

**Novel advances in MDR treatment.
“TO WIN, STOP FIGHTING”**



By:

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Introduction


NOIGEL LLC is a New York based company that was established in 2010.

Our mission is to find new innovative ways to treat MDR infections.

Amongst the company's expertise is utilizing synergistic combinations of FDA approved generic drugs and developing pharmaceutical compositions with new and unique applications.

NOIGEL scientists have published extensive research studies supporting development of their pharmaceutical compositions.

CDC Statistics: Dangers of MDR



MULTIDRUG-RESISTANT PSEUDOMONAS AERUGINOSA

THREAT LEVEL SERIOUS ○○○○○○

This bacteria is a serious concern and requires prompt and sustained action to ensure the problem does not grow.

6,700 MULTIDRUG-RESISTANT PSEUDOMONAS INFECTIONS

440 DEATHS

51,000 PSEUDOMONAS INFECTIONS PER YEAR



DRUG-RESISTANT NEISSERIA GONORRHOEAE

THREAT LEVEL URGENT ○○○○○○

This bacteria is an immediate public health threat that requires urgent and aggressive action.

246,000 DRUG-RESISTANT GONORRHEA INFECTIONS

188,600 RESISTANCE TO TETRACYCLINE

11,480 REDUCED SUSCEPTIBILITY TO CEFIXIME

3,280 REDUCED SUSCEPTIBILITY TO CEFTRIAXONE

2,460 REDUCED SUSCEPTIBILITY TO AZITHROMYCIN

820,000 GONORRHOEAL INFECTIONS PER YEAR



MULTIDRUG-RESISTANT ACINETOBACTER

THREAT LEVEL SERIOUS ○○○○○○


This bacteria is a serious concern and requires prompt and sustained action to ensure the problem does not grow.

7,300 MULTIDRUG-RESISTANT ACINETOBACTER INFECTIONS

500 DEATHS FROM MULTIDRUG-RESISTANT INFECTIONS

12,000 ACINETOBACTER INFECTIONS PER YEAR

AT LEAST THREE DIFFERENT CLASSES OF ANTIBIOTICS **NO LONGER CURE** RESISTANT ACINETOBACTER INFECTIONS



EXTENDED SPECTRUM β-LACTAMASE (ESBL) PRODUCING ENTEROBACTERIACEAE

THREAT LEVEL SERIOUS ○○○○○○

This bacteria is a serious concern and requires prompt and sustained action to ensure the problem does not grow.

26,000 DRUG-RESISTANT INFECTIONS

1,700 DEATHS

140,000 ENTEROBACTERIACEAE INFECTIONS PER YEAR

\$40,000 IN EXCESS MEDICAL COSTS PER YEAR FOR EACH INFECTION



VANCOMYCIN-RESISTANT ENTEROCOCCUS (VRE)

THREAT LEVEL SERIOUS ○○○○○○

This bacteria is a serious concern and requires prompt and sustained action to ensure the problem does not grow.

20,000 DRUG-RESISTANT ENTEROCOCCUS INFECTIONS

1,300 DEATHS FROM DRUG-RESISTANT ENTEROCOCCUS INFECTIONS

66,000 ENTEROCOCCUS INFECTIONS PER YEAR

SOME ENTEROCOCCUS STRAINS ARE RESISTANT TO VANCOMYCIN **LEAVING FEW OR NO TREATMENT OPTIONS**



9,000 DRUG-RESISTANT INFECTIONS PER YEAR

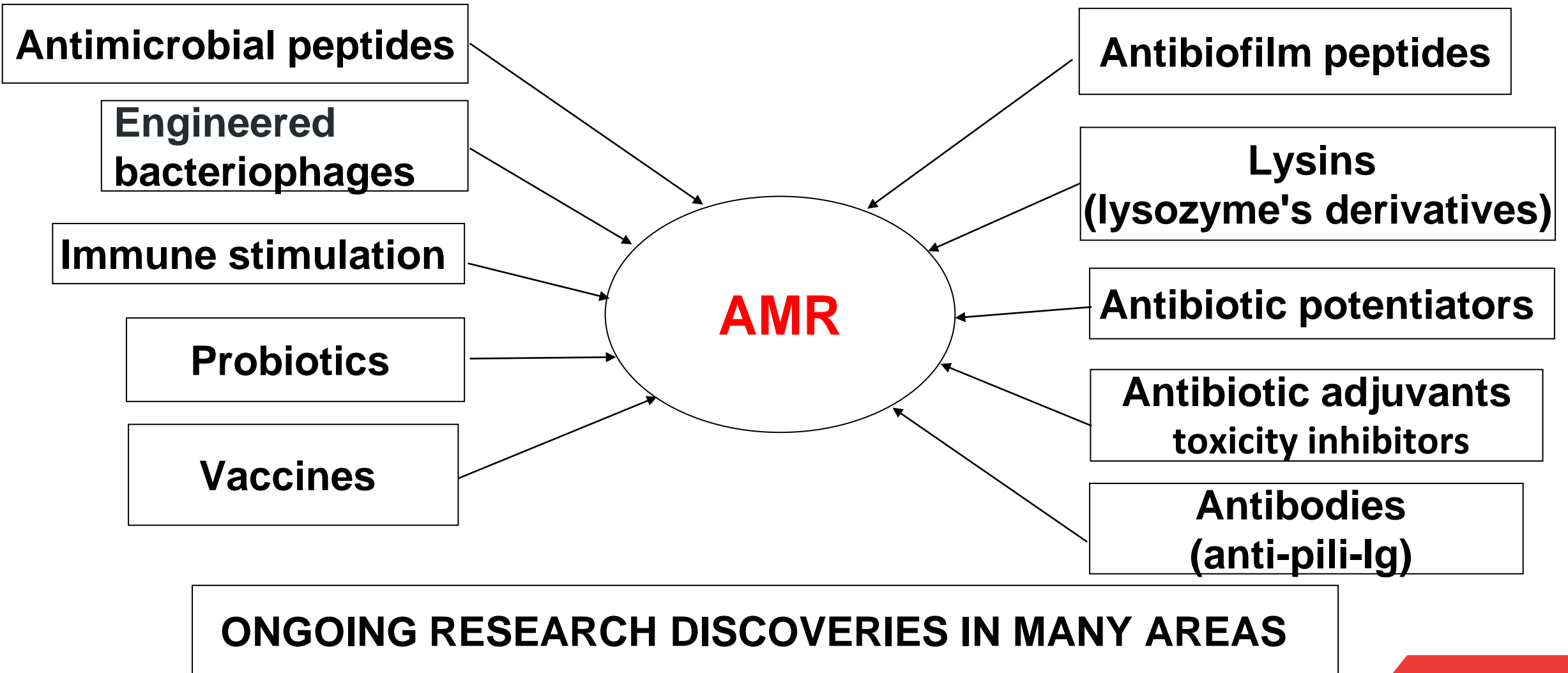
600 DEATHS

7,900 CARBAPENEM-RESISTANT KLEBSIELLA SPP.

1,400 CARBAPENEM-RESISTANT E. COLI

CRE HAVE BECOME RESISTANT TO ALL OR NEARLY ALL AVAILABLE ANTIBIOTICS

Current strategies within scientific community



Market Opportunity

12

12 New antibiotics FDA approved in last 5 years *

4-9%

Annual Increase in global anti-MDR bacteria antibiotic market*

\$35.6 bill. USD

Amount anti-bacterial market will reach by 2022**

US/EU regulatory authorities made Millions in funding available (e.g. CARB-X)

* <https://www.fda.gov/NewsEvents/Newsroom/FDAInBrief/ucm595264.htm>

** <https://www.researchandmarkets.com/research/5x7jmj/global>

NOIGEL pioneers use of TRIZ

- TRIZ was developed by Genrich Altshuller and his colleagues in the former Soviet Union in 1946.
- **TRIZ** (theory of inventive problem solving, modern design and technologies in different fields).
- Some core principles of TRIZ:
 - Problems and solutions are repeated across industries and sciences.
 - Patterns of technical evolution tend to be repeated across industries and sciences.
 - Creative innovations often use scientific effects outside the field where they were developed.

1. <https://www.forbes.com/sites/haydnshaughnessy/2013/03/07/why-is-samsung-such-an-innovative-company/2/#7c5759a87f96>

NOIGEL pioneers use of TRIZ

TRIZ principles have been used in many industries including companies like Samsung¹, General Motors, NASA.

NOIGEL LLC is pioneering the use of TRIZ in the pharmaceutical industry.

1. <https://www.forbes.com/sites/haydnshaughnessy/2013/03/07/why-is-samsung-such-an-innovative-company/2/#7c5759a87f96>

Much research is focused on fighting bacteria as they develop (chasing it).



Through TRIZ, NOIGEL has developed a novel strategy to fight MDR

NOIGEL Breakthrough

- NOIGEL Hypothesis:

If during treatment of infectious diseases we could eliminate the death of microorganisms, we could eliminate development of bacterial resistant strains.

If we could stop bacterial toxin and virulence factors production, we could:

- Make these bacteria less harmful.
- Make the bacteria sensitive to current and future antibiotics.
- Eliminate and decrease the resistant strains selection process.

NOIGEL Proof of Concept

- NOIGEL has developed a novel patent pending pharmaceutical composition of FDA approved generic drugs which will eliminate the death of microorganisms.

NOIGEL refers to this composition as Bacterial Growth Enhancer (BGE30).

- **Instead of killing bacteria**, this composition initiates bacterial growth, resulting in reduced bacterial defense and virulent aggression.
- This will prevent the selection of new dangerous multi-resistant bacterial strains.
- As result of **synergistic combination** of each active components of **BGE30 composition** will significantly diminish the concentration between 0,001% and 0,0001%.

NOIGEL Bacterial Growth Enhancer (BGE30)

Finding the right target:

- NOIGEL identified most suitable candidates as **Bacterial growth enhancer (BGE30)**.
- 550 substances were selected from 38,000 FDA generic drugs.
- NOIGEL selected three substances best suitable as a bacterial growth enhancer (BGE30).

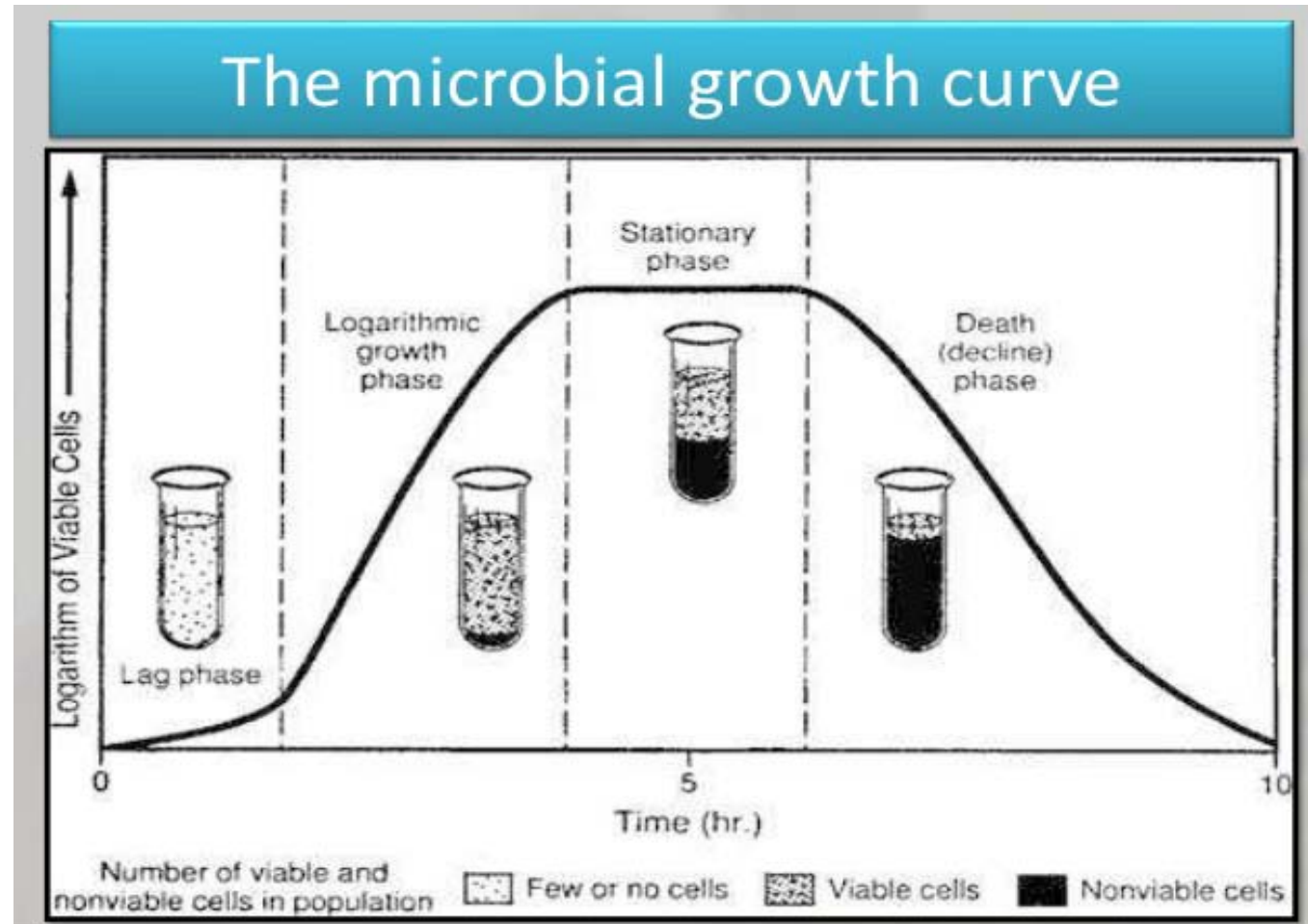
Properties of BGE30:

- BGE is comprised of FDA approved drugs from the **(isoquinoline, imidazole and pyrimidine derivatives)**.
- Decreased bacterial virulence factors and toxins production since BGE create comfort for bacterial growth.
- BGE has minimal spectrum of side effects to host body and doesn't affect Antibiotics activity.

The Key to NOIGEL's breakthrough

Logarithmic growth- bacteria in the absence of competition with each other "**dump**" the majority of **virulence factors** and toxin formation (including factors of acquired antibiotic resistance)

Log phase –
The most perspective phase as a target by antimicrobials.

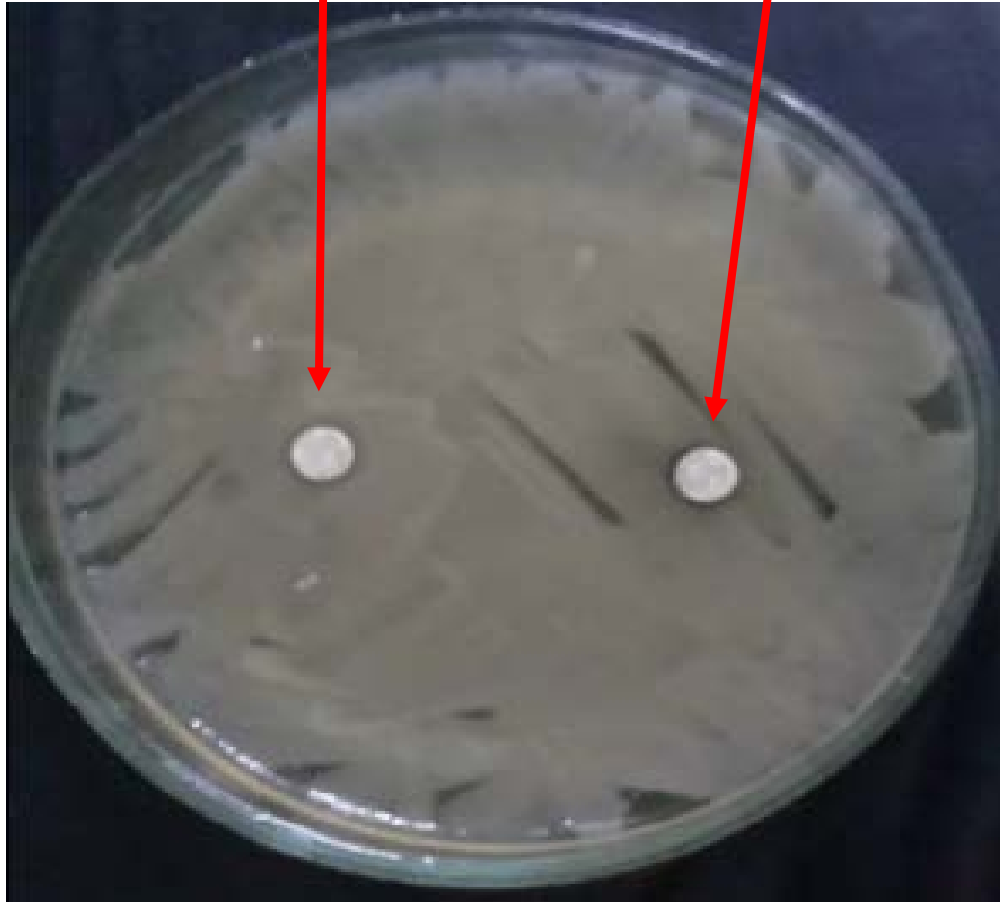


López, S., Prieto, M., Dijkstra, J., Dhanoa, M. S., & France, J. (2004). Statistical evaluation of mathematical models for microbial growth. *International Journal of Food Microbiology*, 96(3), 289-300

Effects in vitro Bacterial growth enhancers (BGE30) on Acinetobacter Baumannii

Polymyxin

Amicacin



d>25 Polymyxin

d<5 mm Amicacin



MDR A. baumannii growth **without** (BGE30): 6 day growth, 2nd passage

MDR A.baumannii growth **with** (BGE30) agents: 6 day growth, 2nd passage

Effect in vitro with (BGE) on Acinetobacter Baumannii

d>25 Polymyxin

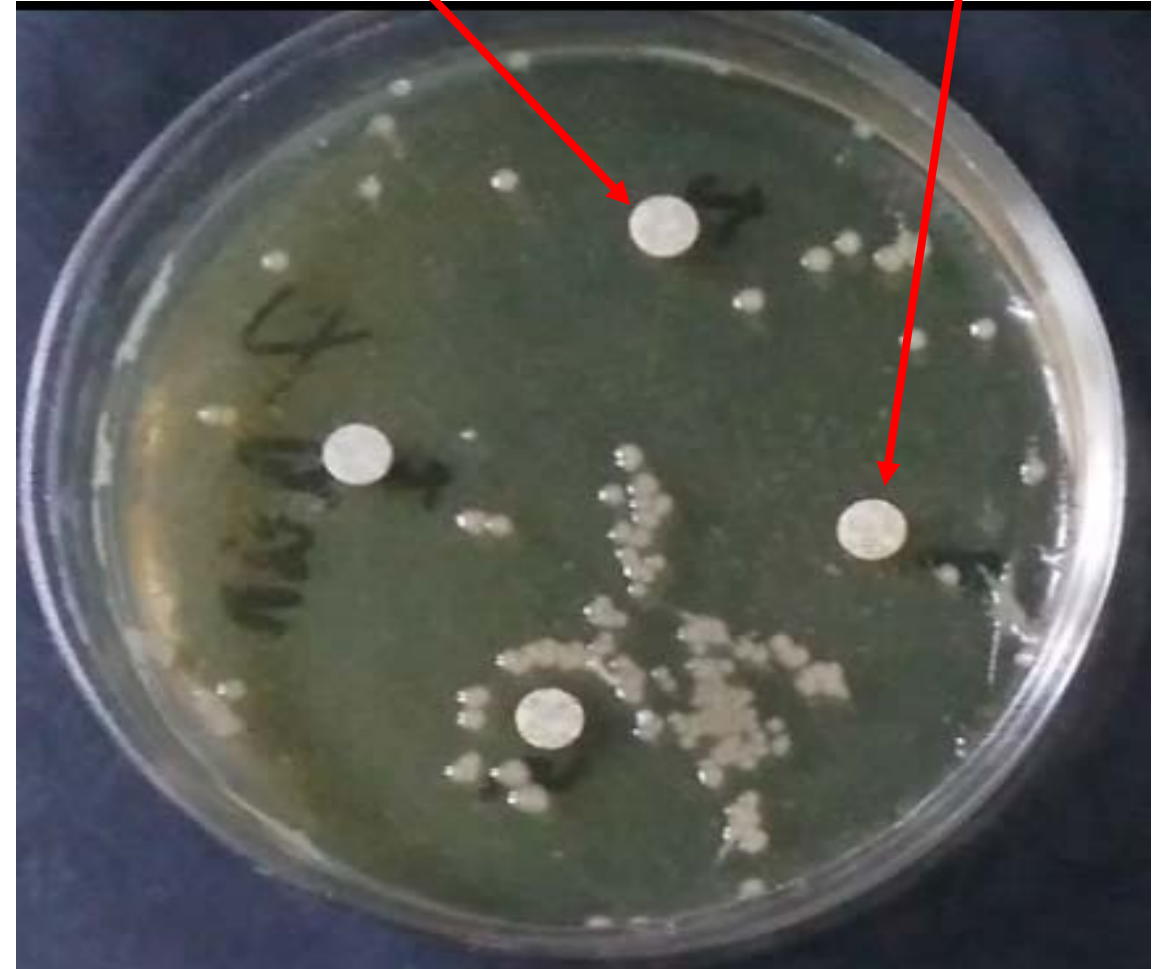
d>25 Amicacin



MDR A.baumannii growth **with (BGE30)**: 9 day growth, 3rd passage.

d>25 Polymyxin

d>25 Amicacin

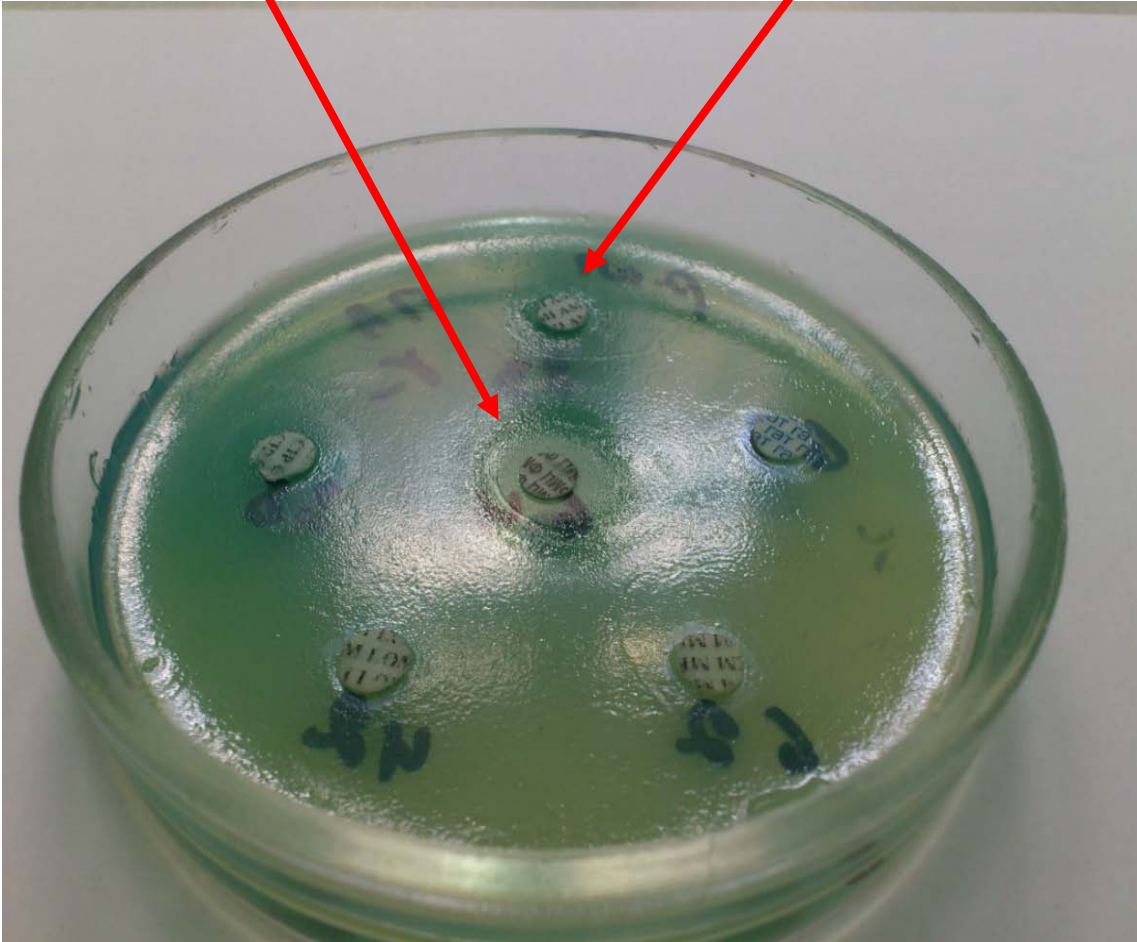


MDR A.baumannii growth **with (BGE30)**: 12 day growth, 4th passage.

Bacterial growth enhancers (BGE30) MDR Pseudomonas Aeruginosa

D < 5 mm Polymyxin

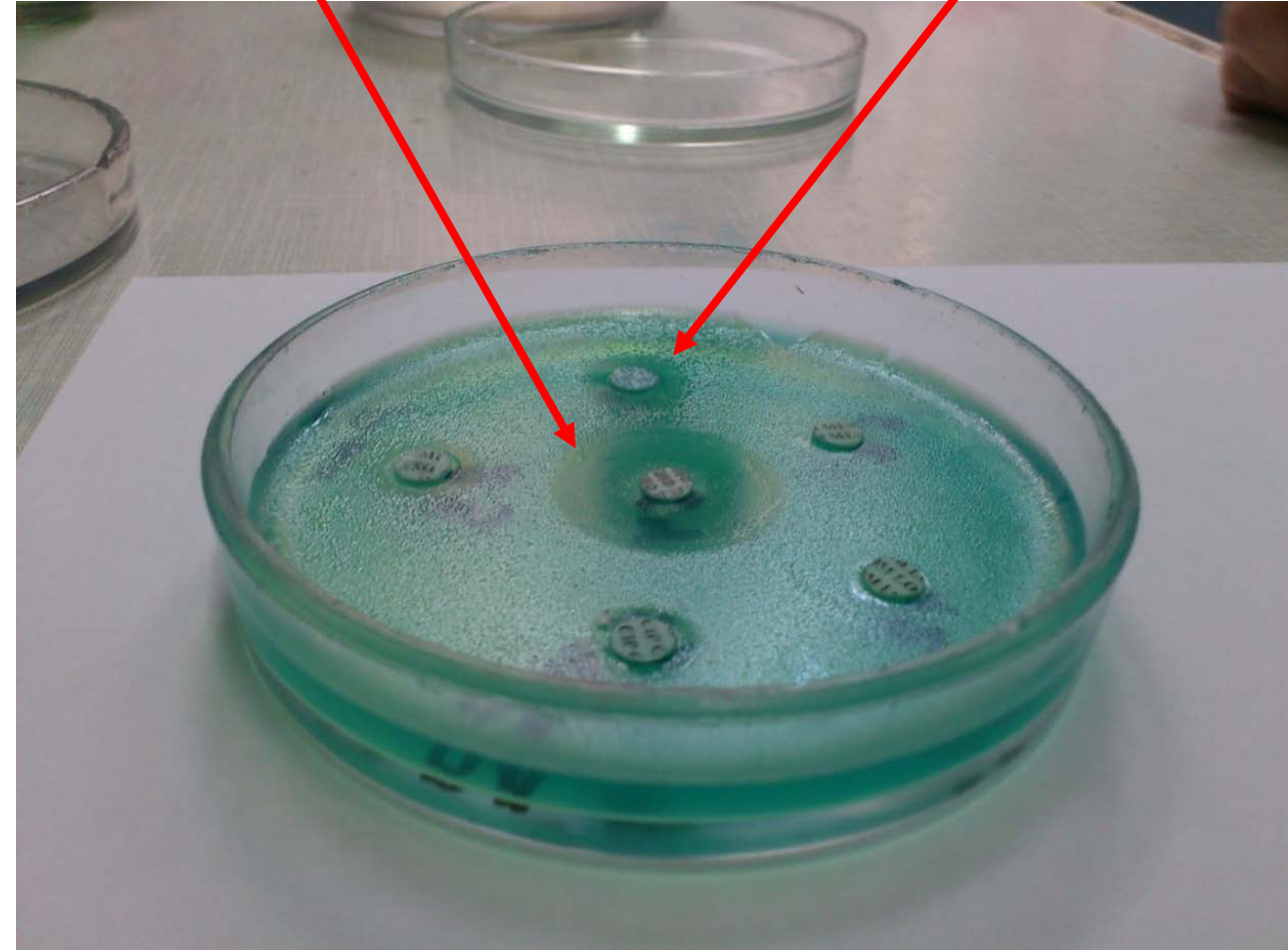
D < 5mm Amicacin



P. Aeruginosa IMI2 (MDR strain) **without** Bacterial growth enhancers (BGE30) 3 day growth, 1st passage

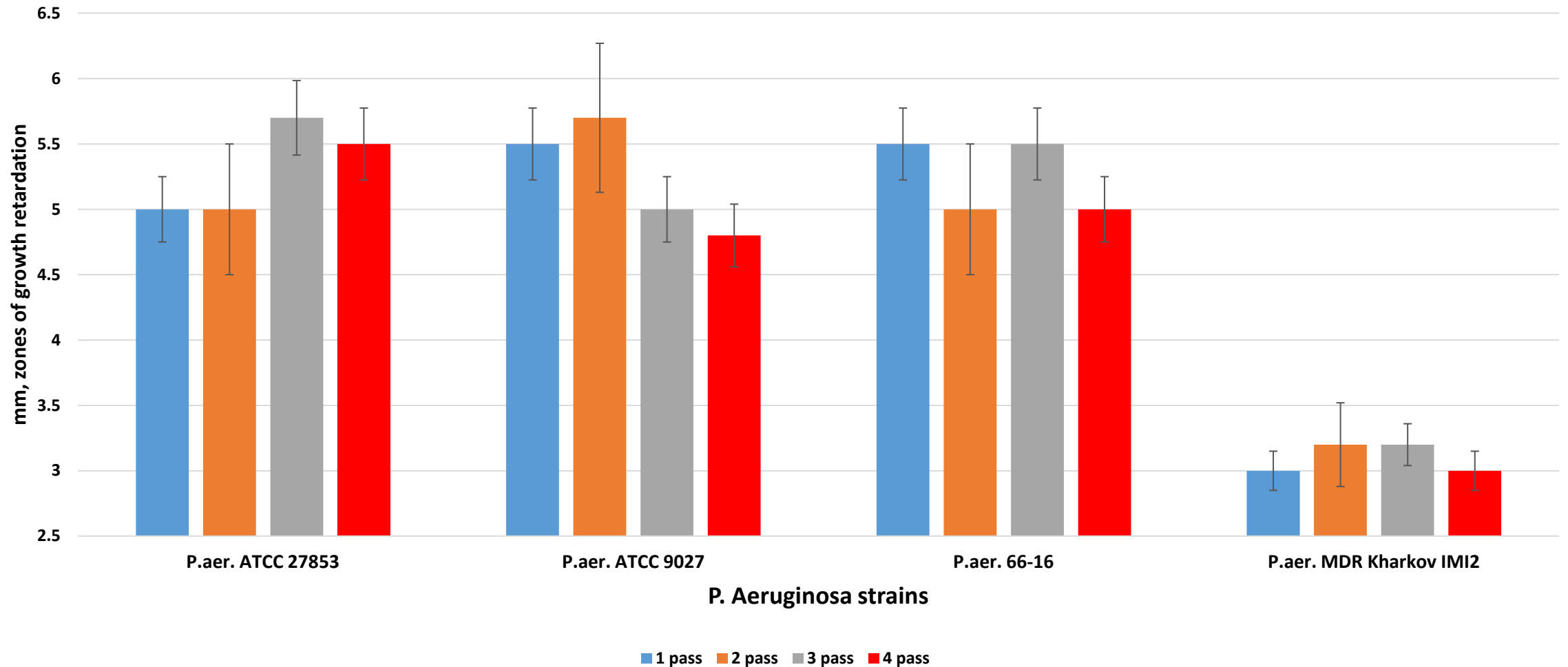
d > 25 mm Polymyxin

d > 10 mm Amicacin



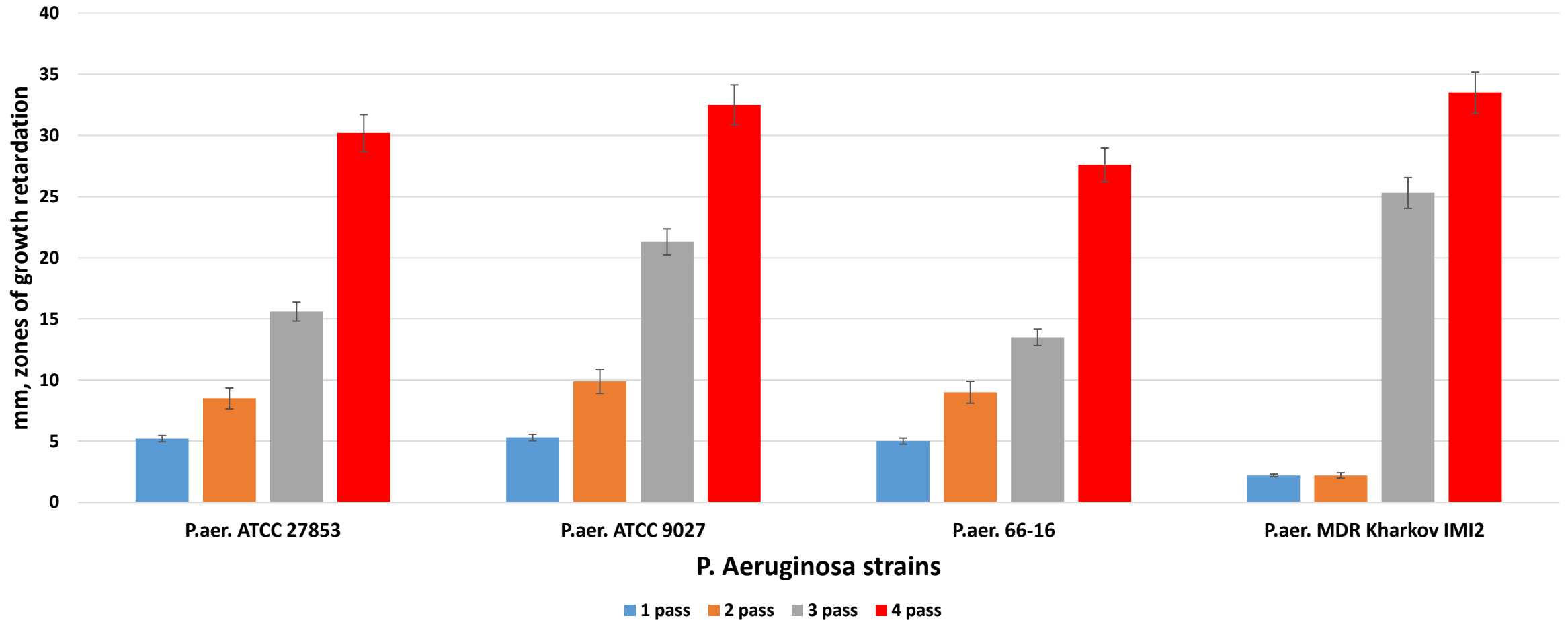
P. Aeruginosa in vitro **with** Bacterial growth enhancers (BGE30) 3 day growth, 1st passage

P. aeruginosa zones of growth retardation (mm) Polymyxin (colistin) in the classic media without (BGE30).



Notes: n=6 for each studies, $P < 0,05$. Stat.hypothesis (dispersion analysis) it is differences between P. aeruginosa sensitivity to polymyxin at classic medium **without BGE30**

P. aeruginosa zones of growth retardation (mm) Polymyxin (colistin) in the classic media with (BGE30).



Notes: n=6 for each studies, $P < 0,05$. Stat. hypothesis (dispersion analysis) it is presence differences between P. aeruginosa sensitivity to polymyxin at medium **with BGE30** along some passages.

Snapshot of NOIGEL activity

- **Successful results in vivo studies:**
 - Microorganisms of target: Pseudomonas aeruginosa, Proteus vulgaris, Acinetobacter baumannii, Klebsiella pneumonia.
 - Antimicrobials: polymyxin, amikacin, fluoroquinolone groups synergistic with Bacterial growth enhancers (BGE30).
- **Planned research projects:**
 - Microorganisms of target: Staphylococcus, Candida albicans, Enterococcus, Enterobacteriaceae, Escherichia coli, Mycobacterium tuberculosis.
 - Antimicrobials: Peniciline, Cephalosporins, Macrolide, Aminoglycoside Tetracycline groups.

Options for further development of NOIGEL research project

1. Pharmaceutical companies currently holding generic antibiotics in their portfolio, could use NOIGEL's approach **to recover bacterial sensitivity to them** and boost sales exponentially.
2. Pharmaceutical companies currently holding generic drugs of **bacterial growth enhancers (BGE30)** will boost their sales due to new application use.
3. Life Sciences private equity groups and venture capital firms could partner with NOIGEL to help create a new company that can manufacture and sell novel method of **bacterial growth enhancers (BGE30)**. Additionally different collaborations may apply.

Publications and IP

IP:

**1. New combinatorial derivatives of antibiotics based on supramolecular structures
PCT/RU2017/000424**

2. Method of accelerating the growth of bacterial biomass and suppression of bacterial virulence PCT/RU2011/001060 ; WO 2013/100792; EA Patent 025623

Publications:

1. Influence Of Non-Metabolic Microbial Growth Promotors (AMP Activators) On The Sensitivity To Antimicrobials In The Actually Multiresistant Microbial Strains Artur Martynov, Tatyana Osolodchenko, Boris Farber, Sophya Farber bioRxiv 143438; doi: <https://doi.org/10.1101/143438>

2. Martynov, AV, Chuprinova, SI, Osolodchenko, T. P., Batrak, O. A., Zavada, N. P., Ryabova, I. S., & Sticker, L. G. (2008). Effect of the combined action of chemical origin stimulants on the growth rate of the microbial mass of *Pseudomonas aeruginosa*. IMI, (3), 20-24.

3. The novel strategy to fight multidrug resistance by multiple drugs synergism, based on docking in drug design and TRIZ/ SMI's Superbugs & Superdrugs, New Jersey, USA. 14-16 NOV 2016/ Farber B., Kleyn I., Martynov A.

4. The novel strategy to fight multidrug resistance by multiple drugs synergism, based on docking in drug design AND TRIZ. Change of paradigm/ Synopsis investors conference, New-York, 15 DEC, 2016/ Ph.D., Sc.D. Boris Farber, Dr. Ilya Kleyn, Dr. Artur Martynov, Tatyana Osolodchenko, Ph.D., Dr. Tatyana Kabluchko, Yury Lisnyak, Ph.D., Tatyana Bomko, Ph.D., Tatyana Nosalskaya, Ph.D., Helen Romanova, Ph.D., Helen Grishina, Ph.D.

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