Inversago Pharma
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The peripheral CB1 blockade: a novel therapeutic avenue to address key metabolic conditions

Montreal-based Inversago Pharma is developing a portfolio of peripherally-acting cannabinoid receptor-1 (CB1) inverse agonists, including its lead candidate INV-101, in development for the treatment of the rare genetic disorder Prader-Willi syndrome (PWS), NASH and other conditions.

Inversago Pharma, based in Montreal, Canada, is working on safer generations of peripherally-acting cannabinoid receptor-1 (CB1) inverse agonists, based on research carried out by George Kunos, Scientific Director of the National Institute on Alcohol Abuse and Alcoholism. The company's ambition is to create blockbuster treatments for a range of metabolic disorders that exploit the clinically-proven biology of CB1, but that aim to avoid the central nervous system toxicity seen with the first generation of centrally-acting drugs.

Following the discovery of CB1 in the brain in the 1980s, many large pharma companies began development of first-generation centrally-acting CB1 antagonists and inverse agonists in the early 2000s. This culminated in the approval of Sanofi's Acomplia (rimonabant) in 2006 for the treatment of obesity, and the large number of clinical trials in non-alcoholic steatohepatitis (NASH), pre-diabetes, type 2 diabetes, and other metabolic diseases. However, the area came crashing down in 2008, when Acomplia was pulled from the market because of its potential to produce severe psychiatric adverse events in some patients, including anxiety, severe depression and suicidal ideation. Albeit rare, this liability had all centrally-acting CB1 development programs halted, and it seemed like the field had nowhere else to go.

This wasn't the end of the CB1 story, however, after more than a decade of work, researchers discovered that peripheral CB1 receptors play a vital role in the wide range of clinical benefits seen with the first-generation drugs. They found that fat, gastrointestinal, liver, pancreatic, muscle, and lung cells all have CB1 receptors, it's the blockade of these that is believed to be responsible for the therapeutic potential of CB1-targeting agents, first and new generations alike.

A new focus: Prader-Willi syndrome

INV-101, Inversago's lead peripherally-acting CB1 inverse agonist, is currently in clinical development for the treatment of the rare genetic disorder Prader-Willi syndrome (PWS) and NASH, while multiple inhibitors are undergoing preclinical work for type 1 diabetes and diabetic nephropathy.

As well as living with a range of cognitive, emotional and motor development delays, people with PWS have an over-activated endocannabinoid system, and their constant hunger, lower energy expenditure and slow metabolism lead to life-threatening obesity and metabolic disorders. There is currently no approved treatment for PWS.

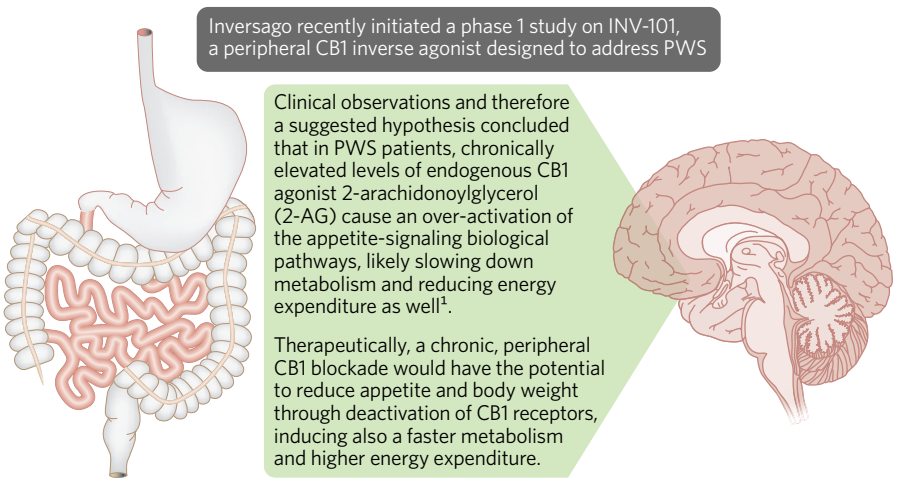

Fig. 1 | Signaling to the brain from the periphery[1]. CB1, cannabinoid receptor-1; PWS, Prader-Willi syndrome.

Signaling to the brain from the periphery

CB1 inverse agonists have been shown to reduce appetite, and induce weight loss by several mechanisms, including increasing energy expenditure and a more rapid metabolism (Fig. 1). Studies with rimonabant in adults with PWS suggested an efficacy comparable to the general obese population. The findings in rimonabant provide proof of concept for a CB1-based approach in PWS, and as Inversago's inverse agonists should not cross the blood–brain barrier, François Ravenelle, CEO and founder, hopes for a significantly improved safety profile, with positive signs of efficacy in the clinic.

"The appetite center in the brain gets its signals from the peripheral nerves—we believe that a peripheral CB1 blockade will induce these endogenous signaling pathways and provide weight loss and hyperphagia reduction," said Ravenelle.

INV-101, which is a small molecule so can be dosed orally, is currently in phase 1 studies.

NASH: A steadily growing metabolic condition with poor therapeutic options

NASH is the most severe form of non-alcoholic fatty liver disease (NAFLD), and has close links with obesity, pre-diabetes, and diabetes. It increases the risk of cardiovascular disease, cirrhosis, liver failure and liver cancer, and its prevalence is increasing worldwide. Data from first-generation CB1 blockers in NASH showed potential in reducing levels of fat in the liver, slowing and even reversing liver fibrosis, and managing insulin and leptin resistance as well as inducing significant weight loss. Inversago is planning a phase 2 trial in NASH with INV-101 in 2022.

Gearing up for milestones

Inversago completed a $35 million Series B funding earlier in 2020, based on the company's preclinical safety data. The money from this second round of funding in two years will fund clinical development of the two lead products, INV-101 and INV-202.

"We expect to gain significance by proving the peripheral CB1 concept through clinical trials in PWS and NASH, and then expand our CB1 franchise to other metabolic indications. This would provide physicians with new options to treat metabolic disorders with effective oral drugs and improve outcomes for patients. Our aim is to build a company that can exploit the full therapeutic potential of a peripheral CB1 blockade, moving projects through late-stage clinical trials," concluded Ravenelle.

1. Knani, I. et al. *Mol. Met.* **5**, 1187–1199(2016).

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