“Dude, where’s my gene therapy?”

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Disclosures

• Consulting
  • Avexis (Gene therapy for Rett Syndrome)
  • Marinus (clinical trials related to CDKL5 deficiency disorder)
  • Anonymous consulting for CDKL5 deficiency disorder
  • International Rett Syndrome Foundation

• Lennox-Gastaut Foundation Board
• Rocky Mountain Rett Association Board
• NIH grant funding (Rett, CDKL5, epileptic encephalopathies)
• Mallinkrodt grant funding (genetic causes of epileptic spasms)
• Other foundation grant funding (Rett, CDKL5)
• Ponzio family chair in neurology research (CHF)
First things first:

• What should be the outcome measure?
  • Dravet Syndrome is not a rapidly “degenerative” disorder: cannot measure decline

• Is there a “severity scale” that is appropriate?
  • What do you measure?
    • Seizures, if so, which ones? What is the best way to accurately count?
    • Cognition
    • Quality of Life

• Why is this important?
  • Clinical trials must have measurable endpoints
  • FDA will not approve if endpoints not met
Types of “gene” therapy

• What are the issues?
• Strategies
  • Gene “replacement”
  • Gene editing
  • Read through
  • Protein replacement
Gene “replacement”

• Excitement!
  • Findings in animal models
    • Artificial turn-off-turn-on in Rett mouse model
    • Gene replacement in Rett mouse model
    • Gene replacement in other diseases (Spinal Muscular Atrophy)
  • Findings in humans
    • Dramatic response in Spinal Muscular Atrophy
Gene “replacement”

• Issues/Questions
  • Addition of new copy (not “replacement”)
    • This does not fix gametes: It can still be passed on
  • Is Dravet “Goldilocks” disease (not too much, not too little, but just right)?
    • Rett is a “Goldilocks” disease (Rett = too little, MeCP2 duplication disorder = too much)
    • CDKL5 may be a “Goldilocks” disease
    • How to not “overshoot”?
  • How to get it (in)to as many cells as possible?
    • Ideal: every cell gets one new copy (currently, this is not the case)
  • How to prevent an immune response?
  • How to prevent other side-effects
Gene “replacement”

- Adeno-associated virus (AAV): the viral vector “of choice”
- Viral vector: used as the taxi to deliver the gene
- Viral vector: the virus is re-engineered to deliver the gene of choice
- Viral vector: need it to cross the blood brain barrier
- Viral vector: the virus can only hold so much (limit to the size of the gene)
  - AAV9: 4.8 kilobases (kb)
  - CDKL5: 3.8 kb
  - MeCP2: 3.6 kb (Rett)
  - SMN1: 1.5 kb (Spinal Muscular Atrophy)
  - SCN1a: 12.5 kb (Dravet syndrome) (It’s too big to fit 😞)
- Promotor region: the business end! (proprietary!)
  - How to ensure the Goldilocks issue: want it to self-regulate (make only enough)
  - This adds to how much you can put in
- AAV9
  - Crosses blood brain barrier
  - AAV10, 11, 12: less immunogenicity?
Gene “replacement”

• Issues/Questions
  • Intravenous versus Intrathecal (spinal tap)
    • Less immune response if intrathecal? More invasive?
  • How many cells in the body need to be altered to have a meaningful change?
    • 10-25% may be the most achievable (with AAV9)
  • Immune response
    • Why “re-dosing” may not get around the 10-25% issue
    • If present, this may be a “one-shot” opportunity
    • Repeat dosing will be reduced by the immune system
  • Gametes not corrected
  • The gene inserts “randomly”
    • What if it inserts into a crucial gene?
    • What if that crucial gene is linked to cell growth (potentially cancer causing)
Clinical trials

• SMA-ongoing phase 2 (phase 1 was promising)
• Cystic fibrosis-phase 1 completed (results?)
• Rett-planned phase 1
  • AveXis press release:
Gene editing

• Issues/Questions
  • Edits the specific genetic change
    • Crispr/Cas9
    • 9: the latest version, why?
      • Cannot (yet) do all possible genetic sequence changes (version 12, 13?)
      • How it works—it cuts and re-assembles.
      • Does not always completely “clean up its mess”
    • 25% maximum efficiency
  • The “guide RNA” and the Crispr/Cas
    • The guide RNA: must be tailor made to patient specific change
      • If not perfect: off-target changes
    • Too big to put both into AAV9
      • See issues associated with Gene Replacement, reduce by 2 (2 different vectors needed)
      • Multiply by 25% (maximum efficiency)
Read Through Drugs

• Relevant ONLY for missense changes that cause a premature stop to translation (only a small protein is made instead)
• This information is in your genetic test result
Read Through Drugs

Normal Translation

Incomplete Translation

Ataluren-Facilitated Translation
Read Through Drugs

• On average, 5-15% of patients with any of at least 1,800 genetic disorders have a nonsense mutation as the underlying cause of the disease, including:
  • DS, CDKL5, Rett
  • DMD, CF
  • SMA
  • Hemophilia
  • Lysosomal storage disorders
  • Retinitis pigmentosa
  • Familial hypercholesterolemia
  • Some cancers

• Successful trials with PTC-124 in DMD and CF may translate into potential therapeutic approaches for other genetic conditions
### Read Through Drugs: DMD experience

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<tr>
<th>Period</th>
<th>Study</th>
<th>Description</th>
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<tr>
<td>2005-2007</td>
<td>Study 004 (Dystrophin Study) 28 days N=38</td>
<td>Production of full length dystrophin</td>
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<td>2008-2009</td>
<td>Study 007 (RCT) 48 weeks N=174</td>
<td>Identified dose Consistent results across multiple endpoints</td>
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<tr>
<td>2013-2015</td>
<td>Study 020 (RCT) 48 weeks N=228</td>
<td>Consistent results across multiple endpoints Benefits in light of natural history</td>
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<td>2012 - 2017</td>
<td>Study 019 (Long-term Study) ~3.5 years*N=94</td>
<td>Preservation of pulmonary function</td>
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**Ongoing Studies**
- Study 025o (Global Registry)
- Study 041 (Post-market Long-term RCT)

Enriched population required for 6MWT
Pre-specified 300-400m subgroup
Read Through Drugs: DMD experience

- Ataluren approved outside the US since 2014
- Available in > 25 countries
  - ~700 patient-years of exposure continues to support positive favorable safety profile
  - ~95% patient retention
- Global registry with real-world evidence generation ongoing
Read Through Drugs: DMD experience

Human Myotubes

Change in 6MWD Mean ± SE (meters)

Ataluren 10, 10, 20 mg/kg (N=57)
Ataluren 20, 20, 40 mg/kg (N=60)
Placebo (N=57)

LS Mean Δ = + 26.4m

Rank transformed p = 0.149
Mixed-model repeated-measures analysis (MMRM)
Read Through Drugs: DMD experience

Baseline 6MWD

Stable Phase

Transition Phase

Accelerated Decline Phase

Most sensitive phase to assess changes in muscle decline within 48 weeks

Time
Read Through Drugs: DMD experience

The U.S. Food and Drug Administration decided not to approve Translarna (ataluren), by PTC Therapeutics, as a treatment for specific types of Duchenne muscular dystrophy caused by "nonsense" mutations.

Although not entirely unexpected, the decision was disappointing to many in the Duchenne community.

On Sept. 28, an FDA advisory panel concluded that evidence to support Translarna’s effectiveness as a therapy was lacking, and more research was needed. That opinion was endorsed by 10 of the panel’s 11 members and echoed by an FDA briefing document given to the advisory panel in advance of the meeting. The brief highlighted problems with research data presented to support the treatment’s marketing application.

The FDA’s Office of Drug Evaluation noted in its recent complete response letter (CRL) that PTC had failed to clearly demonstrate that the treatment worked — a stronger condemnation than that of the advisory group, whose majority voiced its dissatisfaction with inconclusive data.

“Ultimately, no positive results from any prospectively planned analyses that are persuasive have been provided with this application,” the agency memo stated. The CRL calls for additional adequate and well-controlled and clinical trials, at a minimum, to provide substantial evidence of the effectiveness of the treatment.
Read Through Drugs

• What can we learn?
  • Does it depend on the sequence around the premature stop?
  • Not the cure we hoped for (in DMD or CF)
  • You need measureable endpoints
  • You need natural history
  • Even in a disease with decline, it is not straightforward
Protein replacement

• Issues
  • SCN1a is a Big protein
  • How to deliver?
    • Veins? Into cerebrospinal fluid? Into brain?
  • Will it get to where it needs to go?
    • Into cells? Insert into membranes? Go to right place?
• Examples with Big proteins
  • CLN2: loss of a lysosomal enzyme causes degenerative epileptic encephalopathy
    • Enzyme replacement. By replacing enzyme into spinal fluid, a unique feature of this enzyme allows it to be put into cells in the right place.
  • CDKL5: loss of a cytosolic enzyme causes an epileptic encephalopathy
    • Many mysteries around CDKL5 function
Enzyme Replacement Therapy Attenuates Disease Progression in a Canine Model of Late-Infantile Neuronal Ceroid Lipofuscinosis (CLN2 Disease)

Martin L. Katz, Joan R. Coates, Christine M. Sibigroth, Jacob D. Taylor, Melissa Carpentier, Whitney M. Young, Fred A. W inning, Derek Kennedy, Brian R. Vuillemenot, and Charles A. O'Neill

Fig. 1. Survival times of TPPI−/− Dachshunds in the four treatment groups. Two of the dogs given the 16 mg dose were euthanized prior to reaching end-stage disease because they had developed meningitis or obstructive hydrocephalus. The dog receiving the 48 mg dose was euthanized before reaching end-stage disease because it had developed obstructive hydrocephalus. All remaining dogs were euthanized when they reached end-stage disease.
Study of Intraventricular Cerliponase Alfa for CLN2 Disease

Angela Schulz, M.D., Temitayo Ajayi, M.D., Nicola Specchio, M.D., Ph.D., Emily de Los Reyes, M.D., Paul Gissen, M.B., Ch.B., Ph.D., Douglas Ballon, Ph.D., Jonathan P. Dyke, Ph.D., Heather Cahan, M.D., Peter Slasor, Sc.D., David Jacoby, M.D., Ph.D., and Alfried Kohlschütter, M.D., for the CLN2 Study Group®
• CDKL5 deficiency: epileptic encephalopathy, big protein
• CDKL5-knock out male mice, 16 weeks old (adult)
• CDKL5 protein modified with a TAT cap: cell permeable AND crossed blood brain barrier
• Improved: learning and memory, abnormal dendrites, breathing, clasping
• Requires chronic/continuous infusion
Summary: General unknowns

- Cost is unknown
  - Spinraza example (anti-sense oligonucleotide for SMA)
    - hundreds of thousands per year for life
  - Cancer and blood disorders
    - $1-3M, “medical mortgage”
- Long-term consequences of this therapy are unknown
- Is there a critical window of opportunity for treatment?
  - Dravet is a developmental encephalopathy—it happens during a critical period of development and may (permanently?) alter developmental trajectory
Final Summary

• Gene therapy is not here (yet!!!) for Dravet syndrome
• Key elements needed for trials
  • Efficacy in animal models
  • Natural history in humans
  • Measurements of severity or other outcomes measures
  • Established clinical trials network
  • PAG (you!): your input to FDA is crucial
• Gene therapy is likely to be very costly
• Timing of gene therapy may be crucial
Questions?