IMI-ENABLE: A European Antibacterial Drug Discovery Platform

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The rising threat of antimicrobial resistance

Public awareness

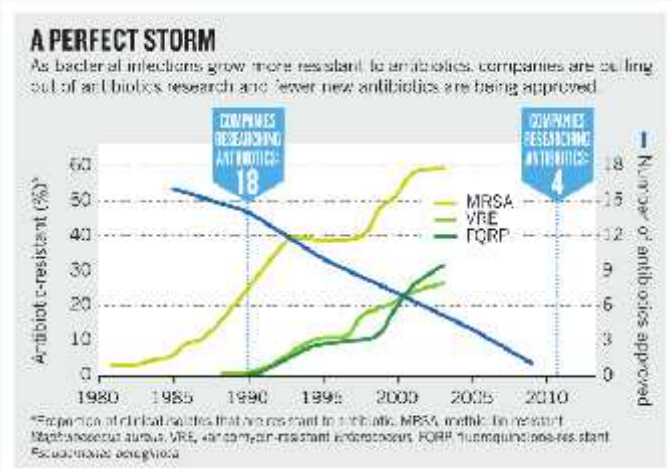
Antibiotic-resistant superbug problem will turn devastating

Antibiotic crisis 'bigger than Aids'

By Rebecca Smith
Medical Editor

Health security, wrote: '

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



Shlaes & Cooper, Nature (2011) **472;** 32

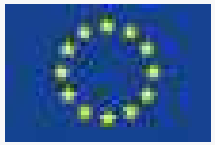
Why no new antibiotics?

- lack of return of investment (short treatment time, low pricing, limited populations infected by resistant strains, restrictions on the use of new antibiotics …)
- regulatory challenges
- scientifically challenging

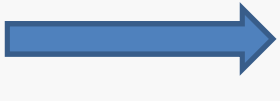
Political awareness

One of the European answers: The ND4BB initiative

EU / EFPIA collaboration created New Drugs for Bad Bugs via IMI to address key bottlenecks in AB R&D



Partnership

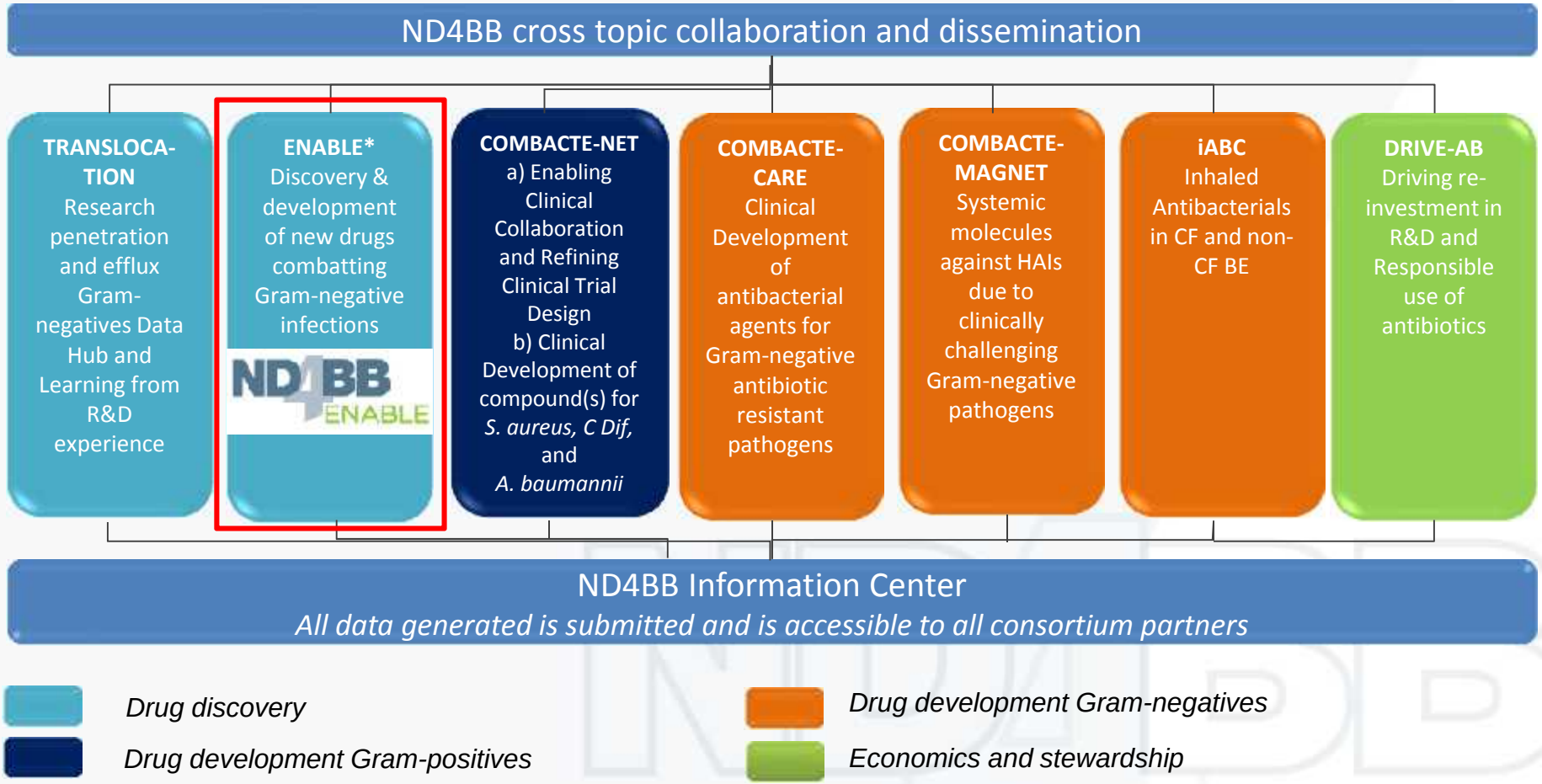


7 Topics

from drug discovery to clinical development

Overall architecture of the ND4BB initiative

ND4BB Program as of 2016



*** The 1st IMI Consortium at Discovery stage**

Total budget: > € 650 million

ENABLE: European Gram Negative Antibacterial Engine

Who are we ?

Consortium with ~40 partners

Public partners

- ***Uppsala University as the managing entity***
- ***20 academics***

Private partners

- ***GlaxoSmithKline (Pennsylvania, US) as the EFPIA coordinator***
- ***Sanofi (co-lead), AstraZeneca & Basilea***
- ***15 SMEs***

Launched Feb 2014,

- ***6-year run time***
- ***Projected budget: €85 million***

Red markers = Public partners (12 European countries)

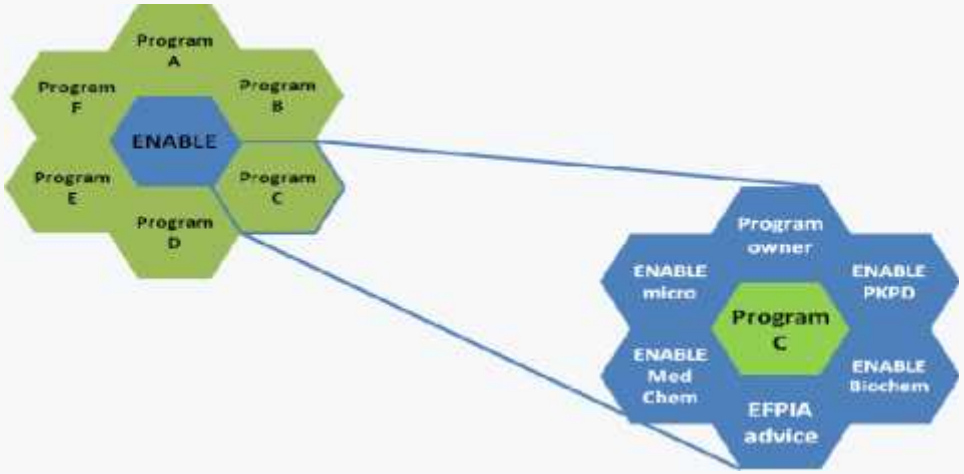
ENABLE: Objectives and philosophy

- Goals
  - create a collaborative antibacterial drug discovery platform across Europe
  - educate the next generation of antibacterial drug discovery European experts
  - identify novel Gram-negative antibacterials
    - three Leads and two Development Candidates
    - at least one compound into Phase 1

- Philosophy
  - multiple programs run in parallel to maximize probability of success
    - including collaboration between Sanofi and GSK
  - rigorous progression criteria to secure success and value of IMI investments
  - Team-centered organization
  - constant support and regular challenges from within the Consortium
  - open sharing of ideas and data: no silos
  - highly supportive of novel approaches

ENABLE: Team mechanics

- Project Teams constituted around the Program owners and including a relevant subset of the Drug Discovery platform partners (3-4)



- Experimental work shared between Program Owner and ENABLE partners
- Regular Team meetings to discuss Science, data and next steps
  - Program owner makes final decisions
- Free access to ENABLE experts (during monthly reviews or on demand)
- Progress presented quarterly to the Portfolio Management Committee by Program Owner for funding-decisions

ENABLE: The Drug Discovery platform

- Medicinal Chemistry
- Microbiology
- ADME/Liability
- *In vivo* Studies
- Preclinical
- Reinforcement Group

ENABLE management (administrative and scientific)

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

ENABLE labs

- Medicinal chemistry, microbiology, ADMET, PK, *in vivo* pharmacology all across Europe and working by disciplines
- representing up to 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

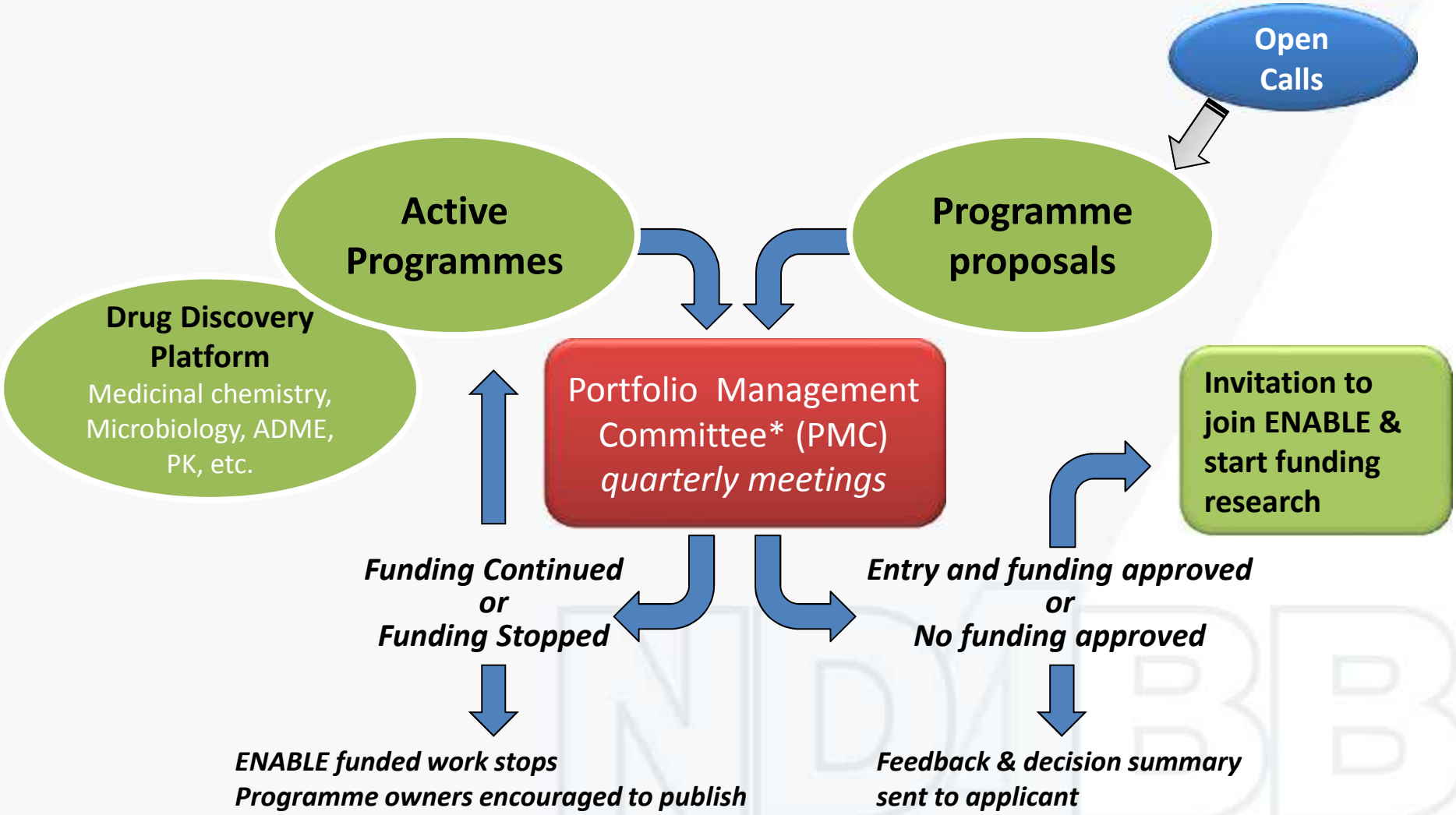
ENABLE: A great proposition for Program Owners (1)

- Applications to ENABLE are easy and with limited risks
  - initially non-confidential data and then CDA protection to show confidential data to PMC
- Limited funding needed to advance project after entering ENABLE
  - research funded at 75% by IMI
- An original and favorable IP framework
  - no IP dilution: new IP invention and data stay with the original “Program Owners”
  - Where/when revenue finally generated (sale / license of product) triggers small (capped) % payment to ENABLE partners
  - IP agreement designed to keep ownership simple and attractive for investors and downstream partners

ENABLE: A great proposition for Program Owners (2)

- Minimal obligations
  - program owners may leave ENABLE anytime
  - no obligation to partner with EFPIA companies represented in ENABLE
- Program owners can greatly benefit from entering ENABLE
  - motivated partners to develop their program and share lab work
  - collaborative (not CRO) spirit striving to move program forward
  - advice and support from academic and EFPIA experts
  - large set of assays generally not accessible by SME/academics
  - strong man power in key disciplines (eg up to 10 chemists at L2C stage)
- Opportunities for publications from collaborative work strongly favored
  - subject to confidentiality/patent constraints

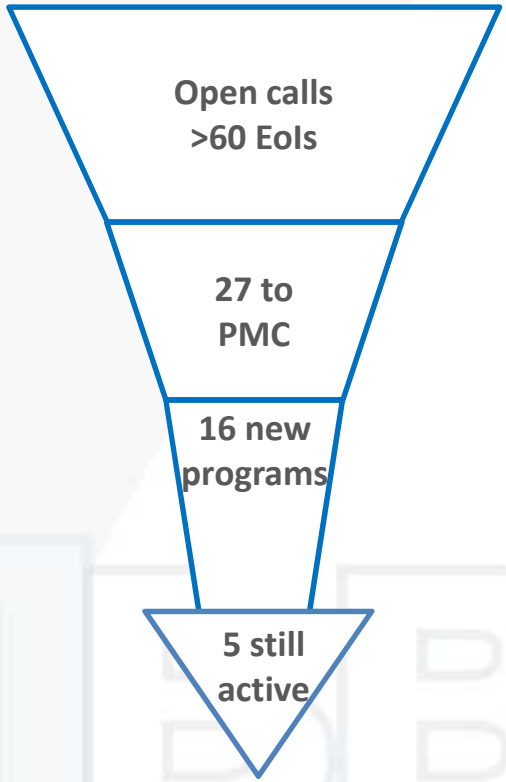
ENABLE: The feeding and funding cycle



* 12 members (4 EFPIA, 4 ENABLE Public and 4 independant experts) making decisions

ENABLE: The Open Calls

- ENABLE operates a continuous Open Call system to fuel ENABLE portfolio
- All European SMEs and academics welcome !
  - systematic survey and contacts with EU-based SMEs attracted many EoIs
- Initial application to Open Call via EoIs
  - 2-3 pages, non-confidential
  - needs to meet **minimum criteria**
  - rapid turnaround of ENABLE response and feedback on science, presentation, etc.
  - application and feedback remains confidential
  - some gaps may be filled by ENABLE (MTA process)
- Long startup phase (up to 6 months from EoI to start)
  - striving to improve



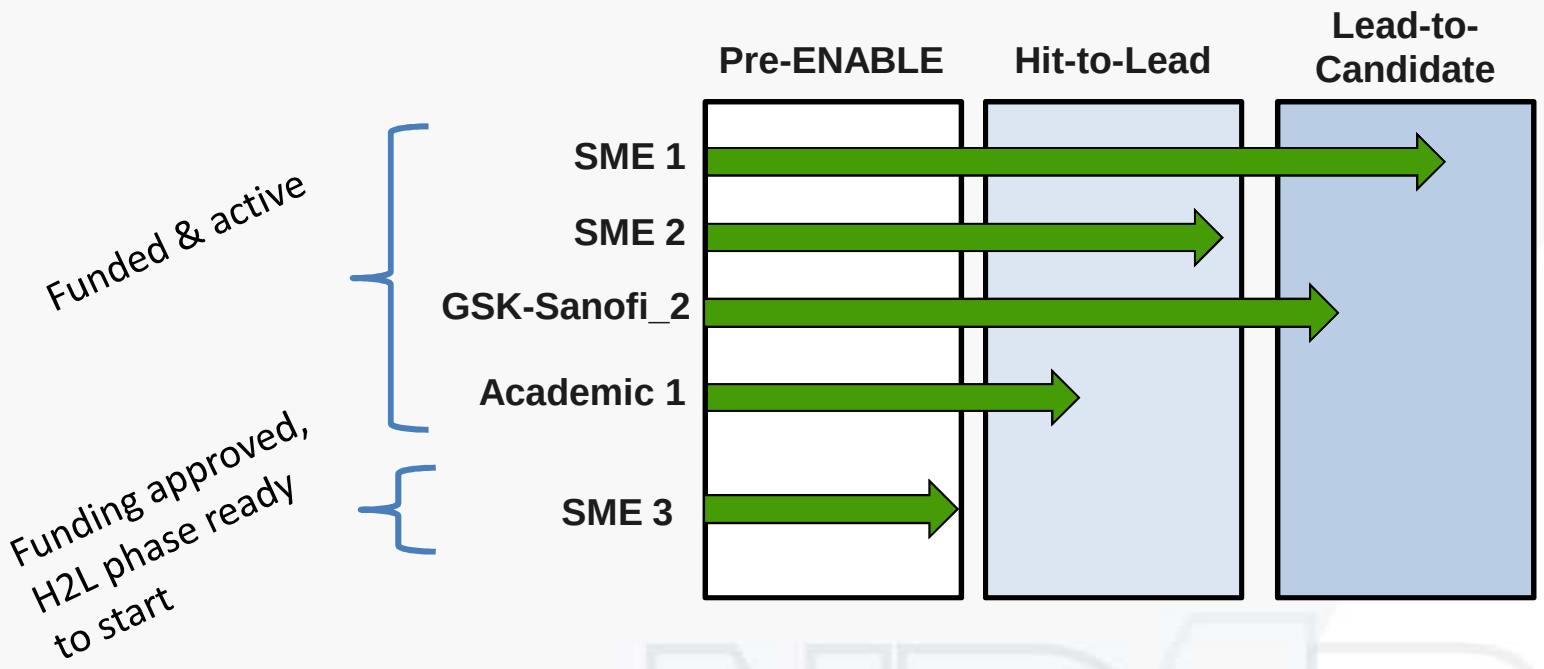
ENABLE: The criteria at time of submission

- Molecules/series with a novel mode of action targeting key Gram-negative
  - direct antibacterial effect or potentiation effect (eg beta-lactamase inhibitors) possible
  - known mechanisms possible provided activity against resistant strains
- MIC ≤ 32 µg/ml vs. at least one of the target Gram-negative pathogens
  - *E. coli, K. pneumoniae, P. aeruginosa* and *A. baumannii*
- Specific antibacterial activities
  - No or limited cytotoxicity and unspecific membrane perturbation not accepted (eg usual Antimicrobial peptides)
- Potential for optimization
  - proven chemical structure and preliminary SAR
  - reasonable route of synthesis (or availability if Natural Product-derived)
  - favorable chemical properties (eg phys-chem properties amenable to iv route)

ENABLE: Achievements since launch

- Consortium mechanics fully operational
  - governance bodies, project teams, discovery platforms, yearly F2F meetings …
- True collaborative spirit mixing different cultures/mindset emerged
- Rigorous management of the portfolio resulting in a robust and continually evolving pipeline
  - 16 programs funded since start and 5 still active (one to become active shortly)
  - 10 programs discontinued over ~2.5 years
  - 1 program transitioned from Hit-to-Lead to Lead-to-Candidate phase
- Open Call process developed and optimized
- Building links with TRANSLOCATION to utilize tools
- Dissemination
  - co-organizing Frontiers in Antibacterial Drug Discovery (FiADD) conference in Stockholm in Sept 2016
  - several communications in various Events and a few publications (more coming)

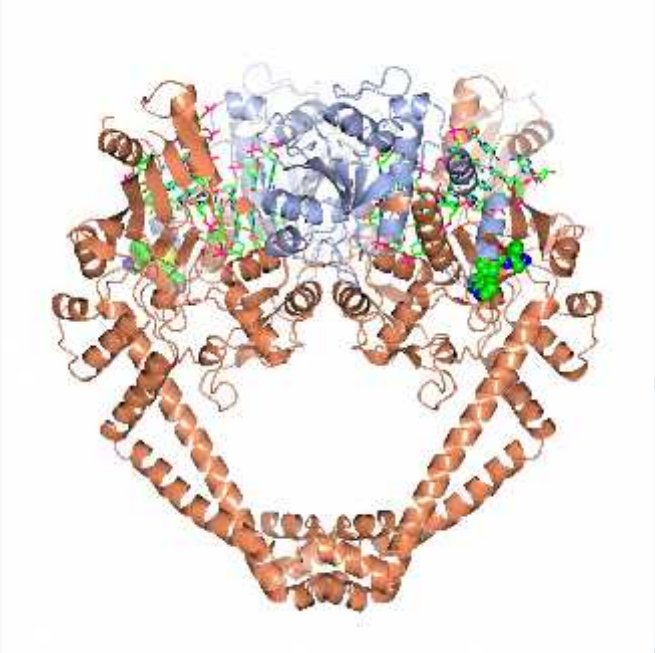
ENABLE Portfolio as of January 2017



- Research efforts are focused on the best bets

ENABLE: Case study (1)

- **GSK/Sanofi topoisomerase inhibitors**
  - GSK and Sanofi pooled their early discovery topoisomerase programs
  - unable to find an acceptable path forward for any series
  - good illustration of the difficulties to optimize a novel anti-Gram-negative scaffold



Series and novel mechanism of action discovered at GSK

Optimized in collaboration with Sanofi and ENABLE partners

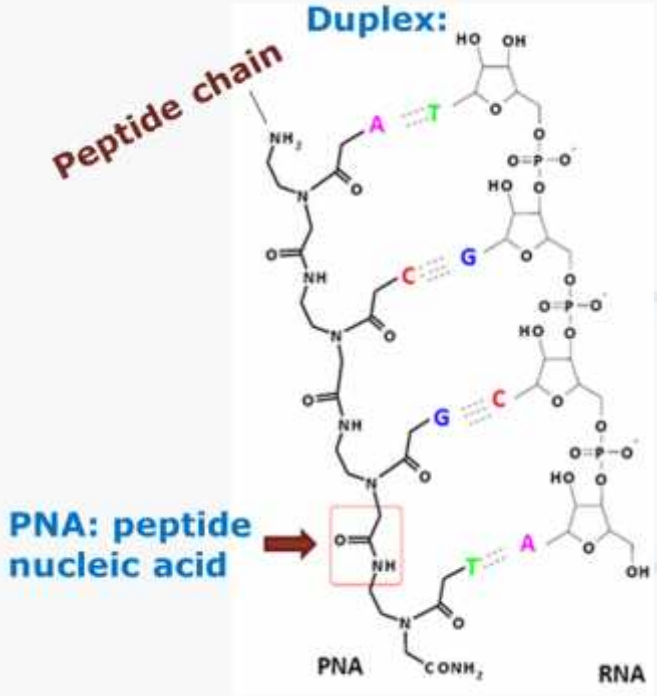
Extensive biochemistry studies in ENABLE

First manuscript submitted

Unprecedented binding mode to DNA-gyrase confirmed with GSK crystallography platform

ENABLE: Case study (2)

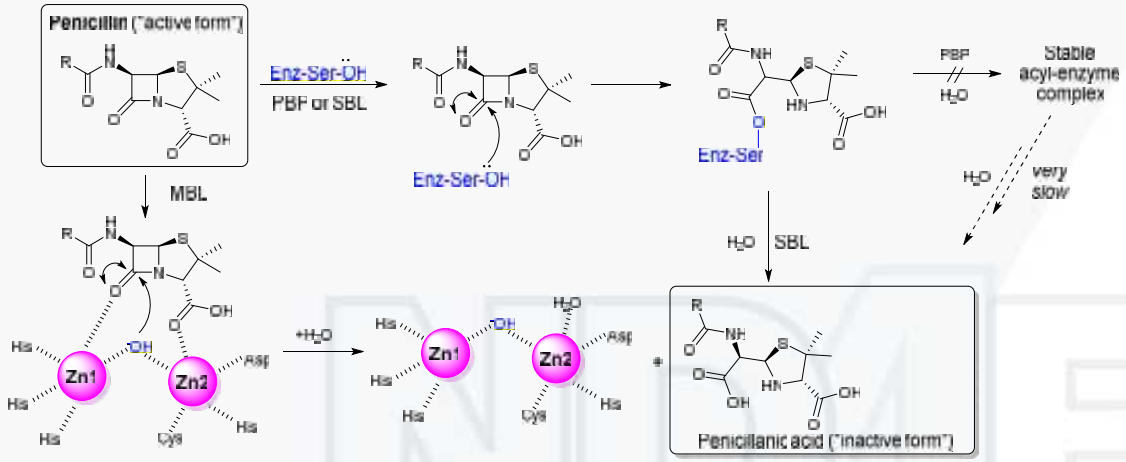
- **University Copenhagen PNA-peptides**
  - Peptide Nucleic Acids (PNAs) can silence essential bacterial target genes
  - conjugation to bacteria-penetrating peptides (BPP) allows delivery of the PNA into Gram-negative bacteria
  - collaboration through ENABLE validated approach but also quickly highlighted liabilities with series



MIC (µg/ml)	Bacteria-penetrating Peptide (BPP)	BPP-matched-PNA	BPP-mis-matched -PNA
E.coli	>64	8	>64
K. pneumoniae	>64	2-4	>64

ENABLE: Case study (3)

- **Oxford metallo-β-lactamase inhibitors**
  - the goal is to identify a first-in-class metallo-beta-lactamase inhibitor able to extend the utility of β-lactam antibiotics (especially carbapenems) active against Gram-negative bacteria
  - program arise from work in another IMI project (European Lead Factory)



Outline mode of action of: PBPs - penicillin binding proteins the targets of β-lactam antibiotics, SBLs and MBLs - serine and metallo-β-lactamases that target the β-lactam antibiotics.

Conclusions (1)

- No single individual/organization can succeed alone in finding rapidly new antibiotics active on resistant Gram-negative bacteria !

- The European consortium ENABLE is an attempt to address this challenge
  - part of the IMI ND4BB initiative
  - relying on a large public-private partnership

- ENABLE combines the skills and expertise from public and private sectors
  - to create a fully integrated antibacterial drug discovery platform
  - to allow experts of the antibacterial field to work synergistically together
  - to educate the next generation of antibacterial drug discovery experts
  - to recruit and help progress the best antibacterial programmes from across Europe

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Web info: www.nd4bb-enable.org

Conclusions (2)

- ENABLE offers great opportunities to Program Owners
  - favourable IP frame, activities largely financed by IMI, motivated partners and benefiting from assays and expertise
- At mid-course, ENABLE is on track to fulfil its objectives
  - 1 lead identified and 1 about to make it (out of 3)
  - first pre-candidate(s) may be identified by end 2017 (out of 2 Development Candidates)
- ENABLE may act as a model for collaborative drug discovery initiatives in other disease areas
- If you are an SME or an academic lab with a promising anti-Gram-negative program, you are invited to apply to ENABLE !

Email: eric.bacque@sanofi.com
Web info: www.nd4bb-enable.org

Acknowledgment

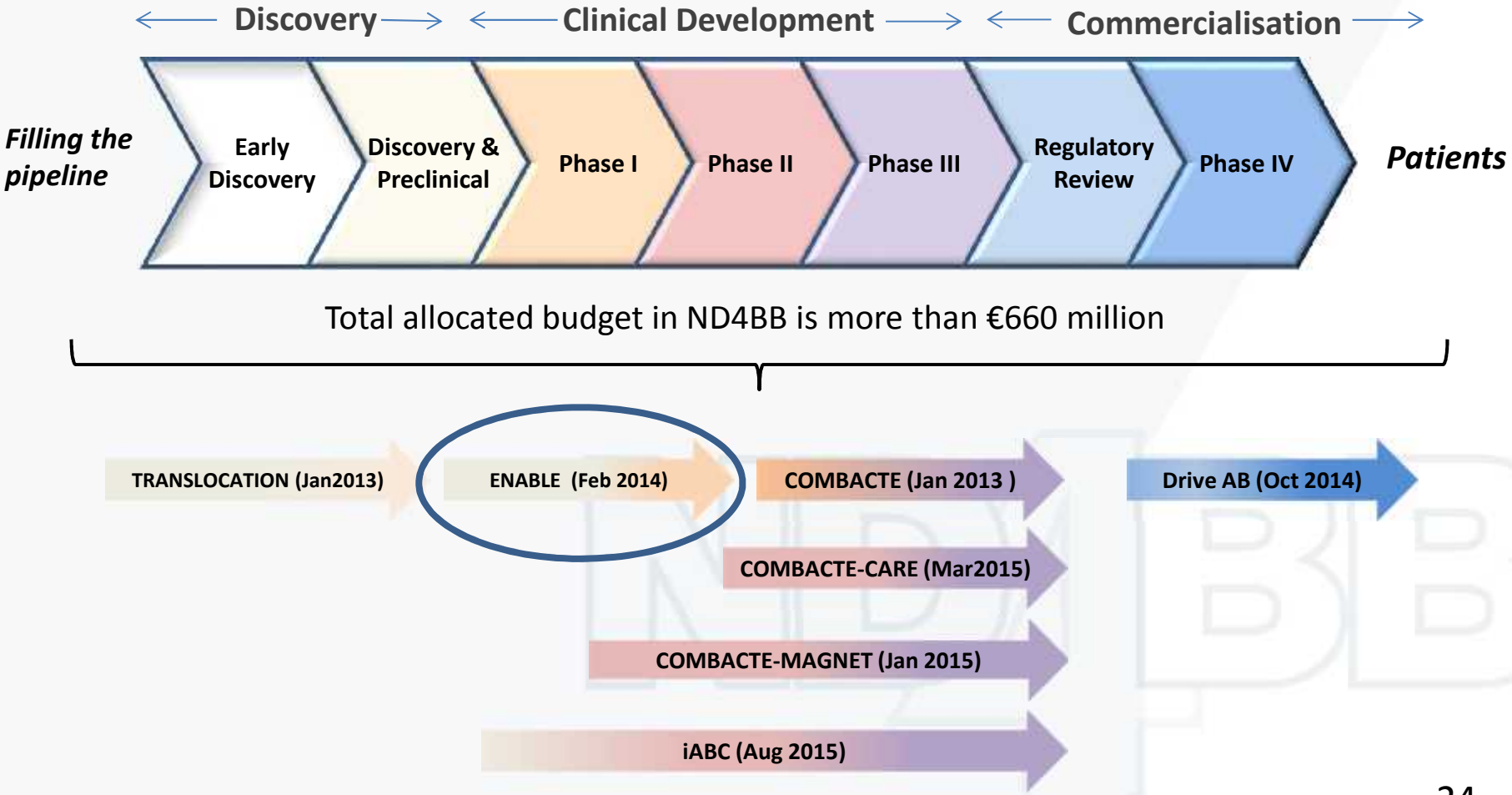
- **CMO members**
  - **UU:** Anders Karlen (Public Head), Diarmaid Hughes (PMC member), Anna Lobell and Cecilia Nilsson
  - **GSK:** Robert Stavenger (EFPIA Head) and Karen Philpot (Alliance Manager)
  - **Other:** Frederik Deroose (Asclepia; PMC member), Claire Skentelbery (European Biotechnology)and Natalia Murillo (Sanofi)

- **Current PMC members**
  - **Independent experts:** Tanjore Balganesh (India), David Pompliano (US), Gerry Wright (Canada) and Malcolm Page (Switzerland)
  - **Public:** Diarmaid Hughes (UU), Frederik Deroose (Asclepia), Pawel Baranczewski (UU) and Tim Walsh (CU)
  - **EFPIA:** Laurenz Kellenberger (Basilea), Laurent Fraisse (Sanofi) and Steve Baker (GSK)

- **and the many other partners that contribute to the daily life of ENABLE !**

Back-ups

ND4BB vision: Delivering a pipeline of new antibiotics to patients via PPPs



ENABLE: PMC mechanics

PMC background

- 12 voting members (see right)
- Meets quarterly by VTC to manage ENABLE pipeline
- Responsible for reviewing new and ongoing programmes
- Deciding body for approval and termination decisions (2/3+ majority)

PMC process

- Meets quarterly by VTC
- All active programmes reviewed + 0-3 new proposals
- Short presentation follow by Q&A
- Closed discussion to finalize decisions
- Written feedback provided to all teams

PMC members

ENABLE partners: EFPIA

Laurenz Kellenberger	(Basilea)
vacant	(AZ / Entasis)
Laurent Fraisse	(Sanofi)
Steve Baker	(GSK)

ENABLE partners: Public

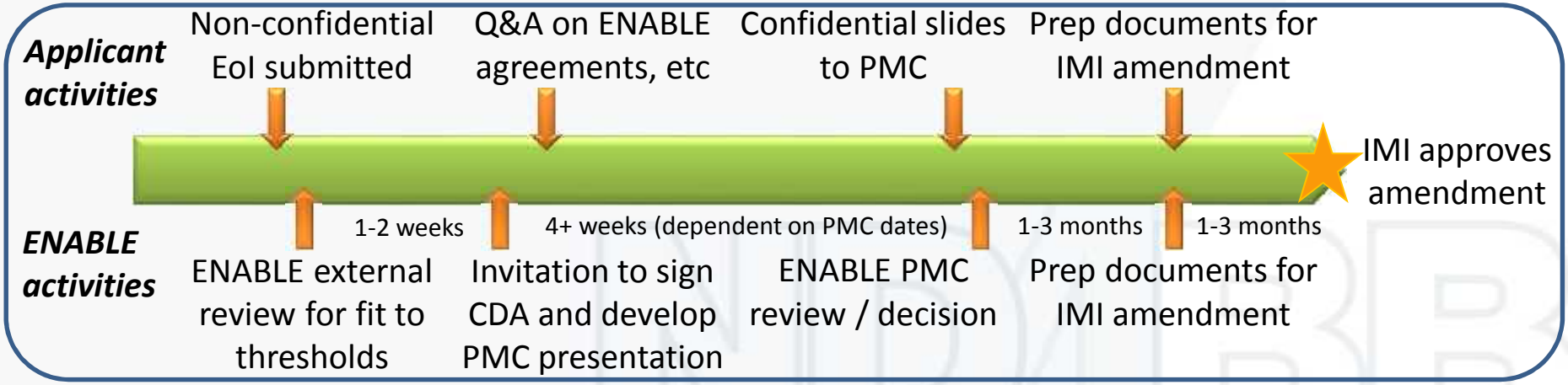
Diarmaid Hughes	(UU)
Frederik Deroose	(Asclepia)
Pawel Baranczewski	(UU)
Tim Walsh	(CU)

Independent experts

Tanjore Balganesh	India
David Pompliano	US
Gerry Wright	Canada
Malcolm Page	Switzerland

ENABLE Open Call process for new programmes

- No deadline; EoIs evaluated upon receipt
- Responsiveness of applicant is a must to maintain momentum
- Small issues can lead to long delays in IMI amendment process



More information on ENABLE website http://www.nd4bb-enable.eu/open-calls

ENABLE: Ongoing challenges

- Currently only open to EU groups

- Focused on ‘traditional approach’ (inhibition of essential targets)
  - same old targets & problems
  - despite misunderstanding, potentiation approaches (membrane disrupters, BLIs, etc) have also always been in scope

- Long startup phase (6 months from EoI to start), always looking for ways to improve this

- Formal amendment prior to new partner starting work
- ENABLE looking internally to simplify processes as well