Gene Therapy: Early Clinical Development Challenges

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What’s different about gene therapy: PK may not apply

- The therapeutic agent is encoded as DNA that is delivered by a viral capsid which must un-coat in the nucleus to release a plasmid that can transcribe a therapeutic RNA.
- The transcribed RNA can code for a protein (or peptide or antibody) and raise its levels or it can cause RNA interference and diminishes levels of the target.
- The administered agent is a vector genome but the ultimate pharmacology is downstream of the molecule that is administered.
- While there can be a dose/response relationship, a conventional PK approach of relating the kinetics of the administered molecule to a therapeutic responses or side effects is not applicable.
Oral administration - capsids don’t survive

Intravenous administration

• Upsides
  • non-invasive
  • could reach the entire CNS

• Downsides
  • doses are very high
  • immune responses are more likely
  • BBB and tropism could hamper reaching the targeted cells
  • systemic exposure could increase the likelihood of off-target effects.

From Maguire et al, 2014
Intrathecal administration

- Upsides
  - Well tolerated
  - Lower doses
  - Reduced systemic exposure

- Downsides
  - Exposure may be best near the site of administration and closer to the surface.

Intraparenchymal administration

- Upsides
  - Doses can be very small
  - Can precisely target specific brain regions
  - Unlikely to elicit an immune response

- Downsides
  - Requires specialized neurosurgery, devices
  - Broad CNS distribution can be difficult

From Hocquemiller et al, 2016
### Table 1. Clinical Trials

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<th>Injection site</th>
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<th>Clinical trial</th>
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From Hocquemiller et al, 2016
What’s different about gene therapy: Dosing

• Gene therapy is delivered once
  • Effects are durable (especially in non-dividing cells)
  • Acquired immunity makes redosing problematic, so adjustments aren’t feasible currently
  • May not be able to improve pharmacology or turn off side effects in an individual other than adjusting other treatments.
  • Ethics require starting with a minimally effective dose and in the target population.
  • Early phase studies can be SAD 😞 but not MAD 😞
What’s different about gene therapy: Time-courses

- Onset of pharmacology is delayed as it may take weeks for the virus to uncoat, for the payload to express and reach a plateau, for secondary effects on the target to also plateau.
- Side effects could be an immediate response to the treatment, could emerge in concert with pharmacology, could emerge late if there is an immune response.
- Assessing safety and pharmacology in early phase studies must account for these timings (spacing of enrollment, timing of assessments, duration of follow-up)
- Because the treatment effects are durable, follow-up is measured in years (FDA guidance is 2-5 years for non-integrating virus, 15 for an integrating virus), beginning with the first patient treated.
What’s different about gene therapy: Safety

• On target effects
• Off-target effects
  • Off-location
  • Off-mechanism
• Immune-responses
• Viral shedding
Pre-existing immunity

- Pre-existing humoral or cellular immunity against a capsid could cause an immediate immune response or block treatment effects.
- Anti-capsid neutralizing antibodies (NAbs) are a subset of anti-capsid antibodies that prevent therapeutic transfection.
- Assays essential to screen animals for use in non-clinical studies to insure validity.
- Screening potential trial participants to exclude those with immunity, depending on ROA.
  - Low serum (1:5) titers have been associated with reduced efficacy for systemic gene therapies.
  - IgG in CSF is 12-1200X lower in children, 300X lower in adults so even high serum titers may be OK for IT or IP delivery.
NAb Seroprevalence
- AAV1 NAb in 15-50%
- AAV2 NAb in 30-60%
- AAV7, AAV8, AAV9 NAb in 15-30%
- AAVrh10 in up to 60%
- Nab cross reactivity between capsids is frequent because of high sequence homology.

Anti-AAV Seroprevalence
- AAV1 Abs in 70%
- AAV2 Abs in 70%
- AAV6 Abs in 45%
- AAV9 Abs in 45%
- AAV8 Abs in 38%.
What’s different about gene therapy: Immunology

Calcedo et al 2009

Narkbunnam et al 2011
Mitigation strategies for pre-existing immunity

- Selection of naïve subjects
- Select or engineer viral subtypes with lower sero-prevalence of NAbs
- Plasmapheresis (for titers < 1:100) or immuno-absorption
- Transient immunosuppression (rituximab, cyclosporine A, methotrexate, mycophenolate, bortezomib)
- Isolated perfusion and saline flushing (not for CNS)
- Competition with empty capsids
What’s different about gene therapy: Immunology

Acquired immunity

• Capsid exposure will lead to the development of immunity
• Transgene product immunity could develop depending on the ‘foreignness’
• Immune attack on tissues that can present antigen can cause damage and loss of the gene therapy if its presence is cleared from the targeted tissue.
  • Monitor with assays for humoral and cellular immunity
  • Immune response in toxicology studies may not be predictive of responses in humans
  • Consider immune-suppression depending on the route of administration.
  • Monitor pharmacodynamics to assess durability of expression
Biomarkers – fit for purpose

- **Diagnostic**: Neutralizing antibodies
- **Shedding**: Capsid
- **Target engagement**: RNAs (shRNA, miRNA, mRNA...)
- **Response**: Targeted protein
- **Safety (?)**: Activated T-cells (Elispot), cytokines...
Since gene therapies are durable, typical Phase 1-3 study progression from safety/PK/PD to preliminary efficacy to definitive efficacy does not apply well.

- Every treated patient contributes to the long-term accumulation of safety and efficacy data.
- For neurodegenerative or other progressive diseases, the earliest patients treated can be the most informative about efficacy since follow-up is longest.
- Early inclusion of controls and blinding can maximize the contribution of all the treated patients.
- Adaptive designs may be especially applicable to enable efficient accumulation of safety and efficacy data.
- Early regulatory discussions about how to demonstrate efficacy and access accelerated approval mechanisms.
What’s different about gene therapy: Ethics

• Cannot treat healthy controls during early development.
• The dose should always have the potential to provide benefit.
• Participation in a gene therapy trial could affect participation in other clinical trials.
• Consent process should inform about these issues and also temper expectations at a time when there are such high hopes for gene therapy.
What’s different about gene therapy: Questions?