Synthesis of antimicrobial polymers with mannose residues as binders for the FimH adhesin of *Escherichia coli*

Atsushi Miyagawa

Department of Life Science and Applied Chemistry, Nagoya Institute of Technology, Aichi, Japan

1. Introduction

1.1. Emergence of drug-resistant bacteria

In USA Antibiotic-resistant infections in 2017[a]
More than **2.8 million** in a year
More than **35,000** people died.

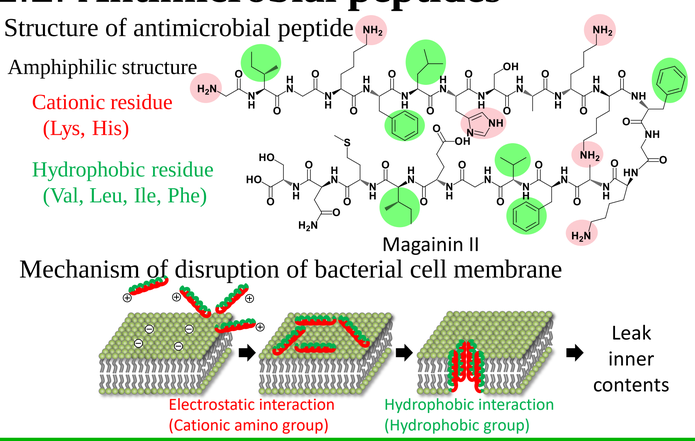
New antibiotic approvals[b]

1983–1987	**16**	2003–2007	**6**
1988–1992	**14**	2008–2012	**2**
1993–1997	**10**	2012–2017	**7**
1998–2002	**7**		

[a] ANTIBIOTIC RESISTANCE THREATS in the United States, 2019
[b] Clinical Infectious Diseases, 2019, 69, 1

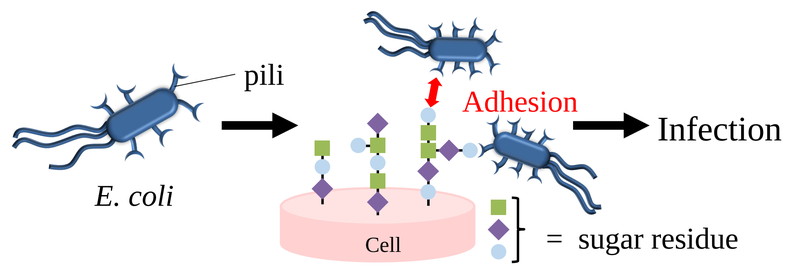
Urgent need to develop new antimicrobial drugs which are acquired resistance difficulty by bacteria.

1.2. Antimicrobial peptides



1.3. FimH adhesin

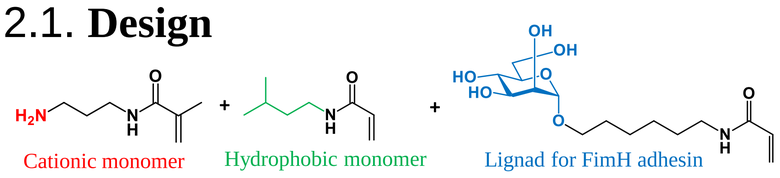
FimH adhesin presents at the tip of bacterial pili.



High binding affinity for FimH adhesin enhance antimicrobial activity and selectivity ?

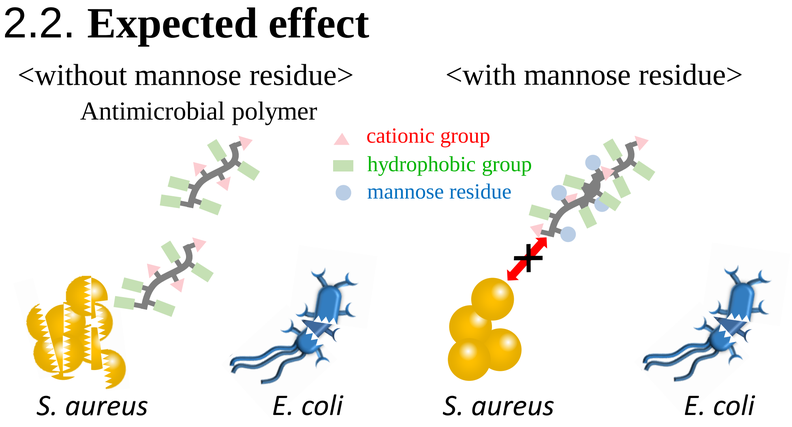
2. Purpose

2.1. Design



Antimicrobial polymers mimic antimicrobial peptides and exhibit antimicrobial activity.

2.2. Expected effect

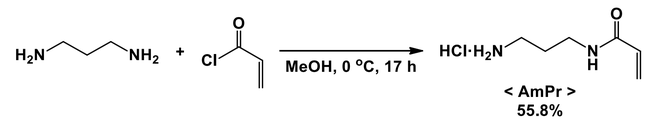


Mannose residue gives selective antimicrobial activity against *E. coli*.

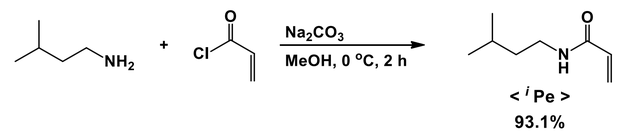
3. Synthesis

3.1. Synthesis of antimicrobial monomers

Synthesis of cationic monomer

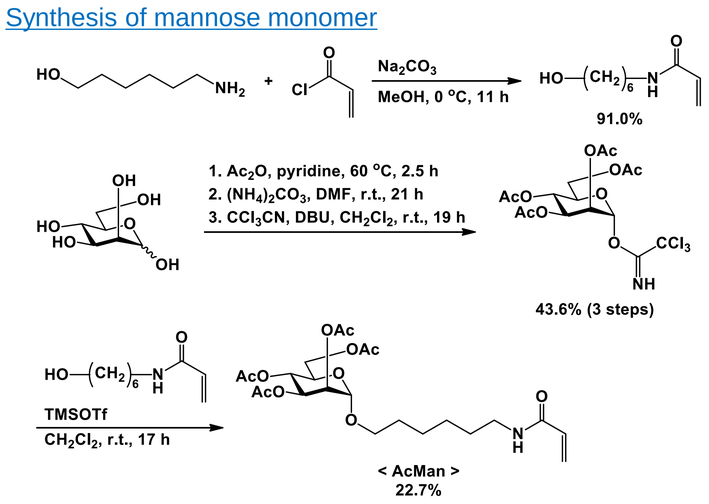


Synthesis of hydrophobic monomer

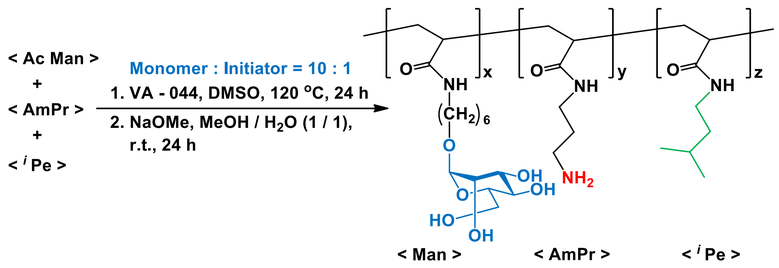


3.2. Synthesis of mannose monomer

Synthesis of mannose monomer



3.3. Polymerization



Polymer	Polymer composition [a]			Yield	Mn [c]	PDI [c]
	Man [b]	AmPr [b]	*i*Pe [b]	(%)	(× 10^3)	
$Man_{1.0}AmPr_{2.5}{}^{i}Pe_{2.0}$	1.0 (1)	2.5 (3)	2.0 (1)	11.4	6.58	1.07
$Man_{1.0}AmPr_{1.0}{}^{i}Pe_{2.2}$	1.0 (1)	1.0 (2)	2.2 (2)	25.1	6.60	1.06
$Man_{3.0}AmPr_{1.0}{}^{i}Pe_{8.3}$	3.0 (1)	1.0 (1)	8.3 (3)	27.9	7.23	1.03

[a] Determined by ^{1}H NMR.
[b] The value in parentheses means initial monomer ratio.
[c] Determined by GPC.

3.4. Evaluation of antimicrobial activity

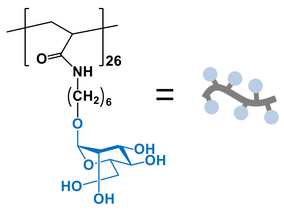
Polymer	MIC (μg / mL)	
	E. coli	*S. aureus*
$Man_{1.0}AmPr_{2.5}{}^{i}Pe_{2.0}$	128	>256
$Man_{1.0}AmPr_{1.0}{}^{i}Pe_{2.2}$	8	256
$Man_{3.0}AmPr_{1.0}{}^{i}Pe_{8.3}$	64	>256
$MAmPr_{1.0}{}^{i}Pe_{1.1}$	8	32
$MAmPr_{1.0}{}^{i}Pe_{2.7}$	32	128

The presence or absence of mannose caused a difference in antimicrobial activity. Introduction of mannose gave high antibacterial activity specifically against *E. coli*.

3.4. Inhibition assay

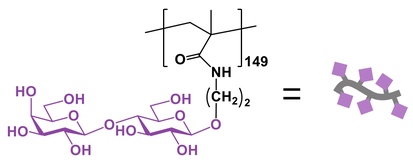
Whether binding to adhesin is functioning effectively by competitive inhibition by inhibitors ?

Mannose polymer uses as inhibiting agent to bind to FimH adhesin instead of mannose residue of antimicrobial polymers



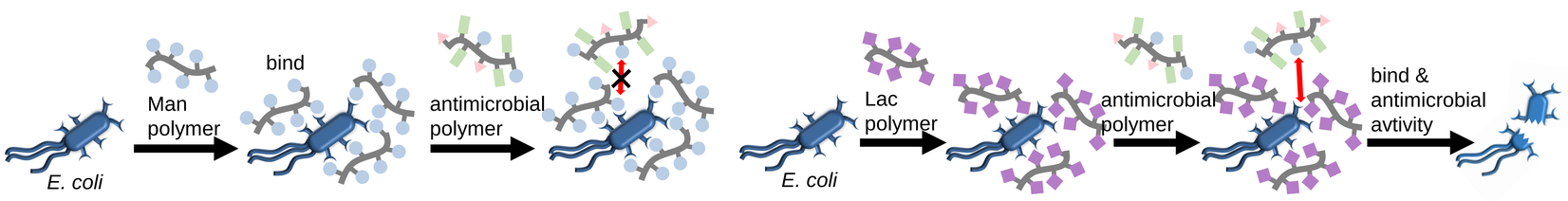
Man polymer (2560 mg / mL),
Mn = 8.77 × 10^3, PDI = 1.40, DP = 26

Lactose polymer uses as negative control not to bind to FimH adhesin



Lac polymer (2560 mg / mL),
Mn = 6.75 × 10^4, PDI = 1.44, DP = 149

Polymer	MIC (μg / mL) against *E. coli*			
	Mannose polymer (2560 μg / mL)		Lactose polymer (2560 μg / mL)	
	(-)	(+)	(-)	(+)
$Man_{1.0}AmPr_{1.0}{}^{i}Pe_{2.2}$	16	32	16	16
$Man_{3.0}AmPr_{1.0}{}^{i}Pe_{8.3}$	128	>256	128	128



- Addition of mannose polymer reduced antimicrobial activity.
- Addition of lactose polymer did not change antimicrobial activity.
- The antimicrobial activity was not reduced by shielding by polymer addition.

This result suggested that mannose residues on the polymer enhanced the antimicrobial activity against *E. coli*.

4. Conclusion

- Antimicrobial polymers containing mannose residues were synthesized using aminopropyl acrylamide, isoalkyl acrylamide, and acetylmannosyl acrylamide.
- Polymers with hexyl mannose residues demonstrated an excellent antimicrobial effect and selectivity against *E. coli*.
- The mannose residues were required to form cluster-like polysaccharides to exploit the bacterial adhesin to mannan and *N*-glycans.

5. References

- Atsushi Miyagawa et al., Journal of Biomaterials Science, Polymer Edition, 33.3 (2022) 299-312.
- Atsushi Miyagawa et al., Journal of Polymer Science, 61(4) (2023) 277-288.