# Séminaire ibs

**Institut de Biologie Structurale J.P. Ebel**
41, rue Jules Horowitz
F-38027 GRENOBLE Cedex 1
Tél. +33 (0)4 38 78 95 50 - Fax +33 (0)4 38 78 54 94
www.ibs.fr

## Conférencier invité

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**A 11h - Salle des séminaires de l'IBS**

**Par Carolin Seuring**

**Swiss Federal Institute of Technology (ETH) Zurich**

Chemistry Department

# A toxicity mechanism in the HET-S/HET-s prion system

The HET-s protein from the filamentous fungus *Podospora anserina* is a prion involved in a limited cell death reaction termed heterokaryon incompatibility (Glass et al., 2000; Saupe, 2000). This reaction is observed at the point of contact between two genetically distinct strains when one harbors prion amyloid aggregates of HET-s and the other one expresses a soluble HET-S protein (96 % identical to HET-s Turcq et al., 1991)). How the interaction of the [Het-s] prion with HET-S brings about cell death remains unknown. It was recently shown that upon interaction with HET-s prion seeds, HET-S relocates from the cytoplasm to the cell periphery and that this relocalization is associated with cell death. Here, we present detailed insights into this mechanism of prion-induced toxicity in which a non-toxic HET-s prion converts a soluble HET-S protein into an integral membrane protein that destabilizes membranes. In liposome leaking assays, we found that HET-S has an innate ability to associate with and disrupt lipid membranes and that this activity is greatly enhanced when HET-S is seeded with HET-s amyloid fibrils. Structurally this can be observed as liposomal membrane defects of 25-60 nm in transmission electron microscopy images of freeze-fractured proteoliposomes that were formed in the presence of both HET-S and HET-s amyloid fibrils. ssNMR analyses reveal that in the presence of HET-s, the HET-S PFD region is converted to the β-solenoid fold which in turn modifies the structure of the globular HeLo domain as detected by proteolytic protection assays and ssNMR. We conclude that the interaction of HET-S with a HET-s prion causes the HeLo domain of HET-S to partially unfold, thereby exposing a 34-residue predicted N-terminal transmembrane (TM) segment from its buried location in the soluble HeLo domain. The liberation of this TM fragment initiates the targeting of the HET-S protein into the membrane. Once embedded in the lipid environment, the HET-S protein can further oligomerize, leading to a loss of membrane integrity and thus displaying features that are reminiscent of a large class of pore-forming toxins (Mueller and Ban, 2010). This study uncovers a novel functional role for amyloids as a specific conformational activation switch for the HeLo pore-forming domain.

**Hôte : D. Bourgeois (IBS/Groupe Dynamop)**