

How We Prepared “Breakthrough”

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Application forms

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Abstract *

Antimicrobial resistance, which is caused by multi-drug-resistant bacterial pathogens is a global health emergency. Gram-negative bacteria (GNB) notably hinder effective treatment because of their impermeable outer membrane (OM). Consequently, many standard-of-care (SOC) antibiotics cannot access intracellular targets in GNB.

The objective of the BREAKthrough European Training Network (ETN) is to sensitise GNB to these antibiotics by making their OM permeable. To this end, we will develop inhibitors of three protein machineries that are responsible for OM maintenance. Importantly, many known antibacterial agents have characteristics different from drugs that are directed against targets in mammalian cells. To define better rules for antibacterial drug development a data hub will be created to assemble information on the physico-chemical characteristics of molecules that can pass the OM.

To achieve these goals, a multi-disciplinary academic-industrial consortium has been assembled with organic chemists, computational chemists and specialists in high-throughput drug screening, zebrafish infection models, bacterial morphogenesis and the molecular biology of the three targets. The expected outcomes of the BREAKthrough ETN include (i) the development of new chemical space rules for drugs that need to cross the OM, (ii) the discovery of new inhibitors that interfere with OM maintenance to overcome the insensitivity of Gram-negative pathogenic bacteria towards SOC antibiotics and (iii) providing 10 Early Stage Researchers with scientific, technical, business and transferable skills to become professional drug developers with a keen eye for the hurdles in the development of these drugs in an industrial context.

1. The team

1.1. Building from a core:

We started from 4, met once to agree on a project and discuss on the consortium, choose a coordinator, etc











1.2. Expand

Complementary expertise: stronger together
(not a group of friends)

Academia-Industry

Different countries

Inclusive

No.	Consortium Member	Short Name	Academic	Non-academic	Awards Doctoral	Country	Department/ Division/ Laboratory	Scientist-in-Charge	Role of Associated Partner
Beneficiaries									
B01	Université catholique de Louvain	UCLouvain	✓		✓	 BE	de Duve Institute	Prof. Jean-François Collet	
B02	Centre National de la Recherche Scientifique	CNRS-IBS	✓		✓	 FR	Institut de Biologie Structurale	Dr. Jean-Pierre Simorre	
B03	University of Newcastle Upon Tyne	UNEW	✓		✓	 UK	Centre for Bacterial Cell Biology, Biosciences Institute	Prof. Waldemar Vollmer	
B04	Università degli Studi di Milano	UNIMI	✓		✓	 IT	Department of Pharmacological and Biomolecular Sciences	Prof. Alessandra Polissi	
B05	Vrije Universiteit Amsterdam	VU	✓		✓	 NL	AIMMS, Department of Molecular Microbiology	Prof. Joen Luirink	
B06	University of Ljubljana	UL FFA	✓		✓	 SI	Faculty of Pharmacy, Pharmaceutical Chemistry	Prof. Stanislav Gobec	
B07	Amsterdam University Medical Centres	AUMC	✓		✓	 NL	Department of Medical Microbiology and Infection control	Prof. Wilbert Bitter	
B08	Institute of Chemical Research of Catalonia	ICIQ	✓			 ES	Martin Research Laboratory	Prof. Ruben Martin Romo	
B09	AiCuris GmbH	AiCuris		✓ Industry		 DE	Bacteriology	Dr. Cuong Vuong	
B10	Naicons Srl	Naicons		✓ SME		 IT	Microbiology	Dr. Margherita Sosio	

1.3. Associated Partners

They can be chosen in a later stage

You need to have enough (secondments !)

2. The proposal

It takes times !

2.1. Scientific Part

1 Excellence

Urgent need: Antimicrobial resistance (AMR) is a **global health emergency**. The United Nations (UN), the World Health Organisation (WHO) and the European Commission (EC), including the G20/G8, have recently declared AMR as a serious global threat to public health that has a tremendous impact on healthcare expenses and productivity¹. AMR may result in an estimate of > 300 million premature deaths and cost the global economy up to €100 trillion by 2050. The most relevant factors (Fig. 1) involved are its continuous spread and the rise of **multi-drug-resistant (MDR)** pathogens with very limited options to treat the infections, resulting in increased morbidity and mortality.¹ Notably, **Gram-negative bacteria (GNB)**, which are resistant to almost all antibiotics, have recently emerged, recreating situations typical of the pre-antibiotic era, with no option left for treatment at all. **MDR GNB** have become a major cause of infections in the past years, also **causing the death of many patients with COVID-19 infections**. Infections by MDR GNB are particularly hard to treat because the **impermeability of the outer membrane (OM) restricts access** of many large-scaffold standard-of-care (SOC) antibiotics. For instance, vancomycin, which blocks peptidoglycan synthesis by binding to the terminal D-Ala-D-Ala in the stem peptide of lipid II, is widely used against Gram-positive bacteria but is ineffective against Gram-negative bacteria because it cannot cross the OM bilayer. **Thus, we want to combat MDR GNB by destabilising their OM, potentiating SOC antibiotics to penetrate and kill bacterial cells.**

Proposed solution: The main research aim of our BREAKthrough Doctoral Network (DN) is to **sensitise GNB to SOC antibiotics by making their OM permeable** through the development of inhibitors of three protein machineries (BAM, Lpt and lipoprotein-peptidoglycan [Lpp-PG] attachment) that are responsible for OM maintenance. Such compounds will **facilitate the entrance of newly developed and existing antibiotics to kill bacterial cells (Fig. 2).**



Figure 1 Need for the BREAKthrough project

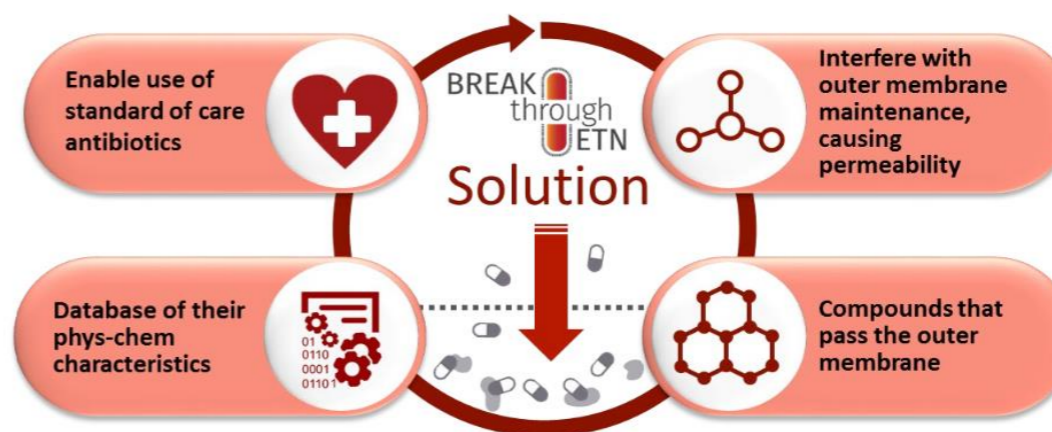


Figure 2 Solution proposed by the BREAKthrough project

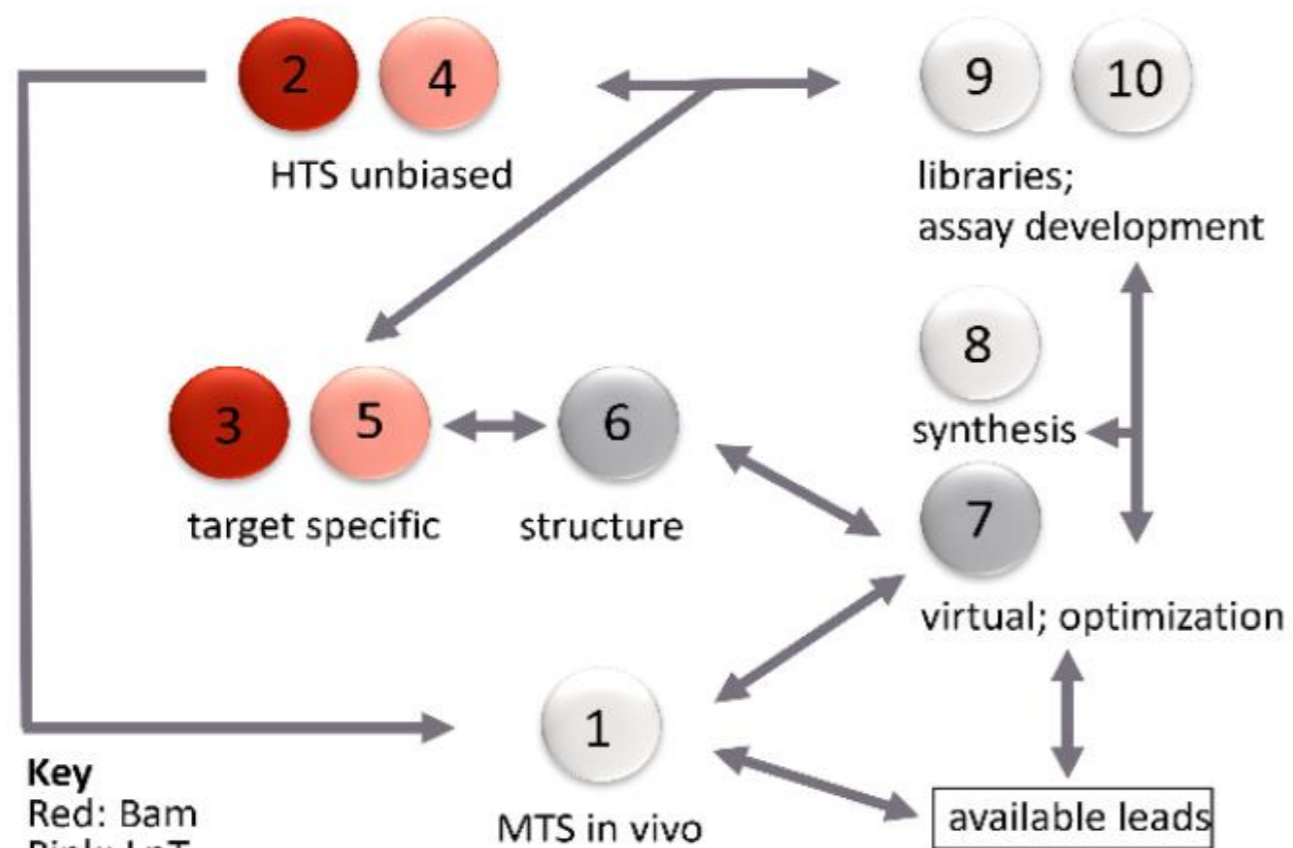


Figure 5 RF projects.

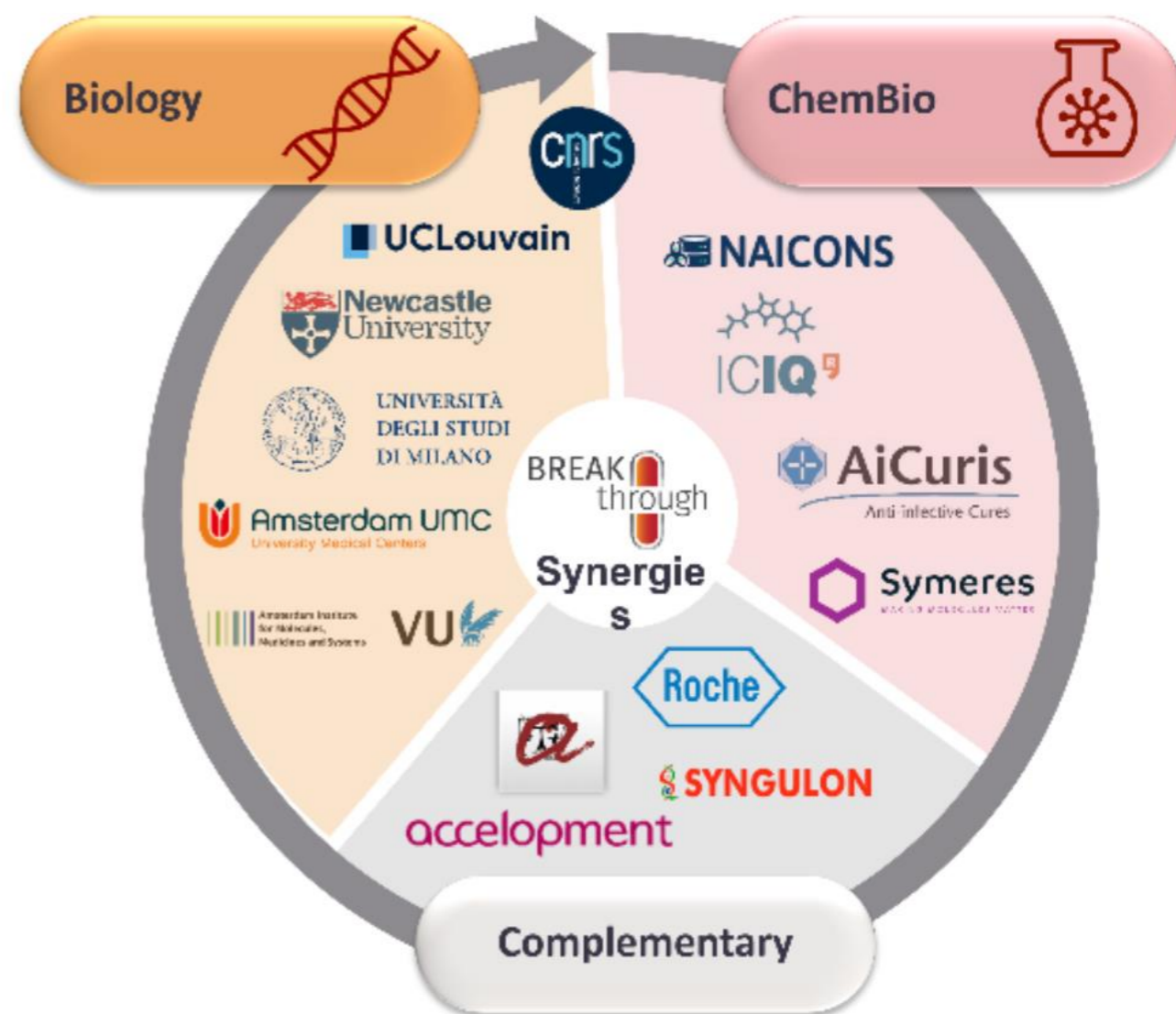


Figure 6
Synergies between the participating organisations

2. The proposal

It takes times !

2.1. Scientific Part

2.2. Non Scientific Part

You need to build a convincing plan
(Data management, training program,
dissemination, career development plan, etc)

3. You need help !

- Ask a colleague for a successful application
- Ask you research administration
- Ask a consultant

It's worth it !

