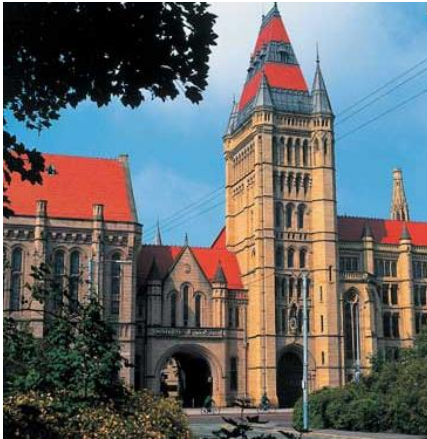


Growing HNF1B mini-kidneys in the laboratory to look for drug treatments

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Research Funding Support

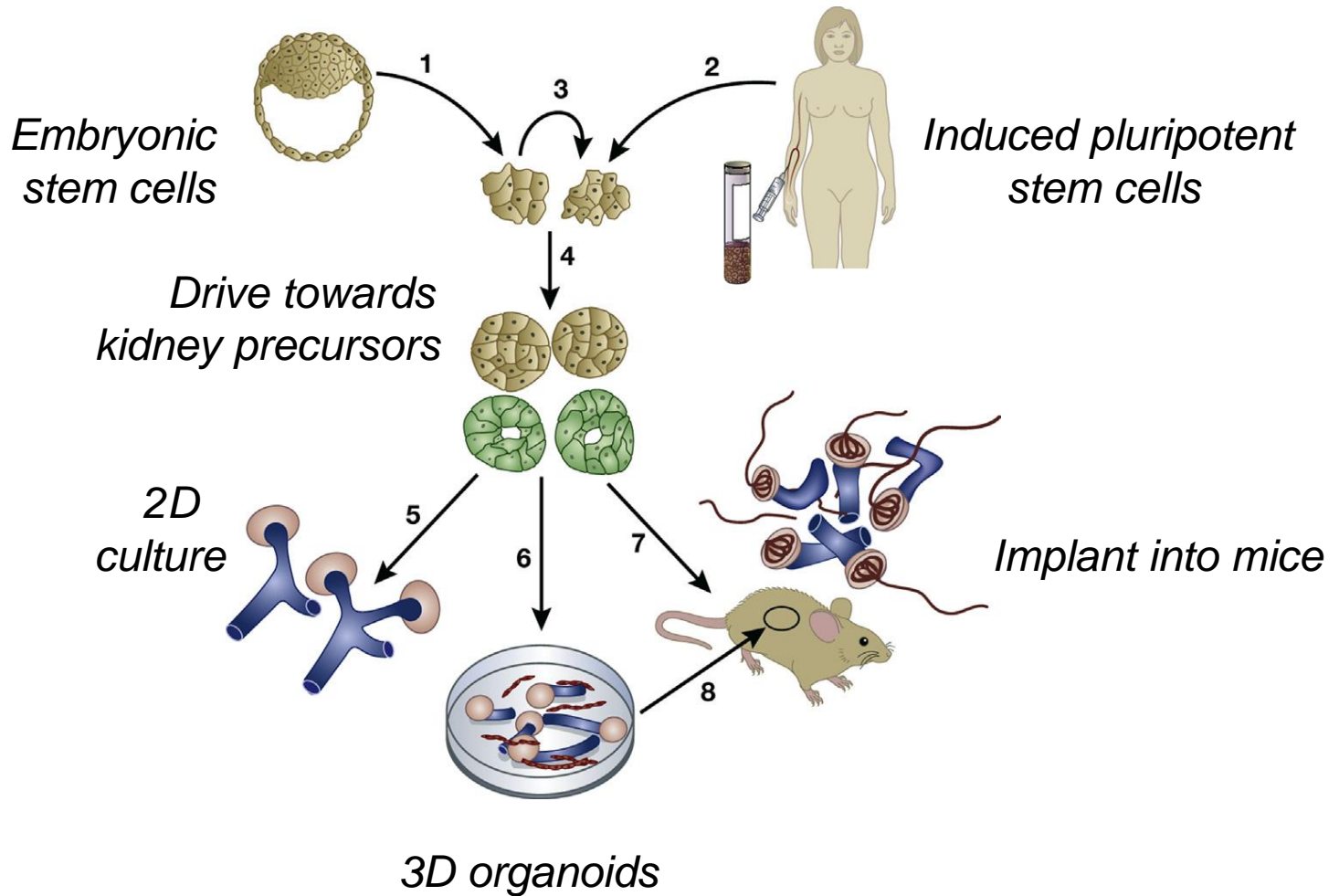
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 - Kidney Research UK
 - Life Arc
 - New Life
 - Welcome Leap
 - Kidneys for Life
 - British Renal Society

Overview of the Talk

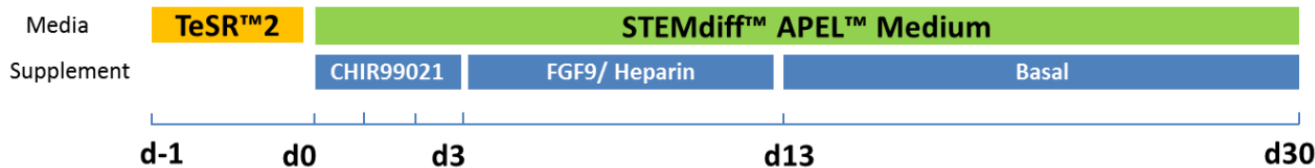
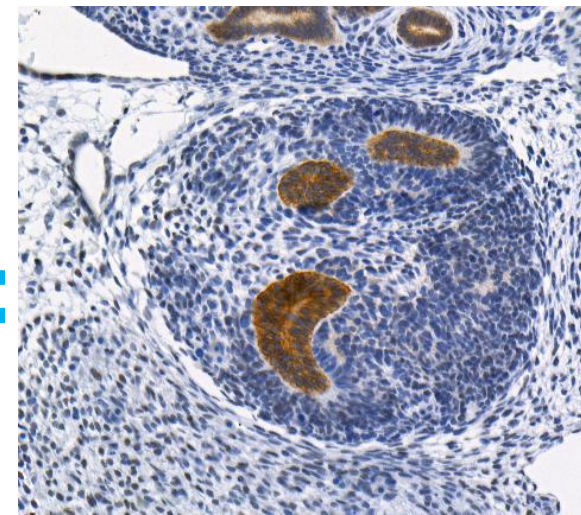
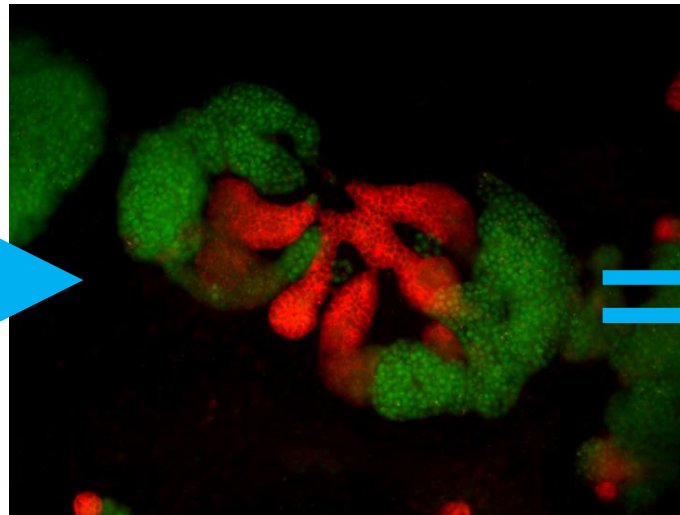
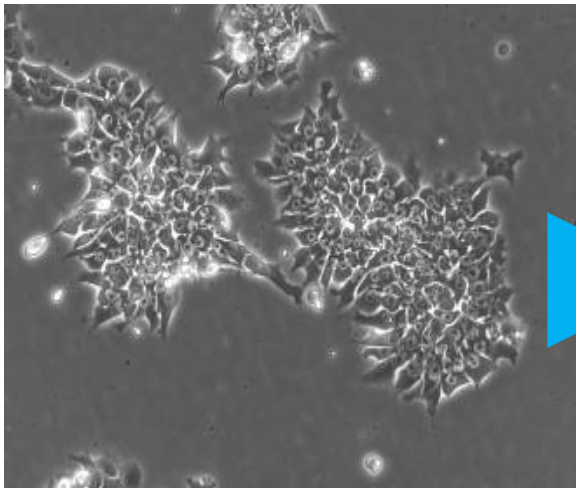
- Can we use stem cell technology to fashion new kidneys and lower urinary tracts?
- Can we use stem cells to model genetic kidney diseases?

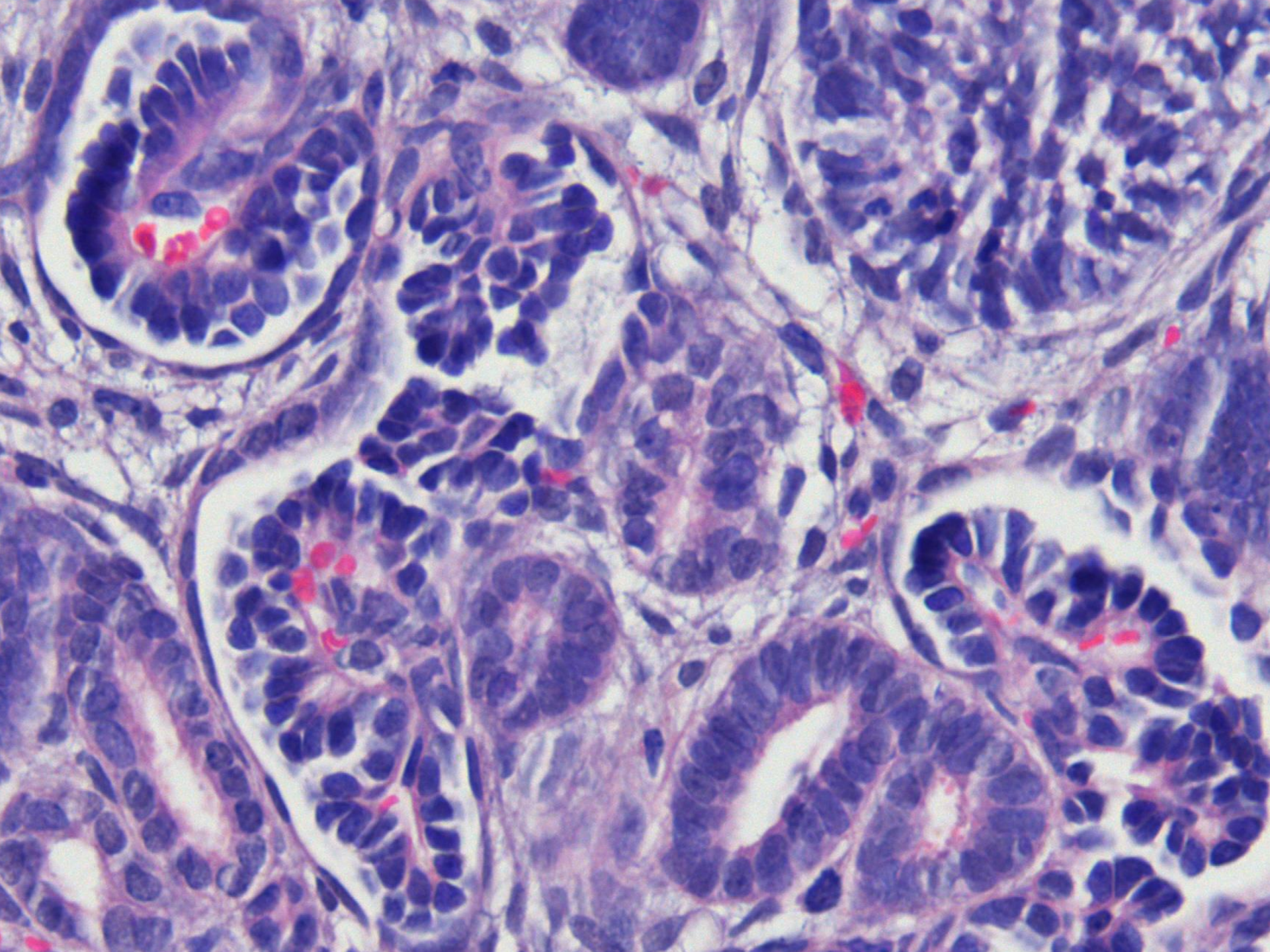
Creating Human Kidney Tissues from Pluripotent Stem Cells



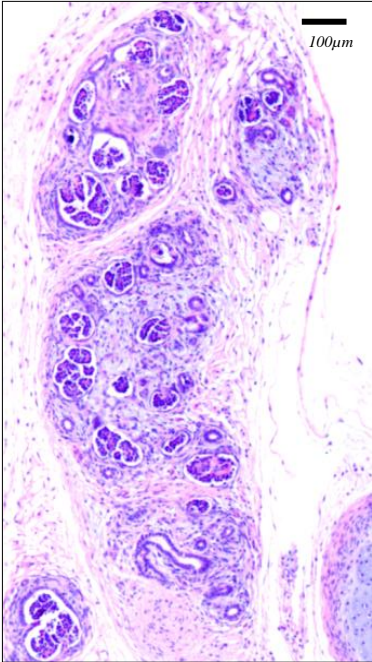
Inducing human pluripotent stem cells: after two week the cells in the dish resemble a six week gestation human kidney

WT1+ nephron precursors
ECAD+ ureteric bud branches



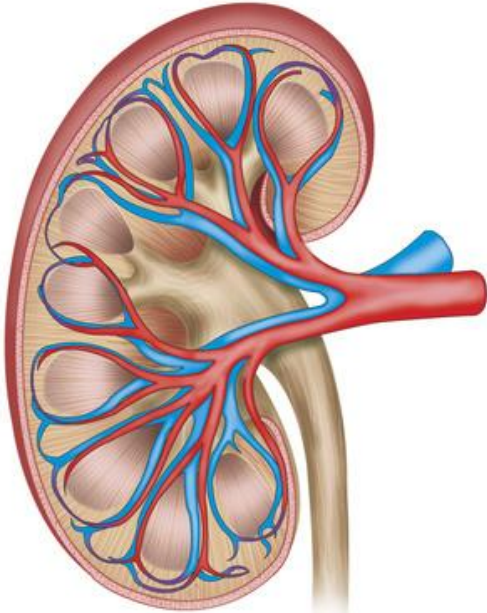


Human 'mini-kidney'



1 cm long

Normal adult human kidney



12 cm long

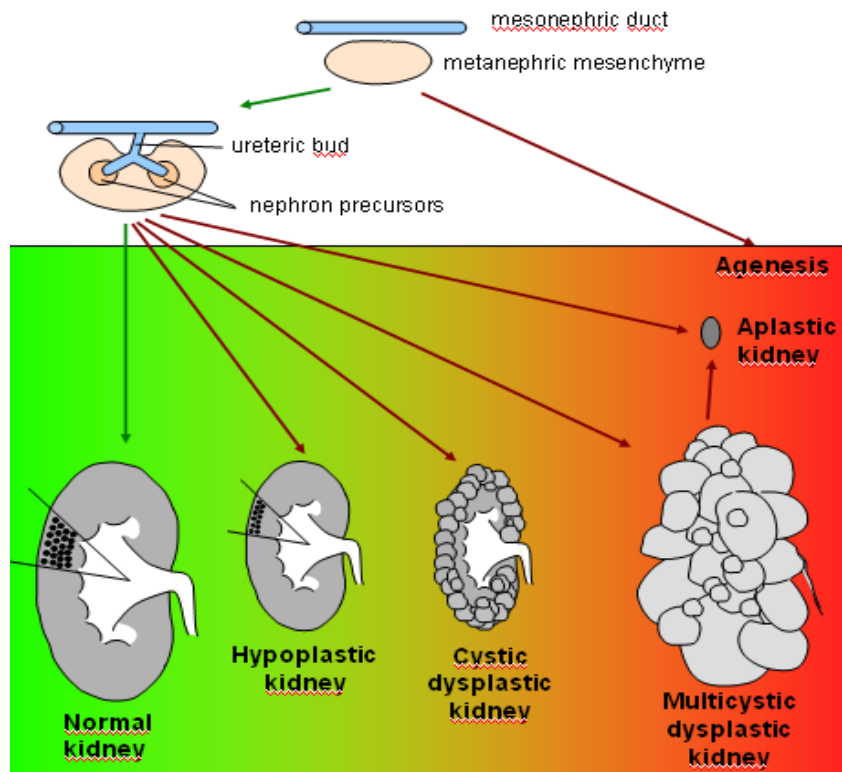
*In terms of volume,
2000
mini-kidneys
= one mature
kidney*



Overview of the Talk

- Can we use stem cell technology to fashion new kidneys and lower urinary tracts?
- **Can we use stem cells to model genetic kidney diseases?**

- Half of all children with severe kidney failure (CKD5) were born with malformed kidneys
- Worldwide, up to 90,000 children have CKD5 and malformed kidneys

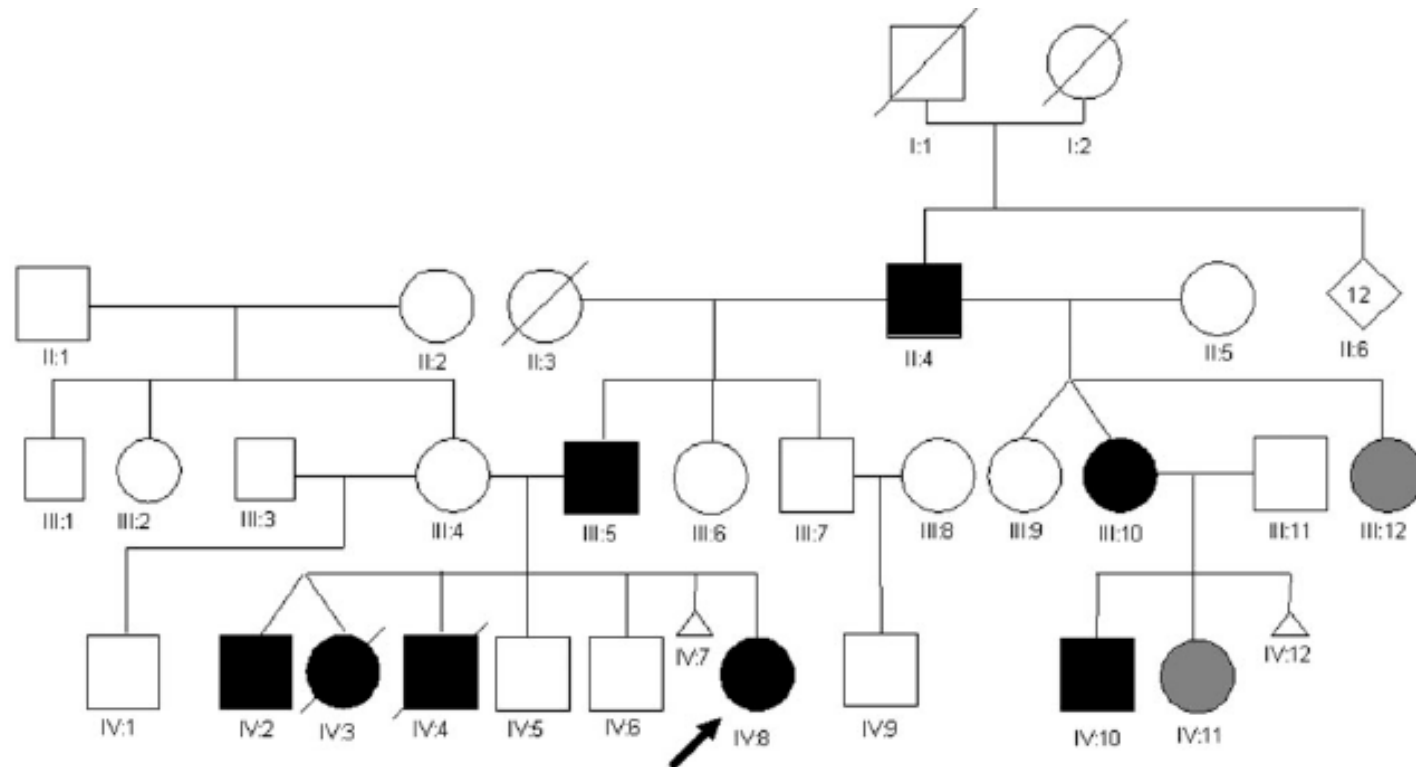


- Around 5% of adults with CKD5 were born with malformed renal tracts

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

Normal **Worsening renal function**

Three Generations born with Malformed Kidneys (autosomal dominant inheritance)



Autosomal dominant genetic disorders featuring malformed kidneys (all feature mutations of transcription factors)

- *HNF1B* - renal cysts and diabetes syndrome (magnesium wasting, gout, diabetes mellitus, & uterus malformations)
- *PAX2* - renal-coloboma syndrome (blindness)
- *EYA1* - branchio-oto-renal syndrome (deafness, & pits in external ear and neck)
- *GATA3* - HDR syndrome (hypoparathyroidism, sensorineural deafness, & renal dysplasia)

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

HNF1B patient from our Renal Genetic Clinic with malformed kidneys & end-stage kidney disease

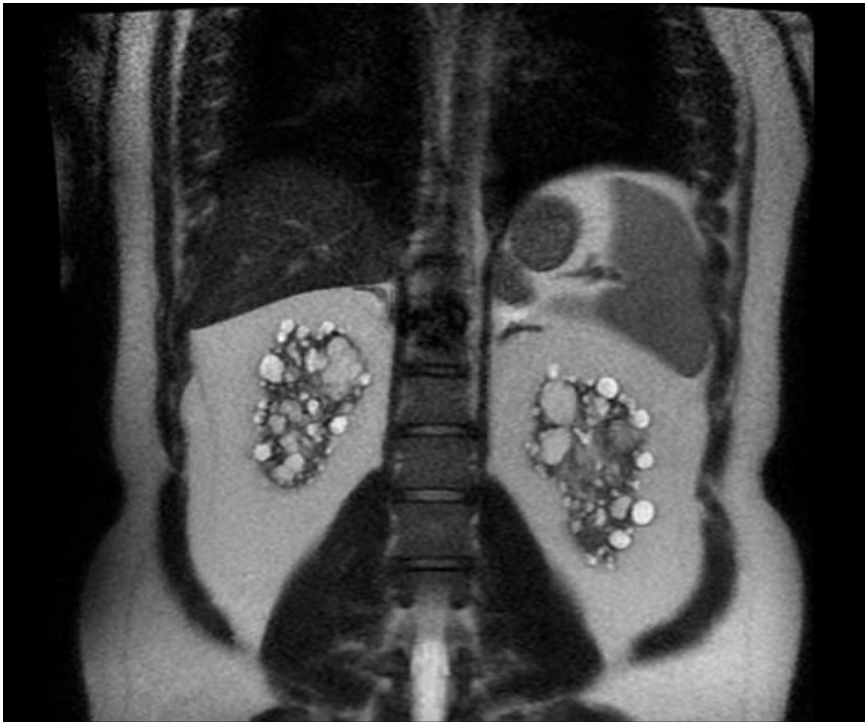
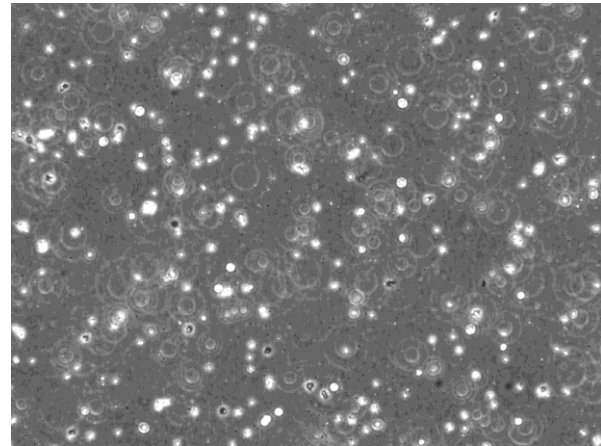
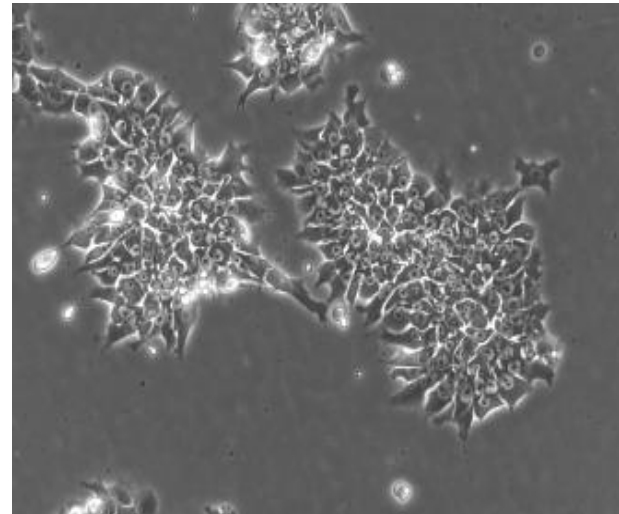


Image provided by Dr KA Hillman

Venous blood donated in clinic...

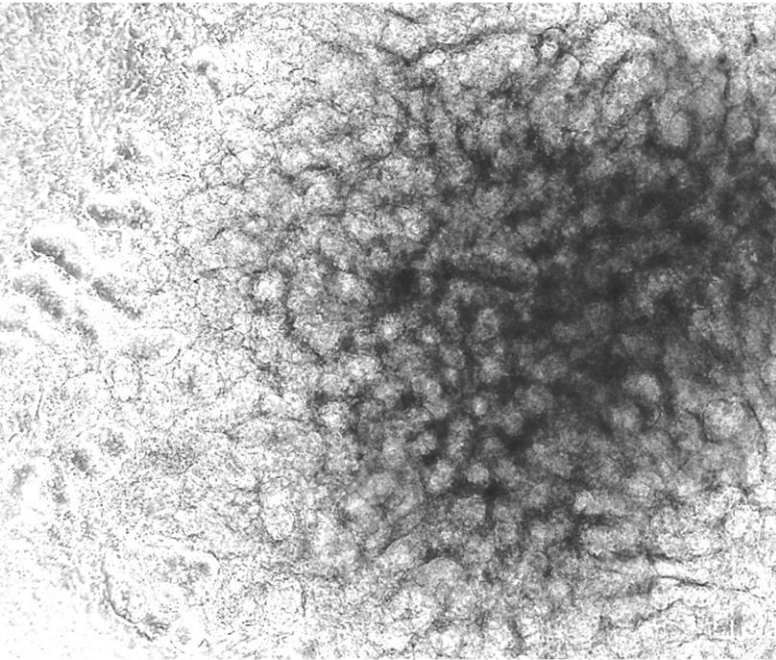


...converted to induced pluripotent stem cells in the laboratory

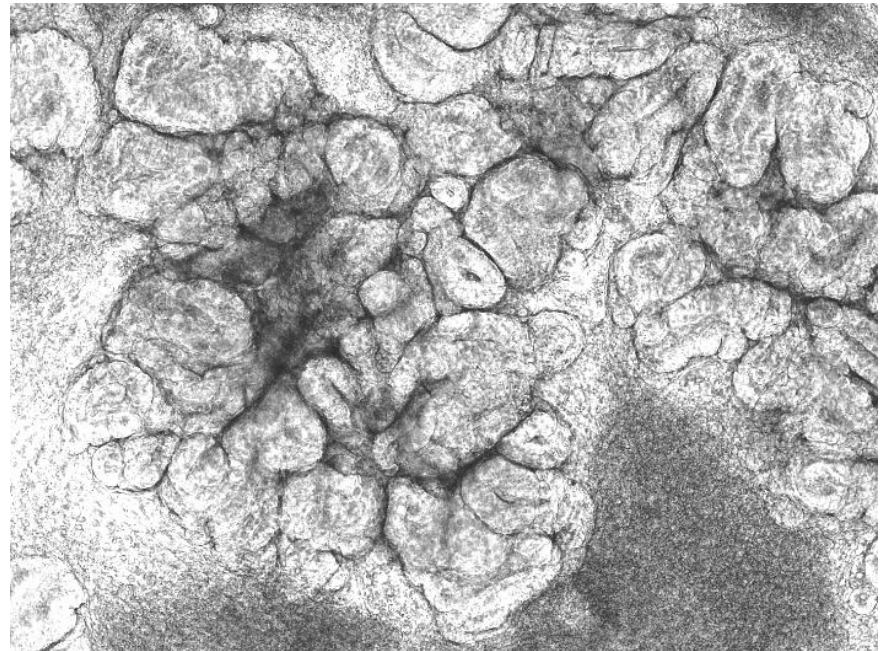


Using human induced pluripotent stem cell kidney organoids to model HNF1B kidney disease

Unaffected relative



Patient with *HNF1B* mutation

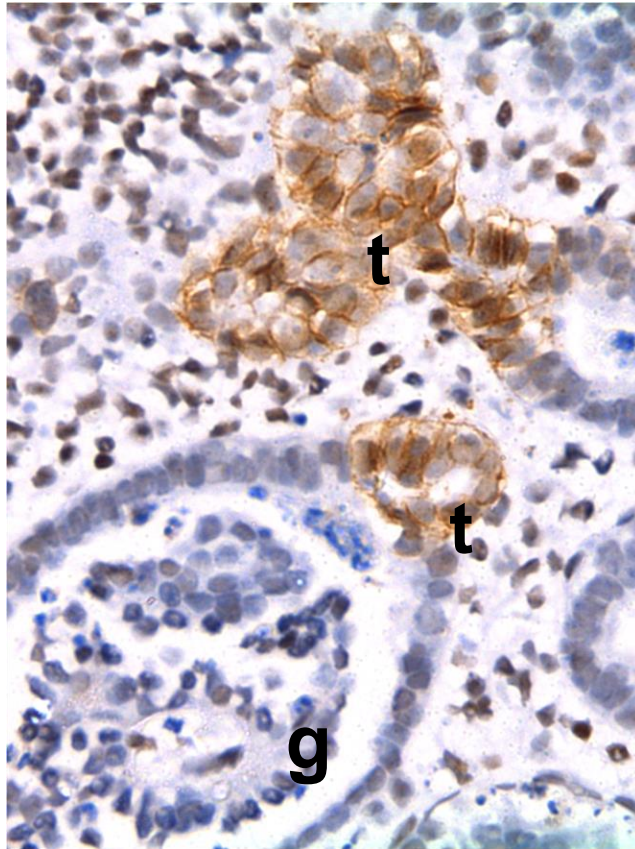


Bantounas I *et al* UK Kidney Week 2022

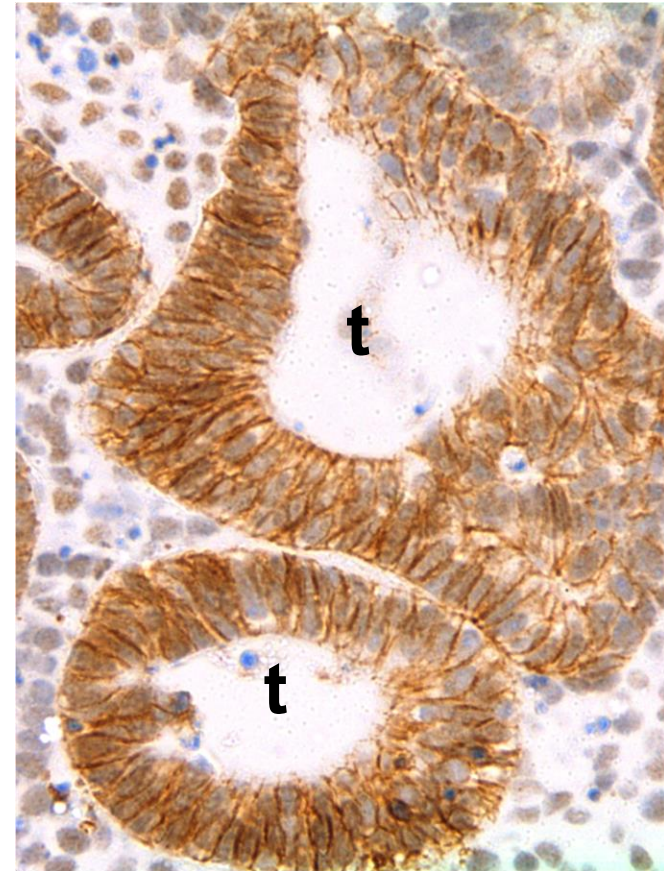
Bantounas I, Rooney KM *et al*
bioRxiv 2023.03.14.532598; doi: <https://doi.org/10.1101/2023.03.14.532598>

Histology of 'wild-type' and *HNF1B* heterozygous mutant mini-kidneys we created from stem cells generated from blood samples donated by a family cared for by our Foundation Trust. Note the abnormal dilated tubules ('t' marked by brown E-cadherin immunostaining) but the lack of glomeruli ('g') in the mutant mini-kidney

Unaffected mother



Mutant son



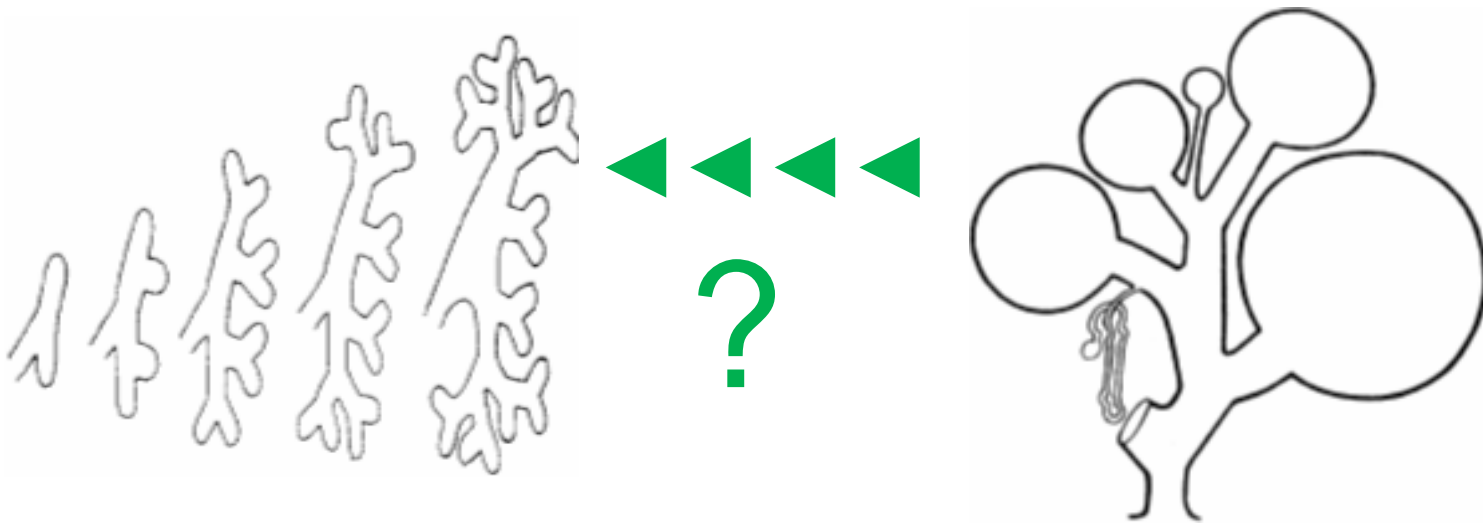
Bantounas I, Rooney KM *et al*

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

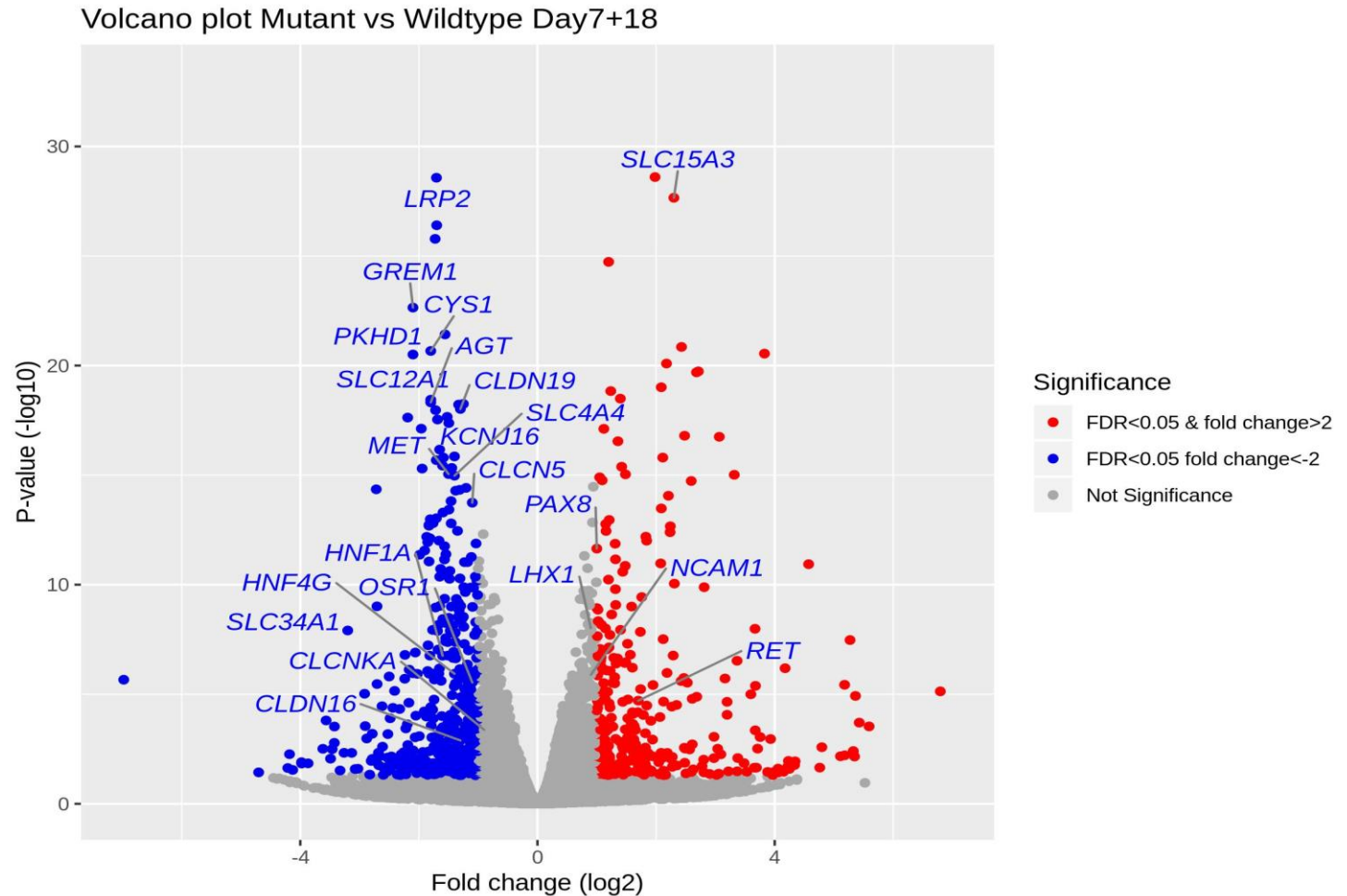
Normal branching tubules

Malformed kidney tubules



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

***HNF1B* heterozygous mutant human organoids have altered transcripts of several developmental, cystic & tubulopathy genes**

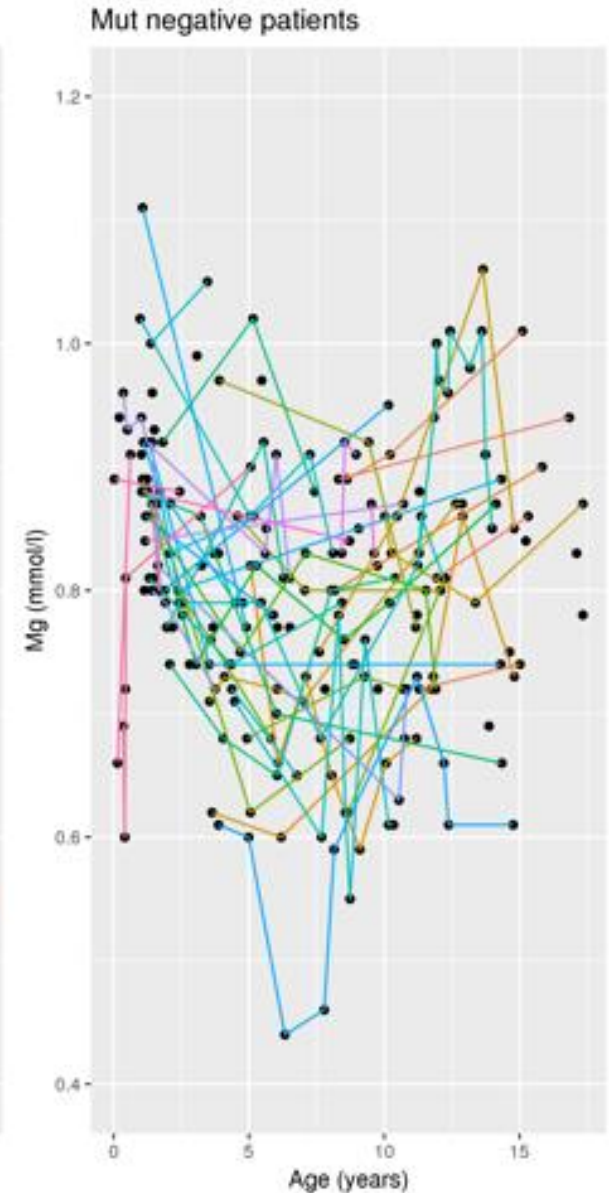
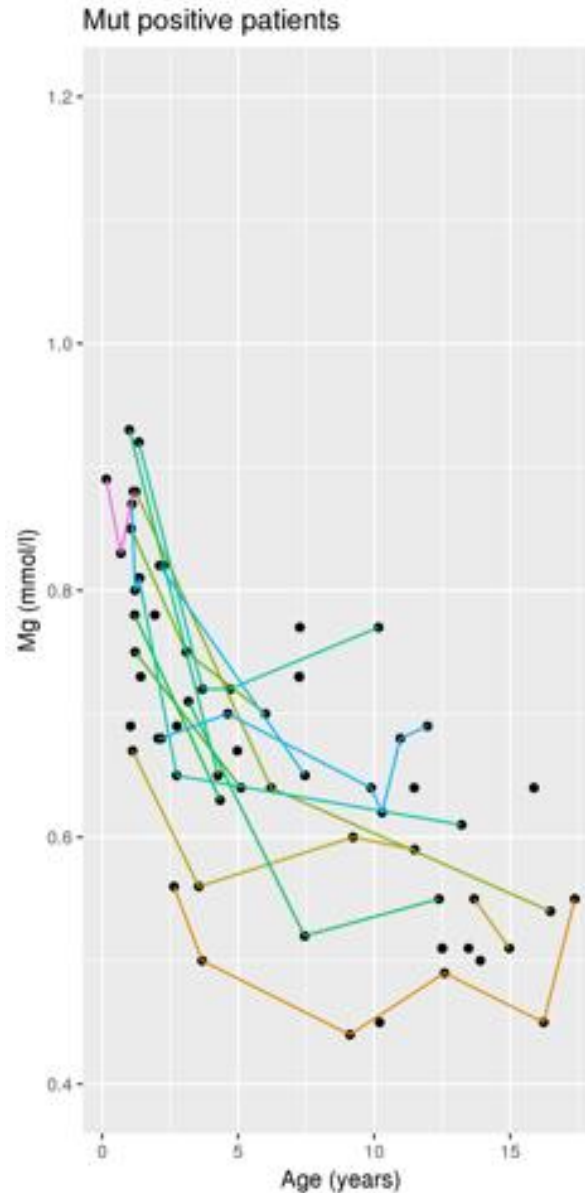


Bantounas I, Rooney KM *et al*

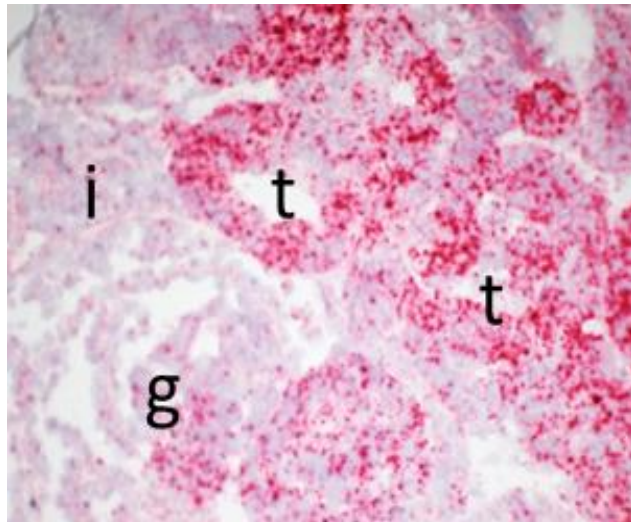
bioRxiv 2023.03.14.532598; doi: <https://doi.org/10.1101/2023.03.14.532598>

Identified 52 *HNF1B* mutations after genetic testing of 199 children with hypo-dysplastic malformations

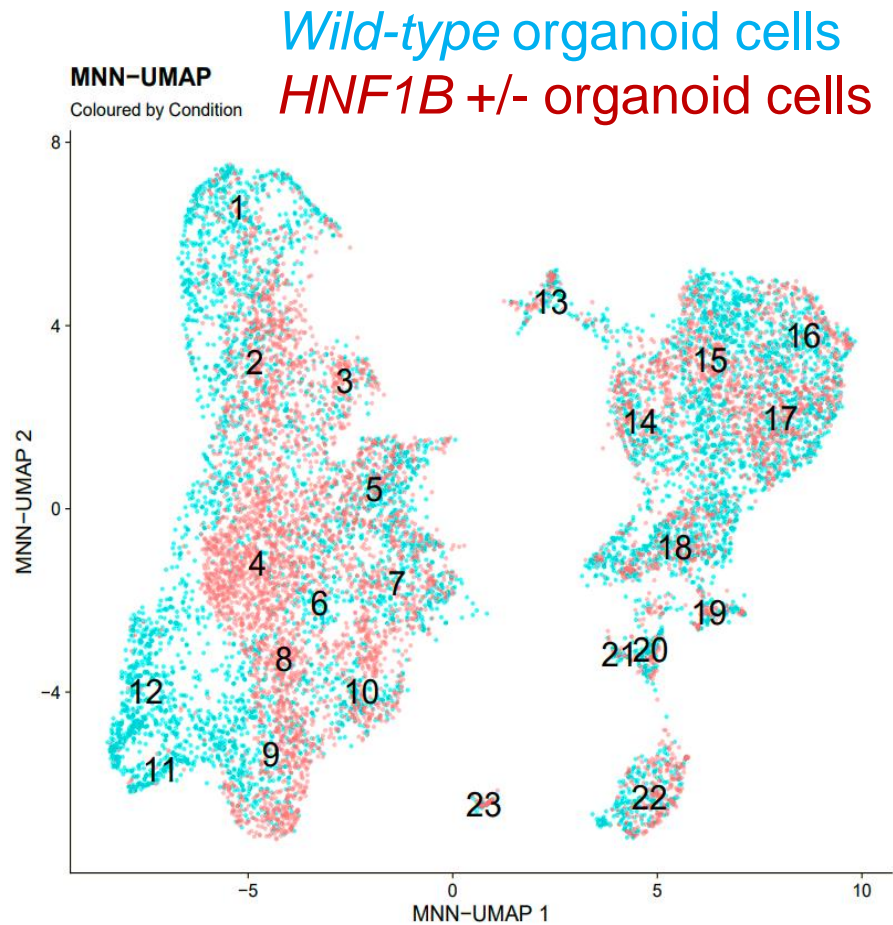
In *HNF1B*-related kidney disease, low blood magnesium and potassium can manifest in the teenage years



HNF1B Mutant Organoids Contain
a Unique Population of Abnormal Tubules (population 4 on scSeq)
that Massively Upregulate the *GRIK3* Glutamate Receptor
This could be a target for future drug therapies



***GRIK3* mRNA**



Bantounas *et al*
bioRxiv 2023.03.14.532598 & unpublished data

Overview of the Talk

- Can we use stem cell technology to fashion new kidneys and lower urinary tracts?
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Our Funders



Medical Research Council



Manchester Regenerative Medicine Network



British Renal Society

registered charity no. 1091024

Kids Kidney Research



UK Regenerative Medicine Platform



Rare Disease Research UK.