# New advances in MDR treatment
# Polymyxin and nephroprotectors


By:
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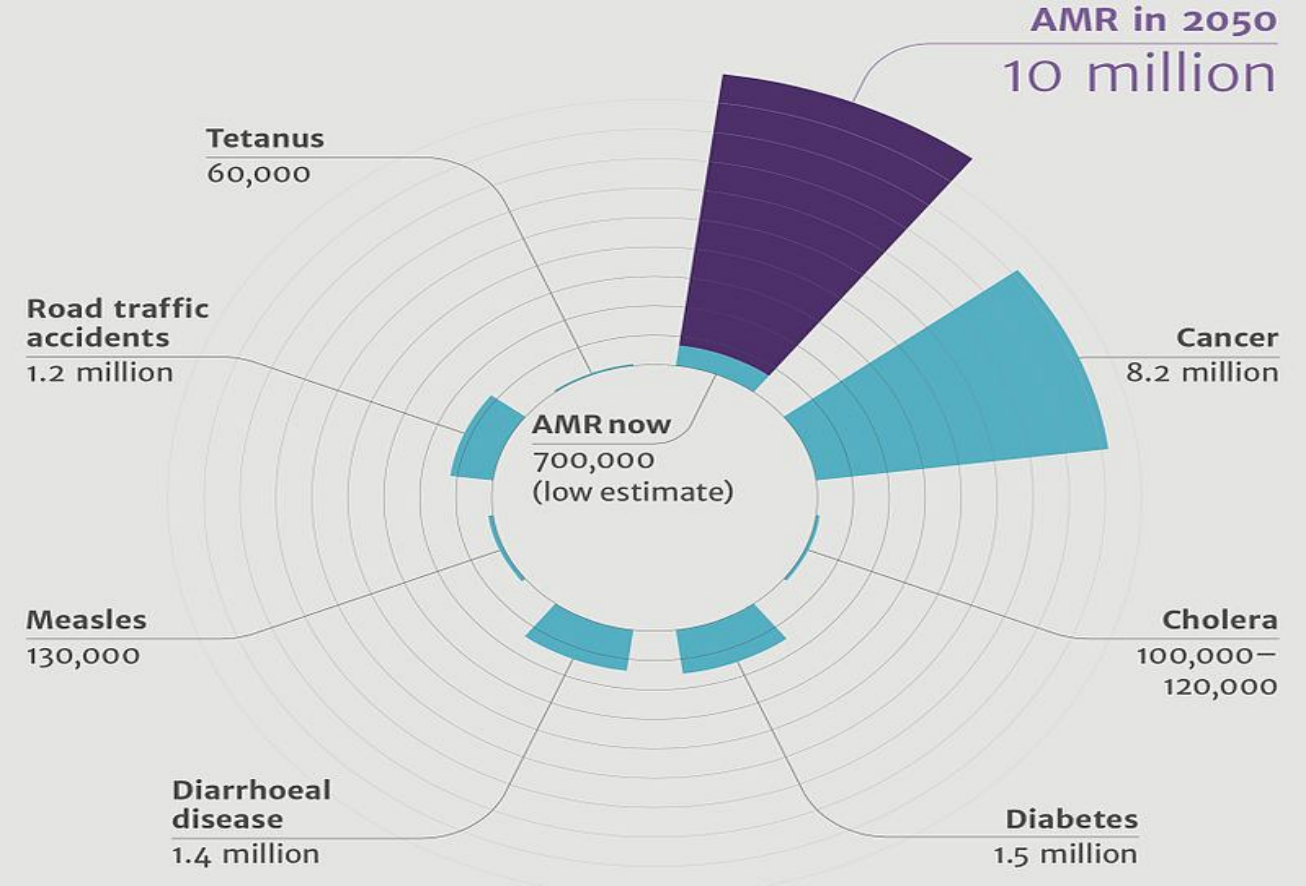
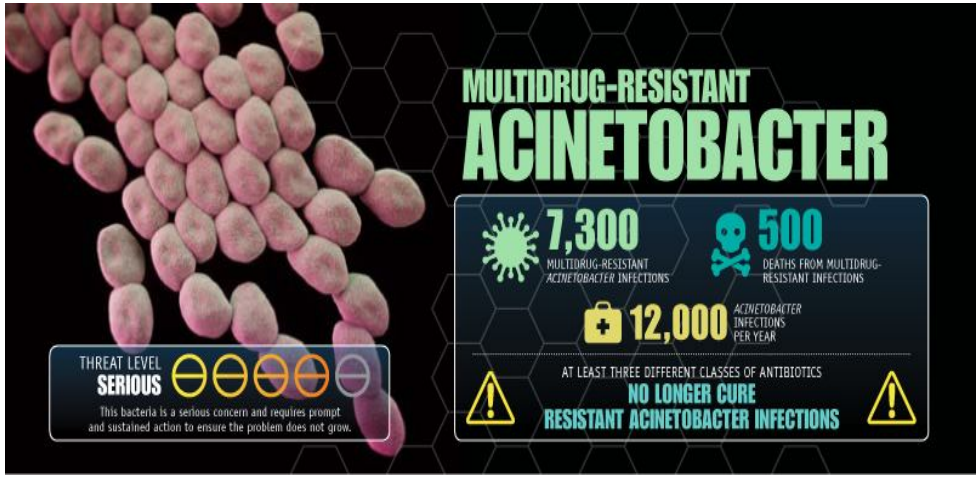
# Antimicrobial resistance AMR threat

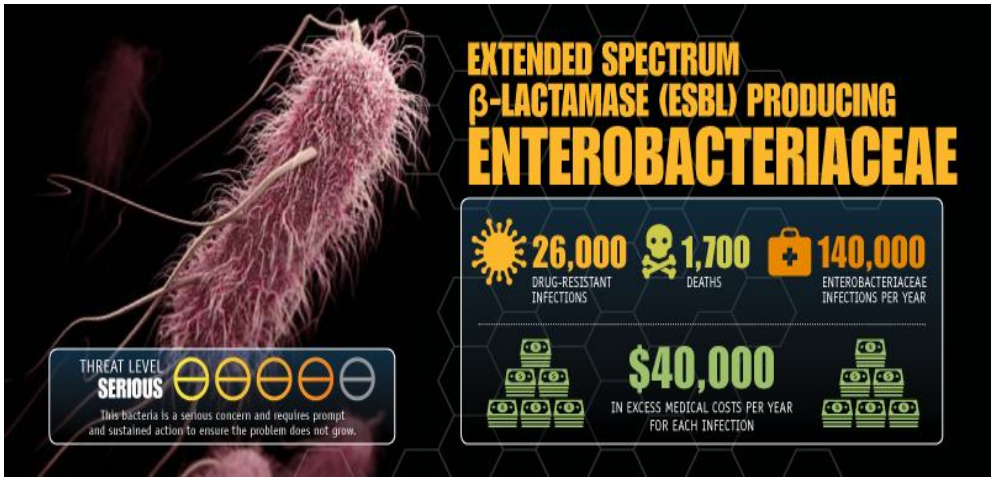
Causes of deaths in the USA compared to antimicrobial resistance death



# CDC Statistics MDR threat





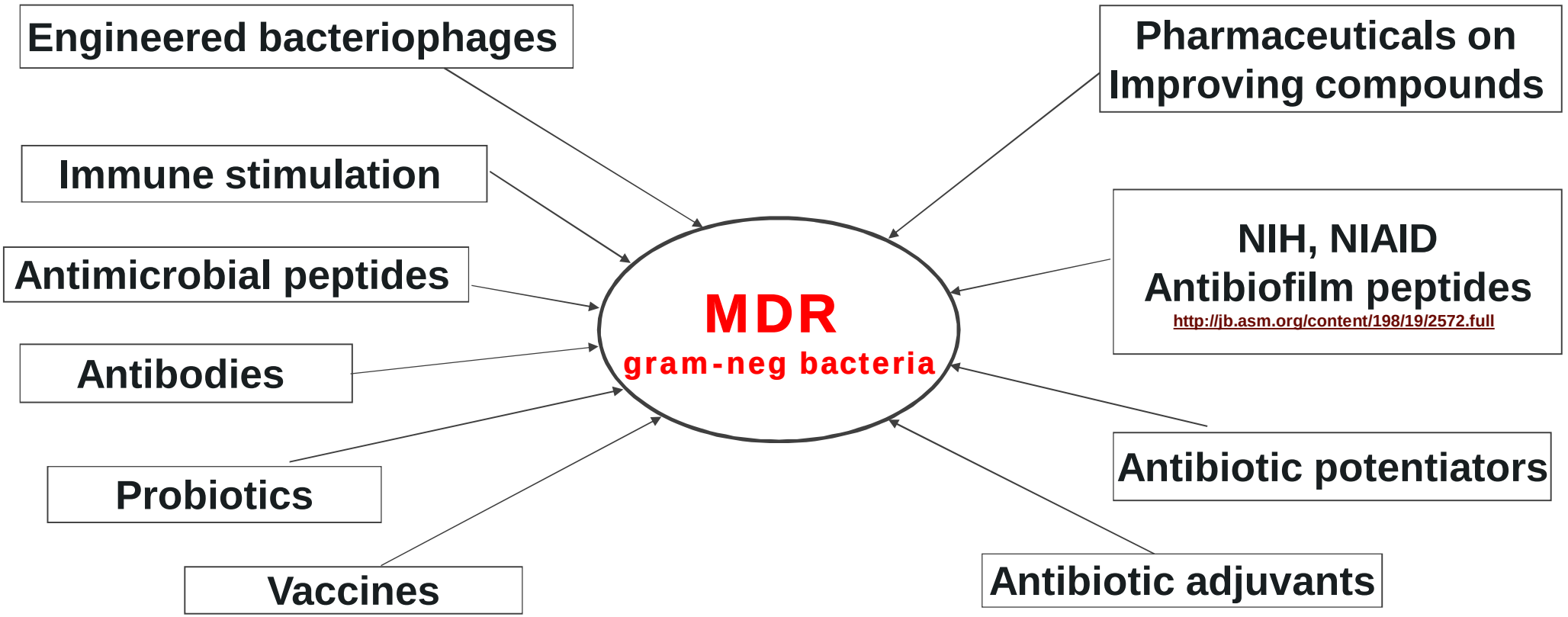

https://www.cdc.gov/drugresistance/biggest_threats.html

# Introduction

- NOIGEL LLC is a New York based company, established in 2010.
- Amongst the company's expertise are:
  - Synergistic combinations of FDA approved generic drugs and
  - Developing pharmaceutical compositions with unique applications.

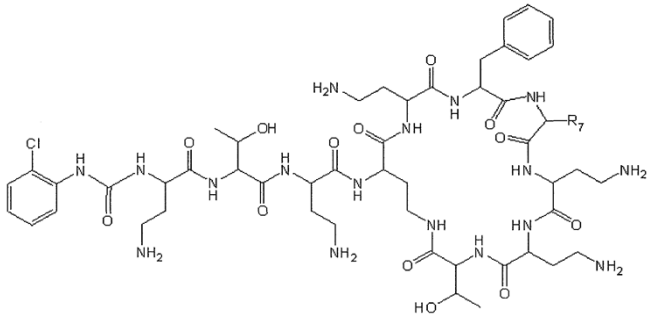
- Executive team:
  - Dr. Boris Farber, Phd. Chief Executive Officer
  - Dr. Ilya Kleyn, M.D. Chief Medical Officer
  - Dr. Artur Martynov, Phd. Executive Vice President of Research
- Key advisors
  - Dr. Daniel Beckles, M.D., Ph.D., FACS, FACC, FCCP
  - Dr. Eduardo Javier Mascareno Ph.D.

# Current research strategies within scientific community.



# Polymyxin and Nephrotoxicity

- **Polymyxin** was discovered in 1947 and introduced to the medical community in the 1950s.
- Polymyxin **nephrotoxicity** has made it a less desirable treatment choice over the years.
- According to the NIH, Polymyxin B has resurged in recent years as a **last resort** therapy for Gram-negative MDR and extremely drug resistant (XDR) pathogens.

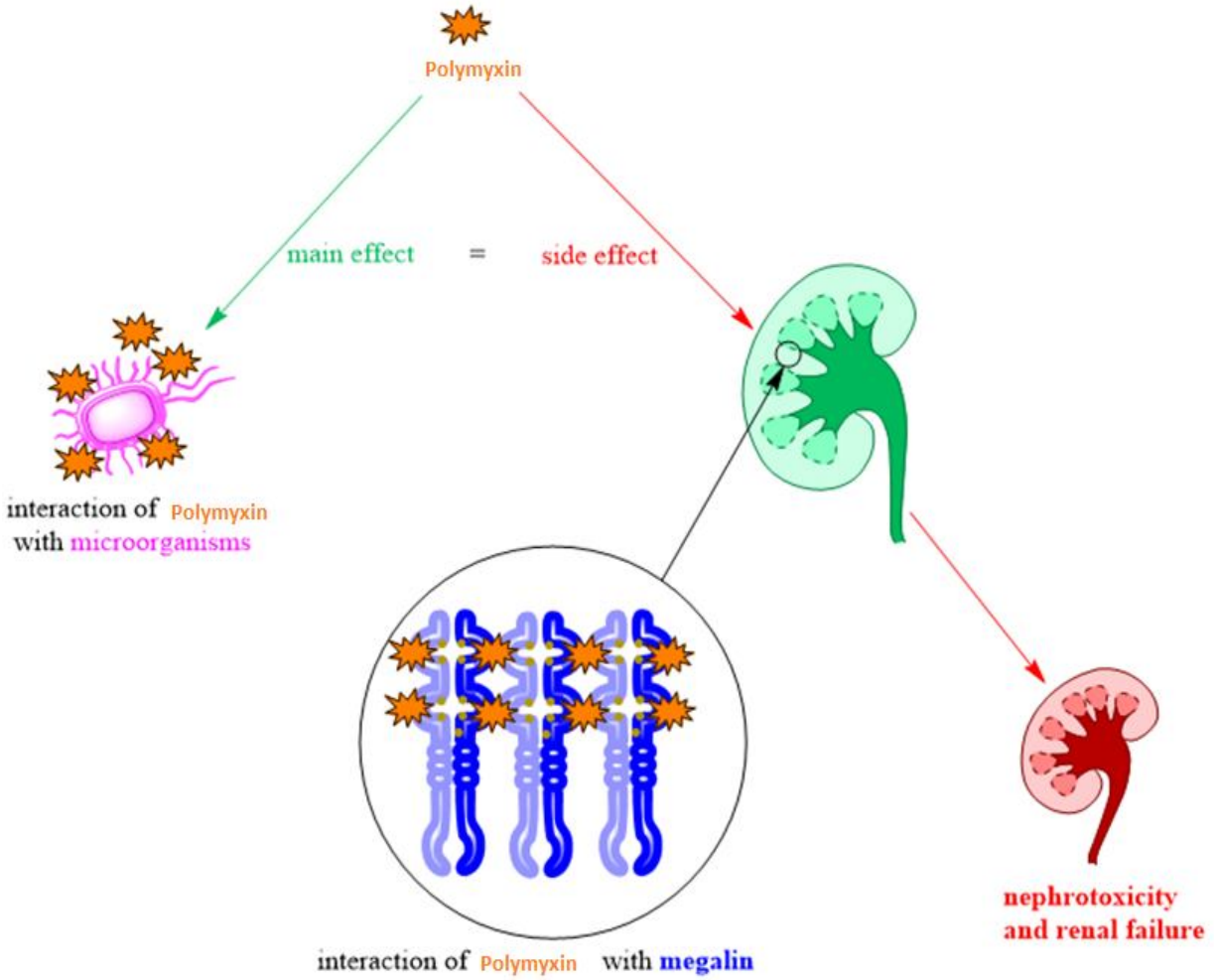



# Past strategies to fight Polymyxin Nephrotoxicity

- Polymyxin IV administration in different doses and different time ranges.[1]
- Analyzing drug delivery methods (e.g.s IV, IM or SQ).[2]
- Diverse methods of Polymyxin production and purification.[3]
- Polymyxin B-immobilized hemoperfusion (PMX-HP).[4]


1. http://www.scielo.br/pdf/ape/v26n1/en_10.pdf
2. http://www.scielo.br/pdf/ramb/v55n6/en_23.pdf
3. https://patents.google.com/patent/WO2010058427A2/en
4. https://www.ncbi.nlm.nih.gov/pubmed/29204670

# Polymyxin nephrotoxicity mechanism




Polymyxin
**high affinity to megalin**
resulting in proteinuria and nephrotoxicity.

# TRIZ and Pharmaceutical Industry

**NOIGEL is the only company, which applying TRIZ[1] for all R&D projects in Pharmaceutical industry.**

- TRIZ method mainly utilized in Industry of technology, product development, design engineering, process management.

- TRIZ principles have been used in many industries and companies including Samsung[2], General Motors[3] , NASA[4] .

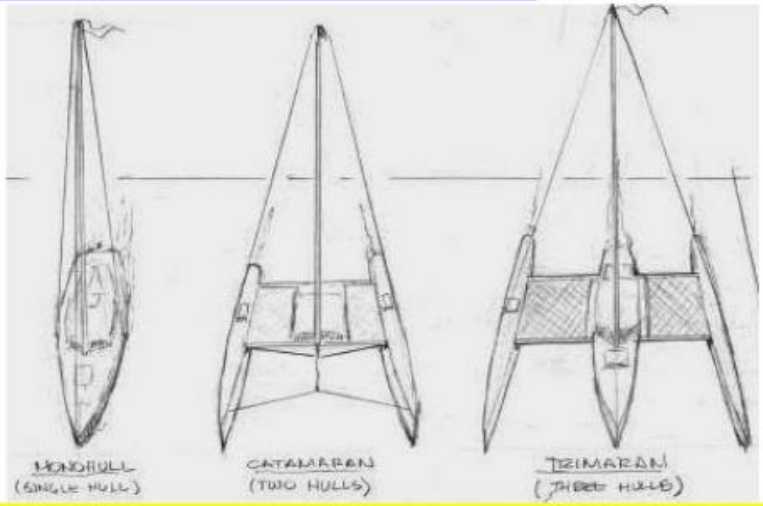
1. https://zenodo.org/record/2547580#.XKKKmJhKhPa
2. **Forbes** https://www.forbes.com/sites/haydnshaughnessy/2013/03/07/why-is-samsung-such-an-innovative-company/#2e46fdb02ad7
3. https://triz-journal.com/axiomatic-design-triz-compatibilities-contradictions/
4. http://www.xtriz.com/publications/AccelerateInnovationWithTRIZ.pdf

# TRIZ contradictions in Polymyxin use.

- From one side, in order to effectively treat infectious disease and save lives, we should use polymyxin.
- From another hand, polymyxin causes kidney toxicity, which prevents polymyxin from full therapeutic use.
- Since polymyxin is under utilized it cause bacterial adaptation and bacterial resistance to polymyxin.

# Example 1:  Mono-Bi-Poly-Hull

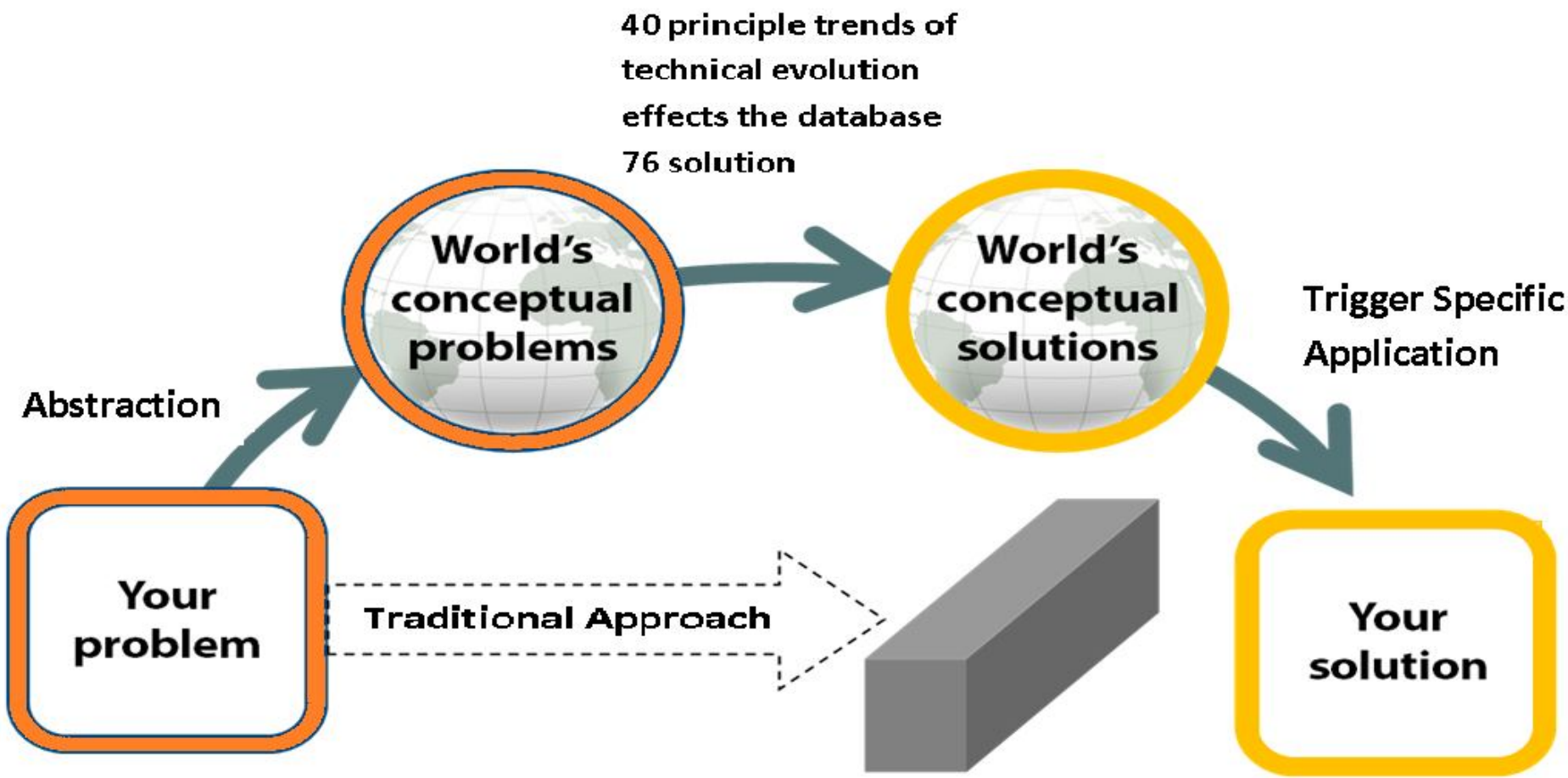
## Monohull, Catamaran, Trimaran





# Example 2: Two materials combination synergy: Steel + Concrete

# PRISM OF TRIZ



# TRIZ principles to solve problem

- **The principle of imposition:**

We separate the “interfering” part from the object (“interfering” property nephrotoxicity) on the contrary, select the only necessary part (the desired property - the antimicrobial activity of polymyxin).

- **The principle of local quality:**

To go from one object structure (or external environment, external influence to a non-uniform.
Different parts of the object should perform different functions.
Each part of the object must be in the conditions most favorable for it to work

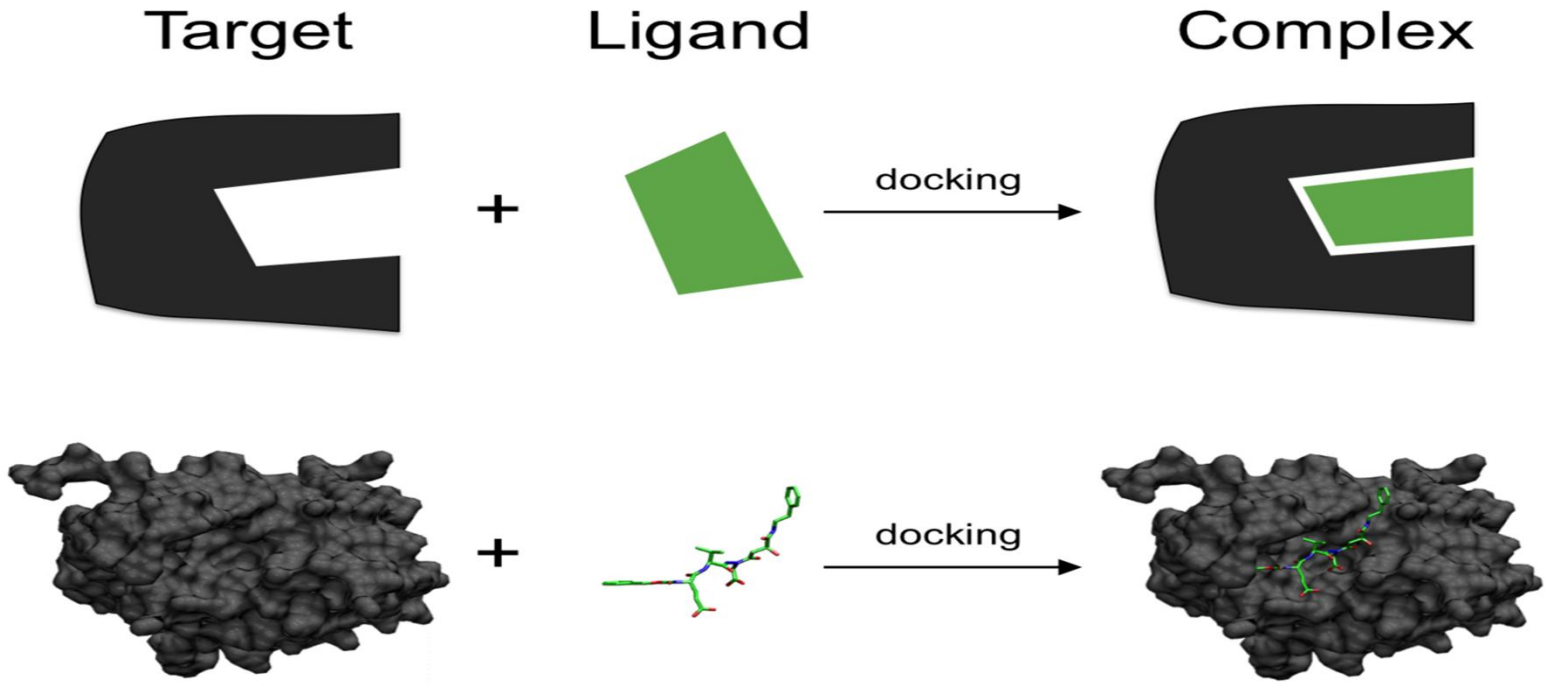
# TRIZ and Nephroprotector discovery

## The principles in research discovery:

**Imposition** was achieved by removing the interference of Polymyxin nephrotoxicity. **Local quality** confirms that our knowledge of microbiology should be focus on the megalin receptors.

**Principle of "pre-planted pillows."**, which tells us to compensate for the relatively low reliability of the facility by prepared emergency means led us to investigating thousands of FDA approved generic drugs and substances to serve as a nephroprotector.

# NOIGEL strategy based on R&D




## Finding the right target:

- To identify candidates to act as nephroprotectors.
- 246 substances were selected from 21,000 FDA generic drugs.
- Two substances synergistically combined to form **NGL022** - nephroprotector.

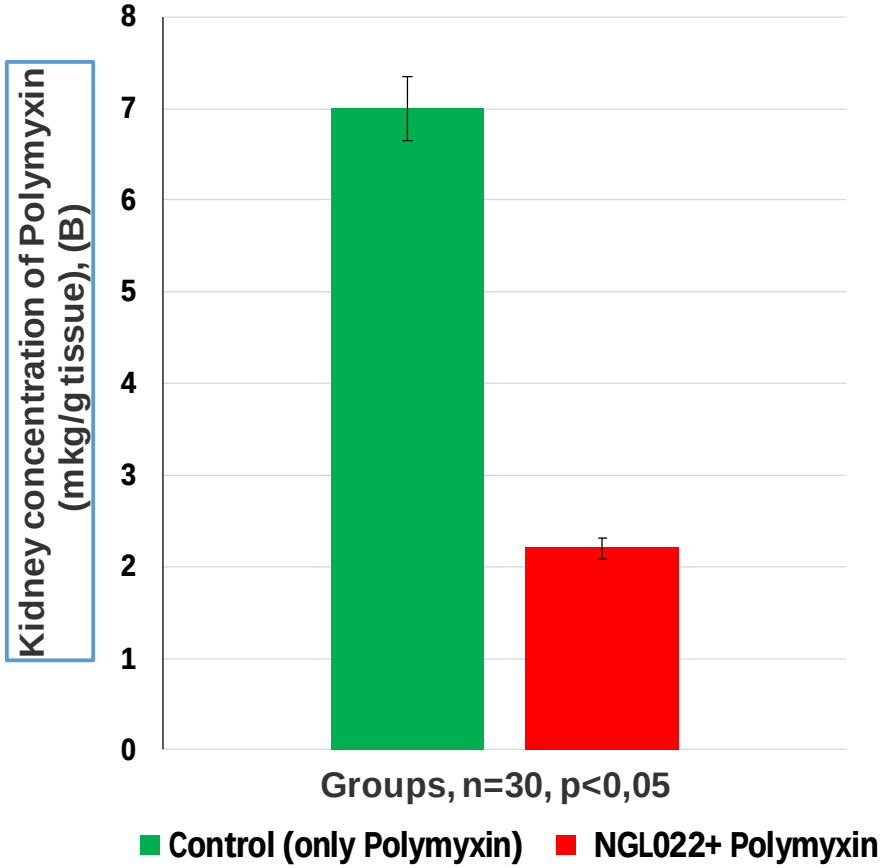
# TRIZ -NGL022 proof of concept

## Properties of NGL022 :

- NGL022 components are comprised of Quinones and Imidazole classes.
- NGL022 has higher affinity to megalin receptor than Polymyxin.
- NGL022 has minimal spectrum of side effects the host body.
- NGL002 doesn’t affect Polymyxin’s antimicrobial activity.

# NOIGEL active research

## Polymyxin's renal accumulation.



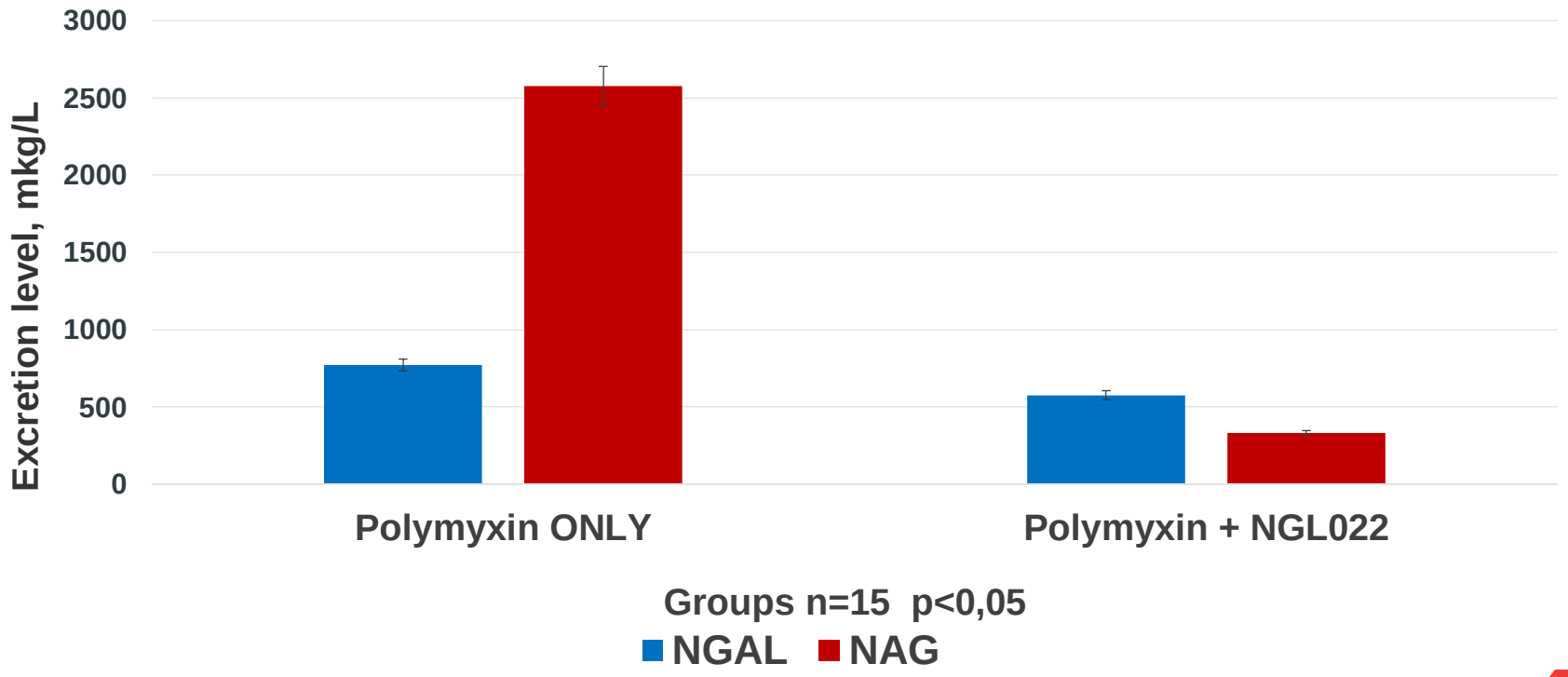

250 rats, ELISA-test and HPLC-systems were used. Studies18 month period (in series).

- 2 groups (30 animals per group)
- NGL022 (15 mg/kg) IV first and colistin (0.5mg/kg) was administered intravenously 45min after.

# Study: Polymyxin + NGL022

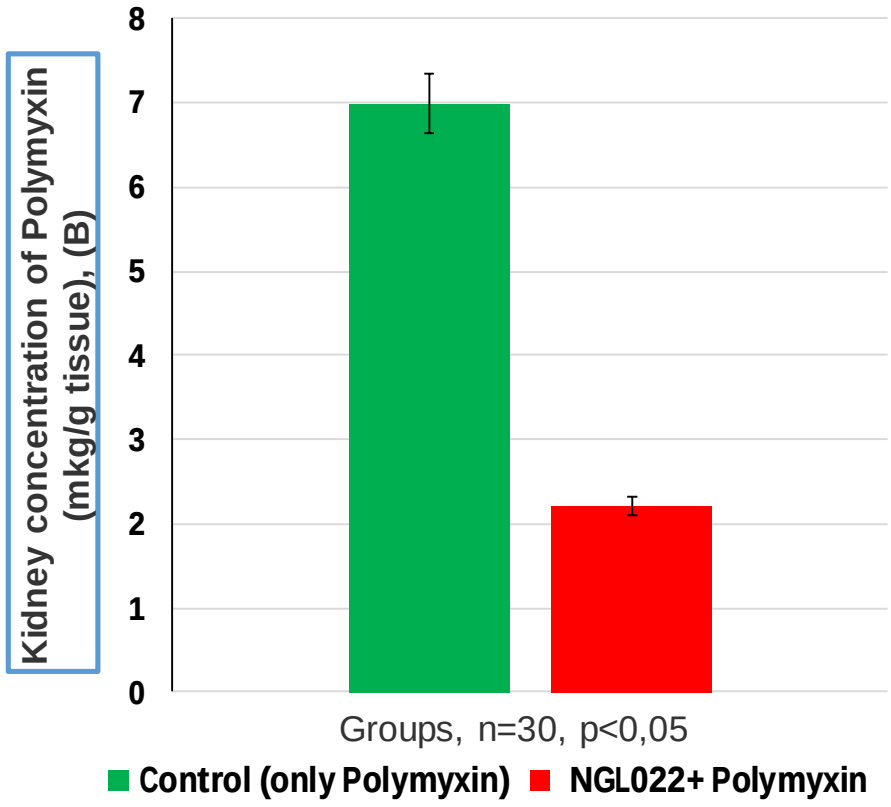
**NGAL** (neutrophil gelatinase-associated lipocalin) - biomarker of acute kidney injury.

**NAG** (N-acetyl-beta-d- glucosaminidase)- biomarkers of kidney disease (the 30 days after the last administration of polymyxin the excretion level of both compounds < 120 mkg /L )

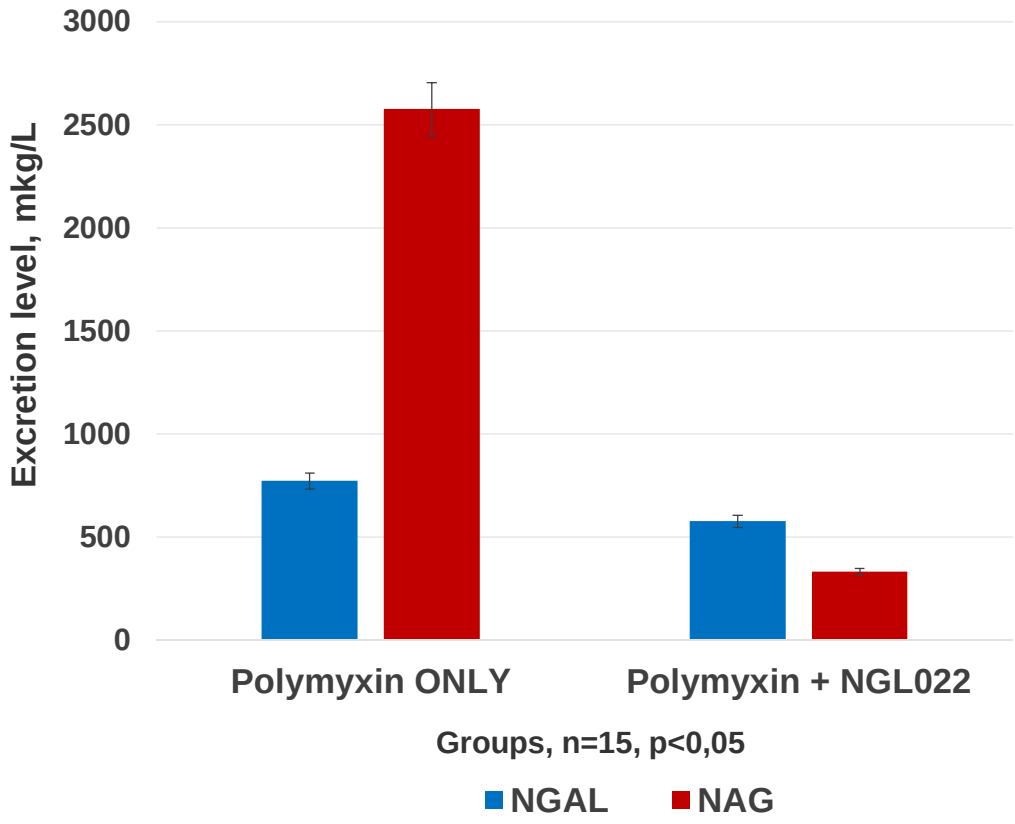


# Results: NGL022 achieves goals

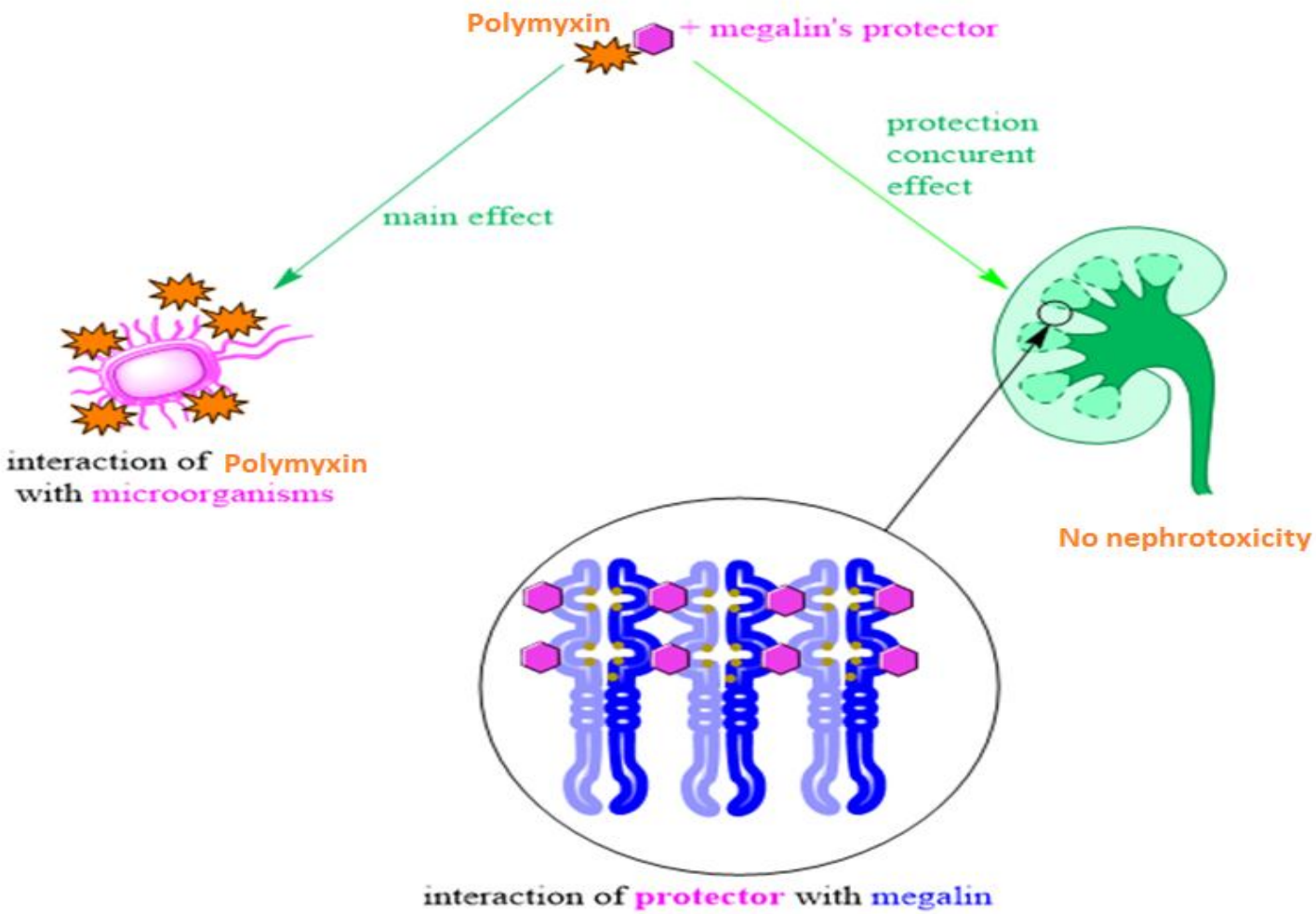
## Polymyxin accumulation in the kidney.




## Polymyxin nephrotoxicity biomarkers.



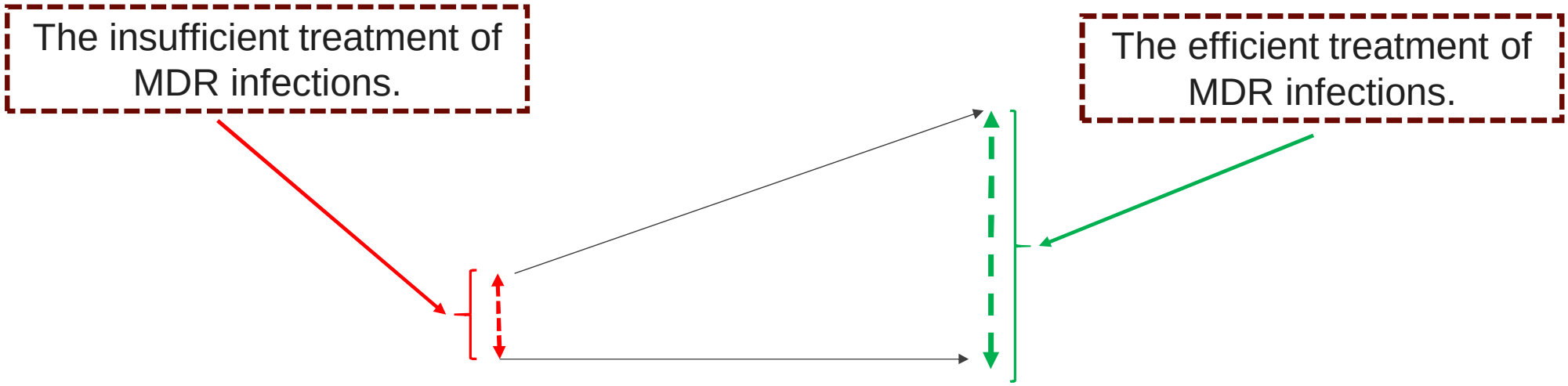
# Polymyxin + NGL022 and Megalin affinity



# Therapeutic Key Takeaways

> 1 week Polymyxin use **without NGL022:** increase risk of nephrotoxicity.

> 1 week Polymyxin use **with NGL022:** mild or No nephrotoxicity




No changes in Polymyxin or NGL022 pharmacological structure.

# Intellectual property and publications.

## IP:

- **New combinatorial derivatives of antibiotics based on supramolecular structures PCT/RU2017/000424**
- **Pharmaceutical composition for the treatment of infectious diseases based on polymyxin with nephroprotectors ( Application filed 05/02/2018 with the PCT Patent Office)**

Publications:


1. Lisnyak Y.V., Martynov AV (2012). Molecular modeling of antimicrobial compounds interactions with cell membrane elements: nystatin-ergosterol membrane pore. *AMI, (*3), 51-56.

2. Lisnyak Yu.V., Martynov A.V., Alhussein M., Prikolotin A.V. Drug-target interactions of polymyxins: A computational structure-toxicity study / 4th International Symposium "Methods and Applications of Computational Chemistry" - Lviv, 28 June - 2 July, 2011. Book of Abstracts.- Lviv-Kharkiv, 2011- P.105.

3. Lisnyak Yu.V. Gubskaya A. V., Martynov A.V. Molecular Modeling Study of Polyene-Sterol Membrane Channel //2nd International Symposium “Methods and Applications of Computational Chemistry”. – Kyiv, 2-4 July, 2007. – Book of Abstracts. – Kyiv-Kharkiv, 2007. – P.90.

# Market Opportunity

**12**

Only 12 New antibiotics FDA approved in last 5 years *

**4-9%**

Annual Increas in global anti-MDR bacteria antibiotic market*

**$246 Mill. USD**

Amount to spend in Pharma and academia to fight MDR bacteria**

* https://www.fda.gov/NewsEvents/Newsroom/FDAInBrief/ucm595264.htm
** http://www.globalopportunitynetwork.org/report-2016/new-business-model-for-antibiotics/

# Market Opportunity

**The true cost of antimicrobial resistance (AMR) and predictive cost of MDR crisis:**

According to Scientific American

**10 million** Deaths from MDR infections each year by 2050

**$35.6 bill** Amount anti-bacterial market will reach by 2022

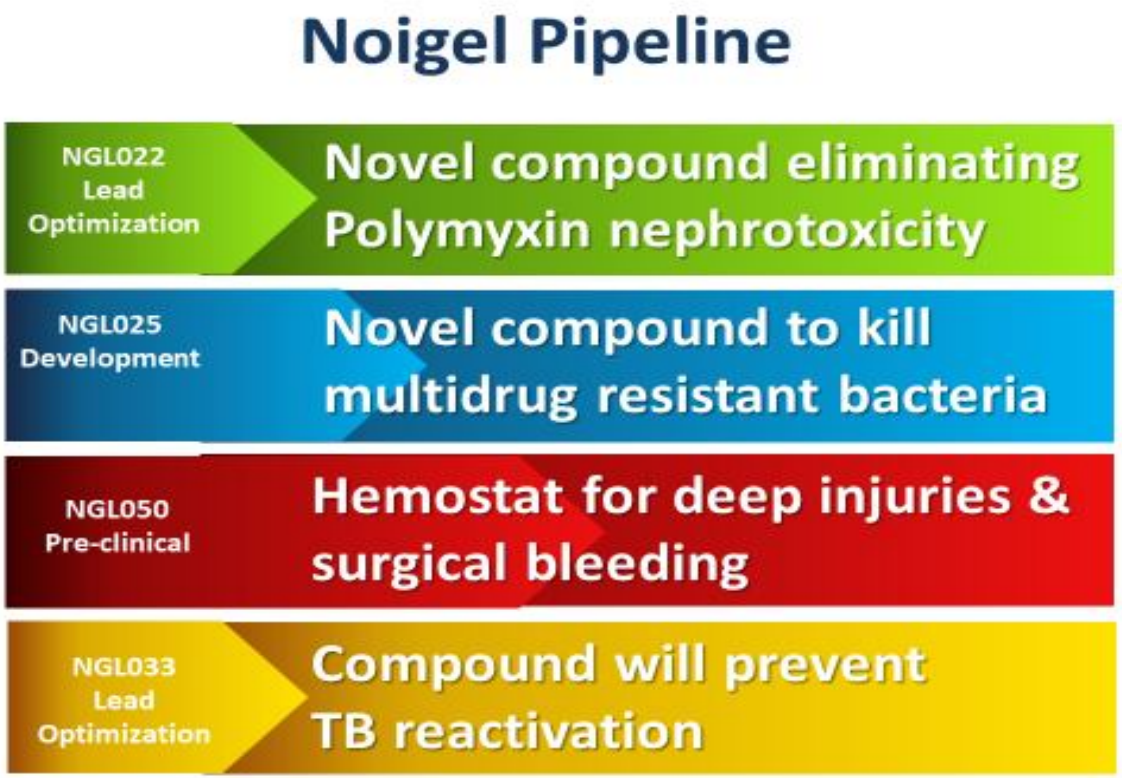
**$100 trill** will be Lost to the global economy by 2050

# Next steps Polymyxin + NGL022 research project

- Noigel looking to partner with VC, Life Science PE group or other interested investors.
- The goal would be to further develop NGL022 to bring it to clinical trial stage.
- Noigel is currently planning further pre-clinical testing and actively seeking funding to ensure all testing necessary to enter Phase I trials by 2020.

# TRIZ method and ongoing pipelines

Company R&D snapshot



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