RÉPUBLIQUE FRANÇAISE
Liberté Égalité Fraternité

INRAE

PrionDif

EXPLORATORY PROJECT

2021-2023

Coordination
Human Rezaei
UMR VIM
human.rezaie@inrae.fr

Key words
Prion
Neurodegeneration
Autocatalytic process
Diffusion reaction
Prion strain

INRAE units involved
VIM
IHAP

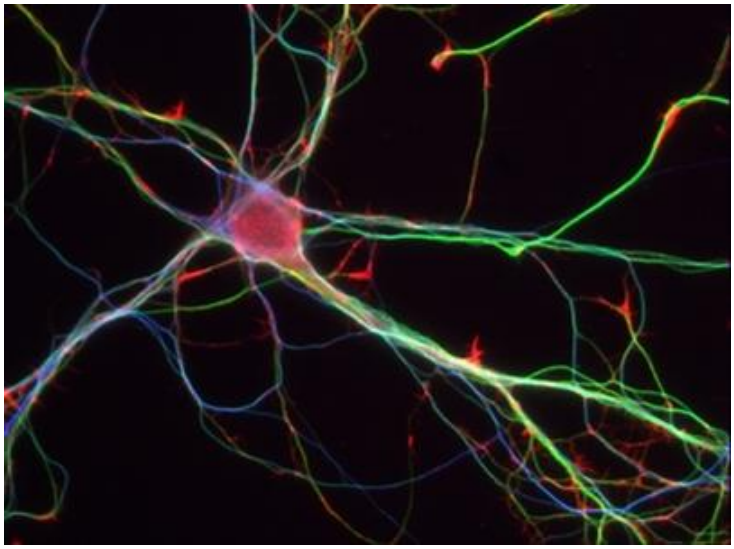
Partnerships
Inria

Prion diseases: modelling the of dissemination and neuroinvasion

Context and challenges

The prion paradigm unifies a number of age-related, devastating neurodegenerative pathologies caused by autocatalytic protein misfolding and aggregation. In the prion paradigm framework, host-encoded monomeric proteins are converted into misfolded aggregated assemblies, which serve as a template for further autocatalytic recruitment and conversion in the brain. Since the late 2000s, the prion paradigm has been extended to other neurodegenerative diseases due to protein misfolding such as Alzheimer's and Parkinson's disease.

In mammalian prion diseases, also known as Transmissible Spongiform Encephalopathies (TSE), prion assemblies (PrPSc), formed from the cellular prion protein (PrPC), contain all the structural information necessary to their replication and their specific stereotyped disease phenotype in the infected host. In TSE, multiple PrPSc conformational variants exist. They define the prion strains and dictate specific physiopathological patterns such as region-specific PrPSc deposits in the same host species. Although self-replicative processes provide a mechanistic framework for the prion paradigm, to date there is no mechanistic link between prion replication, the neuroinvasion process and the strain-specific neuropathological pattern.



© Inserm-L.Peris

Goals

The PrionDif project seeks to develop a multi-scale mechanistic model accounting for the spatiotemporal dynamic of prion spreading within the brain by integrating experimental observations with an effective model of prion replication which takes into account the dynamicity of PrPSc assemblies. By integrating the spatio-temporal mapping of the spread of prion replicative centres with the prion replication/dissemination model, we aim to build

a synthetic multi-scale model of prion structural diversification and lesional propagation. This open-access model will allow us to investigate which parameters of the prion replication process specific to each strain dictate the progression of the disease and the apparition of strain specific PrPSc deposition patterns.

Ultimately, this synthetic approach will allow the identification of key processes to enable therapeutic advances and promote early diagnosis.

Research units involved and partnerships

INRAE scientific division	INRAE research units	Expertises
Animal health	VIM	Macro-Assembly Pathology and Prion Diseases (MAP²) team expertise: molecular biophysics & biochemistry, non-equilibrium kinetics and modelling, stochastic process, Gillespie-type approach, retro-synthetic approach, characterisation of prion assemblies, patterning and prion strains, spatial-temporal evolution of different prion assembly subspecies
	IHAP	Pathogenesis of transmissible spongiform encephalopathies team: physiopathology of prions, tractography, systemic and tissue dissemination of prions, typing of prion strains
External partners		**Expertises**
Inria	Équipe projet Dracula	Modelling of prion diseases: mathematical modelling of reactions under diffusion controls, data integration, synthetic biology, control theory, optimisation, predictive approach