The cutting edge of Nephrology: Personalised Medicine

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Centre for Personalised Medicine

Australian National University

Canberra Health Services

ACT Government

Canberra Hospital

JCSMR, ANU

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Clinical dilemma

- 44 year old female
- RPGN
- Haematuria and proteinuria
- ANA+, dsDNA+, p-ANCA+, RNP+
- Biopsy: crescents and 3+ C3

- What is the diagnosis?

- 23 year old female
- Class III SLE nephritis 2g/d proteinuria
- Rx: High dose prednisone
  - MMF
  - TAC
  - Belimumab
  - Ritux
  - CYC
- No response

- How will you treat?

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That’s unlucky

- Daughter 1 diagnosed with proliferative lupus nephritis
  - Mycophenolate

- Family history:
- Father has rheumatoid arthritis - azathioprine
- Sister has autoimmune hepatitis – prednisone and leflunomide

- Unlucky…?

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Limitations of syndromic medicine

- Pathology (or clinical syndrome) is central to our treatment plans
- Pathology is the consequence of the same pathophysiology
- What if we look closer?

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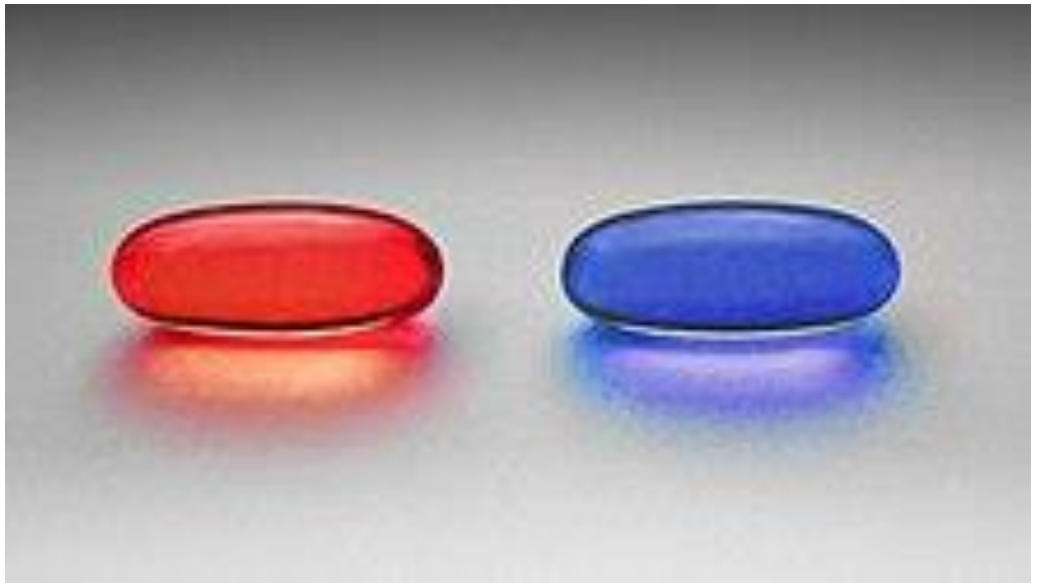
Technologies to understand autoimmunity

- “Omics” – understanding the totality of a biological system

- Genomics
- Transcriptomics
- Proteomics



- Immunophenomics

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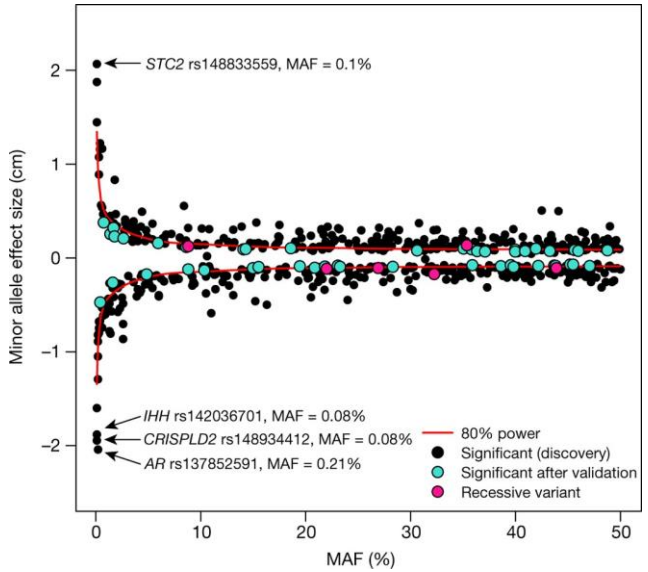
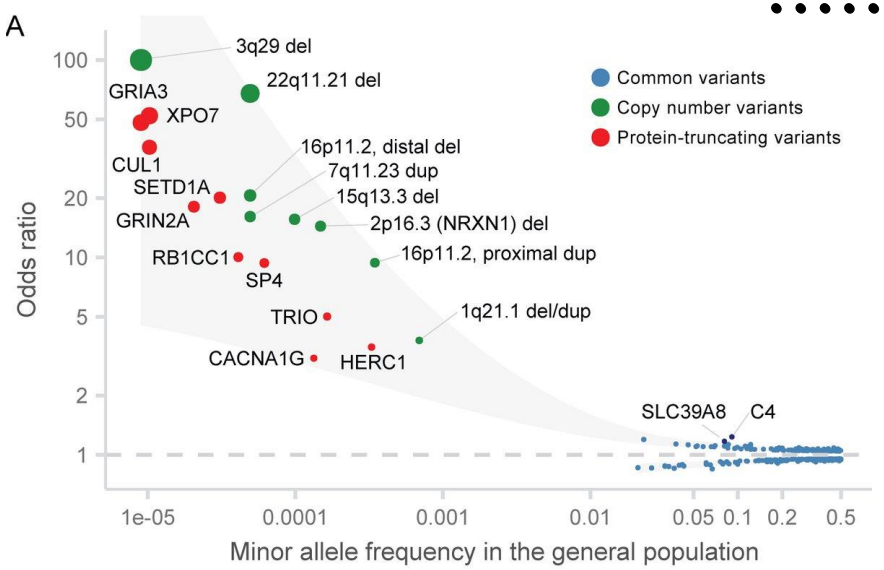
Genomics

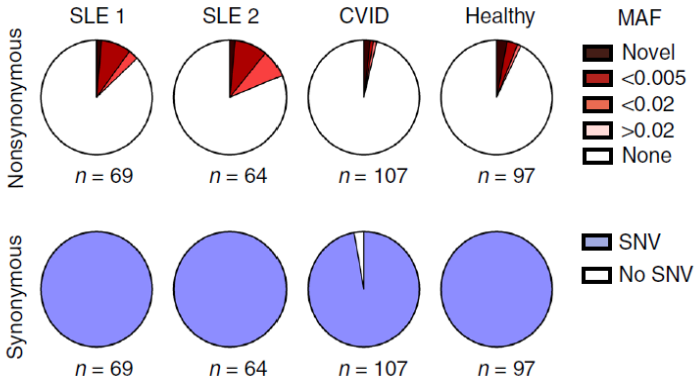
- Whole genome seq
- Rarity
- In silico prediction
- Modelling



Marouli, 2017, *Nature*



Singh, 2022, *Nature*



Jiang, 2019, *Nature Comms*

```
Frog    AIVLKTPPYHDLHITEP
Mouse   AIVFKTPPYEDLEISEP
Human   AIVFKTPPYEDLEIVEP
Cow     AIVFKTPPYEDLEIVEP
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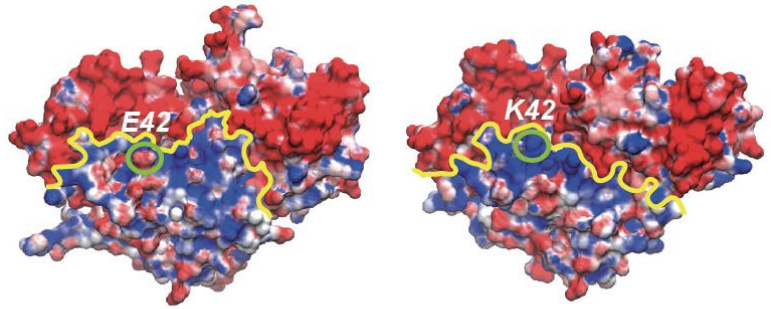

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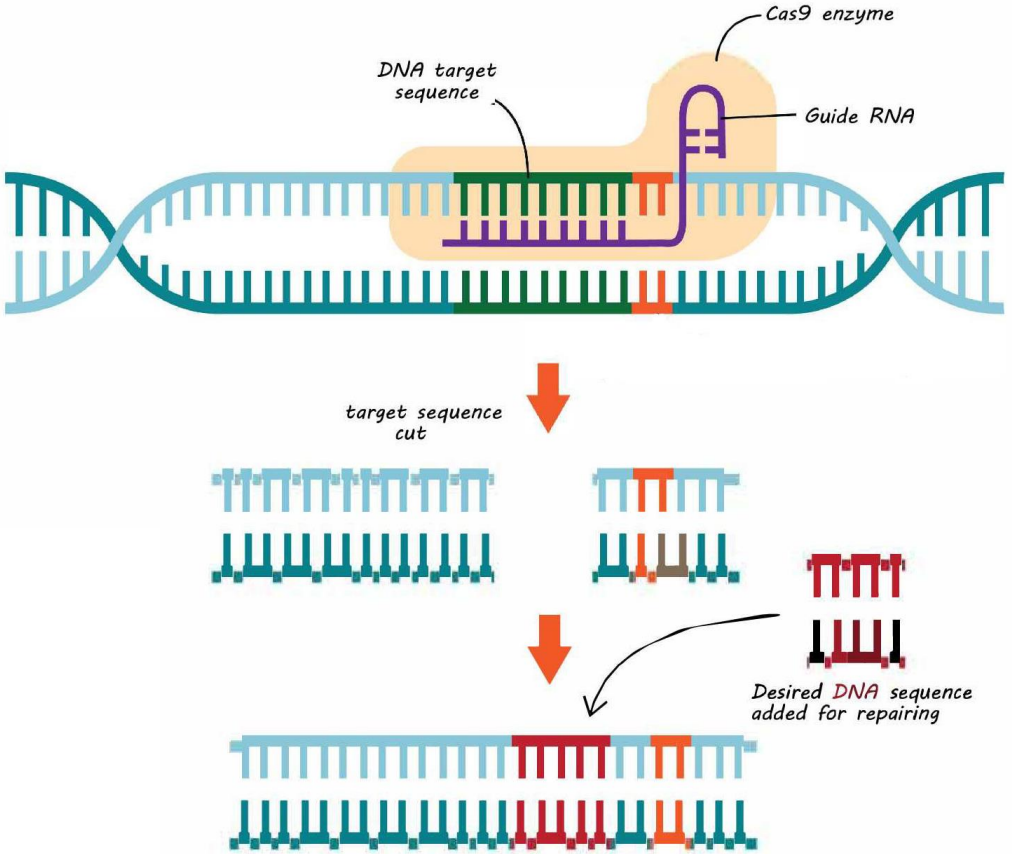
CRISPR models of disease

- Organoids
- Mouse models
- Human cell lines



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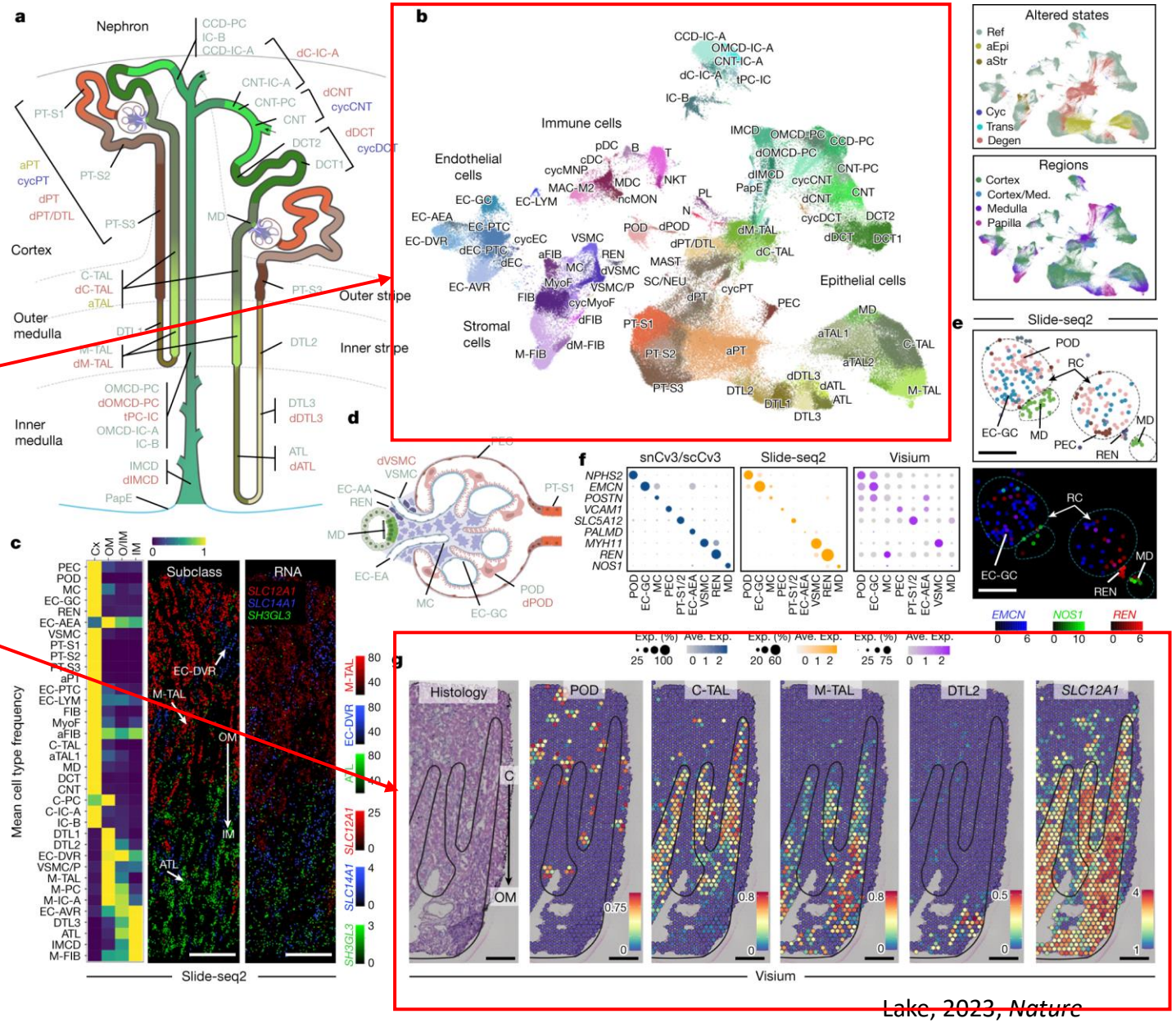
Transcriptomics

- Bulk
- Single cell
- Spatial



Lake, 2023, *Nature*

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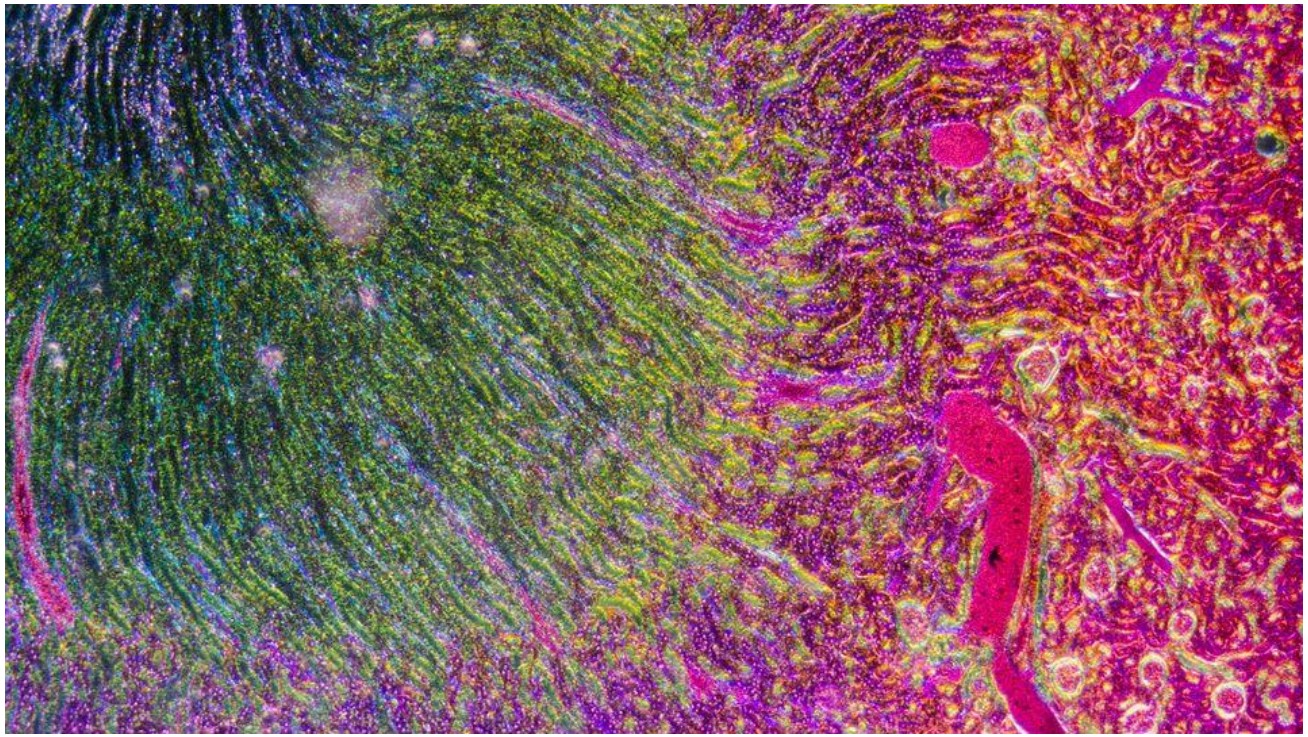
Proteomics

- Molecular biology
- Spatial proteomics



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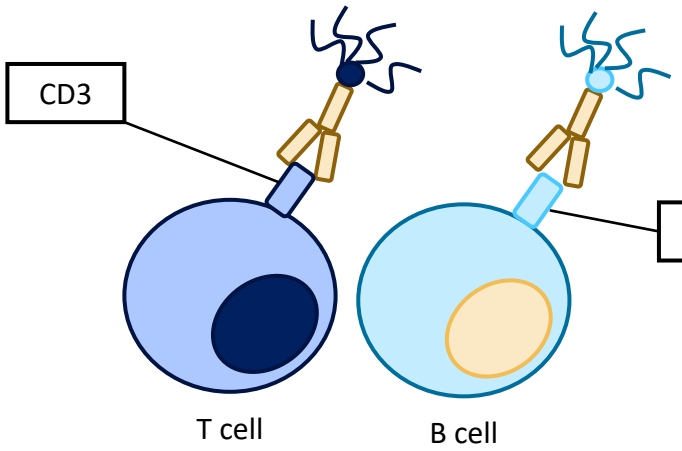
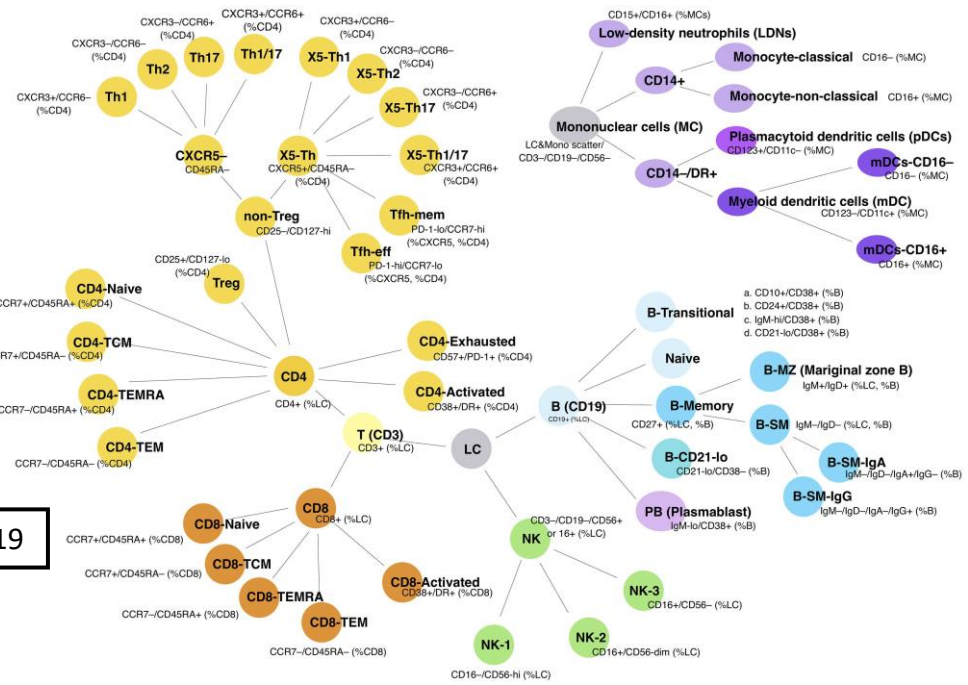
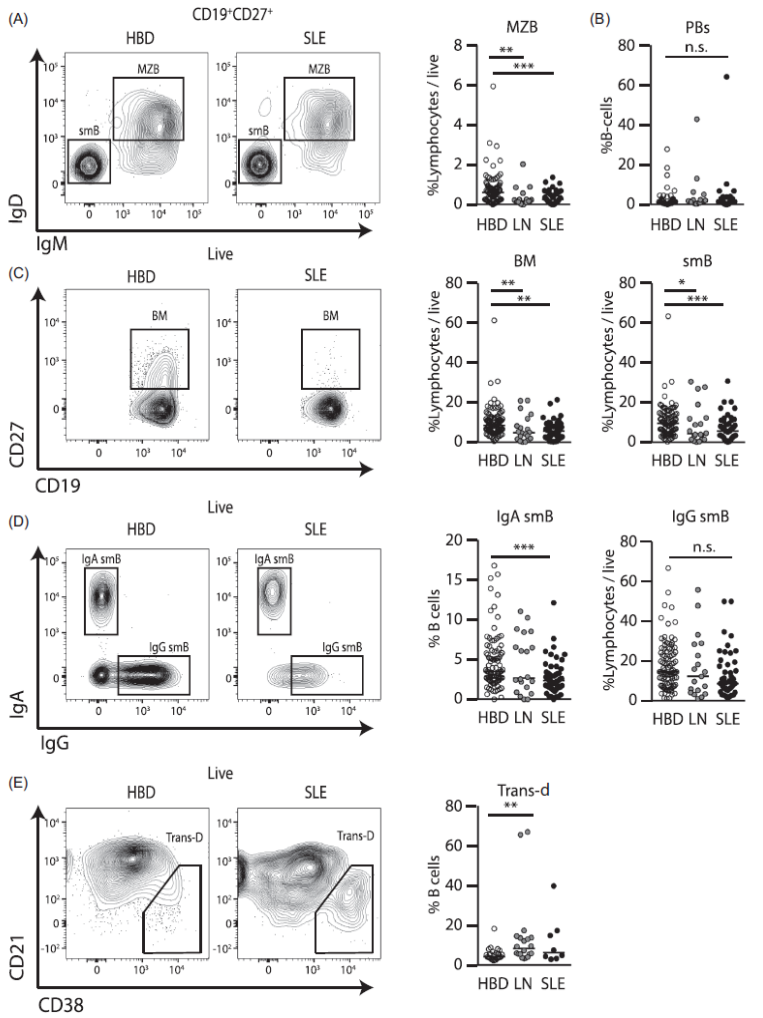
Immunophenomics

- Flow cytometric assessment of circulating lymphocytes







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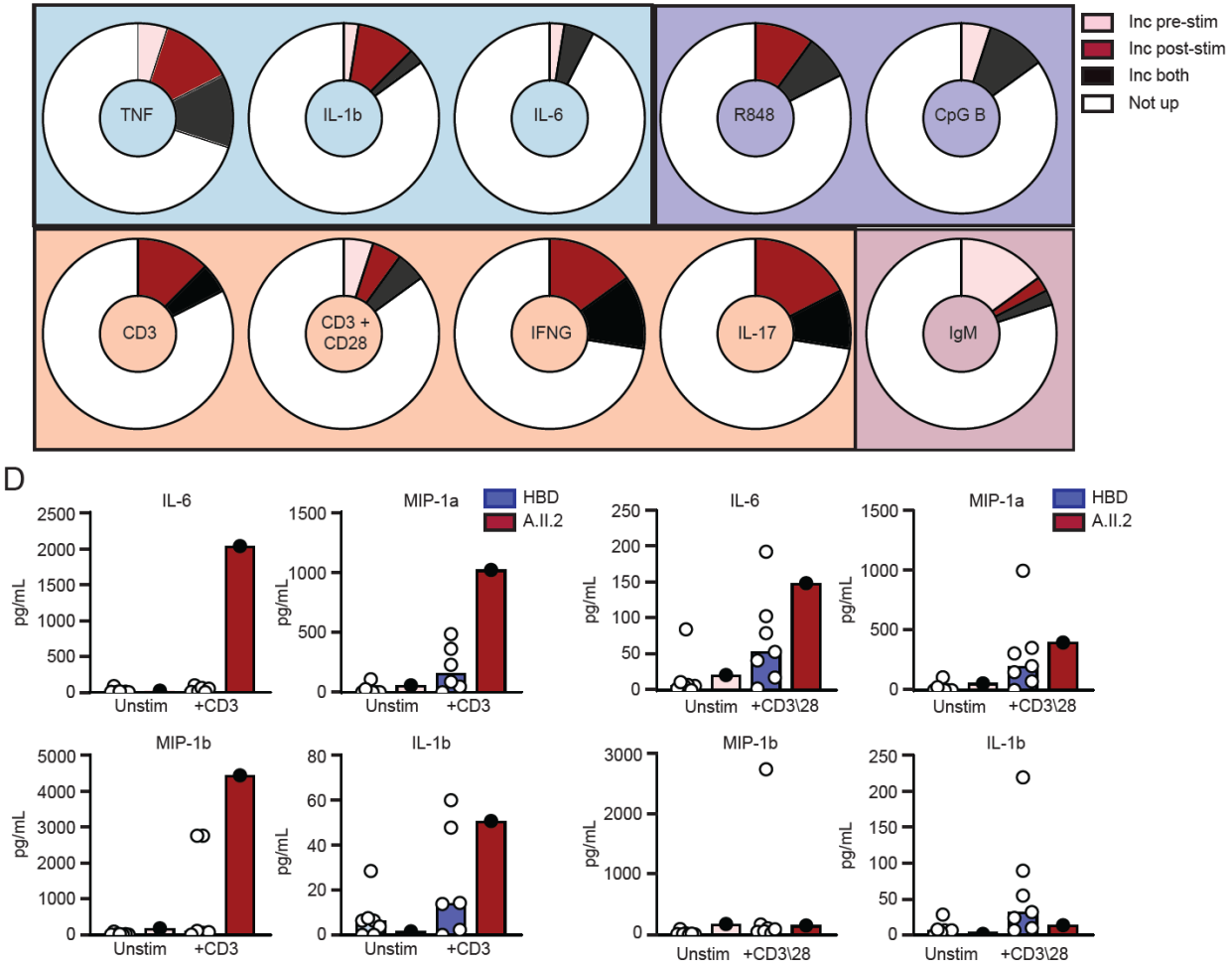
Cytokine response

- Quantify immune response
- Therapeutic targets



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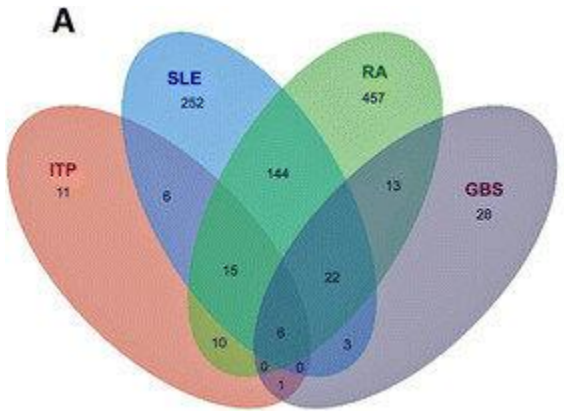
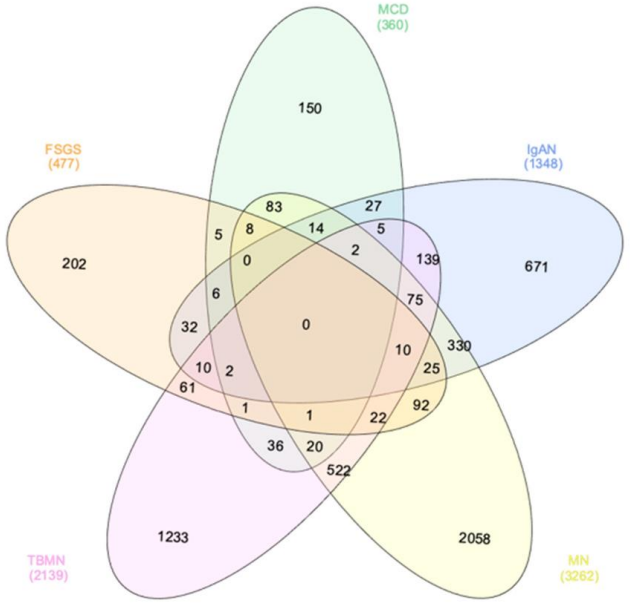
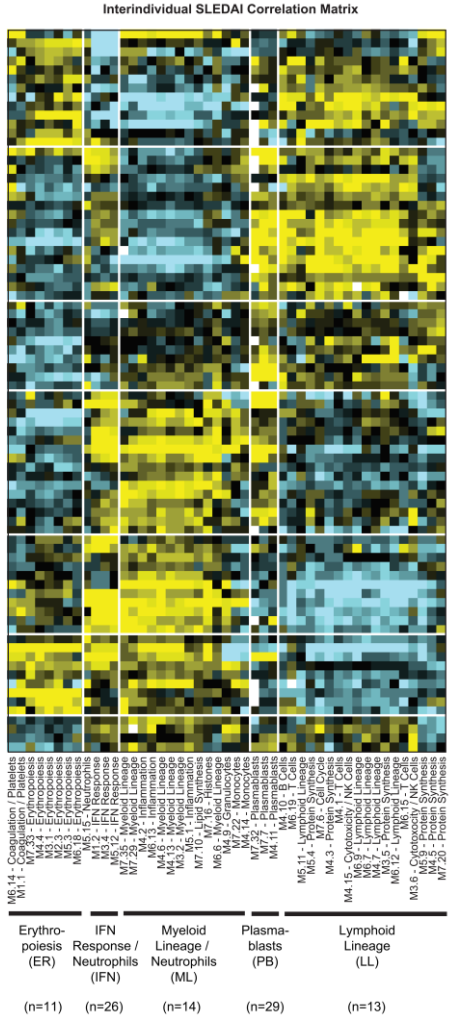
Why is in depth phenotyping useful?

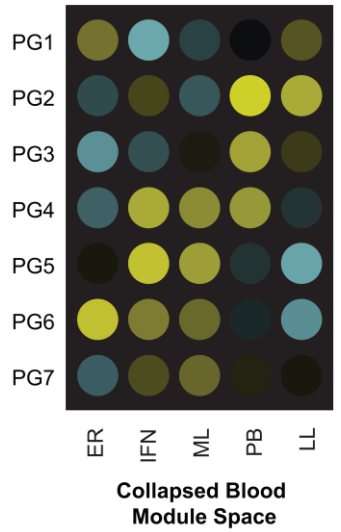
Pathology – different and the same:

- Share genetic and transcriptomic signatures
- But also heterogeneous within disease









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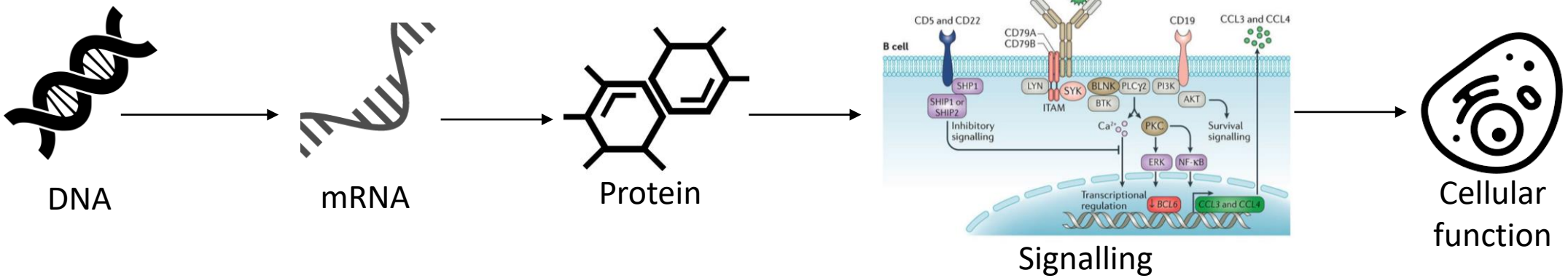
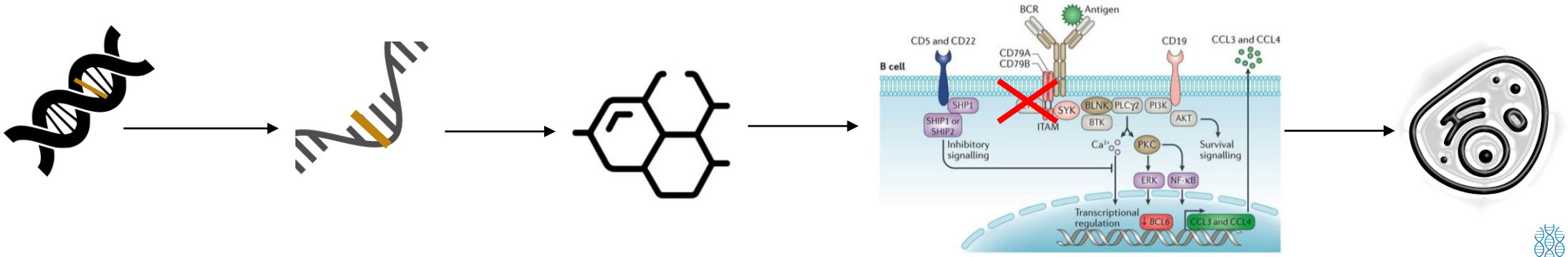
Personalised pathophysiology



Gene variant forward



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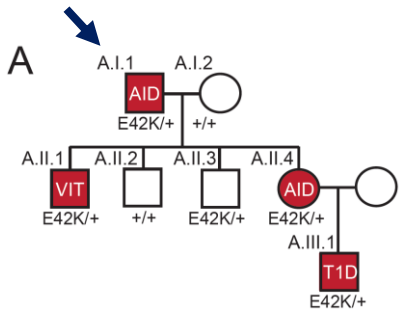
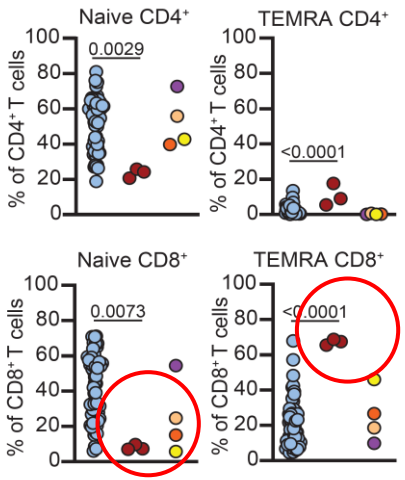
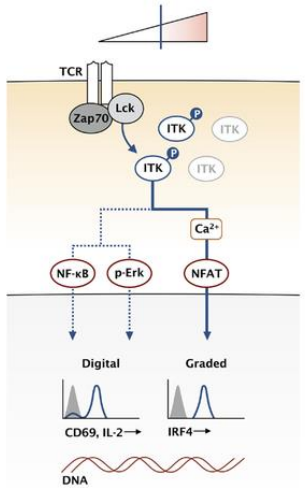
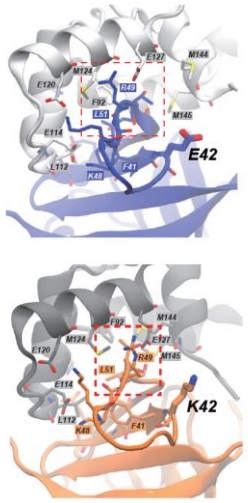
Personalising autoimmunity

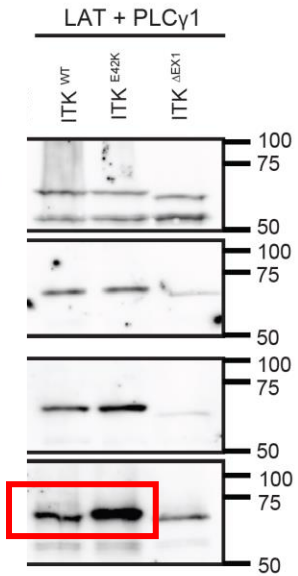


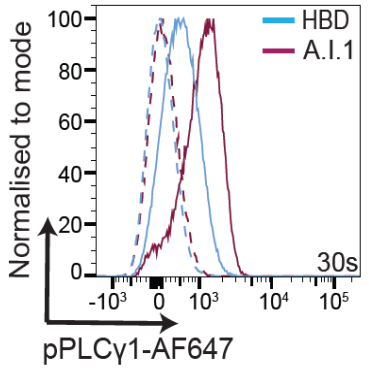
Systemic inflammation
Hypophosphataemia

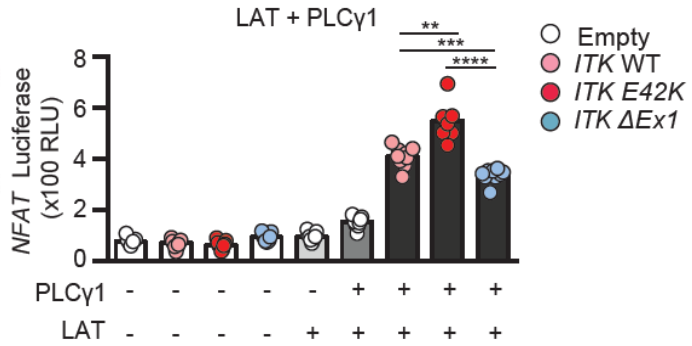


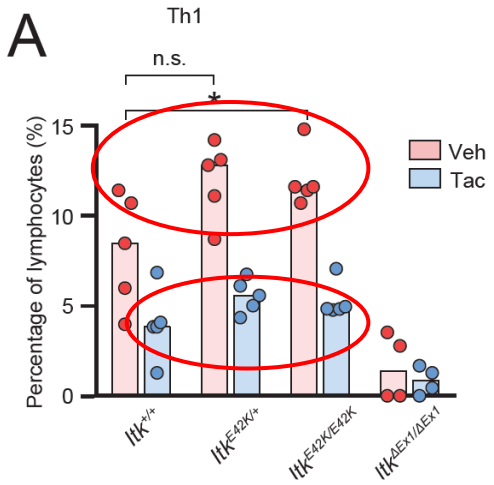


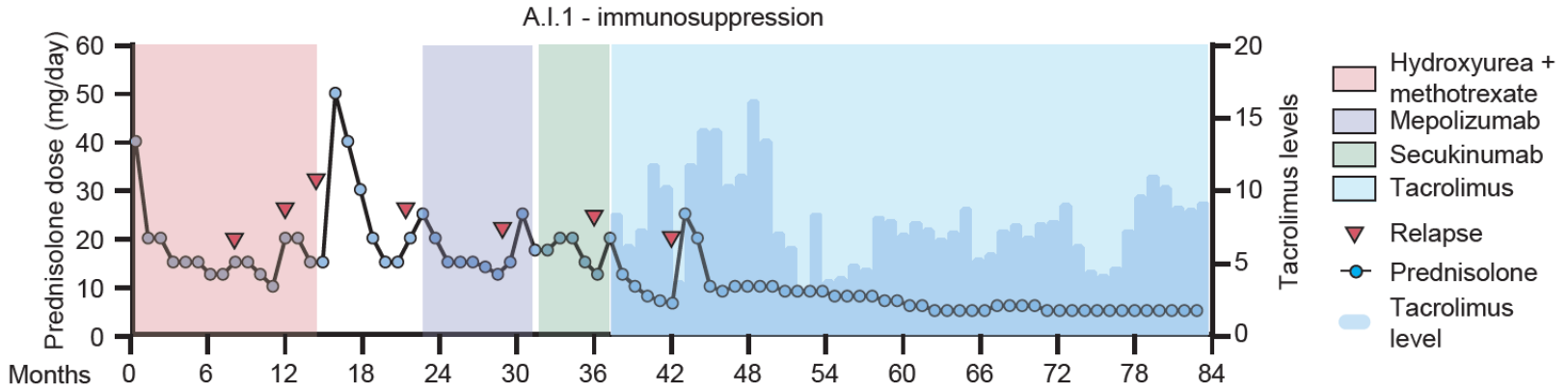












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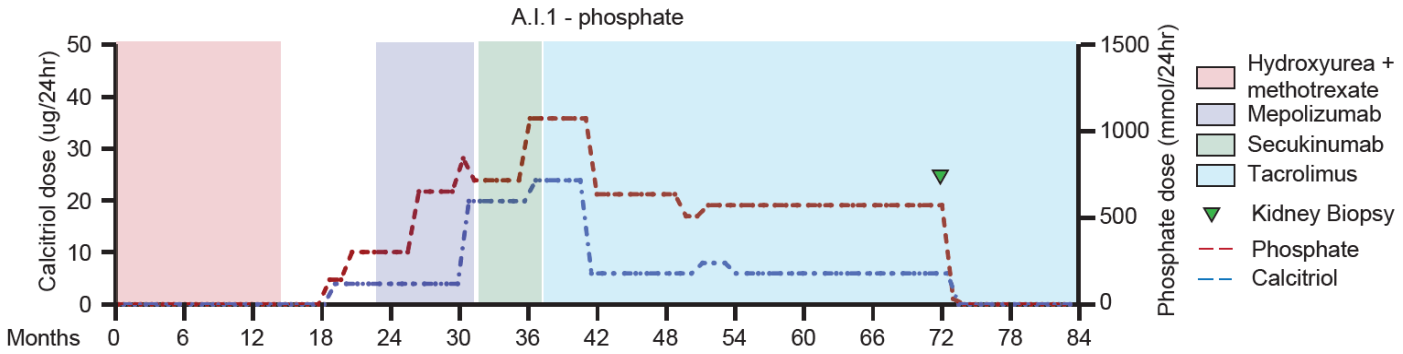
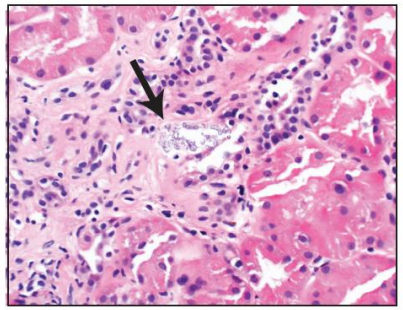
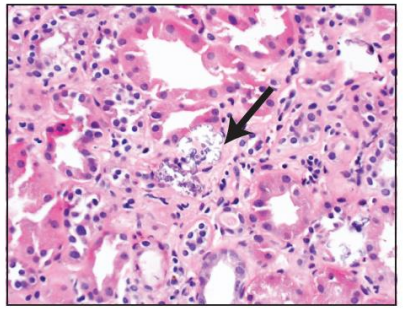
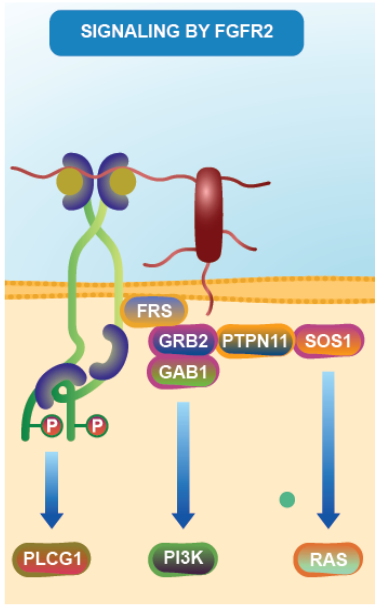
Hypophosphataemia

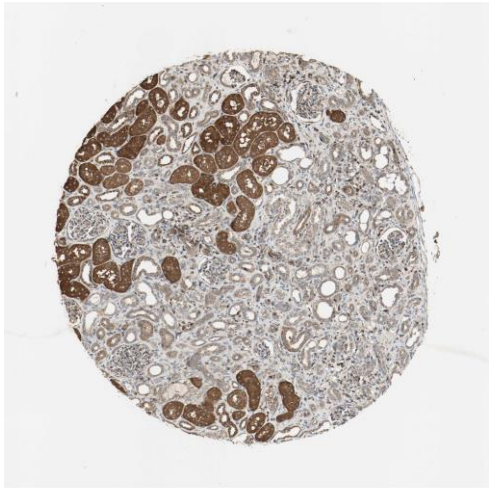








PLCG1



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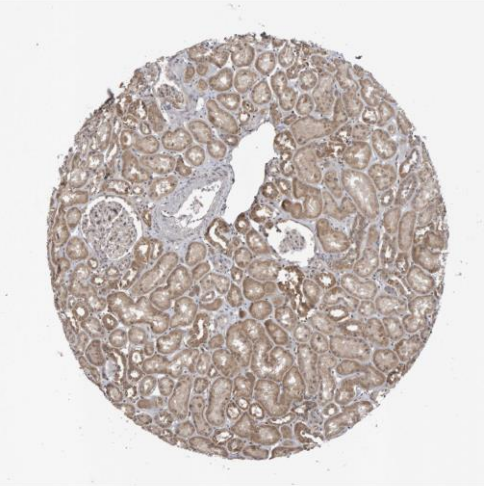
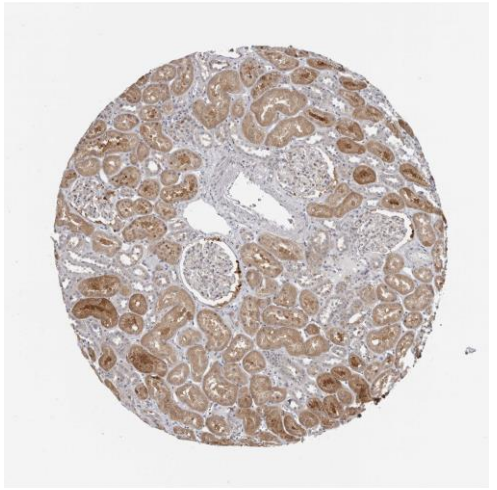
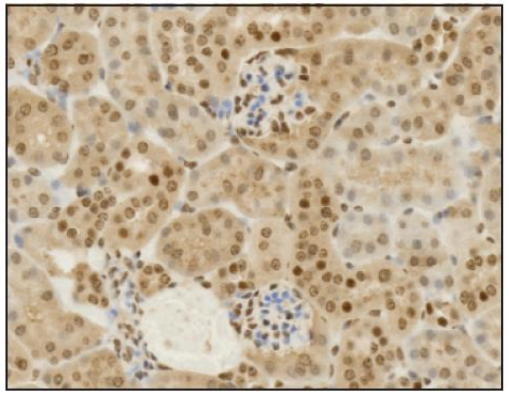


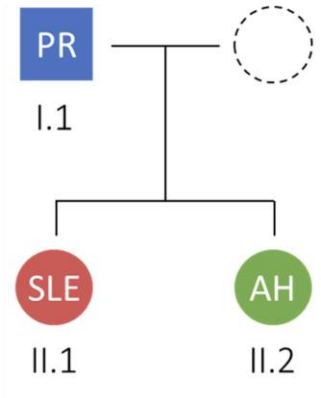
FGFR4

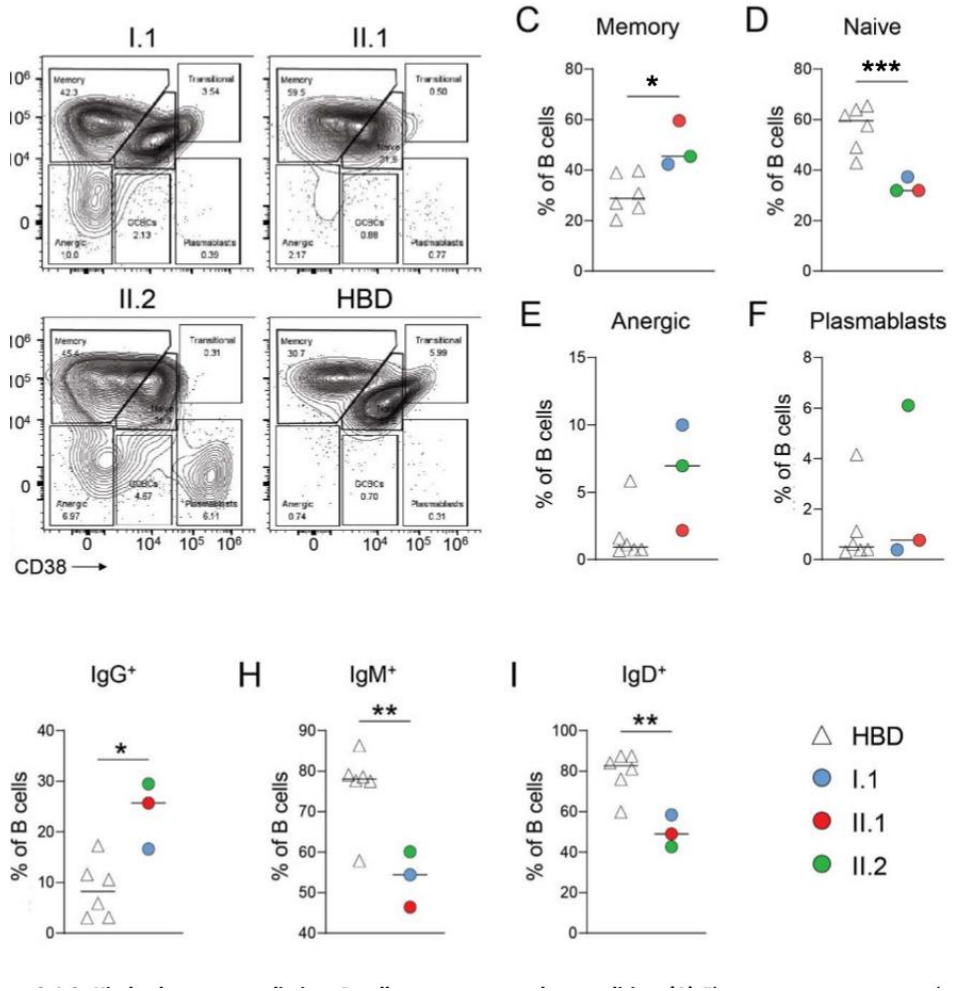


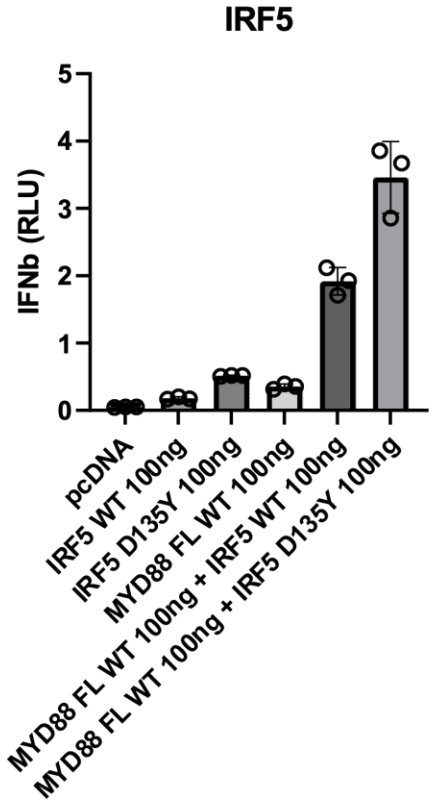
ITK



A complex family (IRF5)







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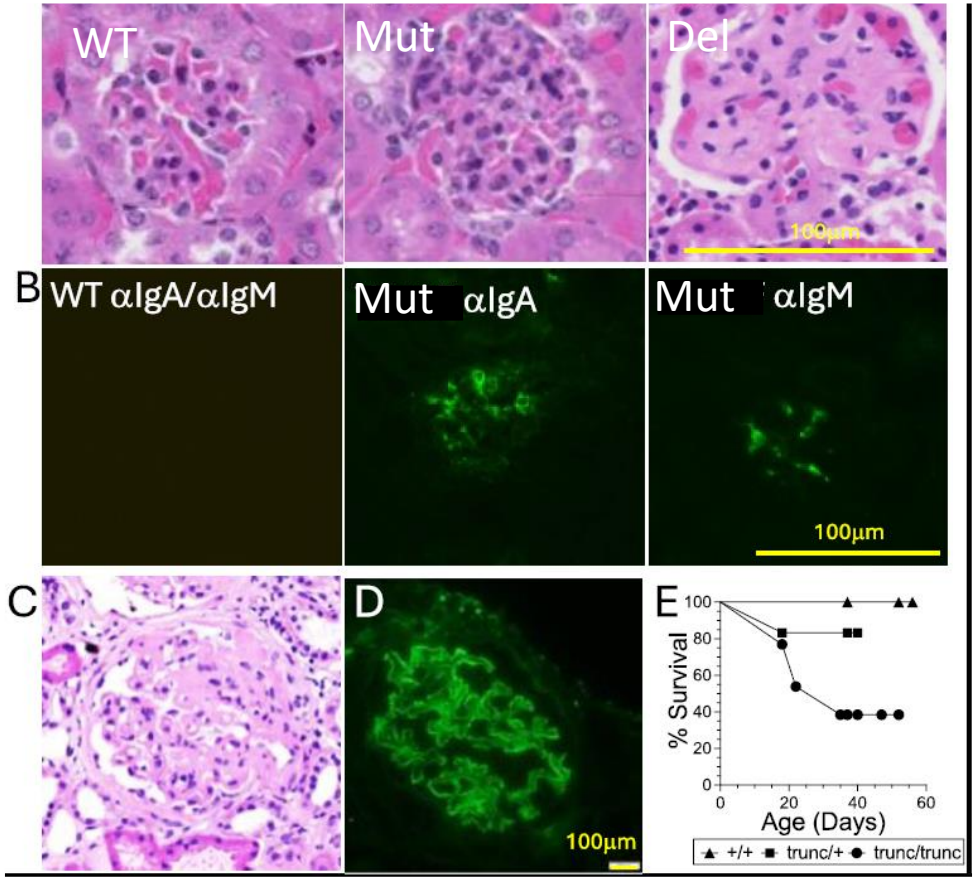
Personalisation at a population level

- Indigenous Australians
  - Highest reported rates of kidney dx
- Mutation in 35%
- CRISPR-Cas9 mice



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Conclusion

- By resolving the genetic and cellular basis of disease we can often provide personalised insights into the basis of immune disease
- Personalised assessment can provide novel treatment targets
- Detailed immune assessment can uncover novel biological processes

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Questions

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Australian National University

Canberra Health Services

ACT Government