Résistance aux antibiotiques :
une approche intégrée
de l'environnement à l'Homme

BIOCITECH, CITÉ DES ENTREPRISES DE SANTÉ ET DE BIOTECHNOLOGIES, ROMAINVILLE

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Session 5: Alternatives innovantes pour lutter contre l'antibiorésistance

17 mars 2016

Session 5: Alternatives innovantes pour lutter contre l'antibiorésistance

Participants à la Table Ronde

- **Hervé AFFAGARD**, MaaT Pharma et **Joël DORÉ**, INRA
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Why do we need Innovative Alternatives to antibiotic resistance ?

- Actions to tackle AMR:
  - more responsible use of antibiotics in humans and animals
  - Develop new antibiotics

    BUT no guarantee that we will be able to find enough new antibiotics to tackle AMR in the long-term!

➔ **We need to implement other strategies that can prevent and treat infections better/ with less impact on resistance increase**

- Current solutions explored:
  - **Vaccines** that prevent infections and so reduce the need to use antibiotics,
  - **Alternative approaches:** phage therapy, antibodies, microbiome protectors , antivirulence products and probiotics, alone or with antibiotics to prevent infections or treat them better, limiting the emergence, rise and dissemination of resistance

➔**Those alternative approaches accompany antibiotic use rather than replace them**

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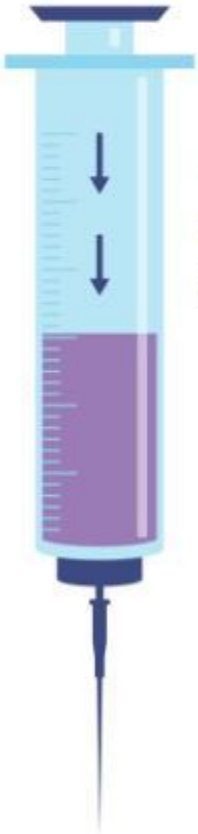
Review on Antimicrobial Resistance

INCREASING COVERAGE OF VACCINES CAN REDUCE ANTIBIOTIC USE

Universal coverage by a pneumococcal conjugate vaccine could potentially avert 11.4 million days of antibiotic use per year in children younger than five, roughly a 47% reduction in the amount of antibiotics used for pneumonia cases caused by *S. pneumoniae*.



47%
reduction in antibiotic use

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Review on Antimicrobial Resistance

ALTERNATIVE PRODUCTS TO TACKLE INFECTIONS

A selection of alternative products that are under development, which could be used for prevention or therapy.

Phage therapy

Natural or engineered viruses that attack and kill bacteria

Lysins

Enzymes that directly and quickly act on bacteria

Antibodies

Bind to particular bacteria or their products, restricting their ability to cause disease

Probiotics

Prevent pathogenic bacteria colonising the gut

Immune stimulation

Boosts the patient's natural immune system

Peptides

Non-mammalian animals' natural defences against infection

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- **Fecal Microbiotherapy**
- **Peptides**
- **Phages**
- **Vaccines**
- **Microbiome Protectors from Antibiotics Damage**

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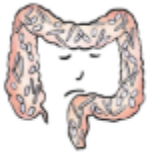
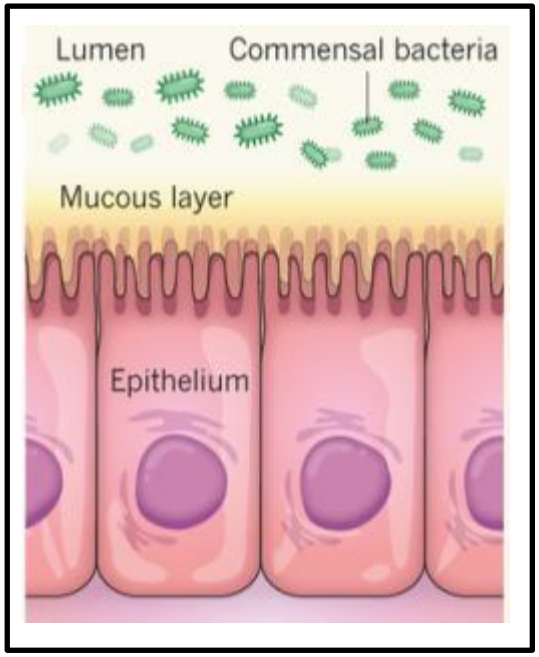
Presentation of the Concept

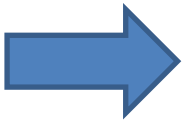
Symbiosis



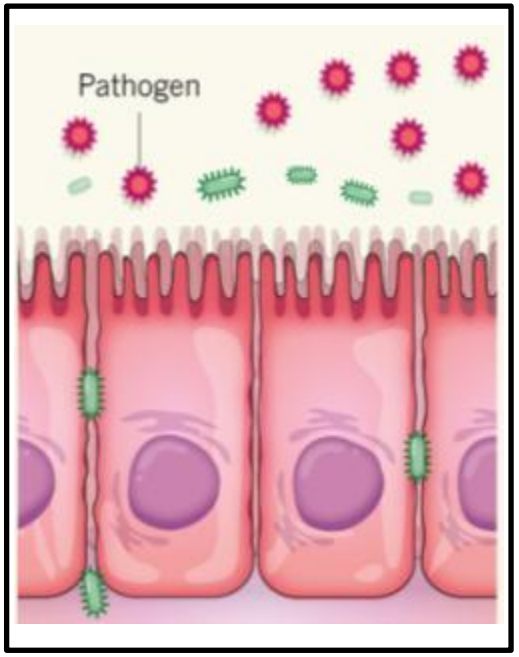
Dysbiosis



Opportunistic pathogens
Multi-drug resistant bacteria
Fungi, yeasts



Increased intestinal permeability



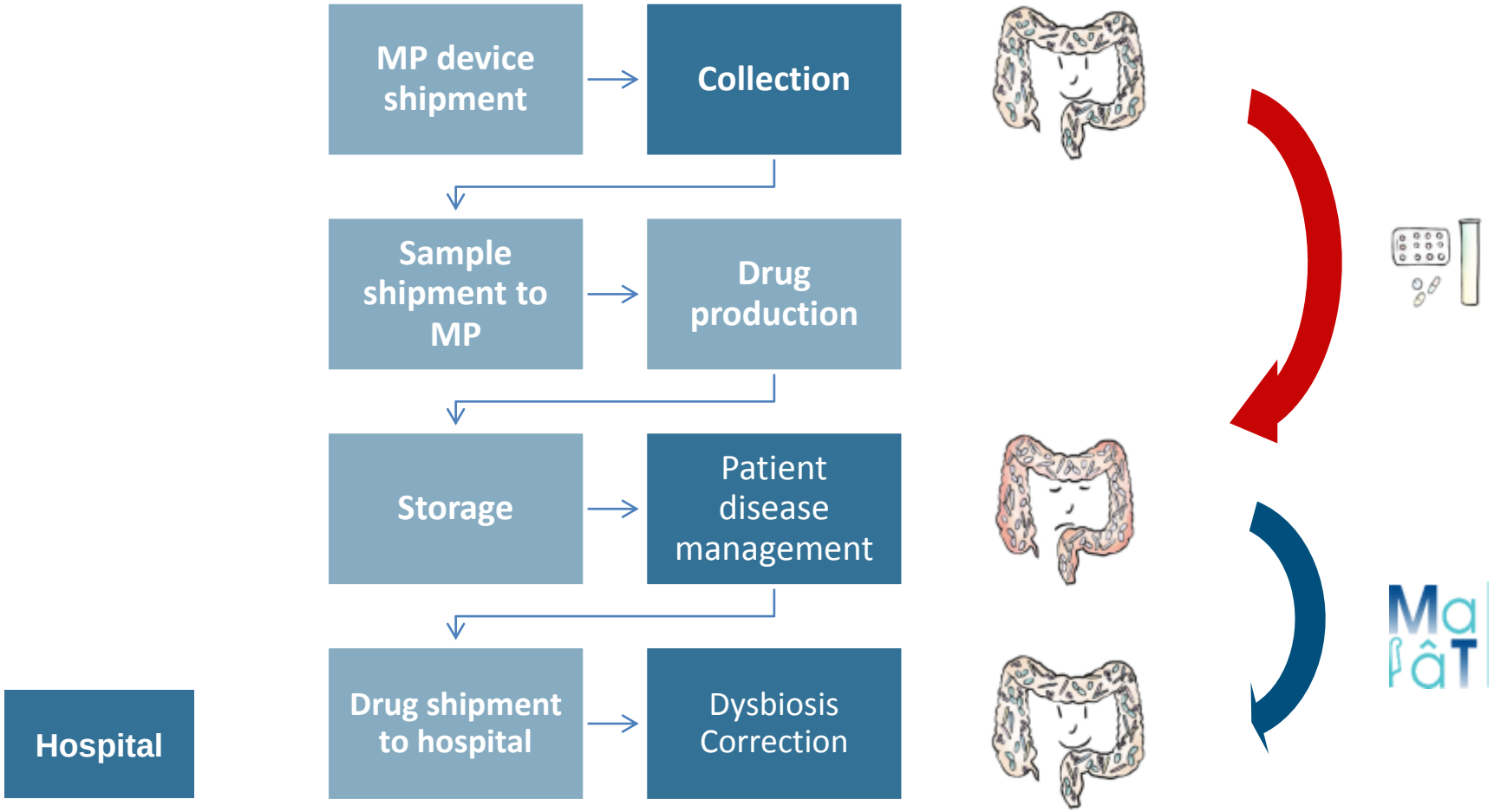
MaaT Pharma INDEX

- **Gut Microbiota Characterization**
- **Biomarkers Identification**
- **Correlation to clinical Symptoms**

Local and systemic inflammation
Pathogen dissemination, sepsis, infectious diseases…

Colonization with MDR bacteria is a consequence of gut dysbiosis

Product Developed



Autologous Microbiotherapy is a novel tool in the battle against MDR bacteria

Key Results obtained up to now

Achievements

- Safety/Dose effect
- 80% microbiota restoration
- No need for bacterial culture
- MVP device developed
- Supply Chain validated
- Oral form under development

Regulatory Progress (Drug)

- Q4/2014: Innovation Task Force
- Q3/2015: Scientific Advice
- Q4/2015: Pre-submission
- Q1/2016: Final Submission
- Q1/2016: Started Scientific Advice at the EMA level

Development / Market Perspectives

1 single product to address **2** untapped markets of enteropathies secondary to hospital massive antibiotics

Targeting drug reimbursement / Initial customers are hospitals

IP expiration : 2035 (4 patents)

Current Hurdles faced ?

- Regulatory framework under construction
- Ick-factor
- More evidences needed to expand technologies to other indications (beyond *c. difficile*)

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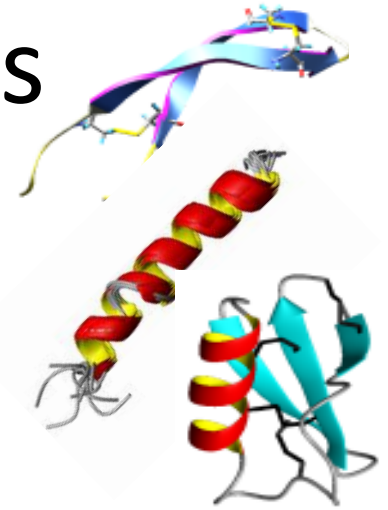
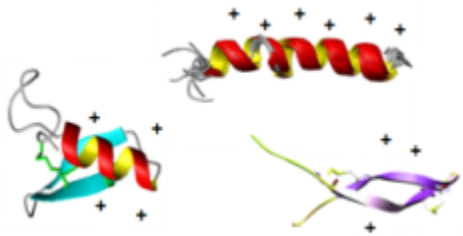
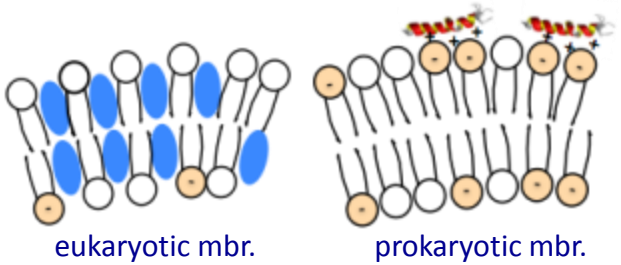
Antimicrobial peptides



Presentation of the Concept

- Conserve during evolution
- Selected under the environmental pressure
- Part of the defence armamentarium of all living organisms
- Circulating, often in contact with eukaryotic cells
- Large variety of structures but conserved motives, size often below 40-50 aa
- A limited number of ≠ PTMs
- High stability to proteolysis
- Different modes of action, selectivity





Different mbr potential:
approx. -70 mV for eukaryotic cells
approx. > -120 mV for prokaryotic cells

Antimicrobial peptides

Key results obtained up to now
Development / market perspectives

Genaera Corp	Magainins	Foot ulcers in diabetics
Ardea Biosciences	Protegrins	oral mucosis, stomatitis, pneumonia
Agennix Inc	Lactoferrin	Sepsis (nosocomial infections), lung cancer, ulcers
Xoma LtD	BPI	Pediatric Bacterial Meningitis
Migenix Inc	Indolicidin	Catheter-associated infections, acne
Pacagent Bio Corp	Histatins	Mouth & dental disorders
Helix Biocides Inc	Cecropins	Acne and skin care
Novozyme	Defensins	Antimicrobial
EntoMed SA	Defensins	Nosocomial infections (fungal)

Antimicrobial peptides

Current Hurdles faced ?

- Cost of production
- Rather multi-targets than single target oriented
- The linear candidates are sensitive to proteolysis
- Formulation remains difficult for a non systemic application
- Half-life is limited in circulation
- Their evolution was dependent of a specific physiological context different from a pathological one

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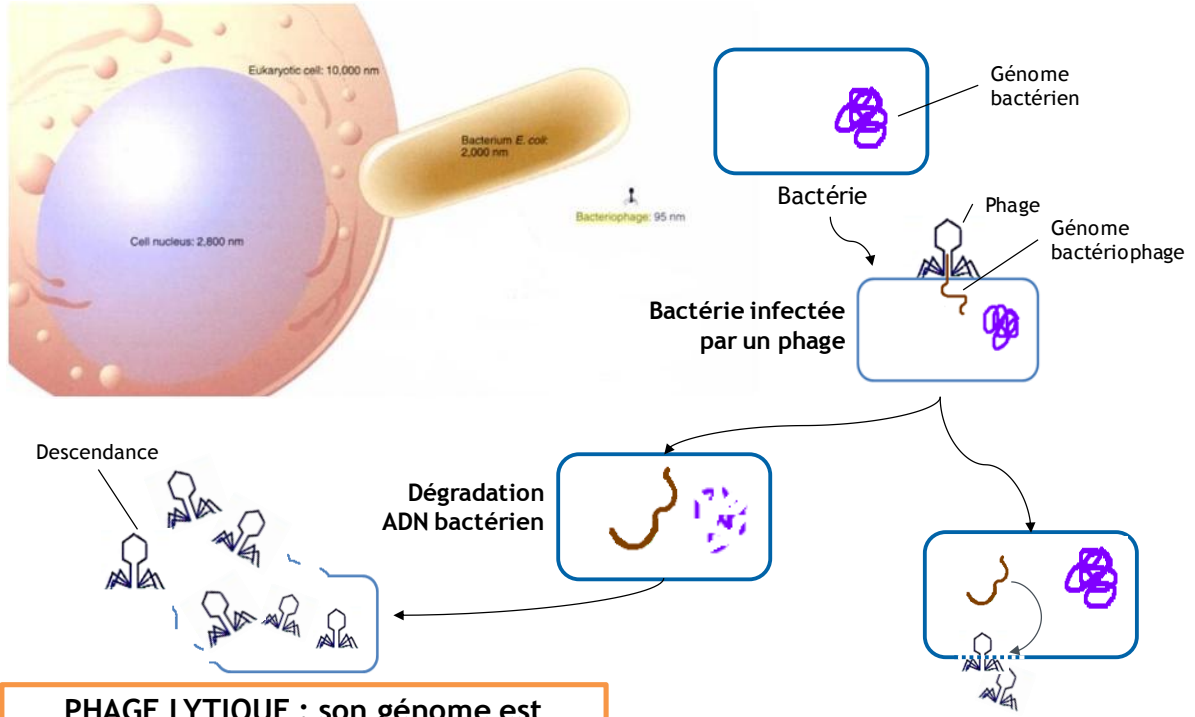
Phagothérapie



PHAGE LYTIQUE : son génome est amplifié. De nouveaux phages sont libérés en détruisant la bactérie

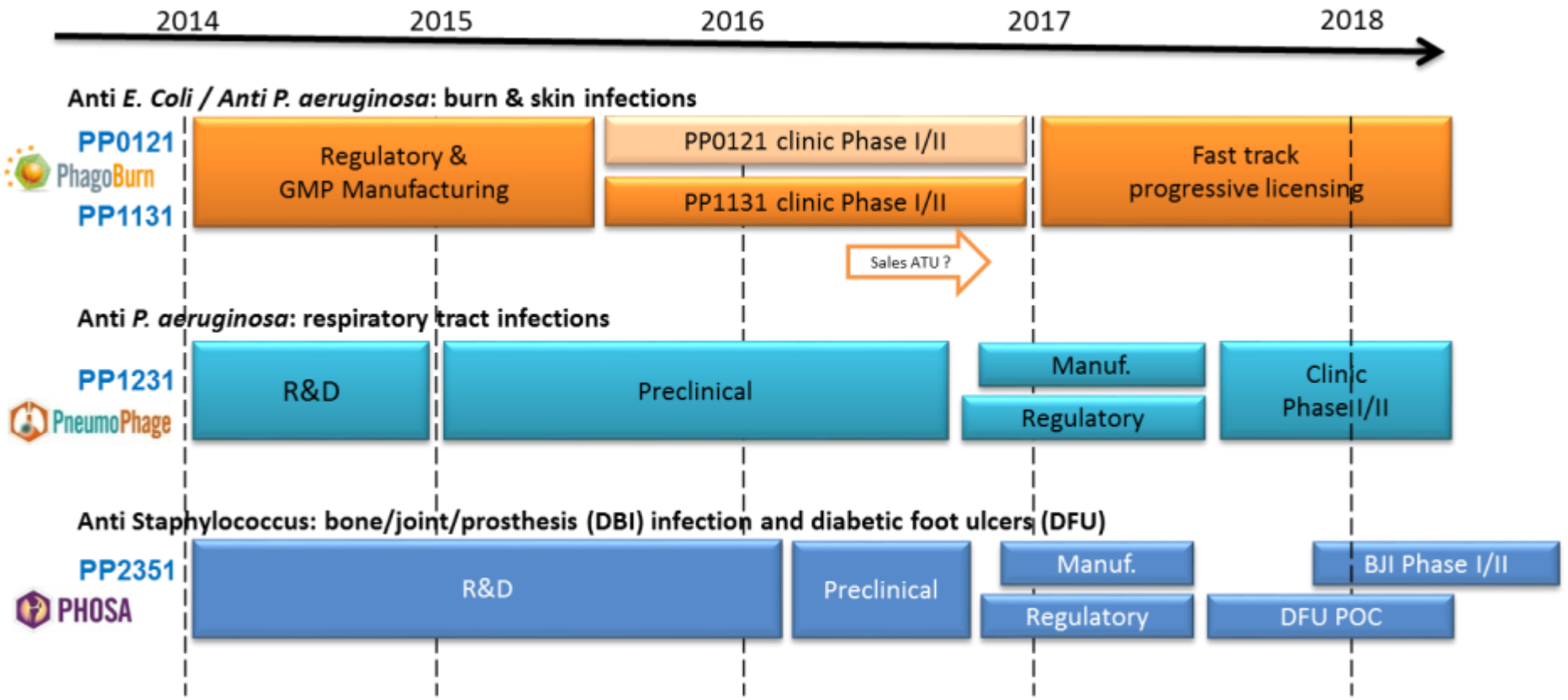
CELUI QUI NOUS INTERESSE !

PHAGE TEMPERE : son génome s'intègre. De nouveaux phages sont à l'occasion libérés dans le milieu avec survie ou pas de la bactérie

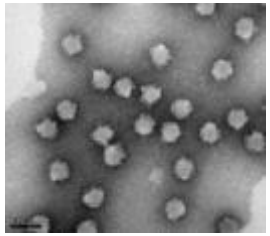
- **Le bactériophage : un prédateur naturel des bactéries.**
- **Des virus totalement inoffensifs pour les cellules eucaryotes mais spécifiques des procaryotes**
- **La phagothérapie ré-émerge en occident mais est éprouvée en Géorgie, Pologne ou Russie**
- **Une approche qui intéresse les hôpitaux militaires et civils en échec thérapeutique et les associations de patients (Le Lien, VLM…).**

PHERECYDES PHARMA

PhagoBurn



Four products in development from topical to systemic applications



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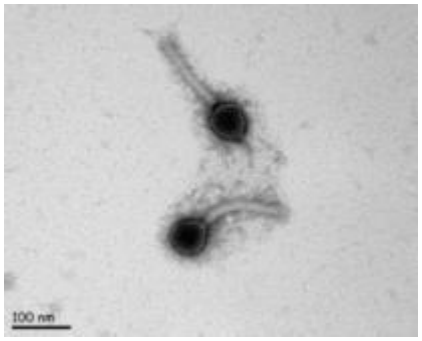
Challenges



- Une nouvelle classe thérapeutique dans la pharmacopée européenne et américaine
  - Cadre réglementaire à définir (CQ, tests…)
- Des procédés de fabrication nouveaux
  - Mise au point et optimisation en BPF
- Une galénique différente des antibiotiques
  - Médicament « vivant » et « auto-propagatif »
- Demande d'ATU auprès de l'ANSM
  - Comité Scientifique Spécialisé Temporaire (CSST)

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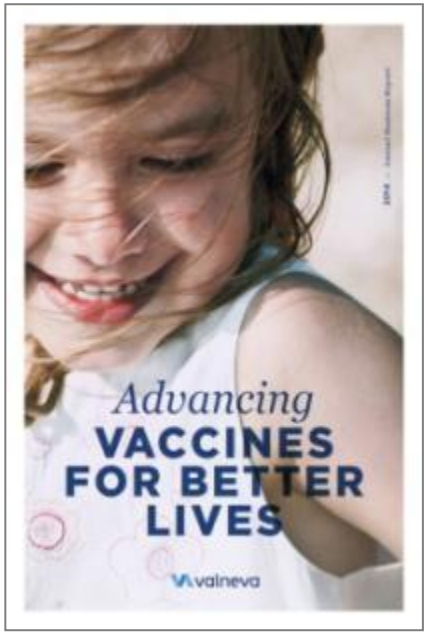
Valneva – Advancing vaccines for better lives

A **vaccine company** with global reach that specializes in the **development, manufacture and commercialization of innovative vaccines**.

Independent, publicly listed S.E. with the ambition to become the single largest, stand-alone vaccine company besides the four dominating pharma companies.

Long-term shareholders support strategy to become a profitable, fully integrated player.



We have already proven success on our strategic pillars:

1 Commercialized vaccines	2 Vaccine candidates	3 Technologies & Services
In-house developed product + Acquired products	Own R&D to marketing approval + Partnered programs	Global partnering + Competence leveraging

Valneva's unique business model dedicated to Vaccines

Marketed products, R&D portfolio and technology platforms

Products/Commercial*

Japanese encephalitis Vaccine

~ €25-28m (2015)[1]

Cholera and ETEC Diarrhea Vaccine

~ €21-23m (2015)[2]

Third Party

Marketing & Distribution

~ €4-8m (2015)[2]

R&D and Technologies

Research & pre-clinical	Ph I / II	Ph II / III

- **Pseudomonas aeruginosa**
- **Clostridium difficile**
- **Lyme borreliosis**
- **New targets***

* viral / travel

Cell-based platform EB66®

GlaxoSmithKline Biologicals, MERIAL, KAKETSUKEN, farvet, JSB IOSCIENCES

IC31® adjuvant / Other laboratory services

AERAS, EU-TBVAC, LUMC, National Institutes of Health, Statens Serum Institut, SANOFI, altimmune, Johnson & Johnson, GlaxoSmithKline Biologicals

- **1** As per Q3 outlook and transition impact from termination of Marketing & Distribution Agreement for Ixiaro® with GSK; **2** from acquired business as of Feb 10th 2015;
  * Net sales revenues to Valneva (differ from in-market sales)

Pre-commercial product: Pseudomonas aeruginosa vaccine

Targeting hospital-acquired pneumonia, with a market potential of $1bn

Pseudomonas aeruginosa

- **Causes ~20% of all hospital-acquired infections** [1,2]
- **Target population: patients in intensive care units on mechanical ventilation**
  - **Up to 1 million in the US and Europe per year**[3]
  - **All-cause mortality rate of 20% to 40% in this target population**[4]

Valneva's vaccine candidate

- **Only clinical program, no vaccine on the market**
- Recombinant OprF/I fusion produced in E.coli
- No preservatives
- 2 injections- days 0 & 7

Current development status VLA 43

- **Phase II/III enrolment completed** (800 patients) (co-financed by GSK)[5]
- **Reduction in mortality as primary endpoint**
- **Interim analysis after 400 patients** confirmed clinically meaningful effect but less pronounced
- **Addition of a secondary endpoint** for a subgroup of patients following Phase II post -hoc analysis

Phase II/III data release expected in Q2 2016

- **Valneva awaits full analysis of the ongoing efficacy trial, including day 180 follow-up time-points, before releasing data**
- **Valneva considers that ≥5% absolute difference in mortality should support the ongoing development of a licensable product**

Picture from www.rtmagazine.com; **1** Pseudomonas Infection, Selina SP Chen, Russell W Steele, MD – Chapter on Epidemiology www.emedicine.medscape.com; **2** Vincent JP et al, JAMA, 1995; p639-644; **3** McConville, M.D., John P. Kress, M.D. Weaning Patients from the Ventilator, N Engl J Med 2012; 367:2233-2239; **4** Vincent et al, JAMA 1995; 274:639-644

Pre-commercial product: Clostridium difficile vaccine

Vaccine targeting healthcare-associated diarrhea, an increasing threat to elderly

Clostridium difficile (C. diff)

- Single most common pathogen of acute healthcare-associated infections in the US[1] (~ 450,000 cases of annually and ~ 30,000 deaths[2])
- ~ 172,000 cases in EU member states per year[3]
- Targeting primary prevention of C. difficile
  - Current antibiotic treatments have significant limitations with recurrence in ~20% of cases[4]

Valneva's vaccine candidate

- Recombinant fusion protein of relevant parts of toxins A and B, not adjuvanted
- Liquid formulation 3 injections on days 0, 7 and 28
- Potential competitive advantage on cost efficiency

Current development status VLA 84

- Positive Phase II results announced in Nov. 2015
- Vaccine dose confirmed in older adults and elderly
- Highly immunogenic in all age groups tested (strong immune responses to both C. diff toxins A & B)
- Good safety and tolerability profile confirmed

Final Phase II data to be announced in Q2 2016

- Next steps to be announced after final study close-out and consultations with regulators and partner
- One of three clinical programs
- Expected to enter market as number two
- GSK opt-in rights[5]

Source picture: www.123rf.com; **1** Magill S, Edwards J R, Bamberg W et al. Multistate Point-Prevalence Survey of Health Care–Associated Infections. New England Journal of Medicine 2014;370:1198-208; **2** Lessa et al, Burden of Clostridium difficile Infection in the United States. N Engl J Med 2015;372:825-34. **3** Clostridium difficile infection in Europe. A CDI Europe Report.; **4** Leffler et al, Clostridium difficile infection. N Engl J Med 2015;372:1539-48; **5** If Phase II successful under pre-defined terms, under SAA with GSK: Intercell Annual report 2012, p. 39,45

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- Peptides
- Phages
- Vaccines
- **Microbiome Protectors from Antibiotics Damage**

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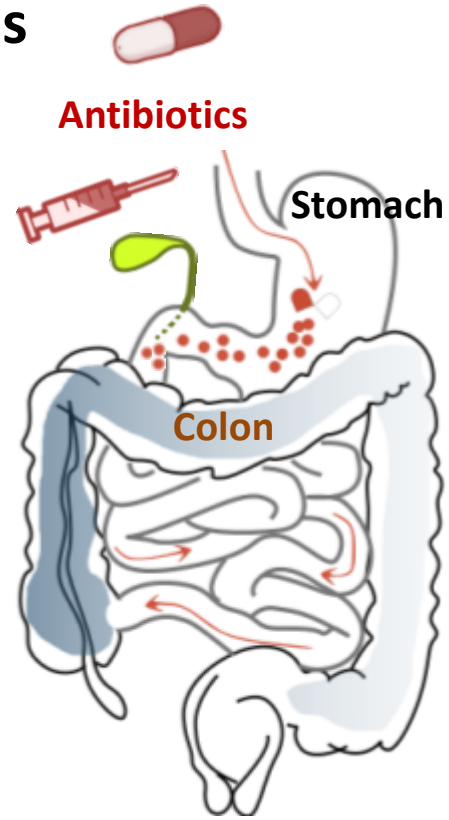
Concept: Antibiotic Treatments Impact the Intestinal Microbiota

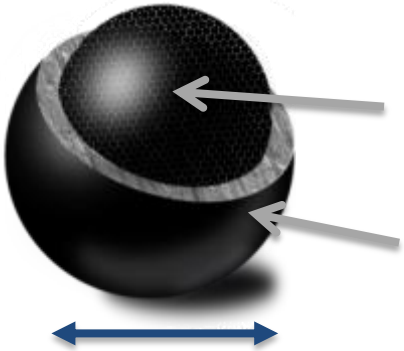
During all antibiotic treatments (oral, i.v., any class of product), a fraction of the dose administered **reaches the colon** either directly (product non absorbed) or via biliary excretion into the Gastro-Intestinal Tract.



As a consequence, **the intestinal microbiota** is **disrupted,** leading to the following consequences:

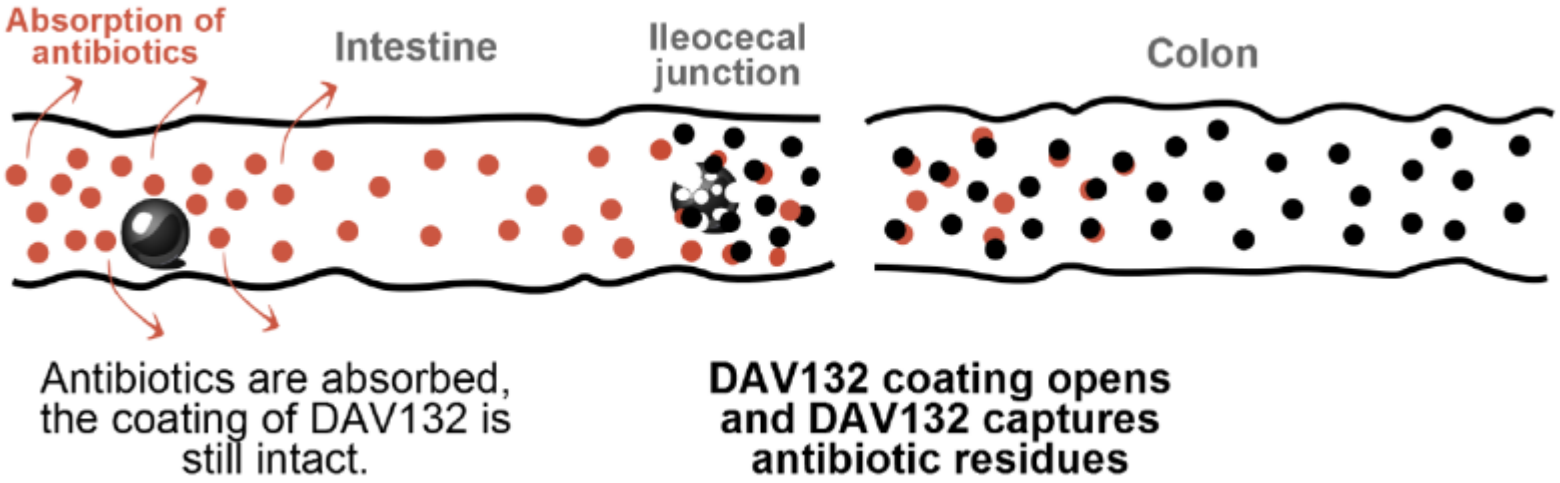
- ✓ **Risk of triggering *C. difficile* infections (CDI) (>70% caused by use of antibiotics)**
- ✓ **Antibiotic-associated Diarrhea (AAD)**
- ✓ **Emergence and spread of resistant bacteria**
- ✓ **Risk factor for common disease** because of the imbalance of the natural flora (*obesity, diabetes, inflammation, …*)

DAV132 Product



Powerful oral adsorbent, which adsorbs antibiotics from all classes under human gut like conditions

Coating for ileo-caecum delivery

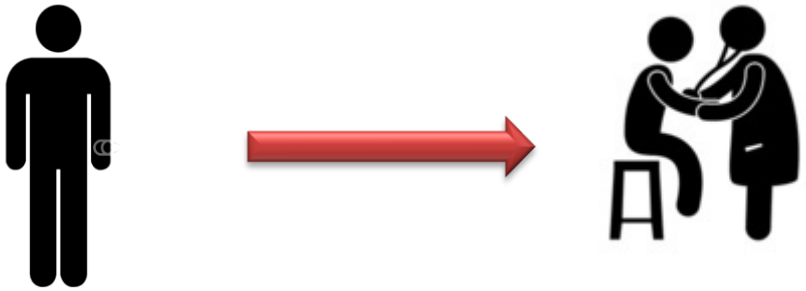


J. De Gunzburg et *al*. J Clin Pharmacol. 2015; 55(1):10-6 Epub 2014 Jul 16

DAV132 on the Market

Current practice

Antibiotics given to treat common infections (β-lactams, quinolones, Clindamycin, Carbapenems…)



***C.Difficile* Infections** treated with Metronidazole, Vancomycin, Fidaxomycin, Fecal transplants…

DAV132 practice = Prevention

Antibiotics

+

DAV132

DAV132 maintains the balance of the Microbiota, and prevents deadly and costly *C.difficile* Infections as well as other consequences of microbiota dysbiosis

DAV132 Key Results

- **Pre-clinical studies**:
  - Proof of prevention of *C. difficile* infection in hamster model when combined with Moxifloxacin, Clindamycin, Ceftriaxone: 100% survival with a dose-dependency of the effect
  - Protection correlated with elimination, through adsorption, of antibiotic residues in the gut + absence of colonization by *C. difficile*
- **Successful PoC Clinical Studies in healthy volunteers** :
  - Captures efficiently antibiotics in the distal intestine (99% decrease in moxifloxacin fecal concentrations)
  - Does not interfere with plasma PK of antibiotics
  - Protects the microbiota (Moxifloxacin causes a 50% drop in gene richness after 6 days of treatment which is abrogated by DAV132)
  - Has an excellent tolerability profile (no SAE in 114 volunteers tested)

J. De Gunzburg et *al*; ID WEEK 2015, San Diego 7-11 Oct; Poster 760
Protective effect of DAV132 on microbiota in human and in animals, article submitted to Nature, Feb 2016

Challenges

- Un concept nouveau avec un double statut réglementaire
  - Dispositif Médical en Europe
  - Médicament aux USA avec un cadre réglementaire unique

- Un bénéfice médical à la fois individuel court terme (prévention de *C.Difficile*), individuel long terme (prévention de maladie chronique) et collectif – écologique (Dissémination de résistance)
  - Validation de la dysbiose antibiotique comme bénéfice médical pour les patients individuellement et collectivement
  - Quelle valorisation « économique » de ces bénéfices collectifs et économiques ? Concept nouveau à prendre en compte dans la pharmacoéconomie des approches alternatives !

Conclusions on Innovative Alternatives

- From a public health perspective these are all important ideas with clear benefits !
  - ➔But, we are not moving anywhere fast enough to develop them, recognize their potential value, and use them appropriately
  - ➔The thinking must start now so that as such products mature and get closer to market, regulators and healthcare purchasers are well positioned to assess their value and make the best use of them.

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Merci !

17 mars 2016