Topic: European Screening Centre: unique library for attractive biology (ESCulab)

All information regarding future IMI Call topics is indicative and subject to change. Final information about future IMI Calls will be communicated after approval by the IMI Governing Board.

Topic details

Action type	Research and Innovation Actions (RIA)
Submission & evaluation process	2 Stages

Specific challenges to be addressed

The translation of novel biological concepts into drug discovery projects critically requires chemical matter that has the potential to become a valuable tool in the treatment of a disease. The leveraging of basic biological research of SMEs, academia and their spin-offs into drug discovery and clinical applications still suffers from a scarcity of suitable chemical starting points that can be optimized into clinical candidate molecules allowing safe evaluation in patients. One of the key barriers is access to high-quality compound libraries and high throughput screening facilities.

Since Jan 2013, the European Lead Factory (ELF) project (www.europeanleadfactory.eu/) a public-private consortium, has offered a unique high quality compound library and state-of-the-art industrial ultra-High Throughput Screening (uHTS) capabilities to targets submitted by the public (public targets). By having their targets screened on the compound library at this top tier screening facility, public target owners[1], including biotechs/SMEs, obtain a Qualified Hit List (QHL) that can be used either as probe compounds to pre-clinically validate a disease hypothesis or as starting point for lead finding and optimisation. Participating pharmaceutical companies benefit from the mutual sharing of their respective libraries and early partnering opportunities with public target owners.

The ELF project is scheduled to finish at the end of 2017, but the necessity for public target owners to access high-quality compound libraries and high throughput screening facilities remains.

Need and opportunity for public-private collaborative research

Universities, research organisations and SMEs have a diverse range of potential drug targets but cannot easily access suitable compound libraries and screening facilities. Pharmaceutical companies need access to high quality targets in order to bring innovative therapies to patients. Combining the large high-quality compound libraries held by the pharmaceutical industry with the innovative targets held by academic organisations in a public-private partnership offers an ideal platform to transform biological discoveries into medicines.

Confirmed HTS hits and leads are the chemical starting points for significant further investment to produce clinical candidates, and, eventually, new medicines. As such, a neutral, trusted honest broker is needed to facilitate sharing of confidential assay and compound data. In addition, all parties bringing targets

[1] The term 'public target owners' used throughout this text refers to academic groups, biotechs, SMEs, charity organizations and patient foundations.

[background] to the project (target owners) must be confident that they retain their rights to that background and are also able, where possible, to further exploit the resulting developments of their contribution.

Facilitating such a platform through a neutral, SME-led compound management and uHTS screening facility will allow all partners to participate in confidence that their targets will be screened in an independent way with maximal protection of their intellectual property. ESCulab will also provide the opportunity for academics/SMEs to collaborate with EFPIA partners and see their projects moving ahead along the value-chain, whereas the pharmaceutical companies have a chance to tap into innovative academic biology. ESCulab will also significantly lower the hurdles for charity organizations or patient foundations that want to initiate drug discovery in their specific field of interest.

Scope

1. **Screening library**
   The core of the ESCulab library will ideally consist of 350 000 compounds from the pharmaceutical companies, and 200 000 compounds provided by the short proposal applicant consortium. Additional compounds may be added if further pharmaceutical companies join. The 200 000 compounds contributed by the applicant consortium must be novel, drug-like, not commercially available, and show a high fraction of sp3 hybridized carbon atoms (sp^3 count > 0.48, MW ~430, clogP ~2.3) without structural overlap with four reference libraries: The Maybridge Screening Collection, Molecular Libraries and Small Molecule Repository (MLSMR), ChEMBL and eMolecules.
2. **Compound Logistics and uHTS screening facilities**
   Appropriate industry-like infrastructure, including laboratory automation/ robotics to support both compound logistics and HTS will be provided, as well as: firewalled IT solutions to support the compound management of the compound library; HTS data management from quality control to chemo-informatic analysis of HTS results; the evaluation and confirmation of hits through medicinal chemistry follow-up activities.
3. **Assay Development**
   In order to access a broad range of innovative biology, ESCulab will support the conversion of public target assays into automation friendly format, both in target-focused and phenotypic approaches.
4. **Screening**
   ESCulab is expected to run 50 public programmes. The project is also expected to develop a strategy to enable the screening of externally funded screens on top of the IMI-funded activities. Each industry partner will schedule 20 programmes or 10 programmes, the associated partner 5 programmes (135 EFPIA screens in total, also phenotypic). The inclusion of phenotypic screening will allow tapping into the ongoing efforts at academia to develop cellular models of increasingly more translational value using, for instance, patient derived material or human iPS cell-derived phenotypes.
5. **Hit Confirmation**

   The outcome of the screening campaign should be a Qualified Hit List (QHLs) with max. 50 compounds.
6. **Long-term sustainability**
   In addition to the IMI-funded screens, ESCulab should offer screening on targets proposed by charity organisations, patient foundations and other organisations against external funding. Thus, it should establish itself as the centre for translating basic biology into chemical matter. Mechanisms and terms and conditions to secure maintenance and continued access to the compound library after termination of ESCulab will be negotiated with the partners providing compounds.

Expected key deliverables

1. **Screening Centre**

   The screening centre will host the compound library and manage the logistic processes around the library to support compound logistic processes for up to 37 HTS projects per year (10 from public projects, 27 from EFPIA projects). The screening centre will also support assay development and perform HTS

campaigns & follow-up tests for academic groups, Biotechs, SMEs, charity organizations and patient foundations.

2. **Hit Confirmation**

   Responsible for providing a list of confirmed hits constituting the QHL which affords medicinal chemistry expertise.

3. **Sustainability plan**

   A business model based on fee-for-service and milestone-based income to ensure self-sustainability at the end of the ESCulab period; the funding of screens by charity organizations or patient foundations already during the ESCulab term serves to explore the business model.
   Establishing the maintenance of the compound library beyond the lifetime of the ESCulab project.

Expected impact

The project is intended to lower the hurdles for academic groups and SMEs to translate early innovative biology into chemical series that have the potential to be optimised into drug candidates. The delivery of up to 50 public and 135 EFPIA QHLs should create value from the libraries and cut timelines to arrive at clinical proof of concept in diseases with unmet medical need, such as cancer, immunological, respiratory, neurological and neurodegenerative diseases[2] anti-infectives and neglected (tropical) diseases.

By including phenotypic screening that mimics cellular events relevant in disease, hit series that show clear structure-activity relationships might trigger target deconvolution activities that ultimately might lead to the discovery of novel pathways/ drug targets.

Including SMEs in the applicant consortium should contribute to strengthening the competitiveness and industrial leadership of Europe.

To maximise impact, at the end of the IMI funding term, there must be a self-sustainable, well recognized screening centre with access to a high-quality library which adopts a business model relying on externally funded screens.

Ideally, for scientists that seriously believe that their discoveries can help patients, ESCulab should be the operational partner of choice in bringing modulation of their targets with small molecules from theory into practice.

Potential synergies with existing Consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of efforts and funding.

Applicants should consider any relevant projects from IMI, FP7, H2020 and other relevant initiatives outside the EU. With respect to IMI projects:

European Lead Factory (www.europeanleadfactory.eu/)

- The ESCulab consortium should liaise with the ELF so that the libraries and target programmes not fully exploited within ELF could be carried through to ESCulab. Also, they should explore whether the ELF database could be used as a resource to support ESCulab hit selection activities.

Projects potentially allowing access to novel screening assays

[2] Council Regulation (EU) No 557/2014, art. 2 (ii) and (iii)). http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32014R0557

- BTCure (www.btcure.eu/), UltraDD (www.ultra-dd.org/), Autism Spectrum Disease for potential targets;
- ND4BB (New Drugs for Bad Bugs, (www.nd4bb.eu/) to discover and develop new, effective antibacterial strategies for the treatment of infections caused by antibiotic-resistant pathogens;
- NEWMEDS (www.newmeds-europe.com/) to identify biomarkers to allow more targeted treatments for schizophrenia and depression;
- EUROPAIN (www.imieuropain.org/), to better understand chronic pain mechanisms to aid the development of novel analgesics;
- IMIDIA (www.imidia.org/) to generate novel tools and fundamental knowledge on β-cell organization to accelerate the path to improved diabetes management;
- PREDECT (www.predect.eu/) to develop new models for novel treatment for cancers of the breast, prostate, and lung;
- PHAGO (www.phago.eu/) to discover novel drug targets along TREM2/CD33 pathway in Alzheimer's Disease.

Indicative duration of the project

The indicative duration of the project is 60 months.

Applicant Consortium

The applicant consortium will be selected on the basis of the submitted short proposals.

The applicant consortium is expected to address all the research objectives and make key contributions to the defined deliverables in synergy with the industry consortium which will join the selected applicant consortium in preparation of the full proposal for stage 2. This may require mobilising, as appropriate, the following expertise:

- Strong European-wide network for public target recruitment with outreach to ongoing and future IMI projects and other European and national initiatives.
- Professional, industry-like management of compound logistics process centred around a single entity for the collection, storage, distribution and management of the ESCulab compound library
- The consortium must include a specialized party ("honest data broker") who can manage and broker (blinded and un-blinded) confidential information on compounds and screening results data according to the Honest Data Broker concept, i.e. one single, centralized unit with dedicated staff bound by confidentiality and non-use obligations.
- Strong experience in assay development, miniaturization, validation for HTS both employing platform techniques and introducing novel experimental approaches. Capabilities to develop HTS/HCS ready target-focused and phenotypic cellular assays.
- Extensive experience in the execution of HTS to industry standards, providing solutions also for complex experimental protocols, e.g. with multiple liquid handling and signal detection steps, kinetic readouts, etc. Necessary expertise in molecular and cellular pharmacology and medicinal chemistry to drive a rigorous hit characterization process.
- Industrial-like experience and proven track record for successful hit confirmation including expertise in medicinal chemistry and, pharmacology.
- Extensive experience in applying IT solutions to the management of compound collections, HTS data management from quality control to chemo-informatic analysis of HTS results.
- Project management capabilities supporting overall governance and steering.

It may also require mobilising, as appropriate, the following resources:

- A library of approximately 200 000 screening compounds. Applicants should demonstrate that their compounds are suitable for HTS, i.e. novel, drug-like, not commercially available, with high sp^3 count (sp^3 count > 0.48, MW ~430, clogP ~2.3), clearly differentiated from vendor libraries.[**Error! Bookmark not defined.**]
- A centralised unit for carrying out the HTS screening operations on the targets originating from public target owners. Preferably, the HTS screening operations are performed in a country with a research exemption limiting IP complexity.

- Software to support the blinding and un-blinding of information
- A firewalled IT infrastructure to handle data related to the compound library.

In their short proposal, applicants should also provide an initial plan for the sustainability of the platform beyond the IMI funding term.

Suggested architecture of the full proposal

The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry participation including their contributions and expertise.

The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 rules and with a view to the achievement of the project objectives.

In the spirit of the partnership, and to reflect how IMI2 Call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, it is envisaged that IMI2 proposals and projects may allocate a leading role within the consortium to an EFPIA beneficiary/large industrial beneficiary. Within an applicant consortium discussing the full proposal to be submitted at stage 2, it is expected that one of the EFPIA beneficiaries/large industrial beneficiaries may elect to become the coordinator or the project leader. Therefore to facilitate the formation of the final consortium, all beneficiaries are encouraged to discuss the weighting of responsibilities and priorities therein. Until the roles are formally appointed through a consortium agreement the proposed project leader shall facilitate an efficient negotiation of project content and required agreements.

The architecture outlined below for the full proposal is a suggestion. Different innovative project designs are welcome, if properly justified.

A plan for aspects related to sustainability, facilitating continuation beyond the duration of the project should also be proposed.

Note on ownership

It is expected that a number of background assets (screening assays or targets) will be screened during this project. To facilitate the development of the results of the screens against these targets into clinical candidate molecules, and eventually into new medicines, the project participants need to be fully comfortable with the principle that ownership of certain deliverables such as the screening results (QHLs) , which would be direct improvements or would be directly related to a specific beneficiaries background, may have to be transferred after their generation, to the party who initially owned the screening assay/target background, according to terms to be negotiated in the Consortium Agreement.

Industry contribution

All EFPIA participants contribute screening compounds as indicated above and will run screens of the compound library in the course of the ESCulab project. Assay development and screening efforts are EFPIA participants' in-kind contributions. With these in-kind contributions, EFPIA participants enhance the database for developing public QHLs and increase the value of hits from the public compound collection. For the sustainability of the platform beyond the ESCulab lifetime, the EFPIA partners will negotiate terms to maintain the compound library after the project ends.

Work package 1 – Programme Recruitment

With a strong emphasis on innovative biology, recruitment of targets and biology amenable to phenotypic screens need to be gathered across Europe intensively with the entrance barriers considerably lowered for ESCulab.

Over a 4 year period of target sourcing, the goal should be to recruit more than 100 proposals.

Programmes from other IMI projects will be proactively sought and will include:

- Proposals that still require assay development activities;
- Phenotypic, target-agnostic programmes;
- Targets from foundations and charities world-wide to reserve screening slots in exchange for a monetary contribution.

Targets can be screened several times, but Qualified Hits will be removed from the compound library.

Expected Applicant consortium contribution

Professional target/programme recruitment acquiring 100+ public proposals from academics/ SMEs over 4 years for selection. Therefore, a strong European-wide network for public target recruitment with focused outreach to ongoing and future IMI projects is essential.

Work package 2 – Review and Selection

The review and selection of target proposals offers an opportunity to connect target owners to pharma partners early on. Therefore, the review body must be staffed with external experts and EFPIA delegates. Targets proposed by charities and foundations who fund the screen are exempt from the review process.

Work package 3 – Compound Logistics

Hosting the physical compound collection, plating and distributing screening decks and samples for retests is the remit of this work package. Costs incurred should be in alignment with benchmarking references.

Once fully operational, the centre will need to accommodate resources sufficient to support compound logistic processes for up to 37 HTS projects per year (10 from public projects, 27 from EFPIA projects) providing plated copies of the compound library for public and pharma screening programmes.

- The pharma companies will receive a copy of the library and perform the screening at their disposal in a blinded fashion.

Expected Applicant consortium contribution:

- Professional, industry-like management of the compound logistics process centred around a single entity for the collection, storage, distribution and management of the ESCulab compound library.

Work package 4 – Assay development

Allowing for target proposals which are not yet assay-ready and phenotypic programmes requires an effort in assay development and screening. The adaption of academic test systems to suitable HTS formats needs professional expertise and needs to be properly staffed. For pharma screens the assay development will be done at the pharma partners' facilities, as follows:

- Development and/or adaptation of target or pathway-specific bioassays for HTS;
- Development and/or adaptation of phenotypic assays.

Expected Applicant consortium contribution:

A proven track-record in assay development. A track-record in automated image capturing and multi-parametric automated image analysis will be crucial to master phenotypic assay development. The Applicant is expected to progress the 5 projects of the associated EFPIA partner from assay development through QHL.

Work package 5a – Target-based Ultra High Throughput Screening

Industry contribution

EFPIA screens will be run at pharma screening sites or their selected subcontractors.

Expected Applicant consortium contribution

Industry-like uHTS infrastructure and expertise (e.g. proven experience in 1536 MTP format HTS)

Work package 5b – (Target-agnostic) Cellular screening

Industry contribution

EFPIA phenotypic screens will be run at pharma screening sites or their selected subcontractors.

Expected Applicant consortium contribution:

Industry-like equipment and know-how (endpoints, counter-screens) to run phenotypic assays in a high throughput format (1536 MTP format, at least 384 low volume MTP format).

Work package 6 – Hit characterization and confirmation

- Re-synthesis of hits and confirmation of activities to assemble a qualified hit list (QHL).
- Support the assembly of a Programme Dossier for an Option Notice for public target owners.

Expected Applicant consortium contribution:

Industrial-like experience and proven track record for successful hit confirmation including respective expertise in medicinal chemistry and pharmacology.

Work package 7 - Information technology

The Honest Data Broker will be the data repository to handle IP sensitive information in a secure manner, and an annotated data source for Hit-to-Lead activities and library analyses.

Work package 8 - Project Management

Overarching project management independent from the day to day consortium activities should steer the administrative aspects referring e.g. to budget and legal aspects including continuous legal support.

References

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