Translational Pharmacology & Biology of Gene Therapy for Heart Failure

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Gene Therapy Overview

Correction of defective gene by insertion of genetic material into cells

- Correct; genetically defined or acquired defects
- Enhance expression, reduce expression, engineered genes/fragments
- Focused on correcting somatic cell defects
- Germ-line modification feasible but ethical issues abound

Payload
Genes
siRNA
Crispr
Talens

Expertise
Vector Design
Delivery
Production/Scale-up
Regulatory/Clinical

Delivery System
Viral:
- Adenovirus
- Adeno-associated virus
- Retrovirus
- Lentivirus

Other:
- Naked DNA
- Lipid-based
- Gene gun
Gene Therapy Brief History

Ashanti DeSilva; 1990
Severe Combined Immunodeficiency:
Gene: Adenosine deaminase
Delivery: Retroviral vector
Ex vivo Gene Tx
White cells fully functional @ 6 mos

Jesse Gelsinger; 1999
Ornithine Decarboxylase Deficiency
Gene: OD
Delivery: Adenovirus
In vivo Gene Tx targeting liver
Died shortly after Tx

First “off the shelf” Gene Tx approved in 2015; for Lipoprotein Lipase deficiency in Familial Chylomicronemia Syndrome
alipogene tiparvovec
New Gene Therapies; Emerging Rapidly

Disease therapies under development

- **Ocular Disease**
  - X-linked retinitis pigmentosa,
  - Diabetic retinopathy
  - 8 others

- **CNS Disease**
  - Parkinsons disease
  - Monogenic ALS
  - Friedrich’s Ataxia

- **Liver Diseases**
  - Hemophilias
  - Pompe disease
  - Mucopolysaccharidoses

- **Ex Vivo Gene Tx**
  - B-Thalassemia
  - Sickle cell anemia
  - Cerebral adrenoleukodystrophy

- **Cancer**
  - p53 mutations
  - CAR-T cells

- **Cardiovascular Disease**
  - Heart failure
  - Familial & Acquired Cardiomyopathies

✓ 67 Biotechs in Gene Tx
✓ Since 2009; 20 alliances
✓ All big pharmas are investing
Gene Therapy For Heart Failure; S100A1

- Multifunctional calcium binding protein; 22 kDa
- Combination of effects has possibility for robust efficacy
- Expression reduced in HF; stimulating S100A1 activity/content via traditional pharmacological therapies not feasible

Brinks, et al, JACC, 2011

*Courtesy P. Most; uniQure, U Heidelberg
AAV9-S100A1 Vector Construction

- Remove viral genes and replace with target transgene
- Viral genes provided in trans to produce transduction-competent particles

- AAV is a naturally occurring non-pathogenic virus
- Does not integrate into host genome
- In non-dividing cells (cardiomyocytes); gene expression 5+ years
- Naturally occurring serotypes allow tissue selective transduction
- Safe history in cardiac gene therapy

\( \text{AAV9-S100A1 Vector Construction} \)
Video Of Cardiac Gene Therapy

Video Courtesy Of
Roger Hajjar, MD
Director Cardiovascular Research Center
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Mt Sinai Medical Center
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Gene Therapy Delivery
Porcine HF Gene Therapy Model; S100A1

- Tx 2 weeks post MI; left circumflex occlusion
- Balloon catheters in left anterior descending artery & anterior cardiac vein.
- Occlude LAD; 3 X 45 sec
- Infuse gene Tx via ACV
- AAV9-S100A1; 1.5 X 10^{13} particles
- Targets anterior wall (5), not posterior wall (4)

Expression levels +14 weeks

Porcine HF Model; Functional Outcome & Survival

Ejection Fraction

One Year Survival

*Courtesy P. Most, uniQure, U of Heidelberg

Translational Considerations

1. Dose
   • Inverted u-shaped dose response?

2. Tissue distribution & expression
   • How to measure viral DNA, expression?
   • Insertion of viral DNA into host genome?

3. Route of administration
   • Direct into tissue, systemically?

4. Pre-existing anti-AAV antibodies
   • Does pre-existing immunity block efficacy?
   • How prevalent are anti-AAV antibodies?
   • Viable work-arounds?

5. Immune/Inflammatory reactions
   • Treatment will likely generate antibodies.
   • Does this limit to one time treatment?
   • Is immunosuppression a good idea?
Translational Considerations

6. Tox/Safety program
   • Dose multiples
   • Single administration paradigm
   • Route of administration same as planned for clinic
   • CRO’s experienced w/gene therapy & appropriate large animals

7. Scale-up & GMP production
   • Many biotechs have not developed this capability
   • Mammalian vs non-mammalian cell production

8. Regulatory
   • Guidance for AAV gene therapy is established
   • RA’s open to early/often interactions as programs approach clinical trials

9. Clinical Trials
   • Straight to patients; no trials in normal human volunteers
   • 2 Trial paradigm; dose range finding, efficacy/safety
   • Requires long term follow up at all stages
Summary

• Gene therapy is rapidly emerging as a viable therapeutic approach
• Large commitment of resources across biotech & pharma on myriad of diseases
• High interest among regulatory authorities in designing development program
• Many considerations & issues not fully resolved
Gene Therapy Partnership; BMS + uniQure