REVIEW ARTICLE

The European lead factory—an experiment in collaborative drug discovery

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Abstract: The European Lead Factory (ELF) is a unique collaborative public–private partnership aiming to deliver innovative drug discovery starting points and improving the value generated by ultra-High Throughput Screening (uHTS) approaches. Composed of a unique compound collection derived from private pharmaceutical company collections and complemented with new chemistries from a unique public collection, it offers a unique uHTS platform accessible to both private companies and publicly funded researchers. One of the key challenges in setting up ELF has been to balance access to screening results with protecting the value of compounds in the collection. Through an 'honest data broker' data management platform and a royalty reward scheme based on achieved milestones, ELF has been able to overcome these challenges. Set up in 2013, it has already accepted 42 targets for screening, submitted by publicly funded researchers, and generated 12 Qualified Hit Lists. In addition, 55,000 new library compounds have been generated by the public partners and added to the 320,000 compounds made available by the companies. Although it faced many challenges in becoming operational, this unique experiment in collaboration is already generating exciting results that will hopefully, eventually lead to better medicines and tools to advance our biological knowledge, and should act as a template for future approaches in the area.

Keywords: drug discovery, public–private partnership, ultra-high throughput screening, biological targets, chemistry scaffolds, honest data broker, qualified hit list, European Screening Centre, Joint European Compound Collection

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1. Introduction

Despite heavy investments into basic and applied pharmaceutical research and steadily increasing public and private efforts, symptomatic and more importantly, curative treatments are still only available for a limited number of known diseases. In nearly all indication areas, the unmet medical need is still enormous[1]. Progress is being made in pharmaceutical research, promising new tools and technologies are being integrated into discovery processes and our understanding of what is going on at the molecular level is growing. Yet even in this post-genomic era, human biology continues to reveal itself as highly complex and the overall success rate in drug discovery remains low[2,3]. Therefore, if we are to

discover new medicines and reduce R&D costs, new avenues and approaches to sharing risks and to reducing attrition rates continue to be of high interest to the pharmaceutical industry, healthcare systems and, most importantly, patients.

One approach that appeared to offer a rapid route to helping understand the complexity of drug targets and accelerate the development of new medicines has been High Throughput Screening (HTS). However, whilst HTS approaches have matured and become an integral part of pharmaceutical research and a cornerstone in the expansion of biomedical knowledge, it has been blamed for failing to provide enough viable leads for many targets. The quality of existing compound collections has often been cited as a reason for the poor quality of hits identified in many HTS campaigns[3,4]. Yet, the challenges faced by HTS extend beyond the quality of existing compound libraries. Corporate compound collections are still heavily safeguarded by pharmaceutical companies and consequently tested against only a fraction of disease-relevant targets determined by a company's therapeutic areas of interest. Furthermore, individual collections provide insufficient coverage of the 'drug-like' chemical space and a comprehensive comparison of the underlying library design strategies is hampered by company boundaries[4,5]. As a result, within the existing competitive framework of safeguarded company compound collections, their corresponding value[6,7] remains incompletely realized.

Therefore, if we are to accelerate the discovery of new drugs to benefit patients, we face a challenge in harnessing the true potential of HTS approaches and the untapped value in company collections, and in building platforms that allow wider access to unique compound collections for both competing companies and public entities alike. Against this backdrop of sharing collections, we must also find ways to protect the rights of the organisations and security of the compound collections involved, while allowing the exploitation of new research results in the form of new drug discovery programmes.

In the following article, we describe a unique public–private partnership called the European Lead Factory (ELF, see Supplementary information S1). ELF aims to address the challenge of delivering innovative ideas and to improve both the quality and value of the hits generated via HTS approaches. It is composed of the European Screening Centre (ESC) and the Joint European Compound Library (JECL). More than 300,000 optimised industrial research compounds have been contributed by seven pharmaceutical companies to the JECL. These compounds from the companies are complemented by an all-new compound collection, based on designs and syntheses by small and medium-sized enterprises (SMEs) and academic institutions. The goal is to build a unique compound collection, unprecedented in current drug discovery platforms, of up to half a million compounds. Screening of such compounds to assess their biological activity is also funded and performed by ELF for both private companies and selected public targets. This means substantial cost savings for contributors as well as a very productive exchange of ideas. State-of-the-art facilities are provided by the newly-established ESC, based in Scotland, Holland and England. The ELF project aims to run up to 240 screens, with third party drug target owners from academia or biotech accounting for up to 120 of the screens.

The ultimate deliverable by ELF is a list of $\leqslant$50 well-characterised HTS hit structures, assembled in a so-called Qualified Hit List (QHL), which is provided to the owner of the related drug target to exploit and develop new drug discovery programmes. Crowdsourced drug target owners can benefit from medicinal chemistry services, including e.g. hit expansion, crystallography and early "absorption, distribution, metabolism, and excretion" (ADME) studies, to identify new tool compounds to enhance biological knowledge or even to further increase the chances of identifying lead compounds that can enter drug development phases. ELF provides researchers with a unique opportunity to screen their innovative targets against JECL, use the results to foster their research and science, and enter into novel collaborative drug discovery projects with EFPIA partner companies.

In order to achieve its goals, ELF is supported by a substantial financial investment of 200 million euros shared by participating partners and Innovative Medicines Initiative (IMI), clearly demonstrating that both public and private parties are strongly committed to the project. It differs from numerous previous academic initiatives in this field by emphasizing the aspect of value generation from its screening activities. The legal framework that underpins ELF promotes the generation of new IP, while encouraging knowledge sharing through dissemination of results and ensuring that the interests of all participating parties are respected. While publication of results is facilitated and welcomed, publications alone are not viewed as a key

measure of success. More tangible value is seen in the exploitation of results to realise their value, whether this be through downstream alliances formed to progress the screening results along the pharmaceutical value chain, license agreements around generated intellectual property or the generation of spin-outs based on assets that originated from external contributors and ELF.

2. Why are Pharmaceutical Companies Involved in ELF?

In response to the increasing challenges faced in drug discovery, large pharmaceutical companies have realized that internal resources are no longer sufficient to increase R&D productivity and, in response, have begun to intensively search for and integrate external innovation[9]. In the search for novel models and strategies, open innovation and crowdsourcing initiatives have attracted tremendous interest from pharmaceutical companies and public institutions in the last decade[10,11]. The transfer and exchange of knowledge between the private and public sector, and on a precompetitive level between pharmaceutical companies, seems to be the current remedy of choice. This zeal to source external innovation has many merits as a higher number of partnerships, genuine collaborations and extended networks will help to cover a much broader span of research across the available chemical and pharmacological universe. By no longer operating in isolation but synergizing activities instead, both academia and pharma will benefit by avoiding duplication of effort and being able to make quicker progress based on more, better quality data. Greater value generation should be a natural consequence for the companies and public institutions that engage in these collaborations, ultimately benefiting patients. Positive experiences from the recent past indicate that particularly in the early high risk phases of drug discovery different stakeholders can strongly profit by collaborating with each other[9,12–14].

At the end of 2012, seven pharmaceutical companies committed to participating in ELF. Both the opportunity to screen against the unique JECL with 300,000 compounds contributed by the pharmaceutical companies complemented by public library programs as well as the prospect of building partnerships with third parties providing targets that are screened at the ESC constitutes an attractive value proposition. With respect to the latter, ELF helps to translate early research into drug discovery programmes, i.e. enabling the identification of high quality hits that can be eventually developed into lead compounds and ultimately, drugs or diagnostic chemical tools. Bringing together excellence in synthetic organic chemistry, screening and logistics expertise, and drug discovery know-how, embedded in a clear legal framework ensures that ELF can achieve its objectives. In summary, the consortium platform represents an excellent avenue for companies to initiate, promote and foster collaborations on the next generation of exciting innovative drug discovery projects.

Another important element in facilitating companies to collaborate in such a commercially sensitive area is ensuring that IP is protected. As ELF allows different companies to access their competitors' compound libraries, clear data and management processes supported by robust IT tools are mandatory to properly protect the intellectual property of all parties participating in ELF. This is accomplished within ELF by means of an Honest Data Broker (HDB), ensuring that the compounds in the composite library remain hidden from individual partners, thus maximizing security. ELF allows a company's targets to be screened against chemotypes that only exist outside of an individual company's library, hence maximizing the opportunity to find potentially interesting compounds and increasing the chance of identifying successful hits[15]. The importance of the HDB system should not be underestimated in facilitating the involvement of normally competitive companies in this type of programme.

3. The European Screening Centre

3.1 Generation of Qualified Hit Lists

(1) ***Operations:*** The screening activities of ELF take place at eight screening centres, one each for the seven participating European Federation of Pharmaceutical Industries and Associations (EFPIA) companies and the last at the ESC (described in supplementary information 1, S1), where the crowdsourced public drug targets are screened. The drug targets screened at the ESC are sourced from researchers at European academic organisations and SMEs. A target programme is defined as a combination of a defined molecular target identified by its unique gene ID and a mode of compound action, i.e. agonist, antagonist, inhibitor, or enhancer. The submitted target proposals are selected based on a number of scientific and technical criteria (Tables 1 and 2) and evaluated by experts from the consortium and independent external reviewers in the Screening Selection Committee.

Table 1. Target Proposal Criteria

Criterion	Defined by
Scientific value	• Scientific quality • Innovation potential of target *or* new chemistry associated with target • Disease relevance • Diversity of portfolio
Different from EU Lead Factory targets	• UniProt ID • Entrez Gene ID *and* • Mode of compound action
Technical feasibility of the assay	The screening assay requirements in Table 2
Transfer to HTS in 3-4 months	The screening assay requirements in Table 2

Table 2. Screening Assay Requirements

Characteristic	Requirement
Assay format	Demonstrated in 384-well plate format, preferably scalable to 1536-well plate format
Homogenous assay	No wash steps
Characterised reference	Available from partner or commercially available
Readout technology	Compatible with mix-and-measure and homogenous formats, e.g.: • Absorbance • Luminescence • Fluorescence intensity • Fluorescence polarization • Fluorescence resonance energy transfer (FRET) • Time resolved fluorescence (TRF) • Homogeneous Time Resolved Fluorescence (HTREF) Or alternatives that give highly specific readouts (e.g. AlphaScreen technology, fluorescence lifetime, fragment complementation or FLIPR for calcium readout)
Signal / Background (S/B) in 384-well plate format, max assay end volume 30 µL, sample end concentration 10^{-5} mol/L	> 3; preferably higher $S/B = \frac{high\ control\ signal}{low\ control\ signal}$
Z′ (*Z* prime) in 384-well format, max assay end volume 30 µL, sample end concentration 10^{-5} mol/L	> 0.6 $Z' = 1 - \frac{3(s.d.\ high\ control + s.d.\ low\ control)}{(mean\ high\ control - meanlow\ control)}$
DMSO tolerance	Minimal tolerance 0.5% DMSO
Stability of each reagent	Stable for at least 8 hours For proteins: proven freeze–thaw cycle stability
Cell lines	Certified *Mycoplasma* free Stable cell lines
Minimal signal pattern on plates	CV <10% across plate filled with reference compounds
Protein	Recombinant protein at least 80% pure Commercially available or feasible to produce on milligram scale
Incubation times	Up to 4 hours
Readout stability	For at least 1 hour
Experimental data	All existing data relating to assay development will be shared. A minimum data package at least shows that the technical specifications are met.

Once a target programme is accepted, a programme team is formed by the target owner and experts from the ESC, who write a comprehensive plan defining the strategy to the retrieve the best ($\leqslant$50) hits i.e., the Qualified Hit List (QHL). All programmes follow the same workflow, described in Figure 1. Once a QHL is generated, the recipient is granted exclusive rights to the compounds on the list, which are from then on excluded from the screening collection. In order to not deplete the quality of the subsequent QHLs, a target programme can only be accepted and screened once. In addition, for most programmes, post-QHL work is done to further validate the initial hit structures and derive structure activity relationships (SARs) of hits or hit series. Wherever possible, this work is supported by structural data from protein crystallography.

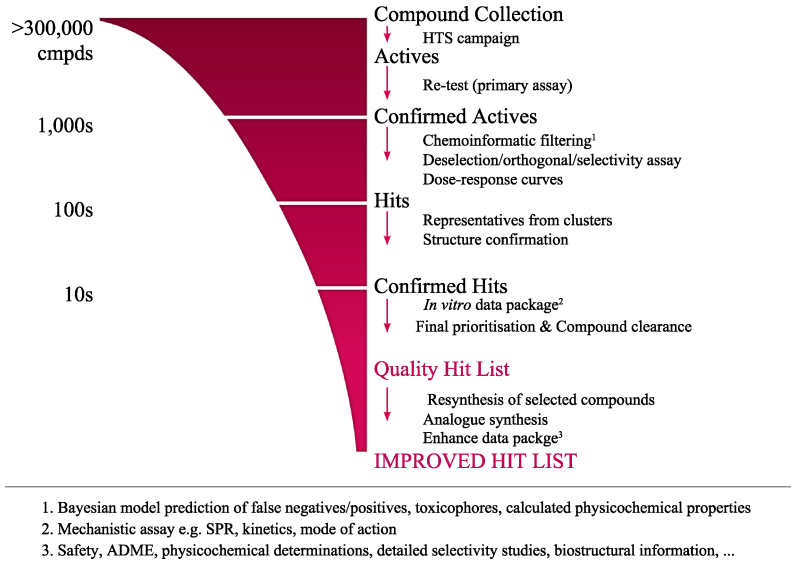

Figure 1. Typical assay cascade for a target programme to move from the original screening results to the generation of an Improved Hit List.

(2) ***Assets:*** The target programme can benefit from some of the most advanced compound management and screening capabilities of Europe, based on the legacy of the Merck, Sharpe & Dohme research sites. The JECL compounds are stored in single use tubes, minimizing freeze–thaw cycles, in a controlled atmosphere at low temperature, minimizing decomposition. In addition, the technology used allows cherry-picking of any combination of samples and plating them in a wide variety of formats, providing rapid access to precise libraries of follow-up samples. The ESC screening activities are state-of-the-art within a ultra-HTS (uHTS) laboratory running bioassays of all the most common read-out methodologies (e.g. luminescence, fluorescence, fluorescence polarization, FRET, FRETTR, alphascreen, luciferase, β-lactamase activity and complementation, and FLIPR assay technology) in either 384- or 1536-well plates. Complementary to this are the protein production and crystallography groups at the University of Oxford associated with Structural Genomics Consortium (SGC) with a world-leading record of producing high-resolution crystal protein–ligand structures.

(3) ***Screening cascade:*** The typical outline of the screening and triaging campaign is shown in Figure 2. After transfer of the assay and materials from the programme owner to the ESC, assay development can start, including miniaturization, optimization for the HTS platform, assay robustness tests and, if necessary, development of deselection/orthogonal assays. If the amount of protein needed for an HTS campaign cannot be produced by the programme owner, the team at the University of Oxford can be involved. uHTS is followed by confirmation of identified actives from the screen by retesting at single-point concentrations and later generation of dose-response curves using the primary assay conditions. False positives are eliminated by testing the primary hits in at least one deselection or orthogonal assay. Biophysical technologies such as Surface Plasmon Resonance (SPR) and Microscale Thermophoresis (MST) have proven particularly useful in the triaging process. Various computational triaging tools are regularly applied to further refine the hits. At this point in the programme, a so-called Preliminary Hit List (PHL) is nominated and for the first time, structural formulae can be viewed, but only by a very limited number of people. The fact that only a small group of nominated individuals are able to see any JECL structures is an essential feature of the HDB system employed by the project. In order not to compromise the value of JECL and other future QHLs, the number of compounds on the PHL is limited to a maximum of 0.1% of the screening set (currently up to 350 compounds). Finally, a maximum of 50 compounds are cherry-picked for the QHL based on the programme owner's background knowledge and wishes as defined in the programme plan, analytic results (LC–MS), prioritisation on activity, visual inspection and clustering.

To further add value to the target programme, the target owner and the programme team can opt to pursue post-QHL work within ELF, leading to a so-called

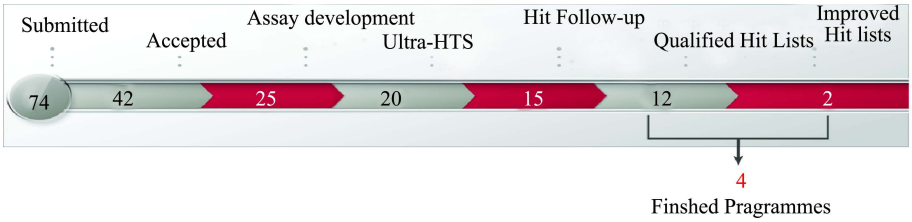

Figure 2. Progress of public programmes submitted to the European Screening Centre. Progress is represented by the number of completed programmes at the respective stages in April 2015.

Improved Hit List with QHL compound analogues. A bespoke medicinal chemistry programme in closer collaboration with the target programme owner is performed at the University of Dundee site in Newhouse. The first steps often involve resynthesis and further characterisation of selected QHL compounds, followed by hit expansion to generate SARs. Thanks to the facilities at the University of Oxford, crystallisation efforts can also be pursued for a limited number of programmes.

3.2 Progress

As of April 2015, a total of 42 public target proposals have been accepted by ELF from 74 submitted proposals. Most proposals are sourced via the networks of people working in ELF, which is reflected in the geographical origin of both submitted and accepted proposals (Figure 3). The majority of both submitted and accepted proposals originate from academic organisations (e.g. universities, medical centres and universities' research institutes) while SMEs are the owners of the remaining quarter (see pie chart in Figure 4(A)).

ELF aims to run programmes related to all human disease areas and all types of defined molecular targets. Compared to the analysis made in the US and UK[16,17], the addressed disease areas (Figure 4(B)) are rather similar, although oncology targets are overrepresented in the current ELF portfolio. However, the type of drug targets (Figure 4(C)) are different. For example, a higher proportion of programmes targeting protein–protein interactions, a target family identified relatively recently and generally considered as associated with higher risks.

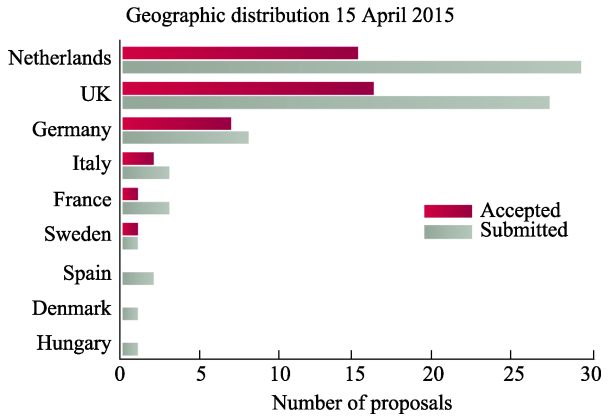

Figure 3. Geographic distribution of accepted and submitted target proposals.

To date, all programmes that have advanced to assay development have been successfully completed and all of them have been converted to run in 1536-well plate format and finished within 1–3 days. All available technologies are represented in the completed screens. At the time of writing, a total of 12 QHL

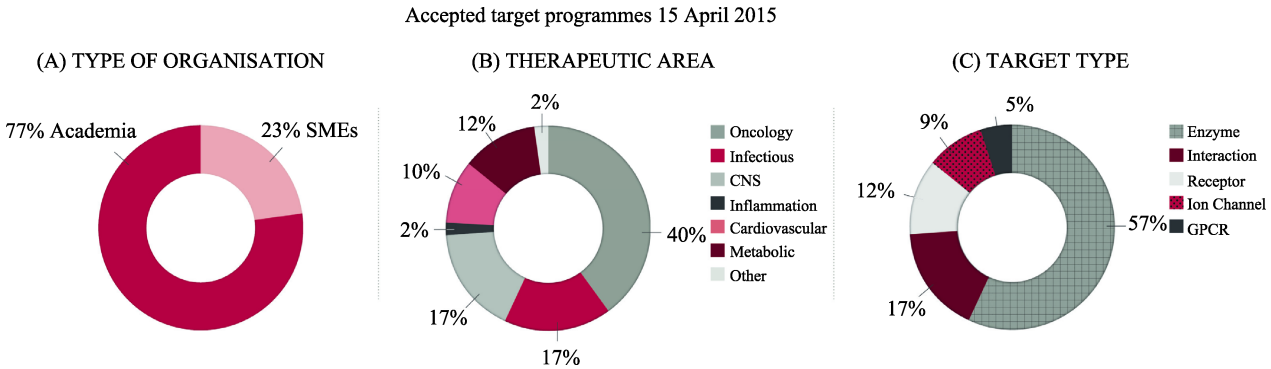

Figure 4. Character of drug target programmes accepted as of 15 April 2015. (A) Type of organisation submitting target proposals. (B) Main therapeutic area addressed by accepted programmes. (C) Nature of molecular drug target.

reports have been written. The associated QHLs include 3–50 compounds with a median of 46 compounds. The compounds represent not only a high fraction of different chemotypes reflected in the relatively many singletons (19 in average), but also clustered compounds from which a budding SAR can be deduced. The QHLs were selected by applying 3–7 different assays for most of which dose–response curves were generated as part of the triaging process. Such extensive and in many cases labour-intensive post-HTS characterisation of hits takes time, on average 165 days but ranging from 40–271 days depending on for example the complexity, maturity and number of assays implemented, as well as the availability of the screening materials needed. In several cases, bespoke assays have been developed in the course of the programme. Additionally, computational models, e.g. Bayesian models, have been used in all 12 programmes to identify not only false positives, but also false negatives. Post-QHL/IHL work is currently going on for seven programmes at different stages. The most advanced ones have provided their programme owners single-digit nanomolar or even picomolar ligands and several protein–ligand crystal structures have been resolved.

As screening of the compounds synthesised within ELF began in February 2015, all QHL compounds so far originate from the EFPIA companies. The distribution over the different sub-collections is very even. Interestingly, compound clusters are in several cases composed of compounds from more than one company, highlighting another advantages of pooling screening collections[15].

3.3 Challenges

It should be admitted that the consortium undertook the crowdsourcing task with a certain naivety. Project partners were convinced that the attractiveness of the incomparable facilities and services offered to the European research community with no upfront costs would result in a number of expected proposals far exceeding the actual submissions in the first two years. Feedback has shown that one of the biggest hurdles for an applicant is the key quality constraints on accepted target assays e.g., proven reproducibility in 384-well plate format. Needless to say, meeting this requirement is a great challenge for many routinely used research assays. Another challenge relates to the accession process. Although the proposal submission form is rather brief, the length and complexity of the legal framework can have a discouraging effect, particularly for academics who would rather focus their attention on their research. However, the correct legal framework is pivotal for any collaboration that wishes to bring new drugs to patients. On the one hand, the need to balance protecting IP, with allowing different partners access to data to ensure that new compounds can be progressed through development. On the other hand, it is recognised as a challenge in all forms of collaboration, equally for both public and private partners. How ELF attempts to find the delicate balance required in this area is further discussed in a later section.

For many programmes, the post-HTS screening cascade has also posed problems. The identification and development of relevant deselection and orthogonal assays were perhaps not stressed enough in the information given to the target owners in the first crowdsourcing calls. For some target classes, several approaches to identify relevant and validated hits can be applied and these have to be agreed upon, slowing down the process for individual targets.

4. The ELF Chemistry Consortium

A second, equally important asset of ELF is its compound collection—the JECL. At the outset of the project, around 320,000 high quality compounds were contributed by the pharmaceutical companies within the consortium[15]. However, a key project goal for the ELF Chemistry Consortium is to complement these compounds with up to an additional 200,000 compounds during the project timeline. JECL is therefore a unique resource not available anywhere else in the world. The ELF Chemistry Consortium offers a unique blend of European chemistry expertise from 6 SMEs and 10 academic centres (described in S1). Together, these 16 partners are tasked with the design, validation and production of the libraries building the Public Compound Collection (PCC), according to the workflow detailed below and summarized in Figure 5.

4.1 Ensuring the Quality and Novelty of Compounds in the Public Compound Collection

The additional 200,000 JECL compounds offer the opportunity to explore new chemical spaces that are not commercially available and typically not addressed in traditional screening collections from chemical vendors or corporate EFPIA collections. This new compound collection is based on proposals that are submitted by academic or industrial chemists—

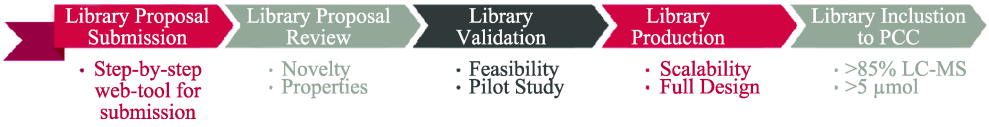

Figure 5. Compound Library workflow in the ELF Chemistry Consortium: key aspects of the various steps are highlighted.

from either within or without the consortium—using a step-by-step procedure via a web-based tool. Monetary incentives in the form of grants are awarded to external contributors, based on the maturity level of the submitted library proposals. More importantly, when submitting library proposals to ELF, the external contributors retain the right to publish their own research and findings. Submitted library proposals are assessed by an eight-strong Library Selection Committee (LSC) of respected chemists from EFPIA, SMEs and academia, all bound by confidentiality, to provide broad and complementary chemistry and drug discovery expertise. The data and information provided at a library proposal stage is used to assess the original design against 6 specific criteria: novelty, molecular properties, synthetic tractability, diversity potential, structural features and innovative library design. Importantly, each submitted library proposal should have a high element of novelty. This is routinely assessed by comparing the proposed library scaffold and enumerated matrix against the existing JECL collection and already submitted JECL libraries, commercial vendor sources (http://emolecules.com/) and additional chemistry-based compound repositories[18–21]. Furthermore, molecular properties and structural features should be preferably aligned to contemporary hit- and lead-like properties (e.g. calculated log *P* less than 4) to ensure a high ratio of soluble compounds at typical screening concentrations in primary target-based HTS assays[22]. Deviations from such properties are considered especially when a strong design concept (e.g. natural product inspiration, target class focus) is provided. Another often underappreciated aspect of library design is practical implementation. The LSC also evaluates the feasibility of submitted library proposals in terms of the subsequent reduction to practice. Here, aspects such as cost of goods, atom economy, length and efficiency of the synthetic route, associated purification and diversification steps are all accounted for based on the information provided by the submitter and the LSC members' experience.

The feasibility of selected proposals is then determined experimentally by academic and industrial consortium partners. During this stage, pilot projects are initiated to verify whether the intended libraries can be effectively produced within the ELF project timeline and budget. The focus of these library validation activities is to establish optimal conditions for critical synthetic and purification steps, and provide experimental proof that these can be carried out on the scale required for the production of the compound library. Another critical aspect of library validation in the ELF Chemistry Consortium is the definition of the reagent scope for each of the intended diversity points in a library. Here, by sampling a subset of available building blocks from the reactivity and physicochemical properties standpoints, valuable information about the accessible library diversity is generated. The new ELF libraries that have been successfully validated are then produced in their entirety by the industrial consortium partners. Modifications to the original design based on diversity and practical considerations, as from the library validation stage, are incorporated into the final library blueprint. The validated synthetic protocol is then executed to standard industrial specifications. Final compounds meeting JECL quality criteria for purity (LC–MS purity >85%) and quantity (>5 µmol) are added to JECL.

4.2 Managing the Process and Progress to Date

Given the size and heterogeneity of the ELF consortium, chemistry project management is critical to success. Real-time monitoring and decision-making is enabled by TarosGate, an informatics platform developed by the consortium coordinator Taros, which seamlessly connects the chemistry laboratories of the sixteen academic and SME partners. Rapid evaluation of progress and productivity with TarosGate has given the ELF chemistry consortium a flying start. Since the recruitment of scientists was completed and synthesis started in late 2013, an efficient pipeline leading to the addition of distinctive screening compounds to the JECL has been established. By the end of March 2015, 564 library proposals had been submitted and 385 of these had been accepted for synthetic validation, equating to a 69% success rate, of which 120 had been successfully validated experimentally. Forty nine of

the submitted library proposals were terminated based on technical failure during validation yielding a 29% attrition rate for that phase. The end result of this efficient process is that more than 55,000 screening compounds had been produced for addition to the JECL, as summarized in Table 3.

Table 3. ELF Chemistry Consortium progress as defined by the number of chemical libraries at different phases of the chemical library selection and validation process. The success rate at each phase is indicated as a percentage in brackets. All figures correct as of 31 March 2015.

Library Proposals	Accepted Library Proposals	Libraries Validated	Successfully Validated Libraries	Failed Libraries
564	385 (69%)	169	120 (71%)	49 (29%)

4.3 Challenges

During the past year and a half of work in the ELF Chemistry Consortium, the foundation for the successful implementation of an innovative compound library factory has been laid. In true collaborative spirit, the chemistry partners have been learning from each other's strengths and expertise and understanding the different chemistry perspectives of leading academic laboratories and pragmatic SMEs. This, together with the persistent focus on quality, has enabled the ELF Chemistry Consortium to improve its success rate at library selection stage from an initial low of 30% to 69% today. Not surprisingly, library validation still represents the most challenging aspect of compound library production for screening purposes. Here, the current 29% attrition rate is still very much in line with industry averages, highlighting once again how critical experimental investigations are and how elusive progress in chemistry research can be. Here, a key lesson is to establish a rigorous progress evaluation mechanism to minimize work in progress, and focus resources on key experiments and decision points. As a rule of thumb, if significant progress or problem resolution in an ELF library validation campaign is not achieved within 8 weeks, then scientists and managers should seriously consider project termination.

An additional challenge faced by the ELF Chemistry Consortium is the engagement of the wider chemistry community in the submission of creative library proposals. This may still reflect the historical reluctance to share chemistry, especially for drug discovery applications, due to the immediate relevance to intellectual property (IP) and value creation. We nevertheless trust that the transparent process established by the ELF consortium in handling IP, owner's rights and responsibilities plus the monetary incentives allocated for submitters can open up opportunities for chemists of any experience level and affiliation to more actively contribute to it, as a way to further enhance the reach and impact of their research.

These challenges notwithstanding, the scientists of ELF Chemistry Consortium have developed key approaches that can facilitate novel bioactive molecule discovery, including diversity-oriented synthesis, biology-oriented synthesis, multicomponent chemistry and activity-directed synthesis, as recently described for selected examples[23–34]. The innovative chemical approaches taken by the ELF Chemistry Consortium are yielding novel, diverse and distinctive compounds that will complement existing large compound collections used for high throughput screening drug discovery applications, thus serving as a blueprint for future compound collection enhancement campaigns.

5. The Challenges of Data Management, IP and Access Rights

The building of such an ambitious drug discovery platform based on novel drug target screens against such a large-scale compound library, composed of compounds from diverse protected sources, has led to some specific data management and legal challenges. While the ELF project is based on the collective effort of a range of pharmaceutical companies, it also aims to collect more biology targets and chemistry scaffolds from SMEs and academic groups either participating directly in the project, or contributing to it as external third parties. A key challenge has been to achieve the right legal approach among the partners in order to ensure the protection of their respective valuable assets while enabling the exploitation of the outputs from the screening activities. To build a consortium with 30 participants and, for now, around 30 external partners, all contributing with potentially patentable information and safely sharing chemical, biochemical and biological data is complex. The need for a data management platform that would enable the uploading of data and use of various triaging tools, yet prevent information leakage that could compromise future IP, was identified at an early stage. HDB has been developed by BIOVIA using the HEOS/ScienceCloud platform and has been up and running since May 2014. The functionalities it provides at this stage are outlined in Figure 6.

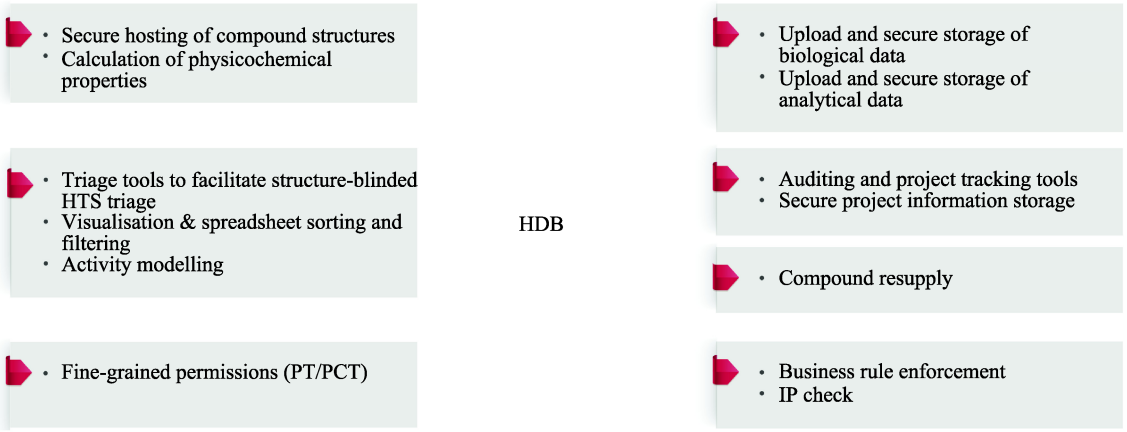

Figure 6. Functions enabled by the bespoke database: the Honest Data Broker.

A second challenge has been to design a sufficiently attractive scheme to encourage potential external compound and target owners to participate. In this context, the ELF partners rightly considered the need to address the IP framework during their negotiations as early as possible. This brought with it the added challenge of facilitating discussions between the scientific and legal/IP communities not only within each organisation but also between the partners. ELF partners acknowledged that a set of basic rules was required and the IMI Intellectual Property legal framework, based on open source collaboration, provides consortium-specific yet flexible working rules, allowing the partners to agree on the basic principles for the most appropriate agreement(s) considering the objective of the project and the legitimate interest of each participant.

It is also important to remember that participating in an IMI project does not affect the initial IP ownership regime. By submitting a chemistry compound or chemical scaffold, each owner is guaranteed the ability to retain the original ownership of its pre-existing know-how brought into the project (while this is referred to as background in the IMI IP policy, such pre-existing know-how may or may not be covered by IP measures). However, it is also known from the start that the partners will also get access to this "background", on a royalty-free basis for project completion, on fair and reasonable terms for any further research and development activities or use, and on conditions to be agreed for commercialisation and exploitation purposes. A mirror approach is also applicable to external contributors, meaning that the ELF consortium partners have agreed to treat direct and indirect partners equally from the outset.

In terms of the IP ownership of results arising from the project, a central question was how to manage the value to be generated during the project (referred to as "foreground" in the IMI IP policy). The objective was not only to protect the initial asset of the owner(s) but also to reward the scientific and intellectual contributions of other partners. As a basic principle, ownership of the foreground belongs in the first instance to the participant(s) who generated it. However, the participants may agree before work commences on a different allocation of ownership. ELF partners agreed on taking full advantage of the flexibility offered by the IMI IP policy and due to the constant close interaction between the drug target programme owners and the consortium partners, a complex joint ownership model was developed especially to accommodate those external contributors. Once again, with the view of attracting external ideas into the project, all target owners whether they are external third parties or members of the consortium abide by the same set of rules and are treated equally.

Another element of complexity arises from the fact that the IMI IP policy provides for any third party, contributing or not, with the opportunity to request access to the foreground generated by the ELF partners as long as they are related to a consortium partner. This is a challenge in a project in which the entities contributing chemical compounds need to protect the IP around these compounds so that their value is maintained. It was therefore very important that the definition of fair and reasonable conditions for access to data that could be used for further research and development uses was correctly formulated, respected all parties' interests and was acceptable to all parties. To that end, a reward scheme was agreed upon for

both internal and external library design contributors to which non-contributing third parties have limited access, the entire process being transparently described on the ELF website[35]. However, experience to date has shown that the complexity of this interesting reward scheme has made communication with the external scientific community difficult and is hindering the engagement of some external parties with the project. The existing communication campaign regarding the rights and obligations of both the drug target and library design contributors provides clear and transparent advice, but the process to formalise the various legal and official agreements to create the binding components is an ongoing challenge.

An attractive dissemination policy is also necessary to convince a wide range of stakeholders to participate. A key element of any research agreement entered into by an academic will be the right to publish the result, for example, in the form of scientific papers and to use the results in connection with teaching, academic research and grant applications. In the case of ELF, however, the partners can prevent premature publication which may infringe the IP rights and their exploitation potential. Ultimately, the goal of the ELF project is to find valuable lead structures that might have previously been inaccessible—structures that could result in the development of novel treatment options for patients. To that end, appropriate confidentiality and protection measures have been put in place in the context of allowing value generation from the results of screens and JECL compound generation. However, in order to facilitate dissemination, the ELF partners agreed to review proposals for publication and/or delay publication by a reasonable period of time during which IP can be sought or subject to licensing agreement for commercialization purposes. In addition, rejection of a publication request can only be made on a few well-defined grounds.

In an attempt to balance the sometimes conflicting demands of value generation and dissemination of research results, items such as IP management, access rights and publication of results have proven to be some of the most difficult challenges of ELF. The current legal agreements covering targets and chemistries constitute a balanced approach and have allowed the project partners to make rapid progress towards achieving the overall objectives of the project. However they are the result of compromises made by each of the partners to ensure that the project can function and achieve its ultimate objectives. The legal framework has also helped to build trust within the consortium across a very diverse set of partners. As such the current legal framework has already served as a template for other IMI projects (e.g. within the antimicrobial resistance programme or for the European Alzheimer platform) and could provide a fair and equitable approach for future collaborative drug discovery research.

6. Conclusion

Although shared platforms for pooling HTS resources and approaches have been tried before and successfully generated interesting lead molecules and chemical probes[36], ELF is a unique initiative in that it is attempting to deliver not just interesting compounds that may result in lead molecules for drug discovery, but real value propositions that can be exploited by public and private partners alike from the outset. The construction of this unique platform has faced many challenges, some of which have been discussed in this article. All of these are being addressed through a combination of hard work and scientific excellence, based on a strong foundation of trust and respect between all consortium partners, irrespective of their background. The management of such an initiative is no easy task, but the pace and amount of progress made in the past two years is a great achievement and reflects a strong, transparent management style. The development and instigation of the HDB, though often difficult, is central to the successful operation of ELF and serves as a model for future initiatives in the drug discovery area, particularly when protected assets are being leveraged on to generate value by different parties. Now with the HDB operational, QHLs and IHLs are being delivered to public and private partners alike. The quality of these lists is also of a high standard as testified by a recent analysis and experience of target owners[35,37].

An interesting aspect of ELF is that it provides a varied, yet centralized resource for early drug discovery, offering advantages at both an operational and innovation level to public and private participants alike. For instance, by leveraging on a diverse and complementary consortium, one ensures a constant flow of different perspectives, ideas and solutions. Pooling resources and talents across different organizations also yields better scalability to tackle problems and volumes that would be difficult to address by single enterprises. Furthermore, the “factory” remit on the successful design and execution of scientific re-

search generates cutting edge expertise and know-how in the various aspects of lead generation (e.g. library design and synthesis, assay development, HTS, hit-to-lead). Together these constitute important steps towards the establishment of ELF as a lead generation center of excellence. However, we still face challenges in establishing a sustainable future for this initiative and ensuring that the high quality results that are being generated are exploited to generate the maximum value as well as ensuring that the maximum benefit is felt by patients.

From the outset, ELF was a novel approach to try and provide better quality leads for future drug discovery programmes. In the first two years of its operation we have seen rapid progress in the establishment of its operations and are now beginning to see the production of high quality results. What was viewed by some as an interesting experiment in collaboration has already delivered on its potential and although many challenges remain and the road ahead may contain many bumps and unexpected turns, ELF is undoubtedly a success and should act as a model for future public–private partnerships in drug discovery.

Conflict of Interest and Funding

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Supplementary information S1

The EU Lead Factory is an entirely new kind of partnership, between public and private organisations, designed to promote innovation by ensuring in-depth collaboration, honest brokerage and enhanced communication.

With 30 international partners and 150 employees, the EU Lead Factory capitalises on the innovation of academia, the agility of SMEs and the experience and resources of EFPIA members.

The seven large pharmaceutical companies partici-

pating are: Bayer, Janssen Pharmaceutica NV, Astrazeneca, H. Lundbeck A/S, Merck KGaA, Sanofi Aventis Deutschland GmbH and UCB Pharma SA

The five partners of the European Screening Centre are Pivot Park Screening Centre (assay development and ultra-high-throughput screening (uHTS)), University of Oxford (protein production and structural biology), University of Dundee, Newhouse, (hit characterisation and medicinal chemistry) BioAscent (compound logistics) and TI Pharma (programme management)

ELF Chemistry Consortium offers a unique blend of European chemistry expertise from 6 SMEs (Taros, Edelris, Lead Discovery Center, Mercachem, Syncom and Sygnature) and 10 academic centers (Max Planck Institute Dortmund, VU University Amsterdam, Netherlands Cancer Institute, University of Duisburg-Essen, University of Groningen, University of Leiden, University of Leeds, University of Nijmegen, University of Nottingham and Technical University of Denmark).(https://www.europeanleadfactory.eu/).

ELF is a unique collaboration between public and private entities under the Innovative Medicines Initiative (IMI). Launched in 2008, the IMI has as its main objective the goal of significantly improving the efficiency and effectiveness of the drug development process with the long-term aim that the pharmaceutical sector produces more effective and safer innovative medicines. The IMI provides a platform where pharmaceutical industrial researchers, academic researchers and other stakeholders can best participate in unique research collaborations and where several traditionally competing companies join forces. In its original guise the IMI's budget of €2 billion for the period 2008–2013 made it the largest life sciences PPP in the world. Half of this budget came from the EU's Seventh Framework Programme (FP7). The rest came in the form of in-kind contributions from EFPIA and its member companies. The IMI now continues as IMI 2, set up under Horizon 2020 and with a total budget of €3.3 billion for the period of 2014–2020. (http://www.imi.europa.eu/)