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Tim Dudgeon

European Lead Factory Web Portal

Successful operation 3 years on

About ELF

Part of the Innovative Medicines Initiative

European Lead Factory

www.europeanleadfactory.eu

IMI supports collaborative research projects and builds networks of industrial and academic experts in order to boost pharmaceutical innovation in Europe.

imi innovative medicines initiative

efpia European Federation of Pharmaceutical Industries and Associations

www.imi.europa.eu

EFPIA members
AZ
Bayer
Lundbeck
Janssen
Merck KGaA
Sanofi
UCB

SME members
ARTTIC S.A.S.
BioAscent
ChemAxon
Edelris
Lead Discovery Center
Lygature
Merachem
Pivot Park Screening Centre
Sygnature Discovery
Syncom
Taros Chemicals

Academic members
University of Dundee
DTU Denmark
University of Groningen
Leiden University
Leiden University Medical Centre
MPI Dortmund
Radboud University, Nijmegen
Pivot Park Screening Center
Technical University of Denmark
University of Duisburg-Essen
University of Leeds
University of Nottingham
University of Oxford
VU University Amsterdam

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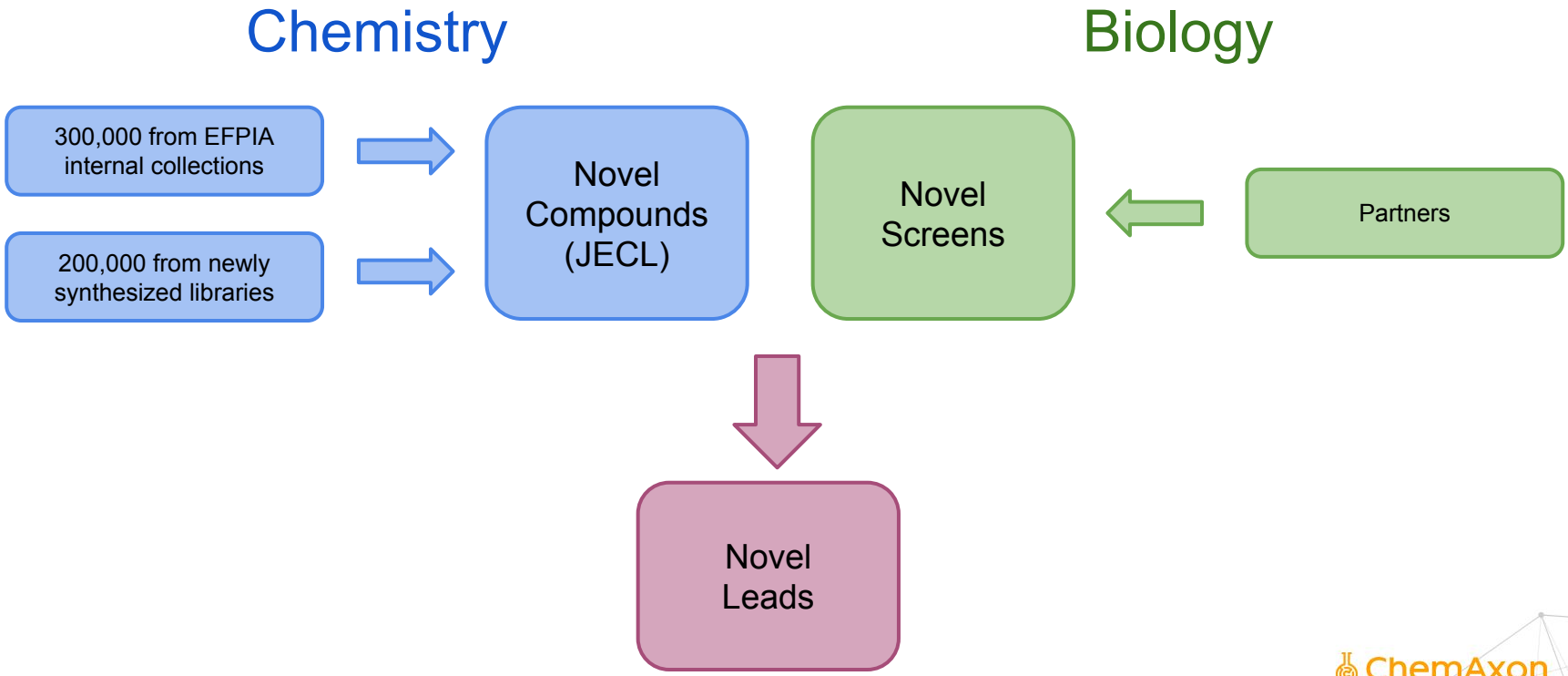
ELF philosophy



13 Work packages

1. Programme Recruitment HTS
2. Compound Logistics
3. Assay Development
4. High Throughput Screening
5. Hit Characterisation
6. Medicinal Chemistry
7. Publication Policy / External Relations
8. Information Technology
9. Sourcing chemical library proposals
10. Review/selection of chemical library proposals
11. Experimental Validation
12. Library Production
13. Project Management

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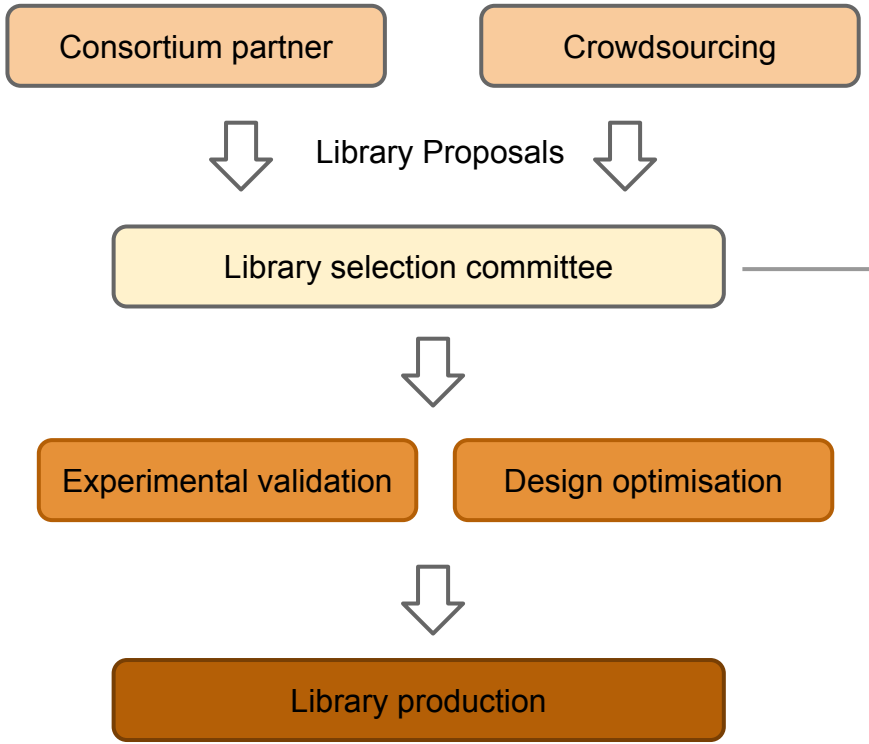
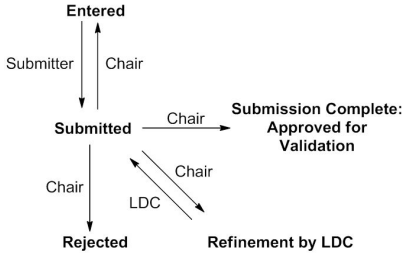
Library generation workflow

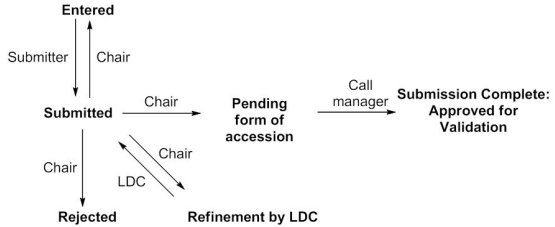


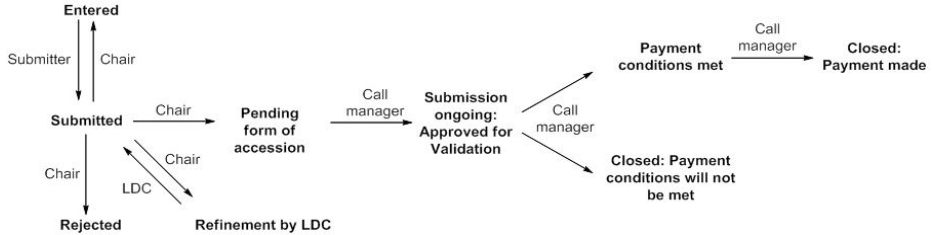
Assessed on:

1. Molecular properties
2. Structural features
3. Novelty
4. Diversity potential
5. Synthetic tractability
6. Innovative design

Workflows and Roles







Three workflows for different types of user:

1. Consortium member
2. Non-EU/EAA citizen
3. EU/EAA citizen

Different levels of access

1. Submitter
2. LSC member
3. LSC Chair
4. ….

UI dynamically generated to ensure that you only see what you're supposed to see and only do what you're supposed to do

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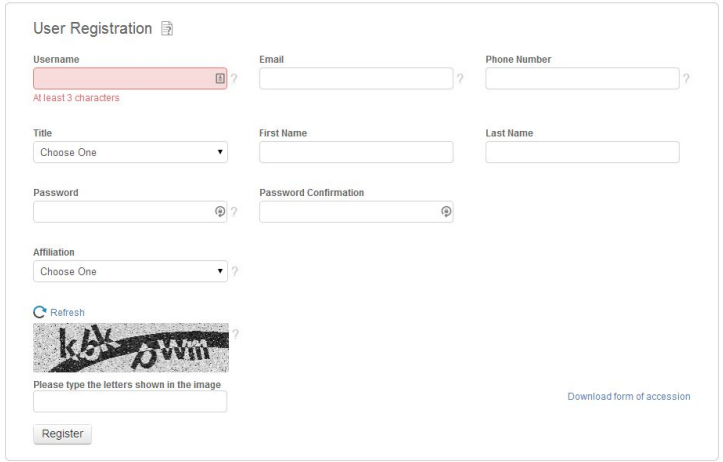
ELF Workflow

Step 1: registration



Users register themselves and provide personal and affiliation details

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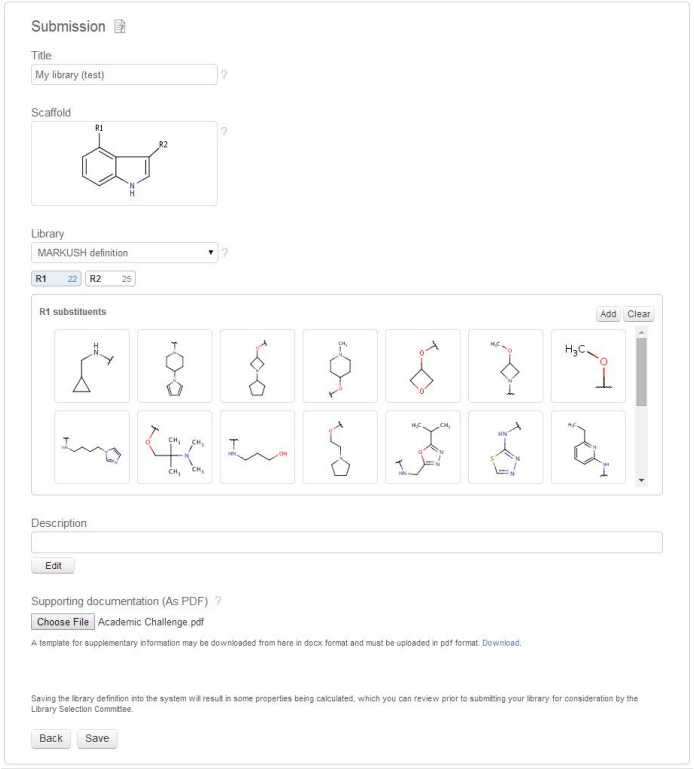
Step 2: enter library



Give it a title

Sketch scaffold with **Marvin JS**

Define your library in one of three ways:

1. Upload SDF
2. Upload MRV with Markush library
3. Pick R-groups from within pre-defined lists and **Markush Enumeration** is used to generate the library

Provide accompanying info including rationale and synthesis validation info

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Step 3: initial property calculations

SSS for scaffold against reference set of 12M structures using **JChem Search**

Exact match search for enumerated structures against reference set of 12M structures

Matching enumerated structures against sets of SMARTS filters provided by EFPIA members using **Chemical Terms** match() and matchCount() functions

Checking enumerated structures against UK MDA legislation database from **Compliance Checker**

Property distributions of enumerated structures. Properties generated with **Chemical Terms** expressions with **Calculator Plugins**

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Step 4: submit proposal

Further round of property calculations performed and library now visible to Library Selection Committee for consideration

At this stage user has handed over ownership of the library idea to the European Lead Factory

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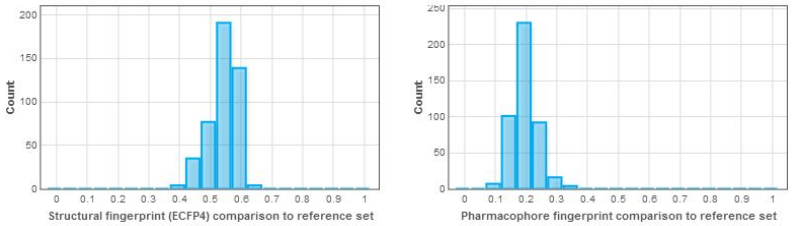
Step 5: final property calculations

ECFP4 fingerprint comparison with 12M structures from reference set

Fuzzy Pharmacophore fingerprint comparison with 12M structures from reference set



Generate histogram of most similar structure in reference set for each compound in the library.

~1000 x 12M x 2 comparisons.

Also, submit structures for comparison against current JECL

“Old” molecular descriptor tables:

- For each search read descriptors from database -> very IO bound.
- Single threaded.
- **-> days for completion**

“Mad fast” similarity search:

- Descriptors generated as binary file.
- Read into memory once
- Search fully multi-threaded.
- **-> minutes for completion**

- **(1M x 1M completes in ~25 min)**

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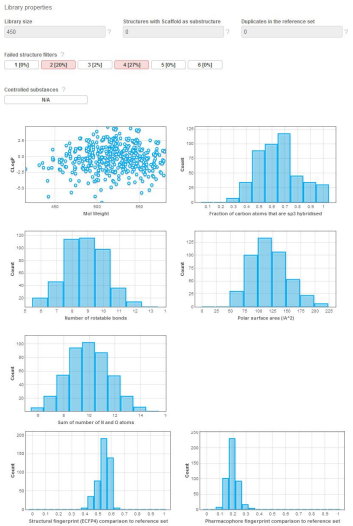
Step 6: assessment



Library Selection Committee

Library Scoring

Molecular properties	Structural features	Novelty
3	2	3
Diversity potential	**Synthetic tractability**	**Innovation**
3	1	2

Comment

Beautiful scaffold which can readily be prepared in a few steps from commercially available starting materials. The molecular properties are strong, low cLogP and the introduction of the stereocenters is controlled during the synthesis.
The chemistry is still paper chemistry and has to be investigated during the validation.

Approve

Reject

Refine

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Once a library design is approved ....

The chemistry is validated

The library is synthesised

Compounds added to JECL

Compounds used for screening

Outcome

The Success Story

*"The web portal has been i**nstrumental to the success** of the overall project. The portal **supports the entire process**, it has supported chemists in the design of libraries that meet the ELF criteria; and in addition **enabled the library selection committee to assess around 1000 library proposals** efficiently and fairly, it has ensured transparent feedback after assessment. The public compound collection is highly distinctive from other small molecule screening collections. **The web portal, developed by ChemAxon, played a key role in this achievement**."*

Prof. Adam Nelson
Chair Library Selection Committee

http://www.aboutpharma.com/blog/2017/03/08/chemaxon-contributing-to-european-lead-factorys-success/

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Details

- 92 users registered, 75 submitted proposals
- 851 Libraries proposals submitted
  - 61% approved
  - 37% rejected
- 192 libraries synthesised and 77 ongoing
- 145k Compounds added to JECL, 200k expected
- Portal expected to be closed once targets met

More details

- Public compounds (PCC) slightly larger but with slightly lower ALogP than EFPIA-contributed ones
- PCC more 3D (fsp3, PMI)
- PCC explores complementary chemical space to EFPIA sets
- PCC and EFPIA compounds similarly likely to be chosen from hit lists
- Biological activity profile of PCC highly distinctive from EFPIA company compounds

Lessons learnt

- Automation has big payback
  - Enabled efficient and transparent assessment of proposed libraries by the LSC
- Good usability needs effort
- Should have invested more in management and error handling functions
- Crowdsourcing of libraries was relatively unsuccessful

THANK YOU

- Gustavo Santucho
- Mario Burdman
- Gabriel Moreno
- María Paz Bisso
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- Zsolt Mohacsi
- Medzi
- Istvan Bagyi
- Agnes Nemth
- Adam Nelson
- Youri Mesmoudi
- Ola Engkvist
- Andrew Pannifer
- Andrei Caracoti

Try it out (while stocks last):
https://elf.chemaxon.com/elf

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