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

J. David Vega, MD
Professor of Surgery
Emory University School of Medicine
Atlanta, GA
Disclosure

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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
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Durable Mechanical Circulatory Support
Future Devices - BiVACOR

Rotary TAH
Still in preclinical testing
Centrifugal flow
Magnetically levitated
Durable Mechanical
Future Devices

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

Circulatory Support
SmartHeart
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

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

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 xenozoanosis 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

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

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

Regenerative Medicine

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

A significant difference in efficiency has been observed in earlier randomized clinical trials involving intracoronary delivery of bone marrow-derived cells, which may be partially explained by variations in patient cohorts, cell type, dosage of delivery, and clinical endpoints evaluated in adult stem cell trials. Trials have been conducted in patients with various cardiac diagnoses including acute myocardial infarction, chronic ischemia, acute coronary syndromes, and nonischemic cardiomyopathy. While such trials do not necessarily show a clear benefit in terms of mortality reduction, they do suggest that bone marrow-derived cells may have beneficial effects on cardiac function, including improved contractility, reduced infarct size, and enhanced neovascularization. Additionally, the use of intramyocardial injection of bone marrow-derived cells has been shown to improve cardiac function, particularly in patients with severe left ventricular dysfunction. Various adult stem cell types have also been tested, including bone marrow-derived cells, bone marrow-derived mesenchymal cells, and umbilical cord blood cells, with varying degrees of success. These trials often involve multiple stages of different delivery approaches, making it difficult to draw definitive conclusions regarding the efficacy and safety of stem cell therapy. Further research is needed to better understand the mechanisms of action of stem cell therapy and to optimize treatment protocols for maximum benefit.
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
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
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

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


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

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

Fig. 5.2 Decellularized porcine heart (right) adjacent to a cadaveric porcine heart
In the immortal words of Yogi Berra
“It’s tough to make predictions, especially about the future.”
Conclusion