

# **(Bio)artificial organs to mimic and / or replace patient failing organs**

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## Potential conflicts of interest declaration

As a speaker, I hereby affirm that there are **no conflicts of interest** concerning the content of the following speech that are the result of employment, an advisory function or financial contributions for research projects, lectures or any other activity.

# WHO organization – Facts on diabetes Type-2 (2016)

- 108 million in 1980 to 422 million in 2014.
- Major cause of blindness, kidney failure, heart attacks, stroke and lower limb amputation.
- In 2012, 1.5 million deaths directly caused by diabetes, 2.2 million deaths attributable to high blood glucose.
- WHO projects that diabetes will be the 7th leading cause of death in 2030 .

**Healthy diet, regular physical activity, maintaining a normal body weight, no tobacco  
CAN PREVENT OR DELAY the onset of type 2 diabetes.**

## Diabetes type 1

Destruction of insulin-producing cells due to an autoimmune reaction

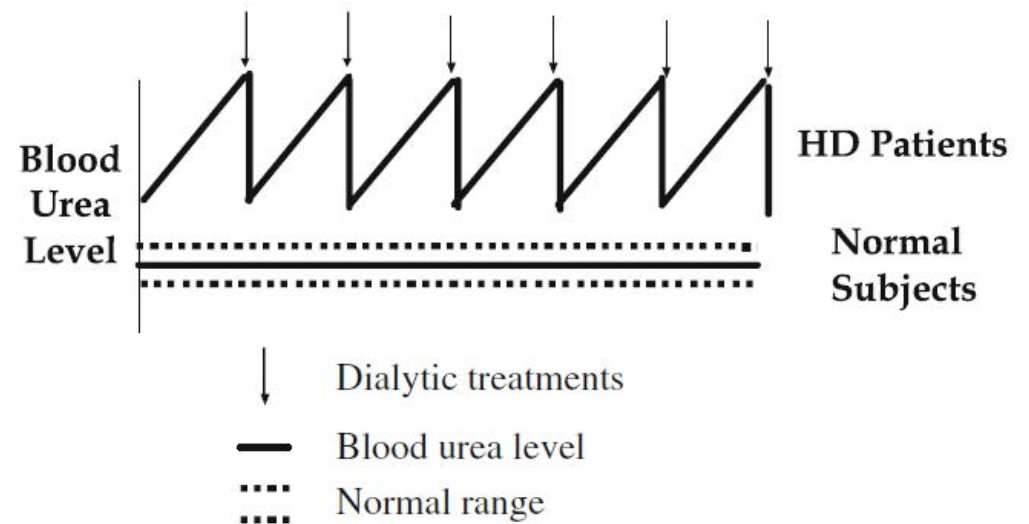
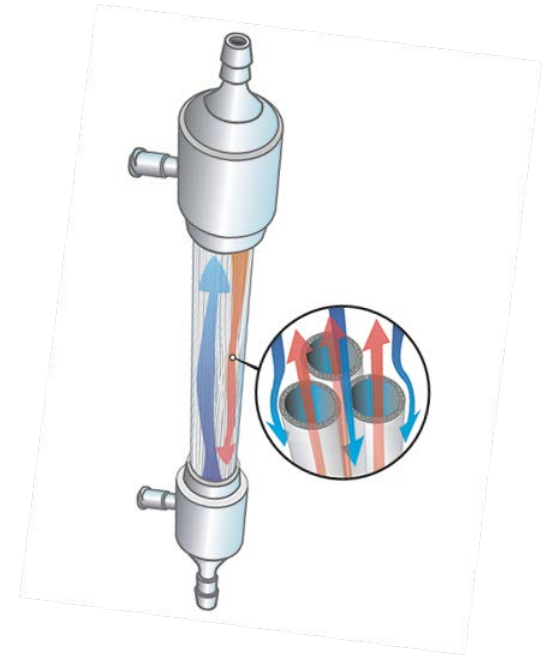
**In The Netherlands >100.000 patients**

# Current therapy

- Clearance of solutes:
  - **water soluble, low molecular weight**
  - **(some) middle molecules**
  - Not - Protein-bound solutes



- Not - continuous cleaning



Vanholder, Kidney International 2003

Lee, Clinical and Experimental Nephrology 2008

# Urgent need for organs

Transplantation is the best option

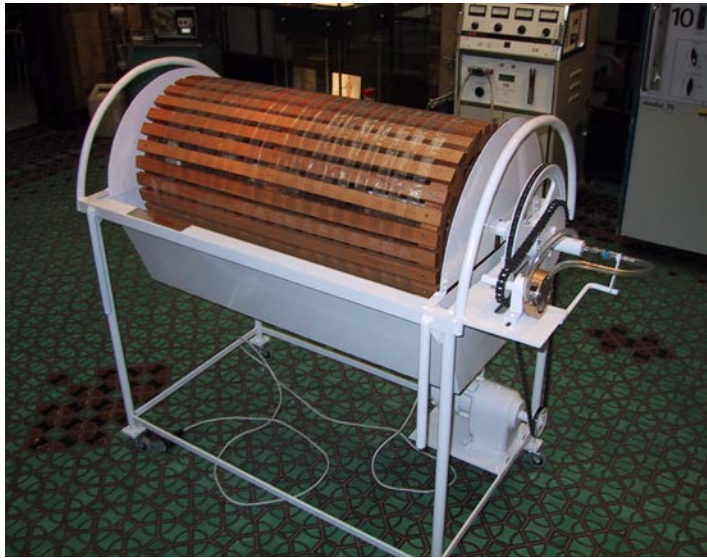
**Kidney:** Waiting list ~4 yrs, Graft survival ~ 10-20 yrs, Not everyone eligible

## (Bio) artificial Organs

**Artificial:** Based on biomaterials, new concepts, new designs

**Bioartificial:** new biomaterials, new concepts, new designs **and cells**

**Extracorporeal and / or Implantable**



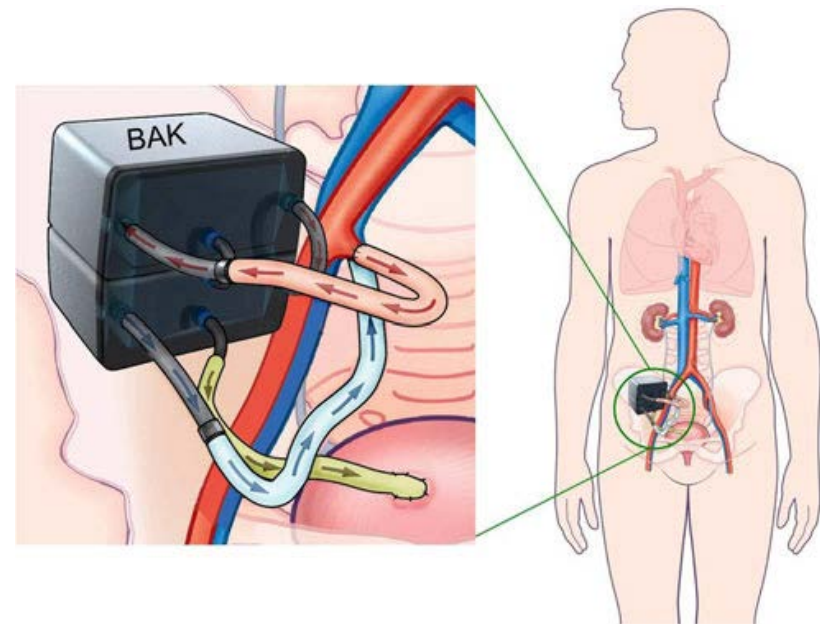
The past



The present



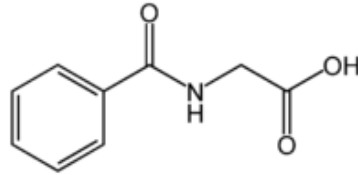
The near future



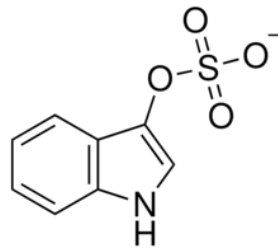
The future

# Protein-bound solutes

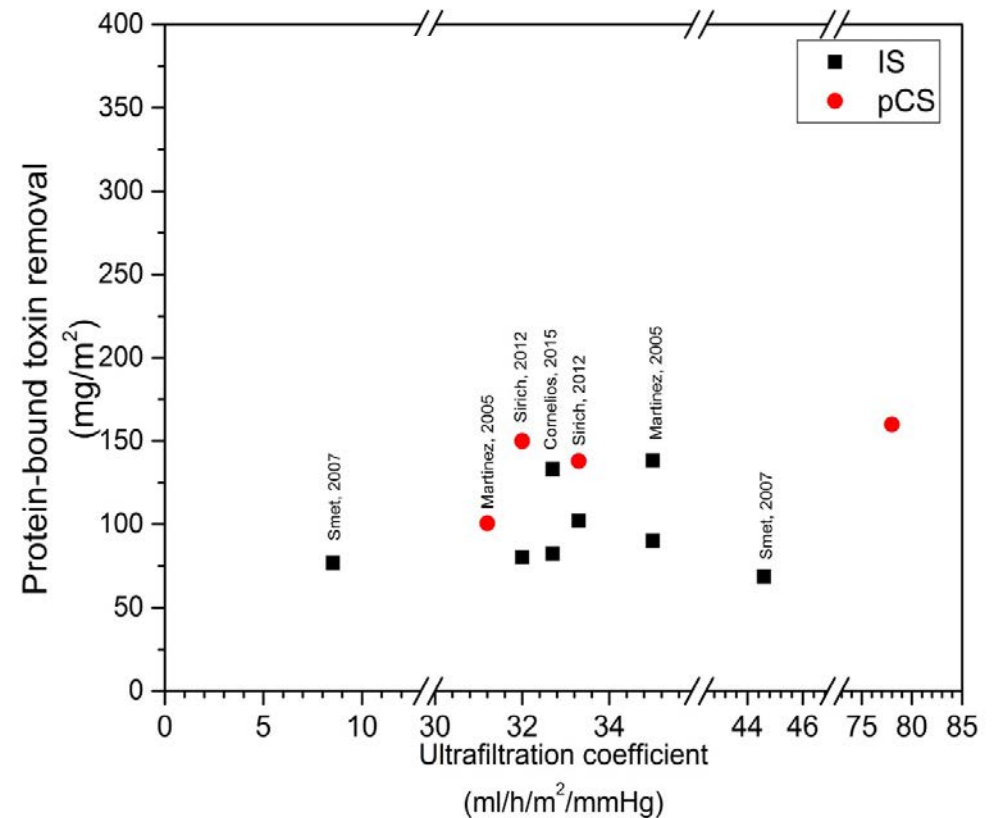
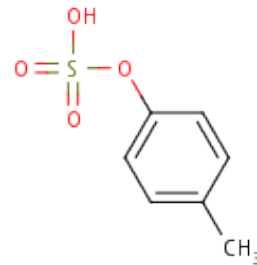
- Hippuric acid  
(40% bound to HSA)



- Indoxyl sulfate  
(> 90 % bound to HSA)



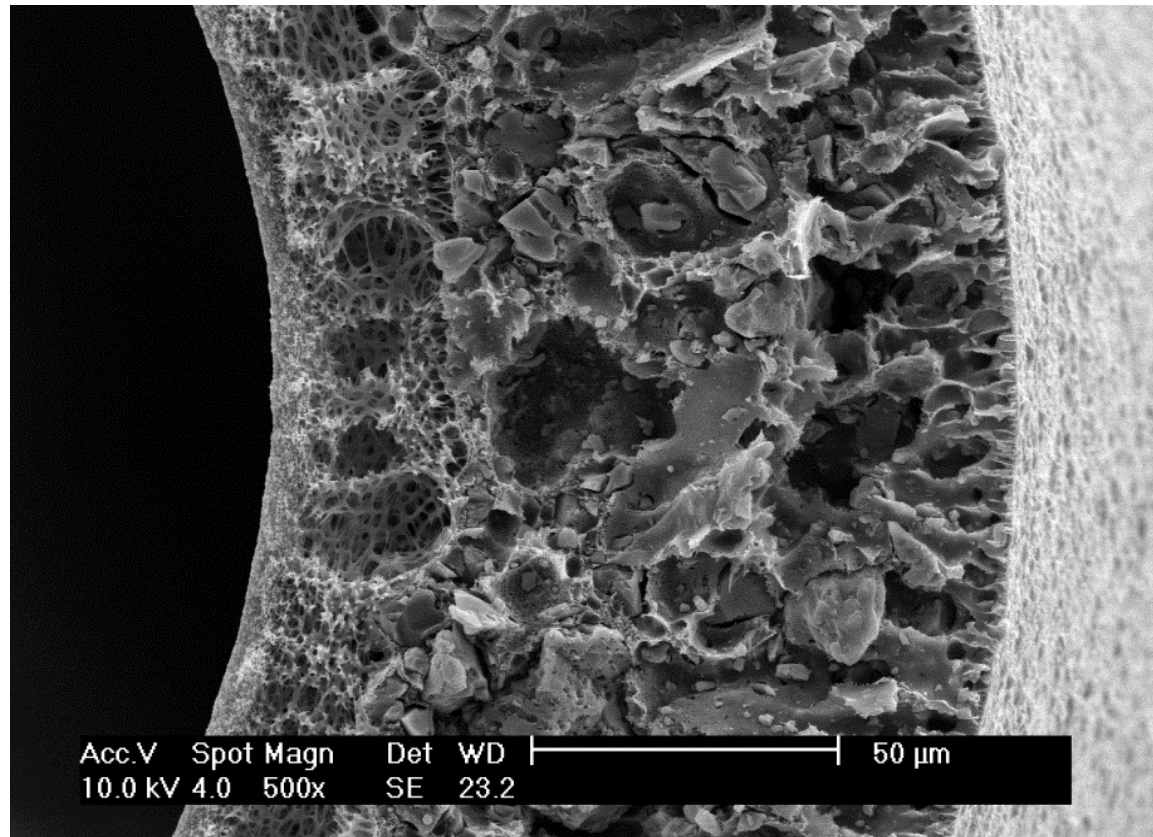
- P-cresyl sulfate  
(> 90 % bound to HSA)



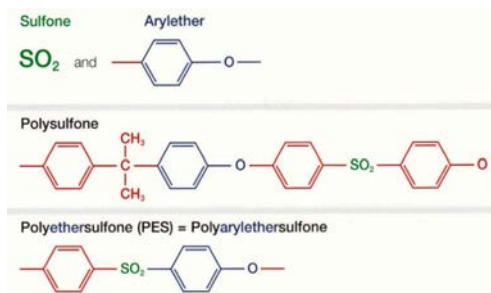
Pavlenko et al, Scien. Reports (2016)



# Better removal of uremic toxins / cytokines



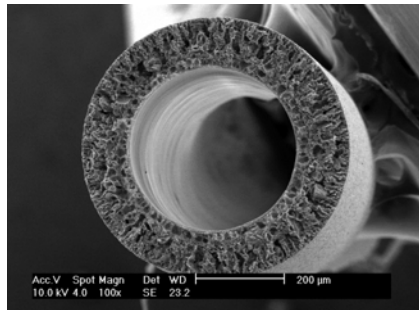
## Mixed Matrix Membrane



**Biomaterials 34 (2013) p7819**  
**Blood Purif., 37 (2014) p1**  
**J. Mater. Chem. B, 1 (44) (2013) p6066**  
**Acta Biomater. 8 (2012) p2279.**

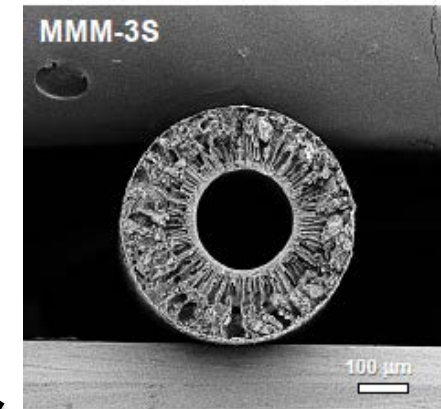


**< 0.15 m<sup>2</sup> MMM for  
complete removal of PBUT**

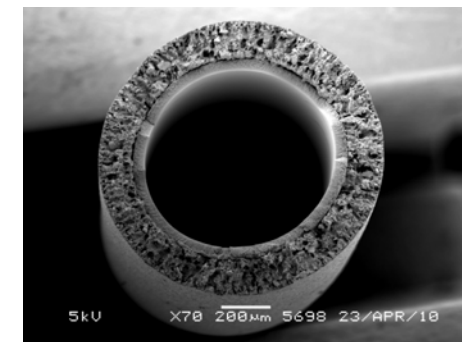
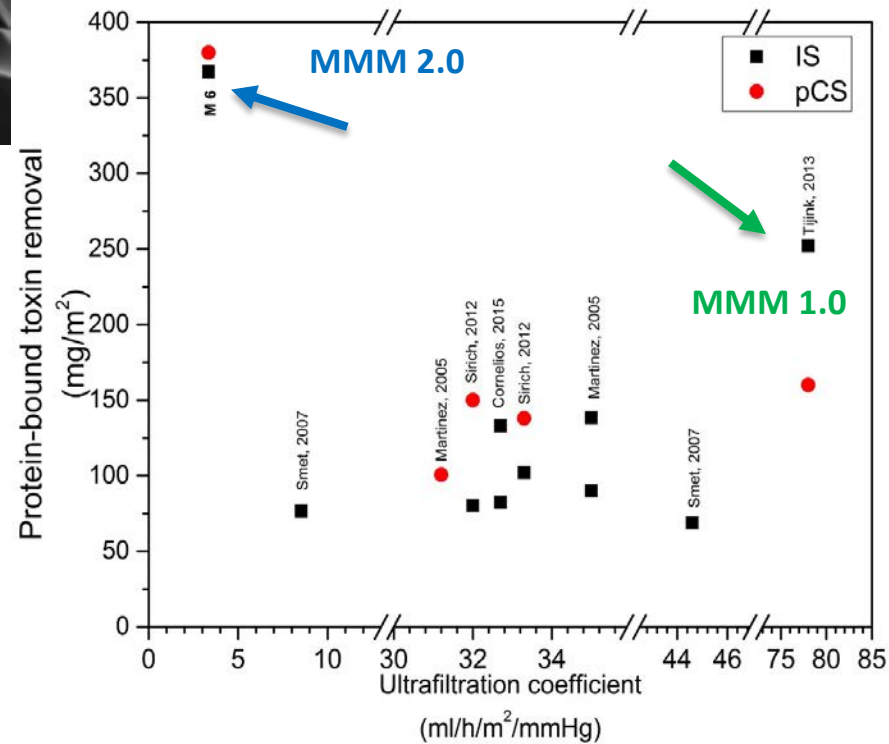


**UC = 5  
MWCO= 14 kDa  
no albumin leakage**

**UC = 80  
MWCO = 59kDa  
No albumin  
leakage**



**MMM 3.0 = 500 mg/m<sup>2</sup>**

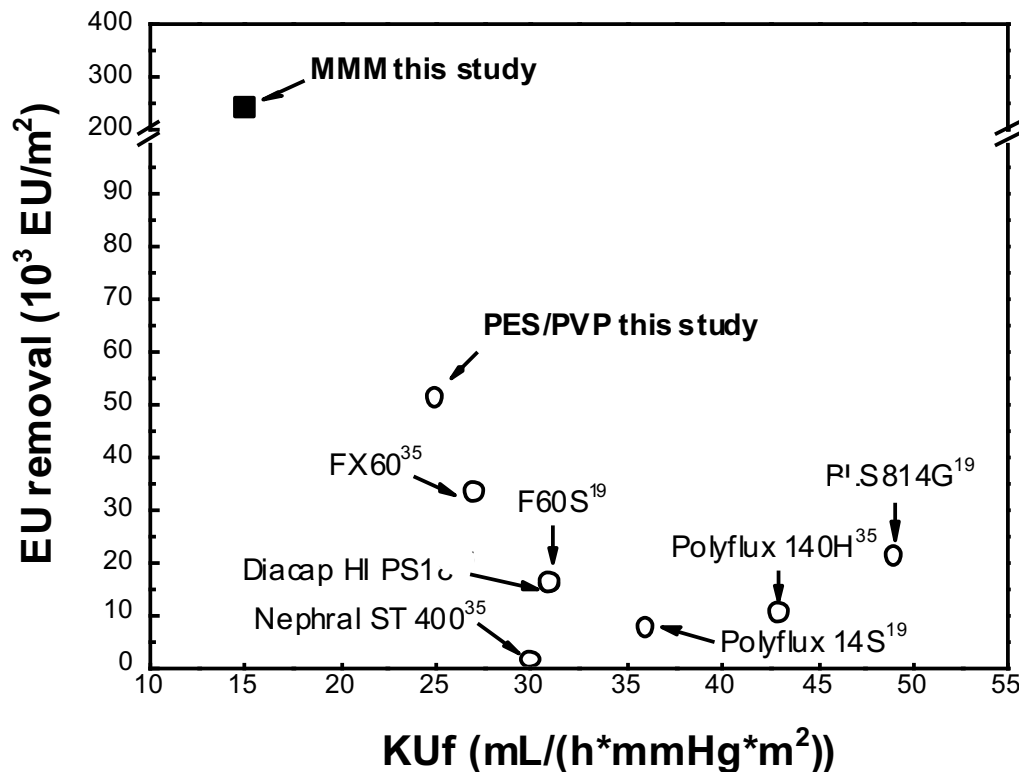


**UC = 75  
Albumin leakage**

# Combined removal of LPS from dialysate and PBTs from human plasma



LPS from *Pseudomonas aeruginosa*



V. Weber, et al., Blood Purification, 2003.

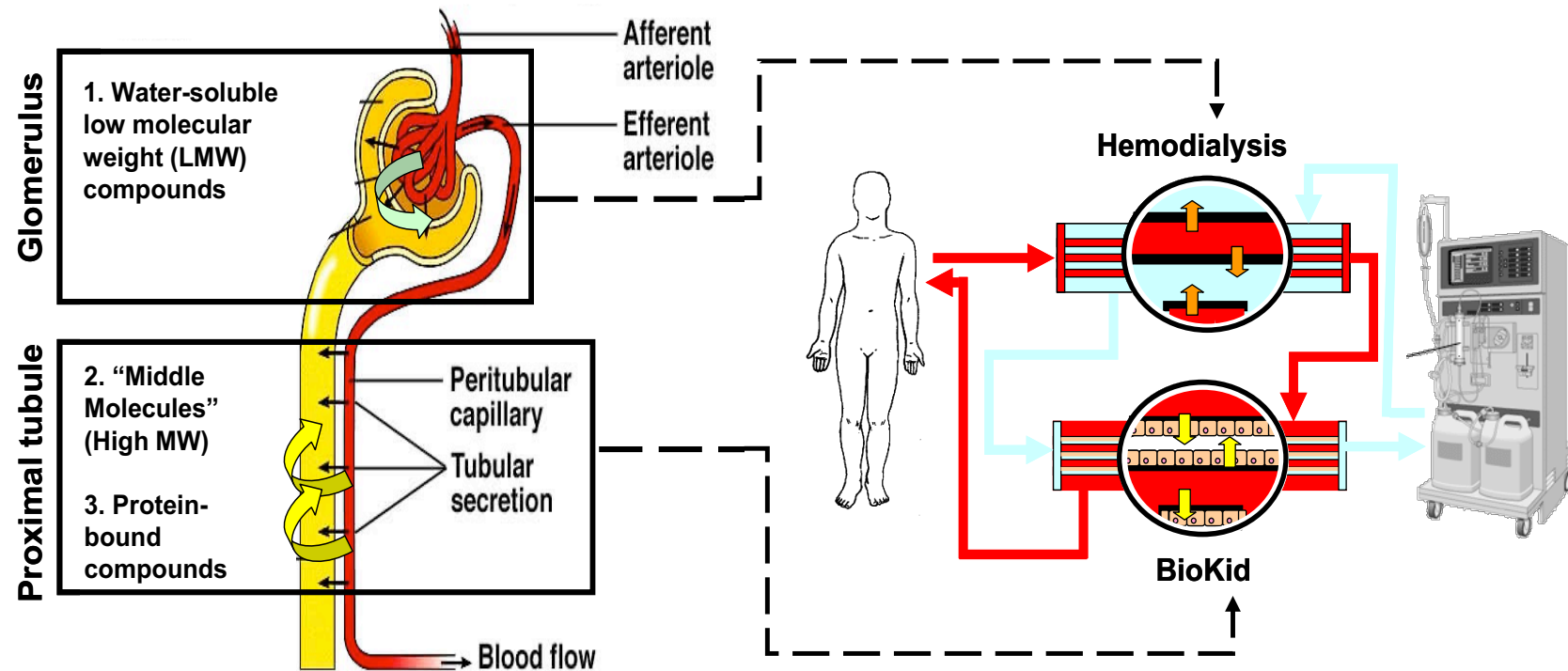
V. Weber, et al., Artif. Organs, 2004.

Geremia et al, Acta Biom., 90 (2019) p100.

Patent application EP18185495.1

**Replace critical transport, metabolic and endocrine kidney function**

# Bioartificial kidney



# Bioartificial Kidney

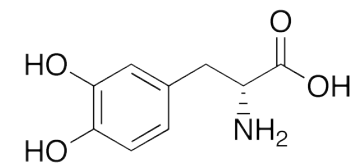
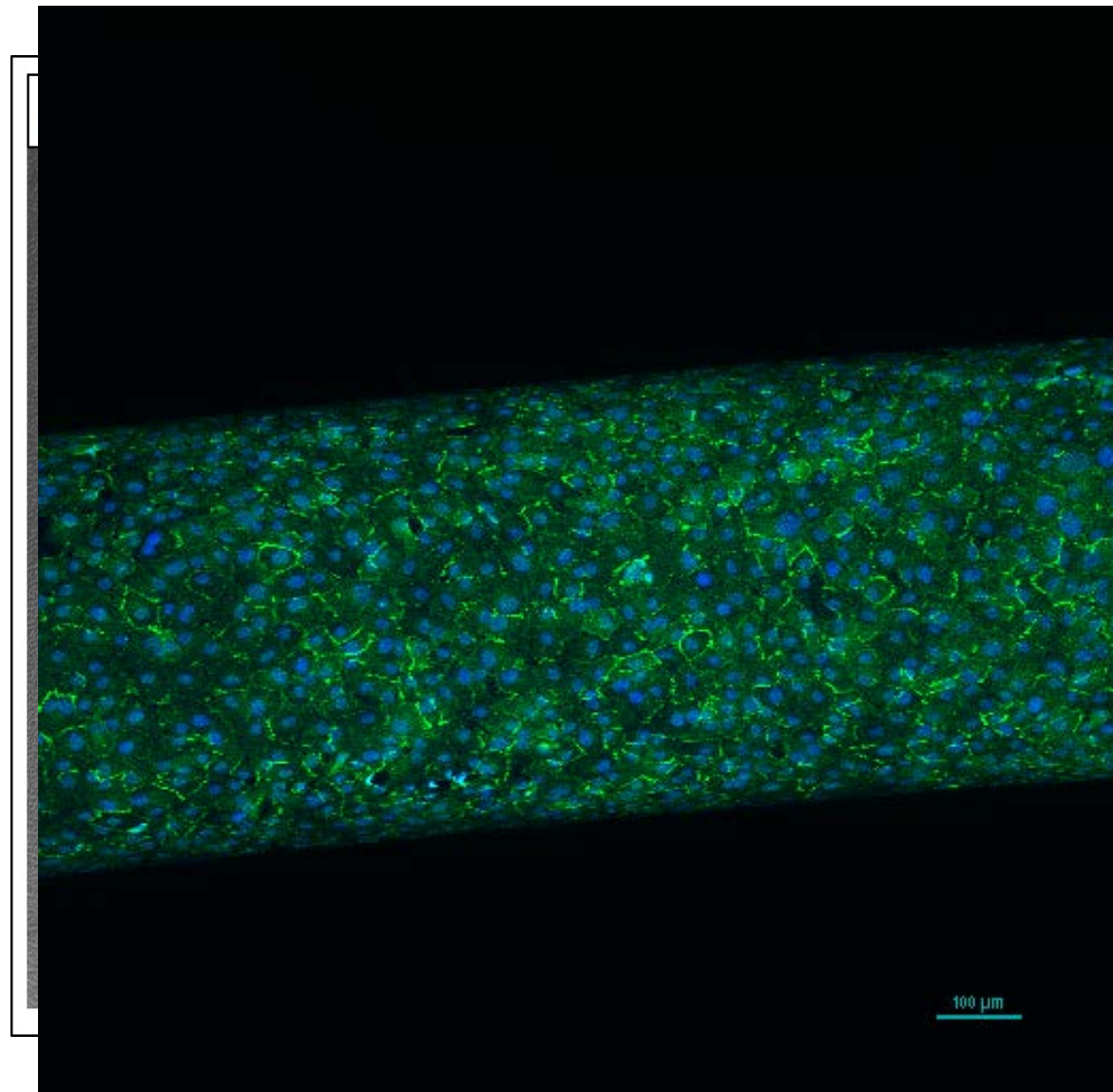
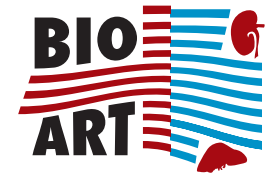


(Bio)Artificial  
Organs

## MIRA

BIOMEDICAL TECHNOLOGY  
AND TECHNICAL MEDICINE

# “Living HFM”

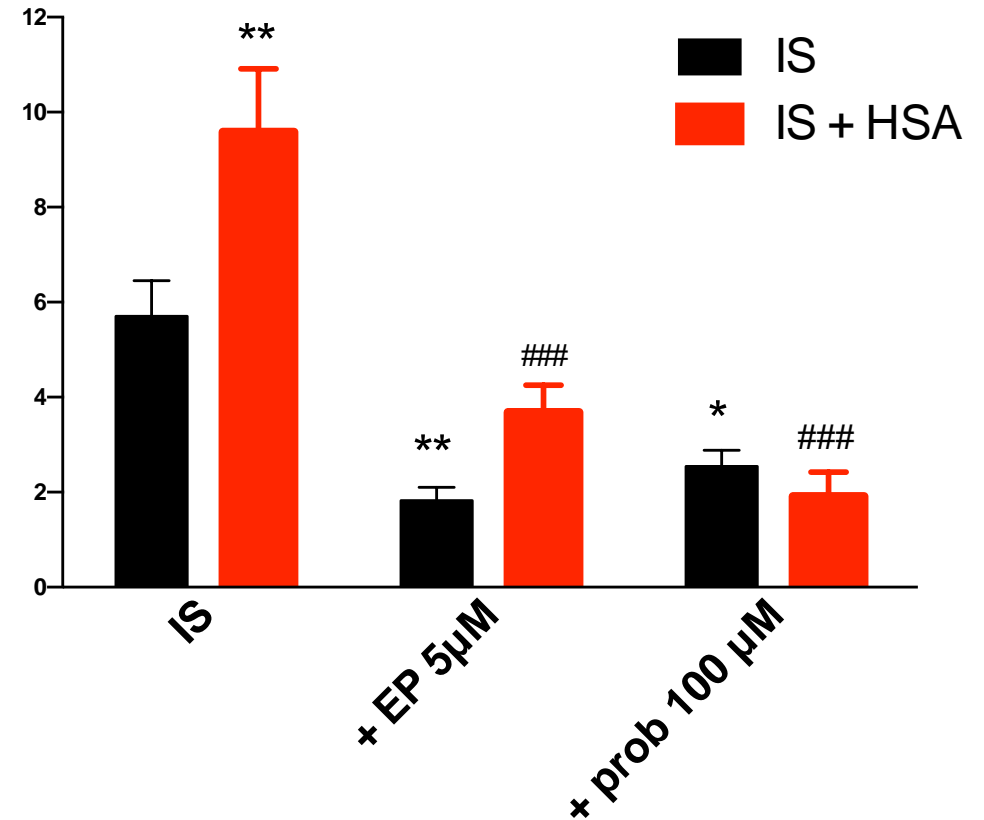
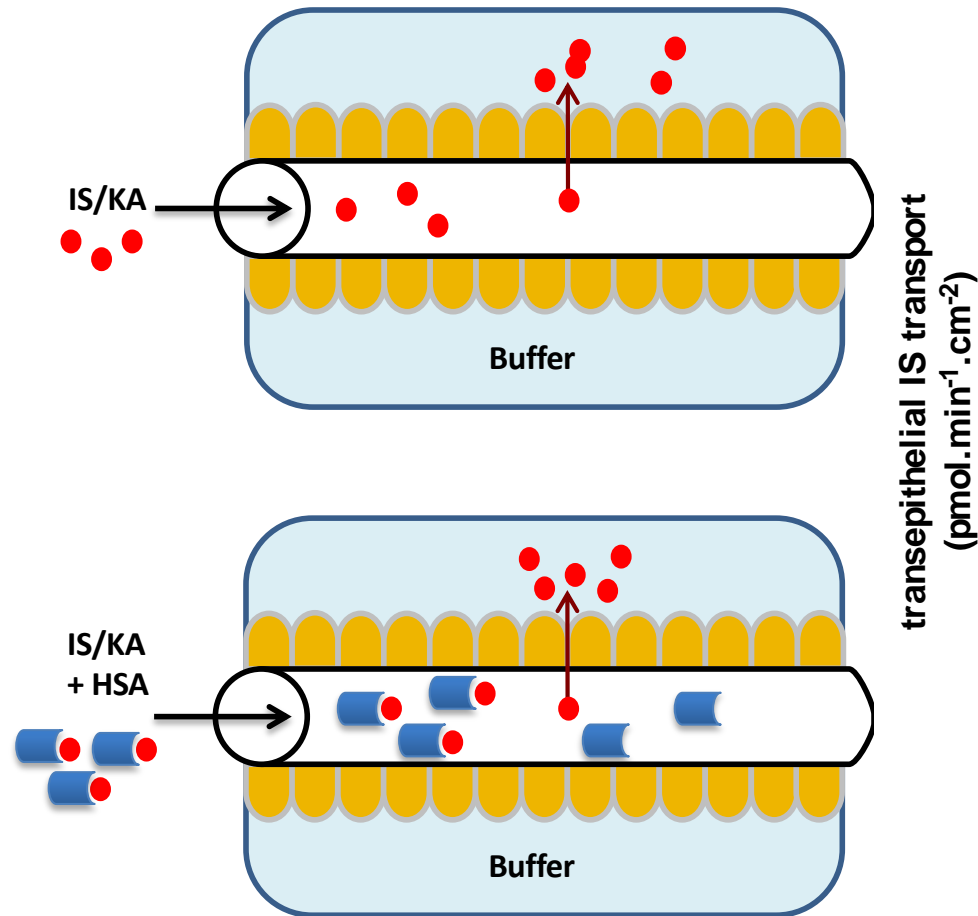


■ Immortalization:

1. SV40T tsA58 U19
2. hTERT

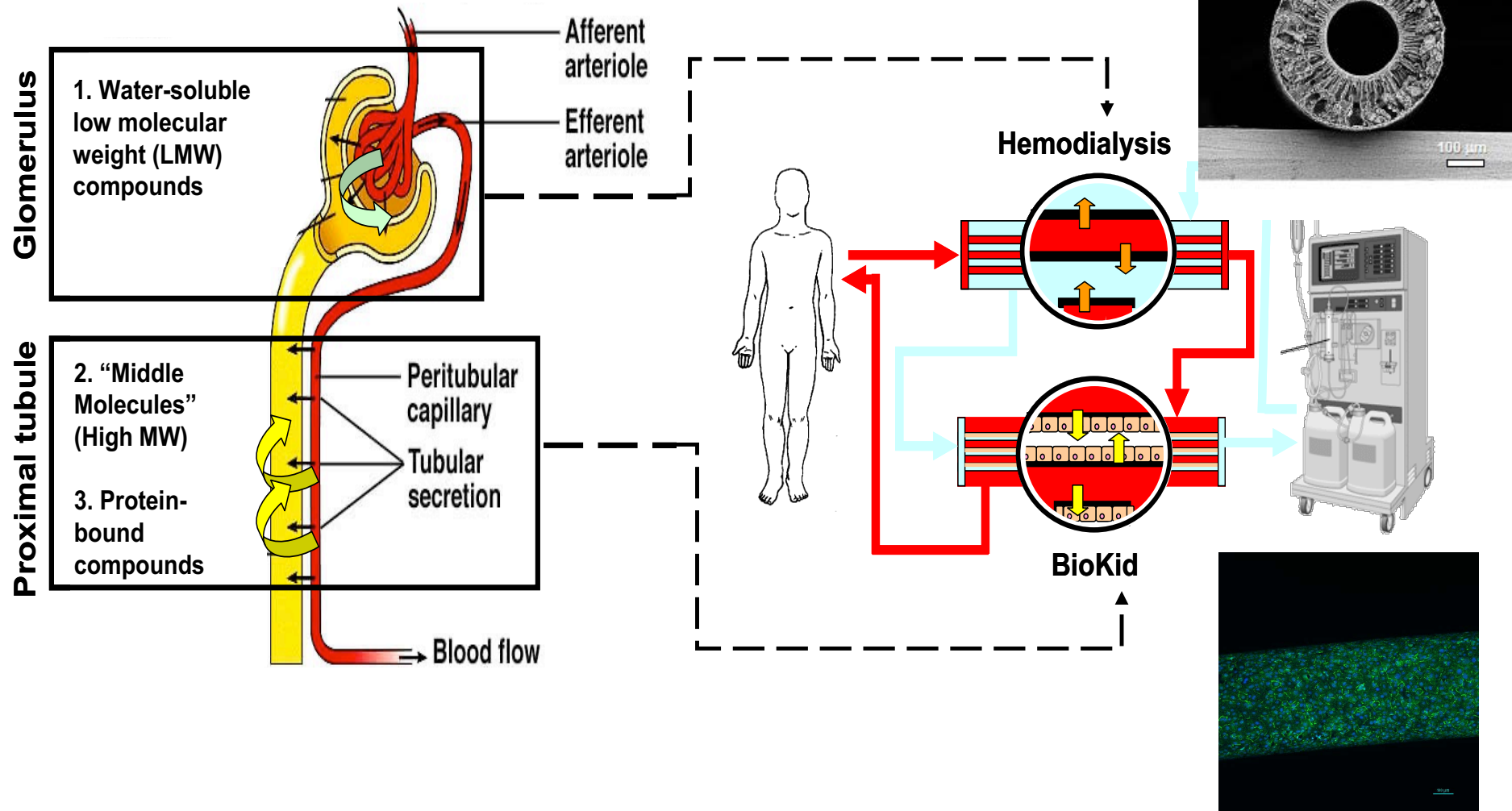
# Functional assays of PTEC on single hollow fibers

## Organic anion transporters (OAT)



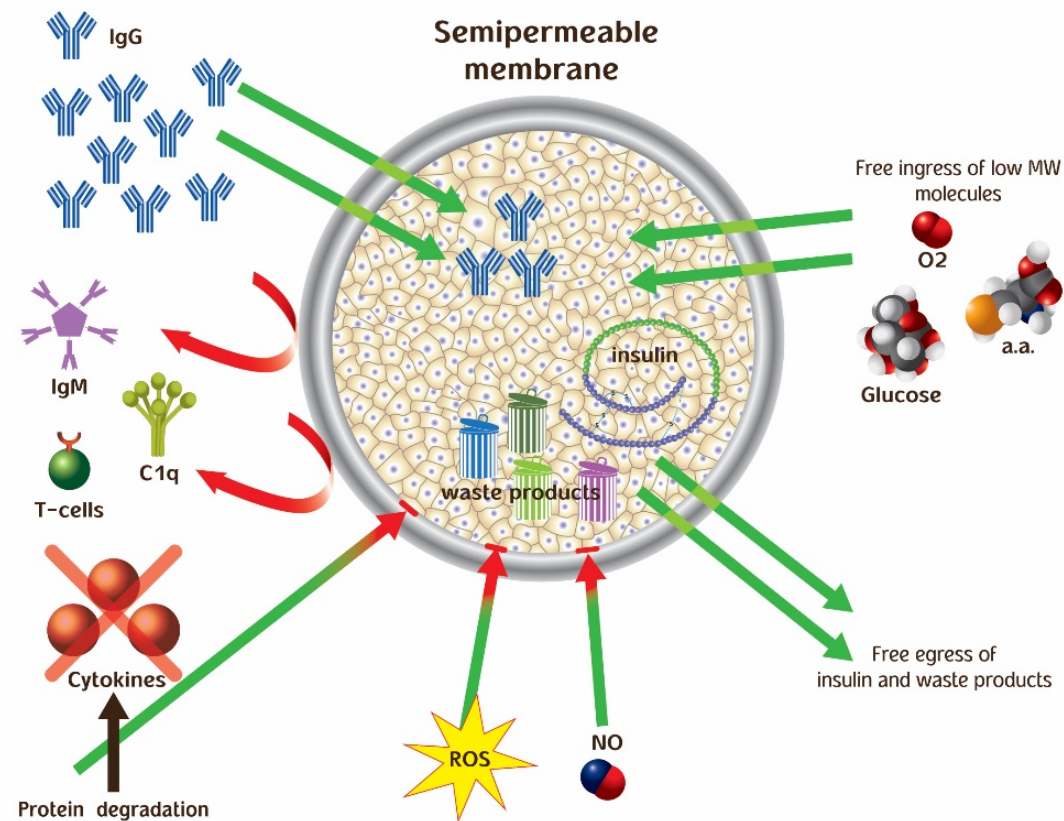


## Mixed matrix membrane



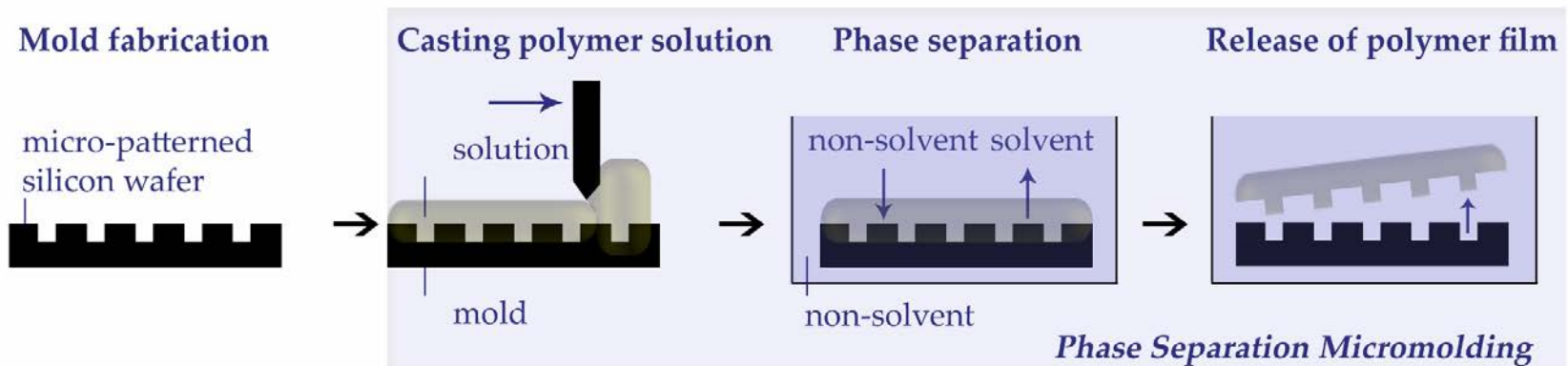
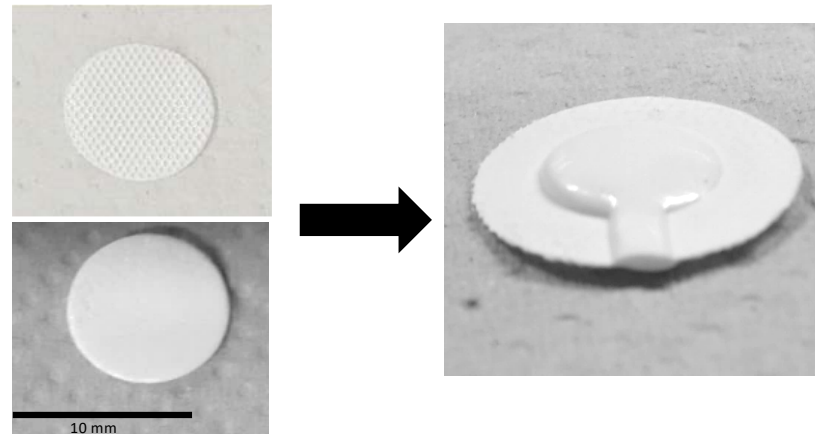


# Bioartificial pancreas

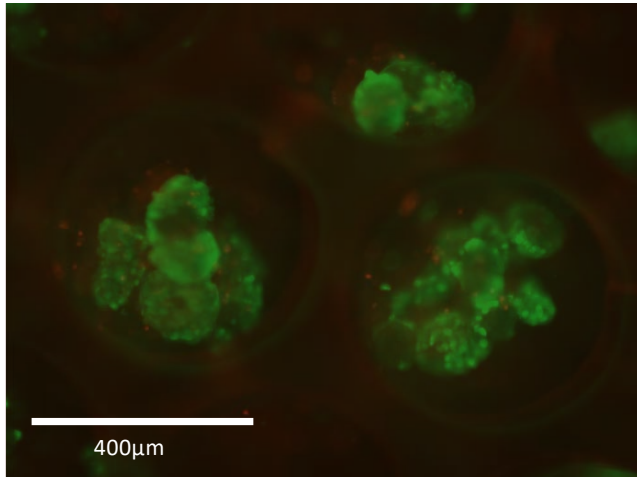


Barkai U, Rotem A, de Vos P. Survival of encapsulated islets: More than a membrane story. World journal of transplantation 2016;6:69-90.

# Micropatterned porous membranes



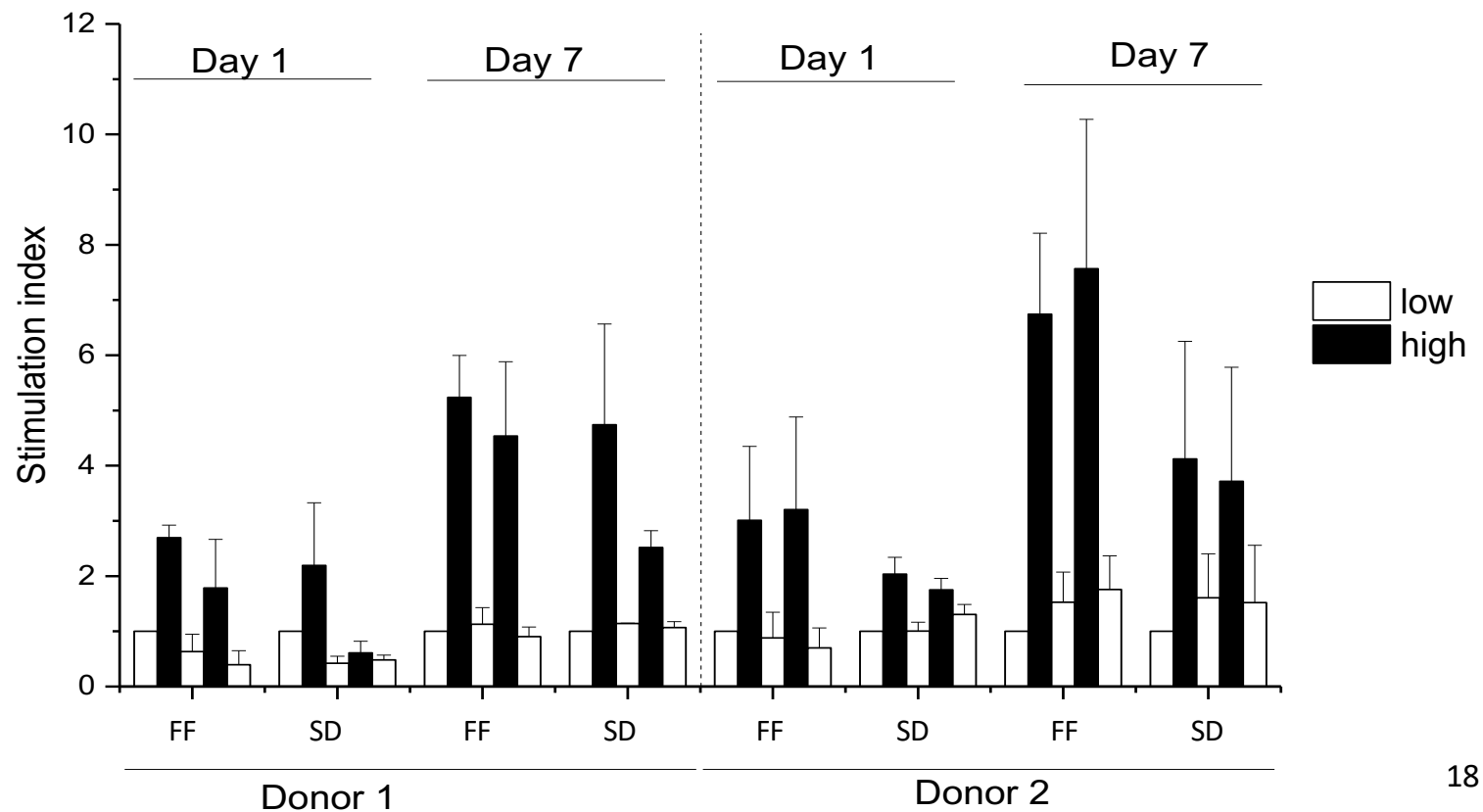
# Human islets encapsulation



Green – live cells  
Red – dead cells

FF – free floating islets

SD- sealed device with  
encapsulated islets



Stim

A



+

B

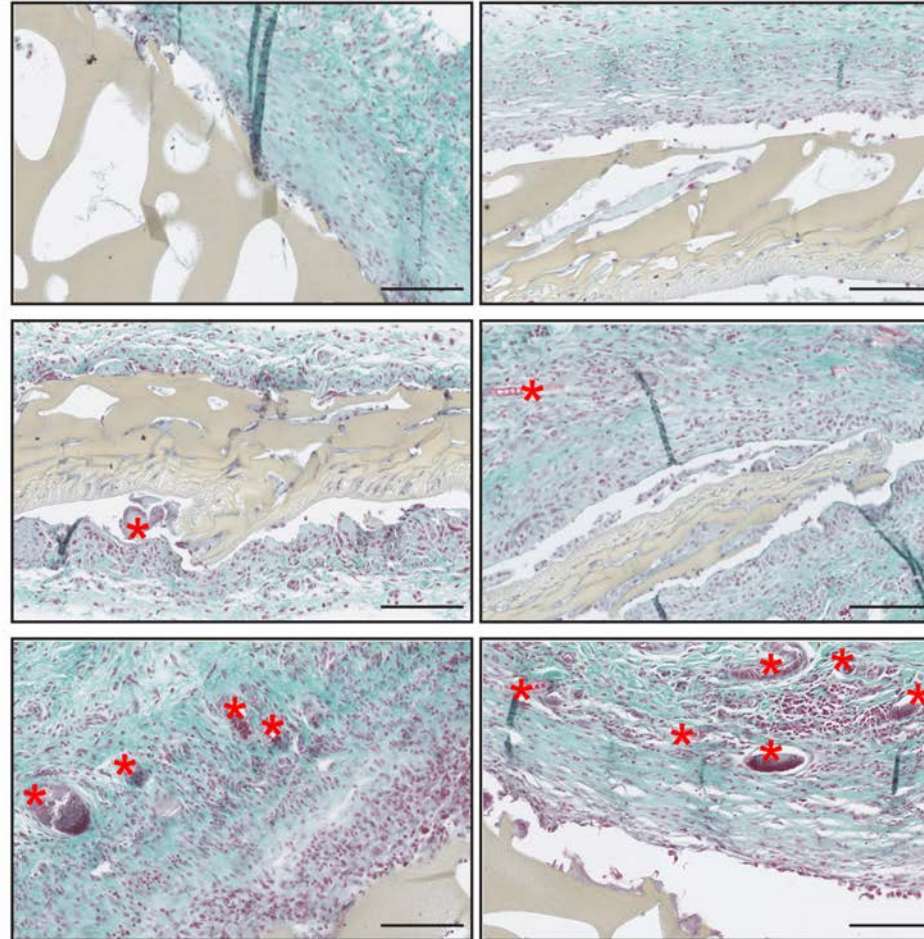


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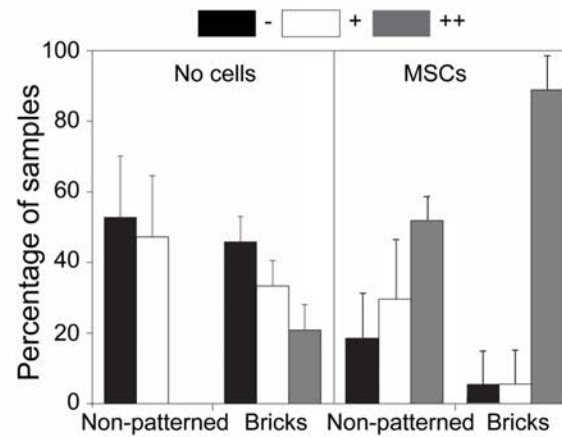
A

No cells

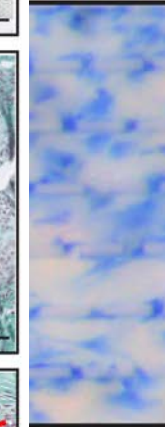
MSCs



B



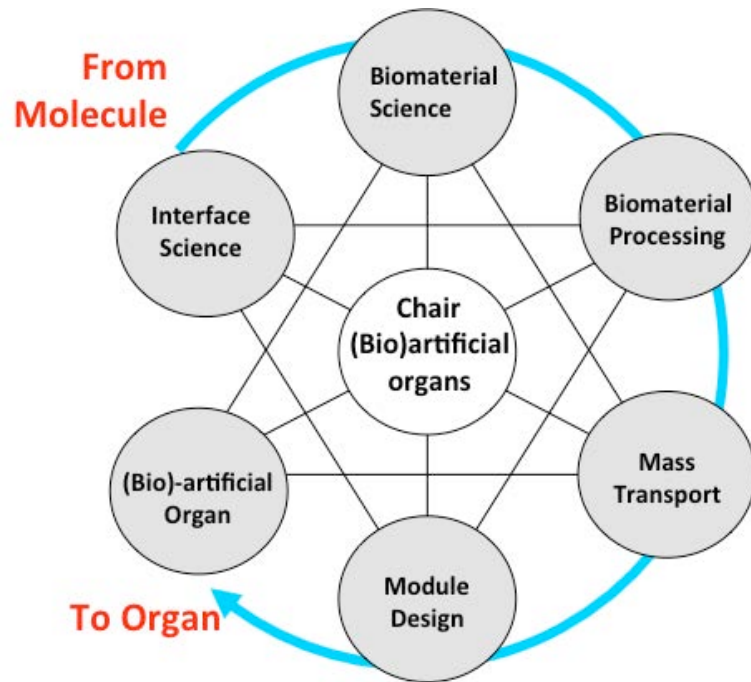
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ne 2018



# It is challenging!



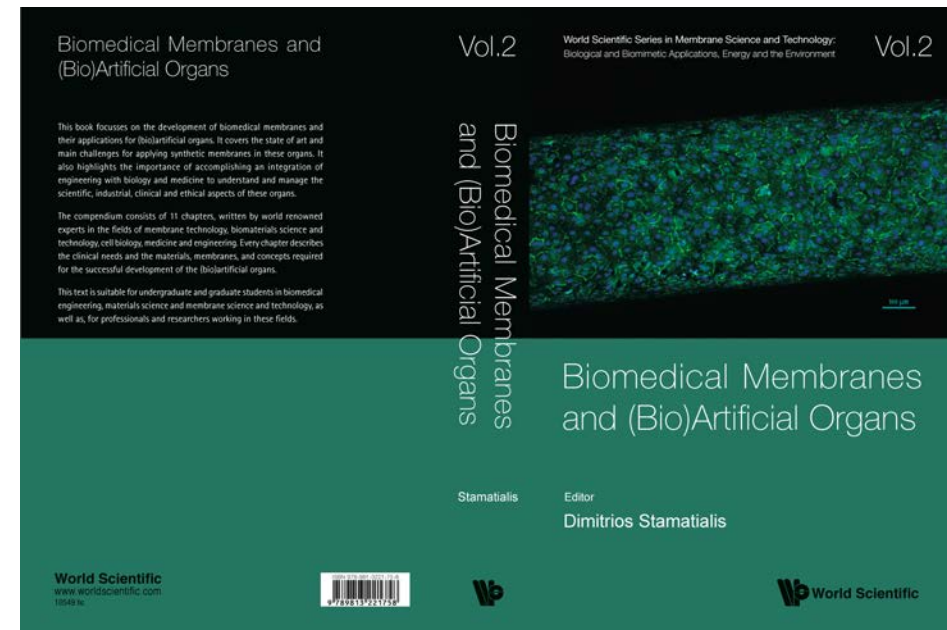
## Complexity increases

Artificial to Bioartificial to.. tissue engineered...

From extracorporeal to implantable...

## It takes time

*In vitro* to *in vivo*



# Acknowledgements

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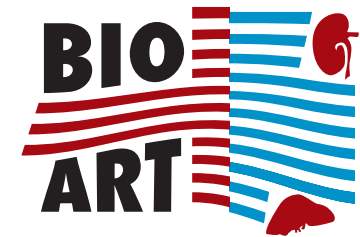
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