

Product Development

Modifying Parkinson's

By **Stephen Hansen**
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Most drugs for Parkinson's disease target dopamine, which provides short-term, palliative treatment but is accompanied by neurological side effects and eventually loses efficacy as patients develop tolerance. Addex Pharmaceuticals S.A. believes its allosteric modulators of metabotropic glutamate receptor subtype 4, which act independently of dopaminergic neurons, may provide physicians with a disease-modifying therapeutic option.

Last week, Merck & Co. Inc. (MRK, Whitehouse Station, N.J.) in-licensed Addex's preclinical positive allosteric modulators of mGluR4 to treat PD and other undisclosed indications. The deal gives Addex (SWX:ADXN, Geneva, Switzerland) \$3 million up front, up to \$167.5 million in milestones, royalties and the opportunity to establish a sales force.

Dopamine functions at the top of the basal ganglia motor circuit, which is composed of two pathways — direct and indirect — that regulate signaling to the thalamus by two parts of the basal ganglia system: the substantia nigra pars reticulata (SNr), and the internal globus pallidus (GPi). The SNr is a mass of neurons in the ventral region of the substantia nigra, while the GPi is a group of neurons in the medial segment of the dorsal pallidum, both of which target the thalamus via GABA signaling.

Because the direct pathway exerts an inhibitory effect on SNr/GPi signaling, while the indirect pathway exerts an excitatory effect, both must operate in balance for the thalamus to function properly, in turn allowing normal motor function.

In PD, dopaminergic neurons begin to die off for reasons unknown, causing a depletion of dopamine in the basal ganglia. This dopamine deficiency leads to an imbalance between the direct and indirect pathways. In the direct pathway, decreased dopamine leads to decreased inhibition of SNr/GPi signaling. In the indirect pathway, it causes an excess release of glutamate, resulting in increased excitation of the SNr/GPi. The effect of this imbalance is the improper motor function seen in PD.

While most therapeutics attempt to restore balance to the system by increasing the amount of dopamine at the top of the circuit, ADXN's mGluR4 modulators decrease glutamate release in the indirect pathway to reduce excitatory signals, effectively matching the reduced inhibition of SNr/GPi signaling in the direct pathway.

According to CSO Mark Epping-Jordan, the belief is that this rebalanced signaling will restore proper motor circuit function.

Since mGluR4 modulators do not result in dopaminergic stimulation, the company hopes that patients would be spared

the neurological side effects associated with dopamine-related therapies, such as the dyskinesia caused by levodopa. Avoiding dopaminergic stimulation also should sidestep problems with tolerance to long-term dopamine-related treatment.

CEO Vincent Mutel said ADXN decided to partner the compounds with MRK for a number of reasons, including that PD requires expensive long-term trials in a large number of patients. In addition, he noted MRK has conducted extensive research into the role of mGluR4 in PD. It also has MK-0657, an undisclosed compound, in Phase I development for PD.

The partners will collaborate on preclinical development, and MRK will be responsible for clinical development. ADXN did not disclose a timeline for when the lead mGluR4 compound would enter the clinic.

The deal also allows ADXN to establish a sales force, as the company has the option to co-promote the mGluR4 modulators in undisclosed European countries.

Mutel said ADXN's strategy is to partner early for large, complicated indications, such as PD or generalized anxiety disorder (GAD), and to wait for

Phase II data in indications where development is less time-consuming and expensive, such as gastroesophageal reflux disease (GERD) or migraine prevention.

ADXN is looking to take compounds with smaller, more manageable indications through to the market itself. One example is ADX71441, a preclinical positive allosteric modulator of GABA B receptor that the company expects to develop itself for spasticity. ADXN may choose to out-license the compound for other indications such as GERD and anxiety.

ADXN's lead compound is ADX10059, a negative allosteric modulator of mGluR5 that is in Phase IIa testing for acute anxiety and is expected to start Phase IIb trials in GERD and migraine in mid-2008. It expects to partner the compound following Phase IIb data.

The company expects to partner three other compounds early due to their large or complicated indications: ADX48621, a negative allosteric modulator of mGluR5 in Phase I for depression and GAD; ADX63365, a positive allosteric modulator of mGluR5 that is expected to start a Phase I trial next year in schizophrenia and cognitive impairment; and ADX68693, a negative allosteric modulator of follicle stimulating hormone (FSH) receptor that is in preclinical testing for osteoporosis and contraception.

ADXN also has positive allosteric modulators of mGluR2 in preclinical development with partner Johnson & Johnson (JNJ, New Brunswick, N.J.).



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