



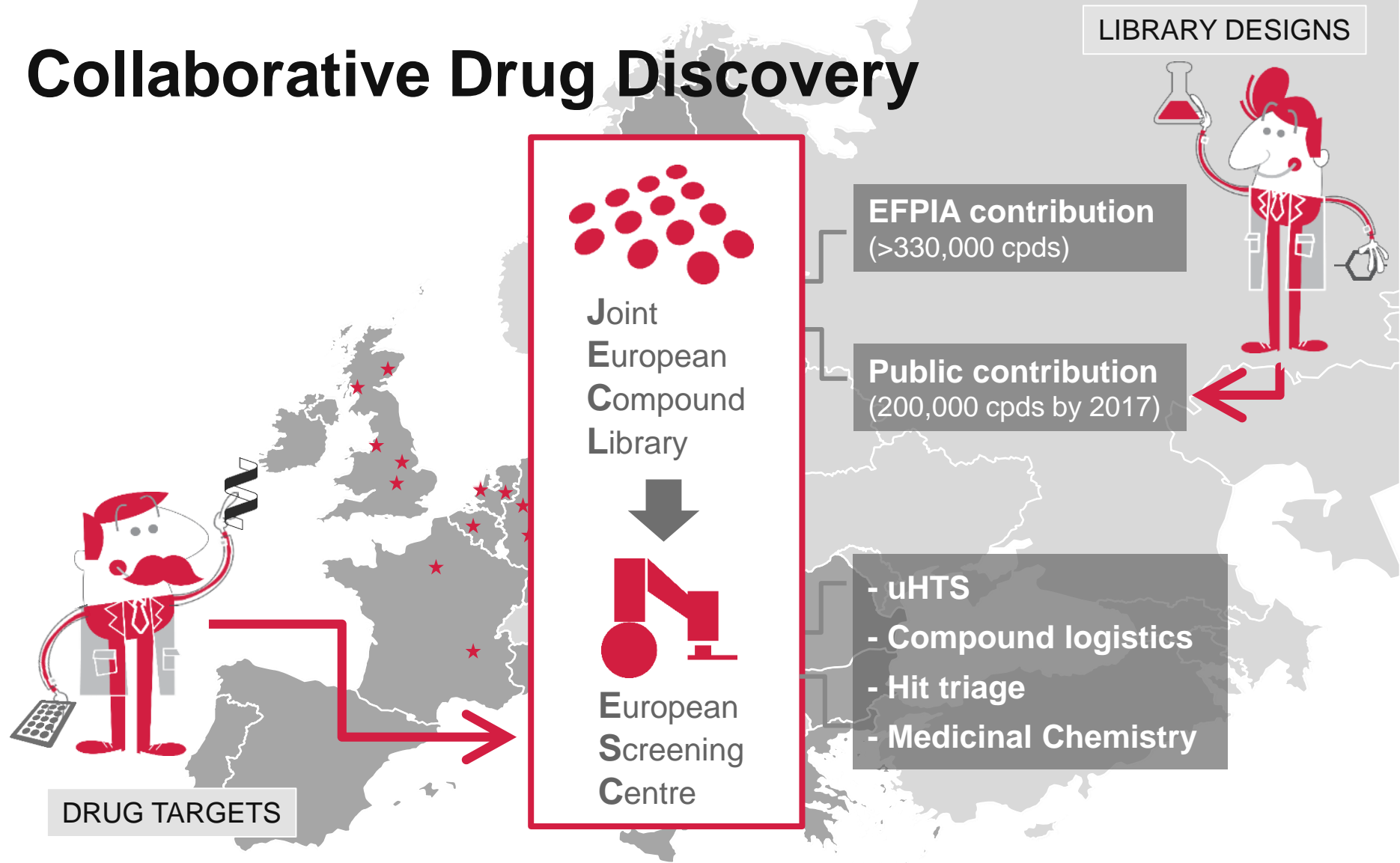
European Lead Factory— making a pan-European compound collection & screening centre a reality

Dimitrios Tzalis (Taros), Head of Chemistry

6th FIP Pharmaceutical Sciences World Congress 2017, Stockholm, Sweden

23 May 2017

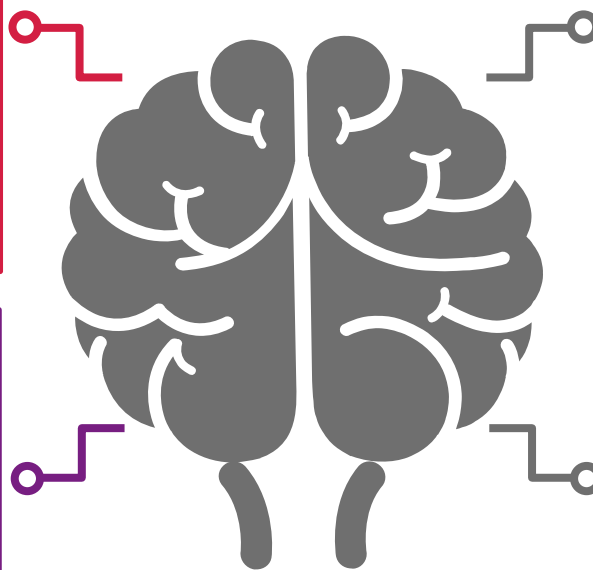
Collaborative Drug Discovery



Made possible by...

European Screening Centre

EFPIA partners



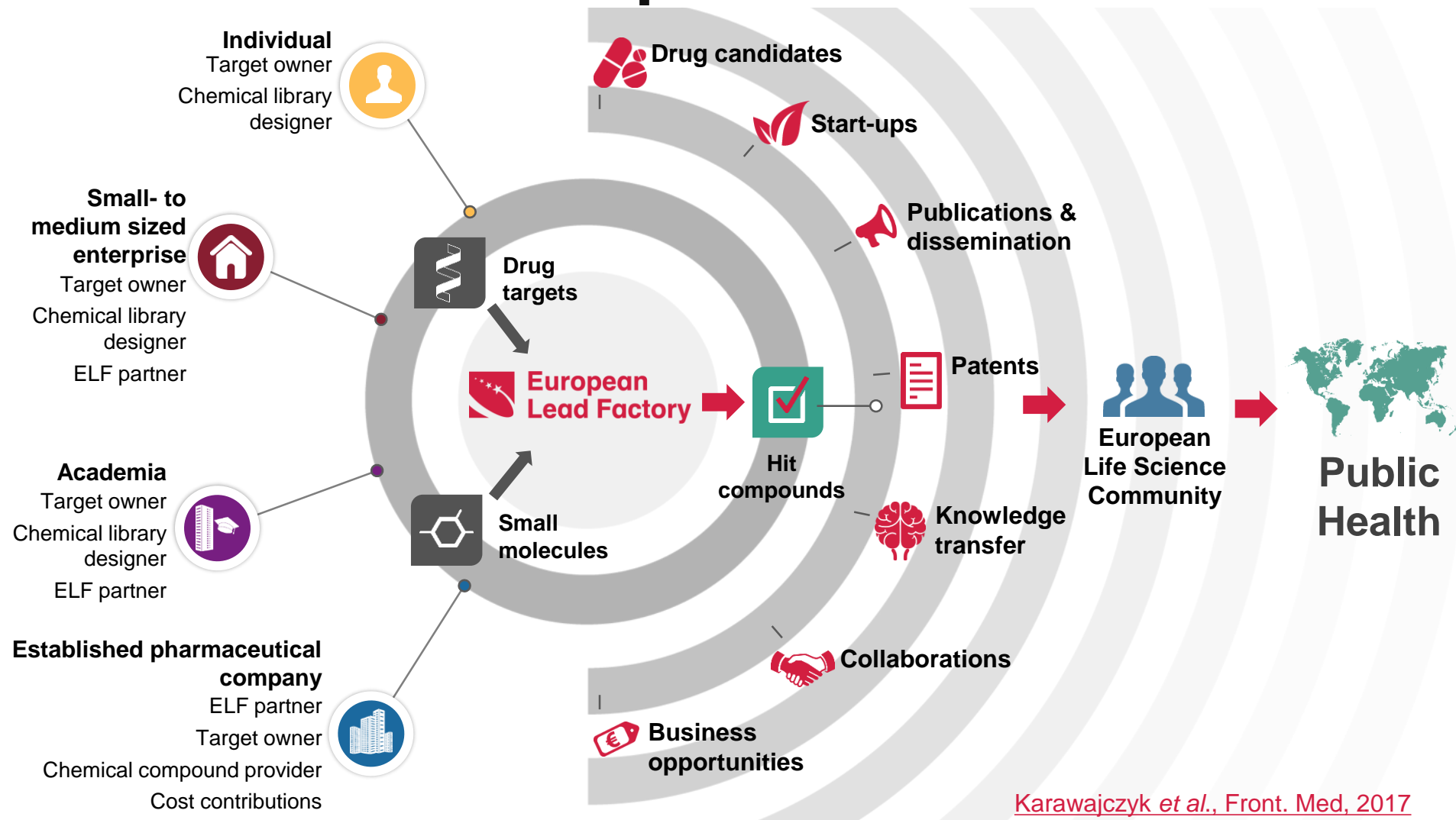
funded by



Public Compound Consortium

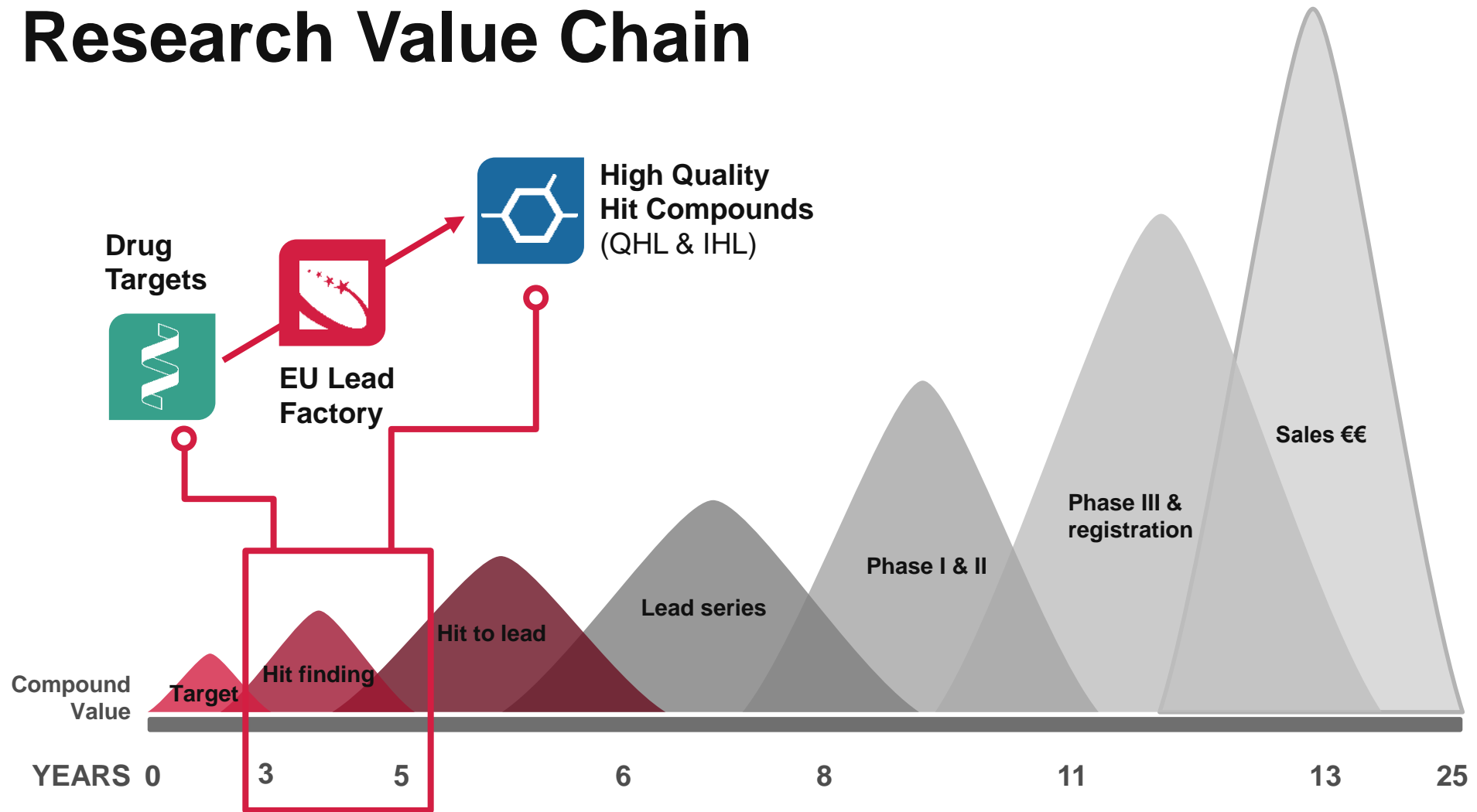
Chemistry CROs

Interactions & Impact



Karawajczyk et al., Front. Med, 2017

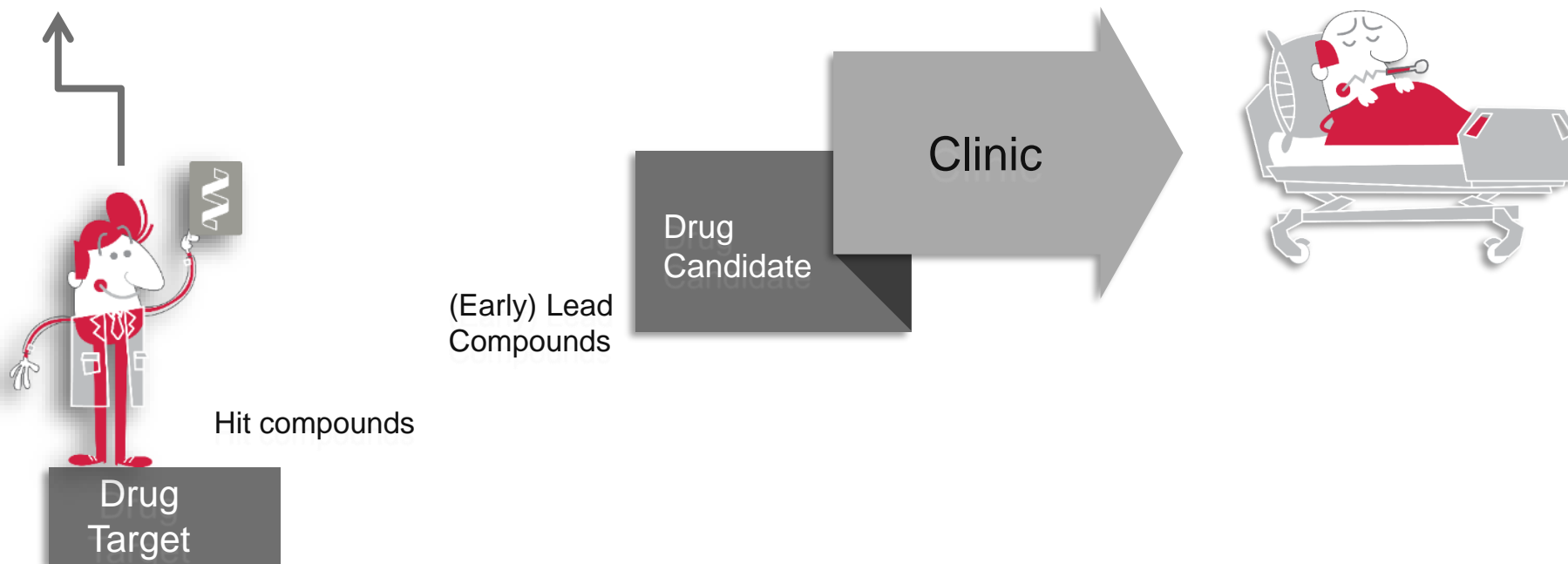
Drug Research Value Chain



The EU Lead Factory Model

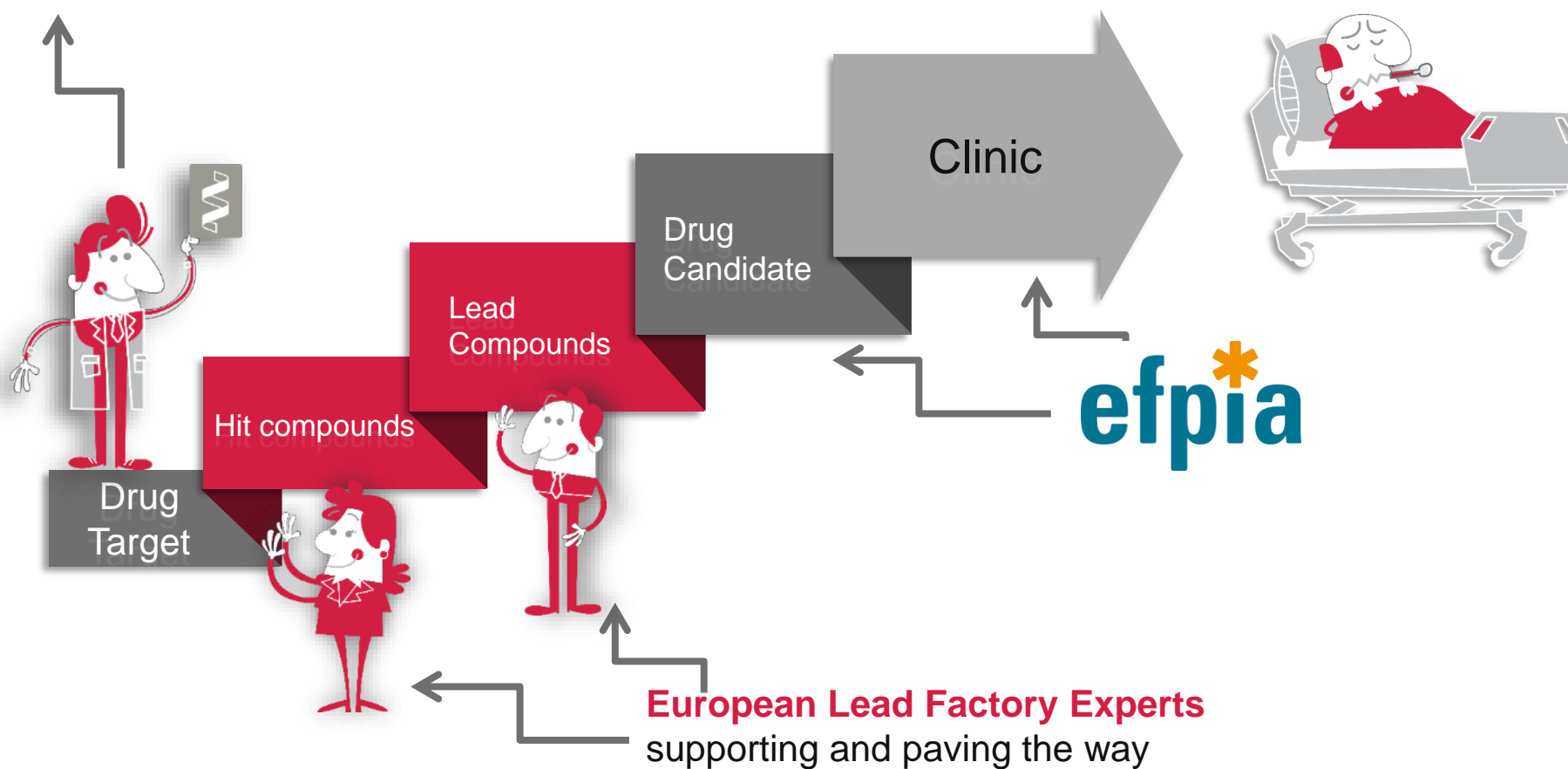
Researcher

in the **lead**



The EU Lead Factory Model

Researcher
in the **lead**



European Lead Factory Experts
supporting and paving the way

Hitting the Targets – and beyond!

Project Objectives

- Produce the best **200 000 screening compounds** in just 5 years
- Use **expertise and infrastructure** to boost innovation in early drug discovery in Europe
- Leverage **combination** of knowledge, strengths, capabilities and assets in **academia, SMEs & big pharma** in Europe

⇒ Building a **factory**

- Defining best practice and governance
- Set up an IT infrastructure

Best practice and governance

- Criteria and workflow for library/target proposal review/selection
- Library/target Selection Committee
- Criteria and workflow for library/target proposal validation
- Library/target Validation Management
- Criteria and workflow for library/assay production and transfer
- Knowledge & data transfer

Defined and fully operational

IT infrastructure

- Web portal for library submission
- Chemoinformatics tool to enable library evaluation and selection
- Chemistry management platform (TarosGate) for library progress and logistics tracking
- Honest Data Broker (HDB) for facilitating the confidential evaluation of biological data

Fully operational

Additional advantages

Collective Intelligence **EU Lead Factory**

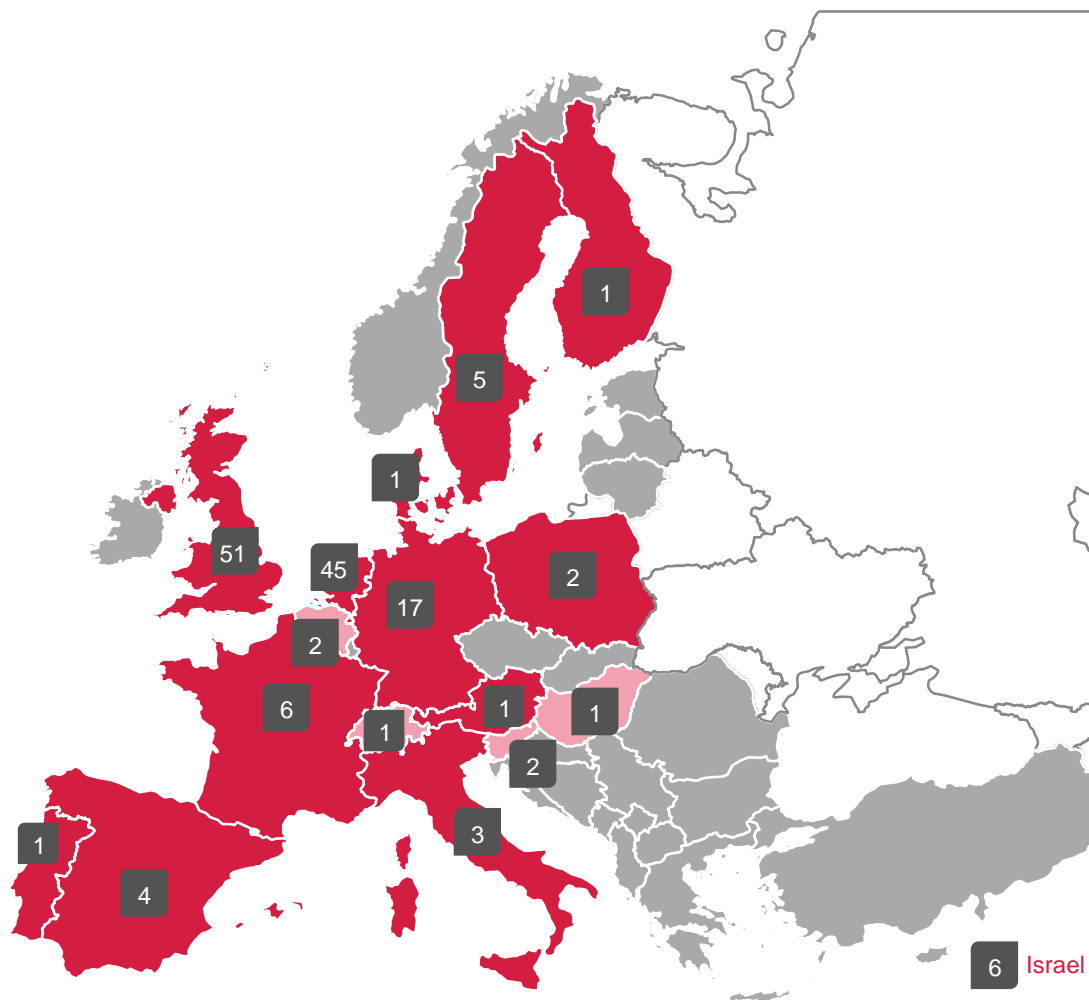


Geographic distribution of public target proposals

Eligible

Submitted (149)

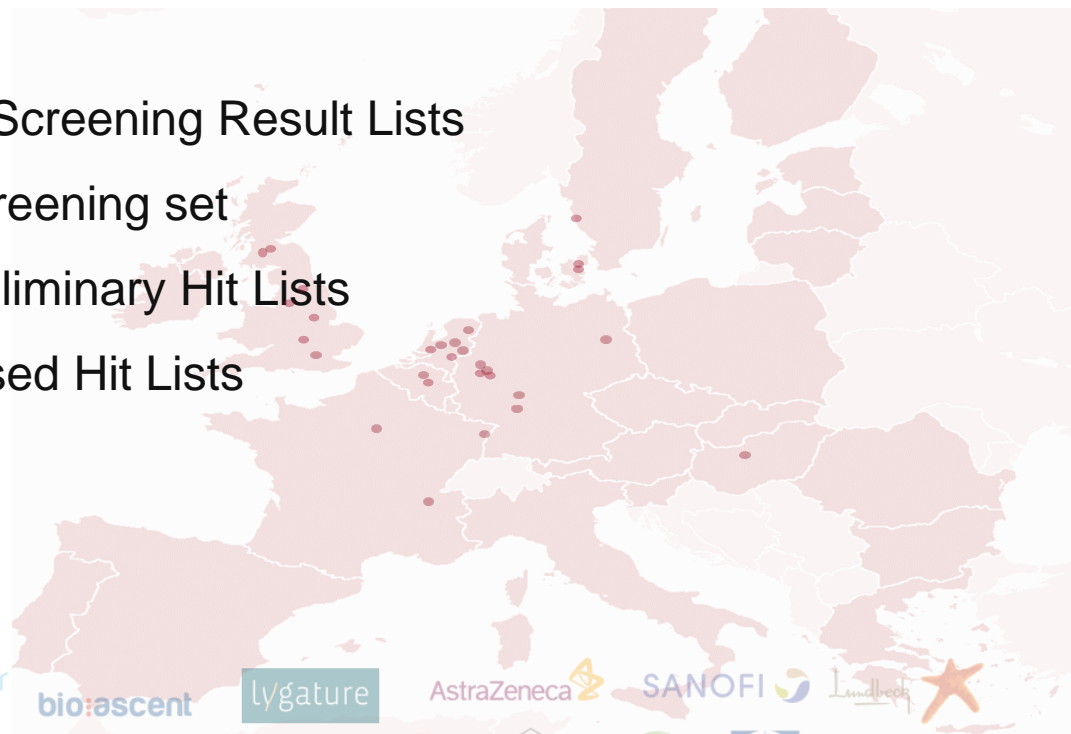
Accepted (85)



Status March 31, 2017

ELF: Collaborative Big Data

- **128,204,242** data points
- **42,522,956** primary HTS entries in Screening Result Lists
- **452,655** compounds in the 2017 screening set
- **26,253** compounds selected for Preliminary Hit Lists
- **4246** compounds selected for Revised Hit Lists
- **73** HDB users across Europe



4th Annual Chemistry Learnings & Achievements Meeting

Goals:

- Exchange of the knowledge
- Integration
- High quality scientific presentations
- Recognition of excellence



> 50 Publications

Figure 2. Progress of public programs submitted & completed programs in the respective stages in April 2015.

Improved Hit List with QHL compound analogs
 bioscience medicinal chemistry programme in collaboration with the target programme on performed at the University of Dundee site in house. The first steps often involve reynolds further characterisation of selected QHL comp followed by hit expansion to generate SARs. to the facilities at the University of Oxford, c sation efforts can also be pursued for a limited of programmes.

3.2 Progress
 As of April 2015, a total of 42 public target po have been accepted by ELF from 74 submit points. Most proposals are sourced via the new people working in ELF, which is reflected in t graphical origin of both submitted and accept points (Figure 2). The majority of both submit accepted proposals originate from academic or tions (e.g. universities, medical centres and u ties' research institutes) while SMEs are the on the remaining quarter (see pie chart in Figure 4).

ELF aims to run programmes related to all disease areas and all types of defined molecu gets. Compared to the analysis made in the 1 UJCI^{16,17}, the addressed disease areas (Figure 4) rather similar, although oncology targets are o

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

Journal of Medicines Development Science (2015) Volume 1, Issue 1

Commentary
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The importance of triaging in determining the quality of output from high-throughput screening

"For small-molecule medicines using a high-quality starting point can have a significant impact on the outcome of the discovery efforts both in terms of time and quality."

Keywords: academic drug discovery • high-throughput screening • HATS

"Quality means doing it right when no one is looking."

Henry Ford

The discovery of new medicines is a complex and expensive process. For small-molecule medicines using a high-quality starting point can have a significant impact on the outcome of the discovery efforts both in terms of speed and quality. High-throughput screening (HTS) is a mature and effective method for identifying chemical starting points; however, due to the need for infrastructure, in terms of robotics and compound libraries, historically this approach has been concentrated in major pharma groups. In addition, interpretation of the output and the design of the subsequent steps to validate that output are also vital in avoiding increasingly well-understood traps that may be overlooked by the unwary. Within major pharma HTS is a mature discipline that has been embedded there since the late 1980s; however, in the wider drug discovery community there is a much lower awareness of the issues associated with this approach. There has been significant growth in academic drug discovery in recent years and the availability of HTS has been identified as a gap. Wider access to HTS expertise and facilities will greatly increase the opportunity to leverage the research that is being carried out in academia and to develop small-molecule medicines that will ultimately benefit patients.

The value of high-quality leads
 The discovery of new medicines is a complex and expensive process. The annual output of 10,455 new molecules in 2014 by Future Med. Chem. (Epub ahead of print)

Future Medicinal Chemistry

feature

Expansion of chemical space in collaborative lead generation discovery: the European Perspective

Anna Karaszajczyk¹, Fabrizio Giordano², Jürg Benishghul³, Kees Power⁴, Remy Morgenthaun⁵, Adam Nelson⁶, Gerhard M. Distenfeld⁷, adam@elf-science.com

High-throughput screening (HTS) represent an innovative, relevant and high-quality tool of a drug discovery campaign. Given that it is practically infinite and sparsely populated, generation and maintenance of a competitive project is addressing this challenge by leveraging groups and small and medium enterprises. Here, we describe the novelty, diversity, size and overall attractiveness of this first batch of 10,455 new molecules in 2014 by Future Med. Chem. (Epub ahead of print)

Introduction
 The continuing discovery and development of novel, safe and effective medicines is expected by contemporary society. Nevertheless, the intellectual, technical and financial challenges associated with it are enormous. Despite the approval of 41 new therapeutics during 2014 (a significant 17-year high) [1], the ability of the pharmaceutical industry to rise to these formidable challenges is periodically questioned and alternative solutions are constantly suggested [2–7]. As a result, the field of drug research has seen significant changes over the past decades and a stronger emphasis on precompetitive, open source models is evident [8]. One such approach, the European Medicines Initiative (EMI) has been established to address these challenges. The EMI is a public-private partnership between the European Commission and the Human Blood Plasma Membrane Consortium, created to build technology platforms supporting drug design and development of biomarkers. However, access by external organisations to the pharmaceutical companies' proprietary source drug collections has, until now, been very limited. The EMI has provided a platform for pharmaceutical companies into a single, open source model, see <http://www.emi.eu>. The EMI has contributed a total of 321,000 compounds to the public domain, which are submitted by academic and pharmaceutical companies into a single, open source model, see <http://www.emi.eu>.

feature

The Joint European Compound driving precompetitive drug discovery: the European Perspective

Jérôme Bernard¹, Philip S. Jones², Andrew L. A. Palmer³, adam@elf-science.com

The Joint European Compound driving precompetitive drug discovery: the European Perspective
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Bioorganic & Medicinal Chemistry

feature

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Bioorganic & Medicinal Chemistry

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Organic Letters

A Universal Isoxanide for Diverse Heterocycle Syntheses

Pravin Pail¹, Karen Khoury^{2,3}, Eberhard Herdtweck⁴ and Alexander Dömling^{4*}

ABSTRACT: Novel scaffolds are of utmost importance for the discovery of functional material. Three different heterocyclic scaffolds easily accessible from isocyanaldehyde dimethyl acetal 1 by multicomponent reaction (MCR) are described. They can be efficiently synthesized by a Ugi tetraamino multicomponent reaction of 1. We discuss the synthesis, 3D structure, and other physicochemical properties.

Scheme 1. Previously Elaborated Heterocyclic Scaffold Using Isoxanide 1 and Our Work toward Three Novel Heterocycles

Block 1 in heterocycle synthesis toward 1-aryl-2-arylimino-1H-imidazole and imidazo[1,5-d]quinoxaline (Scheme 1).¹⁶ Other scaffolds reported include thiazoles and chiral imidazoles both by a thio Ugi reaction.¹⁶ Here we describe the easy synthesis of different scaffolds 2–4 using the same easily accessible building block 1, while not compromising diversity aspects.

From a practical point of view the synthesis of medium sized high quality libraries is demanding. The use of a "universal building block" in the synthesis of diverse scaffolds has great advantages in the parallel synthesis of larger libraries. For example, unprotected amino acids have been used recently in different multicomponent reactions chemistry to stereoselectively afford a diversity of novel cyclic and acyclic scaffolds, including amido-amino phosphonates,¹⁷ benzamide analogues,¹⁸ imino-oxadiazoles,¹⁹ imino-oxazolinones,²⁰ heterocyclic phosphonates,²¹ thiazole and thiomorpholine, dicyclopentanes,²² seleno amino acid,²³ imidazo[1,5-d]quinoxaline,²⁴ or indole derivatives. Isoxanide 1 as its diethyl acetal was first described by Harbison in 1966 and now robust large scale syntheses exist.²⁵ Competitive analysis shows few applications of the building block 1 in heterocycle synthesis.

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A blueprint for public-private partnerships



Nature Reviews Drug Discovery 15,
221–222 (2016)
by Katie Kingwell



The European Lead Factory: A Blueprint for Public-Private Partnerships in Early Drug Discovery

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¹Taros Chemicals GmbH & Co. KG, Dortmund, Germany

²Lygature, Utrecht, Netherlands

The European Lead Factory (ELF) is a public-private partnership (PPP) that provides researchers in Europe with a unique platform for translation of innovative biology and chemistry into high-quality starting points for drug discovery. It combines an exceptional collection of small molecules, high-throughput screening (HTS) infrastructure, and hit follow-up capabilities to advance research projects from both private companies and publicly funded researchers. By active

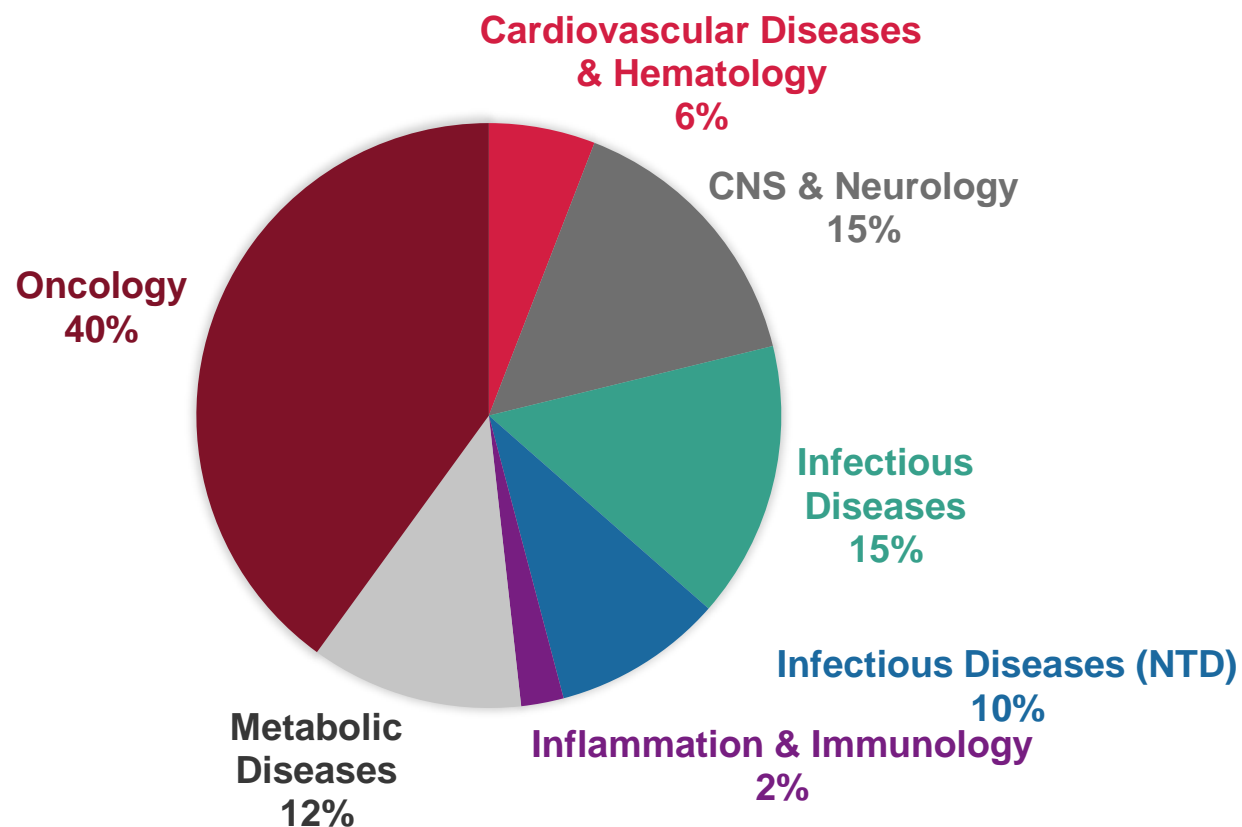
Frontiers in Medicine 3,
75 (2017);
Open Access



Euronews BUSINESS PLANET,
2016-12-28
Jan Skriwanek NKS
Dimitrios Tzalis ELF

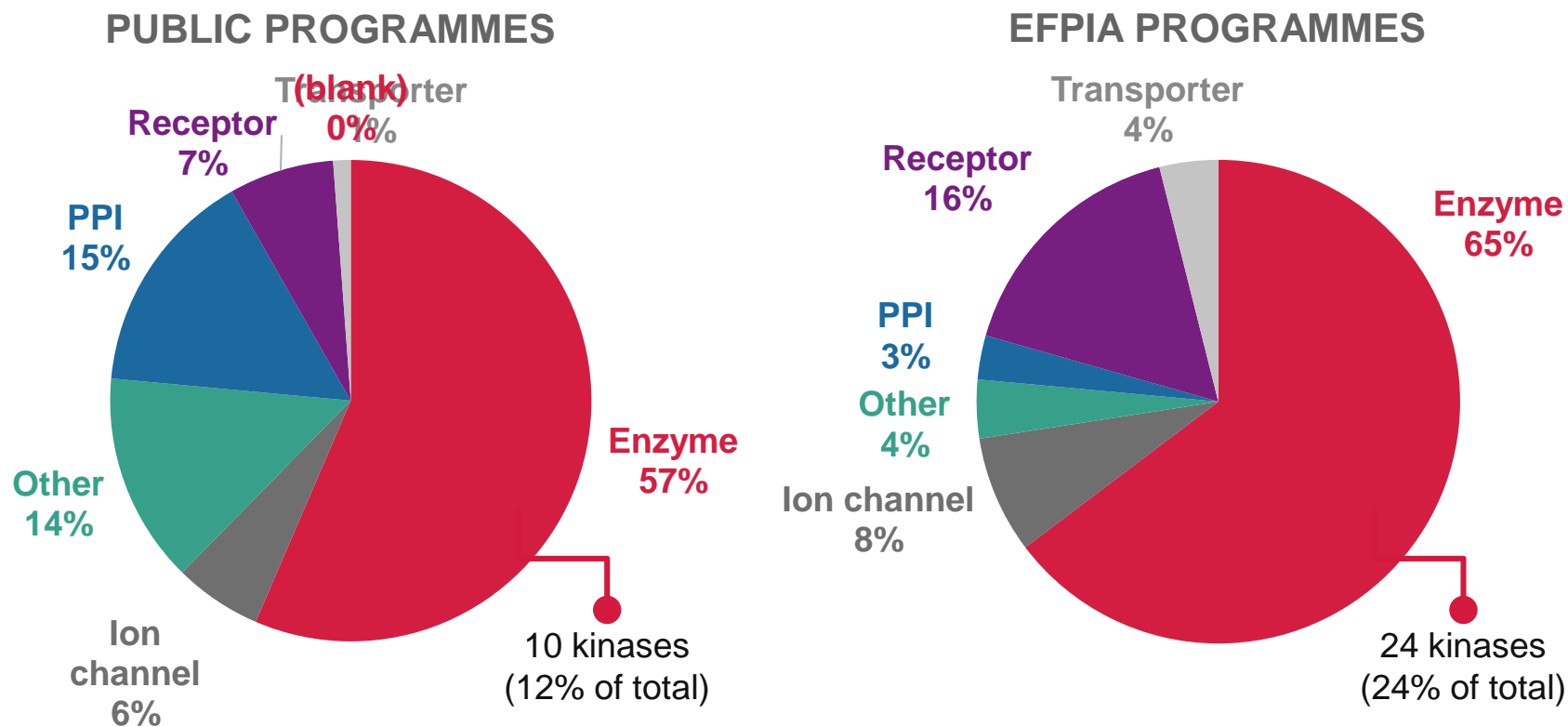
Therapeutic area distribution

ACCEPTED PROGRAMS



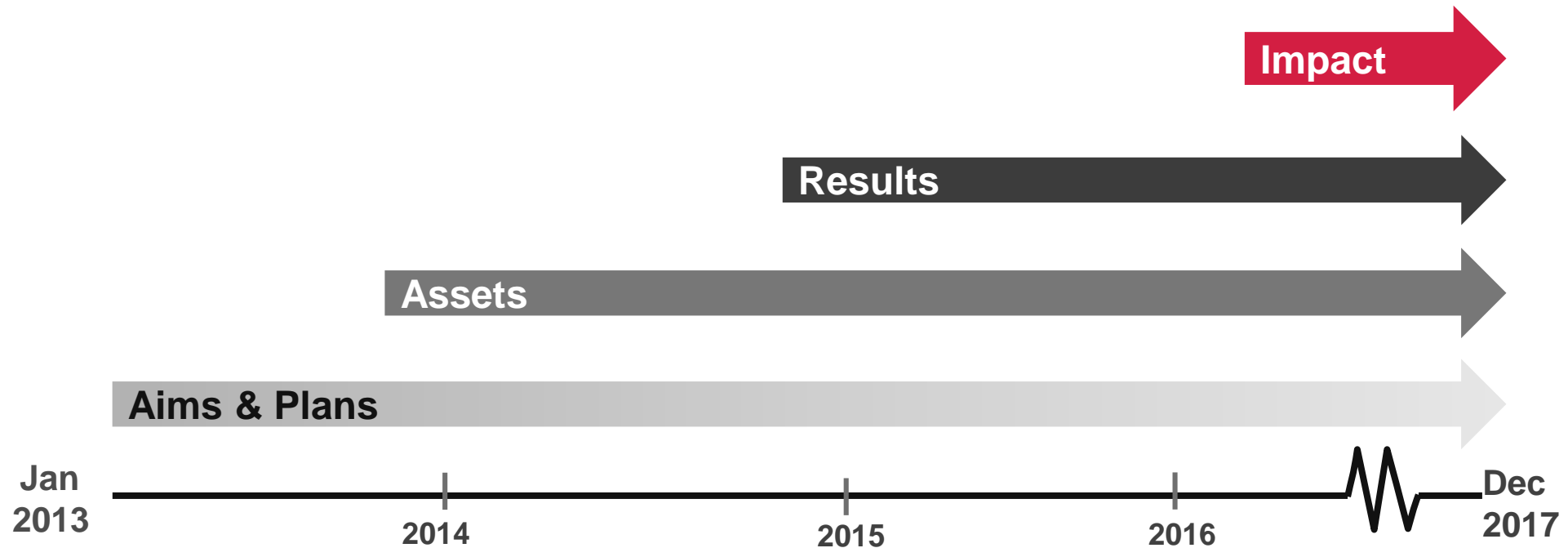
Status March 31, 2017

Comparison of target distribution



Status March 31, 2017

Progress 2013 - 2017



Powerful drug discovery engine!

Life after ELF...

Investment in spin-out from charity

Virtual biotech company launched to battle Parkinson's

PARKINSON'S^{UK}
CHANGE ATTITUDES.
FIND A CURE.
JOIN US.

08.03.2017

In a world-first type of collaboration, Parkinson's UK and the University of Sheffield have launched a joint venture biotech company, Keapstone Therapeutics. Parkinson's UK has allocated 1 million GBP over the next sixteen months to further develop compounds that boost the internal cellular defence mechanisms against oxidative stress. These compounds were

discovered by IMI's European Lead Factory.

New spin-out company & investment

European Lead Factory drug-like hit leads to creation of a spin-out



23.11.2016

Dr. Margit Mahlapuu, one of the academic researchers who has benefited from EU Lead Factory screening activities by identifying a drug candidate series for type 2 diabetes, went on to create a spin-out company based on these results. Dr Mahlapuu's group, based at the University of Gothenburg, first... [Read more](#)

Further development within IMI's ENABLE project



PRESS RELEASE

Promising antibiotic programme gets European boost

Innovative Medicines Initiative projects European Lead Factory and ENABLE create pipeline for novel antibiotics from University of Oxford

**Advancing science, creating new companies,
exploiting IMI project synergies for patient benefit**

Testimonials: Public Target Owners



Dr Margit Mahlapuu
Univ of Gothenburg

*We had already performed a small-scale screen that did not identify a compound with sufficient potency to build on. The **synergy in competencies** between my lab and the EU Lead Factory has given the project a **big push forward**.*

**METABOLIC
DISEASES**



Dr Chris Schofield,
University of Oxford

*'Overall, we are **extremely satisfied** with the progress, from assay optimization to post-hit validation. The work done within ELF is really of **high industry-like standard** and **very professional**.'*

**ANTI-
MICROBIAL
RESISTANCE**

*'It is an **initiative** that needs to be **continued**.'*

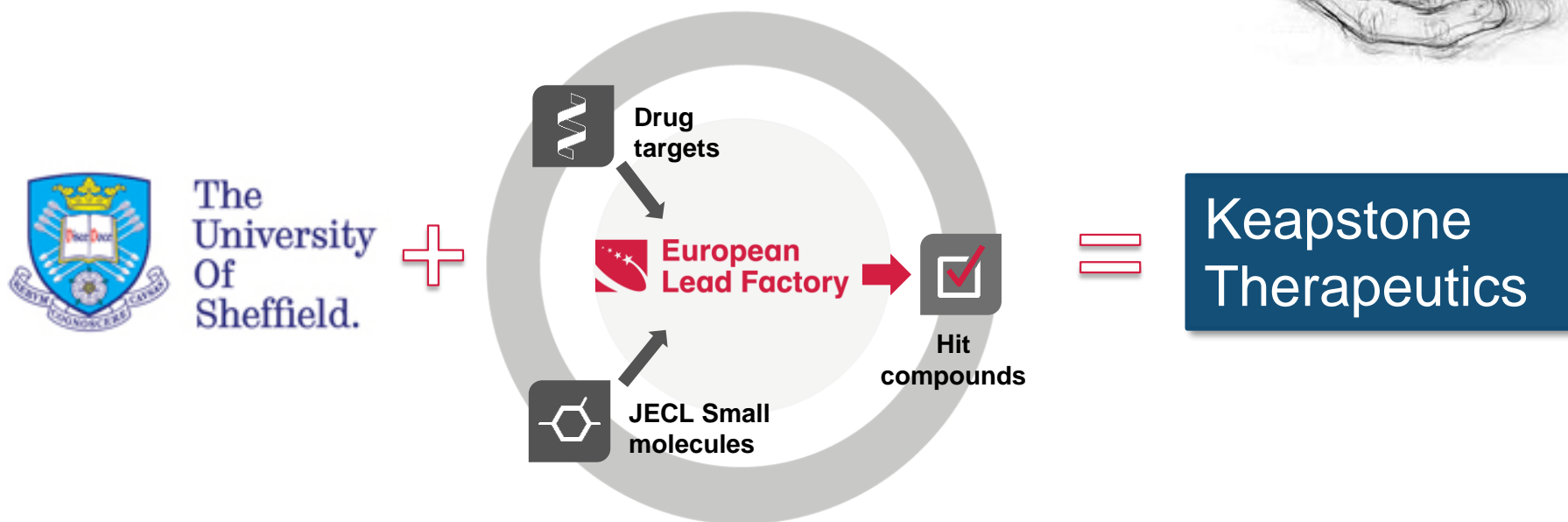


Dr Joost Uitdehaag
NTRC

*'Through ELF we now have access to **unique and tractable chemotypes**. They allowed us to get **proof-of-concept** in vivo and eventually develop a **best-in-class drug candidate**.'*

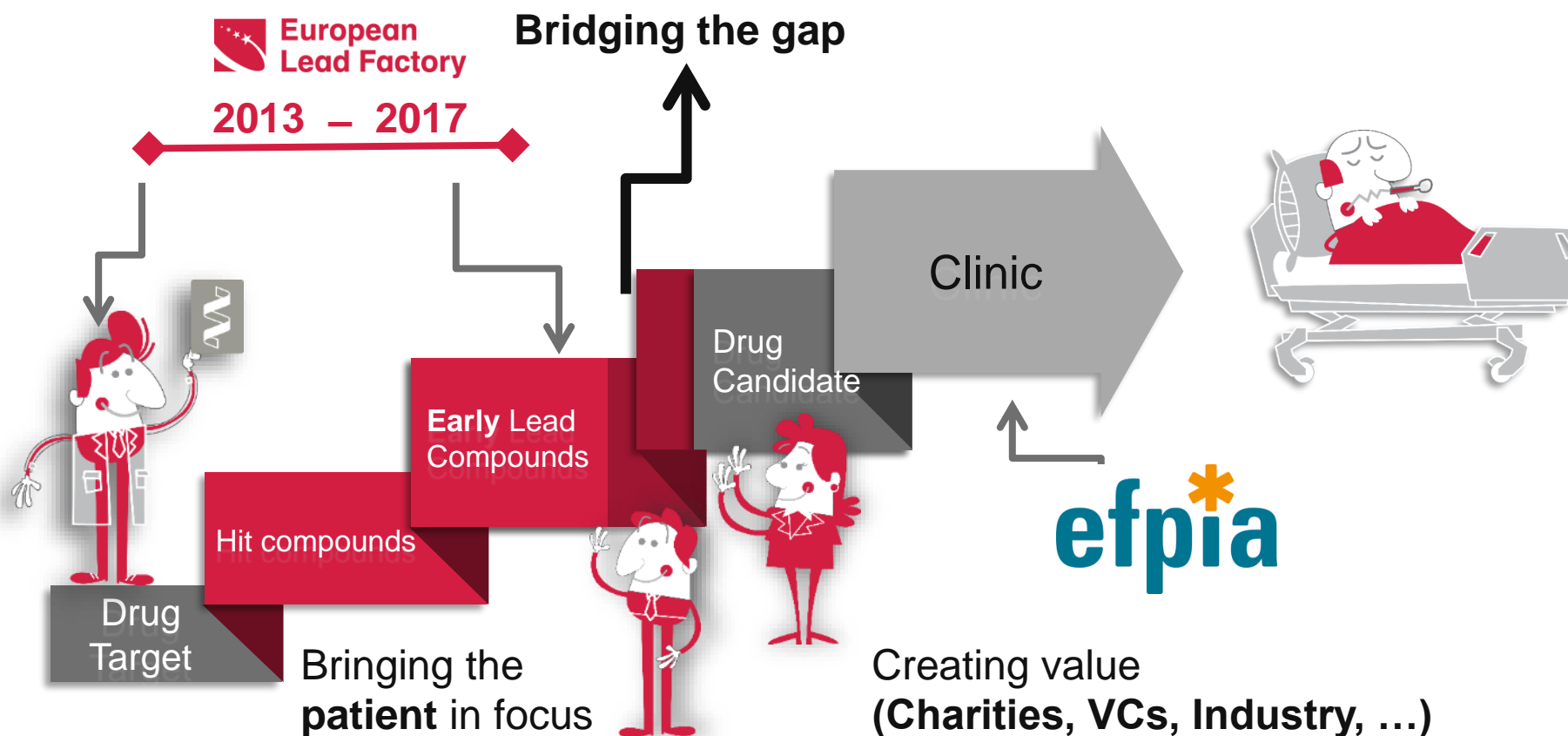
**IMMUNO-
ONCOLOGY**

JECL in the battle against Parkinson's disease

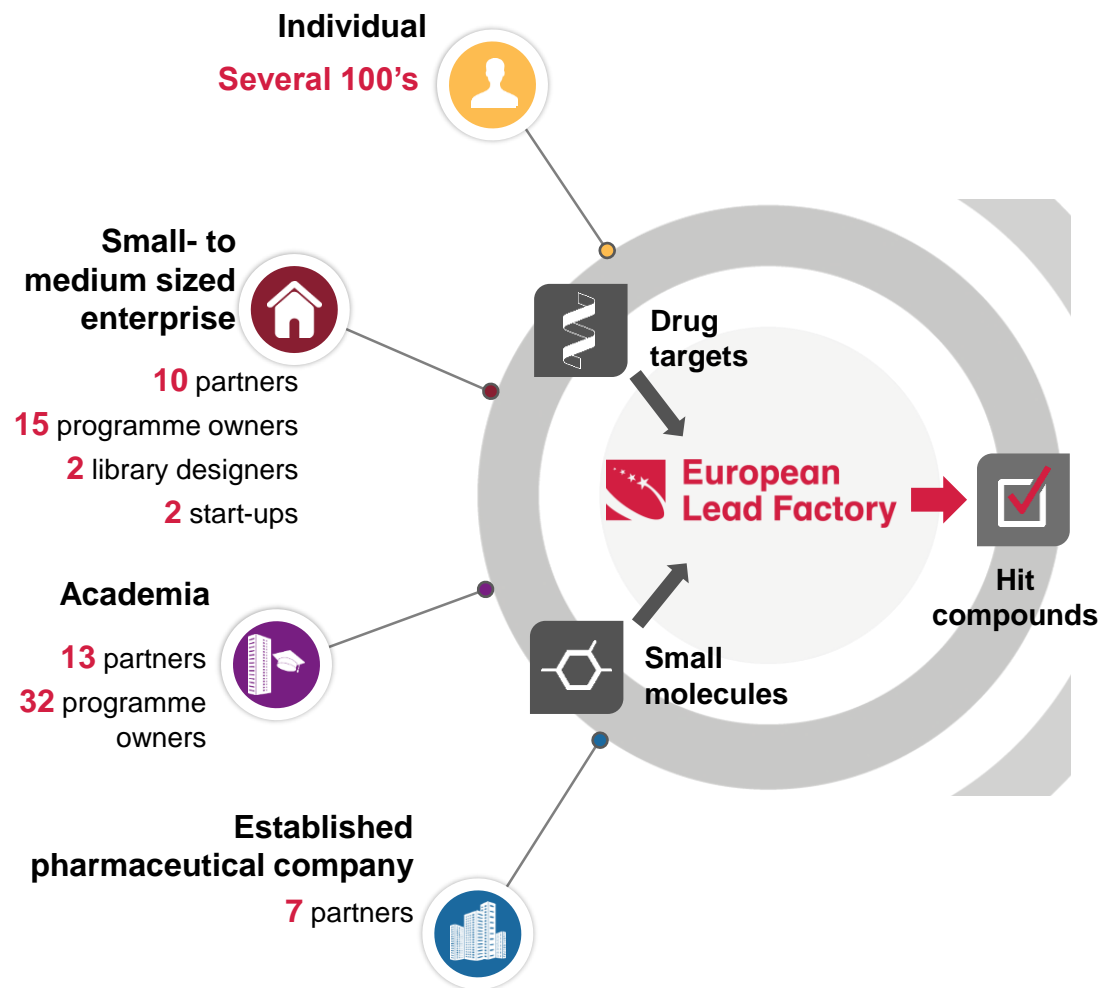


The **University of Sheffield** and **Parkinson's UK** have launched a new £1 million virtual biotech company to create new drugs for Parkinson's disease based on a **JECL** new class of compounds that can activate the brain cell defence system.

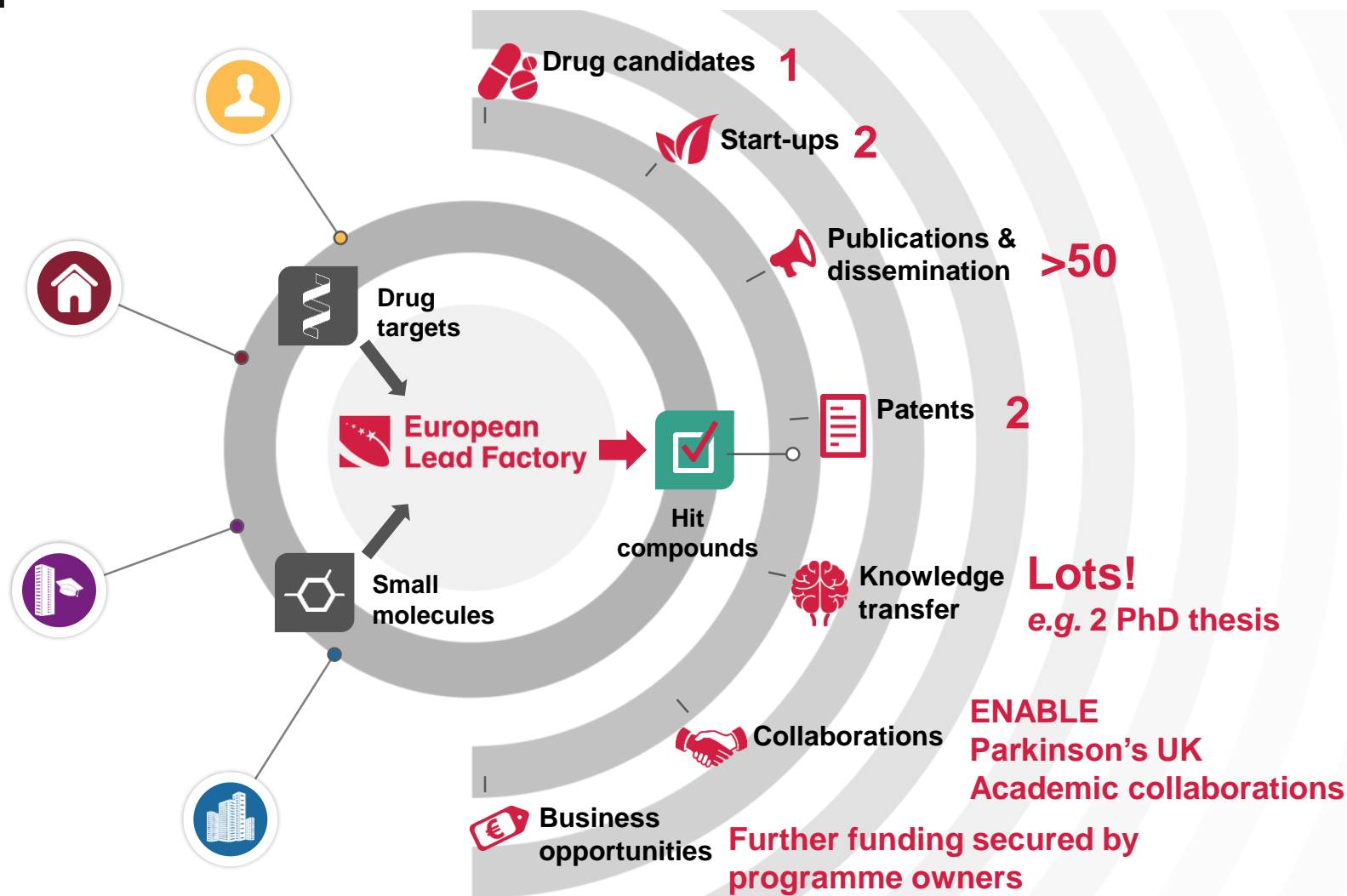
ELF envisions the engagement of all stakeholders to further increase patient benefit



Interactions



Impact





European Lead Factory

www.europeanleadfactory.eu

*Only the official and formally signed contractual documents in relation to the European Lead Factory (Project Agreement, Grant Agreement, Description of Work, and Third Party Access Agreements) have a binding value in relation to the subject matter covered in these slides.
Any information contained in these slides is not binding upon the parties and can in no event be used to interpret or complement the formally signed contractual documents referred to above.*