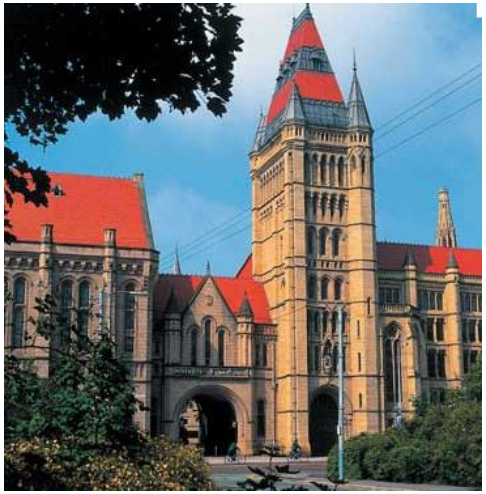
Research update –

Studying *HNF1B* kidneys in a dish



Adrian S. Woolf

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***Adrian has no commercial conflicts of interest to declare*.**

- **In the UK, about 65,000 people have such severe kidney disease that they need long-term dialysis or renal transplantation**

- **Kidney transplants are in short supply**

- **Average life-expectancy on dialysis is less than for some cancer patients**

- **Worldwide, around 2 million people are treated for end-stage kidney disease and as many die each year from this condition, unable to access dialysis or renal transplantation**

The promise of human pluripotent stem cell technology

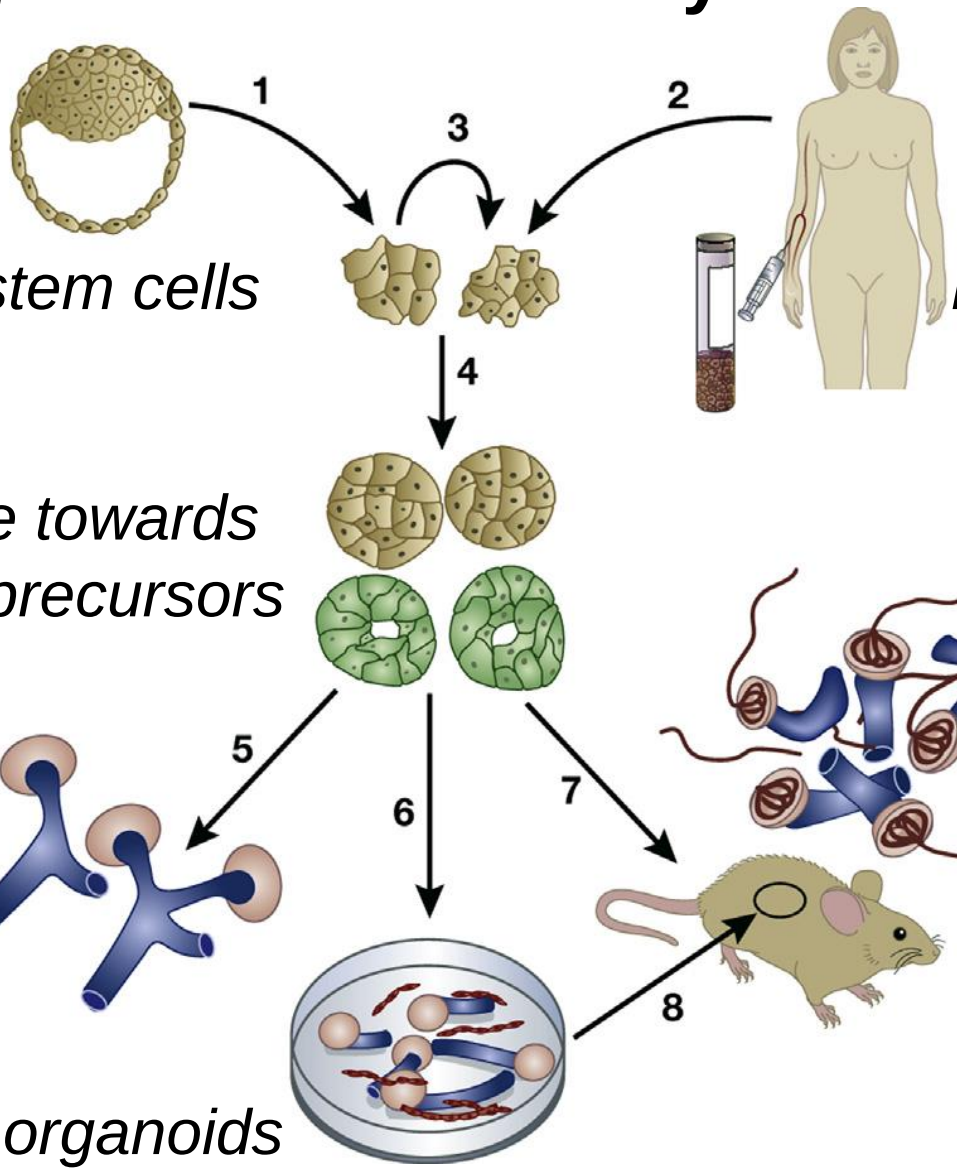
Human stem cells can potentially be used to:

- ***Make normal kidney cells to be used in regenerative medicine therapies.***

- ***Make 'kidney diseases in a dish' to understand mechanisms of disease and test novel therapies.***

…first, some historical background

Ways to grow a human kidney in the laboratory



Woolf AS *Kidney Int* 96:871-882, 2019

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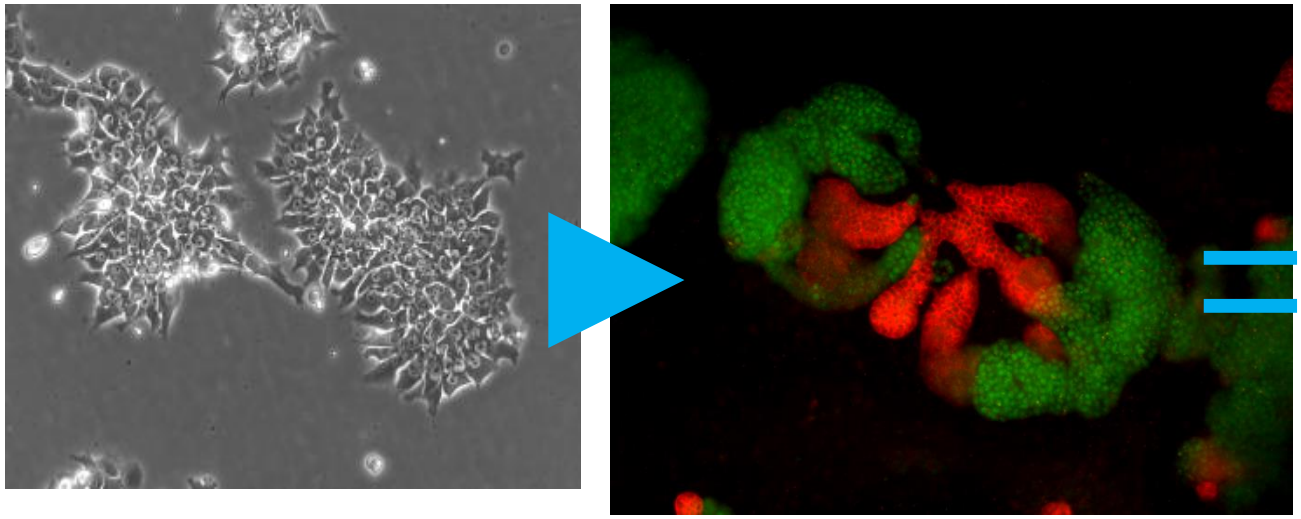
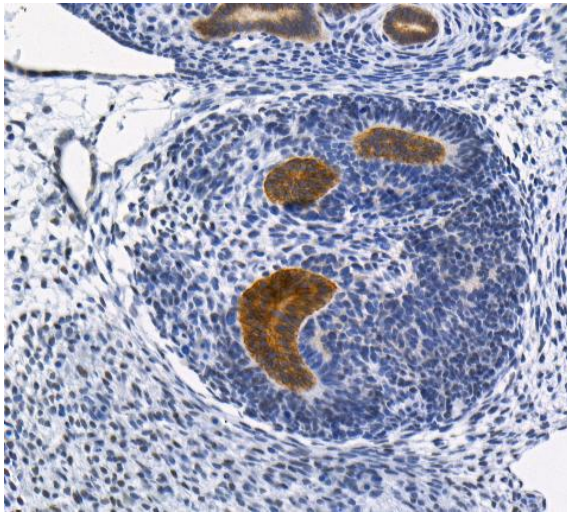
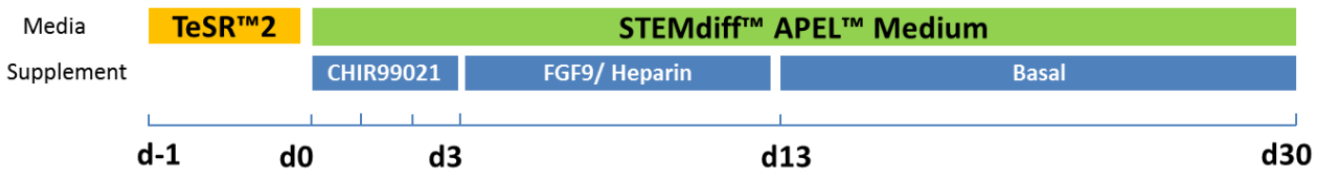
Inducing human pluripotent stem cells *in vitro*: after 30 days the cells in the dish resemble a six week gestation human kidney

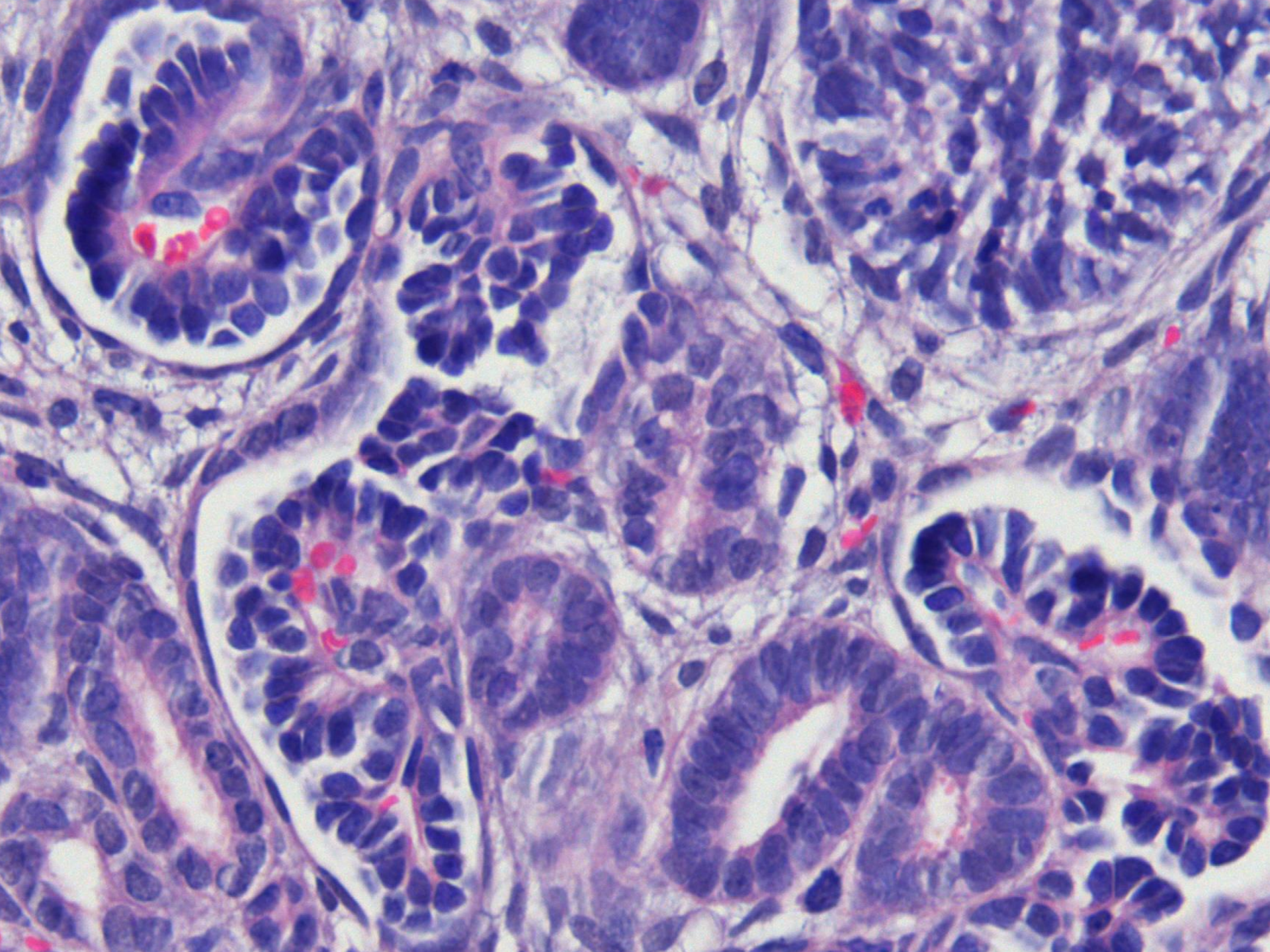
WT1+ nephron precursors
ECAD+ ureteric bud branches



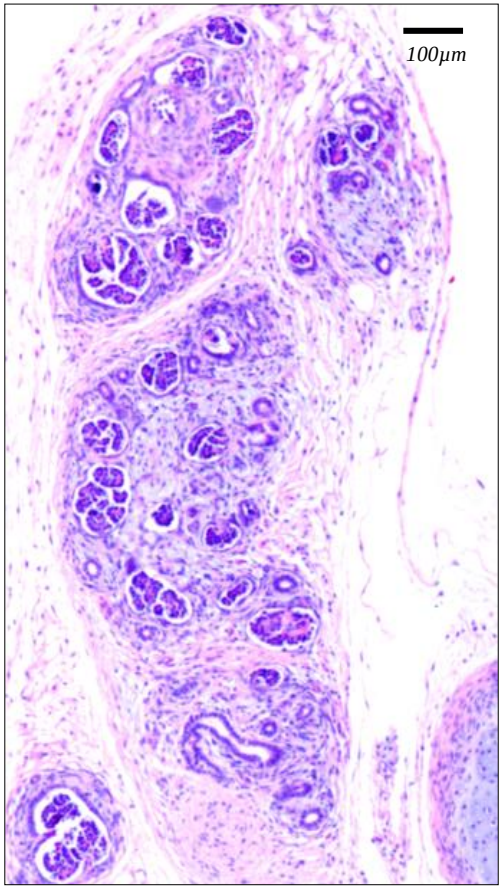




Bantounas I *et al Stem Cell Reports* 2018 & 2021



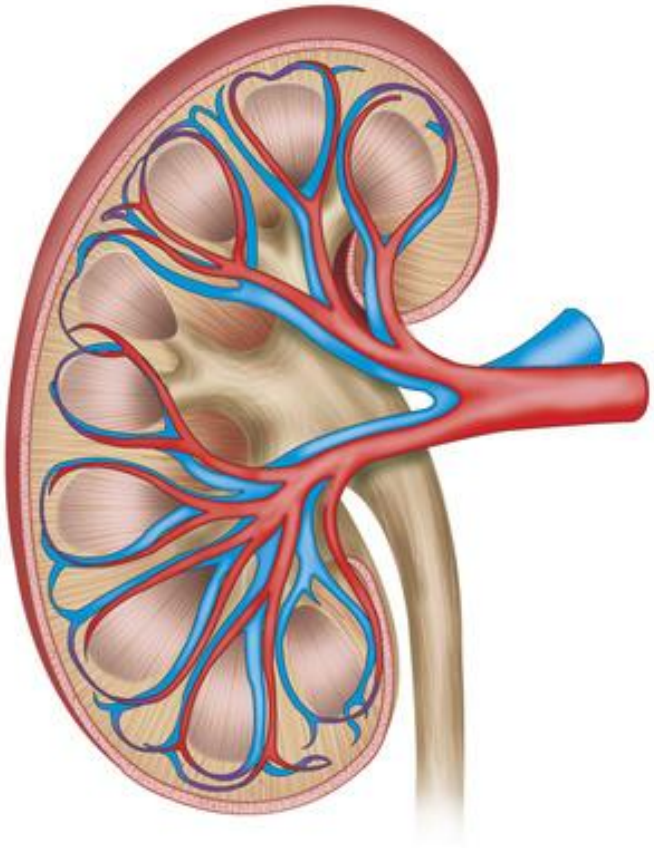
Human ‘mini-kidney’



1 cm long

In terms of volume, 2000 mini-kidneys = one mature kidney

Normal adult human kidney



12 cm long

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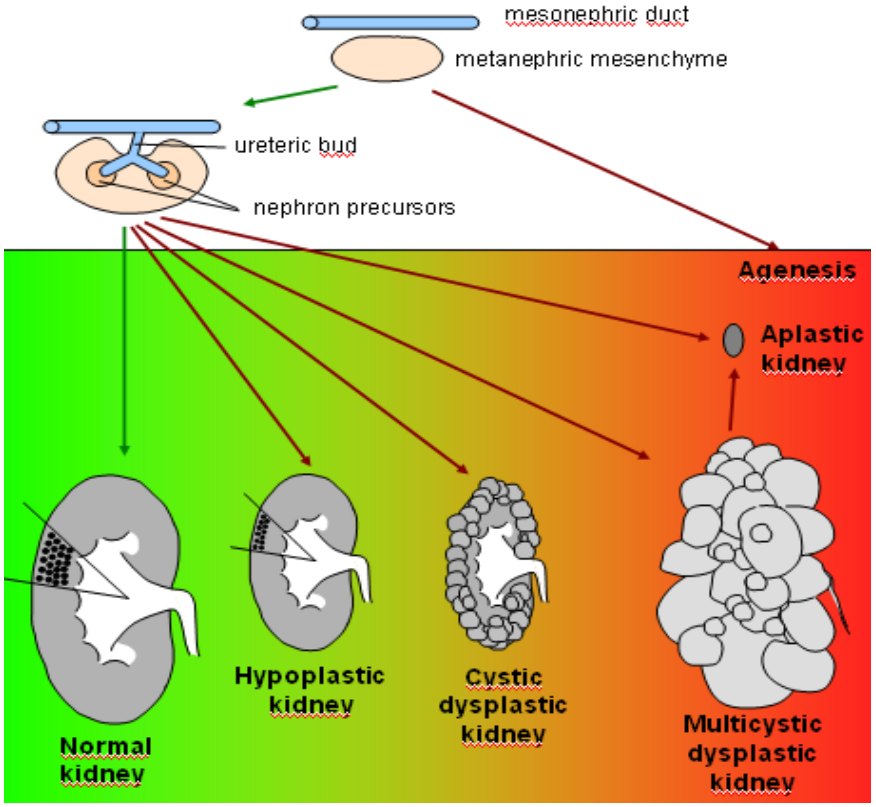
- ***Make 'kidney diseases in a dish' to understand mechanisms of disease and test novel therapies.***

- **Half of all children with end-stage renal disease (ESRD) were born with malformed renal tracts**

- **Worldwide, up to 90,000 children have ESRD and malformed renal tracts**



- **Around 5% of adults with ESRD were born with malformed renal tracts**

- **Many individuals with malformed kidneys carry mutations of genes that normally drive the growth of the renal tract.**

Normal **Worsening renal function**

Making pluripotent stem cells from people with *HNF1B* mutations and malformed kidneys

HNF1B **patient from the our Renal Genetic Clinic with malformed kidneys & end-stage renal disease**

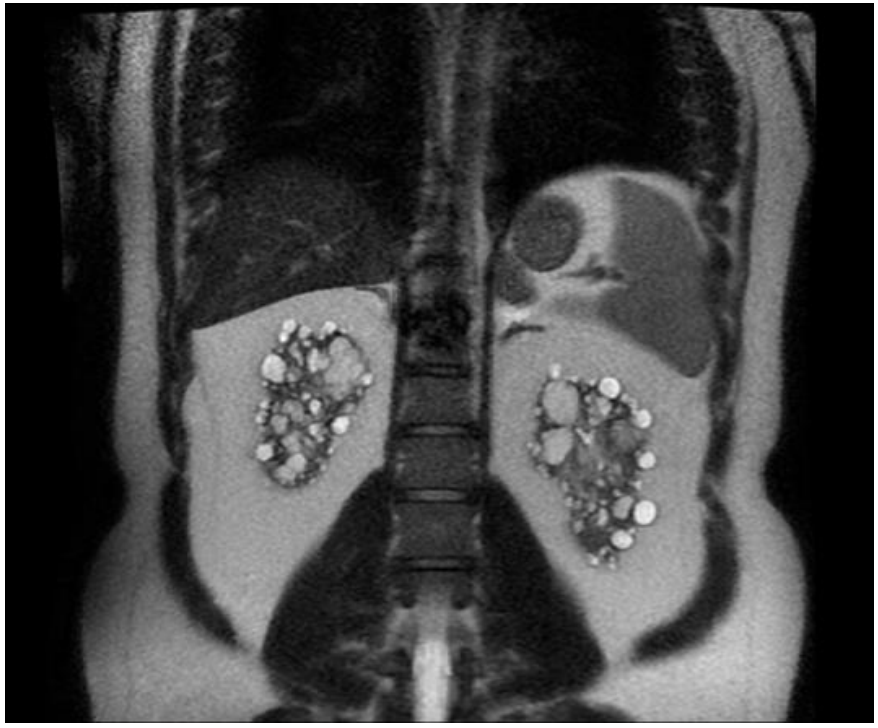
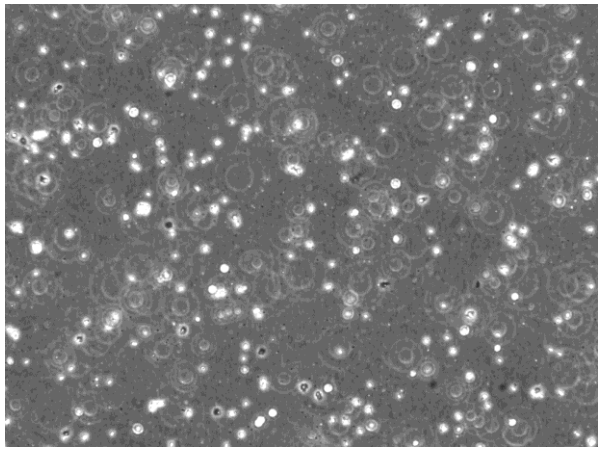
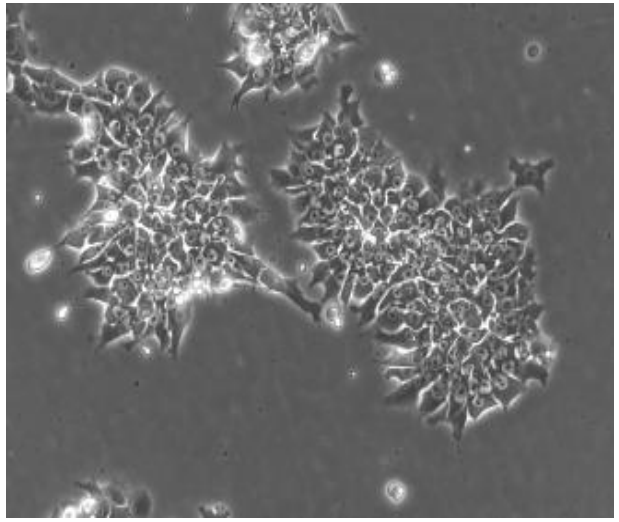


Image from Dr KA Hillman

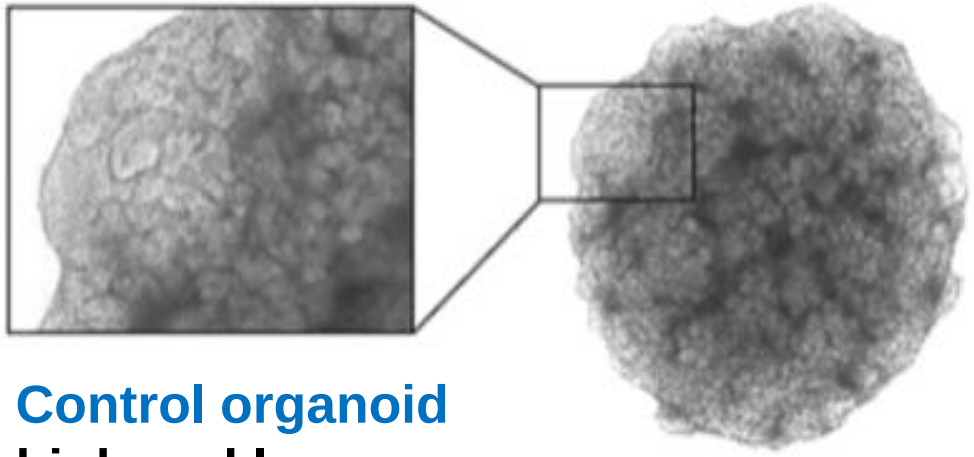
Venous blood donated in clinic….



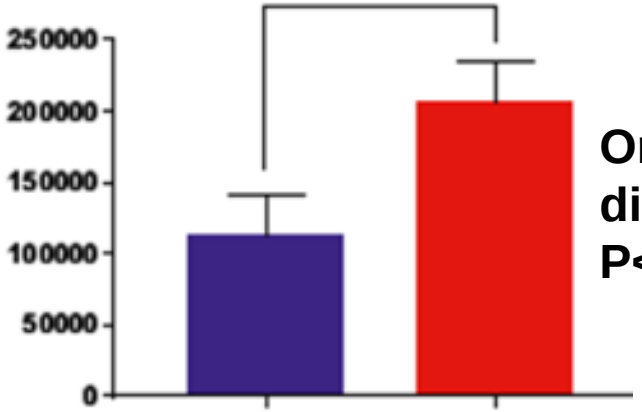
…converted to induced pluripotent stem cells in the laboratory



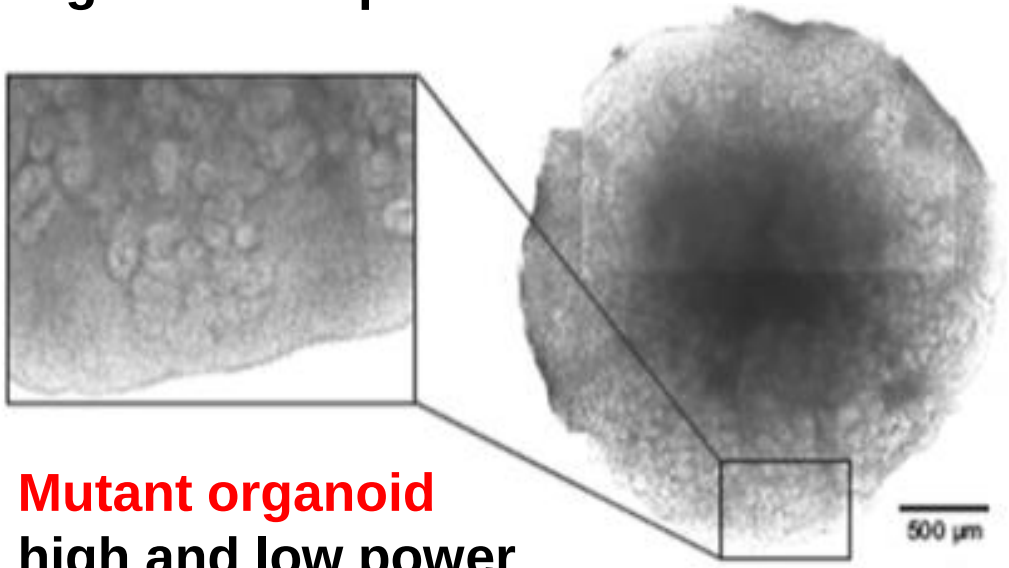
Organoids imaged in culture. Mutant *HNF1B* exon 9 deleted organoids are wider than non mutant control organoids, contain less complex structures and have reduced RNA levels of *HNF1B exon 9*.



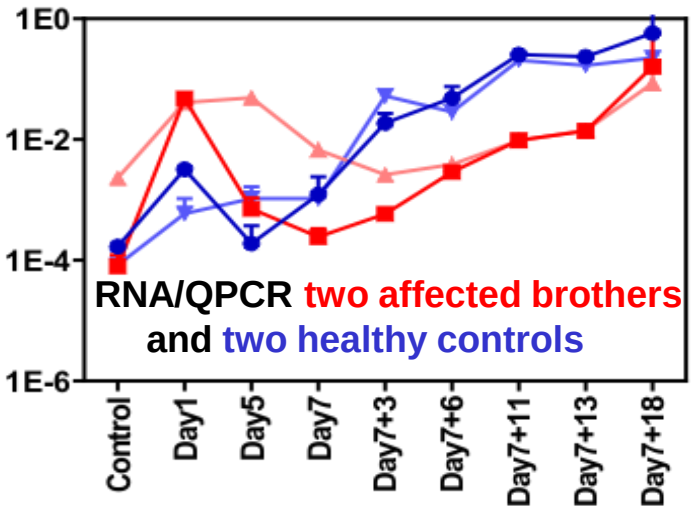
Control organoid
high and low power



Organoid diameter P<0.05

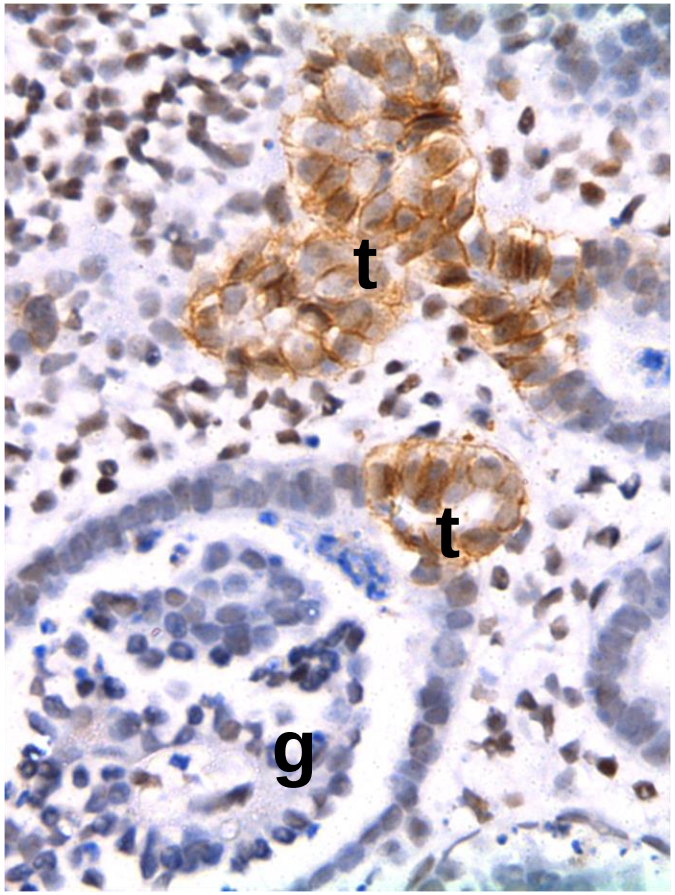


Mutant organoid
high and low power

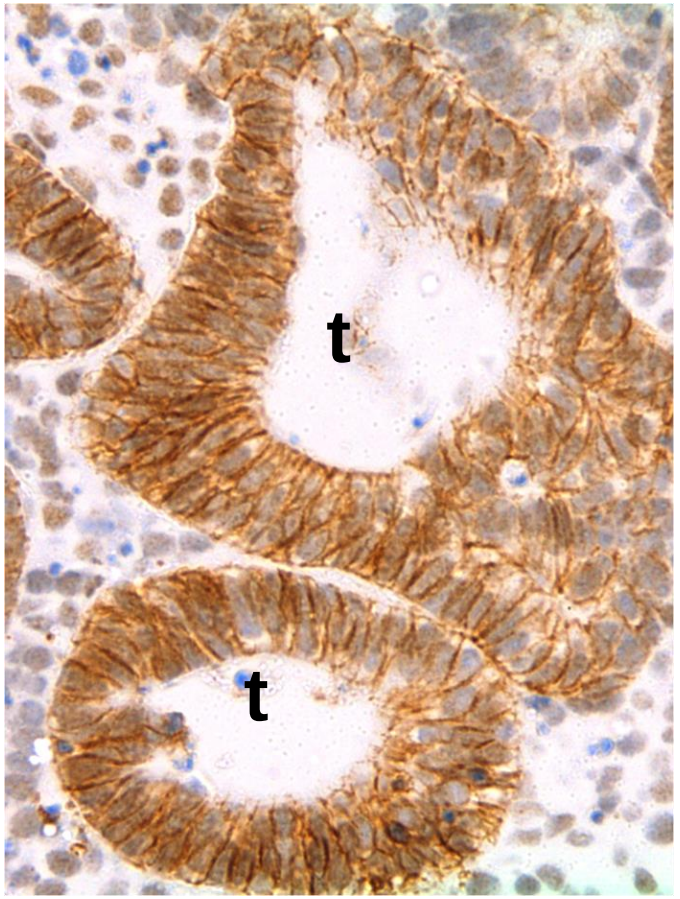


Histology of wildtype and *HNF1B* heterozygous mutant mini-kidneys we created from stem cells generated from blood samples donated by a family followed in our renal genetic clinic. Note the dilated tubules ('**t**' marked by brown E-cadherin immunostaining) but the lack of glomeruli ('**g**') in the mutant mini-kidney

Unaffected mother



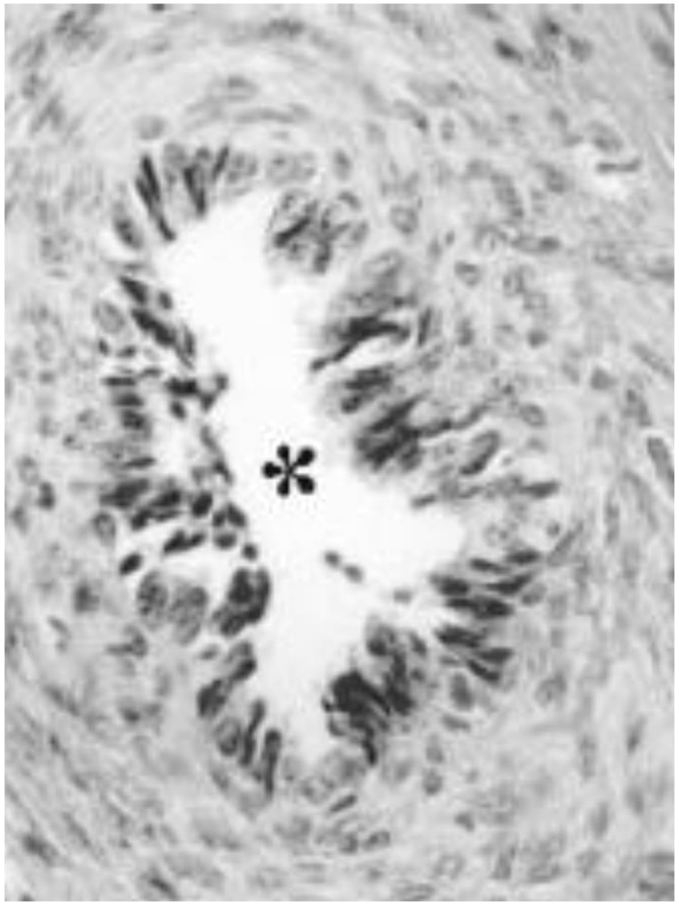
Mutant son

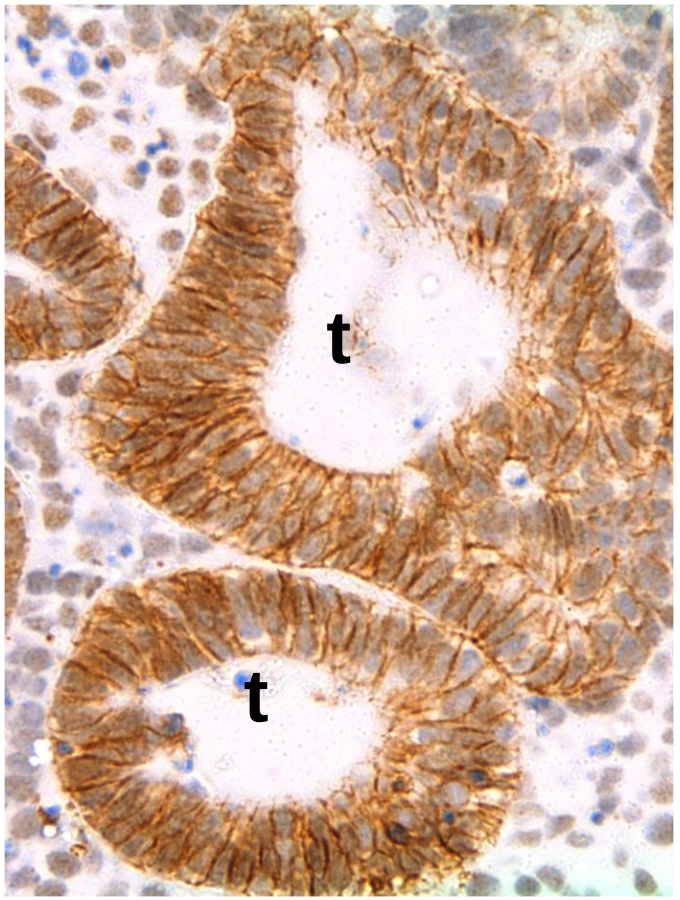


Tengku F - PhD thesis University of Manchester 2020

Dysplastic tubule in vivo

Mutant organoid

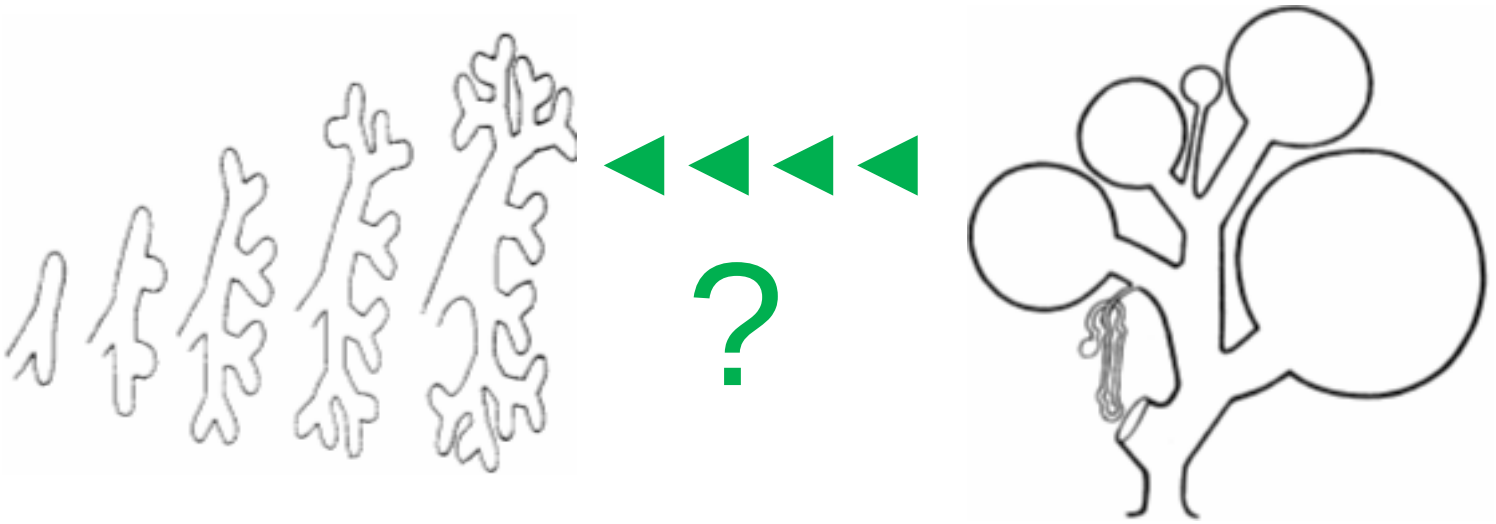




Tengku F - PhD thesis University of Manchester 2020

Our long term aim is to turn dysplastic human kidneys into more normal kidneys

Normal branching tubules ***Malformed kidney tubules***



…..ongoing work e.g. working out the molecular pathways that are going wrong and looking for druggable targets

Summary

Human stem cells can potentially be used to:

- ***Make kidneys to be used in regenerative medicine therapies.***

Perhaps…but problems of small scale, lack of renal artery, and lack of ureter

- ***Make 'kidney diseases in a dish'***

Shows promise for several genetic diseases

…but can it model diabetic nephropathy and progressive fibrosis?

THANKS TO COLLABORATORS AND FAMILIES!

MANCHESTER

Renal Genetics Clinics

Kate Hillman, Bronwyn Kerr, Helen Stuart, Kay Matcalfe, David Keene & Max Cervellione

Human stem cells

Susan Kimber, Ioannis Bantounas, Parisa Ranjzad, Tengku Faris, Amir Salahi, Jason Wong, Sophie Ashley and Kirsty Rooney *et al*

….and many others UK & Worldwide

Our Funders…

MANCHESTER 1824
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MANCHESTER BIOMEDICAL RESEARCH CENTRE

MRC Medical Research Council

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wellcome

leap Human Organs, Physiology, and Engineering

UK Regenerative Medicine Platform

newlife foundation for disabled children

British Renal Society
registered charity no. 1091024

Kids Kidney Research

KIDNEYS FOR LIFE

Kidney Research UK
Funding research to save lives

THE FRAMEWORK PROGRAMME FOR RESEARCH AND INNOVATION
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