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Human commensals producing novel antibiotics impair pathogen colonization

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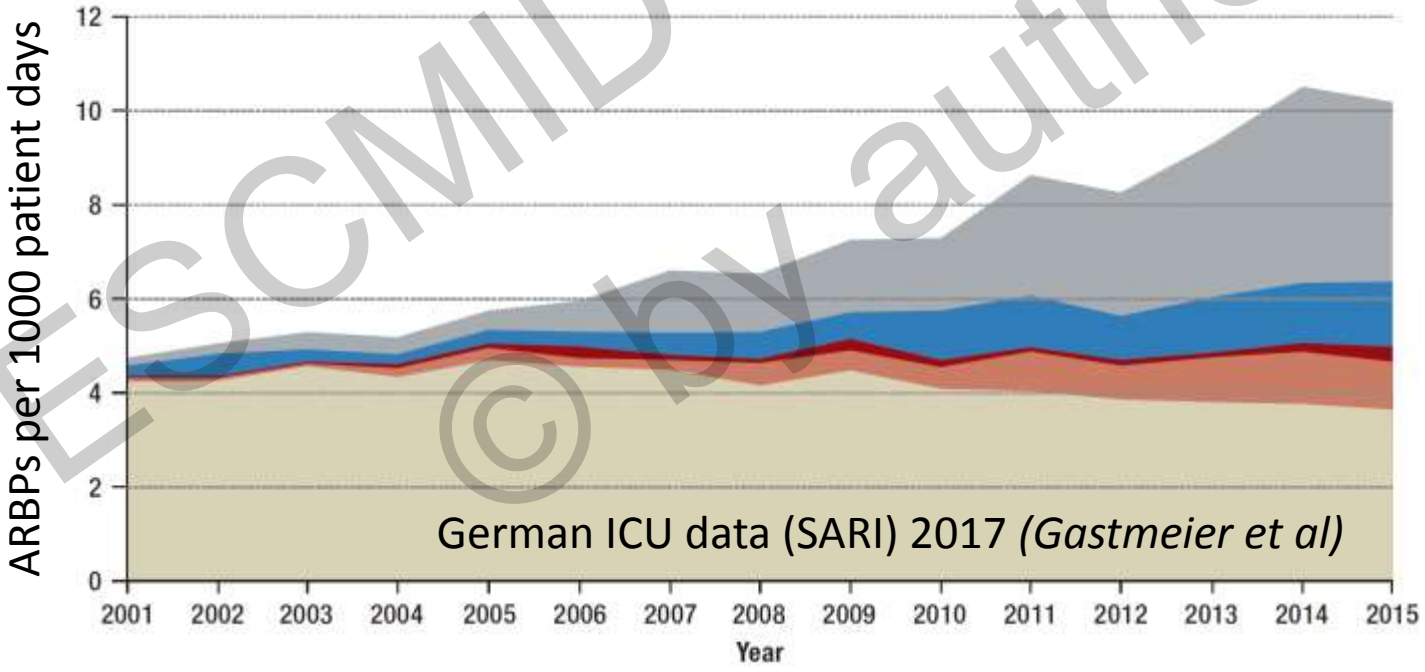
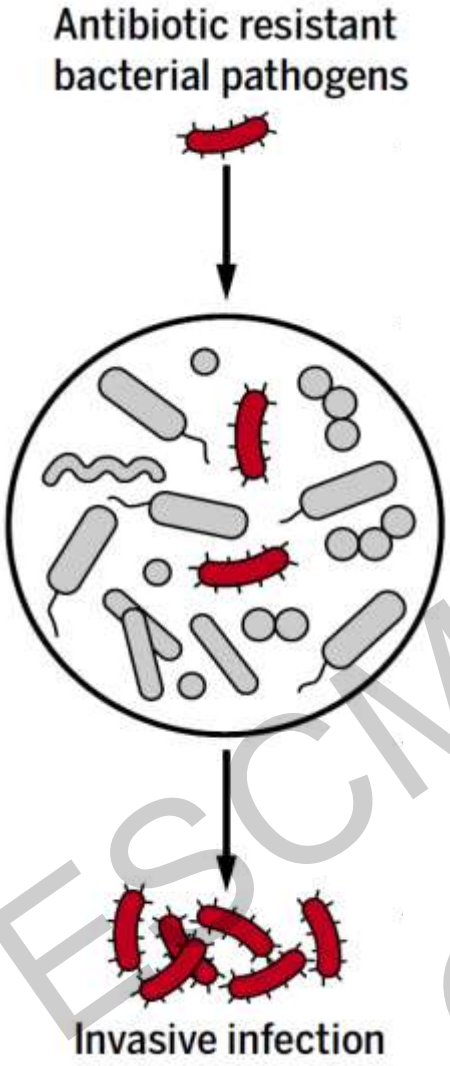
Major ARBPs: the ‘ESKAPE’ pathogens

- **E:** *Enterococcus faecalis/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**, 700,000 deaths per year



Majority of invasive infections start from microbioms



In microbioms of healthy humans:

- *Staphylococcus aureus* CA-MRSA
- *Klebsielle pneumoniae* MDR/XDR
- *Escherichia coli* MDR/XDR
- *Clostridium difficile*

In microbioms of hopitalized patients:

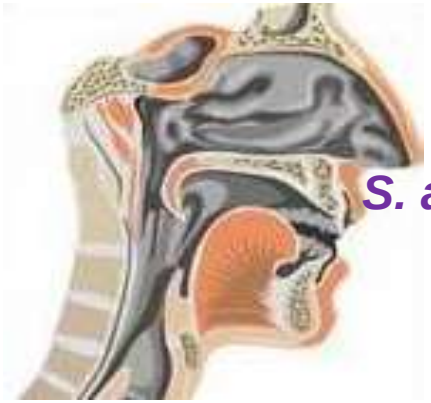
- *Enterococcus faecium* VRE
- *Pseudomonas aeruginosa* MDR/XDR
- *Acinetobacter baumannii* MDR/XDR

→ Should risk patients be screened, isolated, decolonized?

Tacconelli, Autenrieth, Peschel (2017) *Science*

Current ARBP decolonization relies on broad-spectrum antibiotics

S. aureus nasal decolonization:



S. aureus

Wounds

Catheter

Bloodstream

Lung

Selective Digestive Decontamination:

Intestinal opportunists

With **mupirocin**

- Increasing mupirocin resistance (30%)
- Damages microbiomes

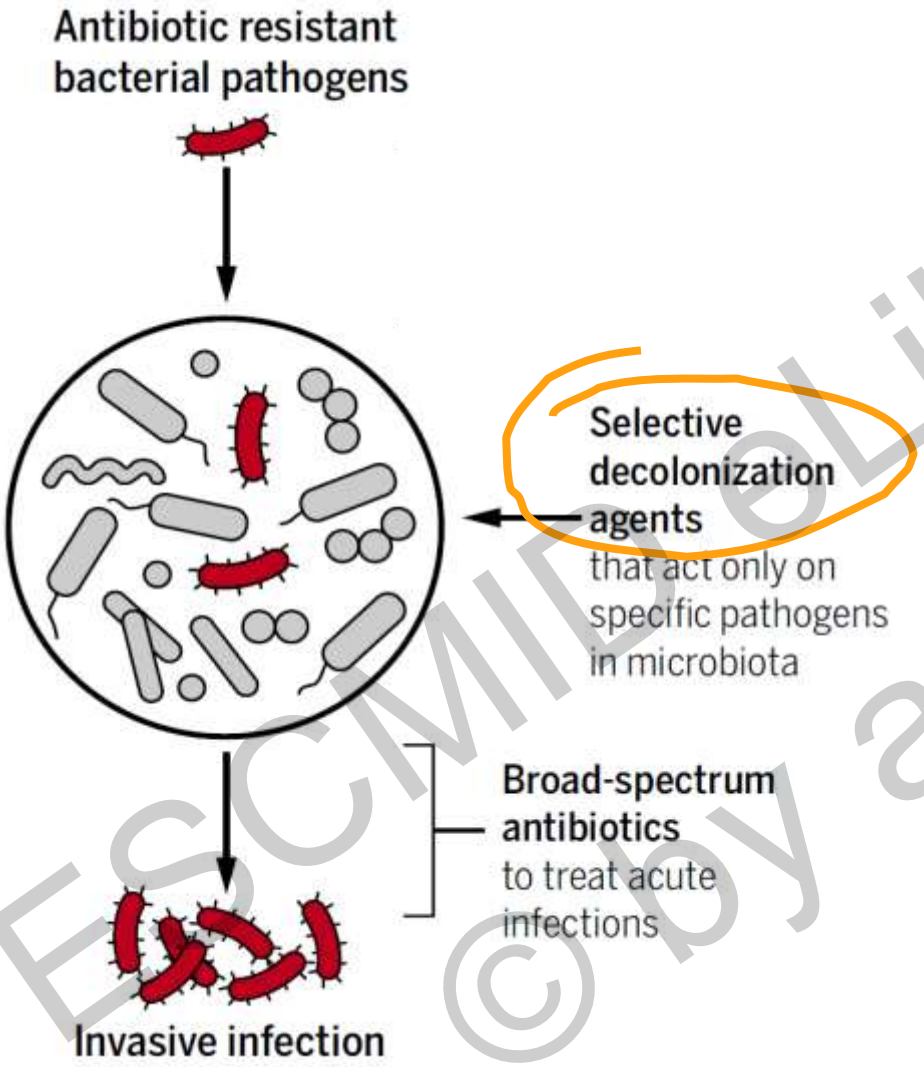
With non-absorbable antibiotics (e.g. **colistin & tobramycin**)

- Endangeres antibiotics of last resort
- Amplifies resistance genes
- Damages microiomes

→ ***How to decolonize in a selective way?***

Tacconelli, Autenrieth, Peschel (2017) *Science*

Decolonization drugs



Properties:

- Non-resorbable
- Narrow activity spectrum
- Fast, bactericidal

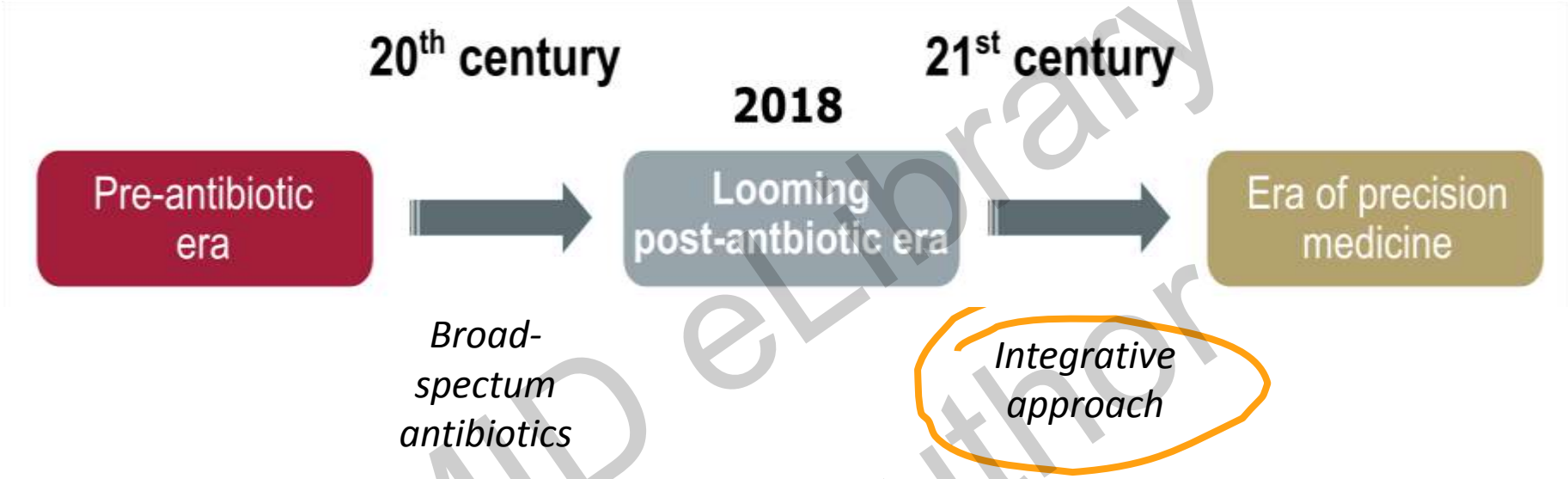
Economically viable?

- Substantial reduction of ICU costs
- Mupirocin (generic): $ >120 mio/a
- *New compounds would yield substantially higher revenues*

→ ***How to develop decolonization drugs?***

Tacconelli, Autenrieth, Peschel (2017) *Science*

New avenues against antibiotic resistance



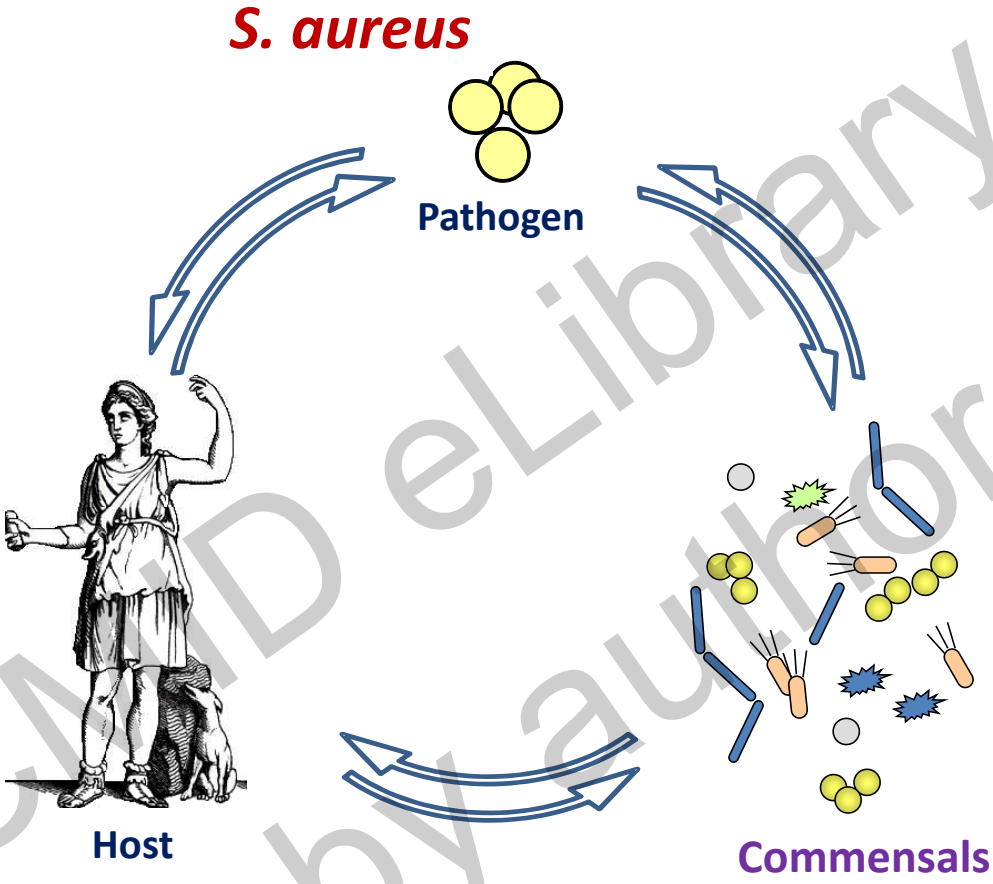
Consider innovative and integrative approaches

Consider **human microbioms** as a source

→ ***for most antibiotic-resistant pathogens***

→ ***for new antimicrobials***

S. aureus colonization governed by nasal microbiome

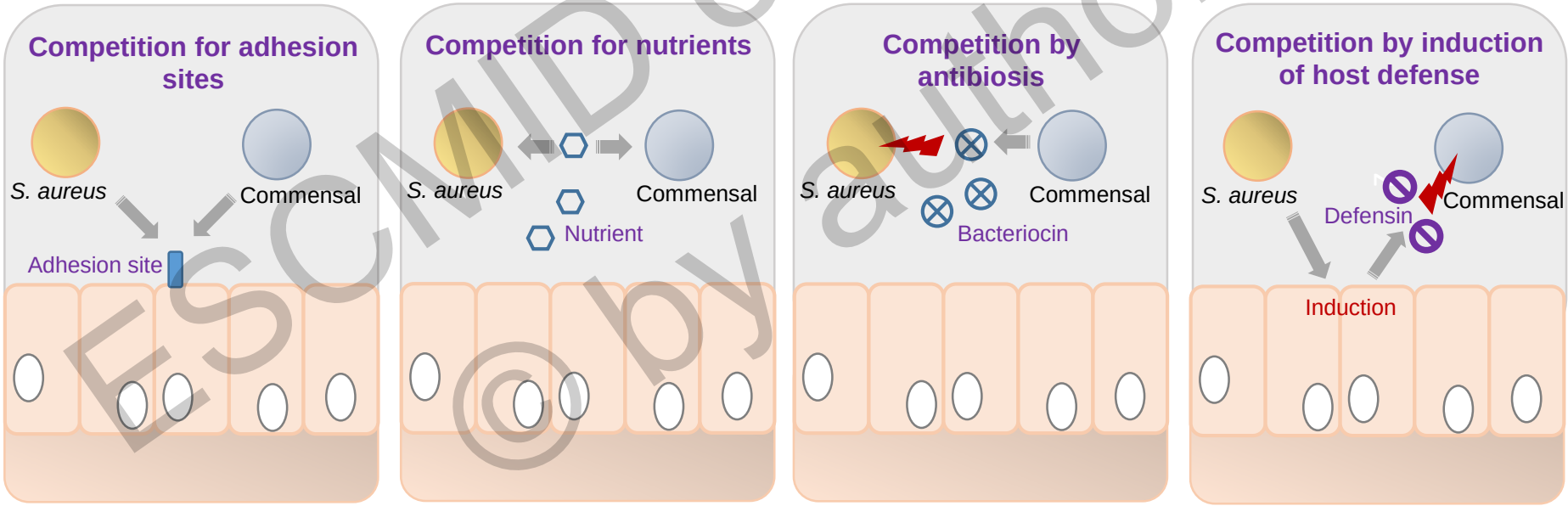


- Major risk factor: **nasal colonization** (30% of the population)
- Antibiotic resistance **(MRSA, CA-MRSA)**
- Colonization governed by **microbiome**

Competition in microbiomes

Nasal commensals:

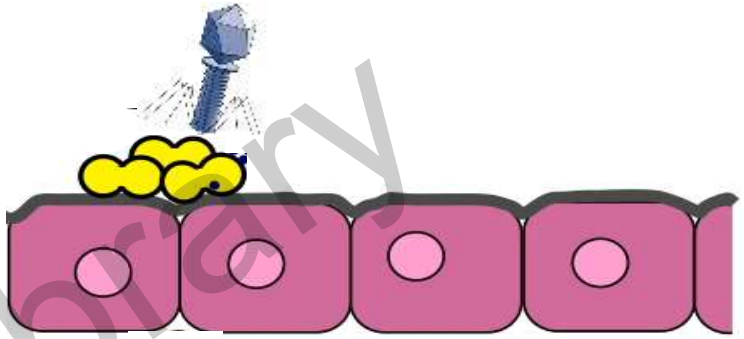
Firmicutes	Coagulase-negative *Staphylococcus* (CoNS)
	Dolosigranulum
	Streptococcus
Actinobacteria	*Corynebacterium*
	Propionibacterium
	Rothia
Proteobacteria	*Moraxella*
	Haemophilus



Krismer, Weidenmeier, Zipperer, Peschel (2017) *Nat Rev Microbiol*

Bacteriophage lysins for selective decolonization

With Hyglos Inc,, Bernried and Karsten Becker, Münster



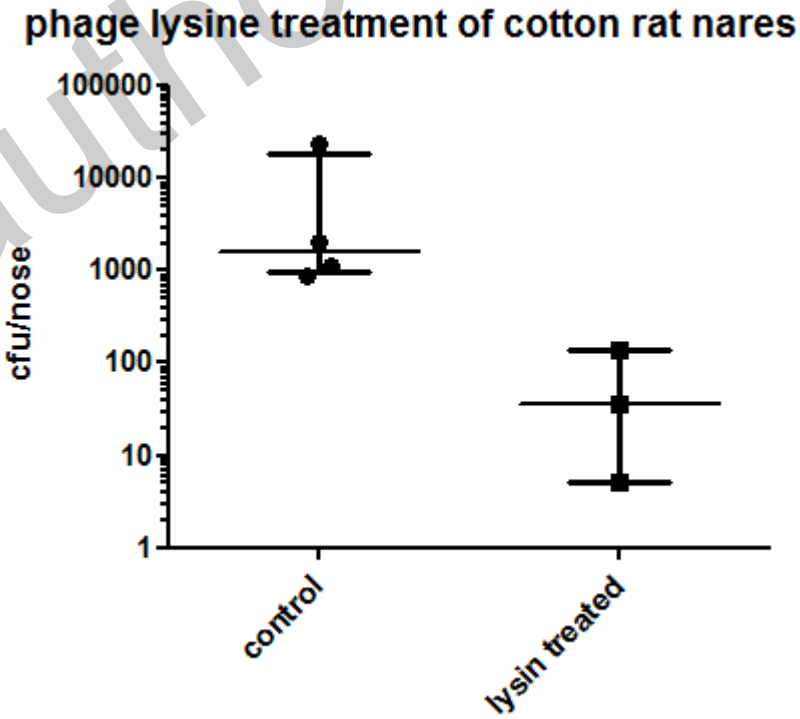
Phage lysins:

- Highly selective for one bacterial species
- Act fast and bactericidal
- Hardly prone to resistance

S. aureus-specific phage lysin PRF-119:

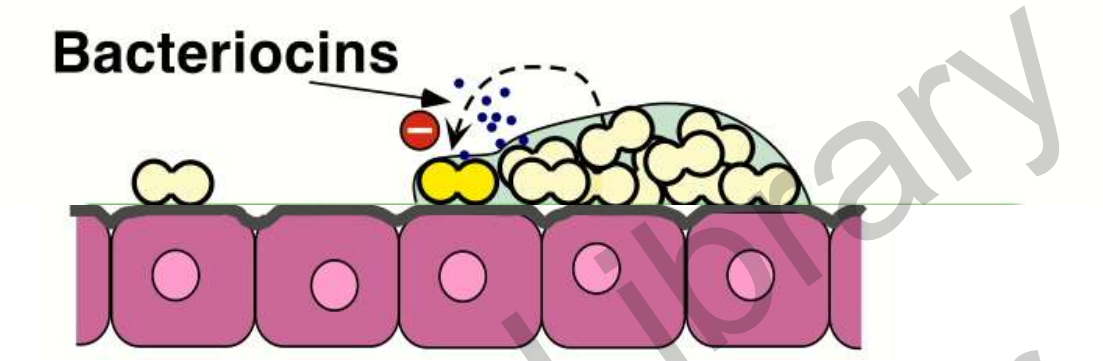
TABLE 1. Antimicrobial activity of PRF-119 against *S. aureus*

Organism[a] (no. of isolates tested)	MIC data (μg/ml)		
	MIC_{50}	MIC_{90}	Range
MSSA (398[b])	0.098	0.391	0.024–0.780
MRSA (776[c])	0.391	0.391	0.024–1.563



Idelevich et al (2011) *Antimicrob Agents Chemother*
Idelevich et al (2016) *Antimicrob Agents Chemother*

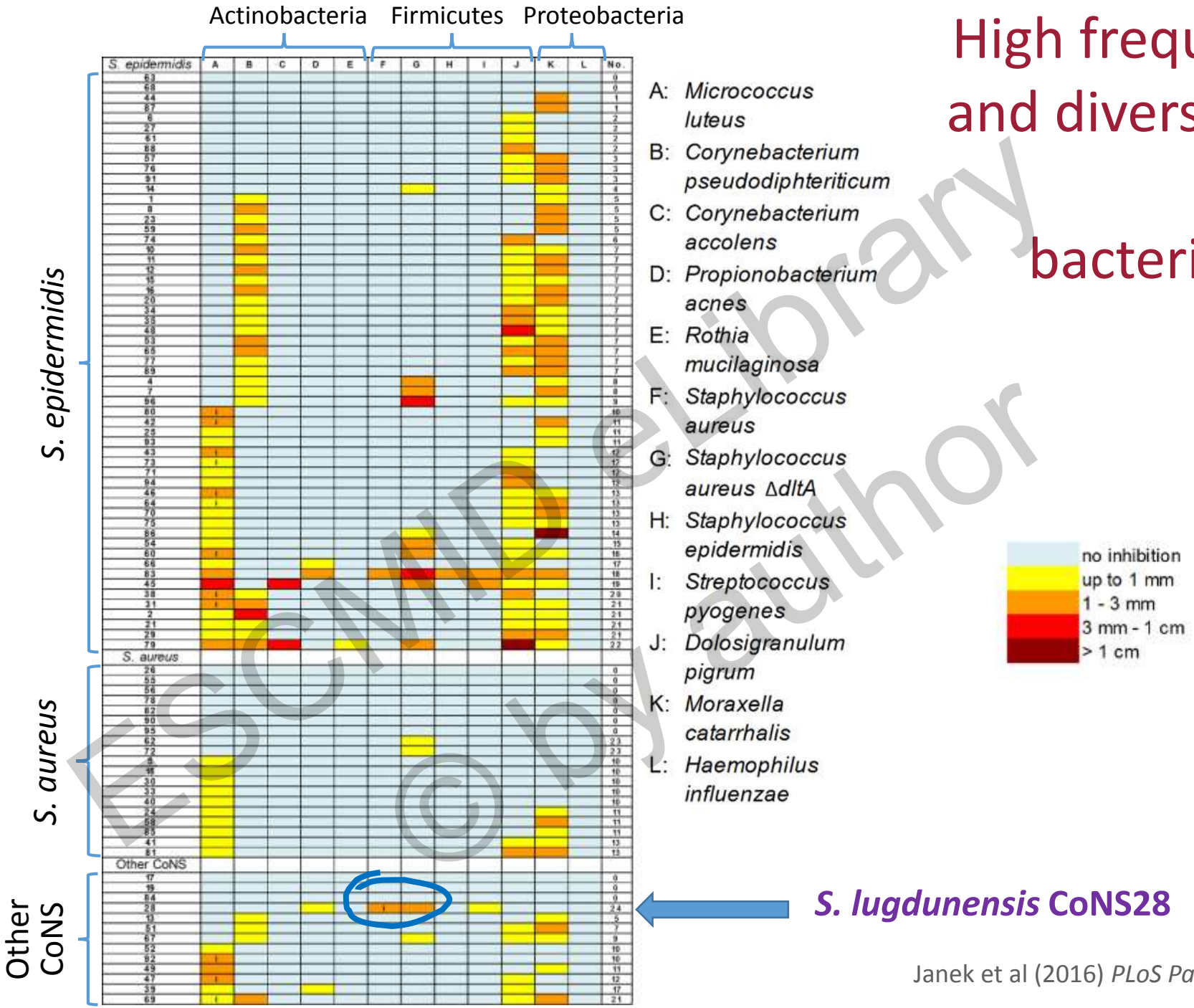
Colonization resistance – roles of bacteriocins?



- **86%** of nasal staphylococcal strains produce bacteriocins
- **Induced by stress** (low iron, H_2O_2,…)
- Most bacteriocins are **inactive against staphylococci and most other *Firmicutes***
- **Highly variable** in structure and activity spectra

Janek et al (2016) *PLoS Pathogens*

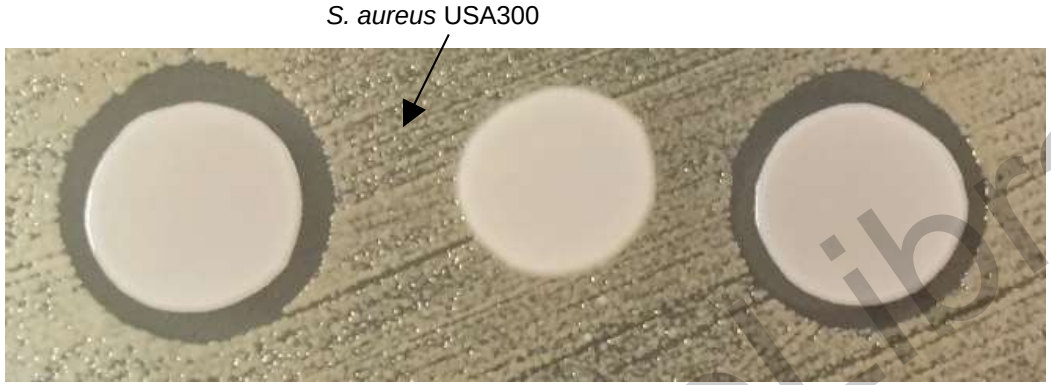
High frequency and diversity of nasal bacteriocins



Janek et al (2016) *PLoS Pathogens*

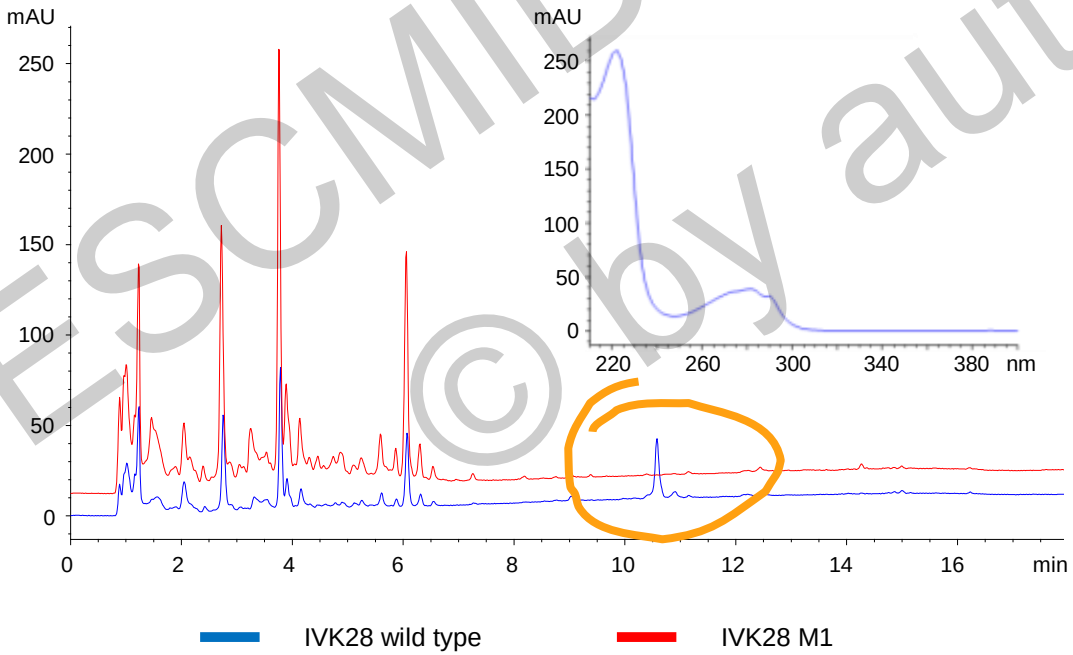
A novel antimicrobial compound from *S. lugdunensis* 28

a



IVK28 wild type | IVK28 Δ*lugD* | IVK28 Δ*lugD*::pRB474/*lugD*

b

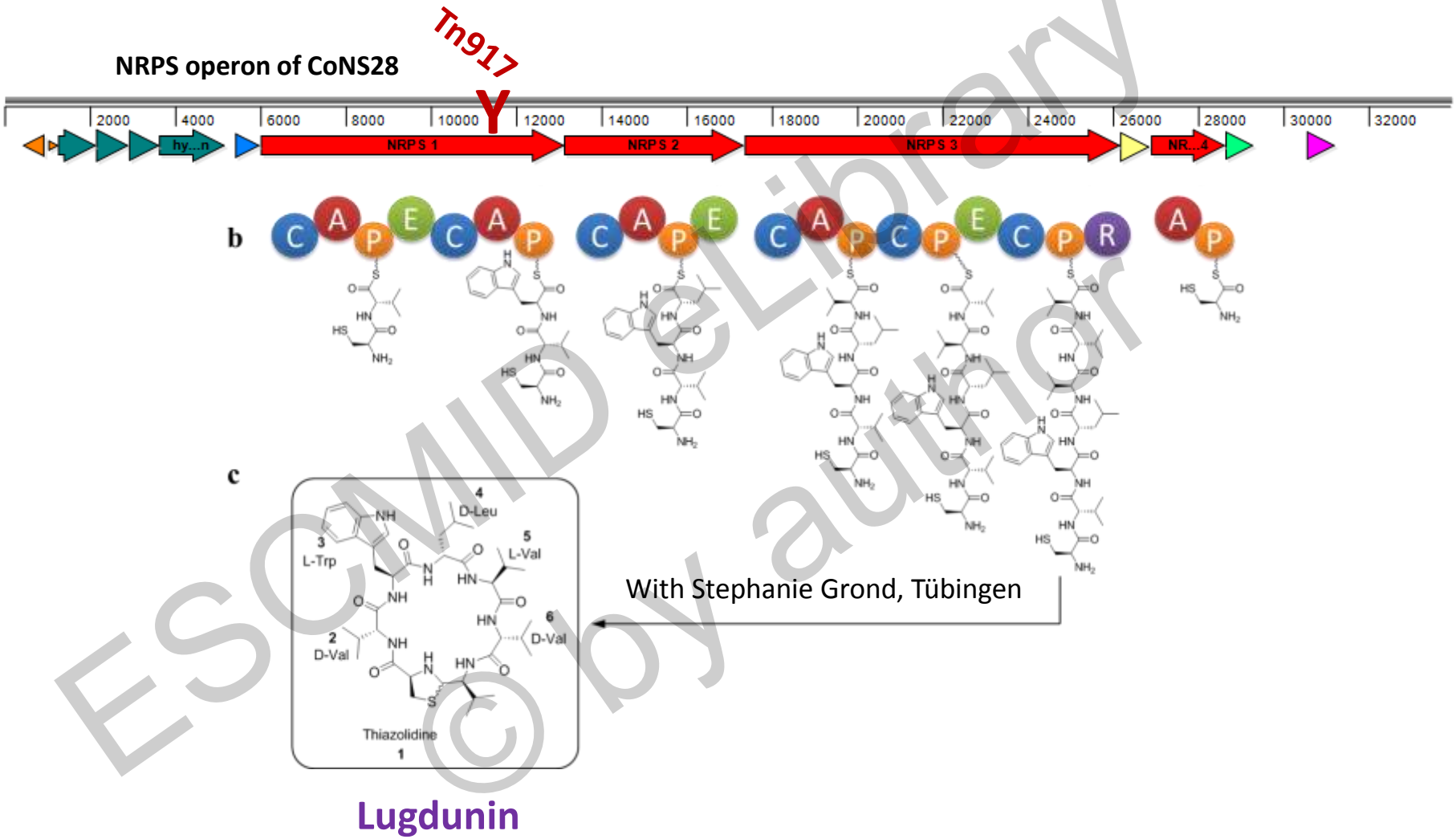


Formula: $C_{40}H_{63}N_8O_6S^+$

Mass: 783.03

"Lugdunin"

Lugdunin is a novel cyclic peptide antibiotic

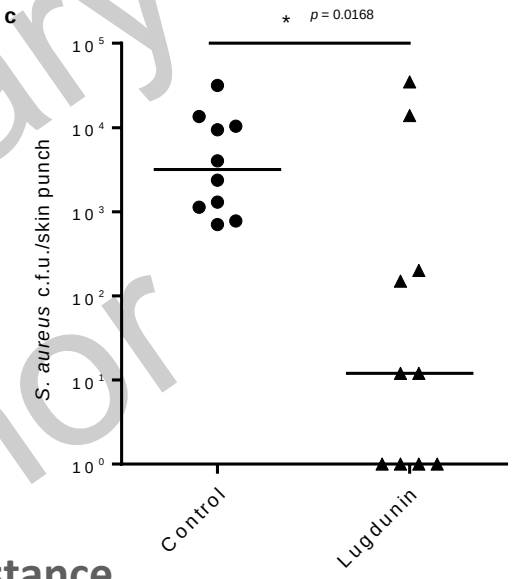


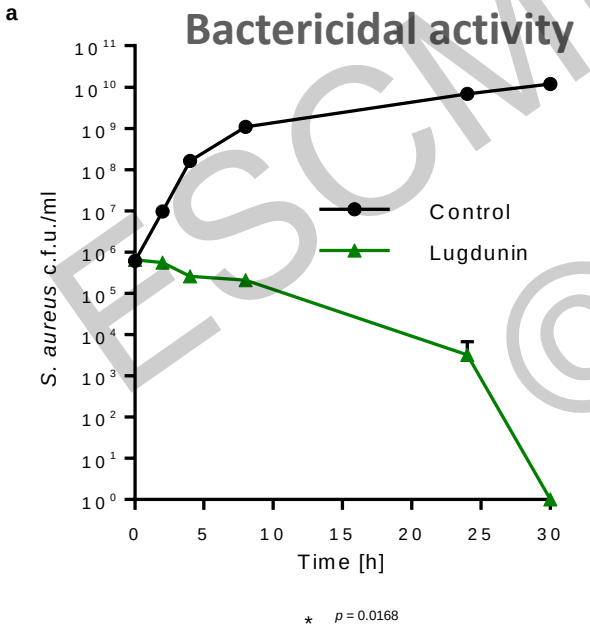
Zipperer et al (2016) *Nature*

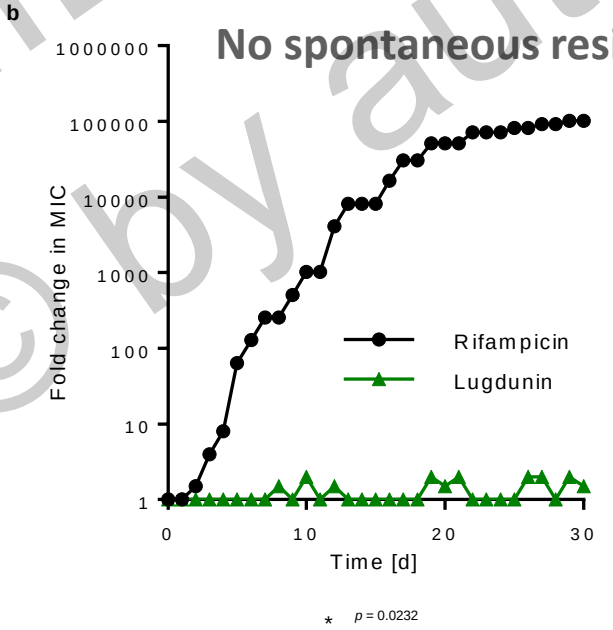
Lugdunin is a promising new antibiotic

Test strain	MIC (µg/ml)
Staphylococcus aureus USA300 (MRSA)	1.5
Staphylococcus aureus MU50 (GISA)	3
Enterococcus faecium BK463 (VRE)	3
Streptococcus pneumoniae ATCC49619	1.5
Pseudominas aeruginosa PAO1	>50
Escherichia coli DH5α	>50

Activity in mouse skin infection model



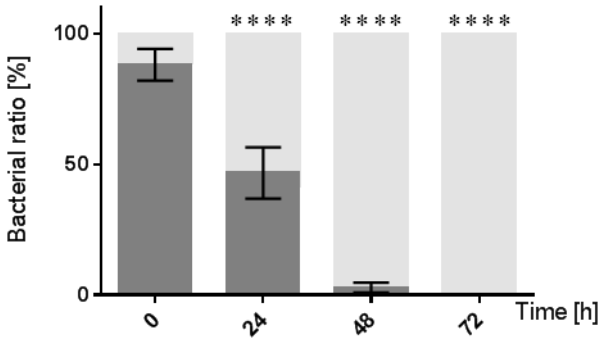




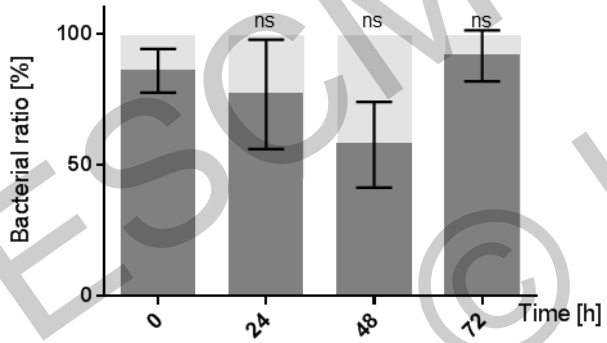
Zipperer et al (2016) *Nature*

Lugdunin-positive *S. lugdunensis* outcompetes *S. aureus*

Growth competition *in vitro*

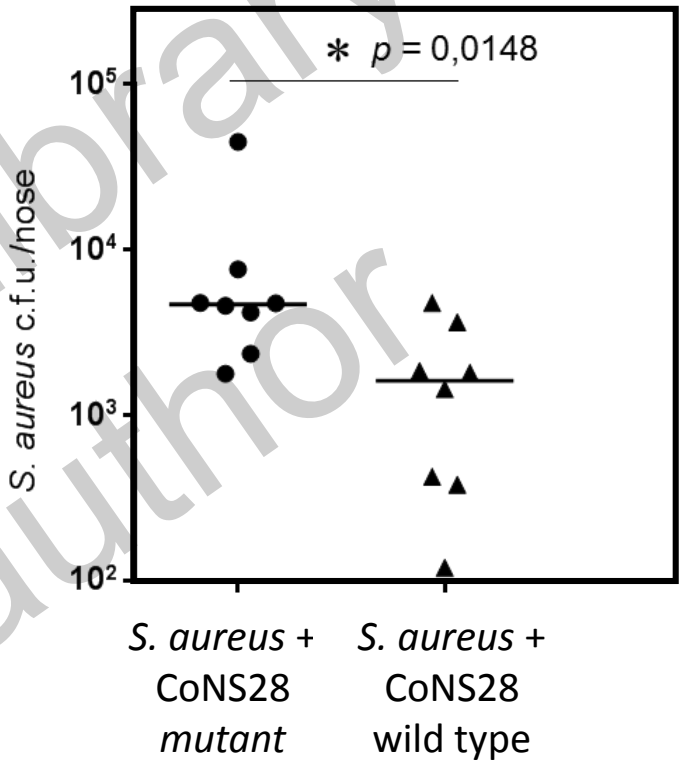


S. aureus +
CoNS28 wild type



S. aureus +
CoNS28 mutant

Co-colonization in cotton rat model



Zipperer et al (2016) *Nature*

Does *S. lugdunensis* shape nasal microbiome composition?

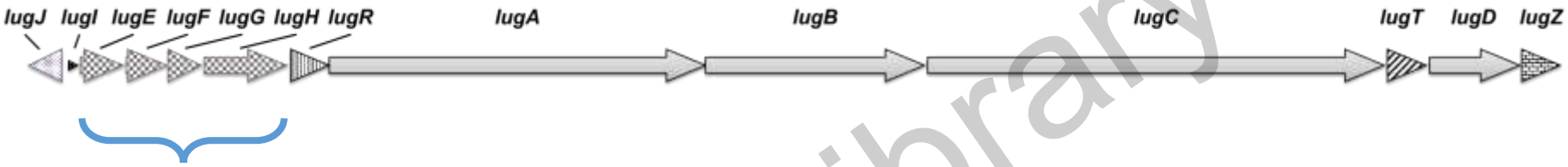
Nasal metagenomes of *S. lugdunensis* carriers / non-carriers

S. lugdunensis: + + + 0 0 + + 0 0 0 0 0 0 0

- Low *Staphylococcus* abundance in *S. lugunensis*-positive noses
- Tendency of high *Corynebacterium* and *Dolosigranulum* counts

Rosenstein et al *In preparation*

ABC transporters confer producer immunity



ABC transporters

LugEFG are required for immunity

	MIC [µg/ml]
S. lugdunensis wild type	6
S. lugdunensis ΔlugEFGH	2
S. aureus wild type	3
S. aureus pRB-lugEFGH	12

Zipperer et al *In preparation*

How about the human nose?

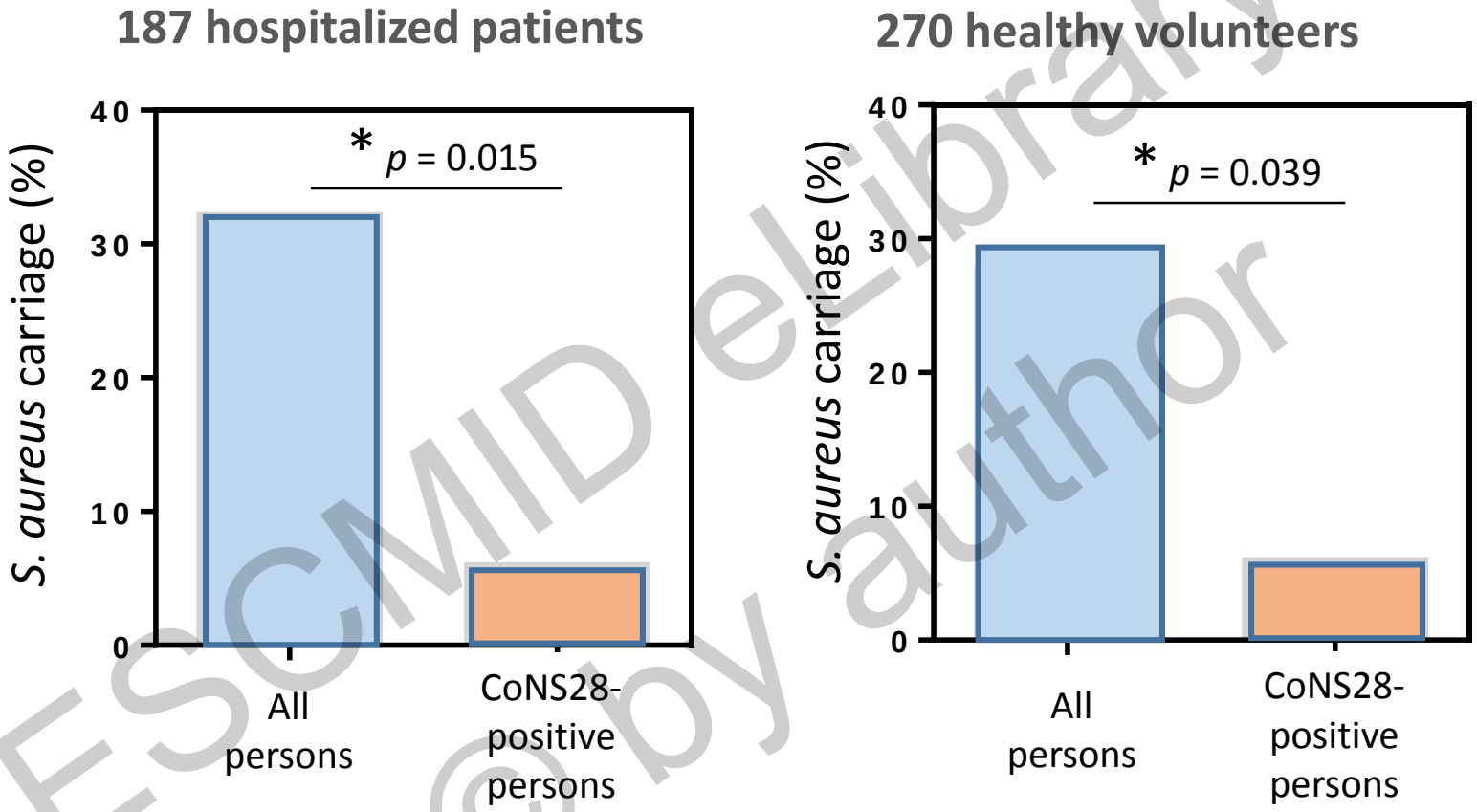
S. aureus prevalence: 30.4%

S. lugdunensis prevalence: 7.7%

- All nasal *S. lugdunensis* contain lugdunin operon
- All nasal *S. aureus* are susceptible to lugdunin

→ Does S. lugdunensis prevent S. aureus colonization?

5-6-fold reduced incidence of *S. aureus* colonization by *S. lugdunensis*

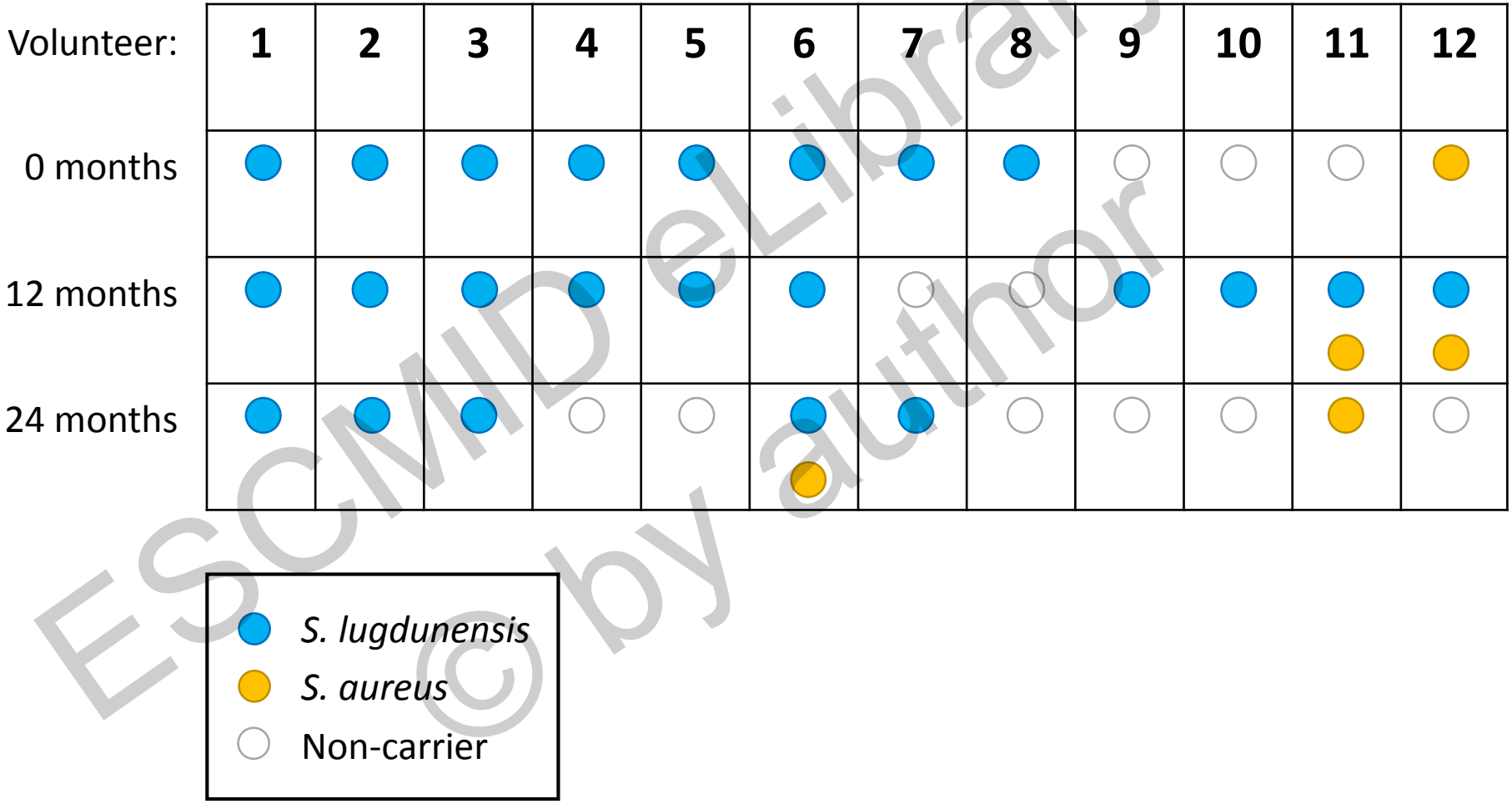


→ ***Lugdunin-producing commensals as anti-S. aureus probiotic?***

Zipperer et al (2016) *Nature*

Laux et al *in preparation*

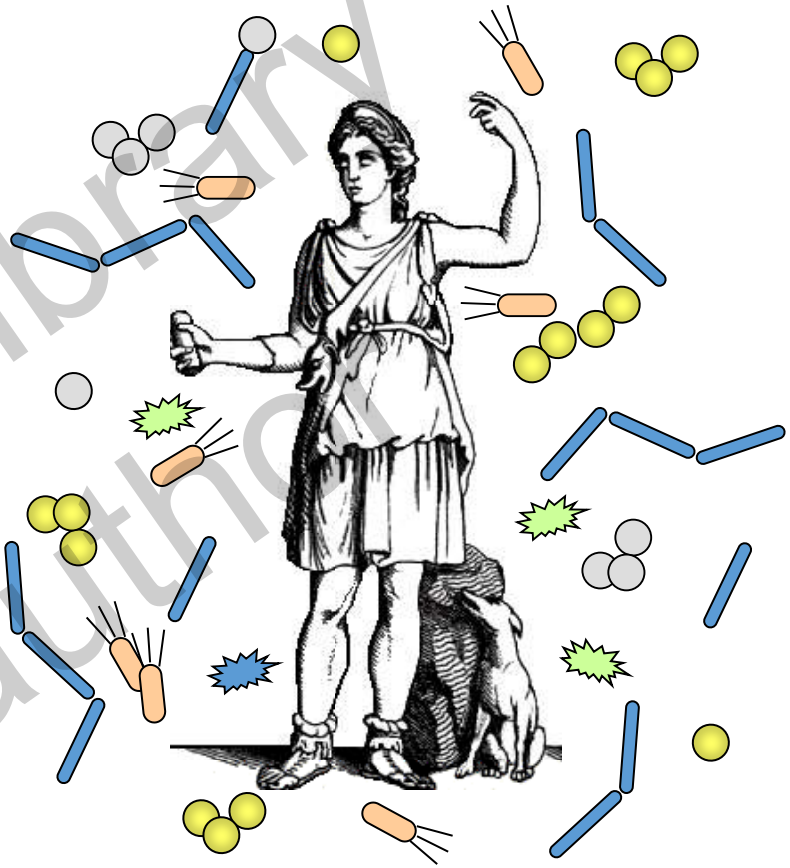
S. lugdunensis nasal persistance



Laux et al *in preparation*

Conclusions:

- Human **microbiome is a major reservoir** for antibiotic-resistant pathogens
- Elucidation of microbial competition may lead to **novel decolonization strategies**
- Human microbiome should be considered as a **source for novel drugs**



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SFB 766
Bacterial Cell Envelope

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