

9. References

* secondary references

- (1) Yang, S.; Chang, R.; Yang, H.; Zhao, T.; Hong, Y.; Kong, H. E.; Sun, X.; Qin, Z.; Jin, P.; Li, S.; Li, X. J. CRISPR/Cas9-Mediated Gene Editing Ameliorates Neurotoxicity in Mouse Model of Huntington's Disease. *J Clin Invest* **2017**, *127* (7), 2719–2724.
- (2) Mercuri, E.; Muntoni, F.; Baranello, G.; Masson, R.; Boespflug-Tanguy, O.; Bruno, C.; Corti, S.; Daron, A.; Deconinck, N.; Servais, L.; Straub, V.; Ouyang, H.; Chand, D.; Tauscher-Wisniewski, S.; Mendonca, N.; Lavrov, A. Onasemnogene Apeparvovec Gene Therapy for Symptomatic Infantile-Onset Spinal Muscular Atrophy Type 1 (STRIVE-EU): An Open-Label, Single-Arm, Multicentre, Phase 3 Trial. *Lancet Neurology* **2021**.
- (3) Christine, C. W.; Bankiewicz, K. S.; Van Laar, A. D.; Richardson, R. M.; Ravina, B.; Kells, A. P.; Boot, B.; Martin, A. J.; Nutt, J.; Thompson, M. E.; Larson, P. S. Magnetic Resonance Imaging-Guided Phase 1 Trial of Putaminal AADC Gene Therapy for Parkinson's Disease. *Ann Neurol* **2019**.
- (4) Griciuc, A.; Federico, A. N.; Natasan, J.; Forte, A. M.; McGinty, D. Gene Therapy for Alzheimer's Disease Targeting CD33 Reduces Amyloid Beta Accumulation and Neuroinflammation. *Hum Mol Genet* **2020**, *29* (17), 2920–2935.
- (5) Mòdol-Caballero, G.; García-Lareu, B.; Herrando-Grabulosa, M.; Sergi Verdés, ·; López-Vales, R.; Pagès, G.; Chillón, · Miguel; Navarro, · Xavier; Bosch, A. Specific Expression of Glial-Derived Neurotrophic Factor in Muscles as Gene Therapy Strategy for Amyotrophic Lateral Sclerosis. *Neurotherapeutics* **2021**.
- (6) Figley, S. A.; Liu, Y.; Karadimas, S. K.; Satkunendrarajah, K.; Fettes, P.; Spratt, S. K.; Lee, G.; Ando, D.; Surosky, R.; Giedlin, M.; Fehlings, M. G. Delayed Administration of a Bio-Engineered Zinc-Finger VEGF-A Gene Therapy Is Neuroprotective and Attenuates Allodynia Following Traumatic Spinal Cord Injury. *PLoS One* **2014**.
- (7) Tanenhaus, A.; Stowe, T.; Young, A.; Mclaughlin, J.; Aeran, R.; Lin, I. W.; Li, J.; Hosur, R.; Chen, M.; Leedy, J.; Chou, T.; Pillay, S.; Vila, M. C.; Kearney, J. A.; Moorhead, M.; Belle, A.; Tagliatela, S. Cell-Selective Adeno-Associated Virus-Mediated SCN1A Gene Regulation Therapy Rescues Mortality and Seizure Phenotypes in a Dravet Syndrome Mouse Model and Is Well Tolerated in Nonhuman Primates. *Hum Gene Ther* **2022**.
- (8) Doudna, J. A.; Charpentier, E. *The New Frontier of Genome Engineering with CRISPR-Cas9*; American Association for the Advancement of Science, 2014; Vol. 346.
- (9) Mendell, J. R.; Al-Zaidy, S. A.; Rodino-Klapac, L. R.; Goodspeed, K.; Gray, S. J.; Kay, C. N.; Boye, S. L.; Boye, S. E.; George, L. A.; Salazar, S.; Corti, M.; Byrne, B. J.; Tremblay, J. P. Current Clinical Applications of In Vivo Gene Therapy with AAVs. *Molecular Therapy* **2021**, *29* (2), 464–488.

- (10) Stödberg, T.; Tomson, T.; Michela Barbaro, |; Stranneheim, H.; Anderlid, B.-M.; Carlsson, S.; Åmark, | Per. Epilepsy Syndromes, Etiologies, and the Use of next-Generation Sequencing in Epilepsy Presenting in the First 2 Years of Life: A Population-Based Study. *Epilepsia* **2020**.
- (11) Miller, J. R.; Zhou, P.; Mudge, J.; Gurtowski, J.; Lee, H.; Ramaraj, T.; Walenz, B. P.; Liu, J.; Stupar, R. M.; Denny, R.; Song, L.; Singh, N.; Maron, L. G.; Mccouch, S. R.; McCombie, W. R.; Schatz, M. C.; Tiffin, P.; Young, N. D.; Silverstein, K. A. T. Hybrid Assembly with Long and Short Reads Improves Discovery of Gene Family Expansions. *BioMed Central Genomics* **2017**.
- (12) Choudhuri, S. *Fundamentals of Molecular Evolution*; Academic Press, 2014.
- (13) Eid, J.; Fehr, A.; Gray, J.; Luong, K.; Lyle, J.; Otto, G.; Peluso, P.; Rank, D.; Baybayan, P.; Bettman, B.; Bibillo, A.; Bjornson, K.; Chaudhuri, B.; Christians, F.; Cicero, R.; Clark, S.; Dalal, R.; Dewinter, A.; Dixon, J.; Foquet, M.; Gaertner, A.; Hardenbol, P.; Heiner, C.; Hester, K.; Holden, D.; Kearns, G.; Kong, X.; Kuse, R.; Lacroix, Y.; Lin, S.; Lundquist, P.; Ma, C.; Marks, P.; Maxham, M.; Murphy, D.; Park, I.; Pham, T.; Phillips, M.; Roy, J.; Sebra, R.; Shen, G.; Sorenson, J.; Tomaney, A.; Travers, K.; Trulson, M.; Vieceli, J.; Wegener, J.; Wu, D.; Yang, A.; Zaccarin, D.; Zhao, P.; Zhong, F.; Korlach, J.; Turner, S. *Real-Time DNA Sequencing from Single Polymerase Molecules.*; 2009; Vol. 323.
- (14) Schadt, E. E.; Banerjee, O.; Fang, G.; Feng, Z.; Wong, W. H.; Zhang, X.; Kislyuk, A.; Clark, T. A.; Luong, K.; Keren-Paz, A.; Chess, A.; Kumar, V.; Chen-Plotkin, A.; Sondheimer, N.; Korlach, J.; Kasarskis, A. Modeling Kinetic Rate Variation in Third Generation DNA Sequencing Data to Detect Putative Modifications to DNA Bases. *Genome Res* **2013**, 23 (1), 129–141.
- (15) Clarke, J.; Wu, H. C.; Jayasinghe, L.; Patel, A.; Reid, S.; Bayley, H. Continuous Base Identification for Single-Molecule Nanopore DNA Sequencing. *Nat Nanotechnol* **2009**, 4 (4), 265–270.
- (16) * Beckett, A. H.; Cook, K. F.; Robson, S. C. A Pandemic in the Age of Next-Generation Sequencing. *Portland Press Limited* **2021**, 43 (6), 10–15.
- (17) Jain, M.; Fiddes, I. T.; Miga, K. H.; Olsen, H. E.; Paten, B.; Akeson, M. Improved Data Analysis for the MinION Nanopore Sequencer. *Nat Methods* **2015**, 12 (4), 351–356.
- (18) Laszlo, A. H.; Derrington, I. M.; Ross, B. C.; Brinkerhoff, H.; Adey, A.; Nova, I. C.; Craig, J. M.; Langford, K. W.; Samson, J. M.; Daza, R.; Doering, K.; Shendure, J.; Gundlach, J. H. Decoding Long Nanopore Sequencing Reads of Natural DNA. *Nat Biotechnol* **2014**, 32 (8), 829–833.
- (19) * *Cost of sequencing a full human genome*. <https://ourworldindata.org/grapher/cost-of-sequencing-a-full-human-genome>.
- (20) N' Songo, A.; Carrasquillo, M. M.; Wang, X.; Nguyen, T.; Asmann, Y.; Younkin, S. G.; Allen, M.; Duara, R.; Greig Custo, M. T.; Graff-Radford, N.; Ertekin-Taner, N. Comprehensive Screening for Disease Risk Variants in Early-Onset Alzheimer's Disease Genes in African Americans Identifies Novel PSEN Variants. *Alzheimers Disease* **2017**.
- (21) Ibilbor, C.; Watson, A. L.; Wang, H.; Gonzalez, G.; Liang, S.; Alonzo, D.; Rodriguez, R. RNA Sequencing in a Penile Cancer Cohort: An Investigation of Biomarkers of Cisplatin Resistance and Potential Therapeutic Drug Targets. *Clin Genitourin Cancer* **2022**, 20 (3), 219–226.

- (22) Barrangou, R.; Fremaux, C.; Deveau, H.; Richards, M.; Boyaval, P.; Moineau, S.; Romero, D. A.; Horvath, P. *CRISPR Provides Acquired Resistance against Viruses in Prokaryotes*; Cambridge Univ. Press, 2007; Vol. 315.
- (23) Brouns, S. J. J.; Jore, M. M.; Lundgren, M.; Westra, E. R.; Slijkhuis, R. J. H.; Snijders, A. P. L.; Dickman, M. J.; Makarova, K. S.; Koonin, E. V.; Van Der Oost, J. *Small CRISPR RNAs Guide Antiviral Defense in Prokaryotes*; Cold Spring Harbor Laboratory Press, 2008; Vol. 321.
- (24) Deltcheva, E.; Chylinski, K.; Sharma, C. M.; Gonzales, K.; Chao, Y.; Pirzada, Z. A.; Eckert, M. R.; Vogel, J.; Charpentier, E. CRISPR RNA Maturation by Trans-Encoded Small RNA and Host Factor RNase III. *Nature* **2011**.
- (25) *A tool for genome editing: CRISPR-Cas9 - BioRender Blog*. <https://www.biorender.com/blog/nobel-prize-chemistry-2020>.
- (26) Mali, P.; Yang, L.; Esvelt, K. M.; Aach, J.; Guell, M.; DiCarlo, J. E.; Norville, J. E.; Church, G. M. *RNA-Guided Human Genome Engineering via Cas9*; American Association for the Advancement of Science, 2013; Vol. 339.
- (27) Walton, R. T.; Christie, K. A.; Whittaker, M. N.; Kleinstiver, B. P. *Unconstrained Genome Targeting with Near-PAMless Engineered CRISPR-Cas9 Variants*; American Association for the Advancement of Science, 2020; Vol. 368.
- (28) Jinek, M.; Chylinski, K.; Fonfara, I.; Hauer, M.; Doudna, J. A.; Charpentier, E. *A Programmable Dual-RNA-Guided DNA Endonuclease in Adaptive Bacterial Immunity*; American Association for the Advancement of Science, 2012; Vol. 337.
- (29) Ran, F. A.; Hsu, P. D.; Lin, C. Y.; Gootenberg, J. S.; Konermann, S.; Trevino, A. E.; Scott, D. A.; Inoue, A.; Matoba, S.; Zhang, Y.; Zhang, F. Double Nicking by RNA-Guided CRISPR Cas9 for Enhanced Genome Editing Specificity. *Cell* **2013**, *154* (6).
- (30) * Pickar-Oliver, A.; Gersbach, C. A. The next Generation of CRISPR–Cas Technologies and Applications. *Nat Rev Mol Cell Biol* **2019**, *20* (8), 490–507.
- (31) Komor, A. C.; Kim, B.; Packer, M. S.; Zuris, J. A.; Liu, D. R. Programmable Editing of a Target Base in Genomic DNA without Double-Stranded DNA Cleavage. *Nature* **2016**.
- (32) Gaudelli, N. M.; Komor, A. C.; Rees, H. A.; Packer, M. S.; Badran, A. H.; Bryson, D. I.; Liu, D. R. Programmable Base Editing of T to G C in Genomic DNA without DNA Cleavage. *Nature* **2017**, *551* (7681), 464–471.
- (33) Anzalone, A. V.; Randolph, P. B.; Davis, J. R.; Sousa, A. A.; Koblan, L. W.; Levy, J. M.; Chen, P. J.; Wilson, C.; Newby, G. A.; Raguram, A.; Liu, D. R. Search-and-Replace Genome Editing without Double-Strand Breaks or Donor DNA. *Nature* **2019**, *576*, 149.
- (34) *Prime editing mechanism*. https://en.wikipedia.org/wiki/Prime_editing#/media/File:Prime_editing_mechanism.png.

- (35) Hilton, I. B.; D, A. M.; Vockley, C. M.; Thakore, P. I.; Crawford, G. E.; Reddy, T. E.; Gersbach, C. A.; Biotechnol, N. Epigenome Editing by a CRISPR/Cas9-Based Acetyltransferase Activates Genes from Promoters and Enhancers. *Nat Biotechnol* **2015**, *33* (5), 510–517.
- (36) Vojta, A.; Dobriní, P.; Tadi, V.; Bočkor, L.; Bočkor, B.; Korá, P.; Julg, B.; Klasí, M.; Zoldoš, V.; Zoldoš, Z. Repurposing the CRISPR-Cas9 System for Targeted DNA Methylation. *Nucleic Acids Res* **2016**, *44* (12), 5615–5628.
- (37) Kearns, N. A.; Pham, H.; Tabak, B.; Genga, R. M.; Silverstein, N. J.; Garber, M.; Maehr, R. Functional Annotation of Native Enhancers with a Cas9-Histone Demethylase Fusion HHS Public Access. *Nat Methods* **2015**, *12* (5), 401–403.
- (38) Gilbert, L. A.; Horlbeck, M. A.; Adamson, B.; Villalta, J. E.; Chen, Y.; Whitehead, E. H.; Guimaraes, C.; Panning, B.; Ploegh, H. L.; Bassik, M. C.; Qi, L. S.; Kampmann, M.; Weissman, J. S. Genome-Scale CRISPR-Mediated Control of Gene Repression and Activation. *Cell* **2014**, *159* (3), 647–661.
- (39) Maeder, M. L.; Linder, S. J.; Cascio, V. M.; Fu, Y.; Ho, Q. H.; Joung, J. K. CRISPR RNA-Guided Activation of Endogenous Human Genes. *Nat Methods* **2013**.
- (40) * Wen, W. S.; Yuan, Z. M.; Ma, S. J.; Xu, J.; Yuan, D. T. CRISPR-Cas9 Systems: Versatile Cancer Modelling Platforms and Promising Therapeutic Strategies. *Int J Cancer* **2016**, *138* (6), 1328–1336.
- (41) Akcakaya, P.; Bobbin, M. L.; Guo, J. A.; Malagon-Lopez, J.; Clement, K.; Garcia, S. P.; Fellows, M. D.; Porritt, M. J.; Firth, M. A.; Carreras, A.; Baccega, T.; Seeliger, F.; Bjursell, M.; Tsai, S. Q.; Nguyen, N. T.; Nitsch, R.; Mayr, L. M.; Pinello, L.; Bohlooly-Y, M.; Aryee, M. J.; Maresca, M.; Keith Joung, J. In Vivo CRISPR Editing with No Detectable Genome-Wide off-Target Mutations. *Nature* **2018**.
- (42) Tsai, S. Q.; Nguyen, N. T.; Malagon-Lopez, J.; Topkar, V. V; Aryee, M. J.; Joung, J. K. CIRCLE-Seq: A Highly Sensitive in Vitro Screen for Genome-Wide CRISPR-Cas9 Nuclease off-Targets. *Nat Methods* **2017**, *14* (6), 607–614.
- (43) Coelho, M. A.; De Braekeleer, E.; Firth, M.; Bista, M.; Lukasiak, S.; Cuomo, M. E.; Taylor, B. J. M. CRISPR GUARD Protects Off-Target Sites from Cas9 Nuclease Activity Using Short Guide RNAs. *Nat Commun* **2020**.
- (44) Yeh, W.-H.; Shubina-Oleinik, O.; Levy, J. M.; Pan, B.; Newby, G. A.; Wornow, M.; Burt, R.; Chen, J. C.; Holt, J. R.; Liu, D. R. In Vivo Base Editing Restores Sensory Transduction and Transiently Improves Auditory Function in a Mouse Model of Recessive Deafness. *Sci Transl Med* **2020**, *12* (546).
- (45) Nagel, G.; Szellas, T.; Huhn, W.; Kateriya, S.; Adeishvili, N.; Berthold, P.; Ollig, D.; Hegemann, P.; Bamberg, E. Channelrhodopsin-2, a Directly Light-Gated Cation-Selective Membrane Channel. *PNAS* **2003**, *100* (SUPPL. 2), 13940–13945.
- (46) Boyden, E. S.; Zhang, F.; Bamberg, E.; Nagel, G.; Deisseroth, K. Millisecond-Timescale, Genetically Targeted Optical Control of Neural Activity. *Nat Neurosci* **2005**, *8* (9), 1263–1268.
- (47) Han, X.; Qian, X.; Bernstein, J. G.; Zhou, H. hui; Franzesi, G. T.; Stern, P.; Bronson, R. T.; Graybiel, A. M.; Desimone, R.; Boyden, E. S. Millisecond-Timescale Optical Control of Neural Dynamics in the Nonhuman Primate Brain. *Neuron* **2009**, *62* (2), 191–198.

- (48) Nagel, G.; Brauner, M.; Liewald, J. F.; Adeishvili, N.; Bamberg, E.; Gottschalk, A. Light Activation of Channelrhodopsin-2 in Excitable Cells of *Caenorhabditis Elegans* Triggers Rapid Behavioral Responses. *Current Biology* **2005**, *15* (24), 2279–2284.
- (49) Klapoetke, N. C.; Murata, Y.; Soo Kim, S.; Pulver, S. R.; Birdsey-Benson, A.; Ku Cho, Y.; Morimoto, T. K.; Chuong, A. S.; Carpenter, E. J.; Tian, Z.; Wang, J.; Xie, Y.; Yan, Z.; Zhang, Y.; Chow, B. Y.; Surek, B.; Melkonian, M.; Jayaraman, V.; Constantine-Paton, M.; Ka-Shu Wong, G.; Boyden, E. S. Independent Optical Excitation of Distinct Neural Populations. *Nat Methods* **2014**, *11* (3), 338–346.
- (50) Chen, R.; Gore, F.; Nguyen, Q. A.; Ramakrishnan, C.; Patel, S.; Kim, S. H.; Raffiee, M.; Kim, Y. S.; Hsueh, B.; Krook-Magnusson, E.; Soltesz, I.; Deisseroth, K. Deep Brain Optogenetics without Intracranial Surgery. *Nat Biotechnol* **2021**, *39* (2), 161.
- (51) Govorunova, E. G.; Sineshchekov, O. A.; Janz, R.; Liu, X.; Spudich, J. L. *Natural Light-Gated Anion Channels: A Family of Microbial Rhodopsins for Advanced Optogenetics*; 2015; Vol. 349.
- (52) Mahn, M.; Gibor, L.; Patil, P.; Cohen-Kashi Malina, K.; Oring, S.; Printz, Y.; Levy, R.; Lampl, I.; Yizhar, O. High-Efficiency Optogenetic Silencing with Soma-Targeted Anion-Conducting Channelrhodopsins. *Nature Communication* **2018**.
- (53) Gradinaru, V.; Thompson, K. R.; Deisseroth, K. ENpHR: A *Neurospora* Halorhodopsin Enhanced for Optogenetic Applications. *Brain Cell Biol* **2008**.
- (54) Diester, I.; Kaufman, M. T.; Mogri, M.; Pashaie, R.; Goo, W.; Yizhar, O.; Ramakrishnan, C.; Deisseroth, K.; Shenoy, K. V. An Optogenetic Toolbox Designed for Primates. *Nat Neurosci* **2011**, 387–397.
- (55) Kralik, J.; van Wyk, M.; Stocker, N.; Kleinlogel, S. Bipolar Cell Targeted Optogenetic Gene Therapy Restores Parallel Retinal Signaling and High-Level Vision in the Degenerated Retina. *Commun Biol* **2022**, *5* (1).
- (56) van Wyk, M.; Pielecka-Fortuna, J.; Löwel, S.; Kleinlogel, S. Restoring the ON Switch in Blind Retinas: Opto-MGluR6, a Next-Generation, Cell-Tailored Optogenetic Tool. *PLoS Biol* **2015**, *13* (5).
- (57) Levskaya, A.; Weiner, O. D.; Lim, W. A.; Voigt, C. A. Spatiotemporal Control of Cell Signalling Using a Light-Switchable Protein Interaction. *Nature* **2009**, 461.
- (58) Müller, K.; Engesser, R.; Metzger, S.; Schulz, S.; Kämpf, M. M.; Busacker, M.; Steinberg, T.; Tomakidi, P.; Ehrbar, M.; Nagy, F.; Timmer, J.; Zubriggen, M. D.; Weber, W. A Red/Far-Red Light-Responsive Bi-Stable Toggle Switch to Control Gene Expression in Mammalian Cells. *Nucleic Acids Res* **2013**, *41* (7).
- (59) Kennedy, M. J.; Hughes, R. M.; Peteya, L. A.; Schwartz, J. W.; Ehlers, M. D.; Tucker, C. L. Rapid Blue Light Induction of Protein Interactions in Living Cells. *Nat Methods* **2010**, *7* (12), 973–975.
- (60) Nihongaki, Y.; Yamamoto, S.; Kawano, F.; Suzuki, H.; Sato, M. CRISPR-Cas9-Based Photoactivatable Transcription System. *Chem Biol* **2015**, *22* (2), 169–174.
- (61) Polstein, L. R.; Gersbach, C. A.; Chem Biol, N. A Light-Inducible CRISPR/Cas9 System for Control of Endogenous Gene Activation. *Nat Chem Biol* **2015**, *11* (3), 198–200.

- (62) Crosson, S.; Moffat, K. Photoexcited Structure of a Plant Photoreceptor Domain Reveals a Light-Driven Molecular Switch. *Plant Cell* **2002**, *14*, 1067–1075.
- (63) Harper, S. M.; Neil, L. C.; Gardner, K. H. *Structural Basis of a Phototropin Light Switch*; 2003; Vol. 301.
- (64) Motta-Mena, L. B.; Reade, A.; Mallory, M. J.; Glantz, S.; Weiner, O. D.; Lynch, K. W.; Gardner, K. H.; Concepcion, K. H. G.; Chem, N.; Author, B. An Optogenetic Gene Expression System with Rapid Activation and Deactivation Kinetics. *Nat Chem Biol* **2014**, *10* (3), 196–202.
- (65) Niopek, D.; Benzinger, D.; Roensch, J.; Draebing, T.; Wehler, P.; Eils, R.; Ventura, B. Di. Engineering Light-Inducible Nuclear Localization Signals for Precise Spatiotemporal Control of Protein Dynamics in Living Cells. *Nat Commun* **2014**.
- (66) Yazawa, M.; Sadaghiani, A. M.; Hsueh, B.; Dolmetsch, R. E. Induction of Protein-Protein Interactions in Live Cells Using Light. *Nat Biotechnol* **2009**, *27* (10), 941–945.
- (67) Zoltowski, B. D.; Crane, B. R. Light Activation of the LOV Protein Vivid Generates a Rapidly Exchanging Dimer. *Biochemistry* **2008**.
- (68) Alexander, G. M.; Rogan, S. C.; Abbas, A. I.; Armbruster, B. N.; Pei, Y.; Allen, J. A.; Nonneman, R. J.; Hartmann, J.; Moy, S. S.; Nicoletis, M. A.; McNamara, J. O.; Roth, B. L. Remote Control of Neuronal Activity in Transgenic Mice Expressing Evolved G Protein-Coupled Receptors. *Neuron* **2009**, *63* (1), 27–39.
- (69) Armbruster, B. N.; Li, X.; Pausch, M. H.; Herlitze, S.; Roth, B. L. Evolving the Lock to Fit the Key to Create a Family of G Protein-Coupled Receptors Potently Activated by an Inert Ligand. *PNAS* **2007**, *104*, 5163–5168.
- (70) Maclaren, D. A. A.; Browne, R. W.; Shaw, J. K.; Radhakrishnan, S. K.; Khare, P.; España, R. A.; Clark, S. D. Clozapine N-Oxide Administration Produces Behavioral Effects in Long-Evans Rats: Implications for Designing DREADD Experiments. *eNeuro* **2016**, *3* (5), 219–235.
- (71) Vardy, E.; Robinson, J. E.; Li, C.; Olsen, R. H. J.; DiBerto, J. F.; Giguere, P. M.; Sassano, F. M.; Huang, X. P.; Zhu, H.; Urban, D. J.; White, K. L.; Rittiner, J. E.; Crowley, N. A.; Pleil, K. E.; Mazzone, C. M.; Mosier, P. D.; Song, J.; Kash, T. L.; Malanga, C. J.; Krashes, M. J.; Roth, B. L. A New DREADD Facilitates the Multiplexed Chemogenetic Interrogation of Behavior. *Neuron* **2015**, *86* (4), 936–946.
- (72) Magnus, C. J.; Lee, P. H.; Atasoy, D.; Su, H. H.; Looger, L. L.; Sternson, S. M. *Chemical and Genetic Engineering of Selective Ion Channel-Ligand Interactions*; 2011; Vol. 333.
- (73) Boehm, M. A.; Bonaventura, J.; Gomez, J. L.; Solís, O.; Stein, E. A.; Bradberry, C. W.; Michaelides, M. Translational PET Applications for Brain Circuit Mapping with Transgenic Neuromodulation Tools. *Pharmacology Biochemistry and Behavior*. Elsevier Inc. May 1, 2021.
- (74) Anthenelli, R. M.; Benowitz, N. L.; West, R.; St Aubin, L.; McRae, T.; Lawrence, D.; Ascher, J.; Russ, C.; Krishen, A.; Evins, A. E. Neuropsychiatric Safety and Efficacy of Varenicline, Bupropion, and Nicotine Patch in Smokers with and without Psychiatric Disorders (EAGLES): A Double-Blind, Randomised, Placebo-Controlled Clinical Trial. *The Lancet* **2016**, *387* (10037), 2507–2520.

- (75) Magnus, C. J.; Lee, P. H.; Bonaventura, J.; Zemla, R.; Gomez, J. L.; Ramirez, M. H.; Hu, X.; Galvan, A.; Basu, J.; Michaelides, M.; Sternson, S. M. *Ultrapotent Chemogenetics for Research and Potential Clinical Applications*; American Association for the Advancement of Science, 2019; Vol. 364.
- (76) Zhang, Y.; Castro, D. C.; Han, Y.; Wu, Y.; Guo, H.; Weng, Z.; Xue, Y.; Ausra, J.; Wang, X.; Li, R.; Wu, G.; Vázquez-Guardado, A.; Xie, Y.; Xie, Z.; Ostojich, D.; Peng, D.; Sun, R.; Wang, B.; Yu, Y.; Leshock, J. P.; Qu, S.; Su, C. J.; Shen, W.; Hang, T.; Banks, A.; Huang, Y.; Radulovic, J.; Gutruf, P.; Bruchas, M. R.; Rogers, J. A. Battery-Free, Lightweight, Injectable Microsystem for in Vivo Wireless Pharmacology and Optogenetics. *Proc Natl Acad Sci U S A* **2019**, *116* (43), 21427–21437.
- (77) Wang, Z.; Hu, M.; Ai, X.; Zhang, Z.; Xing, B. Near-Infrared Manipulation of Membrane Ion Channels via Upconversion Optogenetics. *Adv Biosyst* **2019**, *3* (1).
- (78) Atchison, R. W.; Casto, B. C.; McD Hammon, W. *Adenovirus-Associated Defective Virus Particles*; 1965; Vol. 149.
- (79) Rodney, J.; Muzyczka, N. Mechanism of Rep-Mediated Adeno-Associated Virus Origin Nicking. *J Virol* **2000**, *74* (17), 7762–7771.
- (80) Rodney, J.; Muzyczka, N. Rep-Mediated Nicking of the Adeno-Associated Virus Origin Requires Two Biochemical Activities, DNA Helicase Activity and Transesterification. *J Virol* **1999**, *73* (11), 9325–9336.
- (81) Earley, L. F.; Conatser, L. M.; Lue, V. M.; Dobbins, A. L.; Li, C.; Hirsch, M. L.; Samulski, R. J. Adeno-Associated Virus Serotype-Specific Inverted Terminal Repeat Sequence Role in Vector Transgene Expression. *Hum Gene Ther* **2020**, *31*.
- (82) Xie, Q.; Lerch, T. F.; Meyer, N. L.; Chapman, M. S. Structure-Function Analysis of Receptor-Binding in Adeno-Associated Virus Serotype 6 (AAV-6). *Virology* **2011**, *420* (1), 10–19.
- (83) Wu, Z.; Miller, E.; Agbandje-McKenna, M.; Samulski, R. J. A2,3 and A2,6 N-Linked Sialic Acids Facilitate Efficient Binding and Transduction by Adeno-Associated Virus Types 1 and 6. *J Virol* **2006**, *80* (18), 9093–9103.
- (84) Qing, K.; Mah, C.; Hansen, J.; Zhou, S.; Dwarki, V.; Srivastava, A. *Human Fibroblast Growth Factor Receptor 1 Is a Co-Receptor for Infection by Adeno-Associated Virus 2*; 1999; Vol. 5. <http://medicine.nature.com>.
- (85) Summerford, C.; Bartlett, J. S.; Samulski, R. J. AVb5 Integrin: A Co-Receptor for Adeno-Associated Virus Type 2 Infection. *Nat Med* **1999**, *5*.
- (86) Venkatakrisnan, B.; Yarbrough, J.; Domsic, J.; Bennett, A.; Bothner, B.; Kozyreva, O. G.; Samulski, R. J.; Muzyczka, N.; McKenna, R.; Agbandje-McKenna, M. Structure and Dynamics of Adeno-Associated Virus Serotype 1 VP1-Unique N-Terminal Domain and Its Role in Capsid Trafficking. *J Virol* **2013**, *87* (9), 4974–4984.
- (87) Penaud-Budloo, M.; Le Guiner, C.; Nowrouzi, A.; Toromanoff, A.; Chérel, Y.; Chenuaud, P.; Schmidt, M.; von Kalle, C.; Rolling, F.; Moullier, P.; Snyder, R. O. Adeno-Associated Virus Vector Genomes Persist as Episomal Chromatin in Primate Muscle. *J Virol* **2008**, *82* (16), 7875–7885.

- (88) Chahal, P. S.; Schulze, E.; Tran, R.; Montes, J.; Kamen, A. A. Production of Adeno-Associated Virus (AAV) Serotypes by Transient Transfection of HEK293 Cell Suspension Cultures for Gene Delivery. *J Virol Methods* **2014**, *196*, 163–173.
- (89) Chadeuf, G.; Favre, D.; Tessier, J.; Provost, N.; Nony, P.; Kleinschmidt, J.; Moullier, P.; Salvetti, A. Efficient Recombinant Adeno-Associated Virus Production by a Stable Rep-Cap HeLa Cell Line Correlates with Adenovirus-Induced Amplification of the Integrated Rep-Cap Genome. *Journal of Gene Medicine* **2000**, *2* (4), 260–268.
- (90) Rosenberg, J. B.; Chen, A.; De, B. P.; Dyke, J. P.; Ballon, D. J.; Monette, S.; Ricart Arbona, R. J.; Kaminsky, S. M.; Crystal, R. G.; Sondhi, D. Safety of Direct Intraparenchymal AAVrh.10-Mediated Central Nervous System Gene Therapy for Metachromatic Leukodystrophy. *Hum Gene Ther* **2021**.
- (91) Kim, J. Y.; Grunke, S. D.; Levites, Y.; Golde, T. E.; Jankowsky, J. L. Intracerebroventricular Viral Injection of the Neonatal Mouse Brain for Persistent and Widespread Neuronal Transduction. *Journal of Visualized Experiments* **2014**, No. 91.
- (92) Gong, Y.; Berenson, A.; Laheji, F.; Gao, G.; Wang, D.; Ng, C.; Volak, A.; Kok, R.; Kreouzis, V.; Dijkstra, I. M.; Kemp, S.; Maguire, C. A.; Eichler, F. Intrathecal Adeno-Associated Viral Vector-Mediated Gene Delivery for Adrenomyeloneuropathy. *Hum Gene Ther* **2019**, *30* (5), 544–555.
- (93) Taghian, T.; Marosfoi, M. G.; Puri, A. S.; Cataltepe, O. I.; King, R. M.; Diffie, E. B.; Maguire, A. S.; Martin, D. R.; Fernau, D.; Batista, A. R.; Kuchel, T.; Christou, C.; Perumal, R.; Chandra, S.; Gamlin, P. D.; Bertrand, S. G.; Flotte, T. R.; McKenna-Yasek, D.; Tai, P. W. L.; Aronin, N.; Gounis, M. J.; Sena-Esteves, M.; Gray-Edwards, H. L. A Safe and Reliable Technique for CNS Delivery of AAV Vectors in the Cisterna Magna. *Molecular Therapy* **2020**, *28* (2), 411–421.
- (94) * Kotulska, K.; Fattal-Valevski, A.; Haberlova, J. Recombinant Adeno-Associated Virus Serotype 9 Gene Therapy in Spinal Muscular Atrophy. *Front Neurol* **2021**, *12*.
- (95) Zhang, X.; Chai, Z.; Dobbins, A. L.; Itano, M. S.; Askew, C.; Miao, Z.; Niu, H.; Samulski, R. J.; Li, C. Customized Blood-Brain Barrier Shuttle Peptide to Increase AAV9 Vector Crossing the BBB and Augment Transduction in the Brain. *Biomaterials* **2022**, *281*.
- (96) Carty, N.; Lee, D.; Dickey, C.; Ceballos-Diaz, C.; Jansen-West, K.; Golde, T. E.; Gordon, M. N.; Morgan, D.; Nash, K. Convection-Enhanced Delivery and Systemic Mannitol Increase Gene Product Distribution of AAV Vectors 5, 8, and 9 and Increase Gene Product in the Adult Mouse Brain. *J Neurosci Methods* **2010**, *194* (1), 144–153.
- (97) Felix, M.-S.; Borloz, E.; Metwally, K.; Dauba, A.; Larrat, B.; Matagne, V.; Ehinger, Y.; Villard, L.; Novell, A.; Mensah, S.; Roux, J.-C.; Pouliopoulos, N.; Morse, S. V.; Sheybani, N. D. Ultrasound-Mediated Blood-Brain Barrier Opening Improves Whole Brain Gene Delivery in Mice. *Pharmaceutics* **2021**, *13*.
- (98) Kim, S.; Joon Moon, G.; Oh, Y.-S.; Park, J.; Shin, W.-H.; Yeong Jeong, J.; Shik Choi, K.; Kwan Jin, B.; Kholodilov, N.; Burke, R. E.; Kim, H.-J.; Man Ha, C.; Lee, S.-G.; Ryong Kim, S. Protection of

- Nigral Dopaminergic Neurons by AAV1 Transduction with Rheb(S16H) against Neurotoxic Inflammation in Vivo. *Exp Mol Med* **2018**.
- (99) Spronck, E. A.; Brouwers, C. C.; Vallès, A.; de Haan, M.; Petry, H.; van Deventer, S. J.; Konstantinova, P.; Evers, M. M. AAV5-MiHTT Gene Therapy Demonstrates Sustained Huntingtin Lowering and Functional Improvement in Huntington Disease Mouse Models. *Mol Ther Methods Clin Dev* **2019**, *13*, 334–343.
- (100) Masamizu, Y.; Okada, T.; Ishibashi, H.; Takeda, S.; Yuasa, S.; Nakahara, K. Efficient Gene Transfer into Neurons in Monkey Brain by Adeno-Associated Virus 8. *Neuroreport* **2010**, *21* (6), 447–451.
- (101) Samaranch, L.; Salegio, E. A.; Sebastian, W. S.; Kells, A. P.; Foust, K. D.; Bringas, J. R.; Lamarre, C.; Forsayeth, J.; Kaspar, B. K.; Bankiewicz, K. S. Adeno-Associated Virus Serotype 9 Transduction in the Central Nervous System of Nonhuman Primates. *Hum Gene Ther* **2012**.
- (102) * Manfredsson, F. P.; Rising, A. C.; Mandel, R. J. *AAV9: A Potential Blood-Brain Barrier Buster*; Nature Publishing Group, 2009; Vol. 17.
- (103) Deverman, B. E.; Pravdo, P. L.; Simpson, B. P.; Ravindra Kumar, S.; Chan, K. Y.; Banerjee, A.; Wu, W.-L.; Yang, B.; Huber, N.; Pasca, S. P.; Gradinaru, V.; Biotechnol, N. Cre-Dependent Selection Yields AAV Variants for Widespread Gene Transfer to the Adult Brain. *Nat Biotechnol* **2016**, *34* (2), 204–209.
- (104) Chan, K. Y.; Jang, M. J.; Yoo, B. B.; Greenbaum, A.; Ravi, N.; Wu, W.-L.; Sánchez-Guardado, L.; Lois, C.; Mazmanian, S. K.; Deverman, B. E.; Gradinaru, V.; Author, N. N. Engineered AAVs for Efficient Noninvasive Gene Delivery to the Central and Peripheral Nervous Systems. *Nat Neurosci* **2017**, *20*, 1172–1179.
- (105) Goertsen, D.; Flytzanis, N. C.; Goeden, N.; Chuapoco, M. R.; Cummins, A.; Chen, Y.; Fan, Y.; Zhang, Q.; Sharma, J.; Duan, Y.; Wang, L.; Feng, G.; Chen, Y.; Ip, N. Y.; Pickel, J.; Gradinaru, V. AAV Capsid Variants with Brain-Wide Transgene Expression and Decreased Liver Targeting after Intravenous Delivery in Mouse and Marmoset. *Nat Neurosci* **2022**, *25*, 106–115.
- (106) Ortiz, J. S.; Santiago-Ortiz, J.; Ojala, D. S.; Westesson, O.; Weinstein, J. R.; Wong, S. Y.; Steinsapir, A.; Kumar, S.; Holmes, I.; Schaffer, D. V. AAV Ancestral Reconstruction Library Enables Selection of Broadly Infectious Viral Variants Publication Date AAV Ancestral Reconstruction Library Enables Selection of Broadly Infectious Viral Variants. *Nature* **2015**, *22*, 934–946.
- (107) Tornabene, P.; Trapani, I.; Minopoli, R.; Centrulo, M.; Lupo, M.; De Simone, S.; Tiberi, P.; Dell’aquila, F.; Marrocco, E.; Iodice, C.; Iuliano, A.; Gesualdo, C.; Rossi, S.; Giaquinto, L.; Albert, S.; Hoyng, C. B.; Polishchuk, E.; Cremers, F. P. M.; Surace, E. M.; Simonelli, F.; De Matteis, M. A.; Polishchuk, R.; Auricchio, A. Intein-Mediated Protein Trans-Splicing Expands Adeno-Associated Virus Transfer Capacity in the Retina. *Sci Transl Med* **2019**.
- (108) Schmidt, M. J.; Gupta, A.; Bednarski, C.; Gehrig-Giannini, S.; Richter, F.; Pitzler, C.; Gamalinda, M.; Galonska, C.; Takeuchi, R.; Wang, K.; Reiss, C.; Dehne, K.; Lukason, M. J.; Noma, A.; Park-Windhol, C.; Allocca, M.; Kantardzhieva, A.; Sane, S.; Kosakowska, K.; Cafferty, B.; Tebbe, J.; Spencer, S. J.;

- Munzer, S.; Cheng, C. J.; Scaria, A.; Scharenberg, A. M.; Cohnen, A.; Coco, W. M. Improved CRISPR Genome Editing Using Small Highly Active and Specific Engineered RNA-Guided Nucleases. *Nat Commun* **2021**.
- (109) Fitzpatrick, Z.; Leborgne, C.; Barbon, E.; Masat, E.; Ronzitti, G.; van Wittenberghe, L.; Vignaud, A.; Collaud, F.; Charles, S.; Simon Sola, M.; Jouen, F.; Boyer, O.; Mingozzi, F. Influence of Pre-Existing Anti-Capsid Neutralizing and Binding Antibodies on AAV Vector Transduction. *Mol Ther Methods Clin Dev* **2018**, *9*, 119–129.
- (110) Giles, A. R.; Govindasamy, L.; Somanathan, S.; Wilson, J. M. Mapping an Adeno-Associated Virus 9-Specific Neutralizing Epitope To Develop Next-Generation Gene Delivery Vectors. *J Virol* **2018**, *92*.
- (111) Chowdary, P.; Shapiro, S.; Makris, M.; Evans, G.; Boyce, S.; Talks, K.; Dolan, G.; Reiss, U.; Phillips, M.; Riddell, A.; Peralta, M. R.; Quaye, M.; Patch, D. W.; Tuddenham, E.; Dane, A.; Watissée, M.; Long, A.; Nathwani, A. Phase 1–2 Trial of AAVS3 Gene Therapy in Patients with Hemophilia B. *New England Journal of Medicine* **2022**, *387* (3), 237–247.
- (112) Xu, Y. Z.; Kanagaratham, C.; Jancik, S.; Radzioch, D. Promoter Deletion Analysis Using a Dual-Luciferase Reporter System. *Methods in Molecular Biology* **2013**, *977*, 79–93.
- (113) Wu, M. R.; Nissim, L.; Stupp, D.; Pery, E.; Binder-Nissim, A.; Weisinger, K.; Enghuus, C.; Palacios, S. R.; Humphrey, M.; Zhang, Z.; Maria Novoa, E.; Kellis, M.; Weiss, R.; Rabkin, S. D.; Tabach, Y.; Lu, T. K. A High-Throughput Screening and Computation Platform for Identifying Synthetic Promoters with Enhanced Cell-State Specificity (SPECS). *Nature Communications* **2019**, *10*.
- (114) Cole, S. W.; Arevalo, J. M. G.; Takahashi, R.; Sloan, E. K.; Lutgendorf, S. K.; Sood, A. K.; Sheridan, J. F.; Seeman, T. E. Computational Identification of Gene-Social Environment Interaction at the Human IL6 Locus. *PNAS* **2010**, *107*, 5681–5686.
- (115) Gray, S. J.; Foti, S. B.; Schwartz, J. W.; Bachaboina, L.; Taylor-Blake, B.; Coleman, J.; Ehlers, M. D.; Zylka, M. J.; Mccown, T. J.; Samulski, R. J. Methods Optimizing Promoters for Recombinant Adeno-Associated Virus-Mediated Gene Expression in the Peripheral and Central Nervous System Using Self-Complementary Vectors. *Hum Gene Ther* **2011**, *22*.
- (116) Kügler, S.; Kilic, E.; Bähr, M. Human Synapsin 1 Gene Promoter Confers Highly Neuron-Specific Long-Term Transgene Expression from an Adenoviral Vector in the Adult Rat Brain Depending on the Transduced Area. *Gene Ther* **2003**, *10* (4), 337–347.
- (117) Jin, L.; Lange, W.; Kempmann, A.; Maybeck, V.; Günther, A.; Gruteser, N.; Baumann, A.; Offenhäusser, A. High-Efficiency Transduction and Specific Expression of ChR2opt for Optogenetic Manipulation of Primary Cortical Neurons Mediated by Recombinant Adeno-Associated Viruses. *J Biotechnol* **2016**, *233*, 171–180.
- (118) Cheng, S.; Tereshchenko, J.; Zimmer, V.; Vachey, G.; Pythoud, C.; Rey, M.; Liefhebber, J.; Raina, A.; Streit, F.; Mazur, A.; Bähr, M.; Konstantinova, P.; Déglon, N.; Kügler, S. Therapeutic Efficacy of Regulable GDNF Expression for Huntington’s and Parkinson’s Disease by a High-Induction, Background-Free “GeneSwitch” Vector. *Exp Neurol* **2018**, *309*, 79–90.

- (119) Ekman, F. K.; Ojala, D. S.; Adil, M. M.; Lopez, P. A.; Schaffer, D. V.; Gaj, T. CRISPR-Cas9-Mediated Genome Editing Increases Lifespan and Improves Motor Deficits in a Huntington's Disease Mouse Model. *Mol Ther Nucleic Acids* **2019**, *17*, 829–839.
- (120) Zheng, L.; Wang, Z.; Liu, Y.; Zhao, J.; Huang, S. Activation of the RMTg Nucleus by Chemogenetic Techniques Alleviates the Learning and Memory Impairment in APP/PS1 Mice. *Neuropsychiatr Dis Treat* **2022**, *18*, 2957–2965.
- (121) May, F. J.; Head, P. S. E.; Venturoni, L. E.; Chandler, R. J.; Venditti, C. P. Central Nervous System-Targeted Adeno-Associated Virus Gene Therapy in Methylmalonic Acidemia. *Mol Ther Methods Clin Dev* **2021**, *21*, 765–776.
- (122) Chandler, R. J.; Williams, I. M.; Gibson, A. L.; Davidson, C. D.; Incao, A. A.; Hubbard, B. T.; Porter, F. D.; Pavan, W. J.; Venditti, C. P.; Purpura, D. P. Systemic AAV9 Gene Therapy Improves the Lifespan of Mice with Niemann-Pick Disease, Type C1. *Hum Mol Genet* **2017**, *26* (1), 52–64.
- (123) Colasante, G.; Qiu, Y.; Massimino, L.; Berardino, C. Di; Cornford, J. H.; Snowball, A.; Weston, M.; Jones, S. P.; Giannelli, S.; Lieb, A.; Schorge, S.; Kullmann, D. M.; Broccoli, V.; Lignani, G. In Vivo CRISPRa Decreases Seizures and Rescues Cognitive Deficits in a Rodent Model of Epilepsy. *Brain* **2020**, *43*, 891–905.
- (124) Maubach, G.; Lim, M. C. C.; Zhang, C. Y.; Zhuo, L. GFAP Promoter Directs LacZ Expression Specifically in a Rat Hepatic Stellate Cell Line. *World J Gastroenterol* **2006**, *12*, 723–730.
- (125) Lee, Y.; Messing, A.; Su, M.; Brenner, M. GFAP Promoter Elements Required for Region-Specific and Astrocyte-Specific Expression. *Glia* **2008**, *56* (5), 481–493.
- (126) Do Thi, N. A.; Saillour, P.; Ferrero, L.; Dedieu, J. F.; Mallet, J.; Paunio, T. Delivery of GDNF by an E1,E3/E4 Deleted Adenoviral Vector and Driven by a GFAP Promoter Prevents Dopaminergic Neuron Degeneration in a Rat Model of Parkinson's Disease. *Gene Ther* **2004**, *11* (9), 746–756.
- (127) Tkatch, T.; Rysevaite-Kyguoliene, K.; Sabeckis, I.; Sabeckiene, D.; Pauza, D. H.; Baranauskas, G. *An Efficient RAAV Vector for Protein Expression in Cortical Parvalbumin Expressing Interneurons*; 2022.
- (128) Barnes, S.; Pinto-Duarte, A.; Kappe, A.; Zembrzycki, A.; Metzler, A.; Mukamel, E.; Lucero, J.; Wang, X.; Sejnowski, T.; Markou, A.; Behrens, M. Disruption of MGluR5 in Parvalbumin-Positive Interneurons Induces Core Features of Neurodevelopmental Disorders. *Mol Psychiatry* **2015**, *20*, 1161–1172.
- (129) * Duba-Kiss, R.; Niibori, Y.; Hampson, D. R. GABAergic Gene Regulatory Elements Used in Adeno-Associated Viral Vectors. *Front Neurol* **2021**, *12*.
- (130) Drexel, M.; Rahimi, S.; Sperk, G. Silencing of Hippocampal Somatostatin Interneurons Induces Recurrent Spontaneous Limbic Seizures in Mice. *Neuroscience* **2022**, *487*, 155–165.
- (131) Goff, K. M.; Goldberg, E. M. A Role for Vasoactive Intestinal Peptide Interneurons in Neurodevelopmental Disorders. *Dev Neurosci* **2021**, *43*, 168–180.

- (132) Bechtold, D. A.; Brown, T. M.; Luckman, S. M.; Piggins, H. D. Metabolic Rhythm Abnormalities in Mice Lacking VIP-VPAC2 Signaling. *Am J Physiol Regul Integr Comp Physiol* **2008**, *294* (2), 344–351.
- (133) Hoshino, C.; Konno, A.; Hosoi, N.; Kaneko, R.; Mukai, R.; Nakai, J.; Hirai, H. GABAergic Neuron-Specific Whole-Brain Transduction by AAV-PHP.B Incorporated with a New GAD65 Promoter. *Mol Brain* **2021**.
- (134) DeRosa, B. A.; Belle, K. C.; Thomas, B. J.; Cukier, H. N.; Pericak-Vance, M. A.; Vance, J. M.; Dykxhoorn, D. M. HVGAT-MCherry: A Novel Molecular Tool for Analysis of GABAergic Neurons Derived from Human Pluripotent Stem Cells. *Molecular and Cellular Neuroscience* **2015**, *68*, 244–257.
- (135) Wang, W.; Jia, Y. L.; Li, Y. C.; Jing, C. Q.; Guo, X.; Shang, X. F.; Zhao, C. P.; Wang, T. Y. *Impact of Different Promoters, Promoter Mutation, and an Enhancer on Recombinant Protein Expression in CHO Cells*; Nature Publishing Group, 2017.
- (136) Freundlieb, S.; Schirra-Müller, C.; Bujard, H. A Tetracycline Controlled Activation/Repression System with Increased Potential for Gene Transfer into Mammalian Cells. *Journal of Gene Medicine* **1999**, *1* (1), 4–12.
- (137) Das, A. T.; Tenenbaum, L.; Berkhout, B. Tet-On Systems For Doxycycline-Inducible Gene Expression. *Curr Gene Ther* **2016**, *16*, 156–167.
- (138) Wang, L.; Wang, Z.; Zhang, F.; Zhu, R.; Bi, J.; Wu, J.; Zhang, H.; Wu, H.; Kong, W.; Yu, B.; Yu, X. Enhancing Transgene Expression from Recombinant AAV8 Vectors in Different Tissues Using Woodchuck Hepatitis Virus Post-Transcriptional Regulatory Element. *Int. J. Med. Sci* **2016**, *13* (4), 286–291.
- (139) Glover, C. P. J.; Bienemann, A. S.; Heywood, D. J.; Cosgrave, A. S.; Uney, J. B. Adenoviral-Mediated, High-Level, Cell-Specific Transgene Expression: A SYN1-WPRE Cassette Mediates Increased Transgene Expression with No Loss of Neuron Specificity. *Molecular Therapy* **2002**, *5* (5), 509–516.
- (140) Yang, Y.; Pacia, C. P.; Ye, D.; Zhu, L.; Baek, H.; Yue, Y.; Yuan, J.; Miller, M. J.; Cui, J.; Culver, J. P.; Bruchas, M. R.; Chen, H. Sonothermogenetics for Noninvasive and Cell-Type Specific Deep Brain Neuromodulation. *Brain Stimul* **2021**, *14* (4), 790–800.
- (141) Wang, C. Y.; Wang, S. Astrocytic Expression of Transgene in the Rat Brain Mediated by Baculovirus Vectors Containing an Astrocyte-Specific Promoter. *Gene Ther* **2006**, *13* (20), 1447–1456.
- (142) Muhuri, M.; Zhan, W.; Maeda, Y.; Li, J.; Lotun, A.; Chen, J.; Sylvia, K.; Dasgupta, I.; Arjomandnejad, M.; Nixon, T.; Keeler, A. M.; Manokaran, S.; He, R.; Su, Q.; Tai, P. W. L.; Gao, G. Novel Combinatorial MicroRNA-Binding Sites in AAV Vectors Synergistically Diminish Antigen Presentation and Transgene Immunity for Efficient and Stable Transduction. *Front Immunol* **2021**, *12*.
- (143) Bak, R. O.; Porteus, M. H. CRISPR-Mediated Integration of Large Gene Cassettes Using AAV Donor Vectors. *Cell Rep* **2017**, *20* (3), 750–756.

- (144) Francis, J. S.; Markov, V.; Wojtas, I. D.; Gray, S.; McCown, T.; Samulski, R. J.; Figueroa, M.; Leone, P. Preclinical Biodistribution, Tropism, and Efficacy of Oligotropic AAV/Olig001 in a Mouse Model of Congenital White Matter Disease. *Mol Ther Methods Clin Dev* **2021**, *20*, 520–534.
- (145) Bijlani, S.; Anubhav, ; Nahar, S.; Ganesan, · K. Improved Tet-On and Tet-Off Systems for Tetracycline-Regulated Expression of Genes in *Candida*. *Curr Genet* **2018**, *64*.
- (146) Beghi, E.; Giussani, G.; Abd-Allah, F.; Abdela, J.; Abdelalim, A.; Abraha, H. N.; Adib, M. G.; Agrawal, S.; Alahdab, F.; Awasthi, A.; Ayele, Y.; Barboza, M. A.; Belachew, A. B.; Biadgo, B.; Bijani, A.; Bitew, H.; Carvalho, F.; Chaiah, Y.; Daryani, A.; Do, H. P.; Dubey, M.; Endries, A. Y. Y.; Eskandarieh, S.; Faro, A.; Farzadfar, F.; Fereshtehnejad, S. M.; Fernandes, E.; Fijabi, D. O.; Filip, I.; Fischer, F.; Gebre, A. K.; Tsadik, A. G.; Gebremichael, T. G.; Gezae, K. E.; Ghasemi-Kasman, M.; Weldegewergs, K. G.; Degefa, M. G.; Gnedovskaya, E. V.; Hagos, T. B.; Haj-Mirzaian, A.; Haj-Mirzaian, A.; Hassen, H. Y.; Hay, S. I.; Jakovljevic, M.; Kasaeian, A.; Kassa, T. D.; Khader, Y. S.; Khalil, I.; Khan, E. A.; Khubchandani, J.; Kisa, A.; Krohn, K. J.; Kulkarni, C.; Nirayo, Y. L.; Mackay, M. T.; Majdan, M.; Majeed, A.; Manhertz, T.; Mehndiratta, M. M.; Mekonen, T.; Meles, H. G.; Mengistu, G.; Mohammed, S.; Naghavi, M.; Mokdad, A. H.; Mustafa, G.; Irvani, S. S. N.; Nguyen, L. H.; Nichols, E.; Nixon, M. R.; Ogbo, F. A.; Olagunju, A. T.; Olagunju, T. O.; Owolabi, M. O.; Phillips, M. R.; Pinilla-Monsalve, G. D.; Qorbani, M.; Radfar, A.; Rafay, A.; Rahimi-Movaghar, V.; Reinig, N.; Sachdev, P. S.; Safari, H.; Safari, S.; Safiri, S.; Sahraian, M. A.; Samy, A. M.; Sarvi, S.; Sawhney, M.; Shaikh, M. A.; Sharif, M.; Singh, G.; Smith, M.; Szoeki, C. E. I.; Tabarés-Seisdedos, R.; Temsah, M. H.; Temsah, O.; Tortajada-Girbés, M.; Tran, B. X.; Tsegay, A. A. T.; Ullah, I.; Venketasubramanian, N.; Westerman, R.; Winkler, A. S.; Yimer, E. M.; Yonemoto, N.; Feigin, V. L.; Vos, T.; Murray, C. J. L. Global, Regional, and National Burden of Epilepsy, 1990–2016: A Systematic Analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* **2019**, *18* (4), 357–375.
- (147) Harrington, L. B.; Burstein, D.; Chen, J. S.; Paez-Espino, D.; Ma, E.; Witte, I. P.; Cofsky, J. C.; Kyrpides, N. C.; Banfield, J. F.; Doudna, J. A. Programmed DNA Destruction by Miniature CRISPR-Cas14 Enzymes. *Science* **2018**, *362*, 839–842.
- (148) * Ogbonmide, T.; Rathore, R.; Rangrej, S. B.; Hutchinson, S.; Lewis, M.; Ojilere, S.; Carvalho, V.; Kelly, I. Gene Therapy for Spinal Muscular Atrophy (SMA): A Review of Current Challenges and Safety Considerations for Onasemnogene Apeparvovec (Zolgensma). *Cureus* **2023**, *15* (3).
- (149) Otsuki, N.; Arakawa, R.; Kaneko, K.; Aoki, R.; Arakawa, M.; Saito, K. A New Biomarker Candidate for Spinal Muscular Atrophy: Identification of a Peripheral Blood Cell Population Capable of Monitoring the Level of Survival Motor Neuron Protein. *PLoS One* **2018**, *13*.