αlphanosos

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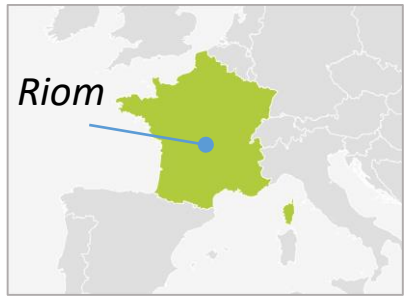

Rapid discovery of highly efficient plant extracts against MDR microbes relevant to humans and animals

Startup, financed by FFF + loans (BpiFrance) + grants (Région Auvergne-Rhône-Alpes)

Operations start : mid-2015

Discovery of and patent application (with very positive EPO search report) on antimicrobial plant mix family with 750 active mixes exemplified

Discovery of plant mix family active on cancer cell lines in collaboration with Swiss EPFL (patent in preparation)

Commercial stage : direct sales (B2B) and through distributors

2018
- cosmetic ingredients
- veterinary hygiene products

2019
- AI based discovery partnerships
- animal feed additives
- dermocosmetics

- First exclusive EffiSkin® distribution agreement signed for Switzerland

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HOW TO OBTAIN SUPERIORLY EFFICIENT AND SAFE "DRUGS"

Edible plant paradox

=> safe despite mix of hundreds of actives

=> mixes of edibles safe too

=> activity against bacteria

Antibacterial activity of vegetables and juices.
Lee YL, Cesario T, Wang Y, Shanbrom E, Thrupp L.; Nutrition. 2003 Nov-Dec;19(11-12):994-6.

System's biology/polypharmacology

=> call for poly-actives

Network medicine and high throughput screening.
Smith RE *, Tran K, Vocque RH. Curr Drug Discov Technol. 2013 Sep;10(3):182-94.

* Total Diet and Pesticide Research Center, U.S. Food and Drug Administration

Proof of the efficacy on bacterial control of polypharmacology based on edible plants:

Consumption of Mediterranean versus Western Diet Leads to Distinct Mammary Gland Microbiome Populations.
Shively CA, Register TC, Appt SE, Clarkson TB, Uberseder B, Clear KYJ, Wilson AS, Chiba A, Tooze JA, Cook KL., Cell Rep. 2018 Oct 2;25(1):47-56.e3.

Alphanosos' WECMEPs (Water Extracts of Complex Mixes of Edible Plants)

Synergistic => patentable, reproducible efficacy, scalable production, safe

BUT from a library of 300-1000+ edibles, there are $10^{10\text{-}40+}$ possible mixes of 5-20 edibles

=> Brute force is not an option

Alphanosos' AI specialized algorithms (re-)enable this revolution

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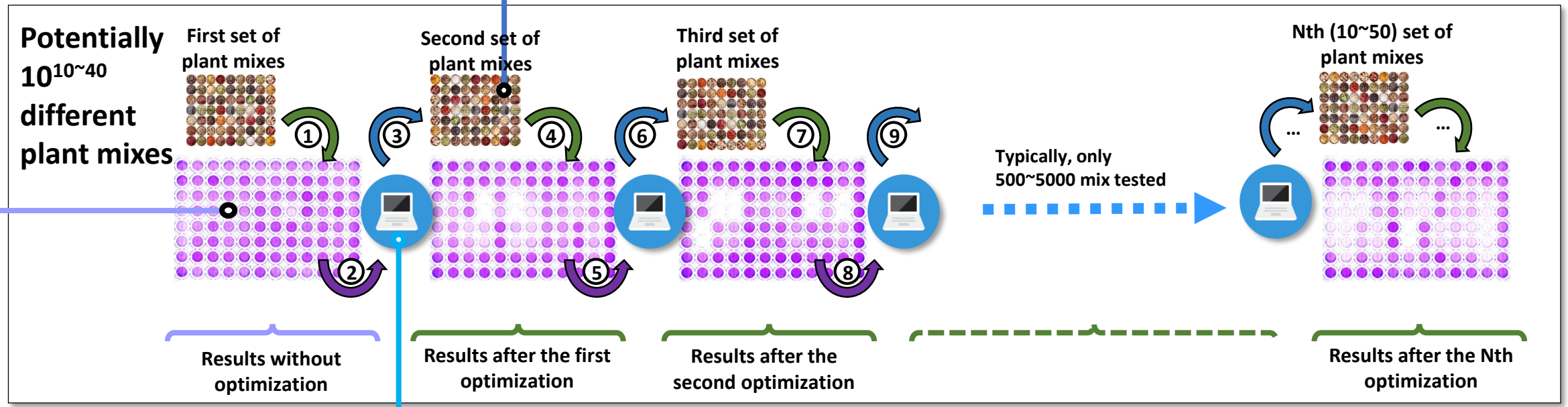
OUR PROPRIETARY AI BASED DISCOVERY METHODOLOGY

(developed by Dr Pascal Mayer, inventor of DNA colony sequencing (now Illumina's technology base))

Target relevant **bacterial strains / (cancer) cell-lines /organism** with high content **phenotypic assays or any other bio/chem/phys/psy/…-assay**

Use **of plants (or drugs) with a history of safe human consumption and with optimal availability** as source of raw material

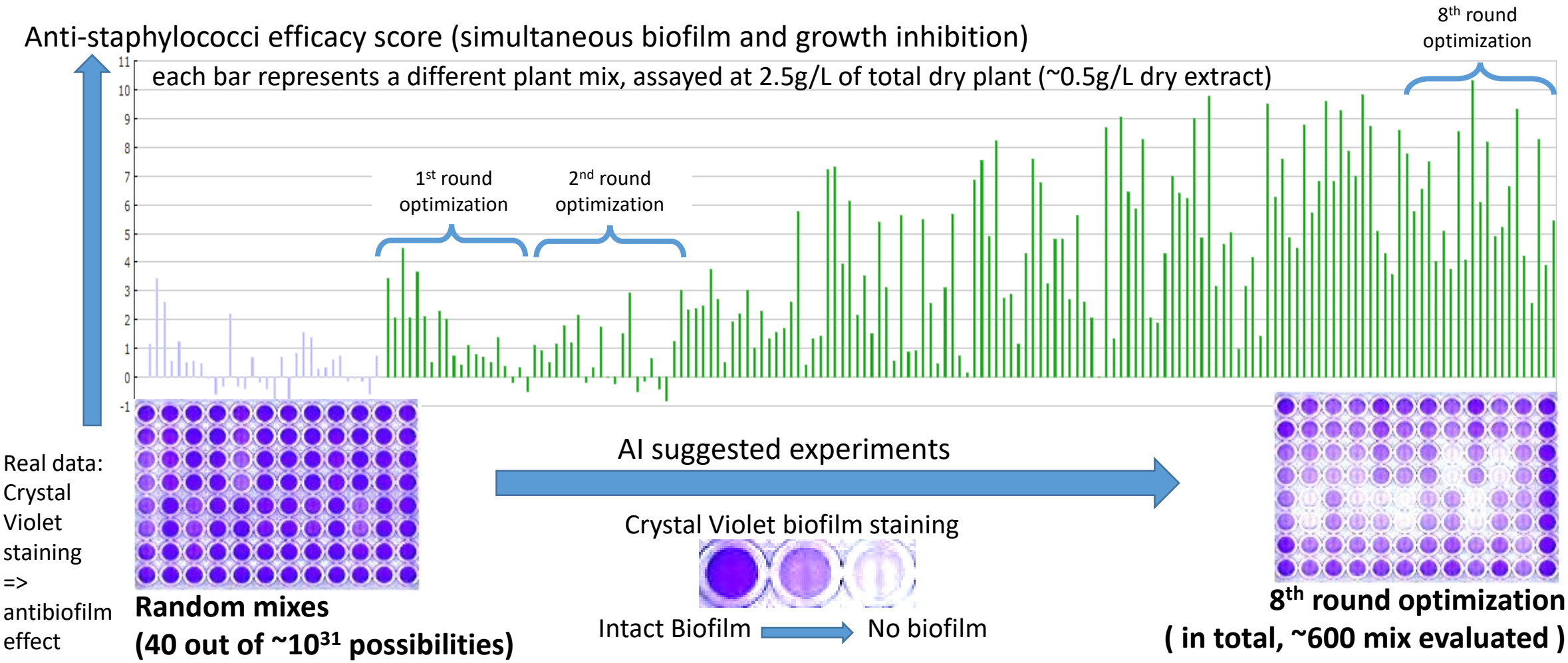
Use the **synergistic and system' potential** of mixes to reduce the risks of toxicity and resistance development => WECMEPs



Use of proprietary and genuine **artificial intelligence algorithms** and software

FAST DEVELOPMENT OF WECMEPs WITH DESIRED PROPERTIES

Alphanosos' AI based compound discovery methodology applied to antimicrobials



Results:

⇒ patent pending family of narrow and broad spectrum mixes (3 to 20 plants) with typical MIC ranging 0.02% – 0.4% (w/v)

⇒ Time from project start to filed patent: 12 months, including technology developments/optimizations (NB: this was our first project)

For Staphylococci (including MRSA) :

MIC90 = 500µg/mL,
MIC100 = 0.2% (w/v)

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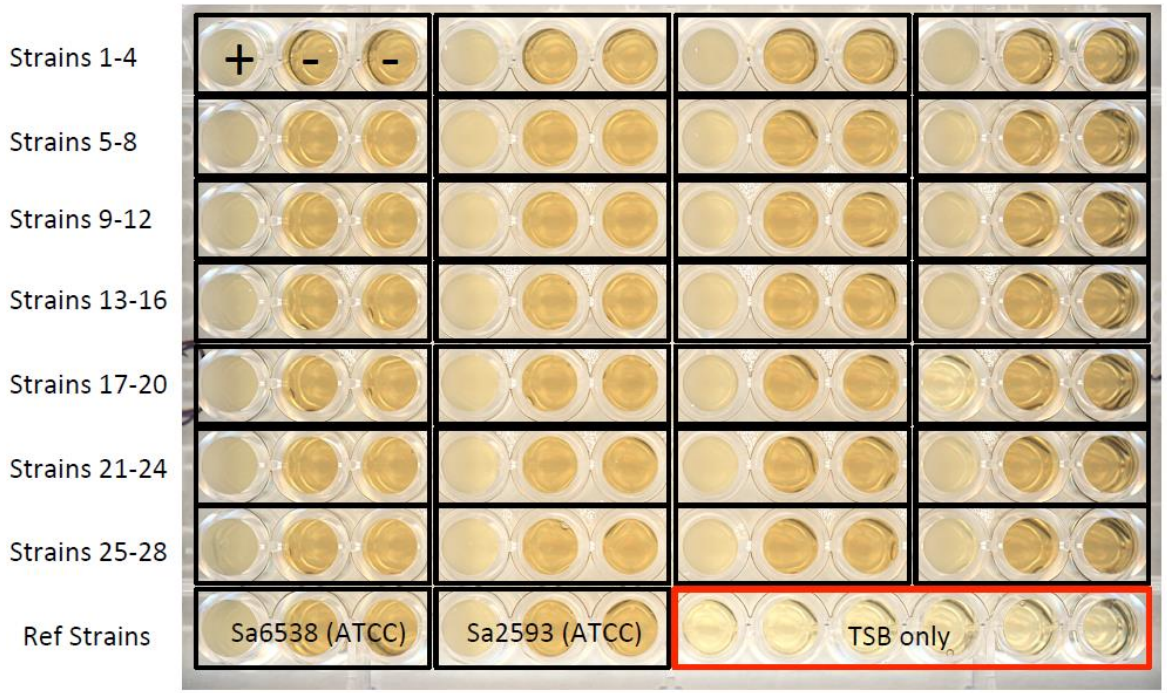
Our Anti-staphylococci discoveries:

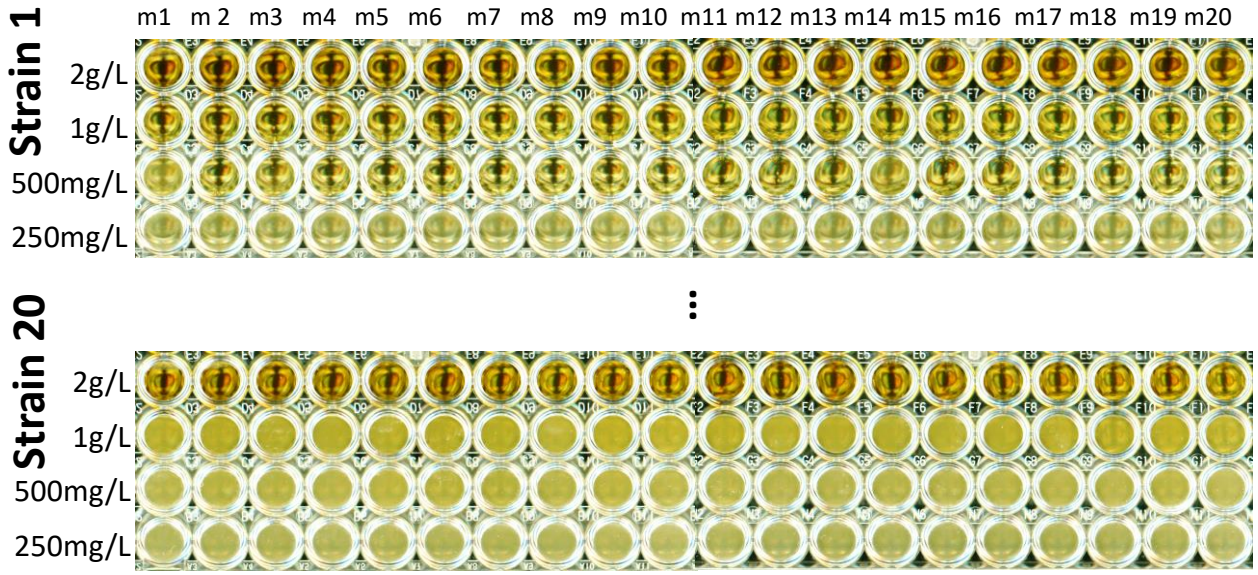
For Staphylococci (including MRSA) → **MIC90 = 500µg/mL**
MIC100 = 0.2% (w/v)

Killing activity of W16P576 against planktonic cells (also preventing biofilm formation)



Experiment by Prof Ensoli's group IFO, Rome, Italy, on clinical strains from severe dermatitis patients (including multiple resistant, MRSA)

Reproducibility of 20 different W16P576 preparations (m1 to m20) with each of 16 plants in a preparation chosen among 3 different batches for each plant (producer, year, conventional or organic…)



Tested on 20 clinical *S. pseudintermedius*, 10 from dog skin infections and 10 from dog ear infections (including multiple resistant, MRSP)

Peer reviewed publications in preparation (4Q2018)

System's biology effect simply stated: targeted dietary imbalance

An untapped mode of action

EDIBLES

⇒ safe unless dietary imbalance is maintained over prolonged period

What is "Prolonged period"? Depends on organism system's dynamics

What is "dietary imbalance" ? System biology notion of robustness

Organism	Diatery time	Generation time	System's Robustness
Humans/pets/farm animals	24h	10-20 years	Very High
Microorganism acute infections	Minutes	0'5-1 hour	Much less than human cells
Microorganism silent/slow infections	Hours?	Day(s)	Much less than human cells
Tumor cells	Hours?	"Months"	Less than non-mutated cells

⇒ *Imbalance in microorganisms (and cancer cells) is much more easy to achieve than in human organisms*

New approach to antimicrobials:

Targeted dietary imbalance

⇒ Will make selected microorganism/tumors extinct before human health is impaired

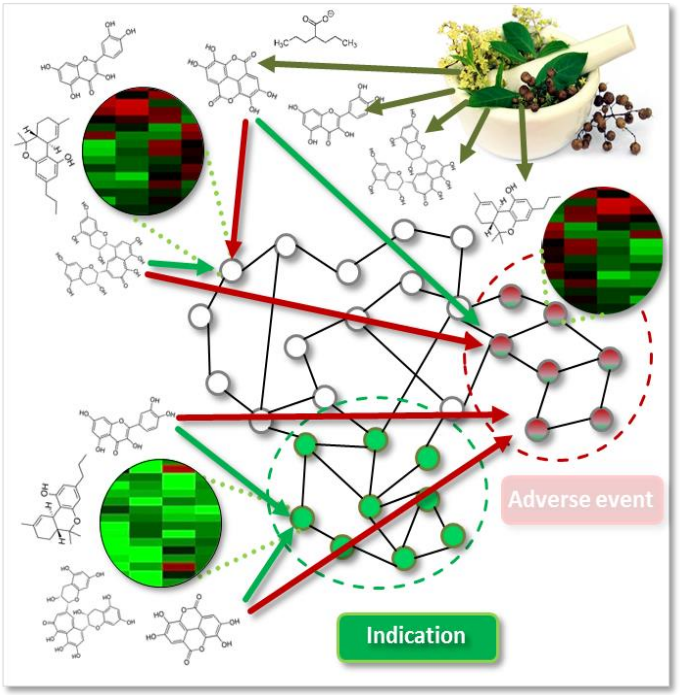
⇒ Will promote desirable microorganisms

⇒ **"EUBIOTICS"**

Alphanosos' solution:
Massively Parallel Phyto-Pharmacology:

From « *miraculous bullet* »
to « *magic*shotgun* »

* : " *Any sufficiently advanced technology is indistinguishable from magic* ", **Arthur C. Clarke**



Taking inspiration from recent science, *e.g.*:

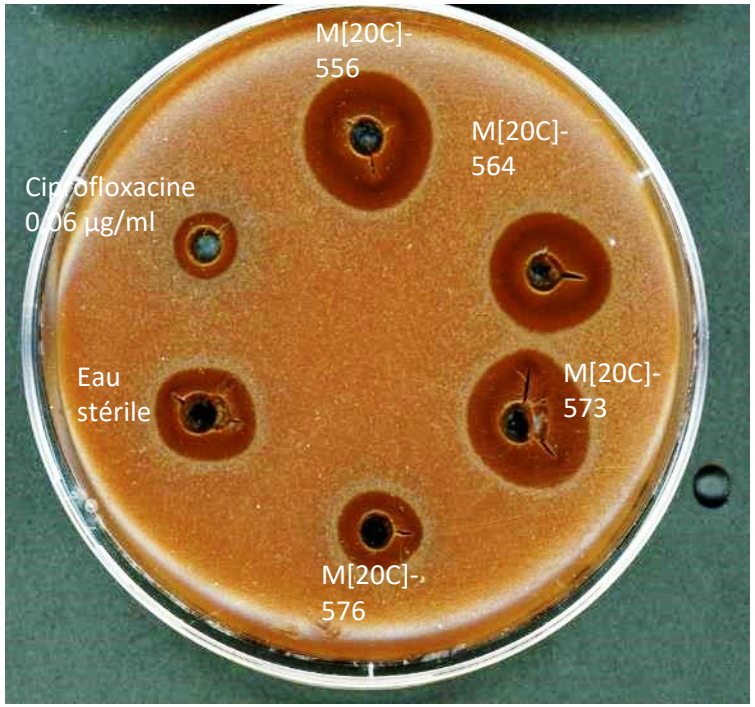
A robustness-based approach to systems-oriented drug design.
Kitano H. Nat Rev Drug Discov. 2007 Mar;6(3):202-10.

Targeting molecular networks for drug research.
Pinto JP, Machado RS, Xavier JM, Futschik ME., Front Genet. 2014 Jun 4;5:160.

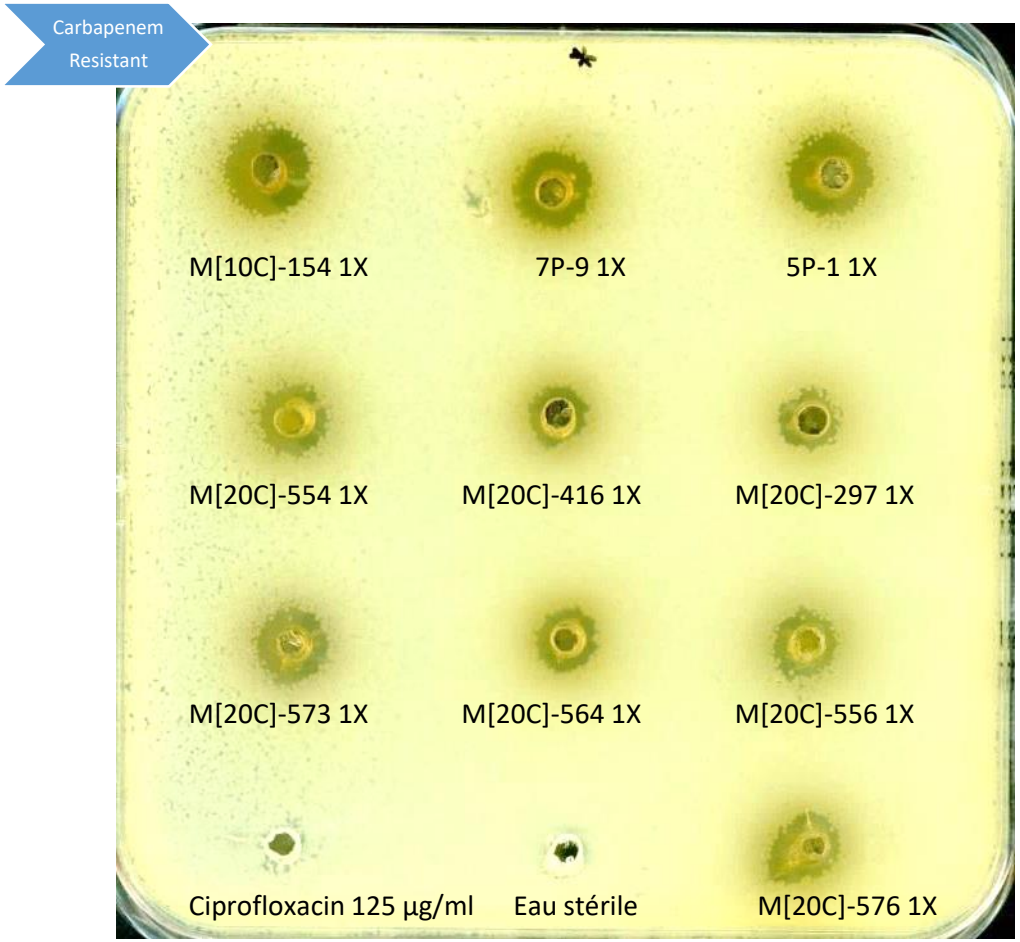
Loss of connectivity in cancer co-expression networks.
Anglani R, Creanza TM, Liuzzi VC, Piepoli A, Panza A, Andriulli A, Ancona N. PLoS One. 2014 Jan 28;9(1):e87075.

ACTIVITY AGAINST CARBAPENEM RESISTANT *Nesseiria gonorrhoeae* AND Acinetobacter baumannii

WECMEPs fighting carbapenem resistant Neisseria gonorrhoeae NCTC 13822



WECMEPs fighting carbapenem resistant Acinetobacter baumannii NCTC 13301



Alphanosos EXTENDED SPECTRUM OF ACTION OF TOP 5 ACTIVE MIXES (AS OF JUNE 2019)

in vitro status: Demonstrated / Préliminary

In red, dermatology indications and « low hanging fruits »

WHO priority pathogens list for R&D of new antibiotics

Priority 1: CRITICAL

- **Wounds** — Demonstrated — ○ ***Acinetobacter baumannii*, carbapenem-resistant**
- **Wounds, Chonic rhinosinusitis** — Demonstrated — ○ ***Pseudomonas aeruginosa*, carbapenem-resistant**
- Préliminary — ○ *Enterobacteriaceae*, carbapenem-resistant, ESBL-producing

Priority 2: HIGH

- **Wounds** — Préliminary — ○ ***Enterococcus faecium*, vancomycin-resistant**
- **Eczema, Psoriasis, Acne, Wounds, Chonic rhinosinusitis** — Demonstrated — ○ ***Staphylococcus aureus*, methicillin-resistant, vancomycin-resistant**
- ND — ○ *Helicobacter pylori*, clarithromycin-resistant
- ND — ○ *Campylobacter* spp., fluoroquinolone-resistant
- Préliminary — ○ *Salmonellae*, fluoroquinolone-resistant
- Demonstrated — ○ ***Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant**

EXTENDED SPECTRUM OF ACTION OF TOP 5 ACTIVE MIXES (AS OF JULY 2018)

in vitro status: Demonstrated / Préliminary

In red, dermatology indications and « low hanging fruits »

Mycobacteria

Mycobacteriosis, leprosy, tuberculosis

- Demonstrated — ○ ***Mycobacterium smegmatis*** (representative organism)
- ND — ○ *Mycobacterium bovis*
- Préliminary — ○ *Mycobacterium tuberculosis* (attenuated)

Miscellaneous

Acne

- Demonstrated — ○ ***Propionibacterium acnes***
- Demonstrated — ○ *Klebsiella pneumonae*

Food industry

- Préliminary — ○ *Listeria monocytogenes*

Lyme's

- Préliminary — ○ ***Borrelia burgdorferi***

- Demonstrated — ○ *Streptococcus uberis* (bovine mastitis)

Dental Caries

- Préliminary — ○ *Streptococcus mutans*

In progress

- ○ *Streptococcus pneumoniae*

Vaginosis

- Demonstrated — ○ *Candida albicans* (***C. albicans / S. aureus mixed biofilms***)

Aquaculture

- Préliminary — ○ *Vibrio parahaemolyticus*
- Préliminary — ○ *Vibrio vulnificus*
- Préliminary — ○ *Vibrio alginolyticus*
- Préliminary — ○ *Vibrio harveyi*

With WECMEPs composed of plants already authorized as feed additives…

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Preliminary in vivo data of antimicrobial plant extracts: no sign of per os toxicity but evidence of per os efficacy

No toxicity in OF1 mice following a 2 times a day **oral treatment** for 12 days with 1.5mg/g, 0.5mg/g and 0.15mg/g plant extract : *mortality, weighing, signs of suffering*

Proof of principle of systemic action *in vivo* despite passage through digestive system

Infection model: **intraperitoneal infection** on 2 groups of 10 OF1 mice

⇒ *S. aureus* Newman at $1.7x10^7$ cfu/mice

Treatment with WECMEP_W16P576:

⇒ ***per os***, oral gavage

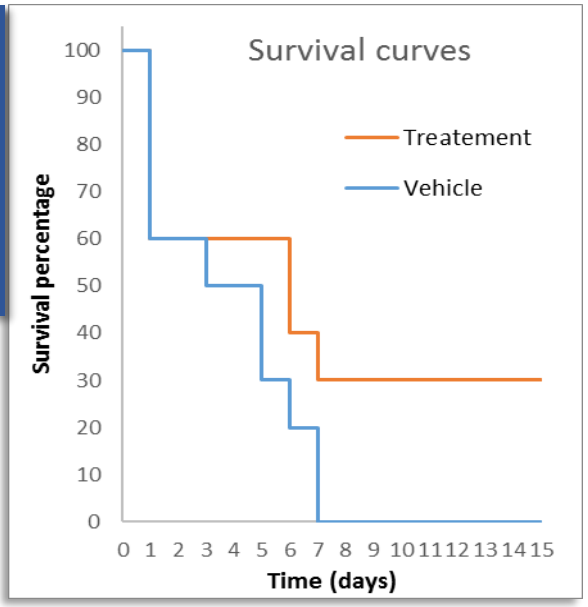
⇒ **1 dose/day**:10 µl/g plant extract at 20g/L (200mg/kg)

⇒ dose = (typical) 6 mg extract from **15 mg total herbs / mouse** (weight adjusted at 0.5mg/g [mix/mouse])

⇒ **Human equivalent could be a "soda can" at 60g/L extract**
(NB: extract mix is an "aromatic preparation" (EU) before drug claim)

30% survival at 15 days with treatment,

0% survival with vehicle



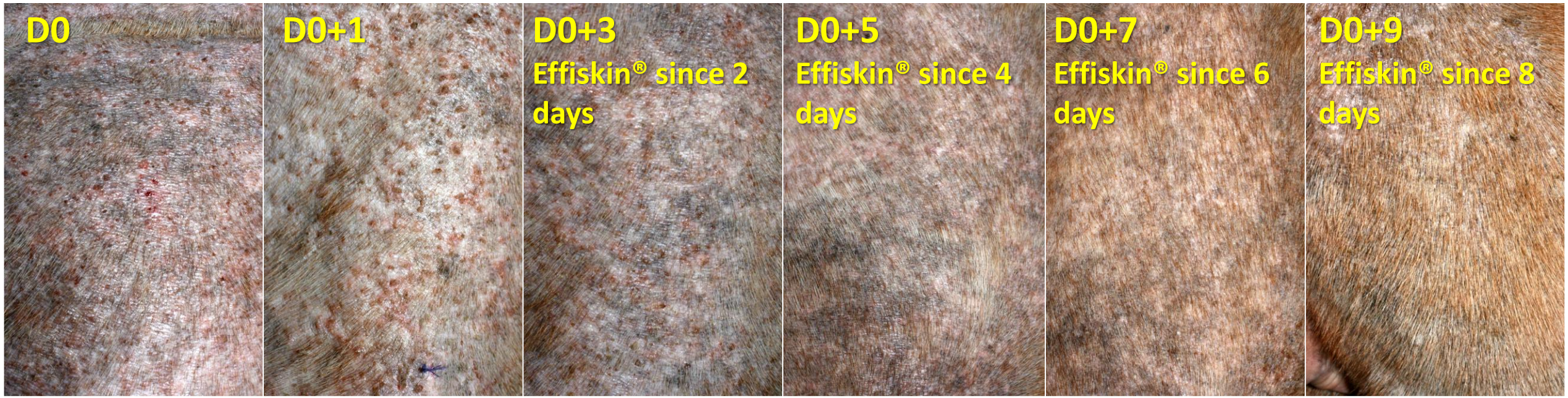
To be seen as proof of principle for systemic effect by ingestion

Alphanosos EffiSkin lotion efficacy assessment clinical case

Generalized Bacterial Folliculitis diagnosed at the Lyon Veterinary School's clinic
Therapeutic failure of chlorhexidine based shampoo and lotions
Therapeutic failure of antibiotic treatment
Bacteria revealed as resistant to ALL antibiotics authorized for the treatment of dogs
Euthanasia envisaged because of signs of suffering resulting from the disease conditions
Last resort option envisaged by the medical team: Effiskin®

J+1

3% chlorhexidine containing shampoo Twice a day (morning and evening)	3% chlorhexidine containing shampoo only mornings + Effiskin® morning (post-shampoo) and evening



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Favorable regulatory situation for botanical drugs (USA/FDA) ⇒ Possibility to go "immediately" to phase II

Botanical Drug Development

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2016
Pharmaceutical Quality/CMC
Revision 1

For a botanical drug that is not currently lawfully marketed in the United States, if it is administered using the route (e.g., topically or orally) and prepared, processed, and used according to methodologies for which there is extensive prior human experience, sufficient information may be available to support initial clinical studies without additional nonclinical pharmacological/toxicological testing. Literature and other available information related to the safety of the drug should be provided.

For example, a botanical dietary supplement marketed under the Dietary Supplement Health and Education Act of 1994 (DSHEA) that has no known safety issues often would require less detailed information on chemistry, manufacturing, and controls (CMC) or toxicological data in an IND for early-phase studies than would a botanical product that is newly discovered, has not been marketed, or has known safety issues. For most botanical drugs, detailed CMC information (e.g., data on comprehensive characterization of the drug substance) may not be warranted for early-phase development (Phase 1 and Phase 2 clinical studies); however, gathering of CMC data should be initiated during these phases because such preliminary information should be submitted prior to initiating Phase 3 studies.

Botanical drug products currently marketed as dietary supplements under DSHEA generally would not require typical Phase 1 tolerability studies if sponsors can provide adequate justification for the relevance of the prior human use.

Biological assay. If the active constituents are not known or quantifiable, a biological assay should be developed, prior to initiation of Phase 3 studies, to assess drug substance batch potency and activity relative to a reference standard (see Section VII.B.2.d).

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The AMR business model dead-end is solved with WECMEPs

- Repurposing possible as
  - ✓ Cosmetics
  - ✓ Hygiene products
  - ✓ Food supplements

Early and sustained non-clinical revenues are possible

- No Hit-2-Lead-2-drug research
- Pre-clinical tox etc… mostly reduced to get convinced of efficacy in animals
- Clinical development is faster: directly into phase II
- Go-to-production is fast, scale-up is universal (same process for every WECMEP)

Drug development costs and timelines are made acceptable again, prolonged patent commercial exploitation

- WECMEPs are environmental friendly:
  - ✓ Fully biodegradable by essence
  - ✓ Do not require organic solvents
  - ✓ Produced in NON-Seveso class production plants

WECMEPs make antibiotics great again!
(easy joke! Thanks Barack)

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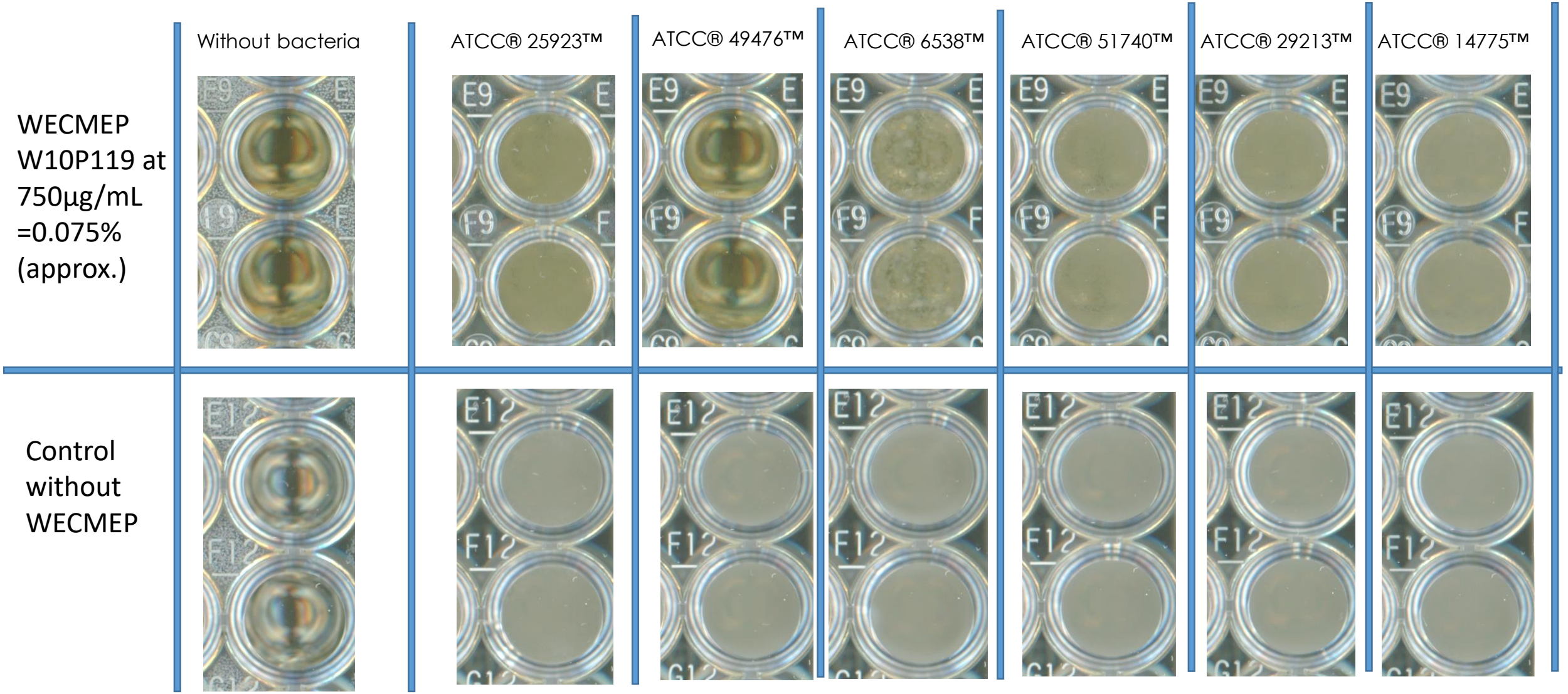
Example of WECMEP with growth and biofilm inhibition activity limited to a single strain within a given specie: growth results



Protocol: Bacteria are inoculated at 3.10^5 in TSB with 0.075% WECMEP and incubated for 17h at 37°C

αlphanosos "1001" ANTIBIOTICS *Based on current and upcoming Anti-Microbial WECMEPs*

"1001" AMR preventing WECMEPs

- narrow spectrum WECMEPs , prescibed after antibiogram
  ⇒ minimize microbiota pertubation
- 1002nd developped in a mattter of days if ever a resistant strain emerges

"1001" microbiota rescuing WECMEPs

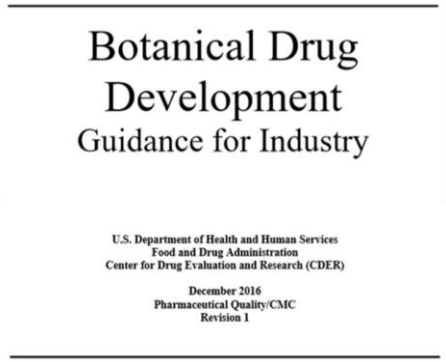
- WECMEPs to promote desirable micro-organisms

« 7(14)/31» antimicrobial WECMEPs

- ❑ Veterinary
- ❑ Humans

- large spectrum WECMEPs: a different treatment started (or switched) each (half-)day of the week / month
  ⇒ Difficult to imagine resistance
  ⇒ Probabilistic prescription less risky: if day 1 morning pill is wrong, day 1 afternoon pill may still save the patient

Regulatory Issue: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WECMEPs are designed to be likely eligible for directly entering phase II

Is there an issue at all?

(for the "1001" products)

In regards of a definitive and sustainable answer to AMR?

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BIODEFENSE AND EMBEDDED SOLUTION

A solution to face antimicrobial emergency

Based on
⇒ WECMEPs
⇒ AI rapid discovery
⇒ Improved throughput (10x)
⇒ Improved rapid instrumentation (3h readout))
⇒ Emergency organization

Unique, no equivalent possible with chemical entities
- Because of costs of infrastructure
- Because of speed of upscale
- Because of speed and costs of diversity generation
- Because of safety (and regulatory) :
  First time in universe compounds vs mix of edible plants

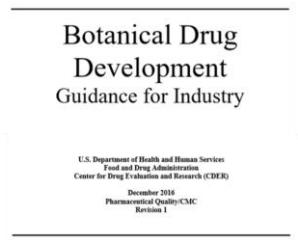
de novo antimicrobial discovery (as proven with *S.a.*) would be performed in 24-36h

Rapid response to bio-terrorism attacks and pandemics

Rapid tool for facing non-envisaged organisms

Adapted for confined crews situations

Regulatory Issue: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Is there an issue at all?

In regards of a definitive and sustainable answer bio-threats?

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LET'S TALK NOW