Laboratory title : CNRS UMR 5297 - Daniel Choquet

Supervisor

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Thesis title :
Development of small antibody mimics for the investigation of glutamate receptors

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Abstract

The identification of the cellular and molecular mechanisms involved in the regulation of glutamate receptor trafficking is crucial to our understanding of synaptic maturation and plasticity. The interactions of AMPA- and NMDA-type glutamate receptor complexes with PDZ domain-containing scaffold proteins are critical for their synaptic stabilization. However, the mechanisms that dynamically govern their respective synaptic retention remain poorly understood. In order to study these interactions and gain a better understanding of the molecular rules involved, the project will be organized around the following aims:

1. Development of a phage display screening method to evolve small size synthetic antibody mimics (<10 kDa) that will be characterized by a strong affinity and specificity for the PDZ domain binding motifs that are critical for the AMPA and NMDA receptor synaptic stabilization.

2. Characterization of the generated tools using biophysical methods (spectroscopy, SPR…) and cellular models (FRET/FLIM) with particular interest in the critical properties that involve affinity and specificity as well as the capacity to disrupt the binding partners from the targeted motifs.

3. Engineering of the selected domains with the aim of providing them with additional properties necessary for the cellular studies (internalization, caging group, fluorophores…).

4. Exploitation of these tools in the context of synaptic transmission studies, primarily using bioimaging technics.

This project is part of a general thematic that aims at developing with a multidisciplinary approach new methods to study the role of specific proteins interactions involved in the regulation of synaptic transmission.

Qualification required

Knowledge in biochemistry and chemistry/biophysics appreciated