



Addex and Merck & Co. Collaborate



Agreement



- Addex and Merck will collaborate to discover and develop positive allosteric modulators (PAM) of metabotropic glutamate receptor 4 (mGluR4)
- The deal includes mGluR4 PAM leads already discovered by Addex
- Merck is responsible for pre-clinical and clinical development
- Addex will participate on joint oversight committees at each stage
- The first indication to be pursued is Parkinson's disease
- Additional indications are undisclosed



Financial Terms



- Addex receives \$3 million upfront
- Addex is eligible to receive \$106.5 million in research, development and regulatory milestones for the first product in multiple indications
- Addex is eligible for an additional \$61 million in research, development and regulatory milestones for a second and third product
- Addex received an option to co-promote marketed products in undisclosed EU countries



Parkinson's Disease

Parkinson's Disease



- Parkinson's disease is a long term degenerative brain disorder
- The cause is unknown
- Characterized by a loss of dopamine producing cells in areas of the brain responsible for control of movement
- Symptoms include tremor, rigidity and slowness
- 1.5 million currently have Parkinson's disease in the U.S.
- About 60,000 new cases are diagnosed in the U.S. every year
- Currently marketed drugs are helpful but there is significant room for improvement
 - No marketed products reduce dependence on L-DOPA
 - No marketed products work via non-dopaminergic mechanisms
 - No marketed products slow disease progression



mGluR4 PAM in Parkinson's Disease

mGluR4 in Parkinson's Disease



- mGluR4 activation has been shown to have an anti-Parkinsonian effect identical to dopamine receptor stimulation in various acute or chronic animal models of Parkinson's (haloperidol-induced catalepsy, 6-OHDA or MPTP lesion)
- Preliminary evidence suggests that mGluR4 PAMs may be as effective as mGluR4 agonists in Parkinson's
- mGluR4 activation exerts a dopamine-like effect via a non-dopaminergic mechanism by reducing transmission at the striato-pallidal synapse
 - Effects of mGluR4 activation at the striato-pallidal synapse is not altered in dopamine-depleted animals
- mGluR4 receptor activation may have direct neuroprotective effects on neurons

Source: *Nature Reviews Neuroscience*, vol 6, Oct. 2005



Another Validation for Addex

Another Validation of the Addex Platform



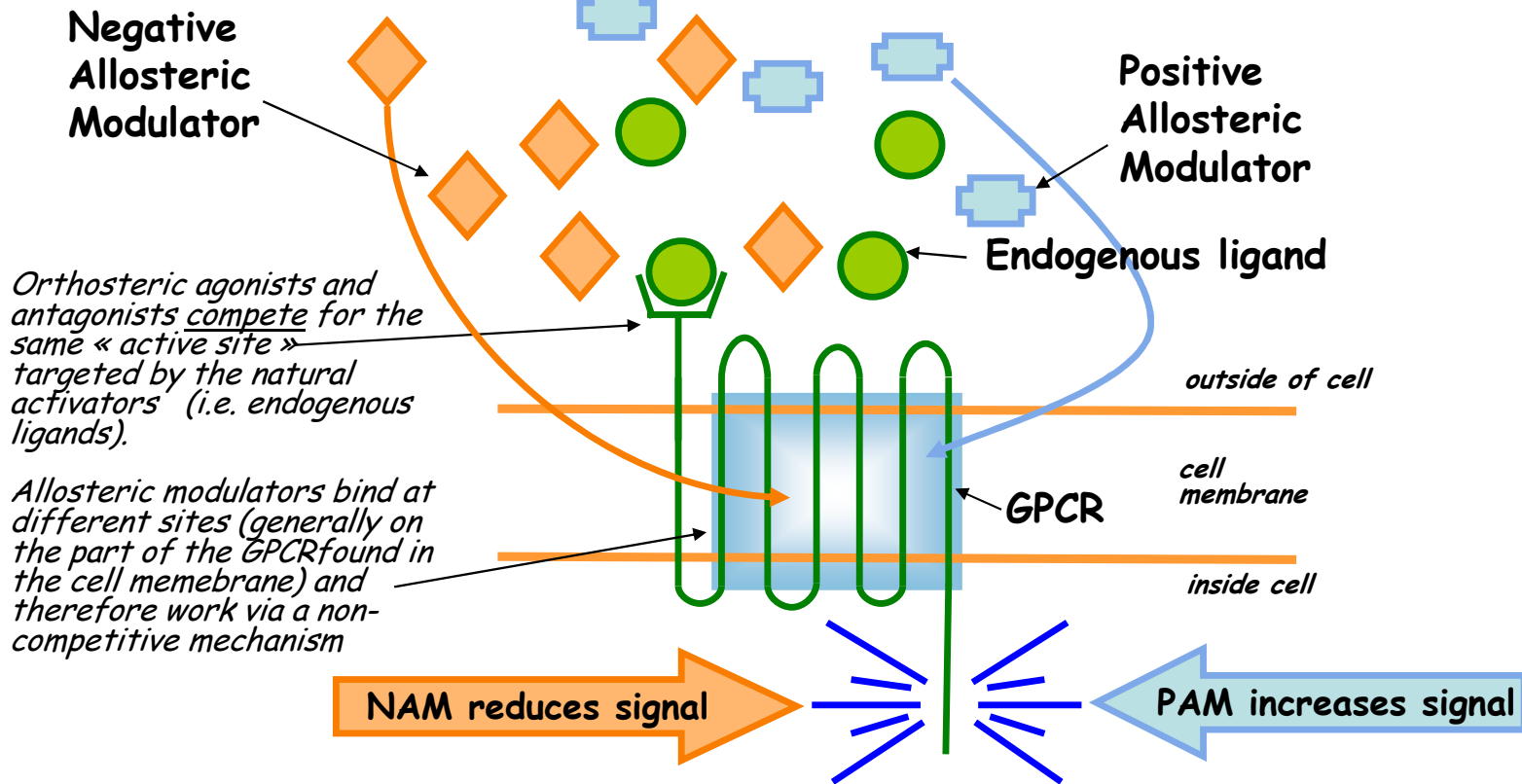
- Although Merck and others have contributed to the elucidation of mGluR4's potential role in Parkinson's disease, finding drug-like mGluR4 PAMs has been challenging
- This collaboration provides Merck with access to selective mGluR4 PAMs and Addex' allosteric modulator development expertise
- Addex signed in 2004 a similar deal around mGluR2 PAMs for anxiety and schizophrenia with Ortho McNeil, a Johnson & Johnson company

Allosteric Modulators

Addex' goal is to become a world class pharmaceutical company by leveraging the specific discovery and optimization capabilities it has built around this unique emerging class of therapeutic agents

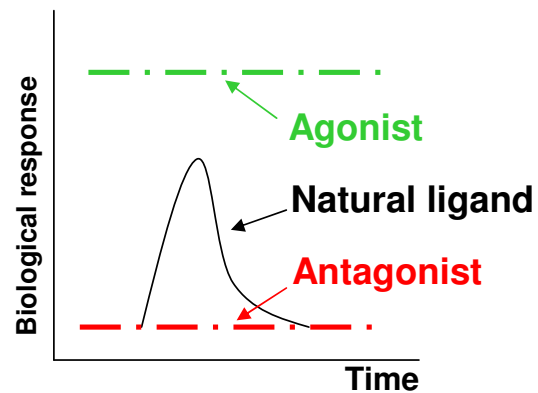
Allosteric Modulation

~a non-competitive approach~

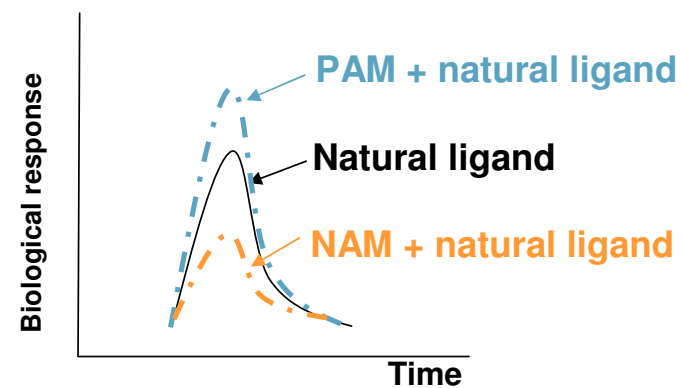


Orthosteric \neq Allosteric

Orthosteric are steady state

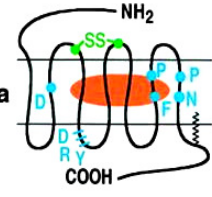
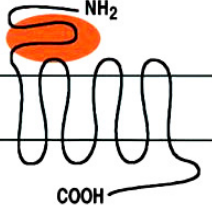
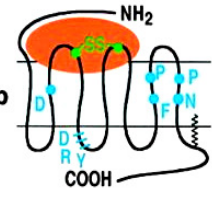
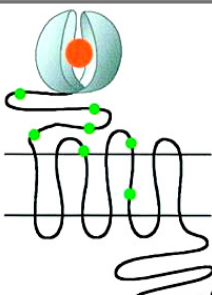
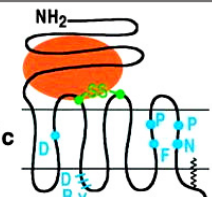


Allostery preserves natural rhythm



- PAMs & NAMs do not activate/deactivate receptors – the natural ligand does
- Natural physiological rhythm may mean fewer side effects and/or better efficacy
- Addex chemists can fine tune how much a PAM/NAM turns the signal up/down
- “Dimmer switch” approach offers more sophisticated therapeutic strategies

Addex can target all GPCR Families

Family 1		Family 2	
 <p>1a</p>	<p>Muscarinic receptors Odorants Catecholamines Adenosine Opioid receptors Anandamide</p>	 <p>NH2 COOH</p>	<p>Calcitonin PTH VIP PACAP GnRH CRF GLP-1 Glucagon GIP</p>
 <p>1b</p>	<p>Peptides Cytokines I₁_B Formyl Met-Leu-Phe fMLP-peptide PAF-acether Thrombin</p>	 <p>NH2 COOH</p>	<p>Family 3</p> <p>mGluR1-8 Ca⁺⁺ GABA_B Pheromones (VR, G_oVN)</p>
 <p>1c</p>	<p>Glycoproteins hormones (LH, TSH, FSH)</p>		

Adapted from Bockaert & Pin, EMBO J, 1999



Addex Pipeline & Partnering Strategy

Allosteric Modulator Pipeline



Discovery	Preclinical	Phase I	Phase IIa	Milestones	Partner
ADX10059 (metabotropic glutamate receptor 5 NAM) Gastroesophageal Reflux Disease (GERD)				Ph IIa endpoint met Ph IIb start: mid 2008	
ADX10059 (mGluR5 NAM) Migraine Prevention				Ph IIa endpoint met Ph IIb start: mid 2008	<i>To be partnered after Ph IIb</i>
ADX10059 (mGluR5 NAM) Acute Anxiety				Ph IIa data: Dec 07 / Jan 08	
ADX48621 (mGluR5 NAM) Depression & Anxiety				Ph I data: 2008	
ADX63365 (mGluR5 PAM) Schizophrenia & Cognitive Impairment				Ph I start: 2008	<i>To be partnered</i>
ADX71441 (GABA _B PAM) Spasticity/GERD/Anxiety				Ph I start: 4Q08 / 1Q09	
ADX68693 (FSH NAM) Contraception / Osteoporosis				Phase I start: 2009	
mGluR2 PAM Schizophrenia/Anxiety					<i>Johnson & Johnson</i>
mGluR4 PAM Parkinson disease					<i>Merck & Co.</i>
GLP1R PAM Type II Diabetes					<i>To be partnered after Ph IIb</i>
GPCR1 NAM Depression					
GPCR2 NAM Depression					

NAM = negative allosteric modulator
PAM = positive allosteric modulator

allosteric modulators for human health

Q&A

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