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IMI European Lead Factory – democratizing access to high-throughput screening

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The European Lead Factory combines assets and experience from major pharma with innovation and agility of academia and SMEs in a collaborative platform to expand access to high-throughput screening. With many successes heading towards the clinic, the organization is broadening its approach to screening and partnering.

Small-molecule drug discovery begins with a therapeutic rationale but rapidly progresses to requiring chemical matter to validate the rationale and provide the chemical basis for a potential new medicine. Multiple strategies exist for generating this chemical matter, but a mainstay for more than 25 years has been diversity-based high-throughput screening (HTS)¹. Due to the considerable infrastructural requirements (including a large, high-quality compound library, compound logistics expertise, and automated assay development and execution) the ability to perform such screening and the expertise to interpret and develop the output has traditionally resided within large pharma companies. The [European Lead Factory](#) (ELF) is a consortium of industry and academic partners that was set up in 2013 to expand access to and increase the application of this critical technique for lead generation.

The ELF model

The original ELF consortium of seven pharma companies, eleven small/medium-sized enterprises (SMEs) and twelve universities created a screening infrastructure across two sites and built a compound screening deck of over 535,000 proprietary compounds. The ELF also created a bespoke informatics system, the 'Honest Data Broker', to protect the intellectual property of the contributed assets and thereby enable the development of resulting leads.

Under the ELF model, academics and SMEs can submit targets for screening via the [ELF website](#). If accepted, the programme is fully or majority funded, and comprises optimization of the proposed assay for robotic screening, screening versus the compound library, and development of further biochemical and biophysical assays specific for the programme to identify up to 50 promising compounds. The most attractive of these are re-synthesized, the biological activities confirmed, and a full package of data and physical samples delivered to the programme owner as potential leads. The ELF thus combines industry's expertise and experience with the innovative strength of the European academic life science community and the agility and creativity of SMEs. Crucially, the ELF widens access to HTS, making this key strategy available across the drug discovery community.

The Innovative Medicines Initiative (IMI) funded the ELF with €196.5 million for the initial 5 years. On the basis of the [success achieved](#), the IMI awarded further funding of €36.7 million to the end of 2023.

A successful large-scale experiment

Since its inception, the ELF compound deck has been screened over 200 times and the output triaged for valuable and patentable chemical matter. As well as over 100 [publications](#) resulting from the ELF, several high-profile successes across a range of indications have led to subsequent development and investment.

Collaboration with the ELF enabled Chris Schofield and Jurgen Brem at the University of Oxford, UK, to identify potent, broad-spectrum metallo- β -lactamase (MBL) inhibitors². MBLs inactivate β -lactam antibiotics and are an increasingly prevalent resistance mechanism in Gram-negative bacteria. Co-administration of the identified MBL inhibitors protected carbapenem β -lactam agents from MBL activity in Gram-negative pathogens². These leads are approaching clinical development and have formed the basis of a continued collaboration within the IMI ENABLE project, which aims to develop clinical candidates against Gram-negative pathogens.

In another successful outcome, by working with the ELF, Margit Mahlapuu at the University of Gothenburg, Sweden, developed novel enzyme inhibitors to address the metabolic complications in type 2 diabetes and non-alcoholic steatohepatitis (NASH). These assets formed the basis of the spin-out company Scandicure, which has entered into an agreement with Servier to advance the compounds through preclinical development.

In addition, a collaboration between the ELF and Richard Mead at the University of Sheffield, UK, identified inhibitors of Kelch-like ECH-associated protein 1 (KEAP1) for the potential treatment of neurodegenerative diseases including Parkinson disease and amyotrophic lateral sclerosis. The further development of these compounds has led to the

creation of a spin-out company, Keapstone Therapeutics, supported by more than €2.6 million from Parkinson's UK and the University of Sheffield.

The ELF's screening programme for the SME Metabomed identified potent and selective acetyl-CoA short-chain synthase 2 (ACSS2) inhibitors for the potential treatment of cancer. The company has secured more than US\$12 million to fund the further development of a clinical candidate. MTB-9655, one of the compounds based on this series, is entering the clinic to allow testing in patients³.

These examples highlight the substantial benefit offered by the ELF to academic and SME partners. Furthermore, as the ELF is a public-private partnership, the pharma partners have used their internal resources to screen the unique compound collection on targets of their choice and different from those screened for the wider scientific community. Industry partners have indicated that such screening campaigns in some cases enabled them to identify superior chemical matter for new programmes. Screening of the ELF compound deck by large pharma partners has also yielded successes on poorly druggable targets. For example, a lead optimization programme by Janssen on hits from the ELF resulted in a first clinical candidate for an undisclosed target in 2018. Furthermore, Merck KGaA is developing a hit originally derived from the ELF, [M4205](#), which is a selective inhibitor of disease-associated cKIT mutants in unresectable metastatic or recurrent gastrointestinal stromal tumours. A phase I trial is in [preparation](#) (see ELF Stakeholder Meeting Report 2019).

Although it is too early to measure the benefit to patients, producing investable and high-quality [leads](#) of the types described above, at scale, suggests that significant patient benefit is likely to result.

Expanding the scope

The ELF's second round of IMI funding began at the end of 2018, under the banner 'ESCulab' (European Screening Centre: unique library for attractive biology). Whereas the first phase of the ELF focused on defined biochemical targets — albeit from a wide range of target families (including enzymes, receptors, ion channels, protein-protein and protein-D(R)NA interactions), the second phase has broadened this scope to target-agnostic phenotypic screens and introduced high-content screening to further increase the range of therapeutic applications.

In the second round, the charity Medicines for Malaria Venture (MMV) joined the consortium to guarantee access to the screening capabilities for multiple programmes. As the ELF's first Product Development Partnership, it is hoped this collaboration will showcase the benefit of combining the considerable scientific expertise of researchers in the charity sector with the ELF's resources to expedite drug development for neglected diseases and other non-commercial indications. In particular, the ELF provides charities such as MMV access to a high-quality, novel, drug-like screening library that is not available 'off-the-shelf' from a commercial vendor.

The ELF has always carefully balanced its portfolio and addressed disease areas with high societal need. In addition to global health programmes on neglected tropical diseases, for which favourable terms such as a full waiver of downstream milestone payments apply, and antimicrobial resistance, the ELF has fast-tracked applications related to [SARS-CoV-2](#). Following direct contact with virology centres in Europe, the first programmes are now progressing as the ELF starts screening for small-molecule protease inhibitors and inhibitors of viral entry into host cells.

So, what is next? Despite the growth in importance of new modalities and advanced therapies, small molecules continue to play a key role⁴. HTS, as a standalone tool or in combination with in silico techniques and, for example, artificial intelligence approaches is well positioned to remain the workhorse in early drug discovery. Not every player involved requires all knowledge and facilities themselves. A number of state-of-art centres could serve as a 'molecular common' for industry and academia, as well as for other organisations such as charities, product development partnerships and philanthropic endeavours. The ELF's public-private nature, the model of risk-sharing and collaborative innovation approach will, in our view, continue to require a mix of funding streams to ensure a balanced portfolio. We believe the ELF consortium model has proven effective as a method for providing valuable output utilizing resources from a wide selection of contributors.

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Competing interests

The following authors are employed by companies as indicated in more detail by their affiliations: P.S.J., S.B., S.P.M., A.M., S.P.V.H., S.H., S.V.B., H.V.D.H., V.M.L., D.B., J.H., S.J., E.O., T.V., J.B., R.H.A.F., F.L., J.S.B.D.V., P.M.K.-V., V.J.M.N., K.M.O., T.R., C.P., O.E., G.P., P.B.S., J.-Y. O., D.R., S.M.K., P.W.M.R., H.V.V., E.J.A.V.W., C.V., P.N., K.B.S., L.T., D.F., M.J., N.A.B.-B., H.H., C.K., H.M., T.D., B.L., F.R.O., D.H., G.J., C.P., A.P., D.T., J.D., D.D., C.V., D.V.B. and A.D.P.