Gabather AB
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Gabather

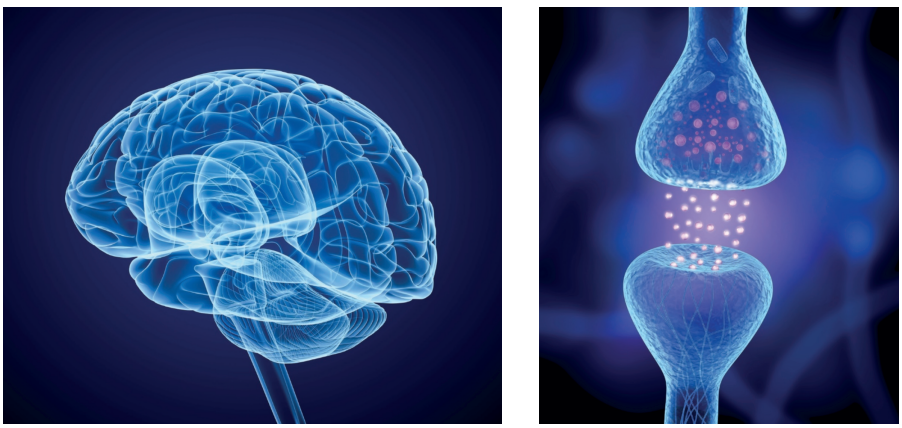
Exploring innovative strategies to restore the balance of excitation and inhibition in the brain

Guided from the start by data from in vivo models, Gabather is discovering new ways to manipulate the neurotransmitter γ-aminobutyric acid (GABA) to more effectively treat patients with psychiatric and neurological disorders, without producing sedative side effects.

Hundreds of millions of people worldwide continue to suffer from psychiatric illness, even though treatments for various mental health conditions have been available for decades. There is a huge unmet need for medications that are more effective and have fewer side effects. One promising target is the brain's main inhibitory signaling chemical, known as γ-aminobutyric acid (GABA). As such, this neurotransmitter plays a crucial role in establishing the balance of excitation and inhibition in the brain. Any disruption in this balance can have a major impact on brain functions such as learning, memory and sleep. This neurotransmitter also plays an important role in a variety of psychiatric and neurological conditions.

Gabather's mission is to introduce novel treatments for psychiatric diseases by developing a pipeline of drug candidates that target $GABA_A$ receptors with greater accuracy and fewer side effects. The Swedish biotech company was founded in 2014 based on a decade of research at Lund University and the University of Copenhagen. Gabather takes a unique approach to identifying promising drug candidates. Instead of starting with a particular indication in mind, Gabather scientists are guided toward potential indications by data from animal models.

"In a world where it can take 12 years and cost $2.6 billion to bring a drug to market, with a clinical success rate of less than 12% for drugs entering clinical development, evaluating in vivo data from the very beginning could help us avoid false leads, streamline the drug development process and increase the chances of success," said Gabather's CEO, Michael-Robin Witt. "We are optimistic that our unique, cost-efficient drug development plan will set the stage for early proof-of-concept studies and positive outcomes in patients."



In the brain (left) Gabather's therapeutic GT-002 targets $GABA_A$ receptors—ligand-gated ion channels present at inhibitory synapses (right).

One target, multiple indications

Leveraging this innovative strategy, the company is developing its lead candidate GT-002 for the treatment of cognitive deficits, which are present in most psychiatric and neurological disorders. The compound is a highly potent and selective stimulator of the $GABA_A$ receptor—the most abundant GABA receptor. It has a unique mechanism of action that minimizes the risk of sedation and convulsive side effects. Studies using in vivo models have shown that GT-002 has antidepressant effects and improves memory, without producing cardiovascular side effects.

Results from a randomized, double-blind, placebo-controlled phase 1a study completed in April 2020 showed that single ascending doses of GT-002 in healthy adults were safe and well tolerated, with promising pharmacokinetic properties and no drug-related adverse events. GT-002 is efficiently absorbed from the intestine into the blood, and plasma levels at the highest dose are several times higher than the estimated effective dose for therapeutic effect in humans at repeated dosing. No adverse effects on blood count, blood chemistry, or on any organ system were observed in any of the subjects. A key differentiator is that GT-002 had no sedative effect, unlike barbiturates, benzodiazepines, non-benzodiazepine Z drugs and other $GABA_A$ receptor modulators on the market.

Building on these positive results, Gabather is now conducting a double-blind and placebo-controlled phase 1 multiple ascending dose study on 16 healthy individuals who will be treated with two dose levels of GT-002 for 7 days, with a follow-up period of 30 days. The objective is to evaluate the drug candidate's pharmacokinetics, safety and tolerability. Preliminary results are expected by the end of the year. A parallel target-engagement study will be conducted to monitor electroencephalography (EEG) and functional MRI (fMRI) signals, and the data acquired will guide the design of future clinical trials in patients.

Portfolio and partnerships

Gabather is conducting in vitro and in vivo experiments on its entire GABA-centered pipeline, including candidates GT-001 to GT-006. The molecules are designed using a proprietary pharmacophore model, and none have sedative side effects.

"Since there are several areas of unmet need as well as many medicines going off-patent, it is an opportune moment to develop new drugs targeting the central nervous system," Witt said. "Our drug candidates show promising development and are patented in several markets."

Gabather's patent portfolio includes quinolone derivatives and triazoloquinazolines such as GT-002—drug candidates in the form of small molecules that interact with the $GABA_A$ receptor complex. Patents have been approved in the USA, China, Canada and Europe, many countries that represent the largest part of the global market.

Currently, Gabather is considering licensing deals for GT-002 as it progresses toward a proof-of-concept study in patients, in addition to joint ventures, development partnerships and other forms of cooperation that have the benefit of shared risks and costs. "Through these collaborations, we look forward to bringing to market next-generation $GABA_A$ stimulators that have tremendous potential for addressing a serious unmet need for millions of patients who suffer from mental illness," concluded Witt.

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