AWP 2-4 – Polymer Chemistry

Polymers in Life Science – B) Antimicrobial Materials

University of Potsdam

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Summer term 2025

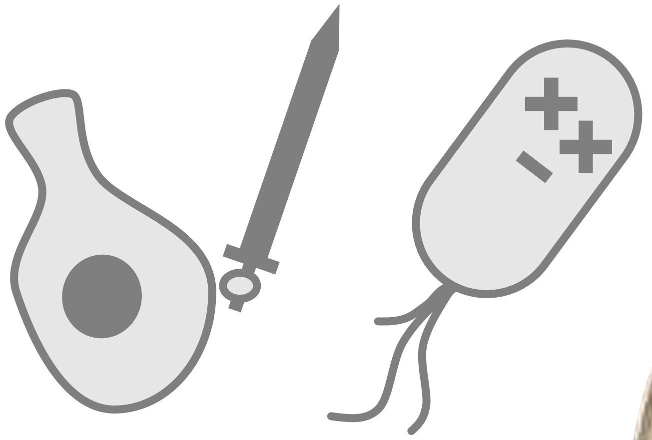
Overview

- Antibiotics and Antimicrobial resistance
- The bacterial cell envelope
- Host-defence Peptides
- Antimicrobial Polymers
- Polymer Disinfectants & Antifouling

Learning objectives

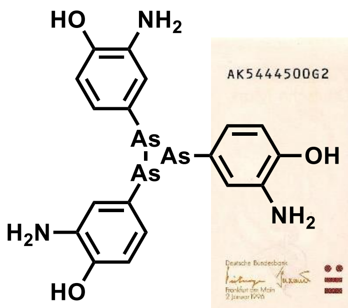
- Understand how grave the problem of AMR is and be able to discuss the reasons behind
- Understand the principal architecture of bacterial cells and how they differ from mammalian cells
- Know how host-defence peptides work
- Understand how antimicrobial polymers work and be able to discuss how their properties are influenced (and connected)
- Be able to explain passive and active antifouling and discuss advantages and downsides

A brief History of Antibiotics

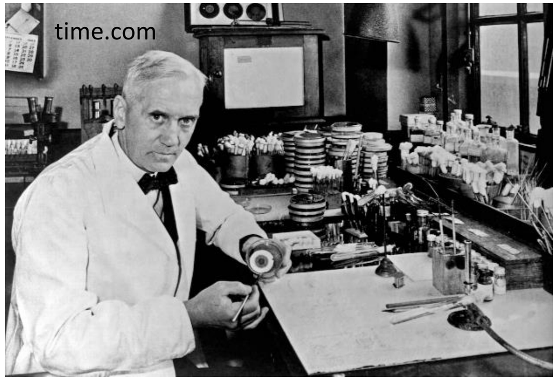


Antibiotics are weapons designed by microorganisms

Wound treatment in ancient cultures

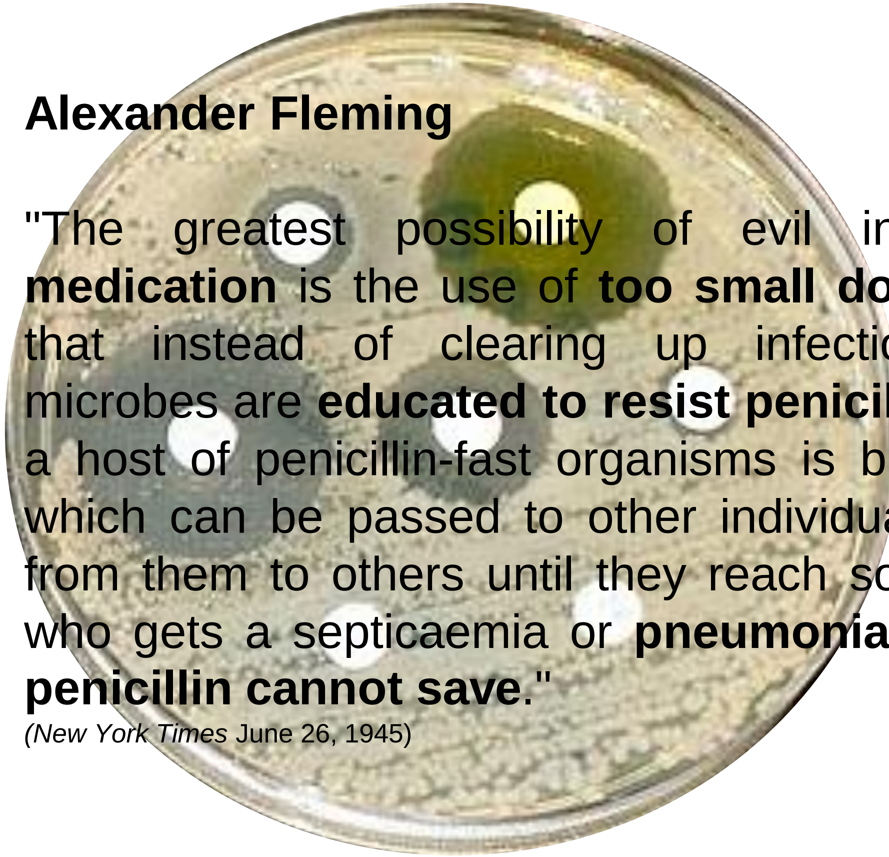


First Antibiotic discovered by Paul Ehrlich (1909): Arsphenamin



Discovery of Penicilin by Alexander Fleming (1928)

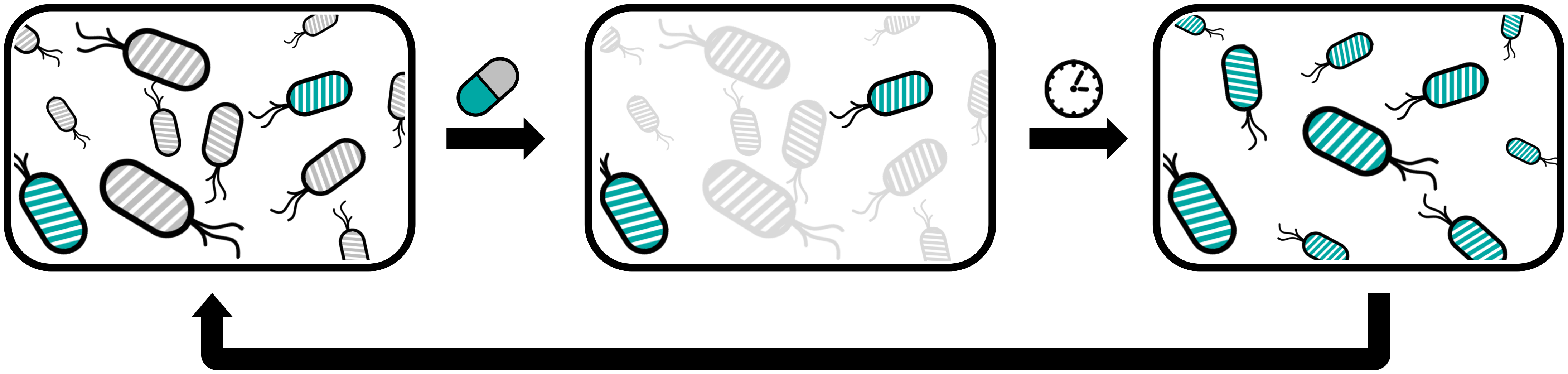
End of the Antibiotic era



Alexander Fleming

"The greatest possibility of evil in **self-medication** is the use of **too small doses** so that instead of clearing up infection the microbes are **educated to resist penicillin** and a host of penicillin-fast organisms is bred out which can be passed to other individuals and from them to others until they reach someone who gets a septicaemia or **pneumonia which penicillin cannot save**."
(*New York Times* June 26, 1945)

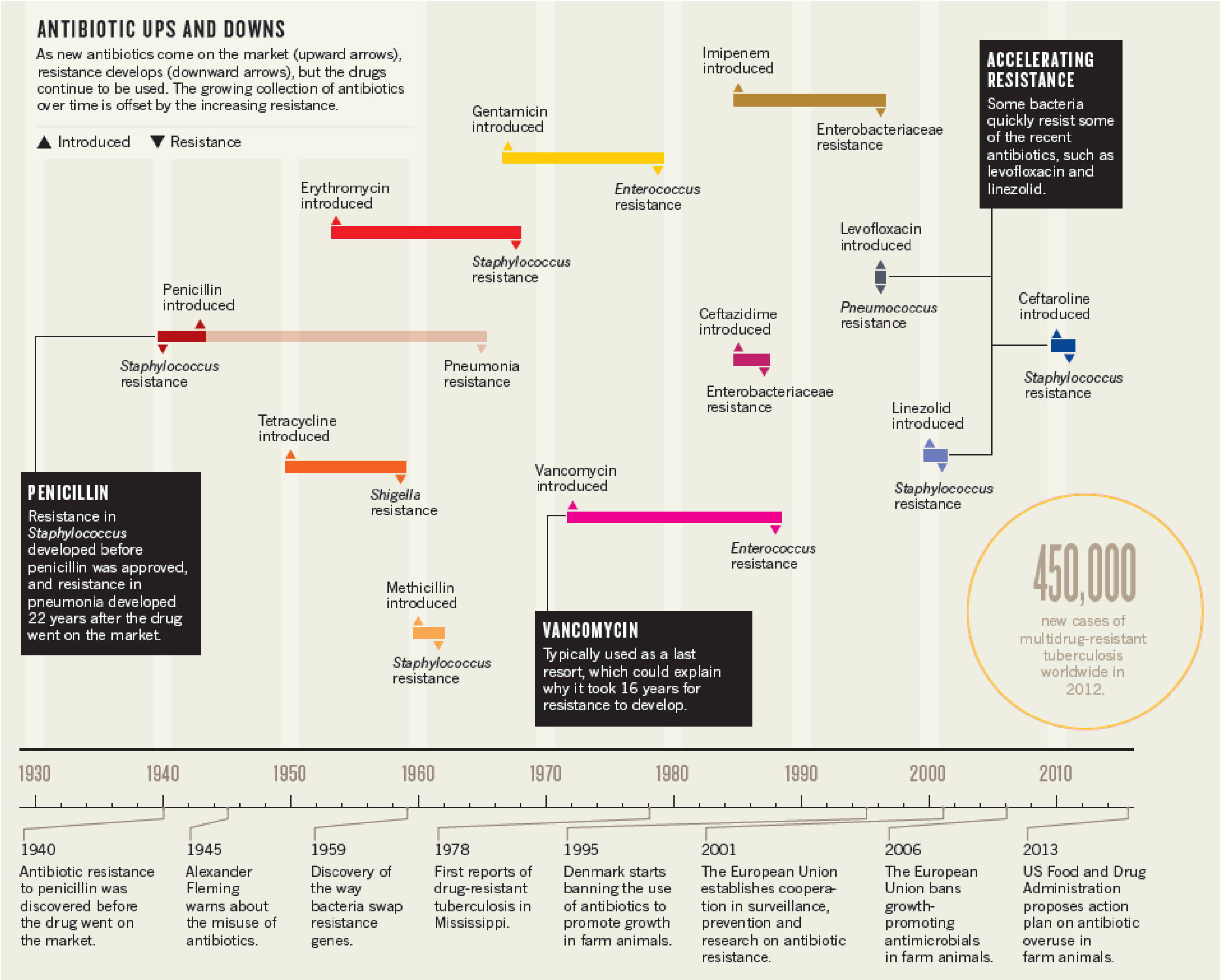
Antimicrobial Resistance (AMR)

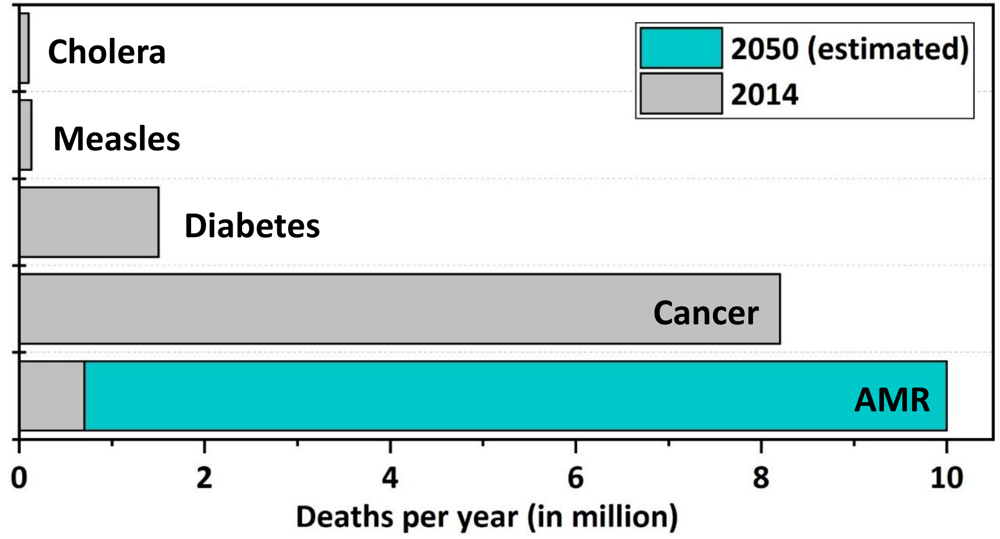


www.who.int/drugresistance

J. O'Neill, *Antimicrobial resistance : tackling a crisis for the health and wealth of nations, Wellcome Trust, London,* ***2014.***
World Health Organization (WHO), **2018**, *Report on Surveillance of Antibiotic Consumption.*

Resistance on the March



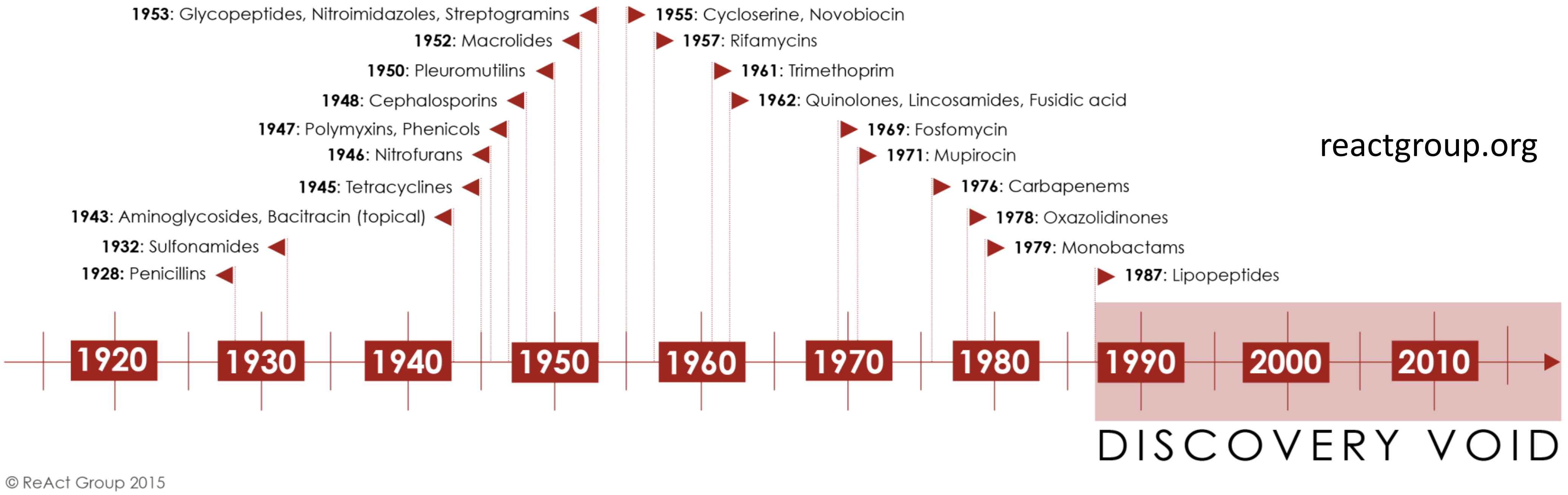


- **Post-antibiotic era threatens our lifestyle and medical advances**
- **1.27 millions deaths attributed to AMR in 2019**
- **New antimicrobial are urgently needed**

„Antibiotic resistance: An infectious arms race“ Nature, 509, doi:10.1038/509S2

J. O'Neill, *Antimicrobial resistance : tackling a crisis for the health and wealth of nations, Wellcome Trust, London,* ***2014.***
World Health Organization (WHO), **2018**, *Report on Surveillance of Antibiotic Consumption.*
Murray CJL, *et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. The Lancet* ***399, 629-655 (2022).***

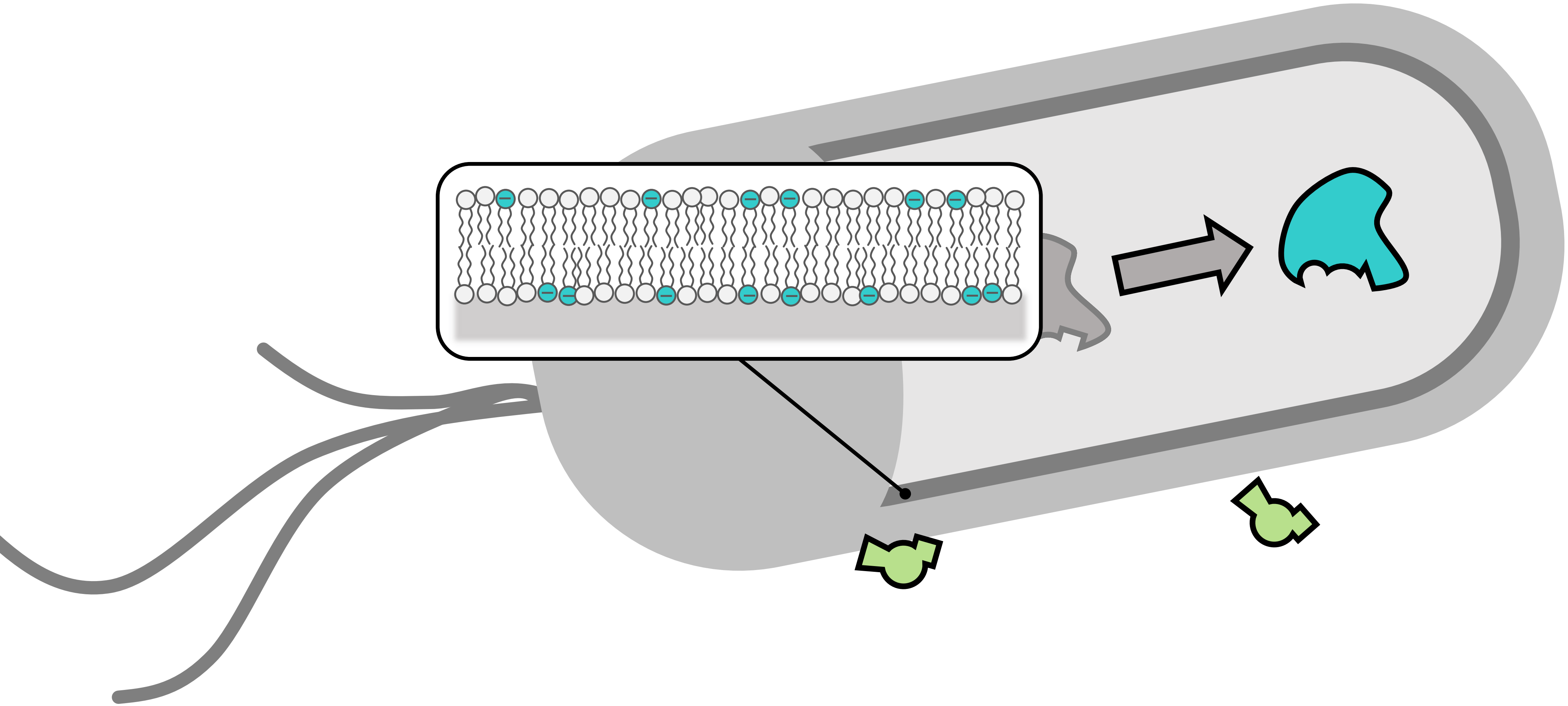
A shrinking Arsenal..



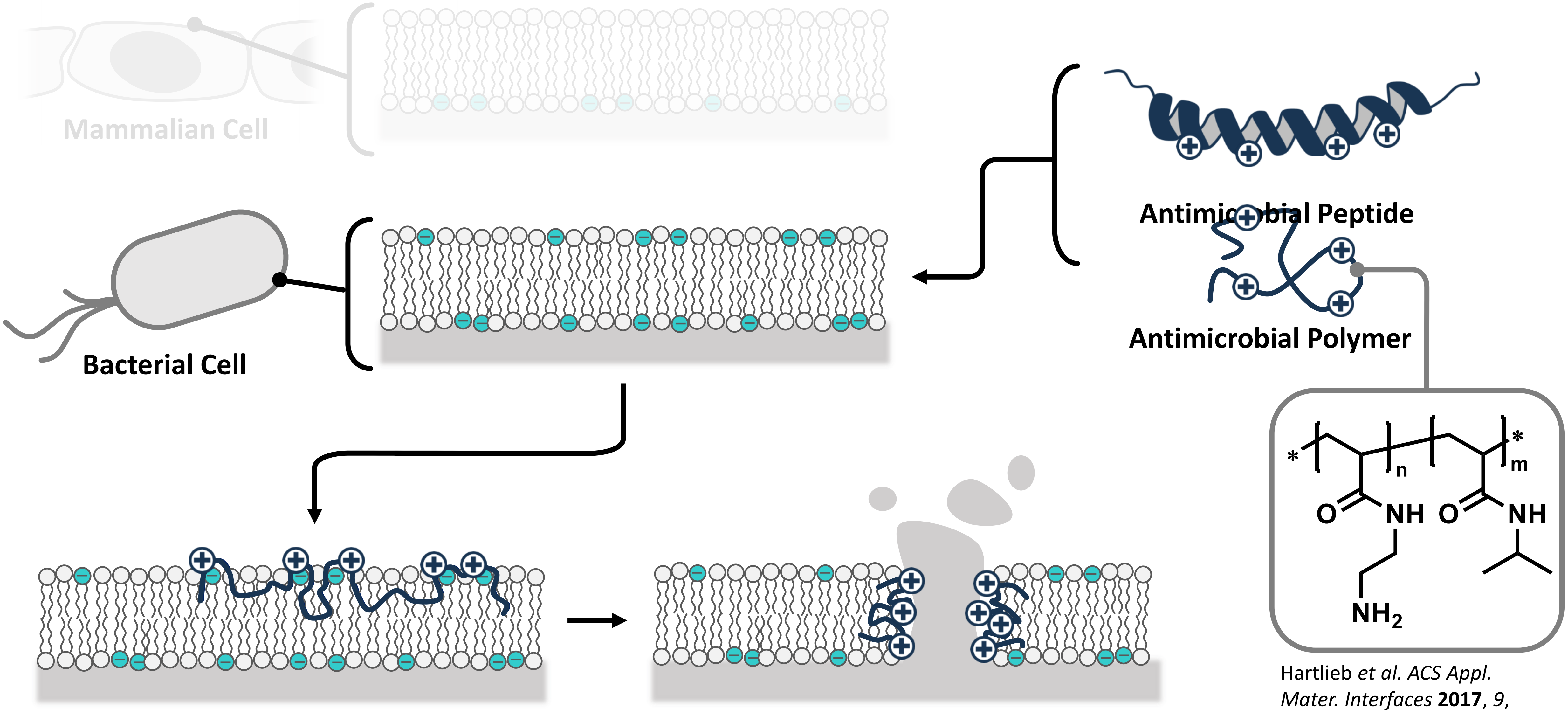
- Most large companies have abandoned antibacterial drug discovery
- Current research is driven by
  - Small companies
  - Academia
  - Public funding

$$$

Antimicrobial Resistance Mechanism



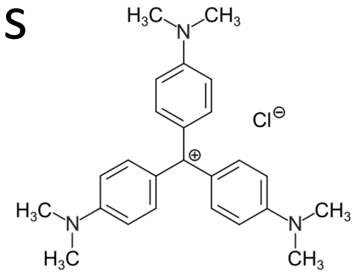
Antimicrobial Peptides and Polymers

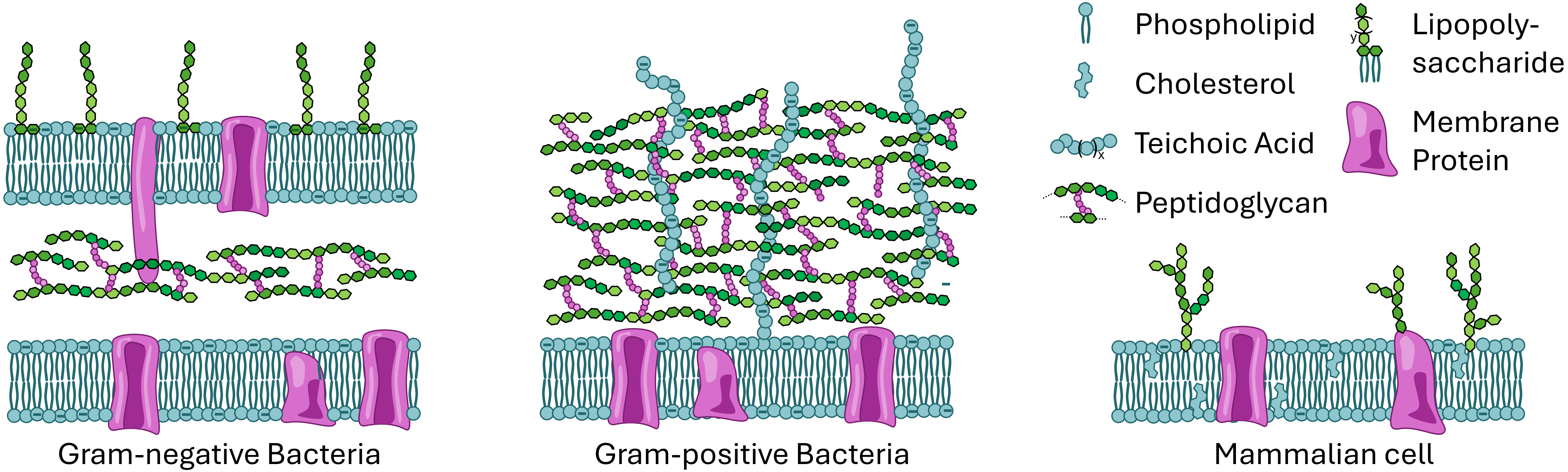


Hartlieb *et al. ACS Appl. Mater. Interfaces* **2017**, *9*, 40117-40126.

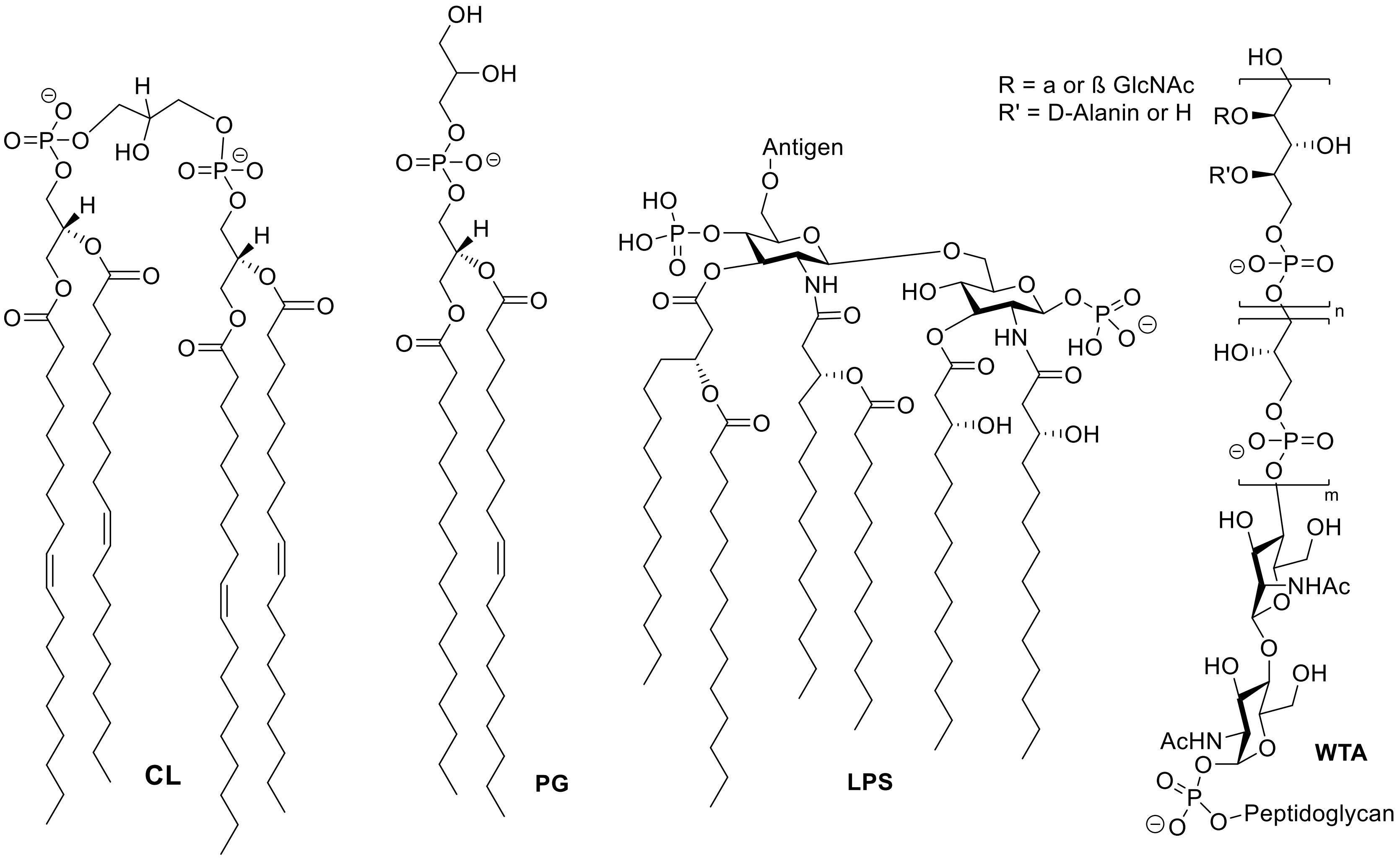
The bacterial cell envelop

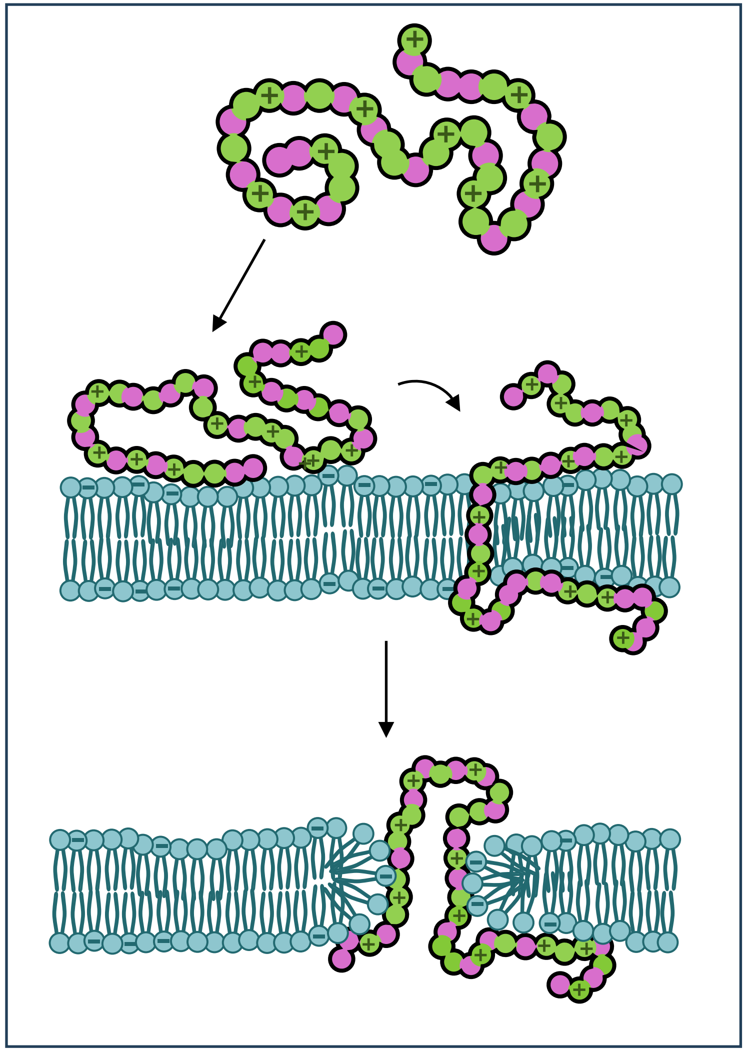
- Bacterial (and fungal) cells are more net-negative than mammalian cells
- However: large difference in architecture between gram pos./neg.





Anionic components of the cell envelop



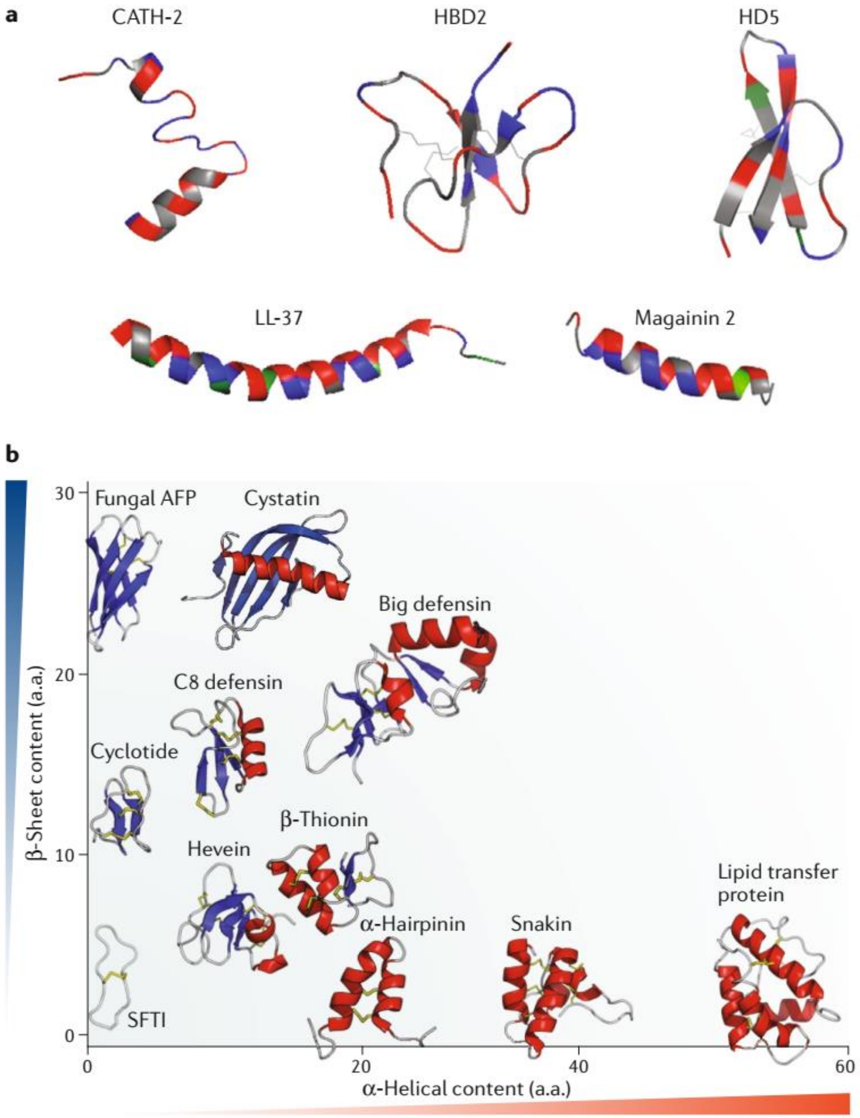


Inspiration: Host-defence peptides (HDPs)

- Ancient motifs to fight microorganism
- Part of innate immunity
- Divers and large class of biomolecules
- Often: Facial amphiphilicity

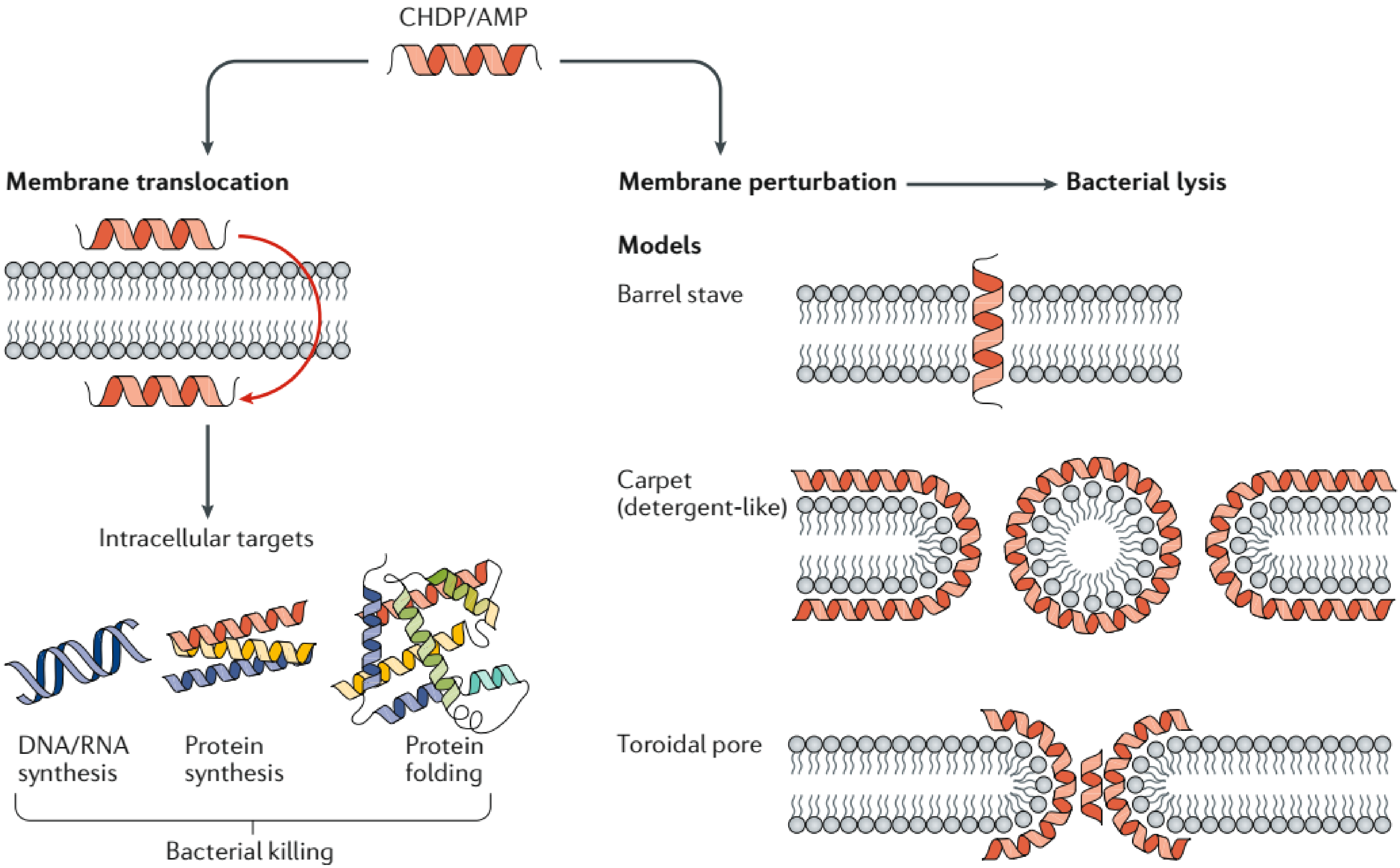
HDP

- Usually managing microbial populations on a local level (e.g. guts, skin)



Mookherjee, N., Anderson, M.A., Haagsman, H.P. *et al.* Antimicrobial host defence peptides: functions and clinical potential. *Nat Rev Drug Discov* **19**, 311–332 (2020). https://doi.org/10.1038/s41573-019-0058-8

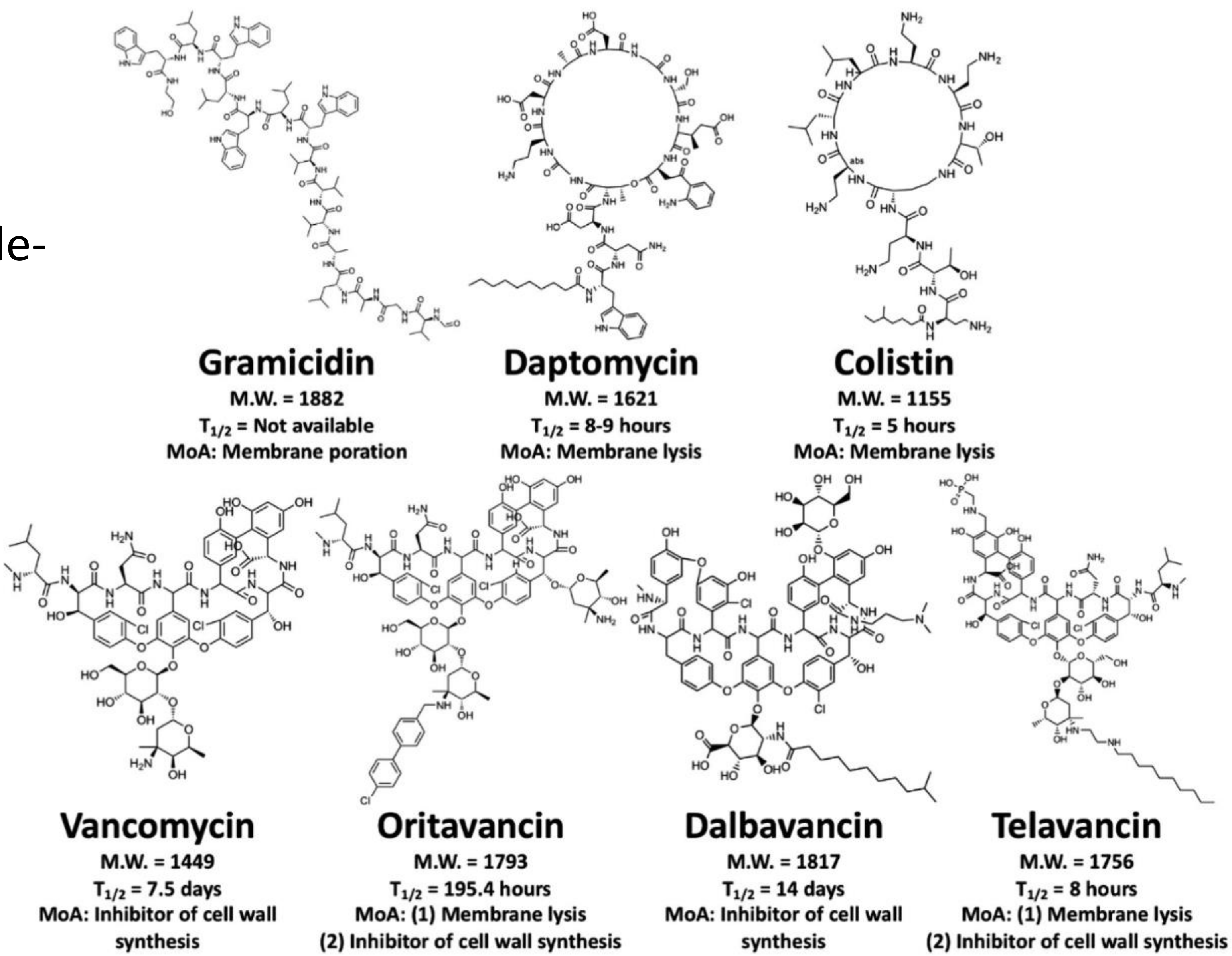
HDP: mechanism of action



Mookherjee, N., Anderson, M.A., Haagsman, H.P. *et al.* Antimicrobial host defence peptides: functions and clinical potential. *Nat Rev Drug Discov* **19**, 311–332 (2020). https://doi.org/10.1038/s41573-019-0058-8

FDA-approved HDPs

- Usually last-resort antibiotic
- Some have significant side-effects



Excurse: MIC & Selectivty

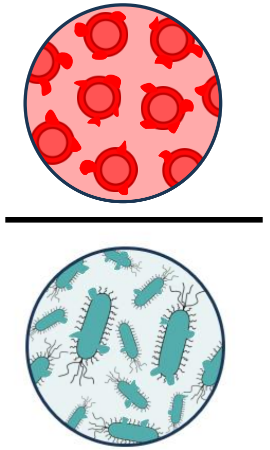
Hemotoxic concentration (Hc_{10})

➡ High concentrations are beneficial

Minimum inhibitory concentration (MIC_{50})

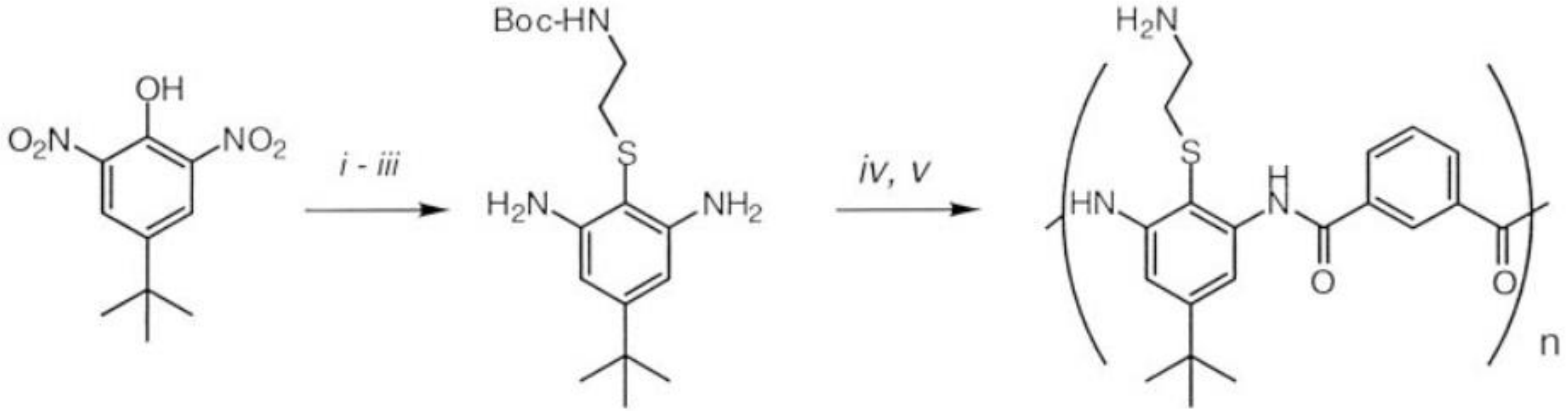
➡ Low concentrations are beneficial

Selectivity =

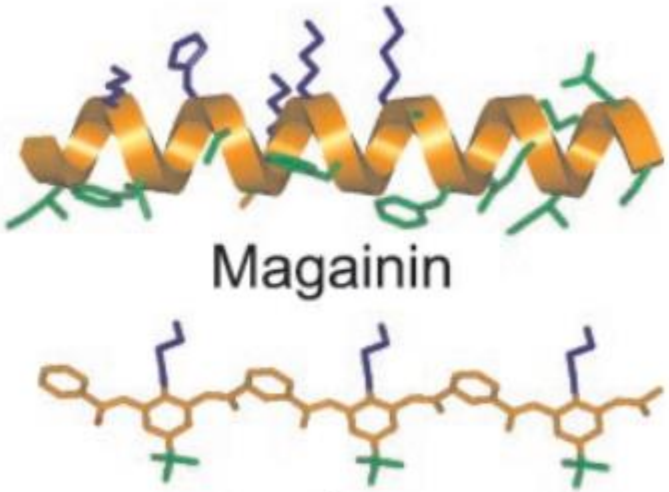


- Selective interaction with bacteria over mammalian cells
- High values are aspired

Antimicrobial polymers: early steps



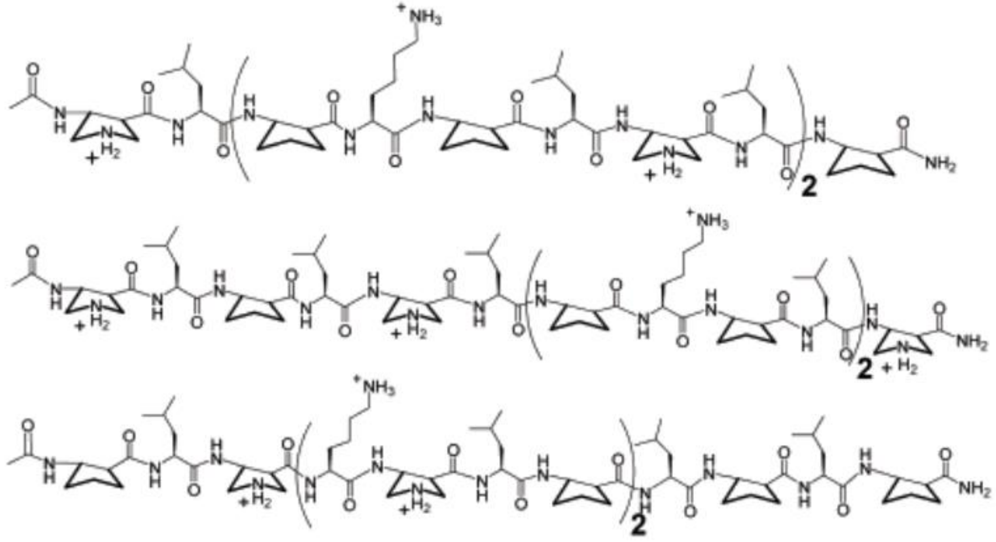
	n	R	MIC, μg/ml§		
			E. coli	*K. pneumoniae*‡	*B. subtilis*¶
2	2	NH_3^+	19	66	12
3	3	NH_3^+	<19	NA	19
4	8*†	NH_3^+	7.5–15	31–50	16
5	60*	NH_3^+	>200	—	—



1

Is a helix necessary?

1, 2, 3



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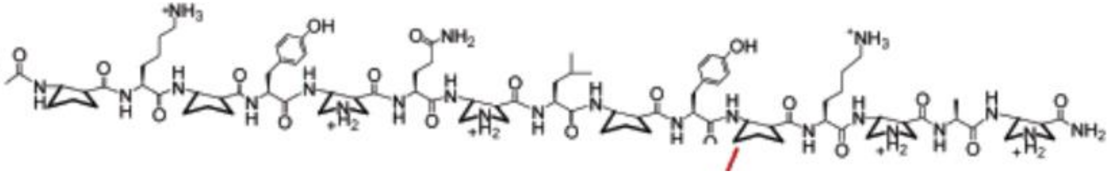
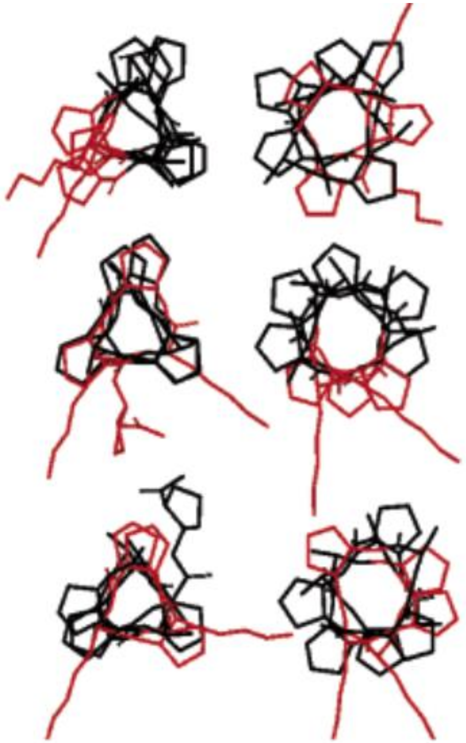
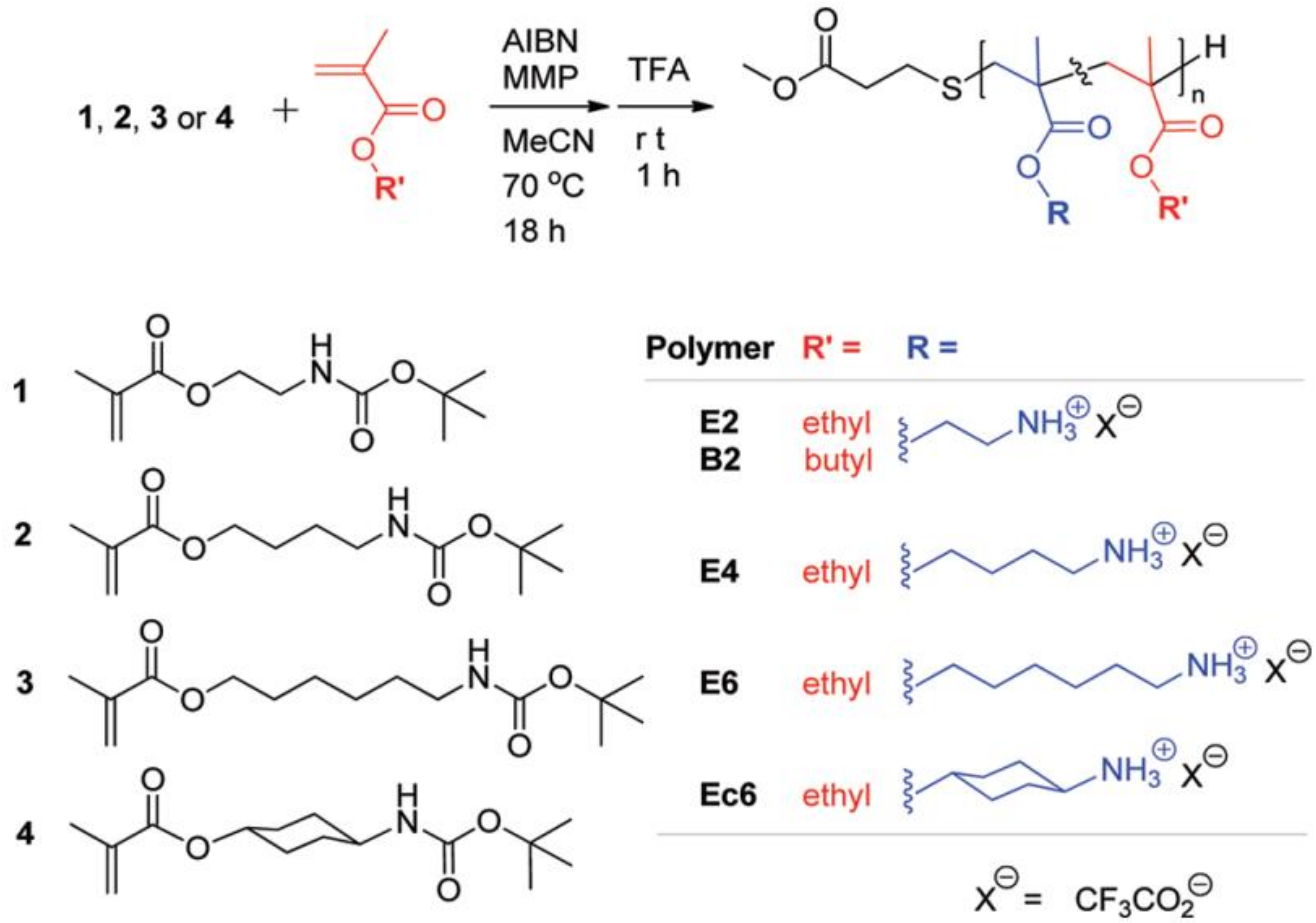


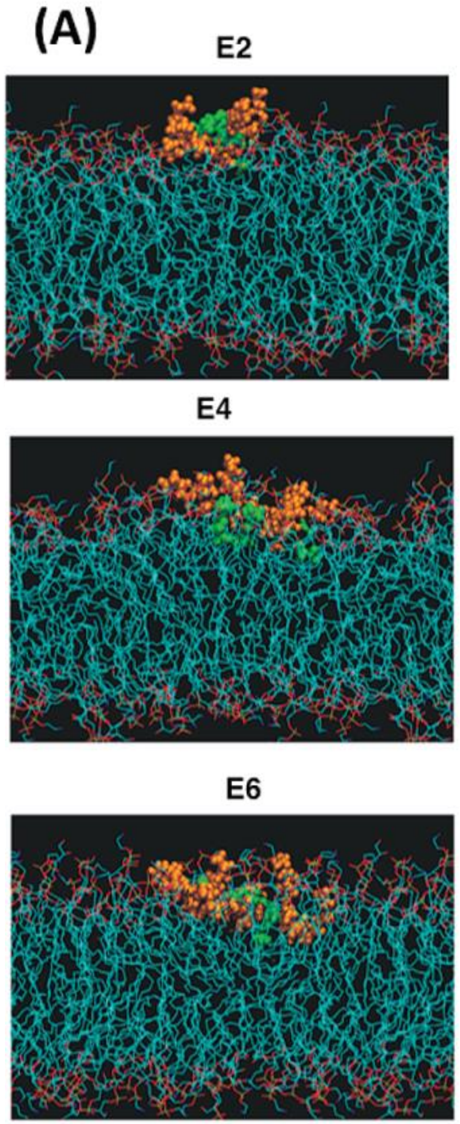


	MIC (E. coli, µg mL^{-1})
1	12.5
2	>100
3	6.3

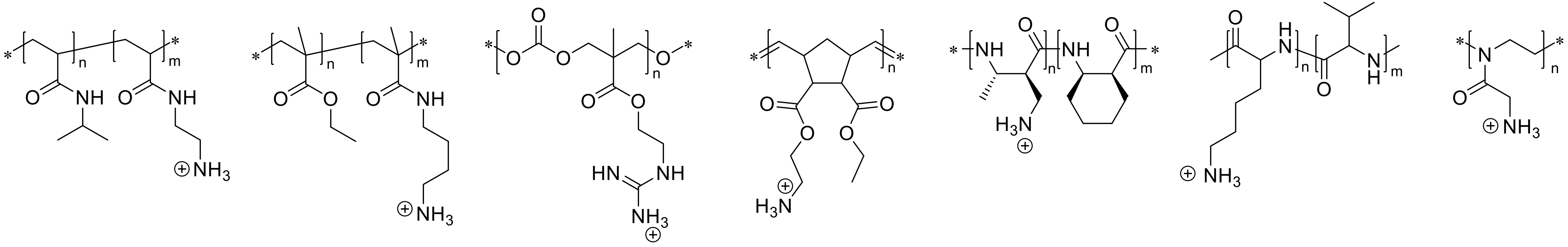
- Facial amphiphilic isomer least active
- Best activity for scrambled sequence

Polymers adopt facial amphiphilic structure on the membrane





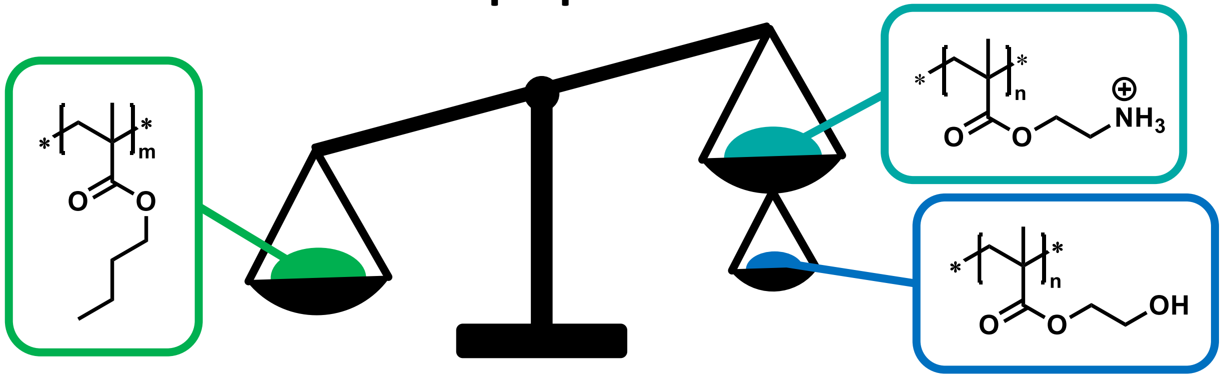
Types of Antimicrobial Polymers



- Usually copolymer from hydrophobic and cationic monomers
- Primary amine and guanidine functions work best

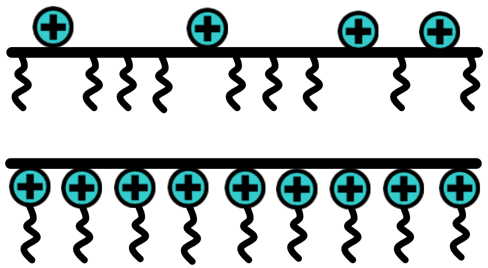
Polymeric Antimicrobial Peptide Mimics

Amphiphilic Balance



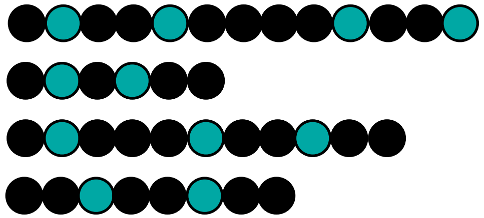
Boyer *et al.*, *Macromolecules* **2020**, *53*, 631-639.
Tiller *et al.*, *Macromol. Biosci.* **2015**, *15*, 1710-1723.
Gellman *et al.*, *J. Am. Chem. Soc.* **2014**, *136*, 4410-4418.

Spatial Organization



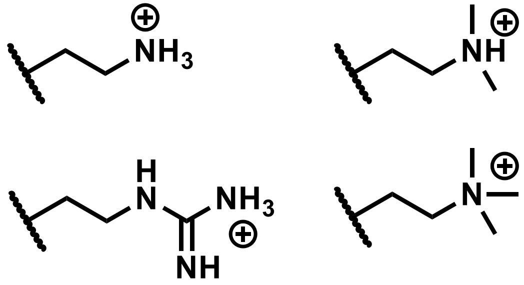
Sen *et al.*, *Angew. Chem. Int. Ed.* **2008**, *47*, 1250-1254.
Lienkamp *et al.*, *Chem. Eur. J.* **2018**, *24*, 8217-8227.
Lienkamp *et al.*, *Macromol. Chem. Phys.* **2019**, *220*, 1900346.

Polymer Length



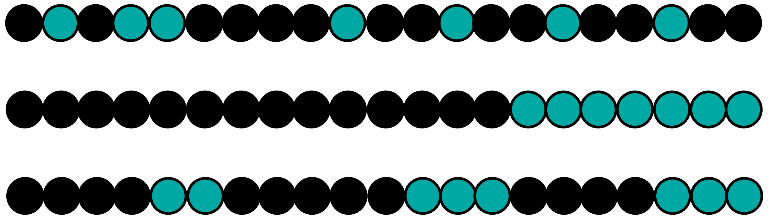
Kuroda *et al.*, *Bioconj. Chem.*, **2017**, *28*, 1340-1350.
Boyer *et al.*, Polym. Chem. **2018**, *9*, 1735-1744.

Type of Charge



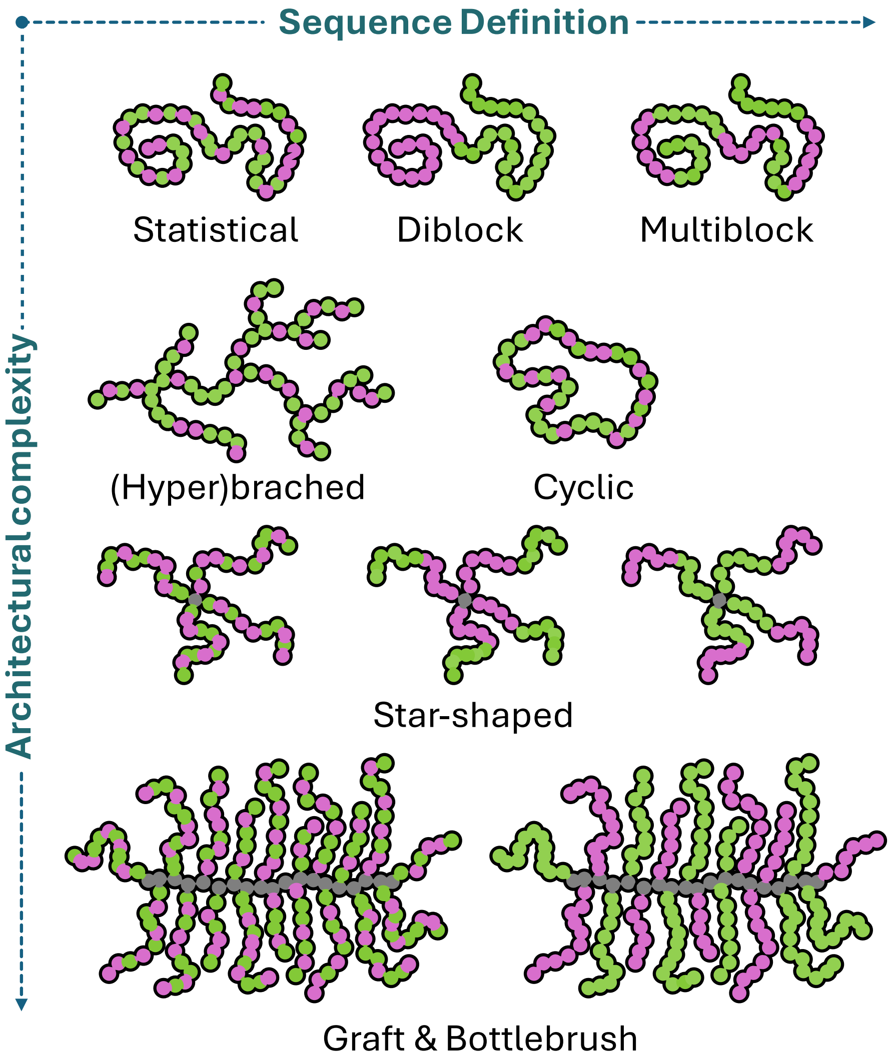
Hedrick, Yang, *et al.*, *Nat. Commun.* **2018**, *9*, 917.
Palermo, Kuroda *et al.*, *Biomacromolecules* **2009**, *10*, 1416-1428.
Agarwal *et al.*, *Macromol. Biosci*. **2013**, *13*, 242-255.

Sequence Control

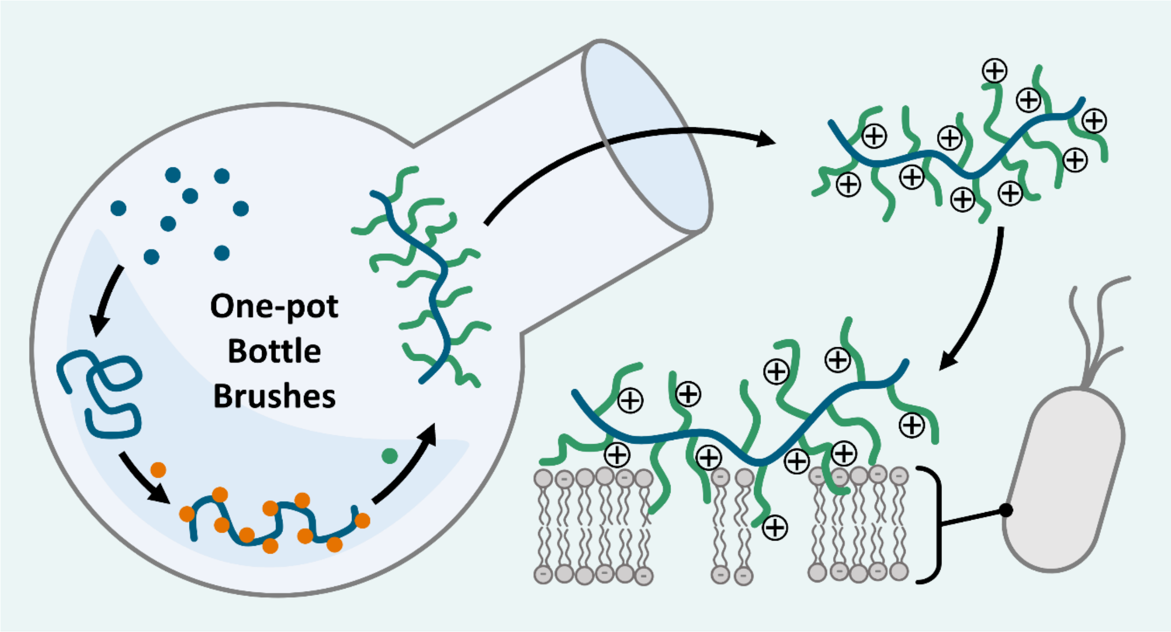


Hartlieb, Perrier *et al.*, *ACS Appl. Mater. Interfaces* **2017**, *9*, 40117-40126.
Boyer et al., *Angew. Chem. Int. Ed.* **2018**, *57*, 4559-4564.
Anastasaki et al., *Polym. Chem.* **2020**, *11*, 84-90.

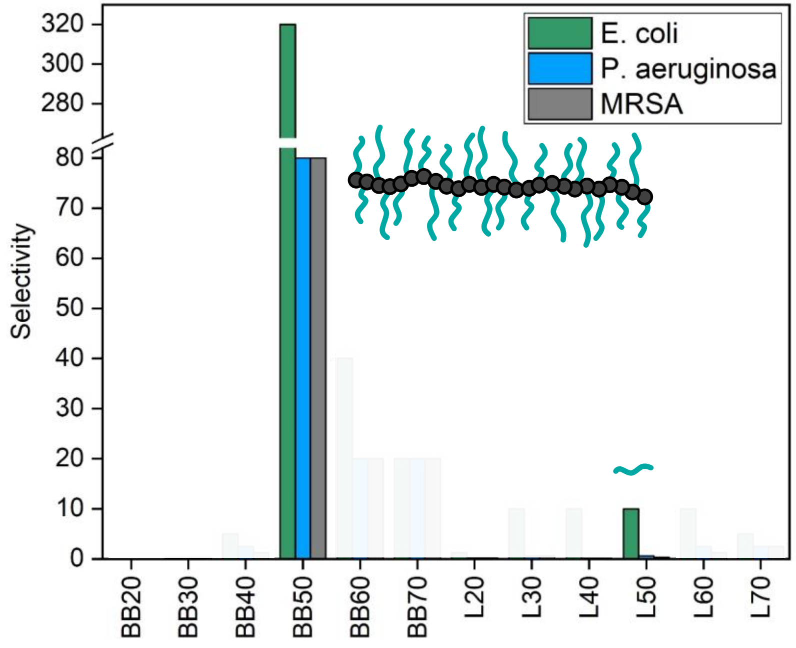
Structural aspects

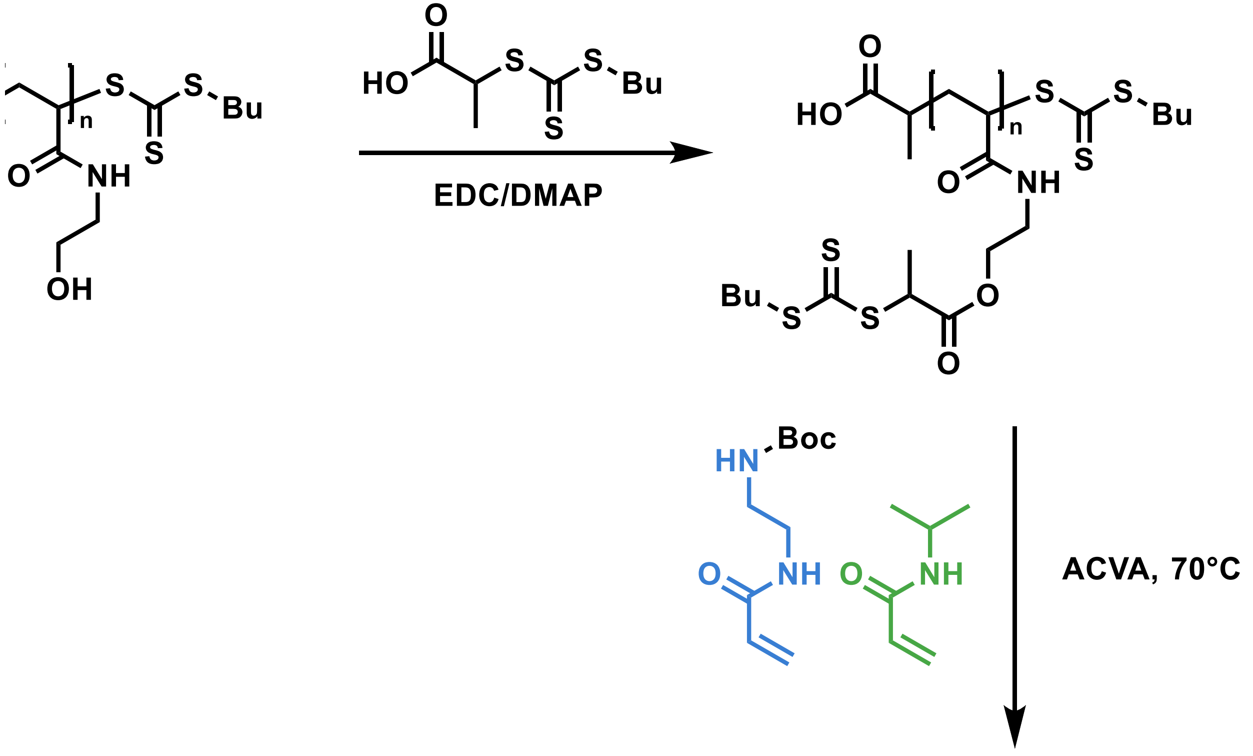


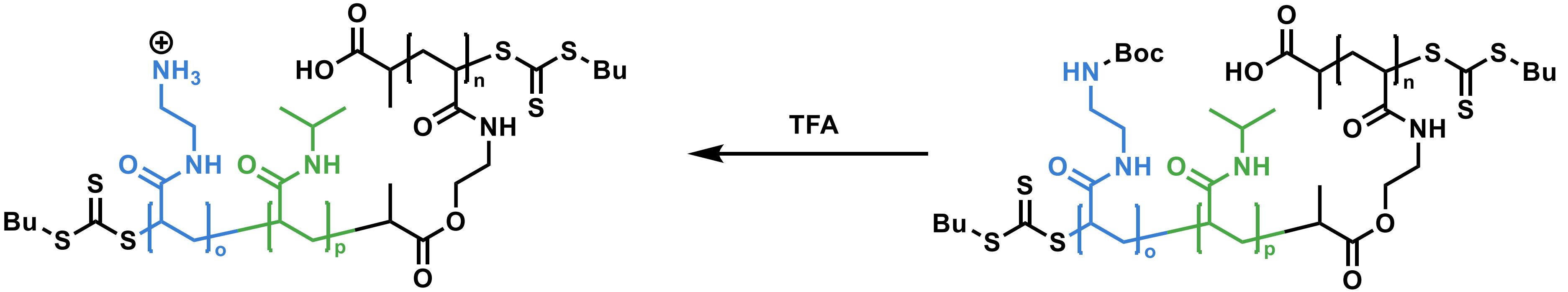
- Polymer topology has a huge impact on activity (selectivity)
- Example: Bottle brush copolymers



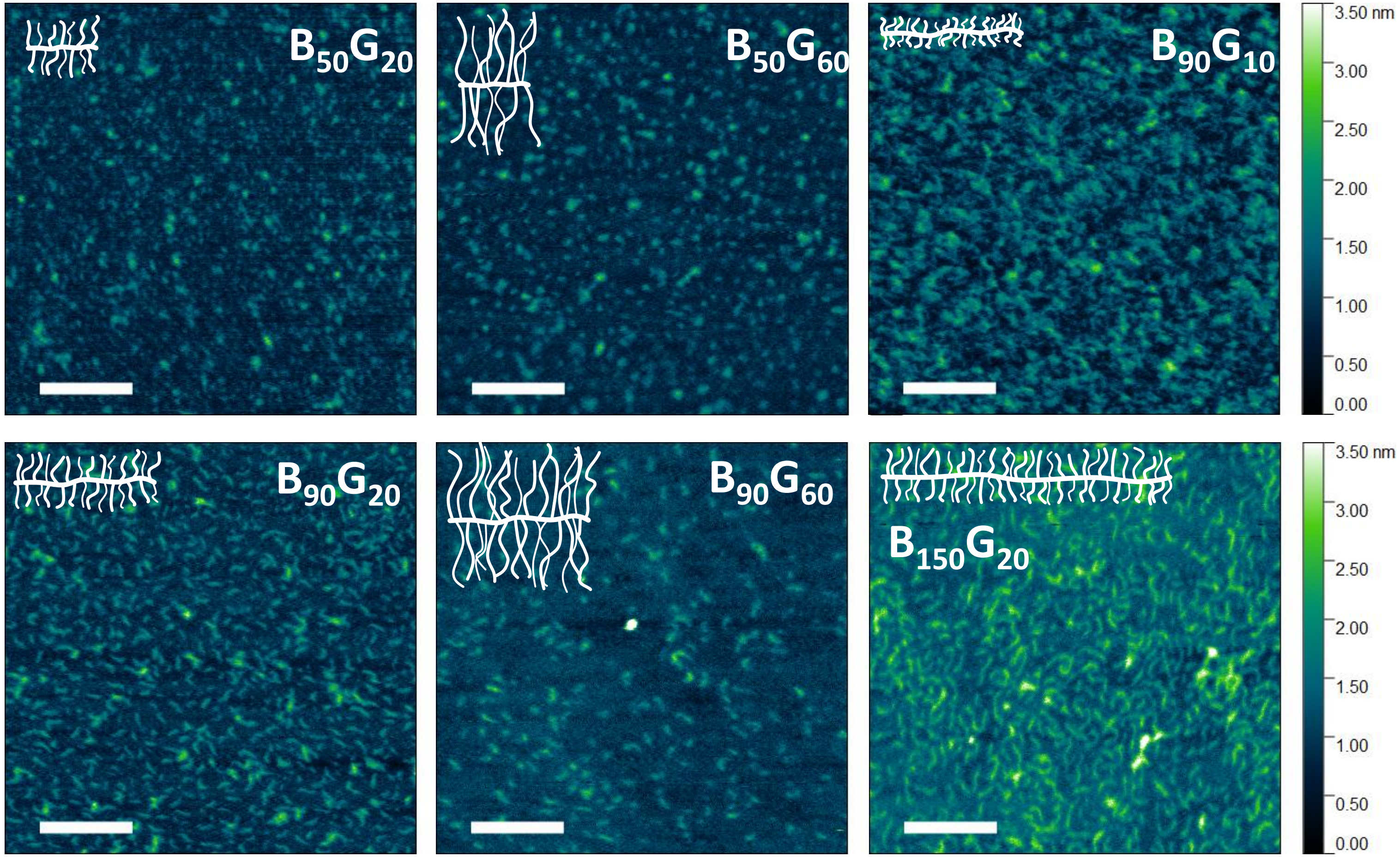
From „grafting-through“ to „grafting-from“

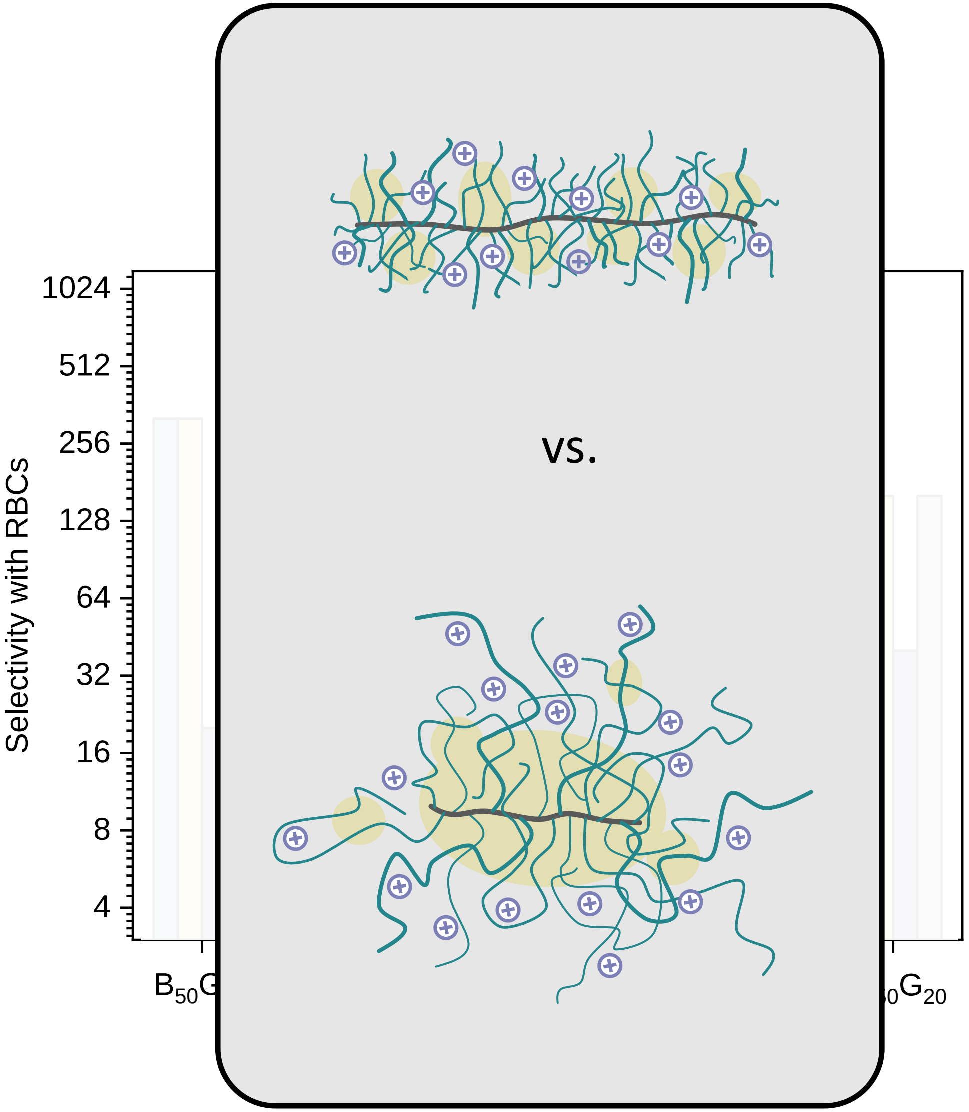




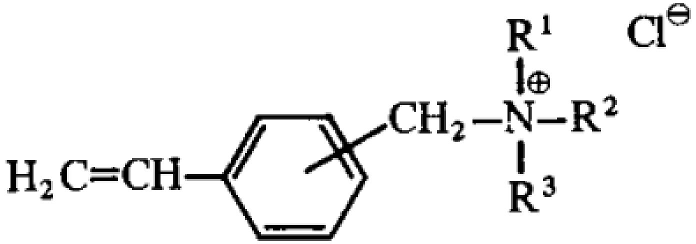


Influence of the Aspect Ratio





Polymer Disinfectants

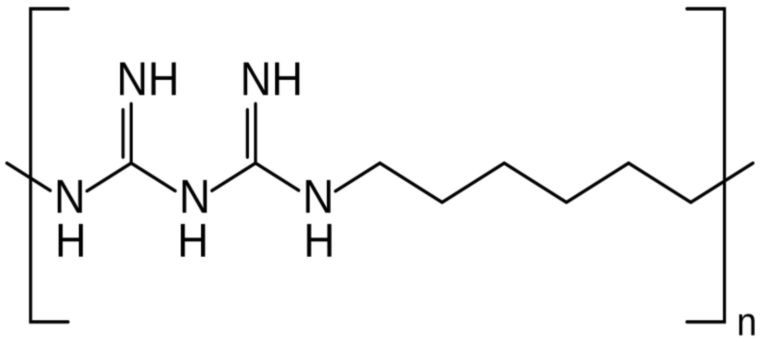


	R^1	R^2	R^3
1	CH_2CH_3	CH_2CH_3	CH_2CH_3
2	CH_3	CH_3	$CH(CH_3)_2$
3	CH_3	CH_3	$(CH_2)_3CH_3$
4	CH_3	CH_3	$(CH_2)_{11}CH_3$

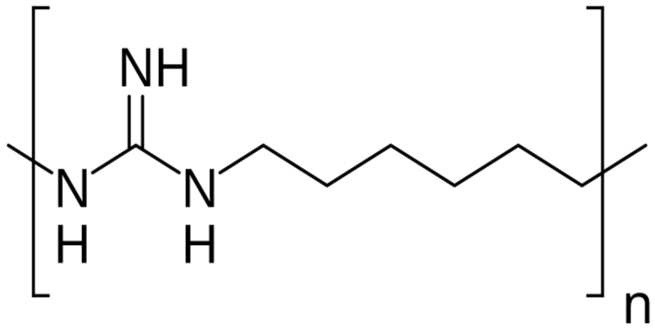
SUMMARY:

Various poly(trialkyl-3-(and 4-)vinylbenzylammonium chloride)s were prepared and their antibacterial activities were assessed by the conventional spread plate method and the viable counting method. They are in general more active against Gram-positive bacteria such as Bacillus subtilis and Staphylococcus aureus than against Gram-negative bacteria such as Escherichia coli, Aerobacter aerogenes and Pseudomonas aeruginosa. Compounds with the longest alkyl chain studied (dodecyl) were found to exhibit particularly high activity, and this was ascribed to the contribution of the increased hydrophobicity of the compounds to the activity. The most significant finding was that the polymers are more active than the corresponding monomers. The higher activity of the polymers was discussed and interpreted in terms of their greater contribution to each elementary process in the cidal action: their favored adsorption onto the bacterial cell surface and the cytoplasmic membrane with subsequent disruption of its integrity.

Polymer Disinfectants II



Polyhexamethylene biguanide (PHMB)



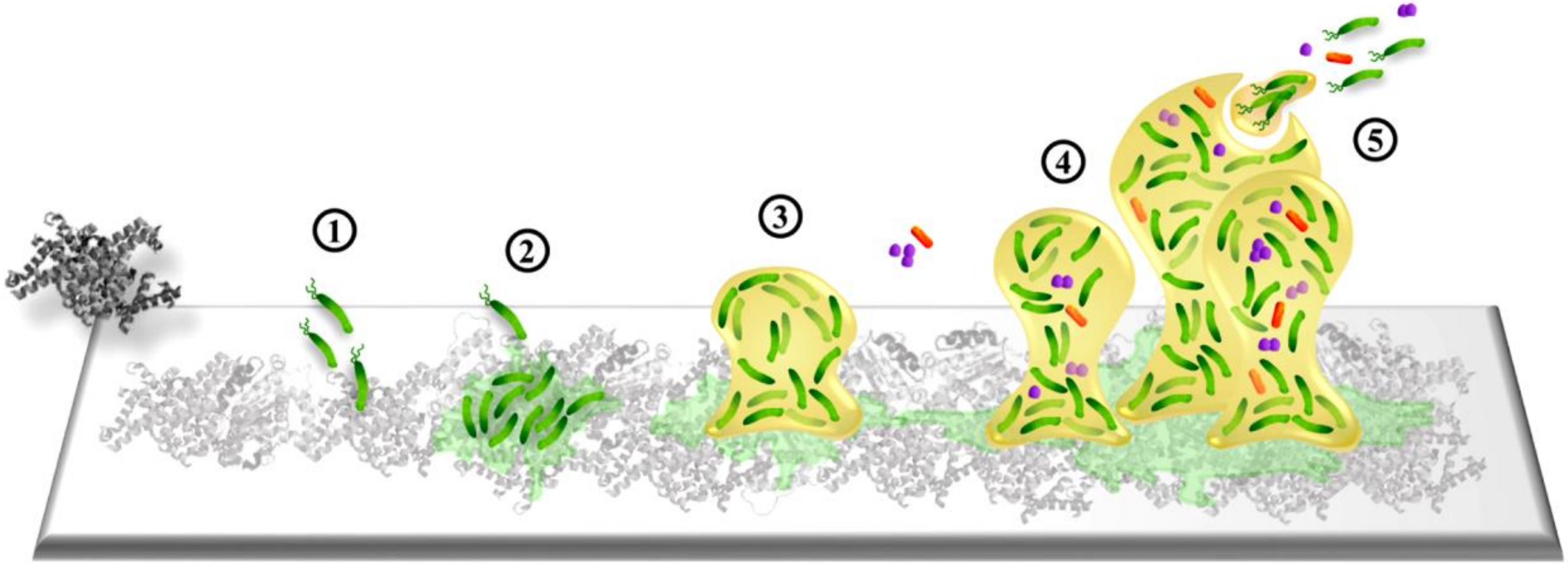
Polyhexamethylene guanidine (PHMG)

- Disinfectants for wounds and skin
- Use in post-surgical treatments and eye drops
- Also used in pool/spa disinfection
- Approved to use as treatment against *Acanthamoeba* keratitis (eye infection)

- Used in humidifier disinfection up to 2011
- pulmonary toxicity of aerosols
- Korean government officially recognized 1,814 dead and 7,837 injured victims (likely more than 20.000 deaths, up to 1 Mio health damages)

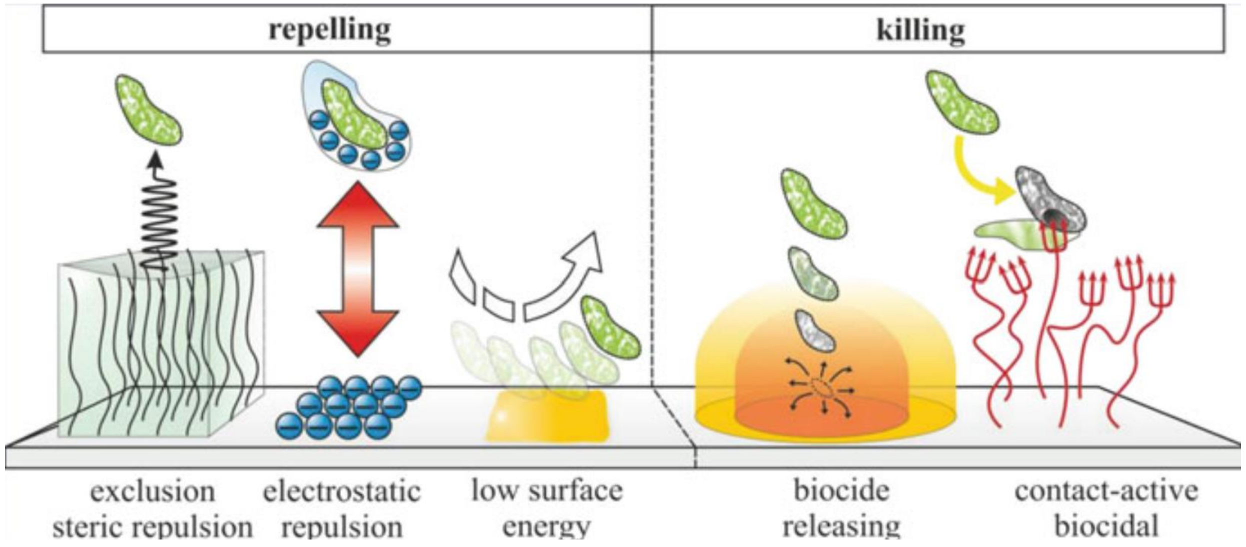
Antifouling: Biofilms

- Biofilms form on almost any surface
- Consist of biomolecules, organisms (bacteria, fungi, ..) and extracellular matrix
- Significant higher treatment resistance of bacteria etc. in biofilms
- Specifically dangerous for implants and medical devices (e.g. catheters)



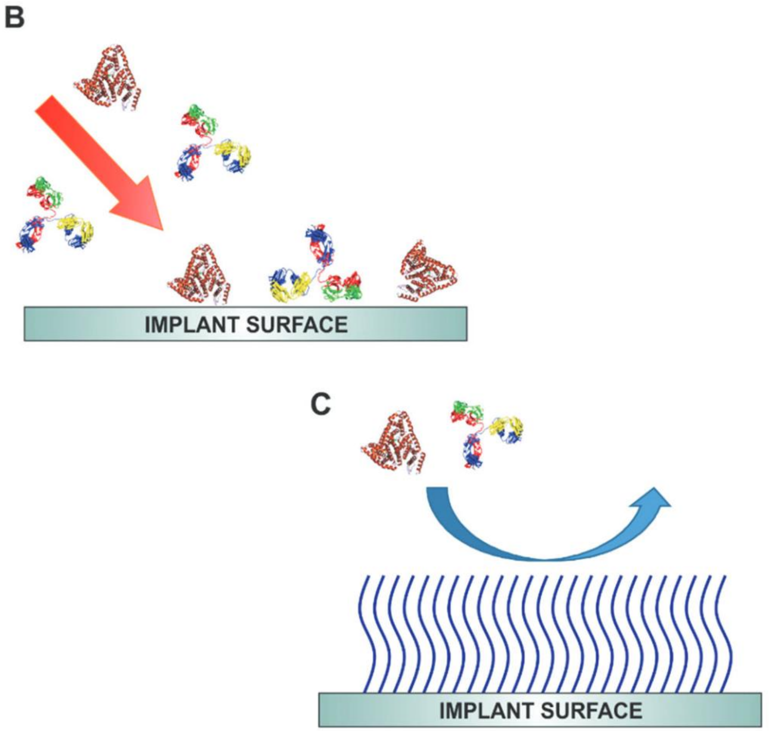
Antifouling strategies

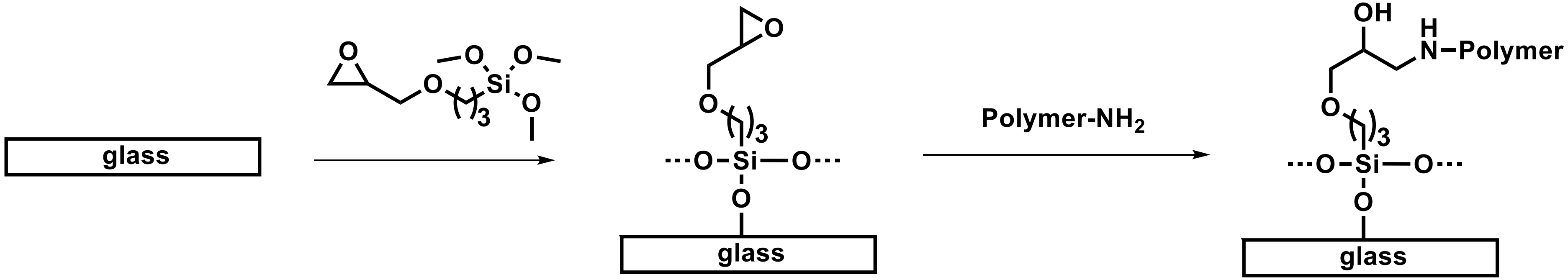
- **Passive Antifouling**
  - Prevention of attachment of biomolecules or organisms
  - No killing of microorganisms
  - Based on strong hydration of the interface
- **Active Antifouling**
  - Biocidal Polymer on the interface or release of biocidal molecules
  - Killing of microorganisms in close vicinity to surface



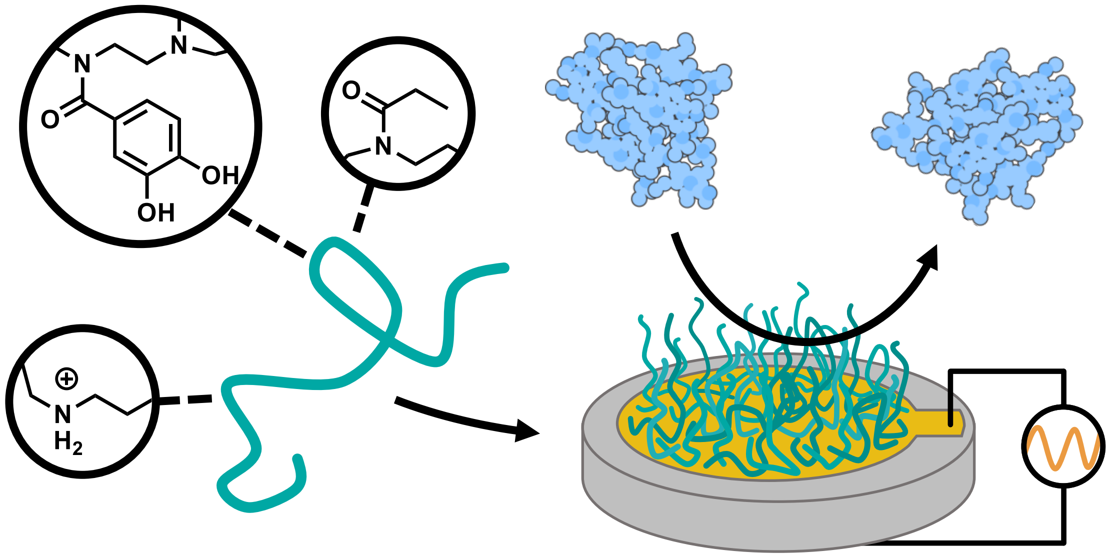
Passives Antifouling

- Hydrated interface
- No sharp boundary but density gradient
- Requires very hydrophilic polymers (PEG, PMeOx, …)
- No anchor points for microorganisms to attach to
- Also reduces binding of biomolecules
- Grafting density is important for efficiency

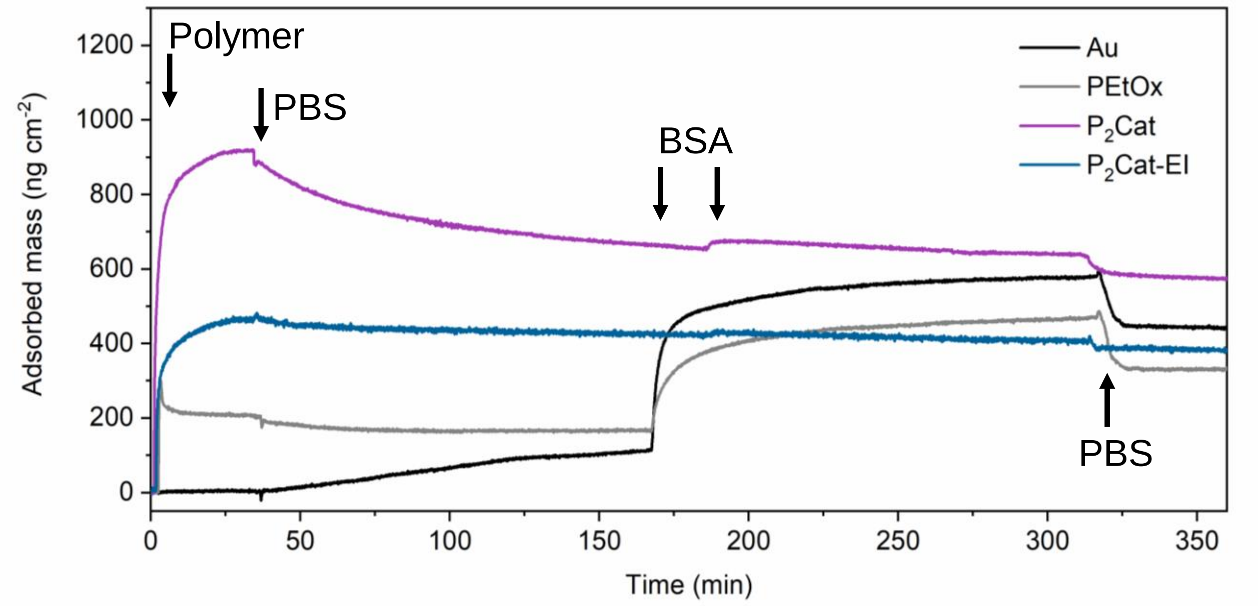




QCM-D



- Quartz-crystal Microbalance with Dissipation measurement
- Piezoelectric measurement of sensor vibration
- Highly sensitive to sensor mass
- Detection of ng/cm² in flow

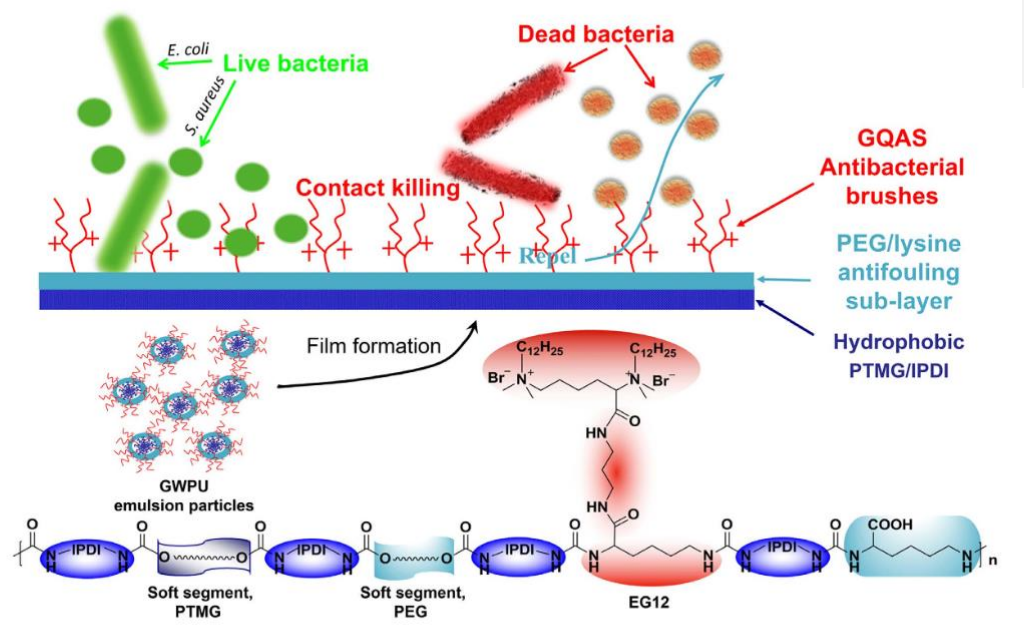


Surface coating	Ads. mass (BSA add.)		Remaining BSA (after PBS wash)	
	ng cm^{-2}	%	ng cm^{-2}	%
Au	555	100	424	76
PEtOx	296	53	154	59
P_2Cat	20	4	-*	-*
P_2Cat-EI	5	1	-*	-*

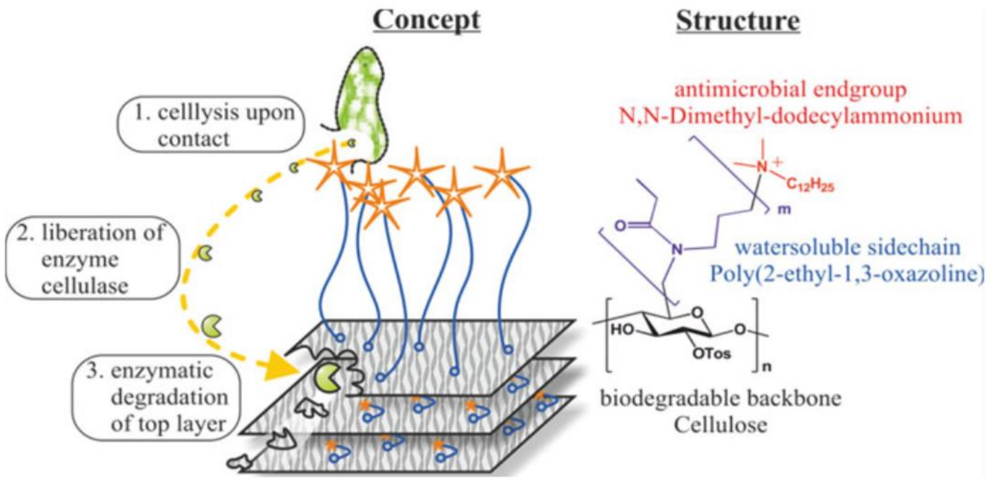
N. Lüdecke, M. Bekir, S. Eickelmann, M. Hartlieb, H. Schlaad. *ACS Appl. Mater. Interfaces* ***2023, 15, 19582-19592.***

Active Antifouling

- Surface-bound antimicrobial polymers
- Often membrane lytic (amphiphilic)
- Selectivity is not so important without leakage of polymer
- Issue: first wave is killed and debris attaches to the surface – perfect ground for biofilm
- Regeneration (detachment of layers or self-cleaning) necessary



He, W., Zhang, Y., Li, J. *et al. Sci Rep* **6,** 32140 (2016)



Bieser AM, Thomann Y, Tiller JC. Macromol Biosci. 2011;11(1):111–21

Take-home message

- **Antimicrobial resistance** is a grave issue endangering the progress of medical science from the last ~ 70 years
- **HDPs** are part of our innate immunity and have a peculiar way to kill bacteria (mostly by **membrane interaction**)
- **Antimicrobial polymer** mimic HDPs but are much more modular
- Different parameters influence their **activity** and **selectivity**, to date there is now AP in clinics
- Polymer disinfectants are used in application but work much less selective (and can be dangerous if used wrong)
- **Biofouling** is a problem in medicine (and far beyond) which requires specifically engineered surfaces to overcome
- **Active** as well as **Passive** strategies exist and have their advantages and disadvantages