Discussion Meeting Report:
Development of MRC's position on research into antimicrobial resistance
July 17th 2013

1 Background

The use of antimicrobials for the treatment and prevention of infections benefits the individual and the whole of society. Antimicrobial resistance (AMR) is increasing and is recognised as a significant global public health issue, compounded by the fact that there are few new antimicrobials in the development pipeline.
Given the importance of increasing resistance, the shortage of new drugs in development and the need for improved diagnostics, the MRC Infections and Immunity Board (IIB) and Strategy Board have reviewed MRC focus in antimicrobial research. It was agreed that rapid coordinated action is needed and that MRC needs to identify how it can best use funding in this area. IIB was tasked with convening a discussion meeting, chaired by Professor Sharon Peacock (University of Cambridge, IIB Deputy Chair) to further shape MRC strategy and delivery in this area.

2 Format of the day

Participants comprised a broad range of expertise, representing scientists from academia, pharma and the biotech industry. The workshop aimed to build understanding of:

- the problems for research in the antimicrobial development pipeline
- the opportunities for MRC to address these challenges
- how to map problems onto funding schemes
- the options to 'think big' to address the issue.

Professor Sir John Savill, MRC CEO, explained that Strategy Board agreed an initial research focus should be on the molecular mechanisms of bacterial resistance and how that is linked to bacterial pathogenesis and the host response, both at the single cell level and the quorum. Sir John noted that antimicrobial research, whilst strong in the UK, is fragmented, with a wealth of experience shared among numerous organisations in the public and private sectors. A consortia-based approach could bring together academic experts with pharma/biotech expertise, but this needs to be focused around a scientific purpose to be effective.

Given this 'starter for ten', the participants were asked to discuss and further shape potential research questions and the value of networks and consortia in their delivery. The discussions did not include the important issues of better stewardship of existing antimicrobials, surveillance of infection or resistance, late phase trials, the regulatory environment or the business model as these are outside the remit of the MRC.

Professor Peacock introduced examples of how MRC funding, at various levels, has been used to bring groups together to address a common research issue as potential models

of working, such as the Addiction Research Clusters[1], or the MRC Population Health Sciences Research Network[2].

Two talks, from Professor Laura Piddock, University of Birmingham and Dr Lloyd Czaplewski, Abgentis Ltd/Chemical Biology Ventures Ltd, helped set the scene around the development of new antibiotics and the unmet needs. There was opportunity for discussion on the problems for research in this area and the opportunities for MRC to address these challenges. This included a presentation on MRCs funding schemes in this area.

3 Overarching research challenges

Given the changing profile of the most hard to treat bacterial infections in both the healthcare environment and the community, the timeline for new drug development and the increasing rise in resistance to exiting drugs, there is a need to both steward the use of existing drugs better and to develop new antibacterials. New antibiotics could be discovered both by screening for new targets, but also by continuing work on the modification of known classes of antibiotics, which may provide a faster route to market.

However, research needed for the discovery and early development of new antibiotics is challenging and the number of large pharmaceutical companies engaged in this area has fallen over recent decades. In part, this is due to the considerable scientific challenges of antibiotic discovery compared with other drugs. For example, the need to selectively target and kill rapidly growing bacteria without harming the host, and to get an antibiotic into a cell through the cell wall, and avoid being removed by the efflux pumps.

Given the decline in the number of larger pharmaceutical companies with active research programmes in antimicrobial research in the UK, there are fewer opportunities for researchers in this space and a challenge exists to train researchers, both in academia and in industry with the interdisciplinary research skills and expertise required.

4 The scientific challenges

4.1 Antibiotic discovery and development

Given the current landscape, the role of academic research in the discovery and development of new antibiotics is of fundamental importance. There is an on-going need for academic research to contribute through basic studies to greater understand bacterial cellular processes and pathways, such as uptake and efflux and the mechanisms and spread of resistance and persistence of important bacterial pathogens. Therefore, it is important that MRC and others continue to fund such work.

Target identification and validation

Fundamental research may also provide the basis for target identification and validation of small molecule antibiotics. For the proportion of academics involved in antibiotic discovery research programmes, target identification is key. A good target needs to be essential to bacterial survival (ideally hitting multiple bacterial targets), absent in humans and drugable. Researchers and funders need to be aware of these characteristics when embarking on, or funding, programmes of early phase discovery research. Rigorous target validation is crucial and so we need to understand:

- the biology of the putative target;

[1] http://www.mrc.ac.uk/Ourresearch/ResearchInitiatives/Addictionresearch/Addictionresearchclusters/index.htm

[2] http://www.populationhealthsciences.org/

- how compounds can get into bacteria, particularly through the bacterial cell wall;
- efflux systems that remove antibiotics;
- mechanisms of resistance and persistence.

Target validation requires better animal models for target validation plus the 'drugability' of the target also needs assessment. For example, novel chemistry can be used to better understand the sensitivity of the target binding pocket. These are all key areas for MRC-funded academic research, which may be addressed in partnership with industry. An early focus on the emergence of resistance *in vitro* is also crucial; if resistance occurs early *in vitro* the compound is unlikely to become a successful antibiotic.

Screening
It was generally agreed that genomic screening by pharmaceutical companies had not yielded new, viable drug targets and that novel screening methods and culture techniques are important to generate leads. Bacterial physiologists have a role in optimising screening conditions and culture techniques. Using whole cell screening provides a measure of how well compounds can get into a cell and stay there, which is particularly important for natural products.

Current clinically useful antibiotics hit relatively few targets, e.g. peptidoglycan synthesis, protein synthesis and DNA replication, and these targets provide a strong basis for further research with the application of the new technologies and tools. The interaction of biologists with chemists will be particularly important in this regard. For example, known structures and scaffolds of effective antibiotics can provide a starting point for chemists to find innovative ways to modify them.

Novel approaches to discovery
The application of chemistry is also vital to discover new targets, to manipulate current drugs to prevent resistance, and to potentially rescue old compounds which have not reached the clinic due to toxicity or lack of efficacy.

In addition to novel chemistry, synthetic biologists can create novel advantageous analogues of known antibiotics and apply structure-informed de novo drug-design. MRC has an opportunity to build on the work funded by EPSRC and BBSRC in natural product synthetic biology to add value by funding human translational application towards the development of novel antimicrobials.

There remains a large untapped resource of microbial, plant and animal sources and underexplored environmental niches to yield novel molecules and scaffolds on which to base new antibiotics. Whilst it is hard not to re-discover existing compounds in a complex mixture of natural products, recent technological advances mean that rediscoveries can be filtered out and allow synthetic tailoring of key natural product scaffolds. Genomics can be used to discover new secondary metabolites as novel antimicrobial targets and it has been estimated that only a fraction of these pathways have been discovered. Novel secondary metabolites could be generated using synthetic biology by recombining known pathways.

4.2 The host response to infection
An alternative to developing small molecule antibiotics is to develop novel antimicrobial strategies which modify the host response; including vaccines, immunotherapy, and anti-virulence or anti-colonisation approaches.

Development of bacterial vaccines has been aided by the completion of bacterial genomic sequencing and the increased understanding of virulence regulatory mechanisms. We recognise the expertise of industry in this area and collaboration with industry partners

would enhance academic investment into bacterial vaccine research. MRC supports high quality vaccine research proposals through a number of mechanisms but most notably DPFS.

Further research to increase our understanding of using immune defence modulation to target bacterial pathogens would be strengthened by facilitating collaboration between bacteriologists and immunologists. Anti-virulence therapies targeting part of virulence or pathogenicity mechanisms required to cause host damage and disease would not be lethal to bacteria, but could be seen as a 'disease modifying' therapy. There was debate as the benefits of agents that would not necessarily clear the infection, but these could be used either alone or in combination with small molecule antibiotics.

4.3 Diagnostics

Advances in point-of-care diagnostics, and particularly the application of rapid whole genome sequencing, are likely to change the antimicrobial market over the next 10-15 years. A faster and more specific diagnosis of the causal bacterial infection may permit the use of narrower spectrum antibiotics. A more rapid identification of the causative infectious agent would enable the correct antibiotic to be prescribed more rapidly. It would also enable patient stratification and the use of narrow spectrum, or pathogen-specific agents in future. MRC should support research in the area of diagnostics and collaboration with EPSRC and TSB would bring together technologists, engineers, chemists, bacteriologists and biotech expertise.

Molecular diagnostic tools can also be used to track the spread of resistance. Infection dynamics, carriage and tracking the spread of resistance are also of vital importance as areas where UK researchers could lead. For example, whole genome sequencing of methicillin-resistant *Staphylococcus aureus* (MRSA) has been shown to define transmission pathways at both global and local levels[3].

5 Mechanisms to address the challenges

5.1 Academic /industry interactions

Given the reduction in the number of pharmaceutical companies working in this space, academia has a pivotal role in the ongoing development of new antimicrobials. Difficulties with the business model for antibiotics have been well described, and were outside the scope of this meeting. For those academics wishing to work in this space, there are lessons to be learned from the pharmaceutical industry to aid the discovery and development of new antibacterial agents[4]. These include the need to focus milestone-driven projects on areas with potential impact on the clinic, and lessons from industry failures such as difficulties in developing antibiotic drugs for Gram negative infections. Academic research looking at antimicrobial targets needs to be aligned with industry and the market pull. Collaboration, both within academia and with pharma and the biotech industry will be important to focus the UK's research strengths.

5.2 Chemists/biologists interaction

The UK has strength and depth in synthetic organic, combinatorial and medicinal chemistry and these skills and knowledge need to be harnessed to develop new antimicrobials. MRC should engage chemists to work with biologists. The integration of novel chemistry with biology, and its application to new and existing antibiotics, could pave the way for new classes of drugs and potentially rescue failed products. MRC should

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[3]Harris SR *et al*. Evolution of MRSA during hospital transmission and intercontinental spread. Science. 2010 Jan 22;327(5964):469-742010 Jan 22;327(5964):469-74. doi: 10.1126/science.1182395 2010 Jan 22;327(5964):469-74

[4] http://antibiotic-action.com/wp-content/uploads/2013/08/Learning-Lessons-report.pdf

take a lead on linking up with BBSRC and EPSRC in this area. Partnership working will ensure that more can be achieved and that innovative multidisciplinary applications will not fall between Research Council boundaries. Workshops on specific themes could bring together chemists and biologists to facilitate new collaborations and applications, modelled on MRC's past experience of bringing together experts from different disciplines, i.e. addiction research clusters [5]or in systems immunology[6].
Review boards assessing applications bringing together chemists and biologists should also appreciate the strategic importance of the application of chemistry to antimicrobial research.

One opportunity could be to establish a cross-Council highlight notice for innovative, multidisciplinary proposals bringing together chemists and biologists. Highlight notices do not require new money and therefore could be quick to instigate. The peer review would need to be developed to ensure there isn't double jeopardy between Councils.

5.3 Research focused consortia

High quality research projects in key areas will bring together academic, and where appropriate, industrial researchers to address common goals. MRC funding should aim to answer broader questions covering basic, applied and translational research.

In those areas where industrial collaboration is beneficial, working in a precompetitive environment could ensure that issues associated with intellectual property could be avoided and would de-risk a project at the early stage. Examples of work that that could be undertaken in such a way are technology platforms, addressing methodological and process issues, PK/PD, screening strategies, hit to lead strategies, developing better animal models, in vivo efficacy, or biomarkers. In such an environment projects could be developed to a point where industry would take them forward. The reduced risk and associated reduced costs at the early stage would provide incentives to industry to engage and then to take forward promising products to later stage development. Successful examples include the MRC stratified medicine consortia[7].

Any newly established foci for research must be driven by scientific questions. These could be organised around groupings of researchers in the public and private sectors and across organisations to draw together UK strengths and multi-disciplinary expertise into topic-specific consortia. As discussed, MRC could facilitate workshops to scope areas of research but the research community, in academia and industry, must coalesce around the scientific areas and develop research proposals to bring to funders. Suggested topics include:

- **Proven antibacterial targets**. Using whole cell screens to examine targets such as DNA replication, RNA synthesis, protein synthesis, cell wall biosynthesis and membrane lipid pathways.
- **Novel antibiotic targets**. Fundamental research on novel targets using innovative approaches.
- **Rescuing old drugs**. Further research should focus on both previous targets that failed to reach the clinic and those drugs which are now of little use due to widespread resistance. Given the recent advance in technologies available, novel chemistry or synthetic biology could be applied to manipulate existing structures to either increase efficient, decrease toxicity or to restore susceptibility.

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[5] http://www.mrc.ac.uk/Ourresearch/ResearchInitiatives/Addictionresearch/Addictionresearchclusters/index.htm

[6] http://www.mrc.ac.uk/consumption/groups/public/documents/content/mrc008986.pdf

[7] http://www.mrc.ac.uk/Newspublications/News/MRC008947

- **Enhancing existing treatments**. Further research can address ways to enhance existing antimicrobials, for example: efflux pump inhibitors to ensure that antibacterial compounds remain in the cell; the development of molecules to disrupt biofilms to increase efficacy of existing antibiotics; the study of existing drugs in combinations; immunomodulation - using and enhancing the body's defence systems against bacteria in the context of the microbiome; anti-virulence strategies, e.g. phage therapy.
- **Genomics and secondary metabolites**. Harnessing genomics to discover new natural products and secondary metabolites as novel antimicrobial targets. Using synthetic biology to generate novel secondary metabolites by recombining known pathways.
- **Mechanism and spread of resistance**. Fundamental research on how resistance and persistence emerge, and resistance spreads.

Focused research consortia will require strong leadership from within and funding for research. No new money is currently on the table from Government so funders and researchers will need to make best use of existing resources and funding mechanisms in the short term. Researchers should be open to wider collaboration with UK experts in their field and beyond and avoid duplication. Existing funding could be used to bring together shared knowledge and align projects addressing similar questions. Researchers should also coordinate proposals around a specific topic when applying for new funding, such as programme grants or Biomedical Catalyst.

MRC should take a lead on initiating discussions with other Research Councils, and potentially other UK and international funders, to discuss mechanisms to provide significant support for new high quality proposals. These could include:

- providing seed funding to bring together established groups to add value to exiting programmes;
- or, as an alternative, fund individuals to work across disciplines;
- initiating a cross-Council highlight notice in antimicrobial research, similar to the recent NIHR call[8];
- ring-fencing a proportion of existing budgets for a new response-mode call. This could be modelled on, for example, the recent cross-Council synthetic biology call.

Establishing consortia would also have a positive knock-on effect on capacity building and expertise in the UK by providing opportunities for cross-training with industry, or training young researchers to work across disciplines.

5.4 Coordination between funders – UK and international

The *UK Health Departments Five Year Antimicrobial Resistance Strategy 2013-2018* was published in September 2013[9] and its implementation will be overseen by the UK Interdepartmental High-level Steering Group (HLSG), on which the Research Councils will sit. The MRC, in partnership with other Research Councils and the wider HLSG membership should ensure successful implementation by continuing to fund high quality research around the agreed high level priorities. The topics listed earlier could form the basis for these priorities. Any future bid for a larger pot of new ring-fenced money from Government would need to show clear deliverables that are beneficial for both the health and wealth of the UK.

Given the global significance of the threat of AMR, MRC should continue to work with international partners in this area. For example:

[8] http://www.themedcalls.nihr.ac.uk/amr

[9] https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/238872/20130902_UK_5_year_AMR_strategy_FINAL.pdf

- Through ongoing participation in the Joint Programming Initiative on AMR [10](JPIAMR) to streamline the European research efforts in AMR by joint planning, implementation and evaluation of national research programmes.
- By building on the statement published in June 2013 by the G8 joint Science Ministers and national science academies [11]which agreed 'to act concertedly on developing the scientific input necessary to reduce antimicrobial resistance working with existing agencies'.

5.5 Overarching coordination

Greater collaboration and coordination within UK researchers could be achieved through a broad overarching network of cross-disciplinary academics, pharma and SMEs. This should be focused around a scientific purpose to coordinate activities, facilitate member interactions, and share data and underpinning technology. A focused network could help prioritise current approaches that have the best chance of advancing down the pipeline and provide a platform for future collaborations.

Antibiotic Discovery UK (ADUK) is an existing network of scientists from academia and industry and may provide a basis for this. It was also noted that BBSRC had previously managed an 'Antibiotic Club' and that MRC and BBSRC could consider reinstating this forum. Either of these examples would require a clear scientific focus and robust management plans.

5.6 Existing funding mechanisms

MRC schemes (and those of other funders) must continue to be the main mechanism to drive forward antimicrobial research. Through these existing schemes, MRC expenditure in antimicrobial research between 2007/08 to 2011/12 has been £24m. For example, basic biology of bacterial cellular processes and pathways, or target identification and validation can be funded through response-mode project and programme grants funded by the Infections and Immunity Board[12]. Specific translational research schemes such as Experimental Medicine Challenge Grants[13], the Confidence in Concept Scheme[14] and the Biomedical Catalyst: Development Pathway Funding Scheme[15] (run in partnership with the Technology Strategy Board, TSB), can support more applied research and provide opportunities to fund the transition from discovery research to translational development of novel antimicrobials and diagnostics. SME-led applications can also be funded under the Biomedical Catalyst, and are administered by TSB[16]. However, the group agreed that significant new funding should be made available and that the MRC was well placed to lead this.

Academic–industry collaborations involving either in-cash or in-kind contributions from industry can add value to antimicrobial research projects. These can be facilitated through an MRC Industry Collaboration Agreement (MICA)[17] which supports the establishment of agreements between the academic and industry partners. MICAs can apply to the majority of MRC funding schemes.

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[10] http://www.jpiamr.eu/
[11] https://www.gov.uk/government/news/g8-science-ministers-statement
[12] http://www.mrc.ac.uk/Ourresearch/Boardpanelsgroups/IIB/index.htm
[13] http://www.mrc.ac.uk/Fundingopportunities/Grants/EMCG/MRC008385
[14] http://www.mrc.ac.uk/Fundingopportunities/Grants/CiC/MRC008619
[15] http://www.mrc.ac.uk/Fundingopportunities/Grants/DPFS/Specification/MRC004553
[16] https://www.innovateuk.org/competition-display-page/-/asset_publisher/RqEt2AKmEBhi/content/biomedical-cataly-1
[17] http://www.mrc.ac.uk/Fundingopportunities/Grants/MICA/Specification/MRC005438

There were also discussions on how MRC could improve the mechanisms for funding proposals in antibiotic development, i.e. should antibiotic focused proposals be assessed by a separate expert panel? Reviewers and funding panels should ensure that antibiotic development grants include all of the information required to judge the potential of a target compound.

6 Recommendations for MRC

1. MRC should engage chemists and synthetic biologists to work with biologists. The integration of novel chemistry with biology, its application and that of synthetic biology, to new and existing antibiotics, could pave the way for new classes of drugs and potentially rescue failed products. This should be achieved by working in partnership with BBSRC and EPSRC where appropriate.

2. MRC should consider holding scoping workshops on the specific themes outlined (proven antibacterial targets; novel antibiotic targets; rescuing old drugs; enhancing existing treatments; genomics and secondary metabolites; mechanism and spread of resistance) to bring together researchers to facilitate new collaborations and funding applications. Review boards assessing such applications should appreciate the strategic importance of the application of chemistry to antimicrobial research.

3. MRC should initiate discussions with other Research Councils, and potentially other UK and international funders, to discuss mechanisms to support new high quality proposals. These could include:
    - the establishment of a cross-Council highlight notice;
    - providing seed funding to bring together established groups to add value to exiting programmes;
    - ring-fencing a proportion of existing budgets for a new response-mode call.

4. MRC should continue to work with international partners in this area. For example:
    - Through ongoing participation in the Joint Programming Initiative on AMR (JPIAMR) to streamline the European research efforts in AMR by joint planning, implementation and evaluation of national research programmes.
    - By building on the statement published in June 2013 by the G8 joint Science Ministers and national science academies which agreed ‘to act concertedly on developing the scientific input necessary to reduce antimicrobial resistance working with existing agencies’.

5. Funders should engage with the community to facilitate a focused cross-disciplinary network of academics, pharma and SMEs in the area around a clear scientific focus.

Workshop on development of MRC's position on research into antimicrobial resistance

Wednesday 17th July, 10am – 4pm
Room 2, Second Floor, MRC Headoffice, One Kemble Street, London

Agenda

10.00 Welcome
Professor Sir John Savill, MRC Chief Executive

10.10 Vision for what we hope to achieve
Professor Sharon Peacock, University of Cambridge and Infections and Immunity Board Deputy Chair

Session 1: Identifying the problems for research in the antimicrobial pipeline

10.30 Setting the scene - Unmet needs; where are the blockages between academic research and new antimicrobials

Introductory comments by Professor Laura Piddock, University of Birmingham and Dr Lloyd Czaplewski, Abgentis Ltd

11.30 Breakout groups: Challenges for academia to feed into drug discovery. What are the questions to be answered?

12.30 Group feedback and discussion

13.00 Lunch

Session 2: Identifying solutions for the problems

13.30 What should funding look like in this area? MRC funding opportunities and potential models of working
Dr Rebecca Ward, MRC Programme Manager for Infections

13.50 Break out groups: Opportunities to address the challenges. What shape should pharma, SME and academia interactions take?

15.00 Tea

15.15 Group feedback and discussion

15.45 Next steps
Professor Sharon Peacock

16.00 Close

Attendees

Dr	Des	Walsh	MRC
Dr	Rebecca	Ward	MRC
Dr	James	Horswill	MRC
Dr	Richard	Alm	AstraZeneca
Dr	Helen	Atkins	Defence Science and Technology Laboratory
Dr	Richard	Bax	Transcript Partners
Professor	Del	Besra	University of Birmingham
Dr	Judith	Bray	CIHR Institute of Infection and Immunity
Dr	David	Brown	Indigix Ltd.
Professor	Anthony	Coates	St Georges London
Professor	Derrick	Crook	University of Oxford
Dr	Lloyd	Czaplewski	Abgentis Ltd.
Dr	Mike	Dawson	Novacta Biosystems Ltd./Cantab Biopharmaceuticals Ltd.
Professor	Chris	Dowson	University of Warwick
Professor	Jeff	Errington	Newcastle University
Professor	Gad	Frankel	Imperial College
Dr	Flic	Gabbay	TranScrip Partners LLP
Dr	David	Harper	AmpliPhi Biosciences Corp.
Professor	David	Holden	Imperial College
Professor	Aras	Kadioglu	University of Liverpool
Dr	Katy	Kettleborough	MRCT
Dr	Chris	Longshaw	Astellas Pharma Ltd.
Dr	Fiona	Marston	Absynth Biologics Ltd.
Professor	Jeremy	Mottram	University of Glasgow
Dr	Alex	O'Neill	University of Leeds
Dr	Pia	Thommes	Euprotec Ltd.
Professor	Sharon	Peacock	University of Cambridge
Professor	Laura	Piddock	University of Birmingham
Professor	Chris	Schofield	University of Oxford
Professor	Mike	Sharland	St Georges London
Dr	David	Simmons	University of Birmingham
Professor	Christoph	Tang	University of Oxford
Professor	Peter	Taylor	University College London
Professor	John	Wain	Discuva Ltd
Professor	Gabriel	Waksman	Birkbeck, University of London
Dr	Ursula	Wells	Department of Health
Dr	Ramesh	Wigneshweraraj	Imperial College London
Professor	Paul	Williams	University of Nottingham
Professor	Brendan	Wren	London School of Hygiene & Tropical Medicine
Dr	Andrew	Zaman	Association of the British Pharmaceutical Industry