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*

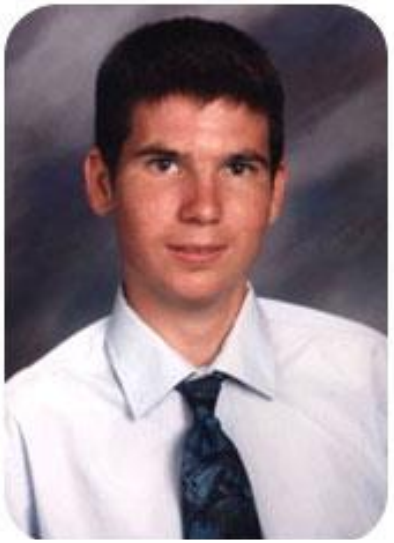
Gene Therapy Brief History

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

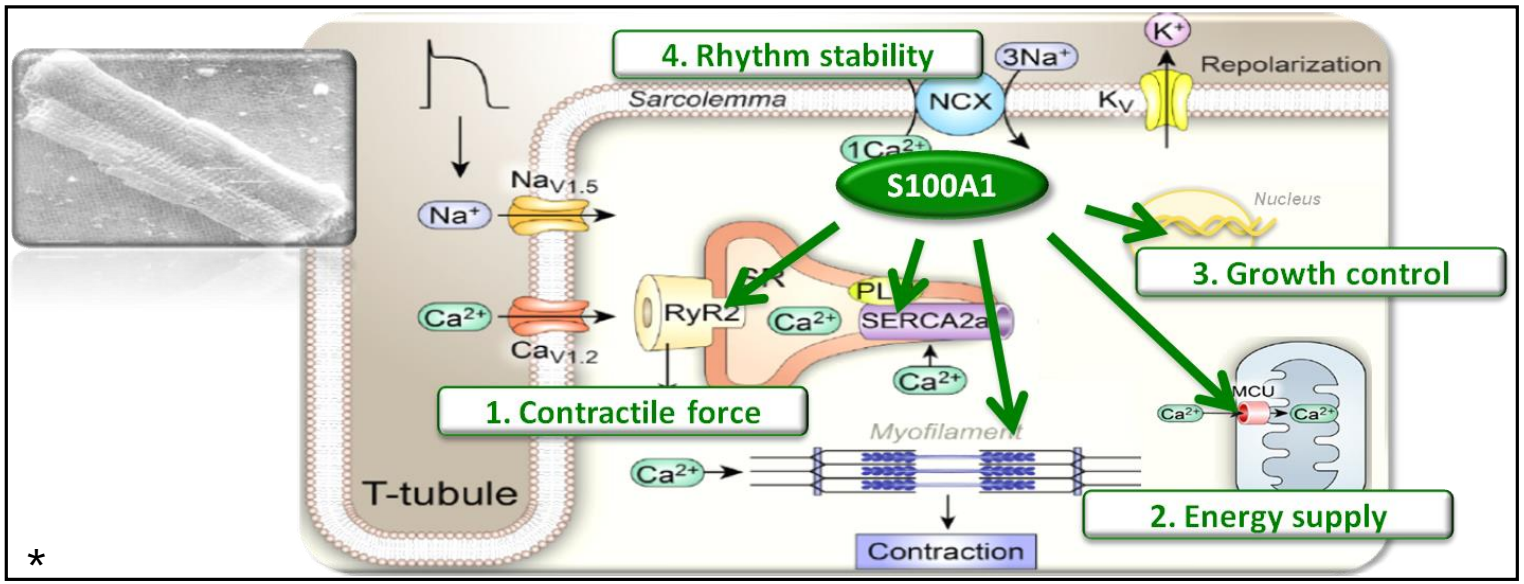
Disease therapies under development

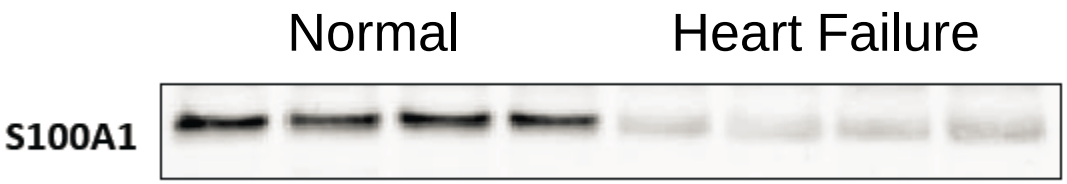
- **Ocular Disease**
  - *X-linked retinitis pigmentosa,*
  - *Diabetic retinopathy*
  - *8 others*
- **CNS Disease**
  - *Parkinsons disease*
  - *Monogenic ALS*
  - *Friedrich's Ataxia*
- **Liver Diseases**
  - *Hemophilias*
  - *Pompe disease*
  - *Mucopolysaccharidoses*
- **Ex Vivo Gene Tx**
  - *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**





Human Heart Tissue Samples

Brinks, et al, JACC, 2011

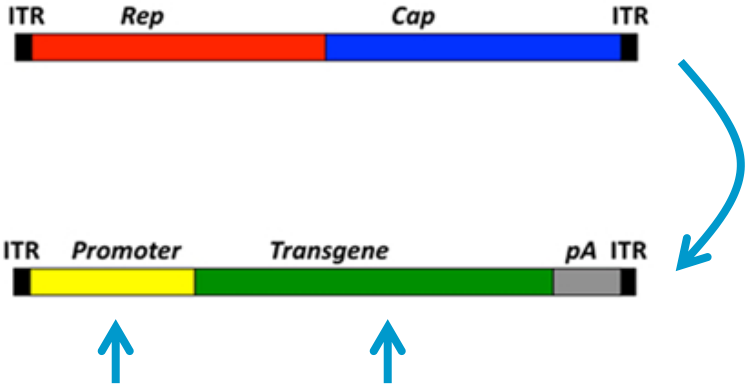
*Courtesy P. Most; uniQure, U Heidelberg

Adeno-Associated Virus Delivery Platform

- 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

AAV9-S100A1 Vector Construction

Adeno-Associated Virus



Heart Specific Promoter

S100A1

Remove viral genes and replace with target transgene

Viral genes provided in trans to produce transduction-competent particles

Video Of Cardiac Gene Therapy

Video Courtesy Of

Roger Hajjar, MD

Director Cardiovascular Research Center

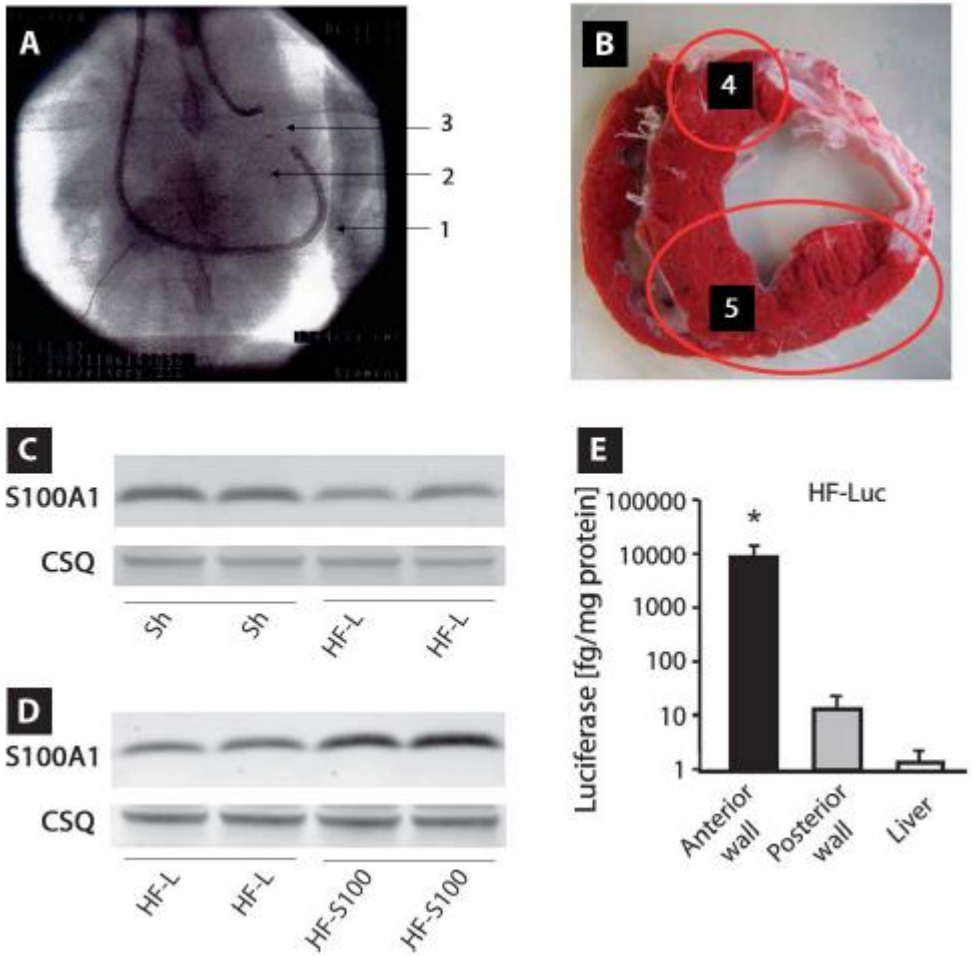
Icahn School Of Medicine

Mt Sinai Medical Center

New York, NY

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)**

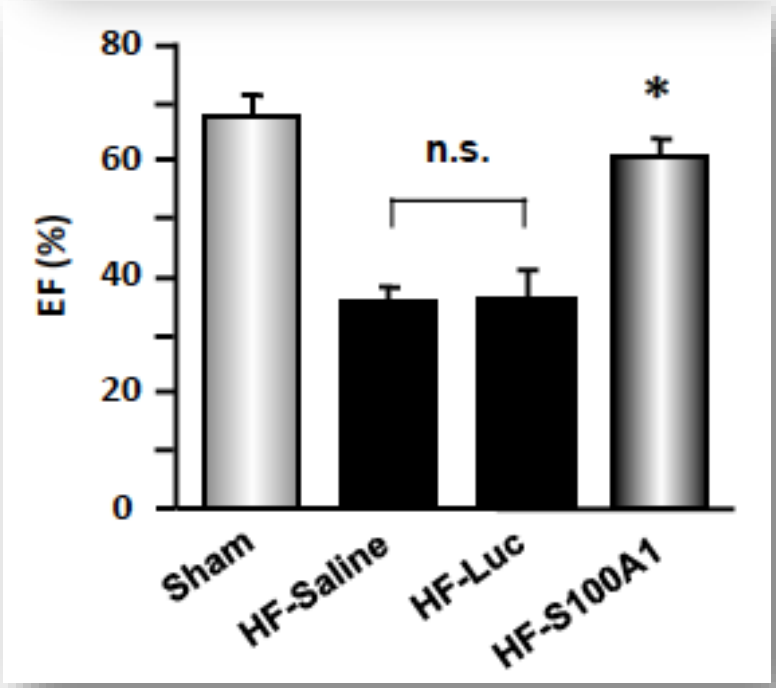


Expression levels +14 weeks

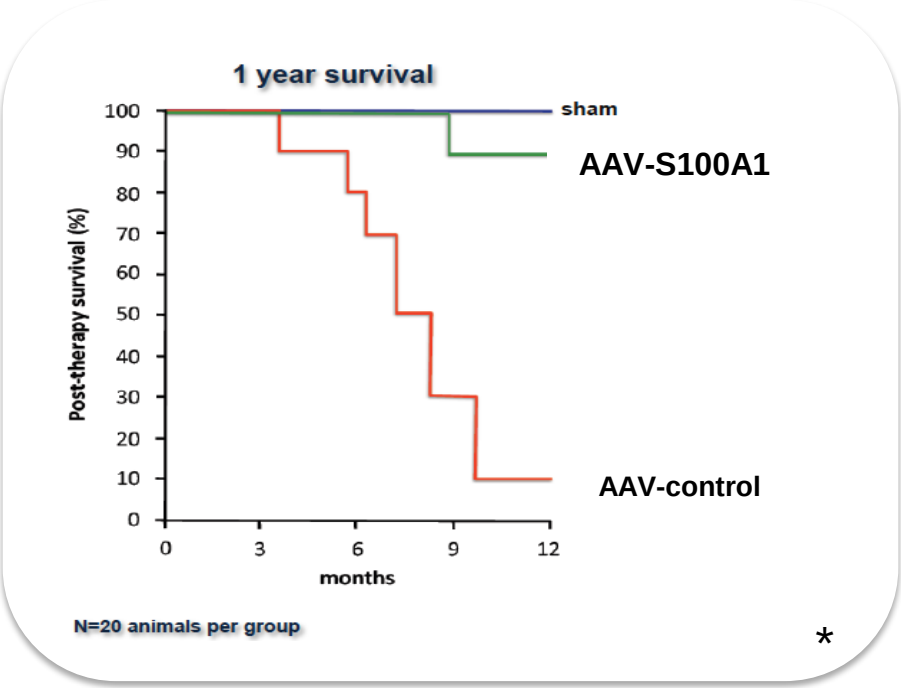
Pleger, et al., *Science TR*, 2011

Porcine HF Model; Functional Outcome & Survival

Ejection Fraction



One Year Survival



Pleger, et al., *Science TR*, 2011

*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