# The ENABLE project: An antibiotic discovery platform

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Putting open innovation into practice –case studies from Europe

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# The rising threat of antimicrobial resistance

## Public awareness

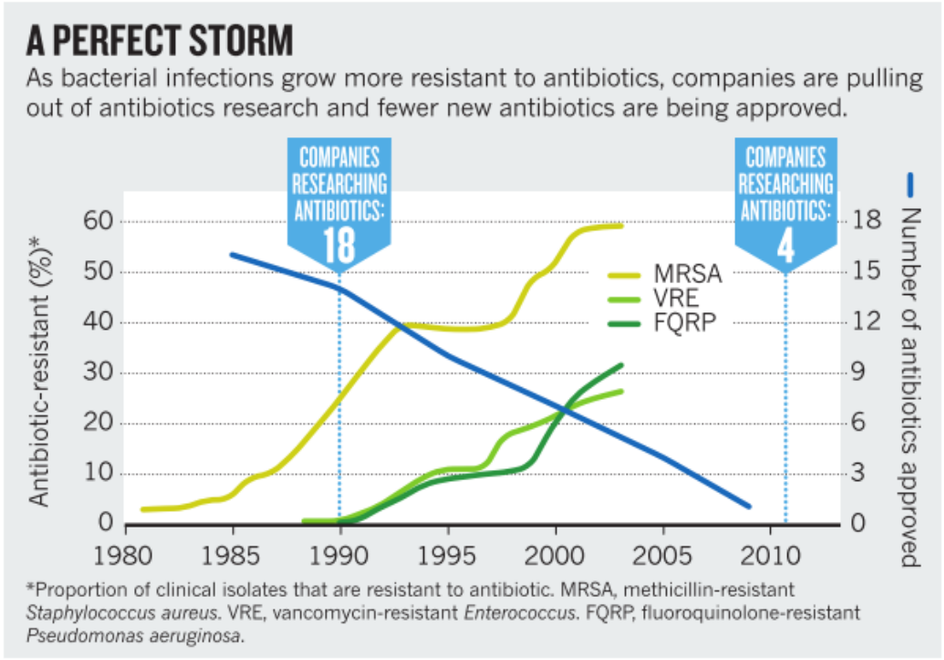

Antibiotic-resistant superbug problem will turn devastating.

**Antibiotic crisis 'bigger than Aids'**

By Rebecca Smith
Medical Editor

health security, wrote: '
post-antibiotic era, in whi

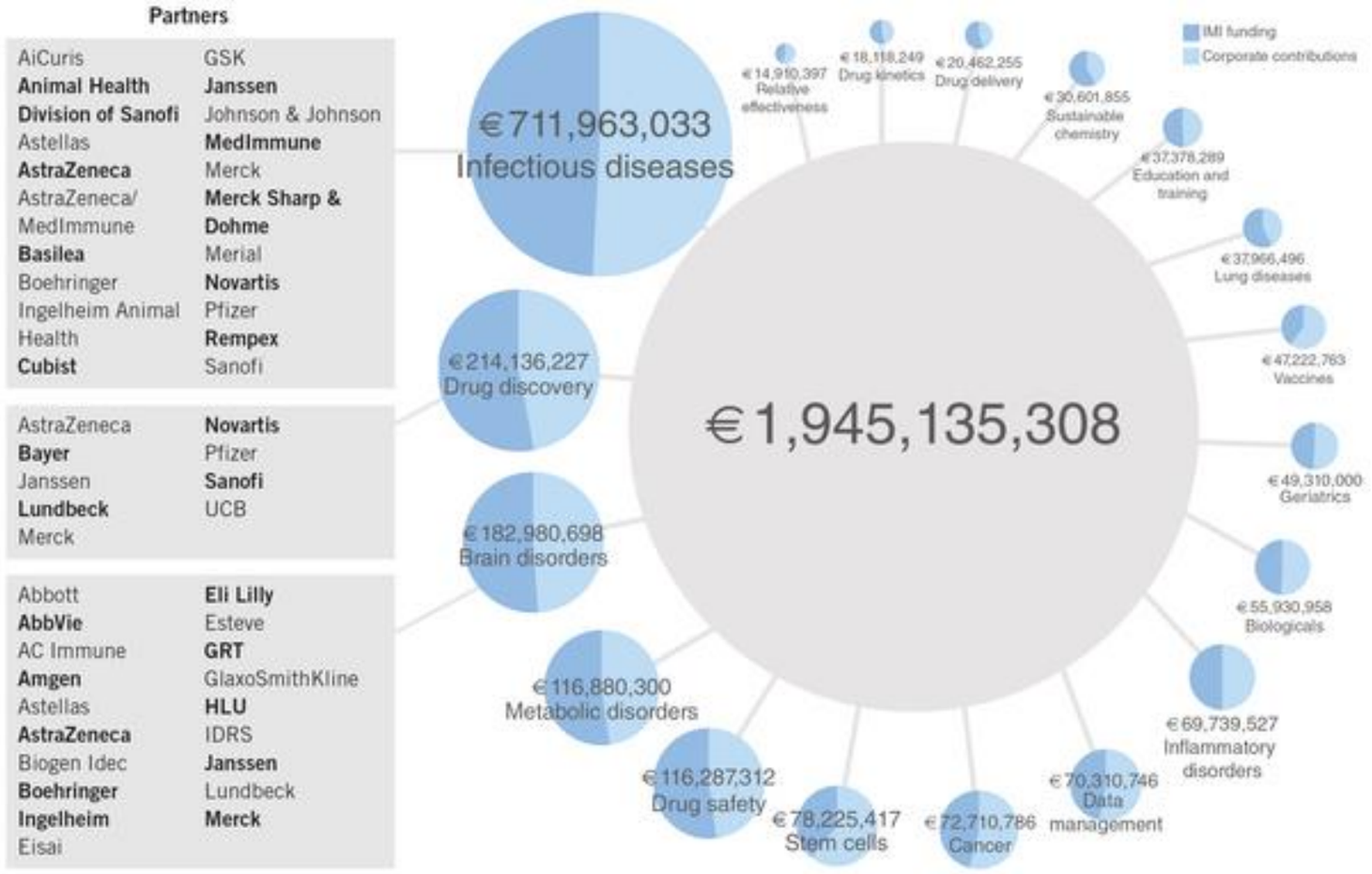
Antibiotics resistance 'as big a risk as terrorism' –
*UK Medical Chief Officer (2013)*




**This growing "antimicrobial resistance" (AMR) is estimated to cause each year some 25 000 deaths and over €1.5 billion in healthcare expenses and productivity losses in Europe alone.**
***ECDC/EMEA Joint Technical Report 2011***

## Political awareness

# The IMI-1 portfolio




*Nature Medicine 2014, Vol 20, no 1*

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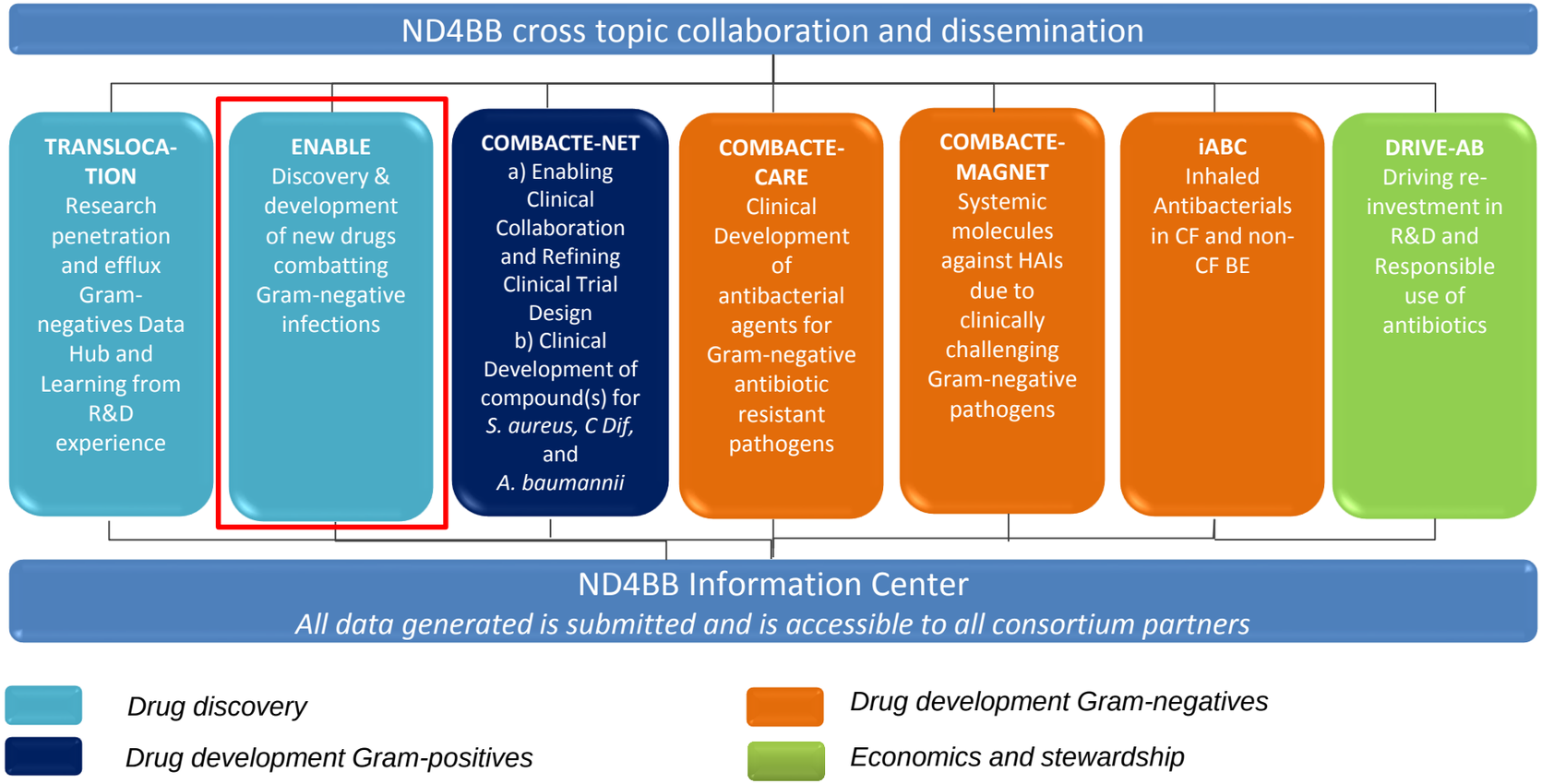
# Overall architecture of ND4BB




***ND4BB Projects as of 2017***

**Total budget: > € 650 million**

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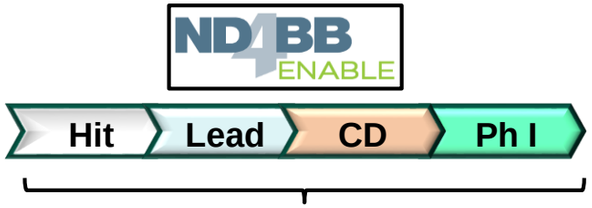
# Developing an antibiotic

| | |
|---|---|
| Chemistry, modelling & microbiology | Design & synthesize new compounds<br>MIC profiling, celltox<br>$MIC_{90}$, Time-kill, WGS |
| Biochemistry<br>Structural Biology | Protein production, assay set-up<br>Crystal structures |
| ADME profiling | CYP inhibition/induction, metabolic stability, protein binding |
| Electrophysiology | e.g. hERG inhibition |
| Bioanalytics, PK, *in vivo* pharmacology | *In vivo* tolerability and efficacy |
| Scale-up chemistry | Compound for toxicology studies |
| Pharmacometry | PK/PD modelling |
| Pharmaceutical development | Formulation, stability |
| Safety | Preclinical safety studies |

**Developing an antibiotic requires;**

- Experienced collaborators
- Expertise in drug discovery and development
- Expertise in antibiotic development
- Time
- Money




**ENABLE has the resources, skills & expertise to perform the work**

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# ENABLE: European Gram Negative Antibacterial Engine

***Consortium with 39 partners:***

***Public partners***

***Uppsala University managing entity***

20 academic/institute/hospital organizations/non-profits

15 SMEs

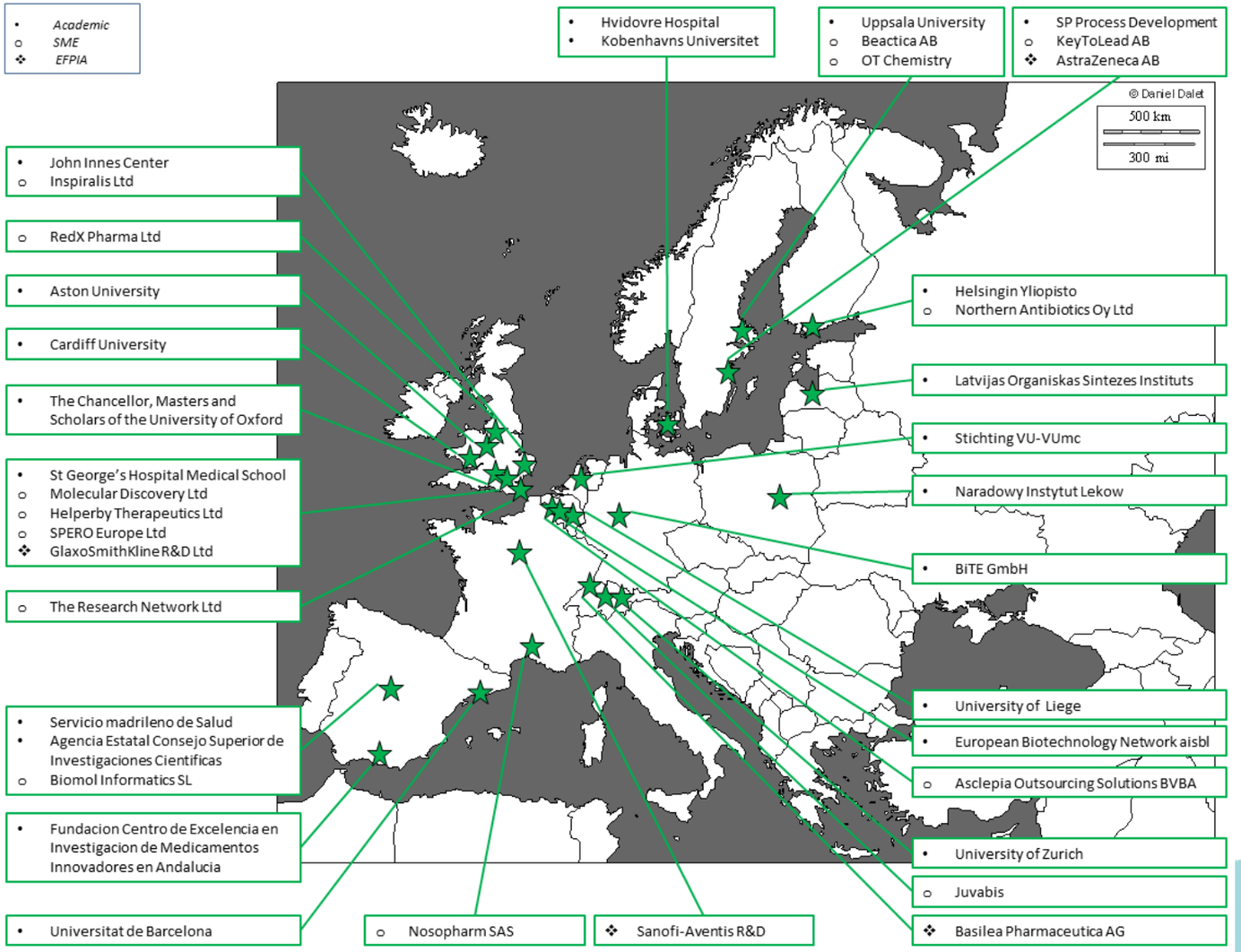
***Private partners (EFPIA)***

***GlaxoSmithKline, Pennsylvania, US***

Sanofi, AstraZeneca & Basilea

***Launched Feb 2014, 6 year run time***

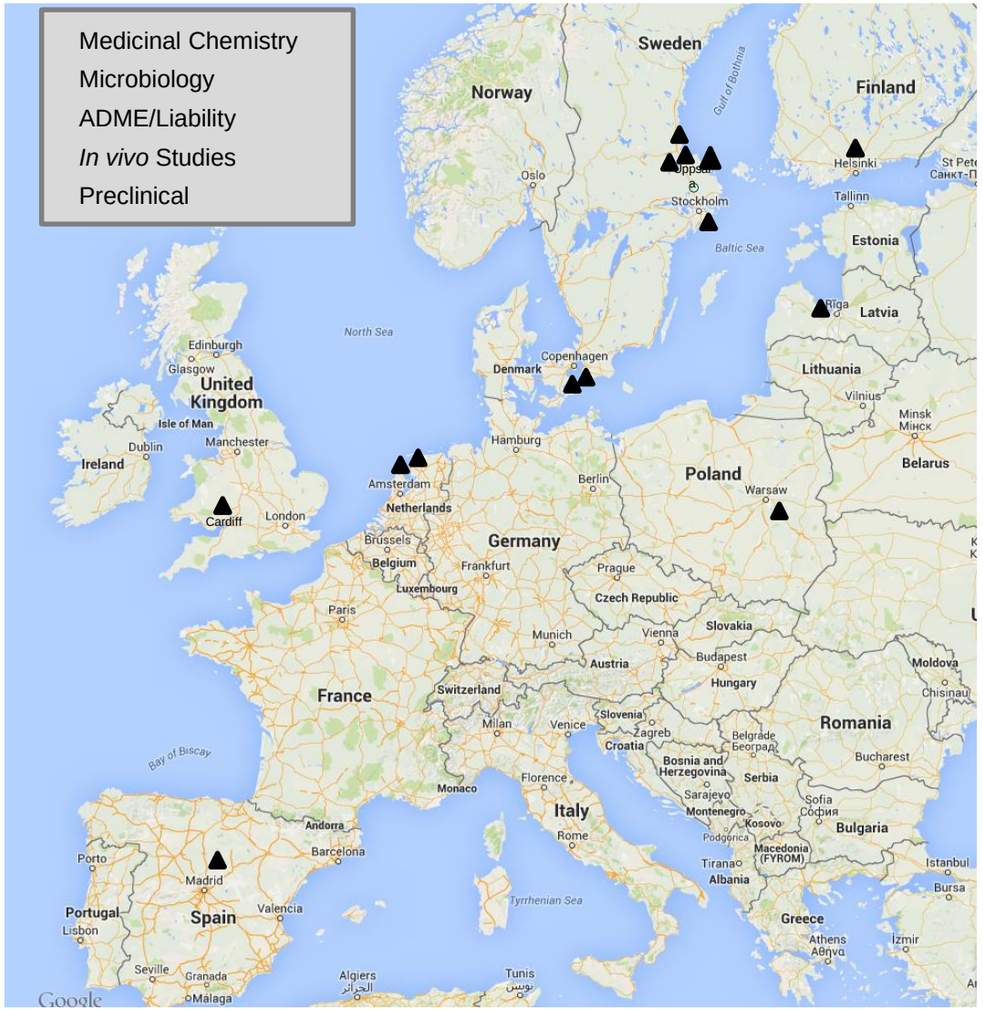
***Projected budget: €85 million***




## Goals

- Create a collaborative drug discovery platform
- Kick start Gram-negative antibacterial discovery:
  - increase overall science base in the area
  - identify three Leads
  - identify two Development Candidates
  - progress at least one compound into Phase 1

# Managing a Drug Discovery platform across Europe




**ENABLE labs**

- Medicinal chemistry, microbiology, ADMET, PK, *in vivo* pharmacology all across Europe and working by disciplines
- Representing more than 50 FTEs

**Compound handling platform**

- Storage of compounds
- ID & Purity control of compounds
- Weigh out of solid material for assays
- Transfer of compounds to microtiter plates/vials
- Distribution of solutions/compounds

**Sharing data in ENABLE**

- Electronic Lab Notebook (ELN)
- Results database
- File Server

**ENABLE management (administrative and scientific)**

- Consortium management office (CMO)
- Finance support (UU)
- Legal support (GSK & UU)

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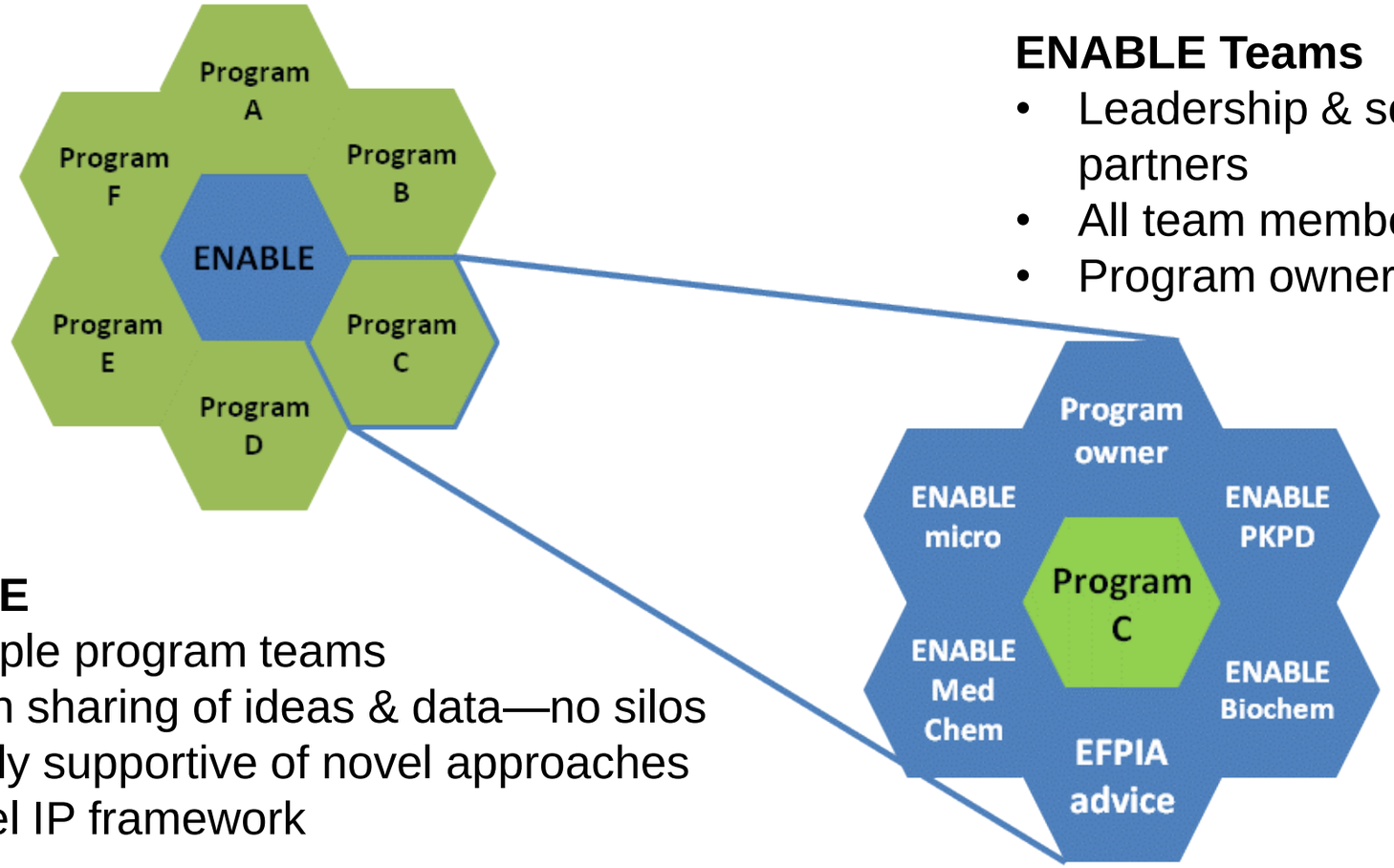
# ENABLE: collaborative antibacterial drug discovery




**ENABLE Teams**

- Leadership & science from multiple partners
- All team members at the table
- Program owner makes final decisions

**ENABLE**

- Multiple program teams
- Open sharing of ideas & data—no silos
- Highly supportive of novel approaches
- Novel IP framework

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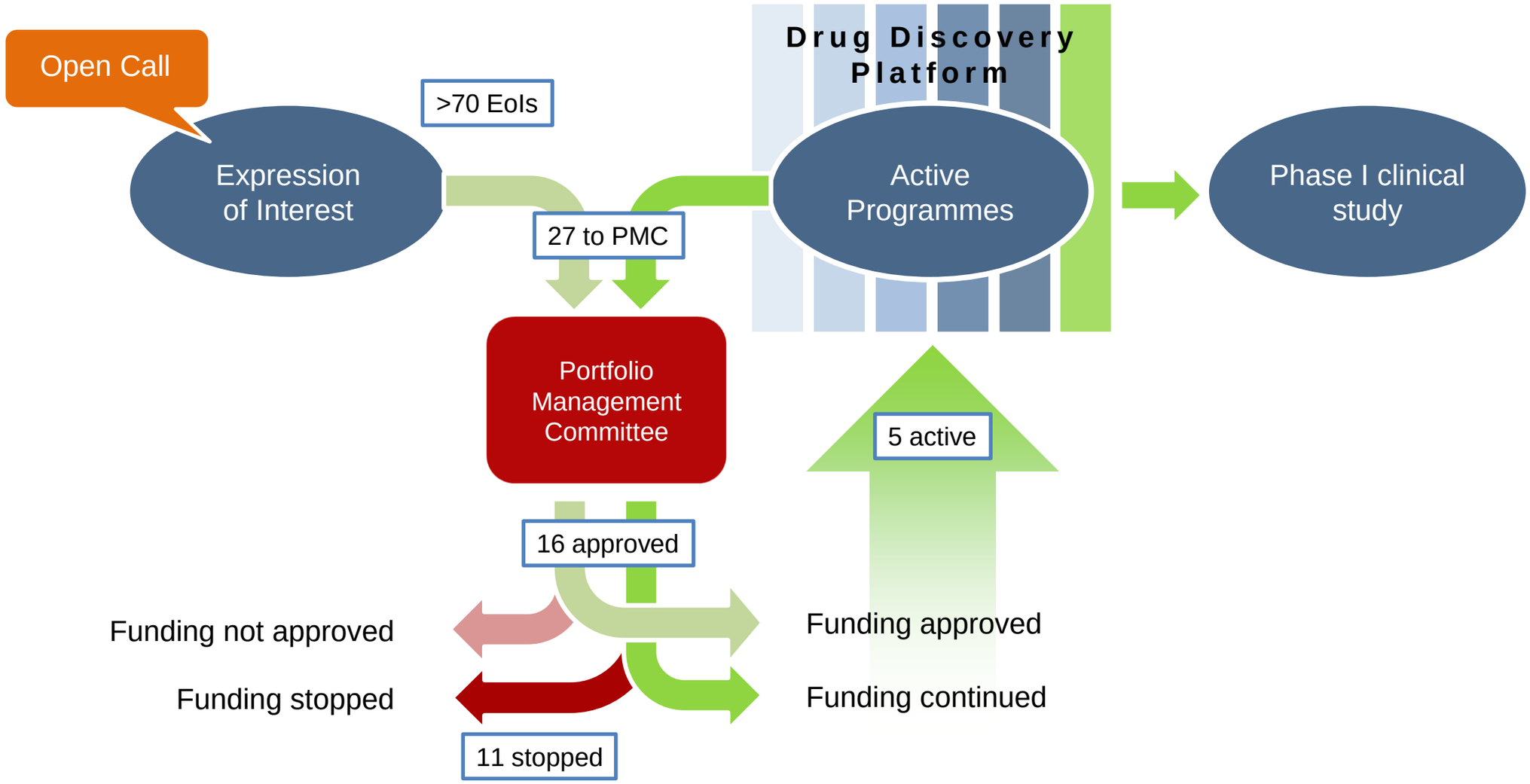
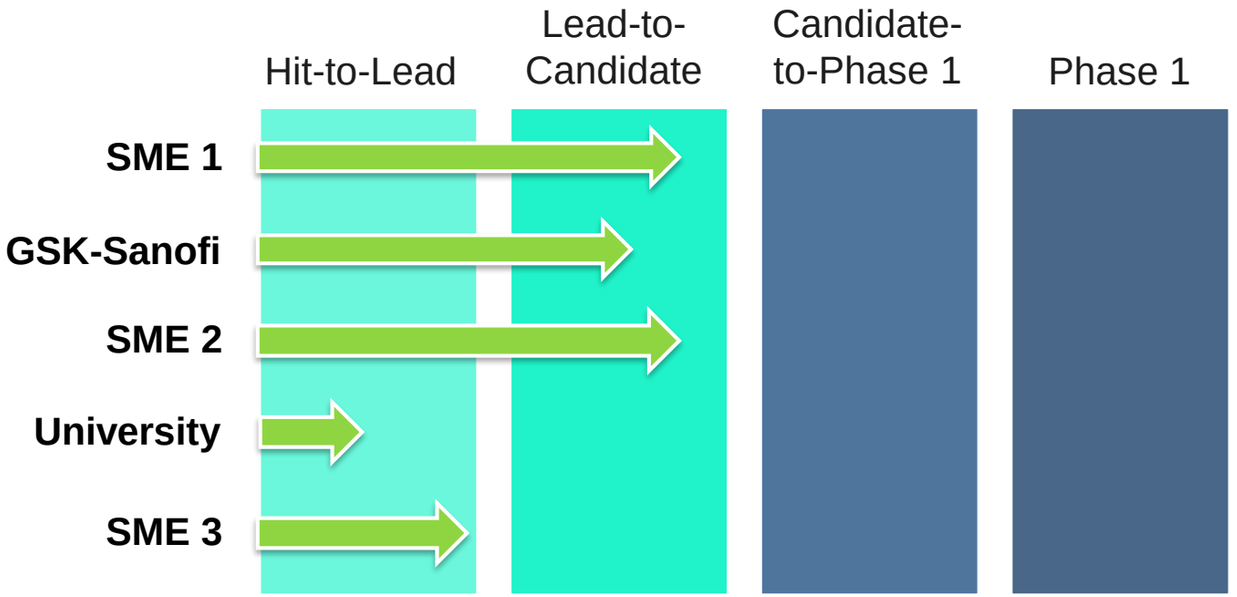
# Heart of ENABLE: PMC (funding) cycle



# ENABLE portfolio May 2017




- 16 programmes approved for funding since start of project
- Over 3 years PMC has stopped funding of 11 programmes

# Aligning IMI projects


## Promising antibiotic programme gets European boost

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

*Utrecht, the Netherlands, 17 November, 2016*

**Researchers at the University of Oxford have been working with two major EU-funded projects to deliver a novel antibiotic programme for clinical development. The development comes thanks to an alignment between the European Lead Factory (ELF) and the European Gram-Negative Antibacterial Engine (ENABLE) projects, both of which are supported by the Innovative Medicines Initiative (IMI), Europe's largest public private partnership in life sciences research.**

The Oxford team, led by Professor Chris Schofield, kick started the process through his group's focus on a potential target within gram negative bacteria that could eliminate resistance against the β-lactam antibiotics, so restoring potency of a group key antibiotics

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# Hit to Lead development of the new family of antibiotics  MDN-0057-0060

- MEDINA compounds (MDN-0057 – 0060) were selected for preclinical Hit-to-Lead (H2L) development within ENABLE
- MEDINA program has involved a multidisciplinary core team from the University of Uppsala (Sweden), SERMAS (Spain), CNB-CSIC (Spain), University of Liège (Belgium), Asclepia (Belgium), MEDINA (Spain) and efpia advisors
- Hit-to-Lead development program focused primarily on:
  - Generation of improved medicinal chemistry series
  - Mood of Action determination
  - *In vivo* Proof of Concept

# MDN57: Good antimicrobial profile

| Species | | MIC ug/ml |
|---|---|---|
| *E. coli* | WT | 8-16 |
| *E. coli* | ΔtolC | 8 |
| *P. aeruginosa* | WT | 16 |
| *P. aeruginosa* | Efflux-defective | 16 |
| *K. pneumoniae* | WT | >64 |
| *K. pneumoniae* | Efflux-defective | 8 |
| *A. baumannii* | WT | 8 |
| *A. baumannii* | Efflux-defective | 8 |

# ….. but high resistance frequencies observed

- **Resistance frequencies :** performed on 4 species using susceptible strains: **$10^{-4}$ to $10^{-6}$ for all key species** at 4-8 x MIC.

- **Whole genome analysis of *E.coli* resistant mutants**:
  - Mutations identified in heme biosynthetic pathway

# Good Stability and Permeability …..

## ADME assessment of MDN-0057:

- **Chemical stability** of compounds at pHs 2.0, 7.4 and 10.0
- **Good solubility** (over 100 µmol/L)
- **Good *in vitro* permeability** (Caco-2)
- **Metabolic stability**: Good metabolic stability in both human and mouse liver microsomes and human hepatocytes
- **Acceptable plasma stability** (after 4 h incubation in human plasma)

# …… and preliminary good safety and in vitro toxicity data

## Good safety window:

- **NO cytotoxic activity** (on HepG2 and Fa2N4 human cell lines at conc > 512 ug/mL)
- **NO cardiotoxic activity** ( 20% hERG inhibition at 50 µM)
- **MODERATE CYP3A4 isoform inhibition** ($IC_{50}$ 2 to 4 µM) and **NO inhibition** of CYP2D6 and CYP2C9 ($IC_{50}$> 86 µM)
- **LOW clearance** in human liver microsomes with $t_{1/2}$ > 60 min (predicted intrinsic clearance <11 µl/min/mg microsomal protein)
- **NO haemolysis** (between 0 and 0.5%)

# …. but unexpected in vivo toxicity in mice

## Preliminary *in vivo* toxicity of MDN-0057

- **Experimental design:**
  - 3 and 30 mg/kg MDN-0057 given *iv* to fed or fasted mice
  - Sample collection before and 15, 60, 120 min after administration
- **Fast kinetics**: Rapid depletion in MDN-0057 concentration after 15 min to reach undetectable levels in 60 min

- Pronounced toxicity and mice lethality 2-20 h after administration

→ **Unexpected acute toxicity and high resistance frequencies recommended the discontinuation of the program (PMC Sept 2014)**

# Summary

- **The ENABLE consortium has brought together the skills and expertise from the public and private sectors to:**
  - Create an antibacterial drug discovery platform
  - Recruit the best programmes from across Europe
  - Educate the next generation of antibacterial drug discovery experts
  - Identify two antibacterial development candidates
  - Progress at least one compound into preclinical and Phase 1 clinical studies
- **A new model for collaborative drug discovery initiatives in other disease areas**

# Thank you

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