Pro: Genetically-Targeted Trials Will Lead Us To Our First Successful Disease Modifying Therapy

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MASSACHUSETTS GENERAL HOSPITAL NEUROLOGY

Disclosures

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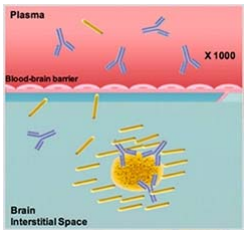
Genetic Trials:

- Steering committee for PD GENEration (Parkinson's Foundation)
- Participating in targeted trial for GBA-PD sponsored by Sanofi/Genzyme (GZ/SAR402671)

Immunotherapy Trials:

- Participating in immunotherapy trials sponsored by Bristol-Myers Squibb/Biogen (BIIB092 anti-tau), Roche (Prasinezumab anti-synuclein) trials

Past immunotherapy trials:



DeMattos et al., Neuron, 2012

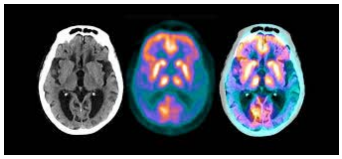
Anti-amyloid:

Bapineuzumab
Solanezumab
Aducanumab
Crenezumab
Ganteneruma

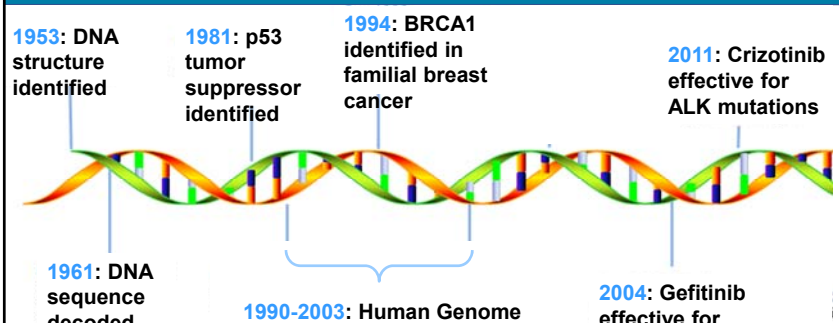
Anti-tau:

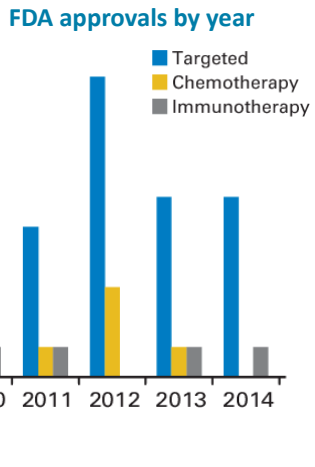
BIIB092
ABBV-8E12

Donanemab

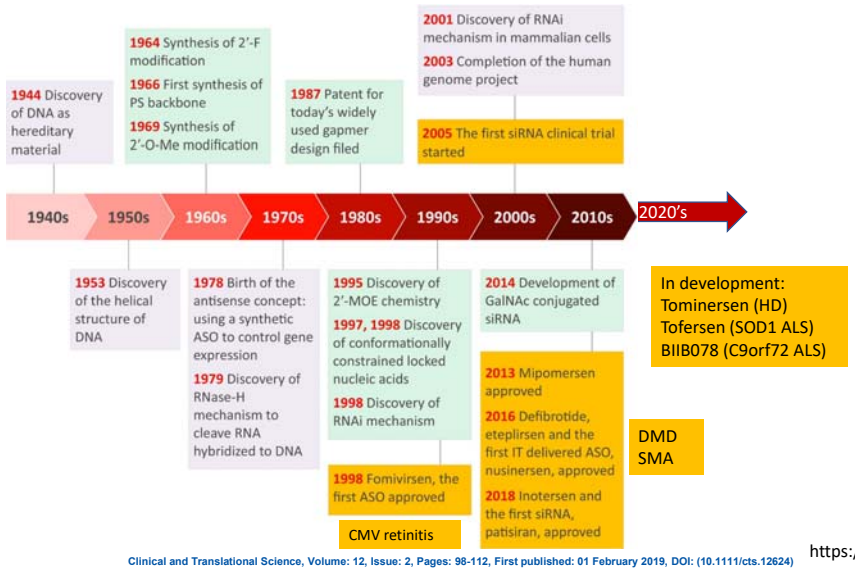


Timeline of Targeted Therapy Development in Cancer

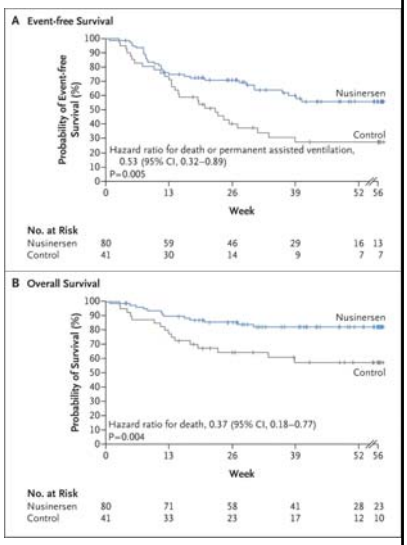




Timeline of antisense oligonucleotide (ASO) trials

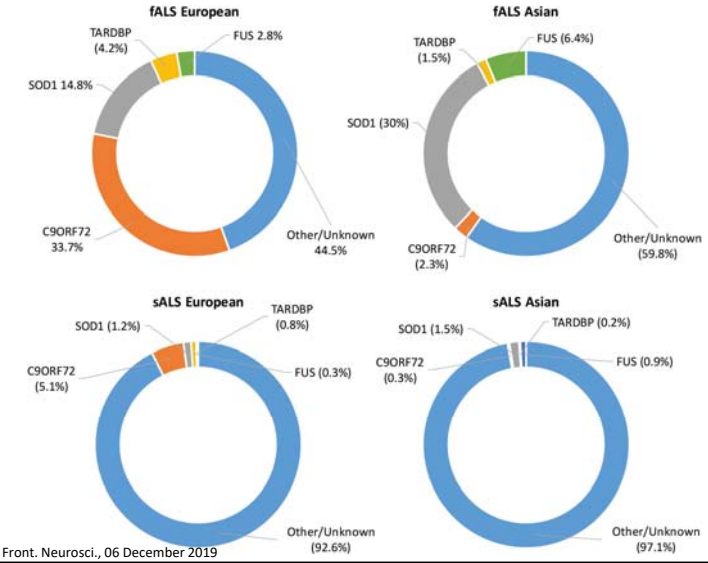


Clinical and Translational Science, Volume: 12, Issue: 2, Pages: 98-112, First published: 01 February 2019, DOI: (10.1111/cts.12624)

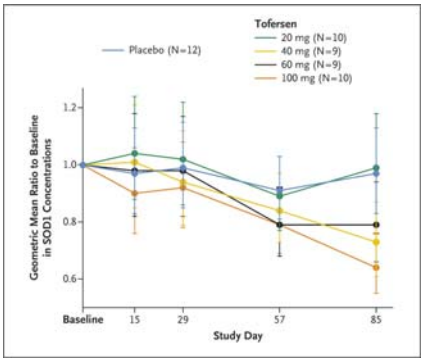


https://www.nejm.org/doi/full/10.1056/NEJMoa1702752

Targeted therapy in ALS



Front. Neurosci., 06 December 2019



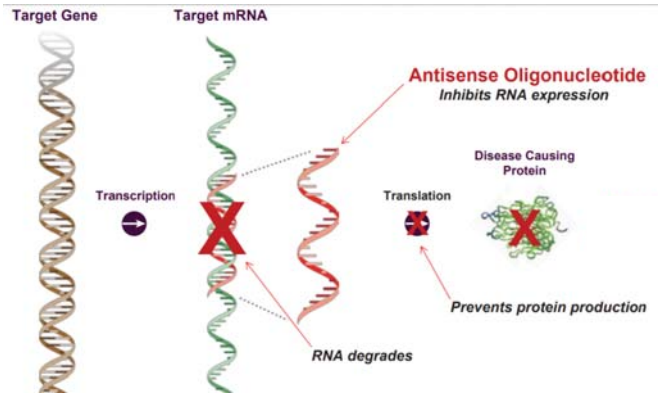
N Engl J Med 2020; 383:109-119

NEALS Northeast Amyotrophic Lateral Sclerosis Consortium

ATGC Advanced Tele-Genetic Counseling

NEALS ALS Genetic Access Program (ALS GAP)

ASO's in Parkinson's Disease

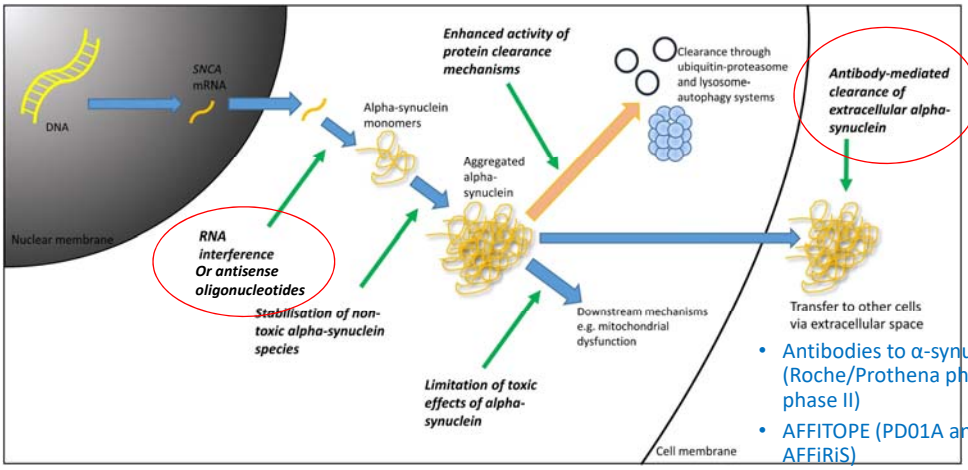


IonisPharma.com

ASO's in development for PD:

- LRRK2 (BIIB094 Ionis/Biogen Phase I)
- α-Synuclein (BIIB101 Ionis/Biogen Phase I in MSA)

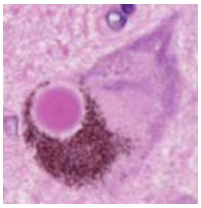
Synuclein targeted therapies

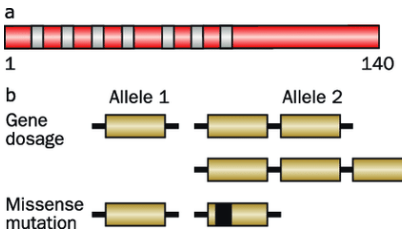


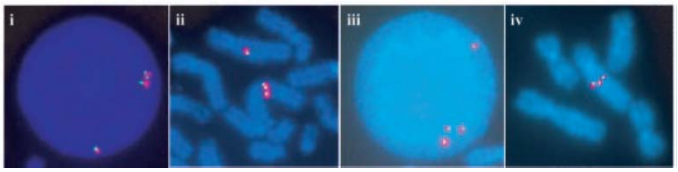
- Antibodies to α-synuclein (Roche/Prothena phase II, Biogen phase II)
- AFFITOPE (PD01A and PD03A, AFFiRiS)

Stoker, Front. Neurosci.,2018

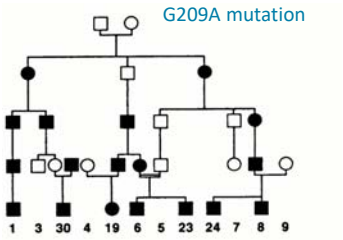
α-Synuclein is a genetic target







Goedart, J Parkinson's Disease 2017, Singleton, Science, 2003



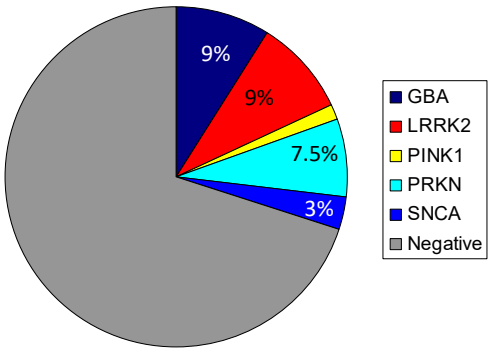
-Polymeropoulos et al, Science, 1997

Cons:

- The majority of PD is "idiopathic" not genetic
- Only 10-15% of PD is thought to be "monogenic"
- Only 30% of monogenic PD is caused by a mutation in a known gene
- Targeted therapies for one type of mutation will not be useful for other genetic mutations
- BBB limits delivery of genetic therapies

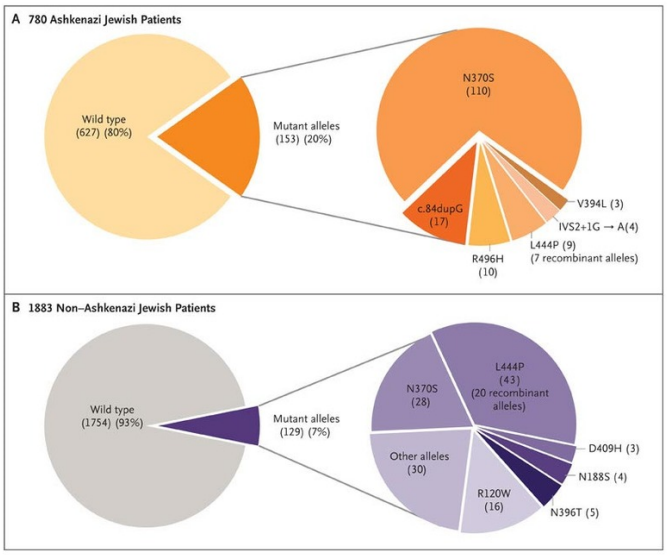
Genetic mutations are not rare

- Out of first 291 participants enrolled in PDGENEration
- 17% reportable mutations in 7 genes
- 30% including VUS
- SNPs associated with increased risk are even more common



Estimated U.S. prevalence

- LRRK2 mutations present in 1-3% of sporadic PD
- Heterozygous GBA mutations:
  - 10.7–31.3% of Ashkenazi patients
  - 2.3% to 9.4% in other ethnicities
- Assuming 1,000,000 PD patients in U.S. alone=
  - 10-30,000 LRRK2 patients
  - 50-100,000 GBA patients
  - 10-25,000 SMA patients



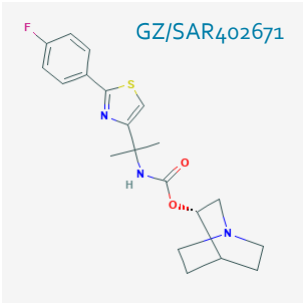
N Engl J Med 2009; 361:1651-1661

Targeted therapies may have broader applications:

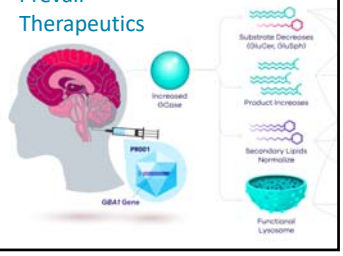
- GCase activity is reduced in DA neurons derived from MSC's from LRRK2 patients
  - Ysselstein D, et al. Nat Commun (2019)
- Inhibition of LRRK2 kinase activity increases GCase activity
- GCase activity is reduced in idiopathic PD SN
  - Gegg ME, et al. Ann Neurol(2012)
- Targeted therapies may be relevant to idiopathic PD

Approaches to BBB

- Immunotherapies also have low CSF:plasma ratios (0.2-0.4%)
- Intrathecal administration (ASOs)
- Small molecule chaperones or inhibitors
- Viral vector approaches



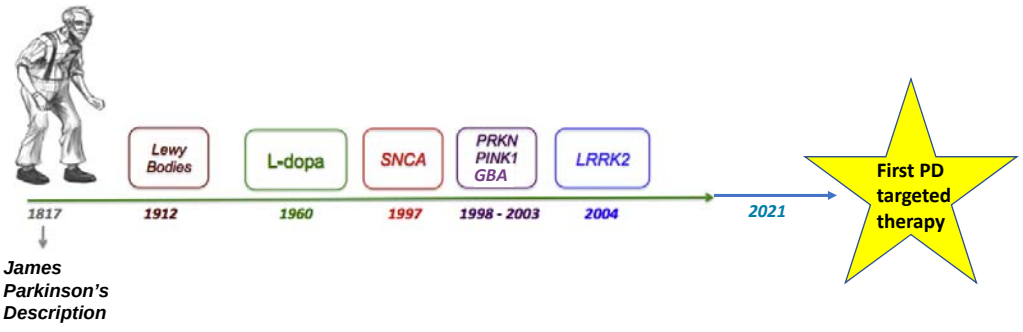
Prevail Therapeutics



Summary:

- Genetically-targeted therapies target the underlying pathophysiology of disease
- ASO trials have shown remarkable success at targeting genetic diseases such as SMA
- Identifiable genetic mutations are relatively common and are expanding rapidly
- Targeted therapies may be relevant to idiopathic disease

Timeline of Parkinson's Genetics



-Mastrangelo, Advances in Genetics, 2017