

How Addex Pharmaceuticals secured two multi-million dollar deals with Merck

A biochemist by training, Vincent Mutel has a long history in drug development and a profound respect for scientists who can take a known concept and successfully execute it. Mr Mutel joined F. Hoffmann-La Roche in 1989, gained broad experience in drug development, and eventually became head of the pharmacology group in Roche's central nervous system diseases department.

For years he worked alongside the industry's most innovative scientists, learning how to discover and develop new drugs. However one day his manager turned to him, and in an ironic tone of voice, declared that henceforth the company would only be producing 'innovative me-too' drugs. For Mr Mutel, the comment had a double meaning.

On the one hand, it was a signal that Roche, like other big pharmaceutical companies at the time, would only support innovation that could promise a substantial return on the company's investment. On the other hand, it was an invitation to would-be entrepreneurs in the company to take up the discovery risk.

"How can you guarantee to your management that by being innovative you are going to make money? I understood portfolio management and I understood the strategic alignment of the company, but I was looking for something else, something different," Mr Mutel said in an interview.

In 2002, Mr Mutel and three other professionals got together in Geneva, Switzerland to found Addex Pharmaceuticals. The goal of the new company was to discover and develop novel compounds to treat addiction and other neuropsychiatric conditions. The other co-founders were François Conquet and Mark Epping-Jordan from GlaxoSmithKline and Timothy Dyer from PricewaterhouseCoopers. Mr Mutel is now Addex's chief executive officer.

The three pharmaceutical founders were all thoroughly versed in drug development and had witnessed first hand the difficulties that big pharma was having in designing new compounds that could work selectively against well-known pharmaceutical targets. They were particularly interested in something known as the G-protein-coupled receptors (GPCRs), a protein family that has been the target of many successful medicinal products.

The GPCRs posed an interesting problem because they were both very well studied but complex. Some of the industry's most experienced scientists were having difficulty

exploiting the target fully. Mr Mutel put this down to the fact that the family consisted of many subtypes and it was difficult, using the traditional methods of drug discovery, to design a molecule that would bind to some subtypes and not to others.

"Speaking for myself, I can tell you that I worked on many targets at Roche, particularly focusing on GPCRs and it was very frustrating because a lot of these targets were resisting our efforts. We were not able to get a satisfying molecule for them because they (the molecules) were lacking selectivity," he recalled.

When the four co-founders came together in 2002 therefore, they were determined to accomplish something

which had thus far eluded their colleagues at the large companies. This was to solve the problem of selectivity. "In other words, could we take these well-known targets, but approach them in a different way," Mr Mutel said.

From the start, the co-founders observed that the GPCR receptor family had a property which had been studied before, but which had not been used for industrial drug discovery. This was the property of 'allosteric' regulation.

The term 'allosteric' comes from the Greek word 'allo' meaning other. Allosteric regulation is the regulation of proteins, like enzymes and receptors, by a molecule which binds to the protein's allosteric site, which is to say, a site other than the protein's active site. The active

site is the primary site where receptors can be activated by the body's endogenous (natural) ligands. It is also the site that has been targeted by most drug makers.

Mr Mutel described the mechanism this way. "It had already been observed that these receptors were sitting in the membrane of the cell and were collecting information from the outside and transducing this information inside. A chemical messenger was coming from the outside, stimulating the system and leading to the production of another chemical messenger, but inside the cell.

"If you think intuitively about this, then you realise something has to happen on the protein structure; it has to be flexible. Information is generated somewhere which is translated all along the pathway and outside the membrane into another signal. Intuitively, there should be a lot of points of modulation.

"The basic question was, as is usual in this type of business, how can you industrialise the process. It is not

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Vincent Mutel

so much how can you identify the molecule once, but how can you guarantee that you can do it several times, and also make sure that your chemists can produce a drug,” the executive commented.

The founders of Addex set themselves the task of acquiring compounds from external providers that met their allosteric criteria. These compounds were all in the public domain and were identified by the company’s scientists using an undisclosed proprietary algorithm. They built up a library which now has about 50,000 compounds.

Mr Mutel said the compounds have been shown to modulate the response of the sub-types of the GPCR target like the ‘dimmer switch’ on a light.

“We are dealing here with targets that are big proteins. They are embedded in the membrane and they are flexible, which means that apart from the binding site of the molecule, which is the natural stimulant, there are a number of points in the protein structure which could be accessible to other molecules.

“You have a different number of binding sites for various GPCRs; it’s not conserved from one to the other. And interestingly because they have evolved without the pressure of selection, these sites are highly specific. So these binding sites are almost unique per sub-type,” he said.

Modulating the system

“We have demonstrated that we are able, with chemistry, to turn the light on or off. Because we know how to modulate the system well, we can design compounds that can either activate or block. I think the real capacity that Addex has today is this deep knowledge of how the system works,” he commented.

In 2002, the Addex scientists started their investigations by looking into addiction. The company licensed in a non allosteric D1 antagonist and developed this up to Phase 2a for smoking cessation. But the compound failed to show efficacy in 2007 and was dropped.

At the end of 2007, the company’s pipeline consisted of 11 products and/or discovery programmes, minus the smoking cessation product.

Its lead product, ADX10059, is an allosteric modulator and recently demonstrated clinically and statistically significant efficacy in separate Phase 2a trials for gastroesophageal reflux disease and migraine. The drug targets metabotropic glutamate receptor 5 (mGluR5) which is a sub-type of the mGluR family and belongs to the GPCRs.

Many start-up companies, with an emphasis on drug discovery, aim to take their compounds to a clinical proof-of-concept stage and then license them out to a large pharmaceutical company. Very few actually do deals with big companies at the preclinical stage. Addex is an exception.

On 3 December 2007, the company announced that it had reached an exclusive collaboration and licensing agreement with the Merck & Co affiliate, Merck Sharp & Dohme (MSD), to develop a new class of orally available drugs, initially as candidates to treat Parkinson’s disease, but later for other undisclosed indications.

The two companies will be discovering and developing allosteric modulators targeting the metabotropic glutamate receptor 4 (mGluR4).

Under the agreement, Addex is set to receive \$3 million

upfront as well as be eligible for up to \$106.5 million in research, development and regulatory milestones for the first product to be developed for multiple indications. Additional milestones of up to \$61 million could be paid if the companies develop a second and third product. Finally, Addex would receive royalties on any product sales.

Then, on 3 January 2008, the company signed an even bigger deal with Merck & Co, this time to investigate a candidate drug for the treatment of schizophrenia and other undisclosed indications. The exclusive licensing agreement is valued at up to \$702 million, including \$22 million upfront; \$455 million in research, development, regulatory and sales milestones for the first product developed for two indications, and \$225 million for a second product developed for two indications. In addition, Addex is eligible for royalties on sales and has an option to co-promote any new product in certain European countries.

The two companies will co-develop Addex’s ADX63365, an allosteric modulator that targets the mGluR5. “It is expected that ADX63365 will not only treat the positive symptoms of schizophrenia, such as hallucination and agitation, but may also decrease the cognitive impairment associated with schizophrenia,” Mr Mutel said.

Pioneering research by Merck

Why would Merck pay hundreds of millions of dollars to have access to two preclinical development programmes?

The answer, said Mr Mutel, is that Merck has been interested in the mGlu receptors for years and, in fact, pioneered research showing that mGluR4 activation could potentially treat Parkinson’s disease.

“If people are willing to invest so much, then it is clear that they understand the target and they see the potential value. Whatever the price they pay us, I think the reality is, they recognise the value of the target,” the executive said.

What Merck has apparently been unable to do thus far is to make drug-like molecules that activate mGluR4 in a specific fashion. “The fact is we were very advanced in our development and we were very knowledgeable in the field. I think this is what Merck has clearly indicated in the first deal that they made with us,” he added.

Mr Mutel describes Addex’s business strategy as essentially knowing what targets are of interest to big pharmaceutical companies and positioning the company accordingly. This means going for partnerships, even very early partnerships.

“This is in our genes. We know that sometimes it is better to partner a molecule, apparently too early for the financial markets, but before it is too late. This is because you are going to compromise the fate of the molecule if you partner too late. If you want to make a blockbuster you have to learn your strategy a long time in advance,” he said.

Vincent Mutel was interviewed by *MedNous* in London, UK on 5 February 2008.