

# ADVENTURES IN GLUTAMATE:

## The Difficult and Expensive Path of Novelty in Drug Discovery

*Efforts to target inscrutable glutamate GPCRs have helped change the way industry discovers small molecule therapeutics, opening up swathes of promising drug targets. But the decades-long effort also reveals problems with today's biotech business model.*

BY CHRISTOPHER MORRISON

- The discovery of metabotropic glutamate receptors in the early '90s opened up a new world of potential drug targets in CNS diseases and beyond.
- But targeting specific mGluRs proved very difficult; eventually the challenge of designing selective molecules led to breakthroughs modulating receptors at sites distinct from the endogenous binding site.
- This so-called allosteric modulation may help to clear a logjam of undruggable GPCRs and other receptors.
- Creating drug-like molecules remains a challenge but industry, after some false starts, is poised to make advances as compounds begin to hit proof-of-concept in man.
- This difficulty underscores the fundamental paradox of financing biotech discovery today: so much cash is required to assemble a platform that few investors will be willing to take such gambles anymore.

Back in the late 1980s and early 1990s, Jeff Conn, PhD, organized symposia to talk about metabotropic glutamate receptors, and nobody would show up. "It was a bit lonely, I guess. We'd be sitting in these large rooms and it would just be the speakers," he laughs.

Conn, then an investigator at **Emory University**, had one big problem: only a few people thought that metabotropic glutamate receptors even existed. Glutamate is the brain's primary excitatory neurotransmitter, a rather simple chemical that binds to ion channel receptors at the synapses where one neuron meets another and is responsible for sending fast excitatory signals along neural circuits. The hypothesized mGluRs, as they're abbreviated, were thought to be G-protein coupled receptors (GPCRs) that modulated this signaling process, independent and distinct from the then relatively well-characterized ion-channel glutamate receptors clustered in the synapse. Before the first gene encoding an mGluR subtype was isolated, there were few papers providing evidence of their existence.

"If glutamate was capable of also modulating cell excitability and transmission at the same synapses where it serves as a fast transmitter, that would have had tremendous impact in terms of novel therapeutics,"

says Conn, recalling the early debate. "There was only a handful of us that really did see it, that believed there were separate receptors coupled to secondary messenger systems," he says. Researchers like Ferdinando Nicoletti, PhD, now head of molecular neuropharmacology at the **University of Rome** and Darryle Schoepp, PhD, then a researcher at **Eli Lilly & Co.** and now SVP and franchise head of neuroscience at **Merck & Co. Inc.**, and a few others.

That debate is now over—these days when Conn and others talk about mGluR, people are listening. Conn's drug discovery program at **Vanderbilt University Medical Center**, where he has worked for six years with an assembled team of ex-pharma discovery stars after a three-year stint at Merck, is a hub of mGluR discovery work. The group has signed several drug discovery deals including a breakthrough \$10 million up front pharmaceutical-academic alliance with **Johnson & Johnson** to discover molecules that target mGluRs. (See "The J&J/ Vanderbilt Tie-Up: Accessing Innovation On The Cheap," *START-UP*, February 2009.) In the past few years these receptors that few thought existed have become some of the hottest drug targets in areas as diverse as psychiatry and neurology, gastro-intestinal disorders and pain. The receptors may play a role in both orphan diseases like Fragile X

Syndrome and in blockbuster-dominated conditions like GERD and schizophrenia.

But the eventual recognition of mGluRs' importance is only half the story. Targeting these receptors' so-called orthosteric binding site, where glutamate itself docked, proved exceptionally difficult for the same reasons the mGluRs were difficult to find in the first place. All the glutamate receptors looked alike. The glutamate binding site is highly conserved in all glutamate receptors, explains **Addex Pharmaceuticals Ltd.** CEO Vincent Mutel, PhD, himself a keen participant in elucidating mGluR pharmacology during his 15 years at **Roche**. "So with any molecule designed to hit the glutamate binding site you're targeting the ion channel receptor, the mGluRs, and also the various glutamate transport systems in the cells," he says. "Glutamate is a very simple molecule, and when nature finds a good solution it has a tendency to reapply that solution to many other problems—this is exactly the case for glutamate." It was nearly impossible to develop a selective molecule against any particular glutamate receptor by targeting the binding site—hit one, hit them all. "It was an idea that rapidly hit the wall. Going after the orthosteric site on mGluRs turned out to be a nightmare."

## THINKING ALLOSTERICALLY

Conn's skeptics began to come around when his lab and Carl Cotman, PhD's lab at **University of California, Irvine**, independently reported in 1991 the discovery of an mGluR selective ligand that would bind mGluRs but not other glutamate binders. By 1995 the case for mGluRs as important drug targets was gaining traction. But to find molecules that weren't binding to the same site as the endogenous receptor ligand, drug discovery outfits needed new ways of screening for drugs. The next breakthrough came in 1999, from a small San Diego biotech called **Sibia Neurosciences**.

Sibia had developed a functional screen for mGluR antagonists. They screened a tiny library, only one thousand compounds, says Conn. And out of that came two antagonists of a single mGluR subtype, mGluR5. "Any larger company probably would have discarded those compounds," says Conn. They didn't follow any of the rules of what people were looking for: primarily, they weren't competitive in a traditional binding assay where molecules that displaced a receptor's natural binder were selected for further interrogation and chemistry in the hopes of creating a drug. That work, done in collaboration

with partner **Novartis AG**, didn't result in a drug but created the first widely used tools in mGluR5 drug discovery.

Those compounds, chemicals abbreviated MTEP and MPEP, did not bind to the receptor's orthosteric site—the site of the natural ligand—but elsewhere. This so-called allosteric binding site was key to their selectivity. And because they bound mGluR5 elsewhere, they didn't inhibit glutamate binding at all. But they nevertheless dampened receptor signaling. (See *Exhibit 1.*) Other researchers including Mutel and colleagues at Roche reasoned that if you could develop allosteric antagonists then surely you could develop allosteric potentiators, molecules that bound to the same or other allosteric sites on the receptor and amplified the signal created by the binding of the endogenous ligand. The search for allosteric sites on mGluRs began in earnest, with a focus on receptor regions that were not thought essential for signaling purposes and therefore unlikely to be as highly conserved by nature. "In 2001 at Roche we reported the first positive allosteric modulator of these receptors," says Mutel; the Roche PAM modulated mGluR1. "Between Novartis' molecules and our molecule, all of pharma stopped targeting the glutamate site and trended toward allosteric modulators," he says.

Merck bought Sibia in 1999 for \$87 million to beef up its CNS discovery efforts and expanded its presence in mGluRs. Conn joined Merck in 2000 and started up a neuroscience effort at the Big Pharma's West Point facilities in North Wales, PA, adding a third site to what became Merck San Diego and an older neuroscience division in Harlow outside London in the UK. In 2002, Merck optioned a group of mGluR agonists from **Taisho Pharmaceutical Co. Ltd.** and the company's mGluR5 work continued apace. The drive toward allosteric modulation of mGluRs, enabled by better functional screening techniques—assays that measured an impact on receptor signaling instead of ligand displacement—would eventually spread beyond this receptor family. In 2009, argue drug hunters in academia, pharma, and biotech alike, allosteric modulation has changed the way industry discovers small molecule therapies against any number of receptors.

Most of this recent work on allosteric modulation has been done on GPCRs, which remain the most tractable of drug targets, and the subject of intense R&D efforts across industry. But of the nearly 850 GPCRs in the genome, fewer than 200 are currently "drugged," says Arthur

Christopoulos, PhD, a leader in receptor allosterism, professor of pharmacology, co-director of the drug discovery biology theme at **Monash University** in Melbourne, Australia, and a member of Addex's scientific advisory board. "In terms of targets, allosteric modulation could at least double the number of GPCRs we can hit, and that doesn't even take into account splice variants, different isoforms, receptor dimers, etc.—the permutations and combinations are essentially untapped," he says. Allosteric modulation didn't just open up previously undruggable targets, it meant companies could attack them using molecules that were not amenable to traditional drug discovery. "Besides the biological beauty of allosteric modulation, allosteric modulators really open up chemical space, big time," says Christopoulos. Sometimes reverting to finding an allosteric binder isn't necessary. And the endogenous binding site may have been a logical starting point, he says, because you have a structure to mimic to begin with: the natural ligand. But in terms of the sort of chemicals drug discoverers can use here, everyone is going after the same molecular characteristics and so the resulting drugs are all variations on the same theme.

What's more, with allosteric mechanisms you can study things that you just couldn't study before, says Schoepp, because these molecules aren't simple on/off switches on receptors. Instead they're more like dimmer switches, reliant only on the presence of the natural ligand to tune up or down. "And so the therapeutic possibilities are really profound relative to where we were before allosteric modulation. Turning possibilities into reality will be a challenge. But it's quite an exciting time to be a pharmacologist."

## A SLOW START

It may be exciting but it hasn't been a smooth ride. Allosteric modulation could untangle the logjam of intractable GPCR targets, with huge impact in a variety of diseases. But as it turned out, allosteric modulators were not easy to find—industry's discovery tools weren't geared for that. And when they were occasionally found they weren't particularly drug-like.

"At Roche we weren't successful," says Mutel, who left Roche and founded Addex in 2002, in part to set up a platform to pursue allosteric modulators (the company's original lead drug candidate was not an allosteric modulator, but Addex shifted gears toward allosterism in 2003). "Roche was aware of the potential but they weren't

prepared to invest systematically in making the screen work. At Addex we had to invent everything—to find out what makes an allosteric modulator an allosteric modulator—because the libraries, the screening systems, the chemical optimization, the mindsets of the chemists, everything was essentially wrong.”

Merck, too, decided to bail; the Big Pharma shut down the ex-Sibia site in San Diego in 2005 and discontinued its alliance with Taisho the same year, after it announced it was focusing its CNS efforts on neurodegenerative diseases (though the company is now back in the psychiatry space). But Merck’s decision—and open mindedness evidenced by a willingness to out-license—created a biotech opportunity. Randy Carpenter, MD, was at the time the CEO of tiny now-defunct Sention, a biotech that was investigating cognitive enhancers and had expanded into studying the role of mGluR5 in Fragile X Syndrome, an inherited form of mental disability and a primary cause of autism. The company had licensed IP from **Brown University** scientist Mark Bear, PhD (now at MIT), related to the phenomenon of long-term depression (LTD), a pruning of neuronal circuitry and the yin to the yang of long-term potentiation. Together these processes formed a pattern of strengthening and weakening neural connections intrinsic to brain development and learning and memory. Excessive LTD was at the center of the pathology of Fragile X, they hypothesized, and mGluR5 was at the center of LTD. As Merck closed its doors in San Diego, Sention took a license to Merck’s mGluR5 compounds.

“Merck’s compounds were the most interesting and advanced,” recalls Carpenter. “Thankfully rather than set them on the shelf or mothball them,” the company was willing to give Sention a chance to test the molecules in a significant unmet need. The deal was signed in early 2005; Sention got rights to develop the mGluR5 antagonists in Fragile X, Down Syndrome, and Huntington’s disease, and Merck hung on to rights in other, larger indications. But not long afterwards, Sention’s lead cognition compound—an amphetamine isomer Carpenter calls “*Viagra for the brain*”—was shown to raise blood pressure in its target elderly population. The VCs got spooked, and Sention was sold for parts. Bear took back his LTD IP and Merck’s mGluR5 allosteric modulators and set up a new shop, **Seaside Therapeutics Inc.** Carpenter was brought on to lead Seaside less than a year after Sention’s original Merck deal, and, after some hiccups in scale-up for clinical

development, the biotech hopes to start Phase I trials of its lead mGluR5 compound STX107 later this year.

Seaside isn’t the only company studying mGluR5 for this orphan disease. Novartis’ AFQ056, also an mGluR5 NAM, is in Phase II for Fragile X (though Carpenter and others had expected to see data earlier this year which never materialized; Novartis declined to comment for this article). And Roche—apparently back in the game—is about where Seaside is with their own mGluR5 program in Fragile X, says Carpenter. Seaside has also allied with Jeff Conn’s drug discovery program. In February 2008, Seaside said it would pay Vanderbilt \$4.5 million in guaranteed research funding over three years to develop mGluR5 allosteric modulators for Fragile X.

### INVENTING NEW TECHNIQUES

Vanderbilt is not working on Seaside’s later stage assets, but on entirely new chemical series. Despite advances made since those early days at Sibia, coming up with acceptable drug candidates remains a complex process, as the chemistry of al-

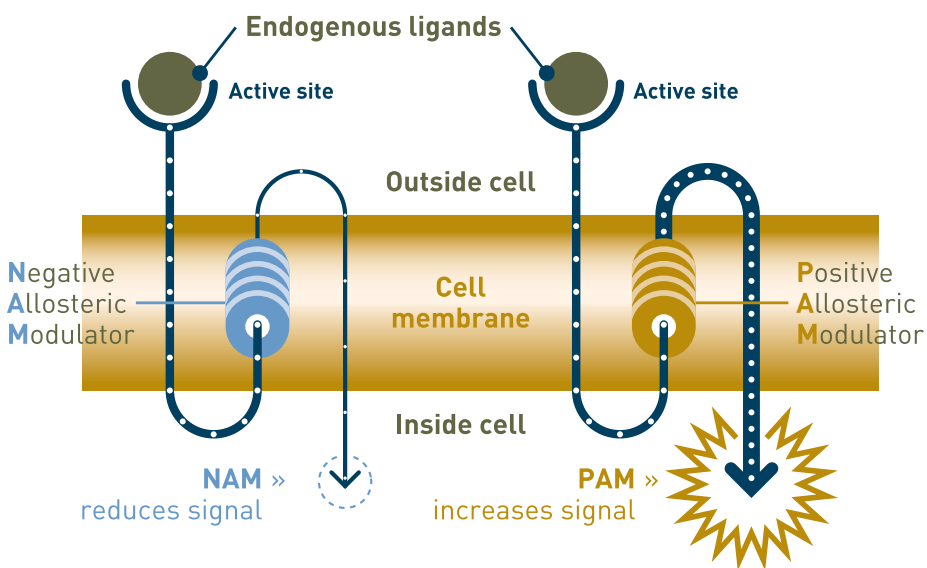
losteric modulation of GPCRs tends to be tricky in a variety of ways. Most obviously it is intrinsically difficult to equip a small molecule with the right set of seemingly disparate characteristics necessary to access an allosteric site in the first place. Neurotransmitter sites have evolved to include the right balance of water and protein interactions, but allosteric modulators tend to bind to sites in the greasy trans-membrane region of the receptor. “Getting molecules that have the right physical-chemical properties and hit the sweet spot between binding in these transmembrane regions with high affinity but actually being water soluble enough” to get there in the first place is tricky, says Merck’s Schoepp.

“A lot of the risk in this whole area is coming up with the right molecules. Some of the failure that will inevitably happen in a new area like this isn’t because it’s a bad idea,” he continues. “You can’t have it all—problems crop up along the way, developing a drug is very different from simply developing a pharmacologically active compound.” For instance, when al-

Exhibit 1

### Allosteric Modulation of GPCRs

Orthosteric agonists and antagonists (not shown here) compete for the same “active site” targeted by natural activators, called endogenous ligands.



Allosteric modulators bind, generally in the cell membrane, via a non-competitive mechanism that exerts its effects on signal transduction primarily after binding by the endogenous ligand at the active site.

SOURCE: Addex Pharmaceuticals

losteric modulators come out of cell-based screening and into *in vivo* studies, new problems can arise. The same reason that some allosteric ligands can be so selective—they're usually targeting poorly conserved regions on receptors—means that allosteric sites can also diverge between species. An allosteric affect may then get lost between a human and a rodent receptor, for example. There are ways around these problems, but they are complications that can make discovery more difficult or take

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longer. Mice can be humanized, a variety of species can be tried, or instead, says Christopoulos, "you can screen for rodent specific molecules in your library. Of course you're not trying to treat rats, but that at least will give you *in vivo* proof of concept for your target."

It may take longer—and may therefore be outside the scope of the patience of most biotech investors—but the opportunities to drug intractable targets with allosteric modulators are now self-evident. "I've yet to see a large pharmaceutical company that doesn't now have an allosteric program," he says. But smaller firms like Addex or even academic groups like Conn's can carve out competitive advantages based on their size, says Christopoulos. Biotechs can move quickly to optimize molecules because they don't have a lot of competing programs internally, they don't have that big company inertia, and they generally have better dialog between chemists and biologists, he says. It's not a simple process. "You need to optimize how well the molecule modulates, not just how well it binds. That means more than one parameter driving structure activity studies and a lot of people don't like that. But it keeps me employed," he says. Besides

his advisory role at Addex, Christopoulos has done contract work or consulted for most if not all of the world's dozen largest pharmaceutical companies.

### A DRIVING FORCE

About two years ago, Darryle Schoepp left Lilly and moved to Merck to run neuroscience research, now consolidated at West Point. Schoepp had been at Lilly for twenty years, holding a series of positions leading up to Lilly's head of neuroscience research. At Lilly—and as a speaker two decades ago at the same empty symposium as Conn—Schoepp helped to pioneer the science of mGluRs, and led efforts to develop the mGluR2/3 orthosteric agonist LY2140023. That promising candidate—one of the few orthosteric molecules targeting the mGluR family and a prodrug of another Lilly compound that looked effective in models but wasn't quite drug-like—has since failed a Phase II schizophrenia study, in March 2009. But oddly, the active comparator in the study, Lilly's olanzapine (*Zyprexa*), also failed to show improvement over placebo in the same trial thanks to a high placebo response, and LY2140023 remains in Phase II development. (See "Lilly's mGlu2/3 Agonist Fails in Phase II for Schizophrenia—But So Does Zyprexa," *The Pink Sheet DAILY*, March 30, 2009.) Lilly is currently recruiting patients for a long-term safety study of the drug candidate, designed to show an improved side effect profile versus *Zyprexa*, aripiprazole (*Abilify*) and risperidone (*Risperdol*).

Lilly's hints at success with its LY2140023 molecule have encouraged others to pursue positive allosteric modulators of mGluR2/3. **AstraZeneca PLC** has a schizophrenia program in the area, as does Johnson & Johnson, which is developing an mGluR2 PAM under the terms of a January 2005 deal with Addex. J&J's compound entered the clinic in June 2009, the first PAM to get tested in humans, though the company has not discussed the program publicly.

Despite the difficulties, "there is clearly a move toward allosteric modulation" within pharmaceutical labs, says AZ's Alan Cross, PhD, chief scientist in the company's neuroscience and pain areas. "It's new pharmacology, there are hurdles to making it work and it takes time to really understand how to run these discovery and development programs," he says. "But compounds are getting into man and the path is getting clearer."

As pharmaceutical companies embrace—or get reacquainted with—target-

ing mGluRs and the concept of allosteric modulation, Addex has benefitted from its early-mover advantage. Not long after Schoepp joined Merck the Big Pharma struck two deals with the Swiss biotech. First, in December 2007, the two companies inked a joint discovery and development deal around mGluR4 PAMs in Parkinson's disease. Merck paid Addex \$3 million up front and pays for the program; should a molecule make it to the clinic Merck takes over development from there. Addex has hung onto an EU co-promotion option and is eligible for milestone and royalty payments. A month later Merck in-licensed worldwide rights to develop and market Addex's preclinical mGluR5 PAM ADX63365, which had shown activity in schizophrenia, and some backup programs. Addex got \$22 million up front and advertised another \$455 million in potential milestones and royalties, and retained another EU commercialization option. It's likely Addex got an above-average price because the deal was competitive: later that same month **Pfizer Inc.** licensed a preclinical mGluR schizophrenia program from Taisho for very similar terms.

"Addex is a pretty small company but they've achieved what many larger companies have failed to do around mGlu receptors," says Schoepp. With allosteric modulation, "It's how you do the experiments, how you set them up and interpret them. It's a fairly new field of pharmacology and Vincent Mutel is one of the people who's spent the time and now understand the nuances," he says. It helped that Addex was able to assemble its library of allosteric modulators without facing the typical roadblocks put up by others' intellectual property, gaining access to others' proprietary chemistries inexpensively because few companies were interested in the sorts of molecules Mutel and company were after.

### HIDING IN PLAIN SIGHT

That isn't to say allosteric modulators didn't exist, for example, within pharmaceutical company libraries. But they were essentially phantoms. Old drugs like diazepam (*Valium*) and other benzodiazepines that act on GABA receptors (GABA is the brain's primary inhibitory neurotransmitter) were unknown allosteric modulators—not particularly selective ones.

There are other drugs recognized as allosterics after discovery. **Amgen Inc.**'s cinalcic (*Sensipar*) is an allosteric modulator of extracellular calcium sensing receptors, discovered by **NPS Pharmaceuticals Inc.**

and licensed to Amgen in 1995. “They had that molecule back before the receptor was even cloned. It was kind of a fluke” that it turned out to act allosterically, says Christopoulos. Nevertheless *Sensipar* has turned out to be a good seller—in 2008 the drug’s global revenue grew 29% to nearly \$600 million. Pfizer Inc.’s CCR5 chemokine receptor antagonist maraviroc (*Selzentry*) is a similar story. That HIV therapy is a so-called entry inhibitor, but it wasn’t known to act allosterically until late in the game.

But for the most part, the typical drug discovery process—searching for a molecule that would bind to an endogenous ligand’s binding site better than the endogenous ligand could—essentially blinded researchers to the existence of allosteric modulators. “Up until the mid-90s the predominant mode of screening was binding-based,” says Christopoulos. “You had a probe, labeled with something, and you’re biasing the screen toward something that disrupts the binding. But a lot of allosteric ligands won’t disrupt binding to appreciable levels even though they can disrupt function in a big way, either positively or negatively,” he says.

With newer functional assays that didn’t measure binding, “a whole different set of molecules started lighting up in the screens. Things that didn’t make sense,” says Christopoulos. In most cases it wasn’t quite the Eureka moment one might hope

for. “Because these were things that would never come out of a binding assay people would say that something was wrong, throw it out. They were picking up allosteric ligands and putting them in the ‘too hard’ basket.” Conn, a big proponent of the role of Big Pharma in drug discovery, nevertheless notes that the patience for complexity in the pharmaceutical world is at an all-time low, thanks to the familiar financial pressures and research and development setbacks many companies have endured over the past few years. “When something comes through that doesn’t fit with a preconceived notion it’s all too easy to just kill a program. The scientists in industry understand the complexity of allosteric modulators but they aren’t often given the opportunity to work through it,” he says.

Eventually, mGluR modulation efforts began to take root regardless of the difficulty; most big companies either persevered in-house or found the technology elsewhere. AstraZeneca began with a biotech alliance; it has a Phase I mGluR5 negative allosteric modulator (AZD2066) that came out of a six-year mGluR collaboration with NPS, says Cross, who notes AZ has focused its discovery program in the pain, psychiatry and GI areas. The pharma has some earlier-stage work in mGluR2, as well as some of the less well characterized mGluRs like 4, 7, and 8; it is also working to discover allosteric modulators of

other receptor families like neuropeptide receptors. In the GI space, says VP and head of cardiology and GI therapy area at AZ, Gunnar Olsson, PhD, AZ is testing its mGluR5 NAM in patients with GERD. That is unsurprising for a company with a \$6.3 billion GERD franchise to protect and expand; the company has several drugs in GERD trials, including its mGluR5 program and AZD3355, a GABA-B agonist. Hitting mGluR5 “inhibits the spontaneous relaxations that occur in the distal part of the esophagus itself, and inhibiting the relaxation reduces reflux in the first place,” explains Olsson. Adding on mGluR5 to PPI therapy with the company’s esomeprazole (*Nexium*) could bring relief to the 30-40% of patients who aren’t fully controlled with PPI therapy alone, he says.

Addex is also working in the GERD space, and its lead compound, ADX10059, may be the furthest along mGluR allosteric modulator in clinical development in any indication. (See *Exhibit 2*.) The candidate is an mGluR5 NAM in Phase IIb studies as both monotherapy and combination therapy; both studies are due to report out in the fourth quarter of 2009. (See “*Girding for new GERD Therapies*,” *IN VIVO*, January 2009.) Interestingly, both AZ’s and Addex’s molecules are also in development outside GERD. AZ is testing its GERD compound in neuropathic pain, says Cross, while Addex’s ’59 is in Phase IIb for migraine prophylaxis. ADX10059

Exhibit 2

### Most Advanced Allosteric Modulators Targeting mGluRs

DRUG CANDIDATE	RECEPTOR/MECHANISM	INDICATION/DEVELOPMENT STAGE	COMPANY
ADX10059	mGluR5 NAM	GERD monotherapy/Phase IIb GERD add-on to PPI/Phase IIb Migraine prophylaxis/Phase IIb	Addex Pharmaceuticals
AFQ056	mGluR5 NAM	Fragile X/Phase II Parkinson’s disease LID/Phase II Undisclosed/Phase II	Novartis
STX107	mGluR5 NAM	Fragile X/Phase I	Seaside Therapeutics
AZD2066	mGluR5 NAM	GERD/Phase I Neuropathic pain/Phase I	AstraZeneca
ADX71149	mGluR2 PAM	Schizophrenia/Phase I Anxiety/Phase I	Johnson & Johnson (from Addex)
ADX48621	mGluR5 NAM	Parkinson’s disease LID	Addex Pharmaceuticals
ADX63365	mGluR5 PAM	Schizophrenia/preclinical	Merck (from Addex)

SOURCE: Company Reports

could also be useful in Parkinson's disease, specifically levodopa-induced dyskinesia, says Mutel, based on the success Novartis has reported with AFQ056 in that indication. But Addex has instead elected to test another mGluR5 compound in that disease, ADX48621, which is in Phase I.

## BEYOND GLUTAMATE

Addex's development decisions for its mGluR5 NAMs are a balancing act between scientific rationale and practical considerations around partnering ('59 is currently on the block and Addex has said it won't itself do Phase III development of the drug in any indications). They also reflect the broader potential of mGluR modulators in a wide variety of disease areas (though so far only the Parkinson's indication, migraine and GERD have achieved POC in man) and the challenge of financing this kind of discovery platform within biotech.

But even as mGluR work has helped to uncover the potential of allosteric modulation, glutamate may soon be eclipsed by work on a variety of GPCR and non-GPCR targets. "There is a really big shift toward allosteric modulation and it has been remarkable to see just how big that shift has been," says Conn. "Most of the industry has really seen the potential." Research in targeting neuropeptide receptors, GABA-B, chemokine receptors, all have benefitted from work done in mGluRs, and not just because allosteric modulators can crack receptor selectivity problems. "Of all the biological advantages of allosteric ligands, the most obvious one is selectivity," says Christopoulos. "But there's also the mechanism itself. Many allosteric ligands will just sit there quiescent and wait for neurotransmission to occur naturally, and that's when they act to boost it or inhibit it. But traditional agonists or antagonists" are active all the time, he says.

Allosteric modulation won't be the answer for every drug discovery problem. But at least in GPCRs "we're at a place where there are many GPCRs that have been intractable to traditional drug discovery and there's a backlog," says Conn. So even if allosteric modulation introduces complexity, "it is a path forward for those targets that have otherwise been intractable," he says.

For Addex the primary challenge may no longer be scientific. The company has raised CHF264 million over three private rounds and a 2007 IPO, and as of the

end of 2008 had about CHF120 million in cash, or two to three years of cash burn—an envious position for a small biotech. Still, it must find a way to conserve its cash while at the same time building on its perceived competitive advantages before pharma catches up; that means moving quickly into new receptors and new therapeutic space, and finding a way to pay for it.

It seems hard to believe that Addex could, in 2009, start up to build out the infrastructure—the assays, the chemistry, the library—that it had to create between 2003 and 2005. Indeed, that Addex didn't start out to build an allosteric modulation platform—its original remit was to in-license and discover drugs to treat addiction, hence its name—suggests it may have been tricky even back then for a start-up to go out trying to create a new way to discover drugs. The biotech financing model of today would hardly support the from-scratch nature of a discovery enterprise where the apparatus itself was difficult to patent (surely Addex has technology IP but not the same kind as, say, an **Alnylam Pharmaceuticals Inc.**, and instead will benefit much more from composition-of-matter patents on drugs themselves).

Biotechs like Addex may be better at this disruptive innovation than Big Pharma, but paying for it is another matter. At its July R&D day the biotech announced it had created metabolic disease and inflammation business units and had programs in place to create allosteric modulators of hot targets like GLP-1 receptor, IL-1 receptor and TNF receptor. Its programs now comprise partial and full negative allosteric modulators, positive allosteric modulators, and allosteric agonists, across a wide variety of targets. mGluR4 alone may have a role in diabetes, pain, Parkinson's, depression, cognition, anxiety, epilepsy, inflammation and neuroprotection, to pick one receptor example where the company has been focused for several years. Out-licensing "is the only way we can maintain the value we've created," says Mutel.

A deal for '59—in any or all indications—would go a long way toward easing Addex's cash burn, and positive Phase IIb data later this year could be the trigger. But it's likely that whatever happens on that later-stage compound Addex will have to forge deals for earlier-stage assets. Mutel isn't concerned about waiting for the kind of value gained from

an IND-ready compound, for example. "Because this is a platform, we don't care too much about licensing out individual programs—there are plenty of interesting targets and each time we partner one we can recreate that value," he says. "If we have to partner early that doesn't matter too much. Our priority is to extend our cash resources to have more shots on goal. The ability to generate innovative, high value shots on goal—which have relatively little target-related risk—is what differentiates our platform. There will be revenue at the end," he says.

Twenty years after nobody wanted to hear about the existence of mGluRs, study of those receptors has led to discoveries that may—as Big Pharmas stumble over one another to tout their biologics pipelines and capabilities—turn the industry spotlight back on novel small molecule drug development. In the GLP-1 space, where the endogenous ligand's "tone" is so tightly regulated—GLP-1 levels increase immediately after eating but then ebb quickly—a small molecule positive allosteric modulator of that peptide receptor may not appear to gain much traction. "But now we're finding allosteric small molecules that can activate the damn thing," says Christopoulos. These allosteric agonists (Addex calls them ago-allosterics) shrug off the need for tone and might eventually muscle in on lucrative markets now dominated by expensive injectable peptides and biologics. In any case they're expanding the definition of what small molecules can do.

"We're only at the tip of the iceberg with allosterics. There is plenty of scope to identify new small molecule behaviors," predicts Christopoulos. "If you can't modulate it, activate it. Anything is possible."

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