ADeBIOTeCH
THINK TANK ONE HEALTH

Colloque
16 Septembre 2021

Approches Innovantes dans la lutte contre l'antibiorésistance

Prof. Djamel Drider
Université de Lille

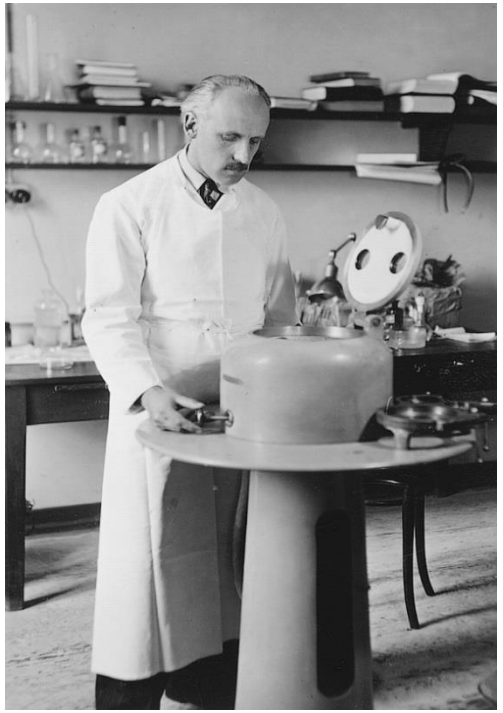
Dr. Philippe Gabant
Co-founder & CSO
Syngulon SA, Seraing (Belgique)

Les peptides antimicrobiens : pourquoi et comment ?
Les bactériocines

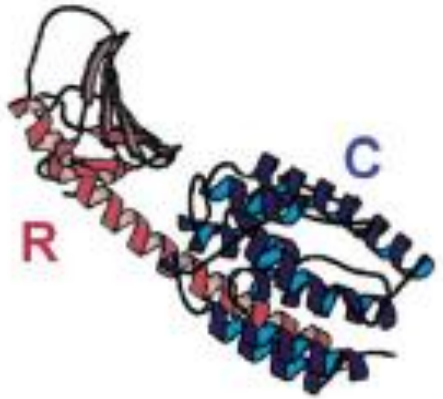
Plan de la présentation

- Eléments généraux sur les bactériocines (D3-D10).
- Partie D. Drider, Université de Lille (D11-D19).
- Partie P. Gabant, Syngulon SA, Seraing, Belgique. D20-D34

Bacteriocins



Prof. André GRATIA (1893-1950)
Prof at ULB and later at ULiège

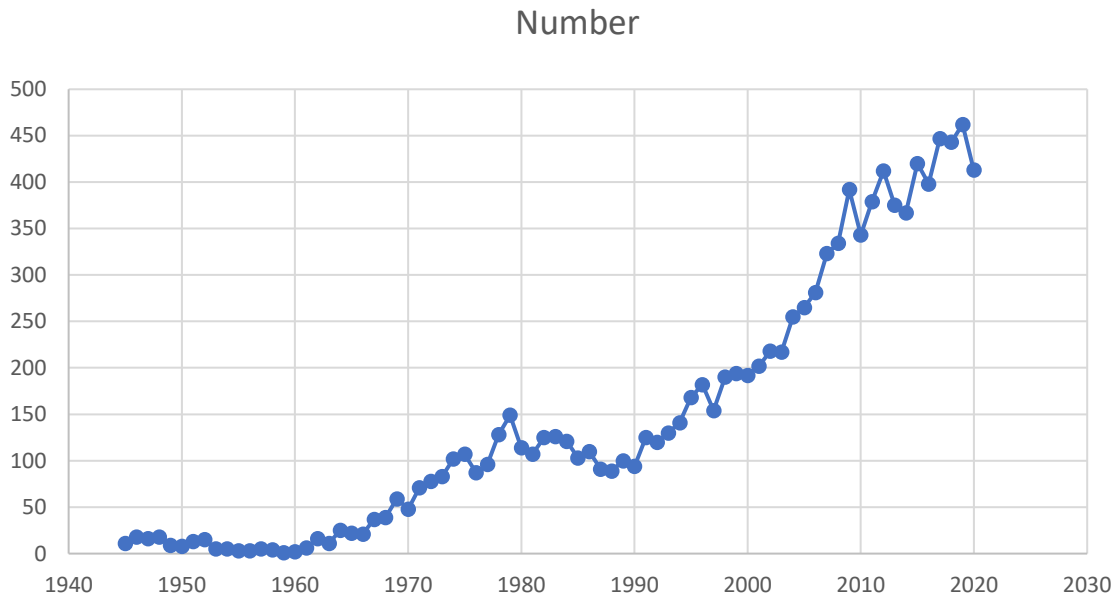


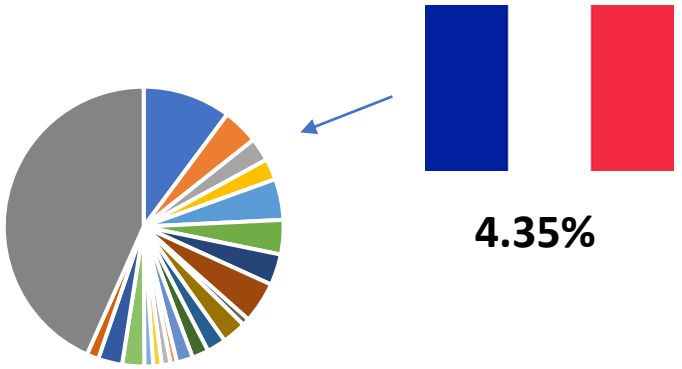
1925 (colicin)

Bacteriocins are Antimicrobial Peptides (AMPs) :

- ribosomally synthesized by **Gram-positive**, **Gram-negative** and *Archaea*
- scheme of production of primary metabolites
- proteinaceous nature
- non-cytotoxic (usually)
- active against bacteria which are phylogenetically close to the producing strains **but**…
- stable at different pHs and temperatures
- no universal classification common scheme

Data and database (s)





APD3. http://aps.unmc.edu/AP **(2016)**
OCINS. http://ocins.cftri.com/ocins/ **(2019)**
BACTIBASE. bactibase.hammamilab.org/main.php (2010 updated)

Mode of action of colicin-like bacteriocins

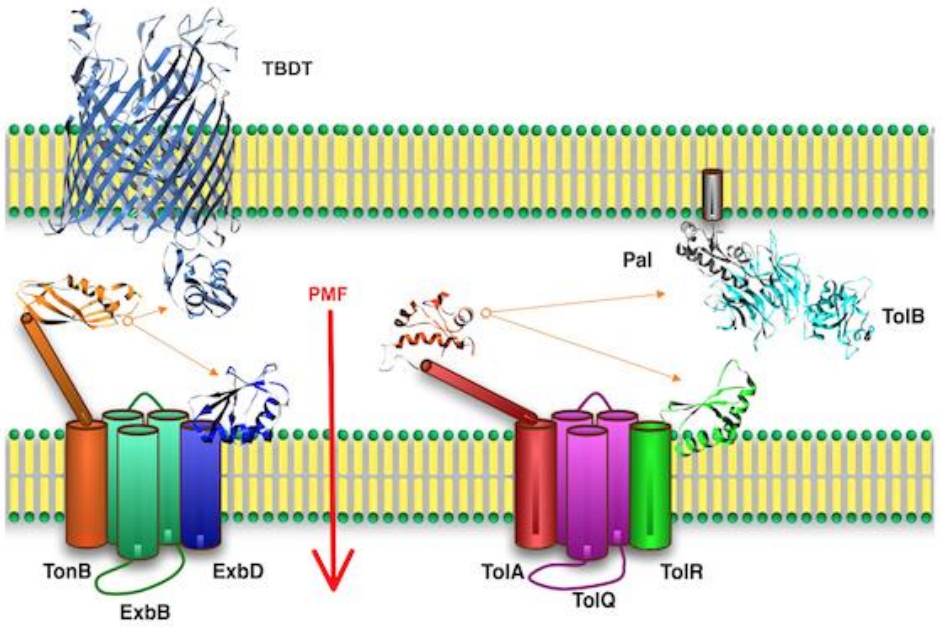
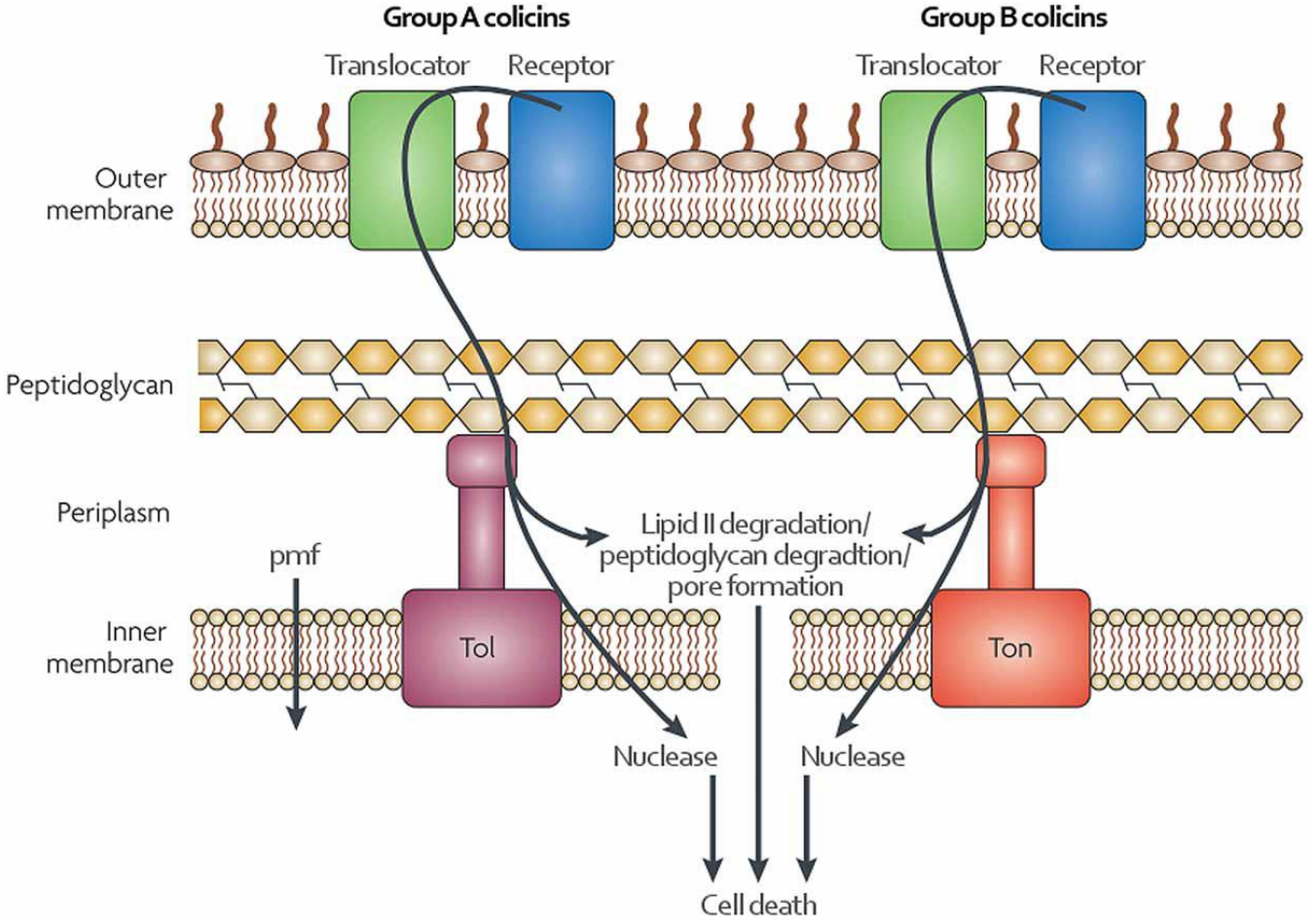
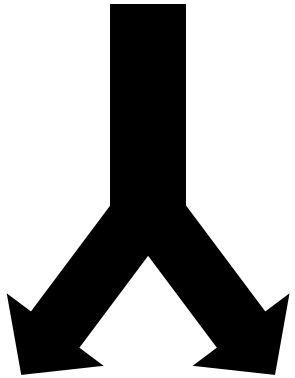


Image: LISM - CNRS (cnrs-mrs.fr)

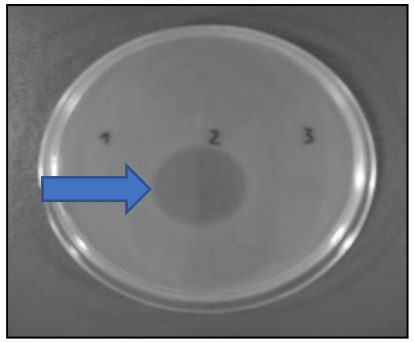


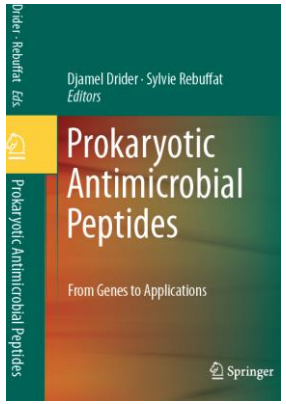
The therapeutic potential of bacteriocins as protein Antibiotics by Hannah M. Behrens et al. 2017. Emerging Topics in Life Sciences (2017) 1 65–74

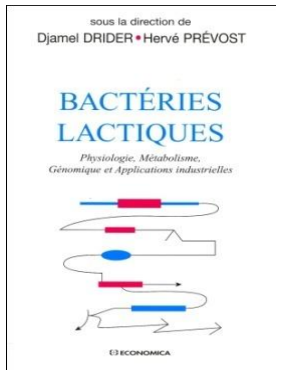
Mode of action of LAB-bacteriocins
Gram-positive bacteria



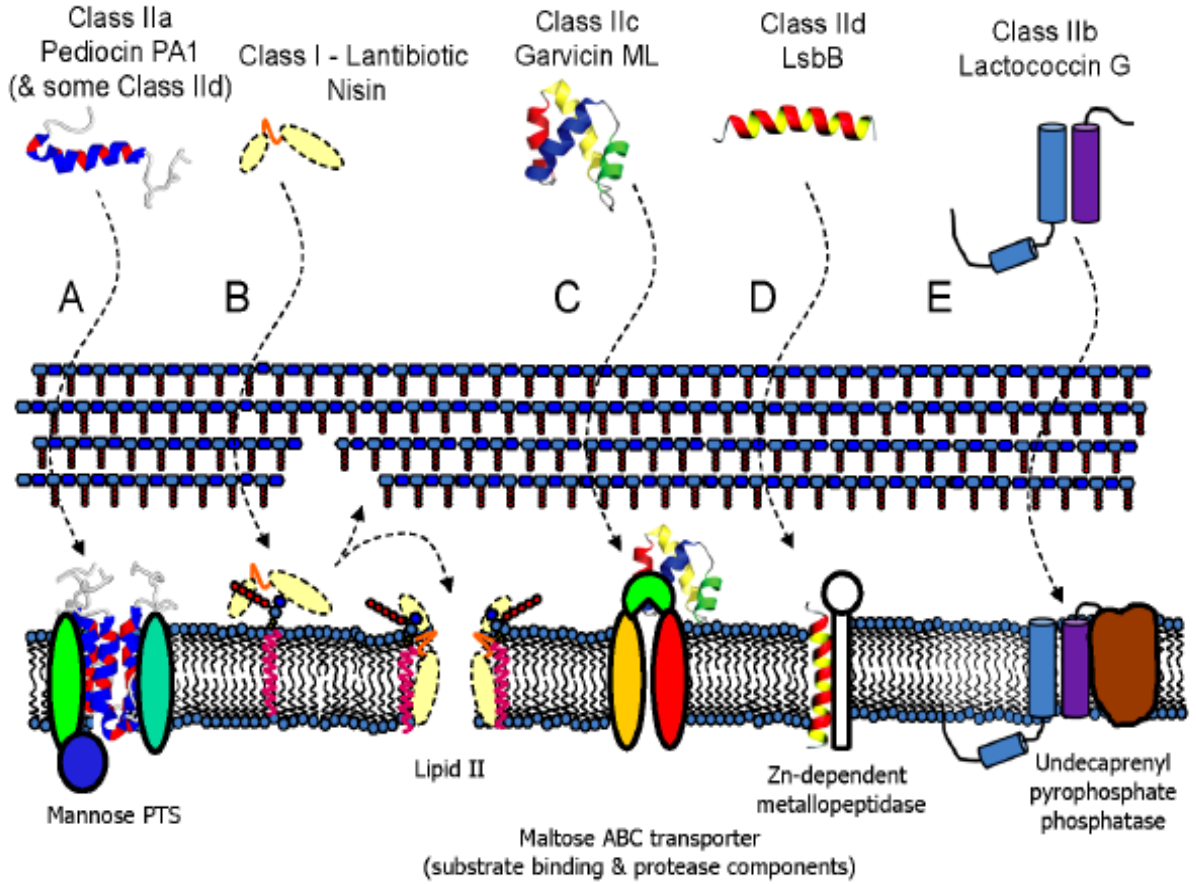
Pore forming	Cell – membrane target
µM CONCENTRATION	**nM CONCENTRATION**







Docking molecules of LAB-Bacteriocins



COTTER et al. (2013). Nature Reviews Microbiology. 11: 95-105

RseP likely serves as the receptor for EntK1 and EntEJ97: stress response membrane-bound Zn dependent protease

Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Biotechnology

Functions and emerging applications of bacteriocins

Michael L Chikindas[1,2], Richard Weeks[1], Djamel Drider[3], Vladimir A Chistyakov[4] and Leon MT Dicks[5]

Probiotics & Antimicro. Prot.
DOI 10.1007/s12602-016-9223-0

Bacteriocins: Not Only Antibacterial Agents

Djamel Drider[1] · Farida Bendali[2] · Karim Naghmouchi[3] · Michael L. Chikindas[4,5]

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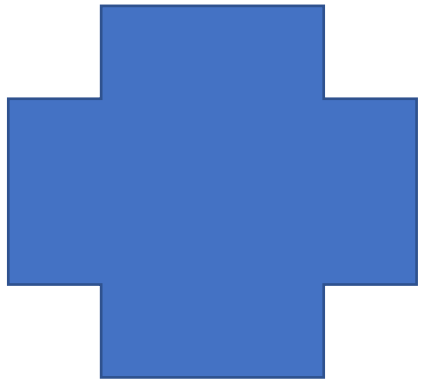
Bacteriocins: Not Only Antibacterial Agents

Djamel Drider[1] · Farida Bendali[2] · Karim Naghmouchi[3] · Michael L. Chikindas[4,5]

LAB-BACTERIOCINS – Prof. D. Drider

Nisin (Nisaplin)
Nisin/colistin combination

Divercin V41
Class IIa
***Carnobacterium divergens* V41**



Enterocin DD14
Leaderless class IIb
***Enterococcus faecalis* 14**

E20 fraction
5 novel class II LAB-bacteriocins
Activity against *Escherichia coli* (*E. coli mcr*-1
EP 19178926.2

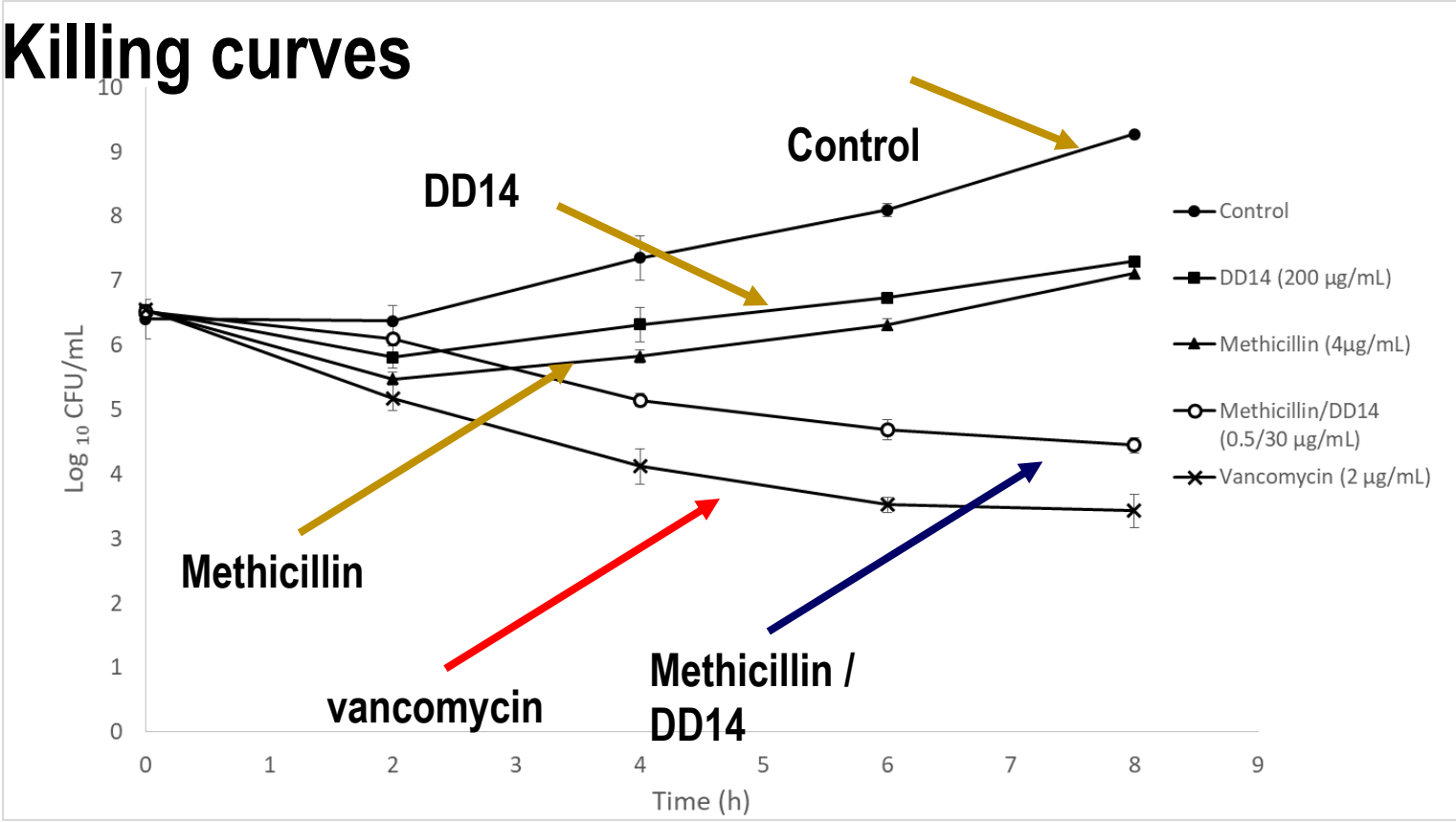
Spectrum of Leaderless class II b Enterocin DD14

Anti-MRSA activity (MRSA-S1)

FICI values

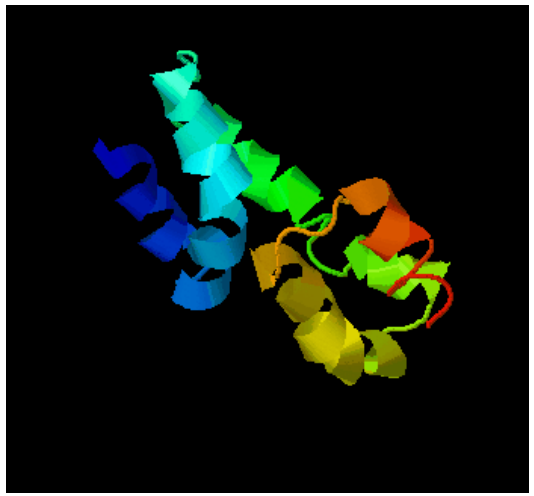
Strains	DD14 (µg/mL)	Methicillin (µg/mL)	Met/DD14 (µg/mL)
S. aureus S1 (MRSA)	>200	4	0.5/30
S. aureus USA300 (MRSA)	>200	16	4/30
S. aureus ATCC 25923 (MSSA)	>200	0.5	0.25/30

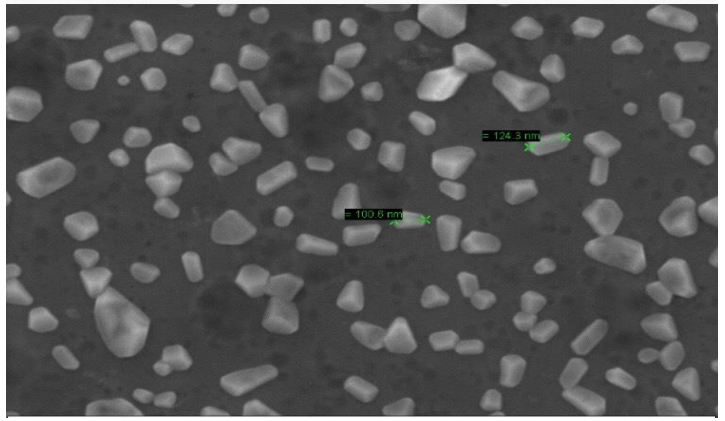
Killing curves



Please remember MRSA-S1 is resistant to Erythromcin & DD14 + Erythromycin have a synergistic interaction

Development of nanobiotics anti-MRSA-S1





Alginate nanoparticles

EntDD14 + Alginate nanoparticles = **Nanobiotics**

- MIC Ent DD14 : 240 µg/ml
- MIC Ent DD14 + Alginate nanoparticules = 60 µg/ml
-

- (EntDD14 + Alginate Nanoparticles) + methicillin,
- MIC methicillin **4 à 0.25 µg/ml**

Anti-biofilm activity

SE

Microbiological Research 252 (2021) 126864

Contents lists available at ScienceDirect

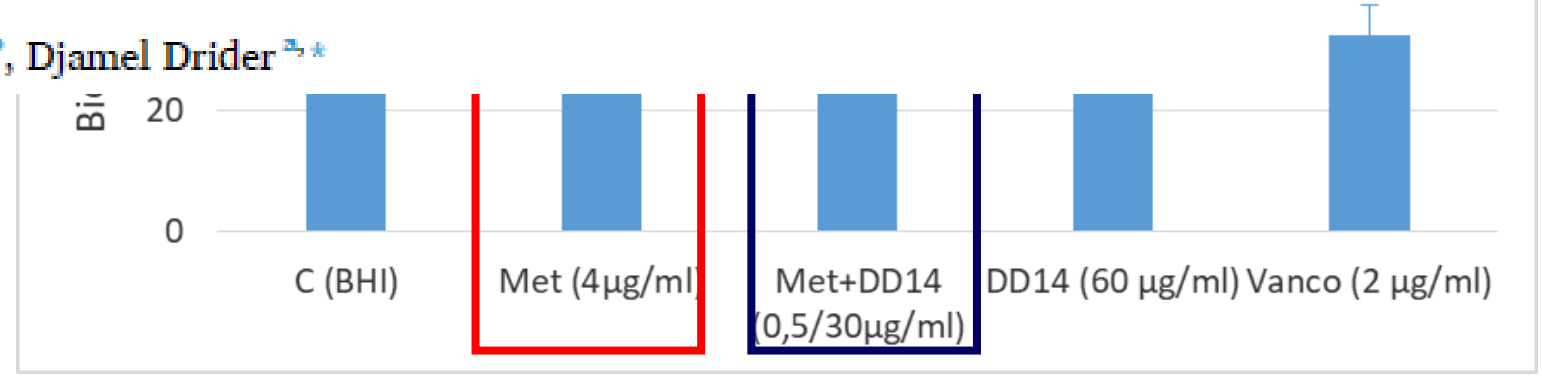
Microbiological Research

journal homepage: www.elsevier.com/locate/micres

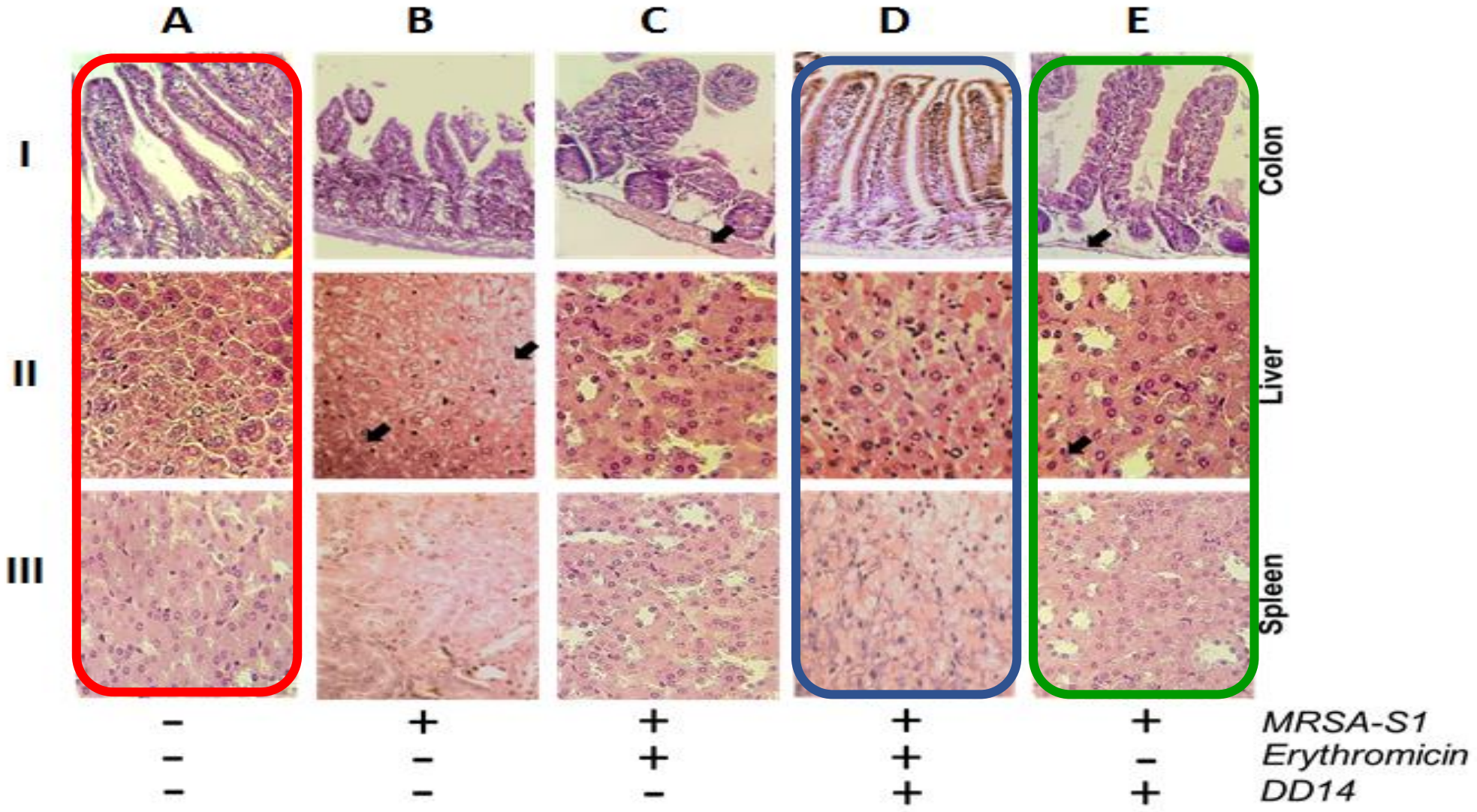
Potentiating effects of leaderless enterocin DD14 in combination with methicillin on clinical methicillin-resistant *Staphylococcus aureus* S1 strain

Yanath Belguesmia [a], Giuseppe Spano [b], Djamel Drider [a,*]

Biofilm: Cristal violet method on polyester plates



Histological alterations following SARM infections, Erythromycin and/or DD14 treatments



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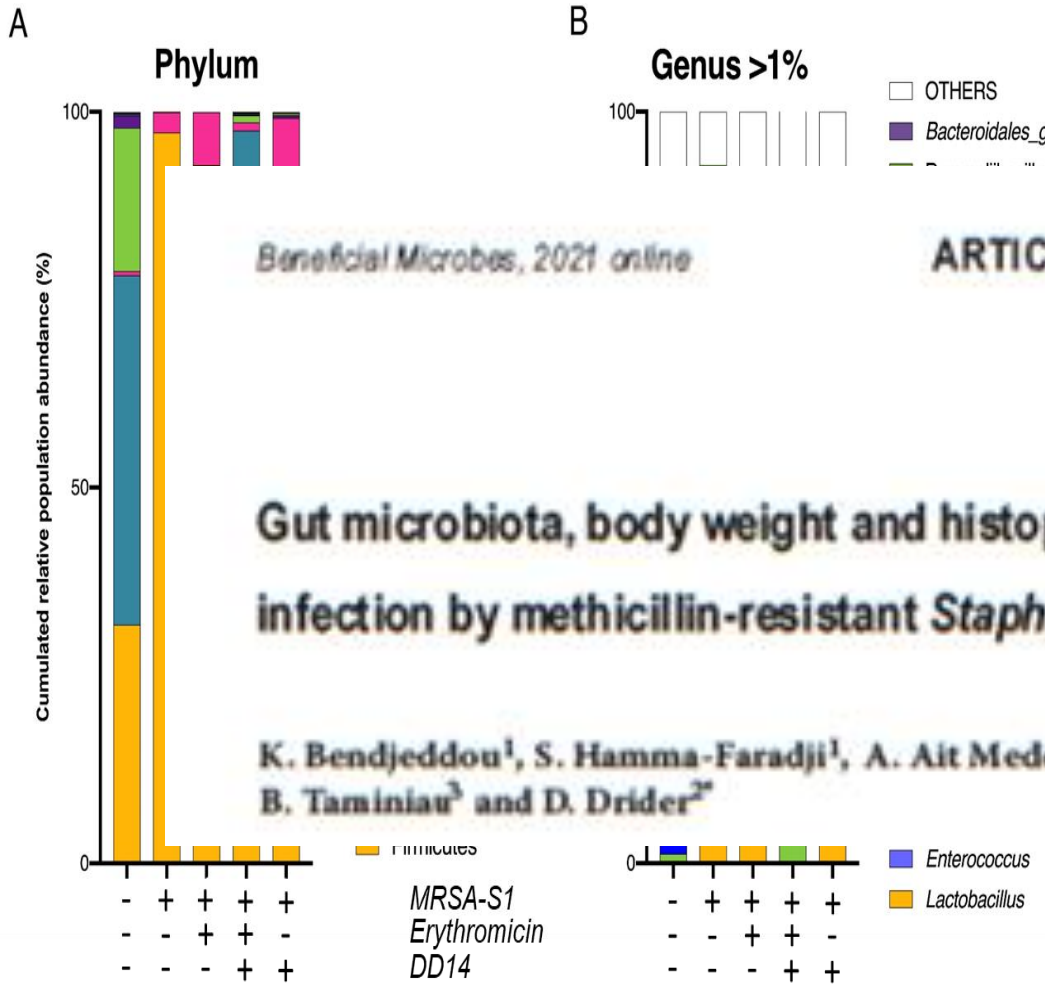


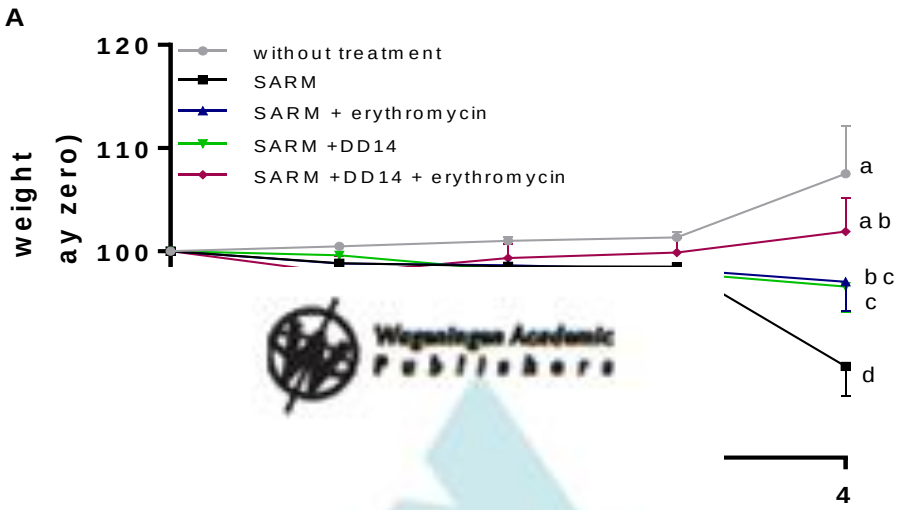
Beneficial Microbes, 2021 online

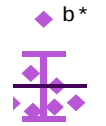
ARTICLE IN PRESS

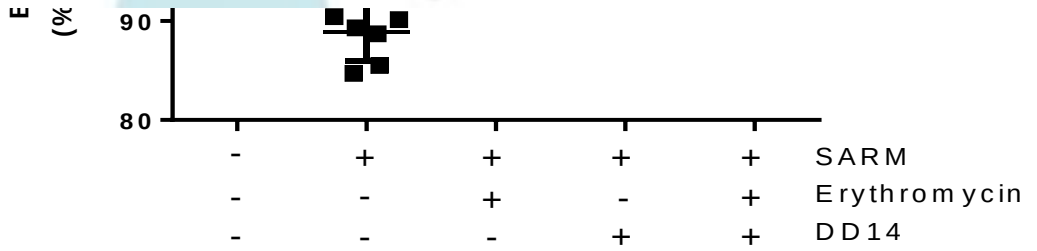
Gut microbiota, body weight and histopathological examinations in experimental infection by methicillin-resistant *Staphylococcus aureus*: antibiotic versus bacteriocin

K. Bendjeddou[1], S. Hamma-Faradji[1], A. Ait Meddour[1], Y. Belguesmia[2], B. Cudennec[2], F. Bendali[1], G. Daube[3], B. Taminiau[3] and D. Drider[2]*

Body weight evolution (statistic analysis)

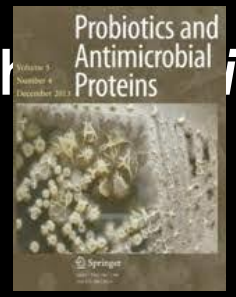






Innovative strategy

Gut microbiota is an important source of bacteriocins and th*itu* expression can be explored for treatment of bacterial infections



Djamel DRIDER
Probiotics and Antimicrobial Proteins (Review in press)

DOI. 10.1007/s12602-021-09843-y

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FACTURE

PHILEO
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International

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Research

La Région des
Hauts de France
Local authorities

Lille University

Colloque
16 Septembre 2021 (Paris)

Approches Innovantes dans la lutte contre l'antibiorésistance

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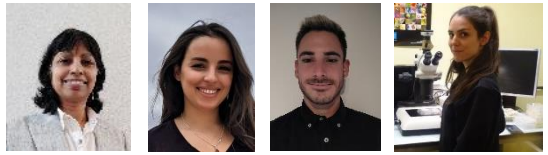
TEAM / SAB / R&D Partners

Team

Guy Hélin, Co-founder, CEO
Dr. Philippe Gabant, Co-Founder, CSO



Dr. Mohamed El Bakkoury, CTO Yeast
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Dr. Baptiste Dumont, R&D Project Manager
Félix Jaumaux, PhD Student
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Hajar Amraoui, PhD Student
Loïc Mues, R&D Scientist
Dr. Silvia Soto Diaz, R&D Project Manager

Collaboration with:
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Dr. Juan Borrero

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IN MEMORIAM
Dr Régis Sodoyer, ex-Sanofi Pasteur, Lyon (FR)

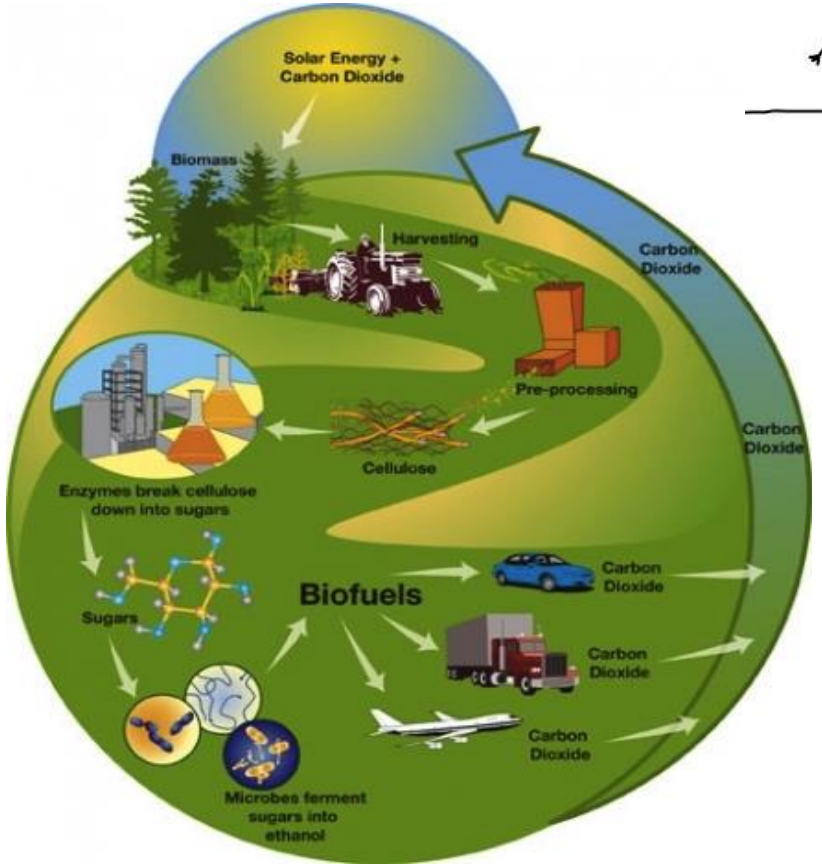
R&D Partners

The importance of microbes for life on our planet

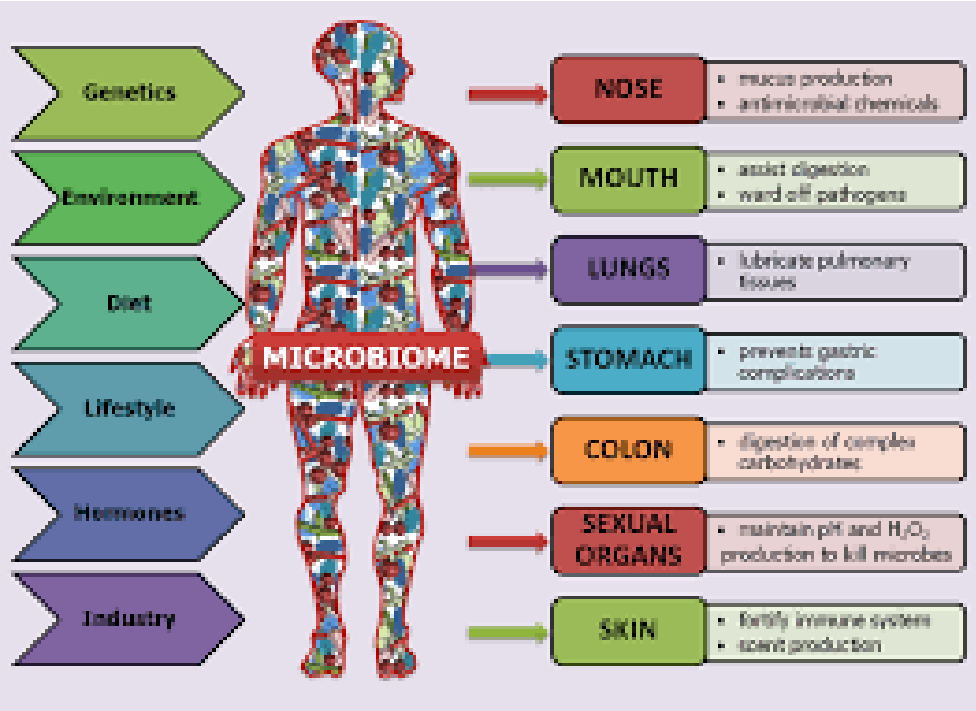
- Microbes are the chemical biocatalysers of our ecosystem
- Microbes are collaborating and fighting with each other to reach certain equilibrium to form communities: « microbiota »
- These microbiota have evolved to generate unique chemical reactions <u>via species synergies</u>

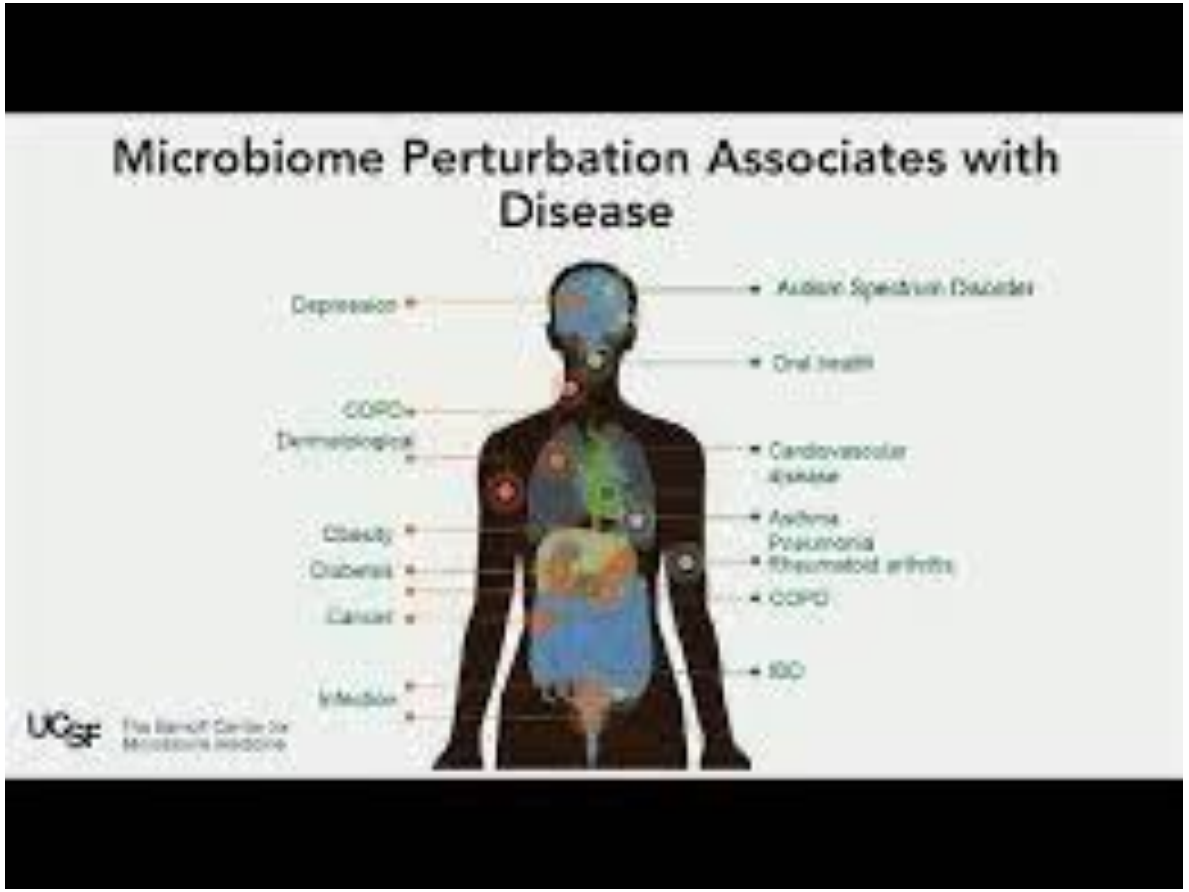
A Biobased Chemistry

- Improvements in energy storage
- An intensification of biotechnological processes

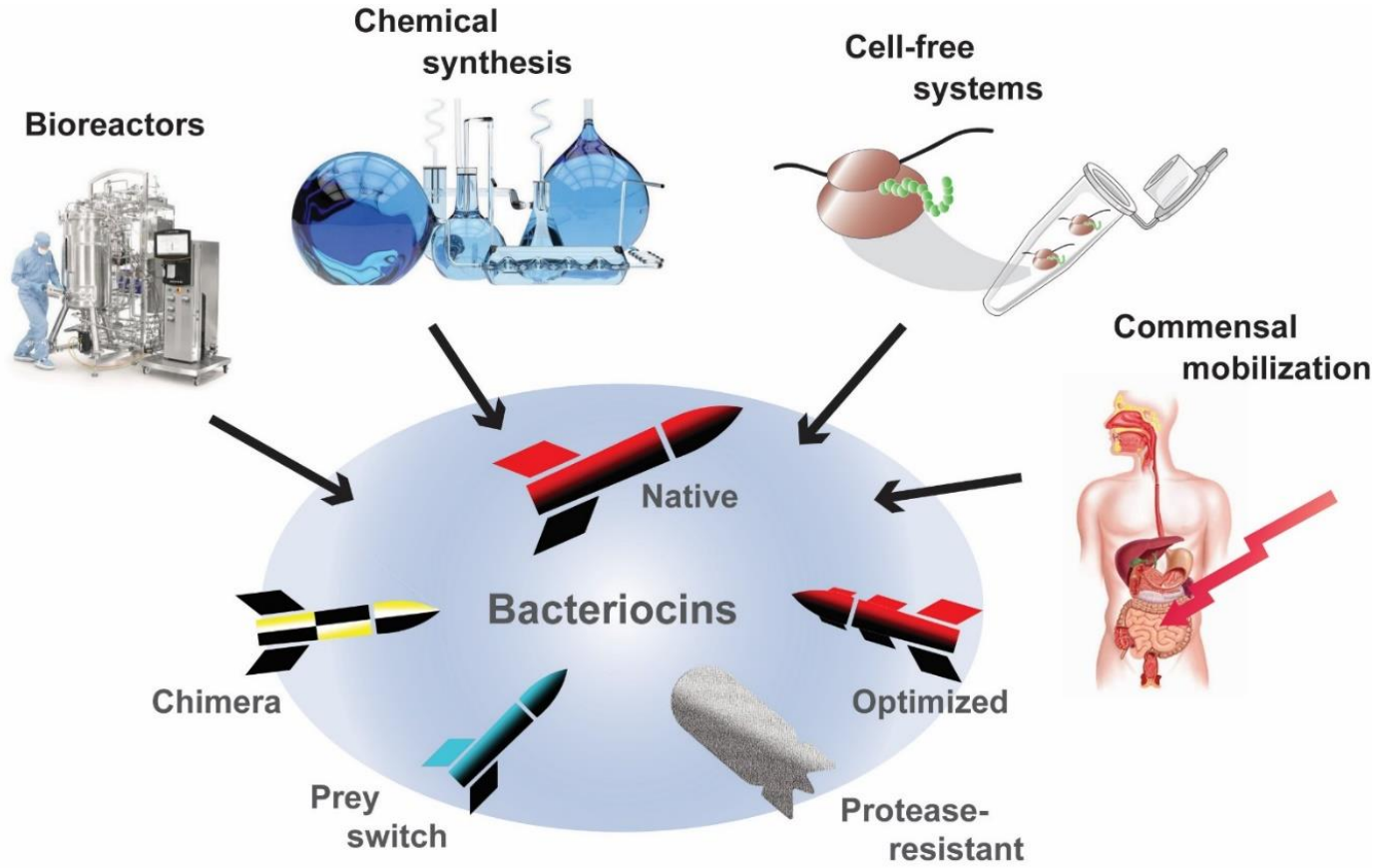


Bacteria and our health





Bacteriocin potential



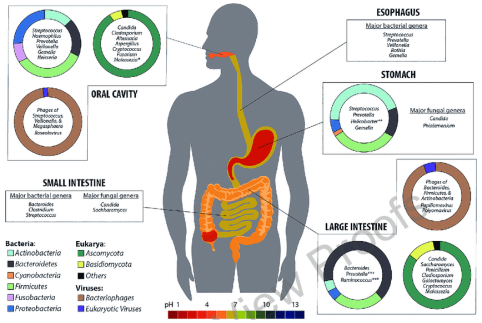
- Production
- Genetic amenability
- Various prey spectrum
- Molecular diversity
- Cyto-friendly
- Stability
- Biological half-life

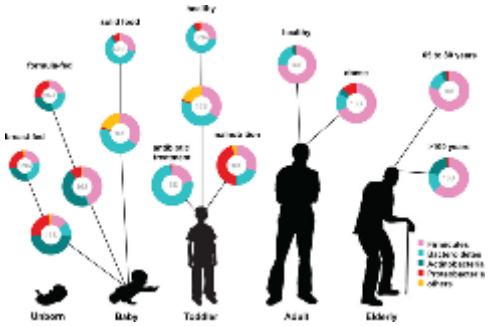
Pascal Hols, Laura Ledesma-García, Philippe Gabant and Johann Mignolet, Trends Microbiology 1685 No. of Pages 13

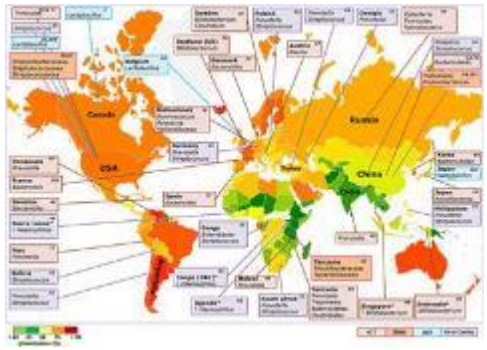
Bacteriocins as alternative to antibiotics

Broad spectrum antibiotics
VS
Narrow spectrum bacteriocins

Human microbiota is very variable

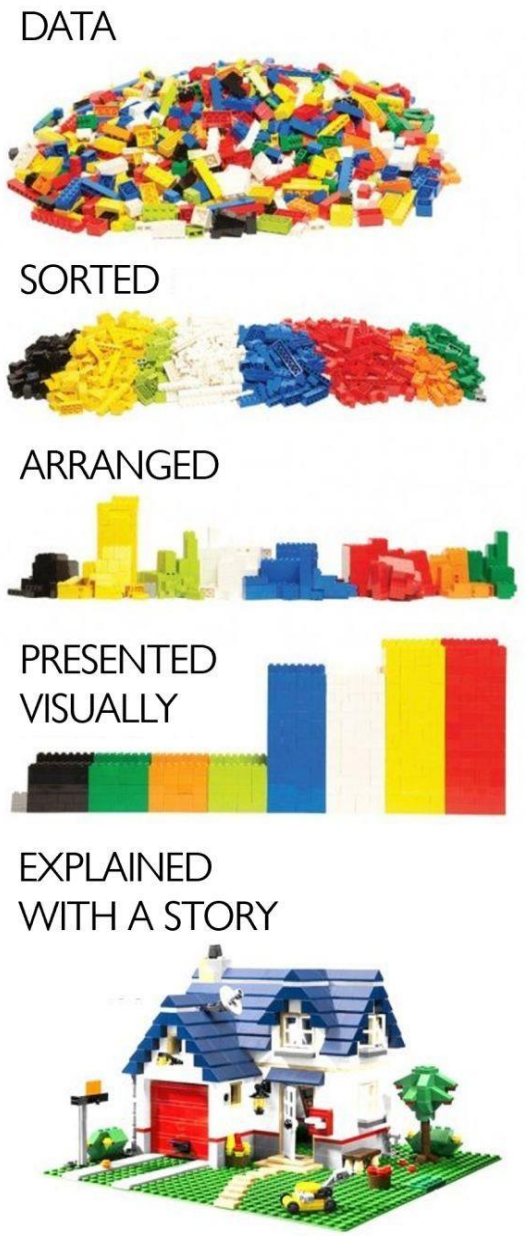


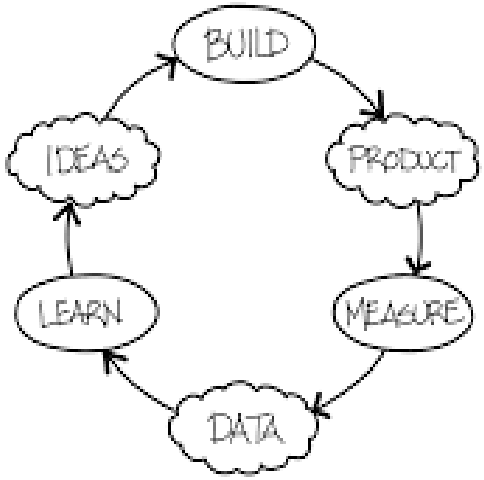




PRECISION MEDICINE

Evolution diversity of bacteriocins





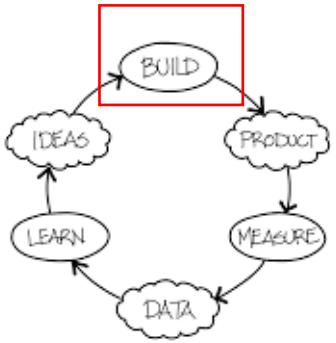
frontiers in Bioengineering and Biotechnology

BRIEF RESEARCH REP
published: 06 September
doi: 10.3389/fbioe.2019.0

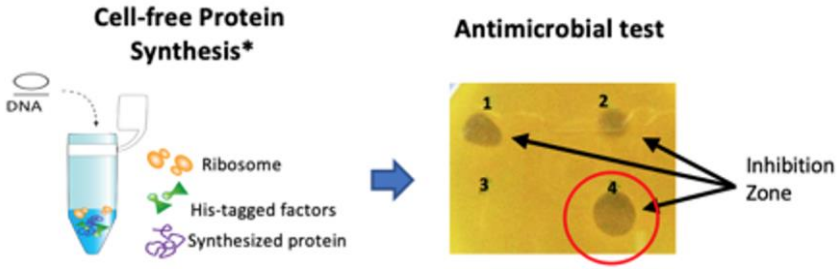
PARAGEN 1.0: A Standardized Synthetic Gene Library for Fast Cell-Free Bacteriocin Synthesis

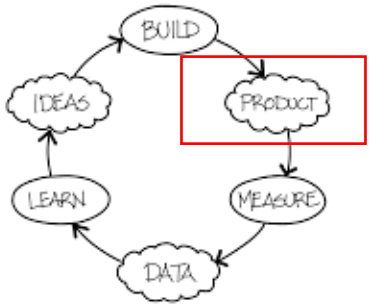
Philippe Gabant and Juan Borrero†*

Syngulon, Seraing, Belgium

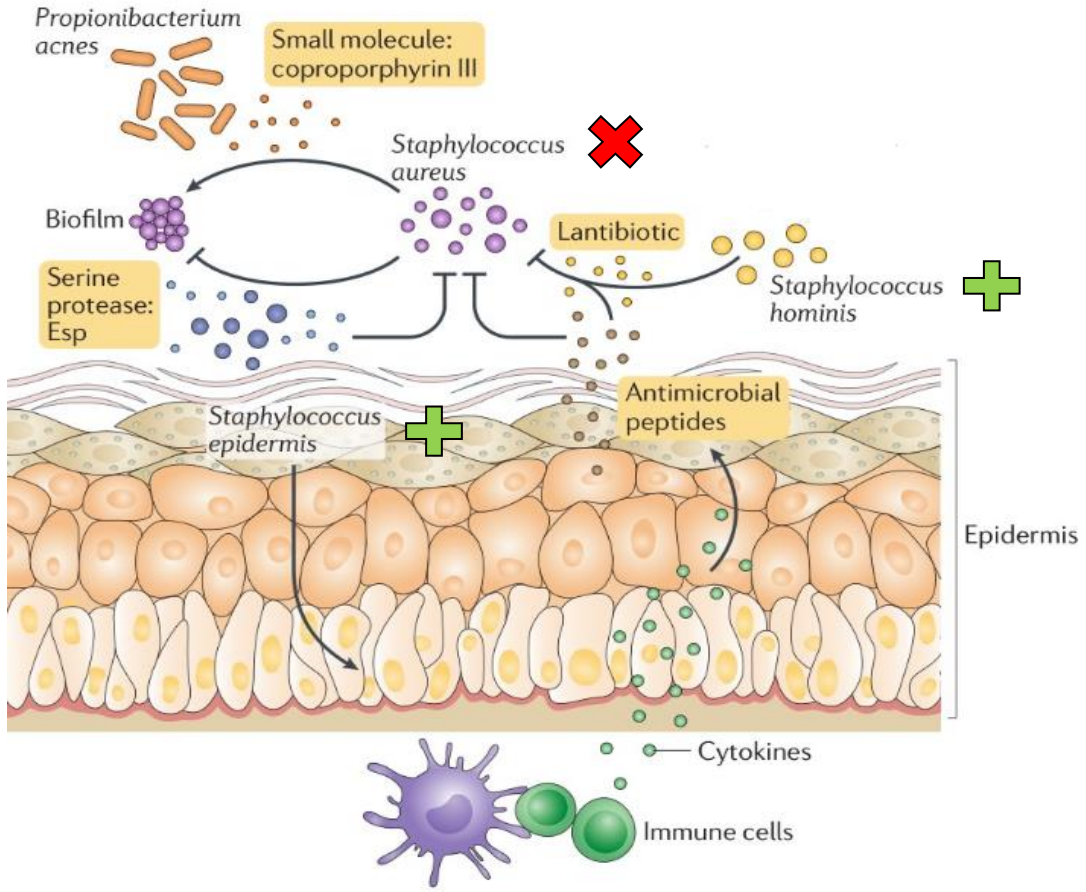


To explore the diversity of bacteriocins we have built a collection of synthetic genes in a standardized format allowing rapid activity measurements of bacteriocins products.

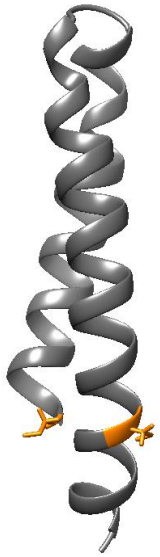


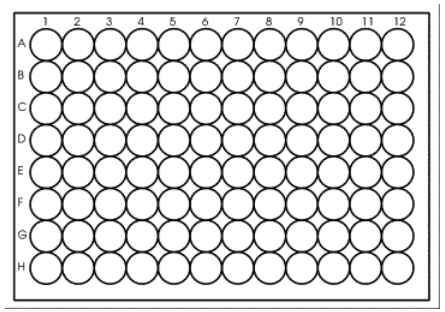


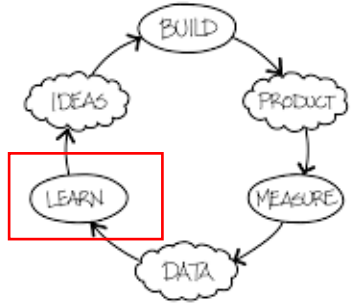
Example of a potential application

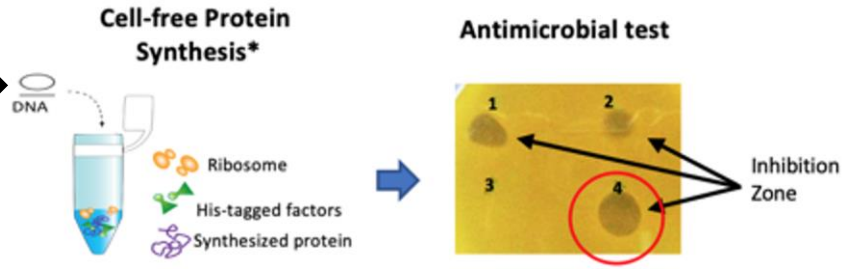


Mutant Library generation to determine structure/function relationships









Type of mutations
- Alanine scan
- Deletion
- Single or multiple amino acid mutation
- (Charge variation)
- (Disulfides bound)

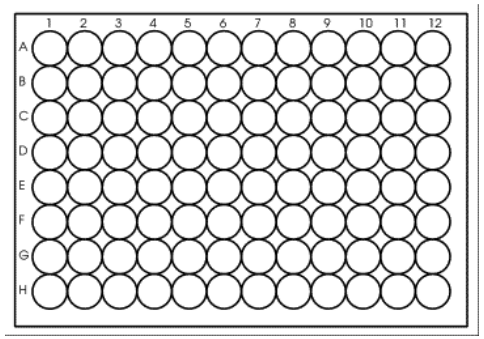
Félix Jaumaux

Prof Cédric Govaerts and Prof Abel Garcia-Pino

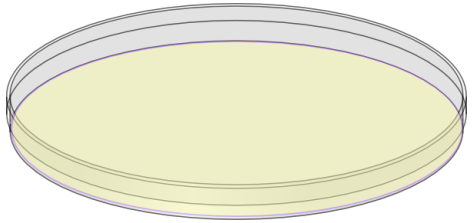
Professor Pascal Hols

Screening of the PARAGEN collection

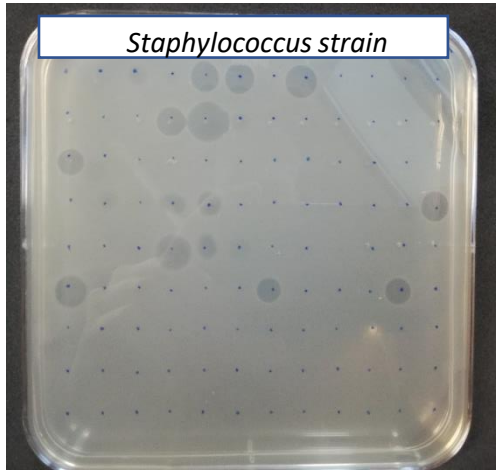
Félix Jaumaux



96 well plate containing chemically synthesized bacteriocins



Petri dish with a homogenous culture of a Staphylococcus strain

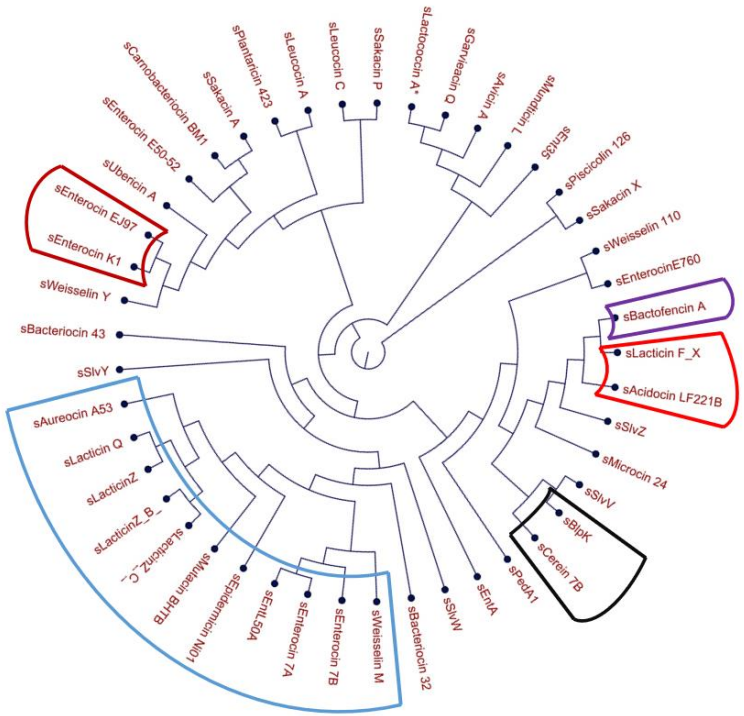


Observation of inhibition halos

Professor Pascal Hols

Professor Jacques Mahillon

Screening looking for bacteriocins active against S. aureus (7 strains tested)



Bacteriocins non active against S. epidermidis (2 strains tested)

A; B; C

Publications

BRIEF RESEARCH REPORT ARTICLE

Front. Bioeng. Biotechnol., 06 September 2019 | https://doi.org/10.3389/fbioe.2019.00213

PARAGEN 1.0: A Standardized Synthetic Gene Library for Fast Cell-Free Bacteriocin Synthesis

Philippe Gabant* and Juan Borrero†

Syngulon, Seraing, Belgium

eLIFE elifesciences.org

RESEARCH ARTICLE

Subtle selectivity in a pheromone sensor triumvirate desynchronizes competence and predation in a human gut commensal

Johann Mignolet[1,2‡*], Guillaume Cerckel[1†], Julien Damoczi[1†], Laura Ledesma-Garcia[1], Andrea Sass[3], Tom Coenye[3], Sylvie Nessler[4], Pascal Hols[1]

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Trends in Microbiology

CellPress REVIEWS

Review

Mobilization of Microbiota Commensals and Their Bacteriocins for Therapeutics

Pascal Hols,[1] Laura Ledesma-García,[1] Philippe Gabant,[2] and Johann Mignolet[1,2,3,*]

Home / Chimica Oggi-Chemistry Today / Vol. 38(4) / Antimicrobial peptides to...

MICHAEL J. BLAND, PHILIPPE GABANT*

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BIOTECHNOLOGY

ANTIMICROBIAL PEPTIDES TO SHAPE BIOBASED CHEMICAL PRODUCTION

Keywords: anti-microbial peptides, antibiotics, bacteriocins, biotechnology, industrial fermentation, microbiome, one health

Open Access Perspective

In the Age of Synthetic Biology, Will Antimicrobial Peptides be the Next Generation of Antibiotics?

by Félix Jaumaux, Luz P. Gómez de Cadiñanos and Philippe Gabant *

Syngulon, Rue du Bois Saint-Jean 15/1, 4102 Seraing, Belgium

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Antibiotics **2020**, *9*(8), 484; https://doi.org/10.3390/antibiotics9080484

Received: 14 July 2020 / Revised: 1 August 2020 / Accepted: 4 August 2020 / Published: 6 August 2020

Other manuscripts in preparation

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Take home message

1. Industries and the health sectors are looking for new ways to control microbial flora (microbiota)
2. Synthetic biology allows to apply biological functions at a new level
3. Bacteriocins are natural antimicrobial peptides (AMP) used by bacteria to protect their ecological niche
4. Syngulon has built PARAGEN a unique collection of synthetic bacteriocin genes (around 500 genes)
5. Via academic collaborations Syngulon is studying the mode of action of bacteriocins
6. Via different industrial/medical partnerships Syngulon is testing applications of bacteriocins