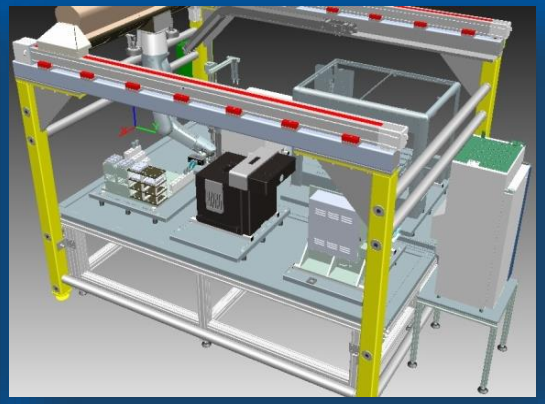


Material Sciences – Cell Biology – Implant Development – Production Technologies – (Pre)Clinical Trials

Berliner Dialyse Seminar 2021

Biologisierte Wege zu neuen Shuntprothesen

Univ.-Prof. Stefan Jockenhövel et al.

- NRW Schwerpunktprofessur Biohybrid & Medical Textiles
- Aachen-Maastricht-Institute for Biobased Materials
- DWI Leibniz Institute for Interactive Materials

Ministerium für
Kultur und Wissenschaft
des Landes Nordrhein-Westfalen
NRW Schwerpunktprofessur

RWTH AACHEN UNIVERSITY
Maastricht University

Berliner DialyseSeminar

Darlegung potentieller Interessenskonflikte

Der Inhalt des folgenden Vortrages ist Ergebnis des Bemühens um größtmögliche Objektivität und Unabhängigkeit.

Als Referent weise ich darauf hin, dass es **persönliche Verbindungen** zu Unternehmen gibt, deren Produkte im Kontext des folgenden Vortrages von Interesse sind. Dabei handelt es sich um die folgenden Unternehmen und Verbindungen:

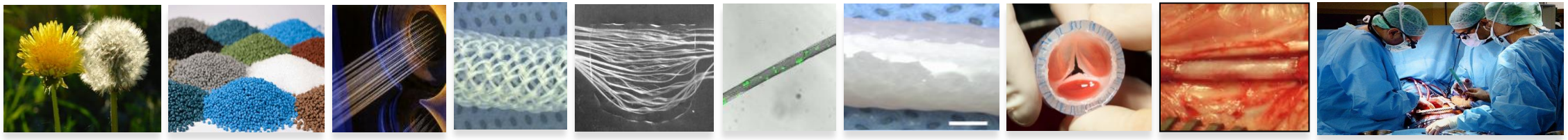
Unternehmen	Verbindungen
Fibrothelium GmbH	Mitgesellschafter
O11 biomedical	Mitgründer
PeraGraft GmbH	Berater

NRW Schwerpunktprofessur Biohybrids & Medical Textiles (BioTex)

Univ.-Prof. Dr. med. Stefan Jockenhövel

Mission: **Knowledge crossing Borders for Translation into Clinic**

Polymer Development → Biomimetic Textiles → (Bio-) Function → Implant Development → Preclinical Testing → Clinical Testing & Certification

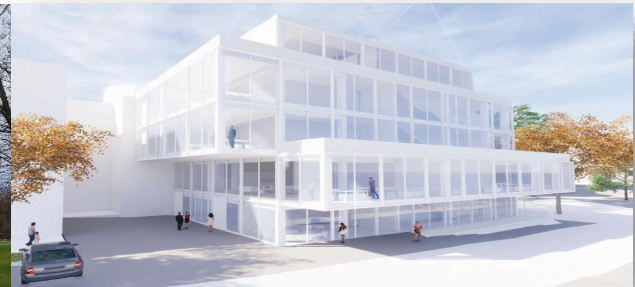


Chemelot Campus, Geleen (NL)

DWI Leibniz Institute for Interactive Materials

Center for Biohybrid Medical Systems

Leibniz Joint Lab – first-in-Translation (*fi*T)



BioTex Research Groups

Dept. of Biohybrid & Medical Textiles (BioTex)
Univ.-Prof. Dr. Stefan Jockenhövel

Biomaterials

Textile Engineering

Bioreactors

Translation

Cardiovascular Tissue Engineering

Respiratory Tissue Engineering

Hard Tissue Engineering

Towards Clinical Translation

Leibniz JointLab
first-in-Translation

BioTex AME | RWTH AACHEN UNIVERSITY

AMI Biobased Materials | Maastricht University

DWI Leibniz-Institut für Interaktive Materialien

Challenges in dialysis shunts

Clinical & technical requirements

- Long-term Stability
  - High Patency rate
  - No Aneurysm formation
  - Constant shunt-flow
  - Physiological hemocompatibility
  - Infection resistant
  - No compliance mismatch
    between shunt and native blood vessels
  - Self-repair mechanism

Learning from Nature

The Nature of Nature

- adapt
- regenerate
- replace

= Nature of Medicine

REGENERATION

Hope of Tissue Engineering

Tissue Engineering

Aims:

- Autologous implants
- Potential of
  - Remodeling
  - Self-repair
  - Infection resistance

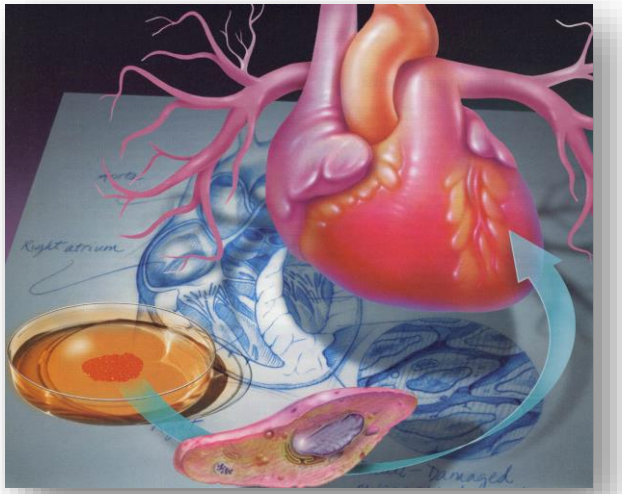
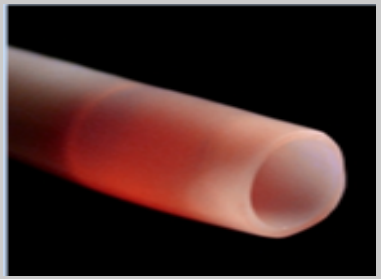


Bild der Wissenschaft 2005

technical solution

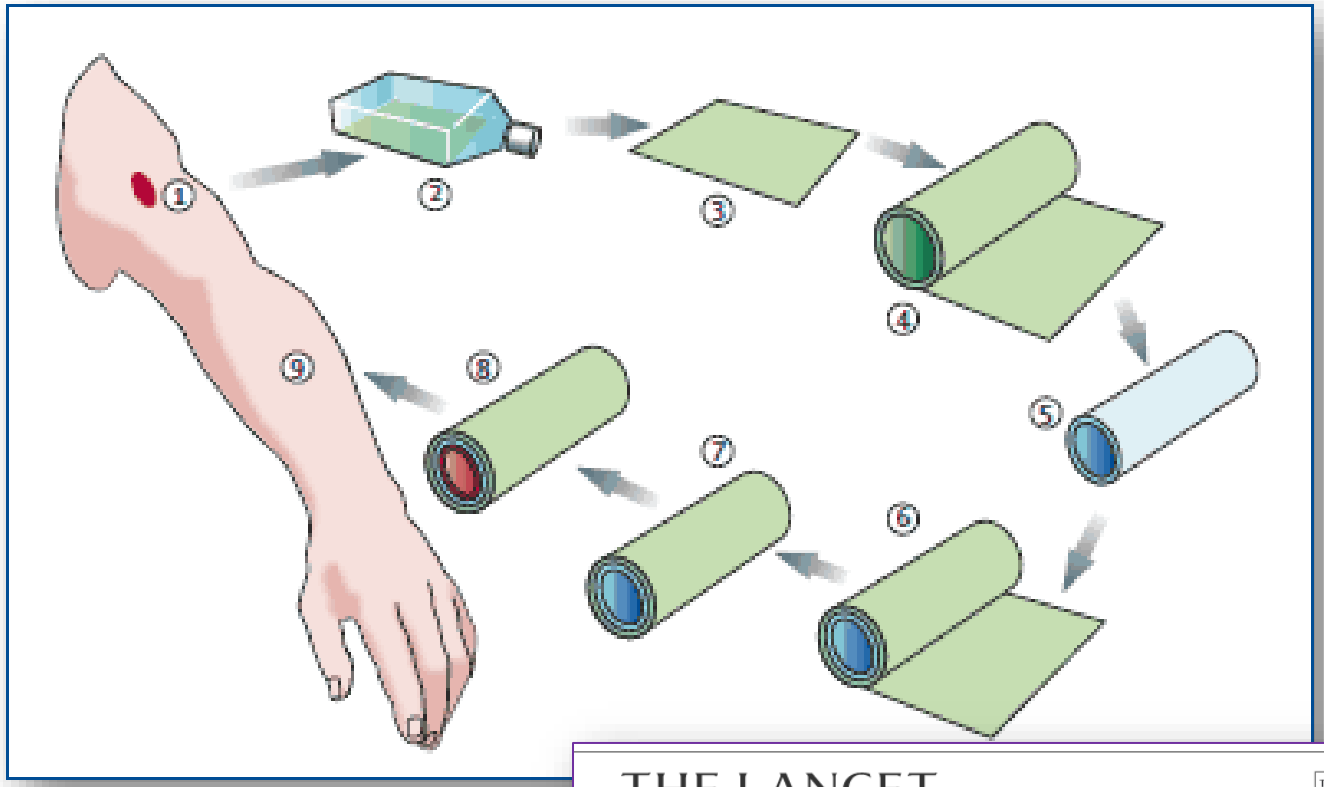
Life-long durability

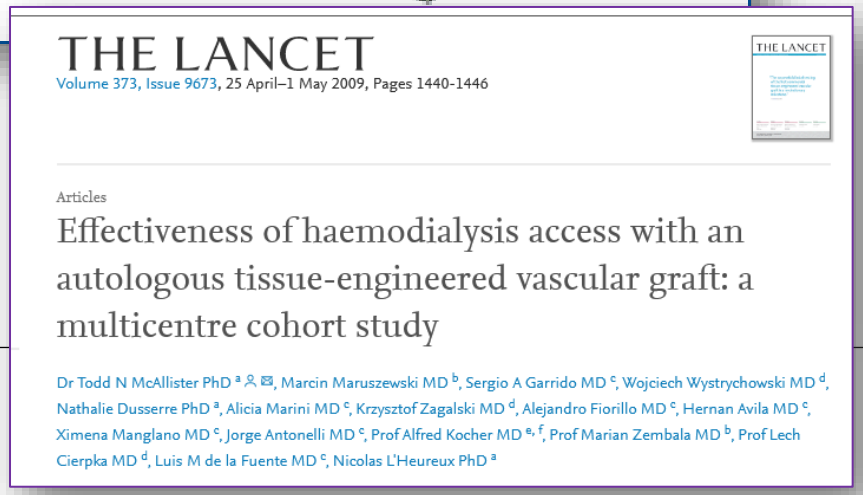
biological solution



www.cytograft.com

Complete Autologous, Tissue-engineered Dialysis Shunt





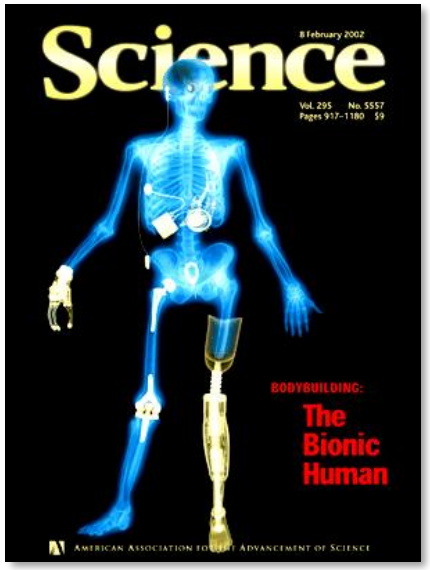
THE LANCET
Volume 373, Issue 9673, 25 April–1 May 2009, Pages 1440-1446

Articles

Effectiveness of haemodialysis access with an autologous tissue-engineered vascular graft: a multicentre cohort study

Dr Todd N McAllister PhD [a], Marcin Maruszewski MD [b], Sergio A Garrido MD [c], Wojciech Wystrychowski MD [d], Nathalie Dusserre PhD [a], Alicia Marini MD [c], Krzysztof Zagalski MD [d], Alejandro Fiorillo MD [c], Hernan Avila MD [c], Ximena Manglano MD [c], Jorge Antonelli MD [c], Prof Alfred Kocher MD [e, f], Prof Marian Zembala MD [b], Prof Lech Cierpka MD [d], Luis M de la Fuente MD [c], Nicolas L'Heureux PhD [a]

The hope of Tissue Engineering



Technical solutions

Design of Living Implants

Limitations

- **mechanical properties**
- **Long-term stability**
- **high complexity**
- **(re)producibility**
- **Long production time = costs**

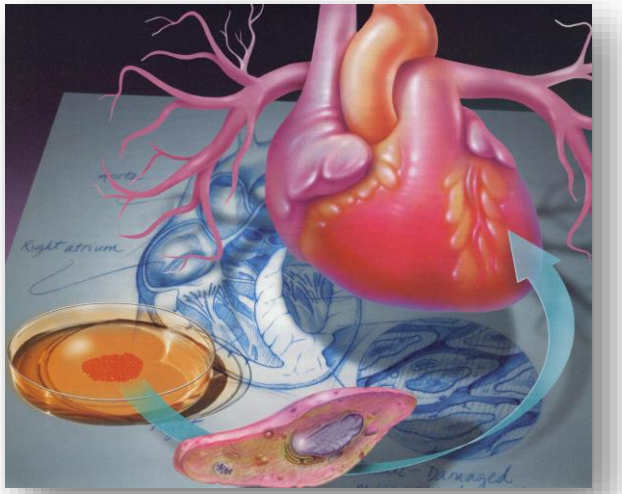
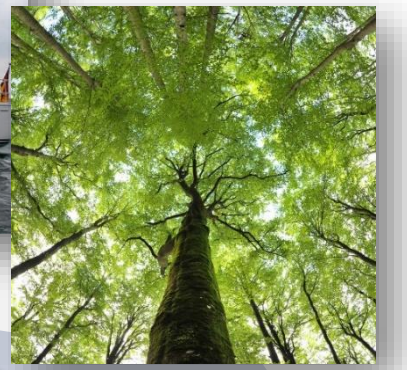


Bild der Wissenschaft 2005

Biological solution

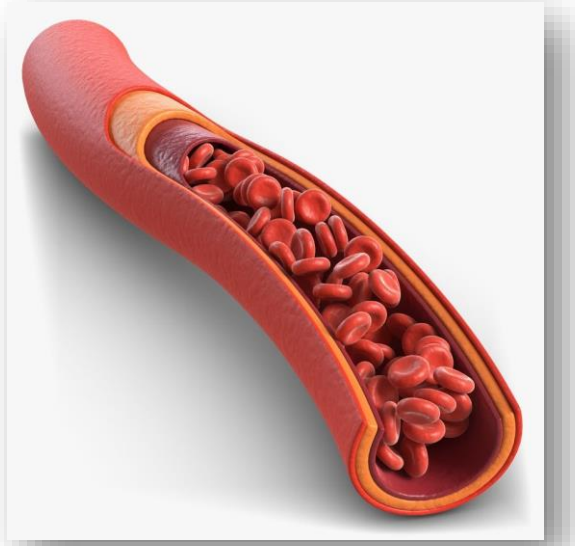
What we can learn more from nature… and engineers!



Textile-reinforced Composite Materials

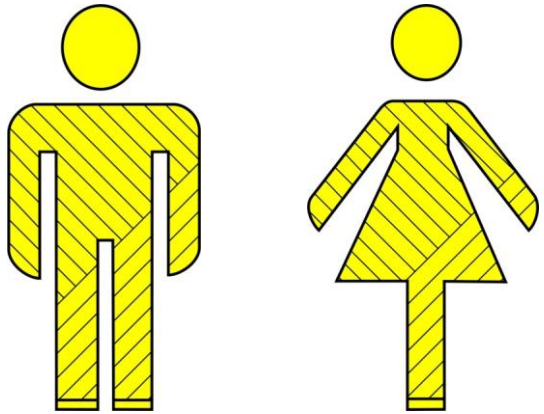
What do these things…

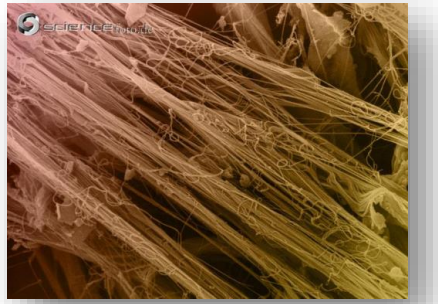
…have in common?

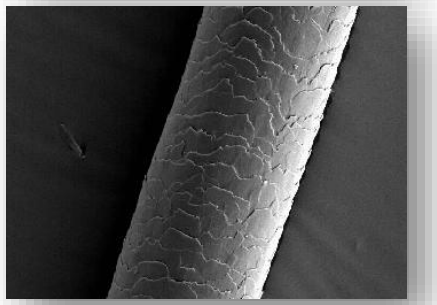


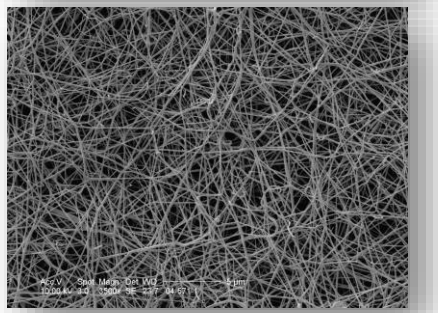
‘WE ARE Textile Products!’ (= Fibre-reinforced Composites)

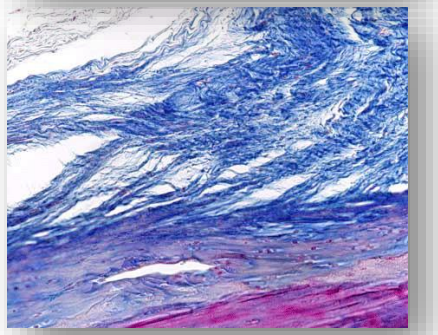
- collagen fibres
- elastic fibres
- fibrin fibres
- fibro cartilage
- muscle filaments
- hairs
- ligaments
- ...





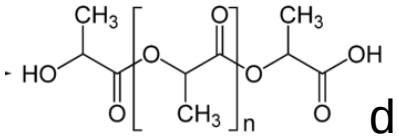






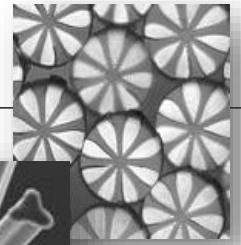
Multi-scale Options in Textile Engineering
From Lab to Industrial Scale

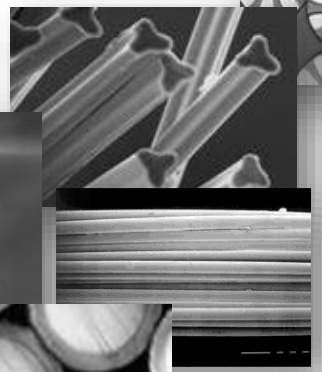
Fibre / Structure



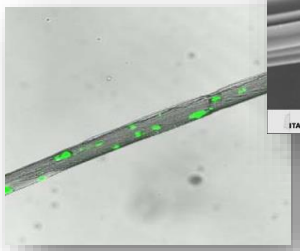
polymers

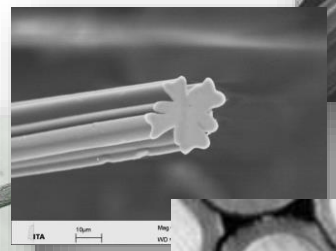
fibre structure





drug-eluting





non-woven fabrics

10^{-9}m

10^{-6}m

10^{-3}m

[nm]

[µm]

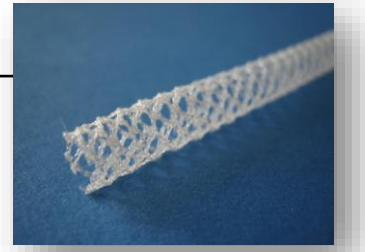
[mm]

Processes

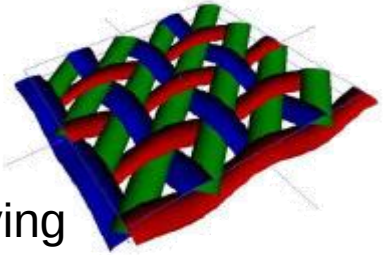
e-spinning

melt &
wet spinning

braiding



knitting



weaving

BioTex AME | RWTH AACHEN UNIVERSITY | Maastricht University

Biohybrid Vascular Prostheses

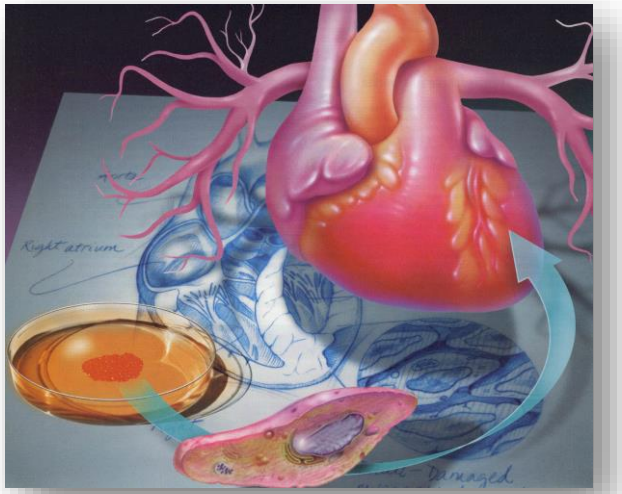
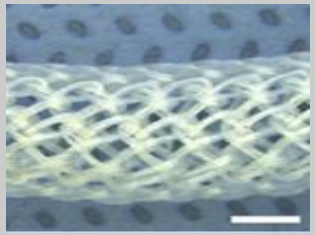
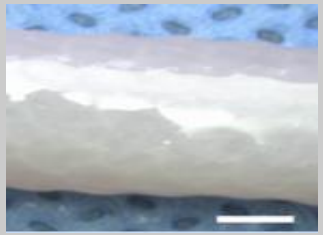
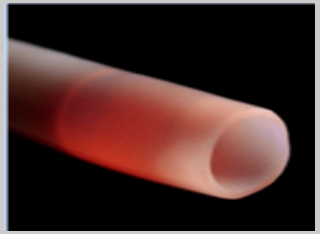


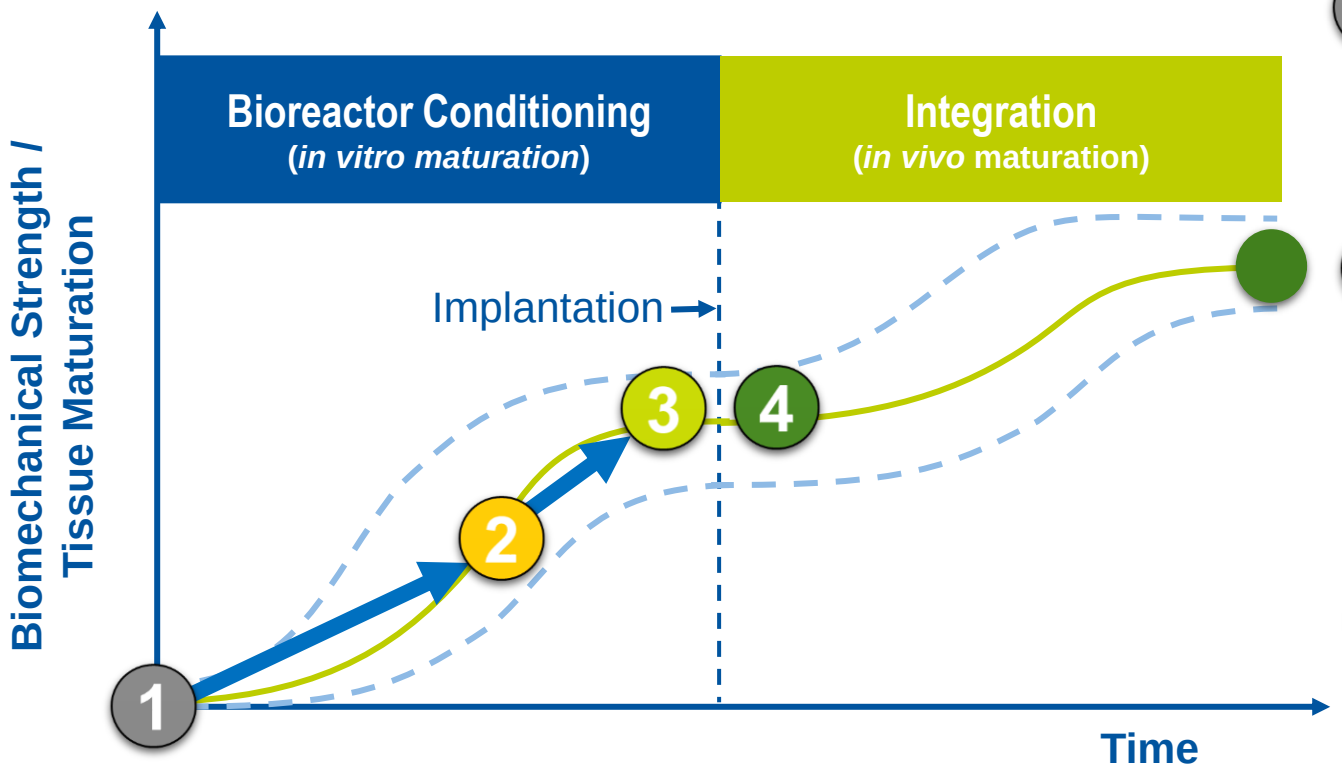
Bild der Wissenschaft 2005

Technical solutions	Biohybrid Solutions	Biological solution
http://img.medicalexpo.de	  Artif. Organs 2008; Tissue Eng. 2009; Biomaterials 2010 Theranostic 2014; Biomaterials 2015, Biomaterials 2019	 www.cytograft.com

Optimal balance between **technical** component …
…and **biological** component!

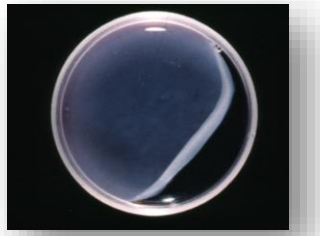
RWTH AACHEN UNIVERSITY
Maastricht University

Form *in vitro* to *peri-operative* approach



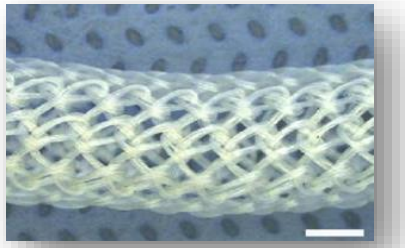
1 Tissue Engineering

- Biodegradable Scaffold



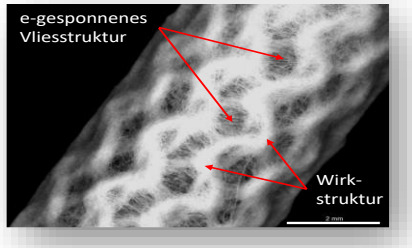
2 Biohybrid Textile Reinforcement

- non-biodegradable warp-knitted backbone



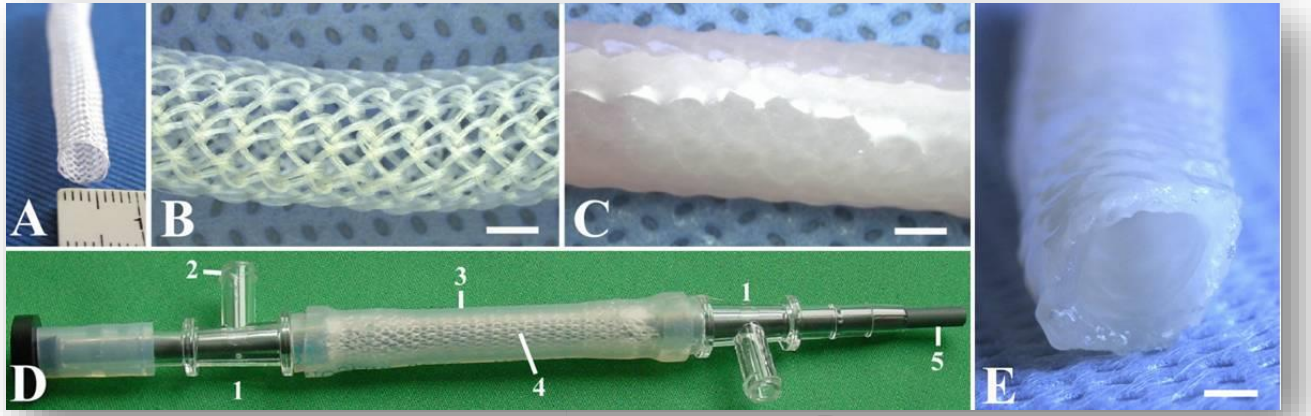
3 *Peri-operative* Tissue Engineering

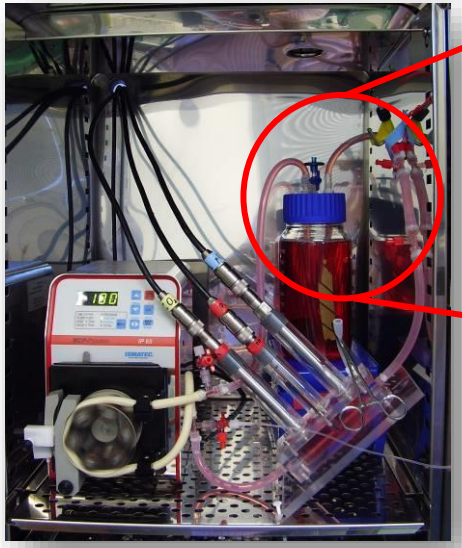
- Non-biodegradable warp-knitted backbone
- Temporay mechanical support (e-spun)

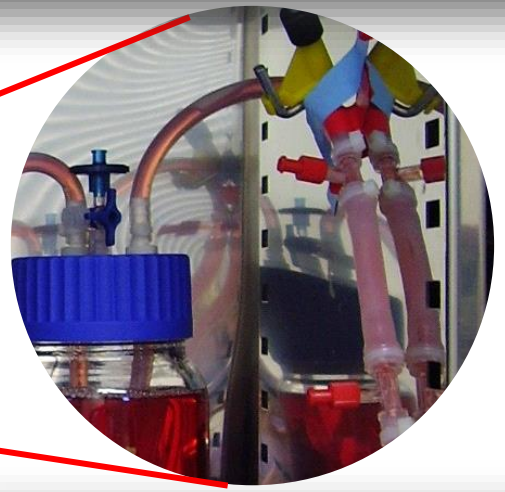


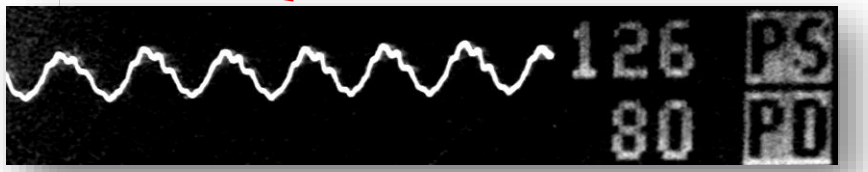
4 *in situ* Tissue Engineering?

Textile Reinforcement of Tissue-Engineered Vascular Grafts









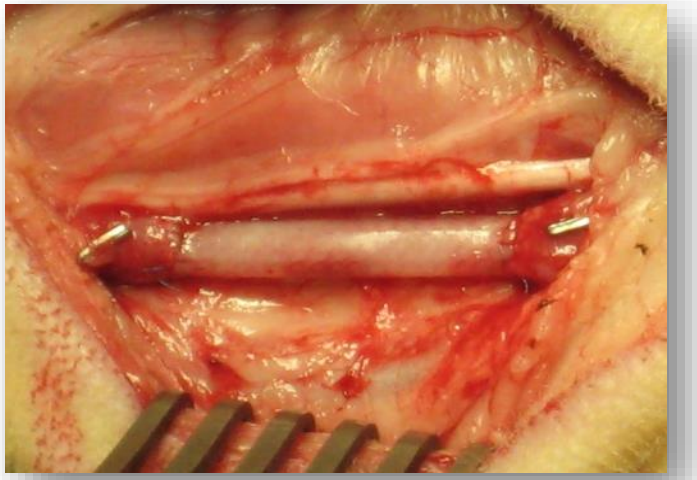
2-Component Co-Scaffold

- PVDF warp-knitted Textile-reinforcement
- Fibrin as cell-carrier
- Cellular components of autologous CCA
  - vSMC
  - EC
- Moulding process

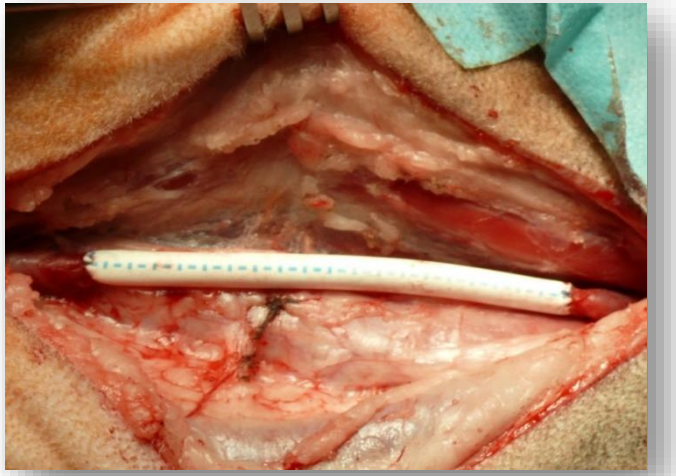
Tschoeke et al. Tissue Engineering 2009

in vivo Evaluation in Carotid Artery Position of Sheep

Biomaterials 2010



day 0

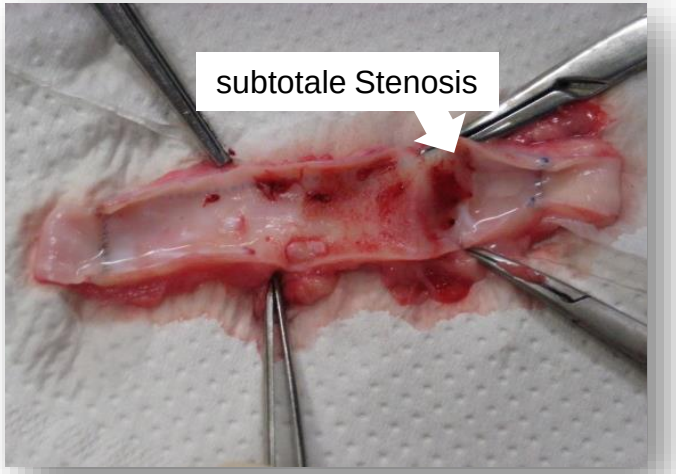


Biohybrid Vascular Graft

VS.

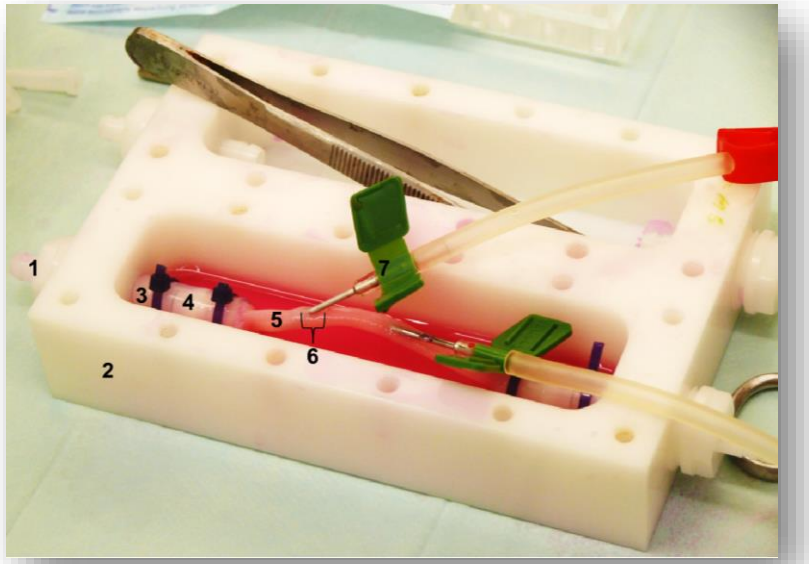
ePTFE Vascular Graft

after
6 month

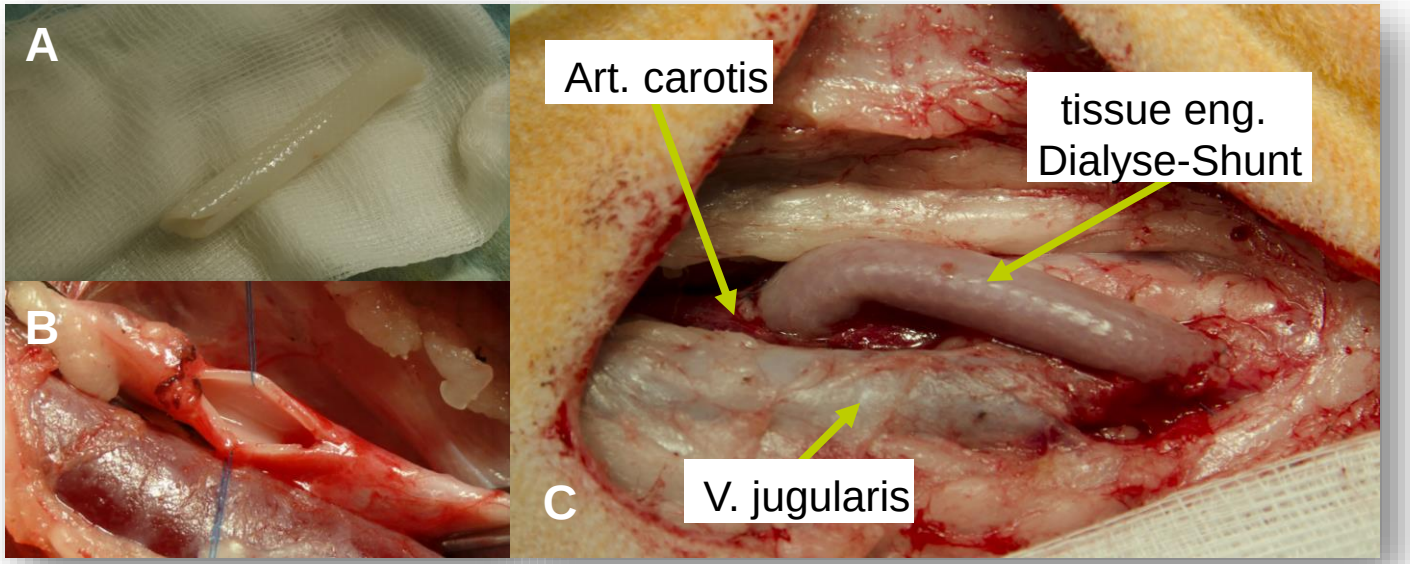


Production Time
42 days

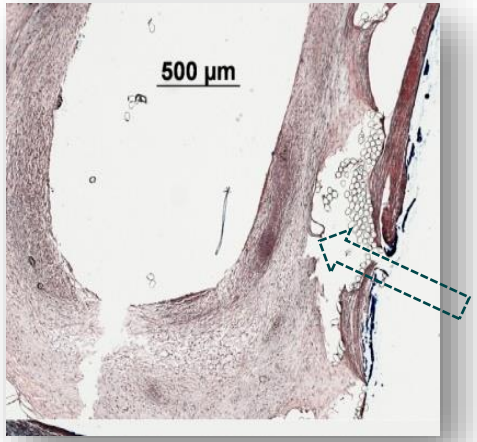
Evaluation as Biohybrid Dialysis Shunt

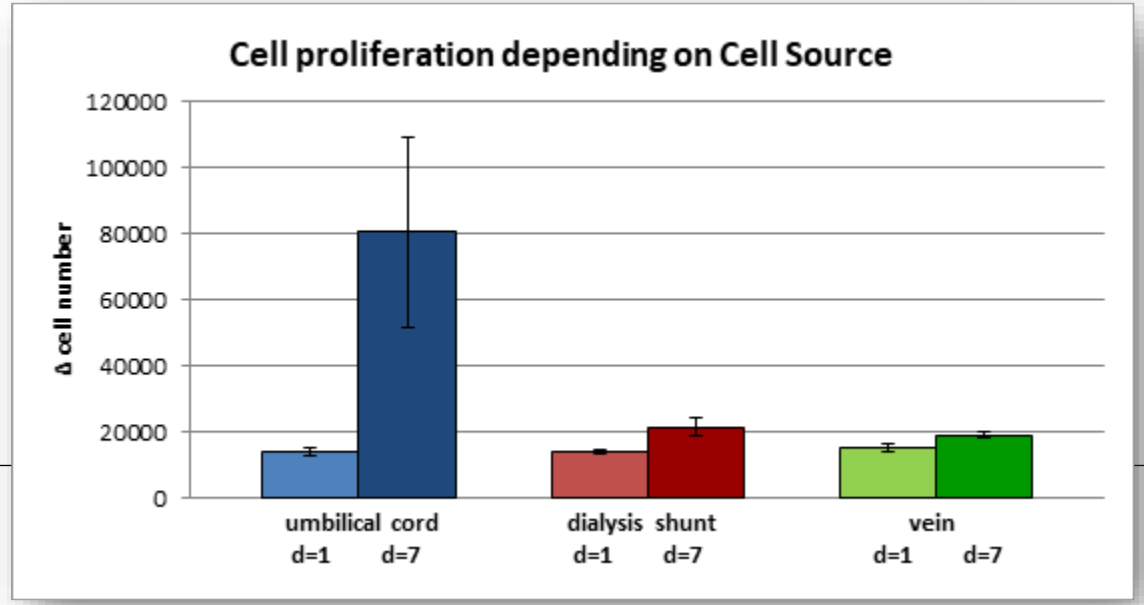


Sterile puncture 2-times per week



Implantation in ovine shunt model





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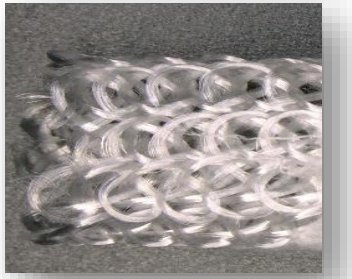
Textile Co-Scaffold for Shortening of in vitro Production Time

Lammers T et al. Chem Mater. 2017
Wolf F et al. Biomaterials 2019
Rama E et al. Adv. Science in revision
Mohapatra, Saurav, et al., in preparation

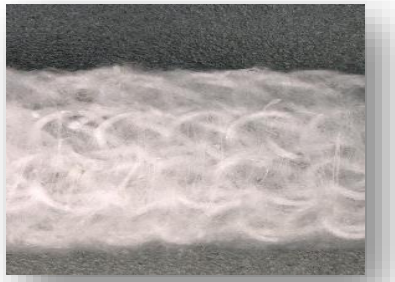
non-biodegradable warp-knitted structure (=long-term stability)
plus **biodegradable e-spun layer** (temporary replaced by ECM)

Improving initial mechanical properties:

Non-biodegradable PLUS biodegradable



warp-knitted mesh



e-spun PLGA layer

Imagable fiber materials:

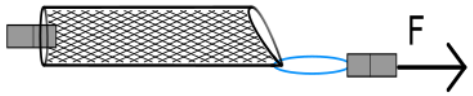
PVDF ⇨ **USPIO-labled**
↳ **^{19}F-TPU**

SPION in e-spun PLGA

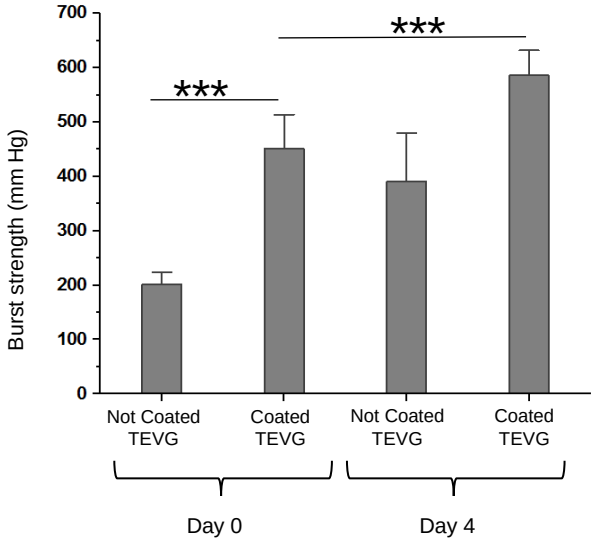
⇨ **Implant imaging**

↳ **degradation imaging**

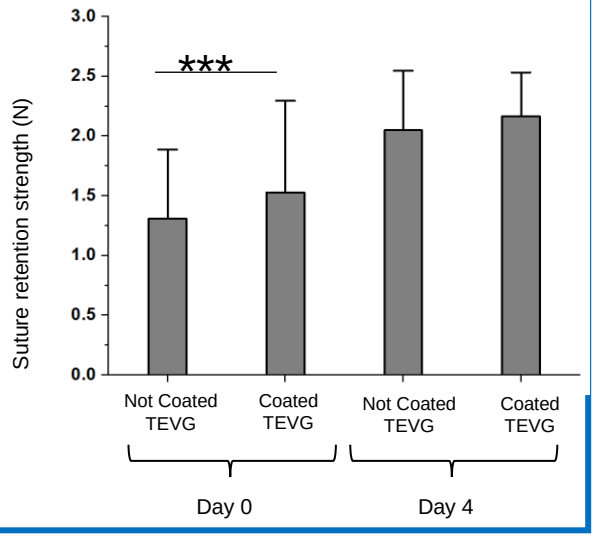
Shortening of in vitro production time from 42 days ⇨ 4 days



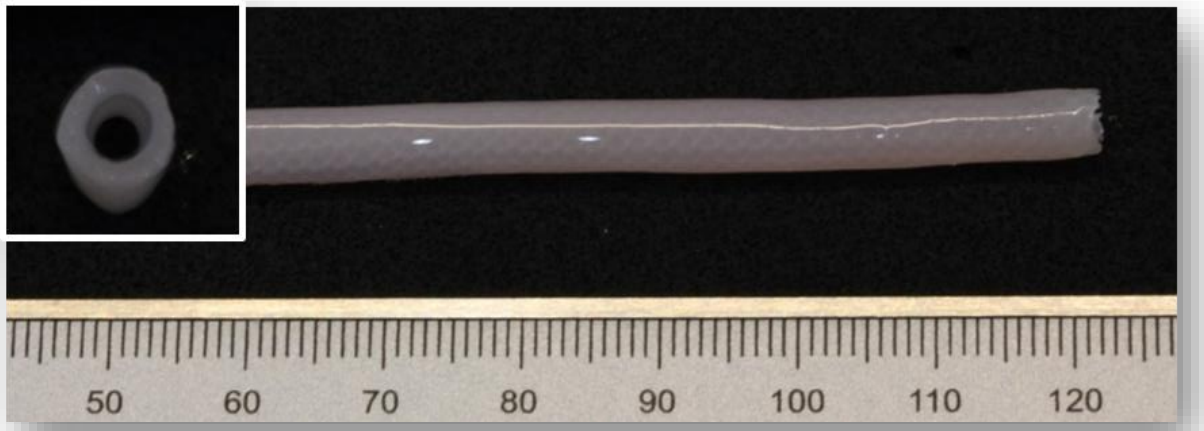
Burst pressure



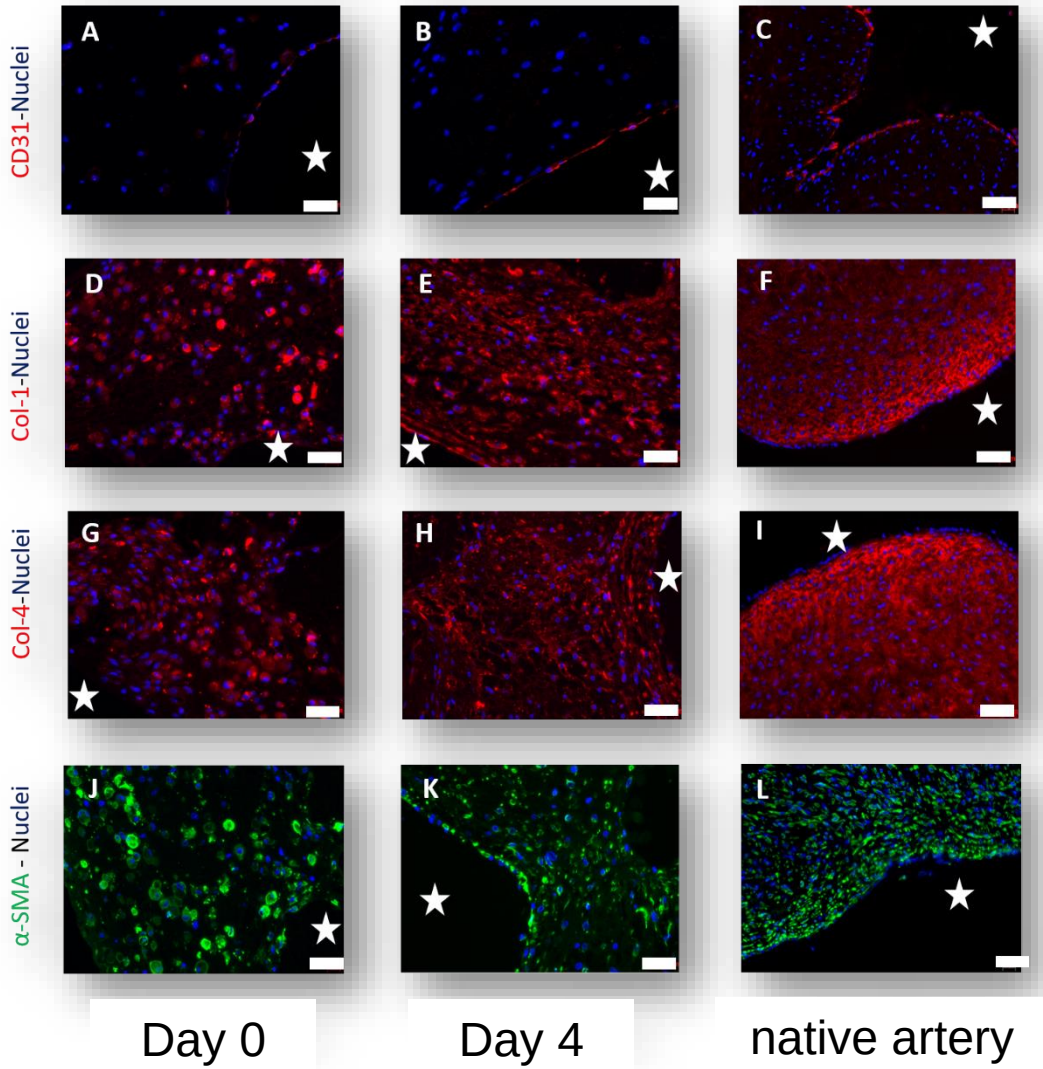
Suture Retention Strength



Achievements – ECM growth in TEVGs after four days



- **after 4 days** tissue-engineered vascular grafts underwent **advanced ECM maturation**
- **adequate mechanical properties** for implantation
- **high confluence of endothelial cell lining**
- **e-spun PLGA layer had no negative impact** on cell morphology & ECM development



Physiological Hemocompatibility by Elastin-like Recombinamers (ELR)

GEFÖRDERT VOM
Bundesministerium für Bildung und Forschung
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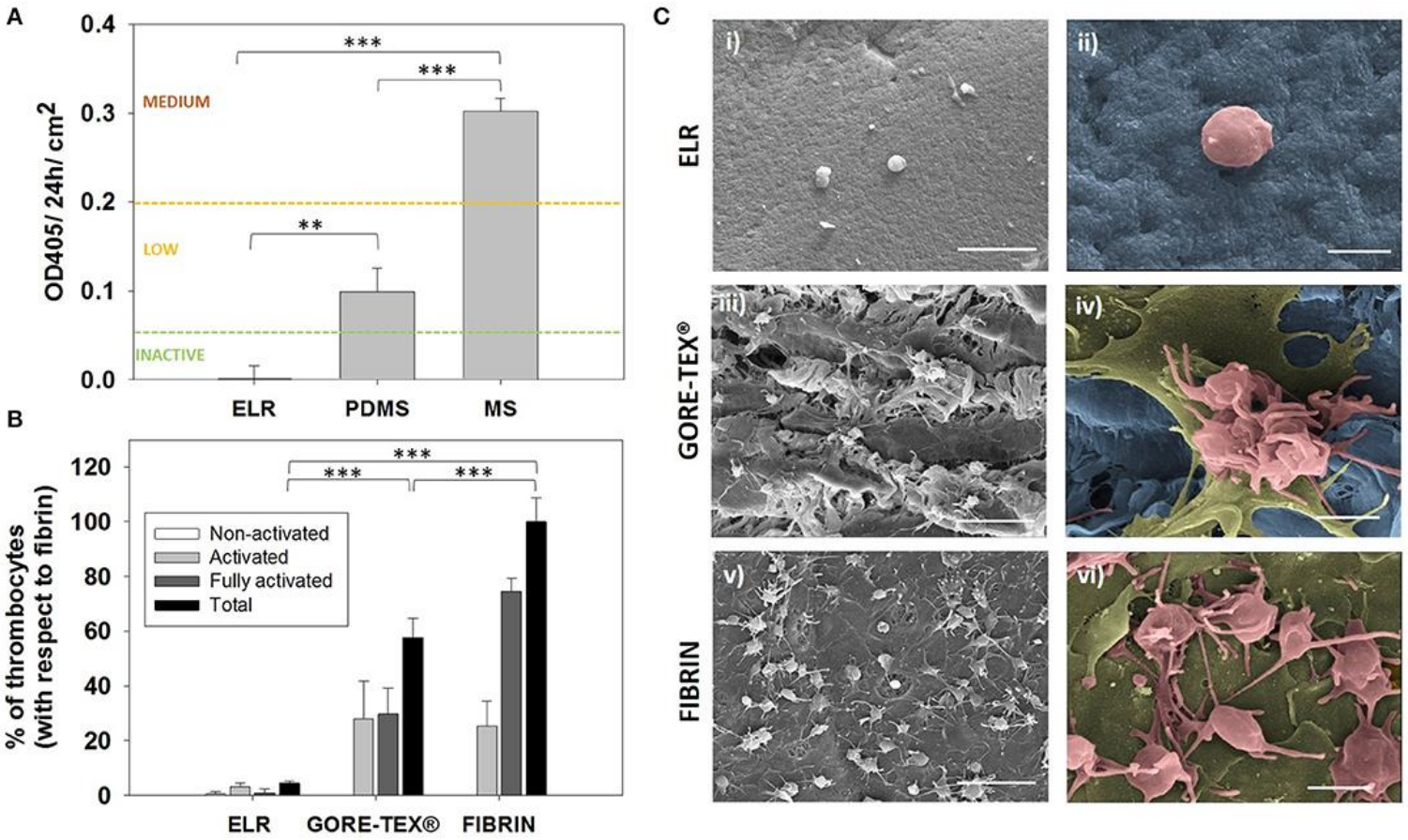
Alicia Fernandez
BioTex/AMIBM

Universidad de Valladolid
Prof. José Carlos Rodríguez Cabello



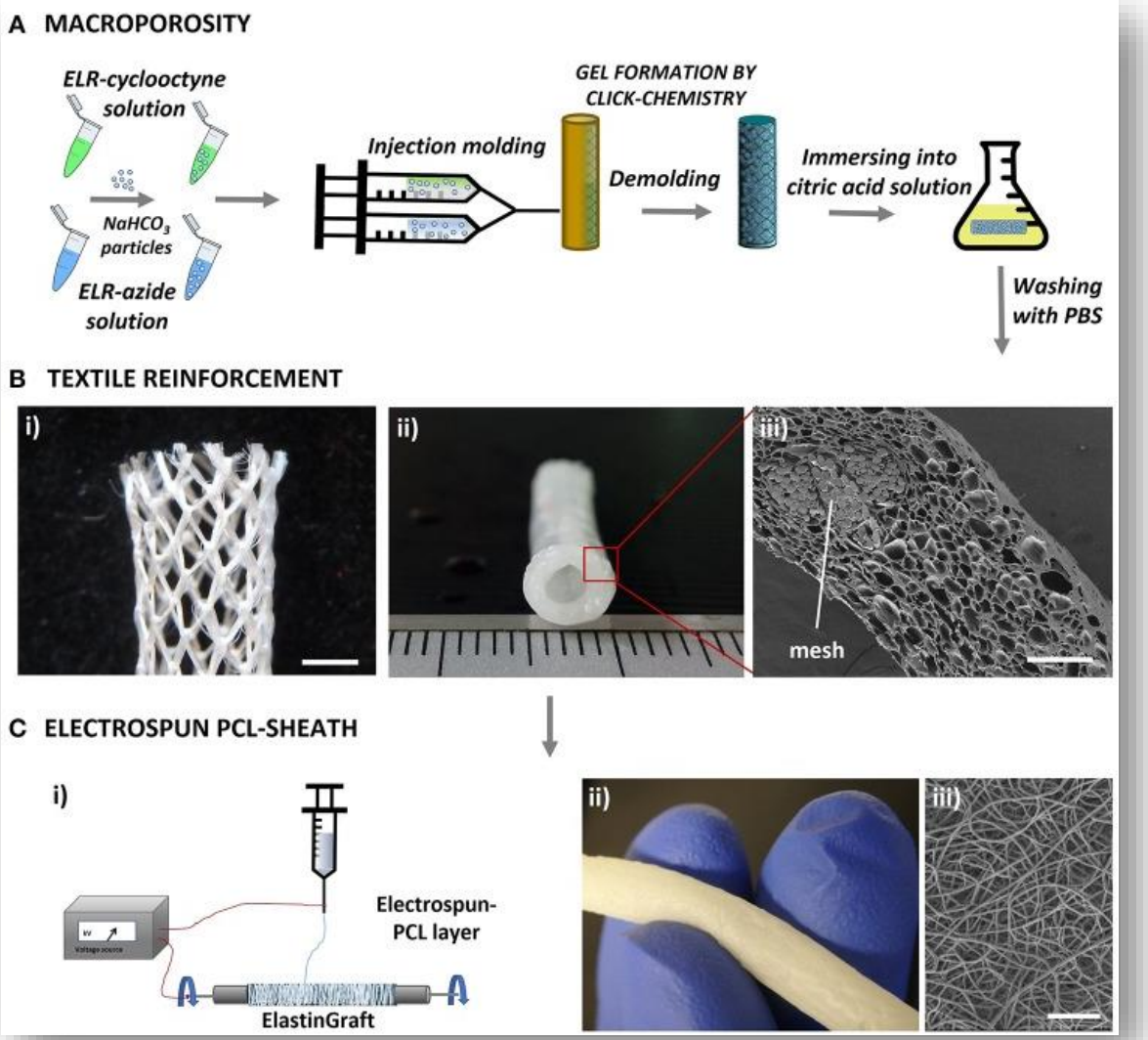
Fernandez-Colino A et al. Front Bioeng Biotechnol. 2019

excellent hemocompatibility
of Elastin-like-recombinamers comparable with endothelial cell lining

enabling
<u>cell-free</u> implants
with physiological hemocompatibility

Fernández-Colino A et al , Macromol Biosci. 2018
Fernández-Colino A et al. Mater Sci Eng C Mater Biol Appl. 2018
Coenen AMJ et al. Acta biomaterialia 2018
Fernández-Colino A et al. Mater Sci Eng C Mater Biol Appl. 2018
Gonzalez de Torre I. Biomater Sci. 2016
Gonzalez de Torre I. et al. Acta Biomaterialia 2015

ElastinGraft towards *in situ* Tissue Engineering



Fernandez-Colino A et al. Front Bioeng Biotechnol. 2019

Co-Scaffold Concept for *in situ* Tissue Eng.

(1) Warp-knitted non-biodegradable Textile Reinforcement (PVDF)

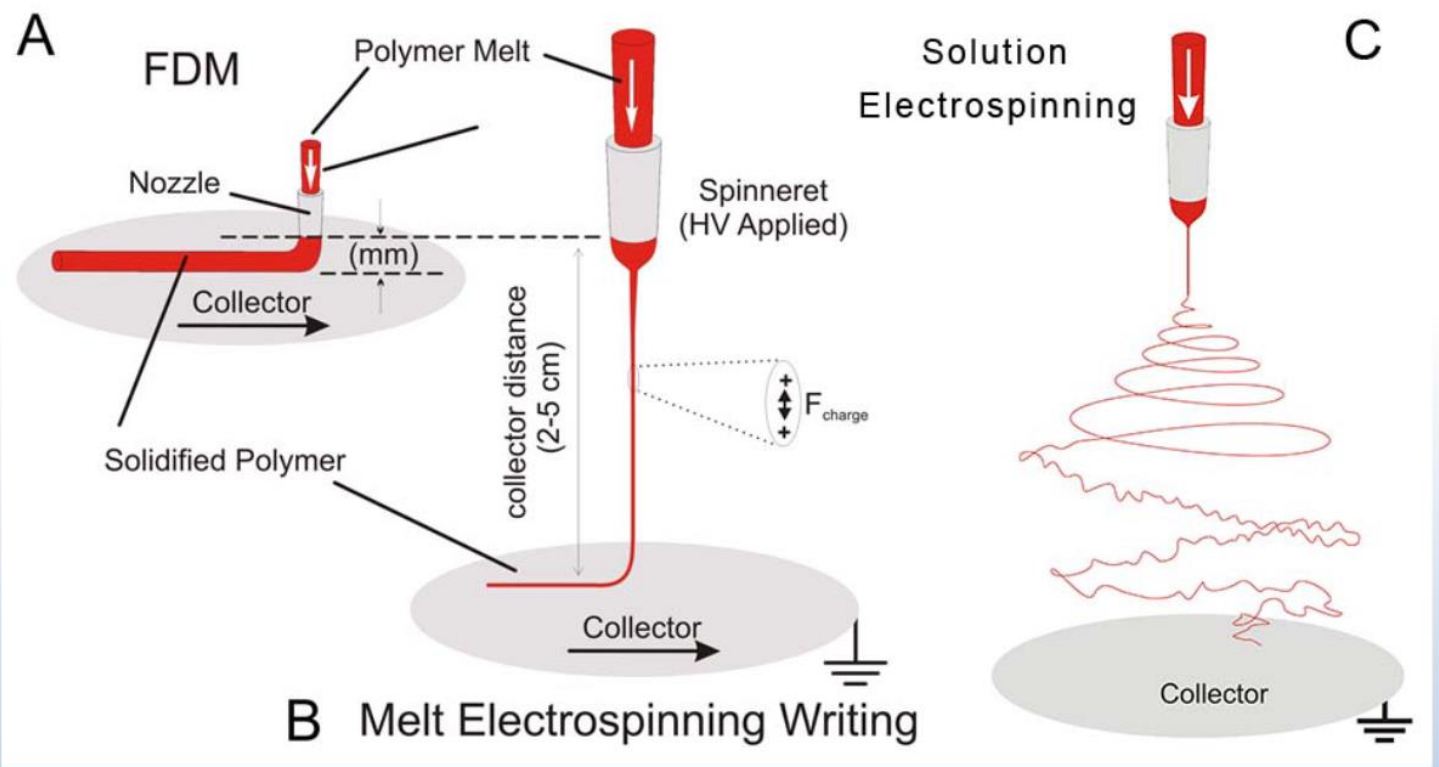
(2) Porous ELR-Scaffold structure for in situ cell ingrowth

(3) Temporary fibre-reinforcement with e-spun PCL (biodegradable)

Outlook: Biomimetic Scaffold Production by Melt Electro Writing (MEW)

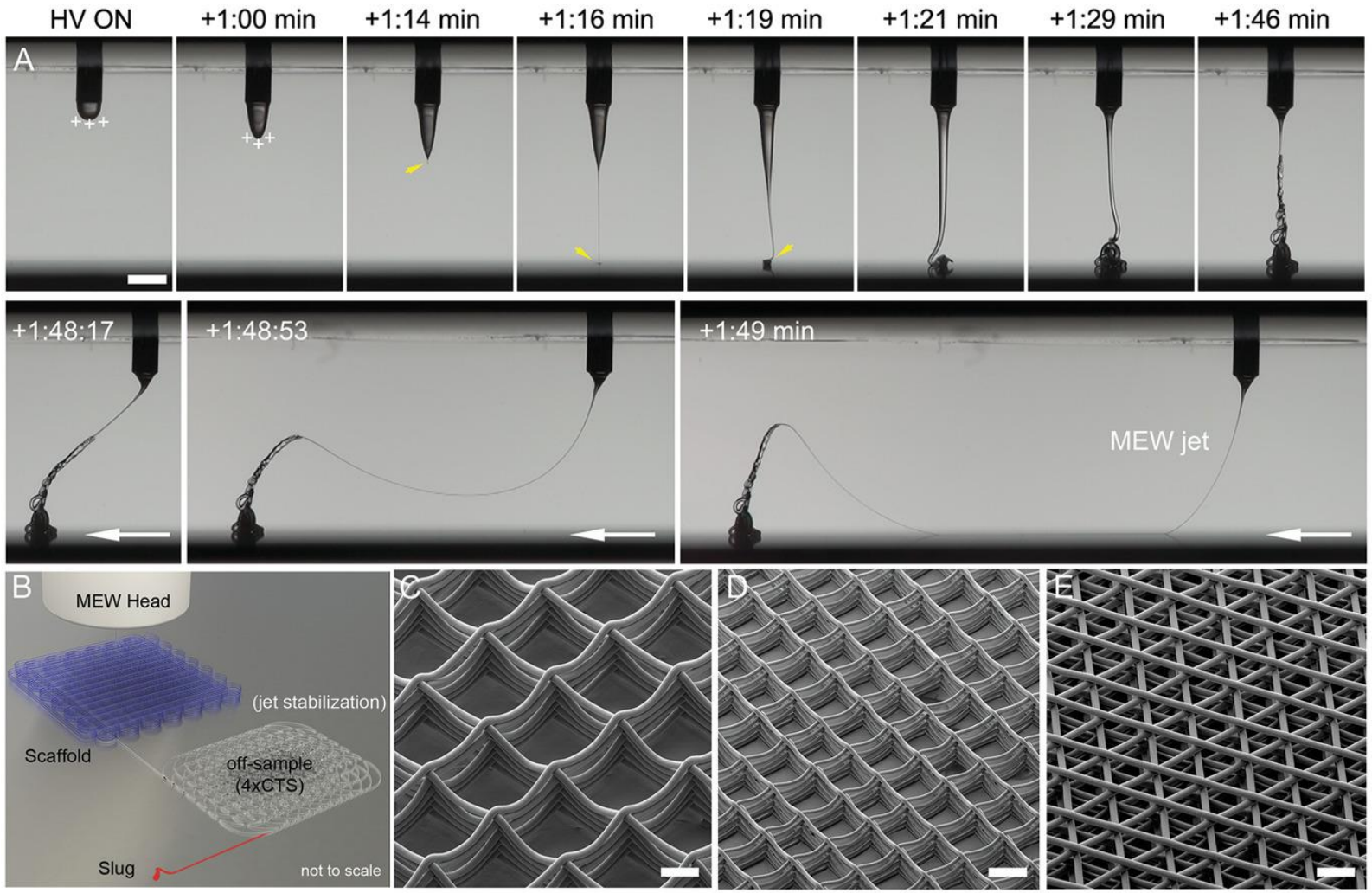
- **Melt-Eletro-Writing**
  - Fibre order in the µm to sub-µm range
  - No field disturbances due to evaporate
    - ↳ stable fibre deposition
    - ↳ high resolution
    - ↳ Complex 3D geometries with defined fibre direction & pore size possible

FDM = Fused Deposition Modelling



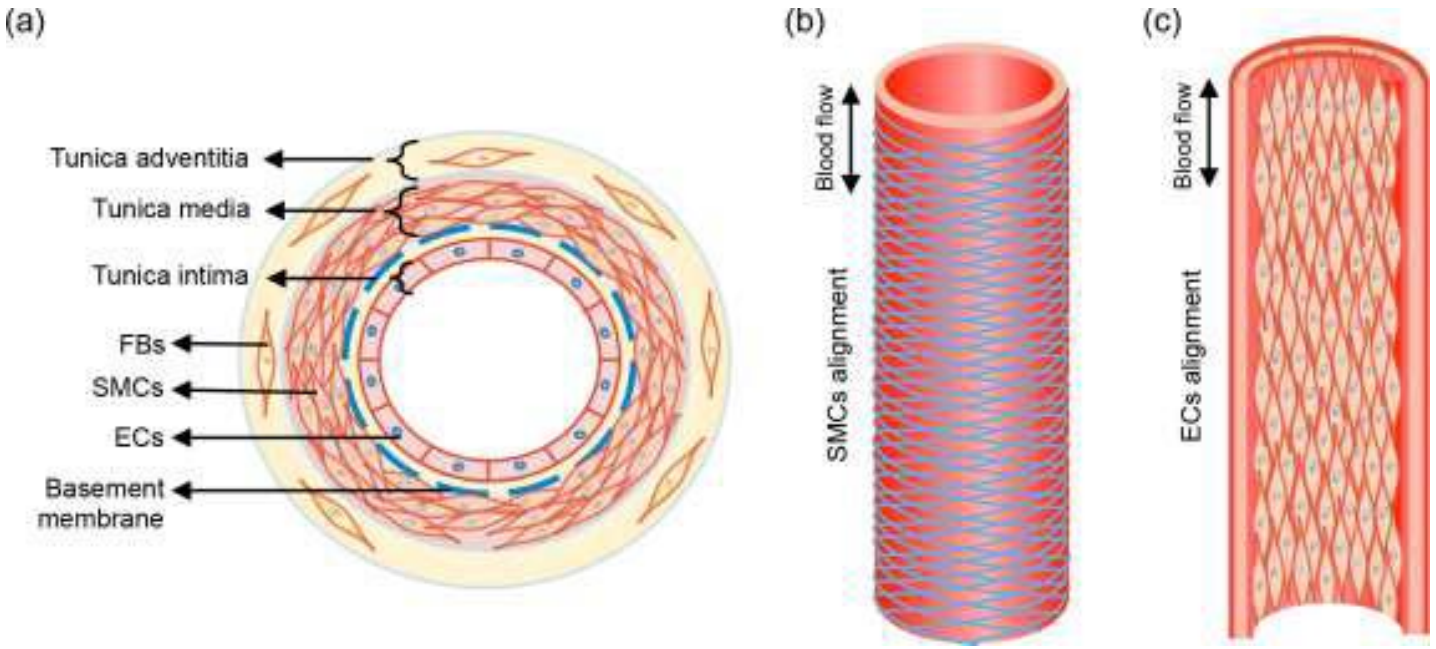
Quelle: D. Hutmacher Gruppe, Brisbane

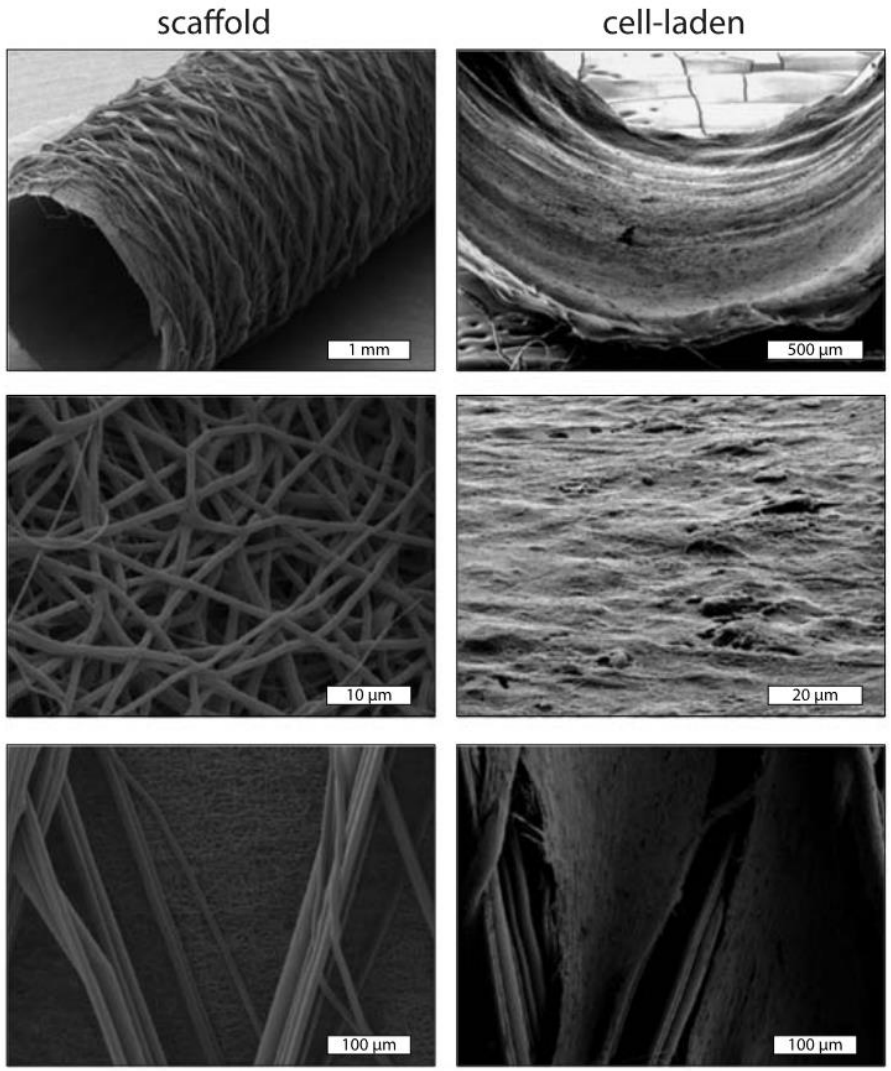
MEW – High resolution and precise fibre placement possible



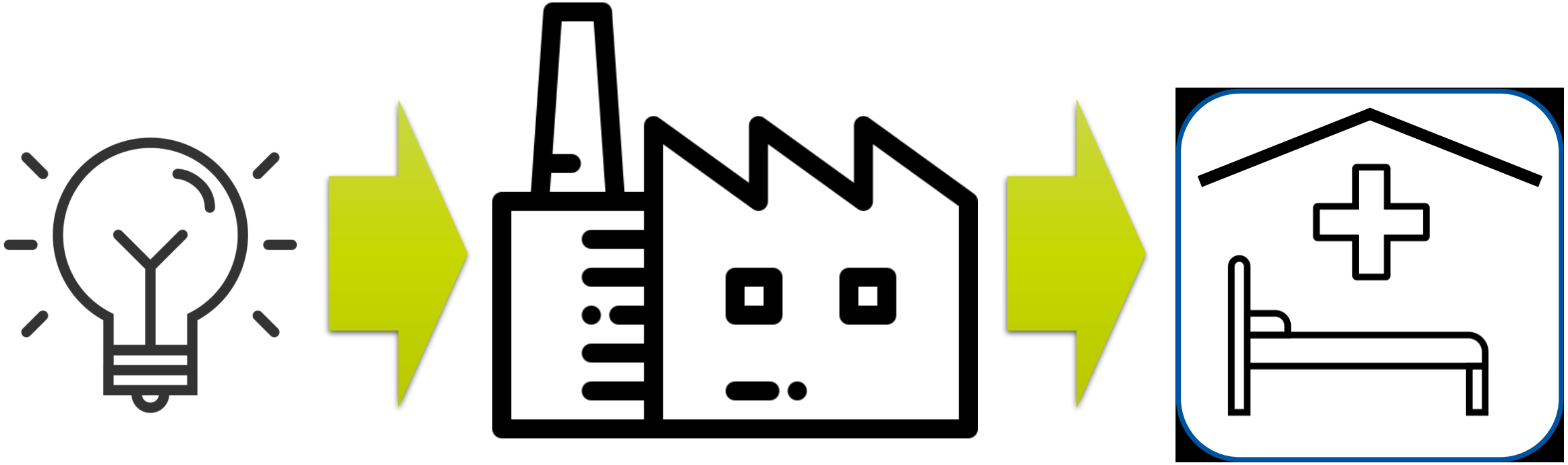
Advanced Healthcare Materials, Volume: 10, Issue: 1, First published: 17 September 2020, DOI: (10.1002/adhm.202001232)

Biomimetic Scaffold Design to guide Cell & Tissue Orientations





From Idea to Innovation = Translation into Clinic



fiT – Facts & Figures

- EFRE-Programs ***Forschungsinfrastruktur.NRW***

  Areas:

  - **425m² Clean Rooms (Class A in B and C) (GMP)**
  - **400m² Laboratories Biology/Chemistry (GLP)**
  - **400m² Office Space & Seminar rooms (GCP & Training)**
- **Total Costs ~15,45 Mio € building costs**

  plus € 2,2 million initial equipment
- **Planned completion 2022**

fiT as a missing link in the academic-industrial value chain

Pre-industrial Production | Industrial Valorization

Material Innovation → Prototypical Production → Pre-clinical Testing → GMP conform Production → First-in-Man Clincal Trials → Up-Scaling & clinical translation

Progress in Medicine

Leibniz Joint-Lab for first-in-man (*fi*T)

DWI Leibniz Institute for Interactive Materials

Center for Biohybrid Medical Systems (CBMS)

Leibniz-Joint-Lab for First-in-Translation (*fi*T)

University Hospital Aachen (UKA)

CLINCAL NEED

Take Home Message: Learning from Nature

The Nature of Nature

- adapt
- regenerate
- replace

= Nature of Medicine

Basic Principles

Be humble,
Observe & Learn

Thanks to the excellent Team

@ Maastricht University

@ RWTH Aachen University

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Stiftung KinderHerz
Mit dem Herzen handeln!

IZKF AACHEN

Deutsche Forschungsgemeinschaft
DFG

tecas

provincie limburg

Brightlands
Knowledge crossing borders

Bundesministerium für Bildung und Forschung

Ministerium für Kultur und Wissenschaft des Landes Nordrhein-Westfalen

European Commission

BioTex AME | RWTH AACHEN UNIVERSITY | Maastricht University