Update in NM medicine: Making sense of Antisense and other genetic/immunotherapies

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Session Learning Outcomes

By the end of this lecture, attendees will be able to:

- Review emerging landscape of targeted therapeutics for genetic neuromuscular disorders
- Discuss practice-relevant issues including access disparities, cost, regulatory burden, and expectations
- Facilitate conversation with neurologist colleagues when sharing and discussing patients with neuromuscular disorders
- Review emerging immunosuppressive and immunomodulating medications in NM

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Genetic treatments 1.01

- Expanding knowledge over the last 40 yrs
- Dystrophin/DMD first sequenced 1987, since then 1000+ genes linked to NM disorders
- Two main types of sequencing errors
  - Gain of Function- change in sequence resulting in change in shape or overexpression of gene
    - CTG repeats in DMPK for myotonic dystrophy I, SOD1 ALS, etc
  - Loss of function: sequence error leading to nonfunctional protein (stop codons, frameshifts)
    - Duchene's MD with stop codon resulting in inability to produce functional/enough dystrophin (biggest gene)

Amado D et al. The Emerging Landscape of Targeted Theraputiecs for Genetic NM disorders, Practical Neurology,22-26 v22n6 (2023)

Compare and contrast Amyotrophic lateral sclerosis and Spinal Muscular Atrophy

Same origin in motor neuron dysfunction

Vastly different diseases and treatments

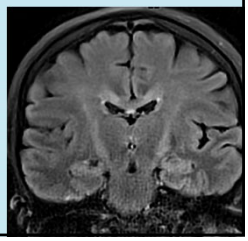
Spinal Muscular Atrophy as a model

- SMA is a devastating disease of the lower motor neurons, with more severe forms leading to flaccid paralysis and death by respiratory failure in infancy
  - SMA Gene: transcriptional regulation, telomerase regeneration and cellular trafficking
  - AR LOF: both copies of SMN1 gene are "bad" resulting in death of motor neuron cells
  - 1:10,000 births
  - Floppy baby, impaired suck, delayed motor milestones,
  - CPK elevated, EMG myopathic, Biopsy degeneration/replacement; now genetic testing
  - SMA0 (birth)-SMA4 (SMN2 copies)
  - Previously no true treatments (**SMA 3&4 normal lifespan/significant weakness)**
    - **Supportive care, steroids**

Adams & Victor Principles of neurologic Disease, 10th Ed. 2015
https://www.fda.gov/media/126109/download

Counter ALS(es) model

- Unknown cause, though approximately 10% is familial and genetic
- Genetic contributions (SOD1, FUS, C9orf72, 40+ identified)
- Pathophysiology: multitude of cellular pathways
  - including altered pre-mRNA splicing, impaired protein homeostasis, nucleocytoplasmic transport defects, glutamate excitotoxicity, mitochondrial dysfunction, increased oxidative stress, impaired axonal transport, and neuroinflammation
- 1-2.6/ 100,000 persons / year
- Progression is continuous with slow, inexorable loss of motor neurons, years, though some genetic forms <1 year
- Dx: Rule out everything else, EMG - denervation, MRI



Talbott https://pubmed.ncbi.nlm.nih.gov/27637961/
https://www.tandfonline.com/doi/pdf/10.1080/21678421.2021.1900259
https://radiopaedia.org/cases/amyotrophic-lateral-sclerosis-10?lang=us

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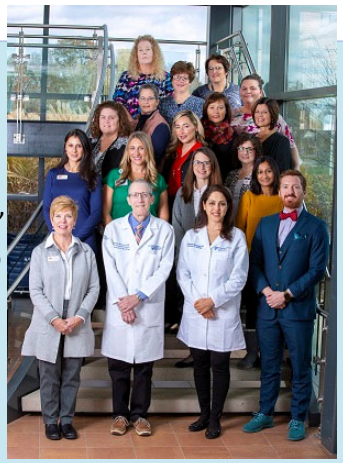
ALS Existing Treatments

- Multidisciplinary clinics
  - Typically involve physical therapists, occupational therapists, speech-language pathologists, dietitians, mental health providers, social work
  - Clinics may also include chaplains, genetic counselors, and palliative care providers
  - Benefits: Survival benefit, specialized care, convenient "one-stop shop"
  - Problem: long visits (often 3-hours or more) can be tiring, expensive to run
- Three FDA-approved therapies existed
  - Riluzole (blocks glutamate excitotoxicity) 1997
  - Edaravone (reduce oxidative stress on motor neurons) 2017
  - Tauroursodeoxycholic acid with sodium phenylbutyrate (limit apoptosis) 2022

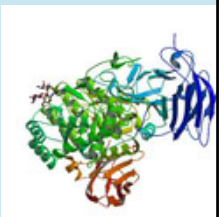


http://webpa.alsa.org/site/PageNavigator/PA_Chapter/Hershey_Clinic/PA_8_Hershey_Clinic_Team.html

Rooney, https://pubmed.ncbi.nlm.nih.gov/25550416/
Traynor, https://pubmed.ncbi.nlm.nih.gov/12933930/
Riluzole: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020599s017lbl.pdf
Edaravone: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209176lbl.pdf

Therapeutic approaches: Protein Replacement

- No/bad proteins, just supplement
- Good: "easier" to accomplish
- Bad: antibodies. Limited effect, organ failure
- Pompe disease (AR) 17q25.2-q25.3 (glycogen storage disease II)
  - Loss of function with gene encoding acid alpha-glucosidase; component for lysosome and leads to build up of glycogen
  - Direct enzyme replacement with alglucosidase alfa (2006) or avalglucosidase **alfa**-ngpt (end 2021)
    - Aes: infections,infusions, hedaches, flu like
    - BLACK BOX: Heart/lung failure, allergic responses
- Studies for other glycogen storage/lysosomal storage diseases



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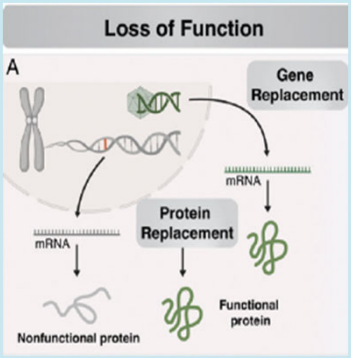
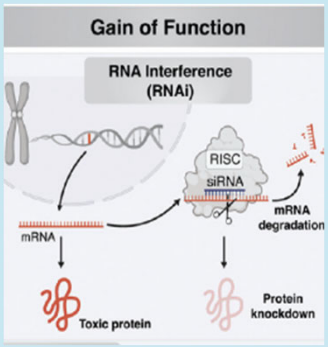
Therapeutic approaches: Gene "Replacement"

- Loss of Function target: bad gene, supplement gene
- Use vector (often adeno-associated virus) to deliver DNA to target cells **without** integration in genome or replication
- Ex: onasemnogene abeparvovec-xioi, FDA approved 2019
  - AAV9 vector carrying SMN1
    - ½ of patients were sitting independently at 18 months (compared to 0 of control)
    - 97% of patients were free of permanent vent support compared to ¼ of control
- Good: great results for bad diseases
- Bad: limited size of vector, costly, delivery issues, immunologic issues
- Current studies: Giant Axonal Neuropathy (GAN) DMD (small dystophin)



Li C, Samulski RJ. Engineering adeno-associated virus vectors for gene therapy. Nat Rev Genet. 2020;21(4):255-272. doi:10.1038/s41576-019-0205-4
AVX STR1VE-EU,Mercuri https://pubmed.ncbi.nlm.nih.gov/34536405/
AVX STR1VE0US update Day https://n.neurology.org/content/94/15_Supplement/1828

Therapeutic approaches: RNA interference



- Replicates/imitates naturally occurring strategy to reduce gene expression (Gain of function treatment)
- Blocks translation or induces degradation
- Delivery via AAV or Lipid nanoparticles (does not cross BBB)
- Drawbacks: same AAV immune issues, unintended targets, can overwhelm RNAi processing
- Ex: Patisaran, 2018
  - LNP delivered, binding to the RNA-induced silencing complex causing TTR destruction prior to release
- Current Studies: CMT1a (PMP22)

Borel F, Kay MA, Mueller C. Recombinant AAV as a platform for translating the therapeutic potential of RNA interference. Mol Ther. 2014;22(4):692-701. doi:10.1038/mt.2013.285

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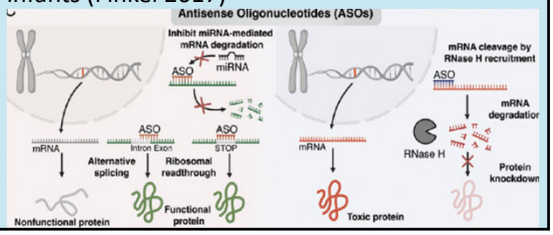
Therapeutic approaches: ASO

- Antisense Oligonucleotide (ASOs) are short single stranded oligonucleotides designed to compliment/augment mRNA with high specificity, unable to cross BBB
- LOF: induce alternative splicing, skip stop codons, or block microRNA sites to prevent their activity/downregulation
- GOF: Trigger enzyme mediated RNAse H destruction of target mRNA
- Ex: (ASO) *nusinersin*, approved by the FDA in 2016
  - Masks splice site to convert SMA2 to SMA1
  - ENDEAR showed improved survival and motor function in infants (Finkel 2017)
  - RISKs: LP risks, stunted growth, headaches, infections
- Current Studies: DMD (5 current drugs)

FSHD (DUX4 suppression), Inotersan (ttr) 2019



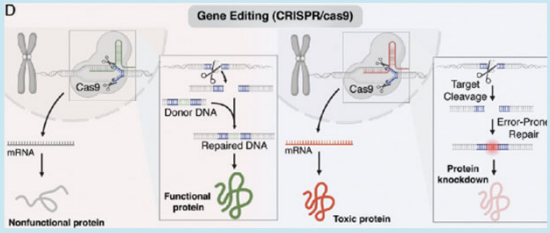
Schoch KM, Miller TM. Antisense oligonucleotides: translation from mouse models to human neurodegenerative diseases. Neuron. 2017;94(6):1056-1070. doi:10.1016/j.neuron.2017.04.010
Himeda CL, Jones PL. FSHD therapeutic strategies: what will it take to get to clinic? J Pers Med. 2022;12(6):865. doi:10.3390/jpm12060865
Nusinersin Endear trial, Finkle, https://www.nejm.org/doi/full/10.1056/nejmoa1702752
Nusinersin Cherish trial, Mercuri https://www.nejm.org/doi/full/10.1056/NEJMoa1710504

Therapeutic approaches: Small Molecule

- 0.1-1 kDa molecules that can suppress genes, affect splicing or affect mRNA stability.
- Orally available, lower cost, easier to store, reversible, small (BBB)
- >40% compounds in 2020 for NM diseases were this variety
- LOF: Ex risdiplam 2019, alters splicing SMN2 into SMN1
- GOF: Dolobid/Vyndaqel prevent TTR aggregation

Therapeutic approaches: Gene Editing

- Directed editing of genome via CRISPR
- 2021 clinical trial LNP CRISP Cas9 on 6 pts with transthyretin amyloidosis – reduced 96%
- Still in infancy: Target issues, immunogenicity, mutations with breaks
- Limitations in Neuro: size, LNPS still not great at passing BBB



Pros & Cons

- Pro: Prolonged life or QOL
- Con: What is the price of life?
  - AEs

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Spinal Muscular Atrophy as a model

- Tremendous cost associated with these treatments and controversies surrounding their FDA review
  - Nusinersin is $125,000 for each intrathecal injection, given every three months after the initial onboarding
  - The genetic therapy is $2,100,000 for the single, one-time dose
- The Institute for Clinical and Economic Review reported nusinersin represented “low longterm value for money” measured as cost per quality-adjusted life year
- Other reports suggest the gene therapy may be cheaper in the long run, by being a one-time treatment with reduced downstream costs

https://icer.org/news-insights/press-releases/icer-issues-final-report-on-sma/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7919869/

ALS genetic treatments

- SOD1 180 unique variants; typical** limb onset, LMD; misfolding SOD1 protein with aggregation in SMN
- RNAi Tofersen, AS0 intrathecal injections
  - Induces RNAse H-mediated degradation of SOD1 mRNA
    - Had to be treated early, if too late reduced amount of NFL but no effect on survival
    - Risks: 7% meningitis, IH, myelitis
- 15+ studies FUS, C9orf72, SOD1, ATXN2 repeat, STMN2 LOF

Miller, T. M. et al. Trial of antisense oligonucleotide tofersen for SOD1 ALS. N. Engl. J. Med 387, 1099–1110 (2022).
Garret, Mark et al. Rise of Genomic Medicine Era in ALS, Practical Neurology,22-26 v22n6 (2023)

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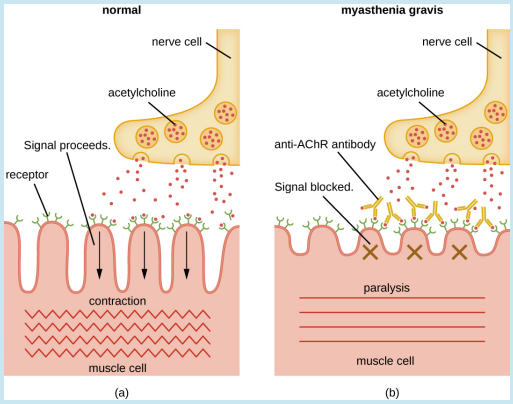
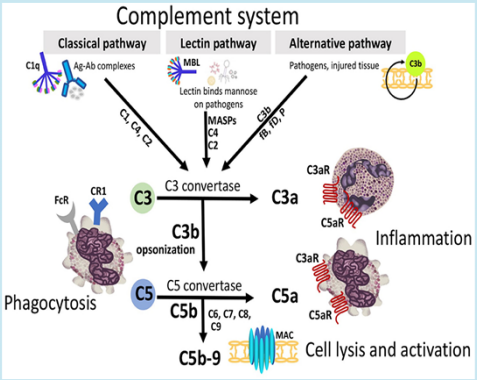
Immunotherapies in Myasthenia



- Myasthenia gravis (MG) is a T cell-dependent, B-cell mediated autoimmune disease caused by antibodies against the **nicotinic acetylcholine receptor** or other components of the post-synaptic muscle endplate at the neuromuscular junction.
- Sx: ptosis, double vision, weakness, dysphagia, SOB
- Old Treatments: immunosupression

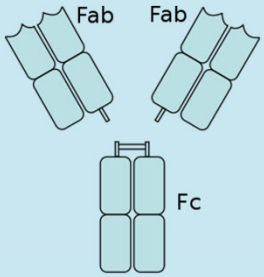
Eculizumab/Ravulizimab (Alexion)

- Recombinant humanized monoclonal antibody against the complement protein C5
- Treats: PNH, NMO, AChR+ MG, HUS
- CHAMPION study 2023:
  - 161pts; 71% reduction in events
- AEs: Headaches>10%, infections (ENCAPSULTED!), HTN



Meisel A, Annane D, Vu T, Mantegazza R, Katsuno M, Aguzzi R, Frick G, Gault L, Howard JF Jr; CHAMPION MG Study Group. Long-term efficacy and safety of ravulizumab in adults with anti-acetylcholine receptor antibody-positive generalized myasthenia gravis: results from the phase 3 CHAMPION MG open-label extension. J Neurol. 2023 Aug;270(8):3862-3875. doi: 10.1007/s00415-023-11699-x. Epub 2023 Apr 27. PMID: 37103755; PMCID: PMC10134722.

Efgartigimod alfa/ Hyaluronidase (ArgenX)



- MOA: antibody fragment that binds to the neonatal Fc receptor (FcRn), preventing FcRn from recycling immunoglobulin G (IgG) back into the blood.
- Treats: AChR+ MG, CIDP
- AEs: Infections, Headaches, numbness and tingling and muscle pain

"Drug Trials Snapshot: Vyvgart". U.S. Food and Drug Administration. 23 May 2023. Retrieved 27 May 2023.

Rozanolixizumab

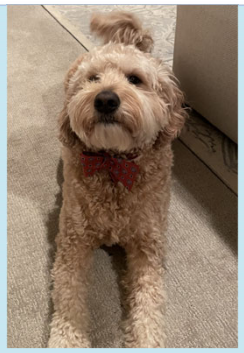
- MOA: humanized IgG4 monoclonal antibody that binds to the neonatal Fc receptor (FcRN)
- Treats: AChR+ MG and MUSK MG
- AE: Headache, infections, diarrhea, pyrexia, hypersensitivity reactions, and nausea
- MyCaring 2023: -5.4 points and -6.7 points in RYSTIGGO-treated group at ≈7mg/kg and ≈10 mg/kg dose level, respectively, vs -1.9 points in the placebo-treated group ($p<0.001$)

Bril V. Efficacy and safety of rozanolixizumab in patients with generalised myasthenia gravis: a randomised, double-blind, placebo-controlled, adaptive Phase 3 study MyCarinG study. Lancet Neurol. 2023;22(5):383-94

Orphan drug status

- Tax incentives
- Exclusivity (enhanced patent protection and marketing rights)
- Research subsidies
- Less expensive to run studies (lower N), lower requirements

THANK YOU!



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