# New Drugs For The Bad Bugs – Introducing IMI-project ENABLE

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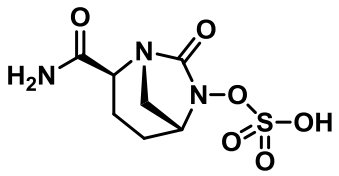
# Outline

- Antibiotics on the pipeline and market
- Introducing IMI and ENABLE
- Polymyxin programme with Northern Antibiotics
- IMI open call criteria
- Conclusions

# Antibacterial drugs to the market during last five years

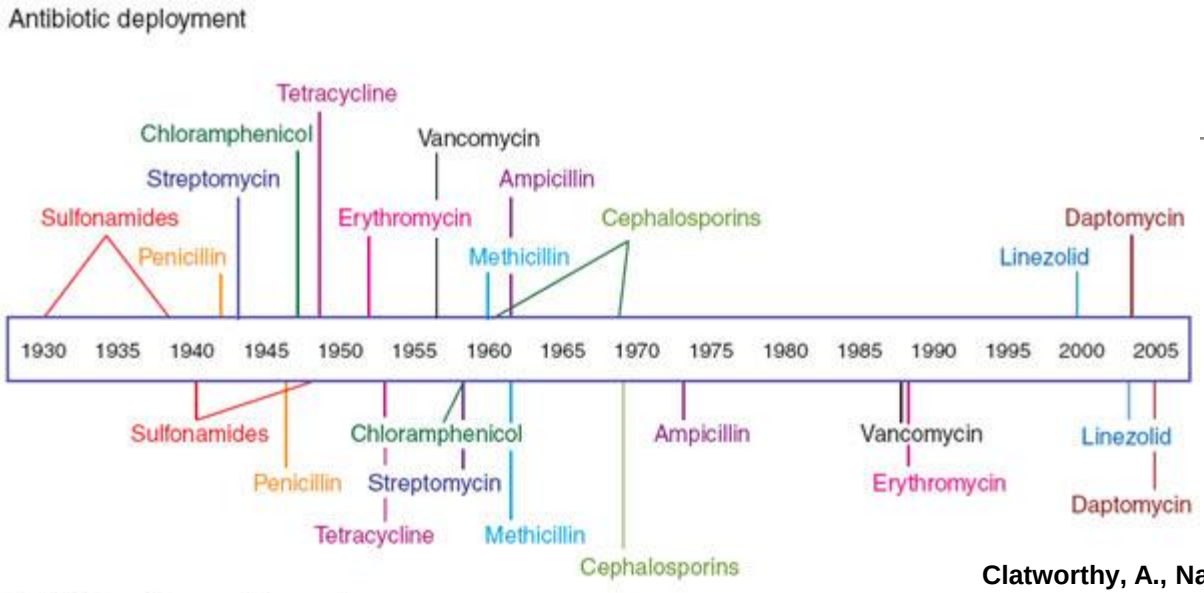


| Year | Drug | Effect | Group | Origin | Organism |
|---|---|---|---|---|---|
| 2011 | Fidaxomycin | G+ (*C. difficile*) | Macrocycle | Natural product | Actinomyces |
| 2012 | Bedaquiline | Tuberculosis | Diarylquinoline | Synthetic | - |
| 2013 | Telavancin | G+ | Lipoglycopeptide, | NP derivative | Actinomyces |
| 2014 | Tedizolid | G+ (MRSA skin) | Oxazolidinone | Synthetic | - |
| | Delamanide | Tuberculosis | Nitroimidazole | Synthetic | - |
| | Dalbavancin | G+ (MRSA skin) | Lipoglycopeptide | NP derivative | Actinomyces |
| | Oritavancin | G+ (MRSA skin) | Lipoglycopeptide | NP derivative | Actinomyces |
| | Finafloxacin | G+/G- | Fluoroquinolone | Synthetic | - |
| | Ceftolozane/ Tazobactam | G+ /G- | Cephalosporine- ß-lactam inhibitor | NP derivative | Fungus |
| 2015 | Ceftazidime/ Avibactam | G- (G+) | Cephalosporine/ non-ß-lactam ß-lactam inhibitor | NP derivative/ synthetic | Fungus |

# Examples of compounds in Phase III clinical trials

| Compound | Group | Target | Bacterium |
|---|---|---|---|
| Omadacycline | Tetracycline | Protein synthesis | G+/G- |
| Eravacycline | Tetracycline | Protein synthesis | G+/G- |
| Solithromycin | Erythromycin | Protein synthesis | G+/G- |
| Surotomycin | Lipopeptide | Cell wall depolarization | G+ |
| Perclozone | Thiosemicarbazone | Unknown | TB |
| SQ109 | Ethambutol | Cell wall synthesis | TB |
| Delafloxacin | Fluoroquinolone | DNA-gyrase and topoIV | G+/G- |
| Avarofloxacin | Fluoroquinolone | DNA-gyrase and topoIV | G+/G- |
| Zabofloxacin | Fluoroquinolone | DNA-gyrase and topoIV | G+/G- |
| Nemonoxacin | Quinolone | DNA-gyrase and topoIV | G+/G- |
| Ozenoxacin | Quinolone | DNA-gyrase and topoIV | G+ |

# Why there is so few novel antibiotics?




Clatworthy, A., Nature Chem Biol, 2007

**Resistance**

**Novel targets needed**

**Novel structures difficult to find**
**Non-drug like molecules, e.g. large MW**

| | % compounds reaching marketing authorisation |
|---|---|
| Phase I | 6,25 |
| Phase II | 25 |
| Phase III | 50 |
| Pre-Registration | 75 |

# Introducing IMI

## Innovative Medicines Initiative

**EU and EFPIA**

IMI2 Budget €3.3 billion

**2014-2024**.

**Pharma Industry**

**Universities**

**SMEs**

**Patient organisations, Medicines regulators**

**Over 50 projects**

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EFPIA (European Federation of Pharmaceutical Industry)

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# IMI: ND4BB
# New Drugs for Bad Bugs

- **ENABLE - a drug-discovery platform for antibiotics**

- TRANSLOCATION – getting drugs into bugs (and keeping them there)
- COMBACTE – creating a pan-European network of clinical sites
- COMBACTE-CARE - taking on the most dangerous resistant bacteria
- COMBACT-MAGNET - help on healthcare-associated infections
- iABC - new treatments to help cystic fibrosis patients
- DRIVE-AB - new economic models for antibiotic development

**http://www.imi.europa.eu/content/nd4bb**

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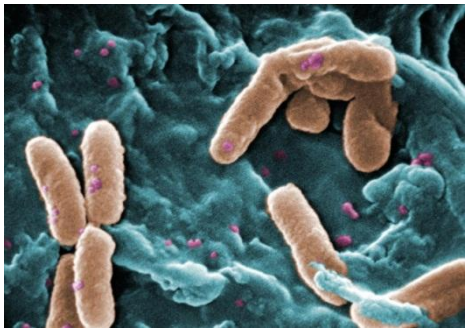
# ENABLE 2014-2020

**European Gram Negative Antibacterial Engine**

## Goals

- Create a collaborative drug discovery platform
- Increase the overall pipeline in the antibacterial area



*Pseudomonas aeruginosa*

## Objectives

Target the systemic treatment of infections due to resistant Gram-negative bacterial pathogens *E. coli, K. pneumoniae, P. aeruginosa and A. baumannii*

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http://nd4bb-enable.eu/

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# ENABLE 2014-2020

**European Gram Negative Antibacterial Engine**

## Project deliverables by 2020:

- Identifying three antibacterial **leads**
- Identifying two antibacterial development **candidates** for preclinical testing
- Progressing at least one compound into **Phase 1 clinical studies**

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# Co-ordination

## Project coordinator

- Robert Stavenger, GlaxoSmithKline Research and Development Ltd

## Managing entity

- Prof. Anders Karlén, Uppsala University, Sweden

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# Consortium

## EFPIA project partners

**GlaxoSmithKline Research and Development Ltd**

**Sanofi-Aventis Research and Development**

**Basilea Pharmaceutica AG**

## SME project partners

- **Asclepia Outsourcing Solutions BVBA, Belgium**
- **Beactica AB, Uppsala, Sweden**
- **Biomol-Informatics SL, Madrid, Spain**
- **Inspiralis Ltd, Norwich, UK**
- **KeytoLead AB, Sodertalje, Sweden**
- **Molecular Discovery Ltd, London, UK**
- **Northern Antibiotics Oy Ltd, Helsinki, Finland**
- **OT Chemistry, Uppsala, Sweden**
- **Redx Pharma Ltd, Manchester, UK**

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# Consortium

## Research organisation, university and non-profit organisation partners

- Agencia Estatal Consejo Superior de Investigaciones Cientificas, Madrid, Spain
- Aston University, UK
- Cardiff University, UK
- European Biotechnology Network AISBL, Belgium
- Fundación Centro de Excelencia en Investigación de Medicamentos Innovadores en Andalucía Medina, Armilla Granada, Spain
- Hvidovre Hospital, Hvidovre, Denmark
- John Innes Centre, Norwich, UK
- Københavns Universitet, Copenhagen, Denmark
- Latvijas Organiskas Sintezes Instituts, Riga, Latvia
- National Medicines Institute (Narodowy Instytut Lekow), Warsaw, Poland
- Servicio Madrileno De Salud, Madrid, Spain
- SP Process Development, Södertälje, Sweden
- Stichting VU-VUMC , Amsterdam, Netherlands
- University of Oxford, UK
- Universitat de Barcelona, Spain
- University of Helsinki, Helsinki, Finland
- University of Liege, Belgium
- Uppsala University, Sweden

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# Project Concept

## ENABLE

**Additional public programmes from open calls**

**EFPIA: expertise & advice**

**Drug Discovery Platform**
Medicinal chemistry, Microbiology, ADME etc.

**Consortium Management Office**

**Programmes with novel mechanisms**

Portfolio Management Committee makes evaluation quarterly

Hit-to-Lead

Lead-to-Candidate

Candidate-to-Phase 1

Phase 1 clinical trial

**Goal 4 Hit-to-Lead Programmes running in parallel**

**2 Lead-to-Candidate Programmes running in parallel**

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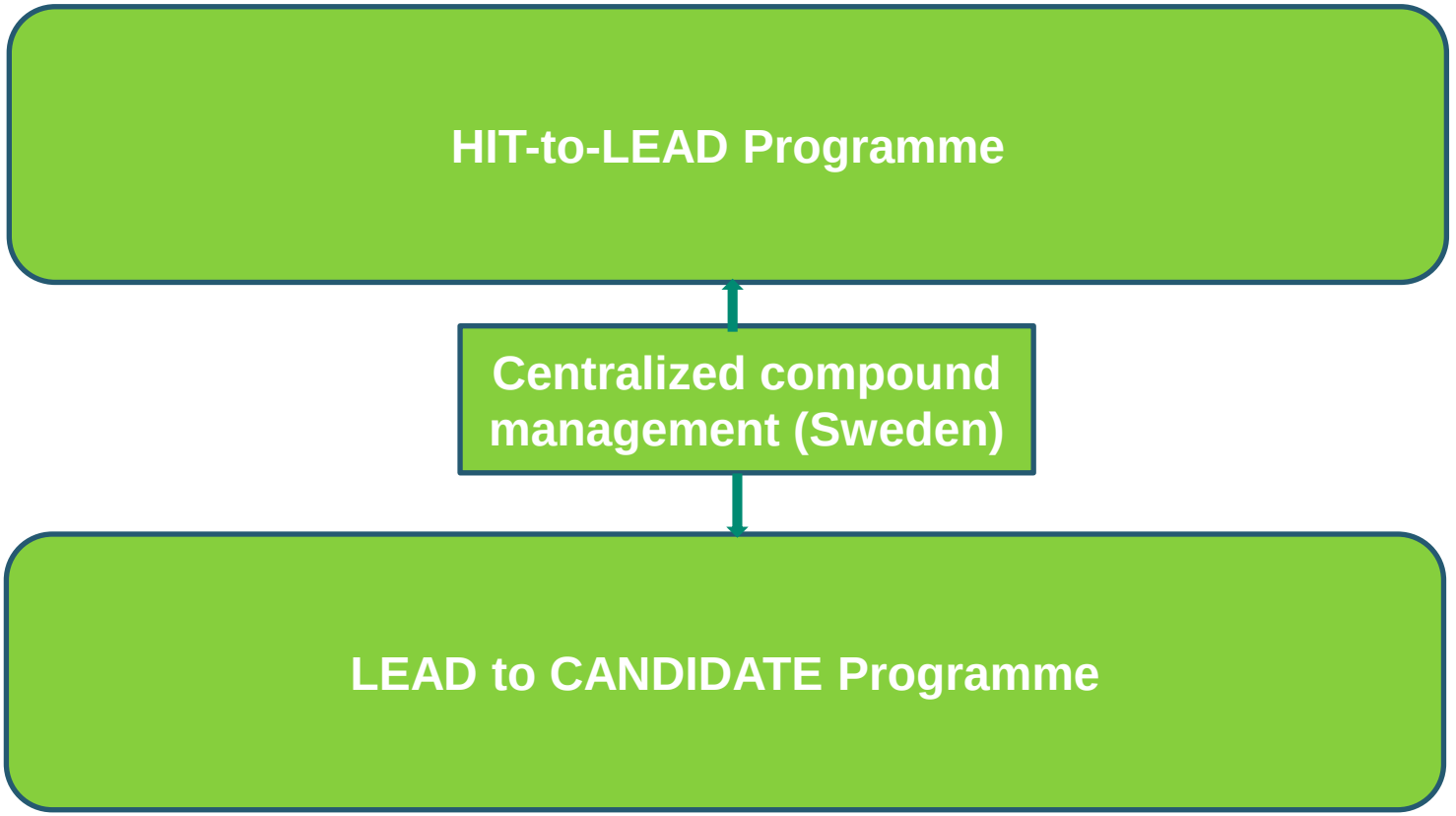
# ENABLE Drug Discovery Platform

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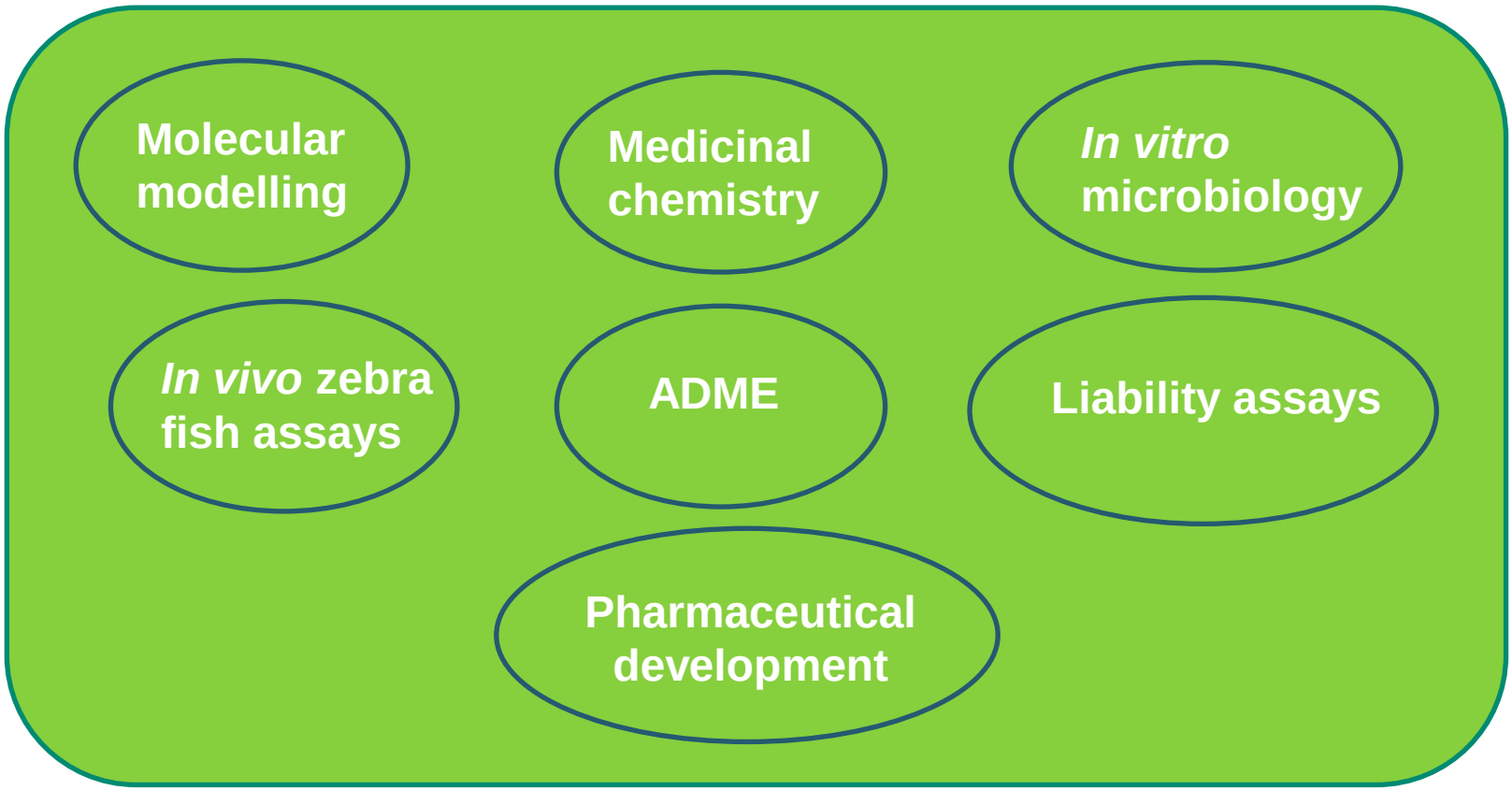
# ENABLE Drug Discovery Platform

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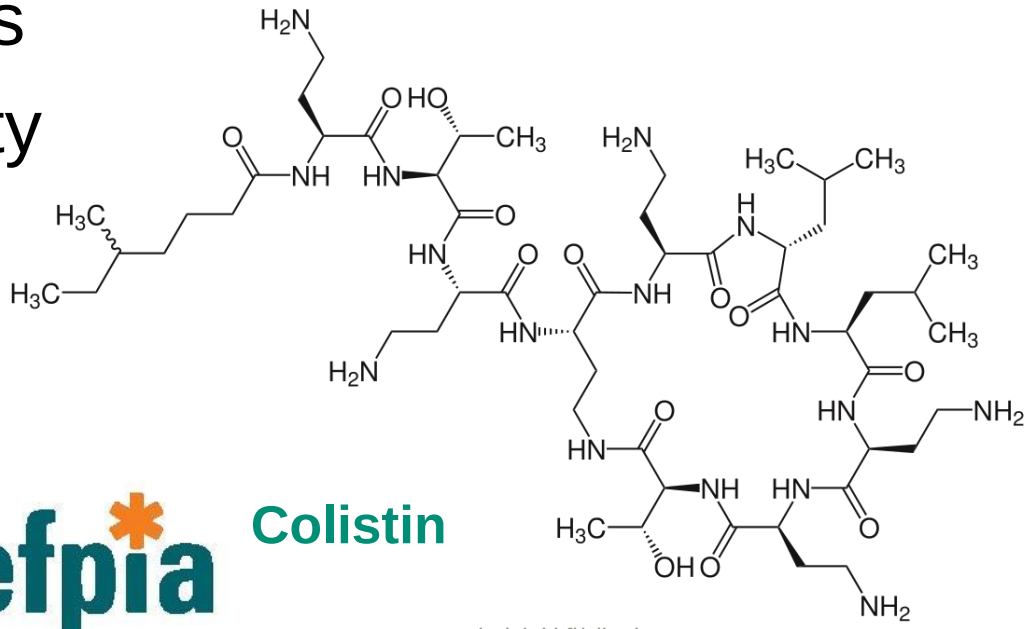
# Programmes

- Expressions of Interest (Eol) that ENABLE has received to date: **56** new and **3** resubmissions
- Programmes presented/approved at the PMC: **26/15**
- Current ongoing programmes: **3**
- Programmes approved by PMC and in the process of joining ENABLE: **6**
- Programs discontinued: **6**

# Last-Resort Antibiotic: Colistin (Polymyxin E)

- From 1949, *Paenibacillus polymyxa var. colistinus*
- Against multidrug-resistant *P. aeruginosa, K. pneumoniae*, and *A. baumannii*
- Belongs to polymyxins
- Problem nephrotoxicity



Colistin

# Last-Resort Antibiotic Colistin: Threat

- Resistance to colistin has been identified last year in the *E. coli* strain SHP45 in China and this spring in the USA
- Polymyxin resistance was shown to be due to the plasmid-mediated mcr-1 gene

Liu, Y-Y. *et al*. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. Lancet Infect Dis, **2015**

McCann, P. *et al*. *Escherichia coli* Harboring *mcr-1* and *bla*$_{CTX-M}$ on a Novel IncF Plasmid: First report of *mcr*-1 in the USA. Antimicrob Agents Chemother, **2016**

# Northern Antibiotics

- Finnish SME, founded 2003

## Portfolio

- Novel compounds that are highly active against difficult-to-treat Gram-negative bacteria such as multi-resistant *E. coli*, *K. pneumoniae*, other species of Enterobacteriaceae, and *A. baumannii*.
- Compounds that sensitize Gram-negative enteric bacteria and *Acinetobacter* by more than 100 times to the action of antibiotics usually used for the treatment of Gram-positive infections only.

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# Northern Antibiotics Polymyxin Programme

- Goal to get better alternative for colistin and polymyxin B
- Novel polymyxin derivative NAB739 is remarkably less cytotoxic
- Role of ENABLE is to provide e.g. *in vivo* efficacy and PK studies, microbiology with many strains
- Synthesis of new polymyxin analogs

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# ENABLE Open Calls:
# Hit-to-Lead project entry

- **MIC ≤32 µg/ml** *vs.* a key Gram-negative pathogen (*E. coli*, *K. pneumoniae*, *P. aeruginosa* and/or *A. baumannii*), with activity against resistant strains, if targeting a known mechanism
- Activity should not be due to detergent-like activity
- Proven chemical structure, preliminary SAR
- Favourable chemical properties and reasonable synthesis pathway
- Promising physchem parameters (e.g. **clogP<4**)

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# ENABLE Open Calls: Lead-to-Candidate project entry

- **MIC90 ≤16 µg/ml** *vs*. a key Gram-negative pathogen
- **MICs ≤64 µg/ml** *vs*. other key Gram-negative pathogens
- Experimentally determined target (or pathway) activity
- Acceptable frequency of resistance
- Time-kill analysis
- Sustainable antibacterial SAR
- Preliminary understanding of DMPK / *in vitro* pharmacology
- Tractable synthetic route with 2 modifiable positions

# Summary

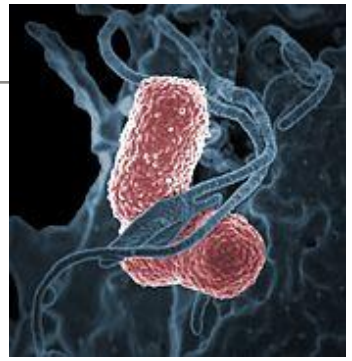

Photo: NIAID

- Developing a drug against Gram-negative bacteria is a great challenge
- ENABLE provides an efficient Drug Discovery Platform
- Polymyxins are a potential class of antibiotics
- If you have promising compounds, consider ENABLE open calls http://nd4bb-enable.eu/open-calls

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# Acknowledgements


- **University of Helsinki**

Prof. Jari Yli-Kauhaluoma, Division of Pharmaceutical Chemistry and Technology, Drug Discovery Unit, Faculty of Pharmacy

- **Northern Antibiotics Ltd, Finland**

Prof. Martti Vaara

Mr. Timo Vaara, M.Sc.


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