

## Dimmer-switch Drugs

By Megan Scudellari | September 1, 2009

A growing number of companies are exploring molecules that modulate targets, rather than just switching them on or off.

It started with an obsession. In 2002, Vincent Mutel began to talk about allosteric modulators, think about allosteric modulators, even dream about them. Few drug companies were pursuing allosteric modulators—small molecules that regulate a receptor or enzyme by binding to a site distinct from the target's active (or orthosteric) site. Such ligands were widely recognized for their role in naturally regulating G protein-coupled receptors (GPCRs), many of which are known drug targets. But at the time, allosteric modulators and their signaling pathways had a reputation of being difficult to work with (they are), the molecules were believed to be insoluble (they are, in fact, soluble), and their efficacy was not proven (it soon would be). Still, Mutel had great hope.

His newly formed company, Addex Pharmaceuticals, was struggling under its original business plan as a specialty pharma focused on addiction therapies, and Mutel realized the company needed to make a radical change. So he thought of a radical solution. While working at Roche a year earlier, Mutel participated in the discovery of the first positive allosteric modulator for a metabotropic glutamate receptor, mGluR1, one in a family of receptors intensively studied for their therapeutic potential in a wide range of neurological disorders, including Parkinson's and schizophrenia. (The modulator is termed positive because it enhances the receptor's activity.) The results convinced Mutel of the power of allosteric modulation. He spoke with the Addex staff, approached investors, and within a year, the company had shifted its business plan from a specialty pharma to a platform biotech exploring allosteric modulation. "Making allosteric modulation work became our mission on Earth," says Mutel.

Addex was one of the earliest and most aggressive companies to pursue allosteric modulation, but it is certainly not the last. "There's a good boatload of biotech companies going in the same direction," says Maik Klasen, a biotech analyst at Frost & Sullivan. And major pharma companies are also jumping aboard: GlaxoSmithKline recently completed a phase I trial of a positive allosteric modulator to treat schizophrenia.



There are several proposed benefits to allosteric modulators. Orthosteric sites, the traditional targets of many drug discovery programs, are highly conserved among protein superfamilies, such as GPCRs and kinases, so it is difficult to specify drugs to subtypes of receptors. Allosteric binding sites, on the other hand, are quite selective. Functionally, allosteric modulators act by enhancing or inhibiting the binding and/or signaling of an orthosteric ligand, mimicking normal physiological rhythms because they have no effect unless an endogenous ligand is bound to the orthosteric site. Orthosteric agonists and antagonists act like light switches, turning receptors constitutively on or off independently of endogenous ligands, but allosteric modulators can function as dimmer switches, modulating a receptor's activity in increments. Because they are quiescent when there is no ligand attached to the orthosteric site, research suggests that large doses of such molecules would not cause toxicity in the same way as high doses of an orthosteric ligand.

The anticipated flood of allosteric modulators to the market will take some time, as most are still in early clinical phases.

Now, the field awaits enough clinical data to prove that the proposed benefits will outweigh any unwanted side effects, such as regulation of other signaling pathways in a cell. Two commercially available allosteric modulators have raised hopes that this category of drugs will have market success, but without more clinical data, the platoon of advantages attributed to allosteric modulators still remains hypothetical, says Klasen. "In biological terms, it makes sense. But in clinical terms, we still have to see how these modulators work in the body."

Slow and steady

In 2003, Addex began a massive effort to transform allosteric modulator discovery from a haphazard, luck-ridden process into an industrialized operation. "Coming from orthosteric development, this was a big challenge. At first, we were lost. We were shooting in the dark," says Mutel. Classical functional assays are cumbersome when used to measure a dynamic change in a GPCR's function rather than simply determining whether it's on or off. What's more, confirming that an allosteric modulator, a noncompetitive molecule, is binding to an expected target requires a great deal of cross-checking, says Mutel. "We had to think from scratch, almost had to rediscover the entire drug development process."

A Sampling of the Allosteric Modulator Pipeline				
Company	Drug	Target	Indication	Phase
Addex Pharmaceuticals	ADX10059	mGluR5	GERD; migraines	IIb
	ADX48621	mGluR5	Parkinson's	Completed I
	ADX71149	mGluR2	Schizophrenia	I
deCODE genetics	DG071	PDE4D	Alzheimer's	IND approved
Evotec	EVT101	NMDA	Depression	Completed I
	EVT201	GABA-A	Insomnia	Completed II
GlaxoSmithKline	GSK729327	AMPA	Schizophrenia	Completed I
Marinus Pharmaceuticals	Ganaxolone	GABA-A	Epilepsy	Completed IIb
Xytis Inc.	XY2401	NMDA	Schizophrenia	Completed I
	XY4083	Alpha-7nAChR	Cognition	IND approved

Today, Addex boasts a library of over 70,000 allosteric modulators for receptors from all three GPCR families and a system of novel, proprietary assays for screening the molecules for clinical potential. The company currently has allosteric modulators against 18 targets in

optimization, preclinical or clinical trials, partnerships with Merck and Johnson & Johnson, and recently expanded its platform to include non-GPCR targets. "Addex has had great success with their program," says Klasen. "Their name comes up all the time."

Yet two larger pharmaceutical companies beat Addex to the market: Amgen's Sensipar (cinacalcet) for hyperparathyroidism, a positive modulator of the calcium-sensing receptor, was approved by the US Food and Drug Administration (FDA) in 2004, and Pfizer's Selzentry (maraviroc) for HIV infection, a negative modulator of the chemokine receptor CCR5, hit the shelves 3 years later.

In 2006, a team of structural biologists and chemists at deCODE genetics pursued an allosteric modulator for a notoriously challenging drug target. Phosphodiesterases are a well-known target class in the pharmaceutical industry, a superfamily of enzymes that hydrolyze cAMP, taking an active part in signal transduction throughout the body. (Viagra, for example, is a PDE5 inhibitor.) But there are no compounds on the market for PDE4, which research suggests plays a role in chronic obstructive pulmonary disease, asthma, inflammation and cognition. Researchers have been unable to target the four unique isoforms of the enzyme because of their highly conserved active sites, says Lance Stewart, head of structural biology at deCODE.

To specifically target the fourth isoform of PDE4, PDE4D, implicated in inflammation and cognition, deCODE researchers took a structural approach. They solved the crystal structure of the enzyme, then identified a binding site for an allosteric ligand. (Compounds that target the PDE4 active site produce significant side effects, such as nausea and vomiting.) Using a real-time kinetic assay, the team assessed the effects of different molecules at the allosteric site and found DG071. The company recently received FDA clearance to begin phase I clinical testing of DG071 in Alzheimer's and other cognitive diseases. A structure-based drug design project normally takes two and a half years, says Stewart, but DG071 took 3 years. "When you're dealing with something complicated like modulation of allosteric sites, you have to do more heavy lifting," he says.

"These are extremely difficult compounds to develop," agrees John Krayacich, CEO of Marinus Pharmaceuticals, which is developing an allosteric modulator for the treatment of epilepsy. But large pharmaceutical companies need to rise to that challenge, say biotech experts. "Big pharma is already quite aware their old drug discovery engine is running out of targets," says Klasen. "They have to go to the next level of complexity, and this includes allosteric drugs."

#### Signing up

Krayacich, who last year joined Marinus from Novartis, believes that's already occurring, estimating that more than half of big pharma's drug discovery programs are now targeted at allosteric modulators. "My impression is there's a lot of work going on," says Ken Rubenstein, principal biotech consultant at Lion Consulting Group.

Early last year, Addex licensed ADX63365, a positive allosteric modulator for mGluR5 for the potential treatment of schizophrenia, to Merck, receiving \$22 million upfront and a promise for \$455 million in milestone payments for the first product in two indications and \$225 million for each additional product in two indications, plus royalties. Such a large investment means Merck expects a big payback, says Klasen. "Merck obviously wants to make money on this drug, so they expect a few billion dollars in market potential."

But that's not to say the market is clamoring for just any allosteric modulator. In 2007, Evotec, a biotech devoted to small molecule therapeutics, completed phase II trials for EVT201, a partial positive allosteric modulator for the GABA-A receptor, licensed from Roche

to treat insomnia. But despite positive efficacy results and a better safety profile than many insomnia drugs on the market, says John Kemp, chief R&D officer at Evotec, the company has been unable to find a partner to advance the drug, which would have to compete with such market giants as Ambien and Lunesta, to the expensive phase III trial.

If a biotech pursues indications in the big therapeutic areas, like the central nervous system, an allosteric drug will drum up a lot of excitement and financing, says Klasen. But an actual flood of allosteric modulators to the market will take some time, he warns, as most are still in early clinical phases. "I would not expect the market to explode before the next 7 to 9 years," he says. "Most of these drugs aren't yet ripe for primetime."