Regenerative Medicine: Therapy for the Troubled Heart

Prof. Simon P. Hoerstrup, MD, PhD (WIEF-AFF Roundtable, May 26th 2015, Tokyo, Japan)
Regeneration – Prometheus Saga

Lakonische Schale ca 530 v. Christus
Principles of Cell-based Therapies

- **CELLS**
  - AUTOGENIC
  - ALLOGENIC
  - XENOGENIC

- **SCAFFOLD**
  - NATURAL
  - SYNTHETIC
  - BIODEGRADABLE

- **IN VITRO CULTURE**
  - STATIC
  - DYNAMIC

- **IMPLANT**
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Example I: Tissue Engineered, Living Heart Valves with Regeneration and Growth Potential

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The Evolution of Heart Valve Prostheses

MECHANICAL

„BIOLOGICAL“

TISSUE ENGINEERED

1960

1990-2000

2010

2015-20
The Native Benchmark

Viable, Autologous

Regeneration

“Growth“

Antithrombogenic

Weber B. et al.
Seminars Immunopathology 2011; 21:307-15
Polymer Scaffold Technologies

Heat welding*        Injection molding        Electro spinning        Rapid prototyping

* HOERSTRUP SP et al. (2000) CIRCULATION 102(III); 44-49
Imaging Based Computation

FSI calculations have enabled identification of the deformations in the heart valve, both in systole and diastole.

*Baaijens, IJNMF* (2001)
Pulse Duplicator (Bioreactor) Systems

* HOERSTRUP SP et al. (1999) TISSUE ENGINEERING
* SODIAN R, HOERSTRUP SP et al. (2002) TIS. ENG.
* MOL A, HOERTRUP SP et al. (2005) ANN BIOMED ENG
Zürich Tissue Engineering Heart Valve Program

Differentiated (Vascular Derived) Cells
* HOERSTRUP SP et al. (2000) CIRCULATION 102(III);44-49
* HOERSTRUP SP et al. (2006) CIRCULATION 114(I);159-166
* MOL A, HOERSTRUP SP et al (2006) CIRCULATION 114(I); 152-158

Mesenchymal Stem/Progenitor Cells
* KADNER A, HOERSTRUP SP et al. (2002) ANNALS THOR SURG 74(4);S1422-8
* KADNER A, HOERSTRUP SP et al. (2004) EJCTS 25(4);635-641
* HOERSTRUP SP et al. (2002) CIRCULATION 106(I); 143-150
* SCHMIDT D, DIJKMAN P, HOERSTRUP SP et al. (2010) JACC 56(6);510-20
* WEBER B, HOERTRUP SP et al (2011) EUROPEAN HEART JOURNAL
* EMMERT M, HOERSTRUP SP et al (2011) JACC INTERVENT.
* EMMERT M, HOERSTRUP SP et al (2012) JACC INTERVENT.
* EMMERT MY, HOERSTRUP SP et al (2013) EUR J CARDIOTHORACIC SURGERY

Blood Derived Stem/Progenitor Cells
* SCHMIDT D, HOERSTRUP SP et al. (2004) AHA
* SCHMIDT D, HOERSTRUP SP et al. (2004) ANNALS THOR SURG 78;2094-98
* SCHMIDT D, HOERSTRUP SP et al (2006) ANNALS THOR SURG 82(4); 1465-71
* SCHMIDT D, HOERSTRUP SP et al (2006) TISSUE ENGINEERING

Prenatal (Placental, Umbilical Blood) Stem Cells
* SCHMIDT D, HOERSTRUP SP et al. (2005) EJCTS 27(5);795-800
* SCHMIDT D, HOERSTRUP SP et al. (2006) CIRCULATION 114(I); 125-131
* SCHMIDT D, HOERSTRUP SP et al. (2007) CIRCULATION 116(11), I64-70
Tissue Engineered Heart Valves (Aortic Position)

**PRE-CLINICAL RESEARCH**

**Stem Cell–Based Transcatheter Aortic Valve Implantation**

First Experiences in a Pre-Clinical Model

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Zurich, Switzerland; and Paris, France


Transcatheter aortic valve implantation using anatomically oriented, marrow stromal cell-based, stented, tissue-engineered heart valves: technical considerations and implications for translational cell-based heart valve concepts

LifeValve/Lifematrix - Living autologous heart valves for minimally invasive implantation procedures

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Example II: Stem Cell based Repair and Regeneration after Heart Attack (Myocardial Infarction)

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Myocardial Infarction: Transcatheter Stem Cell Treatment

Stem Cell-based Microtissues for Myocardial Infarction

- **Bone Marrow Puncture**
- **MSC culture**
- **catheter-based intramyocardial application**

**Microtissue Formation**
- 96 hours
- 36 hours
- 72 hours
- 48 hours
- 24 hours

**Additional cell types/labeled cells**

**Microtissue Size**
- Diameter [μm]

**Microtissue Viability**
- Necrotic
- Apoptotic
- Viable

“Last Mile” of Clinical Translation

Classical Academic Research

Bench / Invention

Basic Research

Pre-Clinical Research / Proof-of-Concept

Wyss Translational Center Zurich

Translational Infrastructure (GLP&GMP)

First-in-Man Trials (GCP)

Clinical Translation / Technology Transfer

Therapy

Products

Services

Bedside / Product

Clinic / Market

Projects / Studies

A Center of ETH Zurich and University of Zurich
Zurich LifeMatrix (Tissue engineered heart structures)

- 1% of newborns have congenital heart malformations (absent heart valves, blood vessels, etc.)
- Current therapies are invasive and require the use of artificial, non-living prosthetic material
  - Limitation in terms of growth and regeneration
  - Multiple reoperations needed
- Autologous, personalized cellular tissues overcome these limitations
  - Capacity of growth and regeneration
  - Applicable both in children and adults
- LifeMatrix platform aims at First-in-Man studies of novel “off-the-shelf” tissue engineered homologous matrices
- Matrix-On-The-Chip platform (ETH), GMP Clinical Translational Platform (UZH), Clinical Pilot Study Platform (USZ)
Zurich VAD (Ventricular Assist Devices)

- Heart failure (HF) is one of the leading causes of death in the world
  - By 2030 > 8m patients will suffer from HF
  - Clinical costs will reach EUR 30bn in Europe
- Current therapies, incl. heart transplantations or arti have limitations:
  - Shortage of donors
  - VADs lack performance and reliability
- Off-the-shelf artificial device similar to human heart in terms of sensing, pumping & biocompatibility
  - Reduction of the need of donor hearts
  - Replacement of existing VADs
- Zurich Heart’s targeted innovations for clinical adoption are, among others, coatings for long term integration, automatic control algorithms for blood pumps
“Last Mile” of Clinical Translation - PPP

Classical Academic Research

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Mechanobiology

Systole

Diastole

* SAUREN F et al. (1983) *J* BIOMECHANICS

* SCHOEN FJ et al. (1997) *J* HEART VALVE DIS