TREK-ing after a new antidepressant

By Lauren Martz, Staff Writer

French researchers have developed a peptide inhibitor of TREK-1 that they think produces antidepressant effects much faster than marketed selective serotonin reuptake inhibitors.¹ **NeuroSearch A/S** is now considering moving into lead optimization with an internal effort to identify small molecule TREK-1 inhibitors.

Approved selective serotonin reuptake inhibitors (SSRIs) typically have a four- to six-week wash-in period, during which the drug shows minimal efficacy. In addition, the drugs only work in 40–50% of patients and can elicit resistance over time.²

“Treatments based on a completely different target than the monoaminergic uptake systems might be able to provide immediate antidepressant effect without the lag time,” said Palle Christophersen, VP and director of *in vitro* pharmacology at NeuroSearch. “Additionally, there is a sizeable proportion of depressed people [who] cannot be treated successfully with available medications. A new type of compound might be able to offer relief for that population.”

Previous studies have provided genetic evidence for an association between depression and potassium channel, subfamily K, member 2 (KCNK2; TREK-1). Mice with the *Trek-1* gene knocked out were significantly less likely to develop depression than were wild-type controls.³

Also, four genetic variations in *TREK-1* associated with resistance to multiple antidepressants were identified in the Sequenced Treatment Alternatives to Relieve Depression (Star*D) clinical trial. The study of 20 approved antidepressants, which was funded by the NIH's National Institute of Mental Health (NIMH), helped confirm the association between TREK-1 activity and depression and suggested that genetic variants might help determine risks of antidepressant resistance.⁴

Now, a paper published in *PLoS Biology* has taken the work on TREK-1 a step further. A team led by Centre National de la Recherche Scientifique (CNRS) researchers at the **University of Nice Sophia Antipolis** validated the antidepressant effects of TREK-1 inhibition and identified a peptide, based on an endogenous one, that antagonizes the channel.

The team includes researchers from CNRS at **University of Lyon, University of Montreal, University of Victor Segalen Bordeaux 2** and **McGill University**.

The team showed that sortilin 1 (SORT1; NTR3), a neurotensin-binding protein, bound and inhibited TREK-1. SORT1 is initially synthesized as a precursor protein and is cleaved to become active and release a 44-amino-acid peptide.

The researchers combined part of the cleaved peptide with extra amino acids for stabilization and showed that the resulting peptide, dubbed spadin, was more effective at inhibiting TREK-1 activity than was the SORT1 precursor protein.

In several neuronal cell types and in brain slices, spadin bound and blocked TREK-1 activity comparably to the SSRI fluoxetine, which is commonly used to treat depression.

Eli Lilly and Co. markets Prozac fluoxetine for depression, bipolar disorder, premenstrual syndrome (PMS) and cachexia.

In five different mouse models of depression, spadin prevented depressed behavior better than saline control did. The peptide's effects were comparable to those seen upon deletion of the *Trek-1* gene in mice or upon treatment of wild-type mice with fluoxetine.

Notably, spadin reduced signs of depression and increased markers of antidepressant action after only four days, whereas four days of fluoxetine had no effect. That finding suggested spadin or other TREK-1 inhibitors might have a faster onset of action than SSRIs.

The researchers obtained similar results in one rat model of depression.

According to Marc Borsotto, a CNRS researcher at the University of Nice Sophia Antipolis and co-principal investigator on the paper, the kinetics of spadin action are faster

than those of other antidepressants, as it acts in 3–4 days instead of 15–21.

Catherine Heurteaux and Jean Mazella, both CNRS researchers at the University of Nice Sophia Antipolis, were also co-principal investigators on the paper.

“Inhibiting this particular target appears to act faster than SSRIs in animals. If this translates over to humans, it could be a strong driver for going forward with the target,” said Christophersen.

Forming a formulation

Borsotto told *SciBX* a key next step is developing a slow-release formulation that dispenses spadin peptide into circulation at a constant rate.

That work is being carried out under a collaborative research contract between the University of Nice and drug delivery company **MedinCell S.A.**

In parallel with the formulation work, Borsotto said the next steps also include safety studies on whether the compound has effects in cardiac, liver and kidney tissues.

Those studies are important, said Christophersen, because the receptor is expressed in peripheral organs. As a result, he said, “you can't exclude the possible long-term side effects. Long-term safety studies do still need to be performed. The side effects of TREK-1

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blockade are not definitely known, but at first sight they appear to be pretty benign.”

Christophersen told *SciBX* that NeuroSearch has an identification program for small molecule TREK-1 inhibitors and that the company is strongly considering going into lead optimization.

Borsotto told *SciBX* that the peptide and its use in treating psychiatric disorders have been patented by the CNRS at the University of Nice Sophia Antipolis and that the IP is available for licensing.

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