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Nosopharm
First-in-class Anti-Infectives

Advancing first-in-class anti-infective therapies to combat multidrug resistance

Nosopharm is an innovative biotechnology company that is focused on exploring untapped microbial biodiversity to discover new drugs to fight antimicrobial resistance.

Infectious diseases are a major cause of global mortality, accounting for more than 9 million deaths each year. The increase in antimicrobial resistance makes these infections much harder to treat. Antimicrobial-resistant organisms are a leading cause of healthcare-associated infections and are considered one of the top ten public health threats worldwide.

Nosopharm is on a mission to discover and develop first-in-class anti-infective therapies to address this critical challenge. Founded in 2009 and headquartered in Lyon, France, the biotechnology company targets antimicrobial-resistant bacteria and fungi that are responsible for the most concerning hospital-acquired infections.

"We are one of the very few biotech companies developing high-potential first-in-class antibiotics," said Philippe Villain-Guillot, Nosopharm's CEO and co-founder. "Novel drugs that can overcome antimicrobial resistance are urgently needed to safeguard public health."

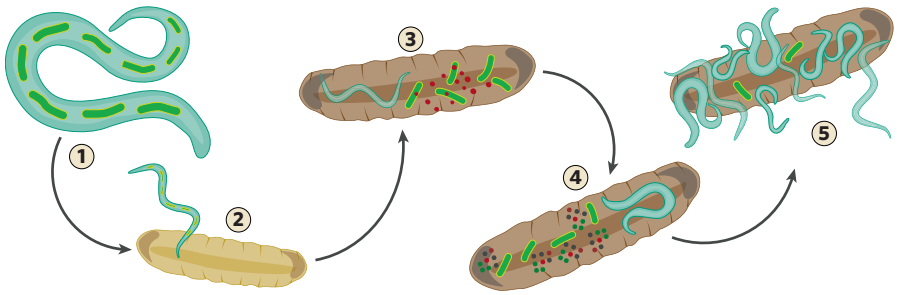

Fig. 1 | ExploRhabdus, Nosopharm's drug discovery platform. The platform harnesses the therapeutic potential of the bacterial genera *Photorhabdus* and *Xenorhabdus*. **1.** *Xenorhabdus* or *Photorhabdus* live in the intestine of the host nematode. **2.** The host nematode infects an insect. **3.** *Xenorhabdus* or *Photorhabdus* are released within the insect and kill it. **4.** *Xenorhabdus* or *Photorhabdus* produce antibiotic molecules that prevent the microbial competitors from degrading the insect's body. **5.** *Xenorhabdus* or *Photorhabdus* colonise the nematode, which along with the bacteria use the insect's biomass as a source of nutrients to reproduce.

Medicinal mining of microbes

Nosopharm has developed an innovative drug discovery platform called ExploRhabdus, which integrates natural products, anti-infective screening, microbiology and medicinal chemistry. The platform harnesses the therapeutic potential of the bacterial genera *Photorhabdus* and *Xenorhabdus*. The complex life cycle of these bacteria, which have a symbiotic relationship with nematodes, requires the production of a broad range of antimicrobial compounds (Fig. 1).

When the nematode infects an insect, the bacteria produce immuno-modulating and toxic compounds that kill the insect. The nematode and the bacteria use the dead insect as a source of nutrients to reproduce. To this end, the bacteria produce antibiotic molecules that prevent microbial competitors from degrading the dead insect. Until recently, the antibiotics made by *Photorhabdus* and *Xenorhabdus* were largely understudied.

Yet these powerful molecules have three key advantages for anti-infective drug discovery. First, they have undescribed chemical scaffolds, suggesting novel mechanisms of action and making them effective at treating infections that are unresponsive to other antibiotics. Second, they are not toxic to the nematode, increasing the likelihood that they are safe for eukaryotic organisms such as humans. Third, they interact with the biological matrices of the dead insect, representing a natural primary filter for drugability.

"*Xenorhabdus* and *Photorhabdus* are a high-value bioresource for anti-infective drug discovery," Villain-Guillot said. "With our unique and ever-expanding expertise in the biomining of these bacteria, the drug discovery platform ExploRhabdus provides a higher probability of obtaining drug candidates by avoiding the main pitfalls of natural product drug discovery."

Aiming for eradication

Nosopharm's drug discovery platform has enabled the discovery of several new antimicrobial molecules such as odilorhabdins. Using a unique antibacterial mechanism, odilorhabdins bind to the bacterial ribosome and disrupt protein synthesis, killing bacteria rather than simply slowing their growth. The most advanced program in Nosopharm's pipeline is NOSO-502—a first-in-class odilorhabdin antibiotic that targets multidrug-resistant Enterobacterales, which are top-priority pathogens according to the World Health Organization.

The main hospital pathogens of the Enterobacterales family are *Escherichia coli* and *Klebsiella pneumoniae*. They have been detected in 20–30% of hospital-acquired infections in Europe and the United States. These pathogens have reached high rates of resistance to multiple drugs, including last-resort antibiotics called carbapenems. In Italy, a G7 member state, carbapenem-resistance rate was 29% in 2019.

NOSO-502 has demonstrated antibacterial activity against multidrug-resistant clinical isolates, including NDM carbapenemase producers. It has also proven to be effective in Enterobacterales infection models, such as peritonitis/sepsis, urinary tract infection and respiratory tract infection. "Upon successful completion of clinical development, NOSO-502 will be the first novel antibiotic class for Enterobacterales infections to be introduced into the clinic in 40 years," Villain-Guillot said.

Expanding the arsenal

Nosopharm's product portfolio includes two additional programs intended for the treatment of systemic *Pseudomonas aeruginosa* infections and *Candida* infections.

The pathogen *P. aeruginosa* is involved in ~10% of hospital-acquired infections in Europe and the United States. Carbapenem-resistant *P. aeruginosa* is considered by the World Health Organization to be a critical priority for the research and development of new antibiotics.

The main fungal hospital pathogens belong to the *Candida* species, which has been detected in 6% of hospital-acquired infections in Europe and the United States. Very few antifungal drug classes are available to treat these infections. This is of particular concern because some multidrug-resistant *Candida* species are rapidly emerging.

"The current therapeutic arsenal, ageing and in need of renewal, no longer enables clinicians to cope with the dire situation posed by these life-threatening multidrug-resistant pathogens," Villain-Guillot said. "We remain firm in our commitment to work with existing and future partners to further develop our entirely new antibiotic classes, which are desperately needed to tackle the growing and global threat of antibiotic resistance."

CONTACT
Philippe Villain-Guillot, CEO
Nosopharm
Lyon, France
Tel: +33 6 26 63 24 89
Email: p.villainguillot@nosopharm.com