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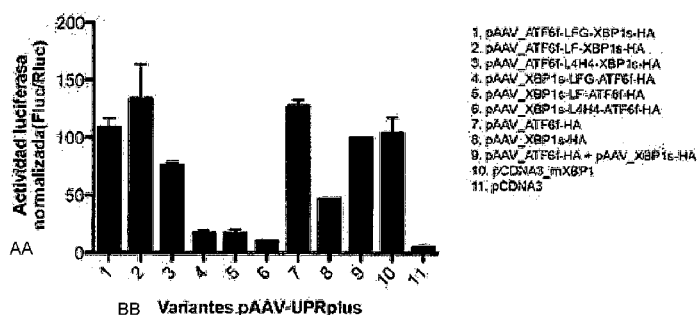
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(54) Title: AAV/UPR-PLUS VIRUS, UPR-PLUS FUSION PROTEIN, GENETIC TREATMENT METHOD AND USE THEREOF IN THE TREATMENT OF NEURODEGENERATIVE DISEASES, SUCH AS PARKINSON'S DISEASE AND HUNTINGTON'S DISEASE, *INTER ALIA*

(54) Título : VIRUS AAV/UPR-PLUS, PROTEINA DE FUSION UPR-PLUS, METODO DE TRATAMIENTO GENETICO Y SU USO EN EL TRATAMIENTO ENFERMEDADES NEURODEGENERATIVAS, TALES COMO LA ENFERMEDAD DE PARKINSON Y HUNTINGTON, ENTRE OTRAS



(57) Abstract: The present invention relates to an AAV/UPR-plus virus sequence, to a genetic treatment method, and to the use thereof in the treatment of neurodegenerative diseases, such as Parkinson's disease and Huntington's disease, *inter alia*, as shown in the *in vitro* studies in figure 14/17.

(57) Resumen: La presente invención presenta una secuencia del virus AAV/UPR-plus, método de tratamiento genético y su uso en el tratamiento enfermedades neurodegenerativas, tales como la enfermedad de Parkinson y Huntington, entre otras, tal como se presenta en los estudios *in vitro* en la figura 14/17.

Plásmido	Experimento 1	Experimento 2	Experimento 3	Promedio	ESM
pAAV-ATF6L-LFG-XBP1s-HA	101.1517	89.62363	125.4241	105.33321	9.367091862
pAAV-ATF6L-LF-XBP1s-HA	80.52831	126.747	191.8758	133.2837033	20.20308089
pAAV-ATF6L-LH4-XBP1s-HA	70.35313	77.71852	74.43257	74.17747	2.416717813
pAAV-XBP1s-LFG-ATF6L-HA	17.81713	12.53327	21.4335	17.2815687	2.59382393
pAAV-XBP1s-LF-ATF6L-HA	19.62822	11.8438	23.48104	16.9825567	3.425142203
pAAV-XBP1s-LH4-ATF6L-HA	9.226968	11.24807	10.3265	10.2681267	0.53383302
pAAV-ATF6L-HA	120.188	122.1534	139.0208	127.3207667	6.17818165
pAAV-XBP1s-HA	47.8101	47.85708	46.66553	47.47787	0.408447887
pAAV-ATF6L-HA + pAAV-XBP1s-HA	100	100	100	100	0
pCDNA3-mXBP1	77.26633	120.5979	116.6251	104.6397767	13.73530344
pCDNA3	4.874095	6.953351	4.208801	6.345455667	0.626583562

Figura 14

AA Normalised luciferase activity (Fluc/Rluc)
BB pAAV-UPRplus variants





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- *antes de la expiración del plazo para modificar las reivindicaciones y para ser republicada si se reciben modificaciones (Regla 48.2(h))*
 - *con la parte de lista de secuencias de la descripción (Regla 5.2(a))*
 - *con (una) indicación(es) relativa(s) a material biológico depositado en virtud de lo dispuesto en la Regla 13bis, aparte de la descripción (Reglas 13bis.4(d)(i) y 48.2(a)(viii))*

“AAV/UPR-plus virus, UPR-plus fusion protein, genetic treatment method and its use in the treatment of neurodegenerative diseases, such as Parkinson's disease and Huntington's disease, among others.”

TECHNICAL FIELD OF THE PRESENT INVENTION

The present invention applies to the field of medicine, specifically in the treatment of neurodegenerative diseases, through the use of adeno-associated viruses (AAVs) that overexpress the fusion protein between XBP1s, a linker peptide and ATF6f in neurons of the central nervous system (CNS), recovering and improving neurodegenerative problems, preferably Parkinson's and Huntington's diseases.

PRIOR ART BACKGROUND AND DESCRIPTION

Scientific research on CNS diseases has been of great interest in recent years, especially diseases related to cognitive and motor disorders. The treatment of diseases related to neurodegenerative problems does not currently have genetic therapeutic approaches to reduce symptoms.

In the search for the treatment of these motor and cognitive diseases, two transcription factors called XBP1 and ATF6 have been identified. They are involved in the biological and molecular mechanisms for improving protein folding and aggregation processes. Mainly the new fusion protein aims to activate the transcription of gene clusters involved in improving protein folding. Then, reduce their aggregation by reprogramming the transcription of the specific genes involved in protein folding, such as chaperones. The phenomenon of protein aggregation is a common feature in neurodegenerative diseases and a cause for selective neuronal death.

Today's existing pharmacological therapies are only palliative, since they are focused on reducing the symptoms of patients suffering from these diseases and fail to stop the selective death of neurons. They generally consist of pharmacological therapies that regulate the levels of altered neurotransmitters because of the death of fundamental neuronal groups, which

ensure the correct functioning of the brain. An example of this type of therapy is the administration of L-dopa and its pharmacological derivatives to Parkinson's patients. This compound is capable of restoring dopamine levels in patients, but does not stop the selective death of dopaminergic neurons causing this disease. The present proposal focuses on curbing neuronal death by means of gene therapy and producing an effective and definitive treatment for this type of pathology.

There are other pathologies related to neuro-motor diseases such as Huntington's disease, where their treatments are limited or non-existent. This disease is a dominant hereditary neurodegenerative pathology caused by a mutation of the IT15 gene, coding the Huntingtin protein. The mutation results in the expansion of a poly-glutamine segment at the N-terminal end of the protein, which generates protein aggregates in the mid-spinal neurons (MSNs) of the striatum region. This triggers neural degeneration and symptoms characteristic of the disease, such as progressive loss of voluntary muscle movement control (chorea), psychiatric symptoms and dementia (Atwal, 2007).

To date, the proposal for the use of a synthetic fusion protein has not been generally addressed. There are publications such as WO2004/111194 and WO2006/028889, which point to the formation of recombinant proteins that encode for XBP1, eIF2 α , S51A and ATF (Post-deletion forms by splicing), separated, not as a fusion protein, which does not seek to optimize the improvement in the control of neurodegenerative diseases in a single construct. On the other hand, there are individual documents that point to the endogenous decrease of XBP1, as presented in patent US2013197023, which correlates with an increased folding capacity of the endoplasmic reticulum (ER) which is required to maintain cellular homeostasis. This individual negative regulation of XBP1 expression has been implicated in the generation of neuroprotection in Huntington's disease and amyotrophic lateral sclerosis (ALS), as filed in patent application WO2010/008860.

Another relevant patent regarding the measurement of ER stress, where the transcription factor XBP1 is involved, is the Japanese patent

JP2007129970.

In general, this development refers to the synthesis and viability of a new peptide conformed by XBP1s, a linker peptide and ATF6f for the treatment of neurodegenerative diseases such as Parkinson's Disease and Huntington's Disease, without being restricted to these alone.

One of the patents nearing this approach is the Chilean patent application 3590-2014, which presents a genetic treatment method to improve memory with a recombinant virus AAV/XBP1S-HA. This treatment brings the XBP1s-HA peptide closer to improving a cognitive function, but not for treating a disease. On the other hand, there is no talk of a functional fusion protein that involves XBP1s within its components.

Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present disclosure as it existed before the priority date of each claim of this application.

INVENTION SUMMARY

Recent studies indicate that the chronic alteration of protein homeostasis in the ER (Endoplasmic Reticulum) is a transversal pathological event observed in practically all neurodegenerative diseases associated with protein folding disorders, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis, among others.

Different conditions interfere with the protein synthesis and folding process in the ER's lumen, resulting in an abnormal accumulation of misfolded proteins. This condition, called ER stress, can be promoted by the expression of certain mutant proteins, as well as by the alteration in the process of protein synthesis and maturation. In response to this phenomenon, an integrated intracellular signaling cascade called UPR is activated. Activation of UPR results in different changes in gene expression

that have global effects on protein homeostasis, decreasing, for example, the levels of abnormal aggregation and protein misfolding resulting from:

- (i) an increased expression of chaperones and foldases;

(ii) improved protein quality control; and

(iii) mass removal of defective proteins.

5 The UPR's initial objective is to recover the protein balance, maintaining cell viability. However, chronic ER stress leads to cell death by apoptosis, a phenomenon observed in several neurodegenerative pathologies.

 The initial UPR phase is mediated by three ER "stress sensors":

10 1) PERK (double-stranded RNA activated protein kinase [PKR] such as endoplasmic reticulum kinase);

 2) ATF6 (activating transcription factor 6); and

15 3) IRE1 (inositol requiring kinase 1)

 Each of these sensors relays information on the folding state in the ER lumen to the nucleus by controlling specific transcription factors, where XBP1 stands out (X-Box binding protein-1). XBP1 regulates a series of genes involved in protein quality control, folding, among other processes. These three adaptive pathways act in unison, maintaining protein homeostasis and cell survival. Unlike the ATF6 and XBP1-dependent responses, signaling mediated by the PERK sensor has also been associated with pro-apoptotic effects. These previous definitions have collaborated in developing this project to define the impact of UPR in the treatment of neurodegenerative diseases, in addition to designing new animal models to measure these responses.

30 Previous evidence has described that a gain in XBP1 function slows the neurodegenerative process in animal models of three neurodegenerative diseases: Huntington's disease, Parkinson's disease and amyotrophic lateral sclerosis. On the other hand, it has also been determined that ATF6 transcription factor deficiency causes a loss of resistance to neuronal death in preclinical models of Parkinson's disease. These antecedents indicate the

importance of these transcription factors in neurodegenerative processes due to the formation of toxic protein aggregates. Therefore, UPRplus® is based on the fusion of two active components of UPR, such as XBP1, ATF6 and a linker peptide.

5 Currently UPRplus has been developed and presents specific transcriptional activity of a group (cluster) of genes related to UPR. UPRplus is a fusion protein and is potentially able to participate in the process of relieving the burden of toxic protein aggregates in neurons.

10 In one aspect, the present invention provides an adeno-associated vector (AAV), comprising a recombinant viral genome where such genome comprises an expression cassette comprising a transcription regulatory region specific for neuronal tissues operatively bound to a polynucleotide of interest encoding a fusion protein, wherein the fusion protein comprises X-Box binding protein 1 (*XBP1s*), activating
15 transcription factor 6 (*ATF6f*) and a bridge or linker sequence.

 In another aspect, the present invention provides a pharmaceutical composition comprising the adeno-associated vector of the invention and pharmaceutically acceptable excipients.

20

 In another aspect, the present invention provides the use of the adeno-associated vector according to the invention or the pharmaceutical composition of the invention, in the manufacture of a medicament for treating Parkinson's and/or Huntington's disease in a subject in need thereof.

25

 In another aspect, the present invention provides a method of treating Parkinson's and/or Huntington's disease comprising administering to a subject the adeno-associated vector according to the invention or the pharmaceutical composition of the invention.

30

 In another aspect, the present invention provides a polynucleotide comprising an expression cassette flanked by the ITRs of an adeno-associated virus, where such expression cassette comprises a promoter, a coding region for immune response, and a polynucleotide of interest that encodes a fusion protein, wherein the fusion protein

comprises XBP1s, ATF6f and a bridge or linker sequence.

In another aspect, the present invention provides a plasmid comprising the sequences of an adeno-associated, an expression cassette flanked by the ITRs of the adeno-associated virus, where such expression cassette comprises a promoter, a coding region for immune response and a polynucleotide of interest, wherein the plasmid comprises the sequence of a plasmid deposited in the international body of biological deposits, Instituto de Investigaciones Agropecuarias de Chile, INIA, under deposit numbers: RGM 2231, , RGM 2232, RGM 2233, RGM 2234, RGM 2235 or RGM 2236.

In another aspect, the present invention provides an adeno-associated virus comprising a viral genome comprising the polynucleotide of the invention.

Also disclosed herein is a method for the treatment of neurodegenerative diseases in cognitive and motor processes in mammals, preferably in humans, using a virus that induces a neuronal overexpression of UPRplus in the central nervous system.

Also disclosed herein is a method to treat neurodegenerative diseases in cognitive and motor processes. The method involves intravenous and/or intraperitoneal and/or intracranial and/or intramedullary and/or intranasal and/or intraneural and/or any pathway that introduces the virus into the brain past the blood-brain barrier of a patient or subject. The virus induces neuronal overexpression of UPRplus in a dose range of 1×10^6 to 1×10^{30} viral units per individual.

Also disclosed herein is a form of intravenous and/or intraperitoneal and/or intracranial and/or intramedullary and/or intranasal and/or intraneural pharmaceutical composition and/or any form that conducts the virus inducing the neuronal overexpression of UPRplus to the brain, passing the blood-brain barrier, with dose ranges as those previously described and a pharmaceutically acceptable vehicle for its use in the treatment of a neurodegenerative disease.

Also disclosed herein is the use of a virus that induces the neuronal

overexpression of UPRplus and its protein-derived compounds, because it can be used to prepare a useful drug for the treatment of a neurodegenerative disease cognitive and motor skills.

5 Also disclosed herein is an adeno-associated virus (AAV) with a sequence of the virus and an insert with a nucleotide sequence described in Table I or any of its variants, contained in the bacterium *Escherichia coli*, and transformed with the plasmid deposited in the International Biological Deposits Organization, Instituto de Investigaciones Agropecuarias de Chile (Chilean Agricultural Research Institute -
10 INIA), under deposit number **RGM 2235**, where the **XBP1s-LFG-ATF6f (UPR-Plus 5)** neural transcription factor is overexpressed, preferably in the central nervous system or any variant of the fragment, which encodes or overexpresses this alternative to the neural transcription factor of UPRplus in mammals, preferably in humans.

15 Also disclosed herein is an adeno-associated virus (AAV) with a sequence of the virus and an insert with a nucleotide sequence described in Table II or any of its variants, contained in the bacterium *Escherichia coli* and transformed with the plasmid deposited in the International Biological Deposits Organization, Instituto de Investigaciones Agropecuarias de Chile (INIA), under deposit number **RGM 2234**,
20 where the **XBP1s-LF-ATF6f (UPR-Plus 4)** neural transcription factor is overexpressed, preferably in the central nervous system or any variant of the fragment, which encodes or overexpresses this alternative to the neural transcription factor of UPRplus in mammals, preferably in humans.

25 Also disclosed herein is an adeno-associated virus (AAV) with a sequence of the virus and an insert with a nucleotide sequence described in Table III or any of its variants, contained in the bacterium *Escherichia coli* and transformed with the plasmid deposited in the International Biological Deposits Organization, Instituto de Investigaciones Agropecuarias de Chile (INIA), under deposit number **RGM 2236**,
30 where the **XBP1s-L4H4-ATF6f (UPR-Plus 6)** neural transcription factor is overexpressed, preferably in the central nervous system or any variant of the fragment, which encodes or overexpresses this alternative to the neural transcription factor of UPRplus in mammals, preferably in humans.

Also disclosed herein is an adeno-associated virus (AAV) with a sequence of

the virus and an insert with a nucleotide sequence described in Table IV or any of its variants, contained in the bacterium *Escherichia coli* and transformed with the plasmid deposited in the International Biological Deposits Organization, Instituto de Investigaciones Agropecuarias de Chile (INIA), under deposit number **RGM 2232**,
5 where the **ATF6f-LFG-XBP1s (UPR-Plus 2)** neural transcription factor is overexpressed, preferably in the central nervous system or any variant of the fragment, which encodes or overexpresses this alternative to the neural transcription factor of UPRplus in mammals, preferably in humans.

10 Also disclosed herein is an adeno-associated virus (AAV) with a sequence of the virus and an insert with a nucleotide sequence described in Table V or any of its variants, contained in the bacterium *Escherichia coli* and transformed with the plasmid deposited in the International Biological Deposits Organization, Instituto de Investigaciones Agropecuarias de Chile (INIA), under deposit number **RGM 2233**,
15 where the **ATF6f-L4H4-XBP1s (UPR-Plus 3)** neural transcription factor is overexpressed, preferably in the central nervous system or any variant of the fragment, which encodes or overexpresses this alternative to the neural transcription factor of UPRplus in mammals, preferably in humans.

20 Also disclosed herein is an adeno-associated virus (AAV) with a sequence of the virus and an insert with a nucleotide sequence described in Table VI or any of its variants, contained in the bacterium *Escherichia coli* and transformed with the plasmid deposited in the International Biological Deposits Organization, Instituto de Investigaciones Agropecuarias de Chile (INIA), under deposit number **RGM 2231**,
25 where the **ATF6f-LF-XBP1s (UPR-Plus 1)** neural transcription factor is overexpressed, preferably in the central nervous system or any variant of the fragment, which encodes or overexpresses this alternative to the neural transcription factor of UPRplus in mammals, preferably in humans.

Throughout this specification the word “comprise”, or variations such as “comprises” or “comprising”, will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

MICROORGANISM DEPOSIT

Plasmid *pAAV_ATF6f-LFG-XBP1s-HA* was deposited on October 7, 2015 at the International Biological Deposits Organization, Instituto de Investigaciones Agropecuarias de Chile (INIA), under deposit number RGM 2232.

Plasmid *pAAV_ATF6f-LF-XBP1s-HA* was deposited on October 7, 2015 at the International Biological Deposits Organization, Instituto de Investigaciones Agropecuarias de Chile (INIA), under deposit number RGM 2231.

Plasmid *pAAV_ATF6f-L4H4-XBP1s-HA* was deposited on October 7, 2015 at the International Biological Deposits Organization, Instituto de Investigaciones Agropecuarias de Chile (INIA), under deposit number RGM 2233.

Plasmid *pAAV_XBP1s-LFG-ATF6f-HA* was deposited on October 7, 2015 at the International Biological Deposits Organization, Instituto de Investigaciones Agropecuarias de Chile (INIA), under deposit number RGM 2235.

Plasmid *pAAV_XBP1s-LF-ATF6f-HA* was deposited on October 7, 2015 at the International Biological Deposits Organization, Instituto de Investigaciones Agropecuarias de Chile (INIA), under deposit number RGM 2234.

Plasmid *pAAV_XBP1s-L4H4-ATF6f-HA* was deposited on October 7, 2015 at the International Biological Deposits Organization, Instituto de Investigaciones Agropecuarias de Chile (INIA), under deposit number RGM 2236.

DETAILED DESCRIPTION OF THE INVENTION

It should be noted that the present invention is not limited to the particular methodology, composites, materials, manufacturing techniques, uses and applications described herein, as these may vary. It should also be understood that the terminology used herein is used for the sole purpose of describing a particular representation and is not intended to limit the invention's perspective and potential.

It should be noted that the use and method of the singular, as expressed in the set of claims and throughout the text, does not exclude the plural, unless within a context that clearly implies it. So, for example, the reference to a "use or method" is a reference to one or more uses or methods and includes equivalents known to those who are knowledgeable of the subject matter (art). Similarly, as another example, the reference to "one step", "one stage" or "one mode" is a reference to one or more steps, stages or modes and may include sub-steps, stages or modes, implicit and/or consequential.

All conjunctions are to be understood in their least restrictive and most inclusive sense possible. Thus, for example, the conjunction 'or' must be understood in its orthodox logical sense, and not as 'or excluding', unless the context or text expressly requires or indicates this. The structures, materials and/or elements described herein are also to be understood as references to functional equivalents to avoid endless, exhaustive enumerations.

Expressions used to indicate approximations or conceptualizations should be understood as stated herein, unless the context requires a different interpretation.

All the names and technical and/or scientific terms used herein have the common meaning as given to them by a common person, qualified in these matters, unless expressly indicated otherwise.

Methods, techniques, elements, compounds and compositions are described, although methods, techniques, compounds and compositions similar and/or equivalent to those described may be used or preferred in practice

and/or in tests for the present invention.

All patents and other publications are cross-referenced for the purpose of describing and/or informing; for example, the methodologies described in such publications, which may be useful in connection with the present invention.

These publications are included only for their pre-patent information, prior to the date of registration of this patent application.

In this regard nothing shall be construed as an admission or acceptance, rejection or exclusion that the authors and/or inventors are not entitled to be so, or that such publications are dated in advance by virtue of previous ones, or for any other reason.

The present invention describes vectors based on serotypes AAV2, AAV6, AAV7, AAV8, AAV9, AAV10, AAV10, AAV11 and pseudo-typed AAVs and from adeno-associated viruses capable of efficiently mediating gene transfer to the central nervous system.

The systemic administration of these vectors also leads to an efficient gene supply to both the brain and spinal cord. The present invention claims that the AAV2 vector with proximal regions of the UPRplus transcription factor promoter allows the generation of a nonspecific response in a cluster of factors in the brain and spine. In particular, the local administration of the AAV2 vector, which comprises a series of expression cassettes in which the heterologous genes XBP1s and ATF6f are under the control of the CMV promoter, improving motor and cognitive abilities in individuals suffering from neurodegenerative mediated diseases. (Figures 16/17 and 17/17 and figure 17/17).

I. Definition of general terms and expressions

The terms "adeno-associated virus", "AAV virus", "AAV virion", "AAV viral particle", and "AAV particle" as used in this document are interchangeable. They refer to a viral particle composed of at least one AAV capsid protein

(preferably all capsid proteins of a particular AAV serotype) and one encapsulated AAV genome polynucleotide. If the particle comprises a heterologous polynucleotide (i.e., a polynucleotide other than a native-type AAV genome such as a transgene to be delivered to a mammalian cell) flanked by inverted terminal repeats of the AAV, which is typically referred to as an 'AAV particle vector' or 'AAV vector'. AAV refers to viruses belonging to the Dependovirus genus of the Parvoviridae family. The AAV genome is approximately 4.7 kilobases long and is composed of single-chain deoxyribonucleic acid (ssDNA) that can be counted as positive or negative. The genome comprises inverted terminal repeats (ITRs) at both ends of the DNA chain, and two open reading frames (ORFs): REP and CAP (Replicase and Capsid). The REP framework consists of four overlapping genes that encode REP proteins (REP 78, REP 68, REP 52 and REP 40) required for the AAV's life cycle. The CAP frame contains overlapping nucleotides of 20 capsid protein sequences: VP1, VP2 and VP3, which interact with each other to form an icosahedral symmetry capsid.

The term "adeno-associated IRT virus" or "AAV IRT", as used herein, refers to the repeating inverted terminal present at both ends of the DNA chain of an adeno-associated virus genome. IRT sequences are required for efficient multiplication of the AAV genome. Another property of these sequences is their ability to form a fork. This feature contributes to its self-copy which allows for independent primary synthesis of the second DNA strand. IRTs also proved to be necessary for both the integration of native AAV DNA into the host cell genome and the rescue of the host cell, as well as for the effective encapsulation of AAV DNA combined with the generation of its complete assembly.

The term 'AAV2', as used in the present invention, refers to serotype 2 of the adeno-associated virus with a genome sequence as defined in GenBank access number AF043303.1, found on the following website: <http://www.ncbi.nlm.nih.gov/nuccore/AF043303.1>.

Currently, about 11 human AAV serotypes and about 100 primate AAV

serotypes that can be used as vectors have been reported. Each serotype represents advantages and disadvantages with respect to stability, productivity, immunogenicity, bioavailability, tropism, etc. However, many laboratories have developed pseudo-typical vectors, i.e. modified AAVs containing cover proteins of different serotypes, in order to obtain the advantages of different serotypes or to avoid the disadvantages of some cover proteins of some serotypes. By way of example, an AAV2/6 virus, in which the characteristics of the two viral serotypes are mixed, are sometimes used in the present invention.

The term 'AAV vector', as used in the present invention, also refers to a vector comprising one or more polynucleotides of interest (or transgenes) that are flanked by AAV terminal repetition sequences (ITRs). Such AAV vectors can be replicated and packaged into infectious viral particles when they are present in a host cell that has been transfected with a vector that encodes and expresses the REP and CAP genes (i.e., the REP and CAP AAV proteins), and where the host cell has been transfected with a vector that encodes and expresses a protein from the E4orf6 adenovirus reading frame. When an AAV vector is incorporated into a larger polynucleotide (for example, a chromosome or other vector such as a plasmid used for cloning or transfection), then the AAV vector is typically referred to as a "pro-vector". The pro-vector can be "rescued" by replication and encapsulation in the presence of the AAV packaging functions and the necessary auxiliary functions provided by E4orf6.

The serotype of the AAV vector provides the specificity of the cell type where it will express the transgene given each serotype's tropism.

The term 'specific binding site for the UPRplus transcription regulatory region' as used in the present invention, refers to a nucleic acid sequence that works as a promoter (i.e. regulates the expression of a selected nucleic acid sequence, operationally bound to the promoter), and that affects the expression of a selected nucleic acid sequence in specific tissue cells, such as neurons. The specific binding site for the regulatory element of neural tissue transcription may be constituent or inducible.

The term 'CAP gene' or 'AAV CAP gene', as used in the present invention, refers to a gene that encodes for a CAP protein. The term 'CAP protein', as used herein, refers to a polypeptide that has activity of at least one functional activity of the CAP protein of a native AAV (VP1, VP2, VP3). Examples of functional activities of the VP1, VP2, and VP3 proteins include the ability to induce capsid formation, facilitate single strand DNA accumulation, facilitate the packaging of AAV DNA into the capsid (i.e., encapsulation), bind to cell receptors, and facilitate the entry of the virus into a host.

The term 'capsid', as used in the present invention, refers to the structure in which the viral genome is packaged. A capsid consists of an oligomeric structure with structural subunits of CAP proteins. For example, AAV has an icosahedral capsid formed by the interaction of three capsid proteins: VP1, VP2 and VP3.

The term 'cell composition', as used in this document, refers to a composite type material comprising the cells of the invention and at least one other component. The composition may be formulated as a single formulation or may be presented as separate formulations of each of the components, which may be combined for joint use as a combined preparation. The composition can be a parts kit, where each of the components is individually formulated and packaged.

The term 'constituent promoter', as used in the present invention, refers to a promoter whose activity is maintained at a relatively constant level throughout an organism, or during most experimental stages, with little or no consideration for the cell's environmental and external conditions.

The term 'expression cassette', as used here, refers to a construction of nucleic acids, generated synthetically or by recombination, with a series of elements specific to nucleic acids, which allow the transcription of a particular nucleic acid into a target cell.

The term 'genes that provide support functions', as used herein, refers to genes

that encode polypeptides, performing functions on the AAV that are dependent for replication (i.e. "support functions"). Auxiliary functions include functions that are necessary for AAV replication, including these fragments involved in the activation of AAV gene transcription, the specific stages of AAV mRNA splicing, AAV DNA replication, synthesis of CAP products, and AAV capsid assembly. Accessory viral functions can be derived from any of the known auxiliary viruses such as adenoviruses, herpes viruses, lentivirus and the vaccinia virus. Auxiliary functions include, but are not limited to, the WHV lentivirus.

The term 'operationally linked', as described in this document, refers to the functional relationship and location of a promoter sequence with respect to a polynucleotide of interest (e.g., a promoter or enhancer is operationally linked to a coding sequence which affects the transcription of that sequence). Generally, an operationally linked developer is adjacent to the sequence of interest. However, an enhancer does not have to be adjacent to the sequence of interest to control its expression.

The term 'locally administered', as used herein, means that the polynucleotides, vectors, polypeptides, and/or pharmaceutical compositions of the invention are administered to the subject at or near a specific site.

The terms 'pharmaceutically acceptable carriers', 'pharmaceutically acceptable diluents', 'pharmaceutically acceptable excipient' or 'pharmaceutically acceptable vehicle' are interchangeable in this document, referring to a non-toxic solid, semi-solid, or filling liquid, diluent or encapsulation material or an auxiliary formulation for any conventional type. A pharmaceutically acceptable carrier is essentially non-toxic to the containers used in the dosages and concentrations and is compatible with other ingredients in the formulation. The number and nature of pharmaceutically acceptable vehicles depends on the desired administration method. Pharmaceutically acceptable vehicles are known and can be prepared by well-known technical methods.

The term 'promoter', as used herein, refers to a nucleic acid that controls

the transcription of one or more polynucleotides, located upstream of the sequence of the polynucleotide(s), and which is structurally identified by the presence of a RNA polymerase dependent DNA binding site, the transcription initiation sites, and any other DNA sequence, including, but not limited to, transcription factor binding sites, repressor, and activator protein binding sites, and any other nucleotide sequences known to the technique to act directly or indirectly to regulate the amount of transcription from the promoter. A 'tissue-specific' promoter is activated only in certain types of differentiated cells or tissues.

The term 'polynucleotide', as used herein, refers to a nucleic acid molecule, either DNA or RNA, containing deoxyribonucleotides or ribonucleotides, respectively. Nucleic acid may be a double strand, single strand, or contain parts of either a double strand or single strand sequence. The term 'polynucleotide' includes, but is not limited to, nucleic acid sequences with the ability to encode a polypeptide and nucleic acid sequences which are partially or wholly complementary to an endogenous polynucleotide of the cell or subject treated with it in a manner that, after transcription, generates an RNA molecule (e.g. microRNA, shRNA, siRNA) capable of hybridizing and inhibiting the endogenous polynucleotide expression.

The term 'bridge or linker', as used herein, refers to a continuous or discontinuous polynucleotide sequence, either DNA or RNA, which allows for the physical separation of objective sequences, positioning them in a suitable manner so that they can be translated and transcribed.

The term 'string' in this document refers to a sequence of continuous nucleotides (including or not modified natural or non-natural nucleotides). The two or more strands may be, or each may be a part of, separate molecules, or they may be covalently interconnected, for example, by means of a coupling (for example, a linker such as polyethylene glycol), to form a molecule. At least one of the strands may include a region that is sufficiently complementary to a target RNA.

A second chain of the dsRNA agent, comprising a complementary region to the antisense chain, is called the "sense strand". However, a siRNA agent can also be formed from a single RNA molecule that is at least partially self-complementary, forming, for example, a hairpin or buttonhole structure, which includes a duplex region. The latter are hereinafter referred to as short hairpin RNAs or shRNAs. In such a case, the term 'strand' refers to one of the RNA molecule's region that is complementary to another region of the same RNA molecule.

The term 'recombinant viral genome', as used herein, refers to an AAV genome in which at least one non-expressive polynucleotide cassette is inserted into the native AAV genome.

The term 'rep gene' or 'AAV rep gene', as used herein, refers to a gene that encodes a Rep protein. The term "Rep protein", as used herein, refers to a polypeptide that has at least one functional activity of a native AAV rep protein (e.g., Rep 40, 52, 68, 78). A "functional activity" of a Rep protein (e.g. Rep 40, 52, 68, 78) is any activity associated with the physiological function of the protein, including the facilitation of DNA replication through the recognition, binding and cutting off of the origin of AAV DNA replication, as well as the helical activity of DNA. Additional functions include modulation of AAV transcription (or other heterologous) promoters and site-specific integration of AAV DNA into a host chromosome.

The term 'subject', as used herein, refers to an individual, plant, mammal or animal, such as a human, a non-human primate (e.g., chimpanzee or other ape and other monkey species), an animal (e.g., birds, fish, livestock, sheep, pigs, goats and horses), a mammal (e.g., dogs and cats), or a laboratory animal (e.g., rodents, such as mice, rats, mice with silenced genes (knockout mice), mice that overexpress a gene (transgenic mice, and guinea pigs). The term does not indicate a particular age or sex. The term 'subject' includes an embryo and a fetus.

The term 'systemically administered' and 'systemically administered', as

used herein, means that the present invention's polynucleotides, vectors, polypeptides, or pharmaceutical compositions are administered to a subject in a non-localized form. The systemic administration of the polynucleotides, vectors, polypeptides, or pharmaceutical compositions of the invention may reach
5 several organs or tissues in the subject's entire body, or may reach new specific organs or tissues. For example, the intravenous administration of a pharmaceutical composition of the invention may result in transduction in more than one tissue or organ in a subject.

10 The term 'transcriptional regulatory element', as used herein, refers to a nucleic acid fragment capable of regulating the expression of one or more genes. The polynucleotide regulatory elements of the invention include a promoter and, optionally, an enhancer.

15 The term 'transduction', as used herein, refers to the process by which a sequence of foreign nucleotides is introduced into a cell into a viral vector.

The term 'transfection', as used in this document, refers to the introduction of DNA into the target eukaryotic cells.

20 The term 'vector', as used herein, refers to a construct capable of delivering, and optionally expressing, one or more polynucleotides of interest in a host cell. Examples of vectors include, but are not limited to, viral vectors, DNA or bare RNA expression vectors, plasmid, cosmic or phage vectors, RNA
25 or DNA expression vectors associated with cationic condensing agents, liposomal encapsulated DNA or RNA expression vectors, and certain eukaryotic cells, such as producing cells. Vectors can be stable and can be self-replicating. There are no limitations as to the type of vector that can be used. The vector may be a cloning vector, suitable for propagation and for obtaining
30 polynucleotides, gene constructs or expression vectors incorporated into several heterologous organisms. Suitable vectors include prokaryotic expression vectors, phage and shuttle vectors and eukaryotic expression vectors based on viral vectors (e.g. adenovirus, adeno-associated viruses as well as retrovirus and lentivirus), as well as non-viral vectors such as pSilencer

4,1-CMV.

The term 'UPRplus', as used in this document, refers to sequences consisting of XBP1s, ATF6f, a promoter, a connection or bridge sequence and an epitope for identification.

The invention's methods and compositions (for example the methods and compositions of the AAV virus with the aforementioned inserts) may be used with any dosage and/or formulation described in the present invention, as well as with any route of administration described in the present invention.

For the term 'cognitive and motor treatment or therapy skills', we refer to cognitive and motor tests performed on different species and/or subjects with a pathology as defined in the present invention.

The term 'cDNA' or 'complementary DNA' refers to a DNA sequence that perfectly complements a RNA sequence, used to form an RT-PCR synthesis.

The phrase 'silencing of a target gene' refers to the process whereby a cell that contains and/or expresses a particular product of the target gene when not in contact with the agent, will contain and/or express at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or less of such gene's product when in contact with the agent, compared to a similar cell that has not been contacted with the agent. This target gene product may, for example, be a messenger RNA (mRNA), a protein, or a regulatory element.

The term 'complementary' as used in this document indicates a sufficient degree of complementarity such that a stable and specific binding takes place between a compound and a target RNA molecule. Specific binding requires a sufficient degree of complementarity to avoid non-specific binding of the oligomeric compound to non-target sequences, under conditions where specific binding is desired, i.e. under physiological conditions in the case of in vivo tests or therapeutic treatment, or in the case of in vitro tests, under conditions where tests have been performed.

The term 'restriction sites' as used in this document refers to the nucleotide sequence to which a specific restriction enzyme for said sequence is attached and cuts or splits off.

5

Ligands

The properties of a virus, including its pharmacological properties, can be influenced and tailored, for example, by the introduction of ligands. In addition,
10 the pharmacological properties of a viral agent can be improved by the incorporation of a ligand into an agent formulation and a virus.

Ligands can be attached to a wide variety of entities, such as ligands that bind to a viral agent, or can be used as a conjugate or formulation additive; for
15 example, with the vehicle of a monomeric subunit attached to the ligand. The examples are described below in the context of a monomeric subunit attached to a ligand, but that is only the preferred one, and entities can be coupled elsewhere with a virus.

20 A ligand alters the distribution, direction, or lifetime of the viral agent into which it is embedded. In the preferred modalities, a ligand provides a better affinity for a selected target; for example, a molecule, cell, or cell type, a compartment (such as a cell or organ compartment, a tissue, or region of the body), as compared to a species in which said ligand is absent.

25

In the present invention, ligands may improve the transport, hybridization, and specificity properties of the target molecule in the virus.

Ligands in general may include therapeutic modifiers, for example to
30 improve absorption of the molecule in the individual; diagnostic compounds or reporter groups, for example, to monitor distribution; crosslinking agents; fractions that confer resistance to immune reactions; and natural or unusual nucleobases.

General examples include lipophilic molecules, lipids, lectins, (e.g. hecigenin, diosgenin), terpenes (e.g. triterpenes, sarsasapogenin, friedelin, lithocholic acid derived from epifriedelanol), vitamins, carbohydrates (e.g. a dextran, pululan, chitin, chitosan), synthetic (e.g., 15-mer oligo-lactate) and
 5 natural (e.g., low and medium molecular weight) polymers, inulin, cyclodextrin, or hyaluronic acid), proteins, protein binding agents, integrin binding molecules, polycations, peptides, polyamines, and peptide mimetics. Other examples include epithelial cell or folic acid receptor ligands, such as transferrin.

10 The ligand can be a naturally occurring or recombinant or synthetic molecule, such as a synthetic polymer (for example, a synthetic poly-amino acid). Examples of poly-amino acids include polylysine (PLL), poly-aspartic acid L-aspartic, poly-acid L-glutamic, styrene-anhydride copolymer of maleic acid, poly-(lactic-co-glycolic) copolymer of divinyl ether-maleic anhydride, copolymer
 15 of N-(2-hydroxy propyl)-methacrylamide (HMPA), polyethylene glycol (PEG), polyvinyl vinyl alcohol (PVA), polyurethane, poly(2-ethylacrylic acid), N-isopropyl-acrylamide polymers, or polyphosphazene. Examples of polyamines include: polyethyleneimine, polylysine (PLL), spermine, spermidine, polyamine, pseudo-peptide polyamine, peptidomimetic polyamine, dendrimer polyamine,
 20 arginine, amidine, protamine, cationic fractions, e.g. cationic lipid, cationic porphyrin, quaternary salt of a polyamine, or an alpha-helical peptide.

Ligands may also include steering groups, for example a steering agent to a cell or tissue, such as a thyrotropin, melanotropin, surfactant protein A,
 25 mucin carbohydrate, a glycosylated polyaminoacid, bisphosphonate, polyglutamate, polyaspartate, an Arg-Gly-Asp peptide (RGD), or a mimetic of RGD peptide.

Ligands can be proteins, for example glycoproteins or lipoproteins such
 30 as low-density lipoprotein (LDL), or albumin, such as serum albumin, or peptides, such as molecules that have a specific affinity for a co-ligand, or antibodies, such as an antibody that binds to a specific cell type. Ligands may also include hormones and hormone receptors. They may also include non-peptide species, such as cofactors, multivalent lactose, multivalent galactose,

N-acetyl-galactosamine, N-acetyl-glucosamine, multivalent mannose, or multivalent fucose.

The ligand can be a substance, such as a drug, that can increase the absorption of the viral agent within the cell; for example, by altering the cell's cytoskeleton, or its microtubules, microfilaments, and/or intermediate filaments.

In one respect, a ligand is a lipid, or a lipid-based molecule. This lipid or lipid-based molecule is preferably bound to a whey protein, such as albumin serum.

Alternatively, viruses may be packaged.

The preparation of injectable virus solutions is performed by diluting the necessary virus concentration in PBS (saline phosphate buffer), which is formulated as follows.

1.- Dissolve the viral dose (previously diluted in PBS 1x) in 800 ml of distilled water with:

- 8 g of NaCl
- 0,2 g of KCl
- 1,44 g of Na_2HPO_4
- 0,24 g of KH_2PO_4
- 2. Adjust pH to 7,4 with HCl.
- 3. Set the volume to 1L with additional distilled water H_2O .
- 4. Sterilize and autoclave.

Design and Selection

Generation of UPRplus molecule variants.

One of the objectives of this patent is to generate the six variants of a recombinant DNA, composed of the human sequences of the active form of XBP1, called XBP1s and the active form of ATF6, called ATF6f. The UPRplus

variants include two variables in their design: the order of the XBP1s and ATF6f molecules (XBP1s-ATF6f and ATF6f-XBP1s) and the binding peptide (also known as linker) between the two sequences. The linkers used are as follows:

- 19-AA Glycine Flexible Linker ("GFL");
- 25-AA Alpha Helix Linker ("AHL4"); and
- 50-AA Flexible Linker ("FL").

It has been shown that these three types of joints or bridges provide the flexibility and adequate distance between the proteins joined at their ends, in order to achieve an interaction between them. The generation and evaluation of these three linkers between the XBP1s and ATF6f molecules allowed to extend the possibilities of generating an active functional transcription factor, which adopts an adequate three-dimensional geometry to join the specific gene elements.

In addition, to better detect the expression of these chimeric proteins, the hemagglutinin peptide (HA) protein sequence (among others, not limited to this epitope) was added to the terminal carboxylic endpoint of all proteins.

The utilized cloning strategy generated the DNA sequences of XBP1s, ATF6f and the three different linkers by de novo synthesis, including restriction sites for subsequent linking to the pAAV expression vector. This expression vector was used to generate viral particles prior to the selection of the UPRplus variant with the highest in vitro neuroprotective activity.

By means of de novo synthesis two sets of gene sequences were obtained. These included the HA sequence at the 3rd end, and depending on the linker, the various restriction sites shown below:

Set 1 XBP1s-linker-ATF6f

SnaBI_XBP1s-LFG-ATF6f_FseI

BspEI_XBPS1s-LF-ATF6f_KpnI

5 BspEI_XBPs-L4H4-Atf6f_KpnI

Set 2 ATF6-linker-XBP1s

SnaBI_ATF6-LFG-XBP1s_FseI

10

KpnI_ATF6-L4H4 -XBP1s_SfiI

KpnI_ATF6 -LF-XBP1s_SfiI

15 The mRNA sequences used for this purpose are described in tables VII and VIII, ATF6f and XBP1s, respectively.

The mRNA sequences of the linkers or jumpers are described in Table IX, which shows the LGF, L4H4 and LF linkers.

20

Along with the generation of these 6 UPRplus variants, the individual versions of XBP1s and ATF6f associated with AAV (tables XI and XII, respectively) were produced, cloned in the pAAV expression vector to correctly compare UPRplus's activity with respect to the individual expression of these transcription factors.

25

The expression of these sequences uses the same promoter of the UPRplus variants and presents the HA peptide, unlike previous studies performed with the transcription factor XBP1s and ATF6f, which did not contain these elements.

30

Once these sequences were obtained by de novo synthesis, they were then linked to the pAAV expression vector through the aforementioned restriction sites. The 8 versions of the generated recombinant DNA were

sequenced, confirming that the sequences were correct and consistent with the expected results.

The de novo synthesis of the aforementioned sequences and the linking
5 of these sequences to the pAAV vector were performed by the GENEWIZ company in the United States.

The sequences obtained in the plasmids can be seen as maps in figures
1/17, 2/17, 3/17, 4/17, 5/17, and 6/17.

10 To confirm these plasmids, a restriction analysis of the obtained sequences was performed by means of plasmid DNA digestion using the EcoR1 restriction enzyme.

15 The fragment sizes obtained in the restriction enzyme assays were as expected, as shown in Figure 7/17.

An analysis of the biomedical scope for its therapeutic use provided an effective and innovative method to treat neurodegenerative diseases, in which
20 the use of this technology produced surprising results in its application.

To explore the involvement of UPRplus, the six recombinant DNA variants described in the previous paragraphs were generated. They encode human sequences of the active form of XBP1, called XBP1s, and the active
25 form of ATF6, called ATF6f, linked by different linkers and linked to an epitope for hemagglutinin (HA), among other possible epitopes.

With respect to the development of the adeno-associated virus (AAV), it comprises the viral recombinant genome that includes an expression cassette
30 with a transcriptional regulatory element operationally linked to the polynucleotide of interest. The AAV serotype type provides part of the tissue selectivity in which the polynucleotide of interest will be expressed, without being exclusive.

According to the present invention, the adeno-associated virus (AAV) includes any known serotype of the 42 types and is derived from parvoviruses. In general, the various AAV serotypes are significantly homologous genomic sequences in terms of amino acids and nucleic acids, which provide identical genetic functions, provide vibrio bacteria that are essentially identical in functional and physical terms, and their replication and assembly use virtually the same mechanisms.

In the present invention in particular, AAV serotype 2 was used (such as those mentioned in GenBank access number ((AAV2) NC_001401.2, (AAV6) AF028704.1, NC006260 (AAV7), NC006261 (AAV8), AX753250.1 (AAV9), (AAV10), (AAV11) and pseudotyped AAVs, as presented for AAV2, in Table X.

For AAV10 and AAV11 viruses, a complete sequence is not available as they differ in capsid proteins.

According to the present invention, the AAV genome normally comprises an actuator in cis 5 and an inverted 3 terminal repeating sequence and an expression cassette. ITR or LTR sequences have a length of 141 base pairs. Preferably, the complete sequence of the LTRs is used in the molecule and only slight modifications of the sequences are allowed. In a preferred form of the present invention, the recombinant genome of the AAV comprises the 5th and 3rd AAV LTRs. In another preferred form of the present invention the 5th and 3rd AAV LTRs are derived from AAV serotype 2. In another more preferable form of the present invention, the recombinant genome of AAVs lacks the Rep and Cap open reading frame.

On the other hand, ITRs can come from other AAV serotypes.

The present invention's AAV comprises a capsid from any serotype. In particular, for the present invention, capsids derived from serotypes 2, 6, 7, 8, 9 and 10 are preferred. However, the AAV capsid of serotype 2 is preferred.

In some implementations, an AAV cap for use in the method of invention

may be generated by mutagenesis (i.e., insertions, deletions or substitutions) of one of the AAV caps or their coding nucleic acids. In some productions, the AAV cap is at least 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% or more similar to one or more of the aforementioned AAV caps.

5

In some implementations, the AAV cap is chimeric, comprising the domains of two, three, four, or more of the aforementioned AAV caps. In some designs, the AAV cap is a mosaic of the monomers VP1, VP2, VP3 and coming from two or three different AAVs or a recombinant AAV (rAAV). In some
10 productions, a composition of rAAV comprises more than one of the above CAPS.

In some implementations, an AAV CAP for use in an rAAV composition is designed to contain a heterologous sequence or other modification. For
15 example, a peptide or protein sequence that confers selective targeting or immune evasion may be genetically engineered on a Cap protein. Alternatively, or in addition, the Cap may be chemically modified so that the surface of the rAAV presents specific chemical modifications, such as polyethylene glycolates, which may facilitate immune evasion. The Cap protein can also be generated
20 by guided mutations (e.g. to remove its natural binding receptor, or to mask an immunogenic epitope).

In one implementation, the AAV vector contains a promoter with the addition of at least one target sequence of at least one sequence of
25 SnaBI_XBP1s-LFG-ATFG-ATF6f_Fsel; or BspEI_XBPS1s-LF-ATF6f_KpnI; or BspEI_XBPs-L4H4-Atf6f_KpnI; or SnaBI_ATF6-LFG-XBP1s_Fsel; or KpnI_ATF6-L4H4 -XBP1s_Sfil or KpnI_ATF6 -LF-XBP1s_Sfil that can be selected from the following tables: Table I (SnaBI_XBP1s-LFG-ATFG-ATF6f_Fsel) or Table II (BspEI_XBPS1s-LF-ATF6f_KpnI) or Table III
30 (BspEI_XBPs-L4H4-Atf6f_KpnI) or Table IV (SnaBI_ATF6-LFG-XBP1s_Fsel) or Table V (KpnI_ATF6-L4H4 -XBP1s_Sfil) or Table VI (KpnI_ATF6 -LF-XBP1s_Sfil), obtained from GenBank.

In one implementation, the AAV vector contains a promoter with the

addition of at least one of the target sequences of SnaBI_XBP1s-LFG-ATF6f_FseI; or BspEI_XBPS1s-LF-ATF6f_KpnI; or BspEI_XBPs-L4H4-Atf6f_KpnI; or SnaBI.

5 In one implementation, the AAV vector contains a promoter with the addition of at least one target sequence that is 85% homologous with a target sequence selected from the aforementioned tables.

10 In one implementation, the AAV vector contains a promoter with the addition of at least one target sequence that is 70% homologous with a target sequence selected from the aforementioned tables.

15 In one implementation, the AAV vector contains a promoter with the addition of at least one target sequence, which is a functional equivalent of a target sequence selected from the aforementioned tables.

The transcription regulatory element may comprise a promoter and, optionally, an enhancer region. The promoter is preferably selected from this list: CMV, PGK1, CAMKII, THY1, GAD34 among others. The enhancer need
20 not be specific to the neural tissue.

In one implementation, the promoter is specific, for example, to the cytomegalovirus, also known as CMV.

25 In a implementation, the promoter is specific, for example, to the phosphoglycerate kinase 1 protein, also known as PGK1.

In one implementation, the promoter is specific, e.g. Calcium Calmodulin Kinase 2, also known as CAMKII.

30

In one implementation, the promoter is specific, e.g. also known as Thy1.

In one implementation, the promoter is specific, for example, the one for glutamic acid decarboxylase 34, also known as GAD34, which normally

operates in GABAergic neurons.

In another implementation, the expression cassette that forms part of the present invention's AAV also comprises a post-transcriptional regulatory element. In a preferred implementation, the post-transcriptional regulatory element is the Woodchuck Hepatitis Virus post-transcriptional regulatory element (WPRE) or functional variants and fragments thereof and the PPT-CTS or functional variants and fragments themselves. In one particular implementation, the post-transcriptional regulatory element is WPRE.

The expression cassette forming part of the AAV in accordance with the invention comprises a 'polynucleotide of interest'. In a preferred realization, the polynucleotide of interest encodes a systemically acting protein. In another implementation, the polynucleotide of interest encodes a protein that acts within a neuron. In a preferred implementation, the protein that acts within that neuron is: XBP1s-LFG-ATF6f; or XBP1s-LF-ATF6f; or XBP1s-LF-ATF6f; or XBP1s-L4H4-ATF6f; or ATF6f-LFG-XBP1s; or ATF6-L4H4 -XBP1s or ATF6f-LF-XBP1s, including any of their isoenzymes that vary in subcellular locations.

The size limit of the AAV vector packaging is limited to the size of the wild-type AAV genome, which varies in size according to the AAV stereotype (namely, between 4087 and 4767). For example, native AAV-2 has a genome size of 5382. In some forms of realization, the cloning capacity of the recombinant RNA vector may be limited, and a desired coding sequence may involve the complete replacement of 4.8 kilobases of the virus genome. Large-sized genes may therefore not be suitable for use in a standard recombinant AAV vector in some cases. The average expert will discern that the options are available in the technique for overcoming a limited coding capacity. For example, the two-genome AAV *IRT* can hybridize to form the head to tail concatemers, almost doubling the vector's capacity. The insertion of the splice sites allows removal of the *IRT* after transcription. Other options for overcoming a limited cloning capacity will be evident to the expert in the subject matter.

As a next objective, the expression of these variants was tested on a

human cell line. In order to carry out this objective, the SHSY5Y neuroblastoma-derived cells were replaced with HEK293 cells, due to the low transfection percentage (30%) of SHSY5Y cells. The HEK293 cells correspond to a human kidney embryonic cell line, which presents a high percentage of transfection
5 (80%) by the CaPO_4 method.

The HEK293 cells were transfected with the 6 variants of UPRplus. As a control, the individual versions of human XBP1s and ATF6f (Tables XI and XII, respectively) that were cloned in the same expression vector were included.
10 Also included was the expression of two versions corresponding to the mouse DNA sequence of XBP1s existing in the laboratory.

The HEK293 cells were transfected using the CaPO_4 method with the respective recombinant DNAs and after 48 hours of expression the protein
15 extraction with RIPA buffer and quantification of total proteins was performed.

Subsequently, different proteins were detected by means of Western Blot (WB), using the antibodies anti-HA, anti-XBP1 and anti-ATF6.

The WB analysis showed that these proteins were expressed correctly,
20 as it was possible to detect all variants of UPRplus with the anti-HA antibody as shown in Figure 8/17. The epitope for hemagglutinin (HA) is present at the terminal C-end of all UPRplus variants and was therefore used as a first approximation. The molecular weights obtained were approximately ~100 kDa
25 for the UPRplus variants and ~50 kDa for the individual proteins.

The molecular size obtained for the individual version of cloned XBP1s in the viral expression of the UPRplus variants does not differ compared to the mouse XBP1s versions already characterized and determined in the same
30 assay (Figure 8/17, lanes 8 and 11). The molecular weights obtained according to the electrophoretic migration were higher than the expected molecular weights (see Figure 8/17), both for the UPRplus proteins and the individual proteins.

On the other hand, the expression of human XBP1s was detected in all UPRplus variants (lanes 1-6, Figure 9/17) as well as in the individual variant (lanes 8, Figure 9/17) using the anti-XBP1 143F (Biolegend) antibody. Since this antibody only recognizes the human form of XBP1s, it was not possible to
 5 detect the expression of the mouse XBP1s sequence (lanes 9, 11 and 12, Figure 9/17).

Finally, the ATF6f protein present in the UPRplus variants was also detected with an anti-ATF6 (abCam) antibody as shown in Figure 10/17. This
 10 antibody recognized both the human and mouse versions of ATF6f (Figure 10/17).

In order to determine the subcellular location of these proteins in HEK293 cells, indirect immunofluorescence assays were conducted on cells expressing
 15 UPRplus proteins and their individual versions. The same antibodies described above, used in the WB analysis, were used. The expression of the epitope HA, of the XBP1 and ATF6 proteins was detected (Figures 11/17, 12/17 and 13/17) in HEK293 cells transiently transfected with the different variants of UPRplus and also in the cells transfected with the individual versions of the XBP1s and
 20 ATF6 proteins. From these results, we determined that the subcellular location of the 6 UPRplus variants corresponds to a nuclear pattern that became evident upon co-marking with the Hoechst probe, which specifically stains the nuclei of cells (Figures 11/17, 12/17 and 13/17). In order to determine the specificity of the anti-HA antibody, cells that were transiently transfected with the
 25 mXBP1s/EGFP plasmid corresponding to the mouse sequence of XBP1s were included as a negative control (Figure 11B/17).

It was also determined that the anti-XBP1 antibody specifically recognizes the XBP1 protein by immunofluorescence in all variants of UPRplus.
 30 The specificity of the anti-XBP1 antibody was determined by the absence of the mark on cells transfected with ATF6 individually or in non-transfected cells. (Figure 12A/17). With this assay, it was possible to detect the mouse sequence of XBP1s using the anti-XBP1 antibody (Figure 12B/17).

The expression of ATF6 was also corroborated by immunofluorescence in HEK293 cells transfected with UPRplus variants. Detection of the ATF6 protein was observed in all protein variants of UPRplus, except in cells that were transfected with XBP1s individually which was used as a negative control (Figure 13/17).

Subsequent to the subcellular localization of the expression of these proteins in transfected HEK293 cells, the activation of the promoter element was evaluated in response to the unfolded protein response, "UPR", mediated by the pAAV-UPRplus virus, using reporters coupled to Luciferase activity.

This analysis of the transcriptional activity of the pAAV-UPRplus variants was conducted using the Luciferase reporter system under the control of the UPR element, called "UPRE", which preferably responds to the heterodimer between ATF6f and XBP1s. For this purpose, HEK293 cells were co-transfected with the plasmids pAAV-UPRplus 1 to 6 in conjunction with the Luciferase-UPRE reporter plasmid. In addition, a Renilla encoding plasmid was transfected, which was used as an internal control for the assay to determine the percentage of cells expressing all plasmids, as it constitutively expresses a chemiluminescent molecule (Promega, Dual-Luciferase® Reporter Assay System). After 48 hours of expression, the luminescence obtained was measured in a luminometer. The activation levels of the response element to UPR by the pAAV-UPRplus variants were compared with those generated by the transfection of the encoding plasmid for the activated form of the XBP1s, called pAAV-XBP1s, and the active form of ATF6, called pAAV-ATF6f, and the co-transfection of both plasmids (pAAV-XBP1s y pAAV-ATF6f). Also included as a positive control of the experiment was the transfection of the pCDNA3-mXBP1s plasmid corresponding to the version of the mouse sequence of XBP1s. The pCDNA3 empty vector transfection was also included as a baseline activity of the XBP1/ATF6 transcriptional activity system of XBP1/ATF6 transcription factors.

Figure 14/17 shows the transcriptional activity of the 6 variants of UPRplus and of the relevant controls. The values shown represent the average

of three independent experiments. As shown in Table XIII:

Table XIII:

Plasmid	Experiment 1	Experiment 2	Experiment 3	Average	ESM
PAAv_ATF6f-LFG-XBP1s-HA	101,1517	99,62383	125,4241	108,73321	8,357091867
PAAv_ATF6f-LF-XBP1s-HA	88,52831	119,747	191,8758	133,3837033	30,60308089
PAAv_ATF6f-L4H4-XBP1s-HA	79,35313	77,71852	71,44357	76,17174	2,410717813
PAAv_XBP1s-LFG-ATF6f-HA	17,81713	12,53527	21,4335	17,26196667	2,583652391
PAAv_XBP1s-LF-ATF6f-HA	15,62922	11,8496	23,48904	16,98928667	3,428142203
PAAv_XBP1s-L4H4-ATF6f-HA	9,228968	11,24907	10,3266	10,26821267	0,583883502
PAAv_ATF6f-HA	120,188	122,1534	139,6209	127,3207667	6,17618165
PAAv_XBP1s-HA	47,8104	47,95798	46,66553	47,47797	0,408447887
PAAv_ATF6f-HA + PAAv_XBP1s-HA	100	100	100	100	0
pCDNA3_mXBP1	77,29633	120,5979	116,0251	104,6397767	13,73530344
pCDNA3	4,874095	6,953351	4,208801	5,345415667	0,826588582

5

The maximum activity (100% of transcriptional activity) was determined as the activation values reached by the co-transfected XBP1s and ATF6f variants, and based on this value the activities of each of the variants in each experiment were normalized.

10

The results obtained show a transcriptional activity of the 1-3 variants similar to the co-expression condition of XBP1s and ATF6f. These variants are capable of binding to the UPRE promoter region and achieve activating the expression of the Luciferase reporter. The 4-6 variants presented levels of transcriptional activity of around 20% with respect to the ATF6f/XBP1s co-expression control, so it is likely that they will not be able to bind to the UPRE promoter region or that the structure of adopting this chimeric protein will alter its binding to the DNA sequence.

15

20

In addition, it was determined that the individual variants are capable of

activating the UPR promoter region and that ATF6f presents a greater activity than the XBP1s protein.

These results verify that three of the mixed variants of “ATF6f-XBP1s”, those assigned as 1, 2 and 3, maintain the activating property of the UPR, indicating that the strategy proposed in the project is viable and is possibly capable of activating target genes related to the transcriptional activity of the heterodimer ATF6f/XBP1s.

The next step in this development was to evaluate the activation of the UPR transcriptional targets mediated by the expression of pAAV-UPRplus.

HEK293 cells were used to conduct this study, which were transfected with the coding plasmids for the six pAAV-UPRplus variants and the individual pAAV-XBP1s and pAAV-ATF6f variants. In addition, the co-transfection of both variants (pAAV-XBP1s and pAAV-ATF6f) was included, a condition that was considered as the maximum activation reached by the heterodimer in these experimental tests.

After 24 hours of expression, the transcriptional activation of genes associated to the UPR pathway was measured by quantifying the mRNA levels of a group of genes described as transcriptional targets modulated by the heterodimer ATF6f-XBP1s using the real-time PCR technique.

The genes analyzed during this project stage were described in a recent study (Shoulders et al., 2013), which determined, by mass sequencing, the genes differentially regulated by XBP1s and/or ATF6 in HEK293 cells. In this study, HEK293 cells were generated that are capable of expressing the XBP1s and/or ATF6f transcription factors in a differential and induced way by the addition of drugs that control the expression of these proteins. This system is capable of expressing XBP1s by adding doxycycline, ATF6f by the drug trimethoprim (TMP), and both proteins (heterodimer) through the incubation with both drugs.

The genes described that are expressed differentially by these transcription factors are shown in the following Table XIV:

Table XIV:

5

XBP1	ATF6	XBP1 /ATF6
Erdj4	HspA5 (BiP)	Creld2
Sec24D	HerpUD	Edem1
Stt3a	Pdia4	Hyou1
	Sel1L	Sulf1

Table XIV above presents the genes regulated by XBP1 and/or ATF6 in inducible HEK293 cells.

10 Based on this information, oligonucleotide sequences were generated to determine the expression levels of the genes shown in Table XIV using real-time PCR in HEK cells treated with the drug tunicamycin, which induces endoplasmic reticulum stress (ER).

15 With this assay we were able to test the amplification efficiency of these genes and corroborate that these genes are activated in response to the ER stress condition.

20 As shown in Figure 15/17, it was determined that the genes were efficiently amplified, and it was also confirmed that they increase their expression in response to the ER stress condition.

25 Subsequently, the mRNA levels of some of the transcriptional UPR targets were compared, obtained from HEK293 cells transfected with each of the six variants of pAAV-UPRplus, pAAV-XBP1s or pAAV-ATF6f individually, and co-transfected with both variants (pAAV-XBP1s and pAAV-ATF6f).

The genes that were chosen for analysis were those associated with the activation of the heterodimer. The chosen genes were: CRELD2, a gene

associated with the degradation of unfolded proteins associated with the ER process called ERAD (“Endoplasmic Reticulum Associated protein Degradation”), HYOU1, related to the protein folding process, and EDEM 1, associated with ERAD and SULF1, a secreted enzyme involved in the formation of the extracellular matrix. In addition, the activation of BIP, associated with the protein folding and HERPUD involved in the ERAD process, was determined. For the messenger RNAs associated with the expression of the heterodimer such as Creld2, Edem1, Hyou1 and Sulf1, it is observed that variants 1, 2 and 3 are capable of activating this group of genes in comparison to the 4, 5 and 6 variants (Figure 16/17). Additionally, in the case of the expression of the SULF1 gene, the UPRplus3 variant presents a greater activation than that obtained when the XBP1s and ATF6f variants are co-expressed.

This result shows us that UPRplus chimeric proteins are capable of activating genes associated with the unfolded protein response. In addition, the activation levels reached by the 1, 2 and 3 variants are similar or greater than those obtained by co-expressing both proteins (Figure 16/17). With respect to the chaperone Bip and the HERPUD genes associated with ERAD, we also observed that the 1, 2 and 3 variants of UPRplus are capable of preferentially activating these genes, reaching induction levels similar to those obtained when co-expressing these transcription factors. The results obtained correspond to the average of three independent experiments.

Routes of administration

The routes of administration of the virus are subject to its passing through the blood-brain barrier to infect the target neurons.

To achieve this objective in the present invention, 2 routes of administration have been mainly defined.

The first of these routes is the nasal route. Generally, drugs administered nasally can enter the bloodstream through general circulation, can penetrate the brain directly, or in some cases can follow both routes. However, many of the

factors that control the flow of the drug through each of these routes are not fully defined. In general, there are three routes by which a drug administered in the nasal cavity can travel. These routes include entry into the systemic circulation directly from the nasal mucosa, entry into the olfactory bulb by axonal transport through the neurons, and direct entry into the brain. Evidence supporting the role of each of these routes for a variety of model substrates is summarized below for the different types of viruses.

Transport routes followed by several viral solutes through nasal administration			
Solute	Animal model	Route of Administration	Route traveled
Virus			
Hepatitis Virus	Mouse	Nasal Inoculation	Olfactory nerve
Herpes Simplex Virus	Mouse	Nasal drops	Direct, Systemic, Olfactory Nerve
Encephalitis Virus	Mouse	Nasal Inoculation	Olfactory Nerve
Pneumococcus	Mouse	Nasal drops	Direct

This table is not intended to be exhaustive in nature, but rather to highlight some of the different kinds of solutes that have been shown to follow one or more routes.

Other routes of administration to the cells in the CNS have included:

Direct injection into fluid compartments, such as the vitreous humor in the eye; or into the cerebral fluid of the spine through different routes, intraventricular or intrathecal (**), for delivery to the choroid plexus, the ependymal/meningeal layers, and from there in the adjacent brain through processes that extend within these layers; and its passage through the blood-brain barrier or blood-tumor barriers by intra-arterial injection combined with a temporary osmotic or pharmacological interruption.

The term (**) Intrathecal (intra + theca, "within a sheath") is an adjective that refers to something that occurs or is introduced into an anatomical space or potential space within a sheath, most commonly the arachnoid membrane of the brain or the spinal cord.

Dosage Calculation

According to Ulusoy et al, vector titration requires a range between 10^9 and 10^{13} genome copies (GC) per ml with a proven dosage of 10^{10} - 10^{12} gc/ml. On the other hand, at any dilution ratio of the vectors to appraise they must have a low-medium range of 10^{11} gc/ml, which results in the disappearance of toxicity.

Dosage in humans:

The dosage range in humans is found between 10^9 and 10^{30} viral units/kg of body weight, without restricting this range to the application in different age groups or with modified volumes of distribution by age or pathology.

The greatest concentration or amount of a substance, found by experiment or observation that causes no detectable adverse alteration of morphology, functional capacity, growth, development, or life span of target organisms distinguishable from those observed in normal (control) organisms of the same species and strain under defined conditions of exposure.

Method of application

The rAAV2 vectors were injected bilaterally into the NS using a 5 μ L Hamilton syringe fitted with a glass capillary with a tip diameter of about 60-80 microns. Two microliters of the buffer containing the appropriate concentrations of viral particles were injected at a speed of 0.4 μ L/minute. The needle was withdrawn slowly 5 minutes after completion of the injection.

Description of Figures

Figure 1/17

This figure shows a restriction map of the pAAV-XBP1s-LFG-ATF6f plasmid, with 7701 bp and the representation of the genetic elements present in the generated recombinant DNA.

5 Figure 2/17

This figure shows a restriction map of the pAAV-XBP1s-LF-ATF6f plasmid, with 7809 bp and the representation of the genetic elements present in the generated recombinant DNA.

10

Figure 3/17

This figure shows a restriction map of the AAV-XBP1s-L4H4-ATF6f plasmid with 7719 bp and the representation of the genetic elements present in the generated recombinant DNA.

15

Figure 4/17

This figure shows a restriction map of the AAV- ATF6f -LFG-XBP1s plasmid with 7701 bp and the representation of the genetic elements present in the generated recombinant DNA.

20

Figure 5/17

This figure shows a restriction map of the pAAV- ATF6f-L4H4-XBP1s plasmid with 7719 bp and the representation of the genetic elements present in the generated recombinant DNA.

25

Figure 6/17

This figure shows a restriction map of the pAAV- ATF6f-LF-XBP1s plasmid with 7809 bp and the representation of the genetic elements present in the generated recombinant DNA.

30

Figure 7/17

This figure shows a photograph of the restriction test of the UPRplus variants. A plasmid DNA digestion was performed with the restriction enzyme
 5 EcoR1 for two hours at 37C.

The fragments obtained were set in a 1% agarose gel. Two types of molecular-weight size markers were used. The sizes are shown at the ends of the gel photograph:

- 10 1. pAAV_ATF6f-LFG-XBP1s-HA
2. pAAV_ATF6f-LF-XBP1s-HA
- 15 3. pAAV_ATF6f-L4H4-XBP1s-HA
4. pAAV_XBP1s-LFG-ATF6f-HA
5. pAAV_XBP1s-LF-ATF6f-HA
- 20 6. pAAV_XBP1s-L4H4-ATF6f-HA
7. pAAV_ATF6f-HA
- 25 8. pAAV_XBP1s-HA

Expected sizes after digestion with Eco R1:

- 30 1. 3895, 1928, 1531, 347 total size: 7701
2. 3895, 1928, 1639, 347 total size: 7809
3. 3895, 1928, 1549, 347 total size: 7719

4. 4262, 1928, 818, 693 total size: 7701

5. 4264, 1928, 926, 693 total size: 7809

5 6. 4264, 1928, 836, 693 total size: 7719

7. 3895, 1928, 693 total size: 6516

8. 4262, 1928, 347 total size: 6537

10

Figure 8/17

This figure shows the expression of UPRplus variants in HEK293 cells and their detection by HA epitope: The HEK293 cells were transiently transfected with the UPRplus variants. Encoding plasmids were used as a control for XBP1s-HA, ATF6-HA and XBP1s/GFP. In addition, an extract of non-transfected cells (NT) was included. After 48 hours of expression, the total proteins were extracted and the HA epitope was detected using the anti-HA Covance antibody (dilution 1:1000). mXBP1-HA was used as a positive control. Hsp90 was used as a load control.

The sizes are shown at the ends of the gel photograph:

1. pAAV_ATF6f-LFG-XBP1s-HA expected molecular weight 83KDa

25

2. pAAV_ATF6f-LF-XBP1s-HA expected molecular weight 87KDa

3. pAAV_ATF6f-L4H4-XBP1s-HA expected molecular weight 82KDa

30

4. pAAV_XBP1s-LFG-ATF6f-HA expected molecular weight 83KDa

5. pAAV_XBP1s-LF-ATF6f-HA expected molecular weight 87KDa

	6.	pAAV_XBP1s-L4H4-ATF6f-HA	expected	molecular	weight
		82KDa			
5	7.	pAAV_ATF6f-HA	expected	molecular	weight
		43KDa			
	8.	pAAV_XBP1s-HA	expected	molecular	weight
		43KDa			
10	9.	pAAV_mXBP1/GFP	expected	molecular	weight
		40KDa			
	10.	NT			
15	11.	pAAV_mXBP1s-HA	expected molecular weight 43KDa		
	12.	pAAV_mXBP1s-HA	expected molecular weight 43KDa		

20 Figure 9/17

This figure shows the expression of the UPRplus variants in HEK293 cells and the detection of XBP1s therein. The HEK293 cells were transiently transfected with the UPRplus variants and with the encoding plasmids for XBP1s-HA, ATF6-HA, XBP1s, and mXBP1s. In addition, extracts of non-transfected cells (NT) were used as a control. After 48 hours of expression, the total proteins were extracted and the XBP1 protein was detected using the Biolegend anti-XBP1 antibody, 143F, (dilution 1:1000). Hsp90 was used as a load control.

30

Identification of the gel lanes:

1. pAAV_ATF6f-LFG-XBP1s-HA

2. pAAV_ATF6f-LF-XBP1s-HA
3. pAAV_ATF6f-L4H4-XBP1s-HA
- 5 4. pAAV_XBP1s-LFG-ATF6f-HA
5. pAAV_XBP1s-LF-ATF6f-HA
6. pAAV_XBP1s-L4H4-ATF6f-HA
- 10 7. pAAV_ATF6f-HA
8. pAAV_XBP1s-HA
- 15 9. pAAV_mXBP1/GFP
- 10.NT
- 11.pAAV_mXBP1s-HA
- 20 12.pAAV_mXBP1s-HA

Figure 10/17

25 This figure shows the expression of the UPRplus variants in HEK293 cells and the detection of ATF6. The HEK293 cells were transiently transfected with the UPRplus variants, and with the coding plasmids for XBP1s-HA, ATF6-HA, XBP1s, mXBP1s. In addition, non-transfected cells (NT) were used as a control. After 48 hours of expression, the total proteins were extracted and the

30 ATF6 protein was detected using the anti-ATF6 antibody abCam (dilution 1:250). The expression of the mouse ATF6 protein was used as a positive control. Hsp90 was used as load control.

Identification of the gel lanes:

1. pAAV_ATF6f-LFG-XBP1s-HA
2. pAAV_ATF6f-LF-XBP1s-HA
3. pAAV_ATF6f-L4H4-XBP1s-HA
4. pAAV_XBP1s-LFG-ATF6f-HA
5. pAAV_XBP1s-LF-ATF6f-HA
6. pAAV_XBP1s-L4H4-ATF6f-HA
7. pAAV_ATF6f-HA
8. pAAV_XBP1s-HA
9. RV ATF6f
10. NT

Figure 11/17

This figure shows two groups of photographs, A and B, where one can observe the subcellular distribution of the UPRplus variants in HEK293 cells.

The group identified as (A) presents the HEK293 cells that were transfected with the different variants of UPRplus, fixed after 48 hours of expression and co-stained with anti-HA antibody (red, top panel) and Hoechst (blue, middle panel) in each condition. The overlay of images is displayed in the bottom panel of each condition.

The group identified as (B) presents the HEK293 cells that were transfected with mXBP1s/EGFP, fixed after 48 hours of expression and co-

stained with anti-HA antibody (red), EGFP intrinsic fluorescence (green), and Hoechst (blue).

The bottom bar of each photograph corresponds to 10 μ m.

5

Figure 12/17

This figure shows two groups of photographs, A and B, which present the subcellular distribution of the UPRplus variants in HEK293 cells.

10

(A) The HEK293 cells were transfected with the different variants of UPRplus, fixed after 48 hours of expression and co-stained with anti-XBP1 antibody (red, top panel), and Hoechst stain (blue, middle panel) in each condition. The overlay of images is displayed in the bottom panel of each condition.

15

(B) The HEK293 cells were transfected with mXBP1s/EGFP, fixed after 48 hours of expression and co-stained with the anti-XBP1 antibody (red), EGFP intrinsic fluorescence (green), and Hoechst stain (blue).

20

The bottom bar of each photograph corresponds to 20 μ m.

Figure 13/17

This figure analyzes the subcellular distribution of the UPRplus variants in HEK293 cells.

25

The HEK293 cells were transfected with the different variants of UPRplus, fixed after 48 hours of expression and co-stained with the anti-ATF6 antibody (red, top panel) and Hoechst stain (blue, middle panel) in each condition. The overlay of images is displayed in the bottom panel of each condition.

30

The lower bar of each photograph corresponds to 20 μ m.

Figure 14/17

This figure presents a bar graph representing the transcriptional activity
5 of the UPRplus variants:

The HEK293 cells were transiently transfected with three different plasmids:

- 10 - the vectors encoding for the UPRplus variants;
- the vector carrying the UPR promoter region that controls luciferase expression; and
- 15 - the renilla encoding plasmid, as an internal control.

The positive controls used were encoding plasmids for ATF6-HA, XBP1s-HA, and co-transfection of ATF6-HA/XBP1s-HA. Also, the transfected pCDNA3 empty vector was used as a negative control. After 48 hours of expression, the
20 transcriptional activity was determined by means of a luciferase assay.

The luminescence measurement was conducted and normalized with the renilla activity.

25 The graph (top panel) represents the average of three independent experiments and the values are the mean and Standard Error of the Mean (SEM).

The table (bottom panel) shows the values obtained in each experiment
30 for each experimental condition.

Figure 15/17

This figure shows an analysis of the expression of UPR target genes in

HEK293 cells where:

The mRNA levels of the UPR-associated transcriptional targets were analyzed by real-time PCR from cDNA obtained from HEK293 cells under
 5 baseline conditions and treated with 1 µg/ml tunicamycin for 8 hours.

All samples were normalized with the expression levels of the constitutively active β -actin gene.

Figure 16/17

This figure shows an analysis of the expression of UPR target genes in HEK293 cells transfected with pAAV-UPRplus where:

15 The mRNA levels of the UPR-associated transcriptional targets were analyzed by real-time PCR from cDNA obtained from HEK293 cells transfected with the encoding plasmids for the six pAAV-UPRplus variants and the individual variants XBP1s and ATF6f, and the co-transfection of both variants (pAAV-XBP1s and pAAV-ATF6f).

20 All samples were normalized with the expression levels of the constitutively active β -actin gene.

1. pAAV_ATF6f-LFG-XBP1s-HA,

2. pAAV_ATF6f-LF-XBP1s-HA,

3. pAAV_ATF6f-L4H4-XBP1s-HA,

4. pAAV_XBP1s-LFG-ATF6f-HA,

5. pAAV_XBP1s-LFATF6f-HA,

6. pAAV_XBP1s-L4H4-ATF6f-HA,

7. pAAV_ATF6f-HA,

8. pAAV_XBP1s-HA,

5

7+8. pAAV_ATF6f-HA + pAAV_XBP1s-HA,

GFP. pAAV-EGFP.

10

Figure 17/17

This figure presents a protein aggregation analysis of the polyQ79 protein (Example of Application) against the expression of UPRplus where:

15

(A) The N2A cells were transiently co-transfected with the pAAV-UPRplus, pAAV-XBP1s or pAAV-ATF6 vectors, and with the pEGFP-poly-Q79 vector. The protein expression was analyzed using Western blot, after 24 hours (right panel) and 48 hours (left panel) of expression. HSP90 was used as a load control.

20

(B) These same samples were analyzed by Filter-trap assay after 24 hours (right panel) and 48 hours (left panel) of expression.

25

(C) Graph that represents the quantification of the protein aggregation of the polyQ79 protein using Western blot after 24 hours (right panel) and 48 hours (left panel) of expression. The mean and standard error of three independent experiments are shown.

30

(D) Graph that represents the quantification of the protein aggregation of polyQ79 using Filter-trap after 24 hours (right panel) and 48 hours (left panel) of expression. The mean and standard error of three independent experiments are shown.

EXAMPLE OF APPLICATION

Parkinson's and Huntington's diseases are related to the formation of protein aggregates that cause selective neuronal death, preferentially in the dopaminergic neurons of the substantia nigra. To observe these effects, a

Western blot test was conducted, as shown in Figure 17/17, where:

3×10^5 N2A cells were seeded in 30 mm wells. After 24 hours, the pAAV-UPRplus, pAAV-XBP1s or pAAV-ATF6 vectors were co-transfected and the pEGFP-poly-Q79 vector was used with the **Effectene method**. 0.6 μ g of each vector plus 3.2 μ l of Enhancer and 100 μ l of EC buffer were mixed. The mixture was shaken by vortex for 15 seconds and incubated at room temperature for 10 minutes. 8 μ l of Effectene (Qiagen) was added, shaken by vortex for 10 seconds, and incubated at room temperature for 15 minutes. The solution was mixed with 500 μ l DMEM 10% SFB medium and added to the drip culture plate covering the entire surface.

After 24 or 48 hours of expression, the cells were removed from the culture plate using a cell scraper, collected, and centrifuged at 2,000 rpm for 5 minutes at 4°C. The precipitate was re-suspended in a PBS buffer with 1% Triton, supplemented with protease inhibitor (Roche). The cells were sonicated 3 times for 5 seconds on ice and, finally, the protein concentration was determined in each sample using the BCA Protein Assay (Pierce, Rockford, IL) (Zhang et al. 2014).

The protein samples were prepared using 25 μ g of total protein, mixed with 4X charge buffer (Tris-HCl 0.2 M [pH 6.8], SDS 10%, bromophenol blue 0.05%, and glycerol 20%) and then heated for 5 minutes at 95°C, which were loaded into 8% denaturant gels. The 8% polyacrylamide separator gel was prepared with Tris-HCl 380 mM [pH 8.3], acrylamide-bis-acrylamide 8%, SDS 0.1%, ammonium persulfate 0.1% and TEMED 0.06%. The compressor polyacrylamide gel was prepared with Tris-HCl 60 mM [pH 6.8], acrylamide-bis-acrylamide 4%, SDS 0.1%, ammonium persulfate 0.1% and TEMED 0.06%.

The electrophoresis was conducted in running buffer (Tris 25 mM,

Glycine 250 mM and SDS 0.1%) at a constant voltage of 100 V. The electrophoretic running was stopped when the blue front left the gel. Subsequently, the proteins were transferred to a PVDF membrane in transfer buffer (Tris 25 mM, Glycine 250 mM and methanol 20%) at a constant voltage of 100 V for 2 hours 30 minutes on ice. The membrane was then incubated in blocking solution (5% milk in PBS) for 1 hour at room temperature and constant agitation. Finally, the membranes were incubated with any of the following antibodies, diluted in 5% milk PBS 0.02% Tween; anti-GFP 1:1000 (Santa Cruz) or anti-HSP90 1:3000 (Santa Cruz), for 16 hours at 4° C while in constant agitation. The following day, the membranes were washed 3 times for 5 minutes with PBS Tween 0.1% and later incubated for 1 hour at room temperature and constant agitation with the relevant secondary antibodies: anti-rabbit-HRP or anti-mouse-HRP (Invitrogen) diluted 1:3000 (Milk 5% in PBS Tween 0.02%). Once this period had transpired, the membranes were washed with PBS Tween 0.1%, this time 3 times for 5 minutes. Finally, protein analysis was done using the Western Blotting Substrate kit (Pierce) and the Chemidoc image detection system (Biorad).

To confirm the above-obtained data, a **Filtertrap assay** was conducted, where 25 µg of total protein mixed with PBS-SDS 4 X buffer was used to conduct this.

These samples were loaded onto a 96 well plate coupled to a vacuum pump containing cellulose acetate filters. After adding the samples, vacuum was applied to retain only high molecular weight species in the filter. Subsequently, the filters were incubated in blocking solution (5% milk in PBS) for 1 hour at room temperature and while in constant agitation. They were later incubated with the anti-GFP antibody 1:1000 (Santa Cruz), diluted in 5% milk PBS Tween 0.02% for 16 hours at 4°C with constant agitation. The following day, the filters were washed 3 times for 5 minutes with PBS Tween 0.1% and later incubated for 1 hour at room temperature and constant agitation with the secondary anti-mouse-HRP antibody (Invitrogen) diluted 1:3000 (5% milk in PBS Tween 0.02%).

After this period, the membranes were washed with PBS Tween 0.1%, this time 3 times for 5 minutes. Finally, protein analysis was done using the Western Blotting Substrate kit (Pierce) and the Chemidoc image detection system (Biorad).

5

Conclusions:

With the expression of the UPRplus, XBP1s and ATF6f proteins for 24 hours, the percentage of aggregation of the polyQ 79-EGFP protein in the N2A cell managed to be reduced. The expression of the UPRplus, XBP1s and ATF6f proteins managed to be reduced to 23.2, 47, and 51.4%, respectively, the percentage of aggregation determined using WB.

10

The anti-aggregation effect was also determined using the Filtertrap technique, in which case the expression of the UPRplus, XBP1s and ATF6f proteins dropped to 15.1, 15, and 39.1% respectively, after 24 hours.

15

In addition, the anti-aggregation effect of the expression of the XBP1s, ATF6f and UPRplus proteins was evaluated using WB after 48 hours. It was observed that the aggregation of polyQ79 dropped significantly only with UPRplus treatment (47% decrease).

20

Moreover, the Filtertrap technique, it was observed that the expression of the XBP1s, ATF6f and UPRplus proteins decreased the protein aggregation of polyQ79-GFP to 48.5; 65.6 and 24% respectively, with respect to the control, after 48 hours.

25

Material and methods

30

Adeno-associated vector production

The AAV virus serotype 2 (AAV2/6) particles were produced by the transfection of 293-AAV cells (Agilent Technologies, Santa Clara, CA) and purified in an iodixanol gradient followed by column affinity chromatography.

The number of AAV particles that the genome contains in the suspension as well as the infectivity of the suspension of the vector in HEK293T cells were determined by TaqMan qPCR assays.

Preparation of the adenoviral plasmids (pAAV) for the 6 variants:

For the development of this target, the XBP1s sequences, human ATF6f sequences, and the respective linkers were synthesized *de novo* and cloned into the adenoviral plasmid pAAV-CMV-MCS, which expresses the transgene under the CMV promoter. The HA tag sequence (Figure 17/17 A) was included in all the generated constructs, which then allowed us to identify the transduced cells. The empty adenoviral plasmid pAAV-CMV-MCS was used as control.

To confirm the expression of the generated constructs we transfected HEK cells with the different constructs, after 48 hours of transfection we performed the extraction of proteins that were evaluated by means of WB using an anti-HA antibody.

As shown in Figure 10/17, we detected a band with the expected molecular weight for the variants UPRplus(130 kDa) along with the expression controls for pAAV-XBP1s-HA (55 kDa), pAAV-ATF6f-HA (55 kDa) and pCDNA-mXBP1s (55 kDa).

Real-time PCR

Total RNA was isolated from HEK 293 cells transfected with the different plasmids. After homogenization in PBS, the Trizol RNA extraction protocol recommended by the manufacturer was followed. The cDNA was synthesized with a high-capacity cDNA reverse transcription kit (Applied Biosystems). SYBR green and a Mx3005P QPCR System (Stratagene) were used for quantitative RT-PCR. The relative quantification of mRNA was calculated by the comparative threshold cycle method with β -actin as control. The primers of the sequences were obtained from the PrimerBank (Table XV).

Table XV

Erdj4	5'-GGAAGGAGGAGCGCTAGGTC-3'	5'-ATCCTGCACCCTCCGACTAC-3'
HspA5 (BiP)	5'-GCCTGTATTTCTAGACCTGCC-3'	5'-TTCATCTTGCCAGCCAGTTG-3'
HerpUD	5'-AACGGCATGTTTTGCATCTG-3'	5'-GGGGAAGAAAGGTTCCGAAG-3'
Hyou 1	5'-GCAGACCTGTTGGCACTGAG-3'	5'-TCACGATCACCGGTGTTTTTC-3'
Pdia4	5'-AGTGGGGAGGATGTCAATGC-3'	5'-TGGCTGGGATTTGATGACTG-3'
Sec24D	5'-AGCAGACTGTCCTGGGAAGC-3'	5'-TTTGTTTGGGGCTGGAAAAG-3'
Sel1L	5'-ATCTCCAAAAGGCAGCAAGC-3'	5'-TGGGAGAGCCTTCCTCAGTC-3'
Stt3a	5'-TTCAACCTGGGTGACCAAGTG-3'	5'-CATGACCTTCGCATCCTCTG-3'
Sulf1	5'-ATTCAAGGAGGCTGCTCAGG-3'	5'-TGTCATGCGTGAAGCAAGTG-3'

Western blot

5 This technique is described in detail in Experiment 1.

Cultures

Neuro2A cells and HEK293T cells were obtained from ATCC and
 10 cultured in DMEM medium supplemented with 10% bovine serum or 5%,
 respectively, and antibiotics (10000 U/ml penicillin, 10 mg/ml streptomycin), at
 37°C and 5% CO₂.

Assays

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Filtertrap assay: 25 ug of total protein are applied to a 96 well plate
 coupled to a vacuum pump (Microfiltration Apparatus, bio-rad, <http://www.bio-rad.com/en-us/applications-technologies/protein-blotting-equipment-cells-power-supplies#3>) containing cellulose acetate filters.

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After adding the samples, vacuum was applied to retain only high molecular weight species in the filter. The filters were then incubated in blocking solution (5% milk in PBS) for 1 hour under agitation at room temperature. They were then incubated with the anti-GFP antibody 1:1000 (Santa Cruz), diluted in 5% milk/PBS Tween 0.02% 16 hours at 4°C under agitation. The next day the filters were washed 3 times for 5 minutes with PBS Tween 0.1% and then incubated for 1 hour at room temperature under constant agitation with the secondary anti-mouse-HRP antibody (Invitrogen) diluted 1:3000 (5% milk/PBS Tween 0.02%).

Effectene Method: This method consists of a method of transfection of plasmids into eukaryotic cells, which is described and standardized by the manufacturer's protocol (Qiagen) (<https://www.qiagen.com/es/shop/assay-technologies/transfection-reagents/effectene-transfection-reagent/>).

This protocol consists of mixing 0.6 µg of each vector plus 3.2 µl of Enhancer and 100 µl of EC buffer. The mixture is shaken by vortex for 10 seconds and incubated at room temperature for 10 minutes. Then, 8 µl of Effectene was added, shaken by vortex for 10 seconds and incubated at room temperature for 15 minutes. This solution is mixed with 500 µl of DMEM 10% FBS medium and added to the 30 mm drip culture plate covering the entire surface.

Statistics

The data are expressed as mean and SEM. Depending on the

experiments, the results were statistically compared using Student's T-test or Mann-Whitney's test, two-way ANOVA, followed by Holm-Sidak or Bonferroni as a post-hoc test or Kruskal-Wallis by one-way ANOVA on ranks followed by the Dunn's test or Bonferroni as a post-hoc test.

CLAIMS

1. An adeno-associated vector (AAV), comprising a recombinant viral genome where such genome comprises an expression cassette comprising a transcription regulatory region specific for neuronal tissues operatively bound to a polynucleotide of interest encoding a fusion protein, wherein the fusion protein comprises X-Box binding protein 1 (*XBP1s*), activating transcription factor 6 (*ATF6f*) and a bridge or linker sequence.
2. The adeno-associated vector according to claim 1, wherein the serotype of the AAV is selected from a group that comprises AAV2, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11 and pseudo-typed AAVs.
3. The adeno-associated vector according to claim 2, wherein the serotype of the AAV is AAV 2 or an AAV 2/6 pseudotyped vector.
4. The adeno-associated vector according to any one of claims 1-3, wherein the transcription regulatory region includes a selected promoter region from the group that comprises *CMV*, *PGK1*, *CAMKII*, *THY1*, *GAD34*.
5. The adeno-associated vector according to claim 4, wherein the selected promoter region of the group is *CMV*.
6. The adeno-associated vector according to any one of claims 1-5, comprising a coding region for an immune response site selected from the *Ha*, *Flag*, *Gfp*, *His* and *Myc* group.

7. The adeno-associated vector according to claim 6, wherein the coding region for an immune response site is *Ha*.
8. The adeno-associated vector according to any one of claims 1-7, wherein the expression cassette comprises a post-transcriptional regulatory region.
9. The adeno-associated vector according to claim 8, wherein the post-transcriptional regulatory region is the post-transcriptional regulatory element of the Woodchuck Hepatitis Virus (WHP).
10. The adeno-associated vector according to any one of claims 1-9, wherein:
- (i) the bridge sequence comprises the sequence of SEQ ID NO: 9, 10 or 11; and/or
 - (ii) the target sequence to be transcribed is encoded by any one of SEQ ID NOs: 1 to 6.
11. The adeno-associated vector according to any one of claims 1-10, wherein the polynucleotide of interest encodes a fusion protein encoded by one of SEQ ID NOs: 1 to 6.
12. A pharmaceutical composition comprising the adeno-associated vector of any one of claims 1-11 and pharmaceutically acceptable excipients.
13. The pharmaceutical composition according to claim 12, comprising a dosage of the virus at a range between 10^9 to 10^{13} genome copies (GC) per ml of compound.

14. Use of the adeno-associated vector according to any one of claims 1-11 or the pharmaceutical composition of claim 12 or claim 13, in the manufacture of a medicament for treating Parkinson's and/or Huntington's disease in a subject in need thereof.

15. A method of treating Parkinson's and/or Huntington's disease comprising administering to a subject the adeno-associated vector according to any one of claims 1-11 or the pharmaceutical composition of claim 12 or claim 13.

16. The use of claim 14 or the method of claim 15, wherein:

- i) the subject is a mammal; and/or
- ii) the mammal is a human.

17. The use of claim 14 or claim 16, wherein the medicament is formulated for administration systemically or locally; or the method of claim 15 or claim 16, wherein the adeno-associated vector or the pharmaceutical composition is administered systemically or locally.

18. A polynucleotide comprising an expression cassette flanked by the ITRs of an adeno-associated virus, where such expression cassette comprises a promoter, a coding region for immune response, and a polynucleotide of interest that encodes a fusion protein, wherein the fusion protein comprises XBP1s, ATF6f and a bridge or linker sequence.

19. The polynucleotide according to claim 18, wherein:

- (i) the promoter region is selected from the group that comprises CMV, PGK1, CAMKII, THY1 and GAD34; and/or
- (ii) the promoter region is CMV; and/or
- (iii) the coding region for an immune response site is selected from the group Ha, Flag, Gfp, His and Myc; and/or
- (iv) the coding region for an immune response site is Ha; and/or
- (v) the type of serotype of the adeno-associated vector is of the number 2 and/or a 2/6 pseudo-typed vector; and/or
- (vi) the expression cassette also comprises a post-transcriptional regulatory region; and/or
- (vii) the expression cassette comprises the post-transcriptional regulatory element of the Woodchuck Hepatitis Virus (WHP); and/or
- (viii) the target sequence to be transcribed is encoded by any one of SEQ ID NOs: 1 to 6; and/or
- (iv) the polynucleotide of interest encodes a fusion protein encoded by any one of SEQ ID NOs: 1 to 6.

20. A plasmid comprising the sequences of an adeno-associated, an expression cassette flanked by the ITRs of the adeno-associated virus, where such expression cassette comprises a promoter, a coding region for immune response and a polynucleotide of interest, wherein the plasmid comprises the sequence of a plasmid deposited in the international body of biological deposits, Instituto de Investigaciones Agropecuarias de Chile, INIA, under deposit numbers: RGM 2231, RGM 2232, RGM 2233, RGM 2234, RGM 2235 or RGM 2236.

21. An adeno-associated virus comprising a viral genome comprising the polynucleotide of claim 18 or claim 19.

Figure 1/17

Restriction map of pAAV_XBP1s-LFG-ATF6f - 7701 nt
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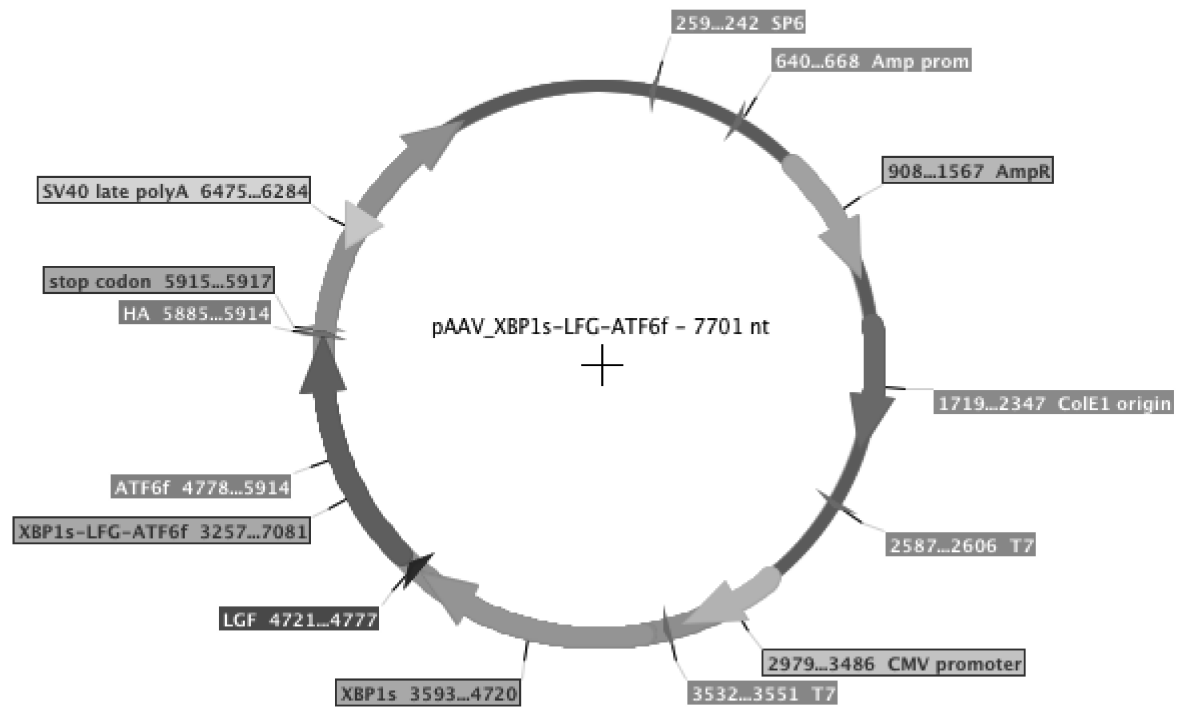


Figure 2/17

Restriction map of pAAV_Xbp1s-LF-ATF6f - 7809 nt
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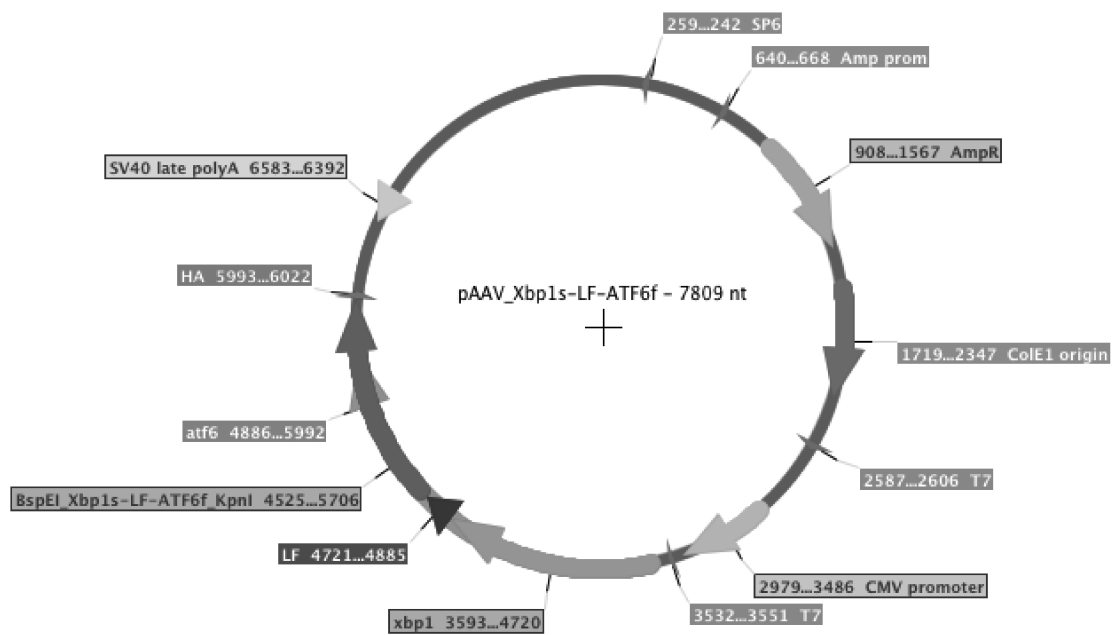


Figure 3/17

Restriction map of pAAV_Xbp1s-L4H4-Atf6f - 7719 nt
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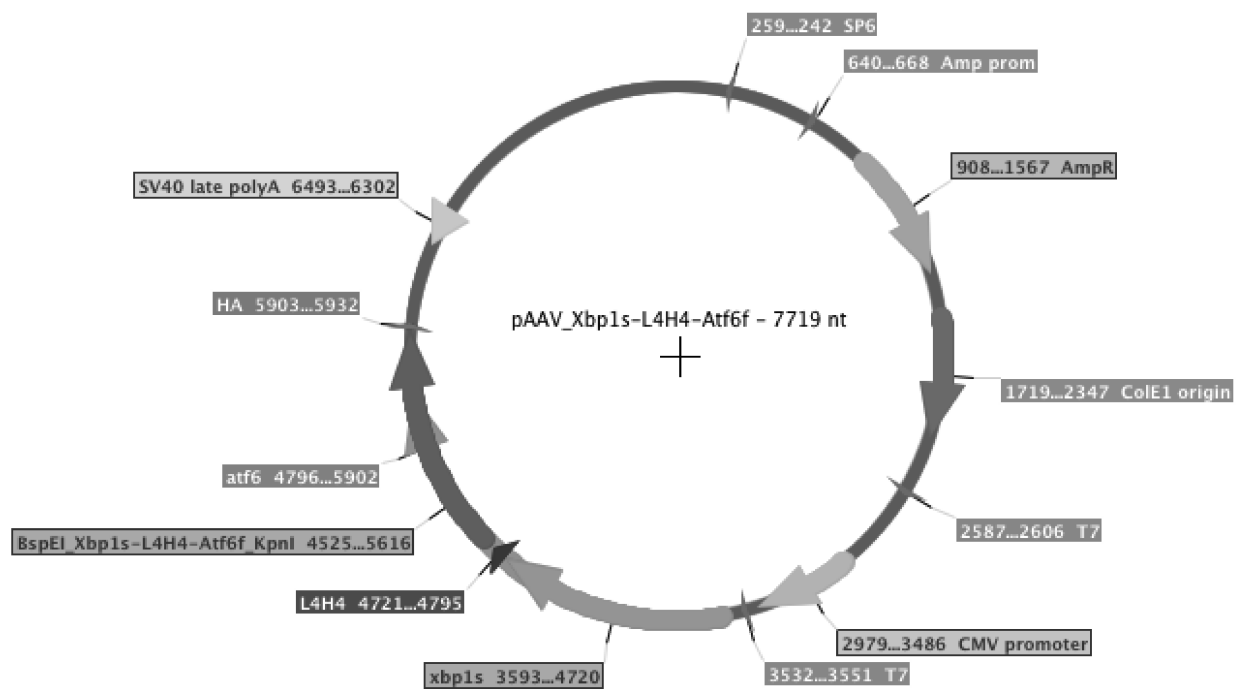


Figure 4/17

Restriction map of pAAV_ATF6 - LFG -XBP1s - 7701 nt
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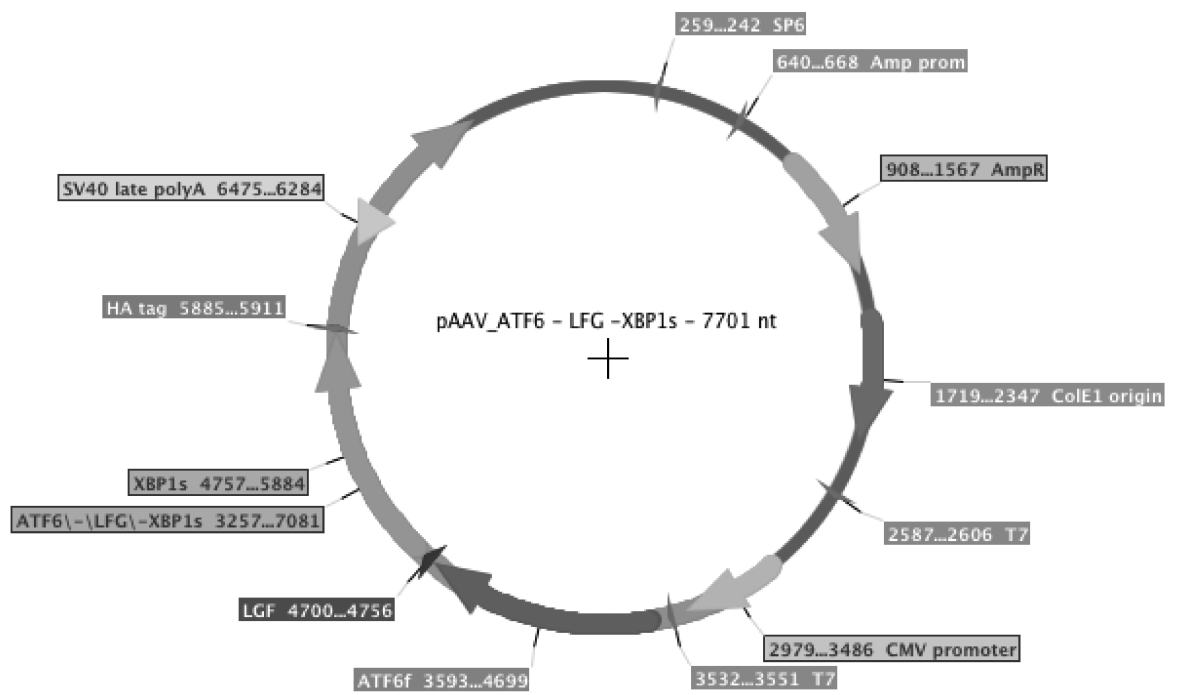


Figure 5/17

Restriction map of pAAV_ATF6- L4H4 - XBP1s - 7719 nt
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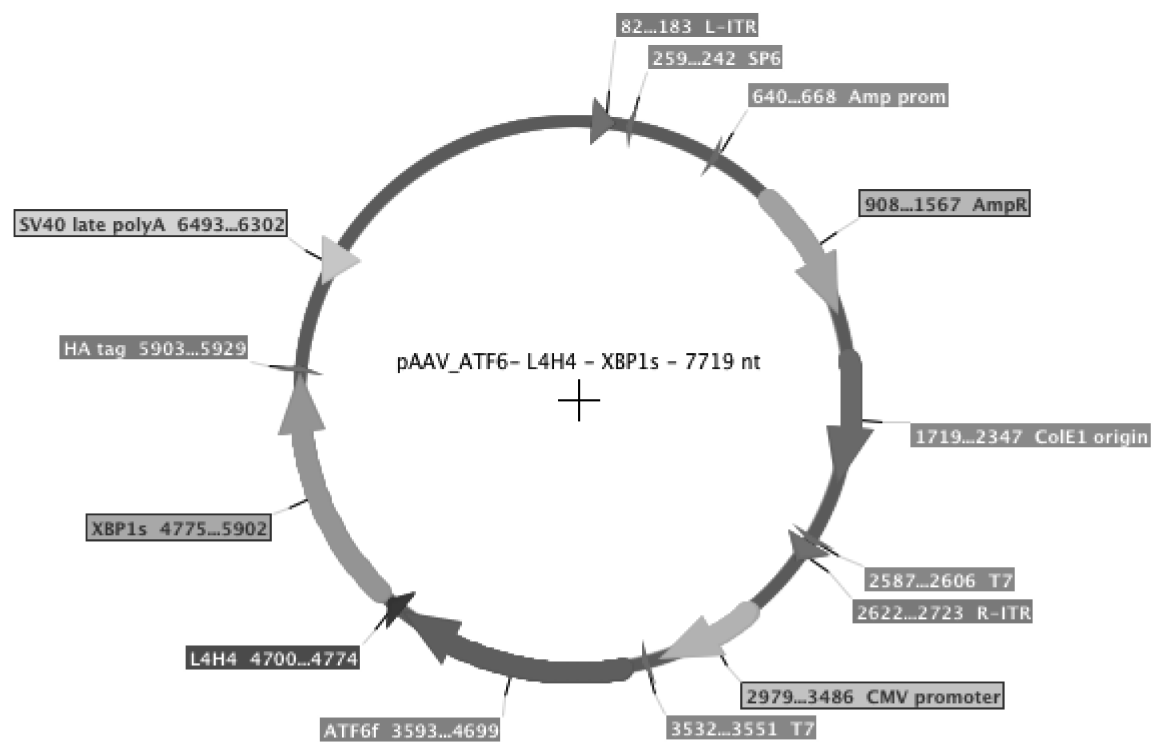


Figure 6/17

Restriction map of pAAV_ATF6 - LF -XBP1s - 7809 nt
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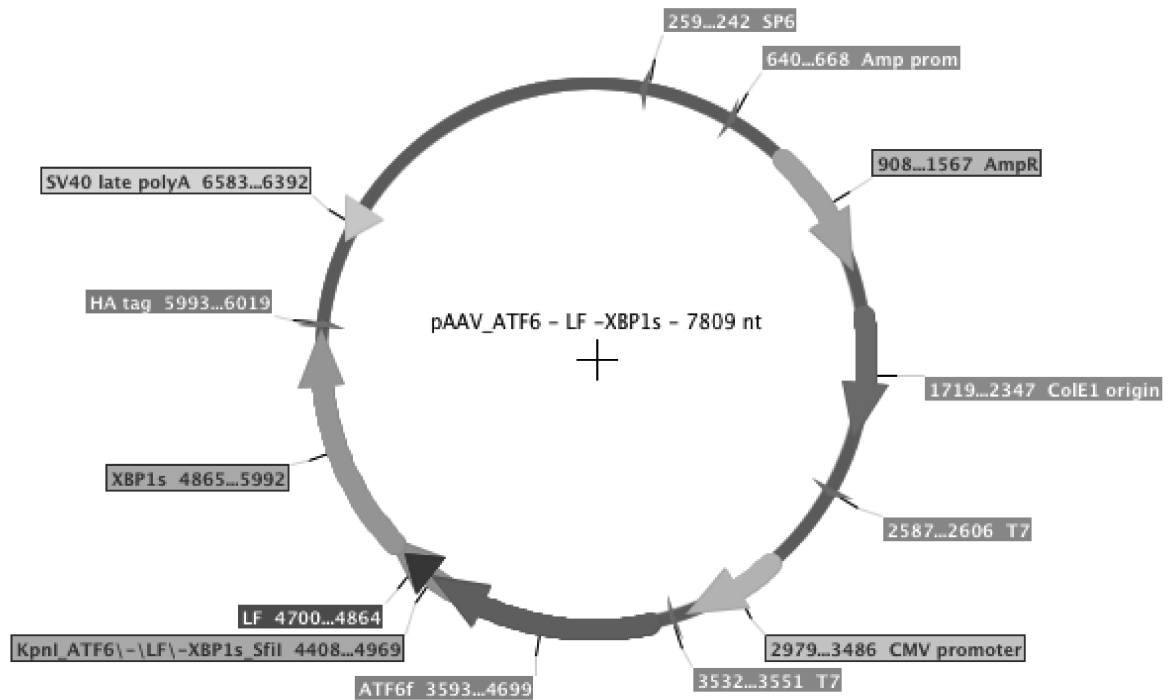


Figure 7/17

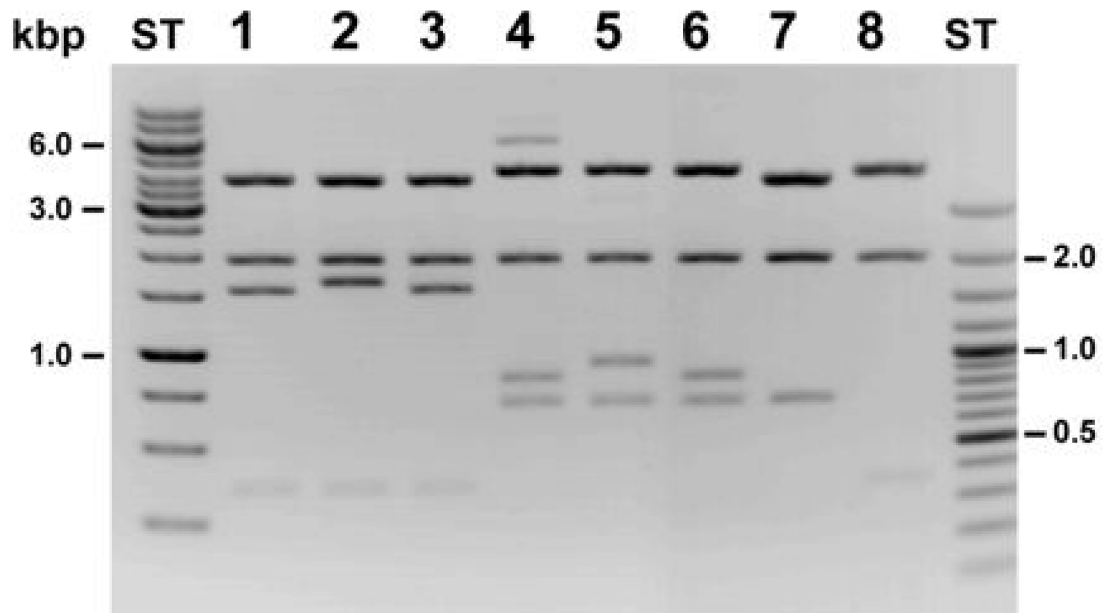


Figure 8/17

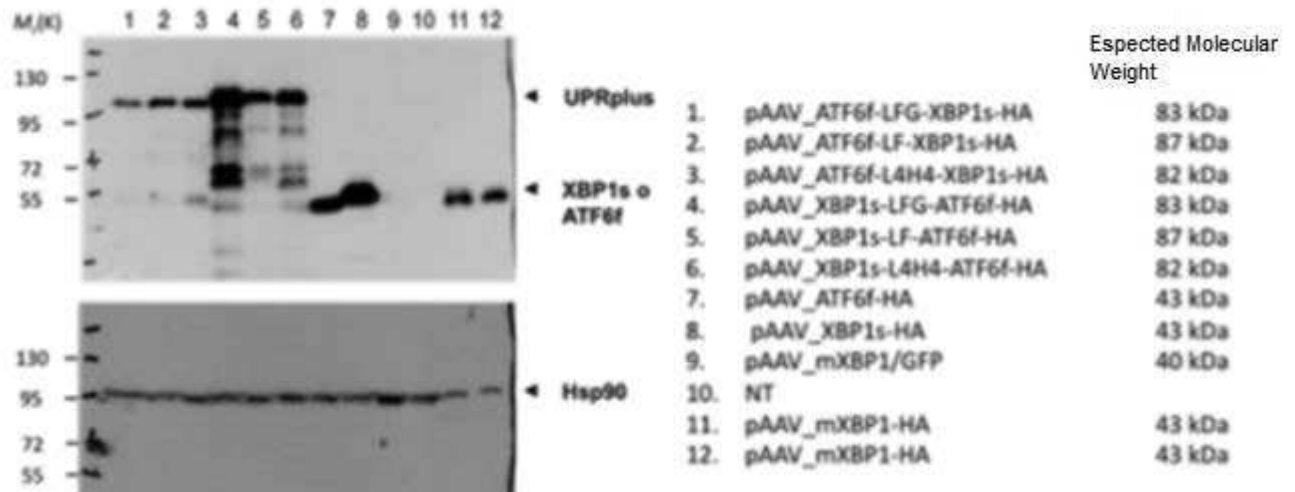


Figure 9/17

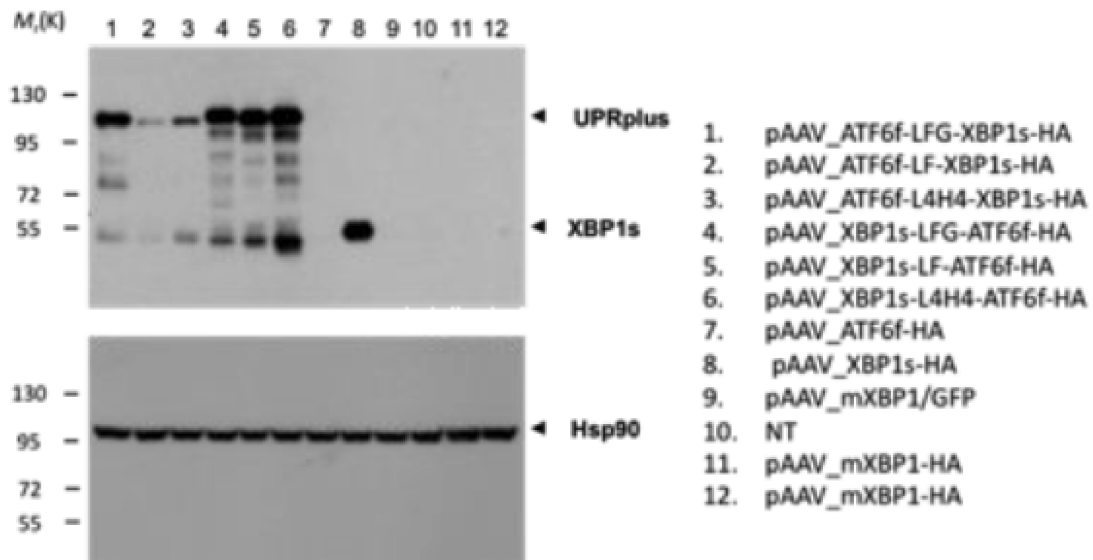


Figure 10/17

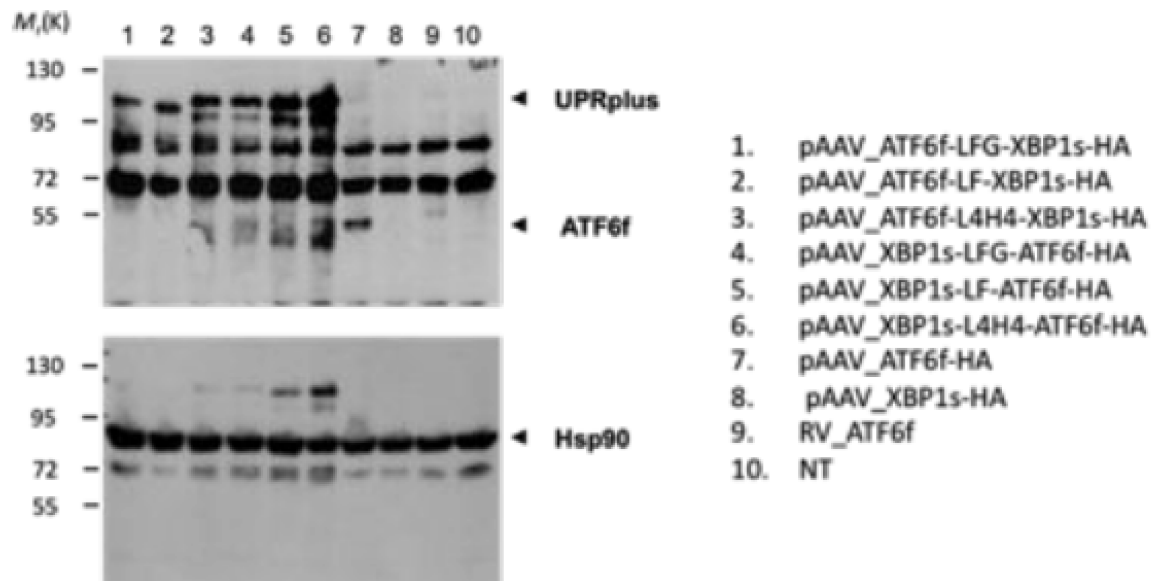


Figure 11/17

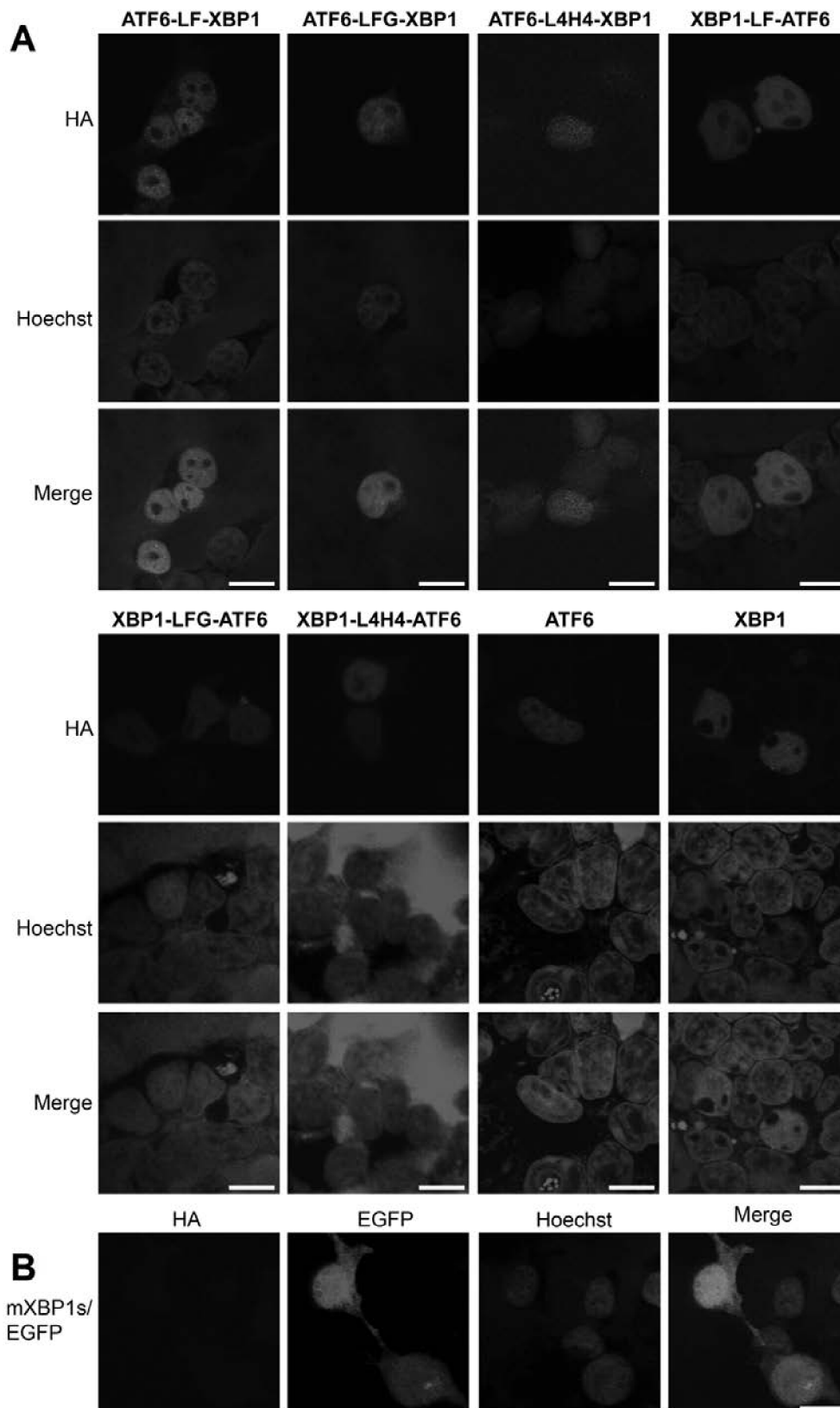


Figure 12/17

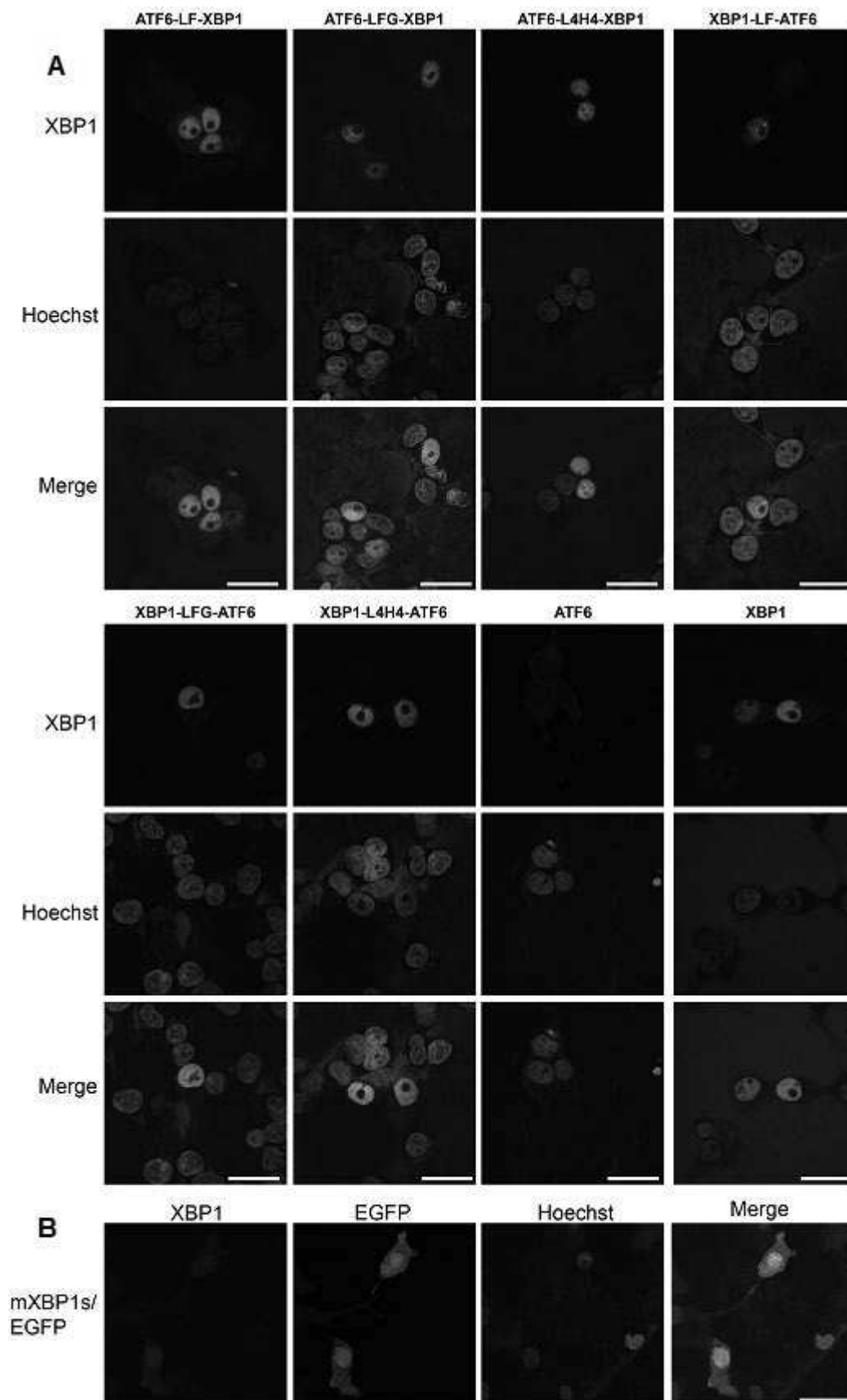


Figure 13/17

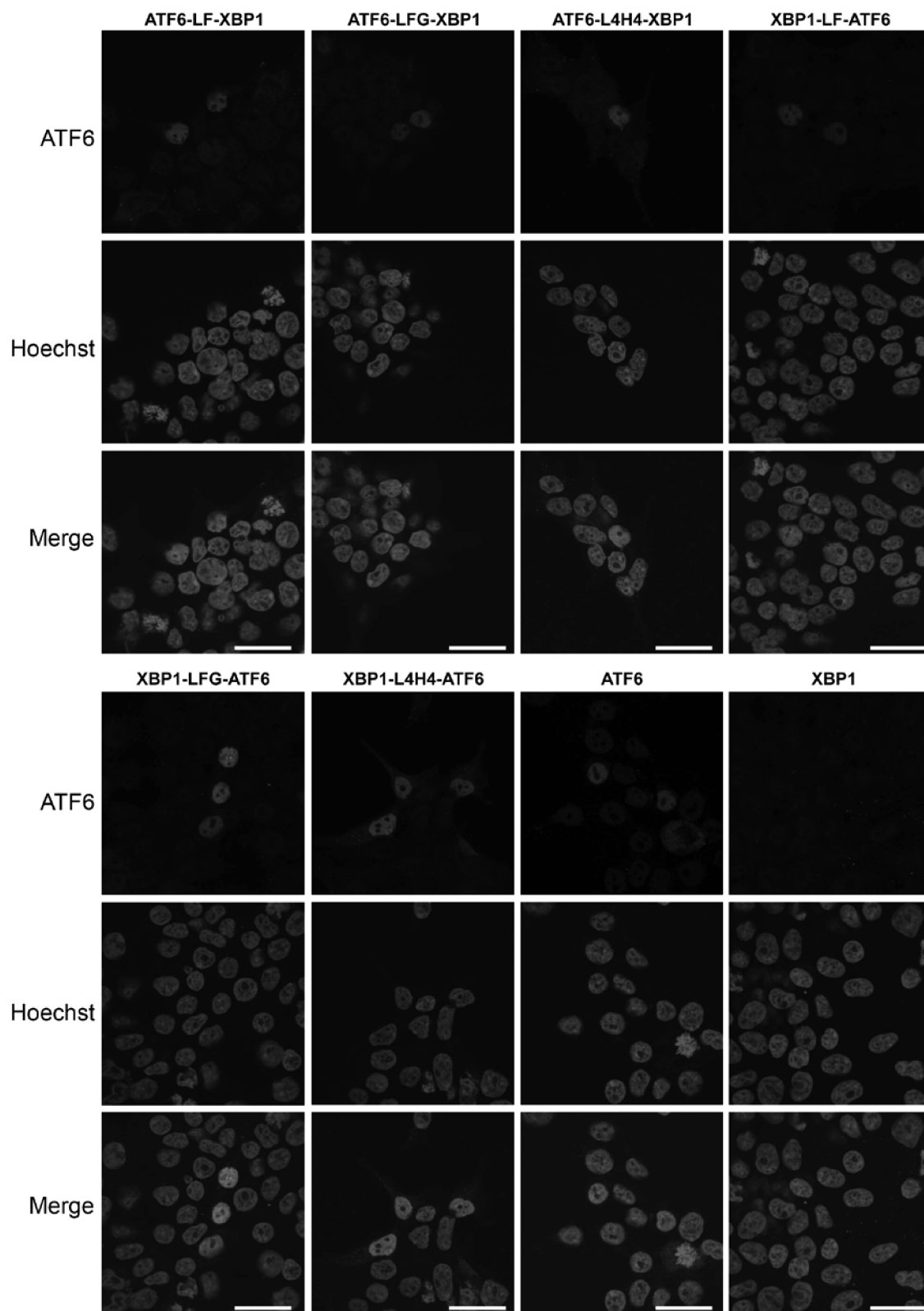
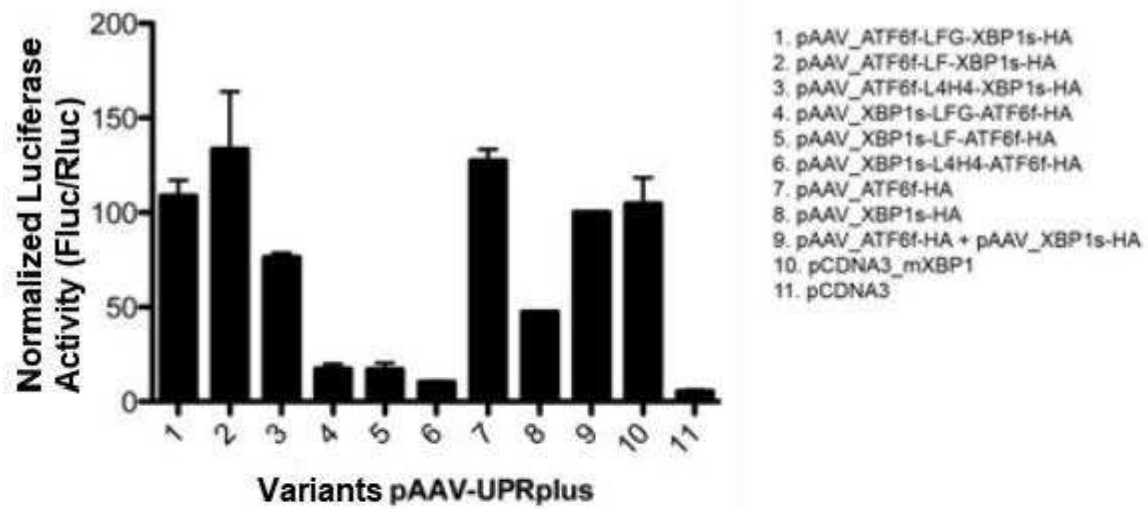


Figure 14/17



Plasmid	Experiment 1	Experiment 2	Experiment 3	Average	ESM
pAAV_ATF6f-LFG-XBP1s-HA	101,1517	99,62383	125,4241	108,73321	6,357091867
pAAV_ATF6f-LF-XBP1s-HA	88,52831	119,747	191,8758	133,3837033	30,60308089
pAAV_ATF6f-L4H4-XBP1s-HA	79,35313	77,71852	71,44357	76,17174	2,410717813
pAAV_XBP1s-LFG-ATF6f-HA	17,81713	12,53527	21,4335	17,26196667	2,583652391
pAAV_XBP1s-LF-ATF6f-HA	15,62922	11,8496	23,48904	16,98928667	3,428142203
pAAV_XBP1s-L4H4-ATF6f-HA	9,228968	11,24907	10,3266	10,26821267	0,583883502
pAAV_ATF6f-HA	120,188	122,1534	139,6209	127,3207667	6,17618165
pAAV_XBP1s-HA	47,8104	47,95798	46,66553	47,47797	0,408447887
pAAV_ATF6f-HA + pAAV_XBP1s-HA	100	100	100	100	0
pCDNA3_mXBP1	77,29633	120,5979	116,0251	104,6397767	13,73530344
pCDNA3	4,874095	6,953351	4,208801	5,345415667	0,826588582

Figure 15/17

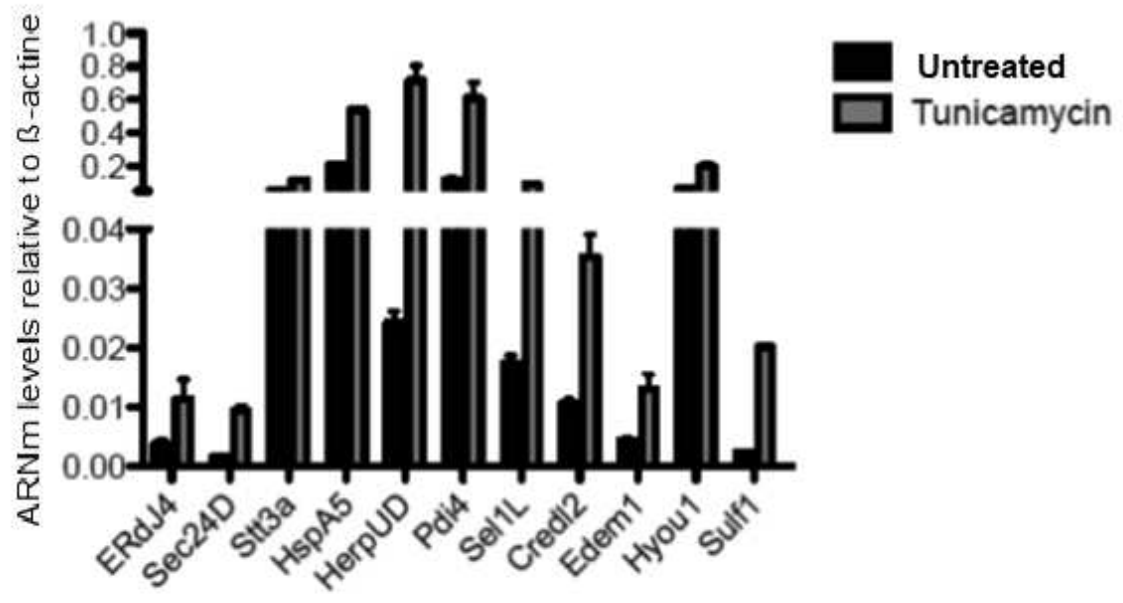


Figure 16/17

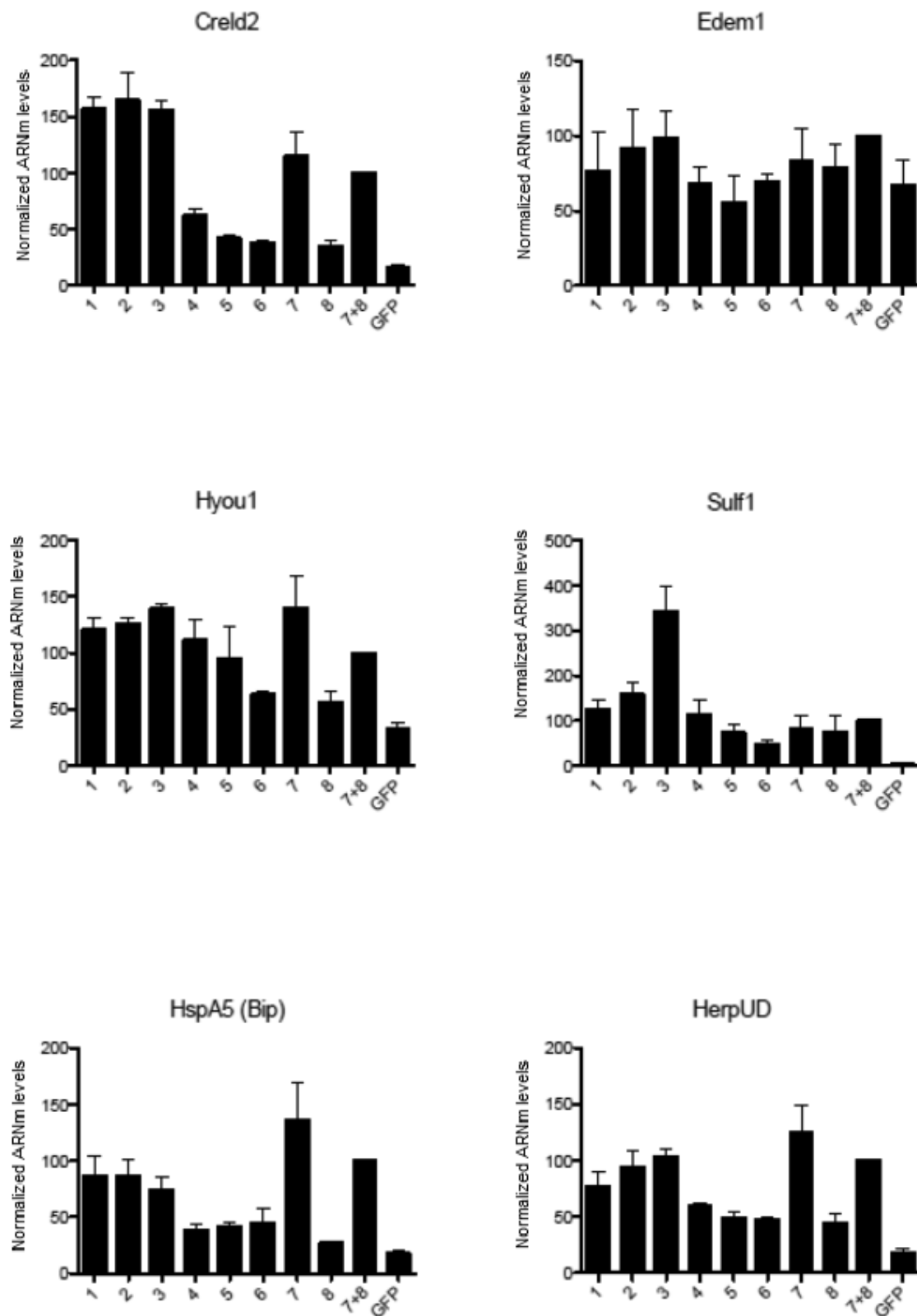
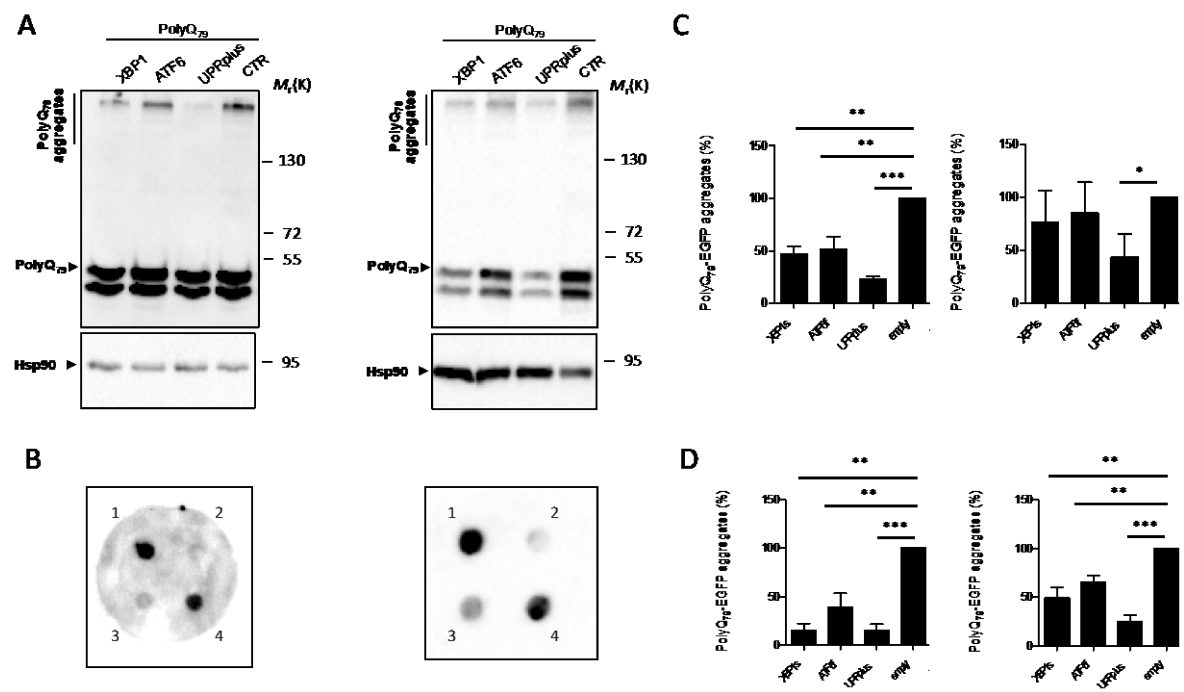


Figure 17/17



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