InfraLife

Workshop Report: Antimicrobial resistance

Workshop on June 2, 2021

EUROPEAN SPALLATION SOURCE

MAX IV

SciLifeLab

Introduction and aims

InfraLife is an initiative between SciLifeLab, MAX IV and European Spallation Source (ESS) in partnership with SwedenBIO and Lif, the trade association for the research-based pharmaceutical industry, with the vision to strengthen Sweden as a leading nation in life science by improving the knowledge about and accessibility to the respective national research infrastructures.

Antimicrobial resistance (AMR) is a major health threat and resistance to common antibiotics is estimated to cause 700,000 deaths each year globally. There is a strong need for new antimicrobials, but also for better diagnostics and non-antibiotic methods to advance the development of new strategies against AMR.

Key stakeholders from industry and academia came together on June 2nd, 2021, to discuss how the national infrastructures, SciLifeLab, MAX IV and ESS, could contribute to accelerating and advancing the AMR field and to provide direction to make the rapidly growing collection of tools and techniques accessible to the AMR research community.

AMR state of the art – dual approach

Due to accelerated AMR, healthcare is facing a shortage of drugs that work effectively against severe infections. Two main strategies to resolve the problems with antimicrobial resistance are available to us: develop new antibiotics and limit the spread of infection and resistance.

WHO's yearly analysis of the AMR clinical antibiotic pipeline recently showed that the current ongoing activities are insufficient in view of the increasing urgency of the spread of microbial resistance. Moreover, only very few of the compounds in clinical trials are active against the critical pathogens that cause the most problems in healthcare.

Public private partnerships such as the Innovative Medicines Initiative (IMI) project ENABLE, led by Professor Anders Karlén at Uppsala University, have engaged to catalyze drug discovery and the development of antimicrobial candidates by bringing attractive candidates to extensive preclinical studies and First-in-Human clinical trials. By its structure, ENABLE gathers small and medium-sized companies, large pharma and academia in collaboration towards a common goal.

ENABLE ends in 2021, and to build on the success of the project, The Swedish Research Council is funding a legacy effort, to build a new Swedish AMR drug discovery pipeline, with a need for both structural biology and novel sequencing techniques. Industry participation in the future effort would be both welcomed and important. ENABLE researchers plan to present the new initiative in August 2021.

Sweden's relatively beneficial AMR situation is largely due to a historical focus on other aspects than drug development. AMR is accelerated by antibiotics overuse, as well as unsatisfactory infection prevention and control. Steps therefore should be taken to reduce the impact and limit the spread of AMR by focusing on limiting the infections (patient control, vaccines) or reduce resistance (using the right antibiotic, at the right place, at the right time). The Centre for Antibiotic Resistance Research at University of Gothenburg, led by Professor Joakim Larsson, focus their research on diagnostics, environment, surveillance, transmission as well as interventions and therapeutics.

There is a growing understanding that the environment plays an important role both in the transmission of antibiotic resistant pathogens and in their evolution. This research field explores the mechanisms and drivers of AMR and identify suitable interventions.

Shotgun metagenomics and sequencing of complex communities to identify resistance genes are key methods to understand transmission of AMR and to understand the risk antibiotics have of selecting for resistance once they are used and released.

Additionally, there are still open questions around the relative efficacy of therapeutical, technological and behavioral interventions to mitigate AMR. This is also the case around the relative contributions of different sources of antibiotics and antibiotic resistant bacteria in the evolution of resistance.

Opportunities offered by the research infrastructures

Sweden's large research infrastructures, MAX IV, ESS and SciLifeLab offer a broad range of research services for both academia and industry across various research fields, several of which are beneficial to AMR research.

SciLifeLab's technologies can be used for studying the molecular aspects of life ranging from the atomic scale up to entire ecosystems. Dr Annika Jenmalm Jensen, Infrastructure Director at SciLifeLab, particularly pointed to the Cryo-EM facilities, mass spectrometry-based proteomics and the screening and sequencing capacities as well suited to answer fundamental AMR questions. In addition, SciLifeLab's Data Driven Life Science (DDLS) program will utilize integrated machine learning techniques to analyse large scale data that can be used for AMR surveillance research.

The SciLifeLab Drug Discovery and Development platform (DDD) is a Swedish national infrastructure distributed to five universities with competence available and a strong and internationally recognized track-record to discover new prototype drugs. Academic scientists as well as industry are encouraged to approach DDD with their ideas for support.

Dr Pawel Baranczewski (DDD) summarized contribution from DDD to the IMI project ENABLE consisting of knowledge and drug discovery project management experience. Possible future support to AMR research could e.g. be to support ENABLE2 with in vitro ADME competence, bioanalysis, in vivo pharmacokinetics knowledge, project scouting, DD project management as well as detailed biophysical studies of ligand-target indications. The DDD platform seems also as natural partner in compound storage and handling as well as in recombinant protein production, assay development and screening of compounds. In their support of drug discovery projects, SciLifeLab DDD collaborates closely with other platforms at SciLifeLab as well as with MAX IV. Need for these close collaborations was also raised by prof Anders Karlén during his introduction to the ENABLE2 project.

MAX IV is a Swedish advanced synchrotron light facility, hosted at Lund University. The majority of the beamlines at the facility, in particular SoftiMAX and NanoMAX are suitable for life science experiments, in particular within the areas of structural biology and imaging, explained Dr Selma Maric at MAX IV. A range of scattering diffraction, as well as spectroscopic and imaging techniques can provide us with not only structural information at various length scales but also provide chemical information in samples, electronic structure, allowing for studies of matter with unprecedented resolution both in time and space. Additionally, the facilities are ideal for the study of new materials capable of inhibiting or killing microbes on the surface. A recent example of antimicrobial clay was given by Dr Karina Thånell at MAX IV, as well as examples of the study of hemozoin crystals in malaria-infected red blood cells.

From a large pharma perspective, Dr Susanna Alami-Abrahmsén of Astra Zeneca, shared that practical aspects, such as ensuring that drug structures are maintained all the way to the patient through the manufacturing and supply chain need to be taken into account. Advanced characterization tools are very important to understand what is happening with drug in processing, in storage and in the body. Prediction models can help to reduce quality checks and rather use resources more efficiently. Moreover, stable drugs that can be delivered to patients are key in countries where conditions are not optimal for all types of drug storage, for instance lack of freezers.

The European Spallation Source (ESS), a pan-European collaboration between 13 member states with its seat in Sweden, is currently under construction in Lund and Copenhagen and will open for users in 2024. The infrastructure, presented by Dr Esko Oksanen, will offer complementary techniques that could be used for cutting edge AMR research, including powerful linear proton accelerators, state-of-the-art neutron instruments, a suite of laboratories, and a supercomputing center.

Neutrons are isotope sensitive, in particular to deuterium and hydrogen. This allows for key components in biology, namely, water, lipids, proteins and DNA and RNA to be visualized within more complex mixtures leading to enhanced structure and function determination. ESS will provide at least a factor of 10 increase in neutron flux, enabling studies previously challenging or not even possible with currently available neutron sources. Examples range from studies of molecular processes such as enzyme mechanisms, protein-ligand interactions and protein transport across membranes, which can be useful in understanding mechanisms of antimicrobial resistance. A specific example from a recent research project illustrated how neutron and high-resolution X-ray crystallography could probe the mechanism by which CTX-M extended-spectrum β-lactamases hydrolyze monobactam antibiotics.

Access and user policies

MAX IV and SciLifeLab are already much engaged in facilitating user access to the infrastructures. 50% of SciLifeLab's users are based outside the founding universities and approximately 15% of users are from health care and industry, and efforts are currently ongoing to increase that proportion. Access for academic users is heavily subsidized whereas access for industry users is associated with a full cost pricing model.

MAX IV is a user facility, open for researchers globally, both from public and private sectors. There are two major access modes: peer-reviewed access and proprietary access. Applications for peer-reviewed access open twice a year, where any user can apply for free beamtime, but with a requirement to publish obtained results. Proprietary access for industry users only is generally faster, comes at a cost, but has on other hand no requirement to publish.

Other ways are possible, such as the example given of the forestry industry that have invested in their own beamline and instruments at MAX IV, or of industry participating in technology development projects to advance the instruments.

ESS will have very much the same setup for users as MAX IV and will open during 2024. It is a user facility and will welcome users both as peer-reviewed access and proprietary access. ESS is in joint discussion with MAX IV on future academic-industrials user platforms as well as with the Swedish Research Council on Swedish initiatives for instruments. Therefore, the discussion about AMR is important to understand what is needed by the community for the future.

Challenges and recommendations

Funding

Among the challenges identified during the meeting, the need for funding and clearer investment strategies from the funding agencies, emerged as two of the top priorities. Larger public and private investments are needed to take big leaps in AMR. The Swedish Research Council is opening a call this summer for AMR projects, with a total budget of 20 million SEK, and have grants available for project initiations and consortium formation. SweLife and Vinnova also have funding available for AMR at different project stages. Larger funding opportunities are available abroad, for instance through the

new European IHI program, or through WHO.

The research infrastructures could be the liaising partner in multistakeholder consortia and collaborations, especially in prevention and diagnostics since those areas are generally less likely to receive funding than drug development projects.

Reasons mentioned for the lack of innovative leads in the pipeline is the withdrawal of large industry from this space and the scientific challenge to identify new starting points and compounds. While the small and medium-sized enterprises (SMEs) largely have taken up the baton, the business models available are not adequate to ensure return of investment and thus hamper further development. Focus should thus be on elucidating the incentive mechanisms available and how these can be refined. Cohesive implementation of policy recommendations, in particular around intellectual property, access and affordability would enable more companies to join consortia and use the infrastructures.

Broader research approaches

Another of the themes that underlay much of the discussion was the necessity of a broad concerted approach to AMR. It is not enough, it was acknowledged, to rely solely on drug development to address antimicrobial challenges, additional focus must be attributed to diagnostics, surveillance, and prevention. A dual approach with therapeutic development of small molecules, exploration of antibodies and screening of insoluble compounds on one hand, must be complemented with substantially funded activities to understand the selection and transfer of resistance. Viral models are also necessary to study, certainly in view of the Covid19 pandemic.

Whether it be surveillance and prevention strategies, material development or sampling techniques, cross-sectoral and cross-thematic collaboration is needed for the academic sector to feed scientific innovation into the innovation system, for the private sector to pursue product development, and for the health care systems to implement new findings and innovation in clinical practice. The need for more industry-industry collaborations between sectors was also highlighted. Subsequently, new national and international collaborations and networks will be necessary, and the research infrastructure were suggested to facilitate consortium formation and coordinate funding applications.

Specific aspects highlighted, where the research infrastructures could play a role, included creating clear entry ways for industry to use the infrastructures and increased expertise support when using the facilities. This could enable a collaborative “idea to results” workflow. The infrastructures could also help forging links between industry and academia by facilitating common data collection, storage, sharing and analysis.

Novel technologies

The need for comprehensive enhanced data storage and data analysis capabilities to exploit the predictive capacity of data, especially from genomics, was emphasized. The approaches available today are inadequate and cost-prohibitive to the users and the community would be aided by development of novel techniques and methods. For instance, a common national antibiotics analysis platform that could be used for complex matrices, such as environmental samples, would enable researchers to understand where resistance genes come from and help link resistance genes to specific bacterial species. Such a national research infrastructure would give Swedish researchers a competitive advantage in the field.

Future efforts

The first InfraLife workshop with focus on antimicrobial resistance provided a unique opportunity to exchange views and to discuss expectations and opportunities for the research infrastructures with members from funding organizations, academic experts within the AMR field and representatives from industry.

In line with the suggestions made during the discussion, InfraLife will now explore how to continue the dialogue within the AMR field based on the workshop's reflections.

Upcoming events and efforts within the InfraLife initiative will be posted on https://www.infralife.se.

Further questions and ideas? Please contact InfraLife coordinators:

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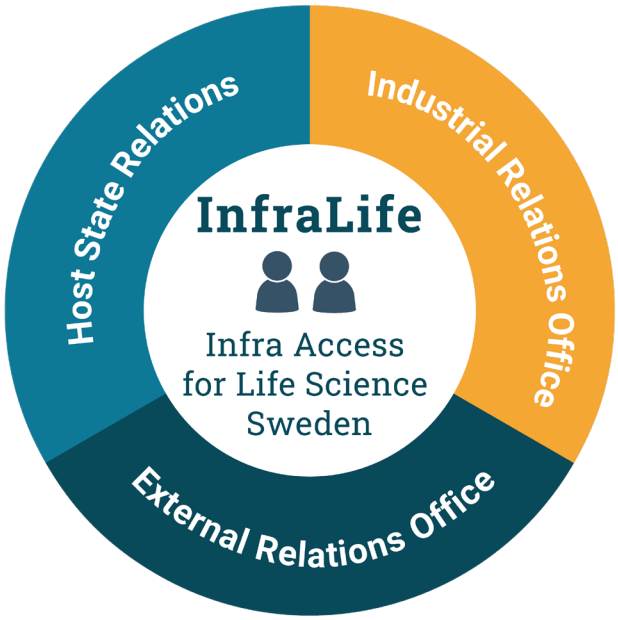

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InfraLife. A new initiative in life science that aims to maximize the benefits of the investments made in Sweden's large scale strategic research infrastructures.

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