

Nanostructural Insights into Cubosome-Mediated Delivery of Neuroprotective Polyphenols

Lucrezia Guarneri¹, Andrew Clulow², Anton Le Brun³, Charlotte Conn⁴ and Leonie van 't Hag^{1*}

¹Department of Chemical and Biological Engineering, Monash University, Clayton, VIC 3800, Australia

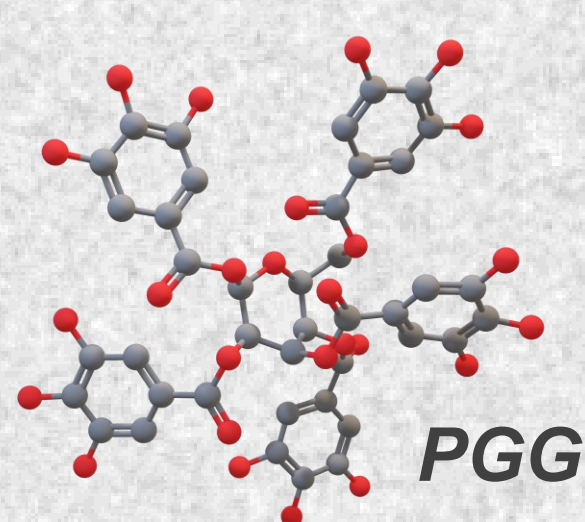
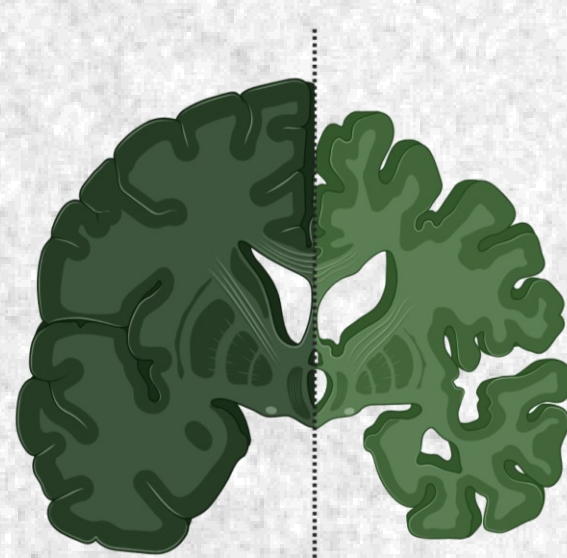
²Australian Synchrotron, ANSTO, 800 Blackburn Road, Clayton, VIC 3168, Australia

³Australian Centre for Neutron Scattering, ANSTO, New Illawarra Road, Lucas Heights, NSW 2234, Australia

⁴School of Science, RMIT University City Campus, Melbourne, VIC 3000, Australia

INTRODUCTION

- Alzheimer's disease (AD): > 57 million people affected worldwide and no curative therapy¹
- Polyphenols such as **pentagalloylglucose** (PGG) target key AD hallmarks *in vitro*²
- Clinical translation limited by **poor bioavailability**³



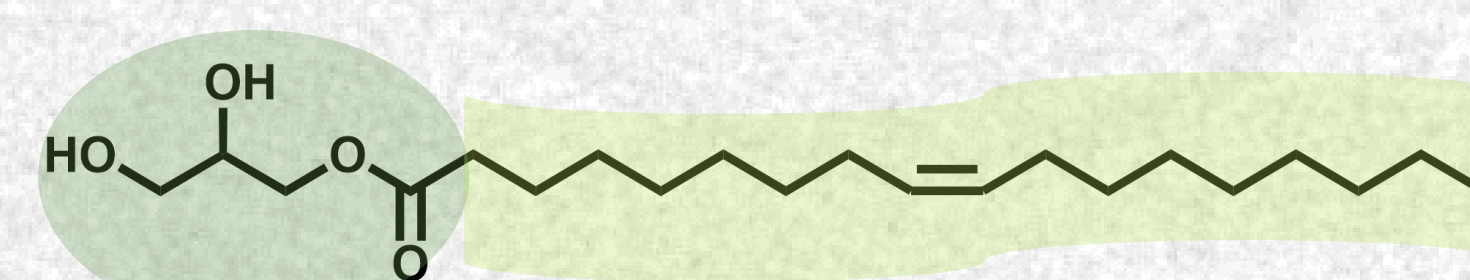
- Cubosomes:** nanocarriers that enhance bioactive stability and **delivery**⁴⁻⁵
- Understanding nanostructure and membrane interactions is key to **optimizing** delivery systems

- This study examines how PGG loading alters cubosome structure and interaction with model neuronal membranes

CUBOSOMES

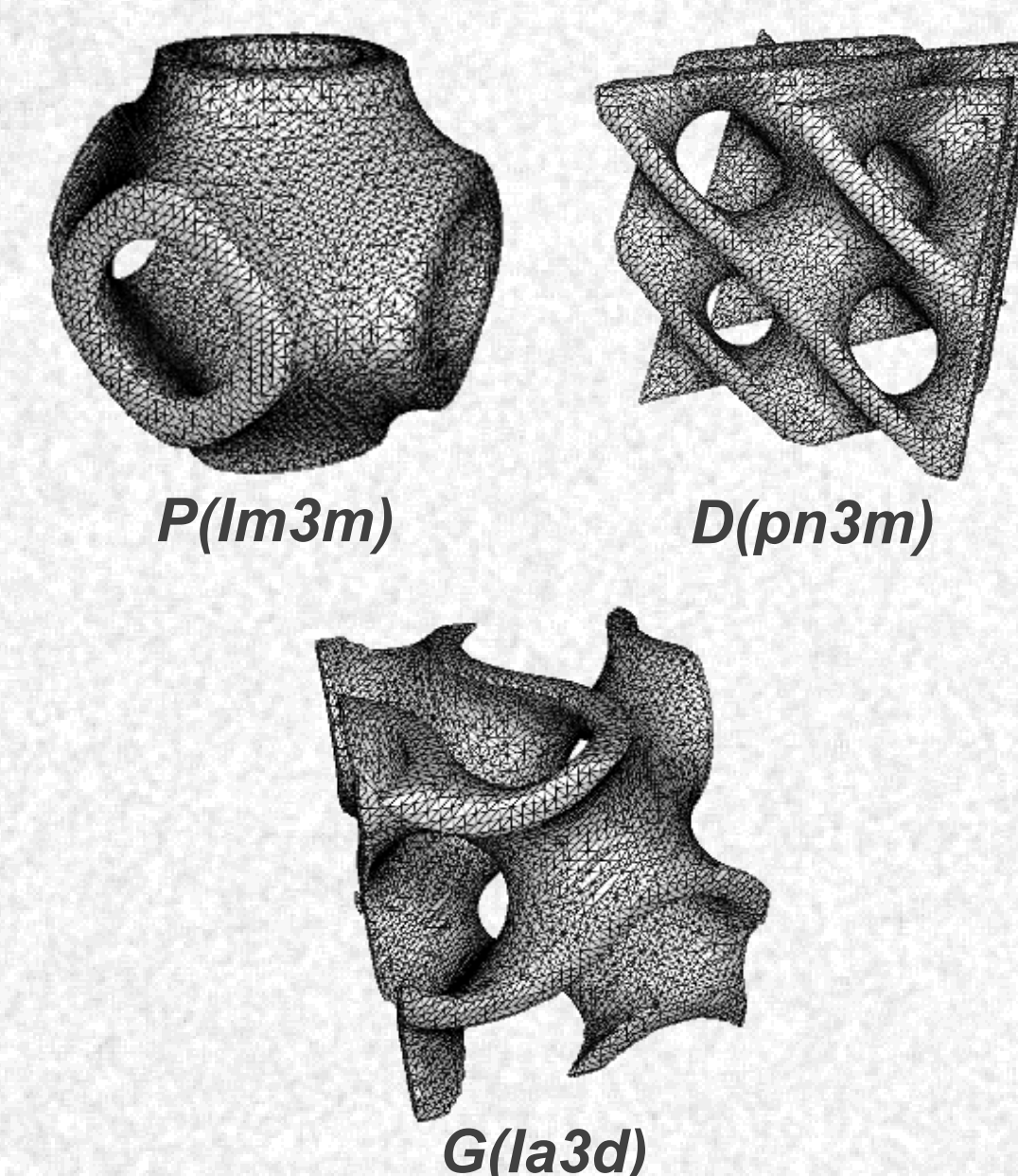
Nanoparticle dispersions of lipid bicontinuous **cubic phases** with a **high surface-area 3D internal structure** that:

- Supports **increased payload** loading across molecular polarities⁶
- Enhance **cellular uptake** via membrane fusion and multiple endocytic pathways⁷



MONOLEIN: cubic phase forming lipid

Cubic phases

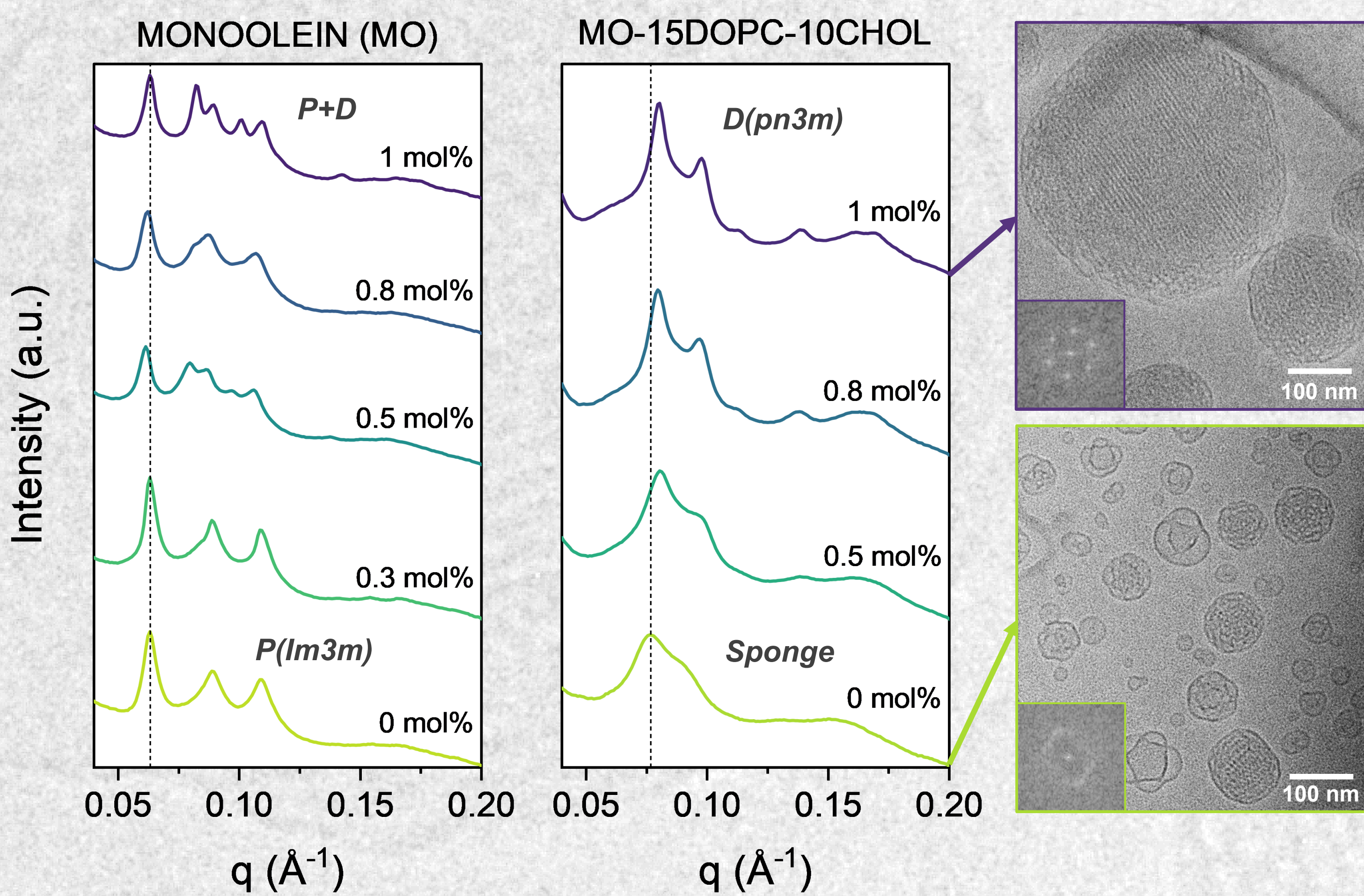


NANOSTRUCTURE

Multi-technique approach:

- Small angle X-ray scattering → internal **cubic ordering** (Bragg peak positions)
- Cryo-TEM → nanoparticle morphology and order **homogeneity**
- Dynamic light scattering → **size** distribution
- Encapsulation efficiency (EE) and **bioactive loading** (BL)

Formulation	Size (nm)	PDI	EE (%)	BL (µg/mL)
MO – Empty	180 ± 5	0.09 ± 0.05		
MO – 1 mol% PGG	215 ± 6	0.08 ± 0.05	97 ± 1	24.1 ± 1.0

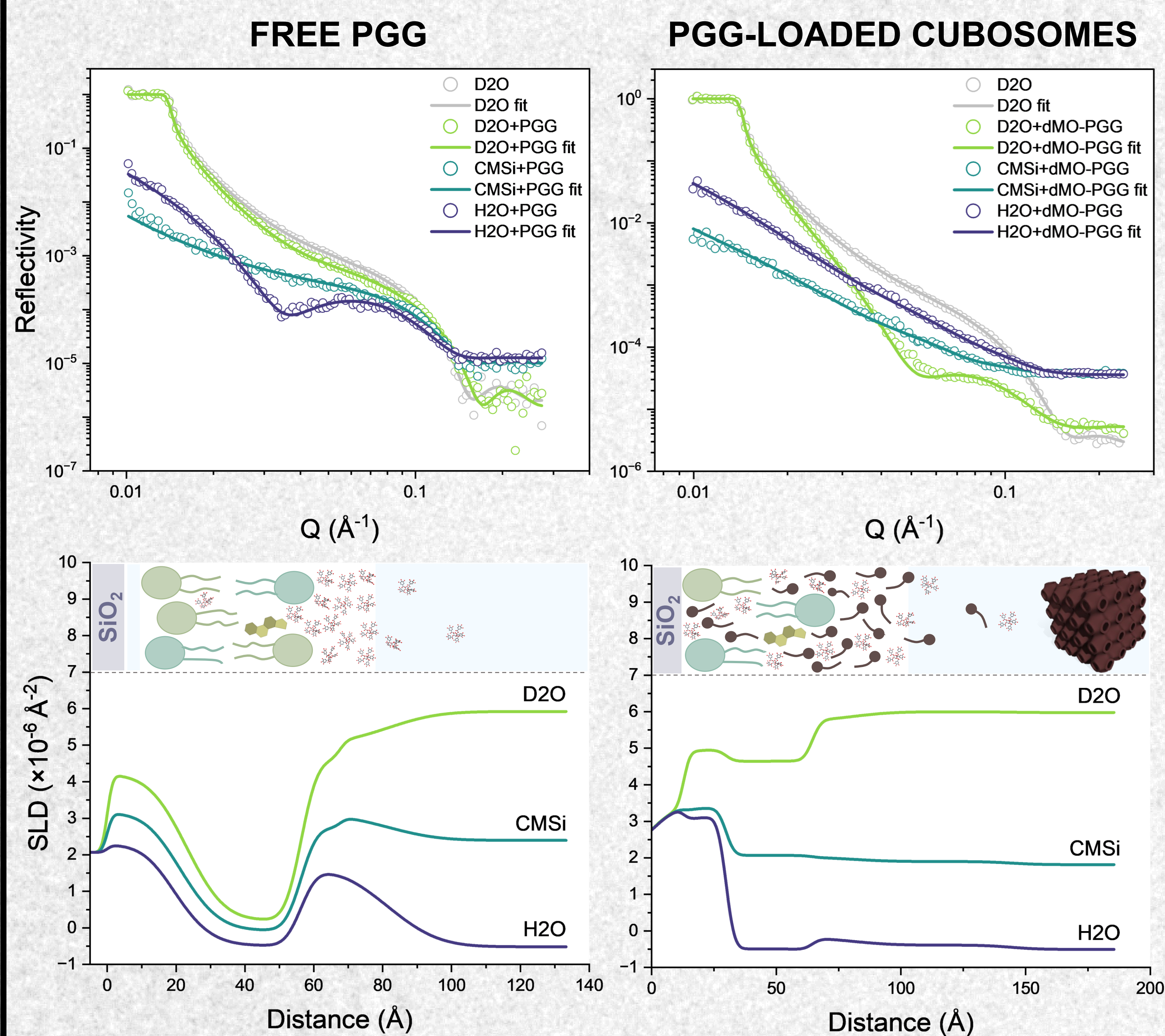


- PGG loading favored internal cubic order of nanoparticles
- PGG resulted in high loading in cubosomes

MEMBRANE INTERACTIONS

Neutron reflectometry → nanoscale interactions between treatments and **model lipid membranes**

Reflectivity(Q) and scattering length density (SLD) profiles → spatial distribution across DOPC-sphingomyelin-cholesterol membranes



- Free PGG adsorbs onto lipid bilayers, with limited membrane permeation
- PGG-loaded cubosomes enhance membrane interaction and permeation

CONCLUSIONS

- PGG **stabilizes** cubic phases by reducing lipid headgroup area via H-bonding, increasing membrane **rigidity** and negative **curvature**
- Small angle scattering** and **neutron reflectometry** link nanostructure to membrane behaviour, enabling mechanism-driven formulation optimization
- Cubosomes **enhance** membrane **permeation**, supporting their use as polyphenol delivery systems

This work connects molecular interactions to cubic phase structure, enabling the rational design of cubosomes for bioactive delivery

REFERENCES

- Alzheimer's and Dementia, 2025, 3708-3821
- Mendonca et al, J Neuroimmunol, 2017, 305, 9–15
- Zhang et al, Pharm Research, 2009, 2066–2080
- Zhai, J. et al. ACS Nano, 2019, 13, 6178–6206
- Cai et al, Advanced Functional Materials, 2024
- Mulet, X. et al Int J Pharm, 2010, 395 (1–2), 290–297
- Yap, S. L., et al JCI, 2024, 656, 409-423

ACKNOWLEDGMENT

My supervisors Dr. Leonie van't Hag, Prof. Charlotte Conn, and Dr. Andrew Clulow. All ANSTO beamline scientists, specifically Dr. Lester Barnsley, Dr. Liliana de Campo and Dr. Anton Le Brun. Dr. Simon Crawford and Dr. Sylvain Trepot at Monash Ramaciotti Cryo EM Facility