

IMI1 Final Project Report Public Summary

Project Acronym: ENABLE

Project Title: European Gram Negative
Antibacterial Engine

Grant Agreement: 115583

Project Duration: 01/02/2014 – 31/10/2021

1. Executive summary

1.1. Project rationale and overall objectives of the project

The current level of unmet need for treating antibiotic resistant Gram-negative bacterial infections is a serious issue for the health care system and will only increase over time. The industrial pipeline of novel agents to treat these infections remains limited and due to the substantial scientific challenges in this area, significant, concerted actions need to be taken. The ENABLE consortium intended to meet these challenges and work in an unprecedented and collaborative way to help populate this important pipeline with new agents ready for testing in patients. The overarching objectives of the ENABLE project were to: 1) create a drug discovery platform with the expertise and resource base to prosecute multiple antibacterial programmes in parallel; and 2) increase the overall pipeline in the antibacterial area by applying this platform to optimise a variety of antibacterial programmes to deliver candidates and phase 1 success. ENABLE could serve as a model for how collaborative Public-Private-Partnership drug discovery projects can be run to accelerate the development of promising therapeutics addressing unmet medical needs. In addition ENABLE has provided robust training for numerous scientists and has improved the overall level of competence in antibacterial drug discovery in Europe and globally.

1.2. Overall deliverables of the project

In line with the overall objectives above, the key deliverables of ENABLE are designed to increase the overall pipeline of high quality, novel mode of action medicines to treat serious systemic Gram-negative infections.

Initial deliverables of the project:

- deliver 3 antibacterial Leads;
- deliver 2 antibacterial clinical Candidates;
- progress at least 1 compound into Phase 1 clinical studies.

ENABLE has progressed 23 European antibacterial programmes in total and strengthened the preclinical pipeline of compounds targeting resistant Gram-negative pathogens. ENABLE has filed 9 patents and published several scientific articles. ENABLE's initial objectives have been surpassed, with:

- **6 leads delivered (WP5b, WP5d, WP5f, WP5g, WP5h, WP4t)**
- **3 development candidates identified (WP5d, WP5f, WP5g)**
- **1 phase I study completed (WP7b)**

1.3. Summary of progress versus plan since last period

Following IMI agreement on a 9-month no-cost extension of the project to compensate for delays due to COVID-19, the end date was moved from 31st of January 2020 to 31st of October 2021. All active programmes completed their work by 31st of July at latest, and the 3 month buffer (Aug, Sep, Oct) was in case of unforeseen delay in a planned Phase 1b study for the UZH/Juvabis programme, which in the end was not undertaken by the programme owners.

At the start of the seventh period there were seven active programmes: Four Hit-to-Lead (H2L) programmes, two Lead-to-CD (L2C) programmes and one programmes in clinical development. During the reporting period, one H2L programme and one L2C programme graduated from ENABLE and continued to progress with funding and support from other antibiotic development initiatives. During the period, one H2L programme made a successful Lead Declaration (hit owner Uppsala University), one L2C programme made a successful Pre-Candidate selection (hit owner University of Oxford) and another a successful Candidate Declaration (Mutabilis-1 programme). In addition, a Phase 1 clinical study was completed (UZH/Juvabis programme).

1.4. Significant achievements since last report

The seventh reporting period of ENABLE saw good progress in the portfolio. Key achievements

- One Lead has been selected (WP4t)
- One Pre-Candidate has been selected (WP5h)
- One Candidate has been selected (WP5f)
- One Phase I study was completed (WP7b)
- The H2L and L2C programmes in the ENABLE portfolio have been substantially advanced during the 7th reporting year

The project has achieved and surpassed its initial goals and has in total identified 6 antibacterial leads, selected 3 antibacterial development candidates and has completed 1 Phase I clinical study.

1.5. Scientific and technical results/foregrounds of the project

ENABLE was formed by the successful fusion of two projects that independently applied to IMI (JEDI and HIEPERACTIV), representing on the one hand management and technical expertise and on the other hand a diverse group of potential antibacterial projects hoping for resources to drive their development. ENABLE was also the result of a successful fusion of inputs from multiple EFPIA partners willing and able to work in collaboration with each other, and with a very diverse set of academic groups, research organizations and SMEs. The smooth transition from being separate projects and groups to functioning as a new antibiotic discovery and development entity that occurred prior to the formal launch of ENABLE in 2014, was the result of months of intense work and close collaborations developed involving key personnel from EFPIA and the public partners. This work resulted in the successful development of all of the legal documents that served to successfully guide ENABLE and its constituent projects through the following seven and a half years. In summary, the rapid and successful establishment of ENABLE as a highly functioning entity with the ability to drive the development of novel antibacterial compounds was a major result of the project.

In setting up ENABLE as a functioning entity we also had to establish a set of technical platforms, each with responsibility for performing the science in a particular area. These were: chemical modelling and database management; chemistry; microbiology; in vitro/in vivo/safety; pharmaceutical development; compound management; and a reinforcement group. Each of these technical platforms (with the

exception of pharmaceutical development and compound management) involved multiple geographically dispersed partners. Establishing efficient lines of communication was an essential requirement for success in ENABLE and this was facilitated by the early establishment of effective management groups and regular meetings at different functional levels. These included the Portfolio Management Committee (PMC) that made decisions on entry and continuation/termination of projects, the Consortium Management Office (CMO) that were responsible for all of the day-to-day management of ENABLE, and the individual Technical Platform Groups that met regularly to discuss division of work, sharing of information, and how to address challenges and bottlenecks.

The international networks established during the seven years of ENABLE, have resulted in bilateral and multilateral collaborations that are continuing after the closure of ENABLE. At the beginning of ENABLE there were approximately 30 different organizations involved which expanded to over 50 by the end. This building of working relationships across Europe is an important result of the project, and is likely to provide continued benefits to science and antibiotic discovery in Europe for years to come.

By working in the ENABLE project a new generation of scientists in Europe have received an invaluable training in the process of discovery and development of novel antibacterial drugs. They have become familiar with the range of assays involved, the key milestones on the development path, the most important liabilities at each stage, and the viewpoints and arguments expressed by leading scientists in major EFPIA companies working in the field. This training extends also to the personnel working in many of the SMEs that had projects within ENABLE. Many SMEs entered ENABLE with very limited knowledge of the totality of the science required for successful antibiotic development. Through their involvement they have been educated and have the ability to work successfully in an independent capacity. In addition, SMEs and academic groups have established valuable contacts with experts within EFPIA.

EFPIA itself has gained from ENABLE by having a unique deep insight into the current state of antibacterial discovery in Europe, and has gained access to academic technical expertise that could be employed to help to enhance their own project development.

Another measure of the value of ENABLE is that it has achieved more than its original set of antibacterial development objectives, including one completed Phase 1 clinical trial. This project is currently scouting for investments to progress programs with potential antibiotics into later stage clinical trials. In addition, three ENABLE programmes have been accepted into other initiatives for continued development: GNA NOW, CARB-X, INEOS Oxford Institute. This continued investment in development is a testament to the quality of the projects developed within ENABLE.

1.6. Potential impact and main dissemination activities and exploitation of results

ENABLE has contributed in several distinct ways to the benefit of European citizens. Firstly, by identifying interesting and novel antibacterial compounds and successfully developing them to a level where they are of interest to other initiatives for further development. ENABLE has contributed directly to increasing the number of potential new antibiotic medicines that may appear on the market

in the coming decade. One or more of these medicines may make an important contribution to saving the lives of European citizens in the future. In one case a potential antibiotic was progressed into phase I human trials.

Secondly, by revitalising knowledge and interest in the area of antibacterial drug discovery and development among European academic laboratories and research organizations, ENABLE has laid the groundwork for future discoveries and collaborations in this critically important area, and in doing so has contributed to making Europe a more attractive area for antibiotic pharmaceutical research and development.

Thirdly, by establishing a successful international project that successfully merged inputs from EFPIA companies, from SMEs, and from academic and research organisations, ENABLE has provided a blueprint for other Public-Private Partnerships (PPPs) to copy and follow. Indeed, the success of ENABLE has motivated the Swedish government to provide seed funding for the continuation of an ENABLE-2 (initially based in Sweden but also involving some of the ENABLE international partners) with the aim of ensuring that this type of collaborative partnership can continue the work on antibacterial drug discovery and development. This may be just the beginning of a larger involvement by other European governments and funding agencies in promoting international collaborations in this critical area. If the success of ENABLE inspires the initiation of one or more similar projects, then that might be its greatest long-term legacy.

1.7. Lessons learned and further opportunities for research

The strong involvement of EFPIA companies in ENABLE has been absolutely essential to its success. They brought knowledge of the management structures needed for building an efficient and effective multidisciplinary collaborative project like ENABLE. In addition, they brought in the knowledge of the huge range of scientific techniques that were required, and importantly, when they would be required during the life of a development project. At later stages in development EFPIA were able and willing to contribute with specialist experts in these areas. Within the PMC, EFPIA and independent experts (who in the main had previously worked within EFPIA companies) contributed a rich knowledge of what had been tried in the past, what had succeeded, and why certain approaches had not succeeded. The public partners quickly learned the importance of identifying liabilities in a development project, the most effective strategies for mitigating liabilities, and the importance of establishing Go/No Go criteria. Together, these strategies rapidly identified projects facing terminal problems which could be wound down and their resources were reallocated to other projects. This knowledge of how to optimally perform drug discovery and development was not or only partially present among the academic groups or the SMEs. One of the most important outcomes from ENABLE has been educational; the transfer of drug discovery and development knowledge from EFPIA experts to academic researchers and SMEs.

Within ENABLE two EFPIA partners collaborated actively on a series of common projects (initially GSK and Sanofi, later GSK and Evotec). In all, they collaborated on three separate development projects, sharing compounds, structures, methods, and technical expertise. This type of collaboration between pharmaceutical companies is highly unusual and reflects positively on their commitment to achieving a common goal, namely the development of new effective antibacterial compounds. The EFPIA

collaboration also had the benefit that it ensured the company management was committed to working within ENABLE, transferring knowledge and advice to SMEs and academic development projects, because they also had their own projects that were benefiting from scientific input from the public partners.