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)
ALD Phenotypes

• 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 (allogeneic)
- 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
Vector Design and Transduction Protocol

- 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
Experienced and Qualified Resources

- ALD is neurodegenerative disorder treated by neurologists
- PI’s inexperienced in gene therapy trials, other scientific disciplines, biotech, industry, regulatory
- Time consuming first time
Professional Support for Clinical Applications

- *Molecular Therapy* journal of ASGT
- 10 issues
- >125 articles
- Very few clinically oriented articles
Financial and Broad Scientific Resources

- Limited funds
- Limited number of scientists
• 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
Agenda

✓ Adrenoleukodystrophy (ALD)
✓ Impediments to Clinical Gene Transfer
✓ Solutions