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Directed protein evolution for the investigation of endogenous proteins in synaptic organization and transmission

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Over the last decades, technological advancements have allowed us to generate a more accurate vision of synapse and its complexity. Despite these progresses, our understanding of a number of structural and functional elements of this specialized neuronal compartment are still incomplete. Indeed, the main features of synapses are their high diversity and plasticity in response to activity. These properties are underlain by a tight dynamic regulation of over 2,000 different protein components. In this context, one of the main current technical hurdles is to be able to directly investigate endogenous proteins of interest and their complexes in their native cellular environment.

To address this challenge, we are exploiting protein engineering methods in order to develop new molecular tools to either monitor or modulate endogenous synaptic proteins. More precisely, by combining directed evolution approaches (phage display), biophysical investigation, structural biology, proteomics, and cellular imaging, we are aiming to:

- develop new probes to monitor proteins involved in the structural organization of neurons and synapses such as Spectrins.
- develop new high affinity binders of PDZ domain binding motifs to inhibit specific PDZ domain partners rather than the PDZ domains themselves.

The probes and the binders that will be generated will allow us to better understand the function and molecular mechanisms that regulate the targeted proteins. We anticipate that this ensemble of new molecular tools, that can be easily shared once fully characterized, will be of high interest to the neuroscience community.