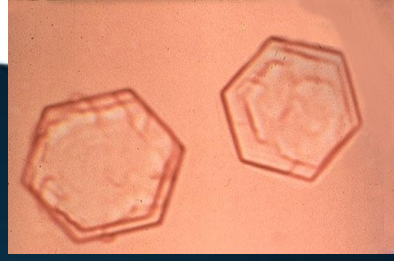
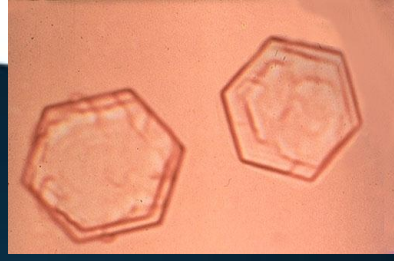


Investigating the Role of Membrane Transport Proteins in the Renal Stone Disease Cystinuria

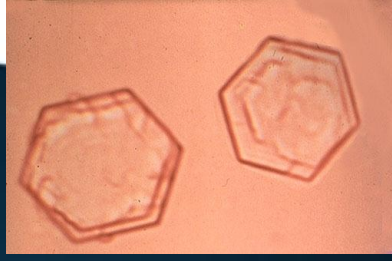
John Sayer
Senior Lecturer in Nephrology



Research Aims

To define precise molecular changes in patients with cystinuria

To characterise functional importance of changes in DNA

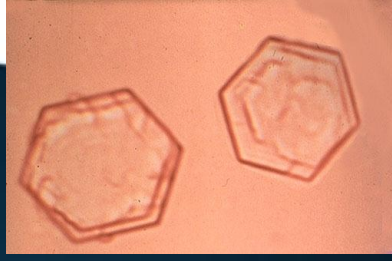


Newcastle cohort

40 individuals or families with cystinuria

Clinical characteristics documented:

- stone episodes (age of onset)
- lithotripsy/PCNL/ureteroscopies
- open surgery
- staghorn calculi
- response to treatment (tiopronin)



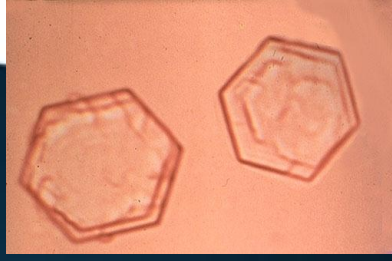
Newcastle cohort

40 individuals or families with cystinuria

Molecular genetic analysis of SLC3A1 and SLC7A9. Sanger sequencing of all exons.

Mutations found in majority of patients (Autosomal recessive and autosomal dominant patterns)

MLPA to solve rest of patients

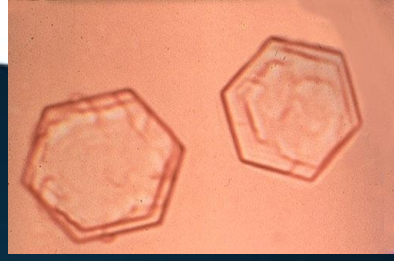


Newcastle cohort

How to deal with multiple variants in same patient, common variants and novel variants?

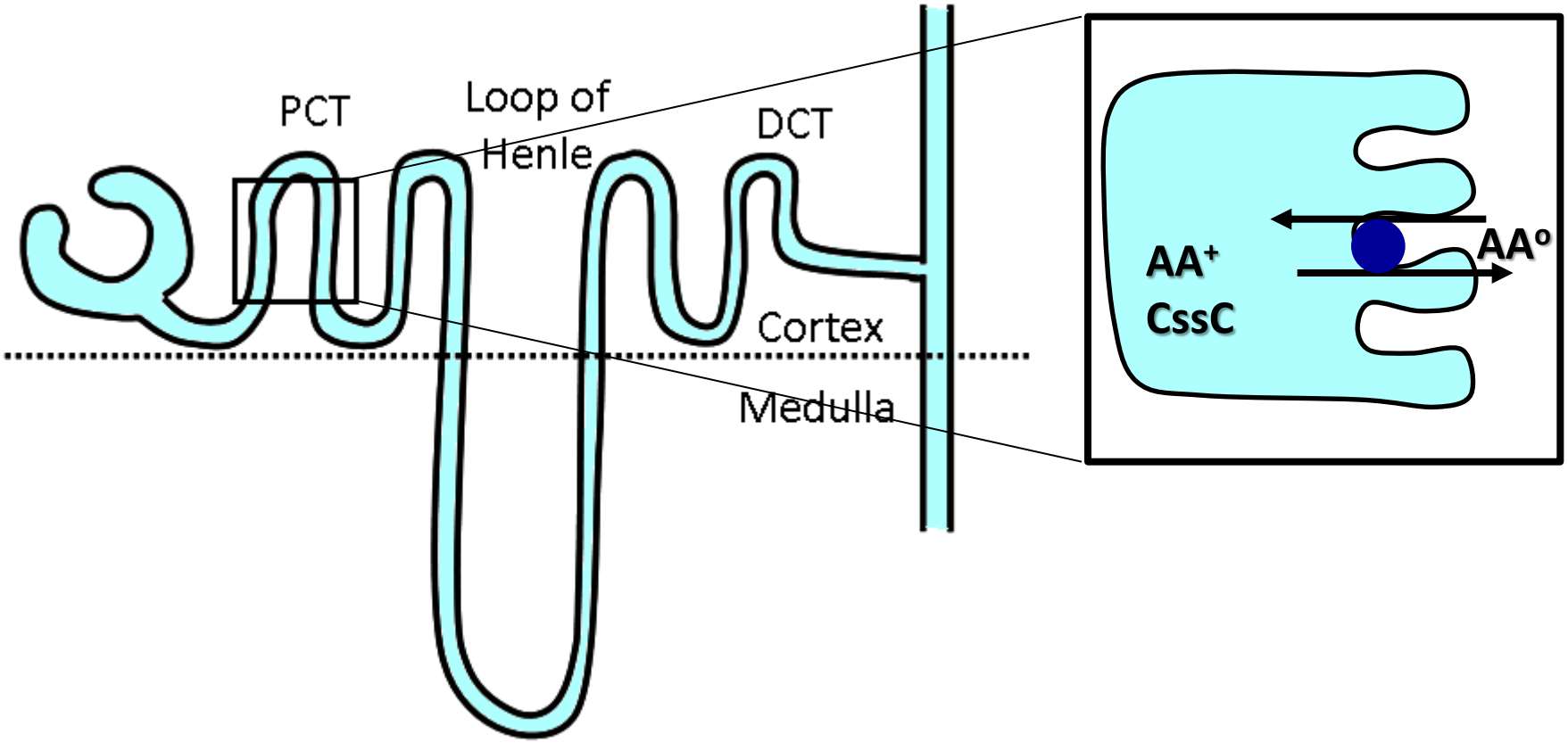
Functional assays required

In silico and in vitro techniques

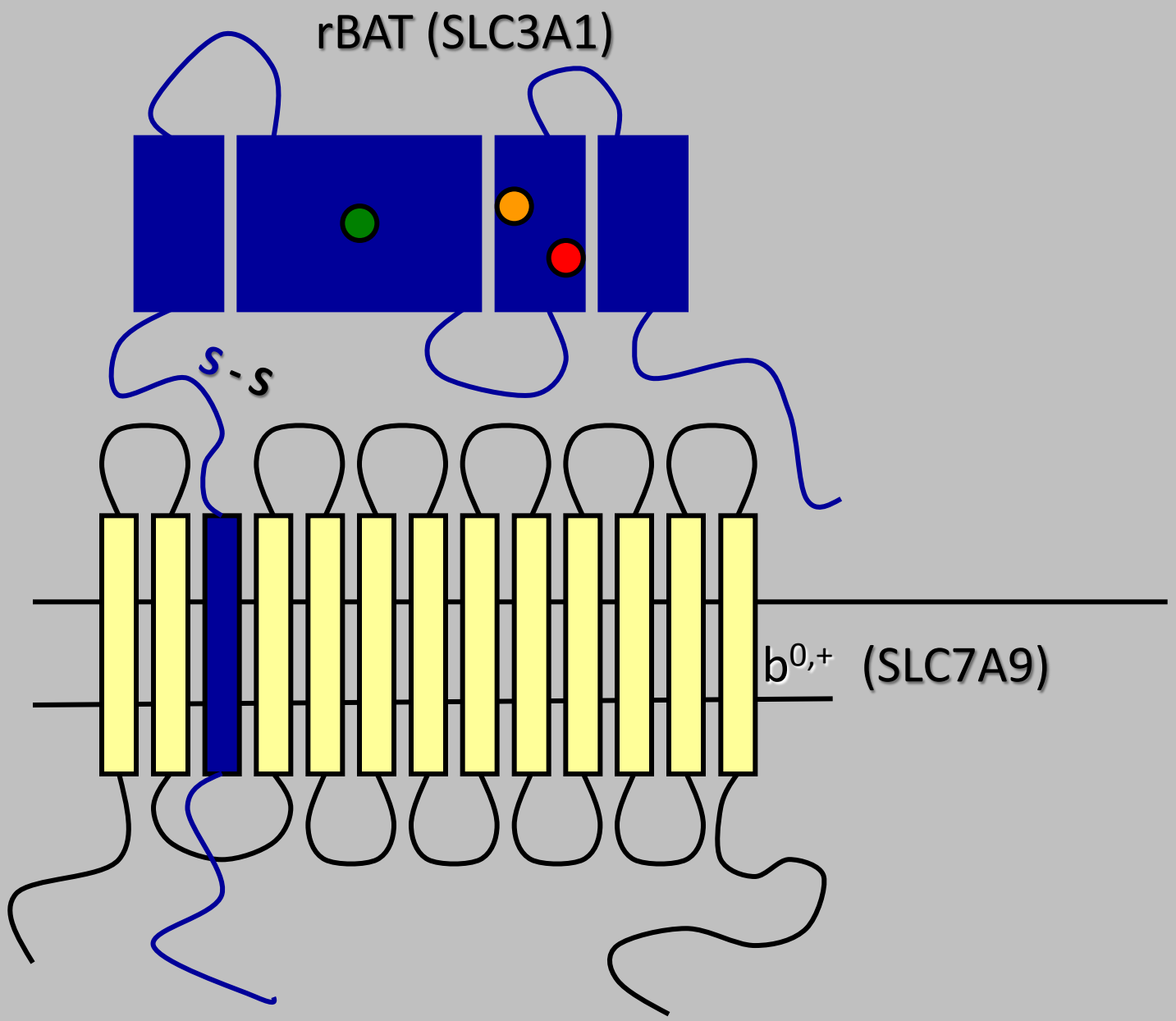


Very few mutations are well-characterised.
The most common mutation in SLC7A9 is V170M, found amongst Libyan Jews.

In SLC3A1, M467T is the most common mutation in Newcastle population (has been reported and characterised amongst Spanish populations)



Do mutant proteins traffic to the membrane?
If they get there do they work well?


rBAT (SLC3A1)
S-S
b0,+ (SLC7A9)

Taking things forward

Share research findings…esp in terms of genetics

Confirm pathogenicity of novel changes

Look for new treatments to enhance membrane protein function