

Challenges in Advancing the Field of Gene Therapy: *A Critical Review of the Science, Medicine, and Regulation*

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Agenda

- ❑ Adrenoleukodystrophy (ALD)
- ❑ Impediments to Clinical Gene Transfer
- ❑ Solutions

Adrenoleukodystrophy (ALD)

- X-linked
- Monogenic disorder
- 1:17,000 incidence
- >600 mutations
- ABCD1 (ALDP)/peroxisomal transporter
- Elevated very long chain fatty acids (VLCFA's)

- 45% Childhood Cerebral Onset
 - Demyelinating disease in boys
 - Death/vegetative state in 2-5 years
- 55% Adrenomyeloneuropathy (AMN)
 - Adults in 20's and beyond
 - Peripheral neuropathy
 - 50% with fatal cerebral involvement

Current ALD Therapy

- Stem cell transplant (allogenic)
- 40% mortality
- Not everyone has a match

ALD Gene Therapy Protocol

- Ex vivo
- Correct autologous CD34+
- Lentiviral vector with ABCD1 payload

Impediments to Clinical Gene Transfer

- Vector design and transduction protocol
- Adverse events
- Risk vs. benefit
- Experienced and qualified resources
- Professional support for clinical applications
- Financial and broad scientific resources

- Constantly evolving
- GMP biologics manufacturing challenges
- Limit to preclinical work
- Translational medicine

Adverse Events

- J. Gelsinger
 - Forum for criticism rather than learning opportunity
 - Impacted risk tolerance adversely
- SCID/leukemic transformations
 - Excellent handling within gene therapy community
 - Additional investigations to insertional oncogenesis
 - Poor public relations effort in broader scientific and lay communities
 - Adversely altered climate in US

Risk vs. Benefit

- Advanced ALD patients (low risk/low benefit)
- Earlier stage ALD patients (higher risk/higher benefit)
- Phase I vs. Phase I/II
- Safety must be in context of medical need

- ALD is neurodegenerative disorder treated by neurologists
- PI's inexperienced in gene therapy trials, other scientific disciplines, biotech, industry, regulatory
- Time consuming first time

- *Molecular Therapy* journal of ASGT
- 10 issues
- >125 articles
- Very few clinically oriented articles

- Limited funds
- Limited number of scientists

Solutions

- Advisory committee of experienced PI's
- "Partner" clinicians with PhDs/basic researchers
- Invest in public relations
- Increase publications of clinical applications
- Select disease amenable to gene therapy
- Use limitations inherent in orphan diseases as opportunities

Disease Amenable to Gene Therapy

- Marry unmet medical need with rational therapeutic approach
- Task force
- Foundation involvement
- Solicit funding
- Take business like approach

Orphan Disease Opportunities

- Small scientific community can speak with united voice
- Pursue external participation
- Harness agenda of foundations

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- ✓ Adrenoleukodystrophy (ALD)
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- ✓ Solutions