

SCIENTIFIC SEMINAR



Szymon Wiktor Manka
University College London (UCL)

Prion strains viewed through the lens of cryo-EM

Despite fundamental advances in prion biology, key knowledge gaps remain. These include precise delineation of prion replication mechanisms, the molecular basis of prion strains and inter-species transmission barriers. We have sought to address these questions by determining structures of highly purified ex vivo prions using cryogenic electron microscopy (cryo-EM). This has been enabled by: 1) the development of an efficient method for obtaining high-specific infectivity preparations of ex vivo prion fibrils from mammalian brain; 2) optimisation of the distribution of infectious prion fibrils on cryo-EM grids; and 3) application of novel computational methods for 3D reconstruction of amyloid fibrils within the Relion software package. Our pipeline has now enabled us to solve the near-atomic resolution structures of infectious prion fibrils from two biologically distinct mouse-adapted prion strains. These data provide the first insight into how divergent prion strains can emerge from an identical prion protein substrate. The fibrils of both mouse prion strains share the same underlying modular architecture, but with markedly altered topology. The same pipeline can be used for structure determination of synthetic prions, which can shed light on prion strain evolution, mutation, replication and cross-species adaptation. We have, therefore, entered a very exciting era for prion research, where definition of prion fibril structures from multiple strains/hosts and various in vitro prion propagation protocols can provide unprecedented mechanistic insights.

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12.00H



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