IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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First Named Inventor	:	Pardis SABETI, *et al.*	
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Docket No.	:	BROD-5215US-CON	
Title	:	ENGINEERED MUSCLE TARGETING COMPOSITIONS	

AMENDMENT AND RESPONSE

FILED VIA EFS-WEB

Commissioner:

In response to the Non-Final Office Action mailed April 17, 2025 ("Office Action"), please enter and consider the following amendments and remarks.

Certificate of EFS-WEB Transmission pursuant to 37 C.F.R. § 1.8

I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office electronic filing system (EFS-Web) to the USPTO, on July 17, 2025.

/Christopher D. Southgate/

Christopher D. Southgate, Ph.D., J.D.

Reg. No. 54,875

AMENDMENT

In the Claims

Please amend the claims as follows. This listing of claims will replace all prior versions and listings of claims in this application.

1. (Currently amended) An engineered adeno-associated virus (AAV) capsid polypeptide comprising:

an n-mer motif inserted in a surface variable region VR-VIII of the engineered AAV capsid polypeptide,

wherein the n-mer motif comprises the amino acid sequence of any one of SEQ ID NOsNO: 2-7, 20-21, 28-33, 49, 51, 53, 55, 57, 59, 61, 64, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 91, 94, 96, 100, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 158, 160, 163, 166, 168, 170, 172, 174, 177, 179, 181, 183, 185, 187, 189, 191, 193, 195, 199, 201, 203, 205, 207, 210, 212, 214, 216, 218, 220, 222, 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 257, 259, 261, 263, 265, 267, 269, 271, 273, 275, 277, 279, 282, 284, 286, 288, 290, 293, 295, 297, 299, 301, 304, 306, 308, 310, 312, 314, 316, 318, 320, 322, 324, 327, 329, 333, 335, 337, 339, 341, 343, 345, 347, 349, 351, 353, 355, 357, 359, 361, 363, 365, 367, 369, 371, 373, 375, 378, 380, 382, 384, 386, 388, 390, 392, 394, 396, 398, 401, 404, 406, 408, 411, 413, 418, 420, 423, 426, 430, 432, 434, 436, 438, 440, 442, 444, 446, 448, 450, 452, 454, 456, 458, 460, 462, 464, 466, 468, 470, 472, 476, 478, 480, 482, 484, 487, 489, 492, 494, 497, 499, 501, 504, 506, 508, 510, 512, 514, 516, 519, 521, 523, 526, 529, 531, 533, 535, 538, 542, 544, 546, 548, 551, 553, 555, 558, 561, 563, 565, 567, 570, 572, 574, 576, 579, 582, 584, 586, 588, 591, 593, 595, 597, 599, 601, 603, 605, 607, 609, 611, 613, 615, 617, 619, 621, 623, 625, 628, 630, 632, 634, 636, 638, 640, 642, 644, 646, 648, 651, 653, 655, 657, 659, 661, 663, 665, 667, 669, 672, 674, 676, 678, 680, 682, 684, 686, 688, 690, 692, 694, 696, 698, 700, 703, 707, 709, 711, 713, 715, 717, 720, 723, 726, 728, 731, 733, 735, 737, 739, 741, 743, 745, 747, 749, 751, 754, 756, 758, 760, 763, and 767.

2. (Previously Presented) The engineered AAV capsid polypeptide of claim 1, wherein the n-

mer motif is inserted between any two amino acids between amino acids 587-591 in an AAV9 capsid polypeptide, or an analogous position in an AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV rh.74 or an AAV rh.10 capsid polypeptide.

3. (Canceled)

4. (Previously Presented) The engineered AAV capsid polypeptide of claim 1, wherein the engineered AAV capsid polypeptide is an engineered AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV rh.74, or AAV rh.10 capsid polypeptide.

5. (Previously Presented) The engineered AAV capsid polypeptide of claim 1, wherein (a) the amino acid at position 588 in an AAV9 capsid polypeptide or in an analogous position in an AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV rh.74, or an AAV rh.10 capsid polypeptide is glycine or alanine, (b) the amino acid at position 592 in an AAV9 capsid polypeptide or in an analogous position in an AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV rh.74, or an AAV rh.10 capsid polypeptide is glutamine, or both (a) and (b).

6. (Canceled)

7. (Previously Presented) The engineered AAV capsid polypeptide of claim 1, wherein the engineered AAV capsid polypeptide further comprises one or more mutations that result in a reduced or an eliminated uptake in a non-muscle cell as compared to an AAV capsid comprising an engineered AAV capsid polypeptide or a wild-type AAV capsid polypeptide that lack the one or more mutations, wherein the one or more mutations are in position 267, in position 269, in position 504, in position 505, in position 590, or any combination thereof in an AAV9 capsid polypeptide (SEQ ID NO: 1) or in one or more positions corresponding thereto in a non-AAV9 capsid polypeptide, wherein the non-AAV9 capsid polypeptide is an AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV rh.74, or AAV rh.10 capsid polypeptide.

8. (Previously Presented) The engineered AAV capsid polypeptide of claim 7, wherein the engineered AAV capsid polypeptide is an engineered AAV9 capsid polypeptide

comprising a mutation at position 267, position 269 or both of a wild-type AAV9 capsid polypeptide (SEQ ID NO: 1), wherein the mutation at position 267 is a G to A mutation and wherein the mutation at position 269 is an S to T mutation, wherein the engineered AAV capsid polypeptide is an engineered AAV9 capsid polypeptide comprising a mutation at position 590 of a wild-type AAV9 capsid polypeptide (SEQ ID NO: 1), wherein the mutation at position 509 is a Q to A mutation, or wherein the engineered AAV capsid polypeptide is an engineered AAV9 capsid polypeptide comprising a mutation at position 504, position 505, or both of a wild-type AAV9 capsid polypeptide (SEQ ID NO: 1), wherein the mutation at position 504 is a G to A mutation and wherein the mutation at position 505 is a P to A mutation.

9. (Canceled)

10. (Canceled)

11. (Canceled)

12. (Canceled)

13. (Previously Presented) A vector system comprising:

a vector comprising:

(a) one or more polynucleotides each encoding one or more engineered adeno-associated virus (AAV) capsid polypeptides, or

(b) one or more polynucleotides encoding one or more engineered AAV capsid polypeptides and a cargo,

wherein each of the one or more polypeptides of (a) and (b) comprises an n-mer motif inserted in a surface variable region VR-VIII of the one or more engineered AAV capsid polypeptides,

wherein the n-mer motif comprises the amino acid sequence of any one of SEQ ID NO: 2-7, 20-21, 28-33, 49, 51, 53, 55, 57, 59, 61, 64, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 91, 94, 96, 100, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 158, 160, 163, 166, 168, 170, 172, 174, 177, 179, 181, 183, 185, 187, 189, 191, 193, 195, 199, 201, 203, 205, 207,

210, 212, 214, 216, 218, 220, 222, 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 257, 259, 261, 263, 265, 267, 269, 271, 273, 275, 277, 279, 282, 284, 286, 288, 290, 293, 295, 297, 299, 301, 304, 306, 308, 310, 312, 314, 316, 318, 320, 322, 324, 327, 329, 333, 335, 337, 339, 341, 343, 345, 347, 349, 351, 353, 355, 357, 359, 361, 363, 365, 367, 369, 371, 373, 375, 378, 380, 382, 384, 386, 388, 390, 392, 394, 396, 398, 401, 404, 406, 408, 411, 413, 418, 420, 423, 426, 430, 432, 434, 436, 438, 440, 442, 444, 446, 448, 450, 452, 454, 456, 458, 460, 462, 464, 466, 468, 470, 472, 476, 478, 480, 482, 484, 487, 489, 492, 494, 497, 499, 501, 504, 506, 508, 510, 512, 514, 516, 519, 521, 523, 526, 529, 531, 533, 535, 538, 542, 544, 546, 548, 551, 553, 555, 558, 561, 563, 565, 567, 570, 572, 574, 576, 579, 582, 584, 586, 588, 591, 593, 595, 597, 599, 601, 603, 605, 607, 609, 611, 613, 615, 617, 619, 621, 623, 625, 628, 630, 632, 634, 636, 638, 640, 642, 644, 646, 648, 651, 653, 655, 657, 659, 661, 663, 665, 667, 669, 672, 674, 676, 678, 680, 682, 684, 686, 688, 690, 692, 694, 696, 698, 700, 703, 707, 709, 711, 713, 715, 717, 720, 723, 726, 728, 731, 733, 735, 737, 739, 741, 743, 745, 747, 749, 751, 754, 756, 758, 760, 763, and 767; and

a regulatory element is operatively coupled to one or more polynucleotide(s), the cargo, or both.

14. (Previously Presented) The vector system of claim 13, wherein the cargo is a cargo polynucleotide and is operatively coupled to one or more of the one or more polynucleotides each encoding one or more engineered AAV capsid polypeptides.

15. (Canceled)

16. (Currently amended) The vector system of claim 13, wherein each of the one or more polypeptides of (a) and (b) ~~the one or more engineered AAV capsid polypeptides are~~ comprise an engineered AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV rh.74, or AAV rh.10 capsid polypeptides.

17. (Previously Presented) The vector system of claim 13, wherein a polynucleotide encoding the n-mer motif is inserted between two codons corresponding to any two amino acids between amino acids 581-593 in an AAV9 capsid polypeptide or in an analogous position in an AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV rh.74, AAV

rh.10 capsid polypeptide; or

is inserted between two codons corresponding to amino acids 588 and 589, in an AAV9 capsid polypeptide or in an analogous position thereto in an AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV rh.74, AAV rh.10 capsid polypeptide, or

is inserted between two codons corresponding to any two amino acids between amino acids 585 and 589 in an AAV9 capsid polypeptide or in an analogous in an AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV rh.74, AAV rh.10 capsid polypeptide.

18. (Canceled)

19. (Previously Presented) The vector system of claim 13, wherein the one or more engineered AAV capsid polypeptides comprise one or more mutations that result in reduced or eliminated uptake of an AAV capsid comprising the one or more engineered AAV capsid polypeptides in a non-muscle cell as compared to an AAV capsid lacking the one or more mutations, wherein the one or more mutations are in position 267, in position 269, in position 504, in position 505, in position 590, or any combination thereof in an AAV9 capsid polypeptide (SEQ ID NO: 1) or in one or more positions corresponding thereto in a non-AAV9 capsid polypeptide, wherein the non-AAV9 capsid polypeptide is an AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV rh.74, or AAV rh.10 capsid polypeptide.

20. (Previously Presented) The vector system of claim 19, wherein the one or more engineered AAV capsid polypeptides is/are engineered AAV9 capsid polypeptide(s) comprising a mutation at position 267, position 269 or both of a wild-type AAV9 capsid polypeptide (SEQ ID NO: 1), wherein the mutation at position 267 is a G to A mutation and wherein the mutation at position 269 is an S to T mutation, wherein the engineered AAV capsid polypeptide is an engineered AAV9 capsid polypeptide comprising a mutation at position 590 of a wild-type AAV9 capsid polypeptide (SEQ ID NO: 1), wherein the mutation at position 509 is a Q to A mutation, or wherein the engineered AAV capsid polypeptide is an engineered AAV9 capsid polypeptide comprising a mutation at position 504, position 505, or both of a wild-type AAV9 capsid polypeptide (SEQ ID NO: 1), wherein the

mutation at position 504 is a G to A mutation and wherein the mutation at position 505 is a P to A mutation.

21. (Previously Presented) The vector system of claim 13, wherein the cargo is capable of treating or preventing a muscle disease or disorder, wherein the muscle disease or disorder is optionally an auto immune disease; a cancer; a muscular dystrophy; a neuro-muscular disease; a sugar or glycogen storage disease; an expanded repeat disease; a dominant negative disease; a cardiomyopathy; a viral disease; a progeroid disease; a disease or disorder associated with a cell expressing both αVβ6 and AAVR, or any combination thereof, and wherein the cargo is optionally a morpholino, a peptide-linked morpholino, an antisense oligonucleotide, a PMO, a therapeutic transgene, a polynucleotide encoding a therapeutic polypeptide or peptide, a PPMO, one or more peptides, one or more polynucleotides encoding a CRISPR-Cas protein, a guide RNA, or both, a ribonucleoprotein, wherein the ribonucleoprotein comprises a CRISPR-Cas system molecule, a therapeutic transgene RNA, or other gene modifying or therapeutic RNA and/or protein, or any combination thereof.

22. (Previously Presented) The vector system of claim 13, wherein the cargo is capable of inducing exon skipping in a gene, optionally a dystrophin gene, or wherein the cargo is a mini- or micro-dystrophin gene and optionally comprises spectrin-like repeats 1, 2, 3, and 24, and optionally an nNOS domain.

23. (Original) The vector system of claim 21, wherein the expanded repeat disease is Huntington's disease, a Myotonic Dystrophy, or Facioscapulohumeral muscular dystrophy (FSHD), wherein the muscular dystrophy is Duchene muscular dystrophy, Becker Muscular dystrophy, a Limb-Girdle muscular dystrophy, an Emery Dreifuss muscular dystrophy, a myotonic dystrophy, or FSH, wherein the myotonic dystrophy is Type 1 or Type 2, wherein the cardiomyopathy is dilated cardiomyopathy, hypertrophic cardiomyopathy, DMD-associated cardiomyopathy, or Dannon disease, wherein the sugar or glycogen storage disease is a MPS type III disease or Pompe disease, wherein the MPS type III disease, is MPS Type IIIA, IIIB, IIIC, or IIID, wherein the neuro-muscular disease is Charcot-Marie-Tooth disease or Friedreich's Ataxia, or any combination thereof.

24. (Previously Presented) A cell or a pharmaceutical formulation comprising the vector system of claim 13.

25. (Previously Presented) A cell, a pharmaceutical formulation, an engineered viral capsid, or an engineered viral particle comprising the engineered AAV capsid polypeptide of claim 1.

26. (Previously Presented) The cell, the pharmaceutical formulation, the engineered viral capsid, or the engineered viral particle of claim 25, wherein the engineered viral capsid, the engineered viral particle, or both comprises modulated transduction via integrin heterodimer αVβ6, AAV receptor (AAVR), or both.

27. (Currently amended) A method of delivering a cargo polynucleotide to a target tissue of a subject in need thereof, comprising:

administering ~~to a subject~~ an engineered viral particle to a subject with a muscle disease or disorder, said engineered viral particle comprising

the engineered AAV capsid polypeptide of claim 1, and

a cargo polynucleotide,

wherein the engineered AAV particle facilitates the delivery of the cargo polynucleotide to the subject's muscle cells. ~~in need thereof, the cell, pharmaceutical formulation, engineered viral capsid, or engineered viral particle of claim 25.~~

28. (Currently amended) The method of claim 27, wherein the cargo polynucleotide is capable of treating or preventing the~~a~~ muscle disease or disorder, wherein the muscle disease or disorder is ~~optionally~~ an auto immune disease; a cancer; a muscular dystrophy; a neuromuscular disease; a sugar or glycogen storage disease; an expanded repeat disease; a dominant negative disease; a cardiomyopathy; a viral disease; a progeroid disease; is a disease or disorder is associated with a cell expressing both αVβ6 and AAVR, or any combination thereof, and wherein the optional cargo is optionally a morpholino, a peptide-linked morpholino, an antisense oligonucleotide, a PMO, a therapeutic transgene, a polynucleotide encoding a therapeutic polypeptide or peptide, a PPMO, one or more peptides, one or more polynucleotides encoding a CRISPR-Cas protein, a guide RNA, or both, a ribonucleoprotein, wherein the ribonucleoprotein comprises a CRISPR-Cas system

molecule, a therapeutic transgene RNA, or other gene modifying or therapeutic RNA and/or protein, or any combination thereof.

29. (Currently amended) The method of claim 28, wherein the expanded repeat disease is Huntington's disease, a Myotonic Dystrophy, or Facioscapulohumeral muscular dystrophy (FSHD), wherein the muscular dystrophy is ~~Duchene~~Duchenne muscular dystrophy, Becker Muscular dystrophy, a Limb-Girdle muscular dystrophy, an Emery Dreifuss muscular dystrophy, a myotonic dystrophy, or FSH, wherein the myotonic dystrophy is Type 1 or Type 2, wherein the cardiomyopathy is dilated cardiomyopathy, hypertrophic cardiomyopathy, DMD-associated cardiomyopathy, or Dannon disease, wherein the sugar or glycogen storage disease is a MPS type III disease or Pompe disease, wherein the MPS type III disease, is MPS Type IIIA, IIIB, IIIC, or IIID, wherein the neuro-muscular disease is Charcot-Marie-Tooth disease or Friedreich's Ataxia, or any combination thereof.

30. (Currently amended) The method of claim 28, wherein the method further comprises ~~modulating transduction of~~ preincubating the engineered viral particle ~~via~~ with an integrin heterodimer αVβ6, ~~via~~ an AAV receptor (AAVR), or both prior to administration to the subject.

31. (Previously Presented) The engineered AAV capsid polypeptide of claim 1, wherein the n-mer motif is inserted between any two amino acids between amino acids 585 and 589 in an AAV9 capsid polypeptide or in an analogous position in an AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV rh.74, AAV rh.10 capsid polypeptide.

32. (Previously Presented) The engineered AAV capsid polypeptide of claim 1, further comprising a cargo, wherein the cargo is coupled to or is otherwise associated with the engineered AAV capsid polypeptide.

33. (Previously Presented) The engineered AAV capsid polypeptide of claim 32, wherein the cargo is a morpholino, a peptide-linked morpholino, an antisense oligonucleotide, a PMO, a therapeutic transgene, a polynucleotide encoding a therapeutic polypeptide or peptide, a PPMO, one or more peptides, one or more polynucleotides encoding a CRISPR-Cas protein, a guide RNA, or both, a ribonucleoprotein, wherein the ribonucleoprotein

comprises a CRISPR-Cas system molecule, a therapeutic transgene RNA, or other gene modifying or therapeutic RNA and/or protein, or any combination thereof.

34. (Previously Presented) The engineered AAV capsid polypeptide of claim 32, wherein the cargo treats or prevents a muscle disease or disorder selected from the group consisting of; an autoimmune disease, a cancer, a muscular dystrophy, a neuromuscular disease, a sugar or glycogen storage disease, an expanded repeat disease, a dominant negative disease, a cardiomyopathy, a viral disease, a progeroid disease, and a disease or disorder associated with a cell expressing both αVβ6 and AAVR; or any combination thereof, and wherein the optional cargo.

35. (Previously Presented) The engineered AAV capsid polypeptide of claim 34, wherein the expanded repeat disease is Huntington's disease, a Myotonic Dystrophy, or Facioscapulohumeral muscular dystrophy (FSHD), wherein the muscular dystrophy is Duchene muscular dystrophy, Becker Muscular dystrophy, a Limb-Girdle muscular dystrophy, an Emery Dreifuss muscular dystrophy, a myotonic dystrophy, or FSH, wherein the myotonic dystrophy is Type 1 or Type 2, wherein the cardiomyopathy is dilated cardiomyopathy, hypertrophic cardiomyopathy, DMD-associated cardiomyopathy, or Dannon disease, wherein the sugar or glycogen storage disease is a MPS type III disease or Pompe disease, wherein the MPS type III disease, is MPS Type IIIA, IIIB, IIIC, or IIID, wherein the neuromuscular disease is Charcot-Marie-Tooth disease or Friedreich's Ataxia, or any combination thereof.

36. (Previously Presented) The engineered AAV capsid polypeptide of claim 32, wherein the cargo is capable of inducing exon skipping in a gene, optionally a dystrophin gene, or wherein the cargo is a mini- or micro-dystrophin gene and comprises spectrin-like repeats 1, 2, 3, and 24.

37. (Previously Presented) The engineered AAV capsid polypeptide of claim 7, wherein the non-muscle cell is a liver cell.

38. (Previously Presented) The engineered AAV capsid polypeptide of claim 19, wherein position 267 in the AAV9 capsid polypeptide (SEQ ID NO: 1), or position

corresponding thereto in a non-AAV9 capsid polypeptide, is mutated to an A;

position 269 in the AAV9 capsid polypeptide (SEQ ID NO: 1) or position corresponding thereto in a non-AAV9 capsid polypeptide, is mutated to a T;

position 504 in the AAV9 capsid polypeptide (SEQ ID NO: 1), or position corresponding thereto in a non-AAV9 capsid polypeptide, is mutated to an A;

position 505 in the AAV9 capsid polypeptide (SEQ ID NO: 1), or position corresponding thereto in a non-AAV9 capsid polypeptide, is mutated to an A;

position 590 in the AAV9 capsid polypeptide (SEQ ID NO: 1), or position corresponding thereto in a non-AAV9 capsid polypeptide, is mutated to an A;

or any combination thereof.

39. (New) An engineered AAV particle comprising

a cargo polynucleotide comprising a mini- or micro-dystrophin gene comprising spectrin-like repeats 1, 2, 3, and 24, and

an engineered AAV capsid polypeptide comprising

a muscle-specific targeting moiety comprising

an n-mer motif of any one of SEQ ID NOs: 28, 29, 30, 31, 32 and 33 inserted between any two amino acids between amino acids 581-593 in an AAV9 capsid polypeptide or an analogous position in an AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV rh.74, or an AAV rh.10 capsid polypeptide.

40. (New) A method of treating a subject with a muscular dystrophy, comprising:

administering the engineered AAV particle of claim 40 to a subject,

wherein the engineered AAV particle facilitates the delivery of the mini- or micro-dystrophin gene to the subject's muscle cells, enhancing the subject's muscle-specific force and decreasing the percent force drop after eccentric contraction.

REMARKS

Status of the Claims

Claims 1–2, 4–5, 7–8, 13–14, 16–17, and 19–40 are pending, with claims 1, 13, and 39 being independent. Claims 1, 16, and 27–30 are amended. Claims 3, 6, 9–12, 15, and 18 are canceled without prejudice or disclaimer as to the subject matter recited therein. Claims 39–40 are new.

Written description for amended claims 27-30 and new claims 39-40 can be found throughout the specification and claims as originally filed, and, for example, in paragraphs [0351], [0584], [0681], [0692], [0702] of the corresponding published U.S. Patent Application No. 2022/0228173.

According to the Examiner, claims 1, 2, 4, 5, 7, 8, 13, 14, 17, and 19-26 are allowable.

No new matter was added by these amendments.

Information Disclosure Statement

The Applicant thanks the Examiner for considering and initialing the Information Disclosure Statements filed on 2/10/2025 and 3/18/2025. On review, the Examiner crossed out references to

1) Choudhury et al., Molecular Therapy, vol. 24, no. 7, 1247-1257, July 2016.
2) Pan et al., Chinese Science Bulletin, vol. 58, 411-418, 2013.

These references are not duplicates, and the attached Electronic Acknowledgement Receipt confirms the publications were submitted on February 10, 2025.

Applicants submit herewith an updated Information Disclosure Statement to comply with 37 CFR 1.97 and 1.98(b) for the following references:

3) Stutika et al., Journal of Virology, Vol. 90(3), pp. 1278-1289, February 2016.
4) Wu et al., Journal of Virology , Vol. 74, No. 18, pp. 8635-8647, September 2000.

The WO 2021/50974 PCT, mistakenly listed as WO 2019/50974, is submitted with this response. The Applicant respectfully requests consideration of these references.

Objections to the Claims

The Office action states that claims 3, 12, and 27 are objected to for minor informalities. Applicant respectfully submits that the objections are rendered moot by the cancellation of claims

3 and 12, and by the amendments to claim 27. Withdrawal of the objections is respectfully requested.

Claim Rejections under 35 U.S.C. § 112(b)

In the Office Action, the Examiner rejected claims 16, 27, and 30 under 35 U.S.C. § 112(b) as allegedly lacking clarity. The Applicant asserts the rejection does not apply to the claims as currently presented. Withdrawal of the rejection is respectfully requested.

Claim Rejections under 35 U.S.C. § 112(b), Enablement

In the Office Action, the Examiner rejected claims 27-30 under 35 U.S.C. § 112(b) as allegedly lacking enablement.

The Applicant respectfully disagrees, but in the interest of advancing prosecution, claim 27 is amended to require:

> A method of delivering a cargo polynucleotide to a target tissue of a subject in need thereof, comprising:
>
> administering an engineered viral particle to a subject with a muscle disease or disorder, said engineered viral particle comprising
>
> the engineered AAV capsid polypeptide of claim 1, and
>
> a cargo polynucleotide,
>
> wherein the engineered AAV particle facilitates the delivery of the cargo polynucleotide to the subject's muscle cells.

At page 8 of the Office Action, the Examiner acknowledges that the engineered AAV particle is "designed to have increased gene delivery to muscle cells and is based on the modifications recited herein."[1] In addition, both the application as filed and the corresponding scientific publication by the inventors [2] provide ample evidence that the claimed invention, as currently presented, is enabled over the full scope of the claims.

New claims 39 and 40

New claim 39 is drawn *inter alia* to an engineered AAV particle comprising

[1] page 8 of the Office Action
[2] Tabebordbar, M. *et al.* Directed evolution of a family of AAV capsid variants enabling potent muscle-directed gene delivery across species. *Cell* **184**, 4919-4938.e22 (2021)(of record).

a cargo polynucleotide comprising a mini- or micro-dystrophin gene, and

an engineered AAV capsid polypeptide comprising a muscle-specific targeting moiety comprising an n-mer motif of any one of SEQ ID NOs: 28, 29, 30, 31, 32, and 33.

New claim 40 is drawn *inter alia* to a method of treating a subject with a muscular dystrophy, comprising:

administering the engineered AAV particle of claim 40 to a subject,

Wherein the engineered AAV particle facilitates the delivery of the mini- or micro-dystrophin gene to the subject's muscle cells, enhancing the subject's muscle-specific force and decreasing the percent force drop after eccentric contraction.

At page 6 of the Office Action, the Examiner concedes the specification is "enabling for intramuscular administration to a subject with Duchenne muscular dystrophy an engineered viral particle which encodes mini-or micro-dystrophin gene comprises spectrin-like repeats 1, 2, 3, and 24 within an AAV capsid comprising an engineered AAV capsid comprising at least one of an n-mer listed in any one of SEQ ID NO: . . 28-33. . .."

The administration of the mini- or micro-dystrophin gene packaged in an engineered AAV particle enhances the subject's muscle-specific force and decreases the percent force drop after eccentric contraction. These results are demonstrated in FIGs. 20E-20F of the application as filed and in FIGs. 3D and 3E of the corresponding Tabebordbar et al. (2021) Cell paper.

Accordingly, the claimed invention is enabled. Applicant respectfully requests the withdrawal of the rejection.

Obviousness-Type Double Patenting

Claims 1-5, 7, 8, 12-14, 16-17, 19-26 and 31-38 are provisionally rejected on the ground of non-statutory obviousness-type double patenting over claims 1, 2, 4-10 and 15-24 of co-pending Application No. 17/707,951, claims 1, 3-5, 7, 8, 11, 13, 16, 18, 19, 21, 23, 31-35, 37-39, 42, 44, 45, 47, 48, 52, 58, 59, 61, 62, 64, 74, and 77 of co-pending application 17/764,509 and claims 1, 9, 11-16 and 18-20 of co-pending application 17/642,541.

According to the Examiner, claims 1, 2, 4, 5, 7, 8, 13, 14, 17, and 19-26 are allowable. Pending claims 16, 27-30, and 39-40 are under examination on the merits.

Solely to expedite the prosecution of this application, a Terminal Disclaimer concerning co-pending applications 17/707,951, 17/764,509, and 17/642,541 is being filed concurrently with

this response.

No Waiver

All of the Applicant's arguments and amendments are without prejudice or disclaimer. The Applicant may not have addressed each specific rejection of the independent and dependent claims because the Applicant submits that the independent claims are allowable, as discussed above. Applicant has not acquiesced to any such rejection and reserves the right to address the patentability of any additional claim features in the future.

CONCLUSION

Applicant submits the preceding as a complete response to the Office Action. Applicant submits that this Amendment and Response place the application in condition for allowance and respectfully requests such action. If any issues can be resolved with an Examiner's Amendment or a telephone conference, please get in touch with the Applicant's representative at (478) 292-5119.

No additional fees are believed to be due for consideration of this paper. However, the Commissioner is hereby authorized to charge any fee deemed necessary for consideration of this paper, including any extension of time fees or additional claim fees, or to credit any overpayment to Deposit Account Number 50-5193, reference number BROD-5215US-CON.

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Respectfully submitted,

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