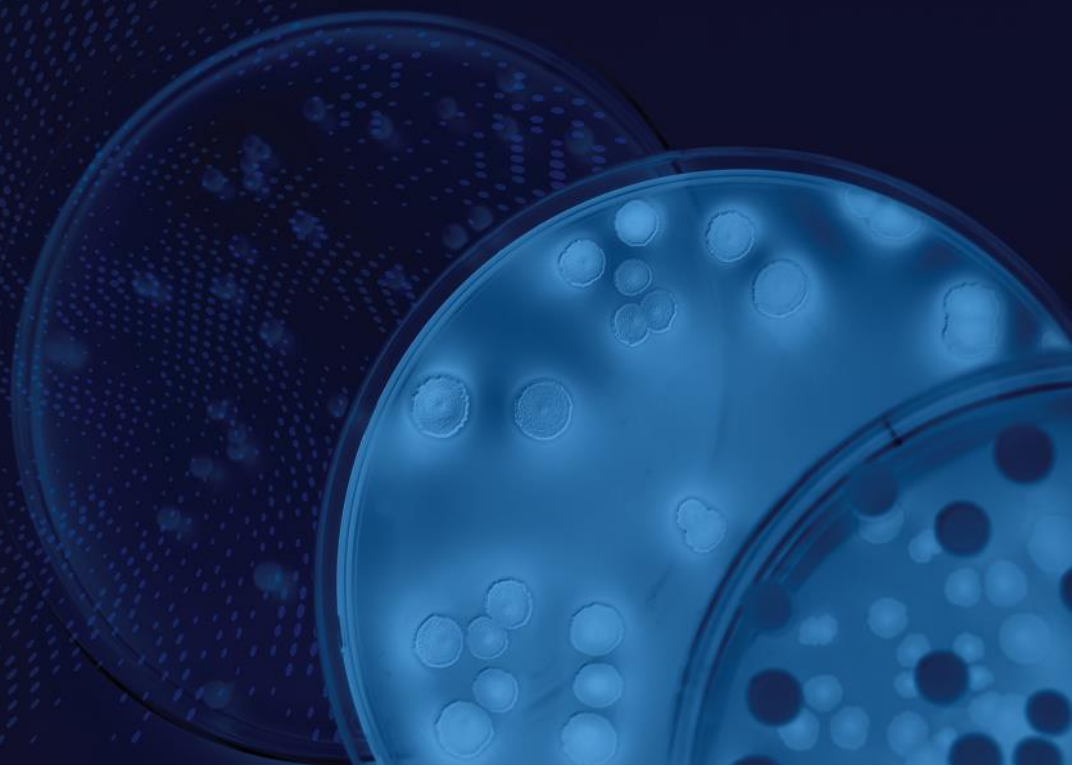
AGIR: Integrated project of discovery of new antibiotics from natural substances

ADEBIOTECH CAMPUS

18 Décembre 2018

Christophe PARSY

Emmanuel PETIOT



DEINOVE

DEINOVE develops innovative compounds based on rare and extremophile microorganisms

Company based in Montpellier, France

1500 m² of Lab facilities

260 patent applications

60 Highly-skilled Staff

Cutting-edge Technological platform

PHARMACEUTICALS

- Antibiotics
- Antifungals

Institut régional de recherche Charles Viollette

DEINOBIOTICS The deinococcus way to antibiotics

bpifrance

Scripps Research

NAICONS

BIOMÉRIEUX

morphochem

COSMETICS

- Phyt-N-Resist®
- Hebelys®
- Bacterial extracts

UNIVAR

SOLVAY

GREENTECH BIOTECHNOLOGIES

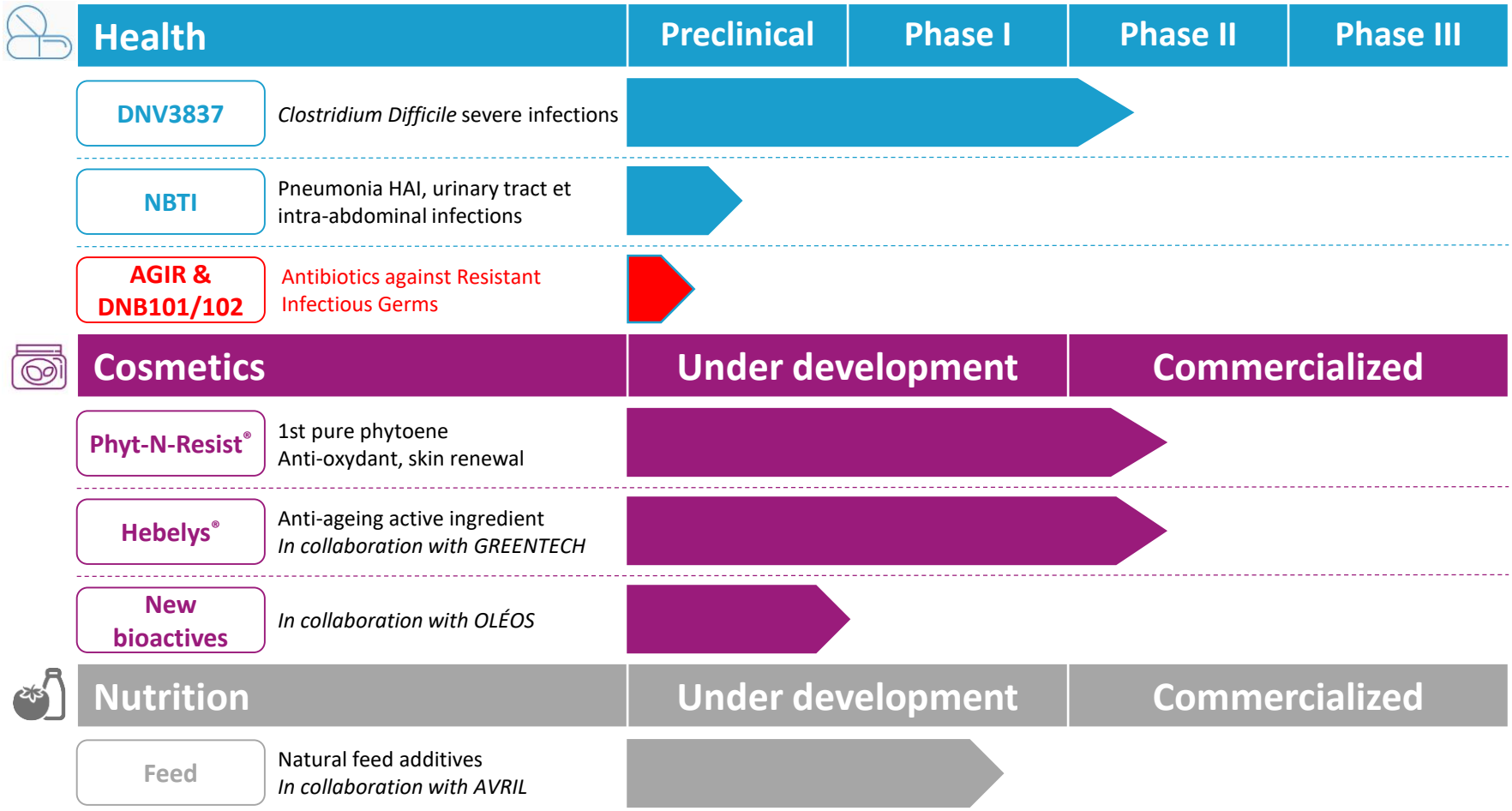
Oléos

NUTRITION

- Dietary supplements
  - Antioxidants
  - UV protection…
- Feed applications
  - Pigments
  - Additives

Avril

Pipeline overview



AGIR:

Alliance Public (ICV) – Private (Groupe Deinove)

Served by a state of the art biotech platform

To fight antimicrobial resistance

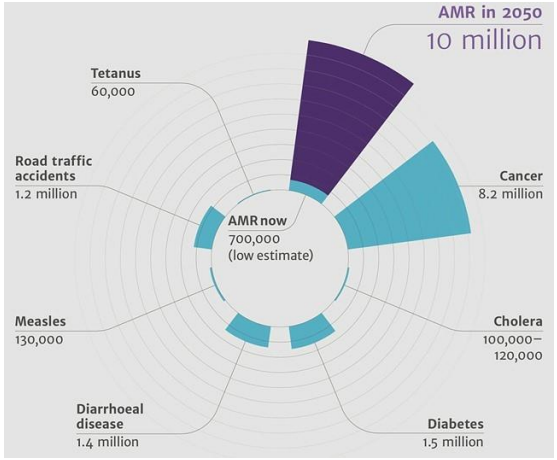
The challenge of antimicrobial resistance

An increasing threat

A GLOBAL HEALTH CHALLENGE

Antimicrobial resistance (AMR) could cause **10 million deaths/year** by 2050

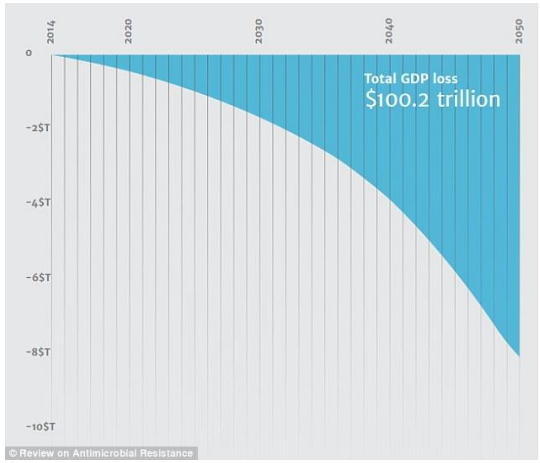
Today 700 000 deaths/year



A RISK FOR THE WORLD ECONOMY

A loss of economic output worth **100 trillion USD** between now and 2050

+healthcare costs +bring into question the ability to continue performing daily medical procedures (transplantations, chemotherapy...)



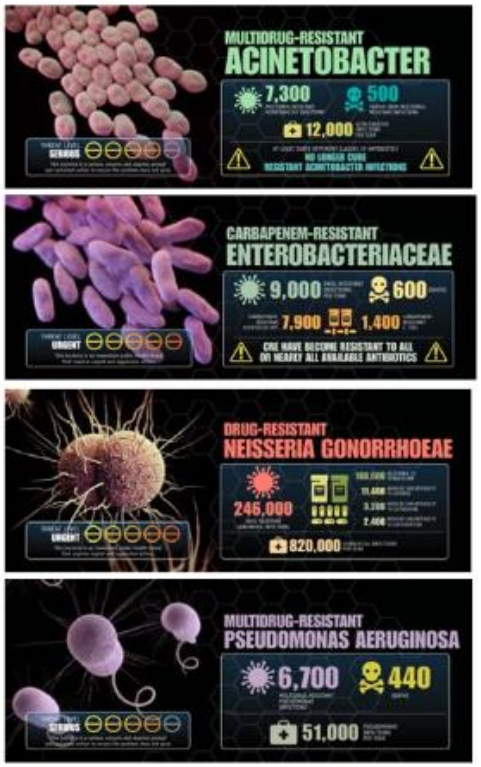
Source: Review on antimicrobial resistance

➤ **URGENT NEED TO FIND NOVEL ANTIBIOTIC STRUCTURES TO FIGHT RESISTANT PATHOGENS (ON THE CDC & WHO LIST)**

The challenge of antimicrobial resistance

Most wanted !

Bacteria (WHO category)	WHO (2017)	CDC (2013)	ESKAPE (2008-9)
Acinetobacter baumannii, carbapenem-R	Critical	Serious (MDR)	Yes
Pseudomonas aeruginosa, carbapenem-R	Critical	Serious (MDR)	Yes
Enterobacteriaceae, carbapenem-R, 3rd-gen ceph-R (ESBL+)	Critical	Urgent (carbapenem-R) Serious (ESBL+)	Yes
Enterococcus faecium, vancomycin-R	High	Serious (VRE)	Yes
Staphylococcus aureus, methicillin-R, vancomycin-I/R	High	Serious (MRSA) Concerning (VRSA)	Yes
Helicobacter pylori, clarithromycin-R	High		
Campylobacter spp., fluoroquinolone-R	High	Serious (drug-R)	
Salmonellae spp., fluoroquinolone-R	High	Serious (drug-R)	
Neisseria gonorrhoeae, 3rd-gen ceph-R, fluoroquinolone-R	High	Urgent (drug-R)	
Streptococcus pneumoniae, penicillin-NS	Medium	Serious (drug-R)	
Haemophilus influenzae, ampicillin-R	Medium		
Shigella spp., fluoroquinolone-R	Medium	Serious	
Clostridium difficile		Urgent	
Candida spp. fluconazole-R		Serious (Flu-R)	
M. tuberculosis		Serious (drug-R)	
Group A *Streptococcus*		Concerning (erythro-R)	
Group B *Streptococcus*		Concerning (clinda-R)	



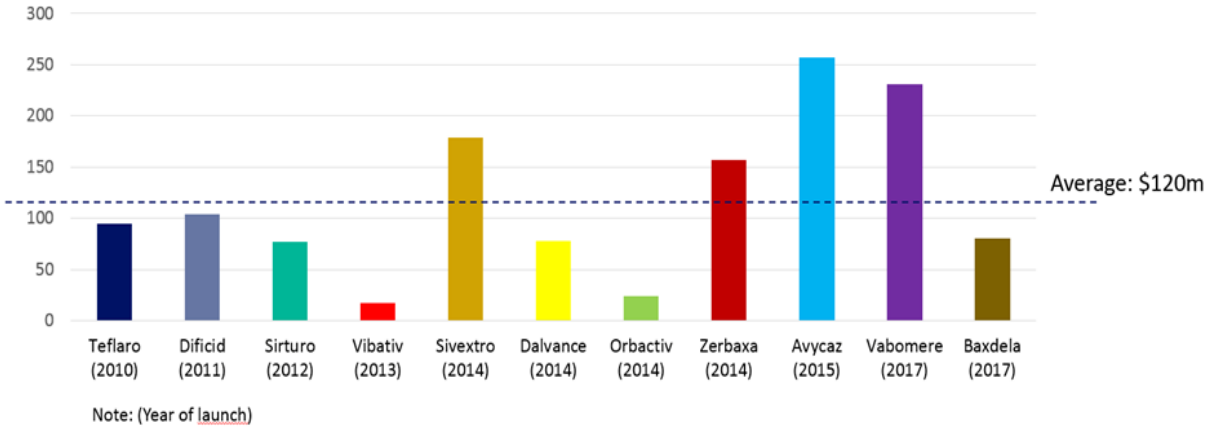
Source: WHO, CDC & ESKAPE

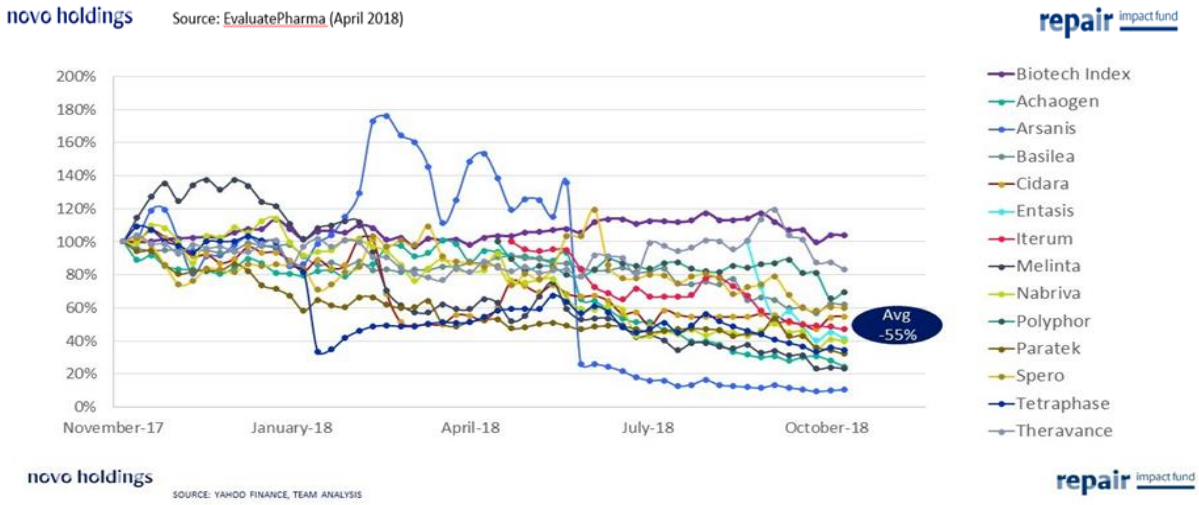
➢ Despite the unmet medical need arising from antimicrobial resistance...

…The current economic model is challenging

The Broken Antibiotics Business Model

The Broken Antibiotics Business Model Part 1-4, 2018, Aleks Engel, Partner, Novo Holdings (Novo Seeds)



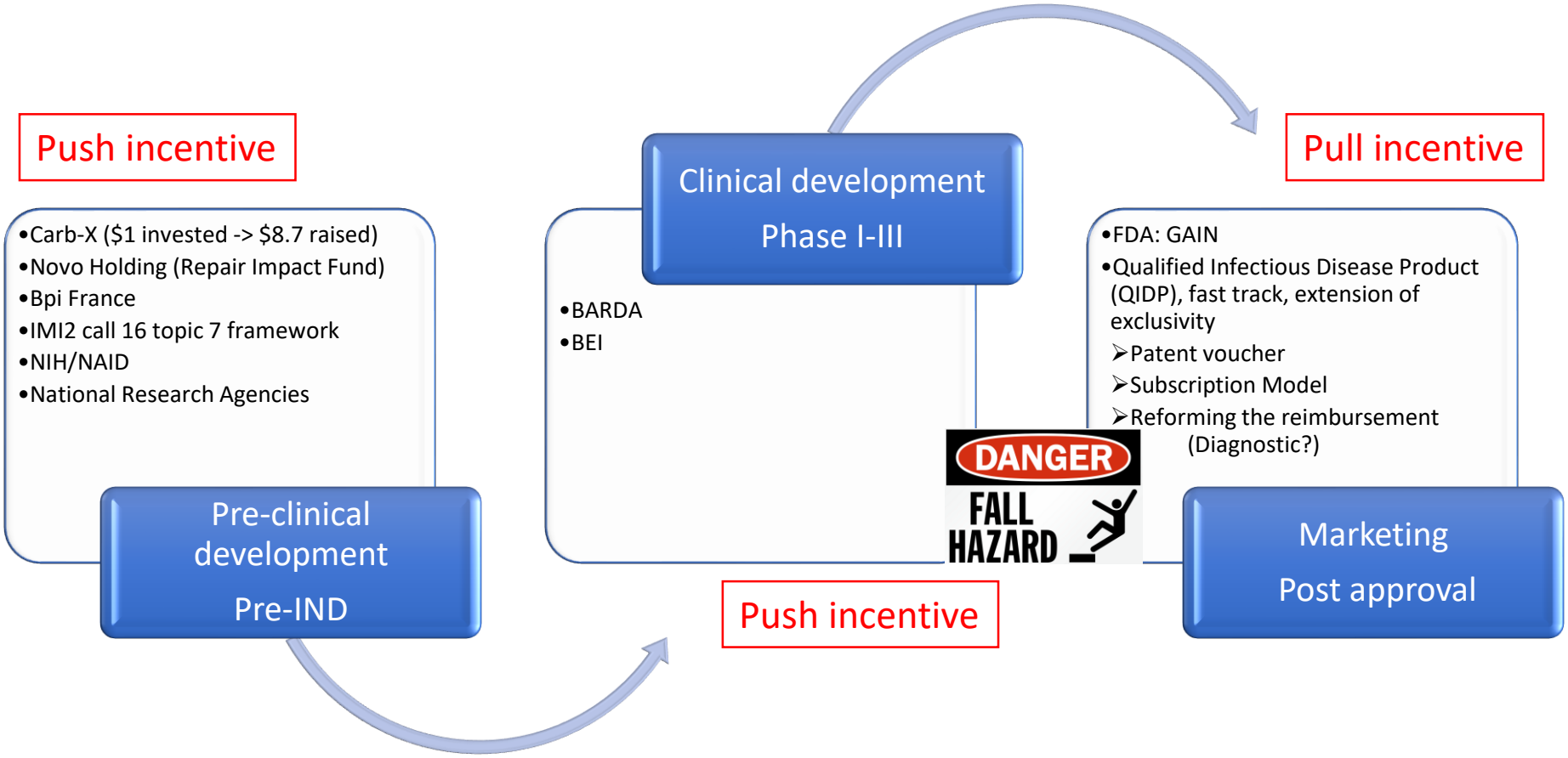


- Today's antibiotic resistance remains a niche market
- ROI is modest as compared to development costs
- Big players are leaving the field (AstraZeneca, The Medicines Company, Novartis, Sanofi)
- Mid size companies are struggling to bring novel drugs to the market: Achaogen (Zemdri), Melinta (Vabomere) and as a results are closing their R&D to focus on commercialization

The business model needs to evolve to brings new drugs to patients

Initiatives to boost novel antibacterial development

Tackling the problem by promoting discovery of new drugs and facilitating market access



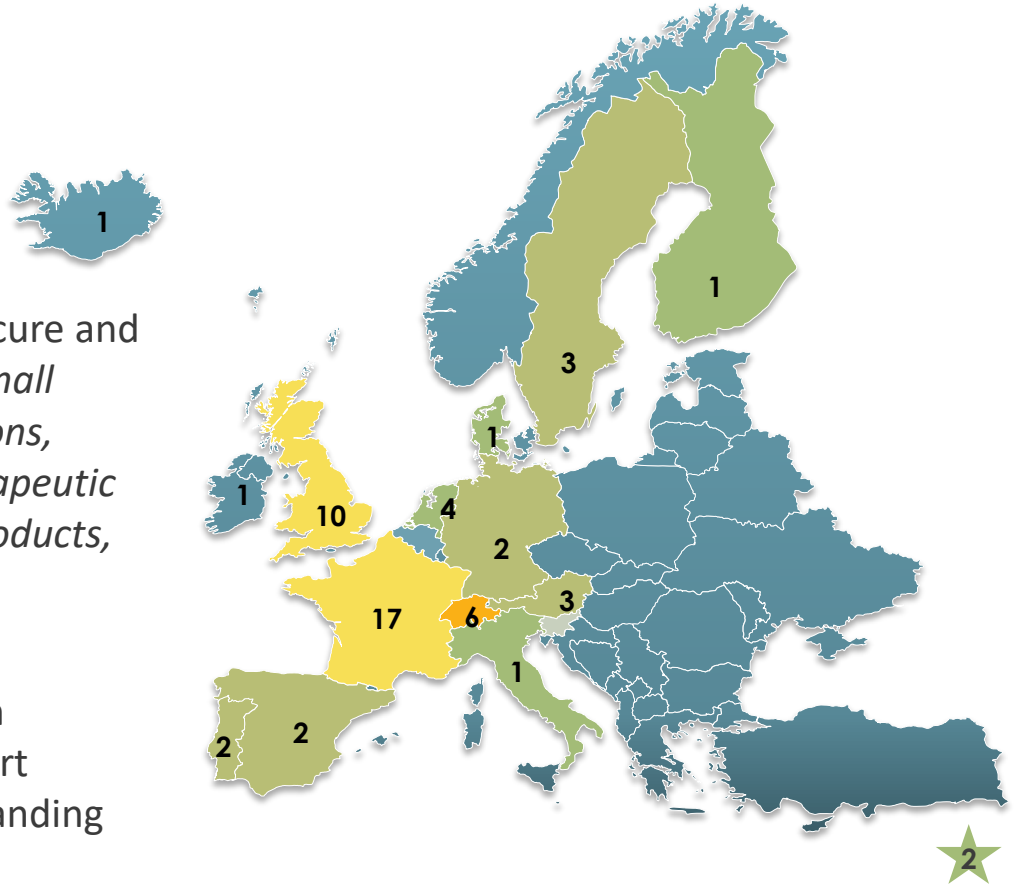
Early Discovery funding is being addressed with Push initiatives…

… the gap in on Phase II to marketing authorization

BEAM Alliance

Launched in 2015

- Association created in **2016**
- **56 European** biotech companies
- **120 new R&D projects** focused upon the cure and prevention of bacterial infections *(from small molecule antibiotics, antibiotic combinations, phages, antibodies, prophylactic and therapeutic vaccines, peptides, prebiotics, other bioproducts, adjunctive therapies, medical devices and diagnostics)*
- **Objective: raise awareness of SME-driven innovation** in the field of AMR, and support policymakers and stakeholders in understanding economic business models around AMR.



AGIR program supported by French government

« AGIR » **A**ntibiotiques contre les **G**ermes **I**nfectieux **R**ésistants

Identify new antibiotic structures from rare or unexploited bacterial strains , by developing new methods of collection, culture, screening, optimization and evaluation.

bpifrance DEINOVE The deinococcus way Institut Charles Viollette Université de Lille

PRESS RELEASE

12 SEPTEMBER 2017

The AGIR project carried out by the DEINOVE group is granted €14.6 million by the 'Investments for the Future' Program (IFP) operated by Bpifrance to develop new antibiotics.

INVESTISSEMENTS D'AVENIR

- The AGIR project will be financed to a level of €14.6 million, for a total budget estimated at €25 million.
- Grants making up almost half of the funding will be spread over the five-year program duration.

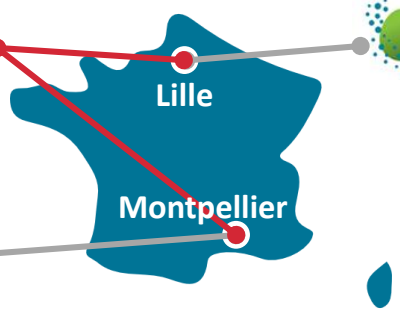
AGIR: 3 partners for a 5 years project

3 Partners

DEINOBIOTICS
The deinococcus way to antibiotics

DEINOVE

Institut régional de recherche Charles Viollette



60 month

T0
01/11/2017

Project AGIR

End
31/10/2022

5 key steps

Project AGIR

Bacteria

- **Development of a discovery platform**
- **Lead optimization of NP and process development**
- **Novel compounds with improved properties**

Antibiotics

Natural Products are back in the game !

Renewed interest using natural products

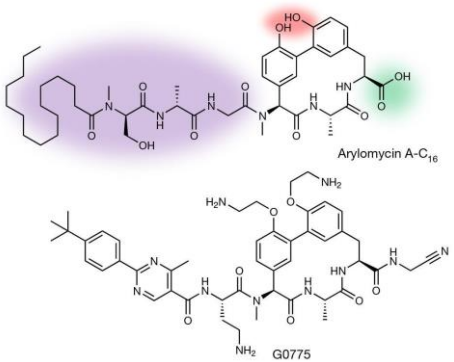
Natural Products remain the main source of :

- Novel Mode of Action
- Diversified chemical space

Natural Products approach is amenable to Hemi-synthesis or Biosynthesis optimization

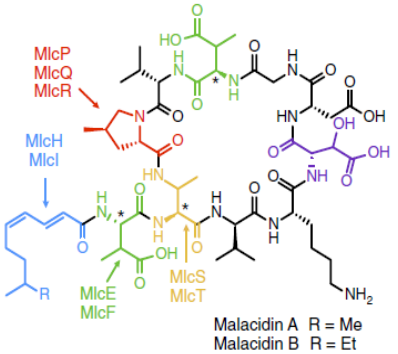
Optimized Arylomycins
Nature 561, pages 189–194 (2018)

Genentech
A Member of the Roche Group



Discovery of the Malacidins
Nature Microbiology, 3, pages 415–422 (2018)

LODO THERAPEUTICS

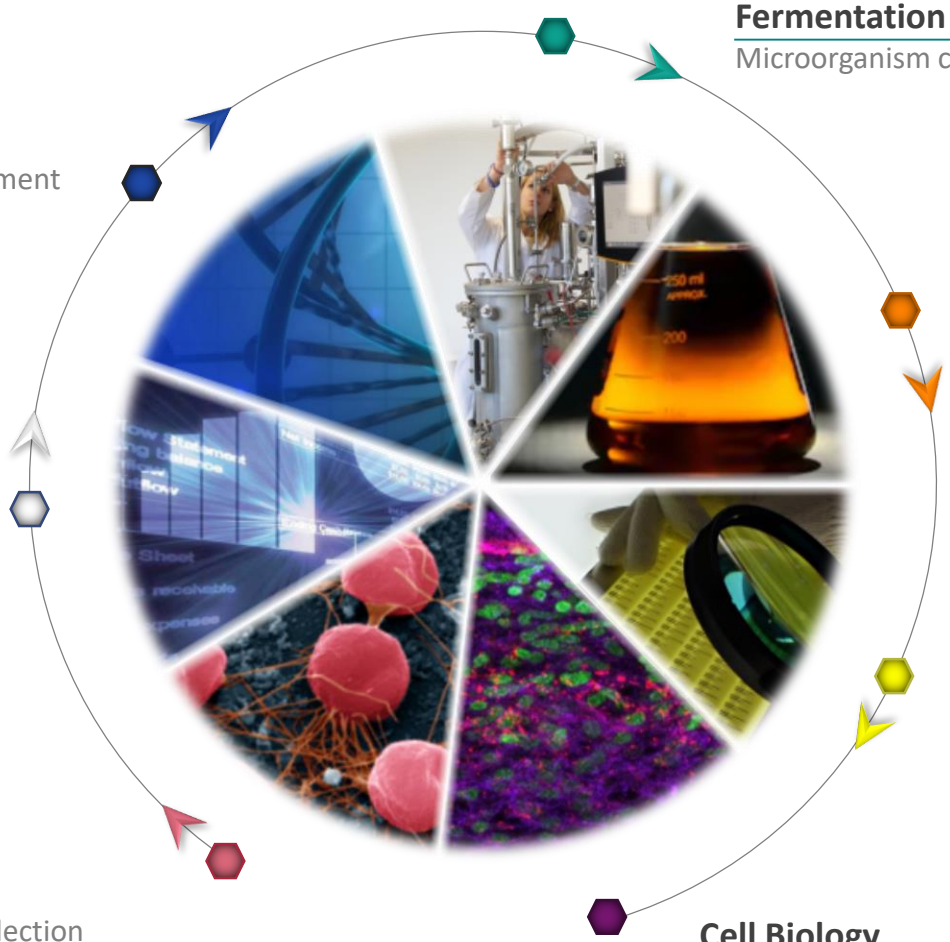


A collaborative high-tech platform

Joint effort between Deinove and ICV to discover novel antibiotics

Fermentation & Purification
Microorganism culture optimization

Molecular Biology
Next Generation Sequencing
Molecule production enhancement
Exploring uncultured bacteria



Medicinal Chemistry
From microorganism to Molecule
Hit2Lead (H2L) and Lead Optimization (LO) approach
Biosynthesis and Structure Activity Relationship (BSAR)

BioInformatics
Data collection and mining
Study of the genetic material
Identification and characterization of novel Biosynthetic Gene Clusters (BGC)

Analyses & Characterizations
Use AI tools on early dereplication
MS/NMR and Electron-Diffraction (Cryo-ED)

Banking
Environmental collection
Private or public Strains collection
Motivation of strains

Cell Biology
Functional activities testing
High content screening MIC & TLC-Bioautography

An integrated platform between Deinove and ICV

A state of the art biotech platform with the financial support of Bpifrance

Extraction of Culture

Extract Activity Characterization

Chemical extraction with solvent
Automated evaporation process

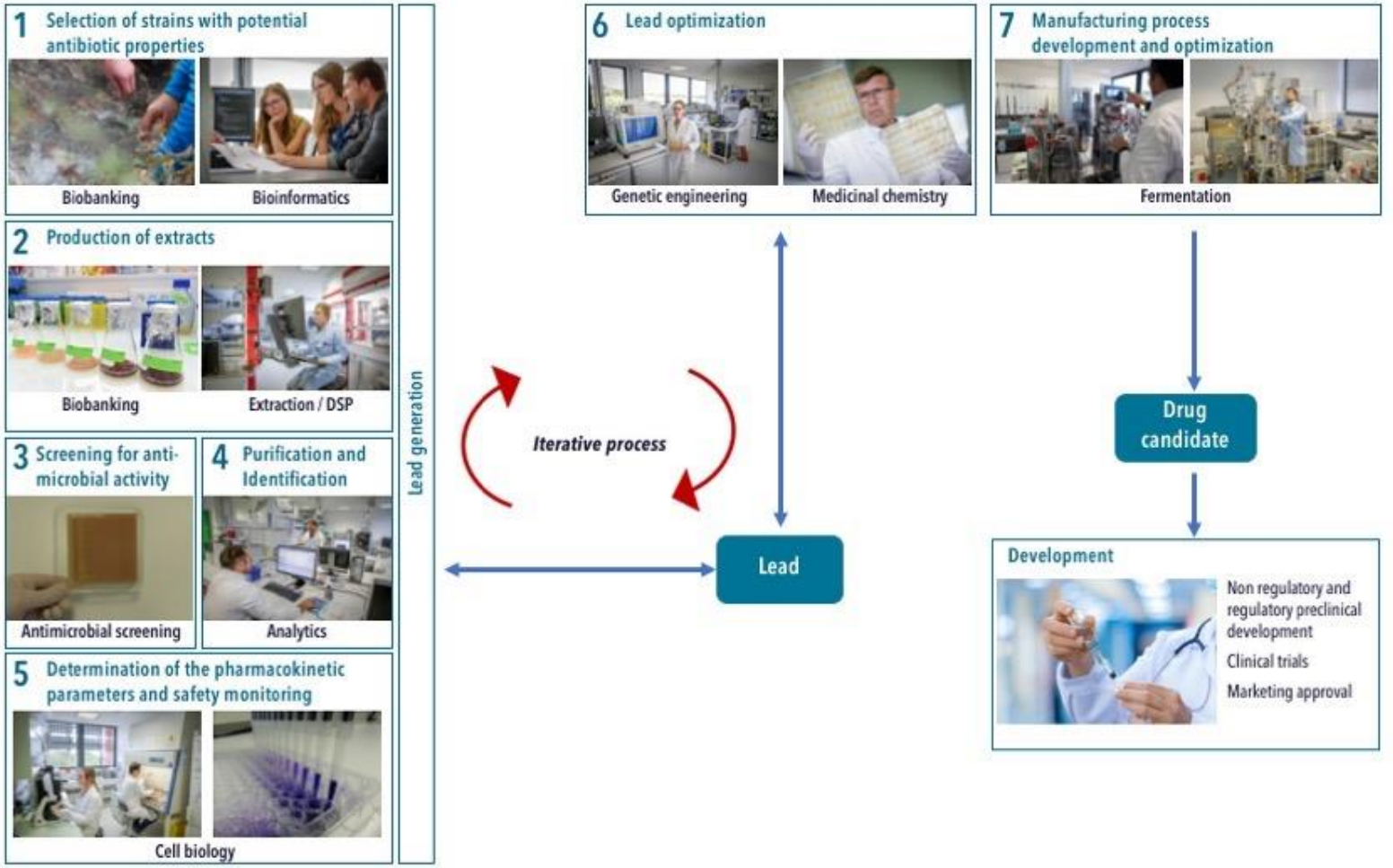
Pathogenic bacteria susceptibility testing
Automated plate incubation and reading

Dereplication with:
Interchim: Puriflash UV-DEDL-MS
Bruker: HPLC Qtof MS/MS with fraction collector

An integrated platform dedicated to discovering new antibiotics

Screening based on **antimicrobial activity**, then search for biosynthesis mechanisms

Collaboratif ICV/Deinove



Discovery Platform " From genome to molecule" co-hosted between ICV and Deinove

Case study of DNB101: A Proof of Concept

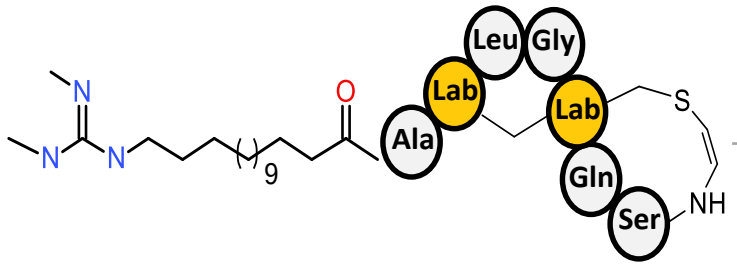
Antibiotic of natural origin isolated from ***Microbacterium arborescens***

- Effective but also partly toxic

Novel chemical structure (NCE)

Activity against dangerous antibiotic-resistant bacteria, identified as a priority by public health authorities

Ongoing tests: efficacy, pharmacology…



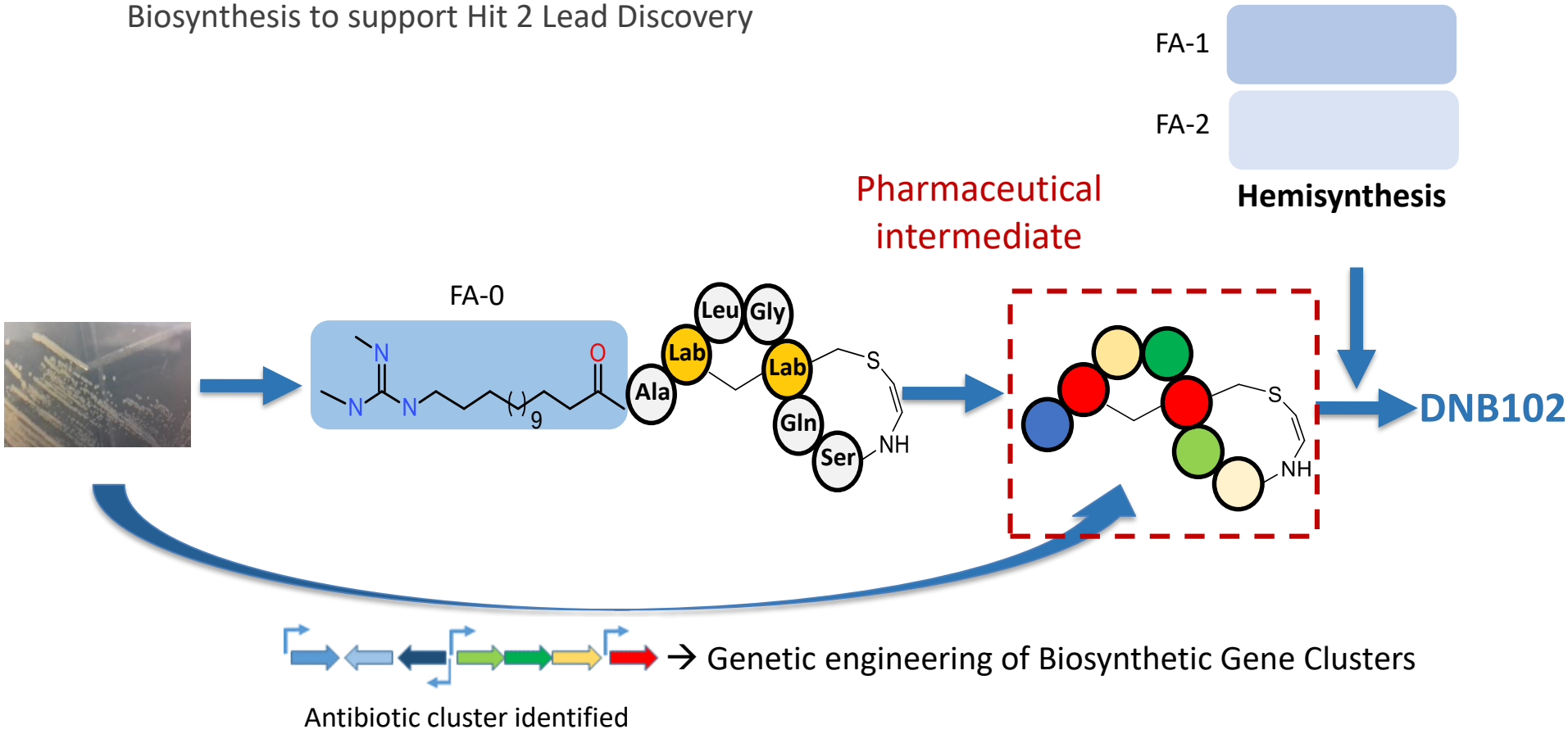
Next step: Develop the lead *via* biosynthesis gene cluster engineering and Med Chem

Two patent applications published

Strains	MIC_{90} (µg/mL)	Strains	MIC_{90} (µg/mL)
S. aureus [MSSA & MRSA]	2	*C. difficile*	0.125
S. epidermidis [MSSA & MRSA]	0.5	*P. acnes*	0.03
E. faecium [Vancomycin S & R]	0.5	*E. coli*	>4
E faecalis	>4	*P. aeruginosa*	>4
S. pneumoniae	0.125	*C. albicans*	>4

Case study: Microvionin series

Biosynthesis to support Hit 2 Lead Discovery



Proprietary chassis well mastered by Deinove, for higher production efficiency:

- Engineered strain able to produce only core nucleus
- Biosynthesis and Structure Activity Relationship (BSAR)

The discovery of novel antibiotics on collaborative mode

Highly challenging and rewarding !

- The discovery of novel antibiotics from natural products with input from:
  - Whole genome sequencing information
  - Exploiting biosynthetic gene clusters from “unculturable” strains
  - Most recent analytical techniques: MS/MS; MS/NMR; Cryo-Electron Diffraction

- Public/Private partnering: Institut Charles Violette – Deinove:
  - Mutualization of technology platform
  - Exchange of competencies at different stages of the drug discovery process
  - Value creation from an educational and scientific point of view

- The financial support of Bpifrance is crucial to develop and promote joint Public/Private push initiatives for the discovery of novel drugs in the antibacterial field

Thank you

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