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(71) Applicant(s)
Sigilon Therapeutics, Inc.

(72) Inventor(s)
MILLER, Robert James;BARNEY, Lauren Emily;JOHNSTON, Erika Ellen;HEIDEBRECHT, Richard;BEAUREGARD, Michael;VEISEH, Omid;CARMONA, Guillaume;GONZALEZ, Francisco Caballero;OBERLI, Matthias Alexander;PERITT, David;SMITH, Devyn Mckinley;WOTTON, Paul Kevin;O'CONNOR, Owen;SEWELL, Jared A.

(74) Agent / Attorney
Pearce IP Pty Ltd, L5, 20 Bond St, SYDNEY, NSW, 2000, AU

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(71) Applicant: SIGILON THERAPEUTICS, INC. [US/US];
100 Binney St, Ste 600, Cambridge, MA 02142 (US).

(72) Inventors: MILLER, Robert, James; 100 Binney St, Ste 600, Cambridge, MA 02142 (US). BARNEY, Lauren, Emily; 100 Binney St, Ste 600, Cambridge, MA 02142 (US). JOHNSTON, Erika, Ellen; 100 Binney St, Ste 600, Cambridge, MA 02142 (US). HEIDEBRECHT, Richard; 100 Binney St, Ste 600, Cambridge, MA 02142 (US). BEAUREGARD, Michael; 100 Binney St, Ste 600, Cambridge, MA 02142 (US). VEISEH, Omid; 100 Binney St, Ste 600, Cambridge, MA 02142 (US). CARMONA, Guillaume; 100 Binney St, Ste 600, Cambridge, MA 02142 (US). GONZALEZ, Francisco, Caballero; 100 Binney St, Ste 600, Cambridge, MA 02142 (US). OBERLI, Matthias, Alexander; 100 Binney St, Ste 600, Cambridge, MA 02142 (US). PERITT, David; 100 Binney St, Ste 600, Cambridge, MA 02142 (US). SMITH, Devyn, McKinley; 100 Binney St, Ste 600, Cambridge, MA 02142 (US). WOTTON, Paul, Kevin; 100 Binney St, Ste 600, Cambridge, MA 02142 (US). O'CONNOR, Owen; 100 Binney St, Ste 600, Cambridge, MA 02142 (US). SEWELL, Jared, A.; 100 Binney St, Ste 600, Cambridge, MA 02142 (US).

(74) Agent: COLLAZO, Diana, M. et al.; Lando & Anastasi, LLP, Riverfront Office Park, One Main Street, Suite 1100, Cambridge, MA 02142 (US).

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(54) Title: IMPLANTABLE PARTICLES AND RELATED METHODS

(57) Abstract: Described herein are particles comprising a first compartment, a second compartment, and a compound of Formula (I), as well as compositions and methods of making and using the same. The particles may comprise a cell capable of expressing a therapeutic agent useful for the treatment of a disease, disorder, or condition described herein.



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IMPLANTABLE PARTICLES AND RELATED METHODS

CLAIM OF PRIORITY

5 This application claims priority to U.S. Provisional Application No. 62/652,880, filed April 4, 2018; U.S. Application No. 62/737,838, filed September 27, 2018; and U.S. Application No. 62/812,568, filed March 1, 2019. The disclosure of each of the foregoing applications is incorporated herein by reference in its entirety.

SEQUENCE LISTING

0 The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on September 26, 2018, is named S2225-7022WO_SL.txt and is 205,145 bytes in size.

BACKGROUND

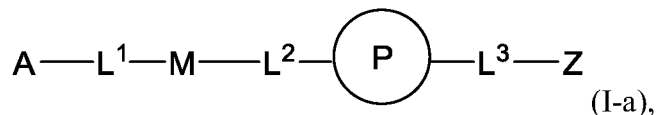
5 The function of implanted particles comprising engineered cells depends on numerous factors including the ability to provide a product and the biological immune response pathway of the recipient (Anderson et al., *Semin Immunol* (2008) 20:86–100; Langer, *Adv Mater* (2009) 21:3235–3236). The performance of such particles after implant will depend to a large extent on their biocompatibility, including the degree to which they are afibrotic, e.g., are able to avoid or
10 mitigate the foreign-body response. Several publications have reported that the foreign body response (FBR) to implanted hydrogel capsules in rodents and non-human primates can be significantly reduced by using spherical capsules that have a size of at least 1 mm in diameter, e.g., millicapsules (Veiseh, O., et al, *Nature Materials* 14:643-652 (2015); WO2014/153126; WO2016/187225) and/or that are prepared using hydrogel-forming polymers that are chemically
25 modified with certain compounds that mitigate the FBR (Vegas, A., et al., *Nature Medicine* 22(3):306-311 (2016), Vegas, A., et al., *Nature Biotechnology* 34(3):345-352 (2016); WO 2012/167223; WO 2017/075631).

Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general
30 knowledge in the field.

SUMMARY

The present invention provides a particle comprising:

- a) a first compartment comprising an alginate polymer and a cell;
- b) a second compartment comprising an alginate polymer; and
- c) a compound of Formula (I-a):



or a pharmaceutically acceptable salt thereof, wherein:

the first compartment is surrounded by the second compartment;

the particle comprises an interface between the first and second compartment;

wherein:

A is alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-O-$, $-C(O)O-$, $-C(O)-$, $-OC(O)-$, $-N(R^C)-$, $-N(R^C)C(O)-$, $-C(O)N(R^C)-$, $-N(R^C)N(R^D)-$, $-NCN-$, $-N(R^C)C(O)(C_1-C_6\text{-alkylene})-$, $-N(R^C)C(O)(C_2-C_6\text{-alkenylene})-$, $-C(=N(R^C)(R^D))O-$, $-S-$, $-S(O)_x-$, $-OS(O)_x-$, $-N(R^C)S(O)_x-$, $-S(O)_xN(R^C)-$, $-P(R^F)_y-$, $-Si(OR^A)_2-$, $-Si(R^G)(OR^A)-$, $-B(OR^A)-$, or a metal, each of which is optionally linked to an attachment group and optionally substituted by one or more R^1 ;

each of L^1 and L^3 is independently a bond, alkyl, or heteroalkyl, wherein each alkyl and heteroalkyl is optionally substituted by one or more R^2 ;

L^2 is a bond;

M is absent, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted by one or more R^3 ;

P is heteroaryl optionally substituted by one or more R^4 ;

Z is alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted by one or more R^5 ;

each R^A , R^B , R^C , R^D , R^E , R^F , and R^G is independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, halogen, azido, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^6 ;

or R^C and R^D , taken together with the nitrogen atom to which they are attached, form a ring, optionally substituted with one or more R^6 ;

each R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 is independently alkyl, alkenyl, alkynyl, heteroalkyl, halogen, cyano, azido, oxo, $-OR^{A1}$, $-C(O)OR^{A1}$, $-C(O)R^{B1}$, $-OC(O)R^{B1}$, $-N(R^{C1})(R^{D1})$, $-N(R^{C1})C(O)R^{B1}$, $-C(O)N(R^{C1})$, SR^{E1} , $S(O)_xR^{E1}$, $-OS(O)_xR^{E1}$, $-N(R^{C1})S(O)_xR^{E1}$, $-S(O)_xN(R^{C1})(R^{D1})$, $-P(R^{F1})_y$, cycloalkyl, heterocyclyl, aryl, heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted by one or more R^7 ;

each R^{A1} , R^{B1} , R^{C1} , R^{D1} , R^{E1} , and R^{F1} is independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl is optionally substituted by one or more R^7 ;

each R^7 is independently alkyl, alkenyl, alkynyl, heteroalkyl, halogen, cyano, oxo, hydroxyl, cycloalkyl, or heterocyclyl;

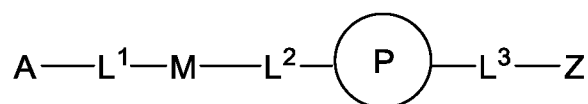
x is 1 or 2; and

y is 2, 3, or 4; and wherein:

the alginate polymer of the second compartment is modified with a compound of Formula (I-a).

Described herein are particles comprising a first compartment, a second compartment, and a compound of Formula (I) (e.g., as described herein), as well as compositions and methods of making and using the same. In some embodiments, the particle comprises a cell (e.g., a cell described herein). In some embodiments, the cell produces a therapeutic agent useful, e.g., for the treatment of a disease, disorder or condition in a subject, e.g., a blood clotting disorder or a lysosomal storage disease. In some embodiments, the particle is capable of modulating the immune response (e.g., FBR) or the effect of an immune response (e.g., FBR) in a subject.

In one aspect, the present disclosure features a particle comprising a) a first compartment; b) a second compartment; and c) a compound of Formula (I):



(I) or a pharmaceutically acceptable salt thereof,

wherein the variables A, L^1 , M, L^2 , P, L^3 , and Z, as well as related subvariables, are defined herein. In some embodiments, the first compartment is surrounded by the second compartment.

In some embodiments, the second compartment forms a barrier around the first compartment.

In some embodiments, the first compartment comprises a compound of Formula (I). In some

embodiments, the second compartment comprises a compound of Formula (I). In some

embodiments, each of the first and second compartments independently comprise a compound of

Formula (I). In some embodiments, a compound of Formula (I) is disposed on the exterior surface of the particle.

In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt thereof (e.g., Formulas (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (II), (II-a), (III), (III-a), (III-b), (III-c), or (III-d)) is a compound described herein. In some embodiments, the compound of Formula (I) is one of the compounds shown in Table 2 herein.

In some embodiments, at least one of the compartments in the particle comprises a polymer. In some embodiments, both the first compartment and the second compartment of the particle comprise a polymer (e.g., a polysaccharide, e.g., alginate). In some embodiments, the first compartment and the second compartment of the particle comprise the same polymer. In some embodiments, the first compartment and the second compartment of the particle comprise a different polymer.

In some embodiments, the polymer is a polysaccharide or other hydrogel-forming polymer (e.g., alginate, hyaluronate or chondroitin). In some embodiments, the polymer is an alginate. In some embodiments, the particle comprises an alginate that is chemically modified with a compound of Formula (I). In some embodiments, the chemically modified alginate has a low molecular weight (e.g., approximate molecular weight of < 75 kD). In some embodiments, the particle comprises a mixture of chemically modified alginate and unmodified alginate. In some embodiments, the particle is a hydrogel capsule. In some embodiments, the particle is a millicapsule or a microcapsule (e.g., a hydrogel millicapsule or a hydrogel microcapsule).

In some embodiments, the particle is spherical. In some embodiments, the total volume (as defined herein) of the second compartment is greater than (e.g. $> 1.5x$, $2x$, $3x$, or $5x$) the volume of the first compartment. In some embodiments, the differential volume (as defined herein) of the second compartment is less than (e.g. $< 1.5x$, $2x$, $3x$, or $5x$) the volume of the first compartment. In some embodiments, the total volume of the second compartment is about 1%, 2%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, or 75% greater than the volume of the first compartment. In some embodiments, the differential volume of the first compartment is greater than (e.g., $> 1.5x$, $2x$, $3x$, or $5x$) the volume of the second compartment. In some embodiments, the total volume of the first compartment is about 1%, 2%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, or 75% greater than the volume of the second compartment.

In some embodiments, the particle has a largest linear dimension (LLD), e.g., diameter, of between about 20 nanometers to about 10 millimeters. In some embodiments, the largest linear dimension (LLD), e.g., diameter, of the particle is between about 500 nanometers to about 10 millimeters, between about 1 millimeter to 10 millimeters, between about 1 millimeter to 5 millimeters, between about 1 millimeter to 4 millimeters, between about 1 millimeter to 3 millimeters, between about 1 millimeter to 2 millimeters, or between about 1.5 millimeters to 2 millimeters or about 1.5 millimeters.

In some embodiments, the average distance between the outer boundary of the second (outer) compartment and the interface is between about 1 nanometers and 1 millimeter, e.g., between about 100 nanometers and 1 millimeter, between about 500 nanometers and about 1 millimeter, or between about 500 nanometers and 500 micrometers.

In some embodiments, the particle comprises a cell. In some embodiments, the first compartment comprises a cell and/or the second compartment comprises a cell. In some embodiments, the first compartment and the second compartment both comprise the same type of cell or different types of cells. In some embodiments, the first compartment comprises a cell and the second compartment does not comprise a cell. A particle described herein may comprise a plurality of cells. The cell or plurality of cells may be present in the particle as single cells, cell clusters (e.g., as spheroids), or attached to a microcarrier. In some embodiments, the particle is formed from a polymer solution and comprises at least any of 5, 10, 15, 20, 30, 40, 50, 75, 100, 150, 200, 250 or 400 million cells/ml of the polymer solution or any number between these values. In some embodiments, the particle comprises an epithelial cell, endothelial cell, fibroblast cell, mesenchymal stem cell, keratinocyte cell or an islet cell or a cell derived from any of the foregoing cell types. In some embodiments, the particle comprises a retinal pigment epithelial (RPE cell) or a mesenchymal stem cell (MSC). In some embodiments, the particle comprises an engineered cell (e.g., an engineered RPE cell or an engineered MSC).

In some embodiments, the particle comprises a cell that expresses a therapeutic agent, such as a nucleic acid (e.g., a nucleotide, DNA, or RNA), a polypeptide, a lipid, a sugar (e.g., a monosaccharide, disaccharide, oligosaccharide, or polysaccharide), or a small molecule. In some embodiments, the therapeutic agent is a replacement therapy or a replacement protein, e.g., useful for the treatment of a blood clotting disorder or a lysosomal storage disease in a subject. In some embodiments, the therapeutic agent is a polypeptide, e.g., a Factor VIII protein or

variant thereof of a Factor IX protein or variant thereof.

In another aspect, the present disclosure features a preparation of a plurality of particles, wherein one or more of the particles in the plurality comprises: a) a first compartment; b) a second compartment; and c) a compound of Formula (I) as described herein. In some 5 embodiments, each particle in the plurality comprises the first and second compartments and a compound of Formula (I). In some embodiments, at least 75%, 80%, 85%, 90%, 95%, 99%, or more of the particles in the plurality are spherical particles. In some embodiments, the preparation is a pharmaceutically acceptable preparation.

In another aspect, the present disclosure features a method of making a particle described 0 herein. In some embodiments, the first compartment of the particle is formed at the same time as the second compartment of the particle. In some embodiments, the method comprises use of an electrostatic droplet generator equipped with a coaxial needle to form multiple droplets from first and second polymer solutions that comprise a hydrogel forming polymer or a mixture of hydrogel forming polymers. In some embodiments, the polymer or mixture of polymers is 5 modified with a compound of Formula (I). In some embodiments, the polymer is an alginate. In some embodiments, the method further comprises contacting the droplets with a cross-linking solution comprising multivalent cations to cross-link each droplet into a particle (e.g., a hydrogel capsule with an inner compartment and an outer compartment). In some embodiments, the cross-linking solution comprises a cross-linking agent, a buffer, and an osmolarity-adjusting 10 agent. In some embodiments, the cross-linking solution further comprises a surfactant.

In another aspect, the present disclosure features a method of implanting a particle described herein into a subject. In another aspect, the present disclosure features a method of providing a substance (e.g., a therapeutic agent, e.g., a polypeptide) to a subject comprising administering to the subject a particle described herein, wherein the particle comprises, or has the 25 ability to produce, the substance. In another aspect, the present disclosure features a method of treating a subject in need of a substance (e.g., a therapeutic agent, e.g., a polypeptide) comprising administering to the subject a particle described herein, wherein the particle comprises, or has the ability to produce, the substance. In some embodiments, the administering step comprises implanting in the subject a pharmaceutically acceptable preparation comprising a plurality of 30 particles, each of which comprises, or has the ability to produce, the substance. In some embodiments, the subject is a mammal (e.g., a human).

In another aspect, the present disclosure features a method of evaluating a particle described herein. In some embodiments, the method comprises providing a particle described herein and evaluating a structural or functional parameter of the particle. In some embodiments, the method comprises evaluating the particle or a plurality of particles described herein for one or more of: a) structural integrity; b) cell viability; c) the production of a therapeutic agent (e.g., a polypeptide); d) the uptake of a nutrient or oxygen; e) the production of a waste product; and f) fibrosis. In some embodiments, the evaluation is performed at least 1, 5, 10, 20, 30, 60, 90 or 120 days after formation of the particle or administration of the particle to a subject. In some embodiments, the subject is a mammal (e.g., a human).

The details of one or more embodiments of the disclosure are set forth herein. Other features, objects, and advantages of the disclosure will be apparent from the Detailed Description, the Figures, the Examples, and the Claims.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 illustrates an exemplary spherical particle of the disclosure, with lines indicating: a first, inner compartment and cells encapsulated therein; a second, outer compartment with an outer boundary; and the interface between the first and second compartments.

FIGS. 2A-2B shows exemplary amino acid sequences encoded by exemplary engineered cells, with **FIG. 2A** showing the amino acid sequence (SEQ ID NO:1) of a Factor VIII-BDD protein encoded by an exemplary engineered cell and **FIG. 2B** showing the amino acid sequence (SEQ ID NO:2) of a human wild-type Factor IX protein.

FIG. 3 is a graph comparing quality of single-compartment and two-compartment hydrogel capsules as a function of equivalent cell loading (million cells/ml alginate), where ml alginate is the sum of alginate used to make the first (inner) compartment and second (outer) compartment of the two-compartment capsules.

FIGS. 4A-4B show the effect of altering the flow rate of extruded alginate on the thickness of the second (outer) compartment of an exemplary particle of the disclosure (i.e., a two-compartment hydrogel millicapsule). **FIG. 4A** is a graph showing the mean second (outer) compartment thickness for particles (about 1.5 millimeter (mm) diameter) produced by varying flow rates of the polymer solutions used to form the first (inner) compartment and second (outer) compartments. **FIG. 4B** is a table of first (inner) compartment and second (outer) compartment

volume percentages and the resulting compartment thicknesses achieved.

FIG. 5 is a graph showing the initial fracture of exemplary particles of the disclosure (i.e., two-compartment hydrogel millicapsules) with varying ratios of inner:outer flow rates (ml/h). The polymer in the first compartment (Inner) is an unmodified high molecular weight alginate and the polymer in the second compartment (Outer) is a mixture of a chemically modified low molecular weight alginate and an unmodified high molecular weight alginate at a 70:30 ratio of chemically modified to unmodified alginate.

FIGS. 6A-6D are brightfield images of exemplary particles (i.e., two-compartment hydrogel millicapsules) with a 50:50 volume ratio of inner:outer compartments. Second (outer) compartments contain low, medium or high conjugation alginate or a control (unmodified), alginate. Exemplary RPE cells engineered to express an exogenous protein were encapsulated in the first (inner) compartment for visualization of the two-compartment architecture.

FIGS. 7A-7F illustrate the effect on fibrosis *in vivo* of varying the level of chemical modification on the alginate comprising the second (outer) compartment of exemplary particles (i.e., two-compartment hydrogel millicapsules). **FIGS. 7A-7E** are brightfield images of particles retrieved from C57/BL6 mice 1 week after implantation. Particles containing the engineered RPE cells within the first (inner) compartment had second (outer) compartments composed of: (i) low, medium or high levels of a compound of Formula (I) conjugated to an alginate, (ii) an unmodified alginate, or (iii) empty capsules composed of medium levels of a compound of Formula (I) conjugated to an alginate. **FIG. 7F** is a graph comparing the mean initial fracture of particles prior to implantation in a mouse model (initial, black bars) and after retrieval following 7 days implantation in C57/BL6 mice (retrieval, gray bars).

FIGS. 8A-8E are images comparing various hydrogel millicapsules and their effect on the fibrotic response. Schematics are shown of the millicapsules retrieved from C57/BL6 mice after a 2-week implantation. **FIG. 8A**: empty capsules comprising no cells. **FIG. 8B**: one-compartment capsules with 5000 cells/capsule; **FIG. 8C**: two-compartment capsules with 5000 cells/particle; **FIG. 8D**: two-compartment capsules with 2500 cells/capsule; **FIG. 8E**: two-compartment capsules with 2500 cells/capsule and a thicker second (outer) compartment.

FIGS. 9A-9K are immunofluorescent staining images comparing the level of macrophage adhesion *in vivo* on exemplary particles (i.e., two-compartment hydrogel millicapsules) with varying (low, medium, or high) amounts of chemically modified alginate in

the second (outer) compartment at 1, 2, and 4 weeks post-implantation in C57/BL6 mice. A positive control (SLG20: unmodified medium MW alginate) and a negative control (empty capsule) were included in these experiments.

FIGS. 10A-10E are brightfield images indicating the level of fibrotic response on exemplary particles (i.e., two-compartment hydrogel millicapsules) 2 weeks post-implantation in C57/BL6 mice. The particles comprised varying (medium, medium high, high, or double high) amounts of chemically modified alginate in the second (outer) compartment. A negative control (empty) capsule with a medium amount of chemically modified alginate in the second (outer) compartment was also included.

FIG. 11 is a graph comparing the mean initial fracture of particles prior to implantation in a mouse model (initial, black bars) and after retrieval following 2 weeks of implantation in C57/BL6 mice (retrieval, gray bars). The particles comprise varying (medium, medium high, high, or double high) amounts of chemically modified alginate in the second (outer) compartment. A negative control (empty) capsule with a medium amount of chemically modified alginate in the second (outer) compartment was included.

FIGS. 12A-12C are brightfield images indicating the level of fibrotic response *in vivo* on exemplary particles (i.e., two-compartment hydrogel millicapsules) with either varying (medium or high) amounts of chemically modified alginate in the second (outer) compartment, or non-conjugated afibrotic small molecules (e.g., a compound of Formula (I)) in the second (outer) compartment (“amine added back” capsules), 2 weeks post-implantation in C57/BL6 mice.

FIGS. 13A-13F are immunofluorescent staining images comparing the level of macrophage adhesion *in vivo* on exemplary particles (i.e., two-compartment hydrogel millicapsules) with differing second (outer) compartments. The second (outer) compartments were prepared from either 70:30 or 60:40 ratio blends of chemically modified low-molecular weight (CM-LMW) alginate to unmodified high-molecular weight (U-HMW) alginate, and also with varying (medium, medium high, or high) amounts of chemically modified alginate in the second (outer) compartment.

FIGS. 14A-14D are brightfield images of encapsulated HEK293F cells in one-compartment or two-compartment hydrogel millicapsules that were cultured for 1 week after encapsulation. **FIGS. 14A-14B** correspond to images of one-compartment or two-compartment capsules. **FIGS. 14C-14D** correspond to images of the culture surface to identify cells not

contained in the capsules following a 1-week incubation at 37 °C.

FIGS. 15A-15C illustrate a correlation between expression levels *in vivo* of FIX by two-compartment hydrogel millicapsules and concentration of ARPE-19:FIX cells in the inner compartment of the capsules. FIGS 15A shows cell numbers in capsules prepared with different cell loading concentration prior to implant into the IP space mice (Initial) and upon retrieval five days after implant (Retrieval). FIG. 15B and 15C show FIX levels in plasma and IP fluid produced by the implanted capsules, respectively.

FIGS. 16A-16C illustrate a correlation between expression levels *in vivo* of FIX by two-compartment hydrogel millicapsules, concentration of ARPE-19:FIX cells in the inner compartment of the capsules and capsule integrity. FIG. 16A shows FIX levels in IP fluid of mice implanted with the capsules. FIG. 16B are brightfield images of the capsules prepared with 646M/ml cells at the pre-implantation (initial) and retrieval time points.

FIG. 17 shows in Tables 4-8 exemplary amino acid sequences and coding sequences for therapeutic polypeptides and nucleotide sequences within an exemplary expression vector useful for engineering RPE cells.

FIG. 18A-18B are brightfield images of exemplary particles (i.e., two-compartment hydrogel capsules about 0.75 mm in diameter (FIG. 18A) or about 1.0 mm in diameter (FIG. 18B) with a 50:50 volume ratio of inner:outer compartments. Each of the first (inner) and second (outer) compartments contain medium conjugation alginate. Exemplary RPE cells engineered to express an exogenous protein were encapsulated in the first (inner) compartment for visualization of the two-compartment architecture.

DETAILED DESCRIPTION

The present disclosure features a particle comprising a first compartment, a second compartment, and a compound of Formula (I) (e.g., as described herein), as well as compositions and methods of making and using the same. In some embodiments, the particles and compositions thereof are useful for the prevention or treatment of a disease, disorder, or condition. In some embodiments, particles configured as hydrogel millicapsules comprising a first hydrogel compartment and a second hydrogel compartment and a compound of Formula (I) exhibit advantageous properties, e.g., they are more afibrotic than similar millicapsules lacking a compound of Formula (I) but comprised of the same type of polymer, and substantially the same

size, and can hold a greater number of cells with minimal detrimental effect on capsule quality compared with millicapsules containing a single compartment. In some embodiments, the particles described herein comprise a cell (e.g., an engineered cell) that produces a therapeutic agent (e.g., a polypeptide) suitable for treating a disease, disorder, or condition in a subject.

Abbreviations and Definitions

Throughout the detailed description and examples of the disclosure the following abbreviations will be used.

CM-Alg	chemically modified alginate
CM-LMW-Alg	chemically modified, low molecular weight alginate
CM-LMW-Alg-101	low molecular weight alginate, chemically modified with Compound 101 shown in Table 2
CM-HMW-Alg	chemically modified, high molecular weight alginate
CM-HMW-Alg-101	high molecular weight alginate, chemically modified with Compound 101 shown in Table 2
CM-MMW-Alg	chemically modified, medium molecular weight alginate
CM-MMW-Alg-101	medium molecular weight alginate, chemically modified with Compound 101 shown in Table 2
HMW-Alg	high molecular weight alginate
MMW-Alg	medium molecular weight alginate
U-Alg	unmodified alginate
U-HMW-Alg	unmodified high molecular weight alginate
U-LMW-Alg	unmodified low molecular weight alginate
U-MMW-Alg	unmodified medium molecular weight alginate
70:30 CM-Alg:U-Alg	70:30 mixture (V:V) of a chemically modified alginate and an unmodified alginate

So that the disclosure may be more readily understood, certain technical and scientific terms used herein are specifically defined below. Unless specifically defined elsewhere in this

document, all other technical and scientific terms used herein have the meaning commonly understood by one of ordinary skill in the art to which this disclosure belongs.

As used herein, including the appended claims, the singular forms of words such as "a," "an," and "the," include their corresponding plural references unless the context clearly dictates otherwise.

"About", when used herein to modify a numerically defined parameter (e.g., a physical description of a hydrogel capsule such as diameter, sphericity, number of cells in a particle, the number of particles in a preparation), means that the parameter may vary by as much as 15% above or below the stated numerical value for that parameter. For example, a hydrogel capsule defined as having a diameter of about 1.5 millimeters (mm) and encapsulating about 5 million (M) cells may have a diameter of 1.275 to 1.725 mm and may encapsulate about 4.25 M to 5.75 M cells. In some embodiments, about means that the parameter may vary by as much as 10% above or below the stated numerical value for that parameter.

"Acquire" or "acquiring", as used herein, refer to obtaining possession of a value, e.g., a numerical value, or image, or a physical entity (e.g., a sample), by "directly acquiring" or "indirectly acquiring" the value or physical entity. "Directly acquiring" means performing a process (e.g., performing an analytical method or protocol) to obtain the value or physical entity. "Indirectly acquiring" refers to receiving the value or physical entity from another party or source (e.g., a third-party laboratory that directly acquired the physical entity or value). Directly acquiring a value or physical entity includes performing a process that includes a physical change in a physical substance or the use of a machine or device. Examples of directly acquiring a value include obtaining a sample from a human subject. Directly acquiring a value includes performing a process that uses a machine or device, e.g., fluorescence microscope to acquire fluorescence microscopy data.

"Administer", "administering", or "administration", as used herein, refer to implanting, absorbing, ingesting, injecting, or otherwise introducing an entity described herein (e.g., a particle comprising a first compartment, a second compartment, and a compound of Formula (I) (including particles encapsulating cells, e.g., engineered RPE cells), or a composition comprising said particles), or providing the same to a subject.

"Afibrotic", as used herein, refers to a compound or material that mitigates the foreign body response (FBR). For example, the amount of FBR in a biological tissue that is induced by

5 implant into that tissue of a particle (e.g., a hydrogel capsule) comprising an afibrotic compound (e.g., a compound of Formula (I), e.g., a compound listed in Table 2) is lower than the FBR induced by implantation of an afibrotic-null reference particle, i.e., a particle that lacks the afibrotic compound or material, but is of substantially the same composition (e.g., same cell type(s)) and structure (e.g., size, shape, no. of compartments, same encapsulating polymers, etc.). In an embodiment, the degree of the FBR is assessed by the immunological response in the tissue containing the implanted particle (e.g., hydrogel capsule), which may include, for example, protein adsorption, macrophages, multinucleated foreign body giant cells, fibroblasts, and angiogenesis, using assays known in the art, e.g., as described in WO 2017/075630, or using one or more of the assays / methods described Vegas, A., et al., *Nature Biotechnol (supra)*, (e.g., subcutaneous cathepsin measurement of implanted capsules, Masson's trichrome (MT), hematoxylin or eosin staining of tissue sections, quantification of collagen density, cellular staining and confocal microscopy for macrophages (CD68 or F4/80), myfibroblasts (alpha-muscle actin, SMA) or general cellular deposition, quantification of 79 RNA sequences of

5 known inflammation factors and immune cell markers, or FACS analysis for macrophage and neutrophil cells on retrieved particles (e.g., capsules) after a set time period (e.g., 14 days) in the intraperitoneal space of a suitable test subject, e.g., an immunocompetent mouse. In an embodiment, the FBR is assessed by measuring the levels in the tissue containing the implant of one or more biomarkers of immune response, e.g., cathepsin, TNF- α , IL-13, IL-6, G-CSF, GM-

10 CSF, IL-4, CCL2, or CCL4. In some embodiments, the FBR induced by a particle described herein (e.g., a two-compartment hydrogel capsule comprising an afibrotic compound disposed in and/or on the surface of the outer compartment), is at least about 80%, about 85%, about 90%, about 95%, about 99%, or about 100% lower than the FBR induced by an FBR-null reference particle, e.g., a particle that is substantially identical to the claimed particle except for lacking the

25 afibrotic compound or material but is otherwise substantially identical to the claimed particle. In some embodiments, the FBR (e.g., FBR biomarker level(s)) induced by an implanted particle is measured after about 30 minutes, about 1 hour, about 6 hours, about 12 hours, about 1 day, about 2 days, about 3 days, about 4 days, about 1 week, about 2 weeks, about 1 month, about 2 months, about 3 months, about 6 months, or longer.

30 "Cell," as used herein, refers to an engineered cell or a cell that is not engineered. In an embodiment, a cell is an immortalized cell.

“Comprise” and variants of the term such as “comprises” or “comprising” are used herein to denote the inclusion of a stated integer or stated integers but not to exclude any other integer or any other integers, unless in the context or usage an exclusive interpretation of the term is required.

“Conservatively modified variants” or conservative substitution”, as used herein, refers to a variant of a reference peptide or polypeptide that is identical to the reference molecule, except for having one or more conservative amino acid substitutions in its amino acid sequence. In an embodiment, a conservatively modified variant consists of an amino acid sequence that is at least 70%, 80%, 85%, 90%, 95%, 97%, 98% or 99% identical to the reference amino acid sequence. A conservative amino acid substitution refers to substitution of an amino acid with an amino acid having similar characteristics (e.g., charge, side-chain size, hydrophobicity/hydrophilicity, backbone conformation and rigidity, etc.) and which has minimal impact on the biological activity of the resulting substituted peptide or polypeptide. Conservative substitution tables of functionally similar amino acids are well known in the art, and exemplary substitutions grouped by functional features are set forth in Table 1 below.

Table 1. Exemplary conservative amino acid substitution groups.

Feature	Conservative Amino Group
Charge/Polarity	His, Arg, Lys
	Asp, Glu
	Cys, Thr, Ser, Gly, Asn, Gln, Tyr
	Ala, Pro, Met, Leu, Ile, Val, Phe, Trp
Hydrophobicity	Asp, Glu, Asn, Gln, Arg, Lys
	Cys, Ser, Thr, Pro, Gly, His, Tyr
	Ala, Met, Ile Leu, Val, Phe, Trp
Structural/Surface Exposure	Asp, Glu, Asn, Aln, His, Arg, Lys
	Cys, Ser, Tyr, Pro, Ala, Gly, Trp, Tyr
	Met, Ile, Leu, Val, Phe
Secondary Structure Propensity	Ala, Glu, Aln, His, Lys, Met, Leu, Arg
	Cys, Thr, Ile, Val, Phe, Tyr, Trp
	Ser, Gly, Pro, Asp, Asn

Evolutionary Conservation	Asp, Glu
	His, Lys, Arg
	Asn, Gln
	Ser, Thr
	Leu, Ile, Val
	Phe, Tyr, Trp
	Ala, Gly
	Met, Cys

“Consists essentially of”, and variations such as “consist essentially of” or “consisting essentially of” as used throughout the specification and claims, indicate the inclusion of any recited elements or group of elements, and the optional inclusion of other elements, of similar or different nature than the recited elements, that do not materially change the basic or novel properties of the specified molecule, composition, particle, or method. As a non-limiting example, a therapeutic protein that consists essentially of a recited amino acid sequence may also include one or more amino acids, including substitutions in the recited amino acid sequence, of one or more amino acid residues, which do not materially affect the relevant biological activity of the therapeutic protein, respectively. As another non-limiting example, a polypeptide that consists essentially of a recited amino acid sequence may contain one or more covalently attached moieties (e.g., a radioactive or fluorescent label) that do not materially change the relevant biological activity of the polypeptide.

“Derived from”, as used herein with respect to a cell or cells, refers to a cell or cells obtained from tissue, a cell line, or other cells, which optionally are then cultured, passaged, immortalized, differentiated and/or induced, to produce the derived cell(s).

“Differential volume,” as used herein, refers to a volume of one compartment within a particle that excludes the space occupied by another compartment(s). For example, the differential volume of the second compartment in a 2-compartment particle refers to a volume within the second (e.g., outer) compartment that excludes space occupied by the first compartment.

“Effective amount” as used herein refers to an amount of a composition of particles (e.g., a particle composition) or a particle component, e.g. a cell, e.g., an engineered cell, or an agent, e.g., a therapeutic agent, produced by a cell, e.g., an engineered cell, sufficient to elicit a

biological response, e.g., to treat a disease, disorder, or condition. In some embodiments, the term “effective amount” refers to the amount of a particle component, e.g., number of cells in the particle, the concentration or density of an afibrotic compound disposed on the particle surface and/or in the outer compartment. As will be appreciated by those of ordinary skill in this art, the effective amount may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the therapeutic agent, composition or particle, the condition being treated, the mode of administration, and the age and health of the subject. An effective amount encompasses therapeutic and prophylactic treatment. For example, to mitigate the FBR induced by a particle, an afibrotic-effective amount of a compound of Formula (I) may reduce the fibrosis or stop the growth or spread of fibrotic tissue on or near the implanted particle. An afibrotic-effective amount of a particle, composition or component thereof (e.g., an afibrotic compound, e.g., an afibrotic polymer) may be determined by any technique known in the art or described herein.

An “endogenous nucleic acid” as used herein, is a nucleic acid that occurs naturally in a subject cell.

An “endogenous polypeptide,” as used herein, is a polypeptide that occurs naturally in a subject cell.

“Engineered cell,” as used herein, is a cell (e.g., an RPE cell) having a non-naturally occurring alteration, and typically comprises a nucleic acid sequence (e.g., DNA or RNA) or a polypeptide not present (or present at a different level than) in an otherwise similar cell under similar conditions that is not engineered (an exogenous nucleic acid sequence). In an embodiment, an engineered cell comprises an exogenous nucleic acid (e.g., a vector or an altered chromosomal sequence). In an embodiment, an engineered cell comprises an exogenous polypeptide. In an embodiment, an engineered cell comprises an exogenous nucleic acid sequence, e.g., a sequence, e.g., DNA or RNA, not present in a similar cell that is not engineered. In an embodiment, the exogenous nucleic acid sequence is chromosomal, e.g., the exogenous nucleic acid sequence is an exogenous sequence disposed in endogenous chromosomal sequence. In an embodiment, the exogenous nucleic acid sequence is chromosomal or extra chromosomal, e.g., a non-integrated vector. In an embodiment, the exogenous nucleic acid sequence comprises an RNA sequence, e.g., an mRNA. In an embodiment, the exogenous nucleic acid sequence comprises a chromosomal or extra-chromosomal exogenous nucleic acid sequence that

comprises a sequence which is expressed as RNA, e.g., mRNA or a regulatory RNA. In an embodiment, the exogenous nucleic acid sequence comprises a chromosomal or extra-chromosomal nucleic acid sequence, which comprises a sequence that encodes a polypeptide, or which is expressed as a polypeptide. In an embodiment, the exogenous nucleic acid sequence comprises a first chromosomal or extra-chromosomal exogenous nucleic acid sequence that modulates the conformation or expression of a second nucleic acid sequence, wherein the second amino acid sequence can be exogenous or endogenous. For example, an engineered cell can comprise an exogenous nucleic acid that controls the expression of an endogenous sequence. In an embodiment, an engineered cell comprises a polypeptide present at a level or distribution which differs from the level found in a similar cell that has not been engineered. In an embodiment, an engineered cell comprises an RPE cell engineered to provide an RNA or a polypeptide. For example, an engineered cell may comprise an exogenous nucleic acid sequence comprising a chromosomal or extra-chromosomal exogenous nucleic acid sequence that comprises a sequence which is expressed as RNA, e.g., mRNA or a regulatory RNA. In an embodiment, an engineered cell (e.g., an RPE cell) comprises an exogenous nucleic acid sequence that comprises a chromosomal or extra-chromosomal nucleic acid sequence comprising a sequence that encodes a polypeptide, or which is expressed as a polypeptide. In an embodiment, an engineered cell (e.g., an RPE cell) comprises an exogenous nucleic acid sequence that modulates the conformation or expression of an endogenous sequence.

“An “exogenous nucleic acid,” as used herein, is a nucleic acid that does not occur naturally in a subject cell.

An “exogenous polypeptide,” as used herein, is polypeptide that does not occur naturally in a subject cell.

“Factor VII protein” or “FVII protein” as used herein, means a polypeptide that comprises the amino acid sequence of a naturally-occurring factor VII protein or variant thereof that has a FVII biological activity, e.g., promoting blood clotting, as determined by an art-recognized assay, unless otherwise specified. Naturally-occurring FVII exists as a single chain zymogen, a zymogen-like two-chain polypeptide and a fully activated two-chain form (FVIIa). In some embodiments, reference to FVII includes single-chain and two-chain forms thereof, including zymogen-like and FVIIa. FVII proteins that may be produced by a particle described herein (e.g., a two-compartment hydrogel capsule containing engineered RPE cells), include

wild-type primate (e.g., human), porcine, canine, and murine proteins, as well as variants of such wild-type proteins, including fragments, mutants, variants with one or more amino acid substitutions and / or deletions. In some embodiments, a variant FVII protein is capable of being activated to the fully activated two-chain form (Factor VIIa) that has at least 50%, 75%, 90% or more (including >100%) of the activity of wild-type Factor VIIa. Variants of FVII and FVIIa are known, e.g., marzeptacog alfa (activated) (MarzAA) and the variants described in European Patent No. 1373493, US Patent No. 7771996, US Patent No. 9476037 and US published application No. US20080058255.

FVII biological activity may be quantified by an art recognized assay, unless otherwise specified. For example, FVII biological activity in a sample of a biological fluid, e.g., plasma, may be quantified by (i) measuring the amount of Factor Xa produced in a system comprising TF embedded in a lipid membrane and Factor X. (Persson et al., *J. Biol. Chem.* 272:19919-19924, 1997); (ii) measuring Factor X hydrolysis in an aqueous system; (iii) measuring its physical binding to tissue factor (TF) using an instrument based on surface plasmon resonance (Persson, *FEBS Letts.* 413:359-363, 1997); or (iv) measuring hydrolysis of a synthetic substrate; and/or (v) measuring generation of thrombin in a TF-independent in vitro system. In an embodiment, FVII activity is assessed by a commercially available chromogenic assay (BIOPHEN FVII, HYPHEN BioMed Neuville sur Oise, France), in which the biological sample containing FVII is mixed with thromboplastin calcium, Factor X and Sxa-11 (a chromogenic substrate specific for Factor Xa.

“Factor VIII protein” or “FVIII protein” as used herein, means a polypeptide that comprises the amino acid sequence of a naturally occurring factor VIII polypeptide or variant thereof that has an FVIII biological activity, e.g., coagulation activity, as determined by an art-recognized assay, unless otherwise specified. FVIII proteins that may be expressed by a particle described herein, e.g., a two-compartment hydrogel capsule containing engineered RPE cells, include wild-type primate (e.g., human), porcine, canine, and murine proteins, as well as variants of such wild-type proteins, including fragments, mutants, variants with one or more amino acid substitutions and / or deletions, B-domain deletion (BDD) variants, single chain variants and fusions of any of the foregoing wild-type or variants with a half-life extending polypeptide. In an embodiment, the cells are engineered to encode a precursor factor VIII polypeptide (e.g., with the signal sequence) with a full or partial deletion of the B domain. In an embodiment, the cells

are engineered to encode a single chain factor VIII polypeptide. A variant FVIII protein preferably has at least 50%, 75%, 90% or more (including >100%) of the coagulation activity of the corresponding wild-type factor VIII. Assays for measuring the coagulation activity of FVIII proteins include the one stage or two stage coagulation assay (Rizza et al., 1982, Coagulation assay of FVIII:C and FIXa in Bloom ed. The Hemophelias. NY Churchill Livingston 1992) or the chromogenic substrate FVIII:C assay (Rosen, S. 1984. *Scand J Haematol* 33:139-145, suppl.)

A number of FVIII-BDD variants are known, and include, e.g., variants with the full or partial B-domain deletions disclosed in any of the following U.S. Patent Nos: 4,868,112 (e.g., col. 2, line 2 to col. 19, line 21 and table 2); 5,112,950 (e.g., col. 2, lines 55-68, FIG. 2, and example 1); 5,171,844 (e.g., col. 4, line 22 to col. 5, line 36); 5,543,502 (e.g., col. 2, lines 17-46); 5,595,886; 5,610,278; 5,789,203 (e.g., col. 2, lines 26-51 and examples 5-8); 5,972,885 (e.g., col. 1, lines 25 to col. 2, line 40); 6,048,720 (e.g., col. 6, lines 1-22 and example 1); 6,060,447; 6,228,620; 6,316,226 (e.g., col. 4, line 4 to col. 5, line 28 and examples 1-5); 6,346,513; 6,458,563 (e.g., col. 4, lines 25-53) and 7,041,635 (e.g., col. 2, line 1 to col. 3, line 19, col. 3, line 40 to col. 4, line 67, col. 7, line 43 to col. 8, line 26, and col. 11, line 5 to col. 13, line 39).

In some embodiments, a FVIII-BDD protein produced by a particle described herein (e.g., expressed by engineered cells contained in the particle) has one or more of the following deletions of amino acids in the B-domain: (i) most of the B domain except for amino-terminal B-domain sequences essential for intracellular processing of the primary translation product into two polypeptide chains (WO 91/09122); (ii) a deletion of amino acids 747-1638 (Hoebein R. C., et al. *J. Biol. Chem.* 265 (13): 7318-7323 (1990)); amino acids 771-1666 or amino acids 868-1562 (Meulien P., et al. *Protein Eng.* 2(4):301-6 (1988); amino acids 982-1562 or 760-1639 (Toole et al., *Proc. Natl. Acad. Sci. U.S.A.* 83:5939-5942 (1986)); amino acids 797-1562 (Eaton et al., *Biochemistry* 25:8343-8347 (1986)); 741-1646 (Kaufman, WO 87/04187)), 747-1560 (Sarver et al., *DNA* 6:553-564 (1987)); amino acids 741-1648 (Pasek, WO 88/00831)), amino acids 816-1598 or 741-1689 (Lagner (Behring Inst. Mitt. (1988) No 82:16-25, EP 295597); a deletion that includes one or more residues in a furin protease recognition sequence, e.g., LKRHRQ at amino acids 1643-1648, including any of the specific deletions recited in US Patent No. 9,956,269 at col. 10, line 65 to col. 11, line 36.

In other embodiments, a FVIII-BDD protein retains any of the following B-domain

amino acids or amino acid sequences: (i) one or more N-linked glycosylation sites in the B-domain, e.g., residues 757, 784, 828, 900, 963, or optionally 943, first 226 amino acids or first 163 amino acids (Miao, H. Z., et al., *Blood* 103(a): 3412-3419 (2004), Kasuda, A., et al., *J. Thromb. Haemost.* 6: 1352-1359 (2008), and Pipe, S. W., et al., *J. Thromb. Haemost.* 9: 2235-2242 (2011)).

In some embodiments, the FVIII-BDD protein is a single-chain variant generated by substitution of one or more amino acids in the furin protease recognition sequence (LKRHRQ at amino acids 1643-1648) that prevents proteolytic cleavage at this site, including any of the substitutions at the R1645 and/or R1648 positions described in U.S. Patent Nos. 10,023,628, 9,394,353 and 9,670,267.

In some embodiments, any of the above FVIII-BDD proteins may further comprise one or more of the following variations: a F309S substitution to improve expression of the FVIII-BDD protein (Miao, H. Z., et al., *Blood* 103(a): 3412-3419 (2004); albumin fusions (WO 2011/020866); and Fc fusions (WO 04/101740).

All FVIII-BDD amino acid positions referenced herein refer to the positions in full-length human FVIII, unless otherwise specified.

“Factor IX protein” or “FIX protein”, as used herein, means a polypeptide that comprises the amino acid sequence of a naturally occurring factor IX protein or variant thereof that has a FIX biological activity, e.g., coagulation activity, as determined by an art-recognized assay, unless otherwise specified. FIX is produced as an inactive zymogen, which is converted to an active form by factor XIa excision of the activation peptide to produce a heavy chain and a light chain held together by one or more disulfide bonds. FIX proteins that may be produced by a particle described herein (e.g., expressed by engineered RPE cells contained in the particle) include wild-type primate (e.g., human), porcine, canine, and murine proteins, as well as variants of such wild-type proteins, including fragments, mutants, variants with one or more amino acid substitutions and / or deletions and fusions of any of the foregoing wild-type or variant proteins with a half-life extending polypeptide. In an embodiment, cells are engineered to encode a full-length wild-type human factor IX polypeptide (e.g., with the signal sequence) or a functional variant thereof. A variant FIX protein preferably has at least 50%, 75%, 90% or more (including >100%) of the coagulation activity of wild-type factor VIX. Assays for measuring the coagulation activity of FIX proteins include the Biophen Factor IX assay (Hyphen BioMed) and

the one stage clotting assay (activated partial thromboplastin time (aPTT), e.g., as described in EP 2 032 607 B2, thrombin generation time assay (TGA) and rotational thromboelastometry, e.g., as described in WO 2012/006624.

A number of functional FIX variants are known and may be expressed by engineered cells encapsulated in a particle described herein, including any of the functional FIX variants described in the following international patent publications: WO 02/040544 A3 at page 4, lines 9-30 and page 15, lines 6-31; WO 03/020764 A2 in Tables 2 and 3 at pages 14-24, and at page 12, lines 1-27; WO 2007/149406 A2 at page 4, line 1 to page 19, line 11; WO 2007/149406 A2 at page 19, line 12 to page 20, line 9; WO 08/118507 A2 at page 5, line 14 to page 6, line 5; WO 09/051717 A2 at page 9, line 11 to page 20, line 2; WO 09/137254 A2 at page 2, paragraph [006] to page 5, paragraph [011] and page 16, paragraph [044] to page 24, paragraph [057]; WO 09/130198 A2 at page 4, line 26 to page 12, line 6; WO 09/140015 A2 at page 11, paragraph [0043] to page 13, paragraph [0053]; WO 2012/006624; WO 2015/086406.

In certain embodiments, the FIX polypeptide comprises a wild-type or variant sequence fused to a heterologous polypeptide or non-polypeptide moiety extending the half-life of the FIX protein. Exemplary half-life extending moieties include Fc, albumin, a PAS sequence, transferrin, CTP (28 amino acid C-terminal peptide (CTP) of human chorionic gonadotropin (hCG) with its 4 O-glycans), polyethylene glycol (PEG), hydroxyethyl starch (HES), albumin binding polypeptide, albumin-binding small molecules, or any combination thereof. An exemplary FIX polypeptide is the rFIXFc protein described in WO 2012/006624, which is an FIXFc single chain (FIXF c-sc) and an Fc single chain (Fc-sc) bound together through two disulfide bonds in the hinge region of Fc.

FIX variants also include gain and loss of function variants. An example of a gain of function variant is the “Padua” variant of human FIX, which has a L (leucine) at position 338 of the mature protein instead of an R (arginine) (corresponding to amino acid position 384 of SEQ ID NO:2), and has greater catalytic and coagulant activity compared to wild-type human FIX (Chang et al., J. Biol. Chem., 273:12089-94 (1998)). An example of a loss of function variant is an alanine substituted for lysine in the fifth amino acid position from the beginning of the mature protein, which results in a protein with reduced binding to collagen IV (e.g., loss of function).

“Interleukin-2 protein” or “IL-2 protein”, as used herein means a polypeptide comprising the amino acid sequence of a naturally occurring IL-2 protein or variant thereof that has an IL-2

biological activity, e.g., activate IL-2 receptor signaling in Treg cells, as determined by an art-recognized assay, unless otherwise specified. IL-2 proteins that may be produced by a particle described herein, e.g., a particle containing engineered RPE cells, include wild-type primate (e.g., human), porcine, canine, and murine proteins, as well as variants of such wild-type proteins. A variant IL-2 protein preferably has at least 50%, 75%, 90% or more (including >100%) of the biological activity of the corresponding wild-type IL-2. Biological activity assays for IL-2 proteins are described in US Patent No. 10,035,836, and include, e.g., measuring the levels of phosphorylated STAT5 protein in Treg cells compared to CD4+CD25-/low T cells or NK cells. Variant IL-2 proteins that may be produced by a particle of the present disclosure (e.g., a particle containing engineered RPE cells) include proteins with one or more of the following amino acid substitutions: N88R, N88I, N88G, D20H, Q126L, Q126F, and C125S or C125A.

“Islet cell” as used herein means a cell that comprises any naturally occurring or any synthetically created, or modified, cell that is intended to recapitulate, mimic or otherwise express, in part or in whole, the functions, in part or in whole, of the cells of the pancreatic islets of Langerhans. The term “islet cells” includes glucose-responsive, insulin producing cells derived from stem cells, e.g., from an induced pluripotent stem cell line.

“Mannitol”, as used herein, refers to D-mannitol unless otherwise explicitly stated.

“Mesenchymal stem function cell” or “MSFC,” as those terms are used herein, refers to a cell derived from, or having at least one characteristic specific to a cell of, mesodermal lineage, and wherein the MSFC is i) not in a terminal state of differentiation and ii) can terminally differentiate into one or more cell types. An MSFC does not comprise a cell of endodermal origin, e.g., a gut cell, or of ectodermal origin, e.g., a cell derived from skin, CNS, or a neural cell. In an embodiment, the MSFC is multipotent. In an embodiment, the MSFC is not totipotent. In an embodiment, an MSFC comprises one or more of the following characteristics:

a) it comprises a mesenchymal stem cell (MSC) or a cell derived therefrom, including a cell derived from a primary cell culture of MSCs, a cell isolated directly (without long term culturing, e.g., less than 5 or 10 passages or rounds of cell division since isolation) from naturally occurring MSCs, e.g., from a human or other mammal, a cell derived from a transformed, a pluripotent, an immortalized, or a long term (e.g., more than 5 or 10 passages or rounds of cell division) MSC culture. In an embodiment, the MSFC is derived from a human source, e.g., the

blood (e.g., peripheral blood), bone marrow (e.g., the iliac crest, femora, tibiae, spine, rib, or knee), synovial tissue, adipose tissue, skin, fetal tissue, umbilical cord, or the placenta;

b) it comprises a cell that has been obtained from a less differentiated cell, e.g., a cell developed, programmed, or reprogramed (e.g., in vitro) into an MSC or a cell that is, except for any genetic engineering, substantially similar to one or more of a naturally occurring MSC or a cell from a primary or long term culture of MSCs, or a cell described in a) above. Examples of less differentiated cells from which MSFC can be derived include IPS cells, embryonic stem cells, or other totipotent or pluripotent cells; see, e.g., Chen, Y.S. et al (2012) *Stem Cells Transl Med* 1(83-95); Frobel, J et al (2014) *Stem Cell Reports* 3(3):414-422; Zou, L et al (2013) *Sci Rep* 3:2243;

c) it is multipotent, e.g., as measured by any assay capable of providing information about cell multipotency, e.g., microscopy;

d) it exhibits a characteristic mononuclear ovoid, stellate shape or spindle shape, with a round to oval nucleus. The oval elongate nucleus may have prominent nucleoli and a mix of heterochromatin and euchromatin. An MSFC (e.g., an MSC) may have little cytoplasm, but many thin processes that appear to extend from the nucleus;

e) it is capable of cell division, e.g., as measured any assay capable of providing information about cell division, e.g., microscopy. In an embodiment, an MSFC is capable of cell division in culture (e.g., prior to being encapsulated or incorporated into a particle described herein). In an embodiment, it is capable of cell division after being encapsulated, e.g., encapsulated as described herein, or incorporated into a particle (e.g., a 2-compartment capsule described herein). In an embodiment, it is incapable of cell division after reaching confluence;

f) it is capable of differentiating into a mesenchymal cell lineage, e.g., an osteoblast, a chondroblast, an adipocyte, or a fibroblast;

g) it expresses a mesenchymal cell marker, e.g., one, two, three, four, five or all of CD105, CD106, CD73, CD90, Stro-1, CD49a, CD29, CD44, CD146, CD166, TNAP+, THY-1+, Stro-2, Stro-4, and alkaline phosphatase;

h) it does not express significant levels of one, two, three, or any of CD34, CD31, VE-cadherin, CD45, HLA-DR, CD11b and a glycophorin or leukocyte differentiation antigen, e.g, CD14, CD33, CD3 and CD19;

i) it expresses one, two, or all of CD75, CD90, and CD105 and does not express one, two,

or any of CD45, CD34, and CD14;

j) it is anti-inflammatory or immune-dampening, e.g., as measured by any method capable of providing information regarding inflammation, e.g., in vivo inhibition of T cell proliferation;

k) it is capable of being adherent, e.g., plastic adherent, e.g., as determined by, e.g., visual inspection; or

l) can grow in three dimensions, e.g., as determined by, e.g., visual inspection.

“Parathyroid hormone” or “PTH” as used herein means a polypeptide or peptide that comprises the amino acid sequence of a naturally occurring parathyroid hormone polypeptide or peptide or variant thereof that has a PTH biological activity, e.g., as determined by an art recognized assay. PTH polypeptides and peptides that may be expressed by encapsulated cells described herein include wild-type primate (e.g., human), porcine, canine, and murine proteins, as well as variants of such wild-type proteins. Such PTH polypeptides and peptides may consist essentially of the wild-type human sequence for pre-pro-PTH polypeptide (115 amino acids), pro-PTH polypeptide (90 amino acids), the mature 84-amino acid peptide (PTH(1-84)), and biologically active variants thereof, such as the truncated variant peptide PTH(1-34). PTH peptide variants with /one or more amino acid substitutions in the human wild-type sequence have been described, e.g., in US Patent Nos. 7410948 and 8563513 and in US published patent application US20130217630. A PTH variant preferably has at least 50%, 75%, 90% or more (including >100%) of a biological activity of the corresponding wild-type PTH. An assay to detect certain PTH variants by tandem mass spectrometry is described in US Patent 8383417. A biological activity assay for PTH peptide variants - stimulation of adenylate cyclase as determined by measuring cAMP levels - is described in US Patent 7410948.

“Poloxamer”, as used herein, refers to the standard generic term for a class of nonionic triblock linear copolymers composed of a central hydrophobic chain of polyoxypropylene (poly(propylene oxide)) flanked by two polyoxyethylene (poly(ethylene oxide)) moieties.

“Poloxamer 188” or “P 188”, as used herein, refers to a poloxamer with an approximate molecular mass of 1800 g/mole for the polyoxypropylene core and an oxyethylene content of about 80% weight percent, e.g., 79.0 to 83.7 percent. In an embodiment, poloxamer 188 has an average molecular weight of 8350 g/mole. In an embodiment, poloxamer 188 has an average molecular weight of 7680 g/mole to 9510 g/mole, e.g., as determined by size exclusion

chromatography, and an oxyethylene content of $81.8 \pm 1.9\%$ weight percent. In an embodiment, each polyoxyethylene chain in poloxamer 188 has 75-85 (e.g., 80) ethylene oxide monomers and the polyoxypropylene core has 25-30 (e.g., 27) propylene oxide monomers. In an embodiment, poloxamer 188 used in a process described herein substantially meets the specifications set forth in a poloxamer monograph published by the United States Pharmacopeia-National Formulary (USP-NF) or the European Pharmacopoeia (Ph. Eur.) that is official at the time the process is performed.

“Poloxamer 407” or “P 407”, as used herein, means a poloxamer with an approximate molecular mass of 4000 g/mole for the polypropylene core and an oxyethylene content of about 70% by weight. In an embodiment, poloxamer 407 has an average molecular weight of 9,840 g/mole to 14,600 g/mole and an oxyethylene content of $73.2 \pm 1.7\%$ by weight. In an embodiment, each polyoxyethylene chain in poloxamer 407 has 95-105 (e.g., 101) ethylene oxide monomers (e.g., and the polyoxypropylene core has 54-60 (e.g., 56) propylene oxide monomers.

“Polypeptide”, as used herein, refers to a polymer comprising amino acid residues linked through peptide bonds and having at least two, and in embodiments, at least 10, 50, 75, 100, 150 or 200 amino acid residues.

“Prevention,” “prevent,” and “preventing” as used herein refers to a treatment that comprises administering or applying a therapy, e.g., administering a composition of particles encapsulating cells (e.g., as described herein), prior to the onset of a disease, disorder, or condition to preclude the physical manifestation of said disease, disorder, or condition. In some embodiments, “prevention,” “prevent,” and “preventing” require that signs or symptoms of the disease, disorder, or condition have not yet developed or have not yet been observed. In some embodiments, treatment comprises prevention and in other embodiments it does not.

A “replacement therapy” or “replacement protein” is a therapeutic protein or functional fragment thereof that replaces or augments a protein that is diminished, present in insufficient quantity, altered (e.g., mutated) or lacking in a subject having a disease or condition related to the diminished, altered or lacking protein. Examples are certain blood clotting factors in certain blood clotting disorders or certain lysosomal enzymes in certain lysosomal storage diseases. In an embodiment, a replacement therapy or replacement protein provides the function of an endogenous protein. In an embodiment, a replacement therapy or replacement protein has the

same amino acid sequence of a naturally occurring variant, e.g., a wild type allele or an allele not associated with a disorder, of the replaced protein. In an embodiment, or replacement therapy or a replacement protein differs in amino acid sequence from a naturally occurring variant, e.g., a wild type allele or an allele not associated with a disorder, e.g., the allele carried by a subject, at no more than about 1, 2, 3, 4, 5, 10, 15 or 20 % of the amino acid residues.

“RPE cell” as used herein refers to a cell having one or more of the following characteristics: a) it comprises a retinal pigment epithelial cell (RPE) (e.g., cultured using the ARPE-19 cell line (ATCC® CRL-2302™)) or a cell derived therefrom, including a cell derived from a primary cell culture of RPE cells, a cell isolated directly (without long term culturing, e.g., less than 5 or 10 passages or rounds of cell division since isolation) from naturally occurring RPE cells, e.g., from a human or other mammal, a cell derived from a transformed, an immortalized, or a long term (e.g., more than 5 or 10 passages or rounds of cell division) RPE cell culture; b) a cell that has been obtained from a less differentiated cell, e.g., a cell developed, programmed, or reprogramed (e.g., in vitro) into an RPE cell or a cell that is, except for any genetic engineering, substantially similar to one or more of a naturally occurring RPE cell or a cell from a primary or long term culture of RPE cells (e.g., the cell can be derived from an IPS cell); or c) a cell that has one or more of the following properties: i) it expresses one or more of the biomarkers CRALBP, RPE-65, RLBP, BEST1, or α B-crystallin; ii) it does not express one or more of the biomarkers CRALBP, RPE-65, RLBP, BEST1, or α B-crystallin; iii) it is naturally found in the retina and forms a monolayer above the choroidal blood vessels in the Bruch’s membrane; iv) it is responsible for epithelial transport, light absorption, secretion, and immune modulation in the retina; or v) it has been created synthetically, or modified from a naturally occurring cell, to have the same or substantially the same genetic content, and optionally the same or substantially the same epigenetic content, as an immortalized RPE cell line (e.g., the ARPE-19 cell line (ATCC® CRL-2302™)). In an embodiment, an RPE cell described herein is engineered, e.g., to have a new property, e.g., the cell is engineered to express a therapeutic protein. In other embodiments, an RPE cell is not engineered.

“Sequence identity” or “percent identical”, when used herein to refer to two nucleotide sequences or two amino acid sequences, means the two sequences are the same within a specified region, or have the same nucleotides or amino acids at a specified percentage of nucleotide or amino acid positions within the specified when the two sequences are compared and aligned for

maximum correspondence over a comparison window or designated region. Sequence identity may be determined using standard techniques known in the art including, but not limited to, any of the algorithms described in US Patent Publication No. 2017/02334455. In an embodiment, the specified percentage of identical nucleotide or amino acid positions is at least about 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or higher.

“Spherical” as used herein, refers to a particle having a curved surface that forms a sphere (e.g., a completely round ball) or sphere-like shape. Spheres and sphere-like objects can be mathematically defined by rotation of circles, ellipses, or a combination around each of the three perpendicular axes, a, b, and c. For a sphere, the three axes a, b, and c are the same length. Generally, a sphere-like shape is an ellipsoid (for its averaged surface) with semi-principal axes a, b, and c that are within 10%, or 5%, or 2.5% of each other. The diameter of a sphere or sphere-like shape is the average diameter, such as the average of the semi-principal axes.

“Subject” as used herein refers to a human or non-human animal. In an embodiment, the subject is a human (i.e., a male or female), e.g., of any age group, a pediatric subject (e.g., infant, child, adolescent) or adult subject (e.g., young adult, middle-aged adult, or senior adult). In an embodiment, the subject is a non-human animal, for example, a mammal (e.g., a primate (e.g., a cynomolgus monkey or a rhesus monkey)). In an embodiment, the subject is a commercially relevant mammal (e.g., a cattle, pig, horse, sheep, goat, cat, or dog) or a bird (e.g., a commercially relevant bird such as a chicken, duck, goose, or turkey). In certain embodiments, the animal is a mammal. The animal may be a male or female and at any stage of development. A non-human animal may be a transgenic animal.

“Total volume,” as used herein, refers to a volume within one compartment of a particle that includes the space occupied by another compartment. For example, the total volume of the second (e.g., outer) compartment of a two-compartment particle refers to a volume within the second compartment that includes space occupied by the first compartment.

“Treatment,” “treat,” and “treating” as used herein refers to one or more of reducing, reversing, alleviating, delaying the onset of, or inhibiting the progress of one or more of a symptom, manifestation, or underlying cause, of a disease, disorder, or condition. In an embodiment, treating comprises reducing, reversing, alleviating, delaying the onset of, or inhibiting the progress of a symptom of a disease, disorder, or condition. In an embodiment, treating comprises reducing, reversing, alleviating, delaying the onset of, or inhibiting the

progress of a manifestation of a disease, disorder, or condition. In an embodiment, treating comprises reducing, reversing, alleviating, reducing, or delaying the onset of, an underlying cause of a disease, disorder, or condition. In some embodiments, “treatment,” “treat,” and “treating” require that signs or symptoms of the disease, disorder, or condition have developed or have been observed. In other embodiments, treatment may be administered in the absence of signs or symptoms of the disease or condition, e.g., in preventive treatment. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (e.g., considering a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example, to delay or prevent recurrence. In some embodiments, treatment comprises prevention and in other embodiments it does not.

“Von Willebrand factor protein” or “VWF protein”, as used herein, means a polypeptide that comprises the amino acid sequence of a naturally occurring VWF polypeptide or variant thereof that has VWF biological activity, e.g., FVIII binding activity, as determined by an art-recognized assay, unless otherwise specified. VWF proteins that may be produced by a particle described herein (e.g., expressed by engineered cells contained in the particle) include wild-type primate (e.g., human), porcine, canine, and murine proteins, as well as variants of such wild-type proteins. The encapsulated cells may be engineered to encode any of the following VWF polypeptides: precursor VWF of 2813 amino acids, a VWF lacking the signal peptide of 22 amino acids and optionally the prepropeptide of 741 amino acids, mature VWF protein of 2050 amino acids, and truncated variants thereof, such as a VWF fragment sufficient to stabilize endogenous FVIII levels in VWF-deficient mice, e.g., a truncated variant containing the D'D3 region (amino acids 764-1247) or the D1D2D'D3 region; and VWF variants with one or more amino acid substitutions, e.g., in the D' region as described in US Patent No. 9458223. A variant VWF protein preferably has at least 50%, 75%, 90% or more (including >100%) of a biological activity of the corresponding wild-type VWF protein. Art-recognized assays for determining the biological activity of a VWF include ristocetin co-factor activity (Federici A B et al. 2004. *Haematologica* 89:77-85), binding of VWF to GP Iba of the platelet glycoprotein complex Ib-V-IX (Sucker et al. 2006. *Clin Appl Thromb Hemost.* 12:305-310), and collagen binding (Kallas & Talpsep. 2001. *Annals of Hematology* 80:466-471).

In some embodiments, the VWF protein produced by a particle of the disclosure

comprises a naturally-occurring or variant VWF amino acid sequence fused to a heterologous polypeptide or non-polypeptide moiety extending the half-life of the VWF protein. Exemplary half-life extending moieties include Fc, albumin, a PAS sequence, transferrin, CTP (28 amino acid C-terminal peptide (CTP) of human chorionic gonadotropin (hCG) with its 4 O-glycans), polyethylene glycol (PEG), hydroxyethyl starch (HES), albumin binding polypeptide, albumin-binding small molecules, or any combination thereof.

Selected Chemical Definitions

Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example, "C₁-C₆ alkyl" is intended to encompass, C₁, C₂, C₃, C₄, C₅, C₆, C₁-C₆, C₁-C₅, C₁-C₄, C₁-C₃, C₁-C₂, C₂-C₆, C₂-C₅, C₂-C₄, C₂-C₃, C₃-C₆, C₃-C₅, C₃-C₄, C₄-C₆, C₄-C₅, and C₅-C₆ alkyl.

As used herein, "alkyl" refers to a radical of a straight-chain or branched saturated hydrocarbon group having from 1 to 24 carbon atoms ("C₁-C₂₄ alkyl"). In some embodiments, an alkyl group has 1 to 12 carbon atoms ("C₁-C₁₂ alkyl"), 1 to 10 carbon atoms ("C₁-C₁₀ alkyl"), 1 to 8 carbon atoms ("C₁-C₈ alkyl"), 1 to 6 carbon atoms ("C₁-C₆ alkyl"), 1 to 5 carbon atoms ("C₁-C₅ alkyl"), 1 to 4 carbon atoms ("C₁-C₄ alkyl"), 1 to 3 carbon atoms ("C₁-C₃ alkyl"), 1 to 2 carbon atoms ("C₁-C₂ alkyl"), or 1 carbon atom ("C₁ alkyl"). In some embodiments, an alkyl

group has 2 to 6 carbon atoms (“C₂-C₆ alkyl”). Examples of C₁-C₆ alkyl groups include methyl (C₁), ethyl (C₂), n-propyl (C₃), isopropyl (C₃), n-butyl (C₄), tert-butyl (C₄), sec-butyl (C₄), isobutyl (C₄), n-pentyl (C₅), 3-pentanyl (C₅), amyl (C₅), neopentyl (C₅), 3-methyl-2-butanyl (C₅), tertiary amyl (C₅), and n-hexyl (C₆). Additional examples of alkyl groups include n-heptyl (C₇), n-octyl (C₈) and the like. Each instance of an alkyl group may be independently optionally substituted, i.e., unsubstituted (an “unsubstituted alkyl”) or substituted (a “substituted alkyl”) with one or more substituents; e.g., for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent.

As used herein, “alkenyl” refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 24 carbon atoms, one or more carbon-carbon double bonds, and no triple bonds (“C₂-C₂₄ alkenyl”). In some embodiments, an alkenyl group has 2 to 12 carbon atoms (“C₂-C₁₂ alkenyl”), 2 to 10 carbon atoms (“C₂-C₁₀ alkenyl”), 2 to 8 carbon atoms (“C₂-C₈ alkenyl”), 2 to 6 carbon atoms (“C₂-C₆ alkenyl”), 2 to 5 carbon atoms (“C₂-C₅ alkenyl”), 2 to 4 carbon atoms (“C₂-C₄ alkenyl”), 2 to 3 carbon atoms (“C₂-C₃ alkenyl”), or 2 carbon atoms (“C₂ alkenyl”). The one or more carbon-carbon double bonds can be internal (such as in 2-butenyl) or terminal (such as in 1-butenyl). Examples of C₂-C₄ alkenyl groups include ethenyl (C₂), 1-propenyl (C₃), 2-propenyl (C₃), 1-butenyl (C₄), 2-butenyl (C₄), butadienyl (C₄), and the like. Examples of C₂-C₆ alkenyl groups include the aforementioned C₂₋₄ alkenyl groups as well as pentenyl (C₅), pentadienyl (C₅), hexenyl (C₆), and the like. Each instance of an alkenyl group may be independently optionally substituted, i.e., unsubstituted (an “unsubstituted alkenyl”) or substituted (a “substituted alkenyl”) with one or more substituents e.g., for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent.

As used herein, the term “alkynyl” refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 24 carbon atoms, one or more carbon-carbon triple bonds (“C₂-C₂₄ alkynyl”). In some embodiments, an alkynyl group has 2 to 12 carbon atoms (“C₂-C₁₂ alkynyl”), 2 to 10 carbon atoms (“C₂-C₁₀ alkynyl”), 2 to 8 carbon atoms (“C₂-C₈ alkynyl”), 2 to 6 carbon atoms (“C₂-C₆ alkynyl”), 2 to 5 carbon atoms (“C₂-C₅ alkynyl”), 2 to 4 carbon atoms (“C₂-C₄ alkynyl”), 2 to 3 carbon atoms (“C₂-C₃ alkynyl”), or 2 carbon atoms (“C₂ alkynyl”). The one or more carbon-carbon triple bonds can be internal (such as in 2-butyne) or terminal (such as in 1-butyne). Examples of C₂-C₄ alkynyl groups include ethynyl (C₂), 1-propynyl (C₃), 2-propynyl (C₃), 1-butyne (C₄), 2-butyne (C₄), and the like. Each instance of an alkynyl

group may be independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted alkynyl”) or substituted (a “substituted alkynyl”) with one or more substituents *e.g.*, for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent.

As used herein, the term “heteroalkyl,” refers to a non-cyclic stable straight or branched chain, or combinations thereof, including at least one carbon atom and at least one heteroatom selected from the group consisting of O, N, P, Si, and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N, P, S, and Si may be placed at any position of the heteroalkyl group. Exemplary heteroalkyl groups include, but are not limited to: -CH₂-CH₂-O-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-CH₂-N(CH₃)-CH₃, -CH₂-S-CH₂-CH₃, -CH₂-CH₂-S(O)-CH₃, -CH₂-CH₂-S(O)₂-CH₃, -CH=CH-O-CH₃, -Si(CH₃)₃, -CH₂-CH=N-OCH₃, -CH=CH-N(CH₃)-CH₃, -O-CH₃, and -O-CH₂-CH₃. Up to two or three heteroatoms may be consecutive, such as, for example, -CH₂-NH-OCH₃ and -CH₂-O-Si(CH₃)₃. Where “heteroalkyl” is recited, followed by recitations of specific heteroalkyl groups, such as -CH₂O, -NR^{C_D}, or the like, it will be understood that the terms heteroalkyl and -CH₂O or -NR^{C_D} are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term “heteroalkyl” should not be interpreted herein as excluding specific heteroalkyl groups, such as -CH₂O, -NR^{C_D}, or the like. Each instance of a heteroalkyl group may be independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted heteroalkyl”) or substituted (a “substituted heteroalkyl”) with one or more substituents *e.g.*, for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent.

The terms “alkylene,” “alkenylene,” “alkynylene,” or “heteroalkylene,” alone or as part of another substituent, mean, unless otherwise stated, a divalent radical derived from an alkyl, alkenyl, alkynyl, or heteroalkyl, respectively. An alkylene, alkenylene, alkynylene, or heteroalkylene group may be described as, *e.g.*, a C₁-C₆-membered alkylene, C₂-C₆-membered alkenylene, C₂-C₆-membered alkynylene, or C₁-C₆-membered heteroalkylene, wherein the term “membered” refers to the non-hydrogen atoms within the moiety. In the case of heteroalkylene groups, heteroatoms can also occupy either or both chain termini (*e.g.*, alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula -C(O)₂R’- may

represent both $-C(O)_2R'$ and $-R'C(O)_2-$.

As used herein, “aryl” refers to a radical of a monocyclic or polycyclic (*e.g.*, bicyclic or tricyclic) $4n+2$ aromatic ring system (*e.g.*, having 6, 10, or 14 π electrons shared in a cyclic array) having 6–14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system (“C₆–C₁₄ aryl”). In some embodiments, an aryl group has six ring carbon atoms (“C₆ aryl”; *e.g.*, phenyl). In some embodiments, an aryl group has ten ring carbon atoms (“C₁₀ aryl”; *e.g.*, naphthyl such as 1–naphthyl and 2–naphthyl). In some embodiments, an aryl group has fourteen ring carbon atoms (“C₁₄ aryl”; *e.g.*, anthracyl). An aryl group may be described as, *e.g.*, a C₆–C₁₀-membered aryl, wherein the term “membered” refers to the non-hydrogen ring atoms within the moiety. Aryl groups include phenyl, naphthyl, indenyl, and tetrahydronaphthyl. Each instance of an aryl group may be independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted aryl”) or substituted (a “substituted aryl”) with one or more substituents.

As used herein, “heteroaryl” refers to a radical of a 5–10 membered monocyclic or bicyclic $4n+2$ aromatic ring system (*e.g.*, having 6 or 10 π electrons shared in a cyclic array) having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur (“5–10 membered heteroaryl”). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl bicyclic ring systems can include one or more heteroatoms in one or both rings. “Heteroaryl” also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on the aryl or heteroaryl ring, and in such instances, the number of ring members designates the number of ring members in the fused (aryl/heteroaryl) ring system. Bicyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.*, indolyl, quinoliny, carbazolyl, and the like) the point of attachment can be on either ring, *i.e.*, either the ring bearing a heteroatom (*e.g.*, 2–indolyl) or the ring that does not contain a heteroatom (*e.g.*, 5–indolyl). A heteroaryl group may be described as, *e.g.*, a 6–10-membered heteroaryl, wherein the term “membered” refers to the non-hydrogen ring atoms within the moiety.

In some embodiments, a heteroaryl group is a 5–10 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5–10

membered heteroaryl”). In some embodiments, a heteroaryl group is a 5–8 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5–8 membered heteroaryl”). In some embodiments, a heteroaryl group is a 5–6 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5–6 membered heteroaryl”). In some embodiments, the 5–6 membered heteroaryl has 1–3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1–2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur. Each instance of a heteroaryl group may be independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted heteroaryl”) or substituted (a “substituted heteroaryl”) with one or more substituents.

Exemplary 5-membered heteroaryl groups containing one heteroatom include, without limitation, pyrrolyl, furanyl and thiophenyl. Exemplary 5-membered heteroaryl groups containing two heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5-membered heteroaryl groups containing three heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5-membered heteroaryl groups containing four heteroatoms include, without limitation, tetrazolyl. Exemplary 6-membered heteroaryl groups containing one heteroatom include, without limitation, pyridinyl. Exemplary 6-membered heteroaryl groups containing two heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6-membered heteroaryl groups containing three or four heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7-membered heteroaryl groups containing one heteroatom include, without limitation, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6-bicyclic heteroaryl groups include, without limitation, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl, and purinyl. Exemplary 6,6-bicyclic heteroaryl groups include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl. Other exemplary heteroaryl groups include heme and heme

derivatives.

As used herein, the terms "arylene" and "heteroarylene," alone or as part of another substituent, mean a divalent radical derived from an aryl and heteroaryl, respectively.

As used herein, "cycloalkyl" refers to a radical of a non-aromatic cyclic hydrocarbon group having from 3 to 10 ring carbon atoms ("C₃-C₁₀ cycloalkyl") and zero heteroatoms in the non-aromatic ring system. In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms ("C₃-C₈cycloalkyl"), 3 to 6 ring carbon atoms ("C₃-C₆ cycloalkyl"), or 5 to 10 ring carbon atoms ("C₅-C₁₀ cycloalkyl"). A cycloalkyl group may be described as, e.g., a C₄-C₇-membered cycloalkyl, wherein the term "membered" refers to the non-hydrogen ring atoms within the moiety. Exemplary C₃-C₆ cycloalkyl groups include, without limitation, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), and the like. Exemplary C₃-C₈ cycloalkyl groups include, without limitation, the aforementioned C₃-C₆ cycloalkyl groups as well as cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), cubanyl (C₈), bicyclo[1.1.1]pentanyl (C₅), bicyclo[2.2.2]octanyl (C₈), bicyclo[2.1.1]hexanyl (C₆), bicyclo[3.1.1]heptanyl (C₇), and the like. Exemplary C₃-C₁₀ cycloalkyl groups include, without limitation, the aforementioned C₃-C₈ cycloalkyl groups as well as cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), spiro [4.5] decanyl (C₁₀), and the like. As the foregoing examples illustrate, in certain embodiments, the cycloalkyl group is either monocyclic ("monocyclic cycloalkyl") or contain a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic cycloalkyl") and can be saturated or can be partially unsaturated. "Cycloalkyl" also includes ring systems wherein the cycloalkyl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is on the cycloalkyl ring, and in such instances, the number of carbons continue to designate the number of carbons in the cycloalkyl ring system. Each instance of a cycloalkyl group may be independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted cycloalkyl") or substituted (a "substituted cycloalkyl") with one or more substituents.

"Heterocyclyl" as used herein refers to a radical of a 3- to 10-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon ("3-10

membered heterocyclyl"). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic ("monocyclic heterocyclyl") or a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic heterocyclyl"), and can be saturated or can be partially unsaturated. Heterocyclyl bicyclic ring systems can include one or more heteroatoms in one or both rings. "Heterocyclyl" also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more cycloalkyl groups wherein the point of attachment is either on the cycloalkyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclyl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heterocyclyl ring system. A heterocyclyl group may be described as, e.g., a 3-7-membered heterocyclyl, wherein the term "membered" refers to the non-hydrogen ring atoms, i.e., carbon, nitrogen, oxygen, sulfur, boron, phosphorus, and silicon, within the moiety. Each instance of heterocyclyl may be independently optionally substituted, i.e., unsubstituted (an "unsubstituted heterocyclyl") or substituted (a "substituted heterocyclyl") with one or more substituents. In certain embodiments, the heterocyclyl group is unsubstituted 3-10 membered heterocyclyl. In certain embodiments, the heterocyclyl group is substituted 3-10 membered heterocyclyl.

In some embodiments, a heterocyclyl group is a 5-10 membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon ("5-10 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5-8 membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-8 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5-6 membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-6 membered heterocyclyl"). In some embodiments, the 5-6 membered heterocyclyl has 1-3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-6 membered heterocyclyl has 1-2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-6 membered heterocyclyl has one ring heteroatom selected from nitrogen, oxygen, and sulfur.

Exemplary 3-membered heterocyclyl groups containing one heteroatom include, without limitation, azirdinyl, oxiranyl, thiorenlyl. Exemplary 4-membered heterocyclyl groups containing one heteroatom include, without limitation, azetidiny, oxetanyl and thietanyl. Exemplary 5-membered heterocyclyl groups containing one heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl and pyrrolyl-2,5-dione. Exemplary 5-membered heterocyclyl groups containing two heteroatoms include, without limitation, dioxolanyl, oxasulfuranyl, disulfuranyl, and oxazolidin-2-one. Exemplary 5-membered heterocyclyl groups containing three heteroatoms include, without limitation, triazoliny, oxadiazoliny, and thiadiazoliny. Exemplary 6-membered heterocyclyl groups containing one heteroatom include, without limitation, piperidinyl, piperazinyl, tetrahydropyranyl, dihydropyridiny, and thianyl. Exemplary 6-membered heterocyclyl groups containing two heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, dioxanyl. Exemplary 6-membered heterocyclyl groups containing two heteroatoms include, without limitation, triazinanyl or thiomorpholinyl-1,1-dioxide. Exemplary 7-membered heterocyclyl groups containing one heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8-membered heterocyclyl groups containing one heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary 5-membered heterocyclyl groups fused to a C₆ aryl ring (also referred to herein as a 5,6-bicyclic heterocyclic ring) include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzoxazolinonyl, and the like. Exemplary 6-membered heterocyclyl groups fused to an aryl ring (also referred to herein as a 6,6-bicyclic heterocyclic ring) include, without limitation, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and the like.

“Amino” as used herein refers to the radical $-NR^{70}R^{71}$, wherein R⁷⁰ and R⁷¹ are each independently hydrogen, C₁–C₈ alkyl, C₃–C₁₀ cycloalkyl, C₄–C₁₀ heterocyclyl, C₆–C₁₀ aryl, and C₅–C₁₀ heteroaryl. In some embodiments, amino refers to NH₂.

As used herein, “cyano” refers to the radical –CN.

As used herein, “halo” or “halogen,” independently or as part of another substituent, mean, unless otherwise stated, a fluorine (F), chlorine (Cl), bromine (Br), or iodine (I) atom.

As used herein, “hydroxy” refers to the radical –OH.

Alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl groups,

as defined herein, are optionally substituted (*e.g.*, “substituted” or “unsubstituted” alkyl, “substituted” or “unsubstituted” alkenyl, “substituted” or “unsubstituted” alkynyl, “substituted” or “unsubstituted” heteroalkyl, “substituted” or “unsubstituted” cycloalkyl, “substituted” or “unsubstituted” heterocyclyl, “substituted” or “unsubstituted” aryl or “substituted” or “unsubstituted” heteroaryl group). In general, the term “substituted”, whether preceded by the term “optionally” or not, means that at least one hydrogen present on a group (*e.g.*, a carbon or nitrogen atom) is replaced with a permissible substituent, *e.g.*, a substituent which upon substitution results in a stable compound, *e.g.*, a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a “substituted” group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. The term “substituted” is contemplated to include substitution with all permissible substituents of organic compounds, such as any of the substituents described herein that result in the formation of a stable compound.

The present disclosure contemplates any and all such combinations to arrive at a stable compound. For purposes of this disclosure, heteroatoms such as nitrogen may have hydrogen substituents and/or any suitable substituent as described herein which satisfy the valencies of the heteroatoms and results in the formation of a stable moiety.

Two or more substituents may optionally be joined to form aryl, heteroaryl, cycloalkyl, or heterocyclyl groups. Such so-called ring-forming substituents are typically, though not necessarily, found attached to a cyclic base structure. In one embodiment, the ring-forming substituents are attached to adjacent members of the base structure. For example, two ring-forming substituents attached to adjacent members of a cyclic base structure create a fused ring structure. In another embodiment, the ring-forming substituents are attached to a single member of the base structure. For example, two ring-forming substituents attached to a single member of a cyclic base structure create a spirocyclic structure. In yet another embodiment, the ring-forming substituents are attached to non-adjacent members of the base structure.

Compounds of Formula (I) described herein can comprise one or more asymmetric centers, and thus can exist in various isomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including

racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high-pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). The disclosure additionally encompasses compounds described herein as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

As used herein, a pure enantiomeric compound is substantially free from other enantiomers or stereoisomers of the compound (i.e., in enantiomeric excess). In other words, an "S" form of the compound is substantially free from the "R" form of the compound and is, thus, in enantiomeric excess of the "R" form. The term "enantiomerically pure" or "pure enantiomer" denotes that the compound comprises more than 75% by weight, more than 80% by weight, more than 85% by weight, more than 90% by weight, more than 91% by weight, more than 92% by weight, more than 93% by weight, more than 94% by weight, more than 95% by weight, more than 96% by weight, more than 97% by weight, more than 98% by weight, more than 99% by weight, more than 99.5% by weight, or more than 99.9% by weight, of the enantiomer. In certain embodiments, the weights are based upon total weight of all enantiomers or stereoisomers of the compound.

Compounds of Formula (I) described herein may also comprise one or more isotopic substitutions. For example, H may be in any isotopic form, including ^1H , ^2H (D or deuterium), and ^3H (T or tritium); C may be in any isotopic form, including ^{12}C , ^{13}C , and ^{14}C ; O may be in any isotopic form, including ^{16}O and ^{18}O ; and the like.

The term "pharmaceutically acceptable salt" is meant to include salts of the active compounds that are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds used in the present disclosure contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition

salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds used in the present disclosure contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent.

5 Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, 0 mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galacturonic acids and the like (see, e.g., Berge et al, *Journal of Pharmaceutical Science* 66: 1-19 (1977)). Certain specific compounds used in the present disclosure contain both basic and acidic functionalities that allow the compounds to be converted 5 into either base or acid addition salts. These salts may be prepared by methods known to those skilled in the art. Other pharmaceutically acceptable carriers known to those of skill in the art are suitable for use in the present disclosure.

The present disclosure may employ compounds of Formula (I) in a prodrug form. Prodrugs are those compounds that readily undergo chemical changes under physiological 10 conditions to provide the compounds useful in the present disclosure. Additionally, prodrugs can be converted to useful compounds of Formula (I) by chemical or biochemical methods in an ex vivo environment.

Certain compounds of Formula (I) described herein can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to 25 unsolvated forms and are encompassed within the scope of the present disclosure. Certain compounds of Formula (I) described herein may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present disclosure and are intended to be within the scope of the present disclosure.

The term "solvate" refers to forms of the compound that are associated with a solvent, 30 usually by a solvolysis reaction. This physical association may include hydrogen bonding. Conventional solvents include water, methanol, ethanol, acetic acid, DMSO, THF, diethyl ether,

and the like. The compounds described herein may be prepared, *e.g.*, in crystalline form, and may be solvated. Suitable solvates include pharmaceutically acceptable solvates and further include both stoichiometric solvates and non-stoichiometric solvates.

The term “hydrate” refers to a compound which is associated with water. Typically, the number of the water molecules contained in a hydrate of a compound is in a definite ratio to the number of the compound molecules in the hydrate. Therefore, a hydrate of a compound may be represented, for example, by the general formula $R \cdot x H_2O$, wherein R is the compound and wherein x is a number greater than 0.

The term “tautomer” as used herein refers to compounds that are interchangeable forms of a compound structure, and that vary in the displacement of hydrogen atoms and electrons. Thus, two structures may be in equilibrium through the movement of π electrons and an atom (usually H). For example, enols and ketones are tautomers because they are rapidly interconverted by treatment with either acid or base. Tautomeric forms may be relevant to the attainment of the optimal chemical reactivity and biological activity of a compound of interest.

The symbol “” as used herein refers to a connection to an entity, *e.g.*, a polymer (*e.g.*, hydrogel-forming polymer such as alginate) or an implantable element (*e.g.*, a particle, device or material). The connection represented by “” may refer to direct attachment to the entity, *e.g.*, a polymer or an implantable element, or may refer to linkage to the entity through an attachment group. An “attachment group,” as described herein, refers to a moiety for linkage of a compound of Formula (I) to an entity (*e.g.*, a polymer or an implantable element as described herein), and may comprise any attachment chemistry known in the art. A listing of exemplary attachment groups is outlined in *Bioconjugate Techniques* (3rd ed, Greg T. Hermanson, Waltham, MA: Elsevier, Inc, 2013), which is incorporated herein by reference in its entirety. In some embodiments, an attachment group comprises alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-C(O)-$, $-OC(O)-$, $-N(R^C)-$, $-N(R^C)C(O)-$, $-C(O)N(R^C)-$, $-N(R^C)N(R^D)-$, $-NCN-$, $-C(=N(R^C)(R^D))O-$, $-S-$, $-S(O)_x-$, $-OS(O)_x-$, $-N(R^C)S(O)_x-$, $-S(O)_xN(R^C)-$, $-P(R^F)_y-$, $-Si(OR^A)_2-$, $-Si(R^G)(OR^A)-$, $-B(OR^A)-$, or a metal, wherein each of R^A , R^C , R^D , R^F , R^G , x and y is independently as described herein. In some embodiments, an attachment group comprises an amine, ketone, ester, amide, alkyl, alkenyl, alkynyl, or thiol. In some embodiments, an attachment group is a cross-linker. In some embodiments, the attachment group is $-C(O)(C_1-C_6\text{-alkylene})-$, wherein alkylene is substituted with R^1 , and R^1 is as described

herein. In some embodiments, the attachment group is $-\text{C}(\text{O})(\text{C}_1\text{-C}_6\text{-alkylene})-$, wherein alkylene is substituted with 1-2 alkyl groups (e.g., 1-2 methyl groups). In some embodiments, the attachment group is $-\text{C}(\text{O})\text{C}(\text{CH}_3)_2-$. In some embodiments, the attachment group is $-\text{C}(\text{O})(\text{methylene})-$, wherein alkylene is substituted with 1-2 alkyl groups (e.g., 1-2 methyl groups). In some embodiments, the attachment group is $-\text{C}(\text{O})\text{CH}(\text{CH}_3)-$. In some embodiments, the attachment group is $-\text{C}(\text{O})\text{C}(\text{CH}_3)-$.

Features of Particles

The present disclosure features particles comprising a first compartment, a second compartment, and a compound of Formula (I), e.g., a described herein. The particle may be spherical (e.g., a hydrogel capsule) or any other shape. The particle may comprise materials such as metals, metallic alloys, ceramics, polymers, fibers, inert materials, and combinations thereof. A particle may be completely made up of one type of material, or may comprise numerous other materials within the second compartment and any first compartments.

In some embodiments, the first compartment is modified with a compound of Formula (I). In some embodiments, the second compartment is modified with a compound of Formula (I). In some embodiments, both the first compartment and the second compartment are independently modified with a compound of Formula (I).

In some embodiments, a particle has a largest linear dimension (LLD), e.g., mean diameter, or size that is greater than 1 millimeter (mm), preferably 1.5 mm or greater. In some embodiments, a particle can be as large as 10 mm in diameter or size. For example, a particle described herein is in a size range of 0.5 mm to 10 mm, 1 mm to 10 mm, 1 mm to 8 mm, 1 mm to 6 mm, 1 mm to 5 mm, 1 mm to 4 mm, 1 mm to 3 mm, 1 mm to 2 mm, 1 mm to 1.5 mm, 1.5 mm to 8 mm, 1.5 mm to 6 mm, 1.5 mm to 5 mm, 1.5 mm to 4 mm, 1.5 mm to 3 mm, 1.5 mm to 2 mm, 2 mm to 8 mm, 2 mm to 7 mm, 2 mm to 6 mm, 2 mm to 5 mm, 2 mm to 4 mm, 2 mm to 3 mm, 2.5 mm to 8 mm, 2.5 mm to 7 mm, 2.5 mm to 6 mm, 2.5 mm to 5 mm, 2.5 mm to 4 mm, 2.5 mm to 3 mm, 3 mm to 8 mm, 3 mm to 7 mm, 3 mm to 6 mm, 3 mm to 5 mm, 3 mm to 4 mm, 3.5 mm to 8 mm, 3.5 mm to 7 mm, 3.5 mm to 6 mm, 3.5 mm to 5 mm, 3.5 mm to 4 mm, 4 mm to 8 mm, 4 mm to 7 mm, 4 mm to 6 mm, 4 mm to 5 mm, 4.5 mm to 8 mm, 4.5 mm to 7 mm, 4.5 mm to 6 mm, 4.5 mm to 5 mm, 5 mm to 8 mm, 5 mm to 7 mm, 5 mm to 6 mm, 5.5 mm to 8 mm, 5.5 mm to 7 mm, 5.5 mm to 6 mm, 6 mm to 8 mm, 6 mm to 7 mm, 6.5 mm to 8 mm, 6.5 mm to 7 mm, 7 mm to 8 mm, or 7.5 mm to 8 mm. In some embodiments, the particle has a mean

diameter or size between 1 mm to 8 mm. In some embodiments, the particle has a mean diameter or size between 1 mm to 4 mm. In some embodiments, the particle has a mean diameter or size between 1 mm to 2 mm. In some embodiments, the particle has a mean diameter or size between 1.5 mm to 2 mm.

In some embodiments, a particle has a largest linear dimension (LLD), e.g., mean diameter, or size that is 1 millimeter (mm) or smaller. In some embodiments, the particle is in a size range of 0.3 mm to 1 mm, 0.4 mm to 1 mm, 0.5 mm to 1 mm, 0.6 mm to 1 mm, 0.7 mm to 1 mm, 0.8 mm to 1 mm or 0.9 mm to 1 mm.

In some embodiments, the second (outer) compartment completely surrounds the first (inner) compartment, and the inner boundary of the second compartment forms an interface with the outer boundary of the first compartment, e.g., as illustrated in FIG. 1. In such embodiments, the thickness of the second (outer) compartment means the average distance between the outer boundary of the second compartment and the interface between the two compartments. In some embodiments, the thickness of the outer compartment is greater than about 10 nanometers (nm), preferably 100 nm or greater and can be as large as 1 mm. For example, the thickness of the outer compartment in a particle described herein may be 10 nanometers to 1 millimeter, 100 nanometers to 1 millimeter, 500 nanometers to 1 millimeter, 1 micrometer (μm) to 1 millimeter, 1 μm to 1 mm, 1 μm to 500 μm , 1 μm to 250 μm , 1 μm to 1 mm, 5 μm to 500 μm , 5 μm to 250 μm , 10 μm to 1 mm, 10 μm to 500 μm , or 10 μm to 250 μm . In some embodiments, the thickness of the outer compartment is 100 nanometers to 1 millimeters, between 1 μm and 1 mm, between 1 μm and 500 μm or between 5 μm and 1 mm.

In some embodiments, a particle comprises at least one pore or opening, e.g., to allow for the free flow of materials. In some embodiments, the mean pore size of a particle is between about 0.1 μm to about 10 μm . For example, the mean pore size may be between 0.1 μm to 10 μm , 0.1 μm to 5 μm , 0.1 μm to 2 μm , 0.15 μm to 10 μm , 0.15 μm to 5 μm , 0.15 μm to 2 μm , 0.2 μm to 10 μm , 0.2 μm to 5 μm , 0.25 μm to 10 μm , 0.25 μm to 5 μm , 0.5 μm to 10 μm , 0.75 μm to 10 μm , 1 μm to 10 μm , 1 μm to 5 μm , 1 μm to 2 μm , 2 μm to 10 μm , 2 μm to 5 μm , or 5 μm to 10 μm . In some embodiments, the mean pore size of a particle is between about 0.1 μm to 10 μm . In some embodiments, the mean pore size of a particle is between about 0.1 μm to 5 μm . In some embodiments, the mean pore size of a particle is between about 0.1 μm to 1 μm . In some embodiments, the mean pore size of the first compartment and the second compartment of the

particle is substantially the same. In some embodiments, the mean pore size of the first compartment and the second compartment of the particle differ by about 1.5%, 2%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, or more. In some embodiments, the mean pore size of the particle (e.g., mean pore size of the first compartment and/or mean pore size of the second compartment) is dependent on a number of factors, such as the material(s) within each compartment and the presence and density of a compound of Formula (I).

In some embodiments, the particle comprises a metal or a metallic alloy. The first compartment, the second compartment, or both compartments may comprise a metal or a metallic alloy. Exemplary metallic or metallic alloys include comprising titanium and titanium group alloys (e.g., nitinol, nickel titanium alloys, thermo-memory alloy materials), platinum, platinum group alloys, stainless steel, tantalum, palladium, zirconium, niobium, molybdenum, nickel-chrome, chromium molybdenum alloys, or certain cobalt alloys (e.g., cobalt-chromium and cobalt-chromium-nickel alloys, e.g., ELGILOY® and PHYNOX®). For example, a metallic material may be stainless steel grade 316 (SS 316L) (comprised of Fe, <0.3% C, 16-18.5% Cr, 10-14% Ni, 2-3% Mo, <2% Mn, <1% Si, <0.45% P, and <0.03% S). In metal-containing particles, the amount of metal (e.g., by % weight, actual weight) can be at least 5%, e.g., at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 99%, or more, e.g., w/w; less than 20%, e.g., less than 20%, 15%, 10%, 5%, 1%, 0.5%, 0.1%, or less.

In some embodiments, the particle comprises a ceramic. The first compartment, the second compartment, or both compartments may comprise a ceramic. Exemplary ceramic materials include oxides, carbides, or nitrides of the transition elements, such as titanium oxides, hafnium oxides, iridium oxides, chromium oxides, aluminum oxides, and zirconium oxides. Silicon based materials, such as silica, may also be used. In ceramic-containing particles, the amount of ceramic (e.g., by % weight, actual weight) can be at least 5%, e.g., at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 99%, or more, e.g., w/w; less than 20%, e.g., less than 20%, 15%, 10%, 5%, 1%, 0.5%, 0.1%, or less.

In some embodiments, the particle comprises a polymer. The first compartment, the second compartment, or both compartments may comprise a polymer. A polymer may be a linear, branched, or cross-linked polymer, or a polymer of selected molecular weight ranges, degree of polymerization, viscosity or melt flow rate. Branched polymers can include one or

more of the following types: star polymers, comb polymers, brush polymers, dendronized polymers, ladders, and dendrimers. A polymer may be a thermoresponsive polymer, e.g., gel (e.g., becomes a solid or liquid upon exposure to heat or a certain temperature) or a photocrosslinkable polymer. Exemplary polymers include polystyrene, polyethylene, polypropylene, polyacetylene, poly(vinyl chloride) (PVC), polyolefin copolymers, poly(urethane)s, polyacrylates and polymethacrylates, polyacrylamides and polymethacrylamides, poly(methyl methacrylate), poly(2-hydroxyethyl methacrylate), polyesters, polysiloxanes, polydimethylsiloxane (PDMS), polyethers, poly(orthoester), poly(carbonates), poly(hydroxyalkanoate)s, polyfluorocarbons, PEEK®, Teflon® (polytetrafluoroethylene, PTFE), PEEK, silicones, epoxy resins, Kevlar®, Dacron® (a condensation polymer obtained from ethylene glycol and terephthalic acid), polyethylene glycol, nylon, polyalkenes, phenolic resins, natural and synthetic elastomers, adhesives and sealants, polyolefins, polysulfones, polyacrylonitrile, biopolymers such as polysaccharides and natural latex, collagen, cellulosic polymers (e.g., alkyl celluloses, etc.), polyethylene glycol and 2-hydroxyethyl methacrylate (HEMA), polysaccharides, poly(glycolic acid), poly(L-lactic acid) (PLLA), poly(lactic glycolic acid) (PLGA), a polydioxanone (PDA), or racemic poly(lactic acid), polycarbonates, (e.g., polyamides (e.g., nylon)), fluoroplastics, carbon fiber, agarose, alginate, chitosan, and blends or copolymers thereof. In polymer-containing particles, the amount of a polymer (e.g., by % weight of the particle, actual weight of the polymer) can be at least 5%, e.g., at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 99%, or more, e.g., w/w; less than 20%, e.g., less than 20%, 15%, 10%, 5%, 1%, 0.5%, 0.1%, or less.

In some embodiments, the polymer comprises a polyethylene. The first compartment, the second compartment, or both compartments may comprise a polyethylene. Exemplary polyethylenes include ultra-low-density polyethylene (ULDPE) (e.g., with polymers with densities ranging from 0.890 to 0.905 g/cm³, containing comonomer); very-low-density polyethylene (VLDPE) (e.g., with polymers with densities ranging from 0.905 to 0.915 g/cm³, containing comonomer); linear low-density polyethylene (LLDPE) (e.g., with polymers with densities ranging from 0.915 to 0.935 g/cm³, contains comonomer); low-density polyethylene (LDPE) (e.g., with polymers with densities ranging from about 0.915 to 0.935 g/m³); medium density polyethylene (MDPE) (e.g., with polymers with densities ranging from 0.926 to 0.940 g/cm³, may or may not contain comonomer); high-density polyethylene (HDPE) (e.g., with

polymers with densities ranging from 0.940 to 0.970 g/cm³, may or may not contain comonomer).

In some embodiments, the particle comprises a polypropylene. The first compartment, the second compartment, or both compartments may comprise a polypropylene. Exemplary polypropylenes include homopolymers, random copolymers (homophasic copolymers), and impact copolymers (heterophasic copolymers), e.g., as described in McKeen, *Handbook of Polymer Applications in Medicine and Medical Devices*, 3- Plastics Used in Medical Devices, (2014):21-53, which is incorporated herein by reference in its entirety.

In some embodiments, the particle comprises a polystyrene. The first compartment, the second compartment, or both compartments may comprise a polystyrene. Exemplary polystyrenes include general purpose or crystal (PS or GPPS), high impact (HIPS), and syndiotactic (SPS) polystyrene.

In some embodiments, the particle comprises a thermoplastic elastomer (TPE). The first compartment, the second compartment, or both compartments may comprise a TPE. Exemplary TPEs include (i) TPA—polyamide TPE, comprising a block copolymer of alternating hard and soft segments with amide chemical linkages in the hard blocks and ether and/or ester linkages in the soft blocks; (ii) TPC—co-polyester TPE, consisting of a block copolymer of alternating hard segments and soft segments, the chemical linkages in the main chain being ester and/or ether; (iii) TPO—olefinic TPE, consisting of a blend of a polyolefin and a conventional rubber, the rubber phase in the blend having little or no cross-linking; (iv) TPS—styrenic TPE, consisting of at least a triblock copolymer of styrene and a specific diene, where the two end blocks (hard blocks) are polystyrene and the internal block (soft block or blocks) is a polydiene or hydrogenated polydiene; (v) TPU—urethane TPE, consisting of a block copolymer of alternating hard and soft segments with urethane chemical linkages in the hard blocks and ether, ester or carbonate linkages or mixtures of them in the soft blocks; (vi) TPV—thermoplastic rubber vulcanizate consisting of a blend of a thermoplastic material and a conventional rubber in which the rubber has been cross-linked by the process of dynamic vulcanization during the blending and mixing step; and (vii) TPZ—unclassified TPE comprising any composition or structure other than those grouped in TPA, TPC, TPO, TPS, TPU, and TPV.

In some embodiments, the particle comprises a polysaccharide, and the polysaccharide is an alginate. Alginate is a polysaccharide made up of β -D-mannuronic acid (M) and α -L-

guluronic acid (G). In some embodiments, the alginate is a high guluronic acid (G) alginate, and comprises greater than about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or more guluronic acid (G). In some embodiments, the alginate is a high mannuronic acid (M) alginate, and comprises greater than about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or more mannuronic acid (M). In some embodiments, the ratio of M:G is about 1. In some embodiments, the ratio of M:G is less than 1. In some embodiments, the ratio of M:G is greater than 1. In alginate-containing particles, the amount of alginate (e.g., by % weight of the particle, actual weight of the alginate) can be at least 5%, e.g., at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 99%, or more, e.g., w/w; less than 20%, e.g., less than 20%, 15%, 10%, 5%, 1%, 0.5%, 0.1%, or less.

In some embodiments, both the first compartment and the second compartment comprise the same polymer. In some embodiments, the first compartment and the second compartment comprise different polymers. In some embodiments, the first compartment comprises an alginate. In some embodiments, the second compartment comprises an alginate. In some embodiments, both the first compartment and the second compartment comprise an alginate. In some embodiments, the alginate in the first compartment is different than the alginate in the second compartment. In some embodiments, the first compartment comprises an alginate and the second compartment comprises a different polymer (e.g., a polysaccharide, e.g., hyaluronate or chitosan). In some embodiments, the second compartment comprises an alginate and the first compartment comprises a different polymer (e.g., a polysaccharide, e.g., hyaluronate or chitosan).

Both the first compartment and the second compartment may include a single component (e.g., one polymer) or more than one component (e.g., a blend of polymers). In some embodiments, the first compartment comprises only alginate (e.g., chemically modified alginate, or a blend of an unmodified alginate and a chemically modified alginate). In some embodiments, the second compartment comprises only alginate (e.g., chemically modified alginate or a blend of an unmodified alginate and a chemically modified alginate). In some embodiments, both the first and the second compartment independently comprise only alginate (e.g., chemically modified alginate or blend of an unmodified alginate and a chemically modified alginate).

In some embodiments, the polymer in one or both of the first and second compartments is

(i) a low-molecular weight alginate, e.g., has an approximate MW < 75 kDa and G:M ratio ≥ 1.5 , (ii) a medium molecular weight alginate, e.g., has approximate molecular weight of 75-150 kDa and G:M ratio ≥ 1.5 , (iii) a high molecular weight alginate, e.g., has an approximate MW of 150 kDa – 250 kDa and G:M ratio ≥ 1.5 , (iv) or a blend of two or more of these alginates. In an embodiment, the polymer in the first (inner) compartment is an unmodified, high molecular weight alginate or an unmodified, medium molecular weight alginate and the polymer in the second (outer) compartment is a blend of a chemically-modified alginate (e.g., alginate modified with Compound 101 shown in Table 2) and an unmodified alginate, e.g, a 70:30 blend or a 60:40 blend of CM-LMW-Alg-101:U-HMW-Alg, which may be prepared as described in the Examples below.

In some embodiments, the particle comprises alginate, and the compound of Formula (I) is covalently attached to some or all the monomers in the alginate. In some embodiments, some or all the monomers in the alginate are modified with the same compound of Formula (I). In some embodiments, some or all the monomers in the alginate are modified with different compounds of Formula (I).

In some embodiments, a polymer of the first compartment of the particle is modified with one compound of Formula (I), and a polymer of the second compartment of the particle is modified with a different compound of Formula (I). In some embodiments, the particle comprises a mixture of polymers modified with a compound of Formula (I) and unmodified polymers (e.g., polymers not modified with a compound of Formula (I)). In some embodiments, the first compartment comprises a mixture of polymers modified with a compound of Formula (I) and unmodified polymers (e.g., polymers not modified with a compound of Formula (I)). In some embodiments, the second compartment comprises a mixture of polymers modified with a compound of Formula (I) and unmodified polymers (e.g., polymers not modified with a compound of Formula (I)).

A polymer of a particle described herein may be modified with a compound of Formula (I) or a pharmaceutically acceptable salt thereof on one or more monomers of the polymer. The modified polymer of the particle may be present in the first (inner) compartment of the particle, the second (outer) compartment of the particle, or both the first (inner) and second (outer) compartments of the particle. In some embodiments, the modified polymer is present only in the second compartment (which includes the exterior particle surface). In some embodiments, at

least 0.5% of the monomers of a polymer are modified with a compound of Formula (I) (e.g., at least 1%, 2.5%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or more of the monomers of a polymer are modified with a compound of Formula (I)). In some embodiments, 0.5% to 50%, 10% to 90%, 10% to 50%, or 25-75%, of the monomers of a polymer are modified with a compound of Formula (I). In some embodiments, 1% to 20% of the monomers of a polymer are modified with a compound of Formula (I). In some embodiments, 1% to 10% of the monomers of a polymer are modified with a compound of Formula (I).

In some embodiments, the polymer (e.g., alginate) (when modified with a compound of Formula (I), e.g., Compound 101 of Table 2) comprises an increase in % N (as compared with unmodified polymer, e.g., alginate) of any of the following values: (i) at least 0.1%, 0.2%, 0.5%, 1.0%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 5.5%, 6%, 6.5%, 7%, 7.5%, 8%, 8.5%, 9%, 9.5%, or 10% N by weight; (ii) 0.1% to 10% by weight, (iii) 0.1% to 2% N by weight; (iv) 2% to 4% N by weight; (v) 4% to 8% N by weight; (vi) 5% to 9% N by weight; (vii) 6% to 9% N by weight, (viii) 6% to 8% N by weight; (ix) 7% to 9% N by weight; and (x) 8% to 9% N by weight where, in each case, % N is determined by combustion analysis (e.g., as described in Example 2 herein) and corresponds to the amount of compound of Formula (I) in the modified polymer.

A particle (e.g., a first compartment or second compartment therein) may comprise a compound of Formula (I) in an amount that confers a specific feature to the particle. For example, the particle surface (e.g., the exterior of the outer compartment) may comprise a concentration or density of a compound of Formula (I) such that the particle is afibrotic (i.e., mitigates the foreign body response) in a subject. In an embodiment, the particle surface comprises an alginate chemically modified with an afibrotic-effective amount of Compound 101. In an embodiment, the afibrotic-effective amount of Compound 101 produces an increase in % N (as compared with the unmodified alginate) of about 0.5% to 2% 2% to 4% N, about 4% to 6% N, about 6% to 8%, or about 8% to 10% N), where % N is determined by combustion analysis (e.g., as described in Example 2 herein) and corresponds to the amount of Compound 101 in the modified alginate.

As described in the examples below, certain higher concentrations of a compound of Formula (I) in the outer-compartment of two-compartment alginate hydrogel capsules compromised the mechanical strength of the capsules, possibly due to a reduction in sites on the

alginate molecules that are available for cross-linking. Thus, in an embodiment, the particle surface (e.g., the exterior of the outer compartment) may comprise a concentration or density of a Formula (I) compound that is high enough to render the particle afibrotic but is lower than a threshold at which a desired mechanical strength is not achieved. In an embodiment, a desired mechanical strength refers to the ability of the particle to maintain its shape and/or remain intact when subjected to any one or more of the following stressors: (i) compression (e.g., at a constant rate); (ii) during administration (e.g., implantation) to a subject; and (iii) after a desired implantation period. The mechanical strength of a particle may be measured prior to implantation of the particle in a subject and/or after retrieval of the implanted particle (e.g., after 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks, 12 weeks, or longer after implant). In an embodiment, the desired mechanical strength of a particle (e.g., a hydrogel capsule) determined after manufacture but before implantation is determined by performing a fracture test using a texture analyzer.

In an embodiment, mechanical testing of hydrogel capsules is performed on a TA.XT plus Texture Analyzer (Stable Micro Systems, Surrey, United Kingdom) using a 5mm probe attached to a 5kg load cell. Individual capsules are placed on a platform and are compressed from above by the probe at a fixed rate of 0.5mm/sec. Contact between the probe and capsule is detected when a repulsive force of 1g is measured. The probe continues to travel 90% of the distance between the contact height of the probe and the platform, compressing the capsule to the point of bursting. The resistance to the compressive force of the probe is measured and can be plotted as a function of probe travel (force v. displacement curve). Typically, before a capsule bursts completely it will fracture slightly and the force exerted against the probe will decrease a small amount. An analysis macro can be programmed to detect the first time a decrease of 0.25-0.5g occurs in the force v. displacement curve. The force applied by the probe when this occurs is termed the initial fracture force. In an embodiment, the desired mechanical strength of a particle described herein (e.g., a two-compartment hydrogel capsule) has an initial fracture force of greater than 1, 1.5, 2, 2.5 or 3 grams or at least 2 grams.

In an embodiment, the desired mechanical strength of a particle is the ability to remain intact at a desired timepoint after implantation in a subject, e.g., both the outer and inner compartments of a hydrogel capsule removed from a subject are visibly intact after retrieval from an immune competent mouse when observed by optical microscopy, e.g., by brightfield imaging

as described in the Examples herein.

In an embodiment, the particle surface comprises an alginate chemically modified with Compound 101 in an amount that provides the particle with both an afibrotic property and a desired mechanical strength, e.g., a concentration or density of Compound 101 in the modified alginate that produces an increase in %N (as compared with the unmodified alginate) of any of the following values: (i) 1% to 3% by weight, (ii) 2% to 4% N by weight; (iii) 4% to 8% N by weight; (iv) 5% to 9% N by weight; (v) 6% to 9% N by weight, (vi) 6% to 8% N by weight; (vii) 7% to 9% N by weight; and (ix) 8% to 9% N by weight; where, in each case, % N is determined by combustion analysis (e.g., as described in Example 2 herein) and corresponds to the amount of compound of Formula (I) in the modified alginate.

When a particle (e.g., a first compartment or second compartment therein) comprises alginate, the alginate can be chemically modified with a compound of Formula (I) using any suitable method known in the art. For example, the alginate carboxylic acid moiety can be activated for coupling to one or more amine-functionalized compounds to achieve an alginate modified with a compound of Formula (I). The alginate polymer may be dissolved in water (30 mL/gram polymer) and treated with 2-chloro-4,6-dimethoxy-1,3,5-triazine (0.5 eq) and N-methylmorpholine (1 eq). To this mixture may be added a solution of the compound of Formula (I) dissolved in a buffer or solvent, such as acetonitrile (0.3 M). The reaction may be warmed, e.g., to 55 °C for 16h, then cooled to room temperature and concentrated via rotary evaporation. The residue may then be dissolved in a buffer or solvent, e.g., water. The mixture may then be filtered, e.g., through a bed of cyano-modified silica gel (Silicycle) and the filter cake washed with water. The resulting solution may then be dialyzed (10,000 MWCO membrane) against a buffer or water for 24 hours, e.g., replacing the buffer or water at least one time, at least two times, at least three times, or more. The resulting solution can be concentrated, e.g., via lyophilization, to afford the desired chemically modified alginate.

In some embodiments, a particle described herein comprises a cell. In some embodiments, the cell is engineered to produce a therapeutic agent (e.g., a protein or polypeptide, e.g., an antibody, protein, enzyme, or growth factor). In some embodiments, the cell is disposed with the first compartment. In some embodiments, the cell is disposed within the second compartment. In some embodiments, the cell is disposed in the first compartment and the second compartment does not comprise a cell. A particle may comprise an active or inactive

fragment of a protein or polypeptide, such as glucose oxidase (e.g., for glucose sensor), kinase, phosphatase, oxygenase, hydrogenase, reductase.

In some embodiments, a particle is capable of preventing materials over a certain size from passing through a pore or opening. In some embodiments, a particle is capable of preventing materials greater than 50 kD, 75 kD, 100 kD, 125 kD, 150 kD, 175 kD, 200 kD, 250 kD, 300 kD, 400 kD, 500 kD, 750 kD, or 1,000 kD from passing through.

A particle described herein may be configured to release a therapeutic agent, e.g., an exogenous substance, e.g., a therapeutic agent described herein. In some embodiments, the therapeutic agent is a compound of Formula (I) or a pharmaceutically acceptable salt thereof. In some embodiments, the therapeutic agent is a biological material. In some embodiments, the therapeutic agent is a nucleic acid (e.g., an RNA or DNA), protein (e.g., a hormone, enzyme, antibody, antibody fragment, antigen, or epitope), small molecule, lipid, drug, vaccine, or any derivative thereof.

A particle (e.g., as described herein) may be provided as a preparation or composition for implantation or administration to a subject. In some embodiments, at least 20%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 100% of the particles in a preparation or composition have a characteristic as described herein, e.g., mean diameter or mean pore size.

In some embodiments, a particle targets or is designed for a certain system of the body, e.g. the nervous system (e.g., peripheral nervous system (PNS) or central nervous system (CNS)), vascular system, skeletal system, respiratory system, endocrine system, lymph system, reproductive system, or gastrointestinal tract. In some embodiments, a particle is targeted to the CNS. In some embodiments, a particle targets or is designed for a certain part of the body, e.g., blood, eye, brain, skin, lung, stomach, mouth, ear, leg, foot, hand, liver, heart, kidney, bone, pancreas, spleen, large intestine, small intestine, spinal cord, muscle, ovary, uterus, vagina, or penis.

A particle may be configured for implantation, or implanted or disposed into or onto any site of the body. In some embodiments, a particle is configured for implantation, implanted or disposed into the omentum of a subject, into the subcutaneous fat of a subject, or into the muscle tissue of a subject. A particle can be configured for implantation, or implanted, or disposed on or in the skin; a mucosal surface, a body cavity, the peritoneal cavity (e.g., the lesser sac); the

central nervous system, e.g., the brain or spinal cord; an organ, e.g., the heart, liver, kidney, spleen, lung, lymphatic system, vasculature, the oral cavity, the nasal cavity, the teeth, the gums, the GI tract; bone; hip; fat tissue; muscle tissue; circulating blood; the eye (e.g., intraocular); breast, vagina; uterus, a joint, e.g., the knee or hip joint, or the spine.

In some embodiments, the particle is configured for implantation or implanted or disposed into the peritoneal cavity (e.g., the omentum). In some embodiments, the particle is configured for implantation or implanted or disposed into or onto the lesser sac, also known as the omental bursa or bursalis omentum. The lesser sac refers to a cavity located in the abdomen formed by the omentum, and is in close proximity to, for example, the greater omentum, lesser omentum, stomach, small intestine, large intestine, liver, spleen, gastrosplenic ligament, adrenal glands, and pancreas. Typically, the lesser sac is connected to the greater sac via the omental foramen (i.e., the Foramen of Winslow). In some embodiments, the lesser sac comprises a high concentration of adipose tissue. A particle may be implanted in the peritoneal cavity (e.g., the omentum, e.g., the lesser sac) or disposed on a surface within the peritoneal cavity (e.g., omentum, e.g., lesser sac) via injection or catheter. Additional considerations for implantation or disposition of a particle into the omentum (e.g., the lesser sac) are provided in M. Pellicciaro et al. (2017) *CellR4* 5(3):e2410, which is incorporated herein by reference in its entirety.

In some embodiments, the particle is configured for implantation or implanted or disposed into the central nervous system (CNS), e.g., the brain or spinal cord and their corresponding tissues and cavities. In vertebrates, the CNS is contained within the dorsal body cavity, including the cranial cavity and the spinal canal. In some embodiments, the particle is configured for implantation or implanted or disposed into an intracerebral space, e.g., the intraparenchymal space, the intraventricular space, or the subdural space. A particle may be implanted in the CNS or disposed on a surface within the CNS through a hole made in the skull and delivered via injection or catheter.

In some embodiments, the particle is configured for implantation or implanted in or disposed into the eye. Exemplary regions suitable for implantation or disposition of the particle include any surface or cavity within the eye, such as the retina, cornea, epithelium, aqueous humor, or vitreal space. In some embodiments, the particle is configured for implantation or implanted or disposed into the vitreal space. A particle may be implanted in the eye or disposed on a surface within the eye through incision and/or injection.

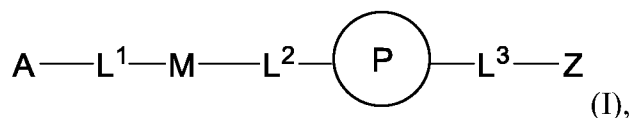
In some embodiments, the particle is easily retrievable from a subject, e.g., without causing injury to the subject or without causing significant disruption of the surrounding tissue. In an embodiment, the particle can be retrieved with minimal or no surgical separation of the particle from surrounding tissue, e.g., via minimally invasive surgical approach, extraction, or resection.

A particle can be configured for limited exposure (e.g., less than 2 days, 1 day, 24 hours, 20 hours, 16 hours, 12 hours, 10 hours, 8 hours, 6 hours, 5 hours, 4 hours, 3 hours, 2 hours, 1 hour or less). A particle can be configured for prolonged exposure (e.g., at least 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, 13 months, 14 months, 15 months, 16 months, 17 months, 18 months, 19 months, 20 months, 21 months, 22 months, 23 months, 24 months, 1 year, 1.5 years, 2 years, 2.5 years, 3 years, 3.5 years, 4 years or more) A particle can be configured for permanent exposure (e.g., at least 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, 13 months, 14 months, 15 months, 16 months, 17 months, 18 months, 19 months, 20 months, 21 months, 22 months, 23 months, 24 months, 1 year, 1.5 years, 2 years, 2.5 years, 3 years, 3.5 years, 4 years or more).

In some embodiments, the particle is not a particle disclosed in any of WO2012/112982, WO2012/167223, WO2014/153126, WO2016/019391, WO2016/187225, US2012-0213708, US 2016-0030359, and US 2016-0030360.

Compounds

In some embodiments, the particles described herein comprise a compound of Formula (I). In some embodiments, the first compartment and/or second compartment of the particle comprise a compound of Formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

A is alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, -O-, -C(O)O-, -C(O)-, -OC(O)-, -N(R^C)-, -N(R^C)C(O)-, -C(O)N(R^C)-, -N(R^C)C(O)(C₁-C₆-alkylene)-, -N(R^C)C(O)(C₂-C₆-alkenylene)-, -N(R^C)N(R^D)-, -NCN-, -C(=N(R^C)(R^D))O-, -S-,

$-\text{S}(\text{O})_{\text{x}}-$, $-\text{OS}(\text{O})_{\text{x}}-$, $-\text{N}(\text{R}^{\text{C}})\text{S}(\text{O})_{\text{x}}-$, $-\text{S}(\text{O})_{\text{x}}\text{N}(\text{R}^{\text{C}})-$, $-\text{P}(\text{R}^{\text{F}})_{\text{y}}-$, $-\text{Si}(\text{OR}^{\text{A}})_2-$, $-\text{Si}(\text{R}^{\text{G}})(\text{OR}^{\text{A}})-$, $-\text{B}(\text{OR}^{\text{A}})-$, or a metal, each of which is optionally linked to an attachment group (e.g., an attachment group described herein) and is optionally substituted by one or more R^1 ;

each of L^1 and L^3 is independently a bond, alkyl, or heteroalkyl, wherein each alkyl and heteroalkyl is optionally substituted by one or more R^2 ;

L^2 is a bond;

M is absent, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted by one or more R^3 ;

P is absent, cycloalkyl, heterocyclyl, or heteroaryl, each of which is optionally substituted by one or more R^4 ;

Z is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, $-\text{OR}^{\text{A}}$, $-\text{C}(\text{O})\text{R}^{\text{A}}$, $-\text{C}(\text{O})\text{OR}^{\text{A}}$, $-\text{C}(\text{O})\text{N}(\text{R}^{\text{C}})(\text{R}^{\text{D}})$, $-\text{N}(\text{R}^{\text{C}})\text{C}(\text{O})\text{R}^{\text{A}}$, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted by one or more R^5 ;

each R^{A} , R^{B} , R^{C} , R^{D} , R^{E} , R^{F} , and R^{G} is independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, halogen, azido, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^6 ;

or R^{C} and R^{D} , taken together with the nitrogen atom to which they are attached, form a ring (e.g., a 5-7 membered ring), optionally substituted with one or more R^6 ;

each R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 is independently alkyl, alkenyl, alkynyl, heteroalkyl, halogen, cyano, azido, oxo, $-\text{OR}^{\text{A}1}$, $-\text{C}(\text{O})\text{OR}^{\text{A}1}$, $-\text{C}(\text{O})\text{R}^{\text{B}1}$, $-\text{OC}(\text{O})\text{R}^{\text{B}1}$, $-\text{N}(\text{R}^{\text{C}1})(\text{R}^{\text{D}1})$, $-\text{N}(\text{R}^{\text{C}1})\text{C}(\text{O})\text{R}^{\text{B}1}$, $-\text{C}(\text{O})\text{N}(\text{R}^{\text{C}1})$, $\text{SR}^{\text{E}1}$, $\text{S}(\text{O})_{\text{x}}\text{R}^{\text{E}1}$, $-\text{OS}(\text{O})_{\text{x}}\text{R}^{\text{E}1}$, $-\text{N}(\text{R}^{\text{C}1})\text{S}(\text{O})_{\text{x}}\text{R}^{\text{E}1}$, $-\text{S}(\text{O})_{\text{x}}\text{N}(\text{R}^{\text{C}1})(\text{R}^{\text{D}1})$, $-\text{P}(\text{R}^{\text{F}1})_{\text{y}}$, cycloalkyl, heterocyclyl, aryl, heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted by one or more R^7 ;

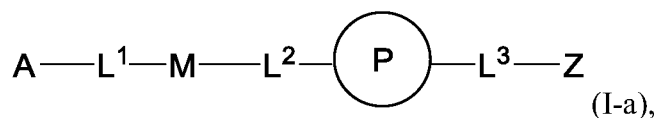
each $\text{R}^{\text{A}1}$, $\text{R}^{\text{B}1}$, $\text{R}^{\text{C}1}$, $\text{R}^{\text{D}1}$, $\text{R}^{\text{E}1}$, and $\text{R}^{\text{F}1}$ is independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl is optionally substituted by one or more R^7 ;

each R^7 is independently alkyl, alkenyl, alkynyl, heteroalkyl, halogen, cyano, oxo, hydroxyl, cycloalkyl, or heterocyclyl;

x is 1 or 2; and

y is 2, 3, or 4.

In some embodiments, the compound of Formula (I) is a compound of Formula (I-a):



5 or a salt thereof, wherein:

A is alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-\text{O}-$, $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})-$, $-\text{OC}(\text{O})-$, $-\text{N}(\text{R}^{\text{C}})-$, $-\text{N}(\text{R}^{\text{C}})\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{N}(\text{R}^{\text{C}})-$, $-\text{N}(\text{R}^{\text{C}})\text{N}(\text{R}^{\text{D}})-$, $-\text{N}(\text{R}^{\text{C}})\text{C}(\text{O})(\text{C}_1-\text{C}_6\text{-alkylene})-$, $-\text{N}(\text{R}^{\text{C}})\text{C}(\text{O})(\text{C}_2-\text{C}_6\text{-alkenylene})-$, $-\text{NCN}-$, $-\text{C}(=\text{N}(\text{R}^{\text{C}})(\text{R}^{\text{D}}))\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{\text{x}}-$, $-\text{OS}(\text{O})_{\text{x}}-$, $-\text{N}(\text{R}^{\text{C}})\text{S}(\text{O})_{\text{x}}-$, $-\text{S}(\text{O})_{\text{x}}\text{N}(\text{R}^{\text{C}})-$, $-\text{P}(\text{R}^{\text{F}})_{\text{y}}-$, $-\text{Si}(\text{OR}^{\text{A}})_2-$, $-\text{Si}(\text{R}^{\text{G}})(\text{OR}^{\text{A}})-$, $-\text{B}(\text{OR}^{\text{A}})-$, or a metal, each of which is optionally linked to an attachment group (e.g., an attachment group described herein) and optionally substituted by one or more R^1 ;

each of L^1 and L^3 is independently a bond, alkyl, or heteroalkyl, wherein each alkyl and heteroalkyl is optionally substituted by one or more R^2 ;

L^2 is a bond;

5 M is absent, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted by one or more R^3 ;

P is heteroaryl optionally substituted by one or more R^4 ;

Z is alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted by one or more R^5 ;

10 each R^{A} , R^{B} , R^{C} , R^{D} , R^{E} , R^{F} , and R^{G} is independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, halogen, azido, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^6 ;

25 or R^{C} and R^{D} , taken together with the nitrogen atom to which they are attached, form a ring (e.g., a 5-7 membered ring), optionally substituted with one or more R^6 ;

each R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 is independently alkyl, alkenyl, alkynyl, heteroalkyl, halogen, cyano, azido, oxo, $-\text{OR}^{\text{A}1}$, $-\text{C}(\text{O})\text{OR}^{\text{A}1}$, $-\text{C}(\text{O})\text{R}^{\text{B}1}$, $-\text{OC}(\text{O})\text{R}^{\text{B}1}$, $-\text{N}(\text{R}^{\text{C}1})(\text{R}^{\text{D}1})-$, $-\text{N}(\text{R}^{\text{C}1})\text{C}(\text{O})\text{R}^{\text{B}1}$, $-\text{C}(\text{O})\text{N}(\text{R}^{\text{C}1})$, $\text{SR}^{\text{E}1}$, $\text{S}(\text{O})_{\text{x}}\text{R}^{\text{E}1}$, $-\text{OS}(\text{O})_{\text{x}}\text{R}^{\text{E}1}$, $-\text{N}(\text{R}^{\text{C}1})\text{S}(\text{O})_{\text{x}}\text{R}^{\text{E}1}$, $-\text{S}(\text{O})_{\text{x}}\text{N}(\text{R}^{\text{C}1})(\text{R}^{\text{D}1})$, $-\text{P}(\text{R}^{\text{F}1})_{\text{y}}$, cycloalkyl, heterocyclyl, aryl, heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally

substituted by one or more R^7 ;

each R^{A1} , R^{B1} , R^{C1} , R^{D1} , R^{E1} , and R^{F1} is independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl is optionally substituted by one or more R^7 ;

each R^7 is independently alkyl, alkenyl, alkynyl, heteroalkyl, halogen, cyano, oxo, hydroxyl, cycloalkyl, or heterocyclyl;

x is 1 or 2; and

y is 2, 3, or 4.

In some embodiments, for Formulas (I) or (I-a), A is alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-O-$, $-C(O)O-$, $-C(O)-$, $-OC(O)-$, $-N(R^C)C(O)-$, $-N(R^C)C(O)(C_1-C_6\text{-alkylene})-$, $-N(R^C)C(O)(C_1-C_6\text{-alkenylene})-$, or $-N(R^C)-$. In some embodiments, A is alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-O-$, $-C(O)O-$, $-C(O)-$, $-OC(O)-$, or $-N(R^C)-$. In some embodiments, A is alkyl, alkenyl, alkynyl, heteroalkyl, $-O-$, $-C(O)O-$, $-C(O)-$, $-OC(O)-$, or $-N(R^C)-$. In some embodiments, A is alkyl, $-O-$, $-C(O)O-$, $-C(O)-$, $-OC(O)-$, or $-N(R^C)-$. In some embodiments, A is $-N(R^C)C(O)-$, $-N(R^C)C(O)(C_1-C_6\text{-alkylene})-$, or $-N(R^C)C(O)(C_1-C_6\text{-alkenylene})-$. In some embodiments, A is $-N(R^C)-$. In some embodiments, A is $-N(R^C)-$, and R^C and R^D is independently hydrogen or alkyl. In some embodiments, A is $-NH-$. In some embodiments, A is $-N(R^C)C(O)(C_1-C_6\text{-alkylene})-$, wherein alkylene is substituted with R^1 . In some embodiments, A is $-N(R^C)C(O)(C_1-C_6\text{-alkylene})-$, and R^1 is alkyl (e.g., methyl). In some embodiments, A is $-NHC(O)C(CH_3)_2-$. In some embodiments, A is $-N(R^C)C(O)(\text{methylene})-$, and R^1 is alkyl (e.g., methyl). In some embodiments, A is $-NHC(O)CH(CH_3)-$. In some embodiments, A is $-NHC(O)C(CH_3)-$.

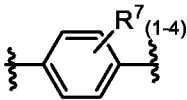
In some embodiments, for Formulas (I) or (I-a), L^1 is a bond, alkyl, or heteroalkyl. In some embodiments, L^1 is a bond or alkyl. In some embodiments, L^1 is a bond. In some embodiments, L^1 is alkyl. In some embodiments, L^1 is C_1-C_6 alkyl. In some embodiments, L^1 is $-CH_2-$, $-CH(CH_3)-$, $-CH_2CH_2CH_2-$, or $-CH_2CH_2-$. In some embodiments, L^1 is $-CH_2-$ or $-CH_2CH_2-$.

In some embodiments, for Formulas (I) or (I-a), L^3 is a bond, alkyl, or heteroalkyl. In some embodiments, L^3 is a bond. In some embodiments, L^3 is alkyl. In some embodiments, L^3 is C_1-C_{12} alkyl. In some embodiments, L^3 is C_1-C_6 alkyl. In some embodiments, L^3 is $-CH_2-$. In some embodiments, L^3 is heteroalkyl. In some embodiments, L^3 is C_1-C_{12} heteroalkyl,

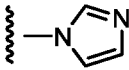
optionally substituted with one or more R^2 (e.g., oxo). In some embodiments, L^3 is C_1 - C_6 heteroalkyl, optionally substituted with one or more R^2 (e.g., oxo). In some embodiments, L^3 is $-C(O)OCH_2-$, $-CH_2(OCH_2CH_2)_2-$, $-CH_2(OCH_2CH_2)_3-$, CH_2CH_2O- , or $-CH_2O-$. In some embodiments, L^3 is $-CH_2O-$.

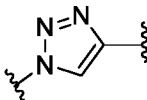
In some embodiments, for Formulas (I) or (I-a), M is absent, alkyl, heteroalkyl, aryl, or heteroaryl. In some embodiments, M is heteroalkyl, aryl, or heteroaryl. In some embodiments, M is absent. In some embodiments, M is alkyl (e.g., C_1 - C_6 alkyl). In some embodiments, M is $-CH_2-$. In some embodiments, M is heteroalkyl (e.g., C_1 - C_6 heteroalkyl). In some embodiments, M is $(-OCH_2CH_2-)_z$, wherein z is an integer selected from 1 to 10. In some embodiments, z is an integer selected from 1 to 5. In some embodiments, M is $-OCH_2CH_2-$, $(-OCH_2CH_2-)_2$, $(-OCH_2CH_2-)_3$, $(-OCH_2CH_2-)_4$, or $(-OCH_2CH_2-)_5$. In some embodiments, M is $-OCH_2CH_2-$, $(-OCH_2CH_2-)_2$, $(-OCH_2CH_2-)_3$, or $(-OCH_2CH_2-)_4$. In some embodiments, M is $(-OCH_2CH_2-)_3$. In some embodiments, M is aryl. In some embodiments, M is phenyl. In some embodiments, M

is unsubstituted phenyl. In some embodiments, M is . In some embodiments, M is

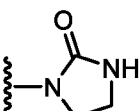
phenyl substituted with R^7 (e.g., 1 R^7). In some embodiments, M is . In some embodiments, R^7 is CF_3 .

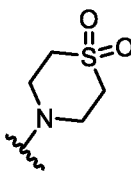
In some embodiments, for Formulas (I) or (I-a), P is absent, heterocyclyl, or heteroaryl. In some embodiments, P is absent. In some embodiments, for Formulas (I) and (I-a), P is a tricyclic, bicyclic, or monocyclic heteroaryl. In some embodiments, P is a monocyclic heteroaryl. In some embodiments, P is a nitrogen-containing heteroaryl. In some embodiments, P is a monocyclic, nitrogen-containing heteroaryl. In some embodiments, P is a 5-membered heteroaryl. In some embodiments, P is a 5-membered nitrogen-containing heteroaryl. In some embodiments, P is tetrazolyl, imidazolyl, pyrazolyl, or triazolyl, pyrrolyl, oxazolyl, or thiazolyl. In some embodiments, P is tetrazolyl, imidazolyl, pyrazolyl, or triazolyl, or pyrrolyl. In some

embodiments, P is imidazolyl. In some embodiments, P is . In some embodiments, P

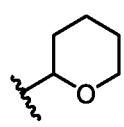
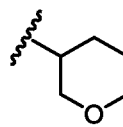
is triazolyl. In some embodiments, P is 1,2,3-triazolyl. In some embodiments, P is .

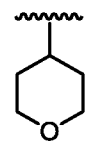
In some embodiments, P is heterocyclyl. In some embodiments, P is a 5-membered heterocyclyl or a 6-membered heterocyclyl. In some embodiments, P is imidazolidinonyl. In

some embodiments, P is . In some embodiments, P is thiomorpholinyl-1,1-dioxidyl.

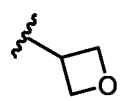
In some embodiments, P is .

In some embodiments, for Formulas (I) or (I-a), Z is alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl. In some embodiments, Z is heterocyclyl. In some embodiments, Z is monocyclic or bicyclic heterocyclyl. In some embodiments, Z is an oxygen-containing heterocyclyl. In some embodiments, Z is a 4-membered heterocyclyl, 5-membered heterocyclyl, or 6-membered heterocyclyl. In some embodiments, Z is a 6-membered heterocyclyl. In some embodiments, Z is a 6-membered oxygen-containing heterocyclyl. In

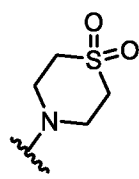
some embodiments, Z is tetrahydropyranyl. In some embodiments, Z is , , or



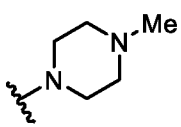
. In some embodiments, Z is a 4-membered oxygen-containing heterocyclyl. In some

embodiments, Z is .

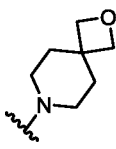
In some embodiments, Z is a bicyclic oxygen-containing heterocyclyl. In some embodiments, Z is phthalic anhydridyl. In some embodiments, Z is a sulfur-containing heterocyclyl. In some embodiments, Z is a 6-membered sulfur-containing heterocyclyl. In some embodiments, Z is a 6-membered heterocyclyl containing a nitrogen atom and a sulfur atom. In

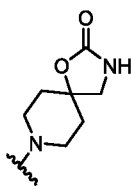
some embodiments, Z is thiomorpholinyl-1,1-dioxidyl. In some embodiments, Z is .

In some embodiments, Z is a nitrogen-containing heterocyclyl. In some embodiments, Z is a 6-

membered nitrogen-containing heterocyclyl. In some embodiments, Z is .

In some embodiments, Z is a bicyclic heterocyclyl. In some embodiments, Z is a bicyclic nitrogen-containing heterocyclyl, optionally substituted with one or more R⁵. In some

embodiments, Z is 2-oxa-7-azaspiro[3.5]nonanyl. In some embodiments, Z is . In some embodiments, Z is 1-oxa-3,8-diazaspiro[4.5]decan-2-one. In some embodiments, Z is



In some embodiments, for Formulas (I) or (I-a), Z is aryl. In some embodiments, Z is monocyclic aryl. In some embodiments, Z is phenyl. In some embodiments, Z is

monosubstituted phenyl (e.g., with 1 R⁵). In some embodiments, Z is monosubstituted phenyl, wherein the 1 R⁵ is a nitrogen-containing group. In some embodiments, Z is monosubstituted phenyl, wherein the 1 R⁵ is NH₂. In some embodiments, Z is monosubstituted phenyl, wherein the 1 R⁵ is an oxygen-containing group. In some embodiments, Z is monosubstituted phenyl, wherein the 1 R⁵ is an oxygen-containing heteroalkyl. In some embodiments, Z is

monosubstituted phenyl, wherein the 1 R⁵ is OCH₃. In some embodiments, Z is monosubstituted phenyl, wherein the 1 R⁵ is in the ortho position. In some embodiments, Z is monosubstituted phenyl, wherein the 1 R⁵ is in the meta position. In some embodiments, Z is monosubstituted phenyl, wherein the 1 R⁵ is in the para position.

In some embodiments, for Formulas (I) or (I-a), Z is alkyl. In some embodiments, Z is C₁-C₁₂ alkyl. In some embodiments, Z is C₁-C₁₀ alkyl. In some embodiments, Z is C₁-C₈ alkyl. In some embodiments, Z is C₁-C₈ alkyl substituted with 1-5 R⁵. In some embodiments, Z is C₁-C₈ alkyl substituted with 1 R⁵. In some embodiments, Z is C₁-C₈ alkyl substituted with 1 R⁵, wherein R⁵ is alkyl, heteroalkyl, halogen, oxo, -OR^{A1}, -C(O)OR^{A1}, -C(O)R^{B1}, -OC(O)R^{B1}, or -N(R^{C1})(R^{D1}). In some embodiments, Z is C₁-C₈ alkyl substituted with 1 R⁵, wherein R⁵ is -OR^{A1}

or $-C(O)OR^{A1}$. In some embodiments, Z is C_1-C_8 alkyl substituted with 1 R^5 , wherein R^5 is $-OR^{A1}$ or $-C(O)OH$. In some embodiments, Z is $-CH_3$.

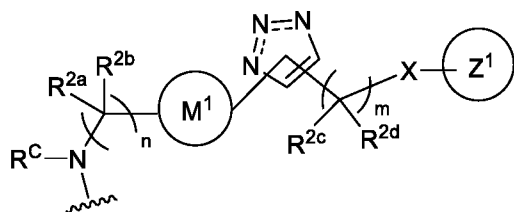
In some embodiments, for Formulas (I) or (I-a), Z is heteroalkyl. In some embodiments, Z is C_1-C_{12} heteroalkyl. In some embodiments, Z is C_1-C_{10} heteroalkyl. In some embodiments, Z is C_1-C_8 heteroalkyl. In some embodiments, Z is C_1-C_6 heteroalkyl. In some embodiments, Z is a nitrogen-containing heteroalkyl optionally substituted with one or more R^5 . In some embodiments, Z is a nitrogen and sulfur-containing heteroalkyl substituted with 1-5 R^5 . In some embodiments, Z is N-methyl-2-(methylsulfonyl)ethan-1-aminyl.

In some embodiments, Z is $-OR^A$ or $-C(O)OR^A$. In some embodiments, Z is $-OR^A$ (e.g., $-OH$ or $-OCH_3$). In some embodiments, Z is $-OCH_3$. In some embodiments, Z is $-C(O)OR^A$ (e.g., $-C(O)OH$).

In some embodiments, Z is hydrogen.

In some embodiments, L^2 is a bond and P and L^3 are independently absent. In some embodiments, L^2 is a bond, P is heteroaryl, L^3 is a bond, and Z is hydrogen. In some embodiments, P is heteroaryl, L^3 is heteroalkyl, and Z is alkyl.

In some embodiments, the compound of Formula (I) is a compound of Formula (I-b):

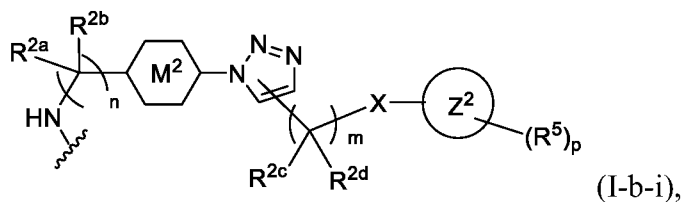


(I-b),

or a salt thereof, wherein Ring M^1 is cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with 1-5 R^3 ; Ring Z^1 is cycloalkyl, heterocyclyl, aryl or heteroaryl, optionally substituted with 1-5 R^5 ; each of R^{2a} , R^{2b} , R^{2c} , and R^{2d} is independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, halo, cyano, nitro, amino, cycloalkyl, heterocyclyl, aryl, or heteroaryl, or each of R^{2a} and R^{2b} or R^{2c} and R^{2d} is taken together to form an oxo group; X is absent, $N(R^{10})(R^{11})$, O, or S; R^C is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each of alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-6 R^6 ; each R^3 , R^5 , and R^6 is independently alkyl, alkenyl, alkynyl, heteroalkyl, halogen, cyano, azido, oxo, $-OR^{A1}$, $-C(O)OR^{A1}$, $-C(O)R^{B1}$, $-OC(O)R^{B1}$, $-N(R^{C1})(R^{D1})$, $-N(R^{C1})C(O)R^{B1}$, $-C(O)N(R^{C1})$, SR^{E1} , cycloalkyl, heterocyclyl, aryl, or heteroaryl; each of R^{10} and R^{11} is independently hydrogen,

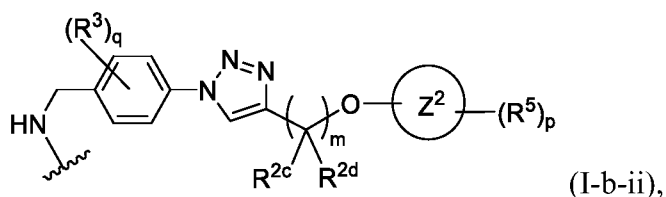
alkyl, alkenyl, alkynyl, heteroalkyl, $-\text{C}(\text{O})\text{OR}^{\text{A1}}$, $-\text{C}(\text{O})\text{R}^{\text{B1}}$, $-\text{OC}(\text{O})\text{R}^{\text{B1}}$, $-\text{C}(\text{O})\text{N}(\text{R}^{\text{C1}})$, cycloalkyl, heterocyclyl, aryl, or heteroaryl; each R^{A1} , R^{B1} , R^{C1} , R^{D1} , and R^{E1} is independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, wherein each of alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl is optionally substituted with 1-6 R^7 ; each R^7 is independently alkyl, alkenyl, alkynyl, heteroalkyl, halogen, cyano, oxo, hydroxyl, cycloalkyl, or heterocyclyl; each m and n is independently 1, 2, 3, 4, 5, or 6; and “ $\sim$ ” refers to a connection to an attachment group or a polymer described herein. In some embodiments, for each R^3 and R^5 , each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally and independently substituted with halogen, oxo, cyano, cycloalkyl, or heterocyclyl.

In some embodiments, the compound of Formula (I-b) is a compound of Formula (I-b-i):



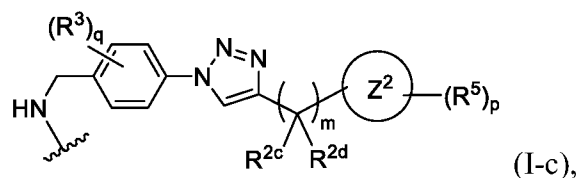
or a pharmaceutically acceptable salt thereof, wherein Ring M^2 is aryl or heteroaryl optionally substituted with one or more R^3 ; Ring Z^2 is cycloalkyl, heterocyclyl, aryl, or heteroaryl; each of R^{2a} , R^{2b} , R^{2c} , and R^{2d} is independently hydrogen, alkyl, or heteroalkyl, or each of R^{2a} and R^{2b} or R^{2c} and R^{2d} is taken together to form an oxo group; X is absent, O , or S ; each R^3 and R^5 is independently alkyl, heteroalkyl, halogen, oxo, $-\text{OR}^{\text{A1}}$, $-\text{C}(\text{O})\text{OR}^{\text{A1}}$, or $-\text{C}(\text{O})\text{R}^{\text{B1}}$, wherein each alkyl and heteroalkyl is optionally substituted with halogen; or two R^5 are taken together to form a 5-6 membered ring fused to Ring Z^2 ; each R^{A1} and R^{B1} is independently hydrogen, alkyl, or heteroalkyl; m and n are each independently 1, 2, 3, 4, 5, or 6; p is 0, 1, 2, 3, 4, 5, or 6; and “ $\sim$ ” refers to a connection to an attachment group or a polymer described herein.

In some embodiments, the compound of Formula (I-b) is a compound of Formula (I-b-ii):



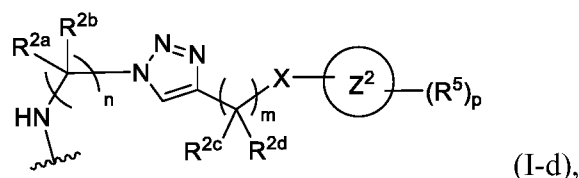
or a pharmaceutically acceptable salt thereof, wherein Ring Z^2 is cycloalkyl, heterocyclyl, aryl or heteroaryl; each of R^{2c} and R^{2d} is independently hydrogen, alkyl, or heteroalkyl, or R^{2c} and R^{2d} and taken together to form an oxo group; each R^3 and R^5 is independently alkyl, heteroalkyl, halogen, oxo, $-OR^{A1}$, $-C(O)OR^{A1}$, or $-C(O)R^{B1}$, wherein each alkyl and heteroalkyl is optionally substituted with halogen; each R^{A1} and R^{B1} is independently hydrogen, alkyl, or heteroalkyl; each of p and q is independently 0, 1, 2, 3, 4, 5, or 6; and “ $\sim$ ” refers to a connection to an attachment group or a polymer described herein.

In some embodiments, the compound of Formula (I) is a compound of Formula (I-c):



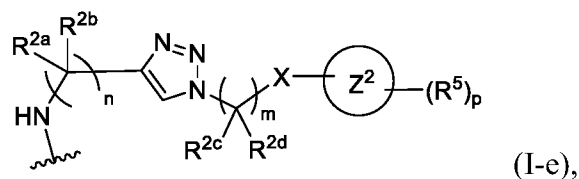
or a pharmaceutically acceptable salt thereof, wherein Ring Z^2 is cycloalkyl, heterocyclyl, aryl or heteroaryl; each of R^{2c} and R^{2d} is independently hydrogen, alkyl, or heteroalkyl, or R^{2c} and R^{2d} is taken together to form an oxo group; each R^3 and R^5 is independently alkyl, heteroalkyl, halogen, oxo, $-OR^{A1}$, $-C(O)OR^{A1}$, or $-C(O)R^{B1}$, wherein each alkyl and heteroalkyl is optionally substituted with halogen; each R^{A1} and R^{B1} is independently hydrogen, alkyl, or heteroalkyl; m is 1, 2, 3, 4, 5, or 6; each of p and q is independently 0, 1, 2, 3, 4, 5, or 6; and “ $\sim$ ” refers to a connection to an attachment group or a polymer described herein.

In some embodiments, the compound of Formula (I) is a compound of Formula (I-d):



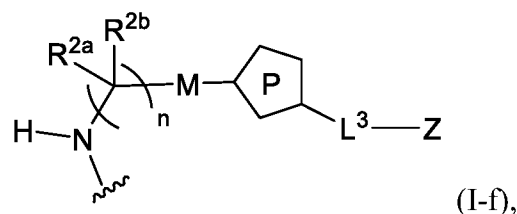
or a pharmaceutically acceptable salt thereof, wherein Ring Z^2 is cycloalkyl, heterocyclyl, aryl or heteroaryl; X is absent, O, or S; each of R^{2a} , R^{2b} , R^{2c} , and R^{2d} is independently hydrogen, alkyl, or heteroalkyl, or each of R^{2a} and R^{2b} or R^{2c} and R^{2d} is taken together to form an oxo group; each R^5 is independently alkyl, heteroalkyl, halogen, oxo, $-OR^{A1}$, $-C(O)OR^{A1}$, or $-C(O)R^{B1}$, wherein each alkyl and heteroalkyl is optionally substituted with halogen; each R^{A1} and R^{B1} is independently hydrogen, alkyl, or heteroalkyl; each of m and n is independently 1, 2, 3, 4, 5, or 6; p is 0, 1, 2, 3, 4, 5, or 6; and “ $\sim$ ” refers to a connection to an attachment group or a polymer described herein.

In some embodiments, the compound of Formula (I) is a compound of Formula (I-e):



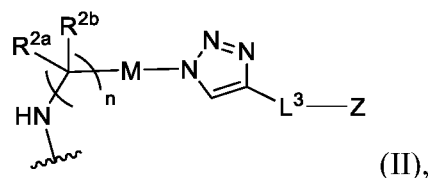
or a pharmaceutically acceptable salt thereof, wherein Ring Z^2 is cycloalkyl, heterocyclyl, aryl or heteroaryl; X is absent, O, or S; each of R^{2a} , R^{2b} , R^{2c} , and R^{2d} is independently hydrogen, alkyl, or heteroalkyl, or each of R^{2a} and R^{2b} or R^{2c} and R^{2d} is taken together to form an oxo group; each R^5 is independently alkyl, heteroalkyl, halogen, oxo, $-OR^{A1}$, $-C(O)OR^{A1}$, or $-C(O)R^{B1}$; each R^{A1} and R^{B1} is independently hydrogen, alkyl, or heteroalkyl; each of m and n is independently 1, 2, 3, 4, 5, or 6; p is 0, 1, 2, 3, 4, 5, or 6; and “ $\sim$ ” refers to a connection to an attachment group or a polymer described herein.

In some embodiments, the compound of Formula (I) is a compound of Formula (I-f):



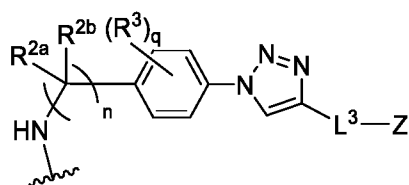
or a pharmaceutically acceptable salt thereof, wherein M is alkyl optionally substituted with one or more R^3 ; Ring P is heteroaryl optionally substituted with one or more R^4 ; L^3 is alkyl or heteroalkyl optionally substituted with one or more R^2 ; Z is alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R^5 ; each of R^{2a} and R^{2b} is independently hydrogen, alkyl, or heteroalkyl, or R^{2a} and R^{2b} is taken together to form an oxo group; each R^2 , R^3 , R^4 , and R^5 is independently alkyl, heteroalkyl, halogen, oxo, $-OR^{A1}$, $-C(O)OR^{A1}$, or $-C(O)R^{B1}$; each R^{A1} and R^{B1} is independently hydrogen, alkyl, or heteroalkyl; n is independently 1, 2, 3, 4, 5, or 6; and “ $\sim$ ” refers to a connection to an attachment group or a polymer described herein.

In some embodiments, the compound of Formula (I) is a compound of Formula (II):



or a pharmaceutically acceptable salt thereof, wherein M is a bond, alkyl or aryl, wherein alkyl and aryl is optionally substituted with one or more R^3 ; L^3 is alkyl or heteroalkyl optionally substituted with one or more R^2 ; Z is hydrogen, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl or $-OR^A$, wherein alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^5 ; R^A is hydrogen; each of R^{2a} and R^{2b} is independently hydrogen, alkyl, or heteroalkyl, or R^{2a} and R^{2b} is taken together to form an oxo group; each R^2 , R^3 , and R^5 is independently alkyl, heteroalkyl, halogen, oxo, $-OR^{A1}$, $-C(O)OR^{A1}$, or $-C(O)R^{B1}$; each R^{A1} and R^{B1} is independently hydrogen, alkyl, or heteroalkyl; n is independently 1, 2, 3, 4, 5, or 6; and “ $\sim$ ” refers to a connection to an attachment group or a polymer described herein.

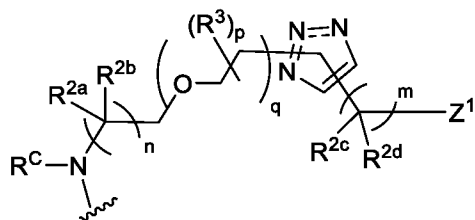
In some embodiments, the compound of Formula (II) is a compound of Formula (II-a):



(II-a),

or a pharmaceutically acceptable salt thereof, wherein L^3 is alkyl or heteroalkyl, each of which is optionally substituted with one or more R^2 ; Z is hydrogen, alkyl, heteroalkyl, or $-OR^A$, wherein alkyl and heteroalkyl are optionally substituted with one or more R^5 ; each of R^{2a} and R^{2b} is independently hydrogen, alkyl, or heteroalkyl, or R^{2a} and R^{2b} is taken together to form an oxo group; each R^2 , R^3 , and R^5 is independently alkyl, heteroalkyl, halogen, oxo, $-OR^{A1}$, $-C(O)OR^{A1}$, or $-C(O)R^{B1}$; R^A is hydrogen; each R^{A1} and R^{B1} is independently hydrogen, alkyl, or heteroalkyl; n is independently 1, 2, 3, 4, 5, or 6; and “ $\sim$ ” refers to a connection to an attachment group or a polymer described herein.

In some embodiments, the compound of Formula (I) is a compound of Formula (III):

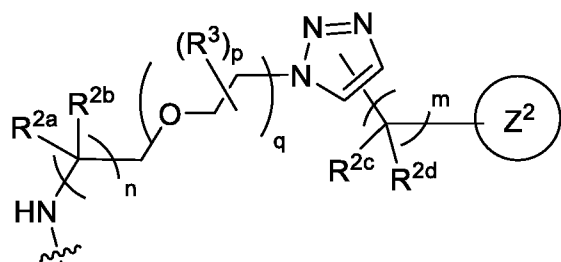


(III),

or a pharmaceutically acceptable salt thereof, wherein Z^1 is alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with 1-5 R^5 ; each of R^{2a} , R^{2b} , R^{2c} , and R^{2d} is independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, halo, cyano, nitro, amino, cycloalkyl, heterocyclyl, aryl, or heteroaryl; or R^{2a} and R^{2b} or R^{2c} and

R^{2d} are taken together to form an oxo group; R^C is hydrogen, alkyl, alkenyl, alkynyl, or heteroalkyl, wherein each of alkyl, alkenyl, alkynyl, or heteroalkyl is optionally substituted with 1-6 R^6 ; each of R^3 , R^5 , and R^6 is independently alkyl, heteroalkyl, halogen, oxo, $-OR^{A1}$, $-C(O)OR^{A1}$, or $-C(O)R^{B1}$; each R^{A1} and R^{B1} is independently hydrogen, alkyl, or heteroalkyl; m and n are each independently 1, 2, 3, 4, 5, or 6; q is an integer from 0 to 25; and “ $\sim$ ” refers to a connection to an attachment group or a polymer described herein.

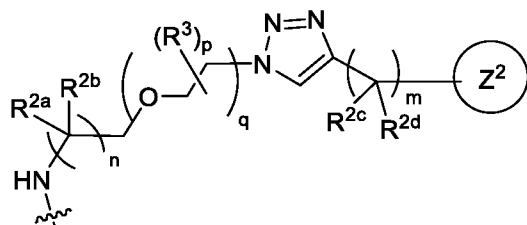
In some embodiments, the compound of Formula (III) is a compound of Formula (III-a):



(III-a),

or a pharmaceutically acceptable salt thereof, wherein Ring Z^2 is cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with 1-5 R^5 ; each of R^{2a} , R^{2b} , R^{2c} , and R^{2d} is independently hydrogen, alkyl, heteroalkyl, halo; or R^{2a} and R^{2b} or R^{2c} and R^{2d} are taken together to form an oxo group; each of R^3 and R^5 is independently alkyl, heteroalkyl, halogen, oxo, $-OR^{A1}$, $-C(O)OR^{A1}$, or $-C(O)R^{B1}$; each R^{A1} and R^{B1} is independently hydrogen, alkyl, or heteroalkyl; m and n are each independently 1, 2, 3, 4, 5, or 6; o and p are each independently 0, 1, 2, 3, 4, or 5; q is an integer from 0 to 25; and “ $\sim$ ” refers to a connection to an attachment group or a polymer described herein.

In some embodiments, the compound of Formula (III-a) is a compound of Formula (III-b):

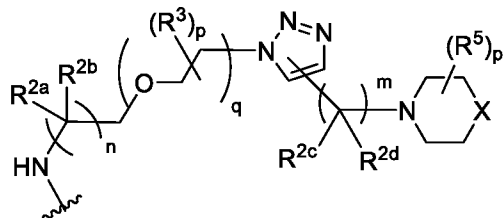


(III-b),

or a pharmaceutically acceptable salt thereof, wherein Ring Z^2 is cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with 1-5 R^5 ; each of R^{2a} , R^{2b} , R^{2c} , and R^{2d} is independently hydrogen, alkyl, heteroalkyl, halo; or R^{2a} and R^{2b} or R^{2c} and R^{2d} are taken together to form an oxo group; each of R^3 and R^5 is independently alkyl, heteroalkyl, halogen,

oxo, $-OR^{A1}$, $-C(O)OR^{A1}$, or $-C(O)R^{B1}$; each R^{A1} and R^{B1} is independently hydrogen, alkyl, or heteroalkyl; m and n are each independently 1, 2, 3, 4, 5, or 6; o and p are each independently 0, 1, 2, 3, 4, or 5; q is an integer from 0 to 25; and “ $\sim$ ” refers to a connection to an attachment group or a polymer described herein.

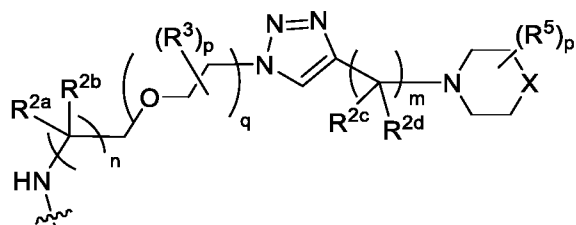
In some embodiments, the compound of Formula (III-a) is a compound of Formula (III-c):



(III-c),

or a pharmaceutically acceptable salt thereof, wherein X is $C(R')(R'')$, $N(R')$, or $S(O)_x$; each of R' and R'' is independently hydrogen, alkyl, halogen, or cycloalkyl; each of R^{2a} , R^{2b} , R^{2c} , and R^{2d} is independently hydrogen, alkyl, heteroalkyl, or halo; or R^{2a} and R^{2b} or R^{2c} and R^{2d} are taken together to form an oxo group; each of R^3 and R^5 is independently alkyl, heteroalkyl, halogen, oxo, $-OR^{A1}$, $-C(O)OR^{A1}$, or $-C(O)R^{B1}$; each R^{A1} and R^{B1} is independently hydrogen, alkyl, or heteroalkyl; m and n are each independently 1, 2, 3, 4, 5, or 6; p is 0, 1, 2, 3, 4, or 5; q is an integer from 0 to 25; x is 0, 1, or 2; and “ $\sim$ ” refers to a connection to an attachment group or a polymer described herein.

In some embodiments, the compound of Formula (III-c) is a compound of Formula (III-d):



(III-d),

or a pharmaceutically acceptable salt thereof, wherein X is $C(R')(R'')$, $N(R')$, or $S(O)_x$; each of R' and R'' is independently hydrogen, alkyl, halogen, or cycloalkyl; each of R^{2a} , R^{2b} , R^{2c} , and R^{2d} is independently hydrogen, alkyl, heteroalkyl, or halo; or R^{2a} and R^{2b} or R^{2c} and R^{2d} are taken together to form an oxo group; each of R^3 and R^5 is independently alkyl, heteroalkyl, halogen, oxo, $-OR^{A1}$, $-C(O)OR^{A1}$, or $-C(O)R^{B1}$; each R^{A1} and R^{B1} is independently hydrogen, alkyl, or heteroalkyl; m and n are each independently 1, 2, 3, 4, 5, or 6; p is 0, 1, 2, 3, 4, or 5; q is an

integer from 0 to 25; x is 0, 1, or 2; and “” refers to a connection to an attachment group or a polymer described herein.

In some embodiments, the compound is a compound of Formula (I). In some embodiments, L^2 is a bond and P and L^3 are independently absent.

In some embodiments, the compound is a compound of Formula (I-a). In some embodiments of Formula (II-a), L^2 is a bond, P is heteroaryl, L^3 is a bond, and Z is hydrogen. In some embodiments, P is heteroaryl, L^3 is heteroalkyl, and Z is alkyl. In some embodiments, L^2 is a bond and P and L^3 are independently absent. In some embodiments, L^2 is a bond, P is heteroaryl, L^3 is a bond, and Z is hydrogen. In some embodiments, P is heteroaryl, L^3 is heteroalkyl, and Z is alkyl.

In some embodiments, the compound is a compound of Formula (I-b). In some embodiments, P is absent, L^1 is $-NHCH_2$, L^2 is a bond, M is aryl (e.g., phenyl), L^3 is $-CH_2O$, and Z is heterocyclyl (e.g., a nitrogen-containing heterocyclyl, e.g., thiomorpholinyl-1,1-dioxide). In some embodiments, the compound of Formula (I-b) is Compound 116.

In some embodiments of Formula (I-b), P is absent, L^1 is $-NHCH_2$, L^2 is a bond, M is absent, L^3 is a bond, and Z is heterocyclyl (e.g., an oxygen-containing heterocyclyl, e.g., tetrahydropyranyl, tetrahydrofuranyl, oxetanyl, or oxiranyl). In some embodiments, the compound of Formula (I-b) is Compound 105.

In some embodiments, the compound is a compound of Formula (I-b-i). In some embodiments of Formula (I-b-i), each of R^{2a} and R^{2b} is independently hydrogen or CH_3 , each of R^{2c} and R^{2d} is independently hydrogen, m is 1 or 2, n is 1, X is O, p is 0, M^2 is phenyl optionally substituted with one or more R^3 , R^3 is $-CF_3$, and Z^2 is heterocyclyl (e.g., an oxygen-containing heterocyclyl, e.g., tetrahydropyranyl, tetrahydrofuranyl, oxetanyl, or oxiranyl). In some embodiments, the compound of Formula (I-b-i) is Compound 100, Compound 106, Compound 107, Compound 108, Compound 109, or Compound 111.

In some embodiments, the compound is a compound of Formula (I-b-ii). In some embodiments of Formula (I-b-ii), each of R^{2a} , R^{2b} , R^{2c} , and R^{2d} is independently hydrogen, q is 0, p is 0, m is 1, and Z^2 is heterocyclyl (e.g., an oxygen-containing heterocyclyl, e.g., tetrahydropyranyl). In some embodiments, the compound of Formula (I-b-ii) is Compound 100.

In some embodiments, the compound is a compound of Formula (I-c). In some embodiments of Formula (I-c), each of R^{2c} and R^{2d} is independently hydrogen, m is 1, p is 1, q is

0, R^5 is $-\text{CH}_3$, and Z is heterocyclyl (e.g., a nitrogen-containing heterocyclyl, e.g., piperazinyl). In some embodiments, the compound of Formula (I-c) is Compound 113.

In some embodiments, the compound is a compound of Formula (I-d). In some embodiments of Formula (I-d), each of R^{2a} , R^{2b} , R^{2c} , and R^{2d} is independently hydrogen, m is 1, n is 3, X is O, p is 0, and Z is heterocyclyl (e.g., an oxygen-containing heterocyclyl, e.g., tetrahydropyranyl, tetrahydrofuranyl, oxetanyl, or oxiranyl). In some embodiments, the compound of Formula (I-d) is Compound 110 or Compound 114.

In some embodiments, the compound is a compound of Formula (I-f). In some embodiments of Formula (I-f), each of R^{2a} and R^{2b} is independently hydrogen, n is 1, M is $-\text{CH}_2-$, P is a nitrogen-containing heteroaryl (e.g., imidazolyl), L^3 is $-\text{C}(\text{O})\text{OCH}_2-$, and Z is CH_3 . In some embodiments, the compound of Formula (I-f) is Compound 115.

In some embodiments, the compound is a compound of Formula (II-a). In some embodiments of Formula (II-a), each of R^{2a} and R^{2b} is independently hydrogen, n is 1, q is 0, L^3 is $-\text{CH}_2(\text{OCH}_2\text{CH}_2)_2$, and Z is $-\text{OCH}_3$. In some embodiments, the compound of Formula (II-a) is Compound 112.

In some embodiments of Formula (II-a), each of R^{2a} and R^{2b} is independently hydrogen, n is 1, L^3 is a bond or $-\text{CH}_2$, and Z is hydrogen or $-\text{OH}$. In some embodiments, the compound of Formula (II-a) is Compound 103 or Compound 104.

In some embodiments, the compound is a compound of Formula (III). In some embodiments of Formula (III), each of R^{2a} , R^{2b} , R^{2c} , and R^{2d} is independently hydrogen, m is 1, n is 2, q is 3, p is 0, R^C is hydrogen, and Z^1 is heteroalkyl optionally substituted with R^5 (e.g., $-\text{N}(\text{CH}_3)(\text{CH}_2\text{CH}_2)\text{S}(\text{O})_2\text{CH}_3$). In some embodiments, the compound of Formula (III) is Compound 120.

In some embodiments, the compound is a compound of Formula (III-b). In some embodiments of Formula (III-b), each of R^{2a} , R^{2b} , R^{2c} , and R^{2d} is independently hydrogen, m is 0, n is 2, q is 3, p is 0, and Z^2 is aryl (e.g., phenyl) substituted with 1 R^5 (e.g., $-\text{NH}_2$). In some embodiments, the compound of Formula (III-b) is Compound 102.

In some embodiments, the compound is a compound of Formula (III-b). In some embodiments of Formula (III-b), each of R^{2a} , R^{2b} , R^{2c} , and R^{2d} is independently hydrogen, m is 1, n is 2, q is 3, p is 0, R^C is hydrogen, and Z^2 is heterocyclyl (e.g., an nitrogen-containing heterocyclyl, e.g., a nitrogen-containing spiro heterocyclyl, e.t., 2-oxa-7-azaspiro[3.5]nonanyl).

In some embodiments, the compound of Formula (III-b) is Compound 121.

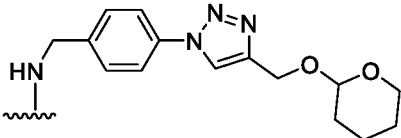
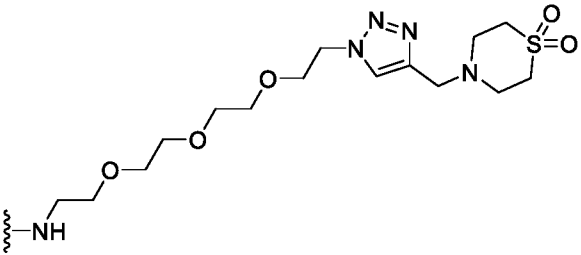
In some embodiments, the compound is a compound of Formula (III-d). In some embodiments of Formula (III-d), each of R^{2a} , R^{2b} , R^{2c} , and R^{2d} is independently hydrogen, m is 1, n is 2, q is 1, 2, 3, or 4, p is 0, and X is $S(O)_2$. In some embodiments of Formula (III-d), each of R^{2a} and R^{2b} is independently hydrogen, m is 1, n is 2, q is 1, 2, 3, or 4, p is 0, and X is $S(O)_2$. In some embodiments, the compound of Formula (III-d) is Compound 101, Compound 117, Compound 118, or Compound 119.

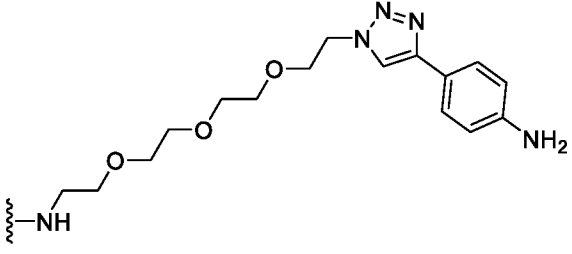
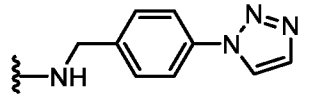
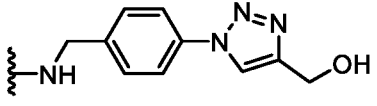
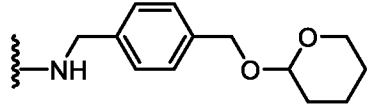
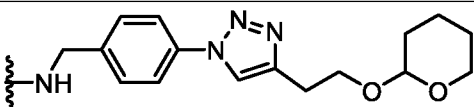
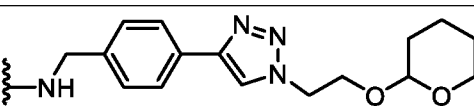
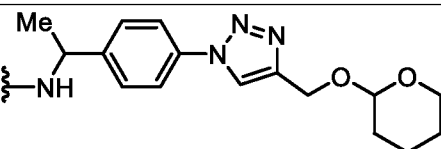
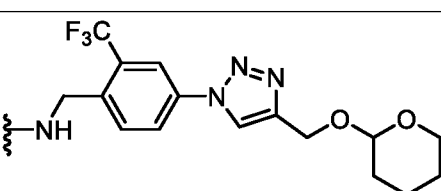
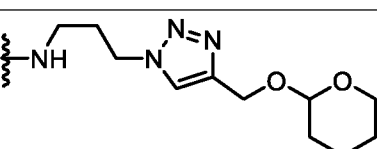
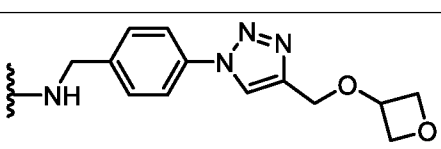
In some embodiments, the compound is a compound of Formula (I-b), (I-d), or (I-e). In some embodiments, the compound is a compound of Formula (I-b), (I-d), or (II). In some embodiments, the compound is a compound of Formula (I-b), (I-d), or (I-f). In some embodiments, the compound is a compound of Formula (I-b), (I-d), or (III).

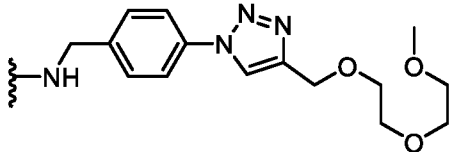
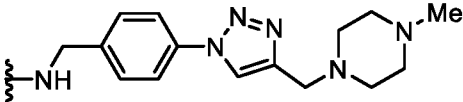
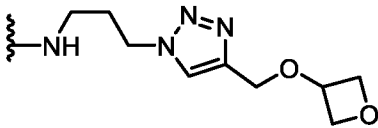
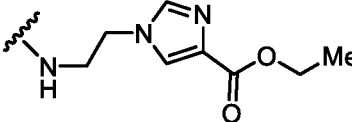
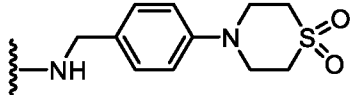
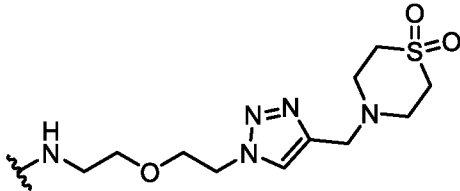
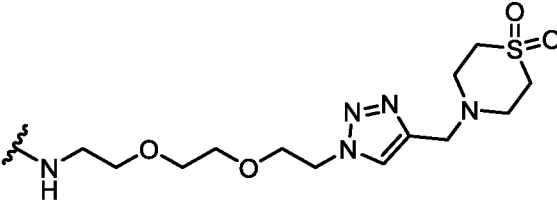
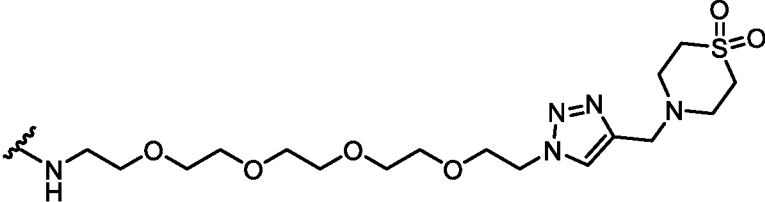
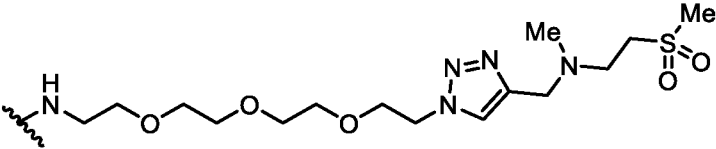
In some embodiments, the compound of Formula (I) is not a compound disclosed in WO2012/112982, WO2012/167223, WO2014/153126, WO2016/019391, WO 2017/075630, US2012-0213708, US 2016-0030359 or US 2016-0030360.

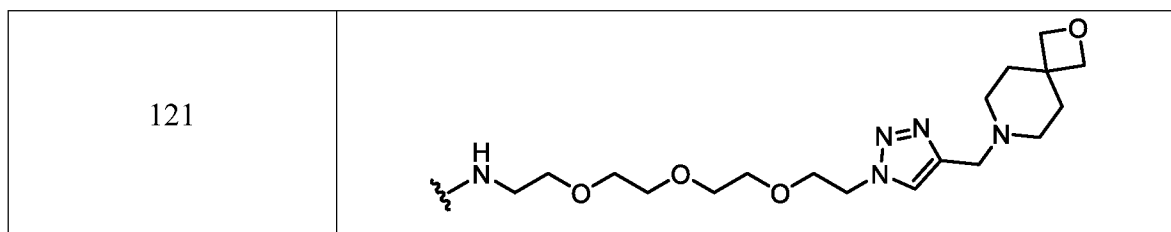
In some embodiments, the compound of Formula (I) comprises a compound shown in Table 2, or a pharmaceutically acceptable salt thereof. In some embodiments, a particle described herein comprises a compound shown in Table 2, or a pharmaceutically acceptable salt thereof.

Table 2: Exemplary compounds

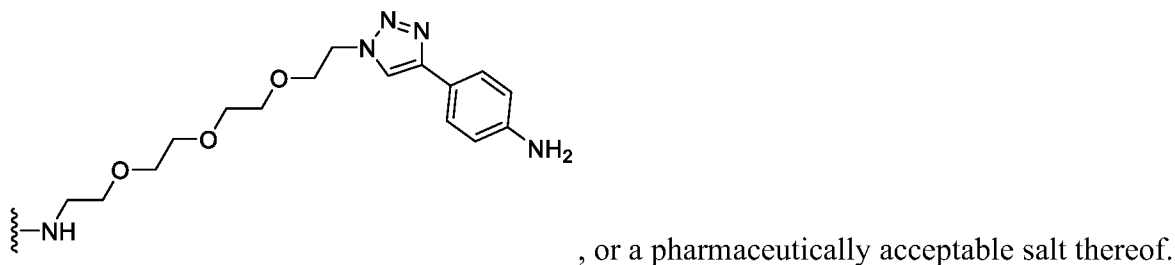
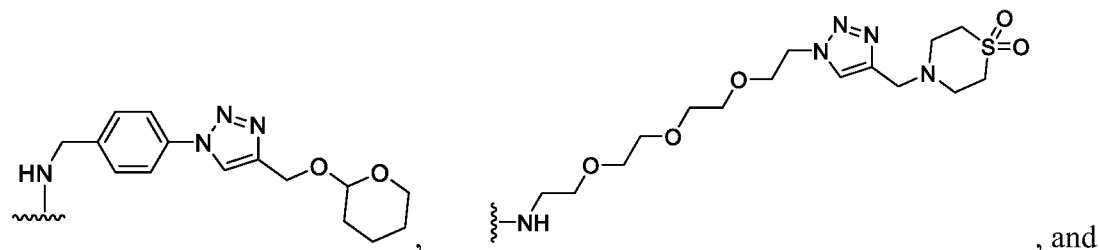
Compound No.	Structure
100	
101	

102	
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104	
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106	
107	
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109	
110	
111	

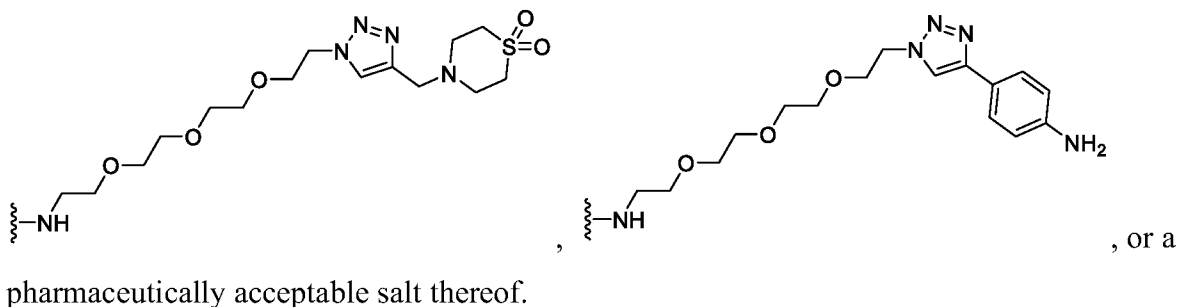
112	
113	
114	
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118	
119	
120	



In some embodiments, the compound is a compound of Formula (I) (e.g., Formulas (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (II), (II-a), (III), (III-a), (III-b), (III-c), or (III-d)), or a pharmaceutically acceptable salt thereof, and is selected from:



In some embodiments, the particle described herein comprises the compound of



10 In an embodiment, a particle described herein comprises a compound of Formula (I) (e.g., a compound shown in Table 2) covalently bound to an alginate polymer. In an embodiment, a particle described herein comprises a compound of Formula (I) (e.g., a compound shown in Table 2, e.g., Compound 101) covalently bound to one or more guluronic acid and/or mannuronic acid monomers in an alginate polymer, e.g., by an amide bond.

15 In some embodiments, a compound of Formula (I) (e.g., Compound 101 in Table 2) is

covalently attached to an alginate (e.g., an alginate with approximate MW < 75 kDa, G:M ratio $\geq$ 1.5) at a conjugation density of at least 2.0 % and less than 9.0 % nitrogen, or 2.0% to 5% nitrogen, 3.0% to 8.0% nitrogen, 5% to 8.0% nitrogen, 4.0% to 7.0% nitrogen, 5.0% to 7.0% nitrogen, or 6.0% to 7.0% nitrogen or about 6.8% nitrogen as determined by combustion analysis for percent nitrogen as described in the Examples below.

Cells

The particles of the present disclosure may comprise a wide variety of different cell types (e.g., human cells), including epithelial cells, endothelial cells, fibroblast cells, mesenchymal stem cells, keratinocyte cells, islet cells, and cells derived from any of the foregoing cell types. The cells may be derived from stem cells or induced pluripotent stem cells. Exemplary cell types include the cell types recited in WO 2017/075631. In some embodiments, the cells are derived from a cell-line shown in Table 3 below.

Table 3: Exemplary cell lines

Cell Line	Cell Type	Germ Layer	Commercial Source
ARPE-19	Epithelial (Retinal)	Ectoderm	ATCC (CRL-2302)
BJ	Fibroblast (Foreskin)	Ectoderm	ATCC (CRL-2522)
CCD-841-CoN	Epithelial (Colon)	Endoderm	ATCC (CRL-1790)
HaCat	Keratinocyte	Ectoderm	Addexbio (T0020001)
HHSEC	Endothelial (Hepatic Sinusoidal)	Endoderm	Sciencellonline.com (#5000)
Huv-EC-C	Endothelial (Embryonic umbilical)	Mesoderm	ATCC (CRL-1730)
MCF-10A	Epithelial (Mammary Gland)	Ectoderm	ATCC (CRL-10317)
MRC-5	Fibroblast (Lung)	Mesoderm	ATCC (CCL-171)
MSC, human	Mesenchyme (Bone Marrow)	Mesoderm	ATCC (PCS-500-012)
MSC, mouse	Mesenchyme (Bone Marrow)	Mesoderm	Cyagen (MU BMX-01001)

WS-1	Fibroblast (Skin)	Ectoderm	ATCC (CRL-1502)
293F	Epithelial (Embryonic Kidney)	Mesoderm	Thermo Fisher (R790007)

In some embodiments, the particle does not comprise any islet cells, as defined herein. In an embodiment, cells contained in a particle of the disclosure, e.g., RPE cells, MSFCs, including engineered RPE cells and MSFCs, have one or more of the following characteristics: (i) are not capable of producing insulin (e.g., insulin A-chain, insulin B-chain, or proinsulin) in an amount effective to treat diabetes or another disease or condition that may be treated with insulin; (ii) not capable of producing insulin in a glucose-responsive manner; or (iii) not an induced pluripotent cell that is engineered into a differentiated insulin-producing pancreatic beta cell.

In an embodiment, the particles described herein comprise a plurality of cells. In an embodiment, the plurality of cells is in the form of a cell suspension prior to being encapsulated within a particle described herein. The cells in the suspension may take the form of single cells (e.g., from a monolayer cell culture), or provided in another form, e.g., disposed on a microcarrier (e.g., a bead or matrix) or as a three-dimensional aggregate of cells (e.g., a cell cluster or spheroid). The cell suspension can comprise multiple cell clusters (e.g., as spheroids) or microcarriers.

In some embodiments, the cells have been engineered to produce a therapeutic agent for the prevention or treatment of a disease, disorder, or condition described, e.g., in WO 2017/075631. The therapeutic agent may be any biological substance, such as a nucleic acid (e.g., a nucleotide, DNA, or RNA), a polypeptide, a lipid, a sugar (e.g., a monosaccharide, disaccharide, oligosaccharide, or polysaccharide), or a small molecule. Exemplary therapeutic agents include the agents listed in WO 2017/075631.

In some embodiments, the therapeutic agent is a peptide or polypeptide (e.g., a protein), such as a hormone, enzyme, cytokine (e.g., a pro-inflammatory cytokine or an anti-inflammatory cytokine), growth factor, clotting factor, or lipoprotein. A peptide or polypeptide (e.g., a protein, e.g., a hormone, growth factor, clotting factor or coagulation factor, antibody molecule, enzyme, cytokine, cytokine receptor, or a chimeric protein including cytokines or a cytokine receptor) produced by an engineered cell can have a naturally occurring amino acid sequence, or may contain a variant of the naturally occurring sequence. The variant can be a naturally occurring or non-naturally occurring amino acid substitution, mutation, deletion or addition relative to the

reference naturally occurring sequence. The naturally occurring amino acid sequence may be a polymorphic variant. The naturally occurring amino acid sequence can be a human or a non-human amino acid sequence. In some embodiments, the naturally occurring amino acid sequence or naturally occurring variant thereof is a human sequence. In addition, a peptide or polypeptide (e.g., a protein) for use with the present disclosure may be modified in some way, e.g., via chemical or enzymatic modification (e.g., glycosylation, phosphorylation). In some embodiments, the peptide has about 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 45, or 50 amino acids. In some embodiments, the protein has an average molecular weight of 5 kD, 10 kD, 25 kD, 50 kD, 100 kD, 150 kD, 200 kD, 250 kD, 500 kD, or more.

In some embodiments, the protein is a hormone. Exemplary hormones include anti-diuretic hormone (ADH), oxytocin, growth hormone (GH), prolactin, growth hormone-releasing hormone (GHRH), thyroid stimulating hormone (TSH), thyrotropin-release hormone (TRH), adrenocorticotrophic hormone (ACTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), luteinizing hormone-releasing hormone (LHRH), thyroxine, calcitonin, parathyroid hormone, aldosterone, cortisol, epinephrine, glucagon, insulin, estrogen, progesterone, and testosterone. In some embodiments, the protein is insulin (e.g., insulin A-chain, insulin B-chain, or proinsulin). In some embodiments, the protein is a growth hormone, such as human growth hormone (hGH), recombinant human growth hormone (rhGH), bovine growth hormone, methionine-human growth hormone, des-phenylalanine human growth hormone, and porcine growth hormone.

In some embodiments, the protein is a growth factor, e.g., vascular endothelial growth factor (VEGF), nerve growth factor (NGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), epidermal growth factor (EGF), transforming growth factor (TGF), and insulin-like growth factor-I and -II (IGF-I and IGF-II).

In some embodiments, the protein is a clotting factor or a coagulation factor, e.g., a blood clotting factor or a blood coagulation factor. In some embodiments, the protein is a protein involved in coagulation, i.e., the process by which blood is converted from a liquid to solid or gel. Exemplary clotting factors and coagulation factors include Factor I (e.g., fibrinogen), Factor II (e.g., prothrombin), Factor III (e.g., tissue factor), Factor V (e.g., proaccelerin, labile factor), Factor VI, Factor VII (e.g., stable factor, proconvertin), Factor VIII (e.g., antihemophilic factor A), Factor VIIC, Factor IX (e.g., antihemophilic factor B), Factor X (e.g., Stuart-Prower factor),

Factor XI (e.g., plasma thromboplastin antecedent), Factor XII (e.g., Hagerman factor), Factor XIII (e.g., fibrin-stabilizing factor), von Willebrand factor, prekallikrein, heparin cofactor II, high molecular weight kininogen (e.g., Fitzgerald factor), antithrombin III, and fibronectin. In some embodiments, the protein is an anti-clotting factor, such as Protein C.

In some embodiments, the protein is an antibody molecule. As used herein, the term "antibody molecule" refers to a protein, e.g., an immunoglobulin chain or fragment thereof, comprising at least one immunoglobulin variable domain sequence. The term "antibody molecule" includes, for example, a monoclonal antibody (including a full-length antibody which has an immunoglobulin Fc region). In an embodiment, an antibody molecule comprises a full-length antibody, or a full-length immunoglobulin chain. In an embodiment, an antibody molecule comprises an antigen binding or functional fragment of a full-length antibody, or a full-length immunoglobulin chain. In an embodiment, an antibody molecule is a monospecific antibody molecule and binds a single epitope, e.g., a monospecific antibody molecule having a plurality of immunoglobulin variable domain sequences, each of which binds the same epitope. In an embodiment, an antibody molecule is a multispecific antibody molecule, e.g., it comprises a plurality of immunoglobulin variable domains sequences, wherein a first immunoglobulin variable domain sequence of the plurality has binding specificity for a first epitope and a second immunoglobulin variable domain sequence of the plurality has binding specificity for a second epitope. In an embodiment, the first and second epitopes are on the same antigen, e.g., the same protein (or subunit of a multimeric protein). In an embodiment, a multispecific antibody molecule comprises a third, fourth or fifth immunoglobulin variable domain. In an embodiment, a multispecific antibody molecule is a bispecific antibody molecule, a trispecific antibody molecule, or tetraspecific antibody molecule.

Various types of antibody molecules may be produced by the encapsulated engineered cells, including whole immunoglobulins of any class, fragments thereof, and synthetic proteins containing at least the antigen binding variable domain of an antibody. The antibody molecule can be an antibody, e.g., an IgG antibody, such as IgG₁, IgG₂, IgG₃, or IgG₄. An antibody molecule can be in the form of an antigen binding fragment including a Fab fragment, F(ab')₂ fragment, a single chain variable region, and the like. Antibodies can be polyclonal or monoclonal (mAb). Monoclonal antibodies may include "chimeric" antibodies in which a portion of the heavy and/or light chain is identical with or homologous to corresponding

sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they specifically bind the target antigen and/or exhibit the desired biological activity. In some embodiments, the antibody molecule is a single-domain antibody (e.g., a nanobody). The described antibodies can also be modified by recombinant means, for example by deletions, additions or substitutions of amino acids, to increase efficacy of the antibody in mediating the desired function. Exemplary antibodies include anti-beta-galactosidase, anti-collagen, anti-CD14, anti-CD20, anti-CD40, anti-HER2, anti-IL-1, anti-IL-4, anti-IL6, anti-IL-13, anti-IL17, anti-IL18, anti-IL-23, anti-IL-28, anti-IL-29, anti-IL-33, anti-EGFR, anti-VEGF, anti-CDF, anti-flagellin, anti-IFN- α , anti-IFN- β , anti-IFN- γ , anti-mannose receptor, anti-VEGF, anti-TLR1, anti-TLR2, anti-TLR3, anti-TLR4, anti-TLR5, anti-TLR6, anti-TLR9, anti-PDF, anti-PD1, anti-PDL-1, or anti-nerve growth factor antibody. In some embodiments, the antibody is an anti-nerve growth factor antibody (e.g., fulranumab, fasinumab, tanezumab).

In some embodiments, the protein is a cytokine or a cytokine receptor, or a chimeric protein including cytokines or their receptors, including, for example tumor necrosis factor alpha and beta, their receptors and their derivatives, renin; lipoproteins; colchicine; corticotrophin; vasopressin; somatostatin; lyppressin; pancreozymin; leuprolide; alpha-1-antitrypsin; atrial natriuretic factor; lung surfactant; a plasminogen activator other than a tissue-type plasminogen activator (t-PA), for example a urokinase; bombesin; thrombin; enkephalinase; RANTES (regulated on activation normally T-cell expressed and secreted); human macrophage inflammatory protein (MIP-1-alpha); a serum albumin such as human serum albumin; mullerian-inhibiting substance; relaxin A-chain; relaxin B-chain; prorelaxin; mouse gonadotropin-associated peptide; chorionic gonadotropin; a microbial protein, such as beta-lactamase; DNase; inhibin; activin; receptors for hormones or growth factors; integrin; protein A or D; rheumatoid factors; platelet-derived growth factor (PDGF); epidermal growth factor (EGF); transforming growth factor (TGF) such as TGF- α and TGF- β , including TGF- β 1, TGF- β 2, TGF- β 3, TGF- β 4, or TGF- β 5; insulin-like growth factor-I and -II (IGF-I and IGF-II); des(1-3)-IGF-I (brain IGF-I), insulin-like growth factor binding proteins; CD proteins such as CD-3, CD-4, CD-8, and CD-19; erythropoietin; osteoinductive factors; immunotoxins; an interferon such as interferon-alpha

(e.g., interferon.alpha.2A), -beta, -gamma, -lambda and consensus interferon; colony stimulating factors (CSFs), e.g., M-CSF, GM-CSF, and G-CSF; interleukins (ILs), e.g., IL-1 to IL-10; superoxide dismutase; T-cell receptors; surface membrane proteins; decay accelerating factor; transport proteins; homing receptors; addressins; fertility inhibitors such as the prostaglandins; fertility promoters; regulatory proteins; antibodies (including fragments thereof) and chimeric proteins, such as immunoadhesins; precursors, derivatives, prodrugs and analogues of these compounds, and pharmaceutically acceptable salts of these compounds, or their precursors, derivatives, prodrugs and analogues. Suitable proteins or peptides may be native or recombinant and include, e.g., fusion proteins.

Examples of a polypeptide (e.g., a protein) produced by particle described herein also include CCL1, CCL2 (MCP-1), CCL3 (MIP-1 α), CCL4 (MIP-1 β), CCL5 (RANTES), CCL6, CCL7, CCL8, CCL9 (CCL10), CCL11, CCL12, CCL13, CCL14, CCL15, CCL16, CCL17, CCL18, CCL19, CCL20, CCL21, CCL22, CCL23, CCL24, CCL25, CCL26, CCL27, CCL28, CXCL1 (KC), CXCL2 (SDF1a), CXCL3, CXCL4, CXCL5, CXCL6, CXCL7, CXCL8 (IL8), CXCL9, CXCL10, CXCL11, CXCL12, CXCL13, CXCL14, CXCL15, CXCL16, CXCL17, CX3CL1, XCL1, XCL2, TNFA, TNFB (LTA), TNFC (LTB), TNFSF4, TNFSF5 (CD40LG), TNFSF6, TNFSF7, TNFSF8, TNFSF9, TNFSF10, TNFSF11, TNFSF13B, EDA, IL2, IL15, IL4, IL13, IL7, IL9, IL21, IL3, IL5, IL6, IL11, IL27, IL30, IL31, OSM, LIF, CNTF, CTF1, IL12a, IL12b, IL23, IL27, IL35, IL14, IL16, IL32, IL34, IL10, IL22, IL19, IL20, IL24, IL26, IL29, IFNL1, IFNL2, IFNL3, IL28, IFNA1, IFNA2, IFNA4, IFNA5, IFNA6, IFNA7, IFNA8, IFNA10, IFNA13, IFNA14, IFNA16, IFNA17, IFNA21, IFNB1, IFNK, IFNW1, IFNG, IL1A (IL1F1), IL1B (IL1F2), IL1Ra (IL1F3), IL1F5 (IL36RN), IL1F6 (IL36A), IL1F7 (IL37), IL1F8 (IL36B), IL1F9 (IL36G), IL1F10 (IL38), IL33 (IL1F11), IL18 (IL1G), IL17, KITLG, IL25 (IL17E), CSF1 (M-CSF), CSF2 (GM-CSF), CSF3 (G-CSF), SPP1, TGFB1, TGFB2, TGFB3, CCL3L1, CCL3L2, CCL3L3, CCL4L1, CCL4L2, IL17B, IL17C, IL17D, IL17F, AIMP1 (SCYE1), MIF, Areg, BC096441, Bmp1, Bmp10, Bmp15, Bmp2, Bmp3, Bmp4, Bmp5, Bmp6, Bmp7, Bmp8a, Bmp8b, C1qtnf4, Ccl21a, Ccl27a, Cd70, Cer1, Cklf, Clcf1, Cmtm2a, Cmtm2b, Cmtm3, Cmtm4, Cmtm5, Cmtm6, Cmtm7, Cmtm8, Crlf1, Ctf2, Ebi3, Edn1, Fam3b, Fasl, Fgf2, Flt3l, Gdf10, Gdf11, Gdf15, Gdf2, Gdf3, Gdf5, Gdf6, Gdf7, Gdf9, Gm12597, Gm13271, Gm13275, Gm13276, Gm13280, Gm13283, Gm2564, Gpi1, Grem1, Grem2, Grn, Hmgb1, Ifna11, Ifna12, Ifna9, Ifnab, Ifne, Il17a, Il23a, Il25, Il31, Iltifb, Inhba, Lefty1, Lefty2,

Mstn, Nampt, Ndp, Nodal, Pf4, Pglyrp1, Prl7d1, Scg2, Scgb3a1, Slurp1, Spp1, Thpo, Tnfsf10, Tnfsf11, Tnfsf12, Tnfsf13, Tnfsf13b, Tnfsf14, Tnfsf15, Tnfsf18, Tnfsf4, Tnfsf8, Tnfsf9, Tslp, Vegfa, Wnt1, Wnt2, Wnt5a, Wnt7a, Xcl1, epinephrine, melatonin, triiodothyronine, a prostaglandin, a leukotriene, prostacyclin, thromboxane, islet amyloid polypeptide, müllerian inhibiting factor or hormone, adiponectin, corticotropin, angiotensin, vasopressin, arginine vasopressin, atriopeptin, brain natriuretic peptide, calcitonin, cholecystokinin, cortistatin, enkephalin, endothelin, erythropoietin, follicle-stimulating hormone, galanin, gastric inhibitory polypeptide, gastrin, ghrelin, glucagon, glucagon-like peptide-1, gonadotropin-releasing hormone, hepcidin, human chorionic gonadotropin, human placental lactogen, inhibin, somatomedin, leptin, lipotropin, melanocyte stimulating hormone, motilin, orexin, oxytocin, pancreatic polypeptide, pituitary adenylate cyclase-activating peptide, relaxin, renin, secretin, somatostatin, thrombopoietin, thyrotropin, thyrotropin-releasing hormone, vasoactive intestinal peptide, androgen, alpha-glucosidase (also known as acid maltase), glycogen phosphorylase, glycogen debrancher enzyme, phosphofructokinase, phosphoglycerate kinase, phosphoglycerate mutase, lactate dehydrogenase, carnitine palmytil transferase, carnitine, and myoadenylate deaminase.

In some embodiments, the protein is a replacement therapy or a replacement protein. In some embodiments, the replacement therapy or replacement protein is a clotting factor or a coagulation factor, e.g., Factor VIII (e.g., comprises a naturally occurring human Factor VIII amino acid sequence or a variant thereof) or Factor IX (e.g., comprises a naturally occurring human Factor IX amino acid sequence or a variant thereof).

In some embodiments, the cell is engineered to express a human Factor VIII protein, e.g., a recombinant Factor VIII. In some embodiments, the recombinant Factor VIII is a B-domain-deleted recombinant Factor VIII (FVIII-BDD). In some embodiments, the cell is derived from a human RPE cell line and comprises an exogenous nucleic acid sequence which encodes the FVIII-BDD amino acid sequence shown in FIG. 2A (SEQ ID NO: 1).

In some embodiments, the cell is engineered to express a FIX, e.g., a wild-type human F IX, such as that shown in FIG. 2B (SEQ ID NO: 2) or a polymorphic variant thereof (e.g., alanine substituted for threonine at amino acid position 148 of SEQ ID NO: 2). In some embodiments, the cell is engineered to express a gain-in-function (GIF) variant of a wild-type FIX protein (FIX-GIF), wherein the GIF variant has higher specific activity than the

corresponding wild-type FIX. In some embodiments, the cell is derived from a human RPE cell line and comprises an exogenous nucleic acid sequence which encodes SEQ ID NO: 2, except for having an amino acid substituted for arginine at a position corresponding to amino acid position 338 of SEQ ID NO: 2. In some embodiments, the substituting amino acid at a position corresponding to amino acid position 338 of SEQ ID NO: 2 is alanine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, histidine, leucine, lysine, or tyrosine. In some embodiments, the FIX protein encoded by cells contained in a particle described herein is a FIX-padua protein and comprises, consists essentially of, or consists of SEQ ID NO:36 (FIG.17) .

In some embodiments, the encapsulated cells are derived from a human RPE cell line and comprise an exogenous nucleic acid sequence which comprises a promoter sequence (e.g., nucleotides 337-2069 of SEQ ID NO:26) operably linked to a coding sequence for a polypeptide. In an embodiment, the coding sequence is a codon-optimized FVIII-BDD coding sequence shown in FIG. 17 (SEQ ID NO: 9, 10, 11, 12, 13, 14, 15, 16 or 17) or a codon-optimized FIX-padua coding sequence shown in FIG. 17 (SEQ ID NO:19, 20 or 21).

In some embodiments, the encapsulated cells are derived from a human RPE cell line and comprise a promoter sequence (e.g., SEQ ID NO:23 or a nucleotide sequence that is at least 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO:23) operably linked to a nucleotide sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:1, 2, 3, 4, 5,6, 7, 29, 30, 31, 32, 33, 34, 35 and 36.

In some embodiments, the particle is a two-compartment hydrogel capsule, in which the inner compartment was formed from a polymer solution comprising about 20 million cells/ml to about 40 million cells/ml, wherein the cells are derived from the ARPE-19 cell line and comprise nucleotides 337-2069 of SEQ ID NO:26 operably linked to a codon-optimized FVIII-BDD coding sequence shown in FIG. 17. In an embodiment, the FVIII-BDD coding sequence is SEQ ID NO:15.

In some embodiments, the replacement therapy or replacement protein is an enzyme, e.g., alpha-galactosidase, alpha-L-iduronidase (IDUA), or N-sulfoglucosamine sulfohydrolase (SGSH). In some embodiments, the replacement therapy or replacement protein is an enzyme, e.g., an alpha-galactosidase A (e.g., comprises a naturally occurring human alpha-galactosidase A amino acid sequence or a variant thereof). In some embodiments, the replacement therapy or replacement protein is a cytokine or an antibody.

In some embodiments, the therapeutic agent is a sugar, e.g., monosaccharide, disaccharide, oligosaccharide, or polysaccharide. In some embodiments, a sugar comprises a triose, tetrose, pentose, hexose, or heptose moiety. In some embodiments, the sugar comprises a linear monosaccharide or a cyclized monosaccharide. In some embodiments, the sugar comprises a glucose, galactose, fructose, rhamnose, mannose, arabinose, glucosamine, galactosamine, sialic acid, mannosamine, glucuronic acid, galactosuronic acid, mannuronic acid, or guluronic acid moiety. In some embodiments, the sugar is attached to a protein (e.g., an N-linked glycan or an O-linked glycan). Exemplary sugars include glucose, galactose, fructose, mannose, rhamnose, sucrose, ribose, xylose, sialic acid, maltose, amylose, inulin, a fructooligosaccharide, galactooligosaccharide, a mannan, a lectin, a pectin, a starch, cellulose, heparin, hyaluronic acid, chitin, amylopectin, or glycogen. In some embodiments, the therapeutic agent is a sugar alcohol.

In some embodiments, the therapeutic agent is a lipid. A lipid may be hydrophobic or amphiphilic, and may form a tertiary structure such as a liposome, vesicle, or membrane or insert into a liposome, vesicle, or membrane. A lipid may comprise a fatty acid, glycerolipid, glycerophospholipid, sterol lipid, prenol lipid, sphingolipid, saccharolipid, polyketide, or sphingolipid. Examples of lipids produced by the encapsulated cells include anandamide, docosahexaenoic acid, a prostaglandin, a leukotriene, a thromboxane, an eicosanoid, a triglyceride, a cannabinoid, phosphatidylcholine, phosphatidylethanolamine, a phosphatidylinositol, a phosphatidic acid, a ceramide, a sphingomyelin, a cerebroside, a ganglioside, estrogen, androsterone, testosterone, cholesterol, a carotenoid, a quinone, a hydroquinone, or a ubiquinone.

In some embodiments, the therapeutic agent is a small molecule. A small molecule may include a natural product produced by a cell. In some embodiments, the small molecule has poor availability or does not comply with the Lipinski rule of five (a set of guidelines used to estimate whether a small molecule will likely be an orally active drug in a human; see, e.g., Lipinski, C.A. et al (2001) *Adv Drug Deliv* 46:2-36). Exemplary small molecule natural products include an anti-bacterial drug (e.g., carumonam, daptomycin, fidaxomicin, fosfomicin, isipamicin, micronomicin sulfate, miocamycin, mupirocin, netilmicin sulfate, teicoplanin, thienamycin, rifamycin, erythromycin, vancomycin), an anti-parasitic drug (e.g., artemisinin, ivermectin), an anticancer drug (e.g., doxorubicin, aclarubicin, aminolaevulinic acid, arglabin, omacetaxine

mepesuccinate, paclitaxel, pentostatin, peplomycin, romidepsin, trabectedin, actinomycin D, bleomycin, chromomycin A, daunorubicin, leucovorin, neocarzinostatin, streptozocin, trabectedin, vinblastine, vincristine), anti-diabetic drug (e.g., voglibose), a central nervous system drug (e.g., L-dopa, galantamine, ziconotide), a statin (e.g., mevastatin), an anti-fungal drug (e.g., fumagillin, cyclosporin), 1-deoxynojirimycin, and theophylline, sterols (cholesterol, estrogen, testosterone). Additional small molecule natural products are described in Newman, D.J. and Cragg, M. (2016) *J Nat Prod* 79:629-661 and Butler, M.S. et al (2014) *Nat Prod Rep* 31:1612-1661, which are incorporated herein by reference in their entirety.

In some embodiments, the cells are engineered to synthesize a non-protein or non-peptide small molecule. For example, in an embodiment an engineered cell can produce a statin (e.g., taurostatin, pravastatin, fluvastatin, or atorvastatin).

In some embodiments, the therapeutic agent is an antigen (e.g., a viral antigen, a bacterial antigen, a fungal antigen, a plant antigen, an environmental antigen, or a tumor antigen). An antigen is recognized by those skilled in the art as being immunostimulatory, i.e., capable of stimulating an immune response or providing effective immunity to the organism or molecule from which it derives. An antigen may be a nucleic acid, peptide, protein, sugar, lipid, or a combination thereof.

The particles comprising a cell may produce a single therapeutic agent or a plurality of therapeutic agents. The plurality of therapeutic agents may be related or may form a complex. In some embodiments, the therapeutic agent secreted or released from a particle comprising a cell is in an active form. In some embodiments, the therapeutic agent is secreted or released from a particle comprising a cell in an inactive form, e.g., as a prodrug. In the latter instance, the therapeutic agent may be activated by a downstream agent, such as an enzyme.

Methods of Treatment

Described herein are methods for preventing or treating a disease, disorder, or condition in a subject through administration or implantation of particles comprising a first compartment, a second compartment, and a compound of Formula (I) (e.g., as described herein), or a composition comprising the same. In some embodiments, the methods described herein directly or indirectly reduce or alleviate at least one symptom of a disease, disorder, or condition. In some embodiments, the methods described herein prevent or slow the onset of a disease, disorder, or condition. In some embodiments, the subject is a human.

In some embodiments, the disease, disorder, or condition affects a system of the body, e.g. the nervous system (e.g., peripheral nervous system (PNS) or central nervous system (CNS)), vascular system, skeletal system, respiratory system, endocrine system, lymph system, reproductive system, or gastrointestinal tract. In some embodiments, the disease, disorder, or condition affects a part of the body, e.g., blood, eye, brain, skin, lung, stomach, mouth, ear, leg, foot, hand, liver, heart, kidney, bone, pancreas, spleen, large intestine, small intestine, spinal cord, muscle, ovary, uterus, vagina, or penis.

In some embodiments, the disease, disorder or condition is a neurodegenerative disease, diabetes, a heart disease, an autoimmune disease, a cancer, a liver disease, a lysosomal storage disease, a blood clotting disorder or a coagulation disorder, an orthopedic condition, an amino acid metabolism disorder.

In some embodiments, the disease, disorder or condition is a neurodegenerative disease. Exemplary neurodegenerative diseases include Alzheimer's disease, Huntington's disease, Parkinson's disease (PD) amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS) and cerebral palsy (CP), dentatorubro-pallidoluysian atrophy (DRPLA), neuronal intranuclear hyaline inclusion disease (NIHID), dementia with Lewy bodies, Down's syndrome, Hallervorden-Spatz disease, prion diseases, argyrophilic grain dementia, corticobasal degeneration, dementia pugilistica, diffuse neurofibrillary tangles, Gerstmann-Straussler-Scheinker disease, Jakob-Creutzfeldt disease, Niemann-Pick disease type 3, progressive supranuclear palsy, subacute sclerosing panencephalitis, spinocerebellar ataxias, Pick's disease, and dentatorubral-pallidoluysian atrophy.

In some embodiments, the disease, disorder, or condition is an autoimmune disease, e.g., scleroderma, multiple sclerosis, lupus, or allergies.

In some embodiments, the disease is a liver disease, e.g., hepatitis B, hepatitis C, cirrhosis, NASH.

In some embodiments, the disease, disorder, or condition is cancer. Exemplary cancers include leukemia, lymphoma, melanoma, lung cancer, brain cancer (e.g., glioblastoma), sarcoma, pancreatic cancer, renal cancer, liver cancer, testicular cancer, prostate cancer, or uterine cancer.

In some embodiments, the disease, disorder, or condition is an orthopedic condition. Exemplary orthopedic conditions include osteoporosis, osteonecrosis, Paget's disease, or a fracture.

In some embodiments, the disease, disorder or condition is a lysosomal storage disease. Exemplary lysosomal storage diseases include Gaucher disease (e.g., Type I, Type II, Type III), Tay-Sachs disease, Fabry disease, Farber disease, Hurler syndrome (also known as mucopolysaccharidosis type I (MPS I)), Hunter syndrome, lysosomal acid lipase deficiency, Niemann-Pick disease, Salla disease, Sanfilippo syndrome (also known as mucopolysaccharidosis type IIIA (MPS3A)), multiple sulfatase deficiency, Maroteaux-Lamy syndrome, metachromatic leukodystrophy, Krabbe disease, Scheie syndrome, Hurler-Scheie syndrome, Sly syndrome, hyaluronidase deficiency, Pompe disease, Danon disease, gangliosidosis, or Morquio syndrome.

In some embodiments, the disease, disorder, or condition is a blood clotting disorder or a coagulation disorder. Exemplary blood clotting disorders or coagulation disorders include hemophilia (e.g., hemophilia A or hemophilia B), Von Willebrand disease, thrombocytopenia, uremia, Bernard-Soulier syndrome, Factor XII deficiency, vitamin K deficiency, or congenital afibrinogenemia.

In some embodiments, the disease, disorder, or condition is an amino acid metabolism disorder, e.g., phenylketonuria, tyrosinemia (e.g., Type 1 or Type 2), alkaptonuria, homocystinuria, hyperhomocysteinemia, maple syrup urine disease.

In some embodiments, the disease, disorder, or condition is a fatty acid metabolism disorder, e.g., hyperlipidemia, hypercholesterolemia, galactosemia.

In some embodiments, the disease, disorder, or condition is a purine or pyrimidine metabolism disorder, e.g., Lesch-Nyhan syndrome.

In some embodiments, the disease, disorder, or condition is diabetes (e.g., Type I or Type II diabetes).

The present disclosure further comprises methods for identifying a subject having or suspected of having a disease, disorder, or condition described herein, and upon such identification, administering to the subject particles comprising a first compartment, a second compartment, and a compound of Formula (I) (e.g., as described herein), or a composition comprising such particles. In an embodiment, the subject is a human.

Pharmaceutical Compositions, Kits, and Administration

The present disclosure further comprises pharmaceutical compositions comprising the particles described herein, as well as kits thereof.

In some embodiments, a pharmaceutical composition comprises a particle comprising a first compartment, a second compartment, and a compound of Formula (I), as well as a pharmaceutically acceptable excipient. In some embodiments, the particles in the pharmaceutical composition comprise a cell (e.g., a human cell, e.g., an engineered human cell) and a pharmaceutically acceptable excipient. In some embodiments, the particles are provided in an effective amount in the pharmaceutical composition. In some embodiments, the effective amount is a therapeutically effective amount. In some embodiments, the effective amount is a prophylactically effective amount.

Pharmaceutical compositions described herein can be prepared by any method known in the art of pharmacology. In general, such preparatory methods include the steps of bringing the particles (e.g., particles, i.e., “the active ingredient”) into association with a carrier and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping and/or packaging the product into a desired single- or multi-dose unit.

Pharmaceutical compositions can be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a “unit dose” is a discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient (i.e., number of particles). The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage.

Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition of the disclosure will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. By way of example, the composition may comprise between 0.1% and 100% (w/w) active ingredient.

The term “pharmaceutically acceptable excipient” refers to a non-toxic carrier, adjuvant, diluent, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable excipients useful in the manufacture of the pharmaceutical compositions of the disclosure are any of those that are well known in the art of pharmaceutical formulation and include inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Pharmaceutically acceptable excipients useful

in the manufacture of the pharmaceutical compositions of the disclosure include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

The particles described herein may be administered orally, parenterally (including subcutaneous, intramuscular, and intradermal), topically, rectally, nasally, intratumorally, intrathecally, buccally, vaginally or via an implanted reservoir. In some embodiments, provided particles or compositions are administrable subcutaneously or by implant.

In some embodiments, the particles and related compositions described herein may be administered or implanted in or on a certain region of the body, such as a mucosal surface or a body cavity. Exemplary sites of administration or implantation include the peritoneal cavity (e.g., lesser sac), adipose tissue, heart, eye, muscle, spleen, lymph node, esophagus, nose, sinus, teeth, gums, tongue, mouth, throat, small intestine, large intestine, thyroid, bone (e.g. hip or a joint), breast, cartilage, vagina, uterus, fallopian tube, ovary, penis, testicles, blood vessel, liver, kidney, central nervous system (e.g., brain, spinal cord, nerve), or ear (e.g., cochlea).

In some embodiments, the particles and related compositions described herein are administered or implanted at a site other than the central nervous system, e.g., the brain, spinal cord, nerve. In some embodiments, the particles and related compositions described herein are administered or implanted at a site other than the eye (e.g., retina).

Sterile injectable forms of the compositions of this disclosure may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

For ophthalmic use, provided pharmaceutically acceptable compositions may be formulated as micronized suspensions or in an ointment such as petrolatum.

Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to animals of all sorts. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with ordinary experimentation.

The particles and related compositions described herein may be formulated in dosage unit form, e.g., single unit dosage form, for ease of administration and uniformity of dosage. It will be understood, however, that the total dosage and usage regimens of the compositions of the present disclosure will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular subject or organism will depend upon a variety of factors including the disease being treated and the severity of the disorder; the activity of the specific active ingredient employed; the specific composition employed; the age, body weight, general health, sex and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific active ingredient employed; the duration of the treatment; drugs used in combination or coincidental with the specific active ingredient employed; and like factors well known in the medical arts.

The exact amount of a treatment required to achieve an effective amount will vary from subject to subject, depending, for example, on species, age, and general condition of a subject, severity of the side effects or disorder, identity of the particular particle(s), mode of administration, and the like. The desired dosage can be delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In certain embodiments, the desired dosage can be delivered using multiple administrations (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations).

It will be appreciated that the particles and related compositions, as described herein, can be administered in combination with one or more additional pharmaceutical agents. The particles or compositions can be administered in combination with additional pharmaceutical

agents that improve their bioavailability, reduce and/or modify their metabolism, inhibit their excretion, and/or modify their distribution within the body. It will also be appreciated that the therapy employed may achieve a desired effect for the same disorder, and/or it may achieve different effects.

Also encompassed by the disclosure are kits (e.g., pharmaceutical packs). The inventive kits may be useful for preventing and/or treating any of the diseases, disorders or conditions described herein. The kits provided may comprise an inventive pharmaceutical composition or particle as described herein and a container (e.g., a vial, ampule, bottle, syringe, and/or dispenser package, or other suitable container). In some embodiments, provided kits may optionally further include a second container comprising a pharmaceutical excipient for dilution or suspension of an inventive pharmaceutical composition or particle described herein. In some embodiments, the inventive pharmaceutical composition or particle described herein provided in the container and the second container are combined to form one unit dosage form.

Methods of Making Particles

The present disclosure further comprises methods for making a particle described herein, e.g., a particle comprising a first compartment, a second compartment, and a compound of Formula (I). In some embodiments where the particle is a hydrogel capsule, the method of making the particle comprises contacting a plurality of droplets comprising first and second polymer solutions (e.g., each comprising a hydrogel-forming polymer) with an aqueous cross-linking solution. The droplets can be formed using any technique known in the art.

Each compartment of a particle described herein may comprise an unmodified polymer, a polymer modified with a compound of Formula (I), or a blend thereof. Briefly, in performing a method of preparing a particle configured as a two-compartment hydrogel capsule, a volume of a first polymer solution (e.g., comprising an unmodified polymer, a polymer modified with a compound of Formula (I), or a blend thereof, and optionally containing cells,) is loaded into a first syringe connected to the inner lumen of a coaxial needle. The first syringe may then be connected to a syringe pump oriented vertically above a vessel containing an aqueous cross-linking solution which comprises a cross-linking agent, a buffer, and an osmolarity-adjusting agent. A volume of the second polymer solution (e.g., comprising an unmodified polymer, a polymer modified with a compound of Formula (I), or a blend thereof, and optionally containing cells) is loaded into a second syringe connected to the outer lumen of the coaxial needle. The

second syringe may then be connected to a syringe pump oriented horizontally with respect to the vessel containing the cross-linking solution. A high voltage power generator may then be connected to the top and bottom of the needle. The syringe pumps and power generator can then be used to extrude the first and second polymer solutions through the syringes with settings determined to achieve a desired droplet rate of polymer solution into the cross-linking solution. The skilled artisan may readily determine various combinations of needle lumen sizes, voltage range, flow rates, droplet rate and drop distance to create 2-compartment hydrogel capsule compositions in which the majority (e.g., at least 80%, 85%, 90% or more) of the capsules are within 10% of the target size and have a sphere-like in shape. After exhausting the first and second volumes of polymer solution, the droplets may be allowed to cross-link in the cross-linking solution for certain amount of time, e.g., about five minutes.

Exemplary process parameters for preparing a composition of millicapsules (e.g., 1.5 mm diameter millicapsules) include the following. A coaxial needle is disposed above the surface of the cross-linking solution at a distance sufficient to provide a drop distance from the needle tip to the solution surface. In an embodiment, the distance between the needle tip and the solution surface is between 1 to 5 cm. In an embodiment, the first and second polymer solutions are extruded through the needle with a total flow rate of between 0.05 mL/min to 5 mL/min, or 0.05 mL/min to 2.5 mL/min, or 0.05 mL/min to about 1 mL/min, or 0.05 mL/min to 0.5 mL/min, or 0.1 mL/min to 0.5 mL/min. In an embodiment, the first and second polymer solutions are extruded through the needle with a total flow rate of about 0.05 mL/min, 0.1 mL/min, 0.15 mL/min, 0.2 mL/min, 0.25 mL/min, 0.3 mL/min, 0.35 mL/min, 0.4 mL/min, 0.45 mL/min, or 0.5 mL/min. In an embodiment, the flow rate of the first and second polymer solutions through the needle are substantially the same. In an embodiment, the flow rate of the first and second polymer solutions through the needle are different.

In an embodiment, the voltage of the instrument is between 1 kV to 20kV, or 1 to 15 kV, or 1 kV to 10 kV, or 5 kV to 10 kV. The voltage may be adjusted until a desired droplet rate is reached. In an embodiment, the droplet rate of the instrument is between 1 droplet/10 seconds to 50 droplets/10 seconds, or 1 droplet/10 seconds to 25 droplets/10 seconds.

In an embodiment, the number of non-particle debris on the surface of the cross-linking solution is determined. Particles that have fallen to the bottom of the cross-linking vessel may then be collected, e.g., by transferring cross-linking solution containing the particles to a separate

container, leaving behind any non-particle debris on the solution surface in the original cross-linking vessel. The removed particles may then be allowed to settle, the cross-linking solution can be removed, and the particles may then be washed one or more times with a buffer (e.g., a HEPES buffer). In an embodiment, one or more aliquots of the resulting particle composition (e.g., preparation of particles) is inspected by microscopy to assess the quality of the composition, e.g., the number of particle defects and satellite particles.

In some embodiments, the cross-linking solution further comprises a process additive (e.g., a hydrophilic, non-ionic surfactant). A process additive may reduce surface tension of the cross-linking solution. Agents useful as the process additive in the present disclosure include polysorbate-type surfactants, copolymer of polyethyleneoxide (PEO) and polypropyleneoxide (PPO), poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO) triblock copolymers, and non-ionic surfactants, such as Tween[®] 20, Tween[®] 80, Triton[™] X-100, IGEPAL[®] CA-630, poloxamer 188, or poloxamer 407, or surfactants with substantially the same chemical and physical properties listed in the Exemplary Surfactant Table immediately below.

Exemplary Surfactant Table			
Brand or Generic Name	Commercial Supplier	Approximate Average Molecular Weight (g/mole)	Hydrophilicity HLB ^a
Tween [®] 20 ^b	Millipore Sigma	1228	16.7
Tween [®] 80 ^c	Millipore Sigma	1310	15
Triton [™] X-100 ^d	Millipore Sigma	625	13.4
IGEPAL [®] CA-630 ^e	Millipore Sigma	603	13
poloxamer 188 ^f	Millipore Sigma	8400	>24
poloxamer 407 ^g	Millipore Sigma	12,500	18-23

^a hydrophilic-lipophilic balance

^b Chemical names and synonyms: polyethylene glycol sorbitan monolaurate, polyoxyethylene (20) sorbitan monolaurate, polysorbate 20, polyoxyethylene 20 sorbitan monododecanoate

^c Chemical names and synonyms: polyethylene glycol sorbitan monooleate, polyoxyethylene (20) sorbitan monooleate, polysorbate 80, (x)-sorbitan mono-9-octadecenoate poly(oxy-1,2-ethanediyl)

^d Chemical names and synonyms: 4-(1,1,3,3-Tetramethylbutyl)phenyl-polyethylene glycol, *t*-octylphenoxy polyethoxyethanol, polyethylene glycol *tert*-octylphenyl ether; octylphenol ethoxylate, octylphenol ethylene oxide condensate

^e Chemical names and synonyms: octylphenoxy polyethoxyethanol, octylphenoxy poly(ethyleneoxy)ethanol, branched

^f Chemical name: Poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol)

^g Chemical name: Poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol)

In some embodiments, the process additive is a non-ionic surfactant. In an embodiment, the process additive comprises more than one surfactant, e.g., more than one hydrophilic surfactant. In some embodiments, the process additive does not contain Tween® 20 (polysorbate 20) or Triton™ X-100. In an embodiment, the process additive is IGEPAL® CA-630 (polyethylene glycol sorbitan monooleate). In some embodiments, the process additive is poloxamer 188.

In some embodiments, the process additive (e.g., surfactant) is present in the cross-linking solution at a concentration of at least 0.0001% or more. In some embodiments, the cross-linking solution comprises at least 0.001%, 0.01%, or 0.1% of the process additive. In some embodiments, the process additive is present at a concentration selected from about 0.001% to about 0.1%, about 0.005% to about 0.05%, about 0.005% to about 0.01%, and about 0.01% to about 0.5%. In an embodiment, the process additive is a surfactant and is present at a concentration that is below the critical micelle concentration for the surfactant.

In some embodiments, the cross-linking agent comprises divalent cations of a single type or a mixture of different types, e.g., one or more of Ba^{2+} , Ca^{2+} , Sr^{2+} . In some embodiments, the cross-linking agent is BaCl_2 , e.g., at a concentration of 1 mM to 100 mM or 7.5 mM to 20 mM. In some embodiments, the cross-linking agent is CaCl_2 , e.g., at a concentration of 50 mM to 100 mM. In some embodiments, the cross-linking agent is SrCl_2 , e.g., at a concentration of 37.5 mM to 100 mM. In some embodiments, the cross-linking agent is a mixture of BaCl_2 (e.g., 5 mM to 20 mM) and CaCl_2 (e.g., 37.5 mM to 12.5 mM) or a mixture of BaCl_2 (e.g., 5 mM to 20 mM) and SrCl_2 (e.g., 37.5 mM to 12.5 mM).

In some embodiments, the cross-linking agent is SrCl_2 , and the process additive is Tween® 80 (or a surfactant with substantially the same chemical and physical properties listed in the Exemplary Surfactant Table) at a concentration of less than 0.1%, e.g., about 0.005% to 0.05%, about 0.005% to about 0.01%. In some embodiments, the concentration of SrCl_2 is about 50 mM. In some embodiments, the cross-linking agent is SrCl_2 and the process additive is poloxamer 188 at a concentration of 1%.

The type and concentration of buffer in the aqueous cross-linking solution is selected to maintain the solution pH at approximately neutral, e.g., from about 6.5 to about 7.5, about 7.0 to

about 7.5, or about 7.0. In an embodiment, the buffer is compatible with a biological material to be encapsulated in the particle, e.g., cells. In some embodiments, the buffer in the aqueous cross-linking solution comprises HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid).

The osmolarity-adjusting agent in the aqueous cross-linking solution is selected to maintain the solution osmolarity at a value similar to the osmolarity of the polymer solution (which in some embodiments comprises a suspension of cells), e.g., an osmolarity that has a higher or lower variance of up to 20%, 10% or 5%. In some embodiments, the osmolarity agent is mannitol at a concentration of 0.1 M to 0.3 M.

In some embodiments, the cross-linking solution comprises 25 mM HEPES buffer, 20 mM BaCl₂, 0.2 M mannitol and 0.01% poloxamer 188.

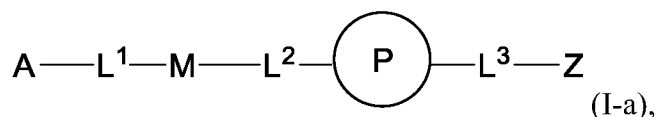
In some embodiments, the cross-linking solution comprises 50 mM strontium chloride hexahydrate, 0.165 M mannitol, 25 mM HEPES and 0.01% of a surfactant with substantially the same chemical and physical properties listed in the Exemplary Surfactant Table for Tween 80.

In an embodiment, the process additive is poloxamer 188, which is present in the particle composition (e.g., preparation of particles) in a detectable amount after the wash steps. Poloxamer 188 may be detected by any technique known in the art, e.g., by partially or completely dissolving the particles in an aliquot of the composition by sodium sulfate precipitation and analyzing the supernatant by LC/MS.

Reduction in the surface tension of the cross-linking solution may be assessed by any method known in the art, for example, through the use of a contact angle goniometer or a tensiometer, e.g., via the du Nouy ring method (see, e.g., Davarci et al (2017) *Food Hydrocolloids* 62:119-127).

ENUMERATED EXEMPLARY EMBODIMENTS

1. A particle comprising:
 - a) a first compartment;
 - b) a second compartment; and
 - c) a compound of Formula (I-a):



or a pharmaceutically acceptable salt thereof, wherein:

A is alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-O-$, $-C(O)O-$, $-C(O)-$, $-OC(O)-$, $-N(R^C)-$, $-N(R^C)C(O)-$, $-C(O)N(R^C)-$, $-N(R^C)N(R^D)-$, $-NCN-$, $-N(R^C)C(O)(C_1-C_6\text{-alkylene})-$, $-N(R^C)C(O)(C_2-C_6\text{-alkenylene})-$, $-C(=N(R^C)(R^D))O-$, $-S-$, $-S(O)_x-$, $-OS(O)_x-$, $-N(R^C)S(O)_x-$, $-S(O)_xN(R^C)-$, $-P(R^F)_y-$, $-Si(OR^A)_2-$, $-Si(R^G)(OR^A)-$, $-B(OR^A)-$, or a metal, each of which is optionally linked to an attachment group (e.g., an attachment group described herein) and optionally substituted by one or more R^1 ;

each of L^1 and L^3 is independently a bond, alkyl, or heteroalkyl, wherein each alkyl and heteroalkyl is optionally substituted by one or more R^2 ;

L^2 is a bond;

M is absent, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted by one or more R^3 ;

P is heteroaryl optionally substituted by one or more R^4 ;

Z is alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted by one or more R^5 ;

each R^A , R^B , R^C , R^D , R^E , R^F , and R^G is independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, halogen, azido, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^6 ;

or R^C and R^D , taken together with the nitrogen atom to which they are attached, form a ring (e.g., a 5-7 membered ring), optionally substituted with one or more R^6 ;

each R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 is independently alkyl, alkenyl, alkynyl, heteroalkyl, halogen, cyano, azido, oxo, $-OR^{A1}$, $-C(O)OR^{A1}$, $-C(O)R^{B1}$, $-OC(O)R^{B1}$, $-N(R^{C1})(R^{D1})$, $-N(R^{C1})C(O)R^{B1}$, $-C(O)N(R^{C1})$, SR^{E1} , $S(O)_xR^{E1}$, $-OS(O)_xR^{E1}$, $-N(R^{C1})S(O)_xR^{E1}$, $-S(O)_xN(R^{C1})(R^{D1})$, $-P(R^{F1})_y$, cycloalkyl, heterocyclyl, aryl, heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted by one or more R^7 ;

each R^{A1} , R^{B1} , R^{C1} , R^{D1} , R^{E1} , and R^{F1} is independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl is optionally substituted by one or more R^7 ;

each R^7 is independently alkyl, alkenyl, alkynyl, heteroalkyl, halogen, cyano, oxo,

hydroxyl, cycloalkyl, or heterocyclyl;

x is 1 or 2; and

y is 2, 3, or 4.

2. The particle of embodiment 1, wherein the first compartment is surrounded by the second compartment.

3. The particle of any one of embodiments 1-2, wherein the first compartment is disposed within the second compartment.

4. The particle of any one of embodiments 1-3, wherein the second compartment forms a barrier around the first compartment.

5. The particle of any one of embodiments 1-4, wherein the total volume of the second compartment is greater than, e.g. 1.5x, 2x, 3x, or 5x, the volume of the first compartment.

6. The particle of any one of embodiments 1-4, wherein the differential volume of the second compartment is greater than, e.g. 1.5x, 2x, 3x, or 5x, the volume of the first compartment.

7. The particle of any one of embodiments 1-4, wherein the total volume of the second compartment is about 1%, 2%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, or 75% greater than the volume of the first compartment.

8. The particle of any one of embodiments 1-4, wherein the differential volume of the second compartment is about 1%, 2%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, or 75% greater than the volume of the first compartment.

9. The particle of any one of embodiments 1-4, wherein the differential volume of the second compartment is less than, e.g. 1.5x, 2x, 3x, or 5x, the volume of the first compartment.

10. The particle of any one of embodiments 1-4, wherein the total volume of the second

compartment is about 1%, 2%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, or 75% less than the volume of the first compartment.

11. The particle of any one of embodiments 1-4, wherein the differential volume of the second compartment is about 1%, 2%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, or 75% less than the volume of the first compartment.

12. The particle of embodiment 1, comprising a property selected from the following:
a) the first compartment comprises a compound of Formula (I-a);
b) the second compartment comprises a compound of Formula (I-a);
c) a compound of Formula (I-a) is disposed on the exterior surface of the particle; and/or
d) the particle comprises an interface between the first and second compartments and a compound of Formula (I-a) is disposed at the interface.

13. The particle of embodiment 12, comprising property a.

14. The particle of any one of embodiments 12-13, comprising property b.

15. The particle of any one of embodiments 12-14, comprising property c.

16. The particle of any one of embodiments 12-15, comprising property d.

17. The particle of embodiment 1, wherein the first compartment or the second compartment is substantially free of a compound of Formula (I-a).

18. The particle of embodiment 1, wherein the outer surface of the particle is substantially free of a compound of Formula (I-a).

19. The particle of embodiment 1, comprising a property selected from the following:
a) the first compartment is substantially free of a compound of Formula (I-a);
b) the second compartment is substantially free of a compound of Formula (I-a);

c) the outer surface of the particle is substantially free of a compound of Formula (I-a); or
d) the particle comprises an interface between the first and second compartment and the interface is substantially free of a compound of Formula (I-a).

20. The particle of embodiment 19, comprising property a.

21. The particle of any one of embodiments 19-20, comprising property b.

22. The particle of any one of embodiments 19-21, comprising property c.

23. The particle of any one of embodiments 19-22, comprising property d.

24. The particle of embodiment 19, comprising properties a and b.

25. The particle of any one of embodiments 1-24, wherein the particle has a largest linear dimension (LLD), e.g., diameter, of between 20 nanometers to 10 millimeters.

26. The particle of any one of embodiments 1-25, wherein the particle has a largest linear dimension (LLD), e.g., diameter, of between 500 nanometers to 10 millimeters.

27. The particle of any one of embodiments 1-26, wherein the particle has a largest linear dimension (LLD), e.g., diameter, of between 1 millimeter to 5 millimeters, e.g., between 1 millimeter to 4 millimeters, 1 millimeter to 3 millimeters, 1 millimeter to 2 millimeters, about 1.5 millimeters to 2 millimeters, or about 1.5 millimeters.

28. The particle of any one of embodiments 1-27, wherein the particle is configured as a hydrogel capsule with the first compartment surrounded by the second compartment.

29. The particle of embodiment 28, wherein the thickness of the second compartment is selected from the group consisting of:

(a) 1 nanometers and 1 millimeter;

- (b) 100 nanometers and 1 millimeter; and
- (c) 500 nanometers and 500 micrometers.

30. The particle of embodiment 29, wherein the thickness of the second compartment is at least about 2.5%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 50%, 60%, 70%, or 80% of the diameter of the particle.

31. The particle of any one of embodiments 1-30, wherein the particle comprises a cell.

32. The particle of any one of embodiments 1-31, wherein the first compartment comprises a cell.

33. The particle of any one of embodiments 1-32, wherein the second compartment comprises a cell.

34. The particle of any one of embodiments 1-33, wherein the first compartment comprises a cell and the second compartment does not comprise a cell.

35. The particle of any one of embodiments 1-34, wherein the first compartment comprises a cell and the second compartment comprises a cell.

36. The particle of embodiment 35, wherein the first compartment and the second compartment comprise the same type of cell.

37. The particle of embodiment 35, wherein the cell in the first compartment is a different type of cell than the cell in the second compartment.

38. The particle of any one of embodiments 31-36, wherein the particle comprises an interface between the first compartment and the second compartment and a cell is disposed at the interface, e.g., a cell contacts both the first and second compartments.

39. The particle of any one of embodiments 31-37, wherein the number or density of cells in the second compartment is less than the number or density of cells in the first compartment.

40. The particle of any one of embodiments 31-39, wherein the first compartment is formed from a polymer solution comprising at least 0.5×10^6 , 1×10^6 , 5×10^6 , 10×10^6 , 15×10^6 or 20×10^6 cells per mL.

41. The particle of any one of embodiments 31-40, wherein the first compartment is formed from a polymer solution comprising at least 0.5×10^6 , 1×10^6 , 5×10^6 , 10×10^6 , 15×10^6 , 20×10^6 or 25×10^6 cells per mL or from a polymer solution comprising 100 to 300 million cells per mL.

42. The particle of any one of embodiments 31-41, wherein the particle comprises at least 100; 250; 500; 750; 1,000; 2,500; 5,000; 10,000; 25,000; or 50,000 cells.

43. The particle of any one of embodiments 31-42, wherein the first compartment comprises at least 100; 250; 500; 750; 1,000; 2,500; 5,000; 10,000; 25,000; or 50,000 cells.

44. The particle of any one of embodiments 31-43, wherein the cells are present as single cells, one or more spheroids, or bound to one or more microcarriers.

45. The particle of any one of embodiments 31-44, wherein the exterior surface of the particle is substantially free of cells.

46. The particle of any one of embodiments 31-45, wherein:

- a) one or a plurality of cells is disposed within the first compartment;
- b) the number or density of cells in the second compartment is at least 2, 5, 10, 10^2 , 10^3 , or 10^4 times less than the number or density of cells in the first compartment;
- c) the first compartment (e.g., the outer boundary of the first compartment) comprises a compound of Formula (I-a); or
- d) the second compartment (e.g., the outer boundary of the second compartment) comprises a compound of Formula (I-a).

47. The particle of embodiment 46, comprising property a.
48. The particle of any one of embodiments 46-47, comprising property b.
49. The particle of any one of embodiments 46-48, comprising property c.
50. The particle of any one of embodiments 46-49, comprising property d.
51. The particle of embodiment 50, comprising properties a and b.
52. The particle of embodiment 50, comprising properties a, b, and c.
53. The particle of embodiment 50, comprising properties a, b, and d.
54. The particle of embodiment 50, comprising properties a, b, c, and d.
55. The particle of any one of embodiments 31-54, wherein the second compartment is substantially free of cells.
56. The particle of any one of embodiments 31-55, wherein the cell is an epithelial cell, endothelial cell, fibroblast cell, mesenchymal stem cell, or keratinocyte cell.
57. The particle of any one of embodiments 31-56, wherein the cell is an RPE (e.g., ARPE-19) cell or an MSC.
58. The particle of any one of embodiments 31-56, wherein the cell is an islet cell.
59. The particle of any one of embodiments 31-58, wherein the cell expresses a therapeutic agent (e.g., a polypeptide).

- 5 60. The particle of embodiment 59, wherein the polypeptide is a Factor VIII protein or a variant thereof or a Factor IX protein or a variant thereof.
61. The particle of any one of embodiments 59-60, wherein the polypeptide comprises SEQ ID NO:1 or a variant thereof.
- 0 62. The particle of any one of embodiments 59-60, wherein the polypeptide comprises SEQ ID NO: 2 or a variant thereof, e.g., an alanine substituted for threonine at amino acid position 148 of SEQ ID NO:2 or a leucine substituted for arginine at amino acid position 338 of SEQ ID NO:2.
63. The particle of embodiment 59, wherein the polypeptide is insulin (e.g., insulin A-chain, insulin B-chain, or proinsulin).
- 5 64. The particle of any one of embodiments 1-63, wherein the particle comprises a polymer.
65. The particle of embodiment 64, wherein the polymer is a polysaccharide.
- 10 66. The particle of any one of embodiments 64-65, wherein the polymer is selected from alginate, chitosan, hyaluronate, gelatin, poly(L-lactic acid) (PLLA), or poly(lactic glycolic acid) (PLGA).
- 25 67. The particle of any one of embodiments 64-66, wherein the first compartment comprises a polymer (e.g., a polysaccharide, e.g., an alginate).
68. The particle of any one of embodiments 64-67, wherein the second compartment comprises a polymer (e.g., a polysaccharide, e.g., an alginate).
- 30 69. The particle of any one of embodiments 64-68, wherein both the first compartment and the second compartment comprise a polymer (e.g., a polysaccharide, e.g., an alginate).

70. The particle of any one of embodiments 64-69, wherein the first compartment and the second compartment comprise the same polymer.
71. The particle of any one of embodiments 64-70, wherein the first compartment and the second compartment comprise a different polymer.
72. The particle of any one of embodiments 64-71, wherein the first compartment does not comprise alginate and the second compartment comprises alginate.
73. The particle of any one of embodiments 64-72, wherein first compartment comprises an alginate and the second compartment comprises a polymer other than alginate.
74. The particle of any one of embodiments 64-73, wherein second compartment comprises an alginate and the first compartment comprises a polymer other than alginate.
75. The particle of embodiment 74, wherein the first compartment comprises hyaluronate or chondroitin and the second compartment comprises an alginate.
76. The particle of any one of embodiments 73-75, wherein the polymer of the first compartment is modified with a compound of Formula (I-a).
77. The particle of any one of embodiments 73-76, wherein the polymer of the second compartment is modified with a compound of Formula (I-a).
78. The particle of any one of embodiments 1-77, wherein the exterior surface of the particle and interior of the second compartment comprise a compound of Formula (I-a).
79. The particle of any one of embodiments 64-78, wherein the polymers of both the first compartment and second compartment are modified with a compound of Formula (I-a).
80. The particle of any one of embodiments 1-79, wherein the compound of Formula (I-a) is

a compound of any one of Formulas (I-b), (I-c), (I-d), (I-e), (I-f), (II), (II-a), (III), (III-a), (III-b), (III-c), or (III-d), or a pharmaceutically acceptable salt thereof.

81. The particle of any one of embodiments 76-80, wherein the compound of Formula (I-a) is selected from Compound 110, Compound 112, Compound 113 or Compound 114 shown in Table 2.

82. The particle of any one of embodiments 76-80, wherein the compound of Formula (I-a) is Compound 112 shown in Table 2.

83. The particle of any one of embodiments 76-80, wherein the compound of Formula (I-a) is Compound 113 shown in Table 2.

84. The particle of any one of embodiments 76-80, wherein the compound of Formula (I-a) is Compound 114 shown in Table 2.

85. The particle of any one of embodiments 76-80, wherein the compound of Formula (I-a) is not Compound 100 shown in Table 2.

86. The particle of any one of embodiments 76-80, wherein the compound of Formula (I-a) is Compound 101 shown in Table 2.

87. The particle of any one of embodiments 76-86, wherein at least 0.5% of the monomers of a polymer are modified with a compound of Formula (I-a) (e.g., at least 1%, 2.5%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or more of the monomers of a polymer are modified with a compound of Formula (I-a)).

88. The particle of any one of embodiments 76-86, wherein at least 0.5% of the monomers of a polymer in the first (inner) compartment of the particle are modified with a compound of Formula (I-a) (e.g., at least 1%, 2.5%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%,

55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or more of the monomers of a polymer in the first (inner) compartment of the particle are modified with a compound of Formula (I-a)).

89. The particle of any one of embodiments 76-86, wherein at least 0.5% of the monomers of a polymer in the second (outer) compartment of the particle are modified with a compound of Formula (I-a) (e.g., at least 1%, 2.5%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or more of the monomers of a polymer in the second (outer) compartment of the particle are modified with a compound of Formula (I-a)).

90. The particle of any one of embodiments 76-86, wherein the polymer (when modified with a compound of Formula (I-a)) comprises an increase in % N (as compared with unmodified polymer) of 0.1% to 10% N by weight (e.g., 0.1% to 2% N, 2% to 4%, or 4% to 8% N by weight), where % N is determined by combustion analysis and corresponds to the amount of compound of Formula (I-a) in the modified polymer.

91. The particle of any one of embodiments 76-86, wherein the first (inner) compartment of the particle comprises a polymer (when modified with a compound of Formula (I-a)) that comprises an increase in % N (as compared with unmodified polymer) of 0.1% to 10% N by weight (e.g., 0.1% to 2% N, 2% to 4%, or 4% to 8% N by weight), where % N is determined by combustion analysis and corresponds to the amount of compound of Formula (I-a) in the modified polymer.

92. The particle of any one of embodiments 76-84, wherein the second (outer) compartment of the particle comprises a polymer (when modified with a compound of Formula (I-a)) that comprises increase in % N (as compared with unmodified polymer) of 0.1% to 10% N by weight (e.g., 0.1% to 2% N, 2% to 4%, or 4% to 8% N by weight), where % N is determined by combustion analysis and corresponds to the amount of compound of Formula (I-a) in the modified polymer.

93. The particle of any one of embodiments 76-84, wherein the particle is a hydrogel capsule

and the second (outer) compartment of the capsule is formed using a mixture of an unmodified alginate and an alginate modified with a compound of Formula (I-a) (e.g., Compound 101) at a conjugation density of at least 2.0 % and less than 9.0 % nitrogen (N) as determined by combustion analysis for percent nitrogen as described in the Examples hereinbelow, or is 3.0 % to 8.0 %, 4.0 % to 7.0%, 5.0 % to 7.0 %, or 6.0 % to 7.0 % or about 6.8%.

94. The particle of any one of embodiments 1-93, wherein the particle is a spherical particle.

95. The particle of any one of embodiments 1-94, wherein the particle is made by a method wherein the second compartment is formed around the first compartment.

96. The particle of any of embodiments 1-95, made by a method comprising contacting a plurality of droplets of a polymer solution with an aqueous cross-linking solution for a period of time sufficient to produce a particle, wherein the cross-linking solution comprises a cross-linking agent, a buffer, and an osmolarity-adjusting agent.

97. The particle of embodiment 96, wherein the cross-linking solution further comprises a process additive.

98. The particle of embodiment 97, wherein the process additive is a surfactant.

99. The particle of embodiment 98, wherein the surfactant is selected from a polysorbate-type surfactant, a copolymer of polyethyleneoxide (PEO) and polypropyleneoxide (PPO), a poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO) triblock copolymer, polysorbate 20, polysorbate 80, 4-(1,1,3,3-Tetramethylbutyl)phenyl-polyethylene glycol, octylphenoxypolyethoxyethanol, poloxamer 188 and poloxamer 407.

100. The particle of any one of embodiments 98-99, wherein the surfactant has a hydrophilic-lipophilic balance (HLB) of at least 18 or at least 24, and optionally wherein the surfactant is poloxamer 188.

101. The particle of any one of embodiments 97-99, wherein the process additive is present in the cross-linking solution at a concentration of at least about 0.001% to about 0.1%, about 0.005% to about 0.05%, about 0.005% to about 0.01%, or about 0.01% to about 0.05%.

102. The particle of any one of embodiments 96-101, wherein the cross-linking agent comprises divalent cations of a single type or a mixture of different types, optionally wherein the cross-linking agent comprises one or more of Ba^{2+} , Ca^{2+} and Sr^{2+} .

103. The particle of any one of embodiments 96-102, wherein the cross-linking agent is selected from the group consisting of:

- a. BaCl_2 at a concentration of 1 mM to 100 mM or 7.5 mM to 20 mM;
- b. CaCl_2 at a concentration of 50 mM to 100 mM;
- c. SrCl_2 at a concentration of 37.5 mM to 100 mM;
- d. a mixture of BaCl_2 at a concentration of 5 mM to 20 mM and CaCl_2 at a concentration of 37.5 mM to 12.5 mM; and
- e. a mixture of BaCl_2 at a concentration of 5 mM to 20 mM and SrCl_2 at a concentration of 37.5 mM to 12.5 mM.

104. The particle of any one of embodiments 96-103, wherein the buffer comprises 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid) (HEPES).

105. The particle of any one of embodiments 96-104, wherein the osmolarity-adjusting agent comprises mannitol at a concentration of 0.1 M to 0.3 M.

106. The particle of any of embodiments 96-105, wherein the cross-linking agent is not SrCl_2 .

107. The particle of any one of embodiments 96-106, wherein the cross-linking agent is BaCl_2 .

108. The particle of any one of embodiments 96-107, wherein the cross-linking solution comprises 25 mM HEPES buffer, 20 mM BaCl_2 , 0.2 M mannitol and 0.01% poloxamer 188.

109. The particle of any one of embodiments 96-108, wherein the cross-linking agent is SrCl_2 and the process additive is a surfactant at a concentration of about 0.01%, wherein the surfactant is polysorbate 80.

110. The particle of embodiment 109, wherein the cross-linking solution comprises 50 mM strontium chloride hexahydrate, 0.165 M mannitol, 25 mM HEPES and 0.01% of polysorbate 80.

111. The particle of any one of embodiments 1 to 110, wherein the particle is a hydrogel millicapsule comprising a hydrogel forming polymer in each of the first and second compartments.

112. The particle of embodiment 111, wherein the only hydrogel forming polymer in the first compartment is a high molecular weight alginate and the hydrogel forming polymer in the second compartment is a mixture of a chemically modified low molecular weight alginate and an unmodified high molecular weight alginate.

113. A preparation of a plurality of particles, wherein the plurality comprises a particle of any one of embodiments 1-112

114. The preparation of embodiment 113, wherein at least 75%, 80%, 85%, 90%, 95%, 99%, or more of the particles in the plurality are spherical particles, and optionally wherein the preparation comprises a detectable amount of the process additive.

115. The preparation of embodiment 113 to 114, wherein the preparation is a pharmaceutically acceptable preparation.

116. A method of making a particle described herein, e.g., a particle of any of embodiments 1-115.

117. The method of embodiment 116, comprising forming the first compartment prior to formation of the second compartment.

118. The method of embodiment 117, comprising forming the first compartment at the same time as the formation of the second compartment.

119. The method of any one of embodiments 116-118, comprising contacting a plurality of droplets of first and second polymer solutions with an aqueous cross-linking solution for a period of time sufficient to produce a hydrogel capsule with first and second compartments, wherein the cross-linking solution comprises a cross-linking agent, a buffer, and an osmolarity-adjusting agent.

120. The method of any one of embodiments 116-119, wherein the method comprises use of a coaxial needle.

121. The method of any one of embodiments 116-120, wherein the first polymer solution comprises cells.

122. A method of implanting a particle in a subject comprising:
providing a particle described herein, e.g., in any of embodiments 1 to 112; and
disposing the particle in the body of the subject.

123. A method of providing a substance, e.g., a therapeutic substance, e.g., a polypeptide, to a subject comprising:

providing a particle described herein, e.g., in any of embodiments 1-112; which comprises or has the ability to produce the substance; and
disposing the particle in the body of the subject.

124. A method of evaluating a particle, e.g., in a subject comprising:
providing a particle described herein, e.g., in any of embodiments 1-112; and
disposing the particle in the body of the subject.

125. A method of treating a subject in need of a substance, e.g., a polypeptide, to a subject

comprising:

providing a particle described herein, e.g., in any of embodiments 1-112; which comprises or has the ability to produce the substance; and disposing the particle in the body of the subject.

126. A composition of particles for use in treating a subject in need of a substance, e.g., a polypeptide, to a subject comprising:

providing a particle described herein, e.g., in any of embodiments 1-112; which comprises or has the ability to produce the substance; and disposing the particle in the body of the subject.

EXAMPLES

In order that the disclosure described herein may be more fully understood, the following examples are set forth. The examples described in this application are offered to illustrate the particles, chemical modifications, compositions and methods provided herein and are not to be construed in any way as limiting their scope.

Example 1: Synthesis of exemplary compounds for preparation of chemically modified implantable elements

General Protocols

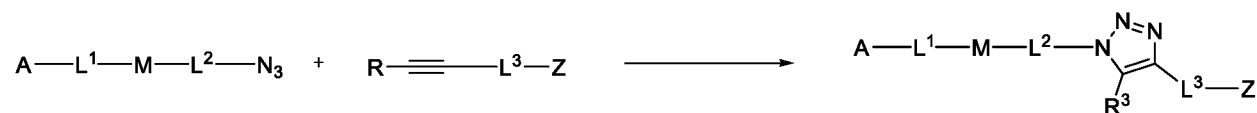
The procedures below describe methods of preparing exemplary compounds for preparation of chemically modified implantable elements. The compounds provided herein can be prepared from readily available starting materials using modifications to the specific synthesis protocols set forth below that would be well known to those of skill in the art. It will be appreciated that where typical or preferred process conditions (*i.e.*, reaction temperatures, times, mole ratios of reactants, solvents, pressures, *etc.*) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvents used, but such conditions can be determined by those skilled in the art by routine optimization procedures.

Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired

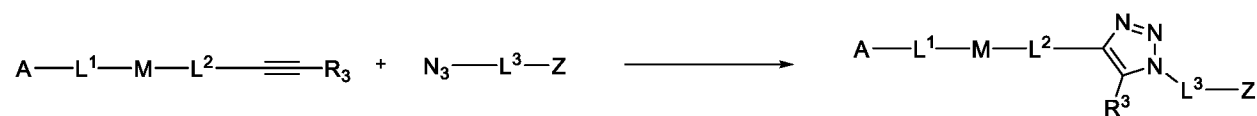
reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions for protection and deprotection are well known in the art. For example, numerous protecting groups, and their introduction and removal, are described in Greene *et al.*, *Protecting Groups in Organic Synthesis*, Second Edition, Wiley, New York, 1991, and references cited therein.

Huisgen cycloaddition to afford 1,4-substituted triazoles

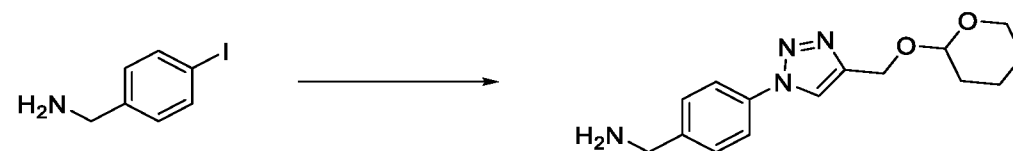
The copper-catalyzed Huisgen [3+2] cycloaddition was used to prepare triazole-based compounds and compositions, devices, and materials thereof. The scope and typical protocols have been the subject of many reviews (e.g., Meldal, M. and Tornøe, C. W. *Chem. Rev.* (2008) 108:2952-3015; Hein, J. E. and Fokin, V. V. *Chem. Soc. Rev.* (2010) 39(4):1302-1315; both of which are incorporated herein by reference).



In the example shown above, the azide is the reactive moiety in the fragment containing the connective element A, while the alkyne is the reactive component of the pendant group Z. As depicted below, these functional handles can be exchanged to produce a structurally related triazole product. The preparation of these alternatives is similar, and do not require special considerations.



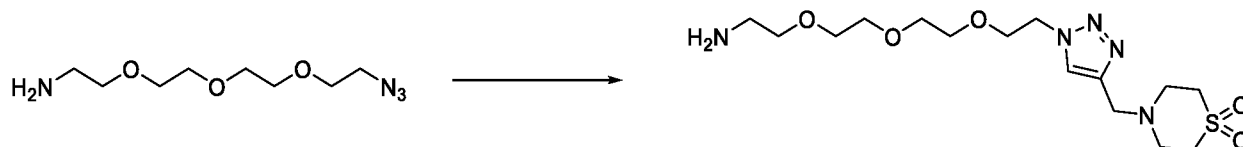
A typical Huisgen cycloaddition procedure starting with an iodide is outlined below. In some instances, iodides are transformed into azides during the course of the reaction for safety.



A solution of sodium azide (1.1 eq), sodium ascorbate, (0.1 eq) trans-*N,N'*-dimethylcyclohexane-1,2-diamine (0.25 eq), copper (I) iodide in methanol (1.0 M, limiting reagent) was degassed with bubbling nitrogen and treated with the acetylene (1 eq) and the aryl iodide (1.2 eq). This mixture was stirred at room temperature for 5 minutes, then warmed to 55 °C for 16 h. The reaction was then cooled to room temperature, filtered through a funnel, and the

filter cake washed with methanol. The combined filtrates were concentrated and purified via flash chromatography on silica gel (120 g silica, gradient of 0 to 40% (3% aqueous ammonium hydroxide, 22% methanol, remainder dichloromethane) in dichloromethane to afford the desired target material.

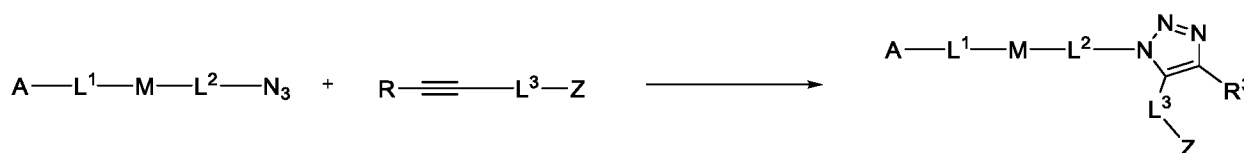
A typical Huisgen cycloaddition procedure starting with an azide is outlined below.



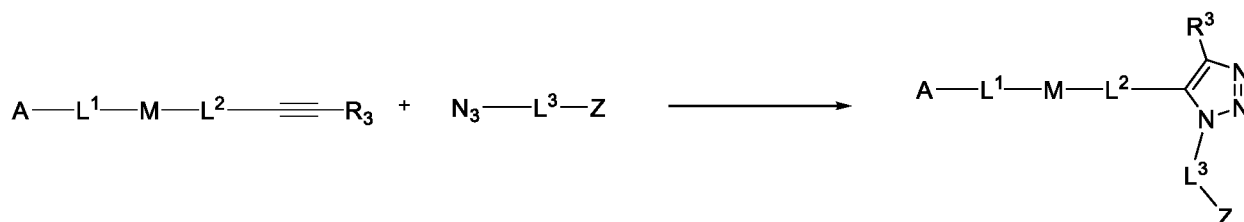
A solution of *tris*[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl]amine (0.2 eq), triethylamine (0.5 eq), copper (I) iodide (0.06 eq) in methanol (0.4 M, limiting reagent) was treated with the acetylene (1.0 eq) and cooled to 0 °C. The reaction was allowed to warm to room temperature over 30 minutes, then heated to 55 °C for 16h. The reaction was cooled to room temperature, concentrated, and purified with HPLC (C18 column, gradient of 0 to 100% (3% aqueous ammonium hydroxide, 22% methanol remainder dichloromethane) in dichloromethane to afford the desired target material.

Huisgen cycloaddition to afford 1,5-substituted triazoles

The Huisgen [3+2] cycloaddition was also performed with ruthenium catalysts to obtain 1,5-disubstituted products preferentially (e.g., as described in Zhang et al, *J. Am. Chem. Soc.*, 2005, 127, 15998-15999; Boren et al, *J. Am. Chem. Soc.*, 2008, 130, 8923-8930, each of which is incorporated herein by reference in its entirety).



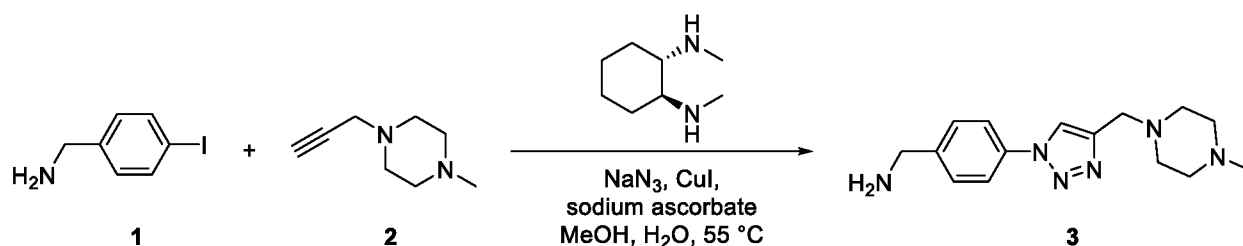
As described previously, the azide and alkyne groups may be exchanged to form similar triazoles as depicted below.



A typical procedure is described as follows: a solution of the alkyne (1 eq) and the azide

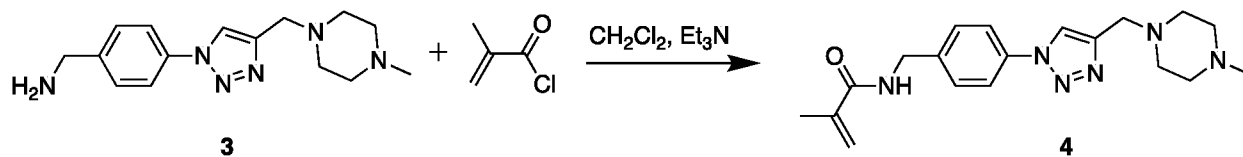
(1 eq) in dioxane (0.8M) were added dropwise to a solution of pentamethylcyclopentadienylbis(triphenylphosphine) ruthenium(II) chloride (0.02eq) in dioxane (0.16M). The vial was purged with nitrogen, sealed and the mixture heated to 60 °C for 12h. The resulting mixture was concentrated and purified via flash chromatography on silica gel to afford the requisite compound.

Experimental Procedure for (4-(4-((4-methylpiperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)phenyl)methanamine (3)



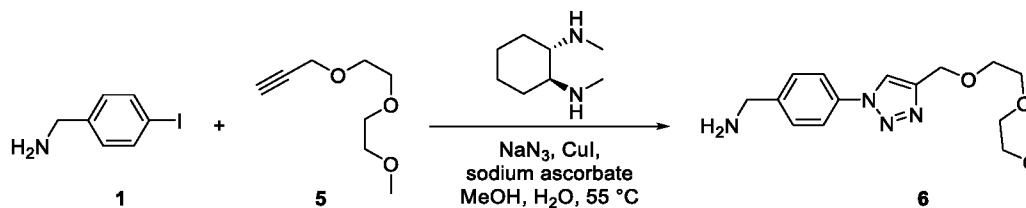
A mixture of (4-iodophenyl)methanamine (**1**, 843 mg, 3.62 mmol, 1.0 eq), (1S,2S)-N1,N2-dimethylcyclohexane-1,2-diamine (74 μ L, 0.47 mmol, 0.13 eq), Sodium ascorbate (72 mg, 0.36 mmol, 0.1 eq), Copper Iodide (69 mg, 0.36 mmol, 0.1 eq), Sodium azide (470 mg, 7.24 mmol, 2.0 eq), and 1-methyl-4-(prop-2-yn-1-yl)piperazine (**2**, 0.5 g, 3.62 mmol, 1.0 eq) in Methanol (9 mL) and water (1 mL) were purged with nitrogen for 5 minutes and heated to 55 °C for over night. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, and the brownish slurry was extracted with dichloromethane. Celite was added to the combined dichloromethane phases and the solvent was removed under reduced pressure. The crude product was purified over silica gel (80 g) using dichloromethane/(methanol containing 12 % (v/v) aqueous ammonium hydroxide) as mobile phase. The concentration of (methanol containing 12 % (v/v) aqueous ammonium hydroxide) was gradually increased from 0 % to 7.5 % to afford (4-(4-((4-methylpiperazin-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)phenyl)methanamine (**3**, 0.45 g, 43 %). LCMS *m/z*: $[M + H]^+$ Calcd for C₁₅H₂₂N₆ 287.2; Found 287.1.

Experimental Procedure for N-(4-(4-((4-methylpiperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)benzyl)methacrylamide (4)



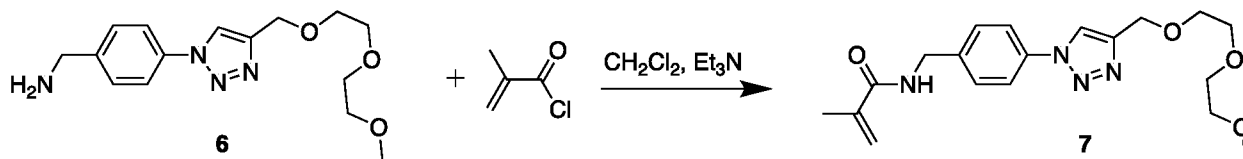
A solution of (4-(4-((4-methylpiperazin-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)phenyl)methanamine (**3**, 1.2 g, 4.19 mmol, 1.0 eq) and triethylamine (0.70 mL, 5.03 mmol, 1.2 eq) in CH₂Cl₂ (50 mL) was cooled to 0 °C with an ice-bath and methacryloyl chloride (0.43 mL, 4.40 mmol, 1.05 eq in 5 mL of CH₂Cl₂) was added. The reaction was stirred for a day while cooled with an ice-bath. 10 grams of Celite were added and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (80 g) using dichloromethane/(methanol containing 12 % (v/v) aqueous ammonium hydroxide) as mobile phase. The concentration of (methanol containing 12 % (v/v) aqueous ammonium hydroxide) was gradually increased from 0 % to 7.5 %. The solvent was removed under reduced pressure and the resulting solid was triturated with diethyl ether, filtered and washed multiple times with diethyl ether to afford *N*-(4-(4-((4-methylpiperazin-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)benzyl)methacrylamide (**4**, 0.41 g, 28 % yield) as a white solid. LCMS *m/z*: [M + H]⁺ Calcd for C₁₉H₂₆N₆O 355.2; Found 355.2.

*Experimental Procedure for (4-(4-((2-(2-methoxyethoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl)phenyl)methanamine (6)*



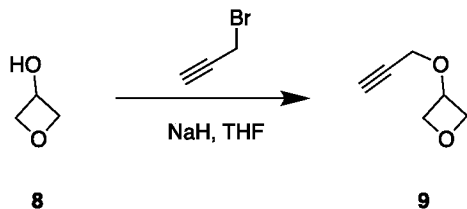
A mixture of (4-iodophenyl)methanamine (**1**, 2.95 g, 12.64 mmol, 1.0 eq), (1*S*,2*S*)-*N*1,*N*2-dimethylcyclohexane-1,2-diamine (259 μL, 1.64 mmol, 0.13 eq), sodium ascorbate (250 mg, 1.26 mmol, 0.1 eq), copper iodide (241 mg, 1.26 mmol, 0.1 eq), sodium azide (1.64 g, 25.29 mmol, 2.0 eq), and 3-(2-(2-methoxyethoxy)ethoxy)prop-1-yne (**5**, 2.0 g, 12.64 mmol, 1.0 eq) in methanol (40 mL) and water (4 mL) was purged with nitrogen for 5 minutes and then heated to 55 °C overnight. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in dichloromethane, filtered, and concentrated with Celite® (10 g). The crude product was purified on silica gel (220 g) using dichloromethane/(methanol containing 12% (v/v) aqueous ammonium hydroxide) as the eluent. The concentration of (methanol containing 12% (v/v) aqueous ammonium hydroxide) was gradually increased from 0% to 6.25% to afford (4-(4-((2-(2-methoxyethoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl)phenyl)methanamine (**6**, 1.37 g, 35%). LCMS *m/z*: [M + H]⁺ Calcd for C₁₅H₂₂N₄O₃ 307.2; Found 307.0.

Experimental Procedure for N-(4-(4-((2-(2-methoxyethoxy)ethoxy)methyl)-1H-1,2,3-triazol-1-yl)benzyl)methacrylamide (7)



A solution of 4-(4-((2-(2-methoxyethoxy)ethoxy)methyl)-1H-1,2,3-triazol-1-yl)phenyl)methanamine (**6**, 1.69 g, 5.52 mmol, 1.0 eq) and triethylamine (0.92 mL, 6.62 mmol, 1.2 eq) in CH₂Cl₂ (50 mL) was cooled to 0 °C with an ice-bath and methacryloyl chloride (0.57 mL, 5.79 mmol, 1.05 eq) was added in a dropwise fashion. The reaction was stirred for 4 h at room temperature. 10 grams of Celite were added and the solvent was removed under reduced pressure. The residue was purified by silica gel (80 g) chromatography using dichloromethane/(methanol containing 12 % (v/v) aqueous ammonium hydroxide) as mobile phase. The concentration of (methanol containing 12 % (v/v) aqueous ammonium hydroxide) was gradually increased from 0 % to 1.25 % to afford *N*-(4-(4-((2-(2-methoxyethoxy)ethoxy)methyl)-1H-1,2,3-triazol-1-yl)benzyl)methacrylamide (**7**, 1.76 g, 85 % yield) as a white solid. LCMS *m/z*: [M + H]⁺ Calcd for C₁₉H₂₆N₄O₄ 375.2; Found 375.0.

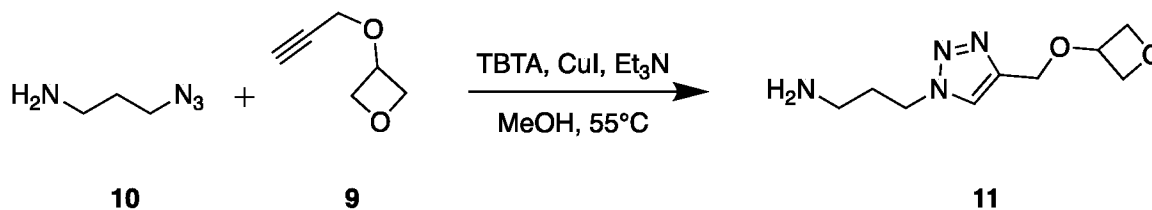
Experimental Procedure for 3-(prop-2-yn-1-yloxy)oxetane (9)



A suspension of sodium hydride (27.0 g, 675 mmol, 60 % purity) in THF (200 mL) was cooled with an ice bath. Oxetan-3-ol (**8**, 25 g, 337 mmol) was added in a dropwise fashion and stirred for 30 minutes at 0 °C. 3-Bromoprop-1-yne (**9**, 41.2 mL, 371 mmol, 80% purity) was then added in a dropwise fashion. The mixture was stirred over night while allowed to warm to room temperature. The mixture was filtered over Celite, washed with THF, and concentrated with Celite under reduced pressure. The crude product was purified over silica gel (220 g) and eluted with Hexanes/EtOAc. The concentration of EtOAc in the mobile phase was increased from 0 to 25% to afford a yellow oil of (**9**, 18.25 g 48 %).

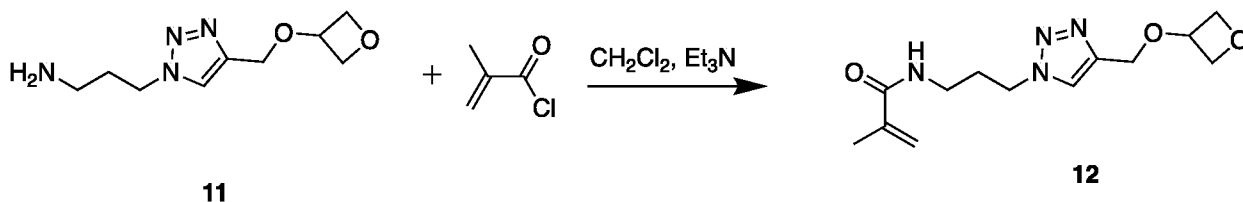
Experimental Procedure for 3-(4-((oxetan-3-yloxy)methyl)-1H-1,2,3-triazol-1-yl)propan-1-

amine (**11**)



A mixture of 3-(prop-2-yn-1-yloxy)oxetane (**9**, 7.96 g, 71 mmol, 1.0 eq), 3-azidopropan-1-amine (**10**, 7.82 g, 78 mmol, 1.1 eq), Tris[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl]-amine (8.29 g, 15.6 mmol, 0.22 eq), Copper Iodide (1.35 g, 7.1 mmol, 0.1 eq), and Triethylamine (2.47 mL, 17.8 mmol, 0.25 eq) in Methanol (80 mL) was warmed to 55 °C and stirred over night under Nitrogen atmosphere. The reaction mixture was cooled to room temperature, Celite (20 g) was added, and concentrated under reduced pressure. The crude product was purified over silica gel (220 g) using dichloromethane/(methanol containing 12 % (v/v) aqueous ammonium hydroxide) as mobile phase. The concentration of (methanol containing 12 % (v/v) aqueous ammonium hydroxide) was gradually increased from 0 % to 15 % to afford 3-(4-((oxetan-3-yloxy)methyl)-1H-1,2,3-triazol-1-yl)propan-1-amine (**11**, 11.85 g, 79 %) as a yellow oil. LCMS m/z: [M + H]⁺ Calcd for C₉H₁₆N₄O₂ 213.1; Found 213.0.

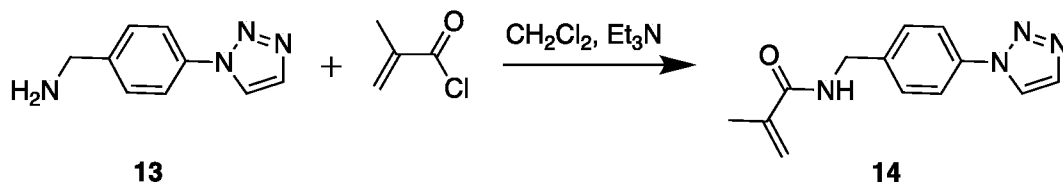
Experimental Procedure for N-(3-(4-((oxetan-3-yloxy)methyl)-1H-1,2,3-triazol-1-yl)propyl)methacrylamide (12)



A solution of 3-(4-((oxetan-3-yloxy)methyl)-1H-1,2,3-triazol-1-yl)propan-1-amine (**11**, 3.94 g, 18.56 mmol, 1.0 eq) and triethylamine (3.1 mL, 22.28 mmol, 1.2 eq) in CH₂Cl₂ (100 mL) was cooled to 0 °C with an ice-bath and methacryloyl chloride (1.99 mL, 20.42 mmol, 1.1 eq) was added in a dropwise fashion. The reaction was stirred over night while allowed to warm to room temperature. 20 grams of Celite were added and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (220 g) using dichloromethane/methanol as mobile phase. The concentration of methanol was gradually increased from 0 % to 5 % to afford N-(3-(4-((oxetan-3-yloxy)methyl)-1H-1,2,3-triazol-1-

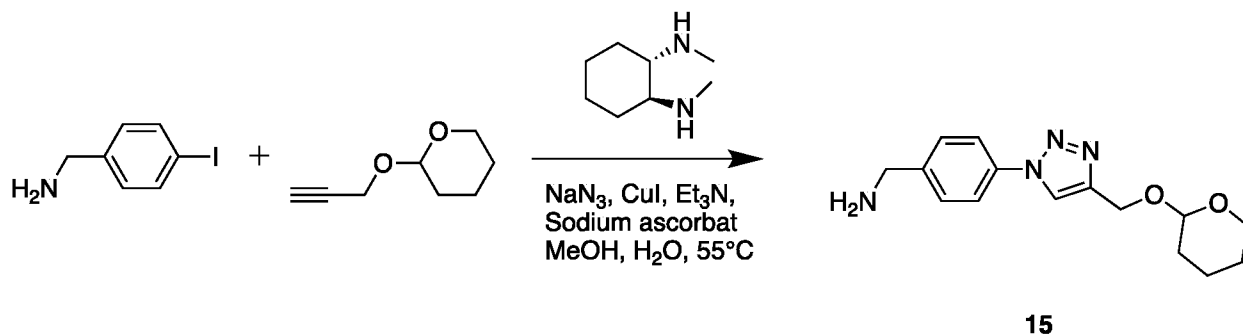
yl)propyl)methacrylamide (**12**, 3.22 g, 62 % yield) as a solid. LCMS m/z : $[M + H]^+$ Calcd for $C_{13}H_{20}N_4O_3$ 281.2; Found 281.0.

Experimental Procedure for N-(4-(1H-1,2,3-triazol-1-yl)benzyl) methacrylamide (14)



To a solution of (4-(1H-1,2,3-triazol-1-yl)phenyl)methanamine (**13**, obtained from WuXi, 1.2 g, 5.70 mmol, 1.0 eq) and triethylamine (15 mL, 107.55 mmol, 18.9 eq) in CH_2Cl_2 (100 mL) was slowly added methacryloyl chloride (893 mg, 8.54 mmol, 1.5 eq) in a dropwise fashion. The reaction was stirred over night. 20 grams of Celite were added and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography using dichloromethane/(methanol containing 12 % (v/v) aqueous ammonium hydroxide) as mobile phase. The concentration of (methanol containing 12 % (v/v) aqueous ammonium hydroxide) was gradually increased from 0 % to 1.25 % to afford N-(4-(1H-1,2,3-triazol-1-yl)benzyl) methacrylamide (**14**, 1.38 g, 40 % yield).

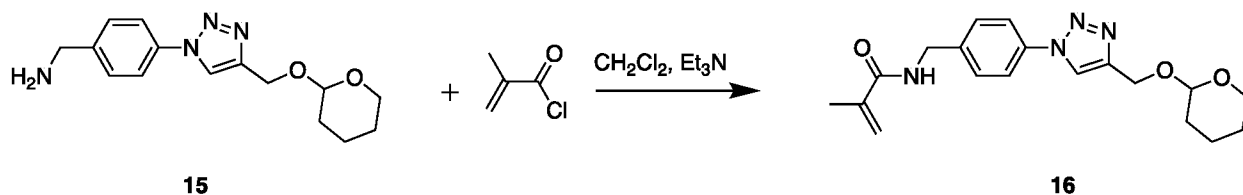
Experimental Procedure for (4-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)phenyl)methanamine (15)



A mixture of (4-iodophenyl)methanamine hydrochloride (5.0 g, 18.55 mmol, 1.0 eq), (1S,2S)-N1,N2- dimethylcyclohexane-1,2-diamine (0.59 mL 3.71 mmol, 0.2 eq), Sodium ascorbate (368 mg, 1.86 mmol, 0.1 eq), Copper Iodide (530 mg, 2.78 mmol, 0.15 eq), Sodium azide (2.41 g, 37.1 mmol, 2.0 eq) , Et_3N (3.11 mL, 22.26 mmol, 1.2 eq) and 2-(prop-2-yn-1-yloxy)tetrahydro-2H-pyran (2.6 g, 18.55 mmol, 1.0 eq) in Methanol (50 mL) and water (12 mL) were purged with Nitrogen for 5 minutes and heated to 55 °C for over night. The reaction mixture was cooled to room temperature and filtered through 413 filter paper. Celite was added and the solvent was

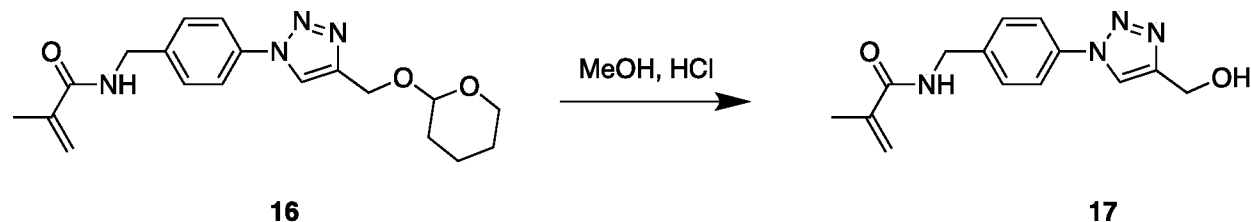
removed under reduced pressure and the residue was purified over silica gel (120 g) using dichloromethane/(methanol containing 12 % (v/v) aqueous ammonium hydroxide) as mobile phase. The concentration of (methanol containing 12 % (v/v) aqueous ammonium hydroxide) was gradually increased from 0 % to 6.25 % to afford (4-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)phenyl)methanamine (**15**, 3.54 g, 66%) as a white solid. LCMS m/z: [M + H]⁺ Calcd for C₁₅H₂₀N₄O₂ 289.2; Found 289.2.

Experimental Procedure for N-(4-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)benzyl)methacrylamide (16)



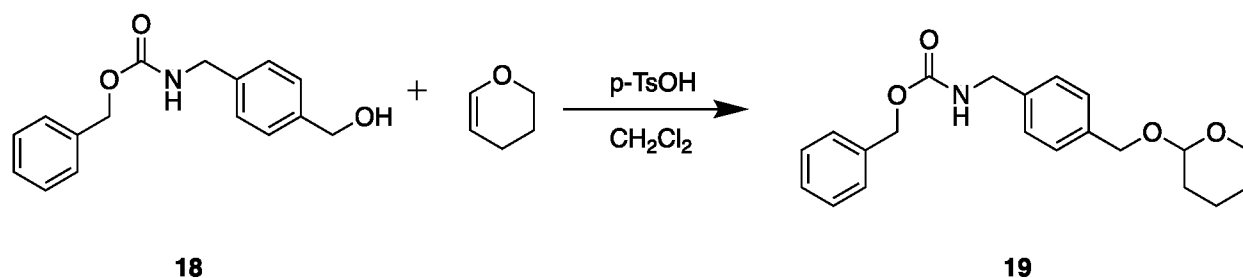
A solution of (4-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)phenyl)methanamin (**15**, 3.46 g, 12.00 mmol, 1.0 eq) and triethylamine (2.01 mL, 14.40 mmol, 1.2 eq) in CH₂Cl₂ (40 mL) was cooled to 0 °C with an ice-bath and methacryloyl chloride (1.23 mL, 12.60 mmol, 1.05 eq, diluted in 5 mL of CH₂Cl₂) was added in a dropwise fashion. The cooling bath was removed and the reaction was stirred for 4 h. 20 grams of Celite was added and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (80 g) using dichloromethane/(methanol containing 12 % (v/v) aqueous ammonium hydroxide) as mobile phase. The concentration of (methanol containing 12 % (v/v) aqueous ammonium hydroxide) was gradually increased from 0 % to 3.75 % to afford *N*-(4-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)benzyl)methacrylamide (**16**, 2.74 g, 64 % yield) as a white solid. LCMS m/z: [M + H]⁺ Calcd for C₁₉H₂₄N₄O₃ 357.2; Found 357.3.

Experimental Procedure for N-(4-(4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)benzyl)methacrylamide (17)



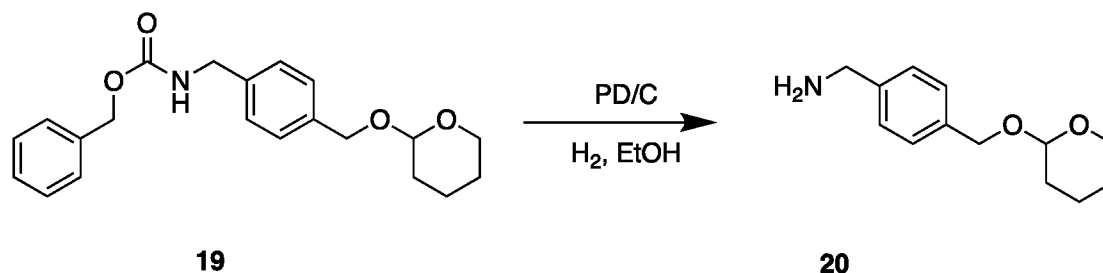
A solution of *N*-(4-(4-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)benzyl)methacrylamide (**16**, 1.2 g, 3.37 mmol, 1.0 eq) was dissolved in Methanol (6 mL) and HCl (1N, aq., 9 mL) for over night at room temperature. Celite was added and the solvent was removed under reduced pressure. The crude product was purified over silica gel chromatography (24 g) using dichloromethane / (methanol containing 12 % (v/v) aqueous ammonium hydroxide) as mobile phase. The concentration of (methanol containing 12 % (v/v) aqueous ammonium hydroxide) was gradually increased from 0 % to 12.5 % to afford *N*-(4-(4-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)benzyl)methacrylamide (**17**, 0.85 g, 92 % yield) as a white solid. LCMS *m/z*: [M + H]⁺ Calcd for C₁₄H₁₆N₄O₂ 273.1; Found 273.1.

*Experimental Procedure for 4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)benzyl)carbamate (19)*



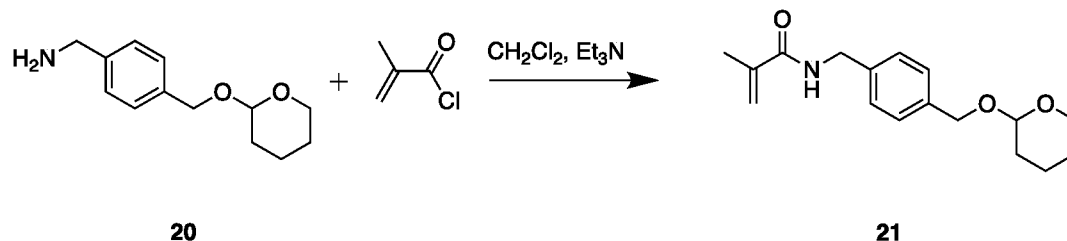
Benzyl 4-(hydroxymethyl)benzylcarbamate (2.71 g, 10 mmol, 1 eq), 3,4-dihydro-2*H*-pyran (1.81 mL, 20 mmol, 2 eq), *p*-Toluenesulfonic acid monohydrate (285 mg, 1.5 mmol, 0.15 eq) in dichloromethane (100 mL) were stirred at room temperature over night. Celite was added and the solvent was removed under reduced pressure. The crude product was purified over silica gel (24 g) using Hexanes/EtOAc as eluent starting at 100 % Hexanes and increasing the concentration of EtOAc gradually to 100 % to afford benzyl 4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)benzylcarbamate (**19**, 2.4 g, 68%) as a colorless oil. LCMS *m/z*: [M + Na]⁺ Calcd for C₂₁H₂₅NO₄ 378.17 Found 378.17.

*Experimental Procedure for 4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-phenyl)methanamine (20)*



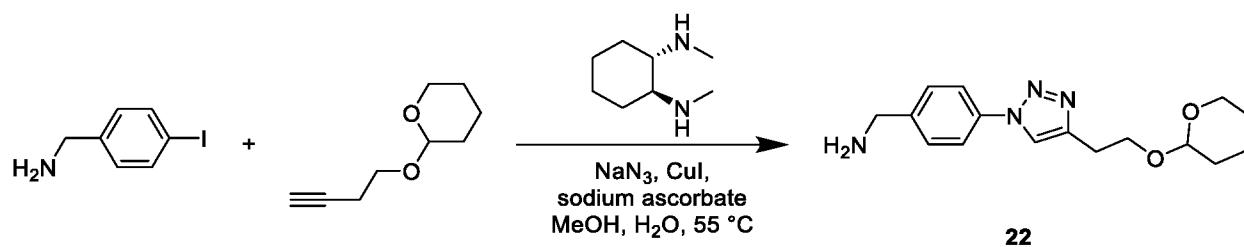
(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)benzyl)carbamate (**19**, 1.5 g, 4.2 mmol, 1 eq), Palladium on carbon (160 mg, 10 wt.%) in EtOH was briefly evacuated and then Hydrogen was added via a balloon and the mixture was stirred for 1 hour at room temperature. Celite was added and the solvent was removed under reduced pressure. The crude product was purified over silica gel (12 g) using dichloromethane/(methanol containing 12 % (v/v) aqueous ammonium hydroxide) as mobile phase. The concentration of (methanol containing 12 % (v/v) aqueous ammonium hydroxide) was gradually increased from 0 % to 25 % to afford (4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)methanamine (**20**, 890 mg, 95%) as a colorless oil. LCMS m/z: $[M + H]^+$ Calcd for $C_{13}H_{19}NO_2$ 222.15 Found 222.14.

Experimental Procedure for N-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)benzyl)-methacrylamide (21)



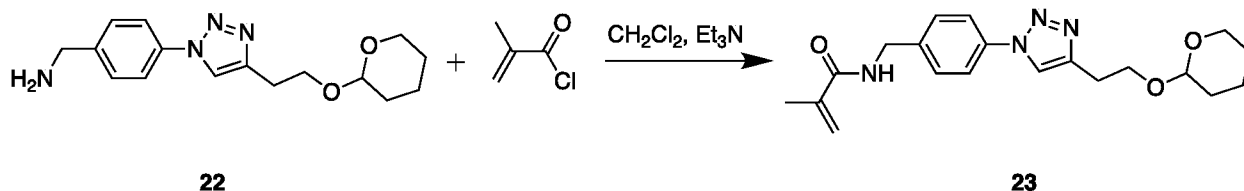
A solution of (4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)methanamine (**20**, 0.5 g, 2.26 mmol, 1.0 eq) and triethylamine (0.47 mL, 3.39 mmol, 1.5 eq) in CH_2Cl_2 (10 mL) were briefly evacuated and flushed with Nitrogen. Methacryloyl chloride (0.33 mL, 3.39 mmol, 1.5 eq) was added in a dropwise fashion. The reaction mixture was stirred over night at room temperature. 10 grams of Celite was added and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (12 g) using Hexanes/EtOAc as eluent starting at 100 % Hexanes and increasing the concentration of EtOAc gradually to 100 % to afford N-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)benzyl)methacrylamide (**21**, 0.47 g, 72 % yield) as a colorless solid. LCMS m/z: $[M + Na]^+$ Calcd for $C_{17}H_{23}NO_3$ 312.16; Found 312.17.

Experimental Procedure (4-(4-(2-(((tetrahydro-2H-pyran-2-yl)oxy)ethyl)-1H-1,2,3-triazol-1-yl)phenyl)methanamine (22)



A mixture of (4-iodophenyl)methanamine (5.0 g, 21.45 mmol, 1.0 eq), (1S,2S)-N1,N2-dimethylcyclohexane-1,2-diamine (0.44 mL 2.79 mmol, 0.13 eq), Sodium ascorbate (425 mg, 2.15 mmol, 0.1 eq), Copper Iodide (409 mg, 2.15 mmol, 0.1 eq), Sodium azide (2.79 g, 42.91 mmol, 2.0 eq), and 2-(but-3-yn-1-yloxy)tetrahydro-2H-pyran (3.36 mL, 21.45 mmol, 1.0 eq) in Methanol (20 mL) and water (5 mL) were purged with Nitrogen for 5 minutes and heated to 55 °C for over night. The reaction mixture was cooled to room temperature and filtered through 413 filter paper. Celite (10 g) was added and the solvent was removed under reduced pressure and the residue was purified over silica gel (220 g) using dichloromethane/(methanol containing 12 % (v/v) aqueous ammonium hydroxide) as mobile phase. The concentration of (methanol containing 12 % (v/v) aqueous ammonium hydroxide) was gradually increased from 0 % to 5 % to afford (4-(4-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)-1H-1,2,3-triazol-1-yl)phenyl)methanamine (**22**, 3.15 g, 49%) as a solid. LCMS m/z: [M + H]⁺ Calcd for C₁₆H₂₂N₄O₂ 303.18; Found 303.18.

Experimental Procedure for N-(4-(4-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)-1H-1,2,3-triazol-1-yl)benzyl)methacrylamide (23)



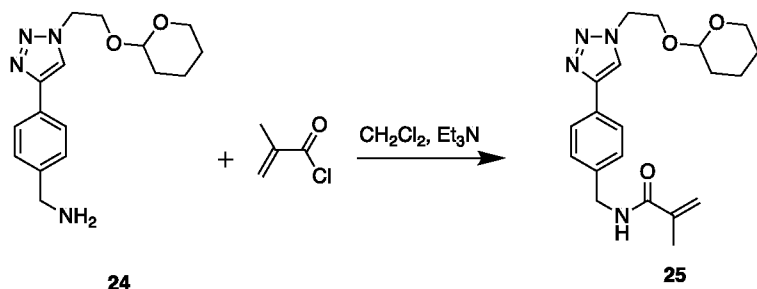
A solution of (4-(4-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)-1H-1,2,3-triazol-1-yl)phenyl)methanamine (**22**, 3.10 g, 10.25 mmol, 1.0 eq) and triethylamine (1.71 mL, 12.30 mmol, 1.2 eq) in CH₂Cl₂ (55 mL) was cooled to 0 °C with an ice-bath and methacryloyl chloride (1.05 mL, 12.30 mmol, 1.2 eq, diluted in 5 mL of CH₂Cl₂) was added in a dropwise fashion. The cooling bath was removed and the reaction was stirred for 4 h. 8 grams of Celite was added and the solvent was removed under reduced pressure. The residue was purified by silica gel

chromatography (80 g) using dichloromethane/(methanol containing 12 % (v/v) aqueous ammonium hydroxide) as mobile phase. The concentration of (methanol containing 12 % (v/v) aqueous ammonium hydroxide) was gradually increased from 0 % to 2.5 % to afford *N*-(4-(4-(2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl)-1*H*-1,2,3-triazol-1-yl)benzyl)methacrylamide (**23**, 2.06 g, 54 % yield) as a white solid. LCMS *m/z*: [M + H]⁺ Calcd for C₂₀H₂₆N₄O₃ 371.2078; Found 371.2085.

*Experimental Procedure (4-(1-(2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl)-1*H*-1,2,3-triazol-4-yl)phenyl)methanamine (24)*

A mixture of (4-ethynylphenyl)methanamine (2.36 g, 18.00 mmol, 1.0 eq), (1*S*,2*S*)-*N*1,*N*2-dimethylcyclohexane-1,2-diamine (0.56 mL, 3.60 mmol, 0.2 eq), Sodium ascorbate (357 mg, 1.80 mmol, 0.1 eq), Copper Iodide (514 mg, 2.70 mmol, 0.15 eq), and 2-(2-azidoethoxy)tetrahydro-2*H*-pyran (3.08, 18.00 mmol, 1.0 eq) in Methanol (24 mL) and water (6 mL) were purged with Nitrogen for 5 minutes and heated to 55 °C for over night. The reaction mixture was cooled to room temperature and filtered over Celite and rinsed with MeOH (3 x 50 mL). The solvent was removed under reduced pressure and the residue was redissolved in dichloromethane, Celite (20 g) was added and the solvent was removed under reduced pressure and the residue was purified over silica gel (120 g) using dichloromethane/(methanol containing 12 % (v/v) aqueous ammonium hydroxide) as mobile phase. The concentration of (methanol containing 12 % (v/v) aqueous ammonium hydroxide) was gradually increased from 0 % to 25 % to afford (4-(1-(2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl)-1*H*-1,2,3-triazol-4-yl)phenyl)methanamine (**24**, 3.51 g, 64%) as a yellowish oil. LCMS *m/z*: [M + H]⁺ Calcd for C₁₆H₂₂N₄O₂ 303.1816; Found 303.1814.

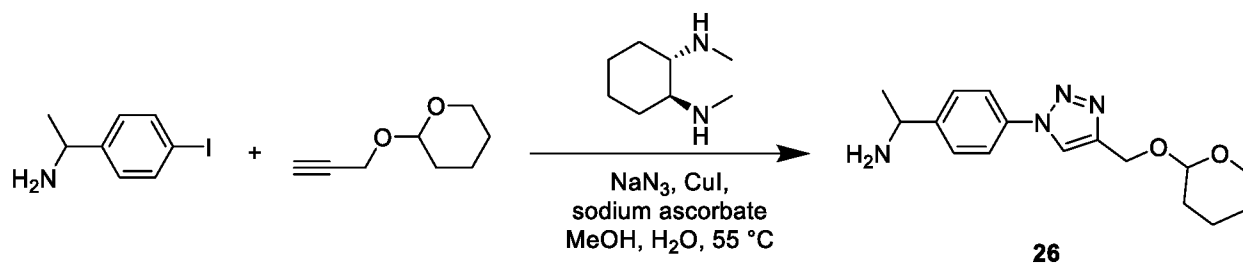
*Experimental Procedure for N-(4-(1-(2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl)-1*H*-1,2,3-triazol-4-yl)benzyl)methacrylamide (25)*



A solution of (4-(1-(2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl)-1*H*-1,2,3-triazol-4-yl)phenyl)methanamine (**24**, 1.5 g, 4.96 mmol, 1.0 eq) and triethylamine (1.04 mL, 7.44 mmol,

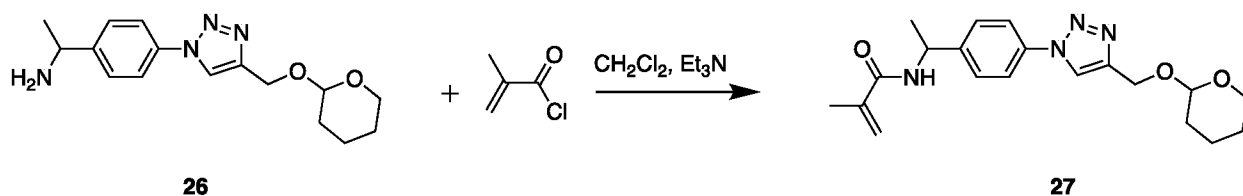
1.5 eq) in CH₂Cl₂ (30 mL) were briefly evacuated and flushed with Nitrogen. Methacryloyl chloride (0.72 mL, 7.44 mmol, 1.5 eq) was added in a dropwise fashion. The reaction mixture was stirred for 2 h at room temperature. 10 grams of Celite was added and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (40 g) using Hexanes/EtOAc as eluent starting at 100 % Hexanes and increasing the concentration of EtOAc gradually to 100 % to afford *N*-(4-(1-(2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl) -1*H*-1,2,3-triazol-4-yl)benzyl)methacrylamide (**25**, 0.9 g, 49% yield) as a colorless solid. LCMS *m/z*: [M + Na]⁺ Calcd for C₂₀H₂₆N₄O₃ 371.2078; Found 371.2076.

*Experimental Procedure for 1-(4-(4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)phenyl)ethan-1-amine (26)*



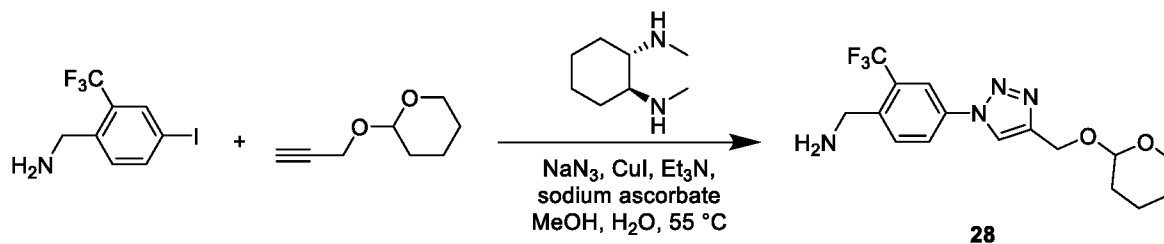
A mixture of 1-(4-iodophenyl)ethan-1-amine hydrochloride (1.0 g, 4.05 mmol, 1.0 eq), (1*S*,2*S*)-*N*1,*N*2- dimethylcyclohexane-1,2-diamine (0.08 mL 0.53 mmol, 0.13 eq), Sodium ascorbate (80 mg, 0.40 mmol, 0.1 eq), Copper Iodide (77 mg, 0.40 mmol, 0.1 eq), Sodium azide (526 g, 8.09 mmol, 2.0 eq), and 2-(prop-2-yn-1-yloxy)tetrahydro-2*H*-pyran (0.57 g, 4.05 mmol, 1.0 eq) in Methanol (9 mL) and water (1 mL) were purged with Nitrogen for 5 minutes and heated to 55 °C for over night. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was redissolved in dichloromethane and filtered over a plug of Celite. Celite was added to the filtrate and the solvent was removed under reduced pressure. The residue was purified over silica gel (40 g) using dichloromethane/(methanol containing 12 % (v/v) aqueous ammonium hydroxide) as mobile phase. The concentration of (methanol containing 12 % (v/v) aqueous ammonium hydroxide) was gradually increased from 0 % to 5 % to afford 1-(4-(4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)phenyl)ethan-1-amine (**26**, 0.62 g, 51%) as a yellowish solid. LCMS *m/z*: [M + H]⁺ Calcd for C₁₆H₂₂N₄O₂ 303.2; Found 303.2.

*Experimental Procedure for N-(1-(4-(4-(((tetrahydro-2*H*-pyran-2-yl)oxy) methyl)-1*H*-1,2,3-triazol-1-yl)phenyl)ethyl)methacrylamide (27)*



A solution of 1-(4-((4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)phenyl)ethan-1-amine (**26**, 0.52 g, 1.7 mmol, 1.0 eq) and triethylamine (0.29 mL, 2.1 mmol, 1.2 eq) in CH₂Cl₂ (11 mL) was cooled to 0 °C with an ice-bath and methacryloyl chloride (0.18 mL, 1.8 mmol, 1.05 eq, diluted in 11 mL of CH₂Cl₂) was added in a dropwise fashion. The cooling bath was removed and the reaction was stirred for 4 h. 5 grams of Celite was added and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (40 g) using dichloromethane/(methanol containing 12 % (v/v) aqueous ammonium hydroxide) as mobile phase. The concentration of (methanol containing 12 % (v/v) aqueous ammonium hydroxide) was gradually increased from 0 % to 2.5 % to afford *N*-(1-(4-((4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)phenyl)ethyl)methacrylamide (**27**, 0.49 g, 76 % yield) as a white solid. LCMS *m/z*: [M + H]⁺ Calcd for C₂₀H₂₆N₄O₃ 371.2078; Found 371.2087.

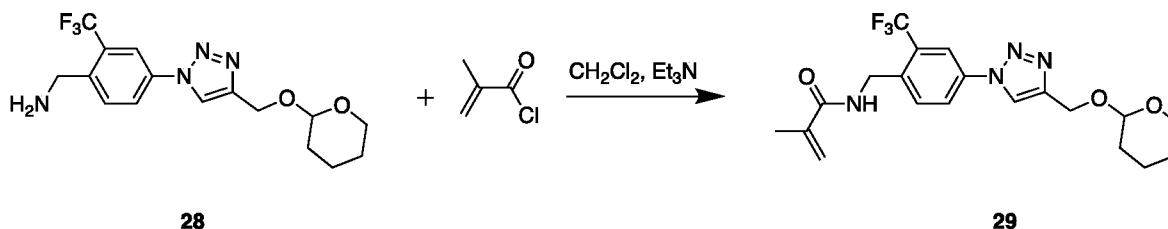
Experimental Procedure for (4-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)-2-(trifluoromethyl)phenyl)methanamine (28)



A mixture of (4-iodo-2-(trifluoromethyl)phenyl)methanamine (3.0 g, 9.97 mmol, 1.0 eq), (1S,2S)-N1,N2-dimethylcyclohexane-1,2-diamine (0.31 mL 1.99 mmol, 0.2 eq), Sodium ascorbate (197 mg, 1.00 mmol, 0.1 eq), Copper Iodide (285 mg, 1.49 mmol, 0.15 eq), Sodium azide (1.30 g, 19.93 mmol, 2.0 eq), Et₃N (1.67 mL, 11.96 mmol, 1.2 eq) and 2-(prop-2-yn-1-yloxy)tetrahydro-2H-pyran (1.40 g, 9.97 mmol, 1.0 eq) in Methanol (24 mL) and water (6 mL) were purged with Nitrogen for 5 minutes and heated to 55 °C for over night. The reaction mixture was cooled to room temperature and filtered through a plug of Celite and rinsed with Methanol (3 x 50 mL). Celite was added to the filtrate and the solvent was removed under

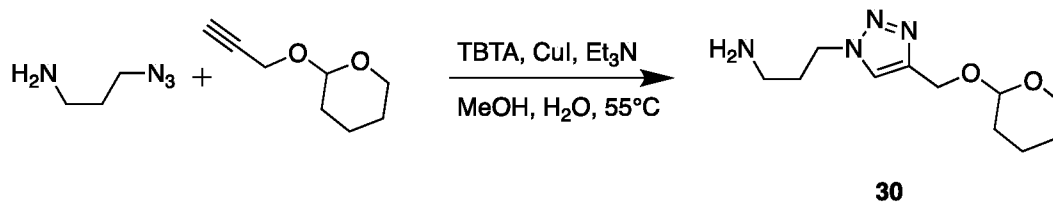
reduced pressure. The residue was purified over silica gel (120 g) using dichloromethane / (methanol containing 12 % (v/v) aqueous ammonium hydroxide) as mobile phase. The concentration of (methanol containing 12 % (v/v) aqueous ammonium hydroxide) was gradually increased from 0 % to 25 % to afford (4-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)-2-(trifluoromethyl)phenyl)methanamine (**28**, 2.53 g, 71%) as a green oil. LCMS m/z: [M + H]⁺ Calcd for C₁₆H₁₉N₄O₂F₃ 357.2; Found 357.1.

Experimental Procedure for N-(4-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)-2-(trifluoromethyl)benzyl) methacrylamide (29)



A solution of (4-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)-2-(trifluoromethyl)phenyl) methanamine (**28**, 1.0 g, 2.81 mmol, 1.0 eq) and triethylamine (0.59 mL, 4.21 mmol, 1.5 eq) in CH₂Cl₂ (25 mL) were briefly evacuated and flushed with Nitrogen. Methacryloyl chloride (0.41 mL, 4.21 mmol, 1.5 eq) was added in a dropwise fashion. The reaction mixture was stirred for 6 h at room temperature. 10 grams of Celite was added and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (40 g) using Hexanes/EtOAc as eluent starting at 100 % Hexanes and increasing the concentration of EtOAc gradually to 100 % to afford N-(4-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)-2-(trifluoromethyl)benzyl) methacrylamide (**29**, 0.65 g, 55% yield) as a colorless solid. LCMS m/z: [M + H]⁺ Calcd for C₂₀H₂₃N₄O₃F₃ 425.2; Found 425.1.

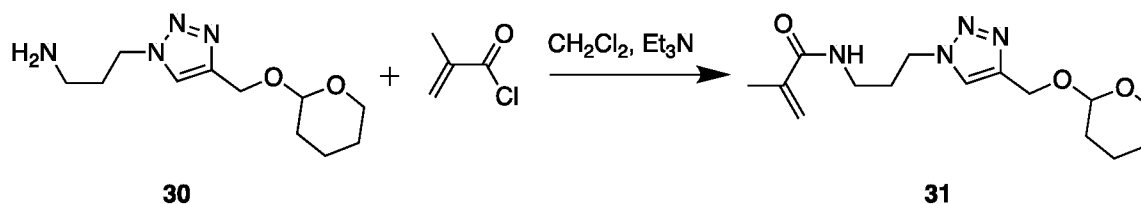
Experimental Procedure for 3-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)propan-1-amine (30)



A mixture of 3-azidopropan-1-amine hydrochloride (1.5 g, 14.98 mmol, 1.0 eq), Tris[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl]-amine (1.99 g, 3.75 mmol, 0.25 eq), Copper Iodide (0.29 g, 1.50

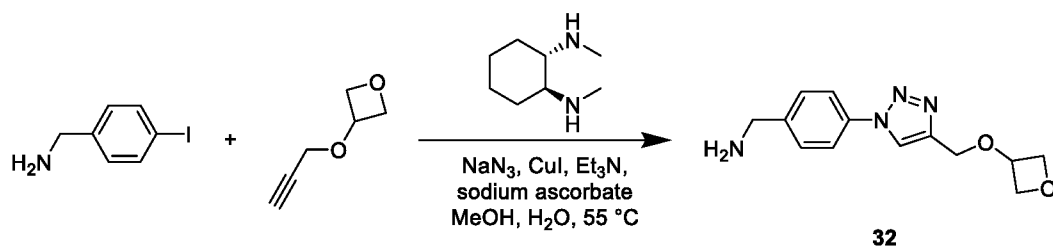
mmol, 0.1 eq), and Triethylamine (0.52 mL, 3.75 mmol, 0.25 eq) in Methanol (50 mL) and water (6 mL) were purged with Nitrogen for 5 minutes and cooled to 0 °C. 2-(prop-2-yn-1-yloxy)tetrahydro-2H-pyran (2.10 g, 14.98 mmol, 1.0 eq) was added and the reaction mixture was warmed to 55 °C and stirred over night under Nitrogen atmosphere. The reaction mixture was cooled to room temperature, filtered over a plug of Celite and rinsed with Methanol (3 x 50 mL). Celite (20 g) was added to the filtrate the solvent was removed under reduced pressure. The residue was purified over silica gel (120 g) using dichloromethane/(methanol containing 12 % (v/v) aqueous ammonium hydroxide) as mobile phase. The concentration of (methanol containing 12 % (v/v) aqueous ammonium hydroxide) was gradually increased from 0 % to 20 % to afford 3-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)propan-1-amine (**30**, 2.36 g, 66%). LCMS m/z: [M + H]⁺ Calcd for C₁₁H₂₀N₄O₂ 241.2; Found 241.2.

Experimental Procedure for N-(3-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)propyl)methacrylamide (31)



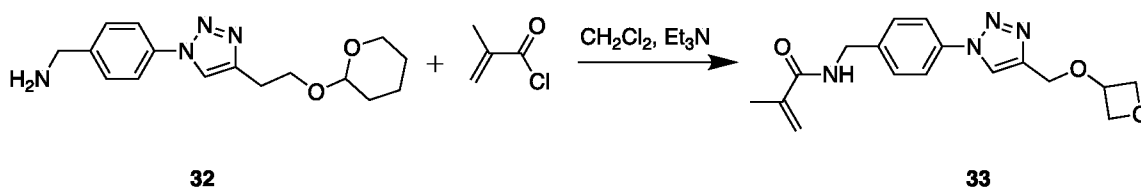
A solution of 3-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)propan-1-amine (**30**, 1.0 g, 4.16 mmol, 1.0 eq) and triethylamine (0.58 mL, 4.16 mmol, 1.0 eq) in CH₂Cl₂ (20 mL) were briefly evacuated and flushed with Nitrogen. Methacryloyl chloride (0.40 mL, 4.16 mmol, 1.0 eq) was added in a dropwise fashion. The reaction mixture was stirred at room temperature over night. 10 grams of Celite was added and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (40 g) using using dichloromethane/(methanol containing 12 % (v/v) aqueous ammonium hydroxide) as mobile phase. The concentration of (methanol containing 12 % (v/v) aqueous ammonium hydroxide) was gradually increased from 0 % to 20 % to afford N-(3-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)propyl)methacrylamide (**31**, 0.96 g, 75% yield) as a colorless oil. LCMS m/z: [M + H]⁺ Calcd for C₁₅H₂₄N₄O₃ 309.2; Found 309.4.

Experimental Procedure for (4-(4-((oxetan-3-yloxy)methyl)-1H-1,2,3-triazol-1-yl)phenyl)methanamine (32)



A mixture of (4-iodophenyl)methanamine hydrochloride (2.64 g, 9.80 mmol, 1.0 eq), (1S,2S)-N1,N2- dimethylcyclohexane-1,2-diamine (0.31 mL 1.96 mmol, 0.2 eq), Sodium ascorbate (198 mg, 0.98 mmol, 0.1 eq), Copper Iodide (279 mg, 1.47 mmol, 0.15 eq), Sodium azide (1.27 g, 19.59 mmol, 2.0 eq) , Et₃N (1.64 mL, 11.75 mmol, 1.2 eq) and 3-(prop-2-yn-1-yloxy)oxetane (**9**, 1.10 g, 9.80 mmol, 1.0 eq) in Methanol (24 mL) and water (6 mL) were purged with Nitrogen for 5 minutes and heated to 55 °C for over night. The reaction mixture was cooled to room temperature and filtered through a plug of Celite and rinsed with Methanol (3 x 50 mL). Celite was added to the filtrate and the solvent was removed under reduced pressure. The residue was purified over silica gel (120 g) using dichloromethane/(methanol containing 12 % (v/v) aqueous ammonium hydroxide) as mobile phase. The concentration of (methanol containing 12 % (v/v) aqueous ammonium hydroxide) was gradually increased from 0 % to 25 % to afford (4-(4-((oxetan-3-yloxy)methyl)-1H-1,2,3-triazol-1-yl)phenyl)methanamine (**32**, 1.43 g, 56%) as an oil. LCMS m/z: [M + H]⁺ Calcd for C₁₃H₁₆N₄O₂ 261.1346; Found 261.1342.

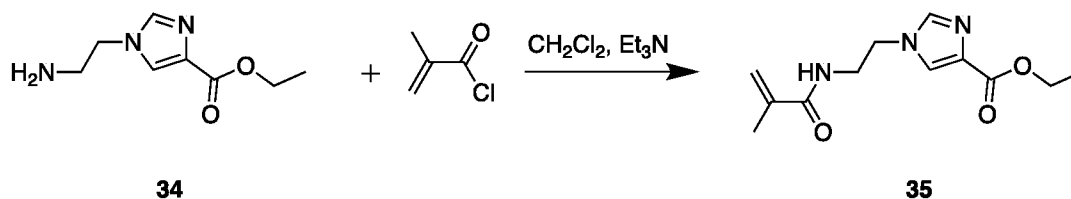
Experimental Procedure for N-(4-(4-((oxetan-3-yloxy)methyl)-1H-1,2,3-triazol-1-yl)benzyl)methacrylamide (33)



A solution of (4-(4-((oxetan-3-yloxy)methyl)-1H-1,2,3-triazol-1-yl)phenyl)methanamine (**32**, 0.58 g, 2.23 mmol, 1.0 eq) and triethylamine (0.47 mL, 3.34 mmol, 1.5 eq) in CH₂Cl₂ (20 mL) were briefly evacuated and flushed with Nitrogen. Methacryloyl chloride (0.32 mL, 3.34 mmol, 1.5 eq) was added in a dropwise fashion. The reaction mixture was stirred for 6 h at room temperature. 10 grams of Celite was added and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (24 g) using Hexanes/EtOAc as eluent starting at 100 % Hexanes and increasing the concentration of EtOAc gradually to 100 % to afford *N*-(4-(4-((oxetan-3-yloxy)methyl)-1H-1,2,3-triazol-1-yl)benzyl)methacrylamide (**33**, 0.48

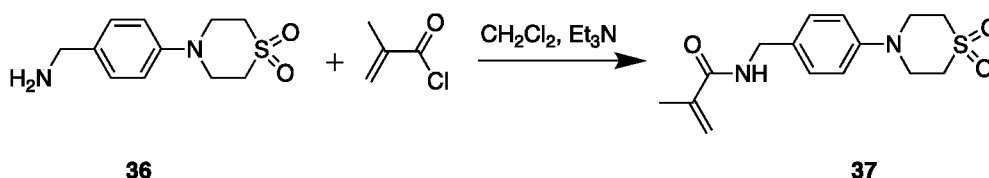
g, 66% yield) as a colorless solid. LCMS m/z: $[M + H]^+$ Calcd for $C_{17}H_{20}N_4O_3$ 329.1608; Found 329.1611.

Experimental Procedure for ethyl 1-(2-methacrylamidoethyl)-1H-imidazole-4-carboxylate (35)



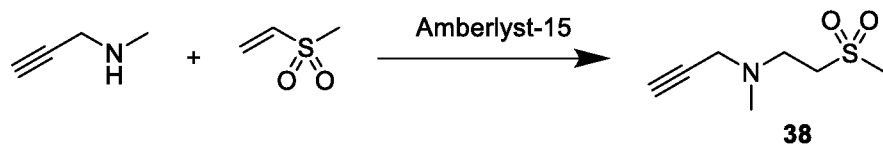
A solution of ethyl 1-(2-aminoethyl)-1H-imidazole-4-carboxylate (**34**, 2.0 g, 10.91 mmol, 1.0 eq) and triethylamine (3.80 mL, 27.29 mmol, 2.5 eq) in CH_2Cl_2 (20 mL) were briefly evacuated and flushed with Nitrogen. Methacryloyl chloride (1.60 mL, 16.37 mmol, 1.5 eq) was added in a dropwise fashion. The reaction mixture was stirred for 3 h at room temperature. 15 grams of Celite was added and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (40 g) using dichloromethane/(methanol containing 12 % (v/v) aqueous ammonium hydroxide) as mobile phase. The concentration of (methanol containing 12 % (v/v) aqueous ammonium hydroxide) was gradually increased from 0 % to 25 % to afford ethyl 1-(2-methacrylamidoethyl)-1H-imidazole-4-carboxylate (**35**, 1.28 g, 47% yield) as a colorless solid. LCMS m/z: $[M + H]^+$ Calcd for $C_{12}H_{17}N_3O_3$ 252.1; Found 252.1.

Experimental Procedure for N-(4-(1,1-dioxidothiomorpholino)benzyl) methacrylamide (37)



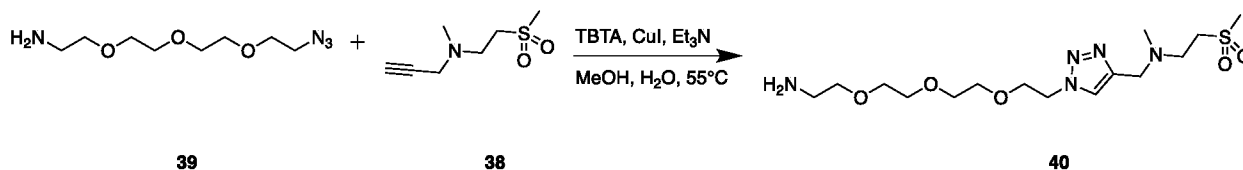
To a solution of 4-(4-(aminomethyl)phenyl)thiomorpholine 1,1-dioxide hydrochloride (**36**, 1.15 g, 4.15 mmol, 1.0 eq) and triethylamine (1.39 mL, 9.97 mmol, 2.4 eq) in CH_2Cl_2 (80 mL) was added a solution of methacryloyl chloride (0.43 mL, 4.36 mmol, 1.05 eq, in CH_2Cl_2 , 5 mL) in a dropwise fashion. The reaction mixture was stirred for 22 h at room temperature. 8 grams of Celite was added and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (80 g) using dichloromethane/(methanol containing 12 % (v/v) aqueous ammonium hydroxide) as mobile phase. The concentration of (methanol containing 12 % (v/v) aqueous ammonium hydroxide) was gradually increased from 0 % to 3.75 % to afford N-(4-(1,1-dioxidothiomorpholino)benzyl) methacrylamide (**37**, 0.32 g, 25% yield) as a solid.

Experimental Procedure for *N*-methyl-*N*-(2-(methylsulfonyl)ethyl)prop-2-yn-1-amine (**38**)



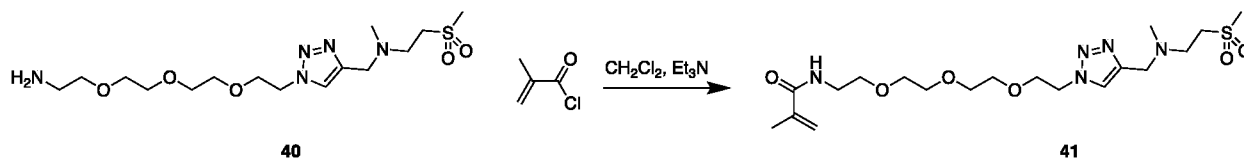
To a mixture of 1-methylsulfonyl-2-methyl-2-propene (4.99 g, 47.03 mmol, 4.13 mL) and Amberlyst-15 ((30% w/w)), *N*-methylprop-2-yn-1-amine (2.6 g, 37.62 mmol) was added in a dropwise fashion. The mixture was stirred at room temperature for 12 hours. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to afford: *N*-methyl-*N*-(2-(methylsulfonyl)ethyl)prop-2-yn-1-amine (**38**, 6.43 g, 98%) as an oil. LCMS *m/z*: [M + H]⁺ Calcd for C₇H₁₃NSO₂ 176.11; Found 176.1.

Experimental Procedure for *N*-((1-(2-(2-(2-(2-aminoethoxy)ethoxy)ethoxy)ethyl)-1*H*-1,2,3-triazol-4-yl)methyl)-*N*-methyl-2-(methylsulfonyl)ethan-1-amine (**40**)



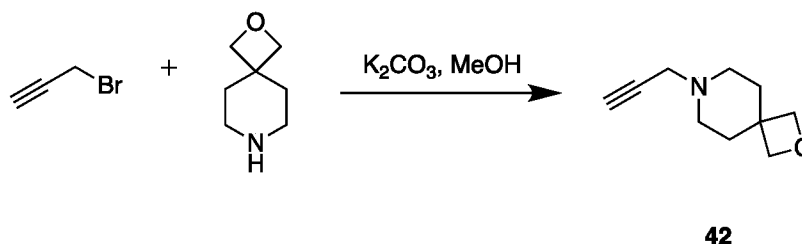
A mixture of *N*-methyl-*N*-(2-(methylsulfonyl)ethyl)prop-2-yn-1-amine (**38**, 5.02 g, 28.64 mmol, 1.25 eq), Tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-amine (3.04 g, 5.73 mmol, 0.25 eq), Copper Iodide (436 mg, 2.29 mmol, 0.1 eq), and Triethylamine (0.8 mL, 5.7 mmol, 0.25 eq) in Methanol (50 mL) and water (6 mL) was evacuated and flushed with Nitrogen (3 times) and cooled with an ice bath. 2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethan-1-amine (**39**, 5.02 g, 22.91 mmol, 1.0 eq) was added in a dropwise fashion, the cooling bath was removed and the mixture was stirred for 5 minutes. The reaction was warmed to 55 °C and stirred over night under Nitrogen atmosphere. The reaction mixture was cooled to room temperature, Celite (20 g) was added, and concentrated under reduced pressure. The crude product was purified over silica gel (220 g) using dichloromethane/(methanol containing 12 % (v/v) aqueous ammonium hydroxide) as mobile phase. The concentration of (methanol containing 12 % (v/v) aqueous ammonium hydroxide) was gradually increased from 0 % to 25 % to afford *N*-((1-(2-(2-(2-(2-aminoethoxy)ethoxy)ethoxy)ethyl)-1*H*-1,2,3-triazol-4-yl)methyl)-*N*-methyl-2-(methylsulfonyl)ethan-1-amine (**40**, 4.98 g, 55 %) as an oil. LCMS *m/z*: [M + H]⁺ Calcd for C₁₅H₃₁N₅O₅S 394.2; Found 394.2.

Experimental Procedure N-(2-(2-(2-(2-(4-((methyl(2-(methylsulfonyl)ethyl) amino)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy) ethyl)methacrylamide (41)



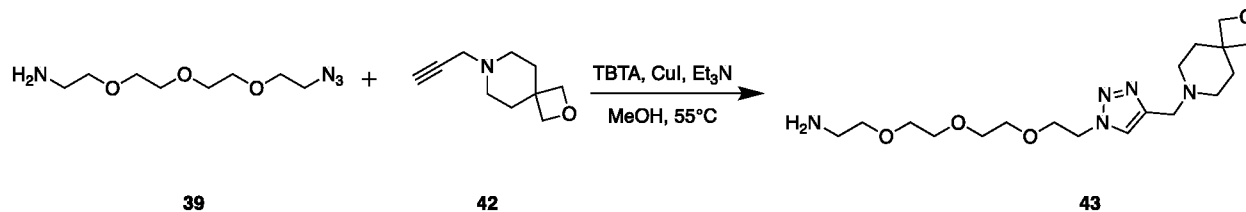
To a solution of *N*-((1-(2-(2-(2-(2-aminoethoxy)ethoxy)ethoxy)ethyl)-1*H*-1,2,3-triazol-4-yl)methyl)-*N*-methyl-2-(methylsulfonyl)ethan-1-amine (**40**, 1.0 g, 2.54 mmol, 1.0 eq) and triethylamine (0.43 mL, 3.05 mmol, 1.2 eq) in CH₂Cl₂ (15 mL) was added a solution of methacryloyl chloride (0.30 mL, 3.05 mmol, 1.5 eq) in a dropwise fashion. The reaction mixture was stirred for 5 h at room temperature. Celite was added and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (40 g) using dichloromethane/(methanol containing 12 % (v/v) aqueous ammonium hydroxide) as mobile phase. The concentration of (methanol containing 12 % (v/v) aqueous ammonium hydroxide) was gradually increased from 0 % to 12.5 % to afford *N*-(2-(2-(2-(2-(4-((methyl(2-(methylsulfonyl)ethyl) amino)methyl)-1*H*-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy) ethyl)methacrylamide (**41**, 0.86 g, 73% yield) as an oil. LCMS *m/z*: [M + H]⁺ Calcd for C₁₉H₃₅N₅O₆S 462.2; Found 462.2.

Experimental Procedure for 7-(prop-2-yn-1-yl)-2-oxa-7-azaspiro[3.5]nonane (42)



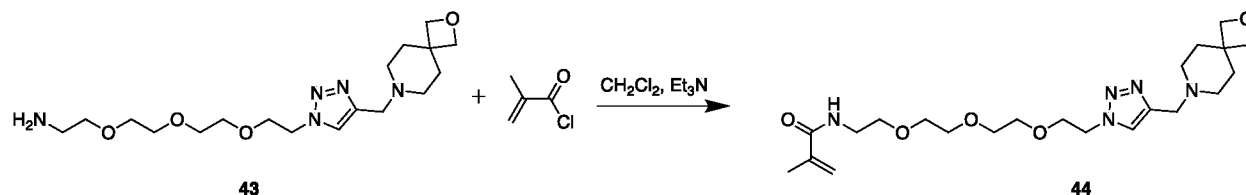
3-Bromoprop-1-yne (4.4 mL, 39.32 mmol 1.0 eq) was added to a mixture of 2-oxa-7-azaspiro[3.5]nonane (8.54 g, 39.32 mmol, 1.0 eq), potassium carbonate (17.9 g, 129.7 mmol, 3.3 eq) in Methanol (200 mL) and stirred over night at room temperature. The mixture was filtered, Celite was added and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (220 g) using dichloromethane/methanol as mobile phase. The concentration of methanol was gradually increased from 0 % to 5 % to afford 7-(prop-2-yn-1-yl)-2-oxa-7-azaspiro[3.5]nonane (**42**, 4.44 g, 68%) as an oil. *Experimental Procedure for 2-(2-(2-(2-*

(4-((2-oxa-7-azaspiro[3.5]nonan-7-yl) methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)ethan-1-amine (43)



A mixture of 7-(prop-2-yn-1-yl)-2-oxa-7-azaspiro[3.5]nonane (**42**, 2.5 g, 15.13 mmol, 1.0 eq), Tris[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl]-amine (1.77 g, 3.33 mmol, 0.22 eq), Copper Iodide (288 mg, 1.51 mmol, 0.1 eq), and Triethylamine (0.53 mL, 3.8 mmol, 0.25 eq) in Methanol (50 mL) was cooled with an ice bath. 2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethan-1-amine (**39**, 3.86 g, 17.70 mmol, 1.17 eq) was added in a dropwise fashion, the cooling bath was removed and the mixture was stirred for 5 minutes. The reaction was warmed to 55 °C and stirred over night under Nitrogen atmosphere. The reaction mixture was cooled to room temperature, Celite (10 g) was added, and concentrated under reduced pressure. The crude product was purified over silica gel (220 g) using dichloromethane/(methanol containing 12 % (v/v) aqueous ammonium hydroxide) as mobile phase. The concentration of (methanol containing 12 % (v/v) aqueous ammonium hydroxide) was gradually increased from 0 % to 10 % to afford for 2-(2-(2-(2-(4-((2-oxa-7-azaspiro[3.5]nonan-7-yl) methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)ethan-1-amine (**43**, 4.76 g, 82 %) as an oil. LCMS m/z: [M + H]⁺ Calcd for C₁₈H₃₃N₅O₄ 384.3; Found 384.2.

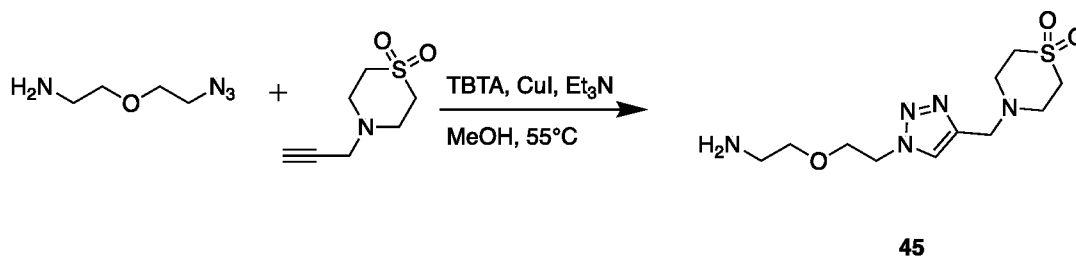
Experimental Procedure for N-(2-(2-(2-(2-(4-((2-oxa-7-azaspiro[3.5]nonan-7-yl) methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)ethyl)methacrylamide (44)



A solution of 2-(2-(2-(2-(4-((2-oxa-7-azaspiro[3.5]nonan-7-yl) methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)ethan-1-amine (**43**, 2.65 g, 6.91 mmol, 1.0 eq) and triethylamine (1.16 mL, 8.29 mmol, 1.2 eq) in CH₂Cl₂ (100 mL) was cooled with an ice-bath under Nitrogen atmosphere. Methacryloyl chloride (0.74 mL, 7.6 mmol, 1.1 eq) was added in a dropwise fashion. The cooling bath was removed and the reaction mixture was stirred for 4 h at room

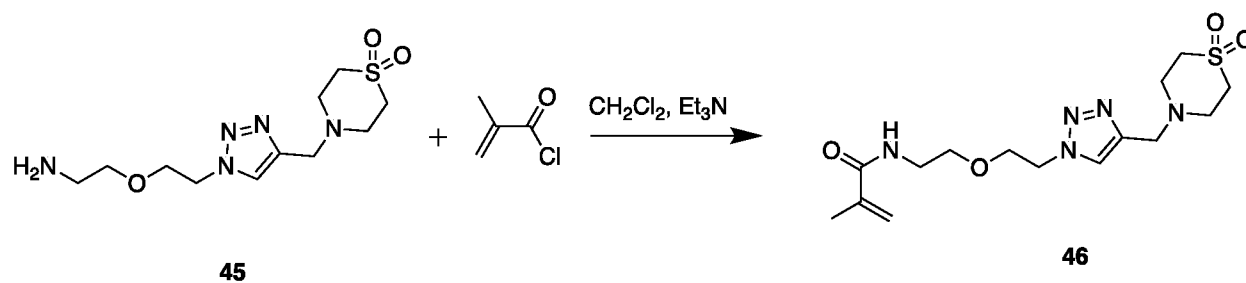
temperature. 10 grams of Celite was added and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (120 g) using dichloromethane/methanol as mobile phase. The concentration of methanol was gradually increased from 0 % to 10 % to afford *N*-(2-(2-(2-(2-(4-((2-oxa-7-azaspiro[3.5]nonan-7-yl)methyl)-1*H*-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)ethyl)methacrylamide (**44**, 1.50 g, 48% yield) as a colorless oil. LCMS m/z : $[M + H]^+$ Calcd for $C_{22}H_{37}N_5O_5$ 452.29; Found 452.25.

*Experimental Procedure for 4-((1-(2-(2-aminoethoxy)ethyl)-1*H*-1,2,3-triazol-4-yl)methyl)thiomorpholine 1,1-dioxide (45)*



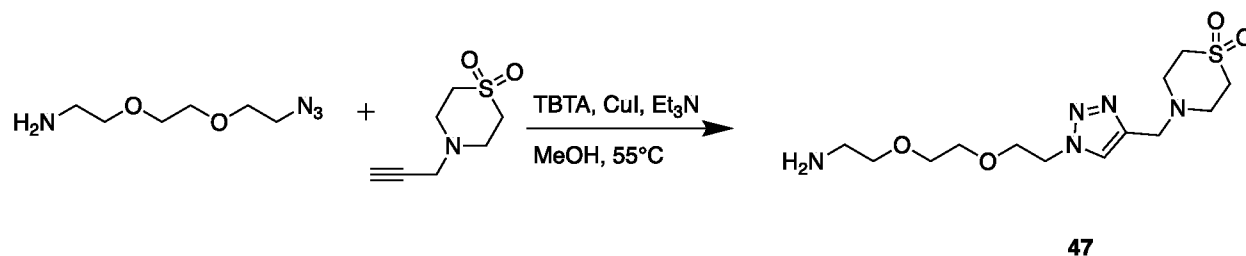
A mixture of 4-(prop-2-yn-1-yl)thiomorpholine 1,1-dioxide (1.14 g, 6.58 mmol, 1.0 eq), Tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-amine (768 mg, 1.45 mmol, 0.22 eq), Copper Iodide (125 mg, 0.66 mmol, 0.1 eq), and Triethylamine (0.23 mL, 1.65 mmol, 0.25 eq) in Methanol (20 mL) was cooled with an ice bath. 2-(2-azidoethoxy)ethan-1-amine (1.00 g, 7.70 mmol, 1.17 eq) was added in a dropwise fashion, the cooling bath was removed and the mixture was stirred for 5 minutes. The reaction was warmed to 55 °C and stirred over night under Nitrogen atmosphere. The reaction mixture was cooled to room temperature, Celite (10 g) was added, and concentrated under reduced pressure. The crude product was purified over silica gel (40 g) using dichloromethane/(methanol containing 12 % (v/v) aqueous ammonium hydroxide) as mobile phase. The concentration of (methanol containing 12 % (v/v) aqueous ammonium hydroxide) was gradually increased from 0 % to 9.5 % to afford for 4-((1-(2-(2-aminoethoxy)ethyl)-1*H*-1,2,3-triazol-4-yl)methyl)thiomorpholine 1,1-dioxide (**45**, 1.86 g, 93 %) as a white solid. LCMS m/z : $[M + H]^+$ Calcd for $C_{11}H_{21}N_5O_4S$ 304.1438; Found 304.1445.

*Experimental Procedure for N-(2-(2-(4-((1,1-dioxidothiomorpholino)methyl)-1*H*-1,2,3-triazol-1-yl)ethoxy)ethyl)methacrylamide (46)*



A solution of 4-((1-(2-(2-aminoethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl)thiomorpholine 1,1-dioxide (**45**, 1.32 g, 4.35 mmol, 1.0 eq) and triethylamine (0.73 mL, 5.22 mmol, 1.2 eq) in CH_2Cl_2 (100 mL) was cooled with an ice-bath under Nitrogen atmosphere. Methacryloyl chloride (0.47 mL, 4.8 mmol, 1.1 eq) was added in a dropwise fashion. The cooling bath was removed and the reaction mixture was stirred for 4 h at room temperature. 10 grams of Celite was added and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (120 g) using dichloromethane/(methanol containing 12 % (v/v) aqueous ammonium hydroxide) as mobile phase. The concentration of (methanol containing 12 % (v/v) aqueous ammonium hydroxide) was gradually increased from 0 % to 1.25 % to afford N-(2-(2-(4-((1,1-dioxidothiomorpholino)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethyl)-methacrylamide (**46**, 0.90 g, 56% yield) as a colorless oil. LCMS m/z: $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{15}\text{H}_{25}\text{N}_5\text{O}_4\text{S}$ 372.17; Found 372.15.

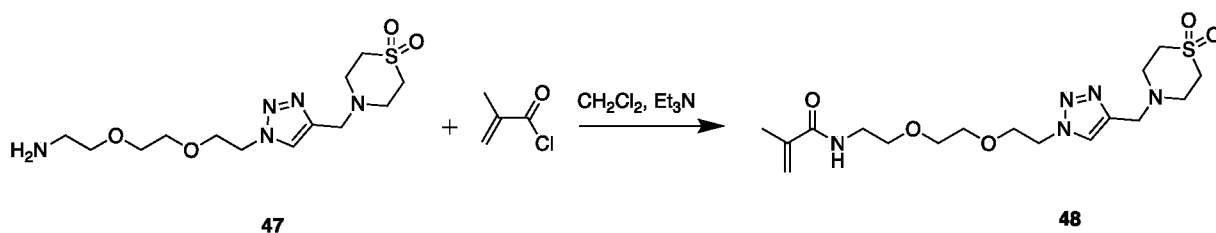
Experimental Procedure for 4-((1-(2-(2-(2-aminoethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl)thiomorpholine 1,1-dioxide (47)



A mixture of 4-(prop-2-yn-1-yl)thiomorpholine 1,1-dioxide (4.6 g, 26.55 mmol, 1.0 eq), Tris[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl]-amine (3.1 g, 5.84 mmol, 0.22 eq), Copper Iodide (506 mg, 2.66 mmol, 0.1 eq), and Triethylamine (0.93 mL, 6.64 mmol, 0.25 eq) in Methanol (80 mL) was cooled with an ice bath. 2-(2-(2-azidoethoxy)ethoxy)ethan-1-amine (5.00 g, 28.68 mmol, 1.08 eq) was added in a dropwise fashion, the cooling bath was removed and the mixture was stirred for 5 minutes. The reaction was warmed to 55°C and stirred over night under Nitrogen atmosphere. The reaction mixture was cooled to room temperature, Celite was added, and

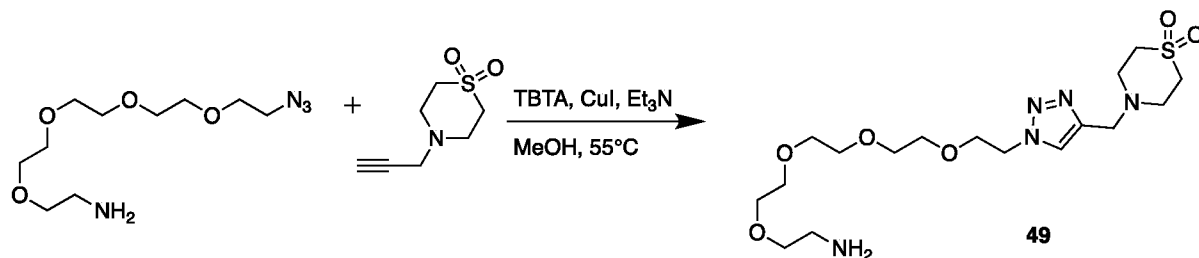
concentrated under reduced pressure. The crude product was purified over silica gel (220 g) using dichloromethane/(methanol containing 12 % (v/v) aqueous ammonium hydroxide) as mobile phase. The concentration of (methanol containing 12 % (v/v) aqueous ammonium hydroxide) was gradually increased from 0 % to 10 % to afford for 4-((1-(2-(2-(2-aminoethoxy)ethoxy)ethyl)-1*H*-1,2,3-triazol-4-yl)methyl)thiomorpholine 1,1-dioxide (**47**, 5.26 g, 57 %) as a yellowish oil. LCMS *m/z*: [M + H]⁺ Calcd for C₁₃H₂₅N₅O₄S 348.1700; Found 348.1700.

Experimental Procedure N-(2-(2-(2-(4-((1,1-dioxidothiomorpholino)methyl)-1*H*-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethyl)methacrylamide (**48**)



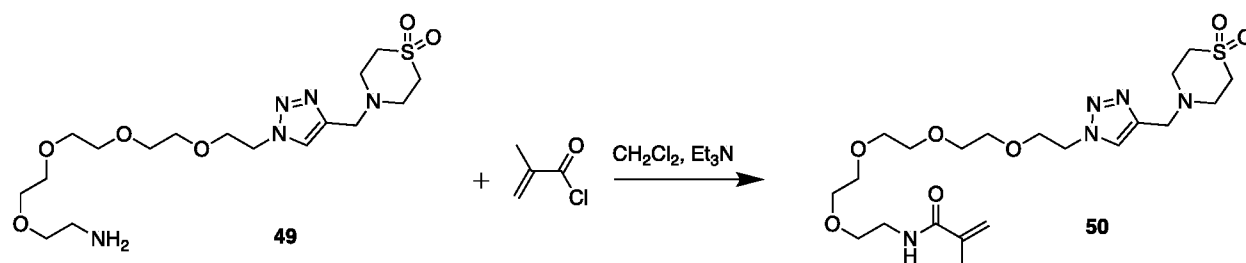
A solution of 4-((1-(2-(2-(2-aminoethoxy)ethoxy)ethyl)-1*H*-1,2,3-triazol-4-yl)methyl)thiomorpholine 1,1-dioxide (**47**, 1.49 g, 4.29 mmol, 1.0 eq) and triethylamine (0.72 mL, 5.15 mmol, 1.2 eq) in CH₂Cl₂ (50 mL) was cooled with an ice-bath under Nitrogen atmosphere. Methacryloyl chloride (0.46 mL, 4.7 mmol, 1.1 eq) was added in a dropwise fashion. The cooling bath was removed and the reaction mixture was stirred for 4 h at room temperature. 10 grams of Celite was added and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (80 g) using dichloromethane/methanol as mobile phase. The concentration of methanol was gradually increased from 0 % to 5 % to afford *N*-(2-(2-(2-(4-((1,1-dioxidothiomorpholino)methyl)-1*H*-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethyl)-methacrylamide (**48**, 0.67 g, 38% yield) as a colorless oil. LCMS *m/z*: [M + H]⁺ Calcd for C₁₇H₂₉N₅O₅S 416.20; Found 416.20.

*Experimental Procedure for 4-((1-(14-amino-3,6,9,12-tetraoxatetradecyl)-1H-1,2,3-triazol-4-yl)methyl)thiomorpholine 1,1-dioxide (**49**)*



A mixture of 4-(prop-2-yn-1-yl)thiomorpholine 1,1-dioxide (5.0 g, 28.86 mmol, 1.0 eq), Tris[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl]-amine (3.37 g, 6.35 mmol, 0.22 eq), Copper Iodide (550 mg, 2.89 mmol, 0.1 eq), and Triethylamine (1.01 mL, 7.22 mmol, 0.25 eq) in Methanol (90 mL) was cooled with an ice bath. 14-azido-3,6,9,12-tetraoxatetradecan-1-amine (8.86 g, 33.77 mmol, 1.17 eq) was added in a dropwise fashion, the cooling bath was removed and the mixture was stirred for 5 minutes. The reaction was warmed to 55 °C and stirred over night under Nitrogen atmosphere. The reaction mixture was cooled to room temperature, Celite (15 g) was added, and concentrated under reduced pressure. The crude product was purified over silica gel (220 g) using dichloromethane/(methanol containing 12 % (v/v) aqueous ammonium hydroxide) as mobile phase. The concentration of (methanol containing 12 % (v/v) aqueous ammonium hydroxide) was gradually increased from 0 % to 10 % to afford 4-((1-(14-amino-3,6,9,12-tetraoxatetradecyl)-1H-1,2,3-triazol-4-yl)methyl)thiomorpholine 1,1-dioxide (**49**, 7.56 g, 60 %) as an oil. LCMS m/z: $[M + H]^+$ Calcd for $C_{17}H_{33}N_5O_6S$ 436.2224; Found 436.2228.

Experimental Procedure N-(14-(4-((1,1-dioxidothiomorpholino)methyl)-1H-1,2,3-triazol-1-yl)-3,6,9,12-tetraoxatetradecyl)methacrylamide (50)



A solution of 4-((1-(14-amino-3,6,9,12-tetraoxatetradecyl)-1H-1,2,3-triazol-4-yl)methyl)thiomorpholine 1,1-dioxide (**49**, 1.95 g, 4.79 mmol, 1.0 eq) and triethylamine (0.80 mL, 5.74 mmol, 1.2 eq) in CH_2Cl_2 (50 mL) was cooled with an ice-bath under Nitrogen atmosphere. Methacryloyl chloride (0.51 mL, 5.26 mmol, 1.1 eq) was added in a dropwise fashion. The cooling bath was removed and the reaction mixture was stirred for 4 h at room temperature. 10 grams of Celite was added and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (80 g) using dichloromethane/methanol as mobile phase. The concentration of methanol was gradually increased from 0 % to 5 % to afford *N*-(14-(4-((1,1-dioxidothiomorpholino)methyl)-1H-1,2,3-triazol-1-yl)-3,6,9,12-tetraoxatetradecyl)methacrylamide (**50**, 0.76 g, 32% yield) as a colorless oil. LCMS m/z: $[M + H]^+$ Calcd for $C_{21}H_{37}N_5O_7S$ 504.25; Found 504.20.

Example 2: Chemical modification of exemplary polymers

A polymeric material may be chemically modified with a compound of Formula (I) (or pharmaceutically acceptable salt thereof) prior to formation of a particle (e.g., a hydrogel capsule described herein). Synthetic protocols of exemplary compounds for modification of polymeric materials are outlined above in Example 1. These compounds, or others, may be used to chemically modify any polymeric material.

For example, in the case of alginate, the alginate carboxylic acid is activated for coupling to one or more amine-functionalized compounds to achieve an alginate modified with an afibrotic compound, e.g., a compound of Formula (I). The alginate polymer is dissolved in water (30 mL/gram polymer) and treated with 2-chloro-4,6-dimethoxy-1,3,5-triazine (0.5 eq) and N-methylmorpholine (1 eq). To this mixture is added a solution of the compound of interest (e.g., Compound 101 shown in Table 2) in acetonitrile (0.3M).

The amounts of the compound and coupling reagent added depends on the desired concentration of the compound bound to the alginate, e.g., conjugation density. A medium conjugation density of Compound 101 typically ranges from 2% to 5% N, while a high conjugation density of Compound 101 typically ranges from 5.1% to 8% N. To prepare a CM-LMW-Alg-101-Medium polymer solution, the dissolved unmodified low molecular weight alginate (approximate MW < 75 kDa, G:M ratio ≥ 1.5) is treated with 2-chloro-4,6-dimethoxy-1,3,5-triazine (5.1 mmol/g alginate) and N-methylmorpholine (10.2 mmol/ g alginate) and Compound 101 (5.4 mmol/ g alginate). To prepare a CM-LMW-Alg-101-High polymer solution, the dissolved unmodified low-molecular weight alginate (approximate MW < 75 kDa, G:M ratio ≥ 1.5) is treated with 2-chloro-4,6-dimethoxy-1,3,5-triazine (10.2 mmol/g alginate) and N-methylmorpholine (20.4 mmol/ g alginate) and Compound 101 (10.8 mmol/ g alginate).

The reaction is warmed to 55°C for 16h, then cooled to room temperature and gently concentrated via rotary evaporation, then the residue is dissolved in water. The mixture is filtered through a bed of cyano-modified silica gel (Silicycle) and the filter cake is washed with water. The resulting solution is then extensively dialyzed (10,000 MWCO membrane) and the alginate solution is concentrated via lyophilization to provide the desired chemically-modified alginate as a solid or is concentrated using any technique suitable to produce a chemically modified alginate solution with a viscosity of 25 cP to 35 cP.

The conjugation density of a chemically modified alginate is measured by combustion analysis for percent nitrogen. The sample is prepared by dialyzing a solution of the chemically modified alginate against water (10,000 MWCO membrane) for 24 hours, replacing the water twice followed by lyophilization to a constant weight.

Example 3: Preparation of exemplary alginate solutions

70:30 mixture of chemically-modified and unmodified alginate. A low molecular weight alginate (PRONOVA™ VLVG alginate, NovaMatrix, Sandvika, Norway, cat. #4200506, approximate molecular weight < 75 kDa; G:M ratio ≥ 1.5) was chemically modified with Compound 101 in Table 2 to produce chemically modified low molecular weight alginate (CM-LMW-Alg-101) solution with a viscosity of 25 cp to 35 cP. A solution of high molecular weight unmodified alginate (U-HMW-Alg) was prepared by dissolving unmodified alginate (PRONOVA™ SLG100, NovaMatrix, Sandvika, Norway, cat. #4202106, approximate molecular weight of 150 kDa – 250 kDa) at 3% weight to volume in 0.9% saline. The CM-LMW-Alg solution was blended with the U-HMW-Alg solution at a volume ratio of 70% CM-LMW-Alg to 30% U-HMW-Alg (referred to herein as a 70:30 CM-Alg:UM-Alg solution).

Unmodified alginate control solution. An unmodified medium molecular weight alginate (SLG20, NovaMatrix, Sandvika, Norway, cat. #4202006, approximate molecular weight of 75-150 kDa), was dissolved at 1.4% weight to volume in 0.9% saline to prepare a U-MMW-Alg solution.

Example 4: Culturing exemplary cells for encapsulation as single cells

4A. ARPE-19 cells. These RPE cells were cultured and subsequently encapsulated in one-compartment or two-compartment hydrogel millicapsules. ARPE-19 cells may be cultured according to any method known in the art, such as according to the following protocol. ARPE-19 cells in a 75 cm² culture flask were aspirated to remove culture medium, and the cell layer was briefly rinsed with 0.05% (w/v) trypsin/ 0.53 mM EDTA solution (“TrypsinEDTA”) to remove all traces of serum containing a trypsin inhibitor. 2-3 mL Trypsin/EDTA solution was added to the flask, and the cells were observed under an inverted microscope until the cell layer was dispersed, usually between 5-15 minutes. To avoid clumping, cells were handled with care and hitting or shaking the flask during the dispersion period was minimized. If the cells did not

detach, the flasks were placed at 37 °C to facilitate dispersal. Once the cells dispersed, 6-8 mL complete growth medium was added and the cells were aspirated by gentle pipetting. The cell suspension was transferred to a centrifuge tube and spun down at approximately 125 x g for 5-10 minutes to remove TrypsinEDTA. The supernatant was discarded, and the cells were re-suspended in fresh growth medium. Appropriate aliquots of cell suspension was added to new culture vessels, which were incubated at 37 °C. The medium was renewed 2-3 times weekly.

4B. HEK293F cells. These cells, marketed as FreeStyle™ 293 F (Thermo Fisher Scientific, Waltham, MA, USA) were grown in suspension using a 125 ml Erlenmeyer flask with a working volume of 25 ml of FreeStyle 293 Expression Medium. Flasks were incubated at 37 °C on a shaker plate set for 125 RPM. Cells were grown to a density between 2 and 3x10⁶ cells/ml at which time the cells are re-seeded to a density between 2 and 3x10⁵ cells/ml, typically every 3-4 days. To avoid clumping, cells were handled with care, placed into a 50ml falcon tube and vortexed for 5-10 seconds to maximize cell homogeneity. After counting the cell density, appropriate aliquots of cell suspension was added to new culture vessels.

Example 5: Preparation of cell clusters for encapsulation

Spheroid clusters of exemplary cells (e.g., ARPE-19 cells) are prepared using AggreWell™ spheroid plates (STEMCELL Technologies) and the protocol outlined herein. On Day 1, rinsing solution (4 mL) is added to each plate, and the plates is spun down for 5 minutes at 3,000 RPM in a large centrifuge. The rinsing solution is removed by pipet, and 4 mL of the complete growth medium is added. The ARPE-19 cells are seeded into the plates at the desired cell density and pipetted immediately to prevent aggregation, with the general rule of thumb that 3.9 million cells per well will generate 150 µm diameter clusters. The plate is spun down for 3 minutes at 800 RPM, and the plate is placed into an incubator overnight.

On Day 2, the plate is removed from incubation. Using wide bore pipet tips, the cells are gently pipetted to dislodge the spheroid clusters. The clusters are filtered through a 40 µm or 80 µm cell strainer to remove extraneous detached single cells and then spun down in a centrifuge for 2 x 1 minute. The clusters are resuspended gently using wide bore pipet tips and are gently stirred to distribute them throughout the medium or another material (e.g., alginate).

Alternatively, ARPE-19 spheroids are prepared using the following protocol. On Day 1, AggreWell™ plates are removed from the packaging in a sterile tissue culture hood. 2 mL of

Aggrewell™ Rinsing solution is added to each well. The plate is centrifuged at 2,000 g for 5 minutes to remove air bubbles, and the AggreWell™ Rinsing Solution is removed from the wells. Each well is rinsed with 2 mL of the complete growth medium, and 2 million ARPE-19 cells in 3.9 mL of the complete growth medium is added to each well. The plate is centrifuged at 100 g for 3 minutes, then the cells are incubated the cells at 37° C for 48 hours. On Day 3, the same protocol described above is used to dislodge the spheroid clusters.

Example 6: Formation of one-compartment and two-compartment hydrogel capsules

Suspensions of single cells (ARPE-19 cells or HEK293F cells as described in Example 4) were encapsulated in one-compartment or two-compartment hydrogel capsules according to the protocols described below.

Immediately before encapsulation, single cells were centrifuged at 1,400 r.p.m. for 1 min and washed with calcium-free Krebs-Henseleit (KH) Buffer (4.7 mM KCl, 25 mM HEPES, 1.2 mM KH₂PO₄, 1.2 mM MgSO₄ × 7H₂O, 135 mM NaCl, pH ≈ 7.4, ≈290 mOsm). After washing, the cells were centrifuged again and all of the supernatant was aspirated. In some experiments, the cell pellet was then resuspended in the 70:30 CM-Alg:UM-Alg solution described in Example 3 at a range of densities of suspended single cells per ml alginate solution. In some experiments, cells were used directly without suspension (e.g, dilution) in the alginate solution (“undiluted cells”).

Prior to fabrication of one-compartment and two-compartment hydrogel capsules, buffers and alginate solutions were sterilized by filtration through a 0.2-μm filter using aseptic processes.

To prepare particles configured as two-compartment hydrogel millicapsules of about 1.5 mm diameter, an electrostatic droplet generator was set up as follows: an ES series 0–100-kV, 20-watt high-voltage power generator (EQ series, Matsusada, NC, USA) was connected to the top and bottom of a coaxial needle (inner lumen of 22G, outer lumen of 18G, Ramé-Hart Instrument Co., Succasunna, NJ, USA). The inner lumen was attached to a first 5-ml Luer-lock syringe (BD, NJ, USA), which was connected to a syringe pump (Pump 11 Pico Plus, Harvard Apparatus, Holliston, MA, USA) that was oriented vertically. The outer lumen was connected via a luer coupling to a second 5-ml Luer-lock syringe which was connected to a second syringe pump (Pump 11 Pico Plus) that was oriented horizontally. When preparing two-compartment capsules that encapsulate cells only in the inner compartment, a first alginate solution comprising

the cells (as single cell suspension) was placed in the first syringe and a second alginate solution lacking cells was placed in the second syringe. The two syringe pumps move the first and second alginate solutions from the syringes through both lumens of the coaxial needle and single droplets containing both alginate solutions are extruded from the needle into a glass dish containing a cross-linking solution. The settings of each Pico Plus syringe pump were 12.06 mm diameter and the flow rates of each pump were adjusted to achieve various test flow rates in the Examples below, but keeping the total flow rate set at 10ml/h.

For fabrication of one-compartment hydrogel capsules of about 1.5 mm diameter, the 70:30 CM-Alg:UM-Alg solution described in Example 3 (with or without a suspension of single cells) was loaded into a syringe and capped with an 18-gauge blunt tipped needle (SAI Infusion Technologies). The syringe was placed into a syringe pump oriented vertically above a dish containing the crosslinking buffer. A high voltage power generator was connected to the needle and grounded to the biosafety cabinet. The syringe pump and power generator were turned on to extrude the alginate solution through the needle with a flow-rate of 0.16 mL/min or 10 mL/hr and adjusting the voltage in a range of 5–9 kV until there was a droplet rate of 12 droplets per 10 seconds.

For fabrication of both the two-compartment and one-compartment millicapsules, after extrusion of the desired volumes of alginate solutions, the alginate droplets were crosslinked for five minutes in a cross-linking solution which contained 25mM HEPES buffer, 20 mM BaCl₂, and 0.2M mannitol. In some experiments, the cross-linking solution also contained 0.01% of poloxamer 188. Capsules that had fallen to the bottom of the crosslinking vessel were collected by pipetting into a conical tube. After the capsules settled in the tube, the crosslinking buffer was removed, and capsules were washed. Capsules without cells were washed four times with HEPES buffer (NaCl 15.428 g, KCl 0.70 g, MgCl₂·6H₂O 0.488 g, 0 ml of HEPES (1 M) buffer solution (Gibco, Life Technologies, California, USA) in 2 liters of deionized water) and stored at 4 °C until use. Capsules encapsulating cells were washed four times in HEPES buffer, two times in 0.9% saline, and two times in culture media and stored in an incubator at 37°C.

In some experiments, the quality of capsules in a composition of two-compartment or one-compartment capsules was examined. An aliquot containing at least 200 capsules was taken from the composition and transferred to a well plate and the entire aliquot examined by optical microscopy for quality by counting the number of spherical capsules out of the total.

In some experiments, the mechanical strength of capsules in a composition of two-compartment capsules was examined using a texture analyzer to determine the initial fracture force as described herein above.

Example 7. Assessing the effect of cell loading on capsule quality

Capsule compositions (comprising two-compartment capsules or one-compartment capsules) were prepared as described in Example 6 using the 70:30 CM-Alg:UM-Alg solution described in Example 3 and various loading amounts of cells in the alginate solution used to form the first (inner) compartment. The cross-linking solution included 0.01% poloxamer 188. Two-compartment capsules (1.5 mm diameter) with equal volume first and second compartments formed from the 70:30 alginate solution were prepared using a flow rate of 5 ml/hour for the alginate solutions in each of the first and second syringes. In addition, a composition of two-compartment, 1.5 mm capsules was prepared in substantially the same manner except the inner compartment was formed using undiluted cells (concentration equiv. to 500 million cells/ml) in the first syringe (e.g., no alginate solution.) Engineered ARPE19 cells expressing Factor VIII were encapsulated at 10-50 million cells/ml alginate solution in one-compartment capsules or 10-500 million cells/ml alginate solution (concentration equiv. to one-compartment capsules) in 2-compartment capsules. The different capsule compositions were examined for quality and the results are shown in Figure 3.

For the one-compartment millicapsules, it was generally observed that capsule quality (i.e., spherical shape) decreased as cell loading increased. Quality of compositions comprising one-compartment millicapsules was below the acceptable threshold of 95% spherical particles in the examined aliquot at cell loadings greater than 20 million cells/ml alginate. Compositions comprising two-compartment millicapsules had very high spherical quality up to a loading cell amount of undiluted cells equivalent to 500 million cells/ml alginate solution, which is about a 25x higher cell loading capacity than the highest acceptable cell loading capacity for the one-compartment particles. For this particular configuration of 70:30 CM-Alg:UM-Alg and capsule size, a cell loading equivalent to 500 million cells/ml alginate solution appears to be the upper loading limit for the first (inner) compartment. Therefore, the two-compartment millicapsules permitted encapsulation of a significantly greater number of cells without affecting the spherical morphology of the capsules.

Example 8: Altering the effect of flow rate ratio on the thickness of the second compartment

Compositions containing two-compartment hydrogel millicapsules (about 1.5mm in diameter) were prepared with a 70:30 mixture of CM-Alg:U-Alg in both compartments. The combined flow rates of alginate solutions through the outer and inner lumens was held constant at 10ml/h, while the ratio of these flow rates was varied to prepare capsules with varying compartment thicknesses. To visualize the compartments in the resulting capsules, ARPE19-FVIII cells were encapsulated at 20 million cells/ml alginate solution in the first (inner) compartment. Compartment thickness was measured via image analysis.

By changing the outer:inner lumen flow rate ratio, the mean thickness of the second (outer) compartment of a 1.5mm two-compartment capsule was varied from 11-267 microns as shown in Figures 4A-4B. In all cases, spherical capsules of about 1.5 mm were formed. The smallest second (outer) compartment created was about 11 microns in diameter, and increasing the ratio of outer:inner lumen flow rates increased the second (outer) compartment thickness from about 11 microns to a maximum of 267 microns. Therefore, the second (outer) compartment thickness of hydrogel capsules may be altered by varying inner and outer flow rates to generate a composition of uniform spherical millicapsules.

Example 9: Effect of varying the composition and size of the first compartment on the mechanical properties of particles

Compositions of two-compartment hydrogel millicapsules were prepared by extruding first and second alginate solutions through a coaxial needle as described in Example 6. The second (outer) compartment was prepared using the 70:30 CM-Alg:U-Alg solution described in Example 3 and the first (inner) compartment was prepared using the U-HMW-Alg solution described in Example 3. While keeping the total (e.g., combined) flow rate at 10ml/h, the inner:outer flow rate ratios (I:O) were varied from 1 ml to 9 ml per hour and 9 ml to 1 ml per hour to produce millicapsules with different inner and outer compartment thicknesses. Control capsule compositions were also prepared. One control contained one-compartment capsules made from the same 70:30 CM-Alg:U-Alg solution. A second control composition contained one-compartment capsules made from the same U-HMW-Alg solution. Mechanical testing was

performed on aliquots from each of the compositions using a texture analyzer to measure initial fracture of individual capsules.

Two-compartment capsules of about 1.5mm in diameter were created in all conditions. One-compartment capsules prepared from the 70:30 mixture had the lowest initial fracture compared to all of the two-compartment capsule configurations. The mechanical strength of two-compartment capsules with an inner compartment of U-HMW-Alg increased with increasing volume fraction of the inner compartment to the entire capsule (see FIG. 5). Capsules in the second control composition (one-compartment U-HMW-Alg capsules) had higher initial fracture than all two-compartment particles with inner and outer compartments composed of U-HMW-Alg and 70:30 CM-Alg:U-Alg, respectively. As the volume fraction of the inner compartment (U-HMW-Alg) increased, mean initial fracture increased. Therefore, changing the configuration of the inner compartment (identity of the alginate and / or thickness) of a 2-compartment millicapsule can alter its mechanical properties. Thus, 2-compartment hydrogel millicapsules can present the same capsule surface with respect to chemical modification (e.g., to mitigate FBR) but have stronger mechanical strength by changing the alginate composition in the first (inner) compartment.

Example 10: Preparation of two-compartment hydrogel capsules with varying amounts of chemical modification in the 2nd (outer) compartment

Chemically modified alginate solutions were prepared with varying amounts of conjugation of compound 101. Polymers were prepared with low (2.03% N), medium (4.42% N), or high (6.72% N) levels of compound 101 conjugation, where % nitrogen is determined by combustion analysis and corresponds to the amount of small molecule conjugated to the polymer. Compositions of two-compartment hydrogel millicapsules were prepared as follows. The outer compartment was formed using (i) a solution containing one of these conjugated polymers blended with U-HMW-Alg at a 70:30 ratio of CM-Alg-101 to U-HMW-Alg or (ii) the U-MMW-Alg solution described in Example 3 as a control. The inner compartment was formed using a solution containing the medium CM-Alg-101 conjugation blended with U-HMW-Alg. The inner and outer flow rates were both 5ml/h. To visualize the first (inner) compartment, 20 million ARPE19-FVIII cells/ml alginate solution were encapsulated in the first (inner) compartment of the capsule.

FIGS. 6A-6D show the capsules created with low, medium, high conjugation CM-Alg polymers or the control (unmodified) polymer in the second (outer) compartment. Compositions of spherical, uniform millicapsules of about 1.5 mm in diameter were formed regardless of which CM-A polymer solution was used to form the outer compartment, demonstrating that high quality capsules can be prepared with the same polymer used in the first (inner) compartment and varying amounts of chemical modification in the second (outer) compartment.

Example 11: Effect of varying the level of chemical modification in the second compartment on biocompatibility

The hydrogel capsules prepared in Example 10 were examined for fibrosis *in vivo* by implanting the capsules into the IP space of C57/BL6 mice for one week. In this mouse model, encapsulated xenogeneic cell lines, such as human RPE cells, generally induce a fibrotic response. At retrieval, particles were imaged for the presence of fibrosis, and initial fracture measured using a texture analyzer. The results are shown in FIGS. 7A-7F.

Upon retrieval, the empty capsules (no cells) had no visible fibrosis (FIG. 7D). Control capsules (U-MMW-Alg outer compartment) had fibrotic buildup surrounding the particles (FIG. 7E). For capsules with a CM-Alg-101 in the outer compartment, a fibrotic response was only observed on the low conjugation CM-Alg capsules (FIG. 7A), with minimal fibrosis observed on the medium and high conjugation CM-Alg capsules (FIGS. 7B-7C). Initial fracture was measured prior to implantation and at retrieval, and all 2-compartment capsules had similar initial fracture at each time point (FIG. 7F). Therefore, altering the chemical modification profile only on the second (outer) compartment of the capsule may be used to modulate an afibrotic property, i.e., increasing the concentration of a compound of Formula I in the outer compartment can substantially reduce fibrosis without affecting mechanical strength.

Example 12: Effect of varying the level of chemical modification in the second compartment on macrophage adhesion over time

The degree of mouse macrophage adhesion *in vivo* over 1-4 weeks on hydrogel capsules with varying amounts (low, medium, or high) of chemical modification in the second (outer) compartment was examined as follows. Capsules were prepared as described in Example 10, and implanted in C57/BL6 mice as in Example 11, then retrieved at 1, 2, and 4 weeks post-

implantation. At retrieval, particles were imaged for the presence of mouse macrophages using immunofluorescent staining (anti-F4/80). The results are shown in FIGS. 9A-9K.

After 1 week of implantation, macrophage adhesion was observed on the positive control capsules (unmodified medium molecular weight alginate) and the low conjugation capsules (FIGS. 9A-9B). Some macrophage adhesion was observed on the medium conjugation capsules (FIG. 9C), and there was minimal macrophage adhesion on the high conjugation (FIG. 9D), or empty capsules (FIG. 9E). At 2 and 4 weeks post-implantation, there was no macrophage adhesion on the empty capsules (FIGS. 9H and 9K), and macrophage adhesion was higher on the medium conjugation capsules (FIGS. 9F and 9I), compared to the high conjugation capsules (FIGS. 9G and 9J), demonstrating a dose response between the level of chemical modification in the second (outer) compartment of the capsule and macrophage adhesion (fibrosis) *in vivo*.

Example 13: Effect of varying the level of chemical modification in the second compartment on fibrosis

The level of chemical modification in the second (outer) compartment of exemplary particles was investigated for its impact on fibrosis using the method described below. The low, medium, and high conjugation capsules prepared in Example 10 were used. Additionally, medium-high (4.79% N) and double-high (9.00% N) conjugation capsules were prepared using methods described in Example 10, where % nitrogen is determined by combustion analysis and corresponds to the amount of small molecule conjugated to the polymer. The capsules were then implanted in C57/BL6 mice as described in Example 11, and retrieved at 2 weeks post-implantation. Fibrosis of the retrieved capsules was analyzed with brightfield imaging, where an opaque layer around the capsule indicates fibrosis. The results are shown in FIGS. 10A-10E.

Empty capsules with medium conjugation were used as a control, and showed no fibrosis (FIG. 10A). Capsules with medium conjugation or medium-high conjugation showed higher levels of fibrosis (FIGS. 10B-10C), compared with the high-conjugation capsules (FIG. 10D). Many of the double high conjugation capsules were not intact spheres after retrieval, some appeared fibrosed, or reduced in size, and there was significant capsule debris (FIG. 10E). This suggests that the second (outer) compartment containing the high levels of a compound of Formula (I) was not intact, demonstrating that there is an upper limit to the amount of a compound of Formula (I) that can effectively resist fibrosis.

Example 14: Effect of varying the level of chemical modification in the second compartment on mechanical strength

The mechanical strength of the capsules used in Example 13 were measured by initial fracture using a texture analyzer. Each of the control, medium, medium high, high, and double high conjugated capsules were tested for mechanical strength at both pre- and post-implantation stages. The results are shown in FIG. 11.

Initial mechanical strength was higher in the control (empty) capsules compared to cell-loaded capsules. The medium, medium-high, and high conjugation capsules had similar strength at both pre- and post-implantation, with a decrease in strength observed after implantation. The capsules with the highest level of conjugation (double high) were the weakest capsules, and most of these capsules were not intact at retrieval (FIG. 11), as noted in Example 13. This further demonstrates that there is an upper limit to the amount of afibrotic small molecule conjugation that is efficacious, as very high levels of conjugation compromise mechanical strength.

Example 15: Effect of covalent and non-covalent chemical modification of the second (outer) compartment on fibrosis

The difference between conjugated or non-conjugated compounds of Formula (I) in the second (outer) compartment of hydrogel capsules as a means to confer resistance to fibrosis was determined using the following experiment.

Capsules with medium and high amounts of compounds of Formula (I) were prepared as in Example 10. In addition, a third type of capsule featuring non-conjugated afibrotic small molecules (denoted “amine added back”) was prepared in a similar manner to the method of Example 10, where the second (outer) compartment of the capsule was made from alginate solution containing unconjugated compounds of Formula (I). This solution was prepared by adding unconjugated small molecule to a medium conjugation alginate solution, using an amount of unconjugated small molecule necessary to achieve an overall amount of compounds of Formula (I) equivalent to the high conjugation alginate solution. The 70:30 CM-Alg:U-Alg was used for the first (inner) compartment of the “amine added back” capsules. All capsules were then implanted *in vivo* using C57/BL6 mice as in Example 11, and were retrieved at 2 weeks post-implantation. Retrieved capsules were imaged with brightfield microscopy to detect the

presence of an opaque outer layer of adhered cells, indicating the beginning of fibrosis. The results are shown in FIGS. 12A-12C.

There was a layer of adhered cells observed on the medium conjugation capsules (FIG. 12A), while only minimal adhesion to the high conjugation capsules was observed (FIG. 12B). The “amine added back” capsules also appeared opaque, indicating a layer of fibrotic cell adhesion on the capsule (FIG. 12C). Therefore, this data demonstrates that only conjugated small molecules contribute to the afibrotic properties of the capsules.

Example 16: Effect of varying level of small molecule conjugation and polymer blend ratio in the second compartment on macrophage adhesion

Capsules prepared from alginate solutions of two polymer blends (containing different ratios of low molecular weight alginate (CM-LMW) to unmodified high molecular weight alginate (U-HMW)), and varying amounts (medium, medium high, or high) of compounds of Formula (I) were compared in terms of their fibrosis resistance *in vivo* with the following experiment.

Three polymer blends were prepared at a 70% CM-LMW-Alg to 30% U-HMW-Alg ratio (70:30) as described in Example 3, with medium, medium high, or high levels of compounds of Formula (I). An additional three polymer blends were also prepared at a 60% CM-LMW-Alg to 40% U-HMW-Alg ratio (60:40), again with medium, medium high, or high levels of compounds of Formula (I). Each polymer blend was then used to form the second (outer) compartment of capsules using the method described in Example 10, providing a set of six hydrogel capsules, featuring medium, medium-high, or high-levels of conjugation from either 70:30 or 60:40 ratio polymer blends. The inner compartments of all the capsules contained the 70:30 CM-Alg:U-Alg solution. The capsules were then implanted *in vivo*, as described in Example 11, and were retrieved at 1 week post-implantation and analyzed via immunofluorescent staining for mouse macrophages adhesion (fibrosis) on the capsules. The results are shown in FIGS. 13A-13F

A trend of decreasing levels of adhered macrophages was observed from the medium to high conjugated capsules, across both the 70:30 (FIGS. 13A-13C) and the 60:40 ratio blends (FIGS. 13D-13F). Also, a larger amount of adhered macrophages was observed in the 60:40 ratio blend capsules, compared with the relatively lower amount of macrophage adhesion in the capsules from the 70:30 ratio blend. As the change in ratio affects the total dose of small

molecules on the capsule, the results infer that the amount of small molecule conjugated to the polymer and the amount of chemically modified polymer used to prepare the capsules can independently alter macrophage adhesion and fibrosis.

Example 17: Comparison of capsule architecture on the fibrotic response

Compositions of one-compartment or two-compartment hydrogel millicapsules encapsulating single ARPE-19 cells expressing FVIII-BDD were prepared by extruding droplets of the 70:30 CM-Alg:U-Alg solution described in Example 3 with various cell loading concentrations into a crosslinking solution. One-compartment capsules with either no cells or 5000 cells dispersed throughout the entire capsule were prepared as the controls. The two-compartment capsules had a cell-free second (outer) compartment and a first (inner) compartment containing 5000 or 2500 cells per capsule. Capsules with 2500 and 5000 cells were prepared using an outer:inner volume ratio of 50%:50%. Capsules with 2500 cells and a thicker second (outer) compartment were prepared using an outer:inner volume ratio of 75%:25%. The capsules were implanted into the IP space of C57/BL6 mice at 0.5ml capsules/mouse. Capsules were retrieved after 14 days and imaged to observe presence or absence of fibrosis. In this mouse model, the xenogeneic ARPE-19 cells in the capsule were expected to induce a FBR.

The results of this experiment showed that all capsules encapsulating ARPE-19 cells, fabricated with either one or two compartments, were fibrosed in the C57/BL6 mouse model (data not shown). No fibrosis was observed on the empty one-compartment control capsules. Thus, in C57/BL6 mice, the configuration of capsules as one-compartment or two-compartments had no apparent effect on FBR induced by the xenogeneic RPE cells.

Example 18: Assessing cell proliferation in exemplary particles configured as two-compartment hydrogel capsules

HEK293F cells, which grow in suspension, were encapsulated within the inner compartment of two-compartment hydrogel millicapsules of about 1.5 mm in diameter. The capsules were prepared using the 70:30 CM-Alg:U-MW-Alg solution described in Example 3 to form both inner and outer compartments. The cell loading concentration in the inner compartment was 20 million HEK293F cells/ml (equivalent of 10 million cells/ml alginate solution in a 1.5 mm one-compartment capsule). Two-compartment capsules were fabricated

using 5ml/h inner and outer flow rates. As a control, one-compartment capsules of about 1.5 mm diameter were prepared using the same 70:30 CM-Alg:U-MW-Alg alginate solution comprising 10 million HEK293F cells/ml. Capsules were incubated at 37 °C, 5% CO₂ for 7 days and then observed by microscopy.

Observation of the capsule edges revealed the presence of cells protruding from the edges of the one-compartment capsules, but not the two-compartment capsules, after one week of culture (FIGS. 14A-9B). Free floating and adhered cells were observed on the surface of the tissue culture plate containing the one-compartment capsules, demonstrating incomplete encapsulation and / or escape of cells (FIG. 14C). In contrast, no cells were observed outside of the two-compartment capsules in the culture plate after one week of culture (FIG. 14D). Similar results were obtained when one-compartment and two-compartment capsules were prepared with ARPE19 cells instead of HEK293F cells (data not shown). Thus, the two-compartment capsules are more effective than one-compartment capsules in containing cells, e.g., without cell leakage or protrusion through the capsule surface.

Example 19: Assessing protein release from one- and two-compartment capsules

To determine if protein molecules expressed by encapsulated cells can be released from two-compartment hydrogel capsules, engineered ARPE19 cells expressing FVIII-BDD were encapsulated in two-compartment capsules and protein secretion was measured after 24 hours.

The capsules were prepared using the 70:30 CM-alg:U-HMW-Alg solution described in Example 3 in each of the first and second syringes and 5 ml/h inner and outer flow rates. The alginate solution to prepare the inner compartment also contained ARPE19-FVIII at 20, 50 or 100 million cells/ml. Capsules were incubated for 24h at 37 °C in a known volume of medium, and medium supernatant was collected and FVIII was detected by FVIII ELISA.

After 24h, FVIII was detected in medium supernatant samples for each cell loading concentration. An increasing trend between cell loading concentration and amount of FVIII detected from the 2-compartment particles was observed (data not shown). These results suggest that FVIII expressed by cells encapsulated in the inner compartment of a two-compartment capsule diffuses through the second compartment and then exits the capsule.

Example 20. Cell concentration in capsules can be increased to increase FIX levels in plasma and IP fluid of nude mice

Compositions of two-compartment hydrogel millicapsules (1.5 mm) encapsulating single ARPE-19:FIX cells were prepared by extruding droplets of the 70:30 CM-Alg:U-Alg solution described in Example 3 with various cell loading concentrations into a crosslinking solution. Cells were encapsulated at 2, 20, 100, 300 million cells/ml alginate in the inner compartment (equivalent of 1, 10, 50, 150 million cells/ml alginate solution in a 1.5mm one-compartment capsule). Capsules were implanted into the IP space of nude mice (0.5ml/mouse) and were retrieved after 5 days. Levels of FIX in the plasma and IP fluid was measured by ELISA.

By varying the encapsulated cell concentration, the total number of encapsulated cells was varied from 500 to 39,000 cells/capsule as shown in FIG. 15A. At all cell concentrations, capsules were created with spherical morphology (data not shown). Some proliferation of cells was observed during implant (FIG. 15A). The levels of FIX in the plasma and IP fluid increased with increasing cell concentration, with the exception of 2 million cells/ml, which was at the lower limit of detection of the ELISA assay (FIG 15. B, C and data not shown). There was an approximately 10-fold increase in FIX levels in the IP fluid, where the capsules are in the local environment, compared to the plasma. Capsules at all cell concentrations were retrieved intact (data not shown). Therefore, a dose response for FIX expression in both the IP and plasma was observed between 2 and 300 M cells/ml alginate solution used to form the inner compartment. In addition, the successful encapsulation of 39,000 cell/capsule is significantly greater than what has been reported in the scientific literature.

Example 21: Optimal cell concentration maximized FIX levels and maintained capsule integrity

Compositions of two-compartment hydrogel millicapsules encapsulating single ARPE-19:FIX cells were prepared as in the previous examples, with cells encapsulated at 100, 200, 300 and 646 million cells/ml of the alginate solution used to form the inner compartment (equivalent of 50, 100, 150, 323 million cells/ml alginate solution in a 1.5mm one-compartment capsule). Capsules were implanted into the IP space of nude mice (0.5ml/mouse) and were retrieved after 4 weeks. Levels of FIX in the IP fluid was measured by ELISA.

By varying the encapsulated cell concentration, the total number of encapsulated cells was varied from 24,000 to 54,000 cells/capsule (data not shown). At all cell concentrations, capsules were created with spherical morphology (data not shown). The levels of FIX in the IP fluid

increased with increasing cell concentration to 150 million cells/ml (FIG 16A). At the highest loading cell concentration (646 million cells/ml), the FIX levels were low and the retrieved capsules were no longer intact (FIG 16B). The majority of the capsules prepared with 100 million cells/ml had greatest number of capsules retrieved intact (data not shown). This demonstrates that there is an optimal cell concentration where protein levels are maximized and capsules maintain their integrity.

Example 22: Preparation of two-compartment capsules with a target size of 0.75 mm diameter or 1.0 mm diameter

Two-compartment capsule compositions with a capsule target size of 1.0 mm or 0.75 mm were prepared as described in the previous examples, but with the following adjustments. The alginate solution used to form the second (outer) compartment contained CM-Alg-101 with a medium conjugation level of Compound 101 (e.g., prepared as described in Example 10) blended with U-HMW-Alg at a 70:30 ratio of CM-Alg-101 to U-HMW-Alg. The same blended alginate solution with a suspension of ARPE19 cells (50 million cells per ml) engineered to express human FVIII was used to form the first (inner) compartment. Capsule compositions with a capsule target size of 1.0 mm capsules were generated using a coaxial needle (20G OD/26G ID), a voltage of 7.3kV, first and second compartment flow rates each of 5mL/h, and a capsule droplet rate of 30-35 droplets per 10 seconds. Capsule compositions with a target size of 0.75 mm were prepared using a coaxial needle (20G OD/26G ID), a voltage of approximately 7.5 kV, first and second compartment flow rates each of 5mL/h, and a capsule droplet rate of 35-40 droplets per 10 seconds.

As shown in FIGS. 18A-18B, spherical 0.75 mm and 1.0 mm two compartment capsules with cells in the inner compartment were produced. These capsules had outer compartments that completely encapsulated the cells in the inner compartment. Therefore, two-compartment capsules can be prepared at 0.75 and 1.0mm mean diameters.

EQUIVALENTS AND SCOPE

This application refers to various issued patents, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference in their entirety. If there is a conflict between any of the incorporated references and the instant specification, the specification shall control. In addition, any particular embodiment of the present disclosure that

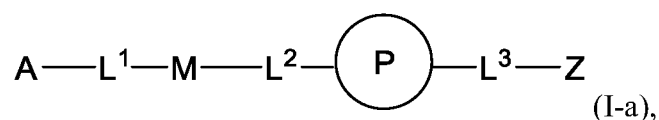
falls within the prior art may be explicitly excluded from any one or more of the claims.

Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the disclosure can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be limited to the above Description, Figures, or Examples but rather is as set forth in the appended claims. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present disclosure, as defined in the following claims.

CLAIMS

1. A particle comprising:
- a) a first compartment comprising an alginate polymer and a cell;
 - b) a second compartment comprising an alginate polymer; and
 - c) a compound of Formula (I-a):



or a pharmaceutically acceptable salt thereof, wherein:

the first compartment is surrounded by the second compartment;

the particle comprises an interface between the first and second compartment;

wherein:

A is alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-O-$, $-C(O)O-$, $-C(O)-$, $-OC(O)-$, $-N(R^C)-$, $-N(R^C)C(O)-$, $-C(O)N(R^C)-$, $-N(R^C)N(R^D)-$, $-NCN-$, $-N(R^C)C(O)(C_1-C_6\text{-alkylene})-$, $-N(R^C)C(O)(C_2-C_6\text{-alkenylene})-$, $-C(=N(R^C)(R^D))O-$, $-S-$, $-S(O)_x-$, $-OS(O)_x-$, $-N(R^C)S(O)_x-$, $-S(O)_xN(R^C)-$, $-P(R^F)_y-$, $-Si(OR^A)_2-$, $-Si(R^G)(OR^A)-$, $-B(OR^A)-$, or a metal, each of which is optionally linked to an attachment group and optionally substituted by one or more R^1 ;

each of L^1 and L^3 is independently a bond, alkyl, or heteroalkyl, wherein each alkyl and heteroalkyl is optionally substituted by one or more R^2 ;

L^2 is a bond;

M is absent, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted by one or more R^3 ;

P is heteroaryl optionally substituted by one or more R^4 ;

Z is alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted by one or more R^5 ;

each R^A , R^B , R^C , R^D , R^E , R^F , and R^G is independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, halogen, azido, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^6 ;

or R^C and R^D , taken together with the nitrogen atom to which they are attached, form a ring, optionally substituted with one or more R^6 ;

each R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 is independently alkyl, alkenyl, alkynyl, heteroalkyl, halogen, cyano, azido, oxo, $-OR^{A1}$, $-C(O)OR^{A1}$, $-C(O)R^{B1}$, $-OC(O)R^{B1}$, $-N(R^{C1})(R^{D1})$, $-N(R^{C1})C(O)R^{B1}$, $-C(O)N(R^{C1})$, SR^{E1} , $S(O)_xR^{E1}$, $-OS(O)_xR^{E1}$, $-N(R^{C1})S(O)_xR^{E1}$, $-S(O)_xN(R^{C1})(R^{D1})$, $-P(R^{F1})_y$, cycloalkyl, heterocyclyl, aryl, heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted by one or more R^7 ;

each R^{A1} , R^{B1} , R^{C1} , R^{D1} , R^{E1} , and R^{F1} is independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl is optionally substituted by one or more R^7 ;

each R^7 is independently alkyl, alkenyl, alkynyl, heteroalkyl, halogen, cyano, oxo, hydroxyl, cycloalkyl, or heterocyclyl;

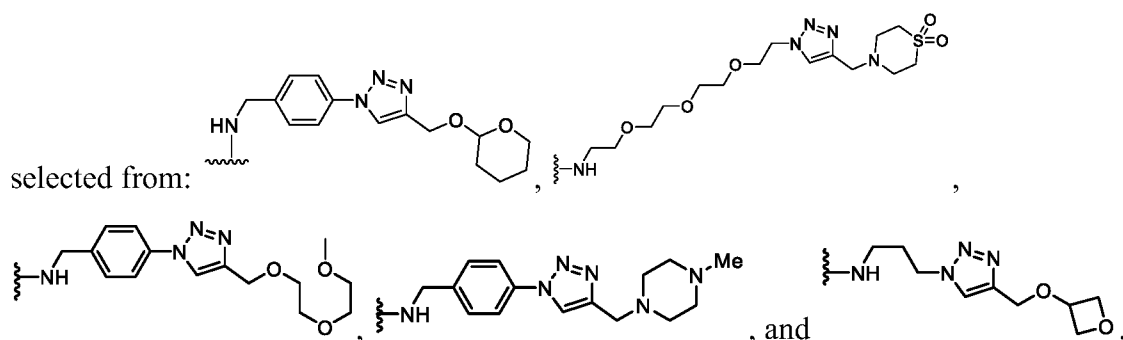
x is 1 or 2; and

y is 2, 3, or 4; and wherein:

the alginate polymer of the second compartment is modified with a compound of Formula (I-a).

2. The particle of claim 1, wherein the differential volume of the second compartment is 1.5x, 2x, 3x, or 5x less than the volume of the first compartment.
3. The particle of claim 1 or 2, wherein the differential volume of the second compartment is about 1%, 2%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, or 75% less than the volume of the first compartment.
4. The particle of any one of the previous claims, wherein the first compartment is substantially free of a compound of Formula (I-a).
5. The particle of any one of the previous claims, wherein the interface is substantially free of a compound of Formula (I-a).
6. The particle of any one of claims 1-5, wherein the particle has a largest linear dimension (LLD or diameter) of between 1 millimeter to 5 millimeters.

7. The particle of any one of claims 1-6, wherein the average distance between the outer boundary of the first compartment and the inner boundary of the second compartment is between 500 nanometers and 500 micrometers.
8. The particle of any one of claims 1-7, wherein the second compartment does not comprise a cell.
9. The particle of claim 8, wherein the particle comprises at least 5×10^6 , 10×10^6 , 15×10^6 or 20×10^6 cells per ml.
10. The particle of claim 8 or claim 9, wherein the cell or cells are present as single cells, one or more spheroids, or bound to one or more microcarriers.
11. The particle of any one of claims 8-10, wherein the cell is an epithelial cell, endothelial cell, fibroblast cell, mesenchymal stem cell, or keratinocyte cell.
12. The particle of any one of claims 8-11, wherein the cell is a retinal pigment epithelial (RPE) cell or an MSC.
13. The particle of any one of claims 8-11, wherein the cell is an islet cell.
14. The particle of any one of claims 8-13, wherein the cell expresses a polypeptide.
15. The particle of claim 14, wherein the polypeptide is a Factor VIII protein or a variant thereof or a Factor IX protein or a variant thereof.
16. The particle of claim 15, wherein the polypeptide is insulin.
17. The particle of any one of claims 1-16, wherein the polymers of both the first compartment and the second compartment are modified with a compound of Formula (I-a).
18. The particle of any one of claims 1-17, wherein the compound of Formula (I-a) is

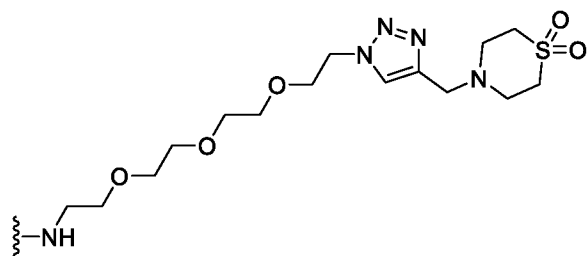


19. The particle of claim 1, wherein the particle is a hydrogel capsule and wherein:

- a) the first compartment comprises a plurality of cells engineered to express a polypeptide;
- b) the first compartment is surrounded by the second compartment;
- c) the second compartment is substantially free of cells; and
- d) wherein the second compartment and exterior surface of the particle comprise an alginate chemically-modified with the compound of Formula (I-a).

20. The particle of claim 19, wherein the chemically-modified alginate comprises the compound of Formula (I-a) in an amount that provides the particle with both an afibrotic property and a desired mechanical strength.

21. The particle of claim 19 or 20, wherein the compound of Formula (I-a) is Compound 101, which has the structure:



22. The particle of claim 21, wherein Compound 101 is present in the chemically-modified alginate at a density of at least 2.0 % and less than 9.0 % nitrogen (N) as determined by combustion analysis for percent nitrogen.

23. The particle of claim 19 or 20, wherein the first compartment is formed from an alginate solution that lacks an afibrotic compound.

24. The particle of any one of claims 19-23, which has a mean diameter of about 1 mm to about 2 mm or a mean diameter of about 0.75 to about 1.0 mm.
25. The particle of any one of claims 19-24, wherein the first compartment is formed from an alginate solution comprising about 10 to about 50 million cells/ml, 50 to about 500 million cells/ml, about 75 million to about 450 million cells/ml, about 100 to about 450 million cells/ml, about 100 to about 400 million cells/ml, or about 100 to about 300 million cells/ml.
26. The particle of any one of claims 19-25, wherein the cells are derived from ARPE19 cells and comprise an exogenous nucleotide sequence which comprises SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, of SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:26, SEQ ID NO:27, and SEQ ID NO:28.
27. The particle of claim 26, wherein the exogenous nucleotide sequence comprises SEQ ID NO:23.
28. The particle of claim 26 or 27, wherein the exogenous nucleotide sequence comprises SEQ ID NO:15 or SEQ ID NO:27.
29. The particle of claim 26 or 27, wherein the exogenous nucleotide sequence comprises SEQ ID NO:19 or SEQ ID NO:28.
30. The particle of any one of claims 1-29, made by a method comprising contacting a plurality of droplets of a polymer solution with an aqueous cross-linking solution for a period of time sufficient to produce a particle, wherein the cross-linking solution comprises a cross-linking agent, a buffer, and an osmolarity-adjusting agent.
31. A preparation of a plurality of particles, wherein the plurality comprises a particle of any one of claims 1-30.
32. The preparation of claim 31, wherein the preparation is a pharmaceutically acceptable preparation.

33. A method of making a particle of any one of claims 1-29 comprising the step of contacting a plurality of droplets of a polymer solution with an aqueous cross-linking solution for a period of time sufficient to produce a particle, wherein the cross-linking solution comprises a cross-linking agent, a buffer, and an osmolarity-adjusting agent.
34. A composition of particles for use in treating a subject in need of a substance comprising:
providing a particle of any one of claims 1-30 or the preparation of claim 31 or 32;
which comprises or has the ability to produce the substance; and
disposing the particle in the body of the subject.
35. A method of treating a subject in need of a substance to a subject comprising:
administering an effective amount of the particle of any one of claims 1-30 or the preparation of claim 31 or 32 to said subject, wherein the particle comprises or has the ability to produce the substance.
36. Use of the particle of any one of claims 1-30, or the preparation of claim 31 or 32, in the manufacture of a medicament for treating a subject in need of a substance, wherein the particle comprises or has the ability to produce the substance, and wherein the medicament is formulated for disposition of the particle in the body of the subject.

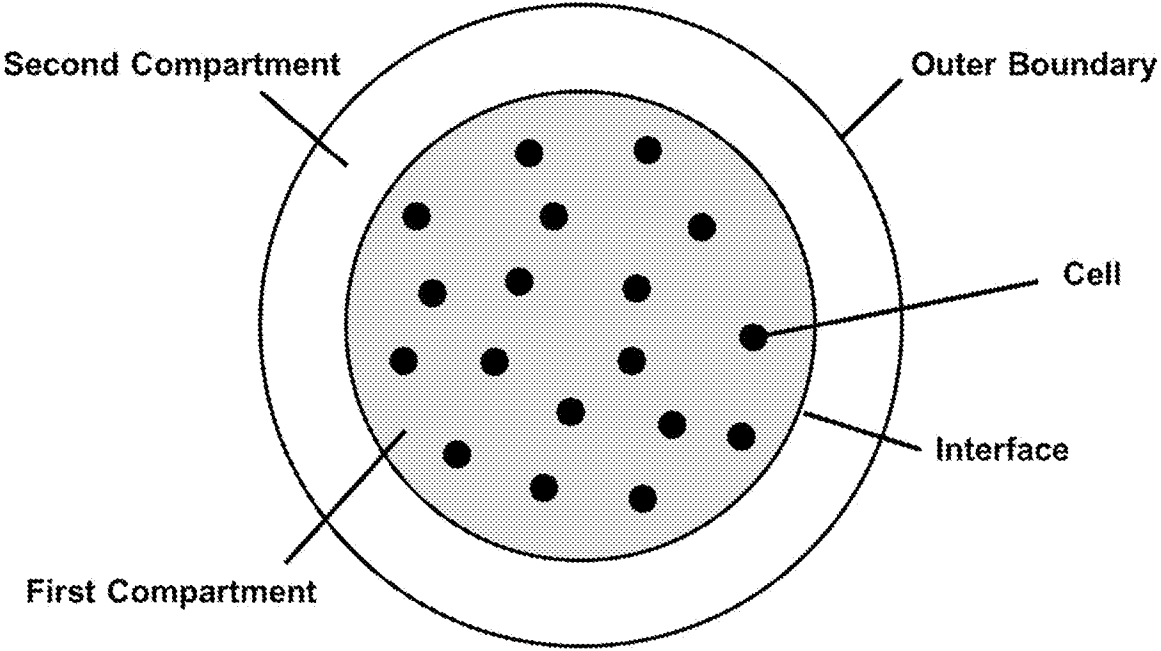


FIG. 1

SEQ ID NO: 1

MQIELSTCFFLCLLRFCFSATTRYYLGAVELSWDYMQSDLGELPVDARFPPRPVKSFPFN
TSVVYKKTLEFVEFTDHLFENIAKPRPPWMGLLGPTIQAEVYDTVVITLKNMASHPVSLHAV
GVSYWKASEGAEYDDQTSQREKEDDKVFPGGSHTYVWQVLKENGPMASDPLCLTYSYLSH
VDLVKDLNSGLIGALLVCREGLAKEKTQTLHKFILLFAVFDEGKSWHSETKNSLMQDRD
AASARAWPKMHTVNGYVNRSLPGLIGCHRKSVYWHVIGMGTTPEVHSIFLEGHTFLVRNH
RQASLEISPITFLTAQTLMDLGQFLLFCHISSHQHDGMEAYVKVDSCPEEPQLRMKNNE
EAEDYDDDLTDSEMDVVRFDNNSPSFIQIRSVAKKHPKTWVHYIAAEEEDWDYAPLVLA
PDDRSYKSQYLNNGPQRIGRKYKKVRFMAYTDETFKTREAIQHESGILGPLLYGEVGDTL
LIIIFKNQASRPYNIYPHGITDVRPLYSRRLPKGVKHLKDFPILPGEIFKYKWTVTVEDGP
TKSDPRCLTRYSSFVNMERDLASGLIGPLLICYESVDQGRNQIMSDKRNVLFSVFDE
NRSWYL TENIQRFLPNPAGVQLEDPEFQASNIMHSINGYVFDSLQLSVCLHEVAYWYILS
IGAQTDFLSVFFSGYTFKHKMVYEDTLTLFPFSGETVFMSMENPGLWILGCHNSDFRNRG
MTALLKVSSCDKNTGDYEDSYEDISAYLLSKNNAIEPRSFQNPVPLKRHQREITRTTL
QSDQEEIDYDDTISVEMKKEDFDIYDEDENQSPRSFQKKTRHYFIAAVERLWDYGMSSSP
HVLNRNAQSGSVPQFKKVVFQEF TDGSFTQPLYRGELNEHLGLLGPYIRAEVEDNIMVTF
RNQASRPYSFYSSLISYEEDQRQGAEPKRFVKNETKTYFWKVQHMAPTKDEFDCKAW
AYFSDVDLEKDVHSGLIGPLL VCHTNTLNPAHGRQVTVQEFALFFTIFDETKSWYFTENM
ERNCRAPCNIQMEDPTFKENYRFHAINGYIMDTLPGLVMAQDQRIRWYLLSMGSNENIHS
IHFSGHVFTVRKKEEYKMALYNLYPGVFETVEMLPKAGIWRVECLIGEHLHAGMSTLFL
VYSNKCQTPLGMASGHIRDFOITASGQYGQWAPKLARLHYSGSINAWSTKEPFSWIKVDL
LAPMIIHGIKTQGARQKFSSLYISQFIIMYSLDGKKWQTYRGNSTGTLMVFFGNVDSSGI
KHNI FNPIIARYIRLHPHYSIRSTLRMELMGCDLNSCSMPLGMESKAISDAQITASSY
FTNMFATWSPSKARLHLQGRSNAWRPQVNNPKEWLQVDFQKTMKVTGVTTQGVKSLLTSM
YVKEFLISSSQDGHQWTLFFQNGKVKV FQGNQDSFTPVVNSLDPPLLTRYLRIHPQSWVH
QIALRMEVLGCEAQDLY

FIG. 2A

SEQ ID NO: 2

YNSGKLEEFVQGNLERECMEEKCSFEEAREVFENTERTEFWKQYVDGDQCESNPCLNG
 GSKDDINSYECWCPFGFEGKNCELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLA
 ENQKSCEPAVPFPCGRVSVSQTSKLTRAETVFPDVDYVNSTEAEITLDNITQSTQSFND
 FTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIIVTAAHCVETGVKITVVAGEH
 NIEETEHTEQKRN VIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIAKEY
 TNIFLKFGSGYVSWGGRV FHKGRSALVLQYLRVPLVDRATCLRSTKFTIYNNMFCAGFH
 EGGRDSCQGD SGGPHVTEVEGTSFLTGIISWGEECAMKGKYG IYTKVSRYVNWIKEKTK
 LT

FIG. 2B

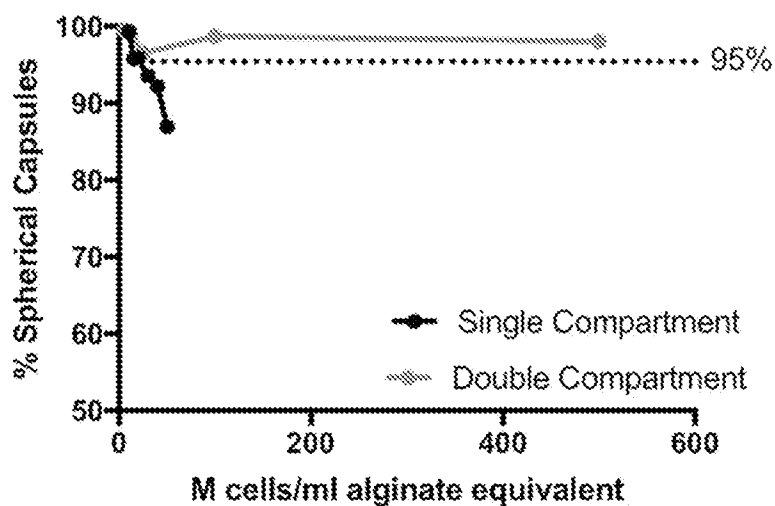


FIG. 3

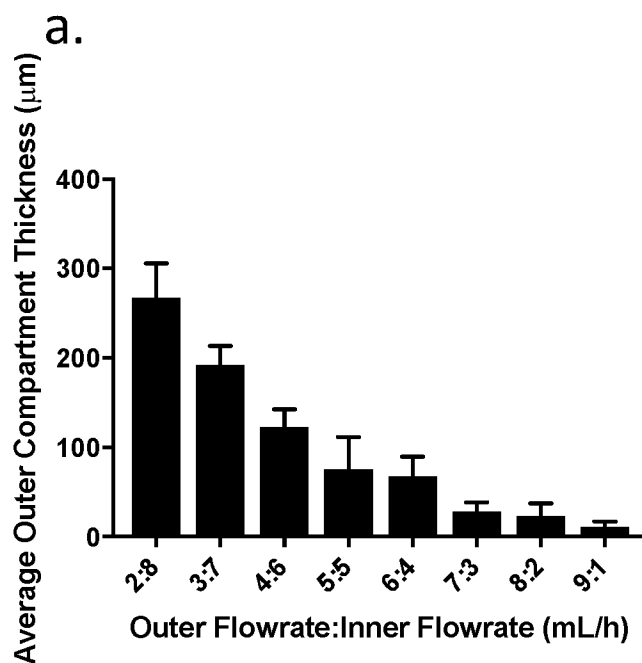


FIG. 4A

b.

Inner Compartment %	Outer Compartment %	Outer Compartment Thickness (μm)
20	80	267
30	70	192
40	60	122
50	50	75
60	40	68
70	30	28
80	20	23
90	10	11

FIG. 4B

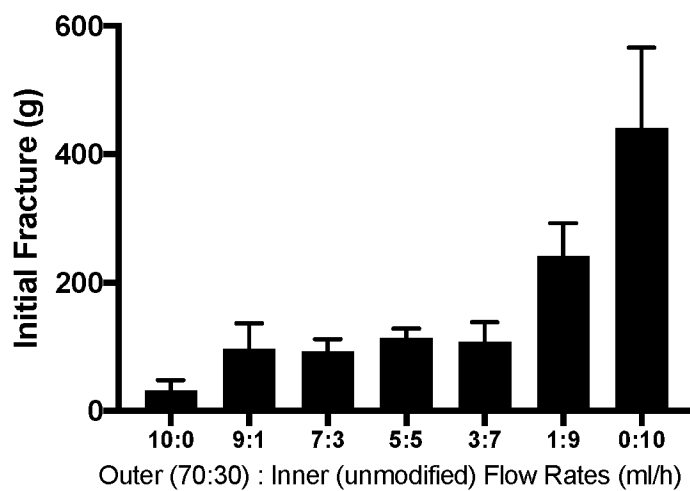


FIG. 5

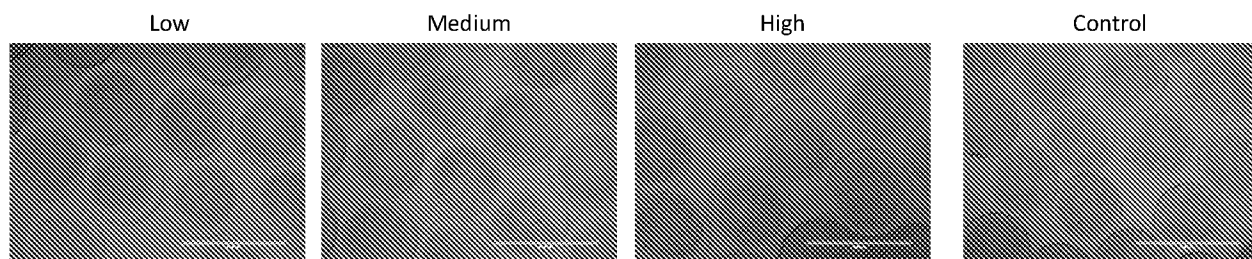


FIG. 6A

FIG. 6B

FIG. 6C

FIG. 6D

FIG. 7A

Low Conjugation

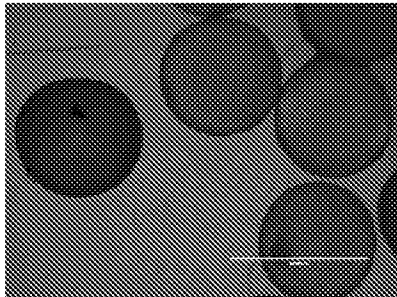


FIG. 7B

Medium Conjugation

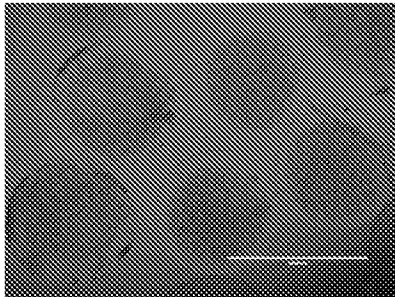
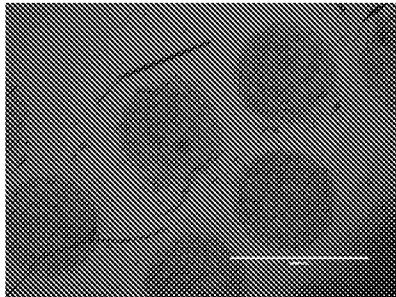
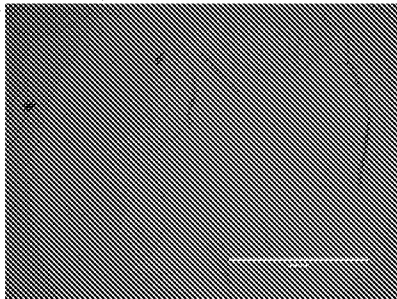


FIG. 7C

High Conjugation



Empty (Medium Conjugation)



Control

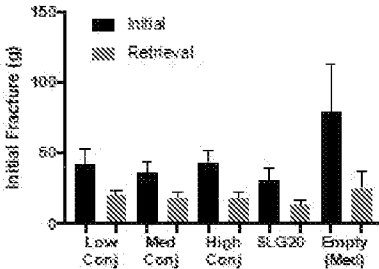
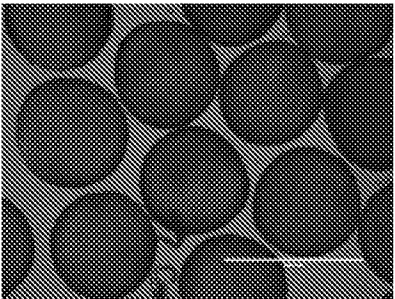


FIG. 7D

FIG. 7E

FIG. 7F

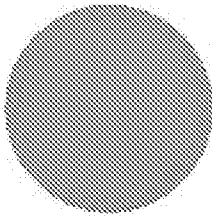


FIG. 8A

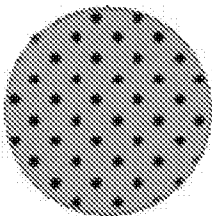


FIG. 8B

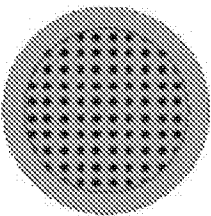


FIG. 8C

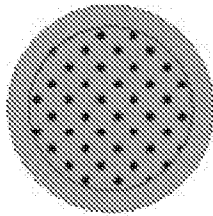


FIG. 8D

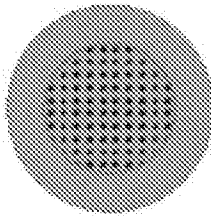
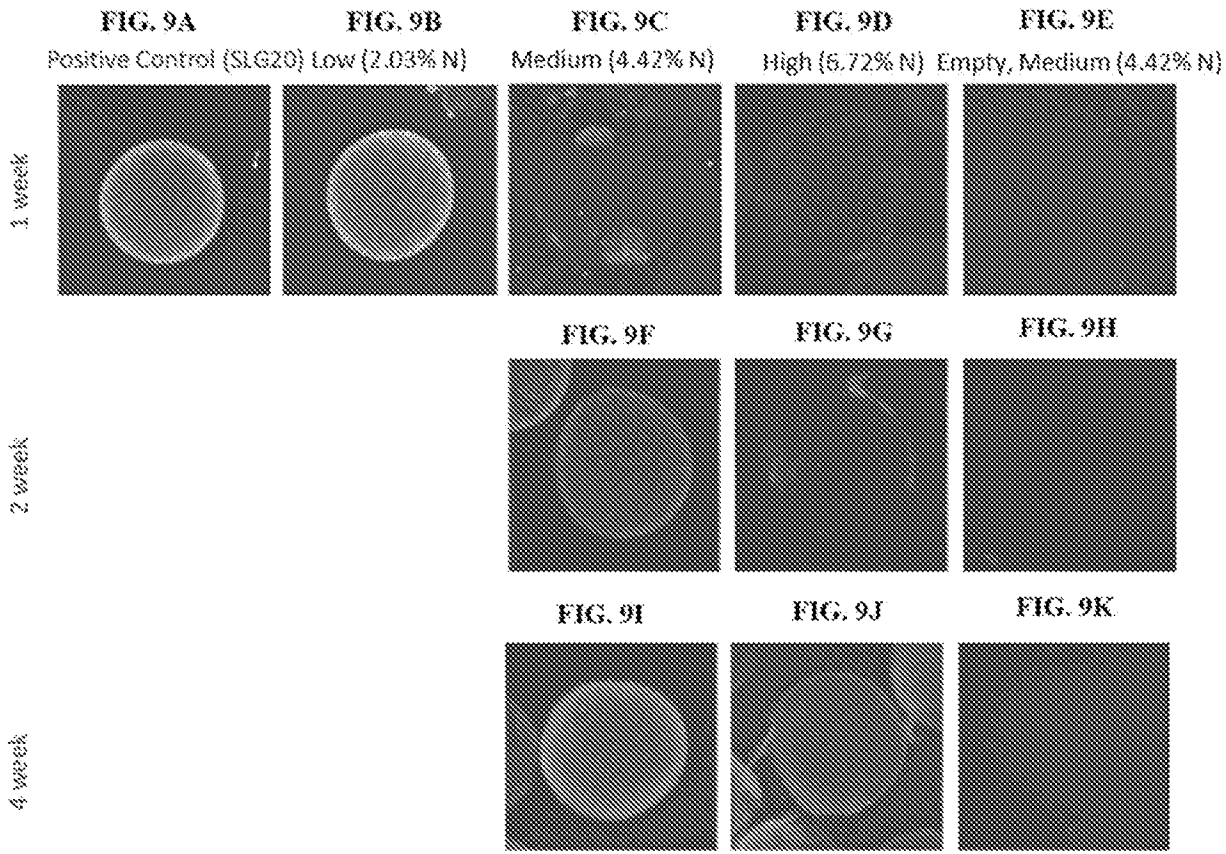


FIG. 8E



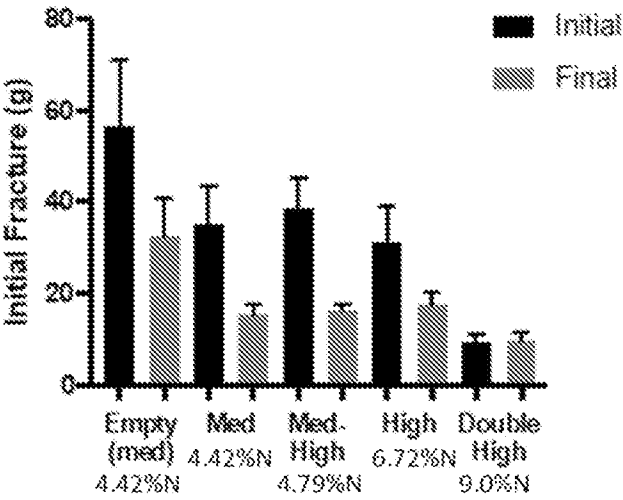
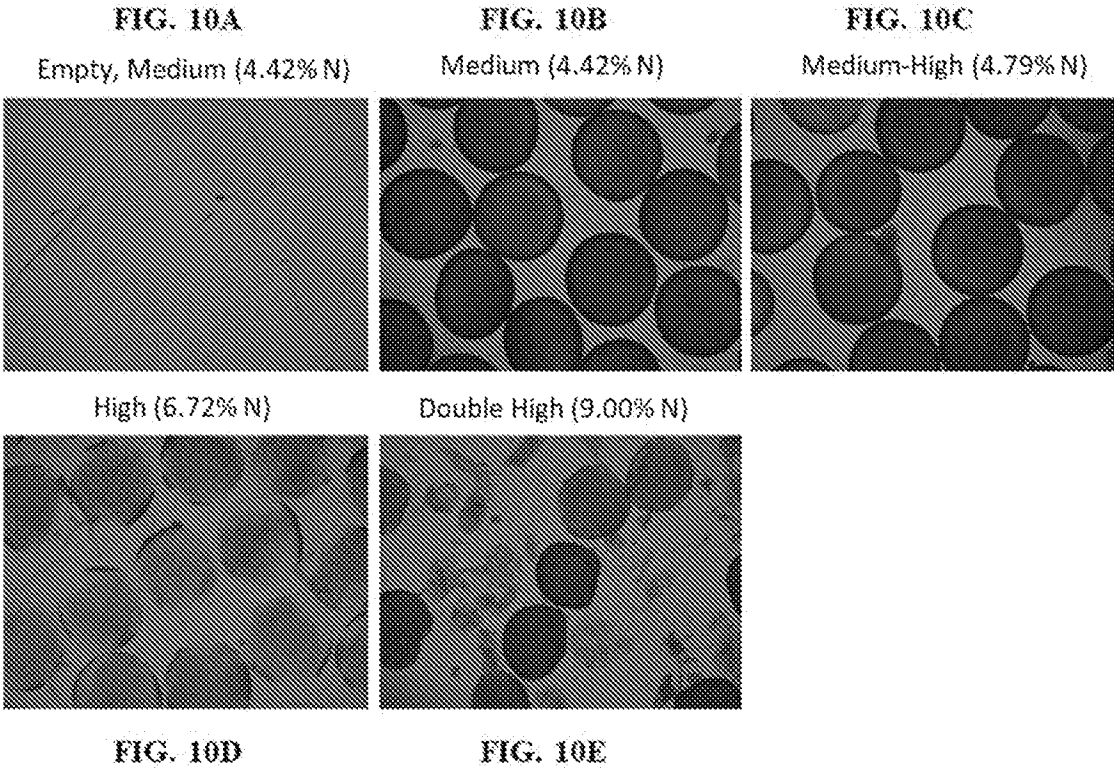


FIG. 11

FIG. 12A

Medium (4.42% N)

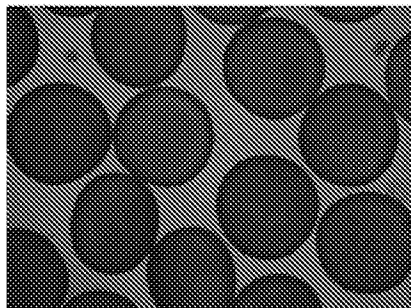


FIG. 12B

High (4.79% N)



FIG. 12C

Amine Added Back (~4.42% N)

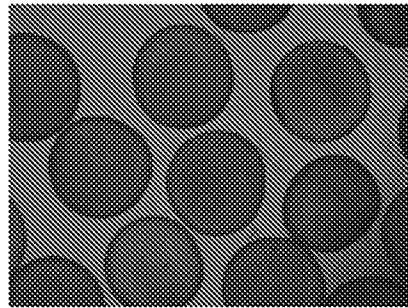


FIG. 13A

Medium (4.42% N)

70:30



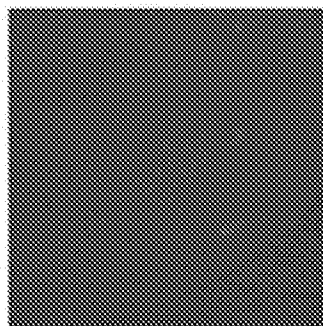
FIG. 13B

Medium-High (4.79% N)



FIG. 13C

High (6.72% N)



60:40

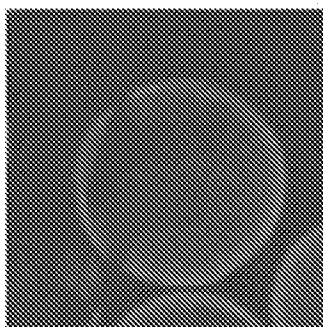
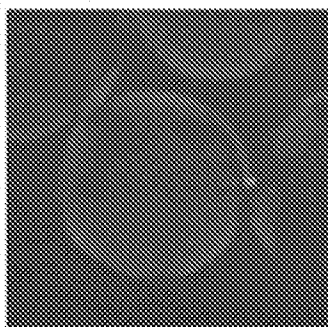
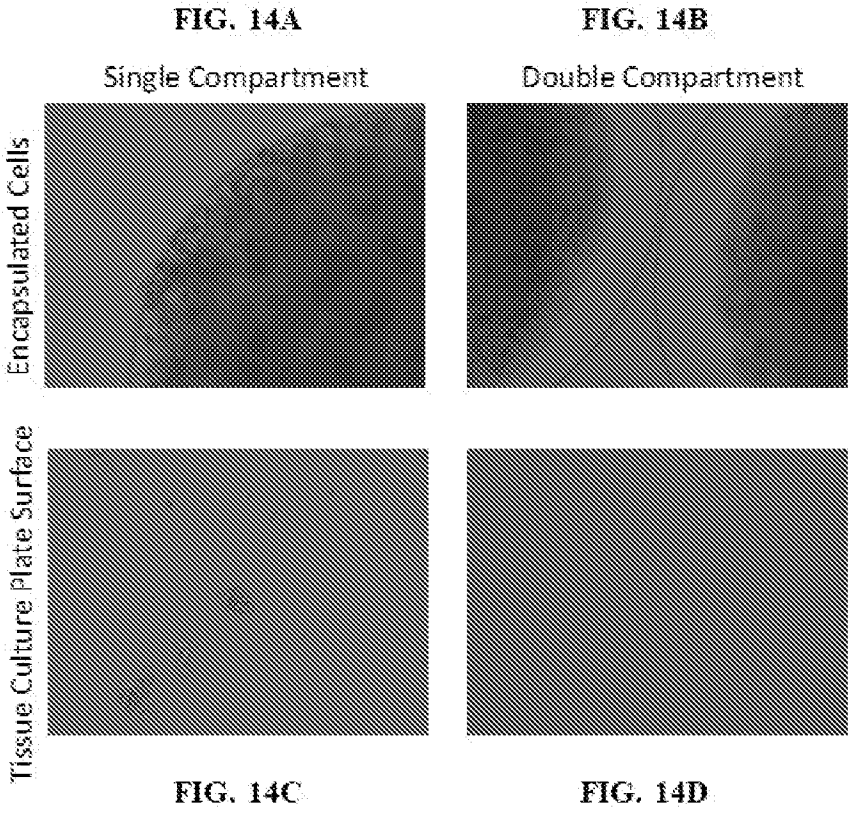


FIG. 13D

FIG. 13E

FIG. 13F



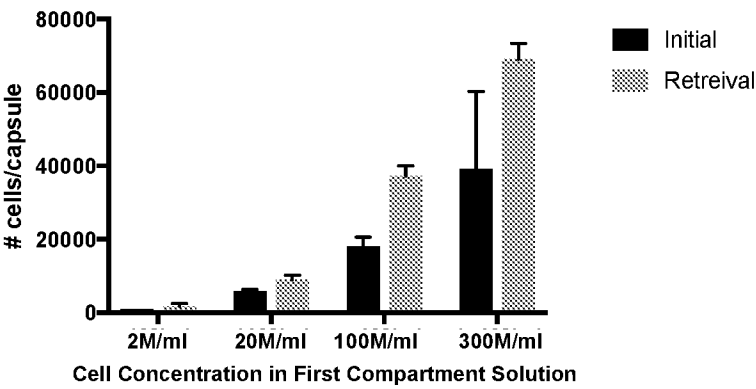


FIG. 15A

Plasma

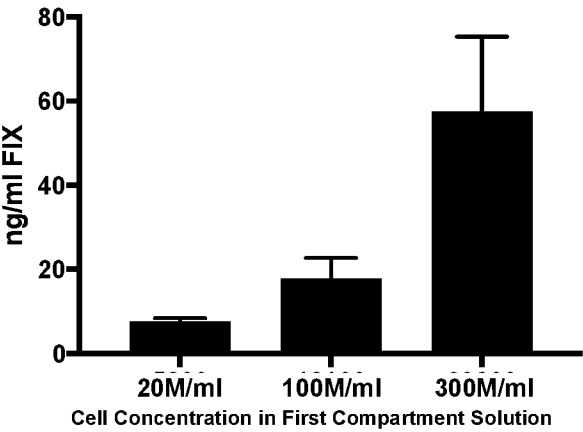


FIG. 15B

IP

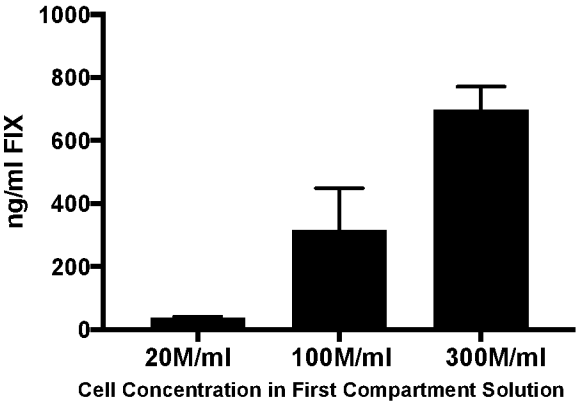


FIG. 15C

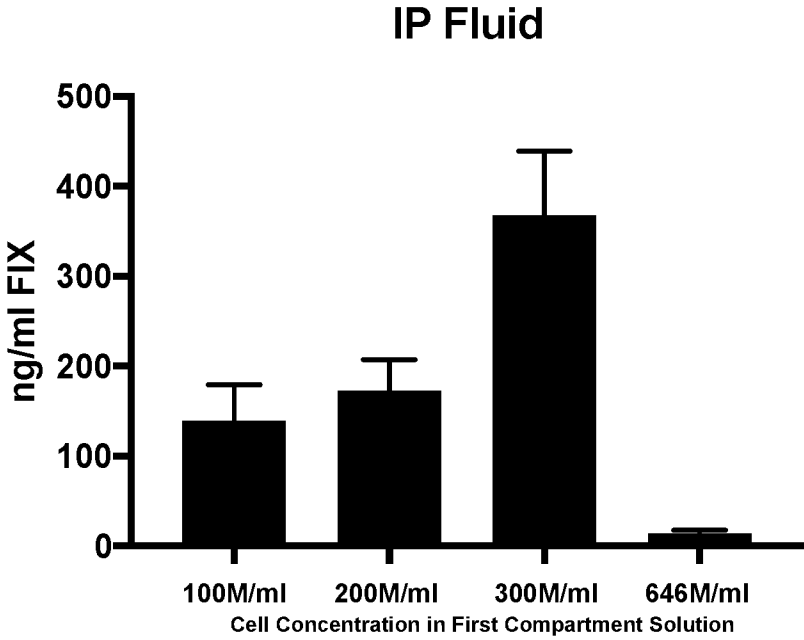


FIG. 16A

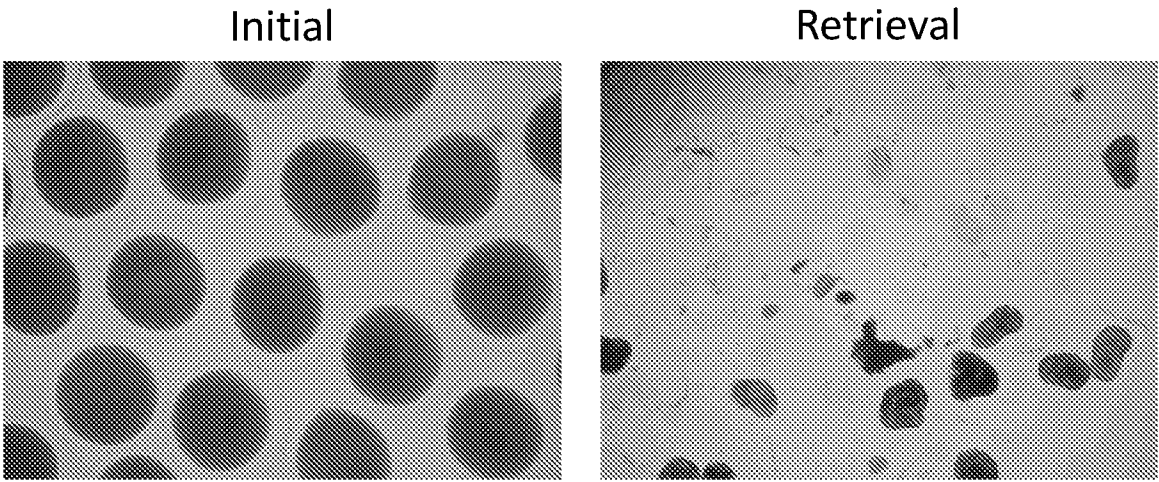


FIG. 16B

FIG. 16C

FIG. 17: Tables 4-8

Table 4:

SEQ ID NO.	Protein	Amino Acid Sequence
1	rhFVIII-BDD	<u>MQIELSTCFF</u> LCLLRFCFSA TRRYYLGA VE LSWDYMQSDL GELPVDARFP
		PRVPKSF PFN TSVVYKKT LF VEFTDHLFNI AKPRPPWMGL LGPTIQAEVY
		DTVVITLKNM ASHPVSLHAV GVS YWKASEG AEYDDQTSQR EKEDDKVFPG
		GSHTYVWQVL KENGPMASDP LCLTYSYLSH VDLVKDLNSG LIGALLVCRE
		GSLAKEKTQT LHKFILLFAV FDEGKSWHSE TKNSLMQDRD AASARAWPKM
		HTVNGYVNRS LPGLIGCHRK SVYWHVIGMG TTPEVHSIFL EGHTFLVRNH
		RQASLEISPI TFLTAQTLLM DLGQFLLFCH ISSHQHDGME AYVKVDSCPE
		EPQLRMKNNE EAEDYDDDLT DSEMDVVRFD DDNSPSFIQI RSVAKKHPKT
		WVHYIAAEEE DWDYAPLVLA PDDRSYKSQY LNNGPQRIGR KYKKVRFMAY
		TDETFKTREA IQHESGILGP LLYGEVGDTL LIIFKNQASR PYNIIYPHGIT
		DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR
		YYSSFVNMER DLASGLIGPL LICYKESVDQ RGNQIMSDKR NVILFSVFDE
		NRSWYLTENI QRFLPNPAGV QLEDPEFQAS NIMHSINGYV FDSLQLSVCL
		HEVAYWYILS IGAQTDFLSV FFSGYTFKHK MVEYEDTLTLF PFSGETVFMS
		MENPGLWILG CHNSDFRNRG MTALLKVSSC DKNTGDYED SYEDISAYLL
		SKNNAIEPRS FSQNPPVLKR HQREITRTTL QSDQEEIDYD DTISVEMKKE
		DFDIYDEDEN QSPRSFQKKT RHYFIAAVER LDWYGMSSSP HVLNRNAQSG
		SVPQFKKVVF QEFTDGSFTQ PLYRGELNEH LGLLGPYIRA EVEDNIMVTF
		RNQASRPYSF YSSLISYEED QRQGAEPKRN FVKPNETKTY FWKVQHMAP
		TKDEFDCKAW AYFSDVDLEK DVHSGLIGPL LVCHTNTLNP AHGRQVTVQE
		FALFFTIFDE TKS WYFTENM ERNCRAPCNI QMEDPTFKEN YRFHAINGYI
		MDTLPGLVMA QDQIRIRWYLL SMGSNENIHS IHFSGHVFTV RKKEEYKMAL
		YNLYPGVFET VEMLPSKAGI WRVECLIGEH LHAGMSTLFL VYSNKCQTPL
		GMASGHIRDF QITASGQYGQ WAPKLARLHY SGSINAWSTK EPFSWIKVDL
		LAPMIIHGK TQGARQKFSS LYISQFIIMY SLDGKKWQTY RGNSTGTLMV
		FFGNVDSSGI KHNI FNPPII ARYIRLHPTH YSIRSTLRME LMGC DLNSCS
		MPLGMESKAI SDAQITASSY FTNMFATWSP SKARLHLQGR SNAWRPQVNN
		PKEWLQVDFQ KTMKVTGVT T QGVKSLLTSM YVKEFLISS QDGHQWTLFF
		QNGKVKVFQG NQDSFTPVVN SLDPPLLTRY LRIHPQSWVH QIALRMEVLG
		CEAQDLY
3	rhScFVIII-BDD 1	<u>MQIELSTCFF</u> LCLLRFCFSA TRRYYLGA VE LSWDYMQSDL GELPVDARFP
		PRVPKSF PFN TSVVYKKT LF VEFTDHLFNI AKPRPPWMGL LGPTIQAEVY
		DTVVITLKNM ASHPVSLHAV GVS YWKASEG AEYDDQTSQR EKEDDKVFPG
		GSHTYVWQVL KENGPMASDP LCLTYSYLSH VDLVKDLNSG LIGALLVCRE
		GSLAKEKTQT LHKFILLFAV FDEGKSWHSE TKNSLMQDRD AASARAWPKM
		HTVNGYVNRS LPGLIGCHRK SVYWHVIGMG TTPEVHSIFL EGHTFLVRNH
		RQASLEISPI TFLTAQTLLM DLGQFLLFCH ISSHQHDGME AYVKVDSCPE
		EPQLRMKNNE EAEDYDDDLT DSEMDVVRFD DDNSPSFIQI RSVAKKHPKT
		WVHYIAAEEE DWDYAPLVLA PDDRSYKSQY LNNGPQRIGR KYKKVRFMAY
		TDETFKTREA IQHESGILGP LLYGEVGDTL LIIFKNQASR PYNIIYPHGIT
		DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR
		YYSSFVNMER DLASGLIGPL LICYKESVDQ RGNQIMSDKR NVILFSVFDE
		NRSWYLTENI QRFLPNPAGV QLEDPEFQAS NIMHSINGYV FDSLQLSVCL
		HEVAYWYILS IGAQTDFLSV FFSGYTFKHK MVEYEDTLTLF PFSGETVFMS

		MENPGLWILG CHNSDFRNRG MTALLKVSSC DKNTGDYED SYEDISAYLL SKNNAIEPRS FSQNPPVLKH HQREITRTTL QSDQEEIDYD DTISVEMKKE DFDIYDEDEN QSPRSFQKKT RHYFIAAVER LDYDGMSSSP HVLRNRAQSG SVPQFKKVVF QEFTDGSFTQ PLYRGELNEH LGLLGPYIRA EVEDNIMVTF RNQASRPYSF YSSLISYEED QRQGAEPKRN FVKPNETKTY FWKVQHMAP TKDEFDCKAW AYFSDVDLEK DVHSGLIGPL LVCHTNTLNP AHGRQVTVQE FALFFTIFDE TKSIFYTENM ERNCRAPCNI QMEDPTFKEN YRFHAINGYI MDTLPGLVMA QDQIRWYLL SMGSNENIHS IHFSGHVFTV RKKEEYKMAL YNLYPGVFET VEMPLPSKAGI WRVECLIGEH LHAGMSTLFL VYSNKCQTPL GMASGHIRDF QITASGQYGQ WAPKLARLHY SGSINAWSTK EPFSWIKVDL LAPMIIHGK TQGARQKFSS LYISQFIIMY SLDGKKWQTY RGNSTGTLMV FFGNVDSSGI KHNIFNPPII ARYIRLHPTH YSIRSTLRME LMGCDLNSCS MPLGMESKAI SDAQITASSY FTNMFATWSP SKARLHLQGR SNAWRPQVNN PKEWLQVDFQ KTMKVTGVT T QGVKSLLTSM YVKEFLISS QDGHQWTLFF QNGKVKVFQG NQDSFTPVVN SLDPPLLTRY LRIHPQSWVH QIALRMEVLG CEAQDLY
4	rhScFVIII-BDD 2	<u>MQIELSTCFF</u> <u>LCLLRFCFSA</u> TRRYLGAIVE LSWDYMQSDL GELPVDARFP PRVPKSFPPN TSVVYKKTFL VEFTDHLFNI AKPRPPWMGL LGPTIQAEVY DTVVITLKNM ASHPVSLHAV GVSYWKASEG AEYDDQTSQR EKEDDKVFP GSHTYVWQVL KENGPMASDP LCLTYSYLSH VDLVKDLNSG LIGALLVCRE GSLAKEKTQT LHKFILLFAV FDEGKSWHSE TKNSLMQDRD AASARAWPKM HTVNGYVNRSLPGLIGCHRK SVYWHVIGMG TTPEVHSIFL EIGHTFLVRNH RQASLEISPI TFLTAQTLLM DLGQFLLFCH ISSHQHDGME AYVKVDSCPE EPQLRMKNNE EAEDYDDDLT DSEMDVVRFD DDNSPSFIQI RSVAKKHPKT WVHYIAAEEE DWDYAPLVLA PDDRSYKSQY LNNGPQRIGR KYKKVRFMAY TDETFTKREA IQHESGILGP LLYGEVGDIT LIIFKNQASR PYNIPHGIT DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR YYSSFVNMER DLASGLIGPL LICYKESVDQ RGNQIMSDKR NVILFSVFDE NRSWYLTENI QRFLPNPAGV QLEDPEFQAS NIMHSINGYV FDSLQLSVCL HEVAYWYILS IGAQTDFLSV FFSGYTFKHK MVEDTLTLF PFSGETVFMS MENPGLWILG CHNSDFRNRG MTALLKVSSC DKNTGDYED SYEDISAYLL SKNNAIEPRS FSQNPPVLKA HQAEITRTTL QSDQEEIDYD DTISVEMKKE DFDIYDEDEN QSPRSFQKKT RHYFIAAVER LDYDGMSSSP HVLRNRAQSG SVPQFKKVVF QEFTDGSFTQ PLYRGELNEH LGLLGPYIRA EVEDNIMVTF RNQASRPYSF YSSLISYEED QRQGAEPKRN FVKPNETKTY FWKVQHMAP TKDEFDCKAW AYFSDVDLEK DVHSGLIGPL LVCHTNTLNP AHGRQVTVQE FALFFTIFDE TKSIFYTENM ERNCRAPCNI QMEDPTFKEN YRFHAINGYI MDTLPGLVMA QDQIRWYLL SMGSNENIHS IHFSGHVFTV RKKEEYKMAL YNLYPGVFET VEMPLPSKAGI WRVECLIGEH LHAGMSTLFL VYSNKCQTPL GMASGHIRDF QITASGQYGQ WAPKLARLHY SGSINAWSTK EPFSWIKVDL LAPMIIHGK TQGARQKFSS LYISQFIIMY SLDGKKWQTY RGNSTGTLMV FFGNVDSSGI KHNIFNPPII ARYIRLHPTH YSIRSTLRME LMGCDLNSCS MPLGMESKAI SDAQITASSY FTNMFATWSP SKARLHLQGR SNAWRPQVNN PKEWLQVDFQ KTMKVTGVT T QGVKSLLTSM YVKEFLISS QDGHQWTLFF QNGKVKVFQG NQDSFTPVVN SLDPPLLTRY LRIHPQSWVH QIALRMEVLG CEAQDLY
5	rhScFVIII-BDD 3 (ΔF)	<u>MQIELSTCFF</u> <u>LCLLRFCFSA</u> TRRYLGAIVE LSWDYMQSDL GELPVDARFP PRVPKSFPPN TSVVYKKTFL VEFTDHLFNI AKPRPPWMGL LGPTIQAEVY DTVVITLKNM ASHPVSLHAV GVSYWKASEG AEYDDQTSQR EKEDDKVFP GSHTYVWQVL KENGPMASDP LCLTYSYLSH VDLVKDLNSG LIGALLVCRE

		GSLAKEKTQT LHKFILLFAV FDEGKSWHSE TKNSLMQDRD AASARAWPKM HTVNGYVNRS LPGLIGCHRK SVYWHVIGMG TTPEVHSIFL EGHTFLVRNH RQASLEISPI TFLTAQTLLM DLGQFLLFCH ISSHQHDGME AYVKVDSCPE EPQLRMKNNE EAEDYDDDLT DSEMDVVRFD DDNSPSFIQI RSVAKKHPKT WVHYIAAEEE DWDYAPLVLA PDDRSYKSQY LNNGPQRIGR KYKKVRFMAY TDETFKTREA IQHESGILGP LLYGEVGDTL LIIFKNQASR PYNIIYPHGIT DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR YYSSFVNMER DLASGLIGPL LICYKESVDQ RGNQIMSDKR NVILFSVFDE NRSWYLTENI QRFLPNPAGV QLEDPEFQAS NIMHSINGYV FDSLQLSVCL HEVAYWYILS IGAQTDFLSV FFSGYTFKHK MVEDTLTLF PFSGETVFMS MENPGLWILG CHNSDFRNRG MTALLKVSSC DKNTGDYED SYEDISAYLL SKNNAIEPRS FSQNPPVLKE ITRTTLQSDQ EEIDYDDTIS VEMKKEDFDI YDEDENQSPR SFQKKTRHYF IAAVERLWDY GMSSSPHVLN NRAQSGSVPQ FKKVVFQEFT DGSFTQPLYR GELNEHLGLL GPYIRAEVED NIMVTFRNQA SRPYSFYSSL ISYEEDQRQG AEPRKNFVKP NETKTYFWKV QHHMAPTKDE FDCKAWAYFS DVDLEKDVHS GLIGPLLCH TNTLNPAHGR QVTVQEFALF FTIFDETKSW YFTENMERN RAPCNIQMED PTFKENYRFH AINGYIMDTL PGLVMAQDQR IRWYLLSMGS NENIHSIHFS GHVFTVRKKE EYKMALYNLY PGVFETVEML PSKAGIWRVE CLIGEHLHAG MSTLFLVYSN KCQTPLGMAS GHIRDFQITA SGQYGQWAPK LARLHYSI NAWSTKEPFS WIKVDLLAPM IIHGIKTQGA RQKFSSLYIS QFIIMYSLDG KKWQTYRGNS TGTLMVFFGN VDSSGIKHNI FNPPIIARYI RLHPHYSIR STLRMELMGC DLNSCSMPLG MESKAISDAQ ITASSYFTNM FATWSPSKAR LHLQGRSNAW RPQVNNPKEW LQVDFQKTMK VTGVTTQGVK SLTSMYVKE FLISSSQDGH QWTLFFQNGK VKVFQGNQDS FTPVNSLDP PLLTRYLRH PQSWVHQIAL RMEVLGCEAQ DLY
6	rhScFVIII-BDD 4	<u>MQIELSTCFE</u> <u>LCLLRFCFSA</u> TRYYLGAVE LSWDYMQSDL GELPVDARFP PRVPKSFPPN TSVVYKKTLE VEFTDHLFNI AKPRPPWMGL LGPTIQAEVY DTVVITLKNM ASHPVSLHAV GVSYWKASEG AEYDDQTSQR EKEDDKVFPG GSHTYVWQVL KENGPMASDP LCLTYSYLSH VDLVKDLNSG LIGALLVCRE GSLAKEKTQT LHKFILLFAV FDEGKSWHSE TKNSLMQDRD AASARAWPKM HTVNGYVNRS LPGLIGCHRK SVYWHVIGMG TTPEVHSIFL EGHTFLVRNH RQASLEISPI TFLTAQTLLM DLGQFLLFCH ISSHQHDGME AYVKVDSCPE EPQLRMKNNE EAEDYDDDLT DSEMDVVRFD DDNSPSFIQI RSVAKKHPKT WVHYIAAEEE DWDYAPLVLA PDDRSYKSQY LNNGPQRIGR KYKKVRFMAY TDETFKTREA IQHESGILGP LLYGEVGDTL LIIFKNQASR PYNIIYPHGIT DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR YYSSFVNMER DLASGLIGPL LICYKESVDQ RGNQIMSDKR NVILFSVFDE NRSWYLTENI QRFLPNPAGV QLEDPEFQAS NIMHSINGYV FDSLQLSVCL HEVAYWYILS IGAQTDFLSV FFSGYTFKHK MVEDTLTLF PFSGETVFMS MENPGLWILG CHNSDFRNRG MTALLKVSSC DKNTGDYED SYEDISAYLL SKNNAIEPRS FSQNPPVLKR EITRTTLQSD QEEIDYDDTI SVEMKKEDFD IYDEDENQSP RSFQKKTRHY FIAAVERLWD YGMSSSPHVL RNRAQSGSVP QFKKVVFQEF TDGSFTQPLY RGELNEHLGL LGPYIRAEVE DNIMVTFRNQ ASRPYSFYSS LISYEEDQRQ GAEPRKNFVK PNETKTYFWK VQHHMAPTKD EFDCKAWAYF SDVDLEKDVH SGLIGPLLVC HTNTLNPAHG RQVTVQEFAL FFTIFDETKS WYFTENMERN CRAPCNIQME DPTFKENYRF HAINGYIMDT LPGLVMAQDQ RIRWYLLSMG SNENIHSIHFS SGHVFTVRKK EYKMALYNL YPGVFETVEM LPSKAGIWRV ECLIGEHLHA GMSTLFLVYS NKCQTPLGMA SGHIRDFQIT ASGQYGQWAP KLARLHYSI INAWSTKEPF SWIKVDLLAP

		MIIHGIKTQG ARQKFSSLYI SQFIIMYSLD GKKWQTYRGN STGTLMVFFG NVDSSGIKHN IFNPPIIARY IRLHPTHYSI RSTLRMELMG CDLNCSMPL GMESKAISDA QITASSYFTN MFATWSPSKA RLHLQGRSNA WRPQVNNPKE WLQVDFQKTM KVTGVTTQGV KSLLTSMYVK EFLISSSQDG HQWTLFFQNG KVKVFQGNQD SFTPVVNSLD PPLLTRYLRI HPQSWVHQIA LRMEVLGCEA QDLY
7	rhFVIII-BDD addback	<u>MQIELSTCFF</u> LCLLRFCFSA TRRYYLGAVE LSWDYMQSDL GELPVDARFP PRVPKSFPPN TSVVYKKTLE VEFTDHLFNI AKPRPPWMGL LGPTIQAEVY DTVVITLKNM ASHPVSLHAV GVSYWKASEG AEYDDQTSQR EKEDDKVFPG GSHTYVWQVL KENGPMASDP LCLTYSYLSH VDLVKDLNSG LIGALLVCRE GSLAKEKTQT LHKFILLFAV FDEGKSWHSE TKNSLMQDRD AASARAWPKM HTVNGYVNRSLPGLIGCHRK SVYWHVIGMG TTPEVHSIFL EGHTFLVRNH RQASLEISPI TFLTAQTLLM DLGQFLLFCH ISSHQHDGME AYVKVDSCPE EPQLRMKNNE EAEDYDDDLT DSEMDVVRFD DDNSPSFIQI RSVAKKHPKT WVHYIAAEEE DWDYAPLVLA PDDRSYKSQY LNNGPQRIGR KYKKVRFMAY TDETFKTREA IQHESGILGP LLYGEVGDIT LIIFKNQASR PYNIIYPHGIT DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR YYSSFVNMER DLASGLIGPL LICYKESVDQ RGNQIMSDKR NVILFSVFDE NRSWYL TENI QRFLPNPAGV QLEDPEFQAS NIMHSINGYV FDSLQLSVCL HEVAYWYILS IGAQTDFLSV FFSGYTFKHK MVEDTLTLF PFSGETVFMS MENPGLWILG CHNSDFRNRG MTALLKVSSC DKNTGDYED SYEDISAYLL SKNNAIEPRS FSQNATNVSN NSNTSNDNSV SPPVLKRHRQ EITRTTLQSD QEEIDYDDTI SVEMKKEDFD IYDEDENQSP RSFQKKTRHY FIAAVERLWD YGMSSSPHVL RNRAQSGSVP QFKKVVQEF TDGSFTQPLY RGELNEHLGL LGPYIRAEVE DNIMVTFRNQ ASRPYSFYSS LISYEEDQRQ GAEPRKNFVK PNETKTYFWK VQHHMAPTKD EFDCKAWAYF SDVDLEKDVH SGLIGPLLVC HTNTLNPAHG RQVTVQEFAL FFTIFDETKS WYFTENMERN CRAPCNIQME DPTFKENYRF HAINGYIMDT LPGLVMAQDQ RIRWYLLSMG SNENIHSIHF SGHVFTVRKK EEYKMALYNL YPGVFETVEM LPSKAGIWRV ECLIGEHLHA GMSTLFLVYS NKCQTPLGMA SGHIRDFQIT ASGQYGQWAP KLARLHYS GS INAWSTKEPF SWIKVDLLAP MIIHGIKTQG ARQKFSSLYI SQFIIMYSLD GKKWQTYRGN STGTLMVFFG NVDSSGIKHN IFNPPIIARY IRLHPTHYSI RSTLRMELMG CDLNCSMPL GMESKAISDA QITASSYFTN MFATWSPSKA RLHLQGRSNA WRPQVNNPKE WLQVDFQKTM KVTGVTTQGV KSLLTSMYVK EFLISSSQDG HQWTLFFQNG KVKVFQGNQD SFTPVVNSLD PPLLTRYLRI HPQSWVHQIA LRMEVLGCEA QDLY

Table 5: FVIII Coding sequences expressed in ARPE-19 cells

SEQ ID NO:	Sequence Name	Nucleotide Sequence
8	rhFVIII-BDD	ATGCAAATAG AGCTCTCCAC CTGCTTCTTT CTGTGCCTTT TGCGATTCTG 50 CTTTAGTGCC ACCAGAAGAT ACTACCTGGG TGCACTGGAA CTGTCATGGG 100 ACTATATGCA AAGTGATCTC GGTGAGCTGC CTGTGGACGC AAGATTTTCT 150 CCTAGAGTGC CAAAATCTTT TCCATTCAAC ACCTCAGTCG TGTACAAAAA 200 GACTCTGTTT GTAGAATTCA CGGATCACCT TTTCAACATC GCTAAGCCAA 250 GGCCACCCTG GATGGGTCTG CTAGGTCCTA CCATCCAGGC TGAGGTTTAT 300 GATACAGTGG TCATTACACT TAAGAACATG GCTTCCCATC CTGTCACTCT 350 TCATGCTGTT GGTGTATCCT ACTGGAAAGC TTCTGAGGGA GCTGAATATG 400 ATGATCAGAC CAGTCAAAGG GAGAAAGAAG ATGATAAAGT CTTCCCTGGT 450 GGAAGCCATA CATATGTCTG GCAGGTCCTG AAAGAGAATG GTCCAATGGC 500

		CTCTGACCCA	CTGTGCCTTA	CCTACTCATA	TCTTTCTCAT	GTGGACCTGG	550
		TAAAAGACTT	GAATTCAGGC	CTCATTGGAG	CCCTACTAGT	ATGTAGAGAA	600
		GGGAGTCTGG	CCAAGGAAAA	GACACAGACC	TTGCACAAAT	TTATACTACT	650
		TTTTGCTGTA	TTTGATGAAG	GGAAAAGTTG	GCACTCAGAA	ACAAAGAACT	700
		CCTTGATGCA	GGATAGGGAT	GCTGCATCTG	CTCGGGCCTG	GCCTAAAATG	750
		CACACAGTCA	ATGGTTATGT	AAACAGGTCT	CTGCCAGGTC	TGATTGGATG	800
		CCACAGGAAA	TCAGTCTATT	GGCATGTGAT	TGGAATGGGC	ACCACTCCTG	850
		AAGTGCACTC	AATATTCCCTC	GAAGGTCACA	CATTTCTTGT	GAGGAACCAT	900
		CGCCAGGCGT	CCTTGGAAT	CTCGCCAATA	ACTTTCTCTTA	CTGCTCAAAC	950
		ACTCTTGATG	GACCTTGGAC	AGTTTCTACT	GTTTTGTCTAT	ATCTCTTCCC	1000
		ACCAACATGA	TGGCATGGAA	GCTTATGTCA	AAGTAGACAG	CTGTCCAGAG	1050
		GAACCCCAAC	TACGAATGAA	AAATAATGAA	GAAGCGGAAG	ACTATGATGA	1100
		TGATCTTACT	GATTCTGAAA	TGGATGTGGT	CAGGTTTGAT	GATGACAAC	1150
		CTCCTTCCTT	TATCCAAATT	CGCTCAGTTG	CCAAGAAGCA	TCCTAAAATG	1200
		TGGGTACATT	ACATTGCTGC	TGAAGAGGAG	GACTGGGACT	ATGCTCCCTT	1250
		AGTCCTCGCC	CCCGATGACA	GAAGTTATAA	AAGTCAATAT	TTGAACAATG	1300
		GCCCTCAGCG	GATTGGTAGG	AAGTACAAAA	AAGTCCGATT	TATGGCATA	1350
		ACAGATGAAA	CCTTTAAGAC	TCGTGAAGCT	ATTCAGCATG	AATCAGGAAT	1400
		CTTGGGACCT	TTACTTTTATG	GGGAAGTTGG	AGACACACTG	TTGATTATAT	1450
		TTAAGAATCA	AGCAAGCAGA	CCATATAACA	TCTACCCTCA	CGGAATCACT	1500
		GATGTCCGTC	CTTTGTATT	AAGGAGATTA	CCAAAAGGTG	TAAAACATTT	1550
		GAAGGATTTT	CCAATTCTGC	CAGGAGAAAT	ATTCAAATAT	AAATGGACAG	1600
		TGACTGTAGA	AGATGGGCCA	ACTAAATCAG	ATCCTCGGTG	CCTGACCCGC	1650
		TATTACTCTA	GTTTCGTTAA	TATGGAGAGA	GATCTAGCTT	CAGGACTCAT	1700
		TGGCCCTCTC	CTCATCTGCT	ACAAAGAATC	TGTAGATCAA	AGAGGAAACC	1750
		AGATAATGTC	AGACAAGAGG	AATGTCATCC	TGTTTTCTGT	ATTTGATGAG	1800
		AACCGAAGCT	GGTACCTCAC	AGAGAATATA	CAACGCTTTC	TCCCCAATCC	1850
		AGCTGGAGTG	CAGCTTGAGG	ATCCAGAGTT	CCAAGCCTCC	AACATCATGC	1900
		ACAGCATCAA	TGGCTATGTT	TTTGATAGTT	TGCAGTTGTC	AGTTTGTGTTG	1950
		CATGAGGTGG	CATACTGGTA	CATTCTAAGC	ATTGGAGCAC	AGACTGACTT	2000
		CCTTTCTGTC	TTCTTCTCTG	GATATACCTT	CAAAACAAA	ATGGTCTATG	2050
		AAGACACACT	CACCCTATTC	CCATTCTCAG	GAGAAACTGT	CTTCATGTCG	2100
		ATGGAAAACC	CAGGTCTATG	GATTCTGGGG	TGCCACAAC	CAGACTTTTCG	2150
		GAACAGAGGC	ATGACCGCCT	TACTGAAGGT	TTCTAGTTGT	GACAAGAACA	2200
		CTGGTGATTA	TTACGAGGAC	AGTTATGAAG	ATATTTTCAGC	ATACTTGCTG	2250
		AGTAAAAACA	ATGCCATTGA	ACCAAGAAGC	TTCTCCCAA	ACCCACCACT	2300
		CTTGAAACGC	CATCAACGGG	AAATAACTCG	TACTACTCTT	CAGTCAGATC	2350
		AAGAGGAAAT	TGACTATGAT	GATACCATAT	CAGTTGAAAT	GAAGAAGGAA	2400
		GATTTTGACA	TTTATGATGA	GGATGAAAAT	CAGAGCCCCC	GCAGCTTTCA	2450
		AAAGAAAACA	CGACACTATT	TTATTGCTGC	AGTGGAGAGG	CTCTGGGATT	2500
		ATGGGATGAG	TAGCTCCCCA	CATGTTCTAA	GAAACAGGGC	TCAGAGTGGC	2550
		AGTGTCCTC	AGTTCAAGAA	AGTTGTTTTT	CAGGAATTTA	CTGATGGCTC	2600
		CTTTACTCAG	CCCTTATACC	GTGGAGAACT	AAATGAACAT	TTGGGACTCC	2650
		TGGGGCCATA	TATAAGAGCA	GAAGTTGAAG	ATAATATCAT	GGTAACTTTC	2700
		AGAAATCAGG	CCTCTCGTCC	CTATTCCTTC	TATTCTAGCC	TTATTTCTTA	2750
		TGAGGAAGAT	CAGAGGCAAG	GAGCAGAACC	TAGAAAAAAC	TTTGTCAAGC	2800
		CTAATGAAAC	CAAACTTAC	TTTTGGAAAG	TGCAACATCA	TATGGCACCC	2850
		ACTAAAGATG	AGTTTGAATG	CAAAGCCTGG	GCTTATTTCT	CTGATGTTGA	2900
		CCTGGAAAAA	GATGTGCACT	CAGGCCTGAT	TGGACCCCTT	CTGGTCTGCC	2950
		ACACTAACAC	ACTGAACCCT	GCTCATGGGA	GACAAGTGAC	AGTACAGGAA	3000
		TTTGCTCTGT	TTTTCAACAT	CTTTGATGAG	ACCAAAAGCT	GGTACTTCAC	3050
		TGAAAATATG	GAAAGAACT	GCAGGGCTCC	CTGCAATATC	CAGATGGAAG	3100
		ATCCCACTTT	TAAAGAGAAT	TATCGCTTCC	ATGCAATCAA	TGGCTACATA	3150
		ATGGATACAC	TACCTGGCTT	AGTAATGGCT	CAGGATCAAA	GGATTGATG	3200
		GTATCTGCTC	AGCATGGGCA	GCAATGAAAA	CATCCATTCT	ATTCATTTCA	3250

		GTGGACATGT GTTCACTGTA CGAAAAAAG AGGAGTATAA AATGGCACTG 3300
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		GGATGAGCAC ACTTTTTCTG GTGTACAGCA ATAAGTGTCA GACTCCCCTG 3450
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		GACTTCACCT CCAAGGGAGG AGTAATGCCT GGAGACCTCA GGTGAATAAT 4050
		CCAAAAGAGT GGCTGCAAGT GGACTTCCAG AAGACAATGA AAGTCACAGG 4100
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		AGTTCCTCAT CTCCAGCAGT CAAGATGGCC ATCAGTGGAC TCTCTTTTTT 4200
		CAGAATGGCA AAGTAAAGGT TTTTCAGGGA AATCAAGACT CCTTCACACC 4250
		TGTGGTGAAC TCTCTAGACC CACCGTTACT GACTCGCTAC CTTCGAATTC 4300
		ACCCCAGAG TTGGGTGCAC CAGATTGCCC TGAGGATGGA GGTCTGGGC 4350
		TGCGAGGCAC AGGACCTCTA CTGA 4374
9	rhFVIII-BDD Sc1	ATGCAAATAG AGCTCTCCAC CTGCTTCTTT CTGTGCCTTT TGCGATTCTG
		CTTTAGTGCC ACCAGAAGAT ACTACCTGGG TGCACTGGAA CTGTCATGGG
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		CCTAGAGTGC CAAAATCTTT TCCATTCAAC ACCTCAGTCG TGTACAAAAA
		GACTCTGTTT GTAGAATTCA CGGATCACCT TTTCAACATC GCTAAGCCAA
		GGCCACCCTG GATGGGTCTG CTAGGTCTTA CCATCCAGGC TGAGGTTTAT
		GATACAGTGG TCATTACACT TAAGAACATG GCTTCCCATC CTGTCACTCT
		TCATGCTGTT GGTGTATCCT ACTGGAAAGC TTCTGAGGGA GCTGAAATATG
		ATGATCAGAC CAGTCAAAGG GAGAAAGAAG ATGATAAAGT CTTCCCTGGT
		GGAAGCCATA CATATGTCTG GCAGGTCTTG AAAGAGAATG GTCCAATGGC
		CTCTGACCCA CTGTGCCTTA CCTACTCATA TCTTTCTCAT GTGGACCTGG
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		GGGAGTCTGG CCAAGGAAAA GACACAGACC TTGCACAAAT TTATACTACT
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		TGATCTTACT GATTCTGAAA TGGATGTGGT CAGGTTTGAT GATGACAAC
		CTCCTTCCTT TATCCAAATT CGCTCAGTTG CCAAGAAGCA TCCTAAACT
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		AGTCCTCGCC CCCGATGACA GAAGTTATAA AAGTCAATAT TTGAACAATG
		GCCCTCAGCG GATTGGTAGG AAGTACAAAA AAGTCCGATT TATGGCATA
		ACAGATGAAA CCTTTAAGAC TCGTGAAGCT ATTCAGCATG AATCAGGAAT
		CTTGGGACCT TTACTTTATG GGGAAAGTTG AGACACACTG TTGATTATAT
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		TGACTGTAGA	AGATGGGCCA	ACTAAATCAG	ATCCTCGGTG	CCTGACCCGC
		TATTACTCTA	GTTTCGTTAA	TATGGAGAGA	GATCTAGCTT	CAGGACTCAT
		TGGCCCTCTC	CTCATCTGCT	ACAAAGAATC	TGTAGATCAA	AGAGGAAACC
		AGATAATGTC	AGACAAGAGG	AATGTCATCC	TGTTTTCTGT	ATTTGATGAG
		AACCGAAGCT	GGTACCTCAC	AGAGAATATA	CAACGCTTTC	TCCCCAATCC
		AGCTGGAGTG	CAGCTTGAGG	ATCCAGAGTT	CCAAGCCTCC	AACATCATGC
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		AGTGTCCCTC	AGTTCAAGAA	AGTTGTTTTT	CAGGAATTTA	CTGATGGCTC
		CTTTACTCAG	CCCTTATACC	GTGGAGAACT	AAATGAACAT	TTGGGACTCC
		TGGGGCCATA	TATAAGAGCA	GAAGTTGAAG	ATAATATCAT	GGTAACTTTC
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		TGAGGAAGAT	CAGAGGCAAG	GAGCAGAACC	TAGAAAAAAC	TTTGTCAAGC
		CTAATGAAAC	CAAAACTTAC	TTTTGGAAAG	TGCAACATCA	TATGGCACCC
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		CCTGGAAAAA	GATGTGCACT	CAGGCCTGAT	TGGACCCCTT	CTGGTCTGCC
		ACACTAACAC	ACTGAACCCT	GCTCATGGGA	GACAAGTGAC	AGTACAGGAA
		TTTGCTCTGT	TTTTCACCAT	CTTTGATGAG	ACCAAAAGCT	GGTACTTCAC
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		AGCTGGAATT	TGGCGGGTGG	AATGCCTTAT	TGGCGAGCAT	CTACATGCTG
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		GGAATGGCTT	CTGGACACAT	TAGAGATTTT	CAGATTACAG	CTTCAGGACA
		ATATGGACAG	TGGGCCCCAA	AGCTGGCCAG	ACTTCATTAT	TCCGGATCAA
		TCAATGCCTG	GAGCACCAAG	GAGCCCTTTT	CTTGGATCAA	GGTGGATCTG
		TTGGCACCAA	TGATTATTCA	CGGCATCAAG	ACCCAGGGTG	CCCGTCAGAA
		GTTCTCCAGC	CTCTACATCT	CTCAGTTTAT	CATCATGTAT	AGTCTTGATG
		GGAAGAAGTG	GCAGACTTAT	CGAGGAAATT	CCACTGGAAC	CTTAATGGTC
		TTCTTTGGCA	ATGTGGATTG	ATCTGGGATA	AAACACAATA	TTTTTAACCC
		TCCAATTATT	GCTCGATACA	TCCGTTTGCA	CCCAACTCAT	TATAGCATTC
		GCAGCACTCT	TCGCATGGAG	TTGATGGGCT	GTGATTTAAA	TAGTTGCAGC
		ATGCCATTGG	GAATGGAGAG	TAAAGCAATA	TCAGATGCAC	AGATTACTGC
		TTTCATCCTAC	TTTACCAATA	TGTTTGCCAC	CTGGTCTCCT	TCAAAAGCTC
		GACTTCACCT	CCAAGGGAGG	AGTAATGCCT	GGAGACCTCA	GGTGAATAAT
		CCAAAAGAGT	GGCTGCAAGT	GGACTTCCAG	AAGACAATGA	AAGTCACAGG
		AGTAACTACT	CAGGGAGTAA	AATCTCTGCT	TACCAGCATG	TATGTGAAGG
		AGTTCCTCAT	CTCCAGCAGT	CAAGATGGCC	ATCAGTGGAC	TCTCTTTTTT
		CAGAATGGCA	AAGTAAAGGT	TTTTTCAGGGA	AATCAAGACT	CCTTCACACC
		TGTGGTGAAC	TCTCTAGACC	CACCGTTACT	GACTCGCTAC	CTTCGAATTC

		ACCCCCAGAG TTGGGTGCAC CAGATTGCCG TGAGGATGGA GGTCTGCGC TGCGAGGCAC AGGACCTCTA CTGA
10	rhFVIII-BDD Sc2	ATGCAAATAG AGCTCTCCAC CTGCTTCTTT CTGTGCCTTT TGCGATTCTG 50 CTTTAGTGCC ACCAGAAGAT ACTACCTGGG TGCAGTGGAA CTGTCATGGG 100 ACTATATGCA AAGTGATCTC GGTGAGCTGC CTGTGGACGC AAGATTTCCCT 150 CCTAGAGTGC CAAAATCTTT TCCATTCAAC ACCTCAGTCG TGTACAAAAA 200 GACTCTGTTT GTAGAATTCA CGGATCACCT TTTCAACATC GCTAAGCCAA 250 GGCCACCCTG GATGGGTCTG CTAGGTCTTA CCATCCAGGC TGAGGTTTAT 300 GATACAGTGG TCATTACACT TAAGAACATG GCTTCCCATC CTGTCACTCT 350 TCATGCTGTT GGTGTATCCT ACTGGAAAGC TTCTGAGGGA GCTGAATATG 400 ATGATCAGAC CAGTCAAAGG GAGAAAGAAG ATGATAAAGT CTTCCCTGGT 450 GGAAGCCATA CATATGTCTG GCAGGTCTCTG AAAGAGAATG GTCCAATGGC 500 CTCTGACCCA CTGTGCCTTA CCTACTCATA TCTTTCTCAT GTGGACCTGG 550 TAAAAGACTT GAATTCAGGC CTCATTGGAG CCTACTAGT ATGTAGAGAA 600 GGGAGTCTGG CCAAGGAAAA GACACAGACC TTGCACAAAT TTATACTACT 650 TTTTGCTGTA TTTGATGAAG GGAAAAGTTG GCACTCAGAA ACAAAGAAGT 700 CCTTGATGCA GGATAGGGAT GCTGCATCTG CTCGGGCCTG GCCTAAAAATG 750 CACACAGTCA ATGGTTATGT AAACAGGTCT CTGCCAGGTC TGATTGGATG 800 CCACAGGAAA TCAGTCTATT GGCATGTGAT TGGAATGGGC ACCACTCCTG 850 AAGTGCACTC AATATTCCTC GAAGGTCACA CATTTCTTGT GAGGAACCAT 900 CGCCAGGCGT CTTTGGAAT CTCGCCAATA ACTTTCCTTA CTGCTCAAAC 950 ACTCTTGATG GACCTTGGAC AGTTTCTACT GTTTTGTCTAT ATCTCTTCCC 1000 ACCAACATGA TGGCATGGAA GCTTATGTCA AAGTAGACAG CTGTCCAGAG 1050 GAACCCCAAC TACGAATGAA AAATAATGAA GAAGCGGAAG ACTATGATGA 1100 TGATCTTACT GATTCTGAAA TGGATGTGGT CAGGTTTGAT GATGACAACT 1150 CTCCTTCCTT TATCCAAATT CGCTCAGTTG CCAAGAAGCA TCCTAAAACT 1200 TGGGTACATT ACATTGCTGC TGAAGAGGAG GACTGGGACT ATGCTCCCTT 1250 AGTCCTCGCC CCCGATGACA GAAGTTATAA AAGTCAATAT TTGAACAATG 1300 GCCCTCAGCG GATTGGTAGG AAGTACAAAA AAGTCCGATT TATGGCATAC 1350 ACAGATGAAA CCTTTAAGAC TCGTGAAGCT ATTCAGCATG AATCAGGAAT 1400 TTTGGGACCT TTACTTTATG GGAAGTTGG AGACACACTG TTGATTATAT 1450 TTAAGAATCA AGCAAGCAGA CCATATAACA TCTACCCTCA CGGAATCACT 1500 GATGTCCGTC CTTTGTATTC AAGGAGATTA CCAAAAGGTG TAAAACATTT 1550 GAAGGATTTT CCAATTCTGC CAGGAGAAAT ATTCAAATAT AAATGGACAG 1600 TGAAGTGTAG AGATGGGCCA ACTAAATCAG ATCCTCGGTG CCTGACCCGC 1650 TATTACTCTA GTTTCGTTAA TATGGAGAGA GATCTAGCTT CAGGACTCAT 1700 TGGCCCTCTC CTCATCTGCT ACAAAGAATC TGTAGATCAA AGAGGAAACC 1750 AGATAATGTC AGACAAGAGG AATGTCATCC TGTTTTCTGT ATTTGATGAG 1800 AACCGAAGCT GGTACCTCAC AGAGAATATA CAACGCTTTC TCCCAATCC 1850 AGCTGGAGTG CAGCTTGAGG ATCCAGAGTT CCAAGCCTCC AACATCATGC 1900 ACAGCATCAA TGGCTATGTT TTTGATAGTT TGCAGTTGTC AGTTTGTTTG 1950 CATGAGGTGG CATACTGGTA CATTCTAAGC ATTGAGGCAC AGACTGACTT 2000 CCTTTCTGTC TTCTTCTCTG GATATACCTT CAAACACAAA ATGGTCTATG 2050 AAGACACACT CACCCTATTC CCATTCTCAG GAGAACTGT CTTCATGTCTG 2100 ATGGAAAACC CAGGTCTATG GATTCTGGGG TGCCACAACCT CAGACTTTCG 2150 GAACAGAGGC ATGACCGCCT TACTGAAGGT TTCTAGTTGT GACAAGAACA 2200 CTGGTGATTA TTACGAGGAC AGTTATGAAG ATATTTTCAGC ATACTTGCTG 2250 AGTAAAAACA ATGCCATTGA ACCAAGAAGC TTCTCCCAA ACCCACCAGT 2300 CTTGAAAGCC CATCAAGCGG AAATAACTCG TACTACTCTT CAGTCAGATC 2350 AAGAGGAAAT TGACTATGAT GATACCATAT CAGTTGAAAT GAAGAAGGAA 2400 GATTTTGACA TTTATGATGA GGATGAAAAT CAGAGCCCCC GCAGCTTTCA 2450 AAAGAAAACA CGACACTATT TTATTGCTGC AGTGGAGAGG CTCTGGGATT 2500 ATGGGATGAG TAGCTCCCCA CATGTTCTAA GAAACAGGGC TCAGAGTGGC 2550 AGTGTCCCTC AGTTCAAGAA AGTTGTTTTT CAGGAATTTA CTGATGGCTC 2600 CTTTACTCAG CCCTTATACC GTGGAGAACT AAATGAACAT TTGGGACTCC 2650

		TGGGGCCATA TATAAGAGCA GAAGTTGAAG ATAATATCAT GGTAACCTTC 2700 AGAAATCAGG CCTCTCGTCC CTATTCCTTC TATTCTAGCC TTATTTCTTA 2750 TGAGGAAGAT CAGAGGCAAG GAGCAGAACC TAGAAAAAAC TTTGTCAAGC 2800 CTAATGAAAC CAAAACCTTAC TTTTGGAAG TGCAACATCA TATGGCACCC 2850 ACTAAAGATG AGTTTGACTG CAAAGCCTGG GCTTATTTCT CTGATGTTGA 2900 CCTGGAAAAA GATGTGCACT CAGGCCTGAT TGGACCCCTT CTGGTCTGCC 2950 ACACTAACAC ACTGAACCCT GCTCATGGGA GACAAGTGAC AGTACAGGAA 3000 TTTGCTCTGT TTTTCACCAT CTTTGATGAG ACCAAAAGCT GGTACTTCAC 3050 TGAAAATATG GAAAGAACT GCAGGGCTCC CTGCAATATC CAGATGGAAG 3100 ATCCCACTTT TAAAGAGAAT TATCGCTTCC ATGCAATCAA TGGCTACATA 3150 ATGGATACAC TACCTGGCTT AGTAATGGCT CAGGATCAAA GGATTGATG 3200 GTATCTGCTC AGCATGGGCA GCAATGAAAA CATCCATTCT ATTCAATTTCA 3250 GTGGACATGT GTTCACTGTA CGAAAAAAG AGGAGTATAA AATGGCCTG 3300 TACAATCTCT ATCCAGGTGT TTTTGAGACA GTGGAAATGT TACCATCCAA 3350 AGCTGGAATT TGGCGGGTGG AATGCCTTAT TGGCGAGCAT CTACATGCTG 3400 GGATGAGCAC ACTTTTTCTG GTGTACAGCA ATAAGTGTCA GACTCCCTG 3450 GGAATGGCTT CTGGACACAT TAGAGATTTT CAGATTACAG CTTCAGGACA 3500 ATATGGACAG TGGGCCCCAA AGCTGGCCAG ACTTCATTAT TCCGGATCAA 3550 TCAATGCCTG GAGCACCAAG GAGCCCTTTT CTTGGATCAA GGTGGATCTG 3600 TTGGCACCAA TGATTATTCA CGGCATCAAG ACCCAGGGTG CCCGTCAGAA 3650 GTTCTCCAGC CTCTACATCT CTCAGTTTAT CATCATGTAT AGTCTTGATG 3700 GGAAGAAGTG GCAGACTTAT CGAGGAAATT CCACTGGAAC CTTAATGGTC 3750 TTCTTTGGCA ATGTGGATTG ATCTGGGATA AAACACAATA TTTTAAACCC 3800 TCCAATTATT GCTCGATACA TCCGTTTGCA CCCAACTCAT TATAGCATTC 3850 GCAGCACTCT TCGCATGGAG TTGATGGGCT GTGATTTAAA TAGTTGCAGC 3900 ATGCCATTGG GAATGGAGAG TAAAGCAATA TCAGATGCAC AGATTACTGC 3950 TTCATCCTAC TTTACCAATA TGTTTGCCAC CTGGTCTCCT TCAAAAGCTC 4000 GACTTCACCT CCAAGGGAGG AGTAATGCCT GGAGACCTCA GGTGAATAAT 4050 CCAAAAGAGT GGCTGCAAGT GGAATTCAGG AAGACAATGA AAGTCACAGG 4100 AGTAACTACT CAGGGAGTAA AATCTCTGCT TACCAGCATG TATGTGAAGG 4150 AGTTCCCTCAT CTCCAGCAGT CAAGATGGCC ATCAGTGGAC TCTCTTTTCT 4200 CAGAATGGCA AAGTAAAGGT TTTTCAGGGA AATCAAGACT CCTTCACACC 4250 TGTGGTGAAC TCTCTAGACC CACCGTTACT GACTCGCTAC CTTGCAATTC 4300 ACCCCCAGAG TTGGGTGCAC CAGATTGCCC TGAGGATGGA GGTTCCTGGG 4350 TGCGAGGCAC AGGACCTCTA CTGA 4374
11	rhFVIII-BDD Sc3	ATGCAAATAG AGCTCTCCAC CTGCTTCTTT CTGTGCCTTT TGCGATTCTG CTTTAGTGCC ACCAGAAGAT ACTACCTGGG TGCAGTGGAA CTGTCATGGG ACTATATGCA AAGTGATCTC GGTGAGCTGC CTGTGGACGC AAGATTTCTT CCTAGAGTGC CAAAATCTTT TCCATTCAAC ACCTCAGTCG TGTACAAAAA GACTCTGTTT GTAGAATTCA CGGATCACCT TTTCAACATC GCTAAGCCAA GGCCACCCTG GATGGGTCTG CTAGGTCCTA CCATCCAGGC TGAGGTTTAT GATACAGTGG TCATTACACT TAAGAACATG GCTTCCCATC CTGTCAGTCT TCATGCTGTT GGTGTATCCT ACTGGAAAGC TTCTGAGGGA GCTGAATATG ATGATCAGAC CAGTCAAAGG GAGAAAGAAG ATGATAAAGT CTTCCCTGGT GGAAGCCATA CATATGTCTG GCAGGTCTCT AAAGAGAATG GTCCAATGGC CTCTGACCCA CTGTGCCTTA CCTACTCATA TCTTTCTCAT GTGGACCTGG TAAAAGACTT GAATTCAGGC CTCATTGGAG CCCTACTAGT ATGTAGAGAA GGGAGTCTGG CCAAGGAAAA GACACAGACC TTGCACAAAT TTATACTACT TTTTGCTGTA TTTGATGAAG GGAAAAGTTG GCACTCAGAA ACAAAGAACT CCTTGATGCA GGATAGGGAT GCTGCATCTG CTCGGGCCTG GCCTAAAATG CACACAGTCA ATGGTTATGT AAACAGGTCT CTGCCAGGTC TGATTGGATG CCACAGGAAA TCAGTCTATT GGCATGTGAT TGGAATGGGC ACCACTCCTG AAGTGCATC AATATTCCTC GAAGGTCACA CATTTCTTGT GAGGAACCAT CGCCAGGCGT CTTTGAAAT CTCGCCAATA ACTTTCCTTA CTGCTCAAAC ACTCTTGATG GACCTTGGAC AGTTTCTACT GTTTTGTCTAT ATCTCTTCCC

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		TGGGTACATT	ACATTGCTGC	TGAAGAGGAG	GACTGGGACT	ATGCTCCCTT
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		TTAAGAATCA	AGCAAGCAGA	CCATATAACA	TCTACCCTCA	CGGAATCACT
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		GAAGGATTTT	CCAATTCTGC	CAGGAGAAAT	ATTCAAATAT	AAATGGACAG
		TGACTGTAGA	AGATGGGCCA	ACTAAATCAG	ATCCTCGGTG	CCTGACCCGC
		TATTACTCTA	GTTTCGTTAA	TATGGAGAGA	GATCTAGCTT	CAGGACTCAT
		TGGCCCTCTC	CTCATCTGCT	ACAAAGAATC	TGTAGATCAA	AGAGGAAACC
		AGATAATGTC	AGACAAGAGG	AATGTCATCC	TGTTTTCTGT	ATTTGATGAG
		AACCGAAGCT	GGTACCTCAC	AGAGAATATA	CAACGCTTTC	TCCCCAATCC
		AGCTGGAGTG	CAGCTTGAGG	ATCCAGAGTT	CCAAGCCTCC	AACATCATGC
		ACAGCATCAA	TGGCTATGTT	TTTGATAGTT	TGCAGTTGTC	AGTTTGTTTG
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		CCTTTCTGTC	TTCTTCTCTG	GATATACCTT	CAAACACAAA	ATGGTCTATG
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		CTTATACCGT	GGAGAATAA	ATGAACATTT	GGGACTCCTG	GGGCCATATA
		TAAGAGCAGA	AGTTGAAGAT	AATATCATGG	TAACTTTCAG	AAATCAGGCC
		TCTCGTCCCT	ATTCCTTCTA	TTCTAGCCTT	ATTTCTTATG	AGGAAGATCA
		GAGGCAAGGA	GCAGAACCTA	GAAAAAACTT	TGTCAAGCCT	AATGAAACCA
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		TTTGACTGCA	AAGCCTGGGC	TTATTTCTCT	GATGTTGACC	TGGAAAAAGA
		TGTGCACTCA	GGCCTGATTG	GACCCCTTCT	GGTCTGCCAC	ACTAACACAC
		TGAACCCTGC	TCATGGGAGA	CAAGTGACAG	TACAGGAATT	TGCTCTGTTT
		TTCAACCATCT	TTGATGAGAC	CAAAAGCTGG	TACTTCACTG	AAAATATGGA
		AAGAACTGC	AGGGCTCCCT	GCAATATCCA	GATGGAAGAT	CCCACTTTTA
		AAGAGAATTA	TCGCTTCCAT	GCAATCAATG	GCTACATAAT	GGATACACTA
		CCTGGCTTAG	TAATGGCTCA	GGATCAAAGG	ATTCGATGGT	ATCTGCTCAG
		CATGGGCAGC	AATGAAAACA	TCCATTCTAT	TCATTTTCAGT	GGACATGTGT
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		CCAGGTGTTT	TTGAGACAGT	GGAAATGTTA	CCATCCAAAG	CTGGAATTTG
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		GGACACATTA	GAGATTTTCA	GATTACAGCT	TCAGGACAAT	ATGGACAGTG
		GGCCCCAAAG	CTGGCCAGAC	TTCATTATTC	CGGATCAATC	AATGCCTGGA
		GCACCAAGGA	GCCCTTTTCT	TGGATCAAGG	TGGATCTGTT	GGCACCAATG
		ATTATTCACG	GCATCAAGAC	CCAGGGTGCC	CGTCAGAAGT	TCTCCAGCCT
		CTACATCTCT	CAGTTTATCA	TCATGTATAG	TCTTGATGGG	AAGAAGTGGC
		AGACTTATCG	AGGAAATTCC	ACTGGAACCT	TAATGGTCTT	CTTTGGCAAT

		GTGGATTCAT CTGGGATAAA ACACAATATT TTTAACCCCTC CAATTATTGC TCGATACATC CGTTTGCACC CAACTCATTAG TAGCATTTCGC AGCACTCTTC GCATGGAGTT GATGGGCTGT GATTTAAATA GTTGCAGCAT GCCATTGGGA ATGGAGAGTA AAGCAATATC AGATGCACAG ATTACTGCTT CATCCTACTT TACCAATATG TTTGCCACCT GGTCTCCTTC AAAAGCTCGA CTTCACCTCC AAGGGAGGAG TAATGCCTGG AGACCTCAGG TGAATAATCC AAAAGAGTGG CTGCAAGTGG ACTTCCAGAA GACAATGAAA GTCACAGGAG TAACTACTCA GGGAGTAAAA TCTCTGCTTA CCAGCATGTA TGTGAAGGAG TTCCTCATCT CCAGCAGTCA AGATGGCCAT CAGTGGACTC TCTTTTTTCA GAATGGCAAA GTAAAGGTTT TTCAGGGAAA TCAAGACTCC TTCACACCTG TGGTGAAGTCC TCTAGACCCA CCGTTACTGA CTCGCTACCT TCGAATTCAC CCCCAGAGTT GGGTGCACCA GATTGCCCTG AGGATGGAGG TTCTGGGCTG CGAGGCACAG GACCTCTACT GA
12	rhFVIII-BDD Sc4	ATGCAAATAG AGCTCTCCAC CTGCTTCTTT CTGTGCCTTT TGCGATTCTG CTTTAGTGCC ACCAGAAGAT ACTACCTGGG TGCAGTGGAA CTGTCATGGG ACTATATGCA AAGTGATCTC GGTGAGCTGC CTGTGGACGC AAGATTTCTT CCTAGAGTGC CAAAATCTTT TCCATTCAAC ACCTCAGTCG TGTACAAAAA GACTCTGTTT GTAGAATTCA CGGATCACCT TTTCAACATC GCTAAGCCAA GGCCACCCTG GATGGGTCTG CTAGGTCCTA CCATCCAGGC TGAGGTTTAT GATACAGTGG TCATTACACT TAAGAACATG GCTTCCCATC CTGTCAGTCT TCATGCTGTT GGTGTATCCT ACTGGAAAGC TTCTGAGGGA GCTGAATATG ATGATCAGAC CAGTCAAAGG GAGAAAGAAG ATGATAAAGT CTTCCCTGGT GGAAGCCATA CATATGTCTG GCAGGTCCTG AAAGAGAATG GTCCAATGGC CTCTGACCCA CTGTGCCTTA CCTACTCATA TCTTTCTCAT GTGGACCTGG TAAAAGACTT GAATTCAGGC CTCATTGGAG CCCTACTAGT ATGTAGAGAA GGGAGTCTGG CCAAGGAAAA GACACAGACC TTGCACAAAT TTATACTACT TTTTGCTGTA TTTGATGAAG GGAAAAGTTG GCACTCAGAA ACAAAGAACT CCTTGATGCA GGATAGGGAT GCTGCATCTG CTCGGGCCTG GCCTAAAATG CACACAGTCA ATGGTTATGT AAACAGGTCT CTGCCAGGTC TGATTGGATG CCACAGGAAA TCAGTCTATT GGCATGTGAT TGGAATGGGC ACCACTCCTG AAGTGCACCT AATATTCCTC GAAGGTCACA CATTTCCTGT GAGGAACCAT CGCCAGGCGT CTTTGGAAAT CTCGCCAATA ACTTTCCTTA CTGCTCAAAC ACTCTTGATG GACCTTGGAC AGTTTCTACT GTTTTGTCTAT ATCTCTTCCC ACCAACATGA TGGCATGGAA GCTTATGTCA AAGTAGACAG CTGTCCAGAG GAACCCCAAC TACGAATGAA AAATAATGAA GAAGCGGAAG ACTATGATGA TGATCTTACT GATTCTGAAA TGGATGTGGT CAGGTTTGAT GATGACAACT CTCCTTCCTT TATCCAAATT CGCTCAGTTG CCAAGAAGCA TCCTAAACT TGGGTACATT ACATTGCTGC TGAAGAGGAG GACTGGGACT ATGCTCCCTT AGTCCTCGCC CCCGATGACA GAAGTTATAA AAGTCAATAT TTGAACAATG GCCCTCAGCG GATTGGTAGG AAGTACAAAA AAGTCCGATT TATGGCATACT ACAGATGAAA CCTTTAAGAC TCGTGAAGCT ATTCAGCATG AATCAGGAAT CTTGGGACCT TTACTTTATG GGGAAAGTTGG AGACACACTG TTGATTATAT TTAAGAATCA AGCAAGCAGA CCATATAACA TCTACCCTCA CGGAATCACT GATGTCCGTC CTTTGTATTC AAGGAGATTA CAAAAGGTG TAAAACATTT GAAGGATTTT CCAATTCTGC CAGGAGAAAT ATTCAAATAT AAATGGACAG TGAATGTAGA AGATGGGCCA ACTAAATCAG ATCCTCGGTG CCTGACCCGC TATTACTCTA GTTTCGTTAA TATGGAGAGA GATCTAGCTT CAGGACTCAT TGGCCCTCTC CTCATCTGCT ACAAAGAATC TGTAAGTCAA AGAGGAAACC AGATAATGTC AGACAAGAGG AATGTCATCC TGTTTTCTGT ATTTGATGAG AACCGAAGCT GGTACCTCAC AGAGAATATA CAACGCTTTC TCCCCAATCC AGCTGGAGTG CAGCTTGAGG ATCCAGAGTT CCAAGCCTCC AACATCATGC ACAGCATCAA TGGCTATGTT TTTGATAGTT TGCAGTTGTC AGTTTGTGTTG CATGAGGTGG CATACTGGTA CATTCTAAGC ATTGGAGCAC AGACTGACTT CCTTTCTGTC TTCTTCTCTG GATATACCTT CAAACACAAA ATGGTCTATG AAGACACACT CACCCTATTC CCATTCTCAG GAGAACTGT CTTCATGTCTG

		ATGGAAAACC CAGGTCTATG GATTCTGGGG TGCCACAAC T CAGACTTTCG GAACAGAGGC ATGACCGCCT TACTGAAGGT TTCTAGTTGT GACAAGAACA CTGGTGATTA TTACGAGGAC AGTTATGAAG ATATTTTCAGC ATACTTGCTG AGTAAAAACA ATGCCATTGA ACCAAGAAGC TTCTCCCAAA ACCCACCAGT CTTGAAACGC GAAATAACTC GTACTACTCT TCAGTCAGAT CAAGAGGAAA TTGACTATGA TGATACCATA TCAGTTGAAA TGAAGAAGGA AGATTTTGAC ATTTATGATG AGGATGAAAA TCAGAGCCCC CGCAGCTTTC AAAAGAAAAAC ACGACACTAT TTTATTGCTG CAGTGGAGAG GCTCTGGGAT TATGGGATGA GTAGCTCCCC ACATGTTCTA AGAAACAGGG CTCAGAGTGG CAGTGTCCCT CAGTTCAGA AAGTTGTTTT CCAGGAATTT ACTGATGGCT CCTTTACTCA GCCCTTATAC CGTGGAGAAC TAAATGAACA TTTGGGACTC CTGGGGCCAT ATATAAGAGC AGAAGTTGAA GATAATATCA TGGTAACTTT CAGAAATCAG GCCTCTCGTC CCTATTCCTT CTATTCTAGC CTTATTTCTT ATGAGGAAGA TCAGAGGCAA GGAGCAGAAC CTAGAAAAAA CTTTGTCAG CCTAATGAAA CCAAACTTA CTTTTGGAAA GTGCAACATC ATATGGCACC CACTAAAGAT GAGTTTGACT GCAAAGCCTG GGCTTATTTT TCTGATGTTG ACCTGAAAAA AGATGTGCAC TCAGGCCTGA TTGGACCCCT TCTGGTCTGC CACACTAACA CACTGAACCC TGCTCATGGG AGACAAGTGA CAGTACAGGA ATTTGCTCTG TTTTTCACCA TCTTTGATGA GACCAAAAGC TGGTACTTCA CTGAAAATAT GGAAAGAAAC TGCAGGGCTC CCTGCAATAT CCAGATGGAA GATCCCACTT TTAAAGAGAA TTATCGCTTC CATGCAATCA ATGGCTACAT AATGGATACA CTACCTGGCT TAGTAATGGC TCAGGATCAA AGGATTTCGAT GGTATCTGCT CAGCATGGGC AGCAATGAAA ACATCCATTC TATTCATTTT AGTGGACATG TGTTCACTGT ACGAAAAAAA GAGGAGTATA AAATGGCACT GTACAATCTC TATCCAGGTG TTTTTGAGAC AGTGGAAATG TTACCATCCA AAGCTGGAAT TTGGCGGGTG GAATGCCTTA TTGGCGAGCA TCTACATGCT GGGATGAGCA CACTTTTTCT GGTGTACAGC AATAAGTGTC AGACTCCCCT GGAATGGCT TCTGGACACA TTAGAGATTT TCAGATTACA GCTTCAGGAC AATATGGACA GTGGGCCCCA AAGCTGGCCA GACTTCATTA TTCCGGATCA ATCAATGCCT GGAGCACCAA GGAGCCCTTT TCTTGATCA AGGTGGATCT GTTGGCACCA ATGATTATTC ACGGCATCAA GACCCAGGGT GCCCGTCAGA AGTTCTCCAG CCTCTACATC TCTCAGTTTA TCATCATGTA TAGTCTTGAT GGAAGAAGT GGCAGACTTA TCGAGGAAAT TCCACTGGAA CCTTAATGGT CTTCTTTGGC AATGTGGATT CATCTGGGAT AAAACACAAT ATTTTTTAACC CTCCAATTAT TGCTCGATAC ATCCGTTTGC ACCCAACTCA TTATAGCATT CGCAGCACTC TTCGCATGGA GTTGATGGGC TGTGATTTAA ATAGTTGCAG CATGCCATTG GGAATGGAGA GTAAAGCAAT ATCAGATGCA CAGATTACTG CTTTCATCTA CTTTACCAAT ATGTTTGCCA CCTGGTCTCC TTCAAAGCT CGACTTCACC TCCAAGGGAG GAGTAATGCC TGGAGACCTC AGGTGAATAA TCCAAAAGAG TGGCTGCAAG TGGACTTCCA GAAGACAATG AAAGTCACAG GAGTAACTAC TCAGGGAGTA AAATCTCTGC TTACCAGCAT GTATGTGAAG GAGTTCCTCA TCTCCAGCAG TCAAGATGGC CATCAGTGGA CTCTCTTTTT TCAGAATGGC AAAGTAAAGG TTTTTCAGGG AAATCAAGAC TCCTTCACAC CTGTGGTGAA CTCTCTAGAC CCACCGTTAC TGAATCGCTA CCTTCGAATT CACCCCAAGA GTTGGGTGCA CCAGATTGCC CTGAGGATGG AGGTTCCTGG CTGCGAGGCA CAGGACCTCT ACTGA
13	rhFVIII-BDD CO2	ATGCAGATCG AGCTGTCTAC CTGCTTCTTC CTGTGCCTGC TCGGGTTCTG 50 CTTCAGCGCC ACCAGAAGAT ATTACCTGGG CGCCGTGGAA CTGAGCTGGG 100 ACTACATGCA GTCTGACCTG GGAGAGCTGC CCGTGGACGC TAGATTTCTT 150 CCAAGAGTGC CCAAGAGCTT CCCCTTCAAC ACCTCCGTGG TGTACAAGAA 200 AACCTGTTC GTGGAATTCA CCGACCACCT GTTCAATATC GCCAAGCCTC 250 GGCCTCCTTG GATGGGACTG CTGGGACCTA CAATTCAGGC CGAGGTGTAC 300 GACACCGTGG TCATCACCTT GAAGAACATG GCCAGCCATC CTGTGTCTCT 350 GCACGCCGTG GGAGTGTCTT ACTGGAAGGC TTCTGAGGGC GCCGAGTACG 400 ACGATCAGAC AAGCCAGAGA GAGAAAGAGG ACGACAAGGT TTTCCCTGGC 450

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		TCAAGGACCT	GAATTCTGGC	CTGATCGGAG	CCCTGCTCGT	GTGTAGAGAA	600
		GGCAGCCTGG	CCAAAGAGAA	AACCCAGACA	CTGCACAAGT	TCATCCTGCT	650
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		GCCTGATGCA	GGACAGGGAT	GCCGCCTCTG	CTAGAGCTTG	GCCTAAGATG	750
		CACACCGTGA	ACGGCTACGT	GAACAGAAGC	CTGCCTGGAC	TGATCGGCTG	800
		CCACAGAAAG	TCCGTGTACT	GGCACGTGAT	CGGCATGGGC	ACAACACCTG	850
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		CCTGCTGATG	GATCTGGGCC	AGTTTCTGCT	GTTCTGCCAC	ATCAGCTCCC	1000
		ACCAGCACGA	TGGCATGGAA	GCCTACGTGA	AGGTGGACAG	CTGCCCCGAA	1050
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		TGGGTGCACT	ATATCGCCGC	CGAGGAAGAG	GACTGGGATT	ACGCTCCTCT	1250
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		GATGTGCGGC	CCCTGTATTG	TAGAAGGCTG	CCCAAGGGCG	TGAAGCACCT	1550
		GAAGGACTTC	CCTATCCTGC	CTGGCGAGAT	CTTCAAGTAC	AAGTGGACCG	1600
		TGACCGTGGA	AGATGGCCCC	ACCAAGAGCG	ACCCTAGATG	TCTGACACGG	1650
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		TGGACCTCTG	CTGATCTGCT	ACAAAGAAAG	CGTGGACCAG	CGGGGCAACC	1750
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		AACCGGTCCT	GGTATCTGAC	CGAGAACATC	CAGCGGTTTC	TGCCCCAATCC	1850
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		ACTCCATCAA	TGGCTATGTG	TTCGACAGCC	TGCAGCTGAG	CGTGTGCCTG	1950
		CACGAAGTGG	CCTACTGGTA	CATCCTGAGC	ATTGGCGGCC	AGACCGCACTT	2000
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		ATCCACCTT	CAAAGAGAAC	TACCGGTTCC	ACGCCATCAA	CGGCTACATC	3150
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		TGTGAAGCTC AGGACCTCTA CTGA 4374
14	rhFVIII-BDD CO3	ATGCAGATCG AGCTGAGCAC CTGCTTCTTC CTGTGCCTGC TGCGCTTCTG 50
		CTTCAGCGCC ACCCGCCGCT ACTACCTGGG CGCCGTGGAG CTGAGCTGGG 100
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		CCCCGCGTGC CCAAGAGCTT CCCCTTCAAC ACCAGCGTGG TGTACAAGAA 200
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		TGACCGTGGA	GGACGGCCCC	ACCAAGAGCG	ACCCCGCTG	CCTGACCCGC	1650
		TACTACAGCA	GCTTCGTGAA	CATGGAGCGC	GACCTGGCCA	GCGGCCTGAT	1700
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		ACAGCATCAA	CGGCTACGTG	TTCGACAGCC	TGCAGCTGAG	CGTGTGCCTG	1950
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		AGCGTGCCCC	AGTTCAAGAA	GGTGGTGTTC	CAGGAGTTCA	CCGACGGCAG	2600
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		TACAACCTGT	ACCCCGGCGT	GTTCGAGACC	GTGGAGATGC	TGCCCAGCAA	3350
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		GCATGAGCAC	CCTGTTCTCTG	GTGTACAGCA	ACAAGTGCCA	GACCCCCCTG	3450
		GGCATGGCCA	GCGGCCACAT	CCGCGACTTC	CAGATCACCG	CCAGCGGCCA	3500
		GTACGGCCAG	TGGGCCCCCA	AGCTGGCCCG	CCTGCACTAC	AGCGGCAGCA	3550
		TCAACGCCTG	GAGCACCAAG	GAGCCCTTCA	GCTGGATCAA	GGTGGACCTG	3600
		CTGGCCCCCA	TGATCATCCA	CGGCATCAAG	ACCCAGGGCG	CCCGCCAGAA	3650
		GTTCAGCAGC	CTGTACATCA	GCCAGTTCAT	CATCATGTAC	AGCCTGGACG	3700
		GCAAGAAGTG	GCAGACCTAC	CGCGGCAACA	GCACCGGCAC	CCTGATGGTG	3750
		TTCTTCGGCA	ACGTGGACAG	CAGCGGCATC	AAGCACAACA	TCTTCAACCC	3800
		CCCCATCATC	GCCCCGCTACA	TCCGCCTGCA	CCCCACCCAC	TACAGCATCC	3850
		GCAGCACCTT	GCGCATGGAG	CTGATGGGCT	GCGACCTGAA	CAGCTGCAGC	3900
		ATGCCCCCTGG	GCATGGAGAG	CAAGGCCATC	AGCGACGCCC	AGATCACCGC	3950
		CAGCAGCTAC	TTCACCAACA	TGTTTCGCCAC	CTGGAGCCCC	AGCAAGGCCC	4000
		GCCTGCACCT	GCAGGGCCGC	AGCAACGCCT	GGCGCCCCCA	GGTGAACAAC	4050
		CCCAAGGAGT	GGCTGCAGGT	GGACTTCCAG	AAGACCATGA	AGGTGACCGG	4100
		CGTGACCACC	CAGGGCGTGA	AGAGCCTGCT	GACCAGCATG	TACGTGAAGG	4150
		AGTTCCTGAT	CAGCAGCAGC	CAGGACGGCC	ACCAGTGGAC	CCTGTTCTTC	4200
		CAGAACGGCA	AGGTGAAGGT	GTTCCAGGGC	AACCAGGACA	GCTTCACCCC	4250
		CGTGGTGAAC	AGCCTGGACC	CCCCCCTGCT	GACCCGCTAC	CTGCGCATCC	4300

		ACCCCCAGAG CTGGGTGCAC CAGATCGCCC TGCGCATGGA GGTGCTGGGC 4350
		TGCGAGGCCC AGGACCTGTA CTGA 4374
15	rhFVIII-BDD CO6	ATGCAGATTG AGCTGAGCAC CTGTTTCTTC CTGTGCCTGC TGAGATTTTG 50 CTTCTCAGCT ACCCGCAGGT ACTACCTGGG AGCCGTTGAG CTGTCTCTGGG 100 ATTACATGCA GTCAGATCTG GGGGAGCTGC CTGTGGACGC TCGGTTTCCC 150 CCCAGAGTGC CAAAGTCCTT TCCCTTCAAC ACCAGCGTGG TGTACAAAAA 200 GACACTTTTT GTTGAATTTA CTGACCACTT GTTCAACATC GCCAAGCCAC 250 GACCCCCATG GATGGGCCTG CTGGGGCCAA CCATTTCAGGC AGAGGTTTAC 300 GACACAGTCG TGATCACACT GAAGAACATG GCCTCCCATC CAGTGTCTCT 350 GCACGCCGTC GGTGTGTCTT ACTGGAAAGC ATCCGAGGGC GCCGAGTATG 400 ACGACCAGAC CAGCCAGAGA GAGAAAGAGG ACGACAAAGT GTTCCCTGGA 450 GGCAGCCACA CCTACGTGTG GCAGGTGTTG AAGGAAAATG GGCCCATGGC 500 CAGTGACCCT TTGTGTCTGA CTTACTCATA CCTGTCTCAT GTGGACTAG 550 TCAAGGACCT GAATTCTGGA CTGATTGGGG CACTGCTTGT GTGCCGCGAA 600 GGCAGCCTGG CCAAAGAAAA GACACAGACC CTTACAAGT TCATCCTGCT 650 GTTCCGCCGTG TTGCAGCAAG GCAAATCCTG GCACTCAGAA ACCAAAAACT 700 CACTGATGCA GGACCGGGAT GCCGCCTCTG CCCGCGCATG GCCAAAAATG 750 CACACCGTCA ACGGCTATGT CAATAGAAGT TTGCCCCGCC TCATTGGATG 800 TCACAGGAAA AGCGTCTATT GGCATGTAAT CGGGATGGGA ACCACACCTG 850 AGGTCCACAG CATATTTCTG GAAGGCCACA CATTTCTGGT GAGAAATCAT 900 CGCCAGGCTT CCCTGGAAAT TTCCCCCATC ACCTTCTTGA CCGCCAGAC 950 ACTGCTCATG GATCTTGGGC AGTTTCTGCT GTTTTGTCTAT ATTTCTTCTC 1000 ACCAACACGA CGGAATGGAG GCCTACGTTA AGGTCGATAG TTGCCCTGAA 1050 GAACCTCAGC TGAGGATGAA GAACAACGAG GAAGCCGAGG ACTACGATGA 1100 CGATTTGACC GATTCCGAAA TGGACGTGGT GCGCTTTGAT GATGACAATT 1150 CTCCATCCTT CATTTCAGATT AGATCCGTCG CCAAGAAGCA CCCCCAGACC 1200 TGGGTGCACT ACATTGCAGC CGAGGAGGAG GATTGGGACT ACGCCCCCT 1250 GGTGCTGGCA CCCGACGACC GAAGCTACAA ATCTCAGTAC CTGAACAATG 1300 GTCCACAACG GATCGGCAGG AAGTACAAGA AAGTGCGGTT CATGGCCTAT 1350 ACAGACGAAA CCTTCAAAAC CAGGGAGGCT ATCCAGCACG AGTCTGGGAT 1400 TCTGGGACCA CTCCTGTACG GCGAAGTGGG CGACACCTTG TTAATTATCT 1450 TCAAGAACCA GGCTAGTAGA CTTATAACA TTTATCCCCA CGGCATTACC 1500 GATGTGCGGC CTCTCTACTC TAGGCGGCTT CCAAAGGGGG TGAAACACCT 1550 GAAGGACTTT CCCATCCTCC CTGGCGAAAT CTTTAAGTAT AAGTGGACAG 1600 TGACCGTGGA GGATGGACCA ACCAAGAGCG ACCCCAGGTG CCTGACACGC 1650 TATTATTCAA GCTTCGTGAA TATGGAAAGG GACCTCGCAT CTGGCTTGAT 1700 CGGCCCTCTG CTGATATGTT ACAAGGAAAG CGTCGATCAG AGAGGAAATC 1750 AGATCATGTC AGACAAAAGG AATGTGATCC TGTTCTCCGT CTTTCGATGA 1800 AACAGGAGCT GGTATCTGAC AGAGAACATC CAGAGATTCC TGCCAAATCC 1850 CGCCGGCGTC CAGCTGGAGG ACCCGGAGTT TCAGGCATCT AACATCATGC 1900 ATTCCATTAA TGGTTACGTG TTCGACTCCC TGCAGCTGAG CGTGTGCCTC 1950 CACGAGGTGG CCTACTGGTA CATCTTGAGC ATCGGCGCCC AGACCGACTT 2000 TCTGAGCGTC TTTTCTCTCC GGTATACTTT CAAACATAAG ATGGTGTACG 2050 AAGATACTCT GACGCTGTTT CCTTTCTCTG GGGAGACTGT GTTTATGTCT 2100 ATGGAGAACC CTGGACTGTG GATTCTCGGA TGCCACAACA GTGACTTTCTG 2150 TAATAGAGGG ATGACTGCAC TGCTGAAGGT GTCCAGCTGT GATAAAAATA 2200 CTGGCGACTA CTACGAAGAT AGCTATGAGG ATATCTCAGC ATACCTGCTG 2250 AGCAAGAATA ACGCCATCGA GCCCCGAAGC TTCTCACAGA ATCCCCCTGT 2300 CCTCAAGAGG CACCAGCGAG AGATCACAAG GACCACACTC CAGTCCGACC 2350 AGGAGGAGAT TGACTACGAT GACACGATTT CTGTGGAGAT GAAAAAAGAG 2400 GACTTTGACA TCTACGATGA GGATGAAAAC CAGAGCCCTA GGTGCTTCCA 2450 GAAGAAAACA AGGCACTACT TCATTGCCGC CGTGGAGAGA CTGTGGGACT 2500 ACGGAATGAG TAGTTCCCCA CACGTGTTGC GGAACAGAGC CCAGAGTGGG 2550 TCCGTCCCAC AGTTCAAGAA GGTTGTTTTT CAGGAGTTCA CAGATGGCTC 2600 CTTCACTCAG CCACTGTATC GCGGCGAGCT GAATGAGCAC TTGGGCTTAT 2650

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		CCAATGAAAC CAAAACCTTAC TTTTGAAGG TGCAGCACCA TATGGCGCCG 2850
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		CTTGGAGAAG GACGTCCACA GCGGCCTGAT TGGCCCTTTG TTGGTCTGCC 2950
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		ACCCTACTTT CAAGGAAAAT TACAGGTTCC ATGCCATTAA TGGCTACATC 3150
		ATGGATACCC TCCCCGGGCT TGTGATGGCT CAGGACCAGC GCATCCGCTG 3200
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		TGGGCCACGT GTTTACCGTG CGCAAGAAGG AGGAGTACAA GATTGCATCA 3300
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		GGCCGGCATC TGGCGCGTGG AGTGCCTCAT TGGGGAGCAC CTCCATGCTG 3400
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		CTCCAGCTAC TTCACCAATA TGTTGCGCCAC CTGGAGCCCC AGCAAGGCCC 4000
		GGCTGCACCT GCAGGGCCGC AGCAACGCCT GGCGGCCTCA GGTGAACAAC 4050
		CCCAAGGAGT GGCTGCAGGT GGAATTCCAG AAAACCATGA AGGTGACTGG 4100
		GGTCACCACC CAGGGAGTCA AGAGCCTGCT GACCAGCATG TATGTGAAGG 4150
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		CAGAACGGTA AGGTGAAAGT GTTCCAGGGA AACCAAGATT CCTTTACACC 4250
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		TGCGAGGCCC AGGACCTGTA CTGA 4374
16	rhFVIII-BDD CO6 sc2	ATGCAGATTG AGCTGAGCAC CTGTTTCTTC CTGTGCCTGC TGAGATTTTG 50
		CTTCTCAGCT ACCCGCAGGT ACTACCTGGG AGCCGTTGAG CTGTCTCTGGG 100
		ATTACATGCA GTCAGATCTG GGGGAGCTGC CTGTGGACGC TCGGTTTCCC 150
		CCCAGAGTGC CAAAGTCCTT TCCCTTCAAC ACCAGCGTGG TGTACAAAAA 200
		GACACTTTTT GTTGAATTTA CTGACCACTT GTTCAACATC GCCAAGCCAC 250
		GACCCCATG GATGGGCCTG CTGGGGCCAA CCATTACAGG AGAGGTTTAC 300
		GACACAGTCG TGATCACACT GAAGAACATG GCCTCCCATC CAGTGTCTCT 350
		GCACGCCGTC GGTGTGTCCT ACTGGAAAGC ATCCGAGGGC GCCGAGTATG 400
		ACGACCAGAC CAGCCAGAGA GAGAAAGAGG ACGACAAAGT GTTCCCTGGA 450
		GGCAGCCACA CCTACGTGTG GCAGGTGTTG AAGGAAAATG GGCCCATGGC 500
		CAGTGACCCT TTGTGTCTGA CTTACTCATA CCTGTCTCAT GTGGATCTAG 550
		TCAAGGACCT GAATTCTGGA CTGATTGGGG CACTGCTTGT GTGCCGCGAA 600
		GGCAGCCTGG CCAAAGAAAA GACACAGACC CTTACAAAGT TCATCCTGCT 650
		GTTCGCCGTG TTCGACGAAG GCAAATCCTG GCACTCAGAA ACCAAAAACT 700
		CACTGATGCA GGACCGGGAT GCCGCCTCTG CCCGCGCATG CCAAAAAATG 750
		CACACCGTCA ACGGCTATGT CAATAGAAGT TTGCCCCGCC TCATTGGATG 800
		TCACAGGAAA AGCGTCTATT GGCATGTAAT CGGGATGGGA ACCACACCTG 850
		AGGTCCACAG CATATTTCTG GAAGGCCACA CATTTCTGGT GAGAAATCAT 900
		CGCCAGGCTT CCCTGGAAAT TTCCCCCATC ACCTTCTTGA CCGCCAGAC 950
		ACTGCTCATG GATCTTGGGC AGTTTCTGCT GTTTTGTCTAT ATTTCTTCTC 1000

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		GAACCTCAGC	TGAGGATGAA	GAACAACGAG	GAAGCCGAGG	ACTACGATGA	1100
		CGATTTGACC	GATTCCGAAA	TGGACGTGGT	GCGCTTTGAT	GATGACAATT	1150
		CTCCATCCTT	CATTTCAGATT	AGATCCGTCG	CCAAGAAGCA	CCCCAAGACC	1200
		TGGGTGCACT	ACATTGCAGC	CGAGGAGGAG	GATTGGGACT	ACGCCCCCCT	1250
		GGTGCTGGCA	CCCGACGACC	GAAGCTACAA	ATCTCAGTAC	CTGAACAATG	1300
		GTCCACAACG	GATCGGCAGG	AAGTACAAGA	AAGTGCGGTT	CATGGCCTAT	1350
		ACAGACGAAA	CCTTCAAAAC	CAGGGAGGCT	ATCCAGCACG	AGTCTGGGAT	1400
		TCTGGGACCA	CTCCTGTACG	GCGAAGTGGG	CGACACCTTG	TTAATTATCT	1450
		TCAAGAACCA	GGCTAGTAGA	CCTTATAACA	TTTATCCCCA	CGGCATTACC	1500
		GATGTGCGGC	CTCTCTACTC	TAGGCGGCTT	CCAAAGGGGG	TGAAACACCT	1550
		GAAGGACTTT	CCCATCCTCC	CTGGCGAAAT	CTTTAAGTAT	AAGTGGACAG	1600
		TGACCGTGGA	GGATGGACCA	ACCAAGAGCG	ACCCGAGCAT	CCTGACACGC	1650
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		AGATCATGTC	AGACAAAAGG	AATGTGATCC	TGTTCTCCGT	CTTCGATGAA	1800
		AACAGGAGCT	GGTATCTGAC	AGAGAACATC	CAGAGATTCC	TGCCAAATCC	1850
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		ATTCCATTAA	TGGTTACGTG	TTCGACTCCC	TGCAGCTGAG	CGTGTGCCTC	1950
		CACGAGGTGG	CCTACTGGTA	CATCTTGAGC	ATCGGCGCCC	AGACCGACTT	2000
		TCTGAGCGTC	TTTTTCTCCG	GGTATACTTT	CAAACATAAG	ATGGTGTACG	2050
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		CTGGCGACTA	CTACGAAGAT	AGCTATGAGG	ATATCTCAGC	ATACCTGCTG	2250
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		TGAGGAGGAT	CAGCGCCAGG	GCGCCGAACC	CCGGAAGAAC	TTTGTGAAGC	2800
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		ATACCAATAC	ACTCAACCCT	GCCCACGGGA	GGCAGGTGAC	CGTGCAGGAG	3000
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		TACAACCTGT	ACCCTGGCGT	GTTTGAGACA	GTGGAGATGC	TGCCATCCAA	3350
		GGCCGGCATC	TGGCGCGTGG	AGTGCCTCAT	TGGGGAGCAC	CTCCATGCTC	3400
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		AGTGGTCAAC	TCTCTGGATC	CTCCCCTGCT	GACACGGTAC	CTGCGGATCC	4300
		ATCCCCAGTC	ATGGGTGCAC	CAGATTGCTC	TGCGCATGGA	GGTGCTTGGC	4350
		TGCGAGGCCC	AGGACCTGTA	CTGA			4374
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		ATTACATGCA	GTCAGATCTG	GGGGAGCTGC	CTGTGGACGC	TCGGTTTCCC	150
		CCCAGAGTGC	CAAAGTCCTT	TCCCTTCAAC	ACCAGCGTGG	TGTACAAAAA	200
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		ACTGCTCATG	GATCTTGGGC	AGTTTCTGCT	GTTTTGTGAT	ATTTCTTCTC	1000
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		TCTGGGACCA	CTCCTGTACG	GCGAAGTGGG	CGACACCTTG	TTAATTATCT	1450
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		GATGTGCGGC	CTCTCTACTC	TAGGCGGCTT	CCAAAGGGGG	TGAAACACCT	1550
		GAAGGACTTT	CCCATCCTCC	CTGGCGAAAT	CTTTAAGTAT	AAGTGGACAG	1600
		TGACCGTGGA	GGATGGACCA	ACCAAGAGCG	ACCCCAGGTG	CCTGACACGC	1650
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		GTCCGTCCCA CAGTTCAAGA AGGTTGTTTT CCAGGAGTTC ACAGATGGCT 2650
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		CAGAGAACAT GGAGAGGAAC TGCAGAGCAC CCTGTAACAT CCAGATGGAG 3150
		GACCCTACTT TCAAGGAAAA TTACAGGTTT CATGCCATTA ATGGCTACAT 3200
		CATGGATACC CTCCCCGGGC TTGTGATGGC TCAGGACCAG CGCATCCGCT 3250
		GGTACCTGCT CTCAATGGGC TCCAACGAGA ACATTCATAG CATCCACTTT 3300
		AGTGGCCACG TGTTTACCGT GCGCAAGAAG GAGGAGTACA AGATGGCACT 3350
		GTACAACCTG TACCCTGGCG TGTTTGAGAC AGTGGAGATG CTGCCATCCA 3400
		AGGCCGGCAT CTGGCGCGTG GAGTGCCTCA TTGGGGAGCA CCTCCATGCT 3450
		GGCATGTCTA CACTGTTCTT GGTGTACAGC AACAAGTGTC AGACTCCACT 3500
		CGGAATGGCC TCCGGGCATA TCCGCGATTT TCAGATCACG GCCTCTGGCC 3550
		AGTATGGCCA ATGGGCTCCC AAGCTGGCCA GGCTGCACTA CAGTGGGAGT 3600
		ATCAACGCTT GGAGACCAA GGAGCCTTTC TCCTGGATCA AGGTGGACCT 3650
		GCTTGCCCCC ATGATTATTC ACGGCATTAA GACACAGGGG GCCAGGCAGA 3700
		AATTCTCCTC CCTGTACATC TCCCAGTTCA TCATCATGTA CAGTCTGGAC 3750
		GGCAAAAAGT GGCAGACCTA CCGCGGGAAC AGTACCGGGA CATTGATGGT 3800
		GTTCTTCGGG AACGTGGACT CTAGCGGCAT TAAACACAAC ATTTTCAACC 3850
		CCCCCATCAT TGCTAGGTAT ATCAGGCTCC ATCCCACCCA CTATAGCATC 3900
		AGGTCCACTC TGCGGATGGA GCTGATGGGC TGCGACCTTA ATTCATGCAG 3950
		CATGCCGCTG GGCATGGAGT CAAAGGCCAT CTCCGACGCC CAAATCACCG 4000
		CCTCCAGCTA CTTACCAAT ATGTTTCGCCA CCTGGAGCCC CAGCAAGGCC 4050
		CGGCTGCACC TGCAGGGCCG CAGCAACGCC TGGCGGCCTC AGGTGAACAA 4100
		CCCCAAGGAG TGGCTGCAGG TGGACTTCCA GAAAACCATG AAGGTGACTG 4150
		GGGTCAACCAC CCAGGGAGTC AAGAGCCTGC TGACCAGCAT GTATGTGAAG 4200
		GAGTTCTTGA TCAGCTCGTC ACAGGATGGC CACCAGTGGA CTTTGTCTT 4250
		TCAGAACGGT AAGGTGAAAG TGTTCCAGGG AAACCAAGAT TCCTTTACAC 4300
		CAGTGGTCAA CTCTCTGGAT CCTCCCCTGC TGACACGGTA CCTGCGGATC 4350
		CATCCCCAGT CATGGGTGCA CCAGATTGCT CTGCGCATGG AGGTGCTTGG 4400
		CTGCGAGGCC CAGGACCTGT ACTAA 4425

Table 6: FIX coding sequences expressed in ARPE-19 cells

SEQ ID NO.	Sequence Name	Nucleotide Sequence
18	rhFIX Padua	ATGCAGCGCG TGAACATGAT CATGGCAGAA TCACCAGGCC TCATCACCAT 50 CTGCCTTTTA GGATATCTAC TCAGTGCTGA ATGTACAGTT TTTCTTGATC 100

		ATGAAAACGC CAACAAAATT CTGAATCGGC CAAAGAGGTA TAATTCAGGT 150
		AAATTGGAAG AGTTTGTTC AAGGGAACCTT GAGAGAGAAT GTATGGAAGA 200
		AAAGTGTAGT TTTGAAGAAG CACGAGAAGT TTTTGAAAAC ACTGAAAGAA 250
		CAACTGAATT TTGGAAGCAG TATGTTGATG GAGATCAGTG TGAGTCCAAT 300
		CCATGTTTAA ATGGCGGCAG TTGCAAGGAT GACATTAATT CCTATGAATG 350
		TTGGTGTCCC TTTGGATTTG AAGGAAAGAA CTGTGAATTA GATGTAACAT 400
		GTAACATTAA GAATGGCAGA TGCGAGCAGT TTTGTAAAA TAGTGCTGAT 450
		AACAAGGTGG TTTGCTCCTG TACTGAGGGA TATCGACTTG CAGAAAACCA 500
		GAAGTCCTGT GAACCAGCAG TGCCATTTCC ATGTGGAAGA GTTTCTGTTT 550
		CACAACTTC TAAGCTCACC CGTGCTGAGA CTGTTTTTCC TGATGTGGAC 600
		TATGTAAATT CTACTGAAGC TGAAACCATT TTGGATAACA TCACTCAAAG 650
		CACCCAATCA TTTAATGACT TCACTCGGGT TGTGTTGTTT TGAATTGTTA AGTTGATGCA 700
		AACCAGGTCA ATTCCCTTGG CAGGTTGTTT TGAATTGTTA AGTTGATGCA 750
		TTCTGTGGAG GCTCTATCGT TAATGAAAA TGGATTGTAA CTGCTGCCCC 800
		CTGTGTTGAA ACTGGTGTTA AAATTACAGT TGTCGCAGGT GAACATAATA 850
		TTGAGGAGAC AGAACATACA GAGCAAAAGC GAAATGTGAT TCGAATTATT 900
		CCTCACCACA ACTACAATGC AGCTATTAAT AAGTACAACC ATGACATTGC 950
		CCTTCTGGAA CTGGACGAAC CCTTAGTGCT AAACAGCTAC GTTACACCTA 1000
		TTTGCATTGC TGACAAGGAA TACACGAACA TCTTCCTCAA ATTTGGATCT 1050
		GGCTATGTAA GTGGCTGGGG AAGAGTCTTC CACAAAGGGA GATCAGCTTT 1100
		AGTTCTTCAG TACCTTAGAG TTCCACTTGT TGACCGAGCC ACATGTCTTC 1150
		TGTCTACAAA GTTCACCATC TATAACAACA TGTTCTGTGC TGGCTTCCAT 1200
		GAAGGAGGTA GAGATTCATG TCAAGGAGAT AGTGGGGGAC CCCATGTTAC 1250
		TGAAGTGGAA GGGACCAGTT TCTTAAGTGG AATTATTAGC TGGGGTGAAG 1300
		AGTGTGCAAT GAAAGGCAAA TATGGAATAT ATACCAAGGT ATCCCGGTAT 1350
		GTCAACTGGA TTAAGGAAAA AACAAAGCTC ACTTAA 1386
19	rhFIX Padua CO2	ATGCAGCGCG TGAACATGAT TATGGCCGAG TCTCCCGGCC TGATCACCAT 50
		CTGTCTGCTG GGCTATCTGC TGAGCGCCGA GTGCACCGTG TTTCTGGATC 100
		ACGAGAACGC CAACAAGATC CTGAACAGAC CCAAGCGGTA CAACAGCGGC 150
		AAGCTGGAAG AGTTCGTGCA GGGCAACCTG GAACGCGAGT GCATGGAAGA 200
		GAAGTGCAGC TTCGAAGAGG CCAGAGAGGT GTTCGAGAAC ACCGAGAGAA 250
		CCACCGAGTT CTGGAAGCAG TACGTGGACG GCGATCAGTG CGAGAGCAAC 300
		CCTTGTCTGA ATGGCGGCAG CTGCAAGGAC GACATCAACA GCTACGAGTG 350
		CTGGTGCCCC TTCGGCTTCG AGGGCAAGAA TTGCGAGCTG GACGTGACCT 400
		GCAACATCAA GAACGGCAGA TGCGAGCAGT TCTGCAAGAA CAGCGCCGAC 450
		AACAAGGTCTG TGTGCTCCTG CACAGAGGGC TACAGACTGG CCGAGAACCA 500
		GAAGTCTTGC GAGCCCGCTG TGCCCTTTCC ATGTGGCAGA GTGTCTGTGT 550
		CCCAGACCAG CAAGCTGACC AGAGCCGAGA CAGTGTTCCC CGACGTGGAC 600
		TACGTGAACA GCACCGAGGC CGAGACAATC CTGGACAACA TCACCCAGAG 650
		CACCCAGTCC TTCAACGACT TCACCAGAGT CGTCGGCGGC GAGGATGCTA 700
		AGCCTGGACA GTTTCCCTTGG CAAGTGGTGC TGAACGGCAA GGTGGACGCT 750
		TTTTGTGGCG GCTCCATCGT GAACGAGAAG TGGATCGTGA CCGCCGCTCA 800
		CTGTGTGGAA ACCGGCGTGA AGATTACAGT GGTGGCCGGC GAGCACAACA 850
		TCGAGGAAAC AGAGCACACC GAGCAGAAAC GGAACGTGAT CAGAATCATC 900
		CCTCACCACA ACTACAACGC CGCCATCAAC AAGTACAACC ACGATATCGC 950
		CCTGCTGGAA CTGGACGAGC CCCTGGTCTT GAACTCTTAC GTGACCCCTA 1000
		TCTGTATCGC CGACAAAGAG TACACCAACA TCTTTCTGAA GTTCGGCAGC 1050
		GGCTACGTGT CCGGCTGGGG AAGAGTTTTC CACAAGGGCA GATCAGCCCT 1100
		GGTGTGTCAG TACCTGAGAG TGCCCCTGGT GGATAGAGCC ACATGCCTGC 1150
		TGAGCACCAA GTTCACCATC TACAACAACA TGTTCTGCGC CGGCTTCCAC 1200
		GAAGGCGGCA GAGATTCTTG TCAAGGCGAT TCTGGCGGCC CTCACGTGAC 1250
		AGAGGTTGAG GGCACAAGCT TTCTGACCGG CATCATCAGC TGGGGCGAAG 1300
		AGTGTGCCAT GAAGGGGAAG TACGGCATCT ACACCAAGGT GTCCAGATAC 1350
		GTGAACTGGA TCAAAGAAAA GACCAAGCTC ACCTGA 1386

20	rhFIX Padua CO3	ATGCAGCGCG	TGAACATGAT	CATGGCCGAG	AGCCCCGGCC	TGATCACCAT	50
		CTGCCTGCTG	GGCTACCTGC	TGAGCGCCGA	GTGCACCGTG	TTCCTGGACC	100
		ACGAGAACGC	CAACAAGATC	CTGAACCGCC	CCAAGCGCTA	CAACAGCGGC	150
		AAGCTGGAGG	AGTTCGTGCA	GGGCAACCTG	GAGCGCGAGT	GCATGGAGGA	200
		GAAGTGCAGC	TTCGAGGAGG	CCCGCGAGGT	GTTTCGAGAAC	ACCGAGCGCA	250
		CCACCGAGTT	CTGGAAGCAG	TACGTGGACG	GCGACCAAGT	CGAGAGCAAC	300
		CCCTGCCTGA	ACGGCGGCAG	CTGCAAGGAC	GACATCAACA	GCTACGAGTG	350
		CTGGTGCCCC	TTCGGCTTCG	AGGGCAAGAA	CTGCGAGCTG	GACGTGACCT	400
		GCAACATCAA	GAACGGCCGC	TGCGAGCAGT	TCTGCAAGAA	CAGCGCCGAC	450
		AACAAGGTGG	TGTGCAGCTG	CACCGAGGGC	TACCGCCTGG	CCGAGAACCA	500
		GAAGAGCTGC	GAGCCC GCCG	TGCCCTTCCC	CTGCGGCCGC	GTGAGCGTGA	550
		GCCAGACCAG	CAAGCTGACC	CGCGCCGAGA	CTGTGTTCCC	CGACGTGGAC	600
		TACGTGAACA	GCACCGAGGC	CGAAACGATC	CTGGACAACA	TCACCCAGAG	650
		CACCCAGAGC	TTCAACGACT	TCACCCGCGT	GGTGGGCGGC	GAGGACGCCA	700
		AGCCCCGGCCA	GTTCCCCTGG	CAGGTGGTGC	TGAACGGCAA	GGTGGACGCC	750
		TTCTGCGGCG	GCAGCATCGT	GAACGAGAAG	TGGATCGTGA	CCGCCGCCCA	800
		CTGCGTGGAA	ACCGGCGTGA	AGATCACCGT	GGTGGCCGGC	GAGCACAACA	850
		TCGAGGAAAC	CGAGCACACC	GAGCAGAAGC	GCAACGTGAT	CCGCATCATC	900
		CCCCACCACA	ACTACAACGC	CGCCATCAAC	AAGTACAACC	ACGACATCGC	950
		CCTGCTGGAG	CTGGACGAGC	CCCTGGTGCT	GAACAGCTAC	GTGACCCCCA	1000
		TCTGCATCGC	CGACAAGGAG	TACACCAACA	TCTTCCTGAA	GTTCCGGCAGC	1050
		GGCTACGTGA	GCGGCTGGGG	CCGCGTGTTT	CACAAGGGCC	GCAGCGCCCT	1100
		GGTGCTGCAG	TACCTGCGCG	TGCCCCCTGGT	GGACCGCGCC	ACCTGCCTGC	1150
		TGAGCACCAA	GTTCACCATC	TACAACAACA	TGTTCTGCGC	CGGCTTCCAC	1200
		GAGGGCGGCC	GCGACAGCTG	CCAGGGCGAC	AGCGGCGGCC	CCCACGTGAC	1250
		CGAGGTGGAG	GGCACCAGCT	TCCTGACCGG	CATCATCAGC	TGGGGCGAGG	1300
		AGTGCGCCAT	GAAGGGCAAG	TACGGCATCT	ACACCAAGGT	GAGCCGCTAC	1350
		GTGAACTGGA	TCAAGGAGAA	AACCAAGCTG	ACCTAA		1386
21	rhFIX Padua CO5	ATGCAGCGGG	TGAACATGAT	CATGGCCGAG	AGCCCCGGGC	TGATCACCAT	50
		CTGTCTGCTG	GGGTACCTGC	TGTCCGCCGA	GTGCACCGTG	TTCCTGGACC	100
		ACGAGAACGC	CAACAAGATC	CTGAATCGCC	CCAAGAGATA	CAATTCGGGA	150
		AAGCTGGAAG	AGTTTGTGCA	GGGCAACCTG	GAGAGAGAGT	CATGGAAGA	200
		GAAGTGCTCC	TTCGAGGAGG	CCCGGGAGGT	GTTTCGAGAAT	ACTGAACGGA	250
		CAACAGAGTT	CTGGAAGCAG	TATGTGGACG	GCGACCAAGT	TGAGAGCAAC	300
		CCCTGTCTGA	ACGGCGGGAG	CTGCAAGGAC	GACATTAATT	CCTACGAATG	350
		CTGGTGCCCC	TTCGGCTTCG	AGGGCAAGAA	CTGCGAGCTG	GACGTGACCT	400
		GCAACATCAA	GAACGGCCGC	TGCGAGCAGT	TTTGCAAGAA	CTCCGCCGAC	450
		AACAAGGTGG	TGTGTTCTTG	CACCGAGGGC	TACCGCCTGG	CCGAAAACCA	500
		GAAGAGCTGT	GAGCCTGCCG	TGCCCTTCCC	CTGCGGCCGG	GTGTCTGTGT	550
		CCCAGACCTC	CAAGCTGACC	AGAGCCGAAA	CCGTGTTTCC	AGATGTGGAC	600
		TACGTGAATA	GCACCGAGGC	CGAGACTATC	CTCGACAACA	TCACCCAGTC	650
		CACCCAGAGC	TTTAACGACT	TCACCCGCGT	GGTGGGCGGC	GAGGACGCCA	700
		AGCCCCGGCCA	GTTCCCCTGG	CAGGTGGTGC	TCAACGGAAA	GGTGGACGCC	750
		TTCTGCGGAG	GCAGCATCGT	GAATGAAAAG	TGGATCGTGA	CAGCCGCCCA	800
		CTGCGTGGAA	ACAGGGGTGA	AGATCACCGT	GGTGGCTGGA	GAGCACAACA	850
		TCGAGGAGAC	AGAGCACACC	GAACAGAAGA	GGAATGTGAT	CAGGATCATC	900
		CCCCACCACA	ACTATAATGC	CGCCATCAAC	AAGTACAACC	ACGACATCGC	950
		CCTGCTGGAG	CTGGATGAGC	CCCTGGTGCT	CAACAGCTAC	GTGACCCCCA	1000
		TCTGCATCGC	TGACAAGGAG	TACACCAACA	TCTTCCTGAA	GTTCCGGCTCC	1050
		GGCTACGTGT	CTGGCTGGGG	CCGCGTGTTT	CACAAGGGAA	GAAGCGCCCT	1100
		CGTGCTGCAG	TACCTGCGGG	TGCCACTGGT	GGACAGGGCC	ACCTGCCTGC	1150
		TGAGCACTAA	GTTCACCAT	TACAACAACA	TGTTCTGCGC	CGGCTTCCAC	1200
		GAGGGCGGCA	GGGACTCCTG	CCAGGGCGAC	AGCGGCGGCC	CCCATGTGAC	1250
		CGAGGTGGAG	GGCACCTCCT	TTCTGACTGG	CATTATCTCC	TGGGGCGAGG	1300
		AGTGCGCCAT	GAAGGGGAAG	TATGGCATCT	ACACCAAGGT	GTCCCGCTAC	1350

		GTGAACTGGA TTAAGGAGAA AACCAAGCTG ACCTGA	1386

Table 7: Expression Vector Sequences

SEQ ID NO.	Component	Nucleotide Sequence
22	5' ITR	TTAACCCTAG AAAGATAGTC TCGTAAAAT TGACGCATGC ATTCTTGAAA TATTGCTCTC TCTTTCTAAA TAGCGCGAAT CCGTCGCTGT GCATTTAGGA CATCTCAGTC GCCGCTTGGA GCTCCCGTGA GGCCTGCTTG TCAATGCGGT AAGTGTCAC TATTGTTGAAC TATAACGACC GCGTGAGTCA AAATGACGCA TGATTATCTT TTACGTGACT TTTAAGATTT AACTCATACG ATAATTATAT TGTATTTC TGTCTACTT ACGTGATAAC TTATTATATA TATATTTTCT TGTATAGAT ATC
23	CAG Promoter	CTCGACATTG ATTATTGACT AGTTATTAAT AGTAATCAAT TACGGGGTCA TTAGTTCATA GCCCATATAT GGAGTTCCGC GTTACATAAC TTACGGTAAA TGGCCCGCCT GGCTGACCGC CCAACGACCC CCGCCCATTTG ACGTCAATAA TGACGTATGT TCCCATAAGTA ACGCCAATAG GGACTTTCCA TTGACGTCAA TGGGTGGAGT ATTTACGGTA AACTGCCCAC TTGGCAGTAC ATCAAGTGTA TCATATGCCA AGTACGCCCC CTATTGACGT CAATGACGGT AAATGGCCCG CCTGGCATTG TGCCAGTAC ATGACCTTAT GGGACTTTCC TACTTGGCAG TACATCTACG TATTAGTCAT CGCTATTACC ATGGTCGAGG TGAGCCCCAC GTTCTGCTTC ACTCTCCCCA TCTCCCCCCC CTCCCCACCC CCAATTTTGT ATTTATTTAT TTTTAAATTA TTTTGTGCAG CGATGGGGGC GGGGGGGGGG GGGGGGCGCG CGCCAGGCGG GCGGGGGCGG GCGGGGGCGG GGGGCGGGGC GAGGCGGAGA GGTGCGGCGG CAGCCAATCA GAGCGGCGCG CTCCGAAAGT TTCCTTTTAT GCGAGGCGG GCGGCGGCGG GGCCCTATAA AAAGCGAAGC GCGCGGCGGG CGGGAGTCGC TCGCGCTGC CTTCGCCCCG TGCCCCGCTC CGCCGCCGCC TCGCGCCGCC CGCCCGGCT CTGACTGACC GCGTTACTCC CACAGGTGAG CGGGCGGGAC GGCCCTTCTC CTCCGGGCTG TAATTAGCGC TTGGTTTAAT GACGGCTTGT TTCTTTTCTG TGGCTGCGTG AAAGCCTTGA GGGGCTCCGG GAGGGCCCTT TGTGCGGGGG GAGCGGCTCG GGGGGTGCCT GCGTGTGTGT GTGCGTGGGG AGCGCCGCGT GCGGCTCCGC GCTGCCCGGC GGCTGTGAGC GCTGCGGGCG CGGCGCGGGG CTTTGTGCGC TCCGCACTGT GCGCGAGGGG AGCGCGGCCG GGGGCGGTGC CCCGCGGTGC GGGGGGGGCT GCGAGGGGAA CAAAGGCTGC GTGCGGGGTG TGTGCGTGGG GGGGTGAGCA GGGGGTGTGG GCGCGTCGGT CGGGCTGCAA CCCCCCTGC ACCCCCCTCC CCGAGTTGCT GAGCACGGCC CGGCTTCGGG TCGGGGGCTC CGTACGGGGC GTGGCGCGGG GCTCGCCGTG CCGGGCGGGG GGTGGCGGCA GGTGGGGGTG CCGGGCGGGG CGGGGCCGCC TCGGGCCGGG GAGGGCTCG GGGAGGGGCG CGGCGGCCCC CGGAGCGCCG GCGGCTGTCG AGGCGCGGCG AGCCGCAGCC ATTGCCTTTT ATGGTAATCG TCGAGAGAGG CGCAGGGACT TCCCTTGTCC CAAATCTGTG CGGAGCCGAA ATCTGGGAGG CGCCGCCGCA CCCCTCTAG CGGGCGCGGG GCGAAGCGGT GCGGCGCCGG CAGGAAGGAA ATGGGCGGGG AGGGCCTTCG TCGCTCGCCG CGCCGCCGTC CCCTTCTCCC TCTCCAGCCT CGGGGCTGTC CGCGGGGGGA CGGCTGCCTT CGGGGGGGAC GGGGAGGGC GGGGTTCCGC TTCTGGCGTG TGACCGGCGG CTCTAGAGCC TCTGCTAACC ATGTTTCATGC CTCTTCTTTT TTCCTACAGC TCCTGGGCAA CGTGCTGGTT ATTGTGCTGT CTCATCATTT TGGCAAAGAA TTG
24	rBG pA	TCCTCAGGTG CAGGCTGCCT ATCAGAAGGT GGTGGCTGGT GTGGCCAATG CCCTGGCTCA CAAATACCAC TGAGATCTTT TTCCCTCTGC CAAAAATTAT GGGGACATCA TGAAGCCCTT TGAGCATCTG ACTTCTGGCT AATAAAGGAA ATTTATTTTC ATTGCAATAG TGTGTTGGAA TTTTGTGT CTCTCACTCG

		GAAGGACATA TGGGAGGGCA AATCATTTTAA AACATCAGAA TGAGTATTTG GTTTAGAGTT TGGCAACATA TGCCCATATG CTGGCTGCCA TGAACAAAGG TTGGCTATAA AGAGGTCATC AGTATATGAA ACAGCCCCCT GCTGTCCATT CCTTATTCCA TAGAAAAGCC TTGACTTGAG GTTAGATTTT TTTTATATTT TGTTTTGTGT TATTTTTTTC TTTAACATCC CTAAAATTTT CCTTACATGT TTTACTAGCC AGATTTTTCC TCCTCTCCTG ACTACTCCCA GTCATAGCTG TCCCTCTTCT CTTATGGAGA TC
25	3' ITR	TTAACCCTAG AAAGATAATC ATATTGTGAC GTACGTTAAA GATAATCATG CGTAAAAATTG ACGCATGTGT TTTATCGGTC TGTATATCGA GGTTTATTTA TTAATTTGAA TAGATATTAA GTTTTATTAT ATTTACACTT ACATACTAAT AATAAAATTC ACAAACAATT TATTTATGTT TATTTATTTA TTAACAAAAA ACAAAAACTC AAAATTTCTT CTATAAAGTA ACAA
26	Vector	TTAACCCTAG AAAGATAGTC TGCCTAAAAT TGACGCATGC ATTCTTGAAA TATTGCTCTC TCTTTCTAAA TAGCGCGAAT CCGTCGCTGT GCATTTAGGA CATCTCAGTC GCCGCTTGGA GCTCCCGTGA GCGGTGCTTG TCAATGCGGT AAGTGTCACT GATTTTGAAC TATAACGACC GCGTGAGTCA AAATGACGCA TGATTATCTT TTACGTGACT TTTAAGATTT AACTCATACG ATAATTATAT TGTTATTTCA TGTTCTACTT ACGTGATAAC TTATTATATA TATATTTTCT TGTTATAGAT ATCATCAACT TTGTATAGAA AAGTTGCTCG ACATTGATTA TTGACTAGTT ATTAATAGTA ATCAATTACG GGGTCATTAG TTCATAGCCC ATATATGGAG TTCCGCGTTA CATAACTTAC GGTAATGGC CCGCCTGGCT GACCGCCCAA CGACCCCGC CCATTGACGT CAATAATGAC GTATGTTCCC ATAGTAACGC CAATAGGGAC TTTCCATTGA CGTCAATGGG TGGAGTATTT ACGGTAAACT GCCCACTTGG CAGTACATCA AGTGTATCAT ATGCCAAGTA CGCCCCCTAT TGACGTCAAT GACGGTAAAT GGCCCGCCTG GCATTATGCC CAGTACATGA CTTTATGGGA CTTTCTACTT TGGCAGTACA TCTACGTATT AGTCATCGCT ATTACCATGG TCGAGGTGAG CCCACGTTT TGCTTCACTC TCCCCATCTC CCCCCCTCC CCACCCCAA TTTTGTATTT ATTTATTTTT TAATTATTTT GTGCAGCGAT GGGGGCGGGG GGGGGGGGGG GGC GCGCGCC AGGCGGGGCG GGGCGGGGCG AGGGGCGGGG CGGGGCGAGG CGGAGAGGTG CGGCGGCAGC CAATCAGAGC GCGCGCTCC GAAAGTTTCC TTTTATGGCG AGGCGGCGGC GGGCGGCGCC CTATAAAAAG CGAAGCTGCC GCGGGGCGGG AGTCGCTGCG CGCTGCCTTC GCCCCGTGCC CCGCTCCGCC GCCGCTCGC GCCGCCCCGCC CCGGCTCTGA CTGACCGCGT TACTCCCACA GGTGAGCGGG CGGGACGGCC CTTCTCTCTC GGGCTGTAAT TAGCGCTTGG TTTAATGACG GCTTGTTTCT TTTCTGTGGC TGCGTGAAAG CTTGAGGGG CTCCGGGAGG GCCCTTTGTG CGGGGGGAGC GGCTCGGGGG GTGCGTGCCT GTGTGTGTGC GTGGGGAGCG CCGCGTGCAG CTCCGCGCTG CCGGCGGGCT GTGAGCGCTG CGGGCGCGGC GCGGGGCTTT GTGCGCTCCG CAGTGTGCGC GAGGGGAGCG CGGCCGGGGG CGGTGCCCCG CGGTGCGGGG GGGGCTGCGA GGGGAACAAA GGCTGCGTGC GGGGTGTGTG CGTGGGGGGG TGAGCAGGGG GTGTGGGCGC GTCGGTCGGG CTGCAACCCC CCCTGCACCC CCCTCCCCGA GTTGCTGAGC ACGGCCCCGC TTCGGGTGCG GGGCTCCGTA CGGGGCGTGG CGCGGGGCTC GCCGTGCCCG GCGGGGGGTG GCGGCAGGTG GGGGTGCCGG GCGGGGCGGG GCCGCCTCGG GCGGGGGAGG GCTCGGGGGA GGGGCGCGGC GGGGGCGGA GCGCCGGCGG CTGTCGAGGC GCGGCGAGCC GCAGCCATTG CCTTTTATGG TAATCGTGCG AGAGGGCGCA GGGACTTCCT TTGTCCCAA TCTGTGCGGA GCCGAAATCT GGGAGGCGCC GCCGCACCC CTCTAGCGGG CGCGGGGCGA AGCGGTGCGG CGCCGGCAGG AAGGAAATGG GCGGGGAGGG CCTTCGTGCG TCGCCGCGCC GCCGTCCCTT TCTCCCTCTC CAGCCTCGGG GTGTCCGCG GGGGGACGGC TGCCTTGCGG GGGGACGGGG CAGGGGCGGG TTCGGCTTCT GGCGTGTGAC CGGCGGCTCT AGAGCCTCTG CTAACCATGT TCATGCCTTC TTCTTTTTCC TACAGCTCCT GGGCAACGTG CTGGTTATTG TGCTGTCTCA TCATTTTGGC AAAGAATTGC AAGTTTGTAC AAAAAAGCAG GCTGCCACCG

		AATTCGCGGC	CGCTAAACCC	AGCTTTCTTG	TACAAAGTGG	CAACTTTATT
		ATACATAGTT	GATCCTCAGG	TGCAGGCTGC	CTATCAGAAG	GTGGTGGCTG
		GTGTGGCCAA	TGCCCTGGCT	CACAAATACC	ACTGAGATCT	TTTTCCCTCT
		GCCAAAAATT	ATGGGGACAT	CATGAAGCCC	CTTGAGCATC	TGACTTCTGG
		CTAATAAAGG	AAATTTATTT	TCATTGCAAT	AGTGTGTTGG	AATTTTTTGT
		GTCTCTCACT	CGGAAGGACA	TATGGGAGGG	CAAATCATTT	AAAACATCAG
		AATGAGTATT	TGGTTTAGAG	TTTGGCAACA	TATGCCCAT	TGCTGGCTGC
		CATGAACAAA	GGTTGGCTAT	AAAGAGGTCA	TCAGTATATG	AAACAGCCCC
		CTGCTGTCCA	TTCCTTATTC	CATAGAAAAG	CCTTGACTTG	AGGTTAGATT
		TTTTTTATAT	TTTGTTTTGT	GTTATTTTTT	TCTTTAACAT	CCCTAAAATT
		TTCCTTACAT	GTTTTACTAG	CCAGATTTTT	CCTCCTCTCC	TGACTACTCC
		CAGTCATAGC	TGTCCCTCTT	CTCTTATGGA	GATCCCCTCG	CCTGCAGCCC
		AAGCTTGGAT	CCCTCGAGTT	AATTAACGAG	AGCATAATAT	TGATATGTGC
		CAAAGTTGTT	TCTGACTGAC	TAATAAGTAT	AATTTGTTTC	TATTATGTAT
		AGGTTAAGCT	AATTACTTAT	TTTATAATAC	AACATGACTG	TTTTTAAAGT
		ACAAAATAAG	TTTATTTTTG	TAAAAGAGAG	AATGTTTAAA	AGTTTTGTTA
		CTTTATAGAA	GAAATTTTGA	GTTTTTGTTT	TTTTTTAATA	AATAAATAAA
		CATAAATAAA	TTGTTTGTTG	AATTTATTAT	TAGTATGTAA	GTGTAAATAT
		AATAAACTT	AATATCTATT	CAAATTAATA	AATAAACCTC	GATATACAGA
		CCGATAAAAC	ACATGCGTCA	ATTTTACGCA	TGATTATCTT	TAACGTACGT
		CACAATATGA	TTATCTTTCT	AGGGTTAAAT	AATAGTTTCT	AATTTTTTTA
		TTATTCAGCC	TGCTGTCGTG	AATACCGAGC	TCCAATTCGC	CCTATAGTGA
		GTCGTATTAC	AATTCACTGG	CCGTCGTTTT	ACAACGTCGT	GACTGGGAAA
		ACCCTGGCGT	TACCCAACCT	AATCGCCTTG	CAGCACATCC	CCCTTTCGCC
		AGCTGGCGTA	ATAGCGAAGA	GGCCCGCACC	GATCGCCCTT	CCCAACAGTT
		GCGCAGCCTG	AATGGCGAAT	GGGACGCGCC	CTGTAGCGGC	GCATTAAGCG
		CGGCGGGTGT	GGTGGTTACG	CGCAGCGTGA	CCGCTACACT	TGCCAGCGCC
		CTAGCGCCCC	CTCCTTTCGC	TTTCTTCCCT	TCCTTCTCG	CCACGTTTCG
		CGGCTTTCCC	CGTCAAGCTC	TAAATCGGGG	GCTCCCTTTA	GGGTTCCGAT
		TTAGTGCTTT	ACGGCACCTC	GACCCCAAAA	AACCTGATTA	GGGTGATGGT
		TCACGTAGTG	GGCCATCGCC	CTGATAGACG	GTTTTTCGCC	CTTTGACGTT
		GGAGTCCACG	TTCTTTAATA	GTGGACTCTT	GTTCCAAACT	GGAACAACAC
		TCAACCCTAT	CTCGGTCTAT	TCTTTTGATT	TATAAGGGAT	TTTGCCGATT
		TCGGCCTATT	GGTTAAAAAA	TGAGCTGATT	TAACAAAAAT	TTAACGCGAA
		TTTTAACAAA	ATATTAACGC	TTACAATTTA	GGTGGCACTT	TTCGGGGAAA
		TGTGCGCGGA	ACCCCTATTT	GTTTTATTTT	CTAAATACAT	TCAAATATGT
		ATCCGCTCAT	GAGACAATAA	CCCTGATAAA	TGCTTCAATA	ATATTGAAAA
		AGGAAGAGTA	TGAGTATTCA	ACATTTCCGT	GTCGCCCTTA	TTCCCTTTTT
		TGCGGCATTT	TGCCTTCCTG	TTTTTGCTCA	CCCAGAAACG	CTGGTGAAAG
		TAAAAGATGC	TGAAGATCAG	TTGGGTGCAC	GAGTGGGTTA	CATCGAACTG
		GATCTCAACA	GCGGTAAGAT	CCTTGAGAGT	TTTCGCCCCG	AAGAACGTTT
		TCCAATGATG	AGCACTTTTA	AAGTTCTGCT	ATGTGGCGCG	GTATTATCCC
		GTATTGACGC	CGGGCAAGAG	CAACTCGGTC	GCCGCATACA	CTATTCTCAG
		AATGACTTGG	TTGAGTACTC	ACCAGTCACA	GAAAAGCATC	TTACGGATGG
		CATGACAGTA	AGAGAATTAT	GCAGTGCTGC	CATAACCATG	AGTGATAACA
		CTGCGGCCAA	CTTACTTCTG	ACAACGATCG	GAGGACCGAA	GGAGCTAACC
		GCTTTTTTGC	ACAACATGGG	GGATCATGTA	ACTCGCCTTG	ATCGTTGGGA
		ACCGGAGCTG	AATGAAGCCA	TACCAAACGA	CGAGCGTGAC	ACCACGATGC
		CTGTAGCAAT	GGCAACAACG	TTGCGCAAAC	TATTAAGTGG	CGAACTACTT
		ACTCTAGCTT	CCCGGCAACA	ATTAATAGAC	TGGATGGAGG	CGGATAAAGT
		TGCAGGACCA	CTTCTGCGCT	CGGCCCTTCC	GGCTGGCTGG	TTTATTGCTG
		ATAAATCTGG	AGCCGGTGAG	CGTGGGTCTC	GCGGTATCAT	TGCAGCACTG
		GGGCCAGATG	GTAAGCCCTC	CCGTATCGTA	GTTATCTACA	CGACGGGGAG
		TCAGGCAACT	ATGGATGAAC	GAAATAGACA	GATCGCTGAG	ATAGGTGCCT

		CACTGATTAA GCATTGGTAA CTGTCAGACC AAGTTTACTC ATATATACTT TAGATTGATT TAAAACTTCA TTTTAAATTT AAAAGGATCT AGGTGAAGAT CCTTTTGTAT AATCTCATGA CCAAATCCC TTAACGTGAG TTTTCGTTCC ACTGAGCGTC AGACCCCGTA GAAAAGATCA AAGGATCTTC TTGAGATCCT TTTTCTCTGC GCGTAATCTG CTGCTTGCAA ACAAAAAAAC CACCGCTACC AGCGGTGGTT TGTGGCCGG ATCAAGAGCT ACCAACTCTT TTTCCGAAGG TAACTGGCTT CAGCAGAGCG CAGATACCAA ATACTGTTCT TCTAGTGTAG CCGTAGTTAG GCCACCACTT CAAGAACTCT GTAGCACC GC CTACATACCT CGCTCTGCTA ATCTGTGTAC CAGTGGCTGC TGCCAGTGGC GATAAGTCGT GTCTTACCGG GTTGGACTCA AGACGATAGT TACCGGATAA GGCGCAGCGG TCGGGCTGAA CGGGGGGTTC GTGCACACAG CCCAGCTTGG AGCGAACGAC CTACACCGAA CTGAGATACC TACAGCGTGA GCTATGAGAA AGCGCCACGC TTCCCGAAGA GAGAAAGGCG GACAGGTATC CGGTAAGCGG CAGGGTCGGA ACAGGAGAGC GCACGAGGGA GCTTCCAGGG GGAAACGCCT GGTATCTTTA TAGTCCTGTC GGGTTTCGCC ACCTCTGACT TGAGCGTCGA TTTTGTGAT GCTCGTCAGG GGGGCGGAGC CTATGGAAAA ACGCCAGCAA CGCGGCCTTT TTACGGTTCC TGGCCTTTTG CTGGCCTTTT GCTCACATGT TCTTTCCTGC GTTATCCCCCT GATTCTGTGG ATAACCGTAT TACCGCCTTT GAGTGAGCTG ATACCGCTCG CCGCAGCCGA ACGACCGAGC GCAGCGAGTC AGTGAGCGAG GAAGCGGAAG AGCGCCCAAT ACGCAAACCG CCTCTCCCCG CGCGTTGGCC GATTCAATTAA TGCAGCTGGC ACGACAGGTT TCCCGACTGG AAAGCGGGCA GTGAGCGCAA CGCAATTAAT GTGAGTTAGC TCACTCATTA GGCACCCAG GCTTTACACT TTATGCTTCC GGCTCGTATG TTGTGTGGAA TTGTGAGCGG ATAACAATTT CACACAGGAA ACAGCTATGA CCATGATTAC GCCAAGCTCG AAATTAACCC TCACTAAAGG GAACAAAAGC TGGTACCTCG CGCGACTTGG TTTGCCATT CTTAGCGCGC GTCGCGTCAC ACAGCTTGGC CACAATGTGG TTTTGTCAA ACGAAGATTC TATGACGTGT TTAAAGTTTA GGTGAGTAA AGCGCAAATC TTTT
27	Transcription Unit for rhScFVIIIBDD CO6	CTCGACATTG ATTATTGACT AGTTATTAAT AGTAATCAAT TACGGGGTCA TTAGTTCATA GCCCATATAT GGAGTTCCGC GTTACATAAC TTACGGTAAA TGGCCCGCCT GGCTGACCGC CCAACGACCC CCGCCCATAG ACGTCAATAA TGACGTATGT TCCCATAGTA ACGCCAATAG GGACTTTCCA TTGACGTCAA TGGGTGGAGT ATTTACGGTA AACTGCCAC TTGGCAGTAC ATCAAGTGTA TCATATGCCA AGTACGCCCC CTATTGACGT CAATGACGGT AAATGGCCCG CCTGGCATT TACCCAGTAC ATGACCTTAT GGGACTTTCC TACTTGGCAG TACATCTACG TATTAGTCAT CGCTATTACC ATGGTCGAGG TGAGCCCCAC GTTCTGCTTC ACTCTCCCCA TCTCCCCCCC CTCCCCACCC CCAATTTTGT ATTTATTTAT TTTTAAATTA TTTTGTGCAG CGATGGGGGC GGGGGGGGGG GGGGGGCGCG CGCCAGGCGG GCGGGGCGG GCGGAGGGGC GGGGCGGGGC GAGGCGGAGA GGTGCGGCGG CAGCCAATCA GAGCGGCGCG CTCCGAAAGT TTCTTTTAT GGCGAGGCGG CGGCGGCGGC GGCCCTATAA AAAGCGAAGC GCGCGGCGGG CGGGAGTCGC TGCGCGCTGC CTTCGCCCCG TGCCCCGCTC CGCCGCCGCC TCGCGCCGCC CGCCCCGGCT CTGACTGACC GCGTTACTCC CACAGGTGAG CGGGCGGGAC GGCCCTTCTC CTCCGGGCTG TAATTAGCGC TTGGTTTAAAT GACGGCTTGT TTCTTTTCTG TGGCTGCGTG AAAGCCTTGA GGGGCTCCGG GAGGGCCCTT TGTGCGGGGG GAGCGGCTCG GGGGGTGCCT GCGTGTGTGT GTGCGTGGGG AGCGCCGCGT GCGGCTCCGC GCTGCCCGGC GGCTGTGAGC GCTGCGGGCG CGGCGCGGGG CTTTGTGCGC TCCGCACTGT GCGCGAGGGG AGCGCGGCCG GGGGCGGTGC CCCGCGGTGC GGGGGGGGCT GCGAGGGGAA CAAAGGCTGC GTGCGGGGTG TGTGCGTGGG GGGGTGAGCA GGGGGTGTGG GCGCGTCGGT CGGGCTGCAA CCCCCCTGC ACCCCCCCTC CCGAGTTGCT GAGCACGGCC CGGCTTCGGG TGCGGGGCTC CGTACGGGGC GTGGCGCGGG GCTCGCCGTG CCGGGCGGGG GGTGGCGGCA GGTGGGGGTG CCGGGCGGGG CGGGGCCGCC TCGGGCCGGG GAGGGCTCGG GGGAGGGGCG CGGCGGCCCC CGGAGCGGCC GCGGCTGTCT AGGCGCGGCG AGCCGAGCC

		ATTGCCTTTT	ATGGTAATCG	TGCGAGAGGG	CGCAGGGACT	TCCTTTGTCC
		CAAATCTGTG	CGGAGCCGAA	ATCTGGGAGG	CGCCGCCGCA	CCCCCTCTAG
		CGGGCGCGGG	GCGAAGCGGT	GCGGCGCCGG	CAGGAAGGAA	ATGGGCGGGG
		AGGGCCTTCG	TGCGTCGCCG	CGCCGCCGTC	CCCTTCTCCC	TCTCCAGCCT
		CGGGGCTGTC	CGCGGGGGGA	CGGCTGCCTT	CGGGGGGGAC	GGGGCAGGGC
		GGGGTTCGGC	TTCTGGCGTG	TGACCGGCGG	CTCTAGAGCC	TCTGCTAACC
		ATGTTTCATG	CTTCTTCTTT	TTCTTACAGC	TCCTGGGCAA	CGTGCTGGTT
		ATTGTGCTGT	CTCATCATTT	TGGCAAAGAA	TTGCAAGTTT	GTACAAAAAA
		GCAGGCTGCC	ACCATGCAGA	TTGAGCTGAG	CACCTGTTTC	TTCTGTGCC
		TGCTGAGATT	TTGCTTCTCA	GCTACCCGCA	GGTACTACCT	GGGAGCCGTT
		GAGCTGTCCCT	GGGATTACAT	GCAGTCAGAT	CTGGGGGAGC	TGCCTGTGGA
		CGCTCGGTTT	CCCCCAGAG	TGCCAAAGTC	CTTTCCCTTC	AACACCAGCG
		TGGTGTACAA	AAAGACACTT	TTTGTGTAAT	TTACTGACCA	CTTGTTCAAC
		ATCGCCAAGC	CACGACCCCC	ATGGATGGGC	CTGCTGGGGC	CAACCATTCA
		GGCAGAGGTT	TACGACACAG	TCGTGATCAC	ACTGAAGAAC	ATGGCCTCCC
		ATCCAGTGTC	TCTGCACGCC	GTCGGTGTGT	CCTACTGGAA	AGCATCCGAG
		GGCGCCGAGT	ATGACGACCA	GACCAGCCAG	AGAGAGAAAG	AGGACGACAA
		AGTGTTCCTT	GGAGGCAGCC	ACACCTACGT	GTGGCAGGTG	TTGAAGGAAA
		ATGGGCCCCAT	GGCCAGTGAC	CCTTTGTGTC	TGACTTACTC	ATACCTGTCT
		CATGTGGATC	TAGTCAAGGA	CCTGAATTCT	GGACTGATTG	GGGCACTGCT
		TGTGTGCCGC	GAAGGCAGCC	TGGCCAAAGA	AAAGACACAG	ACCCTTCACA
		AGTTCATCCT	GCTGTTTCGCC	GTGTTTCGACG	AAGGCAAATC	CTGGCACTCA
		GAAACCAAAA	ACTCACTGAT	GCAGGACCGG	GATGCCGCCT	CTGCCCCGCG
		ATGGCCAAAA	ATGCACACCG	TCAACGGCTA	TGTCAATAGA	AGTTTGCCCG
		GCCTCATTTG	ATGTCACAGG	AAAAGCGTCT	ATTGGCATGT	AATCGGGATG
		GGAACCACAC	CTGAGGTCCA	CAGCATATTT	CTGGAAGGCC	ACACATTTCT
		GGTGAGAAAT	CATCGCCAGG	CTTCCCTGGA	AATTTCCCCC	ATCACCTTCT
		TGACCGCCCCA	GACACTGCTC	ATGGATCTTG	GGCAGTTTCT	GCTGTTTTGT
		CATATTTCTT	CTCACCACAA	CGACGGAATG	GAGGCCTACG	TTAAGGTCTGA
		TAGTTGCCCT	GAAGAACCCT	AGCTGAGGAT	GAAGAACAAC	AGGAGGCCCG
		AGGACTACGA	TGACGATTTG	ACCGATTCCG	AAATGGACGT	GGTGCGCTTT
		GATGATGACA	ATTCTCCATC	CTTCATTGAG	ATTAGATCCG	TGCGCAAGAA
		GCACCCCAAG	ACCTGGGTGC	ACTACATTGC	AGCCGAGGAG	GAGGATTGGG
		ACTACGCCCC	CCTGGTGCTG	GCACCCGACG	ACCGAAGCTA	CAAATCTCAG
		TACCTGAACA	ATGGTCCACA	ACGGATCGGC	AGGAAGTACA	AGAAAGTGCG
		GTTTCATGGCC	TATACAGACG	AAACCTTCAA	AACCAGGGAG	GCTATCCAGC
		ACGAGTCTGG	GATTCTGGGA	CCACTCCTGT	ACGGCGAAGT	GGGCGACACC
		TTGTTAATTA	TCTTCAAGAA	CCAGGCTAGT	AGACCTTATA	ACATTTATCC
		CCACGGCATT	ACCGATGTGC	GGCCTCTCTA	CTCTAGGCGG	CTTCCAAAGG
		GGGTGAAACA	CCTGAAGGAC	TTTCCCATCC	TCCCTGGCGA	AATCTTTAAG
		TATAAGTGGA	CAGTGACCGT	GGAGGATGGA	CCAACCAAGA	GCGACCCCAG
		GTGCCTGACA	CGCTATTATT	CAAGCTTCGT	GAATATGGAA	AGGGACCTCG
		CATCTGGCTT	GATCGGCCCT	CTGCTGATAT	GTTACAAGGA	AAGCGTCGAT
		CAGAGAGGAA	ATCAGATCAT	GTCAGACAAA	AGGAATGTGA	TCCTGTTCTC
		CGTCTTCGAT	GAAAACAGGA	GCTGGTATCT	GACAGAGAAC	ATCCAGAGAT
		TCCTGCCAAA	TCCCGCCGGC	GTCCAGCTGG	AGGACCCGGA	GTTTCAGGCA
		TCTAACATCA	TGCATTCCAT	TAATGGTTAC	GTGTTGCACT	CCCTGCAGCT
		GAGCGTGTGC	CTCCACGAGG	TGGCCTACTG	GTACATCTTG	AGCATCGGCG
		CCCAGACCGA	CTTCTGAGC	GTCTTTTTCT	CCGGGTATAC	TTTCAAACAT
		AAGATGGTGT	ACGAAGATAC	TCTGACGCTG	TTCCCTTTCT	CTGGGGAGAC
		TGTGTTTATG	TCTATGGAGA	ACCCTGGACT	GTGGATTCTC	GGATGCCACA
		ACAGTGACTT	TCGTAATAGA	GGGATGACTG	CACTGCTGAA	GGTGTCCAGC
		TGTGATAAAA	ATACTGGCGA	CTACTACGAA	GATAGCTATG	AGGATATCTC
		AGCATACCTG	CTGAGCAAGA	ATAACGCCAT	CGAGCCCCGA	AGCTTCTCAC
		AGAATCCCCC	TGTCCTCAAG	GCCCACCAGG	CGGAGATCAC	AAGGACCACA

		CTCCAGTCCG	ACCAGGAGGA	GATTGACTAC	GATGACACGA	TTTCTGTGGA
		GATGAAAAAA	GAGGACTTTG	ACATCTACGA	TGAGGATGAA	AACCAGAGCC
		CTAGGTTCGT	CCAGAAGAAA	ACAAGGCACT	ACTTCATTGC	CGCCGTGGAG
		AGACTGTGGG	ACTACGGAAT	GAGTAGTTCC	CCACACGTGT	TGCGGAACAG
		AGCCCAGAGT	GGGTCCGTCC	CACAGTTCAA	GAAGGTTGTT	TTCCAGGAGT
		TCACAGATGG	CTCCTTCACT	CAGCCACTGT	ATCGCGGCCA	GCTGAATGAG
		CACTTGGGCT	TATTGGGCCC	CTACATTTCG	GCAGAAGTCG	AAGATAATAT
		TATGGTGACC	TTCCGCAACC	AGGCCAGCCG	GCCTTACTCA	TTCTACTCCT
		CTCTCATCTC	TTATGAGGAG	GATCAGCGCC	AGGGCGCCGA	ACCCCGGAAG
		AACTTTGTGA	AGCCCAATGA	AACCAAACT	TACTTTTGGG	AGGTGCAGCA
		CCATATGGCG	CCGACGAAAG	ACGAATTTGA	CTGCAAAGCC	TGGGCCTACT
		TCAGCGACGT	CGACTTGGAG	AAGGACGTCC	ACAGCGCCCT	GATTGGCCCT
		TTGTTGGTCT	GCCATACCAA	TACACTCAAC	CCTGCCACAG	GGAGGACGGT
		GACCGTGCG	GAGTTTGCCT	TGTTCTTCAC	CATCTTCGAC	GAAACCAAGA
		GCTGGTACTT	CACAGAGAAC	ATGGAGAGGA	ACTGCAGAGC	ACCCTGTAAC
		ATCCAGATGG	AGGACCCTAC	TTTCAAGGAA	AATTACAGGT	TCCATGCCAT
		TAATGGCTAC	ATCATGGATA	CCCTCCCCGG	GCTTGTGATG	GCTCAGGACC
		AGCGCATCCG	CTGGTACCTG	CTCTCAATGG	GCTCCAACGA	GAACATTTCAT
		AGCATCCACT	TTAGTGGCCA	CGTGTTTACC	GTGCGCAAGA	AGGAGGAGTA
		CAAGATGGCA	CTGTACAACC	TGTACCCTGG	CGTGTTTGAG	ACAGTGGAGA
		TGCTGCCATC	CAAGGCCGGC	ATCTGGCGCG	TGGAGTGCCT	CATTGGGGAG
		CACCTCCATG	CTGGCATGTC	TACACTGTTC	CTGGTGTACA	GCAACAAGTG
		TCAGACTCCA	CTCGGAATGG	CCTCCGGGCA	TATCCGCGAT	TTTCAGATCA
		CGGCCCTCTG	CCAGTATGGC	CAATGGGCTC	CCAAGCTGGC	CAGGCTGCAC
		TACAGTGGGA	GTATCAACGC	TTGGAGCACC	AAGGAGCCTT	TCTCCTGGAT
		CAAGGTGGAC	CTGCTTGCCC	CCATGATTAT	TCACGGCATT	AAGACACAGG
		GGGCCAGGCA	GAAATTCTCC	TCCCTGTACA	TCTCCCAGTT	CATCATCATG
		TACAGTCTGG	ACGGCAAAAA	GTGGCAGACC	TACCGCGGGA	ACAGTACCGG
		GACATTGATG	GTGTTCTTCG	GGAACGTGGA	CTCTAGCGGC	ATTAAACACA
		ACATTTTCAA	CCCCCCCATC	ATTGCTAGGT	ATATCAGGCT	CCATCCCACC
		CACATAGCA	TCAGGTCCAC	TCTGCGGATG	GAGCTGATGG	GCTGCGACCT
		TAATTTCATG	AGCATGCCGC	TGGGCATGGA	GTCAAAGGCC	ATCTCCGACG
		CCCAAATCAC	CGCCTCCAGC	TACTTCACCA	ATATGTTTCG	CACCTGGAGC
		CCCAGCAAGG	CCCGGCTGCA	CCTGCAGGGC	CGCAGCAACG	CCTGGCGGCC
		TCAGGTGAAC	AACCCCAAGG	AGTGGCTGCA	GGTGGACTTC	CAGAAAACCA
		TGAAGGTGAC	TGGGGTCACC	ACCCAGGGAG	TCAAGAGCCT	GCTGACCAGC
		ATGTATGTGA	AGGAGTTCTT	GATCAGCTCG	TCACAGGATG	GCCACCAGTG
		GACTTTGTTC	TTTCAGAACG	GTAAGGTGAA	AGTGTTCAG	GGAAACCAAG
		ATTCCTTTAC	ACCAGTGGTC	AACCTCTCTG	ATCCTCCCCT	GCTGACACGG
		TACCTGCGGA	TCCATCCCCA	GTCTGCGGTG	CACCAGATTG	CTCTGCGCAT
		GGAGGTGCTT	GGCTGCGAGG	CCCAGGACCT	GTACTGAAAT	TCGCGGCCGC
		TAAACCCAGC	TTTCTTGTAC	AAAGTGGCAA	CTTTATTATA	CATAGTTGAT
		CCTCAGGTGC	AGGCTGCCA	TCAGAAGGTG	GTGGCTGGTG	TGGCCAATGC
		CCTGGCTCAC	AAATACCACT	GAGATCTTTT	TCCCTCTGCC	AAAAATTATG
		GGGACATCAT	GAAGCCCCCT	GAGCATCTGA	CTTCTGGCTA	ATAAAGGAAA
		TTTATTTTCA	TTGCAATAGT	GTGTTGGAAT	TTTTTGTGTC	TCTCACTCGG
		AAGGACATAT	GGGAGGGCAA	ATCATTTAAA	ACATCAGAAT	GAGTATTTGG
		TTTAGAGTTT	GGCAACATAT	GCCCATATGC	TGGCTGCCAT	GAACAAAGGT
		TGGCTATAAA	GAGGTCATCA	GTATATGAAA	CAGCCCCCTG	CTGTCCATTC
		CTTATTCCAT	AGAAAAGCCT	TGACTTGAGG	TTAGATTTTT	TTTATATTTT
		GTTTTGTGTT	ATTTTTTTCT	TTAACATCCC	TAAAATTTTC	CTTACATGTT
		TTACTAGCCA	GATTTTTCCCT	CCTCTCCTGA	CTACTCCCAG	TCATAGCTGT
		CCCTCTTCTC	TTATGGAGAT	C		

28	Transcription Unit for rhFIX Padua CO2	CTCGACATTG	ATTATTGACT	AGTTATTAAT	AGTAATCAAT	TACGGGGTCA
		TTAGTTCATA	GCCCATATAT	GGAGTTCCGC	GTTACATAAC	TTACGGTAAA
		TGGCCCGCCT	GGCTGACCGC	CCAACGACCC	CCGCCCATTG	ACGTCAATAA
		TGACGTATGT	TCCCATAGTA	ACGCCAATAG	GGACTTTCCA	TTGACGTCAA
		TGGGTGGAGT	ATTTACGGTA	AAC TGCCAC	TTGGCAGTAC	ATCAAGTGTA
		TCATATGCCA	AGTACGCCCC	CTATTGACGT	CAATGACGGT	AAATGGCCCG
		CCTGGCATT	TGCCCAGTAC	ATGACCTTAT	GGGACTTTCC	TACTTGGCAG
		TACATCTACG	TATTAGTCAT	CGCTATTACC	ATGGTCGAGG	TGAGCCCCAC
		GTTCTGCTTC	ACTCTCCCCA	TCTCCCCCCC	CTCCCCACCC	CCAATTTTGT
		ATTTATTTAT	TTTTTAATTA	TTTTGTGCAG	CGATGGGGGC	GGGGGGGGGG
		GGGGGGCGCG	CGCCAGGCGG	GGCGGGGCGG	GGCGAGGGGC	GGGGCGGGGC
		GAGGCGGAGA	GGTGCGGCGG	CAGCCAATCA	GAGCGGCGCG	CTCCGAAAGT
		TTCTTTTAT	GGCGAGGCGG	CGGCGGCGGC	GGCCCTATAA	AAAGCAAGC
		GCGCGGCGGG	CGGGAGTCGC	TGCGCGCTGC	CTTCGCCCCG	TGCCCCGCTC
		CGCCGCCGCC	TCGCGCCGCC	CGCCCCGGCT	CTGACTGACC	GCCTTACTCC
		CACAGGTGAG	CGGGCGGGAC	GGCCCTTCTC	CTCCGGGCTG	TAATTAGCGC
		TTGGTTTAAT	GACGGCTTGT	TTCTTTTCTG	TGGCTGCGTG	AAAGCCTTGA
		GGGGCTCCGG	GAGGGCCCTT	TGTGCGGGGG	GAGCGGCTCG	GGGGGTGCGT
		GCGTGTGTGT	GTGCGTGGGG	AGCGCCGCGT	GCGGCTCCGC	GCTGCCCGGC
		GGCTGTGAGC	GCTGCGGGCG	CGGCGCGGGG	CTTTGTGCGC	TCCGCAGTGT
		GCGCGAGGGG	AGCGCGGCCG	GGGGCGGTGC	CCCGCGGTGC	GGGGGGGGCT
		GCGAGGGGAA	CAAAGGCTGC	GTGCGGGGTG	TGTGCGTGCG	GGGGTGAGCA
		GGGGGTGTGG	GCGCGTCGGT	CGGGCTGCAA	CCCCCCTGCT	ACCCCCCTCC
		CCGAGTTGCT	GAGCACGGCC	CGGCTTCGGG	TGCGGGGCTC	CGTACGGGGC
		GTGGCGCGGG	GCTCGCCGTG	CCGGGCGGGG	GGTGGCGGCA	GGTGGGGGTG
		CCGGGCGGGG	CGGGGCCGCC	TCGGGCCGGG	GAGGGCTCGG	GGGAGGGGCG
		CGGCGGCCCC	CGGAGCGCCG	GCGGCTGTCT	AGGCGCGGCG	AGCCGCAGCC
		ATTGCCTTTT	ATGGTAATCG	TGCGAGAGGG	CGCAGGGACT	TCCTTTGTCC
		CAAATCTGTG	CGGAGCCGAA	ATCTGGGAGG	CGCCGCCGCA	CCCCCTCTAG
		CGGGCGCGGG	GCGAAGCGGT	GCGGCGCCGG	CAGGAAGGAA	ATGGCTGGGG
		AGGGCCTTCG	TGCGTCGCCG	CGCCGCCGTC	CCCTTCTCCC	TCTCCAGCCT
		CGGGGCTGTC	CGCGGGGGGA	CGGCTGCCTT	CGGGGGGGAC	GGGGCAGGGC
		GGGGTTCGGC	TTCTGGCGTG	TGACCGGCGG	CTCTAGAGCC	TCTGCTAACC
		ATGTTTCATG	CTTCTTCTTT	TTCTTACAGC	TCCTGGGCAA	CGTGCTGGTT
		ATTGTGCTGT	CTCATCATTT	TGGCAAAGAA	TTGCAAGTTT	GTACAAAAAA
		GCAGGCTGCC	ACCATGCAGC	GCGTGAACAT	GATTATGGCC	GAGTCTCCCG
		GCCTGATCAC	CATCTGTCTG	CTGGGCTATC	TGCTGAGCGC	CGAGTGACCC
		GTGTTTCTGG	ATCACGAGAA	CGCCAACAAG	ATCCTGAACA	GACCCAAGCG
		GTACAACAGC	GGCAAGCTGG	AAGAGTTCGT	GCAGGGCAAC	CTGGAACGCG
		AGTGCATGGA	AGAGAAGTGC	AGCTTCGAAG	AGGCCAGAGA	GGTGTTTCGAG
		AACACCGAGA	GAACCACCGA	GTTCTGGAAG	CAGTACGTGG	ACGGCGATCA
		GTGCGAGAGC	AACCCCTTGT	TGAATGGCGG	CAGCTGCAAG	GACGACATCA
		ACAGCTACGA	GTGCTGGTGC	CCCTTCGGCT	TCGAGGGCAA	GAATTGCGAG
		CTGGACGTGA	CCTGCAACAT	CAAGAACGGC	AGATGCGAGC	AGTTCTGCAA
		GAACAGCGCC	GACAACAAGG	TCGTGTGCTC	CTGCACAGAG	GGCTACAGAC
		TGGCCGAGAA	CCAGAAGTCT	TGCGAGCCCC	CTGTGCCCTT	TCCATGTGGC
		AGAGTGTCTG	TGTCCCAGAC	CAGCAAGCTG	ACCAGAGCCG	AGACAGTGTT
		CCCCGACGTG	GACTACGTGA	ACAGCACCGA	GGCCGAGACA	ATCCTGGACA
		ACATCACCCA	GAGCACCCAG	TCCTTCAACG	ACTTCACCAG	AGTCGTCGGC
		GGCGAGGATG	CTAAGCCTGG	ACAGTTTCCT	TGGCAAGTGG	TGCTGAACGG
		CAAGGTGGAC	GCTTTTGTG	GCGGCTCCAT	CGTGAACGAG	AAGTGGATCG
		TGACCGCCGC	TCACTGTGTG	GAAACCGGCG	TGAAGATTAC	AGTGGTGGCC
		GGCGAGCACA	ACATCGAGGA	AACAGAGCAC	ACCGAGCAGA	AACGGAACGT
		GATCAGAATC	ATCCCTCACC	ACAAC TACAA	CGCCGCCATC	AACAAGTACA

		ACCACGATAT CGCCCTGCTG GAACTGGACG AGCCCCTGGT CCTGAACTCT
		TACGTGACCC CTATCTGTAT CGCCGACAAA GAGTACACCA ACATCTTTCT
		GAAGTTCGGC AGCGGCTACG TGTCCGGCTG GGAAGAGTT TTCCACAAGG
		GCAGATCAGC CCTGGTGCTG CAGTACCTGA GAGTGCCCTT GGTGGATAGA
		GCCACATGCC TGCTGAGCAC CAAGTTCACC ATCTACAACA ACATGTTCTG
		CGCCGGCTTC CACGAAGGCG GCAGAGATTC TTGTCAAGGC GATTCTGGCG
		GCCCTCACGT GACAGAGGTT GAGGGCACAA GCTTTCTGAC CGGCATCATC
		AGCTGGGGCG AAGAGTGTGC CATGAAGGGG AAGTACGGCA TCTACACCAA
		GGTGTCCAGA TACGTGAACT GGATCAAAGA AAAGACCAAG CTCACCTGAA
		ATTCGCGGCC GCTAAACCCA GCTTTCTTGT ACAAAGTGGC AACTTTATTA
		TACATAGTTG ATCCTCAGGT GCAGGCTGCC TATCAGAAGG TGGTGGCTGG
		TGTGGCCAAT GCCCTGGCTC ACAAATACCA CTGAGATCTT TTTCCCTCTG
		CCAAAAATTA TGGGGACATC ATGAAGCCCC TTGAGCATCT GACTTCTGGC
		TAATAAAGGA AATTTATTTT CATTGCAATA GTGTGTTGGA ATTTTTGTG
		TCTCTCACTC GGAAGGACAT ATGGGAGGGC AAATCATTTA AAACATCAGA
		ATGAGTATTT GGTTTAGAGT TTGGCAACAT ATGCCCATAT GCTGGCTGCC
		ATGAACAAAG GTTGGCTATA AAGAGGTCAT CAGTATATGA AACAGCCCCC
		TGCTGTCCAT TCCTTATTC ATAGAAAAGC CTTGACTTGA GGTAGATTT
		TTTTTATATT TTGTTTTGTG TTATTTTTTT CTTTAACATC CCTAAAATTT
		TCCTTACATG TTTTACTAGC CAGATTTTTT CTCCTCTCCT GACTACTCCC
		AGTCATAGCT GTCCCTCTTC TCTTATGGAG ATC

Table 8: Additional Amino Acid Sequences

SEQ ID NO.	Protein Name	Amino Acid Sequence
29	Interleukin-2	MYRMQLLSCL ALSLALVTNS APTSSSTKKT QLQLEHLLLD LQMILNGINN 50 YKNPKLTRML TFKFYMPKKA TELKHLQCLE EELKPLEEVL NLAQSKNFHL 100 RPRDLISNIN VIVLELKGSE TTFMCEYADE TATIVEFLNR WITFCQSIIS 150 TLT 153
30	Parathyroid hormone, Truncated	MIPAKDMAKV MIVMLAICFL TKSDGKSVKK RSVSEIQLMH NLGKHLNSME 50 RVEWLRKKLQ DVHNF 65
31	Parathyroid hormone	MIPAKDMAKV MIVMLAICFL TKSDGKSVKK RSVSEIQLMH NLGKHLNSME 50 RVEWLRKKLQ DVHNFVALGA PLAPRDAGSQ RPRKKEDNVL VESHEKSLGE 100 ADKADVNVLK KAKSQ 115
32	Von Willebrand Factor, Truncated 1	MIPARFAGVL LALALILPGT LCSLSCRPP MVKLVC PADN LRAEGLECTK 49 TCQNYDLECM SMGCVSGCLC PPGMVRHENR CVALERCPCF HQGKEYAPGE 99 TVKIGCNTCV CRDRKWNCTD HVCDATCSTI GMAHYLTFDG LKYLFPGEQ 149 YVLVQDYCGS NPGTFRILVG NKGCSHPSVK CKKRVTILVE GGEIELFDGE 199 VNVKRPMDKE THFEVVESGR YIILLGKAL SVVWDRHLSI SVVLKQTYQE 249 KVCGLCGNFD GIQNNDLTSS NLQVEEDPVD FGNSWKVSSQ CADTRKVPLD 299 SSPATCHNNI MKQTMVDSSC RILTSDFVQD CNKLVDPEPY LDVCIYDTCS 349 CESIGDCACF CDTIAAYAHV CAQHGVVITW RTATLCPQSC EERNLRENGY 399 ECEWRYNSCA PACQVTCQHP EPLACPVQCV EGCHAHCPPG KILDELLQTC 449 VDPEDCPVCE VAGRRFASGK KVTLNPSDPE HCQICHCDVV NLTCEACQEP 499 GGLVVP 506
33	Von Willebrand Factor, Truncated 2	MIPARFAGVL LALALILPGT LCAEGTRGRS STARCSLFGS DFNVTDFDGS 50 YSFAGYCSYL LAGGCQKRSF SIIGDFQNGK RVSLSVYLGE FFDIHLFVNG 100 TVTQGDQRV MPYASKGLYL ETEAGYYKLS GEAYGFVARI DSGSNFQVLL 150 SDRYFNKTCG LCGNFNIFAE DDFMTQEGTL TSDPYDFANS WALSSGEQWC 200 ERASPPSSSC NISSGEMQKG LWEQCQLLKS TSVFARCHPL VDPEPFVALC 250

		EKTLCECAGG LECACPALLE YARTCAQEGM VLYGWTDHSA CSPVCPAGME 300
		YRQCVSPCAR TCQSLHINEM CQERCVDGCS CPEGQLLDEG LCVESTTEPC 350
		VHSGKRYPPG TSLSRDCNTC ICRNSQWICS NEECPGECVL TGQSHFKSFD 400
		NRYFTTFSGIC QYLLARDCQD HSFSIVIVTV QCADDRDAVC TRSVTVRLPG 450
		LHNSLVKLKH GAGVAMDGQD VQLPLLKGD L RIQHTVTASV RLSYGEDLQM 500
		DWDGRGRLLV KLSVPYAGKT CGLCGNYNGN QGDDFLTSPG LAEPRVEDFG 550
		NAWKHLHGDCQ DLQKQHSDFC ALNPRMTRFS EEACAVLTSP TFEACHRAVS 600
		PLPYLRNCRY DVCSCSDGRE CLCGALASYA AACAGRGVRV AWREPGRCEL 650
		NCPKGQVYLQ CGTPCNLTCT SLSYPDEECN EACLEGCFCP PGLYMDERGD 700
		CVPKAQCPCY YDGEIFQPED IFSDHHTMCY CEDGFMHCTM SGVPGSLLPD 750
		AVLSSPLSHR SKRSLSCRPP MVKLVC PADN LRAEGLECTK TCQNYDLECM 800
		SMGCVSGCLC PPGMVRHENR CVALERCPCF HQGKEYAPGE TVKIGCNTCV 850
		CRDRKWNCTD HVCDATCSTI GMAHYLTFDG LKYLFPGEQ YVLVQDYCGS 900
		NPGETFRILVG NKGCSHPSVK CKKRVTLVE GGEIELFDGE VNVKRPMDKE 950
		THFEVVESEGR YIIILLGKAL SVVWDRHLSI SVVLKQTYQE KVCGLCGNFD 1000
		GIQNNDLTSS NLQVEEDPVD FGNSWKVSSQ CADTRKVPLD SSPATCHNNI 1050
		MKQTMVDSSC RILTSDFVQD CNKLVDPEPY LDVCIYDTCES SIGDCACF 1100
		CDTIAAYAHV CAQHKGKVVW RTATLCPQSC EERNLRENGY ECEWRYNSCA 1150
		PACQVTCQHP EPLACPVQCV EGCHAHCPPG KILDELLQTC VDPEDCPVCE 1200
		VAGRRFASGK KVTLNPSDPE HCQICHCDVV NLTCEACQEP GGLVVP 1247
34	Fc	EPKSCDKTHT CPPCPAPELL GGPSVFLFPP KPKDTLMISR TPEVTCVVVD 50
		VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN 100
		GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR DELTKNQVSL 150
		TCLVKGFYPS DIAVEWESNG QPENNYKTP PVLDSDGSFF LYSKLTVDKS 200
		RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK 232
35	Albumin	DAHKSEVAHR FKDLGEENFK ALVLIAFAQY LQQCPFEDHV KLVNEVTEFA 50
		KTCVADESAE NCDKSLHTLF GDKLCTVATL RETYGEMADC CAKQEPERNE 100
		CFLQHKDDNP NLPRLVRPEV DVMCTAFHDN EETFLKKYLY EIARRHPYFY 150
		APELLFFAKR YKAAFTTECCQ AADKAACLLP KLDELDEGK ASSAKQRLKC 200
		ASLQKFGERA FKAWAVARLS QRFPKAEFAE VSKLVTDLT K VHTTECHGDL 250
		LECADDRADL AKYICENQDS ISSKLKECCE KPLLEKSHCI AEVENDEMPA 300
		DLPSLAADFV ESKDVCKNYA EAKDVFLGMF LYEYARRHPD YSVVLLLR L 350
		KTYETTLEKC CAAADPHECY AKVFDEFKPL VEEPQNLIKQ NCELFEQLGE 400
		YKFQNALVR YTKKVPQVST PTLVEVSRNL GKVGSKCKH PEAKRMPCAE 450
		DYLSVVLNQL CVLHEKTPVS DRVTKCCTES LVNRRPCFSA LEVDETYVPK 500
		EFNAETFTFH ADICTLSEKE RQIKKQTALV ELVKHKPKAT KEQLKAVMDD 550
		FAAFVEKCK ADDKETCF AE EGKKLVAASQ AALGL 585
36	FIX-Padua	MQRVNMIMAE SPGLITICLL GYLLSAECTV FLDHENANKI LNRPKRYNSG
		KLEEFVQGNL ERECMECKS FEEAREVFEN TERTTEFWKQ YVDGDQCESN
		PCLNGGSKD DINSYECWCP FGFEGKNCEL DVTCNIKNGR CEQFCKNSAD
		NKVVCSTEG YRLAENQKSC EPAVPFPCGR VSVSQTSLT RAETVFPDVD
		YVNSTEAE TI LDNITQSTQS FNDFTRVVGG EDAKPGQFPW QVVLNGKVDA
		FCGGSIVNEK WIVTAAHCVE TGVKITVVG EHNIEETEHT EQKRN VIRII
		PHHNYNAAIN KYNHDIALLE LDEPLVLNSY VTPIC IADKE YTNIFLKFGS
		GYVSGWGRVF HKGRSALVLQ YLRVPLVDRA TCLLSTKFTI YNNMFCAGFH
		EGGRDSCQGD SGGPHVTEVE GTSFLTGIIS WGEECAMKGK YGIYTKVSRY
		VNWIKEKTKL T

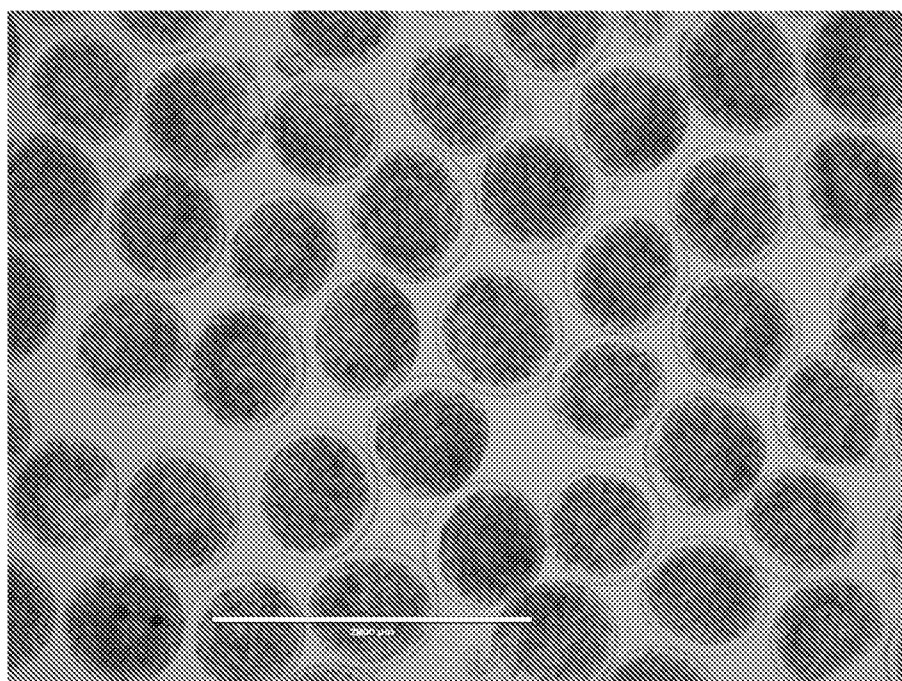


FIG. 18A

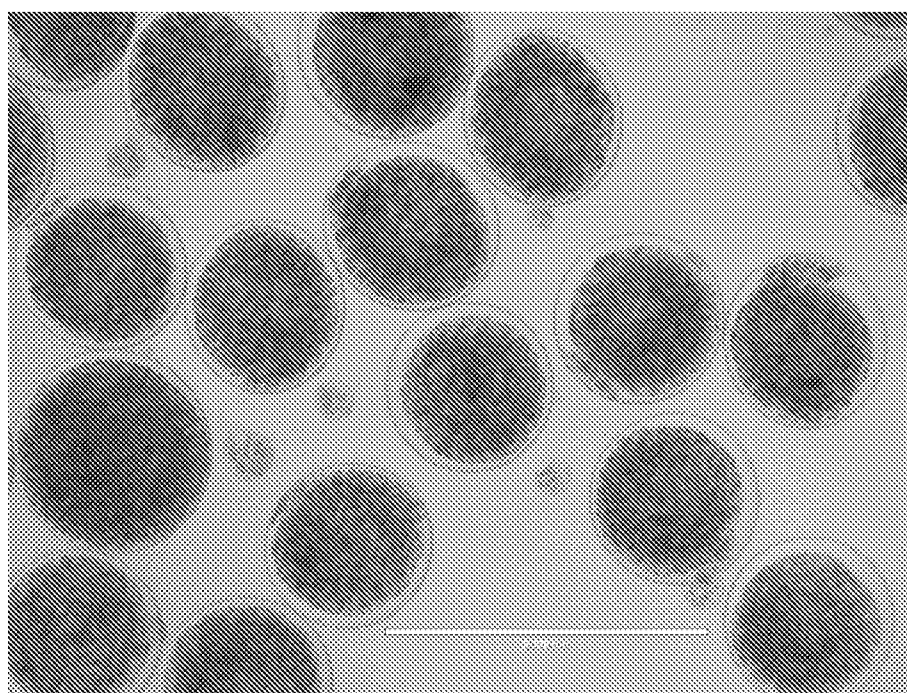


FIG. 18B

Sequence_Listing.txt
SEQUENCE LISTING

<110> SIGILON THERAPEUTICS, INC.

<120> IMPLANTABLE PARTICLES AND RELATED METHODS

<130> S2225-7022WO

<140>

<141>

<150> 62/652,880

<151> 2018-04-04

<150> 62/737,838

<151> 2018-09-27

<150> 62/812,568

<151> 2017-03-01

<160> 36

<170> PatentIn version 3.5

<210> 1

<211> 1457

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<220>

<221> SITE

<222> (1)..(19)

<223> /note="Signal sequence"

<400> 1

Met	Gln	Ile	Glu	Leu	Ser	Thr	Cys	Phe	Phe	Leu	Cys	Leu	Leu	Arg	Phe
1				5					10					15	

Cys	Phe	Ser	Ala	Thr	Arg	Arg	Tyr	Tyr	Leu	Gly	Ala	Val	Glu	Leu	Ser
			20					25					30		

Trp	Asp	Tyr	Met	Gln	Ser	Asp	Leu	Gly	Glu	Leu	Pro	Val	Asp	Ala	Arg
			35				40					45			

Sequence_Listing.txt

Phe Pro Pro Arg Val Pro Lys Ser Phe Pro Phe Asn Thr Ser Val Val
50 55 60

Tyr Lys Lys Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile
65 70 75 80

Ala Lys Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln
85 90 95

Ala Glu Val Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser
100 105 110

His Pro Val Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ala Ser
115 120 125

Glu Gly Ala Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp
130 135 140

Asp Lys Val Phe Pro Gly Gly Ser His Thr Tyr Val Trp Gln Val Leu
145 150 155 160

Lys Glu Asn Gly Pro Met Ala Ser Asp Pro Leu Cys Leu Thr Tyr Ser
165 170 175

Tyr Leu Ser His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile
180 185 190

Gly Ala Leu Leu Val Cys Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr
195 200 205

Gln Thr Leu His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu Gly
210 215 220

Lys Ser Trp His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp
225 230 235 240

Ala Ala Ser Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr
245 250 255

Sequence_Listing.txt

Val Asn Arg Ser Leu Pro Gly Leu Ile Gly Cys His Arg Lys Ser Val
260 265 270

Tyr Trp His Val Ile Gly Met Gly Thr Thr Pro Glu Val His Ser Ile
275 280 285

Phe Leu Glu Gly His Thr Phe Leu Val Arg Asn His Arg Gln Ala Ser
290 295 300

Leu Glu Ile Ser Pro Ile Thr Phe Leu Thr Ala Gln Thr Leu Leu Met
305 310 315 320

Asp Leu Gly Gln Phe Leu Leu Phe Cys His Ile Ser Ser His Gln His
325 330 335

Asp Gly Met Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro
340 345 350

Gln Leu Arg Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp
355 360 365

Leu Thr Asp Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser
370 375 380

Pro Ser Phe Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr
385 390 395 400

Trp Val His Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro
405 410 415

Leu Val Leu Ala Pro Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn
420 425 430

Asn Gly Pro Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met
435 440 445

Ala Tyr Thr Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu
450 455 460

Sequence_Listing.txt

Ser Gly Ile Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu
465 470 475 480

Leu Ile Ile Phe Lys Asn Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro
485 490 495

His Gly Ile Thr Asp Val Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys
500 505 510

Gly Val Lys His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe
515 520 525

Lys Tyr Lys Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp
530 535 540

Pro Arg Cys Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg
545 550 555 560

Asp Leu Ala Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu
565 570 575

Ser Val Asp Gln Arg Gly Asn Gln Ile Met Ser Asp Lys Arg Asn Val
580 585 590

Ile Leu Phe Ser Val Phe Asp Glu Asn Arg Ser Trp Tyr Leu Thr Glu
595 600 605

Asn Ile Gln Arg Phe Leu Pro Asn Pro Ala Gly Val Gln Leu Glu Asp
610 615 620

Pro Glu Phe Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val
625 630 635 640

Phe Asp Ser Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp
645 650 655

Tyr Ile Leu Ser Ile Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe
660 665 670

Sequence_Listing.txt

Ser Gly Tyr Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr
675 680 685

Leu Phe Pro Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro
690 695 700

Gly Leu Trp Ile Leu Gly Cys His Asn Ser Asp Phe Arg Asn Arg Gly
705 710 715 720

Met Thr Ala Leu Leu Lys Val Ser Ser Cys Asp Lys Asn Thr Gly Asp
725 730 735

Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys
740 745 750

Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser Gln Asn Pro Pro Val Leu
755 760 765

Lys Arg His Gln Arg Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln
770 775 780

Glu Glu Ile Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu
785 790 795 800

Asp Phe Asp Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe
805 810 815

Gln Lys Lys Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp
820 825 830

Asp Tyr Gly Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln
835 840 845

Ser Gly Ser Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr
850 855 860

Asp Gly Ser Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His
865 870 875 880

Sequence_Listing.txt

Leu Gly Leu Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile
885 890 895

Met Val Thr Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser
900 905 910

Ser Leu Ile Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg
915 920 925

Lys Asn Phe Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val
930 935 940

Gln His His Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp
945 950 955 960

Ala Tyr Phe Ser Asp Val Asp Leu Glu Lys Asp Val His Ser Gly Leu
965 970 975

Ile Gly Pro Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala His
980 985 990

Gly Arg Gln Val Thr Val Gln Glu Phe Ala Leu Phe Phe Thr Ile Phe
995 1000 1005

Asp Glu Thr Lys Ser Trp Tyr Phe Thr Glu Asn Met Glu Arg Asn
1010 1015 1020

Cys Arg Ala Pro Cys Asn Ile Gln Met Glu Asp Pro Thr Phe Lys
1025 1030 1035

Glu Asn Tyr Arg Phe His Ala Ile Asn Gly Tyr Ile Met Asp Thr
1040 1045 1050

Leu Pro Gly Leu Val Met Ala Gln Asp Gln Arg Ile Arg Trp Tyr
1055 1060 1065

Leu Leu Ser Met Gly Ser Asn Glu Asn Ile His Ser Ile His Phe
1070 1075 1080

Sequence_Listing.txt

Ser Gly His Val Phe Thr Val Arg Lys Lys Glu Glu Tyr Lys Met
1085 1090 1095

Ala Leu Tyr Asn Leu Tyr Pro Gly Val Phe Glu Thr Val Glu Met
1100 1105 1110

Leu Pro Ser Lys Ala Gly Ile Trp Arg Val Glu Cys Leu Ile Gly
1115 1120 1125

Glu His Leu His Ala Gly Met Ser Thr Leu Phe Leu Val Tyr Ser
1130 1135 1140

Asn Lys Cys Gln Thr Pro Leu Gly Met Ala Ser Gly His Ile Arg
1145 1150 1155

Asp Phe Gln Ile Thr Ala Ser Gly Gln Tyr Gly Gln Trp Ala Pro
1160 1165 1170

Lys Leu Ala Arg Leu His Tyr Ser Gly Ser Ile Asn Ala Trp Ser
1175 1180 1185

Thr Lys Glu Pro Phe Ser Trp Ile Lys Val Asp Leu Leu Ala Pro
1190 1195 1200

Met Ile Ile His Gly Ile Lys Thr Gln Gly Ala Arg Gln Lys Phe
1205 1210 1215

Ser Ser Leu Tyr Ile Ser Gln Phe Ile Ile Met Tyr Ser Leu Asp
1220 1225 1230

Gly Lys Lys Trp Gln Thr Tyr Arg Gly Asn Ser Thr Gly Thr Leu
1235 1240 1245

Met Val Phe Phe Gly Asn Val Asp Ser Ser Gly Ile Lys His Asn
1250 1255 1260

Ile Phe Asn Pro Pro Ile Ile Ala Arg Tyr Ile Arg Leu His Pro
1265 1270 1275

Sequence_Listing.txt

Thr His Tyr Ser Ile Arg Ser Thr Leu Arg Met Glu Leu Met Gly
1280 1285 1290

Cys Asp Leu Asn Ser Cys Ser Met Pro Leu Gly Met Glu Ser Lys
1295 1300 1305

Ala Ile Ser Asp Ala Gln Ile Thr Ala Ser Ser Tyr Phe Thr Asn
1310 1315 1320

Met Phe Ala Thr Trp Ser Pro Ser Lys Ala Arg Leu His Leu Gln
1325 1330 1335

Gly Arg Ser Asn Ala Trp Arg Pro Gln Val Asn Asn Pro Lys Glu
1340 1345 1350

Trp Leu Gln Val Asp Phe Gln Lys Thr Met Lys Val Thr Gly Val
1355 1360 1365

Thr Thr Gln Gly Val Lys Ser Leu Leu Thr Ser Met Tyr Val Lys
1370 1375 1380

Glu Phe Leu Ile Ser Ser Ser Gln Asp Gly His Gln Trp Thr Leu
1385 1390 1395

Phe Phe Gln Asn Gly Lys Val Lys Val Phe Gln Gly Asn Gln Asp
1400 1405 1410

Ser Phe Thr Pro Val Val Asn Ser Leu Asp Pro Pro Leu Leu Thr
1415 1420 1425

Arg Tyr Leu Arg Ile His Pro Gln Ser Trp Val His Gln Ile Ala
1430 1435 1440

Leu Arg Met Glu Val Leu Gly Cys Glu Ala Gln Asp Leu Tyr
1445 1450 1455

<210> 2
<211> 461
<212> PRT

Sequence_Listing.txt

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<220>

<221> SITE

<222> (1)..(28)

<223> /note="Signal sequence"

<400> 2

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Sequence_Listing.txt

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

Pro Cys Gly Arg Val Ser Val Ser Gln Thr Ser Lys Leu Thr Arg Ala
180 185 190

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
210 215 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225 230 235 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
245 250 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
260 265 270

Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu
275 280 285

His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn
290 295 300

Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu
305 310 315 320

Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile
325 330 335

Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr
340 345 350

Val Ser Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val
355 360 365

Sequence_Listing.txt

Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Leu
370 375 380

Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His
385 390 395 400

Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val
405 410 415

Thr Glu Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly
420 425 430

Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser
435 440 445

Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr
450 455 460

<210> 3
<211> 1457
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<220>
<221> SITE
<222> (1)..(19)
<223> /note="Signal sequence"

<400> 3
Met Gln Ile Glu Leu Ser Thr Cys Phe Phe Leu Cys Leu Leu Arg Phe
1 5 10 15

Cys Phe Ser Ala Thr Arg Arg Tyr Tyr Leu Gly Ala Val Glu Leu Ser
20 25 30

Trp Asp Tyr Met Gln Ser Asp Leu Gly Glu Leu Pro Val Asp Ala Arg

Sequence_Listing.txt

35

40

45

Phe Pro Pro Arg Val Pro Lys Ser Phe Pro Phe Asn Thr Ser Val Val
 50 55 60

Tyr Lys Lys Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile
 65 70 75 80

Ala Lys Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln
 85 90 95

Ala Glu Val Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser
 100 105 110

His Pro Val Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ala Ser
 115 120 125

Glu Gly Ala Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp
 130 135 140

Asp Lys Val Phe Pro Gly Gly Ser His Thr Tyr Val Trp Gln Val Leu
 145 150 155 160

Lys Glu Asn Gly Pro Met Ala Ser Asp Pro Leu Cys Leu Thr Tyr Ser
 165 170 175

Tyr Leu Ser His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile
 180 185 190

Gly Ala Leu Leu Val Cys Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr
 195 200 205

Gln Thr Leu His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu Gly
 210 215 220

Lys Ser Trp His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp
 225 230 235 240

Ala Ala Ser Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr

Sequence_Listing.txt

245

250

255

Val Asn Arg Ser Leu Pro Gly Leu Ile Gly Cys His Arg Lys Ser Val
 260 265 270

Tyr Trp His Val Ile Gly Met Gly Thr Thr Pro Glu Val His Ser Ile
 275 280 285

Phe Leu Glu Gly His Thr Phe Leu Val Arg Asn His Arg Gln Ala Ser
 290 295 300

Leu Glu Ile Ser Pro Ile Thr Phe Leu Thr Ala Gln Thr Leu Leu Met
 305 310 315 320

Asp Leu Gly Gln Phe Leu Leu Phe Cys His Ile Ser Ser His Gln His
 325 330 335

Asp Gly Met Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro
 340 345 350

Gln Leu Arg Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp
 355 360 365

Leu Thr Asp Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser
 370 375 380

Pro Ser Phe Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr
 385 390 395 400

Trp Val His Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro
 405 410 415

Leu Val Leu Ala Pro Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn
 420 425 430

Asn Gly Pro Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met
 435 440 445

Ala Tyr Thr Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu

Sequence_Listing.txt

450

455

460

Ser Gly Ile Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu
 465 470 475 480

Leu Ile Ile Phe Lys Asn Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro
 485 490 495

His Gly Ile Thr Asp Val Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys
 500 505 510

Gly Val Lys His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe
 515 520 525

Lys Tyr Lys Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp
 530 535 540

Pro Arg Cys Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg
 545 550 555 560

Asp Leu Ala Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu
 565 570 575

Ser Val Asp Gln Arg Gly Asn Gln Ile Met Ser Asp Lys Arg Asn Val
 580 585 590

Ile Leu Phe Ser Val Phe Asp Glu Asn Arg Ser Trp Tyr Leu Thr Glu
 595 600 605

Asn Ile Gln Arg Phe Leu Pro Asn Pro Ala Gly Val Gln Leu Glu Asp
 610 615 620

Pro Glu Phe Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val
 625 630 635 640

Phe Asp Ser Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp
 645 650 655

Tyr Ile Leu Ser Ile Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe

Sequence_Listing.txt

660

665

670

Ser Gly Tyr Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr
 675 680 685

Leu Phe Pro Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro
 690 695 700

Gly Leu Trp Ile Leu Gly Cys His Asn Ser Asp Phe Arg Asn Arg Gly
 705 710 715 720

Met Thr Ala Leu Leu Lys Val Ser Ser Cys Asp Lys Asn Thr Gly Asp
 725 730 735

Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys
 740 745 750

Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser Gln Asn Pro Pro Val Leu
 755 760 765

Lys His His Gln Arg Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln
 770 775 780

Glu Glu Ile Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu
 785 790 795 800

Asp Phe Asp Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe
 805 810 815

Gln Lys Lys Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp
 820 825 830

Asp Tyr Gly Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln
 835 840 845

Ser Gly Ser Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr
 850 855 860

Asp Gly Ser Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His

865 870 875 880

Leu Leu Ser Met Gly Ser Asn Glu Asn Ile His Ser Ile His Phe

Sequence_Listing.txt

1070

1075

1080

Ser Gly His Val Phe Thr Val Arg Lys Lys Glu Glu Tyr Lys Met
 1085 1090 1095

Ala Leu Tyr Asn Leu Tyr Pro Gly Val Phe Glu Thr Val Glu Met
 1100 1105 1110

Leu Pro Ser Lys Ala Gly Ile Trp Arg Val Glu Cys Leu Ile Gly
 1115 1120 1125

Glu His Leu His Ala Gly Met Ser Thr Leu Phe Leu Val Tyr Ser
 1130 1135 1140

Asn Lys Cys Gln Thr Pro Leu Gly Met Ala Ser Gly His Ile Arg
 1145 1150 1155

Asp Phe Gln Ile Thr Ala Ser Gly Gln Tyr Gly Gln Trp Ala Pro
 1160 1165 1170

Lys Leu Ala Arg Leu His Tyr Ser Gly Ser Ile Asn Ala Trp Ser
 1175 1180 1185

Thr Lys Glu Pro Phe Ser Trp Ile Lys Val Asp Leu Leu Ala Pro
 1190 1195 1200

Met Ile Ile His Gly Ile Lys Thr Gln Gly Ala Arg Gln Lys Phe
 1205 1210 1215

Ser Ser Leu Tyr Ile Ser Gln Phe Ile Ile Met Tyr Ser Leu Asp
 1220 1225 1230

Gly Lys Lys Trp Gln Thr Tyr Arg Gly Asn Ser Thr Gly Thr Leu
 1235 1240 1245

Met Val Phe Phe Gly Asn Val Asp Ser Ser Gly Ile Lys His Asn
 1250 1255 1260

Ile Phe Asn Pro Pro Ile Ile Ala Arg Tyr Ile Arg Leu His Pro

Sequence_Listing.txt

1265

1270

1275

Thr His Tyr Ser Ile Arg Ser Thr Leu Arg Met Glu Leu Met Gly
 1280 1285 1290

Cys Asp Leu Asn Ser Cys Ser Met Pro Leu Gly Met Glu Ser Lys
 1295 1300 1305

Ala Ile Ser Asp Ala Gln Ile Thr Ala Ser Ser Tyr Phe Thr Asn
 1310 1315 1320

Met Phe Ala Thr Trp Ser Pro Ser Lys Ala Arg Leu His Leu Gln
 1325 1330 1335

Gly Arg Ser Asn Ala Trp Arg Pro Gln Val Asn Asn Pro Lys Glu
 1340 1345 1350

Trp Leu Gln Val Asp Phe Gln Lys Thr Met Lys Val Thr Gly Val
 1355 1360 1365

Thr Thr Gln Gly Val Lys Ser Leu Leu Thr Ser Met Tyr Val Lys
 1370 1375 1380

Glu Phe Leu Ile Ser Ser Ser Gln Asp Gly His Gln Trp Thr Leu
 1385 1390 1395

Phe Phe Gln Asn Gly Lys Val Lys Val Phe Gln Gly Asn Gln Asp
 1400 1405 1410

Ser Phe Thr Pro Val Val Asn Ser Leu Asp Pro Pro Leu Leu Thr
 1415 1420 1425

Arg Tyr Leu Arg Ile His Pro Gln Ser Trp Val His Gln Ile Ala
 1430 1435 1440

Leu Arg Met Glu Val Leu Gly Cys Glu Ala Gln Asp Leu Tyr
 1445 1450 1455

<210> 4

Sequence_Listing.txt

<211> 1457
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<220>
<221> SITE
<222> (1)..(19)
<223> /note="Signal sequence"

<400> 4
Met Gln Ile Glu Leu Ser Thr Cys Phe Phe Leu Cys Leu Leu Arg Phe
1 5 10 15

Cys Phe Ser Ala Thr Arg Arg Tyr Tyr Leu Gly Ala Val Glu Leu Ser
20 25 30

Trp Asp Tyr Met Gln Ser Asp Leu Gly Glu Leu Pro Val Asp Ala Arg
35 40 45

Phe Pro Pro Arg Val Pro Lys Ser Phe Pro Phe Asn Thr Ser Val Val
50 55 60

Tyr Lys Lys Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile
65 70 75 80

Ala Lys Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln
85 90 95

Ala Glu Val Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser
100 105 110

His Pro Val Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ala Ser
115 120 125

Glu Gly Ala Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp
130 135 140

Sequence_Listing.txt

Asp Lys Val Phe Pro Gly Gly Ser His Thr Tyr Val Trp Gln Val Leu
145 150 155 160

Lys Glu Asn Gly Pro Met Ala Ser Asp Pro Leu Cys Leu Thr Tyr Ser
165 170 175

Tyr Leu Ser His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile
180 185 190

Gly Ala Leu Leu Val Cys Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr
195 200 205

Gln Thr Leu His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu Gly
210 215 220

Lys Ser Trp His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp
225 230 235 240

Ala Ala Ser Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr
245 250 255

Val Asn Arg Ser Leu Pro Gly Leu Ile Gly Cys His Arg Lys Ser Val
260 265 270

Tyr Trp His Val Ile Gly Met Gly Thr Thr Pro Glu Val His Ser Ile
275 280 285

Phe Leu Glu Gly His Thr Phe Leu Val Arg Asn His Arg Gln Ala Ser
290 295 300

Leu Glu Ile Ser Pro Ile Thr Phe Leu Thr Ala Gln Thr Leu Leu Met
305 310 315 320

Asp Leu Gly Gln Phe Leu Leu Phe Cys His Ile Ser Ser His Gln His
325 330 335

Asp Gly Met Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro
340 345 350

Sequence_Listing.txt

Gln Leu Arg Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp
 355 360 365

Leu Thr Asp Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser
 370 375 380

Pro Ser Phe Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr
 385 390 395 400

Trp Val His Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro
 405 410 415

Leu Val Leu Ala Pro Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn
 420 425 430

Asn Gly Pro Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met
 435 440 445

Ala Tyr Thr Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu
 450 455 460

Ser Gly Ile Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu
 465 470 475 480

Leu Ile Ile Phe Lys Asn Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro
 485 490 495

His Gly Ile Thr Asp Val Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys
 500 505 510

Gly Val Lys His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe
 515 520 525

Lys Tyr Lys Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp
 530 535 540

Pro Arg Cys Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg
 545 550 555 560

Sequence_Listing.txt

Asp Leu Ala Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu
565 570 575

Ser Val Asp Gln Arg Gly Asn Gln Ile Met Ser Asp Lys Arg Asn Val
580 585 590

Ile Leu Phe Ser Val Phe Asp Glu Asn Arg Ser Trp Tyr Leu Thr Glu
595 600 605

Asn Ile Gln Arg Phe Leu Pro Asn Pro Ala Gly Val Gln Leu Glu Asp
610 615 620

Pro Glu Phe Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val
625 630 635 640

Phe Asp Ser Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp
645 650 655

Tyr Ile Leu Ser Ile Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe
660 665 670

Ser Gly Tyr Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr
675 680 685

Leu Phe Pro Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro
690 695 700

Gly Leu Trp Ile Leu Gly Cys His Asn Ser Asp Phe Arg Asn Arg Gly
705 710 715 720

Met Thr Ala Leu Leu Lys Val Ser Ser Cys Asp Lys Asn Thr Gly Asp
725 730 735

Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys
740 745 750

Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser Gln Asn Pro Pro Val Leu
755 760 765

Sequence_Listing.txt

Lys Ala His Gln Ala Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln
770 775 780

Glu Glu Ile Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu
785 790 795 800

Asp Phe Asp Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe
805 810 815

Gln Lys Lys Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp
820 825 830

Asp Tyr Gly Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln
835 840 845

Ser Gly Ser Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr
850 855 860

Asp Gly Ser Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His
865 870 875 880

Leu Gly Leu Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile
885 890 895

Met Val Thr Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser
900 905 910

Ser Leu Ile Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg
915 920 925

Lys Asn Phe Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val
930 935 940

Gln His His Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp
945 950 955 960

Ala Tyr Phe Ser Asp Val Asp Leu Glu Lys Asp Val His Ser Gly Leu
965 970 975

Sequence_Listing.txt

Ile Gly Pro Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala His
 980 985 990

Gly Arg Gln Val Thr Val Gln Glu Phe Ala Leu Phe Phe Thr Ile Phe
 995 1000 1005

Asp Glu Thr Lys Ser Trp Tyr Phe Thr Glu Asn Met Glu Arg Asn
 1010 1015 1020

Cys Arg Ala Pro Cys Asn Ile Gln Met Glu Asp Pro Thr Phe Lys
 1025 1030 1035

Glu Asn Tyr Arg Phe His Ala Ile Asn Gly Tyr Ile Met Asp Thr
 1040 1045 1050

Leu Pro Gly Leu Val Met Ala Gln Asp Gln Arg Ile Arg Trp Tyr
 1055 1060 1065

Leu Leu Ser Met Gly Ser Asn Glu Asn Ile His Ser Ile His Phe
 1070 1075 1080

Ser Gly His Val Phe Thr Val Arg Lys Lys Glu Glu Tyr Lys Met
 1085 1090 1095

Ala Leu Tyr Asn Leu Tyr Pro Gly Val Phe Glu Thr Val Glu Met
 1100 1105 1110

Leu Pro Ser Lys Ala Gly Ile Trp Arg Val Glu Cys Leu Ile Gly
 1115 1120 1125

Glu His Leu His Ala Gly Met Ser Thr Leu Phe Leu Val Tyr Ser
 1130 1135 1140

Asn Lys Cys Gln Thr Pro Leu Gly Met Ala Ser Gly His Ile Arg
 1145 1150 1155

Asp Phe Gln Ile Thr Ala Ser Gly Gln Tyr Gly Gln Trp Ala Pro
 1160 1165 1170

Sequence_Listing.txt

Lys	Leu	Ala	Arg	Leu	His	Tyr	Ser	Gly	Ser	Ile	Asn	Ala	Trp	Ser
1175						1180					1185			
Thr	Lys	Glu	Pro	Phe	Ser	Trp	Ile	Lys	Val	Asp	Leu	Leu	Ala	Pro
1190						1195					1200			
Met	Ile	Ile	His	Gly	Ile	Lys	Thr	Gln	Gly	Ala	Arg	Gln	Lys	Phe
1205						1210					1215			
Ser	Ser	Leu	Tyr	Ile	Ser	Gln	Phe	Ile	Ile	Met	Tyr	Ser	Leu	Asp
1220						1225					1230			
Gly	Lys	Lys	Trp	Gln	Thr	Tyr	Arg	Gly	Asn	Ser	Thr	Gly	Thr	Leu
1235						1240					1245			
Met	Val	Phe	Phe	Gly	Asn	Val	Asp	Ser	Ser	Gly	Ile	Lys	His	Asn
1250						1255					1260			
Ile	Phe	Asn	Pro	Pro	Ile	Ile	Ala	Arg	Tyr	Ile	Arg	Leu	His	Pro
1265						1270					1275			
Thr	His	Tyr	Ser	Ile	Arg	Ser	Thr	Leu	Arg	Met	Glu	Leu	Met	Gly
1280						1285					1290			
Cys	Asp	Leu	Asn	Ser	Cys	Ser	Met	Pro	Leu	Gly	Met	Glu	Ser	Lys
1295						1300					1305			
Ala	Ile	Ser	Asp	Ala	Gln	Ile	Thr	Ala	Ser	Ser	Tyr	Phe	Thr	Asn
1310						1315					1320			
Met	Phe	Ala	Thr	Trp	Ser	Pro	Ser	Lys	Ala	Arg	Leu	His	Leu	Gln
1325						1330					1335			
Gly	Arg	Ser	Asn	Ala	Trp	Arg	Pro	Gln	Val	Asn	Asn	Pro	Lys	Glu
1340						1345					1350			
Trp	Leu	Gln	Val	Asp	Phe	Gln	Lys	Thr	Met	Lys	Val	Thr	Gly	Val
1355						1360					1365			

Sequence_Listing.txt

Thr Thr Gln Gly Val Lys Ser Leu Leu Thr Ser Met Tyr Val Lys
1370 1375 1380

Glu Phe Leu Ile Ser Ser Ser Gln Asp Gly His Gln Trp Thr Leu
1385 1390 1395

Phe Phe Gln Asn Gly Lys Val Lys Val Phe Gln Gly Asn Gln Asp
1400 1405 1410

Ser Phe Thr Pro Val Val Asn Ser Leu Asp Pro Pro Leu Leu Thr
1415 1420 1425

Arg Tyr Leu Arg Ile His Pro Gln Ser Trp Val His Gln Ile Ala
1430 1435 1440

Leu Arg Met Glu Val Leu Gly Cys Glu Ala Gln Asp Leu Tyr
1445 1450 1455

<210> 5
<211> 1453
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<220>
<221> SITE
<222> (1)..(19)
<223> /note="Signal sequence"

<400> 5
Met Gln Ile Glu Leu Ser Thr Cys Phe Phe Leu Cys Leu Leu Arg Phe
1 5 10 15

Cys Phe Ser Ala Thr Arg Arg Tyr Tyr Leu Gly Ala Val Glu Leu Ser
20 25 30

Trp Asp Tyr Met Gln Ser Asp Leu Gly Glu Leu Pro Val Asp Ala Arg
35 40 45

Sequence_Listing.txt

Phe Pro Pro Arg Val Pro Lys Ser Phe Pro Phe Asn Thr Ser Val Val
50 55 60

Tyr Lys Lys Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile
65 70 75 80

Ala Lys Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln
85 90 95

Ala Glu Val Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser
100 105 110

His Pro Val Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ala Ser
115 120 125

Glu Gly Ala Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp
130 135 140

Asp Lys Val Phe Pro Gly Gly Ser His Thr Tyr Val Trp Gln Val Leu
145 150 155 160

Lys Glu Asn Gly Pro Met Ala Ser Asp Pro Leu Cys Leu Thr Tyr Ser
165 170 175

Tyr Leu Ser His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile
180 185 190

Gly Ala Leu Leu Val Cys Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr
195 200 205

Gln Thr Leu His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu Gly
210 215 220

Lys Ser Trp His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp
225 230 235 240

Ala Ala Ser Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr
245 250 255

Sequence_Listing.txt

Val Asn Arg Ser Leu Pro Gly Leu Ile Gly Cys His Arg Lys Ser Val
260 265 270

Tyr Trp His Val Ile Gly Met Gly Thr Thr Pro Glu Val His Ser Ile
275 280 285

Phe Leu Glu Gly His Thr Phe Leu Val Arg Asn His Arg Gln Ala Ser
290 295 300

Leu Glu Ile Ser Pro Ile Thr Phe Leu Thr Ala Gln Thr Leu Leu Met
305 310 315 320

Asp Leu Gly Gln Phe Leu Leu Phe Cys His Ile Ser Ser His Gln His
325 330 335

Asp Gly Met Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro
340 345 350

Gln Leu Arg Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp
355 360 365

Leu Thr Asp Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser
370 375 380

Pro Ser Phe Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr
385 390 395 400

Trp Val His Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro
405 410 415

Leu Val Leu Ala Pro Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn
420 425 430

Asn Gly Pro Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met
435 440 445

Ala Tyr Thr Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu
450 455 460

Sequence_Listing.txt

Ser Gly Ile Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu
465 470 475 480

Leu Ile Ile Phe Lys Asn Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro
485 490 495

His Gly Ile Thr Asp Val Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys
500 505 510

Gly Val Lys His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe
515 520 525

Lys Tyr Lys Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp
530 535 540

Pro Arg Cys Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg
545 550 555 560

Asp Leu Ala Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu
565 570 575

Ser Val Asp Gln Arg Gly Asn Gln Ile Met Ser Asp Lys Arg Asn Val
580 585 590

Ile Leu Phe Ser Val Phe Asp Glu Asn Arg Ser Trp Tyr Leu Thr Glu
595 600 605

Asn Ile Gln Arg Phe Leu Pro Asn Pro Ala Gly Val Gln Leu Glu Asp
610 615 620

Pro Glu Phe Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val
625 630 635 640

Phe Asp Ser Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp
645 650 655

Tyr Ile Leu Ser Ile Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe
660 665 670

Sequence_Listing.txt

Ser Gly Tyr Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr
675 680 685

Leu Phe Pro Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro
690 695 700

Gly Leu Trp Ile Leu Gly Cys His Asn Ser Asp Phe Arg Asn Arg Gly
705 710 715 720

Met Thr Ala Leu Leu Lys Val Ser Ser Cys Asp Lys Asn Thr Gly Asp
725 730 735

Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys
740 745 750

Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser Gln Asn Pro Pro Val Leu
755 760 765

Lys Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile Asp
770 775 780

Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu Asp Phe Asp Ile
785 790 795 800

Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys Thr
805 810 815

Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr Gly Met
820 825 830

Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln Ser Gly Ser Val
835 840 845

Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr Asp Gly Ser Phe
850 855 860

Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His Leu Gly Leu Leu
865 870 875 880

Sequence_Listing.txt

Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile Met Val Thr Phe
885 890 895

Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser Ser Leu Ile Ser
900 905 910

Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg Lys Asn Phe Val
915 920 925

Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val Gln His His Met
930 935 940

Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp Ala Tyr Phe Ser
945 950 955 960

Asp Val Asp Leu Glu Lys Asp Val His Ser Gly Leu Ile Gly Pro Leu
965 970 975

Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala His Gly Arg Gln Val
980 985 990

Thr Val Gln Glu Phe Ala Leu Phe Phe Thr Ile Phe Asp Glu Thr Lys
995 1000 1005

Ser Trp Tyr Phe Thr Glu Asn Met Glu Arg Asn Cys Arg Ala Pro
1010 1015 1020

Cys Asn Ile Gln Met Glu Asp Pro Thr Phe Lys Glu Asn Tyr Arg
1025 1030 1035

Phe His Ala Ile Asn Gly Tyr Ile Met Asp Thr Leu Pro Gly Leu
1040 1045 1050

Val Met Ala Gln Asp Gln Arg Ile Arg Trp Tyr Leu Leu Ser Met
1055 1060 1065

Gly Ser Asn Glu Asn Ile His Ser Ile His Phe Ser Gly His Val
1070 1075 1080

Sequence_Listing.txt

Phe Thr Val Arg Lys Lys Glu Glu Tyr Lys Met Ala Leu Tyr Asn
1085 1090 1095

Leu Tyr Pro Gly Val Phe Glu Thr Val Glu Met Leu Pro Ser Lys
1100 1105 1110

Ala Gly Ile Trp Arg Val Glu Cys Leu Ile Gly Glu His Leu His
1115 1120 1125

Ala Gly Met Ser Thr Leu Phe Leu Val Tyr Ser Asn Lys Cys Gln
1130 1135 1140

Thr Pro Leu Gly Met Ala Ser Gly His Ile Arg Asp Phe Gln Ile
1145 1150 1155

Thr Ala Ser Gly Gln Tyr Gly Gln Trp Ala Pro Lys Leu Ala Arg
1160 1165 1170

Leu His Tyr Ser Gly Ser Ile Asn Ala Trp Ser Thr Lys Glu Pro
1175 1180 1185

Phe Ser Trp Ile Lys Val Asp Leu Leu Ala Pro Met Ile Ile His
1190 1195 1200

Gly Ile Lys Thr Gln Gly Ala Arg Gln Lys Phe Ser Ser Leu Tyr
1205 1210 1215

Ile Ser Gln Phe Ile Ile Met Tyr Ser Leu Asp Gly Lys Lys Trp
1220 1225 1230

Gln Thr Tyr Arg Gly Asn Ser Thr Gly Thr Leu Met Val Phe Phe
1235 1240 1245

Gly Asn Val Asp Ser Ser Gly Ile Lys His Asn Ile Phe Asn Pro
1250 1255 1260

Pro Ile Ile Ala Arg Tyr Ile Arg Leu His Pro Thr His Tyr Ser
1265 1270 1275

Sequence_Listing.txt

Ile Arg Ser Thr Leu Arg Met Glu Leu Met Gly Cys Asp Leu Asn
1280 1285 1290

Ser Cys Ser Met Pro Leu Gly Met Glu Ser Lys Ala Ile Ser Asp
1295 1300 1305

Ala Gln Ile Thr Ala Ser Ser Tyr Phe Thr Asn Met Phe Ala Thr
1310 1315 1320

Trp Ser Pro Ser Lys Ala Arg Leu His Leu Gln Gly Arg Ser Asn
1325 1330 1335

Ala Trp Arg Pro Gln Val Asn Asn Pro Lys Glu Trp Leu Gln Val
1340 1345 1350

Asp Phe Gln Lys Thr Met Lys Val Thr Gly Val Thr Thr Gln Gly
1355 1360 1365

Val Lys Ser Leu Leu Thr Ser Met Tyr Val Lys Glu Phe Leu Ile
1370 1375 1380

Ser Ser Ser Gln Asp Gly His Gln Trp Thr Leu Phe Phe Gln Asn
1385 1390 1395

Gly Lys Val Lys Val Phe Gln Gly Asn Gln Asp Ser Phe Thr Pro
1400 1405 1410

Val Val Asn Ser Leu Asp Pro Pro Leu Leu Thr Arg Tyr Leu Arg
1415 1420 1425

Ile His Pro Gln Ser Trp Val His Gln Ile Ala Leu Arg Met Glu
1430 1435 1440

Val Leu Gly Cys Glu Ala Gln Asp Leu Tyr
1445 1450

<210> 6

<211> 1454

<212> PRT

Sequence_Listing.txt

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<220>

<221> SITE

<222> (1)..(19)

<223> /note="Signal sequence"

<400> 6

Met Gln Ile Glu Leu Ser Thr Cys Phe Phe Leu Cys Leu Leu Arg Phe
1 5 10 15

Cys Phe Ser Ala Thr Arg Arg Tyr Tyr Leu Gly Ala Val Glu Leu Ser
20 25 30

Trp Asp Tyr Met Gln Ser Asp Leu Gly Glu Leu Pro Val Asp Ala Arg
35 40 45

Phe Pro Pro Arg Val Pro Lys Ser Phe Pro Phe Asn Thr Ser Val Val
50 55 60

Tyr Lys Lys Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile
65 70 75 80

Ala Lys Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln
85 90 95

Ala Glu Val Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser
100 105 110

His Pro Val Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ala Ser
115 120 125

Glu Gly Ala Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp
130 135 140

Asp Lys Val Phe Pro Gly Gly Ser His Thr Tyr Val Trp Gln Val Leu
145 150 155 160

Sequence_Listing.txt

Lys Glu Asn Gly Pro Met Ala Ser Asp Pro Leu Cys Leu Thr Tyr Ser
165 170 175

Tyr Leu Ser His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile
180 185 190

Gly Ala Leu Leu Val Cys Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr
195 200 205

Gln Thr Leu His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu Gly
210 215 220

Lys Ser Trp His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp
225 230 235 240

Ala Ala Ser Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr
245 250 255

Val Asn Arg Ser Leu Pro Gly Leu Ile Gly Cys His Arg Lys Ser Val
260 265 270

Tyr Trp His Val Ile Gly Met Gly Thr Thr Pro Glu Val His Ser Ile
275 280 285

Phe Leu Glu Gly His Thr Phe Leu Val Arg Asn His Arg Gln Ala Ser
290 295 300

Leu Glu Ile Ser Pro Ile Thr Phe Leu Thr Ala Gln Thr Leu Leu Met
305 310 315 320

Asp Leu Gly Gln Phe Leu Leu Phe Cys His Ile Ser Ser His Gln His
325 330 335

Asp Gly Met Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro
340 345 350

Gln Leu Arg Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp
355 360 365

Sequence_Listing.txt

Leu Thr Asp Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser
370 375 380

Pro Ser Phe Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr
385 390 395 400

Trp Val His Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro
405 410 415

Leu Val Leu Ala Pro Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn
420 425 430

Asn Gly Pro Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met
435 440 445

Ala Tyr Thr Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu
450 455 460

Ser Gly Ile Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu
465 470 475 480

Leu Ile Ile Phe Lys Asn Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro
485 490 495

His Gly Ile Thr Asp Val Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys
500 505 510

Gly Val Lys His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe
515 520 525

Lys Tyr Lys Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp
530 535 540

Pro Arg Cys Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg
545 550 555 560

Asp Leu Ala Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu
565 570 575

Sequence_Listing.txt

Ser Val Asp Gln Arg Gly Asn Gln Ile Met Ser Asp Lys Arg Asn Val
580 585 590

Ile Leu Phe Ser Val Phe Asp Glu Asn Arg Ser Trp Tyr Leu Thr Glu
595 600 605

Asn Ile Gln Arg Phe Leu Pro Asn Pro Ala Gly Val Gln Leu Glu Asp
610 615 620

Pro Glu Phe Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val
625 630 635 640

Phe Asp Ser Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp
645 650 655

Tyr Ile Leu Ser Ile Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe
660 665 670

Ser Gly Tyr Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr
675 680 685

Leu Phe Pro Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro
690 695 700

Gly Leu Trp Ile Leu Gly Cys His Asn Ser Asp Phe Arg Asn Arg Gly
705 710 715 720

Met Thr Ala Leu Leu Lys Val Ser Ser Cys Asp Lys Asn Thr Gly Asp
725 730 735

Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys
740 745 750

Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser Gln Asn Pro Pro Val Leu
755 760 765

Lys Arg Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile
770 775 780

Sequence_Listing.txt

Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu Asp Phe Asp
785 790 795 800

Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys
805 810 815

Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr Gly
820 825 830

Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln Ser Gly Ser
835 840 845

Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr Asp Gly Ser
850 855 860

Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His Leu Gly Leu
865 870 875 880

Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile Met Val Thr
885 890 895

Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser Ser Leu Ile
900 905 910

Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg Lys Asn Phe
915 920 925

Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val Gln His His
930 935 940

Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp Ala Tyr Phe
945 950 955 960

Ser Asp Val Asp Leu Glu Lys Asp Val His Ser Gly Leu Ile Gly Pro
965 970 975

Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala His Gly Arg Gln
980 985 990

Sequence_Listing.txt

Val Thr Val Gln Glu Phe Ala Leu Phe Phe Thr Ile Phe Asp Glu Thr
 995 1000 1005

Lys Ser Trp Tyr Phe Thr Glu Asn Met Glu Arg Asn Cys Arg Ala
 1010 1015 1020

Pro Cys Asn Ile Gln Met Glu Asp Pro Thr Phe Lys Glu Asn Tyr
 1025 1030 1035

Arg Phe His Ala Ile Asn Gly Tyr Ile Met Asp Thr Leu Pro Gly
 1040 1045 1050

Leu Val Met Ala Gln Asp Gln Arg Ile Arg Trp Tyr Leu Leu Ser
 1055 1060 1065

Met Gly Ser Asn Glu Asn Ile His Ser Ile His Phe Ser Gly His
 1070 1075 1080

Val Phe Thr Val Arg Lys Lys Glu Glu Tyr Lys Met Ala Leu Tyr
 1085 1090 1095

Asn Leu Tyr Pro Gly Val Phe Glu Thr Val Glu Met Leu Pro Ser
 1100 1105 1110

Lys Ala Gly Ile Trp Arg Val Glu Cys Leu Ile Gly Glu His Leu
 1115 1120 1125

His Ala Gly Met Ser Thr Leu Phe Leu Val Tyr Ser Asn Lys Cys
 1130 1135 1140

Gln Thr Pro Leu Gly Met Ala Ser Gly His Ile Arg Asp Phe Gln
 1145 1150 1155

Ile Thr Ala Ser Gly Gln Tyr Gly Gln Trp Ala Pro Lys Leu Ala
 1160 1165 1170

Arg Leu His Tyr Ser Gly Ser Ile Asn Ala Trp Ser Thr Lys Glu
 1175 1180 1185

Sequence_Listing.txt

Pro	Phe	Ser	Trp	Ile	Lys	Val	Asp	Leu	Leu	Ala	Pro	Met	Ile	Ile
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His	Gly	Ile	Lys	Thr	Gln	Gly	Ala	Arg	Gln	Lys	Phe	Ser	Ser	Leu
	1205					1210					1215			
Tyr	Ile	Ser	Gln	Phe	Ile	Ile	Met	Tyr	Ser	Leu	Asp	Gly	Lys	Lys
	1220					1225					1230			
Trp	Gln	Thr	Tyr	Arg	Gly	Asn	Ser	Thr	Gly	Thr	Leu	Met	Val	Phe
	1235					1240					1245			
Phe	Gly	Asn	Val	Asp	Ser	Ser	Gly	Ile	Lys	His	Asn	Ile	Phe	Asn
	1250					1255					1260			
Pro	Pro	Ile	Ile	Ala	Arg	Tyr	Ile	Arg	Leu	His	Pro	Thr	His	Tyr
	1265					1270					1275			
Ser	Ile	Arg	Ser	Thr	Leu	Arg	Met	Glu	Leu	Met	Gly	Cys	Asp	Leu
	1280					1285					1290			
Asn	Ser	Cys	Ser	Met	Pro	Leu	Gly	Met	Glu	Ser	Lys	Ala	Ile	Ser
	1295					1300					1305			
Asp	Ala	Gln	Ile	Thr	Ala	Ser	Ser	Tyr	Phe	Thr	Asn	Met	Phe	Ala
	1310					1315					1320			
Thr	Trp	Ser	Pro	Ser	Lys	Ala	Arg	Leu	His	Leu	Gln	Gly	Arg	Ser
	1325					1330					1335			
Asn	Ala	Trp	Arg	Pro	Gln	Val	Asn	Asn	Pro	Lys	Glu	Trp	Leu	Gln
	1340					1345					1350			
Val	Asp	Phe	Gln	Lys	Thr	Met	Lys	Val	Thr	Gly	Val	Thr	Thr	Gln
	1355					1360					1365			
Gly	Val	Lys	Ser	Leu	Leu	Thr	Ser	Met	Tyr	Val	Lys	Glu	Phe	Leu
	1370					1375					1380			

Sequence_Listing.txt

Ile Ser Ser Ser Gln Asp Gly His Gln Trp Thr Leu Phe Phe Gln
1385 1390 1395

Asn Gly Lys Val Lys Val Phe Gln Gly Asn Gln Asp Ser Phe Thr
1400 1405 1410

Pro Val Val Asn Ser Leu Asp Pro Pro Leu Leu Thr Arg Tyr Leu
1415 1420 1425

Arg Ile His Pro Gln Ser Trp Val His Gln Ile Ala Leu Arg Met
1430 1435 1440

Glu Val Leu Gly Cys Glu Ala Gln Asp Leu Tyr
1445 1450

<210> 7
<211> 1474
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<220>
<221> SITE
<222> (1)..(19)
<223> /note="Signal sequence"

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Cys Phe Ser Ala Thr Arg Arg Tyr Tyr Leu Gly Ala Val Glu Leu Ser
20 25 30

Trp Asp Tyr Met Gln Ser Asp Leu Gly Glu Leu Pro Val Asp Ala Arg
35 40 45

Phe Pro Pro Arg Val Pro Lys Ser Phe Pro Phe Asn Thr Ser Val Val

Sequence_Listing.txt

50

55

60

Tyr Lys Lys Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile
 65 70 75 80

Ala Lys Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln
 85 90 95

Ala Glu Val Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser
 100 105 110

His Pro Val Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ala Ser
 115 120 125

Glu Gly Ala Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp
 130 135 140

Asp Lys Val Phe Pro Gly Gly Ser His Thr Tyr Val Trp Gln Val Leu
 145 150 155 160

Lys Glu Asn Gly Pro Met Ala Ser Asp Pro Leu Cys Leu Thr Tyr Ser
 165 170 175

Tyr Leu Ser His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile
 180 185 190

Gly Ala Leu Leu Val Cys Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr
 195 200 205

Gln Thr Leu His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu Gly
 210 215 220

Lys Ser Trp His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp
 225 230 235 240

Ala Ala Ser Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr
 245 250 255

Val Asn Arg Ser Leu Pro Gly Leu Ile Gly Cys His Arg Lys Ser Val

Sequence_Listing.txt

260

265

270

Tyr Trp His Val Ile Gly Met Gly Thr Thr Pro Glu Val His Ser Ile
 275 280 285

Phe Leu Glu Gly His Thr Phe Leu Val Arg Asn His Arg Gln Ala Ser
 290 295 300

Leu Glu Ile Ser Pro Ile Thr Phe Leu Thr Ala Gln Thr Leu Leu Met
 305 310 315 320

Asp Leu Gly Gln Phe Leu Leu Phe Cys His Ile Ser Ser His Gln His
 325 330 335

Asp Gly Met Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro
 340 345 350

Gln Leu Arg Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp
 355 360 365

Leu Thr Asp Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser
 370 375 380

Pro Ser Phe Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr
 385 390 395 400

Trp Val His Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro
 405 410 415

Leu Val Leu Ala Pro Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn
 420 425 430

Asn Gly Pro Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met
 435 440 445

Ala Tyr Thr Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu
 450 455 460

Ser Gly Ile Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu

Sequence_Listing.txt

465 470 475 480
 Leu Ile Ile Phe Lys Asn Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro
 485 490 495
 His Gly Ile Thr Asp Val Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys
 500 505 510
 Gly Val Lys His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe
 515 520 525
 Lys Tyr Lys Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp
 530 535 540
 Pro Arg Cys Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg
 545 550 555 560
 Asp Leu Ala Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu
 565 570 575
 Ser Val Asp Gln Arg Gly Asn Gln Ile Met Ser Asp Lys Arg Asn Val
 580 585 590
 Ile Leu Phe Ser Val Phe Asp Glu Asn Arg Ser Trp Tyr Leu Thr Glu
 595 600 605
 Asn Ile Gln Arg Phe Leu Pro Asn Pro Ala Gly Val Gln Leu Glu Asp
 610 615 620
 Pro Glu Phe Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val
 625 630 635 640
 Phe Asp Ser Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp
 645 650 655
 Tyr Ile Leu Ser Ile Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe
 660 665 670
 Ser Gly Tyr Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr

Sequence_Listing.txt

675

680

685

Leu Phe Pro Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro
 690 695 700

Gly Leu Trp Ile Leu Gly Cys His Asn Ser Asp Phe Arg Asn Arg Gly
 705 710 715 720

Met Thr Ala Leu Leu Lys Val Ser Ser Cys Asp Lys Asn Thr Gly Asp
 725 730 735

Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys
 740 745 750

Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser Gln Asn Ala Thr Asn Val
 755 760 765

Ser Asn Asn Ser Asn Thr Ser Asn Asp Ser Asn Val Ser Pro Pro Val
 770 775 780

Leu Lys Arg His Gln Arg Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp
 785 790 795 800

Gln Glu Glu Ile Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys
 805 810 815

Glu Asp Phe Asp Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser
 820 825 830

Phe Gln Lys Lys Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu
 835 840 845

Trp Asp Tyr Gly Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala
 850 855 860

Gln Ser Gly Ser Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe
 865 870 875 880

Thr Asp Gly Ser Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu

Sequence_Listing.txt

885

890

895

His Leu Gly Leu Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn
 900 905 910

Ile Met Val Thr Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr
 915 920 925

Ser Ser Leu Ile Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro
 930 935 940

Arg Lys Asn Phe Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys
 945 950 955 960

Val Gln His His Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala
 965 970 975

Trp Ala Tyr Phe Ser Asp Val Asp Leu Glu Lys Asp Val His Ser Gly
 980 985 990

Leu Ile Gly Pro Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala
 995 1000 1005

His Gly Arg Gln Val Thr Val Gln Glu Phe Ala Leu Phe Phe Thr
 1010 1015 1020

Ile Phe Asp Glu Thr Lys Ser Trp Tyr Phe Thr Glu Asn Met Glu
 1025 1030 1035

Arg Asn Cys Arg Ala Pro Cys Asn Ile Gln Met Glu Asp Pro Thr
 1040 1045 1050

Phe Lys Glu Asn Tyr Arg Phe His Ala Ile Asn Gly Tyr Ile Met
 1055 1060 1065

Asp Thr Leu Pro Gly Leu Val Met Ala Gln Asp Gln Arg Ile Arg
 1070 1075 1080

Trp Tyr Leu Leu Ser Met Gly Ser Asn Glu Asn Ile His Ser Ile

Sequence_Listing.txt

1085

1090

1095

His Phe Ser Gly His Val Phe Thr Val Arg Lys Lys Glu Glu Tyr
 1100 1105 1110

Lys Met Ala Leu Tyr Asn Leu Tyr Pro Gly Val Phe Glu Thr Val
 1115 1120 1125

Glu Met Leu Pro Ser Lys Ala Gly Ile Trp Arg Val Glu Cys Leu
 1130 1135 1140

Ile Gly Glu His Leu His Ala Gly Met Ser Thr Leu Phe Leu Val
 1145 1150 1155

Tyr Ser Asn Lys Cys Gln Thr Pro Leu Gly Met Ala Ser Gly His
 1160 1165 1170

Ile Arg Asp Phe Gln Ile Thr Ala Ser Gly Gln Tyr Gly Gln Trp
 1175 1180 1185

Ala Pro Lys Leu Ala Arg Leu His Tyr Ser Gly Ser Ile Asn Ala
 1190 1195 1200

Trp Ser Thr Lys Glu Pro Phe Ser Trp Ile Lys Val Asp Leu Leu
 1205 1210 1215

Ala Pro Met Ile Ile His Gly Ile Lys Thr Gln Gly Ala Arg Gln
 1220 1225 1230

Lys Phe Ser Ser Leu Tyr Ile Ser Gln Phe Ile Ile Met Tyr Ser
 1235 1240 1245

Leu Asp Gly Lys Lys Trp Gln Thr Tyr Arg Gly Asn Ser Thr Gly
 1250 1255 1260

Thr Leu Met Val Phe Phe Gly Asn Val Asp Ser Ser Gly Ile Lys
 1265 1270 1275

His Asn Ile Phe Asn Pro Pro Ile Ile Ala Arg Tyr Ile Arg Leu

Sequence_Listing.txt

1280

1285

1290

His Pro Thr His Tyr Ser Ile Arg Ser Thr Leu Arg Met Glu Leu
 1295 1300 1305

Met Gly Cys Asp Leu Asn Ser Cys Ser Met Pro Leu Gly Met Glu
 1310 1315 1320

Ser Lys Ala Ile Ser Asp Ala Gln Ile Thr Ala Ser Ser Tyr Phe
 1325 1330 1335

Thr Asn Met Phe Ala Thr Trp Ser Pro Ser Lys Ala Arg Leu His
 1340 1345 1350

Leu Gln Gly Arg Ser Asn Ala Trp Arg Pro Gln Val Asn Asn Pro
 1355 1360 1365

Lys Glu Trp Leu Gln Val Asp Phe Gln Lys Thr Met Lys Val Thr
 1370 1375 1380

Gly Val Thr Thr Gln Gly Val Lys Ser Leu Leu Thr Ser Met Tyr
 1385 1390 1395

Val Lys Glu Phe Leu Ile Ser Ser Ser Gln Asp Gly His Gln Trp
 1400 1405 1410

Thr Leu Phe Phe Gln Asn Gly Lys Val Lys Val Phe Gln Gly Asn
 1415 1420 1425

Gln Asp Ser Phe Thr Pro Val Val Asn Ser Leu Asp Pro Pro Leu
 1430 1435 1440

Leu Thr Arg Tyr Leu Arg Ile His Pro Gln Ser Trp Val His Gln
 1445 1450 1455

Ile Ala Leu Arg Met Glu Val Leu Gly Cys Glu Ala Gln Asp Leu
 1460 1465 1470

Tyr

Sequence_Listing.txt

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<211> 4374
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
        polynucleotide"

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ggtgagctgc ctgtggacgc aagatttcct cctagagtgc caaaatcttt tccattcaac      180
acctcagtcg tgtacaaaaa gactctgttt gtagaattca cggatcacct tttcaacatc      240
gctaagccaa ggccaccctg gatgggtctg ctaggtccta ccatccaggc tgaggtttat      300
gatacagtgg tcattacact taagaacatg gcttcccatc ctgtcagtct tcatgctgtt      360
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gagaaagaag atgataaagt cttccctggt ggaagccata catatgtctg gcaggctctg      480
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gcttatgtca aagtagacag ctgtccagag gaacccaac tacgaatgaa aaataatgaa     1080
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Sequence_Listing.txt

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aagtacaaaa aagtccgatt tatggcatac acagatgaaa cctttaagac tcgtgaagct	1380
attcagcatg aatcaggaat cttgggacct ttactttatg gggaagttgg agacacactg	1440
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actaaatcag atcctcgggtg cctgaccgcg tattactcta gtttcgtaa tatggagaga	1680
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Sequence_Listing.txt

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Sequence_Listing.txt

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<210> 9

<211> 4374

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
 polynucleotide"

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 gcttatgtca aagtagacag ctgtccagag gaacccaac tacgaatgaa aaataatgaa 1080

Sequence_Listing.txt

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cccgatgaca gaagttataa aagtcaatat ttgaacaatg gccctcagcg gattggtagg	1320
aagtacaaaa aagtccgatt tatggcatac acagatgaaa cttttaagac tcgtgaagct	1380
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Sequence_Listing.txt

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Sequence_Listing.txt

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cagattgccc tgaggatgga ggttctgggc tgcgaggcac aggacctcta ctga 4374
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<210> 10

<211> 4374

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 10

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gatacagtgg tcattacact taagaacatg gcttcccatc ctgtcagtct tcatgctgtt 360
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cgccaggcgt ctttgaaaat ctgcgaata actttcctta ctgctcaaac actcttgatg 960
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Sequence_Listing.txt

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tgggtacatt acattgctgc tgaagaggag gactgggact atgctccctt agtcctcgcc	1260
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aaccgaagct ggtacctcac agagaatata caacgctttc tccccaatcc agctggagtg	1860
cagcttgagg atccagagtt ccaagcctcc aacatcatgc acagcatcaa tggctatgtt	1920
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atggaaaacc caggtctatg gattctgggg tgccacaact cagactttcg gaacagaggc	2160
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Sequence_Listing.txt

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Sequence_Listing.txt

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tctctagacc caccgttact gactcgctac cttcgaattc acccccagag ttgggtgcac	4320
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<210> 11

<211> 4362

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 11

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acctcagtcg tgtacaaaaa gactctgttt gtagaattca cggatcacct tttcaacatc	240
gctaagccaa ggccaccctg gatgggtctg ctaggtccta ccatccaggc tgaggtttat	300
gatacagtgg tcattacact taagaacatg gcttcccatc ctgtcagtct tcatgctgtt	360
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Sequence_Listing.txt

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Sequence_Listing.txt

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Sequence_Listing.txt

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ccgttactga ctcgctacct tcgaattcac cccagagtt gggatgcacca gattgccctg 4320
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<210> 12

<211> 4365

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 12

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Sequence_Listing.txt

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Sequence_Listing.txt

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Sequence_Listing.txt

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aaagtaaagg tttttcaggg aaatcaagac tccttcacac ctgtgggtgaa ctctctagac	4260
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<210> 13

<211> 4374

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 13

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Sequence_Listing.txt

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Sequence_Listing.txt

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Sequence_Listing.txt

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<210> 14

<211> 4374

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 14

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Sequence_Listing.txt

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Sequence_Listing.txt

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Sequence_Listing.txt

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<210> 15

<211> 4374

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 15

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Sequence_Listing.txt

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Sequence_Listing.txt

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Sequence_Listing.txt

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<210> 16

<211> 4374

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 16

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gacacagtcg tgatcacact gaagaacatg gcctcccatc cagtgtctct gcacgccgtc	360
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Sequence_Listing.txt

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gatcttgggc agtttctgct gttttgtcat atttcttctc accaacacga cggaatggag	1020
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gaagccgagg actacgatga cgatttgacc gattccgaaa tggacgtggt gcgctttgat	1140
gatgacaatt ctccatcctt cattcagatt agatccgtcg ccaagaagca cccaagacc	1200
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Sequence_Listing.txt

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gactttgaca	tctacgatga	ggatgaaaac	cagagcccta	ggtcgttcca	gaagaaaaca	2460
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cgcggaaca	gtaccgggac	attgatggtg	ttcttcggga	acgtggactc	tagcggcatt	3780

Sequence_Listing.txt

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<210> 17

<211> 4425

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 17

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aaggaaaatg ggcccatggc cagtgaccct ttgtgtctga cttactcata cctgtctcat	540
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Sequence_Listing.txt

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Sequence_Listing.txt

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Sequence_Listing.txt

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<210> 18

<211> 1386

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 18

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gagagagaat gtatggaaga aaagtgtagt tttgaagaag cacgagaagt ttttgaaaac	240
actgaaagaa caactgaatt ttggaagcag tatgttgatg gagatcagtg tgagtccaat	300
ccatgtttta atggcggcag ttgcaaggat gacattaatt cctatgaatg ttggtgtccc	360
tttggatttg aaggaaagaa ctgtgaatta gatgtaacat gtaacattaa gaatggcaga	420
tgcgagcagt tttgtaaaaa tagtgctgat aacaaggtgg tttgctcctg tactgaggga	480

Sequence_Listing.txt

tatcgacttg cagaaaacca gaagtcctgt gaaccagcag tgccatttcc atgtggaaga	540
gtttctgttt cacaaacttc taagctcacc cgtgctgaga ctgtttttcc tgatgtggac	600
tatgtaaatt ctactgaagc tgaaccatt ttggataaca tcactcaaag cacccaatca	660
tttaatgact tcactcgggt tgttggtgga gaagatgcca aaccagggtca attcccttgg	720
caggttgttt tgaatggtaa agttgatgca ttctgtggag gctctatcgt taatgaaaaa	780
tggattgtaa ctgctgcccc ctgtgttgaa actgggtgta aaattacagt tgtcgcaggt	840
gaacataata ttgaggagac agaacataca gagcaaaagc gaaatgtgat tcgaattatt	900
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tacacgaaca tcttcctcaa atttggatct ggctatgtaa gtggctgggg aagagtcttc	1080
cacaaaggga gatcagcttt agttcttcag taccttagag ttccacttgt tgaccgagcc	1140
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gggaccagtt tcttaactgg aattattagc tgggggtgaag agtgtgcaat gaaaggcaaa	1320
tatggaatat ataccaaggt atcccgggtat gtcaactgga ttaaggaaaa aacaaagctc	1380
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<210> 19

<211> 1386

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 19

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ggctatctgc tgagcgccga gtgcaccgtg tttctggatc acgagaacgc caacaagatc	120
ctgaacagac ccaagcggta caacagcggc aagctggaag agttcgtgca gggcaacctg	180
gaacgcgagt gcatggaaga gaagtgcagc ttcgaagagg ccagagaggt gttcgagaac	240

Sequence_Listing.txt

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accgagagaa ccaccgagtt ctggaagcag tacgtggacg gcgatcagtg cgagagcaac      300
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ttcggcttcg agggcaagaa ttgcgagctg gacgtgacct gcaacatcaa gaacggcaga      420
tgcgagcagt tctgcaagaa cagcgccgac aacaaggctg tgtgctcctg cacagagggc      480
tacagactgg ccgagaacca gaagtcttgc gagcccgctg tgccctttcc atgtggcaga      540
gtgtctgtgt cccagaccag caagctgacc agagccgaga cagtgttccc cgacgtggac      600
tacgtgaaca gcaccgaggc cgagacaatc ctggacaaca tcaccagag caccagttcc      660
ttcaacgact tcaccagagt cgtcggcggc gaggatgcta agcctggaca gtttccttgg      720
caagtgggtg tgaacggcaa ggtggacgct ttttgtggcg gctccatcgt gaacgagaag      780
tggatcgtga ccgccgtca ctgtgtggaa accggcgtga agattacagt ggtggccggc      840
gagcacaaca tcgaggaaac agagcacacc gagcagaaac ggaacgtgat cagaatcatc      900
cctcaccaca actacaacgc cgccatcaac aagtacaacc acgatatcgc cctgctggaa      960
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cacaagggca gatcagccct ggtgctgcag tacctgagag tgcccctggt ggatagagcc     1140
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ggcacaagct ttctgaccgg catcatcagc tggggcgaag agtgtgccat gaaggggaag     1320
tacggcatct acaccaaggt gtccagatac gtgaactgga tcaaagaaaa gaccaagctc     1380
acctga                                           1386

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<210> 20

<211> 1386

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 20

Sequence_Listing.txt

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ggctacctgc tgagcgccga gtgcaccgtg ttcctggacc acgagaacgc caacaagatc	120
ctgaaccgcc ccaagcgcta caacagcggc aagctggagg agttcgtgca gggcaacctg	180
gagcgcgagt gcatggagga gaagtgcagc ttcgaggagg cccgcgaggt gttcgagaac	240
accgagcgca ccaccgagtt ctggaagcag tacgtggacg gcgaccagtg cgagagcaac	300
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tgcgagcagt tctgcaagaa cagcgccgac aacaagggtg tgtgcagctg caccgagggc	480
taccgcctgg ccgagaacca gaagagctgc gagcccgccg tgcccttccc ctgcggccgc	540
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tacggcatct acaccaaggt gagccgctac gtgaactgga tcaaggagaa aaccaagctg	1380
acctaa	1386

<210> 21

<211> 1386

<212> DNA

Sequence_Listing.txt

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 21

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ctgaatcgcc ccaagagata caattccgga aagctggaag agtttgtgca gggcaacctg	180
gagagagagt gcatggaaga gaagtgctcc ttcgaggagg cccgggagggt gttcgagaat	240
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ttcggcttcg agggcaagaa ctgcgagctg gacgtgacct gcaacatcaa gaacggccgc	420
tgcgagcagt tttgcaagaa ctccgccgac aacaagggtg tgtgttcttg caccgagggc	480
taccgcctgg ccgaaaacca gaagagctgt gagcctgccg tgcccttccc ctgcggccgg	540
gtgtctgtgt cccagacctc caagctgacc agagccgaaa ccgtgtttcc agatgtggac	600
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caggtggtgc tcaacggaaa ggtggacgcc ttctgcggag gcagcatcgt gaatgaaaag	780
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gagggcggca gggactcctg ccagggcgac agcggcggcc cccatgtgac cgagggtggag	1260
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Sequence_Listing.txt

tatggcatct acaccaaggt gtcccgctac gtgaactgga ttaaggagaa aaccaagctg	1380
acctga	1386

<210> 22
 <211> 313
 <212> DNA
 <213> Artificial Sequence

<220>
 <221> source
 <223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 22	
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gctcccgtag ggcgtgcttg tcaatgcggt aagtgtcact gatattgaac tataacgacc	180
gcgtgagtca aaatgacgca tgattatctt ttacgtgact ttttaagattt aactcatagc	240
ataattatat tgttatttca tgttctactt acgtgataac ttattatata tatattttct	300
tgttatagat atc	313

<210> 23
 <211> 1733
 <212> DNA
 <213> Artificial Sequence

<220>
 <221> source
 <223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 23	
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ccaacgaccc ccgcccattg acgtcaataa tgacgtatgt tcccatagta acgccaatag	180
ggactttcca ttgacgtcaa tgggtggagt atttacggta aactgcccac ttggcagtag	240
atcaagtgtg tcatatgccg agtacgcccc ctattgacgt caatgacggg aaatggcccc	300
cctggcatta tgcccagtag atgaccttat gggactttcc tacttggcag tacatctacg	360

Sequence_Listing.txt

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ggggcgggggc	gaggcgggaga	ggtgcggcgcg	cagccaatca	gagcgggcgcg	ctccgaaagt	600
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tgaccggcgg	ctctagagcc	tctgctaacc	atgttcatgc	cttcttcttt	ttcctacagc	1680
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<210> 24

<211> 522

<212> DNA

<213> Artificial Sequence

Sequence_Listing.txt

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 24

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tgagcatctg acttctggct aataaaggaa atttattttc attgcaatag tgtgttgga	180
ttttttgtgt ctctcactcg gaaggacata tgggagggca aatcatttaa aacatcagaa	240
tgagtatttg gtttagagtt tggcaacata tgcccatatg ctggctgcca tgaacaaagg	300
ttggctataa agaggtcatc agtatatgaa acagccccct gctgtccatt cttattcca	360
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tttaacatcc ctaaaatfff cttacatgt tttactagcc agatfffcc tcctctcctg	480
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<210> 25

<211> 235

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 25

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gttttattat atttacactt acatactaata aataaattca acaaacaatt tatttatgtt	180
tatttatffa ttaaaaaaaa acaaaaactc aaaatttctt ctataaagta acaaa	235

<210> 26

<211> 6164

<212> DNA

<213> Artificial Sequence

<220>

<221> source

Sequence_Listing.txt

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 26

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gctcccgtga ggctgcttg tcaatgcggt aagtgtcact gatTTTgaac tataacgacc	180
gcgtgagtca aaatgacgca tgattatctt ttacgtgact tTTaagattt aactcatacg	240
ataattatat tgTtatttca Tgttctactt acgtgataac ttattatata tatattttct	300
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ccttatggga ctttcctact tggcagtaca tctacgtatt agtcacgct attaccatgg	720
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Sequence_Listing.txt

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Sequence_Listing.txt

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Sequence_Listing.txt

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Sequence_Listing.txt

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<210> 27

<211> 6721

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 27

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Sequence_Listing.txt

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Sequence_Listing.txt

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Sequence_Listing.txt

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Sequence_Listing.txt

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<210> 28

<211> 3733

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 28

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Sequence_Listing.txt

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Sequence_Listing.txt

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Sequence_Listing.txt

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<210> 29
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<212> PRT
<213> Homo sapiens

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<220>
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<222> (1)..(20)
<223> /note="Signal sequence"

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```

<400> 29
Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu
1          5          10          15

```

```

Val Thr Asn Ser Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu
          20          25          30

```

```

Gln Leu Glu His Leu Leu Leu Asp Leu Gln Met Ile Leu Asn Gly Ile
          35          40          45

```

```

Asn Asn Tyr Lys Asn Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe
          50          55          60

```

```

Tyr Met Pro Lys Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu
65          70          75          80

```

```

Glu Glu Leu Lys Pro Leu Glu Glu Val Leu Asn Leu Ala Gln Ser Lys
          85          90          95

```

```

Asn Phe His Leu Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile

```


Sequence_Listing.txt

100

105

110

Val Leu Glu Leu Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala
 115 120 125

Asp Glu Thr Ala Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe
 130 135 140

Cys Gln Ser Ile Ile Ser Thr Leu Thr
 145 150

<210> 30

<211> 65

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
 polypeptide"

<220>

<221> SITE

<222> (1)..(25)

<223> /note="Signal sequence"

<400> 30

Met Ile Pro Ala Lys Asp Met Ala Lys Val Met Ile Val Met Leu Ala
 1 5 10 15

Ile Cys Phe Leu Thr Lys Ser Asp Gly Lys Ser Val Lys Lys Arg Ser
 20 25 30

Val Ser Glu Ile Gln Leu Met His Asn Leu Gly Lys His Leu Asn Ser
 35 40 45

Met Glu Arg Val Glu Trp Leu Arg Lys Lys Leu Gln Asp Val His Asn
 50 55 60

Phe

65

Sequence_Listing.txt

<210> 31

<211> 115

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<220>

<221> SITE

<222> (1)..(25)

<223> /note="Signal sequence"

<400> 31

Met	Ile	Pro	Ala	Lys	Asp	Met	Ala	Lys	Val	Met	Ile	Val	Met	Leu	Ala
1				5					10					15	

Ile	Cys	Phe	Leu	Thr	Lys	Ser	Asp	Gly	Lys	Ser	Val	Lys	Lys	Arg	Ser
			20					25					30		

Val	Ser	Glu	Ile	Gln	Leu	Met	His	Asn	Leu	Gly	Lys	His	Leu	Asn	Ser
		35					40					45			

Met	Glu	Arg	Val	Glu	Trp	Leu	Arg	Lys	Lys	Leu	Gln	Asp	Val	His	Asn
	50					55					60				

Phe	Val	Ala	Leu	Gly	Ala	Pro	Leu	Ala	Pro	Arg	Asp	Ala	Gly	Ser	Gln
65					70					75					80

Arg	Pro	Arg	Lys	Lys	Glu	Asp	Asn	Val	Leu	Val	Glu	Ser	His	Glu	Lys
				85					90					95	

Ser	Leu	Gly	Glu	Ala	Asp	Lys	Ala	Asp	Val	Asn	Val	Leu	Thr	Lys	Ala
			100					105						110	

Lys	Ser	Gln
		115

<210> 32

<211> 506

<212> PRT

Sequence_Listing.txt

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<220>

<221> SITE

<222> (1)..(22)

<223> /note="Signal sequence"

<400> 32

Met Ile Pro Ala Arg Phe Ala Gly Val Leu Leu Ala Leu Ala Leu Ile
1 5 10 15

Leu Pro Gly Thr Leu Cys Ser Leu Ser Cys Arg Pro Pro Met Val Lys
20 25 30

Leu Val Cys Pro Ala Asp Asn Leu Arg Ala Glu Gly Leu Glu Cys Thr
35 40 45

Lys Thr Cys Gln Asn Tyr Asp Leu Glu Cys Met Ser Met Gly Cys Val
50 55 60

Ser Gly Cys Leu Cys Pro Pro Gly Met Val Arg His Glu Asn Arg Cys
65 70 75 80

Val Ala Leu Glu Arg Cys Pro Cys Phe His Gln Gly Lys Glu Tyr Ala
85 90 95

Pro Gly Glu Thr Val Lys Ile Gly Cys Asn Thr Cys Val Cys Arg Asp
100 105 110

Arg Lys Trp Asn Cys Thr Asp His Val Cys Asp Ala Thr Cys Ser Thr
115 120 125

Ile Gly Met Ala His Tyr Leu Thr Phe Asp Gly Leu Lys Tyr Leu Phe
130 135 140

Pro Gly Glu Cys Gln Tyr Val Leu Val Gln Asp Tyr Cys Gly Ser Asn
145 150 155 160

Sequence_Listing.txt

Pro Gly Thr Phe Arg Ile Leu Val Gly Asn Lys Gly Cys Ser His Pro
165 170 175

Ser Val Lys Cys Lys Lys Arg Val Thr Ile Leu Val Glu Gly Gly Glu
180 185 190

Ile Glu Leu Phe Asp Gly Glu Val Asn Val Lys Arg Pro Met Lys Asp
195 200 205

Glu Thr His Phe Glu Val Val Glu Ser Gly Arg Tyr Ile Ile Leu Leu
210 215 220

Leu Gly Lys Ala Leu Ser Val Val Trp Asp Arg His Leu Ser Ile Ser
225 230 235 240

Val Val Leu Lys Gln Thr Tyr Gln Glu Lys Val Cys Gly Leu Cys Gly
245 250 255

Asn Phe Asp Gly Ile Gln Asn Asn Asp Leu Thr Ser Ser Asn Leu Gln
260 265 270

Val Glu Glu Asp Pro Val Asp Phe Gly Asn Ser Trp Lys Val Ser Ser
275 280 285

Gln Cys Ala Asp Thr Arg Lys Val Pro Leu Asp Ser Ser Pro Ala Thr
290 295 300

Cys His Asn Asn Ile Met Lys Gln Thr Met Val Asp Ser Ser Cys Arg
305 310 315 320

Ile Leu Thr Ser Asp Val Phe Gln Asp Cys Asn Lys Leu Val Asp Pro
325 330 335

Glu Pro Tyr Leu Asp Val Cys Ile Tyr Asp Thr Cys Ser Cys Glu Ser
340 345 350

Ile Gly Asp Cys Ala Cys Phe Cys Asp Thr Ile Ala Ala Tyr Ala His
355 360 365

Sequence_Listing.txt

Val Cys Ala Gln His Gly Lys Val Val Thr Trp Arg Thr Ala Thr Leu
370 375 380

Cys Pro Gln Ser Cys Glu Glu Arg Asn Leu Arg Glu Asn Gly Tyr Glu
385 390 395 400

Cys Glu Trp Arg Tyr Asn Ser Cys Ala Pro Ala Cys Gln Val Thr Cys
405 410 415

Gln His Pro Glu Pro Leu Ala Cys Pro Val Gln Cys Val Glu Gly Cys
420 425 430

His Ala His Cys Pro Pro Gly Lys Ile Leu Asp Glu Leu Leu Gln Thr
435 440 445

Cys Val Asp Pro Glu Asp Cys Pro Val Cys Glu Val Ala Gly Arg Arg
450 455 460

Phe Ala Ser Gly Lys Lys Val Thr Leu Asn Pro Ser Asp Pro Glu His
465 470 475 480

Cys Gln Ile Cys His Cys Asp Val Val Asn Leu Thr Cys Glu Ala Cys
485 490 495

Gln Glu Pro Gly Gly Leu Val Val Pro Pro
500 505

<210> 33
<211> 1247
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<220>
<221> SITE
<222> (1)..(22)

Sequence_Listing.txt

<223> /note="Signal sequence"

<400> 33

Met Ile Pro Ala Arg Phe Ala Gly Val Leu Leu Ala Leu Ala Leu Ile
 1 5 10 15

Leu Pro Gly Thr Leu Cys Ala Glu Gly Thr Arg Gly Arg Ser Ser Thr
 20 25 30

Ala Arg Cys Ser Leu Phe Gly Ser Asp Phe Val Asn Thr Phe Asp Gly
 35 40 45

Ser Met Tyr Ser Phe Ala Gly Tyr Cys Ser Tyr Leu Leu Ala Gly Gly
 50 55 60

Cys Gln Lys Arg Ser Phe Ser Ile Ile Gly Asp Phe Gln Asn Gly Lys
 65 70 75 80

Arg Val Ser Leu Ser Val Tyr Leu Gly Glu Phe Phe Asp Ile His Leu
 85 90 95

Phe Val Asn Gly Thr Val Thr Gln Gly Asp Gln Arg Val Ser Met Pro
 100 105 110

Tyr Ala Ser Lys Gly Leu Tyr Leu Glu Thr Glu Ala Gly Tyr Tyr Lys
 115 120 125

Leu Ser Gly Glu Ala Tyr Gly Phe Val Ala Arg Ile Asp Gly Ser Gly
 130 135 140

Asn Phe Gln Val Leu Leu Ser Asp Arg Tyr Phe Asn Lys Thr Cys Gly
 145 150 155 160

Leu Cys Gly Asn Phe Asn Ile Phe Ala Glu Asp Asp Phe Met Thr Gln
 165 170 175

Glu Gly Thr Leu Thr Ser Asp Pro Tyr Asp Phe Ala Asn Ser Trp Ala
 180 185 190

Leu Ser Ser Gly Glu Gln Trp Cys Glu Arg Ala Ser Pro Pro Ser Ser

Sequence_Listing.txt

195

200

205

Ser Cys Asn Ile Ser Ser Gly Glu Met Gln Lys Gly Leu Trp Glu Gln
 210 215 220

Cys Gln Leu Leu Lys Ser Thr Ser Val Phe Ala Arg Cys His Pro Leu
 225 230 235 240

Val Asp Pro Glu Pro Phe Val Ala Leu Cys Glu Lys Thr Leu Cys Glu
 245 250 255

Cys Ala Gly Gly Leu Glu Cys Ala Cys Pro Ala Leu Leu Glu Tyr Ala
 260 265 270

Arg Thr Cys Ala Gln Glu Gly Met Val Leu Tyr Gly Trp Thr Asp His
 275 280 285

Ser Ala Cys Ser Pro Val Cys Pro Ala Gly Met Glu Tyr Arg Gln Cys
 290 295 300

Val Ser Pro Cys Ala Arg Thr Cys Gln Ser Leu His Ile Asn Glu Met
 305 310 315 320

Cys Gln Glu Arg Cys Val Asp Gly Cys Ser Cys Pro Glu Gly Gln Leu
 325 330 335

Leu Asp Glu Gly Leu Cys Val Glu Ser Thr Glu Cys Pro Cys Val His
 340 345 350

Ser Gly Lys Arg Tyr Pro Pro Gly Thr Ser Leu Ser Arg Asp Cys Asn
 355 360 365

Thr Cys Ile Cys Arg Asn Ser Gln Trp Ile Cys Ser Asn Glu Glu Cys
 370 375 380

Pro Gly Glu Cys Leu Val Thr Gly Gln Ser His Phe Lys Ser Phe Asp
 385 390 395 400

Asn Arg Tyr Phe Thr Phe Ser Gly Ile Cys Gln Tyr Leu Leu Ala Arg

Sequence_Listing.txt

405

410

415

Asp Cys Gln Asp His Ser Phe Ser Ile Val Ile Glu Thr Val Gln Cys
 420 425 430

Ala Asp Asp Arg Asp Ala Val Cys Thr Arg Ser Val Thr Val Arg Leu
 435 440 445

Pro Gly Leu His Asn Ser Leu Val Lys Leu Lys His Gly Ala Gly Val
 450 455 460

Ala Met Asp Gly Gln Asp Val Gln Leu Pro Leu Leu Lys Gly Asp Leu
 465 470 475 480

Arg Ile Gln His Thr Val Thr Ala Ser Val Arg Leu Ser Tyr Gly Glu
 485 490 495

Asp Leu Gln Met Asp Trp Asp Gly Arg Gly Arg Leu Leu Val Lys Leu
 500 505 510

Ser Pro Val Tyr Ala Gly Lys Thr Cys Gly Leu Cys Gly Asn Tyr Asn
 515 520 525

Gly Asn Gln Gly Asp Asp Phe Leu Thr Pro Ser Gly Leu Ala Glu Pro
 530 535 540

Arg Val Glu Asp Phe Gly Asn Ala Trp Lys Leu His Gly Asp Cys Gln
 545 550 555 560

Asp Leu Gln Lys Gln His Ser Asp Pro Cys Ala Leu Asn Pro Arg Met
 565 570 575

Thr Arg Phe Ser Glu Glu Ala Cys Ala Val Leu Thr Ser Pro Thr Phe
 580 585 590

Glu Ala Cys His Arg Ala Val Ser Pro Leu Pro Tyr Leu Arg Asn Cys
 595 600 605

Arg Tyr Asp Val Cys Ser Cys Ser Asp Gly Arg Glu Cys Leu Cys Gly

Sequence_Listing.txt

610

615

620

Ala Leu Ala Ser Tyr Ala Ala Ala Cys Ala Gly Arg Gly Val Arg Val
 625 630 635 640

Ala Trp Arg Glu Pro Gly Arg Cys Glu Leu Asn Cys Pro Lys Gly Gln
 645 650 655

Val Tyr Leu Gln Cys Gly Thr Pro Cys Asn Leu Thr Cys Arg Ser Leu
 660 665 670

Ser Tyr Pro Asp Glu Glu Cys Asn Glu Ala Cys Leu Glu Gly Cys Phe
 675 680 685

Cys Pro Pro Gly Leu Tyr Met Asp Glu Arg Gly Asp Cys Val Pro Lys
 690 695 700

Ala Gln Cys Pro Cys Tyr Tyr Asp Gly Glu Ile Phe Gln Pro Glu Asp
 705 710 715 720

Ile Phe Ser Asp His His Thr Met Cys Tyr Cys Glu Asp Gly Phe Met
 725 730 735

His Cys Thr Met Ser Gly Val Pro Gly Ser Leu Leu Pro Asp Ala Val
 740 745 750

Leu Ser Ser Pro Leu Ser His Arg Ser Lys Arg Ser Leu Ser Cys Arg
 755 760 765

Pro Pro Met Val Lys Leu Val Cys Pro Ala Asp Asn Leu Arg Ala Glu
 770 775 780

Gly Leu Glu Cys Thr Lys Thr Cys Gln Asn Tyr Asp Leu Glu Cys Met
 785 790 795 800

Ser Met Gly Cys Val Ser Gly Cys Leu Cys Pro Pro Gly Met Val Arg
 805 810 815

His Glu Asn Arg Cys Val Ala Leu Glu Arg Cys Pro Cys Phe His Gln

Sequence_Listing.txt

820

825

830

Gly Lys Glu Tyr Ala Pro Gly Glu Thr Val Lys Ile Gly Cys Asn Thr
 835 840 845

Cys Val Cys Arg Asp Arg Lys Trp Asn Cys Thr Asp His Val Cys Asp
 850 855 860

Ala Thr Cys Ser Thr Ile Gly Met Ala His Tyr Leu Thr Phe Asp Gly
 865 870 875 880

Leu Lys Tyr Leu Phe Pro Gly Glu Cys Gln Tyr Val Leu Val Gln Asp
 885 890 895

Tyr Cys Gly Ser Asn Pro Gly Thr Phe Arg Ile Leu Val Gly Asn Lys
 900 905 910

Gly Cys Ser His Pro Ser Val Lys Cys Lys Lys Arg Val Thr Ile Leu
 915 920 925

Val Glu Gly Gly Glu Ile Glu Leu Phe Asp Gly Glu Val Asn Val Lys
 930 935 940

Arg Pro Met Lys Asp Glu Thr His Phe Glu Val Val Glu Ser Gly Arg
 945 950 955 960

Tyr Ile Ile Leu Leu Leu Gly Lys Ala Leu Ser Val Val Trp Asp Arg
 965 970 975

His Leu Ser Ile Ser Val Val Leu Lys Gln Thr Tyr Gln Glu Lys Val
 980 985 990

Cys Gly Leu Cys Gly Asn Phe Asp Gly Ile Gln Asn Asn Asp Leu Thr
 995 1000 1005

Ser Ser Asn Leu Gln Val Glu Glu Asp Pro Val Asp Phe Gly Asn
 1010 1015 1020

Ser Trp Lys Val Ser Ser Gln Cys Ala Asp Thr Arg Lys Val Pro

Sequence_Listing.txt

1025

1030

1035

Leu Asp Ser Ser Pro Ala Thr Cys His Asn Asn Ile Met Lys Gln
 1040 1045 1050

Thr Met Val Asp Ser Ser Cys Arg Ile Leu Thr Ser Asp Val Phe
 1055 1060 1065

Gln Asp Cys Asn Lys Leu Val Asp Pro Glu Pro Tyr Leu Asp Val
 1070 1075 1080

Cys Ile Tyr Asp Thr Cys Ser Cys Glu Ser Ile Gly Asp Cys Ala
 1085 1090 1095

Cys Phe Cys Asp Thr Ile Ala Ala Tyr Ala His Val Cys Ala Gln
 1100 1105 1110

His Gly Lys Val Val Thr Trp Arg Thr Ala Thr Leu Cys Pro Gln
 1115 1120 1125

Ser Cys Glu Glu Arg Asn Leu Arg Glu Asn Gly Tyr Glu Cys Glu
 1130 1135 1140

Trp Arg Tyr Asn Ser Cys Ala Pro Ala Cys Gln Val Thr Cys Gln
 1145 1150 1155

His Pro Glu Pro Leu Ala Cys Pro Val Gln Cys Val Glu Gly Cys
 1160 1165 1170

His Ala His Cys Pro Pro Gly Lys Ile Leu Asp Glu Leu Leu Gln
 1175 1180 1185

Thr Cys Val Asp Pro Glu Asp Cys Pro Val Cys Glu Val Ala Gly
 1190 1195 1200

Arg Arg Phe Ala Ser Gly Lys Lys Val Thr Leu Asn Pro Ser Asp
 1205 1210 1215

Pro Glu His Cys Gln Ile Cys His Cys Asp Val Val Asn Leu Thr

Sequence_Listing.txt

1220 1225 1230

Cys Glu Ala Cys Gln Glu Pro Gly Gly Leu Val Val Pro Pro
1235 1240 1245

<210> 34
<211> 232
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 34
Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
20 25 30

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
35 40 45

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
50 55 60

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65 70 75 80

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
85 90 95

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
100 105 110

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
115 120 125

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
130 135 140

Sequence_Listing.txt

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
145 150 155 160

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
165 170 175

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
180 185 190

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
195 200 205

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
210 215 220

Ser Leu Ser Leu Ser Pro Gly Lys
225 230

<210> 35
<211> 585
<212> PRT
<213> Homo sapiens

<400> 35
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Sequence_Listing.txt

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Sequence_Listing.txt

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Sequence_Listing.txt

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

<210> 36
<211> 415
<212> PRT
<213> Homo sapiens

<400> 36
Tyr Asn Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg
1 5 10 15

Glu Cys Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe
20 25 30

Glu Asn Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly
35 40 45

Asp Gln Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp
50 55 60

Asp Ile Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys
65 70 75 80

Asn Cys Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu
85 90 95

Sequence_Listing.txt

Gln Phe Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr
100 105 110

Glu Gly Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val
115 120 125

Pro Phe Pro Cys Gly Arg Val Ser Val Ser Gln Thr Ser Lys Leu Thr
130 135 140

Arg Ala Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu
145 150 155 160

Ala Glu Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn
165 170 175

Asp Phe Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe
180 185 190

Pro Trp Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly
195 200 205

Ser Ile Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu
210 215 220

Thr Gly Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu
225 230 235 240

Thr Glu His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His
245 250 255

His Asn Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu
260 265 270

Leu Glu Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile
275 280 285

Cys Ile Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser
290 295 300

Sequence_Listing.txt

Gly Tyr Val Ser Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala
305 310 315 320

Leu Val Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys
325 330 335

Leu Arg Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly
340 345 350

Phe His Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro
355 360 365

His Val Thr Glu Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser
370 375 380

Trp Gly Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys
385 390 395 400

Val Ser Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr
405 410 415