SULSA
Scottish Universities Life Sciences Alliance

AMR Conference: 26-27th April 2018

Scotland's Contribution to the Fight Against Antimicrobial Resistance

Highlights from the SULSA AMR Conference

Federica Giordani and Allison Jackson

1. SULSA's AMR Conference

Resistance to the antimicrobials we use to control potentially deadly infections caused by bacteria, fungi, viruses and parasites has become a significant threat to global health. Key points still to be addressed by research and policy, and potential solutions to fight this threat were recently discussed during a meeting held by SULSA in Glasgow.

Over two days 160 delegates; 123 researchers from Universities across Scotland, including 54 early career researchers, plus 37 other representatives from the Wellcome Trust, the Medical Research Council, government bodies and industry came together at the Technology and Innovation Centre at the University of Strathclyde, Glasgow. Delegates shared their expertise and explored how Scotland can work together to address antimicrobial resistance (AMR).

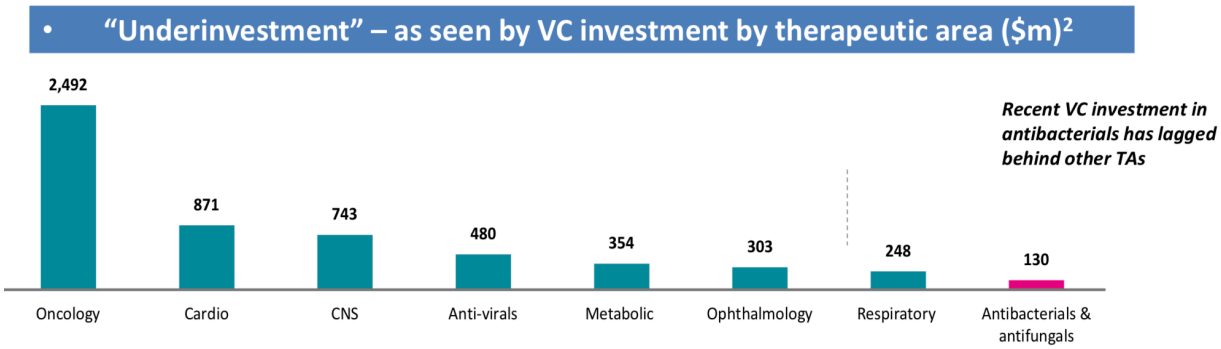
The conference, organised by the Scottish Universities Life Sciences Alliance (SULSA, www.sulsa.ac.uk), aimed at facilitating collaborations and common approaches to tackle what is recognised internationally as a fundamental threat to global health. The first day focused on research, the second on policy and integrating strategies (including funding) to counter drug resistance.

Scotland, with its well-established and highly respected antimicrobial research and product development landscape, has already begun to grapple with the problem of AMR, and is now trying to further boost research and innovation in the field. The meeting afforded delegates the opportunity to discuss issues related to AMR (both from a clinical and a research perspective) and to see an overview of the progress being made.

2. The Search for New Antimicrobials

Since the discovery of penicillin by the Scottish-born Alexander Fleming in 1928 we have taken antibiotics for granted. However, things are now changing. A worrying rise in drug resistant bugs means we risk losing these "wonder drugs" which protect us from potentially life-threatening infections.

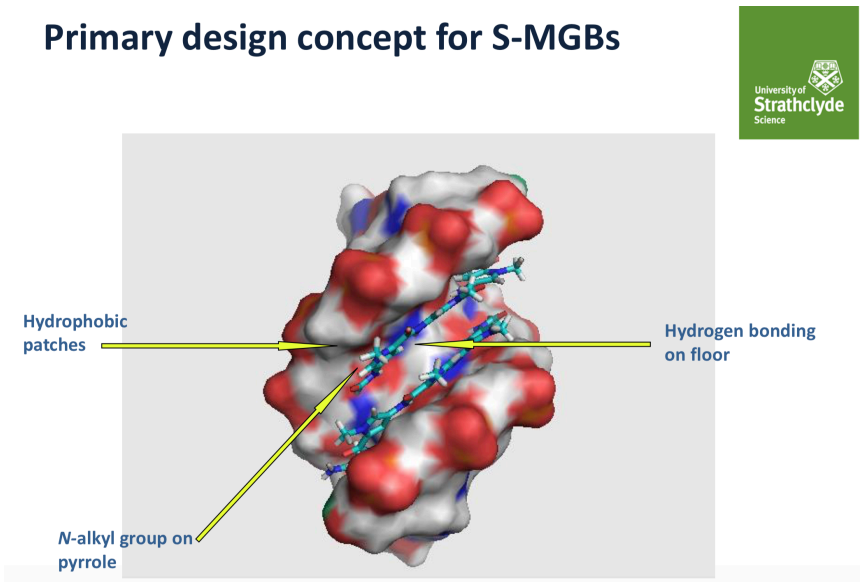
This state of affairs calls for reinvigorated efforts in the pursuit of novel antimicrobials, an area of research which has suffered a pharma "discovery void" since the late 1980s. New weapons are needed to fight resistant pathogenic bacteria but also other nasty microorganisms such as fungi *Candida auris*, the "MRSA of mycology". Unfortunately, as pointed out by Professor Neil Gow from the University of Aberdeen, fungal infections attract little attention or funding, despite affecting over a billion people globally and causing twice as many deaths as malaria.



Source: Slide from Dr Deborah O'Neill, Novabiotics, SULSA AMR Conference (April, 2018)

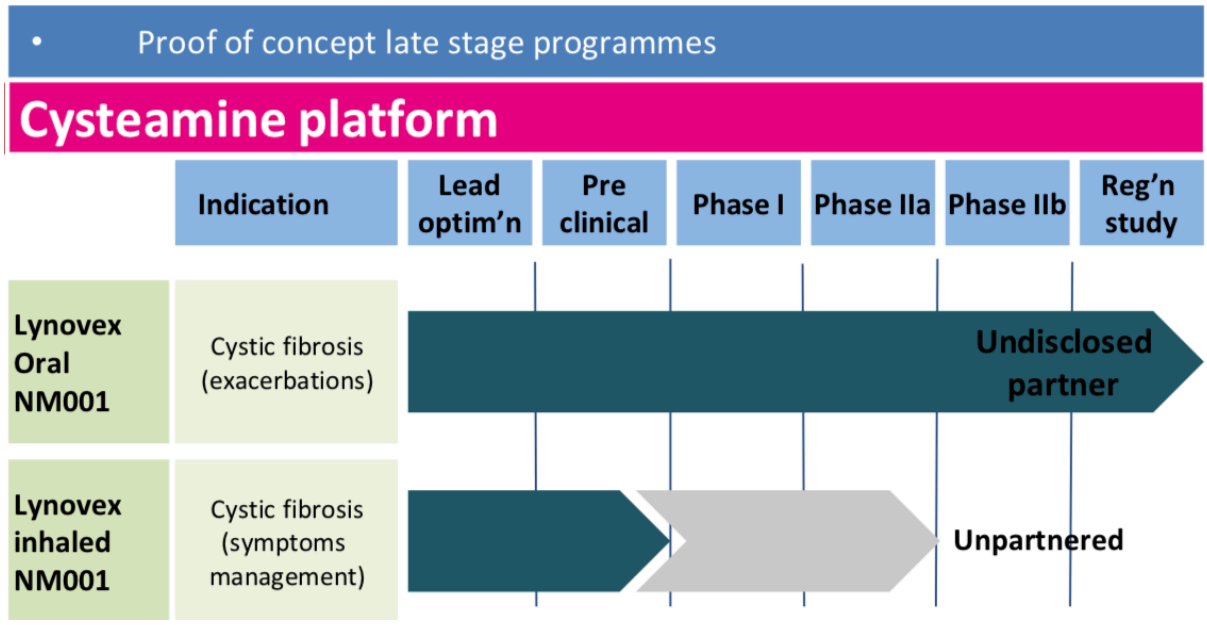
Antibacterial drug discovery is equally challenging. Researchers have to take into account the multiple mechanisms that bugs have evolved to escape being killed, as explained by Professor Ian Gilbert, from the University of Dundee. These defence mechanisms include efflux pumps and the formation of biofilms, which then support persisters: metabolically inactive bacteria either resistant or tolerant to drugs. Dr Alison Mather from the Quadram Institute explained how this new interdisciplinary institute is working at the interface of food science, gut biology, human health and disease to address AMR.

Despite the difficulties, some innovative tools are being developed. Professor Colin Suckling (The University of Strathclyde) presented a collaboration with MGB-Biopharma and their new class of anti-infective minor groove binder compounds against *Clostridium difficile.* These compounds are currently in phase II clinical trials. Suckling believes that S-MGBs, when fully developed, have the potential to make a substantial contribution to anti-infective therapy with a greatly reduced risk of the rapid emergence of resistance. A truly new class of compounds with novel mode of action, like these minor groove binders, was last seen in the year 2000.



Source: Slide from Prof. Colin Suckling, University of Strathclyde, SULSA AMR Conference (April, 2018)

A completely different approach was illustrated by Dr Deborah O'Neil (Novabiotics) who is targeting infection by using host-derived non-antibiotic antimicrobials. Novabiotics is capitalising on host defence systems that have co-evolved with microbes, developed to mitigate resistance. Two of their re-engineered human immune defence molecules are already in clinical trials and more are in preclinical development. In March 2018, the FDA granted Fast Track Designation for NovaBiotics' orally administered form of Lynovex® for the treatment of acute pulmonary exacerbations in cystic fibrosis. Lynovex® is a first-in-class dual mucoactive-antibiotic therapy for CF, currently in a global Phase IIb clinical trial.



Source: Slide from Dr Deborah O'Neill, Novabiotics, SULSA Conference (April, 2018)

In the near future novel medicines might be discovered among the unknown metabolites of actinomycetes, the same bacteria that produce most of the antibiotics we currently use, as shown by the work of Dr Katherine Duncan (The University of Strathclyde). There was a lot of discussion around natural products during the meeting.

During the breakout session *Speeding the antibiotic discovery pipeline*, led by Professor Ian Gilbert, the major questions facing the field were identified and discussed, along with key challenges researchers face. Mapping of Scottish expertise was also done – we are very strong in areas such as drug discovery and natural products. The discussion identified a need for a world-wide facility like the Synchrotron for structure elucidation of natural products. E.g. National Centre for Metabolite Analysis

2.1 Major Questions Facing the Field

- What are the key challenges to developing new antibiotics and how do we solve them?
- How do we find the best drug targets?
- Are there any quick wins?
- How can we speed up the drug discovery process?
- Do we have the right Target Product Profiles/ Compound Progression Criteria?
- Side effects (low tolerance for them)
- Review of drugs that have failed
- Delivery approaches
- De-replication
- Do we need static or cidal antimicrobials? Do we need narrow or broad spectrum?

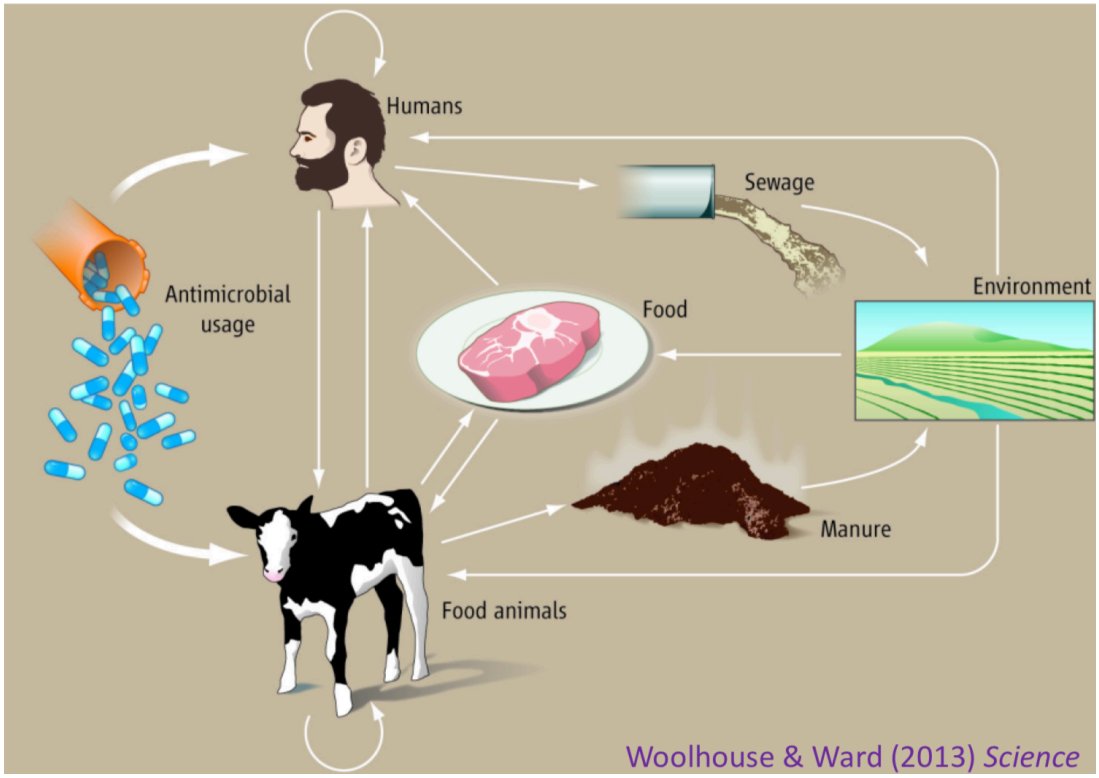
2.2 Key Challenges in Drug Discovery

- Obtaining sufficient compound levels in cells
  - Difficulty getting compounds into bacteria
  - Molecules are often subject to efflux
- Resistance (and its rapid generation)
- Biofilms
- Persisters (dormant or slow growing bacteria that are often resistant to current antibiotics)
- Funding, particularly gaps in funding drug discovery
  - Of note, the SULSA Assay Development Fund run by the European Lead Factory in Newhouse, has had another funding round (closed 1st July 2018). This fund helps researchers progress assays to readiness for industry-standard HTS campaigns.

3. A One Health Problem with Unresolved Dynamics

The introduction of novel antimicrobials is only one part of the solution to combat AMR. History tells us that for every new antibiotic introduced, resistance is soon to be found. AMR is found everywhere in our environment as bugs evolve these defences to compete with other microbes.

Humans, farm animals and the environment interact with each other and their respective bacterial partners. Bacteria, their mobile genetic elements and drug residues can move in between these three interconnected players in ways we are only starting to unravel. AMR is a quintessential One Health issue. Only an integrated approach, with interventions in all three of these domains, will have an impact, Professor Mark Woolhouse (University of Edinburgh) stressed. He pointed out that failures in global surveillance may be preventing early detection of antibiotic resistant isolates.



Source: AMR in a One Health Issue, Woolhouse & Ward (2013)

During the breakout session A *One Health approach to tackling AMR,* led by Professor Dominic Mellor (University of Glasgow), delegates explored what exactly the term "One Health" means, and how the use of this terminology can confuse the issue. Delegates agreed that the AMR community needs to find a way to bring people together to foster networking, to make people aware of each other's work and broaden their own understanding, because of the breadth of topics that come under the One Health umbrella. It was agreed that the lack of consensus in the data format between agencies, and the way in which data is interpreted for people's own use can be a problem. Whilst there is good funding for data generation, there remains very little for data analysis and mining, and integration of data from different sources. Finally, the lack of communication between the research and policy communities should be addressed. Human health is inextricably linked to environmental health, and there was agreement that the AMR community should work together to initiate a strategic formulation of solutions.

4. The Diagnostic Problem – Surveillance is Key

Of all the key points explored during the conference, the ability to have faster, cheaper and more sensitive diagnostic ability was a clear priority. When it comes to the clinic, the first hurdle is the correct and prompt identification of the infectious agent and its potential drug resistance spectrum. This information is needed to allow the selection of the appropriate treatment, avoiding the misuse of antibiotics which is associated with resistance development.

However, as Dr Till Bachman, from The University of Edinburgh, pointed out, rapid diagnostics is still an unmet need in clinical microbiology. He and his team are working

on several projects aimed at shortening the time required for a diagnosis that currently can take up to 72 hours. Professor Stephen Gilliespie from The University of St Andrews reiterated the clinical need stressing how in GP surgeries and clinics most diagnostics fail to make an impact because they take longer than the ideal 30 minutes for a result. Funding challenges such as the £10m Longitude Prize (www.longitudeprize.org/challenge), which is awarded for invention of an affordable, accurate, fast and easy-to-use test for bacterial infections, are helping drive research efforts in diagnostics.

Despite the global recognition of AMR as a problem and the launch of initiatives such as Global AMR Surveillance System (GLASS) and Global PPS we have no clear picture of how AMR spreads. As Professor Dilip Nathwani (NHS Tayside, University of Dundee) emphasised, better surveillance data are required. During the panel session delegated explored the question *Is an AMR Armageddon really upon us or are reports exaggerated?* The answer? We do not really know as exhaustive epidemiological data is not available. So far, most of our data on AMR is based on reported clinical cases with little known on the extent of resistant bacteria in the general population.

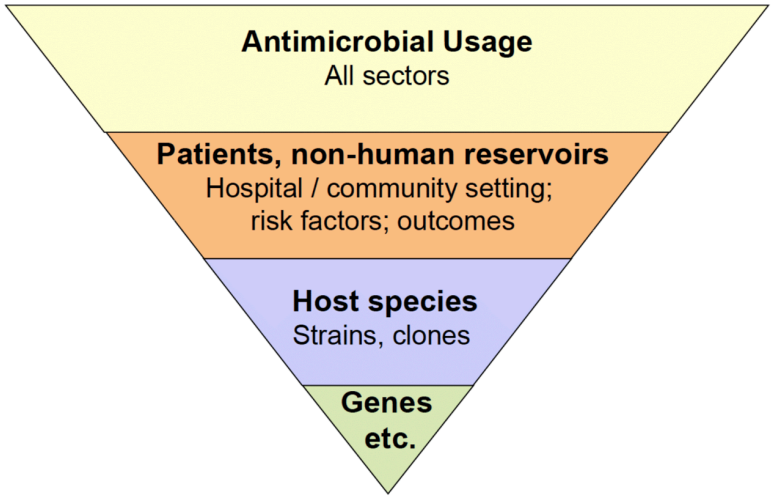
During the *Diagnostics* breakout session, led by Dr Till Bachmann, delegates explored the issue of identifying the microbe, or having enough sensitivity, and how this links to confidence levels required by doctors to *not* prescribe a drug. Attendees also discussed the value of data – and if more was better and if all data was valuable, as bad data can lead to bad choices and sometimes it might be better to not have any data. This is often highlighted in the differences between a researcher and clinician's point of view, as well as how data is interpreted.

5. Antibiotic Stewardship and Education – A Clinical and Public Health Perspective

Professor Dilip Nathwani also explored how we could improve antibiotic stewardship and improve patient outcomes by asking *what data do clinicians need?* It was agreed they require a multitude of information: Good informatics including local epidemiology, genomic and phenotypic information, other data to support risk profiling, rapid diagnostics, backed up by good stewardship which requires learning from implementation science. The effectiveness of interventions must be measured by their impact on patient outcomes. George Leahy from Public Health England (PHE) described the UK's AMR Strategy 2018-2023 and PHE's role in delivering it. PHE does this via surveillance and intelligence, generating and using the evidence-base, analytics and modelling, providing advice on setting ambitions, designing incentive schemes, behavioural insights, marketing, and advocacy through their Antibiotic Guardians and Keep Antibiotics Working campaigns.

Public Health England

The complexities of AMR epidemiology



Source: Public Health England, 2018

Equality and social issues must also be part of the equation when tackling AMR. Professor Eleanor Anderson from Health Protection Scotland pointed out that in Scotland, 1 in 8 people are admitted to a hospital each year, and of those patients, 1 in 3 are prescribed an antibiotic. To reduce this HPS suggests that all practices (not just the high prescribers) should engage in efforts to improve antimicrobial stewardship. Better diagnostic coding, more precise prescribing guidelines, and a deeper understanding of appropriate long-term antibiotic use would allow identification of further possibilities for reductions in use.

Dr Jonathan Pearce from the MRC said "AMR is 'glocal'": a shared problem with different local drivers. Each driver will need to be considered when planning interventions such as restrictions on the use of antibiotics. On the other hand, access to antibiotics for those who cannot afford them should be an international priority.

Dr Clare Taylor (Edinburgh Napier University) showed that education of not just medical staff and veterinarians, but also of the general public on the topic of AMR and the responsible use of antibiotics is essential as part of the effort to prolong the life span of these life-saving drugs. Ultimately, while AMR is primarily the consequence of inappropriate prescribing, it occurs in the wider context of many public health considerations, including an ageing population, multimorbidity and socio-economic drivers on health.

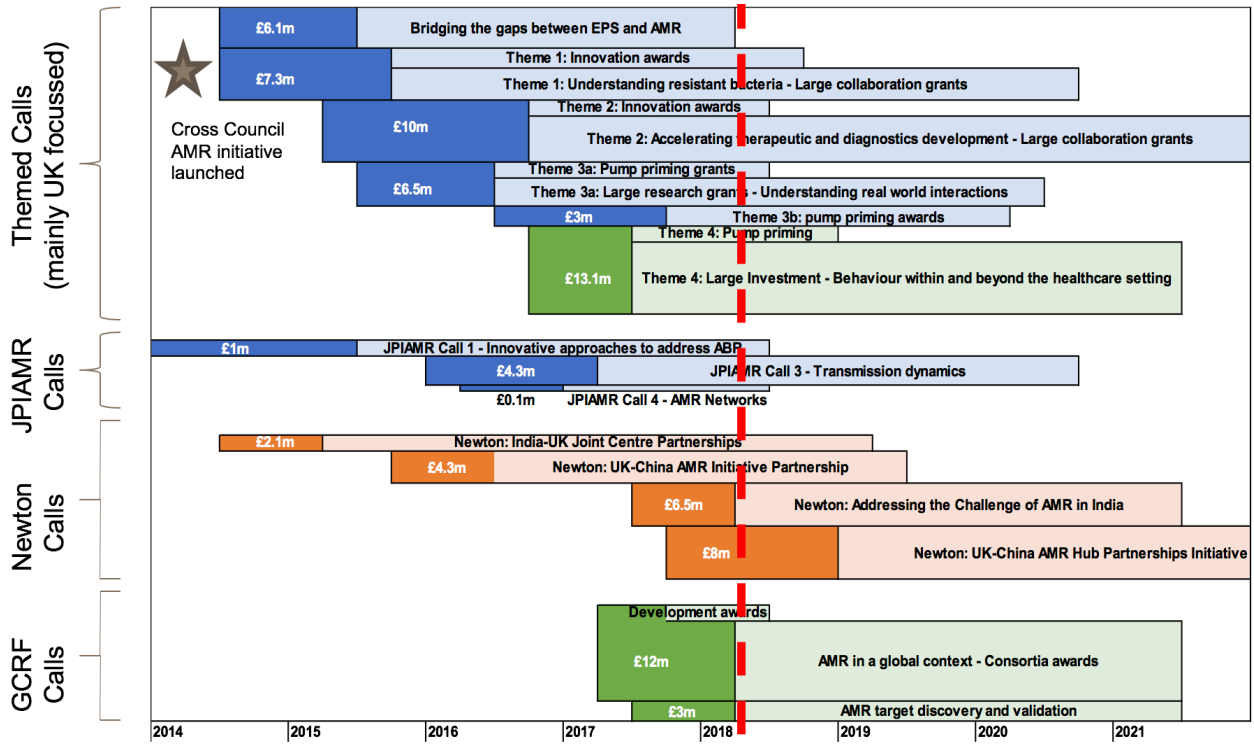
One issue that was discussed throughout the conference, was side-effects of antimicrobials. Patients will tolerate quite severe side-effects of cancer treatment for example, but are not prepared to endure little/any side-effects of an antibiotic, which therefore makes the approval of new treatments even more difficult. During the breakout session*, Clinical considerations in AMR,* led by Professor Dilip Nathwani, delegates explored why doctors are overprescribing

antibiotics, as well as the lack of diagnostic tests available elsewhere - for example in America you can perform a quick diagnostic test to identify if an infection is viral. There was a lot of discussion around why patients are often non-compliant, versus what the evidence is for the duration of treatment, and how these feed the development of resistance.

During the breakout session led by Dr Eleanor Anderson, *Public Health considerations in dealing with AMR*, delegates surveyed ways in which evidence of environmental impact could be integrated into public health. It was agreed that AMR is in effect a "primer" towards a more integrated outcome of public health: eating habits, lifestyle and the gut microbiome, and that AMR needs to be set in the context of socio-economic determinants.

6. Funding AMR Research

Jonathan Pearce of UKRI (Medical Research Council) presented the UKRI's AMR initiative funding portfolio, which spans themed funding calls, JPIAMR calls, Newton funding and Global Challenge Research Funding calls. Jonathan said that it appeared that health economics was being underutilised and that there were prospects for leveraging health record data (and that given Scotland has excellent medical records, this could be an opportunity). In addition, given the value in prioritizing drivers/interventions in a systems approach, multi-scale modelling may be worthy of promoting. He also pointed out there could be better integration of transmission studies whilst ensuring they are linked to impacts (for example on the environment). He also stressed it is important to promote further integration between the social and bio-sciences.



Source: Medical Research Council, 2018

Mike Turner from the Wellcome Trust highlighted that Wellcome's approach to funding AMR generally relied on supporting large-scale initiatives where the consortium is invited to apply for funding, and they have committed £175m over 5 years for targeted, outcome led projects. However, Turner stressed that responsive-mode funding will continue to support AMR research. Wellcome has spent £287m in AMR since 2004, including: basic science (£108), translation (£122m), and epidemiology (£34m). He said that there had been significant investment in translational research for therapeutics in a smaller number of projects compared to basic science, but that they have given little support for diagnostics or public engagement. He highlighted the CARB-X Drug discovery pipeline project, to which Wellcome has given £125m in 5 years, which has supported 34 projects to date in 7 countries.

During the breakout session *Maximising funding opportunities for AMR research*, led by Dr Nick Tucker, delegates explored ways in which AMR research could get further funding, for example via DTP programmes, as well as the need for interdisciplinary working. Whilst there was an agreement that networks were a good idea, a challenge identified was identifying who should be involved. For AMR research, which requires a broad spectrum of disciplines, this can be difficult. One take-home message from the funders' talks was that funders are happy to discuss research ideas and that researchers should not shy away from making contact with the funders to discuss their ideas.

7. Poster Prizes

There were 49 posters displayed during the conference. Prizes were awarded for the best posters as judged by the steering committee:

Winners:

Ruth Bowness (St Andrews) - *Using individual-based mathematical models to study antibiotic resistance*

Rebecca Tonner and Fiona Henriquez (University of the West of Scotland) - *Genes of past, present and future: does legacy pollution contribute to antibiotic resistance in industrialised estuaries?*

Highly Commended:

Madhuri Barge (Glasgow) – *Developing protein antibiotics for treatment of AMR Pseudomonas aeruginosa*

Rebecca McHugh (Strathclyde) – *Exploring Aurodox, A potential anti-virulence compound for the treatment of Escherichia coli infections of the gut*

Image: Prof. Mike Barrett, SULSA Director, and Rebecca McHugh, winner of highly commended prize

8. SULSA Activities to Help Address the Challenges of AMR

8.1 Seed-Funding Call

To continue the momentum started at our AMR conference, the Scottish Universities Life Sciences Alliance (SULSA) are providing funding for collaborative projects to address the challenges surrounding antimicrobial resistance. This funding is to enable researchers from different Scottish Universities to collaborate to gather preliminary data and develop proposals with the aim of attracting further funding from external sources.

The successful applications were:

- Prof. Rosalind Allen (Edinburgh), Prof. Gail McConnell (Strathclyde) and Nicholas Bommer (Edinburgh): Catheter-associated urinary tract infections: linking AMR to biofilm formation.
- Dr Stephen Fox (Glasgow), Dr Cosmika Goswami (Glasgow) and Dr Kerry Pettigrew (St Andrews): Genome Sequencing of Carbapenemase- Producing Enterobacteriaceae (CPE) from Scottish Hospitals for AMR genes and their mobile elements.
- Dr Gillian Halket (Strathclyde) and Prof. Carol Munro (Aberdeen): Antifungal potential of compounds produced by thermophilic Actinobacteria from compost, upon strains of azole resistant Aspergillus fumigatus.
- Dr Charles Knapp (Strathclyde), Dr Fiona Henriques (University of the West of Scotland), Prof. Rosalind Allen (Edinburgh), Dr Andrew Free (Edinburgh), Dr Eulyn Pagaling (James Hutton Institute), Dr Lisa Avery (James Hutton Institute) and Dr Richard Allan (James Hutton Institute): The effect of drinking water treatment on antimicrobial resistance.
- Dr Katherine Duncan (Strathclyde), Dr Eulyn Pagaling (James Hutton Institute), Prof. Tim Daniell (James Hutton Institute), Prof. Rosalind Allen (Edinburgh) and Dr Simon Titmuss (Edinburgh): Microbial microfluidic drug discovery – 21st Century innovation to accelerate the Fleming antibiotic discovery pipeline.
- Dr Till Bachmann (Edinburgh), Prof. Andrew Porter (Aberdeen), Dr Soumya Soman Palliyil (Aberdeen) and Dr Holger Schulze (Edinburgh): Electrochemical biosensor for the detection of bacterial quorum sensing compounds in respiratory diseases.

8.2 Scottish (SULSA) Assay Development Fund

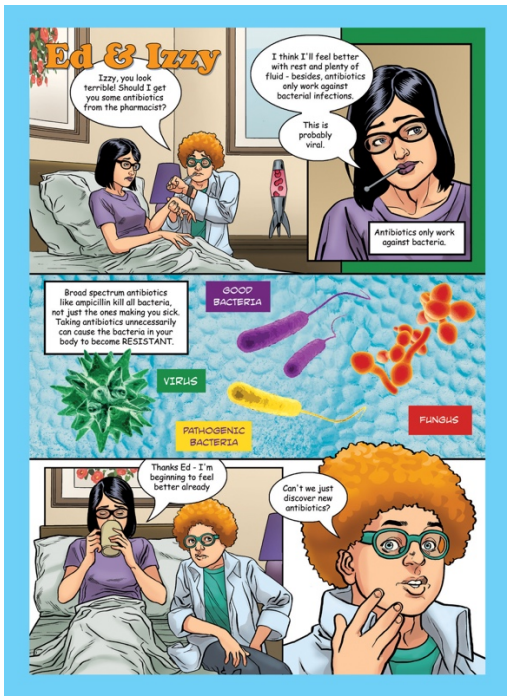
This fund, run by the European Lead Factory in Newhouse, has had another funding round (closed 1st July 2018).

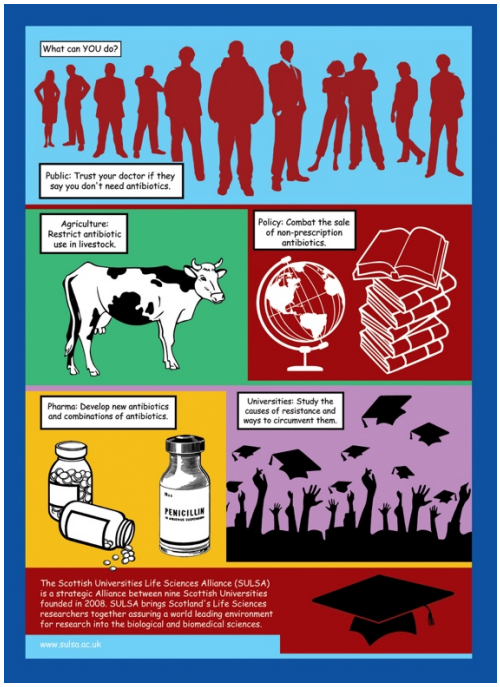
Many scientists in SULSA universities have discovered scientifically interesting, high quality, novel molecular targets and assays. However, they are a long way from being in an HTS compatible assay format. This fund helps researchers progress assays to readiness for industry-standard HTS campaigns.

The fund covers consultancy by experienced screening scientists, a pilot screen of ca. 5000 compounds, and consumables.

8.3 AMR Comic

SULSA has produced a comic highlighting the history of antimicrobial discovery, how antibiotic resistance is spreading, and the impact overuse antibiotics are having. In collaboration with Public Health England, these comics will be freely available for distribution.





Credit: Written by Isabel Vincent, drawn by Gary Erskine and coloured by YelZamor

8.4 SULSA Report: Scotland's War on Germs

SULSA Director, Mike Barrett, has written a SULSA report *Scotland's War on Germs*, detailing Scotland's role in the history of antibiotic discovery, and in assuring an antimicrobial future. This report has been sent to funders, journalists and government officials, and is available to download at www.sulsa.ac.uk/sulsa-reports.

SULSA

SULSA, 2018

Scotland's War on Germs

Michael Barrett
Jill Inkster
Allison Jackson

Summary:

Bacteria are germs that can cause a multitude of diseases.

They are developing resistance to drugs, called antibiotics, that are used to treat them.

This antimicrobial resistance problem threatens many aspects of modern medicine.

Beyond re-awakening the threat of diseases like TB, cholera and typhoid, processes like surgery translation and childbirth are threatened too.

This is because bacteria able to grow in our bodies, that we can generally kill easily with antibiotics, may develop resistance too.

The first great medical leap forward against bacteria came in the mid-nineteenth century in Glasgow, where Lord Lister introduced antiseptic methods to kill bacteria in medical operating rooms.

In 1928, the Scottish doctor, Alexander Fleming, discovered penicillin – and triggered the age of antibiotics.

Scottish scientists, doctors, vets and public health officials remain at the forefront of research into ways to beat antimicrobial resistance today.

In this feature article we discuss the amazing contributions Scotland has made to the war on germs.

Is an antimicrobial resistance Armageddon upon us? Are the drugs that have kept infectious agents at bay for decades about to fail? A report by Lord Jim O'Neill in 2016 predicted that by 2050 we might be seeing as many as 10 million deaths globally caused by antimicrobial resistant infections which will also place an annual economic burden on societies running as high as a hundred trillion pounds per year. O'Neill's report has helped galvanise efforts to combat the threat and Scotland is set to continue its role as a global leader in combating microbial disease.

Sir Alexander Fleming: The Scotsman who discovered penicillin

For over 60 years we have taken it for granted that we are unlikely to be killed by bacterial infections. Just 100 years ago, diseases like tuberculosis, typhoid, cholera, bacterial pneumonia and sepsis accounted for around half of all deaths. Average life expectancy is now twice what it was back then. This change can be attributed, in part, to a serendipitous discovery by a young Scottish doctor, Alexander Fleming, from Darvel in Ayrshire, who is credited with discovering a class of chemicals that we now call antibiotics. In the summer of 1928, while working at St Mary's hospital in London, he went on holiday and left an open plate of bacteria behind. Returning to work, he found a fungus growing on the plate. What's more, the fungus had killed the bacteria. Fleming realised that the fungus was secreting something that was toxic to the bacteria. He set about isolating this substance that he called penicillin. However, without the kind of chemical separation skills needed he found the task too tough and dropped it. It was nearly a decade later that a group in Oxford, working under the Australian pharmacologist and pathologist Howard Florey, purified penicillin, allowing its true potential to be realised.

Figure 1. Sir Alexander Fleming with his Petri dish. Source www.uk.businessinsider.com

8.5 Public Health England's Antibiotic Guardian Awards

SHORTLISTED
ANTIBIOTIC GUARDIAN AWARDS
2018

Because of the conference, SULSA was shortlisted for the 2018 Public Health England's Antibiotic Guardian Awards in the research category. These awards champion those organisations and individuals who have demonstrated achievement in tackling antimicrobial resistance at a local, regional or national level.

9. AMR Consultation SULSA Response

Please see Appendix A to read our AMR consultation response.

10. X-AMR – New Microbiology Society Pop-up Journal

Antimicrobial resistance (AMR) is a cross-disciplinary issue, with ground-breaking studies currently bringing together clinicians and modellers, veterinary and soil scientists, microbiologists and anthropologists. Yet finding a home for the unique publications from this research is difficult. The Microbiology Society is providing such a home with a new pop-up journal for cross-disciplinary research on antimicrobial resistance: X-AMR.

X-AMR is a unique platform for all researchers from microbiologists, clinicians, epidemiologists, social scientists and policymakers to physicists, chemists and engineers, to ensure that cross-disciplinary antimicrobial resistance (AMR) research across disciplines gets the visibility and impact that it deserves. All our content will be free-to-read immediately on publication without any restrictions.

Simply choose the Microbiology Society journal (*Microbiology*, *Journal of General Virology*, *Journal of Medical Microbiology*, or *Microbial Genomics*) that best fits with your article and submit your work as normal through the journal's online submission system, mentioning 'Submission to X-AMR' in the cover letter to help assign it to the correct Editor. Any articles that are outside the typical scope, for example material sciences, should be submitted to *Microbiology*.

For more information see www.microbiologyresearch.org/about/xamr.

11. Special Thanks

We would like to thank the Conference Steering Committee:

- Dr Eleanor Anderson (Health Protection Scotland)
- Dr Till Bachmann (The University of Edinburgh)
- Professor Mike Barrett (SULSA and Wellcome Centre for Molecular Parasitology, The University of Glasgow)
- Professor Tom Evans (University of Glasgow)
- Professor Ian Gilbert (Drug Discovery Unit, The University of Dundee)
- Professor Stephen Gillespie (The University of St Andrews)
- Professor Neil Gow (MRC Centre for Medical Mycology, The University of Aberdeen)
- Dr Paul Herron (University of Strathclyde)
- Professor Dominic Mellor (The University of Glasgow)
- Professor Dilip Nathwani (The University of Dundee and NHS Tayside)
- Professor David Smith (Heriot Watt University)

We would like to thank our speakers:

- **Professor Neil Gow**, University of Aberdeen: Medical Mycology and AMR: A Rapidly Emerging Problem and Global Health Challenge
- **Dr Clare Taylor**, Edinburgh Napier University: Applying Microbiology to the Antimicrobial Problem
- **Professor Mark Woolhouse**, University of Edinburgh: Is There a Link Between Antibiotic Usage in Livestock and AMR in Human Patients?
- **Dr Katherine Duncan**, University of Strathclyde: Omics Guided Antibiotic Discovery from Our Oceans
- **Professor Ian Gilbert**, University of Dundee: Challenges in Antibacterial Drug Discovery
- **Dr Deborah O'Neil**, Novabiotics: Novel, Immune System Based Approaches to Tackling AMR
- **Dr Till Bachmann**, University of Edinburgh: Rapid Diagnostics to Combat Antimicrobial Resistance
- **Dr Alison Mather**, Quadram Institute: Whole Genome Sequencing to Understand the Epidemiology and Transmission of Antimicrobial Resistance
- **Professor Colin J Suckling**, University of Strathclyde: Strathclyde Minor Groove Binders (S-MGBs), A Family of Anti-Infective Agents
- **Professor Mike Turner**, Wellcome Trust: Funding for Antimicrobial Resistance Research at Wellcome
- **Dr Jonathan Pearce**, MRC: AMR – A Cross-Disciplinary and Global Challenge
- **Professor Dilip Nathwani OBE**, University of Dundee, NHS Tayside: Global and UK Epidemiology and Burden of Multi-Drug Resistant Bacteria
- **Dr Eleanor Anderson**, Health Protection Scotland: Control of AMR in Scotland
- **George Leahy**, Public Health England: Shaping PHE's Role in the Development of the Next 5 Year Action Plan

We would like to thank our sponsors for their support:

- Glasgow Polyomics
- Marks and Clerk
- SEFARI
- The Society of Microbiology

Appendix A. SULSA AMR Consultation Response

Written evidence from the Scottish Universities Life Sciences Alliance (SULSA)

Written evidence submitted by Scottish Universities Life Sciences Alliance (SULSA) which highlights the work of SULSA members contributing to the delivery of the AMR strategy.

About SULSA

1. The Scottish Universities Life Sciences Alliance (SULSA; www.sulsa.ac.uk) is a strategic partnership of nine Scottish Universities (Aberdeen, Dundee, Edinburgh, Glasgow, Heriot Watt, Napier, Robert Gordon, Strathclyde, and St Andrews) that aims to drive the life sciences research sector in Scotland to ensure its global competitiveness. Our main strategic aims are to build competitive consortia and win major research funding, support research facilities and networks, and help early career researchers advance their careers. We also provide policy advice on behalf of the Scottish life sciences community.

Response:

2. The UK AMR Strategy 2013-18 set out the following 3 strategic aims:

i) Improve the knowledge and understanding of AMR

ii) Conserve and steward the effectiveness of existing treatments

iii) Stimulate the development of new antibiotics, diagnostics and novel therapies

Within these three aims, there were 7 key areas for future action identified. Below we have given examples of where SULSA members have contributed to these focused strategic areas.

Area 1: Improving infection prevention and control practices

3. SULSA members at the University of Aberdeen[1] have produced findings which have helped underpin the European Food Safety Authority (EFSA) scientific opinion on quantifying the risk of human campylobacteriosis posed by consumption of broiler meat in the EU (EFSA Panel on Biological Hazards (BIOHAZ). This provided the impetus for EFSA to produce an opinion on control options and performance objectives in broiler meat production for *Campylobacter* which resulted in the Commission setting performance objectives for *Campylobacter* in broiler production within the EU. The results from the CaMPS studies have fed into the latest Advisory Committee on the Microbiological Safety of Food report on *Campylobacter* that is due to be released later this year and published/presented/cited by Food Standards Scotland and Food Standards Agency.

[1] www.abdn.ac.uk/smmsn/research/impact/combating-campylobacter.php

Area 2: Optimising prescribing practice

4. SULSA members at the University of Strathclyde have been involved in the development, implementation and evaluation of antibiotic guidelines[2]. Adult guidelines for vancomycin and gentamicin prescribing and monitoring were developed and implemented throughout Scotland in 2009. Evaluation of these guidelines identified practice issues that led to the development and implementation of new prescribing support resources. A recent re-audit has demonstrated improvements in practice. Further development of vancomycin guidelines for obese patients is underway. Other studies have achieved an improvement in the use of vancomycin in neonatal and paediatric intensive care patients. Current work is underway to evaluate amikacin dosing guidelines for the treatment of mycobacterial infections and antibiotic dosage regimens for infection prophylaxis in colorectal surgery.

Area 3: Improving professional education, training and public engagement

5. In April 2018, SULSA held a two-day conference on AMR[3] with the aim of informing and coordinating fundamental and applied research activity on AMR within SULSA universities and other relevant organisations in Scotland. The meeting, with 160 delegates, covering both research and policy related to AMR is featured in a blog[4]. Because of the conference, SULSA was shortlisted for 2018 Public Health England's Antibiotic Guardian Awards[5] in the research category. These awards champion those organisations and individuals who have demonstrated achievement in tackling antimicrobial resistance at a local, regional or national level.

6. SULSA commissioned a comic[6] (Written by Isabel Vincent, drawn by Gary Erskine and coloured by YelZamor) highlighting the history of antimicrobial discovery, how antibiotic resistance is spreading, and the impact overuse antibiotics are having. In collaboration with Public Health England, these comics will be freely available for distribution in the near future.

7. SULSA Director, Mike Barrett, has written a SULSA report Scotland's War on Germs[7], detailing Scotland's role in the history of antibiotic discovery, and in assuring an antimicrobial future. This report has been sent to funders, journalists and Government stakeholders.

8. SULSA members at University of Strathclyde, Edinburgh and Edinburgh Napier University are active within Microbiology Society and Society for Applied Microbiology both of which promote education and engagement with AMR, primarily through Learned Societies Partnership on Antimicrobial Resistance (LeSPAR).

---

[2] http:// impact.ref.ac.uk/CaseStudies/CaseStudy.aspx?Id=42287

[3] http://www.sulsa.ac.uk/amr/

[4] http://blogs.biomedcentral.com/bugbitten/2018/05/18/scotlands-contribution-to-the-fight-against-antimicrobial-resistance-highlights-from-the-sulsa-meeting/

[5] http://antibioticguardian.com/antibiotic-guardian-2018-awards-shortlist/

[6] http://www.sulsa.ac.uk/amrcomic

[7] http://www.sulsa.ac.uk/sulsa-reports/

9. The Microbiology Society's Antibiotics Unearthed[8] programme has been adopted in to undergraduate curricula at Glasgow, Edinburgh and Edinburgh Napier Universities[9] to promote student engagement with AMR.

Area 4: Developing new drugs, treatments and diagnostics

10. Following the two-day AMR conference, SULSA launched a call for seed funding to stimulate collaborative projects to address the challenges surrounding antimicrobial resistance[10].

11. The Scottish Biologics Facility (SBF)[11] at University of Aberdeen has developed a portfolio of monoclonal antibody-based biologics for the early detection, diagnosis and treatment of bacterial and fungal infections. The SBF has a strong research interest in developing novel therapeutics that can prevent bacterial infections by controlling the expression of virulence factors in Gram negative organisms. These 'anti-pathogenic' drugs are less likely to encourage the development of resistance in bacteria compared to conventional antibiotics.

12. With funding from Innovate UK[12], the University of Dundee has created an Antibacterial Drug Discovery Accelerator (ADDA)[13] with the aim of carrying out early phase antibacterial drug discovery. This involves translating fundamental discoveries from microbiologists across the UK into drug discovery projects, to develop novel drug-leads to partner with not-for-profit or commercial partners. This is an area for which it is difficult to obtain funding, but is critical to the AMR agenda to develop novel mode-of-action antibacterials.

13. Researchers at the University of Glasgow[14] have been involved in research to improve the synthesis of Teixobactin-derived compounds with potent activity against *Staphylococcus aureus*.

14. An antibiotic developed at University of Strathclyde is about to enter a phase 2 clinical trial. In collaboration with MGB-BioPharma, Innovate UK has awarded £2.78 million to fund the phase 2 clinical trial of MGB-BP3, the first in a new class of drugs for treating *Clostridium difficile*[15].

---

[8] https://microbiologysociety.org/education-outreach/antibiotics-unearthed.html

[9] https://microbiologysociety.org/education-outreach/antibiotics-unearthed/undergraduate-programme.html

[10] http://www.sulsa.ac.uk/seed-funding/

[11] www.abdn.ac.uk/sbf

[12] https://www.dundee.ac.uk/news/2017/innovate-uk-grant-to-boost-discovery-of-new-antibacterial-drugs.php

[13] http://www.drugdiscovery.dundee.ac.uk/portfolio/antibacterial-drug-discovery-accelerator-adda

[14] http://www.chem.gla.ac.uk/jamiesonlab/#

[15] https://www.strath.ac.uk/whystrathclyde/news/fundingof278mforclinicaltrialsoftreatmentdiscoveredatstrathclyde/

15. SULSA/MSD funding contributed to the development of the studies of minor groove binders for DNA discovered at the **University of Strathclyde** (known as S-MGBs). S-MGBs include individual compounds active against bacteria[16], fungi, and parasites. The SULSA/MSD[17] funding principally paved the way for a successful collaborative bid to BBSRC for the project 'A new drug discovery platform for animal African trypanosomiasis'[18], a project involving the **Universities** of **Edinburgh, Glasgow**, and **Strathclyde**. The drug discovery component of this project is moving well towards identifying development candidates.

16. **Longitude Prize** Discovery Award to researcher at the **University of Strathclyde** to develop 'The Microplate' to a new diagnostic test for antimicrobial susceptibility[19]. Using an interdisciplinary approach (electrical engineering and microfabrication with microbiology), the project combines cutting-edge aspects of these research areas to develop a new antibiotic susceptibility testing that can rapidly test antibiotic sensitivity on a single microchip.

17. Till Bachmann[20] from The **University of Edinburgh** is contributing to the UK strategy on AMR diagnostics through the UK AMR Diagnostics Collaborative and his advisory and judging roles for the Longitude Prize and Discovery Award.

18. Funding from the **Industrial Biotechnology Innovation Centre**[21] in collaboration with GSK is being used to develop stable strains of *Streptomyces* to improve clavulanic acid production at University of Strathclyde.

19. Funding from the Daphne Jackson Trust is supporting a fellow to investigate novel *Actinobacteria* for the production of novel antibiotics at the **University of Strathclyde**.

20. Dr Till Bachmann from The **University of Edinburgh** is the Coordinator of the Transnational Working Group Rapid Diagnostic Tests (AMR-RDT)[22] funded through the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR)[23]. Formed in 2017, AMR-RDT[24] is a multi-sectoral, multi- stakeholder and interdisciplinary working group with global reach. It brings together over 50 key individuals and organisations from 15 countries worldwide that are active in the field of diagnostics and antimicrobial resistance. This group aims to identify barriers for the development and implementation of rapid diagnostic tests to tackle AMR.

---

[16] https://pure.strath.ac.uk/portal/en/projects/the-differing-biological-fates-of-dna-minor-groovebinding-mgb- antibiotics-in-gramnegative-and-grampositive-bacteria(be25e1ea-f41d-48ac-b3f7-48d845d114e7).html

[17] http://www.msd.com/about/our-work/amr.html

[18] https://pure.strath.ac.uk/portal/en/projects/a-new-drug-discovery-pipeline-for-animal-african-trypanosomiasis(ea4465e8-c3b6-4e8e-be03-1131f5c63a1b).html

[19] https://www.strath.ac.uk/whystrathclyde/news/discoveryawardforteamworkingtotackleantibioticresistance/ [20] https://www.research.ed.ac.uk/portal/en/persons/till-bachmann(4c731049-5ce7-4f71-9984-fb216ee36fab).html

[21] http://www.ibioic.com/

[22] https://www.ed.ac.uk/pathway-medicine/antimicrobial-resistance/jpiamr-amrrdt

[23] https://www.jpiamr.eu

[24] https://www.ed.ac.uk/pathway-medicine/antimicrobial-resistance/jpiamr-amrrdt/overview

21.The Scottish (SULSA) Assay Development Fund has a call currently open[25]. Many scientists in SULSA universities have discovered scientifically interesting, high quality, novel molecular targets and assays. However, they are a long way from being in an HTS compatible assay format. This fund helps researchers progress assays to readiness for industry- standard HTS campaigns. The fund covers consultancy by experienced screening scientists, a pilot screen of ca. 5000 compounds, and consumables.

Area 7: Strengthened international collaboration

22.Examples of international collaborations of SULSA members at University of Strathclyde include:

i) Santander/University of Strathclyde International Research Fellowship to Federico Santa María Technical University, Valparaiso, Chile; 2018

ii) SULSA Early Career Research Exchange (PECRE) to Wageningen University, The Netherlands "Bioinformatics approaches to antibiotic discovery); 2017

iii) Marine Alliance of Science and Technology Visiting Fellowship (Mexico), Assessing the biotechnological potential of Antarctic and sub-Arctic sediment cores - a new resource for sustainable antibiotic drug discovery; 2016 – 2017

iv) KMITL Academic Melting Pot, Characterisation of antimicrobial activity from Mangrove Swamps in Thailand; 2018 – 2019

v) Genomic characterisation of antibiotic producing bacteria from the Chilean altiplano; 2015 – 2019

23. International collaboration of SULSA members at University of Glasgow and CIDEIM, Cali, Colombia to examine drug resistance in parasites, bacteria and mosquitoes. Institutional links were achieved by a variety of bilateral training exchanges, together with workshops and symposia (Newton Fund). More than 100 neglected tropical disease researchers benefited, and new inter- institutional collaborations were established, which continue to develop and sustain reciprocal training and research programs between Colombian and the UK towards understanding and mitigating the impact of neglected tropical diseases in Latin America.

24. International collaboration led by University of Edinburgh and researchers at Indian Institute of Technology, Delhi. The project '*User Driven Diagnostics Solutions in a One Health Approach to Tackle AMR'* (Newton Fund)[26] will address the lack of appropriate affordable diagnostics in use in India, by engaging with the user in the community in human healthcare, veterinary and environmental setting to map existing practise and gather user needs to generate target product profiles and user personas. This information will be used to select existing diagnostics and develop novel test in a usable format, and performance and prototype services.

[25] http://www.sulsa.ac.uk/z1x2c3/wp-content/uploads/2018/05/More-Information.pdf

[26] https://esrc.ukri.org/files/funding/funding-opportunities/uk-india-amr-shortlisted-summaries/

25. Dr Till Bachmann (University of Edinburgh) is the founder of the Antimicrobial Resistance Diagnostics Challenge[27] (AMR DxC; @AMR_DxC), an annual international competition and event series that aims to galvanise the next generation of researchers into action. This competition is inspired by the Longitude Prize[28] and driven by the idea that innovation needs interdisciplinary and unbiased thinking as well as international collaboration.

Key actions and priorities for the Government's next AMR strategy that were identified at the SULSA AMR Conference in April 2018 were:

26. Increased funding and support for anti-fungal research and development. This is currently an area of critical concern with the increasing emergence of resistant fungal pathogens.

27. Delegates identified a need for a world-wide facility like the Synchrotron for structure elucidation of natural products. E.g. National Centre for Metabolite Analysis.

28. Gaps in drug discovery funding (particularly in translation into larger screens – SULSA is addressing this via the Scottish SULSA Assay Development Fund).

29. Better surveillance data (capture and assessment), and integration and collaboration across agriculture, healthcare and environment.

30. Increased funding for data: whilst there is good funding for data generation, there remains very little data for analysis and mining, and integration of data from different sources.

31. Improved communication between researchers and policymakers.

32. Increasing support for development of diagnostics: of all the key points explored during the conference, the ability to have faster, cheaper and more sensitive diagnostic ability was a clear priority.

33. Improved education around antibiotics use for veterinary and health workers, as well as the general public.

34. As AMR is a One Health issue, which crosses many disciplinary boundaries, strong networks of researchers from different fields, clinicians, industry and policymakers are essential to drive a coordination, strategic approach to tackling AMR.

[27] https://www.ed.ac.uk/pathway-medicine/antimicrobial-resistance/antimicrobial-resistance-diagnostics-challenge

[28] https://longitudeprize.org

Notes


SULSA
Scottish Universities Life Sciences Alliance