Appendix 1.

SRDC Thematic Research Programme, 2020 - 2022

Title: 'Waging War Against Anti-microbial Resistance'

Aim: To develop and advance research programme in anti-microbial resistant and discovery of new anti-microbials against clinically relevant pathogens

Objectives

1. To elucidate the molecular mechanisms and cellular biology of anti-microbial resistance using systems biology approaches
2. To identify and validate new druggable targets for existing and novel anti-microbials
3. To establish in depth understanding on the complex dynamic interactions between host, pathogens and environment on anti-microbial resistance status, evolution and transmission
4. To accelerate therapeutic discovery and establish pipeline for next generation anti-microbial development

Target infectious agent:

a. Bacteria of clinical relevance - *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp.
b. Soil transmitted helminths

Target compound:

a. Antibiotic
b. Anthelmintics

Problem Statement: Antimicrobials have been used as effective therapy for community associated infections with mild level of bacteria resistance. However, due to extensive and uncontrolled use of antibiotics over the past decades, an alarming trend of antibiotic resistance developed among clinically-important bacteria.[1,2] Consequently, the treatment options for many infections are dwindling and worryingly limited. Antimicrobial resistance (AMR) is a serious emerging global threat. AMR is one of the biggest threats to global health, food security, and development to date. A recent review by Jim O'Neill projected that the annual death toll caused AMR could reach 10 million by the year 2050 if no actions were taken to address the issue.[3] In the United States of America, according to a CDC report, at least 2 million Americans are infected with drug resistant pathogens annually and at least 23,000 of them die from such infection.[4] In Malaysia, the National Surveillance of Antibiotic Resistance 2017 reported similar trend with antibiotic resistance reported to be increasing for *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp. Combined, for which the acronym 'ESKAPE' was devised to

discuss them collectively, they are responsible for a significant global disease burden. Much of their associated morbidity and mortality is due to nosocomial emergence of AMR. Alarmingly in Malaysia is the increasing resistance of certain bacteria against the last line of therapeutic defence such as carbapenem-resistant *Klebsiella pneumoniae* with an increase from 0.3% in 2011 to 2.8% in 2015.[5] Such trend is not unique to just K. *pneumoniae* but in other pathogens such as increasing resistance of *Enterococcus faecium* and *Enterococcus faecalis* to linezolid.[5] AMR is not just isolated to bacterial infection, but that of other pathogenic infection such as soil transmitted helminthiasis. The WHO estimated that around 1.5 billion people around the world is infected with soil-transmitted helminth (STH) including Sarawak.[6,7] The common STHs of clinical importnace are hookworm (*Ancylostoma duodenale* and *Necator americanus*), roundworm (*Ascaris lumbricoides*), and whipworm (*Trichuris trichiura*). However, there are various other STHs that causes various debilitating health conditions particularly in the rural communities and livestock industries. Soil-transmitted helminthiasis, taken as a whole, accounts for a global burden of over 3.3 million disability-adjusted life years[8] associated with various health conditions such as anaemia,[9] malnutrition,[10] and impaired physical and cognitive development.[11-13] Alarmingly, resistance to the limited number drugs available against STHs are on the rise and healthcare and public health workers are running out of treatment options.[14]

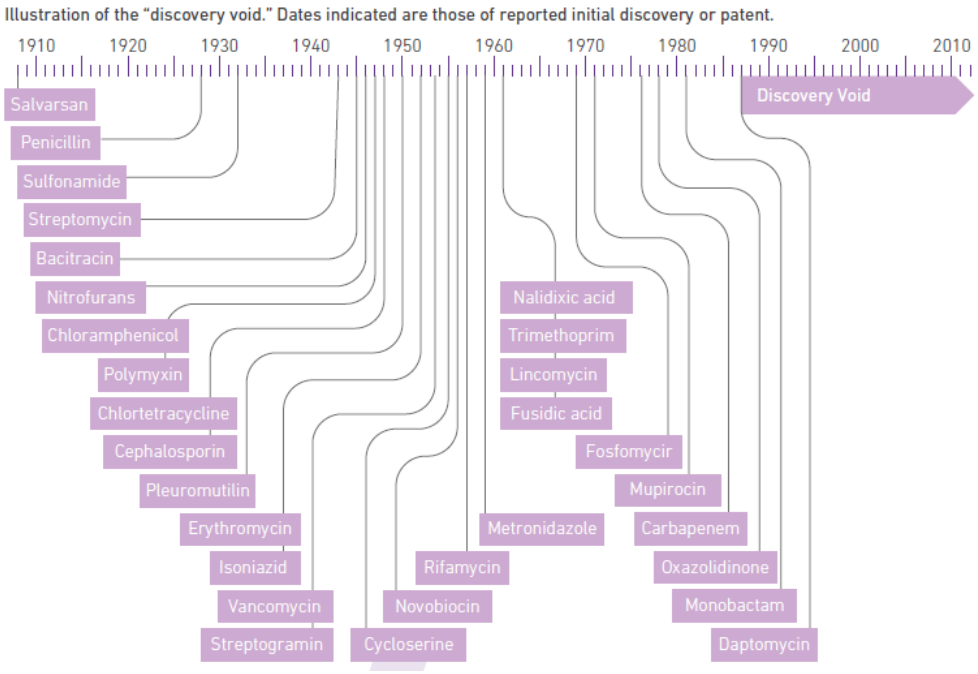

Figure 1. Dates of discovery of distinct classes of antibacterial drugs.[15]

The issue on AMR is potentially catastrophic to global population leading WHO to list AMR as one of the top ten threats to global health in 2019. Adding to the urgency of the problem, current pipeline for development of new antimicrobials is effectively non-existent. Since the discovery of penicillin by Sir Alexander Fleming in 1928, the discovery of new antibiotics reached its peak in the 1950s and 60s (Figure 1).[15] The last completely new class of

antibiotics were discovered in 1980s after which there was a discovery void which coincides with the global therapeutic shift towards combatting non-communicable diseases such as cancer and cardiovascular diseases. With ever increasing incidence of multi-drug resistant bacteria, common infections are getting more difficult to treat and are beginning to cause more severe infections presenting major threats to society. Incidence of community-acquired infections such as pneumonia, which traditionally is treated with penicillin, are getting less responsive to first line antibiotics. Cystitis, a common bacterial infection in women, is usually treated with oral antibiotics, now requiring treatments via other route of administration thus imposing more cost and increasing frequency of treatment failure. Common infections in hospital intensive care and neonatal units are increasingly becoming extremely difficult to treat and threatening the lives of patients.[15]

Thus, there is an urgent need for a concerted global effort to address this ever-increasing threat to the global population. The WHO initiated the Global Action Plan on Antimicrobial Resistance programme in response to the ever-increasing threat of AMR. The long-term goal of the programme is "… to ensure, for as long as possible, continuity of successful treatment and the prevention of infectious with effective and safe medicines that are quality assured, used in a responsible way, and accessible to all who need them."[16] As part of the SRDC initiative to address the current global need and the needs of Sarawak in tackling AMR, echoing the WHO Global Action Plan on Antimicrobial Resistance programme, the SRDC is initiating a targeted research programme tapping into the vast biodiversity of Sarawak aimed at antibiotic discovery, development, disease diagnostics and surveillance. The over-arching aim of this programme is to develop and advance research programme in anti-microbial resistant and discovery of new anti-microbials against clinically relevant pathogens tapping into the richness of Sarawak biodiversity. The SRDC has identified four key objectives which will drive the AMR programme. These objectives are set to promote collaboration between diverse disciplines, encourage sharing of information, skills and knowledge exchanges, and stimulate investments from the public and private sectors, which ultimately accelerate acquisition of new insights into the emergence and spread of antimicrobial resistance, the evolution of resistance and drive the discovery of new diagnostic, preventative and therapeutic strategies for microbial infections. This programme will also provide a real-life test bed for studying the impact of different economic and business models, or development of novel business models, related to the process and drivers of innovation in the development of new antibiotics and diagnostics.

Objectives:

1. **To elucidate the molecular mechanisms and cellular biology of anti-microbial resistance using systems biology approaches**

   Description: A strong fundamental microbiology and in-depth understanding of microbial resistance from the genome, through to cellular and host pathogen interactions in laboratory environment will be established on the initial stage of the programme in order to provide better insights into fundamental mechanisms of resistance development. This will run concurrently with disease surveillance and epidemiology to update the current communicable disease prevalence in Sarawak. Such approach will enable development and testing of new models (*in vitro* and *in vivo*) for anti-microbial testing as well as functional screening on evolution of resistance utilising data generated from the surveillance study. This objective is expected to provide the fundamental knowledge to underpin many of the other activities in subsequent objectives.

   Expected outcomes:

   a. provide better understanding of resistant bacteria in the host context;
   b. define better ways of predicting and influencing the acquisition and evolution of resistance; and
   c. uncover new markers for diagnosing bacterial infection, virulence and resistance.

2. **To identify and validate new druggable targets for existing and novel anti-microbials**

   Description: Working across disciplines, the identification of new "druggable" anti-microbial targets through the application of structural, systems and synthetic biology will be accelerated. Bioinformatics, computational biology and mathematical modelling will facilitate systems-level approaches to better understand resistance mechanisms, their evolution and spread in human- and animal- bacterial pathogens, and drug design. Molecular level understanding of resistance mechanisms and antibacterial mechanisms of action will be investigated using advanced structural and imaging approaches through fostering links between the biological and physical sciences.

   Expected outcomes:

   a. identify new targets for novel anti-microbial testing
   b. reveal new potential binding sites for existing treatment and structural modification (in silico and in vitro) to enhance binding affinity and drug effectiveness

3. **To establish in depth understanding on the complex dynamic interactions between host, pathogens and environment on anti-microbial resistance status, evolution and transmission**

   Description: The environment has been shown to interact with individuals and communities which subsequently influence the way microbes behave and response from the gene level within a microbe to the way resistant genes are transmitted between microbe species. Thus, in depth understanding on the effects of different environmental factors including antimicrobial selection pressure on evolution, acquisition and transmission of anti-microbial resistance must be established. Environmental factors stated here encompass host gut microbiota, hospital and care homes, transport systems, waste water treatment, agricultural practices and the natural environment. It is envisaged that by understanding the role of environmental factors on resistant formation and patterns, better preventive methods and management practices can be formulated.

   Achieving this objective will require active close participation across different disciplines (medicine, life sciences, physical science and engineering) and agencies both from the public and private sectors.

   Expected outcomes:

   a. Greater understanding of how resistant bacteria adapt to their environments and vice versa;
   b. Understanding the dynamics of community interaction and how this affects resistance and transmission in community;
   c. Ways to manipulate environments to prevent resistance evolution and transmission; and
   d. New surveillance networks across different environments in collaboration with federal and state agencies

4. **To accelerate therapeutic discovery and establish pipeline for next generation anti-microbial development**

   Description: This theme will cover the discovery of new and revisit old small molecule approaches as well as developing novel treatments utilising the vast biodiversity and natural product libraries in Sarawak. Building on discoveries in Objective 1 as well as on existing validated targets, elements of this objective will be directed towards strategies designed to exploit chemicals isolated from Sarawak biodiversity for the identification of novel small molecule antibiotics. This objective also covers development of new diagnostic technologies (from Objective 1) for early detection of resistant microbes as well as prognostic utility. In addition, this objective will look into establishing and accelerating anti-microbial discovery and development pipeline. New anti-microbials and existing drug repurposing will be studied using latest scientific findings and technology to improve efficacy and reduce resistant

tendency. Genome mining and metabolic pathway analysis for new synthetic pathways for antibiotics, bioengineering, synthetic biology, small molecule libraries with broader chemical space will be established and used. Further, other potential treatment or management modalities will be studied including but not limited to human vaccine development, passive immunotherapy, bacteriophage technology and probiotics. Long term study will include understanding functional genomics of the microbiome in order to manipulate and prevent evolution and spread of resistant strains.

The research and development activities for this objective will also cover scale up and manufacture of novel antibiotic drugs and vaccine development technology in Sarawak. The interaction with private sector including biotech start-ups will be key to accelerate the translation of such new therapies. Development of next generation diagnostics through the integration of cutting-edge engineering and physical sciences with bacteriology could create simple, reliable, diagnostics for resistant bacteria in clinical and environmental settings. New diagnostics will also allow more targeted use of new antibacterial agents. Development of technological advances into new sensor systems will require partnership between industry and academia, and offers great opportunities for the private sector. Researchers should be mindful of the challenges associated with deploying new technologies in community settings, veterinary practices, care homes, farms etc. Such diagnostics may also form the basis of novel surveillance systems and this objective also includes development of new mathematical models to monitor the spread of resistant bacteria.

Expected outcomes:

a. Establish and accelerate pipeline for antibiotic discovery and development including delivery systems;
b. develop new non-drug-based treatments that can avoid resistance;
c. develop rapid, point of care diagnostics for early detection and targetted therapies;
d. develop innovative diagnostics data networks for community settings to monitor status and spread of anti-microbial resistance; and
e. Study the role of existing and new business models (start-ups and small-medium enterprises) in assisting innovation through public-private partnership.

21st August 2019
Budget:

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