PYLUM BIOSCIENCES

The New Frontier for Precision Antibacterials: Oncology

Medical understanding of bacteria has evolved from "the only good bacteria is a dead bacteria" to the realization that beneficial bacteria are critical to human health and that bacteria are instrumental in the etiology of disease far beyond traditional infectious disease and now includes oncology. These applications demand the need for a tailorable, targeted approach to eliminating only the deleterious bacterial pathogens.

The Company

Pylum Biosciences is developing targeted protein-based bacterial ablation tools (Avidocin™ Proteins) that have therapeutic applications for a range of human diseases. The Pylum story starts with Avidbiotics, founded in 2005, an R&D company with diverse interests. Two valuable projects emerged from Avidbiotics, an immunotherapeutic based on CAR-T, and the Avidocin bacterial targeting platform. Avidbiotics split itno two entities: Xyphos Bio which held the CAR-T platform while the Avidocin IP package was spun out to form Pylum Bio. Soon after the restructuring, Xyphos was acquired by Astellas along with most of the employees for clinical development of the CAR-Ts. Now that all Astellas obligations have been met, Pylum has restarted operations with a fresh approach for the Avidocin protein platform.

The Platform

Avidocins are based on high molecular weight phage tail-like bacteriocins. These structures function to kill bacteria directly upon contact by destroying the cellular membrane potential. Their spectrum is highly targeted, often only killing just a subset of a species of bacteria. The Avidocin technology is based on harnessing this exquisite specificity and retargeting them to a pathogen of choice. This is typically accomplished by engineering the targeting function on the tail fibre (the receptor binding protein, RBP) (Fig. 1). As such, we have developed a portfolio of Avidocins that target various disease-causing species while preserving the normal healthy microbiota. They have been shown to have valuable *in vivo* activity in a variety of animal models, they can be produced by fermentation in standard GRAS production organisms, and have a functional modality distinct from any other antibacterial agent. New Avidocins, targeting newly identified pathogens, can be developed quickly, sometimes within weeks.

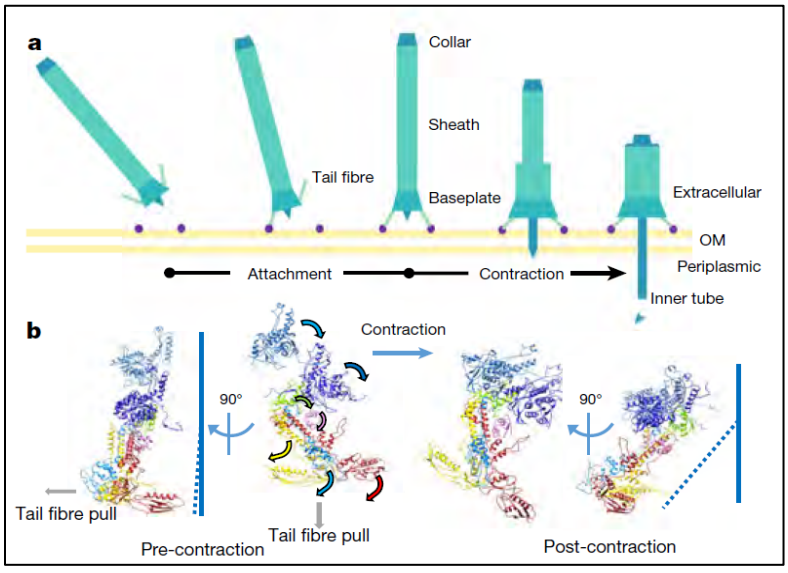

Fig. 1 | Baseplate transition from the pre-contracted to the post-contracted state. **a**, Illustration of an Avidocin landing on a bacterial cell and firing. Release of the spike and hub following injection is postulated based on the lack of these structures on contracted particles that were observed in vitro. **b**, Ribbon diagram of the conserved baseplate components and sheath proteins in their pre-contracted and post-contracted states. Arrows denote potential movements for subunits in the same colors. OM, outer membrane.

The Products

The Avidocin platform was initially conceived 20 years ago with infectious disease in mind, particularly drug-resistant bacteria (aka "ESKAPE" pathogens). Since that time, numerous advances have revealed a much more commercially viable target: cancer. Very recently, the association of oncogenic bacteria with certain cancer types has gained significant scientific merit and it has become obvious that ablation of cancer-associated bacteria could have significant impact on both treating/prevention of cancer, as well as increasing the effectiveness of existing cancer immunotherapies. Our current focus is colorectal cancer (CRC), with two main targets: *Fusobacteium nucleatum* and pks positive *E. coli*. Both have very strong data including not just an association, but also distinct pathologies and mechanisms of tumor promotion. CRC is an ideal low-hanging fruit for Avidocins, we know from animal models that we can formulate and deliver the drug to the colon where it has strong bactericidal activity.

Oncology

Recent publications have detailed intratumoral bacteria niches and how their molecular activities and communication networks impact multiple cancer-related functions. *E. coli* PKS+ has been detected in tumor tissues and linked to the production of secondary metabolites (eg. colibactin) that promote inflammation and DNA damage, contributing to the initiation and growth of tumors. Other bacterial pathobionts such as *Fusobacterium nucleatum*, shown to be exclusively in CRC tumor tissues, may influence the response of tumors to chemotherapy and immunotherapy by metabolizing and inactivating chemotherapeutic drugs.

There is a clear relationship between oncologic drug performance and the presence of pathogenic bacteria in the tumor microenvironment, indicating the targeted removal of the specific pathogens would improve current therapies. Broad spectrum antibiotics do not effectively address the tumor microenvironment and ultimately make the problem worse by driving antimicrobial resistance, exacerbating dysbiosis, and compromising patient immune system and their ability to fight the disease.

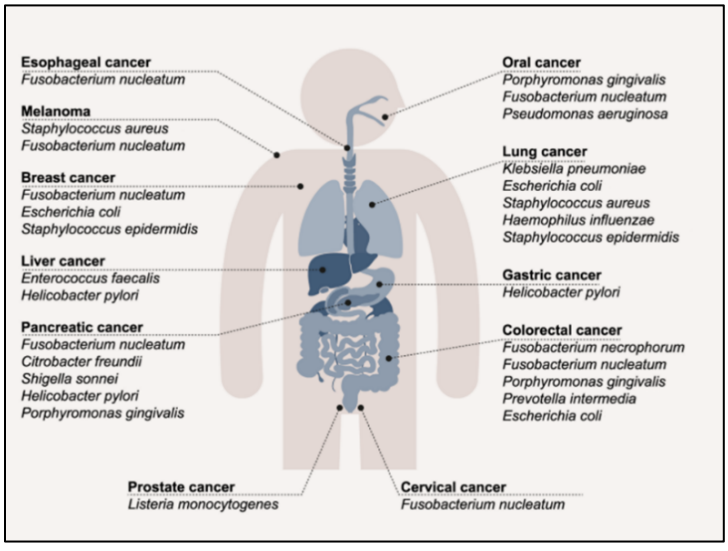

Fig. 2 | Bacteria producing secondary metabolites that promote inflammation and DNA damage contributing to tumor initiation and growth:

Pylum Candidates#	**Cancers**
F. nucleatum ‡	7
E. coli †	3
C. difficile •	1
F. necrophorum ‡	1
P. aeruginosa •	1
K. pneumoniae †	1
E. faecalis †	1
L. monocytogenes †	1

• Pylum candidate validated in vivo
† Pylum candidate validated in vitro
‡ Pylum candidate validation in process

In addition to multiple cancers, *F. nucleatum* has been linked to many diseases, including adverse pregnancy outcomes, gastrointestinal disorders, cardiovascular disease, rheumatoid arthritis, respiratory tract infections, endometriosis, and Alzheimer's disease. Research shows involvement in the progression of some cancers, including colorectal, pancreatic, oesophageal, and breast cancers. A study published in *Nature* showed strong evidence of a causative relationship with *F. nucleatum* with colorectal cancer[3].

Infectious Diseases

Clostridioides difficile infection is one of the highest priority nosocomial infections. It lengthens hospital stays, raises the risk of mortality, and increases costs. Around one-quarter of people who have treatment for a *C. difficile* infection will have another. After three or more infections, 50% of those patients will have yet another infection[2]. Infections can be treated with broad-spectrum antibiotics, but this increases the likelihood of recurrence. The only approved treatments are fecal microbiota transplants, which are marginally effective and haven't yet gained commercial traction.

Avidocin proteins specifically ablate the *C. difficile* bacteria, including antibiotic-resistant strains. Published murine i*n vivo* data showed that the orally delivered *C. difficile* Avidocin (candidate molecule Av-CD291.2) killed the most common clinical isolates while leaving the gut flora unharmed. Unlike vancomycin, a frontline treatment for *C. difficile* infections, Av-CD291.2 did not disrupt colonization resistance or increase susceptibility to infection with *C. difficile* or vancomycin-resistant enterococci (VRE) infection after treatment.

In addition to Av-CD291.2, Pylum has more than 20 additional candidate molecules that have all been cloned, expressed, purified, and *in vitro* validated for killing efficiency of specific pathogenic strains including *Acinetobacter baumannii, CRE, VRE, Pseudomonas aeruginosa, Shigella spp, and Salmonells spp*. These candidates help reduce the business risk by creating multiple opportunities with Orphaned Drug Designations.

Our Strategy

With both a powerful, proprietary platform and attractive, short-term clinical opportunities, our strategy is both simple, compelling and two-pronged:

- Estabish *clinical* 'Proof-of-Platform' in infectious disease (*C. difficile*)
- Estabblish *in vivo* 'Proof-of-Concept' in oncology (Fusobacterium/E. coli pks+)

The next step is to submit a Type B meeting request to meet with the United States Food and Drug Administration (FDA) to align toxicology studies and FIH clinical plans with FDA requirements. Depending on the outcome of that discussion, Av-CD291.2 could be in clinical trials by Q1-2026.

Conclusion

The unique history of Pylum has resulted in a valuable opportunity for investors: with a fully owned and extensive intellectual property portfolio and extensive know-how, we have targeted major unmet medical needs against drug-resistant bacterial infections with expansive medical opportunities. Uniquely in the field of biotech, due to years of applied research, it will take a relatively minor capital investment to reach a critical value-inflection milestones (IND filing and tumor reduction data) in a very short amount of time (<2 years).