The microbiome as a source of and target for novel antibacterial strategies

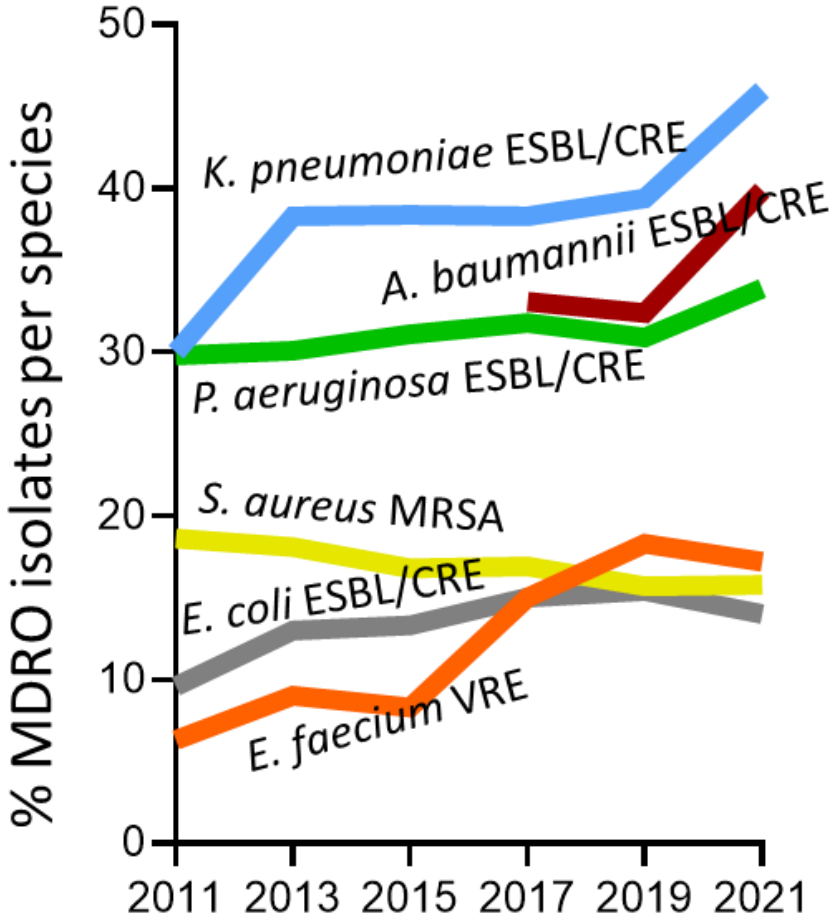
Andreas Peschel

Interfaculty Institute of Microbiology and Infection Medicine Tübingen

Infection Biology

Antibiotic-resistant **"ESKAPE“** pathogens

Invasive ESKAPE isolates in Europe:



ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

E: *Enterococcus faecium* **VRE**
S: *Staphylococcus aureus* **MRSA**
K: *Klebsiella pneumoniae* **ESBL/CRE**
A: *Acinetobacter baumanni* **ESBL/CRE**
P: *Pseudomonas aeruginosa* **ESBL/CRE**
E: *Escherichia coli* **ESBL/CRE**

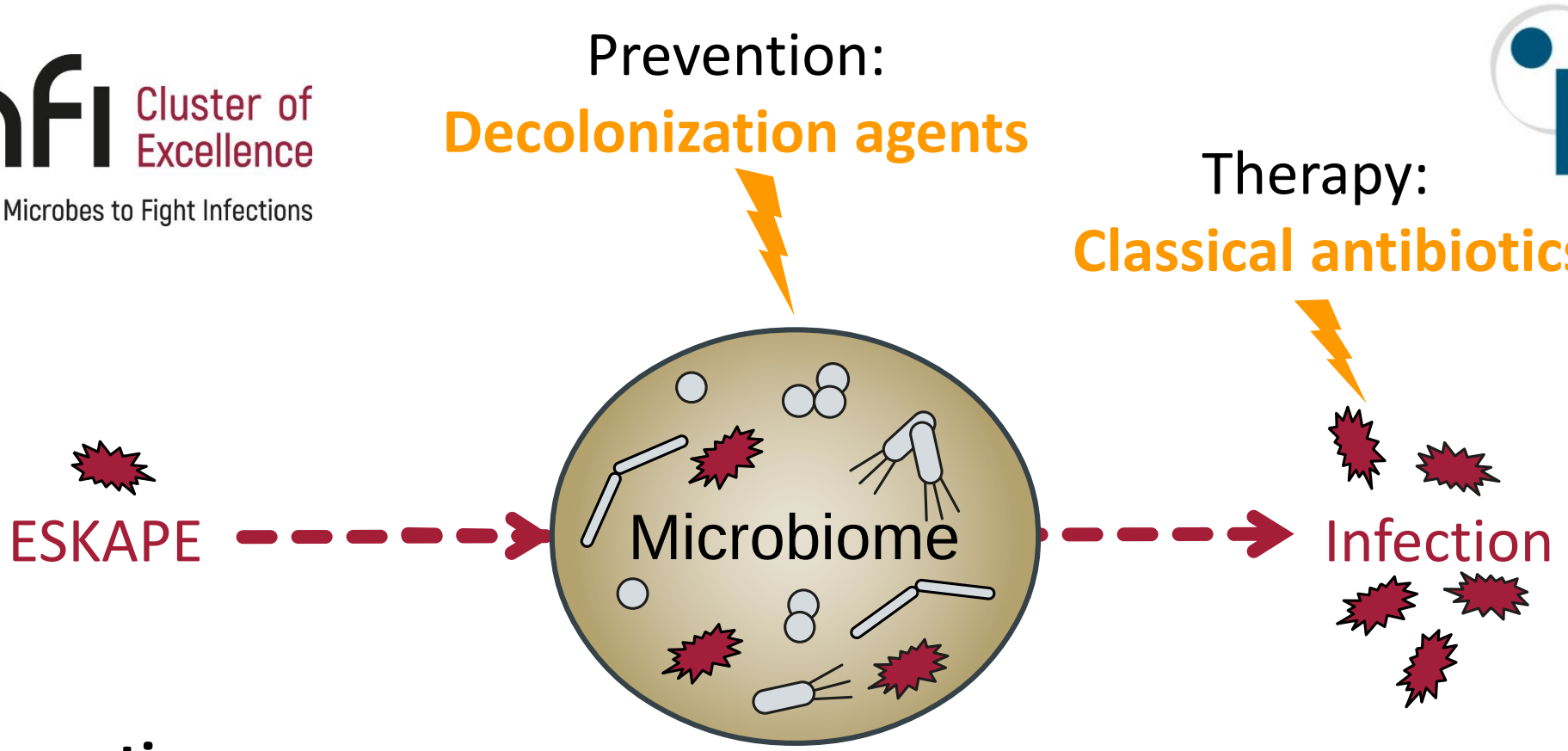
Up to
50% mortality

1,270,000 deaths
per year

ESKAPE pathogens hide in **microbiomes**

Cluster of Excellence
Controlling Microbes to Fight Infections

DZIF



Prevention:

- *'Precision probiotics'*
- *Decolonization drugs, phages*

Tacconelli, Autenrieth, Peschel (2017) *Science*

German Center for Infection Research (**DZIF**)

Funding:
German Research Foundation (DFG)

Funding:
Investors,
Biotech, Pharma

DZIF
Deutsches Zentrum für Infektionsforschung

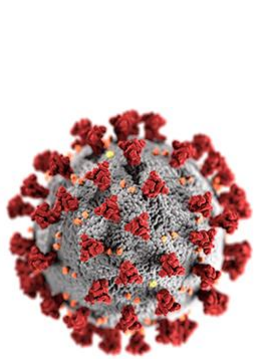
→*Therapeutics*

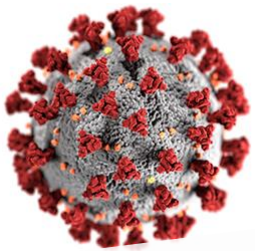
→*Vaccines*

→*Innovative prevention*

→*Clinical guidelines*

“There is glory in prevention”



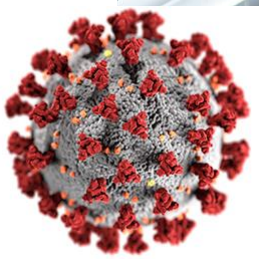


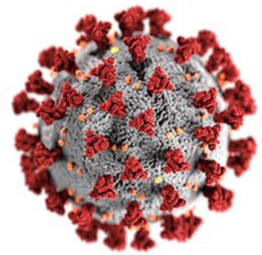
Correspondence

Beyond COVID-19—a paradigm shift in infection management?

Maria J G T Vehreschild [a, b, c], Evelina Tacconelli [d, h, i], Christian G Giske [e, f], Andreas Peschel [g, h, i]

THE LANCET Infectious Diseases





Current ESKAPE decolonization

S. aureus nasal decolonization

'Selective Digestive Decontamination'

S. aureus --> Infections <-- **Intestinal opportunists**

Mupirocin

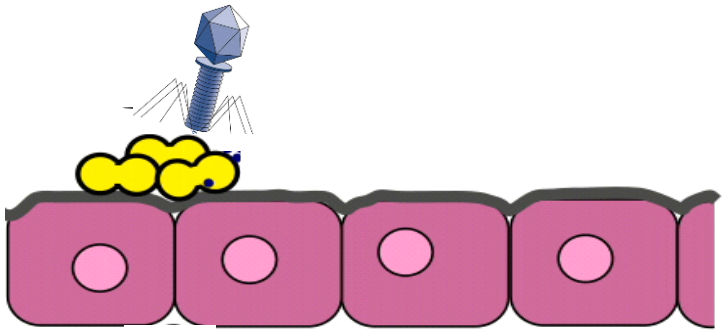
Colistin

Broad-spectum antibiotics

- Damage microbiomes
- Amplify resistance genes
- Endanger treatments of last resort

→ *How to decolonize in a selective, microbiome-preserving way?*

MRSA decolonization by bacteriolytic **phage enzymes**



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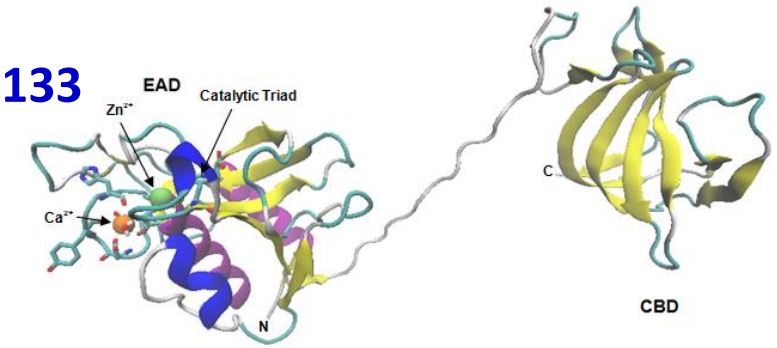
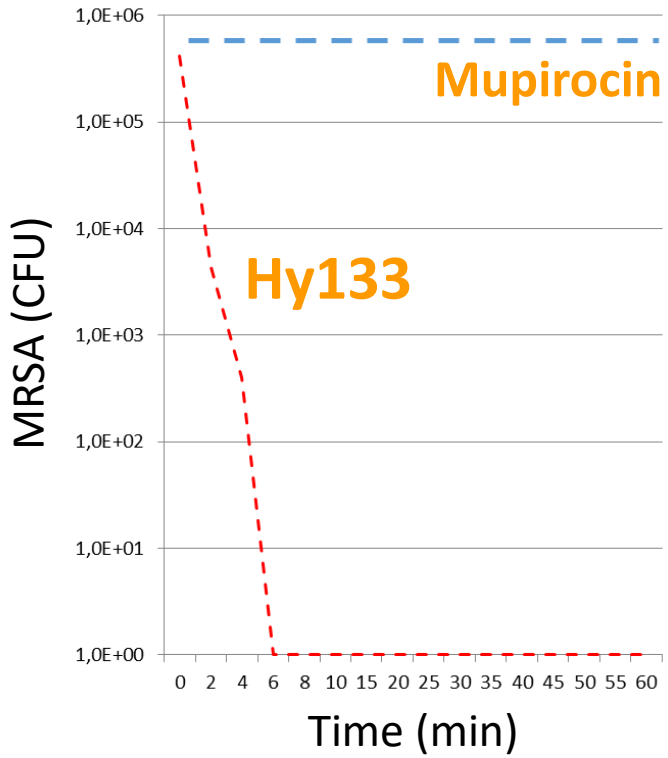
Hypharm

HY-133



Hy133 is bactericidal:

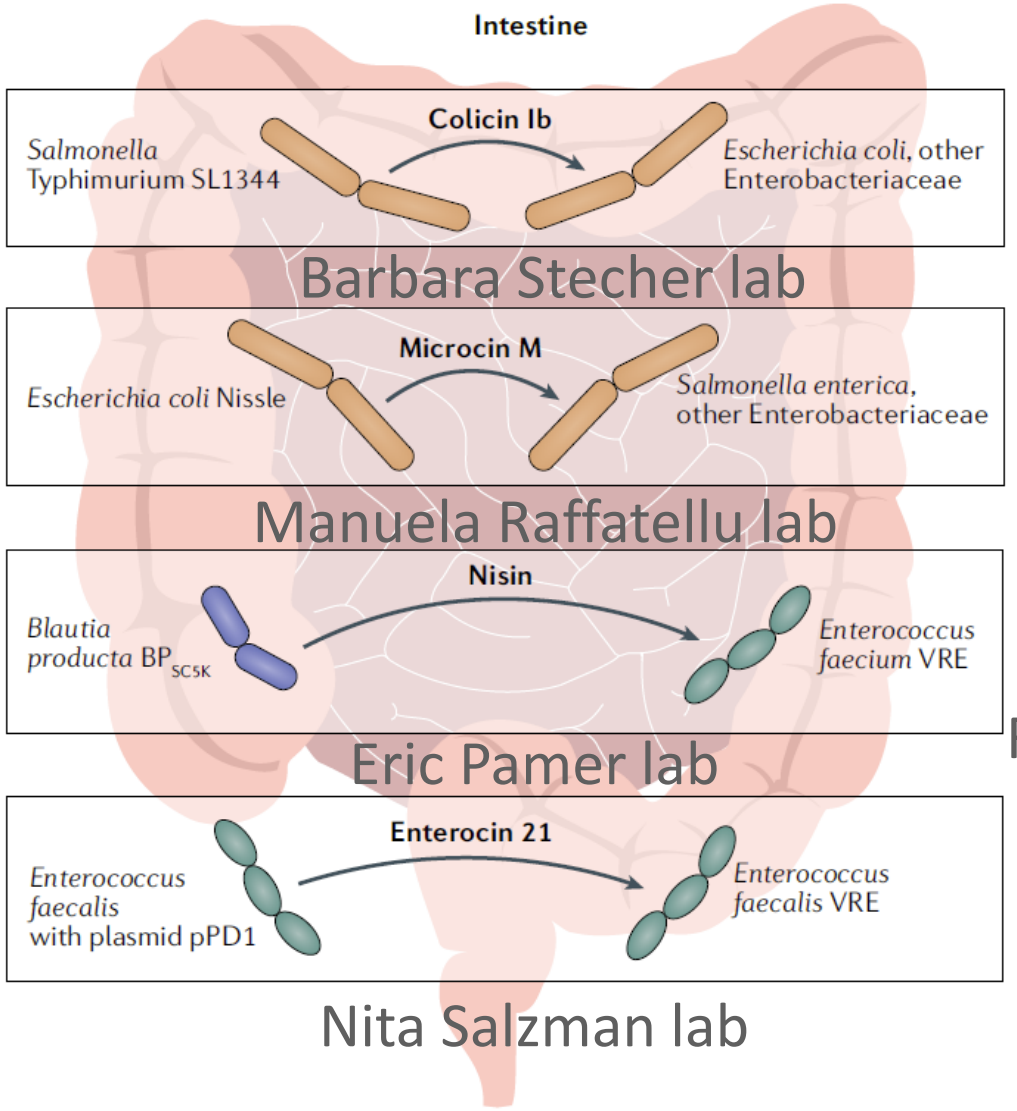


Lytic phage proteins:

- Bactericidal
- Much smaller than full phages
- No resistance induced
- Very good preclinical safety profile

Idelevich et al (2016) *Antimicrob Agents Chemother*

Colonization resistance by '**precision probiotics**'

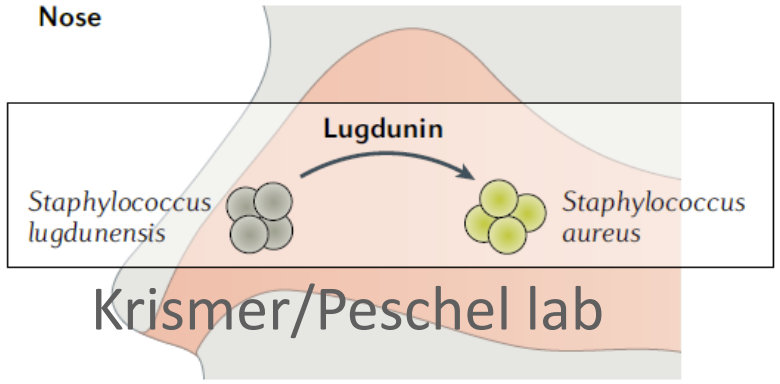


Barbara Stecher lab

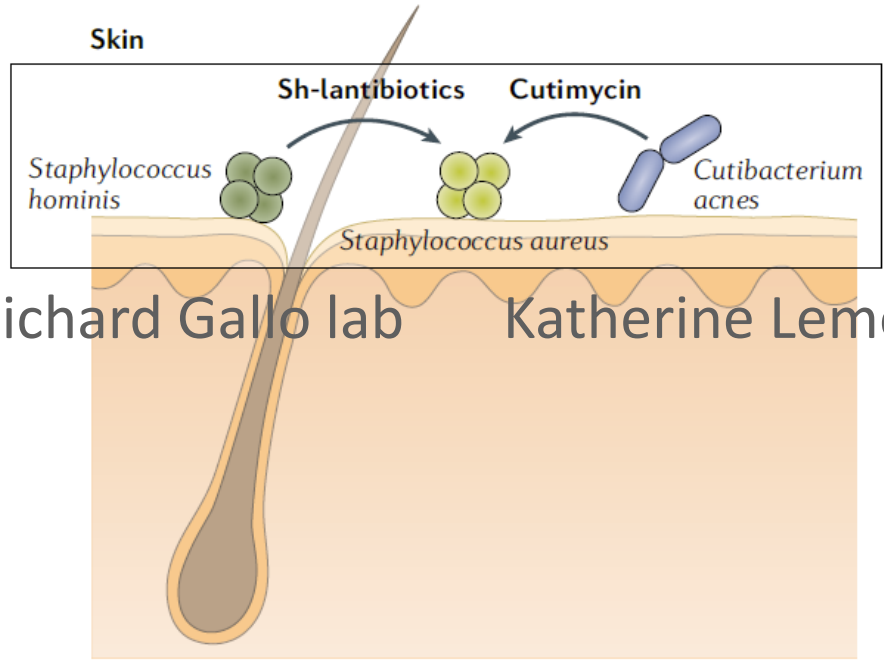
Manuela Raffatellu lab

Eric Pamer lab

Nita Salzman lab



Krismer/Peschel lab



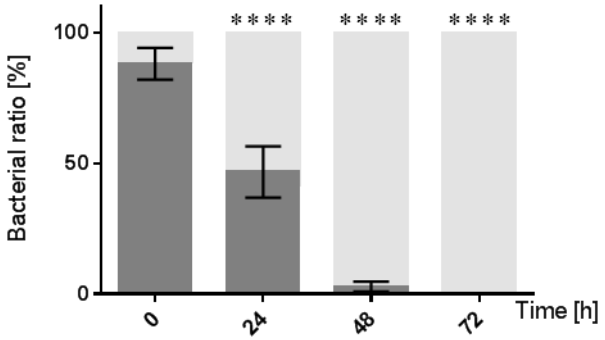
Richard Gallo lab

Katherine Lemon lab

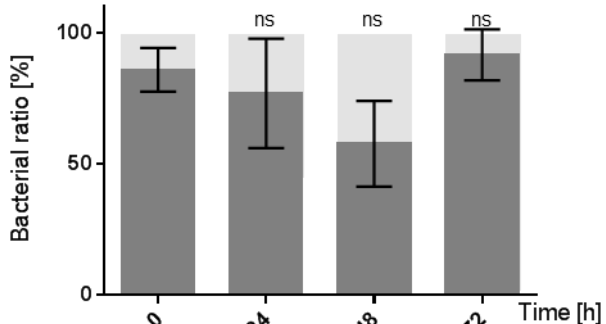
Heilbronner et al (2021) *Nat Rev Microbiol*

Lugunin-producing *S. lugdunensis* prevents *S. aureus* colonization

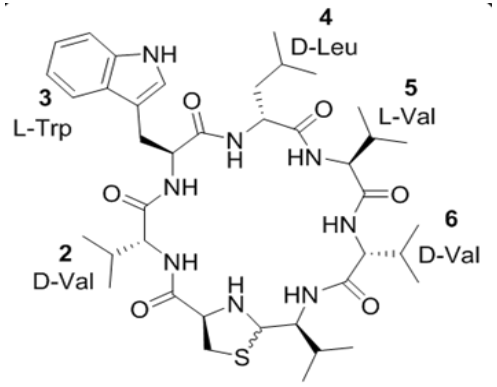
Growth competition *in vitro*



S. aureus +
S. lugdunensis wild type

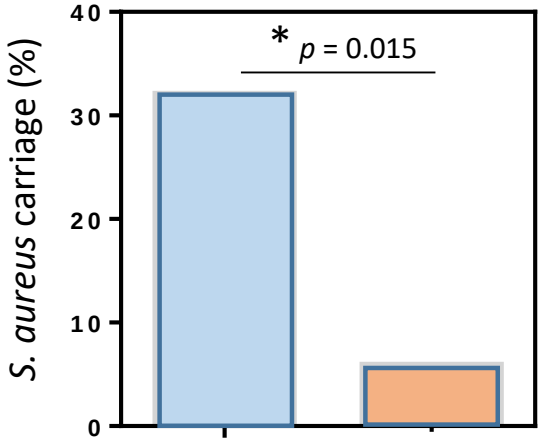


S. aureus +
S. lugdunensis mutant



Lugdunin

***S. aureus* carriage rate**

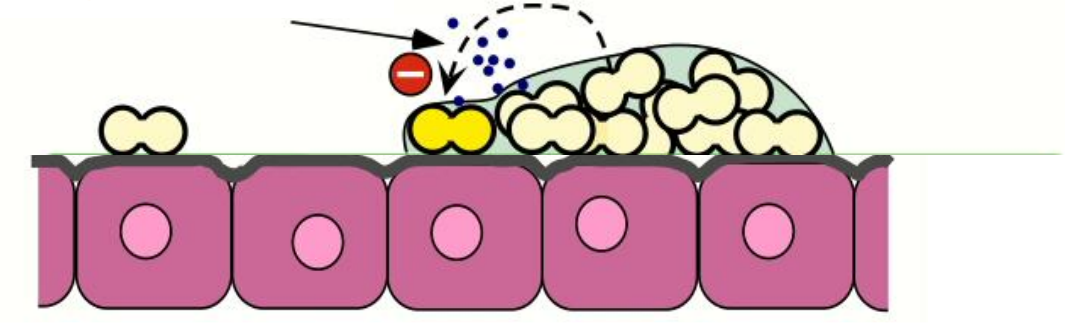


Zipperer et al (2016) *Nature*

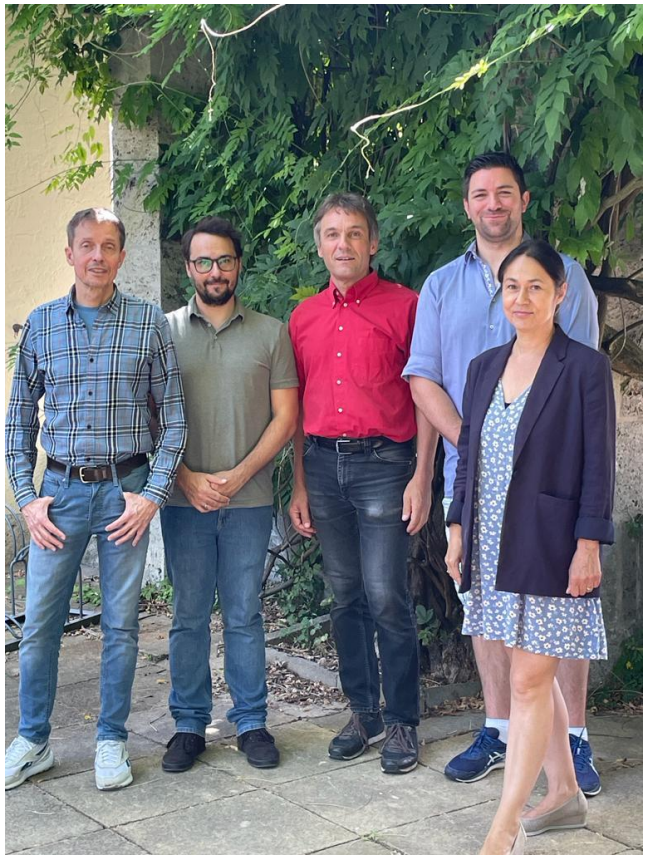
→ *S. lugdunensis reduces risk of S. aurues carriage 6-fold*

Develop the lugdunin producer into a probiotic
“live bacterial product”

Lugdunin



Else Kröner Fresenius Stiftung



- GMP production of live bacterial product
- Phase-I/IIa trial at Univ. Hosp. Tübingen
  - → Safety
  - → Sustained establishmen of LBP
  - → Impact on *S. aureus* carriage

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Controlling Microbes to Fight Infections

Target product profiles:

→ Preventing severe infections by eliminating MRSA/ *S. aureus* from the human nose in at-risk patients

Mupirocin (130 Mio $ per year):

→ *5-6-days treatment, increasing resistance, broad microbiome damage*

***S. lugdunensis* "precision probiotic":**

→ *1-time treatment, sustained exclusion*

Else Kröner Fresenius Stiftung

Cmfi Cluster of Excellence
Controlling Microbes to Fight Infections

Hy133 phage lysin:

→ *1-day treatment, preserves microbiome integrity*

DZIF Deutsches Zentrum für Infektionsforschung

Hypharm

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andreas.peschel@uni-tuebingen.de

@AndreasPeschel1