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Alternatives to Organ Donation
Can we ever solve the donor shortage?

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CEOT CUTTING EDGE OF TRANSPLANTATION

TRANSPLANT SUMMIT 2020
BALANCING EQUITY AND UTILITY IN THE FACE OF AN ORGAN SHORTAGE

Disclosure

Institutional research support from Medtronic and Abbott

Medtronic Physician Quality Improvement Panel

Member, Lifelink Board of Directors

Learning Objectives

1. Identify alternative therapies other than human organ transplantation
2. Describe hurdles to alternative therapies

Alternative Therapies

1. Durable Mechanical Circulatory Support (TAH)
2. Xenotransplantation
3. 3D Bioprinting
4. Regenerative medicine

Durable Mechanical Circulatory Support

TAH requirements

1. Must fit within the mediastinum of a high percentage of patients
2. Ease of implant, avoidance of technical challenges
3. Generate adequate cardiac output
4. Blood-device interface – avoid hemolysis and thromboembolism
5. Must last > 5 years
6. Transcutaneous energy delivery
7. Balance systemic and pulmonary circulations (LV output 10-15% greater than RV output)

Cohn, et al, Nat Rev Cardiol 12,609-617

Graveyard of Past Devices

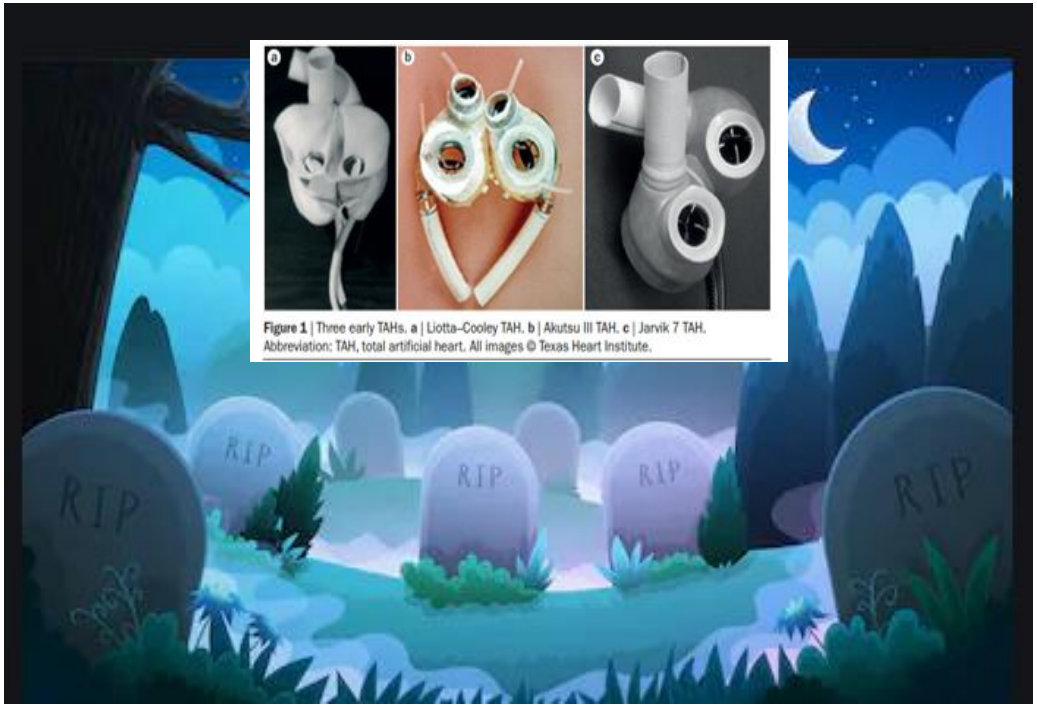


Figure 1 | Three early TAHs. **a** | Liotta–Cooley TAH. **b** | Akutsu III TAH. **c** | Jarvik 7 TAH. Abbreviation: TAH, total artificial heart. All images © Texas Heart Institute.

Graveyard of Past Devices

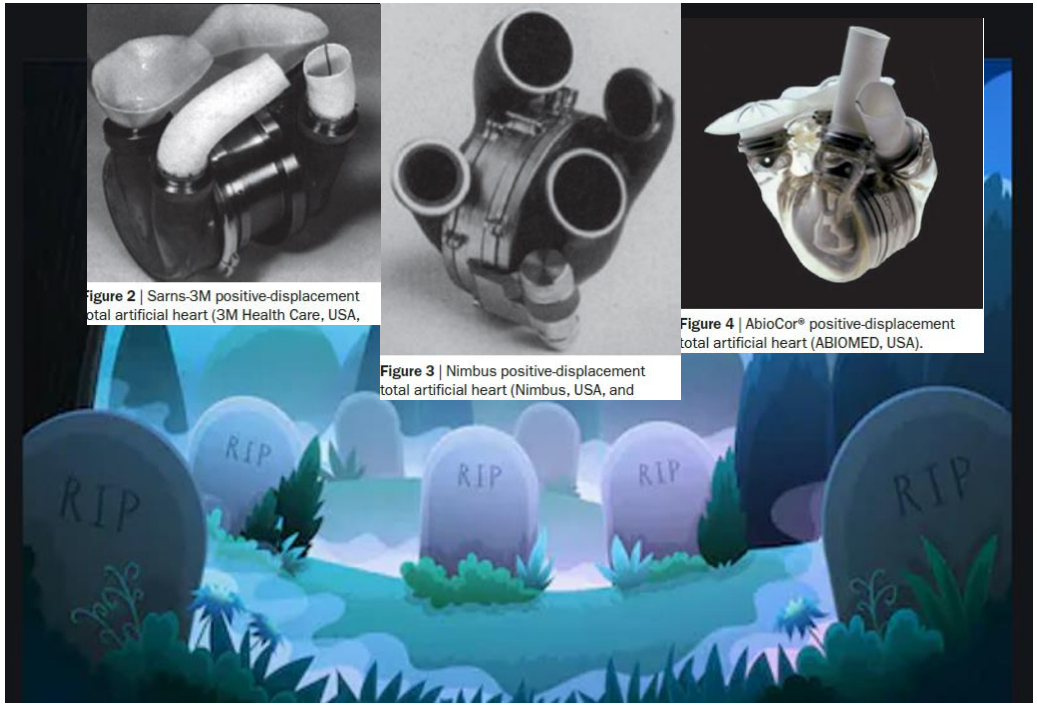
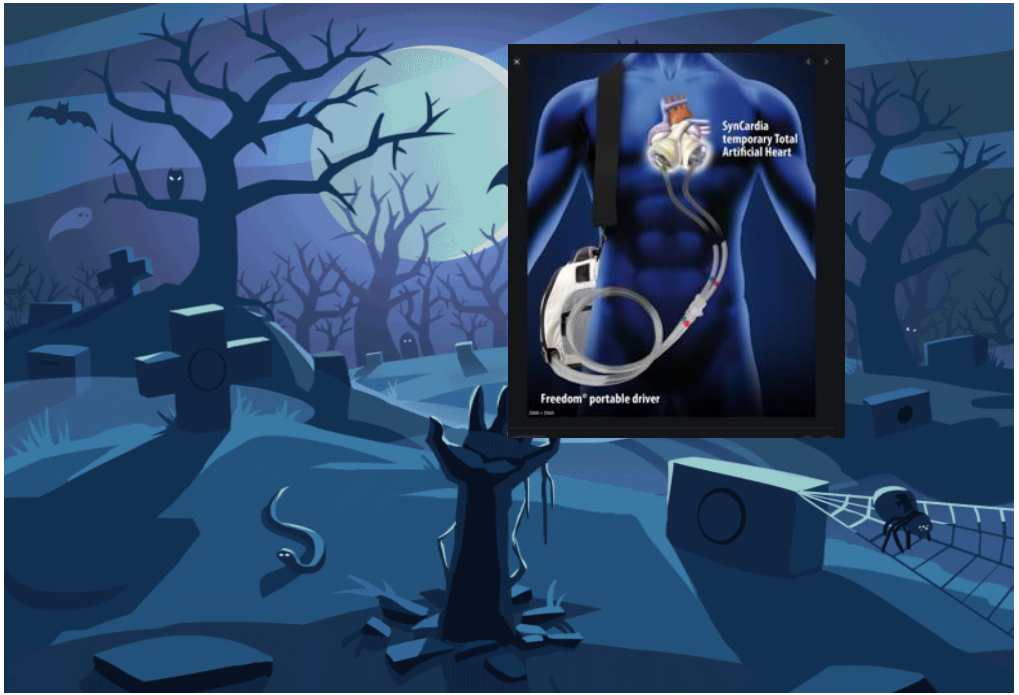


Figure 2 | Sarns-3M positive-displacement total artificial heart (3M Health Care, USA,

Figure 3 | Nimbus positive-displacement total artificial heart (Nimbus, USA, and

Figure 4 | AbioCor® positive-displacement total artificial heart (ABIOMED, USA).

Graveyard of Past Devices



Durable Mechanical Circulatory Support Future Devices - BiVACOR

Rotary TAH

Still in preclinical testing

Centrifugal flow

Magnetically levitated

Powerful
The centrifugal pumps can provide high flows over 12lpm for dynamic activity.

Smart
Smart controllers adapt the pump operation to changes in the patient's activity.

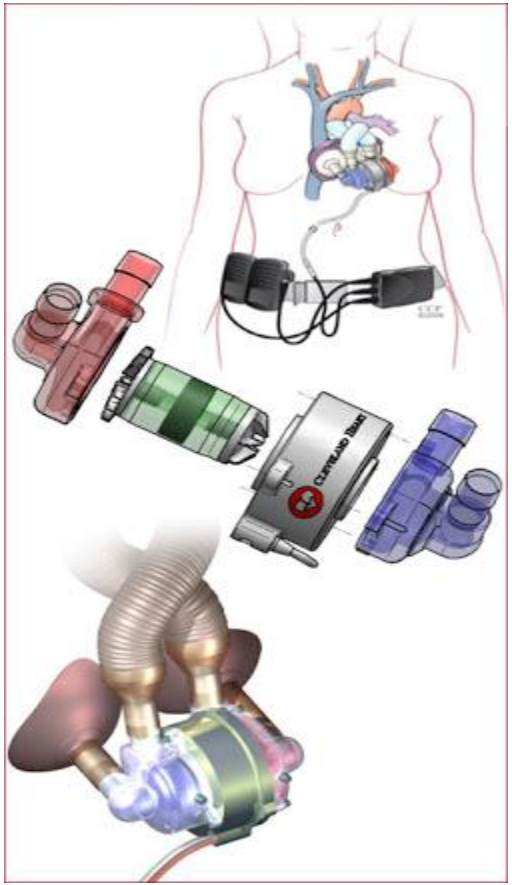
Durable
An expected device life of 5-10 years or more.

Small
Small enough for a child, powerful enough for an adult.

Portable
A small external controller and batteries to give patients freedom.

Durable Mechanical Circulatory Support
Future Devices SmartHeart

Rotary TAH
Still in preclinical testing
Centrifugal flow
Fluid-film hydrodynamic bearing



Durable Mechanical Circulatory Support
Future Devices - CARMAT

Displacement TAH
Human implants
Pulsatile flow
Two reciprocating rotary gear pumps
Biocompatibility
Auto-regulation
FDA approval for feasibility study in US

Alternatives to Organ Donation (as we know it)

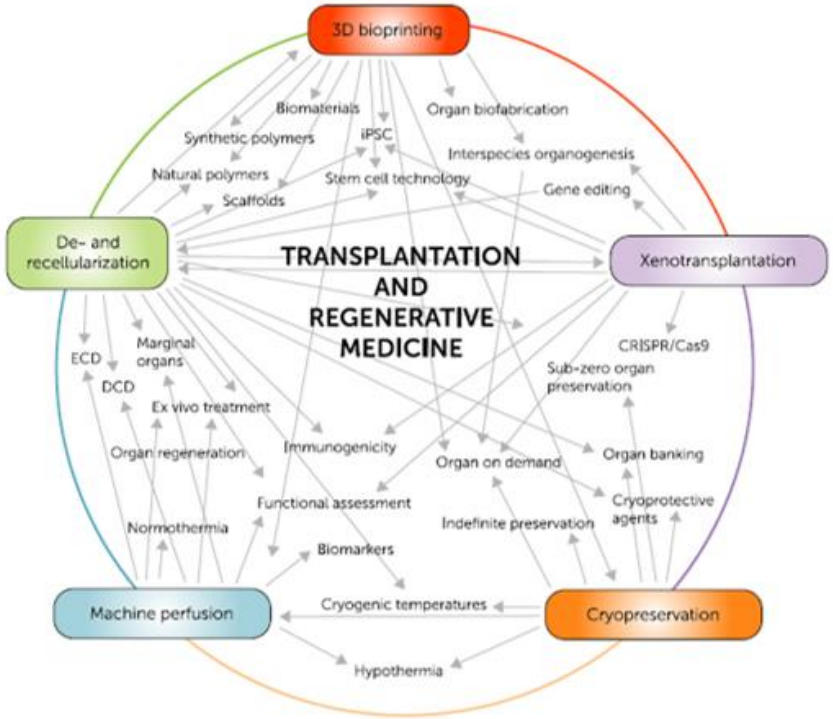


Figure 1 Interactions of different novel technologies in regenerative medicine and organ transplantation.

Messner, et al; Transplant Intl 2019; 32:673-685

Xenotransplantation – Barriers to overcome

1. Presence of 3 known carbohydrate xenoantigens to which humans have preformed antibodies – genetically modified to delete these antigens
2. Genetically modified to express CD46 (human complement regulatory protein) and human thrombomodulin (glycoprotein expressed on surface of endothelial cells
3. Rejection remains primarily a humoral mechanism than a cellular one
4. Utilization of anti-CD40 monoclonal antibody regimen
5. Diagnose impending graft failure – monitoring coagulation dysfunction and increases in the inflammatory response
   - Reductions in platelet count and fibrinogen levels are suggestive of thrombotic microangiopathy, a precursor of graft failure
6. Monitoring of xenograft status – use of xenograft microRNA as a biomarker for organ survival and organ rejection – abundant, quantifiable, and easily differentiated from recipient

Iwase, et al; Intl J of Surgery, 2019 70: 84-91
Zhou. Et al; Int J Mol Sci, 2016 17:E1232

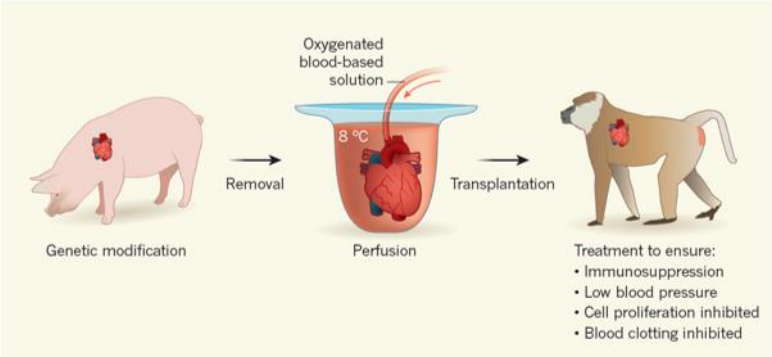
Xenotransplantation – Barriers to overcome

1. Perioperative porcine cardiac xenograft dysfunction – observed in 40-60% of orthotopic cardiac xenotransplantation experiments
2. Diastolic heart failure resulting from massive cardiac overgrowth

Langin, et al; Nature 2018 564:430-433

Xenotransplantation – Modifications

- Pig hearts were perfused with an 8°C blood-based, oxygenated solution containing nutrients and hormones
- Reduced baboon blood pressure to 80 systolic (normal pig BP)
- Rapid taper of steroids over 3 weeks
- Use of temsirolimus to mitigate myocardial hypertrophy



Langin, et al; Nature 2018 564:430-433

Xenotransplantation – Regulatory Barriers

1. Animal sources – closed herds, pathogen-free, regularly screened
2. Careful planning of clinical trials based on preclinical data
3. Transparent regulation of xenotransplantation clinical trials
4. Informed consent for patients
5. Patients must be willing to comply with standards to minimize risk to themselves and society
6. System for surveillance of xenotransplantation related infection must be in place

Goerlich, et al; Curr Opin Organ Transplant 2019, 24:522-526

Xenotransplantation – Surveillance of Donors and Recipients

1. Archiving samples of the source animals for each recipient(s) via necropsy
2. FDA is recommending a storage time-period of **50 years**
3. UK Department of Health recommends 30 years
4. Logistical storage challenge
5. Porcine endogenous retroviruses (PERV) – standard clinical assays do not exist, clinical and societal impact is unknown – can be removed with genome editing
6. Risk of xenozoonosis with other roseoloviruses remains

Goerlich, et al; Curr Opin Organ Transplant 2019, 24:522-526

Xenotransplantation

Preclinical efficacy is supported when a majority (>60%) of transplants of porcine to nonhuman primate models' life sustaining survival is greater than 3 months with some evidence that these organs can sustain life for greater than 6 months – Xenotransplantation advisory committee to the ISHLT

Cooper, et al; J Heart Lung Transplant 2000; 19:1125-1165

First xenotransplantation trial in US approved by FDA and began enrolling patients in March, 2019 – Phase I, open-label, nonrandomized trial, to assess the safety and tolerability of porcine skin xenografts for patients with severe burns

3D Bioprinting

- Introduced 15 years ago as a solution for vascular tissue fabrication
- 1st step – obtain images thru CT or MRI imaging
- Converted into 2D patterns using computer-aided design software
- Bioprinting thru a layer-by-layer process
- Bottom-up printing process in which biomaterials and cells are precisely deposited to targeted location

Gao, et al; Adv Healthcare Mater 2018; 7:1701018

3D Bioprinting

- Biomaterials should mimic native ECM
- Hydrogels most widely used biomaterial for 3D bioprinting – able to support cell survival, proliferation, and maturation
- Promising cell source – pluripotent stem cells
- Bioreactors nurture the bioprinted organ maturation by providing a dynamic culture condition with mechanical and biochemical cues

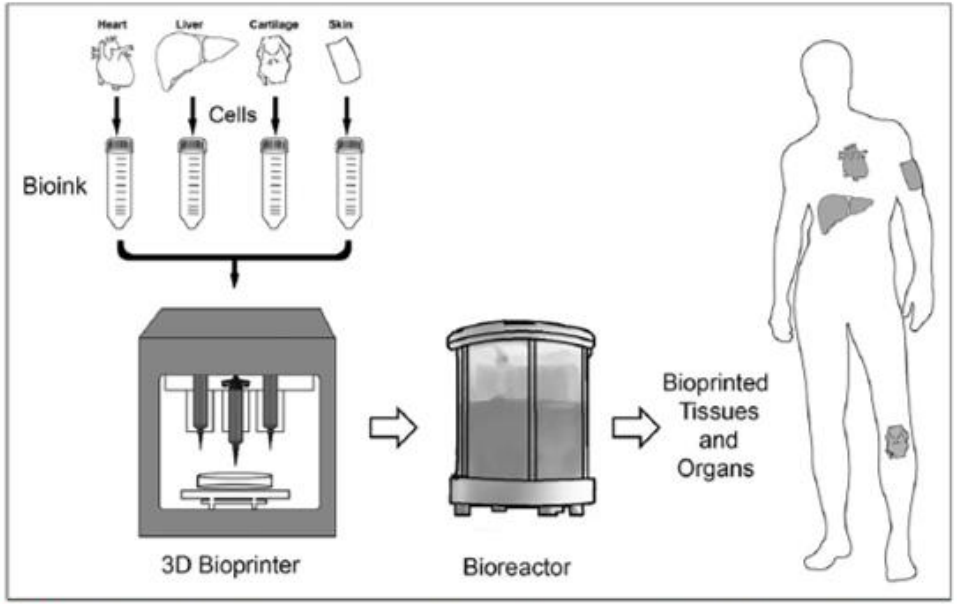


FIGURE 1. An illustration showing the processes involved in 3D bioprinting of tissues and organs including preprinting, printing and post-printing steps.

Ali, et al; Curr Opin Organ Transplant 2018 23:649-656

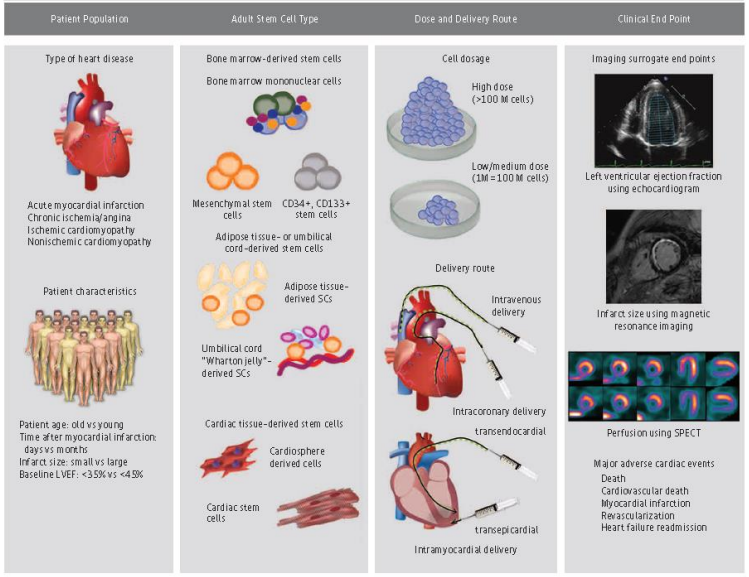
3D Bioprinting Obstacles

- Development of mature bioinks – must be biocompatible, immunocompatible, and support the cells in their desired function
- Cell metabolism requires supply of nutrients and disposal of waste products – both achieved by vessels
- Without proper vascularization, size and complexity of engineered tissues are highly restricted
- Regeneration ability of myocardial tissue is limited as myocytes cease proliferation when they are mature and differentiated
- Mimicking the mechanical and spatial heterogeneity of native cardiac tissue still remains unsolved

Gao, et al; Adv Healthcare Mater 2018; 7:1701018

Regenerative Medicine

Figure 2. Overview of the Various Patient Cohorts, Cell Types, Doses, Routes of Delivery, and Clinical End Points Used in Adult Stem Cell Trials



A significant difference in efficacy has been observed in earlier randomized clinical trials vs later randomized clinical trials, which may be partially explained by variations in patient cohorts, cell types, doses, routes of delivery, and clinical end points evaluated in adult stem cell trials. Trials have been conducted in patients with various cardiac diseases including acute myocardial infarction, chronic ischemia/angina, ischemic cardiomyopathy, and nonischemic cardiomyopathy. Within each cohort, certain patient characteristics may also affect efficacy such as transplanting bone marrow acquired from young vs old patients, delivering cells to patients immediately vs weeks/months post-myocardial infarction, and treating patients who have had small vs large infarct or who have mild (<45%) vs significant (<35%) impairment in left ventricular ejection fraction. Various adult stem cell types have also been evaluated including bone-marrow derived cells (eg, bone marrow–derived mononuclear cells, CD34+ or CD133+ cells, and mesenchymal stem cells) and adipose/umbilical derived stem cells, as well as stem cells derived from cardiac tissue (eg, cardiac stem cells and cardiosphere-derived cells). These cells have been delivered in multiple doses and with different delivery approaches. Finally, most studies have used surrogate end points, such as left ventricular ejection fraction, infarct size, and perfusion defects, which do not always correlate with more definitive end points such as death, myocardial infarction, revascularization, heart failure readmission, and other major adverse cardiovascular events.

Nguyen, et al; JAMA Cardiol 2016;1(7):831-841

Regenerative Medicine

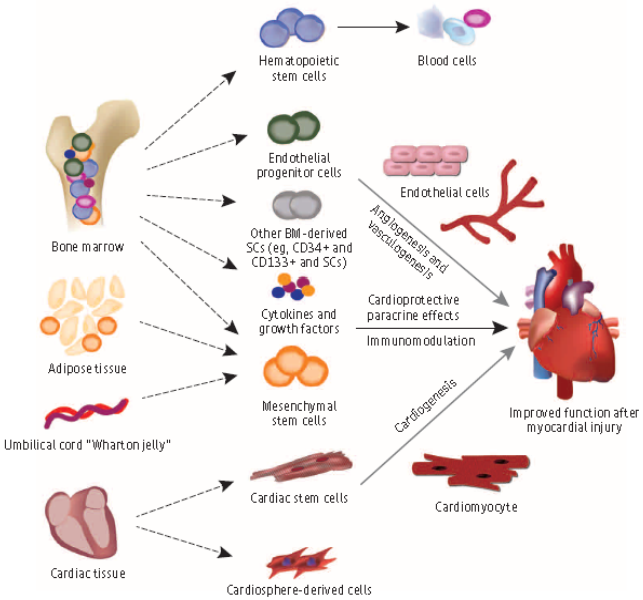
Mounting evidence suggests that adult stem cells may exert paracrine effects by secreting cardioprotective factors

- Stimulate vascular growth and remodeling
- Attenuate fibrosis
- Modulate inflammation
- Regulate cell differentiation and survival
- Recruit stem or progenitor cells

RCTs have found only a modest benefit in patients receiving stem cell therapy

Nguyen, et al; JAMA Cardiol 2016;1(7):831-841

Figure 1. Schematic of the Proposed Mechanism of Action of Stem Cell Therapy



The figure illustrates the theoretical mechanisms of action of various stem cell populations proposed in the literature. Although stem cells can potentially repair the injured myocardium by increasing angiogenesis, releasing factors that reduce cell death or modulate the immune system (eg, paracrine activation) and/or create new heart tissue, thus far only paracrine activation has been proven while the other hypotheses remain controversial. Stem cell (SC) sources include (1) the bone marrow (BM) that contains the most diverse group of cells (eg, hematopoietic stem cells, endothelial progenitor cells, mesenchymal stem cells, and specific stromal cell subpopulations) and factors (eg, cytokine and growth factors) that can potentially regenerate the myocardium; (2) other sources of mesenchymal SCs such as adipose tissue and the umbilical cord; and (3) cardiac tissue that may contain cardiac progenitor cells or cardiospheres.

Regenerative Medicine

- Development of human iPSC
- Cardiac differentiation to artificially generate human cardiomyocytes
- If differentiation is not 100%, increased risk of tumorigenesis due to contamination with non-cardiomyocytes and undifferentiated cells
- Use of glucose and glutamine-free lactic acid supplemented medium to improve efficiency of cardiomyocyte purification
- Production of cardiac spheroids significantly improved engraftment rate
- No human trials yet

Kishino, et al; Inflamm and Regen 2020: (40);1

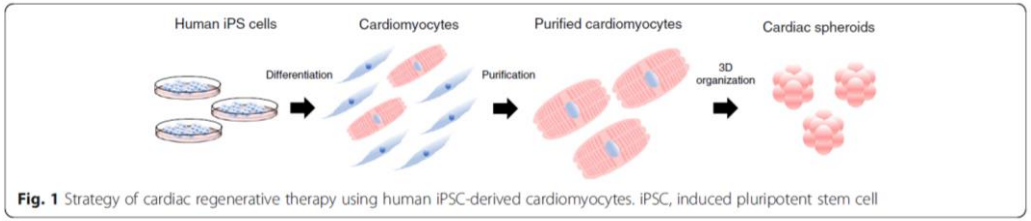


Fig. 1 Strategy of cardiac regenerative therapy using human iPSC-derived cardiomyocytes. iPSC, induced pluripotent stem cell

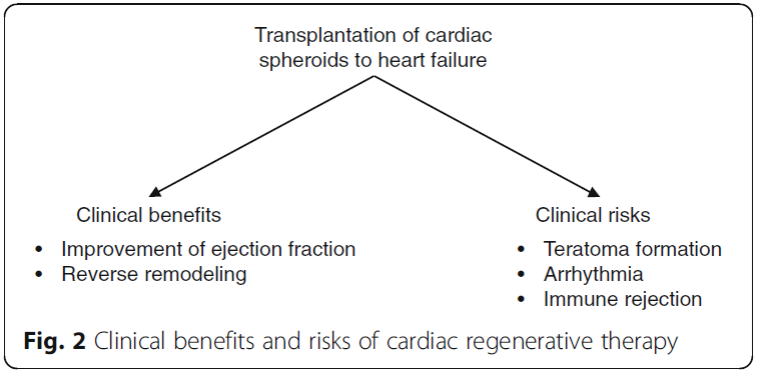


Fig. 2 Clinical benefits and risks of cardiac regenerative therapy

Regenerative Medicine - Bioscaffold

Decellularizing cardiac tissue results in a cell-free ECM that can be used as a cardiac tissue bioscaffold – 1st accomplished in 2008

- Could be derived from human hearts not suitable for transplant
- Retain the native vascular conduits and native ECM macro and micro architecture
- Preserve intrinsic biochemical cues that guide alignment and orientation of cells seeded onto the scaffold
- Theoretically repopulate with recipient's cells for creation of an autologous organ

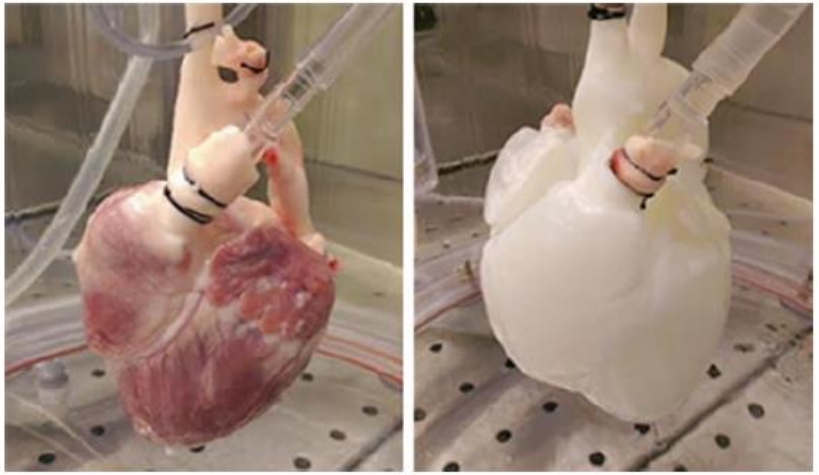


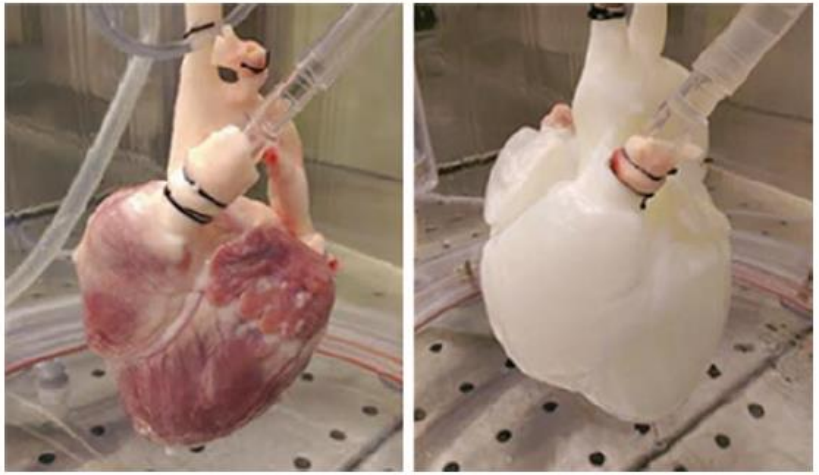
Fig. 5.2 Decellularized porcine heart (right) adjacent to a cadaveric porcine heart

Tang-Quan, et al; Adv Exp Med Biol. 2018;1098:85-114

Regenerative Medicine - Bioscaffold

Thrombus formation is one of the challenges of using whole cardiac dECM in vivo

- dECM scaffolds induce platelet activation, which leads to inflammation and thrombus formation
- Incomplete endothelialization of blood contacting surface of scaffolds induces thrombus formation
- Remnants of cellular and nuclear content in these scaffolds may also induce thrombus formation



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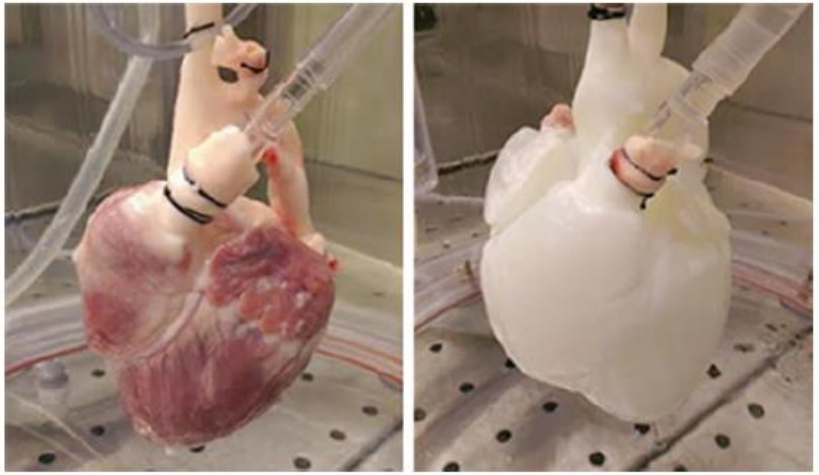
Tang-Quan, et al; Adv Exp Med Biol. 2018;1098:85-114

Regenerative Medicine - Bioscaffold

Other ongoing challenges:

- Precise positioning of seeded cell types inside the organ scaffold
- Adequate oxygen and nutrient supply
- Enabling metabolic waste product removal
- Achieving adequate lymphatic drainage and vascularization of recellularized organs



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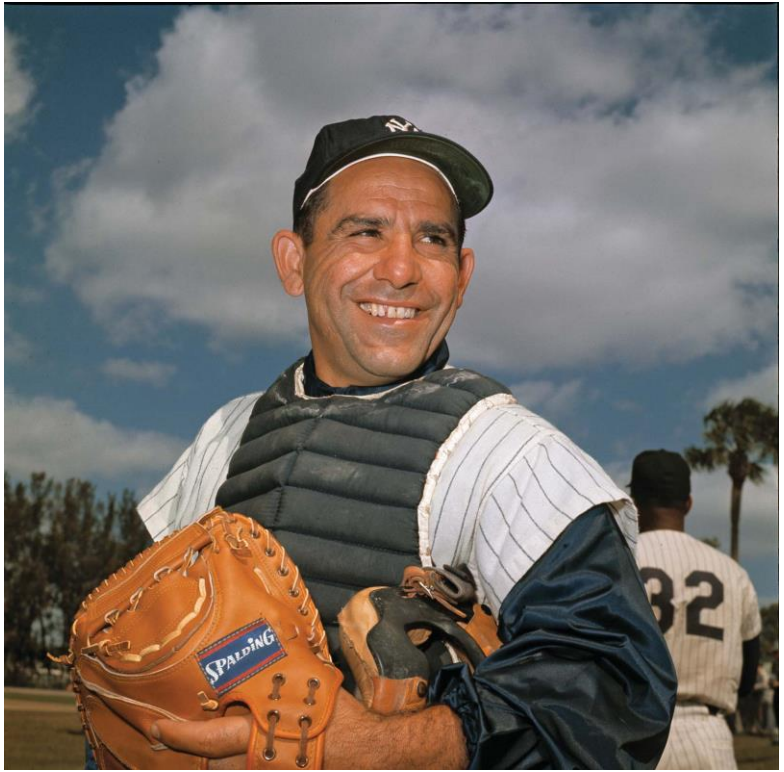
Messner, et al; Transplant Intl 2019; 32:673-685

Conclusion

In the immortal words of Yogi Berra

"It's tough to make predictions, especially about the future."



Conclusion