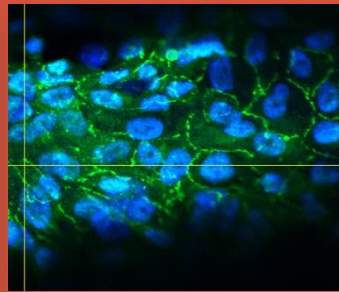
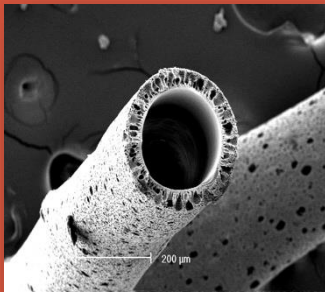


Studying disposition of uremic waste products: can we develop novel therapeutic strategies to treat chronic kidney disease?



Roos Masereeuw, *div. Pharmacology*
Utrecht Institute for Pharmaceutical Sciences, NL



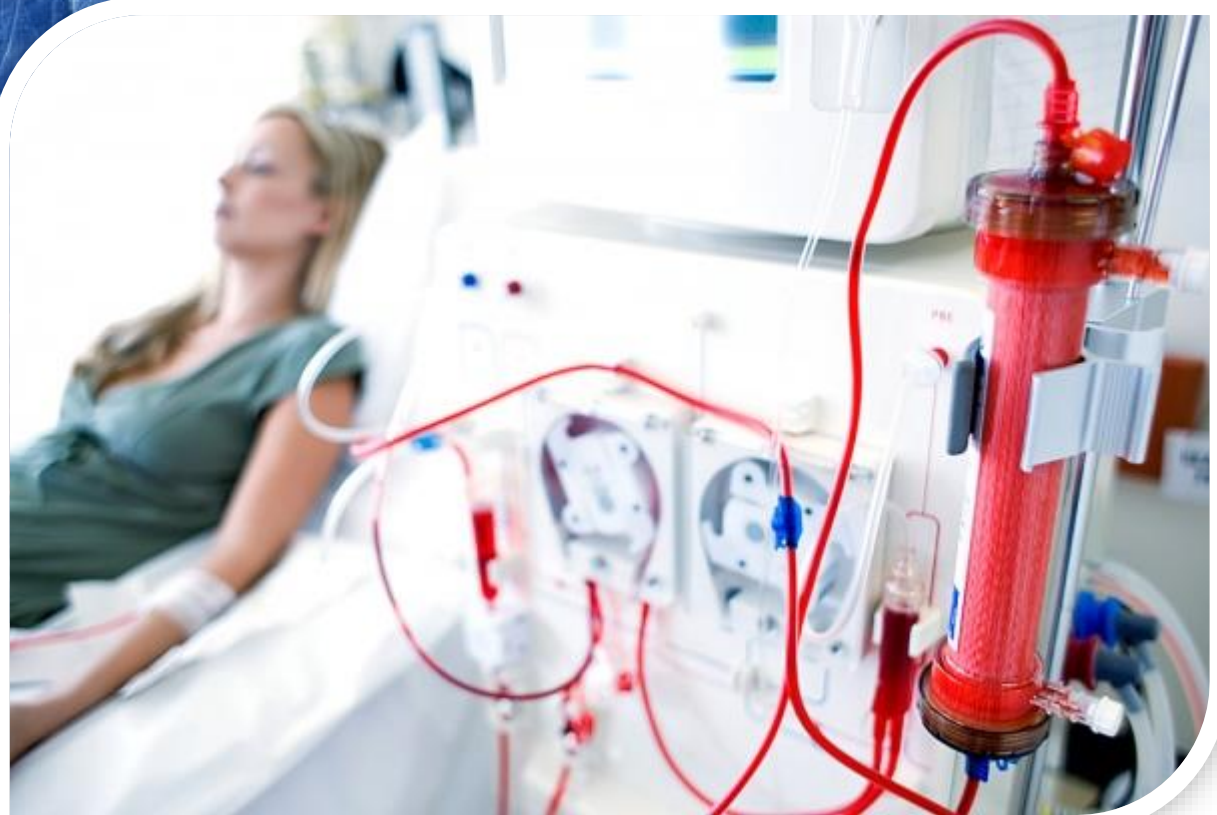
Universiteit Utrecht

27 April 2018

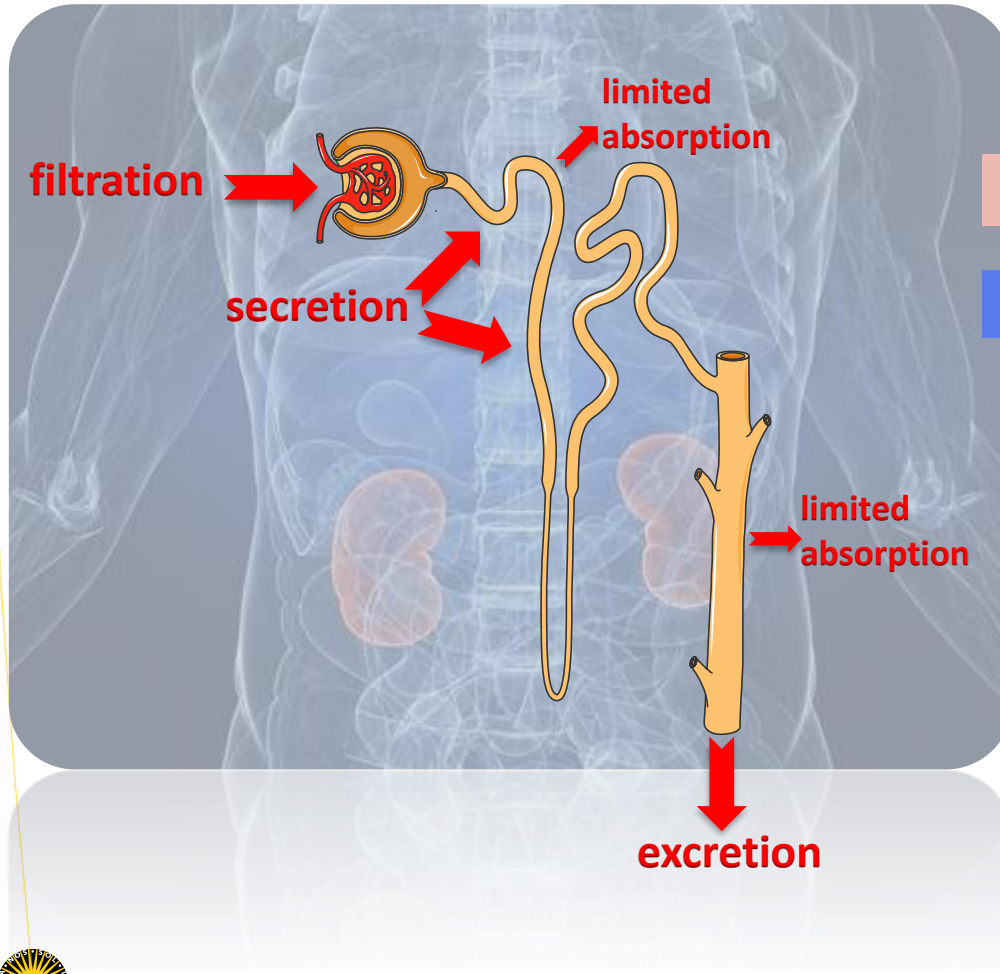


Universiteit Utrecht

Chronic kidney disease

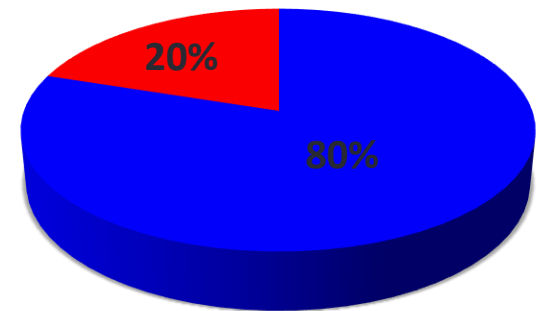


Renal xenobiotic excretion by filtration and secretion

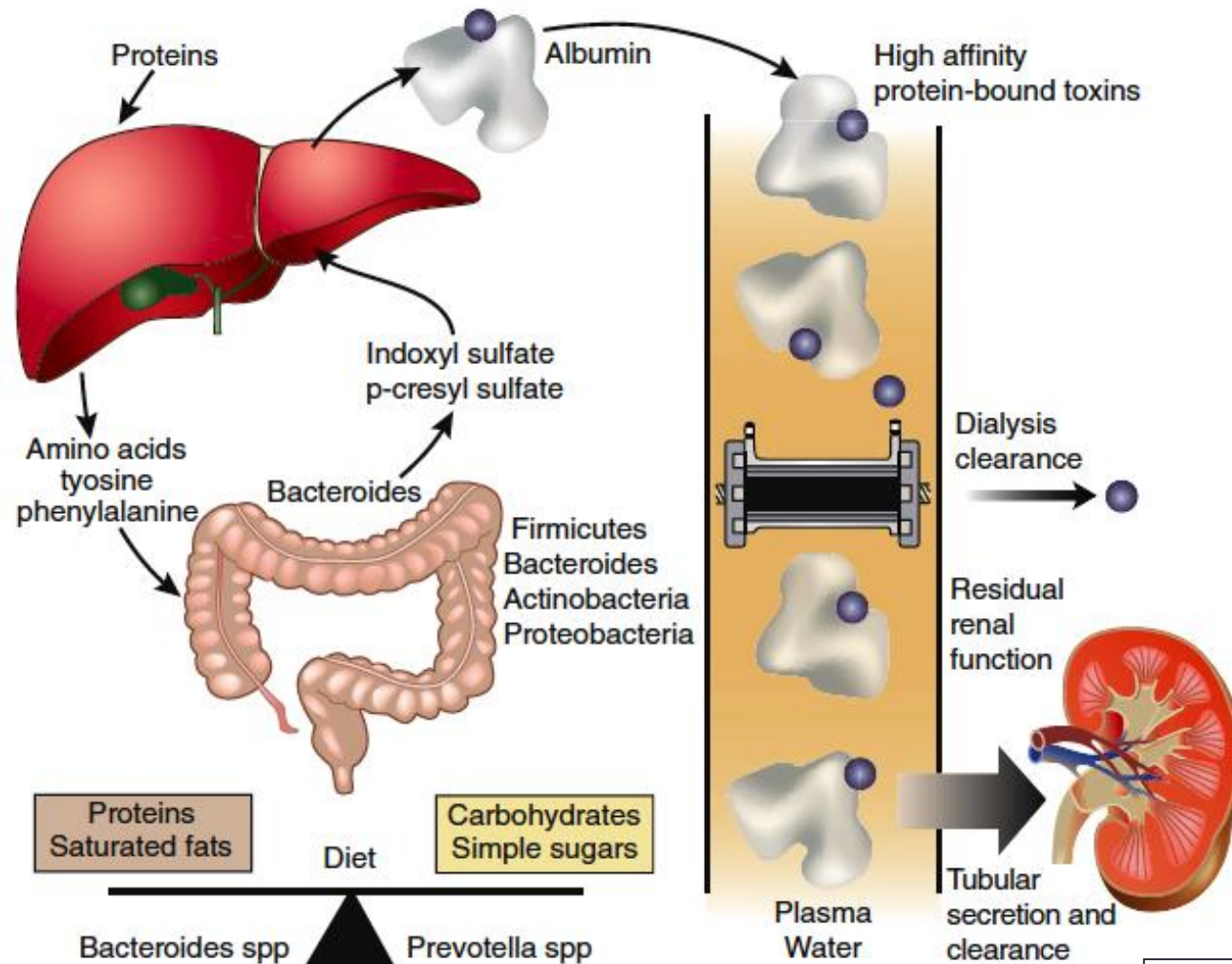


$$\text{Filtration} = f_u [\text{Comp}] \cdot \text{GFR}$$

$$\text{Secretion} = f_u [\text{Comp}] \cdot V_{\text{max}} / (K_m + f_u [\text{Comp}])$$

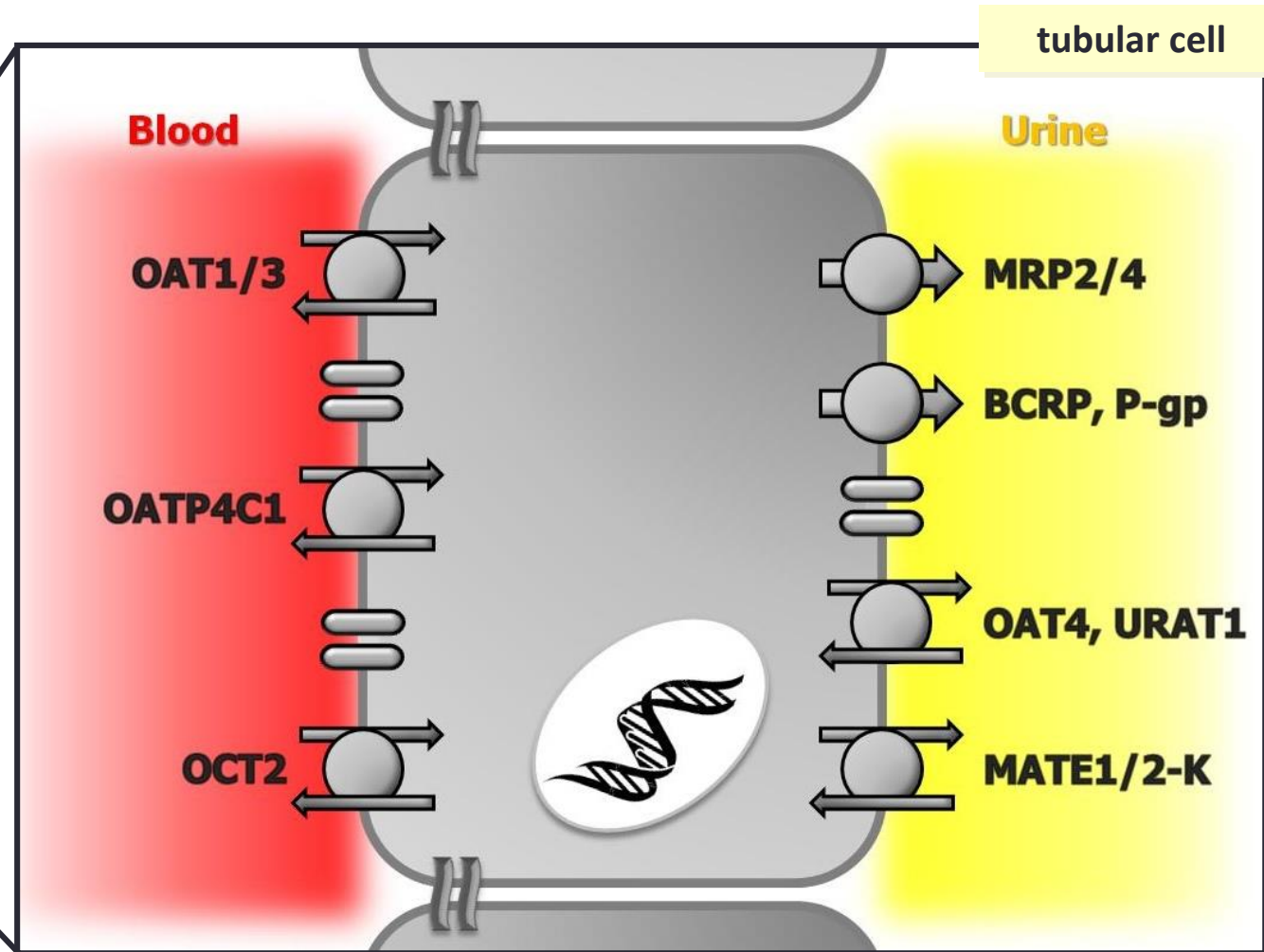
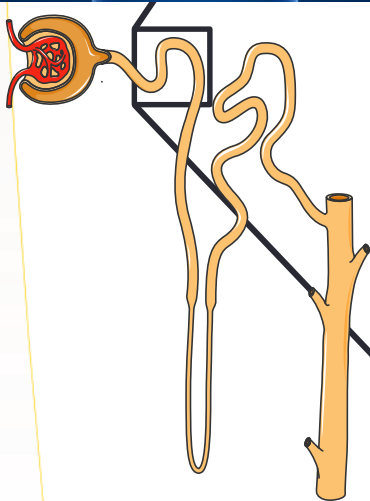
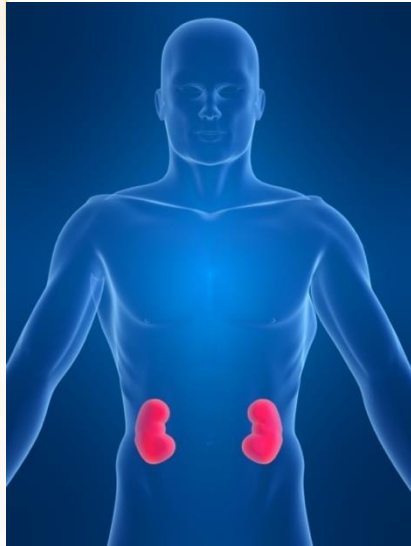


Dialysis clearance is limited for protein-bound uremic toxins

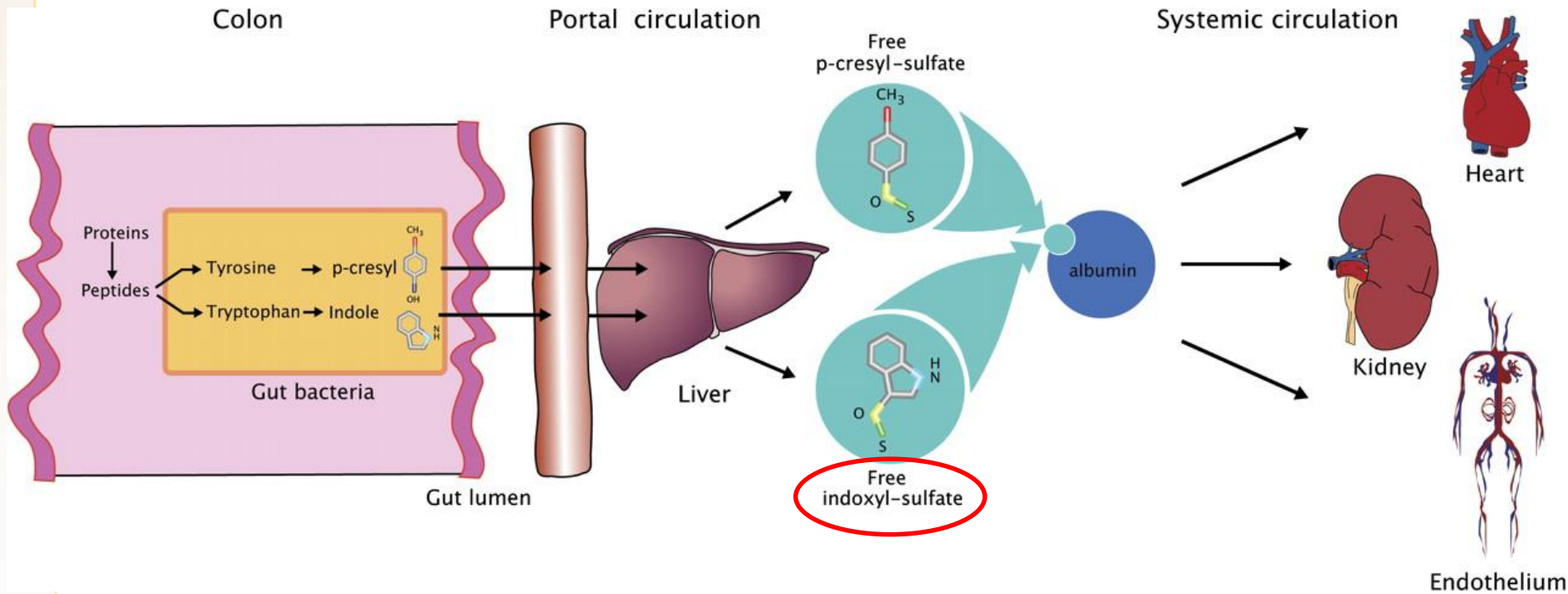




Renal xenobiotic excretion



Chronic kidney disease: uremic toxins



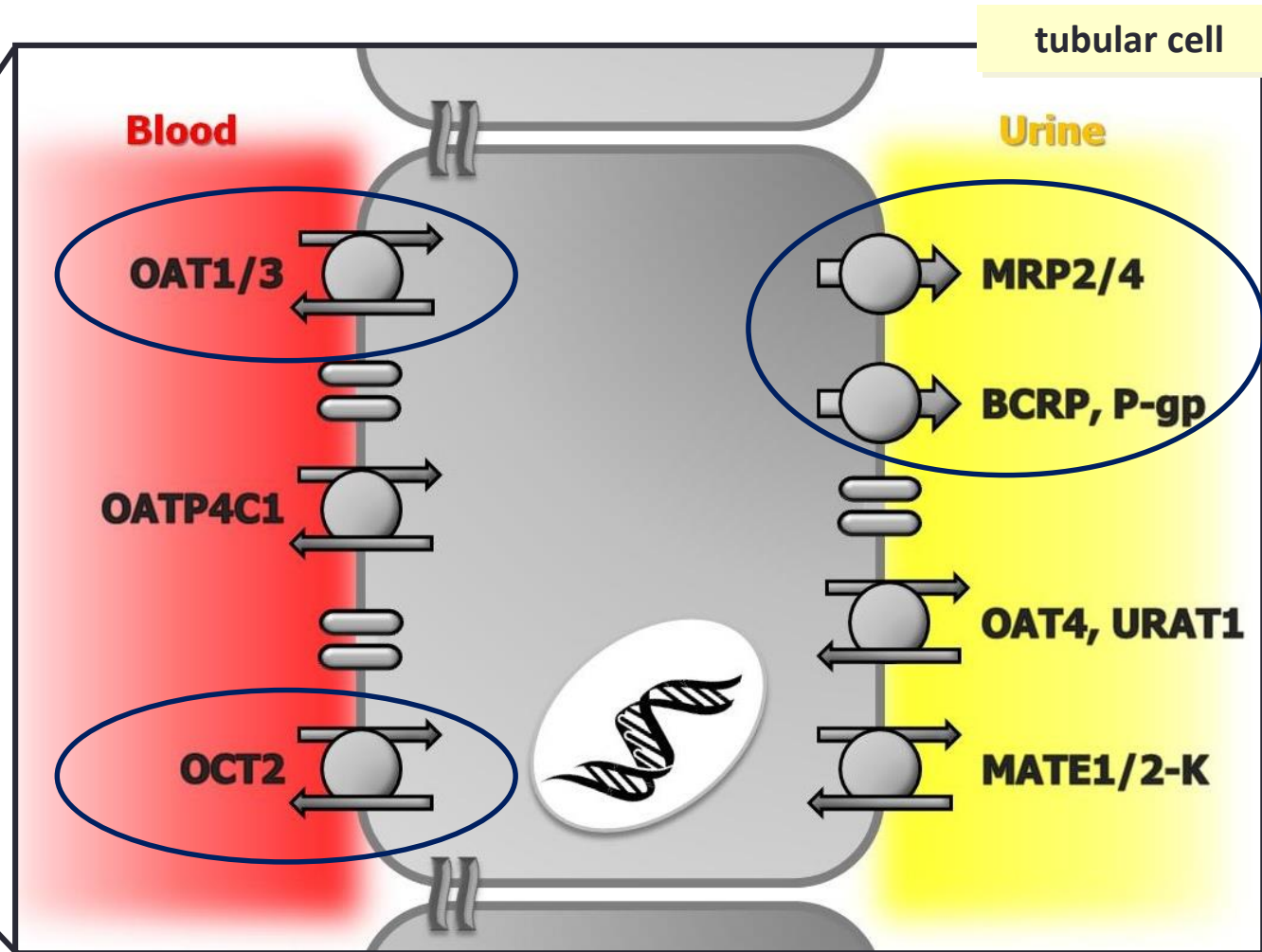
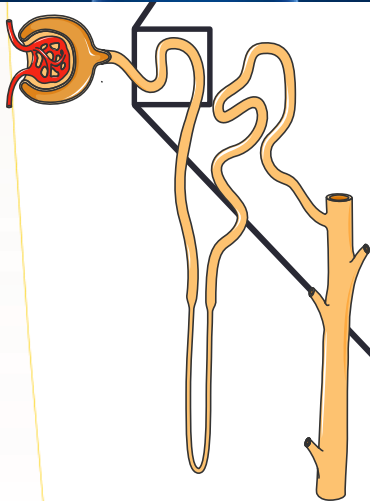
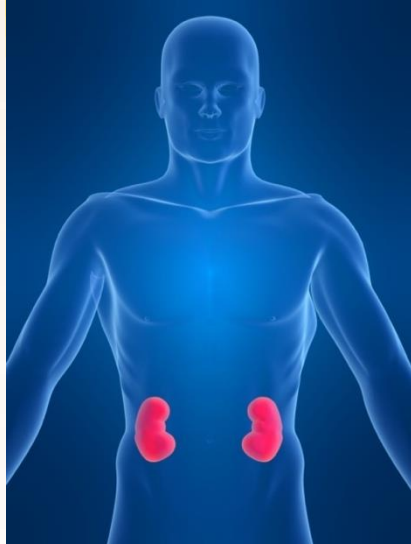
Classification:

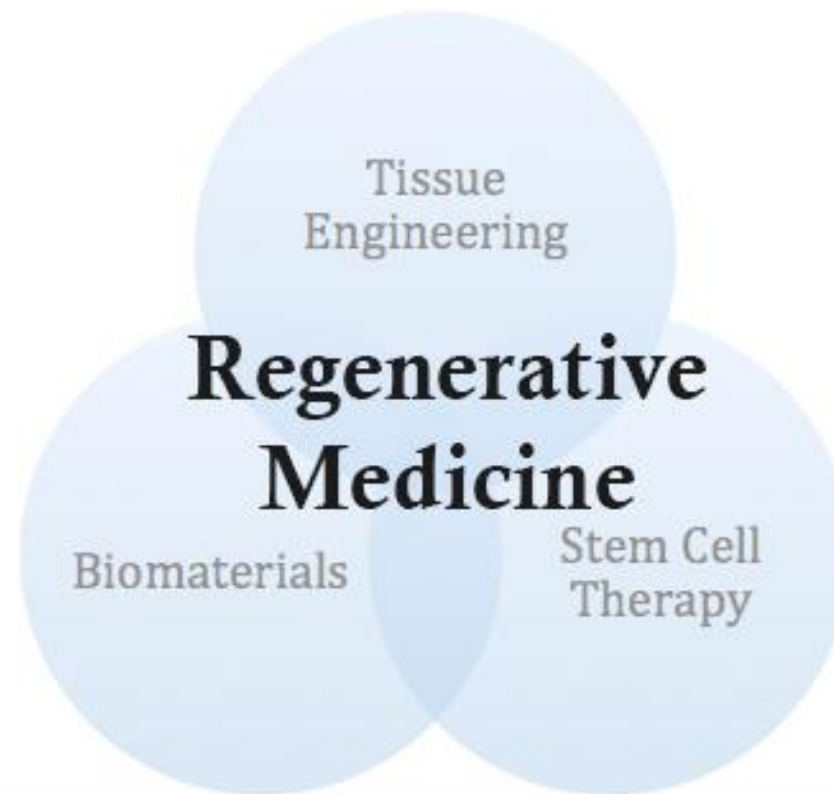
- Small water-soluble compounds (< 500 Da)
- Middle molecules (> 500 Da)
- Protein-bound compounds
e.g. phenols and indoles

Pathologies

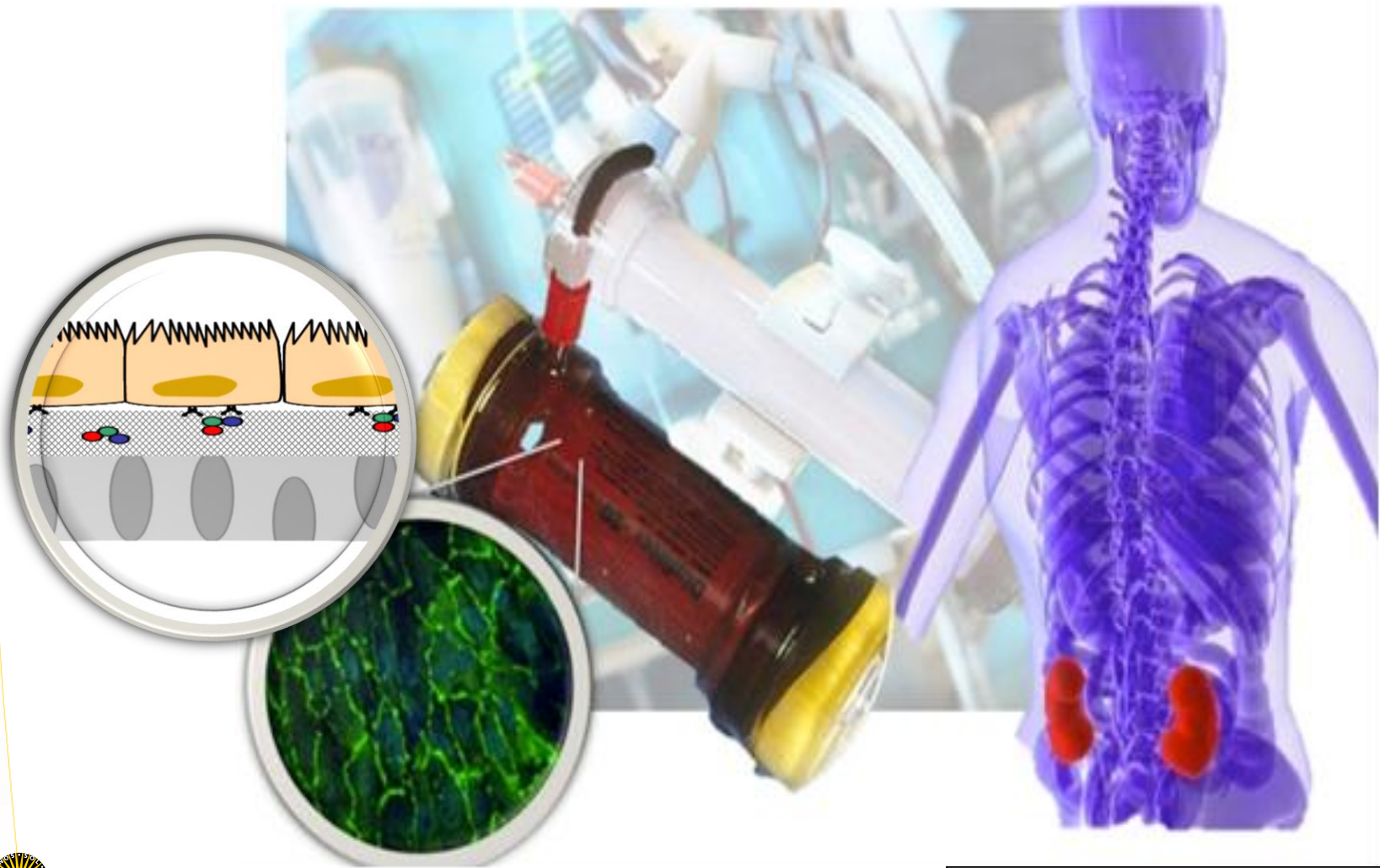
- Renal fibrosis
- Cardiovascular complications
- Cognitive disorders
- ...

Renal uremic toxin handling

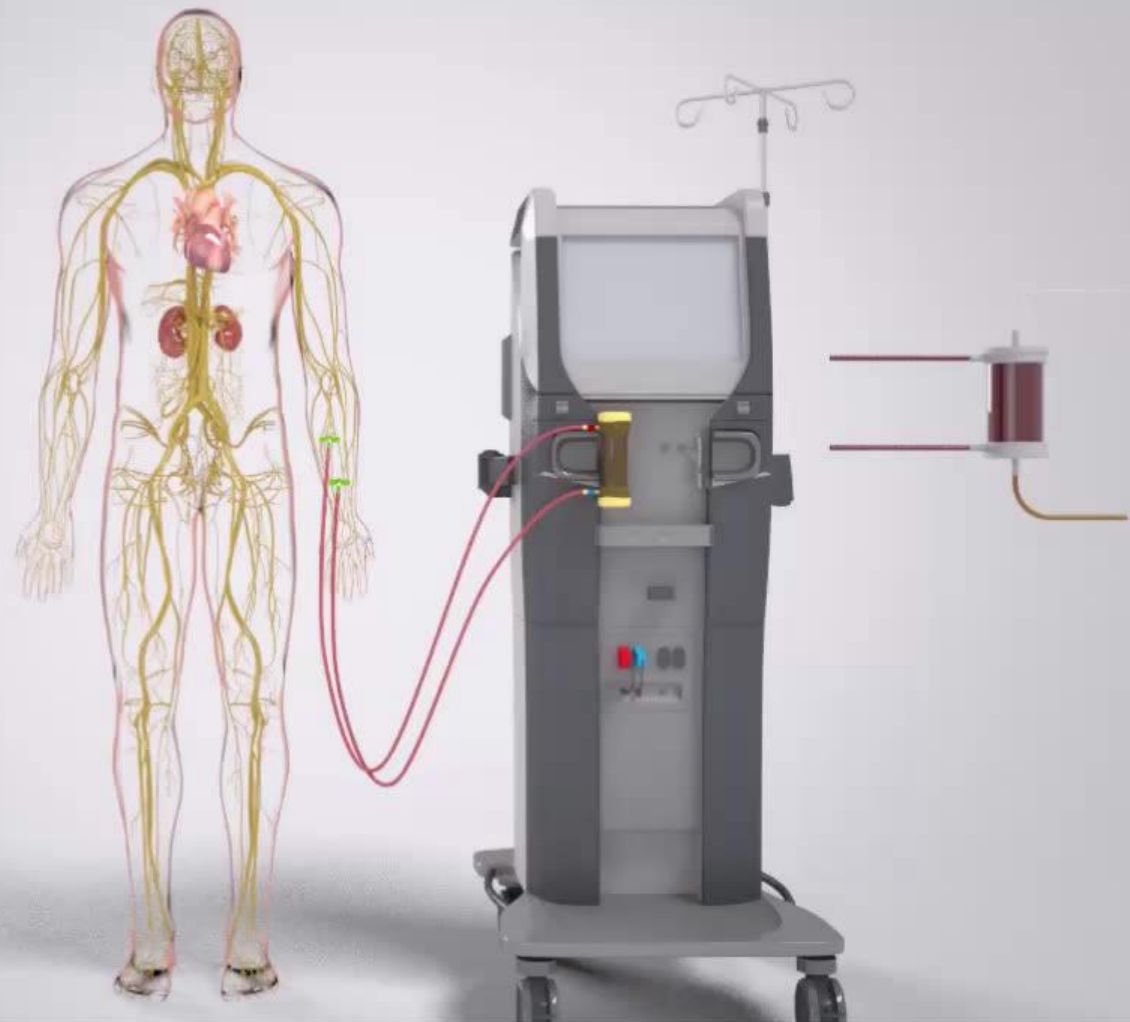




Bioartificial kidney development



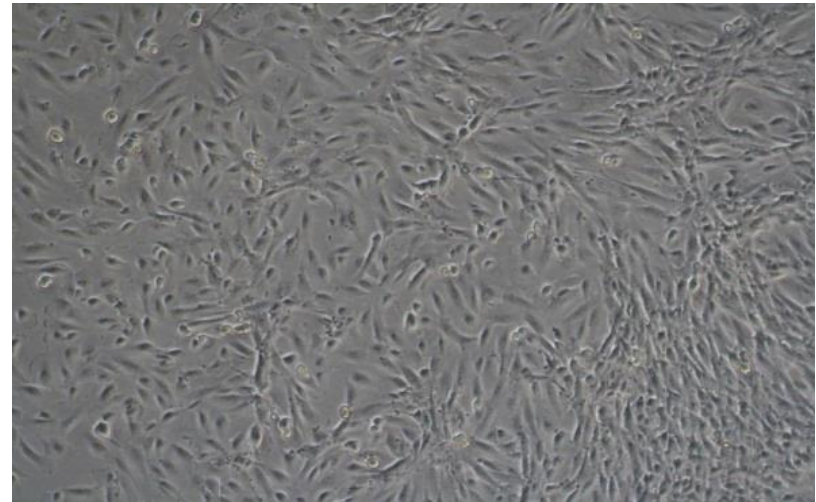
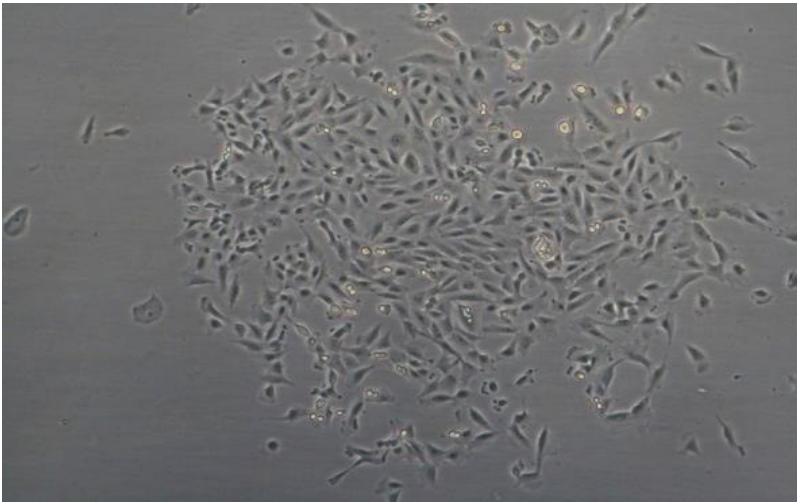
Bioartificial kidney



A unique human renal cell line: ciPTEC

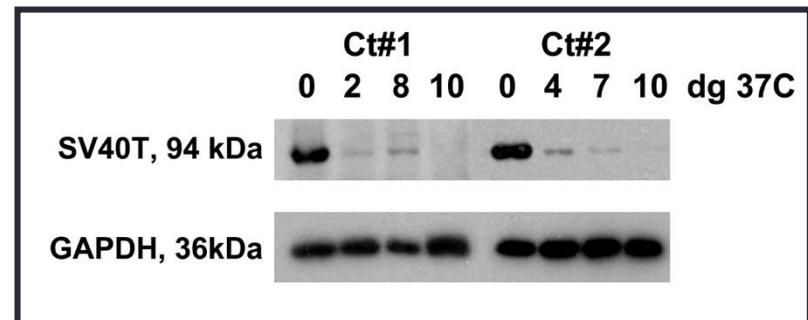


Conditionally Immortalized Proximal Tubular Epithelial Cell (ciPTEC)

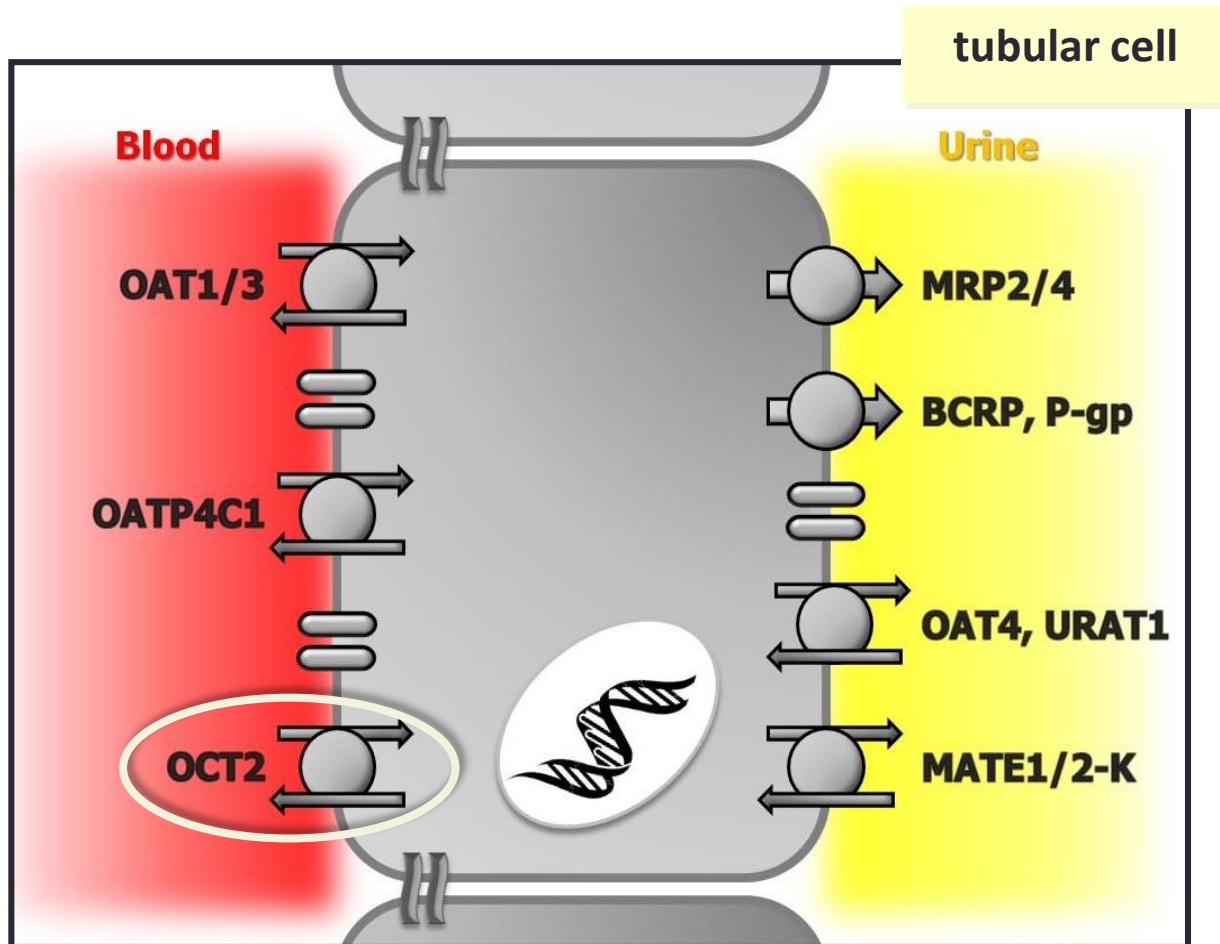


■ Immortalization:

1. SV40T tsA58 U19
2. hTERT

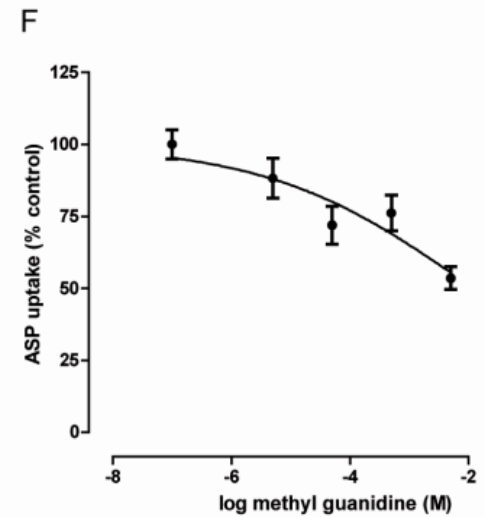
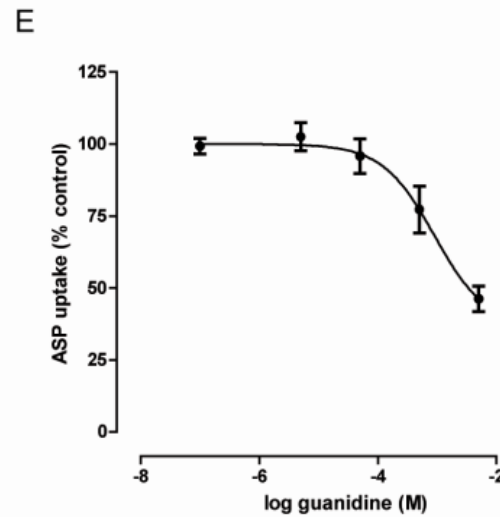
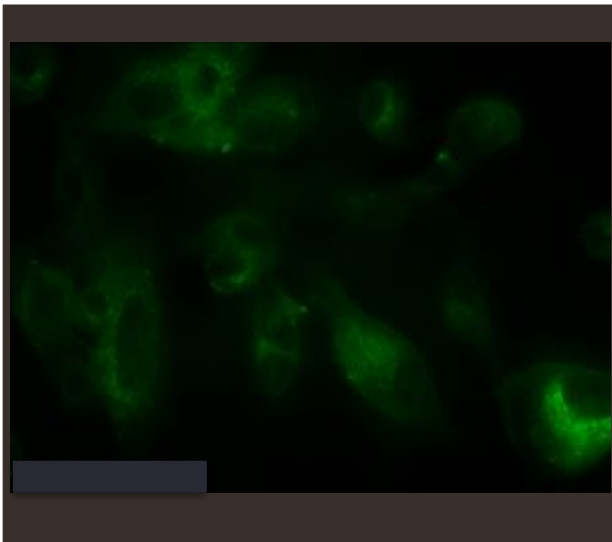
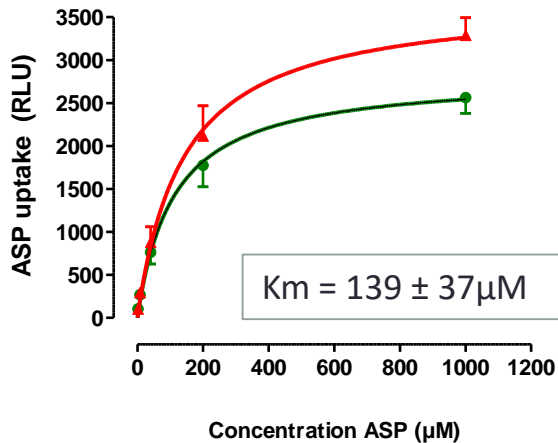


Renal xenobiotic transporters for uremic toxins



Proximal tubule cell OCT2 transport

OCT2 in ciPTEC

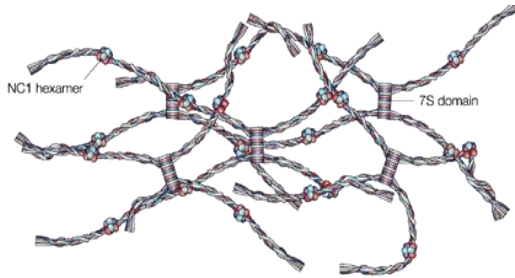


Guanidines inhibit the OCT2 transporters at high doses

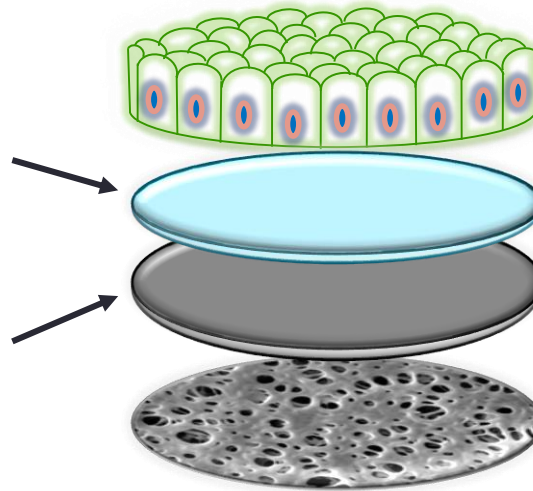


Bioartificial kidney development: living membranes

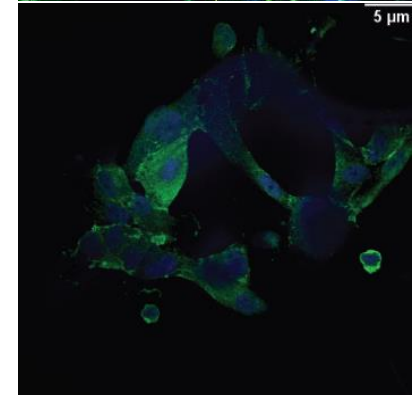
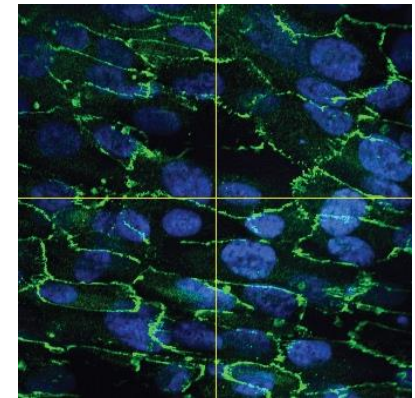
Collagen IV



L-Dopa



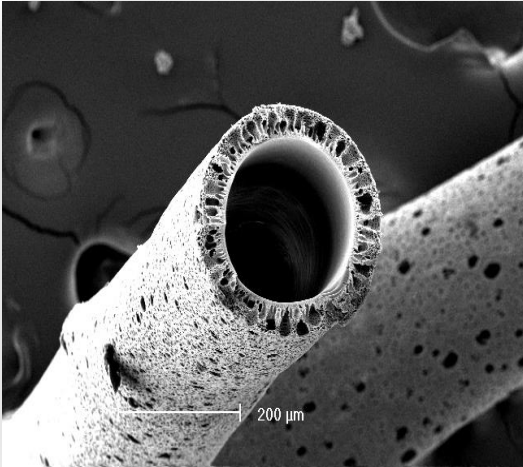
Coated membrane



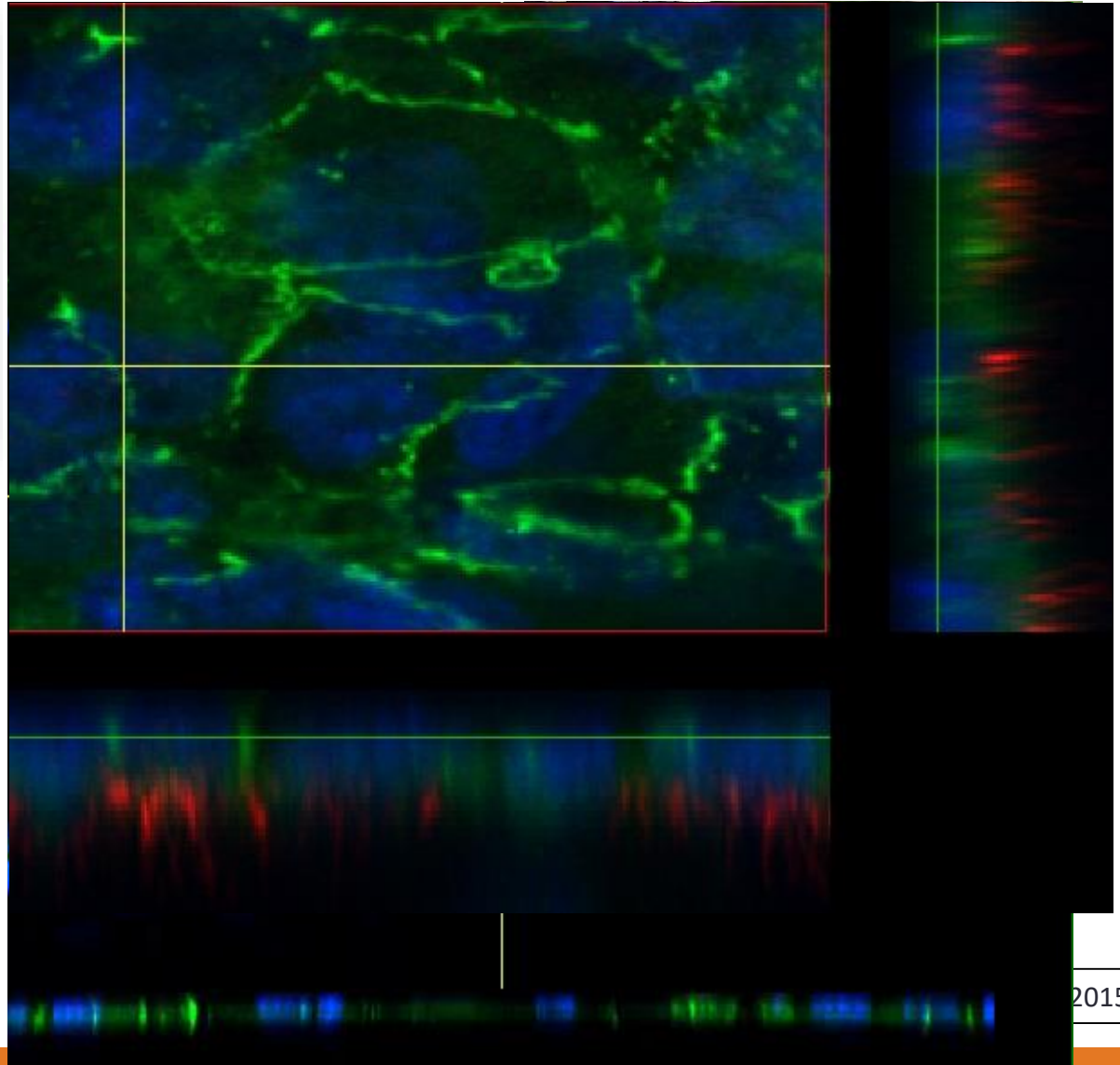
Uncoated membrane



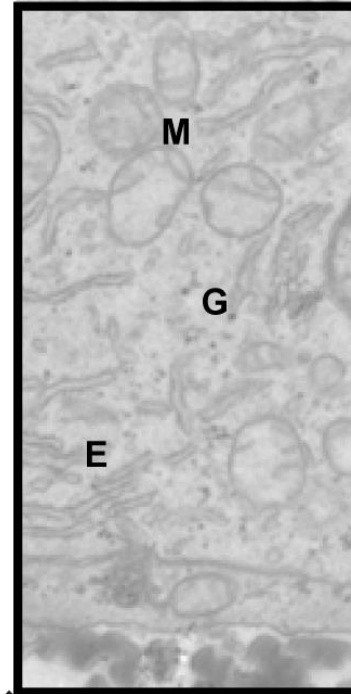
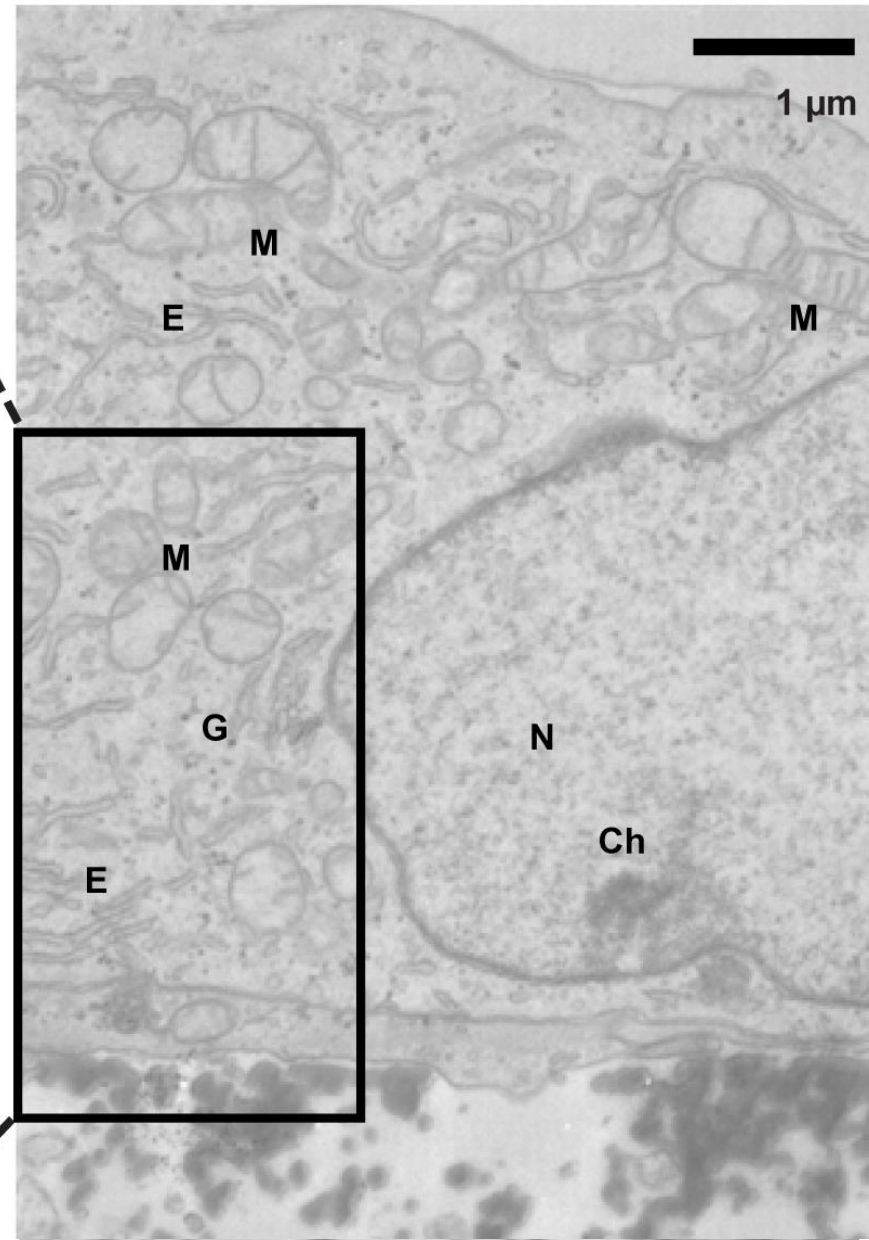
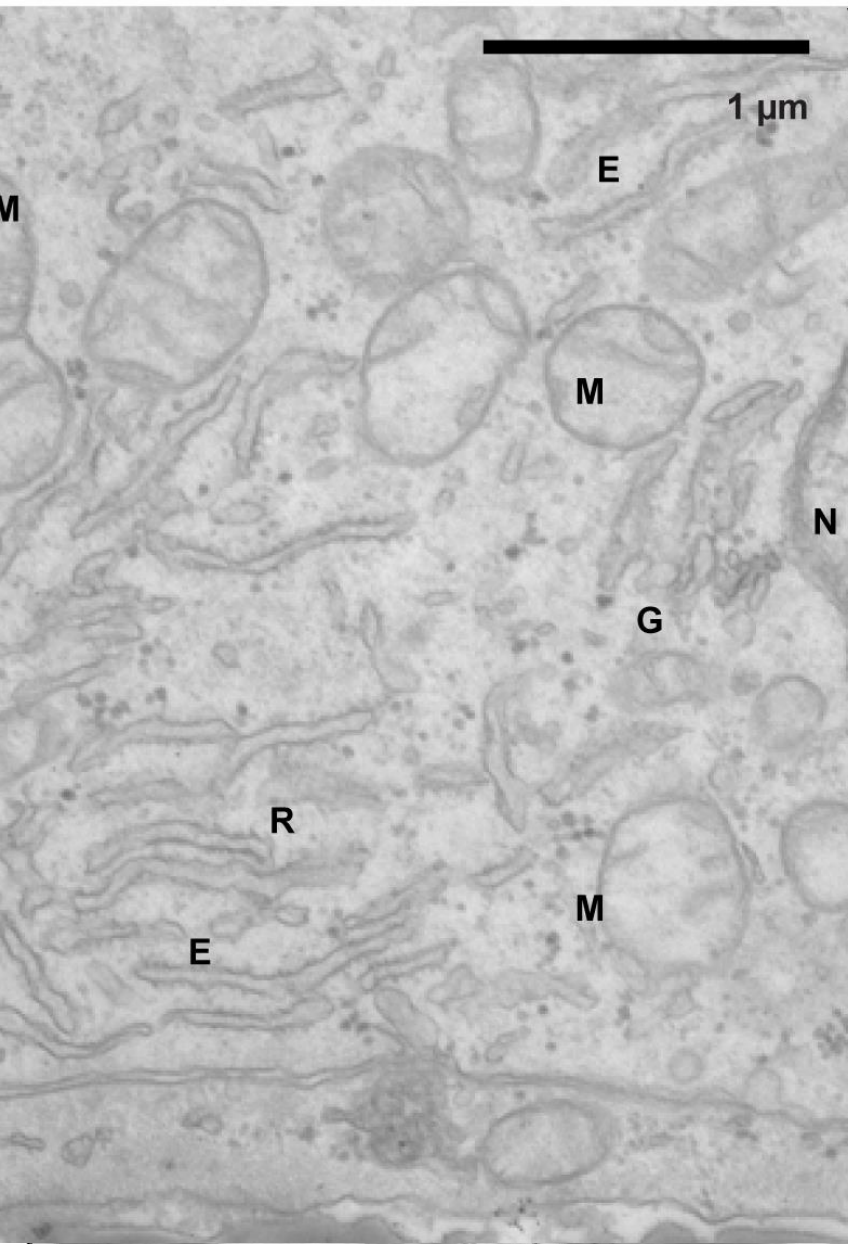
Bioengineered kidney tubules



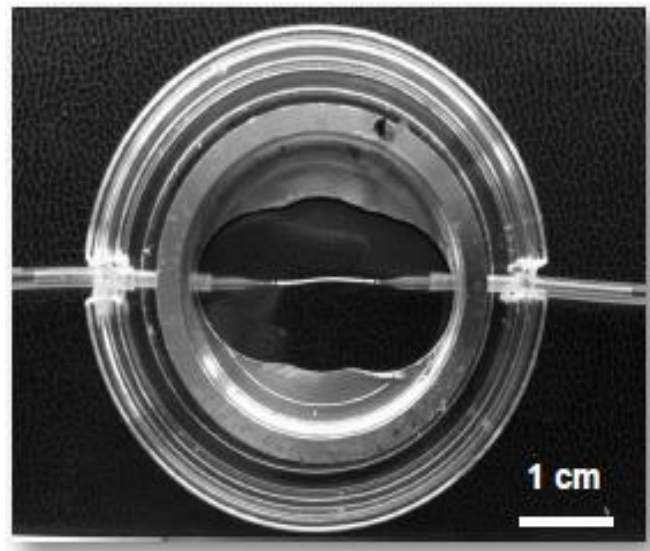
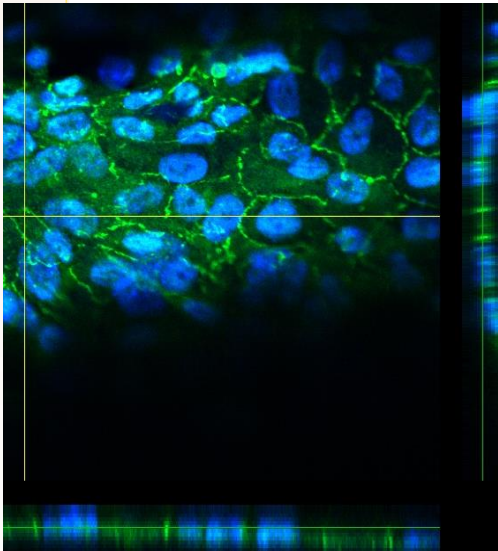
- ZO-1
- Nucleus
- OCT2



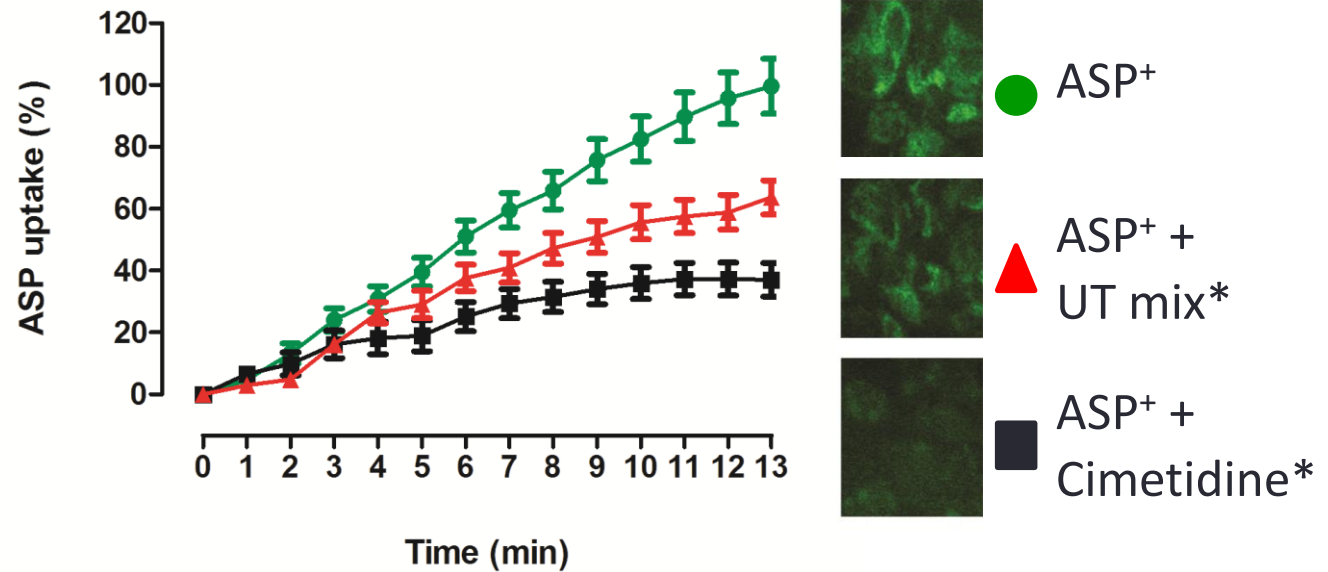
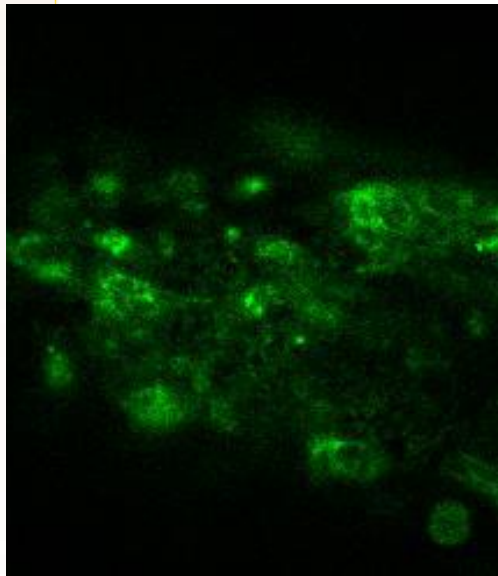
PTEC with intact organelle morphology on hollow fibers



Functional imaging of bioengineered kidney tubules



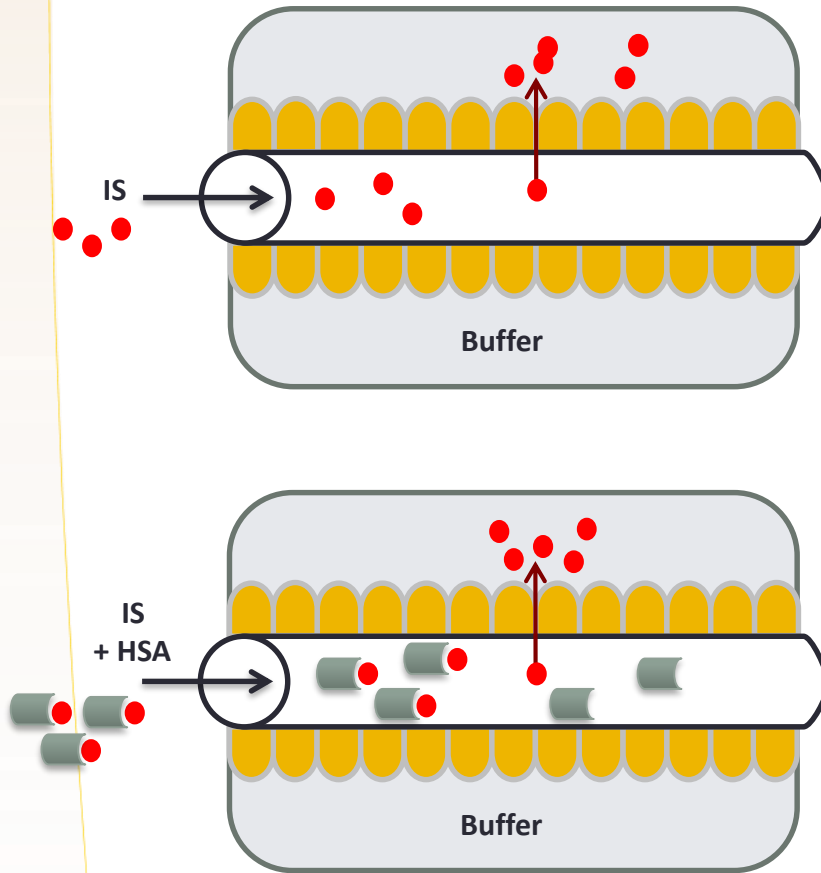
Functional imaging of bioengineered kidney tubules



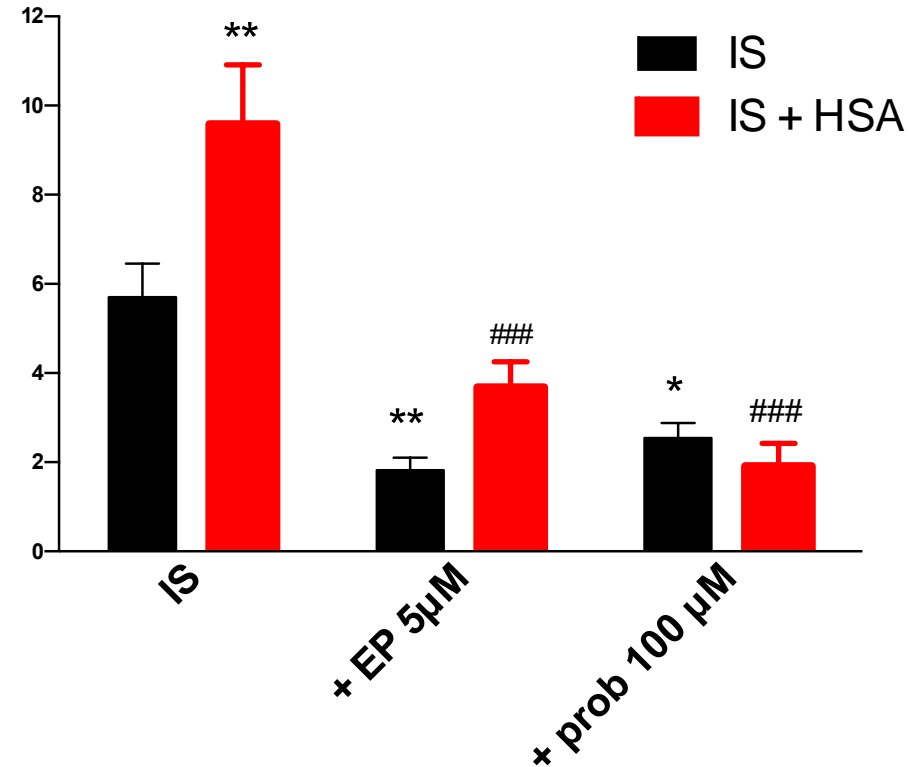
Bioengineered kidney tubules for renal excretion



Transepithelial transport of indoxyl sulfate



transepithelial IS transport
($\text{pmol} \cdot \text{min}^{-1} \cdot \text{cm}^{-2}$)

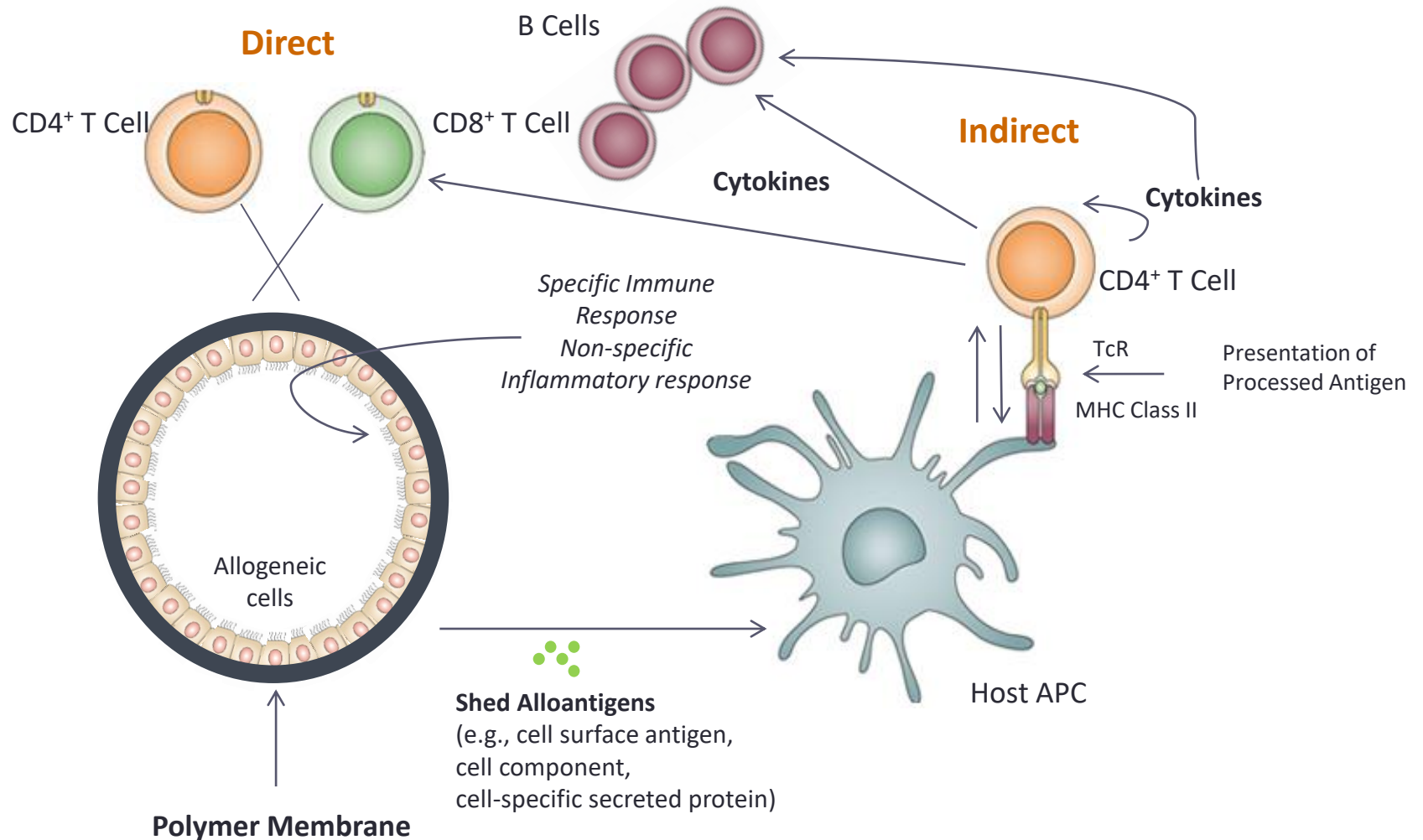


Biokid-current status and future perspectives

- After optimized coating, ciPTEC can grow on hollow fibers and remain functional, and allow for kinetic studies
- Investigate (pre-)clinical safety

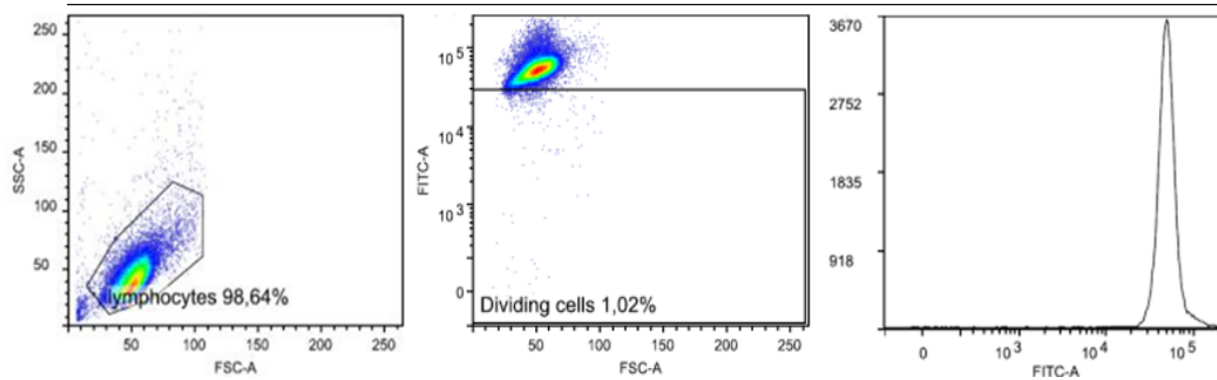


ciPTEC immunogenic response

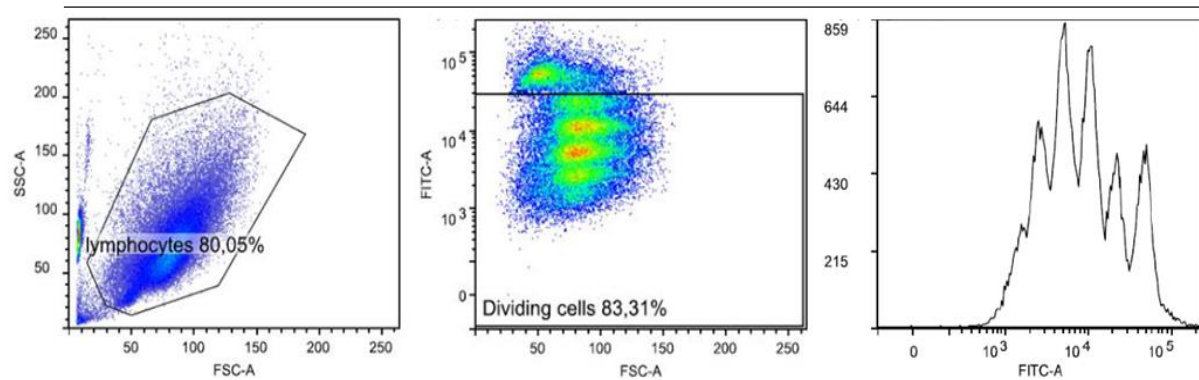


PBMC proliferation

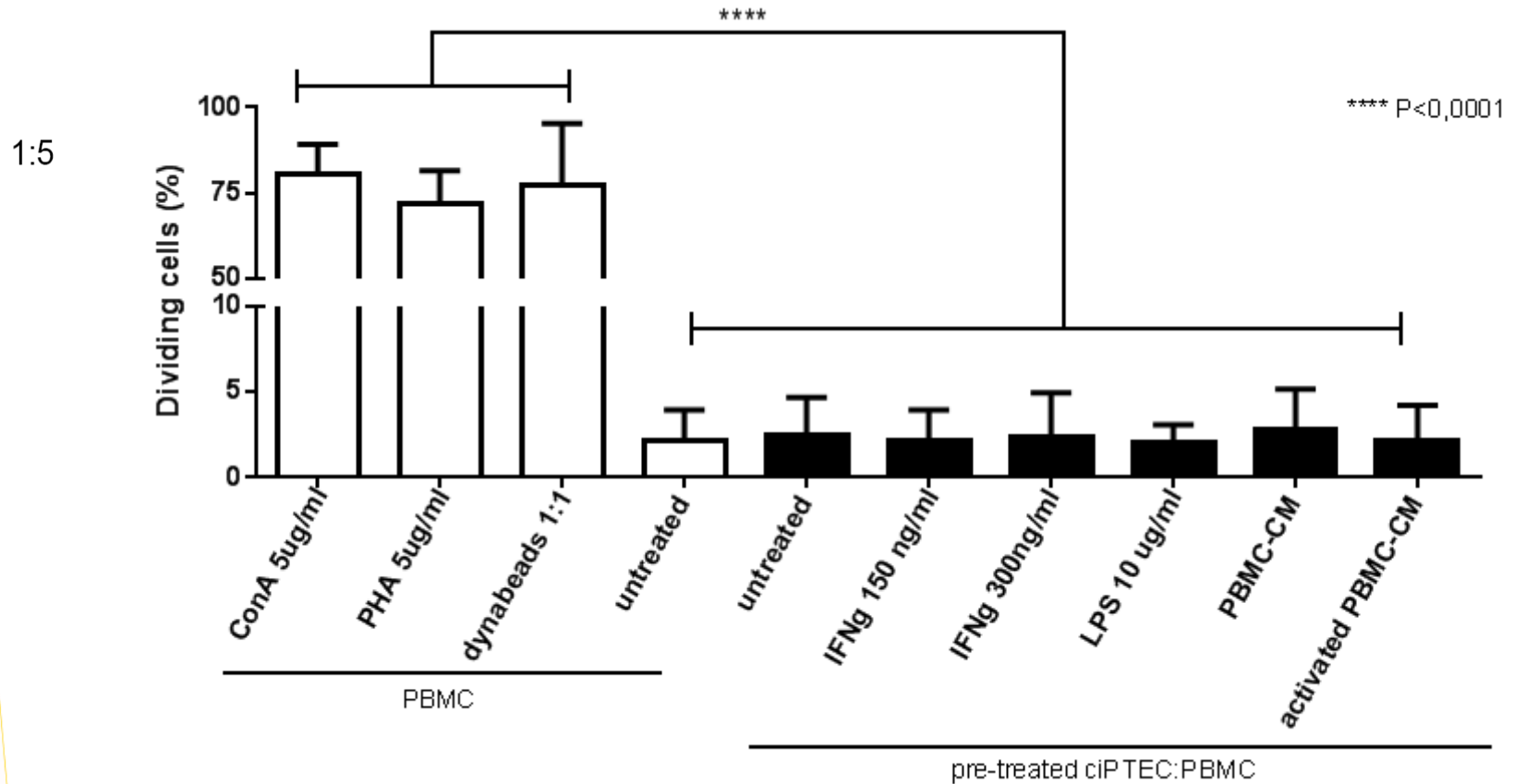
non activated PBMC



activated PBMC



Direct ciPTEC-PBMC co-culture: PBMC proliferation



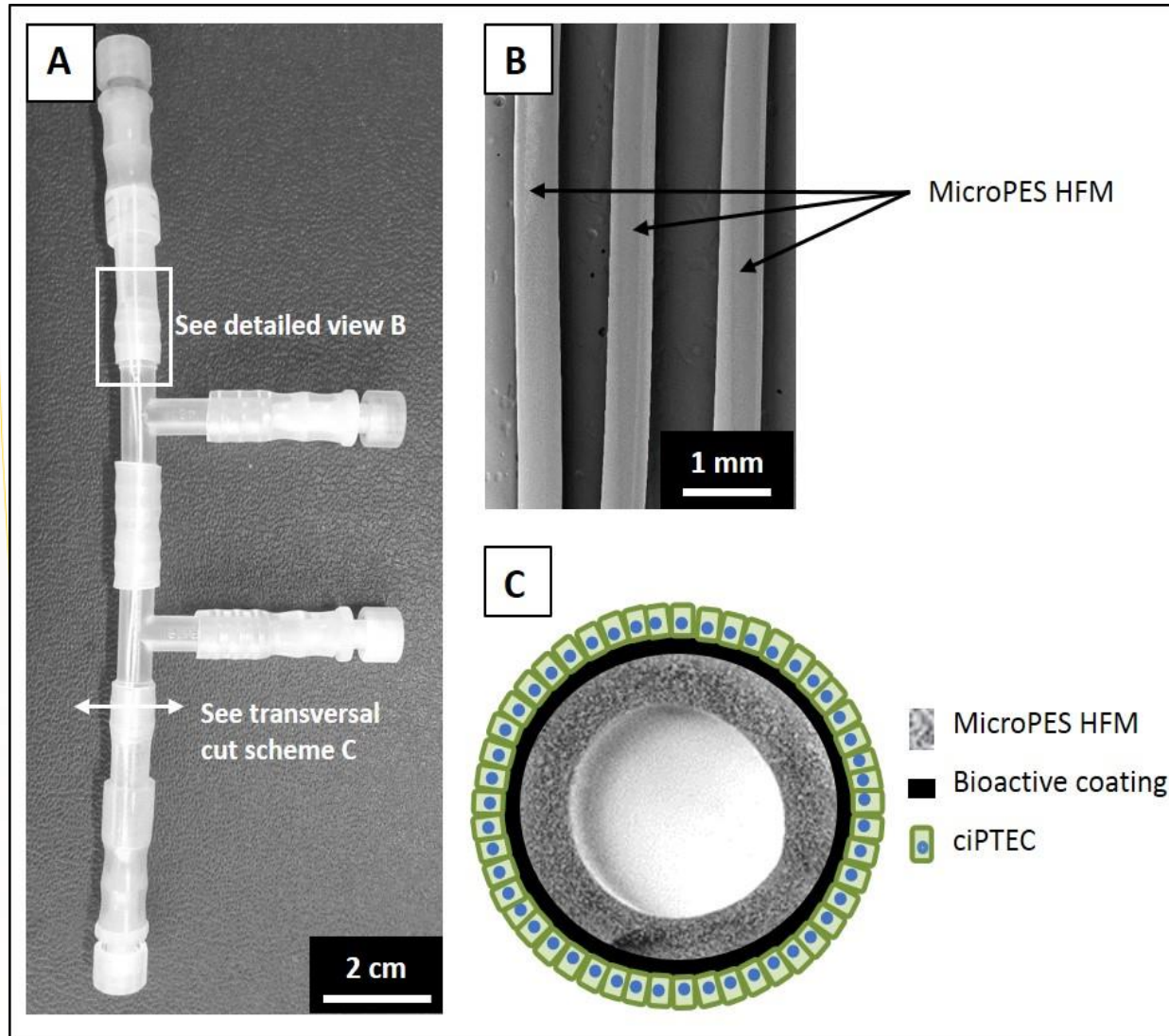
Biokid-current status and future perspectives

- After optimized coating, ciPTEC can grow on hollow fibers and remain functional, and allow for kinetic studies
- Proven *in vitro* safety
- Demonstrating function in upscaled device



Upscaled BAK modules, ongoing

Collaboration UTwente

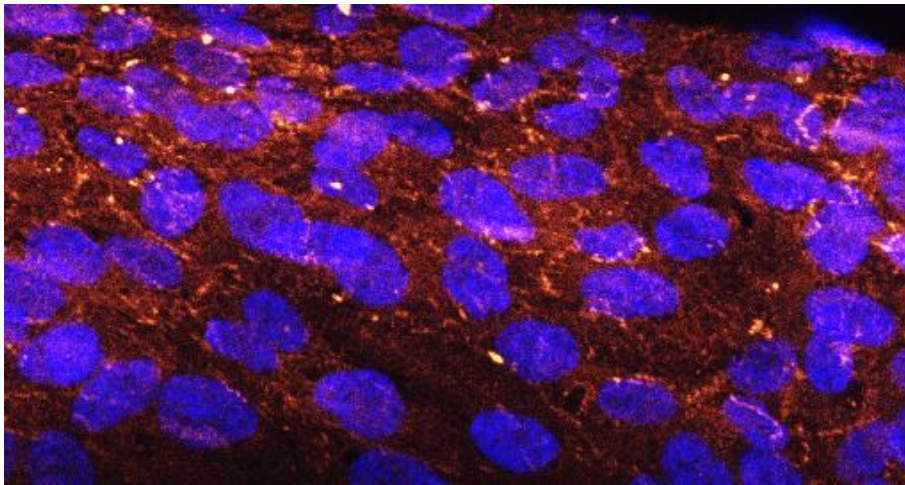


HFM length: 8.5 ± 0.5 cm

Surface: 4.01 ± 0.25 cm²

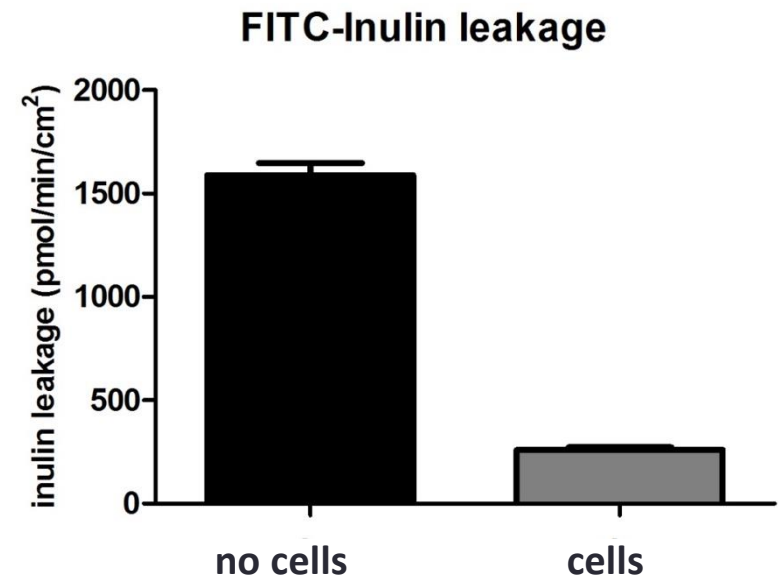
Upscaled BAK modules, ongoing

Collaboration UTwente

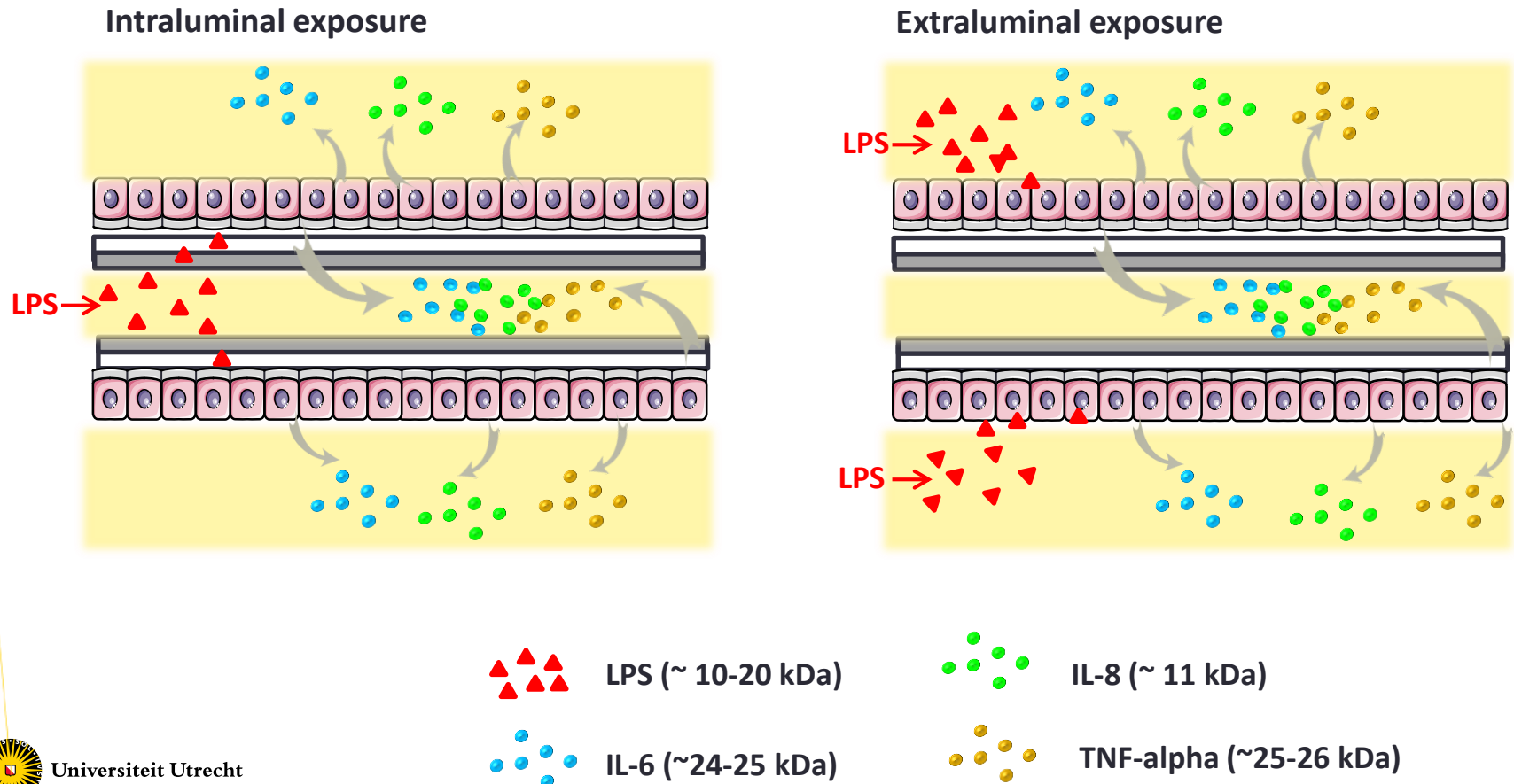


Blue: DAPI (Nuclei)

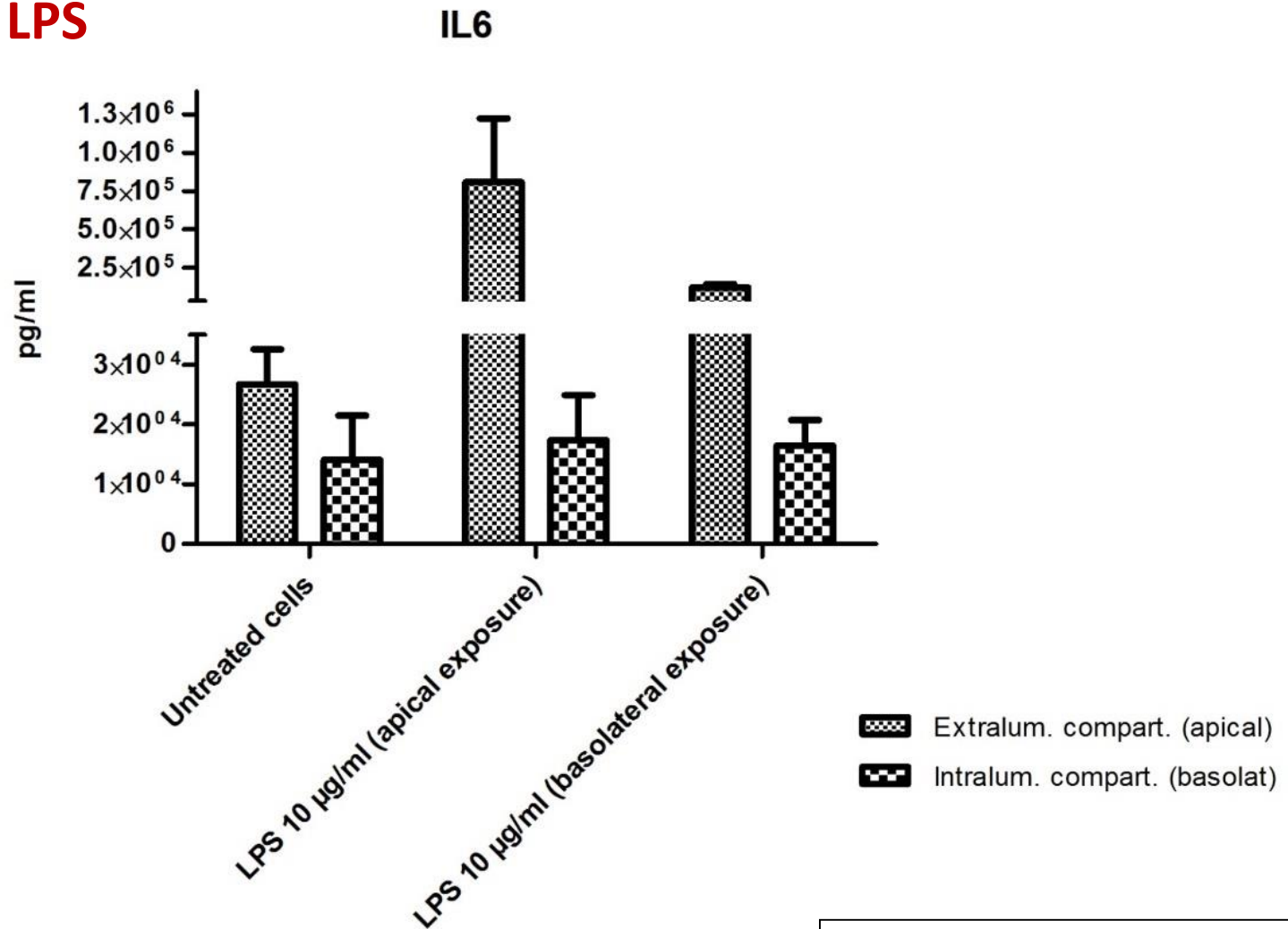
Red: Alexa Fluor 568 (ZO-1)



Response to LPS and IFN- γ in modules



Response to LPS



Biokid-current status and future perspectives

- After optimized coating, ciPTEC can grow on hollow fibers and remain functional, and allow for kinetic studies
- Proven *in vitro* safety
- Function in upscaled device demonstrated
- Future studies directed towards *in vivo* safety and efficacy
- Extra-corporal -> implantable





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Dept. Pediatrics

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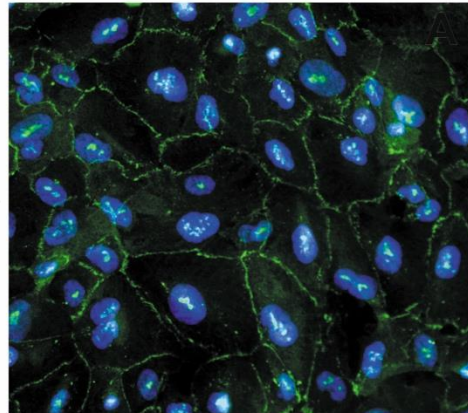
NUTRICIA
RESEARCH



AstraZeneca 

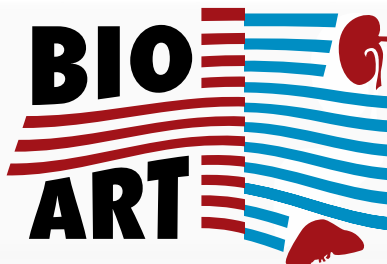


BMM



NIERSTICHTING

Leven gaat voor.



EUtox



Nephrotools