Antimicrobial resistance (AMR) has long been recognized as a threat to treat infections, and in 2019, the World Health Organization (WHO) declared AMR one of the top 10 global public health threats. Global strategies to contain the spread of AMR include a coordinated surveillance network and the development of novel classes of anti-infectives.

In June 2021, the WHO released its fourth Global Antimicrobial Resistance and Use Surveillance System report, revealing alarmingly high rates of resistance to anti-infectives ranging from first-line antibiotics used to treat urinary tract infections (UTIs) to last-resort antimicrobials used to treat a range of nosocomial and mostly Gram-negative bacteria. Meanwhile, the global pipeline of anti-microbials in development lacks compounds with alternative targets to circumvent known AMR mechanisms, hampering the fight against some prevalent resistant bacteria and underscoring the urgent need for new anti-infectives.

An anti-infectives foundry
Forge is pursuing novel classes of anti-infectives by harnessing the company’s MAGNET platform to discover small molecule inhibitors of bacterial and viral metalloenzymes. By focusing on inhibitors of targets with unique mechanisms of action, Forge aims to develop entirely new classes of anti-infectives able to treat patients infected with antimicrobial resistant pathogens. MAGNET includes a library of diverse metal-binding pharmacophore (MBP) fragments covering a wide spectrum of metal-binding geometries and coordination modes. Once a microbe-specific essential metalloenzyme is selected as a target, the library is screened to identify MBPs that potently and selectively inhibit the enzyme. Using structure-based drug design, candidate fragments are incorporated into suitable chemical backbones to optimize potency, selectivity, and drug-like properties, generating full-length inhibitors that undergo preclinical characterization to nominate development candidates (Fig. 1). A key advantage of Forge’s platform is knowing the precise binding site of the target enzyme’s active site metal ion, which accelerates the pace of optimization.

The MAGNET process affords rapid discovery of lead MBPs with exquisite sensitivity to structural differences among metalloenzyme orthologs produced by different pathogens, as evidenced by the distinct LpxC-targeting chemotypes that differentially target bacteria causing UTIs, respiratory tract infections, or sexually transmitted infections.

Bringing down Gram-negatives one LpxC at a time
Forge has built its lead anti-infective program by focusing on LpxC, a key Zn²⁺ metalloenzyme required for Lipid A biosynthesis in Gram-negative bacteria. Lipid A, a component of the outer bacterial membrane, is essential to growth and survival of Gram-negative pathogens, and disruption of lipid A biosynthesis carries bactericidal consequences.

Legacy efforts to develop potent and clinically useful inhibitors of LpxC have not been successful due to their reliance on hydroxamic acid, a MBP that is prone to high plasma drug clearance, poor PK, and toxicity. By contrast, Forge’s lead LpxC compounds rely on novel MBPs that are structurally and chemically differentiated, and do not induce adverse effects in vivo. FG-LpxC leads are effective against the main pathogens responsible for each program’s target indication (i.e., UTIs), and their activity does not extend to Gram-positive bacteria such as those present in the gut microbiome, or to representative human metalloproteins. Encouragingly, Forge’s evaluation of hundreds of contemporary clinical isolates has failed to identify a single instance of pre-existing, target-based resistance, validating the company’s novel target/mechanism strategy. Forge plans to file an IND for FG-LpxC UTI in 2022.

Evergreen platform of anti-infectives
In addition to the FG-LpxC-UTI program, the company’s pipeline includes preclinical LpxC-targeting compounds for Pseudomonas aeruginosa and Neisseria gonorrhoeae infections, as well compounds in early discovery stages targeting the metalloenzymes 1-Deoxy-d-xylulose (DXR), 2-C-methyl-D-erythritol 2,4-cyclopyrophosphate synthase (IspF), phospho-2-dehydro-3-deoxyheptonate aldolase (AroG), succinyl-diaminopimelate desuccinylase (DapE), bacterial RNA polymerase (RNAP), threonyl-tRNA synthetase (ThrRS), and SARS-CoV nonstructural protein 14 (Nsp14).

Forge is developing its portfolio through a global network of external collaborations, including public-private partnerships, and is seeking to expand this network to continue discovering novel classes of anti-infectives to help combat drug resistance.


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