Gene therapy for the treatment of heart failure

Prevalence

Heart Failure (HF) remains a leading cause of mortality (≈50% after 5 years) and hospitalizations throughout the world. It is estimated that over 23 million people worldwide are afflicted with HF.

Gene therapy

Our understanding of the molecular changes in HF has increased significantly in the last 20 years, and novel targets have been identified.

These signalling pathways have been difficult to manipulate pharmacologically and for this reason gene therapy has been used experimentally and clinically for targeting purposes.

Target therapy

- Enhance cardiac muscle contractility
- Enhance angiogenesis
- Enhance cytoprotection
- Enhance stem cell homing

Enhance cardiac muscle contractility

- **Targeting the β-adrenergic system**
  - Downregulated G protein-coupled receptor kinase (GRK)
  - Activation of adenylyl cyclase type 6 (AC6)

- **Targeting Ca^{2+} cycling proteins** (calcium cycling is abnormal in human HF)
  - Over-expression of Ca^{2+}-ATPase (SERCA2a)
  - Over-expression of small ubiquitin-like modifier type 1 (SUMO1)
  - Inhibition of phospholamban (PLN)
  - long-term expression of S100A1 protein

- **Targeting the myofilaments**
  - over-expressing the enzyme of ribonucleotide reductase (R1R2)

    - The production of 2-deoxyATP ⟶ replacing ATP

    ⟶ increasing myosin binding to actin

Enhance angiogenesis

Prolonged over-expression of VEGF-A is associated with leaky vessel formation. Transient over-expression of VEGF-A enhanced formation of functional non-leaky vessels and improved survival in mouse myocardial infarction (MI) model.

Enhance cytoprotection

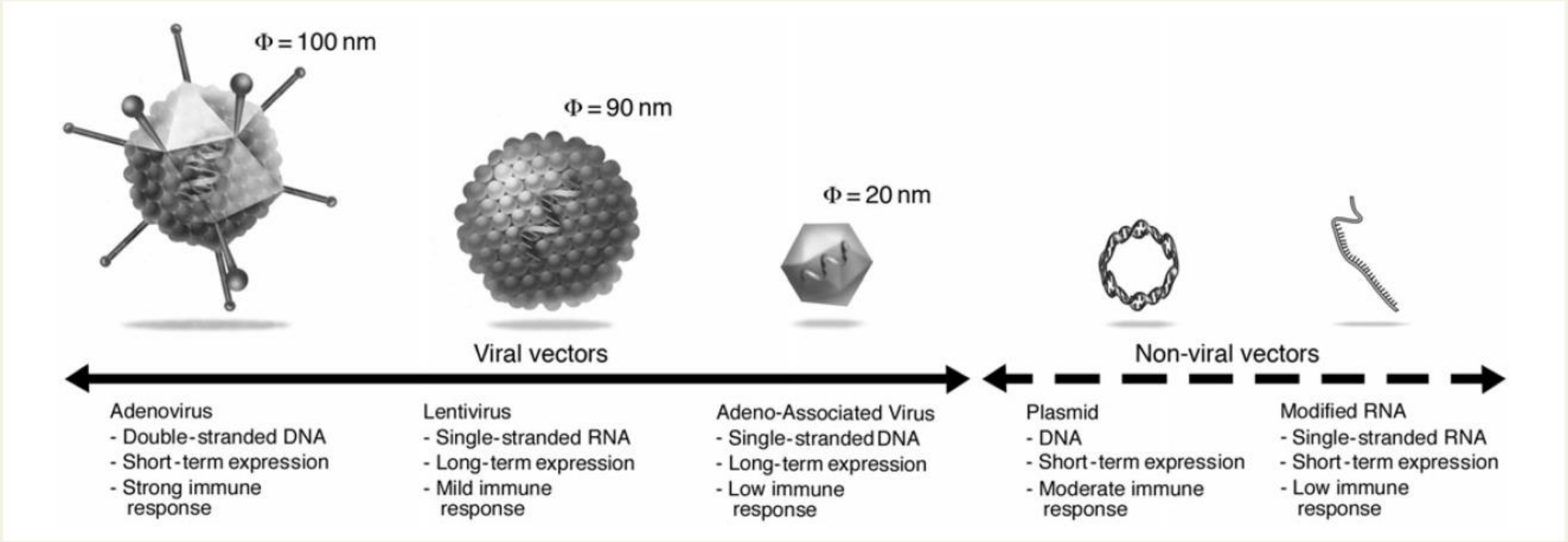
Cytoprotective cardiac gene therapy approaches were recently shown to be promising in clinically relevant large animal models.

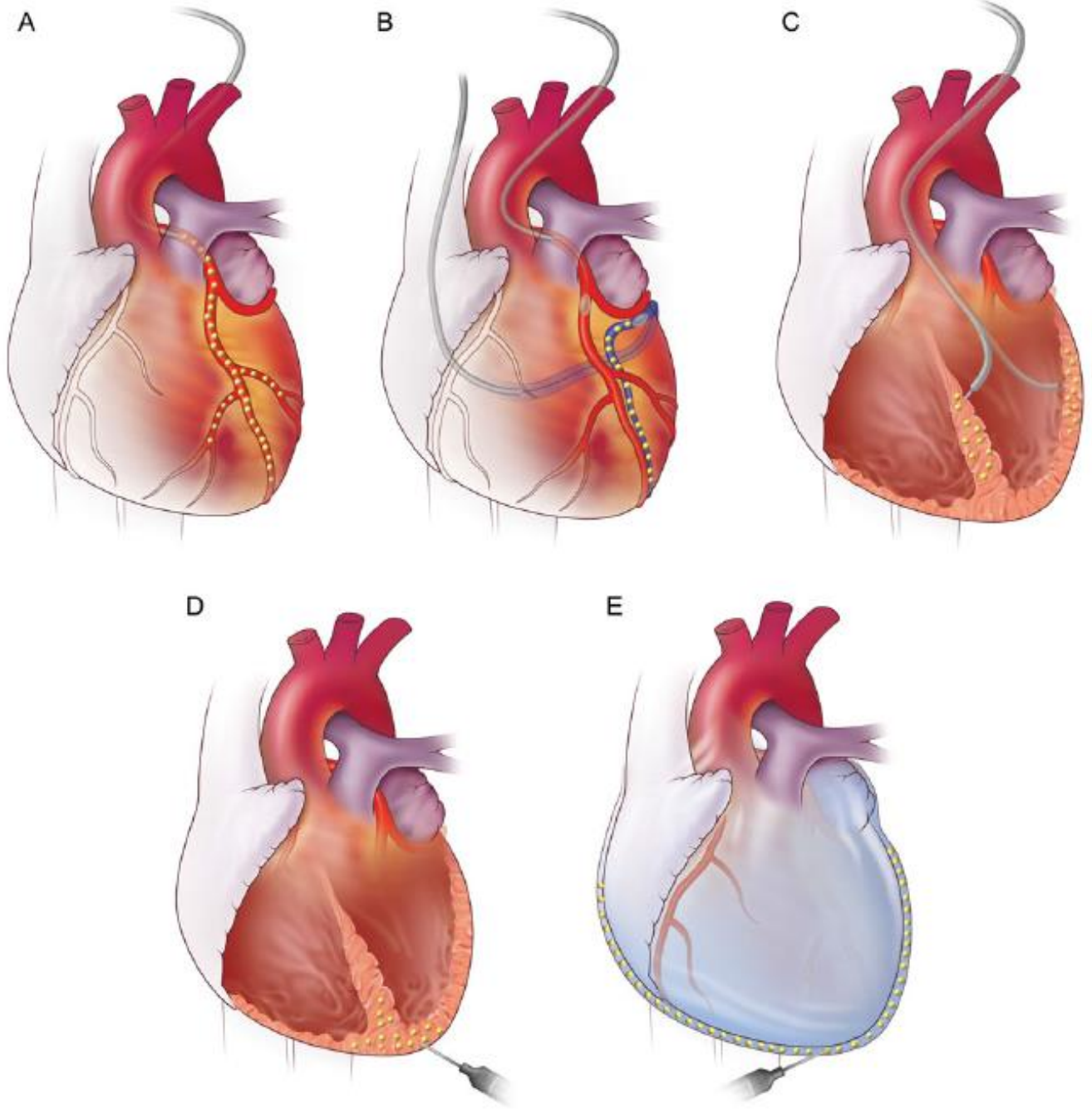
- over-expression haem oxygenase-1
- over-expression VEGF (B and D)

Enhance stem cell homing

The stem cell-derived factor 1 (SDF-1)/C-X-C chemokine receptor (CXCR) type 4 complex has been shown to promote the homing of stem cells to infarcted myocardium.

Vectors and delivery





Methods of gene transfer

(A) Antegrade intracoronary injection.

(B) Retrograde injection through the coronary sinus with simultaneous blockade of the antegrade flow.

(C and D) Direct myocardial injections through the left ventricle using catheter-based and surgical approach.

(E) Intrapericardial injection.

List of clinical cardiac gene therapy trials targeting heart failure

Trial	Phase	Vector	Gene	Delivery	Study design	Target patients	No. of patients	Primary outcome	Study locations	Status
CUPID	I/II	AAV-1	*SERCA2a*	Intracoronary	Phase I: open label; Phase II: randomized, double blinded	NYHA class III/IV, LVEF ≤35%	Phase I: 12; Phase II: 39	Composite endpoint at 6 months: NYHA, 6MWT, VO_2 max, NT-proBNP, QOL, echocardiographic function	USA	Results published
	IIb	AAV-1	*SERCA2a*	Intracoronary	Randomized, double blinded	NYHA class II–IV, LVEF ≤35%	250	Time to recurrent cardiovascular events (12 months)	International	Results published
SERCA-LVAD	II	AAV-1	*SERCA2a*	Intracoronary	Randomized, double blinded	Chronic HF patients on LVAD	24	Safety and feasibility	UK	Not recruiting
AGENT-HF	II	AAV-1	*SERCA2a*	Intracoronary	Randomized, double blinded	NYHA class III/IV, LVEF ≤35%	44	Changes in left ventricular end-systolic volume (6 months)	France	Not recruiting
STOP-HF	I	Plasmid	*SDF-1*	Endomyocardial	Open label	NYHA class III, LVEF ≤40%	17	Major adverse cardiac events (30 days)	USA	Results published
	II	Plasmid	*SDF-1*	Endomyocardial	Randomized, double blinded	Ischaemic cardiomyopathy, LVEF ≤40%	93	6MWT (4 months)	USA	Results published
RETRO-HF	I/II	Plasmid	*SDF-1*	Retrograde	Phase I: open label; Phase II: randomized, double blinded	Ischaemic cardiomyopathy, LVEF ≤40%	Phase I: 12; Phase 2: 40	6MWT (4 months)	USA	Completed recruitment
AC6 Gene Transfer for CHF	I/II	Adenovirus	*hAC6*	Intracoronary	Randomized, double blinded	Chronic HF, LVEF ≤40%	56	Combined (i) exercise time, (ii) cardiac function before and during dobutamine	USA	Completed recruitment

6MWT, 6 min walk test; AAV, adeno-associated virus; *hAC6*, human adenylyl cyclase type 6; HF, heart failure; LVEF, left ventricular ejection fraction; LVAD, left ventricular assist device; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; QOL, quality of life; *SDF-1*, stem cell-derived factor 1; *SERCA2a*, sarcoplasmic reticulum Ca^{2+} ATPase; VO_2 max, maximal oxygen consumption.

Current challenges

- Low viral uptake within the myocardium
- Overcome humoral immunity to viruses

Conclusion

Despite the disappointing results of Gene Therapy in Cardiac Disease, the field of cardiac gene therapy is moving forward. The field has gained valuable knowledge that viral gene delivery can transduce the heart and is safe in advanced HF population. It has become clear that novel reengineered vectors that will escape innate immunity and have higher tropism to the heart will be needed. With improved vectors, novel targets, enhanced gene delivery methods, and specific populations, the therapeutic benefits of gene therapy will be forthcoming in the next few years.