



CHEMICAL DISRUPTION OF THE CLPX CHAPERONE COMPLEX INHIBITS MULTIRESISTANT STAPHYLOCOCCUS AUREUS VIRULENCE

23. April 2018 | Bayerische Patentallianz | Technische Universität München

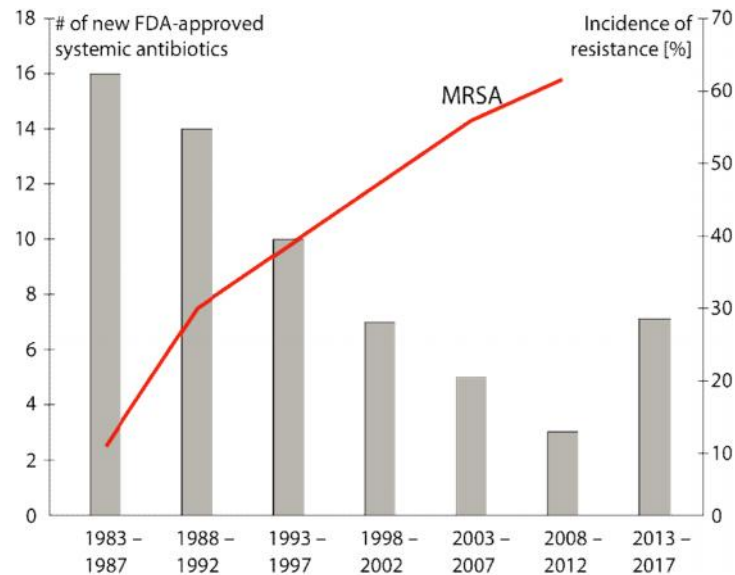
[Dr. Christian Fetzer](#)

Technical University Munich

Heading towards the Post-Antibiotic Era



Rapid spread of methicillin resistant *Staphylococcus aureus* (MRSA)



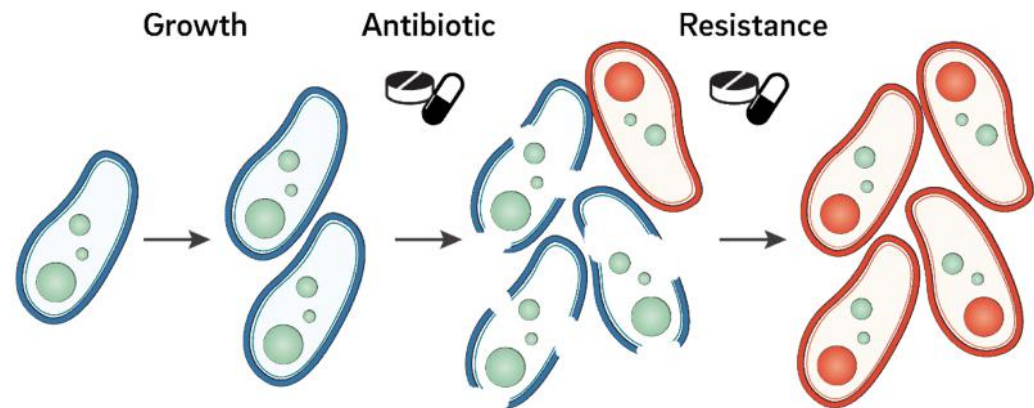
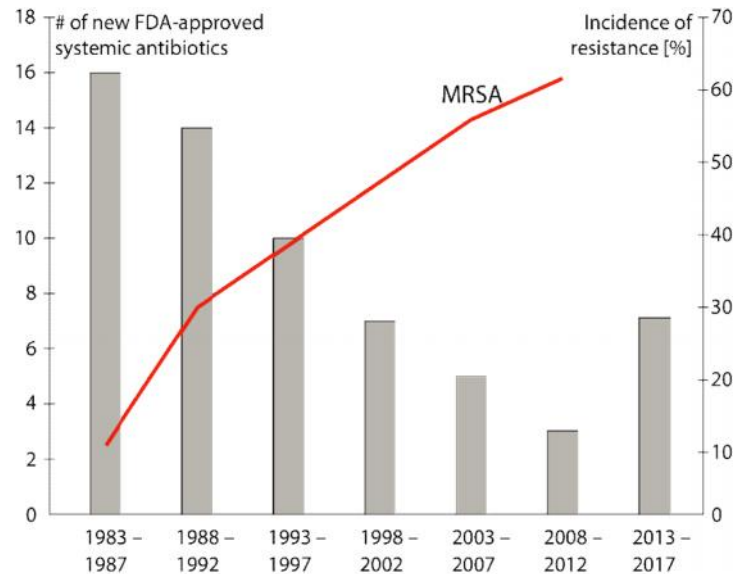
Antimicrob. Agents
Chemother. 2013, 57,
4605-4607

700.000 people die annually worldwide due to multiresistant bacteria

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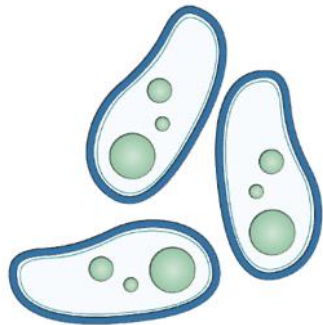
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New Way of Fighting Infections



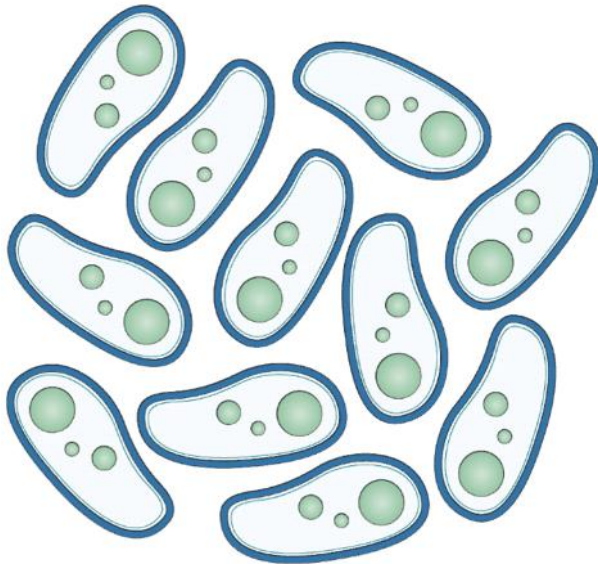
- Waiting for an opportunity to spread



New Way of Fighting Infections



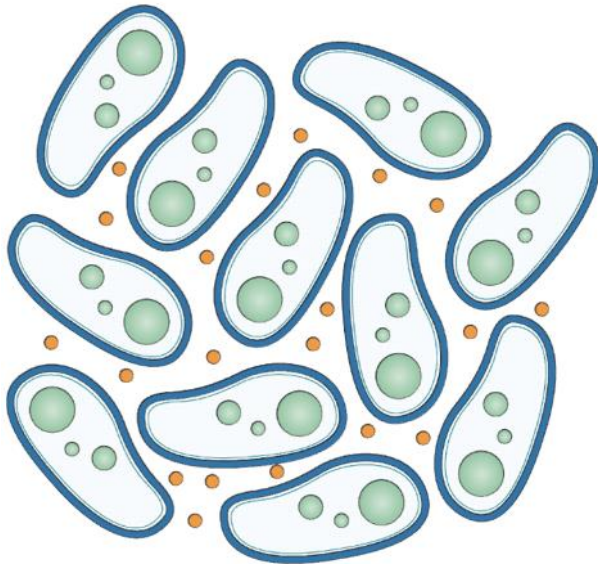
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New Way of Fighting Infections



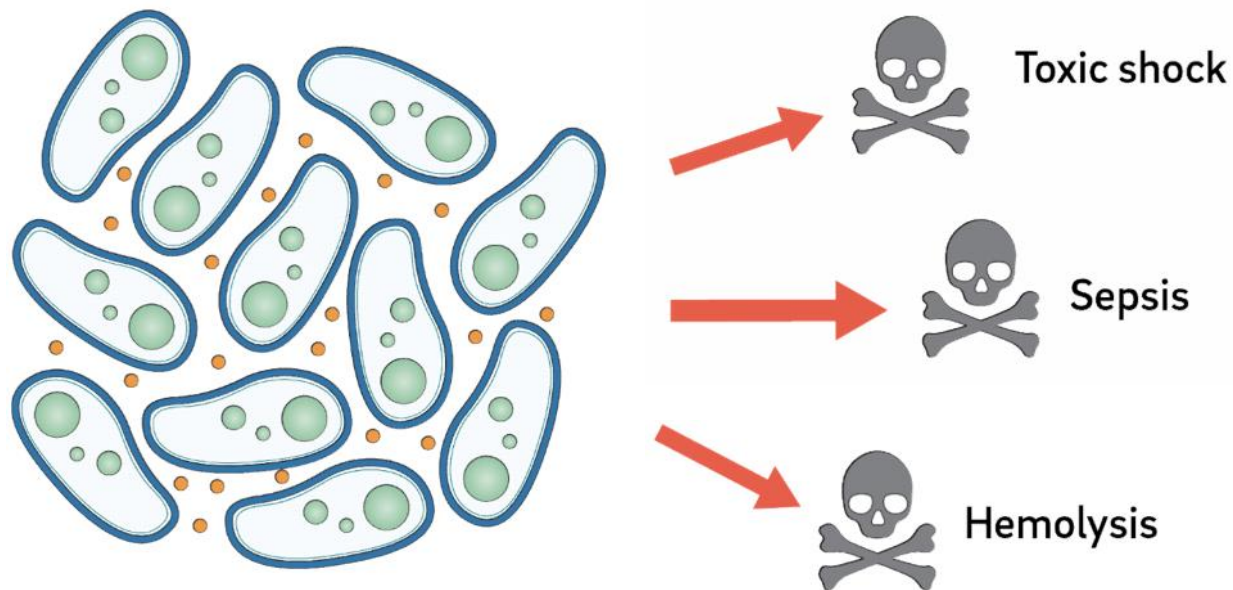
- Waiting for an opportunity to spread
- Communication to coordinate attack



New Way of Fighting Infections



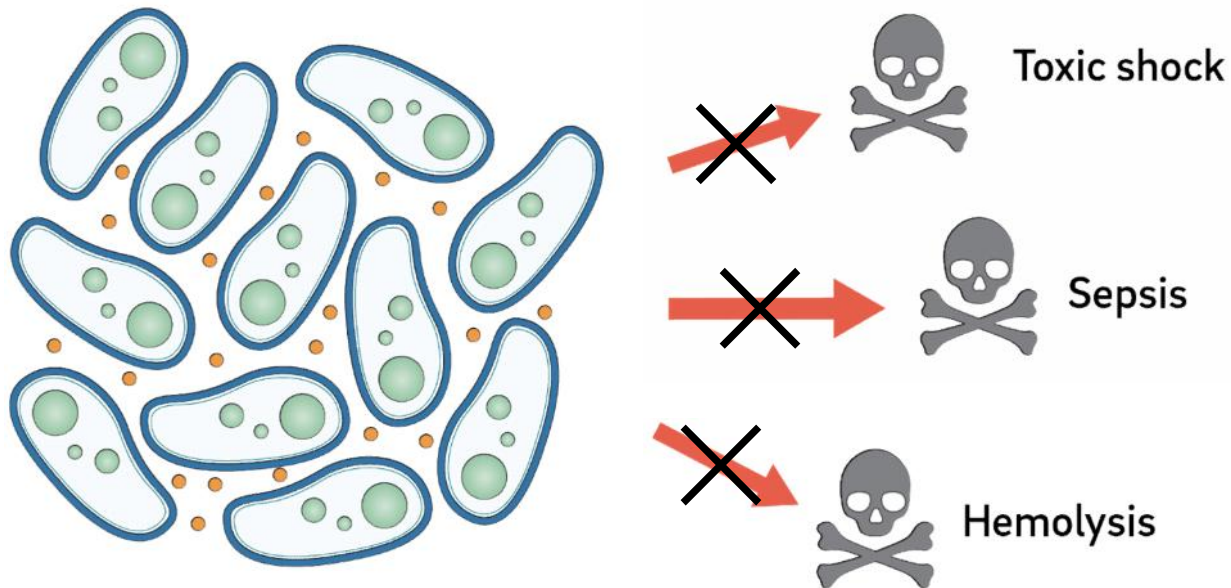
- Waiting for an opportunity to spread
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- Chemical/biological warfare



New Way of Fighting Infections



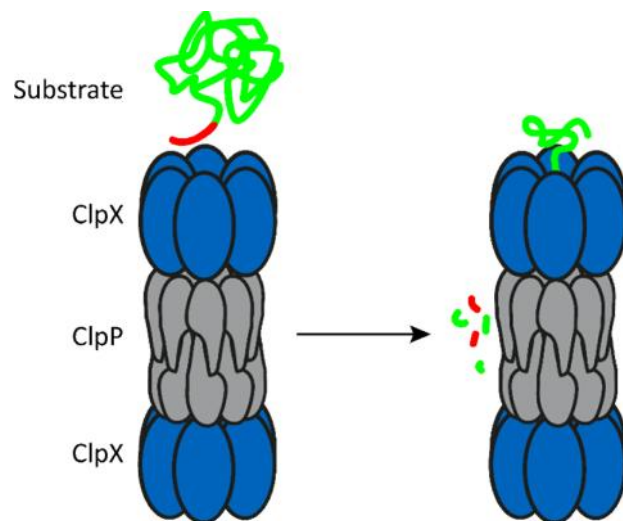
- Waiting for an opportunity to spread
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The Anti-Virulence Approach



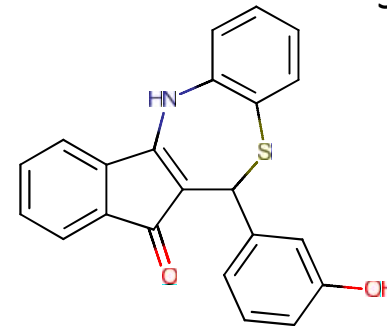
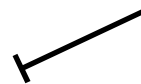
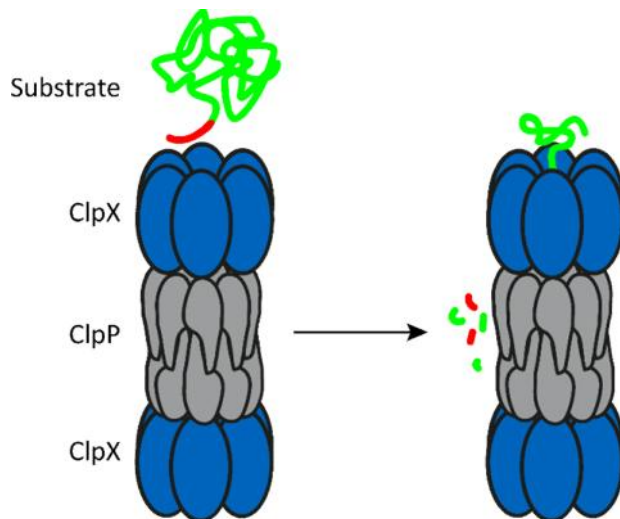
- Inhibition of a central but non-essential regulator
- Not interfering with pathogen's survival
- Reduction of several toxins



The Anti-Virulence Approach



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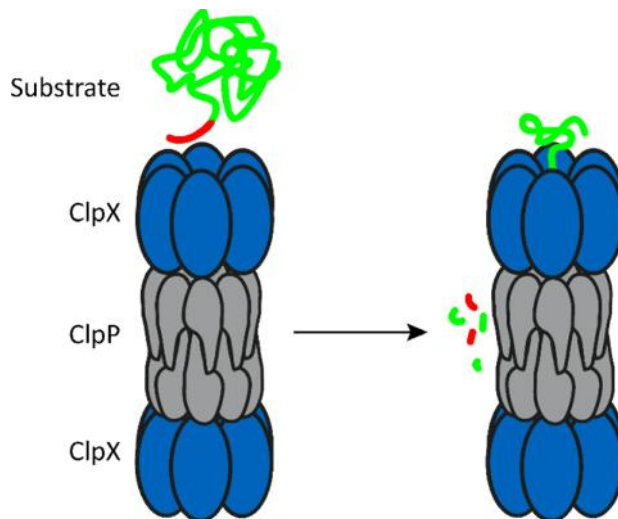


Screening of 40k
substances

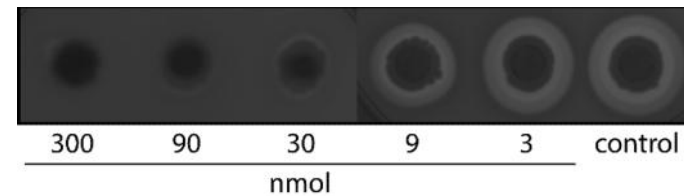
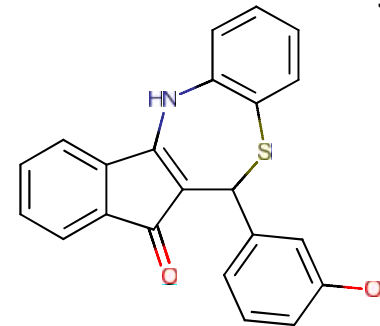
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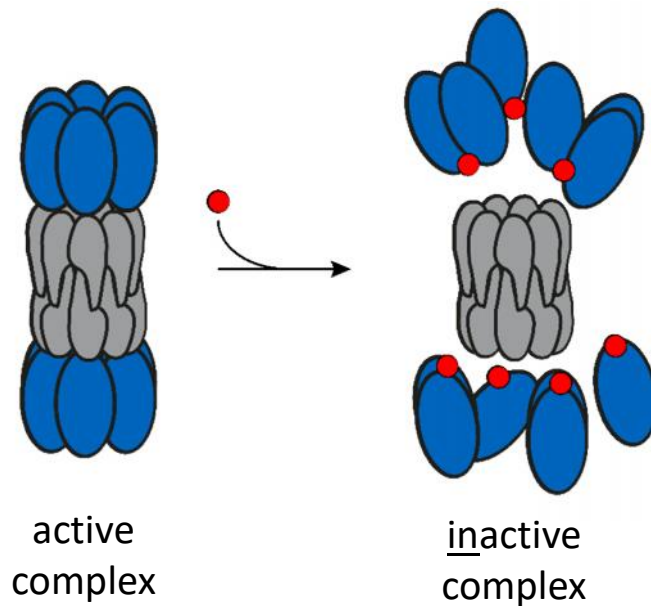
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The Anti-Virulence Approach



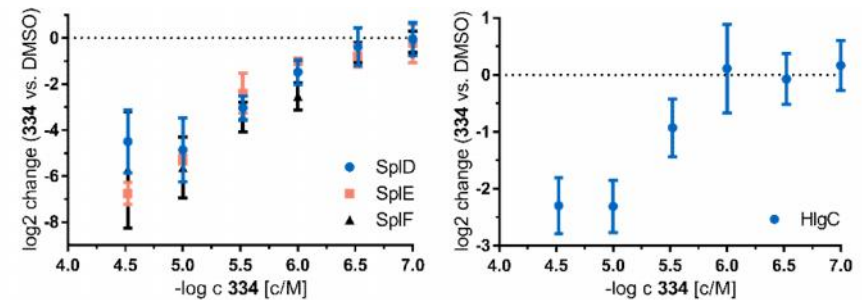
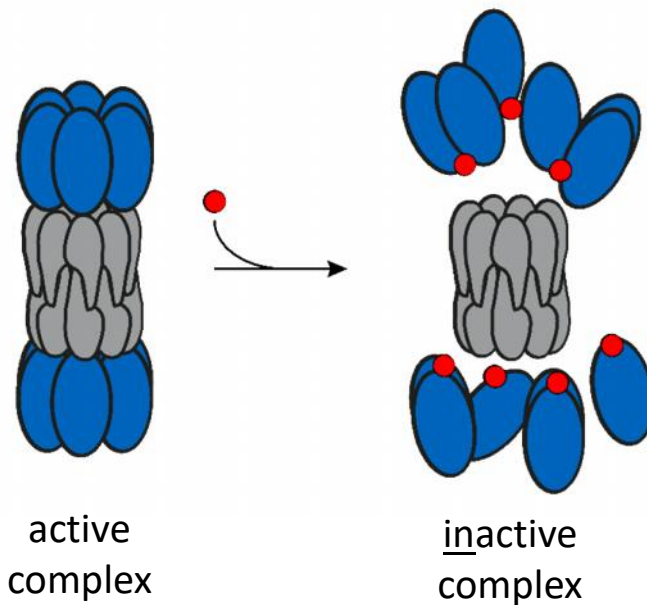
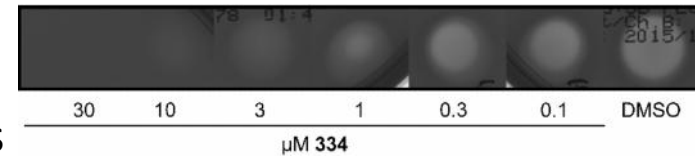
- Inhibitor binds and disrupts complex
- Concentration dependent reduction of toxins
- Virulence factor production strongly reduced



The Anti-Virulence Approach



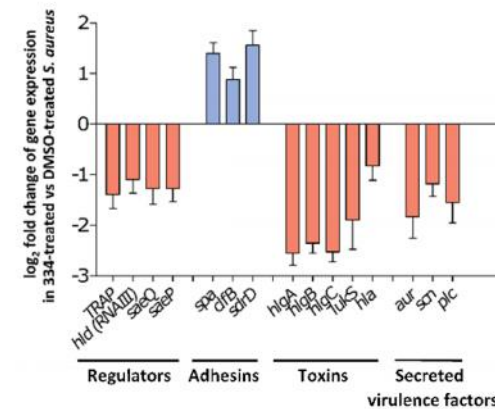
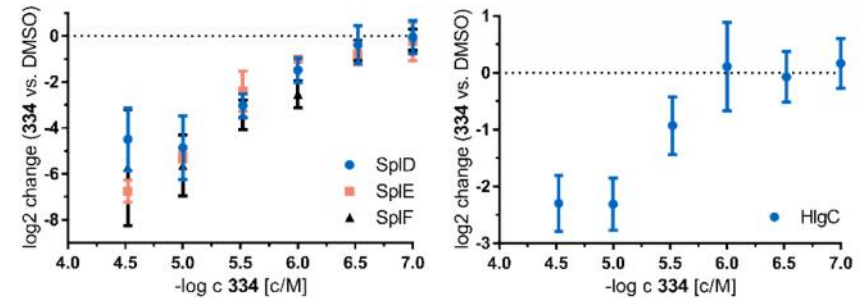
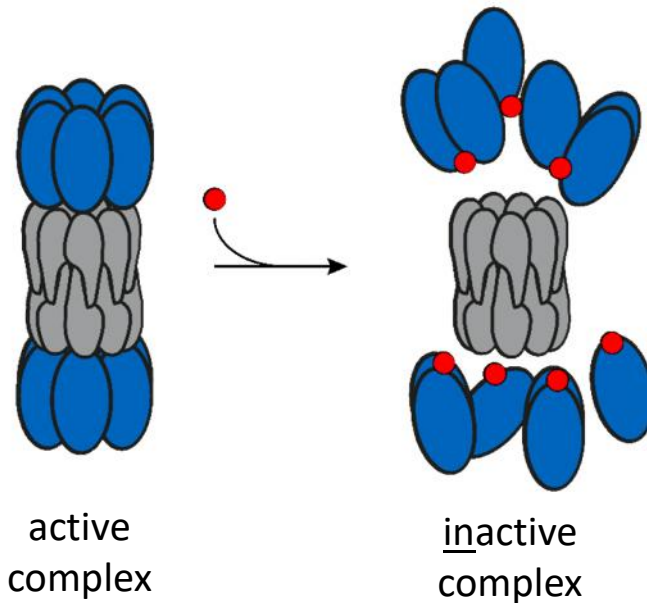
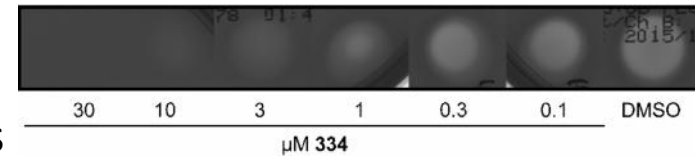
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The Anti-Virulence Approach



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Existing Anti-Virulence Solutions for *S. aureus*?



- Currently in development:
- Targeting of single toxins with antibodies
 - MEDI4893 (clinical phase II)
 - AR-301 (clinical phase II)
 - ASN-100 (clinical phase II)
- Small molecule approaches
 - 6e (Sortase A inhibitor; preclinical development)
 - Savirin (AgrA inhibitor; preclinical development)



- Achieved:
 - Screening and identification of a potent compound class
 - Biochemical Evaluation of Inhibition
 - Synthesis of small compound library to gain insight into structure-activity relationship
 - Monitoring simultaneous reduction of several virulence factors

- In progress:
 - Proof of concept studies in zebrafish and mice
 - Improvement of therapeutic window



Innovative Treatment Options

Anti-
virulence
strategy as a
new
opportunity

Monotherapy
or in
combination
therapy with
approved
antibiotics



IP Status

- PCT application: 19/12/2017

Publication

- C. Fetzer, V. S. Korotkov, R. Thänert, K. M. Lee, M. Neuenschwander, J. P. von Kries, E. Medina, S. A. Sieber, *Angew. Chemie Int. Ed.* **2017**, *56*, 15746–15750. (doi: 10.1002/ange.201708454)

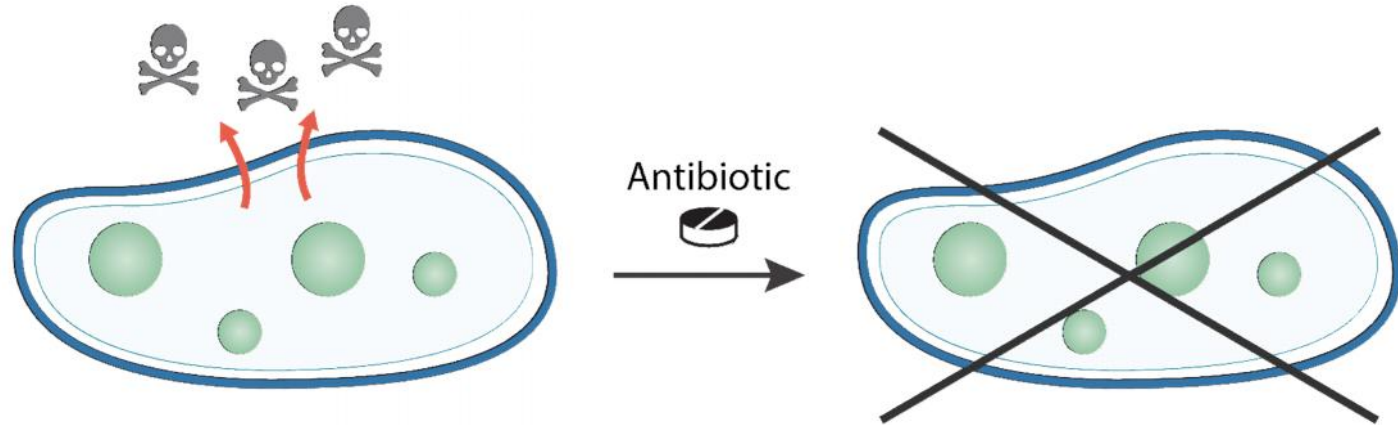
Business Opportunity

- License
- Cooperation
- Option

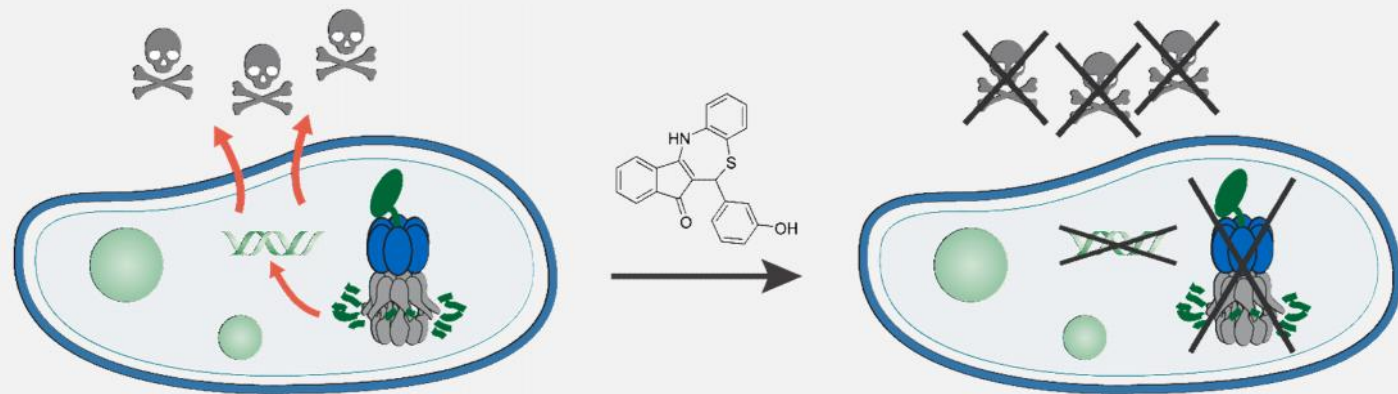
Summary



Current



New



Thank you for your attention!



Meet us at poster **B2**

Scientific expertise



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