NEW DRUGS FOR BAD BUGS

The Innovative Medicines Initiative response to antimicrobial resistance

innovative medicines initiative

efpia

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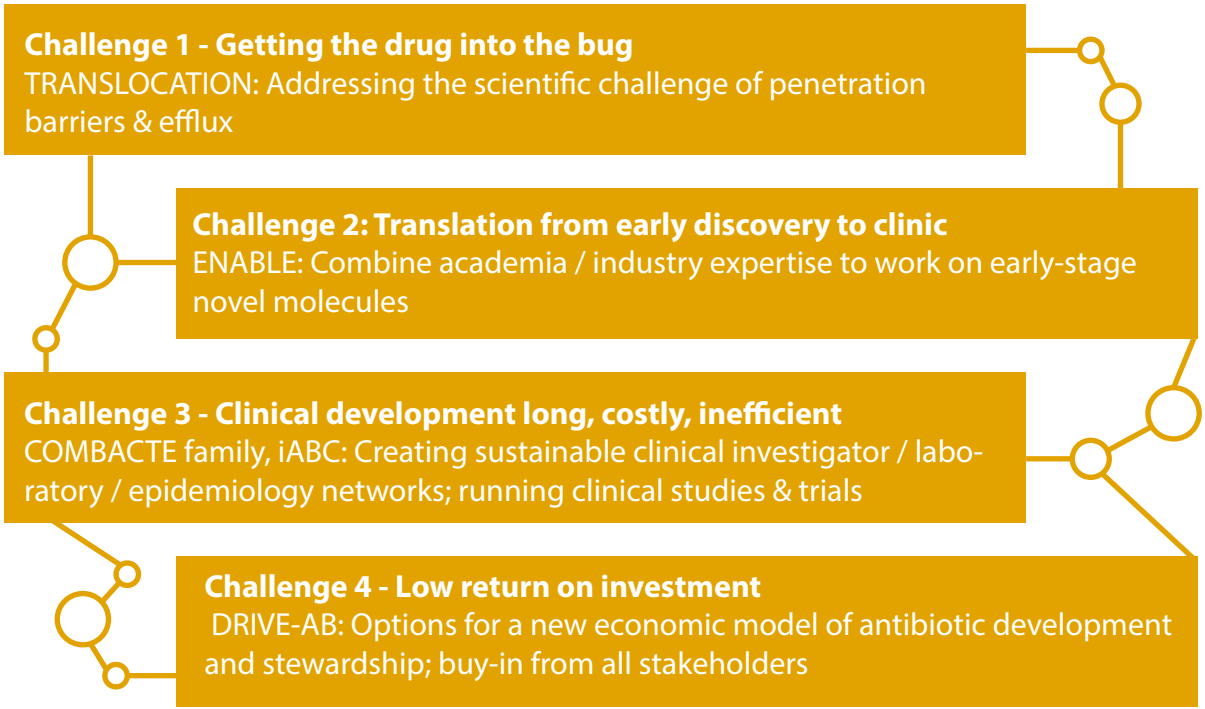
THE ND4BB PROGRAMME

The ND4BB structure



Antimicrobial resistance (AMR) represents a serious and growing threat to human and animal health worldwide. It already kills 700 000 people globally every year, and that figure could rise to 10 million by 2050.

The Innovative Medicines Initiative (IMI) programme New Drugs 4 Bad Bugs (ND4BB) represents an unprecedented partnership between industry, academia and biotech organisations to combat antimicrobial resistance in Europe.

The EUR 700 million programme comprises 7 projects that are finding solutions to the scientific, regulatory, and business challenges that are hampering the development of new antibiotics.

In its 2011 action plan on antimicrobial resistance, the European Commission called for 'unprecedented collaborative research and development efforts to bring new antibiotics to patients' by, among other things, launching an IMI programme in this vitally important area.

The result is New Drugs 4 Bad Bugs (ND4BB). The first projects kicked off in early 2013, and the programme now encompasses seven projects that are starting to deliver exciting results in diverse aspects of antibiotic development. The total budget of the programme now stands at around €700 million.

Between them, the projects address some of the biggest challenges in antibiotic development, covering basic science and early stage drug development, clinical trials, and economics.

BASIC SCIENCE

The science of getting drugs into bugs (and keeping them there)!

The TRANSLOCATION project focuses on identifying new ways of getting potential antibiotics into bacteria and preventing bacteria from destroying or expelling the drugs before they can take effect. It is working primarily on Gram-negative pathogens such as Escherichia coli and Klebsiella pneumoniae; getting antibiotics into these bacteria is particularly challenging.

Key achievements

- Development of **new techniques** to analyse the uptake of antibiotics by bacteria.
- Worked out the **structure of 20 proteins** found in the membranes of bacteria that cause many infections. These proteins play a vital role transporting substances (including, potentially, antibiotics) into and out of bacterial cells.
- **Greater understanding** of the workings of efflux pumps (which bacteria use to expel antibiotics).
- Creation of a **database** to gather data from both new antibiotic research projects and abandoned ones.

Find out more: www.translocation.eu

DRUG DISCOVERY

Building a drug discovery platform for antibiotics

The early stages of antibiotic discovery and development are extremely difficult.

Researchers with promising potential antibiotics that are in the early stages of drug discovery can apply to access the antibiotic development platform created by IMI's ENABLE project.

The platform was set up to test and optimise molecules with the potential to become future drug candidates capable of treating infections due to resistant Gram-negative bacteria.

Applications are assessed for their scientific potential.

Universities and small companies selected to join the project have the opportunity to collaborate with experts in all areas of antibacterial drug discovery, such as microbiology, pharmacology and chemistry, to help advance their molecule through the drug development process, through to clinical testing.

Key achievements

- Since the project started in February 2014, it has **received over 70 applications** to join the project from organisations with **promising anti-infective** research and development programmes.
- As of the end of 2016, **16 programmes** (mainly from academia and small biotech) had been selected to join the project, including one programme that started life in IMI's European Lead Factory project. Of these, **5 remain active**, having been identified as having the highest likelihood of succeeding in the clinic.
- Through these programmes, the project has **identified two advanced molecules** that show particularly promising antibacterial activity and are worthy of further study and optimisation.
- Project partners have also **identified a new way of targeting drug-resistant bacteria**.
- There are **more programmes in the pipeline**. The project has a rolling open Call for proposals and the ENABLE team is continually reviewing submissions.
- The project has attracted the interest of **SMEs working on antibiotic development** both in Europe and beyond; at the end of 2016, there were 15 SMEs in the project.

Find out more: nd4bb-enable.eu | @ND4BB_ENABLE

CLINICAL TRIALS

Establishing a pan-European network of clinical sites

The **COMBACTE family of projects** (COMBACTE-CARE, COMBACTE-MAGNET, COMBACTE-NET) is building a self-sustaining, pan European antibacterial development network and using it to run high-quality clinical studies of new antibiotics for multi-drug resistant bacteria.

COMBACTE-NET is dedicated to building strong clinical, laboratory and research networks across Europe. The hope is that these networks, which bring together vast amounts of expertise from universities, hospitals, the pharmaceutical industry, and more, will become the reference point in Europe for the clinical development of new antibiotics.

COMBACTE-CARE focuses on infections caused by bacteria known as 'carbapenem-resistant enterobacteriaceae' (CRE). CRE are resistant to most available antibiotics and are so difficult to treat they are considered to be one of the most dangerous drug-resistant bacteria in the world. COMBACTE-CARE aims to shed new light on the best ways to understand and treat CRE infections. It will also run clinical trials of a novel antibiotic combination product designed to tackle a sub-type of CRE infections for which there are limited or no treatment options. Further funding for the trial comes from the

US-based Biomedical Advanced Research and Development Authority (BARDA); this will be used to support additional studies needed to advance the development of this urgently-needed treatment.

COMBACTE-MAGNET addresses the need for new approaches to preventing and treating life-threatening infections among patients in intensive care units. This group is particularly vulnerable to infections, for example in their lungs and airways. Increasingly, these infections are resistant to a range of antibiotics, leaving doctors with few options to treat their patients.

Key achievements

- The **CLIN-Net hospital network** includes **over 800 hospitals** in **42 countries** in Europe. The project is now cataloguing these and, where necessary providing training to ensure all are qualified to run high quality clinical studies.
- The **LAB-Net** network counts **over 600 laboratories in 42 countries**.

All three projects are already using the networks to run a number of clinical trials and studies, including:

- **RESCUING** assessed the clinical management and treatment outcomes of hospitalised patients with complicated urinary tract infections. It is the first study within the COMBACTE family to be completed, and the team is now analysing the data gathered.
- **SAATELLITE** is investigating a drug called MEDI4893. MEDI4893 targets a

toxin produced by Staphylococcus aureus, a bacteria often associated with hospital-associated infections and linked to resistance issues.

- **ASPIRE** aims to add to our understanding of the incidence and causes of health-care associated infections (HAIs) caused by two bugs: S. aureus and *Pseudomonas aeruginosa*.
- **ANTICIPATE** aims to determine the incidence of *Clostridium difficile* infections in hospitalised patients on antibiotic treatment.
- **EVADE** is assessing the effectiveness of a drug called MEDI3902 in the prevention of *Pseudomonas aeruginosa* infections, especially in intensive care patients who are on artificial ventilation.
- **REJUVENATE** is testing aztreonam-avibactam for the treatment of complicated intra-abdominal infections (cIAI).
- **EURECA** focuses on patients with serious carbapanem-resistant infections, and aims to learn how patients across Europe are currently treated and which patients respond well to which treatments.
- **Further clinical studies** are ongoing or in the pipeline.

Find out more: www.combacte.com | @COMBACTE

New treatments to help cystic fibrosis patients

Another ND4BB project in the clinical development field is **iABC**. Respiratory infections, frequently caused by drug-resistant bacteria, are the main cause of disease and death in people with cystic fibrosis (CF) and bronchiectasis (BE). Thanks to inhaled antibiotics, patients now live longer than ever before and enjoy a better quality of life. However, infections are increasingly becoming resistant to the few drugs available, putting patients' lives at risk.

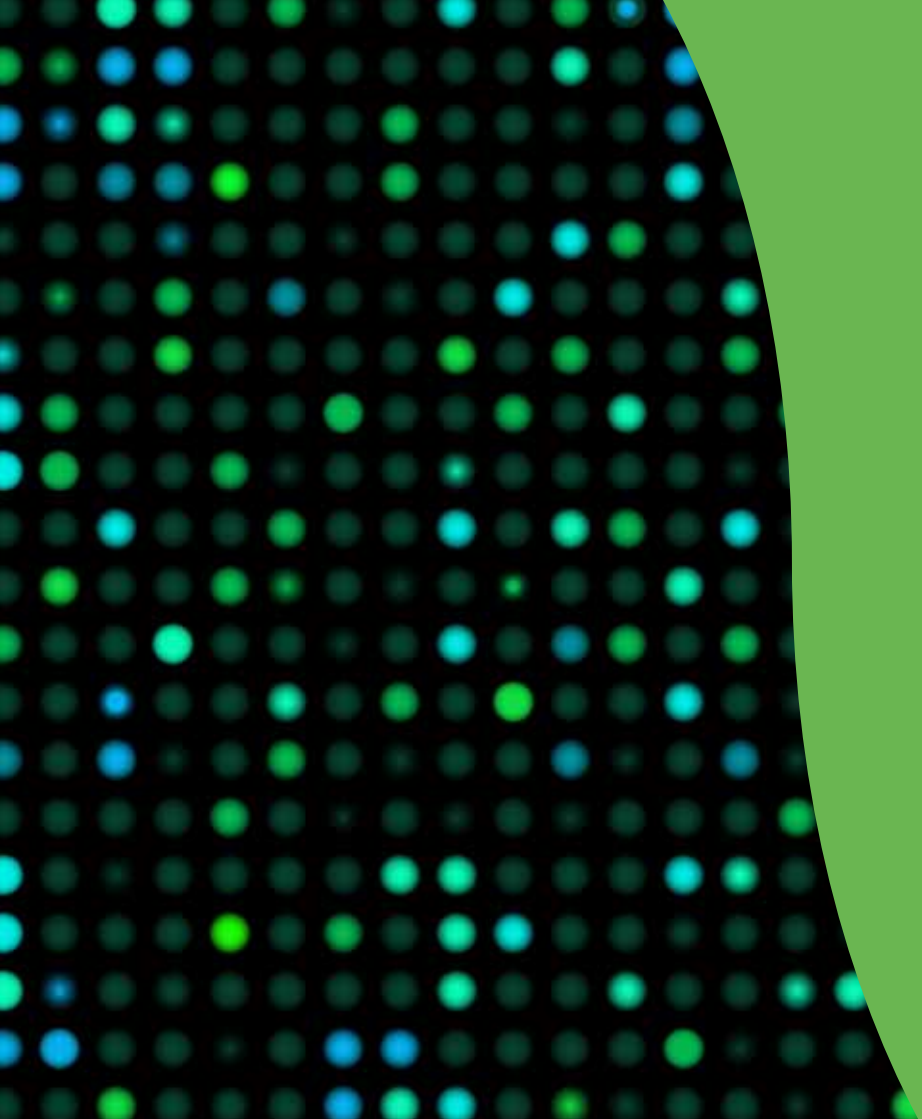
The iABC project is advancing the development of inhaled antibiotics for patients with CF and BE. It is also working to identify ways of improving clinical trials of treatments for these serious diseases.

Find out more: www.iabcproject.com

Coming soon – a new project on *C. difficile*

IMI2 – Call 9, which was launched in April 2016, included a new topic on antimicrobial resistance. Infection with C. difficile bacteria causes diarrhoea and abdominal pain and can prove fatal. In Europe alone, some 172 000 people, many of them elderly, are infected every year.

The goal of this topic is to improve our understanding of the epidemiology and clinical impact of C. difficile infection and to create an EU-wide research platform that will make it easier to test new ways of preventing and treating it. The resulting project will be launched in 2017 and will form part of the 'New Drugs for Bad Bugs' programme.



ECONOMIC MODELS

New economic models for antibiotic development

The DRIVE-AB project focuses on the urgent need to develop a new business model for antibiotic development that will reinvigorate investments in this vital area while also addressing the sustainable use of, and equitable access to, antibiotics. The project is tackling a contradiction at the heart of antibiotic development: on the one hand, pharmaceutical companies make money by selling large volumes of the drugs they develop. On the other hand, the use of new antibiotics should be restricted, so as to minimise the risk of bacteria developing resistance to them. As a result of this situation, sales are low and the costs of development often exceed the potential return on investment. DRIVE-AB is researching and developing the basis for new commercial models that provide industry and other stakeholders with an incentive to invest in this area, while ensuring that new antibiotics are used sustainably. The project will present its final recommendations and discuss their implementation at a conference to be held in Brussels, Belgium on 5-6 September 2017.

Key achievements

- DRIVE-AB achieved international and multidisciplinary **consensus on a global definition of responsible antibiotic use** comprising 22 domains. Consensus was also achieved on quality indicators and quantity metrics for both inpatient and outpatient settings.
- The project **identified the most promising reward models and presented them** to high-level decision-makers, policy experts and economists, as well as regulatory and public health experts and representatives of pharmaceutical companies and research institutions at a specially-organised conference in June 2016.
- The project has also **presented policy briefs to decision-makers** at high-level fora such as the United Nations General Assembly and the World Health Assembly.
- DRIVE-AB scientists discovered that a **30% drop in the efficacy of antibiotics could result in 120 000 additional infections and 6 300 deaths per year** in the US alone among people who undergo common surgeries and chemotherapy treatments. The findings were published in the Lancet Infectious Diseases.
- The project has been recognised by the **United Nations (UN)** Secretary-General's high-level panel on access to medicines and by EU health ministers.
- DRIVE-AB is cited in **EU guidelines on prudent use of antimicrobials in human medicine** as proposed by the European Centre for Disease Prevention and Control (ECDC).

Find out more: drive-ab.eu | @DRIVE_AB

ABOUT IMI

About the Innovative Medicines Initiative

The Innovative Medicines Initiative (IMI) is a partnership between the European Union and the European pharmaceutical industry, represented by EFPIA. IMI was launched in 2008 with the ambitious goal of improving the medicines development process and making it more efficient so that patients will have faster access to better and safer medicines.

IMI projects address challenges in medicines development that can only be addressed by collaborations involving all relevant stakeholders, including universities, small to mid-sized companies, patient organisations, regulatory authorities, the pharmaceutical industry, and companies from other industries such as imaging and diagnostics.

Today, IMI's 70 collaborative projects are delivering promising results in disease areas that are all too familiar to many Europeans, including dementia, infectious diseases, and diabetes.

Globally, IMI is recognised as a pioneer of open innovation and a model for successful public-private partnerships in research.

IMI finances

IMI has a budget of over €5 billion for the period 2008-2024. Half of this comes from the EU's research and innovation programmes.

The other half comes from large companies and organisations, mostly EFPIA companies. These do not receive any EU funding, but contribute to the projects 'in kind', for example by investing their researchers' time or providing access to research facilities or resources.

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