Antibiotic Discovery Accelerator Network (ABX)
July 2019 Meeting Report

Background

There is a growing recognition that the antibiotic discovery pipeline is in need of reinvention. Antibiotics are considered as essential infrastructure, comparable to hospital and ambulance services (Chandler, 2019). The impact of antimicrobial resistance (AMR) is far reaching, and could signify the end of modern medicine; in 2018 the Chief Medical Officer at the UK House of Commons Enquiry into AMR warned that due to its implications on major surgery, cancer treatment and transplants, 'There will be a lot of suffering and modern medicine will be lost' (House of Commons, 2018). The WHO recently issued a fresh warning on the global threat of AMR and their implication on infections (WHO, 2020). According to Sarah Pauline, report author and technical officer of Antimicrobial Resistance and Innovation at the WHO, "We still have a window of opportunity but we need to ensure there is investment now so we don't run out of options for future generations."

According to the UK's five-year national AMR action plan, effective antibiotics are scarce and new drugs are slow to be discovered and developed to commercial stance (HM Government, 2019). Due to the lengthy discovery and developmental processes and low profit margins, pharmaceutical companies are uninterested in the use, and therefore potential development, of antibiotics, and reserve them as a 'last-line defence' (Singer *et al*., 2019). This 'last-line defence' form of drug administration discourages frequent use, and therefore holds low commercial value and therefore interest from investors.

Initiatives such as Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (Carb-X) and the Antimicrobial Resistance (AMR) Centre have engaged in push-pull incentives for the pharmaceutical companies to become interested and invest their resources into the development and manufacture of novel compounds, however these companies are less interested in the early stages of development, and tend to invest in later stages where knowledge becomes patentable (Galkina *et al*., 2018). While drug development is an important step, there is little focus on the discovery of new molecules entering the pipeline, and this signifies a huge bottleneck which compounds hindrance of the development of new antibiotics.

The Antibiotic Discovery Accelerator Network (ABX) aims to address this vital step in the pipeline. The initiative aims to provide a platform to identify discovery bottlenecks as well as detail and combine expertise to facilitate collaboration.

ABX Meeting

The inaugural ABX meeting was held in July 2019 at the Eden Project (Cornwall, UK). The two-day meeting, held in association with the University of Plymouth, marked the launch of the network's initiative to bring together research groups and institutions, with particular emphasis on early career researchers, engaged in antimicrobial discovery across the UK, in an effort to address the gaps and bottlenecks inherent in the pipeline. The meeting provided a platform for researchers to showcase the work that they are involved in, which fostered both

lively discussion and collaborative efforts. Over 40 researchers attended to share their expertise, build connections and discuss ideas, which helped generate future plans for fruitful and meaningful research.

Day 1

The first day was comprised of research-focused talks, with speakers encouraged to identify specific bottlenecks and areas where potential collaboration would be of benefit. The talks contained research across the breadth of the discovery pipeline; from sample collection and isolate recovery to screening efforts, bioinformatic prediction and innovative methods for compound characterisation. The range of topics covered highlighted not only the creativity of the techniques being employed in combating the threat posed by AMR, but also the benefits of collaboration and knowledge-sharing in addressing such important and often inter-disciplinary issues.

Talks:

- Antimicrobial Peptides
- Good Drugs for Bad Bugs: Finding New Antibiotics for Tuberculosis
- DNA Topoisomerases as Targets for Antibacterial Chemotherapy
- Bioprospecting for Novel, Natural Product-Based Antibiotics from Deep-Sea Sponges
- Metagenomic Sample Selection: A Guided Approach to Natural Product Discovery?
- DNA Quadruplexes as Targets for Antimicrobial Gene Regulation
- Integrative Structural Biology of Tripartite Efflux-Pumps and the Cell Envelope in Gram-Negative Bacteria
- Understanding Mechanisms of Antibiotic Toxicity and Searching for New Antimicrobials
- Biologics Drug Discovery – Developing Alternative Therapeutics and Novel Diagnostics for Bacterial and Fungal Infections
- Green Pharmacy in Antibiotic Development – Prolonging Efficacy by Prioritising Compounds Least Likely to Select for Resistance
- Pheromone Based Communication in Enterococci
- Cell-Free Synthetic Biology for Natural Products
- Cross-Resistance and Collateral Sensitivity Between Clinical Antibiotics and Natural Antimicrobials: The Case of Cornish Seaweeds
- Promoting the Antarctic as an Ecosystem for Antibiotic Discovery
- Integrating Interdisciplinary Approaches to Tackle Antibiotic Resistance in Tuberculosis (TB)
- Old Drugs Learn New Tricks: Drug Re-purposing as a Strategy to Uncover Effective Antibacterials
- Boolean Modelling of Pseudomonas Aeruginosa Quorum Sensing and Virulence Networks

Such bottlenecks identified included:

- Development downstream for recovery and preliminary purification of peptides: it is possible to isolate organisms with bioactivity and purify them, but the process following this is often challenging. Such processes include mass spectrometry and NMR. Difficulties arise as there seems to be a lack of experts in these fields with enough interest in antimicrobial peptide analysis to be able to help.
- Early dereplication.
- Lack of medicinal chemistry experts.
- The need for collaborators to help develop systemic as well as topical drug delivery
- Carb-X focus on Gram-negative bacteria, is there access to funding available for Gram-positive bacteria?
- Whole genome sequencing has limitations: it can be used to provide a guide for resistance conferring mutation identification, however there are other strategies such as biochemical and phenotypic which may provide more accurate identification.
- High throughput screening is only as good as the compound library that is being screened.
- Pan-assay interference compounds (PAINs compounds) are highly promiscuous chemical entities that will kill bacteria in phenotypic screens, which have been mistaken for new hit compound. They can cause high attrition rate in small molecule drug discovery.
- Lack of novel and diverse compounds/ new chemistry
- Lack of funding
- The need for ready access to good collaborators in appropriate academic fields rather than pharmaceutical companies
- Having too many samples in storage and not enough human resources to process them
- Lack of specific expertise in environment where samples are collected e.g. deep sea
- Lack of drug libraries and natural extracts to target Gram-negative bacteria
- Lack of bioinformatics tools
- Limited resources to identify novel antimicrobial targets
- The need for more medium throughput bioassays for more rapid identification of functional biologic binders- biological assays that are more suited to smaller labs without the capacity for high-throughput screening, specifically those designed to identify binding targets for novel antimicrobial candidates
- The need of accessing a greater panel of appropriate models of infection
- The fragility of *in vivo* techniques
- The problem that most antimicrobials can't get through cell membrane of Gram-negative bacteria
- The need for more biochemistry experts- there are potentially useful enzymes that are not being worked on

Some solutions offered:

- Only 5% of strains can be picked out using agar plate assays; iChip (isolation Chip) technology can increase this to 50%
- Pre-screening experiments using non-mammalian *in vivo* models
- Using compounds in development to test against assay SAGE: Selective Assay for Growth-based Endpoints, a 12 hour assay that produces quick results, based on long term evolutionary experiments

Day 2

The second day was comprised of a series of round-table discussions focusing on solutions to overcome particular bottlenecks outlined on the first day, addressing topics such as knowledge-gaps, network logistics and sustainable funding.

An area which the ABX initiative has the potential to address is the number of novel drug leads that can be progressed nationally. There are just 42 systemically-acting antibiotic treatments currently in global clinical development. 25 (59.5%) of these have the potential to treat CDC or WHO 'critical threat' pathogens and just 19 (45.2%) have the potential to treat infections caused by Gram-negative pathogens. Current analyses reveal that only 1 in 5 candidate treatments tested for efficacy in humans become approved for clinical use (Pew, 2019).

It became apparent during the meeting's discussion that certain antimicrobial candidates may often not be progressed by smaller labs due to lack of resources in favour of more promising, or 'lead', candidates. It was highlighted that research funding for novel antimicrobials is restricted to only 5 years, with a higher number of smaller funding pots available, as opposed to larger, sustained funding. These restrictions mean that there is often a lack in time and money available to progress candidate compounds to the pre-clinical stage. One of the potential outcomes of ABX will be to explore ways in which to expand the lifespan of smaller grants by collaboration.

Interesting to note however, was the point raised that it may be considered that not enough candidates are discarded at the early stages; that there is a need for more stringent and intelligent selection criteria with a view to producing a smaller number of more viable candidates in later stages of pre-clinical development. Also highlighted was the lack of molecular assays that have the potential to aid in deciding which compounds should be progressed at these early development stages. Other bottlenecks identified were the lack of immediate access to equipment and expertise by certain institutions. Availability of Category 2 facilities for routine testing and collaboration with area specialists, particularly with regard to bioinformatics were among the common themes.

Moving forward

With the idea of groups engaged in antimicrobial discovery becoming more connected across the UK, the meeting succeeded in generating interest regarding how this has the potential to influence funding groups as well as funding policy at a national level. It was touched upon that by harnessing the benefits of multi-institutional collaboration, as well as the position of participating members on advisory boards and research councils, the ABX network has a real potential to raise the profile of AMR research nationally, surplus to the already instrumental O'Neill Report on Antimicrobial Resistance (O'Neill, 2016), produced in May of 2016.

One of the primary outcomes identified by the meeting was the need for a central repository open to all ABX members. The resource will be comprised of a list of strains, compounds and participating members, detailing research expertise and areas for potential collaborative work. The repository will include a list of all 'discarded' or 'B-list' compounds, standard assays used in particular labs, sharing of bioinformatics workflows and a list of funding bodies with an interest in antimicrobial discovery. The central repository aims to provide a one-stop-shop

for ABX members in an effort to encourage, inspire and simplify collaboration. The formalising of a network of researchers from across the UK in this way would also allow both PhD students and Early Career Scientists to visualise the state of the discovery pipeline as a whole, and makes coherent the process of taking an antimicrobial candidate forward from discovery towards pre-clinical characterisation.

The growing need to identify gaps in the antibiotic pipeline has already inspired nationwide and global visual data collation. In 2019 The WHO published its first publicly available comprehensive overview of the preclinical antibacterial products current in the pipeline worldwide, with data on 252 antibacterial diverse agents in development (WHO, 2019). This visual and interactive data resource format may be considered as a model for the ABX network database on a UK scale, with the focus on the very first steps of discovery.

Overall, the inaugural ABX meeting served as a fantastic opportunity for researchers engaged in antimicrobial discovery to meet, network, and to provide an overview of the services and expertise offered to the network. Identifying the bottlenecks inherent in any research field is a vital prerequisite to addressing them, and the ABX meeting provided the first steps of identifying these, creating a solid platform on which to build and move forward into the next stages of its development.

Following a successful first meeting, the ABX team has received further funding to continue and expand the initiative. A second ABX meeting is planned to take place at Aston University (Birmingham, UK) in conjunction with the next Microbiology Society Roadshow, details of which will appear on the ABX webpage:

https://www.plymouth.ac.uk/research/biomedical-research-group/abx

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