Engineering Heart Valve Treatments for Tomorrow*

W. David Merryman, PhD
Departments of Biomedical Engineering, Pharmacology, Medicine, and Pediatrics
http://research.vuse.vanderbilt.edu/mechanobiology/
david.merryman@vanderbilt.edu
Overview

- Heart valve disease
  - Open chest repair or replacement
  - Desire for new strategies that avoid surgery

- Mitral valve disease
  - Devices for percutaneous repair

- Aortic valve disease
  - Tissue engineering for pediatric patients
  - Drug strategies for adult patients
Heart valves

http://www.cts.usc.edu/hpg-valvesoftheheart.html
Open chest surgery

- Retractor
- Pericardium
- Heart

Traditional Open-Heart Surgery | Minimally Invasive Valve Surgery
Mitral valve disease

Prolapse with Regurgitation

Leaflet displacement into left atrium

MV surgical repair

Annuloplasty 96%
Leaflet Resection 73%
Chordal Repair/Replacement 50%

Stats averaged from:

Percutaneous repair devices

Right: NeoChord DS1000. http://www.neochord.com

MitraClip
Edge-to-Edge

Cardioband
Annuloplasty

NeoChord
Chordal Replacement

In trials
(Transapical)

FDA approved

In trials

Right: NeoChord DS1000. http://www.neochord.com
Cryo-anchoring & RF ablation

Aortic Valve

Left atrium
Aortic valve
Left ventricle

Origins of coronary arteries
Right post. valve
Ant. valve
Bicuspid valve
Wall of left ventricle

radial
circumferential
Bimodal focus for aortic valves

Cell activity

Tissue stiffness

Age

Treatment strategies for age-related aortic valve disease

Tissue engineered aortic valves for pediatric patients
Bimodal focus for aortic valves

- Cell activity
  - Quiescent fibroblasts
  - Activated myofibroblasts

- Tissue stiffness
  - Compliant
  - Stiff

- Age
  - Fetal 14-19 wks
  - Fetal 20-39 wks
  - 0-20 yrs
  - 20-60 yrs
  - 60-75 yrs
  - 75-85 yrs
  - 85+ yrs

- Treatment strategies for age-related aortic valve disease

- Tissue engineered aortic valves for pediatric patients
Early success, but we have a problem

...the cells of the valve are unique.

Hildebrand DK, et al, Annals Biomedical Engineering, 2004
How did you do it?

Myocardium

Endocardial cells

Cardiac jelly

Transforming cells

Transformed cells migrating into cardiac cushions
In vitro system of valve development

Stage HH16-17 chick eggs

$Lencinas$ et al. *Birth Defects Res C Embryo Today* 2011
Methacrylated HA (MeHA)

Hyaluronic Acid (HA) + Methacrylic Anhydride → Methacrylated HA (MeHA)

Collagen
MeHA
Irgacure 2959

λ = 365nm

37°C, 5% CO₂
2h

MeHA increases EMT

Sewell-Loftin MK et al, Biomaterials, 2014
Myocardial contraction controls EMT
Moving up to the mouse... then humans?

[Image 1: 500 μm scale bar]

[Image 2: Collagen and Coll-MeHA samples]

[Image 3: Diagram of NFATc1 BAC Locus]

[Graphs C and D: Endocardial Sheet Size and Invasion Depth]

[Images E and F: E8.5 samples]
Bimodal focus for aortic valves

Tissue engineered aortic valves for pediatric patients

Treatment strategies for age-related aortic valve disease
Calcific aortic valve disease

Calcific Aortic Valve Disease (CAVD)

- >20,000 deaths per year
- >65,000 surgeries last year
- Affects 5 million
- Thickening; calcium accumulations
- Surgery is only option
- Mechanism unknown

Can we take a pill to prevent this?

Novaro et al 2010
Antagonizing $5\text{-HT}_{2B}$

- Serotonin (5-HT) and 5-HT agonists cause heart valve disease and pulmonary hypertension
  - Carcinoid syndrome
  - Phen-Fen for weight loss
  - Pergolide and cabergoline for Parkinson’s disease

- Agonists cause excessive cellular activation
  - Myofibroblast phenotype
  - Excessive collagen production
  - By definition, antagonist should reduce/inhibit this activity

- $5\text{-HT}_{2A}$ versus $5\text{-HT}_{2B}$?

Hutcheson JD et al, Pharmacology and Therapeutics, 2011
Hutcheson JD et al, Nature Reviews Cardiology, 2014
Antagonism prevents calcific nodules

**Hutcheson JD et al, Journal of Molecular and Cellular Cardiology, 2012**
Turns off molecular machinery

Vehicle

2B antagonism

*Treatment for 1 h; time lapse over 15 min.*
In the 5-10 years

- Percutaneous options for mitral valve disease – likely to increase significantly

- Tissue engineered heart valve for pediatrics – still a long way off

- Drugs for calcific aortic valve disease – certainly believe it’s possible
Current Group
- Joseph Chen, MS (Notch1-cadherin-11 mechanism)
- Steve Boronyak, MS (Catheter development)
- Nathan Bloodworth, BS (5-HT$_{2B}$ antagonism in PAH)
- Meghan A. Bowler, BS (Targeting cadherin-11)
- Larisa Ryzhova, MD PhD (receptor biochemistry)
- Alison Schroer, MS (Fibroblast focal adhesion mechanobiology)
- Mark Vander Roest, BS (EMT in valve development)
- Cami Johnson, BS (Tie1 mechanosensing in valve dev/disease)

Alumni
- Michael Nilo, MS (currently reviewer at FDA)
- Shaun Price, MD MS (currently medical resident)
- Joshua D. Hutcheson, PhD (currently postdoc at Harvard)
- M.K. Sewell-Loftin, PhD (currently postdoc at WUSTL)
- Charles I. Fisher, PhD (currently scientist at Sanford Burnham)
- Young Wook Chun, PhD (currently postdoc at Vanderbilt)