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Nemesis Bioscience: Delivering the Antibiotic Resurrection

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Abstract: Consistently listed among the greatest current threats to global health, the 'antibiotic resistance crisis' refers to the increasingly worrying emergence and spread of new, antibiotic-resistant strains of pathogenic bacteria. Antibiotics have been transformative for modern medicine and reliance upon them is ubiquitous in healthcare worldwide. However, as the efficacy of available antibiotics diminishes and the rate of novel antibiotic discovery decreases, humanity is on the cusp of a catastrophe that threatens to undermine much of the medical progress of the past century. Nemesis Bioscience is set on solving this problem, harnessing their novel Transmid© technologies to target and eliminate antibiotic-resistance genes, making pathogenic bacteria susceptible once more to existing antibiotics. Their success will bring with it hopes of a new era of medicinal security, turning the 'antibiotic crisis' into the 'antibiotic resurrection'.

Keywords: Antibiotic resistance, Transmid©, CRISPR-Cas9, Phage, Conjugation, Symbiotics©, Microbiome, Babraham Research Campus, Cambridge, Aberystwyth

1. The success story

Headquartered in the heart of the Cambridge biotech ecosystem, on the Babraham Research Campus, with recently acquired facilities on the Aberystwyth Innovation and Enterprise Campus (Fig. 1), Nemesis Bioscience is a rapidly developing company on a mission to tackle antibiotic resistance. Applying their extensive experience from the forefront of academic research and strong track records in developing new technologies and growing businesses, the team has received recognition for their venture, including the King's College, Cambridge Entrepreneurship Award, an Innovate UK SBRI Award and an Innovate UK Smart Award. This has been reflected in success at securing investment, including from Innovate UK, UK2IS and the Development Bank of Wales, as well as amassing £1.5 Million in seed funding. Most recently, this has been supplemented by a major collaboration with Japanese pharmaceutical powerhouse Shionogi, who bring with them over 60 years' industrial expertise in antimicrobial development [1]. Nemesis Bioscience is now poised to expand their CRISPR-Cas9-based "Transmid©" technologies, as companion DNA therapeutics "Symbiotics©", to inactivate

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antibiotic resistance and virulence factors in a wide range of targets, implemented in further preclinical and prospective clinical development.

Figure 1. Nemesis Bioscience office locations. **Left:** Babraham Hall in the centre of the Babraham Research Campus. **Right:** The Aberystwyth Innovation and Enterprise Campus, part of the Institute of Biology, Environmental and Rural Sciences (IBERS).

2. Where did they start

The inspiration behind Nemesis Bioscience, like many great ideas before it, was the product of stimulating conversation over a beer in one of the auspicious pubs of central Cambridge. Co-founders (Fig. 2) Dr Frank Massam (CEO), Professor Conrad Lichtenstein (CSO) and Dr Gi Mikawa (CMO) had previously held senior positions at Population Genetics Technologies, a startup founded by the Nobel Laureate, Professor Sydney Brenner [2], under whom Professor Lichtenstein completed his PhD studies, at the Medical Research Council Laboratory of Molecular Biology, Cambridge. However, motivated by the growing fears over antibiotic-resistant bacteria and accelerating development of CRISPR-Cas9-based genome-editing technologies, the three co-founders were compelled to utilise their combined expertise in translational molecular biology, bacterial genetics and microbiology to combat this new threat. And so, on 3rd March 2014, Nemesis Bioscience was born. Within a month the company had filed its first patent and after swiftly securing Angel Investment to perform proof-of-concept work, they moved in 2015 to their current headquarters on the Babraham Research Campus, Cambridge, UK.

Named for *Nemesis*, the Greek goddess of retribution upon those guilty of hubris, this sentiment effectively captures the company's vision: to turn the tables on those bacteria that might dare to evolve antimicrobial resistance. This is further represented in the company logo (Fig. 2iv), reminiscent of the sword and hourglass often used to symbolise *Nemesis*, it depicts a sword thrust into a DNA double helix - a nod also to the CRISPR-Cas9 genome-editing techniques key to their success.

Figure 2. Nemesis Bioscience founders and logo. **i)** Dr Frank Massam, CEO. **ii)** Professor Conrad Lichtenstein, CSO. **iii)** Dr Gi Mikawa, CMO. **iv)** The Nemesis Bioscience logo.

3. Why are they needed?

Antibiotics have revolutionised healthcare over the past century, contributing greatly to increased life expectancy worldwide [3]. Not only are they instrumental in limiting the severity and spread of many common bacterial infections, but crucially, they have enabled other major medical advancements. Notably they are essential for surgery and treatments that compromise the immune system, where they are required to prevent infection [4]. However, as recognised by the World Health Organisation (WHO) in their 2019 list of top ten 'threats to global health', misuse of antibiotics has resulted in the rapid spread of antibiotic resistance globally, causing the crisis we see today [5]. With the alarming emergence of new multidrug-resistant strains of pathogenic bacteria, infections that might have responded to routine antibiotics decades prior are no longer treatable. Indeed, of the millions of antibiotic-resistant bacterial infections that occur yearly, 700,000 tragically result in loss of life [6], with multidrug-resistant tuberculosis alone causing 250,000 deaths per year [7] and the numbers are growing.

Compounding this issue is the decreasing rate of new antibiotics being approved for use: in the past 20 years only two new antimicrobial drug classes have been approved for Gram-positive bacteria and none for Gram-negative bacteria [7]. As of December 2019, there were only 9 antimicrobials in Phase 3 clinical trials worldwide that might be effective against the US Centers for Disease Control and Prevention (CDC) and WHO-classified 'critical threat pathogens', a pipeline far too small for the growing problem [8]. Even with these efforts it is generally acknowledged that, with the approval of a new antibiotic it will only be a matter of (sometimes frighteningly short periods of) time before resistant strains emerge [9]. This will most likely hold true for any new antimicrobial strategies that rely on directly killing the pathogenic bacteria. Global antibiotic consumption has nevertheless increased by over 65% in the past 20 years [10] and with that number set to increase, interventions to maintain antibiotic efficacy are needed now more than ever. The novel methodology employed by Nemesis Bioscience, to resurrect bacterial sensitivity to pre-existing antibiotics, thus carries game-changing implications.

4. The technology

At the core of the Nemesis Bioscience approach lies their Transmid© technologies [11] (Fig. 3). These utilise the Nobel prize-winning CRISPR-Cas9 genome editing technique [12], encoded on a conjugative plasmid and encapsulated in a pathogen-seeking phage coat. These make use of newly described phages, isolated from the Cam and Ystwyth rivers of Cambridge and Aberystwyth respectively, recruiting the very locations the company calls home to the fight against antimicrobial resistance. Once these phage coats are administered, they enter target pathogenic species and deliver the Transmid©, expressing a specialised, multiplexed CRISPR-Cas9 cassette, currently capable of knocking out resistance to eight β-lactam antibiotic families simultaneously.

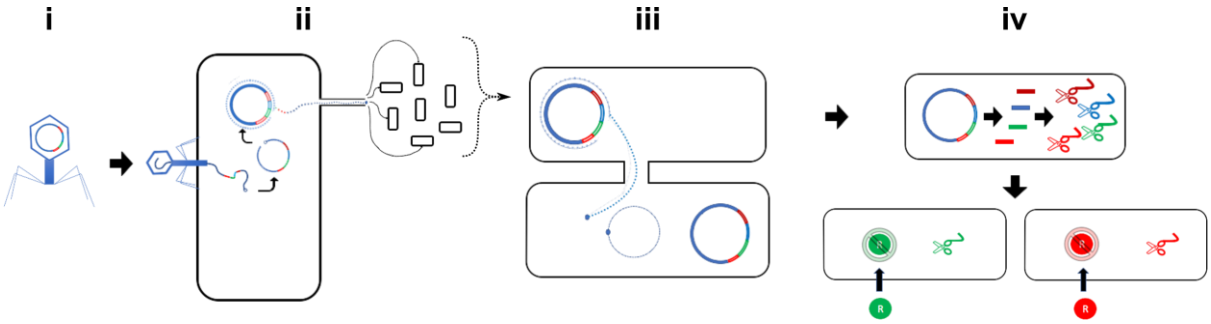

Figure 3. Nemesis Transmid© technologies. **i)** A Nemesis Transmid©, comprising a multiplexed CRISPR-Cas9-expressing conjugative plasmid, within a phage coat. **ii)** Phage coats deliver Transmids© to target bacteria, which replicate and **iii)** spread to other bacteria via promiscuous bacterial conjugation. **iv)** The Transmid© expresses Cas9:guide-RNA complexes (represented by coloured scissors) for targeting antibiotic-resistance genes (represented by coloured 'R' circles). These seek and knock-out antibiotic-resistance genes already in the bacterium and any newly attempting to enter.

Ingeniously, by encoding this mechanism on a conjugative plasmid, the antibiotic-resistance gene-eliminating Transmid© can continue to spread throughout the bacterial population even after the phage coats are cleared by the immune system, exploiting the same mode by which antibiotic resistance is thought to spread: promiscuous bacterial conjugation. Thus, antibiotic-sensitive bacteria are conferred a CRISPR-Cas9 immune system against newly entering antibiotic-resistance genes, while antibiotic-resistant bacteria can only halt spread of the Transmid© if they are conjugation-incompetent and thus also incapable of spreading antibiotic resistance. In addition to these built-in failsafes, due to the uniquely non-lethal nature of the Nemesis Bioscience solution, the strong selective pressure applied by directly killing the bacterial population, from which antimicrobial resistance arises, is absent. This means that unlike other approaches being developed, which chiefly aim to directly kill pathogenic bacteria, the Nemesis Bioscience mode of action should be far less prone to resistance evolving. On the contrary, introduction of the Transmid© instead suppresses the ability to form resistance against subsequent antibiotic treatment.

Re-sensitising the pathogenic bacteria to existing antibiotics also carries distinct advantages for the pharmaceutical industry. The technology enables valorisation of existing antibiotics, the

vast quantities of time and money invested in which may otherwise soon be lost to antibiotic resistance. Furthermore, reuse of previously approved antibiotics will facilitate the prospective clinical trial process, with the availability of reliable datasets with known endpoints, to which results can be compared. Finally, the Nemesis Bioscience approach provides confidence, to pharmaceutical companies and patients alike, that sensitivity to existing and newly developed antibiotics can be maintained for years to come.

5. Looking to the future

Having recently been granted full patent protection by the European Patent Office for their technology in Europe, with further patent applications in the US, Japan, China, Australia and India under review, Nemesis Bioscience is primed for rapid development in the near future. This is evidenced by their 2019 expansion to labs in Aberystwyth and their collaboration with Shionogi announced in 2020. Supported by promising proof-of-concept work, demonstrating the antibiotic re-sensitisation capabilities of Transmids© in mouse models, the expanded facilities will allow for further preclinical animal-model studies to take place. In collaboration with Shionogi, efforts will initially focus on optimising Transmids© to target the WHO 'critical priority' pathogen *Pseudomonas aeruginosa*, with the promise of Phase 1 clinical trials to follow.

In parallel, Nemesis Bioscience aims to isolate and screen more phage coats, expanding their Transmid© library to target other priority pathogens. Symbiotic© capabilities will also be broadened to allow re-sensitisation to other antibiotic families, as well as inactivation of virulence factors. This will not only be limited to application in humans; over 60,000 tonnes of antibiotics are used in the agricultural industry yearly [13], both contributing to- and suffering from rising antimicrobial resistance. As in humans, Transmid© technology will be well-placed to resurrect bacterial antibiotic sensitivity in livestock too. With this in mind, in the near future, Nemesis Bioscience will commence proof-of-concept studies in pigs.

Looking ahead, Nemesis Bioscience is considering a Series A funding round as well as further collaborations with like-minded partners. The technological innovations Nemesis Bioscience brings could have a significant impact on the future of medicine and with their success comes hopes of better global health security with effective antibiotic treatments for all.

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Chris N. Micklem is a PhD student at the University of Cambridge Sainsbury Laboratory and Department of Physics. As an undergraduate at Imperial College London (ICL), he specialised in systems & synthetic biology, co-founding SynBIC (ICL synthetic biology society) to foster enthusiasm for the field. After achieving 2nd place worldwide with Aqualose, the 2014 ICL International Genetically Engineered Machine (iGEM) competition team, his interest in entrepreneurship was sparked while exploring commercialisation of their technology. This occurred as part of team CustoMem, reaching the finals of the 2015 Imperial Enterprise Venture Catalyst Challenge, ultimately giving rise to CustoMem Ltd (now Puraffinity Ltd). Following years in automated strain engineering at Amyris, Inc. and drug discovery at PhoreMost Ltd, he traded industry for PhD studies, undertaking a systems & synthetic biology project on cyanobacterial oscillators. Though now a full-time student, Chris maintains an active interest in early-stage biotech companies. Most recently, this has come through his involvement as a Start-ups Mentor with iGEM Entrepreneurship Program & Innovation Community (EPIC).