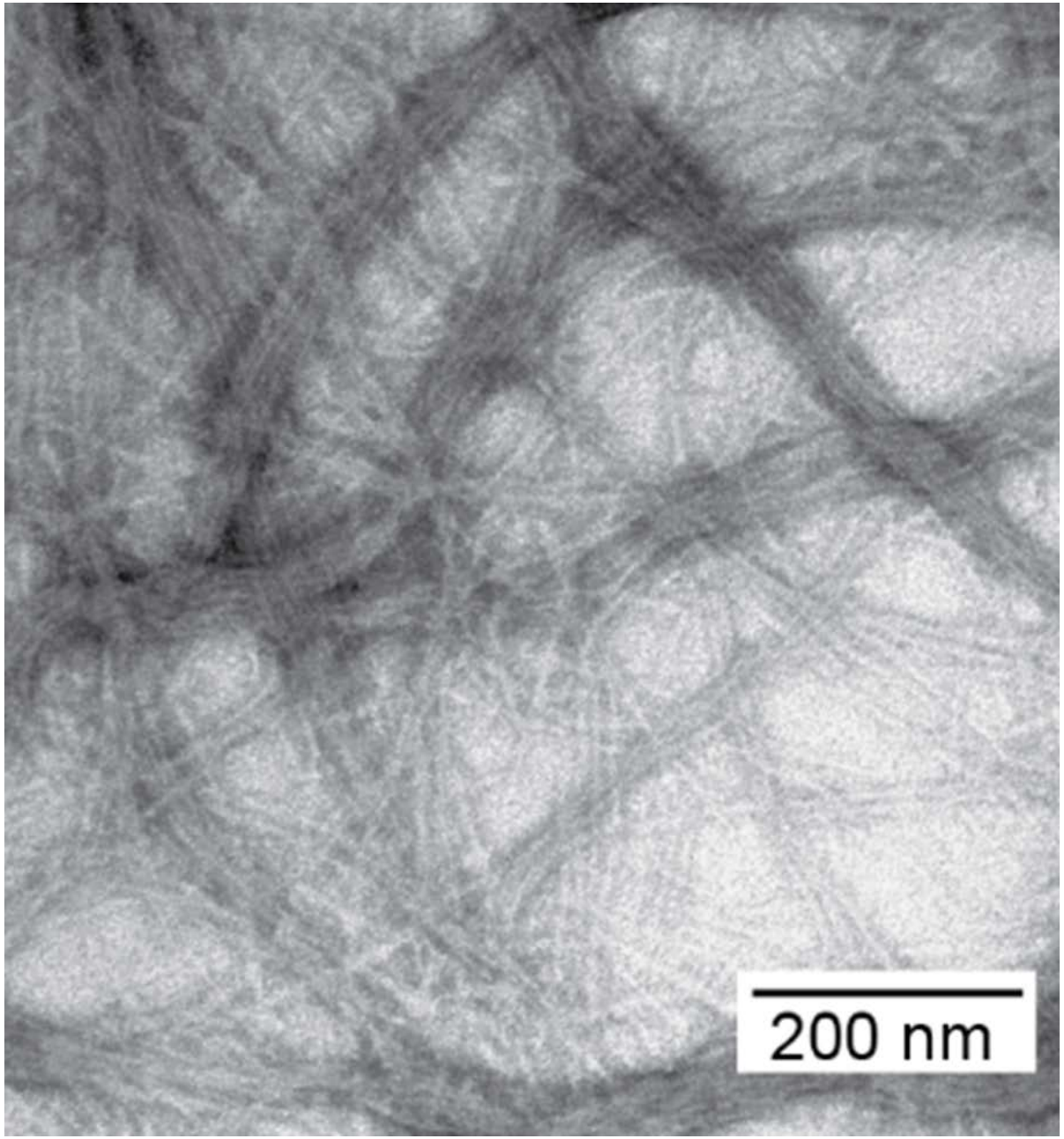
The formation, structure and interactions of disease-associated and functional amyloids

Margie Sunde

Pharmacology, School of Medical Sciences
The University of Sydney

THE UNIVERSITY OF SYDNEY

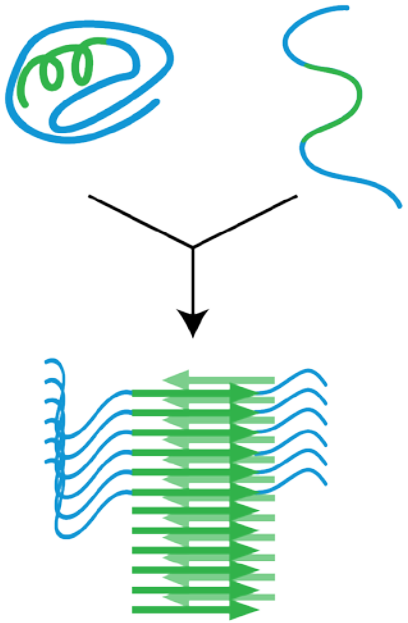


Disease-associated *vs.* functional amyloid fibrils

similar structural characteristics but impact and interactions are different

Fibrillar form is non-functional

Disease- or misfolding-associated amyloid fibril formation



e.g. Asp67His lysozyme, Aβ derived from APP

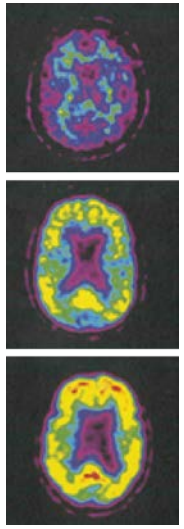
HOMOMERIC

PET brain scans with amyloid-specific probes

Healthy

?

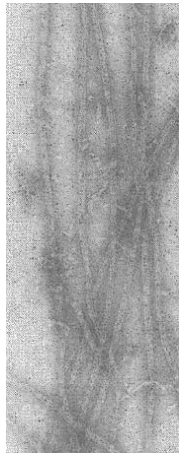
Alzheimer's Disease



Neura Issue 1 (2012)

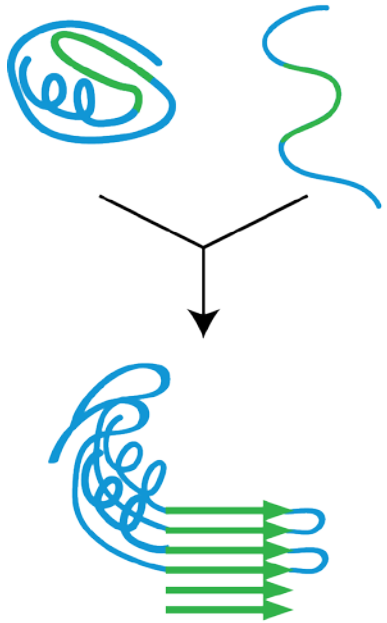
transthyretin fibrils

Familial Amyloidotic Poly—neuropathy And Cardiac Amyloidosis



Functional amyloid fibrils - the fibrillar form has a biological role

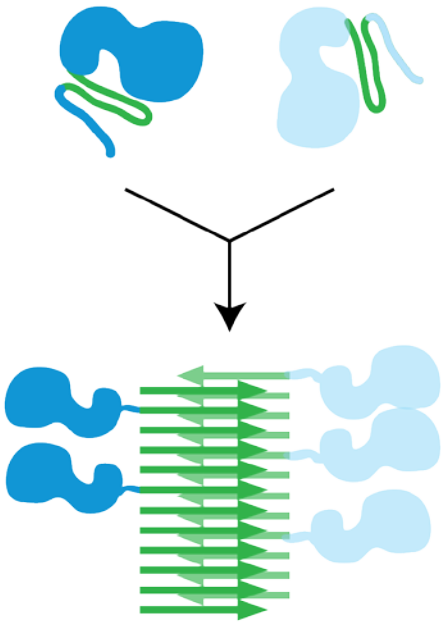
Functional fibrils formed by exposure or generation of amyloidogenic motif



e.g. fungal hydrophobins

HOMOMERIC

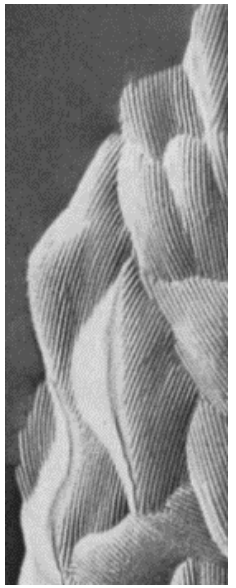
Functional fibrils displaying a separate, active domain



e.g. RIPK1 and RIPK3, HET-s

HETEROMERIC

hydrophobin rodlets on fungal spore

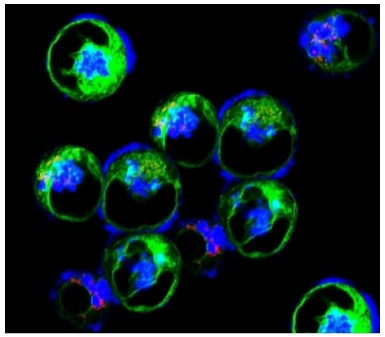


Exp. Mycology 1979: 3: 132-156

curli fibrils on bacteria

Hammer et al. PNAS 2007;104:12494-12499

mammalian cell death by necroptosis



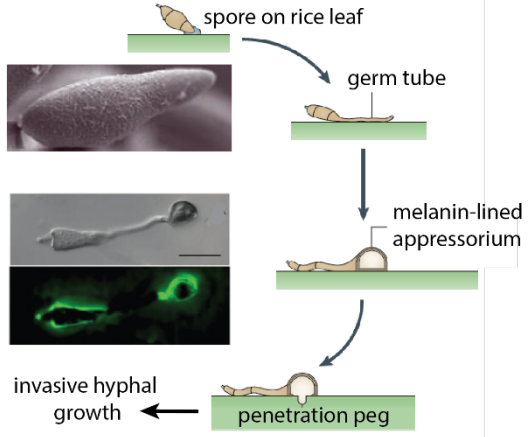
https://www.news-medical.net/life-sciences

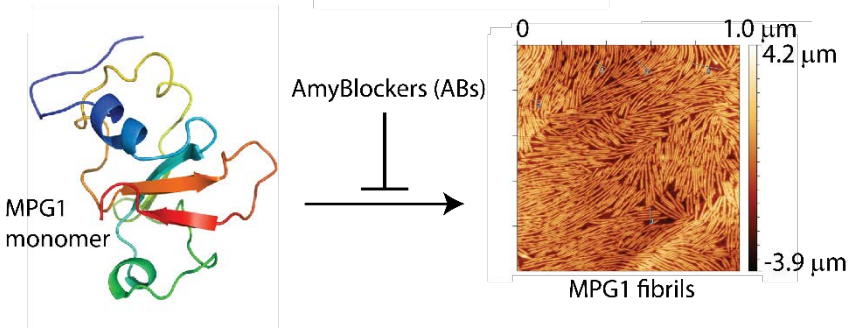
Fungal hydrophobin rodlet amyloid layer facilitates dissemination and infection

Magnaporthe grisea

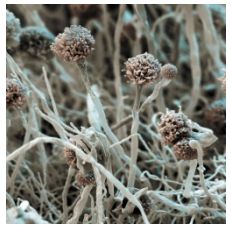
Valent (2004) Nature 431, 516-517

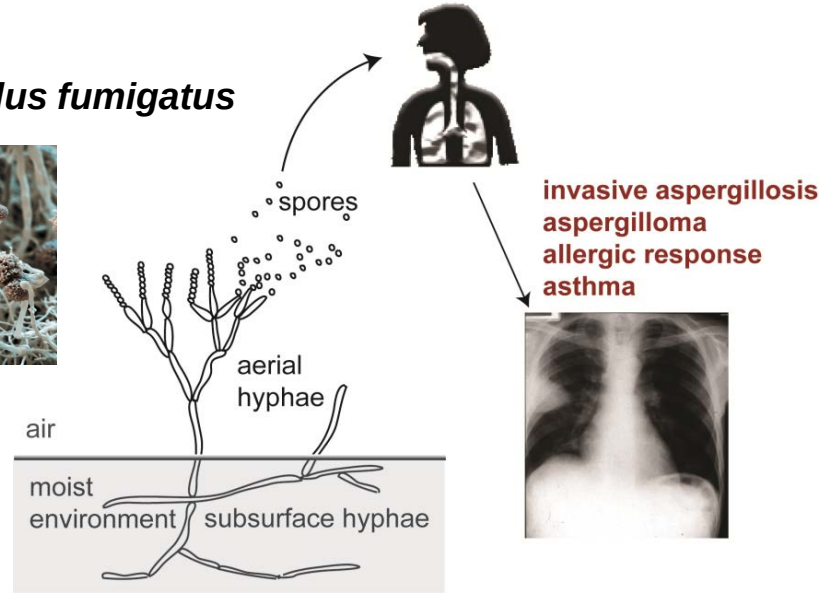
rice blast
most important pathogen of rice
loss of ~25% of global rice crop
food security

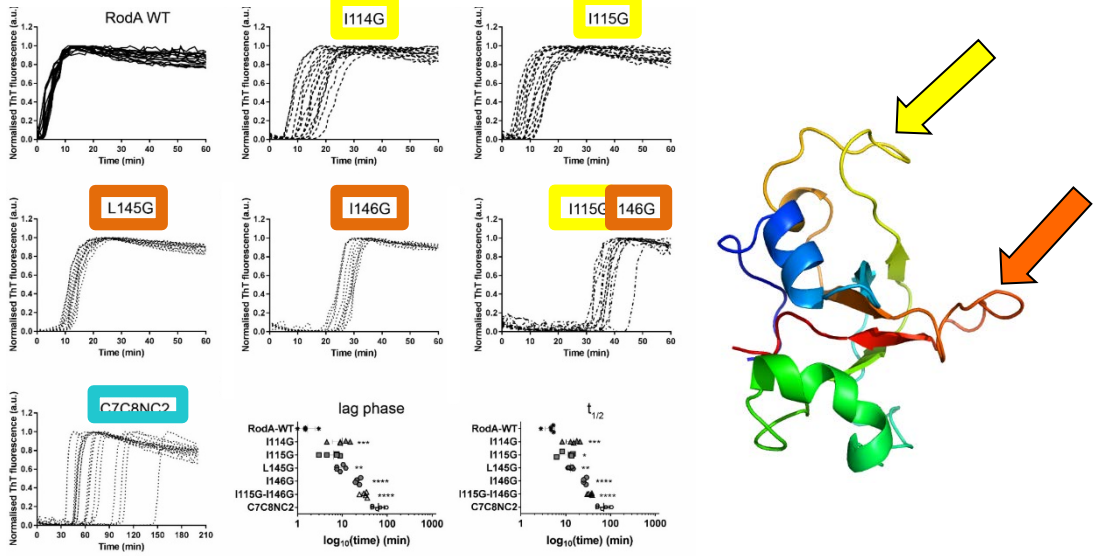




Aspergillus fumigatus



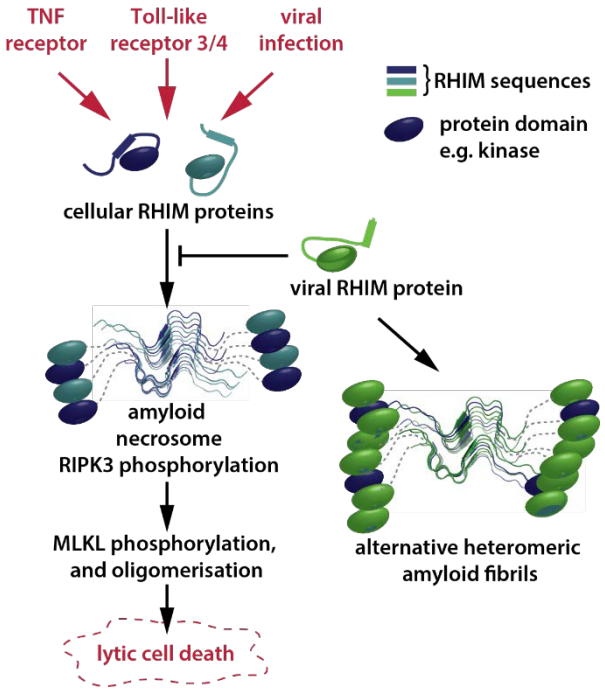


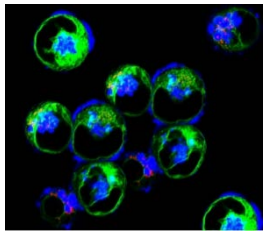


Structural and mechanistic understanding leading to inhibition of hydrophobin assembly for intervention in fungal pathogenesis.

Ann Kwan and Peter Rutledge

Viral proteins inhibit host cell necroptosis by sequestering host signalling amyloids





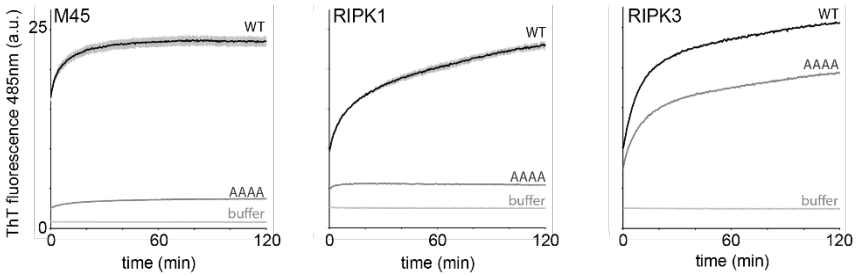
https://www.news-medical.net/life-sciences

Necroptosis associated with:

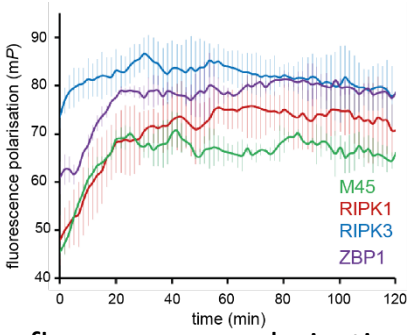
- **Ischaemia reperfusion injury (MI, stroke, transplantation)**
- **Inflammatory bowel disease**
- **Neurodegenerative conditions (ALS, AD)**
- **Liver disease**

- **Potential for biomimicry and therapeutic inhibition of necroptosis**

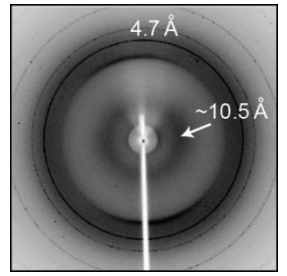
Megan Steain (IDI)



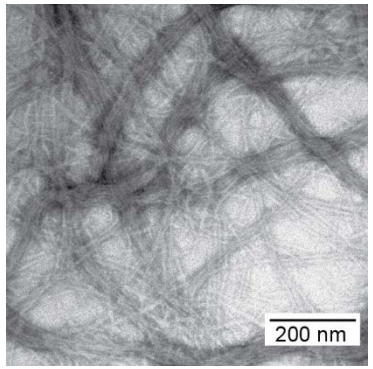
Thioflavin T (and other) assays for amyloid structure



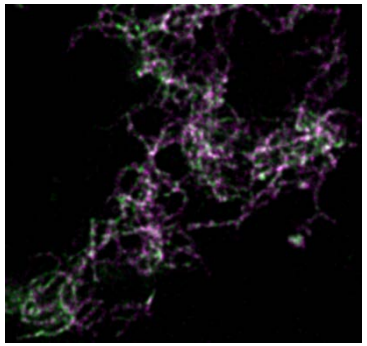
fluorescence polarisation (complex assembly)



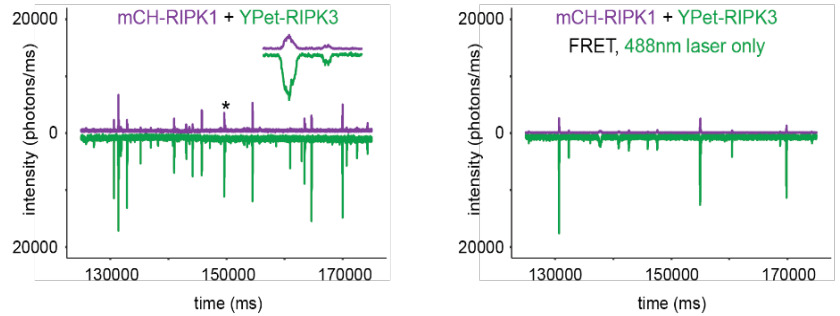
X-ray fibre diffraction

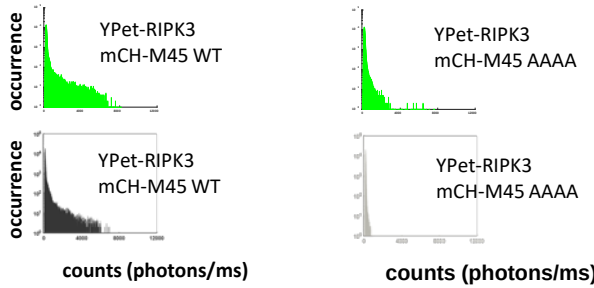


electron microscopy



super-resolution imaging





single molecule spectroscopy approaches (UNSW)