TARGETING PROTEIN-PRTOEIN INTERACTIONS IN RECEPTOR COMPLEXES

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Protein-protein interactions (PPIs) are essential to vital cellular processes, and serve as potential targets for therapeutic intervention. We are particularly interested in the PPIs between integral membrane protein receptors and their intracellular protein partners, so-called 'receptor complexes' and examine how modulation of such receptor complexes PPIs can provide novel biological insight.

We have developed peptide-based inhibitors of the PSD-95/glutamate receptor interaction, by exploiting that PSD-95 contains a tandem PDZ1-2 domain. So we designed and synthesized dimeric peptides with low nanomolar affinities, and have demonstrated that these ligands are potential treatment for ischemic stroke. The lead compound is entering Phase I clinical trials in the spring of 2020. For the same PPI, we examined the importance of backbone hydrogen bond by employing amide-to-ester mutations in peptide ligands and proteins.

Similarly, we have exploited the principle of dimeric peptide-based ligands to perturb the PPI between the scaffolding protein gephyrin and glycine/$GABA_A$ receptors. Most recently we have developed high affinity, cell-permeable peptides and demonstrated how these can modulate inhibitory receptors and used to label synapses. We have used peptide microarrays to more systematically examine receptor/gephyrin interactions, which combined with pull down and mass spectrometry have provided insights into gephyrin protein networks.

Finally, we have targeted G proteins, as alternative ways to target G protein-coupled receptors. Specifically, we have developed synthetic strategies for cyclic depsipeptide natural products, which are potent, cell-permeable and selective for the G_q protein family.