Translational research strategy: an essential approach to fight the spread of antimicrobial resistance

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Translation research strategy in infectious diseases, combining the results from basic research with patient-orientated research, aims to bridge the gap between laboratory findings and clinical infectious disease practice to improve disease management. In an era of increasing antimicrobial resistance, there are four main areas of clinical and scientific uncertainty that need to be urgently addressed by translational research: (i) early diagnosis of antibiotic-resistant infections and the appropriateness of empirical antibiotic therapy; (ii) the identification of reservoirs of antibiotic-resistant pathogens; (iii) the development of new antibiotics with lower propensities to evoke resistance; and (iv) the development of new non-antibiotic drugs to be used in the prevention of the spread of resistant bacterial strains. Strict European collaboration among major stakeholders is therefore essential. Appropriate educational tools to train a new generation of scientists with regard to a multifaceted approach to antimicrobial resistance research should be developed. Key areas include the support and implementation of European networks focused on translational research and related education activities, making potential therapeutics more attractive to investors and helping academic investigators to determine whether new molecules can be developed with clinical applicability.

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Introduction

The definition of translational research according to the US NIH and the Department of Health and Human Services states that it ‘includes two areas of translation. One is the process of applying discoveries generated during research in the laboratory and in preclinical studies to the development of trials and studies in humans. The second area of translation concerns research aimed at enhancing the adoption of best practices for patients in the community’.1 On a practical level, we could easily recognize in medical science two different translational approaches to research: one from basic science, focusing on the development of a new molecule or diagnostic test, and another with a bedside-orientated approach, from clinicians and healthcare agencies, mainly focusing on the improvement of clinical management and outcome of patients. Although clinicians and agencies have successfully worked together on many occasions, they have traditionally been divided by a major cultural gap between the clinic and basic science knowledge. The majority of educational programmes aimed at training physicians or medical scientists are in fact not built according to a translational approach to research and are mainly focused on specific areas. Major consequences of this scientific dualism include, for example, a new molecule or diagnostic test that has lost the potential for real-life application since its development did not combine business expertise and deep understanding of unmet medical needs.2 The implementation of translational research should specifically bridge this gap.

Is a translational approach beneficial to research into antimicrobial-resistant infections?

A major goal of the translation from laboratory findings to clinical infectious disease practice (and vice versa for further testing and development) is the improvement of infectious disease management, combining the results from basic science with a bedside-orientated research approach (see Figure 1). This process should lead to the establishment of a rapid process of discovery, clinical application and public knowledge of a new antibiotic or diagnostic test.

In the last 60 years, increasing antibiotic use has significantly contributed to the development of antimicrobial resistance and related complications, such as mortality and increased length of hospital stay, as well as increased readmission rates and treatment costs.3 New strategies need to be developed to fight the
worldwide spread of antibiotic-resistant bacteria and to increase the number of prevention programmes and treatment effectiveness. There are four areas of clinical and scientific uncertainty that need to be addressed urgently by translational research: (i) early diagnosis of antibiotic-resistant infections; (ii) the definition of reservoirs of antibiotic-resistant pathogens; (iii) the development of new antibiotics with specific antimicrobial spectra and lower propensities to evoke resistance; and (iv) the identification of new non-antibiotic drugs that could improve the prevention of bacterial infections due to antimicrobial-resistant bacteria and treatment efficacy.4

An interesting example of translational research is the German national plan focused on infectious diseases.5 The German Federal Ministry of Education and Research has invested significantly into the foundation of a German Center for Infection Research (Deutsches Zentrum für Infektionsforschung, DZIF). DZIF is a collaborative institutional network of seven sites throughout Germany, including various universities, hospitals and public research institutes with special competencies in the field of infection research and the mission of gleaning insights into pathogens and clinical aspects of infectious diseases and using these to develop approaches for new diagnostics, therapies, drugs, vaccines and immunization protocols, as well as prevention strategies. Translation as a way of improving public health is thus of central significance in the DZIF network. An interesting example of the interdisciplinarity of the DZIF work is the unit focused on the prevention and therapy of healthcare-associated infections. In this unit clinicians, microbiologists, biostatisticians and scientists from seven different universities work together. The projects are strictly related as for example the development of a biobank of samples connected to omics analyses or the synthesis of new molecules for decolonization that could be tested directly in the unit through a dedicated Phase I centre. DZIF also puts emphasis on the interdisciplinary education of clinical and basic infectious diseases experts. Strategic gaps in translational expertise are bridged by substantial funding for new projects, professorships and junior groups.

Do we need specific issues to be addressed by translational research for antimicrobial resistance?

The peculiarity of this research field lies in the fact that antibiotic consumption is composed of myriad physician–patient decisions; therefore it requires specific involvement and collaborations that are different from those needed by other branches of medical science.6 In recent years the integration of all microbiological, epidemiological, ethical and clinical data was partially achieved, for example, in the form of a decision support system.7 From a microbiological point of view, the new spheres of ‘omics’, along with systems and structural biology, substantially advance translational research on multiple aspects of antimicrobial resistance, such as early diagnosis, new indicators of infection outcome and promising new therapies. Novel approaches, including the detection of genes conferring antimicrobial resistance in both commensals and pathogens, by next-generation sequencing methods and metagenomic analyses, might provide a rational basis for stratified antibiotic therapy in patients.8,9 Sophisticated mathematical algorithms then need to be applied to clinical work to bridge the gap between these new data and unmet needs. At present novel tools are being developed allowing the connection of data from omics methods with clinical data and patient diagnostic data. More importantly, real-time data analyses to transfer omics data to clinical application will be possible and will result in personalized medical approaches in the future.10 Preclinical animal models, including those with humanized microbiota, can also play a role, allowing the tracking of horizontal gene transfer in vivo under antibiotic selection pressure and inflammation, or of antibiotic tolerance of pathogens at specific tissue sites.

Translational research also brings new challenges regarding the transformation of large volumes of data into useful medical information. A new conception of repository data is needed as a result of new legal developments in the concept of patient privacy.
Is there a role for European societies in the fight against infectious diseases as well as European organizations and stakeholders?

The process of discovery and development of new antimicrobials can no longer be restricted to the pharmaceutical industry, which has largely abandoned infection-related R&D. Academic institutions can partially step in, but their backgrounds and capacities for compound development are limited and the translational processes need to be reconciled with academic needs. Academic scientists can bring in innovative approaches for the discovery of new antimicrobials, but the enormous resources and time spans required for development processes can only be achieved in public–private partnership schemes. A clear example is the European Gram Negative Antibacterial Engine (ENABLE), part of the Innovative Medicines Initiative (IMI) project, which brings together 32 partners in 13 countries and is currently led by a pharmaceutical company and a university. The main goal of the IMI project is to advance the development of an innovation to the point where it becomes attractive for industry and public–private partnerships to take up the challenge of producing a product for the market.¹¹

In our opinion, a pivotal role should also be played by new educational tools in the field of antimicrobial resistance. An innovative model of teaching based on a translational approach should be developed at European level through the institution of a dedicated Commission providing guidance to the Member States on how to build courses, including multifaceted educational approaches for scientists working in medical fields. In this context European Societies deeply involved in the fight against antimicrobial resistance (European Society of Clinical Microbiology and Infectious Diseases and WHO), as well as other major organizations with extensive experience in education (European Union of Medical Specialists) and research (European Center for Disease Prevention and Control), could provide substantial support. Although the amount of research into antimicrobial resistance has significantly increased, its impact, in terms of the production of new antibiotics, molecules and/or diagnostics, is growing far more slowly. The implementation of translational research in this field could represent a significant contribution, ensuring that the bounty of discoveries from basic science is effectively translated into benefits for patients in real life. European countries should develop clear indications on how to expand scientific work in these areas with broader and more holistic worldviews, as opposed to narrower approaches. Key areas include supporting European networks focused on translational research and education activities applying new educational tools that increase translational approaches to research, making potential therapeutics more attractive to investors and helping academic investigators to determine whether new molecules with clinical applicability can be developed.

Transparency declarations
None to declare.

References
5 DZIF. German Center for Infection Research. http://www.dzif.de/en/ (10 April, date last accessed).