Orthogon Therapeutics, LLC
orthogontherapeutics.com

ORTHOGON THERAPEUTICS

Designing anti-infectives through atomic insights

Orthogon Therapeutics is developing first-in-class anti-infective small molecule drugs using biophysics- and structure-based drug design to optimize compounds that target difficult-to-drug proteins. The company's initial focus is on treating BK and JC polyomavirus infections in transplant patients.

Orthogon Therapeutics, a privately held research and development (R&D) company, uses principles of biophysics and structure-based drug design to develop anti-infective small molecules that selectively bind and neutralize key target proteins at intermolecular contact hotspots with other proteins, DNA or RNA. Orthogon is part of the Pledge Therapeutics family of companies, an enterprise built around a discovery engine and focused on tackling some of the most elusive targets in drug discovery today.

To identify drug candidates with novel mechanisms of action, Orthogon uses a proprietary, iterative drug discovery platform. First, a target protein is screened in its functional conformation using small organic compounds and X-ray crystallography to visualize drug-protein interaction sites. Next, the kinetic and thermodynamic parameters provided by this 'molecular fingerprint' of the binding site(s) power the machine learning–based in silico design and optimization of lead molecules using medicinal chemistry principles. Finally, binding site coordinates and biophysical properties of these lead compounds are experimentally determined and re-incorporated into the in silico design step. This iterative process of integrating and optimizing biophysical and structural parameters drives the design of pharmacologically unique lead compounds typically not found in commercial libraries.

Using this discovery platform, Orthogon has developed first-in-class lead compounds that simultaneously target both BK and JC viruses (Fig. 1), two human polyomaviruses that cause substantial morbidity and mortality in immune-compromised patients, especially in transplant recipients, and represent a large unmet medical need.

"By implementing a discovery engine that uses the highest quality structure and activity data inputs to drive an iterative optimization process, we are exploring opportunities with novel, previously deemed to be difficult-to-drug, targets that will alter the treatment paradigm for a number of unaddressed life-threatening infectious diseases," said Ali Munawar, CEO of Orthogon.

In addition to its two polyomavirus lead compounds, Orthogon has the first ever Glycyl tRNA synthetase–targeting small molecule in preclinical development to treat *Enterobacteriaceae* and *Klebsiella* infections. A novel broad spectrum SARS-CoV-2 spike protein–targeting antibody, also in preclinical development, has promising potent neutralizing activity against the SARS-CoV and SARS-CoV-2 viruses and the Omicron BA.2 variant and is expected to be refractory to resistance in future variants.

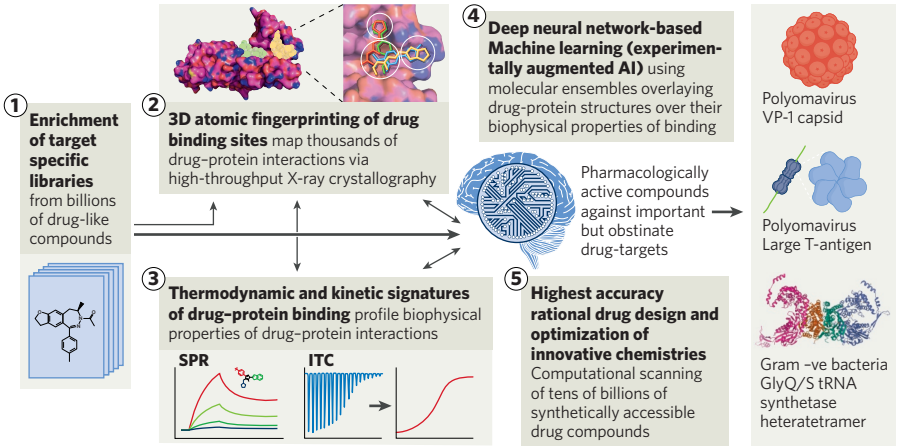

Fig. 1 | Using molecular fingerprinting to design novel anti-infectives. Orthogon's drug discovery platform designs anti-infective small molecules that selectively bind and neutralize key target proteins at hotspots.

Tackling the polyomavirus challenge

A leading cause of severe and often fatal clinical complications in immunocompromised patients is reactivation of the pervasive BK and JC polyomaviruses. Latent infection with these viruses is prevalent in 70–90% of the population, and reactivation leads to nephropathy and kidney complications in the case of the BK virus, and to progressive multifocal leukoencephalopathy (PML) in the case of the neuro-tropic JC virus. Development of small molecule drugs has been challenging due to the absence of conventional antiviral drug targets and a lack of polyomavirus-specific drug development tools and techniques.

Orthogon has used its drug discovery platform to characterize the two main proteins encoded by the small polyomavirus genome—the polyomavirus capsid protein (PyVP1) and the large tumor antigen (LTag) helicase—and to identify new ways to successfully target them.

Orthogon's lead compound is a PyVP1-targeting small molecule that binds to sites critical for virus assembly. The compound is highly potent and exhibits an attractive pharmacokinetic and toxicology profile, positioning it as a first-in-class, orally available drug for treating polyomavirus infections. The compound is in pre-investigational new drug (IND) development for BK virus infections in transplant patients.

A second group of early stage, first-in-class small molecules targets the highly conserved LTag, inhibiting viral replication through a highly selective mechanism of action in both BK and JC viruses. Orthogon's polyomavirus pipeline is complemented by a suite of first-in-class host-targeted antivirals that have the potential for broad-spectrum activity against multiple members of the polyomavirus family.

Further expansion of Orthogon's polyomavirus portfolio is supported by an array of first-ever tools including reporter assays, extensive protein structure data and ongoing work on an animal model of BK polyomavirus.

Translational partnerships in anti-infectives

With a transatlantic footprint in the US and Europe, over 7,500 ft^2 of state-of-the-art research space, and a network of collaborations to complement its in-house capabilities, Orthogon is building a portfolio of de-risked, validated drug candidates ready for co-development partnerships.

"Fighting life threatening infections of viral and bacterial origin requires the development of drugs with novel mechanisms of action that have a high barrier to genetic resistance." said Munawar. "Our platform enables us to access drug targets that have historically remained out of therapeutic reach. We are poised to use our data-driven drug discovery platform in collaboration with partners who share our vision of discovering and advancing revolutionary, first-in-class, medicines that could help improve health outcomes around the globe."

CONTACT
Ali Munawar, CEO
Orthogon Therapeutics, LLC
Canton, MA, USA
Tel: +1-617-304-8914
Email: amunawar@orthogontherapeutics.com