



**UiO : University of Oslo**

**Centre for Integrative Microbial Evolution**

# Bakteriell biofilm – virulens, resistens, og "way of life"

Seksjon for Farmasøytisk Biovitenskap,  
Farmasøytisk institutt og

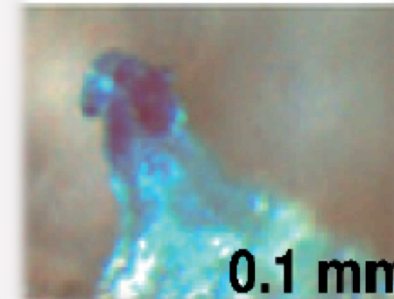
Centre for Integrative Microbial Evolution (CIME)  
Universitetet i Oslo





# San Diego 2001

Functional Genomics of Gram-Positive  
Microorganisms Conference



Shapiro JA. Bacteria as Multicellular Organisms.  
Scientific American. **1988**; 258: 82.

Branda et al., PNAS, 2001

“Throughout the biological world, bacteria thrive predominantly in surface-attached, matrix-enclosed, multicellular communities – or biofilms – as opposed to isolated planktonic cells.”

Tony Romeo. “Bacterial Biofilms”. Curr Top Microbiol Immunol



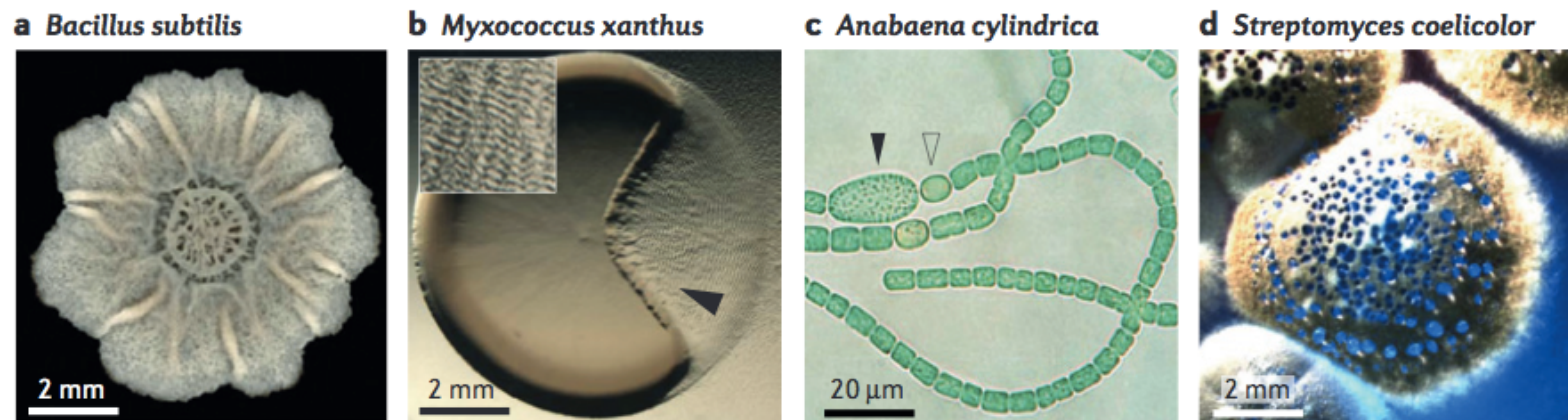
“At the surface of the liquid...The rods adhere together by their sides after the manner of the elements of columnar epithelium, but there is, I think, strong reason to believe that this adhesion is not direct, that is, that they are not in actual contact but glued together by a viscous intermediary substance”

Sanderson, J. B. Appendix no. 5 in *13th Report of the Medical Officer of the Privy Council [John Simon], with Appendix 1870* 56–66 (Her Majesty’s Stationery Office, London, 1871).





## Examples of multicellularity in microbes



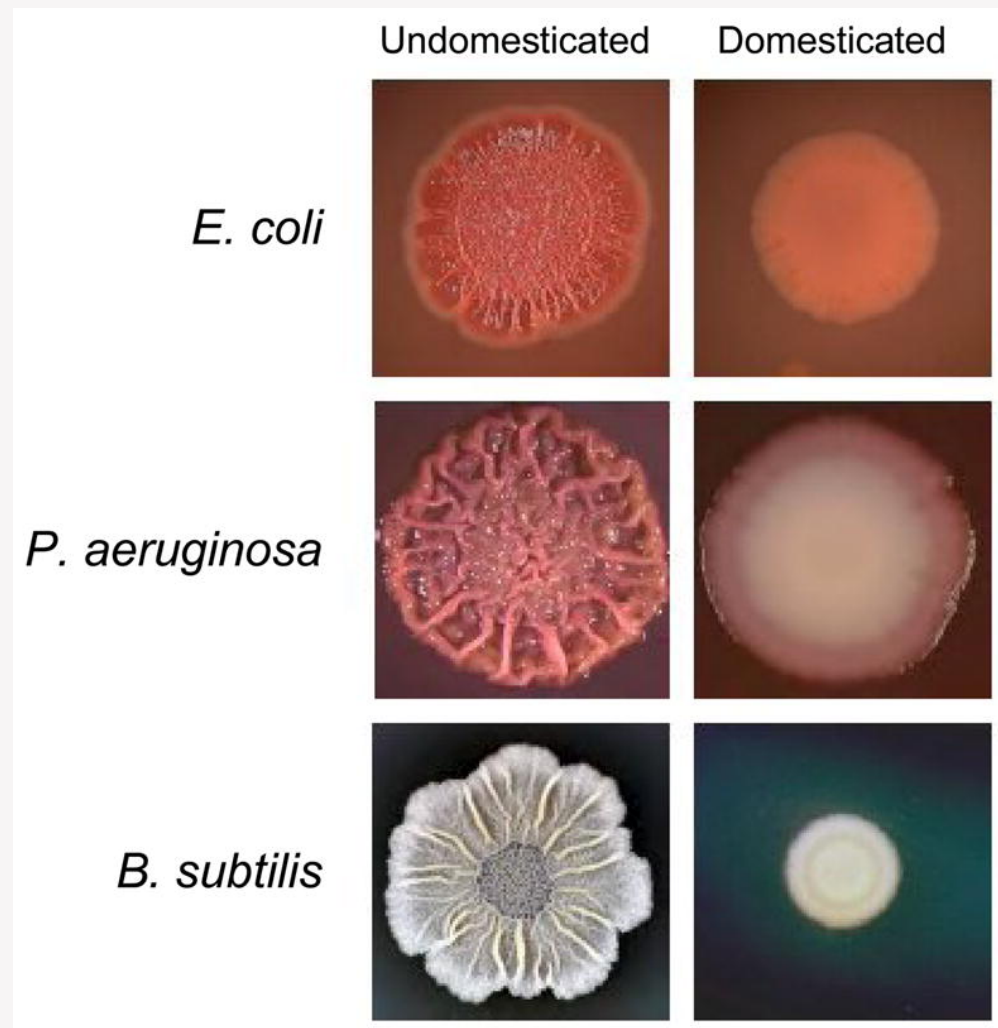
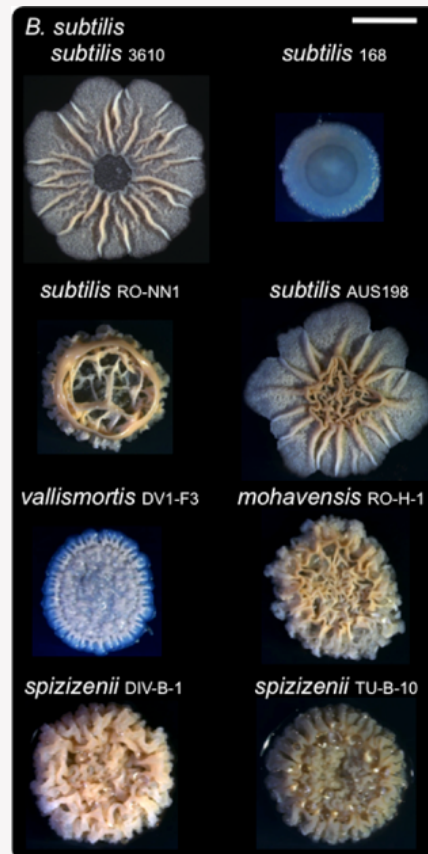
**Figure 1 | Bacterial manifestations of multicellularity.** **a** | A mature *Bacillus subtilis* biofilm. **b** | Predation of an *Escherichia coli* colony (left) by swarming *Myxococcus xanthus* cells (right), which is characterized by a rippling pattern (arrowhead and inset). **c** | Formation of heterocysts (open arrowhead) and akinetes (closed arrowhead) in chains of the filamentous cyanobacterium *Anabaena cylindrica*. **d** | A mature colony of *Streptomyces coelicolor*, which is indicated by the fluffy, grey layer of sporulating aerial mycelium on the colony surface. The colony produces the blue-pigmented polyketide antibiotic actinorhodin. Image in part **a** is reproduced, with permission, from REF. 28 © (2013) Macmillan Publishers Ltd. All rights reserved. Image in part **b** courtesy of S. Müller and J. Kirby, University of Iowa, USA. Image in part **c** courtesy of J. E. Frías and E. Flores, Centro de Investigaciones Científicas, Universidad de Sevilla, Spain.

Claessen et al. (2014). Bacterial solutions to multicellularity: a tale of biofilms, filaments and fruiting bodies. *Nat Rev Microbiol* **12**, 115-124.





# Loss of true multicellularity by domestication

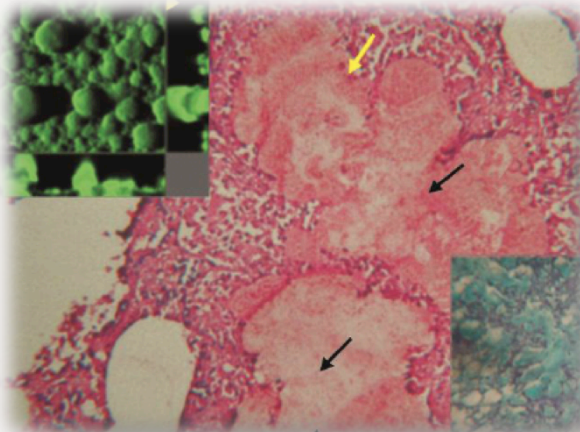






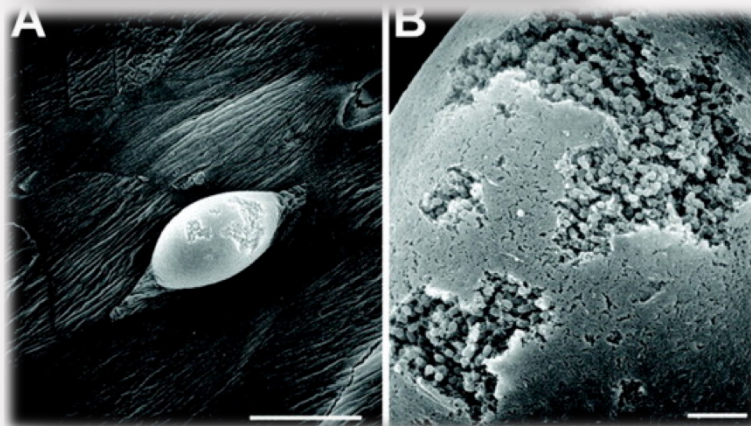
**“Biofilms are medically important, accounting for over 80 percent of microbial infections in the body. Examples include infections of the: ... teeth and dental implants; middle ear; gastrointestinal tract; urogenital tract; airway/lung tissue; eye; urinary tract prostheses; ..... indwelling catheters ... ; cardiac implants such as pacemakers, prosthetic heart valves, ... tracheal and ventilator tubing.”**

NIH, PA: PA-03-047, 2002



*Pseudomonas aeruginosa* i CF lunge

Høiby et al. (2011) Int J Oral Sci



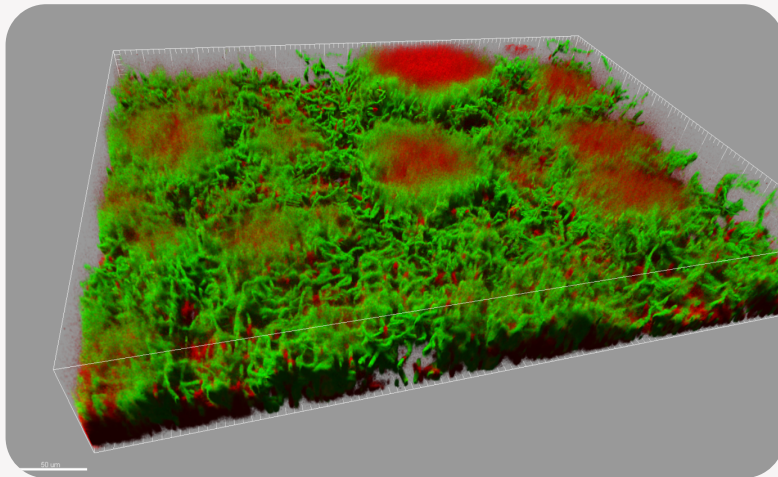
*Escherichia coli* UVI  
biofilm

Andersson et al. (2003) Science

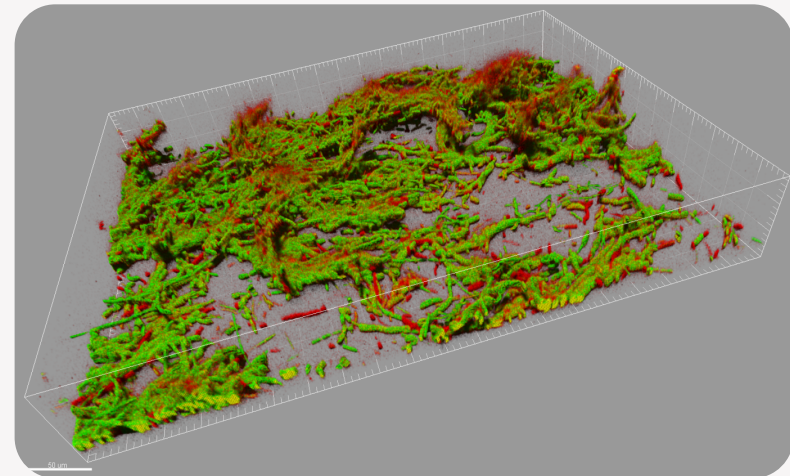


# Biofilm visualization - flow cell

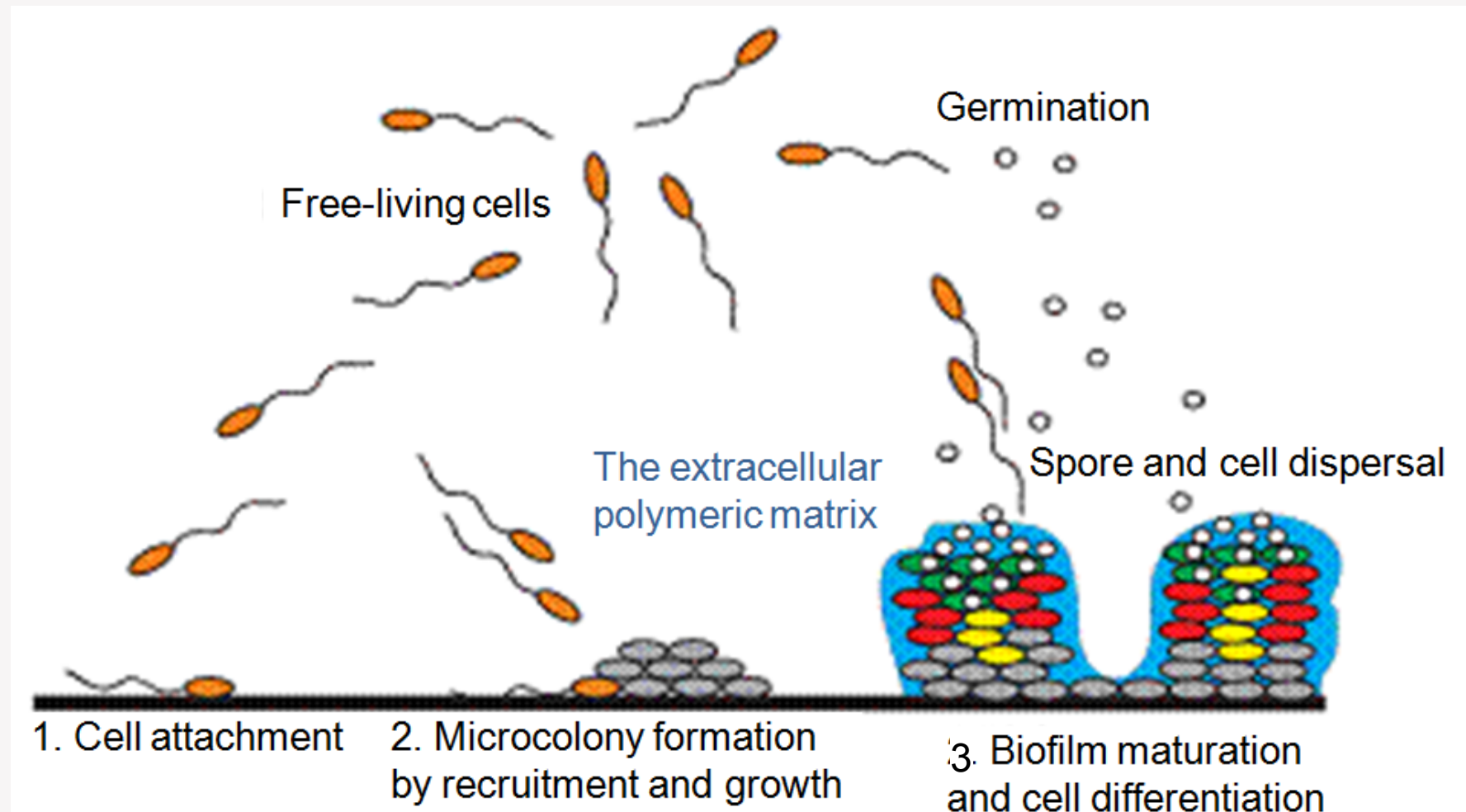
Vector control



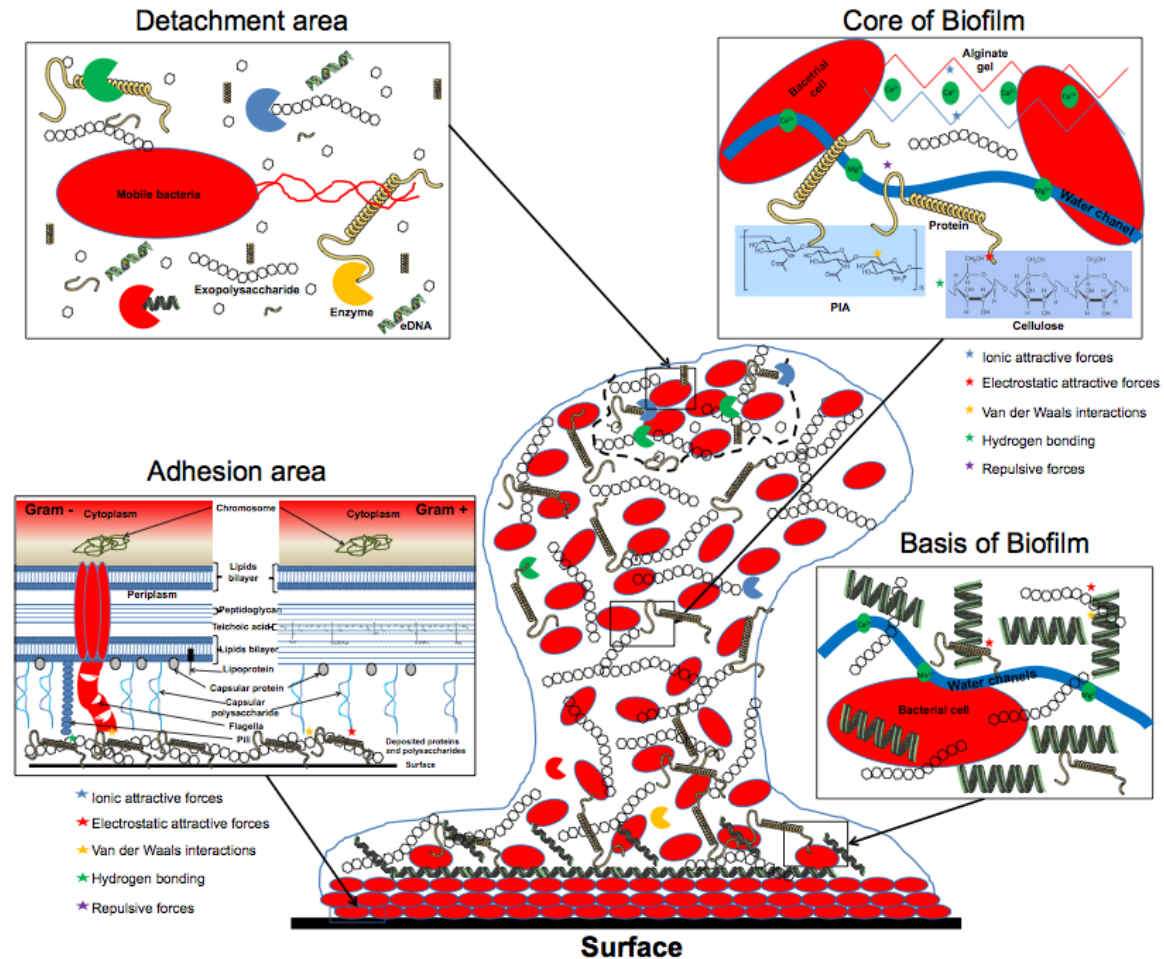
TM protein overexpression



## Biofilm formation – a simplified scheme



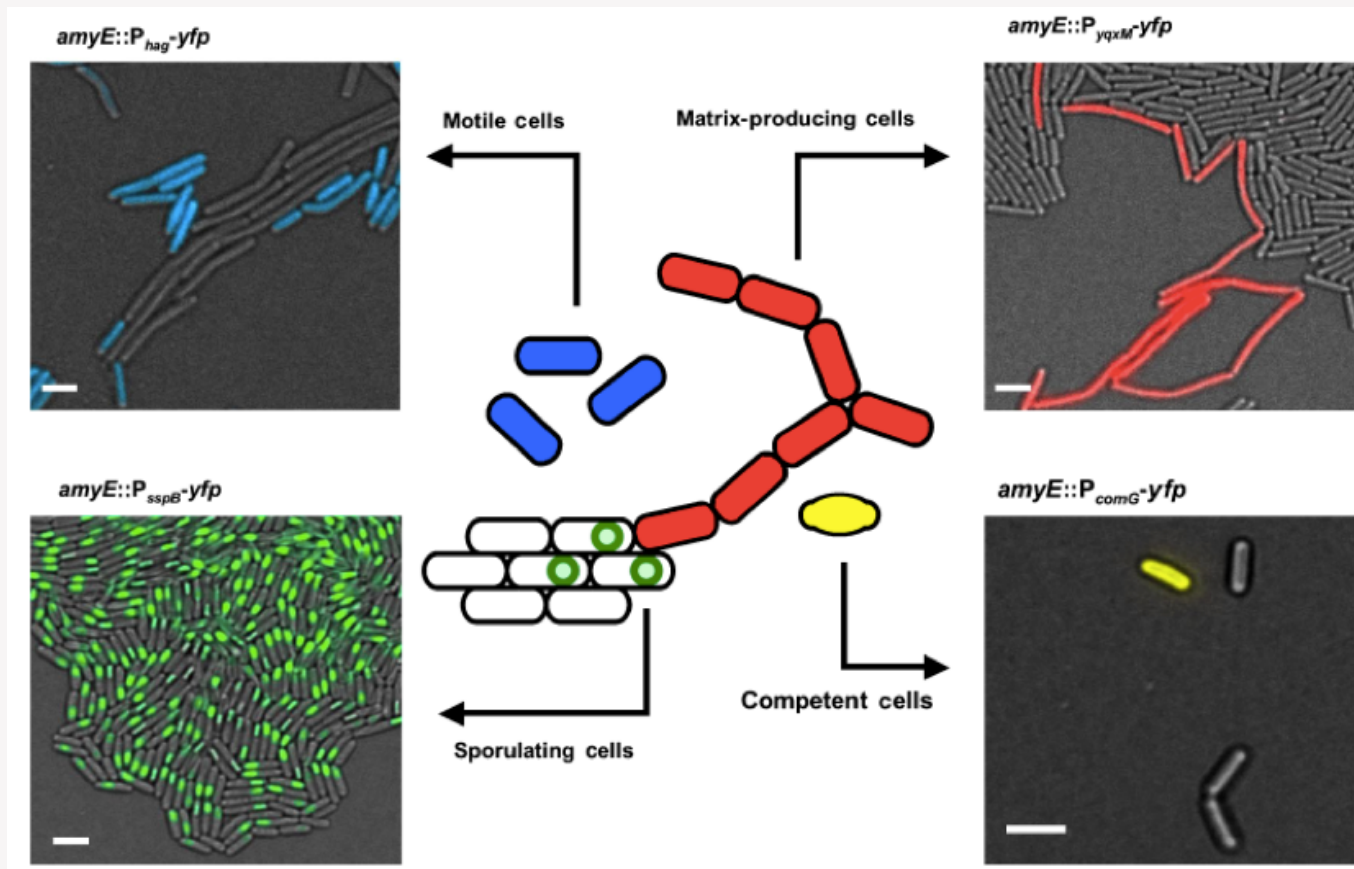
# Biofilm structure



Lembre et al. (2010). <http://dx.doi.org/10.5772/51213>



## Differentiation of cell types (*B. subtilis*)

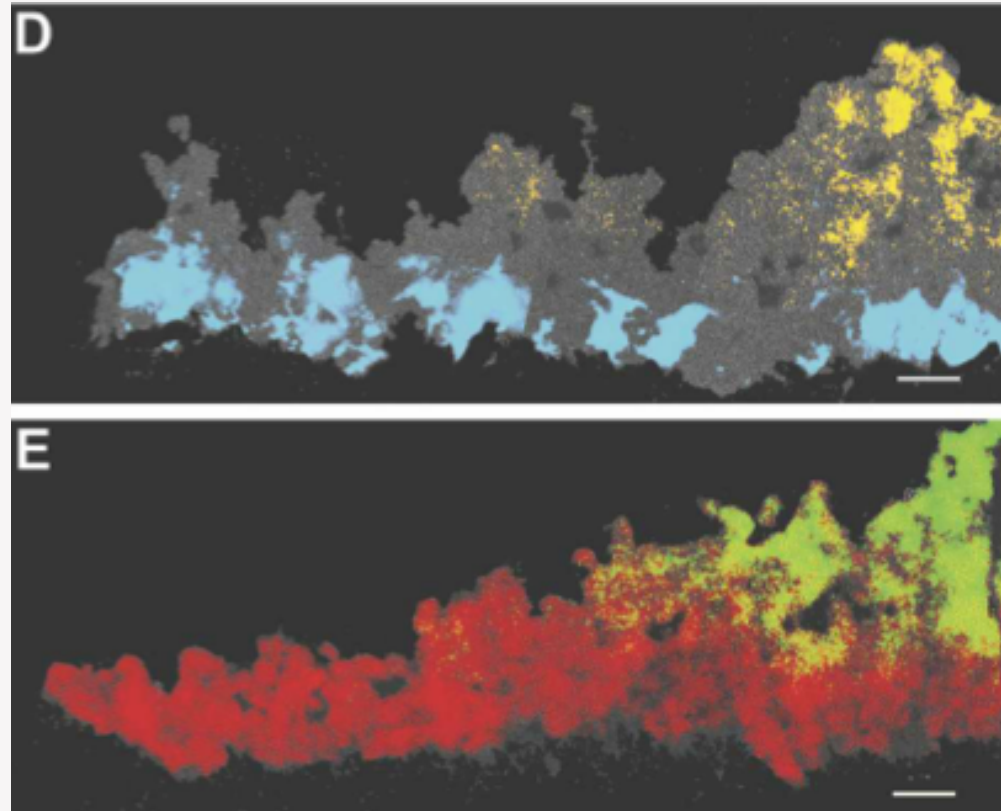


Differensierte  
celletyper

=

Arbeidsdeling!

(Division of labour)



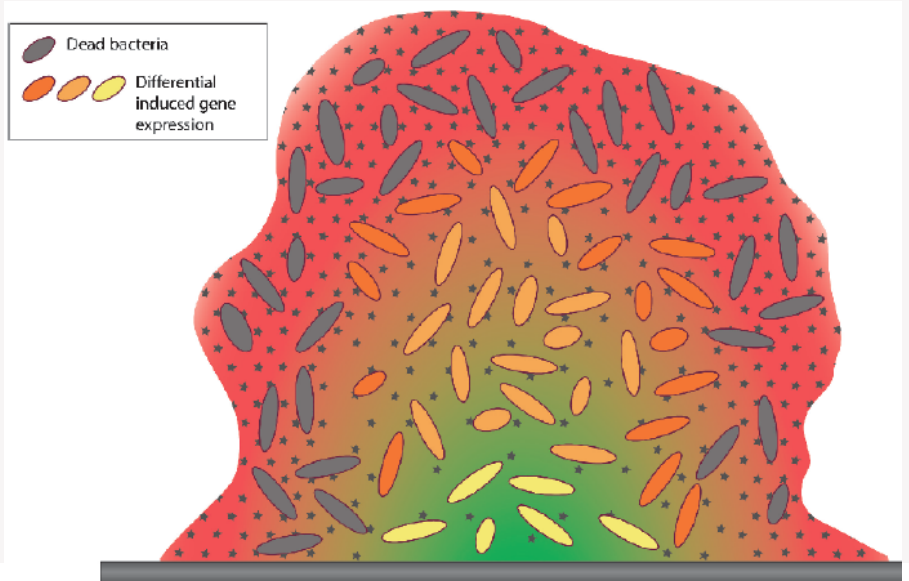
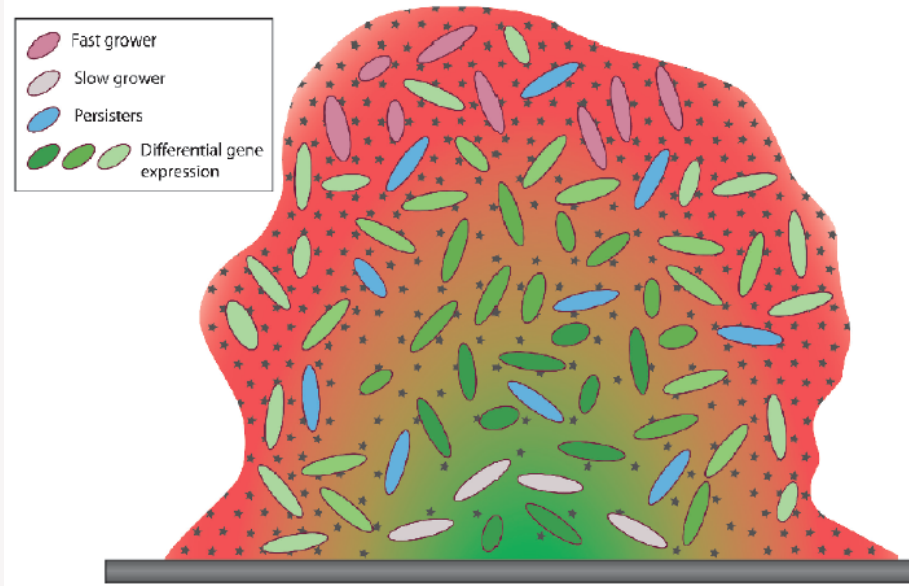
Vlamakis (2008) *Genes and Development*

# Biofilm resistance

Innate resistance

Induced resistance

Lemon et al., 2008  
*Curr Top Microbiol Immunol*







# Antibiotic-resistant diseases pose 'apocalyptic' threat, to

Chief medical officer Dame Sally Davies  
be added to national risk register of

News > Society > Drug resistance

## Antibiotics catastrophe warning from chief medical officer - video

Ian Sample, science correspondent  
The Guardian, Wednesday 23 January 2013 19:00  
[Jump to comments \(503\)](#)



Hospital superbugs such as MRSA are some of the most dangerous diseases, but MPs were warned about infection affecting the general population. Photograph: Getty Images

Britain's most senior medical adviser has warned that drug-resistant diseases could trigger a national catastrophe alongside terrorism, pandemic

Resistant bacteria pose 'a catastrophic threat' to the population ranked alongside terrorism on a list of threats to the nation



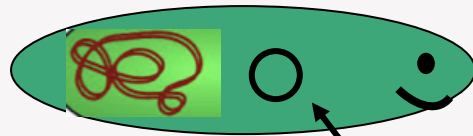
The chief medical officer, Dame Sally Davies, warns of a major increase in the number of bugs resistant to antibiotics. In a report published on Monday she says antibiotic-resistant bacteria with the potential to cause untreatable infections pose 'a catastrophic threat' to the population ranked alongside terrorism on a list of threats to the nation



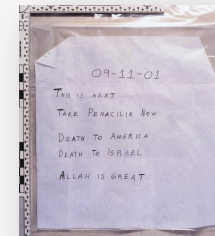
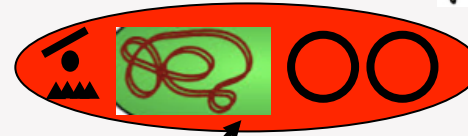
1966

# "The good, the bad, and the ugly"

*B. thuringiensis*



*B. anthracis*



*B. cereus*



## Multicellularity in *B. cereus*?

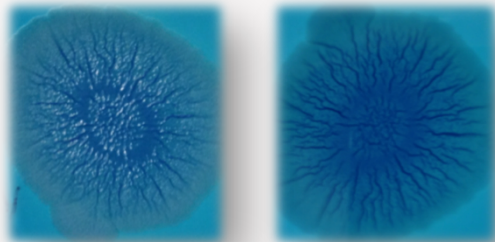
*B. subtilis*



*B. cereus*

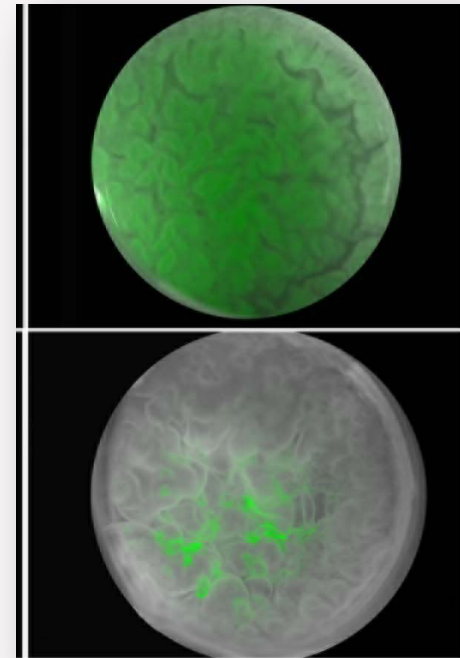


Msgg



Salt free LB + Calcofluor

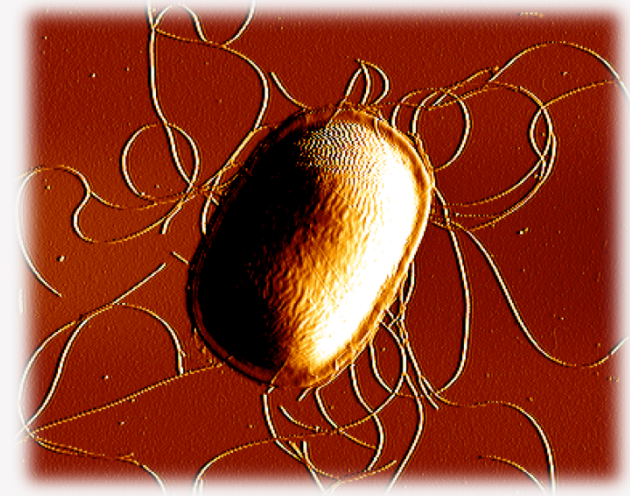
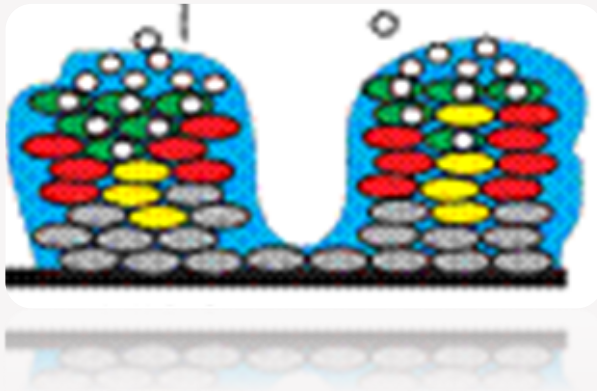
## HBL enterotoxin expression in biofilm



Fagerlund et al.  
(2014) PLoS One

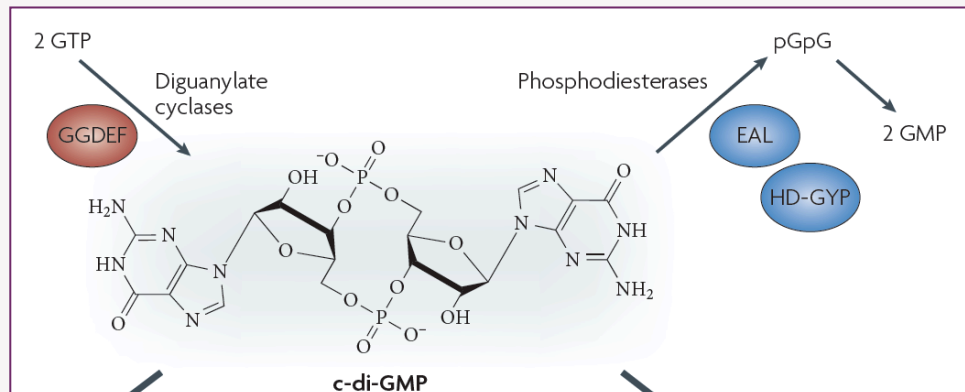


# How do pathogenic Bacilli regulate biofilm formation?



*Bacillus cereus* Bt407  
(Ida Hegna)

c-di-GMP





## ARTICLE

doi:10.1038/nature12790

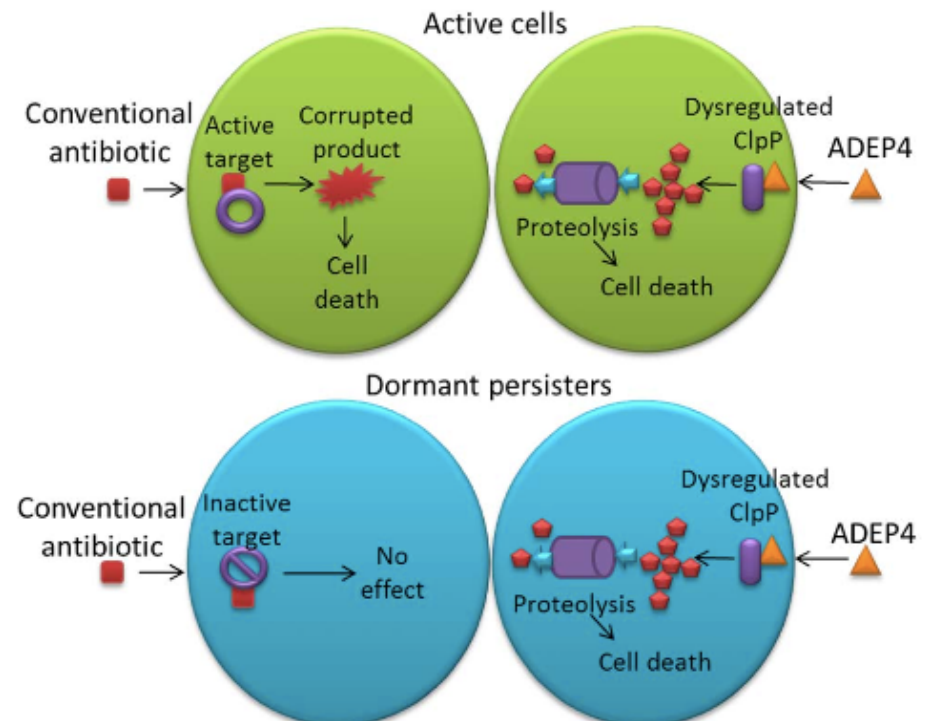
# Activated ClpP kills persisters and eradicates a chronic biofilm infection

B. P. Conlon<sup>1</sup>, E. S. Nakayasu<sup>2†</sup>, L. E. Fleck<sup>1</sup>, M. D. LaFleur<sup>3</sup>, V. M. Isabella<sup>1</sup>, K. Coleman<sup>3</sup>, S. N. Leonard<sup>4</sup>, R. D. Smith<sup>2</sup>, J. N. Adkins<sup>2</sup> & K. Lewis<sup>1</sup>

Chronic infections are difficult to treat with antibiotics but are caused primarily by drug-se... persister cells that are tolerant to killing by antibiotics are responsible for this appar... phenotypic variants of normal cells and pathways leading to dormancy are redundan... develop anti-persister compounds. Biofilms shield persisters from the immune system, s... for treating a chronic infection should be able to eradicate the infection on its own. We reaso... of corrupting a target in dormant cells will kill persisters. The acyldepsipeptide antibiotic... activate the ClpP protease, resulting in death of growing cells. Here we show that ADEP4-act... nonspecific protease and kills persisters by degrading over 400 proteins, forcing cells to self... arise with high probability, but combining ADEP4 with rifampicin produced complete er... *aureus* biofilms *in vitro* and in a mouse model of a chronic infection. Our findings indicate a... dormant cells—activation and corruption of a target, rather than conventional inhibition. I... animal model by activating a protease suggests a realistic path towards developing therapie

Conlon et al., *Nature*, 2013

## Aktivering av dormante celler i biofilm





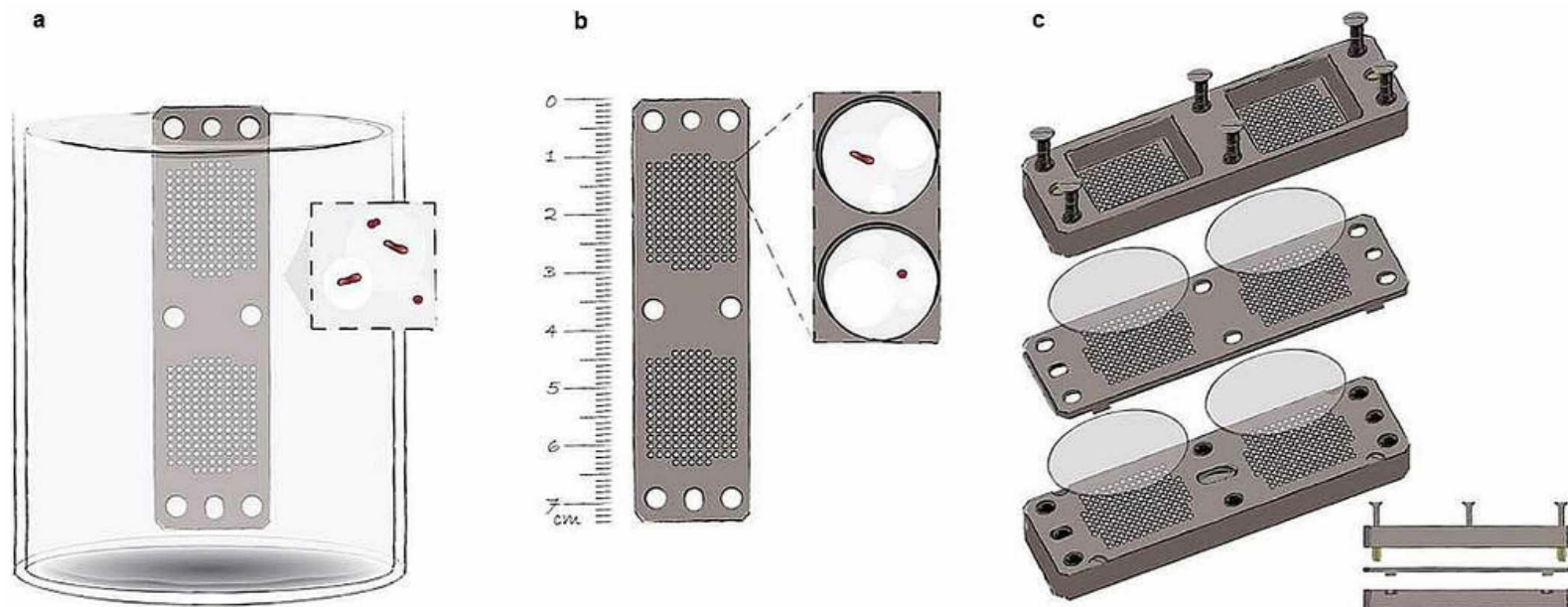
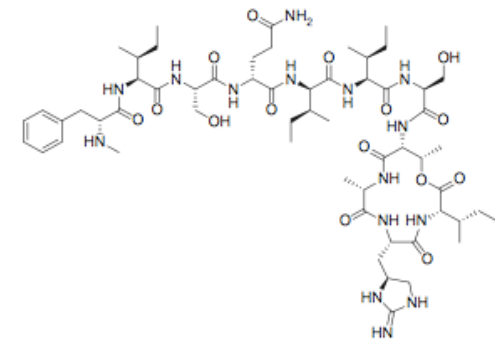
# Nytt prinsipp for 'drug discovery'

Ling et al., *Nature*, 2015

## A new antibiotic kills pathogens without detectable resistance

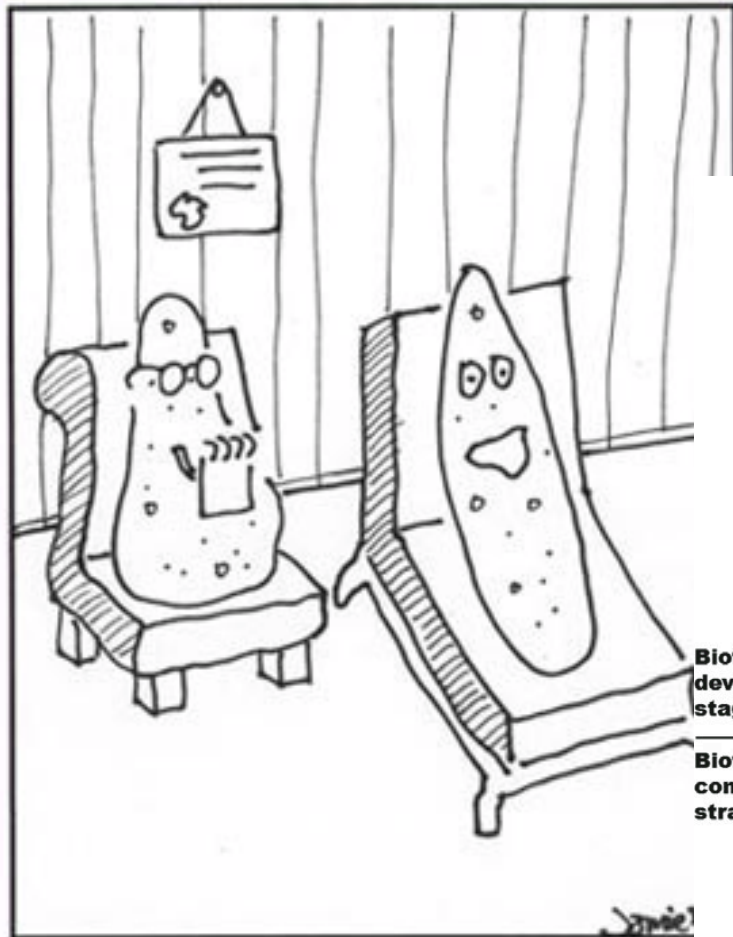
Losee L. Ling<sup>1\*</sup>, Tanja Schneider<sup>2,3\*</sup>, Aaron J. Peoples<sup>1</sup>, Amy L. Spoering<sup>1</sup>, Ina Engels<sup>2,3</sup>, Brian P. Con  
Till F. Schäberle<sup>3,5</sup>, Dallas E. Hughes<sup>1</sup>, Slava Epstein<sup>6</sup>, Michael Jones<sup>7</sup>, Linos Lazarides<sup>7</sup>, Victoria A. Ste  
Cintia R. Felix<sup>1</sup>, K. Ashley Fetterman<sup>1</sup>, William P. Millett<sup>1</sup>, Anthony G. Nitti<sup>1</sup>, Ashley M. Zullo<sup>1</sup>, Chao

Antibiotic resistance is spreading faster than the introduction of new compounds into clinical health crisis. Most antibiotics were produced by screening soil microorganisms, but this limited bacteria was overmined by the 1960s. Synthetic approaches to produce antibiotics have been a platform. Uncultured bacteria make up approximately 99% of all species in external environmental source of new antibiotics. We developed several methods to grow uncultured organisms by culturing specific growth factors. Here we report a new antibiotic that we term teixobactin, discovered in bacteria. Teixobactin inhibits cell wall synthesis by binding to a highly conserved motif in peptidoglycan and lipid III (precursor of cell wall teichoic acid). We did not obtain any mutants of *Staphylococcus aureus* or *Mycobacterium tuberculosis* resistant to teixobactin. The properties of this compound make it a promising candidate for developing antibiotics that are likely to avoid development of resistance.





# Til "krig" mot biofilm



I just can't go with the flow anymore.  
I've been thinking about joining a biofilm.

*This Slime Smile created by Jamie Pennington*

