

Member Profile



Tetra Discovery Partners LLC is an early stage biotechnology company located in Grand Rapids, Michigan. The company uses structure-guided drug design to discover mechanistically novel, allosteric modulators of phosphodiesterase 4 (PDE4). PDE4 allosteric modulators are being developed by Tetra for the treatment of depression and mild cognitive impairment in probable Alzheimer's disease.

The prototypical PDE4 inhibitor, rolipram, has been shown to have pro-cognitive benefit in multiple rodent and monkey models, to improve synaptic and cognitive function in Alzheimer mouse models and to reverse long-term dendritic spine pathology. Rolipram was studied in human clinical trials of depression, but lacked tolerability at the clinical dose due to emesis. PDE4 allosteric modulators have pro-cognitive benefit similar to rolipram with improved tolerability.

Why make allosteric modulators of PDE4? Previous efforts to develop drugs targeting PDE4 focused on the discovery of simple inhibitors that bind in the active site competitively with cAMP. PDE4 allosteric modulators, in contrast, are able to close a PDE4 regulatory domain known as UCR2 over the active site, thereby inhibiting the enzyme. The two UCR2 domains in the PDE4 dimer display negative cooperativity such that only one active site can be closed at a time. This has the consequence that PDE4 enzymatic activity is not completely inhibited by a PDE4 allosteric modulator. Why is this important? This is the differentiating feature of a PDE4 allosteric modulator as compared to a simple, active-site director inhibitor. The allosteric mechanism provides a physiological ceiling on the maximum inhibition of PDE4. This results in better tolerability as it becomes more difficult to increase cAMP in cells to non-physiological concentrations.

Please see the blog on the Tetra Discovery Partners website (<http://tetradiscovery.com/blog/>) for additional information regarding PDE4 allosteric modulators and the use of structure-guided drug design to target protein-protein interactions with small drug molecules.