

Addex Hitting New Targets with Allosteric Modulators

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Addex Pharmaceuticals has unveiled the prospect of oral drugs that directly target the tumor necrosis factor (TNF) inflammatory cascade.

The company outlined at its R&D day last week how it is extending its allosteric modulation platform to include new receptor targets, including Type I transmembrane proteins such as cytokine receptors.

TNF Receptor 1, which binds the pro-inflammatory cytokine TNF-alpha, falls into that category.

"No small molecules have been developed that target this type of receptor so far," CEO Vincent Mutel told attendees at the company's briefing.

Oral drugs in development for treating inflammatory conditions, such as rheumatoid arthritis, act on other targets, such as Syk kinase, Janus Kinase-3 (JAK3) and p38 kinase.

The Geneva-based company developed a proprietary assay – dubbed the "accessory protein relocalization assay" (APRA) – to find negative allosteric modulators of the TNF-RI receptor.

"We can replicate the pharmacology of the receptor using this assay," Robert Lütjens, head of core biology at the company, told *BioWorld International*.

High-throughput screening has already been completed, in fact. "We're in the hit validation process. Lead optimization will start in a couple of months," he said.

His group also is validating an APRA assay for identifying allosteric modulators of interleukin 1 receptor 1 (IL-1RI), which also has proved intractable to orthosteric small-molecule approaches, that is, two small molecules that bind competitively to the receptor's endogenous ligand-binding site rather than to the distal sites to which allosteric modulators bind.

Related assays are in development for two other undisclosed targets, in inflammation and metabolic disease.

Addex also extended its screening capabilities to all G-protein coupled receptor families, having majored in targeting certain GPCRs, most notably metabotropic glutamate receptor 5 (mGluR5), since its formation in 2002. As with its efforts in targeting Type I transmembrane proteins, in-house development of novel biological assays has enabled those efforts. "The GPCR assays that are commercially available from suppliers are not adequate for allosteric modulator discovery," Lütjens said.

The company has developed a cyclic adenosine monophosphate (cAMP) "biosensor," which responds instantly and dynamically to changes in the levels of the signal molecule.

It also developed the so-called ADX tags series 1 and ADX tags series 2 assays, which measure, respectively, activation-dependent association or dissociation of binding partners and conformational changes or multimerization changes that lead to an activation signal. They can be adapted to GPCR and to non-GPCR targets.

The company has employed those technologies to begin new programs based on finding negative allosteric modulators of Orexin, a GPCR associated with sleep disorders. Screening has been completed, and hits have been identified.

"We believe the molecules are going to offer a vast variety of pharmacophores for the industry, which is currently, as we understand, a necessity, and from the interest we have seen from several pharma [companies] that we are talking to, there is something here to be followed," Mutel said.

It also is targeting the Adenosine A2A receptor, a GPCR associated with inflammation. "The beauty of the A2A positive allosteric modulator approach obviously is we're able to target areas where adenosine levels are increased – namely certain inflammation sites," Lütjens said.

The approach does not carry the risk of cardiovascular effects seen with A2A receptor agonists.

The company has begun programs targeting the gastric inhibitor polypeptide (GIP) receptor and glucagon-like peptide (GLP) receptor, neither of which has been tractable to small-molecule approaches before.

Addex already has five programs in the clinic, and several more in full preclinical development.

Its lead drug candidate, ADX10059, a negative allosteric modulator of mGluR5, is undergoing Phase IIb studies in patients with gastroesophageal reflux disease. Those are due to report late this year or early next year.

The company is seeking partners to take at least some of its new projects forward.

"It's clear that we're discussing most if not all of the projects in the pipeline," said Chris Maggos, head of investor relations, although it "will not sell everything," he added. ■