Gilgamesh Pharmaceuticals
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GILGAMESH

A new era for the treatment of psychiatric disorders

Gilgamesh Pharmaceuticals is developing a diverse portfolio of novel, potentially first-in-class and best-in-class medicines targeting mechanisms with demonstrated profound efficacy (onset duration and/or prolonged treatment duration) in humans for the treatment of mental health disorders.

The therapeutic value of highly psychedelic agents in treating a range of psychiatric conditions is becoming increasingly recognized, both in clinical medicine and in the broader culture. Gilgamesh Pharmaceuticals, a central nervous system (CNS)-focused biotech, is positioned at the forefront of an emerging revolution in the treatment of psychiatric disorders, with a pipeline of novel agents that retain or improve on the therapeutic effects of prototypical psychoactive substances, while enhancing their safety and efficacy profile. The development of its innovative and differentiated portfolio is guided by its suite of cutting-edge platform technologies to inform compound selection and optimization.

The most well-established psychedelic drugs for therapeutic purposes include the hallucinogens psilocybin and lysergic acid diethylamide (LSD), the dissociative anesthetic ketamine, and the empathogen 3,4-methylenedioxymethamphetamine (MDMA), all of which have demonstrated rapid onset and/or enduring efficacy. Esketamine, the S isomer of ketamine, has already gained approval for treatment-resistant depression under the trademark Spravato; psilocybin and ketamine have been shown to provide benefits to patients with treatment-resistant depression; and MDMA has demonstrated efficacy in post-traumatic stress disorder.

However, these prototype agents have drawbacks including: profound hallucinogenic or dissociative effects that make them risky for unsupervised use, an inconveniently long duration of action, and in some cases, low oral bioavailability or cardiac risks. Gilgamesh's pipeline of novel molecules is being developed to overcome these limitations and address the enormous unmet medical need presented by psychiatric disorders.

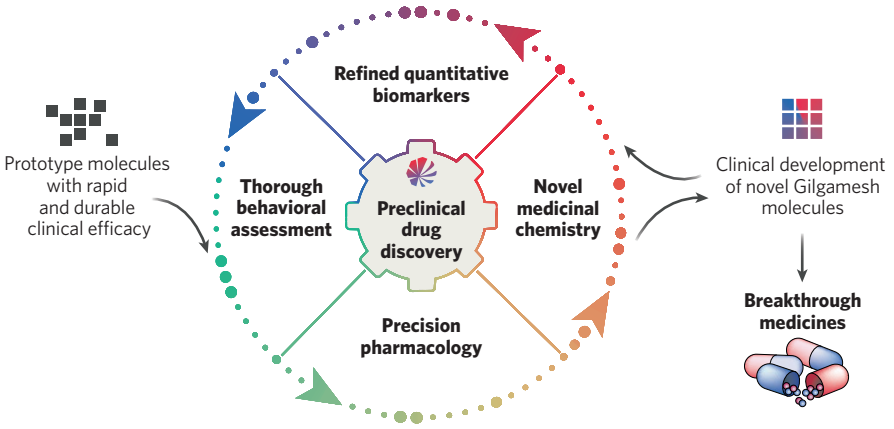

Fig. 1 | Driving the revolution in psychiatric medicine. Gilgamesh has developed a state-of-the-art preclinical platform for characterizing existing molecules and integrating these findings into the development of novel, differentiated psychiatric therapies, creating a drug discovery cycle that couples reverse- and forward-translation expertise. The platform includes high-resolution electrophysiology, disease-relevant models, and unbiased behavioral assessment of entities developed through Gilgamesh's medicinal chemistry expertise.

Active portfolio of programs

Gilgamesh's current portfolio includes four programs with composition of matter intellectual property (IP) coverage. GM-1020 is a small-molecule orally active antagonist of the *N*-methyl-D-aspartate (NMDA) receptor that is under development for depression and other indications. Preclinical studies demonstrate that GM-1020 retains the rapid and robust efficacy of ketamine while avoiding first-pass metabolism, which allows for convenient oral administration and attenuated dissociative side effects relative to those of ketamine and esketamine at therapeutic dosages. Together, these properties may make GM-1020 suitable for at home use, reducing the burden of treatment and increasing compliance. GM-1020 is expected to enter clinical trials before the end of 2022.

Two of Gilgamesh's advanced programs target the 5-HT_{2A} receptor, which is the primary target of classic psychedelics. GM-2505 is a short-acting 5-HT_{2A} receptor agonist/5-HT releaser that is being developed for the treatment of depression and anxiety, and the augmentation of psychotherapy. Like classic psychedelics, GM-2505 produces dramatic changes in perception, emotion, and cognition; however, these effects have a much shorter duration than those of psilocybin, resulting in patients spending less time in therapist-supervised office visits. GM-2505 will enter clinical trials later this year.

A related program, GM-200X, is assessing non-hallucinogenic 5-HT_{2A} receptor agonists for the treatment of depression and anxiety. Preclinical evidence suggests that these compounds lack the hallucinogenic effects of classic psychedelics while retaining their therapeutic benefits, making them safer, suitable for home administration, and free of the potential for misuse associated with classic psychedelics. Due to the expected safety profile, the GM-200X molecules may deliver a long-term or subchronic maintenance therapy in addition to the expected acute efficacy. Gilgamesh expects to nominate a clinical candidate from the GM-200X program this year.

The final advanced program, GM-300X, is focused on novel analogs of ibogaine, which is a naturally occurring, plant-derived atypical psychoactive compound that has shown anecdotal promise in the treatment of substance abuse. Ibogaine has been reported to dramatically reduce cravings for opiates for a period of months after a single administration; however, it has also been linked to QT prolongation and increased risks of cardiac arrhythmia. The GM-300X series of molecules—which target the κ-opioid receptor (KOR) among others but appear to lack ibogaine's adverse cardiac effects—are being developed to help combat the epidemic of substance-use disorders. Lead optimization of GM-300X molecules is currently underway, with candidate nomination expected this year.

The assets in Gilgamesh's pipeline have the shared properties of clinically validated mechanisms of action, rapid onset of effect, and durable therapeutic benefit that persists beyond the pharmacokinetic half-life of the drug, likely via the rapid enhancement of neuroplasticity, which promotes lasting restoration of circuit and synaptic function.

Gilgamesh is also running several early-stage discovery projects to fuel its pipeline over the coming years. Integral to these efforts, Gilgamesh is placing emphasis on quantitative physiological measures to understand target modulation and develop a thorough understanding of the relationship between pharmacokinetics and pharmacodynamics for its molecules. Gilgamesh uses a platform of cutting-edge preclinical technologies (Fig. 1) to guide compound selection, including machine-learning analysis of animal behavior and high-resolution electrophysiology, through collaborations with leading academic laboratories.

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