ECMS 2021

1st International Electronic Conference on Molecular Sciences: Druggable Targets of Emerging Infectious Diseases

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Biocidal Cationic Macromolecules Irrespective of Bacterial Resistance: Our Best Achievements

DIPARTIMENTO DI FARMACIA
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DI GENOVA

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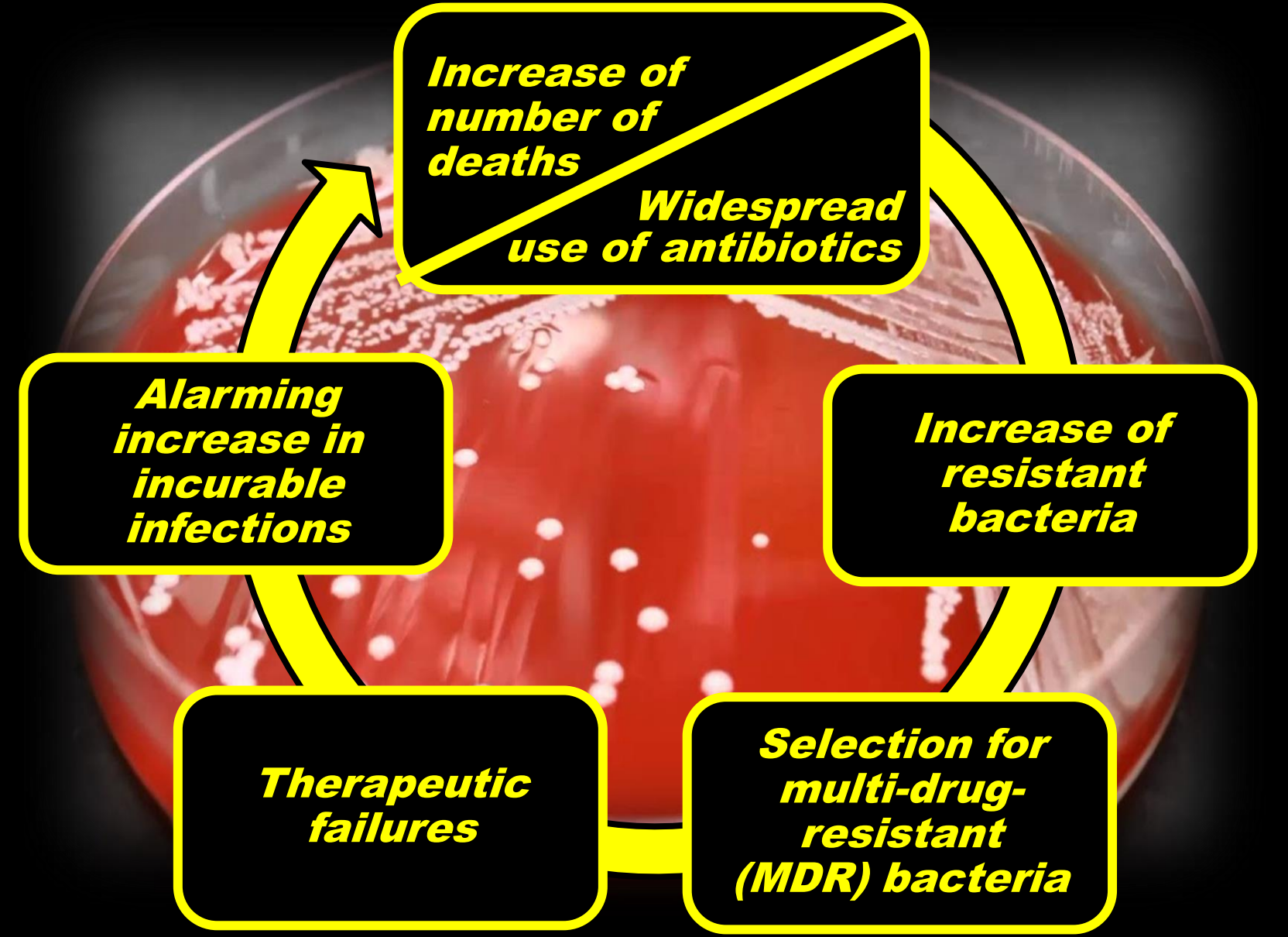
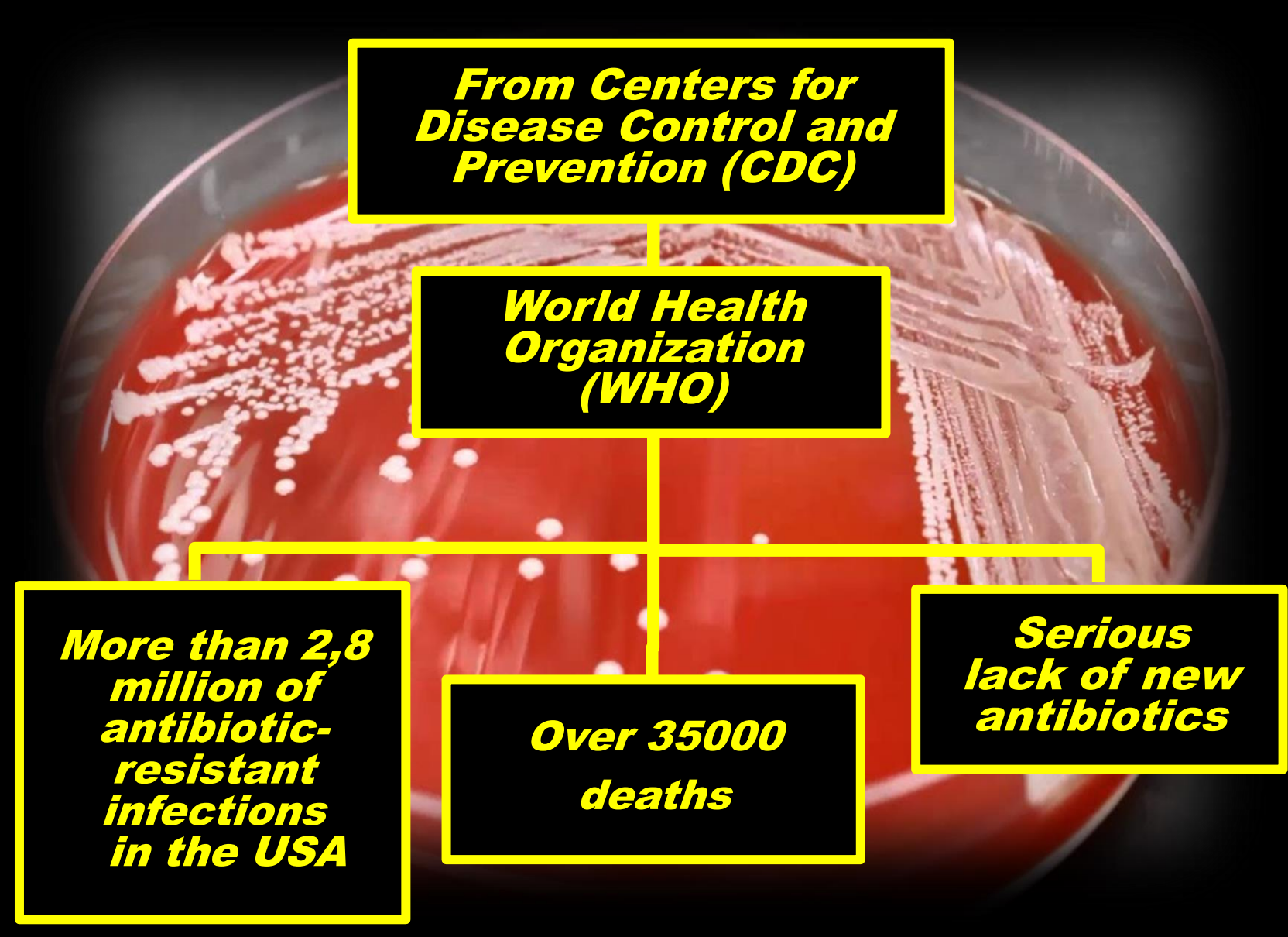

Increase of number of deaths
Widespread use of antibiotics
Increase of resistant bacteria
Selection for multi-drug-resistant (MDR) bacteria
Therapeutic failures
Alarming increase in incurable infections


From Centers for Disease Control and Prevention (CDC)
World Health Organization (WHO)
More than 2,8 million of antibiotic-resistant infections in the USA
Over 35000 deaths
Serious lack of new antibiotics

The Development of New Antimicrobial Agents it's Urgent

Common Strategies to Develop New Antibacterial Agents

Take Natural cationic antimicrobial peptides (AMPs) as model molecules

Synthesis of different types of cationic monomers

Preparation of more stable and low-cost cationic polymers and co-polymers mimic of AMPs

2000-2021

CATIONIC POLYMERS

Further Developments

Development of different types of cationic antimicrobial polymers

2000-2021

From cationic polymers to cationic dendrimers (CDs)

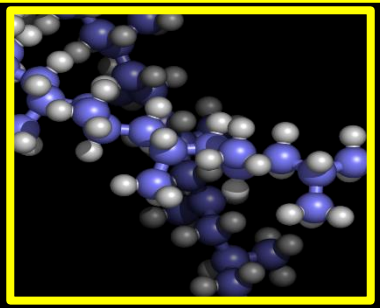
2010-2021

Development of several types of cationic antimicrobial dendrimers

CATIONIC DENDRIMERS

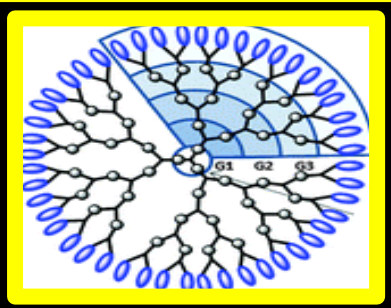
Advantages Provided by Macromolecular Structures

Cationic (Co-)Polymers



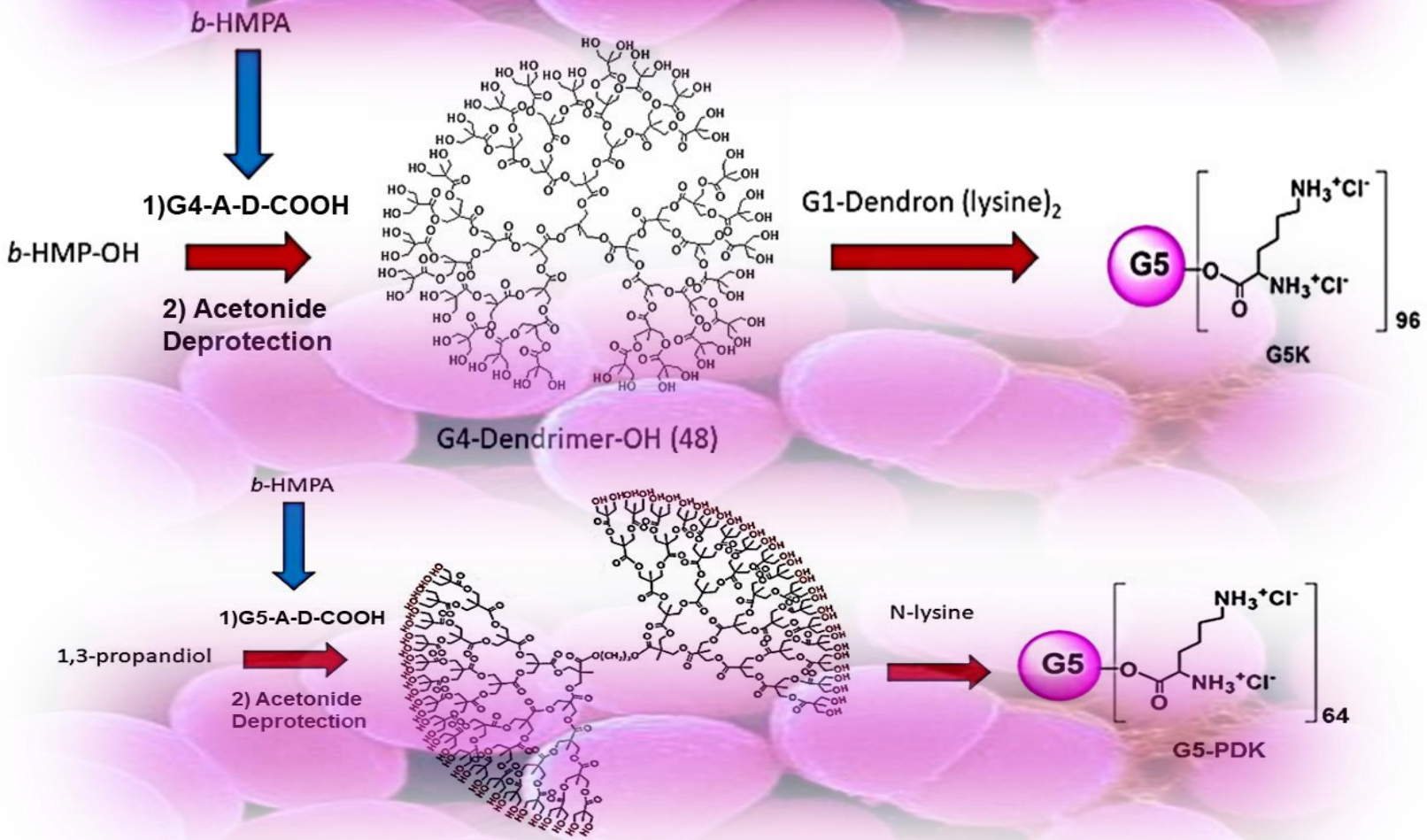
- More long-term activity
- Limited residual toxicity
- Chemical stability
- Non-volatility
- No permeation through the skin thanks to macromolecular structure and high MW

Cationic Dendrimers

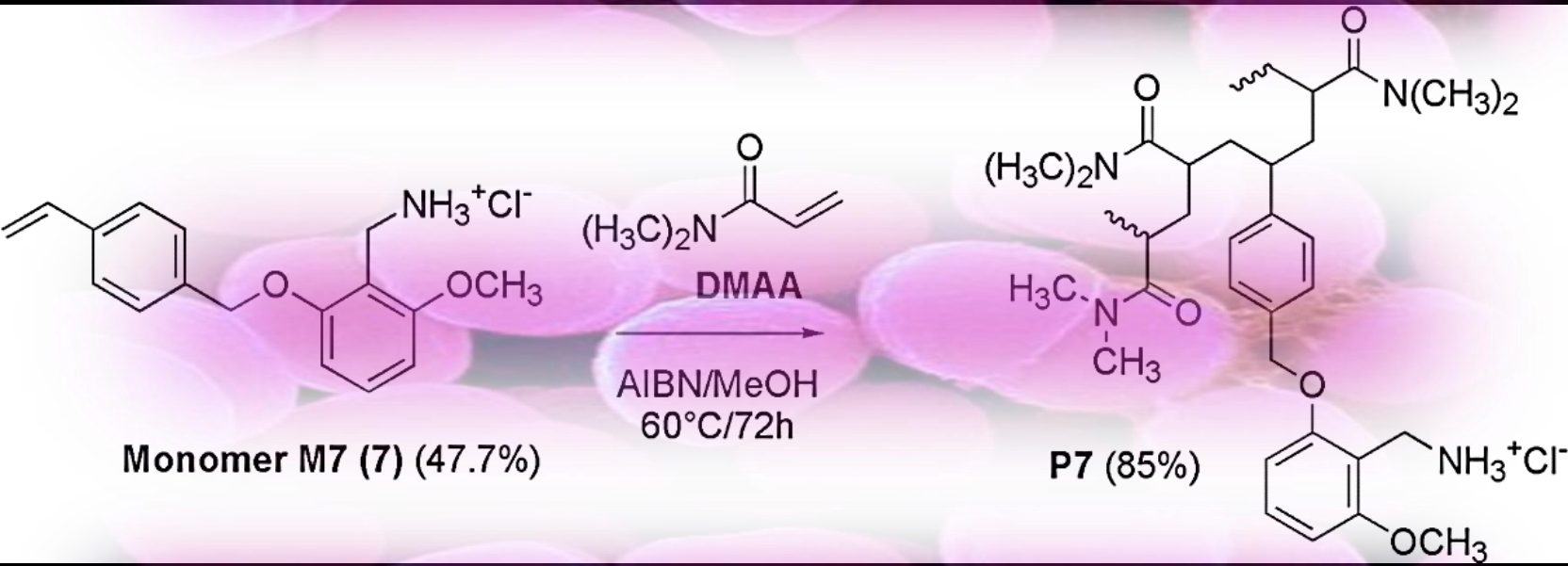


- Tree-like generational structure
- Symmetric spherical architecture
- Monodisperse macromolecules
- Nano dimensions
- Inner cavities to host drugs
- High number of peripheral functional groups

Our Best Fifth Generation Cationic Dendrimers: The Synthesis

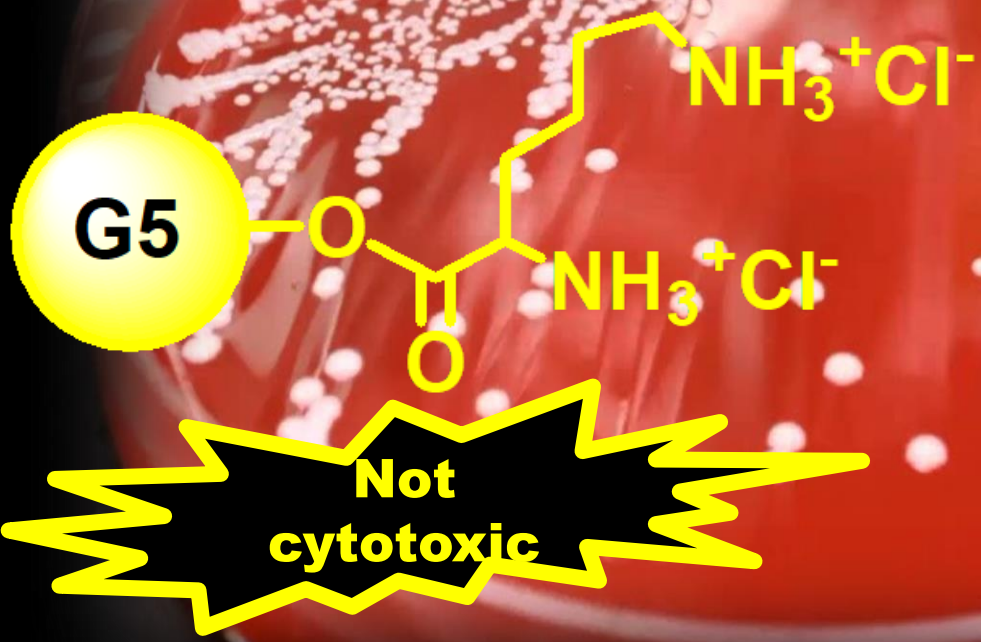


Synthesis of Our Best Cationic Copolymer



Activity of Our Fifth Generation Cationic Dendrimers

Active Against Non-Fermenting Gram-Negative Species



G5K

- *A. Baumannii*
- *P. aeruginosa*
- *S. maltophylia*

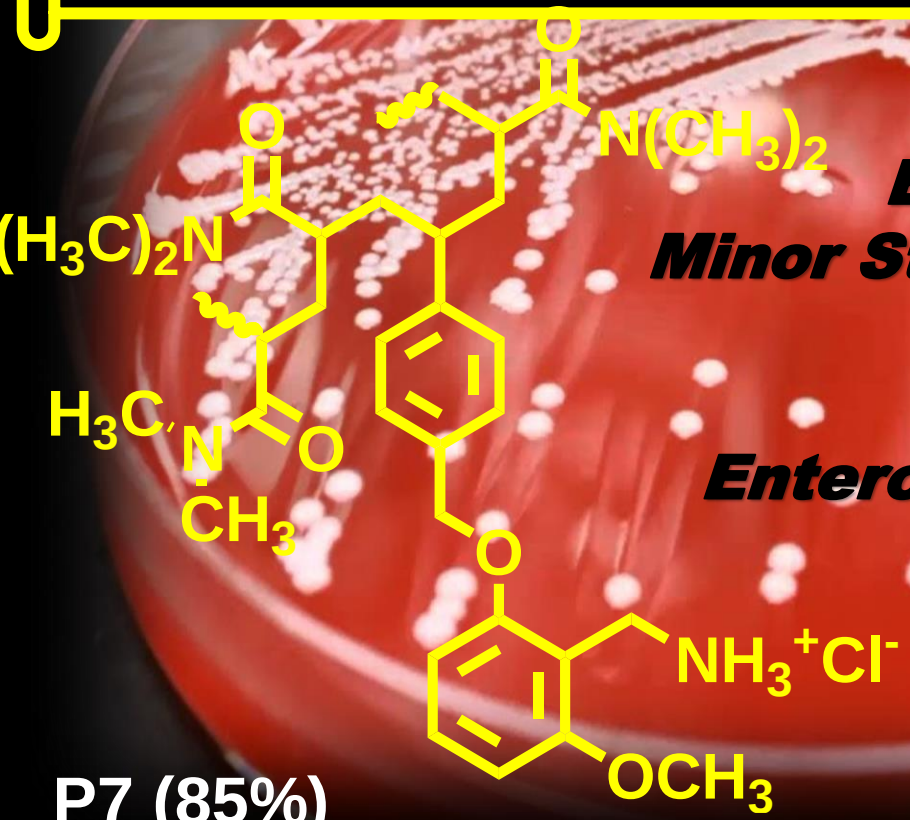
G5PDK

- *A. Baumannii*
- *A. junii*
- *A. johnsonii*
- *A. Ursingii*
- *A. pittii*

K=Lysine

Activity of Copolymer P7

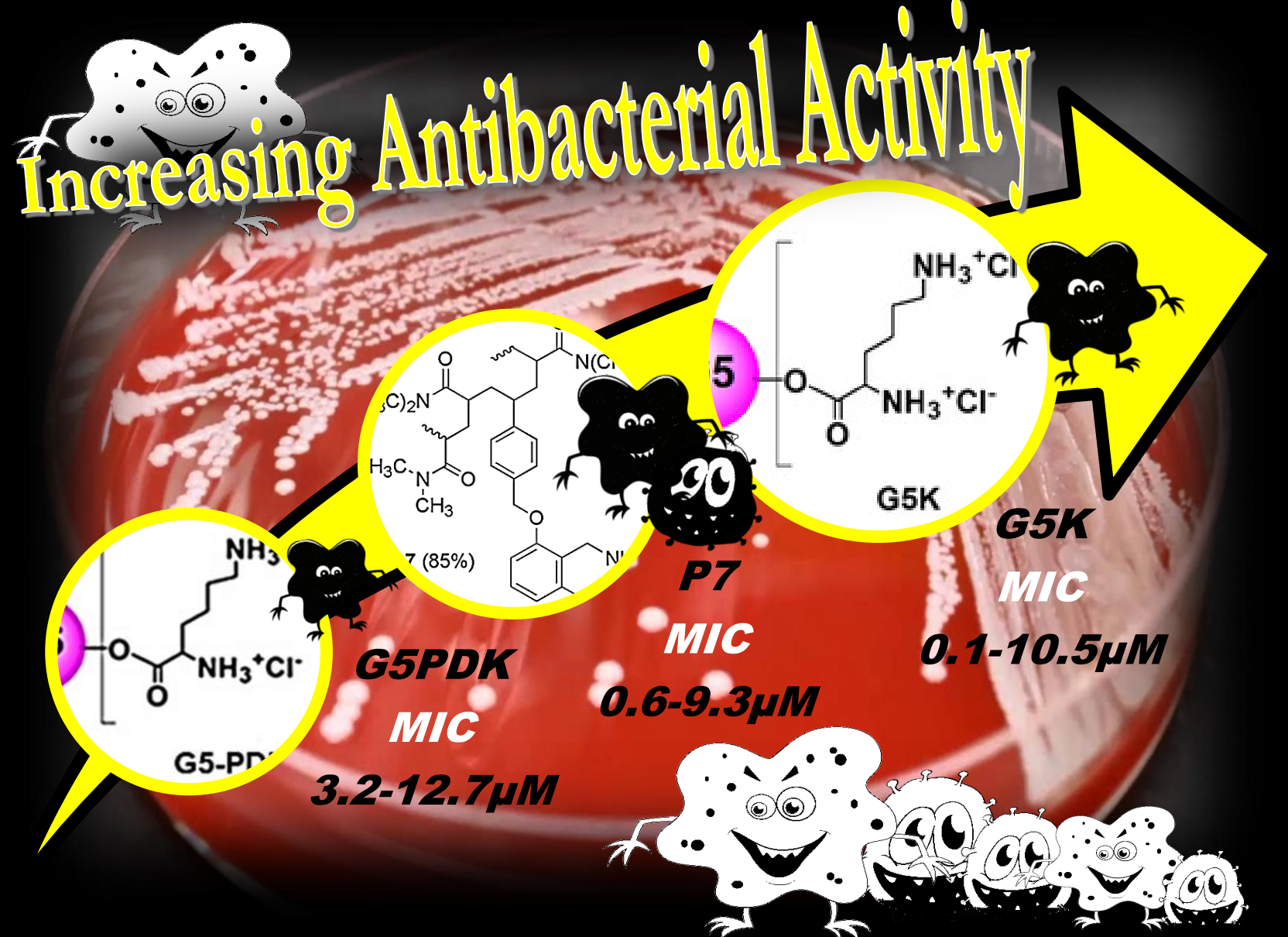
Active Against Several Gram-positive and Gram-negative Species



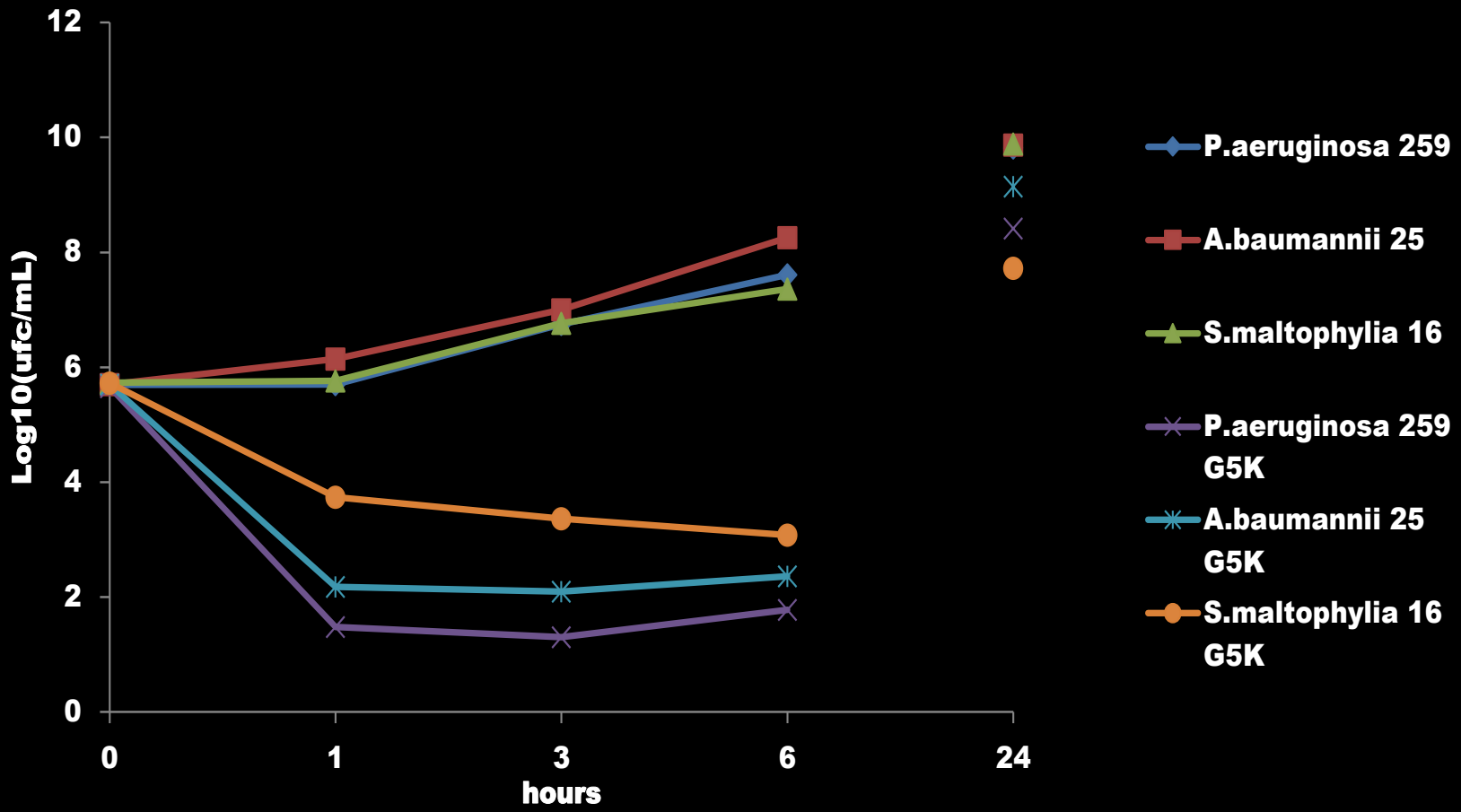
P7 (85%)

- Enterococci SI=1.2-4.7
- Minor Stahylococci SI=2.5-4.7
- S. Epidermidis SI=2.5
- B. Subtilis SI=2.5
- Enterobacteriaceae * * SI<1
- P. aeruginosa * SI<1
- A. baumannii SI<1
- S. maltophylia * SI<1

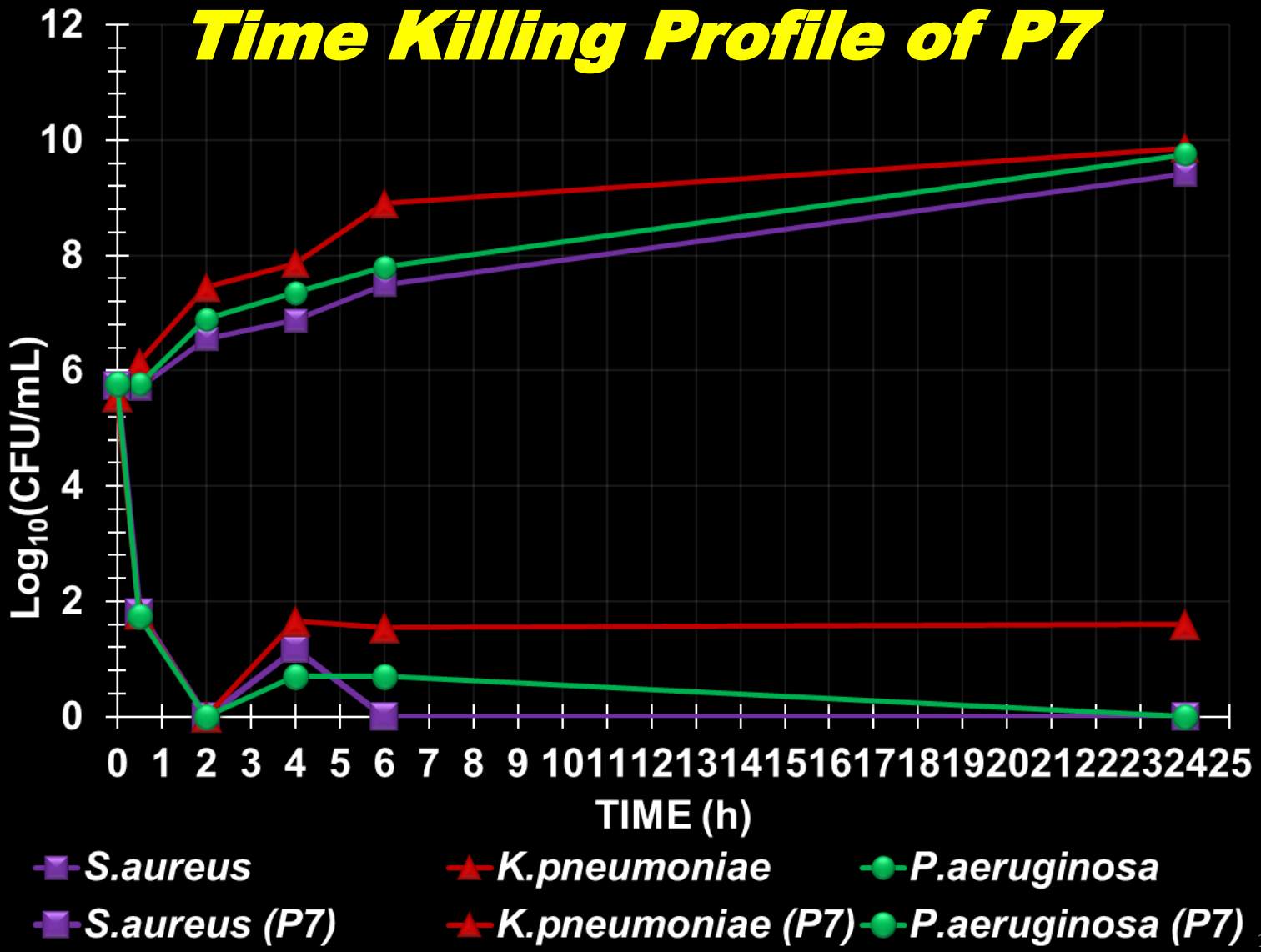
SI = Selectivity Index; * Also cases SI = 1.2; **2 E. coli out of 3 SI = 1.2


Increasing Antibacterial Activity
G5K
MIC
0.1-10.5μM
P7
MIC
0.6-9.3μM
G5PDK
MIC
3.2-12.7μM

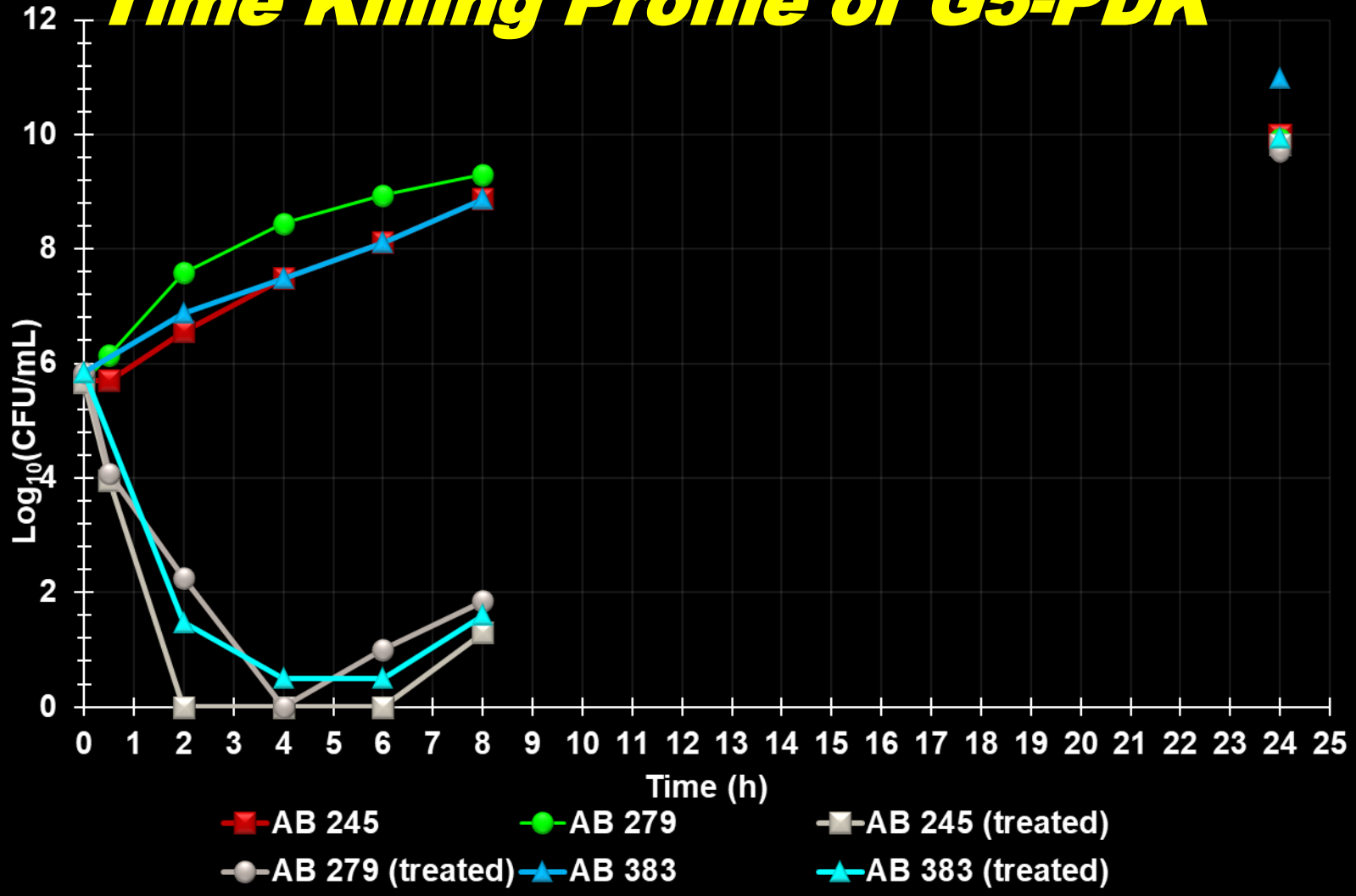
Time Killing Profile of G5K



Time Killing Profile of P7



Time Killing Profile of G5-PDK



Conclusions

K is essential for obtaining potent antimicrobial dendrimers active on Non-fermenting Gram-negative species

G5K with 96 K displayed remarkable antibacterial activity against all major Non-fermenting species

G5-PDK with 64 K displayed remarkable antibacterial activity specifically against the genus *Acinetobacter*

Random copolymer P7 displayed high broad-spectrum antibacterial effects and rapid bactericidal activity

G5K and G5-PDK could represent promising alternatives to no longer effective antibiotics specifically against non-fermenting Gram-negative bacteria

P7 could represent a promising bactericidal agent active on several clinical isolates of both Gram-positive and Gram-negative family

If you are interested in studies currently in progress… look at the poster presented here!

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