

NUCLEIC ACID-BASED REGULATION OF THE MOTOR END PLATE

DESCRIPTION

- 5 The invention relates to the field of biotechnology and genetic therapy, specifically within the areas of gene therapy, neuromuscular modulation, and recombinant protein expression.

The invention relates to a nucleic acid molecule for modulating neuromuscular transmission, the nucleic acid molecule comprising a sequence encoding one or more receptors of the motor end plate or fragments thereof.

- 10 The invention further relates to a nucleic acid vector comprising a nucleic acid molecule according to the present invention, wherein the vector is a viral vector, such as a lentiviral vector or retroviral vector, a transposon, an RNA vector, or a nanoparticle, such as a lipid nanoparticle, a liposome, or a polyethylenimine (PEI).

- The invention relates to a fusion protein, preferably comprising one or more features of any one or more of the preceding claims, said fusion protein comprising a receptor of the motor end plate and/or fragments thereof, wherein said receptor of the motor end plate is an acetylcholine receptor (AChR), a muscle-specific receptor tyrosine kinase (MuSK), and/or a glutamate receptor, and/or fragments thereof, and/or a neurotoxin, wherein the neurotoxin is a botulinum toxin (BoNT) and/or a tetanus toxin.

- 20 The invention relates to an *in vitro* method for modulating neuromuscular transmission, the *in vitro* method comprising transfecting a eukaryotic cell with a nucleic acid molecule according to the present invention.

The invention relates to a genetically modified cell comprising the nucleic acid molecule, a vector, or a fusion protein according to the present invention.

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BACKGROUND OF THE INVENTION

- Neurotoxins are a class of biologically active molecules that disrupt neuronal signaling by targeting critical components of synaptic transmission. Among these, botulinum neurotoxin (BoNT) and tetanus toxin (TeNT) are structurally related clostridial neurotoxins that exert their effects through
- 30 proteolytic cleavage of SNARE proteins, which are essential for synaptic vesicle fusion and neurotransmitter release. While BoNT primarily inhibits acetylcholine release at the neuromuscular junction, inducing localized muscle paralysis, TeNT is retrogradely transported within motor neurons to the central nervous system, where it blocks inhibitory neurotransmission, resulting in spastic paralysis. Despite their shared mechanism of SNARE protein cleavage, their functional outcomes
- 35 differ significantly: BoNT has been widely adopted for therapeutic applications, including the treatment of spasticity, dystonia, hyperhidrosis, and aesthetic medicine, whereas TeNT remains primarily associated with the pathological condition of tetanus infection. The therapeutic efficacy of BoNT arises from its ability to transiently inhibit presynaptic neurotransmitter release at the motor

endplate, leading to muscle paralysis. This is achieved through the cleavage of SNARE proteins, which prevents synaptic vesicle fusion and acetylcholine release, rendering acetylcholine receptors (AChRs) at the neuromuscular junction inactive and thereby inhibiting muscle contraction.

5 Receptors at the motor end plate play a fundamental role in neuromuscular transmission by mediating the conversion of neuronal signals into muscle activation. These receptors are localized within the postsynaptic membrane of the neuromuscular junction, where they regulate synaptic signaling and ensure precise muscle control.

10 The nicotinic acetylcholine receptor (AChR) is a transmembrane receptor expressed in neuronal and muscle cells, where it facilitates synaptic transmission of impulses from motor neurons to muscle fibers. Activation of AChR requires binding two acetylcholine (ACh) molecules, opening its ion channel, and subsequent depolarization of the muscle cell membrane. Structurally, the AChR comprises five subunits, the composition of which varies between developmental stages. The fetal isoform consists of two $\alpha 1$, one $\beta 1$, one γ , and one δ subunit, whereas the adult isoform replaces the γ -subunit with the ϵ -subunit. The fetal isoform exhibits uniform distribution across the sarcolemma, 15 while the adult isoform is concentrated at the neuromuscular junction.

Muscle-specific receptor tyrosine kinase (MuSK) plays a critical role in synapse formation and maintenance at the neuromuscular junction. MuSK comprises three extracellular immunoglobulin-like (Ig-like) domains, a cysteine-rich frizzled-like domain, and an intracellular tyrosine kinase domain, all essential for neuromuscular signaling and synaptic integrity.

20 Neurotoxins such as BoNT and TeNT disrupt this finely tuned system by targeting the presynaptic release of neurotransmitters. BoNT inhibits acetylcholine release at the neuromuscular junction, leading to localized muscle paralysis, which is therapeutically utilized for conditions such as spasticity and dystonia. In contrast, TeNT is transported retrogradely into the central nervous system, where it blocks inhibitory neurotransmission, causing uncontrolled muscle contractions and 25 spastic paralysis.

In light of the prior art, there is an unmet need for developing an approach that enables prolonged and localized BoNT-mediated neuromuscular inhibition while minimizing systemic toxicity, immunogenicity, and the need for frequent administration. Current treatment strategies rely on repeated BoNT injections, associated with dose-dependent diffusion beyond the intended site of 30 action, increasing the risk of adverse effects and reducing treatment efficacy over time. Additionally, repeated exposure to BoNT can lead to the development of immunoresistance, limiting its long-term therapeutic potential. Therefore, there is a critical need for an improved method that ensures sustained, targeted delivery of BoNT or related neurotoxic agents, thereby enhancing treatment efficacy, reducing patient burden, and mitigating systemic side effects.

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SUMMARY OF THE INVENTION

In light of the prior art, the technical problem underlying the invention was providing alternative or improved means for an approach for modulating neuromuscular transmission at the motor end plate. The present invention seeks to provide such means while avoiding the disadvantages known in the 40 prior art.

A further objective of the invention was to provide alternative or improved means to mitigate the risk of overdose associated with prolonged or excessive expression of a neurotoxin, which may lead to systemic adverse effects.

5 A further objective of the invention was to provide alternative or improved means for specific localized modification of synaptic function at the site of action.

A further objective of the invention was to provide alternative or improved means for reducing the risk of side effects due to neurotoxin treatments.

A further objective of the invention was to provide alternative or improved means for precise control mechanisms for BoNT or TeNT expression.

10 A further objective of the invention was to provide alternative or improved means for the treatment or prevention of autoimmune conditions, spasticity, dystonia, hyperhidrosis, and/or aesthetic medicine.

These problems are solved by the features of the independent claims. Preferred embodiments of the present invention are provided by the dependent claims.

15 The present invention, in one aspect, relates to a nucleic acid molecule for modulating neuromuscular transmission, the nucleic acid molecule comprising a sequence encoding one or more receptors of the motor end plate or fragments thereof.

The present invention is derived from advancements in botulinum neurotoxin (BoNT) gene therapy, as disclosed in U.S. Patent No. 11,707,510 B2. One objective of the invention is to mitigate the risk of overdose associated with prolonged or excessive expression of the BoNT or tetanus toxin (TeNT) protein, which may lead to systemic adverse effects. Although the therapeutic window for BoNT or TeNT gene therapy is significantly broader than that of currently approved BoNT or TeNT formulations, uncontrolled or excessive expression presents a potential risk of overdose. For regulatory approval as a pharmaceutical product, it is essential to minimize patient risk to the greatest extent possible by implementing precise control mechanisms for BoNT or TeNT expression.

25 BoNT is widely recognized for its application in aesthetic medicine, yet its critical role in treating spasticity, dystonia, and hyperhidrosis is less well known. Its mechanism of action involves inhibiting neurotransmission at the presynaptic motor endplate, leading to muscle paralysis. However, BoNT is among the most potent toxins known, with lethal doses as low as 1 mg. The duration of its effect depends on the dose and BoNT serotype used (typically BoNT/A). In clinical applications requiring long-lasting effects, higher doses are administered. However, conventional BoNT therapy, delivered in solution, increases systemic exposure and associated risks, including severe side effects and the potential for the patient to develop BoNT immunity over repeated treatments. Hence, targeted gene delivery methods are particularly advantageous in enhancing the duration of BoNT effects while minimizing systemic toxicity.

35 The present invention offers several distinct advantages in modulating neuromuscular transmission through the use of a nucleic acid molecule encoding one or more receptors of the motor end plate or functional fragments thereof. By enabling targeted expression at the neuromuscular junction, systemic side effects can be reduced, thereby enhancing therapeutic specificity and reducing off-target effects. Furthermore, compared to conventional protein-based therapies, the nucleic acid-

based approach allows for improved dosage control and a broader therapeutic window, as expression levels can be finely regulated at the transcriptional or translational level. Additionally, the sustained expression of therapeutic proteins at the motor end plate can extend the duration of therapeutic effects, reducing the need for frequent administrations and improving patient
5 compliance. Collectively, these advantages position the invention as a highly effective and precise strategy for modulating synaptic transmission at the neuromuscular junction.

In embodiments, the receptor of the motor end plate is an acetylcholine receptor (AChR), preferably a nicotinic acetylcholine receptor (nAChR) or fragments thereof.

The nAChR is particularly advantageous for use in this context due to its specialized structure, high
10 density, and essential function at the motor end plate. As the predominant receptor in this region, nAChR is strategically positioned within the deep folds of the muscle cell membrane, which are designed to maximize surface area and optimize receptor availability for neuromuscular transmission. The exceptionally high density of nAChRs at the crests of these folds ensures efficient signal transduction, as millions of receptors are present at each motor end plate, facilitating rapid
15 and robust communication between motor neurons and muscle fibers. Moreover, nAChRs play a critical role in muscle contraction by mediating the effects of acetylcholine, the primary neurotransmitter at the neuromuscular junction. NACHRs initiate a signaling cascade that activates muscle upon acetylcholine binding, underscoring their fundamental importance in neuromuscular function. These characteristics make nAChRs an ideal target for modulating synaptic transmission in
20 therapeutic applications.

In embodiments, the receptor of the motor end plate comprises at least one subunit of the acetylcholine receptor (AChR), preferably an alpha, a beta, a gamma, a delta, and/or an epsilon (ϵ) subunit, more preferably an epsilon subunit.

In a preferred embodiment, the nucleic acid molecule comprises at least one subunit of the AChR. In
25 a preferred embodiment, the nucleic acid molecule comprises at least one epsilon (ϵ) subunit of the AChR. In a further embodiment, the nucleic acid molecule comprises an AChR transmembrane domain of the epsilon (ϵ) subunit. In a further embodiment, the nucleic acid molecule comprises an AChR transmembrane domain of the epsilon (ϵ) subunit that lacks functional AChR activity.

The use of nucleic acids encoding proteins with acetylcholine receptor (AChR) transmembrane
30 domains of the epsilon (ϵ) subunit, but lacking functional receptor activity, particularly provides a novel and inventive competitive inhibition strategy to modulate neuromuscular transmission. By competing with endogenous functional AChRs at the motor end plate, these non-functional receptor variants effectively reduce the number of active AChRs, thereby diminishing synaptic signaling and leading to controlled inhibition of muscle activation.

35 However, also other receptors of the motor end plate may be applicable in this context, such as MuSK or glutamate receptor.

In embodiments, the receptor of the motor end plate is a muscle-specific receptor tyrosine kinase (MuSK) and/or a glutamate receptor or fragments thereof.

In a preferred embodiment, the receptor of the motor end plate is a muscle-specific receptor tyrosine kinase (MuSK) or fragments thereof. In embodiments, the transmembrane domain of MuSK localizes the encoded proteins to the membrane.

In the present invention, MuSK offers significant advantages in modulating neuromuscular transmission through the nucleic acid molecule or the present invention. MuSK is endogenously and specifically expressed in the postsynaptic membrane of the neuromuscular junction, ensuring that its encoded sequence directs precise and localized expression. This specificity makes MuSK an ideal genetic target for interventions to regulate synaptic function, as it plays a central role in neuromuscular synapse formation, maintenance, and signaling.

- 5 Incorporating a MuSK-encoding sequence within the nucleic acid molecule allows for targeted modulation of motor endplate activity, either by enhancing or inhibiting neuromuscular transmission as needed for therapeutic or cosmetic applications. Furthermore, MuSK's transmembrane domain can be leveraged to ensure the membrane localization of encoded proteins, providing structural anchoring within the synapse. This is particularly advantageous in applications where precise receptor positioning is necessary to influence neurotransmission dynamics. Additionally, the Ig-like extracellular domains of MuSK, encoded within the nucleic acid sequence, contribute to synaptic stability and can facilitate interactions with other synaptic components, further enhancing the efficacy of neuromodulatory interventions. Hence, in one embodiment, the nucleic acid molecule comprises a sequence encoding an Ig-like extracellular domain of MuSK.
- 15 By encoding MuSK or its functional domains, the nucleic acid molecule enables the targeted expression of neuromuscular receptors while minimizing off-target effects. This gene-based approach provides a versatile platform for regulating acetylcholine receptor clustering, synapse stability, and signal transduction at the motor endplate, which are critical factors in conditions affecting neuromuscular function. Consequently, the inclusion of MuSK-encoding sequences in the present invention represents a highly precise, receptor-specific strategy for neuromodulatory therapy, allowing for controlled modulation of synaptic activity in both clinical and aesthetic applications.
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In embodiments, the nucleic acid molecule is a DNA or RNA molecule.

In embodiments, the nucleic acid molecule is an mRNA molecule.

- 30 Advantageously, DNA-based approaches enable long-term and sustained expression of the therapeutic protein, as DNA can be stably integrated into the host genome or persist as an episome, reducing the need for repeated administrations. This prolonged expression enhances therapeutic efficacy while improving patient compliance. RNA-based approaches, particularly messenger RNA (mRNA), offer the advantage of transient expression without the risk of genomic integration, making them a safer alternative for precise, controlled therapeutic delivery. Additionally, mRNA therapies can bypass transcriptional regulation, allowing for rapid protein synthesis and immediate therapeutic effects. Advantageously, both DNA and RNA molecules can be designed for targeted expression, ensuring high specificity at the neuromuscular junction while minimizing systemic side effects. Furthermore, advancements in nucleic acid delivery systems, such as lipid nanoparticles and viral vectors, enhance these molecules' stability and cellular uptake, further optimizing their therapeutic potential.
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In embodiments, the nucleic acid molecule comprises a sequence encoding a neurotoxin.

In embodiments, the neurotoxin is a botulinum toxin (BoNT) and/or a tetanus toxin (TeNT).

5 In embodiments, the nucleic acid molecule comprises a sequence encoding a botulinum toxin (BoNT). In embodiments, the nucleic acid molecule comprises a sequence encoding a tetanus toxin (TeNT). In embodiments, the nucleic acid molecule comprising a sequence encoding a neurotoxin, such as BoNT or TeNT, enables neuromuscular modulation. In embodiments, the nucleic acid molecule comprising a sequence encoding a neurotoxin, such as BoNT or TeNT, enables expression of the neurotoxin at the neuromuscular junction.

10 By encoding a neurotoxin such as BoNT or TeNT, the nucleic acid molecule advantageously enables targeted, localized expression of the toxin at the neuromuscular junction, reducing the need for direct protein administration and thereby minimizing systemic distribution and associated side effects. This approach allows for controlled and sustained neurotoxin production, enhancing therapeutic longevity and reducing the frequency of treatments. Additionally, leveraging the cell's translational machinery ensures efficient and regulated synthesis of the neurotoxin at the intended
15 site of action, improving safety and efficacy. Furthermore, nucleic acid-based delivery circumvents direct protein administration's stability and storage challenges, offering a more robust and scalable therapeutic solution. This strategy is particularly beneficial for conditions requiring precise neuromuscular modulation, such as spasticity disorders, dystonias, or chronic pain management.

20 In embodiments, the nucleic acid molecule comprises a sequence encoding scaffold/matrix attachment region (S/MAR) elements. In embodiments, the nucleic acid molecule comprises a sequence encoding a neurotoxin, such as BoNT or TeNT, and scaffold/matrix attachment region (S/MAR) elements.

The administration of nucleic acids encoding recombinant BoNT or TeNT at the target site offers significant advantages, including higher localized concentrations and prolonged therapeutic effects.
25 By incorporating scaffold/matrix attachment region (S/MAR) elements, it is possible to sustain BoNT or TeNT expression, as well as the expression of shRNA, over extended periods, potentially lasting several weeks. This prolonged-expression represents a key advantage over conventional BoNT or TeNT protein administration, which requires repeated injections.

30 To effectively replace protein-based BoNT or TeNT therapy with nucleic acid-based approaches, the distribution of the therapeutic effect must closely mimic that achieved by traditional BoNT or TeNT injections. Clinicians administering BoNT or TeNT injections have developed extensive expertise in selecting precise injection sites and volumes to achieve optimal therapeutic outcomes. However, nucleic acids exhibit fundamentally different diffusion properties compared to proteins. Unlike BoNT or TeNT protein, which readily diffuses in tissue, naked nucleic acids tend to remain localized at the
35 injection site, limiting their spread and overall efficacy.

This challenge can be mitigated through the use of transfection-enhancing vectors that not only improve cellular uptake but also facilitate broader distribution within the target tissue (see below). Various particulate formulations, including liposomes, lipid nanoparticles (LNPs), polyethyleneimine (PEI) particles, and viral vectors, can be employed to enhance nucleic acid delivery. However, these
40 vectors may also increase the risk of off-target transfection, potentially affecting non-target tissues.

For instance, certain LNP formulations exhibit significant tropism for organs such as the liver, spleen, and adjacent lymph nodes following intramuscular administration, raising concerns about unintended systemic effects.

In embodiments, the nucleic acid molecule comprises a sequence encoding a promoter. In
5 embodiments, the nucleic acid molecule comprises a sequence encoding a neurotoxin, such as BoNT or TeNT, scaffold/matrix attachment region (S/MAR) elements, and a promoter.

The use of tissue-specific promoters is a critical strategy to further refine the specificity of nucleic acid-based BoNT or TeNT therapy and mitigate off-target expression. By restricting gene expression to the intended target cells, such promoters ensure that the therapeutic effects remain localized,
10 reducing the likelihood of adverse systemic effects. This approach enhances the safety and efficacy of nucleic acid-based BoNT or TeNT treatments, making them a viable alternative to conventional BoNT or TeNT protein therapy.

In embodiments, the nucleic acid molecule comprises a sequence encoding an antibody.

This approach can effectively neutralize pathological immune responses by encoding an antibody
15 that targets harmful molecules, such as autoantibodies against the AChR. For instance, antibodies designed to bind the Fc region of immunoglobulins or proteins like Protein A can sterically hinder the binding of autoantibodies to AChR, thereby preserving acetylcholine binding and restoring normal neuromuscular transmission. This targeted mechanism offers a highly specific and localized therapeutic effect, minimizing systemic immunosuppression and associated risks. Additionally, the
20 sustained *in vivo* production of therapeutic antibodies through nucleic acid expression reduces the need for repeated antibody administrations, improving patient compliance and treatment efficiency. Another advantage is the potential development of chimeric AChRs that remain functionally active while evading autoantibody recognition, further expanding treatment options.

Another notable advantage is the ability to engineer highly specific antibodies tailored to recognize
25 and neutralize particular pathogenic targets, offering a level of precision that is difficult to achieve with traditional small-molecule drugs or protein therapies. This specificity reduces off-target effects and enhances therapeutic safety. Furthermore, nucleic acid-based antibody production can be easily scaled up, offering a cost-effective and efficient means of generating large quantities of therapeutic antibodies without the complexities associated with traditional antibody manufacturing processes.
30 Another advantage is the flexibility in designing antibodies with enhanced properties, such as increased affinity or reduced immunogenicity, which can improve the treatment's efficacy and safety profile. Additionally, with the potential to encode antibodies directly within the patient's cells, this approach circumvents the need for frequent intravenous administration, thus improving patient compliance and allowing for sustained therapeutic effects over time.

35 In embodiments, the nucleic acid molecule comprises a sequence encoding an siRNA and/or shRNA.

Including a sequence encoding small interfering RNA (siRNA) or short hairpin RNA (shRNA) within the nucleic acid molecule offers significant therapeutic advantages, particularly in neuromuscular modulation using fusion proteins containing neurotoxins. siRNA and shRNA function by triggering
40 RNA interference (RNAi), a natural cellular mechanism that selectively silences specific target genes

at the post-transcriptional level. This gene-silencing capability can enhance the efficacy and specificity of BoNT- or TeNT-based treatments by downregulating genes involved in synaptic recovery, neurotransmitter release, or immune response pathways. For instance, siRNA or shRNA can be designed to suppress SNARE complex proteins that facilitate synaptic vesicle fusion, prolonging the neurotoxic effect and reducing the need for frequent re-administration. Additionally, RNAi elements can be used to target immune-modulatory genes, lowering the risk of the host developing antibodies against BoNT or TeNT, which is a major limitation of repeated neurotoxin treatments. Furthermore, by selectively silencing pro-apoptotic or inflammatory genes, siRNA/shRNA can help minimize off-target toxicity and adverse immune reactions, ensuring a more controlled and localized therapeutic effect. The integration of an siRNA- or shRNA-encoding sequence into the nucleic acid molecule thus represents an advantageous strategy for increasing treatment duration, reducing systemic side effects, and overcoming immunogenicity-related challenges, ultimately enhancing the overall therapeutic potential of neurotoxin-based interventions.

Additionally, incorporating short hairpin RNA (shRNA) sequences targeting AChR expression enables a gene-silencing approach that reduces AChR levels, resulting in a corresponding decrease in neuromuscular signal transduction. This controlled downregulation of AChR expression facilitates precise muscle relaxation, making it a highly adaptable therapeutic strategy for conditions involving excessive or involuntary muscle contractions, such as spasticity, dystonia, or hypertonia. The combinatorial use of various siRNA or shRNA molecules allows for fine-tuned regulation of muscle activity, enabling customized therapeutic effects ranging from mild relaxation to complete muscle paralysis. This flexibility makes the approach suitable for both temporary and long-term neuromodulation, offering advantages over traditional pharmacological treatments by providing localized, sustained, and adjustable muscle inhibition while minimizing systemic side effects.

The use of siRNA presents a particularly advantageous strategy for selectively downregulating endogenous AChR expression while simultaneously enhancing the transgenic expression of a modified AChR. This dual mechanism allows for the targeted replacement of the native receptor with a functionally optimized version at the neuromuscular end plate. By silencing the endogenous AChR through RNA interference, cellular machinery prioritizes the expression and incorporation of the modified receptor, ensuring its efficient integration into the synaptic membrane. This approach facilitates precise neuromodulation and enables the development of customized receptor variants with improved functional properties, such as enhanced stability, reduced autoantibody binding in autoimmune disorders like Myasthenia gravis, or optimized neurotransmission for therapeutic and cosmetic applications. The ability to selectively modulate receptor composition at the motor end plate further enhances the therapeutic specificity of this strategy, minimizing off-target effects while achieving sustained and controlled neuromuscular regulation.

In one embodiment, neuromuscular transmission is inhibited through downregulation of a receptor of the motor end plate. In one embodiment, neuromuscular transmission is inhibited through downregulation of AChR or MuSK expression.

In a further embodiment, the present invention leverages RNA interference to downregulate the expression of AChR or MuSK, thereby inhibiting neuromuscular transmission. This can be achieved through direct transfection with siRNA or by introducing a vector encoding shRNA. The use of siRNA presents several advantages, including a broader range of transfection methods, such as adeno-

associated virus (AAV)-mediated delivery or iontophoresis (e.g., US20110038937A1, Kigasawa et al., Int Journ Pharmac, 2010, Hasan et al., Journ Contr Rel, 2022). These techniques are well-known in the art, and a person skilled in the art is capable of choosing the appropriate method. Additionally, siRNA reduces the risk of an immune response against the therapeutic protein.

- 5 Furthermore, RNAi can facilitate the downregulation of endogenous receptor expression while simultaneously enabling the expression of a modified receptor, which is particularly beneficial for treating neuromuscular disorders such as myasthenia gravis. For BoNT therapy, RNAi-mediated downregulation of AChR presents a viable alternative approach. However, given that BoNT exerts its effect within presynaptic neurons and has a prolonged duration of action, RNAi may not be suitable for all indications, such as neuropathic pain. DNA-encoded shRNA can be employed to extend the therapeutic effect, allowing for prolonged receptor downregulation.

In embodiments, the nucleic acid molecule comprises a sequence encoding a linker.

- In embodiments, the nucleic acid molecule comprises a sequence encoding one or more linker(s). In embodiments, the the nucleic acid molecule comprises a sequence according to SEQ ID NO. 9
15 encoding a linker. In embodiments, the nucleic acid molecule comprises a sequence encoding 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 linker(s), preferably 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 linker(s).

Additional DNA plasmids were constructed to enhance the efficacy of BoNT- or TeNT-mediated effects, incorporating modifications to the linker sequences.

- 20 In one embodiment of the plasmid construct, a single GGGGS linker was replaced by an eightfold linker, thus increasing the flexibility and spatial separation of the linked domains.

In another embodiment, the GGGGS linker was substituted with a quintuple repeat of a human immunoglobulin G (IgG) hinge region, which is known to provide structural stability and flexibility.

- In a further embodiment, a quadruple linker is followed by a thrombin cleavage site,
25 enabling proteolytic processing under specific conditions.

Surprisingly, these modifications were found to result in a significant improvement in BoNT-induced paralysis, demonstrating that linker extension and structural optimization contribute to the enhanced functional activity of the expressed fusion proteins.

- The invention further provides a highly localized and targeted modification of synaptic function,
30 ensuring that therapeutic effects are confined strictly to the treated muscles. This targeted approach significantly reduces the risk of systemic side effects, as the modified protein is primarily expressed within the synaptic cleft, preventing unintended diffusion into surrounding tissues. Furthermore, the invention offers a precise and self-regulating dosing mechanism due to the restricted expression of recombinant proteins at the motor end plate. Because the number of recombinant proteins
35 integrated into the sarcolemma is inherently limited, any excess proteins that are not incorporated into the membrane are rapidly degraded by the proteasomal system within the cytosol. This is particularly advantageous for the expression of potent therapeutic proteins such as BoNT or TeNT, where conventional dosing of recombinant proteins is difficult to control. The invention substantially increases the therapeutic window by restricting expression to the neuromuscular junction, providing

a significantly higher safety margin than direct protein administration. In the case of BoNT- or TeNT-fusion proteins, as outlined below, this approach enables a minimum fivefold increase in the therapeutic range, surpassing any previously established delivery systems. Such a controlled and localized expression strategy represents a breakthrough in neuromuscular modulation, offering
5 unparalleled precision, efficacy, and safety in therapeutic applications.

In one aspect, the present invention relates to a nucleic acid vector comprising a nucleic acid molecule according to the present invention, wherein the vector a viral vector, such as a lentiviral vector or retroviral vector, a transposon, an RNA vector, or a nanoparticle, such as a lipid nanoparticle, a liposome, or a polyethylenimine (PEI).

10 In embodiments, the nucleic acid molecule comprises a sequence according to SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8 or SEQ ID NO. 9, or a sequence of at least 70%, 80%, 90% or 95% sequence identity thereto.

In embodiments, the disclosed constructs may encode a fusion protein comprising at least the transmembrane domain of either the epsilon-subunit (M2) of the acetylcholine receptor (AChR) or
15 the transmembrane domain of muscle-specific kinase (MuSK). In one embodiment, said transmembrane domain is operably linked to a functional protein capable of modulating presynaptic nerve cell activity. Such functional proteins may include, but are not limited to, BoNT or TeNT, which exert neurotoxic effects on presynaptic neurons, or an antibody that specifically binds to synaptically active structures, such as acetylcholine. Through such binding, the antibody may either inhibit the
20 biological activity of the target molecule or facilitate its accumulation at the synapse, thereby modulating neurotransmission.

In one aspect, the present invention relates to a fusion protein, preferably comprising one or more features of the present invention, said fusion protein comprising:

- 25 a) a receptor of the motor end plate and/or fragments thereof, wherein said receptor of the motor end plate is an acetylcholine receptor (AChR), a muscle-specific receptor tyrosine kinase (MuSK), and/or a glutamate receptor, and/or fragments thereof, and/or
b) a neurotoxin, wherein the neurotoxin is a botulinum toxin (BoNT) and/or a tetanus toxin.

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- 30 a) a receptor of the motor end plate and/or fragments thereof, wherein said receptor of the motor end plate is an acetylcholine receptor (AChR), a muscle-specific receptor tyrosine kinase (MuSK), and/or a glutamate receptor, and/or fragments thereof, and/or
b) a neurotoxin, wherein the neurotoxin is a botulinum toxin (BoNT) and/or a tetanus toxin, and/or
35 c) a linker.

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- a) a receptor of the motor end plate and/or fragments thereof, wherein said receptor of the motor end plate is an acetylcholine receptor (AChR), a muscle-specific receptor tyrosine kinase (MuSK), and/or a glutamate receptor, and/or fragments thereof, and/or
 - b) a neurotoxin, wherein the neurotoxin is a botulinum toxin (BoNT) and/or a tetanus toxin, and/or
 - c) a linker, and/or
 - d) an siRNA or shRNA.

In one aspect, the present invention relates to a fusion protein, preferably comprising one or more features of the present invention, said fusion protein comprising:

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- a) a receptor of the motor end plate and/or fragments thereof, wherein said receptor of the motor end plate is an acetylcholine receptor (AChR), a muscle-specific receptor tyrosine kinase (MuSK), and/or a glutamate receptor, and/or fragments thereof, and/or
 - b) a neurotoxin, wherein the neurotoxin is a botulinum toxin (BoNT) and/or a tetanus toxin, and/or
 - 15 c) a linker, and/or
 - d) an siRNA or shRNA, and/or
 - e) scaffold/matrix attachment region (S/MAR) elements and/or
 - f) a promoter.

- 20
- In embodiments, the fusion protein comprises a sequence according to SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8 or SEQ ID NO. 9, or a sequence of at least 70%, 80%, 90% or 95% sequence identity thereto.

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- To mitigate the risk of BoNT or TeNT release, the BoNT or TeNT protein may be conjugated to a transmembrane domain via a linker sequence, thereby anchoring it to the cell membrane. However, the ubiquitous expression of BoNT or TeNT across the entire cellular membrane presents two principal drawbacks. First, BoNT or TeNT molecules displayed on the membrane surface may elicit an immunogenic response, potentially compromising therapeutic efficacy or triggering adverse immune reactions. Second, there exists a risk of unintended extracellular release of BoNT or TeNT, which could lead to off-target effects and reduced localization specificity. Accordingly, the strategy of restricting BoNT or TeNT expression specifically to the motor end plate has been devised to
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- circumvent these limitations, ensuring targeted functionality while minimizing immunogenicity and unintended diffusion.

- Hence, restricting BoNT or TeNT expression specifically to the motor end plate offers several significant advantages. Localizing BoNT to this precise anatomical site enhances targeted delivery and therapeutic efficacy while minimizing systemic exposure. This spatially controlled expression
- 35
- reduces the risk of immunogenic responses that may arise from widespread membrane presentation, thereby improving biocompatibility and reducing potential immune clearance. Furthermore, restricting BoNT or TeNT to the motor end plate advantageously mitigates the risk of unintended extracellular release, ensuring that the neurotoxin remains confined to its intended site of action. This localization also enhances safety by preventing off-target effects that could disrupt
- 40
- neuromuscular function in unintended areas. Collectively, these advantages optimize the therapeutic utility of BoNT or TeNT while addressing key challenges associated with its expression and delivery.

- In further embodiments, proteins that exert their effect within the synaptic cleft are fused, such as acetylcholinesterase, which catalyzes the hydrolysis of acetylcholine. This fusion results in a localized reduction of acetylcholine concentration at the receptor site, thereby diminishing or inhibiting neuromuscular transmission. Additionally, a decrease in excitatory signal transmission and a subsequent reduction in muscle tone can be achieved by expressing modified AChRs. These modified AChRs remain in a closed, non-functional conformation and compete with endogenous wild-type receptors for incorporation into the neuromuscular junction. By displacing functional wild-type receptors, the sensitivity of muscle cells to acetylcholine-mediated stimulation is effectively reduced, thereby modulating neuromuscular activity.

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Preferred sequences

SEQ ID No.	Sequence	Description
1	ATGCCCTTCGTGAACAAGCAGTTCAACTACAAGGACCCCGTGAACGGCGTG GACATCGCCTACATCAAGATCCCCAACGCCGCCAGATGCAGCCCGTGAAG GCCTTCAAGATCCACAACAGATCTGGGTGATCCCCGAGCGCGACACCTTC ACCAACCCCGAGGAGGGCGACCTGAACCCCCCCCCGAGGCCAAGCAGGTG CCCGTGAGCTACTACGACAGCACCTACCTGAGCACCACAACGAGAAGGAC AACTACCTGAAGGGCGTGACCAAGCTGTTCGAGCGCATCTACAGCACCGAC CTGGGCGCGATGCTGCTGACCAGCATCGTGCGCGGCATCCCCCTTCTGGGGC GGCAGCACCATCGACACCGAGCTGAAGGTGATCGACACCAACTGCATCAAC GTGATCCAGCCCGACGGCAGCTACCGCAGCGAGGAGCTGAACCTGGTGATC ATCGGCCCCAGCGCCGACATCATCCAGTTCGAGTGCAAGAGCTTCGGCCAC GAGGTGCTGAACCTGACCCGCAACGGCTACGGCAGCACCCAGTACATCCGC TTCAGCCCCGACTTCACCTTCGGCTTCGAGGAGAGCCTGGAGGTGGACACC AACCCCTGCTGGGCGCCGGCAAGTTCGCCACCGACCCCGCGTGACCCCTG GCCCAGAGCTGATCCACGCCGGCCACCGCCTGTACGGCATCGCCATCAAC CCCAACCGCGTGTTCAGGTGAACACCACGCCTACTACGAGATGAGCGGC CTGGAGGTGAGCTTCGAGGAGCTGCGCACCTTCGGCGGCCACGACGCCAAG TTCATCGACAGCCTGCAGGAGAAGTTCGGCCTGTACTACTACAACAAG TTCAAGGACATCGCCAGCACCCCTGAACAAGGCCAAGAGCATCGTGGGCACC ACCGCCAGCCTGCAGTACATGAAGAAGCTGTTCAGGAGAAGTACCTGCTG AGCGAGGACACCAGCGGCAAGTTCAGCGTGGACAAGCTGAAGTTCGACAAG CTGTACAAGATGCTGACCGAGATCTACACCGAGGACAACTTCGTGAAGTTC TTCAAGGTGCTGAACCGCAAGACCTACCTGAACTTCGACAAGGCCGTGTTC AAGATCAACATCGTGCCCAAGGTGAACTACACCATCTACGACGGCTTCAAC CTGCGCAACACCAACCTGGCCGCCAACTTCAACGGCCAGAACACCGAGATC AACACATGAACTTCACCAAGCTGAAGAAGTTCACCGGCCTGTTTCGAGTTC TACAAGCTGCTGTGCGTGCGCGGCATCATCACCAGCAAGACCAAGAGCCTG GTGCCCCGCGGCGACGAAGGCCCTGAACGACCTGTGCATCAAGGTGAACAAC TGGGACCTGTTCTTCAGCCCCAGCGAGGACAACCTTACCAACGACCTGAAC AAGGGCGAGGAGATCACCAGCGACACCAACATCGAGGCCGCCGAGGAGAAC ATCAGCCTGGACCTGATCCAGCAGTACTACCTGACCTTCAACTTCGACAAC GAGCCCCGAGAATCAGCATCGAGAACCTGAGCAGCGACATCATCGGCCAG CTGGAGCTGATGCCCAACATCGAGCGCTTCCCCAACGGCAAGAAGTACGAG CTGGACAAGTACACCATGTTCCACTACCTGCGCGCCCCAGGAGTTCGAGCAC GGCAAGAGCCGCATCGCCCTGACCAACAGCGTGAACGAGGCCCTGCTGAAC CCCAGCCGCGTGTACACCTTCTTCAGCAGCGACTACGTGAAGAAGGTGAAC AAGGCCACCGAGGCCGCCATGTTCTGCGGTGGGTGGAGCAGCTGGTGTAC GACTTCACCGACGAGACCAGCGAGGTGAGCACCACCGACAAGATCGCCGAC ATCACCATCATCATCCCCTACATCGGCCCCGCCCTGAACATCGGCACATG CTGTACAAGGACGACTTCGTGGGCGCCCTGATCTTCAGCGGCGCCGTGATC CTGGTGGAGTTCATCCCCGAGATCGCCATCCCCGTGCTGGGCACCTTCGCC CTGGTGAGCTACATCGCCACAAGGTGCTGACCGTGAGACCATCGACAAC GCCCTGAGCAAGCGCAACGAGAAGTGGGACGAGGTGTACAAGTACATCGTG	BONT02/03

	ACCAACTGGCTGGCCAAGGTGAACACCCAGATCGACCTGATCCGCAAGAAG ATGAAGGAGGCCCTGGAGAACCAGGCCGAGGCCACCAAGGCCATCATCAAC TACAGTACAACCAGTACACCGAGGAGGAGAAGAACAACATCAACTTCAAC ATCGACGACCTGAGCAGCAAGCTGAACGAGAGCATCAACAAGGCCATGATC AACATCAACAAGTTCTCTGAACCAAGTGCAGCGTGAGCTACCTGATGAACAGC ATGATCCCCCTACGGCGTGAAGCGCCTGGAGGACTTCGACGCCAGCCTGAAG GACGCCCTGCTGAAGTACATCTACGACAACCGCGGCACCCTGATCGGCCAG GTGGACCGCCTGAAGGACAAGGTGAACAACACCCTGAGCACCGACATCCCC TTCCAGCTGAGCAAGTACGTGGACAACCAGCGCCTGCTGAGCACCTTCACC GAGTACATCAAGAACATCATCAACACCAGCATCCTGAACCTGCGCTACGAG AGCAACCACCTGATCGACCTGAGCCGCTACGCCAGCAAGATCAACATCGGC AGCAAGGTGAACCTCGACCCCATCGACAAGAACCAGATCCAGCTGTTCAAC CTGGAGAGCAGCAAGATCGAGGTGATCCTGAAGAACGCCATCGTGTAACA AGCATGTACGAGAAGTTCAGCACCAAGCTTCTGGATCCGCATCCCCAAGTAC TTCAACAGCATCAGCCTGAACAACGAGTACACCATCATCAACTGCATGGAG AACCAACAGCGCTGGAAGGTGAGCCTGAACCTACGGCGAGATCATCTGGACC CTGCAGGACACCCAGGAGATCAAGCAGCGCTGGTGTTCAGTACAGCCAG ATGATCAACATCAGCGACTACATCAACCGCTGGATCTTCGTGACCATCACC AACCAACCGCCTGAACAACAGCAAGATCTACATCAACGGCCGCTGATCGAC CAGAAGCCCATCAGCAACCTGGGCAACATCCACGCCAGCAACAACATCATG TTCAAGCTGGACGGCTGCCGCGACACCCACCGCTACATCTGGATCAAGTAC TTCAACCTGTTCGACAAGGAGCTGAACGAGAAGGAGATCAAGGACCTGTAC GACAACCAGAGCAACAGCGGCATCCTGAAGGACTTCTGGGGCGACTACCTG CAGTACGACAAGCCCTACTACATGCTGAACCTGTACGACCCCAACAAGTAC GTGGACGTGAACAACGTGGGCATCCGCGGCTACATGTACCTGAAGGGCCCC CGCGGCAGCGTGATGACCACCAACATCTACCTGAACAGCAGCCTGTACCGC GGCACCAGTTCATCATCAAGAAGTACGCCAGCGGCAACAAGGACAACATC GTGCGCAACACGACCGCGTGATCATCAACGTGGTGGTGAAGAACAAGGAG TACCGCCTGGCCACCAACGCCAGCCAGCCGGCGTGGAAGAAGATCCTGAGC GCCCTGGAGATCCCCGACGTGGGCAACCTGAGCCAGGTGGTGGTGATGAAG AGCAAGAAGCAGCCAGGGCATCACCAACAAGTGCAAGATGAACCTGCAGGAC AACCAACGGCAACGACATCGGCTTCATCGGCTTCCACCAGTTCAACAACATC GCCAAGCTGGTGGCCAGCAACTGGTACAACCGCCAGATCGAGCGCAGCAGC CGCACCTGGGCTGCAGCTGGGAGTTCATCCCCGTGGACGACGGCTGGGGC GAGCGCCCCCTG	
2	ATGGCGGGCGCTCTCCTGGGAGCCCTGTTGCTGCTTACCCTCTTCGGGAGA TCCCAGGGAAAAAATGAAGAGCTGTCCCTGTACCATCACCTGTTTCGACAAC TACGACCCGGAGTGTCGCCAGTGCGCAGACCTGAGGACACTGTGACTATC ACTTTGAAGGTAAGTCTCACAAATCTTATCTCCCTGAACGAAAAGGAAGAG ACACTCACAAACAGTGTGTGGATTGGTATGATTGGCATGATTACAGACTC AACTACTCCAAGGACGATTTCCGCCGGGTCCGCATCCTGCGTGATCCCTCT GAACACGTGTGGCTGCCAGAAATCGTGCTGGAGAATAACATTGATGGTCAG TTTGGAGTAGCTTACGACAGCAACGTGCTGGTCTACGAAGGCGGATATGTG TCTTGGCTGCCCTCCAGCCATCTACAGGAGCACCTGCGCCGTTGAAGTGACC TATTTCCCGTTCTGACTGGCAGAACTGCTCTCTGATCTTCCGGTCTCAGACC TATAACGCTGAAGAGGTTGAGTTCAATTTTGCAGTTGATGACGATGGAAAT ACCATCAATAAGATTGACATCGACACCGCTGCATTACCGAAAACGGTGAG TGGGCTATCGACTACTGCCCCGGAATGATCCGCCGTTACGAAGGCGGAAGC ACTGACCGCCCTGGCGAGACGGACGTGATCTATACCTCATTATCCGCAGG AAGCCCCCTTTTATGTGATCAACATTATCGTTCCCTTGTGTCTTATCTCT GGGCTTGTGCTTCTGGCTTACTTCTGCCCCGCCAGGCTGGAGGCCAGAAG TGACAGTGAGCATTAACGTTCTGCTCGCCAGACAGTTTTCTCTTCTCTG ATCGCTCAGAAAATTCAGAAACATCCCTCTCCGTTCCACTGTTGGGCCGT TACCTGATCTTCGTATGGTGGTTGCAACCCTGATCGTGATGAATGCGTG ATTGTTCTTAACGTGAGCCTGCGCACGCTACAACCTATGCTACATCCCCA CGCCTGCGGCAAATTCTTCTGGAGTTGCTGCCCCGTTTGTGGGCTCTTCC CCGCCTCCCGAGGACCCCCGCACTGCCTCTCCCGCTCGCCGTGCCAGTTCC GTAGGCATCCTCCTGCGGGCCGAAGAGCTGATCCTGAAAAGCCTCGCTCC GAACTGGTCTTCGAGGGTCAGAGGCACCGTCACGGTACGTGGACCGCTGCC CTGTGTGCAACCTTGGCGCAGCCGCTCCTGAGATCAGATGTTGCGTTGAC GCCGTCAACTTCGTGGCTGAATCCACCCGTGACCAAGAGGCCACTGGCGAA GAGCTGAGCGATTGGGTGAGAATGGGTAAAGGCCCTGGATAACGTGTGTTTC	BoNTANA ALGB (mACHE-L- BONT-02/03)

TGGGCCGCTCTGGTTCTGTTTAGCGTGGGTAGTACCCTCATCTTCCTTGGA GGCTATTTTAAATCAGGTGCCAGACCTGCCATATCCGCCTTGCATCCAGCCA GGCGGTGGCGGTAGTGGGGTGGCGGAAGTGGCGGTGGCGGTAGCGGTGGA GGCGGATCTGAATTCATGCCCTTCGTGAACAAGCAGTTCAACTACAAGGAC CCCGTGccAACGGCGTGGACATCGCCTACATCAAGATCCCCAACGCCGGCC AGATGCAGCCCGTGAAGGCCCTCAAGATCCACAACAAGATCTGGGTGATCC CCGAGCGCGACACCTTCACCAACCCCGAGGAGGGCGACCTGAACCCCCCCC CCGAGGCCAAGCAGGTGCCCGTGAAGTACTACGACAGCACCTACCTGAGCA CCGACAACGAGAAGGACAACCTACCTGAAGGGCGTGACCAAGCTGTTGAGC GCATCTACAGACCGACCTGGGCCGCATGCTGCTGACCAGCATCGTGCGCG GCATCCCCCTTCTGGGGCGGCGAGCACCATCGACACCGAGCTGAAGGTGATCG ACACCAACTGCATCAACGTGATCCAGCCCGACGGCAGCTACCGCAGCGAGG AGCTGAACCTGGTGATCATCGGCCCCAGCGCCGACATCATCCAGTTCGAGT GCAAGAGCTTCGGCCACGAGGTGCTGAACCTGACCCGCAACGGCTACGGCA GCACCCAGTACATCCGCTTCAGCCCCGACTTCACCTTCGGCTTCGAGGAGA GCCTGGAGGTGGACACCAACCCCTGCTGGGCGCCGGCAAGTTCGCCACCG ACCCCGCCGTGACCCTGGCCACGAGCTGATCCACGCCGGCCACCGCCTGT ACGGCATGCCATCAACCCCAACCGCGTGTTCAGGTGAACACCAACGCCT ACTACGAGATGAGCGGCCTGGAGGTGAGCTTCGAGGAGCTGCGCACCTTCG GCGGCCACGACGCCAAGTTCATCGACAGCCTGCAGGAGAACGAGTTCGCGC TGTAATACTACAACAAGTTCAGGACATCGCCAGCACCTGAACAAGGCCA AGAGCATCGTGGGCACCACCGCCAGCCTGCAGTACATGAAGAAGCTGTTCA AGGAGAAGTACCTGCTGAGCGAGGACACCAGCGGCAAGTTCAGCGTGGACA AGCTGAAGTTCGACAAGCTGTACAAGATGCTGACCGAGATCTACACCGAGG ACAACCTTCGTGAAGTTCCTCAAGGTGCTGAACCGCAAGACCTACCTGAAC TCGACAAGGCCGTGTTCAAGATCAACATCGTGCCCAAGGTGAACACACCA TCTACGACGGCTTCACCTGCGCAACACCAACCTGGCCGCCAAGTTCACAG GCCAGAACACCGAGATCAACAACATGAACCTTCACCAAGCTGAAGAAGTTC CCGGCCTGTTGAGTTCACAAGCTGCTGTGCGTGCGCGGCATCATCACCA GCAAGACCAAGAGCCTGGTGCCCGCGGCAGCAAGGCCCTGAACGACCTGT GCATCAAGGTGAACAACCTGGGACCTGTTCTTCAGCCCCAGCGAGGACAAC TCACCAACGACCTGAACAAGGGCGAGGAGATCACCAGCGACACCAACATCG AGGCCGCCGAGGAGAACATCAGCCTGGACCTGATCCAGCAGTACTACCTGA CCTTCAACTTCGACAACGAGCCCGAGAACATCAGCATCGAGAACCTGAGCA GCGACATCATCGGCCAGCTGGAGCTGATGCCCAACATCGAGCGCTTCCCCA ACGGCAAGAAAGTACGAGCTGGACAAGTACACCATGTTCCACTACCTGCGCG CCAGGAGTTCGAGCACGGCAAGAGCCGCATCGCCCTGACCAACAGCGTGA ACGAGGGCCCTGCTGAACCCAGCCGCGTGTACACCTTCTTCAGCAGCGACT ACGTGAAGAAGGTGAACAAGGCCACCGAGGCCGCCATGTTCTTGGGCTGGG TGAGAGCAGCTGGTGACGACTTCACCGACGAGACCAGCGAGGTGAGCACC CCGACAAGATCGCCGACATCACCATCATCATCCCTACATCGGCCCGCCCC TGAACATCGGCAACATGCTGTACAAGGACGACTTCGTGGGCGCCCTGATCT TCAGCGGCGCCGTGATCCTGCTGGAGTTCATCCCCGAGATCGCCATCCCCG TGCTGGGCACCTTCGCCCTGGTGAGCTACATCGCCAACAAGGTGCTGACCG TGAGACCATCGACAACGCCCTGAGCAAGCGCAACGAGAAGTGGGACGAGG TGTAACAAGTACATCGTGACCAACTGGCTGGCCAAGGTGAACACCCAGATCG ACCTGATCCGCAAGAAGATGAAGGAGGCCCTGGAGAACCAGGCCGAGGCCA CCAAGGCCATCATCAACTACCAGTACAACCAGTACACCGAGGAGGAGAAGA ACAACATCAACTTCAACATCGACGACCTGAGCAGCAAGCTGAACGAGAGCA TCAACAAGGCCATGATCAACATCAACAAGTTCCTGAACAGTGCAGCGTGA GCTACCTGATGAACAGCATGATCCCTACGGCGTGAAGCGCCTGGAGGACT TCGACGCCAGCCTGAAGGACGCCCTGCTGAAGTACATCTACGACAACCGCG GCACCTGATCGGCCAGGTGGACCGCTGAAGGACAAGGTGAACAACACCC TGAGCACCGACATCCCTTCCAGCTGAGCAAGTACGTGGACAACCGAGCGCC TGCTGAGCACCTTCACCGAGTACATCAAGAACATCATCAACACCGAGCATCC TGAACCTGCGCTACGAGAGCAACCACCTGATCGACCTGAGCCGCTACGCCA GCAAGATCAACATCGGCAGCAAGGTGAACCTTCGACCCCATCGACAAGAACC AGATCCAGCTGTTCAACCTGGAGAGCAGCAAGATCGAGGTGATCCTGAAGA ACGCCATCGGTACAACAGCATGTACGAGAACTTCAGCACCAGCTTCTGGA TCCGCATCCCCAAGTACTTCAACAGCATCAGCCTGAACAACGAGTACACCA TCATCAACTGCATGGAGAACAACAGCGGCTGGAAGGTGAGCCTGAACACG GCGAGATCATCTGGACCCTGCAGGACACCGAGGATCAAGCAGCGCGTGG	
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	TGTTCAAGTACAGCCAGATGATCAACATCAGCGACTACATCAACCGCTGGA TCTTCGTGACCATCACCAACAACCGCCTGAACAACAGCAAGATCTACATCA ACGGCCGCCTGATCGACCAGAAGCCCATCAGCAACCTGGGCAACATCCACG CCAGCAACAACATCATGTTCAAGCTGGACGGCTGCCGCGACACCCACCGCT ACATCTGGATCAAGTACTTCAACCTGTTTCGACAAGGAGCTGAACGAGAAGG AGATCAAGGACCTGTACGACAACCAGAGCAACAGCGGCATCCTGAAGGACT TCTGGGGCGACTACCTGCAGTACGACAAGCCCTACTACATGCTGAACCTGT ACGACCCCCAACAGTACGTGGACGTGAACAACGTGGGCATCCGCGGTACA TGTACCTGAAGGGCCCCCGCGGCAGCGTGATGACCACCAACATCTACCTGA ACAGCAGCCTGTACC GCGGCACCAAGTTCATCATCAAGAAGTACGCCAGCG GCAACAAGGACAACATCGTGC GCAACAACGACCGCGTGTACATCAACGTGG TGGTGAAGAACAAGGAGTACCGCCTGGCCACCAACGCCAGCCAGGCCGGCG TGGAGAAGATCCTGAGCGCCCTGGAGATCCCCGACGTGGGCAACCTGAGCC AGGTGGTGGTGTGAAGAGCAAGAACGACCAGGGCATCACCAACAAGTGCA AGATGAACCTGCAGGACAACAACGGCAACGACATCGGCTTCATCGGCTTCC ACCAGTTCAACAACATCGCCAAGCTGGTGGCCAGCAACTGGTACAACCGCC AGATCGAGCGCAGCAGCCGACCCCTGGGCTGCAGCTGGGAGTTTCATCCCCG TGGACGACGGCTGGGGCGAGCGCCCCCTGTCTAGATAA	
3	ATGCCCTTCGTGAACAAGCAGTTCAACTACAAGGACCCCGTGAACGGCGTG GACATCGCCTACATCAAGATCCCCAACGCGCGCCAGATGCAGCCCGTGAAG GCCTTCAAGATCCACAACAAGATCTGGGTGATCCCCGAGCGCGACACCTTC ACCAACCCCGAGGAGGGCGACCTGAACCCCCCCCCCGAGGCCAAGCAGGTG CCCGTGAGCTACTACGACAGCACCTACCTGAGCACCAGCAACGAGAAGGAC AACTACCTGAAGGGCGTGACCAAGCTGTTTCGAGCGCATCTACAGCACCGAC CTGGGCGCATGCTGCTGACCAGCATCGTGC GCGGCATCCCCCTTCTGGGGC GGCAGCACCATCGACACCGAGCTGAAGGTGATCGACACCAACTGCATCAAC GTGATCCAGCCCGACGGCAGCTACCGCAGCGAGGAGCTGAACCTGGTGATC ATCGGCCCCAGCGCCGACATCATCCAGTTCGAGTGCAAGAGCTTCGGCCAC GAGGTGCTGAACCTGACCCGCAACGGCTACGGCAGCACCCAGTACATCCGC TTCAGCCCCGACTTCACCTTCGGCTTCGAGGAGAGCCTGGAGGTGGACACC AACCCCTGCTGGGCGCCGGCAAGTTCGCCACCGACCCCGCGTGAACCTG GCCACGAGCTGATCCACGCGCGCCACCGCCTGTACGGCATCGCCATCAAC CCCAACCGCTGTTCAAGGTGAACACCAACGCCTACTACGAGATGAGCGGC CTGGAGGTGAGCTTCGAGGAGCTGCGCACCTTCGGCGGCCACGACGCCAAG TTCATCGACAGCCTGCAGGAGAACGAGTTCGCGCTGTACTACTACACAAG TTCAAGGACATCGCCAGCACCTGAACAAGGCCAAGAGCATCGTGGGCACC ACCGCCAGCCTGCAGTACATGAAGAACGTGTTCAAGGAGAAGTACCTGCTG AGCGAGGACACCAGCGGCAAGTTCAGCGTGGACAAGCTGAAGTTCGACAAG CTGTACAAGATGCTGACCGAGATCTACACCGAGGACAACCTTCGTGAAGTTC TTCAAGGTGCTGAACCGCAAGACCTACCTGAACCTCGACAAGGCCGTGTTT AAGATCAACATCGTGCCCAAGGTGAACCTACACCATCTACGACGGCTCAAC CTGCGCAACACCAACCTGGCCGCCAACCTCAACGGCCAGAACACCGAGATC AACAAATGAACCTCACCAAGCTGAAGAACTTCACCGGCCTGTTTCGAGTTC TACAAGCTGCTGTGCGTGCGCGGCATCATCACCAGCAAGACCAAGAGCCTG GTGCCCCGCGGCAAGGCCCTGAACGACCTGTGCATCAAGGTGAACAAC TGGGACCTGTTCTTCAGCCCCAGCGAGGACAACCTCACCAACGACCTGAAC AAGGGCGAGGAGATCACCAGCGACACCAACATCGAGGCCGCCGAGGAGAAC ATCAGCCTGGACCTGATCCAGCAGTACTACCTGACCTTCAACTTCGACAAC GAGCCCGAGAACATCAGCATCGAGAACCTGAGCAGCGACATCATCGGCCAG CTGGAGCTGATGCCCAACATCGAGCGCTTCCCCAACGGCAAGAAGTACGAG CTGGACAAGTACACCATGTTCCACTACCTGCGCGCCAGGAGTTCGAGCAC GGCAAGAGCCGCATCGCCCTGACCAACAGCGTGAACGAGGCCCTGCTGAAC CCCAGCCGCGTGACACCTTCTTCAGCAGCGACTACGTGAAGAAGGTGAAC AAGGCCACCGAGGCCGCCATGTTCTGGGCTGGGTGGAGCAGCTGGTGTAC GACTTCACCGACGAGACCAGCGAGGTGAGCACCAACCGACAAGATCGCCGAC ATCACCATCATCATCCCCTACATCGGCCCGCCCTGAACATCGGCAACATG CTGTACAAGGACGACTTCGTGGGCGCCCTGATCTTCAGCGGCGCCGTGATC CTGCTGGAGTTCATCCCCGAGATCGCCATCCCCGTGCTGGGCACCTTCGCC CTGGTGAGTACATCGCCAACAAGGTGCTGACCGTGCGAGACCATCGACAAC GCCCTGAGCAAGCGCAACGAGAAGTGGGACGAGGTGTACAAGTACATCGTG ACCAACTGGCTGGCCAAGGTGAACACCCAGATCGACCTGATCCGCAAGAAG ATGAAGGAGGCCCTGGAGAACCAGGCCGAGGCCACCAAGGCCATCATCAAC	BoNTANA BLGA (BONT-02/03- mACHE)

TACCAGTACAACCAAGTACACCGAGGAGGAGAAGAACAACATCAACTTCAAC ATCGACGACCTGAGCAGCAAGCTGAACGAGAGCATCAACAAGGCCATGATC AACATCAACAAGTTCTTGAACCAAGTGCAGCGTGAGCTACCTGATGAACAGC ATGATCCCCTACGGCGTGAAGCGCCTGGAGGACTTCGACGCCAGCCTGAAG GACGCCCTGCTGAAGTACATCTACGACAACCGCGGCCACCTGATCGGCCAG TTGGACCGCCTGAAGGACAAGGTGAACAACACCCCTGAGCACCGACATCCCC TTCCAGCTGAGCAAGTACGTGGACAACCAGCGCCTGCTGAGCACCTTCACC GAGTACATCAAGAACATCATCAACACCAGCATCCTGAACCTGCGCTACGAG AGCAACCACCTGATCGACCTGAGCCGCTACGCCAGCAAGATCAACATCGGC AGCAAGGTGAACCTTCGACCCCATCGACAAGAACCAGATCCAGCTGTTC AAC CTGGAGAGCAGCAAGATCGAGGTGATCCTGAAGAACGCCATCGTGTACAAC AGCATGTACGAGAACTTCAGCACCAAGCTTCTGGATCCGCATCCCCAAGTAC TTCAACAGCATCAGCCTGAACAACGAGTACACCATCATCAACTGCATGGAG AACAACAGCGGCTGGAAGGTGAGCCTGAACCTACGGCGAGATCATCTGGACC CTGCAGGACACCCAGGAGATCAAGCAGCGCGTGGTGTTC AAGTACAGCCAG ATGATCAACATCAGCGACTACATCAACCGCTGGATCTTCGTGACCATCACC AACAACCGCCTGAACAACAGCAAGATCTACATCAACGCCCGCCTGATCGAC CAGAAGCCCATCAGCAACCTGGGCAACATCCACGCCAGCAACAACATCATG TTCAAGCTGGACGGCTGCCGCGACACCCACCGCTACATCTGGATCAAGTAC TTCAACCTGTTTCGACAAGGAGCTGAACGAGAAGGAGATCAAGGACCTGTAC GACAACCAGAGCAACAGCGGCATCCTGAAGGACTTCTGGGGCGACTACCTG CAGTACGACAAGCCCTACTACATGCTGAACCTGTACGACCCCAACAGTAC GTGGACGTGAACAACGTGGGCATCCGCGGCTACATGTACCTGAAGGGCCCC CGCGGCAGCGTGATGACCACCAACATCTACCTGAACAGCAGCCTGTACCGC GGCACAAGTTTCATCATCAAGAAGTACGCCAGCGGCACAAGGACAACATC GTGCGCAACAACGACCGCGTGTACATCAACGTGGTGGTGAAGAACAAGGAG TACCGCCTGGCCACCAACGCCAGCCAGGCCGGCGTGGAGAAGATCCTGAGC GCCCTGGAGATCCCCGACGTGGGCAACCTGAGCCAGGTGGTGGTGTGAAG AGCAAGAACGACCAAGGCATCACCACAAGTGCAAGATGAACCTGCAGGAC AACAACGGCAACGACATCGGCTTCATCGGCTTCACCAAGTTCAACAACATC GCCAAGCTGGTGGCCAGCAACTGGTACAAACCGCCAGATCGAGCGCAGCAGC CGCACCCCTGGGCTGCAGCTGGGAGTTTCATCCCCGTGGACGACGGCTGGGGC GAGCGCCCCCTGTCTAGAATGGCGGGCGCTCTCCTGGGAGCCCTGTGCTG CTTACCCTCTTCGGGAGATCCCAGGGAAAAAATGAAGAGCTGTCCCTGTAC CACCACCTGTTTCGACAACACGACCCGGAGTGTGCGCCAGTGCGCAGACCT GAGGACACTGTGACTATCACTTTGAAGGTAACCTCTCACAATCTTATCTCC CTGAACGAAAAGGAAGAGACACTCACAAACAGTGTGTGGATTGGTATTGAT TGGCAGGATTACAGACTCAACTACTCCAAGGACGATTTGCGCGGGGTGCGC ATCCTGCGTGTACCCTCTGAACACGTGTGGCTGCCAGAAATCGTGCTGGAG AATAACATTGATGGTCAAGTTGGAGTAGCTTACGACAGCAACGTGCTGGTC TACGAAGGCGGATATGTGTCTTGGCTGCCTCCAGCCATCTACAGGAGCACC TGCGCCGTTGAAGTGACCTATTTCCCGTTGCACTGGCAGAACTGCTCTCTG ATCTTCCGCTCTCAGACCTATAACGCTGAAGAGGTTGAGTTTATTTTGTGCA GTTGATGACGATGGAAATACCATCAATAAGATTGACATCGACACCGCTGCA TTCACCGAAAACGGTGAGTGGGCTATCGACTACTGCCCCGGAATGATCCGC CGTTACGAAGGCGGAAGCACTGAGGGCCCTGGCGAGACGGACGTGATCTAT ACCCTCATTATCCGCAGGAAGCCCTCTTTTATGTGATCAACATTATCGTT CCTTGTGTGCTTATCTCTGGGCTTGTGCTTCTGGCTTACTTCTGCCCCGCC CAGGCTGGAGGCCAGAAGTGCACAGTGAGCATTAACGTTCTGCTCGCCCAG ACAGTTTTCTCTCTGATCGCTCAGAAAATTCAGAAAACATCCCTCTCC GTTCCACTGTTGGGCCGTTACCTGATCTTCGTATGGTGGTTGCAACCCTG ATCGTGATGAACGTGCGTATGTTCTTAACGTGAGCCTGCGCACGCCCTACA ACTCACGCTACATCCCCACGCTGCGGCAAAATCTTCTGGAGTTGCTGCCC CGTTTGCTGGGCTCTTCCCCGCCTCCCGAGGACCCCCGCACTGCCTCTCCC GCTCGCCGTGCCAGTTCCGTAGGCATCCTCCTGCGGGCCGAAGAGCTGATC CTGAAAAGCCTCGCTCCGAACTGGTCTTCGAGGGTCAGAGGCACCGTCAC GGTACGTGGACCGCTGCCCTGTGTGAGAACCTTGGCGCAGCCGCTCCTGAG ATCAGATGTTGCGTTGACGCCGTCAACTTCGTGGCTGAATCCACCCGTGAC CAAGAGGCCACTGGCGAAGAGCTGAGCGATTGGGTGAGAATGGGTAAGGCC CTGGATAACGTGTGTTTCTGGGCCGCTCTGGTTCTGTTAGCGTGGGTAGT ACCCTCATCTCTCTTGGAGGCTATTTTAATCAGGTGCCAGACCTGCCATAT CCGCCTTGATCCAGCCATAA	
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4	ATGGCGGGCGCTCTCCTGGGAGCCCTGTTGCTGCTTACCCTCTTCGGGAGA TCCCAGGGAAAAAATGAAGAGCTGTCCCTGTACCATCACCTGTTTCGACAAC TACGACCCGGAGTGTGCGCCAGTGCAGACCTGAGGACACTGTGACTATC ACTTTGAAGGTAACCTCTCACAATCTTATCTCCCTGAACGAAAAGGAAGAG ACACTCACAAACAGTGTGTGGATTGGTATTGATTGGCATGATTACAGACTC AACTACTCCAAGGACGATTTTCGCCGGGGTCGGCATCCTGCGTGTACCCTCT GAACACGTGTGGCTGCCAGAAATCGTGCTGGAGAATAACATTGATGGTCAG TTTGGAGTAGCTTACGACAGCAACGTGCTGGTCTACGAAGGCGGATATGTG TCTTGGCTGCCTCCAGCCATCTACAGGAGCACCTGCGCCGTTGAAGTGACC TATTTCCCGTTCGACTGGCAGAACTGCTCTCTGATCTTCCGGTCTCAGACC TATAACGCTGAAGAGGTTGAGTTCATTTTTCAGTTGATGACGATGGAAAT ACCATCAATAAGATTGACATCGACACCGCTGCATTACCGAAAACGGTGAG TGGGCTATCGACTACTGCCCGGAATGATCCGCGTTACGAAGGCGGAAGC ACTGAGGGCCCTGGCGAGACGGACGTGATCTATAACCCTCATTATCCGCAGG AAGCCCCCTCTTTATGTGATCAACATTATCGTTCCTTGTGTGCTTATCTCT GGGCTTGTGCTTCTGGCTTACTTCCTGCCCGCCAGGCTGGAGGCCAGAAG TGCACAGTGAGCATTAAACGTTCTGCTCGCCAGACAGTTTTCTCTCTCTG ATCGCTCAGAAAATTCCAGAAACATCCCTCTCCGTTCCACTGTTGGGCCGT TACCTGATCTTCGTATGGTGGTTGCAACCCTGATCGTGATGAACGCGTG ATTGTTCTTAACGTGAGCCTGCGCACGCCTACAACCTCATGCTACATCCCCA CGCCTGCGGCAAATTCCTTGGAGTTGCTGCCCCGTTTGTGGGCTCTTCC CCGCCTCCCGAGGACCCCCGCACTGCCTCTCCCGCTCGCCGTGCCAGTTCC GTAGGCATCCTCCTGCGGGCCGAAGAGCTGATCCTGAAAAAGCCTCGCTCC GAACTGGTCTTCGAGGGTCAGAGGCACCGTCACGGTACGTGGACCGCTGCC CTGTGTCAGAACCTTGGCGCAGCCGCTCCTGAGATCAGATGTTGCGTTGAC GCCGTCAACTTCGTGGCTGAATCCACCCGTGACCAAGAGGCCACTGGCGAA GAGCTGAGCGATTGGGTGAGATGGGTAAAGCCCTGGATAACGTGTGTTTC TGGGCCGCTCTGGTTCTGTTAGCGTGGGTAGTACCCTCATCTTCTCTTGA GGCTATTTTAAATCAGGTGCCAGACCTGCCATATCCGCTTGCATCCAGCCA GGCGGTGGCGGTAGTGGGGGTGGCGAAGTGGCGGTGGCGGTAGCGGTGA GGCGGATCTCTGGTGCCCCCGGCGAGCGAATTATGCCCTTCGTGAACAAG CAGTTCAACTACAAGGACCCCGTGAACGGCGTGGACATCGCCTACATCAAG ATCCCCAACGCGGCCAGATGCAGCCCGTGAAGGCCCTCAAGATCCACAAC AAGATCTGGGTGATCCCCGAGCGCACACCTTACCACCCCGAGGAGGGC GACCTGAACCCCCCCCCGAGGCCAAGCAGGTGCCCGTGAGCTACTACGAC AGCACCTACCTGAGCACCGACAACGAGAAGGACAACCTACCTGAAGGGCGTG ACCAAGCTGTTCGAGCGCATCTACAGCACCGACCTGGGCGCATGCTGCTG ACCAGCATCGTGCGCGGCATCCCCTTCTGGGGCGGCAGCACCATCGACACC GAGCTGAAGGTGATCGACACCAACTGCATCAACGTGATCCAGCCCGACGGC AGCTACCGCAGCGAGGAGCTGAACCTGGTGATCATCGGCCCGAGCGCCGAC ATCATCCAGTTCGAGTGCAAGAGCTTCGGCCACGAGGTGCTGAACCTGACC CGCAACGGCTACGGCAGCACCCAGTACATCCGCTTCAGCCCCGACTTCACC TTCGGCTTCGAGGAGAGCCTGGAGGTGGACACCAACCCCTGCTGGGCGCC GGCAAGTTCGCCACCGACCCCGCCGTGACCCTGGCCACGAGCTGATCCAC GCCGGCCACCGCTGTACGGCATCGCCATCAACCCCAACCGCGTGTCAAG GTGAACACCACGCCTACTACGAGATGAGCGGCCTGGAGGTGAGCTTCGAG GAGCTGCGCACCTTCGGCGGCCACGACGCCAAGTTCATCGACAGCCTGCAG GAGAACGAGTTCGCGCTGTACTACTACAACAAGTTCAGGACATCGCCAGC ACCCTGAACAAGGCCAAGAGCATCGTGGGCACCACCGCCAGCCTGCAGTAC ATGAAGAACGTGTTCAAGGAGAAGTACCTGCTGAGCGAGGACACCAGCGGC AAGTTGAGCGTGGACAAGCTGAAGTTCGACAAGCTGTACAAGATGCTGACC GAGATCTACACCGAGGACAACTTCGTGAAGTTCTTCAAGGTGCTGAACCGC AAGGTGAACCTACACCATCTACGACGGCTTCAACCTGCGCAACACCAACCTG GCCGCCAACTTCAACGGCCAGAACACCGAGATCAACAACATGAACCTCACCC AAGCTGAAGAACTTCAACGGCCTGTTTCGAGTTCTACAAGCTGCTGTGCGTG CGCGGCATCATCACCAGCAAGACCAAGAGCCTGGTCCCCCGCGGCAGCAAG GCCCTGAACGACCTGTGCATCAAGGTGAACAACCTGGGACCTGTTCTTCAGC CCCAGCGAGGACAACTTACCAACGACCTGAACAAGGGCGAGGAGATCACC AGCGACACCAACATCGAGGCCGCGGAGGAGAACATCAGCCTGGACCTGATC CAGCAGTACTACCTGACCTTCAACTTCGACAACGAGCCCGAGAACATCAGC ATCGAGAACCTGAGCAGCGACATCATCGGCCAGCTGGAGCTGATGCCCAAC	BoNTANA ALTb (mACHE-L- Thrombin- BONT-02/03)
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	ATCGAGCGCTTCCCCAACGGCAAGAAGTACGAGCTGGACAAGTACACCATG TTCCACTACCTGCGCGCCCAGGAGTTTCGAGCACGGCAAGAGCCGCATCGCC CTGACCAACAGCGTGAACGAGGCCCTGCTGAACCCAGCCGCGTGTACACC TTCTTCAGCAGCGACTACGTGAAGAAGGTGAACAAGGCCACCGAGGCCGCC ATGTTCTCTGGGCTGGGTGGAGCAGCTGGTGTACGACTTCACCGACGAGACC AGCGAGGTGAGCACCACCGACAAGATCGCCGACATCACCATCATCATCCCC TACATCGGCCCCGCCCTGAACATCGGCAACATGCTGTACAAGGACGACTTC GTGGGCGCCCTGATCTTCAGCGGCCCGTGTATCCTGCTGGAGTTCATCCCC GAGATCGCCATCCCCGTGCTGGGCACCTTCGCCCTGGTGTAGCTACATCGCC AACAAGGTGCTGACCGTGCAGACCATCGACAACGCCCTGAGCAAGCGCAAC GAGAAGTGGGACGAGGTGTACAAGTACATCGTGACCAACTGGCTGGCCAAG GTGAACACCCAGATCGACCTGATCCGCAAGAAGATGAAGGAGGCCCTGGAG AACCAGGCCGAGGCCACCAAGGCCATCATCAACTACCAGTACAACCAGTAC ACCGAGGAGGAGAAGAACAACATCAACTTCAACATCGACGACCTGAGCAGC AAGCTGAACGAGAGCATCAACAAGGCCATGATCAACATCAACAAGTTCCTG AACCAGTGCAGCGTGTAGCTACCTGATGAACAGCATGATCCCCTACGGCGTG AAGCGCCTGGAGGACTTCGACGCCAGCCTGAAGGACGCCCTGCTGAAGTAC ATCTACGACAACCGCGGCCACCTGATCGGCCAGGTGGACCGCCTGAAGGAC AAGGTGAACAACACCCCTGAGCACCAGATCCCCTTCCAGCTGAGCAAGTAC GTGGACAACCAGCGCCTGCTGAGCACCTTCACCGAGTACATCAAGAACATC ATCAACACCAGCATCCTGAACCTGCGCTACGAGAGCAACCACCTGATCGAC CTGAGCCGCTACGCCAGCAAGATCAACATCGGCAGCAGGTGAATTCGAC CCCATCGACAAGAACCAGATCCAGCTGTTCAACCTGGAGAGCAGCAAGATC GAGGTGATCCTGAAGAACGCCATCGTGTACAACAGCATGTACGAGAACTTC AGCAGGACTTCTGGATCCGCATCCCCAAGTACTTCAACAGCATCAGCCTG AACAACGAGTACACCATCATCAACTGCATGGAGAACAACAGCGGCTGGAAG GTGAGCCTGAACCTACGGCGAGATCATCTGGACCCTGCAGGACACCCAGGAG ATCAAGCAGCGCGTGGTGTCAAGTACAGCCAGATGATCAACATCAGCGAC TACATCAACCGCTGGATCTTCGTGACCATCACCAACAACCGCCTGAACAAC AGCAAGATCTACATCAACGGCCGCTGATCGACCAGAAGCCATCAGCAAC CTGGGCAACATCCACGCCAGCAACAACATCATGTTCAAGCTGGACGGCTGC CGCGACACCCACCGCTACATCTGGATCAAGTACTTCAACCTGTTTCGACAAG GAGCTGAACGAGAAGGAGATCAAGGACCTGTACGACAACCAGAGCAACAGC GGCATCCTGAAGGACTTCTGGGGCGACTACCTGCAGTACGACAAGCCCTAC TACATGCTGAACCTGTACGACCCCAACAAGTACGTGGACGTGAACAACGTG GGCATCCGCGGCTACATGTACCTGAAGGGCCCCCGCGGCAGCGTGTAGACC ACCAACATCTACCTGAACAGCAGCCTGTACCGCGGCACCAAGTTCATCATC AAGAAGTACGCCAGCGGCAACAAGGACAACATCGTGGCAACAACGACCGC GTGTACATCAACGTGGTGGTGAAGAACAAGGAGTACCGCCTGGCCACCAAC GCCAGCCAGGCCGGCGTGGAGAAGATCCTGAGCGCCCTGGAGATCCCCGAC GTGGGCAACCTGAGCCAGGTGGTGGTGTGAAGAGCAAGAACGACCGGGC ATCACCACAAGTGCAAGATGAACCTGCAGGACAACACGGCAACGACATC GGCTTCATCGGCTTCCACCAGTTCAACAACATCGCCAAGCTGGTGGCCAGC AACTGGTACAACCGCCAGATCGAGCGCAGCAGCCGACCCTGGGCTGCAGC TGGGAGTTCATCCCCGTGGACGACGGCTGGGGCGAGCGCCCCCTGTAA	
5	ATGGCGGGCGCTCTCCTGGGAGCCCTGTTGCTGCTTACCCTCTTCGGGAGA TCCCAGGGAAAAAATGAAGAGCTGTCCCTGTACCATCACCTGTTTCGACAAC TACGACCCGGAGTGTGCGCCAGTGCAGACCTGAGGACACTGTGACTATC ACTTTGAAGTAACTCTCACAATCTTATCTCCCTGAACGAAAAGGAAGAG ACACTCACAAACAGTGTGTGGATTGGTATTGATTGGCATGATTACAGACTC AACTACTCCAAGGACGATTTGCGCGGGGTGGCATCCTGCGTGTACCCTCT GAACACGTGTGGCTGCCAGAAATCGTGCTGGAGAATAACATTGATGGTCAG TTTGGAGTAGCTTACGACAGCAACGTGCTGGTCTACGAAGGCGGATATGTG TCTTGGCTGCCTCCAGCCATCTACAGGAGCACCTGCGCCGTTGAAGTGACC TATTTCCCGTTCGACTGGCAGAACTGCTCTCTGATCTTCCGGTCTCAGACC TATAACGCTGAAGAGGTTGAGTTTATTTTTCAGTTGATGACGATGGAAAT ACCATCAATAAGATTGACATCGACACCGCTGCATTACCGAAAACGGTGAG TGGGCTATCGACTACTGCCCCGGAATGATCCGCCGTTACGAAGGCGGAAGC ACTGAGGGCCCTGGCGAGACGGACGTGATCTATACCCTCATTATCCGCAGG AAGCCCCCTCTTTATGTGATCAACATTATCGTTCCTTGTGTGCTTATCTCT GGGCTTGTGCTTCTGGCTTACTTCTGCCCCGCCAGGCTGGAGGCCAGAAG TGCACAGTGAGCATTAAACGTTCTGCTCGCCAGACAGTTTTCCTCTTCTCTG	BoNTANA AL8GB (mACHE- L8G4S-BONT- 02/03)

	ATCGCTCAGAAAATCCAGAAACATCCCTCTCCGTTCCACTGTTGGGCCGT TACCTGATCTTCGTATGGTGGTTGCAACCTGATCGTGATGAACTGCGTG ATTGTTCTTAACGTACGCTGCGCACGCTACAACATCATGCTACATCCCCA CGCTGCGGCAAATCTTCTGGAGTTGCTGCCCCGTTTGTGGGCTCTTCC CCGCTCCCGAGGACCCCGCACTGCCTCTCCCGCTCGCCGTGCCAGTTC GTAGGCATCCTCCTGCGGGCCGAAGAGCTGATCCTGAAAAAGCCTCGCTCC GAACTGGTCTTCGAGGGTCAGAGGCACCGTCACGGTACGTGGACCGCTGCC CTGTGTGAGAACCTTGGCGCAGCCGCTCCTGAGATCAGATGTTGCGTTGAC GCCGTCAACTTCGTGGCTGAATCCACCCGTGACCAAGAGGCCACTGGCGAA GAGCTGAGCGATTGGGTGAGATGGGTAGGCCCTGGATAACGTGTGTTTC TGGGCCGCTCTGGTCTGTTTAGCGTGGGTAGTACCCTCATCTTCTCTGGA GGCTATTTTAAATCAGGTGCCAGACCTGCCATATCCGCTTGCATCCAGCCA GGCGGAGGTGGCTCTGGAGGCGGTGGATCTGGTGGTGGCGGATCAGGTGGA GGCGGGAGCGGAGGCGGCGGTAGTGGTGGAGGAGGCTCTGGCGGTGGTGGA AGCGGTGGCGGCGGATCTGAATTCATGCCCTTCGTGAACAAGCAGTTC AAC TACAAGGACCCCGTGAACGCGGTGGACATCGCCTACATCAAGATCCCCAAC GCCGGCCAGATGCAGCCCGTGAAGGCCCTCAAGATCCACAACAAGATCTGG TGATCCCCGAGCGCGACACCTTACCAACCCCGAGGAGGGCGACCTGAAC CCCCCCCCGAGGCCAAGCAGGTGCCCGTGAGCTACTACGACAGCACCTAC CTGAGCACCCGACAACGAGAAGGACAACCTACCTGAAGGGCGTGACCAAGCTG TTCGAGCGCATCTACAGCACCGACCTGGGCCGCGATGCTGCTGACCAGCATC GTGCGCGGCATCCCCCTTCTGGGGCGGCAGCACCATCGACACCGAGCTGAAG GTGATCGACACCAACTGCATCAACGTGATCCAGCCCGACGGCAGCTACCGC AGCGAGGAGCTGAACCTGGTGATCATCGGCCCGAGCGCCGACATCATCCAG TTCGAGTGCAAGAGCTTCGCGCCACGAGGTGCTGAACCTGACCCGCAACGGC TACGGCAGCACCCAGTACATCCGCTTCAGCCCCGACTTCACCTTCGGCTTC GAGGAGAGCCTGGAGGTGGACACCAACCCCTGCTGGGCGCCGGCAAGTTC GCCACCGACCCCGCCGTGACCTTGGCCACGAGCTGATCCACGCCGGCCAC CGCTGTACGGCATCGCCATCAACCCCAACCGCGTGTTCAAGGTGAACACC AACGCTACTACGAGATGAGCGGCCCTGGAGGTGAGCTTCGAGGAGCTGCGC ACCTTCGGCGGCCACGACGCCAAGTTTCATCGACAGCCTGCAGGAGAACGAG TTCCGCTGTACTACTACAACAAGTTCAAGGACATCGCCAGCACCCCTGAAC AAGGCCAAGAGCATCGTGGGCACCACCGCCAGCCTGCAGTACATGAAGAAC GTGTTCAAGGAGAAGTACCTGCTGAGCGAGGACACCAGCGGCAAGTTCAGC GTGGACAAGCTGAAGTTCGACAAGCTGTACAAGATGCTGACCGAGATCTAC ACCGAGGACAACCTTCGTGAAGTTCTTCAAGGTGCTGAACCGCAAGACCTAC CTGAACCTTCGACAAGGCCGTGTTCAAGATCAACATCGTGCCCAAGGTGAAC TACACCATCTACGACGGCTTCAACCTGCGCAACACCAACCTGGCCGCCAAC TTCAACGGCCAGAACACCGAGATCAACACATGAACCTTACCAAGCTGAAG AACTTCACCGGCTGTTCGAGTTCTACAAGCTGCTGTGCGTGCGCGGCATC ATCACCAGCAAGACCAAGAGCCTGGTGCCCCGCGGCAGCAAGGCCCTGAAC GACCTGTGCTCAAGGTGAACAACCTGGGACCTGTTCTTCAGCCCCAGCGAG GACAACCTTACCAACGACCTGAACAAGGGCGAGGAGATCACCAGCGACACC AACATCGAGGCGCCGAGGAGAACATCAGCCTGGACCTGATCCAGCAGTAC TACCTGACCTTCAACTTCGACAACGAGCCCGAGAACATCAGCATCGAGAAC CTGAGCAGCGACATCATCGCCAGCTGGAGCTGATGCCAACATCGAGCGC TTCCCCAACGGCAAGAAGTACGAGCTGGACAAGTACACCATGTTCCACTAC CTGCGCGCCCAAGGAGTTCGAGCACGGCAAGAGCCGCATCGCCCTGACCAAC AGCGTGAACGAGGCCCTGCTGAACCCAGCCGCGTGATACCTTCTTCAGC AGCGACTACGTGAAGAAGGTGAACAAGGCCACCGAGGCCGCGCATGTTCTTG GGCTGGGTGGAGCAGCTGGTGACACTTCACCGACGAGACCAGCGAGGTG AGCACACCACGACAAGATCGCCGACATCACCATCATCATCCCTACATCGGC CCCGCCCTGAACATCGGCAACATGCTGTACAAGGACGACTTCGTGGGCGCC CTGATCTTCAGCGGCGCCGTGATCCTGCTGGAGTTTCATCCCGAGATCGCC ATCCCCGTGCTGGGCACCTTCGCCCTGGTGAGCTACATCGCCAACAAGGTG CTGACCGTGCAGACCATCGACAACGCCCTGAGCAAGCGCAACGAGAAGTGG GACGAGGTGTACAAGTACATCGTGACCAACTGGCTGGCCAAGGTGAACACC CAGATCGACCTGATCCGCAAGAAGATGAAGGAGGCCCTGGAGAACCAGGCC GAGGCCACCAAGGCCATCATCAACTACCAGTACAACCAGTACACCGAGGAG GAGAAGAACAACATCAACTTCAACATCGACGACCTGAGCAGCAAGCTGAAC GAGAGCATCAACAAGGCCATGATCAACATCAACAAGTTCCTGAACCAGTGC AGCGTGAGCTACCTGATGAACAGCATGATCCCCTACGGCGTGAAGCGCCTG	
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	GAGGACTTCGACGCCAGCCTGAAGGACGCCCTGCTGAAGTACATCTACGAC AACCGCGGCACCCTGATCGGCCAGGTGGACCGCCTGAAGGACAAGGTGAAC AACACCCTGAGCACCGACATCCCCTTCCAGCTGAGCAAGTACGTGGACAAC CAGCGCCTGCTGAGCACCTTCACCGAGTACATCAAGAACATCATCAACACC AGCATCCTGAACCTGCGCTACGAGAGCAACCACCTGATCGACCTGAGCCGC TACGCCAGCAAGATCAACATCGGCAGCAAGGTGAACCTCGACCCCATCGAC AAGAACCAGATCCAGCTGTTCAACCTGGAGAGCAGCAAGATCGAGGTGATC CTGAAGAACGCCATCGTGTACAACAGCATGTACGAGAAGTTCAGCACCAGC TTCTGGATCCGCATCCCCAAGTACTTCAACAGCATCAGCCTGAACAACGAG TACACCATCATCAACTGCATGGAGAACAACAGCGGCTGGAAGGTGAGCCTG AACTACGGCGAGATCATCTGGACCCTGCAGGACACCCAGGAGATCAAGCAG CGCGTGGTGTCAAGTACAGCCAGATGATCAACATCAGCGACTACATCAAC CGCTGGATCTTCGTGACCATCACCAACAACCGCCTGAACAACAGCAAGATC TACATCAACGGCCGCCTGATCGACCAGAAGCCCATCAGCAACCTGGGCAAC ATCCACGCCAGCAACAACATCATGTTCAAGCTGGACGGCTGCCGCGACACC CACCCTACATCTGGATCAAGTACTTCAACCTGTTGACAAGGAGCTGAAC GAGAAGGAGATCAAGGACCTGTACGACAACAGAGCAACAGCGGCATCCTG AAGGACTTCTGGGGCGACTACCTGCAGTACGACAAGCCCTACTACATGCTG AACCTGTACGACCCCAACAGTACGTGGACGTGAACAACGTGGGCATCCGC GGCTACATGTACCTGAAGGGCCCCCGCGGCAGCGTGTGACCAACACATC TACCTGAACAGCAGCCTGTACCGCGGCACCAAGTTCATCATCAAGAAGTAC GCCAGCGGCAACAAGGACAACATCGTGCACAACAACGACCGCGTGTACATC AACGTGGTGGTGAAGAACAAGGAGTACCGCCTGGCCACCAACGCCAGCCAG GCCGCGGTGGAGAAGATCCTGAGCGCCCTGGAGATCCCCGACGTGGGCAAC CTGAGCCAGGTGGTGGTGTGAAGAGCAAGAACGACCAAGGATCATCAAC AAGTGCAAGATGAACCTGCAGGACAACAACGGCAACGACATCGGCTTCATC GGCTTCCACCAGTTCAACAACATCGCCAAGCTGGTGGCCAGCAACTGGTAC AACCGCCAGATCGAGCGCAGCAGCCGACCCCTGGGCTGCAGCTGGGAGTTC ATCCCCGTGGACGACGGCTGGGGCGAGCGCCCCCTGTAA	
6	ATGGCGGGCGCTCTCCTGGGAGCCCTGTTGCTGCTTACCCTCTTCGGGAGA TCCCAGGGAAAAAATGAAGAGCTGTCCCTGTACCATCACCTGTTGACAAC TACGACCCGGAGTGTGCGCCAGTGCAGCAGACCTGAGGACACTGTGACTATC ACTTTGAAGGTAACCTCTCACAATCTTATCTCCCTGAACGAAAAGGAAGAG ACACTCACAAACAGTGTGTGGATTGGTATTTGATTGGCATGATTACAGACTC AACTACTCCAAGGACGATTTGCGCGGGGTGCGCATCCTGCGTGTACCCTCT GAACACGTGTGGCTGCCAGAAATCGTGTGGAGAATAACATTGATGGTCAG TTTGGAGTAGCTTACGACAGCAACGTGCTGGTCTACGAAGGCGGATATGTG TCTTGGCTGCCTCCAGCCATCTACAGGAGCACCTGCGCCGTTGAAGTGACC TATTTCCCGTTGACTGGCAGAACTGCTCTCTGATCTTCCGGTCTCAGACC TATAACGCTGAAGAGGTTGAGTTTCAATTTTGCAAGTTGATGACGATGGAAT ACCATCAATAAGATTGACATCGACACCGCTGCATTACCGAAAACGGTGAG TGGGCTATCGACTACTGCCCCGAATGATCCGCGTTACGAAGGCGGAAGC ACTGAGGGCCCTGGCGAGACGGACGTGATCTATACCCTCATTATCCGCAGG AAGCCCCCTCTTTATGTGATCAACATTATCGTTCCTTGTGTGCTTATCTCT GGGCTTGTGCTTCTGGCTTACTTCTGCCCCGCCAGGCTGGAGGCCAGAAG TGCACAGTGAGCATTAACGTTCTGCTCGCCCAGACAGTTTTCTCTTCTCTG ATCGCTCAGAAAATTCCAGAAACATCCCTCTCCGTTCCACTGTTGGGCCGT TACCTGATCTTCTCATGGTGGTTGCAACCTGATCGTGATGAACTGCGTG ATTGTTCTTAACGTGAGCCTGCGCACGCTACAACCTCATGCTACATCCCCA CGCTGCGGCAGAAATCTTCTGGAGTTGCTGCCCCGTTTGTGGGCTCTTCC CCGCTCCCCGAGGACCCCGCACTGCCCTCTCCGCTCGCCGTGCCAGTTCC GTAGGCATCTCTCTGCGGGCCGAAGAGCTGATCCTGAAAAAGCCTCGCTCC GAACTGGTCTTCGAGGGTCAGAGGCACCGTCACGGTACGTGGACCGCTGCC CTGTGTGAGAACCTTGGCGCAGCCGCTCCTGAGATCAGATGTTGCGTTGAC GCCGTCAACTTCGTGGCTGAATCCACCCGTGACCAAGAGGCCACTGGCGAA GAGCTGAGCGATTGGGTGAGAAATGGTAAGGCCCTGGATAACGTGTGTTTC TGGGCCGCTCTGTTCTGTTTAGCGTGGTAGTACCCTCATCTTCTTCTGGA GGCTATTTTAAATCAGGTGCCAGACCTGCCATATCCGCTTGCATCCAGCCA GAACTTAAACCCCTTGGGCGACACGACACATACATGCCCCGCTGCCCC GAGCCAAAGTCATGTGATACTCCTCCCCATGCCGAGGTGTCCAGAACCT AAGTCATGCGACACTCTCCCCCTGCCCGAGGTGCCCTGAGCCAAAGTCT TGTGACACACCGCCGCCCTGCCACGCTGCTCTGAGCCTAAGAGCTGCGAT	BoNTANA A5HB (mACHE- 5xHinge-opt- BONT-02/03)

ACACCACCTCCCTGTCTCGATGTCCGGAACCCAAATCTTGTGATACCCCT CCTCCTTGCCCCCGGTGCCCTGAATTCATGCCCTTCGTGAACAAGCAGTTC AACTACAAGGACCCCGTGAACGGCGTGGACATCGCCTACATCAAGATCCCC AACGCCGGCCAGATGCAGCCCGTGAAGGCCTTCAAGATCCACAACAGATC TGGGTGATCCCCGAGCGCGACACCTTCACCAACCCCGAGGAGGGCGACCTG AACCCCCCCCCGAGGCCAAGCAGGTGCCCGTGAGCTACTACGACAGCACC TACCTGAGCACCGACAACGAGAAGGACAACCTACCTGAAGGGCGTGACCAAG CTGTTTCGAGCGCATCTACAGCACCGACCTGGGCGCGCATGCTGCTGACCAGC ATCGTGCGCGGCATCCCCCTTCTGGGGCGGCAGCACCATCGACACCGAGCTG AAGGTGATCGACACCAACTGCATCAACGTGATCCAGCCCGACGGCAGCTAC CGCAGCGAGGAGCTGAACCTGGTGATCATCGGCCCCAGCGCCGACATCATC CAGTTCGAGTGCAAGAGCTTCGGCCACGAGGTGCTGAACCTGACCCGCAAC GGCTACGGCAGCACCCAGTACATCCGCTTCAGCCCCGACTTCACCTTCGGC TTCGAGGAGAGCCTGGAGGTGGACACCAACCCCTGCTGGGCGCCGCAAG TTCGCCACCGACCCCGCCGTGACCCTGGCCACGAGCTGATCCACGCCGGC CACCGCCTGTACGGCATCGCCATCAACCCCAACCGCGTGTTCAGGTGAAC ACCAACGCCTACTACGAGATGAGCGGCCCTGGAGGTGAGCTTCGAGGAGCTG CGCACCTTCGGCGGCCACGACGCCAAGTTCATCGACAGCCTGCAGGAGAAC GAGTTCGCGCTGTACTACTACAACAAGTTCAGGACATCGCCAGCACCTG AACAAGGCCAAGAGCATCGTGGGCACCAACCGCCAGCCTGCAGTACATGAAG AACGTGTTCAAGGAGAAGTACCTGCTGAGCGAGGACACCAGCGGCAAGTTC AGCGTGGACAGCTGAAGTTCGACAAGCTGTACAAGATGCTGACCGAGATC TACACCGAGGACAACCTTCGTGAAGTTCCTCAAGGTGCTGAACCGCAAGACC TACCTGAACCTCGACAAGGCCGTGTTCAAGATCAACATCGTGCCCAAGGTG AACTACACCATCTACGACGGCTTCAACCTGCGCAACACCAACCTGGCCGCC AACTTCAACGGCCAGAACACCGAGATCAACAACATGAACCTTCACCAAGCTG AAGAACCTTCACCGGCCTGTTTCGAGTTCCTACAAGCTGCTGTGCGTGCGCGC ATCATCACCAGCAAGACCAGAGCCTGGTGCCCCGCGGCAGCAAGGCCCTG AACGACCTGTGCATCAAGGTGAACAACCTGGGACCTGTTCTTCAGCCCCAGC GAGGACAACCTTCACCAACGACCTGAACAAGGGCGAGGAGATCACCAGCGAC ACCAACATCGAGGCCGCGCGAGGAGAACATCAGCCTGGACCTGATCCAGCAG TACTACCTGACCTTCAACTTCGACAACGAGCCCCGAGAACATCAGCATCGAG AACCTGAGCAGCGACATCATCGGCCAGCTGGAGCTGATGCCCAACATCGAG CGCTTCCCCAACGGCAAGAGTACGAGCTGGACAAGTACACCATGTTCCAC TACCTGCGCGCCCAGGAGTTCGAGCACGGCAAGAGCCGCATCGCCCTGACC AACAGCGTGAACGAGGCCCTGCTGAACCCAGCCGCGTGTACACCTTCTTC AGCAGCGACTACGTGAAGAGGTGAACAAGGCCACCGAGGCCGCCATGTTTC CTGGGCTGGGTGGAGCAGCTGGTGTACGACTTCACCGACGAGACCAGCGAG GTGAGCACCACCGACAAGATCGCCGACATCACCATCATCATCCCCTACATC GGCCCCGCCCTGAACATCGGCAACATGCTGTACAAGGACGACTTCGTGGGC GCCCTGATCTTCAGCGGCGCCGTGATCCTGCTGGAGTTCATCCCCGAGATC GCCATCCCCGTGCTGGGCACCTTCGCCCTGGTGAGCTACATCGCCAACAAG GTGCTGACCGTGCAGACCATCGACAACGCCCTGAGCAAGCGCAACGAGAAG TGGGACGAGGTGTACAAGTACATCGTGACCAACTGGCTGGCCAAGGTGAAC ACCCAGATCGACCTGATCCGCAAGAAGATGAAGGAGGCCCTGGAGAACCAG GCCGAGGCCACCAAGGCCATCATCAACTACCAAGTACAACCAAGTACACCGAG GAGGAGAAGAACAACATCAACTCAACATCGACGACCTGAGCAGCAAGCTG AACGAGAGCATCAACAAGGCCATGATCAACATCAACAAGTTCCTGAACCAG TGCAGCGTGAGCTACCTGATGAACAGCATGATCCCCTACGGCGTGAAGCGC CTGGAGGACTTCGACGCCAGCCTGAAGGACGCCCTGCTGAAGTACATCTAC GACAACCGCGGCACCCTGATCGGCCAGGTGGACCGCCTGAAGGACAAGGTG AACAACACCCCTGAGCACCGACATCCCCCTCCAGCTGAGCAAGTACGTGGAC AACCAGCGCCTGCTGAGCACCTTCACCGAGTACATCAAGAACATCATCAAC ACCAGCATCCTGAACCTGCGCTACGAGAGCAACACCTGATCGACCTGAGC CGCTACGCCAGCAAGATCAACATCGGCAGCAAGGTGAACCTTCGACCCCATC GACAAGAACCAGATCCAGCTGTTCAACCTGGAGAGCAGCAAGATCGAGGTG ATCCTGAAGAACGCCATCGTGTACAACAGCATGTACGAGAAGTTCAGCACC AGCTTCTGGATCCGCATCCCCAAGTACTTCAACAGCATCAGCCTGAACAAC GAGTACACCATCATCAACTGCATGGAGAACAACAGCGGCTGGAAGGTGAGC CTGAACACGCGAGATCATCTGGACCTGCAGGACACCCAGGAGATCAAG CAGCGCGTGGTGTTCAGTACAGCCAGATGATCAACATCAGCGACTACATC AACCGCTGGATCTTCGTGACCATCACCAACAACCGCCTGAACAACAGCAAG	
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	ATCTACATCAACGGCCGCTGATCGACCAGAAGCCCATCAGCAACCTGGGC AACATCCACGCCAGCAACAACATCATGTTCAAGCTGGACGGCTGCCGCGAC ACCCACCGCTACATCTGGATCAAGTACTTCAACCTGTTGACAAGGAGCTG AACGAGAAGGAGATCAAGGACCTGTACGACAACCAGAGCAACAGCGGCATC CTGAAGGACTTCTGGGGCGACTACCTGCAGTACGACAAGCCCTACTACATG CTGAACCTGTACGACCCCAACAAGTACGTGGACGTGAACAACGTGGGCATC CGCGGCTACATGTACCTGAAGGGCCCCCGCGGCAGCGTGATGACCACCAAC ATCTACCTGAACAGCAGCCTGTACCGCGGCACCAAGTTCATCATCAAGAAG TACGCCAGCGGCAACAAGGACAACATCGTGCACAACAACGACCGCGTGATC ATCAACGTGGTGGTGAAGAACAAGGAGTACCGCCTGGCCACCAACGCCAGC CAGGCCGGCGTGGAGAAGATCCTGAGCGCCCTGGAGATCCCCGACGTGGGC AACCTGAGCCAGGTGGTGGTGATGAAGAGCAAGAACGACAGGGCATCACC AACAAGTGCAAGATGAACCTGCAGGACAACAACGGCAACGACATCGGCTTC ATCGGCTTCCACCAGTTCACAACATCGCCAAGCTGGTGGCCAGCAACTGG TACAACCGCCAGATCGAGCGCAGCAGCCGACCCCTGGGCTGCAGCTGGGAG TTCATCCCCGTGGACGACGGCTGGGGCGAGCGCCCCCTGTAA	
7	ATGCCCTTCGTGAACAAGCAGTTCAACTACAAGGACCCCGTGAACGGCGTG GACATCGCCTACATCAAGATCCCCAACGCCGGCCAGATGCAGCCCGTGAAG GCCTTCAAGATCCACAACAAGATCTGGGTGATCCCCGAGCGCGACACCTTC ACCAACCCCGAGGAGGGCGACCTGAACCCCCCCCCGAGGCCAAGCAGGTG CCCGTGAGCTACTACGACAGCACCTACCTGAGCACCACAACGAGAAGGAC AACTAGCTGAAGGGCGTGACCAAGCTGTTGAGCGCATCTACAGCACCGAC CTGGGCCGCGATGCTGCTGACCAAGCATCGTGCAGCGCATCCCCCTTCGGGGC GGCAGCACCATCGACACCGAGCTGAAGGTGATCGACACCAACTGCATCAAC GTGATCCAGCCGACGGCAGCTACCGCAGCGAGGAGCTGAACCTGGTGATC ATCGGCCCCAGCGCCGACATCATCCAGTTCGAGTGCAAGAGCTTCGGCCAC GAGGTGCTGAACCTGACCCGCAACGGCTACGGCAGCACCCAGTACATCCGC TTCAGCCCCGACTTCACCTTCGGCTTCGAGGAGAGCCTGGAGGTGGACACC AACCCCTGCTGGGGCGCGCAAGTTCGCCACCGACCCCGCCGTGACCCCTG GCCCACGAGCTGATCCACGCCGGCCACCGCCTGTACGGCATCGCCATCAAC CCCAACCGCGTGTTCAGGTGAACACCACGCCTACTACGAGATGAGCGGC CTGGAGGTGAGCTTCGAGGAGCTGCGCACCTTCGGCGGCCACGACGCCAAG TTCATCGACAGCCTGCAGGAGAAGGAGTTCGGCCTGTACTACTACAACAAG TTCAGGACATCGCCAGCACCTGAACAAGGCCAAGAGCATCGTGGGCACC ACCGCCAGCCTGCAGTACATGAAGAACGTGTTCAAGGAGAAGTACCTGCTG AGCGAGGACACCAGCGGCAAGTTCAGCGTGGACAAGCTGAAGTTCGACAAG CTGTACAAGATGCTGACCGAGATCTACACCGAGGACAACTTCGTGAAGTTC TTCAGGTGCTGAACCGCAAGACCTACCTGAACCTTCGACAAGGCCGTGTTT AAGATCAACATCGTGCCCAAGGTGAACACCATCTACGACGGCTTCAAC CTGCGCAACACCAACCTGGCGGCAACTTCAACGGCCAGAACACCGAGATC AACAACATGAACCTCACCAAGCTGAAGAACTTCACCGGCCTGTTGAGTTC TACAAGCTGCTGTGCGTGCAGCGGCATCATCACCAGCAAGACCAAGAGCCTG GTGCCCCGCGGCGAGCAAGGCCCTGAACGACCTGTGCATCAAGGTGAACAAC TGGGACCTGTTCTTCAGCCCCAGCGAGGACAACCTCACCAACGACCTGAAC AAGGGCGAGGAGATCACCAGCGACACCAACATCGAGGCCGCGAGGAGAAC ATCAGCCTGGACCTGATCCAGCAGTACTACCTGACCTTCAACTTCGACAAC GAGCCCAGAACATCAGCATCGAGAACCTGAGCAGCGACATCATCGGCCAG CTGGAGCTGATGCCCCAACATCGAGCGCTTCCCCAACGGCAAGAAGTACGAG CTGGACAAGTACACCATGTTCCACTACCTGCGCGCCAGGAGTTCGAGCAC GGCAAGAGCCGCATCGCCCTGACCAACAGCGTGAACGAGGCCCTGCTGAAC CCCAGCCGCGTGATACCTTCTTCAGCAGCGACTACGTGAAGAAGGTGAAC AAGGCCACCGAGGCCGCCATGTTCTGGGCTGGGTGGAGCAGCTGGTGTAC GACTTCACCGACGAGACCAGCGAGGTGAGCACCAACGACAAGATCGCCGAC ATCACCATCATCATCCCCTACATCGGCCCCGCCCTGAACATCGGCAACATG CTGTACAAGGACGACTTCGTGGGGCGCCCTGATCTTCAGCGGCGCCGTGATC CTGCTGGAGTTCATCCCCGAGATCGCCATCCCCGTGCTGGGCACCTTCGCC CTGGTGAGCTACATCGCCAACAAGGTGCTGACCGTGCAGACCATCGACAAC GCCCTGAGCAAGCGCAACGAGAAGTGGGACGAGGTGTACAAGTACATCGTG ACCAACTGGCTGGCCAAGGTGAACACCCAGATCGACCTGATCCGCAAGAAG ATGAAGGAGGCCCTGGAGAACCAGGCCAGGCCACCAAGGCCATCATCAAC TACCAGTACACCAGTACACCGAGGAGGAGAAGAACAACATCAACTTCAAC ATCGACGACCTGAGCAGCAAGCTGAACGAGAGCATCAACAAGGCCATGATC	BoNTANA BL4GM (BONT02/03- L-MUSK)

	AACATCAACAAGTTCTGTAACCAAGTGCAGCGTGAGCTACCTGATGAACAGC ATGATCCCCCTACGGCGTGAAGCGCCTGGAGGACTTCGACGCCAGCCTGAAG GACGCCCTGCTGAAGTACATCTACGACAACCGGGCACCCTGATCGGCCAG GTGGACCGCTGAAGGACAAGGTGAACAACACCCTGAGCACCGACATCCCC TTCCAGCTGAGCAAGTACGTGGACAACCAGCGCCTGCTGAGCACCTTCACC GAGTACATCAAGAATCATCAACACCAGCATCCTGAACCTGCGCTACGAG AGCAACCACCTGATCGACCTGAGCCGCTACGCCAGCAAGATCAACATCGGC AGCAAGGTGAACCTTCGACCCCATCGACAAGAACCAGATCCAGCTGTTCAAC CTGGAGAGCAGCAAGATCGAGGTGATCCTGAAGAAGCCATCGTGTACAAC AGCATGTACGAGAATTCAGCACCAAGCTTCTGGATCCGCATCCCCAAGTAC TTCAACAGCATCAGCCTGAACAACGAGTACACCATCATCAACTGCATGGAG AACAAACAGCGGCTGGAAGGTGAGCCTGAACTACGGCGAGATCATCTGGACC CTGCAGGACACCCAGGAGATCAAGCAGCGCGTGGTGTCAAGTACAGCCAG ATGATCAACATCAGCGACTACATCAACCGCTGGATCTTCGTGACCATCACC AACAAACCGCTGAACAACAGCAAGATCTACATCAACGGCCGCTGATCGAC CAGAAGCCCATCAGCAACCTGGGCAACATCCACGCCAGCAACAACATCATG TTCAAGCTGGACGGCTGCCGCGACACCCACCGCTACATCTGGATCAAGTAC TTCAACCTGTTGACAAGGAGCTGAACGAGAAGGAGATCAAGGACCTGTAC GACAACAGAGCAACAGCGGCATCCTGAAGGACTTCTGGGGCGACTACCTG CAGTACGACAAGCCCTACTACATGCTGAACCTGTACGACCCCAACAAGTAC GTGGACGTGAACAACGTGGGCATCCGCGGCTACATGTACCTGAAGGGCCCC CGCGGCAGCGTGATGACCACCAACATCTACCTGAACAGCAGCCTGTACCGC GGCACCAGTTTCATCATCAAGAAGTACGCCAGCGGCAACAAGGACAACATC GTGCGCAACAACGACCGCGTGATACATCAACGTGGTGGTGAAGAACAAGGAG TACCGCCTGGCCACCAACGCCAGCCAGCGCGCGTGAGAGAAGATCCTGAGC GCCCTGGAGATCCCCGACGTGGGCAACCTGAGCCAGGTGGTGGTGTATGAAG AGCAAGAACGACCGGCGATCACCACCAAGTGCAAGATGAACCTGCAGGAC AACAAACGGCAACGACATCGGCTTCATCGGCTTCACCAGTTCAACAACATC GCCAAGCTGGTGGCCAGCAACTGGTACAACCGCCAGATCGAGCGCAGCAGC CGCACCTTGGGCTGCAGCTGGGAGTTTCATCCCCGTGGACGACGGCTGGGGC GAGCGCCCCCTGGGCGGTGGCGGTAGTGGGGGTGGCGGAAGTGGCGGTGGC GGTAGCGGTGGAGGCGGATCTATGAGAGAAGTAGTTAACATCCCTCTACTC CAGATGCTGACCCTGGTGGCCTTCTCTGGCACGGAGAAGCTGCCCCAAGGCC CCCCGTATCACCACCCCGCTGGAGACCGTGGATGCACTGGTAGAGGAGGTA GCCACTTTTCATGTGTGCAGTGGAATCTTACCCACAGCCCGAGATTAGCTGG ACACGGAACAAAATACTCATTAAGCTCTTTGACACCCGTTACTCGATCCGA GAAAATGGCCAGCTGCTGACAATACTGTCAAGTGAAGACAGTGATGACGGG ATATACTGCTGCATTGCGAACAATGGCGTGGGTGGCGCTGTGGAGAGCTGT GGGGCTTTGCAAGTGAAGATGAAGCCAAAGATCACCAGGCCTCCCATCAAC GTCAAGATCATCGAAGGACTAAAGGCCGTGTTGCCCTGCACAACCATGGGG AACCCCTAAGCCTTCAGTGTCTTGGATCAAAGGAGACAACGCACTGCGGGAG AACAGCAGGAATCGCCGTGTAGAGTCAGGCAGCCTAAGAATCCATAACGTA CAAAAGGAAGACGCTGGCCAGTACCGTTGCGTAGCCAGAAGAGTCTGGGC ACAGCATAACAGCAAGTTAGTGAAGTGGAGGTGGAGGTCTTCGCACGCATC CTGCGGGCCCCCTGAATCCCATAATGTGACATTTGGGTCTTTCGTACCCCTG CGATGTACCGCAATCGGCATCCCTGTGCCACCATTTTCTGGATAGAAAAT GGGAATGCTGTGAGCTCTGGGAGCATCCAGGAAAGTGTCAAAGACCGGGTG ATTGACAGCAGACTCCAGCTCTTCATCACAAAACCTGGCTTATACACTTGC ATCGCGACTAACAAGCATGGCGAGAAATTCAGCACCGCTAAGGCAGCTGCC ACCGTGTCCATCGCCGAGTGGAGTAAGAGCCAGAAGGACTCCCAAGGCTAC TGTGCCAGTATCGGGGAGAGGTGTGTGACGCAGTGTGGCCAAAGATGCC CTTGTCTTCTTCAACACATCCTACCGAGATCCTGAAGATGCTCAGGAGCTG TTGATCCACACGGCCTGGAATGAGCTCAAGGCGGTGAGCCCCCTGTGCCGG CCTGCCGCCGAGGCCCTGCTCTGCAACCACCTGTTCCAGGAATGTAGCCCT GGTGTGGTGCCTACCCCGATGCCCATTTGCCGGGAGTACTGTCTGGCTGTG AAAGAACTCTTCTGTGCAAAGGAGTGGCAGGCCATGGAAGGAAAAGCCCAC CGGGGCCTATACAGAAGTGGCATGCATCTGCTCCAGTCCCCGAGTGTCTCC AAACTGCCGTCCATGCACAGGGACCCACCGCTGCACTAGATTGCCATAC TTAGACTACAAGAAGGAAAAACATTACGACGTTCCCTTCTATCACATCTAGC AGACCTTCTGCTGACATCCCCAACCTGCCCGCCAGCACATCATCCTTTGCT GTCTCTCCTGCCTACTCTATGACAGTGATCATCTCTATCGTTAGTTCCTTC GCACTGTTTGCTCTGCTTACCATCGCTACCCTGTATTGCTGTAGACGCAGA	
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	AAAGAATGGAAGAACAAGAAGCGGGAGAGTACTGCCGTGACCCTGACCACT CTGCCTTCAGAGCTGCTGCTGGACCGACTGCACCCTAACCTATGTACCAG CGCATGCCACTGCTGCTGAATCCTAACTACTGAGCCTGGAGTACCCTAGA AATAACATTGAATATGTGAGAGACATCGGAGAAGGAGCCTTTGGCCGTGTG TTTCAAGCCCCGAGCCCCCTGGCTTGTGCTGCTTATGAACCTTTCACGATGGTC GCCGTGAAATGCTGAAAGAGGAGGCGAGCGCCGACATGCAAGCTGACTTC CAAAGAGAAGCAGCCCTAATGGCTGAGTTTGATAACCCCAACATCGTGAAG CTCCTGGGTGTGTGCGCCGTGGGCAAACCTATGTGCCTCCTGTTTGAATAC ATGGCCTACGGAGACCTGAATGAGTTCCTGCGGAGCATGTCTCCCCACACA GTTTGCAGCCTGTACACAGCGATCTGAGCACCAGGGCAAGAGTCAGCAGC CCAGGCCCTCCTCCCCTGTCTGTGCGCTGAGCAGTTATGTATTGCTAGACAG GTCGCGCTGGAATGGCTTACCTGAGCGAGAGGAAGTTTGTGCACAGAGAC CTGGCCACCAGAACTGCTTGGTGGGAGAGACCATGGTAGTGAAGATCGCC GACTTTGGACTGTCCAGAAACATCTACTCGGCAGATTACTATAAGGCGGAT GGAAACGATGCCATCCCTATTCGCTGGATGCCTCCTGAAAGTATCTTCTAC AATCGTTACACCACAGAAAGCGATGTGTGGGCTTATGGCGTGGTACTGTGG GAAATCTTTAGCTATGGCCTGCAACCTTACTACGGGATGGCACACGAAGAG GTGATCTATTACGTCCGGGATGGCAATATTTAGCCTGCCAGAGAACTGT CCGCTGGAGCTCTACAACCTCATGCGCCTGTGCTGGAGCAAGCTCCAGCG GATAGGCCCTAGCTTCTGTAGCATTACAGAATCTTGACGCGCATGTGTGAG CGAGCTGAGGGCACGGTGGGGGTATAA	
8	ATGCCCTTCGTGAACAAGCAGTTCAACTACAAGGACCCCGTGACGGCGTG GACATCGCCTACATCAAGATCCCCAACGCGCGCCAGATGCAGCCCGTGAAG GCCTTCAAGATCCACAACAAGATCTGGGTGATCCCCGAGCGGACACCTTC ACCAACCCCGAGGAGGGCGACCTGAACCCCCCCCCGAGGCCAAGCAGGTG CCCGTGAGCTACTACGACAGCACCTACCTGAGCACCACAACGAGAAGGAC AACTACCTGAAGGGCGTGACCAAGCTGTTGAGCGCATCTACAGCACCGAC CTGGGCCGCTGCTGCTGACCAGCATCGTGCGCGGCATCCCCTTCTGGGGC GGCAGCACCATCGACACCGAGCTGAAGGTGATCGACACCAACTGCATCAAC GTGATCCAGCCGACGGCAGCTACCGCAGCGAGGAGCTGAACCTGGTGATC ATCGGCCCCAGCGCCGACATCATCCAGTTCGAGTGCAGAGCTTCGGCCAC GAGGTGCTGAACCTGACCCGCAACGGCTACGGCAGCACCCAGTACATCCGC TTCAGCCCCGACTTCACCTTCGGCTTCGAGGAGAGCCTGGAGGTGGACACC AACCCCTGTGGGCGCCGCAAGTTCCGCCACCGACCCCGCCGTGACCCCTG GCCCACGAGCTGATCCACGCGCGCCACCGCCTGTACGGCATCGCCATCAAC CCCAACCGCGTGTTCAGGTGAACACCAACGCCTACTACGAGATGAGCGGC CTGGAGGTGAGCTTCGAGGAGCTGCGCACCTTCGGCGGCCACGACGCCAAG TTCATCGACAGCCTGCAGGAGAAGAGTTCGCGCTGTACTACTACAACAAG TTCAGGACATCGCCAGCACCTGAACAAGGCCAAGAGCATCGTGGGCACC ACCGCCAGCTGCAGTACATGAAGAAGTGTTCAGGAGAAGTACCTGCTG AGCGAGGACACCAGCGGCAAGTTGAGCGTGGACAAGCTGAAGTTCGACAAG CTGTACAAGATGCTGACCAGATCTACACCGAGGACAACTTCGTGAAGTTC TTCAGGTGCTGAACCGCAAGACCTACCTGAACTTCGACAAGGCCGTGTTC AAGATCAACATCGTGCCCAAGGTGAATACACCATCTACGACGGCTTCAAC CTGCGCAACACCAACCTGGCCGCCAACTTCAACGGCCAGAACACCGAGATC AACAACATGAACTTCACCAAGCTGAAGAAGTTCACCGGCCCTGTTGAGTTC TACAAGCTGCTGTGCGTGCGCGGCATCATCACCAGCAAGACCAAGAGCCTG GTGCCCCGCGGCAGCAAGGCCCTGAACGACCTGTGCATCAAGGTGAACAAC TGGGACCTGTTCTTCAGCCCCAGCGAGGACAACTTCACCAACGACCTGAAC AAGGGCGAGGAGATCACCAGCGACACCAACATCGAGGCCGCGGAGGAGAAC ATCAGCCTGGACCTGATCCAGCAGTACTACCTGACCTTCAACTTCGACAAC GAGCCCAGAGAACATCAGCATCGAGAACCTGAGCAGCGACATCATCGGCCAG CTGGAGCTGATGCCCCAATCGAGCGCTTCCCCAACGGCAAGAAGTACGAG CTGGACAAGTACACCATGTTCCACTACCTGCGCGCCAGGAGTTCGAGCAC GGCAAGAGCCGCATCGCCCTGACCAACAGCGTGAACGAGGCCCTGCTGAAC CCCAGCCGCGTGTACACCTTCTTCAGCAGCGACTACGTGAAGAAGGTGAAC AAGGCCACCGAGGCCCGCATGTTCTGCGGCTGGGTGGAGCAGCTGGTGTAC GACTTCACCGACGAGACCGAGGAGGTGAGCACCAACGACAAGATCGCCGAC ATCACCATCATCATCCCCTACATCGGCCCCGCCCTGAACATCGGCAACATG CTGTACAAGGACGACTTCGTGGGCGCCCTGATCTTCAGCGGCGCCGTGATC CTGCTGGAGTTCATCCCCGAGATCGCCATCCCCGTGCTGGGACCTTCGCC CTGGTGAGCTACATCGCCAACAAGGTGCTGACCGTGACGACCATCGACAAC	BoNTANA BL5HM (BONT02/03- 5xHinge- MUSK)

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In one aspect, the present invention relates to an *in vitro* method for modulating neuromuscular transmission, the *in vitro* method comprising transfecting a eukaryotic cell with a nucleic acid molecule according to the present invention.

- 5 The *in vitro* method for modulating neuromuscular transmission, as disclosed in the present invention, offers several significant advantages for research, therapeutic development, and clinical applications. By transfecting a eukaryotic cell with the nucleic acid molecule of the invention, this method enables the controlled expression of therapeutic proteins, antibodies, neurotoxins, or RNA interference molecules, facilitating the precise investigation of their effects on neuromuscular
- 10 function. This *in vitro* approach provides a reliable and reproducible platform for studying synaptic modulation under defined conditions, allowing for the identification and optimization of effective therapeutic constructs before *in vivo* application. Furthermore, it enables high-throughput screening of various nucleic acid sequences to assess their efficacy, stability, and safety, accelerating the development of novel neuromodulatory treatments. Additionally, by using patient-derived cells, the
- 15 technique offers potential applications in personalized medicine, allowing for individualized treatment strategies based on a patient's specific genetic and molecular profile.

In embodiments, the eukaryotic cell is a skeletal muscle cell, a smooth muscle cell, and/or a skin cell.

Skeletal muscle cells exhibit high transfection efficiency, and intramuscular or intradermal administration of naked plasmid DNA or RNA with suitable transfection vectors enables localized recombinant protein expression in the target tissue. This approach has been extensively studied and validated in prior research (e.g., Davis et al, Hum Gene Ther, 1993, Danko et al, Vaccine, 1994). By
5 employing gene-based strategies for localized BoNT or TeNT expression, this invention addresses critical limitations in current therapeutic approaches, offering a more controlled and sustained modulation of neuromuscular transmission.

Skin cells, including fibroblasts and keratinocytes, serve as an accessible and robust platform for *ex vivo* gene therapy applications, where patient-derived cells can be modified to express therapeutic
10 agents and subsequently reintroduced into the body. Using the nucleic acid molecule in skin cells enables sustained systemic or localized release of therapeutic proteins, antibodies, or RNA interference molecules, offering a non-invasive alternative for neuromuscular modulation. This approach is particularly advantageous for patients requiring long-term treatment, as genetically modified skin cells can function as a continuous source of therapeutic agents without repeated drug
15 administration. Additionally, since skin cells can be easily harvested, modified, and expanded *ex vivo* before transplantation, this strategy allows for personalized and patient-specific therapies, optimizing treatment efficacy while minimizing immune rejection or off-target effects. The use of transfected skin cells also holds potential for cosmetic applications, such as reducing muscular hyperactivity in aesthetic medicine, by providing localized and controlled neuromodulation without the need for
20 repeated toxin injections.

In a preferred embodiment, the present invention relates to an *in vitro* method for modulating neuromuscular transmission, the *in vitro* method comprising transfecting a skeletal muscle cell, a smooth muscle cell and/or a skin cell with a nucleic acid molecule according to the present invention to regulate the transmembrane domains of the acetylcholine receptor (AChR) with the epsilon
25 subunit and/or the transmembrane domain of the muscle-specific receptor tyrosine kinase (MuSK).

In one aspect, the present invention relates to a genetically modified cell comprising the nucleic acid molecule, a vector, and/or a fusion protein according to the present invention.

In embodiments, the cell is a eukaryotic cell selected from the group consisting of a skeletal muscle cell, a smooth muscle cell, or a skin cell.

30 In embodiments, the genetically modified cell according to the present invention is for use in the treatment or prevention of autoimmune conditions, spasticity, dystonia, hyperhidrosis, myasthenia gravis, and/or aesthetic medicine.

In embodiments, the genetically modified cell according to the present invention is for use in cosmetic treatments.

35 An additional advantage of using nucleic acid-based approaches for recombinant protein expression lies in the precise dosage control of specific expression at the motor end plate. This targeted expression inherently limits the number of recombinant proteins integrated into the sarcolemma, as proteins that exceed the membrane's capacity are rapidly degraded in the cytosol via the proteasomal pathway. This mechanism is particularly advantageous for highly potent and potentially

toxic proteins such as BoNT or TeNT, where precise dosage control is critical to ensuring efficacy and safety.

In conventional protein administration, the total amount of BoNT or TeNT delivered to the system can be accurately measured, but the diffusion and localization of the protein remain challenging to control. In contrast, when BoNT- or TeNT-encoding nucleic acids are administered, the exact number of translated proteins cannot be predetermined with the same precision. However, by leveraging the natural limitations of motor end plate expression, the risk of excessive protein accumulation and systemic toxicity is significantly reduced. This results in a substantially expanded therapeutic window compared to protein-based BoNT or TeNT therapy.

The targeted expression strategy enables significantly higher localized dosages at the precise site of action while maintaining systemic safety. Surprisingly, in the case of BoNT fusion proteins, this approach has been shown to expand the therapeutic range by at least fivefold, a level of control and safety that has not been achieved with any other BoNT delivery system to date. Consequently, this innovation represents a major advancement in neuromuscular modulation therapies, offering enhanced efficacy while minimizing the risk of adverse effects.

The various aspects of the invention are unified by, benefit from, are based on and/or are linked by the structural and/or functional features, including functional properties and beneficial technical effects, of the nucleic acid molecule for modulating neuromuscular transmission described herein. The features disclosed in the context of the nucleic acid molecule also apply to and are considered disclosed in the context of the nucleic acid vector, the fusion protein, the in vitro method, the genetically modified cell, and vice versa. Any features disclosed in any further aspects of the invention, such as the nucleic acid vector, the fusion protein, the in vitro method, the genetically modified cell, or medical use thereof, are also considered disclosed in the context of the inventive nucleic acid molecule and vice versa.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a nucleic acid molecule for modulating neuromuscular transmission, the nucleic acid molecule comprising a sequence encoding one or more receptors of the motor end plate or fragments thereof.

The “motor end plate,” also known as the “neuromuscular junction (NMJ),” is a specialized chemical synapse between the terminal end of a motor neuron and a muscle fiber, facilitating the transmission of action potentials from nerve to muscle, thereby initiating muscle contraction. Structurally, the NMJ comprises three key components: the presynaptic nerve terminal, the synaptic cleft, and the postsynaptic motor end plate. The presynaptic nerve terminal contains synaptic vesicles packed with acetylcholine (ACh), which is synthesized from choline and acetyl-CoA via the enzyme choline acetyltransferase. Upon depolarization, voltage-gated calcium channels open, allowing calcium influx that triggers the fusion of synaptic vesicles with the presynaptic membrane, releasing ACh into the synaptic cleft through exocytosis mediated by SNARE proteins. The synaptic cleft, a 50-nanometer space, contains acetylcholinesterase (AChE), which rapidly hydrolyzes ACh to terminate its action. The postsynaptic motor end plate, a highly folded region of the muscle fiber's sarcolemma,

is densely populated with nicotinic acetylcholine receptors (nAChRs) at a density of approximately 10,000 receptors/ μm^2 . These ligand-gated ion channels, composed of α , β , ϵ , and δ subunits, bind ACh, leading to sodium ion influx, membrane depolarization, and the generation of an endplate potential (EPP). If sufficient, the EPP triggers an action potential propagating along the muscle fiber, ultimately inducing muscle contraction via excitation-contraction coupling. Dysfunction at the NMJ, whether due to genetic mutations, autoimmune disorders (e.g., myasthenia gravis, Lambert-Eaton syndrome), or neurotoxins (e.g., botulinum toxin), can disrupt synaptic transmission, leading to neuromuscular diseases characterized by muscle weakness or hyperexcitability.

In the context of the present invention, the motor end plate serves as the critical anatomical and functional site for targeted modulation of neuromuscular transmission. As the postsynaptic membrane of the neuromuscular junction, the motor end plate contains key receptors, including AChR and MuSK, which mediate synaptic transmission from motor neurons to muscle fibers, thereby regulating muscle contraction. The invention leverages the specificity of receptor expression at the motor end plate to achieve localized and controlled therapeutic effects by administering nucleic acids encoding modified receptors, fusion proteins, or RNAi elements. By restricting the expression of therapeutic agents, such as BoNT, TeNT, or acetylcholinesterase, to the motor end plate, the invention mitigates systemic exposure and reduces off-target effects, thereby enhancing both efficacy and safety. Furthermore, the invention enables the downregulation or modification of AChRs to decrease muscle excitability, either by RNA interference mechanisms, including shRNA or siRNA or by expressing dysfunctional receptor variants that competitively inhibit wild-type receptor function. Additionally, by employing genomic elements such as scaffold/matrix attachment regions (S/MAR) and tissue-specific promoters, the invention ensures a sustained yet controlled therapeutic effect, preventing excessive protein expression and associated toxicities. This targeted approach expands the therapeutic window of BoNT- or TeNT-based treatments and offers a novel gene therapy strategy. Consequently, the motor end plate serves as the essential site of action for the invention, enabling precise, localized, and durable modulation of neuromuscular function through genetic intervention.

As used herein, the term "receptor of the motor end plate" refers to any receptor present at the motor end plate. Non-limiting examples are acetyl choline receptors, such as nicotinic acetylcholine receptors (nAChRs) or muscarinic acetylcholine receptors (mAChRs), and non-acetylcholine receptors, such as glutamate receptors, ATP receptors, and neuropeptides.

"Nicotinic acetylcholine receptors (nAChRs)" are ligand-gated ion channels responsive to acetylcholine and certain exogenous agonists such as nicotine. As members of the cys-loop superfamily, nAChRs are pentameric transmembrane proteins composed of various subunit combinations that determine their functional and pharmacological properties. These receptors facilitate synaptic transmission by modulating the flux of Na^+ , K^+ , and, in some cases, Ca^{2+} ions upon agonist binding, leading to cellular depolarization. Two primary classes of nAChRs exist: muscle-type, expressed at the neuromuscular junction (Nm), and neuronal-type (Nn), distributed in the central and peripheral nervous systems. Muscle-type nAChRs mediate excitatory neurotransmission at neuromuscular synapses, whereas neuronal-type receptors contribute to autonomic ganglia signaling, catecholamine release, and cognitive processes. The functional diversity of nAChRs arises from their subunit composition, with vertebrate receptors incorporating α

($\alpha 1$ – $\alpha 10$) and β ($\beta 1$ – $\beta 4$) subunits, forming homomeric or heteromeric assemblies. Acetylcholine binding to two α -subunit sites induces a conformational change, resulting in channel opening and ion conductance. nAChRs are implicated in physiological functions such as neurotransmitter release modulation, synaptic plasticity, and inflammatory responses. Pharmacologically, nAChRs are targeted by agonists (e.g., nicotine, epibatidine), competitive antagonists (e.g., hexamethonium, α -bungarotoxin), and allosteric modulators. Dysregulation of nAChR activity is associated with disorders including myasthenia gravis, congenital myasthenic syndromes, nicotine addiction, and neurodegenerative diseases. subunit of the acetyl choline receptor (AChR)

“Acetylcholine receptor (nAChR) subunits” are the protein components that assemble into pentameric structures to form functional nicotinic acetylcholine receptors, which mediate synaptic transmission by responding to acetylcholine and other ligands. Seventeen nAChR subunits have been identified in mammals, classified into muscle-type ($\alpha 1$, $\beta 1$, δ , γ , and ϵ) and neuronal-type ($\alpha 2$ – $\alpha 10$, $\beta 2$ – $\beta 4$) subunits. These subunits combine in specific stoichiometries to generate receptor subtypes with distinct pharmacological and functional properties. The muscle-type receptors exist as heteropentamers, transitioning from an embryonic form ($\alpha 1$)₂ $\beta 1\delta\gamma$ to an adult form ($\alpha 1$)₂ $\beta 1\delta\epsilon$, where the ϵ subunit replaces the γ subunit shortly after birth. The ϵ subunit, encoded by the CHRNE gene, plays a critical role in stabilizing the receptor complex, enhancing synaptic efficiency, and regulating receptor clustering at the neuromuscular junction. Mutations in CHRNE are a major cause of congenital myasthenic syndrome (CMS), leading to endplate acetylcholine receptor deficiency and altered receptor kinetics. These mutations, often autosomal recessive, impair receptor function by disrupting ligand binding, gating efficiency, and channel opening probability, which can result in severe neuromuscular impairment. The presence of an ϵ subunit-specific mutation that introduces an arginine residue into the ligand-binding pocket exemplifies the profound functional consequences of structural alterations, significantly reducing agonist affinity and gating efficiency. The regulated expression and assembly of nAChR subunits, including the ϵ subunit, are tightly controlled to maintain receptor fidelity and optimal neuromuscular transmission, ensuring proper synaptic signaling and muscle function.

“Muscle-specific kinase” or “Muscle-specific receptor tyrosine kinase” (MuSK) is a receptor tyrosine kinase that is essential for the development, organization, and maintenance of the neuromuscular junction (NMJ), where motor neurons communicate with skeletal muscle fibers. Activation of MuSK occurs through its interaction with low-density lipoprotein receptor-related protein-4 (LRP4), a transmembrane protein, and is enhanced by agrin, a heparan-sulfate proteoglycan released from motor neurons. The activation cascade involves autophosphorylation of MuSK and recruitment of key intracellular signaling molecules, including casein kinase 2 (CK2), downstream of kinase-7 (Dok-7), and rapsyn, leading to the clustering of acetylcholine receptors (AChRs) at the postsynaptic membrane. This process ensures efficient synaptic transmission and muscle contraction. Disruptions in MuSK function, whether due to genetic mutations or autoantibodies, contribute to neuromuscular disorders such as congenital myasthenic syndromes and myasthenia gravis. MuSK-associated myasthenia gravis is characterized by autoantibodies that impair agrin/LRP4-mediated signaling, leading to defective NMJ formation and transmission. MuSK mutations, including frameshift and missense variants, further compromise NMJ integrity by disrupting receptor expression, signaling, or AChR clustering.

As used herein, AChR and MuSK serve as essential molecular targets for the modulation of neuromuscular transmission. The invention exploits the highly specific expression of these receptors to achieve localized gene therapy for neuromuscular disorders. The invention enables precise regulation of neuromuscular excitability by utilizing nucleic acids encoding modified AChR or MuSK, RNAi strategies, or fusion proteins. AChR can be downregulated via siRNA or shRNA to reduce acetylcholine-mediated signaling, decreasing muscle tone in conditions such as spasticity, dystonia, and hyperhidrosis. Additionally, the invention allows for the expression of modified AChR variants that remain in a closed conformation, competitively inhibiting functional wild-type receptors and further reducing muscle responsiveness to neural stimulation. Similarly, MuSK expression can be modulated to influence AChR clustering and synaptic integrity, providing an additional mechanism for fine-tuning neuromuscular transmission. Furthermore, the invention enables the targeted delivery of therapeutic proteins, such as BoNT or TeNT, by fusing them to AChR or MuSK transmembrane domains, ensuring their localized expression at the motor end plate while minimizing systemic exposure and associated risks. Thus, AChR and MuSK are central elements in the invention's strategy to achieve controlled and long-lasting therapeutic effects for neuromuscular disorders through these mechanisms.

"Neurotoxins" are a broad class of exogenous and endogenous compounds that disrupt the structure or function of nervous tissue, leading to neurotoxicity. They interfere with neuronal communication, ion channel function, or neurotransmitter release, often causing excitotoxicity, apoptosis, or systemic nervous system dysfunction. Among neurotoxins, botulinum toxin (BoNT) and tetanus toxin (TeNT), produced by *Clostridium* bacteria, are significant due to their potent effects on synaptic transmission. BoNT inhibits acetylcholine release at neuromuscular junctions by cleaving SNARE proteins essential for vesicle fusion, resulting in flaccid paralysis. Despite being the most potent known biological toxin, it has therapeutic applications in neuromuscular disorders, cosmetics, and pain management. TeNT, structurally similar to BoNT, also cleaves SNARE proteins but targets inhibitory interneurons in the central nervous system, leading to uncontrolled muscle contractions and spastic paralysis. Unlike BoNT, TeNT undergoes retrograde transport to the spinal cord, disrupting inhibitory neurotransmission and causing tetanic contractions characteristic of tetanus. Both toxins exemplify the specificity and potency of neurotoxins in modulating neural function.

The terms and abbreviations "botulinum neurotoxins (BoNTs or BTX)" or "botulinum toxins" can be used interchangeably and refer to a class of highly potent neurotoxic proteins produced by *Clostridium botulinum* and related bacterial species. These toxins function as acetylcholine release inhibitors and neuromuscular blocking agents, preventing neurotransmission at the neuromuscular junction and thereby inducing flaccid paralysis. BoNTs are categorized into seven primary serotypes (A–G), with types A and B being the most clinically relevant due to their capacity to cause botulism in humans and their extensive use in medical and cosmetic applications. The mechanism of action involves receptor-mediated endocytosis, translocation of the light chain into the cytoplasm, and proteolytic cleavage of SNARE proteins, specifically SNAP-25, synaptobrevin, or syntaxin, leading to inhibition of synaptic vesicle fusion and neurotransmitter release. BoNTs are utilized therapeutically for conditions such as muscle spasticity, dystonia, strabismus, chronic migraine, hyperhidrosis, and various neuropathic disorders. Cosmetic applications include temporarily reducing dynamic facial wrinkles through targeted muscle paralysis. Commercial formulations include onabotulinumtoxinA (Botox), abobotulinumtoxinA (Dysport), incobotulinumtoxinA (Xeomin), daxibotulinumtoxinA

(Daxxify), letibotulinumtoxinA (Letybo), and rimabotulinumtoxinB (Myobloc), among others. Adverse effects may result from unintended toxin diffusion, leading to localized or systemic muscle weakness, ptosis, dysphagia, or, in severe cases, respiratory compromise.

BoNT interacts with the presynaptic membrane of neurons at the neuromuscular junction to inhibit neurotransmitter release, leading to flaccid paralysis. This process begins with BoNT binding to specific surface receptors on the presynaptic membrane, including gangliosides (GT1b, GD1b) and protein receptors such as synaptotagmin or SV2, facilitating its uptake through receptor-mediated endocytosis. Once inside the neuron, acidification of the vesicle triggers a conformational change in the toxin, allowing the heavy chain to translocate the light chain into the cytoplasm. The light chain, a zinc-dependent protease, then selectively cleaves essential SNARE proteins, such as SNAP-25, VAMP, or syntaxin, depending on the BoNT serotype, disrupting the synaptic vesicle fusion process required for acetylcholine release. As a result, the neuron cannot transmit signals to the muscle, causing paralysis. The effects of BoNT persist until the neuron regenerates functional SNARE proteins and restores synaptic activity.

“Tetanus toxin (TeNT)” is a potent neurotoxin produced by *Clostridium tetani*, which causes tetanus by interfering with neurotransmitter release in the central nervous system. The toxin comprises a 150 kDa protein cleaved into a 100 kDa heavy (B-chain) and a 50 kDa light (A-chain) subunit. The B-chain binds to specific gangliosides and a GPI-anchored protein on the presynaptic membrane of neurons, facilitating internalization. Once inside, TeNT undergoes retrograde axonal transport to the spinal cord, where it transcytoses into inhibitory interneurons. The A-chain, a zinc-dependent protease, cleaves synaptobrevin (VAMP), a key protein involved in vesicle fusion, thus preventing the release of inhibitory neurotransmitters, such as GABA and glycine. This blockade results in disinhibition of motor neurons, causing muscle rigidity and spasms. The primary clinical manifestations of tetanus include muscle spasms, risus sardonicus, trismus, and opisthotonus. TeNT acts specifically on synaptic vesicles, causing a selective blockade of neurotransmitter release in inhibitory neurons, leading to the pathological muscle activity associated with tetanus.

In the context of the present invention, BoNT and TeNT serve as key therapeutic agents for modulating neuromuscular transmission by selectively inhibiting synaptic vesicle exocytosis at the neuromuscular junction. BoNT functions by cleaving SNARE proteins, thereby preventing the release of acetylcholine from presynaptic nerve terminals and inducing temporary paralysis of the target muscle. This mechanism is widely exploited for treating excessive neuromuscular activity, such as spasticity, dystonia, and hyperhidrosis. However, systemic exposure to BoNT poses a risk of severe side effects, necessitating precise localization of its activity. The invention addresses this challenge by encoding BoNT within nucleic acid constructs that enable targeted expression specifically at the motor end plate using motor end plate-specific promoters, transmembrane domains of AChR or MuSK, and fusion proteins. This targeted approach increases the therapeutic range while reducing systemic toxicity. Additionally, TeNT, produced by acts in an opposing manner to BoNT by preferentially targeting inhibitory interneurons in the central nervous system, leading to unregulated excitatory neurotransmission and sustained muscle contractions. In the invention, TeNT may be utilized in controlled applications to modulate neuronal signaling in therapeutic contexts where enhanced synaptic activity is beneficial. By leveraging the highly specific activity of BoNT and TeNT and refining their delivery through nucleic acid-based expression systems, the invention

achieves precise neuromodulation, significantly improving the safety and efficacy of toxin-based therapies for neuromuscular disorders.

As used herein, a “fusion protein” refers to a genetically engineered chimeric protein composed of two or more distinct functional domains covalently linked to create a single polypeptide with combined or enhanced properties. The fusion protein, as used herein, is designed to improve the pharmacokinetics, specificity, or functionality of therapeutic agents.

Regarding botulinum neurotoxin (BoNT) or tetanus toxin (TeNT), the fusion protein is engineered to optimize its therapeutic potential by enhancing targeting specificity, increasing the duration of action, or modulating its cellular uptake and intracellular activity. In one embodiment, this is achieved by fusing BoNT or TeNT with targeting ligands, receptor-binding domains, or translocation-enhancing sequences that facilitate selective delivery to neuromuscular junctions while reducing off-target effects. Additionally, in one embodiment, the fusion protein can modify the intracellular processing of neurotoxins, ensuring controlled cleavage of SNARE proteins and fine-tuning the degree of neuromuscular inhibition.

In the context of the present invention, fusion proteins serve as a critical component for achieving targeted and controlled modulation of neuromuscular transmission. The fusion proteins are designed to combine functional domains of BoNT or other therapeutic agents with transmembrane domains derived from AChR or MuSK, ensuring precise localization at the motor end plate. By incorporating linker sequences, such as glycine-serine repeats or immunoglobulin-like hinge regions, the invention optimizes the spatial configuration and stability of these fusion constructs, enhancing their therapeutic efficacy. The targeted expression of these fusion proteins at the neuromuscular junction minimizes systemic toxicity and allows for a significantly extended duration of action compared to conventional protein-based therapies. Additionally, fusion proteins may be engineered to include protease-sensitive cleavage sites, enabling controlled activation or deactivation within the synaptic cleft. This approach provides a higher degree of specificity and reduces the risk of unintended diffusion of neurotoxins, thereby increasing the therapeutic range. Through the integration of fusion proteins within nucleic acid constructs, the invention establishes a novel and precise method for neuromodulation, making it particularly advantageous for the treatment of conditions such as spasticity, dystonia, and other disorders associated with aberrant neuromuscular signaling.

In a preferred embodiment, the fusion protein comprises a receptor of the motor end plate, a neurotoxin, an antibody, and/or RNA interference elements, allowing for precise and sustained modulation of neuromuscular transmission. The receptor component may include AChRs, MuSK, and/or glutamate receptors, ensuring targeted localization at the motor end plate. The neurotoxin component may include BoNT and/or TeNT, enabling the selective inhibition of neurotransmitter release and modulation of synaptic activity. Furthermore, the fusion protein may incorporate siRNA or shRNA, which silence specific genes involved in neuromuscular signaling or immune response, potentially reducing immunogenicity, prolonging therapeutic effects, or enhancing selectivity. By combining these elements, such fusion proteins offer a novel approach for improving BoNT-based therapies, ensuring prolonged and localized effects, minimizing systemic toxicity, reducing treatment frequency, and mitigating immune responses that could compromise long-term efficacy.

As used herein, the terms "polynucleotide" or "nucleic acid molecule" refer to any nucleic acid molecule, for example, DNA or RNA, such as messenger RNA (mRNA), RNA, genomic RNA (gRNA), plus-strand RNA (RNA(+)), minus-strand RNA (RNA(-)), genomic DNA (gDNA), complementary DNA (cDNA) or recombinant DNA. Polynucleotides include single and double-stranded polynucleotides. Preferably, polynucleotides of the invention include polynucleotides or variants having at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to any of the reference sequences described herein, typically where the variant maintains at least one biological activity of the reference sequence. In various illustrative embodiments, the present invention contemplates, in part, polynucleotides comprising expression vectors, viral vectors, transfer plasmids and compositions, and cells comprising the same.

Polynucleotides can be prepared, manipulated and/or expressed using a variety of well-established techniques known and available in the art. In order to express a desired polypeptide, a nucleotide sequence encoding the polypeptide can be inserted into an appropriate vector. Examples of vectors are plasmids, autonomously replicating sequences, and transposable elements. Additional exemplary vectors include, without limitation, plasmids, phagemids, cosmids, artificial chromosomes such as yeast artificial chromosome (YAC), bacterial artificial chromosome (BAC), or PI-derived artificial chromosome (PAC), bacteriophages such as lambda phage or M13 phage, and animal viruses. Examples of categories of animal viruses useful as vectors include, without limitation, retrovirus (including lentivirus), adenovirus, adeno-associated virus, herpesvirus (e.g., herpes simplex virus), poxvirus, baculovirus, papillomavirus, and papovavirus (e.g., SV40). Examples of expression vectors are pCneo vectors (Promega) for expression in mammalian cells; pLenti4/V5-DEST™, pLenti6/V5-DEST™, and pLenti6.2/V5-GW/lacZ (Invitrogen) for lentivirus-mediated gene transfer and expression in mammalian cells.

As used herein, the term "retrovirus" refers to an RNA virus that reverse transcribes its genomic RNA into a linear double-stranded DNA copy and subsequently covalently integrates its genomic DNA into a host genome. Once the virus is integrated into the host genome, it is referred to as a "provirus." The provirus serves as a template for RNA polymerase II and directs the expression of RNA molecules, which encode the structural proteins and enzymes needed to produce new viral particles. Illustrative retroviruses suitable for use in particular embodiments include but are not limited to: Moloney murine leukemia virus (M-MuLV), Moloney murine sarcoma virus (MoMSV), Harvey murine sarcoma virus (HaMuSV), murine mammary tumor virus (MuMTV), gibbon ape leukemia virus (GaLV), feline leukemia virus (FLV), spumavirus, Friend murine leukemia virus, Murine Stem Cell Virus (MSCV) and Rous Sarcoma Virus (RSV) and lentivirus.

As used herein, the term "lentivirus" refers to a group (or genus) of complex retroviruses. Illustrative lentiviruses include but are not limited to HIV (human immunodeficiency virus; including HIV type 1, and HIV type 2); visna-maedi virus (VMV) virus; the caprine arthritis-encephalitis virus (CAEV); equine infectious anemia virus (EIAV); feline immunodeficiency virus (FIV); bovine immune deficiency virus (BIV); and simian immunodeficiency virus (SIV).

The term "vector" is used herein to refer to a nucleic acid molecule capable of transferring or transporting another nucleic acid molecule. The transferred nucleic acid is generally linked to, e.g., inserted into, the vector nucleic acid molecule. A vector may include sequences that direct

autonomous replication in a cell or may include sequences sufficient to allow integration into host cell DNA. Useful vectors include, for example, plasmids (e.g., DNA plasmids or RNA plasmids), transposons, cosmids, bacterial artificial chromosomes, and viral vectors. Useful viral vectors include e.g. replication defective retroviruses and lentiviruses.

- 5 As will be evident to one of skill in the art, the term "viral vector" is widely used to refer either to a nucleic acid molecule (e.g., a transfer plasmid) that includes virus-derived nucleic acid elements that typically facilitate the transfer of the nucleic acid molecule or integration into the genome of a cell or to a viral particle that mediates nucleic acid transfer. Viral particles typically include various viral components and sometimes host cell components in addition to nucleic acid(s).
- 10 The term viral vector may refer either to a virus or viral particle capable of transferring a nucleic acid into a cell or to the transferred nucleic acid itself. Viral vectors and transfer plasmids contain structural and/or functional genetic elements that are primarily derived from a virus. The term "retroviral vector" refers to a viral vector or plasmid containing structural and functional genetic elements, or portions thereof, that are primarily derived from a retrovirus.
- 15 In a preferred embodiment, the invention relates to a method for transfecting cells with a nucleic acid molecule according to the present invention.

- Transposable elements are natural, non-viral gene delivery vehicles that mediate stable genomic integration. The Sleeping Beauty (SB) transposon can cut and paste a nucleic acid sequence of interest into the genome, providing the basis for long-term, permanent transgene expression in
- 20 transgenic cells and organisms, in this case for the transformation of immune cells, preferably T cells, with the CAAR-encoding nucleic acid sequences of the present invention. The SB transposon system is relatively well characterized and has been extensively engineered for efficient gene delivery and discovery in various vertebrates, including humans. A skilled person can identify appropriate variants of the SB system and incorporate these into the invention as necessary.
- 25 Specific, non-limiting examples are provided below. The SB system is a safe and simple-to-use vector that enables cost-effective, rapid preparation of therapeutic doses of cell products.

- Generally, a transposon system includes a transposon and a transposase. The transposon acts as a carrier, which carries the gene to be inserted into the genome. The transposase is the so-called "workhorse" of the system, catalyzing the transposition process. The transposase is located between
- 30 the inverted terminal repeats (ITRs) of the transposon. Importantly, the transposase gene can be replaced with any nucleic acid sequence of interest, and the transposase can govern transposition events when encoded by a separate plasmid in trans. Physical separation of the transposon from the transposase enabled optimization of the transposon versus transposase ratio and also provided the freedom of supplying the transposase in the form of mRNA instead of DNA. First, the transposase
- 35 recognizes the transposon and binds the ITRs. During synaptic complex formation, transposase monomers bring the transposon ends together (presumably forming a tetramer). The transposase generates a DNA double-strand break upon excision, while single-stranded gaps at the integration site. The pre-integration complex containing the transposon-bound transposase integrates into the host genome. SB transposition is a highly coordinated reaction that efficiently filters out abnormal,
- 40 toxic transposition intermediates (reviewed in Narayanavari & Izsvák, Cell & Gene Therapy insights, 2017).

Previous optimization of nucleotide residues (including mutations, deletions, and additions) within the ITRs of the original SB transposon (pT) resulted in improved transposon versions, such as pT2, pT3, pT2B, and pT4, which may be employed for the fusion protein-encoding sequences described herein.

- 5 A further aspect of the invention relates to a genetically modified immune cell comprising a nucleic acid molecule or vector as described herein and/or expressing a fusion protein as described herein.

Sequence variants of the claimed nucleic acids, proteins, antibodies, antibody fragments, and/or fusion proteins, for example, those defined by % sequence identity, that maintain similar binding properties of the invention are also included in the scope of the invention. Such variants, which show
10 alternative sequences but maintain essentially the same binding properties, such as target specificity, as the specific sequences provided, are known as functional analogs or functionally analogous. Sequence identity relates to the percentage of identical nucleotides or amino acids when carrying out a sequence alignment.

The recitation "sequence identity," as used herein, refers to the extent to which sequences are
15 identical on a nucleotide-by-nucleotide basis or an amino acid-by-amino acid basis over a comparison window. Thus, a "percentage of sequence identity" may be calculated by comparing two optimally aligned sequences over the window of comparison, determining the number of positions at which the identical nucleic acid base (e.g., A, T, C, G, I) or the identical amino acid residue (e.g., Ala, Pro, Ser, Thr, Gly, Val, Leu, Ile, Phe, Tyr, Trp, Lys, Arg, His, Asp, Glu, Asn, Gln, Cys and Met)
20 occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison (i.e., the window size), and multiplying the result by 100 to yield the percentage of sequence identity. Included are nucleotides and polypeptides having at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to any of the reference sequences described
25 herein, typically where the polypeptide variant maintains at least one biological activity of the reference polypeptide.

It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology or sequence identity to the nucleotide
30 sequence of any native gene. Nonetheless, the present invention specifically contemplates polynucleotides that vary due to differences in codon usage. Deletions, substitutions, and other changes in sequence that fall under the described sequence identity are also included in the invention.

Protein sequence modifications, which may occur through substitutions, are also included within the
35 scope of the invention. Substitutions, as defined herein, are modifications made to the amino acid sequence of the protein, whereby one or more amino acids are replaced with the same number of (different) amino acids, producing a protein that contains a different amino acid sequence than the primary protein. Substitutions may be carried out that preferably do not significantly alter the function of the protein. Like additions, substitutions may be natural or artificial. It is well known in the art that
40 amino acid substitutions may be made without significantly altering the protein's function. This is particularly true when the modification relates to a "conservative" amino acid substitution, which is

the substitution of one amino acid for another of similar properties. Such "conserved" amino acids can be natural or synthetic, which, because of size, charge, polarity, and conformation, can be substituted without significantly affecting the structure and function of the protein. Frequently, many amino acids may be substituted by conservative amino acids without deleteriously affecting the protein's function.

In general, the non-polar amino acids Gly, Ala, Val, Ile, and Leu; the non-polar aromatic amino acids Phe, Trp, and Tyr; the neutral polar amino acids Ser, Thr, Cys, Gln, Asn, and Met; the positively charged amino acids Lys, Arg and His; the negatively charged amino acids Asp and Glu, represent groups of conservative amino acids. This list is not exhaustive. For example, it is well known that Ala, Gly, Ser, and sometimes Cys can substitute for each other even though they belong to different groups.

Substitution variants have at least one amino acid residue in the nucleic acid molecule removed and a different residue inserted.

Potential amino acid substitutions:

Original residue	Preferred conservative substitutions	Examples of exemplary substitutions
Ala (A)	Val	Val; Leu; Ile
Asg (R)	Lys	Lys; Gln; Asn
Asn (N)	Gln	Gln; His; Asp, Lys; Arg
Asp (D)	Glu	Glu; Asn
Cys (C)	Ser	Ser; Ala
Gln (Q)	Asn	Asn, Glu
Glu (E)	Asp	Asp; Gln
Gly (G)	Ala	Ala
His (H)	Arg	Asn; Gln; Lys; Arg
Ile (I)	Leu	Leu; Val; Met; Ala; Phe; Norleucine
Leu (L)	Ile	Norleucine; Ile; Val; Met; Ala; Phe
Lys (K)	Arg	Arg; Gln; Asn
Met (M)	Leu	Leu; Phe; Ile
Phe (F)	Tyr	Leu; Val; Ile; Ala; Tyr
Pro (P)	Ala	Ala
Ser (S)	Thr	Thr
Thr (T)	Ser	Ser
Trp (W)	Tyr	Tyr; Phe
Tyr (Y)	Phe	Trp; Phe; Thr; Ser
Val (V)	Leu	Ile; Leu; Met; Phe; Ala; Norleucine

Substantial modifications in the biological properties of the fusion protein are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain.

Conservative amino acid substitutions are not limited to naturally occurring amino acids but include synthetic ones. Commonly used synthetic amino acids are omega amino acids of various chain lengths and cyclohexyl alanine, which are neutral non-polar analogs; citrulline and methionine sulfoxide, which are neutral non-polar analogs; phenyl glycine which is an aromatic neutral analog; 5 cysteic acid which is a negatively charged analog and ornithine which is a positively charged amino acid analog. Like the naturally occurring amino acids, this list is not exhaustive but merely exemplary of the well-known substitutions in the art.

The present invention contemplates, in particular embodiments, cells genetically modified to express the fusion proteins contemplated herein for use or prevention of autoimmune conditions, spasticity, 10 dystonia, hyperhidrosis, and/or aesthetic medicine.

As used herein, the term "genetically engineered" or "genetically modified" refers to the addition of extra genetic material in the form of DNA or RNA into the total genetic material in a cell. The terms "genetically modified cells," "modified cells," and "redirected cells" are used interchangeably.

As used herein, an "antibody" generally refers to a protein consisting of one or more polypeptides 15 substantially encoded by immunoglobulin genes or fragments of immunoglobulin genes. Where the term "antibody" is used, the term "antibody fragment" may also be considered. The recognized immunoglobulin genes include the kappa, lambda, alpha, gamma, delta, epsilon, and mu constant region genes, as well as the myriad immunoglobulin variable region genes. Light chains are classified as either kappa or lambda. Heavy chains are classified as gamma, mu, alpha, delta, or 20 epsilon, defining the immunoglobulin classes, IgG, IgM, IgA, IgD, and IgE, respectively. The basic immunoglobulin (antibody) structural unit is known to comprise a tetramer or dimer. Each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (L) (about 25 kD) and one "heavy" (H) chain (about 50-70 kD). The N-terminus of each chain defines a variable region of about 100 to 110 or more amino acids, primarily responsible for antigen recognition. The terms 25 "variable light chain" and "variable heavy chain" refer to these variable regions of the light and heavy chains, respectively.

In embodiments, the nucleic acid molecule of the present invention is intended to comprise a sequence encoding a mammalian antibody, in particular human antibodies. In embodiments, the nucleic acid molecule comprises a sequence encoding an antibody or fragments thereof.

30 "Autoantibody" refers to an antibody that is produced by a B cell specific for an autoantigen.

"siRNA (small interfering RNA)" is a short, double-stranded RNA molecule, typically 20-25 nucleotides in length, that promotes the degradation of complementary mRNA, leading to the silencing of specific genes through a process called RNA interference (RNAi).

35 "shRNA (short hairpin RNA)" is an RNA molecule that forms a stem-loop structure and is processed by the cell into siRNA-like fragments, which also induce gene silencing through RNA interference. shRNA is often used for sustained gene silencing when expressed from DNA constructs integrated into the genome.

In the context of the present invention, siRNA and shRNA serve as key molecular tools for the downregulation or silencing of specific genes involved in neuromuscular transmission, particularly 40 AChR and MuSK. siRNA molecules, when directly administered or delivered via suitable transfection

vectors, enable the targeted degradation of mRNA transcripts, thereby preventing the translation of the AChR or MuSK proteins and effectively reducing the sensitivity of muscle cells to acetylcholine-induced excitation. The use of siRNA offers advantages in transient, dose-dependent gene silencing and reduced immune responses due to their short length and ability to be delivered via diverse
5 vehicles, such as lipid nanoparticles or adeno-associated viruses (AAV). On the other hand, shRNA provides a means for more sustained gene silencing by integrating DNA constructs encoding shRNA sequences, which are processed into mature RNA molecules within the cell. These shRNA sequences can be expressed over extended periods, offering a prolonged therapeutic effect, which is advantageous for conditions requiring sustained inhibition of neuromuscular signaling, such as
10 myasthenia gravis. Combining siRNA and shRNA-based approaches with tissue-specific promoters ensures that the silencing is localized to the desired cell types, reducing the risk of off-target effects and enhancing therapeutic specificity. Furthermore, using RNA interference techniques in conjunction with nucleic acid-based therapies, such as those encoding modified receptors or neurotoxins, provides a novel strategy for fine-tuning the therapeutic modulation of neuromuscular
15 function while minimizing adverse systemic effects.

As used herein, a "linker" or "spacer" refers to a short amino acid sequence that connects two or more protein domains or functional units within a single polypeptide chain. The primary function of a linker is to maintain the structural integrity and independent functionality of the fused protein domains while preventing steric hindrance or unwanted interactions. Linkers can be classified as
20 rigid or flexible, with rigid linkers (often rich in proline) serving as structural spacers that minimize domain interference, while flexible linkers (typically Gly-rich) provide mobility and adaptability, facilitating proper folding and functional interactions. Glycine-serine (Gly-Ser or GS) linkers are among the most commonly used flexible linkers, as they enhance protein stability in aqueous environments and provide the necessary spatial separation between domains. By optimizing the
25 linker sequence, it is possible to modulate the structural and functional properties of the fusion protein, ensuring efficient expression, proper domain folding, and retained biological activity. Non-limiting examples of linkers include glycine polymers, glycine-serine polymers, glycine-alanine polymers, alanine-serine polymers, and other flexible linkers known in the art, such as the Whitlow linker. Glycine and glycine-serine polymers are relatively unstructured and, therefore, may be able to
30 serve as a neutral tether between domains of fusion proteins as described herein. However, also rigid linkers, cleavable linkers, affinity linkers, helical linkers, coiled-coil linkers, or linkers with structural motifs may be employed depending on the specific requirement of the fusion protein, including the desired distance and orientation between domains, the need for flexibility or rigidity, and any additional functionalities that may be required.

35 In certain embodiments, the nucleic acid molecule comprises a sequence encoding a linker. In certain embodiments, the fusion protein comprises a linker. In further embodiments, the linker is repetitive.

By conjugating the neurotoxin to a motor end plate receptor, the resulting fusion protein can be selectively expressed at the motor end plate, anchored via the linker sequence. This structural
40 configuration ensures the targeted localization and retention of the protein within the motor end plate, thereby facilitating its directed transport to the presynaptic membrane. This targeted delivery

mechanism enhances the specificity of neurotoxin activity while minimizing off-target effects and systemic distribution.

Thus, in one embodiment, a neurotoxin is conjugated to a motor end plate receptor via a linker sequence. In a further embodiment, BoNT or fragments thereof are fused to the AChR or fragments thereof via a linker.

“Transfection” is the process of introducing nucleic acids, such as DNA or RNA, into eukaryotic cells to achieve the expression or silencing of specific genes. In the context of the present invention, transfection plays a critical role in delivering therapeutic nucleic acids, such as siRNA, shRNA, or plasmid DNA encoding modified receptors or BoNT or TeNT genes, directly into target cells, such as muscle or skin cells. By using transfection techniques, which are well-known in the art, the invention enables the precise modulation of gene expression at the neuromuscular junction, particularly through the targeted expression of receptors like AChR and MuSK or the silencing of specific genes involved in neuromuscular transmission. This method allows for the local and sustained expression of therapeutic proteins, including BoNT or TeNT, while minimizing systemic exposure and associated side effects. Depending on the target cell type and therapeutic goal, transfection can be achieved through various approaches, such as lipid nanoparticles (LNPs), polyethyleneimine (PEI) particles, viral vectors, or electroporation.

Medical conditions

“Autoimmune conditions” are diseases where the immune system mistakenly targets and attacks the body’s healthy tissues, recognizing them as foreign invaders. These conditions arise from a malfunction in the adaptive immune system, distinct from autoinflammatory diseases linked to the innate immune system. Over 80 autoimmune diseases are recognized, with recent research suggesting the presence of more than 100 distinct types. These diseases can affect nearly any part of the body, with symptoms ranging from general fatigue, low-grade fever, and malaise to more specific manifestations such as joint pain, rashes, and neurological disturbances. The causes of autoimmune diseases are multifactorial, involving genetic predispositions and environmental triggers. Common autoimmune diseases include rheumatoid arthritis, systemic lupus erythematosus, type 1 diabetes, multiple sclerosis, and psoriasis. Diagnosis is often complicated by the wide variability in symptoms and their fluctuating nature. Treatment typically focuses on managing symptoms and suppressing the overactive immune response, with options such as immunosuppressants, corticosteroids, and biologics. However, these treatments do not offer cures; long-term management is generally required.

“Myasthenia gravis (MG)” is a chronic autoimmune disorder characterized by skeletal muscle weakness due to impaired neuromuscular transmission. The pathophysiology of MG involves the production of antibodies that target and disrupt the nicotinic acetylcholine receptors (AChR) located at the neuromuscular junction (NMJ), leading to muscle weakness. The predominant antibodies in MG are immunoglobulin G1 (IgG1) and IgG3, which initiate complement-mediated damage or block AChR function, thereby preventing effective communication between nerve and muscle cells. Additionally, antibodies against other proteins such as muscle-specific kinase (MuSK), lipoprotein receptor-related protein 4 (LRP4), and agrin have been identified in certain subsets of MG patients, contributing to the variability in disease presentation and severity. The thymus gland often shows

abnormalities in MG patients, with some individuals developing thymomas or lymphoid hyperplasia. Clinical manifestations of MG vary widely, ranging from ocular symptoms like ptosis and diplopia to generalized muscle weakness, potentially involving respiratory muscles and leading to respiratory failure in severe cases. Diagnosis is supported through serological testing for specific antibodies, electromyography (EMG), and repetitive stimulation tests. Treatment strategies include acetylcholinesterase inhibitors to enhance neuromuscular transmission, immunosuppressive drugs to reduce autoimmune activity, thymectomy in select cases, and interventions such as plasmapheresis during acute exacerbations. In rare cases, certain medications may trigger or worsen MG, including specific antibiotics and immune checkpoint inhibitors.

- 5
- 10 “Spasticity” is a motor disorder characterized by an abnormal increase in muscle tone, typically in response to passive stretch, resulting from damage to the central nervous system (CNS). This condition involves a velocity-dependent rise in resistance to movement, often accompanied by hyperreflexia. It is commonly associated with upper motor neuron syndromes such as cerebral palsy, multiple sclerosis, and spinal cord injury. Spasticity arises from an imbalance between excitatory and inhibitory signals to α motor neurons, leading to heightened muscle excitability. This excessive muscle contraction disrupts coordinated movement, causing functional impairments like decreased range of motion, contractures, and gait abnormalities. Treatment of spasticity aims to reduce muscle tone and improve motor function, with Botulinum toxin type A (BoNT-A) playing a central role in contemporary management. BoNT-A works by inhibiting acetylcholine release at the neuromuscular junction, reducing involuntary muscle activity. This chemodenervation effect provides symptomatic relief, particularly for focal spasticity, and can enhance joint range of motion and muscle function, though its benefits are typically temporary, requiring repeated injections. Despite its efficacy, BoNT-A use may be associated with adverse effects, including muscle weakness in both the targeted and adjacent muscles. The therapeutic window for optimal effects is typically within 4 to 6 weeks post-injection, after which spasticity may return. As such, BoNT-A remains a key intervention in managing spasticity, though careful consideration of its potential for muscle weakness is necessary for effective treatment.

- Dystonia is a neurological movement disorder characterized by sustained or repetitive muscle contractions, leading to twisting, abnormal postures, or involuntary movements. These symptoms may resemble tremors and often worsen with physical activity, potentially spreading to adjacent muscles. The condition may arise from various causes, including genetic factors, infections, trauma, and pharmaceutical reactions. Treatment approaches for dystonia are tailored to the individual's needs and can involve oral medications, physical therapy, and surgical interventions like deep brain stimulation. A key treatment modality is chemodenervation through botulinum neurotoxin (BoNT) injections, which effectively target focal and segmental dystonias. BoNT functions by blocking the release of acetylcholine, inhibiting muscle contraction in the affected areas and thereby reducing dystonic symptoms. In clinical settings, BoNT is recognized as a crucial therapeutic tool, particularly for localized dystonia where targeted muscle groups are injected with the neurotoxin. Additionally, treatment may include oral anticholinergics, dopamine-based therapies for specific forms like dopa-responsive dystonia, and, in severe, refractory cases, deep brain stimulation.

“Hyperhidrosis” is a medical condition characterized by excessive perspiration beyond what is necessary for regulating body temperature. This abnormal sweating often occurs without physical exertion or heat exposure and can affect specific body regions, such as the palms, soles, axillae,

and face, or be generalized throughout the body. The disorder is classified into primary (focal) hyperhidrosis, which is localized and typically hereditary, and secondary hyperhidrosis, which arises from underlying conditions such as endocrine disorders or medications. Diagnosis is often clinical, with tests like the sweat test helping to confirm the condition. Treatment strategies are employed, starting with topical antiperspirants and oral anticholinergics for mild cases. For more severe instances, botulinum toxin (BTX-A) injections represent an effective and FDA-approved option. BTX-A works by cleaving the SNAP-25 protein, preventing the release of acetylcholine, which is responsible for stimulating sweat glands. As a result, sweating is significantly reduced in treated areas for up to 9 months, with repeat treatments required for sustained efficacy. Although highly effective, BTX-A is typically reserved for patients who do not respond to conservative measures due to the associated costs and the need for repeated injections. In addition to BTX-A, other interventions, including iontophoresis, sympathectomy, and various surgical options, may be considered depending on the severity and location of hyperhidrosis.

As used herein, "aesthetic medicine" refers to a branch of medical practice focused on enhancing physical appearance through minimally invasive or non-invasive procedures, often employing pharmacological, biological, or device-based interventions. It encompasses treatments that improve skin texture, volume loss, muscular activity, and overall facial and body aesthetics while maintaining a therapeutic profile. Among these, BoNT, primarily serotype A, is a cornerstone due to its ability to induce temporary chemodenervation by inhibiting acetylcholine release at neuromuscular junctions. BoNT is widely utilized to reduce dynamic rhytides, including glabellar lines, forehead rhytides, lateral canthal lines, perioral lines, nasal rhytides, and platysmal banding. Beyond facial rejuvenation, BoNT is applied for masseter hypertrophy reduction, hyperhidrosis, and other functional aesthetic concerns. Aesthetic medicine also integrates adjunctive modalities such as dermal fillers for volume restoration, laser therapy for resurfacing, chemical peels for epidermal renewal, and energy-based devices for skin tightening. The administration of BoNT and other aesthetic treatments requires precise dosing, targeted injection techniques, and individualized treatment planning to optimize safety and efficacy while minimizing complications such as ptosis, asymmetry, or unintended diffusion. Regulatory approvals, including those by the FDA, define specific indications, while off-label use expands the scope of treatment applications. Combination therapies leveraging BoNT alongside other aesthetic interventions have demonstrated synergistic benefits.

BoNT in aesthetic medicine refers to the clinical application of botulinum neurotoxin, primarily serotype A, to modulate facial musculature and improve the appearance of dynamic wrinkles and other cosmetic concerns. BoNT exerts its effect by inhibiting acetylcholine release at the neuromuscular junction, leading to temporary muscle relaxation and attenuation of expression lines. BoNT-A has been mainly approved for aesthetic indications, such as glabellar lines, while off-label applications extend to forehead rhytides, lateral canthal lines (crow's feet), perioral lines, nasal rhytides (bunny lines), jawline contouring via masseter reduction, and platysmal banding in the neck. Administration techniques vary according to anatomical site, muscle function, and patient-specific factors, requiring precise injection placement to avoid complications such as ptosis, asymmetry, or unintended muscle diffusion. Treatment efficacy is typically observed within days, reaching peak effect in two weeks, with results lasting approximately three to four months. BoNT-A is frequently used with other aesthetic modalities, including dermal fillers for volumization, laser resurfacing for

textural improvement, and thread lifts for tissue repositioning. While adverse effects are generally mild and transient, including localized bruising, swelling, and rare resistance due to antibody formation, proper patient selection and injection technique minimize risks.

Compositions and Formulations

- 5 The compositions contemplated herein may comprise one or more polypeptides, polynucleotides, vectors comprising said polynucleotides, genetically modified immune effector cells, etc., as contemplated herein. Compositions include but are not limited to pharmaceutical compositions.

A "pharmaceutical composition" refers to a composition formulated in pharmaceutically acceptable or physiologically acceptable solutions for administration to a cell or an animal, either alone or in
10 combination with one or more other therapy modalities. It will also be understood that, if desired, the compositions of the invention may be administered in combination with other agents as well, such as e.g. cytokines, growth factors, hormones, small molecules, chemotherapeutics, pro-drugs, drugs, antibodies, or other various pharmaceutically active agents. There is virtually no limit to other components that may also be included in the compositions, provided that the additional agents do
15 not adversely affect the ability of the composition to deliver the intended therapy.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable
20 benefit/risk ratio.

As used herein, "pharmaceutically acceptable carrier, diluent or excipient" includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, surfactant, or emulsifier which has been approved by the United States Food and Drug
25 Administration as being acceptable for use in humans or domestic animals. Exemplary pharmaceutically acceptable carriers include, but are not limited to, to sugars, such as lactose, glucose, and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and cellulose acetate; tragacanth; malt; gelatin; talc; cocoa butter, waxes, animal and vegetable fats, paraffin, silicones, bentonites, silicic
30 acid, zinc oxide; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil, and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol, and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; phosphate buffer solutions; and any other compatible substances
35 employed in pharmaceutical formulations.

In particular embodiments, compositions of the present invention comprise an amount of CAAR-expressing immune effector cells contemplated herein. As used herein, the term "amount" refers to "an amount effective" or "an effective amount" of a genetically modified therapeutic cell, e.g., T cell, to achieve a beneficial or desired prophylactic or therapeutic result, including clinical results.

A "prophylactically effective amount" refers to the amount of a genetically modified therapeutic cell that is effective in achieving the desired prophylactic result. Typically, but not necessarily, since a prophylactic dose is used in subjects prior to or at an earlier stage of disease, the prophylactically effective amount is less than the therapeutically effective amount. The term prophylactic does not necessarily refer to a complete prohibition or prevention of a particular medical disorder. The term prophylactic also refers to reducing the risk of a certain medical disorder occurring or worsening in its symptoms.

A "therapeutically effective amount" of a genetically modified therapeutic cell may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the stem and progenitor cells to elicit a desired response in the individual. A therapeutically effective amount is also one in which the therapeutically beneficial effects outweigh any toxic or detrimental effects of the virus or transduced therapeutic cells. The term "therapeutically effective amount" includes an amount that is effective to "treat" a subject (e.g., a patient). When a therapeutic amount is indicated, the precise amount of the compositions of the present invention to be administered can be determined by a physician considering individual differences in age, weight, tumor size, extent of infection or metastasis, and condition of the patient (subject).

Generally, compositions comprising the cells activated and expanded as described herein may be utilized in the treatment and prevention of diseases such as autoimmune conditions, spasticity, dystonia, hyperhidrosis, and/or aesthetic medicine. The genetically modified cells of the present invention may be administered either alone or as a pharmaceutical composition in combination with carriers, diluents, and/or excipients. In particular embodiments, pharmaceutical compositions contemplated herein comprise an amount of genetically modified cells in combination with one or more pharmaceutically or physiologically acceptable carriers, diluents, or excipients.

Pharmaceutical compositions of the present invention comprising a genetically modified cell according to the present invention may comprise buffers such as neutral buffered saline, phosphate buffered saline, and the like; carbohydrates such as glucose, mannose, sucrose or dextrans, mannitol; proteins; polypeptides or amino acids such as glycine; antioxidants; chelating agents such as EDTA or glutathione; adjuvants (e.g., aluminum hydroxide); and preservatives. Compositions of the present invention are preferably formulated for parenteral administration, e.g., intravascular (intravenous or intraarterial), intraperitoneal, or intramuscular administration.

The liquid pharmaceutical compositions, whether they be solutions, suspensions, or other like forms, may include one or more of the following: sterile diluents such as water for injection, saline solution, preferably physiological saline, Ringer's solution, isotonic sodium chloride, fixed oils such as synthetic mono or diglycerides which may serve as the solvent or suspending medium, polyethylene glycols, glycerin, propylene glycol or other solvents; antibacterial agents such as benzyl alcohol or methylparaben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampoules, disposable syringes, or multiple dose vials made of glass or plastic. An injectable pharmaceutical composition is preferably sterile.

Therapeutic Methods

As used herein, the terms "individual" and "subject" are often used interchangeably and refer to any animal that exhibits a symptom of a disease, disorder, or condition that can be treated with the gene therapy vectors, cell-based therapeutics, and methods disclosed elsewhere herein. In preferred embodiments, a subject includes any animal that exhibits symptoms of a disease, disorder, or condition of the hematopoietic system, e.g., an autoimmune disease, that can be treated with the cell-based therapeutics and methods disclosed herein. Suitable subjects include humans, laboratory animals (such as mice, rats, rabbits, or guinea pigs), farm animals, and domestic animals or pets (such as cats or dogs). Non-human primates and, preferably, human patients are included.

As used herein, "treatment" or "treating" includes any beneficial or desirable effect on the symptoms or pathology of a disease or pathological condition and may include even minimal reductions in one or more measurable markers of the disease or condition being treated. Treatment can optionally involve either the reduction or amelioration of symptoms of the disease or condition or the delaying of the progression of the disease or condition. "Treatment" does not necessarily indicate complete eradication or cure of the disease or condition or associated symptoms thereof.

As used herein, "prevent" and similar words such as "prevented," "preventing," or "prophylactic," etc., indicate an approach for preventing, inhibiting, or reducing the likelihood of the occurrence or recurrence of a disease or condition. It also refers to delaying the onset or recurrence of a disease or condition or delaying the occurrence or recurrence of the symptoms of a disease or condition. As used herein, "prevention" and similar words also include reducing the intensity, effect, symptoms, and/or burden of a disease or condition prior to the onset or recurrence of the disease or condition.

The quantity and frequency of administration will be determined by such factors as the condition of the patient and the type and severity of the patient's disease, although clinical trials may determine appropriate dosages.

The administration of the compositions contemplated herein may be carried out in any convenient manner, including by aerosol inhalation, injection, ingestion, transfusion, implantation, or transplantation. In a preferred embodiment, compositions are administered parenterally. The phrases "parenteral administration" and "administered parenterally," as used herein, refer to modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravascular, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intratumoral, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

General Remarks

All words and terms used herein shall have the same meaning commonly given to them by the person skilled in the art unless the context indicates a different meaning. All terms used in the singular shall include the plural of that term and vice versa.

It will be understood that particular embodiments described herein are shown by way of illustration and not as limitations of the invention. The principal features of this invention can be employed in various embodiments without departing from the scope of the invention. Those skilled in the art will recognize or be able to ascertain, using most routine study, numerous equivalents to the specific

procedures described herein. Such equivalents are considered to be within the scope of this invention and are covered by the claims. All publications and patent applications mentioned in the specification indicate the skill level of those skilled in the art to which this invention pertains. All publications and patent applications are herein incorporated by reference to the same extent as if
5 each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

The use of the word "a" or "an" when used in conjunction with the term "comprising" in the claims and/or the specification may mean "one," but it is also consistent with the meaning of "one or more," "at least one," and "one or more than one." The term "or" in the claims is used to mean "and/or"
10 unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive. However, the disclosure supports a definition of only alternatives and "and/or." Throughout this application, where relevant, the term "about" indicates that a value includes the inherent variation of error for the device, the method employed to determine the value or the variation among the study subjects.

FIGURES

The invention is demonstrated by way of example in the following figures. The figures are to provide a further description of potentially preferred embodiments that enhance the support of one or more non-limiting embodiments of the invention.

Description of the figures:

Figure 1: Exemplary plasmid map for the AChR-BoNT fusion proteins.

Figure 2: Detailed view of the plasmid map for the AChR BoNT fusion protein with a four-fold GGGGS linker.

Figure 3: Detailed view of the plasmid map for the AChR BoNT fusion protein with a eight-fold
25 GGGGS linker.

Figure 4: Section of the plasmid map for the AChR BoNT fusion protein with a quintuple repeat of a human IgG hinge region as a linker.

Figure 5: Schematic representation of an example of a modified MuSK protein with a single repetition of the Ig-like domains and a fusion protein (left), as well as of the normal (wild-type) MuSK
30 (right).

Figure 6: Exemplary plasmid map of a construct with 3 shRNAs for the murine AChR and a control shRNA, as well as a chimeric human AChR and a MYOG promoter.

Figure 7: Exemplary plasmid map of a construct with only one shRNA for the murine AChR and U6 promoter, as well as luciferase as a reporter gene.

EXAMPLES

The invention is demonstrated by way of the examples disclosed below. The examples provide technical support for and a more detailed description of potentially preferred, non-limiting embodiments of the invention.

5 *Summary of the Examples*

In order to demonstrate the functionality and beneficial properties of the nucleic acid molecule and the fusion protein described herein, the following examples are to be considered:

- RNA interference (RNAi)-mediated downregulation of the acetylcholine receptor (AChR) in muscle cells
- 10 - Engineering AChR for Controlled BoNT Expression at the Motor Endplate

Example 1: RNA interference (RNAi)-mediated downregulation of the acetylcholine receptor (AChR) in muscle cells

For RNA interference (RNAi)-mediated downregulation of the acetylcholine receptor (AChR) in muscle cells, two primary approaches are employed: direct injection of
15 siRNA or transfection with an shRNA-encoding vector.

In the case of siRNA administration, the unpackaged siRNA is injected directly into muscle tissue. However, cellular uptake is significantly enhanced through appropriate delivery vehicles, such as liposomes, lipid nanoparticles (LNPs), polyethyleneimine (PEI), or similar transfection agents.

Using shRNA-encoding vectors offers a prolonged RNAi effect, ensuring sustained AChR
20 downregulation over an extended period. This is further optimized by selecting suitable promoters or incorporating a scaffold/matrix attachment region (S/MAR) element. In experimental applications, four distinct shRNA constructs were employed, each individually incorporated into plasmid vectors containing either a U6 promoter or a miR30 precursor in combination with either a cytomegalovirus (CMV) promoter or a muscle-specific MYOG promoter.

25 Additionally, gene constructs containing the shRNA expression cassette are co-integrated with other genetic elements, allowing simultaneous expression of modified AChR sequences resistant to RNAi-mediated degradation. Specifically, modified AChR gene sequences are designed to include target sites for shRNA binding, rendering them immune to endogenous shRNA-mediated knockdown. Such modifications should preferably avoid the transmembrane domain, as alterations in this region could
30 disrupt the targeted integration and functional localization of the AChR at the neuromuscular endplate.

For sequence modifications, heterologous gene sequences from other species serve as templates, with chimeric sequences incorporating species-specific variations in the shRNA target regions. For example, a chimeric AChR sequence was inserted into a plasmid containing the MYOG
35 promoter along with three shRNAs, each embedded within miR30 precursors. This chimeric sequence incorporates rabbit AChR amino acid sequence segments at the shRNA target sites, which differ from human and murine AChR sequences. The shRNA constructs were specifically designed to target the murine AChR, ensuring that in transfected mouse muscle cells,

the endogenous murine AChR is downregulated while the resistant chimeric receptor is effectively expressed, facilitating experimental validation *in vivo* models.

Example 2: Engineering AChR for Controlled BoNT Expression at the Motor Endplate

5 To prevent the unintended release of BoNT, the protein may be fused to a transmembrane domain via a linker sequence. However, ubiquitous expression of BoNT across the entire cell membrane presents two significant drawbacks. First, BoNT proteins displayed on the membrane surface may elicit an immunogenic response, potentially leading to neutralizing antibody formation. Second, despite membrane anchoring, there remains a risk of eventual BoNT release, which could compromise targeted therapeutic efficacy and increase off-target effects.

10 To circumvent these issues, the present invention employs a strategy for the specific expression of BoNT at the neuromuscular junction (NMJ) by leveraging the ϵ -subunit variant of the acetylcholine receptor. In an initial experimental approach, a DNA plasmid was engineered wherein the ϵ -subunit of AChR was C-terminally fused to a BoNT-encoding sequence via a GGGGS linker. This construct was subsequently used to transfect the tibialis muscle of mice, leading to an observable reduction in
15 muscle tone. However, the observed phenotypic effects did not fully align with the expected BoNT-induced paralysis, suggesting that the BoNT fusion protein was not responsible for the observed outcome.

Further analysis indicated that the synaptic cleft width (10–40 nm) was likely too great to allow the BoNT fusion protein to effectively reach the presynaptic nerve terminal and exert its expected
20 pharmacological action. This experimental finding led to the novel concept of achieving a therapeutic effect by modifying AChR itself rather than relying solely on BoNT-mediated neurotoxicity. This approach represents a paradigm shift in neuromuscular modulation, wherein engineered AChR variants could be utilized to achieve targeted pharmacological outcomes at the motor endplate, thereby minimizing systemic side effects and enhancing therapeutic precision.

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CLAIMS

1. A nucleic acid molecule for modulating neuromuscular transmission, the nucleic acid molecule comprising a sequence encoding one or more receptors of the motor end plate or fragments thereof.
2. The nucleic acid molecule according to claim 1, wherein the receptor of the motor end plate is an acetylcholine receptor (AChR), preferably a nicotinic acetylcholine receptor (nAChR) or fragments thereof.
3. The nucleic acid molecule according to claims 1 or 2, wherein the receptor of the motor end plate comprises at least one subunit of the acetyl choline receptor (AChR), preferably an alpha, a beta, a gamma, a delta, and/or an epsilon subunit, more preferably an epsilon subunit.
4. The nucleic acid molecule according to claim 1, wherein the receptor of the motor end plate is a muscle-specific receptor tyrosine kinase (MuSK) and/or a glutamate receptor or fragments thereof.
5. The nucleic acid molecule according to claim 1, wherein the nucleic acid molecule is a DNA or RNA molecule.
6. The nucleic acid molecule according to claim 5, wherein the nucleic acid molecule comprises a sequence encoding a neurotoxin.
7. The nucleic acid molecule according to claim 6, wherein the neurotoxin is a botulinum toxin (BoNT) and/or a tetanus toxin.
8. The nucleic acid molecule according to claim 1, wherein the nucleic acid molecule comprises a sequence encoding an antibody.
9. The nucleic acid molecule according to claim 1, wherein the nucleic acid molecule comprises a sequence encoding an siRNA and/or shRNA.
10. The nucleic acid molecule according to claim 1, wherein the nucleic acid molecule comprises a sequence encoding a linker.
11. A nucleic acid vector comprising a nucleic acid molecule according to claims 1-10, wherein the vector a viral vector, such as a lentiviral vector or retroviral vector, a transposon, an RNA vector, or a nanoparticle, such as a lipid nanoparticle, a liposome, or a polyethylenimin (PEI).
12. A fusion protein, preferably comprising one or more features of any one or more of the preceding claims, said fusion protein comprising:
 - a. a receptor of the motor end plate and/or fragments thereof, wherein said receptor of the motor end plate is an acetylcholine receptor (AChR), a muscle-specific receptor tyrosine kinase (MuSK), and/or a glutamate receptor, and/or fragments thereof, and/or

- b. a neurotoxin, wherein the neurotoxin is a botulinum toxin (BoNT) and/or a tetanus toxin, and/or
 - c. siRNA or shRNA.
- 13. An *in vitro* method for modulating neuromuscular transmission, the *in vitro* method comprising transfecting a eukaryotic cell with a nucleic acid molecule according to any one of claims 1-10,
- 14. The *in vitro* method according to claim 13, wherein the eukaryotic cell is a skeletal muscle cell, a smooth muscle cell, and/or a skin cell.
- 15. A genetically modified cell comprising the nucleic acid molecule according to claims 1-10, a vector according to claim 11, or a fusion protein according to claim 12.
- 16. The genetically modified cell according to claim 15, wherein the cell is a eukaryotic cell selected from the group consisting of a skeletal muscle cell, a smooth muscle cell, or a skin cell.
- 17. The genetically modified cell according to claims 15-16 for use in the treatment or prevention of autoimmune conditions, spasticity, dystonia, hyperhidrosis, myasthenia gravis, and/or aesthetic medicine.