Utrecht University

Wetenschapsdag 14 oktober 2023

nvn nierpatiënten vereniging nederland

Een biologische kunstnier op maat, kan dat wel?

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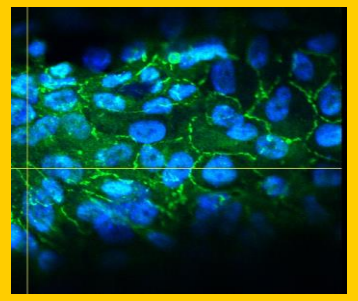
***U**trecht*
***I**nstitute for*
***P**harmaceutical*
***S**ciences*



De nier en zijn functie

- **Gezonde nier**

  Verwijderen van afvalstoffen

  Reguleren vocht- en zoutbalans

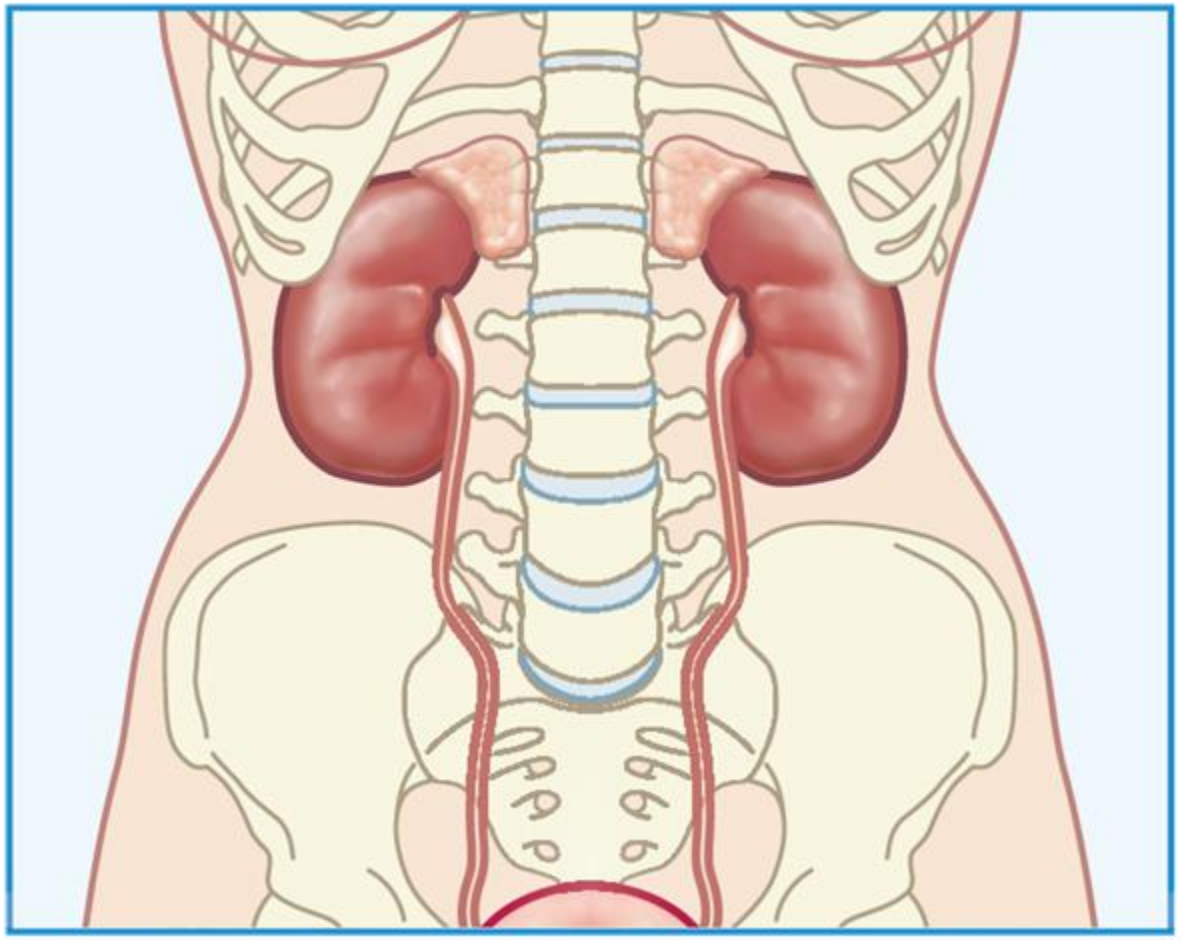
  Productie van hormonen

  Bloeddrukregulatie

- **Nierfalen**

  verlies van nierfunctie

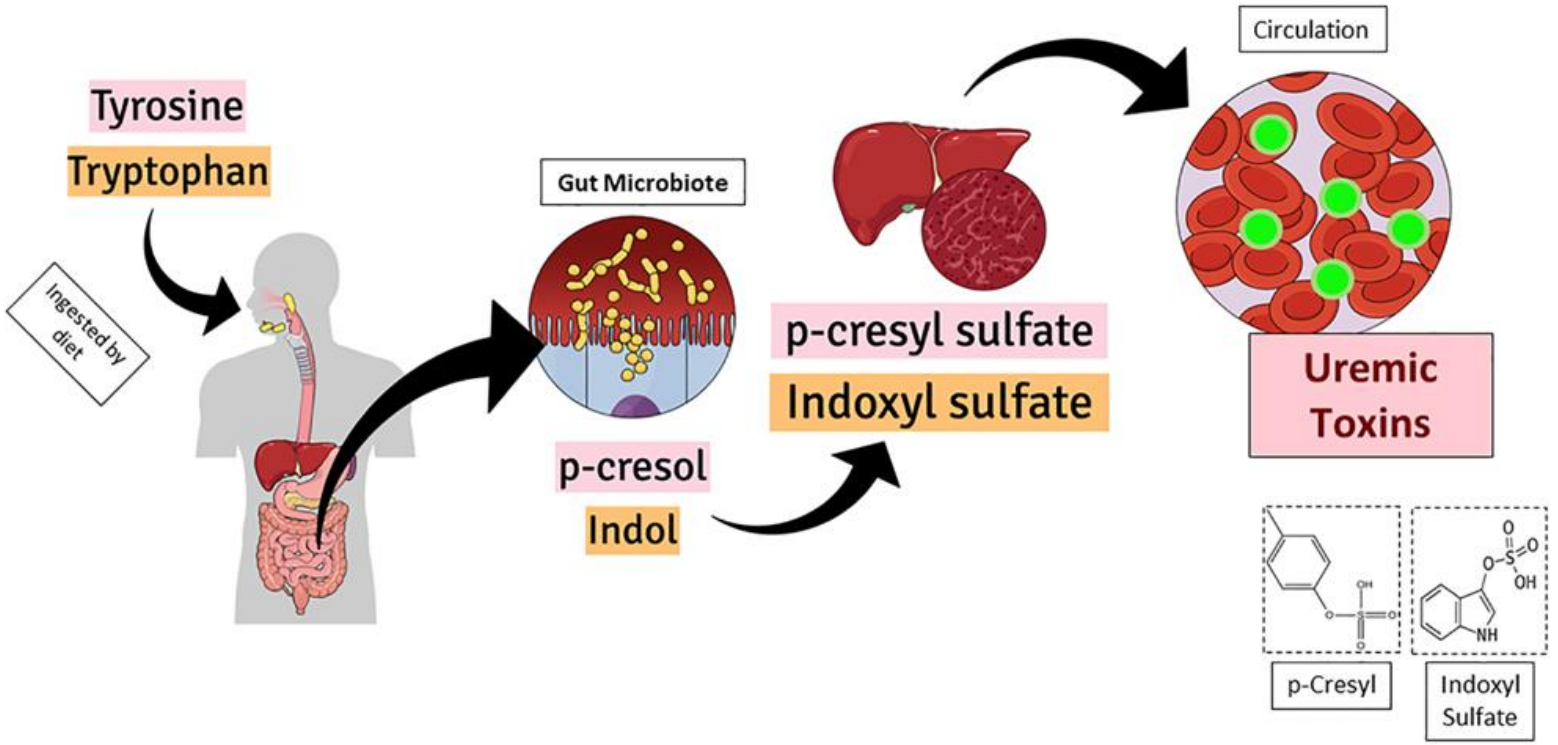
  nierfunctievervangende therapie



Van chronische nierziekte naar eindstadium nierfalen

Uitscheiding van afvalstoffen door filtratie én tubulaire secretie

Ophoping van afvalstoffen: uremische toxines



Producten van ons metabolisme

Classificering:

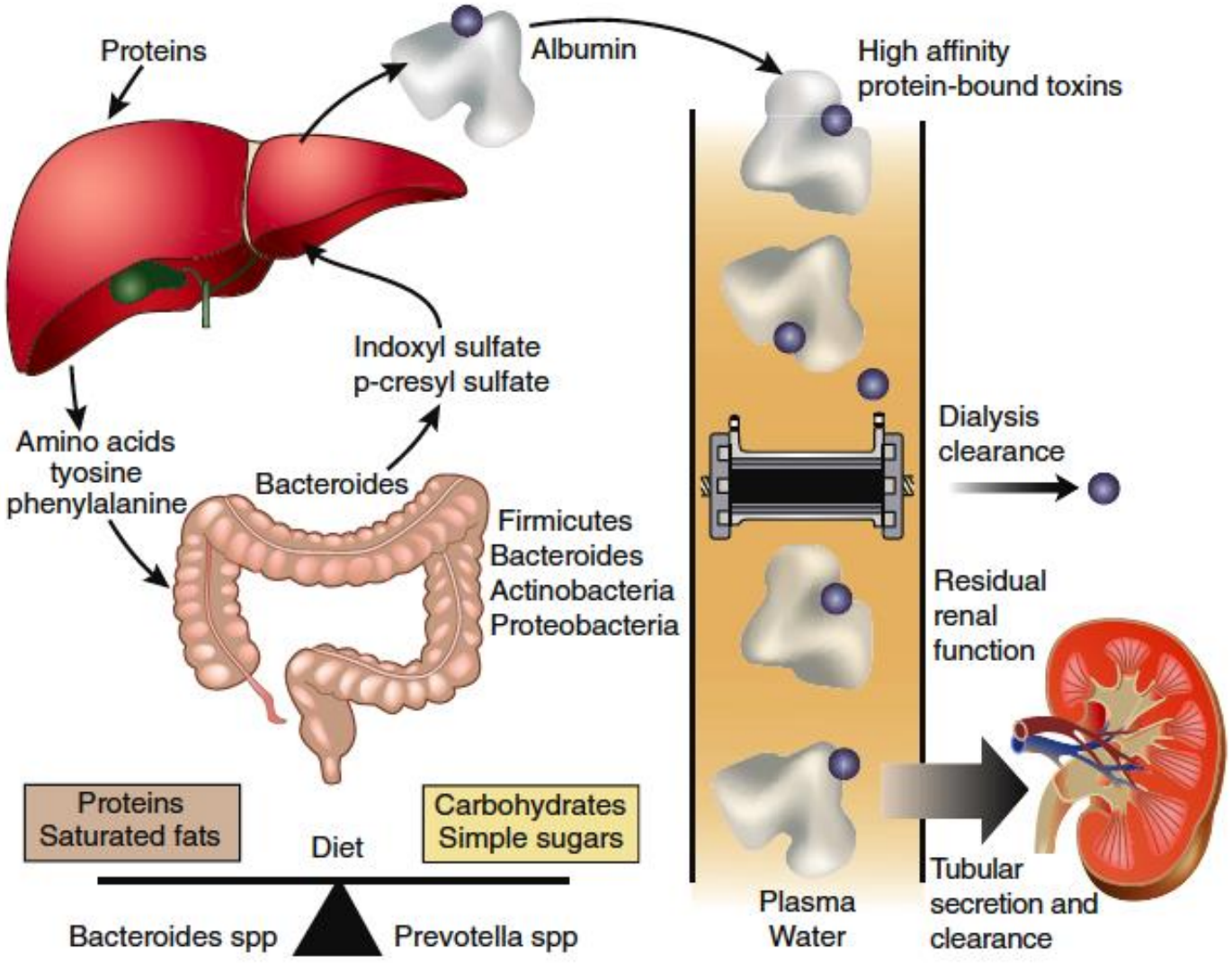
Kleine water-oplosbar stoffen (< 500 Da)
Middelgrote moleculen (> 500 Da)
Eiwitgebonden (kleine) moleculen

Pathologie:

Nierfibrose
Cardiovasculaire complicaties
Cognitieve problemen
…

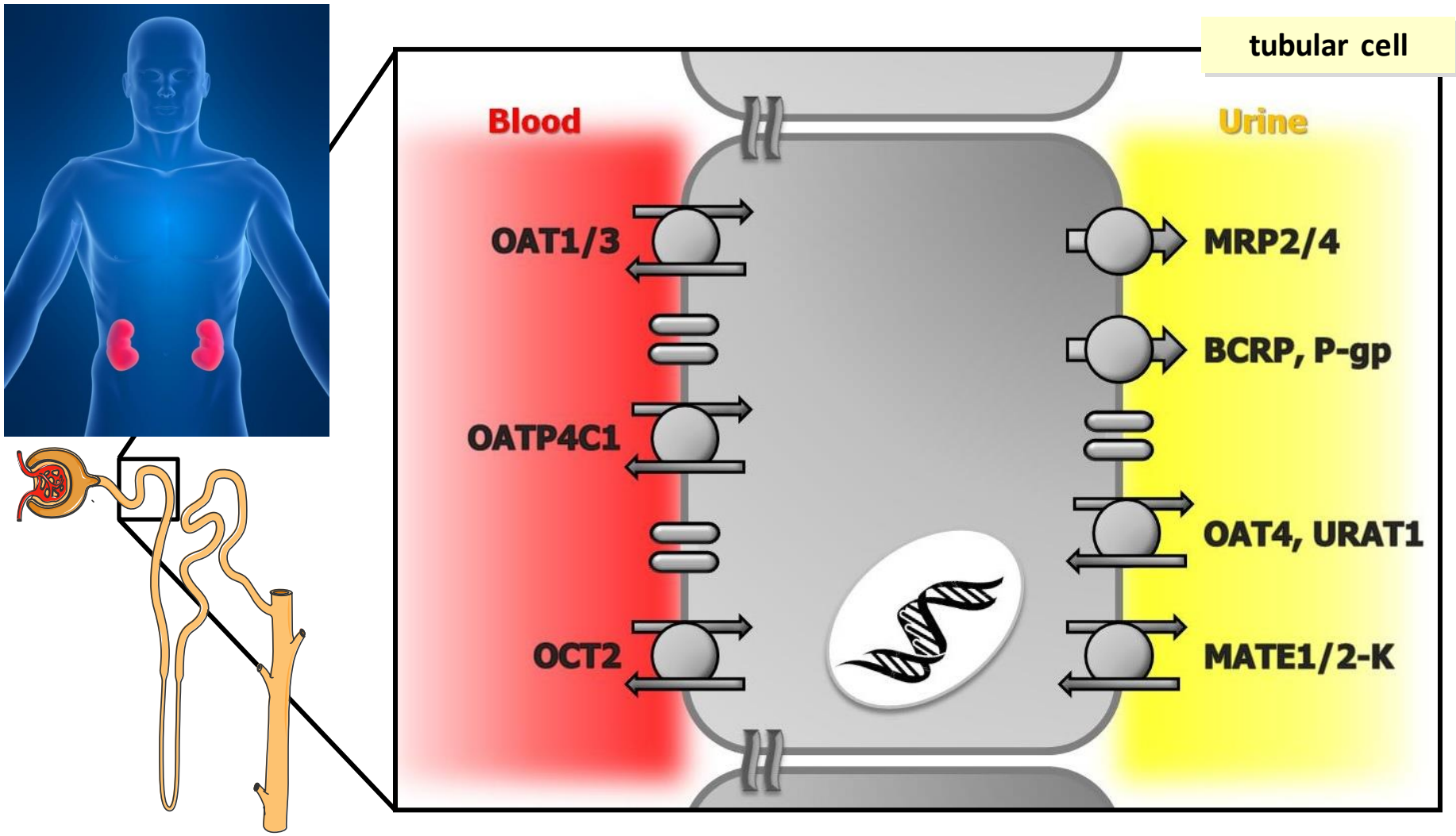
Vanholder *et al*. Pediatr Nephrol 2008
Duranton *et al.* JASN 2012

Eiwitgebonden uremische toxines zijn lastig te verwijderen



Davenport Kidney Int. 2017
Sirich *et al.* Kidney Int. 2017

De nieren zijn goed uitgerust om uremische toxines uit te scheiden

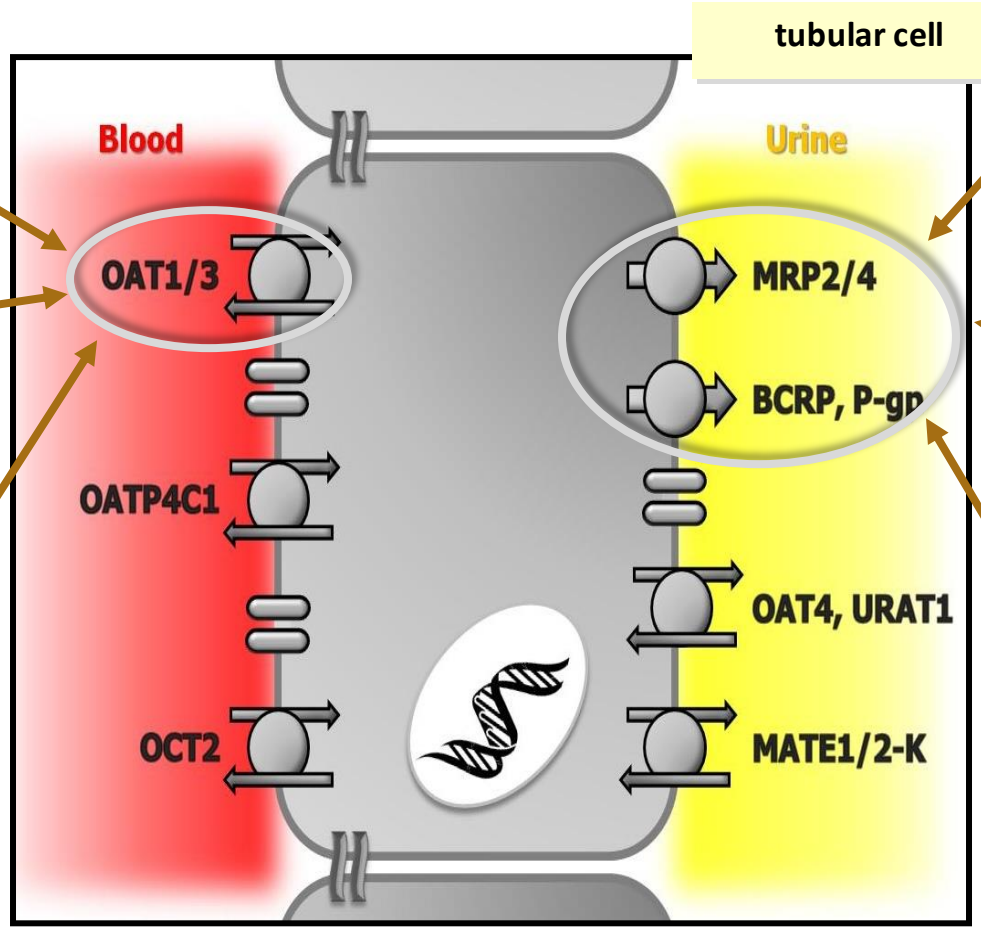


De nieren zijn goed uitgerust om uremische toxines uit te scheiden

Drug
Furosemide
Methotrexate
Tenofovir

Metabolite
Creatinine
Dicarboxylate

Uremic toxin
Indoxyl sulfate
Indoxyl glucuronide
P-cresyl sulfate
P-cresyl glucuronide
Kynurenic acid
Hippurate



Drug
Furosemide
Methotrexate
Thiazides

Metabolite
Urate
Dicarboxylate

Uremic toxin
Indoxyl sulfate
Indoxyl glucuronide
P-cresyl sulfate
P-cresyl glucuronide
Kynurenic acid
Hippurate

Masereeuw R. *et al*. Sem. Nephrol 2014;
Nigam S.K. *et al.* cJASN 2015

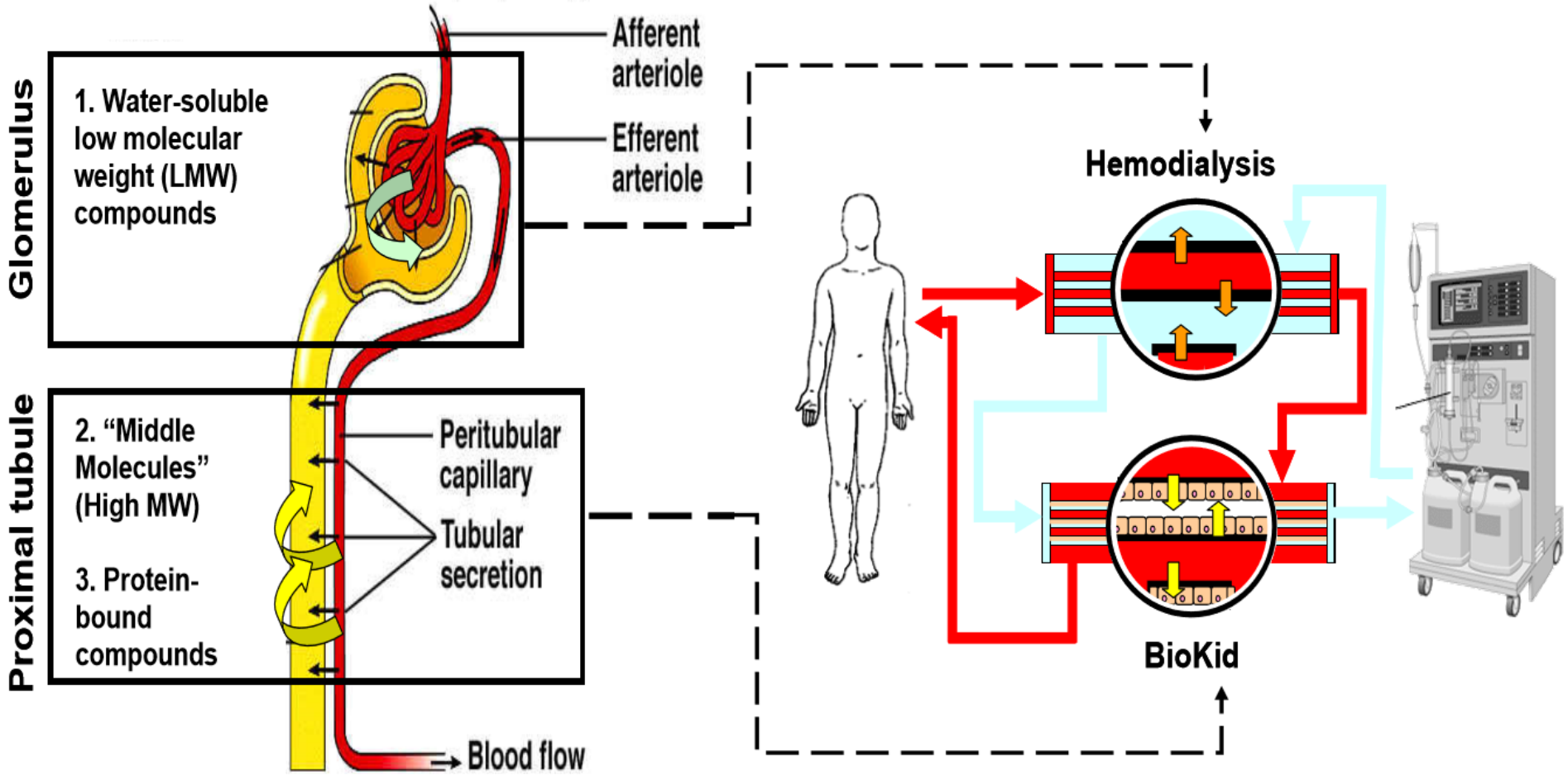
Ontwikkeling van de biologische kunstnier

Jansen, Fedecostante *et al.*, Biotech. Adv., 2014


BMM

Ontwikkeling van de biologische kunstnier

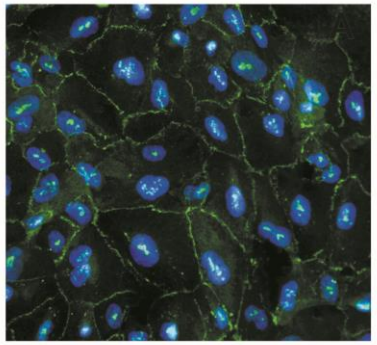
- De ontwikkeling van een prototype dat in staat is om afvalstoffen actief uit te scheiden



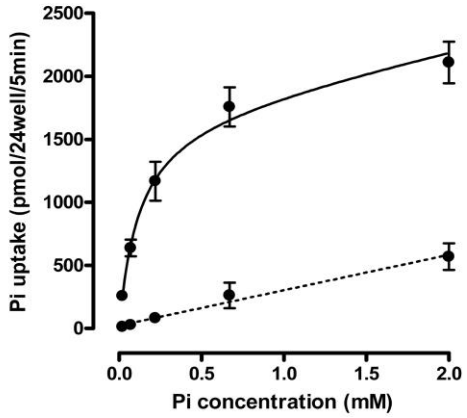
Legallais *et al.* Adv. Healthcare Res. **2018**

Niercellen in kweek brengen

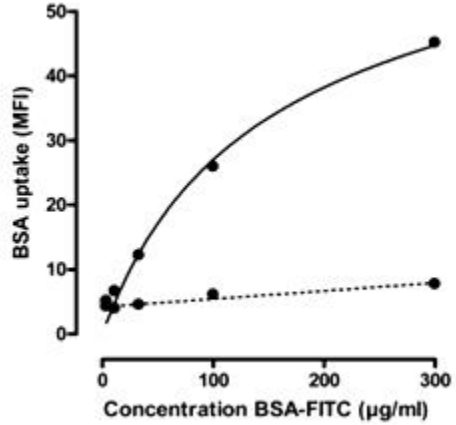
ZO-1

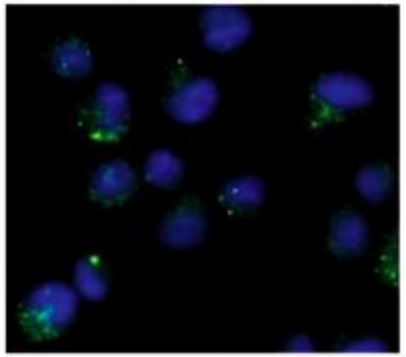


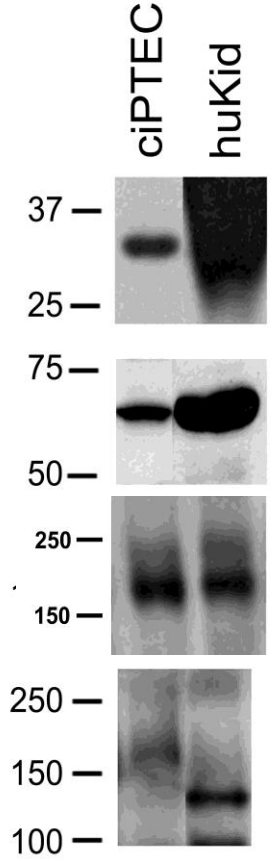
Phosphate uptake



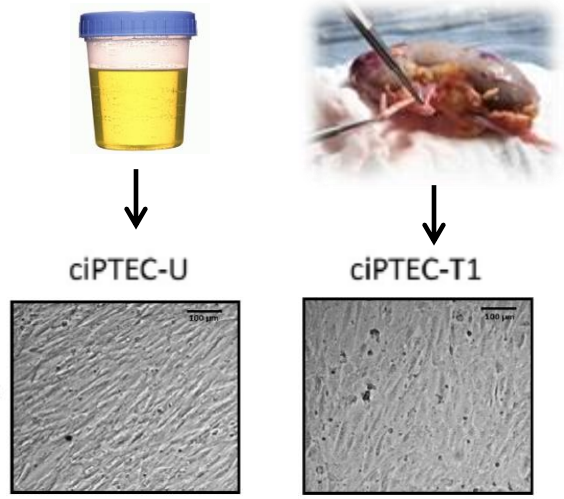
Albumin uptake







ciPTEC cell lines:

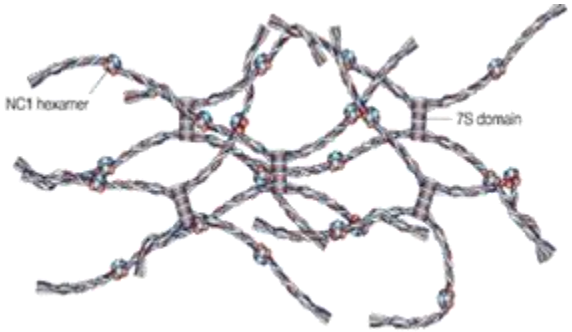


- Conditionally immortalized PTEC:
  - **SV40T** U19tsA58 antigen
  - **hTERT**

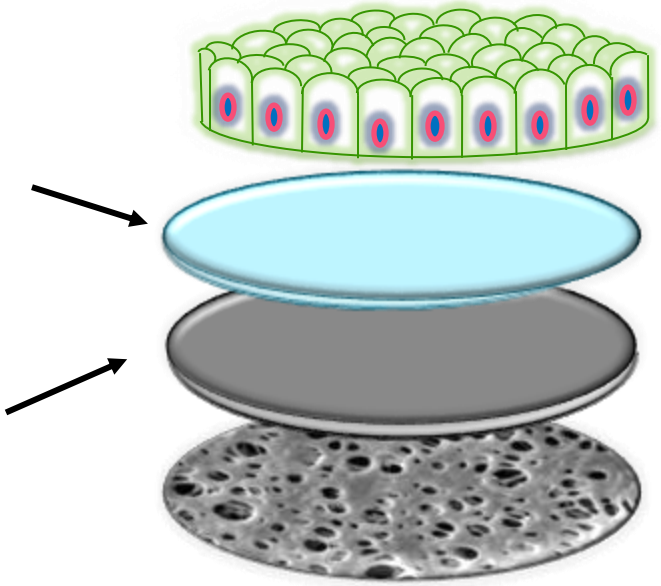
Wilmer *et al.* Cell Tissue Res. **2010**
Jansen *et al.* Exp. Cell Res. **2014**

De eerste stap naar een biologische kunstnier: een levend membraan

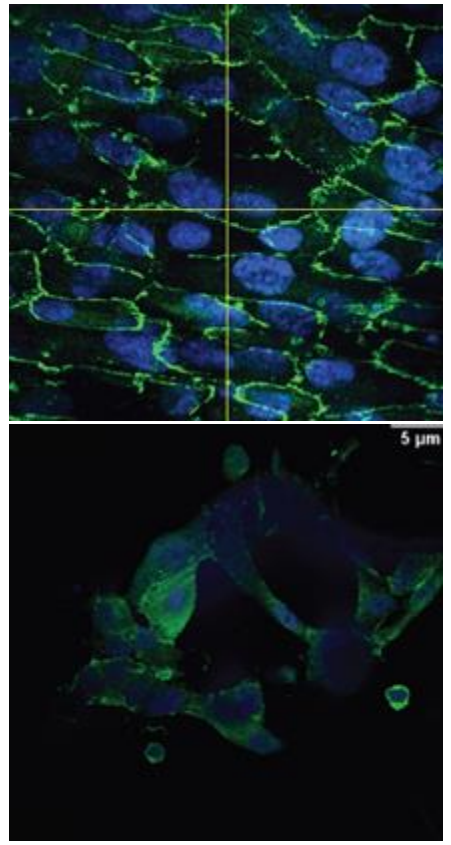
Collagen IV



L-Dopa



Coated membrane

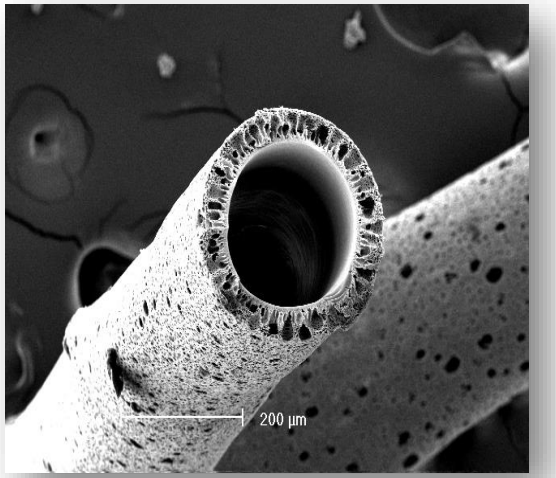


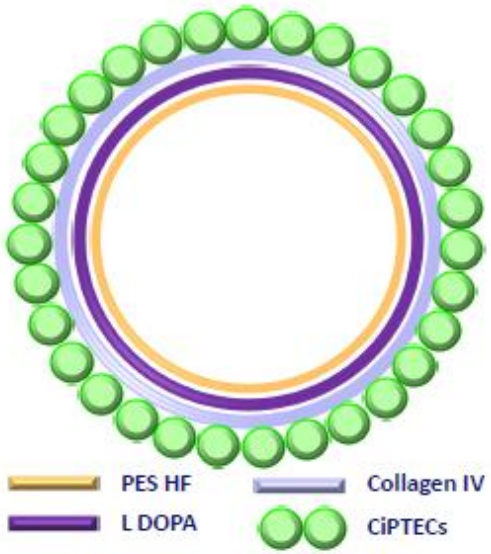
Uncoated membrane

Schophuizen, *et al.*, Acta Biomaterialia, 2015

Ni, *et al.*, Biomaterials, 2011

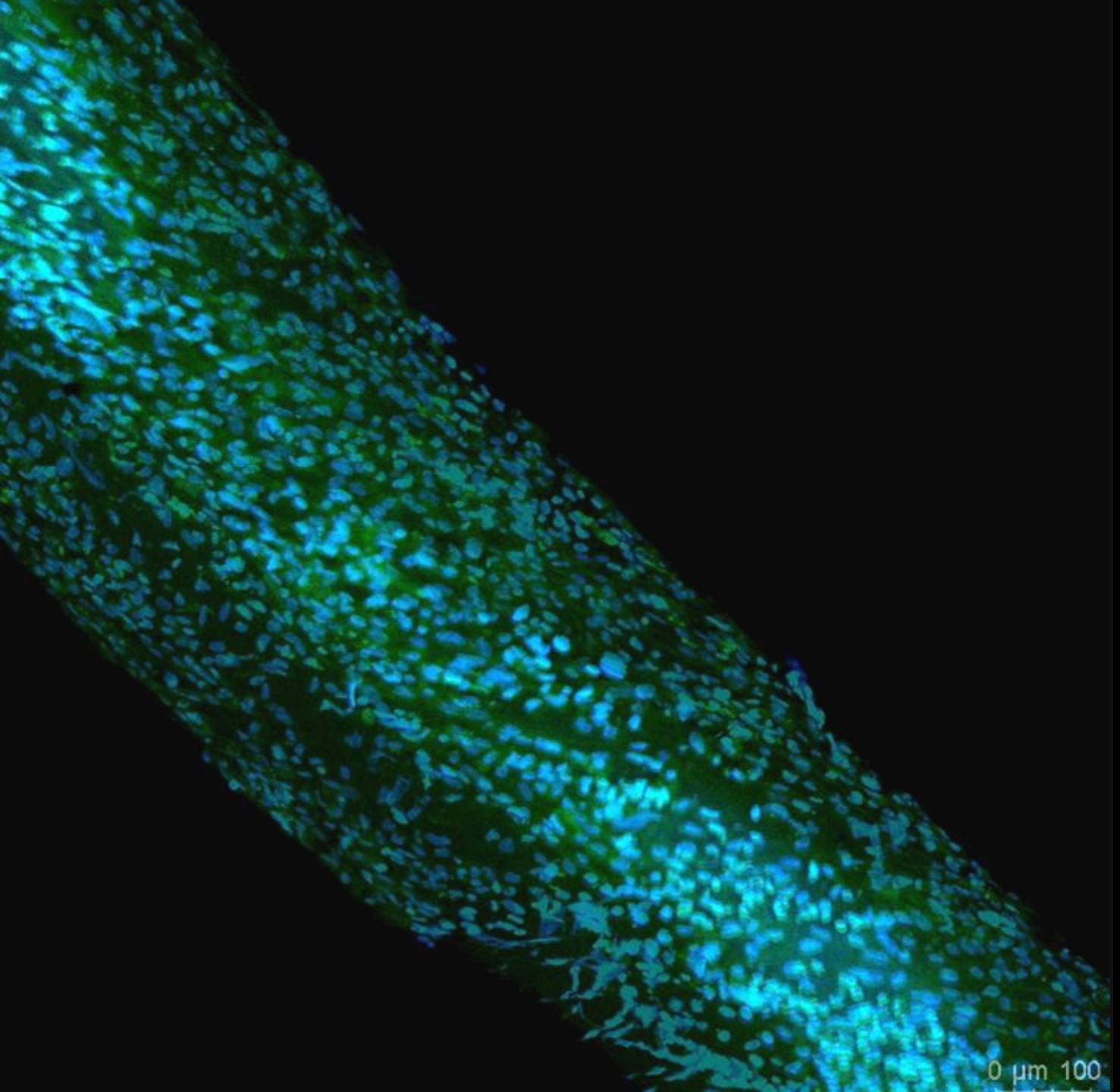
De eerste stap naar een biologische kunstnier: een buisje





- ZO-1
- Nucleus
- OCT2

Jansen *et al.*, Sci. Rep. 2015



Cytoskeleton / Nuclei

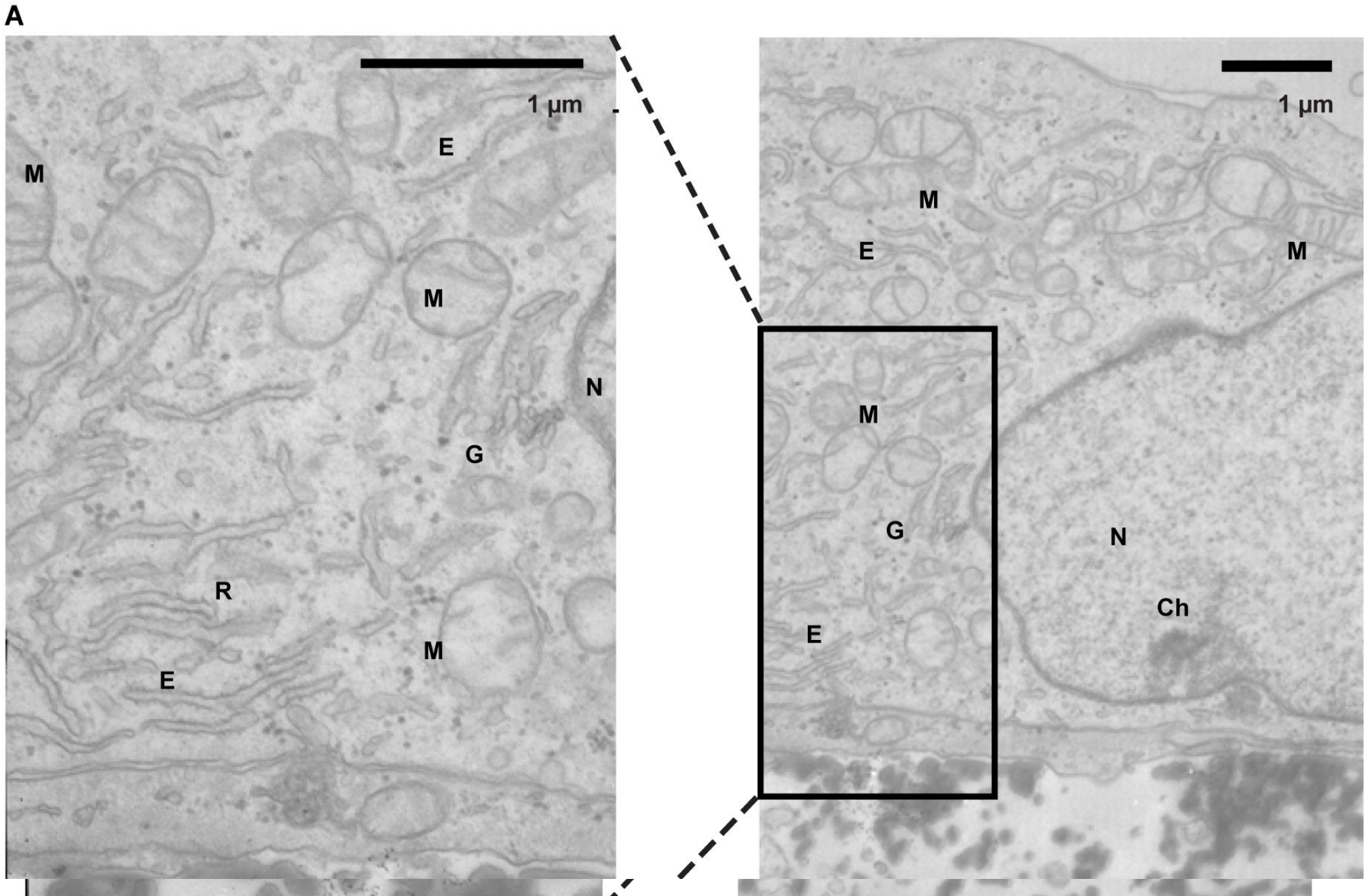
ciPTECs seeded on microPES HFM

(cut off> 65kDa, 100µm wall thickness, 500µm diameter,1.5cm length = 0.2cm²)

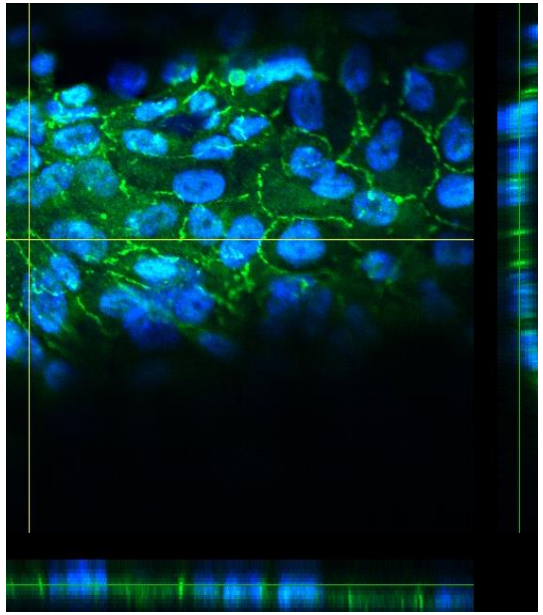
Col IV coating, monolayer formation

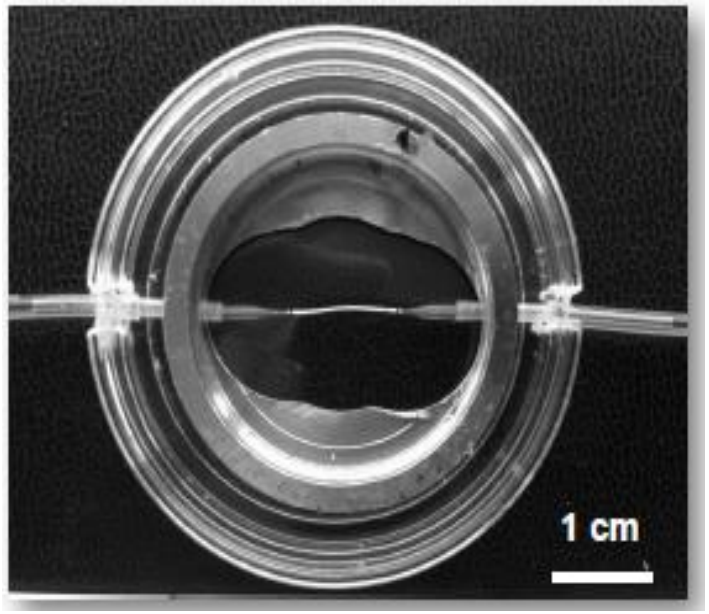
Perfusable (in and out)

Jansen J, *Sci Rep.* **2015**, Jansen J, *Sci Rep*. **2016,** Mihajlovic M, *Oncotarget* **2019,** Chevtchik NV *J Tissue Eng Regen Med*. **2018,** Mihăilă SM, *Toxins,* **2020**


A
1 µm
E
M
M
N
G
R
M
E
1 µm
M
E
M
M
G
N
Ch
E

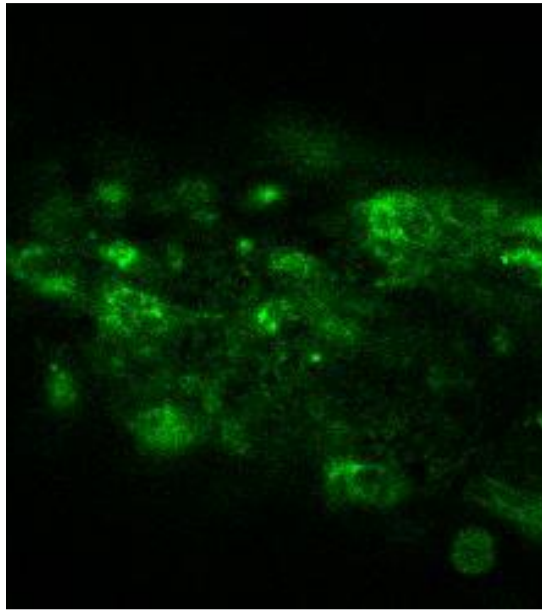
Een functioneel nierbuisje in beeld

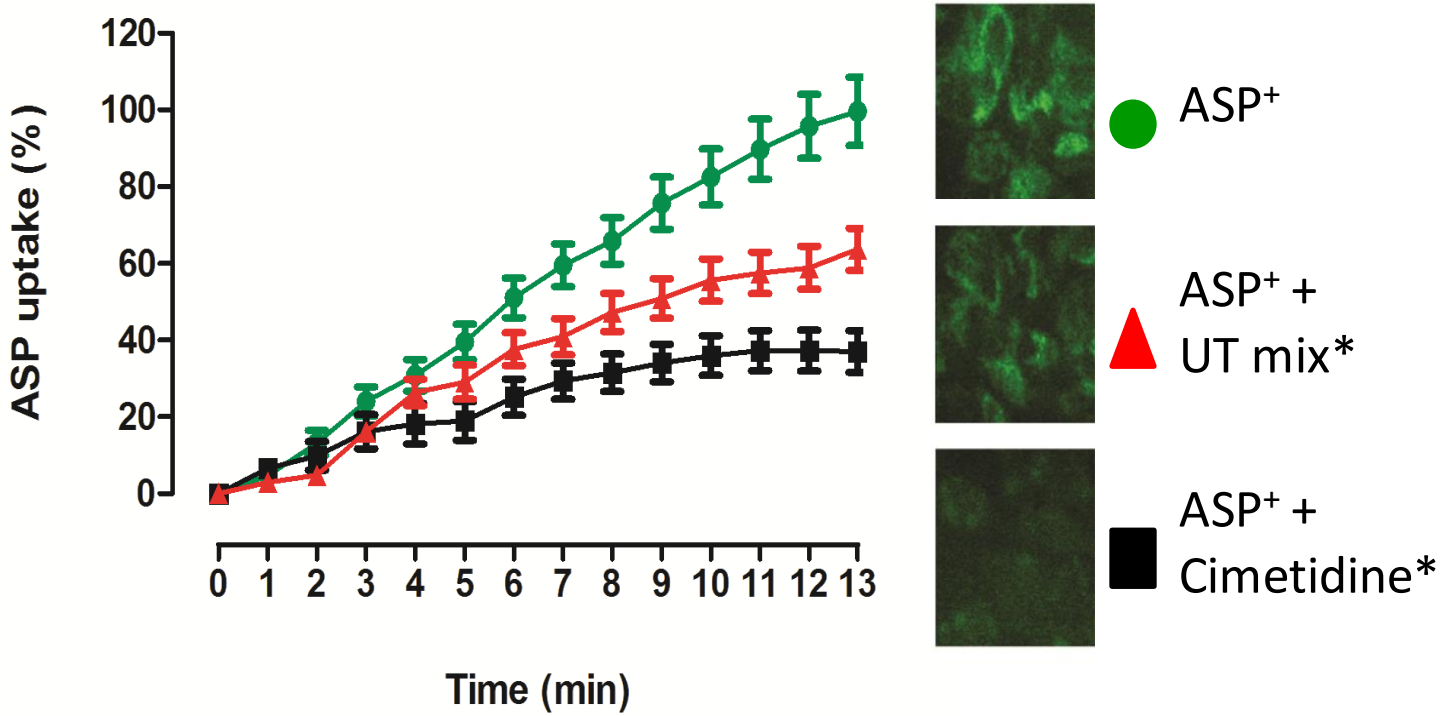




Jansen *et al.*, Sci. Rep. 2015

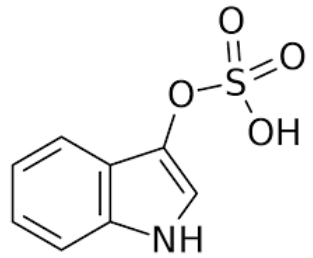
Een functioneel nierbuisje in beeld



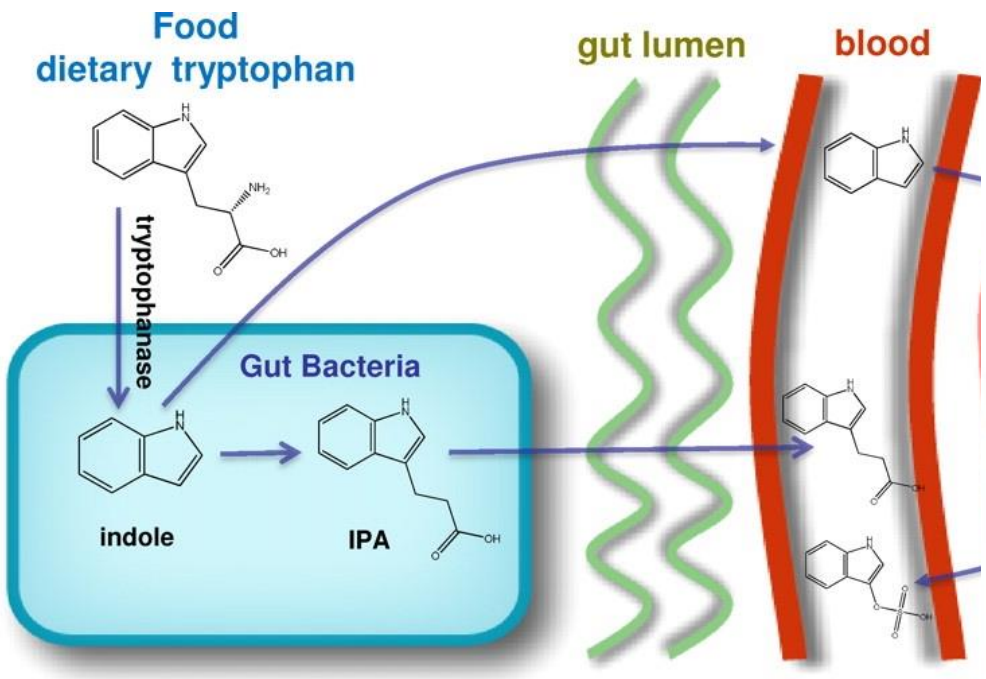


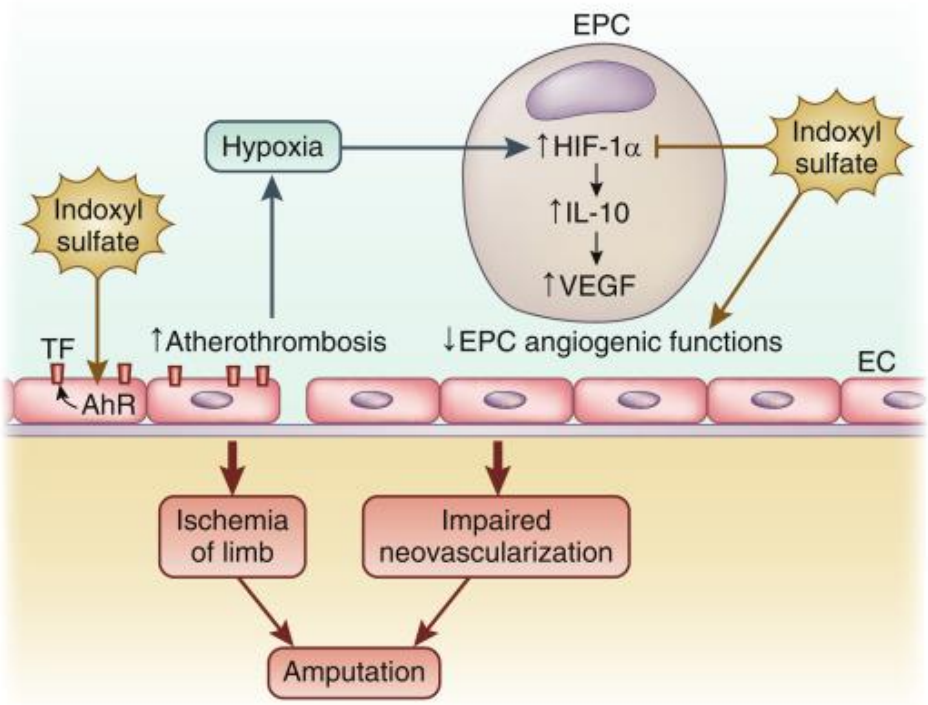
Een functioneel nierbuisje voor de uitscheiding van afvalstoffen

Een functioneel nierbuisje voor de uitscheiding van afvalstoffen



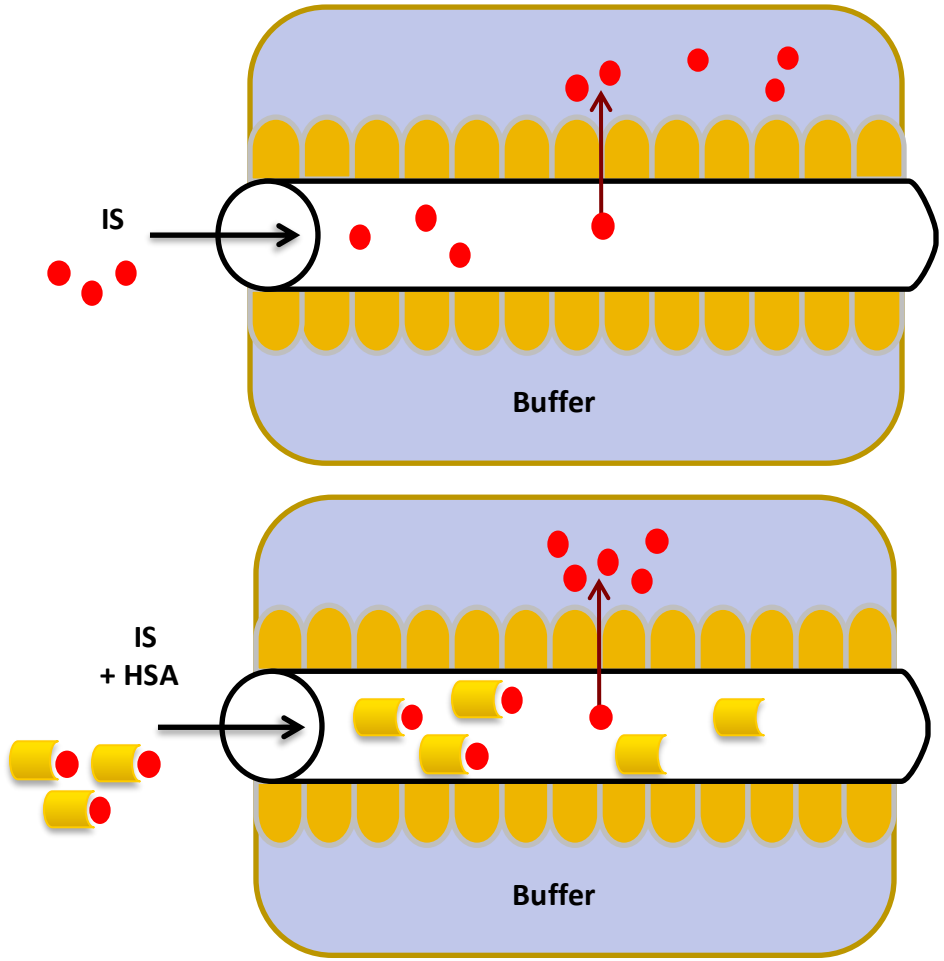
Indoxyl Sulfate

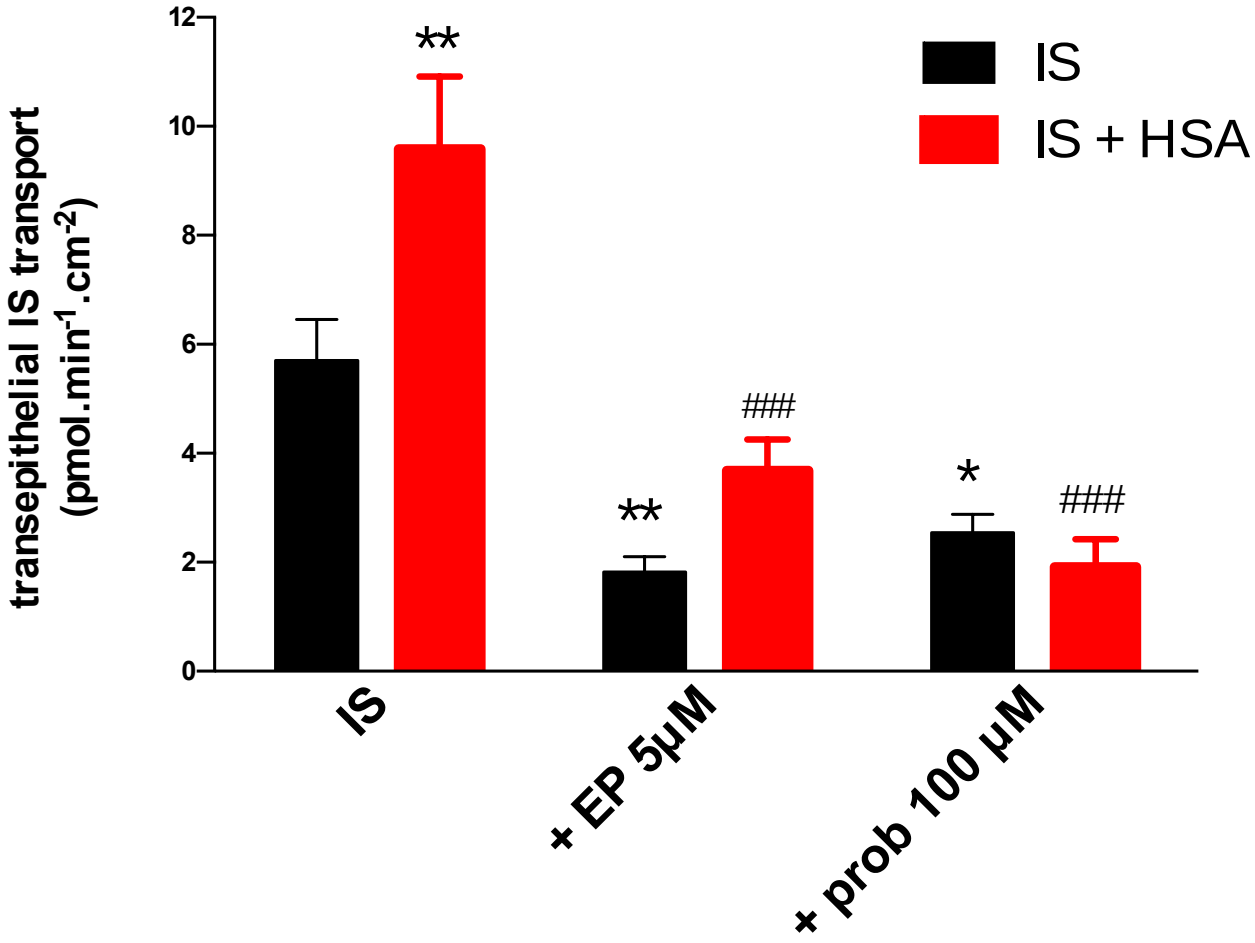




Meijers & Evenepoel, NDT. **2011**;Dou & Burtey, Kidney Int. **2016**

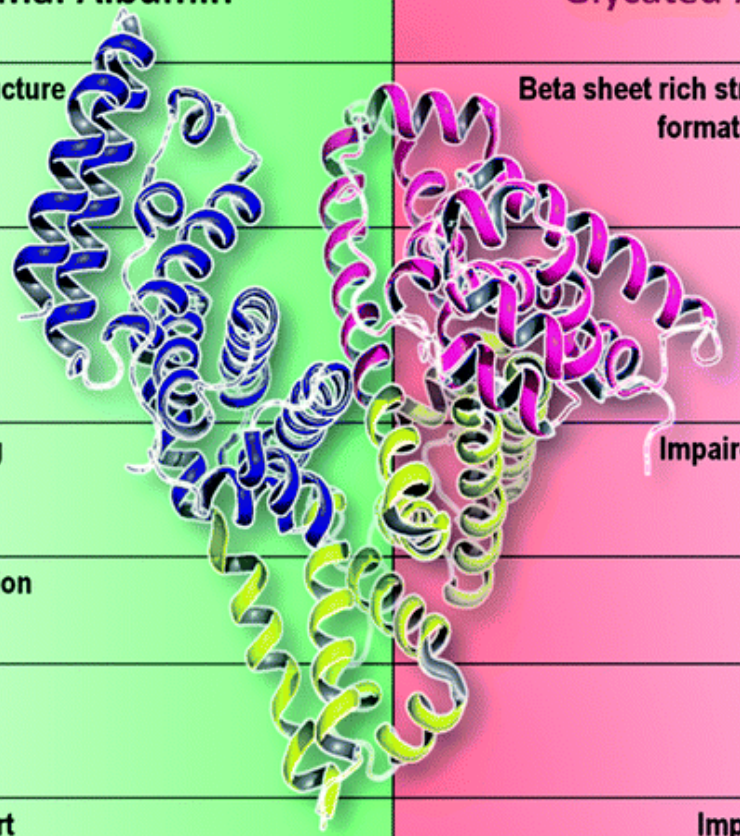
Een functioneel nierbuisje voor de uitscheiding van afvalstoffen





Jansen J., Fedecostante M. *et al*. Sci. Rep. **2016**

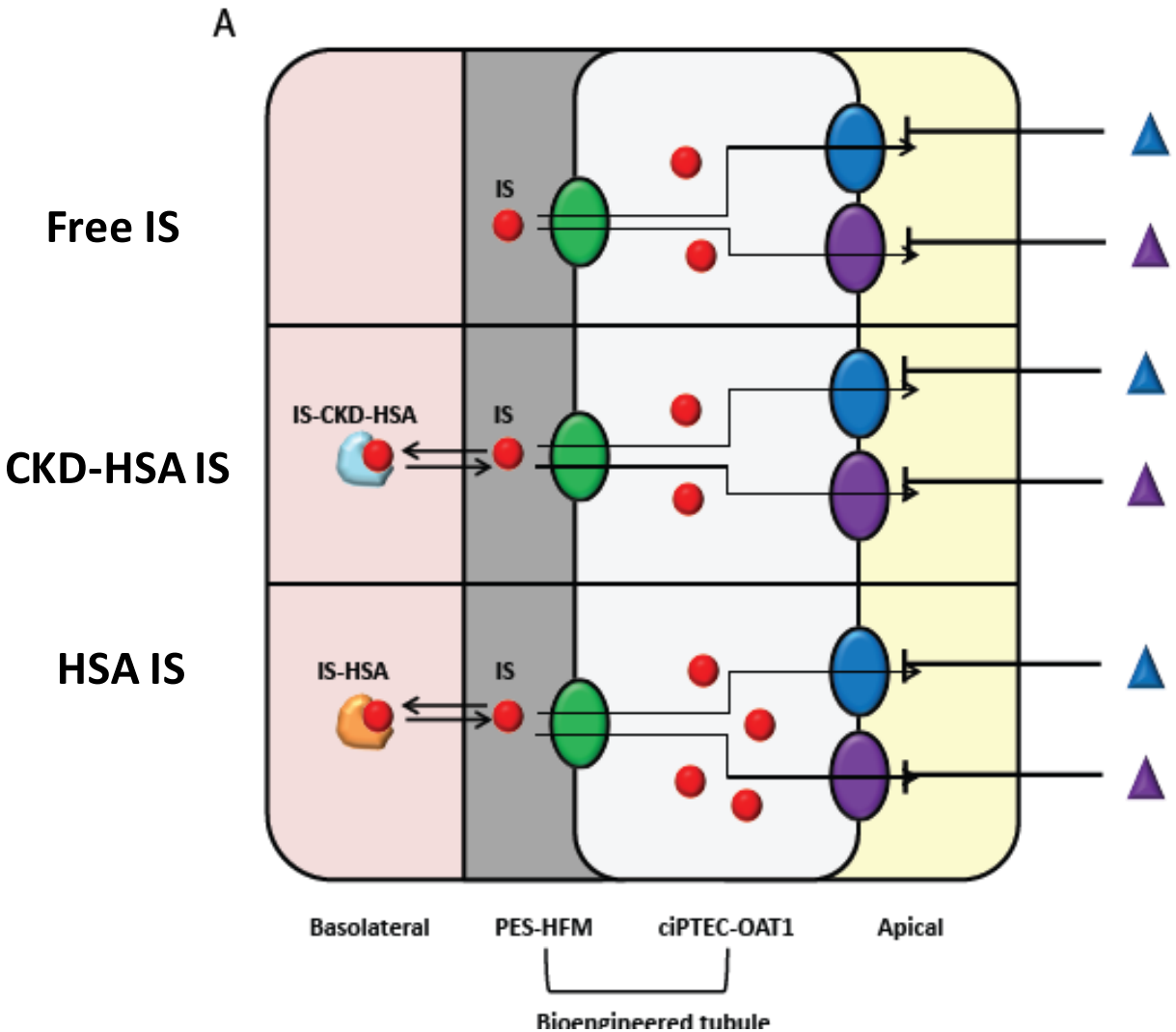
Een functioneel nierbuisje voor de uitscheiding van afvalstoffen

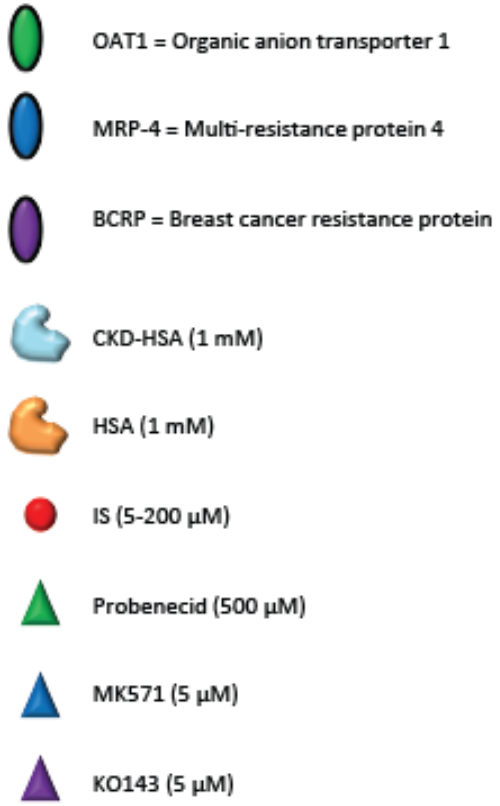


Normal Albumin	Glycated Albumin	Reference
Native helical structure	Beta sheet rich structure, aggregation and formation of cross beta sheets.	Bouma et al. 2003, Obrenovich and Monnier 2004.
Drug binding	Impaired drug binding properties	Baraka-Vidot et al. 2012, Vetter and Indurthi, 2013, Awasthi et al. 2015b.
Fatty acid binding	Impaired fatty acid binding and transport	Yamazaki et al. 2005, Blache et al. 2015.
Antioxidant function	Loss of antioxidant function	Bourdon et al. 1999, Faure et al. 2008.
Esterase function	Loss of esterase activity	Ahmed et al. 2005, Baraka-Vidot et al. 2015.
Hormone transport	Impaired hormone transport	Watanabe et al. 1991, Petitpas et al. 2003.
Protective effect on cells (Endothelial cells, RBCs, Muscle cells etc.)	Deleterious effect on cells (cytotoxicity, inflammation, and membrane damage)	Amore et al. 1997, Hattori et al 2001, Awasthi et al 2015.

Awasthi & Saraswathi, RSC Adv., **2016**

Een functioneel nierbuisje voor de uitscheiding van afvalstoffen

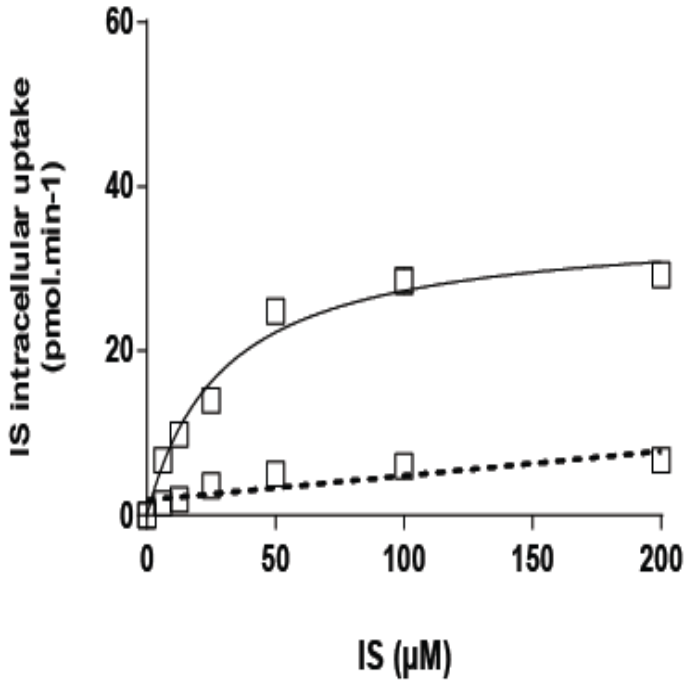




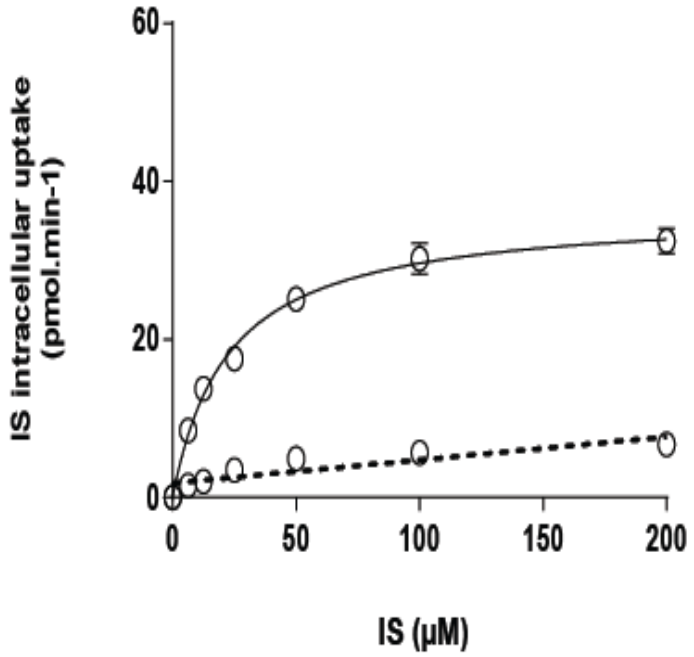
Van der Made, *et al.* Mol. Pharm. **2019**

Een functioneel nierbuisje voor de uitscheiding van afvalstoffen

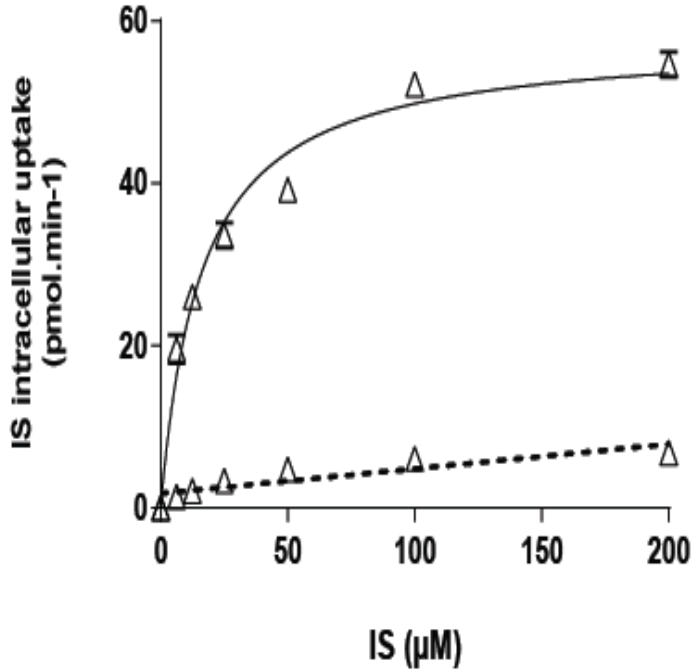
Free IS



CKD-HSA IS

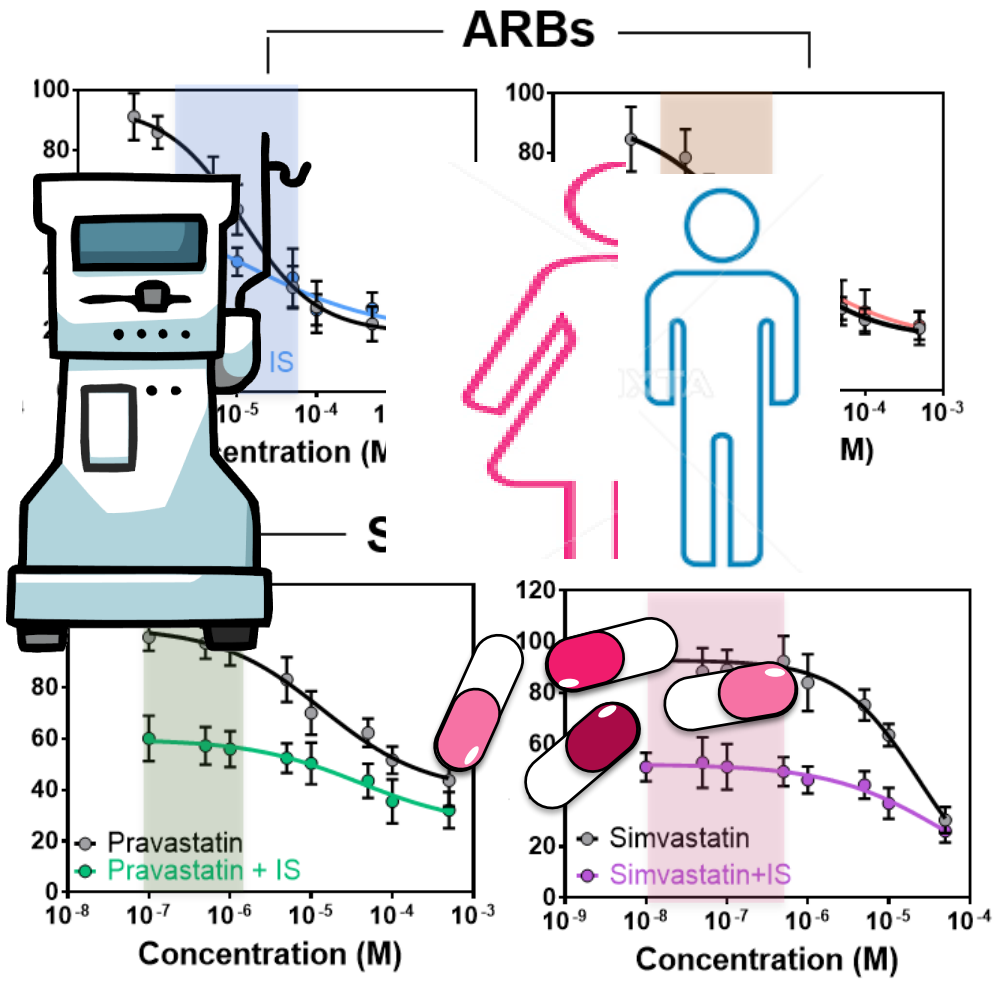


HSA IS



Van der Made, *et al*. Mol. Pharm. **2019**

Interactie tussen geneesmiddelen en afvalstoffen



ARBs = Angiotensin II receptor blockers: valsartan and losartan

Statins= pravastatin, simvastatin

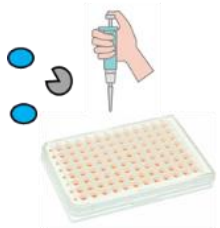
IS= indoxyl sulfate (prototypic protein bound uremic toxin)

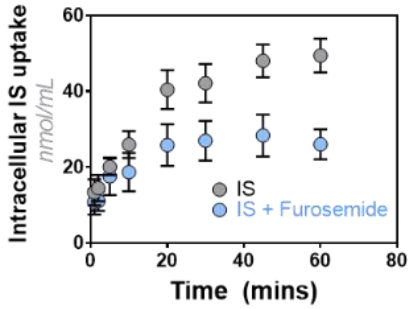
- Drug-toxin and drug-drug interactions lead to their accumulation in blood and could change the management of CKD

UTwente-UMCU-UU-alliance

Miahaila, *et al*. Toxins. **2020**

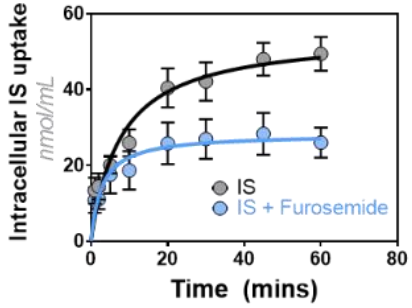
Interactie tussen geneesmiddelen en afvalstoffen: DETOX





Input

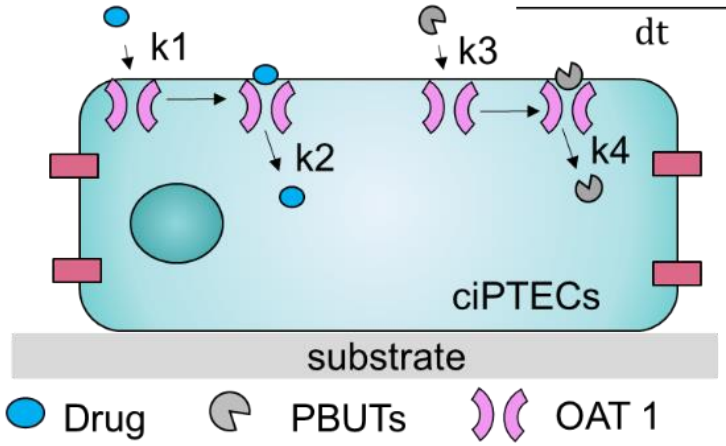
Output

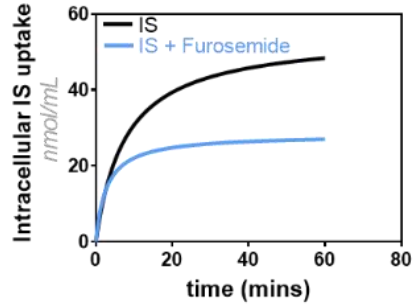


Experimental data

Comparison of kinetics

$$\frac{d[PBUT\_in\_cell]}{dt} = k4.OAT1\_PBUT\_bound$$



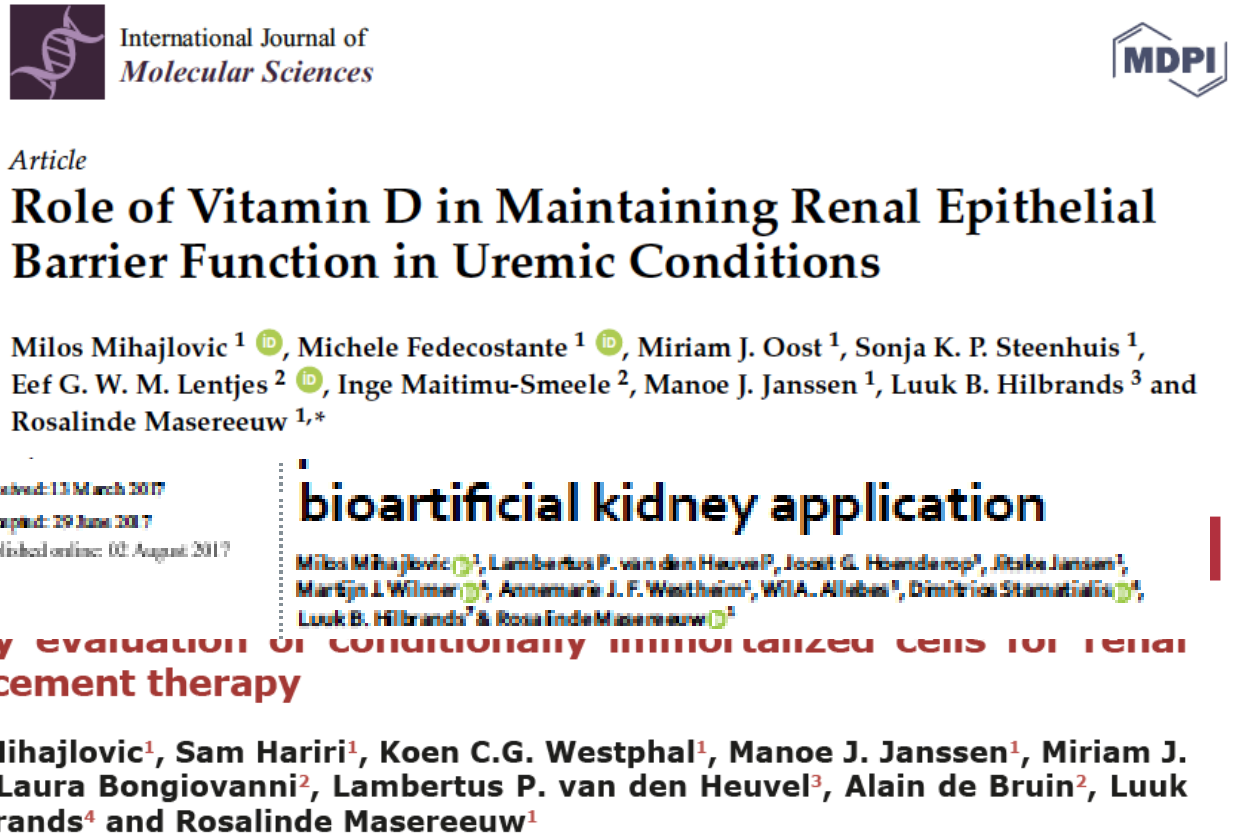


Simulation → Prediction

NIERSTICHTING
Leven gaat voor.

Van nierbuisje naar biologische kunstnier: Kunnen we de nierfunctie voldoende vervangen?

1. Endocrine functions (vitamin D activation)
2. Alloimmune and inflammatory response
3. Tumorigenicity & oncogenicity
4. Upscaled system



International Journal of *Molecular Sciences*

MDPI

Article

Role of Vitamin D in Maintaining Renal Epithelial Barrier Function in Uremic Conditions

Milos Mihajlovic [1], Michele Fedecostante [1], Miriam J. Oost [1], Sonja K. P. Steenhuis [1], Eef G. W. M. Lentjes [2], Inge Maitimu-Smeele [2], Manoe J. Janssen [1], Luuk B. Hilbrands [3] and Rosalinde Masereeuw [1,*]

Received: 13 March 2017
Accepted: 29 June 2017
Published online: 02 August 2017

www.on

bioartificial kidney application

Milos Mihajlovic[1], Lambertus P. van den Heuvel[2], Joost G. Hoenderop[3], Jitske Jansen[1], Marijn J. Wilmer[4], Annemarie J. F. Westheim[3], Wilhelmus A. Allebes[3], Dimitrios Stamatialis[4], Luuk B. Hilbrands[3] & Rosalinde Masereeuw[1]

Safety evaluation of conditionally immortalized cells for renal replacement therapy

Milos Mihajlovic[1], Sam Hariri[1], Koen C.G. Westphal[1], Manoe J. Janssen[1], Miriam J. Oost[1], Laura Bongiovanni[2], Lambertus P. van den Heuvel[3], Alain de Bruin[2], Luuk B. Hilbrands[4] and Rosalinde Masereeuw[1]

From bioengineered tubules to BAK: can we sufficiently replace kidney functions?

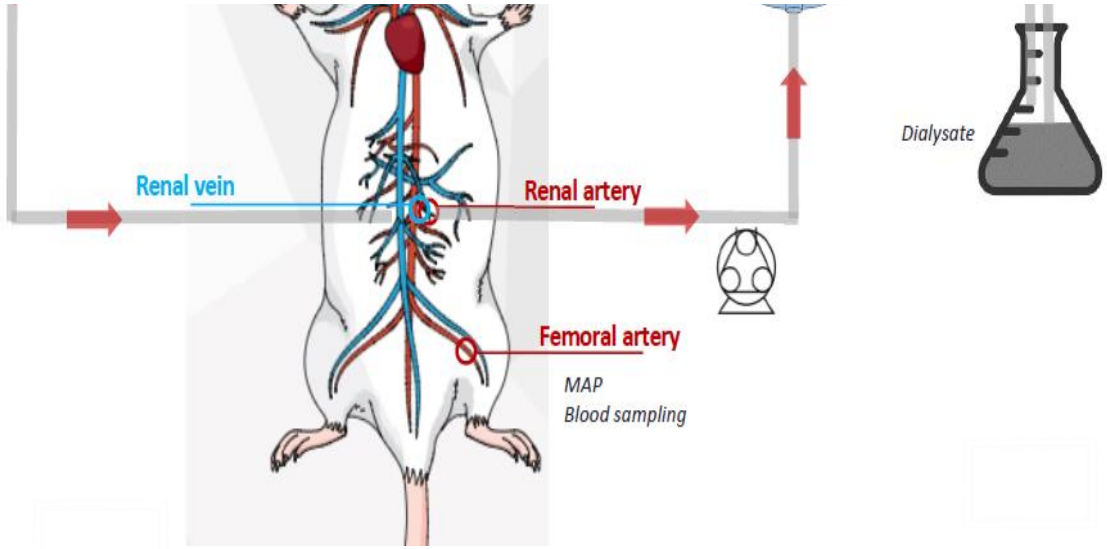
Received: 8 October 2017 | Revised: 4 April 2018 | Accepted: 3 May 2018
DOI: 10.1002/term.2694

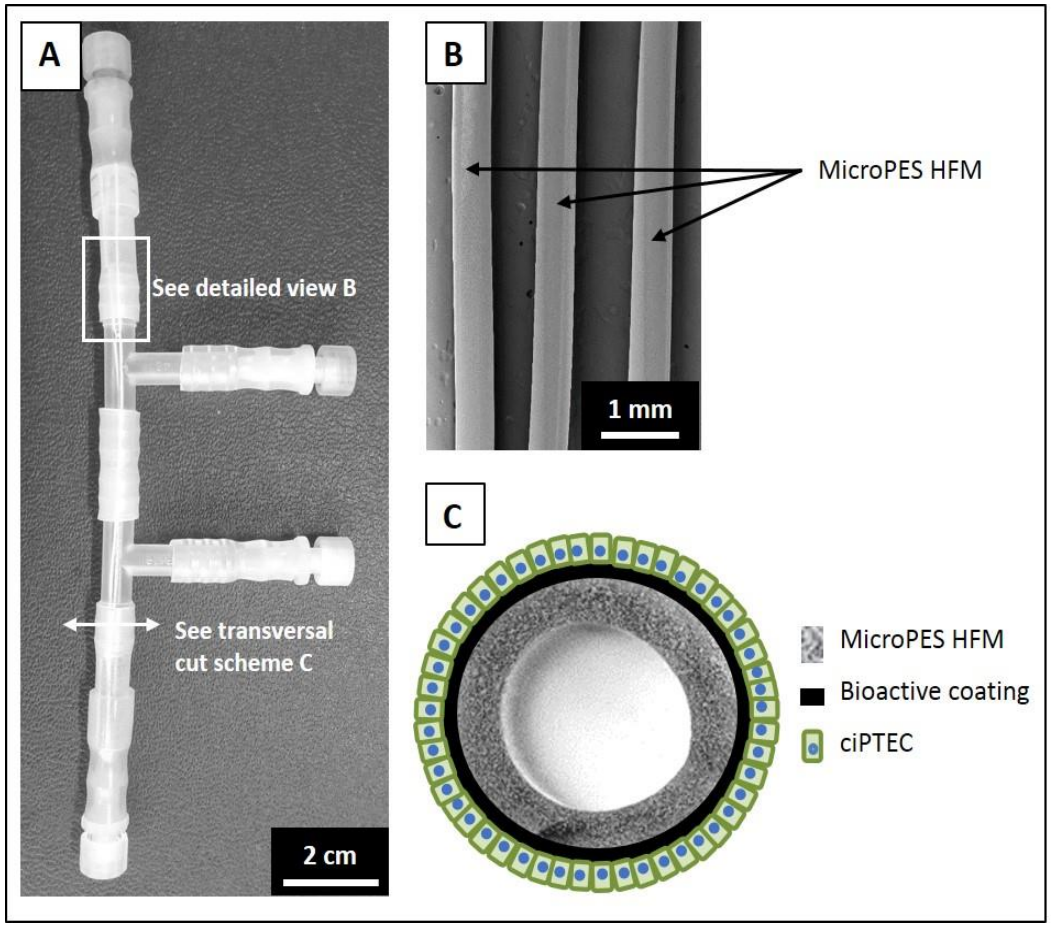
RESEARCH ARTICLE

WILEY

A bioartificial kidney device with polarized secretion of immune modulators

N. V. Chevtchik[1] | M. Mihajlovic[2] | M. Fedecostante[2] | L. Bolhuis-Versteeg[1] | J. Sastre Toraño[3] | R. Masereeuw[2] | D. Stamatialis[1]

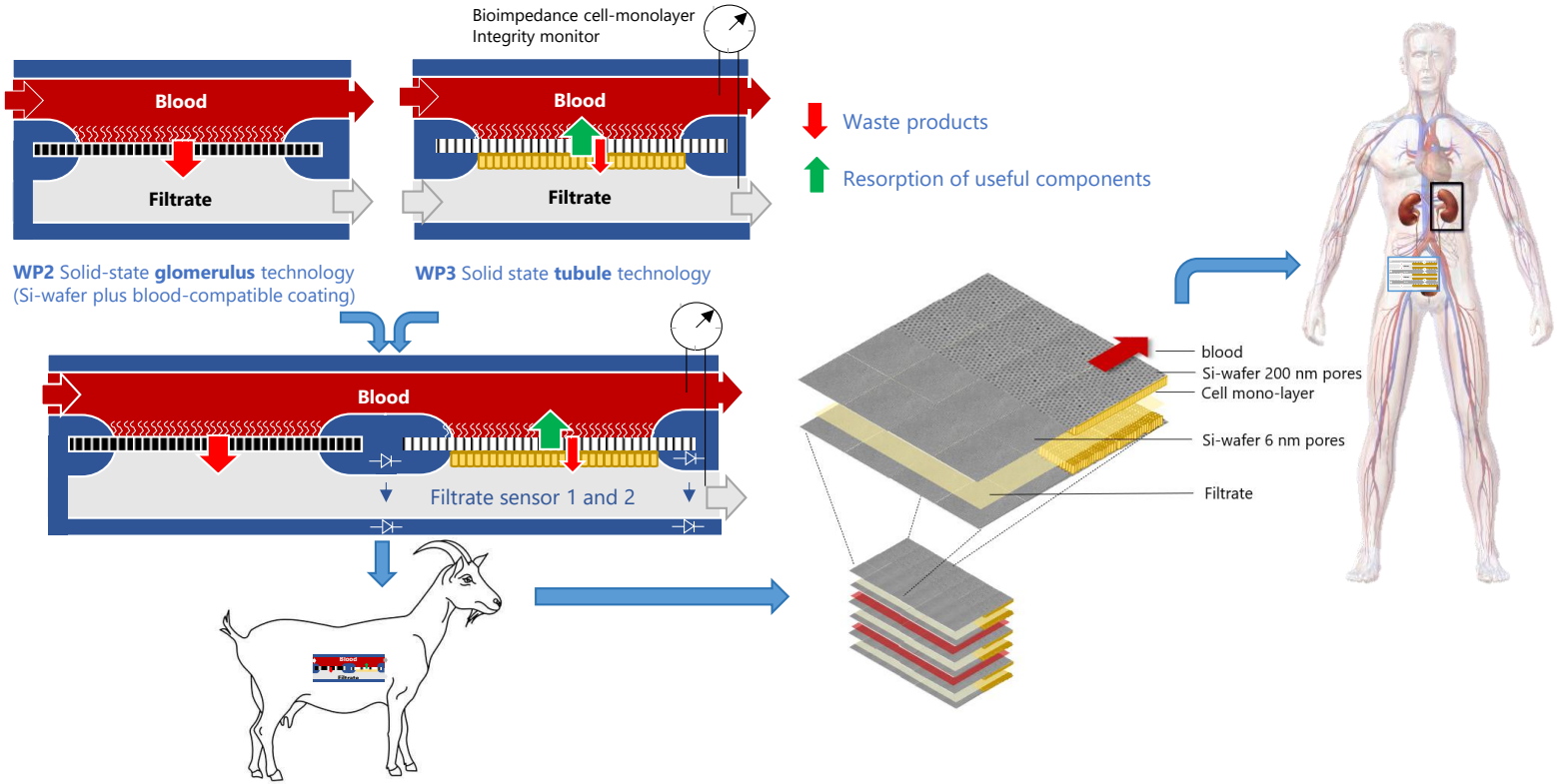




Ongoing collaboration UMCU-UTwente

De huidige status: een stapje terug...

Nierbuisjes blijken onvoldoende stabiel in huidige opzet, dus terug naar de tekentafel



Panel A. KIDNEW development, *serial* integration (linking) and functional validation of biosynthetic glomerulus and tubule technology

Panel B. Beyond KIDNEW development: Miniaturization, *parallel* integration (stacking) and upscaling until implantable KRT

Met dank aan:

Utrecht University

Utrecht Institute for Pharmaceutical Sciences (UIPS)

Div. Pharmacology

Silvia Mihaila
Manoe Janssen
Anne Metje van Genderen
Katja Jansen
Milos Mihajlovic
Koen Westphal
Michele Fedecostante
Thom van der Made
João Faria
Sabbir Ahmed
Rafael Lindoso
Marta Garcia Valverde
Elena Sendino Garvi
Ronald van Gaal
and all Bsc and MSc students

UMC University Medical Center Utrecht

Nephrology & Hypertension

Marianne Verhaar
Karin Gerritsen
Maarten Rookmaaker

Biofabrication Utrecht

Jos Malda
Miguel Dias Castilho

University Twente

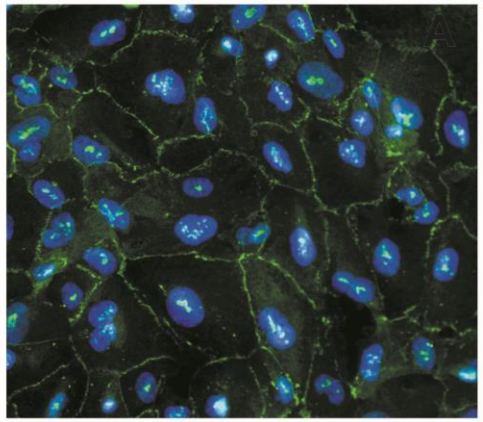
Dimitrios Stamatialis
Ilaria de Napoli
Natalia Chevtchik

Met dank aan:

NIRM
Netherlands Institute of Regenerative Medicine

REGMEDXB
REGENERATIVE MEDICINE CROSSING BORDERS

AstraZeneca



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Leven gaat voor.

BIO ART

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THANK YOU!

Utrecht University

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