Building new models of drug discovery in Europe

the Innovative Medicines Initiative

The discovery and development of a new medicine is time-consuming, risky and expensive. It often takes 10-15 years and an investment of on average >$1 billion for a compound to navigate its way along the drug discovery and development process – and only 8% of drug candidates entering clinical development make it to market and benefiting the patient[1,2]. To mitigate the risk and investment, but also to increase efficiency by pooling resources, experience and expertise, more and more collaborative partnership/open innovation models of R&D have emerged. Founded by the European Commission (EC) and the European Federation of Pharmaceutical Industries and Associations (EFPIA), one such joint undertaking is the Innovative Medicines Initiative (IMI). IMI supports collaborative research projects and builds networks of industrial and academic experts in order to boost pharmaceutical innovation in Europe. Collaborative approaches such as IMI have traditionally focused on pre-competitive areas. Recently, however, we have seen the emergence of projects focused on more competitive areas of research, particularly early drug discovery and hit and lead optimisation.

By Dr Angela Wittelsberger, Dr Hugh Laverty and Dr Michel Goldman

Often the drug discovery process starts with the identification of a new molecule that binds and modulates a biological target. This process of High-Throughput Screening (HTS) frequently represents the first step on the difficult path to the discovery of a new medicine for patients. Since it was embraced in the 1990s, the pharmaceutical industry has become heavily reliant on HTS as a means for identifying new chemical molecules that can bind and modulate biological targets. Over many years millions of compounds were screened against interesting biological targets, yet these screens tended to yield only a small number of hits. Coupled with the high costs associated with setting up HTS, this has led to the perception that HTS has not and will not deliver on its potential.

Unfortunately, the large investments required in HTS preceded the relative drought in drug companies' pipelines and, whether related or not, the combination of a perceived lack of return on investments and a number of late stage failures gave HTS a pretty bad press. However, in a recent publication by Glaser (2009), it is estimated that 55% of the compounds currently in Novartis' lead optimisation pipeline are projects with their roots

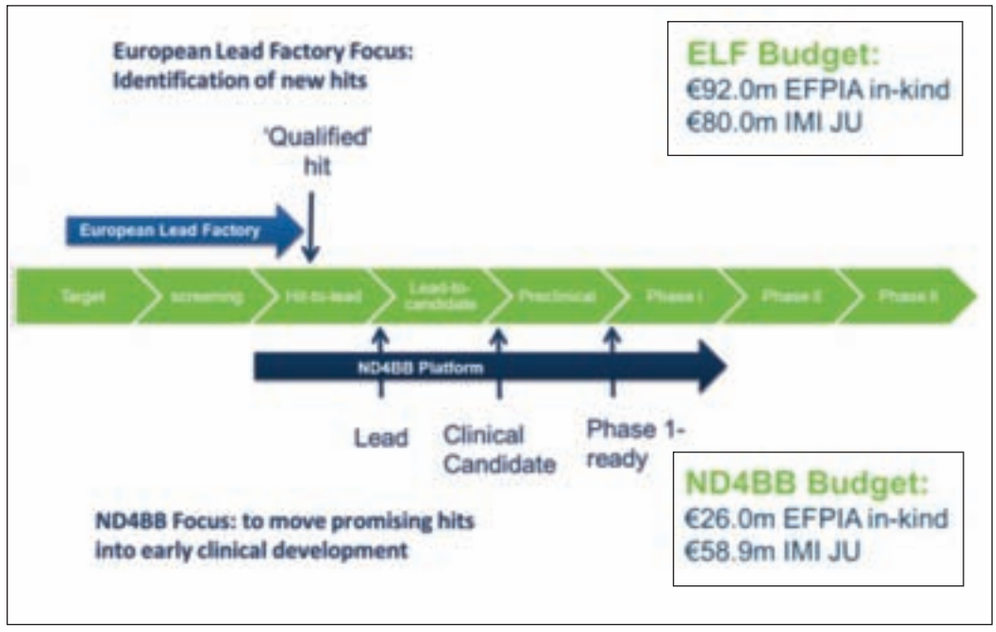

Figure 1
Feeding pharmaceutical companies pipeline. Figure showing where IMI's projects sit on the pharmaceutical company drug development pipeline. European Lead Factory covers the identification of new 'hits' to known targets. ND4BB takes exciting new 'hit to lead' programmes and attempts to progress them into clinical testing

in HTS. Pfizer's antiretroviral agent 'maraviroc', approved by the FDA in 2007, was originally identified as a molecular scaffold in 1997[3].

In the face of the high costs encountered, companies have been increasing the quality of their libraries and refining their HTS processes. But, at the same time, many major companies have retreated from the number of disease areas in which they attempt to discover new medicines. This means that within an individual organisation the number of different disease-related targets that a given high quality library is screened against is declining. Increasingly, companies are seeking new targets from outside their organisations from public research institutions and SMEs, and HTS has become more widely adopted by non-pharma institutions. However, these public entities have limited access to high quality libraries and screens and therefore there is a question mark over whether academic institutions and SMEs will be able to provide the number of new leads expected. Therefore, if we are to ensure that public institutions can be serious players in the HTS arena then we must ensure that the libraries available are of the highest possible quality and contain diverse chemistries covering a wide range of chemical space to prevent the same molecules from appearing in the results of HTS campaigns with different targets. There is also a need for users of libraries to be proactive in their HTS efforts, specifically by validating the chemical identities of their screening hits, a position highlighted by an editorial in Nature Chemical Biology in 2009[4].

Several different initiatives have been instrumental in developing HTS within the public sector. These approaches are facilitating the standardisation of methods; ensuring the quality of the libraries and reducing costs by sharing the burdens of investment through promoting collaboration between different players.

Molecular Libraries Program

The first large scale initiative was the Molecular Libraries Program (MLP) in the US. It was founded with the intention of making the tools of industrial scale drug discovery available to academic investigators. Since the programme started in 2004 the network of nine MLP centres have produced more than 250 probes, produced 342 publications, made its data publically available via PubChem and generated more than 100 potential drug candidates[5]. However, the programme was hampered in the early stages by poor quality compounds, something that was recognised and has been addressed. Unfortunately, the direct funding for MLP is to disappear in 2014 (a direct consequence of the current economic climate), but one of MLP's nine centres, the NIH Chemical Genomics Centre (NCGC), has become part of the NCATS and its services will remain open to both NIH and external scientists. Importantly, the MLP has been instrumental in driving a culture shift with an NIH review in 2010 identifying 32 independent centres in the US alone that have created their own standalone screening facilities[5].

EU-OPENSCREEN

Following the experience in the US and learning from the MLP, Europe has now started several initiatives in this area. Building on existing national networks in 14 European countries to synergise Europe's varied expertise, the European Infrastructure of Open Screening Platforms for Chemical Biology (EU Openscreen), has been set up to deliver new biologically active compounds for all fields of the Life Sciences. These compounds will be used by scientists as molecular tools or probes to investigate the molecular mechanisms of biological processes. It is hoped that the results will yield deep insights into how these compounds act and, thus, inspire the design of new drugs. In addition, the systematic and repeated testing of a large collection of chemicals in different assays and contexts will create a comprehensive knowledge about their impact (benefits and risks) on humans and the environment.

The EU-OPENSCREEN Preparatory Phase project started on November 1, 2010. European researchers from academia and SMEs will obtain access to the most advanced screening technologies. This will allow the researchers to identify compounds affecting new targets. The interdisciplinary approach of EU-OPENSCREEN will bring together chemists, engineers, informaticians and biologists, overcoming the fragmentation of European research in the field of Chemical Biology. EU-OPENSCREEN will primarily support projects on unconventional targets and that address fundamental biological questions. In this respect, the activities of EU-OPENSCREEN will precede commercial development.

European Lead Factory

Both MLP and EU-Openscreen focus very much on harnessing the expertise and infrastructure that already exists within the public sector. This approach has already generated many exciting results and fostered a more open and collaborative approach in the field of HTS. Another initiative taking a more industrial focused approach is the Innovative Medicines Initiative's European Lead Factory (ELF). ELF is a public-private partnership project that involves joint collaboration between public institutions and the pharmaceutical industry[6].

Launched in February 2013, the European Lead Factory is intended to bridge the gap between academic and applied research by providing an industry-like small discovery platform to public investigators with innovative ideas for drug discovery programmes targeting both lead structures for drug development or high quality probes for target research. The ELF is differentiated from other initiatives in that partner EFPIA companies are sharing their compound collections contributing more than 300,000 compounds to a Joint Compound Collection with another 200,000 compounds to be contributed by public partners during the life time of the project. This Joint Compound Collection will be available to be screened against targets not only to other companies but to external partners as well. Uniquely in ELF one company's targets will be screened against a competitor's compounds. Academia or other eligible bodies will be invited to submit proposals for screening of innovative targets and to suggest the design of new and diverse chemical libraries utilising novel concepts and strategies. This innovative approach holds the potential to result in valuable lead structures for thus far unexplored targets by facilitating open innovation around compound collections from pharmaceutical companies, and allow drug discovery programmes from public originators and private consortium members to benefit from otherwise protected assets.

Building on the experience to date in this area, ELF will ensure the highest quality possible for its compound collection and have in place a rigorous selection process for targets to be screened. ELF will provide compounds and support for 48 HTS screens per year. 24 screens will be undertaken by EFPIA partner companies, whereas 24 screens will be made available to IMI eligible partners selected after a rigorous review process. The output from the screens will be a list of the 50 top hits that the target owner will have a three-year exclusivity period to further develop or gain IPR. It is also hoped that projects will be partnered between the target owners and EFPIA partners involved, further accelerating the development of new medicines for the benefit of patients.

ELF's overarching goal is value creation by screening the Joint European Compound Collection against public and private targets. The ELF is a unique experiment in public-private collaboration and has the potential to transform the way in which we approach early drug discovery. The ELF approach has generated a lot of interest and the results of the project will be followed with great interest.

Discovery and development of new drugs combatting Gram-negative infections

The three initiatives described here are very much focused on harnessing HTS and extracting as much value from it as possible by identifying new molecules that bind to or modulate a target. The identification of a promising molecule is only the

beginning, the next challenge in drug discovery is to further develop and optimise the hit into a lead molecule, and then further into a clinical candidate molecule. This is often an iterative and time-consuming process, and indeed the further a drug is developed the greater the obstacles become. This is particularly true in the discovery of new antibiotics where the challenges are multiple. First, huge scientific difficulties have to be overcome, in particular when aiming at a drug to treat Gram-negative bacteria. Next, susceptibility to the development of resistance needs to be analysed and addressed, and third a particularly low return on investment poses a major economic challenge. The scarcity of new antibiotics in the pharmaceutical development pipeline combined with the rise of antibiotic resistant pathogens make antibiotic resistance one of the major public health threats for the next few decades[7,8]. The New Drugs for Bad Bugs (ND4BB) programme by the IMI was launched in 2012 as one out of several actions of the European Commission Action Plan Against the Rising Threats of Antimicrobial Resistance[9]. The goal of the ND4BB research programme is to create an innovative and collaborative public-private partnership-based effort that should positively impact on many aspects of antimicrobial resistance, from addressing basic scientific challenges and discovering novel antibiotic lead and development candidates, to Phase I, Phase II, and Phase III clinical trials, and from the research into new business models of antibiotic R&D to the challenge of responsible use of antibiotics.

The ND4BB project ENABLE, started in February 2014, is an antibiotic drug discovery project in which owners of promising hit or lead molecules active against Gram-negative bacteria are invited to use the resources and expertise brought in by other partners in the project to see their asset further progressed. A programme can enter at 'qualified hit' status, be progressed from hit to lead, then through clinical candidate until maximum a Phase I clinical trial. In order to qualify for entering the project, any novel approach should already have reached a certain level of validation in order to have a realistic chance of reaching clinical candidate status within the six years of the project duration. Therefore, there may be potential synergy with the European Lead Factory, as, in theory, a novel antibacterial hit molecule resulting from an effort under ELF could be further developed in the drug discovery platform provided by ND4BB Topic 3. It is envisaged that up to eight hit-to-lead programmes will be contributed from academic or SME partners. In addition, one lead programme is jointly further developed by Sanofi and GSK within the project using the combined expertise of the platform. The expectation is that up to three novel clinical candidate molecules will be generated, and up to two Phase I clinical trials with novel antibiotics will be conducted within the duration of the project[10].

The main challenge towards making the platform successfully deliver is a solid governance and portfolio management structure and clearly defined terms of ownership and compensation that will be trusted by hit owners and attract the very best European hit-to-lead programmes. This does not prevent the promotion of data and knowledge sharing that should positively impact the entire field of antibiotic drug discovery.

Equally ground-breaking as ELF, this public-private partnership approach to the discovery and development of novel antibiotics drug discovery could prove itself a valuable model for drug discovery/development in general.

Data sharing and IP

A key area of attention for the new drug discovery platforms is data sharing and how the knowledge and intellectual property generated are managed. Whereas the aim is always to maximise outcomes by pooling resources and expertise and sharing data and results as much as possible, there are clearly different approaches that have been adapted depending on the needs and objectives of the initiative. For example, truly 'open' initiatives exist such as India's Open Source Drug Discovery (OSDD) Initiative, a Council of Scientific and Industrial Research (CSIR) Team India Consortium, whose aim is to accelerate the development of new drugs to treat neglected tropical diseases. Committed to affordable healthcare, a potentially discovered new drug under the OSDD initiative would not have any IP constraints but could be manufactured and sold by any company at affordable prices. A 'micro-attribution' rewards system enables contributors to accumulate credit points for their submissions and to subsequently receive monetary rewards as well as increased rights, privileges and responsibilities in the project[11,12].

Many IMI projects focus on pre-competitive areas of research, where IP-related issues can be kept to a minimum. Many projects deal with aggregating data, and newly generated databases and results are made publicly available as much as possible and as soon as possible. For example, the OpenPHACTS project is developing an open access innovation platform that will be comprised of data, vocabularies and infrastructure needed to accelerate drug-oriented research. The aim is to

develop an enabling resource for drug discovery projects which is open to all users and freely available in the public domain[13]. IMI's PROTECT project, co-ordinated by the European Medicines Agency, has published two key databases for pharmacovigilance that are freely available[14]. The Inventory of Drug Consumption Databases in Europe provides a comprehensive and structured source of information on drug consumption in Europe, meanwhile the PROTECT ADR database is a downloadable Excel file listing all adverse drug reactions (ADRs) listed in the Summary of Product Characteristics (SPC) of medicinal products authorised in the EU.

In general, IMI's IP policy aims to promote and reward knowledge creation, disclosure, exploitation and innovation through a fair allocation of rights. Given the diversity of projects supported by IMI and the complexities associated with IP management in public-private partnerships, a 'case-by-case' approach is important. Accordingly, the overall IP policy has been designed to allow for appropriate flexibility to best serve the specific situation of each consortium. As a general provision, each participant remains the exclusive owner of all information and IP rights it holds before becoming a partner in an IMI project. Information and IP that are necessary for the completion of the project are identified prior to the start of the project and defined as 'Background'. This background information is accessible on a royalty-free basis to project participants to the extent necessary for undertaking the project. The results that are generated during the course of the project as part of its objectives are defined as 'Foreground'. Ownership rights to Foreground can be negotiated prior to the start of the project and be adapted to the project needs – and here lies a key flexibility in IMI's IP policy.

ELF and the antibiotic drug discovery platform discussed above are focused on competitive areas of R&D and are aimed at generating value. Importantly, the flexibility of IMI's IP policy allows for collaboration between public and private partners even under competitive conditions in the fields of hit identification and lead optimisation. The agreement negotiated between the different partners needs to make sure that it is attractive for all partners to participate in the project. For example, in ELF, partners have negotiated detailed schemes to allow target owners access rights to chemical compounds provided by other partners and a compensation scheme that rewards the contributions made by the different partners. In ENABLE the different partners have to ensure that both hit owners with an interest to further progress

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their asset and those partners that do not bring in a molecule themselves, but work on the programmes selected for further progression, find it attractive to participate in the project. The IMI IP policy allows for flexible solutions to the extent that different projects can adopt different approaches best suited to the goals of the project. This includes for example the possibility that – in order to attract hit-to-lead programme owners to use the antibiotic drug discovery platform – all improvements made to the hit or lead molecule get assigned to the original hit owner. In return, compensation schemes for those partners contributing to improve the asset can be negotiated for the eventual case that the asset moves on to later stages and starts to generate return. In order to reach an agreement that is attractive for every partner, proper negotiation and flexibility is critical. The neutral platform as provided by the IMI and the flexibilities allowed by IMI's IP policy strongly facilitate the negotiation process and help these complex projects work.

Concluding remarks

To alleviate the challenges of early drug discovery, innovative models of multi-stakeholder collaboration have emerged, that sometimes even operate in the competitive fields of hit identification and further progression towards a novel clinical candidate molecule. These initiatives are ground-breaking and often have as a prerequisite the adoption of a change in mind-set by the different partners. It is early days for many of these initiatives and the coming years will demonstrate whether they are delivering successfully, but by sharing risks and sharing rewards these new collaborations promise exciting future developments in the hope of novel medicines needed for patients.

Disclaimer

The opinions expressed in this article do not necessarily reflect the positions and opinions of the European Commission or the European Federation of Pharmaceutical Industries and Associations. DDW

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