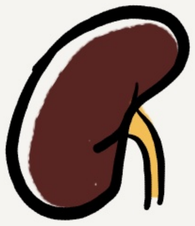
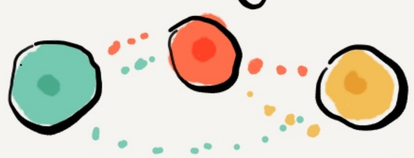
RNA Sequencing and the Kidney Cell Atlas

Understanding the Kidney



Bulk RNA seq
- limitations

Cell-Cell interactions
- who is talking to who?



want to understand cellular heterogeneity

Single Cell RNAseq

- enabling technologies

Barcoding + Droplets

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Menna Clatworthy

University of Cambridge

V1 of the human Kidney Cell Atlas

6 donors

Insights into kidney development

- Appearance of adaptive immune cells

Four distinct Subsets of Kidney MNPs

Compare **fetal** + **adult** kidney
- find popn of pre-natally seeded macrophages

Assess immune functionality in all Kidney cell types

Spatially zonated epithelial antibacterial immunity

Cell-Cell interactions

Nephron-myeloid cell interactions predict pelvic antibacterial defence

Building a Bigger Atlas

Integrating Spatial Data

Towards disease cell atlases

Lupus nephritis

2 distinct groups of macrophages
- Seeded vs monocyte derived

Identify relevant cell types + pathways

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Regulation of nephronectin via miRs in membranous nephropathy

Mario Schiffer

University Hospital Erlangen

The Evolution of Membranous Nephropathy

1946 - first description by Bell et al.

1982 - Megalin identified

1982- **MGN** - Manifestation of multiple pathogenic mechanisms

Hunt for Autoantigenic domain of receptor

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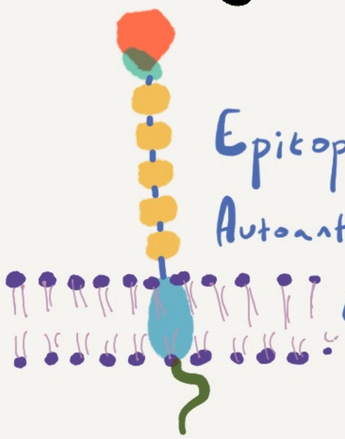


What is the Pathogenic role of the Autoantibodies?

Serum anti-podocyte antibody
- challenging to interpret

Role of miRNAs in pathogenesis of iMGN - link to air pollution?

Hypotheses
> iMGN - initially an endothelial cell disease
> Autoimmunity initiated by posttranscriptional regulation of GBM components
> miRNAs are potential biomarkers / therapeutic targets

Presentation of glomerular antigen
↓
Autoantibody development
↓
Proteinuria

Cell & disease specific miRNA-signatures

Nephronectin

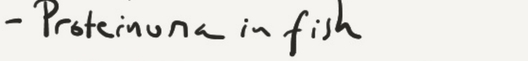
$npnt^{KD}$ and overexpression of miR-378 and -192 induce similar GBM phenotype

- NPNT expression is reduced and overlaps with PLAR2 expression in human iMGN
- Changes in GBM NOT limited to areas of immune complex deposition in human iMGN @ATJCagan

miR screening

Zebrafish model
- Proteinuria in fish

miR-378 injection induces GBM phenotype in zebrafish



fish lose albumin-sized nanoparticles

Widening of GBM SPACE

Nephrin Signalling to Focal Adhesions

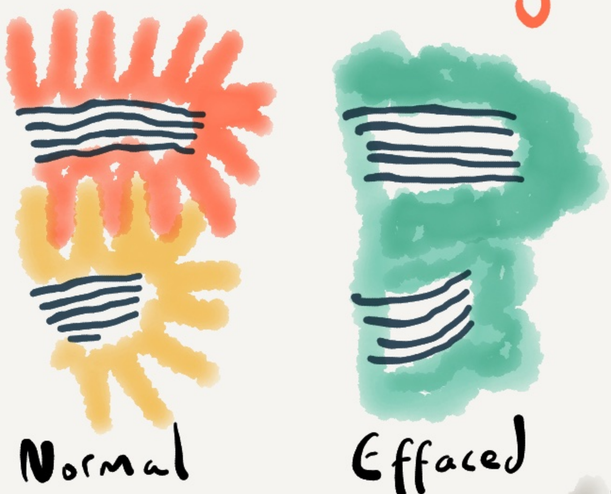
Britta George
University Hospital Münster

A Spectrum of Podocytopathies

Genetic ⟷ Environmental

Many causes remain unknown

The Glomerular Podocyte



The Filtration Barrier

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Nephrin signaling in Podocyte

Nephrin induces lamellipodia

Crk family proteins - loss impairs podocyte development

Healthy Podocytes

Drosophila Nephrocytes

Drosophila RNAi screen

RAP1 - Crk binding protein

Nephrin Activation Model

~~CrkL~~ + ~~Crk1/2~~ double Knockdown abolishes C3G recruitment

Rap1 is necessary for targeting Integrin β

Rap1 is necessary for slit-diophragms

Nephrin induces Rap1 activation

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Gaining a Foothold: How cell-matrix interactions determine glomerular function

Balance is everything

Christoph Schell

University Hospital Freiburg

Podocyte cytomorphology and adhesion

Glomerular basement membrane

Slit diaphragm cell contact
- **generating the filtration barrier**

Podocyte damage = limited ability to repair
- **Protein loss**
- **Scarring**

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Are there Podocyte specific adhesion receptors?

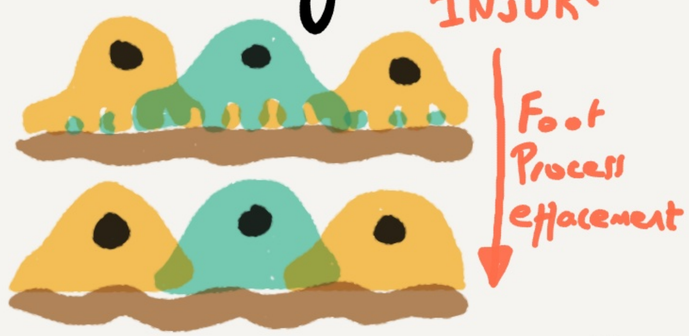
How do podocytes instruct the GBM?

Epb4115 KD mice show defects in the GBM

required for CDM assembly

Podocyte detachment

- common theme in glomerular disease?



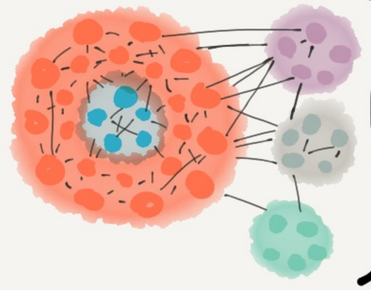
What mediates podocyte adhesion?

Collagen
Actin
Integrin subunits
The 'adhesome'

} Much known from genetics

Epb4115

Loss of Epb4115 causes Massive proteinuria & detachment phenotype



} Mapped focal adhesome of glomerular epithelial cells

Rigidity dependent adhesion maturation

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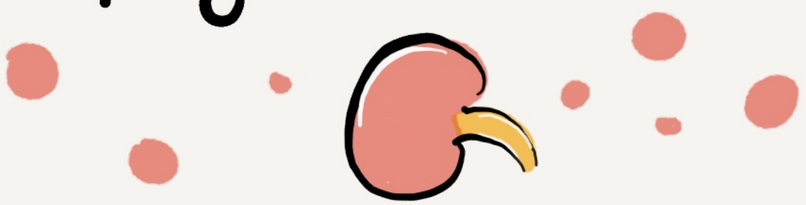
A Molecular Mechanism of Albuminuria

Thomas Benzing
University of Cologne

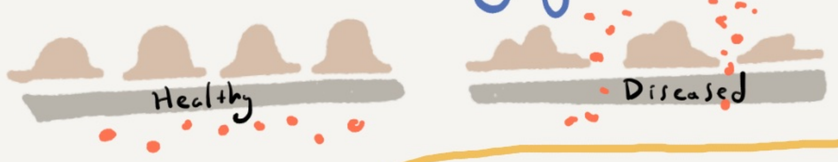
Kidneys are central regulators of organismal homeostasis



There is no validated model of kidney ultrafiltration!

How does glomerular filtration work?

The GBM restricts passage of Macromolecules in healthy glomerulus?



SURPRISE!
Slit diaphragm length inversely correlates with ACR

Mathematical Modeling → GFR = $S^* L_p^*$ net filtration pressure

Conundrums

- multilayered assembly of adhesion proteins unlikely to block albumin
- No nephrotic syndrome without podocyte disease
- why not more severe protein loss?

Generated a mouse model

CRISPR models of late onset disease

Automated Analysis of Morphological Data

→ Albuminuria the result of change in hydraulic conductivity of the GBM

Compression of the GBM prevents albumin diffusion

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The Genetic Architecture of Nephrotic Syndrome from Rare to Common Variants

Data Sharing

Meta Analyses

Matthew Sampson

Harvard Medical School

Precision phenotyping as crucial as genotyping

Contextualise genetic causes and contributors to nephrotic syndrome within framework of...

Genetic architecture

overall composition of variants influencing a given trait, in terms of...

- number
- effect size
- allele frequency
- interactions
  - variants
  - environment

Analysing families + populations

Nephrotic syndrome as a rare, Mendelian disease

COL4A3 + NPHS1 → Paradigmatic or one-offs?

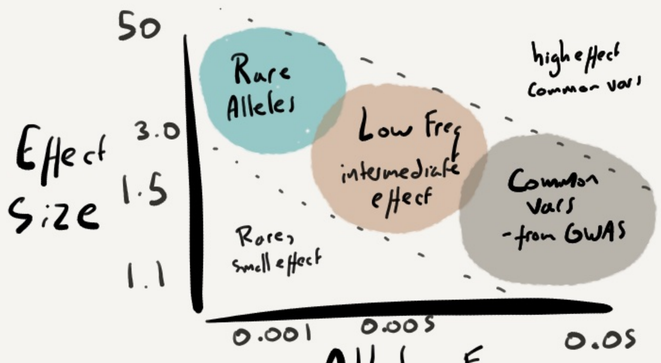
Aim: Map genetic variants

→ Discover mechanisms

→ Learn phenotypic consequences

→ Learn Molecular consequences

Mechanisms → Medicines



GWAS on Membranous Nephropathy

- PLA2R1
- HLA-DQA1

'Quasi-Mendelian'

Need patients from more diverse communities

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New Insights into Galloway-Mowat Syndrome

Corinne Antignac
Imagine Institute, INSERM
University of Paris

A rare, autosomal recessive disorder

Steroid-resistant nephrotic syndrome
Microcephaly + intellectual disability
High clinical heterogeneity - Severe prognosis short life expectancy

11 genes identified to be mutated
- most in RNA metabolism genes

WDR73 mutation - subset of affected children

Severe cerebellar atrophy
→ seizures → optic atroph

Kidney + Brain organoid models

#podocyte2021 PRDM15 + NUP gene mutations

WDR73 - integrator complex
UsnRNA/snoRNA - cell cycle
Crucial role in neural progenitor survival

Implicated in 2 integrator-regulated cellular pathways
Processing of UsnRNA

Does WDR73 maintain neuron + podocyte differentiation state by inhibiting their re-entry into the cell cycle?

KEOPS-related genes
- severe phenotype - 6 month median life expectancy

t^6A modification biosynthetic pathway
Key to accuracy of translation
GON7 → stabilizes KEOPS complex

Animal models don't recapitulate renal phenotypes

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What large-scale genetic cohort studies have taught us about glomerular diseases

Daniel Gale
UCL, Centre for Nephrology

Glomerular diseases typically classified by biopsy morphology

Monogenic
Immune-Mediated
or a mixture

Membranoproliferative GN + C3 glomerulopathy

- Mesangeal proliferation
- often with chronic immune activation
- rare 3-5 per million popn

The Complement System

Familial C3G linked to 3 monogenic complement disorders

- biallelic CFH mutations
- activating C3 muts
- rearrangements in complement factor genes

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The future for genetics of glomerular diseases

Larger cohorts
New technologies
Standardised phenotyping
Large registries

If MPGN/C3G is often a genetic disease of complement regulation...

→ we should sequence complement genes
→ to inform transplant decisions
→ treat patients with complement inhibition not immunosuppression

But observations not explained by monogenic aetiology

Rare Renal Disease Registry - RaDaR
- 26,900 consenting participants

Large Scale Whole Genome Seq
No enrichment of previously reported pathogenic variants

Increase in variants at HLA locus
∴ usually an Autoimmune disorder

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How is Monogenic gene discovery enabling novel therapy for FSGS/SRNS?

Friedhelm Hildebrandt
Harvard Medical School

Monogenic Disease
- mutation in 1 gene only

Single gene causation often with early disease manifestation

However
In different patients different genes may cause a similar disease

Steroid Resistant Nephrotic Syndrome

30% of 1780 SNRS families
- causative mutation found
-26 genes

Identifying Novel monogenic disease genes
Secure entry point to study pathogenesis

1,700 families - Whole Exome Seq

40 novel monogenic disease genes

>10 pathways
- Nucleoporins
- CoQ10 biosynthesis
- slit membrane
- Integrin/Laminin

ADCK4 mutations - new cause for SRNS
- biosynthesis of CoQ10 - in mitochondria

From target identification to gene replacement therapy?

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Linking adjacent basement membrane-insights from C.elegans

B-LINKs

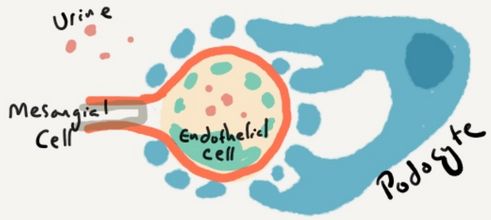
Basement Membrane
to
Basement Membrane
adhesions

Blood brain barrier

Optic cup formation

Lung

A B-link adhesion forms
the glomerular basement membrane



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David Sherwood

Duke University

Utse contributes hemicentin

Type IV collagen + perlecan
stable at B-LINK

Fibulin + Hemicentin are dynamic
↓
recruits other molecules

Long term B-LINK mediates utse
cell-epidermal seam cell tissue adhesion

Identify Membrane encoding genes

Living Basement Membrane Toolkit
> C.elegans genetic screens
Quantitate levels of BM components
Type IV Collagen, fibulin and perlecan enriched at the B-LINK

Relevance to Alport's Syndrome

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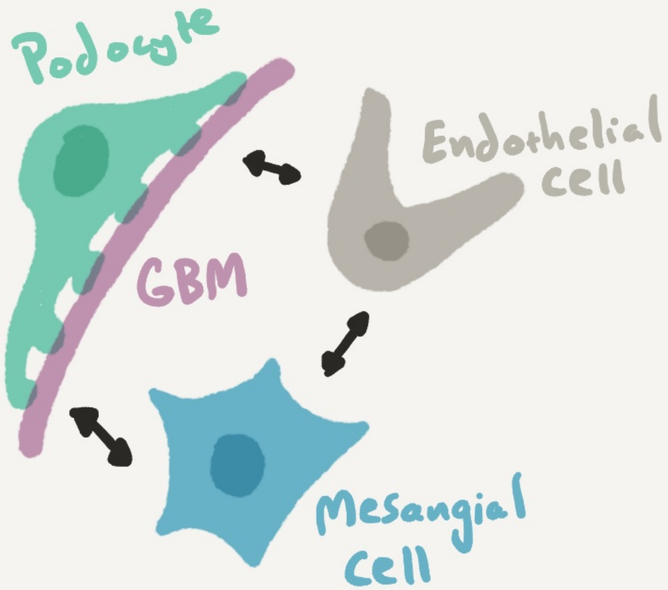
Role of Nephronectin in Glomerular Development

Denise Marciano
UT Southwestern Medical Center

The glomerulus functional unit



Mesangial Cells

Expansion of Mesangial cell area a hallmark of glomerular disease

→ required cells for capillary loop during devo

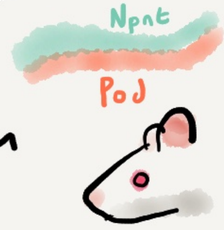
α8β1 highly enriched in mesangial cells

α8β1 integrin ligands

↳ Nephronectin

Deposited into basement membrane by the podocytes

RNA in situ hybridization



Absence of nephronectin causes mesangial expansion

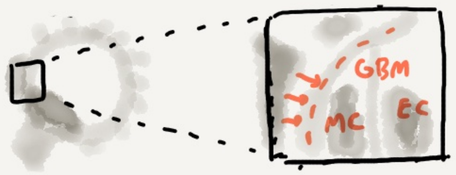
→ increase in mesangial cells

→ Mesangial sclerosis

No impact on serum creatinine or urinary albumin

Nephronectin + α8β1 colocalize & interact at glomerular capillary loops

Mesangial cells have enrichment of α8 at the lateral mesangial junction



Loss of Npnt exacerbates diabetic glomerular disease in mouse model

Nephronectin is required for normal glomerular development

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Basement Membrane Defects in Transplant Glomerulopathy

Hani Suleiman

Washington University School of Medicine

Transplant Glomerulopathy

- Affects ~2% kidney allografts by 5 years post-transplantation

Laminin 521 changes in TG

Collagen α1α1α2 trimers

Double Basement membrane in TG

Super-resolution Microscopy

STORM resolves ~20 nm structures

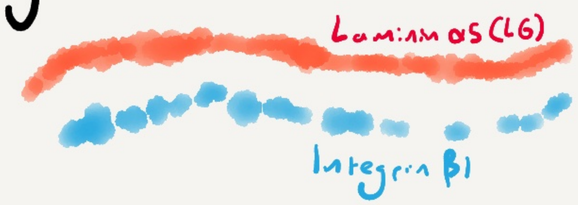
requires ultrathin cryosections

Airyscan resolves ~120 nm structures

- supports 3D imaging

- can be used on paraffin-embedded sections

Mapping GBM molecules with STORM



Aim: • evaluate composition of thickened GM associated with TG

• Identify causes → interventions

Airyscan Microscopy

- GBM markers

Podocalyxin

Agrin

Endothelial cellular protrusions in thickened GBM

Transplant Glomerulopathy is likely due to endothelial + mesangial injury

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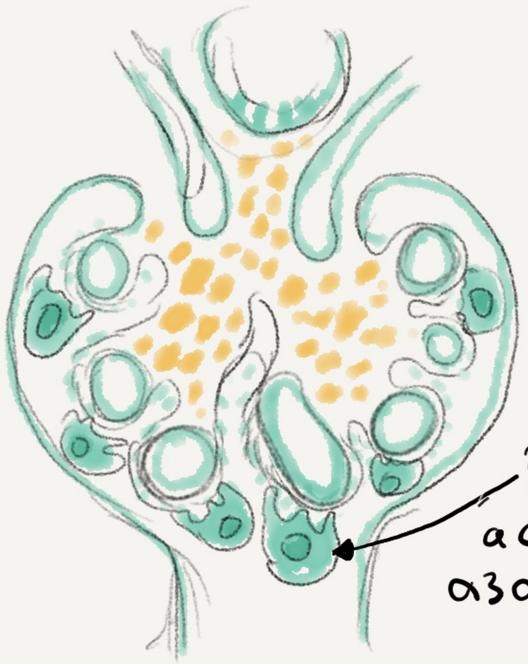
Can We Repair the GBM?

Jeffrey Miner

Washington University School of Medicine

The Kidney Glomerulus

Filters the blood



Podocyte
a collagen IV
α3α4α5 factors

Alport Syndrome

- hereditary glomerular disease
- foot process effacement in Podocytes

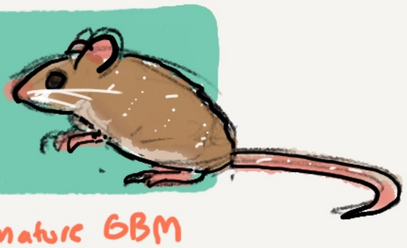
Alport syndrome caused by muts in glomerular basement membrane type IV collagen genes

Alport Syndrome

Therapeutic opportunities

Can the structure (and function) of the abnormal GBM be rescued?

Inducible Col4a3 mouse model



Composition of mature GBM can be changed

Restoration of Collagen IV network slows progression of ESKD

In Vivo tools of the (near) future for 'Gene Therapy'

CRISPR/Cas9

COL4 gene repair

pro-repair gene activation

Pathogenic gene deactivation

Protein Therapy

Viral gene delivery (AAV)

- Mutant COL4 gene replacement

Nonsense Mutation Bypass

- exon skipping
- premature codon readthrough

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Recessive, gain-of-function toxicity in APOL1 BAC transgenic mice

Martin Pollak

Harvard Medical School

APOL1-associated kidney disease

G1 + G2 ⇒ Coding variants
- high risk for kidney disease

Apolipoprotein-L1

APOL1 Nephropathy Spectrum

Key trypanolytic factor

Normal function in kidneys is not known

All models are wrong but some are useful

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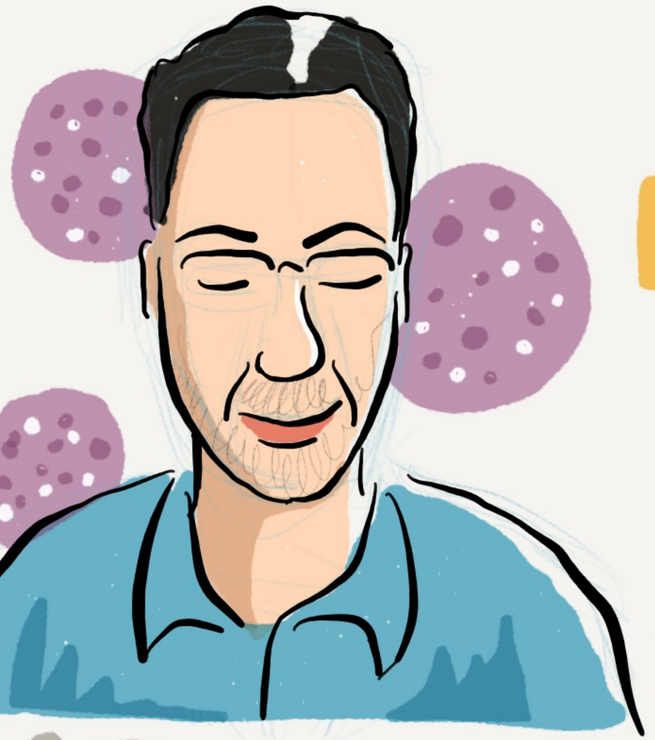

Primate specific gene

APOL1 BAC transgenic mouse

Create G0, G1 + G2 mice
- isogenic with CRISPR induced variants

Uninduced APOL1 expression in these mice
- no spontaneous proteinuria

Induce disease - IFNγ upregulates APOL1

APOL1 expression induced in podocytes post injection with pCpG-Muy

The mice then develop albuminuria + die

G1 + G2 mice develop foot process effacement

Severity of disease correlates with Expression

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Mouse Model

Number of G2 allele matters

Zygosity influences toxicity

Puzzle = Single copy does not induce disease in this model

Searching for Treasure in Big Data

Agnes Fogo

Vanderbilt University Medical Center

Assessing known targets in human specimens

High-risk variants of APOL1 associated with more mesenchymal + less podocyte transition of activated PECs

PEC/podocytes in human arteriolonephrosclerosis

what can we learn from human biopsies?

Do ApoL1 variants affect PEC function?

- assess renal biopsies - genotype >300
- risk stratify

Global Glomerulosclerosis

Risk allele associated with more severe phenotypes

more proteinuria in AA patients with high risk vars of APOL1

Integrating big data with target validation

Mesenchymal transition of activated PECs

more advanced in African Americans with high risk APOL1 alleles

Mining big data for novel podocyte targets

RNA Seq study: Diabetic mouse model

- Differential expression in kidney

Add proteomics

DAAM2 highlighted
- validate in human biopsies
- increased in non-normal samples

DAAM2 regulated by high glucose & Ang II

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Genetic and Pathologic Biomarkers in Glomerular Diseases

Moumita Barua
University of Toronto

Monogenic Studies in Focal and Segmental Glomerulosclerosis (FSGS)

Clinicopathologic entity

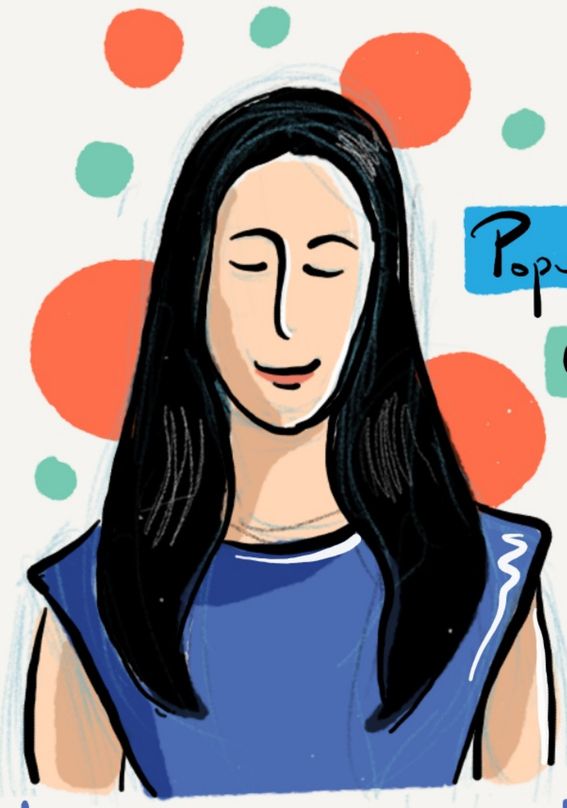
FSGS classification by etiology

Primary | Genetic | Secondary

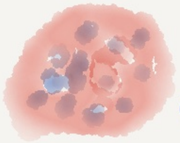
Clinical cues can discriminate primary + secondary FSGS

Serum albumin level | Onset of proteinuria | Podocyte alterations

Need to identify mechanistically informative biomarkers



Integrating genetic testing with other diagnostic tools — improve outcomes



Whole exome seq of 193 adult onset FSGS - COL4A leading cause

- Single gene cause in 11% cohort

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Variability in Alport Syndrome

vulnerable to misdiagnosis

Mild	classic
Hematuria	. Kidney disease
Low grade Albuminuria	. Hearing + eye deformities

Population based studies in Hematuria and Albuminuria

UK Biobank ~500,000 adult volunteers
- genetic + clinical data

Hematuria in Icelandic popn → deCODE

which genetic variants associate with non-GU related haematuria in the UK Biobank?

- 6 loci associated eg: COL4A4 p.Ser969x, TGFB1/CCDC97, HLA-B, PDPN, SORL1, PLLP

Machine Learning to identify Pathological Biomarkers - A Pilot Study

→ whole slide images - cases + controls

10 Key features

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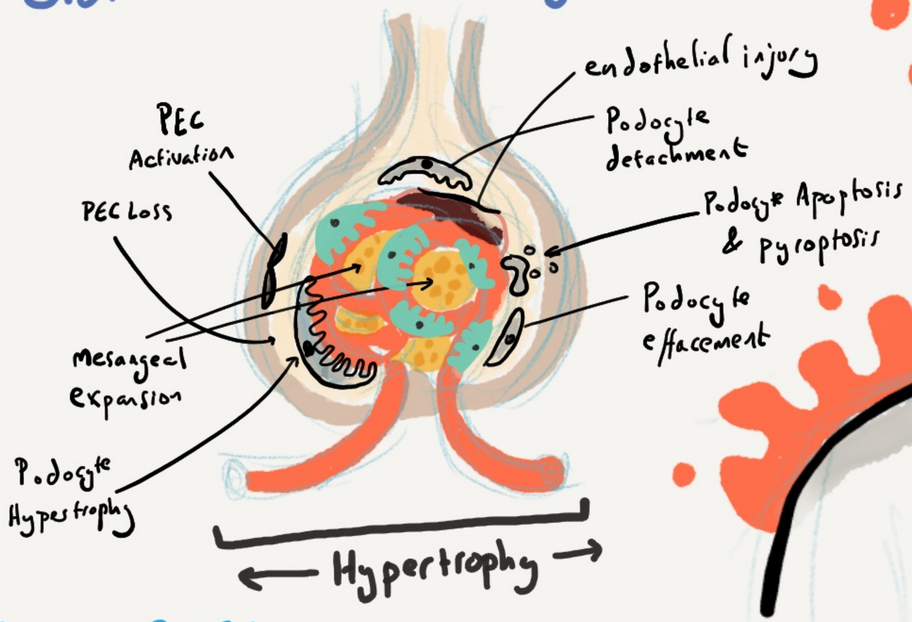
Podocyte Aging - why we should care?

Stuart Shankland
University of Washington Medical Centre

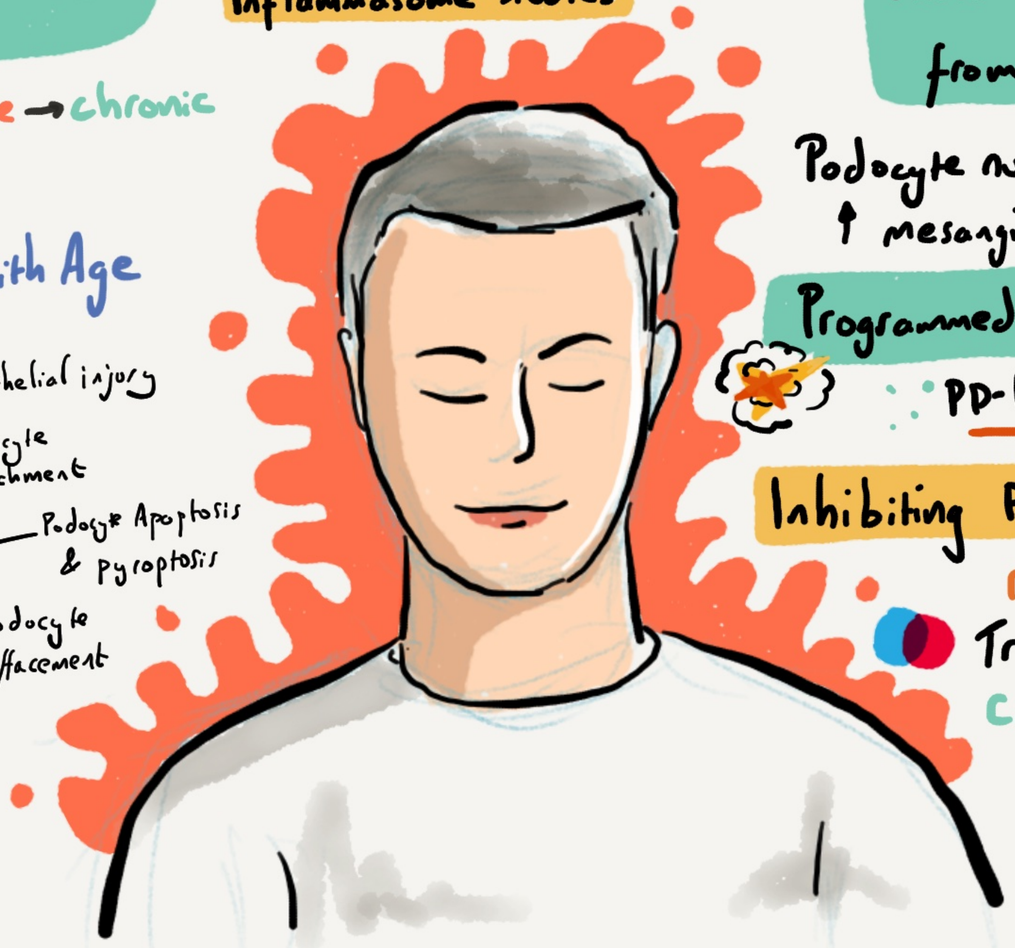
- The global population is Aging
- After age 40 - GFR declines by 0.8-1% per year
- After age 30 - lose ~6000 nephrons a year
- Age accelerates transition from acute → chronic Kidney injury

Glomerular Cellular Changes with Age



Podocyte Replacement Reduced with Aging

Inflammasome studies



Mechanisms of Podocyte Aging?
Can we slow the process?

Aim = Increase Healthspan

RNA-seq young & old podocytes from a reporter mouse

Podocyte number / density decreases with age
↑ mesangial + endothelial cells to compensate

Programmed Cell Death Protein Expression ↑ with age

PD-1 induces death in cultured podocytes

Inhibiting PD-1 in aged mice

Metabolic pathway improvement

Transcriptome comparison

Canonical podocyte genes higher in expression after anti-PD1 antibody

Improved healthspan following treatment - no changes to podocyte density

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Reducing the Inflammasome in aged mice with a NLRP3 inhibitor improves podocyte health

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A Systems Approach to Adhesion Signalling

Martin Humphries
University of Manchester

Mechanisms of cell adhesion

Fidelity of adhesion under variable flow and pressure

How do adhesion receptors sense chemistry and rigidity?

Much we don't know

The Adhesome Network

- proteomic profiling

Multiple mechanisms for integrin–actin linkage

Can we define the adhesome network in vivo?

BioID

protein labelling with biotin

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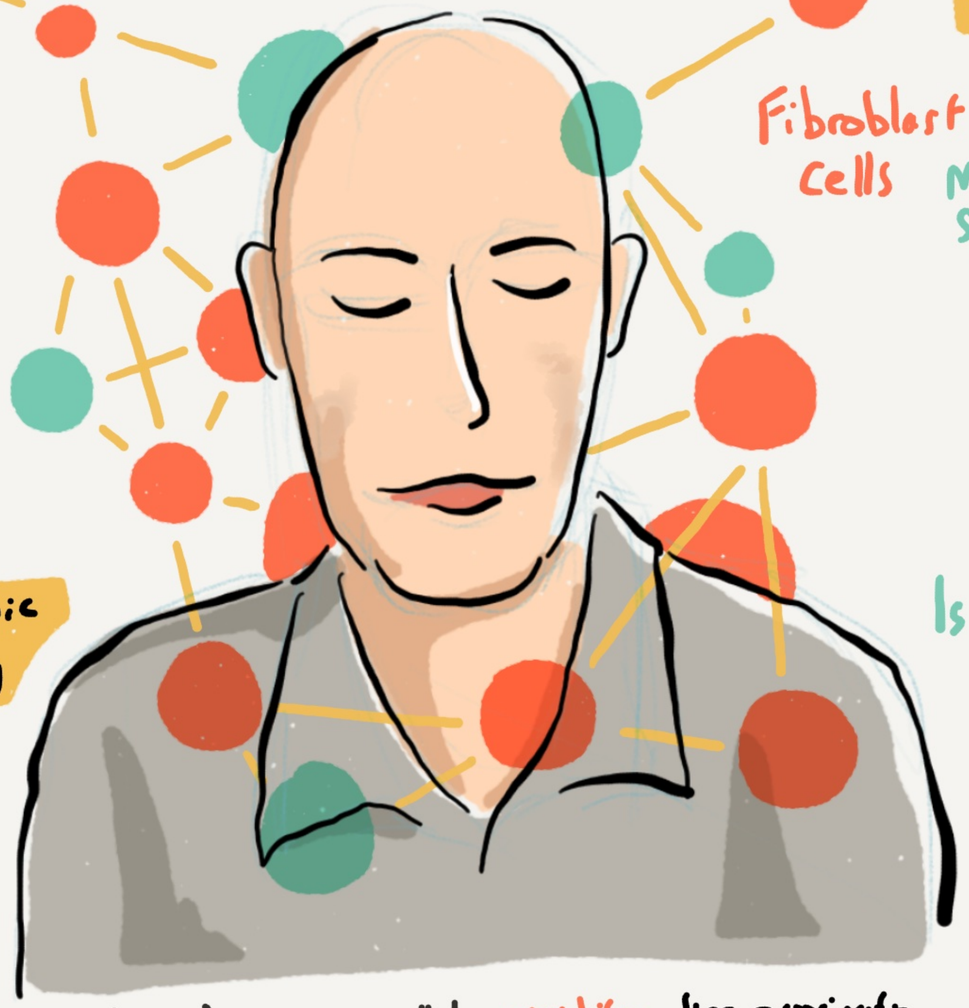


How does extracellular rigidity alter proximity interactions? ≈ Hydrogel experiments ≈

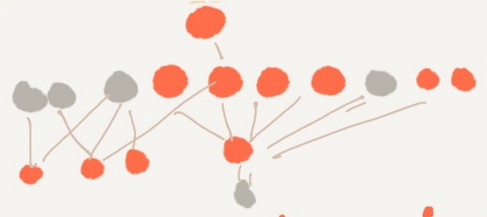
CDK1 a positive regulator of integrin dependent adhesion

CDK1 binds talin via an LD motif

BioID experiments

Labelling to track even transient interactions

Fibroblast Cells — Mass Spec



Bait centric cluster analysis

Unbiased 2D clusters

Reveals 2 main clusters and 5 sub clusters

Is the adhesome spatially segregated?

How is topological organisation achieved?

Mapping function onto the network

Inside-out force modulation

- myosin II inhibition

Blebbistatin altering proximal interactions

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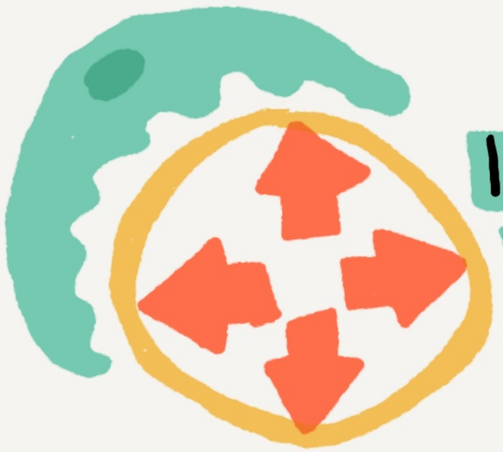
Podocytes under Stress – aspects of the actin cytoskeleton, cell contacts and Matrix

Nicole Endlich
University Medicine Greifswald

Relevance to Diabetic Nephropathy



Inter capillary Pressure can damage podocytes

Designed a stretch apparatus to study impact of pressure changes on podocytes

stretched vs unstretched

OSTEOPONTIN

FASCIN - expressed in podocytes

FASCIN KD – Podocytes more vulnerable to stress

Influences size + number of focal adhesions

FIBRONECTIN

Increased Expression under mechanical stress

↑exp in humans with Diabetic Nephropathy

FILAMIN Actin binding protein

- isoforms
- new binding partner of Synaptopodin

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The Role of Parietal Epithelial Cells in FSGS

Marcus Moeller

RWTH University Hospital
Aachen University

Is it possible to Blow podocytes off the GBM?

Ex-vivo hypecfusion of mouse right kidney

Precile counting of podocytes
- tissue clearing + marked nuclei

It is nearly IMPOSSIBLE to blow off podocytes in healthy mice

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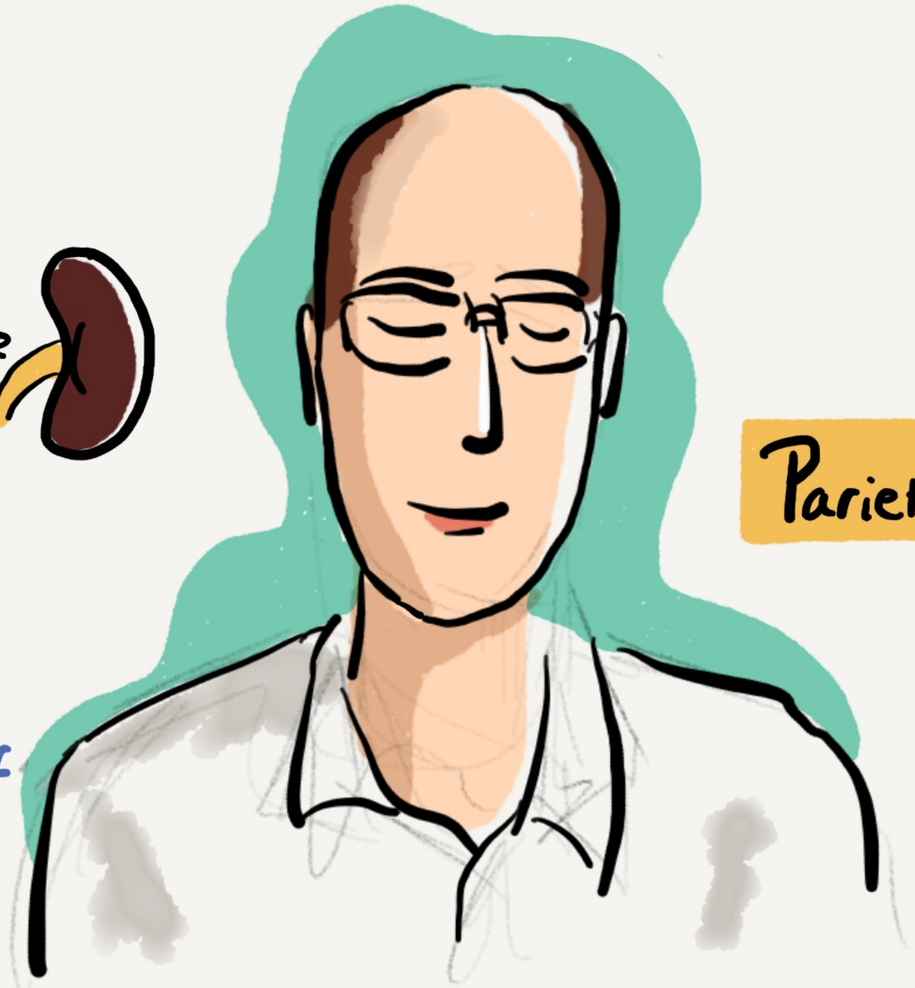

PEC subpopulations

iPECs (intermediate PEC)
Hotspot for lesion formation

1½ year old mice

In aged mice → less podocytes
Few can be blown off

Effaced podocytes are easier to detach

Parietal cells

FSGS - final common pathway to nephron loss
↓
an active cellular process

Glucocortidoids act directly on PECs
Testing the relevance of PEC activation

PECs contribute to CKD Progression

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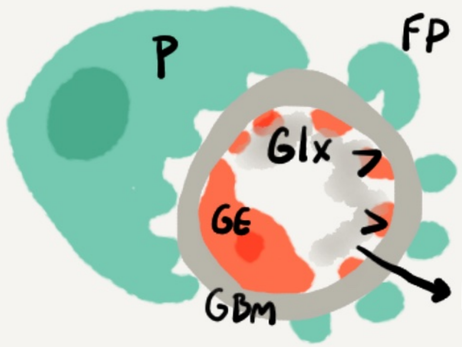
Signals to the Endothelium

Becky Foster

University of Bristol

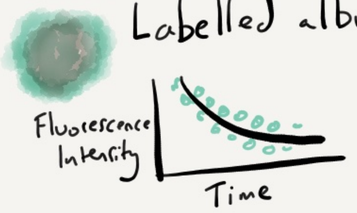
The Glomerular filtration barrier



Glomerular epithelial cells (GEnC) provide an effective primary barrier against protein, via protective glycocalyx lining

Glomerular albumin permeability assay

Labelled albumin



EGlx disruption increases glomerular albumin permeability

Glomerular Paracrine Signalling

Microalbuminuria ↑risk of cardiovascular disorders

Angt restores diabetes-associated eGlx damage & glomerular albumin permeability in rats

Heparanase - HPSE - ↑ in glomerular diseases
- upregulated in podocytes - inhibitors can prevent proteinuria

Heparan sulphate is present in glomerular eGlx
- Influences glomerular albumin permeability

Damage to glomerular endothelial glycocalyx leads to moderate albuminuria

VEGFC protects mice against glomerular endothelial glycocalyx disruption

VEGFC protects against progression of albuminuria in diabetes

Lymphactin = VEGFC gene therapy

Paracrine signals from podocytes to GEnC are important in regulating the eGlx barrier

This crosstalk can be utilised to develop novel therapeutic approaches to target glomerular disease

Podocyte ↔ endothelium Crosstalk

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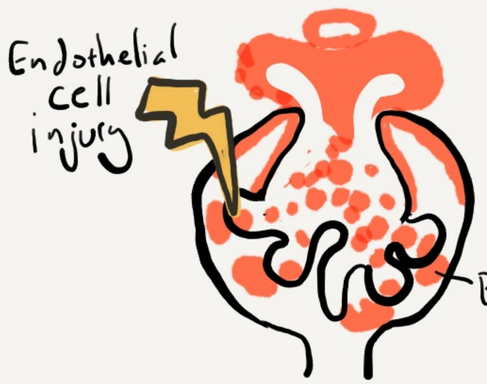
Pathogenesis of Extracapillary Lesions

Pierre-Louix Tharaux

Paris Cardiovascular Research Centre

Extracapillary Glomerular Diseases



"Crescentic" RPGN

insult

adhesion

progression

advanced sclerotic lesion

AAV is a catastrophic disease

We need immediately effective therapies

Crescentic Rapidly Progressive Glomerulonephritis (RPGN)

HB-EGF → expressed in podocytes
- all glomerular epithelial cells.

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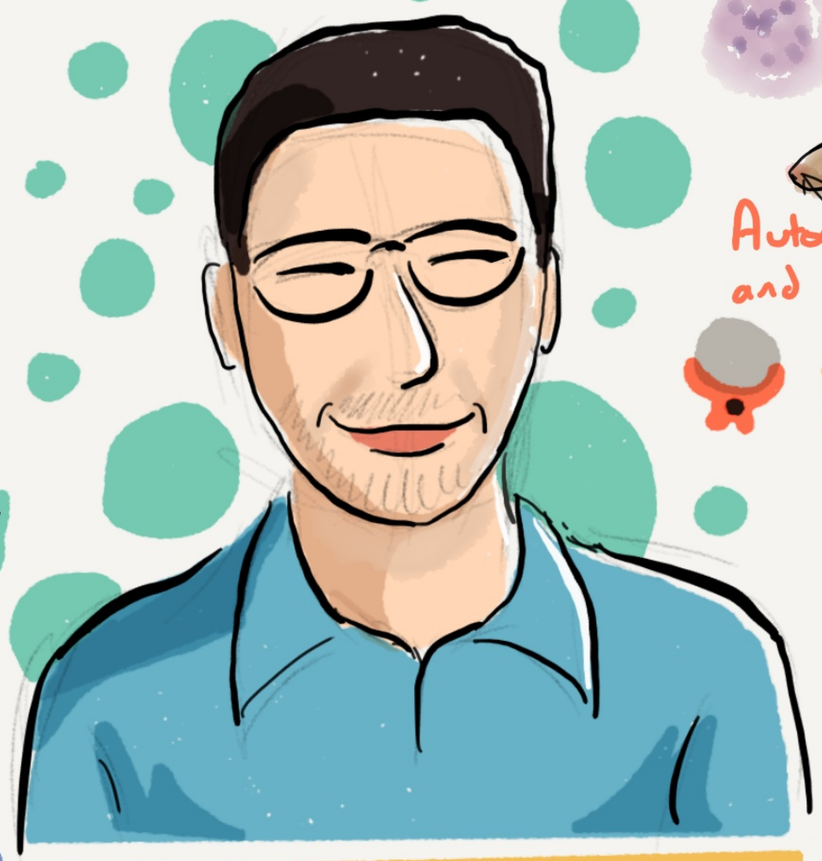

Crescentic and FSGS start after podocyte injury or loss

Majority of cells forming crescents are **NOT** podocytes but PECs!

HB-EGF KO mice

- Prevents fatal renal destruction when deleted in challenged KO mice

Autocrine HB-EGF induces a proliferative and migratory podocyte phenotype in vitro

Conditional deletion of Egfr gene in podocytes limits glomerular inflammatory destruction

Acting locally to stop crescents forming

Targeting PEC recruitment
- CD9/EGFR+PDGFR paths

How does podocyte injury activate PECs?
- HBEGF/EGFR/STAT3 & PPARγ paths

Only about podocyte injury?
- endothelial alteration leading to FSGS

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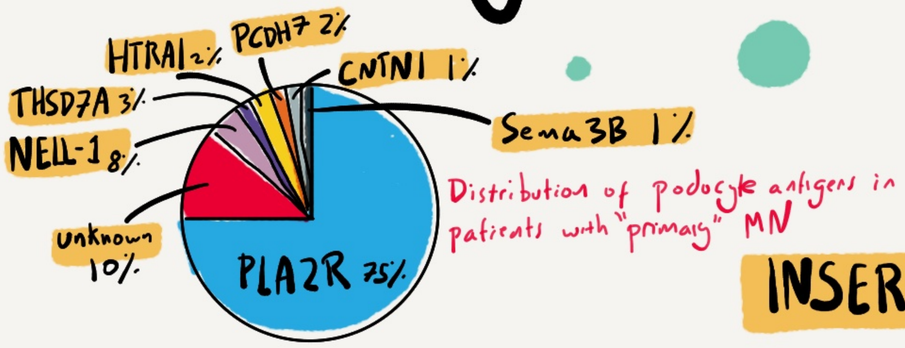
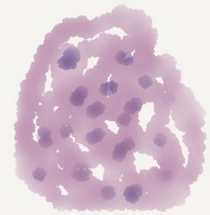
New Antigens and the Podocyte in Membranous Nephropathy



Distribution of podocyte antigens in patients with "primary" MN

Pierre Ronco

INSERM UMRS 1155 & Sorbonne University



Neutral endopeptidase

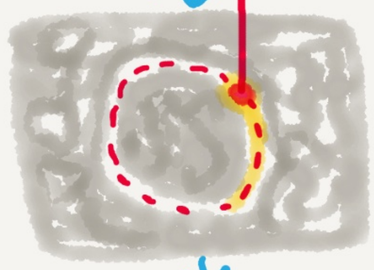
First podocyte target antigen in a rare subset of patients with neonatal MN

PLA2R - Paradigm shift in diagnosis monitoring + stratification of patients

Identified via Western Blotting of Glomerular proteins

Major Technological Leap

Laser Microdissection of glomeruli



MS of trypsin digested proteins

6 new antigens identified

Exostosins 1+2 — NELL-1

NCAM1 — Sema3B

PCDH7

IHC + IF Validation

Validation of antigens in large cohorts

NELL1 - A new marker of K-associated MN?

Target antigen in Malignancy Associated Nephropathy

Contactin-1 = a new antigen in MN with inflammatory neuropathy

HTRA1 - novel target antigen in Primary Membranous nephropathy

Towards antigen defined molecular classification

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Therapeutic Targets in IgA Nephropathy

Jonathan Barratt
University of Leicester

The most common form of primary glomerulonephritis globally

There are **no approved treatments** for IgA nephropathy

Previously = Little interest from Pharma
- Slow progression
- prohibitively expensive

Now - Proteinuria changes as a biomarker for later outcomes

Early change in urine protein

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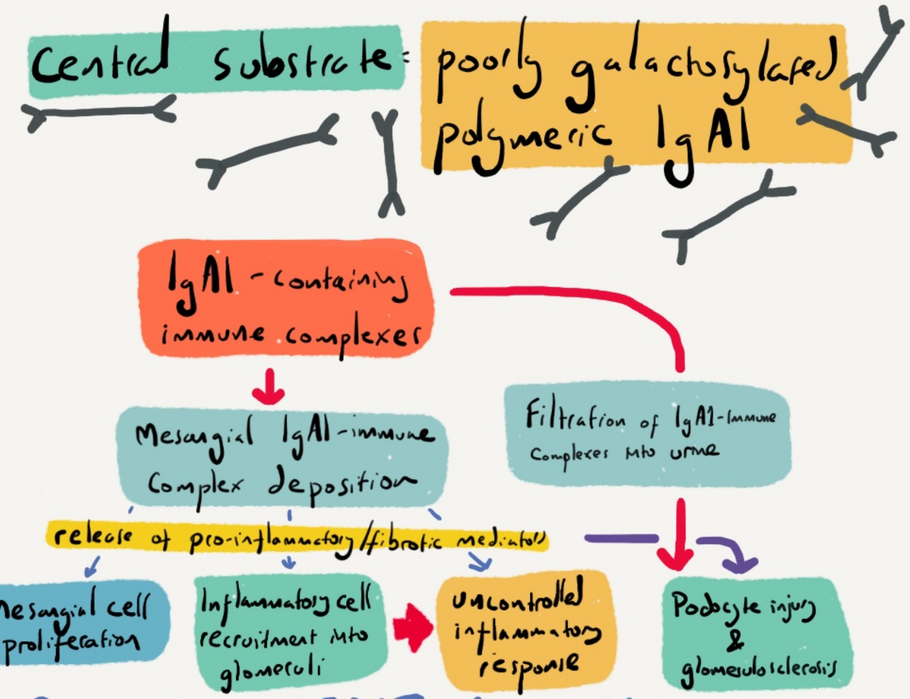
Role of mucosal antibodies

Mucosal Immune system as source of pathogenic IgA molecules

Targeting the gut to treat the kidney
nefIgArd Trial

Patients need treatments

IgA containing Immune complexes



Trials to identify new treatments for IgA nephropathy

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Complement and Podocyte Injury in Glomerular Diseases

Marina Noris

Istituto di Ricerche Farmacologiche Mario Negri- IRCCS

Complement activation can lead to disease

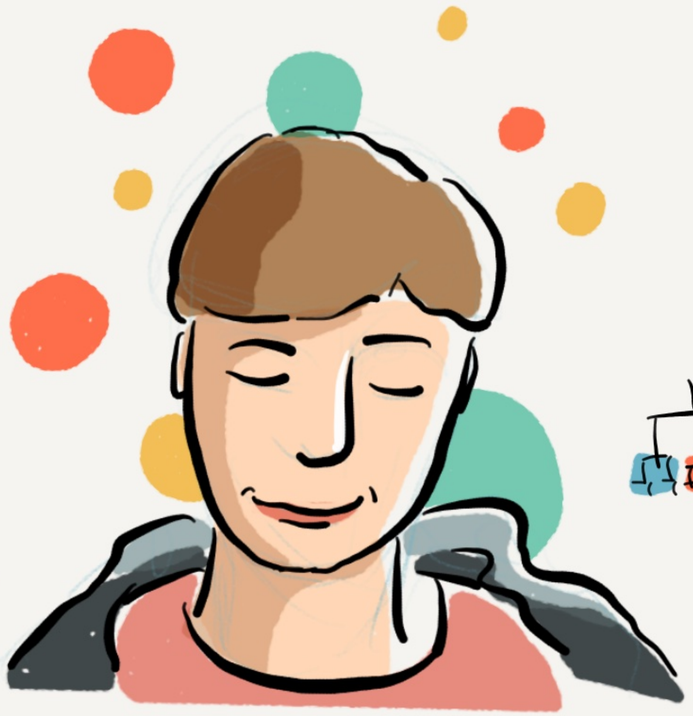
MPGN

- 20-30% cases
- no underlying condition
- idiopathic IC-MPGN

Classical / Lectin / Alternative Pathways

C3 only

Genetic or acquired abnormalities causing AP dysregulation reported in patients with IC-MPGN



Loss of Podocyte **Myosin** ± **Nephrin** staining in IC-MPGN

★ 4 different pathogenic patterns of complement activation

Unsupervised Cluster Analysis

333 patients - Primary IC-MPGN/C3G

Consideration of nephritic factors

Four distinct clusters

1. Fluid phase C3+C5 convertase activation
2. 1 + classical pathway activation
3. Fluid-phase C3 convertase activation only
4. Solid-phase complement activation

Cluster 2 = highest prevalence of nephrotic syndrome

Podocyte injury confirmed in all clusters

C5 activation products => cell injury

Podocyte injury & dysfunction

EAGLE study: Evaluating Morphofunctional effects of Eculizumab Therapy in Primary Membranoproliferative Glomerulonephritis

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Glomerular Injury in ANCA-associated Vasculitis

Silke Brix
University of Manchester

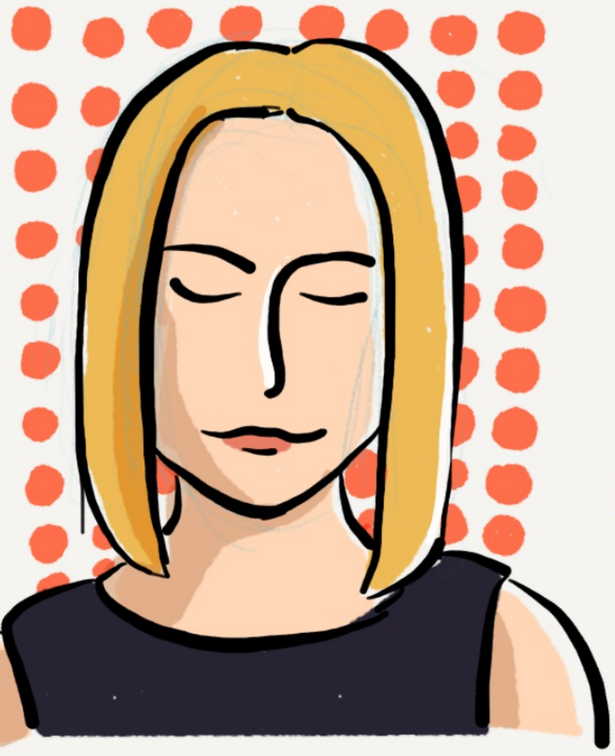
Alternative complement activation in AAV highlights inflammatory pathways involving FHRs

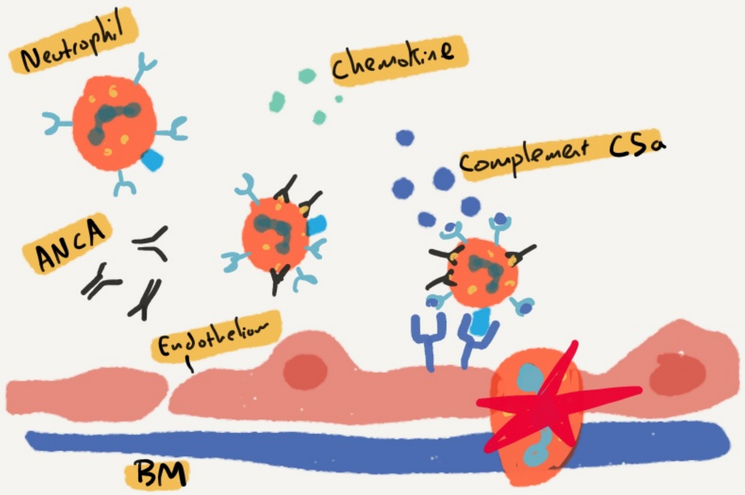
Rapidly Progressive Glomerulonephritis

Type I - Antibody Type

Type II - Immune Complex Type

Type III - Pauci Immune Type





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AAV pathophysiology

Factor H

CFHR5 deposition in ANCA GN

CFHR1 induces monocytic IL1β production and binds necrotic cells

CFHR1 deposits at site of glomerular necrosis

Parietal epithelial cells (PECs) form crescents but mechanisms of extracapillary proliferation remain poorly understood

Pathogenic CD9 expression in PECs as potential driver of glomerular destruction

ANCA Renal Risk Score

Deep learning podometrics
Transitional state found

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Les Souris and a Podocyte potpourri

Susan Quaggin

Feinberg Cardiovascular and Renal Research Institute

The Mouse as a model to study podocyte biology

The Mouse

A fantastic model system

Dissecting pathways

Finding clues to test in patients

Endothelial variability in the Kidney

VEGFR3 - expressed in glomerulus during devo - distinct to VEGFA

Congenital nephrotic syndrome

Podocyte specific expression

Podocyte architecture

Cytoplasmic tail

3 tyrosine residues

- phosphorylation → actin recruitment

Nck2 Nck1 KO

- foot process defects

VEGF - high expression in podocytes during devo

Remove Vegfa from podocytes only

- Develop kidney failure
- Signalling to endothelial cells

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Focus on Myosin: analysing MYO1E mutations with microscopy across Scales

- Organism
- cell
- Molecule

Mira Krendel

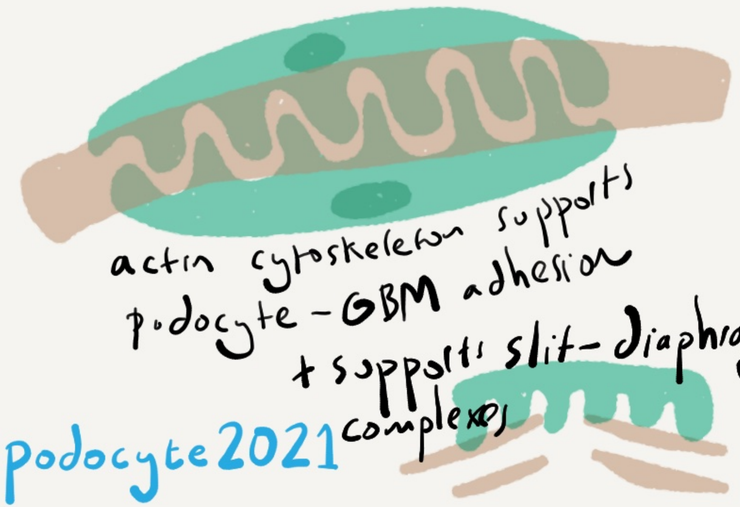
SUNY Upstate Medical University

@KidneyMyosin

Loss of Function actin-associated proteins leads to proteinuria and podocyte effacement

Testing the effects of variants identified in patients with podocytopathies

Cytoskeletal proteins as an example



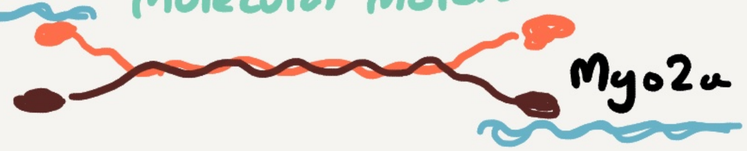
actin cytoskeleton supports podocyte-GBM adhesion + supports slit-diaphragm complexes

Myo1e muts assoc with FSGS/SRNS

Study immortalized mouse podocytes

FRAP: Fluorescence recovery after Photobleaching

Myosins - actin-dependent molecular motors



Analysing Myo1e functions in podocytes

Cytoskeletal proteins play multiple roles

cell-cell adhesion

endocytosis signaling

Mouse Models

Myo1e KO → podocyte dysfunction + proteinuria

- similar to Alport syndrome

Yeast Endocytosis Model

in vitro motility assays @ATJCagan

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The Impact of Genetic Background on Alport Syndrome in Mice

A young male B6 mouse is not ALWAYS a good model

Genetic Background makes a difference

Ron Korstanje

The Jackson Laboratory

Genetically diverse mice...

...to understand diverse humans

Jackson Laboratory - Diversity Outbred
- 8 original strains

Better mouse models for albuminuria
- 20 strain comparison

Mapping modifier genes for Alport Syndrome

Mapping genes that influence albumin levels

The Bilateral wasting kidney (bwk) mutation mapped to **Col4a4**
- part of the glomerular basement membrane

Loss of the GBM in bwk mouse

Large variation in age of onset + severity across mouse strains

Rfx3 Gene identified for changing outcome
- Mouse cross to be +/- KO

Het females possibly diabetic

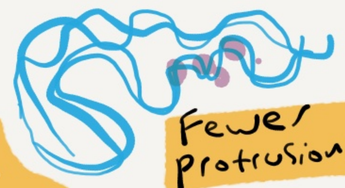
↑ cilia number ↑ cilia length
Disorganized

Primary cilia in the kidney

Dgke + Pik3r1 → actin cytoskeleton

Fmn1 → formin 1 → binds to → drives protrusion?

Testing Fmn1 KO mice
- lower Fmn1



Fewer protrusions

Analysing genetically diverse mice identifies human relevant genes

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C.elegans as a platform to discover new regulators and functions for the FSGS-associated formin INF2

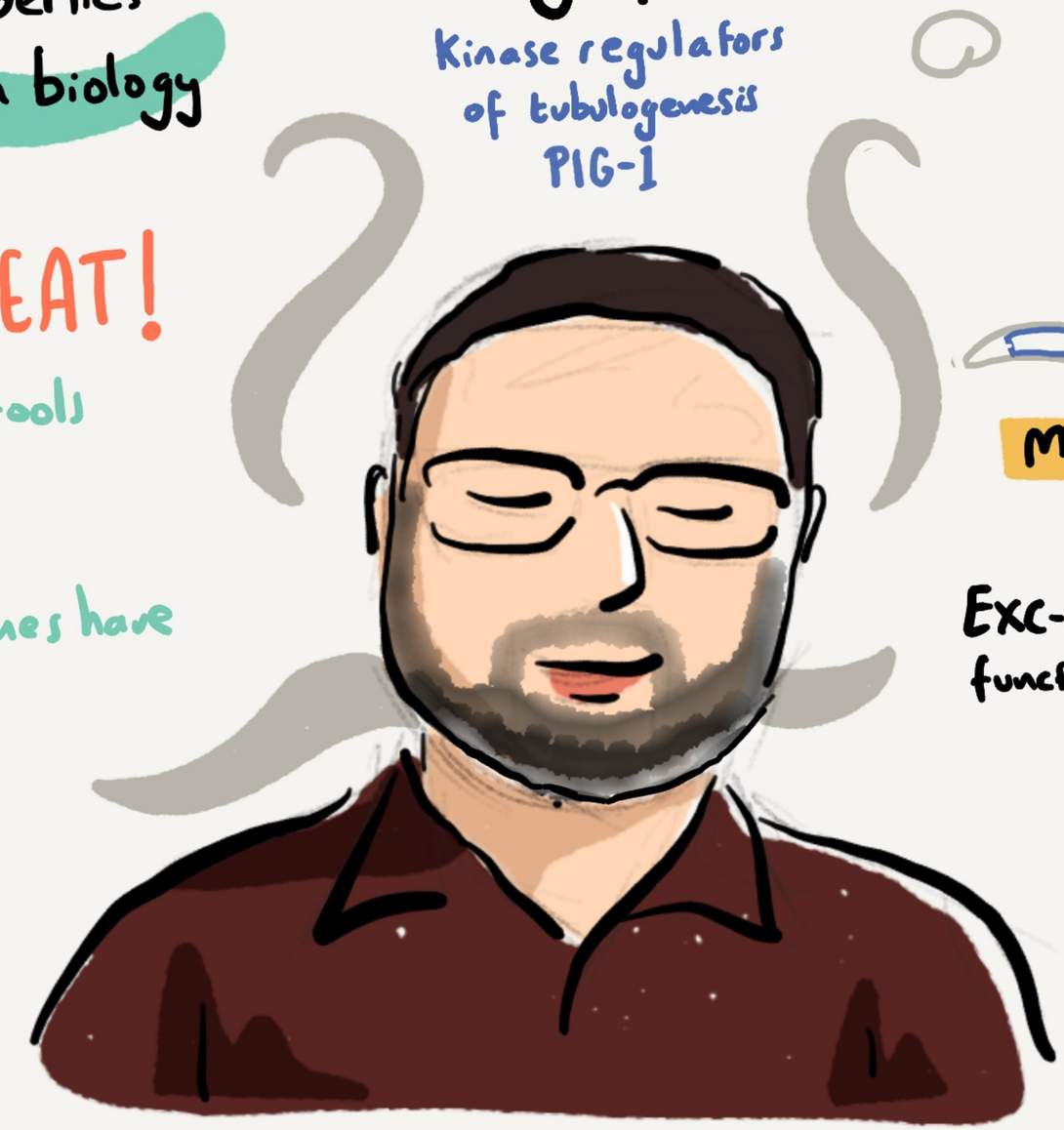
Daniel Shaye
University of Illinois

Tubulogenesis underlies form & function in biology

Kinase regulators of tubulogenesis
PIG-1

Worms are GREAT!

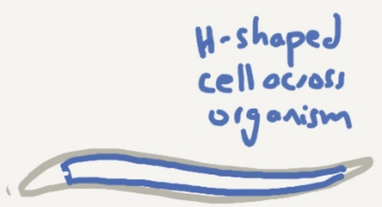
- Powerful genetic tools
- Quick life cycle
- ~50% C.elegans genes have human orthologs
- Transparent



The Excretory Canal

ExCa lumen formation

Coalescence of vesicles



Muts in exc-6 cause ExCa defects

Encodes a formin

- FH2 + FH1 domains
- actin interactions

Exc-6 + INF2 are functionally conserved

Anchoring role

Maintaining the tip

INFT-2 gene regulating F-actin polymerization

inft-2 as a disease model

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APOL1 nephropathy in Kidney Organoids

Benjamin Freedman
University of Washington

Chronic kidney Disease is a Spectrum

Treatment options largely limited to ESRD

Mouse models are low throughput, co$tly and divergent

Need to model specific forms of disease

Human Kidney Organoids resemble kidney tissue

Organoids contain many different cell types

Robotic manufacture of kidney organoids

Podocytes form distinctive epithelia in organoids

Podocalyxin required for podocyte organization

APOL1 - human risk factor for kidney disease
old world primate specific

Generate APOL1 mutants in iPSCs
-interferon gamma induces APOL1 in organoid
mutant is sensitive to ER stress
APOL1 localizes to intracellular & plasma membrane

IFN-γ reduces epithelial markers
Therapeutics can block APOL1 expression

Organoids form glomerulus like structures in mice

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The Challenges of Drug Development for Kidney Disease

Andrey Shaw
Genentech

Developing new drugs for kidney disease

an industry perspective

>1 in 7 US adults have CKD

annual cost > $100 billion

Treatment options are lacking

What is kidney disease
- many different pathologies

Need better phenotyping

Need better understanding of disease mechanisms

Limited diagnostic methods

lack of biopsies or biomarkers

Hard to enroll patients in trials requiring biopsies

Need to improve clinical trial design

FDA approved clinical trial end points before trial starts

SGLT2 inhibitors
- the elephant in the room
- renoprotective
- could cover large fraction of unmet need
- Time will tell

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Drug Development - a regulatory perspective

Aliza Thompson
FDA

Transformation of Drug Development

Clinical Trials for FSGS patients
EXPLOSION of new trials

Drug Development is a global process

Regulators are not a 'black box'

LISTENING TO THE PATIENT VOICE
Smarter trial design
- make it easier for patients

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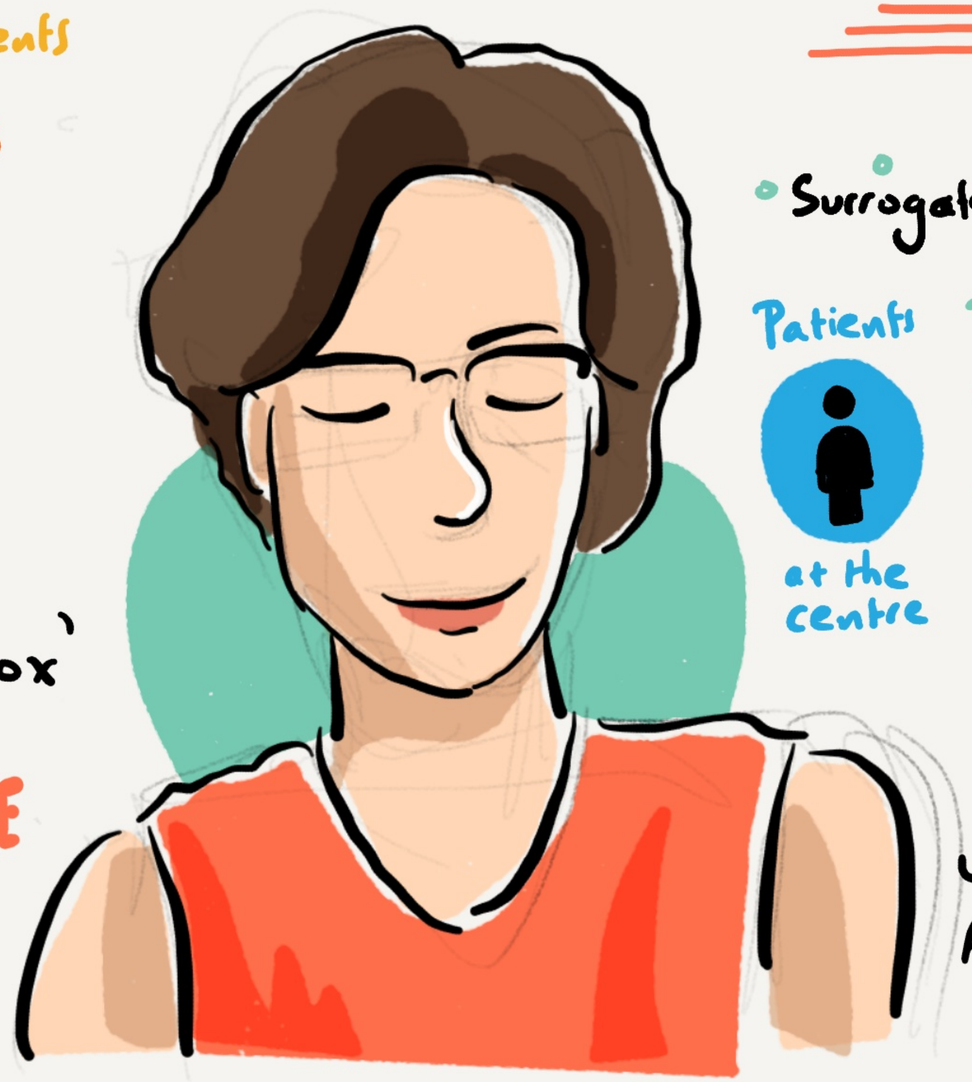

Endpoints & Arrival Pathways
Traditional Approval
Accelerated Approval
endpoint substitutes
- Surrogate biomarkers eg ↓ Proteinuria

Patient Focused Drug Development
Patients at the centre

Patients as experts in their disease
Understanding patient preferences
Appreciate patient heterogeneity

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Mechanisms of response to therapy in Diabetic Kidney Disease

Matthew D. Breyer

Janssen Research and Development LLC

Despite SGLT2: kidney benefit, majority of DKD/CKD subjects still progress to dialysis

What causes resistance to therapy?

Podocyte gene responses to diff drug treatments predominantly do not overlap

Experimental Design

Effects of drug treatment at 2 days + 2 weeks

Albuminuria reduction correlates with improved outcomes

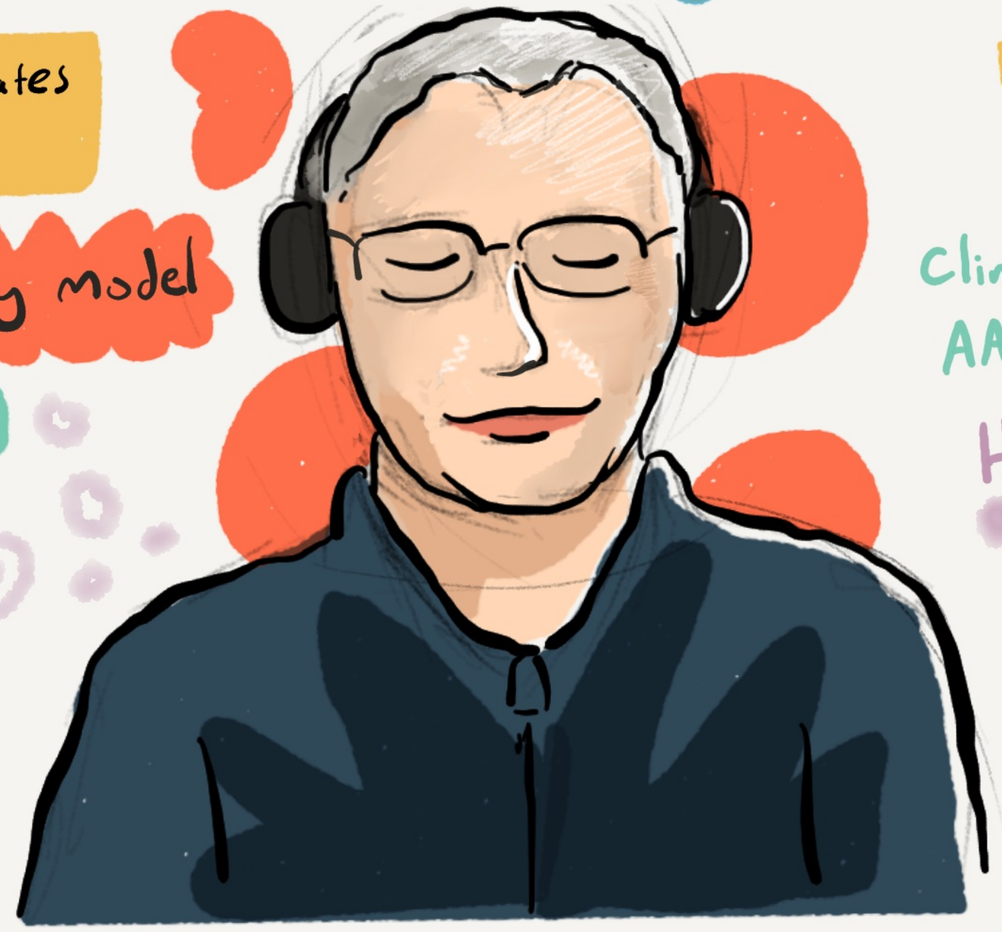
Renin AAV uni-nephrectomy model

Develops renal failure

Tubular degeneration

&

Mesangeal expansion
Glomerulosclerosis



Kidney → Nuclei → 10x Chromium

Clinical biomarkers in db/db renin AAV mice at 2 weeks

- UACR
- SBP
- Glucose

Histopathology + Diff expression RNA

UMAP clusters from ~1 mill kidney cells

PPARγ - top predicted endothelial activated transcription factor activation following ROSI @ 2 days

Ketogenesis pathway

robust data set

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Transplanted human organoids empower PK/PD assessment of drug candidates for the clinic

Chronic kidney disease is a global epidemic in need of novel therapies

Peter Mundel
Goldfinch Bio

Transcriptional profiling of kidney organoids transplanted into rats

- identify best time for transplant

NanoString gene expression quantification in hiPSC
- enabled rapid batch QA

Feasibility of transplanted human organoids

Pharmacokinetics (PK) = what a body does to a drug

Pharmacodynamics (PD) = what a drug does to a body

PK studies with GFB-887

PK/PD studies with transplanted, perfused kidney organoids

Using transplanted kidney organoids for PK/PD studies

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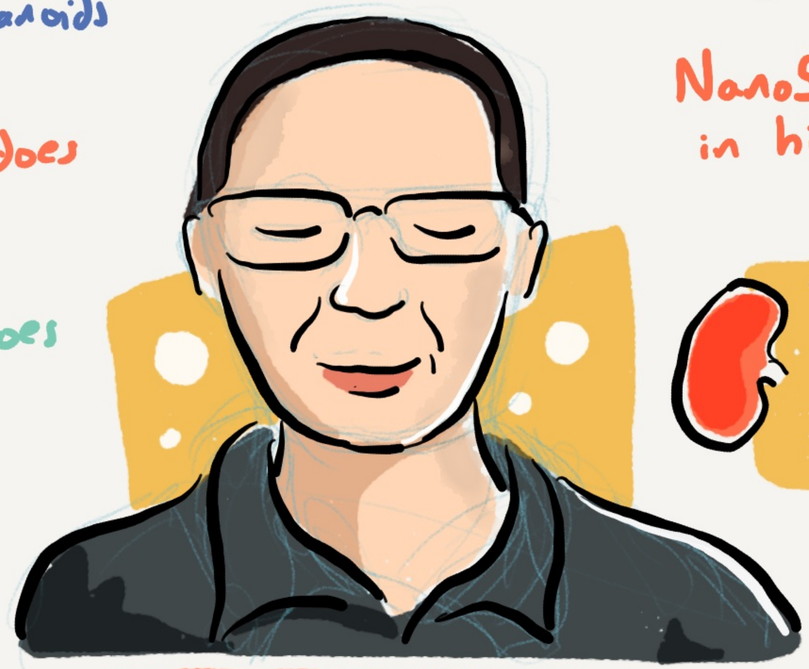

TRPC5 ion channel inhibitors
- GFB-887 - potent, selective human TRPC5 channel blocker

In vivo evaluation in human kidney organoids transplanted in rat

PK analysis | dose → response

In vitro drug evaluation in human kidney organoids grown at scale

High throughput quantification of Podocyte injury

Dawn of new era in drug discovery - confidence in novel drugs via transplanted human organoids

Human Kidney Organoids in Perspective

Melissa Little

Murdoch Children's Research Institute

How might human organoids be used to study glomerular disease

60 genes known to be mutated in podocytopathies

The NEED

- functional validation
- testing treatments

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Organoids — a kidney in a dish → Not an organ, a Model of an organ

Organoid profiles robust + reproducible

NOS1AP mutation - Actin reg promoting CDC42 activation
- Validate novel mutation as causative

Most glomeruli are avascular, but some are vascularizing → in vitro vascularization possible

Limits of Mouse models

Reporter lines to characterise cell types

Accurately patterned glomeruli

Trio exome seq → stem cell line created

Corrected + uncorrected patient lines

- Phenotype characterization
- Abnormal cilia

Replicating known podocytopathies

- NPHS1 point mutation
- Compare glomeruli:- case/control
- loss of podosin protein

Allelic screen of NPHS2 - for drug treatment

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Beyond Podocytes: How Kidneys regulate muscle metabolism

Tobias Huber

University Medical Centre Hamburg-Eppendorf

850m people effected by CKD

Glomerular diseases - multifaceted

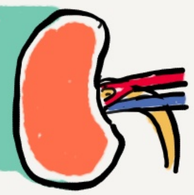
Deep learning-based molecular morphometrics for kidney biopsies

- Can predict many conditions

Healthy epithelia → Epithelial injury → Fibrosis epithelial atrophy

The Podocyte & Glomerular Medicine

From kidney function to organismal health



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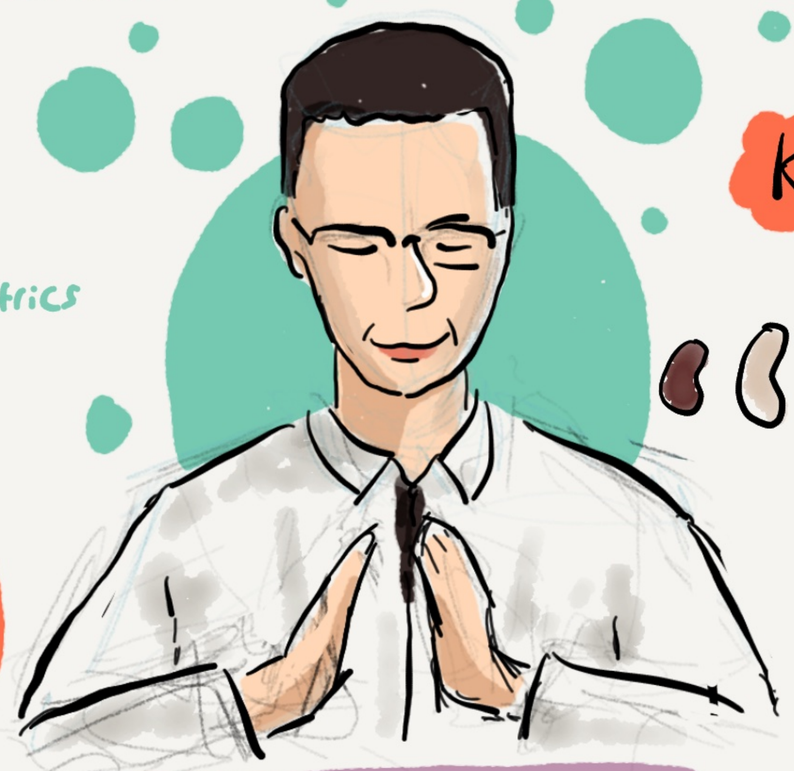
Fibrosis in CKD ⇒ Pro-Cachetic programs



Single-Cell RNA seq from human kidney biopsies confirms animal model results

Therapeutic blockade of Activin A In vivo muscle targeting

75% patients with CKD show muscle wasting

Cachexia ⇒ wasting syndrome

Kidney-Muscle Project

Experimental CKD mouse - leads to functional + structural muscle changes

↓ muscle synthesis ↑ autophagy

Increased kidney production of pro-cachetic factors in CKD

Inhba Activin A

Single Cell RNA-Seq - Fibroblasts upreg Inhba + Activin A

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The podocyte in haemolytic uraemic syndrome

Richard Coward
University of Bristol

- The Podocyte explains why STX HUX has a prediliction for the glomerulus
- CROSS-TALK between podocyte + GEnC causes complement activation

Shiga toxin HUS

- Some conundrums

1 It is species specific

2 It has a predilection for glomeruli in the kidneys

GB3 - implicated receptor

Cows as a reservoir
- lack vascular receptors for E.coli Shiga toxins

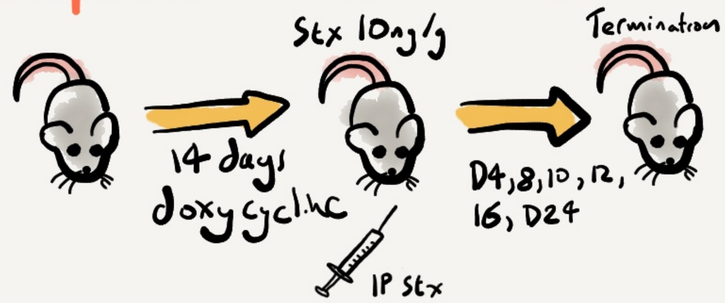
Mouse models
- Murine glomeruli do not express GB3

Generate transgenic Mouse model GB3(synthase) KO

They are Protected from shiga

Induce Gb3 synthase in the mouse model podocyte
- inducible tetracycline-controlled

Confirm with GB3 Immunofluoresence



10 days post Stx (10ng/g)

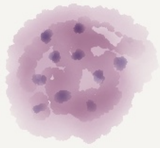
↓ platelets ↓ Haemoglobin ↑ urea

Glomerular C3b
- complement pathway activation

CFH on IF: ↑ factor H in glomerulus

C5 inhibition prevents a TMA in POD-GB3+ STX treated mice

HUS is a Thrombotic Microangiopathy



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Inhibit the Complement Pathway as a treatment

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Novel Insights into Fabry Podocytopathy

Fabian Braun
University Medical Centre Hamburg-Eppendorf
@fab_braun

Fabry Disease

a multi-systemic disorder

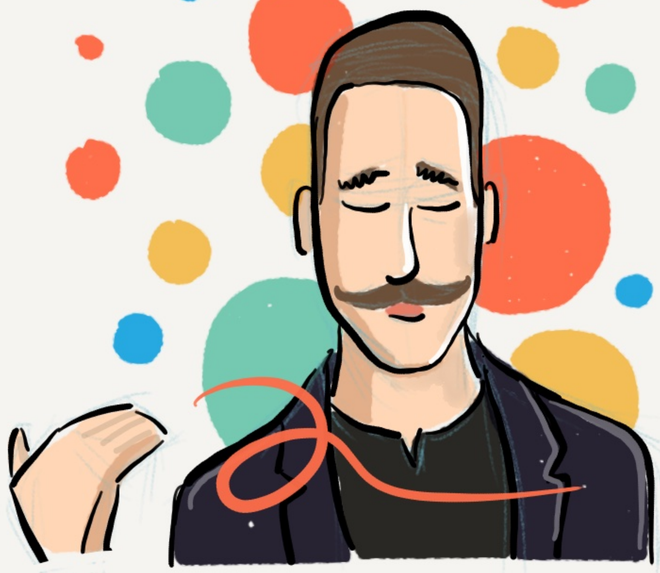
A Lysosomal storage disease

X-chromosamal

Mutation in GLA-gene

- encodes α-Galactosidase A enzyme

Defects in sphingolipid metabolism



Proteinuria, CKD, Albuminuria in kidney

Gb3 accomulation

Complete GLA KO in human podocytes as a novel model

Translational Cycle

Towards a cure for Fabry podocytopathy

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The Lysosome as a central hub of intracellular signalling

Lysosomes are integral for the homeostasis of the entire cell

react dynamically to nutrient status

mTORC1 signalling essential for podocyte

SILAC Proteomics + disease network analysis

GLA KO Podocytes alter lysosomal proteins

20 signif dysreg

SNCA implicated

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A novel detrimental cellular crosstalk in aging glomeruli

Implications for kidney transplants

Fabiola Terzi

Research Institute Necker Enfants Malades

Chronic Kidney Disease

A GLOBAL PROBLEM

Particularly in the elderly

Natural History of CKD Progression

Nephron reduction → compensatory stress

Glomerulosclerosis

role of senescence?

PAI-1 secretion from endothelial cells causes Podocyte detachment

Clearance of senescent cells reduces glomerulosclerosis in mouse

SASP

Senescence-associated secretory phenotype

-cancer progression & aging

Markers to detect senescence

Aging → Senescence → glomerulosclerosis ?

Aging mouse study

Senescence affecting epithelial cells

SASP activated in senescent glomeruli

Accelerated senescence irradiated mice

- supports association of aging with glomerulosclerosis

Secretion of PAI-1 → Podocyte detachment

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Metabolome-proteome crosstalk in glomerular disease

Markus Rinschen

University Medical Centre Hamburg-Eppendorf

&

Aarhus University

@mrins01

What is the podocyte's molecular identity?

How can we IMPROVE podocyte health in stress?

Molecular landscape in Kidney disease

20,000 DNA

RNA

2 mill? Proteins

???? Metabolites

Complexity

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Functional Proteomics

regulation

synthesis

degredation

Prot abundance

Protein Localization

Intermolecular interactions

Post-translational modifications

Mass Spectrometry

Signaling in podocytes

FAC sorting

Podocyte mechanical stress response

↑ YAP1 abundance

The Organoid Proteome

- how similar to native cells?

15-20 human organoids

Investigate changes over time

Podocyte differentiation

changes in extracellular matrix overtime

The Metabolome: From biomarkers to activity

microspheres

Metabolome-proteome cross-talk: new avenues for research

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Mitochondrial reprogramming of podocyte metabolism

Paul Brinkkoetter
University Hospital Cologne

Pathogenic pathways of steroid resistant nephrotic syndrome

-includes a mitochondrial cluster

Are podocytes sensitive to ischemia?

Mitochondria ⇒ Energy supply & Beyond

Targeting mtDNA transcription

TFAM podocyte KO

-No disease phenotype

Podocytes do not rely on mitochondria

Mitochondrial dysfunction enhances insulin signalling

OXPHOS Machinery

OXPHOS machinery as reserve states of stress + injury?

Mitochondria as signalling hubs controlling metabolism?

Nephrocyte Model

Loss of TFAM does not influence nephrocyte morphology

Podocyte specific Phb2 KO mice

Prohibitins- mitochondrial membrane scaffolds

Loss of Phb2 results in impaired anaplerotic feeding of citrate cycle

Loss of Oma1 rescues Phb2^{PKO} mice

Anaerobic glycolosis the main energy source of podocytes

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Mapping Human Fibrotic Disease

Rafael Kramann
Institute of Experimental Medicine and Systems biology RWTH
@rkramann

Fibrosis is Scar tissue

> final common pathway of progressive disease
> leads to organ failure
> Fibrotic disease ⇒ up to 45% of deaths in the developed world

No FDA approved therapies for fibrosis

Single Cell Map of Human CKD

7 patients eGFR >60 4 eGFR<60

Where do myofibroblasts come from?

- a cell that produces extracellular matrix in kidney

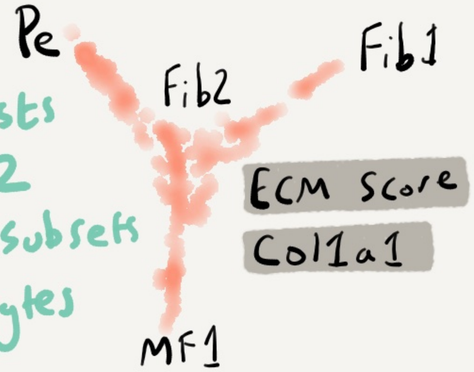
ECM expression score

Spatial transcriptomics of Acute human myocardial infarction (hours) - ischemic zone

Runx1 in fibroblast → myofibroblast

Most ECM coming from Mesenchymal cells

PDGFRb^{+} cells sorted from human kidneys



Myofibroblasts derive from 2 fibroblast subsets and pericytes

Understanding pericyte to myofibroblast differentiation

Nkd2 - potential therapeutic target

KO + overexpression of Nkd2

abolishes ECM expression

validate in kidney organoids

KO ameliorates kidney fibrosis in organoid

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NURTuRE - Integrating big datasets from a nephrotic syndrome cohort to discover phenotypic signatures

Moin Saleem
University of Bristol

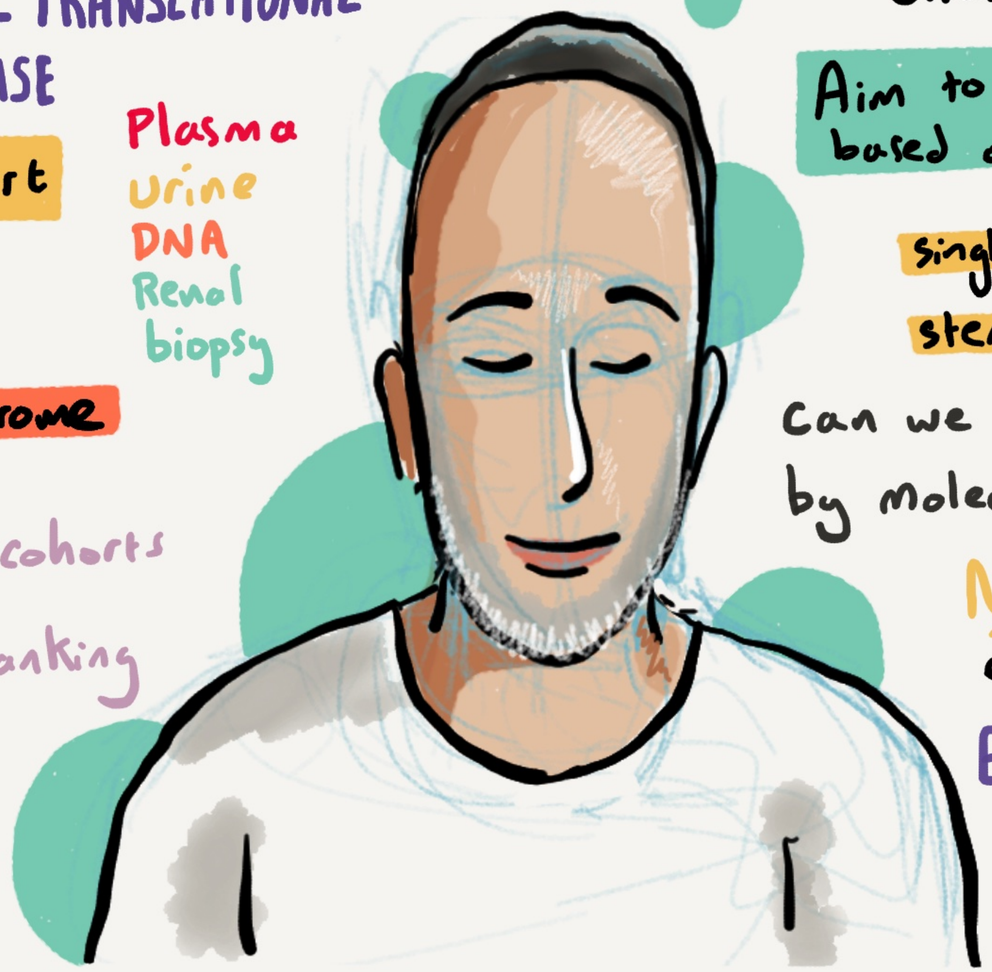
NURTuRE

NATIONAL UNIFIED RENAL TRANSLATIONAL RESEARCH ENTERPRISE

- large patient cohort

Chronic kidney disease & Idiopathic nephrotic syndrome

Plasma
Urine
DNA
Renal biopsy



Prospective multi-centre cohorts

Industry standard biobanking

Rapid recruitment

3000 CKD 800 INS

15 year follow up plan

challenges of integrating large datasets

Aim to improve classification of Nephrotic Syndrome based on underlying mechanisms

Single vs multigene
steroid resistant

circulating factor disease

Can we identify circulating factor disease by molecular phenotyping?

New Tools 3D glomerular 'spheroids'

expose to patient plasma + study response

Epigenetics ⇩ Nephros cohort

can be tissue or cell specific

Manhattan plot - signif loci

Towards new treatments and better diagnoses

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Defining causal gene, cell types and mechanism for kidney disease using multi-omics datasets

Katalin Susztak
University of Pennsylvania

To Mechanism
To Medicine
Transforming Nephrology

Need for advances in how we diagnose & treat kidney disease

Mapping ← gene ← cell type
Mechanism
Medicine → Gene therapy, New drugs

Understanding racial diffs in ESRD development
APOL1 variant - mouse model
Mechanism? altered trafficking

Problem ⇒ Not much to offer patients now

Diabetic hypertensive CKD
- strong heritable component

Mapping eGFR loci to renal transcriptome

Limitations to GWAS - treasure maps

Computational identification of target genes for CKD using cis-eQTL
359 human kidneys
Microdissectio
Single cell RNAseq
Find key cell types
Podocytes
Single nuclear ATAC-Seq } regulatory region annotation

Defining Novel Disease Mechanisms
ACE2 DACH1 DAB2 MANBA
Role of proximal tubules

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Epigenetics in Metabolic memory and Diabetic Kidney Disease

Type 1+2 Diabetes
↑ Prevalence
↑ complications

Diabetic complications can progress despite glucose control
- can't be explained by genetics

Inflammation & Fibrosis
Major culprits

Epigenetics - DNA Methylation & Histone modification

Genome-wide profiling

Exploring biological function

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Rana Natarajan
City of Hope, California

Metabolic Memory

Histone modifications associated with hyperglycemia

Diabetes/obesity

increase pathologic genes by alterations in chromatin marks, chromatin accessibility + methylation

Diabetes

more open chromatin primed for transcription of inflammatory and pathologic genes

Cross-Talk between epigenetic layers may lead to 'metabolic memory'

Epigenetic variations: **EWAS**

Therapeutic Potential

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The Glomerular Proteome in Antibody Mediated Rejection

Ana Konvalinka
Toronto General Hospital

Rates of early kidney allograft rejection have diminished

But Long term allograft survival has not significantly changed

Antibody Mediated rejection

- Poorly understood

Microvascular inflammation
Endothelial interaction with antibody
Circulating donor specific antibodies
Transplant glomerulopathy

HLA DSA - common & deleterious

Pathophysiology of AMR

- Direct injury
- Complement activation
- Antibody dependent cell-mediated toxicity

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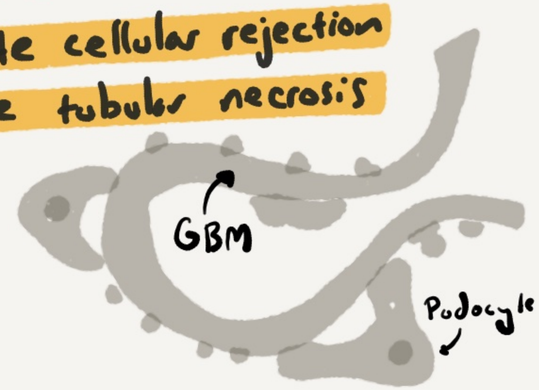
Kidney proteome in AMR

7 AMR donors
11 acute cellular rejection
12 acute tubular necrosis

FFPE biopsies → Laser Capture microdissection → Mass spec → Analysis



Machine Learning + Network Modularity
Elastic-net-based prognosis prediction

Predictive clusters

Glomerular AMR: upregulated proteins
Down regulated proteins - cell adhesion

LGALS1 - Galectin 1

- immunomodulatory
- protective role
- interacts with ECM

Improves graft survival in rodent models

Developing New Models to study AMR

"kidney-on-a-chip"

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SuPAR and COVID and podocyte injury

Jochen Reiser
Rush University Medical Center

SuPAR

60 kDa glycoprotein
3 finger toxins
Multiple Isoforms

muPAR I & II

msuPAR2 recombinant protein

Dimer

Circulating suPAR isoform 1+2 induce proteinuria and kidney disease

suPAR mouse model

innate immune response linked to kidney?

chronic signaling leads to disease?

Integrin Activation
- impacts the podocytes

2 commercial ELISA assays
- quantification

Plasma suPAR as risk factor for FSGS

Low correlation between eGFR & suPAR

suPAR and APOL1 synergy
- Modifies risk of other risk alleles

suPAR in covid associated AKI

Spike S1 protein induces proteinuria in suPAR-tg mice

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Targeting the Fat Podocyte with Small Molecules

Alessia Fornoni
University of Miami

The role of lipids in the Pathophysiology of glomerular diseases

Pathological lipid accumulation } cause or consequence?

Podocyte depletion paradigm

Podocyte target identification in DKD

Cell-based assay
-Podocytes

T1D + T2D cohorts

Lipid metabolism implicated from RNA pathway data

Lipid droplet after serum exposure assessment

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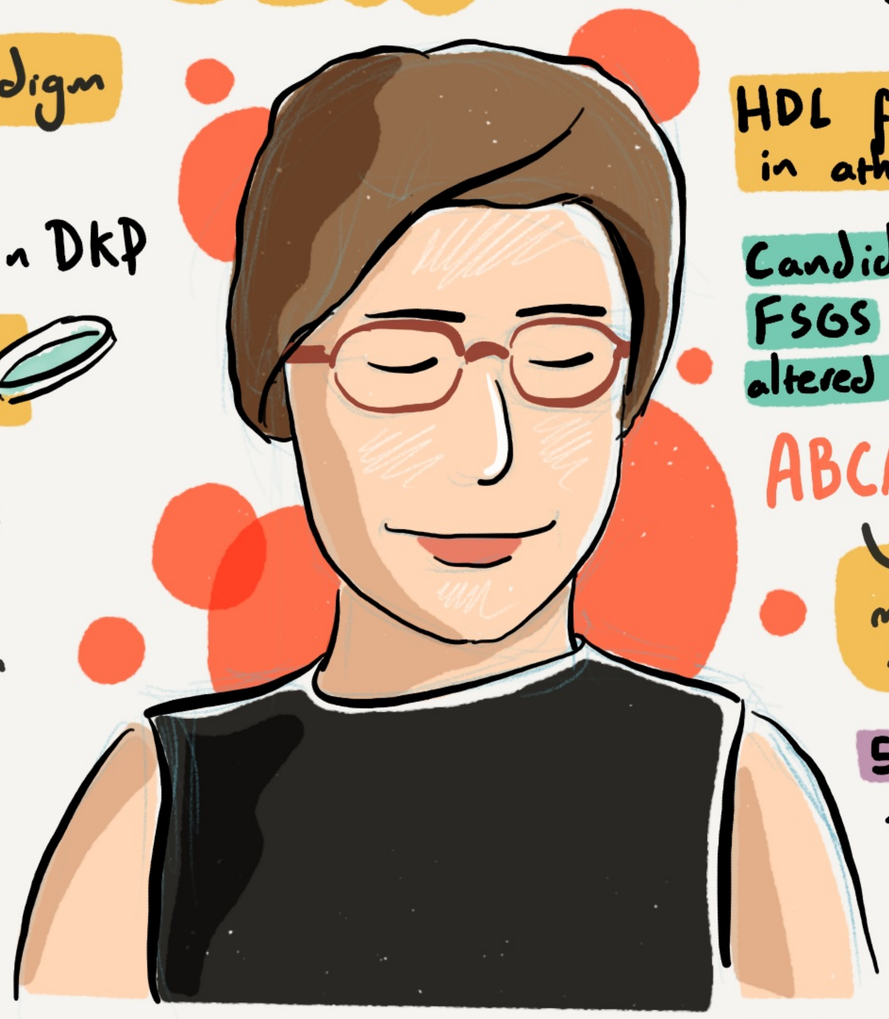

Lipids and the slit diaphragm

Experimental Models →

cholesterol accumulation in kidney cortex

HDL function & cholesterol influx in atherosclerosis

Candidate genes for FSGS associated with altered lipid metabolism

ABCA1 in kidney disease

→ deficiency affects mitochondrial complex formation

Human genetics supports causal role of cholesterol efflux in pathogenesis of proteinuria

Tangier Disease
LCAT Deficiency

→ overexpression of ABCA1 rescues mouse model from proteinuria

5-arylnicotinamides
- compound class mediating ABCA1-induced cholesterol influx

Modeling + site-directed mutagenesis → binding study

ABCA1 inducer is protective

Drug development
Target identification
OSBPL7

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LDL-A liposorber therapy in nephrotic syndrome

Joshua J Zaritsky

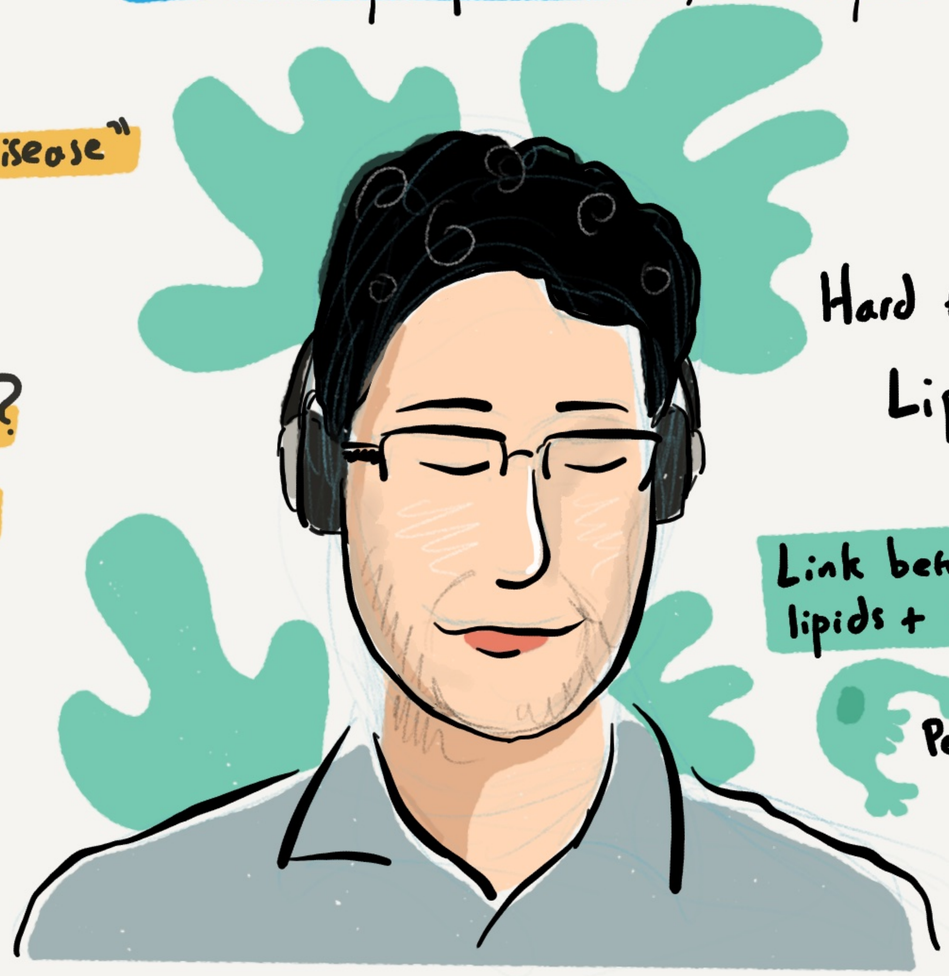
St Chris Hospital for Children, Philadelphia

Why Everyone Hates Focal Segmental Glomerulosclerosis

- 150 years as a "descriptive disease"
- Lack of basic pathophysiology
- Lack of diagnostic tools
- Cure worse than the disease?
- High recurrance rate post-Tx

Treatly is entirely empiric

...Largely ineffective



Liposorber LA-15 system

Plasma filtering

Liposorber studies in FSGS

↳ treatment can lead to remission

Hard to know when Liposorber will be effective

Liposorber mechanism?

- Direct effect of lipid absorption?

Link between disordered lipids + CKD?

Urinary loss of albumin decreases the plasma-lipid buffering capacity

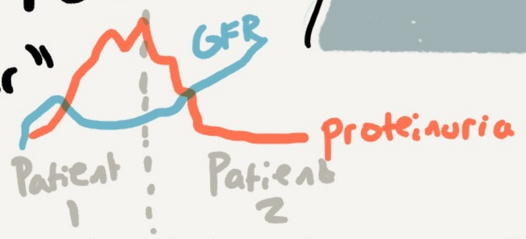
⇩

elevation of unbound FFAs

Persistent podocyte damage + albuminuria converts proteinuria into nephrotic syndrome

Could disordered lipid metabolism in FSGS be causal?

Search for the FSGS "Permeability factor"



why did proteinuria go away in 2nd recipient?

Cytosorb Therapy

- changes to serum lipid profile

Mechanism of action remains unknown

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Molecularly-Targeted Therapies for Kidney Diseases

Anna Greka

Harvard Medical School

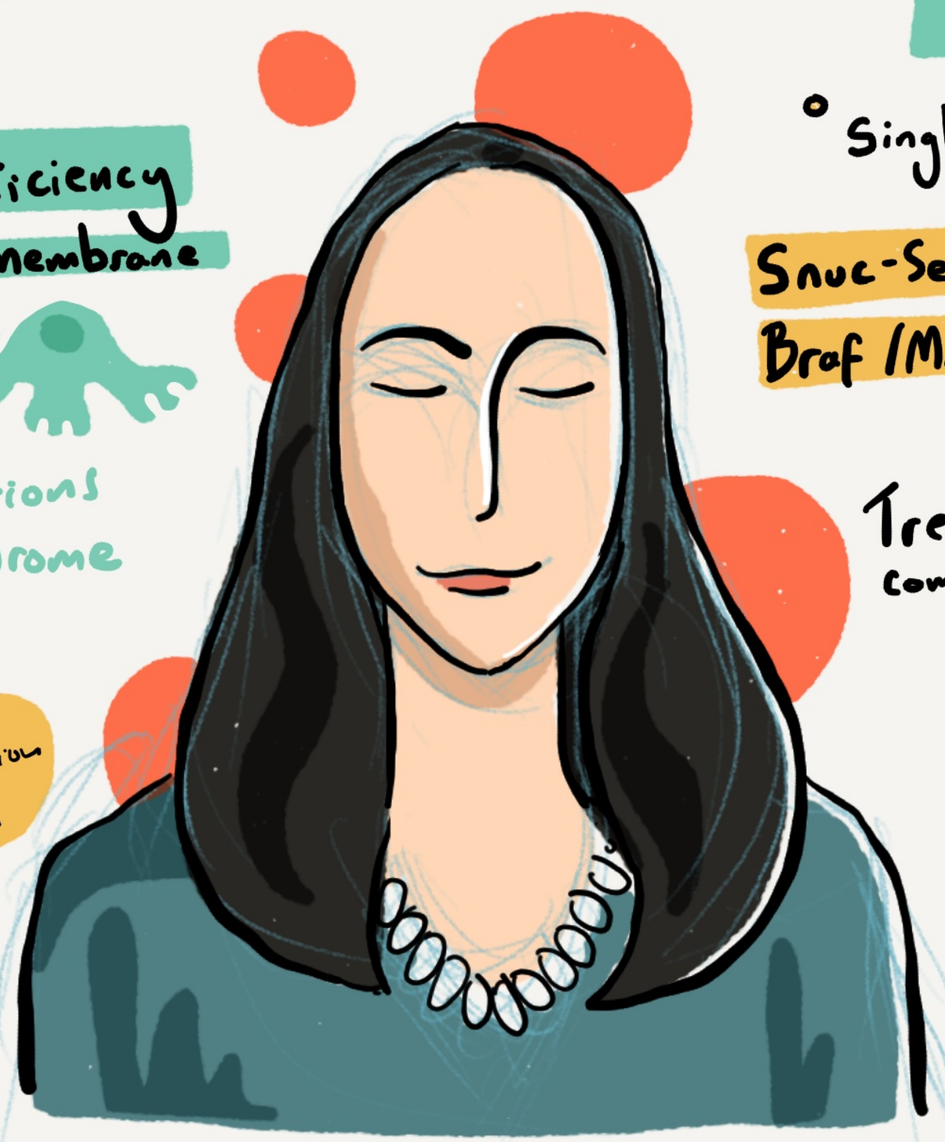
Membrane Proteins

- ~30% of human proteome
- diverse functions

A story about **CoQ deficiency** in the **inner mitochondrial membrane** of **podocytes**

Mitochondrial CoQ mutations can cause nephrotic syndrome

PDSS2 - key gene



★ Integrating transcriptomic + metabolomic data revealed a druggable, podocyte-specific injury pathway

CoQ deficiency in podocytes is sufficient to cause kidney disease in mouse

- Single nuclei RNAseq of KDKD mice

Snuc-Seq reveals a **druggable Braf/Mapk pathway specific to podocytes**

GDC-0879 compound

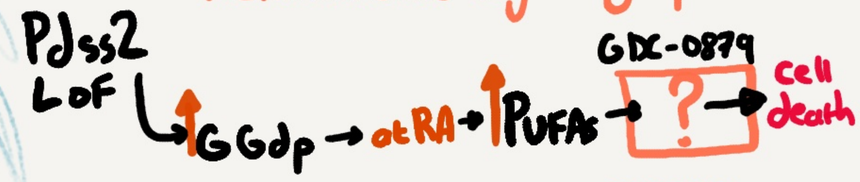
Treatment with this Braf-targeting compound **REVERSES** podocyte injury

How?

Metabolomic Analysis of cell lines

Perturbations in polyunsaturated fatty acid (PUFA) metabolism

Retinoic acid signaling upstream



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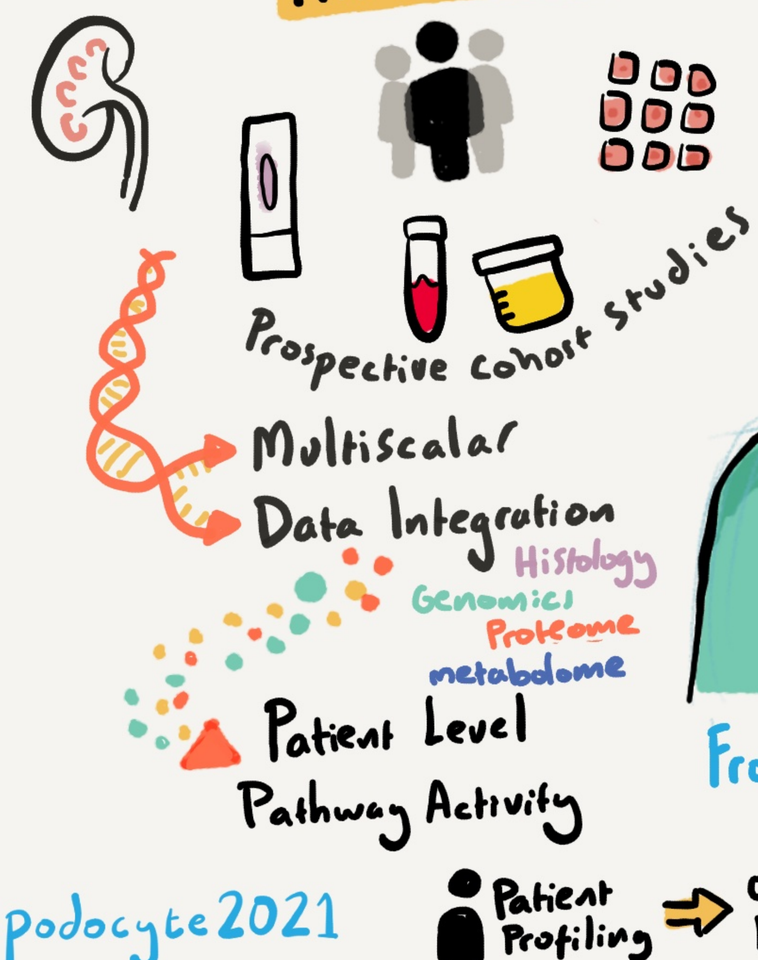
Precision Medicine Trials in FSGS

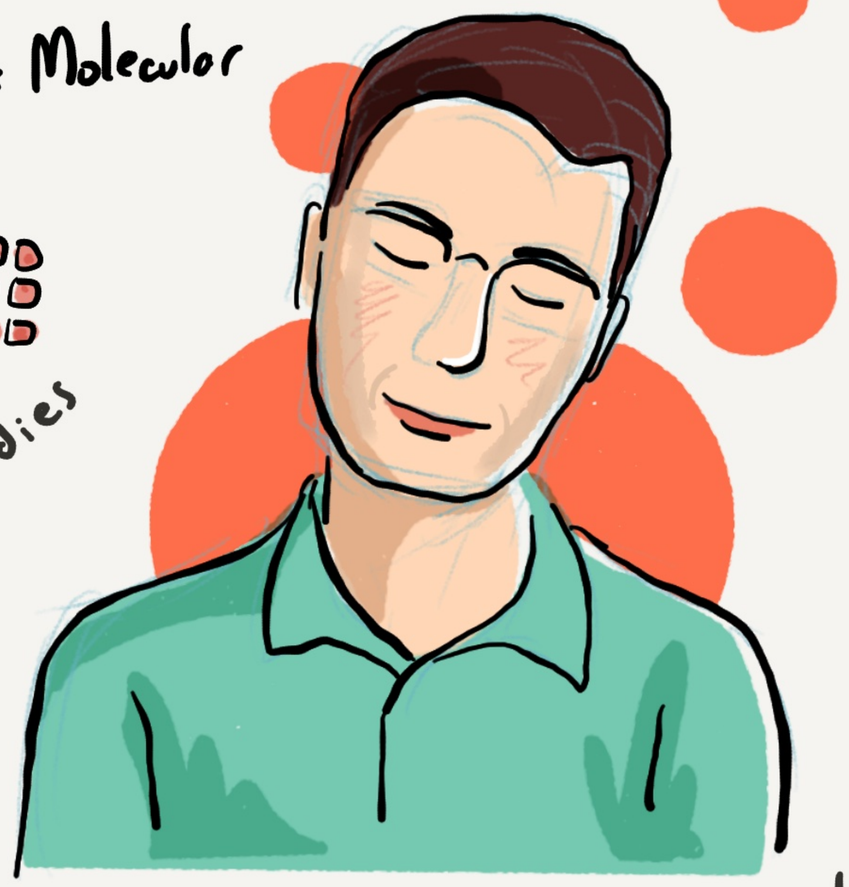
Matthias Kretzler
University of Michigan

neptune

Molecular Targeted Treatments for Glomerular Disease

Biopsy-centred clinical & Molecular PHENOTYPING

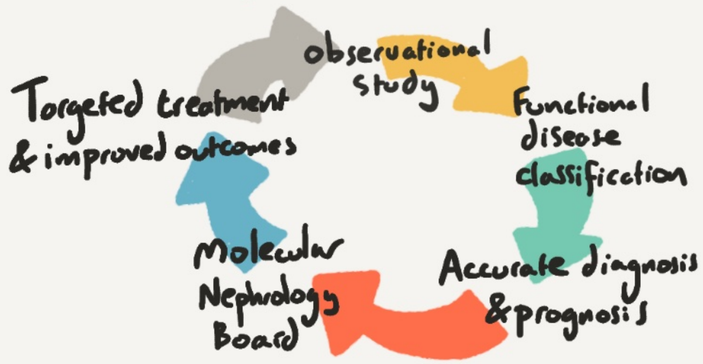




From Association to Causation

Patient Profiling ⇒ Outcome Prediction ⇒ Targeted Therapies

Identifying the right trial for the right patient at the right time



Longitudinal cohorts

A Framework for Translational Research in Nephrotic Syndrome

Identify disease specific molecular pathways

Machine Learning approaches

Multiscalar outcome prediction

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