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## (54) Title: CYTOSOLIC PROTEIN TARGETING ENGINEERED DEUBIQUITINASES AND METHODS OF USE THEREOF

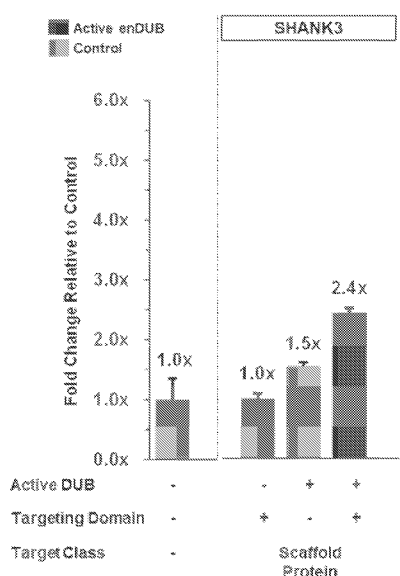


FIG. 3

(57) Abstract: Provided herein are fusion protein comprising: an effector domain comprising a catalytic domain of a deubiquitinase, or a functional fragment or functional variant thereof; and a targeting domain comprising a moiety that specifically binds a cytosolic protein. Also provided herein are methods of using the fusion proteins to treat a disease, including genetic diseases.

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# **CYTOSOLIC PROTEIN TARGETING ENGINEERED DEUBIQUITINASES AND METHODS OF USE THEREOF**

## **CROSS-REFERENCE TO RELATED APPLICATIONS**

This application claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional Patent Application No. 63/110,622, filed November 6, 2020, the entire disclosure of which is incorporated herein by reference.

### **1. FIELD**

[0001] This disclosure relates to fusion proteins comprising an effector domain comprising a catalytic domain of a deubiquitinase, or a functional fragment or functional variant thereof; and a targeting domain comprising a moiety that specifically binds a target cytosolic protein. The disclosure further relates to therapeutic methods of using the same.

### **2. BACKGROUND**

[0002] A subset of genetic diseases are associated with a decrease in the level of expression of a functional cytosolic protein or a decrease in the stability of a cytosolic protein. For example, haploinsufficiency genetic diseases are caused by the presence a single copy of a wild-type allele in heterozygous combination with a loss of function variant allele, wherein the level of functional protein expressed is insufficient to produce the standard phenotype. Haploinsufficiency can arise from a de novo or inherited loss-of-function mutation in the variant allele, such that it produces little or no functional protein. Despite recent developments in gene therapy, there are still no curative treatments for these diseases, and treatment typically centers on the management of symptoms. Therefore, new treatments are needed for diseases, e.g., genetic diseases, that are associated with decreased functional cytosolic protein expression or stability.

### **3. SUMMARY**

[0003] Provided herein are, *inter alia*, engineered deubiquitinases (enDubs) that comprise a targeting moiety that specifically binds a cytosolic target protein and a catalytic domain of a deubiquitinase. The targeting moiety directs that deubiquitinase catalytic domain to the specific target cytosolic protein for deubiquitination. The fusion proteins described herein are particularly

useful in methods of treating genetic diseases, particularly those associated with or caused by decreased expression or stability of a specific cytosolic protein.

[0004] In one aspect, provided herein are fusion proteins comprising: an effector domain comprising a catalytic domain of a deubiquitinase, or a functional fragment or functional variant thereof; and a targeting domain comprising a targeting moiety that specifically binds a cytosolic protein.

[0005] In some embodiments, the deubiquitinase is a cysteine protease or a metalloprotease.

[0006] In some embodiments, the deubiquitinase is a cysteine protease. In some embodiments, the cysteine protease is a ubiquitin-specific protease (USP), a ubiquitin C-terminal hydrolase (UCH), a Machado-Josephin domain protease (MJD), an ovarian tumour protease (OTU), a MINDY protease, or a ZUFSP protease. In some embodiments, the cysteine protease is a USP. In some embodiments, the USP is USP1, USP2, USP3, USP4, USP5, USP6, USP7, USP8, USP9X, USP9Y, USP10, USP11, USP12, USP13, USP14, USP15, USP16, USP17, USP17L2, USP17L3, USP17L4, USP17L5, USP17L7, USP17L8, USP18, USP19, USP20, USP21, USP22, USP23, USP24, USP25, USP26, USP27X, USP28, USP29, USP30, USP31, USP32, USP33, USP34, USP35, USP36, USP37, USP38, USP39, USP40, USP41, USP42, USP43, USP44, USP45, or USP46.

[0007] In some embodiments, the cysteine protease is a UCH. In some embodiments, the UCH is BAP1, UCHL1, UCHL3, or UCHL5.

[0008] In some embodiments, the cysteine protease is a MJD. In some embodiments, the MJD is ATXN3 or ATXN3L.

[0009] In some embodiments, the cysteine protease is an OTU. In some embodiments, the OTU is OTUB1 or OTUB2.

[0010] In some embodiments, the cysteine protease is a MINDY. In some embodiments, the MINDY is MINDY1, MINDY2, MINDY3, or MINDY4.

[0011] In some embodiments, the cysteine protease is a ZUFSP. In some embodiments, the ZUFSP is ZUP1.

[0012] In some embodiments, the deubiquitinase is a metalloprotease. In some embodiments, the metalloprotease is a Jab1/Mov34/Mpr1 Pad1 N-terminal+ (MPN+) (JAMM) domain protease.

[0013] In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%,



97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 1-112.

**[0014]** In some embodiments, the catalytic domain comprises a catalytic domain derived from a deubiquitinase comprising an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 1-112.

**[0015]** In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 113-220 or 286.

**[0016]** In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 286.

**[0017]** In some embodiments, the catalytic domain comprises an amino acid sequence that is a functional fragment of the amino acid sequence of any one of SEQ ID NOS: 1-112.

**[0018]** In some embodiments, the catalytic domain comprises an amino acid sequence that is a functional fragment of the amino acid sequence of any one of SEQ ID NOS: 113-220 or 286.

**[0019]** In some embodiments, the moiety that specifically binds a cytosolic protein comprises an antibody, or functional fragment or functional variant thereof. In some embodiments, the antibody, or functional fragment or functional variant thereof, comprises a full-length antibody, a single chain variable fragment (scFv), a scFv2, a scFv-Fc, a Fab, a Fab', a F(ab')<sub>2</sub>, a F(v), a VHH, or a (VHH)<sub>2</sub>. In some embodiments, the antibody, or functional fragment or functional variant thereof, comprises a VHH or a (VHH)<sub>2</sub>.

**[0020]** In some embodiments, the cytosolic protein is cyclin-dependent kinase-like 5 (CDKL5), copper-transporting ATPase 2 (ATP7B), syntaxin-binding protein 1 (STXBP1), Ras/Rap GTPase-activating protein (SYNGAP1), progranulin (GRN), protein jagged-1 (JAG1), GATOR complex protein DEPDC5 (DEPDC5), tuberlin (TSC2), hamartin (TSC1), kinesin-like protein KIF1A (KIF1A), dynamin-1 (DNM1), SH3 and multiple ankyrin repeat domains protein 3 (SHANK3), dystrophin (DMD), oxygen-regulated protein 1 (RP1), titin (TTN), cytoplasmic dynein 1 heavy chain 1 (DYNC1H1), TRIO and F-actin-binding protein (TRIO), probable ubiquitin carboxyl-terminal hydrolase FAF-X (USP9X), cystatin-B (CSTB), or pterin-4- $\alpha$ -carbinolamine dehydratase (PCBD1).

**[0021]** In some embodiments, the cytosolic protein comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to any one of SEQ ID NOS: 221-328 or 287-289.

**[0022]** In some embodiments, the effector domain is directly fused to the targeting domain. In some embodiments, the effector domain is indirectly fused to the targeting domain. In some embodiments, the effector domain is indirectly fused to the targeting domain via a peptide linker. In some embodiments, the effector domain is indirectly fused to the targeting domain via a peptide linker of sufficient length such that the effector domain and the targeting domain can simultaneously bind the respective target proteins. In some embodiments, the peptide linker comprises the amino acid sequence of any one of SEQ ID NOS: 375-384 or 402-519, or the amino acid sequence of any one of SEQ ID NOS: 375-384 or 402-519 comprising 1, 2, or 3 amino acid modifications. In some embodiments, the peptide linker comprises the amino acid sequence of any one of SEQ ID NOS: 375-384, or the amino acid sequence of any one of SEQ ID NOS: 375-384 comprising 1, 2, or 3 amino acid modifications.

**[0023]** In some embodiments, the effector domain is operably connected either directly or indirectly to the C terminus of the targeting domain. In some embodiments, the effector moiety is operably connected either directly or indirectly to the N terminus of the targeting domain.

**[0024]** In some embodiments, the targeting domain comprises a VHH of any one of claims 62-69, or a (VHH)<sub>2</sub> of any one of claims 70-81.

**[0025]** In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 286.

**[0026]** In some embodiments, the effector domain is indirectly fused to the targeting domain via a peptide linker of sufficient length such that the effector domain and the targeting domain can simultaneously bind the respective target proteins. In some embodiments, the peptide linker comprises the amino acid sequence of any one of SEQ ID NOS: 375-384 or 402-519, or the amino acid sequence of any one of SEQ ID NOS: 375-384 or 402-519 comprising 1, 2, or 3 amino acid modifications. In some embodiments, the peptide linker comprises the amino acid sequence of any one of SEQ ID NOS: 375-384, or the amino acid sequence of any one of SEQ ID NOS: 375-384 comprising 1, 2, or 3 amino acid modifications.

**[0027]** In some embodiments, the effector domain is operably connected either directly or

indirectly to the C terminus of the targeting domain. In some embodiments, the effector moiety is operably connected either directly or indirectly to the N terminus of the targeting domain.

[0028] In some embodiments, the fusion protein comprises an amino acid sequence at least at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 320-367.

[0029] In one aspect, provided herein are nucleic acid molecules encoding a fusion protein described herein. In some embodiments, the nucleic acid molecule is a DNA molecule. In some embodiments, the nucleic acid molecule is an RNA molecule.

[0030] In one aspect, provided herein are vectors comprising a nucleic acid molecule described herein (e.g., a nucleic acid molecule encoding a fusion protein described herein). In some embodiments, the vector is a plasmid or a viral vector.

[0031] In one aspect, provided herein are viral particles comprising a nucleic acid molecule described herein (e.g., a nucleic acid molecule encoding a fusion protein described herein).

[0032] In one aspect, provided herein are in vitro cell or population of cells comprising a fusion protein described herein, a nucleic acid molecule described herein, or a vector described herein.

[0033] In one aspect, provided herein are pharmaceutical compositions comprising a fusion protein described herein, a nucleic acid described herein, a vector described herein, or a viral particle described herein, and an excipient.

[0034] In one aspect, provided herein are methods of making a fusion protein described herein, comprising introducing into an in vitro cell or population of cells a nucleic acid molecule described herein, a vector described herein, or a viral particle described herein; culturing the cell or population of cells in a culture medium under conditions suitable for expression of the fusion protein, isolating the fusion protein from the culture medium, and optionally purifying the fusion protein.

[0035] In one aspect, provided herein are methods of treating or preventing a disease in a subject comprising administering a fusion protein described herein, a nucleic acid molecule described herein, a vector described herein, a viral particle described herein, or a pharmaceutical composition described herein, to a subject in need thereof. In some embodiments, the subject is human.

[0036] In some embodiments, the disease is associated with decreased expression of a

functional version of the cytosolic protein relative to a non-diseased control. In some embodiments, the disease is associated with decreased stability of a functional version of the cytosolic protein relative to a non-diseased control. In some embodiments, the disease is associated with increased ubiquitination of the cytosolic protein relative to a non-diseased control. In some embodiments, the disease is associated with increased ubiquitination and degradation of the cytosolic protein relative to a non-diseased control. In some embodiments, disease is a genetic disease. In some embodiments, the disease is a haploinsufficiency disease.

**[0037]** In some embodiments, the disease is SYNGAP1 encephalopathy, CDKL5 deficiency disorder, STXBP1 encephalopathy, early infantile epileptic encephalopathy type 2, Wilson disease, early infantile epileptic encephalopathy type 4, mental retardation autosomal dominant 5, aphasia, alagille syndrome 1, epilepsy, tuberous sclerosis-2, tuberous sclerosis-1, KIF1A-associated neurological disorder, encephalopathy, Phelan-McDermid syndrome, Becker Muscular Dystrophy, RP1, retinitis pigmentosa 1, dilated cardiomyopathy 1G, DYNC1H1 Syndrome, TRIO-Related intellectual disability (ID), USP9X Development Disorder, epilepsy, progressive myoclonic 1 (EPM1), or hyperphenylalaninemia BH4-deficient D (HPABH4D).

**[0100]** In some embodiments, the target cytosolic protein is SYNGAP1, and the disease is SYNGAP1 encephalopathy; the target cytosolic protein is SYNGAP1, and the disease is Mental retardation autosomal dominant 5; the target cytosolic protein is CDKL5, and the disease is CDKL5 deficiency disorder; the target cytosolic protein is CDKL5, and the disease is an early infantile epileptic encephalopathy; the target cytosolic protein is CDKL5, and the disease is early infantile epileptic encephalopathy type 2; the target cytosolic protein is ATP7B, and the disease is Wilson disease; the target cytosolic protein is STXBP1, and the disease is STXBP1 encephalopathy; the target cytosolic protein is STXBP1, and the disease is an early infantile epileptic encephalopathy; the target cytosolic protein is STXBP1, and the disease is early infantile epileptic encephalopathy type 4; the target cytosolic protein is GRN, and the disease is aphasia primary progressive & FTD (frontotemporal degeneration); the target cytosolic protein is JAG1, and the disease is alagille syndrome 1; the target cytosolic protein is DEPDC5, and the disease is epilepsy (e.g., familial focal, with variable foci 1); the target cytosolic protein is TSC2, and the disease is tuberous sclerosis; the target cytosolic protein is TSC2, and the disease is tuberous sclerosis type 2; the target cytosolic protein is TSC2, and the disease is tuberous sclerosis type 1; the target cytosolic protein is TSC1, and the disease is tuberous sclerosis; the target cytosolic

protein is TSC1, and the disease is tuberous sclerosis type 1; the target cytosolic protein is TSC1, and the disease is tuberous sclerosis type 2; the target cytosolic protein is KIF1A, and the disease is KIF1A-associated neurological disorder; the target cytosolic protein is DNMT1, and the disease is a DNMT1 encephalopathy; the target cytosolic protein is DNMT1, and the disease is encephalopathy; the target cytosolic protein is SHANK3, and the disease is Phelan-McDermid syndrome; the target cytosolic protein is DMD, and the disease is Becker Muscular Dystrophy; the target cytosolic protein is RP1, and the disease is retinitis pigmentosa 1; the target cytosolic protein is TTN, and the disease is dilated cardiomyopathy 1G; the target cytosolic protein is DYNC1H1, and the disease is DYNC1H1 Syndrome; the target cytosolic protein is TRIO, and the disease is TRIO-Related intellectual disability (ID); the target cytosolic protein is USP9X, and the disease is USP9X development disorder; the target cytosolic protein is CSTB, and the disease is epilepsy, progressive myoclonic 1 (EPM1); or the target cytosolic protein is PCBD1, and the disease is hyperphenylalaninemia, BH4-deficient, D (HPABH4D). In some embodiments, the target cytosolic protein is SYNGAP1, and the disease is SYNGAP1 encephalopathy.

**[0038]** In some embodiments, the fusion protein, nucleic acid molecule, vector, viral particle, or pharmaceutical composition is administered at a therapeutically effective dose. In some embodiments, the disease is a haploinsufficiency disease. the fusion protein, nucleic acid molecule, vector, viral particle, or pharmaceutical composition is administered systemically or locally. In some embodiments, the disease is a haploinsufficiency disease. In some embodiments the fusion protein, nucleic acid molecule, vector, viral particle, or pharmaceutical composition is administered intravenously, subcutaneously, or intramuscularly.

**[0039]** In one aspect, provided herein are fusion proteins described herein, polynucleotides described herein, DNA described herein, RNA described herein, vectors described herein, viral particles described herein, and pharmaceutical compositions described herein for use as a medicament.

**[0040]** In one aspect, provided herein are fusion proteins described herein, polynucleotides described herein, DNA described herein, RNA described herein, vectors described herein, viral particles described herein, and pharmaceutical compositions described herein for use in treating or inhibiting a genetic disorder.

**[0041]** In one aspect, provided herein are single variable domain antibodies (VHHs) that specifically binds SYNGAP1 comprising three complementarity determining regions: CDR1,

CDR2, and CDR3, wherein the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 290, 294, 298, 302, 306, or 310, or the amino acid sequence of SEQ ID NO: 290, 294, 298, 302, 306, or 310 comprising 1, 2, or 3 amino acid modifications; the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 291, 295, 299, 303, 307, or 311, or the amino acid sequence of SEQ ID NO: 291, 295, 299, 303, 307, or 311 comprising 1, 2, or 3 amino acid modifications; and/or the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 292, 296, 300, 304, 308, or 312, or the amino acid sequence of SEQ ID NO: 292, 296, 300, 304, 308, or 312 comprising 1, 2, or 3 amino acid modifications.

**[0100]** In some embodiments, the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 290, or the amino acid sequence of SEQ ID NO: 290 comprising 1, 2, or 3 amino acid modifications; the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 291, or the amino acid sequence of SEQ ID NO: 291 comprising 1, 2, or 3 amino acid modifications; and/or the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 292, or the amino acid sequence of SEQ ID NO: 292 comprising 1, 2, or 3 amino acid modifications.

**[0101]** In some embodiments, the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 294, or the amino acid sequence of SEQ ID NO: 294 comprising 1, 2, or 3 amino acid modifications; the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 295, or the amino acid sequence of SEQ ID NO: 295 comprising 1, 2, or 3 amino acid modifications; and/or the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 296, or the amino acid sequence of SEQ ID NO: 296 comprising 1, 2, or 3 amino acid modifications.

**[0102]** In some embodiments, the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 298, or the amino acid sequence of SEQ ID NO: 298 comprising 1, 2, or 3 amino acid modifications; the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 299, or the amino acid sequence of SEQ ID NO: 299 comprising 1, 2, or 3 amino acid modifications; and/or the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 300, or the amino acid sequence of SEQ ID NO: 300 comprising 1, 2, or 3 amino acid modifications.

**[0042]** In some embodiments, the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 302, or the amino acid sequence of SEQ ID NO: 302 comprising 1, 2,

or 3 amino acid modifications; the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 303, or the amino acid sequence of SEQ ID NO: 303 comprising 1, 2, or 3 amino acid modifications; and/or the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 304, or the amino acid sequence of SEQ ID NO: 304 comprising 1, 2, or 3 amino acid modifications.

**[0100]** In some embodiments, the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 306, or the amino acid sequence of SEQ ID NO: 306 comprising 1, 2, or 3 amino acid modifications; the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 307, or the amino acid sequence of SEQ ID NO: 307 comprising 1, 2, or 3 amino acid modifications; and/or the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 308, or the amino acid sequence of SEQ ID NO: 308 comprising 1, 2, or 3 amino acid modifications.

**[0101]** In some embodiments, the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 310, or the amino acid sequence of SEQ ID NO: 310 comprising 1, 2, or 3 amino acid modifications; the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 311, or the amino acid sequence of SEQ ID NO: 311 comprising 1, 2, or 3 amino acid modifications; and/or the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 312, or the amino acid sequence of SEQ ID NO: 312 comprising 1, 2, or 3 amino acid modifications.

**[0043]** In some embodiments, the VHH comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 293, 297, 301, 305, 309, or 313.

**[0044]** In one aspect, provided herein are nucleic acid molecules encoding a VHH described herein. In some embodiments, the nucleic acid molecule is a DNA molecule. In some embodiments, the nucleic acid molecule is an RNA molecule.

**[0045]** In one aspect, provided herein are vectors comprising a nucleic acid molecule described herein (e.g., a nucleic acid molecule encoding a VHH described herein). In some embodiments, the vector is a plasmid or a viral vector.

**[0046]** In one aspect, provided herein are viral particles comprising a nucleic acid molecule described herein (e.g., a nucleic acid molecule encoding a VHH described herein).

**[0047]** In one aspect, provided herein are in vitro cell or population of cells comprising a VHH

described herein, a nucleic acid molecule described herein (e.g., a nucleic acid molecule encoding a VHH described herein), or a vector described herein (e.g., a vector comprising a nucleic acid molecule encoding a VHH described herein).

[0048] In one aspect, provided herein are pharmaceutical compositions comprising a VHH described herein, a nucleic acid molecule described herein (e.g., a nucleic acid molecule encoding a VHH described herein), or a vector described herein (e.g., a vector comprising a nucleic acid molecule encoding a VHH described herein) or a viral particle described herein (e.g., a viral particle comprising a nucleic acid molecule encoding a VHH described herein), and an excipient.

[0049] In one aspect, provided herein are methods of making a VHH polypeptides described herein, comprising introducing into an in vitro cell or population of cells a nucleic acid molecule described herein (e.g., a nucleic acid molecule encoding a VHH described herein), or a vector described herein (e.g., a vector comprising a nucleic acid molecule encoding a VHH described herein) or a viral particle described herein (e.g., a viral particle comprising a nucleic acid molecule encoding a VHH described herein); culturing the cell or population of cells in a culture medium under conditions suitable for expression of the VHH, isolating the VHH from the culture medium, and optionally purifying the VHH.

[0050] In one aspect, provided herein are (VHH)<sub>2</sub>s comprising a first VHH that specifically binds SYNGAP1 comprising three complementarity determining regions: CDR1, CDR2, and CDR3, wherein the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 290, 294, 298, 302, 306, or 310, or the amino acid sequence of SEQ ID NO: 290, 294, 298, 302, 306, or 310 comprising 1, 2, or 3 amino acid modifications; the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 291, 295, 299, 303, 307, or 311, or the amino acid sequence of SEQ ID NO: 291, 295, 299, 303, 307, or 311 comprising 1, 2, or 3 amino acid modifications; and/or the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 292, 296, 300, 304, 308, or 312, or the amino acid sequence of SEQ ID NO: 292, 296, 300, 304, 308, or 312 comprising 1, 2, or 3 amino acid modifications; and a second VHH that specifically binds SYNGAP1 comprising three complementarity determining regions: CDR1, CDR2, and CDR3, wherein the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 290, 294, 298, 302, 306, or 310, or the amino acid sequence of SEQ ID NO: 290, 294, 298, 302, 306, or 310 comprising 1, 2, or 3 amino acid modifications; the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 291, 295, 299, 303, 307, or 311, or



the amino acid sequence of SEQ ID NO: 291, 295, 299, 303, 307, or 311 comprising 1, 2, or 3 amino acid modifications; and/or the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 292, 296, 300, 304, 308, or 312, or the amino acid sequence of SEQ ID NO: 292, 296, 300, 304, 308, or 312 comprising 1, 2, or 3 amino acid modifications; wherein the first VHH and the second VHH are directly or indirectly operably connected.

**[0051]** In some embodiments, the first VHH comprises three CDRs: CDR1, CDR2, and CDR3, wherein the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 290, or the amino acid sequence of SEQ ID NO: 290 comprising 1, 2, or 3 amino acid modifications; the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 291, or the amino acid sequence of SEQ ID NO: 291 comprising 1, 2, or 3 amino acid modifications; and/or the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 292, or the amino acid sequence of SEQ ID NO: 292 comprising 1, 2, or 3 amino acid modifications; and the second VHH comprises three CDRs: CDR1, CDR2, and CDR3, wherein the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 290, or the amino acid sequence of SEQ ID NO: 290 comprising 1, 2, or 3 amino acid modifications; the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 291, or the amino acid sequence of SEQ ID NO: 291 comprising 1, 2, or 3 amino acid modifications; and/or the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 292, or the amino acid sequence of SEQ ID NO: 292 comprising 1, 2, or 3 amino acid modifications.

**[0052]** In some embodiments, the first VHH comprises three CDRs: CDR1, CDR2, and CDR3, wherein the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 294, or the amino acid sequence of SEQ ID NO: 294 comprising 1, 2, or 3 amino acid modifications; the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 295, or the amino acid sequence of SEQ ID NO: 295 comprising 1, 2, or 3 amino acid modifications; and/or the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 296, or the amino acid sequence of SEQ ID NO: 296 comprising 1, 2, or 3 amino acid modifications; and the second VHH comprises three CDRs: CDR1, CDR2, and CDR3, wherein the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 294, or the amino acid sequence of SEQ ID NO: 294 comprising 1, 2, or 3 amino acid modifications; the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID

NO: 295, or the amino acid sequence of SEQ ID NO: 295 comprising 1, 2, or 3 amino acid modifications; and/or the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 296, or the amino acid sequence of SEQ ID NO: 296 comprising 1, 2, or 3 amino acid modifications.

**[0053]** In some embodiments, the first VHH comprises three CDRs: CDR1, CDR2, and CDR3, wherein the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 298, or the amino acid sequence of SEQ ID NO: 298 comprising 1, 2, or 3 amino acid modifications; the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 299, or the amino acid sequence of SEQ ID NO: 299 comprising 1, 2, or 3 amino acid modifications; and/or the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 300, or the amino acid sequence of SEQ ID NO: 300 comprising 1, 2, or 3 amino acid modifications; and the second VHH comprises three CDRs: CDR1, CDR2, and CDR3, wherein the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 298, or the amino acid sequence of SEQ ID NO: 298 comprising 1, 2, or 3 amino acid modifications; the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 299, or the amino acid sequence of SEQ ID NO: 299 comprising 1, 2, or 3 amino acid modifications; and/or the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 300, or the amino acid sequence of SEQ ID NO: 300 comprising 1, 2, or 3 amino acid modifications.

**[0054]** In some embodiments, the first VHH comprises three CDRs: CDR1, CDR2, and CDR3, wherein the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 302, or the amino acid sequence of SEQ ID NO: 302 comprising 1, 2, or 3 amino acid modifications; the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 303, or the amino acid sequence of SEQ ID NO: 303 comprising 1, 2, or 3 amino acid modifications; and/or the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 304, or the amino acid sequence of SEQ ID NO: 304 comprising 1, 2, or 3 amino acid modifications; and the second VHH comprises three CDRs: CDR1, CDR2, and CDR3, wherein the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 302, or the amino acid sequence of SEQ ID NO: 302 comprising 1, 2, or 3 amino acid modifications; the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 303, or the amino acid sequence of SEQ ID NO: 303 comprising 1, 2, or 3 amino acid

modifications; and/or the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 304, or the amino acid sequence of SEQ ID NO: 304 comprising 1, 2, or 3 amino acid modifications.

**[0055]** In some embodiments, the first VHH comprises three CDRs: CDR1, CDR2, and CDR3, wherein the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 306, or the amino acid sequence of SEQ ID NO: 306 comprising 1, 2, or 3 amino acid modifications; the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 307, or the amino acid sequence of SEQ ID NO: 307 comprising 1, 2, or 3 amino acid modifications; and/or the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 308, or the amino acid sequence of SEQ ID NO: 308 comprising 1, 2, or 3 amino acid modifications; and the second VHH comprises three CDRs: CDR1, CDR2, and CDR3, wherein the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 306, or the amino acid sequence of SEQ ID NO: 306 comprising 1, 2, or 3 amino acid modifications; the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 307, or the amino acid sequence of SEQ ID NO: 307 comprising 1, 2, or 3 amino acid modifications; and/or the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 308, or the amino acid sequence of SEQ ID NO: 308 comprising 1, 2, or 3 amino acid modifications.

**[0056]** In some embodiments, the first VHH comprises three CDRs: CDR1, CDR2, and CDR3, wherein the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 310, or the amino acid sequence of SEQ ID NO: 310 comprising 1, 2, or 3 amino acid modifications; the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 311, or the amino acid sequence of SEQ ID NO: 311 comprising 1, 2, or 3 amino acid modifications; and/or the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 312, or the amino acid sequence of SEQ ID NO: 312 comprising 1, 2, or 3 amino acid modifications; and the second VHH comprises three CDRs: CDR1, CDR2, and CDR3, wherein the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 310, or the amino acid sequence of SEQ ID NO: 310 comprising 1, 2, or 3 amino acid modifications; the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 311, or the amino acid sequence of SEQ ID NO: 311 comprising 1, 2, or 3 amino acid modifications; and/or the amino acid sequence of CDR3 comprises the amino acid sequence of

SEQ ID NO: 312, or the amino acid sequence of SEQ ID NO: 312 comprising 1, 2, or 3 amino acid modifications.

**[0057]** In some embodiments, the first VHH comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 293, 297, 301, 305, 309, or 313; and the second VHH comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 293, 297, 301, 305, 309, or 313.

**[0100]** In some embodiments, the first VHH comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 293; and the second VHH comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 293; the first VHH comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 297; and the second VHH comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 297; the first VHH comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 301; and the second VHH comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 301; the first VHH comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 305; and the second VHH comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 305; the first VHH comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 309; and the second VHH comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 309; or the first VHH comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 313; and the second VHH comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%,

95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 313.

**[0058]** In some embodiments, the first VHH is operably connected to the second VHH via a peptide linker.

**[0059]** In some embodiments, the peptide linker comprises the amino acid sequence of any one of SEQ ID NOS: 375-384 or 402-519, or the amino acid sequence of any one of SEQ ID NOS: 375-384 or 402-519 comprising 1, 2, or 3 amino acid modifications.

**[0060]** In one aspect, provided herein are nucleic acid molecules encoding a (VHH)<sub>2</sub> described herein. In some embodiments, the nucleic acid molecule is a DNA molecule. In some embodiments, the nucleic acid molecule is an RNA molecule.

**[0061]** In one aspect, provided herein are vectors comprising a nucleic acid molecule described herein (e.g., a nucleic acid molecule encoding a (VHH)<sub>2</sub> described herein). In some embodiments, the vector is a plasmid or a viral vector.

**[0062]** In one aspect, provided herein are viral particles comprising a nucleic acid molecule described herein (e.g., a nucleic acid molecule encoding a (VHH)<sub>2</sub> described herein).

**[0063]** In one aspect, provided herein are in vitro cell or population of cells comprising a (VHH)<sub>2</sub> described herein, a nucleic acid molecule described herein (e.g., a nucleic acid molecule encoding a (VHH)<sub>2</sub> described herein), or a vector described herein (e.g., a vector comprising a nucleic acid molecule encoding a (VHH)<sub>2</sub> described herein).

**[0064]** In one aspect, provided herein are pharmaceutical compositions comprising a (VHH)<sub>2</sub> described herein, a nucleic acid molecule described herein (e.g., a nucleic acid molecule encoding a (VHH)<sub>2</sub> described herein), or a vector described herein (e.g., a vector comprising a nucleic acid molecule encoding a (VHH)<sub>2</sub> described herein) or a viral particle described herein (e.g., a viral particle comprising a nucleic acid molecule encoding a (VHH)<sub>2</sub> described herein), and an excipient.

**[0065]** In one aspect, provided herein are methods of making a (VHH)<sub>2</sub> polypeptides described herein, comprising introducing into an in vitro cell or population of cells a nucleic acid molecule described herein (e.g., a nucleic acid molecule encoding a (VHH)<sub>2</sub> described herein), or a vector described herein (e.g., a vector comprising a nucleic acid molecule encoding a (VHH)<sub>2</sub> described herein) or a viral particle described herein (e.g., a viral particle comprising a nucleic acid molecule encoding a (VHH)<sub>2</sub> described herein); culturing the cell or population of cells in a culture medium

under conditions suitable for expression of the (VHH)<sub>2</sub>, isolating the (VHH)<sub>2</sub> from the culture medium, and optionally purifying the (VHH)<sub>2</sub>.

[0066] In some embodiments, the peptide linker comprises the amino acid sequence of any one of SEQ ID NOS: 375-384, or the amino acid sequence of any one of SEQ ID NOS: 375-384 comprising 1, 2, or 3 amino acid modifications.

[0067] In one aspect, provided herein, are fusion proteins comprising: (a) an effector domain comprising a catalytic domain of a deubiquitinase, or a functional fragment or functional variant thereof; and (b) a targeting domain comprising a targeting moiety that specifically binds a cytosolic protein.

[0068] In some embodiments, the deubiquitinase is a cysteine protease or a metalloprotease.

[0069] In some embodiments, the deubiquitinase is a cysteine protease. In some embodiments, the cysteine protease is a ubiquitin-specific protease (USP), a ubiquitin C-terminal hydrolase (UCH), a Machado-Josephin domain protease (MJD), an ovarian tumour protease (OTU), a MINDY protease, or a ZUFSP protease.

[0070] In some embodiments, the cysteine protease is a USP. In some embodiments, the USP is selected from the group consisting of USP1, USP2, USP3, USP4, USP5, USP6, USP7, USP8, USP9X, USP9Y, USP10, USP11, USP12, USP13, USP14, USP15, USP16, USP17, USP17L2, USP17L3, USP17L4, USP17L5, USP17L7, USP17L8, USP18, USP19, USP20, USP21, USP22, USP23, USP24, USP25, USP26, USP27X, USP28, USP29, USP30, USP31, USP32, USP33, USP34, USP35, USP36, USP37, USP38, USP39, USP40, USP41, USP42, USP43, USP44, USP45, and USP46.

[0071] In some embodiments, the cysteine protease is a UCH. In some embodiments, the UCH is selected from the group consisting of BAP1, UCHL1, UCHL3, and UCHL5.

[0072] In some embodiments, the cysteine protease is a MJD. In some embodiments, the MJD is selected from the group consisting of ATXN3 and ATXN3L.

[0073] In some embodiments, the cysteine protease is a OTU. In some embodiments, the OTU is selected from the group consisting of OTUB1 and OTUB2.

[0074] In some embodiments, the cysteine protease is a MINDY. In some embodiments, the MINDY is selected from the group consisting of MINDY1, MINDY2, MINDY3, and MINDY4.

[0075] In some embodiments, the cysteine protease is a ZUFSP. In some embodiments, the ZUFSP is ZUP1.

**[0076]** In some embodiments, the deubiquitinase is a metalloprotease. In some embodiments, the metalloprotease is a Jab1/Mov34/Mpr1 Pad1 N-terminal+ (MPN+) (JAMM) domain protease.

**[0077]** In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to any one of SEQ ID NOS: 1-112.

**[0078]** In some embodiments, the catalytic domain comprises a catalytic domain derived from a deubiquitinase at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to any one of SEQ ID NOS: 1-112.

**[0079]** In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to any one of SEQ ID NOS: 113-220.

**[0080]** In some embodiments, the moiety that specifically binds a cytosolic protein comprises an antibody, or functional fragment or functional variant thereof. In some embodiments, the antibody, or functional fragment or functional variant thereof, comprises a full-length antibody, a single chain variable fragment (scFv), a scFv2, a scFv-Fc, a Fab, a Fab', a F(ab')<sub>2</sub>, a F(v), or a VHH. In some embodiments, the antibody, or functional fragment or functional variant thereof, comprises a VHH.

**[0081]** In some embodiments, the cytosolic protein is a transcription factor.

**[0082]** In some embodiments, the cytosolic protein is selected from the group consisting of cyclin-dependent kinase-like 5 (CDKL5), copper-transporting ATPase 2 (ATP7B), syntaxin-binding protein 1 (STXBP1), Ras/Rap GTPase-activating protein (SYNGAP1), progranulin (GRN), protein jagged-1 (JAG1), GATOR complex protein DEPDC5 (DEPDC5), tuberlin (TSC2), hamartin (TSC1), kinesin-like protein KIF1A (KIF1A), dynamin-1 (DNM1), SH3 and multiple ankyrin repeat domains protein 3 (SHANK3), dystrophin (DMD), oxygen-regulated protein 1 (RP1), titin (TTN), cytoplasmic dynein 1 heavy chain 1 (DYNC1H1), TRIO and F-actin-binding protein (TRIO), and probable ubiquitin carboxyl-terminal hydrolase FAF-X (USP9X)

**[0083]** In some embodiments, the cytosolic protein comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to any one of SEQ ID NOS: 221-328.

**[0084]** In some embodiments, the effector domain is directly fused to the targeting domain. In

some embodiments, the effector domain is indirectly fused to the targeting domain. In some embodiments, the effector domain is indirectly fused to the targeting domain via a peptide linker. In some embodiments, the effector domain is indirectly fused to the targeting domain via a peptide linker of sufficient length such that the effector domain and the targeting domain can simultaneously bind the respective target proteins.

[0085] In some embodiments, the effector domain is fused to the C terminus of the targeting domain. In some embodiments, the effector moiety is fused to the N terminus of the targeting domain.

[0086] In one aspect, provided herein are nucleic acid molecules encoding the fusion protein described herein. In some embodiments, the nucleic acid molecule is a DNA molecule. In some embodiments, the nucleic acid molecule is an RNA molecule.

[0087] In one aspect, provided herein are vectors comprising a nucleic acid molecule described herein. In some embodiments, the vector is a plasmid or a viral vector.

[0088] In one aspect, provided herein are viral particles comprising a nucleic acid described herein.

[0089] In one aspect, described herein is an in vitro cell or population of cells comprising a fusion protein described herein, a nucleic acid molecule described herein, or a vector described herein.

[0090] In one aspect, provided herein are pharmaceutical compositions comprising a fusion protein described herein, a nucleic acid molecule described herein, a vector described herein, or a viral particle described herein, and an excipient.

[0091] In one aspect, provided herein are methods of making a fusion protein described herein, comprising (a) introducing into an in vitro cell or population of cells a nucleic acid described herein, a vector described herein, or a viral particle described herein; (b) culturing the cell or population of cells in a culture medium under conditions suitable for expression of the fusion protein, (c) isolating the fusion protein from the culture medium, and (d) optionally purifying the fusion protein.

[0092] In one aspect, provided herein are methods of treating a disease in a subject comprising administering a fusion protein described herein, a nucleic acid described herein, a vector described herein, or a viral particle described herein, or a pharmaceutical composition described herein, to a subject in need thereof.



[0093] In some embodiments, the subject is human.

[0094] In some embodiments, the disease is associated with decreased expression of a functional version of the cytosolic protein relative to a non-diseased control.

[0095] In some embodiments, the disease is associated with decreased stability of a functional version of the cytosolic protein relative to a non-diseased control.

[0096] In some embodiments, the disease is associated with increased ubiquitination and degradation of the cytosolic protein relative to a non-diseased control.

[0097] In some embodiments, the disease is a genetic disease.

[0098] In some embodiments, the disease is a SYNGAP1 encephalopathy, CDKL5 deficiency disorder, STXBP1 encephalopathy early, infantile epileptic encephalopathy type 2, Wilson disease, early infantile epileptic encephalopathy type 4, mental retardation autosomal dominant 5, aphasia (e.g., Aphasia, primary progressive & FTD), alagille syndrome 1, epilepsy (e.g., Familial Focal Epilepsy), tuberous sclerosis-2, tuberous sclerosis-1, KIF1A-associated neurological disorder, encephalopathy, Phelan-McDermid syndrome, Becker Muscular Dystrophy, RP1, retinitis pigmentosa 1, dilated cardiomyopathy 1G, DYNC1H1 Syndrome, TRIO-Related intellectual disability (ID), and USP9X Development Disorder.

[0099] The method of any one of claims 43-48, wherein the disease is early infantile epileptic encephalopathy type 2, Wilson disease, early infantile epileptic encephalopathy type 4, mental retardation autosomal dominant 5, aphasia primary progressive & FTD (frontotemporal degeneration), alagille syndrome 1, epilepsy familial focal with variable foci 1, tuberous sclerosis-2, tuberous sclerosis-1, KIF1A-associated neurological disorder, encephalopathy, Phelan-McDermid syndrome, Becker Muscular Dystrophy, RP1, retinitis pigmentosa 1, dilated cardiomyopathy 1G, DYNC1H1 Syndrome, TRIO-Related intellectual disability (ID), and USP9X Development Disorder.

[00100] In some embodiments, the disease is a haploinsufficiency disease.

[00101] In some embodiments, the fusion protein is administered at a therapeutically effective dose.

[00102] In some embodiments, the fusion protein is administered systematically or locally.

[00103] In some embodiments, the fusion protein is administered intravenously, subcutaneously, or intramuscularly.

#### 4. BRIEF DESCRIPTION OF THE FIGURES

[00104] **FIGS. 1A-1D** provides a schematic representation of exemplary fusion proteins described herein. **FIG. 1A** is a schematic of an engineered deubiquitinase comprising from N' to C' terminus a VHH that specifically binds a cytosolic target protein and the catalytic domain of a deubiquitinase. In this specific embodiment, the C-terminus of the VHH is directly connected to the N-terminus of the catalytic domain of the deubiquitinase. **FIG. 1B** is a schematic of an engineered deubiquitinase comprising from N' to C' terminus the catalytic domain of a deubiquitinase that specifically binds a cytosolic target protein and a VHH that specifically binds a cytosolic target protein. In this specific embodiment, the C-terminus of the catalytic domain of the deubiquitinase is directly connected to the N-terminus of the VHH. **FIG. 1C** is a schematic of an engineered deubiquitinase comprising from N' to C' terminus a VHH that specifically binds a cytosolic target protein and the catalytic domain of a deubiquitinase. In this specific embodiment, the C-terminus of the VHH is indirectly connected to the N-terminus of the catalytic domain of the deubiquitinase through a peptide linker. **FIG. 1D** is a schematic of an engineered deubiquitinase comprising from N' to C' terminus the catalytic domain of a deubiquitinase that specifically binds a cytosolic target protein and a VHH that specifically binds a cytosolic target protein. In this specific embodiment, the C-terminus of the catalytic domain of the deubiquitinase is indirectly connected to the N-terminus of the VHH through a peptide linker.

[00105] **FIG. 2** is a schematic representation of the assay utilized in Example 3, to screen the effect of targeted deubiquitination of different cytosolic proteins on target protein expression.

[00106] **FIG. 3.** is a bar graph depicting the fold change in SHANK3 expression relative to control (as indicated).

[00107] **FIG. 4.** is a bar graph depicting the fold change in SYNGAP1 protein expression relative to control (as indicated).

[00108] **FIG. 5** is a bar graph depicting the fold change in PYDC2 protein expression relative to control (deubiquitinase without the nanobody targeting the alfa-tag).

[00109] **FIG. 6** is a bar graph depicting the fold change in CSTB protein expression relative to control (deubiquitinase without the nanobody targeting the alfa-tag).

[00110] **FIG. 7** is a bar graph depicting the fold change in PCBD1 protein expression relative to control (deubiquitinase without the nanobody targeting the alfa-tag).

[00111] **FIG. 8** is an image of a reduced SDS-PAGE gel stained with Coomassie blue. Two  $\mu$ g

of purified His-SynGAP-EC [1186-1277] obtained from *E. coli* was loaded in the right lane. The left lane labeled “MW” was loaded with a molecular weight marker. The arrow indicates the purified His-SynGAP-EC [1186-1277] protein with a molecular weight of 15.75 kDA.

[00112] FIG. 9 is a bar graph showing the fold change in SYNGAP1 expression relative to control.

## 5. DETAILED DESCRIPTION

### 5.1 Overview

[00113] Ubiquitination is the process by which ubiquitin ligases mediate the addition of ubiquitin, a 76 amino acid regulatory protein, to a substrate protein. Ubiquitination generally starts by the attachment of a single ubiquitin molecule to a lysine amino acid residue of the substrate protein. Mevissen T. et al. Mechanisms of Deubiquitinase Specificity and Regulation Annual Review of Biochemistry 86:1, 159-192 (2017), the entire contents of which is incorporated by reference herein. These monoubiquitination events are abundant and serve various functions. Ubiquitin itself contains seven lysine residues, all of which can be ubiquitinated resulting in polyubiquitinated proteins. Komander, D. et al. Breaking the chains: structure and function of the deubiquitinases. Nat Rev Mol Cell Biol 10, 550–563 (2009), the entire contents of which is incorporated by reference herein. Mono and polyubiquitination can have multiple effects on the substrate protein, including marking the substrate protein for degradation via the proteasome, altering the protein’s cellular location, altering the protein’s activity, and/or promoting or preventing normal protein interactions. See e.g., Hershko A. et al. The ubiquitin system. Annu Rev Biochem. 67:425-79 (1998); Nandi D, et al. The ubiquitin-proteasome system. J Biosci. Mar;31(1):137-55 (2006), the entire contents of each of which is incorporated by reference herein. The effects of ubiquitination can be reversed or prevented by removing the ubiquitin protein(s) from the substrate protein. The removal of ubiquitin from a substrate protein is mediated by deubiquitinase (DUB) proteins. *Id.*

[00114] Numerous genetic diseases are associated with or caused by a decrease in the level of expression of a functional cytosolic protein or the stability of the cytosolic protein. For example, haploinsufficiency genetic diseases are caused by the presence a single copy of a wild-type allele in heterozygous combination with a loss of function variant allele, wherein the level of functional protein expressed is insufficient to produce the standard phenotype. See e.g., Johnson, A. et al,

Causes and effects of haploinsufficiency. Biol Rev, 94: 1774-1785 (2019), the entire contents of which is incorporated by reference herein. Haploinsufficiency can arise from a de novo or inherited loss-of-function mutation in the variant allele, such that it produces little or no functional protein. Other genetic disorders result from the ubiquitination and subsequent degradation of variant but functional proteins, resulting in a decrease in expression of the functional protein.

[00115] The present disclosure provides, *inter alia*, novel fusion proteins that comprise the catalytic domain (or functional fragment thereof) of a deubiquitinase and a targeting moiety, such as a VHH, that specifically binds to a target cytosolic protein. In some embodiments, decreased expression of a functional version of the target cytosolic protein or decreased stability of a functional version of the target cytosolic protein is associated with a disease phenotype. As such, the fusion proteins described herein are particularly useful in the treatment of genetic diseases characterized by a decrease in the level of expression of a functional target cytosolic protein or the stability of the target cytosolic protein. Upon expression of the fusion protein by host cells, the catalytic domain of the deubiquitinase will be specifically targeted to the target cytosolic protein and deubiquitinated, resulting in increased expression of the target cytosolic protein, e.g., to a level sufficient to alleviate the disease phenotype.

## 5.2 Definitions

[00116] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[00117] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure is related. For example, the Concise Dictionary of Biomedicine and Molecular Biology, Juo, Pei-Show, 2nd ed., 2002, CRC Press; The Dictionary of Cell and Molecular Biology, 3rd ed., 1999, Academic Press; and the Oxford Dictionary Of Biochemistry And Molecular Biology, Revised, 2000, Oxford University Press, provide one of skill with a general dictionary of many of the terms used in this disclosure.

[00118] It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of any subject matter claimed. In this application, the use of the singular includes the plural unless specifically stated otherwise.

**[00119]** It must be noted that, as used in the specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. Furthermore, use of the term “including” as well as other forms, such as “include,” “includes,” and “included,” is not limiting.

**[00120]** It is understood that wherever aspects are described herein with the language “comprising,” otherwise analogous aspects described in terms of “consisting of” and/or “consisting essentially of” are also provided.

**[00121]** The term “and/or” where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. Thus, the term “and/or” as used in a phrase such as “A and/or B” herein is intended to include “A and B,” “A or B,” “A” (alone), and “B” (alone). Likewise, the term “and/or” as used in a phrase such as “A, B, and/or C” is intended to encompass each of the following aspects: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

**[00122]** Units, prefixes, and symbols are denoted in their *Système International de Unites* (SI) accepted form. Numeric ranges are inclusive of the numbers defining the range. The headings provided herein are not limitations of the various aspects of the disclosure, which can be had by reference to the specification as a whole. Accordingly, the terms defined immediately below are more fully defined by reference to the specification in its entirety.

**[00123]** As described herein, any concentration range, percentage range, ratio range or integer range is to be understood to include the value of any integer within the recited range and, when appropriate, fractions thereof (such as one tenth and one hundredth of an integer), unless otherwise indicated.

**[00124]** The terms “about” or “comprising essentially of” refer to a value or composition that is within an acceptable error range for the particular value or composition as determined by one of ordinary skill in the art, which will depend in part on how the value or composition is measured or determined, i.e., the limitations of the measurement system. For example, “about” or “comprising essentially of” can mean within 1 or more than 1 standard deviation per the practice in the art. Alternatively, “about” or “comprising essentially of” can mean a range of up to 20%. Furthermore, particularly with respect to biological systems or processes, the terms can mean up to an order of magnitude or up to 5-fold of a value. When particular values or compositions are provided in the application and claims, unless otherwise stated, the meaning of “about” or “comprising essentially

of” should be assumed to be within an acceptable error range for that particular value or composition.

**[00125]** As used herein, the term “catalytic domain” in reference to a deubiquitinase refers to an amino acid sequence, or a variant thereof, of a deubiquitinase that is capable of mediating deubiquitination of a target protein. The catalytic domain may comprise a naturally occurring amino acid sequence of a deubiquitinase or it may comprise a variant amino acid sequence of a naturally occurring deubiquitinase. The catalytic domain may comprise the minimum amino acid sequence of a deubiquitinase to mediate deubiquitination of a target protein. The catalytic domain may comprise more than the minimum amino acid sequence of a deubiquitinase to mediate deubiquitination of a target protein.

**[00126]** The terms “polynucleotide” and “nucleic acid sequence” are used interchangeably herein and refer to a polymer of DNA or RNA. The polynucleotide sequence can be single-stranded or double-stranded; contain natural, non-natural, or altered nucleotides; and contain a natural, non-natural, or altered internucleotide linkage, such as a phosphoroamidate linkage or a phosphorothioate linkage, instead of the phosphodiester found between the nucleotides of an unmodified polynucleotide sequence. Polynucleotide sequences include, but are not limited to, all polynucleotide sequences which are obtained by any means available in the art, including, without limitation, recombinant means, *e.g.*, the cloning of polynucleotide sequences from a recombinant library or a cell genome, using ordinary cloning technology and polymerase chain reaction, and the like, and by synthetic means.

**[00127]** The terms “amino acid sequence” and “polypeptide” are used interchangeably herein and refer to a polymer of amino acids connected by one or more peptide bonds.

**[00128]** The term “functional variant” as used herein in reference to a protein or polypeptide refers to a protein that comprises at least one amino acid modification (*e.g.*, a substitution, deletion, addition) compared to the amino acid sequence of a reference protein, that retains at least one particular function. In some embodiments, the reference protein is a wild type protein. For example, a functional variant of an IL-2 protein can refer to an IL-2 protein comprising an amino acid substitution as compared to a wild type IL-2 protein that retains the ability to bind the intermediate affinity IL-2 receptor but abrogates the ability of the protein to bind the high affinity IL-2 receptor. Not all functions of the reference wild type protein need be retained by the functional variant of the protein. In some instances, one or more functions are selectively reduced

or eliminated.

**[00129]** The term “functional fragment” as used herein in reference to a protein or polypeptide refers to a fragment of a reference protein that retains at least one particular function. For example, a functional fragment of an anti-HER2 antibody can refer to a fragment of the anti-HER2 antibody that retains the ability to specifically bind the HER2 antigen. Not all functions of the reference protein need be retained by a functional fragment of the protein. In some instances, one or more functions are selectively reduced or eliminated.

**[00130]** As used herein, the term “modification,” with reference to a polynucleotide sequence, refers to a polynucleotide sequence that comprises at least one substitution, alteration, inversion, addition, or deletion of nucleotide compared to a reference polynucleotide sequence. Modifications can include non-naturally nucleotides. As used herein, the term “modification,” with reference to an amino acid sequence refers to an amino acid sequence that comprises at least one substitution, alteration, inversion, addition, or deletion of an amino acid residue compared to a reference amino acid sequence. Modifications can include the inclusion of non-naturally occurring amino acid residues.

**[00131]** As used herein, the term “derived from” with reference to an amino acid sequence refers to an amino acid sequence that has at least 80% sequence identity to a reference naturally occurring amino acid sequence. For example, a catalytic domain derived from a naturally occurring deubiquitinase means that the catalytic domain has an amino acid sequence with at least 80% sequence identity to the sequence of the deubiquitinase catalytic domain from which it is derived. The term “derived from” as used herein does not denote any specific process or method for obtaining the amino acid sequence. For example, the amino acid sequence can be chemically or recombinantly synthesized.

**[00132]** The term “fusion protein” and grammatical equivalents as used herein refers to a protein that comprises an amino acid sequence derived from at least two separate proteins. The amino acid sequence of the at least two separate proteins can be directly connected through a peptide bond; or can be operably connected through an amino acid linker. Therefore, the term fusion protein encompasses embodiments, wherein the amino acid sequence of e.g., Protein A is directly connected to the amino acid sequence of Protein B through a peptide bond (Protein A – Protein B), and embodiments, wherein the amino acid sequence of e.g., Protein A is operably connected to the amino acid sequence of Protein B through an amino acid linker (Protein A – linker

– Protein B).

**[00133]** The term “fuse” and grammatical equivalents thereof as used herein refers to the operable connection of an amino acid sequence derived from one protein to the amino acid sequence derived from different protein. The term fuse encompasses both a direct connection of the two amino acid sequences through a peptide bond, and the indirect connection through an amino acid linker.

**[00134]** An “isolated antibody” refers to an antibody that is substantially free of other antibodies having different antigenic specificities (e.g., an isolated antibody that binds specifically to HER2 is substantially free of antibodies that bind specifically to antigens other than HER2). An isolated antibody that binds specifically to HER2 may, however, cross-react with other antigens, such as HER2 molecules from different species. Moreover, an isolated antibody may be substantially free of other cellular material and/or chemicals. By comparison, an “isolated” nucleic acid refers to a nucleic acid composition of matter that is markedly different, i.e., has a distinctive chemical identity, nature and utility, from nucleic acids as they exist in nature. For example, an isolated DNA, unlike native DNA, is a freestanding portion of a native DNA and not an integral part of a larger structural complex, the chromosome, found in nature. Further, an isolated DNA, unlike native DNA, can be used as a PCR primer or a hybridization probe for, among other things, measuring gene expression and detecting biomarker genes or mutations for diagnosing disease or predicting the efficacy of a therapeutic. An isolated nucleic acid may also be purified so as to be substantially free of other cellular components or other contaminants, e.g., other cellular nucleic acids or proteins, using standard techniques well known in the art.

**[00135]** As used herein, the term “antibody” or “antibodies” are used in the broadest sense and encompasses various antibody structures, including but not limited to monoclonal antibodies, polyclonal antibodies, multispecific antibodies (e.g., bispecific antibodies), and antibody fragments so long as they exhibit the desired antigen-binding activity (i.e. antigen binding fragments as defined herein). The term antibody thus includes, for example, include full-length antibodies, antigen-binding fragments of full-length antibodies, molecules comprising antibody CDRs, VH regions, and/or VL regions; and antibody-like scaffolds (e.g., fibronectins). Examples of antibodies include, without limitation, monoclonal antibodies, recombinantly produced antibodies, monospecific antibodies, multispecific antibodies (including bispecific antibodies), human antibodies, humanized antibodies, chimeric antibodies, immunoglobulins, synthetic



antibodies, tetrameric antibodies comprising two heavy chain and two light chain molecules, an antibody light chain monomer, an antibody heavy chain monomer, an antibody light chain dimer, an antibody heavy chain dimer, an antibody light chain- antibody heavy chain pair, intrabodies, heteroconjugate antibodies, antibody-drug conjugates, single domain antibodies (e.g., VHH, (VHH)<sub>2</sub>), monovalent antibodies, single chain antibodies, single-chain Fvs (scFv; (scFv)<sub>2</sub>), camelized antibodies, affybodies, Fab fragments (e.g., Fab, single chain Fab (scFab), F(ab')<sub>2</sub> fragments, disulfide-linked Fvs (sdFv), anti-idiotypic (anti-Id) antibodies (including, e.g., anti-anti-Id antibodies), diabodies, tribodies, and antibody-like scaffolds (e.g., fibronectins), Fc fusions (e.g., Fab-Fc, scFv-Fc, VHH-Fc, (scFv)<sub>2</sub>-Fc, (VHH)<sub>2</sub>-Fc, and antigen-binding fragments of any of the above, and conjugates or fusion proteins comprising any of the above. In certain embodiments, antibodies described herein refer to polyclonal antibody populations. In certain embodiments, antibodies described herein refer to monoclonal antibody populations. Antibodies can be of any type (e.g., IgG, IgE, IgM, IgD, IgA or IgY), any class (e.g., IgG<sub>1</sub>, IgG<sub>2</sub>, IgG<sub>3</sub>, IgG<sub>4</sub>, IgA<sub>1</sub> or IgA<sub>2</sub>), or any subclass (e.g., IgG<sub>2a</sub> or IgG<sub>2b</sub>) of immunoglobulin (Ig) molecule. In certain embodiments, antibodies described herein are IgG antibodies, or a class (e.g., human IgG<sub>1</sub> or IgG<sub>4</sub>) or subclass thereof. In a specific embodiment, the antibody is a humanized monoclonal antibody. In another specific embodiment, the antibody is a human monoclonal antibody.

**[00136]** The term “full-length antibody,” as used herein refers to an antibody having a structure substantially similar to a native antibody structure comprising two heavy chains and two light chains interconnected by disulfide bonds. In some embodiments, the two heavy chains comprise a substantially identical amino acid sequence; and the two light chains comprise a substantially identical amino acid sequence. Antibody chains may be substantially identical but not entirely identical if they differ due to post-translational modifications, such as C-terminal cleavage of lysine residues, alternative glycosylation patterns, etc.

**[00137]** The terms “antigen binding fragment” and “antigen binding domain” are used interchangeably herein and refer to one or more polypeptides, other than a full-length antibody, that is capable of specifically binding to antigen and comprises a portion of a full-length antibody (e.g., a VH, a VL). Exemplary antigen binding fragments include, but are not limited to, single domain antibodies (e.g., VHH, (VHH)<sub>2</sub>), single chain antibodies, single-chain Fvs (scFv; (scFv)<sub>2</sub>), camelized antibodies, affybodies, Fab fragments (e.g., Fab, single chain Fab (scFab), F(ab')<sub>2</sub> fragments, and disulfide-linked Fvs (sdFv). The antigen binding domain can be part of a larger

protein, e.g., a full-length antibody.

**[00138]** The term “(scFv)<sub>2</sub>” as used herein refers to an antibody that comprises a first and a second scFv operably connected (e.g., via a linker). The first and second scFv can specifically bind the same or different antigens. In some embodiments, the first and second scFv are operably connected by an amino via an amino acid linker.

**[00139]** The term “(VHH)<sub>2</sub>” as used herein refers to an antibody that comprises a first and a second VHH operably connected (e.g., via a linker). The first and the second VHH can specifically bind the same or different antigens. In some embodiments, the first and second VHH are operably connected by an amino via an amino acid linker.

**[00140]** The term “Fab-Fc” as used herein refers to an antibody that comprises a Fab operably linked to an Fc domain or a subunit of an Fc domain. A full-length antibody described herein comprises two Fabs, one Fab operably connected to one Fc domain and the other Fab operably connected to a second Fc domain.

**[00141]** The term “scFv-Fc” as used herein refers to an antibody that comprises a scFv operably linked to an Fc domain or subunit of an Fc domain.

**[00142]** The term “VHH-Fc” as used herein refers to an antibody that comprises a VHH operably linked to an Fc domain or a subunit of an Fc domain.

**[00143]** The term “(scFv)<sub>2</sub>-Fc” as used herein refers to a (scFv)<sub>2</sub> operably linked to an Fc domain or a subunit of an Fc domain.

**[00144]** The term “(VHH)<sub>2</sub>-Fc” as used herein refers to (VHH)<sub>2</sub> operably linked to an Fc domain or a subunit of an Fc domain.

**[00145]** “Antibody-like scaffolds” are known in the art, for example, fibronectin and designed ankyrin repeat proteins (DARPin) have been used as alternative scaffolds for antigen-binding domains, *see, e.g.*, Gebauer and Skerra, Engineered protein scaffolds as next-generation antibody therapeutics. *Curr Opin Chem Biol* 13:245-255 (2009) and Stumpp et al., Darpins: A new generation of protein therapeutics. *Drug Discovery Today* 13: 695-701 (2008). Exemplary antibody-like scaffold proteins include, but are not limited to, lipocalins (Anticalin), Protein A-derived molecules such as Z-domains of Protein A (Affibody), an A-domain (Avimer/Maxibody), a serum transferrin (trans-body); a designed ankyrin repeat protein (DARPin), VNAR fragments, a fibronectin (AdNectin), a C-type lectin domain (Tetranectin); a variable domain of a new antigen receptor beta-lactamase (VNAR fragments), a human gamma-crystallin or ubiquitin (Affilin

molecules); a kunitz type domain of human protease inhibitors, microbodies such as the proteins from the knottin family, peptide aptamers and fibronectin (adnectin).

**[00146]** As used herein, the term “CDR” or “complementarity determining region” means the noncontiguous antigen combining sites found within the variable region of both heavy and light chain polypeptides. These particular regions have been described by Kabat *et al.*, J. Biol. Chem. 252, 6609-6616 (1977) and Kabat *et al.*, Sequences of protein of immunological interest. (1991), all of which are herein incorporated by reference in their entireties. Unless otherwise specified, the term “CDR” is a CDR as defined by Kabat *et al.*, J. Biol. Chem. 252, 6609-6616 (1977) and Kabat *et al.*, Sequences of protein of immunological interest. (1991).

**[00147]** As used herein, the term “framework (FR) amino acid residues” refers to those amino acids in the framework region of an antibody variable region. The term “framework region” or “FR region” as used herein, includes the amino acid residues that are part of the variable region, but are not part of the CDRs (*e.g.*, using the Kabat definition of CDRs).

**[00148]** As used herein, the term “heavy chain” when used in reference to an antibody can refer to any distinct type, *e.g.*, alpha ( $\alpha$ ), delta ( $\delta$ ), epsilon ( $\epsilon$ ), gamma ( $\gamma$ ), and mu ( $\mu$ ), based on the amino acid sequence of the constant domain, which give rise to IgA, IgD, IgE, IgG, and IgM classes of antibodies, respectively, including subclasses of IgG, *e.g.*, IgG<sub>1</sub>, IgG<sub>2</sub>, IgG<sub>3</sub>, and IgG<sub>4</sub>.

**[00149]** As used herein, the term “light chain” when used in reference to an antibody can refer to any distinct type, *e.g.*, kappa ( $\kappa$ ) or lambda ( $\lambda$ ) based on the amino acid sequence of the constant domains. Light chain amino acid sequences are well known in the art. In specific embodiments, the light chain is a human light chain.

**[00150]** As used herein, the terms “variable region” refers to a portion of an antibody, generally, a portion of a light or heavy chain, typically about the amino-terminal 110 to 120 amino acids or 110 to 125 amino acids in the mature heavy chain and about 90 to 115 amino acids in the mature light chain, which differ extensively in sequence among antibodies and are used in the binding and specificity of a particular antibody for its particular antigen. The variability in sequence is concentrated in those regions called complementarity determining regions (CDRs) while the more highly conserved regions in the variable domain are called framework regions (FR). Without wishing to be bound by any particular mechanism or theory, it is believed that the CDRs of the light and heavy chains are primarily responsible for the interaction and specificity of the antibody with antigen. In certain embodiments, the variable region is a human variable region. In certain

embodiments, the variable region comprises rodent or murine CDRs and human framework regions (FRs). In particular embodiments, the variable region is a primate (*e.g.*, non-human primate) variable region. In certain embodiments, the variable region comprises rodent or murine CDRs and primate (*e.g.*, non-human primate) framework regions (FRs).

**[00151]** The terms “VL” and “VL domain” are used interchangeably to refer to the light chain variable region of an antibody.

**[00152]** The terms “VH” and “VH domain” are used interchangeably to refer to the heavy chain variable region of an antibody.

**[00153]** As used herein, the terms “constant region” and “constant domain” are interchangeable and are common in the art. The constant region is an antibody portion, *e.g.*, a carboxyl terminal portion of a light and/or heavy chain which is not directly involved in binding of an antibody to antigen but which can exhibit various effector functions, such as interaction with an Fc receptor (*e.g.*, Fc gamma receptor). The constant region of an immunoglobulin (Ig) molecule generally has a more conserved amino acid sequence relative to an immunoglobulin (Ig) variable domain.

**[00154]** The term “Fc region” as used herein refers to the C-terminal region of an immunoglobulin (Ig) heavy chain that comprises from N- to C-terminus at least a CH2 domain operably connected to a CH3 domain. In some embodiments, the Fc region comprises an immunoglobulin (Ig) hinge region operably connected to the N-terminus of the CH2 domain. Examples of proteins with engineered Fc regions can be found in Saunders 2019 (K. O. Saunders, “*Conceptual Approaches to Modulating Antibody Effector Functions and Circulation Half-Life*,” 2019, *Frontiers in Immunology*, V. 10, Art. 1296, pp. 1-20, which is incorporated by reference herein).

**[00155]** As used herein, the term “EU numbering system” refers to the EU numbering convention for the constant regions of an antibody, as described in Edelman, G.M. *et al.*, *Proc. Natl. Acad. USA*, 63, 78-85 (1969) and Kabat *et al.*, *Sequences of Proteins of Immunological Interest*, U.S. Dept. Health and Human Services, 5th edition, 1991, each of which is herein incorporated by reference in its entirety.

**[00156]** As used herein, the term “Kabat numbering system” refers to the Kabat numbering convention for variable regions of an antibody, see *e.g.*, Kabat *et al.*, *Sequences of Proteins of Immunological Interest*, U.S. Dept. Health and Human Services, 5th edition, 1991. Unless otherwise noted, numbering of the variable regions of an antibody are denoted according to the

Kabat numbering system.

**[00157]** As used herein, the terms “specifically binds,” refers to molecules that bind to an antigen (*e.g.*, epitope or immune complex) as such binding is understood by one skilled in the art. For example, a molecule that specifically binds to an antigen can bind to other peptides or polypeptides, generally with lower affinity as determined by, *e.g.*, immunoassays, BIAcore<sup>®</sup>, KinExA 3000 instrument (Sapidyne Instruments, Boise, ID), or other assays known in the art. In a specific embodiment, molecules that specifically bind to an antigen bind to the antigen with a  $K_A$  that is at least 2 logs (*e.g.*, factors of 10), 2.5 logs, 3 logs, 4 logs or greater than the  $K_A$  when the molecules bind non-specifically to another antigen. The skilled worker will appreciate that an antibody, as described herein, can specifically bind to more than one antigen (*e.g.*, via different regions of the antibody molecule). The term specifically binds includes molecules that are cross reactive with the same antigen of a different species. For example, an antigen binding domain that specifically binds human CD20 may be cross reactive with CD20 of another species (*e.g.*, cynomolgus monkey, or murine), and still be considered herein to specifically bind human CD20.

**[00158]** “Affinity” refers to the strength of the sum total of non-covalent interactions between a single binding site of a molecule (*e.g.*, a receptor) and its binding partner (*e.g.*, a ligand). Unless indicated otherwise, as used herein, “binding affinity” refers to intrinsic binding affinity, which reflects a 1 : 1 interaction between members of a binding pair (*e.g.*, an antigen binding moiety and an antigen, or a receptor and its ligand). The affinity of a molecule X for its partner Y can generally be represented by the dissociation constant (KD), which is the ratio of dissociation and association rate constants ( $k_{off}$  and  $k_{on}$ , respectively). Thus, equivalent affinities may comprise different rate constants, as long as the ratio of the rate constants remains the same. Affinity can be measured by well-established methods known in the art, including those described herein. A particular method for measuring affinity is Surface Plasmon Resonance (SPR).

**[00159]** The determination of “percent identity” between two sequences (*e.g.*, amino acid sequences or nucleic acid sequences) can be accomplished using a mathematical algorithm. Identity measures the percent of identical matches between the smaller of two or more sequences with gap alignments (if any) addressed by a particular mathematical model or computer program (*i.e.*, “algorithms”). A specific, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin S & Altschul SF (1990) PNAS 87: 2264-2268, modified as in Karlin S & Altschul SF (1993) PNAS 90: 5873-5877, each of which is herein

incorporated by reference in its entirety. Such an algorithm is incorporated into the BLASTN, BLASTP, BLASTX programs of Altschul SF et al., (1990) J Mol Biol 215: 403, which is herein incorporated by reference in its entirety. BLAST nucleotide searches can be performed with the NBLAST nucleotide program parameters set, e.g., for score=100, wordlength=12 to obtain nucleotide sequences homologous to a nucleic acid molecule described herein. BLAST protein searches can be performed with the BLASTP program parameters set, e.g., default settings; to obtain amino acid sequences homologous to a protein molecule described herein. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul SF et al., (1997) Nuc Acids Res 25: 3389-3402, which is herein incorporated by reference in its entirety. Alternatively, PSI BLAST can be used to perform an iterated search which detects distant relationships between molecules (Id.). When utilizing BLAST, Gapped BLAST, and PSI Blast programs, the default parameters of the respective programs (e.g., of BLASTP and BLASTN) can be used (see, e.g., National Center for Biotechnology Information (NCBI) on the worldwide web, [ncbi.nlm.nih.gov](http://ncbi.nlm.nih.gov)). Another specific, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, 1988, CABIOS 4:11-17, which is herein incorporated by reference in its entirety. Such an algorithm is incorporated in the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used. The percent identity between two sequences can be determined using techniques similar to those described above, with or without allowing gaps. In calculating percent identity, typically only exact matches are counted. As described above, the percent identity is based on the amino acid matches between the smaller of two proteins. Therefore, for example, using NCBI Basic Local Alignment Tool - BLASTP program on the default settings (Search Parameters: word size 3, expect value 0.05, hitlist 100, Gapcosts 11,1; Matrix BLOSUM62, Filter string: F; Genetic Code: 1; Window Size: 40; Threshold: 11; Composition Based Stats: 2; Karlin-Altschul Statistics: Lambda: 0.31293; 0.267; K: 0.132922; 0.041; H: 0.401809; 0.14; and Relative Statistics: Effective search space: 288906); the percent identity between SEQ ID NO: 80 and SEQ ID NO: 286 is 100% identity.

**[00160]** As used herein, the term “operably connected” refers to a linkage of polynucleotide sequence elements or amino acid sequence elements in a functional relationship. For example, a polynucleotide sequence is operably connected when it is placed into a functional relationship with

another polynucleotide sequence. In some embodiments, a transcription regulatory polynucleotide sequence *e.g.*, a promoter, enhancer, or other expression control element is operably-linked to a polynucleotide sequence that encodes a protein if it affects the transcription of the polynucleotide sequence that encodes the protein.

**[00161]** The terms “subject” and “patient” are used interchangeably herein and include any human or nonhuman animal. The term “nonhuman animal” includes, but is not limited to, vertebrates such as nonhuman primates, sheep, dogs, and rodents such as mice, rats and guinea pigs. In some embodiments, the subject is a human.

**[00162]** As used herein, the term “administering” refers to the physical introduction of a therapeutic agent (or a precursor of the therapeutic agent that is metabolized or altered within the body of the subject to produce the therapeutic agent *in vivo*) to a subject, using any of the various methods and delivery systems known to those skilled in the art. Exemplary routes of include intravenous, intramuscular, subcutaneous, intraperitoneal, spinal or other parenteral routes of administration, for example by injection or infusion. The term “parenteral administration” as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intralymphatic, intralesional, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion, as well as *in vivo* electroporation. A therapeutic agent may be administered via a non-parenteral route, or orally. Other non-parenteral routes include a topical, epidermal or mucosal route of administration, for example, intranasally, vaginally, rectally, sublingually or topically. Administering can also be performed, for example, once, a plurality of times, and/or over one or more extended periods.

**[00163]** A “therapeutically effective amount” or “therapeutically effective dose” of a drug or therapeutic agent is any amount of the drug that, when used alone or in combination with another therapeutic agent, protects a subject against the onset of a disease or promotes disease regression evidenced by a decrease in severity of disease symptoms, an increase in frequency and duration of disease symptom-free periods, or a prevention of impairment or disability due to the disease affliction. The ability of a therapeutic agent to promote disease regression can be evaluated using a variety of methods known to the skilled practitioner, such as in human subjects during clinical trials, in animal model systems predictive of efficacy in humans, or by assaying the activity of the

agent in in vitro assays.

[00164] The terms “disease,” “disorder,” and “syndrome” are used interchangeably herein.

[00165] As used herein, the terms “treat,” “treating,” “treatment,” and the like refer to reducing or ameliorating a disease and/or symptom(s) associated therewith or obtaining a desired pharmacologic and/or physiologic effect. It will be appreciated that, although not precluded, treating a disease does not require that the disease or symptoms associated therewith be completely eliminated. In some embodiments, the effect is therapeutic, i.e., without limitation, the effect partially or completely reduces, diminishes, abrogates, abates, alleviates, decreases the intensity of, or cures a disease and/or adverse symptom attributable to the disease. In some embodiments, the effect is preventative, i.e., the effect protects or prevents an occurrence or reoccurrence of a disease. To this end, the presently disclosed methods comprise administering a therapeutically effective amount of a compositions as described herein.

### **5.3 Fusion Proteins**

[00166] In certain aspects, provided herein are fusion proteins that comprise an effector domain comprising a catalytic domain of a deubiquitinase, or a functional fragment or functional variant thereof; and a targeting domain comprising a moiety that specifically binds a target cytosolic protein.

#### **5.3.1 Effector Domain**

[00167] In some embodiments, the effector domain comprises a catalytic domain of a deubiquitinase, or a functional fragment or functional variant thereof. In some embodiments, the deubiquitinase is human. In some embodiments, the catalytic domain is derived from a naturally occurring deubiquitinase (e.g., a naturally occurring human deubiquitinase).

[00168] In some embodiments, the amino acid sequence of the effector domain comprises the amino acid sequence of a full length deubiquitinase. In some embodiments, the amino acid sequence of the effector domain comprises the amino acid sequence of a catalytic domain of a deubiquitinase and an additional amino acid sequence at the N-terminal, C-terminal, or N-terminal and C-terminal end of the catalytic domain.

[00169] In some embodiments, the catalytic domain comprises a naturally occurring amino acid sequence of a deubiquitinase. In some embodiments, the catalytic domain comprises a variant of



a naturally occurring deubiquitinase. In some embodiments, the amino acid sequence of the catalytic domain of the fusion protein is at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of a naturally occurring deubiquitinase. In some embodiments, the amino acid sequence of the catalytic domain of the fusion protein comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, or 20 amino acid modifications compared to the amino acid sequence of the catalytic domain of a naturally occurring deubiquitinase.

**[00170]** In some embodiments, the catalytic domain comprises the minimum amino acid sequence of a naturally occurring deubiquitinase sufficient to mediate deubiquitination of a target protein. In some embodiments, the catalytic domain comprises more than the minimum amino acid sequence of a naturally occurring deubiquitinase sufficient to mediate deubiquitination of a target protein.

**[00171]** In some embodiments, the deubiquitinase is a cysteine protease or a metalloprotease. In some embodiments, the deubiquitinase is a cysteine protease. In some embodiments, the deubiquitinase is a metalloprotease. In some embodiments, the deubiquitinase is a ubiquitin-specific protease (USP), a ubiquitin C-terminal hydrolase (UCH), a Machado-Josephin domain protease (MJD), an ovarian tumor protease (OTU), a MINDY protease, or a ZUFSP protease.

**[00172]** Exemplary deubiquitinases include, but are not limited to, USP1, USP2, USP3, USP4, USP5, USP6, USP7, USP8, USP9X, USP9Y, USP10, USP11, USP12, USP13, USP14, USP15, USP16, USP17, USP17L2, USP17L3, USP17L4, USP17L5, USP17L7, USP17L8, USP18, USP19, USP20, USP21, USP22, USP23, USP24, USP25, USP26, USP27X, USP28, USP29, USP30, USP31, USP32, USP33, USP34, USP35, USP36, USP37, USP38, USP39, USP40, USP41, USP42, USP43, USP44, USP45, USP46, BAP1, UCHL1, UCHL3, UCHL5, ATXN3, ATXN3L, OTUB1, OTUB2, MINDY1, MINDY2, MINDY3, MINDY4, and ZUP1. Exemplary deubiquitinases for use in the present disclosure are also disclosed in Komander, D. et al. Breaking the chains: structure and function of the deubiquitinases. *Nat Rev Mol Cell Biol* 10, 550–563 (2009), the entire contents of which is incorporated by reference herein.

**[00173]** In some embodiments, the deubiquitinase is selected from the group consisting of USP1, USP2, USP3, USP4, USP5, USP6, USP7, USP8, USP9X, USP9Y, USP10, USP11, USP12, USP13, USP14, USP15, USP16, USP17, USP17L2, USP17L3, USP17L4, USP17L5, USP17L7, USP17L8, USP18, USP19, USP20, USP21, USP22, USP23, USP24, USP25, USP26, USP27X,

USP28, USP29, USP30, USP31, USP32, USP33, USP34, USP35, USP36, USP37, USP38, USP39, USP40, USP41, USP42, USP43, USP44, USP45, and USP46.

**[00174]** In some embodiments, the deubiquitinase is BAP1, UCHL1, UCHL3, or UCHL5. In some embodiments, the deubiquitinase is ATXN3 or ATXN3L. In some embodiments, the deubiquitinase is OTUB1 or OTUB2. In some embodiments, the deubiquitinase is MINDY1, MINDY2, MINDY3, or MINDY4. In some embodiments, the deubiquitinase is ZUP1. In some embodiments, the deubiquitinase is a Jab1/Mov34/Mpr1 Pad1 N-terminal+ (MPN+) (JAMM) domain protease.

**[00175]** In some embodiments, the deubiquitinase is a deubiquitinase described in Table 1. In some embodiments, the amino acid sequence of the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of a deubiquitinase in Table 1. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to a catalytic domain of a deubiquitinase in Table 1. In some embodiments, the effector domain comprises a functional fragment of a deubiquitinase in Table 1. In some embodiments, the effector domain deubiquitinase comprises a functional variant of deubiquitinase in Table 1. In some embodiments, the catalytic domain comprises a functional fragment of a catalytic domain of a deubiquitinase in Table 1. In some embodiments, the catalytic domain comprises a functional variant of a catalytic domain of a deubiquitinase in Table 1.

**[00176]** In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical any one of SEQ ID NOS: 1-112. In some embodiments, the deubiquitinase consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical any one of SEQ ID NOS: 1-112.

**[00177]** In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 1. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%,

89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 2. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 3. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 4. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 5. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 6. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 7. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 8. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 9. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 10. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 11. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 12. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 13. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 14. In some

embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 15. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 16. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 17. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 18. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 19. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 20. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 21. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 22. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 23. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 24. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 25. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 26. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%,

84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 27. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 28. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 29. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 30. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 31. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 32. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 33. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 34. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 35. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 36. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 37. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 38. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 39.

100% identical to SEQ ID NO: 39. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 40. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 41. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 42. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 43. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 44. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 45. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 46. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 47. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 48. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 49. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 50. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 51. In some embodiments, the deubiquitinase comprises an amino

acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 52. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 53. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 54. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 55. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 56. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 57. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 58. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 59. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 60. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 61. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 62. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 63. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%,

93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 64. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 65. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 66. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 67. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 68. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 69. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 70. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 71. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 72. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 73. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 74. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 75. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 76. In some



embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 77. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 78. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 79. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 80. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 81. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 82. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 83. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 84. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 85. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 86. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 87. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 88. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%,

84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 89. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 90. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 91. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 92. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 93. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 94. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 95. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 96. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 97. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 98. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 99. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 100. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or

100% identical to SEQ ID NO: 101. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 102. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 103. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 104. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 105. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 106. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 107. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 108. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 109. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 110. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 111. In some embodiments, the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 112.

**[00178]** In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the

catalytic domain of any one of SEQ ID NOS: 1-112. In some embodiments, the amino acid sequence of the effector domain consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of any one of SEQ ID NOS: 1-112.

**[00179]** In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 1. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 2. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 3. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 4. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 5. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 6. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 7. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino

acid sequence of the catalytic domain of SEQ ID NO: 8. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 9. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 10. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 11. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 12. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 13. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 14. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 15. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 16. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 17. In some embodiments, the amino acid

sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 18. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 19. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 20. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 21. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 22. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 23. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 24. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 25. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 26. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%,

84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 27. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 28. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 29. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 30. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 31. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 32. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 33. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 34. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 35. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or

100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 36. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 37. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 38. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 39. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 40. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 41. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 42. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 43. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 44. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 45. In some



embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 46. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 47. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 48. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 49. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 50. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 51. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 52. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 53. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 54. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence

at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 55. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 56. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 57. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 58. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 59. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 60. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 61. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 62. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 63. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%,

95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 64. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 65. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 66. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 67. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 68. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 69. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 70. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 71. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 72. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain

of SEQ ID NO: 73. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 74. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 75. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 76. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 77. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 78. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 79. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 80. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 81. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 82. In some embodiments, the amino acid sequence of the effector domain

comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 83. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 84. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 85. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 86. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 87. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 88. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 89. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 90. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 91. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%,

89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 92. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 93. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 94. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 95. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 96. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 97. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 98. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 99. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 100. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 100.

acid sequence of the catalytic domain of SEQ ID NO: 101. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 102. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 103. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 104. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 105. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 106. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 107. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 108. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 109. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 110. In some embodiments, the amino acid

sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 111. In some embodiments, the amino acid sequence of the effector domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the catalytic domain of SEQ ID NO: 112.

**[00180]** In some embodiments, the catalytic domain is derived from a deubiquitinase that comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 1-112. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 1-112.

**[00181]** In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 1. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 2. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 3. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 4. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 5. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an



amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 6. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 7. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 8. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 9. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 10. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 11. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 12. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 13. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 14. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 15. In some

embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 16. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 17. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 18. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 19. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 20. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 21. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 22. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 23. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 24. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%,

98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 25. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 26. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 27. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 28. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 29. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 30. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 31. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 32. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 33. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 34. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%,

81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 35. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 36. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 37. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 38. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 39. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 40. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 41. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 42. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 43. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 44. In some embodiments, the catalytic

domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 45. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 46. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 47. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 48. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 49. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 50. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 51. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 52. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 53. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%

identical to the amino acid sequence of SEQ ID NO: 54. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 55. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 56. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 57. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 58. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 59. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 60. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 61. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 62. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 63. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%,

85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 64. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 65. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 66. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 67. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 68. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 69. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 70. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 71. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 72. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 73. In some embodiments, the catalytic domain is derived

from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 74. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 75. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 76. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 77. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 78. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 79. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 80. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 81. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 82. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the



amino acid sequence of SEQ ID NO: 83. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 84. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 85. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 86. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 87. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 88. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 89. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 90. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 91. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 92. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%,

88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 93. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 94. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 95. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 96. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 97. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 98. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 99. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 100. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 101. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 102. In some embodiments, the catalytic domain is derived from a deubiquitinase

that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 102. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 104. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 105. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 106. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 107. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 108. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 109. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 110. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 111. In some embodiments, the catalytic domain is derived from a deubiquitinase that consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence

of SEQ ID NO: 112.

**[00182]** In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 113-220 or 286. In some embodiments, the catalytic domain consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 113-220.

**[00183]** In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 113. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 114. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 115. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 116. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 117. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 118. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 119. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 120. In some embodiments, the catalytic domain

comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 121. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 122. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 123. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 124. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 125. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 126. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 127. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 128. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 129. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 130. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 131. In some embodiments, the catalytic domain comprises an

amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 132. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 133. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 134. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 135. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 136. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 137. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 138. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 139. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 140. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 141. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 142. In some embodiments, the catalytic domain comprises an amino acid sequence

at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 143. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 144. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 145. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 146. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 147. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 148. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 149. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 150. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 151. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 152. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 153. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%,

82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 154. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 155. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 156. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 157. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 158. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 159. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 160. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 161. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 162. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 163. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 164. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%,



86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 165. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 166. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 167. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 168. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 169. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 170. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 171. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 172. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 173. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 174. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 175. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%,

89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 176. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 177. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 178. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 179. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 180. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 181. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 182. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 183. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 184. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 185. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 186. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%,

92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 187. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 188. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 189. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 190. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 191. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 192. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 193. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 194. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 195. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 196. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 197. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%,

95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 198. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 199. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 200. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 201. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 202. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 203. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 204. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 205. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 206. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 207. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 208. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%,

99%, or 100% identical to the amino acid sequence of SEQ ID NO: 209. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 210. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 211. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 212. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 213. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 214. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 215. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 216. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 217. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 218. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 219. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical

to the amino acid sequence of SEQ ID NO: 220. In some embodiments, the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 286.

**[00184]** Table 1 below describes, the amino acid sequence of exemplary human deubiquitinases and exemplary catalytic domains of the exemplary human deubiquitinases. The catalytic domains are exemplary. A person of ordinary skill in the art could readily determine a sufficient amino acid sequence of a human deubiquitinase to mediate deubiquitination (e.g., a catalytic domain). Any of the human deubiquitinases (functional fragment or variants thereof) may be used to derive a catalytic domain for use in a fusion protein described herein.

**Table 1.** The amino acid sequence of exemplary human deubiquitinases and exemplary catalytic domains of the same

| Description                                          | SEQ ID NO | Amino Acid Sequence                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | SEQ ID NO | Exemplary Catalytic Domains (Amino Acid Sequence)                                                                                                                                                                                                                                                                                                                                                                                                         |
|------------------------------------------------------|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| UBP27_HUMAN Ubiquitin carboxyl-terminal hydrolase 27 | 1         | MCKDYVYDKDIEQIAKEEQGEA<br>LKLQASTSTEVSHQQCSVPGLG<br>EKFPTWETTKPELELLGHNPRR<br>RRITSSFTIGLRGLINLGNTCF<br>MNCIVQALHTHTPILRDFFLSDR<br>HRCMPSPCLVCEMSSLFRE<br>LYSGNPSPHVVPYKLLHLVWIHA<br>RHLAGYRQQDAHEFLIAALDVL<br>HRHCKGDDVGKAANNPNHCNCI<br>IDQIFTGGLQSDVTCQACHGVS<br>TTIDPCWDISLDLPGSCTSFWP<br>MSPGRESSVNGESHIPGITTTLT<br>DCLRRFTRPEHLGSSAKIKCGS<br>CQSYQESTKQLTMNKLPPVACF<br>HFKRFEHSAKQRRKITTYISFP<br>LELDMPFMASKEARMNGQLQ<br>LPTNSGNNENKYSLFAVNVHQQ<br>TLESGHYTSFIRHHKQWFKCD<br>DAVITKASIKDVLDEGYLLFY<br>HKQVLEHESEKVKEMNTQAY | 113       | SSFTIGLRGLINLGNTCFMN<br>CIVQALHTHTPILRDFFLSDR<br>HRCMPSPCLVCEMSSLF<br>RELYSGNPSPHVVPYKLLHLV<br>WIHARHLAGYRQQDAHEFLI<br>AALDVLHRHCKGDDVGKAAN<br>NPNHCNCIIDQIFTGGLQSD<br>VTCQACHGVSTTIDPCWDIS<br>LDLPGSCTSFWPMSPGRESS<br>VNGESHIPGITTTLTDCLRRF<br>TRPEHLGSSAKIKCGSCQSY<br>QESTKQLTMNKLPPVACFHF<br>KRFEHSAKQRRKITTYISFP<br>LELDMPFMASKEARMNGQ<br>LQLPTNSGNNENKYSLFAVV<br>NHQGTLES GHYTSFIRHHKD<br>QWFKCDDAVITKASIKDVLDE<br>SEGYLLFYHKQVLEHESEKVK<br>KEMNTQAY |
| UBP48_HUMAN Ubiquitin carboxyl-terminal hydrolase 48 | 2         | MAPRLQLEKAAWRWAETVRPEE<br>VSQEHITAYRIWLEPCIRGVC<br>RRNCKGNPNCLVGIGEHILWGE<br>IDENSFHNIDDPNCERRKKNSF<br>VGLTNLGATCYVNTFLQVWFLN<br>LELRQALYLCPSTCSDYMLGDG<br>IQEEKDYEPQTICEHLQYLFAL<br>LQNSNRRYIDPSGFVKALGLDT<br>GQQQDAQEFSKLFMSLLEDTL<br>KQKNPDVRNIVQQQFCGEYAYV                                                                                                                                                                                                                                                                 | 114       | NSFHNIDDPNCERRKKNSFV<br>GLTNLGATCYVNTFLQVWFL<br>NLELRQALYLCPSTCSDYML<br>GDGIQEEKDYEPQTICEHLQ<br>YLFALLQNSNRRYIDPSGFV<br>KALGLDTGQQQDAQEFSKLF<br>MSLLEDTL SKQKNPDVRNIV<br>QQQFCGEYAYVTVCNQC GRE<br>SKLLSKFYELNLNIQGHKQL<br>TDCISEFLKEEKLEGDNRYF                                                                                                                                                                                                            |

|                                                    |   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |     |                                                                                                                                                                                                                                                                                                                                        |
|----------------------------------------------------|---|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                    |   | <p>TVCNQCGRESKLLSKFYELELN<br/>IQGHKQLTDCISEFLKEEKLEG<br/>DNRYFCENCQSKQNATRKRILL<br/>SLPCTLNLQLMRVFDROTGHK<br/>KKLNTYIGFSEILDMEPYVEHK<br/>GGSYVYELSAVLIHRGVSAISG<br/>HYIAHVKDPQSGEWYKFNDEDI<br/>EKMEGKKLQLGIEEDLAEPSKS<br/>QTRKPKCGKGTCHCSRNAYMLVY<br/>RLQTQEKPNNTTVQVPAFLQELV<br/>DRDNSKFEEWCIEMAEMRKQSV<br/>DKGKAKHEEVKELYQRLPAGAE<br/>PYEFVSLEWLQKWLDESTPTKP<br/>IDNHACLCSHDKLHPDKISIMK<br/>RISEYAADIFYSRYGGGPRLTV<br/>KALCKECVVERCRILRLKNQLN<br/>EDYKTVNNLLKAAVKGSDGFWV<br/>GKSSLRSWRQLALEQLDEQDGD<br/>AEQSNGKMNGSTLNKDESKEER<br/>KEEEEELNFNEDILCPHGELCIS<br/>ENERRLSKEAWSKLQYFPKA<br/>PEFPSYKECCSQCKILERESEE<br/>NEALHKMIANEQKTSLPNLFQD<br/>KNRPCLSNWPEDTDVLYIVSQF<br/>FVEEWRKFVRKPTRCSPVSSVG<br/>NSALLCPHGGLMFTFASMTKED<br/>SKLIALIWPSEWQMIQKLFVVD<br/>HVIKITRIEVDVNPSETQYIS<br/>EPKLCPECREGLLCQQQRDLRE<br/>YTQATIYVHKVVDNKKVMKDSA<br/>PELVSSSETEEDKEEAKPDGE<br/>KDPDFNQSNNGGTRQKISHQNY<br/>IAYQKQVIRRSMRHRKVRGEKA<br/>LLVSANQTLKELKIQIMHAFSV<br/>APFDQNLSIDGKILSDDCATLG<br/>TLGVIPESVILLKADEPIADYA<br/>AMDDVMQVCMPEEGFKGTGLLG<br/>H</p> |     | <p>CENCQSKQNATRKRILLSLP<br/>CTLNLQLMRVFDROTGHKK<br/>KLNTYIGFSEILDMEPYVEH<br/>KGSYVYELSAVLIHRGVSA<br/>YSGHYIAHVKDPQSGEWYKF<br/>NDEDIEKMEGKKLQLGIEED<br/>LAEPSKSQTRKPKCGKGTCH<br/>SRNAYMLVYRLQT</p>                                                                                                                                      |
| UBP3_HUMAN Ubiquitin carboxyl-terminal hydrolase 3 | 3 | <p>MECPHLSSSVCIAPDSAKFPNG<br/>SPSSWCCSVCRSNKSPWVCLTC<br/>SSVHCGRYVNGHAKKHVEDAQV<br/>PLTNHKKSEKQDKVQHTVCMDC<br/>SSYSTYCYRCDDFVNDTKLGL<br/>VQKVREHLQNLensaftADRHK<br/>KRKLLNSTLNSKLLKVNGSTT<br/>AICATGLRNLGNTCFMNAILQS<br/>LSNIEQFCCYFKELPAVELRNG<br/>KTAGRRTYHTRSQGDNNVSLVE<br/>EFRKTLCALWQGSQTAFSPESL<br/>FYVVKIMPNGRGYQQQDAHEF<br/>MRYLLDHLHLELQGGFNGVSRS</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 115 | <p>TAICATGLRNLGNTCFMNAIL<br/>LQSLSNIEQFCCYFKELPAV<br/>ELRNGKTAGRRTYHTRSQGD<br/>NNVSLVEEFRKTLCALWQGS<br/>QTAFSPESLFYVVKIMPNG<br/>RGYQQQDAHEFMRYLLDHLH<br/>LELQGGFNGVSRSAILQENS<br/>TLSASNKCCINGASTVVTAI<br/>FGGILQNEVNCLICGTESRK<br/>FDPFLDLSDIPSQFRSKRS<br/>KNQENGPVCSLRDCLRSFTD<br/>LEELDETELYMCHKCKKKQK<br/>STKKFWIQKLPKVLCLHLKR</p> |

|                                                                      |   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |     |                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|----------------------------------------------------------------------|---|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                      |   | AILQENSTLSASNKCCINGAST<br>VVTAIFGGILQNEVNCLICGTE<br>SRKFDPFLDLSLDIPSQFRSKR<br>SKNQENGPVCSLRDCLRSFTDL<br>EELDETELYMCHKCKKKQKSTK<br>KFWIQKLPKVLCLHLKRFHWT<br>YLRNKVDITYVEFPLRGLDMKCY<br>LLEPENSGPESCLYDLAAVVVH<br>HSGVGSGHYTAYATHEGRWFH<br>FNDSTVTLTDEETVVKAKAYIL<br>FYVEHQAKAGSDKL                                                                                                                                                                                                                                                                                             |     | FHWTAYLRNKVDITYVEFPLR<br>GLDMKCYLLEPENSGPESCL<br>YDLAAVVVHHGSGVSGHYT<br>AYATHEGRWFHFNDSVTTLT<br>DEETVVKAKAYILFYVEHQ                                                                                                                                                                                                                                                                                                                         |
| U17LB_HUMAN Ubiquitin carboxyl-terminal hydrolase 17-like protein 11 | 4 | QLAPREKLPLSSRRPAAVGAGL<br>QNMGNTCYVNASLQCLTYTPPL<br>ANYMLSREHSQTCHRHKGCMCLC<br>TMQAHITRALHNPUGHVIQPSQA<br>LAAGFHRGKQEDAHEFLMFTVD<br>AMKKACLPGHKQVDHHSKDTTL<br>IHQIFGGYWRSQIKCLHCHGIS<br>DTFDPYLDIALDIQAAQSVQQA<br>LEQLVKPEELNGENAYHCGVCL<br>QRAPASKTTLTLHTSAKVLILVL<br>KRFSVDVTGNKIAKNVQYPECLD<br>MQPYMSQTNTGPLVYVLYAVLV<br>HAGWSCHNGHYFSYVKAQEGQW<br>YKMDDAEVTASSITSVLSQQAY<br>VLFYIQKSEWERHSESVSRGRE<br>PRALGAEDTDRRATQGELKRDH<br>PCLQAPELDEHLVERATQESTL<br>DHWKFLQEONKTKEFNVRKVE<br>GTLPPDVLVIHQSKYKCGMKNH<br>HPEQQSSLLNLSSTTPTHQESM<br>NTGTLASLRGRARRSKGKNKHS<br>KRALLVCQ | 116 | AVGAGLQNMGNTCYVNASLQ<br>CLTYTPPLANYMLSREHSQT<br>CHRHKGCMCLCTMQAHITRAL<br>HNPUGHVIQPSQALAAGFHRG<br>KQEDAHEFLMFTVDAMKKAC<br>LPGHKQVDHHSKDTTLIHQI<br>FGGYWRSQIKCLHCHGISDT<br>FDPYLDIALDIQAAQSVQQA<br>LEQLVKPEELNGENAYHCGV<br>CLQRAPASKTTLTLHTSAKVL<br>ILVLKRFSVDVTGNKIAKNVQ<br>YPECLDMQPYMSQTNTGPLV<br>YVLYAVLVHAGWSCHNGHYF<br>SYVKAQEGQWYKMDDAEVTA<br>SSITSVLSQQAYVLFYIQKS                                                                    |
| UBP1_HUMAN Ubiquitin carboxyl-terminal hydrolase 1                   | 5 | MPGVIPSESNGLSRGSPSKNR<br>LSLKFFQKKETKRALDFTDSQE<br>NEEKASEYRASEIDQVVPAAQS<br>SPINCEKRENLLPFVGLNNLGN<br>TCYLNSILQVLYFCPGFKSGVK<br>HLFNII SRKKEALKDEANQKDK<br>GNCKEDSLASYELICSLQSLII<br>SVEQLQASFLNPEKYTDELAT<br>QPRLLNLTRELNPMYEGYLQH<br>DAQEVLCILGNIQETCQLLKK<br>EEVKNVAELPTKVVEIIPHPKEE<br>MNGINSIEMDSMRHSEDFKEKL<br>PKNGKRKSDTEFGNMKKKVKL<br>SKEHQSLLENQRQTRSKRKATS<br>DTLESPPKII PKYISENESPRP<br>SQKKSrvKINWLKSATKQPSIL<br>SKFCSLGKITTNQGVKGQSKEN<br>ECDPEEDLGKCESDNTTNGCGL                                                                                                | 117 | LPFVGLNNLGNTCYLNSILQ<br>VLYFCPGFKSGVKHLFNII S<br>RKKEALKDEANQKDKGNCKE<br>DSLASYELICSLQSLII SVE<br>QLQASFLNPEKYTDELATQ<br>PRLLNLTRELNPMYEGYLQ<br>HDAQEVLCILGNIQETCQL<br>LKKEEVKNVAELPTKVVEIIP<br>HPKEEMNGINSIEMDSMRHS<br>EDFKEKLPGKNGKRKSDTEF<br>GNMKKKVKLSKEHQSLLENQ<br>RQTRSKRKATSDTLESPPKI<br>I PKYISENESPRPSQKKSrv<br>KINWLKSATKQPSILSKFCS<br>LGKITTNQGVKGQSKENEC<br>PEEDLGKCESDNTTNGCGL<br>SPGNTVTPVNVNEVKPINKG<br>EEQIGFELVEKLFQGQLVLR |



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|                                                      |   | ESPGNTVTPVNVNEVKPINKGE<br>EQIGFELVEKLFQGGQLVLRTRC<br>LECESLTERREDFQDISVPVQE<br>DELSKVEESSEISPEPKTEMKT<br>LRWAISQFASVERIVGEDKYFC<br>ENCHHYTEAERSLLFDKMPEVI<br>TIHLKCFASGLFDCYGGGLS<br>KINTPLLTPLKLSLEEWSTKPT<br>NDSYGLFAVVMHSGITISSGHY<br>TASVKVTDLNSLELDKGNFVVD<br>QMCEIGKPEPLNEEEARGVVEN<br>YNDEEV SIRVGGNTQPSKVLNK<br>KNVEAIGLLGGQKSKADYELYN<br>KASNPDKVASTAFAENRNSETS<br>DTTGTTHESDRNKESDQTGINI<br>SGFENKISYVVQSLKEYEGKWL<br>LFDDSEVKVTEEKDFLNSLSPS<br>TSPTSTPYLLFYKKL                                                                                                                                                                                                                                                                                                                                                                                                  |     | TRCLECESLTERREDFQDIS<br>VVPVQEDELSKVEESSEISPE<br>PKTEMKTLRWASQFASVER<br>IVGEDKYFCENCHHYTEAER<br>SLLFDKMPEVITIHLKCFAS<br>SGLFDCYGGGLSKINTPLL<br>TPLKLSLEEWSTKPTNDSYG<br>LFAVVMHSGITISSGHYTAS<br>VKVTDLNSLELDKGNFVVDQ<br>MCEIGKPEPLNEEEARGVVE<br>NYNDEEV SIRVGGNTQPSKV<br>LNKNVEAIGLLGGQKSKAD<br>YELYNKASNPDKVASTAFAE<br>NRNSETSDTTGTTHESDRNKE<br>SSDQTGINISGFENKISYVV<br>QSLKEYEGKWL LFDDSEVKV<br>TEEKDFLNSLSPSTSTPTSTP<br>YLLFYKKL                                                                                                                                                                                                                                                                                                                                                                |
| UBP40_HUMAN Ubiquitin carboxyl-terminal hydrolase 40 | 6 | MFGDLFEEYSTVSNNQYGGK<br>KLKTKALEPPAPREFTNLGIR<br>NQGGTCYLNLLQTLHFTPEFR<br>EALFSLGPEELGLFEDKDKPDA<br>KVRIIPQLQRLFAQLLLLDQE<br>AASTADLTDSFGWTSNEEMRQH<br>DVQELNRILFSALETSLVGTSG<br>HDLIYRLYHGTIVNQIVCKECK<br>NVSERQEDFLDLTVAVKNVSGL<br>EDALWNMYVEEEVFDCDNLYHC<br>GTCDRLVKAASAKLRKLPPFL<br>TVSLLRFNFDFVKCERYKETSC<br>YTFPLRINLKPFCQSELDDE<br>YIYDLFSVIIHKGCGYGGHYHV<br>YIKDVDHLGNWQFQEEKSKPDV<br>NLKDLQSEEEIDHPLMILKAIL<br>LEENNLIPVDQLGQKLLKKIGI<br>SWNKYRKQHGFLRKFLQLHSQ<br>IFLSSDESTVRLLKNSSLQAE<br>SDFQRNDQQIFKMLPPESPGLN<br>NSISCPHWFDINDSKVQPIREK<br>DIEQQFQKGESAYMLFYRKSQ<br>QRPPEARANPRYGVPCHELLNEM<br>DAANIELQTKRAECDSANNTFE<br>LHLHLGPQYHFFNGALHPVVSQ<br>TESVWDLTFDKRKTGLDLRQSI<br>FQLLEFWEGDMVLSVAKLVPAG<br>LHIYQSLGGDELTLCETEIADG<br>EDIFVWNGVEVGGVHIQTGIDC<br>EPLLLNVLHLDTSSEGEKCCQV<br>IESPHVFPANAEVGTVLTAI<br>PAGVIFINSAGCPGGEGWTAIP<br>KEDMRKTFREQGLRNGSSILIQ | 118 | FTNLSGIRNQGGTCYLNLL<br>QTLHFTPEFREALFSLGPEE<br>LGLFEDKDKPDAKVRIIPQL<br>LQRLFAQLLLLDQEAASAD<br>LTDSFGWTSNEEMRQHDVQE<br>LNRILFSALETSLVGTSGHD<br>LIYRLYHGTIVNQIVCKECK<br>NVSERQEDFLDLTVAVKNVS<br>GLEDALWNMYVEEEVFDCDN<br>LYHCGTCDRLVKAASAKLR<br>KLPPFLTVSLLRFNFDFVKC<br>ERYKETSCYTFPLRINLKPFC<br>EQSELDDEYIYDLFSVII<br>HKGG<br>CYGGHYHVYIKDVDHLGNWQ<br>FQEEKSKPDVNLKDLQSEEE<br>IDHPLMILKAILLEENNLIP<br>VDQLGQKLLKKIGISWNKKY<br>RKQHGFLRKFLQLHSQIFLL<br>SSDESTVRLLKNSSLQAESD<br>FQRNDQQIFKMLPPESPGLN<br>NSISCPHWFDINDSKVQPIR<br>EKDIEQQFQKGESAYMLFYR<br>KSQQLRPPEARANPRYGVPC<br>HLLNEMDAANIELQTKRAEC<br>DSANNTFELHLHLGPQYHFF<br>NGALHPVVSQTESVWDLTFD<br>KRKTGLDLRQSI FQLLEFWE<br>GDMVLSVAKLVPAGLHIYQS<br>LGGDELTLCETEIADGEDIF<br>VWNGVEVGGVHIQTGIDCEP<br>LLLNVLHLDTSSEGEKCCQV<br>IESPHVFPANAEVGTVLTAI |

|                                                    |   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
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|                                                    |   | <p>DSHDDNSLLTKEEKWVTSMNEI<br/>DWLHVKNLCQLESEEKQVKISA<br/>TVNTMVFDIRIKAIKELKLMKE<br/>LADNSCLRPIDRNGKLLCPVPD<br/>SYTLKEAELKMSSSLGLCLGKA<br/>PSSSQLFLFFAMGSDVQPGTEM<br/>EIVVEETISVRDCLKMLKKSG<br/>LQGDWHLRKMDWCYEAGEPLC<br/>EEDATLKELLICSGDTLLLIIEG<br/>QLPPLGFLKVPPIWWYQLQGPGS<br/>HWESHQDQTNCTSSWGRVWRAT<br/>SSQGASGNEPAQVSLLYLGDIIE<br/>ISEDATLAELKSQAMTLPPFLE<br/>FGVPSPAHLRAWTVERKRPGRRL<br/>LRTDRQPLREYKLGRRIEICLE<br/>PLQKGENLGPQDVLLRTQVRIP<br/>GERTYAPALDLVWNAAQGGTAG<br/>SLRQRVADFYRLPVEKIEIAKY<br/>FPEKFEWLPISWNNQQITKRKK<br/>KKKQDYLQGAPYYLKDGDITIGV<br/>KNLLIDDDDDFSTIRDDTGKEK<br/>QKQALGRRKSQEALHEQSSYI<br/>LSSAETPARPRAPETSLSIHVG<br/>SFR</p>                                          |     | <p>AIPAGVIFINSAGCPGGEGW<br/>TAIPKEDMRKTFREQGLRNG<br/>SSILIQDSHDDNSLLTKEEK<br/>WVTSMNEIDWLHVKNLCQLE<br/>SEEKQVKISATVNTMVFDIR<br/>IKAIKELKLMKELADNSCLR<br/>PIDRNGKLLCPVPDSYTLKE<br/>AELKMSSSLGLCLGKAPSSS<br/>QLFLFFAMGSDVQPGTEMEI<br/>VVEETISVRDCLKMLKKSG<br/>LQGDWHLRKMDWCYEAGEP<br/>LCEEDATLKELLICSGDTLL<br/>LIEGQLPPLGFLKVPPIWWYQ<br/>LQGPGSHWESHQDQTNCTSS<br/>WGRVWRATSSQGASGNEPAQ<br/>VSLLYLGDIIEISEDATLAEL<br/>KSQAMTLPPFLEFGVPSPAHL<br/>LRAWTVERKRPGRLLRTDRQ<br/>PLREYKLGRRIEICLEPLQK<br/>GENLGPQDVLLRTQVRIPGE<br/>RTYAPALDLVWNAAQGGTAG<br/>SLRQRVADFYRLPVEKIEIA<br/>KYFPEKFEWLPISWNNQQIT<br/>KRKKKKKQDYLQGAPYYLKD<br/>GDTIGVKNLLIDDDDDFSTI<br/>RDDTGKEKQKQALGRRKSQ</p> |
| UBP7_HUMAN Ubiquitin carboxyl-terminal hydrolase 7 | 7 | <p>MNHQQQQQQQKAGEQQQLSEPED<br/>MEMEAGDTDDPPRITQNPVING<br/>NVALSDGHNTAEEDMEDDTSWR<br/>SEATFQFTVERFSRLSESVLSP<br/>PCFVRNLPWKIMVMPRFYPDRP<br/>HQKSVGFFLQCNAESDSTSWSC<br/>HAQAVLKIINYRDDEKSFSRRI<br/>SHLFFHKENDWGFNFMAWSEV<br/>TDPEKGFIDDDKVTFEVQVQAD<br/>APHGVAWDSKKHTGYVGLKNQG<br/>ATCYMNSLLQTLFFTNQLRKAV<br/>YMPTEGDDSSKSVPLALQRVF<br/>YELQHSDKPVGTKKLTKSFGWE<br/>TLDSFMQHDVQELCRVLLDNVE<br/>NKMKGTCVEGTIPKLFGRKMVS<br/>YIQCKEVDYRSDRREDYYDIQL<br/>SIKGKKNIFESFVDYVAVEQLD<br/>GDNKYDAGEHGLQEAEKGVKFL<br/>TLPPVLHLQLMRMYDPQTDQN<br/>IKINDRFEFPEQLPLDEFLQKT<br/>DPKDPANYILHAVLVHSGDNHG<br/>GHYVVYLNPKGDGKWCKFDDDV<br/>VSRCTKEEAIEHNYGGHDDLS<br/>VRHCTNAYMLVYIRESKLSEVL<br/>QAVTDHDIPOQLVERLQEEKRI</p> | 119 | <p>TGYVGLKNQGATCYMNSLLQ<br/>TLFFTNQLRKAVYMPTEGD<br/>DSSKSVPLALQRVFYELQHS<br/>DKPVGTKKLTGSFGWETLDS<br/>FMQHDVQELCRVLLDNVENK<br/>MKGTCVEGTIPKLFGRKMVS<br/>YIQCKEVDYRSDRREDYYDI<br/>QLSIKGKKNIFESFVDYVAV<br/>EQLDGDNKYDAGEHGLQEAE<br/>KGVKFLTLPPVLHLQLMRFM<br/>YDPQTDQNIKINDRFEFPEQ<br/>LPLDEFLQKTDPKDPANYIL<br/>HAVLVHSGDNHGGHYVVYLN<br/>PKGDGKWCKFDDDVSRCTK<br/>EEAIEHNYGGHDDLSVRHC<br/>TNAYMLVYIRE</p>                                                                                                                                                                                                                                                                       |

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|                                                                     |   | EAQKRKERQEAHLYMQVQIVAE<br>DQFCGHQGNMYDEEKVKYTVF<br>KVLKNSSLAEFVQSLSQTMGFP<br>QDQIRLWPMQARSNGTKRPAML<br>DNEADGNKTMIELSDNENPWTI<br>FLETVDPELAASGATLPKFDKD<br>HDVMLFLKMYDPKTRSLNYCGH<br>IYTPISCKIRDLLPVMCDRAGF<br>IQDTSILILYEEVKPNLTERIQD<br>YDVSLDKALDELMDGDIIVFQK<br>DDPENDNSELPTAKEYFRDLYH<br>RVDVIFCDKTIPNDPGFVVTLS<br>NRMNYFQVAKTVAQRLNTDPM<br>LQFFKSQGYRDGPGNPLRHNYE<br>GTLRDLLQFFKPRQPKKLYYQQ<br>LKMKITDFENRRSFKCIWLNSQ<br>FREEEITLYPDKHGCVRDLLEE<br>CKKAVELGEKASGKLRLLLEIVS<br>YKIIGVHQEDELLECLSPATSR<br>TFRIEEIPLDQVDIDKENEMLV<br>TVAHFHKEVFGTFGIPFLLRH<br>QGEHFREVMKRIQSLLDIQEKE<br>FEKFKFAIVMMGRHQYINEDEY<br>EVNLKDFEPQPGNMSHPRPWL<br>LDHFNKAPKRSRYTYLEKAIKI<br>HN |     |                                                                                                                                                                                                                                                                                                                                                                                                                             |
| U17L5_HUMAN Ubiquitin carboxyl-terminal hydrolase 17-like protein 5 | 8 | MEDDSLILRGWQFNHFSKLT<br>SRPDAAFAEIQRSTLPEKSPLS<br>CETRVLDLDDAPVARQLAPRE<br>KLPLSSRRPAAVGAGLQNMGNT<br>CYVNASLQCLTYTPPLANMYS<br>REHSQTCRHHKGCMLCTMQAHI<br>TRALHNPBGHVIQPSQALAAGFH<br>RGKQEDAHEFLMFTVDAMKKAC<br>LPGHKQVDHHSKDTTLIHQIFG<br>GYWRSQIKCLHCHGISDTFDPY<br>LDIALDIQAAQSVQQAELQAK<br>PEELNGENAYHCGVCLQAPAS<br>KTLTLHTSAKVLILVLKRFS<br>TGKNIAKNVQYPECLDMQPYMS<br>QPNTGPLVYVLYAVLVHAGWSC<br>HNGHYFSYVKAQEGQWYKMDDA<br>EVTASSITSVLSQQAYVLFYIQ<br>KSEWERHSESVSRRGREPRALGA<br>EDTDRRATQGELKRDHPCLQAP<br>ELDEHLVERATQESTLDHWKFL<br>QEQNKTKEFNVKVEGTLPD<br>VLVIHQSKYKCGMKNHHPEQQS<br>SLNLSSSTPTHQESMNTGT<br>SLRGRARRSKGKNKHSKRALLV<br>CQ                                     | 120 | AVGAGLQNMGNTCYVNASLQ<br>CLTYTPPLANMYSREHSQT<br>CHRHKGCMLCTMQAHITRAL<br>HNPBGHVIQPSQALAAGFHRG<br>KQEDAHEFLMFTVDAMKKAC<br>LPGHKQVDHHSKDTTLIHQI<br>FGGYWRSQIKCLHCHGISDT<br>FDPYLDIALDIQAAQSVQQA<br>LEQLAKPEELNGENAYHCGV<br>CLQAPASKTLTLHTSAKVL<br>ILVLKRFSVTGNKIAKNVQ<br>YPECLDMQPYMSQPNTGPLV<br>YVLYAVLVHAGWSCHNGHYF<br>SYVKAQEGQWYKMDDAEVTA<br>SSITSVLSQQAYVLFYIQKS<br>EWERHSESVSRRGREPRALGA<br>EDTDRRATQGELKRDHPCLQ<br>APEL |

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| U17LL_HUMAN Ubiquitin carboxyl-terminal hydrolase 17-like protein 21 | 9  | MEEDSLYLGGGEWQFNHFSKLTSSRPDAAF AEIQRTSLPEKSPLSCETRVDLCDDLAPVARQLAPREKLPLSNRRPAAVGAGLQNMGNTCYVNASLQCLTYTPPLANYMLSREHSQTCHRHKGCMCTMQAHI TRALHNPGHVIQPSQALAAGFHRG RGKQEDAHEFLMFTVDAMKKAC LPGHKQVDHHSKDTTLIHQIFG GYWRSQIKCLHCHGISDTFDPYLDIALDIQAAQSVQQALEQLVKPEELNGENAYHCGVCLQRAPASKMLTLLTSKAKVLILVLKRFSVTGNKIAKNVQYPECLDMQPYMSQPNTGPLVYVLYAVLVHAGWSC HNGHYFSYVKAQEGQWYKMDDAEVTASSITSVLSQQAYVLFYIQKSEWERHSESVSRRGREPRALGAEDTDRRATQGELKRDHPCLQAP ELDEHLVERATQESTLDHWKFLQEQNKTKEPFNVRKVEGTLPDVLVIHQSKYKCGMKNHHPEQQSSLLNLSSTPTHQESMNTGTLASLRGRARRSKGKNKHSKRALLVCQ      | 121 | AVGAGLQNMGNTCYVNASLQCLTYTPPLANYMLSREHSQTCHRHKGCMCTMQAHI TRALHNPGHVIQPSQALAAGFHRG KQEDAHEFLMFTVDAMKKAC LPGHKQVDHHSKDTTLIHQIFG GYWRSQIKCLHCHGISDTFDPYLDIALDIQAAQSVQQALEQLVKPEELNGENAYHCGVCLQRAPASKMLTLLTSKAKVLILVLKRFSVTGNKIAKNVQYPECLDMQPYMSQPNTGPLVYVLYAVLVHAGWSC HNGHYFSYVKAQEGQWYKMDDAEVTASSITSVLSQQAYVLFYIQKSEWERHSESVSRRGREPRALGAEDTDRRATQGELKRDHPCLQAP EL     |
| U17LA_HUMAN Ubiquitin carboxyl-terminal hydrolase 17-like protein 10 | 10 | MEDDSL YLGGGEWQFNHFSKLTSSRPDAAF AEIQRTSLPEKSPLSCETRVDLCDDLAPVARQLAPREKPPLSSRRPAAVGAGLQNMGNTCYVNASLQCLTYKPPLANYM L F REHSQTCHRHKGCMCTMQAHI TRALHIPGHV IQPSQALAAGFHRG RGKQEDAHEFLMFTVDAMRKAC LPGHKQVDRHSKDTTLIHQIFG GYWRSQIKCLHCHGISDTFDPYLDIALDIQAAQSVQQALEQLVKPEELNGENAYHCGVCLQRAPASKMLTLHNSAKVLILVLKRFPDVTGNKIAKNVQYPECLDMQPYMSQQNTGPLVYVLYAVLVHAGWSC HNGHYSSYVKAQEGQWYKMDDAEVTASSITSVLSQQAYVLFYIQKSEWERHSESVSRRGREPRALGVEDTDRRATQGELKRDHPCLQAP ELDEHLVERATQESTLDHWKFLQEQNKTKEPFNVRRVEGTVPDVLVIHQSKYKCRMKNHHPEQQSSLLNLSSTPTDQESMNTGTLASLRGRTRRSKGKNKHSKRALLVCQ | 122 | AVGAGLQNMGNTCYVNASLQCLTYKPPLANYM L F REHSQTCHRHKGCMCTMQAHI TRALHIPGHV IQPSQALAAGFHRG KQEDAHEFLMFTVDAMRKAC LPGHKQVDRHSKDTTLIHQIFG GYWRSQIKCLHCHGISDTFDPYLDIALDIQAAQSVQQALEQLVKPEELNGENAYHCGVCLQRAPASKMLTLHNSAKVLILVLKRFPDVTGNKIAKNVQYPECLDMQPYMSQQNTGPLVYVLYAVLVHAGWSC HNGHYSSYVKAQEGQWYKMDDAEVTASSITSVLSQQAYVLFYIQKSEWERHSESVSRRGREPRALGVEDTDRRATQGELKRDHPCLQAP EL |

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| UBP41_HUMAN Putative ubiquitin carboxyl-terminal hydrolase 41 | 11 | MDGVLFRAHQCCQYVHPCVHVYV<br>TVGLMDPLCERKEKASKQEREN<br>PLAHLAAWGLVGLHNIGQTCCL<br>NSLIQVFVMNVDFARILKRITV<br>PRGADEQRRSVFPQMLLLEKMQ<br>QDSRQKAVWPLELAYCLQKYNV<br>PLFVQHDAAQLYLKLWNLIKQDQ<br>IADVHLVERLQALYMIIRMKDSL<br>ICLDCAMESSRNSSMLTLRLSF<br>FDVDSKPLKTLEDALHCFQPR<br>ELSSKSKCFCECNGKTRGKQV<br>LKLTHLPQTLTIHLMRFSIRNS<br>QTRKICHSLYFPQSLDFSQILP<br>MKRESCDAEEQSGGQYELFAVI<br>AHVGMADSGHYCVYIRNAVDGK<br>WFCFNDNICLVSWEDIQCTYG<br>NPNYHW                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 123 | WGLVGLHNIGQTCCLNSLIQ<br>VFVMNVDFARILKRITVPRG<br>ADEQRRSVFPQMLLLEKMQ<br>DSRQKAVWPLELAYCLQKYN<br>VPLFVQHDAAQLYLKLWNLI<br>KDQIADVHLVERLQALYMIIR<br>MKDSLICLDCAMESSRNSSM<br>LTLRLSFFDVDSKPLKTLED<br>ALHCFQPRELSSKSKCFCE<br>NCGKTRGKQVQLKLTHLPQT<br>LTIHLMRFSIRNSQTRKICH<br>SLYFPQSLDFSQILPMKRES<br>CDAEEQSGGQYELFAVIAHV<br>GMADSGHYCVYIRNAVDGKW<br>FCFNDNICLVSWEDIQCTY<br>GNPNYHW                                                                                                                                                                                                                                                  |
| UBP38_HUMAN Ubiquitin carboxyl-terminal hydrolase 38          | 12 | MDKILEGLVSSSHPLPLKRVIV<br>RKVVESAHEHWLDEAQCEAMFDL<br>TTRLILEGQDPFQQRQVGHQVLE<br>AYARYHRPEFESFFNKTFVLGL<br>LHQGYHSLDRKDVAILDYIHNG<br>LKLIMSCPSVLDLFSLLQVEVL<br>RMVCERPEPQLCARLSDLLTDF<br>VQCIPKGKLSITFCQQLVRTIG<br>HFQCVSTQERELREYVSQVTKV<br>SNLLQNIWKAEPATLLPSLQEV<br>FASISSTDASFEPVALASLVQ<br>HIPLOMITVLIRSLTDPNVKD<br>ASMTQALCRMIDWLSWPLAQHV<br>DTWVIALLKGLAAVQKFTILID<br>VTLLKIELVFNRLWFPLVRPGA<br>LAVLSHMLLSFQHSPEAFHLIV<br>PHVVNLVHSFKNDGLPSSTAFL<br>VQLTELIHCCMMYHYSGFDPDLYE<br>PILEAIKDFPKPSEEKIKLILN<br>QSAWTSQSNSLASCLSRLSGKS<br>ETGKTGLINLGNTCYMNQSVIQA<br>LFMATDFRRQVLSLNLNGCNSL<br>MKKLQHLFAFLAHTQREAYAPR<br>IFFEASRPPWFPRSQQDCSEY<br>LRFLDLRLHEEEKILKVQASHK<br>PSEILECSETSLQEVASKAAVL<br>TETPRTSDGEKTLEKMFEGGKL<br>RTHIRCLNCRSTSQKVEAFTDL<br>SLAFCPSSLENMSVQDPASSP<br>SIQDGGMLQASVPGPSEEPVVY<br>NPTTAAAFICDSLNEKTIGSPP<br>NEFYCSENTSVPNESNKILVNK<br>DVPQKPGGETTPSVTDLLNYFL<br>APEILTGDNQYYCENCASLQNA | 124 | SETGKTGLINLGNTCYMNQSV<br>IQALFMATDFRRQVLSLNLN<br>GCNSLMKKLQHLFAFLAHTQ<br>REAYAPRIFFEASRPPWFPR<br>RSQQDCSEYLRFLDLRLHEE<br>EKILKVQASHKPEILECSE<br>TSLQEVASKAAVLTTETPRTS<br>DGEKTLEKMFEGGKLRTHIR<br>CLNCRSTSQKVEAFTDLSLA<br>FCPSSLENMSVQDPASSP<br>IQDGGMLQASVPGPSEEPVVY<br>YNPTTAAAFICDSLNEKTIG<br>SPPNEFYCSENTSVPNESNK<br>ILVNKDVPQKPGGETTPSVT<br>DLLNYFLAPEILTGDNQYYC<br>ENCASLQNAEKTMQITEEPE<br>YLILTLLRFSYDQKYHVRK<br>ILDNVSLPLVLELPVKRITS<br>FSSLSESWSVDVDFDLSL<br>LAKKLKPSGTDEASCTKLVP<br>YLLSSVVVHSGISSESGHY<br>SYARNITSTDSSYQMYHQSE<br>ALALASSQSHLLGRDSPSAV<br>FEQDLNEMSKKEWFLFNDS<br>RVTFTSFQSVQKITSRFPKD<br>TAYVLLYKKQH |

|                                                      |    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
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|                                                      |    | <p>EKTMQITEEPEYLILTLRFSY<br/>DQKYHVRKILDNVSLPLVLEL<br/>PVKRITSFSSLSESWSVDVDF<br/>DLSENLAKKLKPSGTDEASCTK<br/>LVPYLLSSVVVHSGISSESGHY<br/>YSYARNITSTDSSYQMYHQSEA<br/>LALASSQSHLLGRDSPSAVFEQ<br/>DLENKEMSKEWFLFNDSRVTF<br/>SFQSVQKITSRFPKDTAYVLLY<br/>KKQHSTNGLSGNNPTSGLWING<br/>DPPLQKELMDAITKDNKLYLQE<br/>QELNARARALQAASASCSEFRPN<br/>GFDDNDPPGSCGPTGGGGGGGF<br/>NTVGRLVF</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| UBP43_HUMAN Ubiquitin carboxyl-terminal hydrolase 43 | 13 | <p>MDLGGDAAGGGPLAPRPRRRR<br/>SLRRLFSRFLALGSRSPGDS<br/>PPRPQPGHCDGDGEGGFACAPG<br/>PVPAAPGSPGEERPPGPQPQLQ<br/>LPAGDGARPPGAQGLKNHGNTC<br/>FMNAVQCLSNTDLLAEFLALG<br/>RYRAAPGRAEVTEQLAALVRAL<br/>WTREYTPQLSAEFKNAVSKYGS<br/>QFQNSQHDALEFLLWLLDRVH<br/>EDLEGSSRGVPSEKLPPEATKT<br/>SENCLSPSAQLPLGQSFVQSHF<br/>QAQYRSSLTCPHCLKQSNTFDP<br/>FLCVSLPIPLRQTRFLSVTLVF<br/>PSKSQRFLRVGLAVPILSTVAA<br/>LRKMVAEEGGVPADEVILVELY<br/>PSGFQRSFFDEEDLNTIAEGDN<br/>VYAFQVPPSPSQGTLSAHLPLGL<br/>SASPRLAAREGQRFSLSLHSES<br/>KVLILFCNLVVGSGQQASRFGPP<br/>FLIREDRAVSWAQLQQSILSKV<br/>RHLMKSEAPVQNLGSLFSIRVV<br/>GLSVACSYLSPKDSRPLCHWAV<br/>DRVLHLRRPGGPPHVKLAVEWD<br/>SSVKERLFGSLQEERAQDADSV<br/>WQQQQAHQHSCITLDECFOFYT<br/>KEEQLAQDDAWKCPHCQVLQQG<br/>MVKLSLWTLDPDILIIHLKRFCQ<br/>VGERRNKLSTLVKFPLSGLNMA<br/>PHVAQRSTSPEAGLGPWPSWKQ<br/>PDCLPTSYPDLFLYDLYAVCNH<br/>HGNLQGGHYTAYCRNSLDGQWY<br/>SYDDSTVEPLREDEVNTRGAYI<br/>LFYQKRNSIPPWSASSSMRGST<br/>SSSLSDHWLLRLGSHAGSTRGS<br/>LLSWSSAPCPSLPQVPDSPIFT<br/>NSLCNQEKGGLEPRRLVRGVKG<br/>RSISMKAPTTSTRAKQGPFTMP</p> | 125 | <p>RPPGAQGLKNHGNTCFMNAV<br/>VQCLSNTDLLAEFLALGRYR<br/>AAPGRAEVTEQLAALVRALW<br/>TREYTPQLSAEFKNAVSKYGS<br/>SQFQNSQHDALEFLLWLLD<br/>RVHEDLEGSSRGVPSEKLPPE<br/>EATKTSENCLSPSAQLPLGQ<br/>SFVQSHFQAQYRSSLTCPHC<br/>LKQSNTFDPFLCVSLPIPLR<br/>QTRFLSVTLVFPSPSKQRFLR<br/>VGLAVPILSTVAALRKMVAE<br/>EGGVPADEVILVELYPSGFQ<br/>RSFFDEEDLNTIAEGDNVYA<br/>FQVPPSPSQGTLSAHLPLGLS<br/>ASPRLAAREGQRFSLSLHSE<br/>SKVLILFCNLVVGSGQQASRF<br/>GPPFLIREDRAVSWAQLQQS<br/>ILSKVRHLMKSEAPVQNLGS<br/>LFSIRVVGLSVACSYLSPKD<br/>SRPLCHWAVDRVLHLRRPGG<br/>PPHVKLAVEWDSSVKERLFG<br/>SLQEERAQDADSVWQQQQA<br/>QQHSCITLDECFOFYTKEEQ<br/>AQDDAWKCPHCQVLQQGMVK<br/>LSLWTLDPDILIIHLKRFCQV<br/>GERRNKLSTLVKFPLSGLNM<br/>APHVAQRSTSPEAGLGPWPS<br/>WKQPDCLPTSYPDLFLYDLY<br/>AVCNHGNLQGGHYTAYCRN<br/>SLDGQWYSYDDSTVEPLRED<br/>EVNTRGAYILFYQKR</p> |

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|                                                      |    | LRWSFGSKEKPPGASVELVEYL<br>ESRRRPRSTSQSIVSLTGTAG<br>EDEKSASPRSNVALPANSEGG<br>RAIERGPAGVPCPSAQPNHCLA<br>PGNSDGPNTARKLKENAGQDIK<br>LPRKFDLPLTMPSVEHEKPAR<br>PEGQKAMNWKESFQMGSKSSPP<br>SPYMGFSGNSKDSRRGTSELDR<br>PLQGTTLTLRSVFRKKENRRNE<br>RAEVSPQVPPVSLVSGGLSPAM<br>DGQAPGSPPALRIPEGLARGLG<br>SRLERDVWSAPSSLRLPRKASR<br>APRGSA LGMSQRTVPGEQASYG<br>TFQRVKYHTLSLGRKKTLPESS<br>F                                                                                                                                                                                                                                                                                                                                                              |     |                                                                                                                                                                                                                                                                                                                                                                                                                     |
| UBP2_HUMAN Ubiquitin carboxyl-terminal hydrolase 2   | 14 | MSQLSSTLKRYTESARYTDAHY<br>AKSGYGAYTPSSYGANLAASLL<br>EKEKLGFKPVPTSSFLTRPTY<br>GPSSLLDYDRGRPLLRPDITGG<br>GKRAESQTRGTERPLGSGLSGG<br>SGFPYGVTTNNCLSYLPINAYDQ<br>GVTLTQKLDSQSDLARDFSSLR<br>TSDSYRIDPRNLGRSPMLARTR<br>KELCTLQGLYQTASCPEYLVLY<br>LENYGRKGSASQVPSQAPPSRV<br>PEIISPTYRPIGRYTLWETGKG<br>QAPGPSRSSSPGRDGMNSKSAQ<br>GLAGLRNLGNTCFMNSILQCLS<br>NTREL RDYCLQRLYMRLHHGS<br>NAHTALVEEFKLIQTIWTSSP<br>NDVVSPSEFKTQIQRYAPRFVG<br>YNQQDAQEFRLRFLLDGLHNEVN<br>RVTLRPKSNPENLDHLPDDEKG<br>RQMWRKYLEREDSRIGDLFVGQ<br>LKSSLTCTDCGYCSTVDFPFDL<br>LSLPIAKRGYPEVTLMDCMRLF<br>TKEDVLDGDEKPTCCRCRGRKR<br>CIKKFSIQRFPKILVLHLKRF<br>ESRIRTSKLTTFVNFPLRDLDL<br>REFASENTNHAVYNLYAVSNHS<br>GTTMGGHYTAYCRSPGTGEWHT<br>FNDSSVTPMSSSQVRTSDAYLL<br>FYELASPPSRM | 126 | SAQGLAGLRNLGNTCFMNSI<br>LQCLSNTREL RDYCLQRLYM<br>RDLHHGSNAHTALVEEFKLI<br>QTIWTSSPNDVVSPSEFKT<br>QIQRYAPRFVGYNQQDAQEF<br>LRFLLDGLHNEVN RVTLRPK<br>SNPENLDHLPDDEKGRQMWR<br>KYLEREDSRIGDLFVGQLKS<br>SLTCTDCGYCSTVDFPFDL<br>SLPIAKRGYPEVTLMDCMRL<br>FTKEDVLDGDEKPTCCRCRG<br>RKRCIKKFSIQRFPKILVLH<br>LKRFSESRIRTSKLTTFVNF<br>PLRDLDLREFASENTNHAVY<br>NLYAVSNHSGTTMGGHYTAY<br>CRSPGTGEWHTFNDSSVTPM<br>SSSQVRTSDAYLLFYELAS |
| UBP45_HUMAN Ubiquitin carboxyl-terminal hydrolase 45 | 15 | MRVKDPTKALPEKAKRSKRPTV<br>PHDEDSSDDIAVGLTCQHVSHA<br>ISVNHVKRAIAENLWSVCSECL<br>KERRFYDGQLVLTSDIWLCLKC<br>GFQCGKNSSEQHSLKHFKSSR<br>TEPHCIIINLSTWIIWCYECDE<br>KLSTHCNKKVLAQIVDFLOKHA<br>SKTQTSAFSRIMKLCEEKCETD                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 127 | LSVRGITNLGNTCFFNAVMQ<br>NLAQTYTLTDLMEIKESST<br>KLKIFPSSDSQLDPLVVELS<br>RPGPLTSALFLHLSMKETE<br>KGPLSPKVLFNQLCQKAPRF<br>KDFQQQDSQELLYLLDAVR<br>TEETKRIQASILKAFNNPTT<br>KTADDETRKKVKAYGKEGVK                                                                                                                                                                                                                           |

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|                                                      |    | <p>             EIQKGGKCRNLSVRGITNLGNT<br/>             CFFNAVMOQLAQTYTLTDLME<br/>             IKESSTKLKIFPSSDSQLDPLV<br/>             VELSRPGPLTSALFLFLHSMKE<br/>             TEKGPLSPKVLFNQLCQKAPRF<br/>             KDFQQQDSQELLHYLLDAVRTE<br/>             ETKRIQASILKAFNNPTTKTAD<br/>             DETRKKVKAYGKEGVKMNFDIR<br/>             IFIGELTSTVMCEEKANISTVK<br/>             DPFIDISLPIIEERVSKPLLWG<br/>             RMNKYRSLRETDHRYSGNVTI<br/>             ENIHQPRAAKKHSSSKDKSOLI<br/>             HDRKCIRKLSSGETVTYQKNEN<br/>             LEMNGDSLMEFASLMNSESRLNE<br/>             SPTDDSEKEASHSESNDADSE<br/>             PSESESASKQTGLFRSSSGSV<br/>             QPDGPLYPLSAGKLLYTKETDS<br/>             GDKEMAEAISELRLSSTVTGDQ<br/>             DFDRENQPLNISNNLCFLEGKH<br/>             LRSYSPQNAFQTLQSYYITTSK<br/>             ECSIQSCLYQFTSMELLMGNNK<br/>             LLCENCTKNKQKYQEETSFAEK<br/>             KVEGVYTNARKQLLISAVPAVL<br/>             ILHLKRFHQAGLSLRKVNHRVD<br/>             FPLMLDLAPFCSATCKNASVGD<br/>             KVLVGLYGLIVEHSGSMREGHYT<br/>             AYVKVRTPSRKLSEHNTKKKNV<br/>             PGLKAADNESAGQVHVSDTYL<br/>             QVPESRALSAQAYLLFYERV           </p> |     | <p>             MNFIDRIFIGELTSTVMCEE<br/>             CANISTVKDPFIDISLPIIE<br/>             ERVSKPLLWGRMNKYRSLRE<br/>             TDHRYSGNVTIENIHQPRA<br/>             AKKHSSSKDKSOLIHDRKCI<br/>             RKLSSGETVTYQKNENLEMN<br/>             GDSLMEFASLMNSESRLNESP<br/>             TDDSEKEASHSESNDADSE<br/>             PSESESASKQTGLFRSSSGS<br/>             GVQPDGPLYPLSAGKLLYTK<br/>             ETDSGDKEMAEAISELRLSS<br/>             TVTGDQDFDRENQPLNISNN<br/>             LCFLEGKHLRSYSPQNAFQT<br/>             LSQSYITTSKECSIQSCLYQ<br/>             FTSMELLMGNNKLLCENCTK<br/>             NKQKYQEETSFAEKKVEGVY<br/>             TNARKQLLISAVPAVLILHL<br/>             KRFHQAGLSLRKVNHRVDFP<br/>             LMLDLAPFCSATCKNASVGD<br/>             KVLVGLYGLIVEHSGSMREGH<br/>             YTAYVKVRTPSRKLSEHNTK<br/>             KKNVPGLKAADNESAGQVHV<br/>             VSDTYLQVPESRALSAQAY<br/>             LLFYERV           </p> |
| UBP32_HUMAN Ubiquitin carboxyl-terminal hydrolase 32 | 16 | <p>             MGAKESRIGFLSYEEALRRVTD<br/>             VELKRLKDAFKRTCGLSYMGO<br/>             HCFIREVLGDGVPPKVAEVIYC<br/>             SFGGTSKGLHFNNLIVGLVLLT<br/>             RGKDEEKAKYIFSLFSSESGNY<br/>             VIREEMERMLHVVDGKVPDTLR<br/>             KCFSEGEKVNYEKFRNWLFLNK<br/>             DAFTFSRWLLSGGVYVTLTDDS<br/>             DTPTFYQTLAGVTHLEESDIID<br/>             LEKRYWLLKAQSRTGRFDLETF<br/>             GPLVSPPIRPSLSEGLFNAFDE<br/>             NRDNHIDFKEISCGLSACCRGP<br/>             LAERQKFCFKVFDVDRDGVLSR<br/>             VELRDMVVALLEVWKNRTDDI<br/>             PELHMDLSDIVEGILNAHDTTK<br/>             MGHLTLEDYQIWSVKNVLANEF<br/>             LNLLFQVCHIVLGLRPATPEEE<br/>             GQIIRGWLERESRYGLQAGHNW<br/>             FIISMQWWQQWKEYVKYDANPV<br/>             VIEPSSVLNGGKYSFGTAAHPM<br/>             EQVEDRIGSSLSYVNTTEEKFS<br/>             DNISTASEASETAGSGFLYSAT           </p>                                                                                                                                                                                                                                                                                      | 128 | <p>             TEKGATGLSNLGNCTCFMNSS<br/>             IQCVSNTQPLTQYFISGRHL<br/>             YELNRTNPIGMKGHMAKCYG<br/>             DLVQELWSGTQKNVAPLKLK<br/>             WTIKAYAPRFNGFQQQDSQE<br/>             LLAFLLDGLHEDLNRVHEKP<br/>             YVELKDSGDRPDWEVAAEAW<br/>             DNHLRRNRSIVVDLFHGQLR<br/>             SQVKCKTCGHISVRFDPFNF<br/>             LSLPLPMDSYMHEITVIKL<br/>             DGTTPVRYGLRLNMDEKYTG<br/>             LKKQLSDLCLNSEQILLAE<br/>             VHGSNIKNFQDNQKVRLLSV<br/>             SGFLCAFEIPVPVSPISASS<br/>             PTQTDSSSPSTNEMFTLTT<br/>             NGDLPRPIFIPNGMPNTVVP<br/>             CGTEKNFTNGMVNGHMPSLP<br/>             DSPFTGYIIAVHRKMMRTEL<br/>             YFLSSQKNRPSLFGMPLIVP<br/>             CTVHTRKKDLYDAVWIVQVSR<br/>             LASPLPPQEASNAHQDCDDS<br/>             MGYQYPFTLRVVQKDGNSCA           </p>                                                                |



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|  |  | PGADVC FARQHNTSDNNNQCLL<br>GANGNILLHLNPQKPGAIDNQP<br>LVTQEPVKATSLTLEGGRLKRT<br>PQLIHGRDYEMVPEPVWRALYH<br>WYGANLALPRPVIKNSKTDIPE<br>LELFPRYLLFLRQQPATRTQQS<br>NIWVNMGNVPSNAPLKRVLAY<br>TGCFSRMQTIKEIHEYLSQRLR<br>IKEEDMRLWLYNSENLYTLDD<br>EDHKLEYLKIQDEQHLVIEVRN<br>KDMSWPEEMSFIANSSKIDRHK<br>VPTEKGATGLSNLGNTCFMNSS<br>IQCVSNTQPLTQYFISGRHLYE<br>LNRTNPIGMKGHMAKCYGDLVQ<br>ELWSGTQKNVAPLKLRTIAKY<br>APRFNGFQQQDSQELLAFLLDG<br>LHEDLNRVHEKPYVELKDSGR<br>PDWEVAAEAWDNHLRRNRSIVV<br>DLFHGQLRSQVKCKTCGHISVR<br>FDPFNFLSLPLPMDSYMHEIT<br>VIKLDGTPVRYGLRLNMDEKY<br>TGLKKQLSDLCGLNSEQILLAE<br>VHGSNIKNFPQDNQKVRLSVSG<br>FLCAFEIPVPVSPISASSPTQT<br>DFSSSPSTNEMFTLTNGDLPR<br>PIFIPNGMPNTVVPCGTEKNFT<br>NGMVNGHMPSLPDSPFTGYIIA<br>VHRKMMRTELYFLSSQKNRPSL<br>FGMPLIVPCTVHTRKKDLYDAV<br>WIQVSRLASPLPPQEASNHAQD<br>CDDSMGYQYPFTLRVVQKDGNS<br>CAWCPWYRFCRGCKIDCGEDRA<br>FIGNAYIAVDWDPTALHLRYQT<br>SQERVVDEHESVEQSRRAQAEP<br>INLDSCRAFTSEEELGENEMY<br>YCSKCKTHCLATKKLDLWRLPP<br>ILIIHLKRFQFVNGRWIKSQKI<br>VKFPRESFDPFAFLVPRDPALC<br>QHKPLTPQGDELSEPRILAREV<br>KKVDAQSSAGEEDVLLSKSPSS<br>LSANIISSPKGSPSSSRKSGTS<br>CPSSKNSSPNSSPRTLGRSKGR<br>LRLPQIGSKNKLSSSKENLDAS<br>KENGAGQICELADALSRGHVLG<br>GSQPELVTPQDHEVALANGFLY<br>EHEACGNGYSNGQLGNHSEEDS<br>TDDQREDTRIKPIYNLYAISCH<br>SGILGGGHYVTYAKNPCKWYC<br>YNDSSCKELHPDEIDTDSAYIL<br>FYEQQGIDYAQFLPKTDGKKMA<br>DTSSMDEDFESDYKKYCVLQ |  | WCPWYRFCRGCKIDCGEDRA<br>FIGNAYIAVDWDPTALHLRY<br>QTSQERVVDEHESVEQSRRA<br>QAEPINLDSCRAFTSEEEL<br>GENEMYCSKCKTHCLATKK<br>LDLWRLPPILIIHLKRFQFV<br>NGRWIKSQKIVKFPRESFDP<br>SAFLVPRDPALCQHKPLTPQ<br>GDELSEPRILAREVKKVDAQ<br>SSAGEEDVLLSKSPSSLSAN<br>IISSPKGSPSSSRKSGTSCP<br>SSKNSSPNSSPRTLGRSKGR<br>LRLPQIGSKNKLSSSKENLD<br>ASKENGAGQICELADALSRG<br>HVLGGSQPELVTPQDHEVAL<br>ANGFLYEHEACGNGYSNGQL<br>GNHSEEDSTDDQREDTRIKP<br>IYNLYAISCHSGILGGGHYV<br>TYAKNPCKWYCYNDSSCKE<br>LHPDEIDTDSAYILFYEQQG<br>IDYAQFLPKTDGKKMADTSS<br>MDEDFESDYKKYCVLQ |
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| U17L6_HUMAN Ubiquitin carboxyl-terminal hydrolase 17-like protein 6 | 17 | MEDDSL YLRGEWQFNHFSKLTSSRPDAAF AEIQRTSLPEKSPLSCETRVDLCDDLAPVARQLAPREKLPLSSRRPAAVGAGLQNMGNTCYVNASLQCLTYTPPLAN YMLSREHSQTCHRHKGCM LCTMQAHI TRALHNPGHVIQPSQAL AAGFHRGRGQEDAHEFLMFTVDAMKKACLPGHKQVDHHSKDTTLIHQIFGGYWRSQIKCLHCHGISDTFDPYLDIALDIQAAQSVQQA LPELVKPEELNGENAYHCGVCLQRAPASKTTLTHTSAKVLILVLKRFSVTGNKIAKNVQYPECLDMQPYMSQQNTGPLVYVLYAVLVHAGWSC HNGHYFSYVKAQEGQWYKMDDAEVTASSITSVLSQQAYVLFYIQKSEWERHSESVS SRGREPRALGSED                                                                                                                                                                                                                                                                                                                       | 129 | AVGAGLQNMGNTCYVNASLQCLTYTPPLAN YMLSREHSQTCHRHKGCM LCTMQAHI TRALHNPGHVIQPSQAL AAGFHRGRGQEDAHEFLMFTVDAMKKACLPGHKQVDHHSKDTTLIHQIFGGYWRSQIKCLHCHGISDTFDPYLDIALDIQAAQSVQQA LPELVKPEELNGENAYHCGVCLQRAPASKTTLTHTSAKVLILVLKRFSVTGNKIAKNVQYPECLDMQPYMSQQNTGPLVYVLYAVLVHAGWSC HNGHYFSYVKAQEGQWYKMDDAEVTASSITSVLSQQAYVLFYIQKSEWERHSESVS SRGREPRALGSED |
| UBP42_HUMAN Ubiquitin carboxyl-terminal hydrolase 42                | 18 | MTIVDKASESSDPSAYQNQPGSSEAVSPGDM DAGSASWGAVSSSLNDVSNHTLSLGPVPGAVVYSSSSVPDKSKPSPQKDQALGDGIAPPQKVLFPSEKICLKWQQTHR VGAGLQNLGNTCFANAALQCLTYTPPLAN YMLSHEHSKTCHAE GFCMMCTMQAHITQALS NPGDVIKPMFVINEMRRIARHFRFGNQEDAEFLQYTV DAMQKACLNGSNK LDRHTQATTLVCQIFGGYLR SRVKCLNCKGVSDTFDPYLDITLEIKAAQSVNKALEQFVKPEQLDGENSYKCSKCKKMVPASKRFTIHRSSNVLTLSLKR FANFTGGKIAKDVKYPEYLDIRPYMSQPNGEPIVYVLYAVLVHTGFNCHAGHYFCYIKASNGLWYQMND SIVSTSDIRSVLSQQAYVLFYIRSHDVKNNGELTHPTHSPGQSSPRPVISQRVVTNKQAAPGFIGPQLPSHMIKNPPHLNGTGPLKDT PSSSMSSP NGNSSVN RASPVNASASVQNWSVNRSSVIPEHPKKQKITISIHNKLPVRQCQSQPNLHSNSLENPTKPVPSSTITNSAVQSTSNASTMSVSSKVTKPIPRSESCSQPVMNGKSKLNSSVLVPYGAESSESD EESKGLGKENGIGTIVSSHSPGQDAEDEEATPHELQEPMTLNGANSADSDSDPKENGLAPDGASCQGQPALHSENPFAKANGLP GKLM | 130 | RVGAGLQNLGNTCFANAALQCLTYTPPLAN YMLSHEHSKTCHAE GFCMMCTMQAHITQALS NPGDVIKPMFVINEMRRIARHFRFGNQEDAEFLQYTV DAMQKACLNGSNK LDRHTQATTLVCQIFGGYLR SRVKCLNCKGVSDTFDPYLDITLEIKAAQSVNKALEQFVKPEQLDGENSYKCSKCKKMVPASKRFTIHRSSNVLTLSLKR FANFTGGKIAKDVKYPEYLDIRPYMSQPNGEPIVYVLYAVLVHTGFNCHAGHYFCYIKASNGLWYQMND SIVSTSDIRSVLSQQAYVLFYIRSHDVKNNGE           |

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|                                                                              |    | <p>PAPLLSLPEDKILETFRLSNKL<br/> KGSTDEMSAPGAERGPPEDRDA<br/> EPQPGSPAAESLEEPDAAAGLS<br/> STKKAPPPRDPGTPATKEGAW<br/> AMAVAPEEPPPSAGEDIVGDTA<br/> PPDLCDPGSLTGDASPLSQDAK<br/> GMIAEGPRDSALAEAEPEGLSPA<br/> PPARSEEPCEQPLLVHPSGDHA<br/> RDAQDPSQSLGAPEAAERPPAP<br/> VLDMAPAGHPEGDAEPSPGERV<br/> EDAAAPKAPGPSPAKEKIGSLR<br/> KVDRGHYRSRRERSSSGEPARE<br/> SRSKTEGHRHRRRRTCPREERDR<br/> QDRHAPEHHHPGHGDRLSPGERR<br/> SLGRCSHHHSRHRSGVELDWVR<br/> HHYTEGERGWGREKFYPDRPRW<br/> DRCRYYHCRYALYAARDWKPFH<br/> GGREHERAGLHERPHKDHNRGR<br/> RGCEPARERERHRPSSPRAGAP<br/> HALAPHPDRFSDRTALVAGDN<br/> CNLSDRFHEHENGKSRKRRHDS<br/> VENS DSHVEKKARRSEQKDPLE<br/> EPKAKKKKKSKKKKKSKDKHRD<br/> RDSRHQQDSDLAACSADLHR<br/> HKKKKKKKKRHSRKSSEDFVKDS<br/> ELHLPRVTSLETVAQFRAQGG<br/> FPLSGGPPLEGVGPFREKTKHL<br/> RMESRDDRCLFEYGQKRRYL<br/> ELGR</p> |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| U17L7_HUMAN Inactive ubiquitin carboxyl-terminal hydrolase 17-like protein 7 | 19 | <p>MEDDSL YLGGDWQFNHFSKLTS<br/> SRLDAAFAEIQR TSLSEKSPLS<br/> SETRFDLCDDLAPVARQLAPRE<br/> KLPLSSRRPAAVGAGLQKIGNT<br/> FYVNVSLQCLTYTLPLSNYMLS<br/> REDSQTCHLHKCCMFCTMQAHI<br/> TVALHSPGHVIQPSQVLAAGFH<br/> RGEQEDAHEFLMFTVDAMKKAC<br/> LPGHKQLDHHSKDTTLIHQIFG<br/> AYWRSQIKYLHCHGVSDTFDPY<br/> LDIALDIQAAQSVKQALEQLVK<br/> PKELNGENAYHCGLCLQKAPAS<br/> KTLTLPTS AKVLILVLKRFS DV<br/> TGNKLAKNVQYPKCRDMQPYMS<br/> QQNTGPLVYVLYAVLVHAGWSC<br/> HNGHYFSYVKAQEGQWKMDDA<br/> EVTASGITSVLSQQAYVLFYIQ<br/> KSEWERHSES VSRGREPRALGA<br/> EDTDRPATQ GELKRDHPCLQVP<br/> ELDEHLVERATQESTLDHWKFP<br/> QEQNKT KPEFNV RKVEGTLPN<br/> VLVIHQSKYKCGMKNHHPEQQS</p>                                                                                                                                                                           | 131 | <p>AVGAGLQKIGNTFYVNVSLQ<br/> CLTYTLPLSNYMLSREDSQT<br/> CHLHKCCMFCTMQAHITWAL<br/> HSPGHVIQPSQVLAAGFHRG<br/> EQEDAHEFLMFTVDAMKKAC<br/> LPGHKQLDHHSKDTTLIHQI<br/> FGAYWRSQIKYLHCHGVSDT<br/> FDPYLDIALDIQAAQSVKQA<br/> LEQLVKPKELNGENAYHCGL<br/> CLQKAPASKTLTLPTS AKVL<br/> ILVLKRFS DV TGNKLAKNVQ<br/> YPKCRDMQPYMSQQNTGPLV<br/> YVLYAVLVHAGWSCHNGHYF<br/> SYVKAQEGQWKMDDAEVT<br/> SGITSVLSQQAYVLFYIQS<br/> EWERHSES VSRGREPRALGA<br/> EDTDRPATQ GELKRDHPCLQ<br/> VPEL</p> |

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|                                                                                        |    | SLNLSSSTKPTDQESMNTGTLA<br>SLQGSTRRSKGNKHSKRSLLV<br>CQ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| U17LH_HUM<br>AN Ubiquitin<br>carboxyl-<br>terminal<br>hydrolase 17-<br>like protein 17 | 20 | MEDDSLYLGGEWQFNHFSKLT<br>SRPDAAFAEIQRSLPEKSPLS<br>CETRVDLCDDLAPVARQLAPRE<br>KLPLSSRRPAAVGAGLQNMNT<br>CYVNASLQCLTYTPPLANYMLS<br>REHSQTCHRHKGCMCTMQAHI<br>TRALHNPGHVIQPSQALAAGFH<br>RGKQEDAHEFLMFTVDAMKKAC<br>LPGHKQVDHHSKDTTLIHQIFG<br>GYWRSQIKCLHCHGISDTFDPY<br>LDIALDIQAAQSVQQAELQVK<br>PEELNGENAYHCGVCLQRPAS<br>KTLTLHTSAKVLILVLKRFSDV<br>TGNKIAKNVQYPECLDMQPYMS<br>QQNTGPLVYVLYAVLVHAGWSC<br>HNGHYFSYVKAQEGQWYKMDDA<br>EVTAASITSVLSQQAYVLFYIQ<br>KSEWERHSESVSREGREPRALGA<br>EDTDRRATQGELKRDHPCLQAP<br>ELDEHLVERATQESTLDHWKFL<br>QEONKTKPEFNVRKVEGTLPD<br>VLVIHQSKYKCGMKNHHPEQQS<br>SLNLSSSTPTHQESMNTGTLA<br>SLRGRARRSKGKNKHSKRALLV<br>CQ | 132 | AVGAGLQNMNTCYVNASLQ<br>CLTYTPPLANYMLSREHSQT<br>CHRHKGCMCTMQAHI<br>HNPGHVIQPSQALAAGFHRG<br>KQEDAHEFLMFTVDAMKKAC<br>LPGHKQVDHHSKDTTLIHQI<br>FGGYWRSQIKCLHCHGISDT<br>FDPYLDIALDIQAAQSVQQA<br>LEQLVKPEELNGENAYHCGV<br>CLQRPASKTLTLHTSAKVL<br>ILVLKRFSDVTGNKIAKNVQ<br>YPECLDMQPYMSQQNTGPLV<br>YVLYAVLVHAGWSCHNGHYF<br>SYVKAQEGQWYKMDDAEVTA<br>ASITSVLSQQAYVLFYIQKS<br>EWERHSESVSREGREPRALGA<br>EDTDRRATQGELKRDHPCLQ<br>APEL                                                                                                                                               |
| UBP13_HUM<br>AN Ubiquitin<br>carboxyl-<br>terminal<br>hydrolase 13                     | 21 | MQRRGALFGMPGGSGGRKMAAG<br>DIGELLVPHMPTIRVPRSGDRV<br>YKNECAFSYDSPNSEGGLYVCM<br>NTFLAFGREHVERHFRKTGQSV<br>YMHLKRHVREKVRGASGGALPK<br>RRNSKIFLDLDTDDDLNSDDYE<br>YEDEAKLVIFFPDHYEIALPNIE<br>ELPALVTIACDAVLSSKSPYRK<br>QDPDTWENELPVSKYANNLTQL<br>DNGVRIPPSGWKCARCDLRENL<br>WLNLTDGSVLCGKWWFDSSGGN<br>GHAEHYRDMGYPLAVKLGTIT<br>PDGADVYSFQEEEPVLDPHLAK<br>HLAHFGIDMLHMHGTENGLQDN<br>DIKLRVSEWEVIQESGTKLKPM<br>YGPYGTGLKKNLGNLSSVMQ<br>AIFSIPEFQRAYVGNLPRIFDY<br>SPLDPTQDFNTQMTKLGHGLLS<br>GQYSKPPVKSELIEQVMKEEHK<br>PQQNGISPRMFKAQVSKSHPEF<br>SSNRQQDAQEFFLHLVNLVERN<br>RIGSENPSDVFRFLVEERIQCC<br>QTRKVRYTERVDYLMQLPVAME                            | 133 | YGPYGTGLKKNLGNLSSVMQ<br>AIFSIPEFQRAYVGNLPR<br>IFDYSPLDPTQDFNTQMTKL<br>GHGLLSGQYSKPPVKSELIE<br>QVMKEEHKPPQQNGISPRMF<br>AFVSKSHPEFSSNRQQDAQE<br>FFLHLVNLVERNRIIGSENPS<br>DVFRFLVEERIQCCQTRKVR<br>YTERVDYLMQLPVAMEAATN<br>KDELIAYELTRREAEANRRP<br>LPELVRAKIPFSACLQAFSE<br>PENVDDFWSSALQAKSAGVK<br>TSRFASFPEYLVVQIKKFTF<br>GLDWVPKKFDVSIIDMPDLLD<br>INHRLRAGLQPGEEELPDIS<br>PPIVIPDDSKDRMLNQLIDP<br>SDIDESSVMQLAEMGFPLEA<br>CRKAVYFTGNMGAEVAFNWI<br>IVHMEEPDFAEPLTMPGYGG<br>AASAGASVFGASGLDNQPPE<br>EIVAIITSMGFQRNQAIQAL<br>RATNNNLERALDWIFSHPEF<br>EEDSDFVIEMENNANANIIS |

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|                                                                    |    | AATNKDELIAYELTRREAEANR<br>RPLPELVRAKIPFSACLQAFSE<br>PENVDFFWSSALQAKSAGVKT<br>RFASFPEYLVVQIKKFTFGLDW<br>VPKKFDVSIIDMPDLLDINHLRA<br>RGLQPGEEELPDISPPIVIPDD<br>SKDRMLNQLIDPSDIDESSVMQ<br>LAEMGFPLEACRKAVYFTGNMG<br>AEVAFNWIIIVHMEEPDAEPLT<br>MPGYGGAASAGASVFGASGLDN<br>QPPEEIVAIITSMGFQRNQAIQ<br>ALRATNNNLERALDWIFSHPEF<br>EEDSDFVIEMENNANANIISEA<br>KPEGPRVKDGSPTYELFAFISH<br>MGTSTMSGHYICHIKKEGRWVI<br>YNDHKVCASERPPKDLGYMYFY<br>RRIPS                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |     | EAKPEGPRVKDGSPTYELFA<br>FISHMGTSTMSGHYICHIKK<br>EGRWVIYNDHKVCASERPPK<br>DLGYMYFYRRIPS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| UBP11_HUM<br>AN Ubiquitin<br>carboxyl-<br>terminal<br>hydrolase 11 | 22 | MAVAPRLFGGLCFRFRDQNP<br>AVEGRPLPIHSCVGCRRERTAM<br>ATVAANPAAAAA AVAAAAVTE<br>DREPQHEELPGLDSQWRQIENG<br>ESGRERPLRAGESWFLVEKHWY<br>KQWEAYVQGGDQDSSTFPGCIN<br>NATLFQDEINWRLKEGLVEGED<br>YVLLPAAAWHYLVSWYGLEHGQ<br>PPIERKVIELPNIQKVEVYPVE<br>LLLVRHNDLGKSHTVQFSHTDS<br>IGLVLRTARERFLVEPQEDTRL<br>WAKNSEGSLDRLYDTHITVLDA<br>ALETGQLIIMETRKKDGTWPSA<br>QLHVMNNNMSEDEDFKGQPGI<br>CGLTNLGNTCFMNSALQCLSNV<br>PQLTEYFLNNCYLEELNFRNPL<br>GMKGEIAEAYADLVKQAWSGHH<br>RSIVPHVFKNKVGHFASQFLGY<br>QQHDSQELLSFLLDGLHEDLNR<br>VKKKEYVELCDAAGRPDQEAQ<br>EAWQNHKRRNDSVIVDTFHGLF<br>KSTLVCPDCGNVSVTFDFPCYL<br>SVPLPISHKRVLEVFFIPMDPR<br>RKPEQHRLVVPKKGKISDLCA<br>LSKHTGISPERMMVADVFSHRF<br>YKLYQLEELPLSSILDRDDIFVY<br>EVSGRIEAIEGSREDIVVPVYL<br>RERTPARDYNNSYYGLMLFGHP<br>LLVSVPRDRFTWEGLYNVLMYR<br>LSRYVTKPNSDDEDDGDEKEDD<br>EEDKDDVPGPSTGGSLRDPEPE<br>QAGPSSGVTNRCFLLDNCLGT<br>SQWPPIRRRRKQLFTLQTVNSNG<br>TSDRTTSPEEVHAQPYIAIDWE | 134 | KGQPGICGLTNLGNTCFMNS<br>ALQCLSNVPQLTEYFLNNCY<br>LEELNFRNPLGMKGEIAEAY<br>ADLVKQAWSGHHRSIVPHVF<br>KNKVGHFASQFLGYQQHDSQ<br>ELLSFLLDGLHEDLNRVKKK<br>EYVELCDAAGRPDQEAQEA<br>WQNHKRRNDSVIVDTFHGLF<br>KSTLVCPDCGNVSVTFDFPC<br>YLSVPLPISHKRVLEVFFIP<br>MDPRRKPEQHRLVVPKKGKI<br>SDLCVALSKHTGISPERMMV<br>ADVFSHRFYKLYQLEELPLSS<br>ILDRDDIFVYEVSGRIEAI<br>GSREDIVVPVYLRETPARD<br>YNNSYYGLMLFGHPLLVSV<br>RDRFTWEGLYNVLMYRLSRY<br>VTKPNSDDEDDGDEKEDDE<br>DKDDVPGPSTGGSLRDPEPE<br>QAGPSSGVTNRCFLLDNCL<br>GTSQWPPIRRRRKQLFTLQTV<br>NSNGTSDRTTSPEEVHAQPY<br>IAIDWEPEMKKRYDEVEAE<br>GYVKHDCVGYVMKKAPVRLQ<br>ECIELFTTVETLEKENPWYC<br>PSCQHQQLATKKLDLWMLPE<br>ILIIHLKRFSYTKFSREKLD<br>TLVEFPIRDLDSEFVIQPPQ<br>NESNPELYKYDLIAVSNHYG<br>GMRDGHYTTFACNKDSGQWH<br>YFDNSVSPVNNENQIESKAA<br>YVLFYQRQD |

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|                                                                     |    | PEMKKRYYYDEVEAEGYVKHDCV<br>GYVMKKAPVRLQECIELFTTVE<br>TLEKENPWYCPSCQHQQLATKK<br>LDLWMLPEILIIHLKRFSYTKF<br>SREKLDTLVEFPIRDLDSEFV<br>IQPQNESNPELYKYDLIAVSNH<br>YGGMRDGHYTTFACNKDSGQWH<br>YFDDNSVSPVNENQIESKAAYV<br>LFYQRQDVARRLLSPAGSSGAP<br>ASPACSSPPSSEFMDVN                                                                                                                                                                                                                                                                                                                                                                                      |     |                                                                                                                                                                                                                                                                                                                                                                                       |
| U17L1_HUMAN Ubiquitin carboxyl-terminal hydrolase 17-like protein 1 | 23 | MGDDSLYLGGEWQFNHFSKLTS<br>SRPDAFAEIQRTSLPEKSPLS<br>SETRVDLCDDLAPVARQLAPRE<br>KLPLSSRRPAAVGAGLQNMGNT<br>CYENASLQCLTYTLPLANMYS<br>REHSQTCQRPKCCMLCTMQAHI<br>TVALHSPGHVIQPSQALAAGFH<br>RGKQEDVHEFLMFTVDAMKKAC<br>LPGHKQVDHHCDDTTLIHQIFG<br>GCWRSQIKCLHCHGISDTFDPY<br>LDIALDIQAAQSVKQALEQLVK<br>PEELNGENAYHCGLCLQRPAS<br>NTLTHTSAKVLILVLKRFSDV<br>AGNKLAKNVQYPECLDMQPYMS<br>QQNTGPLVYVLYAVLVHAGWSC<br>HDGHYFSYVKAQEVQWYKMDDA<br>EVTVCSSIIISVLSQQAYVLFYIQ<br>KSEWERHSESVSRRGREPRALGA<br>EDTDRRAKQGELKRDHPCLQAP<br>ELDEHLVERATQESTLDHWKFL<br>QEQNKTKEPFNVGKVEGTLPN<br>ALVIHQSKYKCGMKNHHPEQQS<br>SLNLSSSTTRTDQESMNTGTLA<br>SLQGRTRRAKGKNKHSKRALLV<br>CQ | 135 | AVGAGLQNMGNTCYENASLQ<br>CLTYTLPLANMYSREHSQT<br>CQRPKCCMLCTMQAHIWAL<br>HSPGHVIQPSQALAAGFHRG<br>KQEDVHEFLMFTVDAMKKAC<br>LPGHKQVDHHCDDTTLIHQI<br>FGGCWRSQIKCLHCHGISDT<br>FDPYLDIALDIQAAQSVKQAL<br>LEQLVKPEELNGENAYHCGL<br>CLQRPASNTLTHTSAKVL<br>ILVLKRFSDVAGNKLAKNVQ<br>YPECLDMQPYMSQQNTGPLV<br>YVLYAVLVHAGWSCHDGHYF<br>SYVKAQEVQWYKMDDAEVTV<br>CSIISVLSQQAYVLFYIQKS                     |
| UBP14_HUMAN Ubiquitin carboxyl-terminal hydrolase 14                | 24 | MPLYSVTVKWGKEKFEGVELNT<br>DEPPMVFKAQLFALTGVQPARQ<br>KVMVKGGLTKDDDWGNIIKING<br>MTLLMGSADALPEEPSAKTVF<br>VEDMTEEQLASAMELPCGLTNL<br>GNTCYMNATVQCIRSVPELKDA<br>LKRYAGALRASGEMASQYITA<br>ALRDLFDSMDKTSSSIPPIILL<br>QFLHMAFPQFAEKGEQGQYLQ<br>DANECWIMMRVLQQKLEAIED<br>DSVKETDSSSASAATPSKKKSL<br>IDQFFGVEFETTMKCTESEEEE<br>VTGKENQLQLSCFINQEVKYL<br>FTGLKLRLQEEITQSPTLQRN<br>ALYIKSSKISRLPAYLTIQMVR<br>FFYKEKESVNAKVLKDVKFPLM                                                                                                                                                                                                                           | 136 | ASAMELPCGLTNLGNTCYMN<br>ATVQCIRSVPELKDALRYA<br>GALRASGEMASQYITAALR<br>DLFDSMDKTSSSIPPIILLQ<br>FLHMAFPQFAEKGEQGQYLQ<br>QDANECWIMMRVLQQKLEA<br>IEDDSVKETDSSSASAATPS<br>KKKSLIDQFFGVEFETTMKC<br>TESEEEVTKGKENQLQLSC<br>FINQEVKYLFTGLKLRLQEE<br>ITQSPTLQRNALYIKSSKI<br>SRLPAYLTIQMVRFFYKEKE<br>SVNAKVLKDVKFPLMLDME<br>LCTPELQEKMSFRSKFKDL<br>EDKKVNQQPNTSDKKSSPQK<br>EVKYEPPSFADDIGSNNGCY |

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|                                                                            |    | LDMYELCTPELQEKMVSFERSKF<br>KDLEDKKVNQQPNTSDKKSSPQ<br>KEVKYEPFSFADDIGSNNGYY<br>DLQAVLTHQGRSSSSGHYVSWV<br>KRKQDEWIKFDDDKVSIIVTPED<br>ILRLSGGGDWHIAYVLLYGPRR<br>VEIMEESEQ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |     | YDLQAVLTHQGRSSSSGHYV<br>SWVKRKQDEWIKFDDDKVSI<br>VTPEDILRLSGGGDWHIAYV<br>LLYGPRR                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Q13107 UBP4<br>_HUMAN<br>Ubiquitin<br>carboxyl-<br>terminal<br>hydrolase 4 | 25 | MAEGGGCRERPDAETQKSELGP<br>LMRTTLQGAQWYLIDSRWFKQ<br>WKKYVGFDSDMYNVGEHNLFP<br>GPIDNSGLFSDPESQTLKEHLI<br>DELDYVLVPTEAWNKLNLWYGC<br>VEGQQPIVRKVVEHGLFVKHCK<br>VEVYLLLELKLCEPNTNVLSC<br>HFSKADTIATIEKEMRKLFNIP<br>AERETRLWNKYMSNTYEQLSKL<br>DNTVQDAGLYQGQVLVIEPQNE<br>DGTWPRQTLQSKSSTAPSRNFT<br>TSPKSSASPYSSVSASLIANGD<br>STSTCGMHSSGVSRGGSGFSAS<br>YNCQEPSSSHIQPGLCGLGNLG<br>NTCFMNSALQCLSNAPLTDYF<br>LKDEYEAEINRDNPLGMKGEIA<br>EAYAEIKQMWSGRDAHVAPRM<br>FKTQVGRFAPQFSGYQQQDSQE<br>LLAFLLDGLHEDLNRVKKPKYL<br>ELKDANGRPDAVVAKEAWENHR<br>LRNDVIVDTFHGLFKSTLVCP<br>ECAKVSVTFDFCYLTLPLPLK<br>KDRVMEVFLVPADPHCRPTQYR<br>VTVPLMGAVSDLCEALSRLSGI<br>AAENMVVADVYNHRFHKIFQMD<br>EGLNHIMPRDDIFVYEVCSSTV<br>DGSECVTLVPYFRERKSRPSST<br>SSASALYGQPLLLSVPKHKLT<br>ESLYQAVCDRISRYVKQPLPDE<br>FGSSPLEPGACNGSRNSCEGED<br>EEEMEHQEEGKEQLSETEGSGE<br>DEPGNDPSETTQKKIKGQPCPK<br>RLFTFSLVNSYGTADINSLAAD<br>GKLLKLNSRSTLAMDWDSETRR<br>LYYDEQSEAYEKHVSMLQPQK<br>KKKTTVALRDCIELFTTMTLGEH<br>EHPWYCPNCKKHQQATKKFDL<br>WSLPKILVVHLKRFSYNRYWRD<br>KLDTVVEFPPIRGLNMSEFVCNL<br>SARPYVYDLIAVSNHYGAMGVG<br>HYTAYAKNKLNGKWYYFDDSNV<br>SLASEDQIVTKAAYVLFYQRRD<br>DEFYKTPSLSSSGSSDGGTRPS<br>SSQQGFGDDEACSMNTN | 137 | SHIQPGLCGLGNLGNTCFMN<br>SALQCLSNAPLTDYFLKDE<br>YEAEINRDNPLGMKGEIAEA<br>YAEIKQMWSGRDAHVAPRM<br>FKTQVGRFAPQFSGYQQQDS<br>QELLAFLLDGLHEDLNRVKK<br>KPYLELKDANGRPDAVVAKE<br>AWENHRLRNDVIVDTFHGL<br>FKSTLVCECAKVSVTFDFPF<br>CYLTLPLPLKKDRVMEVFLV<br>PADPHCRPTQYRVTVPLMGA<br>VSDLCEALSRLSGIAENMV<br>VADVYNHRFHKIFQMDGLN<br>HIMPRDDIFVYEVCSSTVDG<br>SECVTLPVYFRERKSRPSST<br>SSASALYGQPLLLSVPKHKLT<br>TLESYQAVCDRISRYVKQPL<br>LPDEFGSSPLEPGACNGSRN<br>SCEGEDEEEMEHQEEGKEQL<br>SETEGSGEDEPGNDPSETTQ<br>KKKIKGQPCPKRLFTFSLVNS<br>YGTADINSLAADGKLLKLNS<br>RSTLAMDWDSETRRLYYDEQ<br>ESEAYEKHVSMLQPQKKKKT<br>TVALRDCIELFTTMTLGEH<br>DPWYCPNCKKHQQATKKFDL<br>WSLPKILVVHLKRFSYNRYW<br>RDKLDTVVEFPPIRGLNMSEF<br>VCNLSARPYVYDLIAVSNHY<br>GAMGVGHYTAAYAKNKLNGKW<br>YYFDDSNVSLASEDQIVTKA<br>AYVLFYQRRD |

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| UBP26_HUM<br>AN Ubiquitin<br>carboxyl-<br>terminal<br>hydrolase 26 | 26 | MAALFLRGFVQIGNCKTGISKS<br>KEAFIEAVERKKKDRLLVLYFKS<br>GKYSTFRLSDNIQNVVLKSYRG<br>NQNHLLHLTLQNNNGLFIEGLSS<br>TDAEQLKIFLDRVHQNEVQPPV<br>RPGKGGSVFSSTTQKEINKTSF<br>HKVDEKSSSKSFEIAKSGTGV<br>LQRMPLLTSKLTLCGELSENQ<br>HKRRKRLSSSSEMNEEFLKEN<br>NSVEYKKSADCSRCVSYNREK<br>QLKLELEENKKLECESSCIMN<br>ATGNPYLDDIGLLQALTEKMVL<br>VFLQQGYSDGYTKWDKLKLEFF<br>ELFPEKICHGLPNLGNTCYMNA<br>VLQSLLSIPSFADDLLNQSF PW<br>GKIPLNALTMCCLARLLFFKDTY<br>NIEIKEMLLLNKKAISAAAEI<br>FHGNAQNDAHEFLAHCLDQLKD<br>NMEKLNTIWKPKSEFGEDNFPK<br>QVFADDPDTSFGFSCPVTNFEL<br>ELLHSIACKACGQVILKTELNN<br>YLSINLPQRIKAHPSSIQSTFD<br>LFFGAELELEYKCAKCEHKTSGV<br>VHSFSRLPRILIVHLKRYSLNE<br>FCALKKNDQEVIIISKYLKVSSH<br>CNEGTRPPLPLSEGEITDFQL<br>LKVIRKMTSGNISVSWPATKES<br>KDILAPHIGSDKESEQKKGQTV<br>FKGASRRQQQKYLKGNSKPNEL<br>ESVYSGDRAFIEKEPLAHLMTY<br>LEDTS LCQFHKAGGKPASSPGT<br>PLSKVDFQTVPENPKRKKYVKT<br>SKFVAFDRIINPTKDLYEDKNI<br>RIPERFQKVSEQTQQCDGMRIC<br>EQAPQQALPQSFPKPGTQGHTK<br>NLLRPTKLNQKSNRNSLLALG<br>SNKNPRNKDILDKIKSKAKETK<br>RNDDKGDHTYRLISVVS HLGKT<br>LKSGHYICDAYDFEKQIWFTYD<br>DMRVLGIQEAQMQEDRRCTGYI<br>FFYMHNEIFEEMLKREENAQLN<br>SKEVEETLQKE | 138 | KICHGLPNLGNTCYMNAVLQ<br>SLLSIPSFADDLLNQSF PWG<br>KIPLNALTMCCLARLLFFKDT<br>YNIEIKEMLLLNKKAISAA<br>AEIFHGNAQNDAHEFLAHCL<br>DQLKDNMEKLNTIWKPKSEF<br>GEDNFPKQVFADDPDTSFGFS<br>CPVITNFEELELLHSIACKAC<br>GQVILKTELNNYLSINLPQR<br>IKAHPSSIQSTFDLFFGAE<br>LEYKCAKCEHKTSGVHSFS<br>RLPRILIVHLKRYSLNEFCA<br>LKKNQDEVIISKYLKVSSH<br>NEGTRPPLPLSEGEITDFQ<br>LLKVIRKMTSGNISVSWPAT<br>KESKDILAPHIGSDKESEQK<br>KGQTVFKGASRRQQQKYLKG<br>NSKPNELESVYSGDRAFIEK<br>EPLAHLMTYLEDTS LCQFHK<br>AGGKPASSPGTPLSKVDFQT<br>VPENPKRKKYVKT SKFVAFD<br>RIINPTKDLYEDKNI RIPER<br>FQKVSEQTQQCDGMRICEQA<br>PQQALPQSFPKPGTQGHTKN<br>LLRPTKLNQKSNRNSLLAL<br>GSNKNPRNKDILDKIKSKAK<br>ETKRNDKGDHTYRLISVVS<br>HLGKTLKSGHYICDAYDFEK<br>QIWFTYDDMRVLGIQEAQM<br>EDRRCTGYIFFYMHN |
| UBP19_HUM<br>AN Ubiquitin<br>carboxyl-<br>terminal<br>hydrolase 19 | 27 | MSGGASATGPRRGPPGLEDTTS<br>KKKQKDRANQESKDGDPKETG<br>SRYVAQAGLEPLASGDPSASAS<br>HAAGITGSRHRTLFFPSSSGS<br>ASTPQEEQTKEGACEDPHDLLA<br>TPTPELLLDWRQSAEEVIVKLR<br>VGVGPLQLEDVDAFTDTDCVV<br>RFAGGQQWGGVFYAEIKSSCAK<br>VQTRKGSLLHLTLPPKKVPMLTW                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 139 | LPGFTGLVNLGNTCFMNSVI<br>QSLSNTREL R DFFHDRSFEA<br>EINYNPLGTGGRLAIGFAV<br>LLRALWKGTTHAFQPSKLKA<br>IVASKASQFTGYAQHDAQEF<br>MAFLLDGLHEDLNRIQNKP<br>YTETVSDGRPDEVVAEEAWQ<br>RHKMRNDSFIVDLFQGGYKS<br>KLVCPCAKVSITFDPFLYL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |



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|  | PSLLEADEQLCIPPLNSQTCL<br>LGSEENLAPLAGEKAVPPGNDP<br>VSPAMVRSRNPGRKDDCAKEEMA<br>VAADAATLVDEPESMVNLAFVK<br>NDSYEKGPDSVVHVYVKEICR<br>DTSRVLFREQDFTLIFQTRDGN<br>FLRLHPGCGPHTTFRWQVKLRN<br>LIEPEQCTFCFTASRIDICLRK<br>RQSQRWGGLEAPAAVVGAKVA<br>VPTGPTPLDSTPPGGAPHPLTG<br>QEEARAVEKDKSKARSEDGTGLD<br>SVATRTPMEHVT PKPETHLASP<br>KPTCMVPPMPHSPVSGDSVEEE<br>EEEEKKVCLPGFTGLVNLGNTC<br>FMNSVIQSLSNTRERLDFFHDR<br>SFEAEINYNPLGTGGRLAIGF<br>AVLLRALWKGTHHAFQPSKLKA<br>IVASKASQFTGYAQHDAQEFMA<br>FLDDGLHEDLNRIQNKPYTETV<br>DSDGRPDEVVAEEAWQRHKMRN<br>DSFIVDLFQGGYKSKLVCVCA<br>KVSITFDPFLYLPVPLPQKQKV<br>LPVFYFAREPHSKPIKFLVSVS<br>KENSTASEVLDLSQSVHVKPE<br>NLRLAEVIKNRFHRVFLPSHSL<br>DTVSPSDTLLCFELLSSELAKE<br>RVVLEVQQRQPVPSPISKCA<br>ACQRKQQSEDEKLKRCTRCYRV<br>GYCNQLCQKTHWPDHKGLCRPE<br>NIGYPFLVSVPASRLTYARLAQ<br>LLEGYARYSVSVFQPPFQGRM<br>ALESQSPGCTTLLSTGSLEAGD<br>SERDPIQPPELQLVTPMAEGDT<br>GLPRVWAAPDRGPVPSTSGISS<br>EMLASGPIEVGSLPAGERVSRP<br>EAAVPGYQHPSEAMNAHTPQFF<br>IYKIDSSNREQRLEDKGDTPLE<br>LGDDCSLALVWRNNERLQEFVL<br>VASKELECAEDPGSAGEAARAG<br>HFTLDQCLNLFTRPEVLAPEEA<br>WYCPQCKQHREASKQLLLWRLP<br>NVLIVQLKRFSFRSFIWRDKIN<br>DLVEFPVRNLDLSKFCIGQKEE<br>QLPSYDLYAVINHYGGMIGGHY<br>TACARLPNDRSSQRSDVGWRLF<br>DDSTVTTVDESQVVTRYAYVLF<br>YRRRNSPVERPPRAGHSEHHPD<br>LGPAAEAAASQASRIWQEEAE<br>EEPVPEGSGPLGPWGPQDWVGP<br>LPRGPTTPDEGCLRYFVLGTVA<br>ALVALVLNVFYPLVSQSRWR | PVPLPQKQKVLVPVFYFAREP<br>HSKPIKFLVSVSKENSTASE<br>VLDLSQSVHVKPENLRALAE<br>VIKNRFHRVFLPSHSLDTSV<br>PSDTLLCFELLSSELAKEV<br>VVLEVQQRQPVPSPISKCA<br>ACQRKQQSEDEKLKRCTRCY<br>RVGYCNQLCQKTHWPDHKGL<br>CRPENIGYPFLVSVPASRLT<br>YARLAQLLEGYARYSVSVFQ<br>PPFQPGRMALLESQSPGCTTL<br>LSTGSLEAGDSEDPPIQPPE<br>LQLVTPMAEGDTGLPRVWAA<br>PDRGPVPSTSGISSEMLASG<br>PIEVGSLPAGERVSRPEAAV<br>PGYQHPSEAMNAHTPQFFIY<br>KIDSSNREQRLEDKGDTPLE<br>LGDDCSLA<br>LVWRNNERLQEFVLVASKEL<br>ECAEDPGSAGEAARAGHFTL<br>DQCLNLFTRPEVLAPEEAWY<br>CPQCKQHREASKQLLLWRLP<br>NVLIVQLKRFSFRSFIWRDK<br>INDLVEFPVRNLDLSKFCIG<br>QKEEQLPYDLYAVINHYGG<br>MIGGHYTACARLPNDRSSQR<br>SDVGWRLFDDSTVTTVDESQ<br>VVTRYAYVLFYRRRN |
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| UBP10_HUMAN Ubiquitin carboxyl-terminal hydrolase 10 | 28 | MALHSPQYIFGDFSPDEFNQFF<br>VTPRSSVELPPYSGTVLCGTQA<br>VDKLPDGQEYQRIEFGVDEVIE<br>PSDTLPRTPSYSISSTLNPQAP<br>EFILGCTASKITPDGITKEASY<br>GSIDCQYPGSALALDGSSNVEA<br>EVLENDGVSGGLGQREKKKKK<br>RPPGYYSYLDGGDDSI STEAL<br>VNGHANSAPNSVSAEDAEFMG<br>DMPPSVTPRTCNSPQNSTDVS<br>DIVPDSFPFGALGSDTRTAGQP<br>EGGPGADFGQSCFPAEAGRDTL<br>SRTAGAQPCVGTDTTENLGVAN<br>GQILESSGEGTATN<br>GVELHTTESIDLDPKPEASAP<br>PADGTGSASGTLPVSQPKSWAS<br>LFHDSKPSSSSPVAYVETKYSP<br>PAISPLVSEKQVEVKEGLVPVS<br>EDPVAIKIAELLENVTLIHKPV<br>SLQPRGLINKGNWCYINATLQA<br>LVACPPMYHLMKFIPLYSKVQR<br>PCTSTPMIDSFVRLMNEFTNMP<br>VPPKPRQALGDKIVRDIRPGAA<br>FEPTYIYRLLTVNKSSLSEKGR<br>QEDAEYYLGFI LNGLHEEMLNL<br>KKLLSPSNEKLTISNGPKNHSV<br>NEEEQEEQEGSEDEWEQVGPR<br>NKTSVTRQADFVQT<br>PITGIFGGHIRSVVYQQSSKES<br>ATLQPPFTLQLDIQSDKIRTVQ<br>DALESLVARESVQGYTTKTKQE<br>VEISRRVTLEKLPPVLVHLKR<br>FVYEKTGGCQKLIKNI EYPVDL<br>EISKELLSPGVKNKNFKCHRTY<br>RLFVAVVYHHGNSATGGHYTTDV<br>FQIGLNGWLRIDDQTVKVINQY<br>QVVKPTAERTAYLLYRRVDLL | 140 | SLQPRGLINKGNWCYINATL<br>QALVACPPMYHLMKFIPLYS<br>KVQRPCTSTPMIDSFVRLMN<br>EFTNMPVPPKPRQALGDKIV<br>RDIRPGAAFEPTYIYRLLTV<br>NKSSLSEKGRQEDAEYYLGF<br>ILNGLHEEMLNLKKLLSPSN<br>EKLTISNGPKNHSVNEEEQE<br>EQEGSEDEWEQVGPRNKTS<br>VTRQADFVQTPITGIFGGHI<br>RSVVYQQSSKESATLQPPFT<br>LQLDIQSDKIRTVQDALESL<br>VARESVQGYTTKTKQEVEIS<br>RRVTLEKLPPVLVHLKR FV<br>YEKTGGCQKLIKNI EYPVDL<br>EISKELLSPGVKNKNFKCHR<br>TYRLFVAVVYHHGNSATGGHY<br>TTDV FQIGLNGWLRIDDQTV<br>KVINQYQVVKPTAERTAYLL<br>YRRVD |
| UBP49_HUMAN Ubiquitin carboxyl-terminal hydrolase 49 | 29 | MDRCKHVGRRLRLAQDHSILNPQ<br>KWCCLECATTESVWACLKCSHV<br>ACGRYIEDHALKHFEETGHPLA<br>MEVRDLYVFCYLCKDYVLNDNP<br>EGDLKLLRSSLLAVRGQKQDTP<br>VRRGRTLRS MASGEDVVL PORA<br>PQGQPQMLTALWYRRQRL LART<br>LRLWFEKSSRGQAKLEQRRQEE<br>ALERKKEEARRRRREV KRR LLE<br>ELASTPPRKSARLLLHTPRDAG<br>PAASRPAALPTSRRVPAATLKL<br>RRQPAMAPGVTGLRNLGNTCYM<br>NSILQVL SHLQKFRECFLNLD<br>SKTEHLFPKATNGK                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 141 | MDRCKHVGRRLRLAQDHSILN<br>PQKWCCLECATTESVWACLK<br>CSHVACGRYIEDHALKHFEET<br>TGHPLAMEVRDLYVFCYLCK<br>DYVLNDNPEGDLKLLRSSLL<br>AVRGQKQDTPVRRGRTLRS<br>MASGEDVVL PORA PQGQPQML<br>TALWYRRQRL LARTLRLWFE<br>KSSRGQAKLEQRRQEEALER<br>KKEEARRRRREV KRR LLEEL<br>ASTPPRKSARLLLHTPRDAG<br>PAASRPAALPTSRRVPAATL<br>KLRRQPAMAPGVTGLRNLGN<br>TCYMNSILQVL SHLQKFREC                                                                                                                            |

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|                                                                              |    | <p>TQLSGKPTNSSATELSLRNDRA<br/>EACEREGFCWNGRASISRSL<br/>EQNKEPSSKHISLCRELHTLFR<br/>VMWSGKWALVSPFAMLSVWSL<br/>IPAFRGYDQQDAQEFLCELLHK<br/>VQQELESEGTTRRILIPFSQRK<br/>LTKQVLKVVNTIFHGQLLSQVT<br/>CISCNYKSNTIEPFWDLSLEFP<br/>ERYHCIEKGFVPLNQTECLLTE<br/>MLAKFTETEALLEGRIYACDQCN<br/>SKRRKSNPKPLVLSEARKQLMI<br/>YRLPQVLRRLHLKRFRWSGRNHR<br/>EKIGVHVVDQVLTMEPYCCRD<br/>MLSSLDKETFAYDL<br/>SAVVMHHGKGFGSGHYTAYCYN<br/>TEGGFWVHCNDSKLNVCSEEV<br/>CKTQAYILFYTQRTVQGNARIS<br/>ETHLQAQVQSSNNDEGRPQTFS</p>                                                                                                                                                                                |     | <p>FLNLDPSTEHLFPKATNGK<br/>TQLSGKPTNSSATELSLRND<br/>RAEACEREGFCWNGRASISR<br/>SLELIQNKEPSSKHISLCRE<br/>LHTLFRVMWSGKWALVSPFA<br/>MLHSVWSLIPAFRGYDQQDA<br/>QEFLCELLHKVQQELESEGT<br/>TRRILIPFSQRKLTQVLKV<br/>VNTIFHGQLLSQVTCISCNY<br/>KSNTIEPFWDLSLEFPERYH<br/>CIEKGFVPLNQTECLLTEML<br/>AKFTETEALLEGRIYACDQCN<br/>SKRRKSNPKPLVLSEARKQL<br/>MIYRLPQVLRRLHLKRFRWSG<br/>RNHREKIGVHVVDQVLTME<br/>PYCCRDMLSSLDKETFAYDL<br/>SAVVMHHGKGFGSGHYTAYC<br/>YNTEGGFWVHCNDSKLNVCSE<br/>VEEVCKTQAYILFYTQRT</p> |
| U17L8_HUMAN Inactive ubiquitin carboxyl-terminal hydrolase 17-like protein 8 | 30 | <p>MEDDSLYLGGEWQFNHFSKLTS<br/>PRPDAAFAEIQRSTLPEKSPLS<br/>SETRVDLCDDLAPVARQLAPRE<br/>KLPLSSRRPAAVGAGLQNMGNT<br/>CYLNASLQCLTYTPPLANMYS<br/>REHSQTCQRPKCCMLCTMQAHI<br/>TVALHSPGHVIQPSQALAAGFH<br/>RGKQEDAHEFLMFTVDAMKKAC<br/>LPGHKQVDHHSKDTTLIHQIFG<br/>GCWRSQIKCLHCHGISDTFDPY<br/>LDIALDIQAAQSVKQALEQLVK<br/>PEELNGENAYPCGLCLQRPAS<br/>NTLTHTSAKVLILVLKRFCDV<br/>TGNKLAKNVQYPEC<br/>LDMQPYMSQQNTGPLVYVLYAV<br/>LVHAGWSCHNGYYFSYVKAQEG<br/>QWYKMDDAEVTACSITSVLSQQ<br/>AYVLFYIQKSEWERHSESVSRG<br/>REPRALGAEDTDRPATQGELKR<br/>DHPCLQVPELDEHLVERATEES<br/>TLDHWKFPEQNKMKPEFNVRK<br/>VEGTLPNVLVIHQSKYKCGMK<br/>NHHPEQQSSLLNLSSMNSTDQE<br/>SMNTGTLASLQGRTRRSKGKNK<br/>HSKRSLLVQC</p> | 142 | <p>AVGAGLQNMGNTCYLNASLQ<br/>CLTYTPPLANMYSREHSQT<br/>CQRPKCCMLCTMQAHITWAL<br/>HSPGHVIQPSQALAAGFHRG<br/>KQEDAHEFLMFTVDAMKKAC<br/>LPGHKQVDHHSKDTTLIHQI<br/>FGGCWRSQIKCLHCHGISDT<br/>FDPYLDIALDIQAAQSVKQALE<br/>QLVKPEELNGENAYPCGL<br/>CLQRPASNTLTHTSAKVL<br/>ILVLKRFCDVTGNKLAKNVQ<br/>YPECLDMQPYMSQQNTGPLV<br/>YVLYAVLVHAGWSCHNGYYF<br/>SYVKAQEGQWYKMDDAEVTA<br/>CSITSVLSQQAYVLFYIQKS</p>                                                                                                      |
| 6VN6_1                                                                       | 31 | <p>GSKKHTGYVGLKNQGATCYMNS<br/>LLQTLFFTNQLRKAVYMMPT<br/>EGDDSSKSVPLALQRVFYELQHS<br/>KPVGTKKLTKSFGWETLDSFMQ<br/>HDVQELCRVLLDNVENKMKGTC<br/>VEGTIPKLFRGKMVS YIQCKEV<br/>DYRSDRREDY YDIQLSIKGGKN</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 143 | <p>TGYVGLKNQGATCYMNSLLQ<br/>TLFFTNQLRKAVYMMPT<br/>EGDDSSKSVPLALQRVFYELQHS<br/>KPVGTKKLTKSFGWETLDS<br/>FMQHDVQELCRVLLDNVENK<br/>MKGTCVEGTIPKLFRGKMVS<br/>YIQCKEVDYRSDRREDY YDI</p>                                                                                                                                                                                                                                                                                                           |

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|                                                                      |    | IFESFVDYVAVEQLDGDN KYDA<br>GEHGLQEAEKGVKFLTLPPVLH<br>LQLMRMYDPQTDQNIKINDRF<br>EFPEQLPLDEFLQKTDPKDPAN<br>YILHAVLVHSGDNHGGHYVVYL<br>NPKGDGKWCKFDDDVSRCTKE<br>EAIEHNYGGHDDDL SVRHCTNA<br>YMLVYIRESKLSEVLQAVTDHD<br>IPQQLVERLQEEKRIEAQKR                                                                                                                                                                                                                        |     | QLSIKGKKNIFESFVDYVAV<br>EQLDGDN KYDAGEHGLQEAE<br>KGVKFLTLPPVLHLQLMRFM<br>YDPQTDQNIKINDRF EFPEQ<br>LPLDEFLQKTDPKDPANYIL<br>HAVLVHSGDNHGGHYVVYLN<br>PKGDGKWCKFDDDVSRCTK<br>EEAIEHNYGGHDDDL SVRHC<br>TNAYMLVYIRE                                                                                                                                                                                                                                            |
| 6DGF_1                                                               | 32 | AQGLAGLRNLGN TCFMNSILQC<br>LSNTREL RDYCLQRLYMRDLHH<br>GSNAHTALVEEF AKLIQT IWT S<br>SPNDV VSPSEFKTQIQRYAPRF<br>VGYNQQDAQEF LRFLLDGLHNE<br>VNRVTLRPKSNPENLDHLPDDE<br>KGRQMWRKYLEREDSRIGDLFV<br>GQLKSSLTCTDCGYCSTVFDPF<br>WDL SPLIAKRGYPEVTLMDCMR<br>LFTKEDVLDGDEKPTCCRCRGR<br>KRCIKKFSIQRF PKILVLHLKR<br>FSESRI RTSKLTTFVNFPLRDL<br>DLREFASENTNHAVYNLYAVSN<br>HSGTTMGGHYTAYCRSPGTGEW<br>HTFNDSSVTPMSSSQVRTSDAY<br>LLFYELASPPSRM                               | 144 | AQGLAGLRNLGN TCFMNSIL<br>QCLSN TREL RDYCLQRLYMR<br>DLHHGSNAHTALVEEF AKLI<br>QTIWTSSPNDV VSPSEFKTQ<br>IQRYAPRFVGYNQQDAQEF L<br>RFLLDGLHNEVNRVTLRPKS<br>NPENLDHLPDDEKGRQMWRK<br>YLEREDSRIGDLFVGQLKSS<br>LTCTDCGYCSTVFDPFWDL S<br>LPIAKRGYPEVTLMDCMR L F<br>TKEDVLDGDEKPTCCRCRGR<br>KRCIKKFSIQRF PKILVLHL<br>KRFSESRI RTSKLTTFVNF P<br>LRDLDLREFASENTNHAVYN<br>LYAVSNHSGTTMGGHYTAYC<br>RSPGTGEWHTFNDSSVTPMS<br>SSQVRTSDAYLLFYELAS                           |
| 2VHF_1                                                               | 33 | GLEIMIGKKKG IQGHYNSCYLD<br>STLFCLFAFSSVLDTVLLRPKE<br>KNDVEYYSETQELLRTEIVNPL<br>RIYGYVCATKIMKLRKILEKVE<br>AASGFTSEEKDP EEFNLIFHH<br>ILRVEPLLKIRSAGQKVQDCYF<br>YQIFMEKNEKVG VPTIQQLLEW<br>SFINSNLKFAEAPSLIIQMPR<br>FGKDFKLFKKIFPSLELNITDL<br>LEDTPRQCRICGGLAMYECREC<br>YDDPDISAGKIKQFCKTCNTQV<br>HLHPKRLNHKYNPVSLPKDLPD<br>WDWRHGCI PCQNMELFAVLCIE<br>TSHYVAFVKY GKDDSAWLFFDS<br>MADR DGGQNGFNIPQVTPCPEV<br>GEYLKMSLEDLHSLDSRRIQGC<br>ARRLLC DAYMCMYQSPTMSLYK | 145 | MIGKKKG IQGHYNSCYLDST<br>LFCLFAFSSVLDTVLLRPKE<br>KNDVEYYSETQELLRTEIVN<br>PLRIYGYVCATKIMKLRKIL<br>EKVEAASGFTSEEKDP EEF L<br>NILFHILRVEPLLKIRSAG<br>QKVQDCYFYQIFMEKNEKVG<br>VPTIQQLLEWSFINSNLKFA<br>EAPSLIIQMPRFGKDFKLF<br>KKIFPSLELNITDLLEDTPR<br>QCRICGGLAMYECRECYDDP<br>DISAGKIKQFCKTCNTQVHL<br>HPKRLNHKYNPVSLPKDLPD<br>WDWRHGCI PCQNMELFAVLC<br>IETSHYVAFVKY GKDDSAWL<br>FFDSMADR DGGQNGFNIPQV<br>TPCPEVGEYLKMSLEDLHSL<br>DSRRIQGCARRLLC DAYMCM<br>YQS |
| U17LI_HUMAN Ubiquitin carboxyl-terminal hydrolase 17-like protein 18 | 34 | MEDDSLYLGGEWQFNHFSKLTS<br>SRPDAAFAEI QRTSLPEKSPLS<br>CETRVDLCDDLAPVARQLAPRE<br>KLPLSSRRPAAVGAGLQNMGNT<br>CYVNASLQCLTYTPPLAN YMLS<br>REHSQTCHRHKGCM LCTMQAHI                                                                                                                                                                                                                                                                                                 | 146 | AVGAGLQNMGNTCYVNASLQ<br>CLTYTPPLAN YMLSREHSQT<br>CHRHKGCM LCTMQAHITRAL<br>HNPGHVIQPSQALAAGFHRG<br>KQEDAHEFLMFTVDAMKKAC<br>LPGHKQVDHHSKDTTLIHQI                                                                                                                                                                                                                                                                                                           |

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|                                                      |    | <p>TRALHNPBGHVIQPSQALAAGFH<br/>RGKQEDAHEFLMFTVDAMKKAC<br/>LPGHKQVDHHSKDTTLIHQIFG<br/>GYWRSQIKCLHCHGISDTFDPY<br/>LDIALDIQAAQSVQQALEQLVK<br/>PEELNGENAYHCGVCLQRAPAS<br/>KTLTLHTSAKVLILVLKRFSDV<br/>TGNKIAKNVQYPEC<br/>LDMQPYMSQTNTGPLVYVLYAV<br/>LVHAGWSCHNGHYFSYVKAQEG<br/>QWYKMDDAEVTASSITSVLSQQ<br/>AYVLFIYQKSEWERHSESVSRG<br/>REPRALGAEDTDRRAKQGELKR<br/>DHPCLQAPELDEHLVERATQES<br/>TLDHWKFLQEQNKTKEFNVVRK<br/>VEGTLPPDVLVIHQSKYKCGMK<br/>NHHPEQQSSLLNLSSTTPTHQE<br/>SMNTGTLASLRGRARRSKGKNK<br/>HSKRALLVCQ</p>                                                                                                                                                 |     | <p>FGGYWRSQIKCLHCHGISDT<br/>FDPYLDIALDIQAAQSVQQA<br/>LEQLVKPEELNGENAYHCGV<br/>CLQRAPASKTLTLHTSAKVL<br/>ILVLKRFSDVTGNKIAKNVQ<br/>YPECLDMQPYMSQTNTGPLV<br/>YVLYAVLVHAGWSCHNGHYF<br/>SYVKAQEGQWYKMDDAEVTA<br/>SSITSVLSQQAYVLFIYQKS</p>                                                                                                                                                                                                          |
| UBP22_HUMAN Ubiquitin carboxyl-terminal hydrolase 22 | 35 | <p>MVSRPEPEGEAMDAELAVAPPG<br/>CSHLGSFKVDNWKQNLRAIYQC<br/>FVWSGTAEARKRKAKSCICHVC<br/>GVHLNRLHSCLYCVFFGCFTKK<br/>HIHEHAKAKRHNLAIDLMYGGI<br/>YCFLCQDYIYDKDMEIIAKEEQ<br/>RKAWKMQGVGEKFSTWEPTKRE<br/>LELLKHNPKRKITSNCTIGLR<br/>GLINLGNTCFMNCIVQALHTP<br/>LLRDFFLSDRHRCEMQSPSSCL<br/>VCEMSSLFQEFYSGHRSPHIPY<br/>KLLHLVWTHARHLAGYEQQDAH<br/>EFLIAALDVLHRHCKGDDNGKK<br/>ANNPNHCNCIIDQIFTGGLQSD<br/>VTCQVCHGVSTTIDPFWDISLD<br/>LPGSSTPFWPLSPGSEGNVNG<br/>ESHVSGTTTLDCLRRFTRPEH<br/>LGSSAKIKSGCHSYQESTKQL<br/>TMKKLPVACFHLKRFEHSACL<br/>RRKITTYVSFPLELDMTPFMAS<br/>SKESRMNGQYQQPTDSLNDNK<br/>YSLFAVVNHQGTLESGHYTSFI<br/>RQHKDQWFKCDDAIITKASIKD<br/>VLDSEGYLLFYHKQFLEYE</p> | 147 | <p>LGNTCFMNCIVQALHTPPLL<br/>RDFFLSDRHRCEMQSPSSCL<br/>VCEMSSLFQEFYSGHRSPHI<br/>PYKLLHLVWTHARHLAGYEQ<br/>QDAHEFLIAALDVLHRHCKG<br/>DDNGKKANNPNHCNCIIDQI<br/>FTGGLQSDVTCQVCHGVSTT<br/>IDPFWDISLDLPGSSTPFWP<br/>LSPGSEGNVNGESHVSGTT<br/>TLDCLRRFTRPEHLGSSAK<br/>IKCSGCHSYQESTKQLTMKK<br/>LPVACFHLKRFEHSACLRR<br/>KITTYVSFPLELDMTPFMAS<br/>SKESRMNGQYQQPTDSLNDNK<br/>YSLFAVVNHQGTLESGHYTSFI<br/>RQHKDQWFKCDDAIITKASIKD<br/>VLDSEGYLLFYHKQFLEYE</p> |
| UBP18_HUMAN Ubl carboxyl-terminal hydrolase 18       | 36 | <p>MSKAFGLLRQICQSILAESSQS<br/>PADLEEKKEEDSNMKREQPRER<br/>PRAWDPHGLVGLHNIGQTCCL<br/>NSLIQVFVMNVDFTRILKRITV<br/>PRGADEQRRSVPFQMLLLEKEM<br/>QDSRQKAVRPLELAYCLQKCNV<br/>PLFVQHDAALYLYKLWNLIKDQ<br/>ITDVHLVERLQALYTIIRVKDSL</p>                                                                                                                                                                                                                                                                                                                                                                                                                                       | 148 | <p>KGLVPGLVNLGNTCFMNSLL<br/>QGLSACPAFIRWLEEFSTQY<br/>SRDQKEPPSHQYLSLTLLHL<br/>LKALSCQEVTDDEVLDAACL<br/>LDVLRMYRWQISSFEEQDAH<br/>ELFHVITSSLEDERDRQPRV<br/>THLFDVHSLEQQSEITPKQI<br/>TCRTRGSPHPTSNHWKSQHP</p>                                                                                                                                                                                                                                   |

|                                                      |    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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|                                                      |    | <p>ICVDCAMESSRNSSMLTLPPLSL<br/>FDVDSKPLKTLEDALHCFQPR<br/>ELSSKSKCFCENCCKKTRGKQV<br/>LKLTHLPQTTLTIHLMRFSIRNS<br/>QTRKICHSLYFPQSLDFSQILP<br/>MKRESCDAEEQSGG<br/>QYELFAVIAHVGMADSGHYCVY<br/>IRNAVDGKWFCFNDSNICLVSW<br/>EDIQCTYGNPNYHWQETAYLLV<br/>YMKMEC</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |     | <p>FHGRLTSNMVCKHCEHQSPV<br/>RFDTFDSLSLSPAATWGHP<br/>LTLDHCLHHFISSESVRDVV<br/>CDNCTKIEAKGTLNGEKVEH<br/>QRTTFVKQLKLGKLPQCLCI<br/>HLQRLSWSSHGTPLKRHEHV<br/>QFNEFLMMDIYKYHLLGHKP<br/>SQHNPKLNKNPGPTLELQDG<br/>PGAPT PVLNQPGAPKTQIFM<br/>NGACSPSLPTLSAPMPFPL<br/>PVVPDYSSSTYLFRLMAVVV<br/>HHGDMHSGHFVTYRRSPPSA<br/>RNPLSTSNQWLWVSDDTVRK<br/>ASLQEVLSSSAYLLFYERVV</p>                                                                                                                                                                                                                                                                                   |
| UBP28_HUMAN Ubiquitin carboxyl-terminal hydrolase 28 | 37 | <p>MTAELQQDDAAGAADGHGSSCQ<br/>MLLNQLREITGIQDPSFLHEAL<br/>KASNGDITQAVSLLTDERVKEP<br/>SQDTVATEPSEVEGSAANKEVL<br/>AKVIDLTHDNKDDLQAAIALSL<br/>LESPKIQADGRDLNRMHEATSA<br/>ETKRKRKRCEVWGENPNPNPW<br/>RRVDGWVGLKNVGNTCWFSAV<br/>IQSLFQLPEFRRLVLSYSLPQN<br/>VLENCRSHTTEKRNIMFMQELQY<br/>LFALMMGSNRKFVDPSAALDLL<br/>KGAFRSSEEQQQDVSEFTHKLL<br/>DWLEDAFQLAVNVNSPRNKSEN<br/>PMVQLFYGTFLTEG<br/>VREGKPCFNNETFGQYPLQVNG<br/>YRNLDECLEGAMVEGDVELLPS<br/>DHSVKGQERWFTKLPPVLTFE<br/>LSRFEFNQSLGQPEKIHNKLEF<br/>PQIIYMDRYMYRSKELIRNKRE<br/>CIRKLKEEIKILQQKLERYVKY<br/>GSGPARFPLPDMKYVIEFAST<br/>KPASESCPPESDTHMTLPLSSV<br/>HCSVSDQTSKESTSTESSQDV<br/>ESTFSSPEDSLPKSKPLTSSRS<br/>SMEMPSQPAPRTVTDEEINFVK<br/>TCLQRWRSEIEQDIQDLKTCIA<br/>STTQTIEQMYCDPLLQVPYRL<br/>HAVLVHEGQANAGHYWAYIYNQ<br/>PRQSWLKYNDISVTESSWEEVE<br/>RDSYGGLRNV SAYCLMYINDKL<br/>PYFNAEAAPTESDQMSEVEALS<br/>VELKHYIQEDNWRFEQEVEEWE<br/>EEQSCKIPQMESSTNSSSQDYS<br/>TSQEPSVASSHGVRCLSSHAV<br/>IVKEQTAQAIANTARAYEKSGV<br/>EAALSEVMLSPAMQGVILAIK<br/>ARQTFDRDGSEAGLIKAFHEEY</p> | 149 | <p>GWPVGLKNVGNTCWFSAVIQ<br/>SLFQLPEFRRLVLSYSLPQN<br/>VLENCRSHTTEKRNIMFMQEL<br/>QYLFALMMGSNRKFVDPSAA<br/>LDLLKGAFRSSEEQQQDVSE<br/>FTHKLLDWLEDAFQLAVNVN<br/>SPRNKSENPMVQLFYGTFLT<br/>EGVREGKPCFNNETFGQYPL<br/>QVNGYRNLDECLEGAMVEGD<br/>VELLPSDHSVKGQERWFTK<br/>LPPVLT FELSRFEFNQSLGQ<br/>PEKIHNKLEFPQIIYMDRYM<br/>YRSKELIRNKRECIRKLKEE<br/>IKILQQKLERYVKYGS GPAR<br/>FPLPDMKYVIEFASTKPAS<br/>ESCPPESDTHMTLPLSSVHC<br/>SVSDQTSKESTSTESSQDV<br/>ESTFSSPEDSLPKSKPLTSS<br/>RSSMEMPSQPAPRTVTDEEI<br/>NFVKTCLQRWRSEIEQDIQD<br/>LKT CIASTTQTIEQMYCDPL<br/>LRQVPYRLHAVLVHEGQANA<br/>GHYWAYIYNQPRQSWLKYND<br/>ISVTESSWEEVERDSYGGLR<br/>NV SAYCLMYINDKLPY</p> |

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|                                                      |    | <p>SRLYQLAKETPTSHSDPRLQHV<br/>LVYFFQNEAPKRVERTLLEQF<br/>ADKNLSYDERSISIMKVAQAKL<br/>KEIGPDDMNMEYKKWHEDYSL<br/>FRKVSVYLLTGLELYQKGKYQE<br/>ALSYLVYAYQSNAALLMKGPRR<br/>GVKESVIALYRRKCLLELNAKA<br/>ASLFETNDDHSVTEGINVMNEL<br/>IIPCIIHLIINNDISKDDLDAIE<br/>VMRNHWCSYLGQDIAENLQLCL<br/>GEFLPRLLDPSAEIIVLKEPPT<br/>IRPNSPYDLCSRFAAVMESIQG<br/>VSTVTVK</p>                                                                                                                                                                                                                                                                                                                                  |     |                                                                                                                                                                                                                                                                                                                                                                                          |
| U17L2_HUMAN Ubiquitin carboxyl-terminal hydrolase 17 | 38 | <p>MEDDSLVLGGEWQFNHFSKLT<br/>SRPDAAFAEIQRSLPEKSPLS<br/>SEARVDLCDDLAPVARQLAPRK<br/>KLPLSSRRPAAVGAGLQNMGNT<br/>CYENASLQCLTYTPPLANMYS<br/>REHSQTCQRPKCCMLCTMQAHI<br/>TVALHSPGHVIQPSQALAAGFH<br/>RGKQEDAHEFLMFTVDAMKKAC<br/>LPGHKQVDHHSKDTTLIHQIFG<br/>GCWRSQIKCLHCHGISDTFDPY<br/>LDIALDIQAAQSVKQALEQLVK<br/>PEELNGENAYHCGLCLQRPAS<br/>KTLTLHTSAKVLILVLKRFS<br/>TGNKLAKNVQYPEC<br/>LDMQPYMSQQNTGPLVYVLYAV<br/>LVHAGWSCHDGHYFSYVKAQEG<br/>QWYKMDDAKVTACSITSVLSQQ<br/>AYVLFYIQKSEWERHSESVS<br/>RGREPRALGAEDTDRRATQ<br/>GELKRDHPCQLQAPELDERL<br/>VERATQESTLDHWKFPQEQ<br/>NKTKPEFNVRKVEGTLPPN<br/>VLVIHQSKYKCGMKNHHPE<br/>QQSSLLNLSSTTRTDQES<br/>SVNTGTLASLQGRTRRSK<br/>GKNKHSKRALLVCQ</p> | 150 | <p>AVGAGLQNMGNTCYENASLQ<br/>CLTYTPPLANMYSREHSQT<br/>CQRPKCCMLCTMQAHITWAL<br/>HSPGHVIQPSQALAAGFHRG<br/>KQEDAHEFLMFTVDAMKKAC<br/>LPGHKQVDHHSKDTTLIHQI<br/>FGGCWRSQIKCLHCHGISDT<br/>FDPYLDIALDIQAAQSVKQA<br/>LEQLVKPEELNGENAYHCGL<br/>CLQRPASKTLTLHTSAKVL<br/>ILVLKRFSVDVTGNKLAKNVQ<br/>YPECLDMQPYMSQQNTGPLV<br/>YVLYAVLVHAGWSCHDGHYF<br/>SYVKAQEGQWYKMDDAKVT<br/>ACSITSVLSQQAYVLFYIQKS</p> |
| UBP31_HUMAN Ubiquitin carboxyl-terminal hydrolase 31 | 39 | <p>MSKVTAPGSGPPAAASGKEKRS<br/>FSKRLFRSGRAGGGGAGGPGAS<br/>GPAAPSSPSSPSSARSVGSFMS<br/>RVLKTLSTLSHLSSEGAAPDRG<br/>GLRSCFPFGPAAAPTPPPCPPP<br/>PASPAPPACAAEPVPGVAGLRN<br/>HGNTCFMNATLQCLSNTLFAE<br/>YLALGQYRAGRPEPSPDPEQPA<br/>GRGAQGQGEVTEQLAHLVRALW<br/>TLEYTPQHSRDFKTIVSKNALQ<br/>YRGNSQHDAQEFLLWLLDRVHE<br/>DLNHSVKQSGQPPLKPPSETDM</p>                                                                                                                                                                                                                                                                                                                                              | 151 | <p>PVPGVAGLRNHGNTCFMNAT<br/>LQCLSNTLFAEYLALGQYR<br/>AGRPEPSPDPEQPAGRGAQG<br/>QGEVTEQLAHLVRALWTLEY<br/>TPQHSRDFKTIVSKNALQYR<br/>GNSQHDAQEFLLWLLDRVHE<br/>DLNHSVKQSGQPPLKPPSET<br/>DMMPEGPSFPVCSTFVQELF<br/>QAQYRSSLTCPHCQKQSNF<br/>DPFLCISLPIPLPHTRPLYV<br/>TVVYQGKCSHCMRIGVAVPL<br/>SGTVARLREAVSMETKIPTD<br/>QIVLTEMYYDGFHRSFCDTD</p>                                                    |

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|  |  | MPEGPSFPVCSTFVQELFQAQY<br>RSSLTCPHCQKQSN<br>TFDPFLCISLPIPLPHTRPLYV<br>TVVYQGKCSHCMRIGVAVPLSG<br>TVARLREAVSMETKIPTDQIVL<br>TEMYYDGFHRSFCDTDDLET VH<br>ESDCIFAFETPEIFRPEGILSQ<br>RGIHLNNNLNHLKFGLDYHRLS<br>SPTQTAAKQ GKMDSPSRAGSD<br>KIVLLVCNRACTGQQGKRFGLP<br>FVLHLEKTI AWDLLQKEILEKM<br>KYFLRPTVCIQVCPFSLRVVSV<br>VGITYLLPQEEQPLCHPIVERA<br>LKSCGPGGTAHVKL VVEWDKET<br>RDFLFVNTED EYIPDAESVRLQ<br>RERHHQPQTCTLSQ<br>CFQLYTKEERLAPDDAWRCPHC<br>KQLQQGSITLSLWTL PDVLI IH<br>LKRFRQEGDRRMKLQNMVKFPL<br>TGLDMTPHVVKRSQSSWSLPSH<br>WSPWRRPYGLGRDPEDYIYDLY<br>AVCNHHGTMQGGHYTAYCKNSV<br>DGLWYCFDDSDVQQLSEDEVCT<br>QTAYILFYQRRTAIPSWSANSS<br>VAGSTSSSLCEHWVSRLPGSKP<br>ASVTS AASSRRTSLASLSE SVE<br>MTGERSEDDGGFSTRPFVRSVQ<br>RQSLSSRSSVT SPLAVNENCMR<br>PSWSLSAKLQMRSNSPSRFSGD<br>SPIHSSASTLEKIG<br>EAADDKVSI SCFGSLRNLSSSY<br>QEPSDSHSRREHKAVGRAPLAV<br>MEGVFKDESDTRRLNSSVVD TQ<br>SKHSAQGDRLPPLSGPFDNNNQ<br>IAYVDQSDSVDSSPVKEVKAPS<br>HPGSLAKKPESTTKRSPSSKGT<br>SEPEKSLRKGRPALASQESSLS<br>STSPSSPLPVKVSLKPSRSRSK<br>ADSSSRGSGRHSSPAPAQPKKE<br>SSPKSQDSVSSPSPQKQKSASA<br>LTYTASSTS AKKASGPATRSPF<br>PPGKSRTSDHSL SREGSRQSLG<br>SDRASATSTSKPNSPRVSQARA<br>GEGRGAGKHVRSSS<br>MASLRSPSTS IKSGLKRDSKSE<br>DKGLSFFKSALRQKETRRSTD L<br>GKTALLSKKAGSSVKSVCKNT<br>GDDEAERGHQPPASQQPNANTT<br>GKEQLVTKDPASAKHSLLSARK<br>SKSSQLDSGVPSSPGGRQSAEK<br>SSKKLSSSMQTSARPSQKPQ |  | DLET VHESDCIFAFETPEIF<br>RPEGILSQRGIHLNNNLNHL<br>KFGLDYHRLSSPTQTAAKQG<br>KMDSPSRAGSDKIVLLVCN<br>RACTGQQGKRFGLPFVLHLE<br>KTI AWDLLQKEILEKMKYFL<br>RPTVCIQVCPFSLRVVSVVG<br>ITYLLPQEEQPLCHPIVE<br>RALKSCGPGGTAHVKL VVEW<br>DKETRDFLFVNTED EYIPDA<br>ESVRLQRERHHQPQTCTLSQ<br>CFQLYTKEERLAPDDAWRCP<br>HCKQLQQGSITLSLWTL PDV<br>LI IH LKRFRQEGDRRMKLQ N<br>MVKFPLTGLDMTPHVVKRSQ<br>SSWSLPSHSPWRRPYGLGR<br>DPEDYIYDLYAVCNHHGTMQ<br>GGHYTAYCKNSVDGLWYCFD<br>DSDVQQLSEDEVCTQTAYIL<br>FYQRRT |
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| U17LJ_HUMAN Ubiquitin carboxyl-terminal hydrolase 17-like protein 19 | 40 | <p>MEEDSLYLGGGEWQFNHFSKLTSSRPDAAF AEIQRTSLPEKSPLS<br/>CETRVDLCDLAPVARQLAPRE<br/>KLPLSSRRPAAVGAGLQNMGNT<br/>CYVNASLQCLTYTPPLANYM<br/>LSREHSQTCHRHKGCMCTMQAHI<br/>TRALHNPGHVIQPSQALAAGFH<br/>RGKQEDAHEFLMFTVDAMKKAC<br/>LPGHKQVDHHSKDTTLIHQIFG<br/>GYWRSQIKCLHCHGISDTFDPY<br/>LDIALDIQAAQSVQQALEQLVK<br/>PEELNGENAYHCGVCLQRPAS<br/>KTLTLHTSAKVLILVLKRFS<br/>DVTGNKIAKNVQYPEC<br/>LDMQPYMSQTNTGPLVYVLYAV<br/>LVHAGWSCHNGHYFSYVKAQEG<br/>QWYKMDDAEVTASSITSVLSQ<br/>QAYVLFYIQKSEWERHSESVSRG<br/>REPRALGAEDTDRRATQGELKR<br/>DHPCLQAPELDEHLVERATQES<br/>TLDHWKFLQEQNKTKEFNVRK<br/>VEGTLPPDVLVIHQSKYKCGMK<br/>NHHPEQQSSLLKLSSTTPTHQE<br/>SMNTGTLASLRGRARRSKGKNK<br/>HSKRALLVCQ</p>                             | 152 | <p>AVGAGLQNMGNTCYVNASLQ<br/>CLTYTPPLANYM<br/>LSREHSQTCHRHKGCMCTMQAHI<br/>TRALHNPGHVIQPSQALAAGFH<br/>RGKQEDAHEFLMFTVDAMKKAC<br/>LPGHKQVDHHSKDTTLIHQIFG<br/>GYWRSQIKCLHCHGISDTFDPY<br/>LDIALDIQAAQSVQQALEQLVK<br/>PEELNGENAYHCGVCLQRPAS<br/>KTLTLHTSAKVLILVLKRFS<br/>DVTGNKIAKNVQYPEC<br/>LDMQPYMSQTNTGPLVYVLYAV<br/>LVHAGWSCHNGHYFSYVKAQEG<br/>QWYKMDDAEVTASSITSVLSQ<br/>QAYVLFYIQKSEWERHSESVSRG<br/>REPRALGAEDTDRRATQGELKR<br/>DHPCLQAPELDEHLVERATQES<br/>TLDHWKFLQEQNKTKEFNVRK<br/>VEGTLPPDVLVIHQSKYKCGMK<br/>NHHPEQQSSLLKLSSTTPTHQE<br/>SMNTGTLASLRGRARRSKGKNK<br/>HSKRALLVCQ</p>                             |
| U17LF_HUMAN Ubiquitin carboxyl-terminal hydrolase 17-like protein 15 | 41 | <p>MEDDSLYLGGGEWQFNHFSKLTSSRPDAAF AEIQRTSLPEKSPLS<br/>CETRVDLCDLAPVARQLAPRE<br/>KLPLSSRRPAAVGAGLQNMGNT<br/>CYVNASLQCLTYTPPLANYM<br/>LSREHSQTCHRHKGCMCTMQAHI<br/>TRALHNPGHVIQPSQALAAGFH<br/>RGKQEDAHEFLMFTVDAMKKAC<br/>LPGHKQVDHHSKDTTLIHQIFG<br/>GYWRSQIKCLHCHGISDTFDPY<br/>LDIALDIQAAQSVQQALEQLVK<br/>PEELNGENAYHCGVCLQRPAS<br/>KTLTLHTSAKVLILVLKRFS<br/>DVTGNKIDKNVQYPEC<br/>LDMKLYMSQTNSGPLVYVLYAV<br/>LVHAGWSCHNGHYFSYVKAQEG<br/>QWYKMDDAEVTASSITSVLSQ<br/>QAYVLFYIQKSEWERHSESVSRG<br/>REPRALGAEDTDRRATQGELKR<br/>DHPCLQAPELDEHLVERATQES<br/>TLDHWKFLQEQNKTKEFNVRK<br/>VEGTLPPDVLVIHQSKYKCGMK<br/>NHHPEQQSSLLNLSSTTPTHQE<br/>SMNTGTLASLRGRARRSKGKNK<br/>HSKRALLVCQWSQWKYRPTRRG<br/>AHTHAHTQTHT</p> | 153 | <p>AVGAGLQNMGNTCYVNASLQ<br/>CLTYTPPLANYM<br/>LSREHSQTCHRHKGCMCTMQAHI<br/>TRALHNPGHVIQPSQALAAGFH<br/>RGKQEDAHEFLMFTVDAMKKAC<br/>LPGHKQVDHHSKDTTLIHQIFG<br/>GYWRSQIKCLHCHGISDTFDPY<br/>LDIALDIQAAQSVQQALEQLVK<br/>PEELNGENAYHCGVCLQRPAS<br/>KTLTLHTSAKVLILVLKRFS<br/>DVTGNKIDKNVQYPEC<br/>LDMKLYMSQTNSGPLVYVLYAV<br/>LVHAGWSCHNGHYFSYVKAQEG<br/>QWYKMDDAEVTASSITSVLSQ<br/>QAYVLFYIQKSEWERHSESVSRG<br/>REPRALGAEDTDRRATQGELKR<br/>DHPCLQAPELDEHLVERATQES<br/>TLDHWKFLQEQNKTKEFNVRK<br/>VEGTLPPDVLVIHQSKYKCGMK<br/>NHHPEQQSSLLNLSSTTPTHQE<br/>SMNTGTLASLRGRARRSKGKNK<br/>HSKRALLVCQWSQWKYRPTRRG<br/>AHTHAHTQTHT</p> |

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| UBP47_HUMAN Ubiquitin carboxyl-terminal hydrolase 47 | 42 | MVPGEENQLVPKEDVFWRCRQNI<br>IFDEMKKKFLQIENAAEEPRVL<br>CIIQDTTNSKTVNERITLNLPA<br>STPVRKLFEDVANKVGYINGTF<br>DLVWGNNGINTADMAPLDHTSDK<br>SLLDANFEPGKKNFLHLTDKDG<br>EQPQILLEDSSAGEDSVHDFI<br>GPLPREGSGGSTSDYVSQSYSY<br>SSILNKSETGYVGLVNQAMTCY<br>LNSLLQTLFMTPEFRNALYKWE<br>FEESEEDPVT SIPYQLQRLFVL<br>LQTSKKRAIETTDVTRSFQWDS<br>SEAWQQHVDVQELCRMFDALQ<br>KWKQTEQADLINEL<br>YQGKLDYVRCLECGYEGWRID<br>TYLDIPLVIRPYGSSQAFASVE<br>EALHAFIQPEILDGPNQYFCER<br>CKKKCDARKGLRFLHFPYLLTL<br>QLKRFDYDITTMHRIKLNDRMT<br>FPEELDMSTFIDVEDEKSPQTE<br>SCTDSGAENEGSCHSDQMSNDF<br>SNDDGVDEGICLETNSGTEKIS<br>KSGLEKNSLIYELFSVMVHSGS<br>AAGGHYYACIKSFSDEQWYSFN<br>DQHVSRITQEDIKKTHGGSSGS<br>RGYYSSAFASSTNAYMLIYRLK<br>DPARNAKFLEVDEYPEHIKNLV<br>QKERELEEQEKQR<br>EIERNTCKIKLFCLHPTKQVMM<br>ENKLEVHKDKTLKEAVEMAYKM<br>MDLEEVIPLDCCRLVKYDEFHD<br>YLSYEGEEDTPMGLLLGGVK<br>STYMFDLLLETRKPDQVFQSYK<br>PGEVMVKVHVVDLKAESVAAPI<br>TVRAYLNQTVTEFKQLISKAIH<br>LPAETMRIVLERCYNDLRLLSV<br>SSKTLKAEGFFRSNKVFVESSE<br>TLDYQMAFADSHLWKLDRHAN<br>TIRLFVLLPEQSPVSYSKRTAY<br>QKAGGDSGNVDDDCERVKGPVG<br>SLKSVEAILEESTEKLKSLSLQ<br>QQQDGDNGDSSKST<br>ETSDFENIESPLNERDSSASVD<br>NRELEQHIQTSDPENFQSEERS<br>DSDVNNDRSTSSVSDILSSSH<br>SSDTLCNADNAQIPLANGLDH<br>SITSSRRTKANEGKKETWDTAE<br>EDSGTDSEYDESGKSRGEMQYM<br>YFKAEPYAADEGSGEHKLWLMV<br>HVDKRITLAAFKQHLEPFVGV<br>SSHFKVFRVYASNQEFESVRLN | 154 | ETGYVGLVNQAMTCYLNLSLL<br>QTLFMTPEFRNALYKWEFEE<br>SEEDPVT SIPYQLQRLFVLL<br>QTSKKRAIETTDVTRSFQW<br>SSEAWQQHVDVQELCRMFDAL<br>LEQKWKQTEQADLINELYQG<br>KLKDYVRCLECGYEGWRIDT<br>YLDIPLVIRPYGSSQAFASV<br>EALHAFIQPEILDGPNQYF<br>CERCKKKCDARKGLRFLHFP<br>YLLTLQLKRFDYDITTMHRI<br>KLNDRMTFPEELDMSTFIDV<br>EDEKSPQTESCTDSGAENEG<br>SCHSDQMSNDFSNDDGVDEG<br>ICLETNSGTEKISKSGLEKN<br>SLIYELFSVMVHSGSAAGGH<br>YYACIKSFSDEQWYSFNQD<br>VSRITQEDIKKTHGGSSGS<br>GYSSAFASSTNAYMLIYRL<br>KD |
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|                                                      |    | ETLSSFSDDNKITIRLGRALKK<br>GEYRVKVYQLLVNEQEPCKFLL<br>DAVFAKGMTVRQSKEELIPQLR<br>EQCGLELSIDRFRLRKKTWKNP<br>GTVFLDYHIYEEDI<br>NISSNWEVFLEVLDGVEKMMSM<br>SQLAVLSRRWKPMSEKLDPFQE<br>VVLESSSVDELREKLSEISGIP<br>LDDIEFAKGRGTFPCDISVLDI<br>HQDLWDNPKVSTLNWPLYICD<br>DGAVIFYRDKTEELMELTDEQR<br>NELMKKESRLQKTGHRVTYSP<br>RKEKALKIYLDGAPNKDLTQD                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |     |                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| UBP51_HUMAN Ubiquitin carboxyl-terminal hydrolase 51 | 43 | MAQVRETSLPSGSGVRWISGGG<br>GGASPEEAVEKAGMEAAAAGA<br>TKASSRREAEMKLEPLQEREP<br>APEENLTWSSSGGDEKVLPSIP<br>LRCHSSSPVCPRRKPRPRPQP<br>RARSRSQPGLSAPPPPARPPP<br>PPPPPPPPAPRPRAWRGSRRS<br>RPGSRPQTRRSCGDLGSGDP<br>GGLGDWLLEVEFGQGPTGCSHV<br>ESFKVGKNWQKNLRLIYQRFVW<br>SGTPETRRKRAKSCICHVCSTH<br>MNLHLSCLSCVFFGCFTKHIH<br>KHAETKQHHLAVDLYHGVIYCF<br>MCKDYVYDKDIEQI<br>AKETKEKILRLLTSTSTDVSHQ<br>QFMTSGFEDKQSTCETKEQEPK<br>LVKPKKKRRKKSVMYTVGLRGLI<br>NLGNTCFMNCIVQALTHIPLLK<br>DFFLSDKHKCIMTSPSLCLVCE<br>MSSLFHAMYSGRTPHIPYKLL<br>HLIWIHAEHLAGYRQQDAHEFL<br>IAILDVLRHRSKDDSGGQEANN<br>PNCCNCIIDQIFTGGLQSDVTC<br>QACHSVSTTIDPCWDISLDLPG<br>SCATFDSQNPERADSTVSRDDH<br>IPGIPSLTDCLQWFTRPEHLGS<br>SAKIKCNSCQSYQESTKQLTMK<br>KLPIVACFHLKRFE<br>HVGKQRRKINTFISFPLELDMT<br>PFLASTKESRMKEGQPPTDCVP<br>NENKYSLFAVINHHGTLES<br>GHYTSFIRQQKDQWFSCDDAIITKA<br>TIEDLLYSEGYLLFYHKQGLEK<br>D | 155 | YTVGLRGLINLGNTCFMNCI<br>VQALTHIPLLKDFFLSDKHK<br>CIMTSPSLCLVCEMSSLFHA<br>MYSGSRTPHIPYKLLHLIWI<br>HAEHLAGYRQQDAHEFLIAI<br>LDVLRHRSKDDSGGQEANN<br>NCCNCIIDQIFTGGLQSDVT<br>CQACHSVSTTIDPCWDISLD<br>LPGSCATFDSQNPERADSTV<br>SRDDHIPGIPSLTDCLQWFT<br>RPEHLGSSAKIKCNSCQSYQ<br>ESTKQLTMKKLPIVACFHLK<br>RFEHVGKQRRKINTFISFPL<br>ELDMTPFLASTKESRMKEGQ<br>PPTDCVPNENKYSLFAVINH<br>HGTLES<br>GHYTSFIRQQKDQWFSCDDAIITKA<br>TIEDLLYSEGYLLFYHKQGLEK<br>D |
| UBP36_HUMAN Ubiquitin carboxyl-                      | 44 | MPIVDKLKEALKPGRKDSADDG<br>ELGKLLASSAKKVLLQKIEFEP<br>ASKFSYQLEALKSKYVLLNPK<br>TEGASRHKSGDDPPARRQGSEH                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 156 | RVGAGLHNLGNTCFLNATIQ<br>CLTYTPPLANYLLSKEHARS<br>CHQGSFCMLCVMQNHIVQAF<br>ANSGNAIKPVSFIRDLKKIA                                                                                                                                                                                                                                                                                                                                              |

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| terminal<br>hydrolase 36  |    | <p>             TYESCGDGVFAPQKVLFPTERL<br/>             SLRWERVFRVGAGLHNLGNTCF<br/>             LNATIQCLTYTPPLANYYLLSKE<br/>             HARSCHQGSFCMLCVMQNHIVQ<br/>             AFANSGNAIKPVSFIRDLKKIA<br/>             RHFRFGNQEDAHEFLRYTIDAM<br/>             QKACLNCAKLDLDRQTQATTLVH<br/>             QIFGGYLRSRVKCSVCKSVSDT<br/>             YDPYLDVALEIRQAANIVRALE<br/>             L FVKADVLSGENAY<br/>             MCAKCKKKVPASKRFTIHRTSN<br/>             VLTLSLKR FANFSGGKITKDVG<br/>             YPEFLNIRPYMSQNNGDPVMYG<br/>             LYAVLVHSGYSCHAGHYCYVK<br/>             ASNGQWYQMNDSLVHSSNVKVV<br/>             LNQQAYVLFYLRIPGSKKSPEG<br/>             LISRTGSSSLPGRPSVIPDHSK<br/>             KNIGNGIISSEPLTGKRQDSGTM<br/>             KKPHTTEEIGVPISRNGSTLGL<br/>             KSQNGCIPPKLPSGSPSPKLSQ<br/>             TPTHMPTILDDPGKKVKKPAPP<br/>             QHFSPRTAQGLPGTSNSNSSRS<br/>             GSQRQGSWDSRDVVLSTSPKLL<br/>             ATATANGHGLKGND<br/>             ESAGLDRRGSSSSSPEHSASSD<br/>             STKAPQTPRSGAAHLCDSETN<br/>             CSTAGHSKTPPSGADSKTVKLK<br/>             SPVLSNTTTEPASTMSPPPAKK<br/>             LALSAKKASTLWRATGNDLRPP<br/>             PPSPSSDLTHPMKTSHPVVAST<br/>             WPVHRARAVSPAPQSSSRLQPP<br/>             FSPHPTLLSSTPKPPGTSEPRS<br/>             CSSISTALPQVNEDLVSLPHQL<br/>             PEASEPPQSPSEKRKKT FVGEP<br/>             QRLGSETRL PQHIREATAAPHG<br/>             KKRKRRKKRPEDTAASALQEGQ<br/>             TQRQPGSPMYRREGQAQLPAVR<br/>             RQEDGTQPQVNGQQ<br/>             VGCVTDGHHASSRKRKRKGAEG<br/>             LGEEGGLHQDPLRHSCSPMGDG<br/>             DPEAMEESPRKKKKKKRKQETQ<br/>             RAVEEDGHLKCPRSAKPQDAVV<br/>             PESSSCAPSANGWCPGDRMGLS<br/>             QAPPVSWNGERESDVVQELLKY<br/>             SSDKAYGRKVL TWDGKMSAVSQ<br/>             DAIEDSRQARTETVVDWDEEF<br/>             DRGKEKKIKKFKREKRRNFNAF<br/>             QKLQTRNFWSVTHPAKAASLS<br/>             YRR           </p> |     | <p>             RHFRFGNQEDAHEFLRYTID<br/>             AMQKACLNCAKLDLDRQTQAT<br/>             TLVHQIFGGYLRSRVKCSVC<br/>             KSVSDTYDPYLDVALEIRQA<br/>             ANIVRALEL FVKADVLSGEN<br/>             AYMCAKCKKKVPASKRFTIH<br/>             RTSNVLTLSLKR FANFSGGK<br/>             ITKDVGYPEFLNIRPYMSQN<br/>             NG<br/>             DPVMYGLYAVLVHSGYSCHA<br/>             GHYYCYVKASNGQWYQMND<br/>             LVHSSNVKVV LNQQAYVLFY<br/>             LRIP           </p> |
| UBP44_HUM<br>AN Ubiquitin | 45 | <p>             MLAMDTCKHVGQLQLAQDHSSL<br/>             NPQKWHCVDCNTTESIWACLSC           </p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 157 | <p>             TPGVTGLRNLGNTCYMNSVL<br/>             QVLSHLLIFRQCFLKLDLNQ           </p>                                                                                                                                                                                                                                                                                                                                                                                                    |

|                                                    |    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
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| carboxyl-terminal hydrolase 44                     |    | SHVACGRYIEEHALKHFQESSH<br>PVALEVNEMYVFCYLCDDYVLN<br>DNTTGDLKLLRRTLSTAIKSONY<br>HCTTRSGRFLRSMGTGDDSYFL<br>HDGAQSLQLQSEDQLYTALWHR<br>RILMGKIFRTWFEQSPIGRKKQ<br>EPPFQEKIVVKREVKRRQELE<br>YQVKAELSMPPRKSLRLQGLA<br>QSTIIIEIVSVQVPAQTPASPAK<br>DKVLSTSENEISQKVSDDSVKR<br>RPIVTPGVGTGLRNLGNTCYMNS<br>VLQVLSHLLIFRQC<br>FLKLDLNQWLAMTASEKTRSC<br>KHPVTDTVVYQMNECQEKDTGF<br>VCSRQSSLSSGLSGGASKGRKM<br>ELIQPKEPTSQYISLCHELHTL<br>FQVMWSGKWALVSPFAMLSVW<br>RLIPAFRGYAQQDAQEFCELL<br>DKIQRELETTGTSLPALIPTSQ<br>RKLKQVLNVVNNIFHGQLLSQ<br>VTCLACDNKSNTIEPFWDLSLE<br>FPERYQCSGKDIA SQPCLVTEM<br>LAKFTETEALLEGKIYVCDQCNS<br>KRRRFSSKPVVLTEAQKQLMIC<br>HLPQVLRHLHLKRFRWGRNNRE<br>KIGVHVGFEELNM<br>EPYCCRETLKSLRPECFIYDLS<br>AVVMHHGKGFGSGHYTAYCYN<br>S<br>EGGFVWHCND SKLSMCTMDEV<br>C<br>KAQAYILFYTQRTENGH SKLL<br>PPELLLSQH PNEDADTSSNEI<br>LS |     | WLAMTASEKTRSKHPPVTD<br>TVVYQMNECQEKDTGFVCSR<br>QSSLSSGLSGGASKGRKMEL<br>IQPKEPTSQYISLCHELHTL<br>FQVMWSGKWALVSPFAMLS<br>VWRLIPAFRGYAQQDAQEF<br>CELLDKIQRELETTGTSLPA<br>LIPTSQRKLIKQVLNVVNNI<br>FHGQLLSQVTCLACDNKSNT<br>IEPFWDLSLEFPERYQCSGK<br>DIASQPCLVTEMLAKFTETE<br>ALEGKIYVCDQCNSKRRRFS<br>SKPVVLTEAQKQLMICHL<br>PQ<br>VLRHLHLKRFRWGRNNREKI<br>GVHVGFEELNMPEYCCRET<br>LKSLRPECFIYDLSAVVMHH<br>GKGFGSGHYTAYCYNSEGGF<br>WVHCND SKLSMCTMDEVCKA<br>QAYILFYTQRV |
| UBP8_HUMAN Ubiquitin carboxyl-terminal hydrolase 8 | 46 | MPAVASVPKELYLSSSLKDLNK<br>KTEVKPEKISTKSYVHSALKIF<br>KTAEECRLDRDEERAYVLYMKY<br>VTVYNLIKRPDFKQQQDYFHS<br>ILGPGNIKKAVEEAERLSESLK<br>LRYEEAEVRKKLEEKDRQEEAQ<br>RLQQKRQETGREDGGTLAKGSL<br>ENVLDSKDKTQKSNGEKNEKCE<br>TKEKGAITAKELYTMMTDKNIS<br>LIIMDARRMQDYQDSCILHSLS<br>VPEEAI SPGV TASWIEAHL PDD<br>SKDTWKKRGNVEYVLLDWFSS<br>AKDLQIGTTLRSLKDALFKWES<br>KTVLRNEPLVLEGG<br>YENWLLCYPQYTTNAKVTPPPR<br>RQNEEVSI SLDF TYPSLEESIP<br>SKPAAQTTPASIEVDENIELIS<br>GQNERMGPLNISTPVEPVAA<br>SK<br>SDVSPIIQPVPSIKNVPQIDRT                                                                                                                                                                                                                                                                                                                       | 158 | PALTGLRNLGNTCYMNSILQ<br>CLCNAPHLADYFNRNCYQDD<br>INRSNLLGHKGEVAEEFGII<br>MKALWTGQYRYISPKDFKIT<br>IGKINDQFAGYSQQDSQELL<br>LFLMDGLHEDLNKADNRKRY<br>KEENNDHLDDFKAAEHAWQK<br>HKQLNESII VALFQGFKST<br>VQCLTCHKKSRTFEAFMYLS<br>LPLASTSKCTLQDCLRLFSK<br>EEKLTDNNRFYC SHCRARRD<br>SLKKIEIWKLPPVLLVHLKR<br>FSYDGRWKQKLQTSVDFPLE<br>NLDLSQYVIGPKNNLKKNYL<br>FSVSNHYGGLDGGHYTAYCK<br>NAARQRWFKFDDHEVSDISV<br>SSVKSSAAYILFYTSLG                                           |

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|                                                      |    | KKPAVKLP EEHRIKSESTNHEQ<br>QSPQSGKVIPDRSTKPVVFSPT<br>LMLTDEEKARIHAETALLMEKN<br>KQEKELRERQQEEQKEKLRKEE<br>QEQKAKKKQEAENEITEKQQK<br>AKEEMEKKESEQAKKEDKETS<br>KRGKEITGVKRQSKSEHETS<br>KKSVEDRGKRCPTPEIQKKSTG<br>DVPHTSVTGDSGSG<br>KPFKIKGQPESGILRTGTFRED<br>TDDTERNKAQREPLTRARSEEM<br>GRIVPGLPSGWAKFLDPITGTF<br>RYYHSPTNTVHMYPPEMAPSSA<br>PPSTPPTHKAKPQIPAERDREP<br>SKLKRSYSSPDITQAIQEEEEKR<br>KPTVTPTVNRENKPTCYPKAEI<br>SRLSASQIRNLNPVFGGSGPAL<br>TGLRNLGNTCYMNSILQCLCNA<br>PHLADYFNRNCYQDDINRSNLL<br>GHKGEVAEEFGIIMKALWTGQY<br>RYISPKDFKITIGKINDQFAGY<br>SQQDSQELLLFLMDGLHEDLNK<br>ADNRKRYKEENNDH<br>LDDFKAAEHAWQKHQNLNESII<br>VALFQGQFKSTVQCLTCHKKSR<br>TFEAFMYLSLPLASTSKCTLQD<br>CLRLFSKEEKLTNNRFYCSHC<br>RARRDSLKKIEIWKLPPVLLVH<br>LKRFSDGRWKQKLQTSVDFPL<br>ENLDLSQYVIGPKNNLKKNLNF<br>SVSNHYGGLDGGHYTAYCKNAA<br>RQRWFKFDDHEVSDISVSSVKS<br>SAAYILFYTSLGPRVTDVAT |     |                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| UBP37_HUMAN Ubiquitin carboxyl-terminal hydrolase 37 | 47 | MSPLKIHGPIRIRSMQTGITKW<br>KEGSFEIVEKENKVS LVVHYNT<br>GGIPRIFQLSHNIKNVLRPSG<br>AKQSRLMLTLQDNSFLSIDKVP<br>SKDAEEMRLFLDAVHQNRLPAA<br>MKPSQSGSGSFGAILGSRTSQKE<br>TSRQLSYSDNQASAKRGSLETK<br>DDIPFRKVLGNPGRGSIKTAVAG<br>SGIARTIPSLTSTSTPLRSGLL<br>ENRTEKRKRMI STGSELNEDYP<br>KENDSSSNKAMTDPSRKYLT<br>SREKQLSLKQSEENRTSGLLPL<br>QSSSFYGSRAGSKEHSSGGTNL<br>DRTNVSSQTPSAKR<br>SLGFLPQPVPPLSVKKLR CNQDY<br>TGWNKPRVPLSSHQQQLQGFS<br>NLGNTCYMNAI LQSLFSLQSFA<br>NDLLKQGIPWKKIPLNALIRRF                                                                                                                                                                                                                                                                                                                                                                                      | 159 | QQQLQGFSNLGNTCYMNAI LQ<br>SLFSLQS FANDLLKQGIPWK<br>KIPLNALIRRF A HLLVKKDI<br>CNSETKKDLLKKVKNAI SAT<br>AERFSGYMQNDAHEFLSQCL<br>DQLKEDMEKLNKTWKTEPVS<br>GEENSPDISATRAYTCPVIT<br>NLEFEVQHSIICKACGEIIP<br>KREQFNDLSIDLPRRKKPLP<br>PRSIQDSLDFFR AE ELEYS<br>CEKCGGKCALVRHKFNRLPR<br>VLILHLKRYSFNVALSLNNK<br>IGQQVIIIPRYLTLSHCTEN<br>TKP<br>PFTLGWSAHMAISRPLKASQ<br>MVNSCITSPSTPSKKFTFKS<br>KSSLALCLDSDSEDELKRSV<br>ALSQRLCEMLGNEQQQEDLE |

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|                                                                      |    | AHLLVKKDICNSETKKDLLKKV<br>KNAISATAERFSGYMQNDAHEF<br>LSQCLDQLKEDMEKLNKTWKTE<br>PVSGEENSPDISATRAYTCPVI<br>TNLEFEVQHSIICKACGEIIPK<br>REQFNDLSIDLPRRKKPLPPRS<br>IQDSLDFFRAELEEYSCEKCG<br>GKCALVRHKFNRLPRVLILHLK<br>RYSFNVALSLNNKIGQQVVIIPR<br>YLTLSSHCTENTKP<br>PFTLGWSAHMAISRPLKASQMV<br>NSCITSPSTPSKKFTFKSKSSL<br>ALCLDSDSEDELKRSVALSQR<br>CEMLGNEQQQEDLEKSKLCPI<br>EPDKSELENSGFDRMSEEEELLA<br>AVLEISKRDASPSLSHEDDDKP<br>TSSPDTGFAEDDIQEMPENPDT<br>METEKPKTITELDPASFTEITK<br>DCDENKENKTPEGSQGEVDWLQ<br>QYDMEREREEQELQQALASLQ<br>EQEAWEQKEDDDLKRATELSLQ<br>EFNNSFVDALGSEDESGNEDVF<br>DMEYTEAEAEELKRNAETGNLP<br>HSYRLISVVSHIGS<br>TSSSGHYISDVYDIKKQAWFTY<br>NDLEVSKIQEAAVQSDRDRSGY<br>IFFYMHKEIFDELLETEKNSQS<br>LSTEVGKTTRQAL |     | KDSKLCPIEPDKSELENSGF<br>DRMSEEEELLA AVLEISKRDA<br>SPSLSHEDDDKPTSSPDTGF<br>AEDDIQEMPENPDTMETEKP<br>KTITELDPASFTEITKDCDE<br>NKENKTPEGSQGEVDWLQQY<br>DMEREREEQELQQALASLQ<br>EQEAWEQKEDDDLKRATELS<br>LQEFNNSFVDALGSEDESGN<br>EDVFDMEYTEAEAEELKRNA<br>ETGNLPHSYRLISVVSHIGS<br>TSSSGHYISDVYDIKKQAWF<br>TYNDLEVSKIQEAAVQSDRD<br>RSGYIFFYMHK                                 |
| U17LD_HUMAN Ubiquitin carboxyl-terminal hydrolase 17-like protein 13 | 48 | MEEDSLYLGGEWQFNHFSKLT<br>SRLDAFAEIQRTSLPEKSPLS<br>CETRVLDLDDLVPEARQLAPRE<br>KLPLSSRRPAAVGAGLQNMGNT<br>CYVNASLQCLTYTPPLANMYS<br>REHSQTCHRHKGCMCTMQAHI<br>TRALHNPGHVIQPSQALAAGFH<br>RGKQEDAHEFLMFTVDAMKKAC<br>LPHGKQVDHPSKDTTLIHQIFG<br>GYWRSQIKCLHCHGISDTFDPY<br>LDIALDIQAAQSVQQAELQV<br>PEELNGENAYHCGVCLQAPAS<br>KTLTLHTSAKVLILVLKRFS<br>TGNKIAKNVQYPEC<br>LDMQPYMSQQNTGPLVYVLYAV<br>LVHAGWSCHNGHYFSYVKAQEG<br>QWYKMDDAEVTAASITSVLSQ<br>AYVLFYIQKSEWERHSESVSRG<br>REPRALGAEDTDRRATQGELKR<br>DHPCLQAPELDEHLVERATQES<br>TLDRWKFLQEQNKTKPEFNVRK<br>VEGTLPPDVLVIHQSKYKCGMK<br>NHHPEQQSSLLNLSSSTPTHQE                                                                                                                          | 160 | AVGAGLQNMGNTCYVNASLQ<br>CLTYTPPLANMYSREHSQT<br>CHRHKGCMCTMQAHITRAL<br>HNPGHVIQPSQALAAGFHRG<br>KQEDAHEFLMFTVDAMKKAC<br>LPHGKQVDHPSKDTTLIHQI<br>FGGYWRSQIKCLHCHGISDT<br>FDPYLDIALDIQAAQSVQQA<br>LEQLVKPEELNGENAYHCGV<br>CLQRAPASKTLTLHTSAKVL<br>ILVLKRFSVDVTGNKIAKNVQ<br>YPECLDMQPYMSQQNTGPLV<br>YVLYAVLVHAGWSCHNGHYF<br>SYVKAQEGQWYKMDDAEVTA<br>ASITSVLSQQAAYVLFYIQKS |

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|                                                                                       |    | SMNTGTLASLRGRARRSKGKNK<br>HSKRALLVCQ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| U17L3_HUM<br>AN Ubiquitin<br>carboxyl-<br>terminal<br>hydrolase 17-<br>like protein 3 | 49 | MGDDSLYLGGGEWQFNHFSKLT<br>SRPDAAFAEIQRSTSLPEKSPLS<br>SETRVDLCDDLAPVARQLAPRE<br>KLPLSSRRPAAVGAGLQNMGNT<br>CYENASLQCLTYTLPLANYMLS<br>REHSQTCQRPKCCMLCTMQAHI<br>TVALHSPGHVIQPSQALASGFH<br>RGKQEDVHEFLMFTVDAMKKAC<br>LPGHKQVDHHSKDTTLIHQIFG<br>GCWRSQIKCLHCHGISDTFDPY<br>LDIALDIQAAQSVKQALEQLVK<br>PEELNGENAYHCGLCLQRAPAS<br>NTLTHTSAKVLILVLKRFSDV<br>AGNKLAKNVQYPEC<br>LDMQPYMSQQNTGPLVYVLYAV<br>LVHAGWSCHDGHYFSYVKAQEG<br>QWYKMDDAEVTVCSITSVLSQQ<br>AYVLFYIQKSEWERHSESVSRG<br>REPRALGAEDTDRRAKQGELKR<br>DHPCLQAPELDEHLVERATQES<br>TLDHWKFLQEQNKTKPEFNVGK<br>VEGTLPPNALVIHQSKYKCGMK<br>NHHPEQQSSLLNLSSTTRTDQE<br>SMNTGTLASLQGRTRRAKGNK<br>HSKRALLVCQ | 161 | AVGAGLQNMGNTCYENASLQ<br>CLTYTLPLANYMLSREHSQT<br>CQRPKCCMLCTMQAHITWAL<br>HSPGHVIQPSQALASGFHRG<br>KQEDVHEFLMFTVDAMKKAC<br>LPGHKQVDHHSKDTTLIHQI<br>FGGCWRSQIKCLHCHGISDT<br>FDPYLDIALDIQAAQSVKQA<br>LEQLVKPEELNGENAYHCGL<br>CLQRAPASNTLTHTSAKVL<br>ILVLKRFSDVAGNKLAKNVQ<br>YPECLDMQPYMSQQNTGPLV<br>YVLYAVLVHAGWSCHDGHYF<br>SYVKAQEGQWYKMDDAEVTV<br>CSITSVLSQQAYVLFYIQKS                                                                                                                              |
| UBP54_HUM<br>AN Inactive<br>ubiquitin<br>carboxyl-<br>terminal<br>hydrolase 54        | 50 | MSWKRNYFSGGRGSVQGMFAPR<br>SSTSIAPSKGLSNEPGQNSCFL<br>NSALQVLWHLDFRRSFRQLTTH<br>HKCMGDSCIFCALKGIFNQFQC<br>SSEKVLPSDTLRSALAKTFQDE<br>QRFQLGIMDDAAECFENLMRI<br>HFHIADETKEDICTAQHCISHQ<br>KFAMTLFEQCVCCTSCGATSDPL<br>PFIQMVHYISTTSLCNQAICML<br>ERREKPSPSMFGELLQNASTMG<br>DLRNCPSNCGERIRIRRVLMNA<br>PQIITIGLVWDSHSDLAEDVI<br>HSLGTCLKLGDFFRVTDDRAK<br>QSELYLVGMICYYG<br>KHYSTFFFQTKIRKWMYFDDAH<br>VKEIGPKWKDVVTCKIKGHYQP<br>LLLLYADPQGTPVSTQDLPPQA<br>EFQSYSRTCYSDEDSGREPSIS<br>SDTRTDSSTESYPYKSHHESV<br>VSHFSSDSQGTVIYINVENDSMS<br>QSSRDTGHLTDSECNQKHTSKK<br>GSLIERKRSSGRVRRKGDEPQA<br>SGYHSEGETLKEKQAPRNASKP<br>SSSTNRLRDFKETVSNMIHNRP                | 162 | APSKGLSNEPGQNSCFLNSA<br>LQVLWHLDFRRSFRQLTTH<br>KCMGDSCIFCALKGIFNQFQ<br>CSSEKVLPSDTLRSALAKTF<br>QDEQRFQLGIMDDAAECFEN<br>LLMRIHFHIADETKEDICTA<br>QHCISHQKFAMTLFEQCVCCT<br>SCGATSDPLPFIQ<br>MVHYISTTSLCNQAICMLER<br>REKPSPSMFGELLQNASTMG<br>DLRNCPSNCGERIRIRRVLM<br>NAPQIITIGLVWDSHSDLA<br>EDVIHSLGTCLKLGDFFRV<br>TDDRAKQSELYLVGMICYYG<br>KHYSTFFFQTKIRKWMYFDD<br>AHVKEIGPKWKDVVTCKIKG<br>HYQPLLLLLYADPQGTPVSTQ<br>DLPPQAEFQSYSRTCYSDE<br>SGREPSISSDTRTDSSTESY<br>PYKSHHESVVSHFSSDSQG<br>TVIYINVEND |



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|  |  | SLASQTNVGS HCRGRGGDQ PDK<br>KPPRTLPLHSRDWEIESTSSES<br>KSSSSSKYRPTWRPKRESLNID<br>SIFSKDKRKHCYT<br>QLSPFSEDSAKEFIPDEPSKPP<br>SYDIKFGGSPSQYKRWGPARG<br>SHLLEQHPRLIQRMESGYESSE<br>RNSSSPVSLDAALPESNVYRD<br>PSAKRSAGLVPSWRHIPKSHSS<br>SILEVDSTASMGGWTKSQPFSG<br>EEISSKSELDELQEEVARRAQE<br>QELRRKREKELEAAKGFNPHPS<br>RFMDLDELQNGRSDGFERSLQ<br>EAESVFEE SLHLEQKGDCAAAL<br>ALCNEAISKRLALHGASCSTH<br>SRALVDKKLQISIRKARSLQDR<br>MQQQQSPQQPSQPSACLPTQAG<br>TLSQPTSEQPIPLQ<br>VLLSQEAQLESGMDTEFGASSF<br>FHSPASCHESHSSLSPESSAPQ<br>HSSPSRSALKLLTSVEVDNIEP<br>SAFHRQGLPKAPGWTEKNSHHS<br>WEPLDAPEGKLQGSRC DNSSCS<br>KLPPQEGRGIAQEQLFQEKKDP<br>ANPSPVMPIATSERGDEHSLG<br>CSPSNSSAQPSLPLYRTCHPIM<br>PVASSFVLHCPDPVQKTNQCLQ<br>GQSLKTS LTLKVDRGSEETYRP<br>EFPSTKGLVRSLAEQFQRMQGV<br>SMRDSTGFKDRSLSGSLRKNSS<br>PSDSKPPFSQGQEKGHWPWAKQ<br>QSSLEGGDRPLSWE<br>ESTEHSSLALNSGLPNGETSSG<br>GQPRLAEPDIYQEKLSQVRDVR<br>SKDLGSSTD LGTSLPLDSWVNI<br>TRFCDSQLKHGAPRPGMKSSPH<br>DSHTCVTYPERNHILLHPHWNQ<br>DTEQETSELESLYQASLQASQA<br>GCSGWGQQDTAWHPLSQTGSAD<br>GMGRRLHSAHDPGLSKTSTAEM<br>EHGLHEARTVRTSQATPCRGLS<br>RECGEDEQYSAENLRRISRSL<br>GTVVSEREEAPVSSHSDSSNV<br>RKPLETGHRCS SSSSLPVIHDP<br>SVFLLGPQLYLPQPQFLSPDVL<br>MPTMAGEPNRLPGT<br>SRSVQQFLAMCDRGETSQGAKY<br>TGRTLNYQSLPHRSRTDNSWAP<br>WSETNQHIGTRFLTTPGCNPQL<br>TYTATLPERSKGLQVPHTQSW<br>DLFHSPSHPPIVHPVYPPSSSL |  |
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|                                                                    |    | HVPLRSAWNSDPVPGSRTPGPR<br>RVDMPDDDDWRQSSYASHSGHR<br>RTVGEGFLFVLSDAPRREQIRA<br>RVLQHSQW                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| SNUT2_HUM<br>AN U4/U6.U5<br>tri-snRNP-<br>associated<br>protein 2  | 51 | MSGRSKRESRGSTRGKRESESR<br>GSSGRVKRERDREREPEAASSR<br>GSPVRVKREFEPASAREAPASV<br>VPFVRVKREREVDDEDSEPEREV<br>RAKNGRVDSEDRRSRHCPYLDT<br>INRSVLDFDFEKLCSISLSHIN<br>AYACLVCGKYFQGRGLKSHAYI<br>HSVQFSSHVFLNLHTLKFYCLP<br>DNYEIIDSSLEDITYVLKPTFT<br>KQQIANLDKQAKLSRAYDGTTY<br>LPGIVGLNNIKANDYANAVLQA<br>LSNPVPLRNYFLEEDNYKNIKR<br>PPGDIMFLLVQRFGELMRKLWN<br>PRNFKAHVSPHEML<br>QAVVLC SKKTFQITKQGDGVDF<br>LSWFLNALHSALGGTKKKKKTI<br>VTDVFQGSMRIFTKKLPHPDLP<br>AEEKEQLLHNDEYQETMVESTF<br>MYLTLDLPTAPLYKDEKEQLII<br>PQVPLFNILAKFNGITEKEYKT<br>YKENFLKRFQLTCLPPYLIFCI<br>KRFTKNNFFVEKNPTIVNFPIT<br>NVDLREYLSEEVQAVHKNTTYD<br>LIANIVHDGKPSSEGSYRIHVLH<br>HGTGKWYELQDLQVTDILPQMI<br>TLSEAYIQIWKRRDNDETNQQA | 163 | LPGIVGLNNIKANDYANAVL<br>QALSNVPLRNYFLEEDNYK<br>NIKRPPGDIMFLLVQRFGEL<br>MRKLWNPRNFKAHVSPHEML<br>QAVVLC SKKTFQITKQGDGV<br>DFLSWFLNALHSALGGTKKK<br>KKTIVTDVFQGSMRIFTKKL<br>PHPDLPAEEKEQLLHNDEYQ<br>ETMVESTFMYLTLDLPTAPL<br>YKDEKEQLIIPQVPLFNILA<br>KFNGITEKEYKTYKENFLKR<br>FQLTCLPPYLIFCIKRFTKN<br>NFFVEKNPTIVNFPITNVDL<br>REYLSEEVQAVHKNTTYDLI<br>ANIVHDGKPSSEGSYRIHVLH<br>HGTGKWYELQDLQVTDILPQ<br>MITLSEAYIQIWKRRD                                                       |
| UBP35_HUM<br>AN Ubiquitin<br>carboxyl-<br>terminal<br>hydrolase 35 | 52 | MDKILEAVVTSSYPVSVKQGLV<br>RRVLEAARQPLEREQCLALLAL<br>GARLYVGGAEELPRRVGCQLLH<br>VAGRHHPDVFAEFFSARRVLRL<br>LQGGAGPPGPRALACVQLGLQL<br>LPEGPAADEVFALLRREVLRTV<br>CERPGPAACAQVARLLARHPRC<br>VPDGPRLLLFCQQLVRCLGRFR<br>CPAEGEEGAVEFLEQAQQVSGL<br>LAQLWRAQPAAILPCLKELFAV<br>ISCAEEEPSSALASVVQHLPL<br>ELMDGVVRNLSNDDSVTDSQML<br>TAISRMIDWVSWPLGKNIDKWI<br>IALLKGLAAVKKFS<br>ILIEVSLTKIEKVFSKLLYPIV<br>RGAALSVLKYMMLTFQHSHEAF<br>HLLPHIPPMVASLVKEDSNSG<br>TSCLEQLAELVHCMVFRFPGFP<br>DLYEPVMEAIKDLHVPNEDRIK<br>QLLGQDAWTSQKSELAGFYPR                                                                                                                                                                   | 164 | SDTGKIGLINLGNTCYVNSI<br>LQALFMASDFRHCVLRLTEN<br>NSQPLMTKLQWLFGFLEHSQ<br>RPAISPENFLSASWTPWFSP<br>GTQQDCSEYLKYLLDRLHEE<br>EKTGTRICQKLKQSSSPSP<br>EPPAPSSTSVEKMFGGKIV<br>TRICCLCLNVSSREEAFTD<br>LSLAFPPPERCRRRLGSVM<br>RPTEDITARELPPPTSAQGP<br>GRVGPRRQRKHCITEDTPPT<br>SLYIEGLDSKEAGQSSQEE<br>RIEREEEGKEERTEKEEVGE<br>EEESTRGEGEREKEEEVEEE<br>EEKVE<br>KETEKEAEQEKEEDSLGAGT<br>HPDAAIPSGERTCGSEGSRS<br>VLDLVNYFLSPEKLTAENRY<br>YCASCASLQDAEKVVLSQG<br>PCYLILTLRLRFSFDLRTMR |

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|                                                      |    | <p>MAKSDTGKIGLINLGNTCYVNS<br/>ILQALFMASDFRHCVLRLTENN<br/>SQPLMTKLQWLFGFLEHSQRPA<br/>ISPENFLSASWTPWFSPGTQQD<br/>CSEYLKYLDDRLHEEEKTGTRI<br/>CQKLKQSSSPSPPEPPAPSST<br/>SVEKMFGGKIVTRICCLCLNV<br/>SSREEAFTDLSLAF<br/>PPPERCRRRLGSMRPTEDIT<br/>ARELPPPTSAQGPGRVGPRRQR<br/>KHCITEDTPPTSLYIEGLDSKE<br/>AGGQSSQEERIEREEEGKEERT<br/>EKEEVGEEEESTRGEGEREKEE<br/>EVEEEEEKVEKETEKEAEQEKE<br/>EDSLGAGTHPDAAIPSGERTCG<br/>SEGSRSVLDLVNYFLSPEKLTA<br/>ENRYYCESCASLQDAEKVVELS<br/>QGPCYLILTLLRFSFDLRTMRR<br/>RKILDDVSIPLLLRLPLAGGRG<br/>QAYDLCVVVHSGVSSSESGHYY<br/>CYAREGAARPAASLGTADRPEP<br/>ENQWYLFNDTRVSF<br/>SSFESVSNVTSFFPKDTAYVLF<br/>YRQRPREGPEAELGSSRVRTPE<br/>TLHKDLMEAISKNILYLQEQE<br/>KEARSRAAYISALPTSPHWGRG<br/>FDEKDEDEGSPGGCNPAGGNG<br/>GDFHRLVF</p> |     | <p>RKILDDVSIPLLLRLPLAGG<br/>RGQAYDLCVVVHSGVSSSES<br/>GHYYCYAREGAARPAASLGT<br/>ADRPEPENQWYLFNDTRVSF<br/>SSFESVSNVTSFFPKDTAYV<br/>LFYRQRP</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| UBP15_HUMAN Ubiquitin carboxyl-terminal hydrolase 15 | 53 | <p>MAEGGAADLDTQRSDIATLLKT<br/>SLRKGDWYLVDSRWFKQWKY<br/>VGFDWDKYQMGDQNVYPGPID<br/>NSGLLDGDAQSLKEHLIDELD<br/>YILLPTEGWKNLWSYTLMEGQ<br/>EPIARKVVEQGMFVKHCKVEVY<br/>LTELKLCENGNMNNVTRRFSK<br/>ADTIDTIEKEIRKIFSIPEKE<br/>TRLWNKYMSNTFEPLNKPDESTI<br/>QDAGLYQGQVLVIEQKNEDGTW<br/>PRGPSTPKSPGASNFTLPKIS<br/>PSSLSNNYNNMNNRVKNSNYC<br/>LPSYTAYKNYDYSEPGRNNEQP<br/>GLCGLSNLGNTCFM<br/>NSAIQCLSNTPPLTEYFLNDKY<br/>QEELNFDNPLGMRGEIAKSYAE<br/>LIKQMWSGKFSYVTPRAFKTQV<br/>GRFAPQFSGYQQQDCQELLAFL<br/>LDGLHEDLNRIRKKPYIQLKDA<br/>DGRPDKVVAEEAWENHLKRND<br/>SIIVDIFHGLFKSTLVCPECAKI<br/>SVTFDPFCYLTPLPMKKERTL<br/>EVYLVMDPLTKPMQYKVVPK</p>                                                                                                                       | 165 | <p>EQPGLCGLSNLGNTCFMNSA<br/>IQCLSNTPPLTEYFLNDKYQ<br/>EELNFDNPLGMRGEIAKSYA<br/>ELIKQMWSGKFSYVTPRAFK<br/>TQVGRFAPQFSGYQQQDCQE<br/>LLAFLLDGLHEDLNRIRKKP<br/>YIQLKADAGRDPKVVAEEAW<br/>ENHLKRNDSIIVDIFHGLFK<br/>STLVCPECAKISVTFDPFCY<br/>LTLPLPMKKERTLEVYLVRM<br/>DPLTKPMQYKVVPKIGNIL<br/>DLCTALSALSGIPADKMIVT<br/>DIYNHRFHRIFAMDENLSSI<br/>MERDDIYVFEININRTEDTE<br/>HVIIPVCLREKFRHSSYTHH<br/>TGSSLFGQPFMAVPRNNTTE<br/>DKLYNLLLLRMCRYVKISTE<br/>TEETEGSLHCKDQNINGNG<br/>PNGIHEEGSPSEMETDEPDD<br/>ESSQDQELPSENENSQSEDS<br/>VGGDNDSENGLCTEDTCKGQ<br/>LTGHKKRLFTFQFNNLGNTD<br/>INYIKDDTRHIRFDDRQLRL</p> |

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|                                                                    |    | <p>IGNILDLCTALSALSGIPADKM<br/>IVTDIYNHRFHRIFAMDENLSS<br/>IMERDDIYVFEININRTEDTEH<br/>VIIPVCLREKFRHSSYTHHTGS<br/>SLFGQPFLMAVPRN<br/>NTEDKLYNLLLLRMCRYVKIST<br/>ETEETEGSLHCCCKDQNINGNGP<br/>NGIHEEGSPSEMETDEPDDESS<br/>QDQELPSENENSQSEDSVGGDN<br/>DSENGLCTEDTCKGQLTGHKRR<br/>LFTFQFNNLGNTDINYIKDDTR<br/>HIRFDDRQLRLDERSFLALDWD<br/>PDLKKRYFDENAAEDFEKHESV<br/>EYKPPKKPFVVKLKDCIELFTTK<br/>EKLGAEDPWYCPNCKEHQQATK<br/>KLDLWSLPPVLVVHLKRFSYSR<br/>YMRDKLDTLVDFPINDLDMSEF<br/>LINPNAGPCRYNLIASVSNHYGG<br/>MGGGHYTAFANKD<br/>DGKWYYFDDSSVSTASEDQIVS<br/>KAAYVLFYQRQDTFSGTGFFPL<br/>DRETKGASAATGIPLESDEDSN<br/>DNDNDIENENCMHTN</p>                                                                                                                                               |     | <p>DERSFLALDWD PDLKKRYFD<br/>ENAAEDFEKHESVEYKPPKK<br/>PFVVKLKDCIELFTTKEKLG<br/>EDPWYCPNCKEHQQATKKLD<br/>LWSLPPVLVVHLKRFSYSR<br/>MRDKLDTLVDFPINDLDMSE<br/>FLINPNAGPCRYNLIASVSNH<br/>YGGMGGGHYTAFANKDDGK<br/>WYYFDDSSVSTASEDQIVSK<br/>AAYVLFYQRQD</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| UBP29_HUM<br>AN Ubiquitin<br>carboxyl-<br>terminal<br>hydrolase 29 | 54 | <p>MISLKVCGFIQIWSQKTGMTKL<br/>KEALIE TVQRQKEIKLVVTFKS<br/>GKFIRIFQLSNNIRSVVLRHCK<br/>KRQSHLRLTLKNNVFLFIDKLS<br/>YRDAKQLNMFLDIHQNKSQQP<br/>MKSDDDWSVFESRNLKEIDKT<br/>SFYSICNKPSYQKMPLFMSKSP<br/>THVKKGILENQGGKGQNTLSSD<br/>VQTNEDILKEDNPVPNKKYKTD<br/>SLKYIQSNRKNPSSLEDLEKDR<br/>DLKLGPSFNTNCNGNPNDLTV<br/>LATQTLNAKNGLTSPLEPEHSQ<br/>GDPRCNKAQVPLDSHSQQQLQG<br/>FPNLGNTCYMNAVL<br/>QSLFAIPSFADDLLTQGV PWEY<br/>IPFEALIMTLTQLLALKDFCST<br/>KIKRELLGNVKKVISAVAEIFS<br/>GNMQNDAHEFLGQCLDQLKEDM<br/>EKLNATLNTGKECGDENSSPQM<br/>HVGSAATKVVFVCPVVANFEFEL<br/>QLSLICKACGHAVLKVEPNNYL<br/>SINLHQETKPLPLSIQNSLDLF<br/>FKEEELEYNCQMCKQKSCVARH<br/>TFSRLSRVLI IHLKRYSFNNAW<br/>LLVKNNEQVYIPKSLSLSSYCN<br/>ESTKPPLPLSSSAPVGKCEVLE<br/>VSQEMISEINSPLTPSMKLTSE<br/>SSDSLVLVPVEPDKN</p> | 166 | <p>QLQQGFPNLGNTCYMNAVLQ<br/>SLFAIPSFADDLLTQGV PWE<br/>YIPFEALIMTLTQLLALKDF<br/>CSTKIKRELLGNVKKVISAV<br/>AEIFS GNMQNDAHEFLGQCL<br/>DQLKEDMEKLNATLNTGKEC<br/>GDENSSPQMHVGSAAATKV FV<br/>CPVVANFEFELQSLICKAC<br/>GHAVLKVEPNNYLSINLHQE<br/>TKPLPLSIQNSLDLF FKEEE<br/>LEYNCQMCKQKSCVARHTFS<br/>RLSRVLI IHLKRYSFNNAWL<br/>LVKNNEQVYIPKSLSLSSYC<br/>NESTKPPLPLSSSAPVGKCE<br/>VLEVSQEMISEINSPLTPSM<br/>KLTSESSDSLVLVPVEPDKNA<br/>DLQRFQRDCGDASQEQHQ RD<br/>LENGSALESELVHFRDRAIG<br/>EKELPVADSLMDQGDISLPV<br/>MYEDGGKLISSPDTRLVEVH<br/>LQEV PQHPQLQKYEKTNTFV<br/>EFNFDSVTESTNGFYDCKEN<br/>RIPEGSQGM AEQLQQCIEES<br/>IIDEFLQQA PPPGVRKLDAQ<br/>EHTEETLNQSTELRLQKADL<br/>NHLGALGSDNP GNKNILDAE<br/>NTRGEAKELTRNVKMGDPLQ<br/>AYRLISVVSHIGSSPNSGHY</p> |

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|                                                              |    | ADLQRFQRDCGDASQEQHQRDLENGSALESELVHFRDRAIGEKE<br>LPVADSLMDQGDISLPVMYEDG<br>GKLISSPDTRLVEVHLQEVPOH<br>PELQKYEKTNTFVEFNFDSTVE<br>STNGFYDCENRIPEGSQGMAE<br>QLQQCIEESIIDEFLQQAPPPG<br>VRKLDAQEHTEETLNQSTELRL<br>QKADLNHLGALGSDNPGNKNIL<br>DAENTRGEAKELTRNVKMGDPL<br>QAYRLISVVSHIGSSPNSGHYI<br>SDVYDFQKQAWFTYNDLCVSEI<br>SETKMQEARLHSGYIFFYMHNG<br>IFEELLRKAENSRLPSTQAGVI<br>PQGEYEGDSLVRPA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |     | ISDVYDFQKQAWFTYNDLCV<br>SEISETKMQEARLHSGYIFF<br>YMHN                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| UBP6_HUMAN Ubiquitin<br>carboxyl-<br>terminal<br>hydrolase 6 | 55 | MDMVENADSLQAQERKDILMKY<br>DKGHRAGLPEDKGPEPVGINSS<br>IDRFILHETELPPVTAREAKK<br>IRREMTRTSKWMEMLGEWETK<br>HSSKLIDRVYKGIPMNIRGPVW<br>SVLLNIQEIKLKNPGRYQIMKE<br>RGKRSEHIIHIDLVRTTLRN<br>HVFFRDRYGAKQRELFYILLAY<br>SEYNPEVGYCRDLSHITALFLL<br>YLPEEDAFWALVQLLASERHSL<br>PGFHSPNGGTVQGLQDQQEHV<br>PKSQPKTMWHQDKEGLCGQCAS<br>LGCLLRNLIDGISLGLTLRLWD<br>VYLVEGEQVLMPIIT<br>SIALKVQQKRLMKTSRCGLWAR<br>LRNQFFDTWAMNDDTVLKLHRA<br>STKKLTRKQGDLPAPAKREQGS<br>LAPRPVPASRGKTLCKGYRQA<br>PPGPPAQFQRPICASPPWASR<br>FSTPCPGGAVREDTYPVGTQGV<br>PSLALAQQGPQGSWRFLWKSM<br>PRLPTDLDIGGPWFPHYDFEWS<br>CWVRAISQEDQLATCWQAEHCG<br>EVHNKDMSWPEEMSFTANSSKI<br>DRQKVPTEKGATGLSNLGNTCF<br>MNSSIQCVSNTQPLTQYFISGR<br>HLYELNRTNPIGMKGHMAKCYG<br>DLVQELWSGTQKSV<br>APLKLRRRTIAKYAPKFDGFQQQ<br>DSQELLAFLLDGLHEDLNRVHE<br>KPYVELKDS DGRPDWEVAAEAW<br>DNHLRRNRSIIVDLFHGQLRSQ<br>VKCKTCGHISVRFPFNFLSLP<br>LPMSYMDLEITVIKLDGTTVP<br>RYGLRLNMDEKYTGLKKQLRDL<br>CGLNSEQILLAEVHDSNIKNFP | 167 | KGATGLSNLGNTCFMNSSIQC<br>CVSNTQPLTQYFISGRHLYE<br>LNRTNPIGMKGHMAKCYGDL<br>VQELWSGTQKSVAPLKLRRRT<br>IAKYAPKFDGFQQQDSQELL<br>AFLLDGLHEDLNRVHEKPYV<br>ELKDS DGRPDWE<br>VAAEAWDNHLRRNRSIIVDL<br>FHGQLRSQVKCKTCGHISVR<br>FDPNFLSLPLPMSYMDLEI<br>TVIKLDGTTVPVRYGLRLNMD<br>EKYTGLKKQLRDL CGLNSEQ<br>ILLAEVHDSNIKNFPQDNQK<br>VQLSVSGFLCAFEIPVPSSP<br>ISASSPTQIDFSSSPSTNGM<br>FTLTNGDLPKPIFIPNGMP<br>NTVVP CGTEKNFTNGMVNGH<br>MPSLPDSPFTGYIIAVHRKM<br>MRTELYFLSPQENRPSLFGM<br>PLIVPCTVHTRKKDLYDAVW<br>IQVSWLARPLPPQEASIIHAQ<br>DRDNCMGYQYPFTLRVQKD<br>GNSCAWCPQYRFCRGCKIDC<br>GEDRAFIGNAYIAVDWHPTA<br>LHLRYQTSQERVVDKHESVE<br>QSRRAQAEPINLDSCLRAFT<br>SEEELGESEMYYSKCKTHC<br>LATKKLDLWRLPPFLIIHLK<br>RFQFVNDQWIKSQKIVRFLR<br>ESFDPSAFLVPRDPALCQHK<br>PLTPQGDELSKPRILAREVK<br>KVDAQSSAGKEDMLLSKSPS<br>SLSANISSSPKSPSSSRKS<br>GTSCPSSKNSSPNSSPRTL<br>RSKGRRLRPQIGSKNKPSSS<br>KKNL DASKENGAGQICELAD |

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|                                                                                |    | <p>QDNQKVQLSVSGFLCAFEIPVP<br/>SSPISASSPTQIDFSSSPSTNG<br/>MFTLTNGDLPKPIFIPNGMPN<br/>TVVPCGTEKNFTNGMVNGHMPS<br/>LPDSPFTGYIIAVHRKMMRTEL<br/>YFLSPQENRPSLFG<br/>MPLIVPCTVHTRKKDLYDAVWI<br/>QVSWLARPLPPQEASIIHAQDRD<br/>NCMGYQYPFTLRVVQKDGNSCA<br/>WCPQYRFCRGCKIDCGEDRAFI<br/>GNAYIAVDWHPTALHLRYQTSQ<br/>ERVVDKHESVEQSRRAQAEPIN<br/>LDSCLRAFTSEEELGESEMYYC<br/>SKCKTHCLATKKLDLWRLPPFL<br/>IIHLKRFQFVNDQWIKSQKIVR<br/>FLRESFDPSAFLVPRDPALCQH<br/>KPLTPQGDELSKPRILAREVKK<br/>VDAQSSAGKEDMLLSKSPSSLS<br/>ANISSSPKGSPPSSSRKSGTSCP<br/>SSKNSSPNSSPRTL<br/>GRSKGRLRLPQIGSKNKPSSSK<br/>KNLDASKENGAGQICELADALS<br/>RGHMRGGSQPELVTPQDHEVAL<br/>ANGFLYEHEACGNGCGDGYSNG<br/>QLGNHSEEDSTDDQREDTHIKP<br/>IYNLYAISCHSGILSGGHYITY<br/>AKNPNCWKWYCYNDSSCEELHPD<br/>EIDTDSAYILFYEQQGIDYAQF<br/>LPKIDGKKMADTSSTDEDES<br/>YEKYSMLQ</p> |     | <p>ALSRGHMRGGSQPELVTPQD<br/>HEVALANGFLYEHEACGNGC<br/>GDGYSNGQLGNHSEEDSTDD<br/>QREDTHIKPIYNLYAISCHS<br/>GILSGGHYITYAKNPNCWKWY<br/>CYNDSSCEELHPDEIDTDSA<br/>YILFYEQQG</p>                                                                                                                                                                                                                                                                                                                                                                      |
| UBP53_HUM<br>AN Inactive<br>ubiquitin<br>carboxyl-<br>terminal<br>hydrolase 53 | 56 | <p>MAWVKFLRKPGGNLGKVYQPGS<br/>MLSLAPTKGLLNEPGQNSCFLN<br/>SAVQVLWQLDIFRRSLRVLTHG<br/>VCQGDACIFCALKTIFAQFQHS<br/>REKALPSDNIRHALAESFKDEQ<br/>RFQLGLMDDAAECFENMLERIH<br/>FHIVPSRDADMCTSKSCITHQK<br/>FAMTLYEQCVCRSCGASSDPLP<br/>FTEFVRYISTTALCNEVERMLE<br/>RHERFKPEMFAELLQAANTTDD<br/>YRKCPNSCGQKIKIRRVLMNCP<br/>EIVTIGLVWDSEHSDLTEAVVR<br/>NLATHLYLPGLFYRVTDENAKN<br/>SELNLVGMICYTSQ<br/>HYCAFAFHTKSSKWVFFDDANV<br/>KEIGTRWKDVVSKCIRCHFQPL<br/>LLFYANPDGTAVSTEDALRQVI<br/>SWSHYKSAENMGCEKPVHKS<br/>DNLKENGFGDQAKQRENQKFPT<br/>DNISSNRSHSHTGVGKPAKL<br/>SHIDQREKIKDISRECALKAIE</p>                                                                                                                                                                                                                                  | 168 | <p>APTKGLLNEPGQNSCFLNSA<br/>VQVLWQLDIFRRSLRVLTHG<br/>VCQGDACIFCALKTIFAQFQ<br/>HSREKALPSDNIRHALAESF<br/>KDEQRFQLGLMDDAAECFEN<br/>MLERIHFHIVPSRDADMCTS<br/>KSCITHQKFAMTLYEQCVCR<br/>SCGASSDPLPFTEFVRYIST<br/>TALCNEVERMLERHERFKPE<br/>MFAELLQAANTTDDYRKCP<br/>NCGQKIKIRRVLMNCP EIVT<br/>IGLVWDSEHSDLTEAVVRNL<br/>ATHLYLPGLFYRVTDENAKN<br/>SELNLVGMICYTSQHYCAFA<br/>FHTKSSKWVFFDDANVKEIG<br/>TRWKDVVSKCIRCHFQPLLL<br/>FYANPDGTAVSTEDALRQVI<br/>SWSHYKSAENMGCEKPVH<br/>KSDNLKENGFGDQAKQRENQ<br/>KFPTDNISSNRSHSHTGVG<br/>KGPAKLSHIDQREKIKDISR</p> |

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|                                                                                                         |    | <p>QKNLLSSQRKDLEKGQRKDLGR<br/> HRDLVDEDLSHFQSGSPAPNG<br/> FKQHGNPHLYHSQGKGSYKHDR<br/> VVPQSRASAQIISSSKSQILAP<br/> GEKITGKVKSDNGTGYDTDSSQ<br/> DSRDRGNSCDSSSKSRNRGWKP<br/> MRETNLNVDISIFSES<br/> EKRQHSPRHKPNISNPKSSKD<br/> PSFSNWPKENPKQKGLMTIYED<br/> EMKQEIGSRSSLESNGKGAEN<br/> KGLVEGKVHGDNWQMQRTEGY<br/> ESSDHISNGSTNLDSPVIDGNG<br/> TVMDISGVKETVCFSDQITTSN<br/> LNKERGDCTSLQSQHHLEGFRK<br/> ELRNLEAGYKSHEFHPESHLQI<br/> KNHLIKRSHVHEDNGKLFPS<br/> LQIPKDHNAHEHIHQSDQKLE<br/> KPNECKFSEWLNIENTERTGLP<br/> FHVDNSASGKRVNSNEPSSLWS<br/> SHLRTVGLKPEAPLIQQQNM<br/> DQCYFENSLSTECI<br/> IRSASRSDGCQMPKLCQNLPP<br/> PLPPKYYAITSVPQSEKSESTP<br/> DVKLTEVFKATSHLPKHSLSA<br/> SEPSLEVSTHMNDERHKETFQV<br/> RECFGNTPNCPSSSSTNDFQAN<br/> SGAIDAFQPELDSISTCPNET<br/> VSLTTYFSVDSCMTDTYRLKYH<br/> QRPKLSFPESGFCNNSLS</p> |     | <p>ECALKAIEQKNLLSSQRKDL<br/> EKGQRK</p>                                                                                                                                                                                                                                                                                                                       |
| <p>U17LO_HUM<br/> AN Ubiquitin<br/> carboxyl-<br/> terminal<br/> hydrolase 17-<br/> like protein 24</p> | 57 | <p>MEDDSLILRGEWQFNHFSKLT<br/> SRPDAAFAEIQRSLPEKSP<br/> CETRVLDLDDAPVARQLAP<br/> KLPLSSRRPAAVGAGLQNM<br/> CYVNASLQCLTYTPPLAN<br/> REHSQTCRHHKGCMLCTM<br/> TRALHNPQHVIVQPSQAL<br/> RGKQEDAHEFLMFTVDAM<br/> LPGHKQVDHHSKDTTLIH<br/> GYWRSQIKCLHCHGISDT<br/> LDIALDIQAAQSVQQA<br/> PEELNGENAYHCGVCLQ<br/> KTLTLHTSAKVLILVLR<br/> TGNKIAKNVQYPEC<br/> LDMQPYMSQPNTG<br/> LVHAGWSCHNGHYFSYV<br/> QWYKMDDAEVTASSIT<br/> AYVLFYIQKSEWERHSE<br/> REPRALGAEDTDRRATQ<br/> DHPCLQAPELDEHLVER<br/> TLDHWKFLQEQNKTKPE<br/> VEGTLPPDVLVIHQSKY</p>                                                                                                                                                                                                                                                                              | 169 | <p>AVGAGLQNMNTCYVNASLQ<br/> CLTYTPPLANMLSREHSQ<br/> CHRHKGCMCTMQAHITRA<br/> HNPQHVIVQPSQALAA<br/> KQEDAHEFLMFTVDAM<br/> LPGHKQVDHHSKDTTLI<br/> FGGYWRSQIKCLHCHGIS<br/> FDPYLDIALDIQAAQSV<br/> LEQLVKPEELNGENAYH<br/> CLQRAPASKTLTLHTSA<br/> ILVLRFSQVTGNKIAKN<br/> YPECLDMQPYMSQPNT<br/> YVLYAVLVHAGWSCHNG<br/> SYVKAQEGQWYKMDDAE<br/> SSITSVLSQQAYVLFYIQ</p> |

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|                                                                                           |    | NHHPEQQSSLLNLSSSTPTHQE<br>SMNTGTLASLRGRARRSKGKNK<br>HSKRALLVCQ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| U17LM_HU<br>MAN<br>Ubiquitin<br>carboxyl-<br>terminal<br>hydrolase 17-<br>like protein 22 |    | MEDDSLYLGGEWQFNHFSKLT<br>SRPDAAFAEIQRSTLPEKSPLS<br>CETRVDLCDDLAPVARQLAPRE<br>KLPLSSRRPAAVGAGLQNMNT<br>CYVNASLQCLTYTPPLANYMLS<br>REHSQTCHRHKGCMCTMQAHI<br>TRALHNPQHVVIQPSQALAAGFH<br>RGKQEDAHEFLMFTVDAMKKAC<br>LPGHKQVDHHSKDTTLIHQIFG<br>GYWRSQIKCLHCHGISDTFDPY<br>LDIALDIQAAQSVQQAQLEQLVK<br>PEELNGENAYHCGVCLQRAPAS<br>KTLTLHTSAKVLILVLKRFS<br>TGNKIAKNVQYPEC<br>LDMQPYMSQQNTGPLVYVLYAV<br>LVHAGWSCHNGHYFSYVKAQEG<br>QWYKMDDAEVTASSITSVLSQQ<br>AYVLFYIQKSEWERHSESVSRG<br>REPRALGAEDTDRRATQGELKR<br>DHPCLQAPELDEHLVERATQES<br>TLDHWKFLQEQNKTKPEFNVRK<br>VEGTLPPDVLVIHQSKYKCGMK<br>NHHPEQQSSLLKLSSTPTHQE<br>SMNTGTLASLRGRARRSKGKNK<br>HSKRALLVCQ |     | AVGAGLQNMNTCYVNASLQ<br>CLTYTPPLANYMLSREHSQT<br>CHRHKGCMCTMQAHI<br>TRALHNPQHVVIQPSQALAAGFH<br>RGKQEDAHEFLMFTVDAMKKAC<br>LPGHKQVDHHSKDTTLIHQIFG<br>GYWRSQIKCLHCHGISDTFDPY<br>LDIALDIQAAQSVQQAQLEQLVK<br>PEELNGENAYHCGVCLQRAPAS<br>KTLTLHTSAKVLILVLKRFS<br>TGNKIAKNVQYPEC<br>LDMQPYMSQQNTGPLVYVLYAV<br>LVHAGWSCHNGHYFSYVKAQEG<br>QWYKMDDAEVTASSITSVLSQQ<br>AYVLFYIQKSEWERHSESVSRG<br>REPRALGAEDTDRRATQGELKR<br>DHPCLQAPELDEHLVERATQES<br>TLDHWKFLQEQNKTKPEFNVRK<br>VEGTLPPDVLVIHQSKYKCGMK<br>NHHPEQQSSLLKLSSTPTHQE<br>SMNTGTLASLRGRARRSKGKNK<br>HSKRALLVCQ |
| UBP5_HUM<br>AN Ubiquitin<br>carboxyl-<br>terminal<br>hydrolase 5                          | 58 | MAELSEEALLSVLPTIRVPKAG<br>DRVHKDECAFSFDTPESGGGLY<br>ICMNTFLGFGKQYVERHFNTKG<br>QRVYLHLRRTTRPKEEDPATGT<br>GDPPRKKPTRLAIGVEGGFDLS<br>EEKFELDEDVKIVILPDYLEIA<br>RDGLGGLPDIVRDRVTSVEAL<br>LSADSASRKQEVQAWDGEVRQV<br>SKHAFSLKQLDNPARIPPCGWK<br>CSKCDMRENWLNLTDGSI<br>LCGRYFDGSGGNNAVEHYRETGY<br>PLAVKLGTITPDGADVSYDED<br>DMVLDPSLAEHLSHFGIDMLKM<br>QKTDKTMTELEIDM<br>NQRIGEWELIQESGVPLKPLFG<br>PGYTGIRNLGNSCYLNSVVQVL<br>FSIPDFQQRKYVDKLEKIFQNAP<br>TDPTQDFSTQVAKLGHGLLSGE<br>YSKVPESGDGERVPEQKEVQD<br>GIAPRMFKALIGKGHPFSTNR<br>QQDAQEFFLHLINMVERNCRSS<br>ENPNEVFRFLVEEKIKCLATEK<br>VKYTQRVYIMQLPVPMDAALN                                            | 170 | FGPGYTGIRNLGNSCYLNSV<br>VQVLFSDIPDFQQRKYVDKLEK<br>IFQNAPTDPTQDFSTQVAKL<br>GHGLLSGEYSKVPESGDGE<br>RVPEQKEVQDGIAPRMFKAL<br>IGKGHPFSTNRQQDAQEFF<br>LHLINMVERNCRSS<br>ENPNEVFRFLVEEKIKCLATEK<br>VKYTQRVYIMQLPVPMDAALN                                                                                                                                                                                                                                                                                                                                       |



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|                                                      |    | KEELLEYEEKKRQAEEEKMALP<br>ELVRAQVPFSSCLEAYGAPEQV<br>DDFWSTALQAKSVAVKTTRFAS<br>FPDYLVIIQIKKFTFGLDWVPKK<br>LDVSIEMPEELDIS<br>QLRGTGLQPGEEELPDIAPPLV<br>TPDEPKGSLGFYGNEDEDSFCS<br>PHFSSPTSPMLDESVIIQLVEM<br>GFPMDACRKAVYYTGNSGAEAA<br>MNWVM SHMDDPDFANPLILPGS<br>SGPGSTSAAADPPPEDCVTTIV<br>SMGFSRDQALKALRATNNSLER<br>AVDWIFSHIDDLDAEAAMDISE<br>GRSAAADSISESVPVGPVKVRDGP<br>GKYQLFAFISHMGTSTMCGHYV<br>CHIKKEGRWVIYNDQKVCASEK<br>PPKDLGYIIFYQQRVAS                                                                                                                                                                                                                                                                                                                                                                                                                                               |  | ADSISESVPVGPVKVRDGPVK<br>YQLFAFISHMGTSTMCGHYV<br>CHIKKEGRWVIYNDQKVCAS<br>EKPPKDLGYIIFYQQRVA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| UBP25_HUMAN Ubiquitin carboxyl-terminal hydrolase 25 | 59 | MTVEQNVLQQSAAQKHQQTFLN<br>QLREITGINDTQILQQALKDSN<br>GNLELAVAFLTAKNAKTPQQEE<br>TTYQTALPGNDRIISVGSQAD<br>TNVIDLTGDDKDDLQRAIALSL<br>AESNRAFRETGITDEEQAISRV<br>LEASIAENKACLKRTPTVWRD<br>SRNPYDRKRQDKAPVGLKNVGN<br>TCWFSAVIQSLFNLLEFRRLVL<br>NYKPPSNAQDLPRNQKEHRNLP<br>FMRELRYLFALLVGTKRKYVDP<br>SRAVEILKDAFKSNDSSQQQDVS<br>EFTHKLLDWLEDAFQMKAEET<br>DEEKPKNPMVELFY<br>GRFLAVGVLEGKKFENTEMFGQ<br>YPLQVNGFKDLHECLEAAMIEG<br>EIESLHSENSGKSGQEHWFTEL<br>PPVLTFFELSRFEFNQALGRPEK<br>IHNKLEFPQVLYLDHYMRNRE<br>ITRIKREEIKRLKDYLTVLQQR<br>LERYLSYSGSGPKRFPLVDVLQY<br>ALEFASSKPVCTSPVDDIDASS<br>PPSGSIPTLSTTEQQGALS<br>SELPSTSPSSVAAISSRSVIHK<br>PFTQSRIPDLPMHPAPRHITE<br>EELSVLESCLHRWRTEIENDTR<br>DLQESISRIHRTIELMYSDKSM<br>IQVPYRLHAVLVHE<br>GQANAGHYWAYIFDHRESRWMK<br>YNDIAVTKSSWEELVRDSFGGY<br>RNASAYCLMYINDKAQFLIQEE<br>FNKETGQPLVGIETLPPDLRDF<br>VEEDNQRFEEKELEEWDAQLAQK<br>ALQEKLLASQKLRSETSSTTA |  | KAPVGLKNVGNTCWFSAVIQ<br>SLFNLLEFRRLVLNYKPPSN<br>AQDLPRNQKEHRNLPFMREL<br>RYLFALLVGTKRKYVDPSSRA<br>VEILKDAFKSNDSSQQQDVSE<br>FTHKLLDWLEDAFQMKAEET<br>TDEEKPKNPMVELFYGRFLA<br>VGVLEGKKFENTEMFGQYPL<br>QVNGFKDLHECLEAAMIEG<br>IESLHSENSGKSGQEHWFTE<br>LPPVLTFFELSRFEFNQALGR<br>PEKIHNKLEFPQVLYLDHYM<br>HRNREITRIKREEIKRLKDY<br>LTVLQQRLELYLSYSGSGPKR<br>FPLVDVLQYALEFASSKPVCT<br>TSPVDDIDASSPPSGSIPTSQ<br>TLPSTTEQQGALSSELPTST<br>PSSVAAISSRSVIHKPFTQS<br>RIPDLPMHPAPRHITEEEL<br>SVLESCLHRWRTEIENDTRD<br>LQESISRIHRTIELMYSDKS<br>MIQVPYRLHAVLVHEGQANA<br>GHYWAYIFDHRESRWMKYND<br>IAVTKSSWEELVRDSFGGYR<br>NAS |

|                                                                    |    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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|                                                                    |    | QAAGDPEYLEQPSRSDFSKHLK<br>EETIQIITKASHEHEDKSPETV<br>LQSAIKLEYARLVKLAQEDTPP<br>ETDYRLHHVVVYFIQNQAPKKI<br>IEKTLLEQFGDRNLSFDERCHN<br>IMKVAQAKLEMIKPEEVNLEEY<br>EEWHQDYRKFFRETMYLIIGLE<br>NFQRESYIDSLLFL<br>ICAYQNNKELLSKGLYRGHDEE<br>LISHYRRECLLKLNEQAELFE<br>SGEDREVNNGLIIMNEFIVPFL<br>PLLLVDEMEEKDILAVEDMRNR<br>WCSYLGQEMEPHLQEKLTDFLP<br>KLLDCSMEIKSFHEPPKLPSYS<br>THELCERFARIMLSLSRTPADG<br>R                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| UBP33_HUM<br>AN Ubiquitin<br>carboxyl-<br>terminal<br>hydrolase 33 | 60 | MTGSNSHITILTLKVLPHFESL<br>GKQEKIPNKMSAFRNHCPHLD<br>VGEITKEDLIQKSLGTCQDCKV<br>QGPNLWACLENRCSYVCGESQ<br>VDHSTIHSQETKHYLTVNLTTL<br>RVWCYACSKFVFLDRKLGTQPS<br>LPHVRQPHQIQENSVQDFKIPS<br>NTTLKTPLVAVFDDLDIEADEE<br>DELRARGLTGLKNIGNTCYMNA<br>ALQALSNCPPLTQFFLDCGGLA<br>RTDKKPAICKSYLKLMTLWHL<br>SRPGSVVPTTLFQGIKTVNPTF<br>RGYSQQDAQEFRLCLMDLLHEE<br>LKEQVMEVEEDPQT<br>ITTEETMEEDKSQSDVDFQSCE<br>SCSNSDRAENENGSRCSFEDNN<br>ETTMLIQDDENNSEMSEKDWQKE<br>KMCNKINKVNSEGEFDKDRDSI<br>SETVDLNNQETVKVQIHSRASE<br>YITDVHSNDLSTPQILPSNEGV<br>NPRLSASPCKSGNLWPGLAPPH<br>KKAQSASPKRKKQHKKYRSVIS<br>DIFDGTIISSVQCLTCDRVSVT<br>LETFQDLSLPIPGKEDLAKLHS<br>SSHPTSIVKAGSCGEAYAPQGW<br>IAFFMEYVKRFVSVCPVSWFWG<br>PVVTLQDCLAFFARDELKGDN<br>MYSCEKCKKLRNGV<br>KFCKVQNFPEILCIHLKRFRHE<br>LMFSTKISTHVSFPLEGLDLQP<br>FLAKDSPAQIVTYDLLSVICHH<br>GTASSGHYIAYCRNNLNLWYE<br>FDDQSVTEVSESTVQNAEAYVL<br>FYRKSSEEAQKERRRISNLLNI<br>MEPSLLQFYISRQWLNKFKTFA | 171 | ARGTLGLKNIGNTCYMNAAL<br>QALSNCPPLTQFFLDCGGLA<br>RTDKKPAICKSYLKLMTLWHL<br>HKSRPGSVVPTTLFQGIKTV<br>NPTFRGYSQQDAQEFRLCLM<br>DLLHEELKEQVMEVEEDPQT<br>ITTEETMEEDKSQSDVDFQS<br>CESCNSDRAENENGSRCSF<br>EDNNETTMLIQDDENNSEMSE<br>KDWQKEKMCNKINKVNSEGE<br>FDKDRDSISETVDLNNQETV<br>KVQIHSRASEYITDVHSNDL<br>STPQILPSNEGVNPRLSASP<br>PKSGNLWPGLAPPHKKAQSA<br>SPKRKKQHKKYRSVISDIFD<br>GTIISSVQCLTCDRVSVTLE<br>TFQDLSLPIPGKEDLAKLHS<br>SSHPTSIVKAGSCGEAYAPQ<br>GWIAFFMEYVKRFVSVCPVS<br>WFWGPVVTLQDCLAFFARDEL<br>ELKGDNMYSCEKCKKLRNGV<br>KFCKVQNFPEILCIHLKRFR<br>HELMFSTKISTHVSFPLEGL<br>DLQPFLAKDSPAQIVTYDLL<br>SVICHHTASSGHYIAYCRN<br>NLNNLWYEFDDQSVTEVSES<br>TVQNAEAYVLFYRKSS |

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|                                                                              |    | EPGPISNNDFLCIHGGVPPRKA<br>GYIEDLVLMPLQNIWDNLYSRY<br>GGGPAVNHLYICHTCQIEAEKI<br>EKRRKTELEIFIRLNRAFQKED<br>SPATFYCISMQWFREWESFVKG<br>KDGDPPGPIDNTKIAVTKCGNV<br>MLRQGADSGQISEETWNFLQSI<br>YGGGPEVILRPPVVHVDPDILQ<br>AEEKIEVETRSL                                                                                                                                                                                                                                                                                                                                                                                                                                                         |     |                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| UBP21_HUMAN Ubiquitin carboxyl-terminal hydrolase 21                         | 61 | MPQASEHRLGRTREPPVNIQPR<br>VGSKLPFAPRARSKERNPASG<br>PNMLRPLPPRGLPDERLKKL<br>ELGRGRTSGPRPRGPLRADHGV<br>PLPGSPPTVALPLPSRTNLAR<br>SKSVSSGDLRPMGIALGGHRGT<br>GELGAALSRLALRPEPPTLRRS<br>TSLRRLGGFPGPPTLFSIRTEP<br>PASHGSFHMISARSSEPFFYSDD<br>KMAHHTLLLGSGHVGLRNLGNT<br>CFLNAVLQCLSSSTRPLRDFCLR<br>RDFRQEVPGGGRAQELTEAFAD<br>VIGALWHPDSCEAVNPTRFRAV<br>FQKYVPSFSGYSQQ<br>DAQEFLKLMLERLHLEINRRGR<br>RAPPILANGPVPSPRRGGALL<br>EEPESDDDRANLMWKRYLERE<br>DSKIVDLFVGQLKSKLKQACG<br>YRSTTFEVFCDLSLPIPKKGFA<br>GGKVSRLRDCFNLFTEKEELESE<br>NAPVCDRCRQKTRSTKKLTVQR<br>FPRILVLHLNRFASRGSIKKS<br>SVGVDPLQRLSLGDFASDKAG<br>SPVYQLYALCNHSGSVHYGHYT<br>ALCRCQTGWHVYNDSPVSE<br>NQVASSEGYVLFYQLMQEPPRC<br>L | 172 | LGSGHVGLRNLGNTCFLNAV<br>LQCLSSTRPLRDFCLRRDFR<br>QEVPGGGRAQELTEAFADVI<br>GALWHPDSCEAVNPTRFRAV<br>FQKYVPSFSGYSQQDAQEFL<br>KLLMERLHLEINRRGRRAPP<br>ILANGPVPSPRRGGALLEE<br>PELSDDDRANLMWK<br>RYLEREDSKIVDLFVGQLKS<br>CLKCQACGYRSTTFEVFCDL<br>SLPIPKKGFAAGKVSRLRDCF<br>NLFTKEEELESENAPVCDRC<br>RQKTRSTKKLTVQRFPRILV<br>LHLNRFASRGSIKKSSVGV<br>DFPLQRLSLGDFASDKAGSP<br>VYQLYALCNHSGSVHYGHYT<br>ALCRCQTGWHVYNDSPVSE<br>SENQVASSEGYVLFYQLMQ |
| U17L4_HUMAN Inactive ubiquitin carboxyl-terminal hydrolase 17-like protein 4 | 62 | MGDDSLYLGGEWQFNHFSKLTS<br>SRPDAAFAEIQRTSLPEKSPLS<br>SETRVDLCDDLPAPVARQLAPRE<br>KLPLSSRRPAAVGAGLQNMGNT<br>CYENASLQCLTYTLPLANMYS<br>REHSQTCQRPKCCMLCTMQAHI<br>TVALHSPGHVIQPSQALAAGFH<br>RGKQEDVHEFLMFTVDAMKKAC<br>LPGHKQVDHHSKDTTLIHQIFG<br>GCWRSQIKCLHCHGISDTFDPY<br>LDIALDIQAAQSVKQALEQLVK<br>PEELNGENAYHCGLCLQAPAS<br>NTLTLHTSAKVLILVLKRFSVD<br>AGNKLAKNVQYPEC                                                                                                                                                                                                                                                                                                                      | 173 | AVGAGLQNMGNTCYENASLQ<br>CLTYTLPLANMYSREHSQT<br>CQRPKCCMLCTMQAHITWAL<br>HSPGHVIQPSQALAAGFHRG<br>KQEDVHEFLMFTVDAMKKAC<br>LPGHKQVDHHSKDTTLIHQI<br>FGGCWRSQIKCLHCHGISDT<br>FDPYLDIALDIQAAQSVKQA<br>LEQLVKPEELNGENAYHCGL<br>CLQAPASNTLTLHTSAKVL<br>ILVLKRFSVDVAGNKLAKNVQ<br>YPECLDMQPYMSQQNTGPLV<br>YVLYAVLVHAGWSCHDGYF<br>SYVKAQEGQWYKMDDAEVT<br>CSITSVLSQQAYVLFYIQKS                                                                   |

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|                                                                                        |    | LDMQPYMSQQNTGPLVYVLYAV<br>LVHAGWSCHDGYYSYVKAQEG<br>QWYKMDDAEVTVCSITSVLSQQ<br>AYVLFYIQKSEWERHSESVSRG<br>REPRALGAEDTDRPATQGELKR<br>DHPCLQVPELDEHLVERATEES<br>TLDHWKFPQEQNKMKPEFNVRK<br>VEGTLPPNVLVHQSXYKCGMK<br>NHHPEQQSSLLNLSMNSTDQE<br>SMNTGTLASLQGRTRRSKGKNK<br>HSKRSLLVCO                                                                                                                                                                                                                                                                                                                                                             |     |                                                                                                                                                                                                                                                                                                                                                                   |
| U17LK_HUM<br>AN Ubiquitin<br>carboxyl-<br>terminal<br>hydrolase 17-<br>like protein 20 | 63 | MEDDSLVLGGWQFNHFSKLT<br>SRPDAAFAEIQRSLPEKSPLS<br>CETRVDLCDLAPVARQLAPRE<br>KLPLSSRRPAAVGAGLQNMGNT<br>CYVNASLQCLTYTPPLANMYS<br>REHSQTCHRHKGCMCTMAHI<br>TRALHNPQHVIVPSQALAGFH<br>RGKQEDAHEFLMFTVDAMKKAC<br>LPGHKQVDHHSKDTTLIHQIFG<br>GYWRSQIKCLHCHGISDTFDPY<br>LDIALDIQAAQSVQQAELQVK<br>PEELNGENAYHCGVCLQAPAS<br>KTLTLHTSAKVLILVLKRFSDV<br>TGNKIAKNVQYPECLDMQPYMS<br>QPNTGPLVYVLYAVLVHAGWSC<br>HNGHYFSYVKAQEGQWYKMDDA<br>EVTASSITSVLSQQAYVLFYIQ<br>KSEWERHSESVSRGREPRALGA<br>EDTDRRATQGELKRDHPCLQAP<br>ELDEHLVERATQESTLDHWKFL<br>QEQNKTKPEFNVRKVEGTLPPD<br>VLVHQSXYKCGMKNHHPEQQS<br>SLLNLSSTTPTHQESMNTGTLA<br>SLRGRARRSKGKNKHSKRALLV<br>CQ | 174 | AVGAGLQNMGNTCYVNASLQ<br>CLTYTPPLANMYSREHSQT<br>CHRHKGCMCTMAHITRAL<br>HNPQHVIVPSQALAGFH<br>KQEDAHEFLMFTVDAMKKAC<br>LPGHKQVDHHSKDTTLIHQIFG<br>GYWRSQIKCLHCHGISDT<br>FDPYLDIALDIQAAQSVQQA<br>LEQLVKPEELNGENAYHCGV<br>CLQAPASKTLTLHTSAKVL<br>ILVLKRFSDVTGNKIAKNVQ<br>YPECLDMQPYMSQPNTGPLV<br>YVLYAVLVHAGWSCHNGHYF<br>SYVKAQEGQWYKMDDAEVTA<br>SSITSVLSQQAYVLFYIQKS     |
| UBP12_HUM<br>AN Ubiquitin<br>carboxyl-<br>terminal<br>hydrolase 12                     | 64 | MEILMTVSKFASICTMGANASA<br>LEKEIGPEQFPVNEHYFGLVNF<br>GNTCYCNSVLQALYFCRPFREK<br>VLAYKSQPRKKESLLTCLADLF<br>HSIATQKKKVGVIKKFITRL<br>RKENELFDNYMQQDAHEFLNYL<br>LNTIADILQEERKQEKQNGRLP<br>NGNIDNENNNSTPDPTWVHEIF<br>QGTLTNETRCLTCETISSKDED<br>FLDLSVDVEQNTSITHCLRGFS<br>NTETLCSEYKYCEECRSKQEA<br>HKRMKVKKLPMILALHLKRFKY<br>MDQLHRYTKLSYRVVFPLELRL<br>FNTSGDATNPDRMY                                                                                                                                                                                                                                                                           | 175 | EHYFGLVNFNTCYCNSVLQ<br>ALYFCRPFREKVLAYKSQPR<br>KKESLLTCLADLFHSIATQK<br>KKVGVIPKKFITRLRKENE<br>LFDNYMQQDAHEFLNYLLNT<br>IADILQEERKQEKQNGRLPN<br>GNIDNENNNSTPDPTWVHEI<br>FQGTLTNETRCLTCETISSK<br>DEDFLDLSVDVEQNTSITHC<br>LRGFSNTETLCSEYKYCEE<br>CRSKQEAHKRMKVKKLPMIL<br>ALHLKRFKYMDQLHRYTKLS<br>YRVVFPLELRLFNTSGDATN<br>PDRMYDLVAVVVHCGSGPNR<br>GHYIAIVKSHDFWLLFDDDI |

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|                                                                                        |    | DLVAVVVHCGSGPNRGHYIAIV<br>KSHDFWLLFDDDDIVEKIDAQAI<br>EEFYGLTSDISKNSESGYILFY<br>QSRD                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |     | VEKIDAQAIIEEFYGLTSDIS<br>KNSSESGYILFYQSR                                                                                                                                                                                                                                                                                                                                                              |
| UL17C_HUM<br>AN Ubiquitin<br>carboxyl-<br>terminal<br>hydrolase 17-<br>like protein 12 | 65 | MEEDSLYLGGGEWQFNHFSKLTS<br>SRPDAAFAEIQRSLPEKSPLS<br>CETRVDLCDDLAPVARQLAPRE<br>KLPLSNRRPAAVGAGLQNMNT<br>CYVNASLQCLTYTPPLANYM<br>REHSQTCHRHKGCMCTMQAHI<br>TRALHNPQHVIQPSQALAAGFH<br>RGKQEDAHEFLMFTVDAMKKAC<br>LPGHKQVDHHSKDTTLIHQIFG<br>GYWRSQIKCLHCHGISDTFDPY<br>LDIALDIQAAQSVQQAELQV<br>PEELNGENAYHCGVCLQRPAS<br>KMLTLLTSKVLILVLKRFSDV<br>TGNKIAKNVQYPEC<br>LDMQPYMSQPNTGPLVYVLYAV<br>LVHAGWSCHNGHYFSYVKAQEG<br>QWYKMDDAEVTASSITSVLSQQ<br>AYVLFYIQKSEWERHSESVSRG<br>REPRALGAEDTDRRATQGELKR<br>DHPCLQAPELDEHLVERATQES<br>TLDHWKFLQEQNKTKPEFNVRK<br>VEGTLPPDVLVIHQSKYKCGMK<br>NHHPEQQSSLLKLSSTTPTHQE<br>SMNTGTLASLRGRARRSKGKNK<br>HSKRALLVCQ | 176 | AVGAGLQNMNTCYVNASLQ<br>CLTYTPPLANYM<br>SREHSQT<br>CHRHKGCMCTMQAHITRAL<br>HNPQHVIQPSQALAAGFHRG<br>KQEDAHEFLMFTVDAMKKAC<br>LPGHKQVDHHSKDTTLIHQI<br>FGGYWRSQIKCLHCHGISDT<br>FDPYLDIALDIQAAQSVQQA<br>LEQLVKPEELNGENAYHCGV<br>CLQRPASKMLTLLTSKVL<br>ILVLKRFSDVTGNKIAKNVQ<br>YPECLDMQPYMSQPNTGPLV<br>YVLYAVLVHAGWSCHNGHYF<br>SYVKAQEGQWYKMDDAEVT<br>SSITSVLSQQAYVLFYIQKS                                    |
| UBP20_HUM<br>AN Ubiquitin<br>carboxyl-<br>terminal<br>hydrolase                        | 66 | MGDSRDLCPHLDSIGEVTKEDL<br>LLKSKGTCQSCGVTGPNLWACL<br>QVACPYPVCGESFADHSTIHAQ<br>AKKHNLTVNLTTFRLWCYACEK<br>EVFLEQRLAAPLLGSSSKFSEQ<br>DSPPPSHPLKAVPIAVALDEGES<br>ESEDDDLKPRGLTGMKNLGN<br>SCYMNAALQALSNCPLTQFFLEC<br>GGLVRTDKKPALCKSYQKL<br>VSEVWHKKRPSYVVP<br>TSLSHGIKLVNPMFRGYAQQDTQEF<br>LRLCLMDQLHEELKEPVVATV<br>ALTEARDSSDTDEKREGDRSPSE<br>DEFLSCDSSSDRGE<br>GDGQGRGGSSQAETELLIPDEAGRAIS<br>EKERMKDRKFSWGQQRTNSEQV<br>DEDADVDTAMAALDDQPAEAQP<br>PSPRSSPCRTPEPDNDALHRS<br>SSRPCSPVHHHEGHAKLSSSP<br>RASPVMAPSYVLKKAQVLSAG<br>SRRRKEQRYRSVISDIFDGSIL<br>SLVQCLTCDRVSTTVETFDLS                                                                 | 177 | PRGLTGMKNLGNSCYMN<br>AALQALSNCPLTQFFLEC<br>GGLVRTDKKPALCKSYQKL<br>VSEVWHKKRPSYVVP<br>TSLSHGIKLVNPMFRGYAQQDTQEF<br>LRLCLMDQLHEELKEPVVATV<br>ALTEARDSSDTDEKREGDRSPSE<br>DEFLSCDSSSDRGE<br>GDGQGRGGSSQAETELLIPDEAGRAIS<br>EKERMKDRKFSWGQQRTNSEQV<br>DEDADVDTAMAALDDQPAEAQP<br>PSPRSSPCRTPEPDNDALHRS<br>SSRPCSPVHHHEGHAKLSSSP<br>RASPVMAPSYVLKKAQVLSAG<br>SRRRKEQRYRSVISDIFDGSIL<br>SLVQCLTCDRVSTTVETFDLS |

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|                                                       |    | <p>LPIPGKEDLAKLHSAIYQNVPA<br/>KPGACGDSYAAQGWLA FIVEYI<br/>RRFVVSCTPSWFWGPVVTLED<br/>LAFFFADELKGDNMYS CERCK<br/>KLRNGVKYCKVLRRLPEILCIHL<br/>KRFRHEVMYSFKIN<br/>SHVSFPLEGLDLRPFLAKECTS<br/>QITTYDLLSVICHHG TAGSGHY<br/>IAYCQNVINGQWYEFDDQYVTE<br/>VHETVVQNAEGYVLFYRKSSEE<br/>AMRERQQVVSLAAMREPSLLRF<br/>YVSREWLNKFNTFAEPGPITNQ<br/>TFLCSHGGIPPHKYHYIDDLVV<br/>ILPQNVWEHLYNRFGGPAVNH<br/>LYVCSICQVEIEALAKRRRIEI<br/>DTFIKLNKAFQAEESPGVIYCI<br/>SMQWFRWEAFVKGKDNEPPGP<br/>IDNSRIAQVKGSGHVQLKQGAD<br/>YGQISEETWTYLN SLYGGGPEI<br/>AIRQSAQPLGPENLHGEQKIE<br/>AETRAV</p> |     | <p>ILCIHLKRFRHEVMYSFKIN<br/>SHVSFPLEGLDLRPFLAKEC<br/>TSQITTYDLLSVICHHG TAG<br/>SGHYIAYCQNVINGQWYEF<br/>DQYVTEVHETVVQNAEGYV<br/>LFYRKSS</p>                                                                                                                                                                                                                                                                                        |
| UBP46_HUMAN Ubiquitin carboxyl-terminal hydrolase 46  | 67 | <p>MTVRNIASICNMGTNASALEKD<br/>IGPEQFPINEHYFGLVNF GNTC<br/>YCNSVLQALYFCRPFRENVLAY<br/>KAQQKKKENLLTCLADLFHSIA<br/>TQKKKGVIPPKKFISRLRKEND<br/>DLFDNYMQQDAHEFLNYLLNTI<br/>ADILQEEKKQEKQNGKLKNGNM<br/>NEPAENNKPELTWVHEIFQGT<br/>LTNETRCLNCETVSSKDEDFDL<br/>SVDVEQNTSITHCLRDFSNTET<br/>LCSEQKYCETCCSKQEAQKRM<br/>RVKKLPMILALHLKRFKYMEQL<br/>HRYTKLSYRVVFPELRLFNTS<br/>SDAVNLDRMYDLVA<br/>VVVHCGSGPNRGHYITIVKSHG<br/>FWLLFDDDI VEKIDAQAIEEFY<br/>GLTSDISKNSESGYILFYQSRE</p>                                                                                              | 178 | <p>EHYFGLVNF GNTCYCNSVLQ<br/>ALYFCRPFRENVLAYKAQQK<br/>KKENLLTCLADLFHSIATQK<br/>KKVGVIPPKKFISRLRKEND<br/>LFDNYMQQDAHEFLNYLLNT<br/>IADILQEEKKQEKQNGKLKKN<br/>GNMNEPAENNKPELTWVHEI<br/>FQGTLTNETRCLNCETVSSK<br/>DEDFDLSDVEQNTSITHC<br/>LRDFSNTETLCSEQKYCET<br/>CCSKQEAQKRMVKKLPMIL<br/>ALHLKRFKYMEQLHRYTKLS<br/>YRVVFPELRLFNTSSDAVN<br/>LDRMYDLVAVVHCGSGPNR<br/>GHYITIVKSHGFWLLFDDDI<br/>VEKIDAQAIEEFYGLTSDIS<br/>KNSESGYILFYQSR</p> |
| CYLD_HUMAN Ubiquitin carboxyl-terminal hydrolase CYLD | 68 | <p>MSSGLWSQEKVTSPYWEERIFY<br/>LLLQECSVTDKQTQKLLKVPKG<br/>SIGQYIQDRSVGHSRIPSAKGK<br/>KNQIGLKILEQPHAVLFVDEKD<br/>VVEINEKFTELLLAITNCEERF<br/>SLFKNRNRLSKGLQIDVGCPVK<br/>VQLRSGEEKFPGVVRFRGPLLA<br/>ERTVSGIFFGVELLEEGRGQGF<br/>TDGVYQ GKQLFQCDEDCGVFVA<br/>LDKLELIEDDDTALES DYAGPG<br/>DTMQVELPPLEINSRVSLKVGE<br/>TIESGTVIFCDVLPKGESLGYF</p>                                                                                                                                                                                                                          | 179 | <p>GKKKGIQGHYNSCYLDSTLF<br/>CLFAFSSVLDTVLLRPKEKN<br/>DVEYYSETQELLRTEIVNPL<br/>RIYGYVCATKIMKLRKILEK<br/>VEAASGFTSEEKDPEEFLNI<br/>LFHHILRVEPLLKIRSAGQK<br/>VQDCYFYQIFME<br/>KNEKVGVP TIQQLEWSFIN<br/>SNLKFAEAPSCLIIQMPRFG<br/>KDFKLFKKI FPSLELNITDL<br/>LEDTPRQCRICGGLAMYECR<br/>ECYDDPDISAGKIKQFCKTC<br/>NTQVHLHPKRLNHKNPVSL</p>                                                                                                   |

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|                                                      |    | <p>VGVDMDNPIGNWDGRFDGVQLC<br/>SFACVESTILLHIN<br/>DIIPALSESVTQERRPPKLAFM<br/>SRGVGDKGSSSHNPKATGSTS<br/>DPGNRNRSELYFTLNGSSVDSQ<br/>PQSKSKNTWYIDEVAEDPAKSL<br/>TEISTDFDRSSPPLQPPPVNSL<br/>TTENRFHSLPFSLTKMPNTNGS<br/>IGHSPLSLSAQSVMEELNTAPV<br/>QESPPLAMPPGNSHGLEVGSLA<br/>EVKENPPFYGVIRWIGQPPGLN<br/>EVLAGLELEDECAGCTDGTFRG<br/>TRYFTCALKKALFVKLKSCRPD<br/>SRFASLQPVSNQIERCNSLAFG<br/>GYLSEVVEENTPPKMEKEGLEI<br/>MIGKKKGIQGHYNS<br/>CYLDSTLFLCLFAFSSVLDTVLL<br/>RPKEKNDVEYYSETQELLRTEI<br/>VNPLRIYGYVCATKIMKLRKIL<br/>EKVEAASGFTSEEKDPPEEFLNI<br/>LFHHILRVEPLLKIRSAGQKVQ<br/>DCYFYQIFMEKNEKVGVPITQQ<br/>LLEWSFINSNLKFAEAPSCLII<br/>QMPRFGKDFKLFKKIFPSLELN<br/>ITDLEDTPRQCRICGGLAMYE<br/>CRECYDDPDISAGKIKQFCKTC<br/>NTQVHLHPKRLNHKYNPVSLPK<br/>DLPDWDWRHGCIPCQNMELFAV<br/>LCIETSHYVAFVKYKDDSAWL<br/>FFDSMADRDRGGQNGFNIPQVTP<br/>CPEVGEYLMKSLEDLHSLDSRR<br/>IQGCARRLLCDAYMCMYQSPTM<br/>SLYK</p> |     | <p>PKDLPDWDWRHGCIPCQNME<br/>LFAVLCIETSHYVAFVKYK<br/>DDSAWLFFDSMADRDRGGQNG<br/>FNIPQVTPCPEVGEYLMKSL<br/>EDLHSLDSRRIQGCARRLLC<br/>DAYMCMYQSPT</p>                                                                                                                                                                                                                                                                                                                   |
| UBP16_HUMAN Ubiquitin carboxyl-terminal hydrolase 16 | 69 | <p>MGKKRTKGKTVPIDDSSETLEP<br/>VCRHIRKGLEQGNLKKALVNVE<br/>WNICQDCKTDNKVKDKAEETE<br/>EKPSVWLCLKCGHQGCGRNSQE<br/>QHALKHYLTTPRSEPHCLVLSLD<br/>NWSVWCYVCDNEVQYCSSNQLG<br/>QVVDYVRKQASITTPKPAEKDN<br/>GNIELENKKLEKESKNEQEREK<br/>KENMAKENPPMNSPCQITVKGL<br/>SNLGNTCFFNAVMQNLSQTPVL<br/>RELLKEVKMSGTIVKIEPPDLA<br/>LTEPLEINLEPPGPLTLAMSQF<br/>LNEMQETKKGVVTPKELFSQVC<br/>KKAVRFKGYQQQDS<br/>QELRLYLLDGMRAEEHQRVSKG<br/>ILKAFGNSTEKLDEELKNKVKD<br/>YEKKKSMPSFVDRIFGGELTSM<br/>IMCDQCRTVSLVHESFLDLSLP</p>                                                                                                                                                                                                                                                                                                                                                                                            | 180 | <p>ITVKGLSNLGNTCFFNAVMQ<br/>NLSQTPVLRELLKEVKMSGT<br/>IVKIEPPDLALTEPLEINLE<br/>PPGPLTLAMSQFLNEMQETK<br/>KGVVTPKELFSQVCKKAVRF<br/>KGYQQQDSQELRLYLLDGM<br/>AEEHQRVSKGILKAFGNSTE<br/>KLDEELKNKVKDYEKKKSMP<br/>SFVDRIFGGELTSMIMCDQC<br/>RTVSLVHESFLDLSLPVLDD<br/>QSGKKSVDNKNLKKTVDEDE<br/>QDSEEEKDND SYIKERSDIP<br/>SGTSKHLQKKAKKQAKKQAK<br/>NQRRQKIQGKVLHLNDICT<br/>IDHPEDSEYEAMSLQGEVN<br/>IKSNHISQEGVMHKEYCVNQ<br/>KDLNGQAKMIESVTDNQKST<br/>EEVDMKNINMDNDLEVLTS</p> |

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|                                                                                                                                              |    | <p>VLDDQSGKKS VNDKNL KKTVED<br/>EDQDSEEEKD NDSY I KERSDIP<br/>SGTSKHLQKKAKKQAKKQAKNQ<br/>RRQQKIQQKVLHLNDICTIDHP<br/>EDSEYEAEMSLQGEVNIKSNIH<br/>SQEGVMHKEYCVNQKDLNGQAK<br/>MIESVTDNQKSTEEVDMKNINM<br/>DNDLEVLTS SPTRNLNGAYLTE<br/>GSNGEVDISNGFKNLNLNAALH<br/>PDEINIEILNDSHT<br/>PGTKVYEVVNEDPETAFACTLAN<br/>REVNTDECSIQHCLYQFTRNE<br/>KLRDANKLLCEVCTRRQCNGPK<br/>ANIKGERKHVYTNAKKQMLISL<br/>APPVLT LHLKRFQQAGFNLRKV<br/>NKHIKFPEILDLAPFCTLKCKN<br/>VAEENTRVLYSLYGVVEHSGTM<br/>RSGHYTAYAKARTANSHLSNLV<br/>LHGDIPQDFEMESKGQWFHISD<br/>THVQAVPTTKVLNSQAYLLFYE<br/>RIL</p>                                                                                                                                                                                                                                                              |     | <p>PTRNLNGAYLTEGSNGEVDI<br/>SNGFKNLNLNAALHPDEINI<br/>EILNDSHTPGTKVYEVVNED<br/>PETAFACTLANREVNTDECS<br/>IQHCLYQFTRNEKLRDANKL<br/>LCEVCTRRQCNGPKANIKGE<br/>RKHVYTNAKKQMLISLAPPV<br/>LTLHLKRFQQAGFNLRKVNK<br/>HIKFPEIL<br/>DLAPFCTLKCKNVAEENTRV<br/>LYSLYGVVEHSGTMRS GHYT<br/>AYAKARTANSHLSNLVLHGD<br/>IPQDFEMESKGQWFHISDTH<br/>VQAVPTTKVLNSQAYLLFYE<br/>RIL</p>                     |
| <p>ALG13_HUM<br/>AN Putative<br/>bifunctional<br/>UDP-N-<br/>acetylglucosa<br/>mine<br/>transferase<br/>and<br/>deubiquitinase<br/>ALG13</p> | 70 | <p>MKCVFVTVGTTSFDDLIACVSA<br/>PDSLQKIESLGYNRLILQIGRG<br/>TVVPEPFSTESFTLDVYRYKDS<br/>LKEDIQKADLVISHAGAGSCLE<br/>TLEKGKPLVVVINEKLMNNHQL<br/>ELAKQLHKEGHLFYCTCRVLT<br/>PGQAKSIASAPGKCQDSAALTS<br/>TAFSGLDFGLLSGYLHKQALVT<br/>ATHPTCTLLFPSCHAFFPLPLT<br/>PTLYKMHKGWKNYCSQKSLNEA<br/>SMDEYLGSGLFRKLTAKDASC<br/>LFRAISEQLFCSQVHHLEIRKA<br/>CVSYMRENQQT FESYVEGSFEK<br/>YLERLGDPKESAGQ<br/>LEIRALSLIYNRDFILYRFP GK<br/>PPTYVTDNGYEDKILLCYSSSG<br/>HYDSVYSKQFQSSAAVCQAVLY<br/>EILYKDV FVVDEELKTAIKLF<br/>RSGSKKNRNNAV TGSEDAHTDY<br/>KSSNQNRMEEWGACYN AENIPE<br/>GYNKGTEETKSPENPSKMPFPY<br/>KVLKALDPEIYRNVEFDVWLDS<br/>RKELQKSDYMEYAGRQYYLGDK<br/>CQVCLESEGRYYNAHIQEVGNE<br/>NNSVTVFIEELAEKHVVPLANL<br/>KPVTQVMSVPAWNAMP SRKGRG<br/>YQKMPGGYVPEIIVISEMDIKQQ<br/>KKMFKKIRGKEVYM<br/>TMAYGKGDP LLP PRLQHSMHYG<br/>HDPPMHYSQTAGNVMSNEHFHP</p> | 181 | <p>YRYKDSLKEDIQKADLVISH<br/>AGAGSCLETLEKGKPLVVVI<br/>NEKLMNNHQL ELAKQLHKEG<br/>HLFYCTCRVLTCPGQAKSIA<br/>SAPGKCQDSAALTSTAFSGL<br/>DFGLLSGYLHKQALVTATHP<br/>TCTLLFPSCHAFFPLPLTPT<br/>LYKMHKGWKNYCSQKSLNEA<br/>SMDEYLGSGLFRKLTAKDA<br/>SCLFRAISEQLFCSQVHHLE<br/>IRKACVSYMRENQQT FESYV<br/>EGSFEKYLERLGDPKESAGQ<br/>LEIRALSLIYNRDFILYRFP<br/>GKPPTYVTDNGYEDKILLCY<br/>SSSGHYDSVYS</p> |



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|                                             |    | <p>QHPSPRQGRGYGMPRNSSRFIN<br/> RHNMPGPKVDFYPGPGKRCCQS<br/> YDNFSYRSRSFRRSHRQMSCVN<br/> KESQYGFTPGNGQMPRGLEETI<br/> TFYEVEEGDETAIPTLPNHGGP<br/> STMVPATSGYCVGRRGHSSGKQ<br/> TLNLEEGNGQSENGRYHEEYLY<br/> RAEPDYETSGVYSTTASTANLS<br/> LQDRKSCSMSPQDVTVTSYNYPQ<br/> KMMGNIAAVAASCANNVPAPVL<br/> SNGAAANQAISTTSVSSQNAIQ<br/> PLFVSPPTHGRPVI<br/> ASPSYPCHSAIPHAGASLPPPP<br/> PPPPPPPPPPPPPPPPPPPPPP<br/> PALDVGETSNLQPPPPPLPPPPY<br/> SCDPSGSDLPQDQTKVLQYYFNL<br/> GLQCYHSHYWHSMVYVPQMQQQ<br/> LHVENYPVYTEPPLVDQTVPQC<br/> YSEVRREDGIQAEASANDTFPN<br/> ADSSSVPHGAVYYPVMSDPYGQ<br/> PPLPGFDSCLPVVPDYSCVPPW<br/> HPVGTAYGGSSQIHGAINPGPI<br/> GCIAPSPASHYVPQGM</p> |     |                                                                                                                                                                                                                                                                                                                         |
| OTU1_HUMAN Ubiquitin thioesterase OTU1      | 71 | <p>MFGPAKGRHFGVHPAPGFPGGV<br/> SQQAAGTKAGPAGAWPVGSRTD<br/> TMWRLRCKAKDGTHVLQGLSSR<br/> TRVRELQGQIAAITGIAPGGQR<br/> ILVGYPPECLDLSNGDTILEDL<br/> PIQSGDMLIIIEEDQTRPRSSPA<br/> FTKRGAASSYVRETLPLVLRTRVV<br/> PADNSCLFTSVYVVEGGVNLN<br/> ACAPEMRRLIAQIVASDPDFYS<br/> EAILGKTNQEYCDWIKRDDTWG<br/> GAIEISILSKFYQCEICVVDQ<br/> TVRIDRFGEDAGYTKRVLLIYD<br/> GIHYDPLQRNFPDPDTPPLTIF<br/> SSNDDIVLVQALELADARRRR<br/> QFTDVNRFTLRMCVCQKGLTGQ<br/> AEAREHAKETGHTNFGEV</p>                                                                                                                                                                                              | 182 | <p>QGLSSRTRVRELQGQIAAIT<br/> GIAPGGQRILVGYPPECLDL<br/> SNGDTILEDLPIQSGDMLII<br/> EEDQTRPRSSPAFTKRGAASS<br/> YVRETLPLVLRTRVVPADNSC<br/> LFTSVYVVEGGVNLNACAP<br/> EMRRLIAQIVASDPDFYSEA<br/> ILGKTNQEYCDWIKRDDTWG<br/> GAIEISILSKFYQCEICVVD<br/> TQTVRIDRFGEDAGYTKRVL<br/> LIYDGIHYDPLQ</p>                                |
| OTUD1_HUMAN OTU domain-containing protein 1 | 72 | <p>MQLYSSVCTHYPAGAPGPTAAA<br/> PAPPAAATPFKVSLQPPGAAGA<br/> APEPETGECQAAAAEHREAAA<br/> VPAAKMPAFSSCFEVVSGAAAP<br/> ASAAAGPPGASCKPPLPPHYTS<br/> TAQITVRALGADRLLHGPDPV<br/> PGAAGSAAAPRGRCLLLAPAPA<br/> APVPPRRGSSAWLLEELLRPDC<br/> PEPAGLDATREGPDNRNRLSEH<br/> RQALAAAKHRGPAATPGSPDPG<br/> PGPWGEEHLAERGPRGWERGGD<br/> RCDAPGGDAARRPDPEAEAPPA</p>                                                                                                                                                                                                                                                                                                            | 183 | <p>HREAAVPAAKMPAFSSCFE<br/> VVSGAAAPASAAAGPPGASC<br/> KPPLPPHYTSTAQITVRALG<br/> ADRLLHGPDPVPGAAGSAA<br/> APRGRCLLLAPAPAAPVPPR<br/> RGSSAWLLEELLRPDCPEPA<br/> GLDATREGPDNRNRLSEHRQ<br/> ALAAAKHRGPAATPGSPDPG<br/> PGPWGEEHLAERGPRGWERG<br/> GDRCDAPGGDAARRPDPEAE<br/> APPAGSIEAAPSSAAEPVIV<br/> SRSDPRDEKLALYLAEVEKQ</p> |

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|                                              |    | GSIEAAPSSAAEPVIVSRSDPR<br>DEKLALYLAEVEKQ<br>DKYLRQRNKYRFHIIIPDGNCLY<br>RAVSKTVYGDQSLHRELREQTV<br>HYIADHLDHFSPLIEGDVGEFI<br>IAAAQDGAWAGYPELLAMGQML<br>NVNIHLTTGGRLESPTVSTMIH<br>YLGPEDSLRLPSIWLSWLSNGHY<br>DAVFDHSYPNPEYDNWCKQTQV<br>QRKRDEELAKSMAISLSKMYIE<br>QNACS                                                                                     |     | DKYLRQRNKYRFHIIIPDGNCLY<br>RAVSKTVYGDQSLHRELREQTV<br>HYIADHLDHFSPLIEGDVGEFI<br>IAAAQDGAWAGYPELLAMGQML<br>NVNIHLTTGGRLESPTVSTMIH<br>YLGPEDSLRLPSIWLSWLSNGHY<br>DAVFDHSYPNPEYDNWCKQTQV<br>QRKRDEELAKSMAISLSKMYIE<br>QNACS                                                                 |
| OTU6B_HUMAN<br>Deubiquitinase OTUD6B         | 73 | MEAVLTEELDEEEQLLRHRKE<br>KKELQAKIQGMKNVAPKNDKKR<br>RKQLTEDVAKLEKEMEOKHREE<br>LEQLKLTTKENKIDSVAVNISN<br>LVLENQPPRISKAQKRREKKAA<br>LEKEREERIAEAEIENLTGARH<br>MESEKLAQILAAARQLEIKQIPS<br>DGHCMYKAIEDQLKEKDCALTV<br>VALRSQTAEYMQSHVEDFLPFL<br>TNPNTGDMYTPEEFQKYCEDIV<br>NTAAWGGQLELRALSHILQTPI<br>EIIQADSPPIIVGEEYSKKPLI<br>LVYMRHAYGLGEHYNVTRLVN<br>IVTENC | 184 | QKHREELEQLKLTTKENKID<br>SVAVNISNLVLENQPPRISK<br>AQKRREKKAALEREERIEA<br>EAEIENLTGARHMESEKLAQ<br>ILAAARQLEIKQIPSDGHCMY<br>KAIEDQLKEKDCALTVVALR<br>SQTAEYMQSHVEDFLPFLTN<br>PNTGDMYTPEEFQKYCEDIV<br>NTAAWGGQLELRALSHILQT<br>PIEIIQADSPPIIVGEEYSK<br>KPLILVYMRHAYG                           |
| OTU6A_HUMAN OTU domain-containing protein 6A | 74 | MDDPKSEQQRILRRHQERQEL<br>QAQIRSLKNSVPKTDKTKRKQL<br>LQDVARMEAEMAQKHRQELEKF<br>QDDSSIESVVEDLAKMNLENRP<br>PRSSKAHRKRERMESEERERQE<br>SIFQAEMSEHLAGFKREEEEKL<br>AAILGARGLEMKAIPADGHCMY<br>RAIQDQLVFSVSVEMLRCRTAS<br>YMKKHVDEFLPFFSNPETSDFS<br>GYDDFMIYCDNIVRTTAWGGQL<br>ELRALSHVLKTPIEVIQADSPT<br>LIIGEEYVKKPIILVYLRYAYS<br>LGEHYNVTPLEAGAAGGVLPRL           | 185 | QELEKFQDDSSIESVVEDLA<br>KMNLENRPPRSSKAHRKRER<br>MESEERERQESIFQAEMSEH<br>LAGFKREEEEKLAAILGARG<br>LEMKAIPADGHCMYRAIQDQ<br>LVFSVSVEMLRCRTASYMKK<br>HVDEFLPFFSNPETSDFSFGY<br>DDFMIYCDNIVRTTAWGGQL<br>ELRALSHVLKTPIEVIQADS<br>PTLIIGEEYVKKPIILVYLRYAYS                                       |
| OTUB1_HUMAN<br>Ubiquitin thioesterase OTUB1  | 75 | MAAEEPQQQKQEPLGSDSEGVN<br>CLAYDEAIMAQDRIQQEIAVQ<br>NPLVSRLELSVLYKEYAEDDN<br>IYQQKIKDLHKKYSYIRKTRPD<br>GNCFYRAFGFSLHLEALLDDSK<br>LQRFKAVSAKSKEDLVSQGFTE<br>FTIEDFHNTFMDLIEQVEKQTS<br>VADLLASFNDQSTSDYLVVYLR<br>LLTSGYLQRESKFFEHFIEGGR<br>TVKEFCQQEVEPMCKESDHIHI<br>IALAQALSVS IQVEYMDRGE                                                                 | 75  | MAAEEPQQQKQEPLGSDSEGVN<br>CLAYDEAIMAQDRIQQEIAVQ<br>NPLVSRLELSVLYKEYAEDDN<br>IYQQKIKDLHKKYSYIRKTRPD<br>GNCFYRAFGFSLHLEALLDDSK<br>LQRFKAVSAKSKEDLVSQGFTE<br>FTIEDFHNTFMDLIEQVEKQTS<br>VADLLASFNDQSTSDYLVVYLR<br>LLTSGYLQRESKFFEHFIEGGR<br>TVKEFCQQEVEPMCKESDHIHI<br>IALAQALSVS IQVEYMDRGE |

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|                                                            |    | TTNPHFPEGSEPKVYLLYRPG<br>HYDILYK                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |     | GGTTNPHFPEGSEPKVYLL<br>YRPGHYDILYK                                                                                                                                                                                                                                                                                                                                               |
| OTU7A_HU<br>MAN OTU<br>domain-<br>containing<br>protein 7A | 76 | MVSSVLPNPTSAECWAALLHDP<br>MTLDMDAVLSDFVRSTGAEPGL<br>ARDLLEGKNWDLTAALSDYEQL<br>RQVHTANLPHVFNEGRGPKQPE<br>REPQPGHKVERPCLQRQDDIAQ<br>EKRLSRGISHASSAIVSLARSH<br>VASECNNEQFPLEMPIYTFQLP<br>DLSVYSEDFRSFIERDLIEQAT<br>MVALEQAGRLNWWSTVCTSCKR<br>LLPLATTGDGNCLLHAASLGMW<br>GFHDRDLVLRKALYTMMRTGAE<br>REALKRRWRWQQTQQNKEEWE<br>REWTELLKLASSEPRTHFSKNG<br>GTGGGVDSNSEDVY<br>ESLEEFHVFLAHILRRPIVVV<br>ADTMLRDSGGEAFAPIPFGGIY<br>LPLEVPPNRCHCSPLVLAYDQA<br>HFSALVSMEQRDQQREQAVIPL<br>TDSEHKLLPLHFAVDPGKDWEW<br>GKDDNDNARLAHLILSLEAKLN<br>LLHSYMNVTWIRIPSETRAPLA<br>QPESPTASAGEDVQSLADSLDS<br>DRDSVCSNSNSNNGKNGKDEK<br>EKQRKEKDKTRADSVANKLGSF<br>SKTLGIKLKKNMGGGLVHGK<br>MGRANSANGKNGDSAERGKEKK<br>AKSRKGSKEESGASASTSPSEK<br>TTPSPTDKAAGASP<br>AEKGGGPRGDAWKYSTDVKLSL<br>NILRAAMQGERKFI FAGLLTS<br>HRHQFHEEMIGYYLTSAQERFS<br>AEQEQRRRDAATAAAAAAAAAA<br>ATAKRPPRRPETEGVPVPERAS<br>PGPPTQLVLKLERPSPGPAAG<br>RAARAAAGGTASPGGGARRASA<br>SGPVPGRSPPAPARQSVIHVQA<br>SGARDEACAPAVGALRPCATYP<br>QQNRSLSSQSYSPARAAALRTV<br>NTVESLARAVPGALPGAAGTAG<br>AAEHKSQTYTNGFGALRDGLEF<br>ADADAPTARSNGECGRGGPGPV<br>QRRQCRENCAFYGRAETEHYCS<br>YCYREELRRRREARGARP | 186 | SDYEQLRQVHTANLPHVFNE<br>GRGPKQPEREPQPGHKVERP<br>CLQRQDDIAQEKRLSRGISH<br>ASSAIVSLARSHVASECNNE<br>QFPLEMPIYTFQLPDLVYS<br>EDFRSFIERDLIEQATMVAL<br>EQAGRLNWWSTVCTSCKRLL<br>PLATTGDGNCLLHAASLGMW<br>GFHDRDLVLRKALYTMMRTG<br>AEREALKRRWRWQQTQQNKE<br>EEWEREWTELLKLASSEPR<br>HFSKNGGTGGGVDSNSEDVY<br>ESLEEFHVFLAHILRRPIV<br>VVADTMLRDSGGEAFAPIPF<br>GGIYLPLEVPPNRCHCSPLV<br>LAYDQAHFSAL |
| OTUD4_HU<br>MAN OTU<br>domain-<br>containing<br>protein 4  | 77 | MEAAVGVPDGGDQGGAGPREDA<br>TPMDAYLRKLGLYRKLVAKDGS<br>CLFRAVAEQVLHSQSRHVEVRM<br>ACIHYLRENREKFEAFIEGSFE<br>EYLKRLNPQEWVGQVEISALS<br>LMYRKDFI IYREPNVSPSQVTE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 187 | MEAAVGVPDGGDQGGAGPRE<br>DATPMDAYLRKLGLYRKLVA<br>KDGSCLFRAVAEQVLHSQSR<br>HVEVRMACIHYLRENREKFE<br>AFIEGSFEEYLRLENPQEW<br>VGQVEISALS LMYRKDFI IY                                                                                                                                                                                                                                    |

|                                                   |    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |                                                                                                                                       |
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|                                                   |    | <p>NNFPEKVL LCF SNGNHYDIVP<br/> IKYKESSAMCQSLLYELLYEKV<br/> FKTDVSKI VMELDTLEVADEDN<br/> SEISDSEDDSCSKTAAAAADV<br/> NGFKPLSGNEQLKNNGNSTSLP<br/> LSRKVLKSLNPAVYRNVEYEIW<br/> LKSKQAQQKRDYSIAAGLQYEV<br/> GDKCQVRLDHNGKF<br/> LNADVQGIHSENGPVLVEELGK<br/> KHTSKNLKAPPPESWNTVSGKK<br/> MKKPSTSGQNFHSDVDYRGPKN<br/> PSKPIKAPSALPPRLQHPSGVR<br/> QHAFSSHSSGSQSQKFSSEHKN<br/> LSRTPSQIIRKPDRERVEDFDH<br/> TSRESNYFGLSPEERREKQAIE<br/> ESRLLYEIQNRDEQAFPALSSS<br/> SVNQ SASQSSNPCVQRKSSHVG<br/> DRKGSRRRMDTEERKDKDSIHG<br/> HSQLDKRPEPSTLENITDDKYA<br/> TVSSPSKSKKLECPSPAEQKPA<br/> EHVSLSNPAPLLVSPEVHLTPA<br/> VPSLPATVPAWPSE<br/> PTTFGPTGVPAPIPVLSVTQTL<br/> TTGPDSAVSQAHLTPSPVPVSI<br/> QAVNQPLMPLPQTL SLYQDPLY<br/> PGFPCNEKGDRAIVPPYSLCQT<br/> GEDLPKDKNILRFFFN LGVKAY<br/> SCPMWAPHSYLYPLHQAYLAAC<br/> RMYPKVPVPVYPHNPWFQEAPA<br/> AQNESDCTCTDAHFPMT EASV<br/> NGQMPQPEIGPPTFSSPLVIP<br/> SQVSESHGQLSYQADLESETPG<br/> QLLHADYEESLSGKNMFPQSFG<br/> PNPFLGPVPIAPFFPHVWYGY<br/> PFQGF IENPVMRQNI VLP SDEK<br/> GELDLSLENLDLS<br/> KDCGSVSTVDEFPEAR GEHVHS<br/> LPEASVSSKPDEGRTEQSSQTR<br/> KADTALASIPPVAEGKAHPPTQ<br/> ILNRERETVPVELEPKRTIQSL<br/> KEKTEKV KDPKTAADV VSPGAN<br/> SVDSRVQRPKEESSEDENEVSN<br/> ILRSGRSKQFYNQTYGSRKYKS<br/> DWGYSGRGGYQHVRSEESWKQ<br/> PSRSRDEGYQYHRNVRGRPF RG<br/> DRRRSGMGDGH RGQHT</p> |    | <p>REPNVSPSQVTENN FPEKVL<br/> LCF SNGNHYDIVP</p>                                                                                      |
| OTUB2_HUMAN<br>Ubiquitin<br>thioesterase<br>OTUB2 | 78 | <p>MSETSFNLI SEKCDILSILRDH<br/> PENRIYRRKIEELSKRFTAIRK<br/> TKGDGNCFYRALGYSY LESLLG<br/> KSREIFKFKERVLTQTPNDLLAA<br/> GFEHKFRNFNAFYSVVELVE</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 78 | <p>MSETSFNLI SEKCDILSILR<br/> DHPENRIYRRKIEELSKRFT<br/> AIRKTKGDGNCFYRALGYSY<br/> LESLLGKSREIFKFKERVLTQ<br/> TPNDLLAAGFEHKFRNFNFN</p> |

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|                                                                                   |    | KDGSVSSLLKVFNDQSASDHIV<br>QFLRLLTSAFIRNRADFFRHF<br>DEEMDIKDFCTHEVEPMATECD<br>HIQITALSQALSIALQVEYVDE<br>MDTALNHHVFPEAATPSVYLLY<br>KTSHYNILYAADKH                                                                                                                                                                                                                                                                                                                                      |     | AFYSVVELVEKDGSVSSLLK<br>VFNDQSASDHIVQFLRLLTS<br>AFIRNRADFFRHFIDEEMDI<br>KDFCTHEVEPMATECDHIQI<br>TALSQALSIALQVEYVDEMD<br>TALNHHVFPEAATPSVYLLY<br>KTSHYNILYAADKH                                                                                                                                                                                                                                                                                        |
| OTUD3_HUMAN OTU domain-containing protein 3                                       | 79 | MSRKQAAKSRPGSGSRKAEAE<br>KRDERAARRALAKERRNRPE<br>SGGGGCEEEFVSFANQLQALGL<br>KLREVPDGNCLFRALGDQLEGH<br>SRNHLKHRQETVDYMIKQREDF<br>EPFVEDDIPFEKHVASLAKPGT<br>FAGNDAIVAFARNHQLNVVIHQ<br>LNAPLWQIRGTEKSSVRELHIA<br>YRYGEHYDSVRRINDNSEAPAH<br>LQTDQFQMLHQDESNKREKIKTK<br>GMDSEDDLRLDEVEDAVQKVCNA<br>TGCSDFNLIQVQNEAENYNIES<br>AIIAVLRMNQGKRNNAEENLEP<br>SGRVLKQCGPLWEE<br>GGSGARIFGNQGLNEGRTENNK<br>AQASPSEENKANKNQLAKVTNK<br>QRREQQWMEKKKRQEERHRHKA<br>LESRGSHRDNNRSEAEANTQVT<br>LVKTFALNI | 188 | MSRKQAAKSRPGSGSRKAEAE<br>ERKRDERAARRALAKERRNR<br>PESGGGGGCEEEFVSFANQL<br>QALGLKLREVPDGNCLFRA<br>LGDQLEGHSRNHLKHRQETV<br>DYMIKQREDFEPFVEDDIPF<br>EKHVASLAKPGTFAGNDAIV<br>AFARNHQLNVVIHQNLAPLW<br>QIRGTEKSSVRELHIAIRYGE<br>HYDSVRR                                                                                                                                                                                                                      |
| OTU7B_HUMAN OTU domain-containing protein 7B (Also referred to herein as Cezanne) | 80 | MTLDMDAVLSDVFVRSTGAEPGL<br>ARDLLEGKNWDVNAALSDFEQL<br>RQVHAGNLPPSFSESGGSRT<br>PEKGFSDREPTRPPRPILQRQDD<br>IVQEKRLSRGISHASSIVSLA<br>RSHVSSNGGGGGSNEHPLEMPI<br>CAFQLPDLTVYNEDFRSFIERD<br>LIEQSMVLVALEQAGRLNWWVSV<br>DPTSQRLLPLATTGDGNCLLHA<br>ASLGMWGFHDRDLMLRKALYAL<br>MEKGVEKEALKRRWRWQQQTQ<br>QNKESGLVYTEDEWQKEWNE<br>LIKLASSEPRMHLGTNGANC<br>GGVESSEEPVYESLEEFHVF<br>VLAHVLRRLPIVVVADTMLRD<br>SGGEAFAPIPFGGIYLPLEV<br>PASQCHRSPVLVLAHQHFS<br>AL                                      | 189 | MTLDMDAVLSDVFVRSTGAEP<br>GLARDLLEGKNWDVNAALSD<br>FEQLRQVHAGNLPPSFSEGS<br>SGSRTPEKGFSDREPTRPPR<br>PILQRQDDIVQEKRLSRGIS<br>HASSIVSLARSHVSSNGGG<br>GSNEHPLEMPICAFQLPDL<br>TVYNEDFRSFIERDLIEQSM<br>VLVALEQAGRLNWWVSVDP<br>TSPQRLLPLATTGDGNCLLHA<br>ASLGMWGFHDRDLMLRKALY<br>ALMEKGVEKEALKRRWRWQQ<br>QTQQNKESGLVYTEDEWQKE<br>WNELIKLASSEPRMHLGTNG<br>ANC GGVESSEEPVYESLEEF<br>HVFVLAHVLRRLPIVVVADT<br>MLRDSGGEAFAPIPFGGIYL<br>PLEVPASQCHRSPVLVLAHQ<br>HFSAL |
|                                                                                   |    | EVKLHLLHSYMNVKWIPLSSDA<br>QAPLAQPESPTASAGDEPRSTP<br>ESGSDKESVGSSTSNEGGRR<br>KEKSKRDREKDKKRADSVANKL<br>GSFGKTLGSKLKNMGGLMHSK<br>GSKPGGVGTGLGGSSGTETLEK                                                                                                                                                                                                                                                                                                                                | 286 | PPSFSESGGSRTPEKGFSD<br>REPTRPPRPILQRQDDIVQE<br>KRLSRGISHASSIVSLARS<br>HVSSNGGGGGSNEHPLEMPI<br>CAFQLPDLTVYNEDFRSFIE<br>RDLIEQSMVLVALEQAGRLN                                                                                                                                                                                                                                                                                                            |

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|                                                                        |    | KKKNSLKSWKGGKEEAAGDGPV<br>SEKPPAESVGNNGSKYSQEV MQ<br>SLSILRTAMQGEGKFI FVGTLK<br>MGHRHQYQEEMI QRYLSDAEER<br>FLAEQKQKEAERKIMNGGIGGG<br>PPPAKKPEPDAREEQPTGPPAE<br>SRAMAFSTGY PGDFTI PRPSGG<br>GVHCQEPRRQLAGGPCVGG LPP<br>YATFPRQC PPGRPY PHQDSIPS<br>LEPGSHSKDGLHRGALLPPPYR<br>VADSY SNGYREPP EPDGWAGGL<br>RGLPPTQTCKKQPNCSFYGHPE<br>TNNFCSCCYREELRRRERE PDG<br>ELLVHRF                                                                                                                                                                                                                                                                                                                                      |     | WVSVDPTSQRLLPLATTGDG<br>NCLLHAASLGMWGFHDRDLM<br>LRKALYALMEKGVEKEALKR<br>RWRWQQTQQNKESGLVYTED<br>EWQKEWNELIKLASSEPRMH<br>LGTNGANCGGVESEEPVYE<br>SLEEFHV FVLAHVLR RPIVV<br>VADTMLRDSGGEAFAPI PFG<br>GIYLPLEVPASQCHR SPLVL<br>AYDQAHFSALVSMEQKENTK<br>EQAVIPLTDSEYKLLPLHFA<br>VDPGKGWEWGKDDSDNVRLA<br>SVILSLEVKLHLLHSYMN VK<br>WIPLSSDAQAPLAQ                                                                             |
| OTUD5_HU<br>MAN OTU<br>domain-<br>containing<br>protein 5              | 81 | MTILPKKKPPPPDADPANEP PP<br>PGPMPPAPRRGGGVGVGGGTG<br>VGGGDRDRDSGVVGARPRASPP<br>PQG PLPGPPGALHRWALAVPPG<br>AVAGPRPQQASPPPCGGPGGP<br>GGPGDALGAAAAGVGAAGVVVG<br>VGGAVGVGGCCSGPGH SKRRRQ<br>APGVGAVGGGSPERE EVGAGYN<br>SEDEYEAAAARIEAMDPATVEQ<br>QEHWF EKALRDKKGFII KQMK<br>DGACLFRAVADQVYGDQDMHEV<br>VRKHCM DYLMKNADYFSNYVTE<br>DFTTYINRKRKNNCHGNHIEMQ<br>AMAEMYNRPVEVYQ<br>YSTGTSAVEPINTFHGIHQNE<br>EPIRVSYHRNIHNSV VNP NKA<br>TIGVGLGLPSFKPGFAEQSLMK<br>NAIKTSEESWIEQQMLEDKKRA<br>TDWEATNEAIEEQVARES YLQW<br>LRDQEKQARQVRGPSQPRKASA<br>TCSSATAAASSGLEEWTSRSPR<br>QRSSASSPEHP ELHAELGMKPP<br>SPGTVLALAKPPSPCAPGTSSQ<br>FSAGADRATSPLVSLYPALECR<br>ALIQQMSPSAFGLNDWDDDEIL<br>ASVLAVSQQEYLD SMKKNKVHR<br>DPPPKS | 190 | MTILPKKKPPPPDADPANEP<br>PPPGPMPPAPRRGGGVGVGG<br>GGTGVGGGDRDRDSGVVGAR<br>PRASPPPGPLPGPPGALHR<br>WALAVPPGAVAGPRPQQASP<br>PPCGGPGGPGGGPGDALGAA<br>AAGVGAAGVVVG VGGAVGVG<br>GCCSGPGH SKRRRQAPGVGA<br>VGGGSPERE EVGAGYNSEDE<br>YEAAAARIEAMDPATVEQQE<br>HWF EKALRDKKGFII KQMK<br>DGACLFRAVADQVYGDQDMH<br>EVVRKHCM DYLMKNADYFSN<br>YVTE DFTTYINRKRKNNCHG<br>NHIEMQAMAEMYNRPVEVYQ<br>YSTGTSAVEPINTFHGIHQN<br>EDEPIRVSYHRNIHNSV |
| TNAP3_HUM<br>AN Tumor<br>necrosis factor<br>alpha-induced<br>protein 3 | 82 | MAEQVLPQALYLSNMRKAVKIR<br>ERTPEDI FKPTNGIIHHEKTMH<br>RYTLEMFR TCQFCPQFREIIHK<br>ALIDRNIQATLESQKKLNWCRE<br>VRKLVALKTNGDGNCLMHATSQ<br>YMWGVQD TDLVLRKALFSTLKE<br>TDTRNFKFRWQLESLSQEFVE<br>TGLCYDTRNWNDEWDNL IKMAS<br>TDTPMARSGLQYNSLEEIHIFV<br>LCNILRRPIIIVISDKMLRSLES                                                                                                                                                                                                                                                                                                                                                                                                                                      | 191 | MAEQVLPQALYLSNMRKAVK<br>IRERTPEDI FKPTNGIIHHE<br>KTMHRYTLEMFR TCQFCPQF<br>REIIHKALIDRNIQATLESQ<br>KKLNWCREVRKLVALKTNGD<br>GNCLMHATSQYMWGVQD TDL<br>VLRKALFSTLKETDTRNFKF<br>RWQLESLSQEFVETGLCYD<br>TRNWNDEWDNL IKMASTDP<br>MARSGLQYNSLEEIHIFVLC                                                                                                                                                                         |

|                                                              |    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
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|                                                              |    | <p>GSNFAPLKVGGIYLPLHWP AQE<br/>CYRYP IVLGYDSHHFVPLVTLK<br/>DSGPEIRAVPLVNRDRGRFEDL<br/>KVHFLTDPENEMKE<br/>KLLKEYLMVIEIPVQGDHGT<br/>HLINAAKLDEANLPKEINLVDD<br/>YFELVQHEYKKWQENSEQGRRE<br/>GHAQNPMEPSVPQLSLMDVKCE<br/>TPNCPFFMSVNTQPLCHECSE<br/>RQKNQNKLPKLNSKPGPEGLPG<br/>MALGASRGEAYEPLAWNPEEST<br/>GGPHSAPPTAPSPFLFSETTAM<br/>KCRSPGCPFTLNQHNNGFCERC<br/>HNARQLHASHAPDHRHLDPGK<br/>CQACLQDVTRTFNGICSTCFKR<br/>TTAEASSSLSTSLPPSCHQRSK<br/>SDPSRLVRSPSPHSCHRAGNDA<br/>PAGCLSQAARTPGD<br/>RTGT SKCRKAGCVYFGTPENKG<br/>FCTLCFIEYRENKHFAAASGKV<br/>SPTASRFQNTIPCLGRECGTLG<br/>STMFEGYCQKCFIEAQNR FHE<br/>AKRTEEQLRSSQRRDVPRTTQS<br/>TSRPKCARASCKNILACRSEEL<br/>CMECQHPNQRMGPGAHRGEPAP<br/>EDPPKQRCRAPACDHFNGNAKCN<br/>GYCNECFQFKQMYG</p> |     | <p>NILRRPIIVISDKMLRSLES<br/>GSNFAPLKVGGIYLPLHWP AQE<br/>QECYRYP IVLGYDSHHFVPL</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <p>ZRAN1_HUMAN<br/>Ubiquitin<br/>thioesterase<br/>ZRANB1</p> | 83 | <p>MSEGIKWACEYCTYENWPSAI<br/>KCTMCRAQRPSGTIITEDPFKS<br/>GSSDVGRDWDPSSTEGGSSPLI<br/>CPDSSARPRVKSSYSMENANKW<br/>SCHMCTYLNWPRAIRCTQCLSQ<br/>RRTRSPTESPQSSGSGSRP VAF<br/>SVDPC EEYNDRNKLNTRTQHWT<br/>CSVCTYENWAKAKRCVVC DHP<br/>PNNIEAIELAETEEASSIINEQ<br/>DRARWRGSCSSGNSQRRSP PAT<br/>KRDSEVKMDFQRIELAGAVGSK<br/>EELEVDFKKLKQIKNRMKKT DW<br/>LFLNACVG VVEGDLAAIEAYKS<br/>SGGDIARQLTADEV<br/>RLLNRPSAFDVGYTLVHLAIRF<br/>QRQDMLAILL TEVSQQAACIP<br/>AMVCP ELTEQIRREIAASLHQR<br/>KGDFACYFLTDLVTFTLPADIE<br/>DLPPTVQEKLFDEVLDRDVQKE<br/>LEEESPIINWSLELATRLDSRL<br/>YALWNRTAGDCLLDSVLQATWG<br/>IYDKDSVLRKALHDSLHDCSHW<br/>FYTRWKDWESWYSQS FGLHFSL<br/>REEQWQEDWAFILSLASQPGAS</p>                                                            | 192 | <p>MSEGIKWACEYCTYENWPS<br/>AIKCTMCRAQRPSGTIITED<br/>PFKSGSSDVGRDWDPSSTEG<br/>GSSPLICPDSSARPRVKSSY<br/>SMENANKWSCHMCTYLNWPR<br/>AIRCTQCLSQRRTSPTESP<br/>QSSGSGSRP VAFSVDPC EEY<br/>NDRNKLNTRTQHWTCSVCTY<br/>ENWAKAKRCVVC DHPNPN<br/>EAEI LAETEEASSIINEQDR<br/>ARWRGSCSSGNSQRRSP PAT<br/>KRDSEVKMDFQRIELAGAVG<br/>SKEELEVDFKKLKQIKNRMK<br/>KTDWLFLNACVG VVEGDLAA<br/>IEAYKSSGGDIARQLTADEV<br/>RLLNRPSAFDVGYTLVHLAI<br/>RFQRQDMLAILL TEVSQQA<br/>KCIPAMVCP ELTEQIRREIA<br/>ASLHQRKGDFACYFLTDLVT<br/>FTLPADIEDLPPTVQEKLF<br/>EVLDRDVQKELEEESPIINW<br/>SLELATRLDSRLYALWNRTA<br/>GDCLLDSVLQATWGIYDKDS<br/>VLRKALHDSLHDCSHWFYTR</p> |

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|                                                    |    | LEQTHIFVLAHILRRPIIVYGV<br>KYYKSFRGETLGYTRFQGVYLP<br>LLWEQSFQWKSPIALGYTRGHF<br>SALVAMENDGYGNR<br>GAGANLNTDDDTITFLPLVDS<br>ERKLLHVHFLSAQELGNEEQQE<br>KLLREWLDCCVTEGGVLVAMQK<br>SSRRRNHPLVTQMVEKWLDYR<br>QIRPCTSLSDGEDEDEDE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |     | WKDWESWYSQSFGHLHFSLRE<br>EQWQEDWAFILSLASQPGAS<br>LEQTHIFVLAHILRRPIIVY<br>GVKYYKSFRGETLGYTRFQG<br>VYLPLLWEQSFQWKSPIALG<br>YTRGHFSAL                                                                                                                                                                                                                                |
| VCIP1_HUMAN<br>Deubiquitinating protein<br>VCIP135 | 84 | MSQPPPPPPPLPPPPPPPEAPQ<br>TPSSLASAAASGGLLKRRDRRI<br>LSGSCPDPKCQARLFFPASGSV<br>SIECTECGQRHEQQQLLGVEEV<br>TDPDVVLHNLRLNALLGVTGAP<br>KKNTLVKVMGLSNYHCKLLSP<br>ILARYGMDKQTGRAKLLRDMNQ<br>GELFDCALLGDRAFLIEPEHVN<br>TVGYGKDRSGSLLYLHDTLEDI<br>KRANKSQECLIPVHVDGDGHCL<br>VHAVSRALVGRELFWHALRENL<br>KQHFQQHLARYQALFHDFIDAA<br>EWEDIINECDPLFVPPEGVPLG<br>LRNIHIFGLANVLH<br>RPIILLDSLSGMRSSGDYSATF<br>LPGLIPAEKCTGKDGHLNKPIC<br>IAWSSSGRNHYIPLVGKGAAL<br>PKLPMNLLPKAWGVPQDLIKKY<br>IKLEEDGGCVIGGDRSLQDKYL<br>LRLVAAMEEVFMDKHGIHPSLV<br>ADVHQYFYRRTGVIQVQPEEVT<br>AAAKKAVMDNRLHKCLLCGALS<br>ELHVPPEWLAPEGKLYNLAKST<br>HGQLRTDKNYSFPLNNLVCSYD<br>SVKDVLPDYGMSNLTACNWCH<br>GTSVRKVRGDGSIVYLDGDRTN<br>SRSTGGKCGCGFKHFDGKEYD<br>NLPEAFPITLEWGG<br>RVVRETVYWFQYESDSSLNSNV<br>YDVAMKLVTKHFPGEFGSEILV<br>QKVVHTILHQTAKNPDDYTPV<br>NIDGAHAQRVGDVQGQESQSL<br>PTKIILTQKTKTLHKEELNMS<br>KTERTIQQNITEQASVMQKRKT<br>EKLKQEQKGQPRTVSPSTIRDG<br>PSSAPATPTKAPYSPTTSKEKK<br>IRITTNDGRQSMVTLKSSTTFF<br>ELQESIAREFNIPPYLQCIYRG<br>FPPKELMPPQAGMEKEPVPLQH<br>GDRITIEILKSKAEGGQSAAAH<br>SAHTVKQEDIAVTGKLSSKELQ<br>EQAEKEMYSLCLLA | 193 | PASGSVSIECTECGQRHEQQ<br>QLLGVEEVTDPDVVLHNLRL<br>NALLGVTGAPKKNTLVKVM<br>GLSNYHCKLLSPILARYGMD<br>KQTGRAKLLRDMNQGELFDC<br>ALLGDRAFLIEPEHVNTVGY<br>GKDRSGSLLYLHDTLEDIKR<br>ANKSQECLIPVHVDGDGHCL<br>VHAVSRALVGRELFWHALRE<br>NLKQHFQQHLARYQALFHDF<br>IDAAEWEDIINECDPLFVPP<br>EGVPLGLRNIHIFGLANVLH<br>RPIILLDSLSGMRSSGDYSA<br>TFLPGLIPAEKCTGKDGHLN<br>KPICIAWSSSGRNHYIPL |



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|                                                                                                                                                                                                     |    | <p>             TLMGEDVWSYAKGLPHMFQQGG<br/>             VFYSIMKKTMGMDGKHCTFPH<br/>             LPGKTFVYNASEDRLELCVDAA<br/>             GHFPIGPDVEDLVKEAVSQVRA<br/>             EATTRSRESSPSHGLLLKLGSGG<br/>             VVKKKSEQLHNVTAFQKGHSL<br/>             GTASGNPHLDPRARETSVVRKH<br/>             NTGTDFSNSSTKTEPSVFTASS<br/>             SSELIRIAPGVVTMRDGRQLD<br/>             PDLVEAQRKKLQEMVSSIQASM<br/>             DRHLRDQSTEQSPSDLPQRKTE<br/>             VVSSSAKSGSLQTGLPESFPLT<br/>             GGTEENLNTETTDGCVADALGAA<br/>             FATRSKAQRGNSVEELEEMDSQ<br/>             DAEMTNTTEPMDHS           </p> |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <p>             UCHL3_HU<br/>             MAN<br/>             Ubiquitin<br/>             carboxyl-<br/>             terminal<br/>             hydrolase<br/>             isozyme L3           </p> | 85 | <p>             MEGQRWLPLEANPEVTNQFLKQ<br/>             LGLHPNWQFVDVYGMPELLSM<br/>             VPRPVCVALLLPITEKEYEVR<br/>             TEEEEIKISQGGQDVTSSVYFMK<br/>             QTISNACGTIGLIHAIANNKDK<br/>             MHFESGSTLKKFLEESVSMSP<br/>             ERARYLENYDAIRVTHETSAHE<br/>             GQTEAPSIDEKVDLHFIALVHV<br/>             DGHLYELDGRKFPFINHGETSD<br/>             ETLLDAIEVCKKFMERDPDEL<br/>             RFNAIALSAA           </p>                                                                                                                                                                       | 194 | <p>             QRWLPLEANPEVTNQFLKQL<br/>             GLHPNWQFVDVYGMPELLS<br/>             MVRPVCVALLLPITEKEYE<br/>             VFRTEEEIKISQGGQDVTSS<br/>             VYFMKQTISNACGTIGLIHA<br/>             IANNKDKMHFESGSTLKKFL<br/>             EESVSMSPERARYLENYDA<br/>             IRVTHETSAHEGQTEAPSID<br/>             EKVDLHFIALVHVDGHLYEL<br/>             DGRKFPFINHGETSDETLL<br/>             DAIEVCKKFMERDPDELRFN<br/>             AIALSAA           </p> |
| <p>             UCHL1_HU<br/>             MAN<br/>             Ubiquitin<br/>             carboxyl-<br/>             terminal<br/>             hydrolase<br/>             isozyme L1           </p> | 86 | <p>             MQLKPMEinPEMLNKVLSRLGV<br/>             AGQWRFDVVLGLEEESLGSVPA<br/>             PACALLLLFPLTAQHENFRKKQ<br/>             IEELKGQEVSPKVYFMKQTIGN<br/>             SCGTIGLIHAVANNQDKLGFED<br/>             GSVLKQFLSETEKMSPEDRAKC<br/>             FEKNEAIIQAADAVAQEGQCRV<br/>             DDKVNFHFIFFNNVDGHLYELD<br/>             GRMPFPVNHGASSEDTLKDAAC<br/>             KVCREFTEREQGEVRFSAVALC<br/>             KAA           </p>                                                                                                                                                                           | 86  | <p>             MQLKPMEinPEMLNKVLSRL<br/>             GVAGQWRFDVVLGLEEESLG<br/>             SVPAPACALLLLFPLTAQHE<br/>             NFRKKQIEELKGQEVSPKVY<br/>             FMKQTIGNSCGTIGLIHAVA<br/>             NNQDKLGFEDGSVLKQFLSE<br/>             TEKMSPEDRAKCFEKNEAIQ<br/>             AAADAVAQEGQCRVDDKVNF<br/>             HFILFNNVDGHLYELDGRMP<br/>             FPNHGHGASSEDTLKDAACV<br/>             CREFTEREQGEVRFSAVALC<br/>             KAA           </p> |
| <p>             UCHL5_HU<br/>             MAN<br/>             Ubiquitin<br/>             carboxyl-<br/>             terminal<br/>             hydrolase<br/>             isozyme L5           </p> | 87 | <p>             MTGNAGEWCLMESDPGVFTELI<br/>             KGFGCRGAQVEEIIWSLEPENFE<br/>             KLKPVHGLIFLFWQPGEEPAG<br/>             SVVQDSRLDTIFFAKQVINNAC<br/>             ATQAIVSVLLNCTHGDVHLGET<br/>             LSEFKEFSQSFDAAMKGLALSN<br/>             SDVIRQVHNSFARQQMFEDTK<br/>             TSAKEEDAFHFVSYPVNGRLY<br/>             ELDGLREGPIDLGACNQDDWIS<br/>             AVRPVIEKRIQKYSEGEIRFNL<br/>             MAIVSDRKMIYEQKIAELQRQL<br/>             AEEPMDDTDQGSMLSIAIQSEV           </p>                                                                                                                  | 195 | <p>             GEWCLMESDPGVFTELIKGF<br/>             GCRGAQVEEIIWSLEPENFEK<br/>             LKPVHGLIFLFWQPGEEPAG<br/>             GSVVQDSRLDTIFFAKQVIN<br/>             NACATQAIVSVLLNCTHGDV<br/>             HLGETLSEFKEFSQSFDAAM<br/>             KGLALSNSDVIRQVHNSFAR<br/>             QQMFEDTKTSAKEEDAFHF<br/>             VSYYPVNGRLYELDGLREGP<br/>             IDLGACNQDDWISAVRPVIE<br/>             KRIQKYSEGEIRFNLMAIVS<br/>             DRK           </p> |

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|                                   |    | AKNQMLIEEEVQKLKRYKIENI<br>RRKHNYLPFIMELLKTLAEHQQ<br>LIPLVEKAKEKQNAKKAQETK                                                                                                                                                                                                                                                                                                                                                                              |     |                                                                                                                                                                                                                     |
| ATX3_HUMAN Ataxin-3               | 88 | MESIFHEKQEGSLCAQHCLNNL<br>LQGEYFSPVELSSIAHQLDDEE<br>RMRMAEGGVTSEDYRTFLQQPS<br>GNMDDSGFFSIQVISNALKVGW<br>LELILFNSPEYQRLRIDPINER<br>SFICNYKEHWF <sup>T</sup> VRKLGKQWFN<br>LNSLLTGPELISDTYLALFLAQ<br>LQQEGYSIFVVKGDLPDCEADQ<br>LLQMIRVQQMHRPKLIGEELAQ<br>LKEQRVHKTDLERVLEANDGSG<br>MLDEDEEDLQRALALSRQEIDM<br>EDEEADLRRAIQLSMQGSSRNI<br>SQDMTQTS GTNLTSEELRKRE<br>AYFEKQQQKQQQQQQQQQQGDL<br>SGQSSHPCERPATSSGALGSDL<br>GDAMSEEDMLQAAVTMSLETVR<br>NDLKTEGKK | 196 | ESIFHEKQEGSLCAQHCLNN<br>LLQGEYFSPVELSSIAHQLD<br>EEERMRMAEGGVTSEDYRTF<br>LQQPSGNMDDSGFFSIQVIS<br>NALKVGWGLELILFNSPEYQR<br>LRIDPINERSFICNYKEHWF <sup>T</sup><br>TVRKLKGQWFNLNSLLTGPE<br>LISDTYLALFLAQLQQEGYS<br>IFVVK |
| JOS2_HUMAN Josephin-2             | 89 | MSQAPGAQSPPTVYHERQRLE<br>LCAVHALNNVLQQQLFSQEAA<br>EICKRLAPDSRLNPHRSLGTG<br>NYDVNVIMAALQGLGLAAVWWD<br>RRRPLSQLALPQVLGLILNLPS<br>PVSGLLLSLPLRRRHVVALRQV<br>DGVYYNLD SKLRAPEALGDEDG<br>VRAFLAAALAQGLCEVLLVVTK<br>EVEEKGSWLRTD                                                                                                                                                                                                                             | 197 | PTVYHERQRLELCAVHALNN<br>VLQQQLFSQEAADEICKRLA<br>PDSRLNPHRSLGTGNYDVN<br>VIMAALQGLGLAAVWWD<br>RRRPLSQLALPQVLGLILNLPS<br>PVSGLLLSLPLRRRHVVALRQ<br>VGVYYNLD SKLRAPEALGD<br>EDGVRAFLAAALAQGLCEVL<br>LVV                  |
| JOS1_HUMAN Josephin-1             | 90 | MSCVPWKGD KAKSESLPQAA<br>PPQIYHEKQRRELCALHALNNV<br>FQDSNAFTRDTLQEIFQRLSPN<br>TMVTPHKKSMLGNGNYDVNVIM<br>AALQTKGYEAVWWDKRRDVGVI<br>ALTNVMGFIMNLPSSLCWGPKL<br>LPLKRQHWICVREVGGAYYNLD<br>SKLKMP EWIGGESELRKFLKHH<br>LRGKNCELLLVVPEEVEAHQSW<br>RTDV                                                                                                                                                                                                         | 198 | PQAAPPQIYHEKQRRELCAL<br>HALNNVFQDSNAFTRDTLQE<br>IFQRLSPNTMVT PHKKSMLG<br>NGNYDVNVIMAALQTKGYEA<br>VWWDKRRDVGVI ALTNVMGF<br>IMNLPSSLCWGPKLPLKRQ<br>HWICVREVGGAYYNLD SKLK<br>MPEWIGGESELRKFLKHHLR<br>GKNCELLLVV        |
| ATX3L_HUMAN Ataxin-3-like protein | 91 | MDFIFHEKQEGFLCAQHCLNNL<br>LQGEYFSPVELASIAHQLDDEE<br>RMRMAEGGVTSEEYLAFLQQPS<br>ENMDDTGFFSIQVISNALKFWG<br>LEIIHFNNPEYQKL GIDPINER<br>SFICNYKQHWFTIRKFGKHWFN<br>LNSLLAGPELISDTCLANFLAR<br>LQQQAYS VFVVKGDLPDCEADQ<br>LLQIIISVEEMDTPKLN GKKLVK<br>QKEHRVYKTVLEKVSEESDESG<br>TSDQDEEDFQRALELSRQETNR<br>EDEHLRSTIELSMQGSSGNTSQ                                                                                                                               | 199 | DFIFHEKQEGFLCAQHCLNN<br>LLQGEYFSPVELASIAHQLD<br>EEERMRMAEGGVTSEEYLAFL<br>LQQPS ENMDDTGFFSIQVIS<br>NALKFWGLEIIHFNNPEYQK<br>LGIDPINERSFICNYKQHWFT<br>IRKFGKHWFNLSLLAGPE<br>LISDTCLANFLARLQQQAYS<br>VFVVK              |

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|                                                                           |    | DLPKTSCVTPASEQPKKIKEDY<br>FEKHQQEQKQQQQSDLP GHSS<br>YLHERPTTSSRAIESDLSDDIS<br>EGTVQAAVD TILEIMRKNL KIK<br>GEK                                                                                                                                                                                                                                                                                                                                                                                                                                                             |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| MINY3_HUMAN<br>Ubiquitin<br>carboxyl-<br>terminal<br>hydrolase<br>MINDY-3 | 92 | MSELTKELMELVWG TKSSPGLS<br>DTIFCRWTQGFVFSESEGSAL E<br>QFEGGPCAVIAPVQAFL LKKLL<br>FSSEKSSWRDCSEEEQKELLCH<br>TLC DILESACCDHSGSYCLVSW<br>LRGKTTEETASISGSPAESSCQ<br>VEHSSALAVEELGFERFH ALIQ<br>KRSFRSLPELKDAVL DQYSMWG<br>NKFGLVLLFLYSVLLTKGIENIK<br>NEIEDASEPLIDPVYGHGSQSL<br>INLLLTGHAVSNVWDGDRECSG<br>MKLLGIHEQAAVGFL TLM EALR<br>YCKVGSYLKSPKFPIWIVGSET<br>HLTVFFAKDMALVA<br>PEAPSEQARRVFQTYDPEDNGF<br>IPDSLLEDVMKALDLVSDPEYI<br>NLMKNKLDPEGLGI ILLGPFLQ<br>EFFPDQGSSGPESFTVYHYNGL<br>KQSNYNEKVMYVEGTAVVMGFE<br>DPM LQTDDTP IKRCLQTKWPYI<br>ELLWTTDRSPSLN                 | 200 | CRWTQGFVFSESEGSAL EQF<br>EGGPCAVIAPVQAFL LKKLL<br>FSSEKSSWRDCSEEEQKELL<br>CHTLC DILESACCDHSGSYC<br>LVSWLRGKTTEETASISGSP<br>AESSCQVEHSSALAVEELGF<br>ERFH ALIQKRSFRSLPELKD<br>AVLDQYSMWGNKFG<br>VLLFLYSVLLTKGIENIKNE<br>IEDASEPLIDPVYGHGSQSL<br>INLLLTGHAVSNVWDGDREC<br>SGMKLLGIHEQAAVGFL TLM<br>EALRYCKVGSYLKSPKFPIW<br>IVGSETHLTVFFAKDMALVA<br>PEAPSEQARRVFQTYDPEDN<br>GFIPDSLLEDVMKALDLVSD<br>PEYINLMKNKLDPEGLGI ILL<br>LGPFLQEFFPDQGSSGPESF<br>TVYHYNGLKQSNYNEKVMYV<br>EGTAVVMGFEDPMLQTDDTP<br>IKRCLQTKWPYIELLWTTDR<br>SPSLN |
| MINY1_HUMAN<br>Ubiquitin<br>carboxyl-<br>terminal<br>hydrolase<br>MINDY-1 | 93 | MEYHQPEDPAPGKAGTAEAVIP<br>ENHEVLAPDEHPQD TDARDAD<br>GEAREREPADQALLPSQCGDNL<br>ESPLPEASSAPPGPTLGTLP EV<br>ETIRAC SMPQELPQSPRTRQPE<br>PDFYCVKWIPWKGEQTPI ITQS<br>TNGPCPLLAIMNIFLQWKVKL<br>PPQKEVITSDELMAHLGNCLLS<br>IKPQEKSEGLQLNFQQNVDDAM<br>TVLPKLATGLDVNVRFTGVSD F<br>EYTPECSVFDLLGIPLYHGWLV<br>DPQSPEAVRAVGKLSYNQLVER<br>IITCKHSSDTNLVTEGLIAEQF<br>LETTAAQLTYHGLC<br>ELTAAAKEGELS VFFRNHFST<br>MTKHKSHLYLLVTDQGFLQEEQ<br>VWESLHNVDGDS CFDSDFHL<br>SHSLGKPGAEGSGSPETQLQ<br>VDQDYLI ALSLQQQQPRG PLGL<br>TDLELAQQLQEEYQQQQAQP<br>VRMRTRVLSLQGRGATSGRPAG<br>ERRQRPKHESDCILL | 201 | YCVKWIPWKGEQTPI ITQST<br>NGPCPLLAIMNIFLQWKVK<br>LPPQKEVITSDELMAHLGN C<br>LLSIKPQEKSEGLQLNFQQN<br>VDDAMTVLPKLATGLDVNVR<br>FTGVSDFEYTPECSVFDLLG<br>IPLYHGWLVDPQSP EAVRAV<br>GKLSYNQLVERIITCKHSSD<br>TNLVTEGLIAEQFLETTAAQ<br>LTYHGLCELTA AAKEGELS V<br>FFRNHFSTMTKHKSHLYLL<br>VTDQGFLQEEQVWESLHN V<br>DGDSCFCDSDFHL SHSLGKG<br>PGAEGSGSPETQLQVDQDY<br>LIALSLQQQQPRG PLGLTDL<br>ELAQQLQEEYQQQQAQP V<br>RMRTRVLSLQGRGATSGRPA<br>GERRQRPKHESDCILL                                                                                    |
| MINY2_HUMAN                                                               | 94 | MESSPELQPLEHGVAAGPASG<br>TGSSQEG LQETRLAAGDGPVW                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 202 | YHIKWIQWKEENTPI ITQNE<br>NGPCPLLA I LNVLLLA WKVK                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

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| Ubiquitin<br>carboxyl-<br>terminal<br>hydrolase<br>MINDY-2                                |    | AAETSGGNGLGAAAARRSLPDS<br>ASPAGSPEVPGPCSSSAGLDLK<br>DSGLES PAAAEAPLRGQYKVTA<br>SPETAVAGVGHELGTAGDAGAR<br>PDLAGTCQAELTAAGSEEPSSA<br>GGLSSSCSDPSPPGESPSLDL<br>ESFSNLHSFPSSCEFNSSEEGAE<br>NRVPEEEEGAAVLP GAVPLCKE<br>EEGEETAQVLAASKERFPGQSV<br>YHIKWIQWKEENTPIITQNG<br>PCPLLAILNVLLLAWKVKLPPM<br>MEIITAEQLMEYLG<br>DYMLDAKPKEISEIQRLNQEON<br>MSDAMAILHKLQTGLDVNVRFT<br>GVRVFEYTPCEIVFDLLDIPLY<br>HGWLVD PQIDDIVKAVGNC SYN<br>QLVEKIIISCKQSDNSELVSEGF<br>VAEQFLNNTATQ LTYHGLCELT<br>STVQEGELCVFFRNNHFSTMTK<br>YKGQLYLLVTDQGFLTEEKVVW<br>ESLHNVDGDNFCDSEFHLRPP<br>SDPETVYKGQDQIDQDYL MAL<br>SLQQEQQSQEINWEQIPEGISD<br>LELAKKLQEEEDRRASQYYQE<br>EQAAAAAAAAASTQAQGGQPAQA<br>SPSSGRQSGNSERKRKEPREKD<br>KEKEKEKNSCVIL |     | LPPMMEIITAEQLMEYLG DY<br>MLDAKPKEISEIQRLNQEON<br>MSDAMAILHKLQTGLDVNVR<br>FTGVRVFEYTPCEIVFDLLD<br>IPLYHGWLVD PQIDDIVKAV<br>GNC SYNQLVEKIIISCKQSDN<br>SELVSEGFVAEQFLNNTATQ<br>LTYHGLCELTSTVQEGELCV<br>FFRNNHFSTMTKYKGQLYLL<br>VTDQGFLTEEKVVWESLHN<br>VDGDNFCDSEFHLRPPSDPE<br>TVYKGQDQIDQDYL MALSL<br>QQEQQSQEINWEQIPEGISD<br>LELAKKLQEEEDRRASQYYQE<br>EQEQAAAAAAAAASTQAQGGQ<br>PAQASPSGRQSGNSERKRK<br>EPREKDKEKEKEKNSCVIL |
| MINY4_HU<br>MAN<br>Probable<br>ubiquitin<br>carboxyl-<br>terminal<br>hydrolase<br>MINDY-4 | 95 | MDSL FVEEVAASLVREFLSRKG<br>LKKTCVTMDQERPRSDL S INNR<br>NDLRKVLHLEFLYKENKAKENP<br>LKTSLELITRYFLDHFGNTANN<br>FTQDTPIPALSVPKNNKVPSR<br>CSETTLVNIYDLSD EDAGWRTS<br>LSETSKARHDNLDGDVLGNFVS<br>SKRPPHKSKPMQTVGETPVL<br>SAWEKIDKLHSEPSLDVKRMGE<br>NSRPKSLIVRGMSGPIASSP<br>QDSFHRHYLRSSPSSSSTQPQ<br>EESRKVPELFVCTQDILASSN<br>SSPSRTSLGQSEL TVERQKT<br>ASSPPLPSKRLPP<br>WDRARPRDPS EDTPAVDGSTDT<br>DRMPLKLYLP GGNSRMTQERLE<br>RAFKRQGSQPAPVRKNQLLPSD<br>KVDGELGALRLEDVEDELIREE<br>VILSPVPSVLKLQTASKPIDLS<br>VAKEIKTLLFGSSFCCFNEEWK<br>LQSF SFSNTASLKYGIVQNKGG<br>PCGVLA AVQGCVLQKLLFEGDS<br>KADCAQGLQPSDAHRTRCLVLA<br>LADIVWRAGGRERAVVALASRT                                                                          | 203 | FCCFNEEWKLQSF SFSNTAS<br>LKYGIVQNKGGPCGVLA AVQ<br>GCVLQKLLFEGDSKADCAQG<br>LQPSDAHRTRCLVLA LADIV<br>WRAGGRERAVVALASRTQQF<br>SPTGKYKADGVLETTLTHSL<br>TCYEDLVTF LQQSIHQFEVG<br>PYGCILLTLSAILSRSTELI<br>RQDFDVPTSHLIGAHGYCTQ<br>ELVNLLLTGKAVSNVFN DVV<br>ELDSGDGNITLLRGIAARSD<br>IGFLSLFEHYNMCQVGCFLK<br>TPRFPIWVVCSESHFSILFS<br>LQPGLLRDWRTERLFDLYYY<br>DGLANQQEQIRLTIDTTQTI<br>SEDTDN DLVPPLELCIRTKW<br>KGASVNWNGSDPIL    |

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|                                          |    | <p>QQFSPTGKYKADGVLETTLTHS<br/> LTCYEDLVTFLLQQSIHQFEVGP<br/> YGCILLTLSAILSRSTELIRQD<br/> FDVPTSHLIGAHGY<br/> CTQELVNLLLTGKAVSNVFNDV<br/> VELDSGDGNITLLRGIAARSDI<br/> GFLSLFEHYNMCQVGCFLKTPR<br/> FPIWVVCSESHFSILFSLQPGL<br/> LRDWRTERLFDLYYYDGLANQQ<br/> EQIRLTIDTTQTISEDNDNDLV<br/> PPELCIRTKWKGASVNWNGSD<br/> PIL</p>                                                                                                                                                                                                                                            |     |                                                                                                                                                                                                                                                                          |
| STABP_HUMAN STAM-binding protein         | 96 | <p>MSDHGDVSLPPEDRVRALSQLG<br/> SAVEVNEDIPPRYFRSGVEII<br/> RMASIYSEEGNIEHAFILYNKY<br/> ITLFIEKLPHRDYKSAVIEPK<br/> KDTVKKLKEIAFPKAEELKAEL<br/> LKRYTKEYTEYNEKKKEAEEL<br/> ARNMAIQQELEKEKQ RVAQQKQ<br/> QQLEQEQFHAF EEMIRNQELEK<br/> ERLKIVQEF GKVDPLGGPLVP<br/> DLEKPSLDVFP TLT VSSI QPSD<br/> CHTTVRPAKPPVDRSLKPGAL<br/> SNSESIPTIDGLRHVVVPGRLC<br/> PQFLQLASANTARGVETCGILC<br/> GKLMRNEFTITHVL<br/> IPKQSAGSDYCNTEEEELFLI<br/> QDQQGLITLGWIHTHTPTQTAF<br/> SSVDLHHTCSYQMMLPESVAIV<br/> CSPKFQETGFFKLTDHGLEEIS<br/> SCRQKGFHPH SKDPPLFCSCSH<br/> VTVDRAVTITDLR</p> | 204 | <p>VVPGRLCPPQFLQLASANTAR<br/> GVETCGILCGKLMRNEFTIT<br/> HVLIPKQSAGSDYCNTEEE<br/> ELFLIQDQQGLITLGWIHTH<br/> PTQTAFLLSSVDLHHTCSYQM<br/> MLPESVAIVCSPKFQETGFF<br/> KLTDHGLEEISSCRQKGFHP<br/> HSKDPPLFCSCSHVTVDRA<br/> VTITDLR</p>                                           |
| MPND_HUMAN MPN domain-containing protein | 97 | <p>MAAPEPLSPAGGAGEEAP EDE<br/> DEAEAEDPERPNAGAGGGRSGG<br/> GGSSVSGGGGGGAGAGCGGP<br/> GGALTRRAVTLRVLLKDALLEP<br/> GAGVLSIYYLGKKFLGDLQPDG<br/> RIMWQETGQTFNSPSAWATHCK<br/> KLVNPAKKS GCGWASVKYKGQK<br/> LDKYKATWLRHLQLHTPATAAD<br/> ESPASEGEEEEELMEEEEEDVL<br/> AGVSAEDKSRRPLGKSPSEPAH<br/> PEATTPGKRVD SKIRVPVRYCM<br/> LGS RDLARNPHTLVEVTSFAAI<br/> NKFQPFNVAVSSNVLFLLDFHS<br/> HLTRSEVVG YLGGR<br/> WDVNSQMLTVLRAFP CRSRLGD<br/> AETAAAIEEEIYQSLFLRGLSL<br/> VGWYHSHPHSPALPSLQDIDAQ<br/> MDYQLRLQGSSNGFQPC LALLC<br/> SPYYSGNPGPESKISPFWMPP</p>                  | 205 | <p>VAVSSNVLFLLDFHSHLTRS<br/> EVVGYLGGRWDVNSQMLTVL<br/> RAFP CRSRLGDAETAAAIEE<br/> EIIYQSLFLRGLSLVGWYHSH<br/> PHSPALPSLQDIDAQMDYQL<br/> RLQGSSNGFQPC LALLCSPY<br/> YSGNPGPESKISPFWMPPP<br/> EMLLVEFYKGSPDLVRLQEP<br/> WSQEHTYLDKLIKISLASRTP<br/> KDQSLCHVLEQVCGVLKQGS</p> |

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|                                                                        |     | PEMLLVEFYKGS PDLVRLQEPW<br>SQEHTYLDKLIKISLASRTPKDQ<br>SLCHVLEQVCGVLKQGS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |     |                                                                                                                                                                                                                                                                                                                                              |
| EMC9_HUMAN ER<br>membrane<br>protein<br>complex<br>subunit 9           | 98  | MGEVEISALAYVKMCLHAARYP<br>HAAVNGLFLAPAPRSGECLCLT<br>DCVPLFHS HLALSVMLEVALNQ<br>VDVWGAQAGLVVAGYYHANAAV<br>NDQSPGPLALKIAGRIAEFFPD<br>AVLIMLDNQKLVPQPRVPPVIV<br>LENQGLRWVPKDKNLVMWRDWE<br>ESRQMGALLEDRAHQHLVDFD<br>CHLDDIRQDWTNQRLNTQITQW<br>VGPTNGNGNA                                                                                                                                                                                                                                                                                                                                 | 206 | ALAYVKMCLHAARYPHAAVN<br>GLFLAPAPRSGECLCLTDCV<br>PLFHS HLALSVMLEVALNQV<br>DVWGAQAGLVVAGYYHANAA<br>VNDQSPGPLALKIAGRIAEF<br>FPDAVLIMLDNQKLVPQPRV<br>PPVIVLENQGLRWVPKDKNL<br>VMWRDWEESRQMGALLEDRA<br>HQHLVDFDCHLDDIRQDWT<br>NQRLNTQITQWVGPTNGNGN<br>A                                                                                            |
| PSDE_HUMAN 26S<br>proteasome<br>non-ATPase<br>regulatory<br>subunit 14 | 99  | MDRLLRLGGGMPGLGQGPPTDA<br>PAVDTAEQVYISSLALLKMLKH<br>GRAGVPMEVMGLMLGEFVDDYT<br>VRVIDVFAMPQSGTGVSVEAVD<br>PVFQAKMLDMLKQTGRPEMVG<br>WYHSHPGFGCWLSGVDINTQQS<br>FEALSERAVAVVVDPIQSVKKG<br>VVIDAFRLINANMMVLGHEPRQ<br>TTSNLGHLNKP SIQALIHGLNR<br>HYYSITINRKNLEQKMLLNL<br>HKKSWMGLTLQDYSECHKHNE<br>SVVKEMLELAKNYNKAVEEEDK<br>MTPEQLAIKNVGKQDPKRHLEE<br>HVDVLMTSNIVQCLAAMLDTVV<br>FK                                                                                                                                                                                                          | 207 | QVYISSLALLKMLKHGRAGV<br>PMEVMGLMLGEFVDDYT<br>IDVFAMPQSGTGVSVEAVD<br>VFQAKMLDMLKQTGRPEMVG<br>GWYHSHPGFGCWLSGVDINT<br>QQSFEALSERAVAVVVDPIQ<br>SVKKGVIDAFRLINANMMV<br>LGHEPRQTTSNLGHLNKP SI<br>QALIHGLNRHYYSITINRKN<br>LEQKMLLNLHKKSWMGLTL<br>QDYSECHKHNE SVVKEMLE<br>ELAKNYNKAVEEEDKMTPEQ<br>LAIKNVGKQDPKRHLEE<br>HVDVLMTSNIVQCLAAMLDTVV<br>FK |
| MYSM1_HUMAN Histone<br>H2A<br>deubiquitinase<br>MYSM1                  | 100 | MAAEEADV DIEGDVVAAGAQP<br>GSGENTASVLQKDHYLDSSWRT<br>ENGLIPWTL DNTISEENRAVIE<br>KMLLEEEYYLSKKSQPEKVWLD<br>QKEDDKKYMKS LQKTAKIMVHS<br>PTKPASYSVKWTIEEKELFEQG<br>LAKFGRRWTKISK LIGSRTVLQ<br>VKSARQYFKNKVKCGLDKETP<br>NQKTGHN LQVKNE DKGTAWTP<br>SCLRGRADPNLNAVKIEKLSDD<br>EEVDITDEVDELSSQTPQKNSS<br>SDLLLD FPN SKMHETNQGEFIT<br>SDSQEALFSKSSRGCLQNEKQD<br>ETLSSEITLWTEK<br>QSNQDKKSIELNDQKFNELIKN<br>CNKHDGRGIIVDARQLPSPEPC<br>EIQKNLNDNEMLFHSCQMVEES<br>HEEEELKPPEQEIEIDRNIIQE<br>EEKQAIPEFFEGRQAKTPERYL<br>KIRNYILDQWEICKPKYLNKTS<br>VRPGLKNCGDVNCIGRIHTYLE<br>LIGAINFGCEQAVYNRPQTVDK | 208 | QVKVASEALLIMDLHAHVSM<br>AEVIGLLGGRYSEVDKVVEV<br>CAAEP CNSLSTGLQCEMDPV<br>SQTQASETLAVRGF SVIGWY<br>HSHPAFDPNPSLRDIDTQAK<br>YQSYFSRGGA KFIGMIVSPI<br>NRNNPLPYSQITCLVISEEI<br>SPDGSYRLPYKFEVQQMLEE<br>PQWGLVFEKTRWII EK YRLS<br>HSSVPMDKIFRRDSDLTCLQ<br>KLLCEMRKTL SKVTNCFMAE<br>EFLTEIENLFLSNYKSNQEN<br>GVTEENCTKELLM                          |

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|                                                  |     | <p>VRIRDRKDAVEAYQLAQRLQSM<br/>RTRRRRVDPWGNWCDAKDLEG<br/>QTFEHLSAEELAKRREEEEKGRP<br/>VKSLKVP RPTKSSFDPFQLIPC<br/>NFFSEEKQEPFQVKVASEALLI<br/>MDLHAHV SMAEVIG<br/>LLGGRYSEVDKVVEVCAAEPCN<br/>SLSTGLQCEMDPVSQTQASETL<br/>AVRGFSVIGWYHSHPAFDPNPS<br/>LRDIDTQAKYQSYFSRGGAKFI<br/>GMIVSPYNRRNNPLPYSQITCLV<br/>ISEEISPDGSYRLPYKFEVQQM<br/>LEEPQWGLVFEKTRWIEKYRL<br/>SHSSVPMDKIFRRDSDLTCLQK<br/>LLECMRKTL SKVTNCFMAEEFL<br/>TEIENLFLSNYKSNQENGVT EE<br/>NCTKELLM</p>                                                                           |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| ABRX2_HUMAN BRISC complex subunit Abraxas 2      | 101 | <p>MAASISGYTFSAVCFHSANSNA<br/>DHEGFLLEVRQEETFSISDSQ<br/>ISNTEFLQVIEIHNHQPCSKLF<br/>SFYDYASKVNEESLDRILKDRR<br/>KKVIGWYRFRNTQQQMSYREQ<br/>VLHKQLTRILGVPDLVFLLEFSF<br/>ISTANNSTHALEYVLFRRPNRRY<br/>NQRISLAIPNLGNTSQQEYKVS<br/>SVPNTSQSYAKVIKEHGTDFD<br/>KDGVMKDIRAIYQVYNALQEKV<br/>QAVCADVEKSERVVESCQAEVN<br/>KLRRQITQRKNEKEQERRLQQA<br/>VLSRQMPSES LDPAFSPRMPSS<br/>GFAAEGRSTLGDAE<br/>ASDPPPPYSDFHPNNQESTLSH<br/>SRMERSVFM PRPQAVGSSNYAS<br/>TSAGLKYPGSGADLPPQRAAG<br/>DSGEDSDSDYENLIDPTEPSN<br/>SEYSHSKDSRPM AHPDEDPRNT<br/>QTSQI</p> | 209 | <p>AVCFHSANSNADHEGFLLEGE<br/>VRQEETFSISDSQISNTEFL<br/>QVIEIHNHQPCSKLFSFYDY<br/>ASKVNEESLDRILKDRRKKV<br/>IGWYRFRNTQQQMSYREQV<br/>LHKQLTRIL<br/>GVPDLVFLLEFSFISTANNST<br/>HALEYVLFRRPNRRYNQRISL<br/>AIPNLGNTSQQEYKVSSVPN<br/>TSQSYAKVIKEHGTDFD<br/>KDGVMKDIRAIYQVYNALQEKV<br/>QAVCADVEKSERVVESCQAE<br/>VNKLRRQITQRKNEKEQERR<br/>LQQAVLSRQMPSES LDPAFS<br/>PRMPSSGFAAEGRSTLGDAE<br/>ASDPPPPYSDFHPNNQESTL<br/>SHSRMERSVFM PRPQAVGSS<br/>NYASTSAGLKYPGSGADLPP<br/>PQRAAGDSGEDSDSDYENL<br/>IDPTEPSNSEYSHSKDSRPM<br/>AHPDEDPRNTQTSQI</p> |
| PRP8_HUMAN Pre-mRNA-processing-splicing factor 8 | 102 | <p>MAGVFPYRGPGNPVPGPLAPLP<br/>DYMSEEKLEKARKWQQLQAKR<br/>YAEKRKFGFVDAQKEDMPPEHV<br/>RKIIRDHGD MTNRKFRHDKRVY<br/>LGALKYMPH AVLKLENMPMPW<br/>EQIRDVPVLYHITGAISFVNEI<br/>PWVIEPVYISQWGSMMIMRRE<br/>KRDRRHFKRMRFPPFDDEEPPL<br/>DYADNILDVEPLEAIQLELDPE<br/>EDAPVLDWFYDHQPLRDSRKYV<br/>NGSTYQRWQFTLPMMSTLYRLA<br/>NQLLTDLVDDNYFYLFDLKAFF</p>                                                                                                                                                                                                 | 210 | <p>FNPRTGQLFLKIIHTSVWAG<br/>QKRLGQLAKWKTAEEVAALI<br/>RSLPVEEQPKQIIIVTRKGML<br/>DPLEVHLLDFPNIVIKGSEL<br/>QLPFQACLKVEKFGDLILKA<br/>TEPQMVLFNLYDDWLKTISS<br/>YTAFSRLILILRALHVNNDR<br/>AKVILKPKDKTTITEPHHIWP<br/>TLTDEEWIKVEVQLKDLILA<br/>DYGKKNVNVASLTQSEIRD<br/>IILGMEISAPSQQRQQIAEI<br/>EKQTKEQSQLTATQTRTVNK<br/>HGDEIITSTTSNYETQTFSS</p>                                                                                                                                                                                          |

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|  |  | <p>TSKALNMAIPGGPKFEPLVRDI<br/> NLQDEDWNEFNDIN<br/> KIIIRQPIRTEYKIAFPYLYNN<br/> LPHHVHLTWYHTPNVFIKTED<br/> PDLPAFYFDPLINPISHRHSVK<br/> SQEPLPDDDEEFELPEFVEPFL<br/> KDTPLYTDNTANGIALLOWAPRP<br/> FNLRSGRTRRALDIPLVKNWYR<br/> EHCPAGQPVKVRVSYQKLLKYY<br/> VLNALKHRPPKAQKKRYLFRSF<br/> KATKFFQSTKLDWVEVGLQVCR<br/> QGYNMLNLLIHRKNLNYLHLDY<br/> NFNLPVKTLTTKERKKSFRGN<br/> AFHLCREVLRLTKLVVDHSVQY<br/> RLGNVDAFQLADGLQYIFAHV<br/> QLTGMRYRYKYKLMR<br/> QIRMCKDLKHLIYYRFNTGPVG<br/> KGP GCGFWAAGWRVWLFFMRGI<br/> TPLLERWLGNLLARQFEGRHSK<br/> GVAKTVTKQRVESHFDLELRAA<br/> VMHDILDMMPEGIKQNKARTIL<br/> QHLSEAWRCWKANIPWKVPGLP<br/> TPIENMILRYVKAKADWWTNTA<br/> HYNRERIRRGATVDKTVCKKNL<br/> GRLTRLYLKAEQERQHNYLKDG<br/> PYITAEAVAVYTTTVHWLESR<br/> RFSPIFPPLSYKHDTKLLILA<br/> LERLKEAYSVKSRLNQSOREEL<br/> GLIEQAYDNPHEALSRIKRHLL<br/> TQRAFKEVGIEFMD<br/> LYSHLVPVYDVEPLEKITDAYL<br/> DQYLWYEADKRRLFPPWIKPAD<br/> TEPPPLLKYKWCQGINNLQDVW<br/> ETSEGECEVMLESRFKMYEKI<br/> DLTLLNRLRLIVDHNIADYMT<br/> AKNNVVINYKDMNHTNSYGIIR<br/> GLQFASFIVQYYGLVMDLVLG<br/> LHRASEMAGPPQMPNDFLSFQD<br/> IATEAAHPIRLFCRYIDRIHIF<br/> FRFTADEARDLIQRYLTEHPDP<br/> NNENIVGYNNKKCWPRDARMRL<br/> MKHDVNLGRAVFWDIKNRLPRS<br/> VTTVQWENSFVSVYSKDNPNLL<br/> FNMCGFECRILPKC<br/> RTSYEEFTHKDGVMNLQNEVTK<br/> ERTAQCFLRVDDSMQRFHNRV<br/> RQILMASGSTTFTKIVNKWNTA<br/> LIGLMTYFREAVVNTQELLDLL<br/> VKCENKIQTIRIKIGLNSKMPSR<br/> FPPVVFYTPKELGGLGMLSMGH<br/> VLIPQSDLRWSKQTDVGITHFR</p> |  | <p>KTEWRVRAISAANLHLRTNH<br/> IYVSSDDIKETGYTYILPKN<br/> VLKKFICISDLRAQIAGYLY<br/> GVSPDPNPQVKEIRCIVMVP<br/> QWGTHQTVHLPGQLPQHEYL<br/> KEMEPLGWIHTQPNESPQLS<br/> PQDVTTHAKIMADNPSWDGE<br/> KTIIITCSFTPGSCTLTAYK<br/> LTPSGYEWGRQNTDKGNPNK<br/> GYLP SHYERVQMLLSDRFLG<br/> FFMVPAQSSWNYNFMGVRHD<br/> PNMKYELQLANPKEFYHEVH<br/> RPSHFLNFALLQEGEVYSAD<br/> REDLYA</p> |
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|                                         |     | <p>SGMSHEEDQLIPNLYRYIQPWE<br/>SEFIDSQRVWAEYALKRQEAIA<br/>QNRRLTLEDLEDSDRGIPRIN<br/>TLFQKDRHTLAYDKGWRVRTDF<br/>KQYQVLKQNPFWWTHQRHDGKL<br/>WNLNNYRTDMIQALGGVEGILE<br/>HTLFKGTYPFTWEG<br/>LFEKASGFEESEMKWKKLTNAQ<br/>RSGLNQIPNRRFTLWWSPTINR<br/>ANVYVGFQVQLDLTGIFMHGKI<br/>PTLKISLIQIFRAHLWQKIHES<br/>IVMDLCQVFDQELDALEIETVQ<br/>KETIHPKRSYKMNSSCADILLF<br/>ASYKWNVSRPSLLADSKDVMS<br/>TTTQKYWIDIQLRWGDYDSHDI<br/>ERYARAKFLDYTTDNMSIYPSP<br/>TGVLIAIDLAYNLHSAYGNWFP<br/>GSKPLIQQAMAKIMKANPALYV<br/>LRERIRKGLQLYSSEPTPEYLS<br/>SQNYGELFSNQIIWFVDDTNVY<br/>RVTIHKTFEGNLTT<br/>KPINGAIFIFNPRTGQLFLKII<br/>HTSVWAGQKRLGQLAKWKTAEE<br/>VAALIRSLPVEEQPKQIIIVTRK<br/>GMLDPLEVHLLDFPNIVIKGSE<br/>LQLPFQACLKVEKFGDLILKAT<br/>EPQMVLFNLYDDWLKTISSYTA<br/>FSRLILILRALHVNNDRAKVIL<br/>KPDKTTITEPHHIWPTLTDEEW<br/>IKVEVQLKDLILADYGKKNNVN<br/>VASLTQSEIRDIIILGMEISAPS<br/>QQRQQIAEIEKQTKEQSQLTAT<br/>QTRTVNKHGDEIITSTTSNYET<br/>QTFSSKTEWRVRAISAANLHLR<br/>TNHIYVSSDDIKET<br/>GYTYILPKNVLKKFICISDLRA<br/>QIAGYLYGVSPDPNPQVKEIRC<br/>IVMVPQWGTHQTVHLPGLPQH<br/>EYLKEMEPLGWIHTQPNESPQL<br/>SPQDVTTHAKIMADNPSWDGEK<br/>TIIITCSFTPGSCTLTAYKLTP<br/>SGYEWGRQNTDKGNNPKGYLPS<br/>HYERVQMLLSDRFLGFFMVPAQ<br/>SSWNYNFMGVRHDPNMKYELQL<br/>ANPKEFYHEVHRPSHFLNFALL<br/>QEGEVYSADREDLYA</p> |     |                                                                                                                                 |
| NPL4_HUMAN Nuclear protein localization | 103 | <p>MAESIIIRVQSPDGVKRITATK<br/>RETAATFLKKVAKEFGFQNNGF<br/>SVYINRNKTGEITASSNKSINL<br/>LKIKHGDLLFLFPSSLAGPSSE<br/>METSVPPGFKVFGAPNVVEDEI</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 211 | <p>QPSAITLNRQKYRHVDNIMF<br/>ENHTVADRFLDFWRKTGNQH<br/>FGYLYGRYTEHKDIPLGIRA<br/>EVAAIYEPPQIGTQNSLELL<br/>EDPKAEVVDEIAAKLGLRKV</p> |

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| protein 4 homolog                                |     | DQYLSKQDGKIYRSRDPQLCRH<br>GPLGKCVHCVPLEPFDELYLNH<br>LEPPVKHMSFHAYIRKLTGGAD<br>KGKFVALENISCKIKSGCEGHL<br>PWPNGICTKCQPSAITLNRQKY<br>RHVDNIMFENHTVADRFLDFWR<br>KTGNQHFGYLYGRYTEHKDIPL<br>GIRAEVAAIYEPPQIGTQNSLE<br>LLEDPKAEVVDEIA<br>AKLGLRKVGWIFTDLVSEDTRK<br>GTVRYSRNKDTYFLSSEECITA<br>GDFQNKHPNMCRLSPDGHFGSK<br>FVTAVATGGPDNQVHFEGYQVS<br>NQCMALVRDECLLPCKDAPELG<br>YAKESSEQYVPDVFYKDVKDF<br>GNEITQLARPLPVEYLIIDITT<br>TFPKDPVYTFSSISQNPFPNIENR<br>DVLGETQDFHSLATYLSQNTSS<br>VFLDTISDFHLLLFLVTNEVMP<br>LQDSISLLLEAVRTRNEELAQT<br>WKRSEQWATIEQLCSTVGGQLP<br>GLHEYGAVGGSTHTATAAMWAC<br>QHCTFMNQPGTGHCCEMCSLPRT |     | GWIFTDLVSEDTRKGTVRYS<br>RNKDTYFLSSEECITAGDFQ<br>NKHPNMCRLSPDGHFGSKFV<br>TAVATGGPDNQVHFEGYQVS<br>NQCMALVRDECLLPCKDAPE<br>LGAKESSEQYVPDVFYKD<br>VDKFGNEITQLARPLPVEYL<br>IIDITTTFPKDPVYTFSSISQ<br>NPFPNIENRDVLGETQDFHSL<br>ATYLSQNTSSVFLDTISDFH<br>LLLFLVTNEVMPLQDSISLL<br>LEAVRTRNEELAQTWKRSEQ<br>WATIEQLCSTVGGQLPGLHE<br>YGAVGGSTHTATAAMWACQH<br>CTFMNQPGTGHCCEMCSLPRT                                         |
| EMC8_HUMAN ER membrane protein complex subunit 8 | 104 | MPGVKLTTQAYCKMVLHGAKYP<br>HCAVNGLLVAEKQKPRKEHLPL<br>GGGAHHTLFVDCIPLFHGTLA<br>LAPMLEVALTLIDSWCKDHSYV<br>IAGYYQANERVKDASPNQVAEK<br>VASRIAEGFSDTALIMVDNTKF<br>TMDCVAPTIVHYEHENRWRCR<br>DPHHDYCEDWPEAQRIASALLD<br>SRSYETLVDFDNHLDDIRNDWT<br>NPEINKAVLHLC                                                                                                                                                                                                                                                                                                                                                         | 212 | TQAYCKMVLHGAKYPHCAVN<br>GLLVAEKQKPRKEHLPLGGP<br>GAHHTLFVDCIPLFHGTLAL<br>APMLEVALTLIDSWCKDHSY<br>VIAGYYQANERVKDASPNQV<br>AEKVASRIAEGFSDTALIMV<br>DNTKFTMDCVAPTIVHYEHH<br>ENRWRCRDPHHDYCEDWPEA<br>QRIASALLDSRSYETLVDFD<br>NHLDDIRNDWTNPEINKAVL<br>HLC                                                                                                                                                           |
| ABRX1_HUMAN BRCA1-A complex subunit Abraxas 1    | 105 | MEGESTSAVLSGFVLGALAFQH<br>LNTDSDETEGFLLEVKGEAKNS<br>ITDSQMDDVEVVYTIQKYIP<br>CYQLFSFYNSSGEVNEQALKKI<br>LSNVKKNVVGWYKFRRHSDQIM<br>TFRERLLHKNLQEHFSNQDLV<br>LLLTPSIITESCSTHRLEHSLY<br>KPQKGLFHRVPLVVANLGMSEQ<br>LGKTVSGSCMSTGFSAVQTH<br>SSKFEEEDGSLKEVHKINEMYA<br>SLQEELKSICKKVEDSEQAVDK<br>LVKDVNRLKREIEKRRGAQIQ<br>AREKNIQKDPQENIFLCQALRT<br>FFPNSEFLHSCVMS<br>LKNRHVSKSSCNYNHHLDVVDN<br>LTLMEHTDIPEASPASTPQII<br>KHKALDLDDRWFKRSRLLDQTQ                                                                                                                                                                      | 213 | GFVLGALAFQHLNTDSDETEG<br>FLLGEVKGEAKNSITDSQMD<br>DVEVVYTIQKYIPCYQLF<br>SFYNSSGEVNEQALKKILSN<br>VKNVVGWYKFRRHSDQIMT<br>FRERLLHKNLQEHFSNQDLV<br>FLLTPSIITESCSTHRLEH<br>SLYKPQKGLFHRVPLVVANL<br>GMSEQLGKTVSGSCMSTGF<br>SAVQTHSSKFEEEDGSLKE<br>VHKINEMYASLQEELKSICK<br>KVEDSEQAVDKLVKDVNRLK<br>REIEKRRGAQIQAREKNIQ<br>KDPQENIFLCQALRTFFPNS<br>EFLHSCVMSLKNRHVSKSSC<br>NYNHHLDVVDNLTLMEHTD<br>IPEASPASTPQIIKHKALDL |

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|                                                                                     |     | DKRSKADTGSSNQDKASKMSSP<br>ETDEEIEKMKGFGEYSRSPTF                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |     | DDRWQFKRSRLDQTQDKRSK<br>ADTGSSNQDKASKMSSPETD<br>EEIEKMKGFGEYSRSPTF                                                                                                                                                                                                                                                                                       |
| STALP_HUM<br>AN AMSH-<br>like protease                                              | 106 | MDQPFTVNSLKKLAAMPDHTDV<br>SLSPEERVRLSKLGCNITISE<br>DITPRRYFRSGVEMERMAVYL<br>EEGNLENAFVLYNKFITLFVEK<br>LPNHRDYQQCAVPEKQDIMKKL<br>KEIAFPRTDELKNDLLKKYNVE<br>YQEYLQSKNKYKAEILKKLEHQ<br>RLIEAERKRIAQMRQQLESEQ<br>FLFFEDQLKKQELARGQMRSQQ<br>TSGLSEQIDGSALSCEFSTHQQN<br>SLLNVFADQPNKSDATNYASHS<br>PPVNRALTPAATLSAVQNLVVE<br>GLRCVVLPEDLCHKFLQLAESN<br>TVRGIETCGILCGK<br>LTHNEFTTITHVIVPKQSAGPDY<br>CDMENVEELFNVQDQHDLLTLG<br>WIHTHTPTQTAFLLSSVDLHCHS<br>YQLMLPEAIAIVCSPKHKDTGI<br>FRLTNAGMLEVSACKKKGFH<br>TKEPRLFSICKHVLVKDIKIIV<br>LDLR | 214 | VVLPEDLCHKFLQLAESNTV<br>RGIETCGILCGKLTHNEFTI<br>THVIVPKQSAGPDYCDMENV<br>EELFNVQDQHDLLTLGWIHT<br>HPTQTAFLLSSVDLHCHSYQ<br>LMLPEAIAIVCSPKHKDTGI<br>FRLTNAGMLEVSACKKKGFH<br>PHTKEPRLFSICKHVLVKDI<br>KIIVLDLR                                                                                                                                                 |
| CSN6_HUM<br>AN COP9<br>signalosome<br>complex<br>subunit 6                          | 107 | MAAAAAAAAAATNGTGGSSGMEV<br>DAAVVPSVMACGVTGSVSVALH<br>PLVILNISDHWIRMRSQEGRPV<br>QVIGALIGKQEGRNIEVMNSFE<br>LLSHTVEEKI IIDKEYYYTKEE<br>QFKQVFKELEFLGWYTTGGPPD<br>PSDIHVHKQVCEIIESPLFLKL<br>NPMTKHTDLPVSVFESVIDIIN<br>GEATMLFAELTYTLATEEAERI<br>GVDHVARMTATGSGENSTVAEH<br>LIAQHSIAIKMLHSRVKLILEYV<br>KASEAGEVPFNHEILREAYALC<br>HCLPVLSTDKFKTDFYDQCNDV<br>GLMAYLGTITKTCNTMNQFVNK<br>FNVLYDRQGIGRRMRGLFF                                                                                                                                 | 215 | VALHPLVILNISDHWIRMRS<br>QEGRPVQVIGALIGKQEGRN<br>IEVMNSFELLSHTVEEKI I<br>DKEYYYTKEEQFKQVFKELE<br>FLGWYTTGGPPDPSDIHVHK<br>QVCEIIESPLFLKLNPMTKH<br>TDLPSVVFESVIDIINGEAT<br>MLFAELTYTLATEEAERIGV<br>DHVARMTATGSGENSTVAEH<br>LIAQHSIAIKMLHSRVKLILE<br>YVKASEAGEVPFNHEILREA<br>YALCHCLPVLSTDKFKTDFY<br>DQCNDVGLMAYLGTITKTCN<br>TMNQFVNKFNVLYDRQGIGR<br>RMRGLFF |
| EIF3F_HUM<br>AN<br>Eukaryotic<br>translation<br>initiation<br>factor 3<br>subunit F | 108 | MATPAVPVSAPPATPTPVPAAA<br>PASVPAPTAPAAAAPVPAAPAA<br>SSSDPAAAAAATAAPGQTPASA<br>QAPAQTPAPALPGPALPGPFPG<br>GRVVRHLHPVILASIVDSYERRN<br>EGAARVIGTLLGTVDKHSVEVT<br>NCFVSPHNESEDEVAVDMEFAK<br>NMYELHKKVSPNELILGWYATG<br>HDITEHSVLIHEYYSREAPNPI<br>HLTVDTSLQNGRMSIKAYVSTL<br>MGVPGRTMGVMFTPLTVKYAYY<br>DTERIGVDLIMKTCFSPNRVIG                                                                                                                                                                                                              | 216 | VRLHPVILASIVDSYERRNE<br>GAARVIGTLLGTVDKHSVEV<br>TNCFSVPHNESEDEVAVDME<br>FAKNMYELHKKVSPNELILG<br>WYATGHDITEHSVLIHEYYS<br>REAPNPIHLTVDTSLQNGRM<br>SIKAYVSTLMGVPGRTMGVM<br>FTPLTVKYAYYDTERIGVDL<br>IMKTCFSPNRVIGLSSDLQQ<br>VGGASARIQDALSTVLQYAE<br>DVLSGKVSADNTVGRFLMSL<br>VNQVPKIVPDDFETMLNSNI                                                             |

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|                                                                  |     | LSSDLQQVGGASARIQDALSTV<br>LQYAEDVLSGKVSADNTVGRFL<br>MSLVNQVPKIVPDDFETMLNSN<br>INDLLMVTYLANLTQSQIALNE<br>KLVNL                                                                                                                                                                                                                                                                                                                |     | NDLLMVTYLANLTQSQIALN<br>EKLVLN                                                                                                                                                                                                                                                                                                                                                         |
| PSMD7_HUMAN 26S proteasome non-ATPase regulatory subunit 7       | 109 | MPELAVQKVVVHPLVLLSVVDH<br>FNRIGKVGNGKRVVGVLLGSWQ<br>KKVLDVSNFSAVPFDEDDKDDSVW<br>VWFLDHDYLENMYGMFKKVNAR<br>ERIVGWYHTGPKLHKNDIAINE<br>LMKRYCPNSVLVIIDVKPKDLG<br>LPTEAYISVEEVHDDGTPTSTKT<br>FEHVTSEIGAEAEAEVGVHLL<br>RDIKDTTVGTLSQRITNQVHGL<br>KGLNSKLLDIRSYLEKVATGKL<br>PINHQIYYQLQDVFNLLPDVSL<br>QEFVKAFFYLKTNQMVVYLAS<br>LIRSVVALHNLINNKKIANRDAE<br>KKEGQEKEESKKDRKEDKEKDK<br>DKEKSDVKKEEKKEKK                               | 217 | VVVHPLVLLSVVDHFNRIK<br>VGNQKRVVGVLLGSWQKKVL<br>DVSNSFAVPFDEDDKDDSVW<br>FLDHDYLENMYGMFKKVNAR<br>ERIVGWYHTGPKLHKNDIAI<br>NELMKRYCPNSVLVIIDVKP<br>KDLGLPTEAYISVEEVHDDG<br>TPTSTKTFEHVTSEIGAEAE<br>EVGVHLLRDIKDTTVGTLS<br>QRITNQVHGLKGLNSKLLDI<br>RSYLEKVATGKLPINHQIYY<br>QLQDVFNLLPDVSLQEFVKA<br>FFYLKTNQMVVYLASLIRS<br>VVALHNLINNKKIANRDAEKK<br>EGQEKEESKKDRKEDKEKDK<br>DKEKSDVKKEEKKEKK |
| EIF3H_HUMAN Eukaryotic translation initiation factor 3 subunit H | 110 | MASRKEGTGSTATSSSSTAGAA<br>GKGKGGSGDSAVKQVQIDGL<br>VVLKIIKHYYQEEGQTEVVQGV<br>LLGLVVEDRLEITNCFPPQHT<br>EDDADFDEVQYQMEMMRSLRHV<br>NIDHLHVGWYQSTYYGSFVTRA<br>LLDSQFSYQHAIEESVVLIIYDP<br>IKTAQGSLSLKAYRLTPKLMEV<br>CKEKDFSPEALKKANITFEYMF<br>EEVPIVINKNSHLINVLMELEK<br>KSAVADKHELLSLASSNHLG<br>KNLQLLMDRVDEMSQDIVKYNT<br>YMRNTSKQQQKHQYQRRQPE<br>NMQRQSRGEPPLPEEDLSKLFK<br>PPQPPARMDSLLIAGQINTYCQ<br>NIKEFTAQNLGKLFMAQALQEY<br>NN | 218 | VQIDGLVVLKIIKHYYQEEGQ<br>GTEVVQGVLLGLVVEDRLEI<br>TNCFFPPQHTEDDADFDEVQ<br>YQMEMMRSLRHVNIDHLHVG<br>WYQSTYYGSFVTRALLDSQF<br>SYQHAIEESVVLIIYDPIKTA<br>QGSLSLKAYRLTPKLMEVCK<br>EKDFSPEALKKANITFEYMF<br>EEVPIVINKNSHLINVLMELEK<br>KSAVADKHELLSLASSNHLG<br>KNLQLLMDRVDEMSQDIVKYNT<br>YMRNTSKQQQKHQYQRRQPE<br>NMQRQSRGEPPLPEEDLSKLFK<br>PPQPPARMDSLLIAGQINTYCQ<br>NIKEFTAQNLGKLFMAQALQEY<br>NN |
| CSN5_HUMAN COP9 signalosome complex subunit 5                    | 111 | MAASGSGMAQKTWELANNMQEA<br>QSIDEIYKYDKKQQQEILAAKP<br>WTKDHHYFKYCKISALALLKMMV<br>MHARSGGNLEVMGLMLGKVDGE<br>TMIIMDSFALPVEGTETRVNAQ<br>AAAYEYMAAYIENAKQVGRLEN<br>AIGWYHSHPGYGCWLSGIDVST<br>QMLNQFQEPFVAVVIDPRTI<br>SAGKVNLGAFRTYTPKGYKPPDE<br>GPSEYQTIPLNKIEDFGVHCKQ<br>YYALEVSYFKSSLDKLELLW<br>NKYWNTLSSSSLLTNADYTTG<br>QVFDLSEKLEQSEAQLGRGSFM                                                                                  | 219 | YCKISALALLKMMHARSGG<br>NLEVMGLMLGKVDGETMIIM<br>DSFALPVEGTETRVNAQAAA<br>YEYMAAYIENAKQVGRLENA<br>IGWYHSHPGYGCWLSGIDVS<br>TQMLNQFQEPFVAVVIDPT<br>RTISAGKVNLGAFRTYTPKGY<br>KPPDEGPSEYQTIPLNKIED<br>FGVHCKQYYALEVSYFKSSL<br>DRKLELLWNTLVNTLSSSS<br>SLLTNADYTTGQVFDLSEKL<br>EQSEAQLGRGSFMLGLETHD<br>RKSEDKLAKATRDCKTTIE                                                                      |

|                                                         |     |                                                                                                                                                                                                                                                                                                                                                                                 |     |                                                                                                                                                                                                                                                                                                                                                                         |
|---------------------------------------------------------|-----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                         |     | LGLETHDRKSEDKLAKATRDSC<br>KTTIEAIHGLMSQVIKDKLFNQ<br>INIS                                                                                                                                                                                                                                                                                                                        |     | AIHGLMSQVIKDKLFNQINI<br>S                                                                                                                                                                                                                                                                                                                                               |
| BRCC3_HUMAN Lys-63-specific<br>deubiquitinase<br>BRCC36 | 112 | MAVQVVQAVQAVHLESDAFLVC<br>LNHALSTEKEEVMGLCIGELND<br>DTRSDSKFAYTGTEMRTVAEKV<br>DAVRIVHIHSVILRRSDKRKD<br>RVEISPEQLSAASTEAEERLAE<br>TGRPMRVVGVYHSHPHITVWPS<br>HVDVRTQAMYQMDQGFVGLIF<br>SCFIEDKNTKTGRVLYTCFQSI<br>QAQKSSESLHGPRDFWSSSQHI<br>SIEGQKEEERYERIEIPIHIVP<br>HVTIGKVCLES AVELPKILCQE<br>EQDAYRRIHSLTHLDSVTKIHN<br>GSVFTKNLCSQMSAVSGPLLQW<br>LEDRLQEQHLQELQKEEL<br>MQELSSLE | 220 | VHLESDAFLVCLNHALSTEK<br>EEVMGLCIGELNDDTRSDSK<br>FAYTGTEMRTVAEKVDAVRI<br>VHIHSVILRRSDKRKDRVE<br>ISPEQLSAASTEAEERLAE<br>TGRPMRVVGVYHSHPHITVW<br>SHVDVRTQAMYQMDQGFVGL<br>LIFSCFIEDKNTKTGRVLYT<br>CFQSIQAQKSSESLHGPRDF<br>WSSSQHISIEGQKEEERYER<br>IEIPIHIVPHVTIGKVCLES<br>AVELPKILCQEEQDAYRRIH<br>SLTHLDSVTKIHN<br>GSVFTKNLCSQMSAVSGPLLQW<br>LEDRLQEQHLQELQKEEL<br>MQELSSLE |

### 5.3.2 Targeting Domain

**[00185]** In some embodiments, the targeting domain comprises a targeting moiety that specifically binds to a target cytosolic protein. In some embodiments, the targeting moiety comprises an antibody (or antigen binding fragment thereof). In some embodiments, the antibody is a full-length antibody, a single chain variable fragment (scFv), a (scFv)<sub>2</sub>, a scFv-Fc, a Fab, a Fab', a (Fab')<sub>2</sub>, a F(v), a single domain antibody, a single chain antibody, a VHH, or a (VHH)<sub>2</sub>. In some embodiments the targeting moiety comprises a VHH. In some embodiments the targeting moiety comprises a (VHH)<sub>2</sub>.

**[00186]** In some embodiments, the targeting moiety specifically binds to a wild type target cytosolic protein. In some embodiments, the targeting moiety specifically binds to a wild type target cytosolic protein, but does not specifically binds to a variant of the target cytosolic protein associated with a genetic disease. In some embodiments, the targeting moiety specifically binds to a naturally occurring variant of a target cytosolic protein. In some embodiments, the targeting moiety specifically binds to a naturally occurring variant of a target cytosolic protein that is associated with a genetic disease (e.g., a genetic disease described herein). In some embodiments, the targeting moiety specifically binds to a naturally occurring variant of a target cytosolic protein that is a cause of a genetic disease (e.g., a genetic disease described herein). In some embodiments, the targeting moiety specifically binds a naturally occurring variant of a target cytosolic protein that is a loss of a function variant. In some embodiments, the targeting moiety specifically binds a

naturally occurring variant of a target cytosolic protein that is a loss of a function variant associated with a genetic disease (e.g., a genetic disease described herein). In some embodiments, the targeting moiety specifically binds a naturally occurring variant of a target cytosolic protein that is a loss of a function variant that causes a genetic disease (e.g., a genetic disease described herein).

### **5.3.2.1 Exemplary Target Cytosolic Proteins**

[00187] In some embodiments, targeting moiety specifically binds a target cytosolic protein (e.g., a cytosolic protein described herein). Exemplary target cytosolic proteins include, but are not limited to, Ras/Rap GTPase-activating protein (SYNGAP1), cyclin-dependent kinase-like 5 (CDKL5), copper-transporting ATPase 2 (ATP7B), syntaxin-binding protein 1 (STXBP1), progranulin (GRN), protein jagged-1 (JAG1), GATOR complex protein DEPDC5 (DEPDC5), tuberlin (TSC2), hamartin (TSC1), kinesin-like protein KIF1A (KIF1A), dynamin-1 (DNM1), SH3 and multiple ankyrin repeat domains protein 3 (SHANK3), dystrophin (DMD), oxygen-regulated protein 1 (RP1), titin (TTN), cytoplasmic dynein 1 heavy chain 1 (DYNC1H1), TRIO and F-actin-binding protein (TRIO), probable ubiquitin carboxyl-terminal hydrolase FAF-X (USP9X), Cystatin-B (CSTB), and Pterin-4-alpha-carbinolamine dehydratase (PCBD1).

[00188] In some embodiments, the target cytosolic protein is SYNGAP1. In some embodiments, the target cytosolic protein is CDKL5. In some embodiments, the target cytosolic protein is ATP7B. In some embodiments, the target cytosolic protein is STXBP1. In some embodiments, the target cytosolic protein is GRN. In some embodiments, the target cytosolic protein is JAG1. In some embodiments, the target cytosolic protein is DEPDC5. In some embodiments, the target cytosolic protein is TSC2. In some embodiments, the target cytosolic protein is TSC1. In some embodiments, the target cytosolic protein is KIF1A. In some embodiments, the target cytosolic protein is DNM1. In some embodiments, the target cytosolic protein is SHANK3. In some embodiments, the target cytosolic protein is DMD. In some embodiments, the target cytosolic protein is TNT. In some embodiments, the target cytosolic protein is DYNC1H1. In some embodiments, the target cytosolic protein is TRIO. In some embodiments, the target cytosolic protein is USP9X. In some embodiments, the target cytosolic protein is TRIO. In some embodiments, the target cytosolic protein is USP9X. In some embodiments, the target cytosolic protein is CSTB. In some embodiments, the target cytosolic protein is USP9X. In some embodiments, the target cytosolic protein is PCBD1.

[00189] In some embodiments, the target cytosolic protein comprises an amino acid sequence

[illegible]

the target cytosolic protein comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 235. In some embodiments, the target cytosolic protein comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 236. In some embodiments, the target cytosolic protein comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 237. In some embodiments, the target cytosolic protein comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 238. In some embodiments, the target cytosolic protein comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 287. In some embodiments, the target cytosolic protein comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 288. In some embodiments, the target cytosolic protein comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 289.

**[00190]** Table 2 below, provides the wild type amino acid sequence of exemplary proteins to target for deubiquitination utilizing the fusion proteins described herein.

**Table 2.** The amino acid sequence of exemplary cytosolic proteins to target for deubiquitination utilizing the fusion proteins described herein and exemplary disease associations

| Description                            | Disease Associations                                                               | SEQ ID NO | Wild Type Amino Acid Sequence                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|----------------------------------------|------------------------------------------------------------------------------------|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cyclin-dependent kinase-like 5 (CDKL5) | CDKL5 Deficiency Disorder;<br><br>Epileptic encephalopathy, early infantile Type 2 | 221       | MKIPNIGNVMNKFEILGVVGEAYGVVLKCRHKETHE<br>IVAIAKKFKDSEENEEVKETTLRELKMLRTLKQENIVE<br>LKEAFRRRGKLYLVFEYVEKNMLELLEEMPNGVPPEK<br>VKSYYQLIKAIHWCHKNNDIVHRDIKPENLLISHNDV<br>LKLCDFGFARNLSEGNNANYTEYVATRWYRSPPELLLG<br>APYGKSVDMWVSGCILGELSDGQPLFPGESEIDQLFT<br>IQKVLGPLPSEQMKLFYSNPRFHGLRFPVNHQPQSLE<br>RRYLGILNSVLLDLMKNLLKLDPADRYLTEQCLNHPT<br>FQTQRLLDRSPSRSAKRKPYHVESSTLSNRNQAGKST<br>ALQSHHRSNSKDIQNLSVGLPRADEGLPANESFLNGN<br>LAGASLSPLHTKTYQASSQPGSTSKDLTNNNIPHLLS<br>PKEAKSKTEFDENIDPKPSEGPGTKYLKSNRSRQQNR<br>HSFMESSQSKAGTLQPNEKQSRHSYIDTIPQSSRSPS<br>YRTKAKSHGALSDSKSVSNLSEARAQIAEPSTSRYP<br>SSCLDLNSPTSPTPTRHSDTRTLLSPSGRNNRNEGTL<br>DSRRTTTRHSKTMEELKLPEHMDSSHSHSLSAPHESF |



|                                                |                |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|------------------------------------------------|----------------|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                |                |     | SYGLGYTSPFSSQQRPHRHSMYVTRDKVRAKGLDGSL<br>SIGQGMAARANSLQLLSPQPGEQLPPEMTVARSSVKE<br>TSREGTSSFHTRQKSEGGVYHDPHSDDGTPAKENRHL<br>YNDPVPRRVGSFYRVPSRPDNSFHENNVSTRVSSLP<br>SESSSGTNHRSKRQPAFDPWKSPENISHSEQLKEKEKQ<br>GFFRSMKKKKKKSQTVPNSDSPDLLTLQKSIHASTP<br>SSRPKEWRPEKISDLQTQSQPLKSLRKLLHLSSASNH<br>PASSDPRFQPLTAQQTKNSFSEIRIHPLSQASGGSSN<br>IRQEPAPKGRPALQLPGQMDPGWHVSSVTRSATGSPS<br>YSEQLGAKSGPNGHPYNRTNRSRMPNLNDLKETAL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Copper-<br>transporting<br>ATPase 2<br>(ATP7B) | Wilson disease | 222 | MPEQERQITAREGASRKILSKLSLPTRAWEPAKKSF<br>AFDNGVYEGGLDGLGPSSQVATSTVRILGMTCCQSCVK<br>SIEDRISNLKGIISMKVSLQGSATVKYVPSVVCLOQ<br>VCHQIGDMGFEASIAEGKAASWPSRSLPAQEAVVKLR<br>VEGMTCCQSCVSSIEGKVRKLQGVVRVKVSLSNQEAVI<br>TYQPYLIQPEDLRDHVNDMGFEAAIKSKVAPLSLGP<br>DIERLQSTNPKRPLSSANQNFNNSETLGHQGS HVVTL<br>QLRIDGMHCKSCVLNIEENIGQLLGVQSIQVSLENKT<br>AQVKYDPSCTSPVALQRAIEALPPGNFKVSLPDGAEG<br>SGTDHRSSSSHSPGSPPRNQVQGTCTTLIAIAGMTC<br>ASCVHSIEGMISQLEGVQQISVSLAEGTATVLYNPSV<br>ISPEELRAAIEDMGFEASVVSESCSTNPLGNHSAGNS<br>MVQTTDGTPTSVQEVAPHTGRLPANHAPDILAKSPQS<br>TRAVAPQKCFLOIKGMTCASCVSNIERNLQKEAGVLS<br>VLVALMAGKAEIKYDPEVIQPLEIAQFIQDLGFEAAV<br>MEDYAGSDGNIELTITGMTCASCVHNIESKLTRTNGI<br>TYASVALATSKALVKFDPEIIGPRDIIKIEEIGFHA<br>SLAQRNPNAHHLDHKMEIKQWKKSFLCSLVFGIPVMA<br>LMIYMLIPSNEPHQSMVLDHNIIPGLSILNLIFFILC<br>TFVQLLGGWYFYVQAYKSLRHRANMDVLIVLATSIA<br>YVYSLVILVVAVAEKAERSPVTFFDTPPMLFVFIALG<br>RWLEHLAKSKTSEALAKLMSLQATEATVVTLGEDNLI<br>IREEQVPMELVQRGDIVKVVPGGKFPVDGKVLEGNTM<br>ADESLITGEAMPVTKKPGSTVIAGSINAHGSVLIKAT<br>HVGNDTTLAQIVKLVEEAQMSKAPIQQALADRFSGYFV<br>PFIIIMSTLTLVWVIVIGFIDFGVVQRYFPNPNKHIS<br>QTEVIRFAFQTSITVLCIACPCSLGLATPTAVMVG<br>GVAAQNGILIKGGKPLEMAHKIKTMFMDKTGTITHGV<br>PRVMRVLLLDGVATLPLRKVLAVVGTAEEASSEHPLGV<br>AVTKYCKEELGTETLGYCTDFQAVPGCGIGCKVSNVE<br>GILAHSERPLSAPASHLNEAGSLPAEKDAVPQTFSVL<br>IGNREWLRRNGLTISSDVSDAMTDHEMKGQTAILVAI<br>DGVLCGMIAIADAVKQEAALAVHTLQSMGVDVVLITG<br>DNRKTARAIATQVGINKVFAEVLPSHKVAKVQELQNK<br>GKKVAMVG DGVDNDSPALAQADMGVAIGTGTDAIEAA<br>DVVLI RNDLLDVVASIHL SKRTVRRIRINLVLALIYN<br>LVGIPIAAGVFMPIGIVLQPWMGSAAMAASSVS VLS<br>SLQLKCYKKPDLERYEAQAHGHMKPLTASQVSVHIGM<br>DDRWRDSPRATPWDQVSYVSQVSLSSLTSDKPSRHS<br>AADDGDGKWSLLNLRDEEQYI |

|                                             |                                                                                    |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|---------------------------------------------|------------------------------------------------------------------------------------|-----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Syntaxin-binding protein 1 (STXBP1)         | STXBP1<br>Encephalopathy;<br><br>Epileptic encephalopathy, early infantile, Type 4 | 223 | MAPIGLKAVVGEKIMHDVIKKVKKKGEWKVLVVDQLS<br>MRMLSSCCKMTDIMTEGITIIVEDINKRREPLPSLEAV<br>YLITPSEKSVHSLISDFKDPPTAKYRAAHVFFTDSCP<br>DALFNELVKSRAAKVIKTLTEINIAFLPYESQVYSLD<br>SADSFQSFYSPHKAQMKNPILERLAEQIATLCATLKE<br>YPAVRYRGEYKDNALLAQLIQDKLDAYKADDPMTGEG<br>PDKARSQLLILDRGFDPPSPVLHELTFQAMSYDLLPI<br>ENDVYKYETSGIGEARVKEVLLDEDDDLWIALRHKHI<br>AEVSQEVTRSLKDFSSSKRMNTGEKTTMRDLSQMLKK<br>MPQYQKELSKYSTHLHLAEDCMKHYQGTVDKLCRVEQ<br>DLAMGTDAEGEKIKDPMRAIVPILLDANVSTYDKIRI<br>ILLYIFLKNGITENLNKLIQHAQIPPEDSEIITNMA<br>HLGVPIVTDSTLRRRSKPERKERISEQTYQLSRWTP<br>IKDIMEDTIEDKLDTKHYPYISTRSSASFSTTAVSAR<br>YGHWHKNKAPGEYRSGPRLIIFILGGVSLNEMRCAYE<br>VTQANGKWEVLIGSTHILTPQKLLDTLKKLNKTDEE<br>SS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Ras/Rap GTPase-activating protein (SYNGAP1) | SYNGAP1<br>Encephalopathy;<br><br>Mental retardation, autosomal dominant 5         | 224 | MSRSRASIHRGSIPAMSYAPFRDVRGSPSMHRTQYVHS<br>PYDRPGWNPRFCIIISGNQLMLLEDEDEIHPLLIIRDRS<br>ESSRNKLLRRTVSVVPEGRPHGEHEYHLGRSRRKSVP<br>GGKQYSMEGAPAAPFRPSQGFLSRRLKSSIKRTKSQP<br>KLDRTSSFRQILPRFRSADHDRARLMQSFKESHSHES<br>LLSPSSAAEALELNLEDEDSIIKPVHSSILGQEFCEV<br>TTSSGTCFCACRSAAERDKWIENLQRAVKPNKDNSRR<br>VDNVLKLWII EARELPKKRYCELCDDMLYARTTS<br>KPRSASGDTVFWGEHFEFNNLPVRLALRLHLYRDSK<br>KRKKDKAGYVGLVTVPVATLAGRHFTQWYPVTLPTG<br>SGGSGGMGSGGGGGSGGGSGGKGKGGCPAVRLKARYQ<br>TMSILPMELYKEFAEYVTNHYRMLCAVLEPALNVKKG<br>EEVASALVHILQSTGKAKDFLSDMAMSEVDRFMEREH<br>LIFRENTLATKAIEEYMRIGQKYLKDAIGEFIRALY<br>ESEENCEVDPIKCTASSLAHQANLRMCCELALCKVV<br>NSHCVFRELKEVFASWRLRCAERGREDIADRLISAS<br>LFLRFLCPAIMSPSLFGLMQEYPDEQTSRTLTLIAKV<br>IQNLANFSKFTSKEDFLGFMNEFLELEWGSMMQFLYE<br>ISNLDTLTNSSSFEGYIDLGRELSTLHALLWEVLPQL<br>SKEALLKLGLPLRLLNDISTALRNPNIQRQPSRQSER<br>PRPQPVVLRGPSAEMQGYMMRDLNSSIDLQSFMARGL<br>NSSMDMARLPSPTEKPPPPPPGGGKDLFYVSRPPLA<br>RSSPAYCTSSSDITEPEQKMLSVNKSVMMLDLQGDGP<br>GGRLNSSSVSNLAAVGDLLHSSQASLTAALGLRPAPA<br>GRLSQGSGSSITAAGMRLSQMGVTTDGVPAQQRLRIPL<br>SFQNPLFHMAADGPGPPGGHGGGGGGHGPSSHHHHHH<br>HHHHRGGEPPGDTFAPFHGYSKSEDLSSGVPKPPAAS<br>ILHSHSYSDEFGPSGTDFTTRQLSLQDNLQHMLSPQ<br>ITIGPQRPAPSGPGGGSGGGSGGGGGQPPPLQRGKS<br>QQLTVSAAQKPRPSSGNLLQSPEPSYGPAPRQQSLS<br>KEGSIGGSGGGSGGGGGGLKPSITKQHSQTPSTLNPT<br>MPASERTVAWVSNMPLSADIESAHIEREEYKLKEYS<br>KSMDESRLDRVKEYEEEEIHSLKERLHMSNRKLEEYER<br>RLLSQEEQTSKILMQYQARLEQSEKRLRQQQAEDSQ |

|                                |                                             |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|--------------------------------|---------------------------------------------|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                |                                             |     | IKSIIGRLMLVEEELRRDHPAMAEPLPEPKKRLLDAQ<br>ERQLPPLGPTNPRVTLAPPWNLAPPAPPPPRQLQIT<br>ENGEFRNTADH                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Progranulin<br>(GRN)           | Aphasia,<br>primary<br>progressive &<br>FTD | 225 | MWTLVSWVALTAGLVAGTRCPDGQFCPVACCLDPGGA<br>SYSCCRPLLDKWPTTTLRHLGGPCQVDAHCSAGHSCI<br>FTVSGTSSCCPFPEAVACGDGHHCCPRGFHCSADGRS<br>CFQRSGNNSVGAIQCPDSQFECPDFSTCCVMVDGSWG<br>CCPMPQASCCEDRVHCCPHGAFCDLVHTRCITPTGTH<br>PLAKKLPAQRTNRAVALSSSVMPDARSRCPDGSTCC<br>ELPSGKYGCCPMPNATCCSDHLHCCPQDTVCDLIQSK<br>CLSKENATTDLTKLPAHTVGDVKCDMEVSCPDGYTC<br>CRLQSGAWGCCPFTQAVCCEDHIHCCPAGFTCDTQKG<br>TCEQGP HQVPWMEKAPAHLSLPDPQALKRDPVPCDNVS<br>SCPSSDTCCQLTSGEWGCCPIPEAVCCSDHQHCCPQG<br>YTCVAEQQCQRGSEIVAGLEKMPARRASLSHPRDIGC<br>DQHTSCPVGQTCCPSLGGSWACCQLPHAVCCEDRQHC<br>CPAGYTCNVKARSCEKEVVSQAQPATFLARSPHVGVKD<br>VECGEGHFCHDNQTCCRDNRQGWACCOPYRQGVCCADR<br>RHCCPAGFRCAARGTKCLRREAPRWDAPLRDPALRQL<br>L                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Protein jagged-<br>1<br>(JAG1) | Alagille<br>syndrome 1                      | 226 | MRSRTRGRSGRPLSLLLALLCALRAKVC GASGQFEL<br>EILSMQNVN GELQNGNCCGGARNPGDRKCTRDECDTY<br>FKVCLKEYQSRVTAGGPCSFGSGSTPVIGGNTFNLKA<br>SRGNDNRNRIVL PFSFAWPRS YTLLEAWDSSNDTVQP<br>DSIIEKASHSGMINPSRQWQTLKQNTGVAHF EYQIRV<br>TCDDY YYGFGCNKFCRPRDDFFGHYACDQNGNKT CME<br>GWMGPECNRAICRQGCS PKHGSKCLPGDCRCQYGWQG<br>LYCDKCI PHPGCVHGICNEPWQCLCETNWWGGQLCDKD<br>LNYCGTHQPC LNGGTCSNTGPDKYQCSCPEGYSGPNC<br>EIAEHACLSDPCHNRGSKETSLGFECECSPGWTGPT<br>CSTNIDDCSPNNCSHGGTCQDLVNGFKVCVCPQWTGK<br>TCQLDANECEAKPCVNAKSCKNLIASYCDCLPGWMG<br>QNC DININDCLGQCQNDASCRDLVNGYRCICPPGYAG<br>DHCERDIDECASNPC LGGHCQNEINRFQCLCPTGFS<br>GNLCQLDIDYCEPNPCQNGAQCYNRASDY FCKCPEDY<br>EGKNC SHLKDHCRTTPCEVIDSCTVAMASNDTPEGVR<br>YISSNVCGPHGKCKSQSGGKFTCDCNKGFTGT YCHEN<br>INDCESNPCRNNGGTCIDGVNSYKICSDGWEGAYCET<br>NINDCSQNPCHNGGTCRDLVNDFYCDCKNGWKGTCH<br>SRDSQCDEATCNNGGTCYDEGDAFKCMCPGGWEGTTC<br>NIARNSSCLPNPCHNGGTCVVNGESFTCVCKEGWEGP<br>ICAQNTNDCSPHPCYNSGT CVDGDNWYRCECAPGFAG<br>PDCRININECQSSPCAFGATCVDEINGYRCVCPGHS<br>GAKCQEVSGRPCITMGSVIPDGA KWDDDCNTCQCLNG<br>RIACSKVWCGPRPCLLHKGHSECPSGQSCIPILDDQC<br>FVHPCTGVGECRSSLQPVKTKTSDSYQDNCANIT<br>FTFNKEMMS PGLTTEHICSELRLNLILKNVSAEYSIY<br>IACEPSPSANNEIHVAISAEDIRDDGNPIKEITDKII<br>DLVSKRDGNSSLIAAVAEVRVQRRPLKNRTDFLVPLL<br>SSVLTVAWICCLVTAFYWCLRRKRP GSHTHSASEDN<br>TTNNVREQLNQIKNPIEKHGANTVPIKDYENKNSKMS |

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|---------------------------------------------------|---------------------------------------------------------|-----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                   |                                                         |     | KIRTHNSEVEEDDMDKHQQKARFAKQPAYTLVDREEK<br>PPNGTPTKHPNWTNKQDNRDLESAQSLNRMEYIV                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| GATOR<br>complex<br>protein<br>DEPDC5<br>(DEPDC5) | Epilepsy,<br>familial focal,<br>with variable<br>foci 1 | 227 | MRTTKVYKLVIIHKKGFGGSDDDELVVNPKVFPHIKLG<br>IVEIAHPNDEYSPLLLQVKSLKEDLQKETISVDQTVT<br>QVFRRLRPYQDVYVNVVDPKDVTLDLVELTFKDQYIGR<br>GDMWRLKKSLVSTCAYITQKVEFAGIRAQAGELWVKN<br>EKVMCGYISEDTRVVFRSTSAMVYIFIQMSCEMWDFD<br>IYGDLYFEKAVNGFLADLFTKWKEKNC SHEVTVVLF<br>RTFYDAKSVDEFPEINRASIRQDHKGRFYEDFYKVVV<br>QNERREEWTSLLVTIKKLFIQYPVLVRLEQAEGFPQG<br>DNSTSAQGNYLEAINLSFNVFDKHYINRNFDRTGQMS<br>VVITPGVGVEVDRLLMILTKQRMIDNGIGVDLVC<br>EQPLHAVPLFKLHNRSAPRDSRLGDDYNIPHWINHSF<br>YTSKSQLFCNSFTPRIKLAGKKPASEKAKNGRDTSLG<br>SPKESENALPIQVDYDAYDAQVFRLLPGPSRAQCLTTC<br>RSVRERESHRSKSASSCDVSSSPSLPSRTLPTTEEVR<br>QASDDSSLGKSANILMIPHPHLHQYEVSSSLGYTSTR<br>DVLENMMEPPQRDSSAPGRFHVGSASMLHVRPGGYT<br>PQRALINPFAPSRMPMKLT SNRRRWMTFPVGPGEA<br>IQIHHQTRQNMALQSGSQRDPTHSSAELLELAYHEA<br>AGRHSNSRQPGDGMSFLNFSGTEELSVGLLSNSGAGM<br>NPRTQNKDSLEDSVSTSPDPILTLSAPPVVPFGCCTV<br>GVDWKSLLTPACPLTDDYFPDRQGLQNDYTEGCYDL<br>LPEADIDRRDEEDGVQMTAQQVFEEFICQRLMQGYQII<br>VQPKTQKPNPAVPPPLSSSPLYSRGLVSRNRPEEDQ<br>YWL SMGRTFHKVTLKDKMITVTRYLPKYPYESAQIHY<br>TYSLCPSHSDSEFVSCWVEFSHERLEEYKWNLYDQYI<br>CSAGSEDFSLIESLKFWRTRFLLLPACVTATKRITEG<br>EAHCDIYGDRPRADEDEWQLLDGFVRFEGLNRIRRR<br>HRSDRMMRKGTAMKGLQMTGP ISTHSLESTAPPVGKK<br>GTSALSALLEMEASQKCLGEQQA AVHGGKSSAQSAES<br>SSVAMTPTYMDSPRKDGAFFMEFVRSPRTASSAFYPQ<br>VSVDQTATPMLDGTSLGICTGQSM DRGNSQTFGNSQN<br>IGEQQYSSTNSSDSSQQLVASSLTSSSTLTEILEAM<br>KHPSTGVQLLSEQKGLSPYCFISAEVVHVLVNHVEGI<br>QTQAM AIDIMQKMLEEQ LITHASGEAWRTFIYGFYFY<br>KIVTDKEPDRVAMQQPATTWHTAGVDDFASFQRKWE<br>VAFVAEELVHSEIPAFLLPWLPSRPASYASRHSSFSR<br>SFGGRSQAALLAATVPEQRTVTLDVDVNNRTDRLEW<br>CSCYYHGNFSLNAAFEIKLHWM AVTA AVL FEMVQGW<br>RKATSCGFLLPVLEGPALPSYLYGDPLRAQLFIPL<br>NISCLLKEGSEHLFDSFEPETYWDRMHLFQEAIAHRF<br>GFVQDKY SASAFNFPAENKPQYIHVTGTVFLQLPYSK<br>RKFSGQQRRRRNSTSSTNQNMFC EERVGYNWAYNTML<br>TKTWRSSATGDEKFADRL LKDF TDFCINRDNRLVTFW<br>TSCLEKMHASAP |
| Tuberin<br>(TSC2)                                 | Tuberous<br>sclerosis-2                                 | 228 | MAKPTSKDSGLKEKFKILLGLGTPRPNPRSAEGKQTE<br>FIITAEILRELSMECGLNNRIRMIGQICEVAKTKKFE<br>EHAVEALWKAVADLLQPERPLEARHAVLALLKAIVQG<br>QGERLGVLRALFFKVIKDYPSNEDLHERLEVFKALTD<br>NGRHITYLEEELAD FVLQWMDVGLSSEFLLVLVNLVK                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

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|                    |                         |     | <p> FNSCYLDEYIARMVQMICLLCVRTASSVDIEVSLQVL<br/> DAVVCYNCLPAESLPLFIVTLCRTINVKELCEPCWKL<br/> MRNLLGTHLGHSIYNMCHLMEDRAYMEDAPLLRGAV<br/> FFVGMALWGAHRLYSLRNSPTSVLPSFYQAMACPNEV<br/> VSYEIVLSITRLIKKYRKELQVVAWDILLNIIERLLQ<br/> QLQTLDSPELRTIVHDLTTVEELCDQNEFHGSQERY<br/> FELVERCADQRPESSLLNLISYRAQSIHPAKDGWIQN<br/> LQALMERFFRSESRGAVRIKVLVDVLSFVLLINRQFYE<br/> EELINSVVISQLSHIPEDKDHQVRKLATQLLDLAEG<br/> CHTHHFNSLLDIEKVMARSLSPPELEERDVAAYSA<br/> SLEDVKTAVLGLLVILQTKLYTLPASHATRVYEMLV<br/> HIQLHYKHSYTLPIASSIRLQAFDFLLLLRADSLHRL<br/> GLPNKDGVVRFSPYCVCDYMEPERGSEKKTSGPLSPP<br/> TGPPGPAPAGPAVRLGSVPYSLLFRVLLQCLKQESDW<br/> KVLKLVGLRPESLRYKVLIFTSPCSVDQLCSALCSM<br/> LSGPKTLERLRGAPEGFSRTDLHLAVVPVLTALISYH<br/> NYLDKTKQREMVYCLEQGLIHRCASQCVVALSICSVE<br/> MPDIIKALPVLVVKLTHISATASMAVPLLEFLSTLA<br/> RLPHLYRNFAAEQYASVFAISLPYTNPSKFNQYIVCL<br/> AHHVIAMWFIRCLPFRKDFVPFITKGLRSNVLLSFD<br/> DTPEKDSFRARSTSLNERPKSLRIARPPKQGLNNSPP<br/> VKEFKESSAAEAFCRSISVSEHVRSRIQTSLTAS<br/> LGSADENSVAQADDSLKNLHLELTETCLDMMARYVFS<br/> NFTAVPKRSPVGEFLLAGGRKTWLVGNKLVTVTTSV<br/> GTGTRSLGLDSGELQSGPESSSSPGVHVRQTKEAPA<br/> KLESQAGQQVSRGARDVRMSGGHGLRVGALDVPAS<br/> QFLGSATSPGPRTAPAAKPEKASAGTRVPVQEKTNLA<br/> AYVPLLTQGWAEILVRRPTGNTSWLMSLENPLSPFSS<br/> DINNMPQLQELSNALMAAERFKEHRDTALYKSLVPA<br/> STAKPPPLPRSNTVASFSSLYQSSCQGQLHRVSWAD<br/> SAVVMEEGSPGEVPVLVEPPGLEDVEAALGMDRRTDA<br/> YSRSSSVSSQEEKSLHAEELVGRGIPIERVVSSEGGR<br/> PSVDLSFQPSQPLSKSSSSPELQTLQDILGDPGDKAD<br/> VGRLSPEVKARSQSGTLDGESAAWSASGEDSRGQPEG<br/> PLPSSSPRSPGLRPRGYTISDSAPSRGRKVERDAL<br/> KSRATASNAEKVPGINPSFVFLQLYHSPFFGDESNKP<br/> ILLPNESQS FERSVQLLDQIPSYDTHKIAVLYVGEQ<br/> SNSELA ILSNEHGSYRYTEFLTGLGRLIELKDCQPK<br/> VYLGGLDVCGEDGQFTYCWHDDIMQAVFH IATLMPTK<br/> DVDKHRC DKKRHLGNDFVSIVYNDSGEDFKLGTIKGQ<br/> FNFVHVIVTPLDYECNLVSLQCRKDMEGLVDTSVAKI<br/> VSDRNLPFVARQMALHANMASQVHHSRSNPTDIYPSK<br/> WIARLRHIKRLRQRICEEAAAYSNPSLPLVHPPSHSKA<br/> PAQTPAEPTPGYEVGQRKRLISSVEDFTEFV </p> |
| Hamartin<br>(TSC1) | Tuberous<br>sclerosis-1 | 229 | <p> MAQQANVGELLAMLDS PMLGVRDDVTAVFKENLNSDR<br/> GPMLVNTLV DYYLETSSQPALHILTTLQEPHDKHLLD<br/> RINEYVGKAATRLSILSLLGHVIRLQPSWKHKLSQAP<br/> LLPSLLKCLKMDTDVVVLTTGVLVLITMLPMIPQSGK<br/> QHLLDFFDI FGR LSSWCLKKPGHVAEVYLVHLHASVY<br/> ALFHRLYGMYPCNFVSFLRSHYSMKENLET FEEVVKP<br/> MMEHVRIHP ELVTGSKDHELDPRRWKRLETHDVVIEC </p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

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|------------------------------------------|--------------------------------------------------|-----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                          |                                                  |     | AKISLDPTEASYEDGYSVSHQISARFPHRSADVTTSP<br>YADTQNSYGCATSTPYSTSRMLLNMPGQLPQTLSSP<br>STRLITEPPQATLWSPSMVCGMTTPPTSPGNVPPDLS<br>HPYSKVFGTTAGGKGTPLGTPATSPPPAPLCHSDDYV<br>HISLPQATVTPPRKEERMDSARPCLHRQHHLNDRGS<br>EPPGSGKGSVTLSDLPGFLGDLASEEDSIEKDKEEAA<br>ISRELSEITTAEEAEPPVPRGGFDSPFYRDSLPGSQRK<br>THSAASSSQGASVNPEPLHSSLDKLGPDTPKQAFPTPI<br>DLPCGSADESPAGDRECQTSLETSIFTPSPCKIPPT<br>RVGFGSGQPPPYDHLFEVALPKTAHHFVIRKTEELLK<br>KAKGNTEEDGVPSTSPMEVLDRLIQQGADAHSKELNK<br>LPLPSKSVDWTHFGGSPPSDEIRTLRDQLLLHLNQLL<br>YERFKRQQHALRNRLLRKVIKAAALEEHNAAMKDQL<br>KLQEKDIQMWKVSQKEQARYNQLQEQRDMVTKLHS<br>QIRQLQHDREEFYNNQSQELQTKLEDCRNMAIELRIEL<br>KKANNKVCHELLELSQVSQKLSNSESQVQQMEFLNRQ<br>LLVLGEVNELYLEQLQNKHSDTTKEVEMMKAAAYRKEL<br>EKNRSHVLQQTQRLDTSQKRILELESHLAKKDHLLE<br>QKKYLEDVKLQARGQLQAAESRYEAQKRITQVFELEI<br>LDLYGRLEKDGLLKKLEEEKAEAAEAAEERLDCCNDG<br>CSDSMVGHNEEASGHNGETKTPRPSSARGSSGSRGGG<br>GSSSSSELSTPEKPPHQRAGPFSSRWETTMGEASAS<br>IPTTVGSLPSSKSFLGMKARELFRNKSESQCDEGMT<br>SSLSESLKTELKDLGVEAKIPLNLDGPHPSPTPDS<br>VGQLHIMDYNETHHEHS                                                                              |
| Kinesin-like<br>protein KIF1A<br>(KIF1A) | KIF1A-<br>Associated<br>Neurological<br>Disorder | 230 | MAGASVKVAVRVRPFNSREMSRDSKCI IQMSGSTTTI<br>VNPQKPKETPKSFSFDYSYWSHTSPEDINYASQKQVY<br>RDIGEEMQLQHA FEGYNVCI FAYGQTGAGKSYTMMGKQ<br>EKDQQGIIPQLCEDLFSRINDTTNDNMSYSVEVSYME<br>IYCERVRDLLNPKNKGNLVRVREHPLLGPYVEDLSKLA<br>VTSYNDIQDLMDSGNKARTVAATNMNETSSSRSHAVFN<br>IIFTQKRHDAETNITTEKVS KISLVDLAGSERADSTG<br>AKGTRLKEGANINKSLTTLGKVISALAEMDSGPKNK<br>KKKKTDFIPYRDSVLTWLLREN LGNSRTAMVAALSP<br>ADINYDETTLSTLRYADRAKQIRCNAVINEDPNNKLIR<br>ELKDEVTRLRDLLYAQGLGDITDMTNALVGMSPSSSL<br>SALSSRAASVSSLHERILFAPGSEEAIERLKETEKII<br>AELNETWEEKLRRTEAIRMEREALLAEMGVAMREDGG<br>TLGVFSPKKT PHLVNLNEDPLMSECLLYYIKDGITRV<br>GREDGERRDIVLSGHFIKEEHCVFRSDSRGGSEAVV<br>TLEPCEGADTYVNGKKVTEPSILRSGNRIIMGKSHVF<br>RFNHPEQARQERERTPCAETPAEPVDWAFQAQRELLEK<br>QGIDMKQEMEQRLELEDQYRRERE EATYLLQQRRLD<br>YESKLEALQKQMDSRYYPEVNEEEEEPEDEVQWTERE<br>CELALWAFRKWKWYQFTSLRDLLWGNAIFLKEANAIS<br>VELKKKVQFQFVLLTDTLYSPLPPDLLPPEAAKDRET<br>RPFPRTI VAVEVQDQKNGATHYWTLEKLRQRLDLMRE<br>MYDRAAEVPSSVIEDCDNVVTGGDPFYDRFPWFRLVG<br>RAFVYLSNLLYPVPLVHRVAIVSEKGEVKGFLRVAVQ<br>AISADEEAPDYGSGVRQSGTAKISFDDQHFEKFQSES<br>CPVVGMSRSGTSQEELRIVEGQGQGADVGPSADEVNN |

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|---------------------------------------------------------------------------|---------------------------------|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                           |                                 |     | <p>NTCSAVPPEGLLLDSSEKAALDGPLDAALDHLRLGNT<br/> FTFRVTVLQASSISAEYADIFCQFNFIHRHDEAFSTE<br/> PLKNTGRGPPLGFYHVQNIAVEVTKSFIIEYIKSQPIV<br/> FEVFGHYQQHPFPPLCKDVLSPLRPSRRHFPRVMPLS<br/> KPV PATKLSTLTRPCPGPCHCKYDLLVYFEICELEAN<br/> GDYIPAVVDHRGGMPCMGTFLLHQGIQRRITVTLLE<br/> TGSHIRWKEVREL VVGRI RNTPETDESLIDPNILSLN<br/> ILSSGYIHPAQDDRTFYQFEAAWDSSMHNSLLNRVT<br/> PYREKIYMTLSAYIEMENCTQPAVVTKDFCMVFYSRD<br/> AKLPASRSIRNLFSGSLRASESNRVTGVYELSLCHV<br/> ADAGSPGMQRRRRRVLDTSVAYVRGEENLAGWRPRSD<br/> SLILDHQWELEKLSLLQEVEKTRHYLLLRKLETAQR<br/> PVPEALSPA FSEDES HGSASSPLSAEGRSPLEA<br/> PNERQRELAVKCLRLTHTFNREYTHSHVCVSASESK<br/> LSEMSVTLLRDPMSPLGVATLTPSSTCPSLVEGRYG<br/> ATDLRTPQPCSRPASPEPELLPEADSKKLPSPARATE<br/> TDKEPQRLLPDIQEIRVSPIVSKKGYLHFLEPHTSG<br/> WARRFVVRRPYAYMYNSDKDTVERFVLNLATAQVEY<br/> SEDQQAMLKTPNTFAVCTEHRGILLQAASDKMDHDL<br/> YAFNPLLAGTIRSKLSRRRSAQMRV</p>                                                                                                                                                                            |
| Dynamin-1<br>(DNM1)                                                       | Encephalopathy                  | 231 | <p>MGNRGMEDLIPLVNRLQDAFSAIGQNADLDLPQIAVV<br/> GGQSAGKSSVLENFVGRDFLPRGSGIVTRRPLVLQLV<br/> NATTEYAEFLHCKGKKFTDFEEVRLEIEAETDRVTGT<br/> NKGISPVPINLRVYSPHVLNLTLVDLPGMTKVPVGDQ<br/> PPDIEFQIRDMLMQFVTKENCLILAVSPANSDLANS<br/> ALKVAKEVDPQGQRTIGVITKLDLMDEGTDARDVLEN<br/> KLLPLRRGYIGV VNR SQKDIDGKKDITAAALAEKFF<br/> LSHPSYRHLADRMGTPYLQKVLNQQLTNHIRDTPGL<br/> RNKLQSQLLSIEKEVEEYKNFRPDDPARKTKALLQMV<br/> QQFAVD FEKRIEGSGDQIDTYELSGGARINRIFHERF<br/> PFELVKMEFDEKELRREISYAIKNIHGIRTGLFTPDM<br/> AFETIVKKQVKKIREPCLKCVD MVI SELISTVRQCTK<br/> KLQQYPR LREEMERIVTTHIREREGRTKEQVMLLIDI<br/> ELAYMNTNHEDFIGFANAQQRSNQMNKKKTSNGQDEI<br/> LVIRKGWLTINNIGIMKGSKEYWFVLTAENLSWYKD<br/> DEEKEKKYMLSVDNLKLRDVEKGFMSKHI FALFNTE<br/> QRNVYKDYRQLELACETQEEVDSWKASFLRAGVYPER<br/> VGDK EKASETEENGSDSFMHSM DPQLERQVETIRNLV<br/> DSYMAIVNKTVRDLMPKTIHMLMINNTKEFI FSELLA<br/> NLYSCGDQNTLMEE SAEQAQRDEMLRMYHALKEALS<br/> IIGDINTTTVSTPMPPPVDDSWLQVQSV PAGRRSPTS<br/> SPTPQRRAPAVPPARPGSRGPAGPP PAGSALGGAPP<br/> VPSRPGASPDFGPPPVPSRPNRAPPGVPSRSGQAS<br/> PSRPESPRPPFDL</p> |
| SH3 and<br>multiple<br>ankyrin repeat<br>domains<br>protein 3<br>(SHANK3) | Phelan-<br>McDermid<br>syndrome | 232 | <p>MDGPGASAVVVRVGIPDLQQTKCLRLDPAAPVWAAKQ<br/> RVL CALNHSLQDALNYGLFQPPSRGRAGKFLDEERLL<br/> QEYPPNLDTPLPYLEFRYKRRVYAQNLI DDKQFAKLH<br/> TKANLKKFMDYVQLHSTDKVARLLDKGLDPNFHDPS<br/> GECPLSLAAQLDNATDLLKVLKNGGAHLDFRTRDGLT<br/> AVHCATRQRNAAALTLLDLGASPDYKDSRGLTPLYH<br/> SALGGGDALCCELLLDHAQLGITDENGWQEIHQACR</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

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|                     |                                 |     | <p>FGHVQHLEHLLFYGADMGAQNASGNTALHICALYNQE<br/> SCARVLLFRGANRDVRNYSQTAFQVAIIAGNFELAE<br/> VIKTHKDSDVVPFRETPSYAKRRRLAGPSGLASPRPL<br/> QRSASDINLKGEAQPAASPGPSLRSLPHQLLLQRLQE<br/> EKDRDRDADQESNISGPLAGRAGQSKI SPSGPGGPGP<br/> APGPGPAPPAPPAPPPRGPKRKLYSAVPGRKFIAVKA<br/> HSPQGEGEIPLHRGEAVKVLSIGEGGFWEGETVKGRGTG<br/> WFPADCVEEVQMRQHDTRPETREDRTKRLFRHYTVGS<br/> YDSLTSYSDYVIDDKVAVLQKRDHEGFVLRGAKAE<br/> TPIEEFTPTPAFPALQYLESVDVEGVAVRAGLRTGDF<br/> LIEVNGVNVVKVGHKQVVALIRQGGNRLVMKVSVTR<br/> KPEEDGARRRAPPKRAPSTTLRLRSKSMATAELEEL<br/> ASIRRRKGEKLDEMLAAAAEPTLRPDIADADSRAATV<br/> KQRPTSRRTITPAEISSLFERQGLPGPEKLPGLSKGI<br/> PRTKSGEDEKLASLLEGRFPRSTSMQDPVREGRGIP<br/> PPPQTAPPPPPAPYYFDSGPPPAFSPPPPPGRAYDTV<br/> RSSFKPGLEARLGAGAAGLYEPGAALGPLPYPERQKR<br/> ARSMIILQDSAPESGDAPRPPPAATPPERPKRRPRPP<br/> GPDSPYANLGAFSASLFAPSKPQRRKSPLVKQLQVED<br/> AQERAALAVGSPGPGGGSFAREPSPTHGRPRPGGLDY<br/> GAGDGPGLAFGGPGPAKDRRLEERRRSTVFLSVGAIE<br/> GSAPGADLPSLQPSRSIDERLLGTGPTAGRDLLLPSP<br/> VSALKPLVSGPSLGPSTFIHPLTGKPLDPSSPLAL<br/> ALAARERALASQAPSRSPTPVHSPDADRPGLFVDVQ<br/> ARDPERGLASPAFSPRSPAWIPVPARREAEKVPREE<br/> RKSPEDKKSMILSVLDTSLQRPAGLIVVHATSNGQEP<br/> SRLGGAEERPGTPELAPAPMQSAVAEPLPSRAQP<br/> PGGTPADAGPGQGSSEEEPELVFAVNLPPAQLSSSDE<br/> ETREELARIGLVPPPEEFANGVLLATPLAGPGPSPTT<br/> VPSPASGKPSSEPPPAPEESAADSGVEEADTRSSSDPH<br/> LETTSTISTVSSMSTLSSESSELTDTHTSFADGHTFL<br/> LEKPPVPPKPKLKSPLGKGPVTFRDPLLKQSSDSELM<br/> AQQHHAASAGLASAAGPARPRYLFQRRSKLWGDPVES<br/> RGLPGPEDDKPTVISELSSRLQQLNKDTRSLGEEPVG<br/> GLGSLLDPAKKSPIAAARLFSSLGELSSI SAQRSPGG<br/> PGGGASYSVRPSGRYPVARRAPSPVKPASLERVEGLG<br/> AGAGGAGRPFGLTPPTILKSSSL SIPHEPKVRFVVR<br/> SVSARSRSPPSPPLPSPASGPGPGAPGPRRPFQQKPL<br/> QLWSKFDVGDWLESIHLEGEHRDRFEDHEIEGAHLPAL<br/> TKDDFVELGVTRVGHMNIERLRQLDGS</p> |
| Dystrophin<br>(DMD) | Becker<br>Muscular<br>Dystrophy | 233 | <p>MLWWEVEEDCYEREDVQKKTFTKWNVAQFSKFGKH<br/> ENLFSDLQDGRRLDLLLEGLTGQKLKKEKGSTRVHAL<br/> NNVNKALRVLQNNNVLDVNIGSTDIVDGNHKLTLGLI<br/> WNIILHWQVKVMKNIMAGLQQTNSEKILLSWVRQST<br/> RNPQVNVINFTTSWSDGLALNALIHSHRPDLFDWNS<br/> VVCQQSATQRLEHAFNIARYQLGIEKLLDPEDVDTTY<br/> PDKKSILMYITSLFQVLPQQVSI EAIQEVEMLRPPK<br/> VTKEEHFQLHHQMHSQQITVSLAQGYERTSSPKPRF<br/> KSYAYTQAAYVTTSDPTRSPFPSPQHLEAPEDKSFSS<br/> LMESEVNLDRYQTALEEVLSWLLSAEDTLQAQGEISN<br/> DVEVVKDQFHTHEGYMMDLTAHQGRVGNILQLGSKLI</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |



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|  |  |  | <p>             GTGKLSSEDEETEVEQEQMNNLLNSRWECLRVASMEKQSN<br/>             LHRVLMDLQNQKLKELNDWLTKTEERTRKMEEEPLG<br/>             PDLEDLKRQVQQHKVLQEDLEQEQVRVNSLTHMVVVV<br/>             DESSGDHATAALEEQKVLGDRWANICRWTEDRWVLL<br/>             QDILLKWQRLTEEQCLFSAWLSEKEDAVNKIHTTGFK<br/>             DQNEMLSSLQKLAVLKADLEKKKQSMGKLYSLKQDLL<br/>             STLKNKSVTQKTEAWLDNFARCWDNLVQKLEKSTAQI<br/>             SQAVTTTQPSLTQTTVMETVTTVTTRREQILVKHAQEE<br/>             LPPPPPQKKRQITVDSEIRKRLDVDITELHSWITRSE<br/>             AVLQSPEFAIFRKEGNFSDLKEKVNAIEREKA EKFRK<br/>             LQDASRSAQALVEQMVNEGVNADSIKQASEQLNSRWI<br/>             EFCQLLSERLNLWLEYQNNIIAFYNQLQOLEQMTTTAE<br/>             NWLKIQTTPSEPTAIKSQLKICKDEVNRLSDLQPQI<br/>             ERLKIQSIALKEKGQGPFLDADFVAFTNHFKQVFSD<br/>             VQAREKELQTI FDTLPPMRYQETMSAIRTWVQQSETK<br/>             LSIPQLSVTDYEIMEQRLGELQALQSSSLQEQQSGLYY<br/>             LSTTVKEMSKKAPSEISRKYQSEFEEIEGRWKKLSSQ<br/>             LVEHCQKLEEQMNKLKRIQNHQITLKKWMAEVDVFLK<br/>             EEWPA LGDSEILKKQLKQCRLLVSDIQTIQPSLNSVN<br/>             EGGQKIKNEAEPEFASRLETTELKELNTQWDHMCQQVY<br/>             ARKEALKGGLKTVSLQKDLSEMHEWMTQAE EYLER<br/>             DFEYKTPDELQKAVEEMKRAKEEAQQKEAKVKLLTES<br/>             VNSVIAQAPPVAQEALKKELETLT TNYQWLCTRLNGK<br/>             CKTLEEVWACWHELLSYLEKANKWLNEVEFKLKT TEN<br/>             IPGGAE EISEVLDLENLMRHSEDNPNQIRILAQT LT<br/>             DGGVMDELIN ELET FNSRWRELHEEAVRRQK LLEQS<br/>             IQSAQETEKSLHLIQESLTFIDKQLAAYIADKVDA AQ<br/>             MPQEAQKIQSDLTSHEISLEEMKKHNQGEAAQRVLS<br/>             QIDVAQKKLQDVSMKFRLFQKPANFEQRLQESKMILD<br/>             EVKMHLPALET KSVEQEVVQSQLNHCVNLYKSLSEVK<br/>             SEVEMVIKTGRQIVQKKQTENPKELDERVTALKLHYN<br/>             ELGAKVTERKQQLEKCLKLSRKMRKEMNVLT EWLAAT<br/>             DMELTKRSAVEGMPSNLDSEVAWGKATQKEIEKQKVH<br/>             LKSITEVGEALKTVLGKKETLVEDKLSLLNSNWI AVT<br/>             SRAEEWLNLLLEYQKHMETFQNVDHITKWI IQADTL<br/>             LDESEKKKPQQKEDVLKRLKAELNDIRPKVDSTRDQA<br/>             ANLMANRGDHCRLVEPQISELNHRFAAISHRIKTGK<br/>             ASIPLKELEQFNSDIQKLLPLEAEIQQGVNLKEEDF<br/>             NKDMNEDNEGTVKELLQRGDNLQQRITDERKREEIKI<br/>             KQQLLQTKHNALKDLRSQRRKKALEISHQWYQYKRQA<br/>             DDLLKCLDDIEKKLASLPEPRDERKIKEIDRELQKKK<br/>             EELNAVRRQAEGLS EDGAAMAVEPTQIQLSKRWREIE<br/>             SKFAQFRRLNFAQIHTVREETMMVMTE DMPL EISYVP<br/>             STYLTEITHVSQALLEVEQLLNAPDLCAKDFEDLFKQ<br/>             EESLKNIKDSLQQSSGRIDI IHSKKTAALQSATPVER<br/>             VKLQEALSQ LDFQWEKV NMYKDRQGRFDRSVEKWRR<br/>             FHYDIKIFNQWLTEAEQFLRKTQIPENWEHAKYKWYL<br/>             KELQDGIGQRQTVVRTLNATGEEIIQQSSKTDASILQ<br/>             EKLGSNLNRWQEVCKQLSDRKKRLEEQKNILSEFQRD<br/>             LNEFVLWLEEADNIASIPLEPGKEQQLKEKLEQVKLL<br/>             VEELPLRQGILKQLNETGGPVLVSAPISPEEQDKLEN           </p> |
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|                                  |                        |     | KLIKQTNLQWIKVSRALPEKQGEIEAQIKDLGQLEKKL<br>EDLEEQLNHLLLLWLSPIRNQLEIYNQPNQEGPFDVKE<br>TEIAVQAKQPDVEEILSKGQHLYKEKPATQPVKRKLE<br>DLSSEWKAVNRLLQELRAKQPD LAPGLTTIGASPTQT<br>VTLVTQPVVTKETAISKLEMPSSLMLEVPALADFNRA<br>WTELTDWLSLLDQVIKSQRVMVGDLLEDINEMI IKQKA<br>TMQDLEQRRPQLEELITAAQNLKNKTSNQEARTIITD<br>RIERIQNQWDEVQEHQNRQQLNEMLKDSTQWLEAK<br>EEAEQVLGQARAKLESWKEGPYTVDAIQKKITETKQL<br>AKDLRQWQTNVDVANDLALKLLRDYSADDTRKVMHMIT<br>ENINASWRSIHKRVSERAAL EETHRLLQQFPLDLEK<br>FLAWLTEAETTANVLQDATRKERLLED SKGVKELMKQ<br>WQDLQGEIEAHTDVYHNLDENSQKILRSLEGSDDAVL<br>LQRRLDNMNFKWSELRKSLNIRSHLEASSDQWKRLH<br>LSLQELLVWLQKDDLSRQAPIGGDFPAVQKQNDVH<br>RAFKRELKTKEPVIMSTLETVRIFLTEQPLEGLEKLY<br>QEPRELPPPEERAQNVTRLLRKQAEVNT EWEKLNLS<br>ADWQRKIDETLERLQELQEATDELDLKL RQAEVIKGS<br>WQPVGDLLIDSLQDHLEKVKALRGEIAPLKENVSHVN<br>DLARQLTTLGIQLSPYNLSTLEDLNTRWKLLQVAVED<br>RVRQLHEAHRDFGPASQHFLSTSVQGPWERAISPKNV<br>PYYINHETQTT CWDHPKMTELYQSLADLNNVRF SAYR<br>TAMKLRRLLQKALCLDLLSLAACDALDQHNLKQNDQP<br>MDILQIINCLTTIYDRLEQEHNNLVNVL CVDMLCNW<br>LLNVYDTGRTGRIRVLSFKTGII SLCKAHLEDKYRYL<br>FKQVASSTGFCDQRRLLGLLLHDSIQIPRQLGEVASFG<br>GSNIEPSVRSCFQFANNKPEIEAALFLDWMRLEPQSM<br>VWLPVLHRVAAAETAKHQAKCNICKECPIIGFRYRSL<br>KHFNIDICQSCFFSGRVAKGHKMHYPMVEYCTPTTSG<br>EDVRDFAKVLKNKFRTKRYFAKHPRMGYLPVQTVLEG<br>DNMETPVTLINFWPVDSAPASSPQLSHDDTHSRIEHY<br>ASRLAEMENSNGSYLND SISPNESIDDEHLLIQHYCQ<br>SLNQDSPLSQPRSPAQILISLESEERGERILADLE<br>EENRNLAQAYDRLKQQHEHKGLSPLSPPEMMPTSPQ<br>SPRDAELIAEAKLLRQHKGRL EARMQILEDHNKQLES<br>QLHRLRQLLEQPQAEAKVNGTTVSSPSTSLQRSDSSQ<br>PMLLRVVGSTSDSMGEEDLLSPQDTSTGLEEVMEQ<br>LNNSFPSSRGRNTPGKPMREDTM |
| Oxygen-regulated protein 1 (RP1) | Retinitis Pigmentosa 1 | 234 | MSDTPSTGFSTI IHPTSSEGVPPPRHLSLTHPVVAKR<br>ISFYKSGDPQFGGVRVVVNPRSFKSF DALLDNL SRKV<br>PLPFGVRNISTPRGRHSITRLEELEDGESYLC SHGRK<br>VQPVLDLKARRRPRPWLSSRAISAHSPHPVAVAAPG<br>MPRPPRSLVVFRNGDPKTRRAVLLSRRVTQSFEAFLQ<br>HLTEVMQRPVVKLYATDGRRVPSLQAVILSSGAVVAA<br>GREPFKPGNYDIQKYLLPARLPGISQRVYPKGNAKSE<br>SRKISTHMSSSSRSQIYSVSSEKTHNND CYLDYSFVP<br>EKYLALEKND SQNLPIYPS EDDIEKSIIFNQDGTMTV<br>EMKVRFRIKEEETIKWTTTVSKTGPSNNDEKSEMSFP<br>GRTESRSSGLKLAACSF SADVSPMERSSNQEGSLAEE<br>INIQMTDQVAETCSSASWENATVDTDI IQGTQDQAKH<br>RFYRPPTPGLRRVRQKKS VIGSVTLVSETEVQEKMIG                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

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|                |                                 |     | <p>QFSYSEERESGENKSEYHMFTHSCSKMSSSVSNKPVLV<br/> QINNNDQMEESSLERKKENSLLKSSAISAGVIEITSQ<br/> KMLEMSHNGLPSTISNNSIVEEDVVDVDCVVLNKTGI<br/> KNFKTYGNTNDRFSPISADATHFSSNNSGTDKNISEA<br/> PASEASSTVTARIDRLINEFAQCGLTKLPKNEKKILS<br/> SVASKKKKSRQQAINSRYPQDQGLATKGILNKNERIN<br/> TKGRITKEMIVQDSDSPLKGGILCEEDLQKSDTVIES<br/> NTFCSKSNLNSTISKNFHRNKLNTTQNSKVQGLLTR<br/> KSRSLNKISLGAPKKREIGQRDKVFPHNESKYCKSTF<br/> ENKSLFHVFNILEQKPKDFYAPQSQAEVASGYLRGMA<br/> KKSLSVKVTDSHITLKSQKKRKGDVKVASAILSKQHA<br/> TTRANSLASLKKPDFPEAIAHHSIQNYIQSWLQNNINP<br/> YPTLKPIKSAPVCRNETSVVNCSNNSFSGNDPHTNSG<br/> KISNFMESNKHITKIAGLTGDNLCKEGDKSFIANDT<br/> GEEDLHETQVGSNDAYLVPLHEHCTLSQSAINDHNT<br/> KSHIAAEKSGPEKKLVYQEINLARKRQSVEAAIQVDP<br/> IEEETPKDLLPVLMLHQLQASVPGIHKQTQNGVVQMPG<br/> SLAGVPFHSAICNSSTNLLLAWLLVLNLKGSMNFCQ<br/> VDAHKATNKSSETLALLEILKHIAITEEADDLKAABA<br/> NLVESTTSHFGLSEKEQDMVPIDLSANCSTVNIQSV<br/> KCSNERTQGISSLDGGCSASEACAPEVCVLEVTCS<br/> CEMCTVNKAYSPKETCNPSDTFFPSDGYGVDQTS<br/> ACFLGEVCSLTDTVFSDKACAQKENHTYEGACPIDET<br/> YVPVNVNCTIDFLNSKENTYTDNLDSTEELERGGDIQ<br/> KDLNILTDPYKNGFNTLVSHQNVSNLSSCGLCLSEK<br/> EAELDKKHSSLDDEFENC SLRKFQDENAYTSFDMEEPR<br/> TSEEPGSITNSMTSSERNISELESFELENHDTDIFN<br/> TVVNGGEQATEELIQEEVEASKTLELIDISSKNIMEE<br/> KRMNGIIEYIISKRLATPPSLDFCYDSKQNSEKETNE<br/> GETKMVKMMVKTMETGSYSESSPDLKKCIKSPVTS<br/> SDYRPDSSEQPYKTSSDDPNDSGELTQEKEYNIGFV<br/> KRAIEKLYGKADI IKPSFFPGSTRKSQVCPYNSVEFQ<br/> CSRKASLYDSEGQSFGSSEQVSSSSSMLQEFQEERQD<br/> KCDVSAVRDNYCRGDIVEPGTKQNDSDRILTDIEEGV<br/> LIDKGKWLLENHLLRMSENPGMCGNADTTSDVTL<br/> DNNSSEVPYSHFGNLAPGPTMDELSSSELEELTQPLE<br/> LKCNYFNMPHGSDSEPFHEDLLDVRNETCAKERIANH<br/> HTEEKGS HQSERVCTSVTHSFISAGNKVYPVSDDAIK<br/> NQPLPGSNMIHGT LQEADSLDKLYALCGQHCPILT<br/> VI IQPMNEEDRGFAYRKESDIENFLGFYLMWKIHPYLLQ<br/> TDKNV FREENNKASMRQNLIDNAIGDIFDQFYFSNTF<br/> DLMGKRRKQKRINFLGLEEEGNLKKFQPD LKERFCMN<br/> FLHTSLLVVG NVDSNTQDL SGQTNEIFKAVDENNNLL<br/> NNRFQGSRTNLNQVRENINCHYFFEMLGQACLLDIC<br/> QVETSLNISNRNILELCMFEGENLFIWEEEDILNLTD<br/> LESSREQEDL</p> |
| Titin<br>(TTN) | Dilated<br>Cardiomyopathy<br>1G | 235 | <p>MTTQAPTFTQPLQSVVVLEGSTATFEAHISGFPVPEV<br/> SWFRDQGVISTSTLPGVQISFSDGRAKLTIPAVTKAN<br/> SGRYS LKATNGSGQATSTAELLVKAETAPPNFVQRLQ<br/> SMTVRQGSQVRLQVRVTGIPTPVVKFYRDGA EIQSSL<br/> DFQISQEGDLYSLLIAEAYPEDSGTYSVNATNSVGRA</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

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|  |  |  | TSTAELLVQGEEEVPAKKTIVSTAQISESRQTRIE<br>KKIEAHFDARS IATVEMVIDGAAGQQLPHKTPPRIPP<br>KPKSRSPTPPSIAAKAQLARQQSPSPIRHSPSPVRHV<br>RAPTPSPVRSVSPAARISTSPIRSVRSPLLMRKTQAS<br>TVATGPEVPPPWKQEGYVASSSEAEMRETTLTSTQI<br>RTEERWEGRYGVQEQVTISGAAGAAASVSASASYAAE<br>AVATGAKEVKQDADKSAAVATVVAAVDMARVREPVIS<br>AVEQTAQRTTTTAVHIQPAQEQRKEAEKTAVTKVVV<br>AADKAKEQELKSRTKEVITTKQE QMHVTHEQIRKETE<br>KTFVPKVVISAAKAKEQETRIS EITKKQKQVTQEAI<br>RQETEITAASMVVVATAKSTKLETVPGAQEETTTQOD<br>QMHLSEYKIMKETRKT VVPKVIVATPKVKEQDLVSRG<br>REGITTKREQVQITQE KMRKEAEKTALSTI AVATAKA<br>KEQETILRTRET MATRQEQIQVTHGKVDVGKAEAVA<br>TVVAAVDQARVREPREPGHLEESYAQQTTLEYGYKER<br>ISAAKVAEPPQRPASEPHVVPKAVKPRVIQAPSETHI<br>KTDDQKGMHISSQIKKTTDLTTERLVHVDKRPRASP<br>HFTVSKISVPKTEHG YEASIAGSAIATLQKELSATSS<br>AQKITKSVKAPT VKPSETRVRAEPTPLPQFPFADTPD<br>TYKSEAGVEVKKEVGVSITGTTVREERFEVLHGREAK<br>VTETARVPAPVEIPVTPPTLV SGLKNVTVIEGESVTL<br>ECHISGYPSPTVTWYREDYQIESSIDFQITFQSGIAR<br>LMIREAFAEDSGRFTCSAVNEAGTVSTSCYLAVQVSE<br>EFEKETTA VTEKFTTEEKRFVESRDVVM TDTSLTEEQ<br>AGPGEPAPYFITKPVVQKLVEGGSVVFGCQVGGNPK<br>PHVYWKKSGVPLTTGYRYKVSYNKQTGECKLVISMTF<br>ADDAGEYTI VVRNKHGETSASASLLEEADYELLMKSQ<br>QEMLYQTQVTA FVQEPKVGETAPGFVYSEYEKEYEKE<br>QALIRKKMAKDTVVVRTYVEDQEFHISSFEERLIKEI<br>EYRIIKTTLEELLEEDGEEKMAVDISESEAVESGFDS<br>RIKNYRILEGMGVT FHCMSGYPLPKIAWYKD GKRIK<br>HGERYQMDFLQDGRASLRIPVVLPEDEGIYTA FASNI<br>KGNAICSGKLYVEPAAPLGAPTYIPTLEPVSRIRSL<br>PRSVSRSPIRMSPARMSPARMSPARMSPARMSPGRRL<br>EETDESQLERLYKPVFVLKPV SFKCLEGQTARFDLKV<br>VGRPMPETFWFHDGQQI VNDYTHKVVIKEDGTQSLII<br>VPATPSDSGEWTVVAQNRAGRSSISVILTVEAVEHQV<br>KPMFVEKLKNVNIKEGSRLEMKV RATGNPNPDIVWLK<br>NSDII VPHKYPKIRIEG TKGEAALKIDSTVSQDSAWY<br>TATAINKAGRD TTRCKVNVEVEFAEPEPERKLIIPRG<br>TYRAKEIAAPELEPLHLRYGQE QWEEGDLYDKEKQOK<br>PFFKKKLTSLRLKRFGPAHFECRLTPIGDPTMVVEWL<br>HDGKPLEAANRLRMINEFGYCSLDYGVAYS RDSGIIT<br>CRATNKYGT DHTSATLIVKDEKSLVEESQLPEGRKGL<br>QRIEELERMAHEGALTGVTTDQKEKQKPDIVLYPEPV<br>RVLEGETARFR CRVTGYPQPKVNWYLNGLIRKSKRF<br>RVRYDGIHYLDIVDCKSYDTGEVKVTAENPEGVIEHK<br>VKLEIQQREDFRSVLRRAPEPRPEFHVHEPGKLQFEV<br>QKVDRPVDTTETKEVVKLKRAERITHEKVPEESEELR<br>SKFKRRTEEGYEAITAVELKSRKKDESYEELLRKTK<br>DELLHWTKELTEEEKKALAE EGKITIPTFKPDKIELS |
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|  |  |  | <p> PSMEAPKIFERIQSQTVGQGSDAHFRVRVVGKPDPEC<br/> EWYKNGVKIERSDRIYWYPEDNVCELVIDVTAEDS<br/> ASIMVKAINIAGETSSHAFLLVQAKQLITFTQELQDV<br/> VAKEKDTMATFECETSEPFVKVKWKDGMVEHGEDKY<br/> RMHSDRKVHFLSILTIDTSDAEDYSCVLVEDENVKTT<br/> AKLIVEGAVVEFVKELQDIEVPESYSGELECIVSPEN<br/> IEGKWHNDVELKSNGKYTITSRRGRQNLTVKDVTKE<br/> DQGEYSFVIDGKKTTCCLKMKPRPIAILQGLSDQKVC<br/> EGDIVQLEVKVSLESVEGVWMKDGQEVQPSDRVHIVI<br/> DKQSHMLLIEDMTKEDAGNYSFTIPALGLSTSGRVS<br/> YSVDVITPLKDVNVIEGTKAVLECKVSVPDVTSVKWY<br/> LNDEQIKPDDRVQAI VKGTKQRLVINRTHASDEGPYK<br/> LIVGRVETNCNLSVEKIKIRGLRDLTCTETQNVVFE<br/> VELSHSGIDVLWNFKDKEIKPSSSKYKIEAHGKIYKLT<br/> VLNMMKDDEGKYTFYAGENMTSGKLTVAGGAISKPLT<br/> DQTVAESQEA VFECEVANPDSKGEWLRDGHPLTNN<br/> IRSESDGHKRRLIIAATKLDDIGEYTYKVATSKTSKAK<br/> LKVEAVKIKKTLKNLTVTETQDAVFTVELTHPNVKG<br/> QWIKNGVVLESNEKYAISVKGTIYSLRIKNCAIVDES<br/> VYGFRGLRGASARLHVETVKI IKKPKDVTALENATV<br/> AFEVSVSHDTPVKWFHKSVEIKPSDKHRLVSEKRVH<br/> KLMLQNI SPSDAGEYTAVVGQLECKAKL FVETLHITK<br/> TMKNIEVPETKTASFCEVSHFNVP SMWLKNGVEIEM<br/> SEKFKIVVQGLHQLIIMNTSTEDSAEYTFVCGNDQV<br/> SATLTVTPIMITSMLKDINAEEKDTITFEVTVNYEGI<br/> SYKWLKNGVEIKSTDKCQMRTKKLTHSLNIRNVHFGD<br/> AADYTFVAGKATSTATLYVEARHIEFRKH IKDIKVL<br/> KKRAMFECEVSEPDITVQWMKDDQELQITDRIKIQKE<br/> KYVHRLIPSTRMSDAGKYTVVAGGNVSTAKLFVEGR<br/> DVRIRSIKKEVQVIEKQRAVVEFEVNEDDVAHWYKD<br/> GIEINFQVQERHKYVVERRIHRMFISETRQSDAGEYT<br/> FVAGRNRSSVTLYVNAPEPPQVLQELQPVTVQSGKPA<br/> RCAVISGRPPQPKISWYKEEQLLSTGFKCKFLHDGQE<br/> YTLLLIEAFPEDAAYTCEAKNDYGVATT SASLSVEV<br/> PEVSPDQEMPVYPPAIITPLQDVTVTSEGQPARFQCR<br/> VSGTDLKVSWSKDKKIKPSRFFRMTQFEDTYQLEIA<br/> EAYPEDEGTYTFVASNAVQVSSSTANLSLEAPESILH<br/> ERIEQEIEMEMKEFSSSFLSAEEGLHSAELQLSKIN<br/> ETLELLSESPVYPTKFDSEKEGTGPIFIKEVSNADIS<br/> MGDVATLSVTVIGIPKPKIQWFFNGVLLTPSADYKFV<br/> FDGDDHSLIILFTKLEDEGEYTCMASNDYGKTIC SAY<br/> LKINSKGEHGKDTETESAVAKSLEKLGGPCPPHFLKE<br/> LKPIRCAQGLPAIFEYTVVGEPAPTVTWFKENKQLCT<br/> SVYYTIIHNPNNGSGTFIVNDPQREDSGLYICKAENML<br/> GESTCAAELLVLEDTDMTDTPCAKSTPEAPEDFPQ<br/> TPLKGPAVEALDSEQEIIATFVKDTILKAALITEENQQ<br/> LSYEHIAKANELSSQLPLGAQELQSILEQDKLTPEST<br/> REFLCINGSIH FQPLKEPSPNLQLQIVQSQKTF SKEG<br/> ILMPEEPETQAVLSDTEKIFPSAMSIEQINSLTVEPL<br/> KTL LAEPEGNY PQSSIEPPMHSYLT SVAEEVLSPKEK<br/> TVSDTNREQRVTLQKQEAQSALILS QSLAEGHVESLQ </p> |
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|  |  |  | SPDVMISQVNYEPLVPSEHSCTEGGKILIESANPLEN<br>AGQDSAVRIEEGKSLRFPLALEEKQVLLKEEHSNDVV<br>MPPDQIIIESKREPVAIKKVQEVQGRDLLSKESLLSGI<br>PEEQRLNLKIQICRALQAAVASEQPGLFSEWLRNIEK<br>VEVEAVNITQEPRHIMCMYLVTSAKSVTEEVTTIIED<br>VDPQMANLKMELRDALCAIIEEIDILTAEGPRIQQG<br>AKTSLQEEMDSFSGSQKVEPITEPEVESKYLISTEEV<br>SYFNVQSRVKYLDATPVTKGVASAVVSDEKQDESLKP<br>SEEKEESSSESGETEEVATVKIQEAEGGLIKEDGPMIH<br>TPLVDTVSEEGDIVHLTTSITNAKEVNWYFENKLVPS<br>DEKFKCLQDQNTYTLVIDKVNTEHDQGEYVCEALNDS<br>GKTATSAKLTVVKRAAPVIKRKIEPLEVALGHLAKFT<br>CEIQSAPNVRWFQWKAGREIYESDKCSIRSSKYISSL<br>EILRTQVVDCGEYTCKASNEYGSVSCTATLTVTEAYP<br>PTFLSRPKSLTTFVGKAAKFICTVTGTPVETIWIQKD<br>GAALSPSPNWRISDAENKHILELSNLTIQDRGVYSCK<br>ASNKFGADICQAEIIIDKPHFIKELEPVQSAINKKV<br>HLECQVDEDRKVTVTWSKDGQKLPPGKDYKICFEDKI<br>ATLEIPLAKLKDSGTIVCTASNEAGSSSSCSATVTVRE<br>PPSFVKKVDPSYMLPGESARLHCKLKGSFVIQVTWF<br>KNNKELSESNTVRMYFVNSEAILDITDVKVEDSGSYS<br>CEAVNDVGSDSCSTEIVIKEPPSFIKTLEPADIVRGT<br>NALLQCEVSGTGPFIEISWFKDKKQIRSSKKYRLFSQK<br>SLVCLEIFSFNSADVGEYECVVANEVGKCGCMATHLL<br>KEPPTFVKKVDDLIALGGQTVTLQAAVRGSEPISVTW<br>MKGQEVIREDGKIKMSFSNGVAVLIIPDVQISFGGKY<br>TCLAENEAGSQTSVGELIVKEPAKIIERAELIQVTAG<br>DPATLEYTVAGTPELKPKWKYKDGRLPLVASKKYRISFK<br>NNVAQLKFYSAELHDSGQYTFEISNEVGSSSCETTFT<br>VLDRDIAPFFTKPLRNVDSVVNGTCRLDCKIAGSLPM<br>RVSWFKDGKEIAASDRYRIAFVEGTASLEIIRVDMND<br>AGNFTCRATNSVGSKDSSGALIVQEPPSFVTKPGSKD<br>VLPGSVAVCLKSTFQGSTPLTIRWFKGNKELVSGGSCY<br>ITKEALESSLELYLVKTSDSGTYTCKVSNVAGGVECS<br>ANLFVKEPATFVEKLEPSQLLKKGDATQLACKVTGTP<br>PIKITWTFANDREIKESSKHRMSFVESTAVLRITDVGI<br>EDSGEYMCEAQNEAGSDHCSSIVIVKESPYFTKEFKP<br>IEVLKEYDVMLLAEVAGTPPFETWFKDNTILRSGRK<br>YKTFIQDHLVSLQILKFVAADAGEYQCRVTNEVGSSI<br>CSARVTLREPPSFIKKIESTSSLRGGTAAAFQATLKGS<br>LPITVTWLKDSDEITEDDNIRMTFENNVASLYLSGIE<br>VKHDGKYVCQAKNDAGIQRCALLSVKEPATITEEAV<br>SIDVTQGD PATLQVKFSGTKEITAKWFKDGQELTLGS<br>KYKISVTDTVSILKIIISTEKKDSGEYTFEVQNDVGRS<br>SCKARINVLDLIIPPSFTKKLKKMDSIKGSFIDLECI<br>VAGSHPI SIQWFKDDQEISASEKYKFSFHDNTAFLEI<br>SQLEGTDSGTYTCSATNKAGHNQCSGHLTVKEPPYFV<br>EKPQSQDVNPNTRVQLKALVGGTAPMTIKWFKDNKEL<br>HSGAARSVWKDDTSTLELFAAKATDSGTYICQLSND<br>VGTATSKATL FVKEPPQFIKKPSPVLVLRNGQSTTFE<br>CQITGTPKIRVSWYLDGNEITAIQKHGISFIDGLATF |
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|  |  | <p> QISGARVENSGTYVCEARNDA GTASCSIELKVKEPPT<br/> FIRELKPVEVVKYSDVELECEVTGTPPFEVTWLKNNR<br/> EIRSSKKYTLTDRVSVFNLHITKCDPSDTGEYQCIVS<br/> NEGGSCSCSTRVALKEPPSFIKKIENTTTVLKSSATF<br/> QSTVAGSPPI SITWLKDDQILDEDDNVYISFVDSVAT<br/> LQIRSVDNHSGRYTCQAKNESGVERCYAFLLVQEPA<br/> QIVEKAKSVDTVTEKDPMTLECVVAGTPELKVWLKDG<br/> KQIVPSRYFSMSFENNVASFRIQSVMKQDSGQYTFKV<br/> ENDFGSSSCDAYLRVLDQNIPPSFTKKLT KMDKVLGS<br/> SIHMECKVSGSLPISAQWFKDGKEISTSAKYRLVCHE<br/> RSVSLEVN NLELEDTANYTCKVSNVAGDDACSGILTV<br/> KEPPSFLVKPGRQQAIPDSTVEFKAILKGT PPFKIKW<br/> FKDDVELVSGPKCFIGLEGSTSFNLYSVDASKTGQY<br/> TCHVTNDVGS DSCTTMLLVTEPPKFVKKLEASKIVKA<br/> GDSSRLECKIAGSPEIRVVWFRNEHEL PASDKYRMTF<br/> IDSVAVIQMNNLSTEDSGDFICEAQNPAGSTSCSTKV<br/> IVKEPPVFSSFPPIVETLKNAEVSLECELSGTPPFEV<br/> VWYKDKRQLRSSKKYKIASKNFHTSIHILNVDTS DIG<br/> EYHCKAQNEVGSDTCVCTVKLKEPPRFVSKLNSLTVV<br/> AGEPAELQASIEGAQPIFVQWLKEKEEVIRESENIRI<br/> TFVENVATLQFAKAEPANAGKYICQIKNDGGMRENMA<br/> TLMVLEPAVIVEKAGPMTVTVGETCTLECKVAGTPEL<br/> SVEWYKDGKLLTSSQKHKFSFYNKISSRLILSVERQD<br/> AGTYTFQVQNNVGKSSCTAVVDVSDRAVPPSFTRRLK<br/> NTGGVLGASCILECKVAGSSPISVAWFHEKT KIVSGA<br/> KYQTTFSDNVCTLQLNSLDSSDMGNYTCVAANVAGSD<br/> ECRAVLTVQEPPSFVKEPEPLEVLPGKNVTFTSVIRG<br/> TPPFKVNWFRGARELVKGDRCNIFYEDTVAELELFNI<br/> DISQSGEYTCVVSNNAGQASCTTRLFVKEPAAFLKRL<br/> SDHSVEPGKSIILESTYTGTLPISVTWKKDGFNITTS<br/> EKCNIVTTEKTCILEILNSTKR DAGQYSCEIENEAGR<br/> DVCALVSTLEPPYFVTELEPLEAAVGDSVSLQCQVA<br/> GTPEITVSWYKGD TKLRPTPEYRTYFTNNVATLVFNK<br/> VNINDSGEYTCKAENSIGTASSKTVFRIQERQLPPSF<br/> ARQLKDIEQTVGLPVT LTCRLNGSAPIQVCWYRDGVL<br/> LRDDENLQTSFVDNVATLKILQTDLSHSGQYSCSASN<br/> PLGTASSSARLTAREPKKSPFFDIKPVSIDVIAGESA<br/> DFECHVTGAQPMRITWSKDNKEIRPGGNYTITCVGNT<br/> PHLRILKVGKGDSGQYTCQATNDVGKDMCSAQLSVKE<br/> PPKFVKKLEASKVAKQGESI QLECKISGSPEIKVSWF<br/> RNDSELHESWKYNMSFINSVALLTINEASAEDSGDYI<br/> CEAHNGVG DASCSTALT VKAPPVFTQKPSPVGALKGS<br/> DVILQCEISGTPPFEVVWVKDRKQVRNSKKFKITSKH<br/> FDTSLHILNLEASDVGEYHCKATNEVGSDTCSCSVKF<br/> KEPPRFVKKLSDTSTLIGDAVELRAIVEGFQPI SVVW<br/> LKDRGEVIRESENTRISFIDNIATLQLGSP EASNSGK<br/> YICQIKNDAGMRECSAVLTVLEPARIIEKPEPMTVTT<br/> GNPFALECVVTGTPELSAKWFKD GRELSADSKHHITF<br/> INKVASLKIPCAEMSDKGLYSFEVKN SVGKSNCTVSV<br/> HVSDRIVPPSFIRKLKDVNAILGASVVLECRVSGSAP<br/> ISVGWFQD GNEIVSGPKCQSSFSENVCTLNLSLLEPS </p> |
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|  |  |  | DTGIYTCVAANVAGSDECSAVLTVQEPPSFEQTPDSV<br>EVLPGMSLTFTSVIRGTPPFVKVWFKGSRELVPGES<br>NISLEDFVTELELFEVQPLESGDYSCLVTNDAGSASC<br>TTHLFVKEPATFVKRLADFSVETGSPIVLEATYTGTP<br>PISVSWIKDEYLISQSERCSTMTTEKSTILEILESTI<br>EDYAQYSCLIEAGQDICEALVSVLEPPYFIEPLEH<br>VEAVIGEPATLQCKVDGTPEIRISWYKEHTKLRSAPA<br>YKMQFKNNVASLVINKVDHSDVGEYSCKADNSVGAVA<br>SSAVLVIKARKLPFFFARKLKDVHETLGFPVAFECRI<br>NGSEPLQVSWYKDGVLKDDANLQTSFVHNVATLQIL<br>QTDQSHIGQYNCSASNPLGTASSSAKLILSEHEVPPF<br>FDLKPVSVDLALGESGTFKCHVTGTAPIKITWAKDNR<br>EIRPGGNYKMTLVENTATLTVLVKGKGDAGQYTCYAS<br>NIAGKDSCSAQLGVQEPPRFIKKLEPSRIVKQDEFTR<br>YECKIGGSPEIKVLWYKDETEIQESSKFRMSFVDSVA<br>VLEMHNLSVEDSGDYTCEAHNAAGSASSSTSLKVKEP<br>PIFRKKPHPIETLKGADVHLECELQGTTPPFHVSWKD<br>KRELRSKGKYMIMSENFLTSTHILNVDAADIGEYQCK<br>ATNDVGS DTCVGSIALKAPPRFVKKLSDISTVVGKEV<br>QLQTTIEGAEPISVVWFKDKGEIVRES DNIWISYSEN<br>IATLQFSRVEPANAGKYTCQIKNDAGMQECFATLSVL<br>EPATIVEKPESIKVTTGDTCTLECTVAGTPELSTKWF<br>KDGKELTSDNKYKISFFNKVSGLKIINVAPSDSGVYS<br>FEVQNPVGKDSCTASLQVSDRTVPPSFTRKLKETNGL<br>SGSSVMECKVYGSPPIVSWFHEGNEISSGRKYQTT<br>LTDNTCALTVMLEESDSGDYTCIATNMAGSDECSAP<br>LTVREPPSFVQKPDPMDLTGTNVTFTSIVKGTPPFS<br>VSWFKGSSELVPGDRCNVSLSDVAELELFDVDTSSQS<br>GEYTCIVSNEAGKASCTTHLYIKAPAKFVKRLNDYSI<br>EKGKPLILEGTFTGTPIVSWTKKNGINVTSPQRNI<br>TTTEKSAILEIPSSTVEDAGQYNKYIENASGKDSCSA<br>QILILEPPYFVKQLEPVKVSVDGDSASLQCQLAGTPEI<br>GVSWYKGDTKLRPTTTYKMHFRNNVATLVFNQVDIND<br>SGEYICKAENSVGEVSASTFLTVQEQLPPSFQRQLR<br>DVQETVGLPVVFDCAISGSEPIVSWYKDGKPLKDSP<br>NVQTSFLDNTATLNI FKTDRLAGQYSCTATNPISGA<br>SSSARLILTEGKNPPFFDIRLAPVDAVVGESADFECH<br>VTGTQPIKVSWAKDSREIRSGGKYQISYLENSAHLTV<br>LKVDKGD SGQYTCYAVNEVGKDSCTAQLNIKERLIPP<br>SFTKRLSETVEETEGNSFKLEGRVAGSQPITVAWYKN<br>NIEIQPTSNCEITFKNNTLVQLVRKAGMNDAGLYTCK<br>VSNDAGSALCTSSIVIKEPKKPPVFDQHLTPVTVSEG<br>EYVQLSCHVQGSEPIRIQWLKAGREIKPSDRCSFSFA<br>SGTAVLELRDVAKADSGDYVCKASNVAGSDTTKSKVT<br>IKDKPAVAPATKKA AVDGRLEFFVSEPQSIRVVEKTTA<br>TFIAKVGGDPIPNVKWTKGKWRQLNQGRVFIHQKGD<br>EAKLEIRDTTKTDSGLYRCVAFNEHGEIESNVNLQVD<br>ERKKQEKIEGDLRAMLKKTPI LKKGAGEEEEEIDIMEL<br>LKNVDPKEYEKYARMYGITDFRGLLQAFELLKQSQEE<br>ETHRLEIEEIERSERDEKEFEELVSFIQQRLSQTEPV<br>TLIKDIENQTVLKDND AVFEIDIKINYPEIKLSWYKG |
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|  |  |  | <p>           TEKLEPSDKFEISIDGDRHTLRVKNQCQLKDQGNRYRLV<br/>           CGPHIASAKLTVIEPAWERHLQDVTLEKQGCTCTMTCQ<br/>           FSVPNVKSEWFRNGRILKPQGRHKTEVEHKVHKLTIA<br/>           DVRAEDQGGYTCKYEDLETSaelRIEAEPIQFTKRIQ<br/>           NIVVSEHQSATFECEVSFDDAIVTWYKGPTELTESQK<br/>           YNFRNDGRCHYMTIHNVTDPDEGVYSVIARLEPRGEA<br/>           RSTAElyLTtKEIKLELKPPDIPDSRVPIPTMPIRAV<br/>           PPEEIPPVVAPPiPLLLPTPEEKKPPPKRIEVTkkAV<br/>           KKDAKKVVAkpKEMTPREEIVKKPPPTTLIPAKAPE<br/>           I IDVSSKAEEVKIMTITRKKEVQKEKEAVYEKKQAVH<br/>           KEKRVFIESFEePYDELEVEPYTEPFEPQPYEEPDed<br/>           YEEIKVEAKKEVHEEWEEDFEEGQeYYEREeGYDEGE<br/>           EEWEEAYQEREVIQVQKEVYEEESHerkVPAKVPEKKA<br/>           PPPPKVIKKPVIEKIEKTSRRMEEEKVQVTKVPEVSK<br/>           KIVPQKPSRTPVQEEVIEVKVPAVHTKKMVISEEKMF<br/>           FASHTEEEVSVTVPEVQKEIVTEEKIHVAISKRVePP<br/>           PKVPELPEKPAPEEVAPVPIPKKVEPPAPKVPEVPPK<br/>           PVPEEKKPVVPVKKEPAAPPKVPEVPPKPVPEEKIPV<br/>           PVAKKKEAPPAKVPEVQKGVVTEEKITIVTQREESPP<br/>           PAVPEIPKKKVPEERKPVPRKEEEVPPPPKVPALPKK<br/>           PVPEEKVAVPVPVAKKAPPRAEVSKKTvVEEKRFVA<br/>           EEKLSFAVPQRVEVTRHEVSAEEeWSYSEEEEGVSIS<br/>           VYREEEEREEEEAEVTEYEVMEePEEYVVEEKLHIIS<br/>           KRVEAEPAEVTERQEKKIVLKPKIPAKIEEPppAKVP<br/>           EAPKKIVPEKKVPAPVPKKEKVPPPKVPEEPKKPVPE<br/>           KKVPPKVIKMEePLPAKVTERHMQITQEEKVLVAVTK<br/>           KEAPPKARVPEEPKRAVPEEKVLKLKPKREEEPpAKV<br/>           TEFRKRvVKEEKVSIEAPKREPQPIKEVTIMEEKERA<br/>           YTL EEeAVSVQREEEYEEYEEYDYKEFEeYEPTEEYD<br/>           QYEEYEEREYERYEEHEEYITEPEKPIPVKPVPEEPV<br/>           PTKPKAPPAKVLKKAVPEEKVPVPIPKKLKPPPPKVP<br/>           EEPPKKVFEEKIRISITKREKEQVTEPAAKVPMKPKRV<br/>           VAEEKVPVPRKEVAPPVRVPEVPKELEPEEEVAFEEEV<br/>           VTHVEEYLVEEEEEYIHEEEEFITEEEVVPVPIPVKVP<br/>           EVPRKPVPEEKKPVVPKKEAPPAAKVPEVPKKPEEK<br/>           VPVLI PKKEKPPPAKVPEVPKKPVPEEKVPVPVPPKV<br/>           EAPPAAKVPEVPKKPVPEKKVPVPAPKKVEAPPAAKVPE<br/>           VPKKLIPEEKKPTVPVKKEAPPKVPKKREPVPVPV<br/>           ALPQEEeVLFEEeIVPEEEVLPEEEeVLPEEEeVLPE<br/>           EEeVLPEEEeIPPEEEeVPPEEeYVPEEEeFVPEEEV<br/>           LPEVKPKVPVPAPVPEIKKKVTEKKVVIPKKEEAPPA<br/>           KVPEVPKKVEEKRIILPKEEEVLPEVEVTEEPEEEPIs<br/>           EEeIPEEPPSIEEVEEVAPPRVPEVIKKAVPEAPTpv<br/>           PKKVEAPPAAKVSKKIPEEKVPVPVQKKEAPPAAKVPEV<br/>           PKKVPEKKVLVPKKEAVPPAKGRTVLEEKVSVAFRQE<br/>           VVVKERLELEVVEAEVEeIPEEEeFHEVEeYFEEGEF<br/>           HEVEeFIKLEQHRVEEEHRVEKvHRVIEVFEEAEVEV<br/>           FEKPKAPPKGPEISEKIIPPKKPPTKVVPKKEPPAAKV<br/>           PEVPKKIVVEEKVRVPEEPRVPPTKVPEVLPPKEVVP<br/>           EKKVPVPPAKKPEAPPKVPPEAPKEVVPEKKVPVPPP<br/>           KKPEVPPTKVPEVPKAAVPEKKVPEAIPPKPESPPE         </p> |
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|  |  |  | VPEAPKEVVPEKKVPAAPPKKPEVTPVKVPEAPKEVV<br>PEKKVPVPPPKKPEVPPTKVPEVPKVAVPEKKVPEAI<br>PPKPESPPPEVFEEPEEVALEEPPEAEVVEEPEPAAPP<br>QVTVPPKKPVPEKKAPAVVAKKPELPPVKVPEVPKEV<br>VPEKKVPLVVPKKPEAPPKAVPEVPKEVVPEKKVAVP<br>KKPEVPPAKVPEVPKKPVLEEKPAVPVPERAESPPPE<br>VYEEPEEIIAPEEEIIAPEEEKPVPAEEEEPEVPPPAV<br>PEEPKKIIPEKKVPVIKKPEAPPKPEPEPEKVKIEKPK<br>LKPRPPPPPPAPPKEDVKEKIFQLKAIPKKKVPEKPQ<br>VPEKVELTPLKVPGGEEKVRKLLPERKPEPKKEEVVLK<br>SVLRKRPEEEEPKVEPKKLEKVKKPAVPEPPPPKPV<br>EVEVPTVTKRERKIEPTKVPEIKPAIPLPAPEPKPK<br>PEAEVKTIKPPPVEPEPTPIAAPVTVPVVGKKA EAKA<br>PKEEAAKPKGPIKGVPKKTPSPIEAERRKL RPSGSGE<br>KPPDEAPFTYQLKAVPLKFVKEIKDIIILTESEFVGSS<br>AIFECVSPSTAITTWMKDGSNIRESPKHRFIADGKD<br>RKLHIIDVQLSDAGEYTCVLRRLGNKEKTSTAKLVVEE<br>LPVRFVKTLEEEVTVVKGQPLYLSCELNKERD VVWRK<br>DGKIVVEKPGRIVPGVIGLMRALTINDADDT DAGTYT<br>VTVENANNLECSSCVKVVEVIRDWLVKPIRDQHVKPK<br>GTAIFACDIAKDTPNIKWFKGYDEIPAEPNDKTEILR<br>DGNHLYLKIKNAMPEDIAEYAVEIEGKRYPAKLT LGE<br>REVELLKPIEDVTIYEKESASFDAEISEADIPGQWKL<br>KGELLRPSPTCEIKAEGGKRFTLHKVKLDQAGEVLY<br>QALNAITTAILTVKEIELDFAVPLKDVTVPERRQARF<br>ECVLTREANVIWSKGPDI IKSSDKFDI IADGKKHILV<br>INDSQFDDEGVYTAEVEGKKT SARLFVTGIRLKFMS<br>LEDQTVKEGETATFVCELSHEKMHVVWFKNDAKLHTS<br>RTVLISSEGKTHKLEMKEVTLDDISQIKAQVKELSST<br>AQLKVLEADPYFTVKLHDKTAVEKDEITLKCEVSKDV<br>PVKWFKDGEEIVPSPKYSIKADGLRRILKIKKADLKD<br>KGEYVCD CGTDKTKANVTVEARLIKVEKPLYGVEV FV<br>GETAHFEIELSEPDVHGQWKLKGQPLTASPDCEI IED<br>GKKHILILHNCQLGMTGEVSFQAANAKSAANLKV KEL<br>PLIFITPLSDVKVF EKDEAKFECEVSREP KTFRWLKG<br>TQEITGDDR FELIKDGTKHSMVIKSAAFED EAKYMF<br>AEDKHTSGKLIIEGIRLKFLTPLKDVTAKEKESAVFT<br>VELSHDNIRVKWFKNDQRLHTTRSVSMQDEGKTHSIT<br>FKDLSIDDT SQIRVEAMGMSSEAKLTVLEGDPYFTGK<br>LQDYTGVEKDEVILQCEISKADAPVKWFKDGKEIKPS<br>KNAVIKADGKKRMLILKKALKSDIGQYTCDCGTDKTS<br>GKLDIEDREIKLVRPLHSVEVMETETARFETEISEDD<br>IHANWKLKGEALLQTPDCEIKEEGKIHSLVLHNCRLD<br>QTGGVDFQAANVKSSAHLRVKPRVIGLLRPLKDVTVT<br>AGETATFDCELSYEDIPVEWYLGKKLEPSDKV VPRS<br>EGKVHTLTLRDVKLEDAGEVQLTAKDFKTHANL FVKE<br>PPVEFTKPLEDQTVEEGATAVLECEVSRENAKVWFK<br>NGTEILKSKKYEIVADGRVRKLV IHDCTPEDIKTYTC<br>DAKDFKTS CNLNVVPPHVEFLRPLTDLQVREKEMARF<br>ECELSRENAKVWFKDGAEIKKGKKYDIIISKGAVRIL<br>VINKCLLDDEAEYSCEVRTARTSGMLTVLEEEAVFTK |
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|  |  | NLANIEVSETDTIKLVCEVSKPGAEEVIWYKGDEEIIIE<br>TGRYEILTEGRKRILVIQNAHLEDAGNYNCRLPSSRT<br>DGKVKVHELAAEFISKPNLEILEGEKAEFVCSISKE<br>SFPVQWKRDDKTLES GDKYDVIADGKKRVLVVKDATL<br>QDMGTYVVMVGAARAAAHLTVIEKLRIVPLKDTRVK<br>EQQEVVFNCEVNTGAKAKWFRNEEAI FDSSKYIILQ<br>KDLVYTLRIRDAHLDDQANYNVSLTNHRGENVKSAAN<br>LIVEEEDLRIVEPLKDIETMEKKS VTFWCKVNRLNVT<br>LKWTKNGEEVPFDNRVSYRVDKYKHMLTIKDCGFPDE<br>GEYIVTAGQDKSVAELLIIIEAPTEFVEHLEDQTVTEF<br>DDAVFSCQLSREKANVKWYRNGREIKEGKKYKFEKDG<br>SIHRLIIKDCRLDDECEYACGVEDRKSARLFVEEIP<br>VEIIRPPQDILEAPGADVFLAELNKDKVEVQWLNN<br>MVVVQGDQKQMMSEGKIHRLQICDIKPRDQGEYRFIA<br>KDKEARAKLELAAAPKIKTADQDLVVDVGKPLTMVVP<br>YDAYPKAAEFKENEPLSTKTIDTTAEQTSFRILEA<br>KKGDKGRYKIVLQNKHGKAEGFINLKVIDVPGPVRNL<br>EVTETFDGEVSLAWEEPLTDGGSKIIGYVVERRDIKR<br>KTWVLATDRAESCEFTVTGLQKGGVEYLFVRVSARNRV<br>GTGEPVETDNPVEARSKYDVPGPPLNVTITDVNRFGV<br>SLTWEPPEYDGGAEITNYVIELRDKTSIRWDTAMTVR<br>AEDLSATVTDVVEGQEYSFRVRAQNRIGVGKPSAATP<br>FVKVADPIERPSPVNLTS SDQTQSSVQLKWEPLKD<br>GGSPILGYIIERCEEGKDNWIRCNMKLVPETYKVTG<br>LEKGNKYLYRVS AENKAGVSDPSEILGPLTADDAFVE<br>PTMDLSAFKDGLEVIVPNPITILVPSTGYPRPTATWC<br>FGDKVLETGDRVKMKTLSAYAELVISPSERSDKGIYT<br>LKLENRVKTI SGEIDVNVIARPSAPKELKFGDITKDS<br>VHLTWEPDDDDGGSPLTGYVVEKREVS RKTWTKVMDF<br>VTDLEFTVPDLVQGKEYLFKVCARNKCGPGEPAVDE<br>PVNMSTPATVPDPPENVKWRDRTANSIFLTWDPPKND<br>GGSRIKGYIVERCPRGSDKWVACGEPVAETKMEVTGL<br>EEGKWYAYRVKALNRQGASKPSRPTEEIQAVDTQEAP<br>EIFLDVKLLAGLTVKAGTKIELPATVTGKPEPKITWT<br>KADMILKQDKRIT IENVPKKSTVTIVDSKRSDTGTYI<br>IEAVNVCGRATAVVEVNVLDKPGPPAAFDITDVTNES<br>CLLTWNPPRDDGGSKITNYVVERRATDSEVWHKLSST<br>VKDTNFKATKLIPNKEYIFRVAAENMYGVGEPVQASP<br>ITAKYQFDPPGPPTRLPSDITKDAVTLTWCEPDDDG<br>GSPITGYWVERLDPDTDKWVRCNKMPVKDTTYRVKGL<br>TNKKKYRFRVLAENLAGPGKPSKSTEPILIKDPIDPP<br>WPPGKPTVKDVGKTSVRLNWTKEHDGGAKIESYVIE<br>MLKTGTDEWVRVAEGVPTTQHLLPGLMEGQEYSFRVR<br>AVNKAGESEPSEPSDPVLCREKLYPPSPPRWLEVINI<br>TKNTADLKWTVPEKDGGSPITNYIVEKRDVRRKGWQT<br>VDTTVKDKTKCTVTPLTEGSLYVFRVAAENAIGQSDYT<br>EIEDSVLAKDTFTTPGPPYALAVVDVTKRHVDLKWEP<br>PKNDGGRPIQRYVIEKKERLGTRWVKAGKTAGPCNF<br>RVTDVIEGTEVQFQVRAENEAGVGHPSPEPTEILSIED<br>PTSPPSPPLDLHVT DAGRKHIAIAWKPPKNGGSPII<br>GYHVEMCPVGTEKWMRVNSRP IKDLKFKVEEGVVPDK |
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|  |  | <p> EYVLRVRAVNAIGVSEPSEISENVVAKDPDCKPTIDL<br/> ETHDIIVIEGEKLSIPVPFRAVPVPTVSWHKDGKEVK<br/> ASDRLTMKNDHISAHLEVPKSVRADAGIYTITLENKL<br/> GSATASINVKVIGLPGPCKDIKASDITKSSCKLTWEP<br/> PEFDGGTPILHYVLERREAGRRTYIPVMSGENKLSWT<br/> VKDLIPNGEYFFRVKAVNKVGGGEYIELKNPVIAQDP<br/> KQPPDPPVDVEVHNPTAEAMTITWKPPLYDGGSKIMG<br/> YIIEKIAKGEERWKRCNEHLVPILTYTAKGLEEGKEY<br/> QFRVRAENAAGISEPSRATPPTKAVDPIDAPKVIILRT<br/> SLEVKRGDEIALDASISGSPYPTITWIKDENVIVPEE<br/> IKKRAAPLVRRRKGEVQEEEPFVLPLTQRLSIDNSKK<br/> GESQLRVRDSLRLPDHGLYMIKVENDHGIAPACTVSV<br/> LDTPGPPINFVFEDIRKTSVLCKWEPLDDGGSEIIN<br/> YTLEKKDKTKPDSEWIVVTSTLRHCKYSVTKLIEGKE<br/> YLFRVRAENRFGPGPPCVSKPLVAKDPFGPPDAPDKP<br/> IVEDVTSNSMLVKWNEPKDNGSPILGYWLEKREVNST<br/> HWSRVNKSLLNALKANVDGLLEGLTYVFRVCAENAAG<br/> PGKFSPPSDPKTAHDPISPPGPPIPRVTDTSSTTIEL<br/> EWEPPAFNGGGEIVGYFVDKQLVGTNEWSRCTEKMIL<br/> VRQYTVKEIREGADYKLRVSAVNAAGEGPPGETQPVT<br/> VAEPQEPPAVELDVSVKGGIQIMAGKTLRIPAVVTGR<br/> PVPTKVWTKEEGELDKDRVVIDNVGTKSELI IKDALR<br/> KDHGRYVITATNSCGSKFAAARVEVFDVPGPVLDLKP<br/> VVTNRKMCLLNWSDPEDDGGSEITGFI IERKDAKMHT<br/> WRQPIETERSKCDITGLLEGQYKFRVIAKNKFGCGP<br/> PVEIGPILAVDPLGPPTSPERLTYTERTKSTITLDWK<br/> EPRSNGGSPIQGYIIEKRRHDKPDFERVNKRCLCPTTS<br/> FLVENLDEHQMYEFRVKAVNEIGESEPSLPLNVVIQD<br/> DEVPTIKLRLSVRGDTIKVKAGEPVHIPADVTGLPM<br/> PKIEWSKNETVIEKPTDALQITKEEVSRSSEAKTELSI<br/> PKAVREDKGTYYTVTASNRLGSVFRNVHVEVYDRPSPP<br/> RNLAVTDIKAESCYLETWDAPLDNGGSEITHYVIDKRD<br/> ASRKKAEWEEVTNTAVEKRYGIWKLIPNGQYEFVRVA<br/> VNKYGISDECKSDKVVIQDPYRLPGPPGKPKVLARTK<br/> GSMLVSWTPPLDNGGSPITGYWLEKREEGSPYWSRVS<br/> RAPITKVGLKGVEFNVPRLLEGVKYQFRAMAINAAGI<br/> GPPSEPSDPEVAGDPIFPFGPPSCPEVKDKTKSSISL<br/> GWKPPAKDGGSPIKGYIVEMQEEGTTDWKRVNEPDKL<br/> ITTCECVVPNLKELRKYRFRVKAVNEAGESEPSDTTG<br/> EIPATDIQEEPEVFIDIGAQDCLVCKAGSQIRIPAVI<br/> KGRPTPKSSWEFDGKAKKAMKDGVDHIDPEDAQLETAE<br/> NSSVII IPECKRSHTGKYSITAKNKAGQKTANCRVKV<br/> MDVPGPPKDLKVSDITRGSCRLSWKMPDDDGGDRIKG<br/> YVIEKRTIDGKAATKVNPDGSGSTTFVVPDLLSEQQYF<br/> FRVRAENRFGIGPPVETIQRTTARDPIYPPDPPIKLLK<br/> IGLITKNTVHLSWKPPKNDGGSPVTHYIVECLAWDPT<br/> GTKKEAWRQCCKNRDVEELQFTVEDLVEGGGEYEFVRKA<br/> VNAAGVSKPSATVGPVTVKDQTCPPSIDLKEFMEVEE<br/> GTNVNIVAKIKGVFPPTLTWFKAPPKKPDNKEPVLYD<br/> THVNKLVDVDDTCTLVIPQSRSDTGLYTITAVNNLGT<br/> ASKEMRLNVLGRPGPPVGPIKFESVSADQMTLSWFPP </p> |
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|  |  |  | <p> KDDGGSKITNYVIEKREANRKTWVHVSSEPKECTYTI<br/> PKLLEGHEYVFRIMAQNKYGIGEPLDSEPETARNLFS<br/> VPGAPDKPTVSSVTRNSMTVNWEEPEYDGGSPVTGYW<br/> LEMKDTTSKRWKRVNRDPIKAMTLGVSYKVTGLIEGS<br/> DYQFRVYAINAAGVGPASLPSDPATARDPIAPPGPPF<br/> PKVTDWTKSSADLEWSPPLKDGGSKVTGYIVEYKEEG<br/> KEEWEKGKDKEVRGTKLVVTGLKEGAFYKFRVRAVNI<br/> AGIGEPGEVTDVIEMKDRLVSPDLQLDASVRDRIVVH<br/> AGGVIRIIAYVSGKPPPTVTWNMNERTLPQEATIIETT<br/> AISSSMVIKNCQRSHQGVYSLAKNEAGERKKTIIVD<br/> VLDVPGPVGTPFLAHLNLTNESCKLTWFSPEDDGGSPI<br/> TNYVIEKRESDRRAWTPVTYTVTRQONATVQGLIQGKA<br/> YFFRIAAENSIGMGPFVETSEALVIREPITVPERPED<br/> LEVKEVTKNVTTLTWNPPKYDGGSEIINYVLESRLIG<br/> TEKFHKVTNDNLLSRKYTVKGLKEGDTYEYRVSAVNI<br/> VGQGKPSFCTKPICTCKDELAPPTLHLDLFRDKLTIRVG<br/> EAFALTGRYSGKPKPKVSWFKDEADVLEDDRTHIKTT<br/> PATLALAKIKAKRSDSGKYCVVVENSTGSRKGFCQVN<br/> VVDRPGPPVGPVSFDEVTKDYMVISWKPLDDGGSKI<br/> TNYIIIEKKEVGKDVWMPVTSASAKTTCKVSKLLEGKD<br/> YIFRIHAENLYGISDPLVSDSMKAKDRFRVPDAPDQP<br/> IVTEVTKDSALVTWNKPHDGGKPITNYILEKRETMASK<br/> RWARVTKDPIHPYTKFRVPDLLEGQCYEFRVSAENEI<br/> GIGDPSPPSKPVFAKDPIAKPSPPVNPEAIDTTCNSV<br/> DLTWQPPRHDGGSKILGYIVEYQKVGDEEWRRANHTP<br/> ESCPETKYKVTGLRDGQTYKFRVLAVNAAGESDPAHV<br/> PEPVLVKDRLEPPELILDANMAREQHIIKVGDTLRLSA<br/> IIKGVFPFKVTWKEDRDAPTKARIDVTPVGSKLEIR<br/> NAAHEDGGIYSLTVENPAGSKTVSVKVLVLDKPGPPR<br/> DLEVSEIRKDSYLTWKEPLDDGGSVITNYVVERRDV<br/> ASAQWSPLSATSKKKSHFAKHLNEGNQYLFRAAENQ<br/> YGRGPFVETPKPIKALDPLHPPGPPKDLHHVDVDKTE<br/> VSLVWNKPDRDGGSPITGYLVEYQEEGTQDWIKFKTV<br/> TNLECVVTGLQQGKTYRFRVKAENIVGLGLPDTTIPI<br/> ECQEKLVPPSVELDVKLIEGLVVKAGTTVRFPPIIRG<br/> VPVPTAKWTTDGSEIKTDEHYTVETDNFSSVLTIKNC<br/> LRRDTGEYQITVSNAAGSKTVAVHLTVLDVPGPPTGP<br/> INILDVTPEHMTISWQPPKDDGGSPVINYIVEKQDTR<br/> KDTWGVVSSGSSKTKLKIPLHLQKGCEYVFRVRAENKI<br/> GVGPPLDSTPTVAKHKFSPPSPGKPVVTDITENAAT<br/> VSWTLPKSDGGSPITGYMERREVTGKWVRVNKTPIA<br/> DLKFRVTGLYEGNTYEFVFAENLAGLSKPSPPSSD<br/> PIKACRPIKPPGPPINPKLKDKSRETADLVWTKPLSD<br/> GGSPILGYVVECQKPGTAQWNRINKDELIRQCAFRVP<br/> GLIEGNEYRFRIKAANIVGEGEPRELAESVIAKDILH<br/> PPEVELDVTCRDVITVRVGQTIIRILARVKGRPEPDIT<br/> WTKEGKVLVREKRVDLIQDLPRVELQIKEAVRADHGK<br/> YIISAKNSSGHAQGSAINVLDLDRPGPCQNLKVTNVTK<br/> ENCTISWENPLDNGGSEITNFIVEYRKPNQKGWSIVA<br/> SDVTKRLIKANLLANNEYFRVCAENKVGVGPTIETK<br/> TPILAINPIDRPGEPENLHIADKGTFFVYLKWRRPDY </p> |
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|  |  |  | DGGSPNLSYHVERRLKGSDDWERVHKSGSIKETHYMVD<br>RCVENQIYEFVRVQTKNEGGESDWVKTEEVVVKEDLQK<br>PVLDLKLSGVLTVKAGDTIRLEAGVRGKPFPEVAWTK<br>DKDATDLTRSPRVKIDTRADSSKFSLTKAKRSDGGKY<br>VVTATNTAGSFVAYATVNVLDKPGPVRNLKIVDVSSD<br>RCTVCWDPPEDDGGCEIQNYILEKCETKRMVWSTYSA<br>TVLTPGTTVTRLIEGNEYIFRVRAENKIGTGPPTESK<br>PVIAKTKYDKPGRDPPEVTKVSKEEMTVVWNPPEYD<br>GGKSITGYFLEKKEKHSTRWVPVNKSAIPERRMKVQN<br>LLPDHEYQFRVKAENEIGIGEPSLPSRPVVAKDPIEP<br>PGPPTNFRVVDTTKHSITLWGKPVYDGGAPIIGYVV<br>EMRPKIADASPDEGWKRCNAAQLVRKEFTVTSLDEN<br>QEYEFRVCAQNQVGIGRPAELKEAIKPKEILEPPEID<br>LDASMRKLVIVRAGCPIRLFAIVRGRPAPKVTWRKVG<br>IDNVVRKGQVDLVDTMAFLVIPNSTRDDSGKYSLTLV<br>NPAGEKAVFVNVRLDTPGPVSDLKVSDVTKTSCHVS<br>WAPPENDGGSQVTHYIVEKREADRKTWSTVTPPEVKKT<br>SEHVTNLVPGNEYIFRVTAVNEYGPGVPTDVPKPVLA<br>SDPLSEPDPPRKLEVTEMTKNSATLAWLPPLRDGGAK<br>IDGYITSYREEEQPADRWTEYSVVKDLSLVVTGLKEG<br>KKYKFRVAARNAVGVSLPREAEGVYEAKEQLLPKIL<br>MPEQITIKAGKKLRIEAHVYGKPHPTCKWKKGEDEVV<br>TSSHLAVHKADSSSILIIKDVTRKDSGYYSLTAEISS<br>GTDQKIKVVVMDAPGPPQPPFDISDIDADACSLSWH<br>IPLDGGSNITNYIVEKCDVSRGDWVTALASVTKTSC<br>RVGKLIPGQEYIFRVRAENRFGISEPLTSPKMVAQFP<br>FGVPSEPKNARVTKVNKDCIFVAWDRPDSGGSPPIIG<br>YLIERKERNSSLWVKANDTLVRSTEYPCAGLVEGLE<br>SFRIYALNKAGSSPPSKPTEYVTARMPVDPPGKPEVI<br>DVTKSTVSLIWARPKHDGGSKIIGYFVEACKLPGDKW<br>VRCNTAPHQIPQEEYTATGLEEKAQYQFRAIARTAVN<br>ISPPSEPSDPVTILAENVPPRIDLSVAMKSLLTVKAG<br>TNVCLDATVFGKPMPTVSWKKDGTLLKPAEGIKMAMQ<br>RNLCTLELFSVNRKDSGDYTTITAENSSGSKSATIKLK<br>VLDPGPPASVKINKMYSDRAMLSWEPPLDGGSEIT<br>NYIVDKRETSRPNWAQVSATVPITSCSVEKLIIEGHEY<br>QFRICAENKYGVGDPVFTEPAIAKNPYDPPGRCDPPV<br>ISNITKDHMTVSWKPPADDGGSPITGYLLEKRETQAV<br>NWTKVNRKPIIERTLKATGLQEGTEYEFVTAINKAG<br>PGKPSDASKAAYARDPQYPPGPPAFPKVYDTRSSVS<br>LSWGKPAYDGGSPIIGYLVEVKRADSDNWVRCNLPQN<br>LQKTRFEVTGLMEDTQYQFRVYAVNKIGYSDPSDVPD<br>KHYPKDILIPPEGELDADLRKTLILRAGVTMRLYVPV<br>KGRPPPKITWSKPNVNLDRIGLDIKSTDFDTFLRCE<br>NVNKYDAGKYILTLENSCGKKEYTIVVKVLDTPGPPV<br>NVTVKEISKDSAYVTWEPPIIDGGSPIINYVQKRDA<br>ERKSWSTVTTECSKTSFRVANLEEGKSYFFRVFAENE<br>YGIGDPGETRDAVKASQTPGPVVDLKVRSVSKSSCSI<br>GWKKPHSDGGSRIIGYVVDLFTENKWQRMKSLSLQ<br>YSAKDLTEGKEYTFRVSAENENEGETPSEITVVARDD<br>VVAPDLDLKGLPDLCYLAKENSNFRLKIPKGPAPS |
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|  |  |  | VSWKKGEDPLATDTRVSVESSAVNTTLIVYDCQKSDA<br>GKYTITLKNVAGTKEGTISIKVVGKPGIPTGPIKFDE<br>VTAEAMTLKWAPPKDDGGSEITNYILEKRDSVNNKWV<br>TCASAVQKTTFRVTRLHEGMEYTFRVSAENKYGVGEG<br>LKSEPIVARHPFDVPDAPPPPNIVDVRHDSVSLTWT<br>PKKTGGSPITGYHLEFKERNSSLWKRANKTPIRMRDF<br>KVTGLTEGLEYEFRVMAINLAGVGKPSLPSEPVVALD<br>PIDPPGKPEVINITRNSVTLIWTEPKYDGGHKLTGYI<br>VEKRDLPSSWMMKANHVNVPECAFTVTDLVEGGKYE<br>RIRAKNTAGAISAPSESTETIICKDEYEAPTIVLDPT<br>IKDGLTIKAGDTIVLNAISILGKPLPKSSWSKAGKDI<br>RPSDITQITSTPTSSMLTIKYATRKDAGEYTITATNP<br>FGTKVEHVKVTVLDVPGPPGPVEISNVSAEKATLTWT<br>PPLEDGGSPIKSYILEKRETSRLLWTVVSEDIQSCRH<br>VATKLIQGNEYIFRVSAVNHYGKGEVPQSEPVKMVDR<br>FGPPGPPEKPEVSNVTKNATVSWKRPVDDGGSEITG<br>YHVERREKKSLRWVRAIKTPVSDLRCKVTGLQEGSTY<br>EFRVSAENRAGIGPPSEASDSVLMKDAAYPPGPPSNP<br>HVTDTTKKSASLAWGKPHYDGGLEITGYVVEHQKVG<br>EAWIKDTTGTALRITQFVVPDLQTKKEYNFRISAIND<br>AGVGEPAPIPDVEIVEREMAPDFELDAELRRTLTVRA<br>GLSIRIFVPIKGRPAPEVTWTKDNINLNKRANIENTE<br>SFTLLIIEPCNRYDTGKFVMTIENPAGKKSGFVNVRV<br>LDTPGPVLNLRPTDITKDSVTLHWDLPLIDGGSRTN<br>YIVEKREATRKSYSTATTKCHKCTYKVTGLSEGCEYF<br>FRVMAENEYGIGEPTETTEPVKASEAPSPPDNLNMD<br>ITKSTVSLAWPKPKHDGGSKITGYVIEAQKRGSDQWT<br>HITTVKGLECVVRNLTEGEEYTFQVMAVNSAGRSAPR<br>ESRPVIVKEQTMLELDLRGIYQKLVIKAGDNKVE<br>IPVLGRPKPTVTWKKGDQILKQTQRVNFETTATSTIL<br>NINECVRSDSGPYPLTARNIVGEVGDVITIQVHDIPG<br>PPTGPIKFDEVSSDFVTFSWDPPENDGGVPISNYVVE<br>MRQTDSTTWVELATTVIRTTYKATRLTTGLEYYQFRVK<br>AQNRYGVGPGITSACIVANYPFKVPGPPTGPQVAVT<br>KDSMTISWHEPLSDGGSPILGYHVERKERNGILWQTV<br>SKALVPGNIFKSSGLTDGIAYEFRVIAENMAGKSKPS<br>KPSEPMLALDPIDPPGKPVPLNITRHTVTLKWAKPEY<br>TGGFKITSYIVEKRDLPNGRWLKNFNSILENEFTVS<br>GLTEDAAYEFRVIAKNAAGAISPPSEPSDAITCRDDV<br>EAPKIKVDVKFKDTVILKAGEAFRLEADVSGRPPPTM<br>EWSKDGELEGTAKEIKIADFSTNLVNKDSTRDSDG<br>AYTLTATNPGGFAKHIFNVKVLDRPGPPEGPLAVTEV<br>TSEKCVLSWFPPLDDGGAKIDHYIVQKRETSRLAWN<br>VASEVQVTKLKVTLLKGNEYIFRVMAVNKYGVGEPL<br>ESEPVLAVNYPGPPDPPKNPEVTTITKDSMVVCWHP<br>DSDGGSEIINYIVERRDKAGQRWIKCNKKTTLTLDRYK<br>VSGLTEGHEYEFRIANAAGISAPSPTSPFYKACDT<br>VFKPGPPGNPRVLDTSRSSISIAWNKPIYDGGSEITG<br>YMVEIALPEEDEVQIVTPPAGLKATSYTTITGLTENQE<br>YKIRIYAMNSEGLGEPALVPGTPKAEDRMLPPEIELD<br>ADLRKVVTIRACCTLRLFVPIKGRPAPEVKWARDHGE |
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|  |  | SLDKASIESTSSYTLLIVGNVNRFD SGKY ILTVENSS<br>GSKSAFVNVRVLDTPGPPQDLKVKEVTKTSVTLTWDP<br>PLLDGGSKIKNYIVEKRESTRKAYSTVATNCHKTSWK<br>VDQLQEGCSYYFRVLAENEYGIGLPAETAESVKASER<br>PLPPGKITLMDVTRNSVSLSWEKPEHDGGSRLGYIV<br>EMQTKGSDKWATCATVKVTEATITGLIQGEEYSFRVS<br>AQNEKGISDPRQLSVPVIAKDLVIPP AFKLLFNTFTV<br>LAGEDLKVDVPFIGRPTPAVTWHKDNVPLKQTTRVNA<br>ESTENNSLLTIKDACREDVGHYVVKLTNSAGEAIETL<br>NVIVLDKPGPPTGPVKMDEVTADSITLSWGP PKYDGG<br>SSINNYIVEKRDTSTTTWQIVSATVARTTIKACRLKT<br>GCEYQFRIAAENRYGKSTYLNSEPTVAQY PFKVPGPP<br>GTPVVTLSRDSMEVQWNEPISDGGSRVIGYHLERKE<br>RNSILWVKLNKTPIPQTKFKTTGLEEGVEYEFVRS AE<br>NIVGIGKPSKVSECYVARDPDPPGRPEAIIVTRNSV<br>TLQWKKPTYDGGSKITGYIVEKKELPEGRWMKASFTN<br>IIDTHFEVTGLVEDHRYEFVRIARNAAGVFSEPEST<br>GAITARDEVDP PRISMDPKYKDTIVVHAGESFKVDAD<br>IYGKPIPTIQWIKGDQELSNTARLEIKSTDFATSLSV<br>KDAVRVDSGNYILKAKNVAGERSVTVNVKVLDRPGPP<br>EGPVVISGVTAEKCTLAWKPPLQDGGSDIINYIVERR<br>ETSRLVWTVVDANVQTLSCKVTKLLEGNEYTFRIMAV<br>NKYGVGEPLESEPVVAKNPFVVPDAPKAPEVTTVTKD<br>SMIVVWERPASDGGSEILGYVLEKRDKEGIRWTRCHK<br>RLIGELRLRV TGLIENHDYEFVRS AENAAGLSEPSPP<br>SAYQKACDPIYKPGPPNNPKVIDITRSSVFLSWSKPI<br>YDGGCEIQGYIVEKCDVSVGEWTMCTPPTGINKTNIE<br>VEKLEKHEYNFRICAINKAGVGEHADVP GPIIVEEK<br>LEAPDIDL DLELRKIINIRAGGSLRLFVPIKGRPTPE<br>VKWGV DGEIRDAAIIDVTSSFTSLVLDNVNRYDSGK<br>YTLTLENSSGTKSAFVTVRVLDTPSPPVNLKVTEITK<br>DSVSITWEPPLLDGGSKIKNYIVEKREATRKSAAVV<br>TNCHKNSWKIDQLQEGCSYYFRVTAENEYGIGLPAQT<br>ADPIKVAEVPQPPGKITVDDVTRNSVSLSWTKPEHDG<br>GSKIIQYIVEMQAKHSEKWSECARVKS LQAVITNLTQ<br>GEEYLF RVVAVNEKGRSDPRSLAVPIVAKDLVIEPDV<br>KPAFSSYSVQVGQDLKIEVPISGRPKPTITWT KDGLP<br>LKQTT RINVTDSLDTLTSIKETHKDDGGQYGITVAN<br>VVGQKTASIEIVTLDKPDPPKGPVKFDDVSAESITLS<br>WNPPLYTGQCQITNYIVQKRDTTTTVWDVVSATVART<br>TLKVTKLKTGTEYQFRIFAENRYGQSFALES DP IVAQ<br>YPYKEPGPPGTPFATAISKDSMVIQWHEPVNNGGSPV<br>IGYHLERKERN SILWTKVNKTI IHDTQFKAQNLEEGI<br>EYEF RVYAENIVGVGKASKNSECYVARDPDPPGTPE<br>PIMVKRNEITLQWTKPVYDGGSMITGYIVEKRDL PDG<br>RWMKASFTNVIETQFTVSGLTEDQRYEFVRIAKNAAG<br>AISKPSDSTGPITAKDEVELPRISMDPKFRDTIVVNA<br>GETFRLEADVHGKPLPTIEWLRGDKEIEESARCEIKN<br>TDFKALLIVKDAIRIDGGQYILRASNVAGSKSFPVNV<br>KVLDRPGPPEGPVQVTGVTSEKCSLTWSPPLQDGGSD<br>ISHYVVEKRETSRLAWTVVASEVVTNSLKVTKLLEGN |
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|  |  | <p> EYVFRIMAVNKYGVGEPLESAPVLMKNPFVLPGPPKS<br/> LEVNTNIAKDSMTVCWNRPDSDGGSEIIGYIVEKRDRS<br/> GIRWIKCNKRITDLRLRVTGLTEDHEYEFRVSAENA<br/> AGVGEPSPATVYYKACDPVFKPGPPTNAHIVDTTKNS<br/> ITLAWGKPIYDGGSEILGYVVEICKADEEEWQIVTPQ<br/> TGLRVTRFEISKLTEHQEYKIRVCALNKVGLGEATSV<br/> PGTVKPEDKLEAPELDDLSELRKGI VVRAGGSARIHI<br/> PFKGRPTPEITWSREEGEFTDKVQIEKGVNYTQLSID<br/> NCDNRNDAGKYILKLENSSGSKSAFVTVKVLDTPGPPQ<br/> NLAVKEVRKDSAFLVWEPPIIDGGAKVKNYVIDKRES<br/> TRKAYANVSSKSKTSFKVENLTEGAIYYFRVMAENE<br/> FGVGVPVETVDAVKAAPPSPPGKVTLTDVQSQTASL<br/> MWEKPEHDGGSRLGYVVMQPKGTEKWSIVAESKVC<br/> NAVVTGLSSGQEQFRVKAYNEKGKSDPRVLGVPVIA<br/> KDLTIQPSLKLPFNTYSIQAGEDLKIEIPVIGRPRPN<br/> ISWVKDGEPLKQTTTRVNVEETATSTVLHIKEGNKDDF<br/> GKYTVTATNSAGTATENLSVIVLEKPGPPVGPVRFDE<br/> VSADFVVISWEPPAYTGGCQISNYIVEKRDTTTTTWH<br/> MVSATVARTTIKITKLKTGTEYQFRIFAENRYGKSAP<br/> LDSKAVIVQYPFKEPGPPGTPFVTSISKDQMLVQWHE<br/> PVNDGGTKIIGYHLEQKEKNSILWVKLNKTPIQDTKF<br/> KTTGLDEGLEEYEFKVSAENIVGIGKPSKVSECFVARD<br/> PCDPPGRPEAIVITRNNVTWKWKPAYDGGSKITGYI<br/> VEKKDLPDGRWMKASFTNVLETEFTVSGLVEDQRYEF<br/> RVIARNAAGNFSEPSDSSGAITARDEIDAPNASLDPK<br/> YKDVI VVHAGETVLEADIRGKPIPDVVWSKDGKELE<br/> ETAARMEIKSTIQKTTLVVKDCIRTDGGQYILKLSNV<br/> GGTKSIPITVKVLDRPGPPEGPLKVTGVTAEKCYLAW<br/> NPPLQDGGANISHYII EKRETSRLSWTQVSTEVQALN<br/> YKVTKLLPGNEYIFRMAVNKYGIGEPLESGPVTACN<br/> PYKPPGPPSTPEVSAITKDSMVVTWARPVDDGGTEIE<br/> GYILEKRDKEGVRWTKCNKKTITDLRLRVTGLTEGHS<br/> YEFRVA AENAAGVGEPSEPSVFYRACDALYPPGPPSN<br/> PKVTDTSRSSVSLAWSKPIYDGGAPVKGYVVEVKEAA<br/> ADEWTTCTPPTGLQGKQFTVTKLKENTEYNFRICAIN<br/> SEGVGEPATLPGSVVAQERIEPPEIELDADLRKVVL<br/> RASATLRLFVTIKGRPEPEVKWEKAEGILTDRAQIEV<br/> TSSF TMLVIDNVTRFDSGRYNLTLENNSGSKTAFVNV<br/> RVLDSPSAPVNLTIREVKKDSVTLSWEPPLIDGGAKI<br/> TNYIVEKRETTTRKAYATITNNCTKTTFRIENLQEGCS<br/> YYFRVLASNEYGIGLPAETTEPVKVSEPPLPPGRVTL<br/> VDVTRNTATIKWEKPESDGGSKITGYVVMQTKGSEK<br/> WSTCTQVKTEATISGLTAGEEYVFRVA AVNEKGRSD<br/> PRQLGVPVIARDIEIKPSVELPFHTFNVKAREQLK<br/> IDVPFKGRPQATVNWRKDGQTLKETTRVNVSSSKTVT<br/> SLSIKEASKEDVGTYELCVSNSAGSITVPITIIIVLDR<br/> PGPPGPIRIDEVSCDSITISWNPPEYDGGCQISNYIV<br/> EKKETTSTTWHIVSQAVARTSIKIVRLTTGSEYQFRV<br/> CAENRYGKSSYSESSAVVAEYPFSPPGPPGTPKVVHA<br/> TKSTMLVTWQVPVNDGGSRVIGYHLEYKERS SILWSK<br/> ANKILIADTQMKVSGLDEGLMYEYRVYAENIAGIGKC </p> |
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|  |  | <p>             SKSCEPVPARDPCDPPGQPEVTNITRKSVSLSKWSKPH<br/>             YDGGAKITGYIVERRELPDGRWLKCNYTNIQETYFEV<br/>             TELTEDQRYEFRVFARNAADSVSEPESTGPIIVKDD<br/>             VEPPRVMMMDVKFRDVIIVVKAGEVLKINADIAGRPLPV<br/>             ISWAKDIEIEERARTEIISTDNHTLLTVKDCIRRD<br/>             GQYVLTLLKNVAGTRSVAVNCKVLDKPGPPAGPLEING<br/>             LTAEKCSLSWGRPQEDGGADIDYIIVEKRETSHLAWT<br/>             ICEGELQMTSCKVTKLLKGNEYIFRVTGVNKGVGEP<br/>             LESVAIKALDPFTVPSPTSLTITSVTKESMTLCWSR<br/>             PESDGGSEISGYIERREKNSLRWVRVNKKPVYDLRV<br/>             KSTGLREGCEYEYRVYAENAAGLSLPSETSPILRAED<br/>             PVFLPSPPSKPKIVDSGKTTITIAWVKPLFDGGAPIT<br/>             GYTVEYKKSDDTDWKTISIQLRGTEYTIISGLTTGAAY<br/>             VFRVKS VNKVGASDPDSSDPQIAKERE EEP LFDIDS<br/>             EMRKT LIVKAGASFTMTVPFRGRPVPNVLWSKPD TDL<br/>             RTRAYVDTTDSRTSLTIENANRNDSGKYTLTIQNVLS<br/>             AASLT LVVKVLDTPGPPTNITVQDVTKESAVLSWDVP<br/>             ENDGGAPVKNYHIEKREASKAWVSVTNNCNRLSYKV<br/>             TNLQEGAIYYFRVSGENEFGVGIPAETKEGVKITEKP<br/>             SPPEKLGVTSSISKDSVSLTWLKEHDGGSRIVHYVVE<br/>             ALEKGQKNWVKCAVAKSTHHVVSGLRENSEYFFRVFA<br/>             ENQAGLSDPRELLLPVLIKEQLEPPEIDMKNFPSHTV<br/>             YVRAGSNLKVDIPISGKPLPKVTLSRDGVPLKATMRF<br/>             NTEITAENLTINLKE SVTADAGRYEITAANSSGTTKA<br/>             FINIVLDRPGPPTGPVVISDITEESVTLKWEPKYD<br/>             GGSQVTNYILLKRETSTAVWTEVSATVARTMMKVMKL<br/>             TTGEEYQFRIKAENRFGISDHIDSACVTVKLPYTTPG<br/>             PPSTPWVTNVTRESITVGWHEPVSNNGGSAVVGYLEM<br/>             KDRNSILWQKANKLVIRTTTHFKVTTISAGLIYEFVRY<br/>             AENAAGVGKPSHPSEPVLAIDACEPPRNVRITDISKN<br/>             SVSLSWQQPAFDGGSKITGYIVERRDLPDGRWTKASF<br/>             TNVTETQFIISGLTQNSQYEFRVFARNAVGSISNPSE<br/>             VVGPI TCIDSYGGPVIDLPLEYTEVVKYRAGTSVKLR<br/>             AGISGKPAPTIEWYKDDKELQTNALVCVENTTDLASI<br/>             LIKDADRLNSGCYELKLRNAMGSASATIRVQILDKPG<br/>             PPGPIEFKTVTAEKITLLWRPPADDGGAKITHYIVE<br/>             KRETSRVVWSMVSEHLEECIITTTKIIKGNEYIFRVR<br/>             AVNKYGIGEPLESDSVVAKNAFVTPGPPGPIPEVTKIT<br/>             KNSMTVVWSRPIADGGSDISGYFLEKRDKKS LGWFKV<br/>             LKETIRDTRQKVTGLTENS DYQYRVCAVNAAGQGPF<br/>             EPSEFYKAADPIDPPGPPAKIRIADSTKSSITLGWSK<br/>             PVYDGGSAVTGYVVEIRQGE EEEWTTVSTKGEVRTTE<br/>             YVVS NLKPGVNYFRVSAVNCAGQGEP IEMNEPVQAK<br/>             DILEAPEIDL DVALRTSVIAKAGEDVQVLIPFKGRPP<br/>             PTVTWRKDEKNLGS DARYSIENTDSSSLLTIPQVTRN<br/>             DTGKYILTIENG VGEPKSSTVSVKVLDTPAACQKLQV<br/>             KHVSRGTVTLLWD PPLIDGGSP IINYVIEKR DATKRT<br/>             WSVVSHKCSSTSFKLIDLSEKTPFFFRVLAENEIGIG<br/>             EPCETTEPVKAAEVPAPIRDLSMKDSTKTSVILSWTK<br/>             PDFDGGSVITEYVVERKGKGEQTWSHAGISKCEIEV<br/>             SQLKEQSVLEFRVFAKNEKGLSDPVTIGPITVKELII           </p> |
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|  |  |  | <p> TPEVDLSDIPGAQVTVRIGHNVHLELPYKGKPKPSIS<br/> WLKDG LPLKESEFVRFSKTENKITLSIKNAKKEHGGK<br/> YTVILDNAVCR IAVPITVITLGPPSKPKGPIRFDEIK<br/> ADSVILSWDVPEDNNGGEITCYSIEKRETSQTNWKMV<br/> CSSVARTTFKVPNLVKDAEYQFRVRAENRYGVSQPLV<br/> SSIIVAKHQFRIPGPPGKPV IYNVTS DGMSLTWDAPV<br/> YDGGSEVTGFHVEKKERN SILWQKVNTSPISGREYRA<br/> TGLVEGLDYQFRVYAENSAGLSSPSDPSKFTLAVSPV<br/> DPPGTPDYIDVTRETITLKWNPPLRDGGSKI VGY SIE<br/> KRQGN ERWVR CNFTDVSECQYTVTGLSPGDRYEFRII<br/> ARNAVGTISP PSQSSGIIMTRDENVPPIVEFGPEYFD<br/> GLIIKSGESLRIKALVQGRPVPRVTWFKD GVEIEKRM<br/> NMEITDVLGSTSLFVRDATRDHRGVYTV EAKNASGSA<br/> KAEIKVKVQDTPGKVVGPIRFTNITGEKMTLWWDAPL<br/> NDGCAPITHYII EKRETSRLAWALIEDKCEAQSYTAI<br/> KLINGNEYQFRVSAVNKFGVGRPLDSDPVVAQIQYTV<br/> PDAPGIPEPSNITGNSITLTWARPESDGGSEIQQYIL<br/> ERREKKSTRWVKVISKRPISETRFKVTGLTEGNEYEF<br/> HVMAENAAGVGPASGISRLIKCREPVNPPGPPTVVKV<br/> TDTSKTTVSLEWSKP VFDGGMEIIGYIIEMCKADLGD<br/> WHKVNAEACVKTRYTVTDLQAGEEYKFRVSAINGAGK<br/> GDSCEVTGTIKAVDRLTAPELDIDANFKQTHVVRAGA<br/> SIRLFIAYQGRPTPTAVWSKPDSNLSLRADIHTTDSF<br/> STLTVENCNRNDAGKYTLTVENNSGSKSITFTVKVLD<br/> TPGPPGPITFKDVTRGSATLMWDAPLLDGGARIHHYV<br/> VEKREASRRSWQVISEKCTRQIFKVNDLAEGVPYYFR<br/> VSAVNEYGVGEPEYEMPEPIVATEQPAPPRRLDVVDT<br/> KSSAVLAWLKPDHDGGSRITGYLLEMQRKGSDFWVEA<br/> GHTKQLTFTVERLVEKTEYEFRVKAKN DAGYSEPREA<br/> FSSV IIEKPQIEPTADLTGITNQLITCKAGSPFTIDV<br/> PISGRPAPKVTWKLEEMRLKETDRVSITTTKDRTTLT<br/> VKDSMRGDSGRYFLTLENTAGVKTFSVTVVVIGRPGP<br/> VTGPIEVSSVSAESC VLSWGE PKDGGGTEITNYIVEK<br/> RESGTTAWQLVNSSVKRTQIKVTHLT KYMEYSFRVSS<br/> ENRFGVSKPLESAPIIAEHFPVPPSAPTRPEVYHVSA<br/> NAMSIRWEEPYHDGGSKIIGYWVEKKERN TILWVKEN<br/> KVPCLECN YKVTGLVEGLE YQFRTYALNAAGVSKASE<br/> ASRPIM AQNPVDAPGRPEVTDVTRSTVSLIWSAPAYD<br/> GGSKVGYIIERKPVSEVGDGRWLKCN YTI VSDNFFT<br/> VTALSEGDTYEFRLAKNAAGVISKGSESTGPVTCRD<br/> EYAPPKAELDARLHGD LVTIRAGSDLVLDAAVGGKPE<br/> PKIIWTKGDKELDLCEK VSLQYTGKRATAVIKFCDRS<br/> DSGKYTLTVKNASGTKAVSVMVKVLDSPGPGKLTVS<br/> RVTQEKCTLAWSLPQEDGGAEITHYIVERRETSRLNW<br/> VIVEGECPTLSYVVTRLIKNNEYIFRVRAVNKYGPGV<br/> PVESEPIVARN SFTIPSPPGIPEEVGTGKEHIIQWT<br/> KPESDGGNEISNYLV DKREKKS LRWTRVN KDYVVYDT<br/> RLKVTSLMEGCDYQFRVTAVNAAGNSEPSEASN FISC<br/> REPSYTPGPPSAPRVVDTTKHSISLAWTKPMYDGGTD<br/> IVGYVLEMQEKD TDQWYRVHTNATIRNTEFTVPDLKM<br/> GQKYSFRVA AVNVKGMSEYSESIAEIEPVERIEIPDL </p> |
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|  |  |  | <p>             ELADDLKKTVTIRAGASLRMLVSVSGRPPPVITWSKQ<br/>             GIDLASRAIIDTTESYSLLIVDKVNRYDAGKYTIEAE<br/>             NQSGKKSATVLVKVYDTPGPCPSVKVKEVSRDSVTIT<br/>             WEIPTIDGGAPVNNYIVEKREAAAMRAFKTVTTKCSKT<br/>             LYRISGLVEGTMYYFRVLPENIYGIGEPCETSDAVLV<br/>             SEVPLVPAKLEVVDVTKSTVTLAWEKPLYDGGSRLTG<br/>             YVLEACKAGTERWMKVVTLKPTVLEHTVTSLNEGEQY<br/>             LFRIRAQNEKGVSEPRETVTAVTVQDLRVLPIDLST<br/>             MPQKTIHVPAGRPVELVIPIAGRPPPAASWFFAGSKL<br/>             RESERVTVETHTKVAKLTIRETTIRDTGEYTLLEKNV<br/>             TGTSETIKVILDKPGPPTGPIKIDEIDATSITISW<br/>             EPPELDGGAPLSGYVVEQRDAHRPGWLPVSESVTRST<br/>             FKFTRLTEGNEYVFRVAATNRFGIGSYLQSEVIECRS<br/>             SIRIPGPPETLQIFDVSRDGMTLTWYPPEDDGGSQVT<br/>             GYIVERKEVRADRWVRVNKVPVTMTRYRSTGLTEGLE<br/>             YEHRVTAINARGSGKPSRPSKPIVAMDPIAPPKQPON<br/>             PRVTDTRTSVSLAWSVPEDEGGSKVTGYLIEMQKVD<br/>             QHEWTKCNTTPTKIREYTLTHLPQGAERYFRVLACNA<br/>             GGPGEPAEVPPTVKVTEMLEYPDYELDERYQEGIFVR<br/>             QGGVIRLTIPIKKGKFPICKWTKEGQDISKRAMIATS<br/>             ETHTELVIKEADRGDSGTYDLVLENKCGKKAVYIKVR<br/>             VIGSPNSPEGPLEYDDIQVRSVRVSWRPPADDGGADI<br/>             LGYILERREVPKAAWYIDSRRVGTSLVVKGLKENVE<br/>             YHFRVSAENQFGISKPLKSEEPVTPKTPLNPPEPPSN<br/>             PPEVLDVTKSSVSLWSRPKDDGGSRVGTGYIYERKET<br/>             STDKWVRHNKTQITTTMYTGTGLVPDAEYQFRIIAQN<br/>             DVGLSETSPASEPVVCKDPFDKPSQPGELEILSISKD<br/>             SVTLQWEKPECDGGKEILGYWVEYRQSGDSAWKKSNNK<br/>             ERIKDKQFTIGGLLEATEYEFRVFAENETGLSRPRRT<br/>             AMSIKTKLTSGEAPGIRKEMKDVTTKLGEAAQLSCQI<br/>             VGRPLPDIKWYRFGKELIQSRKYMSSDGRTHTLTVM<br/>             TEEQEDEGVYTCIATNEVGEVETSSKLLLQATPQFHP<br/>             GYPLKEKYYGAVGSTLRLHVMYIGRPVPAMTWFGQK<br/>             LLQNSENITIENTEHYTHLVMKNVQRKTHAGKYKVQL<br/>             SNVFGTVDAILDVEIQDKPDKPTGPIVIEALLKNSAV<br/>             ISWKPPADDGGSWITNYVVEKCEAKEGAEWQLVSSAI<br/>             SVTTCRIVNLTENAGYYFRVSAQNTFGISDPLEVSSV<br/>             VIKSPFEKPGAPGKPTITAVTKDSCVVAWKPPASDG<br/>             GAKIRNYYLEKREKKQNKWISVTTEEIRETVFSVKNL<br/>             IEGLEYEFRVKCENLGGESEWSEISEPITPKSDVP IQ<br/>             APHFKEELRNLNVRYQSNATLVCKVTGHPKPIVKWYR<br/>             QGKEIIADGLKYRIQEFKGGYHQLIIASVTDDDATVY<br/>             QVRATNQGGSVSGTASLEVEVPAKIHLPKTLEGMGAV<br/>             HALRGEVVSIIKIPFSGKPDPVITWQKGQDLIDNNGHY<br/>             QVIVTRSFTSLVFPNGVERKDAGFYVCAKNRFGIDQ<br/>             KTVELDVADVDPDPRGVKVS DVS RDSVNLTWTEPASD<br/>             GGSKITNYIVEKCATTAEERWLRVGQARETRYTVINLF<br/>             GKTSYQFRVIAENKFGLSKPSEPSEPTITKEDKTRAM<br/>             NYDEEVDRETVSMTKASHSSTKELYEKYMIADLGR<br/>             GEFGIVHRCVETSSKKT YMAKFVKVKGTDQVLVKKEI<br/>             SILNIARHRNILHLHESFESMEELVMI FEFISGLDIF           </p> |
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|  |  | <p> ERINTSAFELNEREIVSYVHQVCEALQFLHSHNIGHF<br/> DIRPENIIYQTRRSSTIKIIIEFGQARQLKPGDNFRL<br/> FTAPEYYAPEVHQHDVVSTATDMWSLGLVYVLLSGI<br/> NPFLAETNQOIENIMNAEYTFDEEAFKEISIEAMDF<br/> VDRLLVKERKSRMTASEALQHPWLKQKIERVSTKVIR<br/> TLKHRRYYHTLIKKDLNMVVSAAARISCGGAIRSQKGV<br/> SVAKVKVASIEIGPVSGQIMHAVGEEGGHVKYVCKIE<br/> NYDQSTQVTWYFGVRQLENSEKYEITYEDGVAILYVK<br/> DITKLDDGTYRCKVVNDYGEDSSYAELEFVKGVREYD<br/> YYCRRTMKKIKRRDTMRLLEPPEFTLPLYNKTAIV<br/> GENVRFGVTITVHPEPHVTWYKSGQKIKPGDNDKKYT<br/> FESDKGLYQLTINSVTDDDAEYTVVARNKYGEDSCK<br/> AKLTVTLHPPPTDSTLRPMFKRLLANAECQEGQSVCF<br/> EIRVSGIPPPPTLKWEKDGQPLSLGPNIEIIHEGLDYY<br/> ALHIRDTLPEDTGYRVTATNTAGSTSCQAHQLQVERL<br/> RYKKQEFKSKEEHERHVQKQIDKTLRMAEILSGTESV<br/> PLTQVAKEALREAAVLYKPAVSTKTVKGEFRLEIEEK<br/> KEERKLMPYDVPEPRKYKQTTIEEDQRIKQFVPMSD<br/> MKWYKKIRDQYEMPGKLDREVQKRPKRIRLSRWEQFY<br/> VMPLPRITDQYRKPWRIPKLSQDDLEIVRPARRRTPS<br/> PDYDFYRPRRRSLGDISDEELLLPIDDYLAMKRTEE<br/> ERLRLEEELELGFSAAPPSRSPHFELSSLRYSSPQA<br/> HVKVEETRKFDFRYSTYHIPTKAEASTSYAELRERHAQ<br/> AAYRQPKQRQRIMAEREDEELLRPVTTTQHLSEYKSE<br/> LDFMSKEEKSRKKSRRQREVTEITEIEEEYEISKHAQ<br/> RESSSSASRLRRRRSLSPYIELMRPVSELIRSRPQ<br/> PAEYEDDTERRSPTPERTRPRSPSPVSSERSLSRFE<br/> RSARFDIFSRYESMKAALKTQKTSEKYEVLSSQQPFT<br/> LDHAPRITLRMRSHRVPCGQNTFRILNVQSKPTAEVK<br/> WYHNGVELQESSKIHNTNTSGVLTLEILDCHTDDSGT<br/> YRAVCTNYKGEASDYATLDVTGGDYTTYASQRRDEEV<br/> PRSVFPELTRTEAYAVSSFKKTSEMEASSSVREVKSQ<br/> MTETRESLSSYEHSAEMKSAALEEKSLEEKSTTRK<br/> IKTTLAARILTKPRSMTVYEGESARFSCDTDGEPVPT<br/> VTWLRKGQVLSTSARHQVTTTKYKSTFEISSVQASDE<br/> GNYSVVVENSEGKQEAFTLTIQKARVTEKAVTSPPR<br/> VKSPEPRVKSPKAVKSPKRVKSPKPSHPKAVSPTETK<br/> PTPTEKVQHLPVSAPPKITQFLKAEASKEIAKLTCVV<br/> ESSVLRKEVTVYKDGKKLKENGHFQFHYSADGTYEL<br/> KINNLTESDQGEYVCEISGEGGTSTNLQFMGQAFKS<br/> IHEKVSKISETKKSDQKTTESTVTRKTEPKAPEPISS<br/> KPVIVTGLQDQTVSSDSVAKFAVKATGEPRTAIWTK<br/> DGKAITQGGKYKLSEDKGGFFLEIHKTDTSDSGLYTC<br/> TVKNSAGSVSSSSCKLTIKAIKDTEAQKVSTQKTSEIT<br/> PQKKAVVQEEISQKALRSEEIKMSEAKSQEKLALKEE<br/> ASKVLISEEVKSAATSLEKSIVHEEITKTSQASEEV<br/> RTHAEIKAFSTQMSINEGQRLVLKANIAGATDVKWVL<br/> NGVELTNSEERYGVSGSDQTLTIKQASHRDEGILTC<br/> ISKTEGIVKCQYDLTLSKELSDAPAFISQPRSQNIN<br/> EGQNVLFTCEISGEPSPKIEWFKNNLPISISSNVSIS<br/> RSRNVYSLEIRNASVSDSGKYTIKAKNFRGQCSATAS </p> |
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|-------------------------------------------------------|---------------------|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                       |                     |     | LMVLPLVEEPSREVLRRTSGDTSLQGSFSSQSVQMSA<br>SKQEASFSSSFSSSSASSMTEMKFASMSAQSMSSMQES<br>FVEMSSSSFMGISNMTQLESSTSKMLKAGIRGIPPKI<br>EALPSDISIDEGKVLTVACAFTGEPTPEVTWSCGGRK<br>IHSQEQGRFHIENTDDLTTLIIMDVQKQDGGLYTSL<br>GNEFGSDSATVNIHIRSI                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Cytoplasmic<br>dynein 1 heavy<br>chain 1<br>(DYNC1H1) | DYNC1H1<br>Syndrome | 236 | MSEPGGGGGEDGSAGLEVSQNVADVSVLQKHLRKL<br>VPLLEDGGEAPAALEAALEEKSALEQMRKFLSDPQV<br>HTVLVERSTLKEDVGDEGEEKEFISYNINIDIHYGV<br>KSNSLAFIKRTPVIDADKPVSSQLRVLTLSEDSPYET<br>LHSFISNAVAPFFKSYIRESGKADRGDGKMAPSVEKK<br>IAELEMGLLHLQQNIEIPEISLPIHPMITNVAKQCYE<br>RGEKPKVTDGDKVEDPTFLNQLQSGVNRWIREIQKV<br>TKLDRDPASGTALQEISFWNLRLALYRIQEKRESPE<br>VLLTLDILKHGKRFBATVSFDTDTGLKQALETVNDYN<br>PLMKDFPLNDLLSATELTKIRQALVAIFTHLRKIRNT<br>KYPiQRALRLVEAISRDLSQLLKVLGTRKLMHVAYE<br>EFEKVMVACFEVFQTDDEYEKLQVLLRDIVKRREE<br>NLKMVWRINPAHRKLQARLDQMRKFRRQHEQLRAVIV<br>RVLRPQVTAVAQQNQGEVPEPQDMKVAEVLFDAADAN<br>AIEEVNLAYENVKEVDGLDVSKEGTEAWEAAMKRYDE<br>RIDRVETRITARLDQLGTAKNANEMFRIFSRFNALF<br>VRPHIRGAIREYQTQLIQRVKDDIESLHDKFKVQYPQ<br>SQACKMSHVRDLPPVSGSIWAKQIDRQLTAYMKRVE<br>DVLGKGWENHVEGQKLKQDGDSEFRMKNLTQEIFDDWA<br>RKVQQRNGLGVSGRIFTIESTRVRGRTGNVLKLVNLF<br>PEIITLSKEVRNLKWLGRVPLAIVNKAHQANQLYPF<br>AISLIESVRTYERTCEKVEERNTISLLVAGLKKEVQA<br>LIAEGIALVWESYKLDPYVQRLAETVFNQEKVDDLL<br>IIEEKIDLEVRSLCTCMYDHKTFSEILNRVQKAVDDL<br>NLHSYSLNPIWVNKLDMIEIERILGVRLQAGLRAWTQV<br>LLGQAEDKAEVDMDTDAPQVSHKPGGEPKIKNVVHEL<br>RITNQVIYLNPPIEECRYKLYQEMFAWKMVVLSLPRI<br>QSQRVQGVHYELTEEEKFYRNALTRMPDGPVALEES<br>YSAVMGIVSEVEQYVKVWLQYQCLWDMQAENIYNRLG<br>EDLNKWQALLVQIRKARGTFDNAETKKEFGPVVIDYG<br>KVQSKVNLKYDSWHKEVLSKFGQMLGSNMTEFHSQIS<br>KSRQELEQHSVDTASTSDAVTFITYVQSLKRKIKQFE<br>KQVELYRNGQRLLEKQRFQFPPSWLYIDNIEGEWGAF<br>NDIMRRKDSAIQQQVANLQMKIVQEDRAVESRTTDL<br>TDWEKTKPVTGNLRPEEALQALTIEGKFGRLKDDRE<br>KCAKAKEALELTDTGLLSGSEERVQVALEELQDLKGV<br>WSELSKVWEQIDQMKEQPWVSVQPRKLRQNLDAALLN<br>LKSFPARLRQYASYEFVQRLLKGYMKINMLVIELKSE<br>ALKDRHWKQLMKRLHVNWVSELTLGQIWDVDLQKNE<br>AIVKDVLLVAQGEMALEEFLKQIREVWNTYELDLVNY<br>QNKCRILIRGWDDLFNKVKEHINSVSAMKLSPIYKVF<br>EDALSWEDKLNRMALFDVWIDVQRRWVYLEGIFTGS<br>ADIKHLLPVETQRFQSISTEFLALMKKVSXSPLVMDV<br>LNIQGVQRSRLERLADLLGKIQKALGEYLERERSFP<br>FYFVGDEDLLEIIGNSKNVAKLQKHFKKMFAVSSII |

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|  |  | <p>             LNEDNSVVLGISSREGEEVMFKTPVSSITEHPKINEWL<br/>             TLVEKEMRVTLAKLLAESVTEVEIFGKATSIDPNTYI<br/>             TWIDKYQAQLVVLSAQIAWSENVETALSSMGGGGDAA<br/>             PLHSVLSNVEVTLNVLADSVLMEQPPLRRRKLEHLIT<br/>             ELVHQRDVTRSLIKSKIDNAKSFEWLSQMRFYFDPKQ<br/>             TDVLQQLSIQMANAKFNYGFEYLGVDKLVQTPLTDR<br/>             CYLTMTQALEARLGGSPFGPAGTGKTESVKALGHQLG<br/>             RFVLVFNCDET FDFQAMGRI FVGLCQVGAWGCFDEFN<br/>             RLEERMLS AVSQVQCIQEALREHSNPNYDKTSAPIT<br/>             CELLNKQVKVSPDMAIFITMNPYAGRSNLPDNLKKL<br/>             FRSLAMTKPDRQLIAQVMLYSQGFRTAEVLANKIVPF<br/>             FKLCEQLSSQSHYDFGLRALKSVLVSAGNVKRERIQ<br/>             KIKREKEERGEAVDEGEIAENLPEQEILIQSVCEMTV<br/>             PKLVAEDIPLLFSLSDVFPVQYHRGEMTALREELK<br/>             KVCQEMYLT YGDGEEVGMWVEKVLQLYQITQINHGL<br/>             MMVGPSGSGKSMARVLLKALERLEGVEGVAHIIDPK<br/>             AISKDHLYGTLDPNTREWTDGLFTHVLRKIIDSVRGE<br/>             LQKRQWIVFDGDVDPEWVENLNSVLDDNKLTLPLNGE<br/>             RLSLPPNVRIMFEVQDLKYATLATVSRCGMVWFSEDV<br/>             LSTDMI FNNFLARLRSIPLDEGEDEAQRRRKGKEDEG<br/>             EEAAS PMLQIQRDAATIMQPYFTSNGLVTKALEHAFQ<br/>             LEHIMDLTRLRCLGSLFSMLHQACRNVAQYNANHPDF<br/>             PMQIEQLERYIQRYLVYAILWSLSGDSRLKMAELGE<br/>             YIRRITTVPLPTAPNIPIDIYEVSI SGEWSPWQAKVP<br/>             QIEVETHKVAAPDVVPTLDTVRHEALLYTWLAEHKP<br/>             LVLGPPGSGKTMTLFSALRALPDMEVVGLNFSSATT<br/>             PELLKTFDHYCEYRRTPNGVVLAPVQLGKWLVLFCDE<br/>             EINLPDMDKYGTQRVISFIRQMVEHGGFYRTSDQTW<br/>             VKLERIQFVGACNPPTDPGRKPLSHRFLRHVPVVYVD<br/>             YPGPASLTQIYGTFNRAMLRLIPSLRTYAEPLTAAMV<br/>             EFYTMSQERFTQDTQPHYIYSPREMTRWVRGIFEALR<br/>             PLETLPVEGLIRIWAHEALRLFQDRLVEDEERRWTDE<br/>             NIDTVALKHFPNIDREKAMSRPILYSNWLSKDYIPVD<br/>             QEELRDYVKARLKV FYEEELDVPLVLFNEVL DHVLR<br/>             DRIFRQPQGHLLLIGVSGAGKTTLSRFVAMNGLSVY<br/>             QIKVHRKYTGEDFDEDLRTVLRSGCKNEKIAFIMDE<br/>             SNVLD SGFLERMNTLLANGEVPGLFEGDEYATLMTQC<br/>             KEGAQKEGLMLDSHEELYKWFTSQVIRNLHVFTMNP<br/>             SSEGLKDRAATSPALFNRCVLNWFWDWSTEALYQVGK<br/>             EFTSKMDLEKPNYIVPDYMPVVYDKLPQPPSHREAI<br/>             NSCVFVHQTLHQANARLAKRGGRMTAITPRHYLDFIN<br/>             HYANLFHEKRSELEEQQMHLNVGLRKIKETVDQVEEL<br/>             RRDLR IKSQELEVKNAAANDKLKMKVQDQQAEEKKV<br/>             MSQEIQEQLHKQQEVIADKQMSVKEDLDKVEPAVIEA<br/>             QNAVKS IKKQHLVEVRSMANPPAAVKLALESICLLLG<br/>             ESTTDWKQIRSIIMRENFIPTIVNFSAEEISDAIREK<br/>             MKKNYMSNPSYNYEIVNRASLACGPMVKWAIAQLNYA<br/>             DMLKRVEPLRNELQKLEDDAKDNQQKANEVEQMIRDL<br/>             EASIARYKEEYAVLISEAQA IKADLA AVEAKVNRSTA<br/>             LLKSLSAERERWEKTSETFKNQMSTIAGDCLLSAAFI<br/>             AYAGYFDQQMRQNLF TTWSHHLQQANIQFRTDIARTE           </p> |
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|                                         |                 |     | <p>YLSNADERLRWQASSLPADDLCTENAIMLKRFNRYPL<br/> IIDPSGQATEFIMNEYKDRKITRITSFLDDAFRKNLES<br/> ALRFGNPLLVDVESYDPVLNPVLNREVRRTGGRVLI<br/> TLGDQDIDLSPSFVIFLSTRDPTVEFPPDLCSRVTFV<br/> NETVTRSSLQSQCLNEVLKAERPVDVEKRSDLLKLQG<br/> EFQLRLRQLEKSLQALNEVKGRILDDDTIITTLLENL<br/> KREAAEVTRKVEETDIVMQEVETVSQQYLPLSTACSS<br/> IYFTMESLKQIHFLYQYSLQFFLDIYHNVLYENPNLK<br/> GVTDHTQRLSIITKDLFQVAFNRVARGMLHQDHITFA<br/> MLLARIKLGTVGEPTYDAEFQHFLRGNEIVLSAGST<br/> PRIQGLTVEQAEAVVRLSCLPAFKDLIAKVQADEQFG<br/> IWL DSSSEPTVPYLWSEETPATPIGQAIHRLLLIQA<br/> FRPDRLLAMAHMFVSTNLGESFMSIMEQPLDLTHIVG<br/> TEVKPNTPVLMCSVPGYDASGHVEDLAAEQNTQITSI<br/> AIGSAEGFNQADKAINAVKSGRWVMLKNVHLAPGWL<br/> MQLEKKLHSLQPHACFRLFLTMEINPKVPVNNLLRAGR<br/> IFVFEPPPGVKANMLRTFSSIPVSRICKSPNERARLY<br/> FLLAWFHAI IQERLRYAPLGWSKKYEFGESDLRSACD<br/> TVDTWLDDTAKGRQNI SPDKIPWSALKTLMAQSIYGG<br/> RVDNEFDQRLNNTFLERLFTTRSFDSEFKLACKVDGH<br/> KDIQMPDGI RREEFVQWVELLPDTQTPSWLGLPNNAE<br/> RVLLTTQGVD MISKMLKMOMLEDEDDLAYAETEKKTR<br/> TDSTSDGRPAWMRTLHTTASNWLHLIPQTL SHLKRTV<br/> ENIKDPLFRFFEREVKMGAKLLQDVRQDLADVQVCE<br/> GKKKQTNYLRTLINELVKGILPRSWSHYTV PAGMTVI<br/> QWVSDFSERIKQLQNISLAAASGGAKELKNIHVCLGG<br/> LFVPEAYITATRQYVAQANSWSLEELCLEVNVTTSQG<br/> ATLDACSFVGTGLKLQGATC NNNKLSLSNAISTALPL<br/> TQLRWVKQTNTEKKASVVTLPVYLNFTRADLIFTVDF<br/> EIA TKEDPRS FYERGVAVLCTE</p> |
| TRIO and F-actin-binding protein (TRIO) | TRIO-Related ID | 237 | <p>MEEVPGDALCEHFEANILTQNRQCNCFHPEEAHGARY<br/> QELRSPSGAEVPHYCDLPRCPPAPEDPLSASTSGCQSV<br/> VDPGLRPGPKRGPSPSAGLP EEGPTAAPRSRSRELEA<br/> VPYLEGLTTS LCGSCNEDPGSDPTSSPDSATPDDTSN<br/> SSSV DWD TVERQEEEAPSWDELAVMIPRRPREGPRAD<br/> SSQRAPSLLTRSPVGGDAAGQKKEDTGGGGRSAGQHW<br/> ARLRGESGLSLERHRSTLTQASSMTPHSGPRSTTSQA<br/> SPAQRDTAQAASTREIPRASSPHRITQRDTSRASSTQ<br/> QEISRASSTQQETSRASSTQEDTPRASSTQEDTPRAS<br/> STQWNTPRASSPSRSTQLDNPRTSSTQQDNPQTSFPT<br/> CTPQRENPRTPCVQQDDPRASSPNRTTQRENSRTSCA<br/> QRDNPKASRTSSPNRATRDNPRTSCAQRDNPRASSPS<br/> RATRDNPPTTSCAQRDNPRASRTSSPNRATRDNPRTSC<br/> AQRDNPRASSPSRATRDNPPTTSCAQRDNPRASRTSSP<br/> NRATRDNPRTSCAQRDNPRASSPNRAARDNPPTTSCAQ<br/> RDNPRASRTSSPNRATRDNPRTSCAQRDNPRASSPNR<br/> ATRDNPPTTSCAQRDNPRASRTSSPNRATRDNPRTSCA<br/> QRDNPRASSPNRTTQQDSPRTSCARRDDPRASSPNRT<br/> IQQENPRTSCALRDNPASSPSRTIQQENPRTSCAQR<br/> DDPRASSPNRTTQQENPRTSCARRDNPRASSRNRTIQ<br/> RDNPRTSCAQRDNPRASSPNRTIQQENLRTSCTRQDN</p>                                                                                                                                                                                                                                                                                                                                                                                    |



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|                                                              |                            |     | <p>             PRTSSPNRATRDNPRTSCAQRDNLRASSPIRATQQDN<br/>             PRTCIIQQNIIPRSSSTQQDNPKTSCTKRDNLRPTCTQR<br/>             DRTQSFQSDNRDNPGTSSSQCCCTQKENLRPSSPHRSTQ<br/>             WNNPRNSSPHRTNKDIPWASFPLRPTQSDGPRSTSSPS<br/>             RSKQSEVPWASIALRPTQGDRPQTSSPSRPAQHDP<br/>             PQSSFGPTQYNLPSRATSSSHNPGHQSTSRSTSSPVYP<br/>             AAYGAPLTSPEPSQPPCAVCIGHRDAPRASSPPRYLQ<br/>             HDPFPPFFPEPRAPSEPPHHEPPYIPPAVCIGHRDAP<br/>             RASSPPRHTQFDPFPPFLPDTSDAEHQCSQSPQHEPLQL<br/>             PAPVCIGYRDAPRASSPPRQAPEPSLLFQDLPRASTE<br/>             SLVPSMDSLHECPHIPTPVCIGHRDAPSFSSPPRQAP<br/>             EPSLFFQDPPGTSMESLAPSTDSLHGSPVLIPQVCIG<br/>             HRDAPRASSPPRHPPSDLAFLAPSPSPGSSGSGRSGA<br/>             PPGETRHNLEREEYTVLADLPPPRRLAQRQPGPQAQC<br/>             SSGGRTHSPGRAEVERLFGQERRKSEAAGAFQAQDEG<br/>             RSQQPSQGSQQLRRQSSPAPSRQVTMLPAKQAELTR<br/>             RSQAEPHPWSPPEKRPEGDRQLQGSPLPPRTSARTPE<br/>             RELRTQRPLESQAGPRQPLGVWQSQEPPPGSQGPH<br/>             RHLERSWSSQEGGLPGGWGCGEPSSLGAAKAPEGAW<br/>             GGTSTREYKESWGQPEAWEEKPTHELPRELGKRSPLTS<br/>             PPENWGGPAESSQSWHSGTPTAVGWGAEGACPYPRGS<br/>             ERRPELDWRDLGLLRAPGEGVWARVPSLDWEGLLEL<br/>             LQARLPRKDPAGHRDDLARALGPELGPPGTNDVPEQE<br/>             SHSQPEGWAEATPVNGHSPALQSQSPVQLPSACTSTQ<br/>             WPKIKVTRGPATATLAGLEQTGPLGSRSTAKGPSLPE<br/>             LQFQPEEPEESEPSRGDPLTDQKQADSADKRAEGKA<br/>             GSPLKGRVLTWRMPGDRPTLFPFLSLGLVLRWRRP<br/>             DLLNFKKGWMSILDEPGEPSPSLTTTSTSQWKKHWF<br/>             VLTDSCLKYYRDSTAEAEDELDEIDLRSCDVTVEYA<br/>             VQRNYGFQIHTKDAVYTLSTAMTSGIRRNWIEALRKT<br/>             RPTAPDVTKLSDSNKENALHSYSTQKGPLKAGEQRA<br/>             GSEVISRGGPRKADGQRQALDYVELSPLTQASPQRRAR<br/>             TPARTPDRLAKQEELERDLAQRSEERRKWFEATDSRT<br/>             PEVPAGEGPRRGLGAPLTEDQQNRLSEEIEKKWQELE<br/>             KLPLRENKRVPPLTALLNQSRGERRGPPSDGHEALEKE<br/>             VQALRAQLEAWRLQGEAPQSALRSQEDGHIPPGYISQ<br/>             EACERSLAEMESSHQVMEELQRHHERELQRLQQEKE<br/>             WLLAEETAATASAIAMKKAYQEELSRELSKTRSLQQ<br/>             GPDGLRKQHQSDEALKRELQVLSEQYSQKCLEIGAL<br/>             MRQAEEREHTLRRCCQEGQELLRHNQELHGRLESEID<br/>             QLRGFIAQGMNGCGRSNERSSCLEVLRLRVKENEL<br/>             QYLKKEVQCLRDELQMMQKDKRFTSGKYQDVYVELSH<br/>             IKTRSEREIEQLKEHLRLAMAALQEKESSMRNSLAE           </p> |
| Probable ubiquitin carboxyl-terminal hydrolase FAF-X (USP9X) | USP9X Development Disorder | 238 | <p>             MTATTRGSPVGGNDNQGPAPDGQSQPPLQQNQTSPPD<br/>             SSNENSPATPPDEQGGQDAPPQLEDEEPAFPHTDLAK<br/>             LDDMINRPRWVVPVLPKGELEVLLEAAIDLSKKGLDV<br/>             KSEACQRRFFRDGLTISFTKILTDEAVSGWKFEIHRCI<br/>             INNTHRLVELCVAKLSQDWFPLELLAMALNPHCKFH<br/>             IYNGTRPCESVSSSVQLPEDELFAKSPDPRSPKGWLV<br/>             DLLNKFGLTLNGFQILHDFRINGSALNVQIIAALIKPF<br/>             GQCYEFLTLHTVKKYFLPIIEMVPQFLENLTDEELKK           </p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

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|  |  |  | EAKNEAKNDALSMIIKSLKNLASRVPGQEETVKNLEI<br>FRLKMILRLLQISSFNGKMNALNEVNKVISSVSYYTH<br>RHGNPEEEEWLTAERMAEWIQQNNILSIVLRDSLHQP<br>QYVEKLEKILRFVIKEKALTLDLDNIWAAQAGKHEA<br>IVKNVHDLAKLAWDFSPEQLDHLFDCFASWTNAS<br>KKQREKLLELIRRLAEDDKDGMMAHKVLNLLWNLAS<br>DDVPVDIMDLALSAHIKILDYSCSQDRDTQKIQWIDR<br>FIEELRTNDKWVIPALKQIREICSLFGEAPQNLSQTQ<br>RSPHFVYRHDLINQLQHNHALVTLVAENLATYME<br>SMRLYARDHEDYDPQTVRLGSRYSHVQEVQERLNF<br>RFLFKDGQLWLCAPOAKQIWKCLAENAVYLC<br>DREACFKWYSKLMGDEPDLPDINKDFESNV<br>LQLDPSLLTENGMKCFERFFKAVNCREGKL<br>VAKRRAYMMDDLELIGLDYLWRVVIQSNDDI<br>ASRAIDLLEIYTNLGPRLQVNQVVIHEDFIQ<br>SCFDRLKASYDTLCVLDGDKDSVNCARQEAV<br>RMRVRVLTVLREYINECDSYHEERTILPMSRA<br>FRGKHLSEFVVRFPNQGRQVDDLEVWSHTND<br>TIGSVRRCILNRIKANVAHTKIELFVGELIDP<br>ADDRKLIGQLNLKDKSLITAKLTQISSNMPSS<br>PDSSSDSSTGSPGNHGNHYSDBGPNPEVES<br>CLPGVIMSLHPYISFLWQVADLGSSLNMP<br>PLRDGARVLMKLMPPDSTTIEKLRAICLDHAK<br>LGESSLSPSLDSLFFGPSASQVLYLTEVVYAL<br>LMPAGAPLADSSDFQFHFLKSGGLPLVLSML<br>TRNNFLPNADMETRRGAYLNALKIAKLLLT<br>AIGYGHVRAVAEACQPGVEGVNPMTQINQV<br>THDQAVVLQSALQSI PNPSSECM LRNVSV<br>RLAQQISDEASRYMPDICVIRAIQKIIWASG<br>CGSLQLVFSPNEEITKIYEKTNAGNEPDLE<br>DEQVCCEALEVMTLCFALIPTALDALSKEK<br>AWQTFIIDLLHCHSKTVRQVAQEQFFLMCT<br>RCCMGHRPLLEFFITLLFTVLGSTARERAK<br>HSGDYFTLLRHLLNYAYNSNINVPNAEVLL<br>NNEIDWLKRIRDDVKRTGETGIEETILEGHL<br>GVTKELLAFQTSKKFHHIGCEKGGANLIKEL<br>IDDFIFPASNVYLQYMRNGELPAEQAI<br>PVCSPPTINAGFELLVALAVGCVRN<br>LKQIVDSLTEMYYIGTAITTCALTEWEY<br>LPPVGPRPPKGFVGLKNAGATCYMNSVIQ<br>QLYMI PSIRNGILAIEGTGSDVDDDM<br>SGDEKQDNESNVDP RDDVF GYPQQFED<br>KPALSKTEDRKEYNIGVLRHLQVIFGHLA<br>ASRLQYYVPRGFWKQFRLWGEPVNLRE<br>QHDALEFFNSLVDSLDEALKALGHPAMLS<br>KVLGGSFADQKICQGC P HRYECEESFT<br>TLNVDIRNHQNLDSLEQYVKGDLL<br>LEGANAYHCEKCNKKVDTVKRLLIK<br>KLPPVLAIQLKRFDYDWERECAIKFNDY<br>FEFPRELDMEPYTVAGVAKLEGDNVNP<br>ESQLIQQSEQSESETAGSTKYRLVGVL<br>VHSGQASGGHYYSYIIQRNGGDGER<br>NRWYKFDDGDVTECKMDDDEEMKNQCF<br>GG EYMGEVFDHMMKRMSYRRQKRWW<br>NAYILFYERMDTIDQDDELIRYISELA<br>ITTRPHQIIMP SAIERSVRKQNVQFM<br>HNRMQYSMEYFQFMKKLLTCNGVYLN<br>PPPGQDHLLPEAE EITMISIQLAARFL<br>FTTG FHTKKVV RGSASDWYDALCILL<br>RHSKNVRFWFAHNVL FNVSNRFSEYLL<br>ECP SAEVRGAFAKLIVFIAHFSLQDGP<br>CPSPFASPGSSQAYDNLSLSDHLLRA<br>VLNLLRREVSEHGRHLQQYFNL |
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|                                                            |                                                              |     |                                                                                                                                                                                                                                                                                                                                                                                                                            |
|------------------------------------------------------------|--------------------------------------------------------------|-----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                            |                                                              |     | VMYANLGVAEKTQLLKLSPATFMLVSLDEGPGPPIK<br>YQYAEELGKLYSVVSQIRCCNVSSRMQSSINGNPPLP<br>NPFQDPNLSQPIMPIQQNVADILFVRTSYVKKI IEDC<br>SNSEETVKLLRFCCWENPQFSSTVLSELLWQVAYSYT<br>YELRPYLDLLLQILLIEDSWQTHRIHNALKGIPDDRD<br>GLFDTIQRSKNHYQKRAYQCIKCMVALFSNCPVAYQI<br>LQNGDLKRKWTWAVEWLGDELERRPYTGPNPQYTYNN<br>WSPPVQSNETSNGYFLERSHSARMTLAKACELCPEEE<br>PDDQDAPDEHESPPPEDAPLYPHSPGSQYQQNNHVHG<br>QPYTGPAAHMNNPQRTGQRAQENYEGSEEVSPQTK<br>DQ |
| Pyrin domain-<br>containing<br>protein 2<br>(PYDC2)        | -                                                            | 287 | MASSAELDFNLQALLEQLSQDEL SKFKSLIRTISLGK<br>ELQTVPQTEVDKANGKQLVEIFTSHSCSYWAGMAAIQ<br>VFEKMNQTHLSGRADEHCVMPPP                                                                                                                                                                                                                                                                                                                 |
| Cystatin-B<br>(CSTB)                                       | Epilepsy,<br>progressive<br>myoclonic 1<br>(EPM1)            | 288 | MMCGAPSATQPATAETQHIADQVRSQLEEKENKKFPV<br>FKAVSFKSQVVAGTNYFIKVHVGDEDFVHLRVFQSLP<br>HENKPLTLSNYQTNKAKHDELTYF                                                                                                                                                                                                                                                                                                                 |
| Pterin-4-alpha-<br>carbinolamine<br>dehydratase<br>(PCBD1) | Hyperphenylala<br>ninemia, BH4-<br>deficient, D<br>(HPABH4D) | 289 | MAGKAHRLSAEERDQLLPNLRAVGWNELEGRDAIFKQ<br>FHFKDFNRAFGFMTRVALQAEKLDHHPWFVNVNKHVH<br>ITLSTHECAGLSERDINLASFIEQVAVSMT                                                                                                                                                                                                                                                                                                           |

### 5.3.2.2 Anti-SYNGAP1 Single Domain Antibodies

**[00191]** In one aspect, provided herein is a single domain antibody (e.g., a VHH) that specifically binds SYNGAP1 (e.g., human SYNGAP1). In some embodiments, the single domain antibody is a VHH (i.e. a nanobody). In some embodiments, the VHH comprises three complementarity determining regions: VH CDR1, VH CDR2, and VH CDR3. The CDRs below are defined according to Kabat.

**[00192]** In some embodiments, the VHH comprises a CDR1 that comprises the amino acid sequence of SEQ ID NO: 290, 294, 298, 302, 306, or 310, or the amino acid sequence of SEQ ID NO: 290, 294, 298, 302, 306, or 310 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); a CDR2 that comprises the amino acid sequence of SEQ ID NO: 291, 295, 299, 303, 307, or 311, or the amino acid sequence of SEQ ID NO: 291, 295, 299, 303, 307, or 311 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); and/or a CDR3 that comprises the amino acid sequence of SEQ ID NO: 292, 296, 300, 304, 308, or 312 or the amino acid sequence of SEQ ID NO: 292, 296, 300, 304, 308, or 312 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition).

**[00193]** In some embodiments, the VHH comprises a CDR1 that comprises the amino acid

sequence of SEQ ID NO: 290, or the amino acid sequence of SEQ ID NO: 290 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); a CDR2 that comprises the amino acid sequence of SEQ ID NO: 291, or the amino acid sequence of SEQ ID NO: 291 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); and a CDR3 that comprises the amino acid sequence of SEQ ID NO: 292, or the amino acid sequence of SEQ ID NO: 292 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition).

**[00194]** In some embodiments, the VHH comprises a CDR1 that comprises an amino acid sequence at least 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 290; a CDR2 that comprises an amino acid sequence at least 95%, 96%, 97%, 98%, 99%, or 100% to the amino acid sequence of SEQ ID NO: 291; and a CDR3 that comprises an amino acid sequence at least 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 292.

**[00195]** In some embodiments, the VHH comprises a CDR1 that comprises the amino acid sequence of SEQ ID NO: 294, or the amino acid sequence of SEQ ID NO: 294 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); a CDR2 that comprises the amino acid sequence of SEQ ID NO: 295, or the amino acid sequence of SEQ ID NO: 295 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); and a CDR3 that comprises the amino acid sequence of SEQ ID NO: 296, or the amino acid sequence of SEQ ID NO: 296 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition).

**[00196]** In some embodiments, the VHH comprises a CDR1 that comprises an amino acid sequence at least 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 294; a CDR2 that comprises an amino acid sequence at least 95%, 96%, 97%, 98%, 99%, or 100% to the amino acid sequence of SEQ ID NO: 295; and a CDR3 that comprises an amino acid sequence at least 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 296.

**[00197]** In some embodiments, the VHH comprises a VH CDR1 that comprises the amino acid sequence of SEQ ID NO: 298, or the amino acid sequence of SEQ ID NO: 298 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); a CDR2 that comprises the amino acid sequence of SEQ ID NO: 299, or the amino acid sequence of SEQ ID NO: 299 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); and a CDR3 that comprises the amino acid sequence of SEQ ID NO: 300, or the amino acid sequence of SEQ ID

NO: 300 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition).

**[00198]** In some embodiments, the VHH comprises a CDR1 that comprises an amino acid sequence at least 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 298; a CDR2 that comprises an amino acid sequence at least 95%, 96%, 97%, 98%, 99%, or 100% to the amino acid sequence of SEQ ID NO: 299; and a CDR3 that comprises an amino acid sequence at least 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 300.

**[00199]** In some embodiments, the VHH comprises a CDR1 that comprises the amino acid sequence of SEQ ID NO: 302, or the amino acid sequence of SEQ ID NO: 302 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); a CDR2 that comprises the amino acid sequence of SEQ ID NO: 303, or the amino acid sequence of SEQ ID NO: 303 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); and a CDR3 that comprises the amino acid sequence of SEQ ID NO: 304, or the amino acid sequence of SEQ ID NO: 304 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition).

**[00200]** In some embodiments, the VHH comprises a CDR1 that comprises an amino acid sequence at least 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 302; a CDR2 that comprises an amino acid sequence at least 95%, 96%, 97%, 98%, 99%, or 100% to the amino acid sequence of SEQ ID NO: 303; and a CDR3 that comprises an amino acid sequence at least 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 304.

**[00201]** In some embodiments, the VHH comprises a CDR1 that comprises the amino acid sequence of SEQ ID NO: 306, or the amino acid sequence of SEQ ID NO: 306 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); a CDR2 that comprises the amino acid sequence of SEQ ID NO: 307, or the amino acid sequence of SEQ ID NO: 307 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); and a CDR3 that comprises the amino acid sequence of SEQ ID NO: 308, or the amino acid sequence of SEQ ID NO: 308 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition).

**[00202]** In some embodiments, the VHH comprises a CDR1 that comprises an amino acid sequence at least 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 306; a CDR2 that comprises an amino acid sequence at least 95%, 96%, 97%, 98%, 99%, or 100% to the amino acid sequence of SEQ ID NO: 307; and a CDR3 that comprises an

amino acid sequence at least 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 308.

**[00203]** In some embodiments, the VHH comprises a CDR1 that comprises the amino acid sequence of SEQ ID NO: 310, or the amino acid sequence of SEQ ID NO: 310 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); a CDR2 that comprises the amino acid sequence of SEQ ID NO: 311, or the amino acid sequence of SEQ ID NO: 311 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); and a CDR3 that comprises the amino acid sequence of SEQ ID NO: 312, or the amino acid sequence of SEQ ID NO: 312 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition).

**[00204]** In some embodiments, the VHH comprises a CDR1 that comprises an amino acid sequence at least 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 310; a CDR2 that comprises an amino acid sequence at least 95%, 96%, 97%, 98%, 99%, or 100% to the amino acid sequence of SEQ ID NO: 311; and a CDR3 that comprises an amino acid sequence at least 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 312.

**[00205]** In some embodiments, the VHH comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 293, 297, 301, 305, 309, or 312.

**[00206]** In some embodiments, the VHH comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 293.

**[00207]** In some embodiments, the VHH comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 297.

**[00208]** In some embodiments, the VHH comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 301.

**[00209]** In some embodiments, the VHH comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 305.

**[00210]** In some embodiments, the VHH comprises an amino acid sequence at least 90%, 91%,

92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 309.

**[00211]** In some embodiments, the VHH comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 313.

**[00212]** Also provided herein are (VHH)<sub>2</sub> antibodies that specifically bind SYNGAP1. The first VHH and the second VHH of a (VHH)<sub>2</sub> may be directly connected or indirectly connected via an amino acid linker. Exemplary amino acid linkers include the amino acid sequence of any one of SEQ ID NOS: 375-384. In some embodiments, the amino acid sequence of the linker is at least 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 375-384. In some embodiments, the amino acid sequence of the linker is at least 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 375. In some embodiments, the amino acid sequence of the linker is at least 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 376. In some embodiments, the amino acid sequence of the linker is at least 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 377. In some embodiments, the amino acid sequence of the linker is at least 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 378. In some embodiments, the amino acid sequence of the linker is at least 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 379. In some embodiments, the amino acid sequence of the linker is at least 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 380. In some embodiments, the amino acid sequence of the linker is at least 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 381. In some embodiments, the amino acid sequence of the linker is at least 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 382. In some embodiments, the amino acid sequence of the linker is at least 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 383. In some embodiments, the amino acid sequence of the linker is at least 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 384.

**[00213]** In some embodiments, the (VHH)<sub>2</sub> comprises a first VHH comprising a CDR1 that comprises the amino acid sequence of SEQ ID NO: 290, 294, 298, 302, 306, or 310, or the amino acid sequence of SEQ ID NO: 290, 294, 298, 302, 306, or 310 with 1, 2, or 3 amino acid

modifications (e.g., a substitution, deletion, or addition); a CDR2 that comprises the amino acid sequence of SEQ ID NO: 291, 295, 299, 303, 307, or 311, or the amino acid sequence of SEQ ID NO: 291, 295, 299, 303, 307, or 311 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); and/or a CDR3 that comprises the amino acid sequence of SEQ ID NO: 292, 296, 300, 304, 308, or 312 or the amino acid sequence of SEQ ID NO: 292, 296, 300, 304, 308, or 312 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); and a second VHH comprising a CDR1 that comprises the amino acid sequence of SEQ ID NO: 290, 294, 298, 302, 306, or 310, or the amino acid sequence of SEQ ID NO: 290, 294, 298, 302, 306, or 310 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); a CDR2 that comprises the amino acid sequence of SEQ ID NO: 291, 295, 299, 303, 307, or 311, or the amino acid sequence of SEQ ID NO: 291, 295, 299, 303, 307, or 311 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); and/or a CDR3 that comprises the amino acid sequence of SEQ ID NO: 292, 296, 300, 304, 308, or 312 or the amino acid sequence of SEQ ID NO: 292, 296, 300, 304, 308, or 312 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition).

**[00214]** In some embodiments, the (VHH)<sub>2</sub> comprises a first VHH comprising a CDR1 that comprises the amino acid sequence of SEQ ID NO: 290, or the amino acid sequence of SEQ ID NO: 290 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); a CDR2 that comprises the amino acid sequence of SEQ ID NO: 291, or the amino acid sequence of SEQ ID NO: 291 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); and a CDR3 that comprises the amino acid sequence of SEQ ID NO: 292, or the amino acid sequence of SEQ ID NO: 292 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition), operably connected (optionally via an amino acid linker) to a second VHH, wherein the second VHH comprises a CDR1 that comprises the amino acid sequence of SEQ ID NO: 290, or the amino acid sequence of SEQ ID NO: 290 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); a CDR2 that comprises the amino acid sequence of SEQ ID NO: 291, or the amino acid sequence of SEQ ID NO: 291 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); and a CDR3 that comprises the amino acid sequence of SEQ ID NO: 292, or the amino acid sequence of SEQ ID NO: 292 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition).

**[00215]** In some embodiments, the (VHH)<sub>2</sub> comprises a first VHH that comprises a CDR1 that



comprises the amino acid sequence of SEQ ID NO: 294, or the amino acid sequence of SEQ ID NO: 294 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); a CDR2 that comprises the amino acid sequence of SEQ ID NO: 295, or the amino acid sequence of SEQ ID NO: 295 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); and a CDR3 that comprises the amino acid sequence of SEQ ID NO: 296, or the amino acid sequence of SEQ ID NO: 296 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition), operably connected (optionally via an amino acid linker) to a second VHH, wherein the second VHH comprises a CDR1 that comprises the amino acid sequence of SEQ ID NO: 294, or the amino acid sequence of SEQ ID NO: 294 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); a CDR2 that comprises the amino acid sequence of SEQ ID NO: 295, or the amino acid sequence of SEQ ID NO: 295 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); and a CDR3 that comprises the amino acid sequence of SEQ ID NO: 296, or the amino acid sequence of SEQ ID NO: 296 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition).

**[00216]** In some embodiments, the (VHH)<sub>2</sub> comprises a first VHH that comprises a CDR1 that comprises the amino acid sequence of SEQ ID NO: 298, or the amino acid sequence of SEQ ID NO: 298 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); a CDR2 that comprises the amino acid sequence of SEQ ID NO: 299, or the amino acid sequence of SEQ ID NO: 299 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); and a CDR3 that comprises the amino acid sequence of SEQ ID NO: 300, or the amino acid sequence of SEQ ID NO: 300 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition), operably connected (optionally via an amino acid linker) to a second VHH, wherein the second VHH comprises a CDR1 that comprises the amino acid sequence of SEQ ID NO: 298, or the amino acid sequence of SEQ ID NO: 298 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); a CDR2 that comprises the amino acid sequence of SEQ ID NO: 299, or the amino acid sequence of SEQ ID NO: 299 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); and a CDR3 that comprises the amino acid sequence of SEQ ID NO: 300, or the amino acid sequence of SEQ ID NO: 300 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition).

**[00217]** In some embodiments, the (VHH)<sub>2</sub> comprises a first VHH that comprises a CDR1 that comprises the amino acid sequence of SEQ ID NO: 302, or the amino acid sequence of SEQ ID

NO: 302 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); a CDR2 that comprises the amino acid sequence of SEQ ID NO: 303, or the amino acid sequence of SEQ ID NO: 303 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); and a CDR3 that comprises the amino acid sequence of SEQ ID NO: 304, or the amino acid sequence of SEQ ID NO: 304 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition), operably connected (optionally via an amino acid linker) to a second VHH, wherein the second VHH comprises a comprising a VH CDR1 that comprises the amino acid sequence of SEQ ID NO: 302, or the amino acid sequence of SEQ ID NO: 302 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); a CDR2 that comprises the amino acid sequence of SEQ ID NO: 303, or the amino acid sequence of SEQ ID NO: 303 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); and a CDR3 that comprises the amino acid sequence of SEQ ID NO: 304, or the amino acid sequence of SEQ ID NO: 304 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition).

**[00218]** In some embodiments, the (VHH)<sub>2</sub> comprises a first VHH that comprises a CDR1 that comprises the amino acid sequence of SEQ ID NO: 306, or the amino acid sequence of SEQ ID NO: 306 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); a CDR2 that comprises the amino acid sequence of SEQ ID NO: 307, or the amino acid sequence of SEQ ID NO: 307 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); and a CDR3 that comprises the amino acid sequence of SEQ ID NO: 308, or the amino acid sequence of SEQ ID NO: 308 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition), operably connected (optionally via an amino acid linker) to a second VHH, wherein the second VHH comprises a comprising a CDR1 that comprises the amino acid sequence of SEQ ID NO: 306, or the amino acid sequence of SEQ ID NO: 306 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); a CDR2 that comprises the amino acid sequence of SEQ ID NO: 307, or the amino acid sequence of SEQ ID NO: 307 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); and a CDR3 that comprises the amino acid sequence of SEQ ID NO: 308, or the amino acid sequence of SEQ ID NO: 308 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition).

**[00219]** In some embodiments, the (VHH)<sub>2</sub> comprises a first VHH that comprises a CDR1 that comprises the amino acid sequence of SEQ ID NO: 310, or the amino acid sequence of SEQ ID NO: 310 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); a

CDR2 that comprises the amino acid sequence of SEQ ID NO: 311, or the amino acid sequence of SEQ ID NO: 311 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); and a CDR3 that comprises the amino acid sequence of SEQ ID NO: 312, or the amino acid sequence of SEQ ID NO: 312 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition), operably connected (optionally via an amino acid linker) to a second VHH, wherein the second VHH comprises a CDR1 that comprises the amino acid sequence of SEQ ID NO: 310, or the amino acid sequence of SEQ ID NO: 310 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); a CDR2 that comprises the amino acid sequence of SEQ ID NO: 311, or the amino acid sequence of SEQ ID NO: 311 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); and a CDR3 that comprises the amino acid sequence of SEQ ID NO: 312, or the amino acid sequence of SEQ ID NO: 312 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition).

**[00220]** In some embodiments, the (VHH)<sub>2</sub> comprises a first VHH that comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 293, 297, 301, 305, 309, or 313; and a second VHH that comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 293, 297, 301, 305, 309, or 313.

**[00221]** In some embodiments, the (VHH)<sub>2</sub> comprises a first VHH that comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 293; and a second VHH that comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 293.

**[00222]** In some embodiments, the (VHH)<sub>2</sub> comprises a first VHH that comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 297; and a second VHH that comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 297.

**[00223]** In some embodiments, the (VHH)<sub>2</sub> comprises a first VHH that comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 301; and a second VHH that comprises an amino acid

sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 301.

**[00224]** In some embodiments, the (VHH)<sub>2</sub> comprises a first VHH that comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 305; and a second VHH that comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 305.

**[00225]** In some embodiments, the (VHH)<sub>2</sub> comprises a first VHH that comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 309; and a second VHH that comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 309.

**[00226]** In some embodiments, the (VHH)<sub>2</sub> comprises a first VHH that comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 313; and a second VHH that comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 313.

**[00227]** In some embodiments, the (VHH)<sub>2</sub> comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 314. In some embodiments, the (VHH)<sub>2</sub> comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 315. In some embodiments, the (VHH)<sub>2</sub> comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 316. In some embodiments, the (VHH)<sub>2</sub> comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 317. In some embodiments, the (VHH)<sub>2</sub> comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 318. In some embodiments, the (VHH)<sub>2</sub> comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 319.

**[00228]** In some embodiments, the anti-SYNGAP1 VHH is one described in Table 3.

[00229] The amino acid sequence of anti-SYNGAP1 VHHs is provided in Table 3 below.

**Table 3.** Amino Acid Sequence of Anti- SynGAP1 VHHs. The CDRs are defined according to Kabat.

| Description |      | SEQ ID NO | Amino Acid Sequence                                                                                                                        |
|-------------|------|-----------|--------------------------------------------------------------------------------------------------------------------------------------------|
| FLX00152    | CDR1 | 290       | GFSFSNFP                                                                                                                                   |
|             | CDR2 | 291       | INQDGRNT                                                                                                                                   |
|             | CDR3 | 292       | QAIRTTTHFDS                                                                                                                                |
|             | VHH  | 293       | QVQLVESGGGLVQPGGSLRLSCAASGFSFSNFPMMWVR<br>QAPGKGREWVADINQDGRNTYYADSVKGRFTISRDN<br>AKTTVYLQMNINLPEDTAVYYCQAIRTTTHFDSWGQGTQV<br>TVSS         |
| FLX00153    | CDR1 | 294       | GFTFSNYR                                                                                                                                   |
|             | CDR2 | 295       | IDRSGTYT                                                                                                                                   |
|             | CDR3 | 296       | AADRRLIVDLTPEVYDH                                                                                                                          |
|             | VHH  | 297       | QLQLVESGGGLVQPGESLRLSCAASGFTFSNYRMYWVR<br>MAPGKGLEWVSDIDRSGTYTYADSVKGRFAISRDN<br>AKNTVYLQMNLSLKPEDTAVYYCAADRRLIVDLTPEVYD<br>HWGQGTQVTVSS   |
| FLX00154    | CDR1 | 298       | GFIFSSYQ                                                                                                                                   |
|             | CDR2 | 299       | INTGGWNT                                                                                                                                   |
|             | CDR3 | 300       | AADRWMVAKIVGGDLDFDS                                                                                                                        |
|             | VHH  | 301       | QVQLVESGGGLVQPGGSLRLSCAASGFIFSSYQMAWVR<br>QAPGKGLEWVADINTGGWNTYYADSVKGRFTISRDN<br>AKNTLYLEMNSLKPEDTAVYYCAADRWMVAKIVGGDLDF<br>DSWGQGTQVTVSS |
| FLX00155    | CDR1 | 302       | GFAFGSYD                                                                                                                                   |
|             | CDR2 | 303       | ITPGGGGT                                                                                                                                   |
|             | CDR3 | 304       | YYCAKNFYGNNG                                                                                                                               |
|             | VHH  | 305       | QVQLVESGGGLVQPGGSLRLSCAASGFAFGSYDMSWVR<br>QAPGQGPEWVSATITPGGGGTIFYAYSDSVKGRFAISR<br>D NAKNTLTQLMNSLKPDDTAMYYCAKNFYGNNGRGHGT<br>QVTVSS      |
| FLX00156    | CDR1 | 306       | GFTFGTHA                                                                                                                                   |
|             | CDR2 | 307       | ISSGGGGT                                                                                                                                   |
|             | CDR3 | 308       | NSPSNIANDN                                                                                                                                 |
|             | VHH  | 309       | QVQLVESGGGLVQPGGSLRLACAASGFTFGTHAMHWVR<br>WAPGKGFEWVSTISSGGGGTRYADSVKGRFTISRDN<br>AKNTVYLQMDNLKPEDTAVYYCNSPSNIANDNNGQGTQV<br>TVSS          |
| FLX00157    | CDR1 | 310       | ERTFGHYA                                                                                                                                   |
|             | CDR2 | 311       | ISWKGGTT                                                                                                                                   |
|             | CDR3 | 312       | AARNTMSGSMSSSAYPY                                                                                                                          |
|             | VHH  | 313       | QVQLVESGGGLVQAGASLRLSCAASERTFGHYAMGWFR<br>QAPGKEREFVATISWKGGTTGYAHSVKGRFTISRDS<br>AKNMVYLQMNLSLKPEDTAVYYCAARNTMSGSMSSSAY<br>PYWGQGTQVTVSS  |

[00230] The amino acid sequence of anti-SYNGAP1 VHH<sub>2</sub>'s is provided in Table 4 below.

**Table 4.** Amino Acid Sequence of Anti- SynGAP1 VHH<sub>2</sub>s

| Description | SEQ ID NO: | Amino Acid Sequence                                                                                                                                                                                                                                                                               |
|-------------|------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| FLX00152    | 314        | QVQLVESGGGLVQPGGSLRLSCAASGFSFSNFPMMWVRQAPGKGRE<br>WVADINQDGRNTYYADSVKGRFTISRDNAKTTVYLQMNNLNPEDTA<br>VYYCQAIRTTTHFDSWGQGTQVTVSSGGGGSGGGSGGGSGGGGS<br>QVQLVESGGGLVQPGGSLRLSCAASGFSFSNFPMMWVRQAPGKGRE<br>WVADINQDGRNTYYADSVKGRFTISRDNAKTTVYLQMNNLNPEDTA<br>VYYCQAIRTTTHFDSWGQGTQVTVSS                |
| FLX00153    | 315        | QLQLVESGGGLVQPGESLRLSCAASGFTFSNYRMYWVRMAPGKGLE<br>WVSDIDRSGTYTYADSVKGRFAISRDNAKNTVYLQMNSLKPEDTA<br>VYYCAADRRLIVDLTPEVYDHWGQGTQVTVSSGGGGSGGGSGGGG<br>SGGGGSQQLVESGGGLVQPGESLRLSCAASGFTFSNYRMYWVRMA<br>PGKGLEWVSDIDRSGTYTYADSVKGRFAISRDNAKNTVYLQMNSL<br>KPEDTAVYYCAADRRLIVDLTPEVYDHWGQGTQVTVSS      |
| FLX00154    | 316        | QVQLVESGGGLVQPGGSLRLSCAASGFIFSSYQMAWVRQAPGKGLE<br>WVADINTGGWNTYYADSVKGRFTISRDNAKNTLYLEMNSLKPEDTA<br>VYYCAADRWMVAKIVGGDLDFDSWGQGTQVTVSSGGGGSGGGSGG<br>GGGGGSQVQLVESGGGLVQPGGSLRLSCAASGFIFSSYQMAWVR<br>QAPGKGLEWVADINTGGWNTYYADSVKGRFTISRDNAKNTLYLEMN<br>SLKPEDTAVYYCAADRWMVAKIVGGDLDFDSWGQGTQVTVSS |
| FLX00155    | 317        | QVQLVESGGGLVQPGGSLRLSCAASGFAFGSYDMSWVRQAPGQGPE<br>WVSAITPGGGGT FYAYYSDSVKGRFAISRDNAKNTLTLMNSLKP<br>DTAMYYCAKNFYGNNGRGHGTQVTVSSGGGGSGGGSGGGSGGGG<br>SQVQLVESGGGLVQPGGSLRLSCAASGFAFGSYDMSWVRQAPGQGP<br>EWVSAITPGGGGT FYAYYSDSVKGRFAISRDNAKNTLTLMNSLKP<br>DDTAMYYCAKNFYGNNGRGHGTQVTVSS               |
| FLX00156    | 318        | QVQLVESGGGLVQPGGSLRLACAASGFTFGTHAMHWVRWAPGKGFE<br>WVSTISSGGGGTRYADSVKGRFTISRDNAKNTVYLQMDNLKPEDTA<br>VYYCNSPSNIANDNWGQGTQVTVSSGGGGSGGGSGGGSGGGGSQ<br>VQLVESGGGLVQPGGSLRLACAASGFTFGTHAMHWVRWAPGKGFEW<br>VSTISSGGGGTRYADSVKGRFTISRDNAKNTVYLQMDNLKPEDTAV<br>YYCNSPSNIANDNWGQGTQVTVSS                  |
| FLX00157    | 319        | QVQLVESGGGLVQAGASLRLSCAASERTFGHYAMGWFRQAPGKERE<br>FVATISWKGGTTGYAHSVKGRFTISRDSAKNMVYLQMNSLKPEDTA<br>VYYCAARNTMSGMSSSAYPYWGQGTQVTVSSGGGGSGGGSGGGG<br>SGGGGSQVQLVESGGGLVQAGASLRLSCAASERTFGHYAMGWFRQA<br>PGKERE FVATISWKGGTTGYAHSVKGRFTISRDSAKNMVYLQMNSL<br>KPEDTAVYYCAARNTMSGMSSSAYPYWGQGTQVTVSS    |

### 5.3.3 Orientation and Linkers

[00231] In some embodiments, the effector domain is N-terminal of the targeting domain in the fusion protein. In some embodiments, the targeting domain is N-terminal of the effector domain in the fusion protein. In some embodiments, the effector domain is operably connected (directly

or indirectly) to the C terminus of the targeting domain. In some embodiments, the effector domain is operably connected (directly or indirectly) to the N terminus of the targeting domain. In some embodiments, the effector domain is directly operably connected to the C terminus of the targeting domain. In some embodiments, the effector domain is directly operably connected to the N terminus of the targeting domain.

**[00232]** In some embodiments, the effector domain is indirectly operably connected to the C terminus of the targeting domain. In some embodiments, the effector domain is indirectly operably connected to the N terminus of the targeting domain. One or more amino acid sequences comprising e.g., a linker, or encoding one or more polypeptides may be positioned between the effector moiety and the targeting moiety. In some embodiments, the effector domain is indirectly operably connected to the C terminus of the targeting domain through a peptide linker. In some embodiments, the effector domain is indirectly operably connected to the N terminus of the targeting domain through a peptide linker.

**[00233]** Each component of the fusion protein described herein can be directly linked to the other to indirectly linked to the other via a peptide linker. In some embodiments, the linker is one or any combination of a cleavable linker, a non-cleavable linker, a peptide linker, a flexible linker, a rigid linker, a helical linker, or a non-helical linker. In some embodiments, the linker is a peptide linker. In some embodiments, the linker is a peptide linker that comprises glycine or serine, or both glycine and serine amino acid residues. In some embodiments, the peptide linker comprises from or from about 2-25, 5-25, 10-25, 15-25, 20-25, 2-20, 5-20, 10-20, 15-20, 2-15, 5-15, 10-15, 2-10, or 5-10 amino acids. In some embodiments, the linker is a peptide linker that consists of glycine or serine, or both glycine and serine amino acid residues. In some embodiments, the peptide linker consists of from or from about 2-25, 5-25, 10-25, 15-25, 20-25, 2-20, 5-20, 10-20, 15-20, 2-15, 5-15, 10-15, 2-10, or 5-10 amino acids. In some embodiments, the peptide linker comprises at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 amino acid residues. In some embodiments, the linker is at least 11 amino acids in length. In some embodiments, the linker is at least 15 amino acids in length. In some embodiments, the linker is 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 amino acid residues in length.

**[00234]** In some embodiments, the linker is a glycine/serine linker, e.g., a peptide linker substantially consisting of the amino acids glycine and serine. In some embodiments, the linker is

a glycine/serine/proline linker, e.g., a peptide linker substantially consisting of the amino acids glycine, serine, and proline.

**[00235]** In some embodiments, the amino acid sequence of the linker comprises the amino acid sequence of any one of SEQ ID NOS: 375-384 or 402-519, or the amino acid sequence of any one of SEQ ID NOS: 375-384 or 402-519 comprising 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition). In some embodiments, the amino acid sequence of the linker consists of the amino acid sequence of any one of SEQ ID NOS: 375-384 or 402-519, or the amino acid sequence of any one of SEQ ID NOS: 375-384 or 402-519 comprising 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition).

**[00236]** In some embodiments, the amino acid sequence of the linker comprises the amino acid sequence of any one of SEQ ID NOS: 375-384, or the amino acid sequence of any one of SEQ ID NOS: 375-384 comprising 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition). In some embodiments, the amino acid sequence of the linker consists of the amino acid sequence of any one of SEQ ID NOS: 375-384, or the amino acid sequence of any one of SEQ ID NOS: 375-384 comprising 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition).

**[00237]** The amino acid sequence of exemplary linkers for use in any one or more of the fusion proteins described herein is provided in Table 5 below.

**Table 5.** Amino Acid Sequence of Exemplary Linkers

| Amino Acid Sequence            | SEQ ID NO |
|--------------------------------|-----------|
| GGGGSGGGSGGGSGGGSGGGGS         | 375       |
| GGGGSGGGSGGGSGGGGS             | 376       |
| GGGGSGGGSGGGGS                 | 377       |
| GGGGSGGGS                      | 378       |
| GGGGS                          | 379       |
| SGGGSGGGSGGGGS                 | 380       |
| SGGGSGGGSGGGG                  | 381       |
| SGGGSGGGG                      | 382       |
| SGGGG                          | 383       |
| GGSGG                          | 384       |
| AHFKISGEKRPSTDPGKKAKNPKKKKKKDP | 402       |
| AHRAKKMSKTHA                   | 403       |
| ASPEYVNLPIINGNG                | 404       |
| CTKRPRW                        | 405       |
| DKAKRVSRNKSEKKRR               | 406       |
| EELRLKEELLKGIYA                | 407       |
| EEQLRRRKNSRLNNTG               | 408       |
| EVLKVIRTGKRKKKAWKRMVTKVC       | 409       |



|                                                     |     |
|-----------------------------------------------------|-----|
| HHHHHHHHHHHHQPH                                     | 410 |
| HKKKHDPASVNFSEFSK                                   | 411 |
| HKRTKKNLS                                           | 412 |
| I INGRKLKLLKSSRRSSQTSNNSFTSRRS                      | 413 |
| KAEQERRK                                            | 414 |
| KEKRKRREELFIEQKKRK                                  | 415 |
| KKGKDEWFSRGKKP                                      | 416 |
| KKGPSVQKRKKTNLS                                     | 417 |
| KKKTVINDLLHYKKEK                                    | 418 |
| KKNGGKGKNKPSAKIKK                                   | 419 |
| KKPKWDDFKKKKK                                       | 420 |
| KKRKKDNLS                                           | 421 |
| KKRRKRRRK                                           | 422 |
| KKRRRRARK                                           | 423 |
| KKSKRGR                                             | 424 |
| KKSRKRG                                             | 425 |
| KKSTALSRELGKIMRRR                                   | 426 |
| KKSYQDPEIIAHSRPRK                                   | 427 |
| KKTGKNRKLKSKRVKTR                                   | 428 |
| KKVSIAGQSGKLWRWKR                                   | 429 |
| KKYENVVIKRSRKRGRPRK                                 | 430 |
| KNKKRK                                              | 431 |
| KPKKKR                                              | 432 |
| KRAMKDDSHGNSTSPKRRK                                 | 433 |
| KRANSNLVAAYEKAKKK                                   | 434 |
| KRASEDTTSGSPKKSSAGPKR                               | 435 |
| KRFKRRWMVRKMKTCK                                    | 436 |
| KRGLNSSFETSPKKVK                                    | 437 |
| KRGNSSIGPNDLSKRKQKK                                 | 438 |
| KRIHSVLSQSQIDPSKKVKRAK                              | 439 |
| KRKGKLKNKGSKRKK                                     | 440 |
| KRRRRRRREKRKR                                       | 441 |
| KRSNDRTYSPEEEKQORRA                                 | 442 |
| KRTVATNGDASGAHRAKMSK                                | 443 |
| KRVYNKGEDEQEHLPGKKKR                                | 444 |
| KSGKAPRRRAVSMDNSNK                                  | 445 |
| KVNFLDMSLDDIIIIYKELE                                | 446 |
| KVQHRIAKKTTRRRR                                     | 447 |
| LSPSLSPL                                            | 448 |
| MDSLLMNRKFLYQFKNVRWAKGRRETYLC                       | 449 |
| MPQNEYIELHRKRYGYRLDYHEKKRKESREAHERSKKAKKMIGLKAKLYHK | 450 |
| MVQLRPRASR                                          | 451 |
| NNKLLAKRRKGGASPKDDPMDDIK                            | 452 |
| NYKRPMGTYGPPAKRHEGE                                 | 453 |
| PDTKRAKLDSETTMVKKK                                  | 454 |
| PEKRTKI                                             | 455 |
| PGGRGKKK                                            | 456 |
| PGKMDKGEHRQERRDRPY                                  | 457 |
| PKKGDKYDKTD                                         | 458 |

|                         |     |
|-------------------------|-----|
| PKKKSrk                 | 459 |
| PKKNKPE                 | 460 |
| PKKRAKV                 | 461 |
| PKPKKLKVE               | 462 |
| PKRGRGR                 | 463 |
| PKRRLVDDA               | 464 |
| PKRRRTY                 | 465 |
| PLFKRR                  | 466 |
| PLRKAKR                 | 467 |
| PPAKRKCI F              | 468 |
| PPARRRRL                | 469 |
| PPKKKRKV                | 470 |
| PPNKRMKVKH              | 471 |
| PPRIYPQLPSAPT           | 472 |
| PQRSPFPKSSVKR           | 473 |
| PRPRKVPR                | 474 |
| PRRRVQRKR               | 475 |
| PRRVRLK                 | 476 |
| PSRKRPR                 | 477 |
| PSSKKRKV                | 478 |
| PTKKRVK                 | 479 |
| QRPGPYDRP               | 480 |
| RGKGGKGLGKGGAKRHRK      | 481 |
| RKAGKGGGGHKTTKKRSKDEKVP | 482 |
| RKIKLKRAK               | 483 |
| RKIKRKRAK               | 484 |
| RKKEAPGPREELRSRGR       | 485 |
| RKKRKGGK                | 486 |
| RKKRRQRRR               | 487 |
| RKKSIPLSIKNLKRKHKRKNKTR | 488 |
| RKLVKPKNTKMKTCLRTPY     | 489 |
| RKRLILSDKGQLDWKK        | 490 |
| RKRLKSK                 | 491 |
| RKRRVRDNM               | 492 |
| RKRSPKDKKEDLDGAGKRRKT   | 493 |
| RKRTPRVDGQTGENDMNKRRRK  | 494 |
| RLPVRRRRRR              | 495 |
| RLRFRKPKSK              | 496 |
| RQQRKR                  | 497 |
| RRDLNSSFETSPKKVK        | 498 |
| RRDRAKLR                | 499 |
| RRGDGRRR                | 500 |
| RRGRKRKAEKQ             | 501 |
| RRKKRR                  | 502 |
| RRKRSKSEDMDSVESKRRR     | 503 |
| RRKRSR                  | 504 |
| RRPKGKTLQKRKPK          | 505 |
| RRRGFERFGPDNMGRKRRK     | 506 |
| RRRGKNKVAAQNCRK         | 507 |

|                                                                  |     |
|------------------------------------------------------------------|-----|
| RRRKRRNLS                                                        | 508 |
| RRRQKQKGGASRRR                                                   | 509 |
| RRRREGPRARRRR                                                    | 510 |
| RRTIRLKLVDKCDRSCIKQKKNRNKCQYCRFHKCLSVGMSHNAIRFGRMPRSEKAKL<br>KAE | 511 |
| RRVPQRKEVSRCKCRK                                                 | 512 |
| RVGGRRQAVECIEDLLNEPGQPLDLSCKRPRP                                 | 513 |
| RVVKLRAP                                                         | 514 |
| RVVRRR                                                           | 515 |
| SKRKTKISRKTR                                                     | 516 |
| SYVKTVPNRTRTYIKL                                                 | 517 |
| TGKNEAKKRKIA                                                     | 518 |
| TLSPASSPSSVSCPVIPASTDESPGSALNI                                   | 519 |

### 5.3.3.1 Conditional Constructs

**[00238]** Also described herein are constructs that comprise a targeting domain (e.g., a VHH, (VHH)<sub>2</sub>) bound to an effector domain (e.g., an effector domain that comprises a catalytic domain of a deubiquitinase, or an effector domain that comprises a deubiquitinase). In some embodiments, the association of the targeting domain and the effector domain is mediated by binding of a first agent (e.g., a small molecule, protein, or peptide) attached to the targeting domain and a second agent (e.g., a small molecule, protein, or peptide) attached to the effector domain. For example, in one embodiment, the targeting domain may be attached to a first agent that specifically binds to a second agent that is attached to the effector domain. In some embodiments, specific binding of the first agent to the second agent is mediated by addition of a third agent (e.g., a small molecule).

**[00239]** For example, a conditional construct includes an KBP/FRB-based dimerization switch, e.g., as described in US20170081411 (the entire contents of which are incorporated by reference herein), can be utilized herein. FKBP12 (FKBP or FK506 binding protein) is an abundant cytoplasmic protein that serves as the initial intracellular target for the natural product immunosuppressive drug, rapamycin. Rapamycin binds to FKBP and to the large PI3K homolog FRAP (RAFT, mTOR), thereby acting to dimerize these molecules. In some embodiments, an FKBP/FRAP based switch, also referred to herein as an FKBP/FRB based switch, can utilize a heterodimerization molecule, e.g., rapamycin or a rapamycin analog. FRB is a 93 amino acid portion of FRAP, that is sufficient for binding the FKBP-rapamycin complex (Chen, J., Zheng, X. F., Brown, E. J. & Schreiber, S. L. (1995) Identification of an 11-kDa FKBP12-rapamycin-binding domain within the 289-kDa FKBP12-rapamycin-associated protein and characterization of a

critical serine residue. Proc Natl Acad Sci USA 92: 4947-51), the entire contents of which is incorporated by reference herein. For example, the targeting domain can be attached to FKBP and the effector domain attached to FRB. Thereby, the association of the targeting domain and the effector domain is mediated by rapamycin and only takes place in the presence of rapamycin.

**[00240]** Exemplary conditional activation systems that can be used here include, but are not limited to those described in US20170081411; Lajoie MJ, et al. Designed protein logic to target cells with precise combinations of surface antigens. Science. 2020 Sep 25;369(6511):1637-1643. doi: 10.1126/science.aba6527. Epub 2020 Aug 20. PMID: 32820060; Farrants H, et al. Chemogenetic Control of Nanobodies. Nat Methods. 2020 Mar;17(3):279-282. doi: 10.1038/s41592-020-0746-7. Epub 2020 Feb 17. PMID: 32066961; and US20170081411, the entire contents of each of which is incorporated by reference herein for all purposes.

#### **5.3.4 Exemplary Fusion Proteins**

**[00241]** Exemplary fusion proteins are described below. Exemplary fusion proteins of the present disclosure include, but are not limited to, those described below. In some embodiments, the fusion protein comprises an effector domain comprising a catalytic domain of a cysteine protease deubiquitinase, or a functional fragment or functional variant thereof; and a targeting domain comprising a targeting moiety that specifically binds a cytosolic protein, wherein the cytosolic protein is CDKL5, ATP7B, STXBP1, SYNGAP1, GRN, JAG1, DEPDC5, TSC2, TSC1, KIF1A, DNMT1, SHANK3, DMD, RP1, TTN, DYNC1H1, TRIO, USP9X, PYDC2, CSTB, or PCBD1.

**[00242]** In some embodiments, the fusion protein comprises an effector domain comprising a catalytic domain of a metalloprotease deubiquitinase, or a functional fragment or functional variant thereof; and a targeting domain comprising a targeting moiety that specifically binds a cytosolic protein, wherein the cytosolic protein is CDKL5, ATP7B, STXBP1, SYNGAP1, GRN, JAG1, DEPDC5, TSC2, TSC1, KIF1A, DNMT1, SHANK3, DMD, RP1, TTN, DYNC1H1, TRIO, or USP9X, PYDC2, CSTB, or PCBD1.

**[00243]** In some embodiments, the fusion protein comprises an effector domain comprising a catalytic domain of a deubiquitinase, or a functional fragment or functional variant thereof, wherein the deubiquitinase is a ubiquitin-specific protease (USP), a ubiquitin C-terminal hydrolase (UCH), a Machado-Josephin domain protease (MJD), an ovarian tumour protease (OTU), a

MINDY protease, or a ZUFSP protease; and a targeting domain comprising a targeting moiety that specifically binds a cytosolic protein, wherein the cytosolic protein is CDKL5, ATP7B, STXBP1, SYNGAP1, GRN, JAG1, DEPDC5, TSC2, TSC1, KIF1A, DNMI, SHANK3, DMD, RP1, TTN, DYNC1H1, TRIO, USP9X, PYDC2, CSTB, or PCBD1.

**[00244]** In one embodiment, the fusion protein comprises an effector domain comprising a catalytic domain of a deubiquitinase, or a functional fragment or functional variant thereof, wherein the deubiquitinase is USP1, USP2, USP3, USP4, USP5, USP6, USP7, USP8, USP9X, USP9Y, USP10, USP11, USP12, USP13, USP14, USP15, USP16, USP17, USP17L2, USP17L3, USP17L4, USP17L5, USP17L7, USP17L8, USP18, USP19, USP20, USP21, USP22, USP23, USP24, USP25, USP26, USP27X, USP28, USP29, USP30, USP31, USP32, USP33, USP34, USP35, USP36, USP37, USP38, USP39, USP40, USP41, USP42, USP43, USP44, USP45, USP46, BAP1, UCHL1, UCHL3, UCHL5, ATXN3, ATXN3L, OTUB1, OTUB2, MINDY1, MINDY2, MINDY3, MINDY4, or ZUP1; and a targeting domain comprising a targeting moiety that specifically binds a cytosolic protein, wherein the cytosolic protein is CDKL5, ATP7B, STXBP1, SYNGAP1, GRN, JAG1, DEPDC5, TSC2, TSC1, KIF1A, DNMI, SHANK3, DMD, RP1, TTN, DYNC1H1, TRIO, USP9X, PYDC2, CSTB, or PCBD1.

**[00245]** In one embodiment, the fusion protein comprises an effector domain comprising a catalytic domain of a deubiquitinase, or a functional fragment or functional variant thereof, wherein the deubiquitinase is described in Table 1; and a targeting domain comprising a targeting moiety that specifically binds a cytosolic protein, wherein the cytosolic protein is CDKL5, ATP7B, STXBP1, SYNGAP1, GRN, JAG1, DEPDC5, TSC2, TSC1, KIF1A, DNMI, SHANK3, DMD, RP1, TTN, DYNC1H1, TRIO, USP9X, PYDC2, CSTB, or PCBD1.

**[00246]** In one embodiment, the fusion protein comprises an effector domain comprising a catalytic domain of a deubiquitinase, or a functional fragment or functional variant thereof, wherein the catalytic domain is described in Table 1; and a targeting domain comprising a targeting moiety that specifically binds a cytosolic protein, wherein the cytosolic protein is CDKL5, ATP7B, STXBP1, SYNGAP1, GRN, JAG1, DEPDC5, TSC2, TSC1, KIF1A, DNMI, SHANK3, DMD, RP1, TTN, DYNC1H1, TRIO, USP9X, PYDC2, CSTB, or PCBD1.

**[00247]** In one embodiment, the fusion protein comprises an effector domain comprising a catalytic domain of a deubiquitinase, or a functional fragment or functional variant thereof, wherein the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%,

85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 1-112; and a targeting domain comprising a targeting moiety that specifically binds a cytosolic protein, wherein the cytosolic protein is CDKL5, ATP7B, STXBP1, SYNGAP1, GRN, JAG1, DEPDC5, TSC2, TSC1, KIF1A, DNMT1, SHANK3, DMD, RP1, TTN, DYNC1H1, TRIO, USP9X, PYDC2, CSTB, or PCBD1.

**[00248]** In one embodiment, the fusion protein comprises an effector domain comprising a catalytic domain of a deubiquitinase, or a functional fragment or functional variant thereof, wherein the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 113-220 or 286; and a targeting domain comprising a targeting moiety that specifically binds a cytosolic protein, wherein the cytosolic protein is CDKL5, ATP7B, STXBP1, SYNGAP1, GRN, JAG1, DEPDC5, TSC2, TSC1, KIF1A, DNMT1, SHANK3, DMD, RP1, TTN, DYNC1H1, TRIO, USP9X, PYDC2, CSTB, or PCBD1.

**[00249]** In one embodiment, the fusion protein comprises an effector domain comprising a catalytic domain of a deubiquitinase, or a functional fragment or functional variant thereof, wherein the deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 1-112; and a targeting domain comprising a targeting moiety that specifically binds a cytosolic protein, wherein the cytosolic protein comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 221-238 or 287-289.

**[00250]** In one embodiment, the fusion protein comprises an effector domain comprising a catalytic domain of a deubiquitinase, or a functional fragment or functional variant thereof, wherein the catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 113-220 or 286; and a targeting domain comprising a targeting moiety that specifically binds a cytosolic protein, wherein the cytosolic protein comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS:

221-238 or 287-289.

[00251] The amino acid sequence of exemplary SYNGAP1 targeting fusion proteins are provided in Table 6 below.

**Table 6.** Amino acid sequence of exemplary SYNGAP1 targeting enDub fusion proteins

| Description        | SEQ ID NO: | Amino Acid Sequence                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|--------------------|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| FLX00152 – Cezanne | 320        | QVQLVESGGGLVQPGGSLRLSCAASGFSFSNFPMMWVR<br>QAPGKGREWVADINQDGRNTYYADSVKGRFTISRDNK<br>TTVYLQMNINLPEDTAVYYCQAIKRTTTHFDSWGQGTQV<br>TVSSPPSFSESGGSRTPEKGFSDREPTRPPRPILQRQ<br>DDIVQEKRLSRGISHASSIVSLARSHVSSNGGGGGSN<br>EHPLLEMPICAFQLPDLTVYNEDFRSFIERDLIEQSMLV<br>ALEQAGRLNWWVSDPTSQRLLPLATTGDNCLLHAAS<br>LGMWGFHDDRDLMLRKALYALMEKGVEKEALKRRWRWQQ<br>TQQNKESGLVYTEDEWQKEWNELIKLASSEPRMHLGTN<br>GANC GGVSSEEPVYESLEEFHVFVLAHVLRPIVVVA<br>DTMLRDSGGGEAFAPIPFGGIYLPLEVPASQCHRSPLVL<br>AYDQAHFSALVSMEQKENTKEQAVIPLTDSEYKLLPLH<br>FAVDPGKGWEWGKDDSDNVRLASVILSLEVKLHLLHSY<br>MNVKWIPLSSDAQAPLAQ            |
| FLX00153 – Cezanne | 321        | QLQLVESGGGLVQPGE SLRLSCAASGFTFSNYRMYWVR<br>MAPGKGLEWVSDIDRSGTYTYADSVKGRFAISRDNK<br>NTVYLQMNINLPEDTAVYYCAADRRLIVDLTPPEVDHW<br>GQGTQVTVSSPPSFSESGGSRTPEKGFSDREPTRPPR<br>PILQRQDDIVQEKRLSRGISHASSIVSLARSHVSSNG<br>GGGGSNEHPLLEMPICAFQLPDLTVYNEDFRSFIERDLI<br>EQSMLVALEQAGRLNWWVSDPTSQRLLPLATTGDNCL<br>LLHAASLGMWGFHDDRDLMLRKALYALMEKGVEKEALKR<br>RWRWQQTQQNKESGLVYTEDEWQKEWNELIKLASSEPR<br>MHLGTNGANC GGVSSEEPVYESLEEFHVFVLAHVLR<br>PIVVVADTMLRDSGGGEAFAPIPFGGIYLPLEVPASQCH<br>RSPLVLAYDQAHFSALVSMEQKENTKEQAVIPLTDSEY<br>KLLPLHFAVDPGKGWEWGKDDSDNVRLASVILSLEVKL<br>HLLHSYMNVKWIPLSSDAQAPLAQ      |
| FLX00154 – Cezanne | 322        | QVQLVESGGGLVQPGGSLRLSCAASGFI FSSYQMAWVR<br>QAPGKGLEWVADINTGGWNTYYADSVKGRFTISRDNK<br>NTLYLEMNINLPEDTAVYYCAADRWMVAKIVGGDLDFD<br>SWGQGTQVTVSSPPSFSESGGSRTPEKGFSDREPTRP<br>PRPILQRQDDIVQEKRLSRGISHASSIVSLARSHVSS<br>NGGGGGSNEHPLLEMPICAFQLPDLTVYNEDFRSFIERD<br>LIEQSMLVALEQAGRLNWWVSDPTSQRLLPLATTGDN<br>NCLLHAASLGMWGFHDDRDLMLRKALYALMEKGVEKEAL<br>KRRWRWQQTQQNKESGLVYTEDEWQKEWNELIKLASSE<br>PRMHLGTNGANC GGVSSEEPVYESLEEFHVFVLAHVLR<br>RRPIVVVADTMLRDSGGGEAFAPIPFGGIYLPLEVPASQ<br>CHRSPLVLAYDQAHFSALVSMEQKENTKEQAVIPLTDS<br>EYKLLPLHFAVDPGKGWEWGKDDSDNVRLASVILSLEV<br>KLHLLHSYMNVKWIPLSSDAQAPLAQ |
| FLX00155 – Cezanne | 323        | QVQLVESGGGLVQPGGSLRLSCAASGFAGFSYDMSWVR<br>QAPGQGP EWVSAITPGGGGT FYAYYSDSVKGRFAISR                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

|                                      |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|--------------------------------------|-----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                      |     | NAKNTLTLMNSLKPDDTAMYYCAKNFYGNNGRGHGTQ<br>VTVSSPPSFSESGGSRTPEKGFSDREPTRPPRPILQR<br>QDDIVQEKRLSRGISHASSIVSLARSHVSSNGGGGGS<br>NEHPLEMPICAFQLPDLTVYNEDFRSFIERDLIEQSML<br>VALEQAGRLNWWVSDPTSQRLLPLATTGDGNCLLHAA<br>SLGMWGFHDRDLMLRKALYALMEKGVEKEALKRRRWQ<br>QTQQNKESGLVYTEDEWQKEWNELIKLASSEPRMHLGT<br>NGANCGVESSEEPVYESLEEFHVFLAHVLRPIVVV<br>ADTMLRDSGGEAFAPIPFGGIYLPLEVPASQCHRSPLV<br>LAYDQAHFSALVSMEQKENTKEQAVIPLTDSEYKLLPL<br>HFAVDPGKGWEWGKDDSDNVRLASVILSLEVKLHLLHS<br>YMNVKWIPLSSDAQAPLAQ                                                                                            |
| FLX00156 – Cezanne                   | 324 | QVQLVESGGGLVQPGGSLRLACAASGFTFGTHAMHWVR<br>WAPGKGFWEVSTISSGGGGTRYADSVKGRFTISRDNK<br>NTVYLQMDNLKPEDTAVYYCNSPSNIANDNWGQGTQVT<br>VSSPPSFSESGGSRTPEKGFSDREPTRPPRPILQRQD<br>DIVQEKRLSRGISHASSIVSLARSHVSSNGGGGGSNE<br>HPLEMPICAFQLPDLTVYNEDFRSFIERDLIEQSMLVA<br>LEQAGRLNWWVSDPTSQRLLPLATTGDGNCLLHAASL<br>GMWGFHDRDLMLRKALYALMEKGVEKEALKRRRWQQT<br>QQNKESGLVYTEDEWQKEWNELIKLASSEPRMHLGTNG<br>ANCGVESSEEPVYESLEEFHVFLAHVLRPIVVVAD<br>TMLRDSGGEAFAPIPFGGIYLPLEVPASQCHRSPLVLA<br>YDQAHFSALVSMEQKENTKEQAVIPLTDSEYKLLPLHF<br>AVDPGKGWEWGKDDSDNVRLASVILSLEVKLHLLHSYM<br>NVKWIPLSSDAQAPLAQ          |
| FLX00157 – Cezanne                   | 325 | QVQLVESGGGLVQAGASLRLSAASERTFGHYAMGWFR<br>QAPGKEREVATISWKGGTTGYAHSVKGRFTISRDSAK<br>NMVYLQMNLSLKPEDTAVYYCAARNTMSGSMSSSAYPYW<br>GQGTQVTVSSPPSFSESGGSRTPEKGFSDREPTRPPR<br>PILQRQDDIVQEKRLSRGISHASSIVSLARSHVSSNG<br>GGGGSNEHPLEMPICAFQLPDLTVYNEDFRSFIERDLI<br>EQSMLVALEQAGRLNWWVSDPTSQRLLPLATTGDGNC<br>LLHAASLGMWGFHDRDLMLRKALYALMEKGVEKEALKR<br>RWRWQQTQQNKESGLVYTEDEWQKEWNELIKLASSEPR<br>MHLGTNGANCGVESSEEPVYESLEEFHVFLAHVLR<br>PIVVVADTMLRDSGGEAFAPIPFGGIYLPLEVPASQCH<br>RSPLVLAYDQAHFSALVSMEQKENTKEQAVIPLTDSEY<br>KLLPLHFHAVDPGKGWEWGKDDSDNVRLASVILSLEVKL<br>HLLHSYMNVKWIPLSSDAQAPLAQ |
| FLX00152 – GSSSS<br>linker – Cezanne | 326 | QVQLVESGGGLVQPGGSLRLSAAAGFSFSNFPMMWVR<br>QAPGKGREWVADINQDGRNTYYADSVKGRFTISRDNK<br>TTVYLQMNNLNPEDTAVYYCQAIPTTTHFDSWGQGTQV<br>TVSSGSSSSPPSFSESGGSRTPEKGFSDREPTRPPRP<br>ILQRQDDIVQEKRLSRGISHASSIVSLARSHVSSNGG<br>GGGSNEHPLEMPICAFQLPDLTVYNEDFRSFIERDLIE<br>QSMLVALEQAGRLNWWVSDPTSQRLLPLATTGDGNCL<br>LHAASLGMWGFHDRDLMLRKALYALMEKGVEKEALKRR<br>WRWQQTQQNKESGLVYTEDEWQKEWNELIKLASSEPRM<br>HLGTNGANCGVESSEEPVYESLEEFHVFLAHVLR<br>PIVVVADTMLRDSGGEAFAPIPFGGIYLPLEVPASQCHR                                                                                                                   |



|                                      |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|--------------------------------------|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                      |     | SPLVLAYDQAHFSALVSMEQKENTKEQAVIPLTDSEYK<br>LLPLHFAVDPGKGWEWGKDDSDNVRLASVILSLEVKLH<br>LLHSYMNVKWIPLSSDAQAPLAQ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| FLX00153 – GSSSS<br>linker – Cezanne | 327 | QLQLVESGGGLVQPGESLRLSCAASGFTFSNYRMYWVR<br>MAPGKGLEWVSDIDRSGTYTYYYADSVKGRFAISRDN<br>NTVYLQMNLSLKPEDTAVYYCAADRRLIVDLTPEDVYDHW<br>GQGTQVTVSSGSSSSPPSFSEGSGGSRTPEKGFSDREP<br>TRPPRPILQRQDDIVQEKRLSRGISHASSSIVSLARSH<br>VSSNGGGGGSNEHPLEMPICAFQLPDLTVYNEDFRSFI<br>ERDLIEQSMLVALEQAGRLNWWVSVDPDTSQRLPLATT<br>GDGNCLLHAASLGMWGFHDDRDLMLRKALYALMEKGV<br>EALKRRWRWQQTQQNKESGLVYTEDEWQKEWNELIKLA<br>SSEPRMHLGTNGANCGGVESSEEPVYESLEEFHVFVLA<br>HVLRRPIVVVADTMLRDSGGEAFAPIPFGGIYLPLEVP<br>ASQCHRSPLVLAYDQAHFSALVSMEQKENTKEQAVIPL<br>TDSEYKLLPLHFAVDPGKGWEWGKDDSDNVRLASVILS<br>LEVKLHLLHSYMNVKWIPLSSDAQAPLAQ |
| FLX00154 – GSSSS<br>linker – Cezanne | 328 | QVQLVESGGGLVQPGGSLRLSCAASGFIFSSYQMAWVR<br>QAPGKGLEWVADINTGGWNTYYADSVKGRFTISRDN<br>NTLYLEMNSLKPEDTAVYYCAADRWMVAKIVGGDLDFD<br>SWGQGTQVTVSSGSSSSPPSFSEGSGGSRTPEKGFSDR<br>EPTRPPRPILQRQDDIVQEKRLSRGISHASSSIVSLAR<br>SHVSSNGGGGGSNEHPLEMPICAFQLPDLTVYNEDFRS<br>FIERDLIEQSMLVALEQAGRLNWWVSVDPDTSQRLPLA<br>TTGDGNCLLHAASLGMWGFHDDRDLMLRKALYALMEKV<br>EKEALKRRWRWQQTQQNKESGLVYTEDEWQKEWNELIK<br>LASSEPRMHLGTNGANCGGVESSEEPVYESLEEFHVFV<br>LAHVLRRPIVVVADTMLRDSGGEAFAPIPFGGIYLPLE<br>VPASQCHRSPLVLAYDQAHFSALVSMEQKENTKEQAVI<br>PLTDSEYKLLPLHFAVDPGKGWEWGKDDSDNVRLASVI<br>LSLEVKLHLLHSYMNVKWIPLSSDAQAPLAQ |
| FLX00155 – GSSSS<br>linker – Cezanne | 329 | QVQLVESGGGLVQPGGSLRLSCAASGFAGSYDMSWVR<br>QAPGQGPWEVSAITPGGGGTFYAYYSDSVKGRFAISR<br>NAKNTLTLMNSLKPDDTAMYYCAKNFYGNNGRGHGTQ<br>VTVSSGSSSSPPSFSEGSGGSRTPEKGFSDREPTRPPR<br>PILQRQDDIVQEKRLSRGISHASSSIVSLARSHVSSNG<br>GGGGSNEHPLEMPICAFQLPDLTVYNEDFRSFIERDLI<br>EQSMLVALEQAGRLNWWVSVDPDTSQRLPLATTGDGNC<br>LLHAASLGMWGFHDDRDLMLRKALYALMEKGVKEALKR<br>RWRWQQTQQNKESGLVYTEDEWQKEWNELIKLASSEPR<br>MHLGTNGANCGGVESSEEPVYESLEEFHVFVLAHVLRR<br>PIVVVADTMLRDSGGEAFAPIPFGGIYLPLEVPASQCH<br>RSPLVLAYDQAHFSALVSMEQKENTKEQAVIPLTDSEY<br>KLLPLHFAVDPGKGWEWGKDDSDNVRLASVILSLEVKL<br>HLLHSYMNVKWIPLSSDAQAPLAQ         |
| FLX00156 – GSSSS<br>linker – Cezanne | 330 | QVQLVESGGGLVQPGGSLRLACAASGFTFGTHAMHWVR<br>WAPGKGFEWVSTISSGGGGTRYADSVKGRFTISRDN<br>NTVYLQMDNLKPEDTAVYYCNSPSNIANDNWGQGTQVT<br>VSSGSSSSPPSFSEGSGGSRTPEKGFSDREPTRPPRP<br>LQRQDDIVQEKRLSRGISHASSSIVSLARSHVSSNGG<br>GGGGSNEHPLEMPICAFQLPDLTVYNEDFRSFIERDLIEQ                                                                                                                                                                                                                                                                                                                                          |

|                                         |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-----------------------------------------|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                         |     | SMLVALEQAGRLNWWVSVDPTSQRLLPLATTGDGNCLL<br>HAASLGMWGFHDRDLMLRKALYALMEKGVEKEALKRRW<br>RWQQTQQNKESGLVYTEDEWQKEWNELIKLASSEPRMH<br>LGTNGANCGVESSEEPVYESLEEFHVFLAHVLRRI<br>VVVADTMLRDSGGEAFAPIPFGGIYLPLEVPASQCHRS<br>PLVLAYDQAHFSALVSMEQKENTKEQAVIPLTDSEYKL<br>LPLHFAVDPGKGWEWGKDDSDNVRLASVILSLEVKLHL<br>LHSYMNVKWIPLSSDAQAPLAQ                                                                                                                                                                                                                                                                       |
| FLX00157 – GSSSS<br>linker – Cezanne    | 331 | QVQLVESGGGLVQAGASLRLSAASERTFGHYAMGWFR<br>QAPGKERE FVATISWKGGTTGYAHSVKGRTISRDAK<br>NMVYLQMNSLKPEDTAVYYCAARNTMSGSMSSSAYPYW<br>GQGTQVTVSSGSSSSPPSFSESGGSRTPEKGFSDREP<br>TRPPRPILQRQDDIVQEKRLSRGISHASSSIVSLARSH<br>VSSNGGGGGSNEHPLEMPICAFQLPDLTVYNEDFRSFI<br>ERDLIEQSMLVALEQAGRLNWWVSVDPTSQRLLPLATT<br>GDGNCLLHAASLGMWGFHDRDLMLRKALYALMEKGVEK<br>EALKRRRWQQTQQNKESGLVYTEDEWQKEWNELIKLA<br>SSEPRMHLGTNGANCGVESSEEPVYESLEEFHVFLA<br>HVLRRPIVVVADTMLRDSGGEAFAPIPFGGIYLPLEVP<br>ASQCHRSPLVLAYDQAHFSALVSMEQKENTKEQAVIPL<br>TDSEYKLLPLHFAVDPGKGWEWGKDDSDNVRLASVILS<br>LEVKLHLHLSYMNVKWIPLSSDAQAPLAQ       |
| FLX00152 – (GSSSS)2<br>linker – Cezanne | 332 | QVQLVESGGGLVQPGGSLRLSAAAGFSFNFPMWVR<br>QAPGKGREWVADINQDGRNTYYADSVKGRFTISRDNK<br>TTVYLQMNNLNPEDTAVYYCQAIRTTTHFDSWGQGTQV<br>TVSSGSSSSGSSSSPPSFSESGGSRTPEKGFSDREPT<br>RPPRPILQRQDDIVQEKRLSRGISHASSSIVSLARSHV<br>SSNGGGGGSNEHPLEMPICAFQLPDLTVYNEDFRSFIE<br>RDLIEQSMLVALEQAGRLNWWVSVDPTSQRLLPLATTG<br>DGNCLLHAASLGMWGFHDRDLMLRKALYALMEKGVEKE<br>ALKRRRWQQTQQNKESGLVYTEDEWQKEWNELIKLA<br>SEPRMHLGTNGANCGVESSEEPVYESLEEFHVFLAH<br>VLRRIPIVVVADTMLRDSGGEAFAPIPFGGIYLPLEVPA<br>SQCHRSPLVLAYDQAHFSALVSMEQKENTKEQAVIPLT<br>DSEYKLLPLHFAVDPGKGWEWGKDDSDNVRLASVILSL<br>EVKLHLHLSYMNVKWIPLSSDAQAPLAQ          |
| FLX00153 – (GSSSS)2<br>linker – Cezanne | 333 | QLQLVESGGGLVQPGESLRLSAASGFTFSNYRMYWVR<br>MAPGKGLEWVSDIDRSGTYTYADSVKGRFAISRDNK<br>NTVYLQMNSLKPEDTAVYYCAADRRLIVDLTPEVYDHW<br>GQGTQVTVSSGSSSSGSSSSPPSFSESGGSRTPEKGF<br>SDREPTRPPRPILQRQDDIVQEKRLSRGISHASSSIVS<br>LARSHVSSNGGGGGSNEHPLEMPICAFQLPDLTVYNED<br>FRSFIERDLIEQSMLVALEQAGRLNWWVSVDPTSQRLL<br>PLATTGDGNCLLHAASLGMWGFHDRDLMLRKALYALME<br>KGVEKEALKRRRWQQTQQNKESGLVYTEDEWQKEWNE<br>LIKLASSEPRMHLGTNGANCGVESSEEPVYESLEEFH<br>VFVLAHVLRRIPIVVVADTMLRDSGGEAFAPIPFGGIYL<br>PLEVPASQCHRSPLVLAYDQAHFSALVSMEQKENTKEQ<br>AVIPLTDSEYKLLPLHFAVDPGKGWEWGKDDSDNVRLA<br>SVILSLEVKLHLHLSYMNVKWIPLSSDAQAPLAQ |
| FLX00154 – (GSSSS)2                     | 334 | QVQLVESGGGLVQPGGSLRLSAAAGFI FSSYQMAWVR                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

|                                         |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
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| linker – Cezanne                        |     | QAPGKGLEWVADINTGGWNTYYADSVKGRFTISRDN<br>AKNTLYLEMNSLKPEDTAVYYCAADRWMVAKIVGGDLDFD<br>SWGQGTQVTVSSGSSSSSGSSSSPPSFSESGGSRTPEK<br>GFSDREPTRPPRPILQRQDDIVQEKRLSRGISHASSSI<br>VSLARSHVSSNGGGGGSNEHPLEMPICAFQLPDLTVYN<br>EDFRSFIERDLIEQSMLVALEQAGRLNWWVSDPTSQR<br>LLPLATTGDGNCLLHAASLGMWGFHDRDLMLRKALYAL<br>MEKGVEKEALKRRWRWQQTQQNKESGLVYTEDEWQKEW<br>NELIKLASSEPRMHLGTNGANCGGVESSEEPVYESLEE<br>FHVFLAHVLRRPVVVADTMLRDSGGEAFAPIPFGGI<br>YLPLEVPASQCHRSPLVLAYDQAHFSALVSMEQKENTK<br>EQAVIPLTDSEYKLLPLHFAVDPGKGWEWGKDDSDNVR<br>LASVILSLEVKLHLLHSYMNVKWIPLSSDAQAPLAQ                                   |
| FLX00155 – (GSSSS)2<br>linker – Cezanne | 335 | QVQLVESGGGLVQPGGSLRLSCAASGFAFGSYDMSWVR<br>QAPGQGPWEVSAITPGGGGTIFYAYSDSVKGRFAISR<br>DNANTLTLMNSLKPDDTAMYYCAKNFYGNNGRGHTQ<br>VTVSSGSSSSSGSSSSPPSFSESGGSRTPEKGFSDREP<br>TRPPRPILQRQDDIVQEKRLSRGISHASSIIVSLARSH<br>VSSNGGGGGSNEHPLEMPICAFQLPDLTVYNEDFRSFI<br>ERDLIEQSMLVALEQAGRLNWWVSDPTSQRLLPLATT<br>GDGNCLLHAASLGMWGFHDRDLMLRKALYALMEKGVEK<br>EALKRRWRWQQTQQNKESGLVYTEDEWQKEWNELIKLA<br>SSEPRMHLGTNGANCGGVESSEEPVYESLEEFHVFLA<br>HVLRRPVIIVVADTMLRDSGGEAFAPIPFGGIYLPLEVP<br>ASQCHRSPLVLAYDQAHFSALVSMEQKENTKEQAVIPL<br>TDSEYKLLPLHFAVDPGKGWEWGKDDSDNVRLASVILS<br>LEVKLHLLHSYMNVKWIPLSSDAQAPLAQ |
| FLX00156 – (GSSSS)2<br>linker – Cezanne | 336 | QVQLVESGGGLVQPGGSLRLACAASGFTFGTHAMHWVR<br>WAPGKGFEWVSTISSGGGGTRYADSVKGRFTISRDN<br>AKNTVYLQMDNLKPEDTAVYYCNSPSNIANDNWQGTQVT<br>VSSGSSSSSGSSSSPPSFSESGGSRTPEKGFSDREPTR<br>PPRPILQRQDDIVQEKRLSRGISHASSIIVSLARSHVS<br>SNGGGGGSNEHPLEMPICAFQLPDLTVYNEDFRSFI<br>ERDLIEQSMLVALEQAGRLNWWVSDPTSQRLLPLATTGD<br>GNCLLHAASLGMWGFHDRDLMLRKALYALMEKGVEKEA<br>LRRWRWQQTQQNKESGLVYTEDEWQKEWNELIKLASS<br>EPRMHLGTNGANCGGVESSEEPVYESLEEFHVFLAHV<br>LRRPVIIVVADTMLRDSGGEAFAPIPFGGIYLPLEVPAS<br>QCHRSPLVLAYDQAHFSALVSMEQKENTKEQAVIPLTD<br>SEYKLLPLHFAVDPGKGWEWGKDDSDNVRLASVILS<br>LEVKLHLLHSYMNVKWIPLSSDAQAPLAQ  |
| FLX00157 – (GSSSS)2<br>linker – Cezanne | 337 | QVQLVESGGGLVQAGASRLSCAASERTFGHYAMGWFR<br>QAPGKEREVATISWKGGTTGYAHSVKGRFTISRDSAK<br>NMVYLQMNLSLKPEDTAVYYCAARNTMSGSMSSSAYPYW<br>GQGTQVTVSSGSSSSSGSSSSPPSFSESGGSRTPEKGF<br>SDREPTRPPRPILQRQDDIVQEKRLSRGISHASSIIVS<br>LARSHVSSNGGGGGSNEHPLEMPICAFQLPDLTVYNED<br>FRSFIERDLIEQSMLVALEQAGRLNWWVSDPTSQRLL<br>PLATTGDGNCLLHAASLGMWGFHDRDLMLRKALYALME<br>KGVEKEALKRRWRWQQTQQNKESGLVYTEDEWQKEWNE<br>LIKLASSEPRMHLGTNGANCGGVESSEEPVYESLEEFH                                                                                                                                                              |

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|                                         |     | VFVLAHVLRRPPIVVVADTMLRDSGGEAFAPIPFGGIYLP<br>PLEVPASQCHRSPLVLAYDQAHFSALVSMEQKENTKEQ<br>AVIPLTDSEYKLLPLHFAVDPGKGWEWGKDDSDNVRLA<br>SVILSLEVKLHLLHSYMNVKWIPLSSDAQAPLAQ                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| FLX00152 – (GSSSS)3<br>linker – Cezanne | 338 | QVQLVESGGGLVQPGGSLRLSCAASGFSFSNFPMMWVR<br>QAPGKGREWVADINQDGRNTYYADSVKGRFTISRDN<br>AKTTVYLMNNLNPEDTAVYYCQAIKRTTTHFDSWGQGTQV<br>TVSSGSSSSGSSSSGSSSSPSPSFSESGSGSRTPEKGF<br>SDREPTRPPRPILQRQDDIVQEKRLSRGISHASSSIVSL<br>ARSHVSSNNGGGGSNEHPLEMPICAFQLPDLTVYNEDF<br>RSFIERDLIEQSMLVALEQAGRLNWWVSDPTSQRLLP<br>LATTGDNCLLHAASLGMWGFHNRDLMLRKALYALMEK<br>GVEKEALKRRRWQQTQQNKESGLVYTEDEWQKEWNE<br>LIKLASSEPRMHLGTNGANCGGVESSEEPVYESLEE<br>FHV FVLAHVLRRPPIVVVADTMLRDSGGEAFAPIPFGGIYLP<br>LEVPASQCHRSPLVLAYDQAHFSALVSMEQKENTKEQ<br>AVIPLTDSEYKLLPLHFAVDPGKGWEWGKDDSDNVRLA<br>SVILSLEVKLHLLHSYMNVKWIPLSSDAQAPLAQ              |
| FLX00153 – (GSSSS)3<br>linker – Cezanne | 339 | QLQLVESGGGLVQPGESLRLSCAASGFTFSNYRMYWVR<br>MAPGKGLEWVSDIDRSGTYTYADSVKGRFAISRDN<br>AKNTVYLMNSLKPEDTAVYYCAADRRLIVDLTPEVYDHW<br>GQGTQVTVSSGSSSSGSSSSGSSSSPSPSFSESGSGSRT<br>PEKGFSDREPTRPPRPILQRQDDIVQEKRLSRGISHAS<br>SSIVSLARSHVSSNNGGGGSNEHPLEMPICAFQLPDLT<br>VYNEDFRSFIERDLIEQSMLVALEQAGRLNWWVSDPT<br>SQRLLPLATTGDNCLLHAASLGMWGFHNRDLMLRKAL<br>YALMEKGVEKEALKRRRWQQTQQNKESGLVYTEDEWQ<br>KEWNELIKLASSEPRMHLGTNGANCGGVESSEEPVYES<br>LEE FHV FVLAHVLRRPPIVVVADTMLRDSGGEAFAPIP<br>FGGIYLPLEVPASQCHRSPLVLAYDQAHFSALVSMEQKE<br>NTKEQAVIPLTDSEYKLLPLHFAVDPGKGWEWGKDDSD<br>NVRLASVILSLEVKLHLLHSYMNVKWIPLSSDAQAPLA<br>Q     |
| FLX00154 – (GSSSS)3<br>linker – Cezanne | 340 | QVQLVESGGGLVQPGGSLRLSCAASGFIFSSYQMAWVR<br>QAPGKGLEWVADINTGGWNTYYADSVKGRFTISRDN<br>AKNTLYLEMNSLKPEDTAVYYCAADRWMVAKIVGGDLDFD<br>SWGQGTQVTVSSGSSSSGSSSSGSSSSPSPSFSESGSGS<br>RTPEKGFSDREPTRPPRPILQRQDDIVQEKRLSRGISH<br>ASSSIVSLARSHVSSNNGGGGSNEHPLEMPICAFQLPD<br>LTVYNEDFRSFIERDLIEQSMLVALEQAGRLNWWVSD<br>PTSQRLLPLATTGDNCLLHAASLGMWGFHNRDLMLRK<br>ALYALMEKGVEKEALKRRRWQQTQQNKESGLVYTEDE<br>WQKEWNELIKLASSEPRMHLGTNGANCGGVESSEEPVY<br>ESLEE FHV FVLAHVLRRPPIVVVADTMLRDSGGEAFAPI<br>PFGGIYLPLEVPASQCHRSPLVLAYDQAHFSALVSMEQ<br>KENTKEQAVIPLTDSEYKLLPLHFAVDPGKGWEWGKDD<br>SDNVRLASVILSLEVKLHLLHSYMNVKWIPLSSDAQAP<br>LAQ |
| FLX00155 – (GSSSS)3<br>linker – Cezanne | 341 | QVQLVESGGGLVQPGGSLRLSCAASGFAGSYDMSWVR<br>QAPGQGPEWVSATIPGGGGTFYAYYSDSVKGRFAISR<br>DNKNTLTLMNSLKPDDTAMYYCAKNFYGNNGRGHGTQ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

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|                                         |     | <p>VTVSSGSSSSSGSSSSSGSSSSPPSFSESGSGSRTPEKGF<br/> SDREPTRPPRPILQRQDDIVQEKRLSRGISHASSSIVS<br/> LARSHVSSNGGGGGSNEHPLEMPICAFQLPDLTVYNED<br/> FRSFIERDLIEQSMLVALEQAGRLNWWVSDPTSQRLL<br/> PLATTGDGNCLLHAASLGMWGFHDRDMLRKAALYALME<br/> KGVEKEALKRRRWQQTQQNKESGLVYTEDEWQKEWNE<br/> LIKLASSEPRMHLGTNGANCGGVESSEEPVYESLEEFH<br/> VFVLAHVLRRPVVVADTMLRDSGGEAFAPIPFGGIYL<br/> PLEVPASQCHRSPLVLAYDQAHFSALVSMEQKENTKEQ<br/> AVIPLTDSEYKLLPLHFAVDPGKGWEWGKDDSDNVRLA<br/> SVILSLEVKLHLLHSYMNWKWIPLSSDAQAPLAQ</p>                                                                                                                                             |
| FLX00156 – (GSSSS)3<br>linker – Cezanne | 342 | <p>QVQLVESGGGLVQPGGSLRLACAASGFTFGTHAMHWVR<br/> WAPGKGFVWSTISSGGGGTRYADSVKGRFTISRDNK<br/> NTVYLQMDNLKPEDTAVYYCNSPSNIANDNWGQGTQVT<br/> VSSGSSSSSGSSSSSGSSSSPPSFSESGSGSRTPEKGFSD<br/> REPTRPPRPILQRQDDIVQEKRLSRGISHASSSIVSLA<br/> RSHVSSNGGGGGSNEHPLEMPICAFQLPDLTVYNEDFR<br/> SFIERDLIEQSMLVALEQAGRLNWWVSDPTSQRLLPL<br/> ATTGDGNCLLHAASLGMWGFHDRDMLRKAALYALMEKG<br/> VEKEALKRRRWQQTQQNKESGLVYTEDEWQKEWNELI<br/> KLASSEPRMHLGTNGANCGGVESSEEPVYESLEEFHVF<br/> VLAHVLRRPVVVADTMLRDSGGEAFAPIPFGGIYLPL<br/> EVPASQCHRSPLVLAYDQAHFSALVSMEQKENTKEQAV<br/> IPLTDSEYKLLPLHFAVDPGKGWEWGKDDSDNVRLASV<br/> ILSLEVKLHLLHSYMNWKWIPLSSDAQAPLAQ</p>             |
| FLX00157 – (GSSSS)3<br>linker – Cezanne | 343 | <p>QVQLVESGGGLVQAGASRLSCAASERTFGHYAMGWFR<br/> QAPGKEREVATISWKGGTTGYAHSVKGRFTISRDSAK<br/> NMVYLQMNLSLKPEDTAVYYCAARNTMSGMSSSAYPYW<br/> GQGTQVTVSSGSSSSSGSSSSSGSSSSPPSFSESGSGSRT<br/> PEKGFSDREPTRPPRPILQRQDDIVQEKRLSRGISHAS<br/> SSIVSLARSHVSSNGGGGGSNEHPLEMPICAFQLPDLT<br/> VYNEDFRSFIERDLIEQSMLVALEQAGRLNWWVSDPT<br/> SQRLLPLATTGDGNCLLHAASLGMWGFHDRDMLRKAL<br/> YALMEKGVEKEALKRRRWQQTQQNKESGLVYTEDEWQ<br/> KEWNELIKLASSEPRMHLGTNGANCGGVESSEEPVYES<br/> LEEFHVFVLAHVLRRPVVVADTMLRDSGGEAFAPIPF<br/> GGIYLPLEVPASQCHRSPLVLAYDQAHFSALVSMEQKE<br/> NTKEQAVIPLTDSEYKLLPLHFAVDPGKGWEWGKDDSD<br/> NVRLASVILSLEVKLHLLHSYMNWKWIPLSSDAQAPLA<br/> Q</p> |
| FLX00152 VHH <sub>2</sub> –<br>Cezanne  | 344 | <p>QVQLVESGGGLVQPGGSLRLSCAASGFSFSNFPMMWVR<br/> QAPGKGREWVADINQDGRNTYYADSVKGRFTISRDNK<br/> TTVYLQMNNLNPEDTAVYYCQAIRTTTHFDSWGQGTQV<br/> TVSSGGGGSGGGGSGGGGSGGGGSGVQLVESGGGLVQPG<br/> GGSLRLSCAASGFSFSNFPMMWVRQAPGKGREWVADIN<br/> QDGRNTYYADSVKGRFTISRDNKTTVYLQMNNLNPED<br/> TAVYYCQAIRTTTHFDSWGQGTQVTVSSPPSFSESGSG<br/> SRTPEKGFSDREPTRPPRPILQRQDDIVQEKRLSRGIS<br/> HASSSIVSLARSHVSSNGGGGGSNEHPLEMPICAFQLP<br/> DLTVYNEDFRSFIERDLIEQSMLVALEQAGRLNWWVSV<br/> DPTSQRLLPLATTGDGNCLLHAASLGMWGFHDRDMLR</p>                                                                                                                                          |

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|                                        |     | KALYALMEKGVEKEALKRRWRWQQQTQQNKESGLVYTED<br>EWQKEWNELIKLASSEPRMHLGTNGANCGVESSEEPV<br>YESLEE FHVFLAHVLRRIPIVVVADTMLRDSGGEAFAP<br>IPFGGIYLPLEVPASQCHRSPLVLAYDQAHFSALVSME<br>QKENTKEQAVIPLTDSEYKLLPLHFAVDPGKGWEWGKD<br>DSDNVRLASVILSLEVKLHLLHSYMNVKWIPLSSDAQA<br>PLAQ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| FLX00153 VHH <sub>2</sub> –<br>Cezanne | 345 | QLQLVESGGGLVQPGESLRLSCAASGFTFSNYRMYWVR<br>MAPGKGLEWVSDIDRSGTYTYADSVKGRFAISRDNK<br>NTVYLQMNSLKPEDTAVYYCAADRRLIVDLTPEVYDHW<br>GQGTQVTVSSGGGGSGGGSGGGSGGGSSQLQLVESG<br>GGLVQPGESLRLSCAASGFTFSNYRMYWVRMAPGKLE<br>WVSDIDRSGTYTYADSVKGRFAISRDNKNTVYLQMN<br>SLKPEDTAVYYCAADRRLIVDLTPEVYDHWGQGTQVTV<br>SSPPSFSESGGSRTPEKGFSDREPTRPPRPILQRQDD<br>IVQEKRLSRGISHASSSIVSLARSHVSSNGGGGGSNEH<br>PLEMPICAFQLPDLTVYNEDFRSFIERDLIEQSM LVAL<br>EQAGRLNWWVSDPTSQRLLPLATTGDGNCLLHAASLG<br>MWGFHDRDLMLRKALYALMEKGVEKEALKRRWRWQQTQ<br>QNKESGLVYTEDEWQKEWNELIKLASSEPRMHLGTNGA<br>NCGVESSEEPVYESLEE FHVFLAHVLRRIPIVVVADT<br>MLRDSGGEAFAPIPFGGIYLPLEVPASQCHRSPLVLAY<br>DQAHFSALVSMEQKENTKEQAVIPLTDSEYKLLPLHFA<br>VDPGKGWEWGKDDSDNVRLASVILSLEVKLHLLHSYMN<br>VKWIPLSSDAQAPLAQ    |
| FLX00154 VHH <sub>2</sub> –<br>Cezanne | 346 | QVQLVESGGGLVQPGGSLRLSCAASGFIFSSYQMAWVR<br>QAPGKGLEWVADINTGGWNTYYADSVKGRFTISRDNK<br>NTLYLEMNSLKPEDTAVYYCAADRWMVAKIVGGDLDFD<br>SWGQGTQVTVSSGGGGSGGGSGGGSGGGSSQVQLVE<br>SGGGLVQPGGSLRLSCAASGFIFSSYQMAWVRQAPGK<br>LEWVADINTGGWNTYYADSVKGRFTISRDNKNTLYLE<br>MNSLKPEDTAVYYCAADRWMVAKIVGGDLDFDSWGQGT<br>QVTVSSPPSFSESGGSRTPEKGFSDREPTRPPRPILQ<br>RQDDIVQEKRLSRGISHASSSIVSLARSHVSSNGGGG<br>SNEHPLEMPICAFQLPDLTVYNEDFRSFIERDLIEQSM<br>LVALEQAGRLNWWVSDPTSQRLLPLATTGDGNCLLHA<br>ASLGMWGFHDRDLMLRKALYALMEKGVEKEALKRRWRW<br>QQTQQNKESGLVYTEDEWQKEWNELIKLASSEPRMHLG<br>TNGANCGVESSEEPVYESLEE FHVFLAHVLRRIPIV<br>VADTMLRDSGGEAFAPIPFGGIYLPLEVPASQCHRSPL<br>VLAYDQAHFSALVSMEQKENTKEQAVIPLTDSEYKLLP<br>LHFAVDPGKGWEWGKDDSDNVRLASVILSLEVKLHLLH<br>SYMNVKWIPLSSDAQAPLAQ |
| FLX00155 VHH <sub>2</sub> –<br>Cezanne | 347 | QVQLVESGGGLVQPGGSLRLSCAASGFAGSYDMSWVR<br>QAPGQGP EWVSAITPGGGGT FYAYYSDSVKGRFAISR<br>NAKNTLT LQMNSLKPDDTAMYYCAKNFYGNNGRGHTQ<br>VTVSSGGGGSGGGSGGGSGGGSSQVQLVESGGGLVQ<br>PGGSLRLSCAASGFAGSYDMSWVRQAPGQGP EWVSAI<br>TPGGGGT FYAYYSDSVKGRFAISRDNKNTLT LQMN<br>SLKPDDTAMYYCAKNFYGNNGRGHTQVTVSSPPSFSEGS<br>GSRTPEKGFSDREPTRPPRPILQRQDDIVQEKRLSRG                                                                                                                                                                                                                                                                                                                                                                                                             |

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|                                                       |     | ISHASSSIVSLARSHVSSNGGGGGSNEHPLEMPICAFQ<br>LPDLTVYNEDFRSFIERDLIEQSMLVALEQAGRLNWWV<br>SVDPTSQRLLPLATTGDNCLLHAASLGMWGFHDRDLM<br>LRKALYALMEKGVEKEALKRRRWRWQQTQQNKESGLVYT<br>EDEWQKEWNELIKLASSEPRMHLGTNGANCGVESSEE<br>PVYESLEE FHVFLAHVLRRI VVVADTMLRDSGGEAF<br>APIPFGGIYLPLEVPASQCHRSPLVLAYDQAHFSALVS<br>MEQKENTKEQAVIPLTDSEYKLLPLHFAVDPGKGWEWG<br>KDDSDNVRLASVILSLEVKLHLLHSYMNVKWIPLSSDA<br>QAPLAQ                                                                                                                                                                                                                                                                                                                                                      |
| FLX00156 VHH <sub>2</sub> –<br>Cezanne                | 348 | QVQLVESGGGLVQPGGSLRLACAASGFTFGTHAMHWVR<br>WAPGKGFVWSTISSGGGGTRYADSVKGRFTISRDNK<br>NTVYLQMDNLKPEDTAVYYCNSPSNIANDNWGQGTQVT<br>VSSGGGGSGGGSGGGSGGGSSQVQLVESGGGLVQPG<br>GSLRLACAASGFTFGTHAMHWVRWAPGKGFVWSTISS<br>GGGGTRYADSVKGRFTISRDNKNTVYLQMDNLKPEDT<br>AVYYCNSPSNIANDNWGQGTQVTVSSPPSFSESGGSR<br>TPEKGFSDREPTRPPRPILQRQDDIVQEKRLSRGISHA<br>SSSIVSLARSHVSSNGGGGGSNEHPLEMPICAFQLPDL<br>TVYNEDFRSFIERDLIEQSMLVALEQAGRLNWWVSVD<br>TSQRLLPLATTGDNCLLHAASLGMWGFHDRDLMRLKA<br>LYALMEKGVEKEALKRRRWRWQQTQQNKESGLVYTEDEW<br>QKEWNELIKLASSEPRMHLGTNGANCGVESSEEPVYE<br>SLEEFHVFLAHVLRRI VVVADTMLRDSGGEAFAPIP<br>FGGIYLPLEVPASQCHRSPLVLAYDQAHFSALVSMEQK<br>ENTKEQAVIPLTDSEYKLLPLHFAVDPGKGWEWGKDDSD<br>NVRLASVILSLEVKLHLLHSYMNVKWIPLSSDAQAPL<br>AQ                   |
| FLX00157 VHH <sub>2</sub> –<br>Cezanne                | 349 | QVQLVESGGGLVQAGASLRLSCAASERTFGHYAMGWFR<br>QAPGKERE FVATISWKGGTTGYAHSVKGRTISRDSAK<br>NMVYLQMNLSLKPEDTAVYYCAARNTMSGMSSSAYPYW<br>GQGTQVTVSSGGGGSGGGSGGGSGGGSSQVQLVESG<br>GGLVQAGASLRLSCAASERTFGHYAMGWFRQAPGKERE<br>FVATISWKGGTTGYAHSVKGRTISRDSAKNMVYLQMN<br>SLKPEDTAVYYCAARNTMSGMSSSAYPYWGQGTQVT<br>SSPPSFSESGGSRTPPEKGFSDREPTRPPRPILQRQDD<br>IVQEKRLSRGISHASSSIVSLARSHVSSNGGGGGSNEH<br>PLEMPICAFQLPDLTVYNEDFRSFIERDLIEQSMLVAL<br>EQAGRLNWWVSVDPTSQRLLPLATTGDNCLLHAASLG<br>MWGFHDRDLMRLKALYALMEKGVEKEALKRRRWRWQQTQ<br>QNKESGLVYTEDEWQKEWNELIKLASSEPRMHLGTNGA<br>NCGVESSEEPVYESLEE FHVFLAHVLRRI VVVADT<br>MLRDSGGEAFAPIPFGGIYLPLEVPASQCHRSPLVLAY<br>DQAHFSALVSMEQKENTKEQAVIPLTDSEYKLLPLHFA<br>VDPGKGWEWGKDDSDNVRLASVILSLEVKLHLLHSYMN<br>VKWIPLSSDAQAPLAQ |
| FLX00152 VHH <sub>2</sub> –<br>GSSSS linker – Cezanne | 350 | QVQLVESGGGLVQPGGSLRLSCLASGFSFSNFPMMWVR<br>QAPGKGREWVADINQDGRNTYYADSVKGRFTISRDNK<br>TTVYLQMNLSLNPEDTAVYYCQAIRTTTHFDSWGQGTQV<br>TVSSGGGGSGGGSGGGSGGGSSQVQLVESGGGLVQPG<br>GSLRLSCLASGFSFSNFPMMWVRQAPGKGREWVADIN                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

|                                                       |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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|                                                       |     | QDGRNTYYADSVKGRFTISRDNAKTTVYLQMNLPED<br>TAVYYCQAIRTTTHFDSWGQGTQVTVSSGSSSSPPSFS<br>EGSGGSRTPEKGFSDREPTRPPRPILQRQDDIVQEKRL<br>SRGISHASSSIVSLARSHVSSNGGGGGSNEHPLEMPIC<br>AFQLPDLTVYNEDFRSFIERDLIEQSMLVALEQAGRLN<br>WWVSDPTSQRLLPLATTGDGNCLLHAASLGMWGFHDR<br>DLMLRKALYALMEKGVEKEALKRRRWQQTQQNKESGL<br>VYTEDEWQKEWNELIKLASSEPRMHLGTNGANCGVES<br>SEEPVYESLEEFHVFLAHVLRPIVVADTMLRDSGG<br>EAFAPIPFGGIYLPLEVPASQCHRSPVLAYDQAHFSA<br>LVSMEQKENTKEQAVIPLTDSEYKLLPLHFAVDPGKGW<br>EWGKDDSDNVRLASVILSLEVKLHLLHSYMNVKWIPLS<br>SDAQAPLAQ                                                                                                                                                                                                                               |
| FLX00153 VHH <sub>2</sub> –<br>GSSSS linker – Cezanne | 351 | QLQLVESGGGLVQPGESLRLSCAASGFTFSNYRMYWVR<br>MAPGKGLEWVSDIDRSPTYTYADSVKGRFAISRDN<br>NTVYLQMNLSKPEDTAVYYCAADRRLIVDLTPEVYDHW<br>GQGTQVTVSSGGGGSGGGSGGGSGGGSQLQLVESG<br>GGLVQPGESLRLSCAASGFTFSNYRMYWVRMAPGKLE<br>WVSDIDRSPTYTYADSVKGRFAISRDNANTVYLQMN<br>SLKPEDTAVYYCAADRRLIVDLTPEVYDHWGQGTQVTV<br>SSGSSSSPPSFSESGGSRTPEKGFSDREPTRPPRPIL<br>QRQDDIVQEKRLSRGISHASSSIVSLARSHVSSNGGGG<br>GSNEHPLEMPICAFQLPDLTVYNEDFRSFIERDLIEQS<br>MLVALEQAGRLNWWVSDPTSQRLLPLATTGDGNCLLH<br>AASLGMWGFHDRDLMLRKALYALMEKGVEKEALKRRWR<br>WQQTQQNKESGLVYTEDEWQKEWNELIKLASSEPRMHL<br>GTNGANCGVESSEEPVYESLEEFHVFLAHVLRPIV<br>VVADTMLRDSGGEAFAPIPFGGIYLPLEVPASQCHRSP<br>LVLAYDQAHFSALVSMEQKENTKEQAVIPLTDSEYKLL<br>PLHFAVDPGKGWEWGKDDSDNVRLASVILSLEVKLHLL<br>HSYMNVKWIPLSSDAQAPLAQ      |
| FLX00154 VHH <sub>2</sub> –<br>GSSSS linker – Cezanne | 352 | QVQLVESGGGLVQPGGSLRLSCAASGFIFSSYQMAWVR<br>QAPGKGLEWVADINTGGWNTYYADSVKGRFTISRDN<br>NTLYLEMNSLKPEDTAVYYCAADRWMVAKIVGGDLDFD<br>SWGQGTQVTVSSGGGGSGGGSGGGSGGGSQVQLVE<br>SGGGLVQPGGSLRLSCAASGFIFSSYQMAWVRQAPGK<br>LEWVADINTGGWNTYYADSVKGRFTISRDNANTLYLE<br>MNSLKPEDTAVYYCAADRWMVAKIVGGDLDFDSWGQGT<br>QVTVSSGSSSSPPSFSESGGSRTPEKGFSDREPTRPP<br>RPILQRQDDIVQEKRLSRGISHASSSIVSLARSHVSSN<br>GGGGGSNEHPLEMPICAFQLPDLTVYNEDFRSFIERDL<br>IEQSMLVALEQAGRLNWWVSDPTSQRLLPLATTGDGN<br>CLLHAASLGMWGFHDRDLMLRKALYALMEKGVEKEALK<br>RRRWQQTQQNKESGLVYTEDEWQKEWNELIKLASSEP<br>RMHLGTNGANCGVESSEEPVYESLEEFHVFLAHVLR<br>RPIVVADTMLRDSGGEAFAPIPFGGIYLPLEVPASQC<br>HRSPLVLAYDQAHFSALVSMEQKENTKEQAVIPLTDSE<br>YKLLPLHFAVDPGKGWEWGKDDSDNVRLASVILSLEV<br>KLHLLHSYMNVKWIPLSSDAQAPLAQ |
| FLX00155 VHH <sub>2</sub> –<br>GSSSS linker – Cezanne | 353 | QVQLVESGGGLVQPGGSLRLSCAASGFAGSYDMSWVR<br>QAPGQGPEWVSATPGGGGTIFYAYYSDSVKGRFAISR                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |



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|                                                       |     | <p>NAKNTLTLQMNSLKPDDTAMYYCAKNFYGNNGRGHGTQ<br/> VTVSSGGGSGGGSGGGSGGGSGGGSSQVQLVESGGGLVQ<br/> PGGSLRLSCAASGFAFGSYDMSWVRQAPGQGPWEVSAI<br/> TPGGGGTFYAYYSDSVKGRFAISRDNKNTLTLQMNSL<br/> KPDDTAMYYCAKNFYGNNGRGHGTQVTVSSGSSSSPPS<br/> FSEGSRTPEKGFSDREPTRPPRPILQRQDDIVQEK<br/> RLSRGISHASSIVSLARSHVSSNGGGGGSNEHPLEMP<br/> ICAFQLPDLTVYNEDFRSFIERDLIEQSMLVALEQAGR<br/> LNWWWVSDPTSQRLLPLATTGDGNCLLHAASLGMWGFH<br/> DRDLMLRKALYALMEKGVEKEALKRRWRWQQTQONKES<br/> GLVYTEDEWQKEWNELIKLASSEPRMHLGTNGANCGGV<br/> ESSEEPVYESLEEFHVFLAHVLRPIVVVADTMLRDS<br/> GGEAFAPIPFGGIYLPLEVPASQCHRSPVLAYDQAHF<br/> SALVSMEQKENTKEQAVIPLTDSEYKLLPLHFAVDPGK<br/> GWEWGKDDSDNVRLASVILSLEVKLHLLHSYMNVKWIP<br/> LSSDAQAPLAQ</p>                                                                                      |
| FLX00156 VHH <sub>2</sub> –<br>GSSSS linker – Cezanne | 354 | <p>QVQLVESGGGLVQPGGSLRLACAASGFTFGTHAMHWVR<br/> WAPGKGFWEVSTISSGGGGTRYADSVKGRFTISRDNK<br/> NTVYLQMDNLKPEDTAVYYCNSPSNIANDNWGQGTQVT<br/> VSSGGGSGGGSGGGSGGGSGGGSSQVQLVESGGGLVQPG<br/> GSLRLACAASGFTFGTHAMHWVRWAPGKGFWEVSTISS<br/> GGGGTRYADSVKGRFTISRDNKNTVYLQMDNLKPEDT<br/> AVYYCNSPSNIANDNWGQGTQVTVSSGSSSSPPSFSEG<br/> SGGSRTPEKGFSDREPTRPPRPILQRQDDIVQEKRLSR<br/> GISHASSIVSLARSHVSSNGGGGGSNEHPLEMPICAF<br/> QLPDLTVYNEDFRSFIERDLIEQSMLVALEQAGRLNWW<br/> VSDPTSQRLLPLATTGDGNCLLHAASLGMWGFHDRDL<br/> MLRKALYALMEKGVEKEALKRRWRWQQTQONKESGLVY<br/> TEDEWQKEWNELIKLASSEPRMHLGTNGANCGGVESSE<br/> EPVYESLEEFHVFLAHVLRPIVVVADTMLRDSGGEA<br/> FAPIPFGGIYLPLEVPASQCHRSPVLAYDQAHFSALV<br/> SMEQKENTKEQAVIPLTDSEYKLLPLHFAVDPGKGWEW<br/> GKDDSDNVRLASVILSLEVKLHLLHSYMNVKWIP<br/> LSSDAQAPLAQ</p> |
| FLX00157 VHH <sub>2</sub> –<br>GSSSS linker – Cezanne | 355 | <p>QVQLVESGGGLVQAGASRLSCAASERTFGHYAMGWFR<br/> QAPGKEREVATISWKGGTTGYAHSVKGRFTISRDSAK<br/> NMVYLQMNSLKPEDTAVYYCAARNTMSGMSSSSAYPYW<br/> GQGTQVTVSSGGGSGGGSGGGSGGGSSQVQLVESG<br/> GGLVQAGASRLSCAASERTFGHYAMGWFRQAPGKERE<br/> FVATISWKGGTTGYAHSVKGRFTISRDSAKNMVYLQMN<br/> SLKPEDTAVYYCAARNTMSGMSSSSAYPYWGQGTQVTV<br/> SSGSSSSPPSFSEGSRTPEKGFSDREPTRPPRPIL<br/> QRQDDIVQEKRLSRGISHASSIVSLARSHVSSNGGGG<br/> GSNEHPLEMPICAFQLPDLTVYNEDFRSFIERDLIEQS<br/> MLVALEQAGRLNWWWVSDPTSQRLLPLATTGDGNCLLH<br/> AASLGMWGFHDRDLMLRKALYALMEKGVEKEALKRRWR<br/> WQQTQONKESGLVYTEDEWQKEWNELIKLASSEPRMHL<br/> GTNGANCGGVESSEEPVYESLEEFHVFLAHVLRPIV<br/> VVADTMLRDSGGEAFAPIPFGGIYLPLEVPASQCHRSP<br/> LVLAYDQAHFSALVSMEQKENTKEQAVIPLTDSEYKLL<br/> PLHFAVDPGKGWEWGKDDSDNVRLASVILSLEVKLHLL</p>                    |

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|                                                             |     | HSYMNVKWIPLSSDAQAPLAQ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| FLX00152 VHH <sub>2</sub> –<br>(GSSSS)2 linker –<br>Cezanne | 356 | QVQLVESGGGLVQPGGSLRLSCAASGFSFSNFPMMWVR<br>QAPGKGREWVADINQDGRNTYYADSVKGRFTISRDN<br>AKTTVYQLQMNNLNPEDTAVYYCQAIRTTTHFDSWGQGTQV<br>TVSSGGGGSGGGSGGGSGGGSGGGSGVQLVESGGGLVQP<br>GGSRLRLSCAASGFSFSNFPMMWVRQAPGKGREWVADIN<br>QDGRNTYYADSVKGRFTISRDNKTTVYQLQMNNLNPED<br>TAVYYCQAIRTTTHFDSWGQGTQVTVSSGSSSSSGSSSS<br>PPSFSESGSGSRTPEKGFSDREPTRPPRPILQRQDDIV<br>QEKRLSRGISHASSSIVSLARSHVSSNGGGGGSNEHPL<br>EMPICAFQLPDLTVYNEDFRSFIERDLIEQSMLVALEQ<br>AGRLNWWVSVDPQSRLLPLATTGDNCLLHAASLGMW<br>GFHDRDLMLRKALYALMEKGVEKEALKRRWRWQQTQQN<br>KESGLVYTEDEWQKEWNELIKLASSEPRMHLGTNGANC<br>GGVESSEEPVYESLEE FHFVLAHVLRPIVVVADTML<br>RDSGGEAFAPIPFGGIYLPLEVPASQCHRSPLVLAYDQ<br>AHFSALVSMEQKENTKEQAVIPLTDSEYKLLPLHFAVD<br>PGKGWEWGKDDSDNVRLASVILSLEVKLHLLHSYMNVK<br>WIPLSSDAQAPLAQ             |
| FLX00153 VHH <sub>2</sub> –<br>(GSSSS)2 linker –<br>Cezanne | 357 | QLQLVESGGGLVQPGESLRLSCAASGFTFSNYRMYWVR<br>MAPGKGLEWVSDIDRSGTYTYADSVKGRFAISRDN<br>AKNTVYQLQMNSLKPEDTAVYYCAADRRLIVDLTPEVYDHW<br>GQGTQVTVSSGGGGSGGGSGGGSGGGSGGGSQLQLVESG<br>GGLVQPGESLRLSCAASGFTFSNYRMYWVRMAPGKGLE<br>WVSDIDRSGTYTYADSVKGRFAISRDNKNTVYQLQMN<br>SLKPEDTAVYYCAADRRLIVDLTPEVYDHWGQGTQVTV<br>SSGSSSSSGSSSSPPPSFSESGSGSRTPEKGFSDREPTRP<br>PRPILQRQDDIVQEKRLSRGISHASSSIVSLARSHVSS<br>NGGGGGSNEHPLEMPICAFQLPDLTVYNEDFRSFIERD<br>LIEQSMLVALEQAGRLNWWVSVDPQSRLLPLATTGDN<br>NCLLHAASLGMWGFHDRDLMLRKALYALMEKGVEKEAL<br>KRRWRWQQTQQNKESGLVYTEDEWQKEWNELIKLASSE<br>PRMHLGTNGANCGGVESSEEPVYESLEE FHFVLAHVLR<br>RPIVVVADTMLRDSGGEAFAPIPFGGIYLPLEVPASQ<br>CHRSPLVLAYDQAHFSALVSMEQKENTKEQAVIPLTDS<br>EYKLLPLHFAVDPGKGWEWGKDDSDNVRLASVILSLEV<br>KLHLLHSYMNVKWIPLSSDAQAPLAQ |
| FLX00154 VHH <sub>2</sub> –<br>(GSSSS)2 linker –<br>Cezanne | 358 | QVQLVESGGGLVQPGGSRLRLSCAASGFIFSSYQMAWVR<br>QAPGKGLEWVADINTGGWNTYYADSVKGRFTISRDN<br>AKNTLYLEMNLSLKPEDTAVYYCAADRWMVAKIVGGDLDFD<br>SWGQGTQVTVSSGGGGSGGGSGGGSGGGSGGGSQLQLVE<br>SGGGLVQPGGSRLRLSCAASGFIFSSYQMAWVRQAPGKG<br>LEWVADINTGGWNTYYADSVKGRFTISRDNKNTLYLE<br>MNLSLKPEDTAVYYCAADRWMVAKIVGGDLDFDSWGQGT<br>QVTVSSGSSSSSGSSSSPPPSFSESGSGSRTPEKGFSDRE<br>PTRPPRPILQRQDDIVQEKRLSRGISHASSSIVSLARS<br>HVSSNGGGGGSNEHPLEMPICAFQLPDLTVYNEDFRSF<br>IERDLIEQSMLVALEQAGRLNWWVSVDPQSRLLPLAT<br>TGDGNCLLHAASLGMWGFHDRDLMLRKALYALMEKGVE<br>KEALKRRWRWQQTQQNKESGLVYTEDEWQKEWNELIK<br>LASSEPRMHLGTNGANCGGVESSEEPVYESLEE FHFVFL                                                                                                                                                        |

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|                                                             |     | AHVLRRPIVVVADTMLRDSGGEAFAPIPFGGIYLPLEV<br>PASQCHRSPLVLAYDQAHFSALVSMEQKENTKEQAVIP<br>LTDSEYKLLPLHFAVDPGKGWEWGKDDSDNVRLASVIL<br>SLEVKLHLLHSYMNVKWIPLSSDAQAPLAQ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| FLX00155 VHH <sub>2</sub> –<br>(GSSSS)2 linker –<br>Cezanne | 359 | QVQLVESGGGLVQPGGSLRLSCAASGFAFGSYDMSWVR<br>QAPGQGPEWVSAITPGGGGT FYAYYSDSVKGRFAISR<br>NAKNTLTLMNSLKPDDTAMYYCAKNFYGNNGRGHGTQ<br>VTVSSGGGSGGGGSGGGGSGGGGSGVQLVESGGGLVQ<br>PGGSLRLSCAASGFAFGSYDMSWVRQAPGQGPEWVSAI<br>TPGGGGT FYAYYSDSVKGRFAISRDNANTLTLMNSL<br>KPDDTAMYYCAKNFYGNNGRGHGTQVTVSSGSSSSGSS<br>SSPFSFSESGGSRTPEKGFSDREPTRPPRPILQRQDD<br>IVQEKRLSRGISHASSSIVSLARSHVSSNGGGGGSNEH<br>PLEMPICAFQLPDLTVYNEDFRSFIERDLIEQSMLVAL<br>EQAGRLNWWVSDPTSQRLLPLATTGDGNCLLHAASLG<br>MWGFHDRDLMLRKALYALMEKGVKEALKRRWRWQQTQ<br>QNKESGLVYTEDEWQKEWNELIKLASSEPRMHLGTNGA<br>NCGGVESSEEPVYESLEEFHVFLAHVLRRPIVVVADT<br>MLRDSGGEAFAPIPFGGIYLPLEV PASQCHRSPLVLAY<br>DQAHFSALVSMEQKENTKEQAVIPLTDSEYKLLPLHFA<br>VDPGKGWEWGKDDSDNVRLASVILSLEVKLHLLHSYMN<br>VKWIPLSSDAQAPLAQ |
| FLX00156 VHH <sub>2</sub> –<br>(GSSSS)2 linker –<br>Cezanne | 360 | QVQLVESGGGLVQPGGSLRLACAASGFTFGTHAMHWVR<br>WAPGKGF EWVSTISSGGGGTRYADSVKGRFTISRDN<br>AKNTVYLQMDNLKPEDTAVYYCNSPSNIANDNWGQGTQVT<br>VSSGGGSGGGGSGGGGSGGGGSGVQLVESGGGLVQPG<br>GSLRLACAASGFTFGTHAMHWVRWAPGKGF EWVSTISS<br>GGGGTRYADSVKGRFTISRDNANTVYLQMDNLKPEDT<br>AVYYCNSPSNIANDNWGQGTQVTVSSGSSSSGSSSSP<br>SFSESGGSRTPEKGFSDREPTRPPRPILQRQDDIVQE<br>KRLSRGISHASSSIVSLARSHVSSNGGGGGSNEHPLEM<br>PICAFQLPDLTVYNEDFRSFIERDLIEQSMLVALEQAG<br>RLNWWVSDPTSQRLLPLATTGDGNCLLHAASLG MWGF<br>HDRDLMLRKALYALMEKGVKEALKRRWRWQQTQ QNKE<br>SGLVYTEDEWQKEWNELIKLASSEPRMHLGTNGANCGG<br>VESSEEPVYESLEEFHVFLAHVLRRPIVVVADTMLRD<br>SGGEAFAPIPFGGIYLPLEV PASQCHRSPLVLAYDQAH<br>FSALVSMEQKENTKEQAVIPLTDSEYKLLPLHFAVDPG<br>KGWEWGKDDSDNVRLASVILSLEVKLHLLHSYMNVKWI<br>PLSSDAQAPLAQ |
| FLX00157 VHH <sub>2</sub> –<br>(GSSSS)2 linker –<br>Cezanne | 361 | QVQLVESGGGLVQAGASRLSCAASERTFGHYAMGWFR<br>QAPGKERE FVATISWKGGTTGYAHSVKGRTISRDS<br>AKNMVYLQMNLSLKPEDTAVYYCAARNTMSGMS<br>SSSAYPYWGQGTQVTVSSGGGSGGGGSGGGGSGGGGSGVQLVESG<br>GGLVQAGASRLSCAASERTFGHYAMGWFRQAPGKERE<br>FVATISWKGGTTGYAHSVKGRTISRDSAKNMVYLQMN<br>SLKPEDTAVYYCAARNTMSGMS<br>SSSAYPYWGQGTQVTVSSGSSSSGSSSSP<br>SFSESGGSRTPEKGFSDREPTRPPRPILQRQDDIVQE<br>KRLSRGISHASSSIVSLARSHVSSNGGGGGSNEH<br>PLEMPICAFQLPDLTVYNEDFRSFIERDLIEQSMLVALEQAG<br>RLNWWVSDPTSQRLLPLATTGDG                                                                                                                                                                                                                                                                             |

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|                                                             |     | NCLLHAASLGMWGFHDRDLMLRKALYALMEKGVEKEAL<br>KRRWRWQQQTQQNKESGLVYTEDEWQKEWNELIKLASSE<br>PRMHLGTNGANCGVESSEEPVYESLEEFHVFLAHVL<br>RRPIVVVADTMLRDSGGEAFAPIPFGGIYLPLEVPASQ<br>CHRSPLVLAYDQAHFSALVSMEQKENTKEQAVIPLTDS<br>EYKLLPLHFAVDPGKGWEWGKDDSDNVRLASVILSLEV<br>KLHLLHSYMNVKWIPLSSDAQAPLAQ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| FLX00152 VHH <sub>2</sub> –<br>(GSSSS)3 linker –<br>Cezanne | 362 | QVQLVESGGGLVQPGGSLRLSCAASGFSFSNFPMMWVR<br>QAPGKGREWVADINQDGRNTYYADSVKGRFTISRDNAK<br>TTVYLQMNINLPEDTAVYYCQAIRTTTHFDSWGQGTQV<br>TVSSGGGGSGGGSGGGSGGGSGGGSGVQLVESGGGLVQPG<br>GGSLRLSCAASGFSFSNFPMMWVRQAPGKGREWVADIN<br>QDGRNTYYADSVKGRFTISRDNAKTTVYLQMNINLPED<br>TAVYYCQAIRTTTHFDSWGQGTQVTVSSGSSSSSGSSSS<br>GSSSSPPSFSESGSGSRTPEKGFSDREPTRPPRPILQR<br>QDDIVQEKRLSRGISHASSIVSLARSHVSSNNGGGGGS<br>NEHPLEMPICAFQLPDLTVYNEDFRSFIERDLIEQSML<br>VALEQAGRNLNWWVSDPTSQRLPLATTGDGNCLLHAA<br>SLGMWGFHDRDLMLRKALYALMEKGVEKEALKRRWRWQ<br>QTQQNKESGLVYTEDEWQKEWNELIKLASSEPRMHLGT<br>NGANCGVESSEEPVYESLEEFHVFLAHVLRRPIVVV<br>ADTMLRDSGGEAFAPIPFGGIYLPLEVPASQCHRSPLV<br>LAYDQAHFSALVSMEQKENTKEQAVIPLTDSEYKLLPL<br>HFAVDPGKGWEWGKDDSDNVRLASVILSLEVKLHLLHS<br>YMNVKWIPLSSDAQAPLAQ              |
| FLX00153 VHH <sub>2</sub> –<br>(GSSSS)3linker –<br>Cezanne  | 363 | QLQLVESGGGLVQPGESLRLSCAASGFTFSNYRMYWVR<br>MAPGKGLEWVSDIDRSGTYTYADSVKGRFAISRDNAK<br>NTVYLQMNLSLKPEDTAVYYCAADRRLIVDLTPEVYDHW<br>GQGTQVTVSSGGGGSGGGSGGGSGGGSGGGSQLQLVESG<br>GGLVQPGESLRLSCAASGFTFSNYRMYWVRMAPGKGLE<br>WVSDIDRSGTYTYADSVKGRFAISRDNAKNTVYLQMN<br>SLKPEDTAVYYCAADRRLIVDLTPEVYDHWGQGTQVTV<br>SSGSSSSSGSSSSSGSSSSPPSFSESGSGSRTPEKGFSDR<br>EPTTRPPRPILQRQDDIVQEKRLSRGISHASSIVSLAR<br>SHVSSNNGGGGGSNEHPLEMPICAFQLPDLTVYNEDFRS<br>FIERDLIEQSMLVALEQAGRNLNWWVSDPTSQRLPLA<br>TTGDGNCLLHAASLGMWGFHDRDLMLRKALYALMEKGV<br>EKEALKRRWRWQQQTQQNKESGLVYTEDEWQKEWNELIK<br>LASSEPRMHLGTNGANCGVESSEEPVYESLEEFHVFL<br>LAHVLRPIVVVADTMLRDSGGEAFAPIPFGGIYLPLE<br>VPASQCHRSPLVLAYDQAHFSALVSMEQKENTKEQAVI<br>PLTDSEYKLLPLHFAVDPGKGWEWGKDDSDNVRLASVI<br>LSLEVKLHLLHSYMNVKWIPLSSDAQAPLAQ |
| FLX00154 VHH <sub>2</sub> –<br>(GSSSS)3linker –<br>Cezanne  | 364 | QVQLVESGGGLVQPGGSLRLSCAASGFIFSSYQMAWVR<br>QAPGKGLEWVADINTGGWNTYYADSVKGRFTISRDNAK<br>NTLYLEMNSLKPEDTAVYYCAADRWMVAKIVGGDLDFD<br>SWGQGTQVTVSSGGGGSGGGSGGGSGGGSGGGSGVQLVE<br>SGGGLVQPGGSLRLSCAASGFIFSSYQMAWVRQAPGKG<br>LEWVADINTGGWNTYYADSVKGRFTISRDNAKNTLYLE<br>MNSLKPEDTAVYYCAADRWMVAKIVGGDLDFDSWGQGT<br>QVTVSSGSSSSSGSSSSSGSSSSPPSFSESGSGSRTPEKG                                                                                                                                                                                                                                                                                                                                                                                                                            |

|                                                             |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
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|                                                             |     | FSDREPTRPPRPILQRQDDIVQEKRLSRGISHASSSIV<br>SLARSHVSSNGGGGSNEHPLEMPICAFQLPDLTVYNE<br>DFRSFIERDLIEQSMLVALEQAGRLNWWVSDPTSQRL<br>LPLATTGDGNCLLHAASLGMWGFHDRDLMLRKALYALM<br>EKGVEKEALKRRRWQQTQQNKESGLVYTEDEWQKEWN<br>ELIKLASSEPRMHLGTNGANCGGVESSEEPVYESLEEF<br>HVFVLAHVLRRIPIVVADTMLRDSGGEAFAPIPFGGIY<br>LPLEVPASQCHRSPLVLAYDQAHFSALVSMEQKENTKE<br>QAVIPLTDSEYKLLPLHFAVDPGKGWEWGKDDSDNVRL<br>ASVILSLEVKLHLLHSYMNWKWIPLSSDAQAPLAQ                                                                                                                                                                                                                                                                                                                                   |
| FLX00155 VHH <sub>2</sub> –<br>(GSSSS)3 linker –<br>Cezanne | 365 | QVQLVESGGGLVQPGGSLRLSCAASGFAFGSYDMSWVR<br>QAPGQGPEWVSATITPGGGGTIFYAYYSDSVKGRFAISR<br>NAKNTLTLMNSLKPDDTAMYICAKNFYGNNGRGHGTQ<br>VTVSSGGGGSGGGSGGGSGGGSGGGSGVQLVESGGGLVQ<br>PGGSLRLSCAASGFAFGSYDMSWVRQAPGQGPEWVSAT<br>ITPGGGGTIFYAYYSDSVKGRFAISRDAKNTLTLMNSL<br>KPDDTAMYICAKNFYGNNGRGHGTQVTVSSGSSSSGSS<br>SSGSSSSPPSFSESGGSRTPEKGFSDREPTRPPRPIL<br>QRQDDIVQEKRLSRGISHASSSIVSLARSHVSSNGGGG<br>GSNEHPLEMPICAFQLPDLTVYNEDFRSFIERDLIEQS<br>MLVALEQAGRLNWWVSDPTSQRLPLATTGDGNCLLH<br>AASLGMWGFHDRDLMLRKALYALMEKGEKEALKRRWR<br>WQQTQQNKESGLVYTEDEWQKEWNELIKLASSEPRMHL<br>GTNGANCGGVESSEEPVYESLEEFHVFVLAHVLRRIPI<br>VVADTMLRDSGGEAFAPIPFGGIYLPLEVPASQCHRS<br>PLVLAYDQAHFSALVSMEQKENTKEQAVIPLTDSEYKLL<br>PLHFAVDPGKGWEWGKDDSDNVRLASVILSLEVKLHLL<br>HSYMNWKWIPLSSDAQAPLAQ |
| FLX00156 VHH <sub>2</sub> –<br>(GSSSS)3 linker –<br>Cezanne | 366 | QVQLVESGGGLVQPGGSLRLACAASGFTFGTHAMHWVR<br>WAPGKGFEWVSTISSGGGGTRYADSVKGRFTISRDAK<br>NTVYLQMDNLKPEDTAVYYCNSPNSNIANDNWGQGTQVT<br>VSSGGGGSGGGSGGGSGGGSGGGSGVQLVESGGGLVQPG<br>GSLRLACAASGFTFGTHAMHWVRWAPGKGFEWVSTISS<br>GGGGTRYADSVKGRFTISRDAKNTVYLQMDNLKPEDT<br>AVYYCNSPNSNIANDNWGQGTQVTVSSGSSSSGSSSSGS<br>SSSPSFSESGGSRTPEKGFSDREPTRPPRPILQRQD<br>DIVQEKRLSRGISHASSSIVSLARSHVSSNGGGGSNE<br>HPLEMPICAFQLPDLTVYNEDFRSFIERDLIEQSMLVA<br>LEQAGRLNWWVSDPTSQRLPLATTGDGNCLLHAASL<br>GMWGFHDRDLMLRKALYALMEKGEKEALKRRRWQQT<br>QQNKESGLVYTEDEWQKEWNELIKLASSEPRMHLGTNG<br>ANCGGVESSEEPVYESLEEFHVFVLAHVLRRIPIVVAD<br>TMLRDSGGEAFAPIPFGGIYLPLEVPASQCHRSPLVLA<br>YDQAHFSALVSMEQKENTKEQAVIPLTDSEYKLLPLHF<br>AVDPGKGWEWGKDDSDNVRLASVILSLEVKLHLLHSY<br>MNWKWIPLSSDAQAPLAQ        |
| FLX00157 VHH <sub>2</sub> –<br>(GSSSS)3 linker –<br>Cezanne | 367 | QVQLVESGGGLVQAGASLRLSCAASERTFGHYAMGWFR<br>QAPGKEREVATISWKGGTTGYAHSVKGRFTISRDAK<br>NMVYLQMNLSLKPEDTAVYYCAARNTMSGMSSSAYPYW<br>GQGTQVTVSSGGGGSGGGSGGGSGGGSGGGSGVQLVESG<br>GGLVQAGASLRLSCAASERTFGHYAMGWFRQAPGKERE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

|  |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|--|--|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  |  | FVATISWKGTTGYAHSVKGRFTISRDSAKNMVYLQMN<br>SLKPEDTAVYYCAARNTMSGSMSSSAYPYWGQGTQVTV<br>SSGSSSSGSSSSGSSSSPPSFSESGSGSRTPEKGFSDR<br>EPTRPPRPILQRQDDIVQEKRLSRGISHASSIVSLAR<br>SHVSSNGGGGSNEHPLEMPICAFQLPDLTVYNEDFRS<br>FIERDLIEQSMLVALEQAGRLNWWVSVDP TSQRLLPLA<br>TTGDGNCLLHAASLGMWGFHDRDLMLRKALYALMEKGV<br>EKEALKRRRWQQTQQNKESGLVYTEDEWQKEWNELIK<br>LASSEPRMHLGTNGANC GGVESSEEPVYESLEEFHV FV<br>LAHVLR RP I V V V A D T M L R D S G G E A F A P I P F G G I Y L P L E<br>VPASQCHRSPVLVAYDQAHFSALVSMEQKENTKEQAVI<br>PLTDSEYKLLPLHFAVDPGKGWEWGKDDSDNVRLASVI<br>LSLEVKLHLLHSYMNVKWIPLSSDAQAPLAQ |
|--|--|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

**[00252]** In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 320-367. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 320. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 321. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 322. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 323. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 324. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 325. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the

amino acid sequence of SEQ ID NO: 326. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 327. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 328. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 329. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 330. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 331. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 332. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 333. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 334. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 335. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 336. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 337. In some embodiments, the fusion

[illegible]



84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 349. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 350. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 351. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 352. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 353. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 354. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 355. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 356. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 357. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 358. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 359. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%,

96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 360. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 361. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 362. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 363. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 364. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 365. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 366. In some embodiments, the fusion protein comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 367.

**[00253]** In some embodiments, the fusion protein consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 320-367. In some embodiments, the fusion protein consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 320. In some embodiments, the fusion protein consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 321. In some embodiments, the fusion protein consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%,

[illegible]

100% identical to the amino acid sequence of SEQ ID NO: 333. In some embodiments, the fusion protein consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 334. In some embodiments, the fusion protein consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 335. In some embodiments, the fusion protein consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 336. In some embodiments, the fusion protein consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 337. In some embodiments, the fusion protein consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 338. In some embodiments, the fusion protein consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 339. In some embodiments, the fusion protein consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 340. In some embodiments, the fusion protein consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 341. In some embodiments, the fusion protein consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 342. In some embodiments, the fusion protein consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 343. In some embodiments, the fusion protein consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 344. In some

embodiments, the fusion protein consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 345. In some embodiments, the fusion protein consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 346. In some embodiments, the fusion protein consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 347. In some embodiments, the fusion protein consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 348. In some embodiments, the fusion protein consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 349. In some embodiments, the fusion protein consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 350. In some embodiments, the fusion protein consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 351. In some embodiments, the fusion protein consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 352. In some embodiments, the fusion protein consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 353. In some embodiments, the fusion protein consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 354. In some embodiments, the fusion protein consists of an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 355. In some embodiments, the fusion protein consists of an amino acid sequence at

[illegible]

92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 367.

#### **5.3.4.1 Additional Exemplary Embodiments**

**[00254]** Additional exemplary embodiments of fusion proteins described herein are provided below, which should not be construed as limiting.

**[00255]** Embodiment 1. A fusion protein comprising: (a) an effector moiety comprising a functional fragment of a human deubiquitinase that is capable of mediating deubiquitination, wherein the human deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 1-112, and a targeting moiety comprising a VHH, (VHH)<sub>2</sub>, or scFv that specifically binds to a cytosolic protein.

**[00256]** Embodiment 2. A fusion protein comprising an effector moiety comprising a functional fragment of a human deubiquitinase that is capable of mediating deubiquitination that comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 113-220 or 286, and a targeting moiety comprising a VHH, (VHH)<sub>2</sub>, or scFv that specifically binds to a cytosolic protein.

**[00257]** Embodiment 3. A fusion protein comprising an effector moiety comprising a functional fragment of a human deubiquitinase that is capable of mediating deubiquitination that comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 286, and a targeting moiety comprising a VHH, (VHH)<sub>2</sub>, or scFv that specifically binds to a cytosolic protein.

**[00258]** Embodiment 4. The fusion protein of any one of Embodiments 1-3, wherein the cytosolic protein is cyclin-dependent kinase-like 5 (CDKL5), copper-transporting ATPase 2 (ATP7B), syntaxin-binding protein 1 (STXBP1), Ras/Rap GTPase-activating protein (SYNGAP1), progranulin (GRN), protein jagged-1 (JAG1), GATOR complex protein DEPDC5 (DEPDC5), tuberlin (TSC2), hamartin (TSC1), kinesin-like protein KIF1A (KIF1A), dynamin-1 (DNM1), SH3 and multiple ankyrin repeat domains protein 3 (SHANK3), dystrophin (DMD), oxygen-regulated protein 1 (RP1), titin (TTN), cytoplasmic dynein 1 heavy chain 1 (DYNC1H1), TRIO and F-actin-binding protein (TRIO), probable ubiquitin carboxyl-terminal hydrolase FAF-

X (USP9X), Pyrin domain-containing protein 2 (PYDC2), cystatin-B (CSTB), or pterin-4-alpha-carbinolamine dehydratase (PCBD1).

**[00259]** Embodiment 5. The fusion protein of any one of Embodiments 1-4, wherein said cytosolic protein is SHANK3, SYNGAP1, PYCD2, CSTB, or PCBD1.

**[00260]** Embodiment 6. The fusion protein of any one of Embodiments 1-5, wherein said cytosolic protein is SHANK3, SYNGAP1, CSTB, or PCBD1.

**[00261]** Embodiment 7. The fusion protein of any one of Embodiments 1-6, wherein said cytosolic protein is SYNGAP1.

**[00262]** Embodiment 8. The fusion protein of any one of Embodiments 1-7, wherein said targeting moiety is a VHH or (VHH)<sub>2</sub>.

**[00263]** Embodiment 9. The fusion protein of any one of Embodiments 1-8, wherein said targeting moiety comprises a VHH described in Table 3.

**[00264]** Embodiment 10. The fusion protein of any one of Embodiments 1-9, wherein said targeting moiety comprises a VHH that comprises a CDR1, CDR2, and CDR3 of a VHH that is described in Table 3.

**[00265]** Embodiment 11. The fusion protein of any one of Embodiments 1-10, wherein said VHH comprises a CDR1 that comprises the amino acid sequence of SEQ ID NO: 290, 294, 298, 302, 306, or 310, or the amino acid sequence of SEQ ID NO: 290, 294, 298, 302, 306, or 310 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); a CDR2 that comprises the amino acid sequence of SEQ ID NO: 291, 295, 299, 303, 307, or 311, or the amino acid sequence of SEQ ID NO: 291, 295, 299, 303, 307, or 311 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); and/or a CDR3 that comprises the amino acid sequence of SEQ ID NO: 292, 296, 300, 304, 308, or 312 or the amino acid sequence of SEQ ID NO: 292, 296, 300, 304, 308, or 312 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition).

**[00266]** Embodiment 12. The fusion protein of any one of Embodiments 1-11, wherein said targeting moiety comprises a VHH that comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of a VHH that is described in Table 3.

**[00267]** Embodiment 13. The fusion protein of any one of Embodiments 1-12, wherein said targeting moiety comprises a VHH that comprises an amino acid sequence at least 80%, 81%,



82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 293, 297, 301, 305, 309, or 313.

**[00268]** Embodiment 14. The fusion protein of any one of Embodiments 1-13, wherein said targeting moiety comprises a (VHH)<sub>2</sub> comprising a first VHH described in Table 3 and a second VHH described in Table 3.

**[00269]** Embodiment 15. The fusion protein of Embodiment 14, wherein the amino acid sequence of said first VHH is 100% identical to the amino acid sequence of said second VHH.

**[00270]** Embodiment 16. The fusion protein of any one of Embodiments 14-15, wherein said first (VHH)<sub>2</sub> comprises a CDR1, CDR2, and CDR3 of a VHH that is described in Table 3; and said second (VHH)<sub>2</sub> comprises a CDR1, CDR2, and CDR3 of a VHH that is described in Table 3.

**[00271]** Embodiment 17. The fusion protein of any one of Embodiments 14-16, wherein said first (VHH)<sub>2</sub> comprises a CDR1 that comprises the amino acid sequence of SEQ ID NO: 290, 294, 298, 302, 306, or 310, or the amino acid sequence of SEQ ID NO: 290, 294, 298, 302, 306, or 310 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); a CDR2 that comprises the amino acid sequence of SEQ ID NO: 291, 295, 299, 303, 307, or 311, or the amino acid sequence of SEQ ID NO: 291, 295, 299, 303, 307, or 311 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); and/or a CDR3 that comprises the amino acid sequence of SEQ ID NO: 292, 296, 300, 304, 308, or 312 or the amino acid sequence of SEQ ID NO: 292, 296, 300, 304, 308, or 312 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); and said first (VHH)<sub>2</sub> comprises a CDR1 that comprises the amino acid sequence of SEQ ID NO: 290, 294, 298, 302, 306, or 310, or the amino acid sequence of SEQ ID NO: 290, 294, 298, 302, 306, or 310 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); a CDR2 that comprises the amino acid sequence of SEQ ID NO: 291, 295, 299, 303, 307, or 311, or the amino acid sequence of SEQ ID NO: 291, 295, 299, 303, 307, or 311 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition); and/or a CDR3 that comprises the amino acid sequence of SEQ ID NO: 292, 296, 300, 304, 308, or 312 or the amino acid sequence of SEQ ID NO: 292, 296, 300, 304, 308, or 312 with 1, 2, or 3 amino acid modifications (e.g., a substitution, deletion, or addition).

**[00272]** Embodiment 18. The fusion protein of any one of Embodiments 14-17, wherein said first (VHH)<sub>2</sub> comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence

of a VHH that is described in Table 3; and said second (VHH)<sub>2</sub> comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of a VHH that is described in Table 3.

**[00273]** Embodiment 19. The fusion protein of any one of Embodiments 14-18, wherein said first (VHH)<sub>2</sub> comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 293, 297, 301, 305, 309, or 313; and said second (VHH)<sub>2</sub> comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 293, 297, 301, 305, 309, or 313.

**[00274]** Embodiment 21. The fusion protein of any one of Embodiments 1-19, wherein said effector moiety comprising a functional fragment of a human deubiquitinase that is capable of mediating deubiquitination that comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 286, and a targeting moiety; and said targeting moiety comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 293, 297, 301, 305, 309, 313, or 314-319.

**[00275]** Embodiment 20. The fusion protein of any one of Embodiments 1-19, comprising an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 320-367.

### 5.3.5 Methods of Making Fusion Proteins

**[00276]** Fusion proteins described herein can be made by any conventional technique known in the art, for example, recombinant techniques or chemical synthesis (*e.g.*, solid phase peptide synthesis). In some embodiments, the fusion protein is made through recombinant expression in a cell (*e.g.*, a eukaryotic cell, *e.g.*, a mammalian cell). Briefly, the fusion protein can be made by synthesizing the DNA encoding the fusion protein and cloning the DNA into any suitable expression vector. Numerous cloning vectors are known to those of skill in the art, and the selection of an appropriate cloning vector is a matter of choice. The gene can be placed under the control of

a promoter, ribosome binding site (for bacterial expression) and, optionally, an operator and/or one or more enhancer elements, so that the DNA sequence encoding the fusion protein is transcribed into RNA in the host cell transformed by a vector containing this expression construction. The coding sequence may or may not contain a signal peptide or leader sequence. Heterologous leader sequences can be added to the coding sequence that causes the secretion of the expressed polypeptide from the host organism. Other regulatory sequences may also be desirable which allow for regulation of expression of the protein sequences relative to the growth of the host cell. Such regulatory sequences are known to those of skill in the art, and examples include those which cause the expression of a gene to be turned on or off in response to a chemical or physical stimulus, including the presence of a regulatory compound. Other types of regulatory elements may also be present in the vector, for example, enhancer sequences. The control sequences and other regulatory sequences may be ligated to the coding sequence prior to insertion into a vector, such as the cloning vectors described above. Alternatively, the coding sequence can be cloned directly into an expression vector which already contains the control sequences and an appropriate restriction site.

**[00277]** The expression vector may then be used to transform an appropriate host cell. A number of mammalian cell lines are known in the art and include immortalized cell lines available from the American Type Culture Collection (ATCC), such as, but not limited to, Chinese hamster ovary (CHO) cells, CHO-suspension cells (CHO-S), HeLa cells, HEK293, baby hamster kidney (BHK) cells, monkey kidney cells (COS), VERO, HepG2, MadinDarby bovine kidney (MDBK) cells, NOS, U2OS, A549, HT1080, CAD, P19, NIH3T3, L929, N2a, MCF-7, Y79, SO-Rb50, DUKX-X11, and J558L.

**[00278]** Depending on the expression system and host selected, the fusion protein is produced by growing host cells transformed by an expression vector described above under conditions whereby the fusion protein is expressed. The fusion protein is then isolated from the host cells and purified. If the expression system secretes the fusion protein into growth media, the fusion protein can be purified directly from the media. If the fusion protein is not secreted, it is isolated from cell lysates. The selection of the appropriate growth conditions and recovery methods are within the skill of the art. Once purified, the amino acid sequences of the fusion proteins can be determined, i.e., by repetitive cycles of Edman degradation, followed by amino acid analysis by HPLC. Other methods of amino acid sequencing are also known in the art. Once purified, the functionality of

the fusion protein can be assessed, *e.g.*, as described herein, *e.g.*, utilizing a bifunctional ELISA.

[00279] As described above, functionality of the fusion protein can be tested by any method known in the art. Each functionality can be measured in a separate assay. For example, binding of the targeting domain to the target protein can be measured using an enzyme linked immunosorbent assay (ELISA). Catalytic activity of the effector domain can be measured using any standard deubiquitinase activity assay known in the art. For example, BioVision Deubiquitinase Activity Assay Kit (Fluorometric) Catalog # K485-100 according to the manufacturer's instructions. The deubiquitinase activity of a fusion protein described herein can be measured for example by using a fluorescent deubiquitinase substrate to detect deubiquitinase activity upon cleavage of the fluorescent substrate. The deubiquitinase activity can also be measured according to the materials and methods set forth in the Examples provided herein.

#### 5.4 Nucleic Acids, Host Cells, Vectors, and Viral Particles

[00280] In one aspect, provided herein are nucleic acid molecules encoding a fusion protein described herein. In some embodiments, the nucleic acid molecule is a DNA molecule. In some embodiments, the nucleic acid molecule is an RNA molecule. In some embodiments, the nucleic acid molecule contains at least one modified nucleic acid (*e.g.*, that increases stability of the nucleic acid molecule), *e.g.*, phosphorothioate, N6-methyladenosine (m6A), N6,2'-O-dimethyladenosine (m6Am), 8-oxo-7,8-dihydroguanosine (8-oxoG), pseudouridine (Ψ), 5-methylcytidine (m5C), and N4-acetylcytidine (ac4C).

[00281] In one aspect, provided herein is a host cell (or population of host cells) comprising a nucleic acid encoding a fusion protein described herein. In some embodiments, the nucleic acid is incorporated into the genome of the host cell. In some embodiments, the nucleic acid is not incorporated into the genome of the host cell. In some embodiments, the nucleic acid is present in the cell episomally. In some embodiments, the host cell is a human cell. In some embodiments, the host cell is a mammalian cell. In some embodiments, the host cell is a mouse, rat, hamster, guinea pig, cat, dog, or human cell. In some embodiments, the host cell is modified *in vitro*, *ex vivo*, or *in vivo*.

[00282] The nucleic acid can be introduced into the host cell by any suitable method known in the art (*e.g.*, as described herein). For example, a viral delivery system (*e.g.*, a retrovirus, an adenovirus, an adeno associated virus, a herpes virus, a lentivirus, a pox virus, a vaccinia virus, a

vesicular stomatitis virus, a polio virus, a Newcastle's Disease virus, an Epstein-Barr virus, an influenza virus, a reoviruses, a myxoma virus, a maraba virus, a rhabdovirus, or a coxsackie virus delivery system) can be utilized to deliver a nucleic acid (e.g., DNA or RNA molecule) encoding the fusion protein for expression with the host cell. In some embodiments, the nucleic acid encoding the fusion protein is present episomally within the host cell. In some embodiments, the nucleic acid encoding the fusion protein is incorporated into the genome of the host cell. In some embodiments, the virus replication competent. In some embodiments, the virus is replication deficient.

**[00283]** In some embodiments, a nucleic acid (DNA or RNA) is delivered to the host cell using a non-viral vector (e.g., a plasmid) encoding the fusion protein. In some embodiments, the nucleic acid encoding the fusion protein is present episomally within the host cell. In some embodiments, the nucleic acid encoding the fusion protein is incorporated into the genome of the host cell. Exemplary non-viral transfection methods known in the art include, but are not limited to, direct delivery of DNA such as by ex vivo transfection, by injection (e.g., microinjection), electroporation, liposome mediated transfection, receptor-mediated transfection, microprojectile bombardment, by agitation with silicon carbide fibers Through the application of techniques such as these cells may be stably or transiently transfected with a nucleic acid encoding a fusion protein described herein to express the encoded fusion protein.

**[00284]** In one aspect, provided herein are vectors comprising a nucleic acid encoding a fusion protein described herein (e.g., a nucleic acid described herein). In some embodiments, the vector is a viral vector. Exemplary viral vectors include, but are not limited to, retroviral vectors, adenoviral vectors, adeno associated viral vectors, herpes viral vectors, lentiviral vectors, pox viral vectors, vaccinia viral vectors, vesicular stomatitis viral vectors, polio viral vectors, Newcastle's Disease viral vectors, Epstein-Barr viral vectors, influenza viral vectors, reovirus vectors, myxoma viral vectors, maraba viral vectors, rhabdoviral vectors, and coxsackie viral vectors. In some embodiments, the vector is a non-viral vector. In some embodiments, the non-viral vector is a plasmid.

**[00285]** In one aspect, provided herein is a viral particle (or population of viral particles) that comprise a nucleic acid encoding a fusion protein described herein (e.g., a nucleic acid described herein). In some embodiments, the viral particle is an RNA virus. In some embodiments, the viral particle is a DNA virus. In some embodiments, the viral particle comprises a double stranded

genome. In some embodiments, the viral particle comprises a single stranded genome. Exemplary viral particles include, but are not limited to, a retrovirus, an adenovirus, an adeno associated virus, a herpes virus, a lentivirus, a pox virus, a vaccinia virus, a vesicular stomatitis virus, a polio virus, a Newcastle's Disease virus, an Epstein-Barr virus, an influenza virus, a reoviruses, a myxoma virus, a maraba virus, a rhabdovirus, or a coxsackie.

## 5.5 Pharmaceutical Compositions

[00286] In one aspect, provided herein are pharmaceutical compositions comprising 1) a fusion protein described herein, a nucleic acid encoding a fusion protein described herein, a vector comprising a nucleic acid encoding a fusion protein described herein, or a viral particle comprising a nucleic acid encoding a fusion protein described herein; and 2) at least one pharmaceutically acceptable carrier, excipient, stabilizer buffer, diluent, surfactant, preservative and/or adjuvant, etc (see, e.g., Remington's Pharmaceutical Sciences (1990) Mack Publishing Co., Easton, PA). A person of ordinary skill in the art can select suitable excipient for inclusion in the pharmaceutical composition. For example, the formulation of the pharmaceutical composition may differ based on the route of administration (e.g., intravenous, subcutaneous, etc.), and/or the active molecule contained within the pharmaceutical composition (e.g., a viral particle, a non-viral vector, a nucleic acid not contained within a vector).

[00287] Acceptable carriers, excipients, or stabilizers are preferably nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, or other organic acids; antioxidants including ascorbic acid or methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; or m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, or other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as TWEEN™, PLURONICS™ or polyethylene glycol (PEG).

[00288] In one embodiment, the present disclosure provides a pharmaceutical composition comprising a fusion protein described herein for use as a medicament. In another embodiment, the disclosure provides a pharmaceutical composition for use in a method for the treatment of cancer. In some embodiments, pharmaceutical compositions comprise a fusion protein disclosed herein, and optionally one or more additional prophylactic or therapeutic agents, in a pharmaceutically acceptable carrier.

[00289] A pharmaceutical composition may be formulated for any route of administration to a subject. Specific examples of routes of administration include parenteral administration (*e.g.*, intravenous, subcutaneous, intramuscular). In some embodiments, the pharmaceutical composition is formulated for intravenous administration. In some embodiments, the pharmaceutical composition is formulated for subcutaneous administration. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions. The injectables can contain one or more excipients. Exemplary excipients include, for example, water, saline, dextrose, glycerol or ethanol. In addition, if desired, the pharmaceutical compositions to be administered can also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents, stabilizers, solubility enhancers, or other such agents, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate or cyclodextrins.

[00290] In some embodiments, the pharmaceutical composition is formulated for intravenous administration. Suitable carriers for intravenous administration include physiological saline or phosphate buffered saline (PBS), or solutions containing thickening or solubilizing agents, such as glucose, polyethylene glycol, or polypropylene glycol or mixtures thereof.

[00291] The compositions to be used for *in vivo* administration can be sterile. This is readily accomplished by filtration through, *e.g.*, sterile filtration membranes.

[00292] Pharmaceutically acceptable carriers used in the parenteral preparations described herein include for example, aqueous vehicles, nonaqueous vehicles, antimicrobial agents, isotonic agents, buffers, antioxidants, local anesthetics, suspending and dispersing agents, emulsifying agents, sequestering or chelating agents or other pharmaceutically acceptable substances. Examples of aqueous vehicles, which can be incorporated in one or more of the formulations described herein, include sodium chloride injection, Ringer's injection, isotonic dextrose injection, sterile water injection, dextrose or lactated Ringer's injection. Nonaqueous parenteral vehicles,

which can be incorporated in one or more of the formulations described herein, include fixed oils of vegetable origin, cottonseed oil, corn oil, sesame oil or peanut oil. Antimicrobial agents in bacteriostatic or fungistatic concentrations can be added to the parenteral preparations described herein and packaged in multiple-dose containers, which include phenols or cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoic acid esters, thimerosal, benzalkonium chloride or benzethonium chloride. Isotonic agents, which can be incorporated in one or more of the formulations described herein, include sodium chloride or dextrose. Buffers, which can be incorporated in one or more of the formulations described herein, include phosphate or citrate. Antioxidants, which can be incorporated in one or more of the formulations described herein, include sodium bisulfate. Local anesthetics, which can be incorporated in one or more of the formulations described herein, include procaine hydrochloride. Suspending and dispersing agents, which can be incorporated in one or more of the formulations described herein, include sodium carboxymethylcellulose, hydroxypropyl methylcellulose or polyvinylpyrrolidone. Emulsifying agents, which can be incorporated in one or more of the formulations described herein, include Polysorbate 80 (TWEEN<sup>®</sup> 80). A sequestering or chelating agent of metal ions, which can be incorporated in one or more of the formulations described herein, is EDTA. Pharmaceutical carriers, which can be incorporated in one or more of the formulations described herein, also include ethyl alcohol, polyethylene glycol or propylene glycol for water miscible vehicles; orsodium hydroxide, hydrochloric acid, citric acid or lactic acid for pH adjustment.

[00293] The precise dose to be employed in a pharmaceutical composition will also depend on the route of administration, and the seriousness of the condition caused by it, and should be decided according to the judgment of the practitioner and each subject's circumstances. For example, effective doses may also vary depending upon means of administration, target site, physiological state of the subject (including age, body weight, and health), other medications administered, or whether therapy is prophylactic or therapeutic. Therapeutic dosages are preferably titrated to optimize safety and efficacy.

## 5.6 Methods of Therapeutic Use

[00294] In one aspect, provided herein are methods of treating a disease in a subject by administering to the subject having the disease a fusion protein described herein, a nucleic acid encoding a fusion protein described herein, a vector comprising a nucleic acid encoding a fusion



protein described herein, or a viral particle comprising a nucleic acid encoding a fusion protein described herein.

**[00295]** The fusion protein can be delivered to host cells via any method known in the art. For example, a viral delivery system (e.g., a retrovirus, an adenovirus, an adeno associated virus, a herpes virus, a lentivirus, a pox virus, a vaccinia virus, a vesicular stomatitis virus, a polio virus, a Newcastle's Disease virus, an Epstein-Barr virus, an influenza virus, a reoviruses, a myxoma virus, a maraba virus, a rhabdovirus, an enadenotucirev or a coxsackie) can be utilized to deliver a nucleic acid (e.g., DNA or RNA molecule) encoding the fusion protein for expression within a population of cells of a subject. In some embodiments, the nucleic acid encoding the fusion protein is present episomally within the population of cells of the subject. In some embodiments, the nucleic acid encoding the fusion protein is incorporated into the genome of the population of cells of the subject. In some embodiments, the virus is replication competent. In some embodiments, the virus is replication deficient.

**[00296]** In some embodiments, the fusion protein is administered to the subject. In some embodiments, a nucleic acid (DNA or RNA) is administered to the subject. In some embodiments, the nucleic acid (DNA or RNA) is complexed within a carrier (e.g., a nanoparticle, a liposome, a microsphere). In some embodiments, a nucleic acid (DNA or RNA) within a non-viral vector (e.g., a plasmid) encoding the fusion protein is administered to the subject.

### **5.6.1 Administration**

**[00297]** The fusion protein can be delivered to host cells via any method known in the art. For example, a viral delivery system (e.g., a retrovirus, an adenovirus, an adeno associated virus, a herpes virus, a lentivirus, a pox virus, a vaccinia virus, a vesicular stomatitis virus, a polio virus, a Newcastle's Disease virus, an Epstein-Barr virus, an influenza virus, a reoviruses, a myxoma virus, a maraba virus, a rhabdovirus, an enadenotucirev or a coxsackie) can be utilized to deliver a nucleic acid (e.g., DNA or RNA molecule) encoding the fusion protein for expression within a population of cells of a subject. In some embodiments, the nucleic acid encoding the fusion protein is present episomally within the population of cells of the subject. In some embodiments, the nucleic acid encoding the fusion protein is incorporated into the genome of the population of cells of the subject. In some embodiments, the virus is replication competent. In some embodiments, the virus is replication deficient.

[00298] In some embodiments, the fusion protein is administered to the subject. In some embodiments, a nucleic acid (DNA or RNA) is administered to the subject. In some embodiments, the nucleic acid (DNA or RNA) is complexed within a carrier (e.g., a nanoparticle, a liposome, a microsphere). In some embodiments, a nucleic acid (DNA or RNA) within a non-viral vector (e.g., a plasmid) encoding the fusion protein is administered to the subject.

[00299] In some embodiment, the fusion protein is administered parenterally. In some embodiments, the fusion protein is administered via intravenous, intramuscular, intraarterial, intrathecal, intralymphatic, intralesional, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural or intrasternal injection or infusion. In some embodiments, the fusion protein is intravenously administered. In some embodiments, the fusion protein is subcutaneously administered. In some embodiments, the fusion protein is administered via a non-parenteral route, or orally. Other non-parenteral routes include a topical, epidermal or mucosal route of administration, for example, intranasally, vaginally, rectally, sublingually or topically. Administering can also be performed, for example, once, a plurality of times, and/or over one or more extended periods.

[00300] In some embodiments, the methods disclosed herein are used in place of standard of care therapies. In certain embodiments, a standard of care therapy is used in combination with any method disclosed herein. In some embodiments, the methods disclosed herein are used after standard of care therapy has failed. In some embodiments, the fusion protein is co-administered, administered prior to, or administered after, an additional therapeutic agent. In some embodiments, the disease is a genetic disease.

### **5.6.2 Exemplary Genetic Diseases**

[00301] In some embodiments, the disease is associated with decreased expression of a functional target cytosolic protein. In some embodiments, the disease is associated with decreased stability of a functional target cytosolic protein. In some embodiments, the disease is associated with increased ubiquitination of a target cytosolic protein. In some embodiments, the disease is associated with increased ubiquitination and degradation of a target cytosolic protein. In some embodiments, the disease is a haploinsufficiency disease.

[00302] In some embodiments, the disease is a genetic disease. In some embodiments, the

genetic disease is associated with decreased expression of a functional target cytosolic protein. In some embodiments, the genetic disease is associated with decreased stability of a functional target cytosolic protein. In some embodiments, the genetic disease is associated with increased ubiquitination of a target cytosolic protein. In some embodiments, the genetic disease is associated with increased ubiquitination and degradation of a target cytosolic protein. In some embodiments, the genetic disease is a haploinsufficiency disease.

**[00303]** In some embodiments, the disease is an epileptic encephalopathy. In some embodiments, the epileptic encephalopathy is an early infantile epileptic encephalopathy. In some embodiments, the early infantile epileptic encephalopathy is early infantile epileptic encephalopathy type 4, or early infantile epileptic encephalopathy type 4.

**[00304]** In some embodiments, the disease is SYNGAP1 encephalopathy, CDKL5 deficiency disorder, STXBP1 encephalopathy early, early infantile epileptic encephalopathy type 2, Wilson disease, early infantile epileptic encephalopathy type 4, Mental retardation, autosomal dominant 5, aphasia, primary progressive & FTD (frontotemporal degeneration), alagille syndrome 1, Epilepsy, familial focal, with variable foci 1, Tuberous sclerosis-2, Tuberous sclerosis-1, KIF1A-associated neurological disorder, encephalopathy, Phelan-McDermid syndrome, Becker Muscular Dystrophy, RP1, retinitis pigmentosa 1, dilated cardiomyopathy 1G, DYNC1H1 Syndrome, TRIO-Related intellectual disability (ID), or USP9X development disorder.

**[00305]** In some embodiments, the target cytosolic protein is SYNGAP1, and the disease is SYNGAP1 encephalopathy. In some embodiments, the target cytosolic protein is SYNGAP1, and the disease is Mental retardation, autosomal dominant 5. In some embodiments, the target cytosolic protein is CDKL5, and the disease is CDKL5 deficiency disorder. In some embodiments, the target cytosolic protein is CDKL5, and the disease is an early infantile epileptic encephalopathy. In some embodiments, the target cytosolic protein is CDKL5, and the disease is early infantile epileptic encephalopathy type 2. In some embodiments, the target cytosolic protein is ATP7B, and the disease is Wilson disease. In some embodiments, the target cytosolic protein is STXBP1, and the disease is STXBP1 encephalopathy. In some embodiments, the target cytosolic protein is STXBP1, and the disease is an early infantile epileptic encephalopathy. In some embodiments, the target cytosolic protein is STXBP1, and the disease is early infantile epileptic encephalopathy type 4. In some embodiments, the target cytosolic protein is GRN, and the disease is aphasia, primary progressive & FTD (frontotemporal degeneration). In some embodiments, the target cytosolic

protein is JAG1, and the disease is alagille syndrome 1. In some embodiments, the target cytosolic protein is DEPDC5, and the disease is epilepsy (e.g., familial focal, with variable foci 1). In some embodiments, the target cytosolic protein is TSC2, and the disease is tuberous sclerosis. In some embodiments, the target cytosolic protein is TSC2, and the disease is tuberous sclerosis type 2. In some embodiments, the target cytosolic protein is TSC2, and the disease is tuberous sclerosis type 1. In some embodiments, the target cytosolic protein is TSC1, and the disease is tuberous sclerosis. In some embodiments, the target cytosolic protein is TSC1, and the disease is tuberous sclerosis type 1. In some embodiments, the target cytosolic protein is TSC1, and the disease is tuberous sclerosis type 2. In some embodiments, the target cytosolic protein is KIF1A, and the disease is KIF1A-associated neurological disorder. In some embodiments, the target cytosolic protein is DNM1, and the disease is a DNM1 encephalopathy. In some embodiments, the target cytosolic protein is DNM1, and the disease is encephalopathy. In some embodiments, the target cytosolic protein is SHANK3, and the disease is Phelan-McDermid syndrome. In some embodiments, the target cytosolic protein is DMD, and the disease is Becker Muscular Dystrophy. In some embodiments, the target cytosolic protein is RP1, and the disease is retinitis pigmentosa 1. In some embodiments, the target cytosolic protein is TTN, and the disease is dilated cardiomyopathy 1G. In some embodiments, the target cytosolic protein is DYNC1H1, and the disease is DYNC1H1 Syndrome. In some embodiments, the target cytosolic protein is TRIO, and the disease is TRIO-Related intellectual disability (ID). In some embodiments, the target cytosolic protein is USP9X, and the disease is USP9X development disorder. In some embodiments, the target cytosolic protein is CSTB, and the disease is epilepsy, progressive myoclonic 1 (EPM1). In some embodiments, the target cytosolic protein is PCBD1, and the disease is hyperphenylalaninemia, BH4-deficient, D (HPABH4D).

## 5.7 Kits

**[00306]** In one aspect, provided herein are kits comprising a fusion protein described herein, a nucleic acid encoding a fusion protein described herein, a vector comprising a nucleic acid encoding a fusion protein described herein, or a viral particle comprising a nucleic acid encoding a fusion protein described herein, for therapeutic uses. Kits typically include a label indicating the intended use of the contents of the kit and instructions for use. The term label includes any writing, or recorded material supplied on or with the kit, or which otherwise accompanies the kit.

Accordingly, this disclosure provides a kit for treating a subject afflicted with a disease (*e.g.*, a genetic disease), the kit comprising: (a) a dosage of a fusion protein, a nucleic acid encoding a fusion protein described herein, a vector comprising a nucleic acid encoding a fusion protein described herein, or a viral particle comprising a nucleic acid encoding a fusion described herein; and (b) instructions for using the fusion protein in any of the therapy methods disclosed herein.

## 6. EXAMPLES

[00307] The present invention is further illustrated by the following examples which should not be construed as further limiting.

### 6.1 Example 1. Generation of Targeted Engineered Deubiquitinases

[00308] This example provides general experimental methods of using fluorescent tagged target proteins together with fluorophore tagged engineered deubiquitinases (enDUBs) to demonstrate up-regulation of expression in the context of an enDUB. For illustrative purposes the constructs disclosed below will be synthesized in a suitable vector for mammalian expression. Generally, the target protein will be expressed with a C-terminal YFP followed by a P2A cleavage signal and an mCherry protein as a second reporter (Target protein – YFP – P2A – mCherry). This construct will be co-transfected in the presence of a trifunctional fusion protein comprising of a CFP protein followed by a P2A signal and a nanobody specifically binding to YPF followed by the engineered DUB (CFP – P2A - Anti-YFPnanobody – enDUB). In applications for drug treatment the targeting nanobodies (or other specific binders) will be directed to the wild type (or disease-causing mutant) protein in the cell to be upregulated while the enDUB is fused to a binding protein directed to the target protein. Target protein binding moieties could be any antibody or antibody fragments, nanobodies, or any other non-antibody scaffold such as fibronectins, anticalins, ankyrin repeats or natural binding proteins interacting specifically with the target protein to be upregulated. The amino acid sequence of the components of the test fusion proteins is provided in Table 7 below.

**Table 7.** Amino Acid Sequence of Components of test fusion proteins

| Description            | SEQ ID NO | Amino Acid Sequence                                                                                                                                 |
|------------------------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Target Proteins</b> |           |                                                                                                                                                     |
| LCK kinase             | 239       | MGCGCSSHPEDDWMENIDVCENCHYPIVPLDGKGTLLIRNGSEVRD<br>PLVTYEGSNPPASPLQDNLVIALHSYEP SHDGLGF EKGEQLRILE<br>QSGEWWKAQSLTTGQEGFIPFNFVAKANSLEPEPWFFKNLSRKDAE |

|                             |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-----------------------------|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                             |     | RQLLAPGNTHGSFLIRESESTAGSFSLSVRDFDQNNQGEVVKHYKIR<br>NLDNGGFYISPRITFPGLHELVRHYTNASDGLCTRLSRPCQTQKPQ<br>KPWWEDEWEVPRETLKLVERLGAGQFGEVWMGYINGHTKVAVKSLK<br>QGSMSPD AFLAEANLMKQLQHQRLLVRLYAVVTQEPIYIITEYMENG<br>SLVDFLKTTPSGIKLTINKLLDMAAQIAEGMAFIEERNYIHRDLRAA<br>NILVSDTLSCKIADFGRLARLIEDNEYTAREGAKFPIKWTAPAINY<br>GTFTIKSDVWSFGILLTEIVTHGRIPYPGMTNPEVIQNLERGYRMV<br>RPDNCPEELYQLMRLCWKERPEDRPTFDYLRVLEDDFTATEGQYQ<br>PQP                                                                                                                                                                                |
| YES1 kinase                 | 240 | MGCIKSKENKSPAICYRPENTPEPVSTSVSHYGAEPPTVSPCPSSS<br>AKGTAVNFSSLSMTPFSGSSGVTPFSGASSSFVVPSSYPAGLTGG<br>VTIFVALYDYEARTTEDLSFKKGERFQIINNTEGDWWEARSATGK<br>NGYIPSNYVAPADSIQAEWYFGKMGRKDAERLLLLNPGNQRGIFLV<br>RESETTKGAYSLSIRDWDEIRGDNVVKHYKIRKLDNGGYITTRAQF<br>DTLQKLKHYTEHADGLCHKLTTCVPTVKPQTQGLAKDAWEIPRES<br>LRLEVKLGGCFGEVWMGTWNGTTKVAIKTLKPGTMMPEAFLQEAQ<br>IMKKLRHDKLVPLYAVVSEEPYIVTEFMSKGSLLDFLKEGDGKYL<br>KLPQLVDMAAQIADGMAYIERMNYIHRDLRAANILVGENLVCKIAD<br>FGLARLIEDNEYTARQGAKEPIKWTAPEAALYGRFTIKSDVWSFGI<br>LQTELVTKGRVPYPGMVNREVLEQVERGYRMPCPQGCPESLHELMN<br>LCWKKDPDERPTFEYIQSFLEDYFTATEPQYQGENL |
| Aurora kinase A             | 241 | MDRSKENCISGPVKATAPVGGPKRVLVTQQFPCQNPLPVSNGQAQR<br>VLCPSNSSQRVPLQAQKLVS SHKPVQNKQKQLQATSVPHVSRPL<br>NNTQKSKQPLPSAPENNPEEELASKQKNEESKKRQWALEDFEIGRP<br>LGKKGFGNVYLAREKQSKFILALKVLFKAQLEKAGVEHQLRREVEI<br>QSHLRHPNILRLYGYFHDATRVYLILEYAPLGTVYRELQKLSKFDE<br>QRTATYITELANALSYCHSKRVIHRDIKPENLLLGSAGELKIADFG<br>WSVHAPSSRRTTLCGTLDYLPPEMIEGRMHDEKVDLWSLGLCYEF<br>LVGKPPFEANTYQETYKRISRVEFTFPDFVTEGARDLISRLLKHNP<br>SQRPMLREVLEHPWITANSSKPSNCQNKESASKQS                                                                                                                                                     |
| <b>Fluorescent Proteins</b> |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| YFP                         | 242 | VSKGEELFTGVVPILVELDGDVNGHKFSVS GEGEGDATYGKLTCLKF<br>ICTTGKLPVPWPPTLVTTFGYGLQCFARYPDHMKQHDFFKSAMPEGY<br>VQERTIFFKDDGNYKTRAEVKFEGDTLVNRIELKGIDFKEDGNILG<br>HKLEYNNSHNHYIMADKQKNGIKVNFKIRHNIEDGVSQVLADHYQQ<br>NTPIGDGPVLLPDNHYLSYQSALS KDPNEKRDHMLVLEFVTAAGIT<br>LGMDELYK                                                                                                                                                                                                                                                                                                                                |
| mCherry                     | 243 | MVSKGEEDNMAIIKEFMRFKVHMEGSVNGHEFEIEGEGEGRPYEGT<br>QTAKLKVTKGGPLPFAWDILSPQFMYGSKAYVKHPADIPDYCLKSF<br>PEGFKWERVMNFEDGGVVTVTQDSSLQDGEFIYKVKLRGTNFPSDG<br>PVMQKKTMGWEASSERMPEDGALKGEIKQRLKLDGGHYDAEVKT<br>TYKAKKPVQLPGAYNVNIKLDITSHNEDYTIVEQYERAEGRHSTGG<br>MDELYK                                                                                                                                                                                                                                                                                                                                        |
| CFP                         | 244 | MVSKGEELFTGVVPILVELDGDVNGHKFSVS GEGEGDATYGKLTCLKF<br>FICTTGKLPVPWPPTLVTTLTWGVQCFSRYPDHMKQHDFFKSAMPEG<br>YVQERTIFFKDDGNYKTRAEVKFEGDTLVNRIELKGIDFKEDGNIL<br>GHKLEYNYISHNHYITADKQKNGIKANFKIRHNIEDGVSQVLADHYQ<br>QNTPIGDGPVLLPDNHYLSTQSALS KDPNEKRDHMLVLEFVTAAGI<br>TLGMDELYK                                                                                                                                                                                                                                                                                                                             |

| A2 Peptides                       |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-----------------------------------|-----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| P2A                               | 245 | GSGATNFSLLKQAGDVEENPGP                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| T2A                               | 246 | GSGEGRGSLTTCGDVEENPGP                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| E2A                               | 247 | GSGQCTNYALLKLAGDVESNPGP                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Target Binders                    |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| YFP targeting nanobody            | 248 | QVQLVESGGALVQPGGSLRLSCAASGFPVNRYSMRWYRQAPGKERE<br>WVAGMSSAGDRSSYEDSVKGRFTISRDDARNTVYLQMNSLKPEDTA<br>VYYCNVNVGFEYWGQGTQVTVSS                                                                                                                                                                                                                                                                                                                                                                         |
| LCK binder (monobody)             | 249 | GSVSSVPTKLEVVAATPTSLLSISWDAPAVTVDFYHITYGETGGNSP<br>VQEFTVPGSKSTATISGLKPGVDYTITVYAYVSYPEYYFPSPISIN<br>YRT                                                                                                                                                                                                                                                                                                                                                                                            |
| YES1 Kinase binder (monobody)     | 250 | GSVSSVPTKLEVVAATPTSLLSISWDAPAVTVDYFYFITYGETGGNSP<br>VQEFTVPGSKSTATISGLKPGVDYTITVYAWYYDDDEYMNNESSPI<br>SINYRT                                                                                                                                                                                                                                                                                                                                                                                        |
| Aurora kinase A binder (monobody) | 251 | GSVSSVPTKLEVVAATPTSLLSISWDAPAVTVVHYVITYGETGGNSP<br>VQEFTVPGSKSTATISGLKPGVDYTITVYAI DFYWGSYSPISIN YR<br>T                                                                                                                                                                                                                                                                                                                                                                                            |
| EnDUBS                            |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Cezanne                           | 252 | PPSFSEGGSGSRTPEKGFSDREPTRPPRPILQRQDDIVQEKRLSRG<br>ISHASSSIVSLARSHVSSNGGGGGSNEHPLEMPICAFQLPDLTVYN<br>EDFRSFIERDLIEQSMLVALEQAGRLNWWVSDPTSQRLLPLATTG<br>DGNCLLHAASLGMWGFHDRDLMLRKALYALMEKGEKEALKRRRW<br>QQTQQNKESGLVYTEDEWQKEWNELIKLASSEPRMHLGTNGANCGG<br>VESSEEPVYESLEEFHVFLAHVLRPIVVVADTMLRDSGGEAFAP<br>IPFGGIYLPLEVPASQCHRSPLVLAYDQAHFSALVSMEQKENTKEQ<br>AVIPLTDSEYKLLPLHFAVDPGKGWEWGKDDSDNVRLASVILSLEV<br>KLHLLHSYMNWKIPLSSDAQAPLAQ                                                                |
| OTUD1                             | 253 | DEKLALYLAEVEKQDKYLQRNKYRFHIIIPDGNCLYRAVSKTVYGD<br>QSLHRELREQTVHYIADHLDFHSPLEIGDVGEFIIAAAQDGAWAGY<br>PELLAMGQMLNVNIHLTTGGRLESPTVSTMIHYLGPEDSLRPSIWL<br>SWLSNGHYDAVFDHSYPNPEYDNWCKQTQVQRKRDEELAKSMAISL<br>SKMYIEQNACS                                                                                                                                                                                                                                                                                 |
| TRABID                            | 254 | LEVDFKKLKQIKNRMKKTDLWFLNACVGVVEGDLAAIEAYKSSGGD<br>IARQLTADEVRLNRPISAFDVGTYTLVHLAIRFQRQDMLAILLTEVS<br>QQAACIPAMVCPTEQIRREIAASLHQKRGDFACYFLTDLVTF<br>LPADIEDLPPTVQEKLFDEVLD RDVQKELEEEESPIINWSLELATRL<br>DSRLYALWNRTAGDCLLDSVLQATWGIYDKDSVLRKALHDSLHDCS<br>HWFYTRWKDWESWYSQSFGHLHFSLREEQWQEDWAFILSLASQPGAS<br>LEQTHIFVLAILRRPIIVYGVKYKSFRRGETLGYTRFQGVYLP<br>WEQSFCWKSPIALGYTRGHFSALVAMENDGYGNRGAGANLNTDDDV<br>TITFLPLVDSEKLLHVHFLSAQELGNEEQQEKLLREWLDCCVTEG<br>GVLVAMQKSSRRRNHPLVTQMVEKWLDYRQIRPCTSL |
| USP21                             | 255 | SDDKMAHHTLLLGSGHVGLRNLGNTCFLNAVLQCLSSTRPLRDFCL<br>RRDFRQEVPGGGRAQELTEAFADVIGALWHPDSCEAVNPTRFRAVF<br>QKYVPSFSGYSQQDAQEFLLKLMERLHLEINRRGRRAPPILANGPV                                                                                                                                                                                                                                                                                                                                                  |

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|                                                |     | PSPPRRGGALLEEPELSDDDRANLMWKRYLEREDSKIIVDLFVGQLK<br>SCLKCQACGYRSTTFEVFCDLSLPIPKKGFAGGKVSRLDCFNLF TK<br>EEEESEENAPVCDRCRQKTRSTKKLTVQRFPRILVLHLNRFASRG<br>SIKKSSVGVDFFLQRLSLGDFASDKAGSPVYQLYALCNHSGSVHYG<br>HYTALCRCQTGWHVYND SRVSPVSENQVASSEGYVLFYQLMQEPPR<br>CL                                                                                                                                                                                                                                                                                                                    |
| OTUD4                                          | 256 | ATPMDAYLRKLGLYRKLVAKDGSCLFRAVAEQVLHSQSRHVEVRMA<br>CIHYLRENREKFEAFIEGSFEEYLKRLNPQEWVGQVEISALSLMY<br>RKDFIIYREPNVSPSQVTENNFPKVLCCFSNGNHYDIVYPIKYKE<br>SSAMCQSLLYELLYEKVFKTDVSKI VMELDTLEVADE                                                                                                                                                                                                                                                                                                                                                                                        |
| Human USP3<br>(full length)<br>nuclear located | 257 | MECPHLSSSSVCIAPDSAKFPNGSPSSWCCSVCRSNKSPWVCLTCSS<br>VHCGRYVNGHAKKHYEDAQVPLTNHKKSEKQDKVQHTVCMDCSSYS<br>TYCYRCDDFVNDTKLGLVQKVREHLQNLNSAFTADRHKRKLLE<br>NSTLNSKLLKVNGSTTAICATGLRNLGNTCFMNAILOSLSNIEQFC<br>CYFKELPAVELRNGKTAGRRTYHTRSQGDNNVSLVEEFRKTLALW<br>QGSQTAFFSPESLFYVWVKIMPNFRGYQQQDAHEFMRYLLDHLHLEL<br>QGGFNGVSRSAILOENSTLSASNKCCINGASTVVTAIFGGILQNEV<br>NCLICGTESRKFDPFDLDSLIPSQFRSKRSKNQENGPVCSLRDCL<br>RSFTDLEELDETELYMCHKCKKKQKSTKKFWIQKLPKVLCLHLKRF<br>HWTAYLRNKVDITYVEFPLRGLDMKCYLLEPENSGPESCLYDLAAVV<br>VHHGSGVSGHYTAYATHEGRWFHFNDSTVTLTDEETVVKAKAYIL<br>FYVEHQAKAGSDKL |

[00309] The amino acid sequence of the test fusion proteins is provided in Table 8 below.

**Table 8.** Amino acid sequence of exemplary test fusion proteins

| Description                                  | SEQ ID NO | Amino Acid Sequence                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|----------------------------------------------|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| LCK Kinase<br>Target – YFP-<br>P2A – mCherry | 258       | MGCGCSSHPEDDWMENIDVCENCHYPIVPLDGKGTLLIRNGSEVRD<br>PLVTYEGSNPPASPLQDNLVIALHSYEP SHDGLGFEKGEQLRILE<br>QSGEWWKAQSLTTGQEGFIPFNFAKANSLEPEPWF FKNLSRKDAE<br>RQLLAPGNTHGSFLIRESESTAGSFSLSVRDFDQNGQEVVKHYKIR<br>NLDNGGFYISPRITFPGLHELVRHYTNASDGLCTRLSRPCQTQKPQ<br>KPWWEDEWEVPRETLKLVERLGAGQFGEVWMGYNGHTKVAVKSLK<br>QGSMSPD AFLAEANLMKQLQHQLVRLYAVVTQEPYIITEYMENG<br>SLVDFLKTPSGIKLTINKLLDMAAQIAEGMAFIEERNYIHRDLRAA<br>NILVSDTLCKIADFGARLIEDNEYTAREGAKFPKWTAPAINY<br>GTFTIKSDVVSFGILLTEIVTHGRIPYPGMTNPEVIQNLERG YRMV<br>RPDNCPEELYQLMRLCWKERPEDRPTFDYLRSVLEDDFTATEGQYQ<br>PQPVSKEELFTGVVPILVELDGDVNGHKFSVSGEGEGDATY GKLT<br>LKFICTTGKLPVPWPPTLVTTFGYGLQC FARYPDHMKQHDFFKSAMP<br>EGYVQERTIFFKDDGNYKTRAEVKFEGDTLVNRIELKGIDFKEDGN<br>ILGHKLEYNYN SHNVYIMADKQKNGIKVNFKIRHNIEDG SVQLADH<br>YQQNTPIGDGPVLLPDNHYLSYQSALSKDPNEKRDHMLLEFVTAA<br>GITLGMDELYKSGATNFSLLKQAGDVEENPGPMVSKGEEDNMAII<br>KEFMRFKVHMEG SVNGHEFEIEGEGEGRPYEGTQTAKLKVTKGGPL<br>PFAWDILSPQFMYGSKAYVKHPADIPDYLKLSFPEGFKWERVMNFE<br>DGGVTVTQDSSLQDGEFIYKVKLRGTNFPSDGPVMQKKTMGWEAS<br>SERMPEDGALKGEIKQRLKLKDGGHYDAEVKTTYKAKKPVQLPGA<br>YNVNIKLDITSHNEDYTIVEQYERAEGRHSTGGMDELYK |



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|---------------------------------------------------|-----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| YES1 Kinase<br>Target – YFP-<br>P2A – mCherry     | 259 | <p>MGCIKSKENKSPAICYRPENTPEPVSTSVSHYGAEPPTTVSPCPSSS<br/>AKGTAVNFSSLSMTFPGGSSGVTPFPGGASSSFVVPSSYPAGLTGG<br/>VTIFVALYDYEARTTEDLSFKKGERFQIINNTEGDWWEARSIATGK<br/>NGYIPSNYVAPADSIQAEEWYFGKMGRKDAERLLLNPGNQRGIFLV<br/>RESETTKGAYSLSIRDWDEIRGDNVKHYKIRKLDNGGYIITTRAQF<br/>DTLQKLKHYTEHADGLCHKLTTCPTVKPQTQGLAKDAWEIPRES<br/>LRLEVKLGGQCFGEVWMGTWNGTTKVAIKTLKPGTMMPEAFLEQEAQ<br/>IMKKLRHDKLVPLYAVVSEEPYIVTEFMSKGSLLDFLKEGDGKYL<br/>KLPQLVDMAAQIADGMAYIERMNYIHRDLRAANILVGENLVCKIAD<br/>FGLARLIEDNEYTARQGAKEPIKWTAPAAALYGRFTIKSDVWSFGI<br/>LQTELVTKGRVPYPGMVNREVLEQVERGYRMPCPQGCPESLHELMN<br/>LCWKKDPDERPTFEYIQSFLEDYFTATEPQYQPGENLVSKGEELFT<br/>GVVPILVELDGDVNGHKFSVSSEGEEDATYGKLTCLKFICTTGKLPV<br/>PWPTLVTTFGYGLQCFARYPDHMKQHDFFKSAMPEGYVQERTIFFK<br/>DDGNYKTRAEVKFEGDTLVNRIELKGIDFKEDGNILGHKLEYNYS<br/>HNVEIMADKQKNGIKVNFKIRHNIEDGSVQLADHYQQNTPIGDGPV<br/>LLPDNHYLSYQSALS KDPNEKRDHMLLEFVTAAGITLGMDELYKG<br/>SGATNFSLLKQAGDVEENPGPMVSKGEEDNMAIIKEFMRFKVHMEG<br/>SVNGHEFEIEGEGEGRPYEGTQTAKLKVTKGGPLPFAWDILSPQFM<br/>YGSKAYVKHPADIPDYLKLSFPEGFKWERVMNFEDGGVVTVTQDSS<br/>LQDGEFIYKVKLRGTNFPDGPVMQKKTMGWEASSERMPEDGALK<br/>GEIKQRLKLDGGHYDAEVKTTYKAKKPVQLPGAYNVNIKLDITSH<br/>NEDYTIVEQYERAEGRHSTGGMDELYK</p> |
| Aurora Kinase<br>A Target – YFP-<br>P2A – mCherry | 260 | <p>MDRSKENCISGPVKATAPVGGPKRVLVTQQFPCQNPLPVNSGQAQR<br/>VLCPSNSSQRVPLQAQKLVSSHKPVQNQKQKQLQATSVPHVSRPL<br/>NNTQKSKQPLPSAPENNPEEELASKQKNEESKKRQWALEDFEIGRP<br/>LGKKGKFGNVYLAREKQSKFILALKVLFKAQLEKAGVEHQLRREVEI<br/>QSHLRHPNIRLYGYFHDATRVYLLILEYAPLGTVYRELQKLSKFDE<br/>QRTATYITELANALSYCHSKRVIHRDIKPENLLLGSAGELKIADFG<br/>WSVHAPSSRRITLCGTLDYLPPEMIEGRMHDEKVDLWSLGLVLCYEF<br/>LVGKPPFEANTYQETYKRISRVEFTFPDFVTEGARDLISRLKHNP<br/>SQRPMLREVLEHPWITANSSKPSNCQNKESASKQSVSKGEELFTGV<br/>VPILVELDGDVNGHKFSVSSEGEEDATYGKLTCLKFICTTGKLPVPW<br/>PTLVTTFGYGLQCFARYPDHMKQHDFFKSAMPEGYVQERTIFFKDD<br/>GNYKTRAEVKFEGDTLVNRIELKGIDFKEDGNILGHKLEYNYS<br/>VYIMADKQKNGIKVNFKIRHNIEDGSVQLADHYQQNTPIGDGPVLL<br/>PDNHYLSYQSALS KDPNEKRDHMLLEFVTAAGITLGMDELYKGS<br/>ATNFSLLKQAGDVEENPGPMVSKGEEDNMAIIKEFMRFKVHMEGS<br/>VNGHEFEIEGEGEGRPYEGTQTAKLKVTKGGPLPFAWDILSPQFMYG<br/>SKAYVKHPADIPDYLKLSFPEGFKWERVMNFEDGGVVTVTQDSSLQ<br/>DGEFIYKVKLRGTNFPDGPVMQKKTMGWEASSERMPEDGALKGE<br/>IKQRLKLDGGHYDAEVKTTYKAKKPVQLPGAYNVNIKLDITSHNE<br/>DYTIVEQYERAEGRHSTGGMDELYK</p>                                                                                                                                                              |
| CFP- P2A-<br>Cezanne enDUB                        | 261 | <p>MVSKGEELFTGVVPILVELDGDVNGHKFSVSSEGEEDATYGKLTCLK<br/>FICTTGKLPVPWPPTLVTTLTWGVQCFSRYPDHMKQHDFFKSAMPEG<br/>YVQERTIFFKDDGNYKTRAEVKFEGDTLVNRIELKGIDFKEDGNIL<br/>GHKLEYNYSIHNVEITADKQKNGIKANFKIRHNIEDGSVQLADHYQ<br/>QNTPIGDGPVLLPDNHYLSTQSALS KDPNEKRDHMLLEFVTAAGI<br/>TLGMDELYKSGATNFSLLKQAGDVEENPGPPPSFSESGSGSRTPE<br/>KGFSDREPTRPPRPILQRQDDIVQEKLRSRGISHASSIVSLARSH<br/>VSSNGGGGGSNEHPLEMPICAFQLPDLTVYNEDFRSFIERDLIEQS</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

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|------------------------------|-----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                              |     | MLVALEQAGRLNWWVSVDPTSQRLLPLATTGDGNCLLHAASLGMWG<br>FHDRDLMLRKALYALMEKGVEKEALKRRWRWQQQTQQNKESGLVYTE<br>DEWQKEWNELIKLASSEPRMHLGTNGANCGVESSEEPVYESLEEF<br>HVFVLAHVLRRIVVVADTMLRDSGGEAFAPIPFGGIYLPLEVPAS<br>QCHRSPLVLAYDQAHFSALVSMEQKENTKEQAVIPLTDSEYKLLPL<br>HFAVDPGKGWEWGKDDSDNVRLASVILSLEVKLHLLHSYMNVKWIP<br>LSSDAQAPLAQ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| CFP- P2A-<br>OTUD1 enDUB     | 262 | MVSKGEELFTGVVPILVELDGDVNGHKFSVSGEGEGDATYGKLT<br>FICTTGKLPVPWPPTLVTTLTWGVQCFSRYPDHMKQHDFFKSAMPEG<br>YVQERTIFFKDDGNYKTRAEVKFEGDTLVNRIELKGIDFKEDGNIL<br>GHKLEYNYISHNVYITADKQKNGIKANFKIRHNIEDGSGVQLADHYQ<br>QNTPIGDGPVLLPDNHYLSTQSALS KDPNEKRDHMLLEFVTAAGI<br>TLGMDELYKSGGATNFSLLKQAGDVEENPGPDEKLALYLAEVEKQD<br>KYL RQRNKYRFHIIIPDGNCLYRAVSKTVYGDQSLHRELREQTVHYI<br>ADHLDHFSPLIEGDVGEFIIAAAQDGAWAGYPELLAMGQMLNVNIH<br>LTTGGRLESPTVSTMIHYLGPEDSLRPSIWL SWLSNGHYDAVFDHS<br>YPNPEYDNWCKQTQVQRKRDEELAKSMAISLSKMYIEQNACS                                                                                                                                                                                                                                                                                              |
| CFP- P2A-<br>TRABID<br>enDUB | 263 | MVSKGEELFTGVVPILVELDGDVNGHKFSVSGEGEGDATYGKLT<br>FICTTGKLPVPWPPTLVTTLTWGVQCFSRYPDHMKQHDFFKSAMPEG<br>YVQERTIFFKDDGNYKTRAEVKFEGDTLVNRIELKGIDFKEDGNIL<br>GHKLEYNYISHNVYITADKQKNGIKANFKIRHNIEDGSGVQLADHYQ<br>QNTPIGDGPVLLPDNHYLSTQSALS KDPNEKRDHMLLEFVTAAGI<br>TLGMDELYKSGGATNFSLLKQAGDVEENPGPLEVDFFKKLKQIKNRM<br>KKTDLWFLNACVGVVEGDLAAIEAYKSSGGDIARQLTADDEVRLNR<br>PSAFDVGYTLVHLAIRFQRQDMLAILLTEVSQQAACIPAMVCPEL<br>TEQIRREIAASLHQKRGDFACYFLTDLVFTLPADIEDLPPTVQEK<br>LFDEVLD RDVQKELEEEESP IINWSLELATRLDSRLYALWNRTAGDC<br>LLDSVLQATWGIYDKDSVLRKALHDSLHDCSHWFYTRWKDWESWYS<br>QSFGHLHFSRLREEQWQEDWAFILSLASQPGASLEQTHIFVLAHILRR<br>PIIVYGVKYYKSFRGETLGYTRFQGVYLP LLWEQSF CWKSPIALGY<br>TRGHFSALVAMENDGYGNRGAGANLNTDDDVTITFLPLVDSEKLL<br>HVHFLSAQELGNEEQQEKLLEWLDCCVTEGGVLVAMQKSSRRRNH<br>PLVTQMVEKWLD RYRQIRPCTSL S |
| CFP- P2A-<br>USP21 enDUB     | 264 | MVSKGEELFTGVVPILVELDGDVNGHKFSVSGEGEGDATYGKLT<br>FICTTGKLPVPWPPTLVTTLTWGVQCFSRYPDHMKQHDFFKSAMPEG<br>YVQERTIFFKDDGNYKTRAEVKFEGDTLVNRIELKGIDFKEDGNIL<br>GHKLEYNYISHNVYITADKQKNGIKANFKIRHNIEDGSGVQLADHYQ<br>QNTPIGDGPVLLPDNHYLSTQSALS KDPNEKRDHMLLEFVTAAGI<br>TLGMDELYKSGGATNFSLLKQAGDVEENPGPSDDKMAHHTLLLGS<br>HVGLRNLGNTCFLNAVLQCLSSTRPLRDFCLRRDFRQEVPPGGGRAQ<br>ELTEAFADVIGALWHPDSCEAVNPTRFRAVFQKYVPSFSGYSQQDA<br>QEFLKLLMERLHLEINRRGRRAPPILANGPVPSPPRRGGALLEEPE<br>LSDDDRANLMWKRYLEREDSKIIVDLFVGQLKSKLCQACGYRSTTF<br>EVFCDSLPIPKKFAGGKVS LRDCFNLF TKEEELESENAPVCDRC<br>RQKTRSTK KLT VQRFPRI LVHLNRF SASRGS IKKSSVGVD FPLQR<br>LSLGDFASDKAGSPVYQLYALCNHSGSVHYGHYTALC RCQTGW HVY<br>NDSRVSPVSENQVASSEGYVLFYQLMQEPPRCL                                                                                           |
| CFP- P2A-<br>OTUD4 enDUB     | 265 | MVSKGEELFTGVVPILVELDGDVNGHKFSVSGEGEGDATYGKLT<br>FICTTGKLPVPWPPTLVTTLTWGVQCFSRYPDHMKQHDFFKSAMPEG<br>YVQERTIFFKDDGNYKTRAEVKFEGDTLVNRIELKGIDFKEDGNIL<br>GHKLEYNYISHNVYITADKQKNGIKANFKIRHNIEDGSGVQLADHYQ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

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|-----------------------------------------------|-----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                               |     | QNTPIGDGPVLLPDNHYLSTQSALS KDPNEKRDMVLLEFVTAAGI<br>TLGMDELYKGSGATNFSLLKQAGDVEENPGPATPMDAYLRKLGLYR<br>KLVAKDGSCLFRAVAEQVLHSQSRHVEVRMACIHYLRENREKFEAF<br>IEGSFEEYLKRLNPQEWVGQVEISALS LMYRKDFI IYREPNVSPS<br>QVTENNFPKVL LCF SNGNHYDIVYPIKY KESSAMCQSLLYELLYE<br>KVFKTDVSKIVMELDTLEVADE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| CFP-P2A-a-<br>YFPnanobody-<br>Cezanne enDUB   | 266 | MVSKGEELFTGVVPILVELDGDVNGHKFSVSGEGEGDATY GKLTLK<br>FICTTGKLPVPWPPTLVTTLTWGVQCFSRYPDHMKQHDFFKSAMPEG<br>YVQERTIFFKDDGNYKTRAEVKFEGDTLVNRIELKGIDFKEDGNIL<br>GHKLEYNYISHNVYITADKQKNGIKANFKIRHNIEDGSGVQLADHYQ<br>QNTPIGDGPVLLPDNHYLSTQSALS KDPNEKRDMVLLEFVTAAGI<br>TLGMDELYKGSGATNFSLLKQAGDVEENPGPQVQLVESGGALVQPG<br>GSLRLSCAASGFPVNRYSMRWYRQAPGKEREWVAGMSSAGDRSSYE<br>DSVKGRFTISRDDARNTVYLQMNSLKPEDTAVYYCNVNVGFEYWGQ<br>GTQVTVSSPPSFSESGGSRTPEKGFSDREPTRPRPILQRQDDIV<br>QEKRLSRGISHASSSIVSLARSHVSSNGGGGGSNEHLEMPICAFQ<br>LPDLTVYNEDFRSFIERDLIEQSMLVALEQAGRLNWWVSVDPSTSQR<br>LLPLATTGDGNCLLHAASLGMWGFHDRDLMLRKALYALMEKGVEKE<br>ALKRRRWQQTQQNKESGLVYTEDEWQKEWNELIKLASSEPRMHLG<br>TNGANCGVESSEEPVYESLEEFHVFLAHVLRRIIVVADTMLRD<br>SGGEAFAPIPFGGIYLPLEVPASQCHRSPLVLAYDQAHFSALVSME<br>QKENTKEQAVIPLTDSEYKLLPLHFAVDPGKGWEWGKDDSDNVRLA<br>SVILSLEVKLHLLHSYMNWKWIPLSSDAQAPLAQ |
| CFP-P2A-a-<br>YFPnanobody-<br>OTUD1 enDUB     | 267 | MVSKGEELFTGVVPILVELDGDVNGHKFSVSGEGEGDATY GKLTLK<br>FICTTGKLPVPWPPTLVTTLTWGVQCFSRYPDHMKQHDFFKSAMPEG<br>YVQERTIFFKDDGNYKTRAEVKFEGDTLVNRIELKGIDFKEDGNIL<br>GHKLEYNYISHNVYITADKQKNGIKANFKIRHNIEDGSGVQLADHYQ<br>QNTPIGDGPVLLPDNHYLSTQSALS KDPNEKRDMVLLEFVTAAGI<br>TLGMDELYKGSGATNFSLLKQAGDVEENPGPQVQLVESGGALVQPG<br>GSLRLSCAASGFPVNRYSMRWYRQAPGKEREWVAGMSSAGDRSSYE<br>DSVKGRFTISRDDARNTVYLQMNSLKPEDTAVYYCNVNVGFEYWGQ<br>GTQVTVSSDEKLALYLAEVEKQDKYLRQRNKYRFHIIPDGNCLYRA<br>VSKTVYGDQSLHRELREQTVHYIADHLDHFSPLIEGDVGEFI IAAA<br>QDGAWAGYPELLAMGQMLNVNIHLTTGGRLESPTVSTMIHYLGPED<br>SLRPSIWLSWLSNGHYDAVFDHSYPNPEYDNWCKQTQVQRKRDEEL<br>AKSMAISLSKMYIEQNACS                                                                                                                                                                                                                 |
| CFP-P2A-a-<br>YFPnanobody-<br>TRABID<br>enDUB | 268 | MVSKGEELFTGVVPILVELDGDVNGHKFSVSGEGEGDATY GKLTLK<br>FICTTGKLPVPWPPTLVTTLTWGVQCFSRYPDHMKQHDFFKSAMPEG<br>YVQERTIFFKDDGNYKTRAEVKFEGDTLVNRIELKGIDFKEDGNIL<br>GHKLEYNYISHNVYITADKQKNGIKANFKIRHNIEDGSGVQLADHYQ<br>QNTPIGDGPVLLPDNHYLSTQSALS KDPNEKRDMVLLEFVTAAGI<br>TLGMDELYKGSGATNFSLLKQAGDVEENPGPQVQLVESGGALVQPG<br>GSLRLSCAASGFPVNRYSMRWYRQAPGKEREWVAGMSSAGDRSSYE<br>DSVKGRFTISRDDARNTVYLQMNSLKPEDTAVYYCNVNVGFEYWGQ<br>GTQVTVSSLEVDFKKLKQIKNRMKKTDWLFNLACVGVVEGDLAAIE<br>AYKSSGDIARQLTADDEVRLNRPFAFDVGYTLVHLAIRFQRQDML<br>AILLTEVSQQAACIPAMVCPTELTEQIRREIAASLHQRKGFACFYF<br>LTDLVTFITLPADIEDLPPTVQEKLFDEVLD RDVQKELEESPIINW<br>SLELATRLDSRLYALWNRTAGDCLLDSVLQATWGIYDKDSVLRKAL<br>HDSLHDCSHWFYTRWKDWESWYSQSFGHLHFSLREEQWQEDWAFILS<br>LASQPGASLEQTHIFVLAHILRRPIIVYGVKYKYSFRGETLGYTRF                                                                                  |

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|                                                         |     | QGVYLP LLWEQSFCWKSPIALGYTRGHFSALVAMENDGYGNRGAGANLNTDDDDVTITFLPLVDSERKLLHVHFLSAQELGNEEQQEKLLREWLDCCVTEGGVLVAMQKSSRRRNHPLVTQMVEKWLDYRQIRPCTSL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| CFP-P2A-a-YFPnanobody-USP21 enDUB                       | 269 | MVSKGEELFTGVVPILVELDGDVNGHKFSVSGEGEGDATYGKLTCLKFICTTGKLPVPWPPTLVTTTLTWGVQCFSRYPDHMKQHDFFKSAMPEGYVQERTIFFKDDGNYKTRAEVKFEGDTLVNRIELKGIDFKEDGNILGHKLEYNYISHNVYITADKQKNGIKANFKIRHNIEDGQSVQLADHYQQNTPIGDGPVLLPDNHYLSTQSALS KDPNEKRDMVLLFEFVTAAGITLGMDELYKSGGATNFSLLKQAGDVEENPGPQVQLVESGGALVQPGGSLRLSCAASGFPVNRYSMRWYRQAPGKEREWVAGMSSAGDRSSYEDSVKGRFTISRDDARNTVYLMNSLKPEDTAVYYCNVNVGFYWGQGTQVTVSSSDDKMAHHTLLLGSGHVGLRNLGNTCFLNAVLQCLSTTRPLRDFCLRRDFRQEVPGGGRAQELTEAFADVIGALWHPDSCEAVNPTRFRAVFQKYVPSFSGYSQQDAQEFLKLLMERLHLEINRRGRRAPPILANGPVPSPRRGGALLEEPELSDDDRANLMWKRYLEREDSKIVDLFVGQLKSKLCKQACGYRSTTFEVFCDLSLPIPKKGFAGGKVSLRDCFNLFTEKEEELESENAPVCDRCRQKTRSTKKLTQVRFPRILVLHLNRFSAASRGSIKKSSVGVDFPLQRLSLGDFASDKAGSPVYQLYALCNHSGSVHYGHYTALCRCQTGWHVYND SRVSPVSENQVASSEGYVLFYQLMQEPPRCL      |
| CFP-P2A-a-YFPnanobody-OTUD4 enDUB                       | 270 | MVSKGEELFTGVVPILVELDGDVNGHKFSVSGEGEGDATYGKLTCLKFICTTGKLPVPWPPTLVTTTLTWGVQCFSRYPDHMKQHDFFKSAMPEGYVQERTIFFKDDGNYKTRAEVKFEGDTLVNRIELKGIDFKEDGNILGHKLEYNYISHNVYITADKQKNGIKANFKIRHNIEDGQSVQLADHYQQNTPIGDGPVLLPDNHYLSTQSALS KDPNEKRDMVLLFEFVTAAGITLGMDELYKSGGATNFSLLKQAGDVEENPGPQVQLVESGGALVQPGGSLRLSCAASGFPVNRYSMRWYRQAPGKEREWVAGMSSAGDRSSYEDSVKGRFTISRDDARNTVYLMNSLKPEDTAVYYCNVNVGFYWGQGTQVTVSSATPMDAYLRKLGLYRKLVAKDGSCLFRAVAEQVLHSQSRHVEVRMACIHYLRENREKFEAFIEGSFEEYLKRLNPQEWVGQVEISALSLMYRKDFIYREPNVSPSQVTENNPFPEKVLCCFSNGNHYDIVYPIKYKESSAMCQSLLYELLYEKVFKTDVSKIVMELDTLEVADE                                                                                                                                                                                                            |
| CFP-P2A -anti-LCK Kinase targeting binder-Cezanne enDUB | 271 | MVSKGEELFTGVVPILVELDGDVNGHKFSVSGEGEGDATYGKLTCLKFICTTGKLPVPWPPTLVTTTLTWGVQCFSRYPDHMKQHDFFKSAMPEGYVQERTIFFKDDGNYKTRAEVKFEGDTLVNRIELKGIDFKEDGNILGHKLEYNYISHNVYITADKQKNGIKANFKIRHNIEDGQSVQLADHYQQNTPIGDGPVLLPDNHYLSTQSALS KDPNEKRDMVLLFEFVTAAGITLGMDELYKSGGATNFSLLKQAGDVEENPGPGSVSSVPTKLEVVAATPTSLLSISWDAPAVTVLYYLITYGETGDHWSGHQAFEVPGSKSTATISGLKPGVDYITITVYAAESYGESYSPISINRYTPPSFSEGSGGSRTPKEGFS DREPTRPPRPILQRQDDIVQEKRLSRGISHASSSIVSLARSHVSSNGGGGGSNEHPLEMPICAFQLPDLTVYNEDFRSFIERDLIEQSMLVALEQAGRLNWWWVSDPTSQRLPLATTGDGNCLLHAASLG MWGFHDDRDLMLRKALYALMEKGV EKEALKRRRWQQQTQONKESGLVYTEDEWQKEWNELIKLASSEPRMHLGTNGANCGVESSEEPVYESLEEFHVFLAHVLRRIIVVADTMLRDSGGEAFAPIPFGGIYLPLEV PASQCHRSPLVLAYDQAHFSALVSMEQKENTKEQAVIPLTDSEYKLLPLHFAVDPGKGWEWGKDDSDNVRLASVILSLEVKLHLLHSYMNKWIPLSSDAQAPLAQ |
| CFP-P2A -anti-LCK Kinase                                | 272 | MVSKGEELFTGVVPILVELDGDVNGHKFSVSGEGEGDATYGKLTCLKFICTTGKLPVPWPPTLVTTTLTWGVQCFSRYPDHMKQHDFFKSAMPEG                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

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| targeting binder-OTUD1 enDUB                           |     | YVQERTIFFKDDGNYKTRAEVKFEGDTLVNRIELKGIDFKEDGNIL<br>GHKLEYNYISHNVYITADKQKNGIKANFKIRHNIEDGSVQLADHYQ<br>QNTPIGDGPVLLPDNHYLSTQSALS KDPNEKRDMVLLEFVTAAGI<br>TLGMDELYKGSGATNF SLLKQAGDVEENPGPGSVSSVPTKLEVVA<br>TPTSLLISWDAPAVTVLYYLITYGETGDHWSGHQAFEVPGSKSTAT<br>ISGLKPGVDYTTITVYAHAE SYGESYSPISIN YRTDEKLALYLA EVE<br>KQDKYLRQRNKYRFHII PDGNCLYRAVSKTVYGDQSLHRELREQTV<br>HYIADHLDHFSPLIEGDVGEFIIAAAQDGAWAGYPELLAMGQMLNV<br>NIHLTTGGRLESPTVSTMIHYLGPEDSLRPSIWLSWLSNGHYDAVF<br>DHSYPNPEYDNWCKQTQVQQRKDEELAKSMAISLSKMYIEQNACS                                                                                                                                                                                                                                                                                                                                                                                                     |
| CFP-P2A -anti-LCK Kinase targeting binder-TRABID enDUB | 273 | MVSKGEELFTGVVPILVELDGDVNGHKFSVSGEGEGDATY GKLTLK<br>FICTTGKLPVPWPPTLVTTLTWGVQCFSRYPDHMKQHDFFKSAMPEG<br>YVQERTIFFKDDGNYKTRAEVKFEGDTLVNRIELKGIDFKEDGNIL<br>GHKLEYNYISHNVYITADKQKNGIKANFKIRHNIEDGSVQLADHYQ<br>QNTPIGDGPVLLPDNHYLSTQSALS KDPNEKRDMVLLEFVTAAGI<br>TLGMDELYKGSGATNF SLLKQAGDVEENPGPGSVSSVPTKLEVVA<br>TPTSLLISWDAPAVTVLYYLITYGETGDHWSGHQAFEVPGSKSTAT<br>ISGLKPGVDYTTITVYAHAE SYGESYSPISIN YRTLEVDFKKLKQIK<br>NRMKKTDLWFLNACVGVVEGDLAAIEAYKSSGGDIARQLTADDEVRL<br>LNRPSAFDVG YTLVHLAIRFQRQDMLAILLTEVSQQAACIPAMVC<br>PELTEQIRREIAASLHQKRGDFACYFLTDLVTFTLPADIEDLPPTV<br>QEKLFDEVLDRDVQKELEEEESP IINWSLELATRLDSRLYALWNRTA<br>GDCLLDSVLQATWGIYDKDSVLRKALHDSLHDCSHWFYTRWKDWES<br>WYSQSFGHLHFSRLREEQWQEDWAFILSLASQPGASLEQTHIFVLAHI<br>LRRPIIVYGVKYYKSFRTGETLGYTRFQGVYLP LLWEQSFCWKSPIA<br>LGYTRGHFSALVAMENDGYGNRGAGANLNTDDVTITFLPLVD SER<br>KLLHVHFLSAQELGNEEQQEKLLREWLDCCVTEGGVLVAMQKSSRR<br>RNHPLVTQMVEKWLDRYRQIRPCTSL |
| CFP-P2A -anti-LCK Kinase targeting binder-USP21 enDUB  | 274 | MVSKGEELFTGVVPILVELDGDVNGHKFSVSGEGEGDATY GKLTLK<br>FICTTGKLPVPWPPTLVTTLTWGVQCFSRYPDHMKQHDFFKSAMPEG<br>YVQERTIFFKDDGNYKTRAEVKFEGDTLVNRIELKGIDFKEDGNIL<br>GHKLEYNYISHNVYITADKQKNGIKANFKIRHNIEDGSVQLADHYQ<br>QNTPIGDGPVLLPDNHYLSTQSALS KDPNEKRDMVLLEFVTAAGI<br>TLGMDELYKGSGATNF<br>GSVSSVPTKLEVVAATPTSLLISWDAPAVTVLYYLITYGETGDHWS<br>GHQAFEVPGSKSTATISGLKPGVDYTTITVYAHAE SYGESYSPISIN<br>YRTSDDKMAHHTLLLGSGHVGLRNLGNTCFLNAVLQCLSSTRPLRD<br>FCLRRDFRQEVPGGGRAQELTEAFADVIGALWHPDSCEAVNPTRFR<br>AVFQKYVPSFSGYSQQDAQEFLKLLMERLHLEINRRGRRAPPI LAN<br>GPVPSPPRRGGALLEEPELSDDDRANLMWKRYLEREDSKIVDLFVG<br>QLKSKLCQACGYRSTTFEVFCDL SLP I PKKG FAGGKVS LRDCFNL<br>FTKEEELESENAPVCDRCRQKTRSTKKLTVQRFPRILVLHLNRFSA<br>SRGSIKKSSVGVD FPLQRLSLGDFASDKAGSPVYQLYALCNHSGSV<br>HYGHYTALCRCQTGWHVYND SRVSPVSENQVASSEGYVLFYQIMQE<br>PPRCL                                                                                                       |
| CFP-P2A -anti-LCK Kinase targeting binder-OTUD4 enDUB  | 275 | MVSKGEELFTGVVPILVELDGDVNGHKFSVSGEGEGDATY GKLTLK<br>FICTTGKLPVPWPPTLVTTLTWGVQCFSRYPDHMKQHDFFKSAMPEG<br>YVQERTIFFKDDGNYKTRAEVKFEGDTLVNRIELKGIDFKEDGNIL<br>GHKLEYNYISHNVYITADKQKNGIKANFKIRHNIEDGSVQLADHYQ<br>QNTPIGDGPVLLPDNHYLSTQSALS KDPNEKRDMVLLEFVTAAGI<br>TLGMDELYKGSGATNF SLLKQAGDVEENPGPGSVSSVPTKLEVVA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

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|                                                                       |     | TPTSLLISWDAPAVTVLYYLITYGETGDHWSGHQAFEVPGSKSTAT<br>ISGLKPGVDYTTITVYAHAEASYGESYSPISINYRTATPMDAYLRKLG<br>LYRKLVAKDGSCLFRAVAEQVLHSQSRHVEVRMACIHYLRENREKF<br>EAFIEGSFEEYLKRLNPQEWVGQVEISALSMLYRKDFIITYREPNV<br>SPSQVTENNPFKEKVLCLFSNGNHYDIVYPIKYKESSAMCQSLLYEL<br>LYEKVFKTDVSKI VMELDTLEVADE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| CFP-P2A -anti-<br>YES1 Kinase<br>targeting binder-<br>Cezanne enDUB   | 276 | MVSKGEELFTGVVPILVELDGDVNGHKFSVSGEGEGDATYGKLT<br>FICTTGKLPVPWPPTLVTTLTWGVQCFSRYPDHMKQHDFFKSAMPEG<br>YVQERTIFFKDDGNYKTRAEVKFEGDTLVNRIELKGIDFKEDGNIL<br>GHKLEYNYISHNVYITADKQKNGIKANFKIRHNIEDGVSQVLADHYQ<br>QNTPIGDGPVLLPDNHYLSTQSALS KDPNEKRDMVLLFVTAAGI<br>TLGMDELYKSGGATNFSLLKQAGDVEENPGPGSVSSVPTKLEVVA<br>TPTSLLISWDAPAVTVDYFFITYGETGGNSPVQFETVPGSKSTATI<br>SGLKPGVDYTTITVYAWYYYDDEEYMNESPI SINYRTPPSFSEGS<br>GSRTPEKGFSDREPTRPPRPILQRQDDIVQEKRLSRGISHASSSIV<br>SLARSHVSSNGGGGGSNEHPLEMPICAFQLPDLTVYNEDFRSFIER<br>DLIEQSMVLVALEQAGRLNWWVSVDPTSQRLLPLATTGDGNCLLHAA<br>SLGMWGFHDDRDLMLRKALYALMEKGVEKEALKRRWRWQQTQQNKES<br>GLVYTEDEWQKEWNELIKLASSEPRMHLGTNGANCGGVESSEEPVY<br>ESLEEFHVFLAHVLRPIVVVADTMLRDSGGEAFAPIPFGGIYLP<br>LEVPAQCHRSPVLVLAHQAHFSALVSMEQKENTKEQAVIPLTDSE<br>YKLLPLHFAVDPGKGWEWGKDDSDNVRLASVILSLEVKLHLLHSYM<br>NVKWIPLSSDAQAPLAQ |
| CFP-P2A -anti-<br>YES1 Kinase<br>targeting binder-<br>OTUD1 enDUB     | 277 | MVSKGEELFTGVVPILVELDGDVNGHKFSVSGEGEGDATYGKLT<br>FICTTGKLPVPWPPTLVTTLTWGVQCFSRYPDHMKQHDFFKSAMPEG<br>YVQERTIFFKDDGNYKTRAEVKFEGDTLVNRIELKGIDFKEDGNIL<br>GHKLEYNYISHNVYITADKQKNGIKANFKIRHNIEDGVSQVLADHYQ<br>QNTPIGDGPVLLPDNHYLSTQSALS KDPNEKRDMVLLFVTAAGI<br>TLGMDELYKSGGATNFSLLKQAGDVEENPGPGSVSSVPTKLEVVA<br>TPTSLLISWDAPAVTVDYFFITYGETGGNSPVQFETVPGSKSTATI<br>SGLKPGVDYTTITVYAWYYYDDEEYMNESPI SINYRTDEKLALYLA<br>EVEKQDKYLRQRNKYRFHIIPDGNCLYRAVSKTVYGDQSLHRELRE<br>QTVHYIADHLDFHSPLIEGDVGEFIIAAQDGAWAGYPELLAMGQM<br>LNVNIHLTTGGRLESPTVSTMIHYLGPEDSLRPSIWLSWLSNGHYD<br>AVFDHSYPNPEYDNWCKQTQVQRKRDEELAKSMAISLSKMYIEQNA<br>CS                                                                                                                                                                                                                       |
| CFP-P2A -anti-<br>YES1 Kinase<br>targeting binder-<br>TRABID<br>enDUB | 278 | MVSKGEELFTGVVPILVELDGDVNGHKFSVSGEGEGDATYGKLT<br>FICTTGKLPVPWPPTLVTTLTWGVQCFSRYPDHMKQHDFFKSAMPEG<br>YVQERTIFFKDDGNYKTRAEVKFEGDTLVNRIELKGIDFKEDGNIL<br>GHKLEYNYISHNVYITADKQKNGIKANFKIRHNIEDGVSQVLADHYQ<br>QNTPIGDGPVLLPDNHYLSTQSALS KDPNEKRDMVLLFVTAAGI<br>TLGMDELYKSGGATNFSLLKQAGDVEENPGPGSVSSVPTKLEVVA<br>TPTSLLISWDAPAVTVDYFFITYGETGGNSPVQFETVPGSKSTATI<br>SGLKPGVDYTTITVYAWYYYDDEEYMNESPI SINYRTLEVDFKKLK<br>QIKNRMKKTDLWFLNACVGVEGDLAAIEAYKSSGGDIARQLTADE<br>VRLNLRPSAFDVGYTLVHLAIRFQRQDMLAILLTVESQQAACIPA<br>MVCPELTEQIRREIAASLHQKRGDFACYFLTDLVFTFLPADIEDLP<br>PTVQEKLFDEVLD RDVQKELEESPIINWSLELATRLDSRLYALWN<br>RTAGDCLDSVLQATWGIYDKDSVLRKALHDSLHDCSHWFYTRWKD<br>WESWYSQSFGHLHFSLREEQWQEDWAFILSLASQPGASLEQTHIFVL<br>AHILRRPIIVYGVKYKYSFRGETLGYTRFQGVYLLPLWEQSFCWKS                                                                        |

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|                                                                           |     | PIALGYTRGHFSALVAMENDGYGNRGAGANLNTDDDDVTITFLPLVD<br>SERKLLHVHFLSAQELGNEEQQEKLLEWLDCCVTEGGVLVAMQKS<br>SRRRNHPLVTQMVEKWLDTRYRQIRPCTSLS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| CFP-P2A -anti-<br>YES1 Kinase<br>targeting binder-<br>USP21 enDUB         | 279 | MVSKGEELFTGVVPILVELDGDVNGHKFSVSSEGEEDATYGKLT<br>FICTTGKLPVPWPPTLVTTLTWGVQCFSRYPDHMKQHDFFKSAMPEG<br>YVQERTIFFKDDGNYKTRAEVKFEGDTLVNRIELKGIDFKEDGNIL<br>GHKLEYNYISHNVYITADKQKNGIKANFKIRHNIEDGSVQLADHYQ<br>QNTPIGDGPVLLPDNHYLSTQSALS KDPNEKRDMVLLFVTAAGI<br>TLGMDELYKSGGATNFSLLKQAGDVEENPGPGSVSSVPTKLEVAA<br>TPTSLLSWDAPAVTVDYFFITYGETGGNSPVQEFVTPGSKSTATI<br>SGLKPGVDYTTITVYAWYYDDDEYMNNESSPISINYRTSDDKMAHHT<br>LLLGSGHVGLRNLGNTCFLNAVLQCLSSTRPLRDFCLRRDFRQVEP<br>GGGRAQELTEAFADVIGALWHPDSCEAVNPTRFRAVFQKYVPSFSG<br>YSQQDAQEFLKLLMERLHLEINRRGRRAPPI LANGPVPSPPRRGGA<br>LLEPELSDDDRANLMWKRYLEREDSKIIVDLFVGQLKSKLCQACG<br>YRSTTFEVFCDSLPIPKKGFAGGKVSRLRDCFNLFTKEEELESENA<br>PVCDRCRQKTRSTKKLTVQRFPRILVLHLNRFASARGSIKKSSVGV<br>DFPLQRLSLGDFASDKAGSPVYQLYALCNHSGSVHYGHYTALCRCQ<br>TGWHVYNDSRVSPVSENQVASSEGYVLFYQLMQEPPRCL                |
| CFP-P2A -anti-<br>YES1 Kinase<br>targeting binder-<br>OTUD4 enDUB         | 280 | MVSKGEELFTGVVPILVELDGDVNGHKFSVSSEGEEDATYGKLT<br>FICTTGKLPVPWPPTLVTTLTWGVQCFSRYPDHMKQHDFFKSAMPEG<br>YVQERTIFFKDDGNYKTRAEVKFEGDTLVNRIELKGIDFKEDGNIL<br>GHKLEYNYISHNVYITADKQKNGIKANFKIRHNIEDGSVQLADHYQ<br>QNTPIGDGPVLLPDNHYLSTQSALS KDPNEKRDMVLLFVTAAGI<br>TLGMDELYKSGGATNFSLLKQAGDVEENPGPGSVSSVPTKLEVAA<br>TPTSLLSWDAPAVTVDYFFITYGETGGNSPVQEFVTPGSKSTATI<br>SGLKPGVDYTTITVYAWYYDDDEYMNNESSPISINYRTATPMDAYLR<br>KLGLYRKLVAKDGSCLFRAVAEQVLHSQSRHVEVRMACIHYLREN<br>EKFEAFIEGSFEEYLRLENPQEWVGQVEISALSLMYRKDFIYRE<br>PNVSPSQVTENNFPKVLCCFSNGNHYDIVYPIKYKESSAMCQSL<br>YELLYEKVFKTDVSKI VMELDTLEVADE                                                                                                                                                                                                                                       |
| CFP-P2A -anti-<br>Aroua Kinase<br>A targeting<br>binder- Cezanne<br>enDUB | 281 | MVSKGEELFTGVVPILVELDGDVNGHKFSVSSEGEEDATYGKLT<br>FICTTGKLPVPWPPTLVTTLTWGVQCFSRYPDHMKQHDFFKSAMPEG<br>YVQERTIFFKDDGNYKTRAEVKFEGDTLVNRIELKGIDFKEDGNIL<br>GHKLEYNYISHNVYITADKQKNGIKANFKIRHNIEDGSVQLADHYQ<br>QNTPIGDGPVLLPDNHYLSTQSALS KDPNEKRDMVLLFVTAAGI<br>TLGMDELYKSGGATNFSLLKQAGDVEENPGPGSVSSVPTKLEVAA<br>TPTSLLSWDAPAVTVVHYVITYGETGGNSPVQEFVTPGSKSTATI<br>SGLKPGVDYTTITVYIDFYWGSYSPISINYRTPPSFSESGGSRT<br>EKGFSREPTRP RPILQRQDDIVQEKRLSRGISHASSIVSLARS<br>HVSSNGGGGGSNEHPLEMPICAFQLPDLTVYNEDFRSFIERDLIEQ<br>SMLVALEQAGRLNWWVSVDPTSQRLLPLATTGDGNCLLHAASLGMW<br>GFHDRDLMLRKALYALMEKGVEKEALKRRWRWQQTQQNKESGLVYT<br>EDEWQKEWNELIKLASSEPRMHLGTNGANCGGVESEEPVYESLEE<br>FHVFLAHVLR RPVVVADTMLRDSGGEAFAPIPFGGIYLPLEVPA<br>SQCHRSPLVLAYDQAHFSALVSMEQKENTKEQAVIPLTDSEYKLLP<br>LHFAVDPGKGWEWGKDDSDNVRLASVILSLEVKLHLLHSYMNKWI<br>PLSSDAQAPLAQ |
| CFP-P2A -anti-<br>Aroua Kinase<br>A targeting                             | 282 | MVSKGEELFTGVVPILVELDGDVNGHKFSVSSEGEEDATYGKLT<br>FICTTGKLPVPWPPTLVTTLTWGVQCFSRYPDHMKQHDFFKSAMPEG<br>YVQERTIFFKDDGNYKTRAEVKFEGDTLVNRIELKGIDFKEDGNIL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

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| binder- OTUD1<br>enDUB                                                      |     | GHKLEYNYISHNVYITADKQKNGIKANFKIRHNIEDGSVQLADHYQ<br>QNTPIGDGPVLLPDNHYLSTQSALS KDPNEKRDHMLLEFVTAAGI<br>TLGMDELYKSGGATNFSLKQAGDVEENPGPGSVSSVPTKLEVVA<br>TPTSLLSWDAPAVTVVHYVITYGETGGNSPVQFETVPGSKSTATI<br>SGLKPGVDYTITVYAIDFYWGSYSPISINYRTDEKLALYLAEVEKQ<br>DKYLRQRNKYRFHIIIPDGNCLYRAVSKTVYGDQSLHRELREQTVHY<br>IADHLDHFSPLIEGDVGEFIIAAAQDGAWAGYPELLAMGQMLNVNI<br>HLTTGGRLESPTVSTMIHYLGPEDSLRPSIWLSWLSNGHYDAVFDH<br>SYPNPEYDNWCKQTQVQRKRDEELAKSMAISLSKMYIEQNACS                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| CFP-P2A -anti-<br>Aroua Kinase<br>A targeting<br>binder-<br>TRABID<br>enDUB | 283 | MVSKGEELFTGVVPILVELDGDVNGHKFSVS GEGEGDATY GKLTLK<br>FICTTGKLPVPWPPTLVTTLTWGVQCFSRYPDHMKQHDFFKSAMPEG<br>YVQERTIFFKDDGNYKTRAEVKFEGDTLVNRIELKGIDFKEDGNIL<br>GHKLEYNYISHNVYITADKQKNGIKANFKIRHNIEDGSVQLADHYQ<br>QNTPIGDGPVLLPDNHYLSTQSALS KDPNEKRDHMLLEFVTAAGI<br>TLGMDELYKSGGATNFSLKQAGDVEENPGPGSVSSVPTKLEVVA<br>TPTSLLSWDAPAVTVVHYVITYGETGGNSPVQFETVPGSKSTATI<br>SGLKPGVDYTITVYAIDFYWGSYSPISINYRTLEVDFKKLKQIKNR<br>MKKTDWLFNLACVGVVEGDAAIEAYKSSGGDIARQLTADEVRLN<br>RPSAFDVGTYTLVHLAIRFQRQDMLAILLTVESQQAACIPAMVCPE<br>LTEQIRREIAASLHQKGFACFLTDLTFTLTPADIEDLPPTVQE<br>KLFDEVLD RDVQKELEEEESPIINWSLELATRLDSRLYALWNRTAGD<br>CLLDSVLQATWGIYDKDSVLRKALHDSLHDCSHWFYTRWKDWESWY<br>SQSFGHLHFSLREEQWQEDWAFILSLASQPGASLEQTHIFVLAHILR<br>RPIIVYGKYYKSFRTGLGYTRFQGVYLLPWEQSFCKWSPIALG<br>YTRGHFSALVAMENDGYGNRGAGANLNTDDVTITFLPLVDSEKRL<br>LHVHFLSAQELGNEEQQEKLLREWLDCCVTEGGVLVAMQKSSRRRN<br>HPLVTQMVEKWLDRYRQIRPCTSL |
| CFP-P2A -anti-<br>Aroua Kinase<br>A targeting<br>binder- USP21<br>enDUB     | 284 | MVSKGEELFTGVVPILVELDGDVNGHKFSVS GEGEGDATY GKLTLK<br>FICTTGKLPVPWPPTLVTTLTWGVQCFSRYPDHMKQHDFFKSAMPEG<br>YVQERTIFFKDDGNYKTRAEVKFEGDTLVNRIELKGIDFKEDGNIL<br>GHKLEYNYISHNVYITADKQKNGIKANFKIRHNIEDGSVQLADHYQ<br>QNTPIGDGPVLLPDNHYLSTQSALS KDPNEKRDHMLLEFVTAAGI<br>TLGMDELYKSGGATNFSLKQAGDVEENPGPGSVSSVPTKLEVVA<br>TPTSLLSWDAPAVTVVHYVITYGETGGNSPVQFETVPGSKSTATI<br>SGLKPGVDYTITVYAIDFYWGSYSPISINYRTSDDKMAHHTLLLS<br>GHVGLRNLGNCTFLNAVLQCLSSTRPLRDFCLRRDFRQEVPGGGR<br>QELTEAFADVIGALWHPDSCEAVNPTRFRAVFQKYVPSFSGYSQQD<br>AQEFLKLLMERLHLEINRRGRRAPPI LANGVPVSPPRRGALLEEP<br>ELSDDDRANLMWKRYLEREDSKIVDLFVGLKSKCLKCQACGYRSTT<br>FEVFCDSLPIPKKGFAGGKVSRLDCFNLFTEKEEELSENAPVCDR<br>CRQKTRSTKKLTVQRFPRIILVLHLNRFSSASRGSIKKSSVGVDFFLQ<br>RLSLGDFASDKAGSPVYQLYALCNHSGSVHYGHYTALCQCQTGWVH<br>YNDSRVSPVSENQVASSEGYVLFYQLMQEPPRCL                                                                                      |
| CFP-P2A -anti-<br>Aroua Kinase<br>A targeting<br>binder- OTUD4<br>enDUB     | 285 | MVSKGEELFTGVVPILVELDGDVNGHKFSVS GEGEGDATY GKLTLK<br>FICTTGKLPVPWPPTLVTTLTWGVQCFSRYPDHMKQHDFFKSAMPEG<br>YVQERTIFFKDDGNYKTRAEVKFEGDTLVNRIELKGIDFKEDGNIL<br>GHKLEYNYISHNVYITADKQKNGIKANFKIRHNIEDGSVQLADHYQ<br>QNTPIGDGPVLLPDNHYLSTQSALS KDPNEKRDHMLLEFVTAAGI<br>TLGMDELYKSGGATNFSLKQAGDVEENPGPGSVSSVPTKLEVVA<br>TPTSLLSWDAPAVTVVHYVITYGETGGNSPVQFETVPGSKSTATI<br>SGLKPGVDYTITVYAIDFYWGSYSPISINYRTATPMDAYLRKGLY                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |



|  |  |                                                                                                                                                                                |
|--|--|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  |  | RKLVAKDGSCLFRAVAEQVLHSQSRHVEVRMACIHYLRENREKFEA<br>FIEGSFEEYLKRLLENPQEWVGQVEISALSLMYRKDFIIYREPNVSP<br>SQVTENNFPKVLCLCFSGNHYDIVYPIKYKESSAMCQSLLYELLY<br>EKVFKTDVSKI VMELDTLEVADE |
|--|--|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

## 6.2 Example 2. Testing of Targeted Engineered Deubiquitinases

[00310] To demonstrate upregulation of a target protein in the context of a specific targeting enDUB the following experiments will be performed.

Schematic constructs used:

- Control experiment using non-targeting enDUB fusion
  - Target – YFP- P2A – mCherry
  - CFP- P2A- enDUB (nontargeting control enDUB)
- Test constructs for up-regulation:
  - Target- YFP-P2A-mCherry
  - CFP-P2A-a-YFPnanobody-enDUB
- Or specific targeting enDUB fusion composed of
  - CFP-P2A -anti-targeting binder-enDUB

[00311] Co-transfection of both plasmids carrying the YFP tagged target protein together with the enDUB fused to a target binding protein into HEK cells will be performed. A control construct carrying the enDUB in the absence of the targeting binder will also be co-transfected together with the labeled target protein. After 24-48 hours the transfected cells will be analyzed by FACS or upregulation over the control. The mCherry signal on the target protein will be used to normalize for transfection efficiency while the CFP signal will be used to normalize for the transfection efficiency of the enDUB constructs. The YFP fused to the target protein is the read-out for target gene expression and will be plotted vs the signal in the control transfection. Relative increase in the YFP fluorescence over control will demonstrate upregulation in the presence of the enDUB.

## 6.3 Example 3. Screening Assay for Testing Fusion Proteins

[00312] The following example describes an assay to analyze the ability of a targeted engineered deubiquitinase (enDub) (e.g., an enDub described herein) to increase expression of a target protein. Generally, the assay involves tagging the target protein with a fluorescent tag (e.g., NanoLuciferase (NLuc)) and an alfa-tag ( $\alpha$ -Tag); and tagging a fusion protein of the enDub and

an anti-alfa Tag nanobody with a different fluorescent tag (e.g., Firefly Luciferase (FLuc)) through a cleavable linker. The use of two different fluorescent tags enables normalization of the signal to compensate for variation in transfection/expression, as the second fluorescent tag is rapidly cleaved from the enDub-anti-alfa tag fusion protein inside the cell through cleavage of the cleavable linker. FIG. 2 provides a general schematic of the cellular aspects of the assay. The protocol, including materials and methods is described below.

**[00313]** CHO-K1 cells were digested with 0.25% (w/v) Trypsin-EDTA, at 37°C, for 5min. Complete medium was added for the CHO-K1 cell cultures to stop the digestion. The CHO-K1 cells were centrifuges at 800 rpm for 5 minutes. After centrifugation, the supernatant was discarded and the CHO-K1 cells were resuspend in 2 mL culture medium and counted.  $10^6$  CHO-K1 cells were electroporated under 440V with 0.5ug of a plasmid encoding the target protein tagged with NLuc and alfa-tag, and 1ug of a plasmid encoding a) enDub-anti-alfa tag nanobody-FLuc fusion protein (experimental), b) the enDub (control), or the anti-alfa tag nanobody (control).  $5E+4$  cells/well were placed in in 24 well plates and cultured for 24h, at 37°C, 5% CO<sub>2</sub>. The cells were digested with 0.25% (w/v) Trypsin-EDTA, at 37°C for 5min. Complete medium was added to the culture to stop the digestion and the cells were counted for use in NanoGlo® Dual Luciferase® Assay (Promega), which enables detection of FLuc and NLuc® in a single sample. The NanoGlo® Dual Luciferase® Assay was carried out according to manufacturer's instructions (Promega, Nano-Glo® Dual-Luciferase® Reporter Assay Technical Manual #TM426). Briefly,  $1E+4$  cells/well were placed in 96 well black plates and cultured for 24h, at 37°C, 5% CO<sub>2</sub>. The plates were removed from the incubator and allowed to equilibrate to room temperature. The samples were modified as needed to have a starting volume of 80µl per well. All sample wells were injected with 80µl of ONE-Glo™ EX Reagent and incubated for 3 minutes. The firefly luminescence was read in all sample wells using a 1-second integration time. All sample wells were injected with 80µl of NanoDLR™ Stop & Glo® Reagent; and incubated for 5 minutes. The NanoLuc® luminescence of all sample wells was read using a 1-second integration time. The dispensing lines were cleaned according to manufacturer's instructions (Nano-Glo® Dual-Luciferase® Reporter Assay Technical Manual #TM426.) and the data analyzed.

**[00314]** The amino acid sequence of the components of the fusion proteins used in the assay are detailed in Table 9 below.

**Table 9.** Amino acid sequence of components of test fusion proteins

| Description                          |                    | SEQ ID NO | Amino Acid Sequence                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|--------------------------------------|--------------------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Fluorescent Protein                  | NanoLuc            | 385       | VFTLEDFVGDWRQTAGYNLDQVLEQGGVSSSLFQ<br>NLGVSVTPPIQRIVLSGENGLKIDIHVIIPYEGL<br>SGDQMGQIEKIFKVVPVDDHHFKVILHYGTLV<br>IDGVTPNMIDYFGRPYEGIAVFDGKKITVTGTL<br>WNGNKIIDERLINPDGSLFRVTINGVTGWRLC<br>ERILA                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                      | Firefly Luciferase | 386       | MEDAKNIKKGPAPFFYPLEDGTAGEQLHKAMKRY<br>ALVPGTIAFTDAHIEVDITYAEYFEMSVRLAEA<br>MKRYGLNTNHRIVVCSNSLQFFMPVLGALFIG<br>VAVAPANDIYNERELLSMGSISQPTVVFVSKKG<br>LQKILNVQKKLP I I Q K I I I M D S K T D Y Q G F Q S M Y<br>TFVTSHLPFGFNEYDFVPESFDRDKTIALIMNS<br>SGSTGLPKGVALPHRTACVRFSHARDPIFGNQI<br>IPDTAILSVPFHHGFGMFTTLGYLICGFRVVL<br>MYRFEELFLRSLQDYKIQSALLVPTLFSFFAK<br>STLIDKYDLSNLHEIASGGAPLSKEVGEAVAKR<br>FHLPGIRQGYGLTETTSAILITPEGDDKPGAVG<br>KVVPFFEAKVVDLDTGKTLGVNQRGELCVRGPM<br>IMSGYVNNPEATNALIDKGWLHSGDIAYWDED<br>EHFFIVDRKSLIKYQYQVAPAELESILLQHP<br>NIFDAGVAGLPDDDAGELPAVVVLEHGKTMTE<br>KEIVDYVASQVTTAKKLRGGVVFVDEVPKGLTG<br>KLDARKIREILIKAKKGGKIAVTRLK |
| Alfa Tag                             |                    | 387       | PSRLEELRRRLTEP                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| P2A                                  |                    | 388       | GSGATNFSLLKQAGDVEENPGP                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Cezanne (Exemplary Catalytic Domain) |                    | 389       | PPSFSESGGSRTPEKGFSDREPTRPPRPILQR<br>QDDIVQEKRLSRGISHASSIVSLARSHVSSNG<br>GGGGSNEHPLEMPICAFQLPDLTVYNEDFRSFI<br>ERDLIEQSMLVALEQAGRLNWWWVSDPTSQRLL<br>PLATTGDGNCLLHAASLGMWGFHDRDLMLRKAL<br>YALMEKGVEKEALKRRRWQQTQONKESGLVYT<br>EDEWQKEWNELIKLASSEPRMHLGTNGANCGGV<br>ESSEEPVYESLEEFHVFLAHVLRPIVVVADT<br>MLRDSGGEAFAPIPFGGIYLPLEVPASQCHRSP<br>LVLAYDQAHFSALVSMEQKENTKEQAVIPLTDS<br>EYKLLPLHFAVDPGKGWEWGKDDSDNVRLASVI<br>LSLEVKLHLLHSYMNVKWIPLSSDAQAPLAQ                                                                                                                                                                                                         |

[00315] The amino acid sequence of exemplary target fusion proteins comprising a target protein, NLuc, and the alfa tag are detailed in Table 10 below.

**Table 10.** Amino Acid Sequence of exemplary Target Protein – NLuc – Alfa Tag Fusion Proteins

| Test Protein                       | SEQ ID NO | Amino Acid Sequence                                                                                                                                                                                                                              |
|------------------------------------|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Shank3-nanoluc-<br>alfa-tag-fusion | 390       | MDGPGASAVVVRVGIPDLQQTCKLRDPAAPVWAAKQRVLCALNH<br>SLQDALNYGLFQPPSRGRAGKFLDEERLLQEYPPNLDTPLPYLEF<br>RYKRRVYAQNLIIDKQFAKLHTKANLKKFMDYVQLHSTDQKVARLL<br>DKGLDPNFHDPDSGECPLSLAAQLDNATDLLKVLKNGGAHLDFRT<br>RDGLTAVHCATRQRNAAALTLLDLGASPDYKDSRGLTPLYHSAL |

|                                   |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-----------------------------------|-----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                   |     | GGGDALCCCELLLDHHAQLGITDENGWQEIHQACRFGHVQHLEHLL<br>FYGADMGAQNASGNTALHICALYNQESCARVLLFRGANRDVRNYN<br>SQTAFQVAIIAGNFELAEVIKTHKDSDVVPFRETPSYAKRRRLAG<br>PSGLASPRPLQRSASDINLKGEAQPAASPGPSLRSPLHQLLLQRL<br>QEEKDRDRDADQESNISGPLAGRAGQSKISPSGPGGPGPAPGPGP<br>APPAPPAPPGRPKRKLYSAVPGRKFIIVKAHSPQGEGEIPLHRG<br>EAVKVL SIGEGGFWEFTVKGRTGWFPADCVVEEVQMRQHDTRPETR<br>EDRTKRLFRHYTVGSYDSLTSYSDYVIDDKVAVLQKRDHEGFGFV<br>LRGAKAETPIEEFTPTPAFPALQYLESVDVEGVAVRAGLRGTGDFL<br>IEVNGVNVVKVGHKQVVALIRQGGNRLVMKVSVTRKPEEDGARR<br>RAPPPPKRAPSTTLTLRSKSMATAELEELASIRRRKGEKLDEMLAA<br>AAEPTLRPDIADADSRAATVKQRPTSRRITPAEISSLFERQGLPG<br>PEKLPGSLRKGIPTKSVGEDEKLASLLEGRFPRSTSMQDPVREG<br>RGIPPPPTAPPPPPAPYYFDSGPPPAFSPPPPPGRAYDTVRSSF<br>KPGLEARLGAGAAGLYEPGAALGPLPYPERQKRARSMIILQDSAP<br>ESGDAPRPPPAATPPERPKRRPRPPGPDSPYANLGAFSASLFAPS<br>KPQRRKSPLVKQLQVEDAQERAALAVGSPGPGGGSFAREPSPTH<br>GPRPGGLDYGAGDGPGLAFGGPGPAKDRRLEERRRSTVFLSVGAI<br>EGSAPGADLPSLQPSRSIDERLLGTGPTAGRDLLLSPVSAKPL<br>VSGPSLGPSTFIHPLTGKPLDPSSPLALALAARERALSQAPS<br>RSPTPVHSPDADRPGLFVDVQARDPERGSLASPAFSPRSPAWIP<br>VPARREAEKVPREERKSPEDKKSMILSVLDTSLQRPAGLIVVHAT<br>SNGQEPSRLGGAEERPGTPELAPAPMQSAVAEPLSPRAQPPG<br>GTPADAGPGQGSSEEEPELVFAVNLPPAQLSSSDEETREELARIG<br>LVPPPEEFANGVLLATPLAGPGSPPTVPSPASGKPSSEPPPAPE<br>SAADSGVEEADTRSSSDPHLETTSTISTVSSMSTLSSESGLTDT<br>HTSFADGHTFLLKPPVPPKPKLKSPGKGPVTRDPLLKQSSDS<br>ELMAQQHHAASAGLASAAGPARPRYLFQRRSKLWGDVPSRGLPG<br>PEDDKPTVISELSSRLQQLNKDTRSLGEEPVGGLGSLDPAKKSP<br>IAAARLFSSLGELSSISAQRSPGGPGGGASYSVRPSGRYPVARRA<br>PSPVKPASLERVEGLGAGAGGAGRPFGLTPTTILKSSSLSPHEP<br>KEVRFVVRSVSARSRSPPSPPLSPASGPGPGAPGPRRPFQKPL<br>QLWSKFDVGDWLES IHLGEHRDRFEDHEIEGAHLPALTKDDFVEL<br>GVTRVGHMNIERALRQLDGSKVPVFTLEDFVGDWRQTAGYNLDQ<br>VLEQGGVSSLFQNLGVSVTPIQRIVLSGENGLKIDIHV IIPYEG<br>SGDQMGQIEKIFKVVPVDDHHFKVILHYGTLVIDGVTN MIDYF<br>GRPYEGIAVFDGKKITVTGTLWNGNKIIDERLINPDGSLFRVTI<br>NGVTGWRLCERILAGGGGSPSRLEEEELRRRLTEP |
| CDKL5-nanoluc-<br>alfa-tag-fusion | 391 | MKIPNIGNVMNKFEILGVVGEAYGVVLKCRHKETHEIVAIKKFK<br>DSEENEEVKETTLRELKMLRTLKQENIVELKEAFRRRGKLYLVFE<br>YVEKNMLELLEEMPNGVPPEKVKSYIYQLIKAIHWCHKNDIVHRD<br>IKPENLLISHNDVLKLCDFGFARNLSEGNNANYTEYVATRWRSP<br>ELLGAPYGKSDMWSVGCILGELSDGQPLFPGESEIDQLFTIQK<br>VLGPLPSEQMKLFYSNPRFHGLRFPVNHQPQSLERRYLGLNSVL<br>LDLMKNLLKLDPADRYLTEQCLNHPTFQTQRLLDSPRSRKRKP<br>YHVESSTLSNRNQAGKSTALQSHHRSNSKDIQNLSVGLPRADEGL<br>PANESFLNGNLGASLSPLHTKTYQASSQPGSTSKDLTNNNIPHL<br>LSPKEAKSKTEFDNFIDPKPSEGPGTKYLSNSRSQQNRHSFMES<br>SQSKAGTLQPNKQSRHSYIDTIPQSSRSPSYRTKAKSHGALS<br>KSVSNLSEARAQIAEPSTSRYPSSCLDLNSPTSPTPTRHSDTRT<br>LLSPSGRNNRNEGTLDSRRTTTRHSTMEELKLPEHMDSSHSHSL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

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|------------------------------------|-----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                    |     | SAPHESFSYGLGYTSPFSSQQRPHRHSMYVTRDKVRAKGLDGSL<br>IGQGMAARANSLQLLSPQPGEQLPPEMTVARSSVKETSREGTSSF<br>HTRQKSEGGVYHDPHSDDGTAPEKNRHLNDPVPRRVGSFYRVPS<br>PRPDNSFHENNVSTRVSSLPSESSSGTNHRSKQPAFDPWKSPENI<br>SHSEQLKEKEKQGFRRSMKKKKKKSQTVPNSDSPDLLTLQKSIHS<br>ASTPSSRPKEWRPEKISDLQTQSQPLKSLRKLHLSSASNHPASS<br>DPRFQPLTAQQTKNSEIRIHPLSQASGGSSNIRQEPAPKGRPA<br>LQLPGQMDPGWHVSSVTRSATGEPSEQLGAKSGPNGHPYNRTN<br>RSRMPNLNDLKETALKVPVFTLEDFVGDWRQTAGYNLDQVLEQGG<br>VSSLFQNLGVSVTPIQIRIVLSGENGLKIDIHVPIPYEGLSGDQMG<br>QIEKIFKVVPVDDHHFKVILHYGTLVIDGVTNPMIDYFGRPYEG<br>IAVFDGKKITVTGTLWNGNKIIDERLINPDGSLLFRVTINGVTGW<br>RLCERILAGGGGSPSRLEEELRRRLTEP                                                                                                                                                                                                                                                                                                                                                                        |
| STXBP1-nanoluc-<br>alfa-tag-fusion | 392 | MAPIGLKAVVGEKIMHDVIKKVKKKGWVVLVVDQLSMRMLSSCC<br>KMTDIMTEGITIVEDINKRREPLPSLEAVYLITPSEKSVHSLISD<br>FKDPPTAKYRAAHVFFTDSCPDALFNELVKSRAAKVIKTLTEINI<br>AFLPYESQVYSLDSADSFQSFYSPHKAQMKNPILERLAEQIATLC<br>ATLKEYPAVRYRGEYKDNALLAQLIQDKLDAYKADDPMTGEGPDK<br>ARSQLLILDRGFDPSSPVLHELTFQAMSYDLLPIENDVYKYETSG<br>IGEARVKEVLLDEDDDLWIALRHKHIAEVSQEVTRSLKDFSSSKR<br>MNTGEKTTMRDLSQMLKKMPQYQKELSKYSTHLHLAEDCMKHYQG<br>TVDKLCRVEQDLAMGTDAEGEKIKDPMRAIVPILLDANVSTYDKI<br>RIILLYIFLKNGITENLNKLIQHAQIPPEDSEIITNMAHLGVPI<br>VTDSTLRRRSKPERKERISEQTYQLSRWTPIIKDIMEDTIEDKLD<br>TKHYPYISTRSSASFSTTAVSARYGHWKKNKAPGEYRSGPRLIIF<br>ILGGVSLNEMRCAYEVTQANGKWEVLIGSTHILTPQKLLDTLKKL<br>NKTDEEISSKVPVFTLEDFVGDWRQTAGYNLDQVLEQGGVSSLFQ<br>NLGVSVTPIQIRIVLSGENGLKIDIHVPIPYEGLSGDQMGQIEKIF<br>KVVPVDDHHFKVILHYGTLVIDGVTNPMIDYFGRPYEGIAVFDG<br>KKITVTGTLWNGNKIIDERLINPDGSLLFRVTINGVTGWRLCERI<br>LAGGGGSPSRLEEELRRRLTEP                                                                                                                    |
| DNM1-nanoluc-<br>alfa-tag-fusion   | 393 | MGNRGMEDLIPLVNRLQDAFSAIGQNADLDLPQIAVVGQSAGKS<br>SVLENFVGRDFLPRGSGIVTRRPLVLQLVNATTEYAEFLHCKGKK<br>FTDFEEVRLEIEAETDRVTGTNKGISPVPINLRVYSPHVLNLTIV<br>DLPGMTKVPVGDQPPDIEFQIRDMLMQFVTKENCLILAVSPANS<br>LANSDALKVAKEVDPPGQRTIGVITKLDLMDGTDARDVLENKLL<br>PLRRGYIGVVNRSQKDIDGKKDITAALAAERKFFLSHPYSYRHLAD<br>RMGTPYLQKVLNQQLTNHIRDTLPGLRNKLQSLLSIEKEVEEYK<br>NFRPDDPARKTKALLQMVQQFAVDFEKRIEGSGDQIDTYELSGGA<br>RINRIFHERFPFELVKMEFDEKELRREISYAIKNIHGIRTGLFTP<br>DMAFETIVKKQVKKIREPCLKCVDMVISLISTVRQCTKKLQQYP<br>RLREEMERIVTTHIREREGRTKEQVMLLIDIELAYMNTNHEDFIG<br>FANAQQRSNQMKNKKTSGNQDEILVIRKGWLTINNIGIMKGSKE<br>YWFVLTAENLSWKDDEEKEKKYMLSVDNLKLKRDVEKGFMSKHI<br>FALFNTEQRNVYKDYRQLELACETQEEVDSWKASFLRAGVYPERV<br>GDKEKASETEENGSDSFMHSMDPQLERQVETIRNLVDSYMAIVNK<br>TVRDLMPKTIMHLMINNTKEFIFSELLANLYSCGDQNTLMEEAE<br>QAQRDEMLRMYHALKEALSIIIGDINTTTVSTPMPPPVDDSWLQV<br>QSVPAARRSPTSSPTPQRRAPAVPPARPGSRGPAPGPPAGSALG<br>GAPPVPSRPGASDPDFGPPPQVPSRPNRAPPGVPSRSGQASPSRP<br>ESPRPPFDLKVPVFTLEDFVGDWRQTAGYNLDQVLEQGGVSSLFQ |

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|------------------------------------------|-----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                          |     | NLGVSVTPIQRIVLSGENGLKIDIHV IIPYEGLSGDQMGQIEKIF<br>KVVYPVDDHHFKVILHYGTLVIDGVTPNMIDYFGRPYEGIAVFDG<br>KKITVTGTLWNGNKI IIDERLINPDGSLLFRVTINGVTGWRLCERI<br>LAGGGGSPSRLEEEELRRRLTEP                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| KIF1A-nanoluc-<br>alfa-tag-fusion        | 394 | MAGASVKVAVRVRPFNSREMSRDSKCI IQMSGSTTTIVNPKQPKPKE<br>TPKSFSFDYSYWSHTSPEDINYASQKQVYRDIGEEMLQHAFEGYN<br>VCIFAYGQTGAGKSYTMMGKQEKDQQGIIPQLCEDLFSRINDTTN<br>DNMSYSVEVSYMEIYCERVRDLLNPKNKGNLRVREHPPLGPYVED<br>LSKLAVTSYNDIQDLMDSGNKARTVAATNMNETSSRSHAVFNII F<br>TQKRHDAETNITTEKVS KISLVDLAGSERADSTGAKGTRLKEGAN<br>INKSLTTLGKVISALAE MDSGPNKNKKKKKTDFIPYRDSVLTWLL<br>RENLGGNSRTAMVAALSPADINYDET LSTLRYADRAKQIRCNAVI<br>NEDPNNKLIRELKDEVTRLRDLLYAQGLGDITDMTNALVGMSPSS<br>SLSALSSRAASVSSLHERILFAPGSEEAIERLKETEKI I AELNET<br>WEEKLRRTAIRMEREALLAEMGVAMREDGGT LGVFSPPKTPHLV<br>NLNEDPLMSECLLYYIKDGITRVGREDGERRQDIVLSGHFIKEEH<br>CVFRSDSRGGSEAVVTLEPCEGADTYVNGKKVTEPSILRSGNRI I<br>MGKSHVFRFNHPEQARQERERTPCAETPAEPVDWAFQAQRELLEKQ<br>GIDMKQEMEQR LQLELEDQYRREREEATYLL EQQLDYESKLEALQ<br>KQMDSRYYPEVNEEEEEPEDEVQWTERECELALWAFRKWKWYQFT<br>SLRDLLWGN AIFLKEANAISVELKKKVQFQVLLTDTLYSPLPPD<br>LLPPEAAKDRETRPFPR TIVAVEVQDQKNGATHYWTLEKLQRDL<br>LMREMYDRAAEVPSSVIEDCDNVVTGGDPFYDRFPWFRLVGRAFV<br>YLSNLLYPVPLVHRVAIVSEKGEVKGFRLVAVQAI SADEEAPDYG<br>SGVRQSGTAKISFDDQHFEKFQSESCPVVGMSRSGTSQEELRIVE<br>GQGQGADVGP SAEVNNTCSAVPPEGLLLDSSEKAALDGPLDAA<br>LDHLRLGNTFTFRVTVLQASSISAEYADIFCQFNFIHRHDEAFST<br>EPLKNTGRGPPLGFYHVQNI AVEVTKSFIEYIKSQPIVFEVFGHY<br>QQHPFPPLCKDVLSPLRPSRRHFPRVMPLSKPVPATKLSTLTRPC<br>PGPCHCKYDLLVYFEICELEANGDYIPAVVDHRGGMPMCGTFL LH<br>QGIQRRITVTLLHETGSHIRWKEVREL VVGRI RNTPETDESLIDP<br>NILSLNILSSGYIHPAQDDRTFYQFEAAWDSSMHN SLLLNRVT<br>PYREKIYMTLSAYIEMENCTQPAVVTKDFCMVFYSRDAKL PASRSIR<br>NLFGSGSLRASESNRV TGVYELSLCHVADAGSPGMQRRRRRVLD<br>T SVAYVRGEENLAGWRPRSDSLILDHQWELEKLSLLQEVEKTRHYL<br>LLREKLETAQRVPPEALSPAFSEDSHSGSSASSPLSAEGRPSP<br>LEAPNERQRELAVKCLRLLTHTFNREYTHSHVCVSASESKLSEMS<br>VTLLRDPSMSPLGVATLTPSSTCPSLVEGRYGATDLRTPQPCSRP<br>ASPEPELLPEADSKKLPSPARATETDKEPQRLLPDIQEIRVSP I<br>VSKKGYLHFLEPHTSGWARRFVVVRRPYAYMYNSDKDTVERFVLN<br>LATAQVEYSEDQQAMLKTPNTFAVCTEHRGILLQAASDKMDHDL<br>WLYAFNPLLAGTIRSKLSRRRSAQMRVKVPVFTLEDFVGDWRQTAGY<br>NLDQVLEQGGVSSLFQNLGVSVTPIQRIVLSGENGLKIDIHV IIP<br>YEGLSGDQMGQIEKIFKVVYPVDDHHFKVILHYGTLVIDGVTPNM<br>IDYFGRPYEGIAVFDGKKITVTGTLWNGNKI IIDERLINPDGSLLF<br>RVTINGVTGWRLCERILAGGGGSPSRLEEEELRRRLTEP |
| SYNGAP1 -<br>nanoluc-alfa-tag-<br>fusion | 395 | MSRSRASIHRSIPAMSYAPFRDVRGPSMHRTQYVHSPYDRPGWN<br>PRFCIIISGNQLMLDEDEIHPLLI RDRSESSRNKLLRRTVSVPV<br>EGRPHGEHEYHLGRSRRKSVPGGKQYSMEGAPAAPFRPSQGFLSR<br>RLKSSIKRTKSQPKLDRTSSFRQILPRFRSADHDRARLMQSFKES                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

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|-----------------------------------|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                   |     | <p>HSHESSLSPSSAAEALELNLEDEDSIIKPVHSSILGQEFCEVTTS<br/>SGTKCFACRSAAERDKWIENLQRAVKPNKDNSRRVDNVKLWII<br/>ARELPPKKRYCYCELCLDDMLYARTTSKPRSASGDTVFWGEHFEFN<br/>NLPVAVRALRLHLYRDSDDKKRKKDKAGYVGLVTVPVATLAGRHFE<br/>QWYPVTLPTGSGGSGGMGSGGGGSGGGSGGKGKGGCPAVRLKAR<br/>YQTMSSILPMELYKEFAEYVTNHYRMLCAVLEPALNVKGKEEVASA<br/>LVHILQSTGKAKDFLSDMAMSEVDRFMEREHLIFRENTLATKAIE<br/>EYMRLIGQKYLKDAIGEFIRALYESEENCEVDPIKCTASSLAHQ<br/>ANLRMCCELALCKVVNSHCVPRELKEVFASWRLRCAERGREDIA<br/>DRLISASLFLRFLCPAIMPSPSLFGLMQEYYPDEQTSRTLTTLIAKVI<br/>QNLANFSKFTSKEDFLGFMNEFLELEWGSMMQQLYEISNLDTLTN<br/>SSSFEGYIDLGRELSTLHALLWEVLPQLSKEALLKLGPLPRLND<br/>ISTALRNPNIQRQPSRQSERPRPQPVVLRGPSAEMQGYMMRDLS<br/>SIDLQSEFMARGLNSSMDMARLPSPTEKPPPPPPGGGKDLFYVSR<br/>PPLARSSPAYCTSSSDITEPEQKMLSVNKSVMMLDLQGDGPGGRL<br/>NSSSVSNLAAVGDLLHSSQASLTAALGLRPAPAGRLSQSGSSIT<br/>AAGMRLSQMGVTTDGVPAQQLRIPLSFQNPLFHMAADGPGPPGGH<br/>GGGGGHGPPSSHHHHHHHHHRGGEPPGDTFAPFHGYSKSEDLSS<br/>GVPKPPAASILHSHSYSDEFGPSGTDFTRRQLSLQDNLQHMLSPP<br/>QITIGPQRPAPSGPGGGSGGGSGGGGGGQPPPLQRGKSQQLTVSA<br/>AQKPRPSSGNLLQSPEPSYGPAPRQQSLSKEGSI GGSGGSGGGG<br/>GGGLKPSITKQHSQTPSTLNPTMPASERTVAWVSNMPLHSADIES<br/>AHIEREEYKLKEYSKSMDESRLDRVKEYEEEIHSLKERLHMSNRK<br/>LEEYERRLLSQEEQTSKILMQYQARLEQSEKRLRQQQAEDSQIK<br/>SIIGRLMLVEEELRRDHPAMAEPLPEPKRLLDAQERQLPPLGPT<br/>NPRVTLAPPWNGLAPPAPPPPRLOITENGEFRNTADHKVPVFTL<br/>EDFVGDWRTAGYNLDQVLEQGGVSSLFQNLGVSVTPIQIRIVLSG<br/>ENGLKIDIHVIIPEYGLSGDQMGQIEKIFKVVPVDDHDFKVLH<br/>YGTLVIDGVTNPMIDYFGRPYEGIAVFDGKKITVTGTLWNGNKII<br/>DERLINPDGSLLFRVTINGVTGWRLCERILAGGGGSPSRLEEELR<br/>RRLTEP</p> |
| PYDC2-nanoluc-<br>alfa-tag-fusion | 396 | <p>MASSAELDFNLQALLEQLSQDELSKFKSLIRTISLGKELQTVPQT<br/>EVDKANGKQLVEIFTSHSCSYWAGMAAIQVFEKMNQTHLSGRADE<br/>HCVMPPPKVPVFTLEDFVGDWRTAGYNLDQVLEQGGVSSLFQNL<br/>GVSVTPIQIRIVLSGENGLKIDIHVIIPEYGLSGDQMGQIEKIFKV<br/>VYPVDDHDFKVLHYGTLVIDGVTNPMIDYFGRPYEGIAVFDGKK<br/>ITVTGTLWNGNKIIDERLINPDGSLLFRVTINGVTGWRLCERILA<br/>GGGGSPSRLEEELRRRLTEP</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| CSTB-nanoluc-<br>alfa-tag-fusion  | 397 | <p>MMCGAPSATQPATAETQHIADQVRSQLEEKENKKFPVFKAVSFKS<br/>QVVAGTNYFIKVHVGDEDFVHLRVFQSLPHENKPLTSLNYQTNKA<br/>KHDELTYFKVPVFTLEDFVGDWRTAGYNLDQVLEQGGVSSLFQNL<br/>LGVSVTPIQIRIVLSGENGLKIDIHVIIPEYGLSGDQMGQIEKIFK<br/>VVYPVDDHDFKVLHYGTLVIDGVTNPMIDYFGRPYEGIAVFDGK<br/>KITVTGTLWNGNKIIDERLINPDGSLLFRVTINGVTGWRLCERIL<br/>AGGGGSPSRLEEELRRRLTEP</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| PCBD1-nanoluc-<br>alfa-tag-fusion | 398 | <p>MAGKAHRLSAEERDQLLPNLRVAVGWNELEGRDAIFKQFHFKDFNR<br/>AFGFMTRVALQAEKLDHHPWFNVYNKVHITLSTHECAGLSERDI<br/>NLASFIEQVAVSMTKVVPVFTLEDFVGDWRTAGYNLDQVLEQGGV<br/>SSLFQNLGVSVTPIQIRIVLSGENGLKIDIHVIIPEYGLSGDQMGQ<br/>IEKIFKVVPVDDHDFKVLHYGTLVIDGVTNPMIDYFGRPYEGI</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

|  |  |                                                                            |
|--|--|----------------------------------------------------------------------------|
|  |  | AVFDGKKITVTGTLWNGNKIIDERLINPDGSLFRVTINGVTGWR<br>LCERILAGGGGSPSRLEELRRRLTEP |
|--|--|----------------------------------------------------------------------------|

[00316] The amino acid sequence of exemplary fusion proteins comprising a control or a targeted engineered deubiquitinase are detailed in Table 11 below.

**Table 11.** Amino Acid Sequence of exemplary enDub Control and Screening Fusion Proteins

| Description                                              | SEQ ID NO | Amino Acid Sequence                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|----------------------------------------------------------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| FireflyLuciferase-<br>P2A-nano<br><br>(Control)          | 399       | MEDAKNIKKGPAPFYPLEDGTAGEQLHKAMKRYALVPGTIAFTDA<br>HIEVDITYAEYFEMSVRLAEAMKRYGLNTNHRIVVCSENSLQFFM<br>PVLGALFIGVAVAPANDIYNERELLNSMGISQPTVVFVSKKGLQK<br>ILNVQKKLP I IQK I IIMDSKTDYQGFQSMYTFVTSHLPPGFNEYD<br>FVPESFDRDKTIALIMNSSGSTGLPKGVALPHRTACVRFSHARDP<br>IFGNQIIPDTAILS SVVPFHHGFGMFTTLGYLICGFRVVL MYRFEE<br>ELFLRSLQDYKIQSALLVPTLFSFFAKSTLIDKYDLNLHEIASG<br>GAPLSKEVGEAVAKRFHLP GIRQGYGLTETTSAILITPEGDDKPG<br>AVGKVVPFFFEAKVVDLDTGKTLGVNQRGELCVRGPMIMSGYVNNP<br>EATNALIDKDGWLHSGDIAYWDEDEHFFIVDRLKSLIKYKGYQVA<br>PAELESILLQHPNIFDAGVAGLPDDDAGELPAAVVLEHGKTMTE<br>KEIVDYVASQVTTAKKL RGGVVFVDEV PKGLTGKLDARKIREILI<br>KAKKGGKIAVTRLKSGATNFSLLKQAGDVEENPGPRSGTGSSGE<br>VQLQESGGGLVQPGGSLRLSCTASGVTISALNAMAMGWYRQAPGE<br>RRVMVA AVSERGNAMYRESVQGRFTVTRDFTNKMVSLQMDNLKPE<br>DTAVYYCHVLEDRVDSFHDYWGQGTQVTVSS                                                                                                                                                                                                                                                                                                   |
| FireflyLuciferase-<br>P2A-Cezanne<br><br>(Control)       | 400       | MEDAKNIKKGPAPFYPLEDGTAGEQLHKAMKRYALVPGTIAFTDA<br>HIEVDITYAEYFEMSVRLAEAMKRYGLNTNHRIVVCSENSLQFFM<br>PVLGALFIGVAVAPANDIYNERELLNSMGISQPTVVFVSKKGLQK<br>ILNVQKKLP I IQK I IIMDSKTDYQGFQSMYTFVTSHLPPGFNEYD<br>FVPESFDRDKTIALIMNSSGSTGLPKGVALPHRTACVRFSHARDP<br>IFGNQIIPDTAILS SVVPFHHGFGMFTTLGYLICGFRVVL MYRFEE<br>ELFLRSLQDYKIQSALLVPTLFSFFAKSTLIDKYDLNLHEIASG<br>GAPLSKEVGEAVAKRFHLP GIRQGYGLTETTSAILITPEGDDKPG<br>AVGKVVPFFFEAKVVDLDTGKTLGVNQRGELCVRGPMIMSGYVNNP<br>EATNALIDKDGWLHSGDIAYWDEDEHFFIVDRLKSLIKYKGYQVA<br>PAELESILLQHPNIFDAGVAGLPDDDAGELPAAVVLEHGKTMTE<br>KEIVDYVASQVTTAKKL RGGVVFVDEV PKGLTGKLDARKIREILI<br>KAKKGGKIAVTRLKSGATNFSLLKQAGDVEENPGPRSGTGSPPS<br>FSEGSGGSRTPEKGFSDREPTRPPRPILQRQDDIVQEKRLSRGIS<br>HASSIVSLARSHVSSNGGGGGSNEHPLEMPICAFQLPDLTVYNE<br>DFRSFIERDLIEQSMLVALEQAGRLNWWVSVDPTSQRLLPLATTG<br>DGNCLLHAASLGMWGFHDDRDLMLRKALYALMEKGVEKEALKRRWR<br>WQQTQONKESGLVYTEDEWQKEWNELIKLASSEPRMHLGTNGANC<br>GGVESSEEPVYESLEEFHVFLAHVLRPIVVVADTMLRDSGGEA<br>FAPIPFGGIYLPLEVPASQCHRSPVLAYDQAHFSALVSMEQKEN<br>TKEQAVIPLTDSEYKLLPLHFAVDPGKGWEWGKDDSDNVRLASVI<br>LSLEVKLHLLHSYMNVKWIPLSSDAQAPLAQ |
| FireflyLuciferase-<br>P2A-<br>a_alfatag_nano-<br>Cezanne | 401       | MEDAKNIKKGPAPFYPLEDGTAGEQLHKAMKRYALVPGTIAFTDA<br>HIEVDITYAEYFEMSVRLAEAMKRYGLNTNHRIVVCSENSLQFFM<br>PVLGALFIGVAVAPANDIYNERELLNSMGISQPTVVFVSKKGLQK                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |



|  |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|--|--|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  |  | ILNVQKKLP I I Q K I I I M D S K T D Y Q G F Q S M Y T F V T S H L P P G F N E Y D<br>F V P E S F D R D K T I A L I M N S S G S T G L P K G V A L P H R T A C V R F S H A R D P<br>I F G N Q I I P D T A I L S V V P F H H G F G M F T T L G Y L I C G F R V L M Y R F E E<br>E L F L R S L Q D Y K I Q S A L L V P T L F S F F A K S T L I D K Y D L S N L H E I A S G<br>G A P L S K E V G E A V A K R F H L P G I R Q G Y G L T E T T S A I L I T P E G D D K P G<br>A V G K V V P F F E A K V V D L D T G K T L G V N Q R G E L C V R G P M I M S G Y V N N P<br>E A T N A L I D K D G W L H S G D I A Y W D E D E H F F I V D R L K S L I K Y K G Y Q V A<br>P A E L E S I L L Q H P N I F D A G V A G L P D D D A G E L P A A V V V L E H G K T M T E<br>K E I V D Y V A S Q V T T A K K L R G G V V F V D E V P K G L T G K L D A R K I R E I L I<br>K A K K G G K I A V T R L K G S G A T N F S L L K Q A G D V E E N P G P R S G T G S S G E<br>V Q L Q E S G G G L V Q P G G S L R L S C T A S G V T I S A L N A M A M G W Y R Q A P G E<br>R R V M V A A V S E R G N A M Y R E S V Q G R F T V T R D F T N K M V S L Q M D N L K P E<br>D T A V Y Y C H V L E D R V D S F H D Y W G Q G T Q V T V S S G A P G S G P P S F S E G S<br>G G S R T P E K G F S D R E P T R P P R P I L Q R Q D D I V Q E K R L S R G I S H A S S S<br>I V S L A R S H V S S N G G G G S N E H P L E M P I C A F Q L P D L T V Y N E D F R S F<br>I E R D L I E Q S M L V A L E Q A G R L N W W V S V D P T S Q R L L P L A T T G D G N C L<br>L H A A S L G M W G F H D R D L M L R K A L Y A L M E K G V E K E A L K R R W R W Q Q T Q<br>Q N K E S G L V Y T E D E W Q K E W N E L I K L A S S E P R M H L G T N G A N C G G V E S<br>S E E P V Y E S L E E F H V F V L A H V L R R P I V V A D T M L R D S G G E A F A P I P<br>F G G I Y L P L E V P A S Q C H R S P L V L A Y D Q A H F S A L V S M E Q K E N T K E Q A<br>V I P L T D S E Y K L L P L H F A V D P G K G W E W G K D D S D N V R L A S V I L S L E V<br>K L H L L H S Y M N V K W I P L S S D A Q A P L A Q |
|--|--|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

[00317] The assay was conducted with utilizing the tagged proteins and targeted enDubs described above in Tables 7 and 8. The results of the SHANK3 targeting are shown in FIG. 3, showing a 2.4-fold increase in SHANK3 protein expression relative to the control. The results from the SYNGAP1 targeting are shown in FIG. 4, showing a 3.1-fold increase in SYNGAP1 protein expression relative to the control. The results of the PYDC2 targeting are shown in FIG. 5, showing a 2.64-fold increase in PYDC2 protein expression. The results of the CSTB targeting are shown in FIG. 6, showing a 1.61-fold increase in CSTB protein expression. The results of the PCBD1 targeting are shown in FIG. 7, showing a 1.13-fold increase in PCBD1 protein expression. The control used for the PYDC2, CSTB, and PCBD1 experiments is the engineered deubiquitinase without the nanobody targeting the alfa-tag. Normalization of transduction efficiency was performed using the firefly luciferase signal as the reference and the ratio between NLuc signal divided by firefly luciferase signal plotted on the y axes.

#### 6.4 Example 4. Generation of Anti-SYNGAP-1 VHH

[00318] Anti-SYNGAP-1 VHHs (i.e. nanobodies) were generated according to the materials and methods below.

#### 6.4.1 Antigen Expression

[00319] cDNA of His-SynGAP-EC[1186-1277] (Uniprot #Q96PV0) with 6His tag at 5'/N-terminal was chemically synthesized with codon optimization for bacterial systems, then sub-cloned in an expression vector. Full protein sequence is as follows: MGSHHHHHSGKSMDESRLDRVKEYEEEEIHSLKERLHMSNRKLEEYERRLLSQEEQTSKILMQY QARLEQSEKRLRQQQA EKDSQIKSIIGRLMLVEEELRRDHPAMAEPLPEPKKRLLLDAQERQLPP LGPT (SEQ ID NO: 368). His-SynGAP-EC[1186-1277] was expressed in *E. coli*, then purified by affinity against 6His-tag using Nickel resin. Purification test results of His-SynGAP-EC [1186-1277] in *E. coli* are shown in FIG. 8. 4.08MG of His-SynGAP-EC [1186-1277] was produced with a molecular weight of 15.75kDA and a pI of 7.38.

#### 6.4.2 Phage Display

[00320] A series of camelid VHHs were screened for binding to the His-SynGAP-EC[1186-1277] produced above. Briefly, a tube was coated with His-SynGAP-EC[1186-1277], washed, blocked, washed, incubated with a phage library expressing camelid VHHs, washed, and the phages expressing camelid VHH binders that bound to His-SynGAP-EC[1186-1277] were eluted from the tube with glycine-HCL. The concentration of the eluted phages was determined. First, the eluted phages were added to *E. Coli* TG1. TG1 was poured onto a plate and cultured upside down. The PFU was calculated based on the number of plaques (i.e. dead TG1) on the plate. The eluted phages were added to TG1 followed infection by helper phage and cultured. Phages were precipitated with PEG/NaCl and subsequently resuspended. The phages were screened using a polyclonal ELISA and a monoclonal ELISA. Briefly, the polyclonal ELISA was carried out utilizing a plate coated with His-SynGAP-EC[1186-1277] (4µg/mL) or control buffer. The coated plate was washed, blocked, washed, and incubated with the amplified eluted phages. Subsequently the plate was washed and incubated with anti-phage-HRP antibody, washed, and incubated with TMB followed by HCL. The result readings were taken at 450nm. The monoclonal phase ELISA was carried out according to the following. Single TG1 clones randomly selected from plates (described above) were cultured with helper phage. A total of 192 clones from round 3 +96 clones from round 4+ 96 clones from round 5 were selected. The clones were centrifuged and the supernatant (i.e. the phages) were collected. A plate was coated with His-SynGAP-EC[1186-1277] (4 µg/ml) or control buffer. The plate was washed, blocked, washed, incubated with the selected

phages, washed, incubated with anti-phage-HRP antibody, washed, and incubated with TMB followed by HCL. The results were read of 450nm.

[00321] Six anti-His-SynGAP-EC[1186-1277] VHHs were identified and sequenced from the above. The amino acid sequence of the six anti-His-SynGAP-EC[1186-1277] VHHs is disclosed in Table 12 below.

**Table 12.** Amino Acid Sequence of Anti- SynGAP VHHs

| Description |      | SEQ ID NO | Amino Acid Sequence                                                                                                                        |
|-------------|------|-----------|--------------------------------------------------------------------------------------------------------------------------------------------|
| FLX00152    | CDR1 | 290       | GFSFSNFP                                                                                                                                   |
|             | CDR2 | 291       | INQDGRNT                                                                                                                                   |
|             | CDR3 | 292       | QAIRTTTHFDS                                                                                                                                |
|             | VH   | 293       | QVQLVESGGGLVQPGGSLRLSCAASGFSFSNFPMMWVR<br>QAPGKGREWVADINQDGRNTYYADSVKGRFTISRDN<br>AKTTVYLQMNNLPEDTAVYYCQAIRTTTHFDSWGQGTQV<br>TVSS          |
| FLX00153    | CDR1 | 294       | GFTFSNYR                                                                                                                                   |
|             | CDR2 | 295       | IDRSGTYT                                                                                                                                   |
|             | CDR3 | 296       | AADRRLIVDLTPEVYDH                                                                                                                          |
|             | VH   | 297       | QLQLVESGGGLVQPGESLRLSCAASGFTFSNYRMYWVR<br>MAPGKGLEWVSDIDRSGTYTYADSVKGRFAISRDN<br>AKNTVYLQMNSLKPEDTAVYYCAADRRLIVDLTPEVYD<br>HWGQGTQVTVSS    |
| FLX00154    | CDR1 | 298       | GFIFSSYQ                                                                                                                                   |
|             | CDR2 | 299       | INTGGWNT                                                                                                                                   |
|             | CDR3 | 300       | AADRWMVAKIVGGDLDFDS                                                                                                                        |
|             | VH   | 301       | QVQLVESGGGLVQPGGSLRLSCAASGFIFSSYQMAWVR<br>QAPGKGLEWVADINTGGWNTYYADSVKGRFTISRDN<br>AKNTLYLEMNSLKPEDTAVYYCAADRWMVAKIVGGDL<br>DFDSWGQGTQVTVSS |
| FLX00155    | CDR1 | 302       | GFAFGSYD                                                                                                                                   |
|             | CDR2 | 303       | ITPGGGGT                                                                                                                                   |
|             | CDR3 | 304       | YYCAKNFYGNNG                                                                                                                               |
|             | VH   | 305       | QVQLVESGGGLVQPGGSLRLSCAASGFAFGSYDMSWVR<br>QAPGQGPEWVSAITPGGGGTIFYAYYSDSVKGRFAISR<br>DNNAKNTLTLMNSLKPDDTAMYYCAKNFYGNNGR<br>GHGTQVTVSS       |
| FLX00156    | CDR1 | 306       | GFTFGTHA                                                                                                                                   |
|             | CDR2 | 307       | ISSGGGGT                                                                                                                                   |
|             | CDR3 | 308       | NSPSNIANDN                                                                                                                                 |
|             | VH   | 309       | QVQLVESGGGLVQPGGSLRLACAASGFTFGTHAMHWVR<br>WAPGKGFWEVSTISSGGGGTRYADSVKGRFTISRDN<br>AKNTVYLQMDNLKPEDTAVYYCNSPSNIANDN<br>WQGTQVTVSS           |
| FLX00157    | CDR1 | 310       | ERTFGHYA                                                                                                                                   |
|             | CDR2 | 311       | ISWKGTT                                                                                                                                    |
|             | CDR3 | 312       | AARNTMSGSMSSSAYPY                                                                                                                          |

|  |    |     |                                                                                                                                          |
|--|----|-----|------------------------------------------------------------------------------------------------------------------------------------------|
|  | VH | 313 | QVQLVESGGGLVQAGASLRSLCAASERTFGHYAMGWFR<br>QAPGKERE FVATISWKGGTTGYAHSVKGRFTISRDSA<br>NMVYLQMNSLKPEDTAVYYCAARNTMSGSMSSSAYPYW<br>GQGTQVTVSS |
|--|----|-----|------------------------------------------------------------------------------------------------------------------------------------------|

## 6.5 Example 5. Deubiquitinase Activity of Anti-SYNGAP1 targeted enDubs

[00322] EnDubs targeting SYNGAP1 were constructed using the anti-SYNGAP1 nanobodies described in above in Example 4. The experimental fusion proteins contained from N to C terminus: FireflyLuciferase-P2A-anti-syngap1 nanobody-Cezanne catalytic domain. The amino acid sequence of each of the experimental anti-SYNGAP1 enDubs is provided below in Table 13.

[00323] Table 13 provides the amino acid sequence of exemplary anti-SYNGAP1 enDubs.

**Table 13.** Amino Acid Sequence of Anti-SYNGAP1 enDubs

| Description                                             | SEQ ID NO | Amino Acid Sequence                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|---------------------------------------------------------|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| FireflyLuciferase-P2A-anti-syngap1_FLX0015<br>7-Cezanne | 369       | MEDAKNIKKGPAPFYPLEDGTAGEQLHKAMKRYALVPGTIAFTD<br>AHIEVDITYAEYFEMSVRLAEAMKRYGLNTNHRIVVCSNSLQF<br>FMPVLGALFIGVAVAPANDIYNERELNSMGISQPTVVFVSKKG<br>LQKILNVQKKLPPIIQKIIIMDSKTDYQGFQSMYTFVTSHLPPGF<br>NEYDFVPESFDRDKTIALIMNSSGSTGLPKGVALPHRTACVRF<br>HARDPIFGNQIIPDTAILSVPVFFHHGFGMFTTLGYLICGFRVVL<br>MYRFEEELFLRSLQDYKIQSALLVPTLFSFFAKSTLIDKYDLN<br>LHEIASGGAPLSKEVGEAVAKRFHLPGIRQGYGLTETTSAILIT<br>PEGDDKPGAVGKVVPPFEAKVVDLDTGKTLGVNQRGELCVRGPM<br>IMSGYVNNPEATNALIDKDWLHSGDIAYWDEDEHFFIVDR LKS<br>LIKYGQYQVAPAELESILLQHPNIFDAGVAGLPDDAGELPAAV<br>VVLEHGKTMTEKEIVDYVASQVTTAKKLGGVVFVDEVPKGLTG<br>KLDARKIREILIKAKKGGKIAVTRLKSGGATNFSLLKQAGDVEE<br>NPGPRSGTGSSGQVQLVESGGGLVQAGASLRSLCAASERTFGHY<br>AMGWFRQAPGKERE FVATISWKGGTTGYAHSVKGRFTISRDSA<br>NMVYLQMNSLKPEDTAVYYCAARNTMSGSMSSSAYPYWGQGTQV<br>TVSSGGGGSGGGSGGGSGGGSGGGSGVQLVESGGGLVQAGASLR<br>SLCAASERTFGHYAMGWFRQAPGKERE FVATISWKGGTTGYAHSV<br>KGRFTISRDSAKNMVYLQMNSLKPEDTAVYYCAARNTMSGSMSS<br>SAYPYWGQGTQVTVSSGAPGSGPPSFSESGGSRTPEKGFSDRE<br>PTRPPRPILQRQDDIVQEKR LSRGISHASSIVSLARSHVSSNG<br>GGGSNEHPLEMPICAFQLPDLTVYNEDFRSFIERDLIEQSMLV<br>ALEQAGRLNWWVSVDPTSQRLLPLATTGDGNCLLHAASLGMWGF<br>HDRDLMLRKALYALMEKGVEKEALKRRWRWQQTQONKESGLVYT<br>EDEWQKEWNELIKLASSEPRMHLGTNGANCGVESSEEPVYESL<br>EEFHVFLAHVLRPIVVVADTMLRDSGGEAFAPIPFGGIYLP<br>EVPASQCHRSPLVLAYDQAHFSALVSMEQKENTKEQAVIPLTDS<br>EYKLLPLHFVDPGKGWEGKDDSDNVRLASVILSLEVKLHLLH<br>SYMNVKWIPLSSDAQAPLAQ |
| FireflyLuciferase-P2A-anti-syngap1_FLX0015              | 370       | MEDAKNIKKGPAPFYPLEDGTAGEQLHKAMKRYALVPGTIAFTD<br>AHIEVDITYAEYFEMSVRLAEAMKRYGLNTNHRIVVCSNSLQF<br>FMPVLGALFIGVAVAPANDIYNERELNSMGISQPTVVFVSKKG                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

|                                                                 |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-----------------------------------------------------------------|-----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 6-Cezanne                                                       |     | <p>LQKILNVQKKLPPIIQKIIIMDSKTDYQGFQSMYTFVTSHLPPGF<br/> NEYDFVPESFDRDKTIALIMNSSGSTGLPKGVALPHRTACVRFS<br/> HARDPIFGNQIIPDTAILSVPFHHGFGMFTTLGYLICGFRVVL<br/> MYRFEEELFLRSLQDYKIQSALLVPTLFSFFAKSTLIDKYDLN<br/> LHEIASGGAPLSKEVGEAVAKRFHLPGIRQGYGLTETTSAILIT<br/> PEGDDKPGAVGKVVPFFFEAKVVDLDTGKTLGVNQRGELCVRGPM<br/> IMSGYVNNPEATNALIDKDGWLHSGDIAYWDEDEHFFIVDRLKS<br/> LIKYGQYQVAPAELESILLQHPNIFDAGVAGLPDDDAGELPAAV<br/> VVLEHGKTMTEKEIVDYVASQVTTAKKLGGVVVFVDEVPKGLTG<br/> KLDARKIREILIKAKKGGKIAVTRLKSGGATNFSLLKQAGDVEE<br/> NPGPRSGTGSSGQVQLVESGGGLVQPGGSLRLACAASGFTFGTH<br/> AMHWVRWAPGKGFVWSTISSGGGGTRYADSVKGRFTISRDNK<br/> NTVYLQMDNLKPEDTAVYYCNSPSNIANDNWGQGTQVTVSSGGG<br/> GSGGGGSGGGGSGGGGSQVQLVESGGGLVQPGGSLRLACAASGF<br/> TFGTHAMHWVRWAPGKGFVWSTISSGGGGTRYADSVKGRFTIS<br/> RDNKNTVYLQMDNLKPEDTAVYYCNSPSNIANDNWGQGTQVTV<br/> SSGAPGSGPPSFSESGSGSRTPEKGFSDREPTRPPRPILQRQDD<br/> IVQEKRLSRGISHASSIVSLARSHVSSNGGGGGSNEHPLEMPI<br/> CAFQLPDLTVYNEDFRSFIERDLIEQSMLVALEQAGRLNWWVSV<br/> DPTSQRLLPLATTGDGNCLLHAASLGMWGFHDDRDLMLRKALYAL<br/> MEKGVEKEALKRRRWQQTQQNKESGLVYTEDEWQKEWNELIK<br/> ASSEPRMHLGTNGANCGGVESSEEPVYESLEE FHV FVLAHVLR<br/> PIVVVADTMLRDSGGEAFAPIPFGGIYLPLEVPASQCHRSPLVL<br/> AYDQAHFSALVSMEQKENTKEQAVIPLTDSEYKLLPLHFAVDPG<br/> KGWEWGKDDSDNVRLASVILSLEVKLHLLHSYMNKWIPLSSDA<br/> QAPLAQ</p> |
| FireflyLuciferase-<br>P2A-anti-<br>syngap1_FLX0015<br>5-Cezanne | 371 | <p>MEDAKNIKKGPAPFYPLEDGTAGEQLHKAMKRYALVPGTIAFTD<br/> AHIEVDITYAEYFEMSVRLAEAMKRYGLNTNHRIVVCSNSLQF<br/> FMPVLGALFIGVAVAPANDIYNERELLSMGISQPTVVFVSKKG<br/> LQKILNVQKKLPPIIQKIIIMDSKTDYQGFQSMYTFVTSHLPPGF<br/> NEYDFVPESFDRDKTIALIMNSSGSTGLPKGVALPHRTACVRFS<br/> HARDPIFGNQIIPDTAILSVPFHHGFGMFTTLGYLICGFRVVL<br/> MYRFEEELFLRSLQDYKIQSALLVPTLFSFFAKSTLIDKYDLN<br/> LHEIASGGAPLSKEVGEAVAKRFHLPGIRQGYGLTETTSAILIT<br/> PEGDDKPGAVGKVVPFFFEAKVVDLDTGKTLGVNQRGELCVRGPM<br/> IMSGYVNNPEATNALIDKDGWLHSGDIAYWDEDEHFFIVDRLKS<br/> LIKYGQYQVAPAELESILLQHPNIFDAGVAGLPDDDAGELPAAV<br/> VVLEHGKTMTEKEIVDYVASQVTTAKKLGGVVVFVDEVPKGLTG<br/> KLDARKIREILIKAKKGGKIAVTRLKSGGATNFSLLKQAGDVEE<br/> NPGPRSGTGSSGQVQLVESGGGLVQPGGSLRLSCAASGFAFGSY<br/> DMSWVRQAPGQGPWVSAITPGGGGT FYAYYSDSVKGRFAISR<br/> NAKNTLTLMNSLKPDDTAMYYCAKNFYGNNGRGHGTQVTVSSG<br/> GGGSGGGGSGGGGSGGGGSQVQLVESGGGLVQPGGSLRLSCAAS<br/> GFAFGSYDMSWVRQAPGQGPWVSAITPGGGGT FYAYYSDSVKGR<br/> FAISRDNKNTLTLMNSLKPDDTAMYYCAKNFYGNNGRGHGT<br/> QVTVSSGAPGSGPPSFSESGSGSRTPEKGFSDREPTRPPRPILQ<br/> RQDDIVQEKRLSRGISHASSIVSLARSHVSSNGGGGGSNEHPL<br/> EMPICAFQLPDLTVYNEDFRSFIERDLIEQSMLVALEQAGRLNW<br/> WVSDPTSQRLLPLATTGDGNCLLHAASLGMWGFHDDRDLMLRKA<br/> LYALMEKGVEKEALKRRRWQQTQQNKESGLVYTEDEWQKEWNE<br/> LIKLASSEPRMHLGTNGANCGGVESSEEPVYESLEE FHV FVLAH</p>             |

|                                                                 |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-----------------------------------------------------------------|-----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                 |     | VLRRPIVVVADTMLRDSGGEAFAPIPFGGIYLPLEVPASQCHRS<br>PLVLAYDQAHFSALVSMEQKENTKEQAVIPLTDSEYKLLPLHFA<br>VDPGKGWEWGKDDSDNVRLASVILSLEVKLHLLHSYMNVKWIPL<br>SSDAQAPLAQ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| FireflyLuciferase-<br>P2A-anti-<br>syngap1_FLX0015<br>4-Cezanne | 372 | MEDAKNIKKGPAPFYPLEDGTAGEQLHKAMKRYALVPGTIAFTD<br>AHIEVDITYAEYFEMSVRLAEAMKRYGLNTNHRIVVCSENSLQF<br>FMPVLGALFIGVAVAPANDIYNERELNSMGISQPTVVFVSKKG<br>LQKILNVQKKLP I I Q K I I IMDSKTDYQGFQSMYTFVTSHLPPGF<br>NEYDFVPESFDRDKTIALIMNSSGSTGLPKGVALPHRTACVRFS<br>HARDPIFGNQ I I P D T A I L S V V P F H H G F G M F T T L G Y L I C G F R V V L<br>MYRFEEELFLRSLQDYKIQSALLVPTLFSFFAKSTLIDKYDLSN<br>LHEIASGGAPLSKEVGEAVAKRFHLPGIRQGYGLTETTSAILIT<br>PEGDDKPGAVGKVVPFFFEAKVVDLDTGKTLGVNQRGELCVRGPM<br>IMSGYVNNPEATNALIDKDGWLHSGDIAWDEDEHFFIVDRLKS<br>LIKYGKYQVAPAELESILLQHPNIFDAGVAGLPDDDAGELPAAV<br>VVLEHGKTMTEKEIVDYVASQVTTAKKL RGGVVFVDEV PKGLTG<br>KLDARKIREILIKAKKGGKIAVTRLKSGGATNFSLLKQAGDVEE<br>NPGPRSGTGSSGQVQLVESGGGLVQPGGSLRLSCAASGFI FSSY<br>QMAWVRQAPGKGLEWVADINTGGWNTYYADSVKGRFTISRDNK<br>NTLYLEMNSLKPEDTAVYYCAADRWMVAKIVGGDLDFDSWGQGT<br>QVTVSSGGGGSGGGSGGGSGGGSGQVQLVESGGGLVQPGGSL<br>RLSCAASGFI FSSYQMAWVRQAPGKGLEWVADINTGGWNTYYAD<br>SVKGRFTISRDNKNTLYLEMNSLKPEDTAVYYCAADRWMVAKI<br>VGGDLDFDSWGQGTQVTVSSGAPGSGPPSFSESGGSRTPEKGF<br>SDREPTRPPRPILQRQDDIVQEKRLSRGISHASSSIVSLARSHV<br>SSNGGGGGSNEHPLEMPICAFQLPDLTVYNEDFRSFIERDLIEQ<br>SMLVALEQAGRLNWWVSVDPTSQRLLPLATTGDGNCLLHAASLG<br>MWGFHDRDLMLRKALYALMEKGVEKEALKRRWRWQQTQQNKESG<br>LVYTEDEWQKEWNELIKLASSEPRMHLGTNGANCGGVESSEEPV<br>YESLEEFHVFLAHVLRPIVVVADTMLRDSGGEAFAPIPFGGI<br>YLPLEVPASQCHRSPLVLAYDQAHFSALVSMEQKENTKEQAVI<br>PLTDSEYKLLPLHFAVDPGKGWEWGKDDSDNVRLASVILSLEVKL<br>HLLHSYMNVKWIPLSSDAQAPLAQ |
| FireflyLuciferase-<br>P2A-anti-<br>syngap1_FLX0015<br>3-Cezanne | 373 | MEDAKNIKKGPAPFYPLEDGTAGEQLHKAMKRYALVPGTIAFTD<br>AHIEVDITYAEYFEMSVRLAEAMKRYGLNTNHRIVVCSENSLQF<br>FMPVLGALFIGVAVAPANDIYNERELNSMGISQPTVVFVSKKG<br>LQKILNVQKKLP I I Q K I I IMDSKTDYQGFQSMYTFVTSHLPPGF<br>NEYDFVPESFDRDKTIALIMNSSGSTGLPKGVALPHRTACVRFS<br>HARDPIFGNQ I I P D T A I L S V V P F H H G F G M F T T L G Y L I C G F R V V L<br>MYRFEEELFLRSLQDYKIQSALLVPTLFSFFAKSTLIDKYDLSN<br>LHEIASGGAPLSKEVGEAVAKRFHLPGIRQGYGLTETTSAILIT<br>PEGDDKPGAVGKVVPFFFEAKVVDLDTGKTLGVNQRGELCVRGPM<br>IMSGYVNNPEATNALIDKDGWLHSGDIAWDEDEHFFIVDRLKS<br>LIKYGKYQVAPAELESILLQHPNIFDAGVAGLPDDDAGELPAAV<br>VVLEHGKTMTEKEIVDYVASQVTTAKKL RGGVVFVDEV PKGLTG<br>KLDARKIREILIKAKKGGKIAVTRLKSGGATNFSLLKQAGDVEE<br>NPGPRSGTGSSGQLQLVESGGGLVQPGESLRLSCAASGFTFSNY<br>RMYWVRMAPGKGLEWVSDIDRSGTYTYADSVKGRFAISRDNK<br>NTVYLQMNSLKPEDTAVYYCAADRRLIVDLTPEVYDHWGQGTQV<br>TVSSGAPGSGPPSFSESGGSRTPEKGFSDREPTRPPRPILQRQ<br>DDIVQEKRLSRGISHASSSIVSLARSHVSSNGGGGGSNEHPLEM                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

|                                                                 |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-----------------------------------------------------------------|-----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                 |     | PICAFQLPDLTVYNEDFRSFIERDLIEQSMLVALEQAGRLNWWV<br>SVDPTSQRLLPLATTGDNCLLHAASLGMWGFHDRDLMLRKALY<br>ALMEKGVEKEALKRRRWQQTQQNKESGLVYTEDEWQKEWNELI<br>KLASSEPRMHLGTNGANCGVESSEEPVYESLEEFHVFLAHVL<br>RRPIVVVADTMLRDSGGEAFAPIPFGGIYLPLEVPASQCHRSPL<br>VLAYDQAHFSALVSMEQKENTKEQAVIPLTDSEYKLLPLHFAVD<br>PGKGWEWGKDDSDNVRLASVILSLEVKLHLLHSYMNVKWIPLSS<br>DAQAPLAQ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| FireflyLuciferase-<br>P2A-anti-<br>syngap1_FLX0015<br>2-Cezanne | 374 | MEDAKNIKKGPAPFYPLEDGTAGEQLHKAMKRYALVPGTIAFTD<br>AHIEVDITYAEYFEMSVRLAEAMKRYGLNTNHRIVVCSENSLQF<br>FMPVLGALFIGVAVAPANDIYNERELNSMGISQPTVVFVSKKG<br>LQKILNVQKKLPITQKIIIMDSKTDYQGFQSMYTFVTSHLPPGF<br>NEYDFVPESFDRDKTIALIMNSSGSTGLPKGVALPHRTACVRFS<br>HARDPIFGNQIIPDTAILSVPVFFHHGFGMFTTLGYLICGFRVVL<br>MYRFEELFLRSLQDYKIQSALLVPTLFSFFAKSTLIDKYDLN<br>LHEIASGGAPLSKEVGEAVAKRFHLPGIRQGYGLTETTSAILIT<br>PEGDDKPGAVGKVVPFFFEAKVVDLDTGKTLGVNQRGELCVRGPM<br>IMSGYVNNPEATNALIDKDGWLHSGDIAWDEDEHFFIVDRLKS<br>LIKYGQYQVAPAELESILLQHPNIFDAGVAGLPDDDAGELPAAV<br>VVLEHGKTMTEKEIVDYVASQVTTAKKLGGVVFVDEVPKGLTG<br>KLDARKIREILIKAKKGGKIAVTRLKSGGATNFSLLKQAGDVEE<br>NPGPRSGTGSSGQVQLVESGGGLVQPGGSLRLSCAASGFSFSNF<br>PMMWVRQAPGKGREWVADINQDGRNTYYADSVKGRFTISRDNK<br>TTVYLQMNINLPEDTAVYYCAIRTTTHFDSWGQGTQVTVSSGA<br>PGSGPPSFSESGGSRTPEKGFSDREPTRPPRPILQRQDDIVQE<br>KRLSRGISHASSIVSLARSHVSSNGGGGGSNEHPLEMPICAFQ<br>LPDLTVYNEDFRSFIERDLIEQSMLVALEQAGRLNWWVSVDPTS<br>QRLLPLATTGDNCLLHAASLGMWGFHDRDLMLRKALYALMEKG<br>VEKEALKRRRWQQTQQNKESGLVYTEDEWQKEWNELIKLASSE<br>PRMHLGTNGANCGVESSEEPVYESLEEFHVFLAHVLRRPIVV<br>VADTMLRDSGGEAFAPIPFGGIYLPLEVPASQCHRSPLVLAYDQ<br>AHFSALVSMEQKENTKEQAVIPLTDSEYKLLPLHFAVDPGKGWE<br>WGKDDSDNVRLASVILSLEVKLHLLHSYMNVKWIPLSSDAQAPL<br>AQ |

[00324] Each of the constructs in Table 13 was tested as described in Example 3. As shown in FIG. 9, each of the SYNGAP1 targeted nanobodies showed an increase in SYNGAP1 expression of at least 2-fold over the control.

\* \* \*

[00325] The invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

[00326] All references (e.g., publications or patents or patent applications) cited herein are

incorporated herein by reference in their entireties and for all purposes to the same extent as if each individual reference (e.g., publication or patent or patent application) was specifically and individually indicated to be incorporated by reference in its entirety for all purposes.

Other embodiments are within the following claims.



## CLAIMS

What is claimed is:

1. A fusion protein comprising:
  - a. an effector domain comprising a catalytic domain of a deubiquitinase, or a functional fragment or functional variant thereof; and
  - b. a targeting domain comprising a targeting moiety that specifically binds a cytosolic protein.
2. The fusion protein of claim 1, wherein said deubiquitinase is a cysteine protease or a metalloprotease.
3. The fusion protein of claim 2, wherein said deubiquitinase is a cysteine protease.
4. The fusion protein of claim 3, wherein said cysteine protease is a ubiquitin-specific protease (USP), a ubiquitin C-terminal hydrolase (UCH), a Machado-Josephin domain protease (MJD), an ovarian tumour protease (OTU), a MINDY protease, or a ZUFSP protease.
5. The fusion protein of claim 4, wherein said cysteine protease is a USP.
6. The fusion protein of claim 5, wherein said USP is USP1, USP2, USP3, USP4, USP5, USP6, USP7, USP8, USP9X, USP9Y, USP10, USP11, USP12, USP13, USP14, USP15, USP16, USP17, USP17L2, USP17L3, USP17L4, USP17L5, USP17L7, USP17L8, USP18, USP19, USP20, USP21, USP22, USP23, USP24, USP25, USP26, USP27X, USP28, USP29, USP30, USP31, USP32, USP33, USP34, USP35, USP36, USP37, USP38, USP39, USP40, USP41, USP42, USP43, USP44, USP45, or USP46.
7. The fusion protein of claim 4, wherein said cysteine protease is a UCH.
8. The fusion protein of claim 7, wherein said UCH is BAP1, UCHL1, UCHL3, or UCHL5.
9. The fusion protein of claim 4, wherein said cysteine protease is a MJD.
10. The fusion protein of claim 9, wherein said MJD is ATXN3 or ATXN3L.
11. The fusion protein of claim 4, wherein said cysteine protease is an OTU.
12. The fusion protein of claim 11, wherein said OTU is OTUB1 or OTUB2.
13. The fusion protein of claim 4, wherein said cysteine protease is a MINDY.
14. The fusion protein of claim 13, wherein said MINDY is MINDY1, MINDY2, MINDY3, or MINDY4.
15. The fusion protein of claim 4, wherein said cysteine protease is a ZUFSP.
16. The fusion protein of claim 15, wherein said ZUFSP is ZUP1.

17. The fusion protein of claim 2, wherein said deubiquitinase is a metalloprotease.
18. The fusion protein of claim 17, wherein said metalloprotease is a Jab1/Mov34/Mpr1 Pad1 N-terminal+ (MPN+) (JAMM) domain protease.
19. The fusion protein of any one of the preceding claims, wherein said deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 1-112.
20. The fusion protein of any one of the preceding claims, wherein said catalytic domain comprises a catalytic domain derived from a deubiquitinase comprising an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 1-112.
21. The fusion protein of any one of the preceding claims, wherein said catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 113-220 or 286.
22. The fusion protein of any one of the preceding claims, wherein said catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 286.
23. The fusion protein of any one of the preceding claim, wherein said catalytic domain comprises an amino acid sequence that is a functional fragment of the amino acid sequence of any one of SEQ ID NOS: 1-112.
24. The fusion protein of any one of the preceding claim, wherein said catalytic domain comprises an amino acid sequence that is a functional fragment of the amino acid sequence of any one of SEQ ID NOS: 113-220 or 286.
25. The fusion protein of any one of the preceding claims, wherein said moiety that specifically binds a cytosolic protein comprises an antibody, or functional fragment or functional variant thereof.

26. The fusion protein of claim 25, wherein said antibody, or functional fragment or functional variant thereof, comprises a full-length antibody, a single chain variable fragment (scFv), a scFv2, a scFv-Fc, a Fab, a Fab', a F(ab')<sub>2</sub>, a F(v), a VHH, or a (VHH)<sub>2</sub>.
27. The fusion protein of claim 26, wherein said antibody, or functional fragment or functional variant thereof, comprises a VHH or a (VHH)<sub>2</sub>.
28. The fusion protein of any one of the preceding claims, wherein said cytosolic protein is cyclin-dependent kinase-like 5 (CDKL5), copper-transporting ATPase 2 (ATP7B), syntaxin-binding protein 1 (STXBP1), Ras/Rap GTPase-activating protein (SYNGAP1), progranulin (GRN), protein jagged-1 (JAG1), GATOR complex protein DEPDC5 (DEPDC5), tuberlin (TSC2), hamartin (TSC1), kinesin-like protein KIF1A (KIF1A), dynamin-1 (DNM1), SH3 and multiple ankyrin repeat domains protein 3 (SHANK3), dystrophin (DMD), oxygen-regulated protein 1 (RP1), titin (TTN), cytoplasmic dynein 1 heavy chain 1 (DYNC1H1), TRIO and F-actin-binding protein (TRIO), probable ubiquitin carboxyl-terminal hydrolase FAF-X (USP9X), cystatin-B (CSTB), or pterin-4-alpha-carbinolamine dehydratase (PCBD1).
29. The fusion protein of any one of the preceding claims, wherein said cytosolic protein comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to any one of SEQ ID NOS: 221-328 or 287-289.
30. The fusion protein of any one of the preceding claims, wherein said effector domain is directly operably connected to said targeting domain.
31. The fusion protein of any one of claims 1-29, wherein said effector domain is indirectly operably connected to said targeting domain.
32. The fusion protein of claim 31, wherein said effector domain is indirectly operably connected to said targeting domain via a peptide linker.
33. The fusion protein of claim 32, wherein said effector domain is indirectly fused to said targeting domain via a peptide linker of sufficient length such that said effector domain and said targeting domain can simultaneous bind the respective target proteins.
34. The fusion protein of claim 32 or 33, wherein said peptide linker comprises the amino acid sequence of any one of SEQ ID NOS: 375-384 or 402-519, or the amino acid sequence of any one of SEQ ID NOS: 375-384 or 402-519 comprising 1, 2, or 3 amino acid modifications.

35. The fusion protein of claim 34, wherein said peptide linker comprises the amino acid sequence of any one of SEQ ID NOS: 375-384, or the amino acid sequence of any one of SEQ ID NOS: 375-384 comprising 1, 2, or 3 amino acid modifications.
36. The fusion protein of any one of the preceding claims, wherein said effector domain is operably connected either directly or indirectly to the C terminus of said targeting domain.
37. The fusion protein of any one of claims 1-35, wherein said effector moiety is operably connected either directly or indirectly to the N terminus of said targeting domain.
38. A nucleic acid molecule encoding the fusion protein of any one of claims 1-37.
39. The nucleic acid molecule of claim 38, wherein said nucleic acid molecule is a DNA molecule.
40. The nucleic acid molecule of claim 38, wherein said nucleic acid molecule is an RNA molecule.
41. A vector comprising the nucleic acid molecule of any one of claims 38-40.
42. The vector of claim 41, wherein said vector is a plasmid or a viral vector.
43. A viral particle comprising the nucleic acid molecule of any one of claims 38-40.
44. An in vitro cell or population of cells comprising the fusion protein of any one of claims 1-37, the nucleic acid molecule of any one of claims 38-40, or the vector of any one of claims 41-42.
45. A pharmaceutical composition comprising the fusion protein of any one of claims 1-37, the nucleic acid molecule of any one of claims 38-40, the vector of any one of claims 41-42, or the viral particle of claim 43, and an excipient.
46. A method of making the fusion protein of any one of claims 1-37, comprising
- introducing into an in vitro cell or population of cells the nucleic acid molecule of any one of claims 38-40, the vector of any one of claims 41-42, the viral particle of claim 43;
  - culturing the cell or population of cells in a culture medium under conditions suitable for expression of the fusion protein,
  - isolating the fusion protein from the culture medium, and
  - optionally purifying the fusion protein.
47. A method of treating or preventing a disease in a subject comprising administering the fusion protein of any one of claims 1-37, the nucleic acid molecule of any one of claims 38-40,

the vector of any one of claims 41-42, the viral particle of claim 43, or the pharmaceutical composition of claim 45, to a subject in need thereof.

48. The method of claim 47, wherein the subject is human.

49. The method of claim 47 or 48, wherein said disease is associated with decreased expression of a functional version of the cytosolic protein relative to a non-diseased control.

50. The method of any one of claims 47-49, wherein the disease is associated with decreased stability of a functional version of the cytosolic protein relative to a non-diseased control.

51. The method of any one of claims 47-50, wherein said disease is associated with increased ubiquitination of the cytosolic protein relative to a non-diseased control.

52. The method of any one of claims 47-51, wherein said disease is associated with increased ubiquitination and degradation of the cytosolic protein relative to a non-diseased control.

53. The method of any one of claims 47-52, wherein said disease is a genetic disease.

54. The method of any one of claims 47-53, wherein said disease is SYNGAP1 encephalopathy, CDKL5 deficiency disorder, STXBP1 encephalopathy, early infantile epileptic encephalopathy type 2, Wilson disease, early infantile epileptic encephalopathy type 4, mental retardation autosomal dominant 5, aphasia, alagille syndrome 1, epilepsy, tuberous sclerosis-2, tuberous sclerosis-1, KIF1A-associated neurological disorder, encephalopathy, Phelan-McDermid syndrome, Becker Muscular Dystrophy, RP1, retinitis pigmentosa 1, dilated cardiomyopathy 1G, DYNC1H1 Syndrome, TRIO-Related intellectual disability (ID), USP9X Development Disorder, epilepsy, progressive myoclonic 1 (EPM1), or hyperphenylalaninemia BH4-deficient D (HPABH4D).

55. The method of any one of claims 47-54, wherein

- a. said target cytosolic protein is SYNGAP1, and said disease is SYNGAP1 encephalopathy;
- b. said target cytosolic protein is SYNGAP1, and said disease is Mental retardation autosomal dominant 5.
- c. said target cytosolic protein is CDKL5, and said disease is CDKL5 deficiency disorder;
- d. said target cytosolic protein is CDKL5, and said disease is an early infantile epileptic encephalopathy

- e. said target cytosolic protein is CDKL5, and said disease is early infantile epileptic encephalopathy type 2;
- f. said target cytosolic protein is ATP7B, and said disease is Wilson disease;
- g. said target cytosolic protein is STXBP1, and said disease is STXBP1 encephalopathy;
- h. said target cytosolic protein is STXBP1, and said disease is an early infantile epileptic encephalopathy;
- i. said target cytosolic protein is STXBP1, and said disease is early infantile epileptic encephalopathy type 4;
- j. said target cytosolic protein is GRN, and said disease is aphasia primary progressive & FTD (frontotemporal degeneration);
- k. said target cytosolic protein is JAG1, and said disease is alagille syndrome 1;
- l. said target cytosolic protein is DEPDC5, and said disease is epilepsy (e.g., familial focal, with variable foci 1);
- m. said target cytosolic protein is TSC2, and said disease is tuberous sclerosis;
- n. said target cytosolic protein is TSC2, and said disease is tuberous sclerosis type 2;
- o. said target cytosolic protein is TSC2, and said disease is tuberous sclerosis type 1;
- p. said target cytosolic protein is TSC1, and said disease is tuberous sclerosis;
- q. said target cytosolic protein is TSC1, and said disease is tuberous sclerosis type 1;
- r. said target cytosolic protein is TSC1, and said disease is tuberous sclerosis type 2;
- s. said target cytosolic protein is KIF1A, and said disease is KIF1A-associated neurological disorder;
- t. said target cytosolic protein is DNMI, and said disease is a DNMI encephalopathy;
- u. said target cytosolic protein is DNMI, and said disease is encephalopathy;
- v. said target cytosolic protein is SHANK3, and said disease is Phelan-McDermid syndrome;
- w. said target cytosolic protein is DMD, and said disease is Becker Muscular Dystrophy;
- x. said target cytosolic protein is RP1, and said disease is retinitis pigmentosa 1;

- y. said target cytosolic protein is TTN, and said disease is dilated cardiomyopathy 1G;
  - z. said target cytosolic protein is DYNC1H1, and said disease is DYNC1H1 Syndrome;
  - aa. said target cytosolic protein is TRIO, and said disease is TRIO-Related intellectual disability (ID);
  - bb. said target cytosolic protein is USP9X, and said disease is USP9X development disorder;
  - cc. said target cytosolic protein is CSTB, and the disease is epilepsy, progressive myoclonic 1 (EPM1); or
  - dd. the target cytosolic protein is PCBD1, and the disease is hyperphenylalaninemia, BH4-deficient, D (HPABH4D).
56. The method of any one of claims 47-55, wherein said disease is a haploinsufficiency disease.
57. The method of any one of claims 47-56, wherein said fusion protein, nucleic acid molecule, vector, viral particle, or pharmaceutical composition is administered at a therapeutically effective dose.
58. The method of any one of claims 47-57, wherein said fusion protein, nucleic acid molecule, vector, viral particle, or pharmaceutical composition is administered systematically or locally.
59. The method of any one of claims 47-58, wherein said fusion protein, nucleic acid molecule, vector, viral particle, or pharmaceutical composition is administered intravenously, subcutaneously, or intramuscularly.
60. The fusion protein of any one of claims 1-37, the polynucleotide of claim 38, the DNA of claim 39, the RNA of claim 40, the vector of any one of claims 41-42, the viral particle of claim 43, or the pharmaceutical composition of claim 45 for use as a medicament.
61. The fusion protein of any one of claims 1-37, the polynucleotide of claim 38, the DNA of claim 39, the RNA of claim 40, the vector of any one of claims 41-42, the viral particle of claim 43, or the pharmaceutical composition of claim 45 for use in treating or inhibiting a genetic disorder.

62. A single variable domain antibody (VHH) that specifically binds SYNGAP1 comprising three complementarity determining regions: CDR1, CDR2, and CDR3, wherein
- a. the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 290, 294, 298, 302, 306, or 310, or the amino acid sequence of SEQ ID NO: 290, 294, 298, 302, 306, or 310 comprising 1, 2, or 3 amino acid modifications;
  - b. the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 291, 295, 299, 303, 307, or 311, or the amino acid sequence of SEQ ID NO: 291, 295, 299, 303, 307, or 311 comprising 1, 2, or 3 amino acid modifications; and/or
  - c. the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 292, 296, 300, 304, 308, or 312, or the amino acid sequence of SEQ ID NO: 292, 296, 300, 304, 308, or 312 comprising 1, 2, or 3 amino acid modifications.
63. The VHH of claim 62, wherein
- a. the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 290, or the amino acid sequence of SEQ ID NO: 290 comprising 1, 2, or 3 amino acid modifications;
  - b. the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 291, or the amino acid sequence of SEQ ID NO: 291 comprising 1, 2, or 3 amino acid modifications; and/or
  - c. the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 292, or the amino acid sequence of SEQ ID NO: 292 comprising 1, 2, or 3 amino acid modifications.
64. The VHH of claim 62, wherein
- a. the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 294, or the amino acid sequence of SEQ ID NO: 294 comprising 1, 2, or 3 amino acid modifications;
  - b. the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 295, or the amino acid sequence of SEQ ID NO: 295 comprising 1, 2, or 3 amino acid modifications; and/or



- c. the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 296, or the amino acid sequence of SEQ ID NO: 296 comprising 1, 2, or 3 amino acid modifications.
- 65. The VHH of claim 62, wherein
  - a. the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 298, or the amino acid sequence of SEQ ID NO: 298 comprising 1, 2, or 3 amino acid modifications;
  - b. the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 299, or the amino acid sequence of SEQ ID NO: 299 comprising 1, 2, or 3 amino acid modifications; and/or
  - c. the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 300, or the amino acid sequence of SEQ ID NO: 300 comprising 1, 2, or 3 amino acid modifications.
- 66. The VHH of claim 62, wherein
  - a. the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 302, or the amino acid sequence of SEQ ID NO: 302 comprising 1, 2, or 3 amino acid modifications;
  - b. the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 303, or the amino acid sequence of SEQ ID NO: 303 comprising 1, 2, or 3 amino acid modifications; and/or
  - c. the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 304, or the amino acid sequence of SEQ ID NO: 304 comprising 1, 2, or 3 amino acid modifications.
- 67. The VHH of claim 62, wherein
  - a. the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 306, or the amino acid sequence of SEQ ID NO: 306 comprising 1, 2, or 3 amino acid modifications;
  - b. the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 307, or the amino acid sequence of SEQ ID NO: 307 comprising 1, 2, or 3 amino acid modifications; and/or

- c. the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 308, or the amino acid sequence of SEQ ID NO: 308 comprising 1, 2, or 3 amino acid modifications.
68. The VHH of claim 62, wherein
- a. the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 310, or the amino acid sequence of SEQ ID NO: 310 comprising 1, 2, or 3 amino acid modifications;
  - b. the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 311, or the amino acid sequence of SEQ ID NO: 311 comprising 1, 2, or 3 amino acid modifications; and/or
  - c. the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 312, or the amino acid sequence of SEQ ID NO: 312 comprising 1, 2, or 3 amino acid modifications.
69. The VHH of any one of claims 62-68, wherein said VHH comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 293, 297, 301, 305, 309, or 313.
70. A (VHH)<sub>2</sub> comprising a first VHH that specifically binds SYNGAP1 comprising three complementarity determining regions: CDR1, CDR2, and CDR3, wherein
- a. the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 290, 294, 298, 302, 306, or 310, or the amino acid sequence of SEQ ID NO: 290, 294, 298, 302, 306, or 310 comprising 1, 2, or 3 amino acid modifications;
  - b. the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 291, 295, 299, 303, 307, or 311, or the amino acid sequence of SEQ ID NO: 291, 295, 299, 303, 307, or 311 comprising 1, 2, or 3 amino acid modifications; and/or
  - c. the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 292, 296, 300, 304, 308, or 312, or the amino acid sequence of SEQ ID NO: 292, 296, 300, 304, 308, or 312 comprising 1, 2, or 3 amino acid modifications; and
- a second VHH that specifically binds SYNGAP1 comprising three complementarity determining regions: CDR1, CDR2, and CDR3, wherein

- d. the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 290, 294, 298, 302, 306, or 310, or the amino acid sequence of SEQ ID NO: 290, 294, 298, 302, 306, or 310 comprising 1, 2, or 3 amino acid modifications;
- e. the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 291, 295, 299, 303, 307, or 311, or the amino acid sequence of SEQ ID NO: 291, 295, 299, 303, 307, or 311 comprising 1, 2, or 3 amino acid modifications; and/or
- f. the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 292, 296, 300, 304, 308, or 312, or the amino acid sequence of SEQ ID NO: 292, 296, 300, 304, 308, or 312 comprising 1, 2, or 3 amino acid modifications;

wherein the first VHH and the second VHH are directly or indirectly operably connected.

71. The (VHH)<sub>2</sub> of claim 70, wherein the first VHH comprises three CDRs: CDR1, CDR2, and CDR3, wherein

- a. the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 290, or the amino acid sequence of SEQ ID NO: 290 comprising 1, 2, or 3 amino acid modifications;
- b. the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 291, or the amino acid sequence of SEQ ID NO: 291 comprising 1, 2, or 3 amino acid modifications; and/or
- c. the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 292, or the amino acid sequence of SEQ ID NO: 292 comprising 1, 2, or 3 amino acid modifications; and

the second VHH comprises three CDRs: CDR1, CDR2, and CDR3, wherein

- d. the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 290, or the amino acid sequence of SEQ ID NO: 290 comprising 1, 2, or 3 amino acid modifications;
- e. the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 291, or the amino acid sequence of SEQ ID NO: 291 comprising 1, 2, or 3 amino acid modifications; and/or
- f. the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 292, or the amino acid sequence of SEQ ID NO: 292 comprising 1, 2, or 3 amino acid modifications.

72. The (VHH)<sub>2</sub> of claim 70, wherein the first VHH comprises three CDRs: CDR1, CDR2, and CDR3, wherein

- a. the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 294, or the amino acid sequence of SEQ ID NO: 294 comprising 1, 2, or 3 amino acid modifications;
- b. the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 295, or the amino acid sequence of SEQ ID NO: 295 comprising 1, 2, or 3 amino acid modifications; and/or
- c. the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 296, or the amino acid sequence of SEQ ID NO: 296 comprising 1, 2, or 3 amino acid modifications; and

the second VHH comprises three CDRs: CDR1, CDR2, and CDR3, wherein

- d. the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 294, or the amino acid sequence of SEQ ID NO: 294 comprising 1, 2, or 3 amino acid modifications;
- e. the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 295, or the amino acid sequence of SEQ ID NO: 295 comprising 1, 2, or 3 amino acid modifications; and/or
- f. the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 296, or the amino acid sequence of SEQ ID NO: 296 comprising 1, 2, or 3 amino acid modifications.

73. The (VHH)<sub>2</sub> of claim 70, wherein the first VHH comprises three CDRs: CDR1, CDR2, and CDR3, wherein

- a. the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 298, or the amino acid sequence of SEQ ID NO: 298 comprising 1, 2, or 3 amino acid modifications;
- b. the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 299, or the amino acid sequence of SEQ ID NO: 299 comprising 1, 2, or 3 amino acid modifications; and/or

- c. the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 300, or the amino acid sequence of SEQ ID NO: 300 comprising 1, 2, or 3 amino acid modifications; and

the second VHH comprises three CDRs: CDR1, CDR2, and CDR3, wherein

- d. the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 298, or the amino acid sequence of SEQ ID NO: 298 comprising 1, 2, or 3 amino acid modifications;
- e. the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 299, or the amino acid sequence of SEQ ID NO: 299 comprising 1, 2, or 3 amino acid modifications; and/or
- f. the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 300, or the amino acid sequence of SEQ ID NO: 300 comprising 1, 2, or 3 amino acid modifications.

74. The (VHH)<sub>2</sub> of claim 70, wherein the first VHH comprises three CDRs: CDR1, CDR2, and CDR3, wherein

- a. the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 302, or the amino acid sequence of SEQ ID NO: 302 comprising 1, 2, or 3 amino acid modifications;
- b. the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 303, or the amino acid sequence of SEQ ID NO: 303 comprising 1, 2, or 3 amino acid modifications; and/or
- c. the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 304, or the amino acid sequence of SEQ ID NO: 304 comprising 1, 2, or 3 amino acid modifications; and

the second VHH comprises three CDRs: CDR1, CDR2, and CDR3, wherein

- d. the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 302, or the amino acid sequence of SEQ ID NO: 302 comprising 1, 2, or 3 amino acid modifications;
- e. the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 303, or the amino acid sequence of SEQ ID NO: 303 comprising 1, 2, or 3 amino acid modifications; and/or

- f. the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 304, or the amino acid sequence of SEQ ID NO: 304 comprising 1, 2, or 3 amino acid modifications.

75. The (VHH)<sub>2</sub> of claim 70, wherein the first VHH comprises three CDRs: CDR1, CDR2, and CDR3, wherein

- a. the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 306, or the amino acid sequence of SEQ ID NO: 306 comprising 1, 2, or 3 amino acid modifications;
- b. the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 307, or the amino acid sequence of SEQ ID NO: 307 comprising 1, 2, or 3 amino acid modifications; and/or
- c. the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 308, or the amino acid sequence of SEQ ID NO: 308 comprising 1, 2, or 3 amino acid modifications; and

the second VHH comprises three CDRs: CDR1, CDR2, and CDR3, wherein

- d. the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 306, or the amino acid sequence of SEQ ID NO: 306 comprising 1, 2, or 3 amino acid modifications;
- e. the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 307, or the amino acid sequence of SEQ ID NO: 307 comprising 1, 2, or 3 amino acid modifications; and/or
- f. the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 308, or the amino acid sequence of SEQ ID NO: 308 comprising 1, 2, or 3 amino acid modifications.

76. The (VHH)<sub>2</sub> of claim 70, wherein the first VHH comprises three CDRs: CDR1, CDR2, and CDR3, wherein

- a. the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 310, or the amino acid sequence of SEQ ID NO: 310 comprising 1, 2, or 3 amino acid modifications;

- b. the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 311, or the amino acid sequence of SEQ ID NO: 311 comprising 1, 2, or 3 amino acid modifications; and/or
- c. the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 312, or the amino acid sequence of SEQ ID NO: 312 comprising 1, 2, or 3 amino acid modifications; and

the second VHH comprises three CDRs: CDR1, CDR2, and CDR3, wherein

- d. the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 310, or the amino acid sequence of SEQ ID NO: 310 comprising 1, 2, or 3 amino acid modifications;
- e. the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 311, or the amino acid sequence of SEQ ID NO: 311 comprising 1, 2, or 3 amino acid modifications; and/or
- f. the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 312, or the amino acid sequence of SEQ ID NO: 312 comprising 1, 2, or 3 amino acid modifications.

77. The (VHH)<sub>2</sub> of any one of claims 70, wherein said first VHH comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 293, 297, 301, 305, 309, or 313; and said second VHH comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 293, 297, 301, 305, 309, or 313.

78. The (VHH)<sub>2</sub> of any one of claims 70, wherein

- a. said first VHH comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 293; and said second VHH comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 293;
- b. said first VHH comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 297; and said second VHH comprises an amino acid sequence at

- least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 297;
- c. said first VHH comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 301; and said second VHH comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 301;
  - d. said first VHH comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 305; and said second VHH comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 305;
  - e. said first VHH comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 309; and said second VHH comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 309; or
  - f. said first VHH comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 313; and said second VHH comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 313.

79. The (VHH)<sub>2</sub> of any one of claims 62-78, wherein said first VHH is operably connected to said second VHH via a peptide linker.

80. The (VHH)<sub>2</sub> of claim 62-78, wherein said peptide linker comprises the amino acid sequence of any one of SEQ ID NOS: 375-384 or 402-519, or the amino acid sequence of any one of SEQ ID NOS: 375-384 or 402-519 comprising 1, 2, or 3 amino acid modifications.

81. The (VHH)<sub>2</sub> of claim 80, wherein said peptide linker comprises the amino acid sequence of any one of SEQ ID NOS: 375-384, or the amino acid sequence of any one of SEQ ID NOS: 375-384 comprising 1, 2, or 3 amino acid modifications.



82. The (VHH)<sub>2</sub> of any one of claims 70-81, wherein said (VHH)<sub>2</sub> comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 314-319.
83. A nucleic acid molecule encoding the VHH of any one of claims 62-69 or the (VHH)<sub>2</sub> of any one of claims 70-82.
84. The nucleic acid molecule of claim 83, wherein said nucleic acid molecule is a DNA molecule.
85. The nucleic acid molecule of claim 83, wherein said nucleic acid molecule is an RNA molecule.
86. A vector comprising the nucleic acid molecule of any one of claims 83-85.
87. The vector of claim 86, wherein said vector is a plasmid or a viral vector.
88. A viral particle comprising the nucleic acid molecule of any one of claims 83-85.
89. An in vitro cell or population of cells comprising the VHH of any one of claims 62-69 or the (VHH)<sub>2</sub> of any one of claims 70-82, the nucleic acid molecule of any one of claims 83-85, or the vector of any one of claims 86-87.
90. A pharmaceutical composition comprising the VHH of any one of claims 62-69 or the (VHH)<sub>2</sub> of any one of claims 70-82, the nucleic acid molecule of any one of claims 83-85, the vector of any one of claims 86-87, or the viral particle of claim 88, and an excipient.
91. A method of making the VHH of any one of claims 62-69 or the (VHH)<sub>2</sub> of any one of claims 70-82, comprising
- introducing into an in vitro cell or population of cells the nucleic acid molecule of any one of claims 83-85, the vector of any one of claims 86-87, the viral particle of claim 88;
  - culturing the cell or population of cells in a culture medium under conditions suitable for expression of the fusion protein,
  - isolating the fusion protein from the culture medium, and
  - optionally purifying the fusion protein.
92. The fusion protein of any one of claims 1-37, wherein said targeting domain comprises a VHH of any one of claims 62-69, or a (VHH)<sub>2</sub> of any one of claims 70-82.

93. The fusion protein of claim 92, wherein said catalytic domain comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 286.
94. The fusion protein of any one of claims 92-93, wherein said effector domain is indirectly fused to said targeting domain via a peptide linker of sufficient length such that said effector domain and said targeting domain can simultaneously bind the respective target proteins.
95. The fusion protein of claim 94, wherein said peptide linker comprises the amino acid sequence of any one of SEQ ID NOS: 375-384 or 402-519, or the amino acid sequence of any one of SEQ ID NOS: 375-384 or 402-519 comprising 1, 2, or 3 amino acid modifications.
96. The fusion protein of claim 95, wherein said peptide linker comprises the amino acid sequence of any one of SEQ ID NOS: 375-384, or the amino acid sequence of any one of SEQ ID NOS: 375-384 comprising 1, 2, or 3 amino acid modifications.
97. The fusion protein of any one of claims 92-96, wherein said effector domain is operably connected either directly or indirectly to the C terminus of said targeting domain.
98. The fusion protein of any one of claims 92-97, wherein said effector moiety is operably connected either directly or indirectly to the N terminus of said targeting domain.
99. The fusion protein of any one of claims 9-98, wherein said fusion protein comprises an amino acid sequence at least at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 320-367.
100. A nucleic acid molecule encoding the fusion protein of any one of claims 92-99.
101. The nucleic acid molecule of claim 100, wherein said nucleic acid molecule is a DNA molecule.
102. The nucleic acid molecule of claim 100, wherein said nucleic acid molecule is an RNA molecule.
103. A vector comprising the nucleic acid molecule of any one of claims 99-102.
104. The vector of claim 103, wherein said vector is a plasmid or a viral vector.
105. A viral particle comprising the nucleic acid molecule of any one of claims 99-102.

106. An in vitro cell or population of cells comprising the fusion protein of any one of claims 92-99, the nucleic acid molecule of any one of claims 100-102, or the vector of any one of claims 103-104.
107. A pharmaceutical composition comprising the fusion protein of any one of claims 92-99, the nucleic acid molecule of any one of claims 100-102, the vector of any one of claims 103-104, or the viral particle of claim 105, and an excipient.
108. A method of making the fusion protein of any one of claims 92-99, comprising
- introducing into an in vitro cell or population of cells the nucleic acid molecule of any one of claims 100-102, the vector of any one of claims 103-104, the viral particle of claim 105;
  - culturing the cell or population of cells in a culture medium under conditions suitable for expression of the fusion protein,
  - isolating the fusion protein from the culture medium, and
  - optionally purifying the fusion protein.
109. A method of treating or preventing a disease in a subject comprising administering the fusion protein of any one of claims 92-99, the nucleic acid molecule of any one of claims 100-102, the vector of any one of claims 103-104, the viral particle of claim 105, or the pharmaceutical composition of claim 107, to a subject in need thereof.
110. The method of claim 109, wherein the subject is human.
111. The method of any one of claims 109-110, wherein said disease is SYNGAP1 encephalopathy.
112. The method of any one of claims 108-110, wherein said fusion protein, nucleic acid molecule, vector, viral particle, or pharmaceutical composition is administered at a therapeutically effective dose.
113. The method of any one of claims 109-112, wherein said fusion protein, nucleic acid molecule, vector, viral particle, or pharmaceutical composition is administered systematically or locally.
114. The method of any one of claims 109-113, wherein said fusion protein, nucleic acid molecule, vector, viral particle, or pharmaceutical composition is administered intravenously, subcutaneously, or intramuscularly.

115. The fusion protein of any one of claims 92-99, the polynucleotide of claim 100, the DNA of claim 101, the RNA of claim 102, the vector of any one of claims 103-104, the viral particle of claim 105, or the pharmaceutical composition of claim 107 for use as a medicament.

116. The fusion protein of any one of claims 92-99, the polynucleotide of claim 100, the DNA of claim 101, the RNA of claim 102, the vector of any one of claims 103-104, the viral particle of claim 105, or the pharmaceutical composition of claim 107 for use in treating or inhibiting a genetic disorder.

**FIG. 1A****FIG. 1B****FIG. 1C****FIG. 1D**

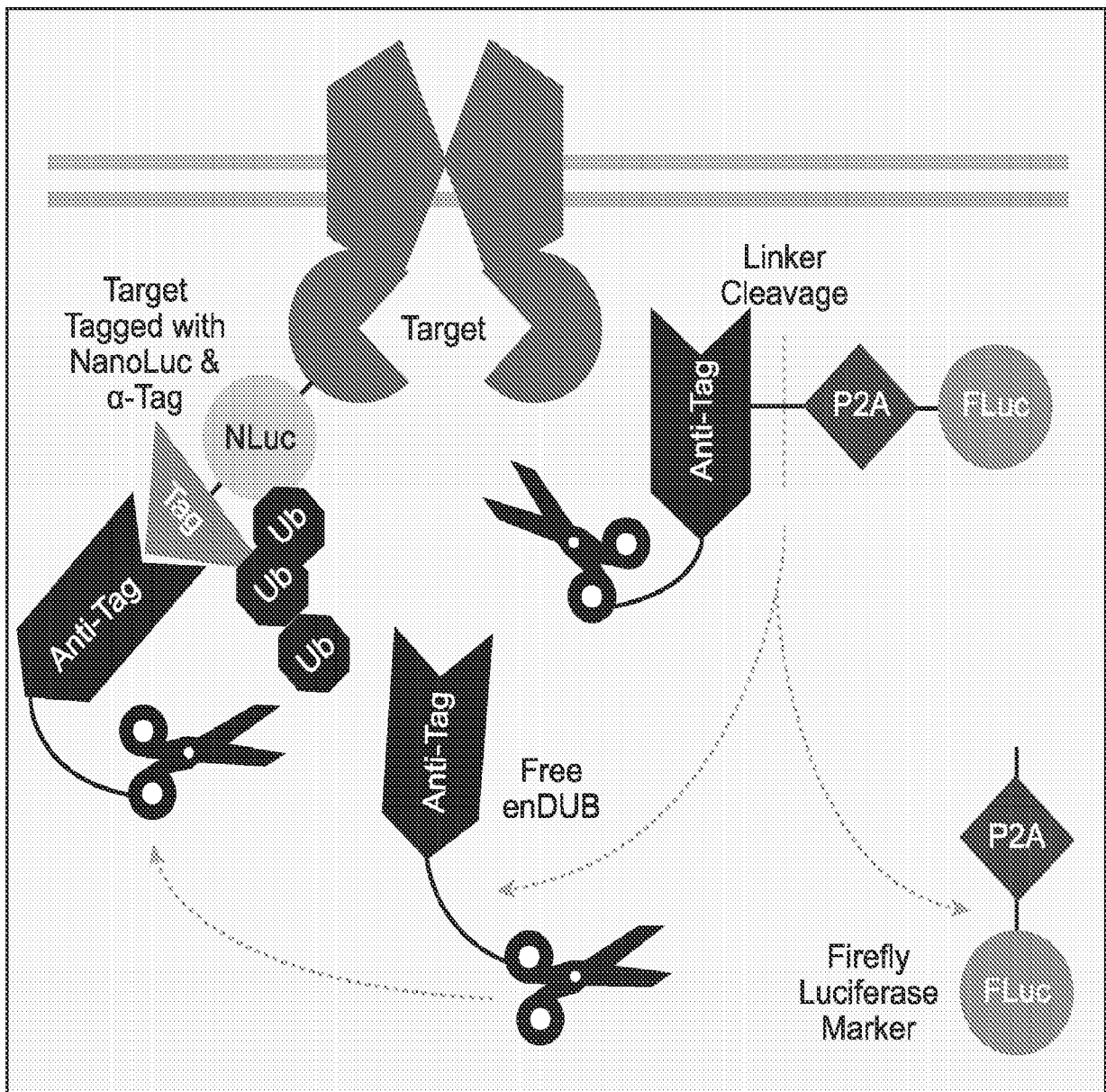


FIG. 2

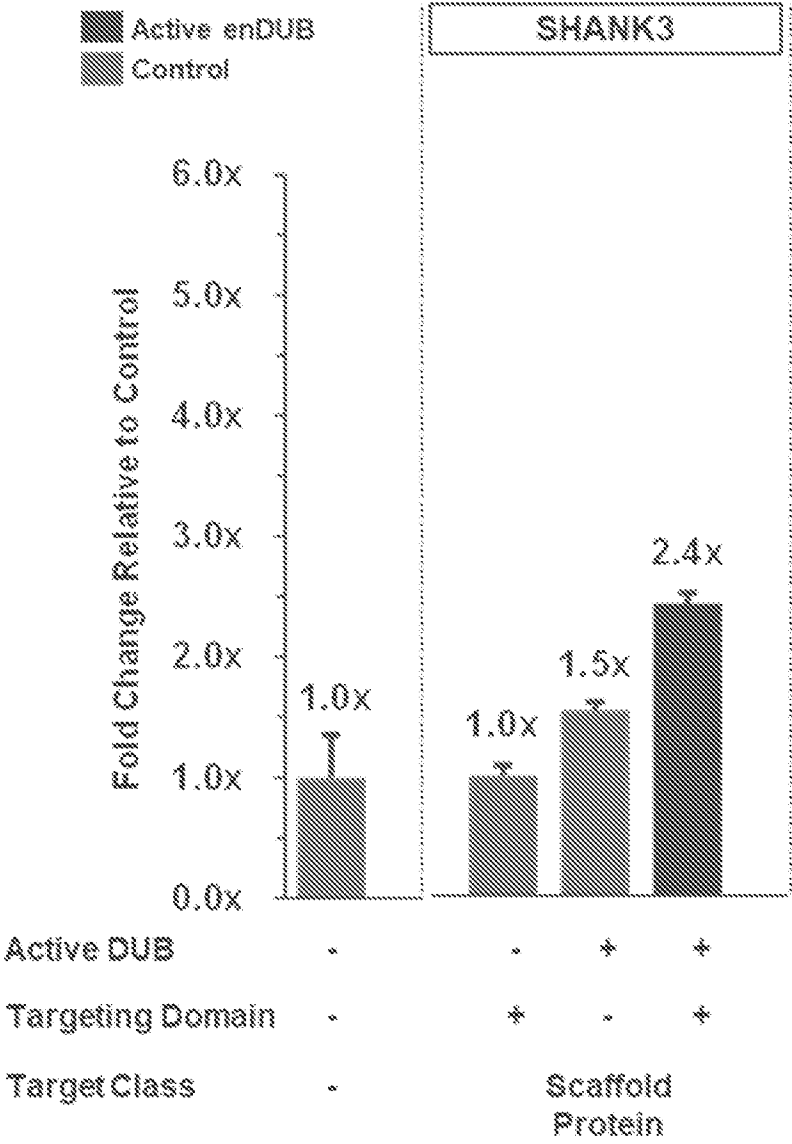


FIG. 3

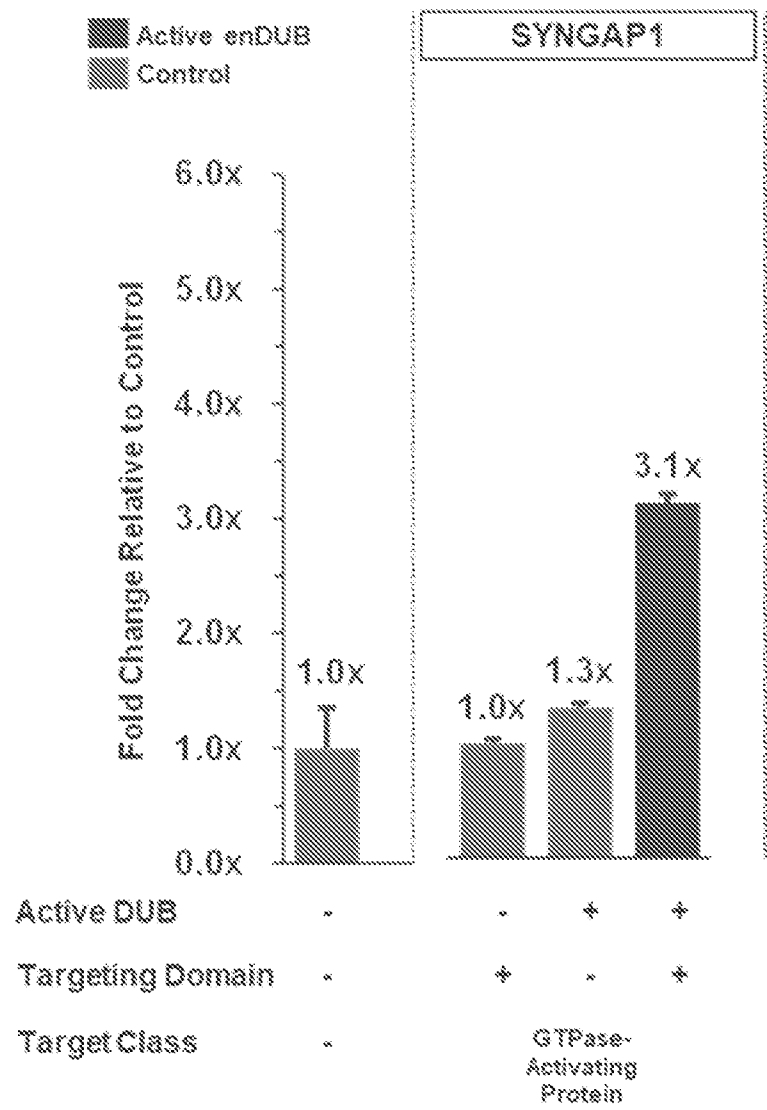


FIG. 4



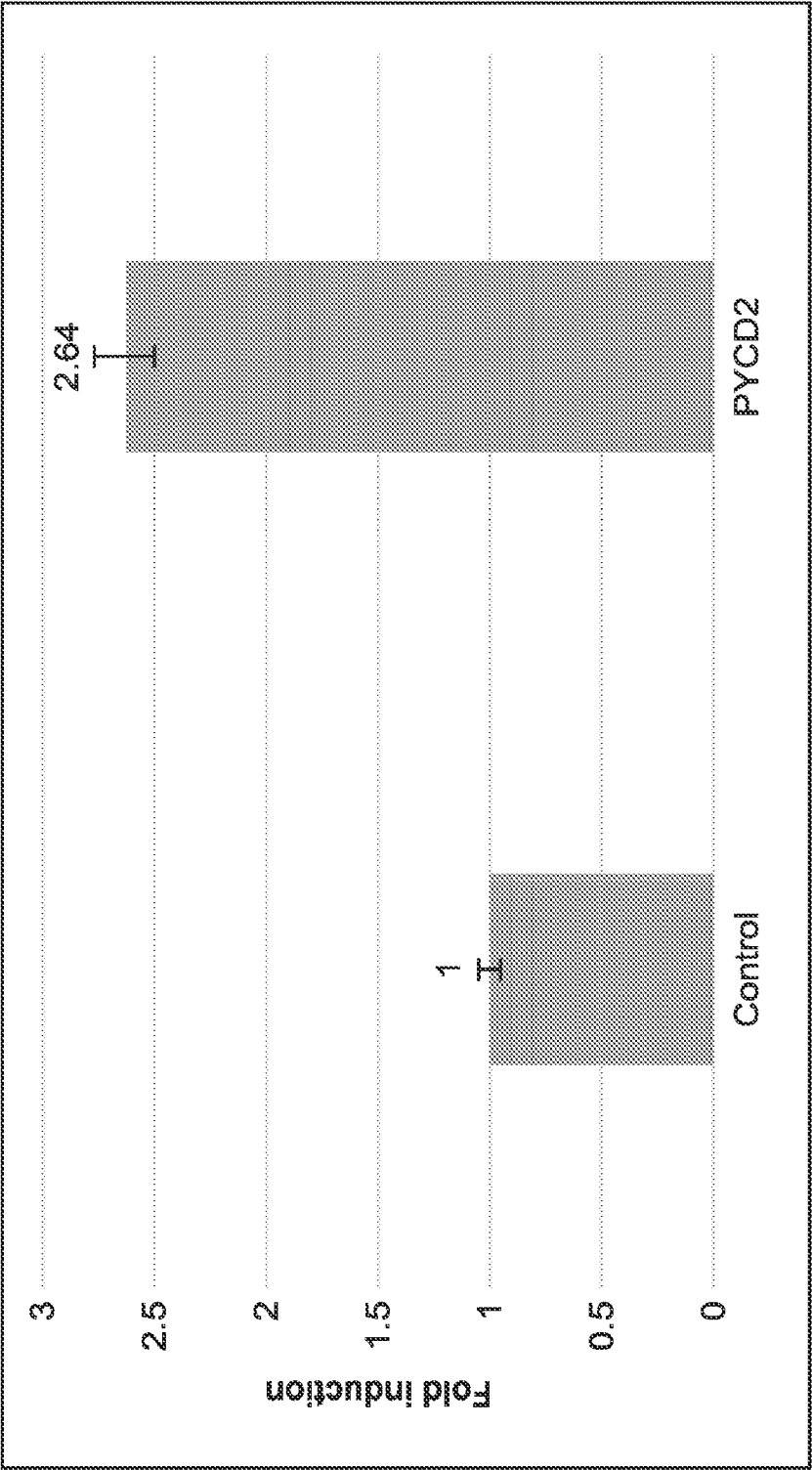


FIG. 5

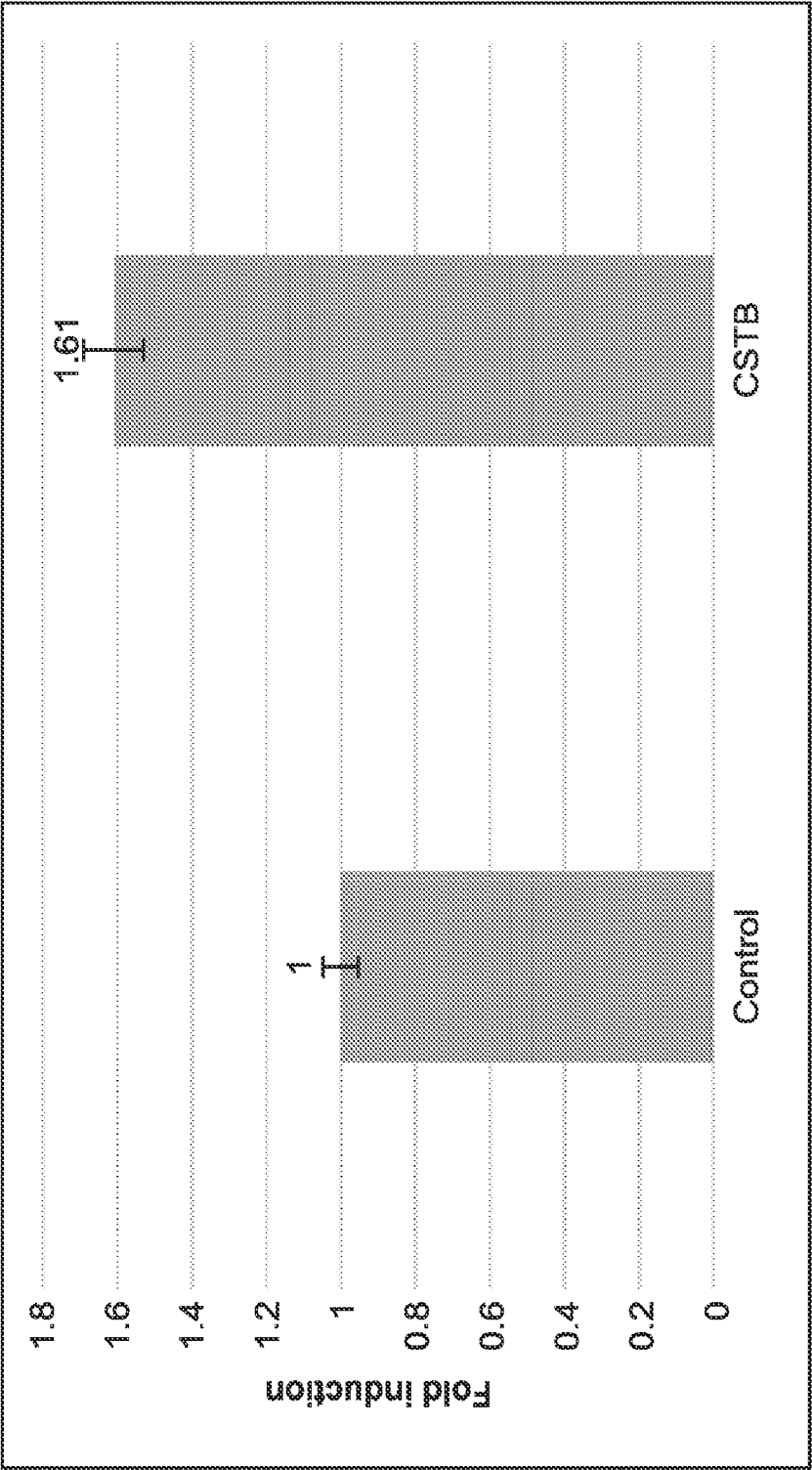


FIG. 6

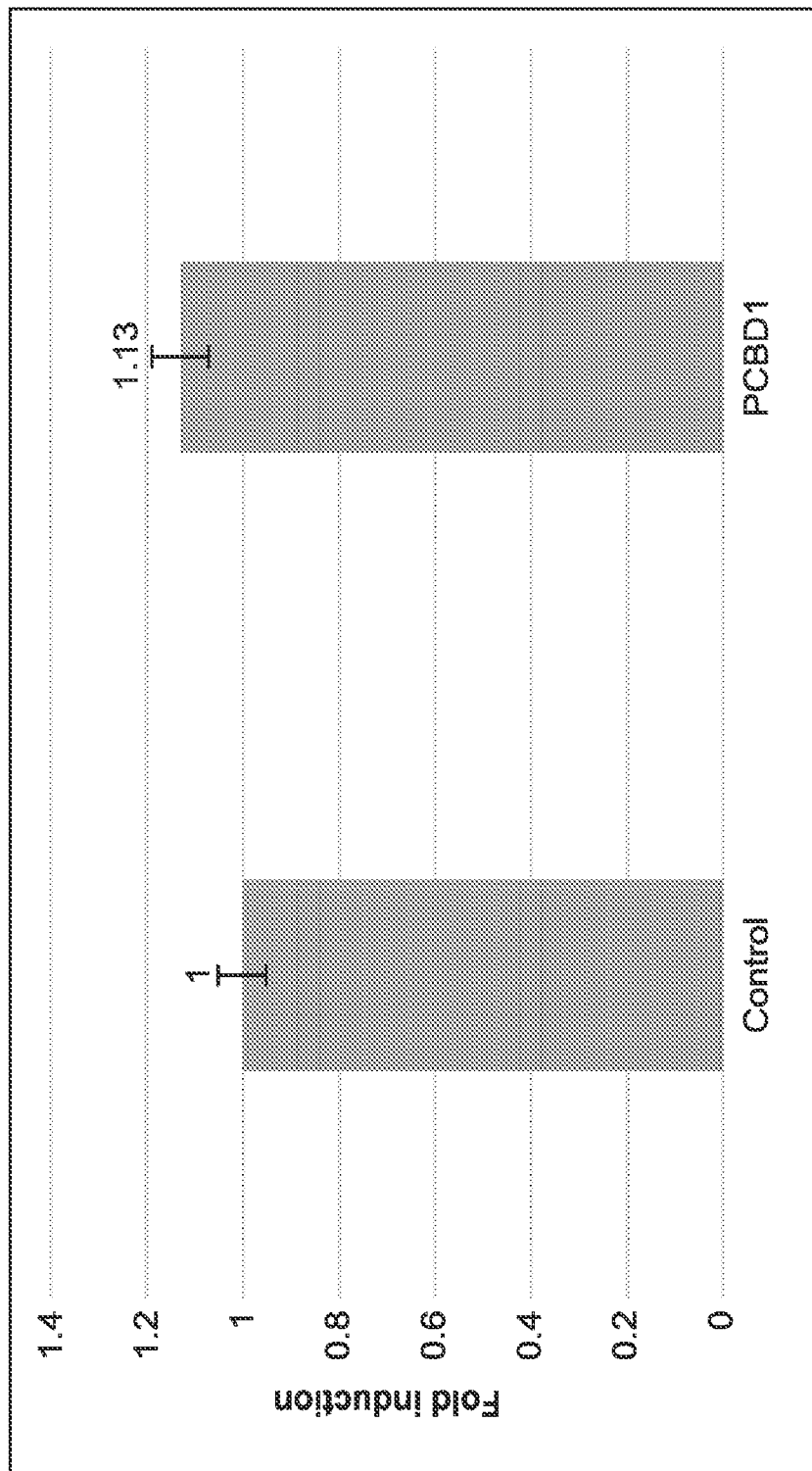


FIG. 7

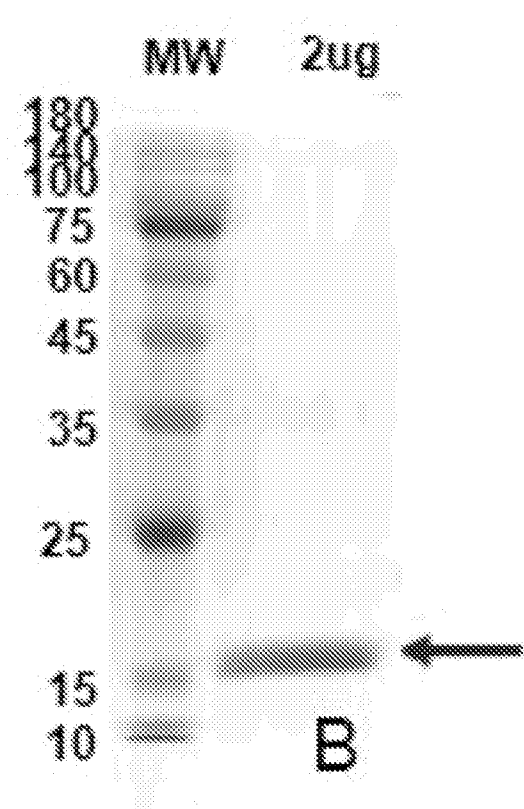


FIG. 8

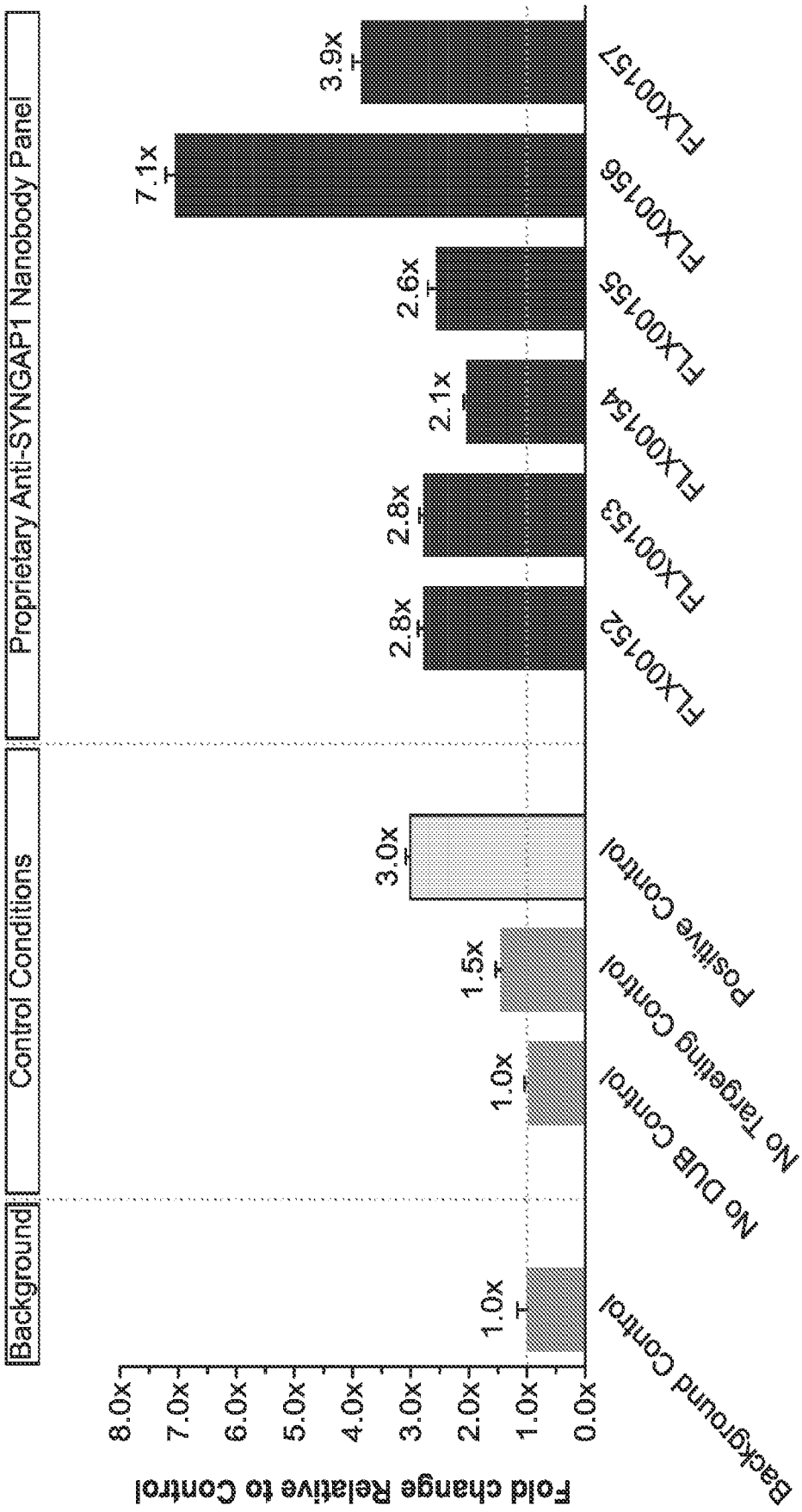


FIG. 9

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2021/058285

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C07K 14/415; C12N 9/22; C12N 15/86 (2022.01)

CPC - C07K 14/415; C12N 9/22; C12N 15/86 (2022.02)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

see Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

see Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

see Search History document

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages           | Relevant to claim No. |
|-----------|----------------------------------------------------------------------------------------------|-----------------------|
| A         | WO 2019/126762 A2 (THE BROAD INSTITUTE INC. et al) 27 June 2019 (27.06.2019) entire document | 1                     |
| A         | WO 2009/143622 A1 (CHUM) 03 December 2009 (03.12.2009) entire document                       | 1                     |

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

Date of the actual completion of the international search

05 April 2022

Date of mailing of the international search report

APR 18 2022

Name and mailing address of the ISA/US

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Facsimile No. 571-273-8300

Authorized officer

Harry Kim

Telephone No. PCT Helpdesk: 571-272-4300

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2021/058285

**Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)**

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

- a. ☐ forming part of the international application as filed:
    - ☐ in the form of an Annex C/ST.25 text file.
    - ☐ on paper or in the form of an image file.
  - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
  - c. ☒ furnished subsequent to the international filing date for the purposes of international search only:
    - ☒ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
    - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

SEQ ID NOs: 1, 293, and 390 were searched.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2021/058285

## Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 20-61, 79-116  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See extra sheet(s).

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.



Continued from Box No. III Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-19 are drawn to fusion proteins.

Group II+: claims 62-78 are drawn to single variable domain antibodies which bind SYNGAP1.

The first invention of Group I+ is restricted to a fusion protein selected to be SEQ ID NO:390. It is believed that claim 1 reads on this first named invention and thus these claims will be searched without fee to the extent that they read on SEQ ID NO:390.

The first invention of Group II+ is restricted to a single variable domain antibody (VHH) selected to be SEQ ID NO:293.

Applicant is invited to elect additional fusion proteins and their respective, corresponding, SEQ ID NOS to be searched in a specific combination by paying additional fee for each set of election. An exemplary election would be a fusion protein selected to be SEQ ID NO:391. Additional fusion proteins and their respective, corresponding, SEQ ID NOS will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ and group II+ formulas do not share a significant structural element responsible for treating genetic diseases requiring the selection of alternative fusion proteins where "The fusion protein of any one of the preceding claims, wherein said deubiquitinase comprises an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOS: 1-112," or alternative single domain antibodies where "A single variable domain antibody (VHH) that specifically binds SYNGAPI comprising three complementarity determining regions: CDR1, CDR2, and CDR3, wherein a. the amino acid sequence of CDR1 comprises the amino acid sequence of SEQ ID NO: 290, 294, 298, 302, 306, or 310, or the amino acid sequence of SEQ ID NO:290, 294, 298, 302, 306, or 310 comprising 1, 2, or 3 amino acid modifications; b. the amino acid sequence of CDR2 comprises the amino acid sequence of SEQ ID NO: 291, 295, 299, 303, 307, or 311, or the amino acid sequence of SEQ ID NO:291, 295, 299, 303, 307, or 311 comprising 1, 2, or 3 amino acid modifications; and/or c. the amino acid sequence of CDR3 comprises the amino acid sequence of SEQ ID NO: 292, 296, 300, 304, 308, or 312, or the amino acid sequence of SEQ ID NO:292, 296, 300, 304, 308, or 312 comprising 1, 2, or 3 amino acid modifications."

The special technical features of Groups I+, a fusion protein comprising an effector domain and a targeting domain, are not present in Groups II+; the special technical features of Groups II+, a single variable domain antibody, are not present in Groups I+.

Additionally, even if Groups I+ were considered to share the technical features of a fusion protein comprising: a. an effector domain comprising a catalytic domain of a deubiquitinase, or a functional fragment or functional variant thereof, and b. a targeting domain comprising a targeting moiety that specifically binds a cytosolic protein. However, these shared technical features do not represent a contribution over the prior art.

Specifically, WO 2019/126762 A2 to The Broad Institute Inc. et al. discloses a fusion protein (a fusion protein, Para. [0123]) comprising: a. an effector domain comprising a catalytic domain of a deubiquitinase, or a functional fragment or functional variant thereof, and b. a targeting domain comprising a targeting moiety that specifically binds a cytosolic protein (wherein the RNA targeting domain comprises a catalytically inactive CpfI or CpfI nickase protein, Para. [0036]; at least one or more half-monomers specifically ordered to target the genomic locus of interest linked to at least one or more effector domains are further linker to a chemical or energy sensitive protein, Para. [0553]; the functional domain may be selected from ...deubiquitinase, Para. [0174]; NUPR1 (nuclear protein, transcriptional regulator, 1), Para. [1809]; abundant in cells, especially in the cytosol, Para. [0964]).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical features.