Generation of Kidney Organoids from human iPS cells

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RIKEN BDR

28/9/2021 Glycoforum

What is Organoid?

Organoid = Organ + oid (something similar to a real organ)

A common definition: Self-organizing tissues from stem cells

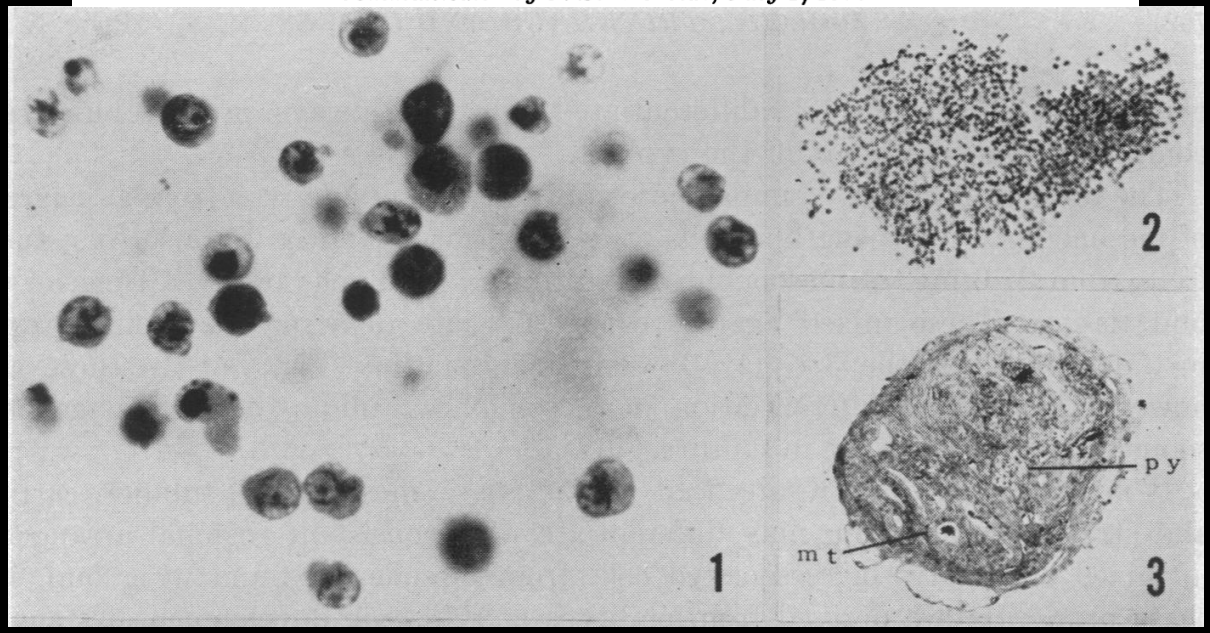
Originally, it was an aggregate of embryonic cells.

*DIFFERENTIATION IN CULTURE OF MIXED AGGREGATES OF DISSOCIATED TISSUE CELLS**

By J. P. Trinkaus and Peggy W. Groves

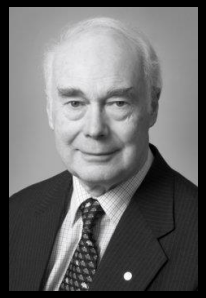
Osborn Zoological Laboratory, Yale University

Communicated by J. S. Nicholas, July 1, 1955



(Trinkaus et al., *PNAS* 1955)

Embryoid body



Sir Martin J. Evans

Establishment in culture of pluripotential cells from mouse embryos

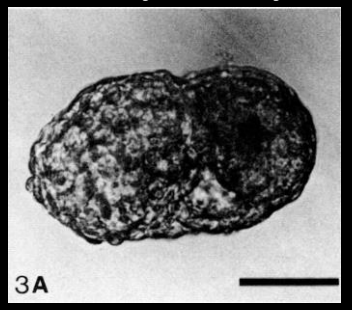
M. J. Evans* & M. H. Kaufman†

Departments of Genetics* and Anatomy†, University of Cambridge, Downing Street, Cambridge CB2 3EH, UK

Pluripotential cells are present in a mouse embryo until at least an early post-implantation stage, as shown by their ability to take part in the formation of chimaeric animals[1] and to form teratocarcinomas[2]. Until now it has not been possible to establish progressively growing cultures of these cells *in vitro*, and cell lines have only been obtained after teratocarcinoma formation *in vivo*. We report here the establishment in tissue culture of pluripotent cell lines which have been isolated directly from *in vitro* cultures of mouse blastocysts. These cells are able to differentiate either *in vitro* or after innoculation into a mouse as a tumour *in vivo*. They have a normal karyotype.

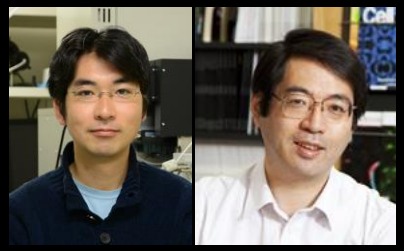
(Evans et al., *Nature* 1981)

Embryoid body



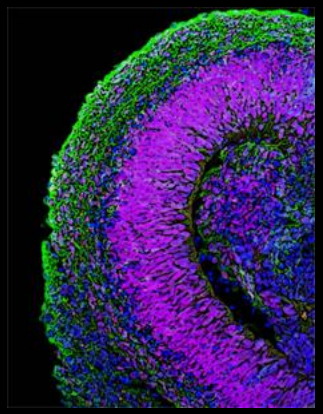
(Doetschman et al., *Development* 1985)

Organoid from stem cells



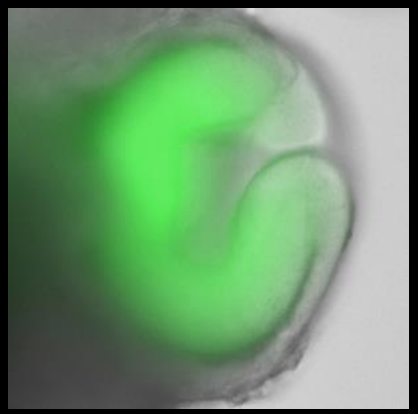
M. Eiraku Y. Sasai

Self-Organizing
Polarized Cortical Tissues



(Eiraku et al., *Cell Stem Cell* 2008)

Self-Organizing Optic-cup



(Eiraku et al., *Nature* 2011)

Organoids are not only interesting tools for studying organogenesis but also could be useful platforms for medical applications

Potential of organoid technologies

CellPress

Cell Stem Cell

Short Article

Zika Virus Depletes Neural Progenitors in Human Cerebral Organoids through Activation of the Innate Immune Receptor TLR3

Jason Dang,[1,2,6] Shashi Kant Tiwari,[1,6] Gianluigi Lichinchi,[1,3] Yue Qin,[1] Veena S. Patil,[1] Alexey M. Eroshkin,[4] and Tariq M. Rana[1,5,*]

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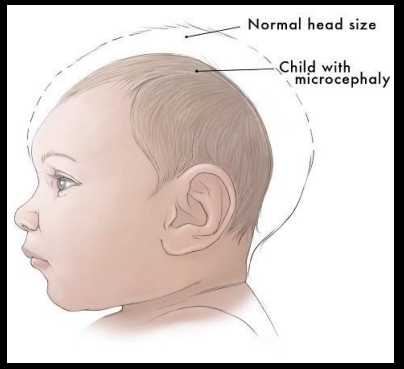
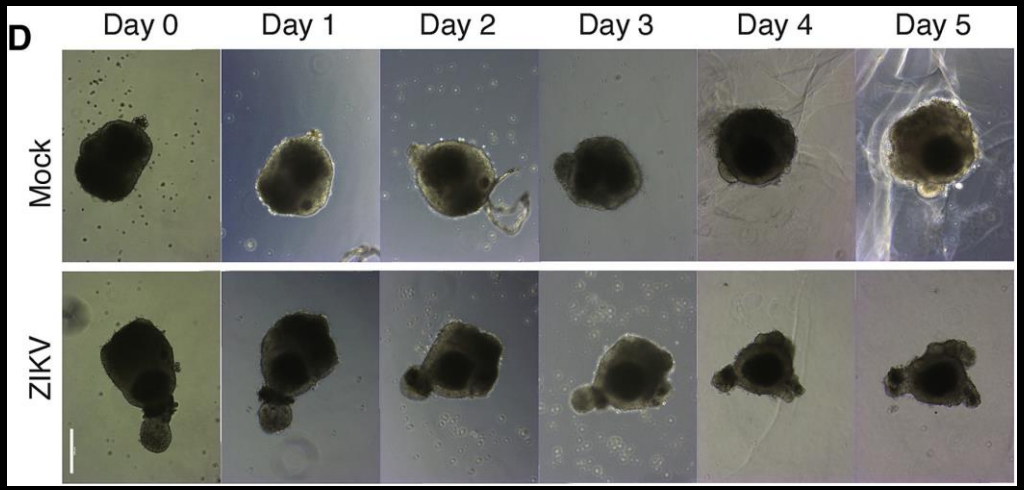
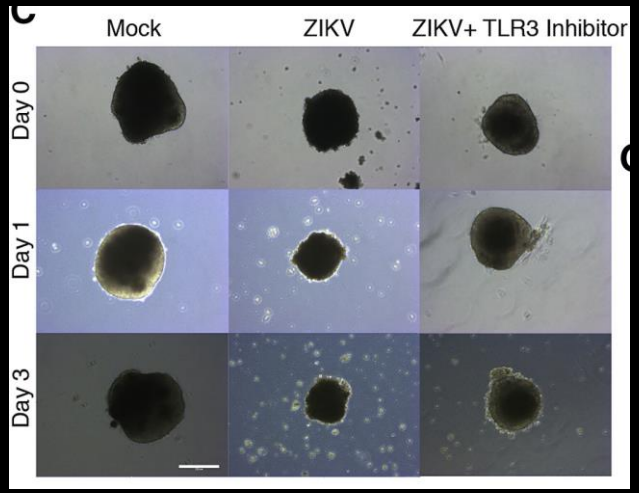
[5]Institute for Genomic Medicine, University of California San Diego, La Jolla, CA 92093, USA
[6]Co-first author
*Correspondence: trana@ucsd.edu
http://dx.doi.org/10.1016/j.stem.2016.04.014



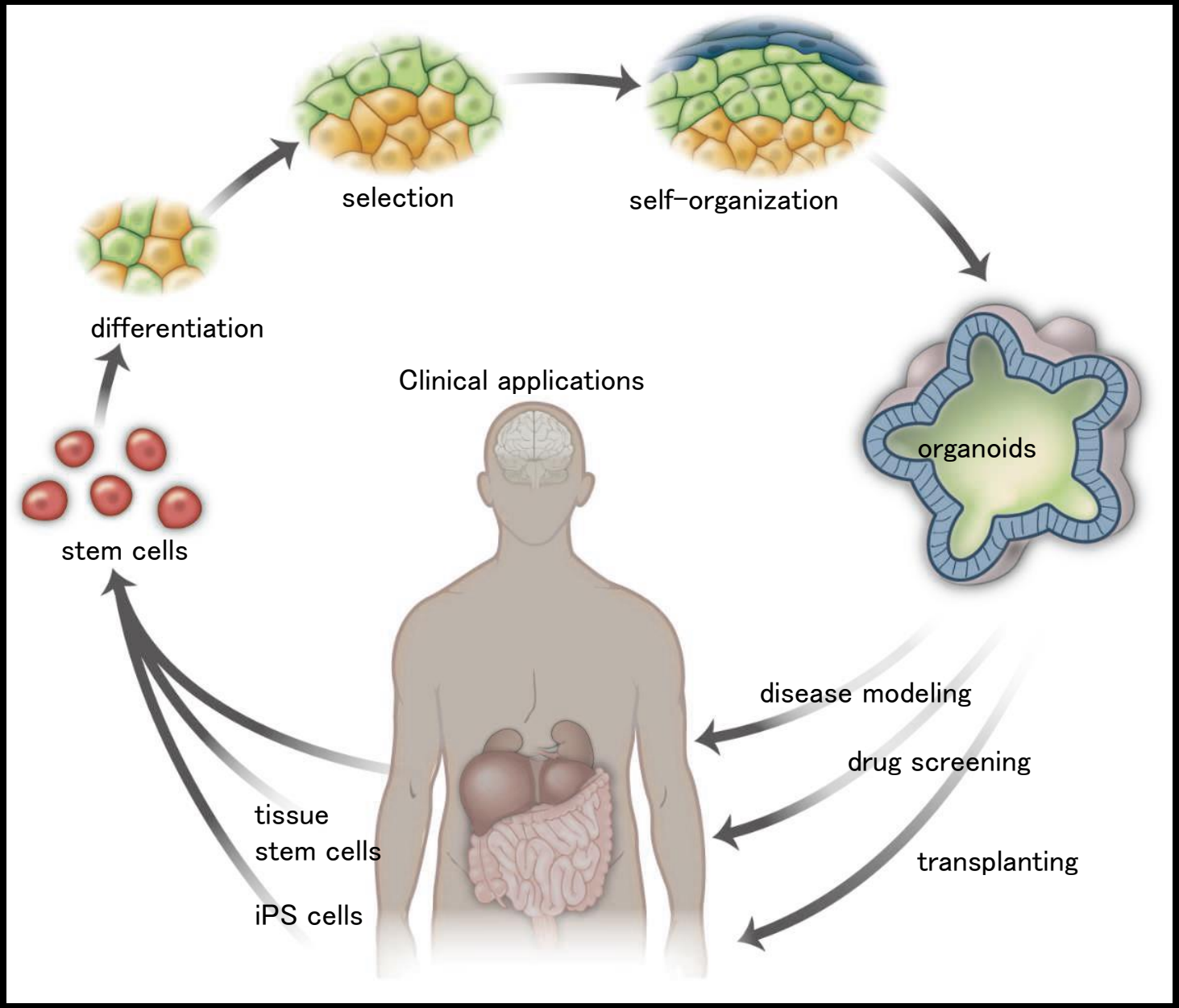
Zika virus infection during pregnancy causes microcephaly in a baby





(J. Dong et al., *Cell Stem Cell* 2016)

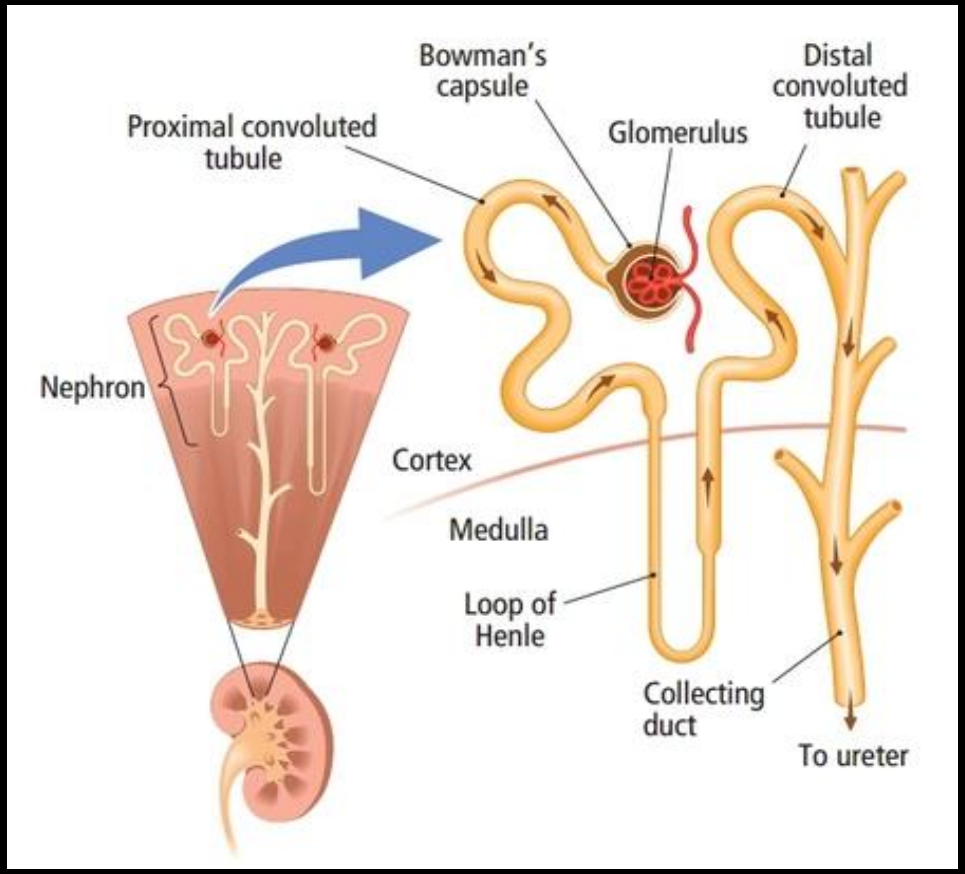
Potential of organoid technologies



(modified from Lancaster and Knoblich, Science 2014)

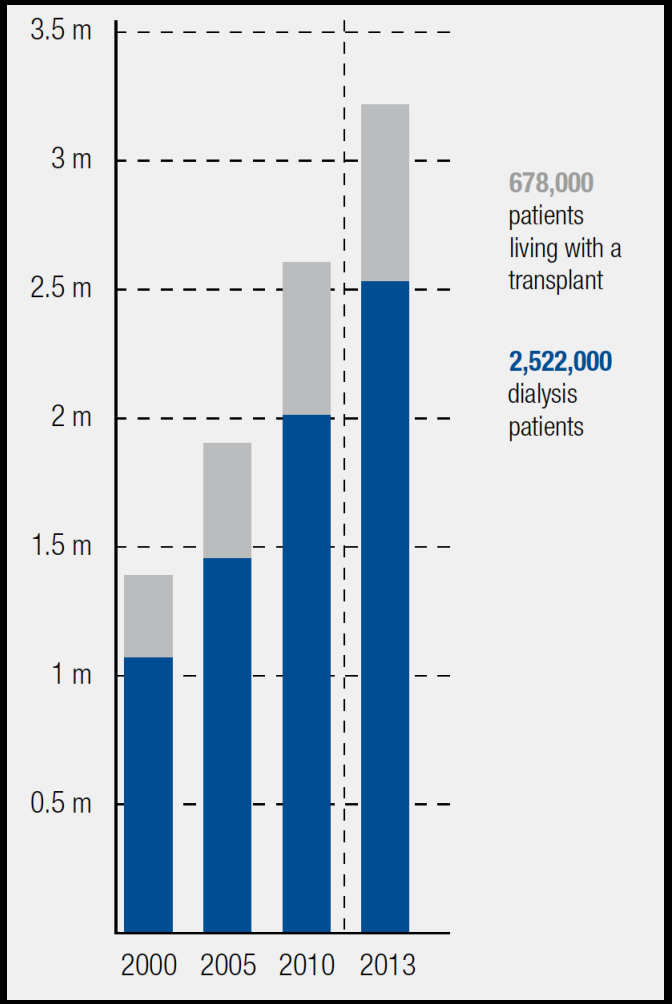
Kidney anatomy

Structure



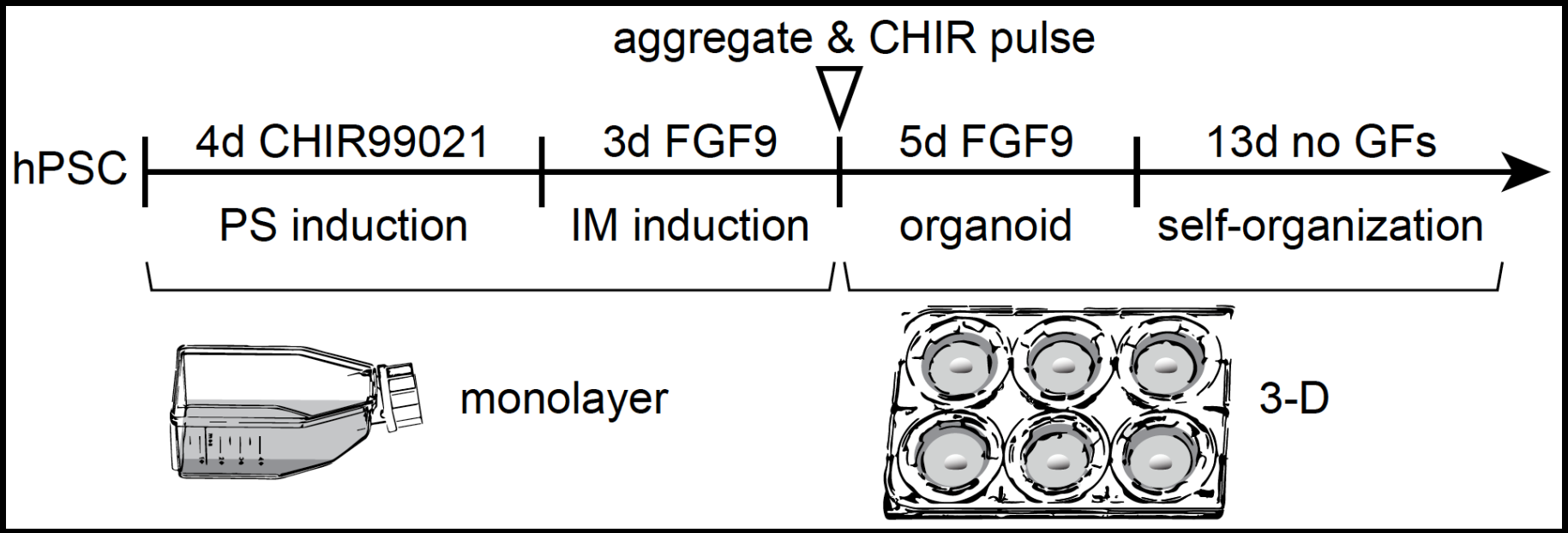
leavingcertbiology.net (Chapter 37: The Human Urinary System)

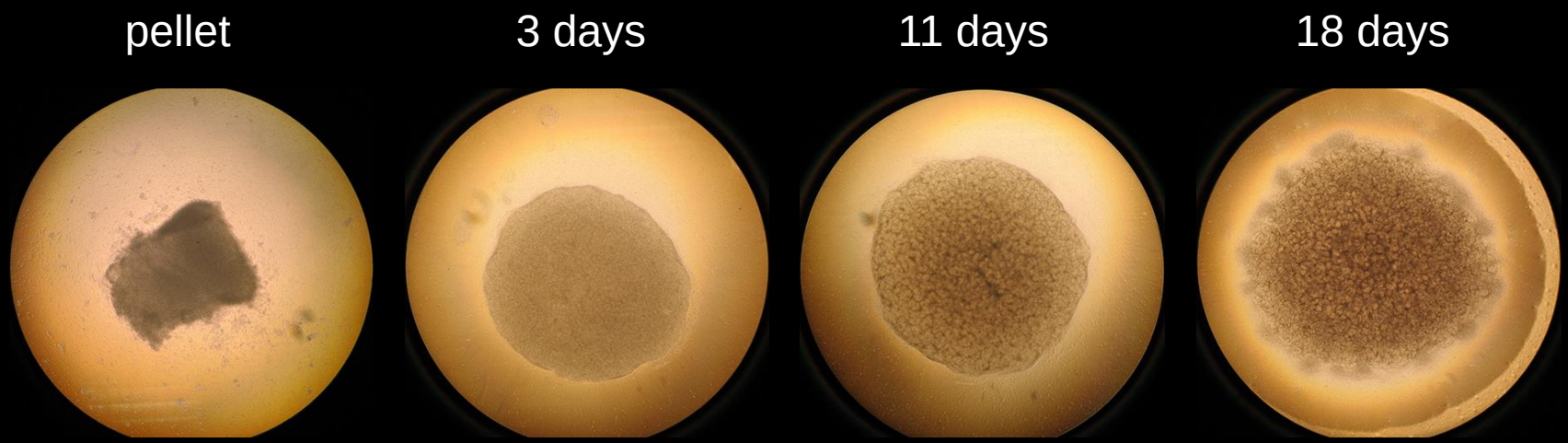
of ESKD patients in the world



(Fresenius Medical Care Deutschland. 2014)

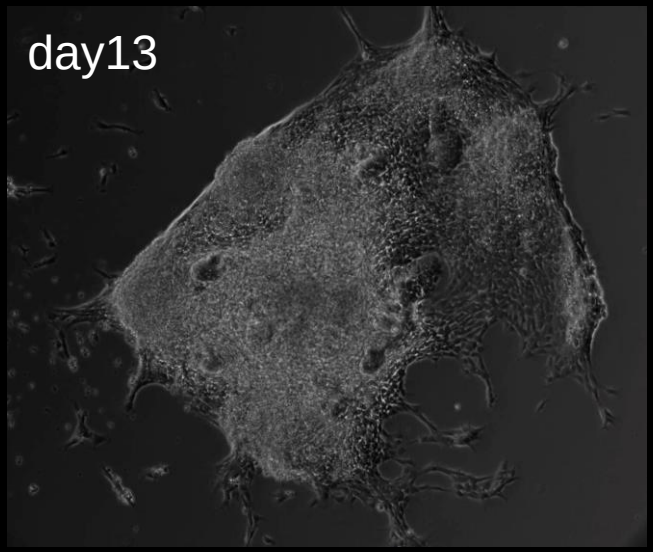
A mixture of AI + PI generated kidney organoids

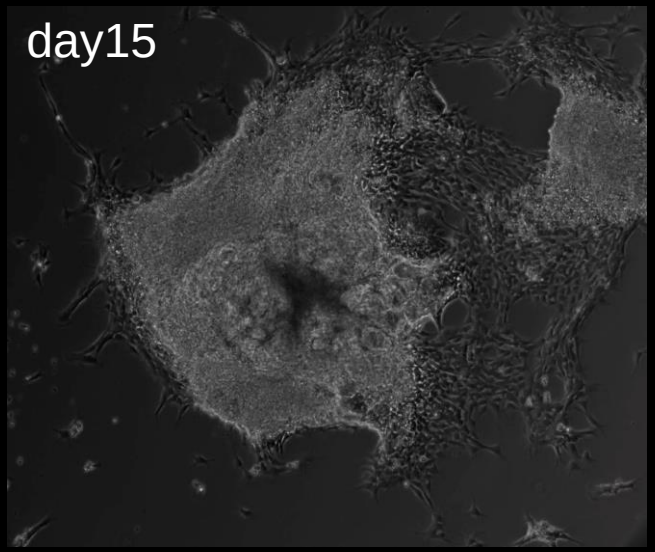


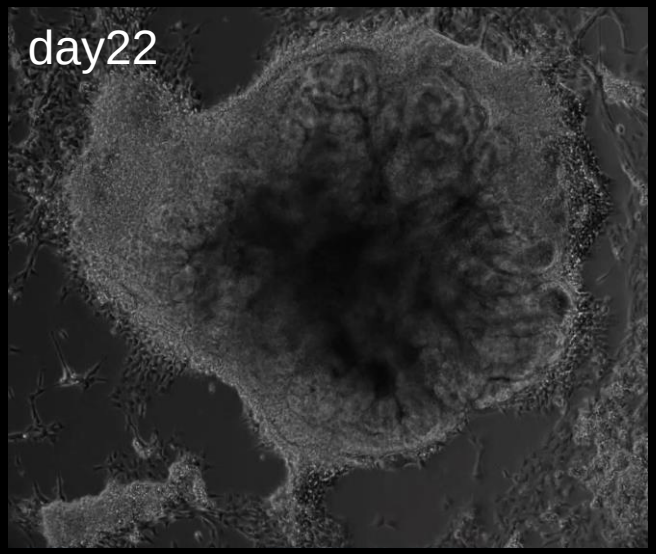


(Takasato et al., *Nature* 2015)

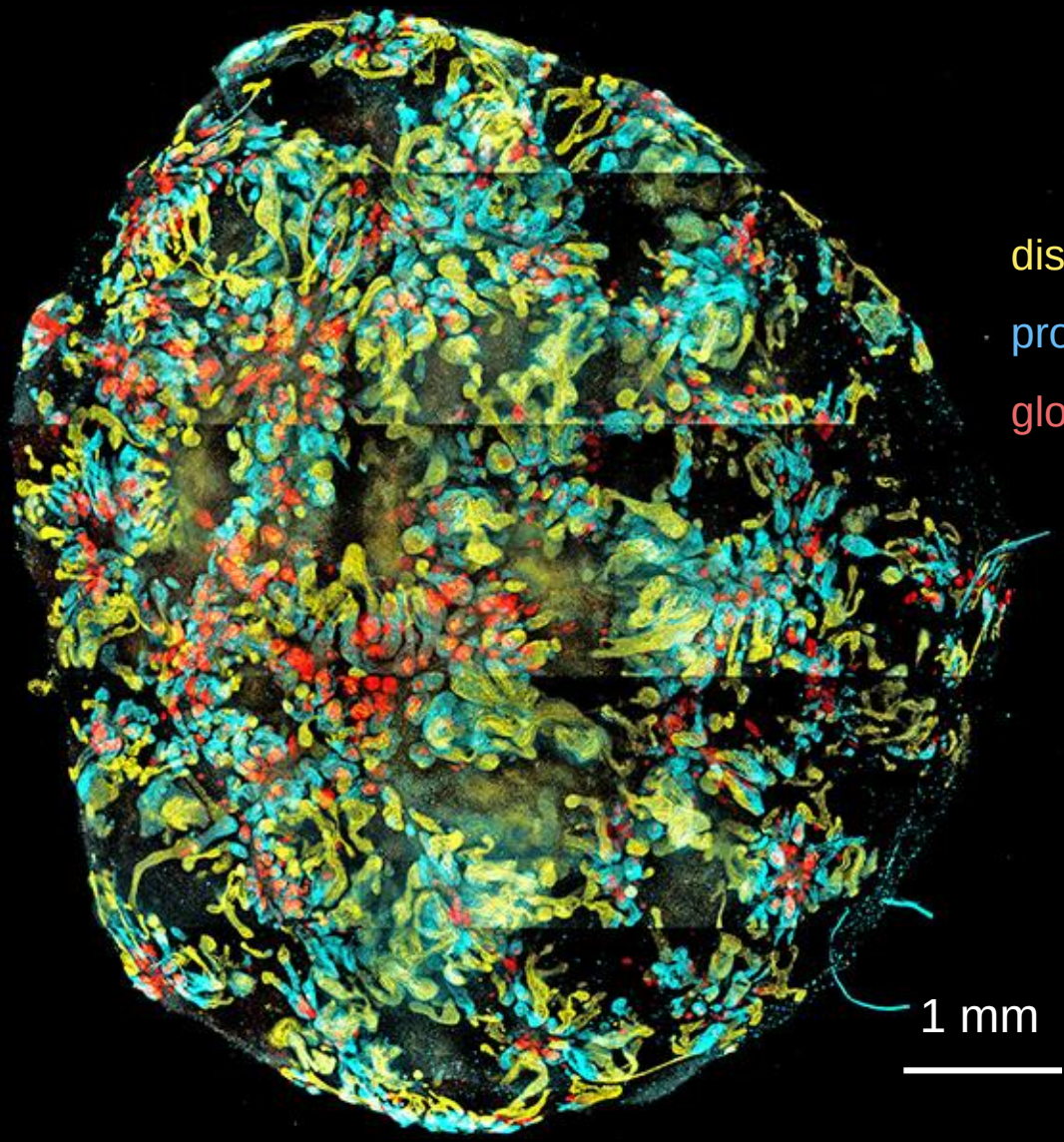
Time-lapse of a developing kidney organoid







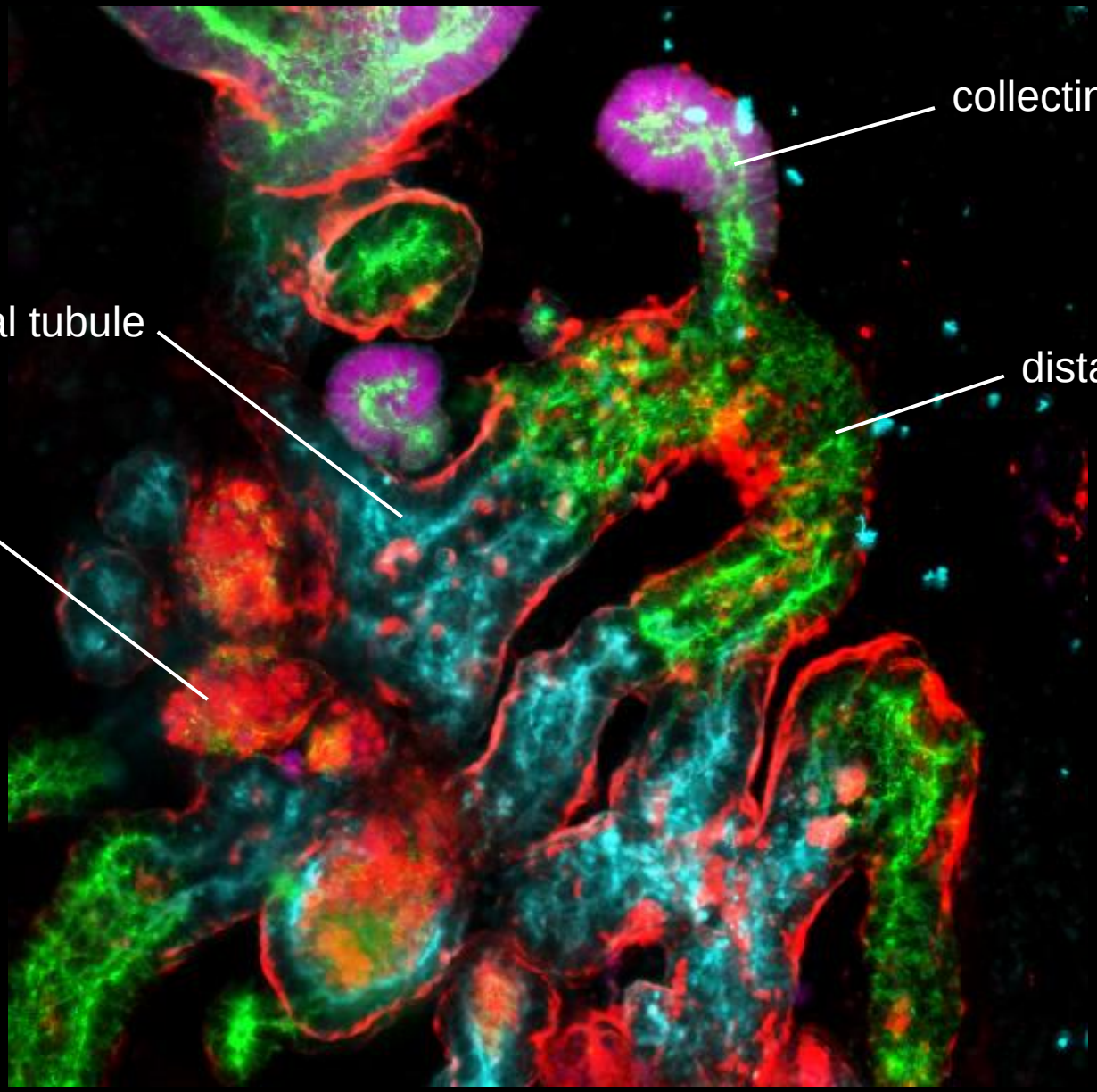
Kidney organoids comprised nephrons



(Takasato et al., *Nature* 2015)

Self-organizing nephrons consisted of 4 segments

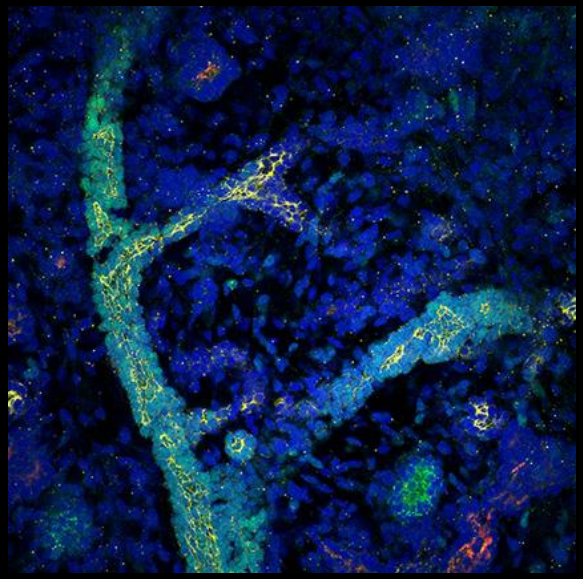
GATA3
ECAD
LTL
WT1



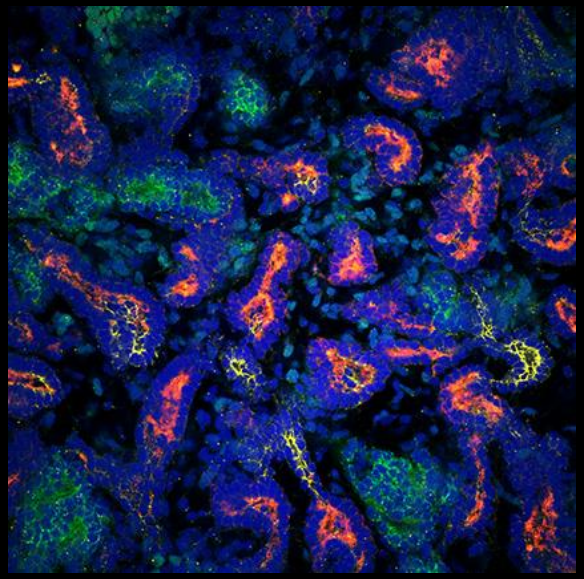
(Takasato et al., *Nature* 2015)

Ducts in the bottom layer, Glomeruli in the outer layer

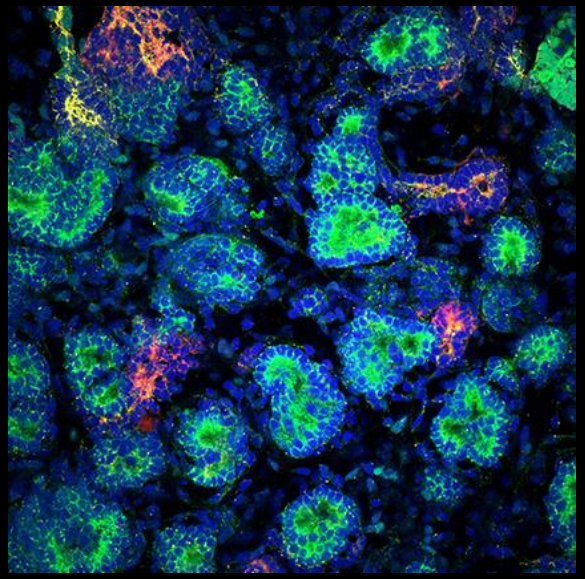
Bottom



Middle



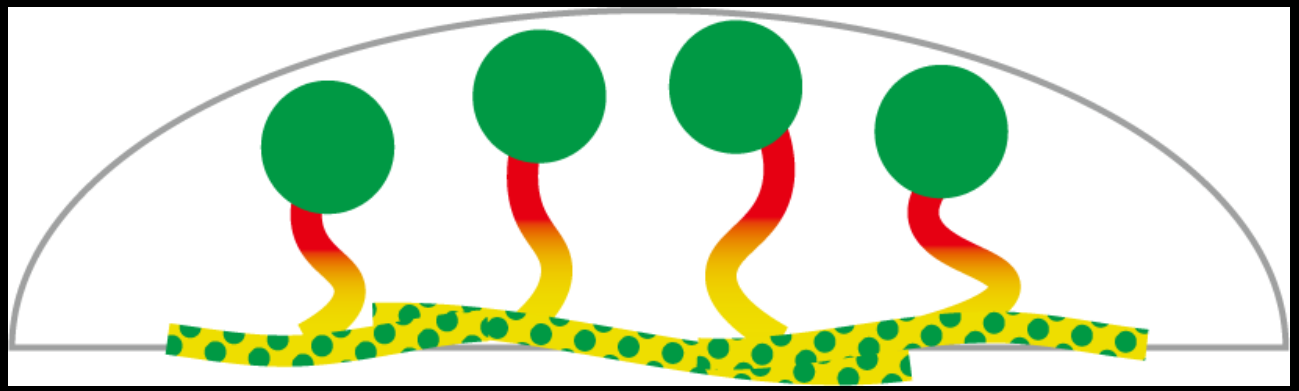
Top



Top

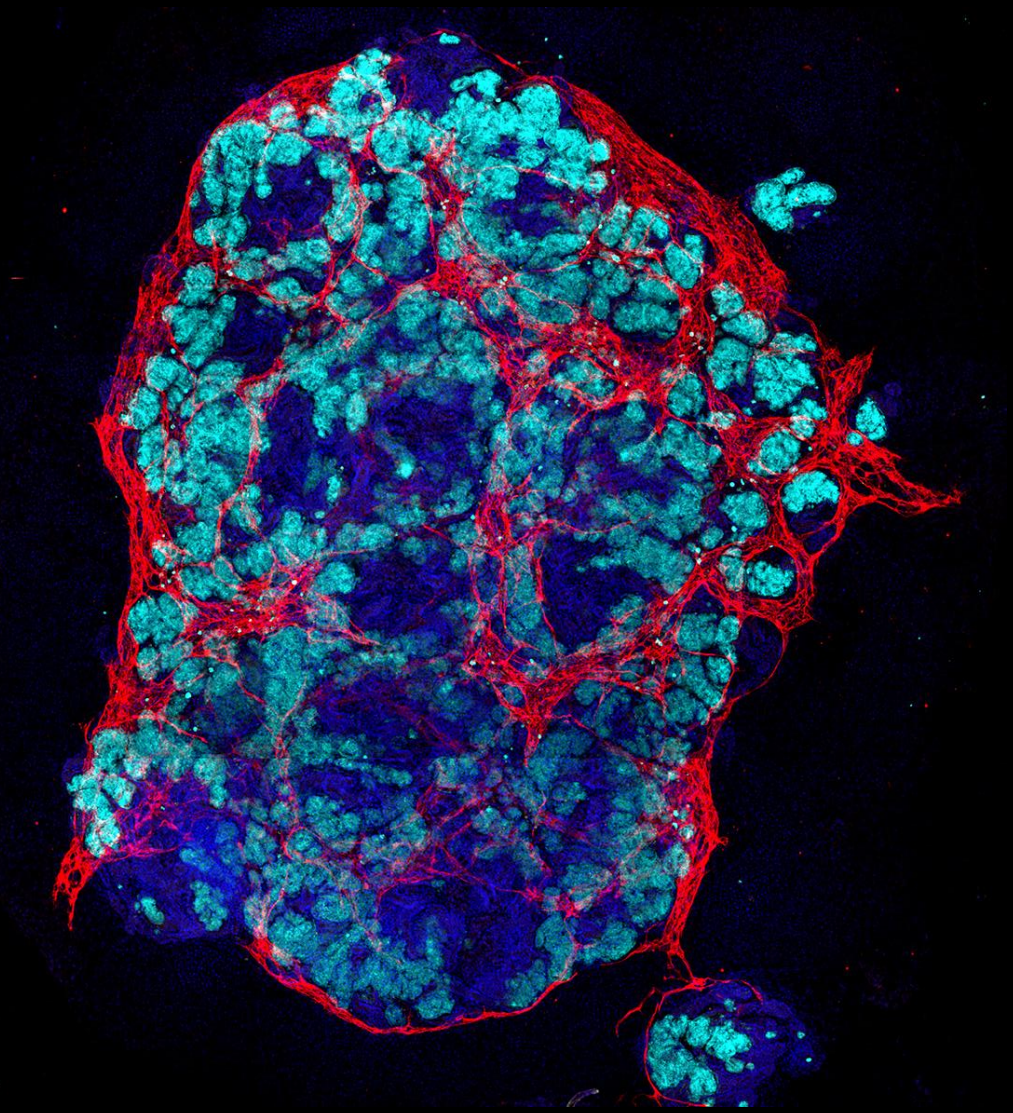
Middle

Bottom



(Takasato et al., *Nature* 2015)

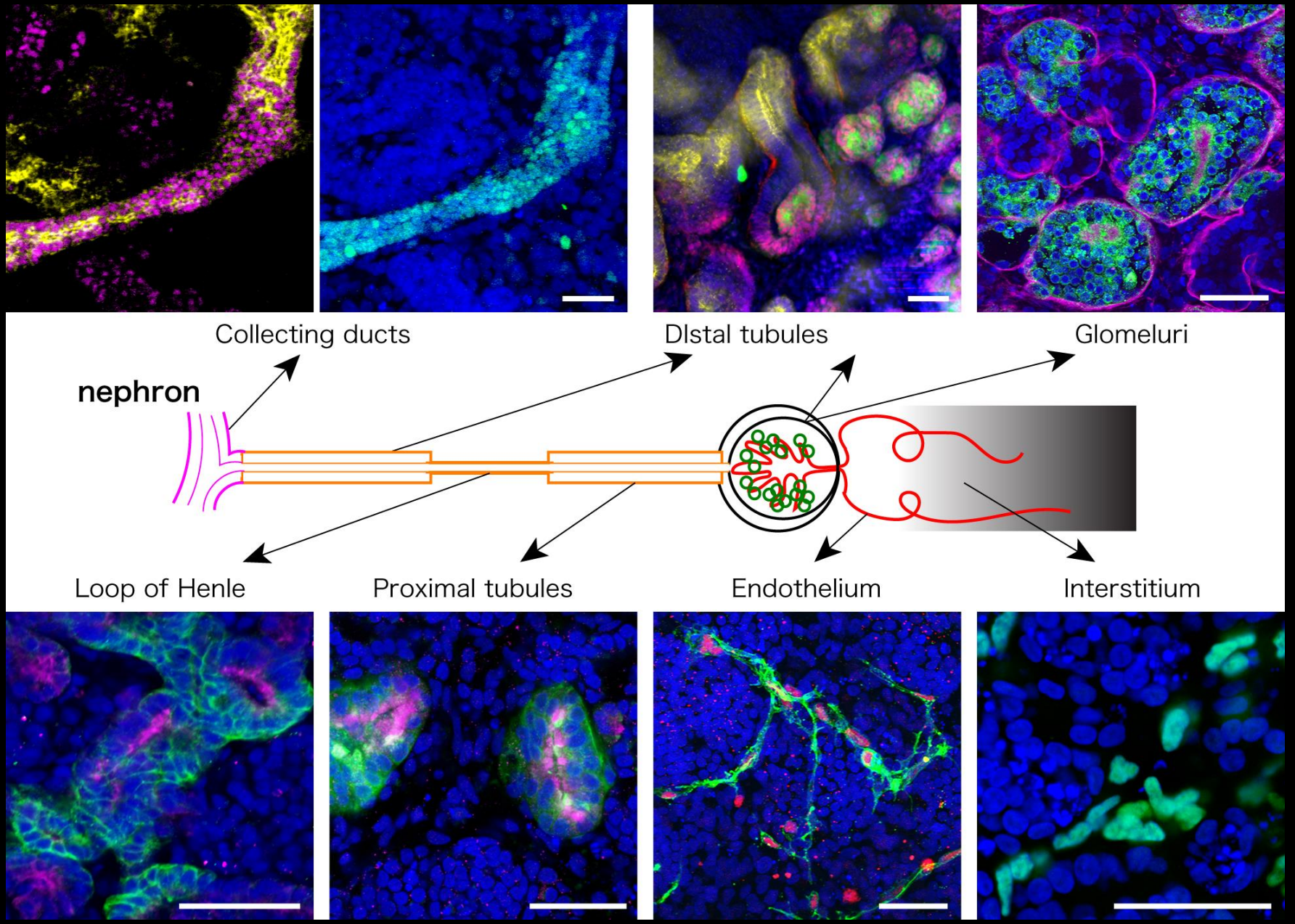
Kidney organoids contain vascular network



Glomerulus Vasculature

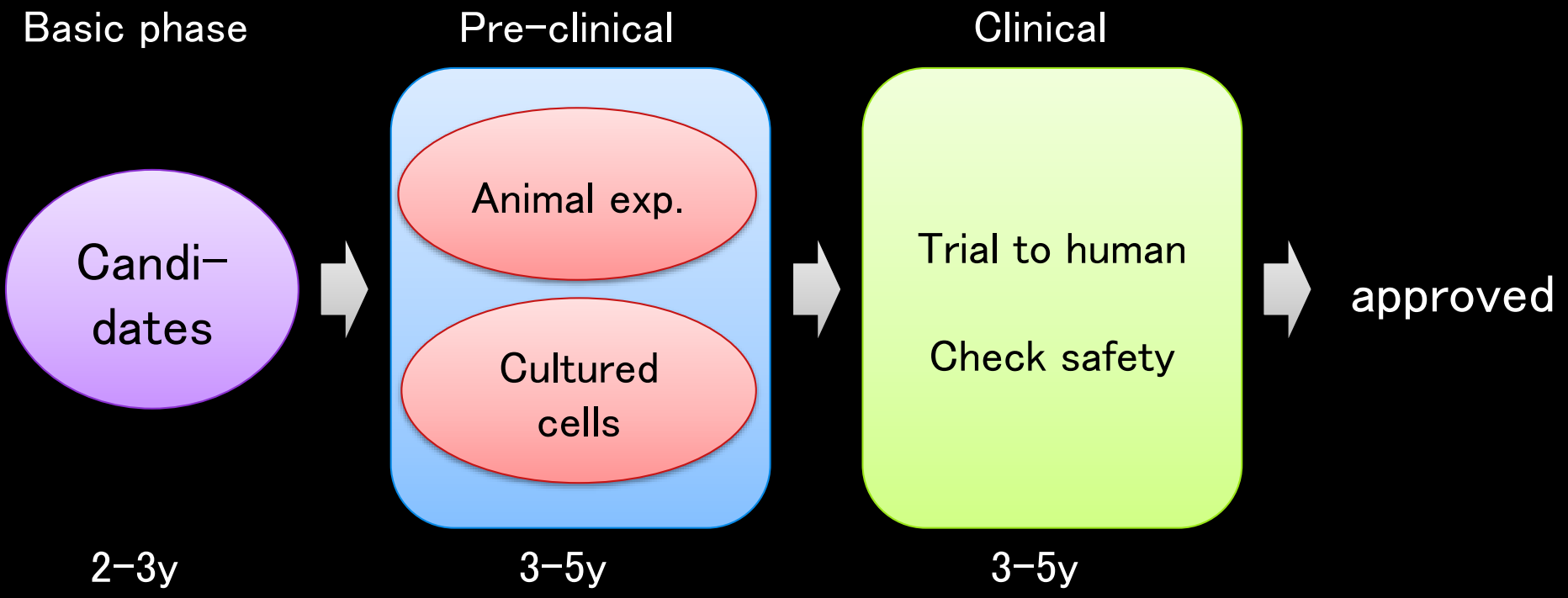
(Takasato et al., *Nature Protocols* 2016)

All anticipated renal structures developed in kidney organoids



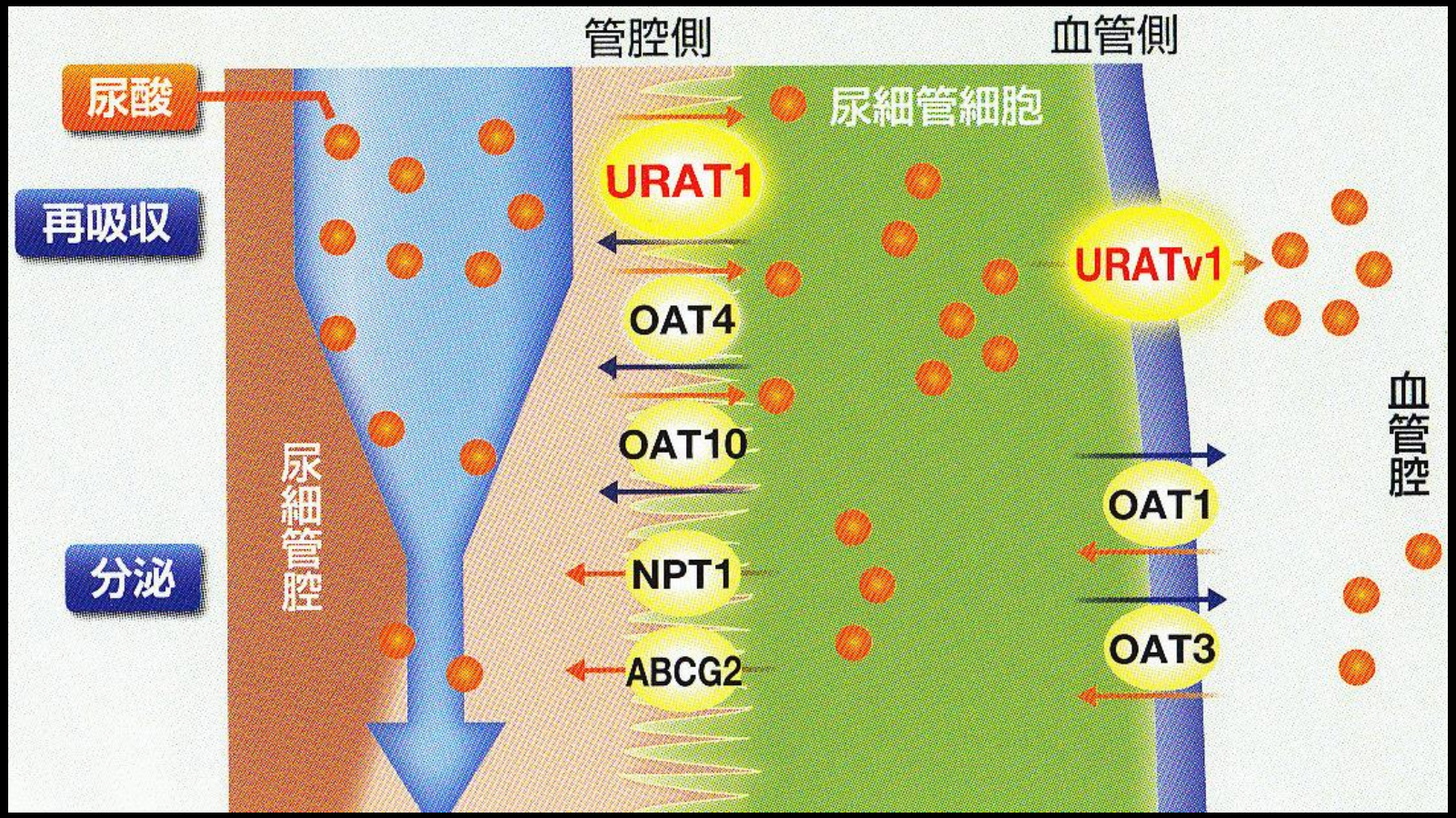
Scale = 100 μm

Nephrotoxicity assay for drug development



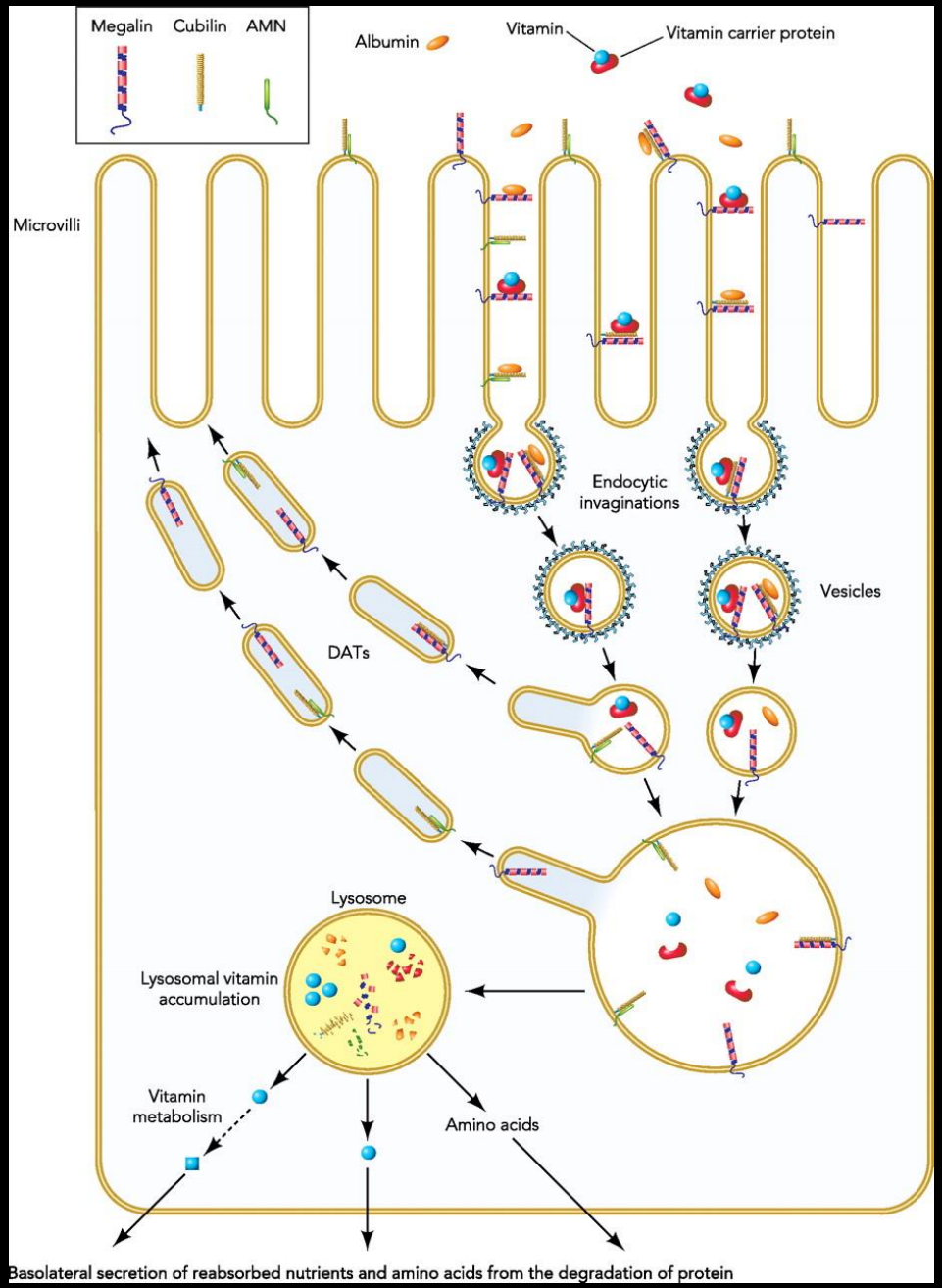
Success rate：1 / 30,000
Cost：Billions of Yen

Reabsorption function of renal proximal tubules



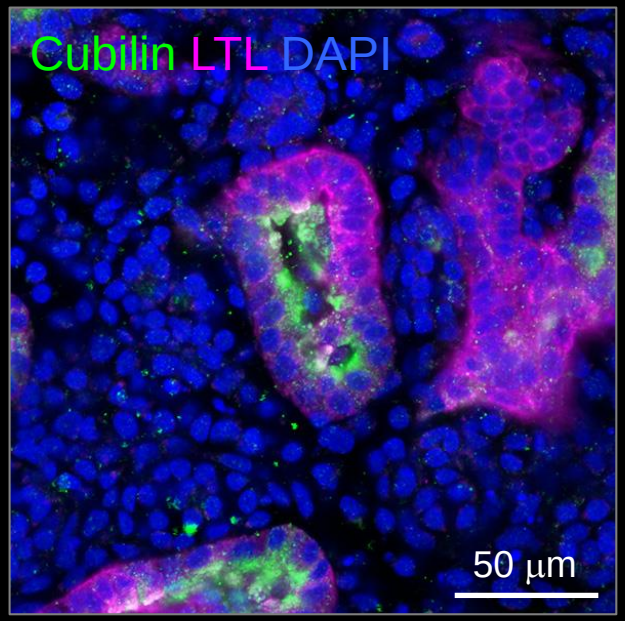
Physiological function drives pharmacokinetics

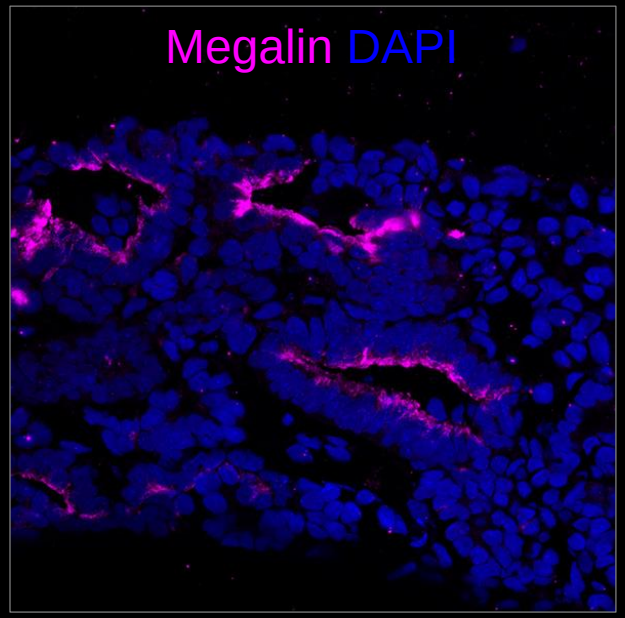
Megalin-Cubilin mediated endocytosis in PT

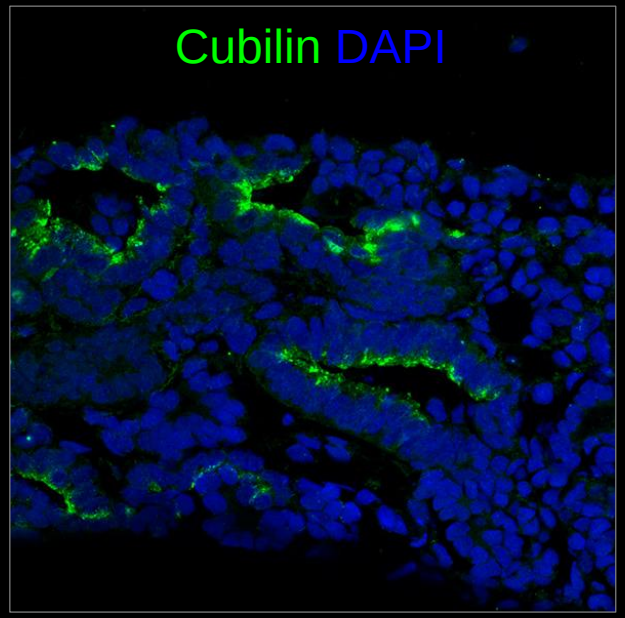


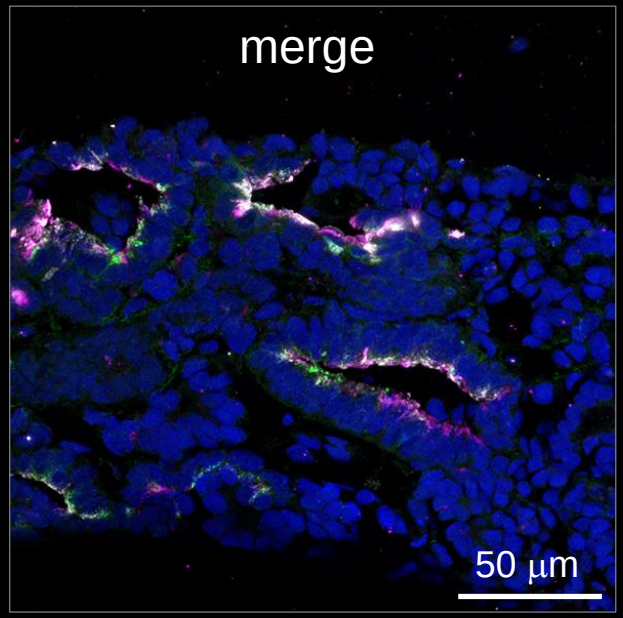
(Christensen et al, *Physiology* 2012)

PT expresses both Megalin and Cubilin

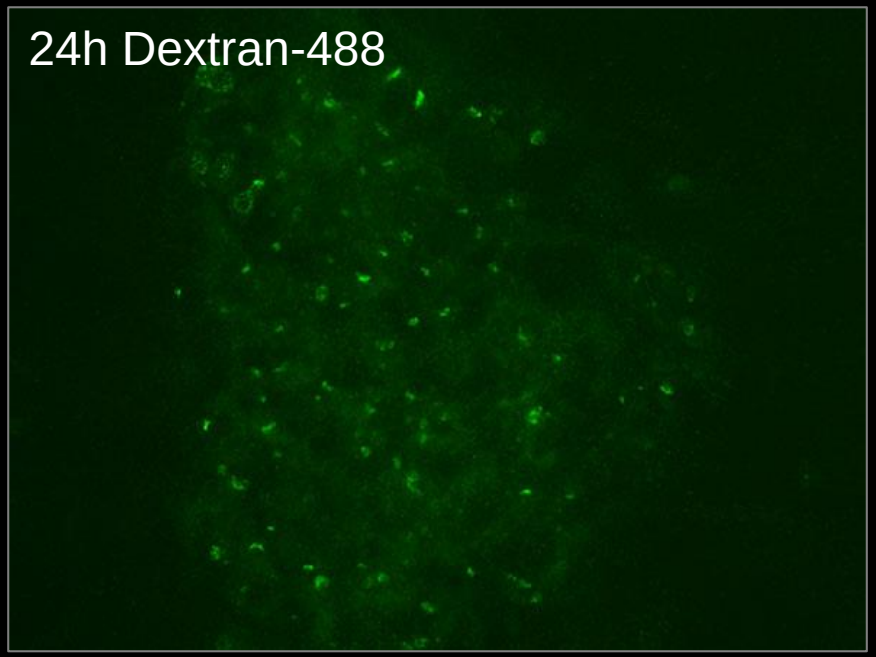




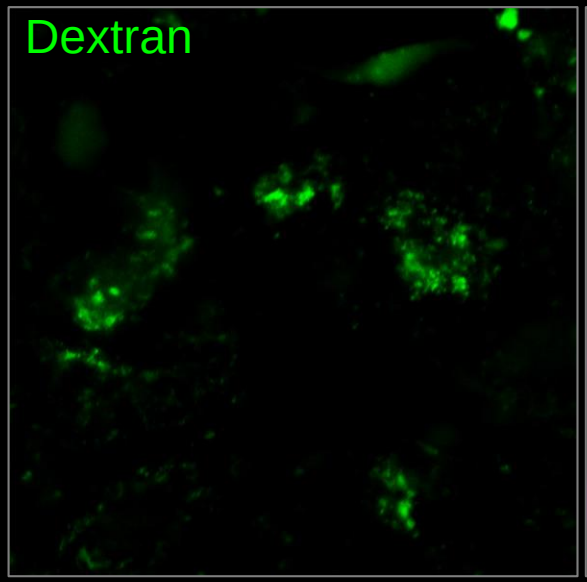


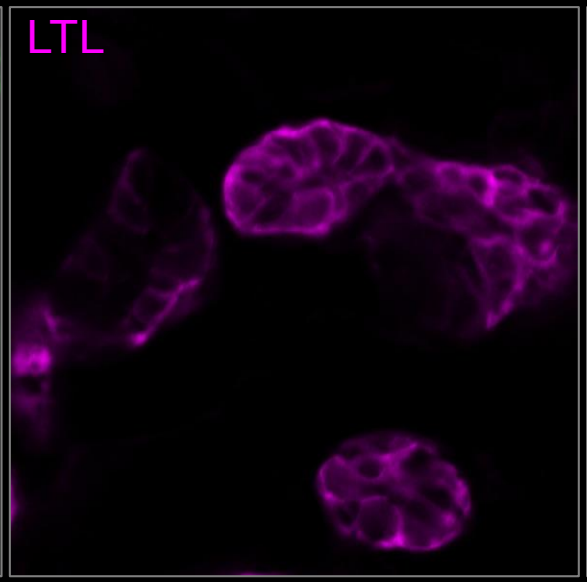


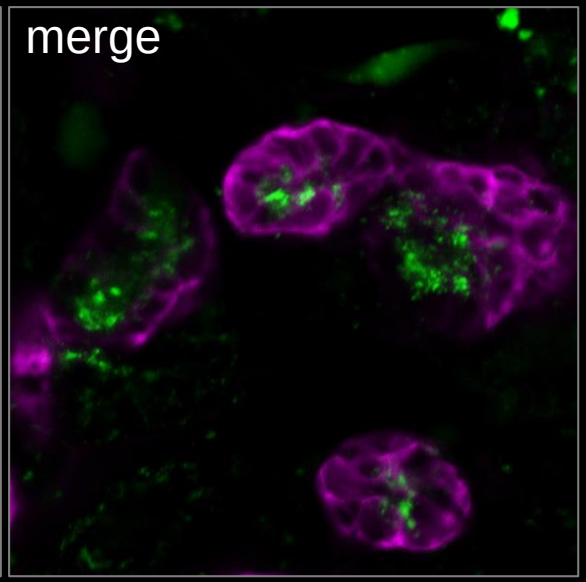
Dextran uptake in proximal tubules



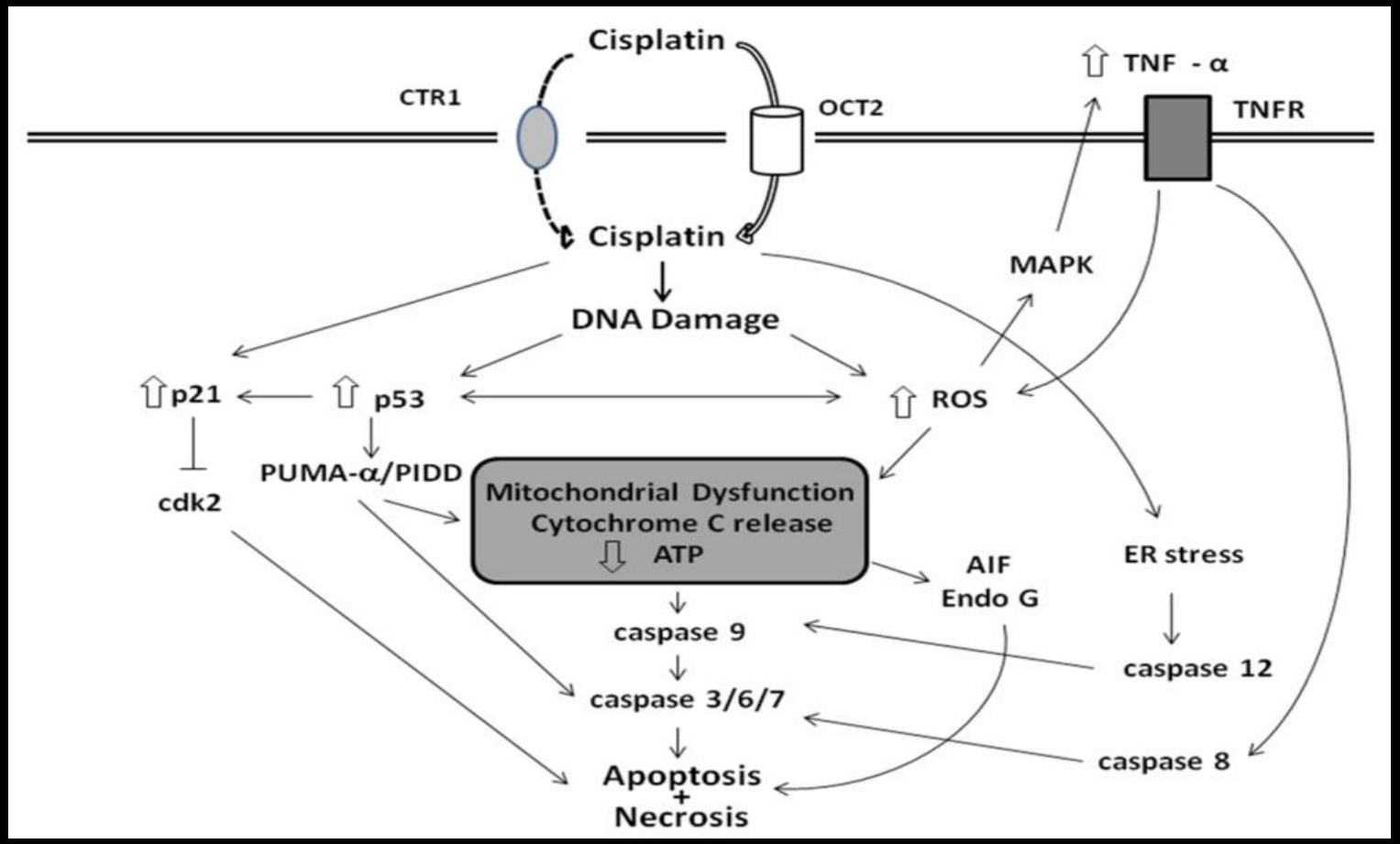
Dextran: a polysaccharide endocytosed by the PT







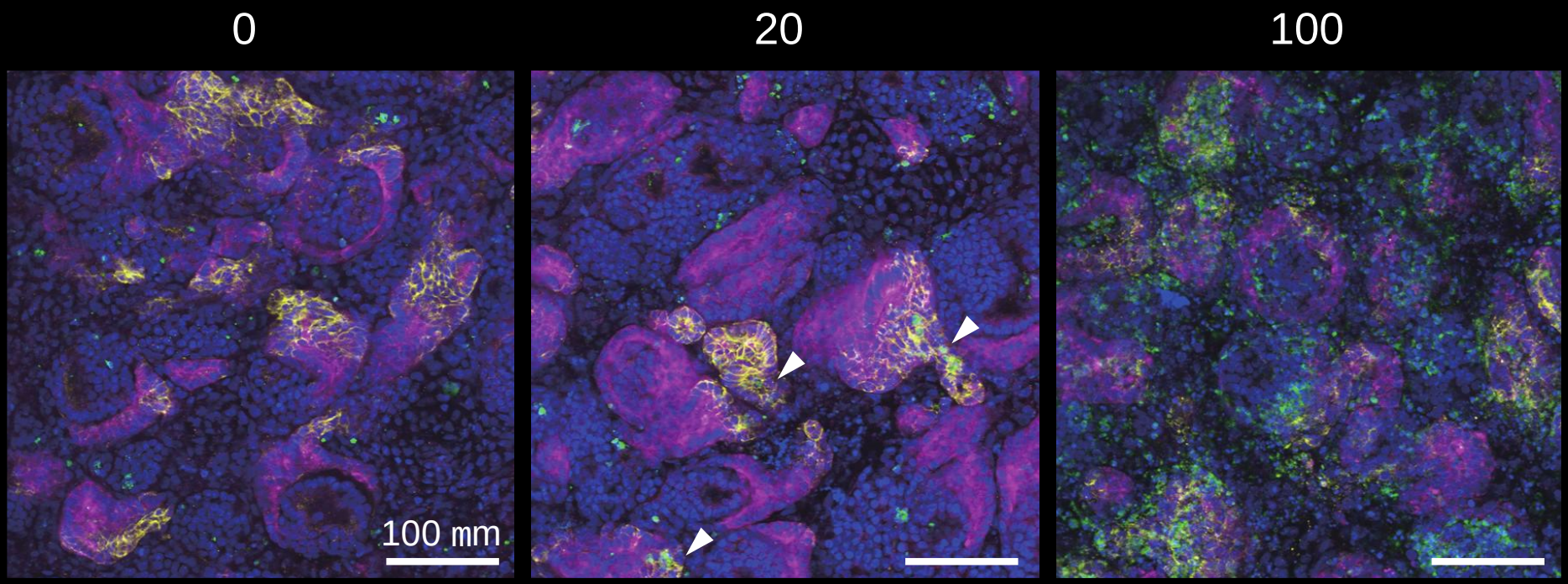
Cisplatin induces acute apoptosis in PT



(RP Miller et al, *Toxins* 2010)

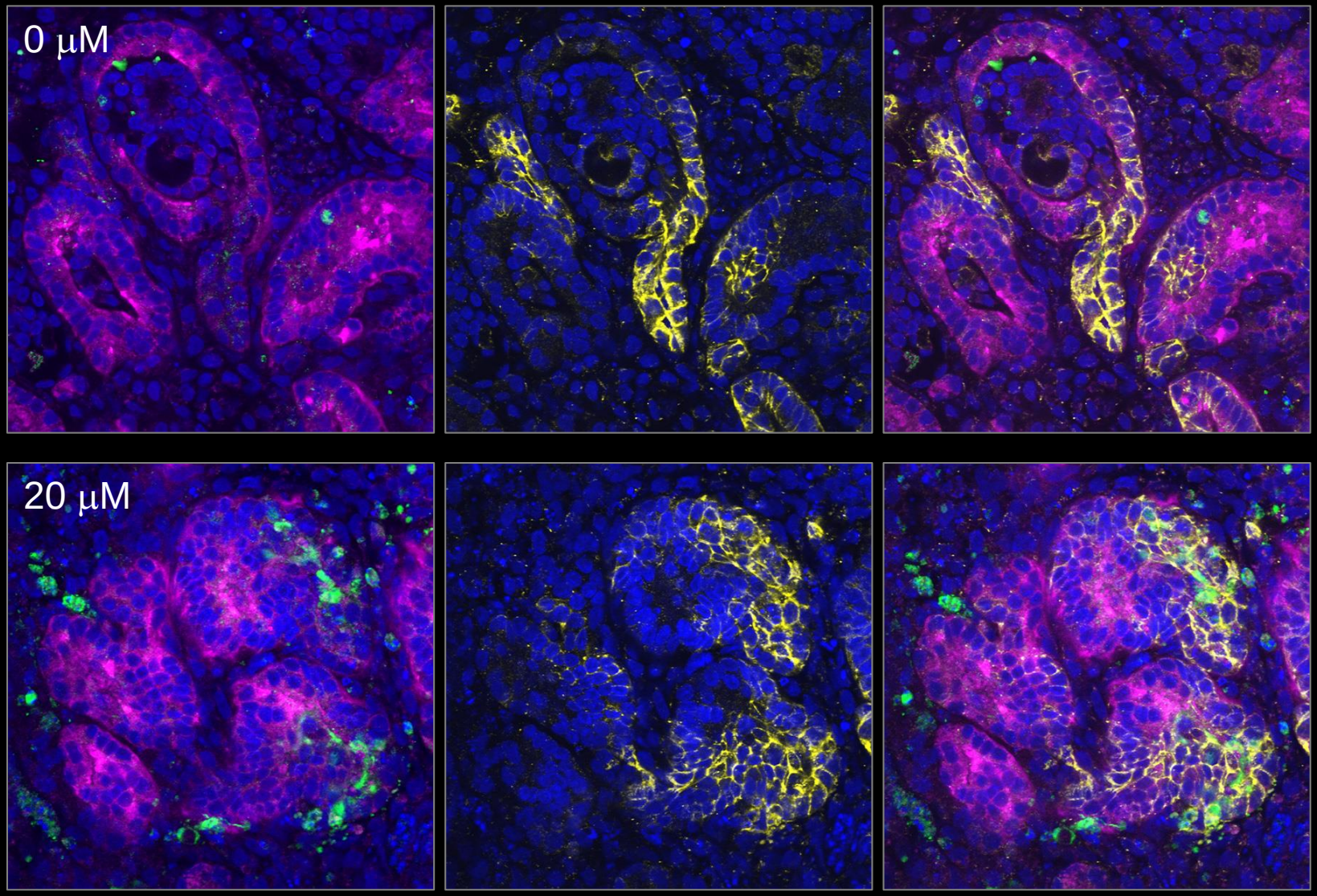
Low dose Cisplatin induced tissue specific cell death

24h Cisplatin [μM]

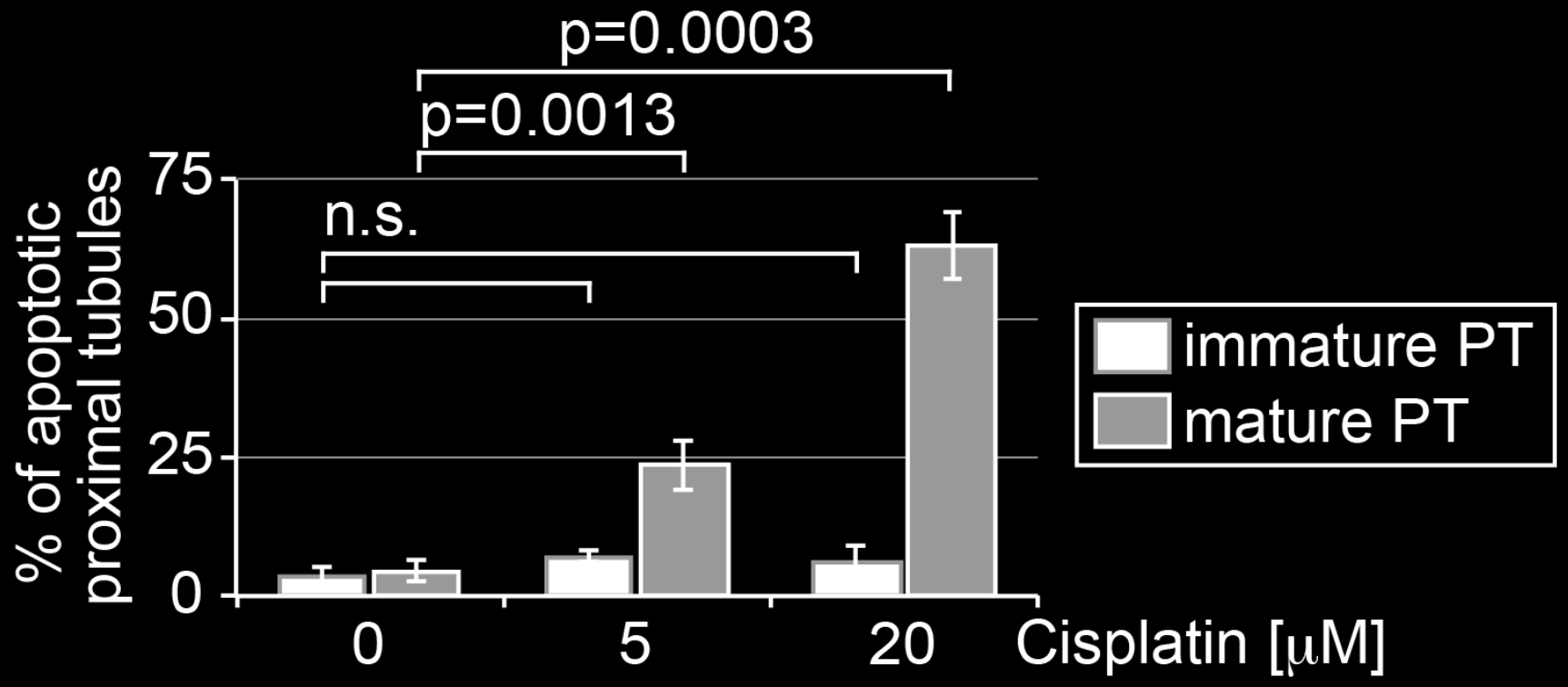


LTL ECAD cleaved-CASP3 DAPI

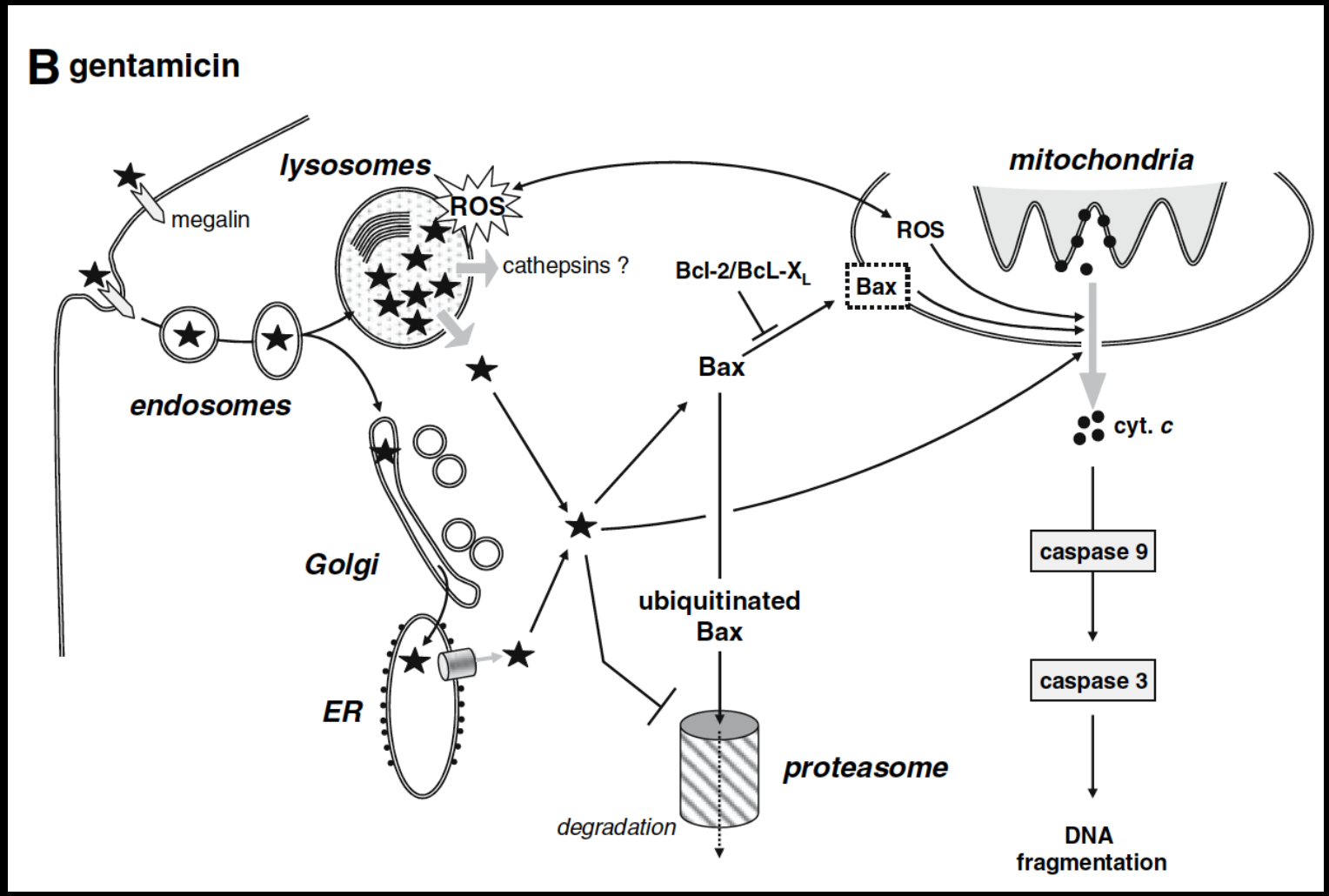
Low Cisplatin induced matured PT-specific apoptosis



Low Cisplatin induced matured PT-specific apoptosis



Renal tubules uptake gentamicin by endocytosis

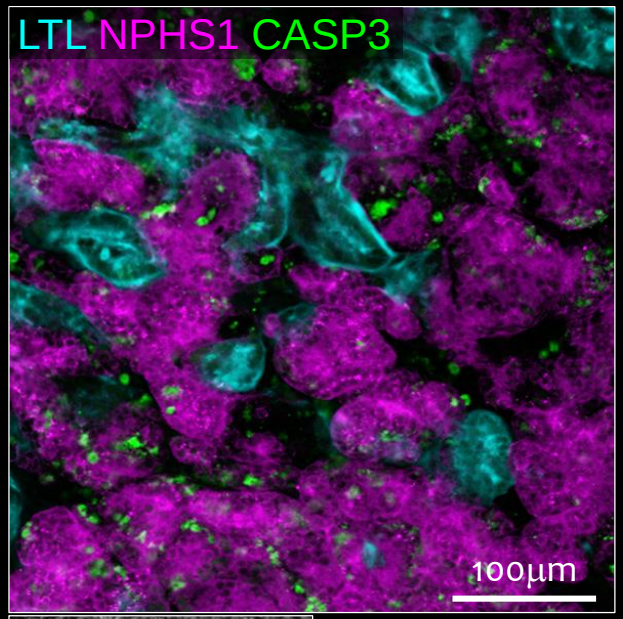


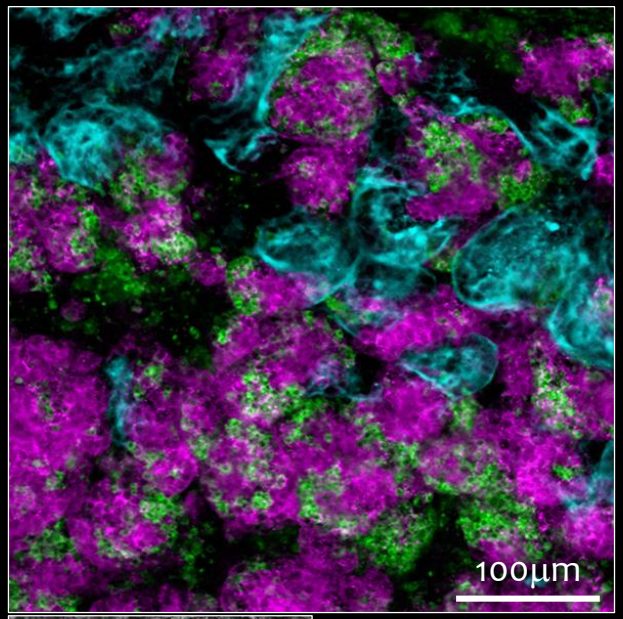
(Servais H. Apoptosis 2008)

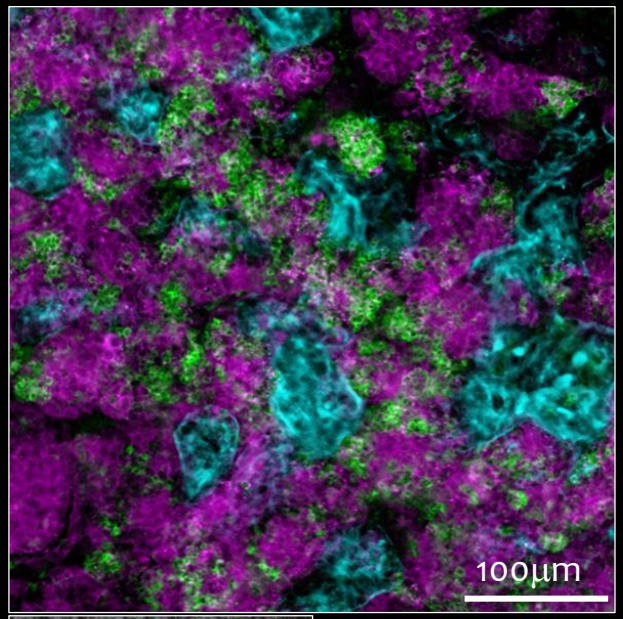
Gentamicin induced podocyte specific cell death

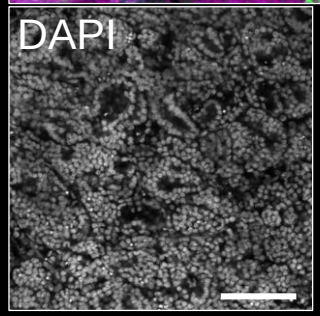
0mM Gentamicin 48h

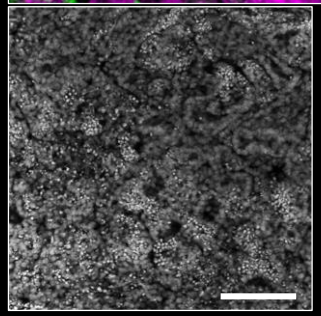
10mM Gentamicin 48h

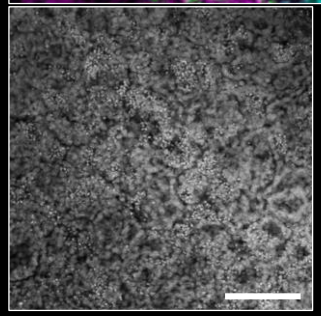








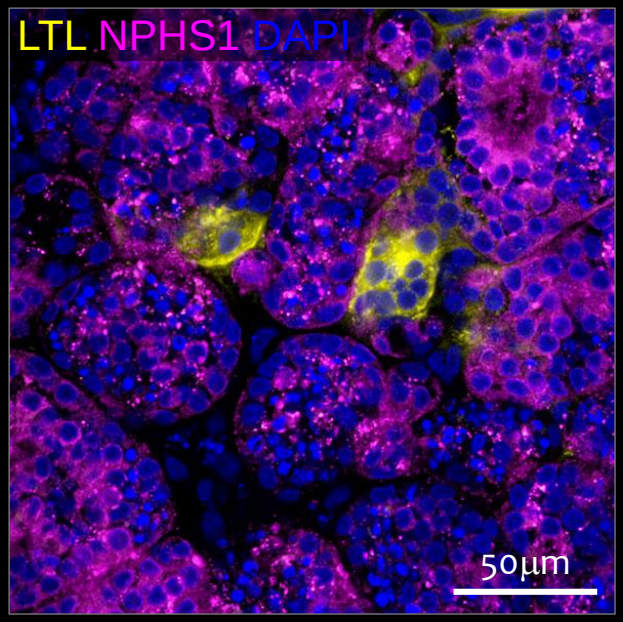


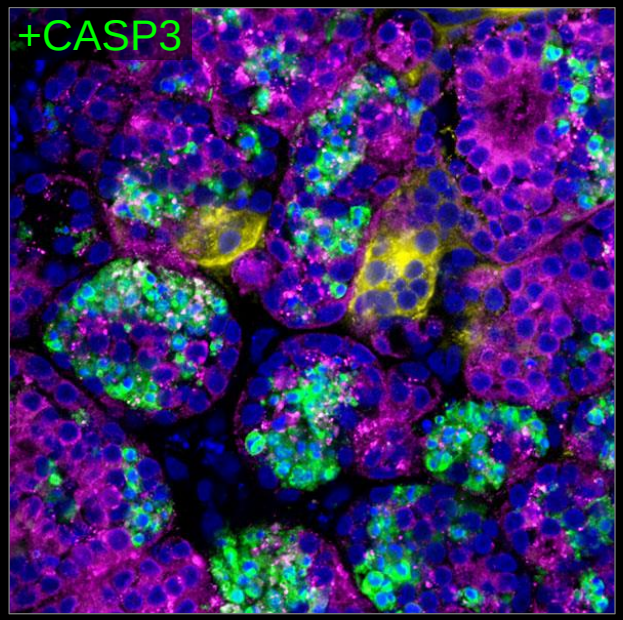


(*Unpublished*)

Gentamicin induced podocyte specific cell death

#1





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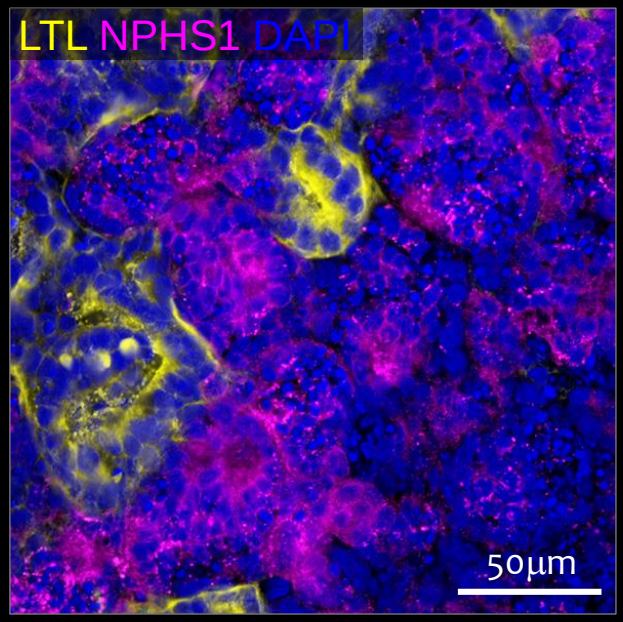
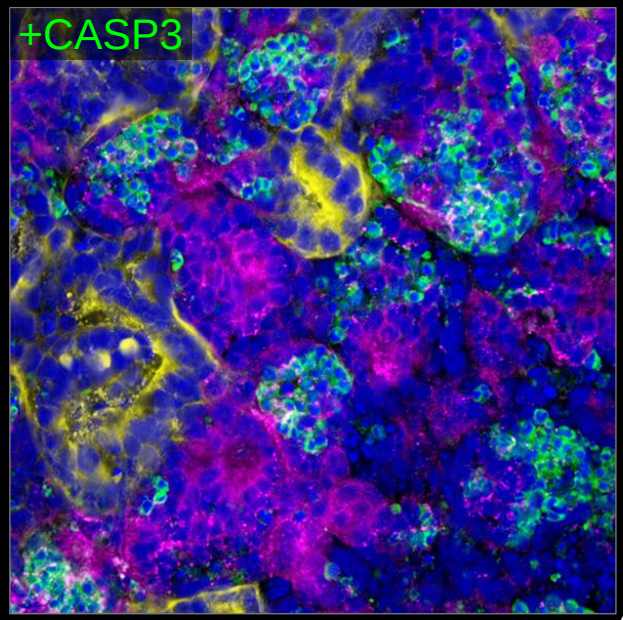
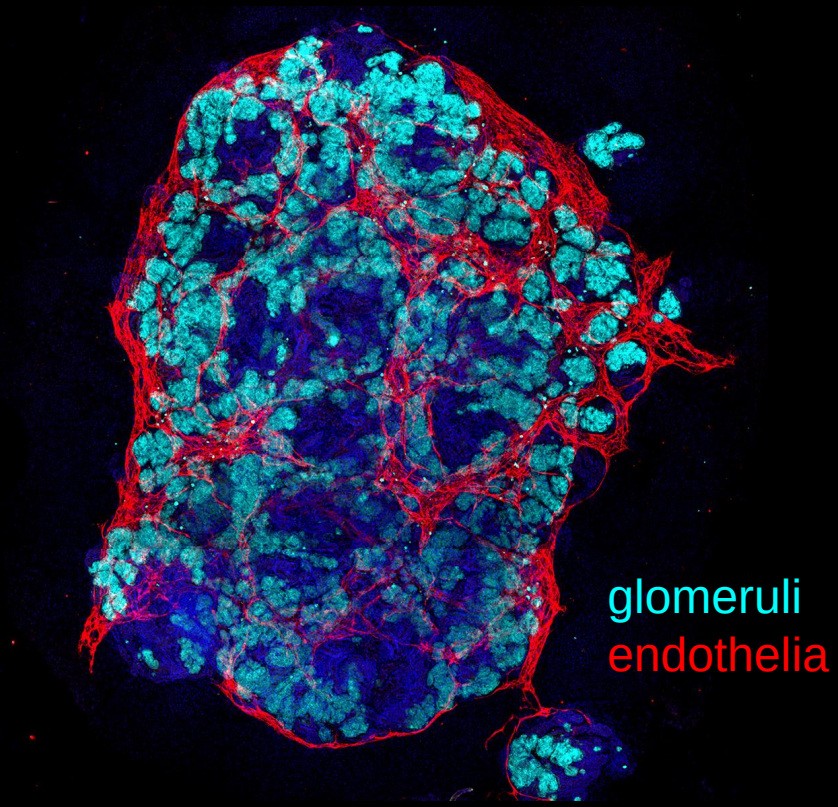




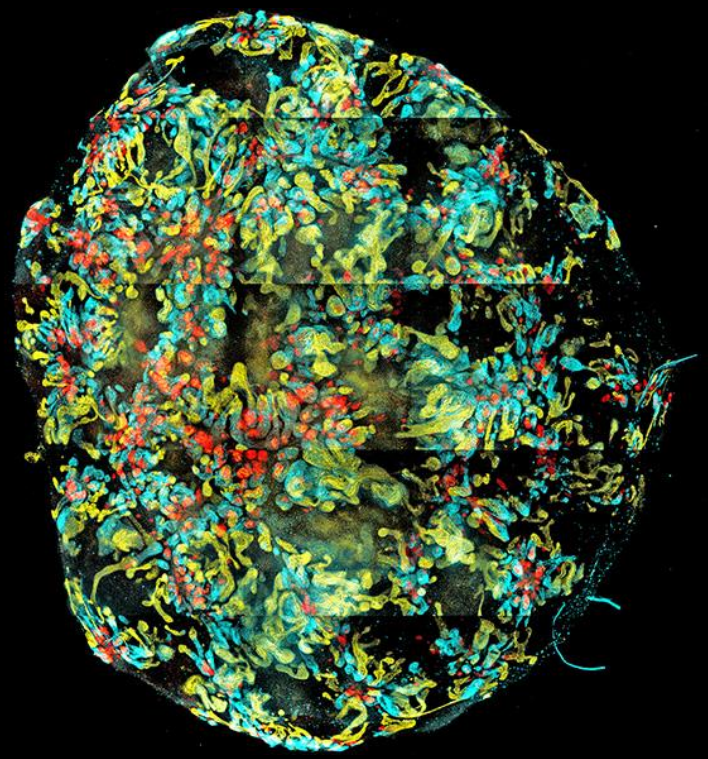
(*Unpublished*)

kidney organoids are not transplantable yet

1. Glomeruli are not fully vascularized



2. Ureter does not develop in the organoid

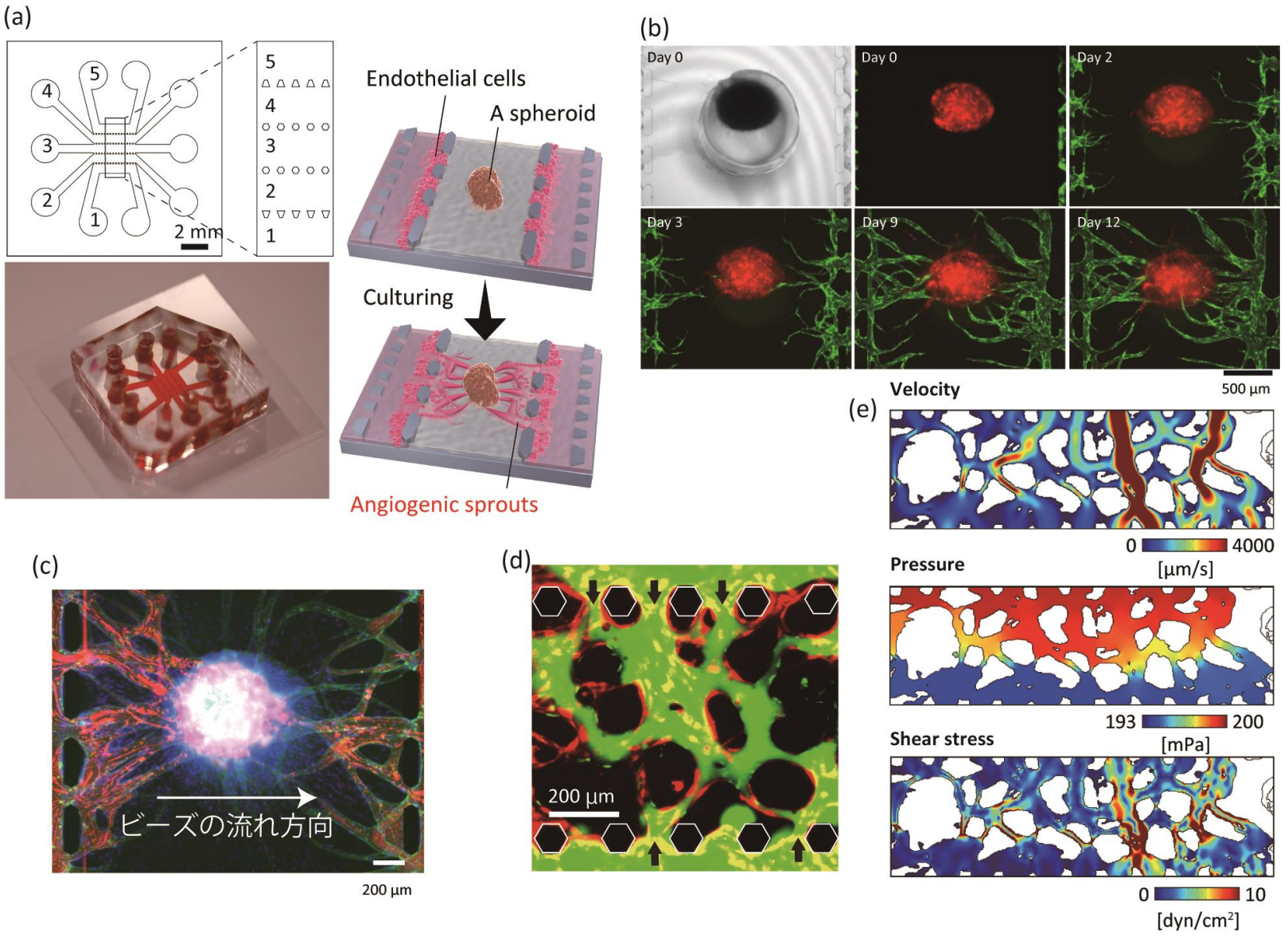


3. Cell heterogeneity is not perfectly controlled.

4. Cells are not well matured

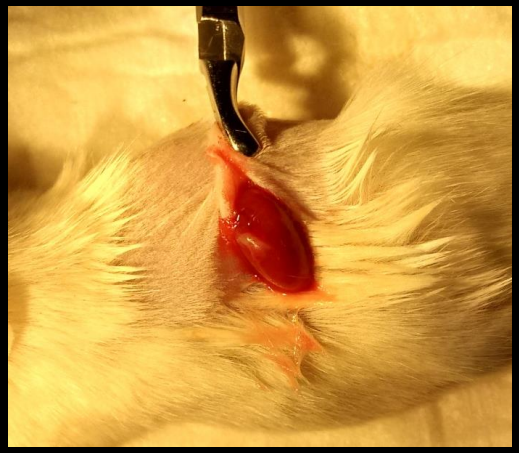
Organo-on-a-chip for vascularisation of organoids

代表：横川 隆司、分担：荒岡（CiRA）、山下（CiRA）、高里（理研）、榎木（タカラバイオ）



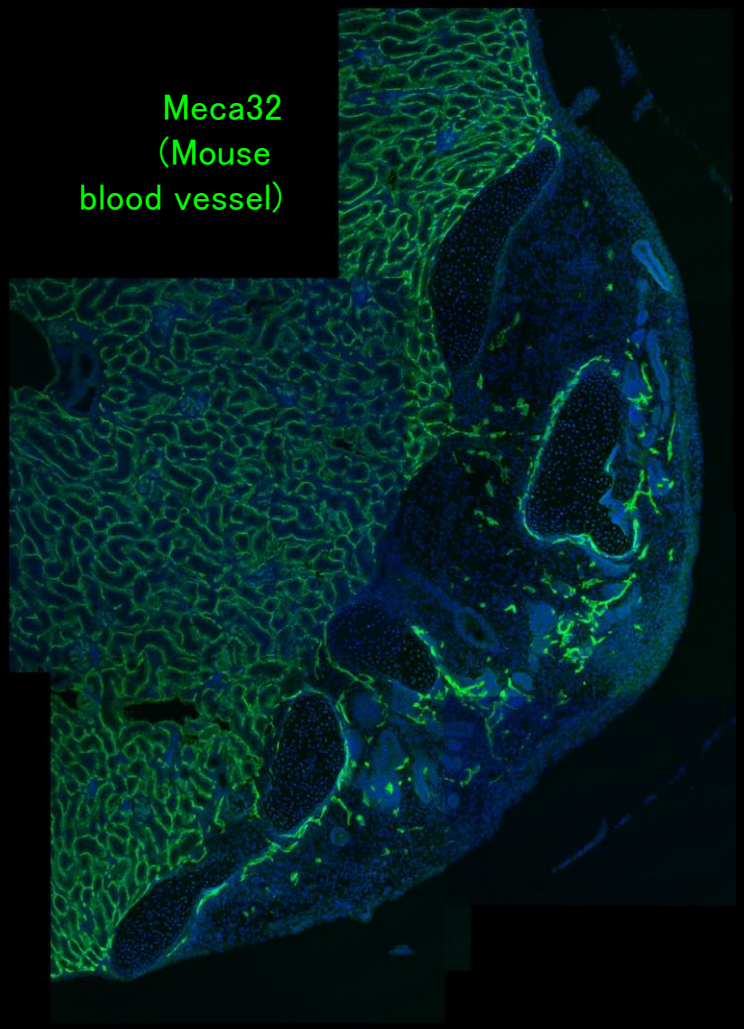
Transplanted kidney organoids were vascularized

Transplanted under renal capsule

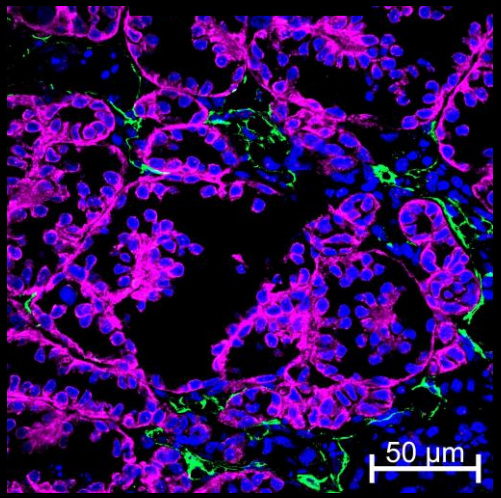


7 days after

(*Stem Cell Reports, 2018*)

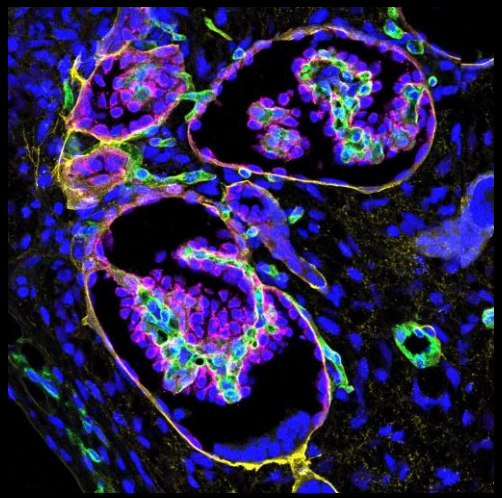


In vitro



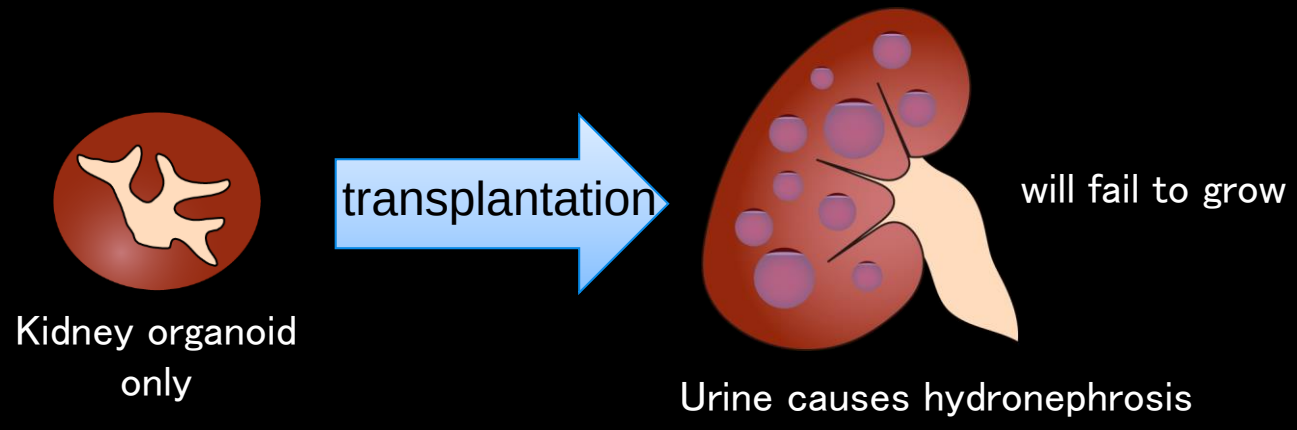
Glomerulus Blood vessels

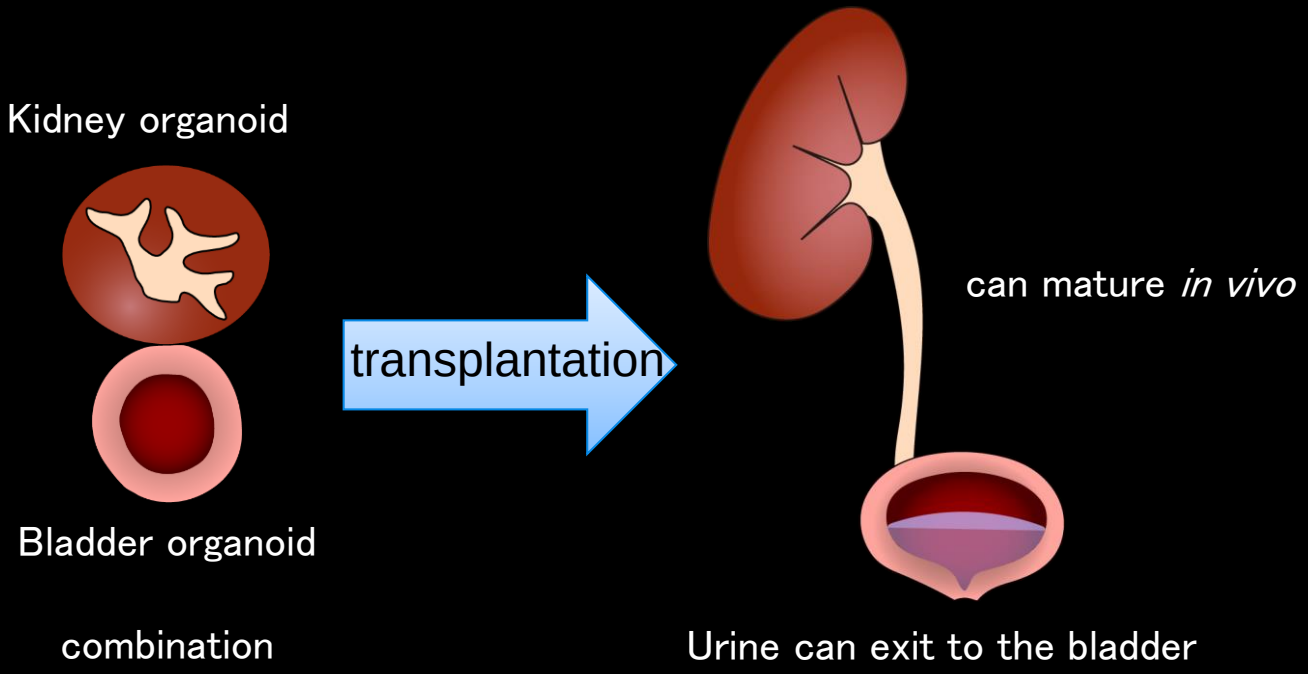
transplantation



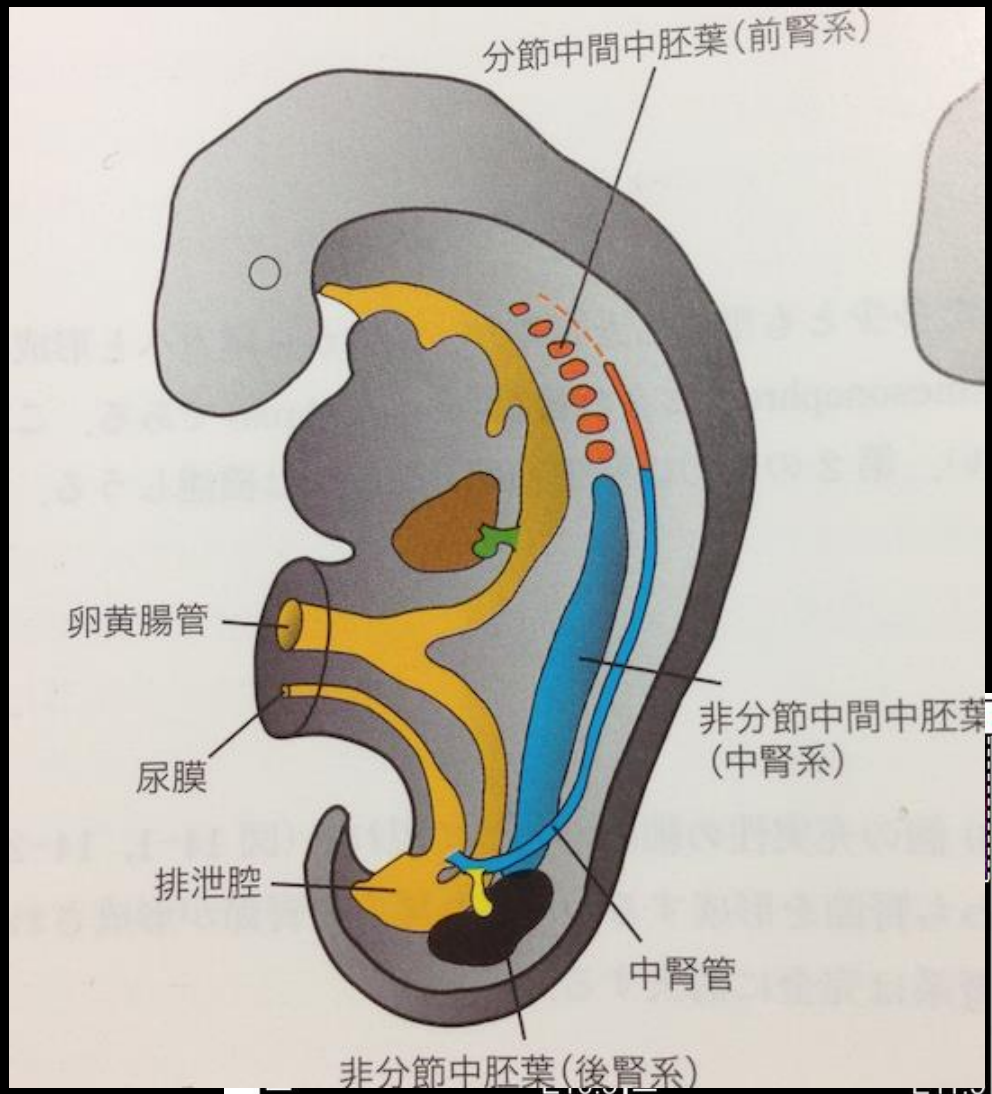
(Yabuuchi, Unpublished data)

Kidney organoids can survive with the bladder under transplantation



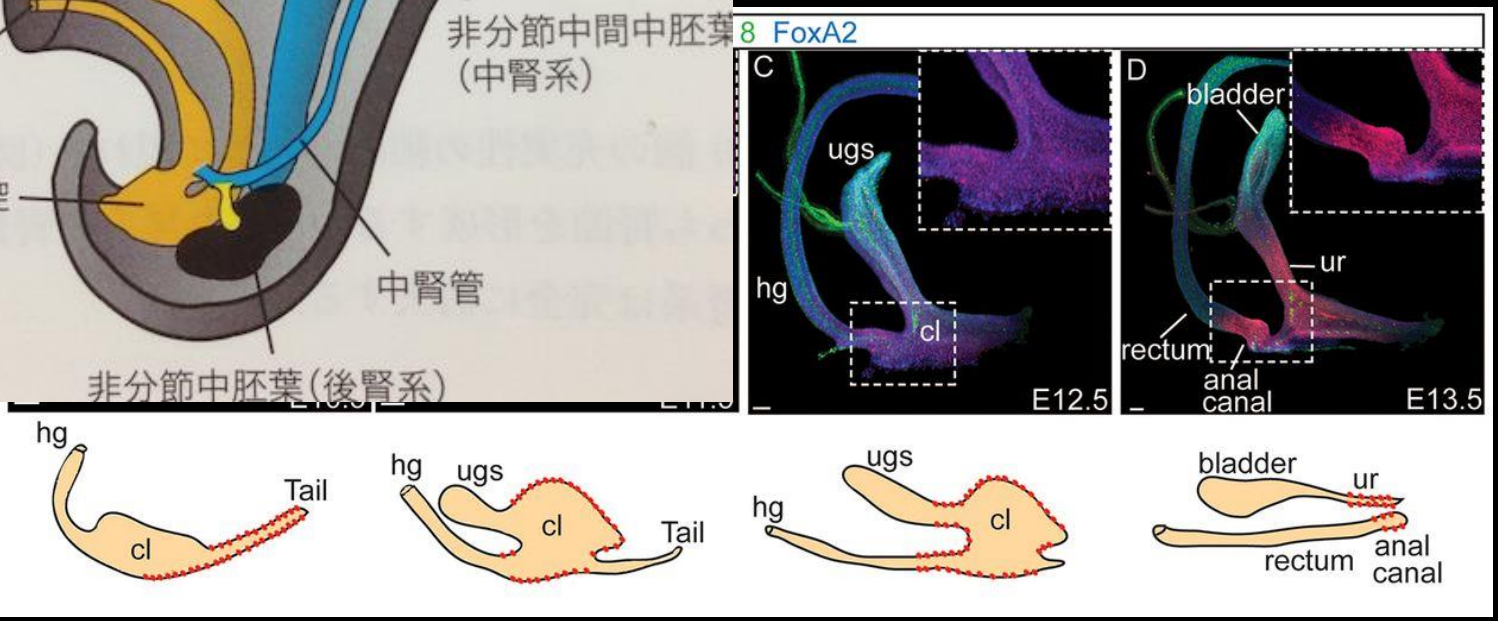


Bladder Development



iPS → endoderm → hind gut

→ Cloaca→ urothelium



謝辞

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Filip Wymeersch（PD）
Junichi Taniguchi （PD）
Olena Trush (PD)
Chie Fukui (TS)
Kensuke Yabuuchi（D4）
Yoshiki Sahara（D3）
Kazuhiro Ofuji（D3）
Rio Noto（D4）
Wataru Uno（D3）
Masaya Goto (M2)
Hiroki Matsunaga（OB）
Thomas Kluiver (visiting stu.)

Otsuka Pharmaceutical Co.

Ryuji Yokokawa, Kyoto University

Murdoch Children's Research Institute

Leiden University Medical Center

Yokogawa Electric Corp.(CQ1)

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