# Structural and functional characterisation of lipid transport and metabolism


**Joseph Lyons lab**

**Section for Protein Science (MBG) and iNANO**

MBG Bldg 1874, 5th floor

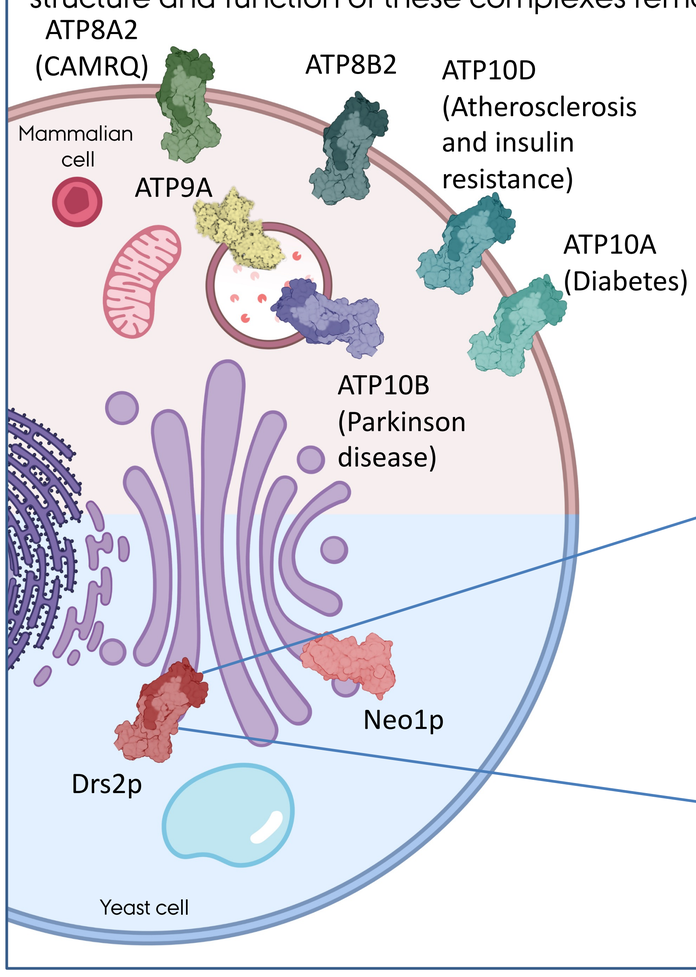
Group: 3 postdocs, 2 PhD students, 1 Bachelor student


We focus on characterising and investigating molecular mechanisms in lipid and polyamine transport and metabolism in humans and fungi.

**Research Areas:** membrane proteins, membrane transport, lipid synthesis, electron microscopy, X-ray crystallography, biochemistry.

## Lipid flippases

Lipid flippases play a central role in membrane modelling and cell homeostasis by driving the inward transport of lipids in the membrane and are localised throughout the membranes of the secretory pathway. A number of lipid flippases recruit a variety of proteins involved in membrane remodelling, however the structure and function of these complexes remain unknown.




**What are we interested in?**

Our research examines the molecular interactions dictating lipid specificity and transport, the mechanisms behind transporter regulation and activation, and the structural and functional role of discrete mutations implicated in rare neurological disorders.

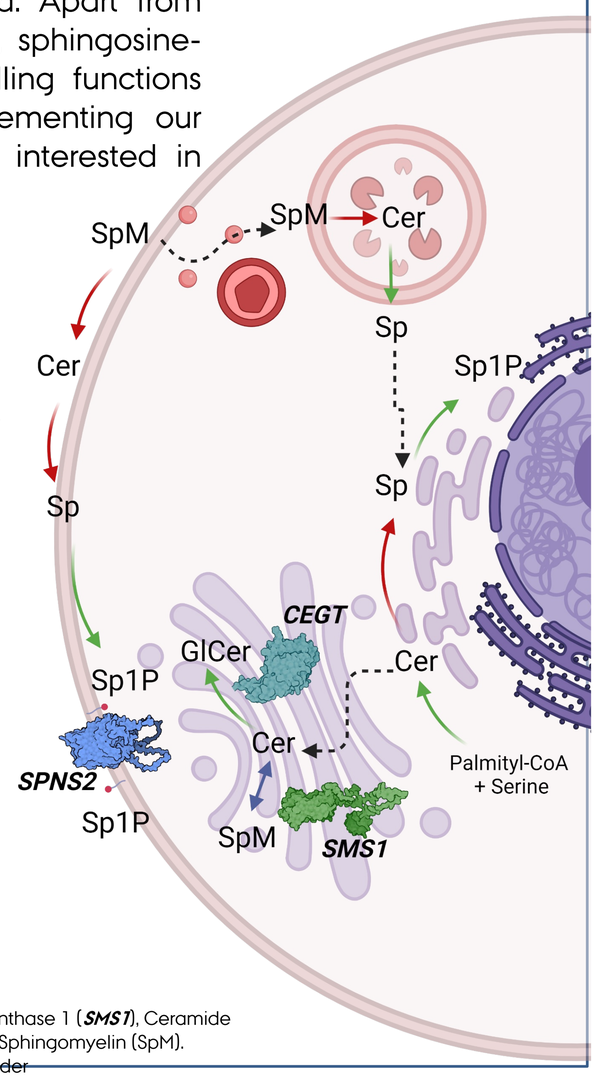
## Sphingolipid metabolism and transport

Sphingolipid transport and metabolism is complex, highly regulated and compartmentalized. Apart from being important cellular building blocks, sphingosine-based molecules, have important signalling functions inside and outside of the cell. Complementing our interest on lipid flippases (left), we are interested in sphingolipid homeostasis.

**What are we interested in?**

Our research focuses on understanding the mechanism of glucosylceramide and sphingomyelin synthesis performed by ceramide glycosyltransferase (CEGT) and sphingomyelin synthase (SMS1).
We want to examine 1) structural features underlying their reaction mechanism, 2) drug binding, 3) substrate specificity, 4) regulation of their activity.

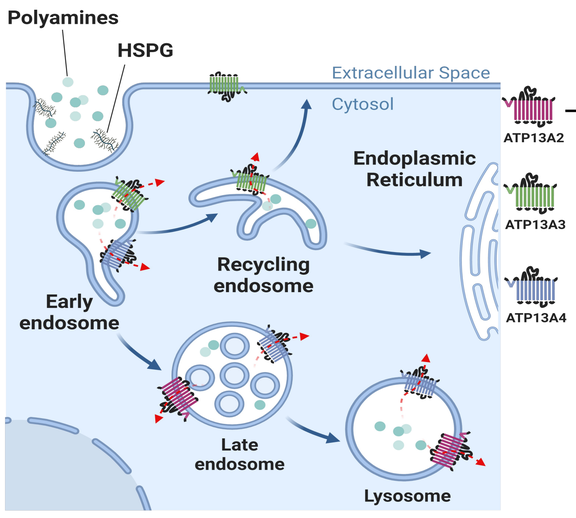
Moreover, we are exploring the structural and functional interplay between these proteins in sphingolipid homeostasis.

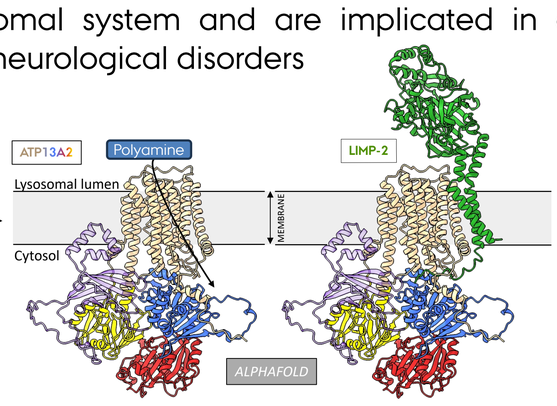



**Legend**: Sphingosine-1-phosphate transporter (***SPNS2***), Sphinomyelin synthase 1 (***SMS1***), Ceramide glucosyltransferase (***CEGT***), Ceramide (Cer), Glucosylceramide (GlCer), Sphingomyelin (SpM). Sphingosine (Sp). Sphingosine-1-phosphate (Sp1P). Created wtih Biorender

## Polyamine transporters

P5B-ATPases are ATP driven polyamine transporters exclusive to eukaryotes. They are located throughout the endo-lysosomal system and are implicated in a spectrum of human disease, in particular neurological disorders such as Parkinson's disease.



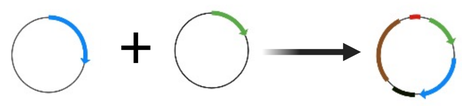

**P5B-ATPases in disease**

| | Related diseases | Tissue distribution (mRNA) |
|---|---|---|
| ATP13A2 | Neurodegenerative disorders | Ubiquitous, highest in brain |
| ATP13A3 | Cancer, pulmonary arterial hypertension | Ubiquitous, highest in liver |
| ATP13A4 | Neurodevelopmental disorders | Brain and glandular epithelial cells |

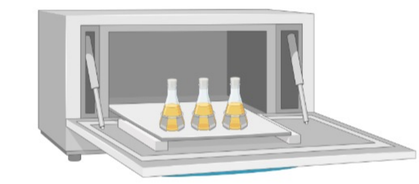
**What are we interested in?**

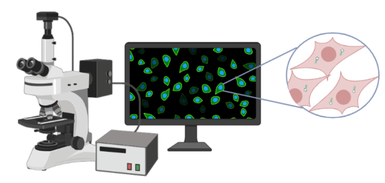
Our research examines the mechanisms underlying 1) substrate specificity and transport, 2) transporter regulation and activation, 3) Heterocomplex formation and, 4) the structural and functional role of disease associated mutations.

## Methods



**Cloning**



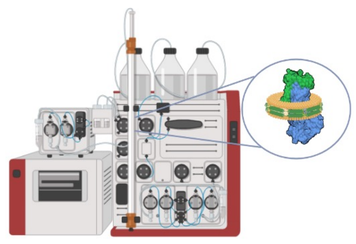


**Fluorescence Microscopy**

Immuno-staining, GFP-signal

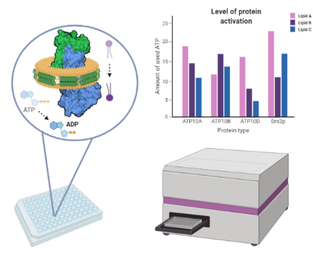
**Protein expression**

E. coli, yeast, mammalian, insect cells



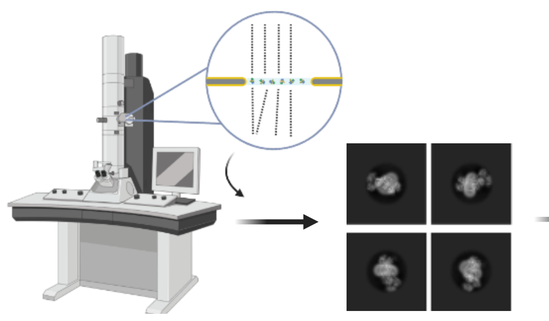
**Protein purification**

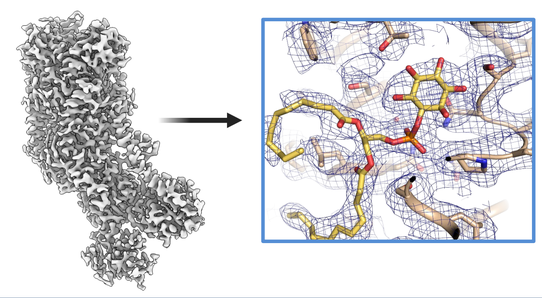
Affinity chromatography, SEC, FSEC




**Activity Assays**

Colorimetric, chemiluminescence, fluorescence, in cell assays, FACS





**Single-particle cryo-EM**

## Projects

A variety of BSc and MSc projects are available with a focus on transmembrane transport of lipids and polyamines. As a BSc/MSc student in our group, you will get a proper research project, working together with a day-to-day supervisor, with the opportunity to develop your competences in Molecular Biology, Biophysics, Biochemistry and Structural Biology.

We have openings for BSc and MSc students – join us and have fun!

If interested, contact: lyons@inano.au.dk

## References


1) Timcenko et al, **Nature**, 2019,
2) Timcenko et al, **J. Mol. Biol.**, 2021,
3) Lyons et al, **Curr. Opin. Struct. Biol.**, 2020,
4) Martin et al, **Acta Neuropathol**, 2020,
5) Moliere et al, **J. Cell. Sci.**, 2022
6) Van Veen et al, **Nature**, 2020
7) Spiegel et al, **J. Lipid Res**. 2019
8) Montigny et al, **BBA**, 2016



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