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# *S E M I N A I R E*

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## « Pharmacology in a membrane: Interactions of lipophilic small molecules with pentameric ligand-gated ion channels »

Pentameric ligand-gated ion channels are a critical component of the post-synaptic membrane, and numerous lipophilic small molecules, including general anesthetics, endogenous neurosteroids, hormones, and lipids, exert their effects at least partially via direct interactions with the pLGIC transmembrane domain. Experimental efforts to identify relevant binding modes or quantify binding affinities frequently encounter obstacles associated with membrane-based mechanisms, including challenging crystallization and weak control of ligand concentration local to the protein. Computational approaches for rigorous prediction of likely binding sites and associated affinities circumvent many of these experimental obstacles, but have been developed almost exclusively for use with soluble proteins and an isotropic reference state. I will present our recent extension of these methods to a randomly-mixed membrane reference state and resulting predictions for binding modes of lipids, neurosteroids, and general anesthetics for eukaryotic pLGICs, and corresponding evidence from subsequent experimental tests. Finally, I will discuss implications of non-random mixing and domain formation in quasi-native membranes for direct binding mechanisms.

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**Jeudi 24 mars 2016**
**14h30**

**Salle de Conférence**