SYNERGETIC COMBINATION S-CURVE AND TRANSITION TO A HIGHER-LEVEL SYSTEM FOR MULTI DRUG RESISTANT(MDR) BACTERIA

Dr. Boris Farber,CEO Noigel. LLC, TRIZ Biopharma International LLC, TRIZ Master

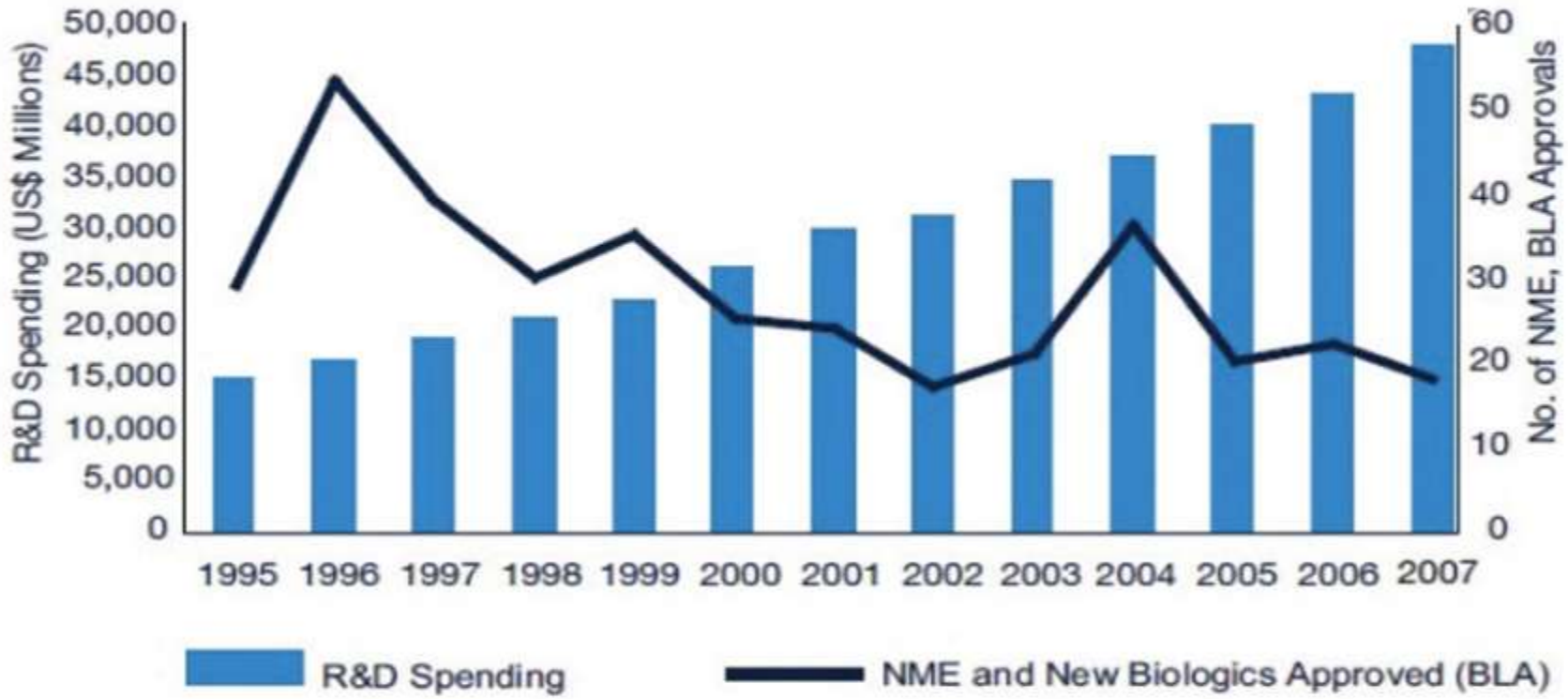
Company background

- **NOIGEL LLC is a New York based company, established** by a group of scientists and experts to study and develop **New Paradigms in pharmaceutical industry based on TRIZ and modern technologies**- is the only company in the World which applied TRIZ methods for all R&D in pharmaceuticals.

Amongst the company's expertise are:

  - Synergistic combinations of FDA approved generic drugs
  - Developing pharmaceutical compositions with unique applications.

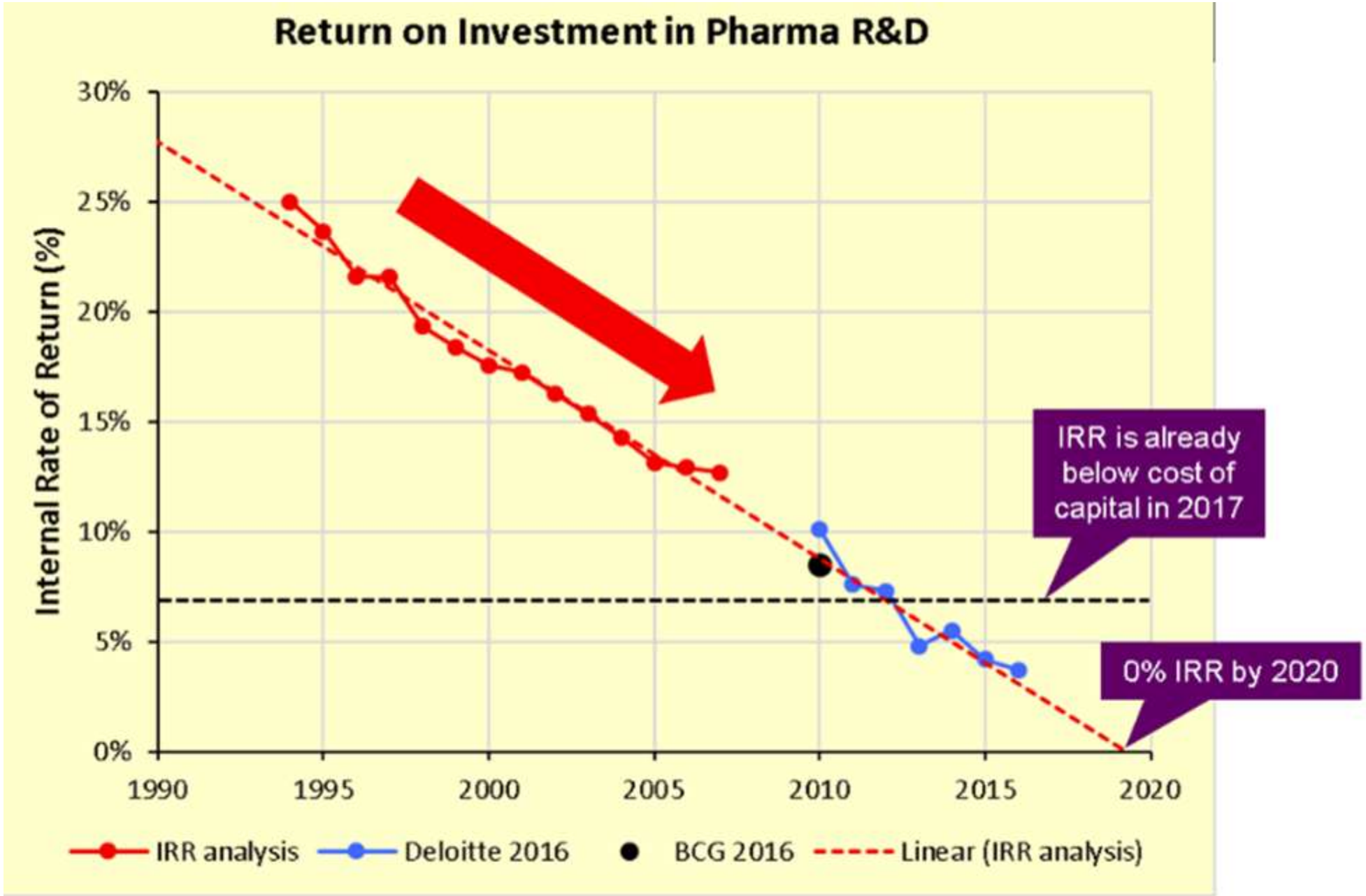
- **Executive team:**
  - Dr. Boris Farber, Dr.Sc.,Phd, CEO
  - Dr. Ilya Kleyn, M.D. CM0
  - Dr. Artur Martynov, Dr.Sc., Phd, CSO
- **Key advisors**
  - Dr. Daniel Beckles, M.D., Ph.D., FACS, FACC, FCCP
  - Dr. Eduardo Javier Mascareno Ph.D.
  - Dr. Harold Haines Ph.D.



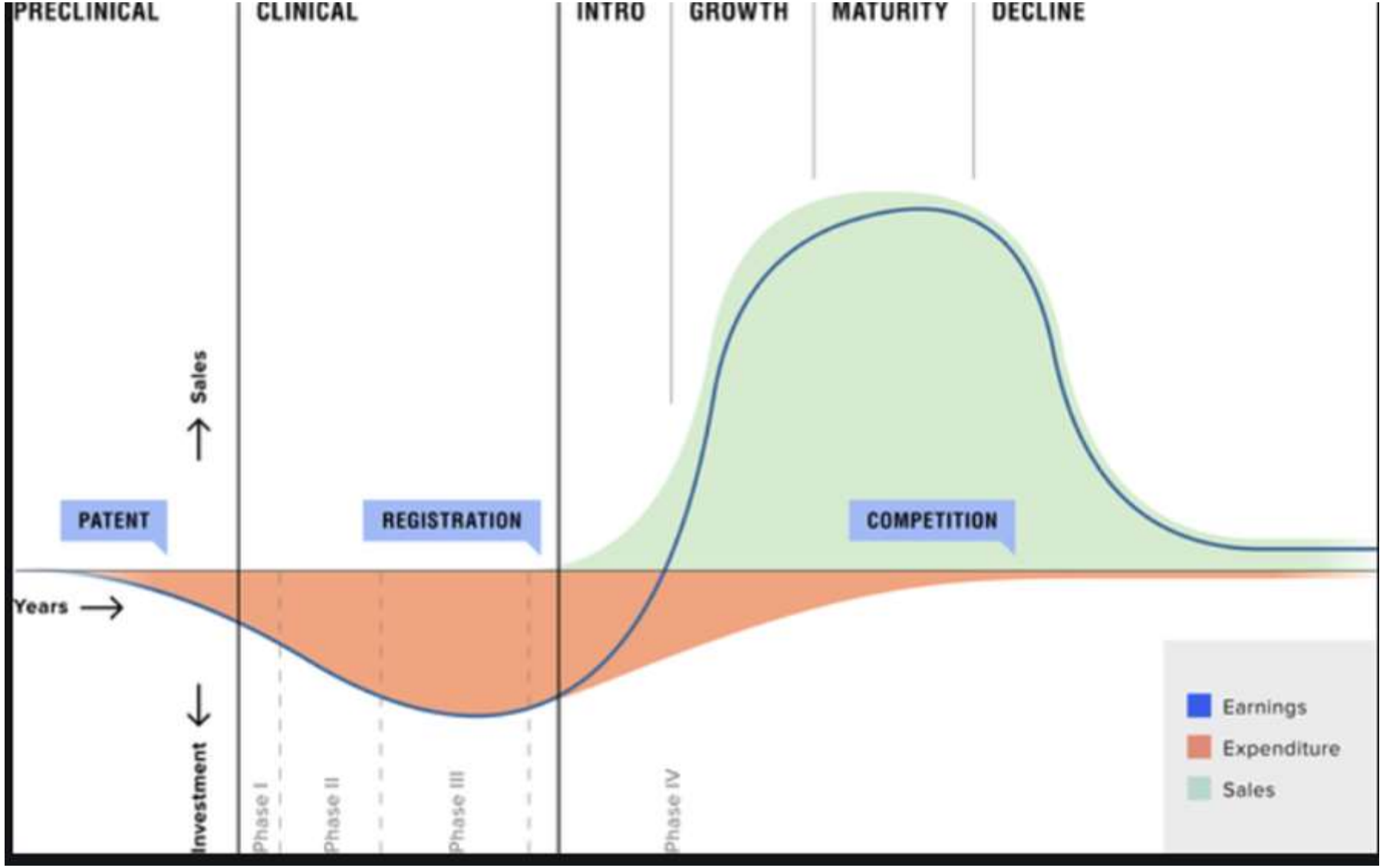
NME:
New chemical or biological prescription therapeutic: excludes vaccines, antigens and combination therapies which do not include at least one new constituents

Source: FDA CDER, PhRMA and PricewaterhouseCoopers analysis

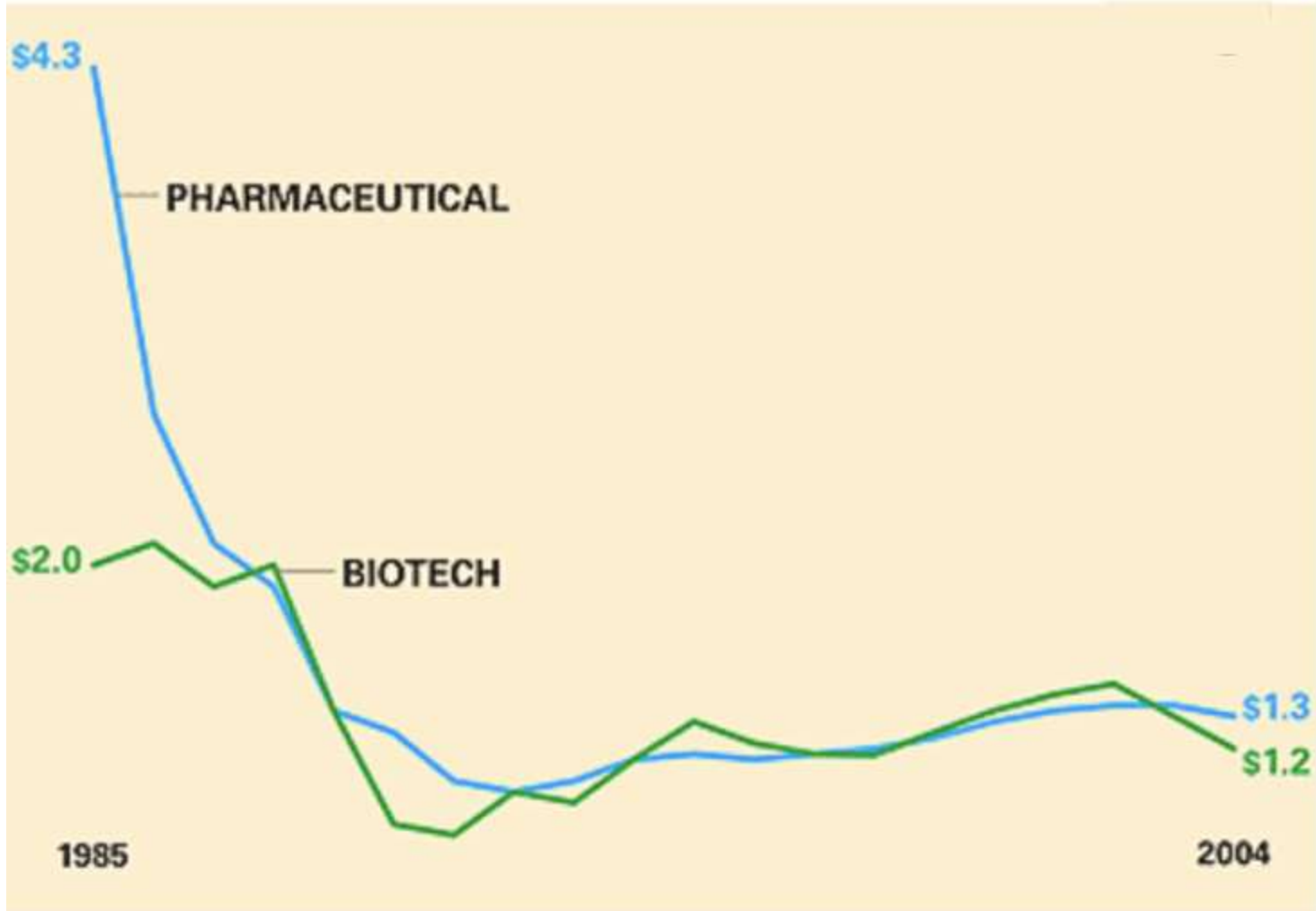
Note: Data on R&D spending for non-PhRMA companies are not included here.



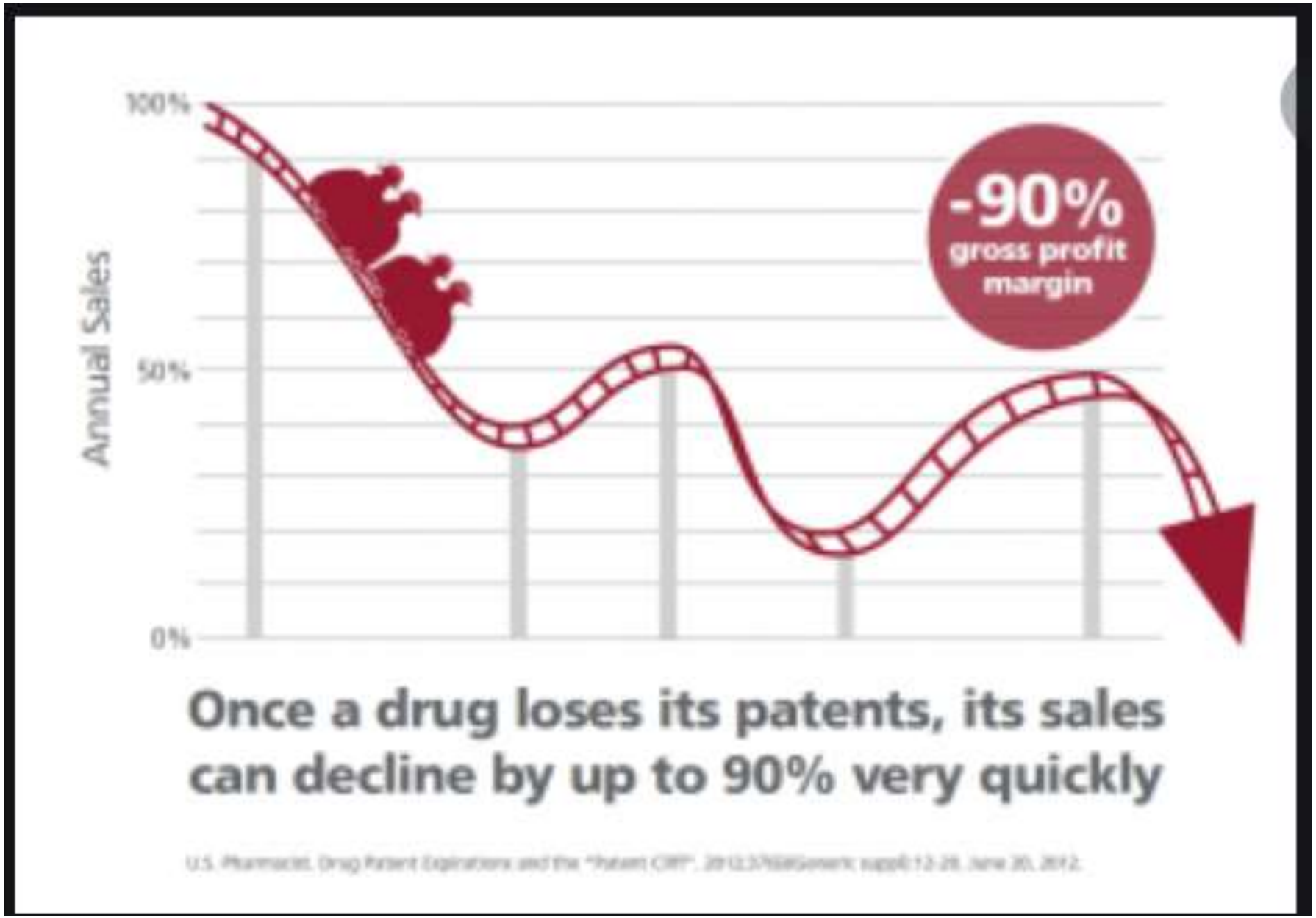
Source: EvaluatePharma, IRR analysis


PRECLINICAL
CLINICAL
INTRO
GROWTH
MATURITY
DECLINE
Sales
PATENT
REGISTRATION
COMPETITION
Years
Investment
Phase I
Phase II
Phase III
Phase IV
Earnings
Expenditure
Sales

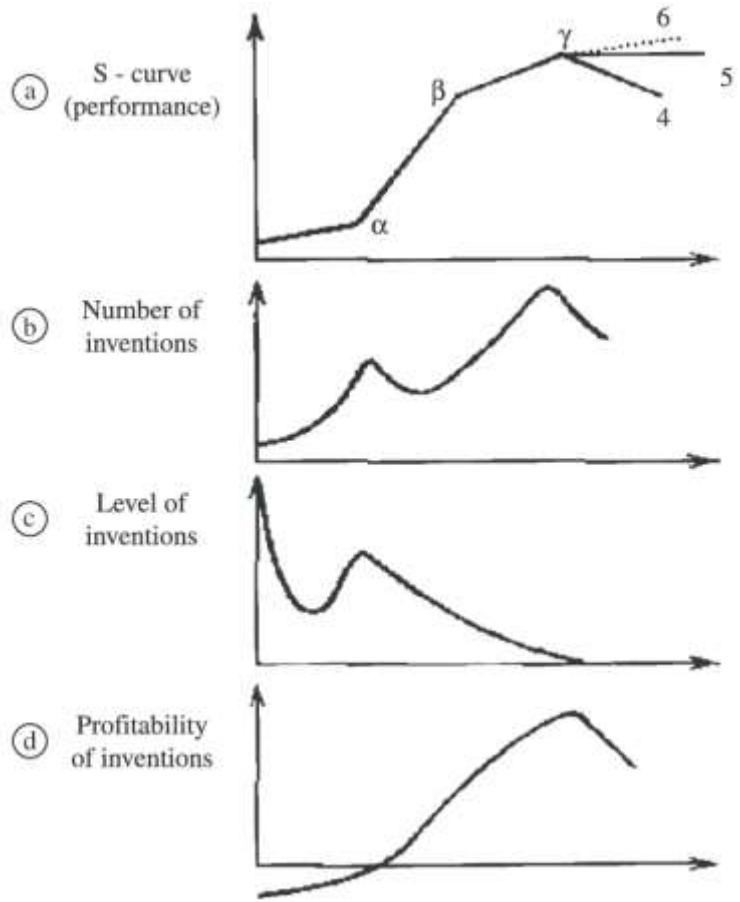
R&D spending per new drug launched ($ billions 2004)

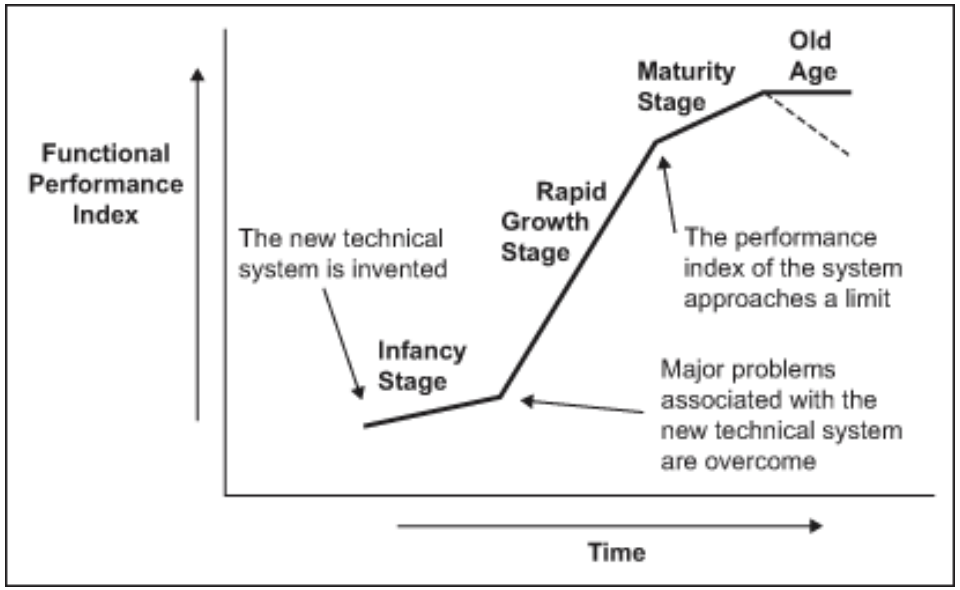


The sample of biotech companies includes all publicly held companies that tried to develop new drugs. The sample of pharmaceutical companies includes the top 20 companies in the world according to their R&D spending. The drugs do not include line extensions, reformulations, or approvals for new uses. Every annual data point represents the cumulative R&D expenditures from 1985 through the given year divided by the cumulative number of drugs launched during the same period. The first four and last four years of data were adjusted to account for the lag between R&D spending and the resultant output. Credit for a jointly developed new drug was divided equally between the biotech firm and its partner, the established pharmaceutical company.


100%
50%
0%
Annual Sales
-90%
gross profit
margin
Once a drug loses its patents, its sales
can decline by up to 90% very quickly

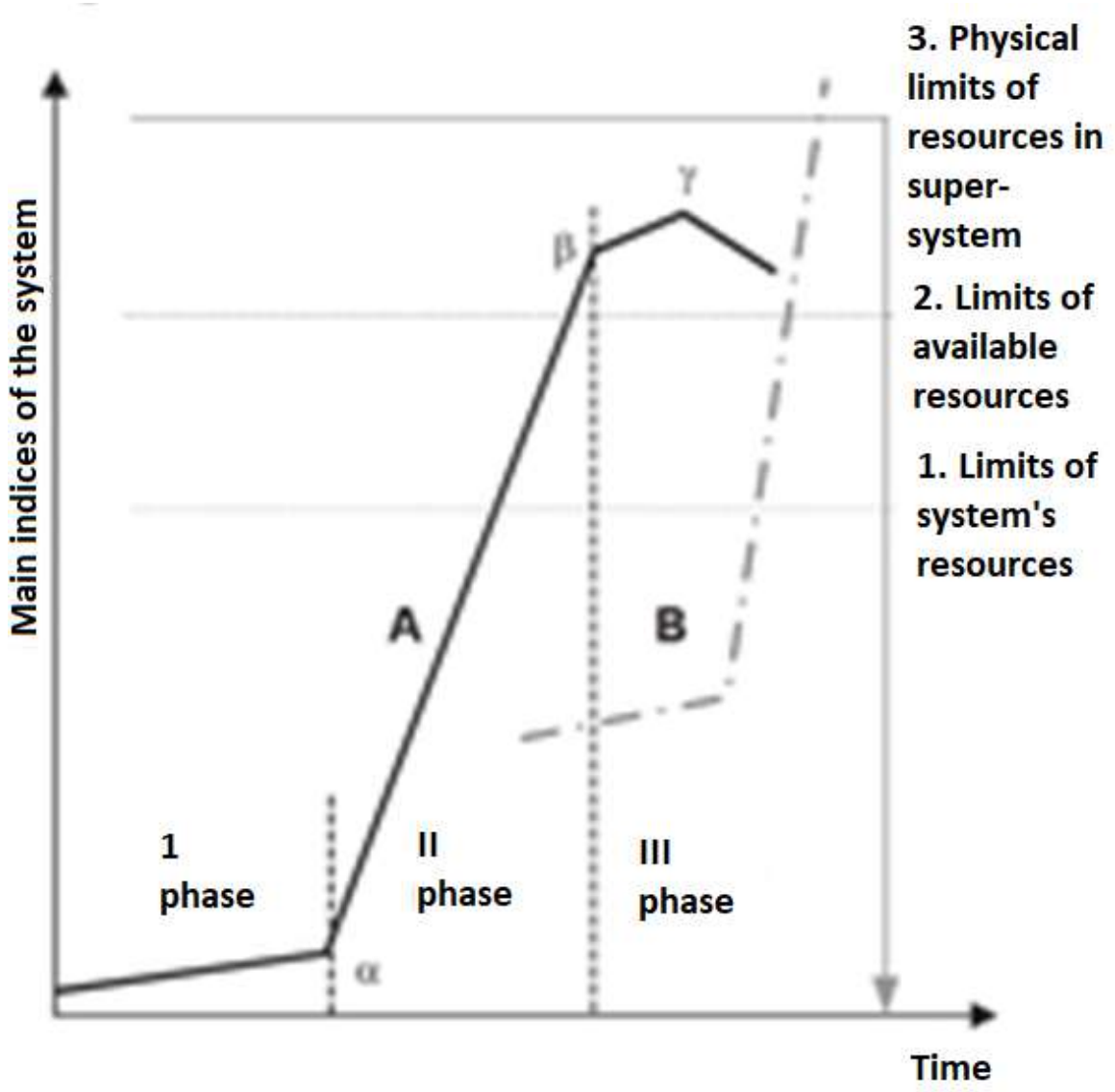
S-Curve TRIZ: Three ASPECTS: Heuristics, Synergy, Dynamics





S-curve characterizes the whole system life cycles. There are four stages: infancy, rapid growth, maturity and decline. **TRIZ** introduces four indicators in determining where a product or system is in its evolutionary **S-curve** In addition, each stage has its own features.

S-Curve TRIZ: Three ASPECTS: Heuristics, Synergy, Dynamics



Some NOIGEL'S PROJECTS

Line 1. Potentiating and applying a new and unique applications for FDA approved generic drugs (6 Projects).

Project1: Polymyxin and Nephroprotectors to reduce polymyxin nephrotoxicity.
Project 2: Multiple drug resistance bacteria (MDR) new paradigm to fight MDR , use of potentiators (enhancers).
Project 3: Anti-tuberculosis drugs based on the completed phagocytosis stimulants.
Project 4: Pharmaceutical composition to activate tissue regeneration by stimulating autologous stem cells growth, migration and differentiation stem cells.
Project 5: Binary hemostatic, based on the self-assembled modified polysaccharides and self dissolving in the wound. Without damage to wound tissue.
Project 6: New approach of Metformin use with reduced Gastrointestinal side effects.

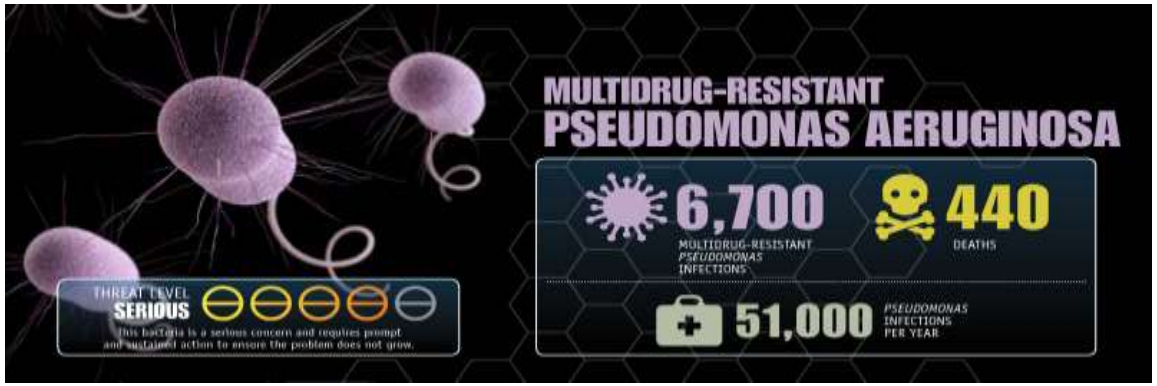
Line 2. Creating new generation of drugs with dynamic structures (Dynamic drugs) based onFDA approved generic "static" drugs. (4 Projects)

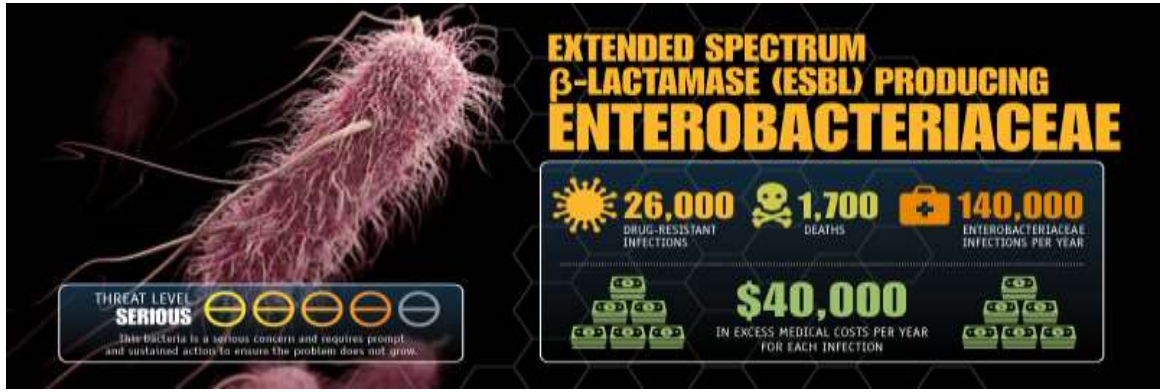
Project 1. Anticancer strategy based on the self-assembled target RNA (tRNA).
Project 2. Strategy for development the Dynamic Antivirals based on the self-assembled modified peptides.
Project 3. Strategy for development the Dynamic vaccines based on the self-assembled modified peptides.
Project 4. Dynamic insulin based on the self-assembled modified peptides.

Line 3. New diagnostic approach for early cancer detection and early prediction of atherosclerosis and it's complications.

Line 1. Applying a New and Unique application to FDA approved generic drugs and improving their efficacy. (6 Projects)

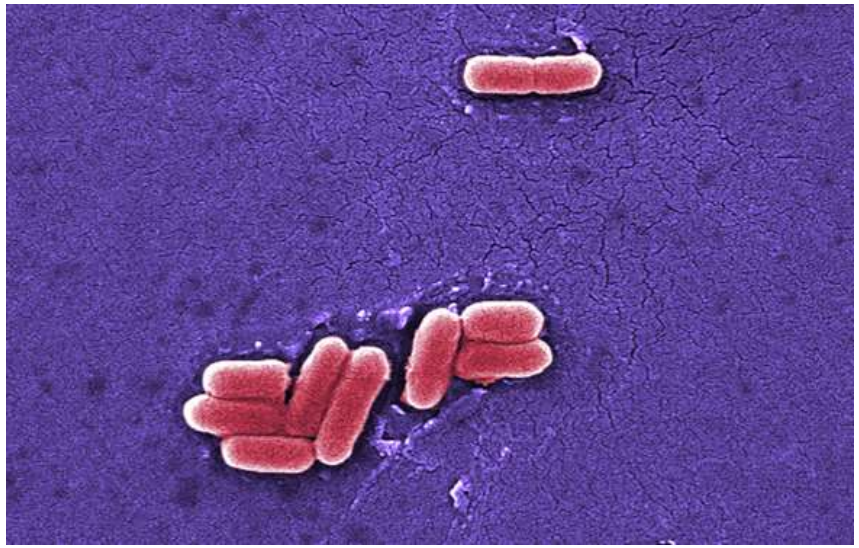
CDC statistics on some MDR

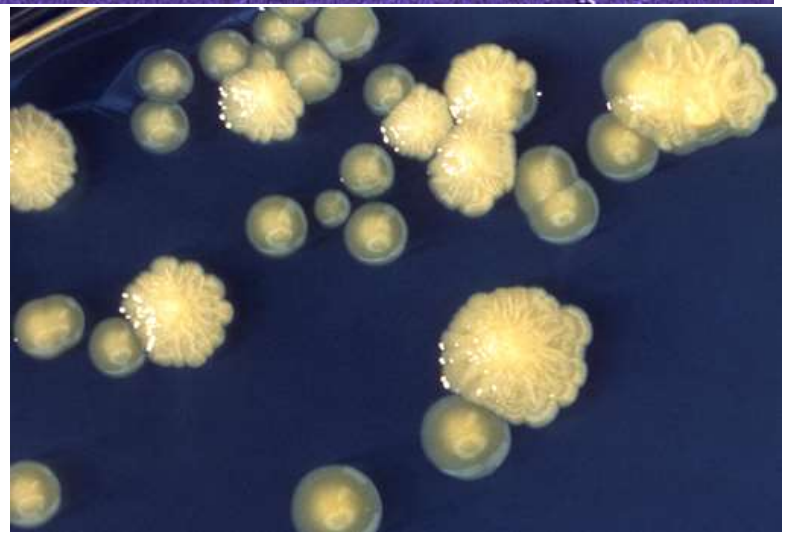




Bad Bugs: No ESKAPE

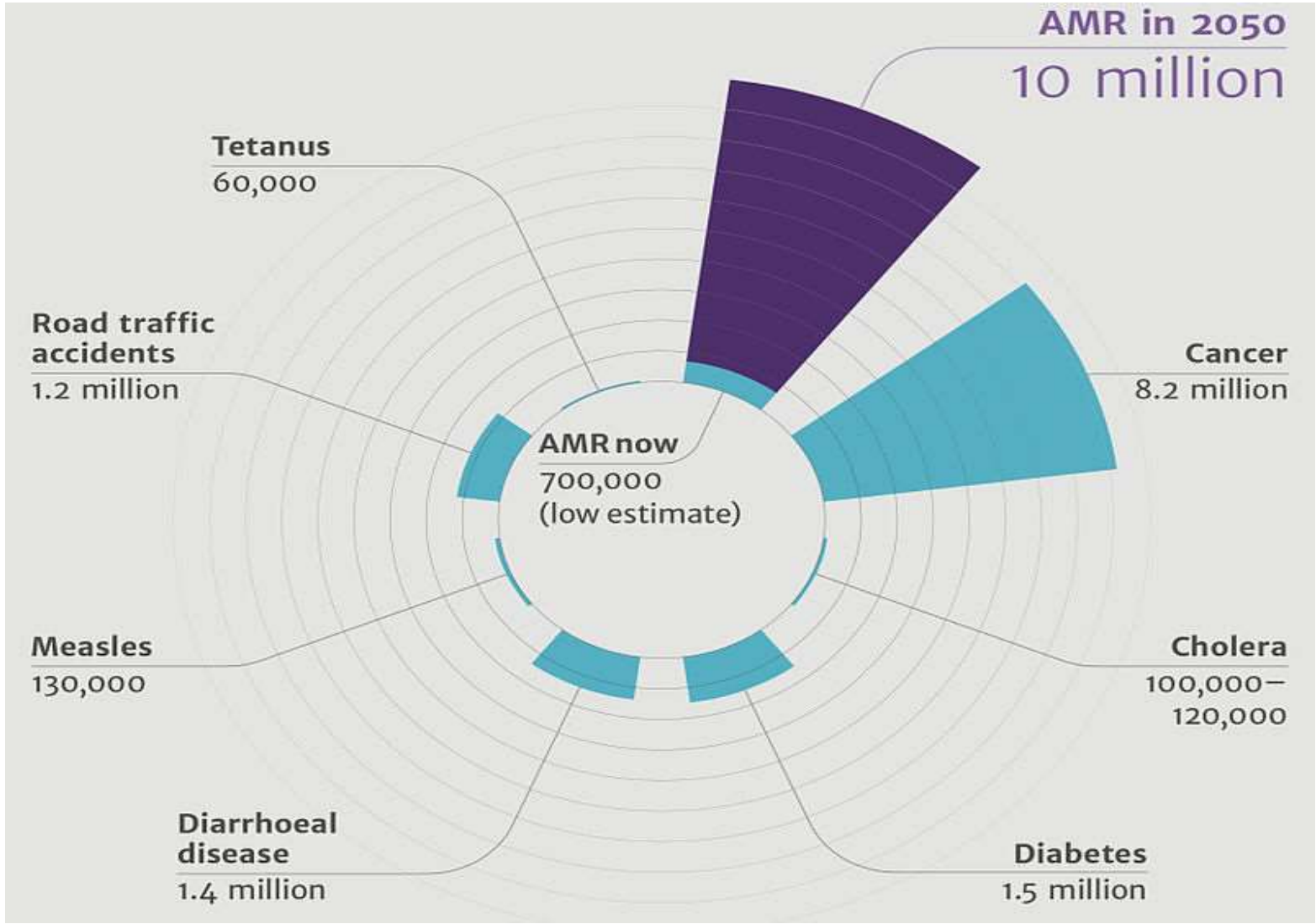
- *Enterococcus*
- *S. aureus*
- *Klebsiella spp.*
- *Acinetobacter*
- *P. aeruginosa*
- *Enterobacter spp.*





Boucher H, et al, Clin Infect Dis 2009;48:1-12

MAJOR Causes OF DEATHS IN USA COMPARED TO antimicrobial resistance (AMR) DEATH

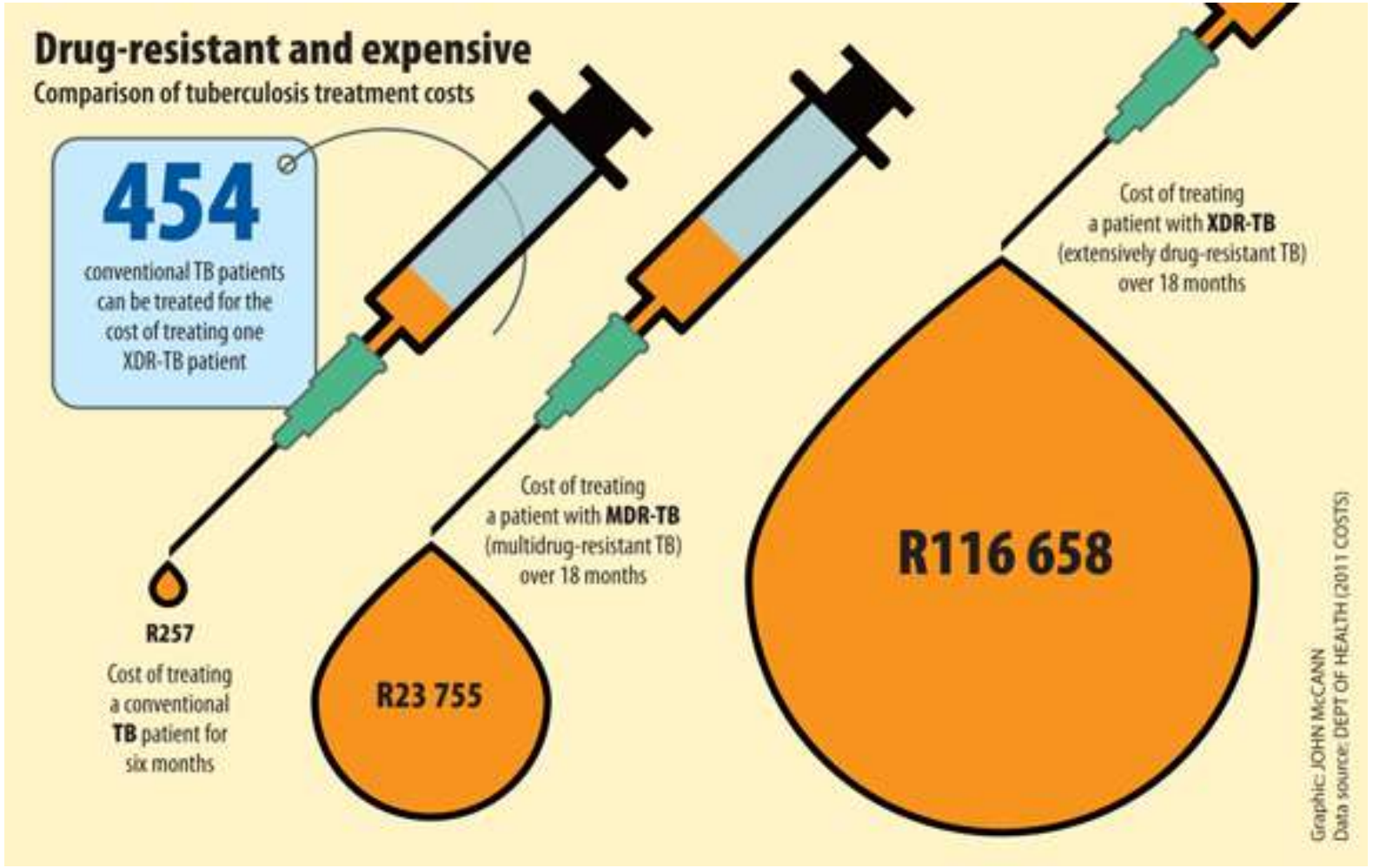


CDC Statistics: Dangers of MDR

$ 26 BILLION
annual cost of antibiotic-resistant infection to U.S. health care

23,000 Americans
die from resistant infection each year

10 million deaths
&
$100 trillion lost by 2050 in the World



In his 1945 Nobel prize lecture, Fleming warned of the dangers of antimicrobial resistance:

“The time may come when penicillin can be bought by anyone in the shops.

Then there is the danger that the ignorant man may easily under dose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant.”


MICROBIOLOGY LAB
IT'S WORSE THAN WE THOUGHT. THAT ANTIBIOTIC-RESISTANT BACTERIA IS READING NIETZSCHE!
6-24
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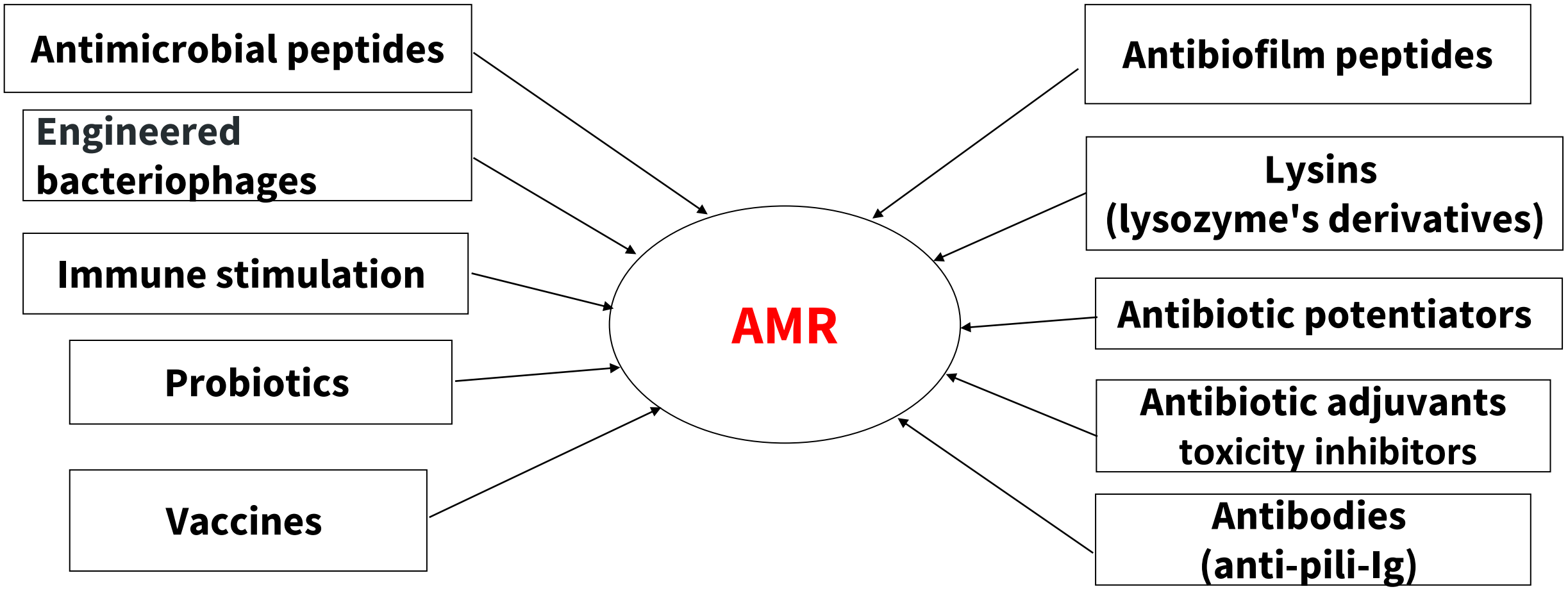
Current strategies within scientific community



Market Opportunity

12

12 New antibiotics FDA approved in last 5 years *

4-9%

Annual Increase in global anti-MDR bacteria antibiotic market*

$35.6bill. 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

- **To fight and conquer in all your battles is not supreme excellence; supreme excellence consists in breaking the enemy's resistance without fighting.**

Sun Tzu

- **For to win one hundred victories in one hundred battles is not the acme of skill. To subdue the enemy without fighting is the acme of skill.**

Sun Tzu

- **You must not fight too often with one enemy, or you will teach him all your art of war.**

Napoleon Bonaparte

Example1: Project 6: A New Paradigm for fighting Multiple drug resistance (MDR)microorganisms.

Based on TRIZ Principle # 13 “Inversion” or do the opposite” or "The other way round":

• Instead of killing bacteria, lets provide a suitable environment in which case the bacteria will produce less virulent toxins and defense factors. This in turn leads to more bacterial sensitivity to the antibiotics currently in use to which they were previously resistant to.

•Noigel developed the pharmaceutical composition based on FDA-approved substances (enhancers) to halt bacterial toxicity and virulence factors production.

TRIZ PRINCIPLES COMBINATIONS, CHOSEN BY ALGORITHMS (ARIZ) , COULD BE USED TO SOLVE A PROBLEM FOR MDR FIGHTING (RED COLOR ON SLIDE 13)

Principle #13: Invert the action(s) used to solve the problem

(e.g. instead of cooling an object, heat it; instead of suppressing- enhancing growths).

Addition principles from TRIZ 40 PRINCIPLES MATRIX (FROM SLIDE 13)

- 9 Preliminary anti-action
- 13 "The other way round"
- 21 Skipping
- 25 Self-service
- 36 Phase transitions

10 Preliminary action

15 Dynamics

24 Intermediary

35 Parameter changes

TRIZ principles:
#9.Preliminary anti-action
#10.Preliminary action

"Preliminary tests indicate a substance similar to an unpaid bill."

Researches are focused on fighting bacteria as they develop (by chasing it).

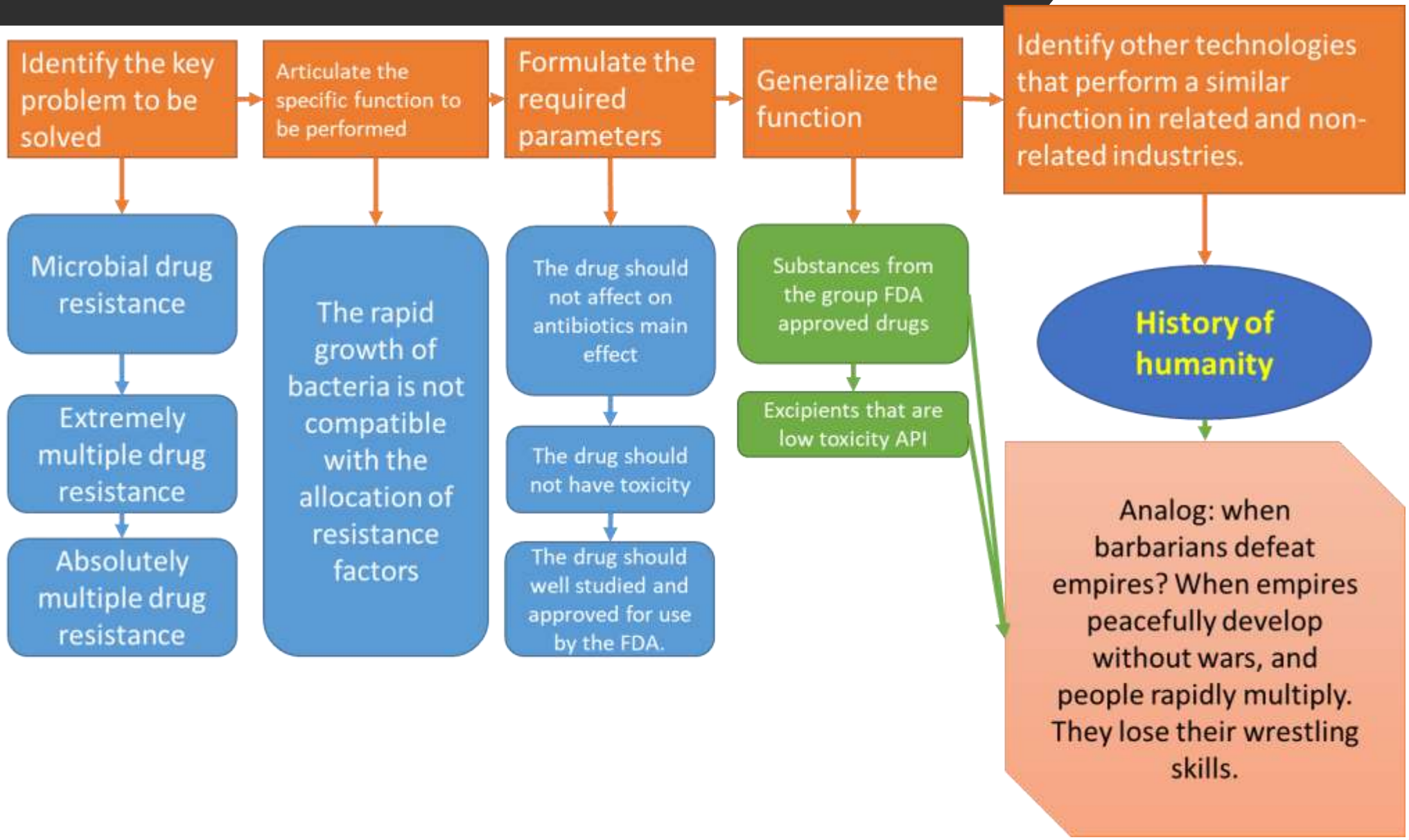
NOIGEL'S novel strategy is to stop bacterial virulence factor, toxin production, and restore antibiotic effectiveness against MDR bacteria.

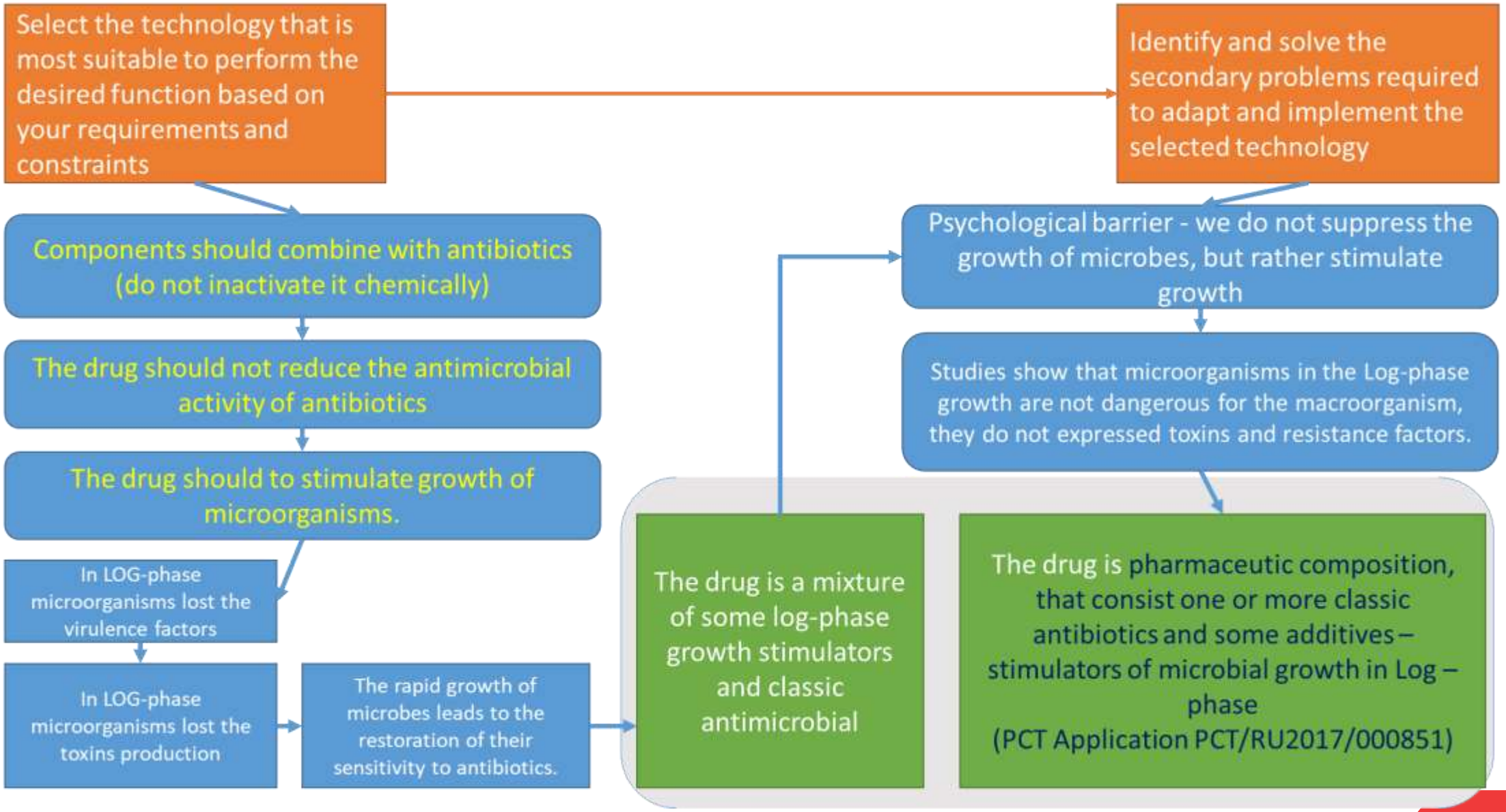
NOIGEL Hypothesis

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

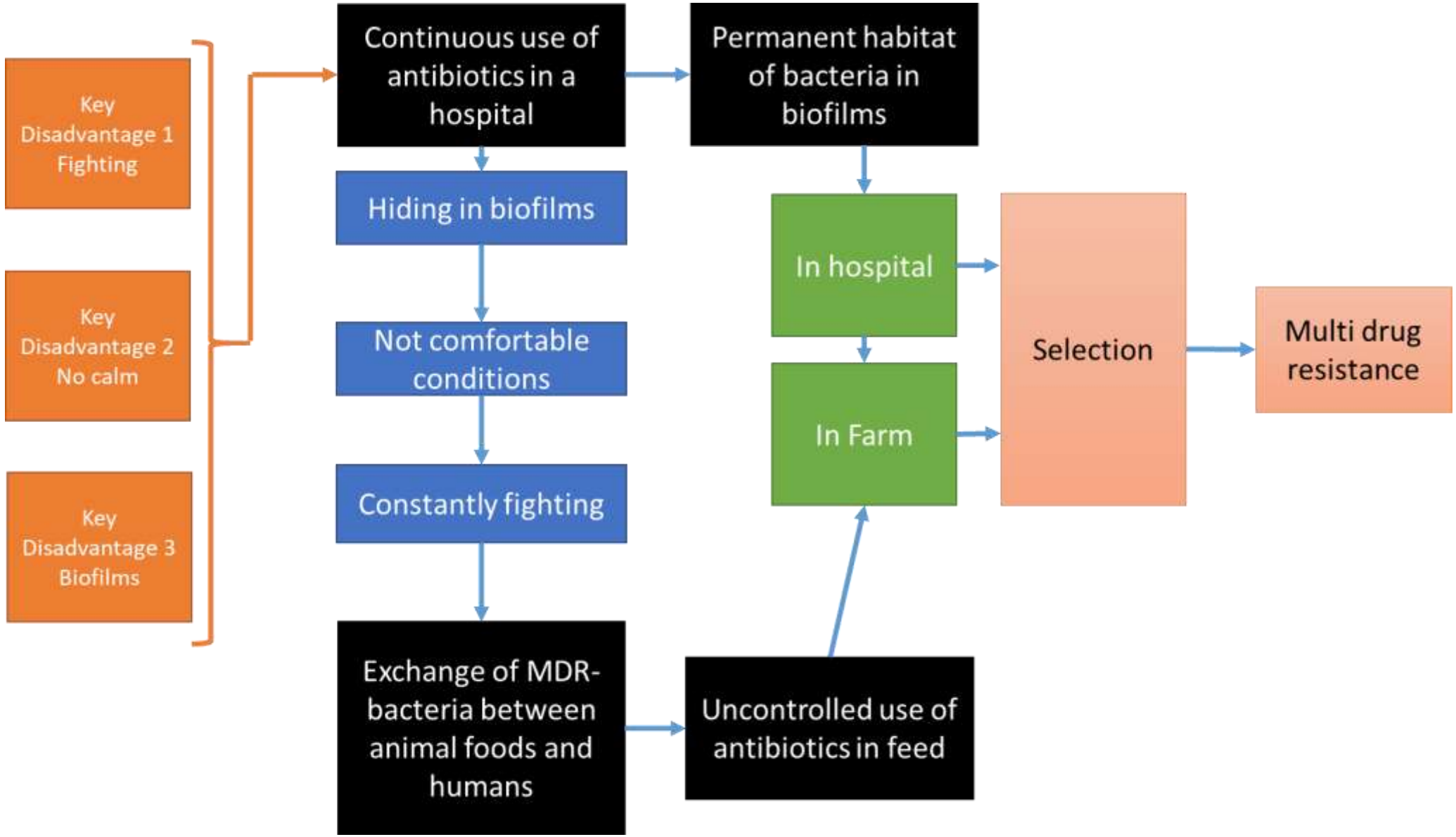
- Make MDR bacteria less harmful.
- Make MDR bacteria sensitive to current and future antibiotics.
- Eliminate and decrease the resistant strains selection process.

Function-Oriented Search for method for restore the sensitivity of bacteria to antibiotics

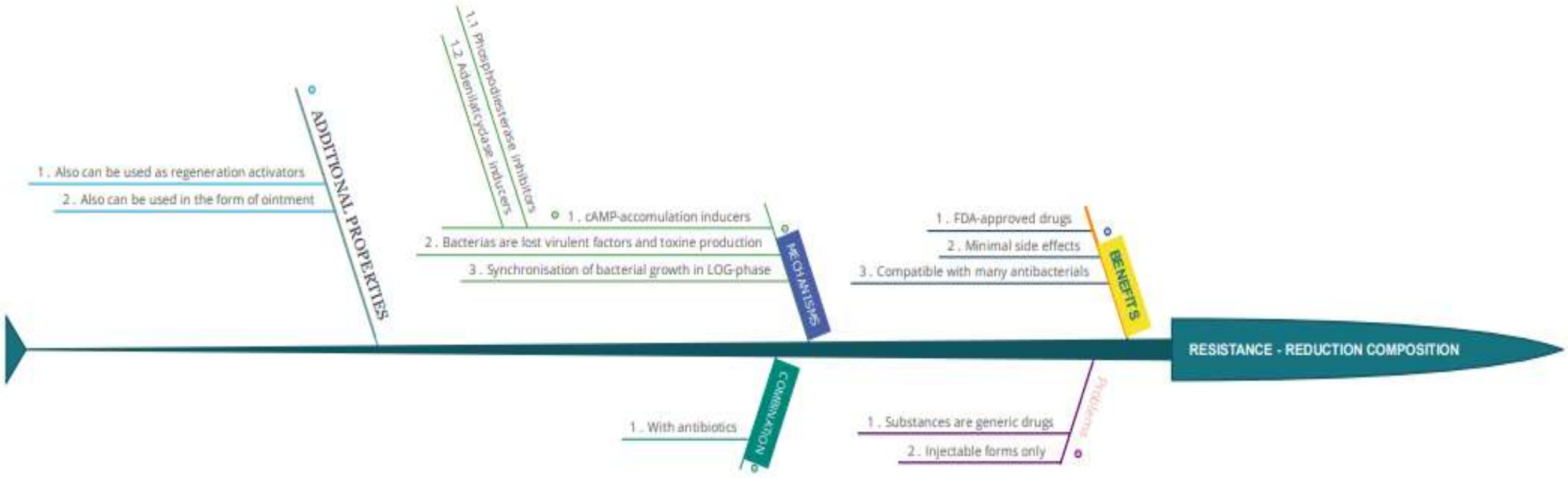


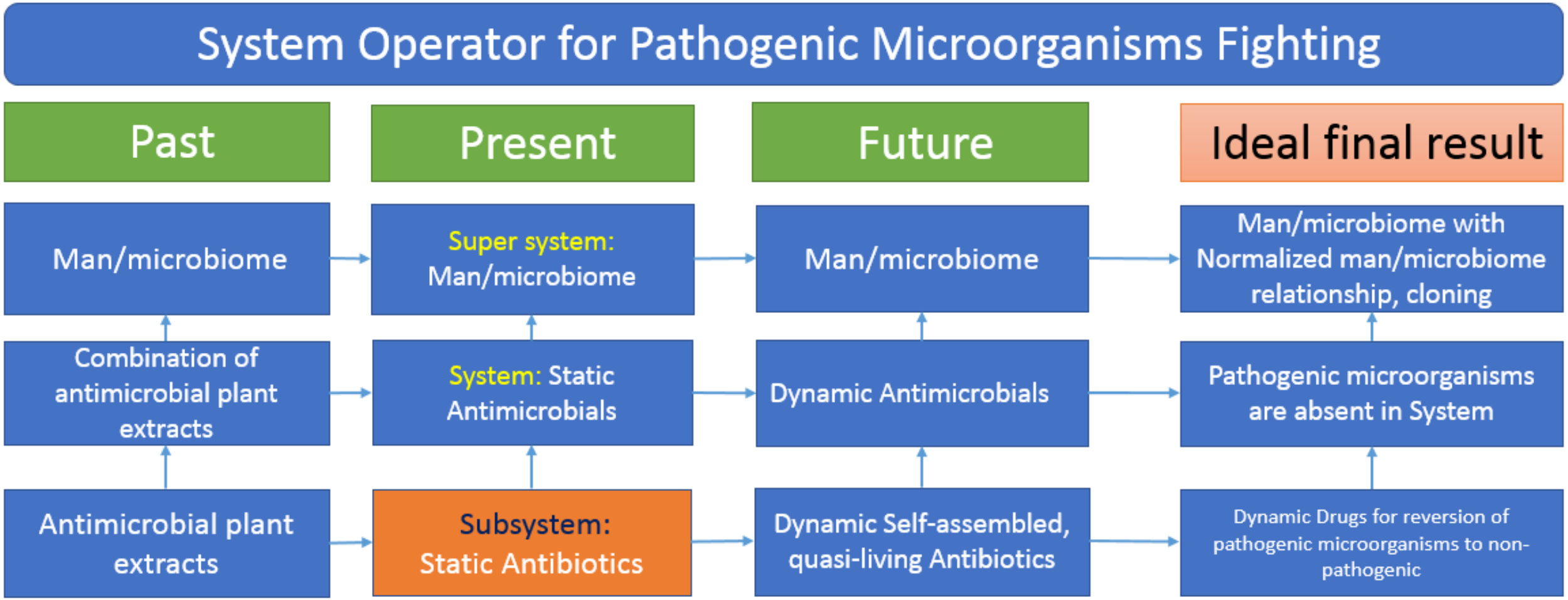

Select the technology that is most suitable to perform the desired function based on your requirements and constraints
Identify and solve the secondary problems required to adapt and implement the selected technology
Components should combine with antibiotics (do not inactivate it chemically)
The drug should not reduce the antimicrobial activity of antibiotics
The drug should to stimulate growth of microorganisms.
In LOG-phase microorganisms lost the virulence factors
In LOG-phase microorganisms lost the toxins production
The rapid growth of microbes leads to the restoration of their sensitivity to antibiotics.
Psychological barrier - we do not suppress the growth of microbes, but rather stimulate growth
Studies show that microorganisms in the Log-phase growth are not dangerous for the macroorganism, they do not expressed toxins and resistance factors.
The drug is a mixture of some log-phase growth stimulators and classic antimicrobial
The drug is pharmaceutic composition, that consist one or more classic antibiotics and some additives – stimulators of microbial growth in Log – phase (PCT Application PCT/RU2017/000851)

Cause-Effect Chains Analysis for Multi Drug Resistance

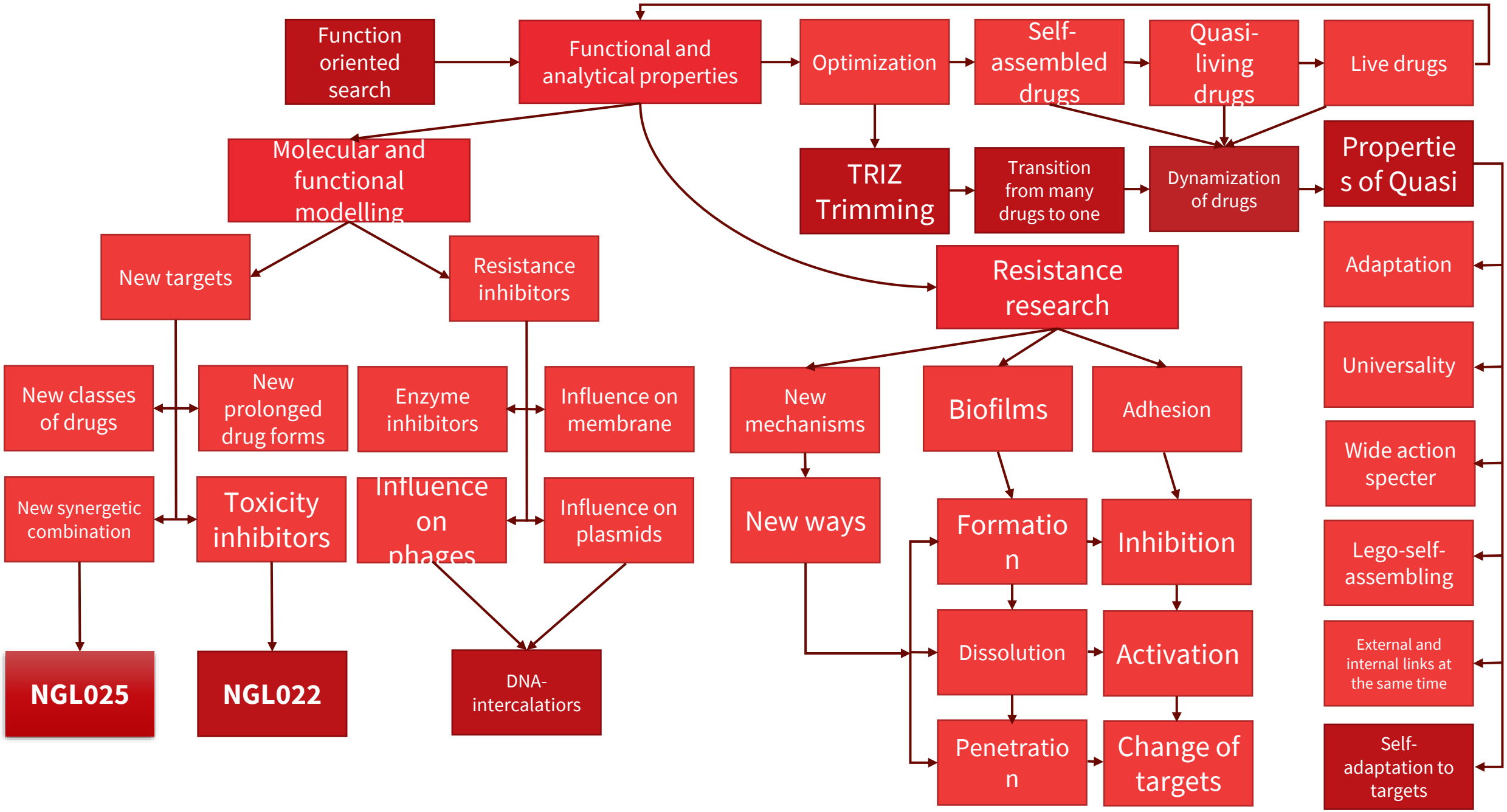


ISHIKAVA DAIAGRAM FOR MDR

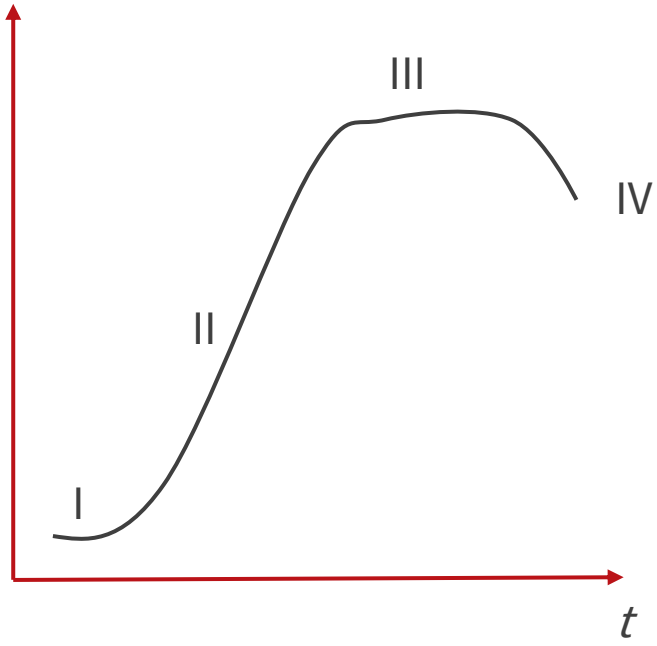



System Operator for Pathogenic Microorganisms Fighting
Past
Present
Future
Ideal final result
Man/microbiome
Super system: Man/microbiome
Man/microbiome
Man/microbiome with Normalized man/microbiome relationship, cloning
Combination of antimicrobial plant extracts
System: Static Antimicrobials
Dynamic Antimicrobials
Pathogenic microorganisms are absent in System
Antimicrobial plant extracts
Subsystem: Static Antibiotics
Dynamic Self-assembled, quasi-living Antibiotics
Dynamic Drugs for reversion of pathogenic microorganisms to non-pathogenic

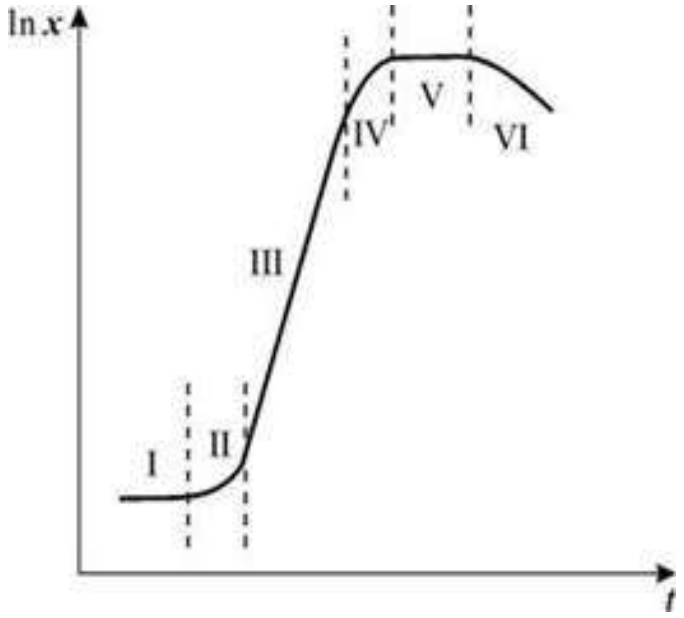
TRIZ structure of the functional-analytical method of improving the system “man - microbiome- environment”



Development cycle of technical systems



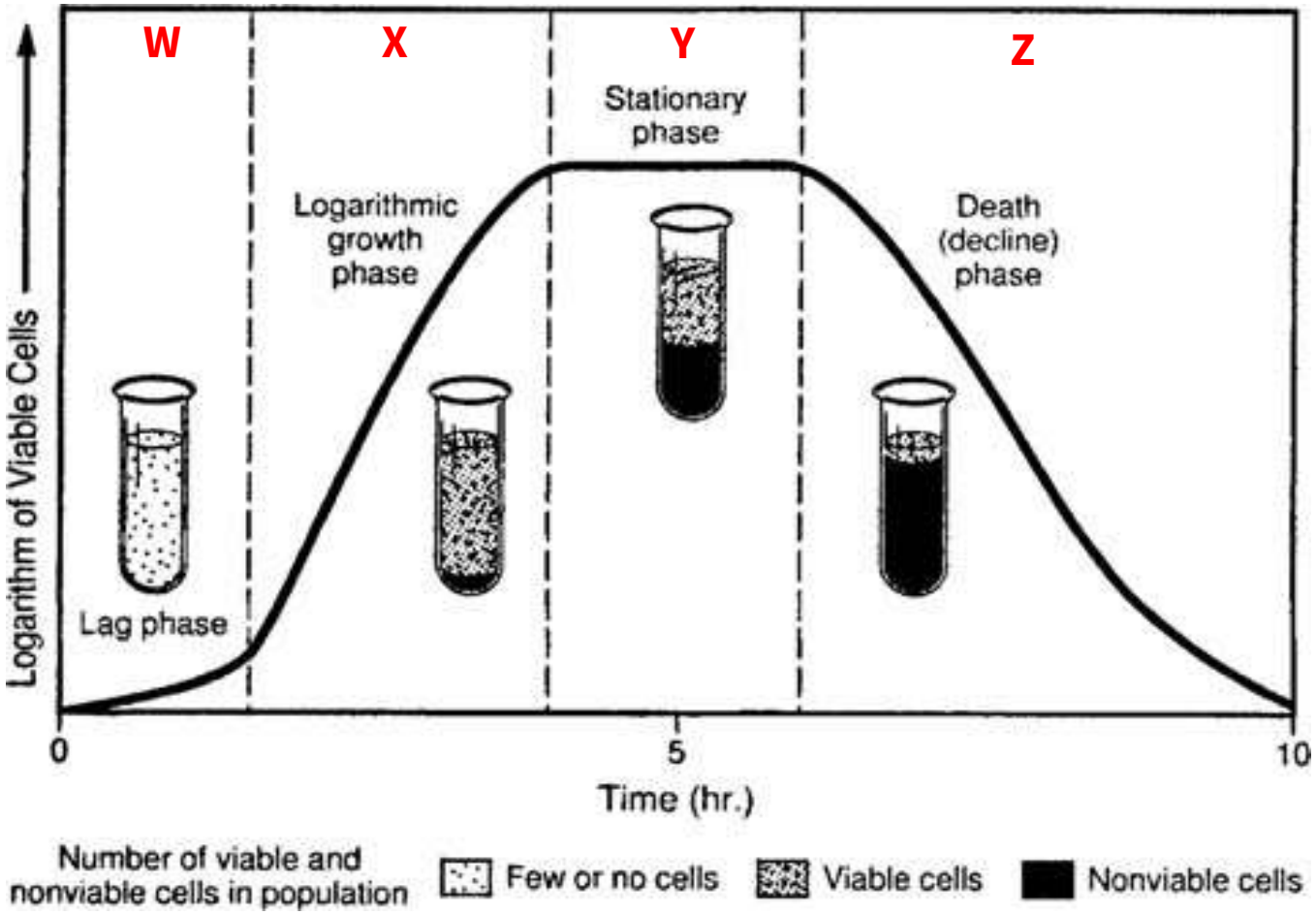
Growth curve of microorganisms in a nutrient medium



The Key to NOIGEL's breakthrough

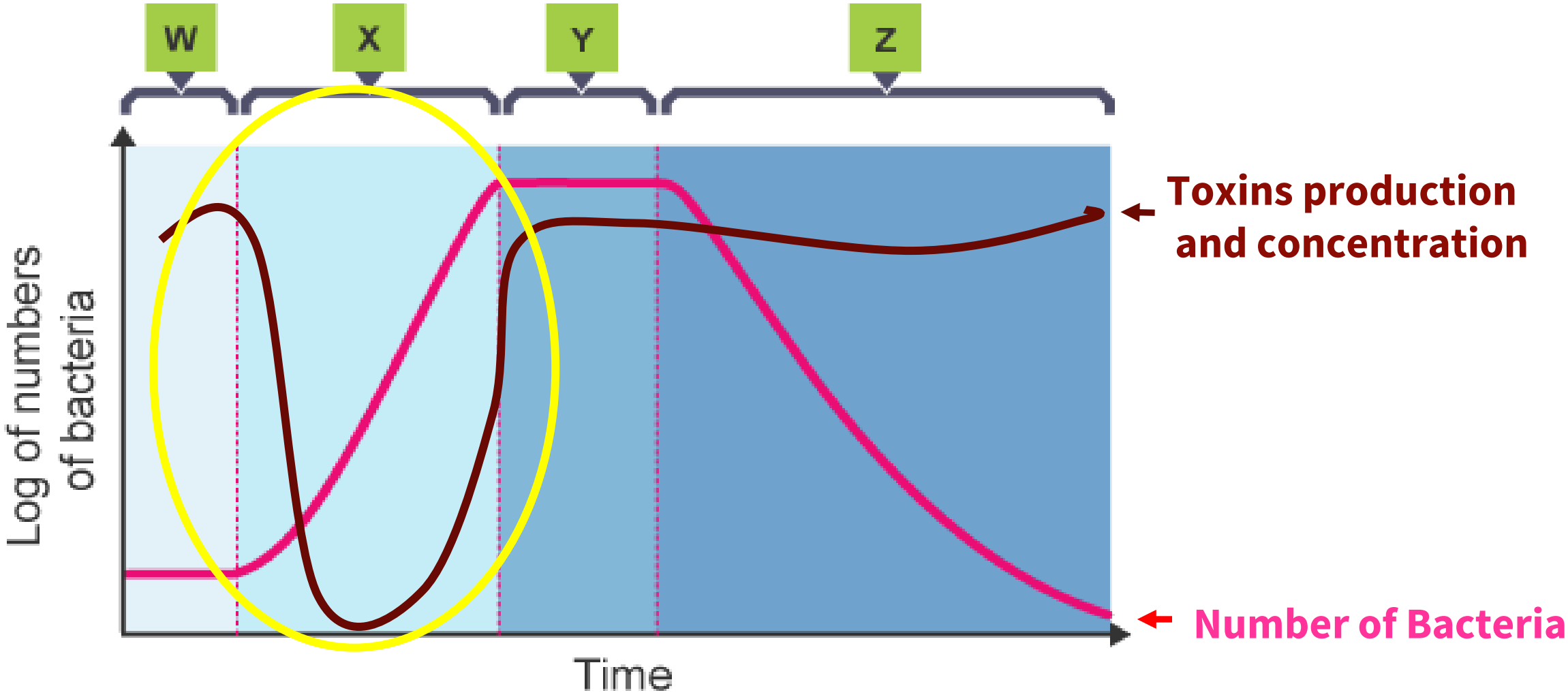
Logarithmic growth-
bacteria in the absence of competition with each other **"dump" the majority of virulence factors and toxin formation.** It also may eliminate factors of acquired antibiotic resistance.

Log phase –
The most receptive phase for treatment with anti-biotics



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

Virulence factors dynamics



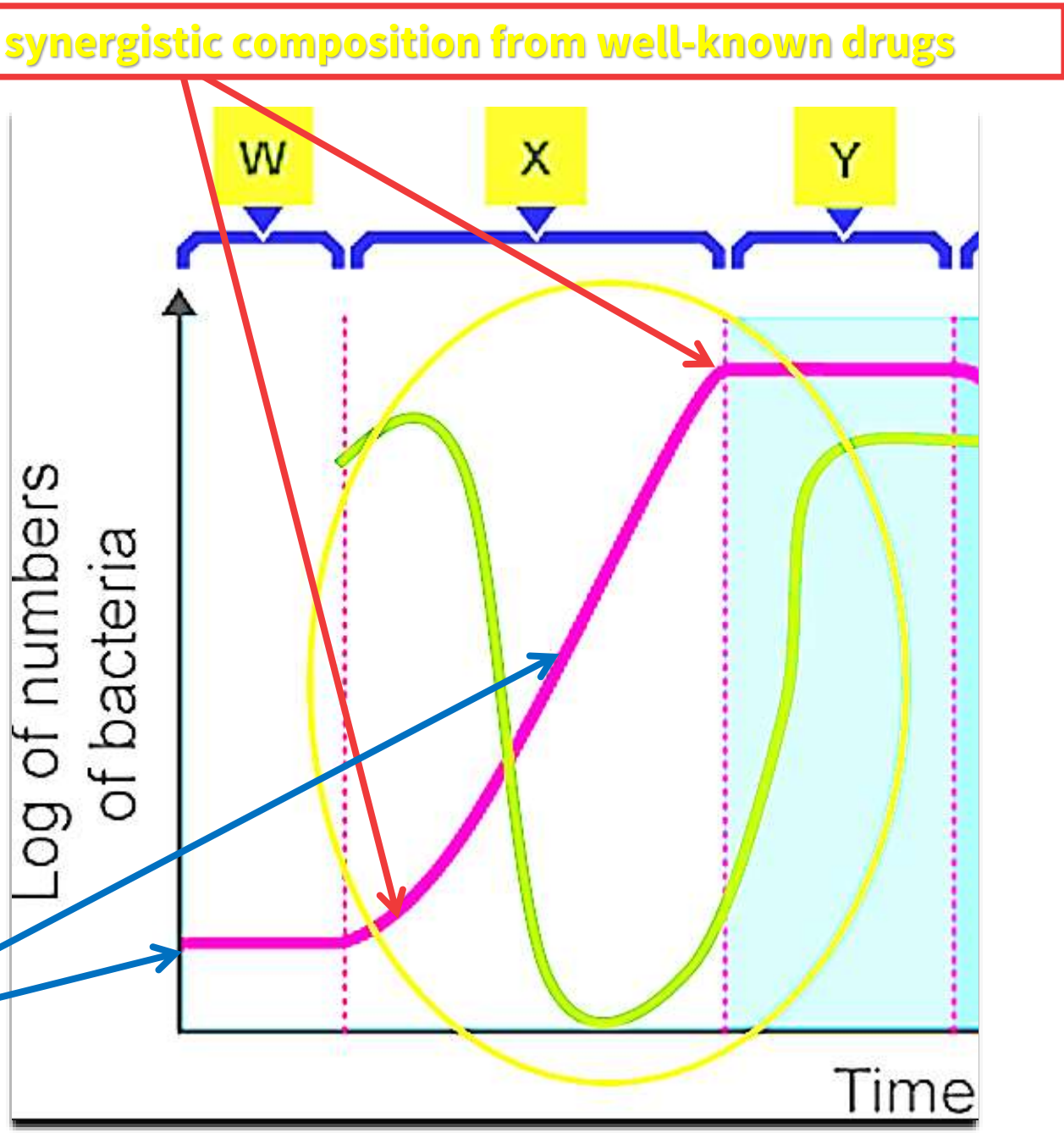
Sivonen, K. (1990). Effects of light, temperature, nitrate, orthophosphate, and bacteria on growth of and hepatotoxin production by Oscillatoria agardhii strains. *Applied and environmental microbiology*, *56*(9), 2658-2666.

Herbert, D., Elsworth, R., & Telling, R. C. (1956). The continuous culture of bacteria; a theoretical and experimental study. *Microbiology*, *14*(3), 601-622.13

What ARE STRATEGIES ?

- Our strategy is to“fool" bacteria in order to eliminate biofilms and to destroy multiresistant bacteria by sending false signals making them think that there is an absence of danger. It will bring to initiation of logarithmic phase of bacterial growth.
- It is well known fact that the intensive growth of the bacterial mass in Log-phase does not cause a release of more toxins, virulence factors or cause a formation of biofilm. Based on this phenomenon, a combination of well known medications and compositions expressed in synergistic effect to stimulate growth of bacteria we were able to find a method to stop bacterial toxicity and

long-known classical antibacterial



BACTERIA “LIFE CYCLE” -STAGE “W”

- At the stage “W”, bacteria that are “armed” with a huge number of factors necessary to “clean up” the habitat of old-timers get to the new place of residence.
- Factors of resistance to antibiotics (analogy - a shield to protect against enemy weapons).

BACTRIA “LIFE CYCLE” -STAGE “X”

- When the “field” at the stage “X” is cleared, the enemies have fallen - it makes no sense to carry a ton of weapons on themselves - there are plenty of nutrients, they can be multipled and spread.
- Bacteria practically lose their ability to secrete exotoxins, antibiotic resistance factors, and adhesion factors.

BACTRIA “LIFE CYCLE” STAGE “X”

- If we add some supplements to the environment the bacteria will rapidly multiply, but the toxin will not be synthesized anymore.
- It is the conditions when the bacterium "feels" itself comfortably and ceases to synthesize virulence factors and is the most interesting for finding the means to combat resistance.

IDEALITY: Right phase, right time

- 1. Bacteria must be constantly in the growth phase of the phase ”X” in order to be sensitive to antibiotics.
- 2. Substances synchronizing bacteria in the phase “X” should not be toxic to the bacteria themselves and to the human body.
- 3. It is desirable that such substances be in the FDA database of well-studied compounds.

Hypothesis

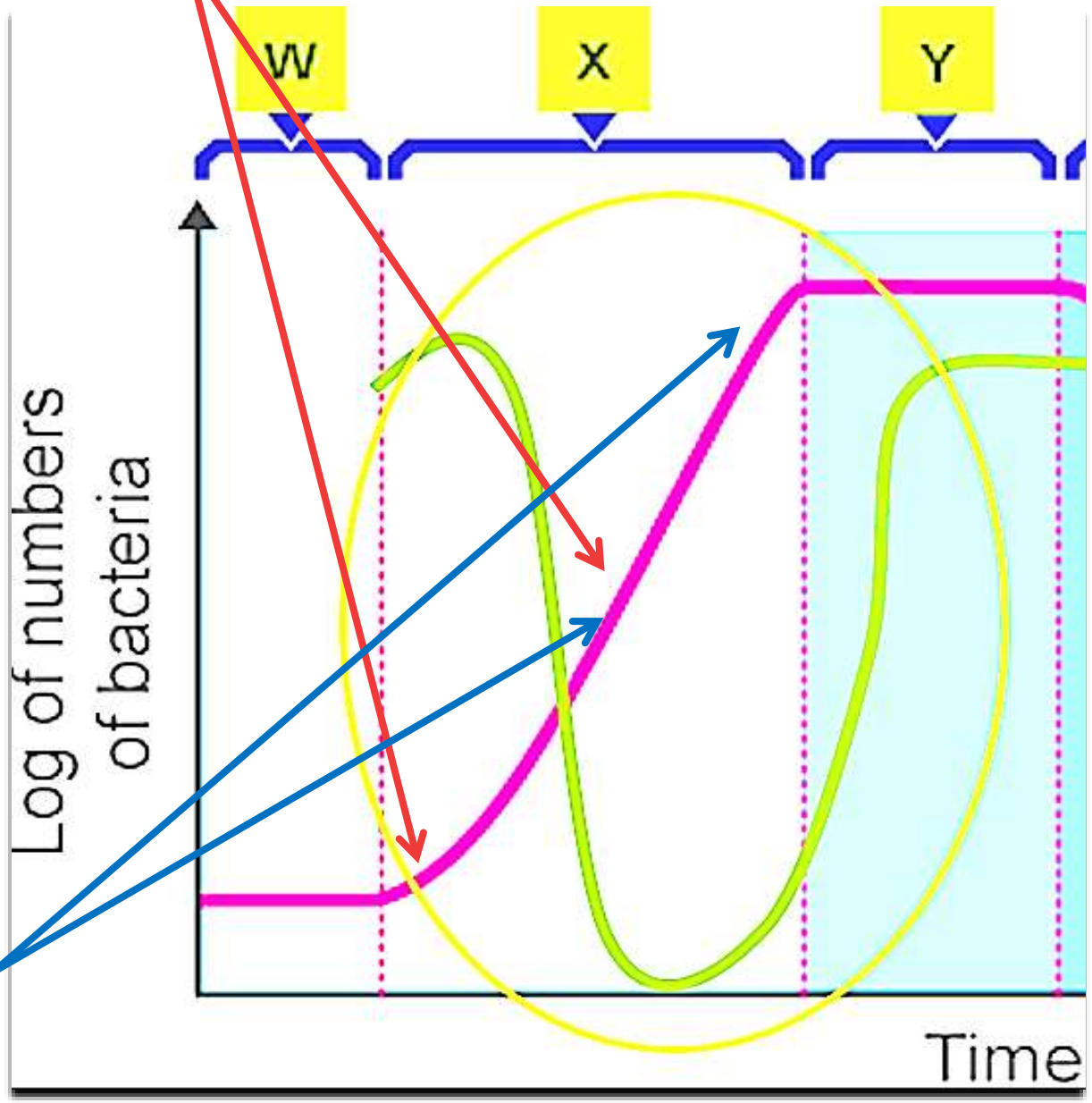
- If during treatment of infectious diseases, we could eliminate the death of microorganisms, we could eliminate the selection process of resistant strains.
- The factors of microorganisms virulence include both exo- and endotoxins and acquired antibiotic resistance factors (like beta-lactamase).
- The loss of toxin production and antibiotic resistance factors make these bacteria is not only less harmful, but also sensitive to antibiotics and eliminate the resistant strains selection process.

What are the Strategies ?

- Our strategy **to "fool" bacteria** in order to eliminate biofilms and to destroy multiresistant bacteria by sending false signals making them think that there is an absence of danger. It will bring to initiation of logarithmic phase of bacterial growth.
- It is well known fact that the intensive growth of the bacterial mass in Log-phase does not cause a release of toxins, virulence factors or cause a formation of biofilm.
- Based on this phenomenon, we have studied a combination of well known medications and compositions expressed in synergistic effect to stimulate growth of bacteria.

- We have developed the method to stop bacterial toxicity and virulence.

Our synergistic composition from well-known drugs



Well known classical antibacterials

A NEW SYSTEM WITH SYNERGISTIC PROPERTIES FROM AVAILABLE RESOURCES

- We have developed pharmaceutical composition from known drugs utilized for other purposes.
- **Instead of killing bacteria,** this composition initiate their fast growth resulting in reduced bacterial protection and virulent abilities.
- **Resulting synergistic** effect is so strong that the concentration of each active component sufficient for growth stimulation is between 0,001% and 0,0001%.

“Reformed” as a result of enhancers bacteria could be quickly killed using known means, these bacteria had prior resistance for.

NOIGEL, LLC

Discovery process of potentiator (NGL025)

- Using TRIZ methodology, NOIGEL discovered the key to fight MDR bacteria lied mainly in synchronizing bacteria to the Log growth phase. In this stage biofilms, toxins and virulence factors are not released.

- NOIGEL set out to discover a compound that would accomplish this goal. 38,000 FDA generic drugs were analyzed and 550 substances were selected for further testing.

- **Discovery NGL025 is a synergistic combination of three substances from the isoquinoline, imidazole, and pyrimidine derivatives classes.** With pronounced bacterial response in minimum concentrations between (0,001% and 0,0001%).

Proof of Concept and Mechanism of Action

- NOIGEL'S composition (NGL025) inhibits phosphodiesterase and activates adenylate cyclase (causing growth synchronization) in a non-toxic manner. These activities cause the inhibition of biofilm and toxin production.

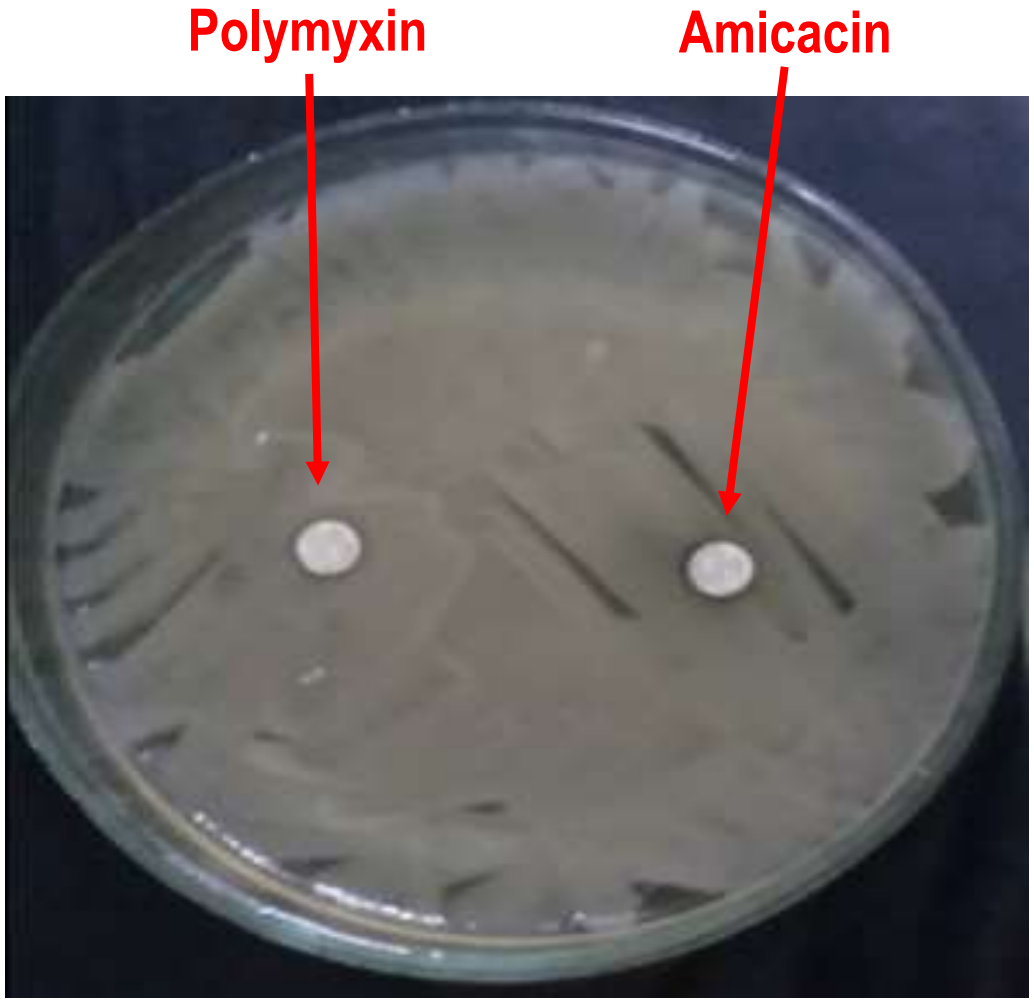
- Unlike current potentaitors, NGL025 effects inhibition of resistance mechanisms, inhibits virulence factors, and at the same time interferes with quorum sensing. As a result of these three mechanisms, antibiotics regain efficacy and are able to kill the bacteria.

- NOIGEL tested co-administration of NGL025 with antibiotics in vitro.

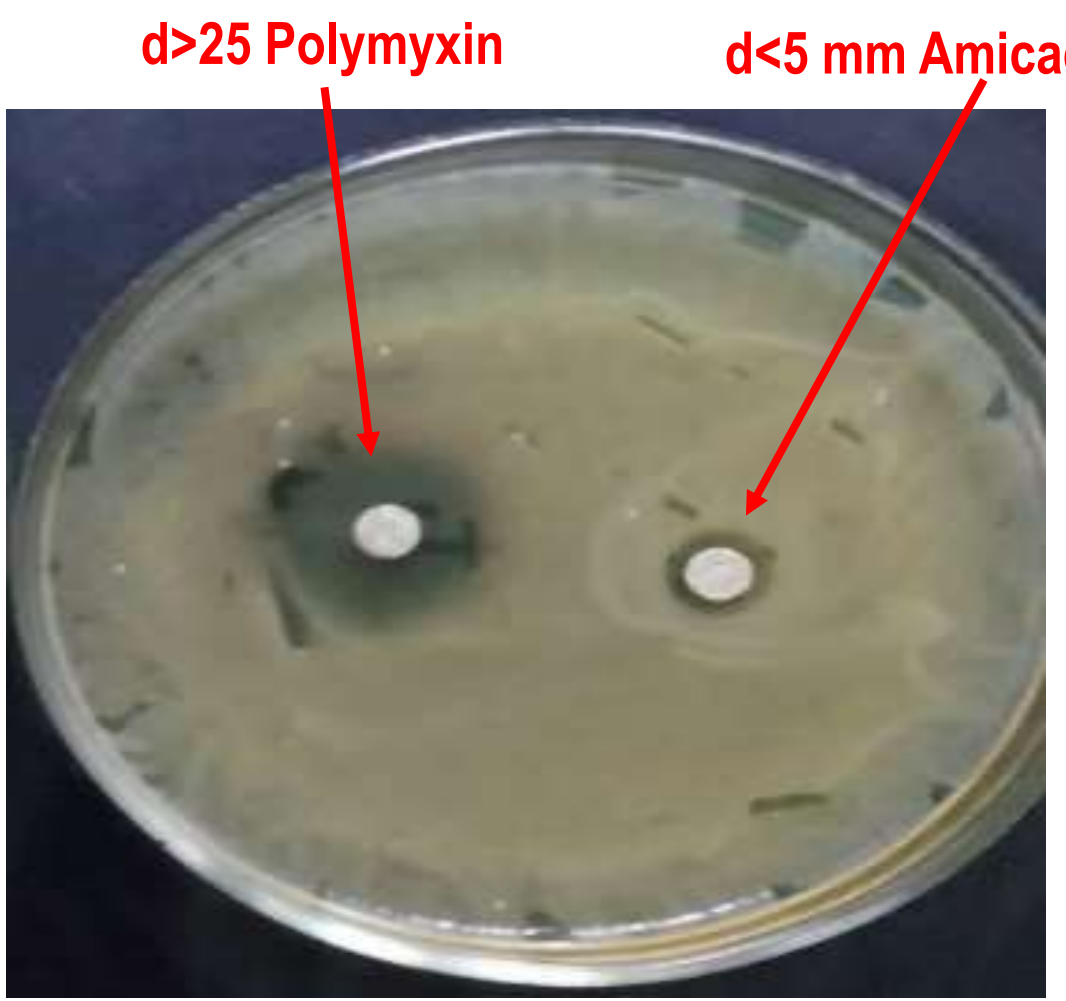
Results of testing

- Slides 17-19 show NGL025 effects in vitro as compared to other widely used antibiotics on their own.
- Slides 20-25 provide data summaries in graph form, showing success of NGL025 in potentiating existing antibiotics.

Effects in vitro NGL025 potentiation on Acinetobacter Baumannii

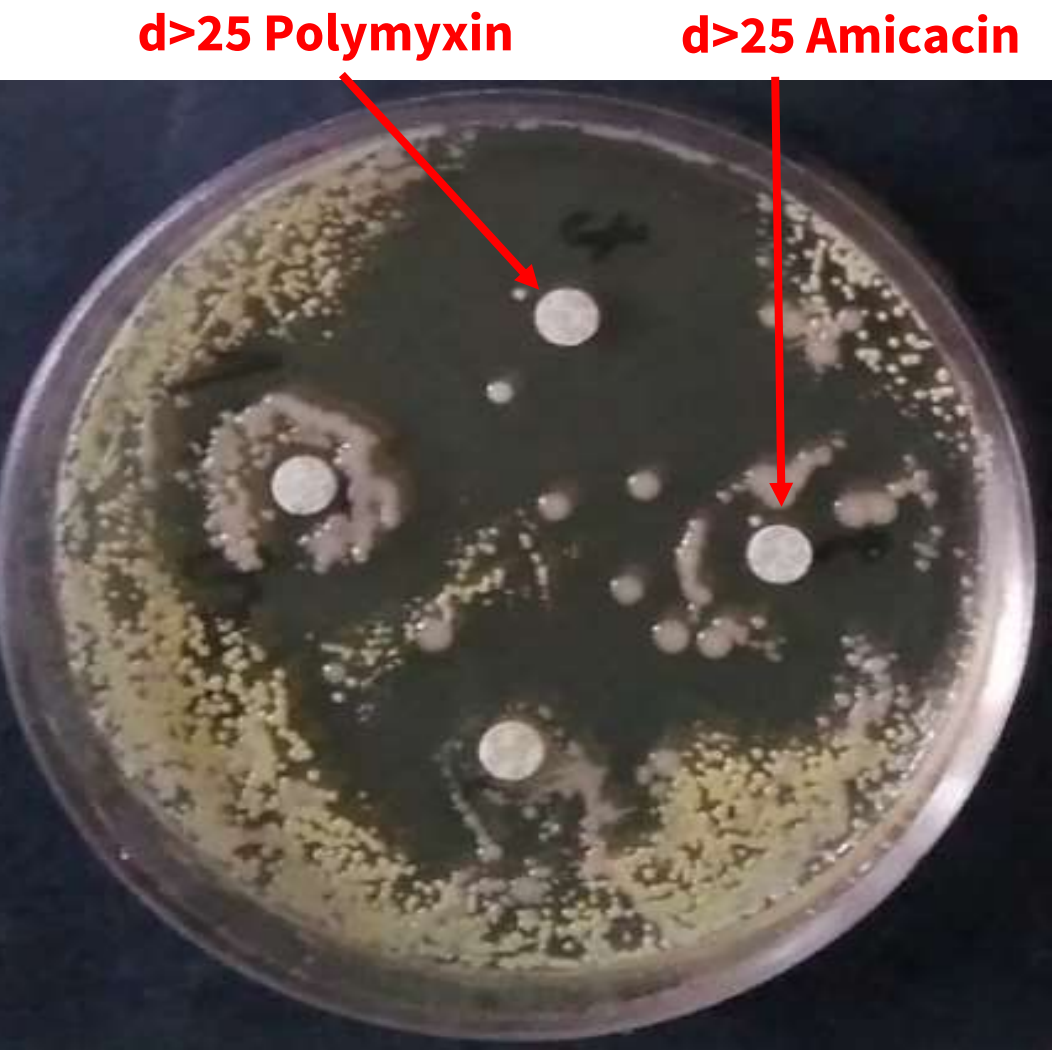


MDR *A.baumannii* growth **without NGL025:** 6 day growth, 2nd passage.

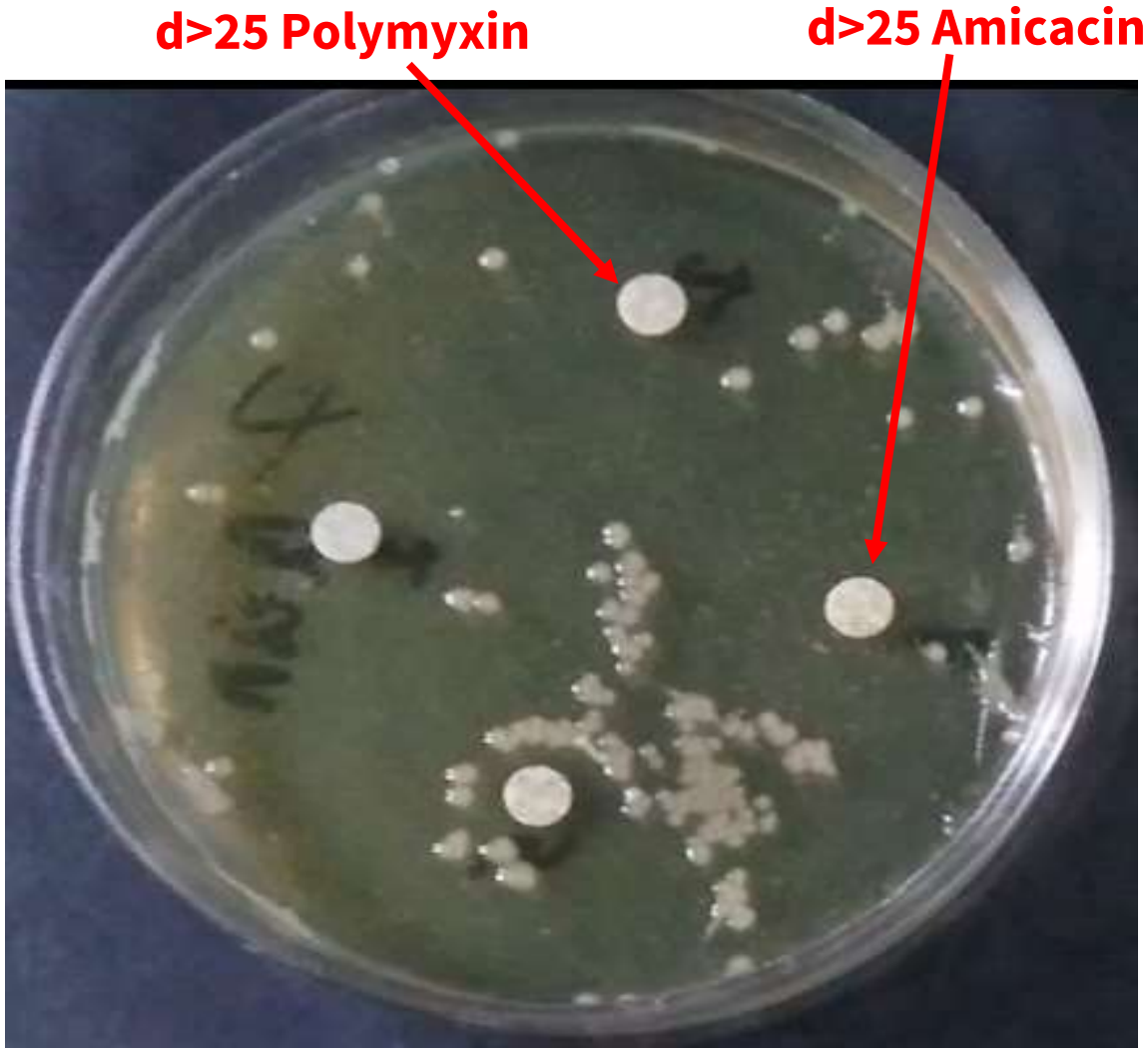


MDR *A.baumannii* growth **with NGL025**: 6 day growth, 2nd passage.

Effects in vitro NGL025 potentiation on Acinetobacter Baumannii

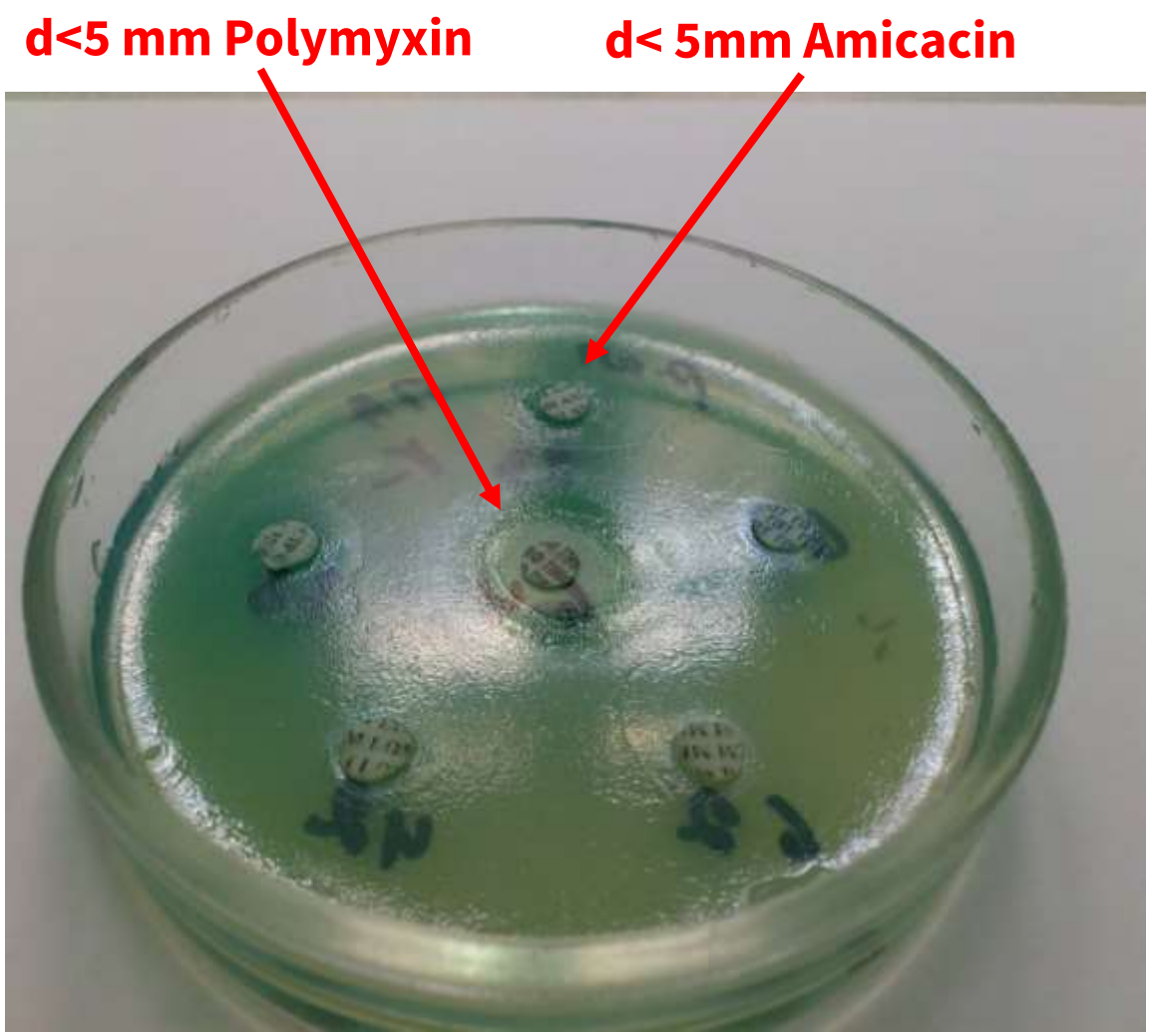


MDR *A.baumannii* growth **with NGL025:**
9 day growth, 3rd passage.

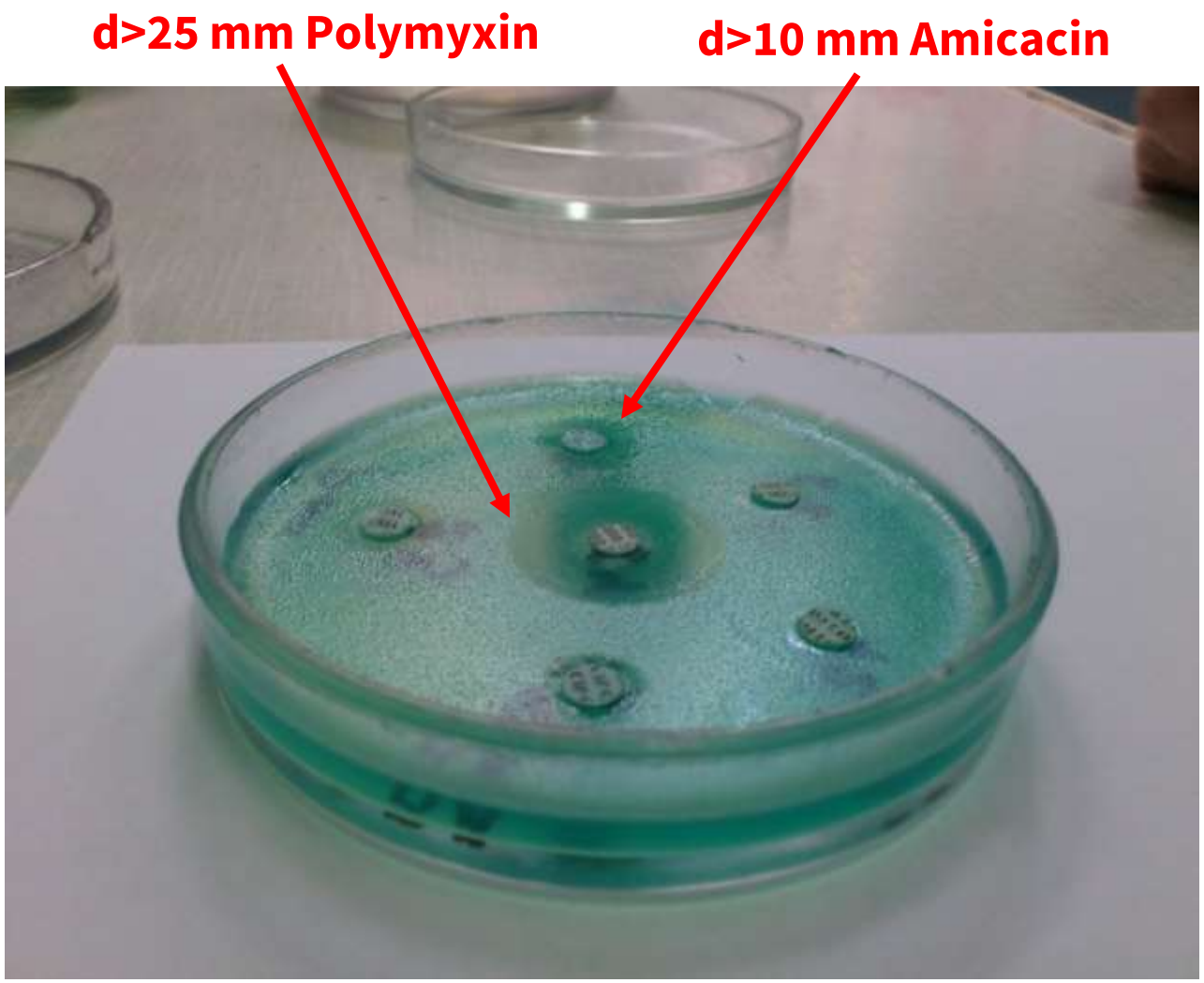


MDR *A.baumannii* growth **with NGL025:**
12 day growth, 4th passage.

Effect in vitro NGL025 potentiation on MDR strain *Pseudomonas aeruginosa*



P. aeruginosa IMI2 **without NGL025** 3day growth,1st passage



P. aeruginosa IMI2 **with NGL025** 3 day growth,1st passage

Potentiators suppressing adhesive properties of *P. aeruginosa*

Potentiators	Adhesion index (AI)		
	***Pseudomonas aeruginosa* ATCC 27853**	***Pseudomonas aeruginosa* ATCC 9027**	***Pseudomonas aeruginosa* 12-76**
0.01±0.005 % A	2.6±0.3*	3.4±0.2*	3.5±0.3*
0.01±0.005 % B	2.5±0.2*	3.5±0.2*	3.5±0.3*
0.01±0.005 % C	2.6±0.2*	3.3±0.2*	3.6±0.3*
0.001±0.0005% A	2.6±0.3*	3.4±0.1*	3.7±0.4*
0.001±0.0005% B	2.7±0.4*	3.6±0.3*	3.8±0.3*
0.001±0.0005% C	2.4±0.4*	3.5±0.3*	3.7±0.3*
0.01±0.005% A 0.01±0.005% B 0.01±0.005% C	**1.4 ± 0.3***	**1.5 ± 0.3***	**1.4 ± 0.3***
0.001±0.0005 %A 0.001±0.0005 %B 0.001±0.0005 %C	**1.8 ± 0.2***	**1.9 ± 0.4***	**1.7 ± 0.4***
Control	**3.2 ± 0.3**	**3.1 ± 0.3**	**3.2 ± 0.3**

Table Comparative adhesive properties (IA) in *P.aeruginosa*
*Notes: * - (p <0.05)*

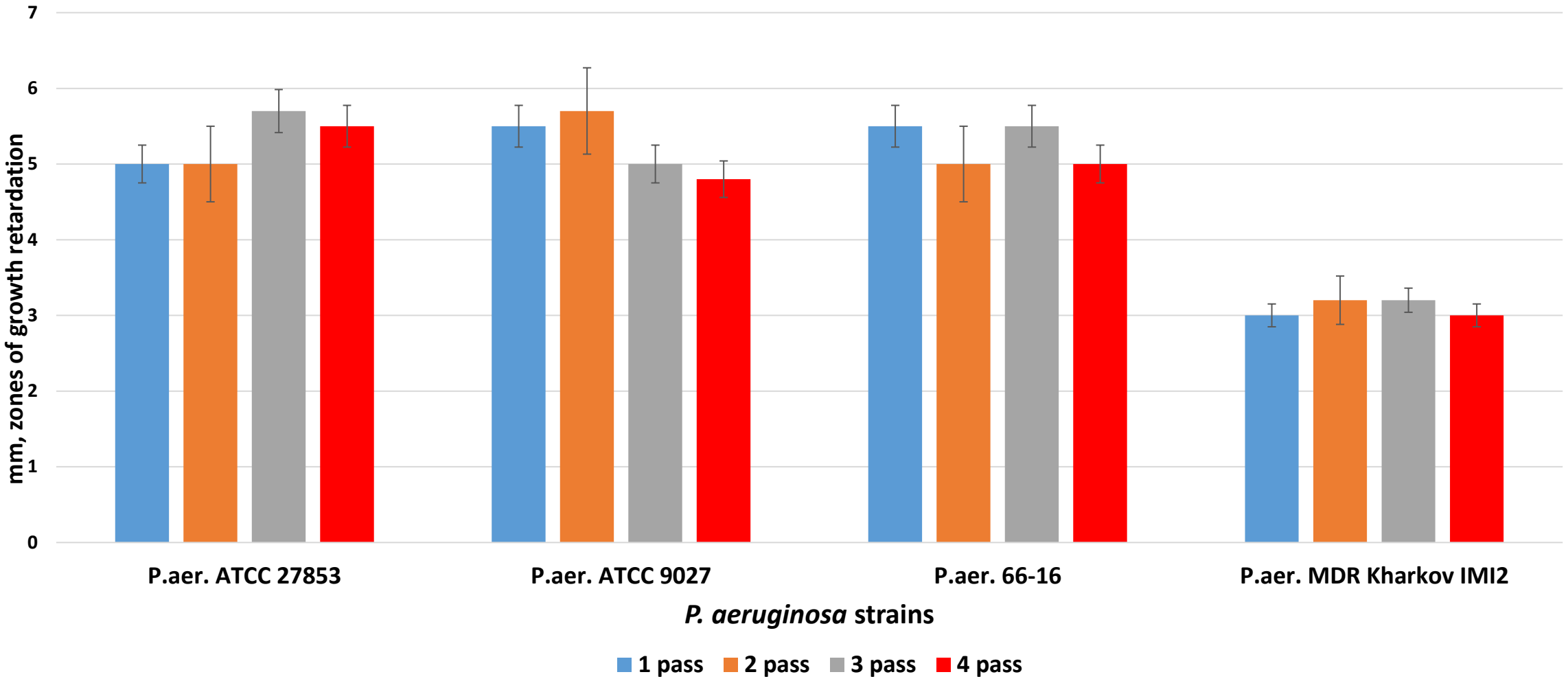
Potentiators and microbial growth

Table -Number of microbial cells P. aeruginosa after influence of potentiators combination on at a dose of inoculum 10^6

Nutrient media - packed red blood cells			
Potentiators, concentration	***Pseudomonas aeruginosa* ATCC 27853**	***Pseudomonas aeruginosa* ATCC 9027**	***Pseudomonas aeruginosa* 66-16**
	N ± n	**N ± n**	**N ± n**
0,01±0,005 % B 0,01±0,005 % C	4,2 ± 0,5*	4,8 ±0,7*	4,7 ± 0,7*
0,01±0,005 % A 0,01±0,005 % B 0,01±0,005 % C	5,3 ± 0,7*	5,4 ±0,8*	5,8 ± 0,5*
0,001±0,0005 %A 0,001±0,0005 % B 0,001±0,0005 %C	**6,2 ± 0,6***	**6,4 ±0,7***	**6,3 ± 0,5***
Control	**2,2 ± 0,1**	**3,1 ±0,2**	**2,8 ± 0,1**

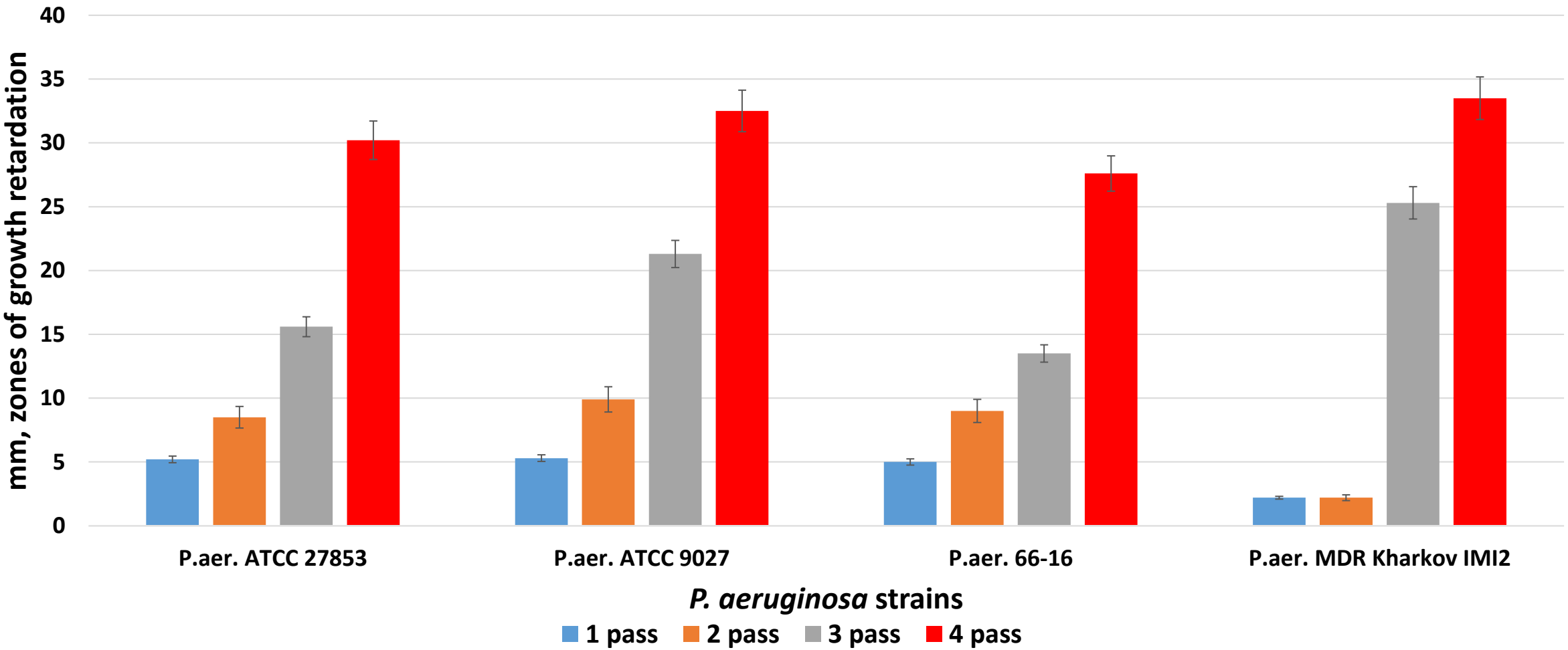
Notes: N - the average number of microbial organisms billion / ml, n - the average deviation,A -, B -,C - synergistic composition of potentiators, * (p <0.05).

P. aeruginosa zones of growth retardation by Polymyxin **without** NGL025



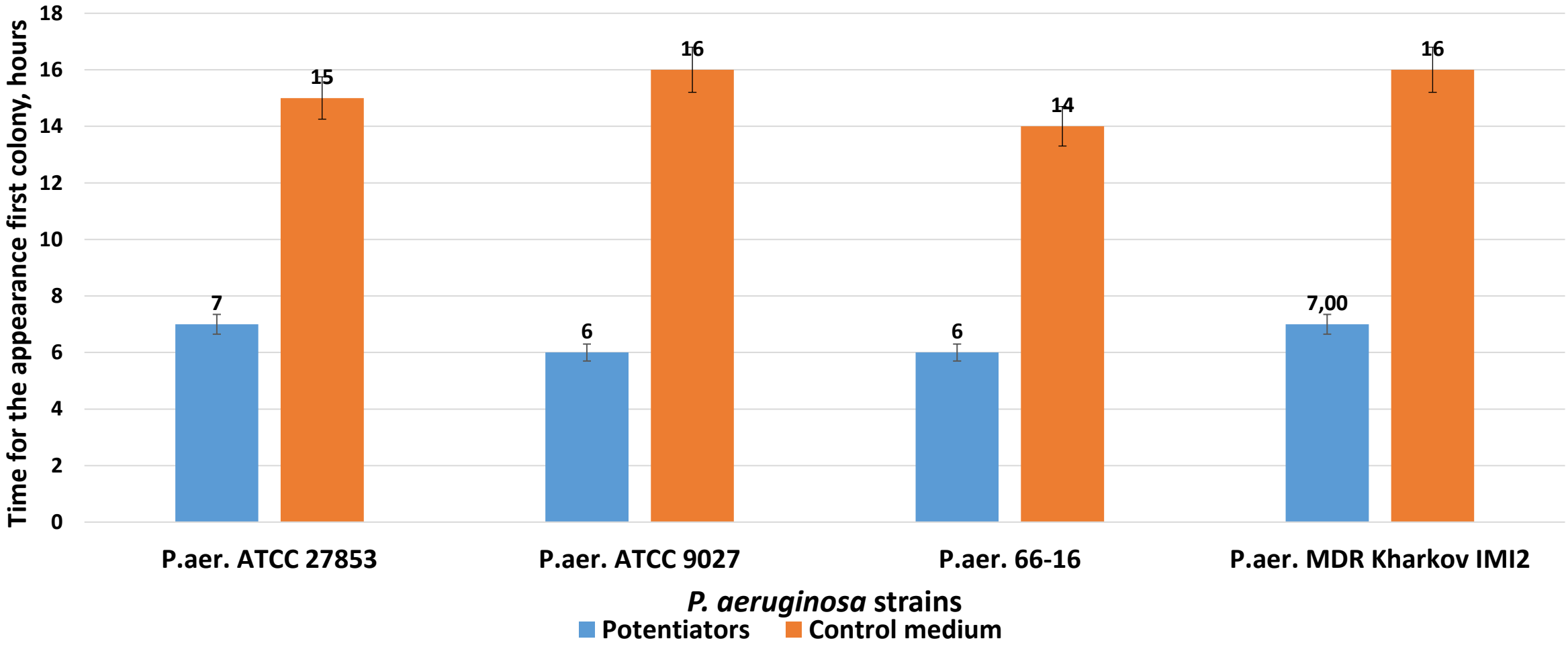
Notes: n=6 for each studies, P<0,05. Stat.hypothesis (dispersion analysis) it is differences between *P. aeruginosa* sensitivity to polymyxin at classic medium **without** **NGL025**

P. aeruginosa zones of growth retardation by Polymyxin with NGL025

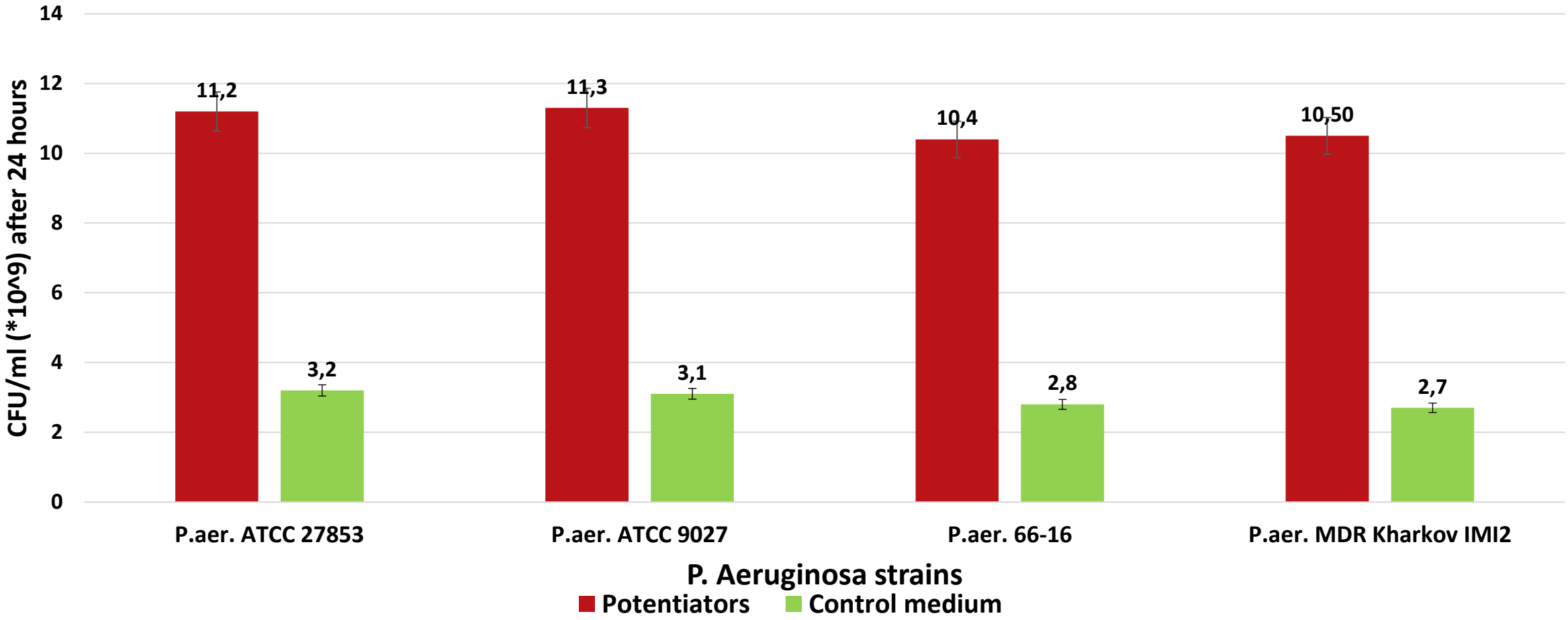


Notes: n=6 for each studies, P<0,05. Stat. hypothesis (dispersion analysis) it is presence differences between P. aeruginosa sensitivity to polymyxin at medium **with NGL025** along some passages.

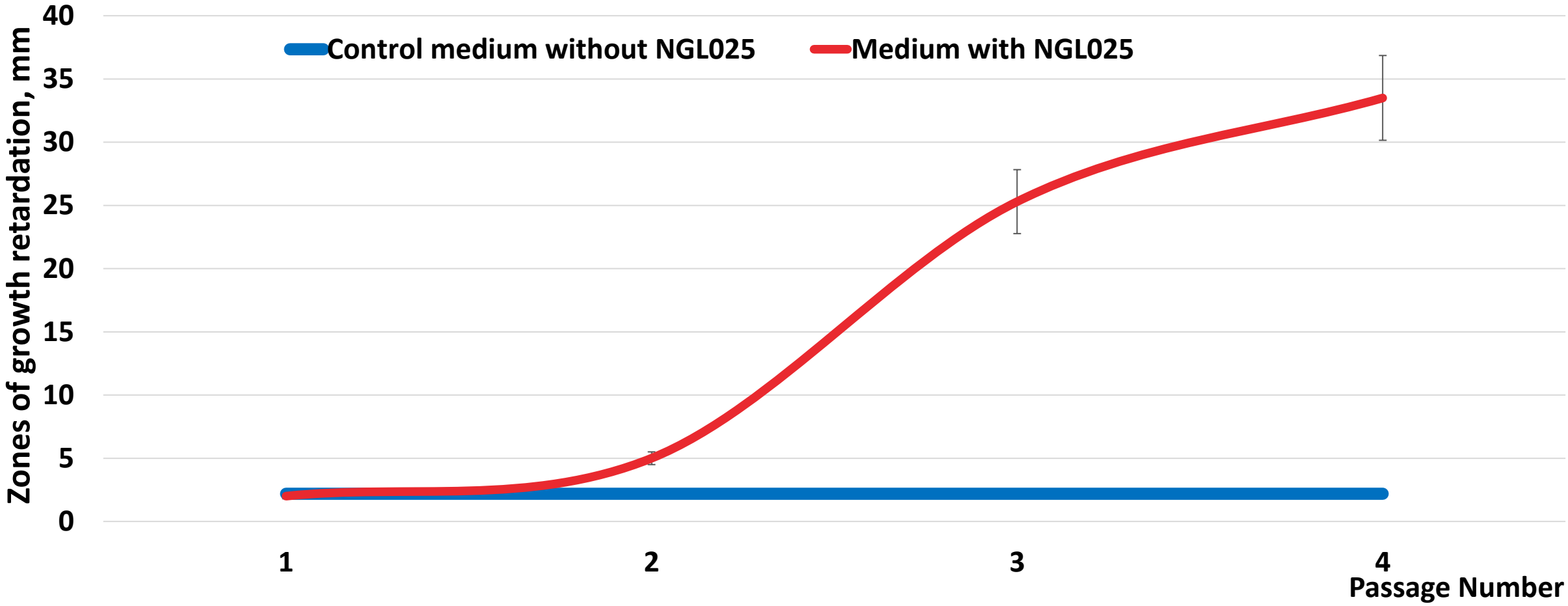
NGL025 potentiation based on *P. aeruginosa* growth



Quantity of microorganisms after 24 hours of incubation in vitro.

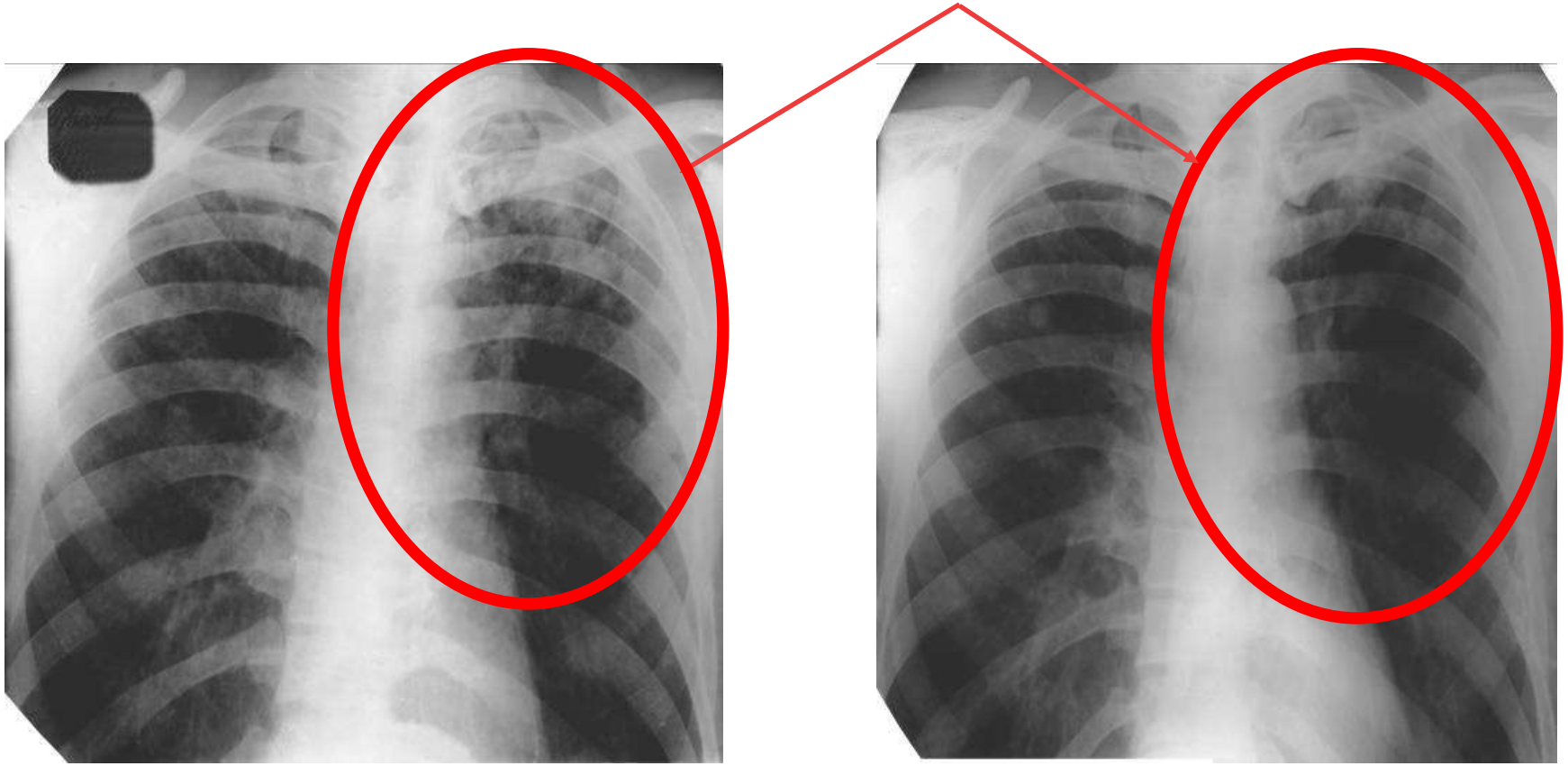


Dependence between *P. aeruginosa* growth retardation by Polymyxin with NGL025 and without




WHEN WE TESTED THIS DRUG ON MICE, NOBODY NOTICED ANY SIDE EFFECTS.
SCHWADRON

Clinical case of active MDR pulmonary TB



There has been a positive result: on the radiograph in the upper parts of both lungs there was a significant resorption of focal and infiltrative shadows cavity of the lung, tissue decay was not detected.

HRZE- (isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E))

Patient 42 years old male was diagnosed with active MDR pulmonary tuberculosis. Patient received first and then second-line drugs therapy according to WHO criteria : (HRZE) , and second line later generation quinolones, ethionamide etc. He had poor response on standard therapy.

Patient was given enhancers intravenously in 500cc 0.9%NS once a day for 3 days and then he continued HRZE therapy. After 15 day of therapy cough, SOB and low grade fever subsided, patient's symptoms improved. CXR was done and compared prior to enhancers therapy as shown above . Patient had clinical and radiological improvement. Patient followed within a year with no recurrence.

Snapshot of NGL025 activity

Successful results in vitro studies NGL025 as of October 2018:

Microorganisms of target:

- *Pseudomonas aeruginosa,*
- *Acinetobacter baumannii*
- *Klebsiella pneumonia,*
- *Proteus vulgaris*

Antimicrobials with restored sensitivity to MDR bacteria:

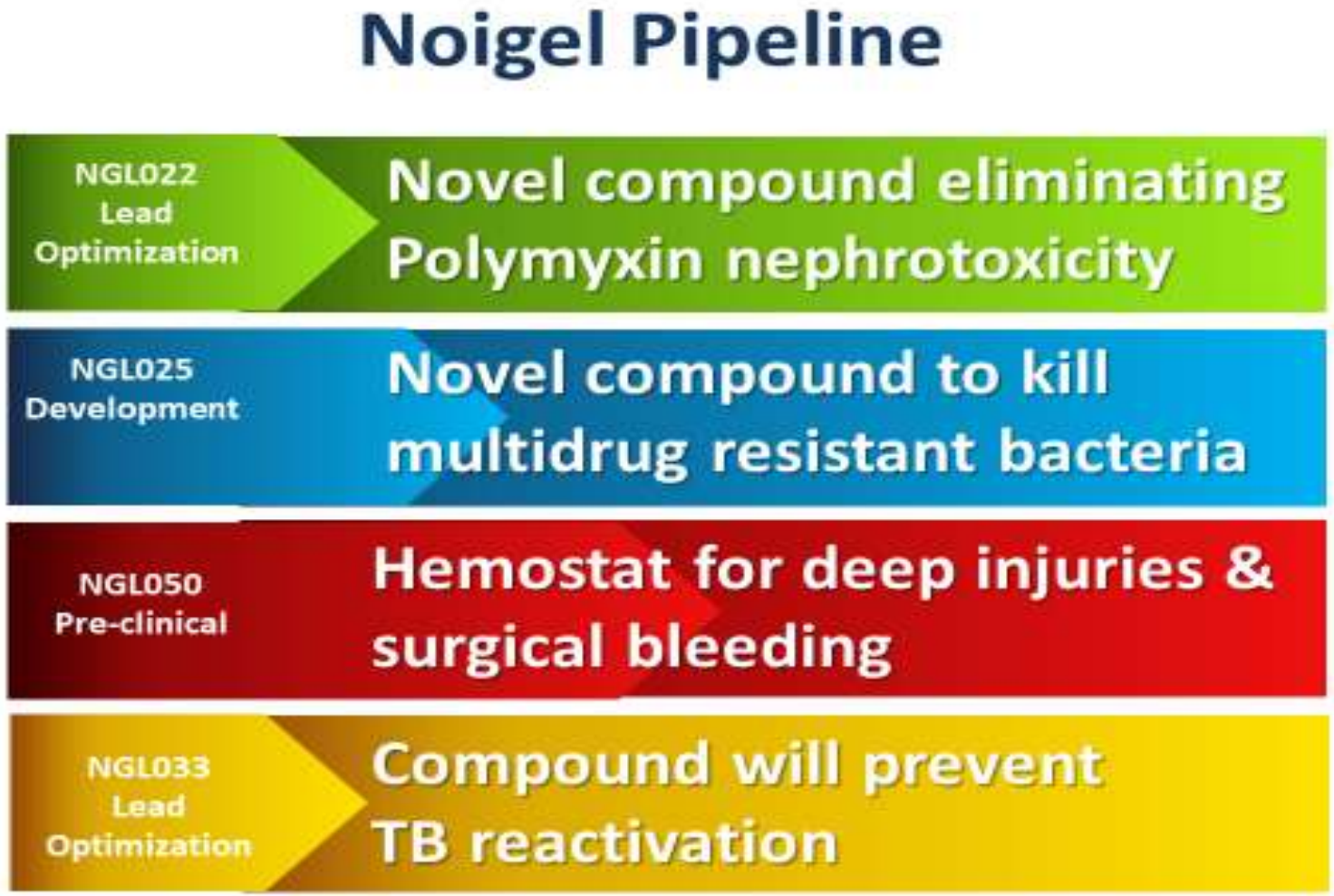
- Polymyxin
- Amikacin
- Fluoroquinolone groups

Next planned MDR microorganisms as a target:

Staphylococcus, Candida albicans, Enterococcus, Enterobacteriaceae, Escherichia coli, Mycobacterium tuberculosis.

NOIGEL's ongoing pipelines

Company R&D snapshot



A conservative structure: Statics

- A conservative structure of a classical drug (like one“key”) cannot match a specific receptor (“many different, though similar, locks”) in all individuals of one species equally and with equal affinity.
- Increase drug effectiveness, related to enhance the concept of drug development and approaches to this process

Some disadvantages of Classic (static) drugs.

1) **Static** conservative chemical structures.

2) The presence of a “slippage effect” (change in the receptor sensitivity and response to the same medication over time) :

a) Diminished or loss of efficacy drugs over the time treating Hypertension, Diabetes etc.

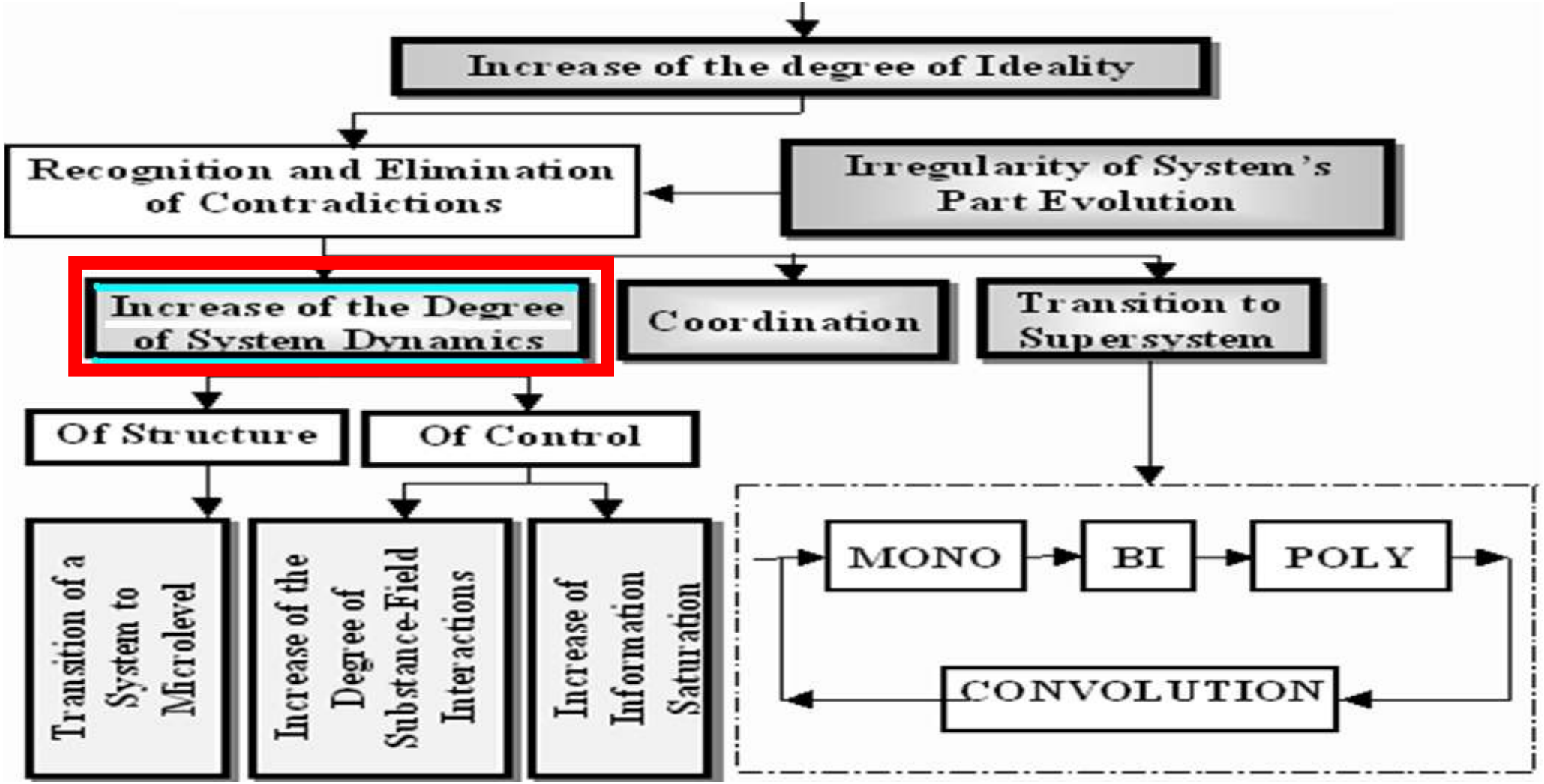
b) The Multidrug resistant (MDR) infections due to antibiotics inability to adapt to new receptors and new microorganisms defense factors and mutations as result antibiotic function develop **“slippage effect”.** Similar development tumor resistance to therapy over time observed in oncology related to chemotherapeutic drugs **“slippage effect”.**

"Don't forget to take a handful of our complimentary antibiotics on your way out."

Line 2

New generation of drugs with dynamic structures (Dynamic drugs) based on TRIZ (5 Projects)

LAWS OF BIO-TECHNICAL AND BIO-MEDICAL SYSTEMS EVOLUTION



Evolution of medicine / pharmacy

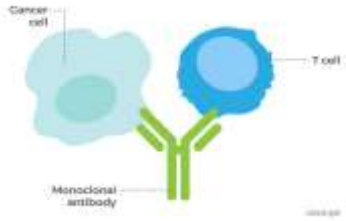
1. Drug dynamization - drugs with elements of a living organism that can adapt to the disease and the body of a particular person (an example is the antiviral drug Albuvir, highly effective for treating more than 20 viral infections in animals and humans, registered as a veterinary medicinal product in Ukraine)

2. Personalization of treatment - when each individual person is given vaccination and complex complex treatment with small doses of different drugs on the basis of a whole range of diagnostic procedures, and the same drug is not massively prescribed to all patients in a high dose according to the standard protocol.

3. The advantage will be given to means of prevention, rather than treatment. For example, vaccinating against the same COVID-19 is cheaper than burying. You can also use tools to rejuvenate a healthy body and restore immunity in a healthy body, maintaining it in good shape. Preventing the onset of disease, not curing disease, this will be a new trend. Priorities will shift to the effects of drugs on a healthy body, not on a sick one. Accordingly, the methods of clinical trials will undergo significant changes, as healthy people without illness are not in the clinic. Such methods have not yet been developed, and the response to vaccines is not perfect, a high level of antibodies in response to the vaccine is sometimes dangerous for the body itself (for example, with the Ebola virus and HIV virus).

4. Many doctors are beginning to return to old, long-tested drugs that have been forgotten in the pursuit of expensive, patented, but not very effective means. This picture is observed for antihypertensive drugs. Many expensive asartans proved to be ineffective, while banal amlodipine, even in monotherapy, was more effective in combination with other patent expiration remedies. The same picture is with antiulcer drugs - 5 generations of proton pump inhibitors, starting with omeprazole, turned out to be equally effective with the penny drug famotidine, which is used to treat almost all of Asia. The resurrection of old drugs in new combinations will be revived.

1. Pharmaceutical companies are reorienting to biological products that do not produce toxic metabolites at all - immunoglobulins and peptides (because mabs) and targeted drugs (because mibs) that act in very small doses and selectively on one enzyme. The effectiveness of the latter was not very justified and did not pay off (they are expensive, the efficiency drops sharply due to the polymorphism of receptors within the population and the difference between enzymes between races).



2. Auto vaccines will be manufactured in micro-factories the size of a printer within a day for a specific person. For example, if a person is sick with pseudomonosis, then a sample of bacteria will be introduced into the device, and on the second day, the ampoules with an auto vaccine for treatment in a specific person and with a specific strain will already be output.

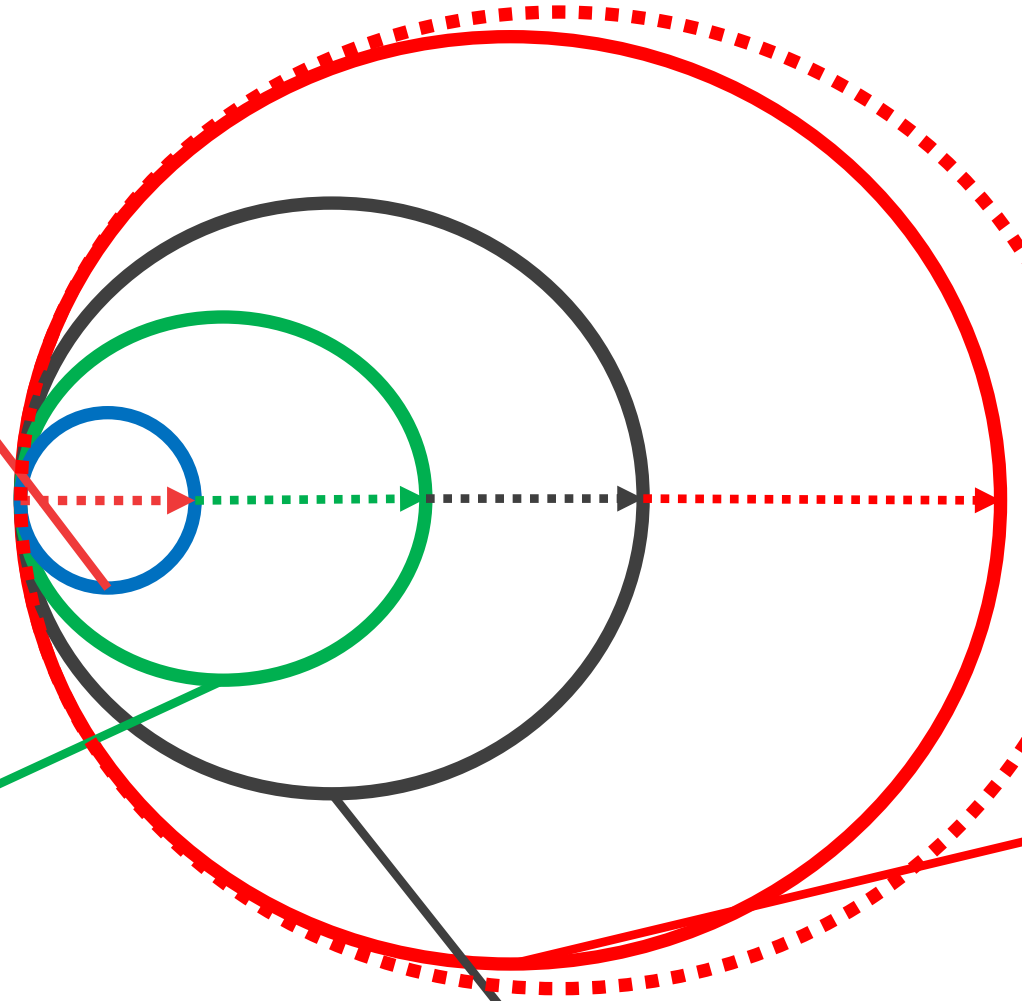
3. The same picture can be for personalization of treatment with adaptation of bacteriophages - at the entrance to the micro-factory - a phage-insensitive bacterium, after 2 days at the exit - an adapted bacteriophage highly sensitive to this particular bacterium in this patient.

To survive, rate of bacteria's "innovations" faster than rate of new drugs development.
This is time to find another, NON traditional way to for drug design

NOIGEL, LLC

The degree of freedom (variability, adaptability)

Classical Drugs based on static structure. Use of 2-5 drugs in combination for synergy effect.



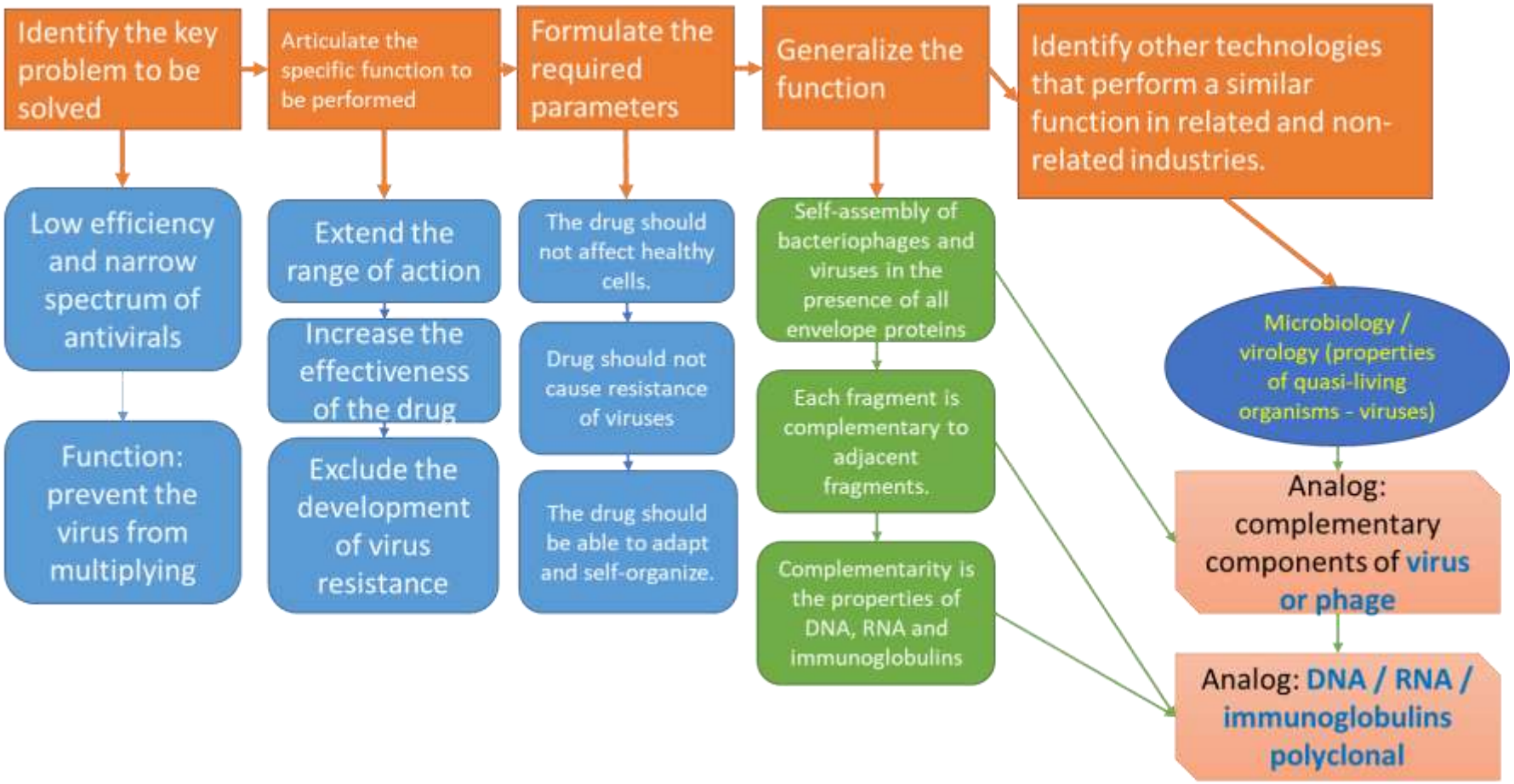
Future dynamic drugs Self- adapted dynamic Vaccines.

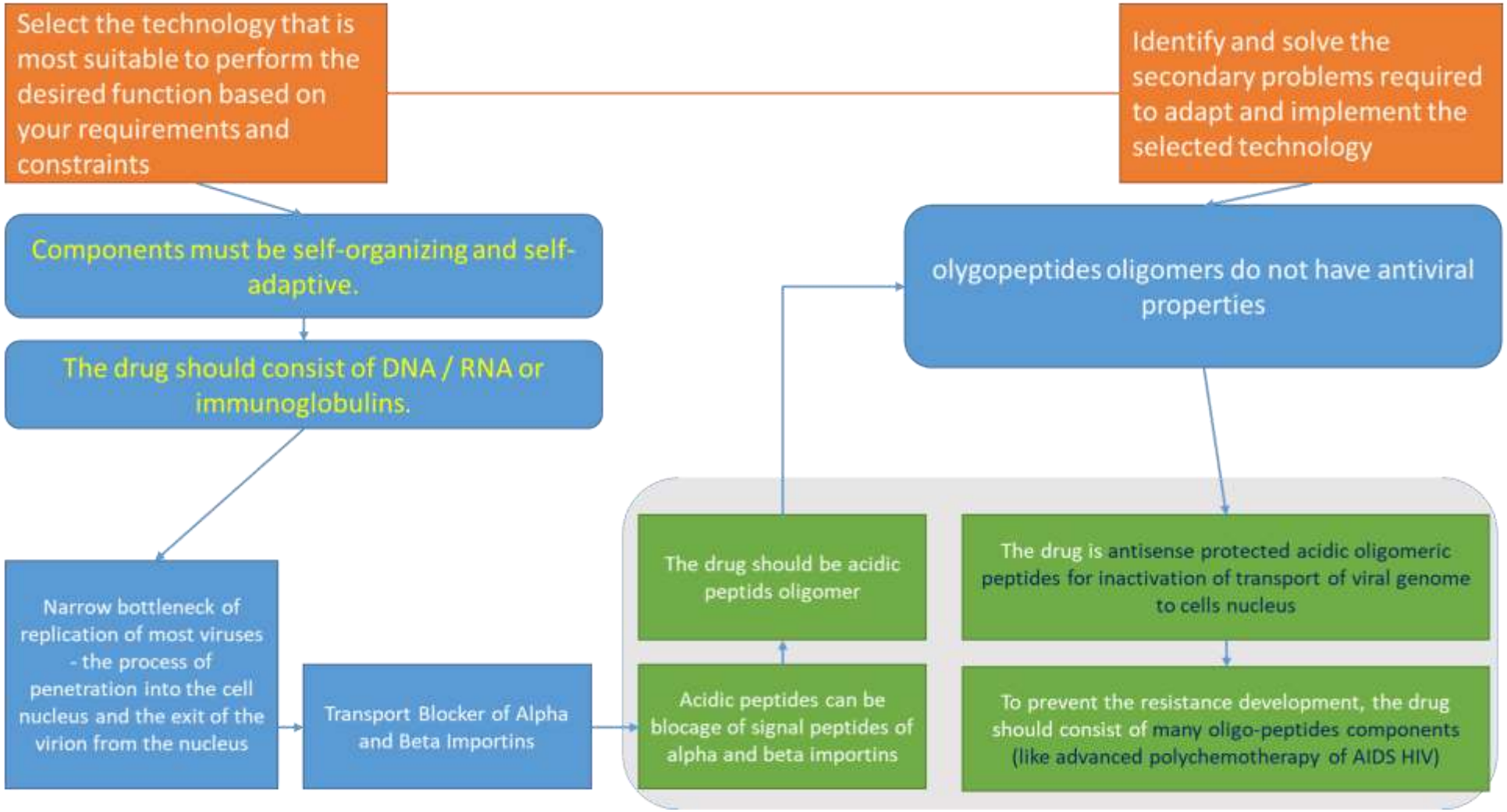
Dynamic Drugs (Self-assembly from an excess amount of different fragments) Self-adaptation

Human Organism (Slippage Effect) Mutation in Aging

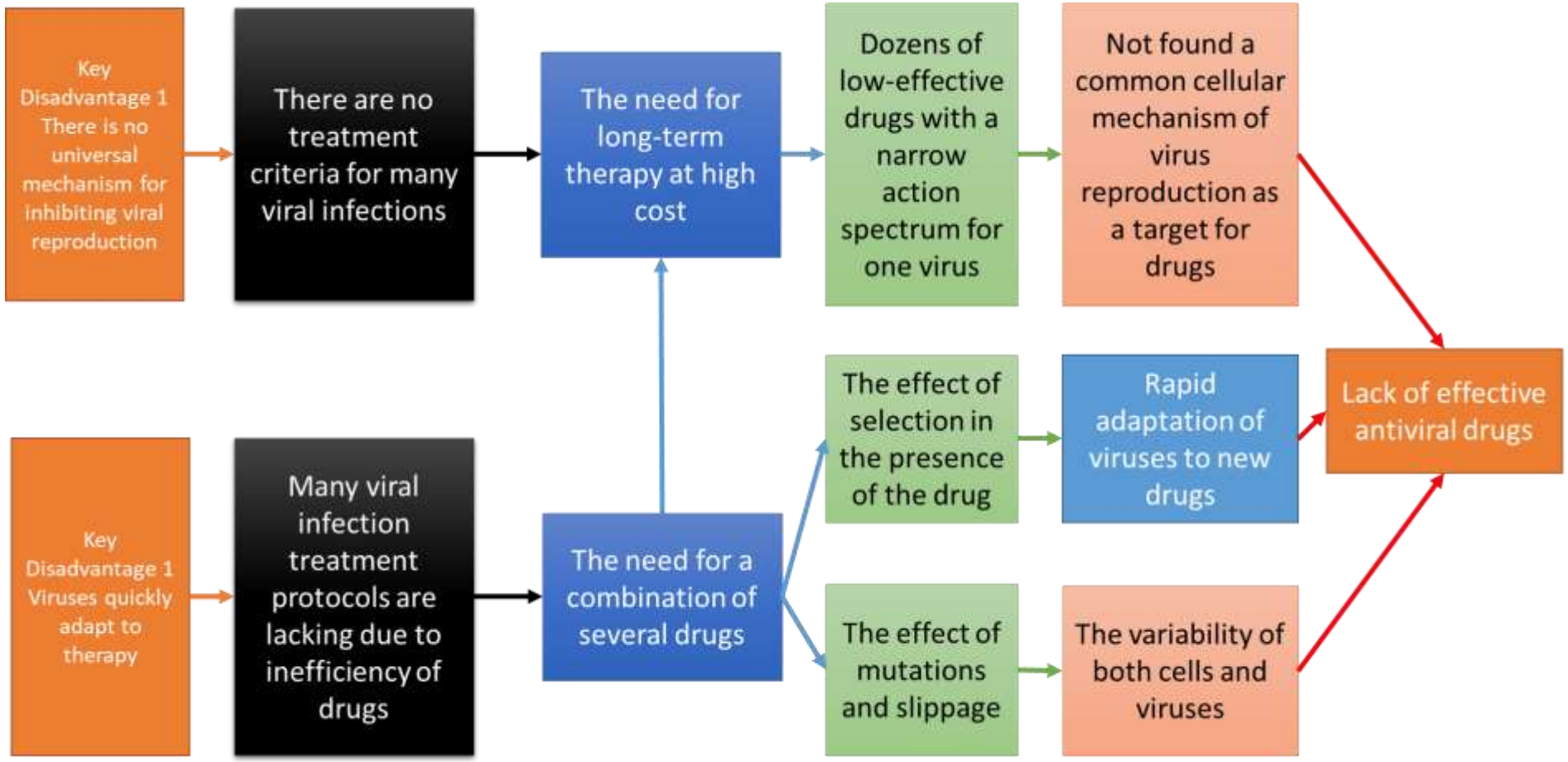
Microorganisms, Viruses mutations, drug resistance

Function-Oriented Search for Ideal Antiviral Drug




Select the technology that is most suitable to perform the desired function based on your requirements and constraints
Identify and solve the secondary problems required to adapt and implement the selected technology
Components must be self-organizing and self-adaptive.
The drug should consist of DNA / RNA or immunoglobulins.
olygopeptides oligomers do not have antiviral properties
Narrow bottleneck of replication of most viruses - the process of penetration into the cell nucleus and the exit of the virion from the nucleus
Transport Blocker of Alpha and Beta Importins
The drug should be acidic peptids oligomer
Acidic peptides can be blocage of signal peptides of alpha and beta importins
The drug is antisense protected acidic oligomeric peptides for inactivation of transport of viral genome to cells nucleus
To prevent the resistance development, the drug should consist of many oligo-peptides components (like advanced polychemotherapy of AIDS HIV)

Cause-Effect Chains Analysis for Antiviral Drug



Used TRIZ-principles

TRIZ contradiction: from one side – produced drugs are static individual substances and cannot be effective for treatment of many viral infections, from another side, different viruses have many different signals of importins and for treatment of those viral infections we need many different drugs (one drug – one virus). This one drug must be "smart", substitute many drugs and self-adjust to any of the viruses.

principles of TRIZ: ***fragmentation*** (to divide an object into independent fragments — fragmentation of whole proteins into oligopeptides with replacement of their charge);

The principle of rejection and regeneration of parts (having fulfilled its purpose or become an unnecessary part of an object must be discarded (dissolved, evaporated, etc.)

The principle of copying (instead of an inaccessible, complicated, expensive, inconvenient or fragile object to use its simplified and cheap copies - instead of synthesizing a highly specific and expensive non-peptide inhibitor of nuclear import signals, use a mixture of oligopeptides with different sequences from available raw materials);

The principle of homogeneity (objects interacting with this object should be made from the same material or close to it in properties - instead of synthesizing complex highly specific xenobiotic, use fully biodegrading peptides from natural sources, but with preliminary replacement from charges with opposite ones);

The principle of dissociation-association ("Dissociation-association" is stronger than the "separation-association"

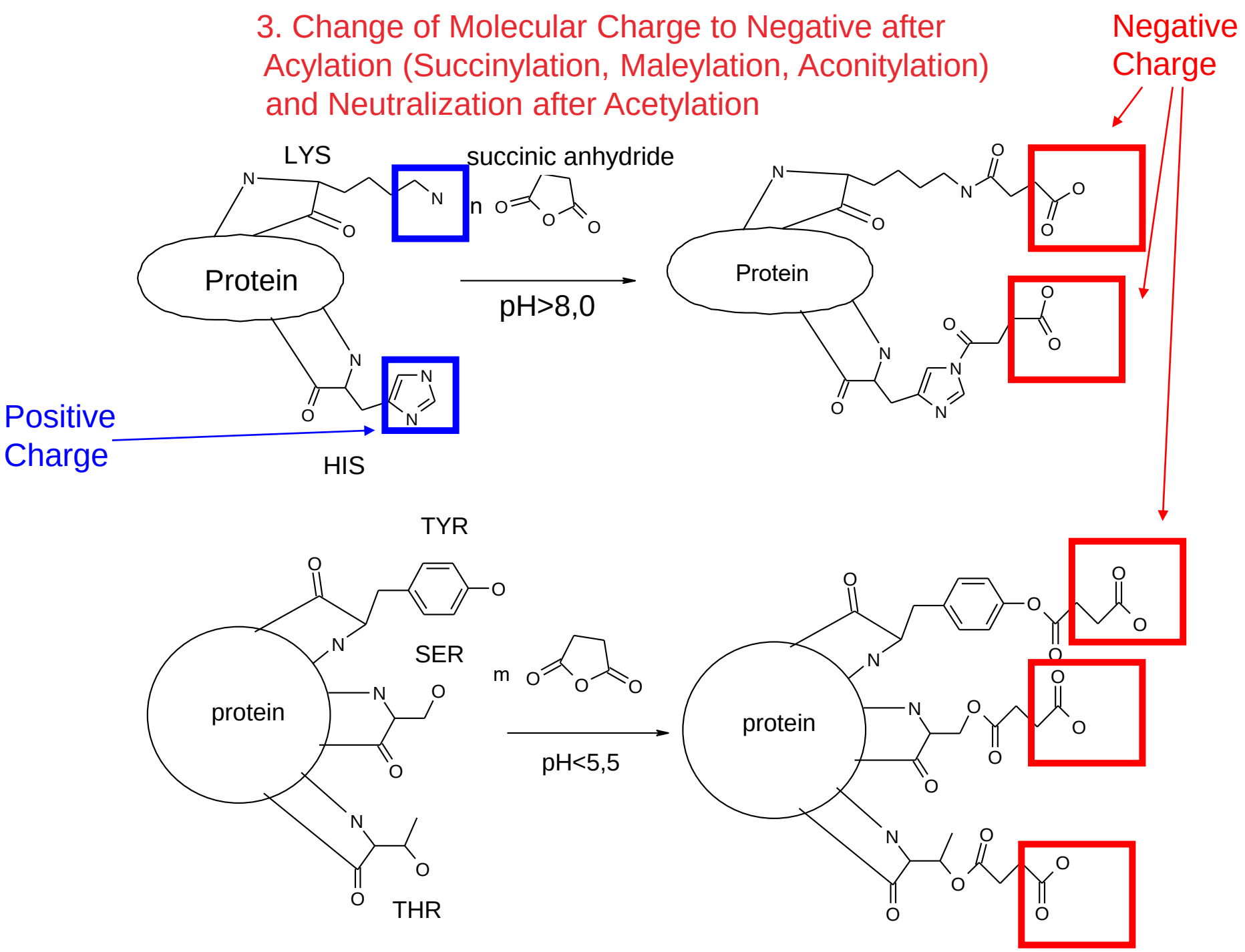
The principle of self-organization (self-assembling of an active substance from inactive precursors - out of thousands of synthesized Albuvir peptides, only a small number of high-affinity fragments will be associated with the signal peptides of beta-importins, and for each virus these will be their peptides)

Dynamic self-assembled, quasi live, self-adapted drugs

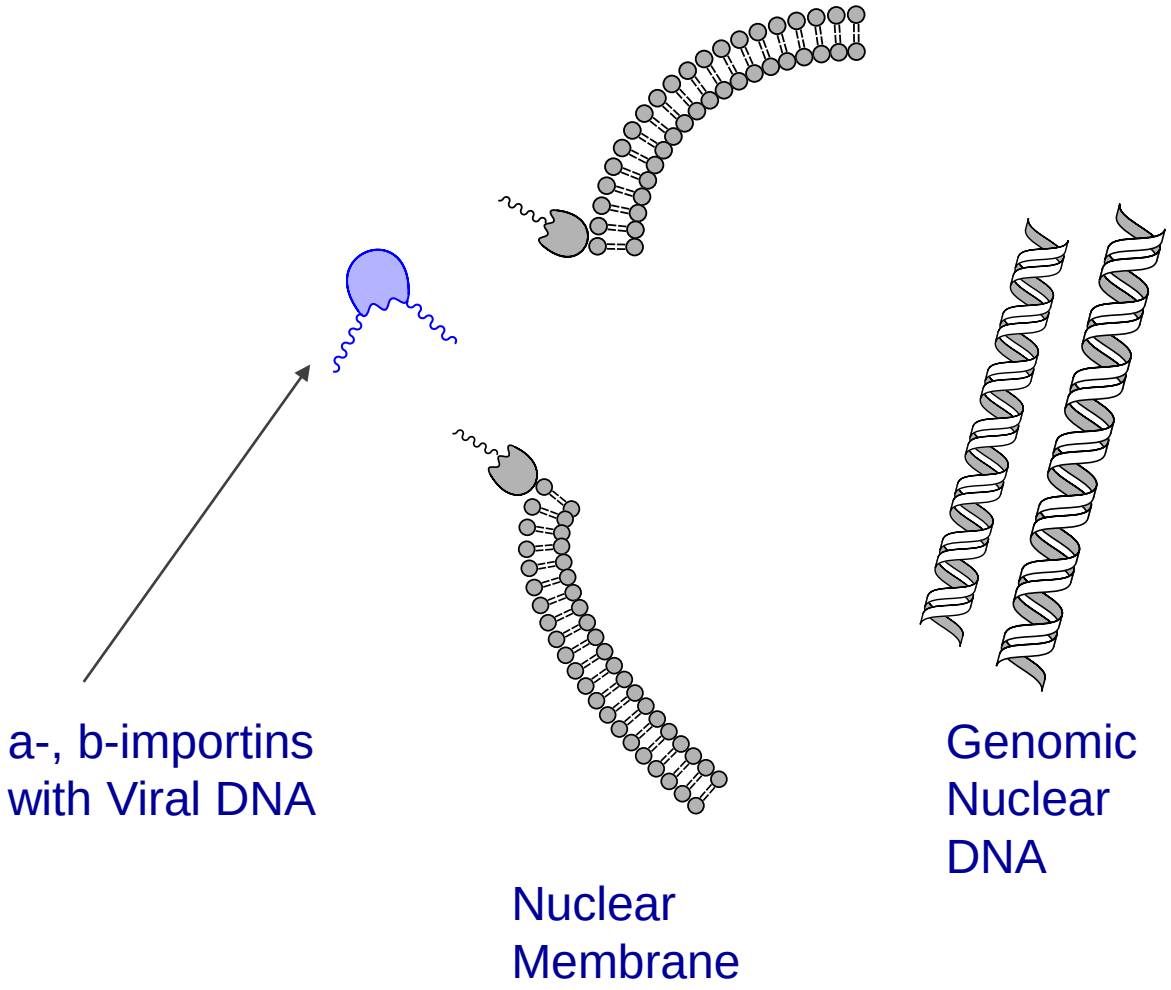
Instead of one "key" for one "lock" (the principle of a classic drug with a conservative structure), we propose a selection of "skeleton keys": a group of many similar molecules that "open" many "locks" and adapt to the target. This facilitates a practically 100% effectiveness rate and a maximally wide spectrum of drug activity.

ALBUVIR Contains more than 1 million partially acylated peptides. It effectively inhibits the process of nuclear importation of viral polynucleotides from those viruses that depend on the cell nucleus (FLU, HERPES VIRUSES, HIV/AIDS)

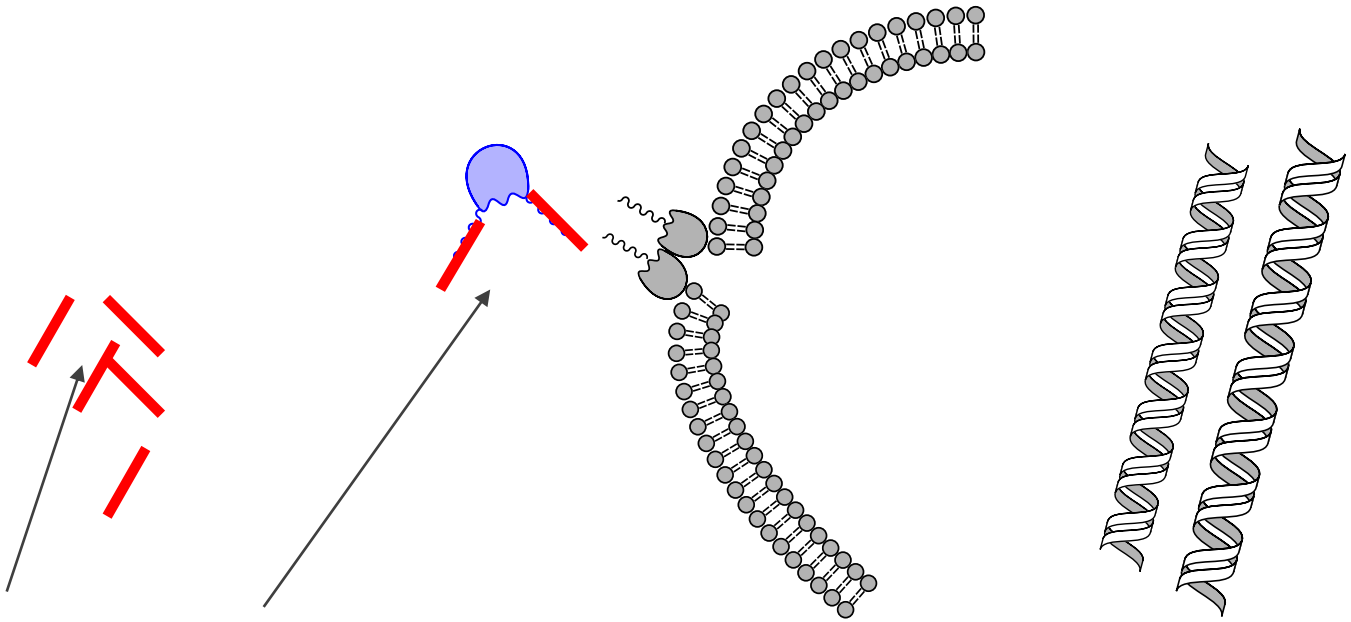
3. Change of Molecular Charge to Negative after Acylation (Succinylation, Maleylation, Aconitylation) and Neutralization after Acetylation



4. The Mechanism of the Penetration of a Viral Genome through the Nuclear Membrane



5. Albuvir's Mechanism of Action



Albuvir

a-, b-importins
with Viral DNA

Nuclear
Membrane

Genomic
Nuclear
DNA

6. Pharmacological Properties of the Proposed Drugs

Albuvir:

LD50=**2880** mg/kg

ED50=25 mg/kg

Ti=115.2

T1/2=29 min

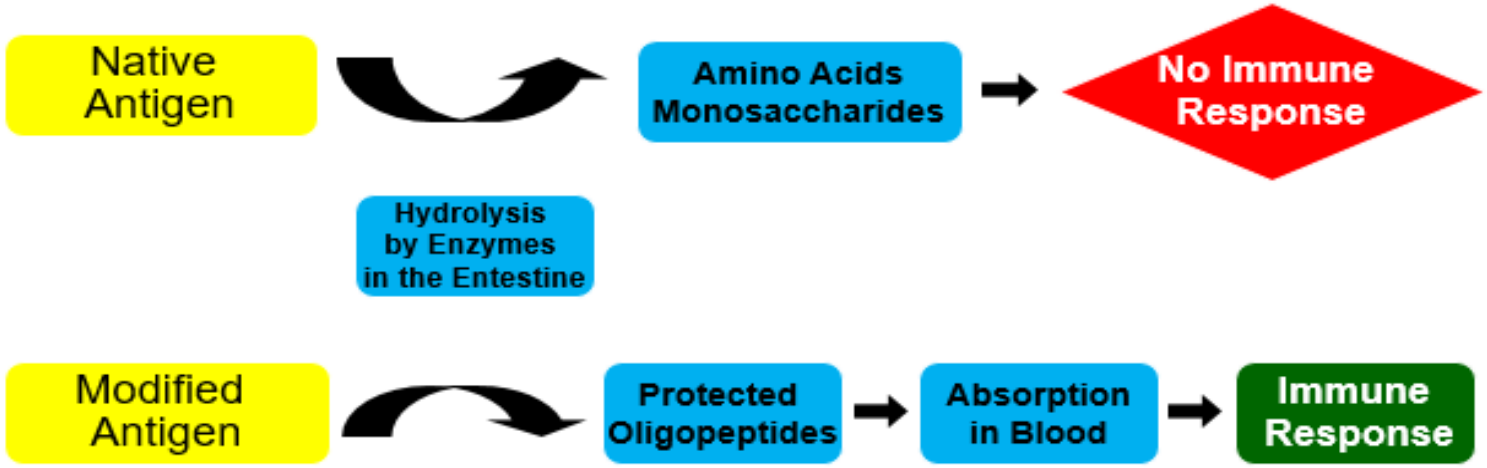
Application Method:

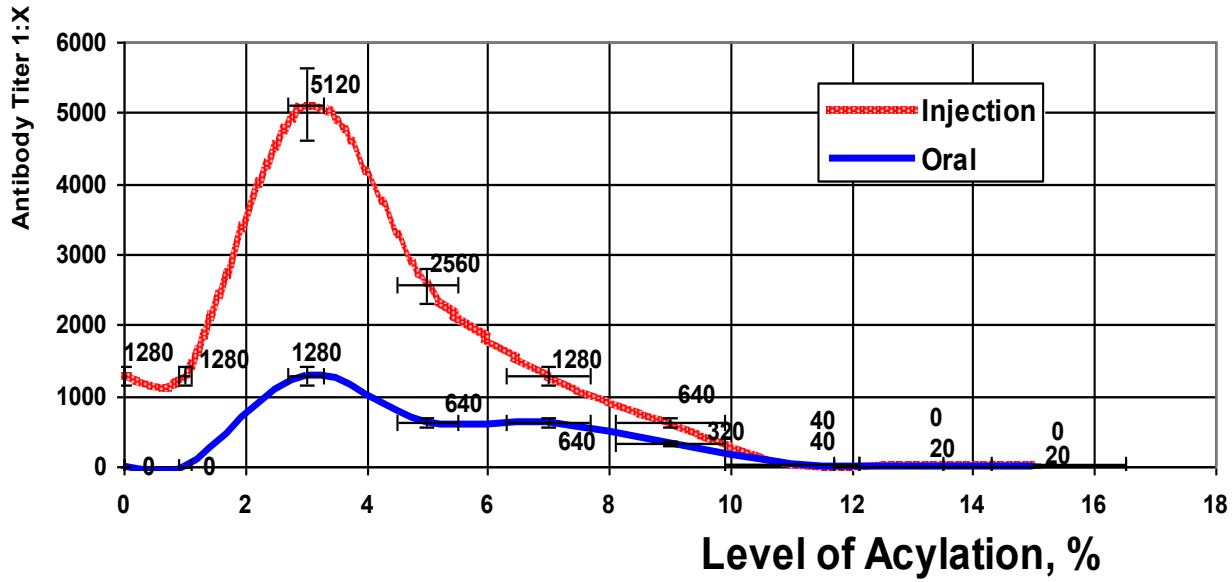
peroral

Effective in the Treatment of:

1. **Influenza**
2. **Herpes Types 1 and 2**
3. **Cytomegalovirus Infection**
4. **Herpes Zoster Virus**
5. **Epstein-Barr Virus**
6. **Coronavirus**

Project 3. Strategy for development the Dynamic vaccines based on the self-assembled modified peptides





The mechanism of action of oral vaccines with partially modified antigens

Line 3.
New diagnostic approach for early cancer detection and early prediction of atherosclerosis and it’s complications.

Human Herpesvirus (HHV) classification

Type	Synonym	Subfamily	Pathophysiology
HHV-1	Herpes simplex virus-1 (HSV-1)	α (Alpha)	Oral and/or genital herpes (predominantly orofacial)
HHV-2	Herpes simplex virus-2 (HSV-2)	α	Oral and/or genital herpes (predominantly genital)
HHV-3	Varicella zoster virus (VZV)	α	Chickenpox and shingles

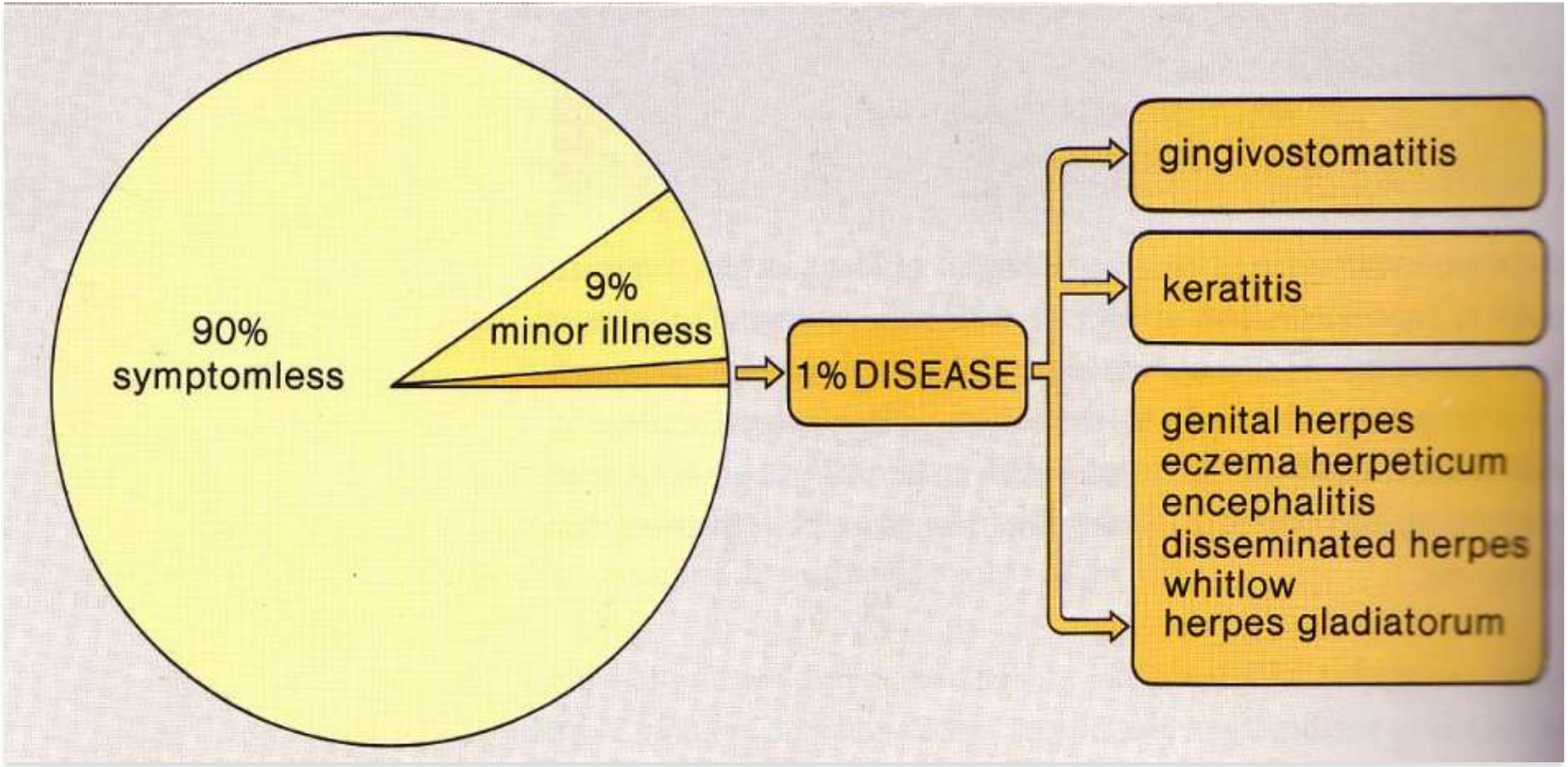
Human Herpesvirus (HHV) classification

Type	Synonym	Subfamily	Pathophysiology
HHV-4	Epstein-Barr virus (EBV), lymphocryptovirus	γ (Gamma)	Infectious mononucleosis, Burkitt's lymphoma, CNS lymphoma in AIDS patients, post-transplant lymphoproliferative syndrome (PTLD), nasopharyngeal carcinoma
HHV-5	Cytomegalovirus (CMV)	β (Beta)	Infectious mononucleosis-like syndrome, retinitis, etc.

Human Herpesvirus (HHV) classification

Type	Synonym	Subfamily	Pathophysiology
HHV-6, -7	Roseolovirus	β	*Sixth disease* (roseola infantum or *exanthem subitum*)
HHV-8	Kaposi's sarcoma-associated herpesvirus (KSHV), a type of rhadinovirus	γ	Kaposi's sarcoma, primary effusion lymphoma, some types of multicentric Castlem

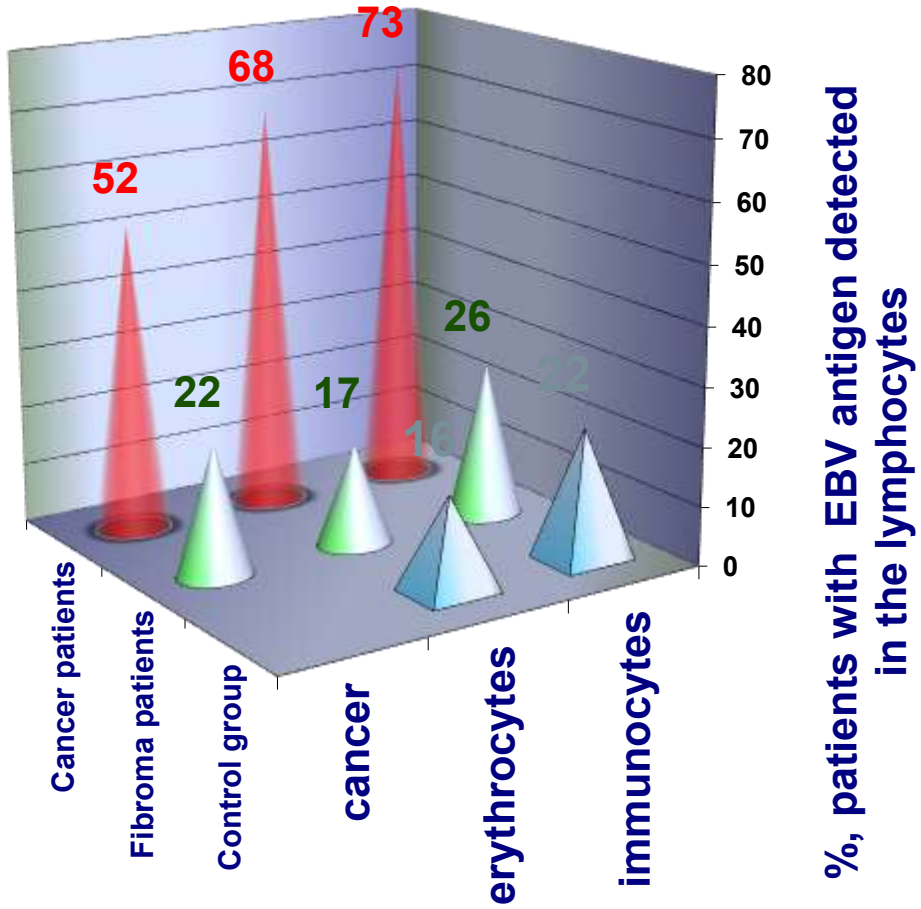
Clinical manifestations of Herpes virus



Herpes virus Statistics

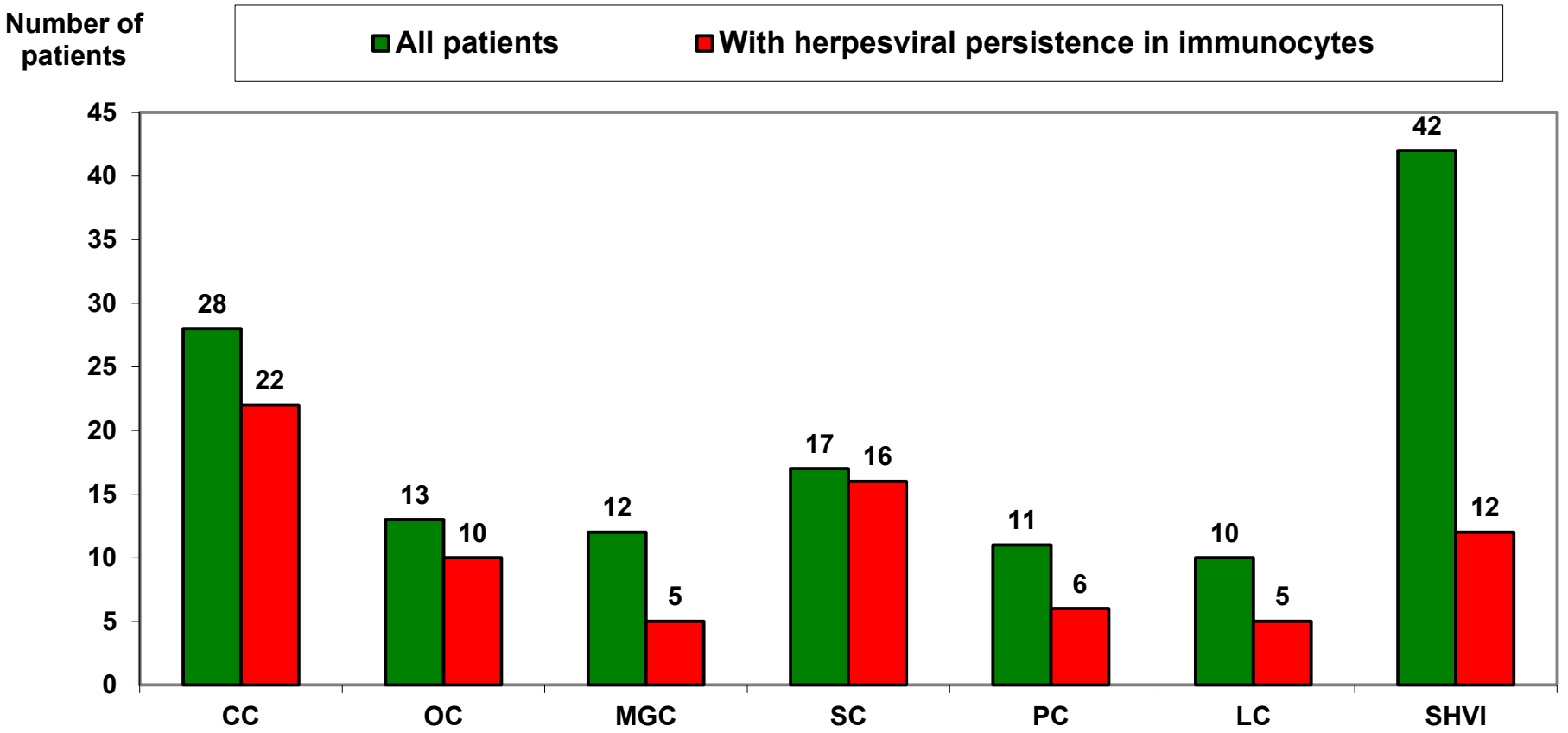
- More than 80% of the adult population has oral herpes and a recent study suggests this number could be 98% exposure among adults.
- One in five Americans have genital herpes (yet at least 80 percent of those with herpes are **unaware they have it).**
- One in five Americans have genital herpes (yet at least 80 percent of those with herpes are **asymptomatic).**
- There are approximately one million new cases of herpes each year.
- 25 percent of American adults have symptomatic genital herpes.

Amount in % Epstein-Barr virus (EBV) infected population



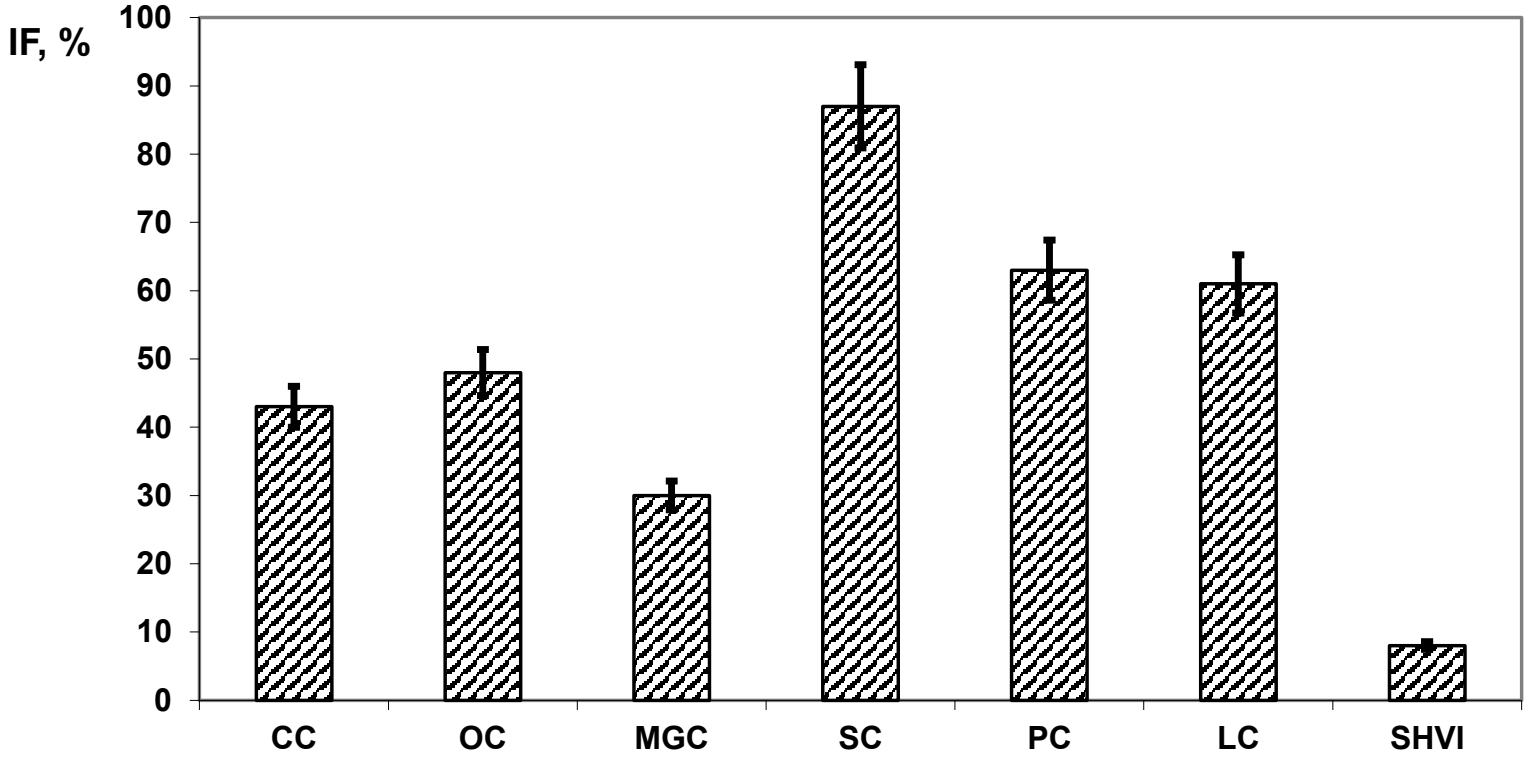
Cancer patients – patients with cancer of uterus
Control group- patients with acute Epstein-Barr virus,
EBV-infection without cancer (mononucleosis, lymphadenitis etc.)
Criteria is infection by 50% or more by EBV

Statistical correlation of Epstein-Barr virus and patients with different type of cancer



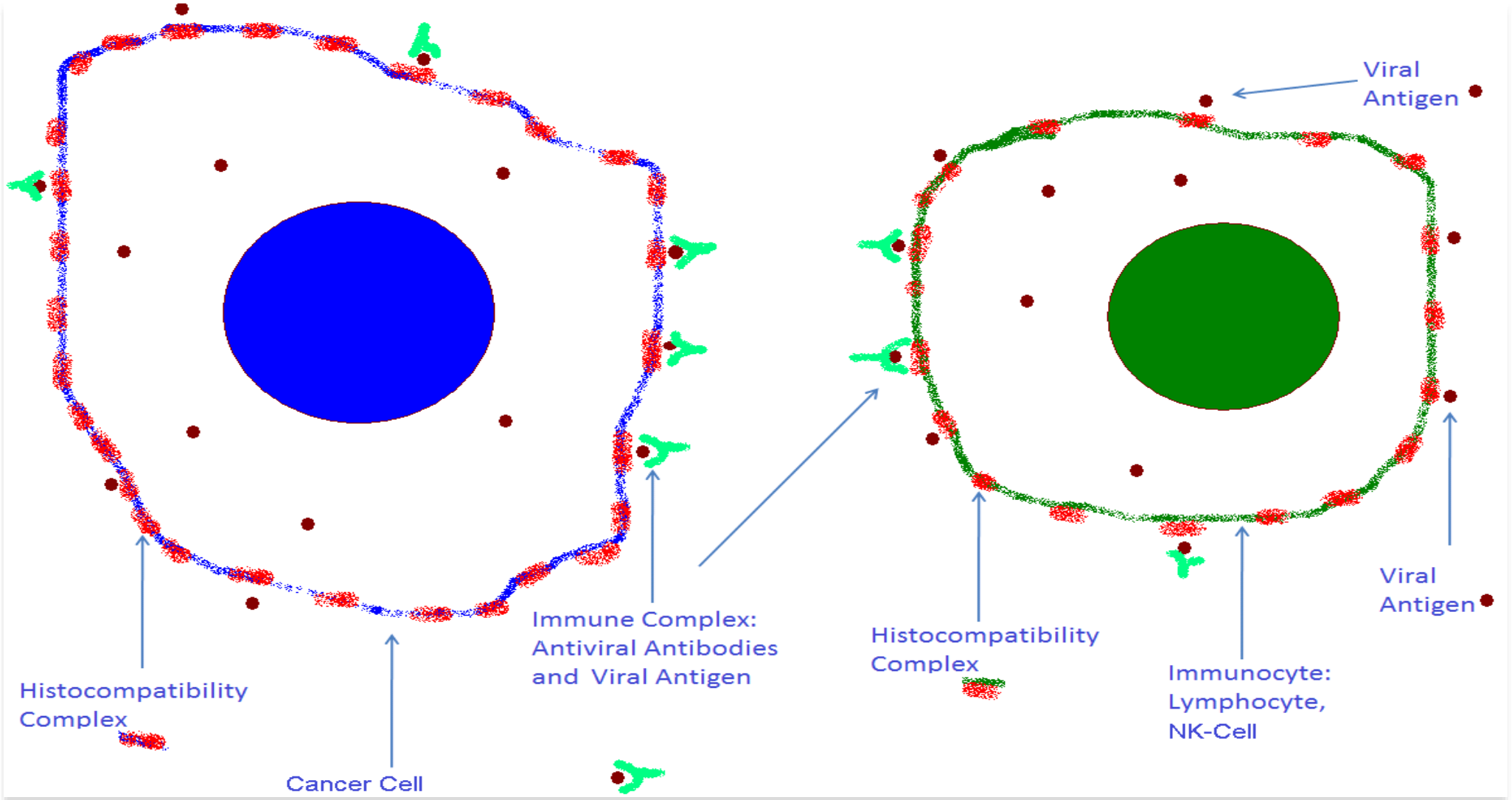
CC – Cervical Cancer
OC – Ovarian Cancer
MGC – Mammary Gland Cancer
SC – Stomach Cancer
PC – Pancreatic Cancer
LC – Lung Cancer
SHVI – Severe Herpesvirus Infection (HSV1,2)

Distribution groups of patients with HSV1, 2 and the fluorescence index

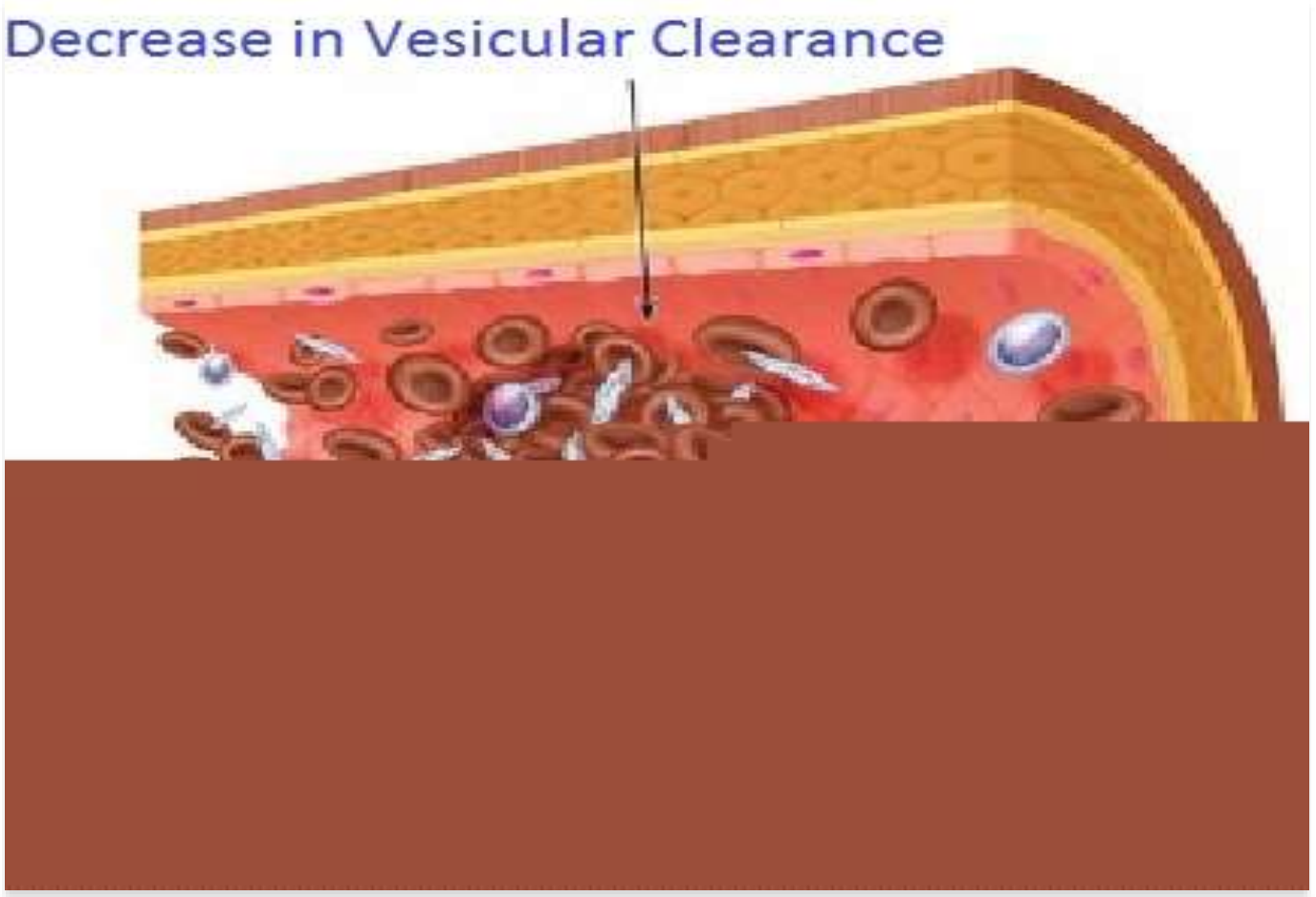


IF – Immunofluorescence index, or the percentage of cells infected with viruses
CC – Cervical Cancer
OC – Ovarian Cancer
MGC – Mammary Gland Cancer
SC – Stomach Cancer
PC – Pancreatic Cancer
LC – Lung Cancer
SHVI – Severe Herpesvirus Infection (HSV1,2)

Cancer cells are become invisible to immunocytes during herpes virus intracellular persistence.

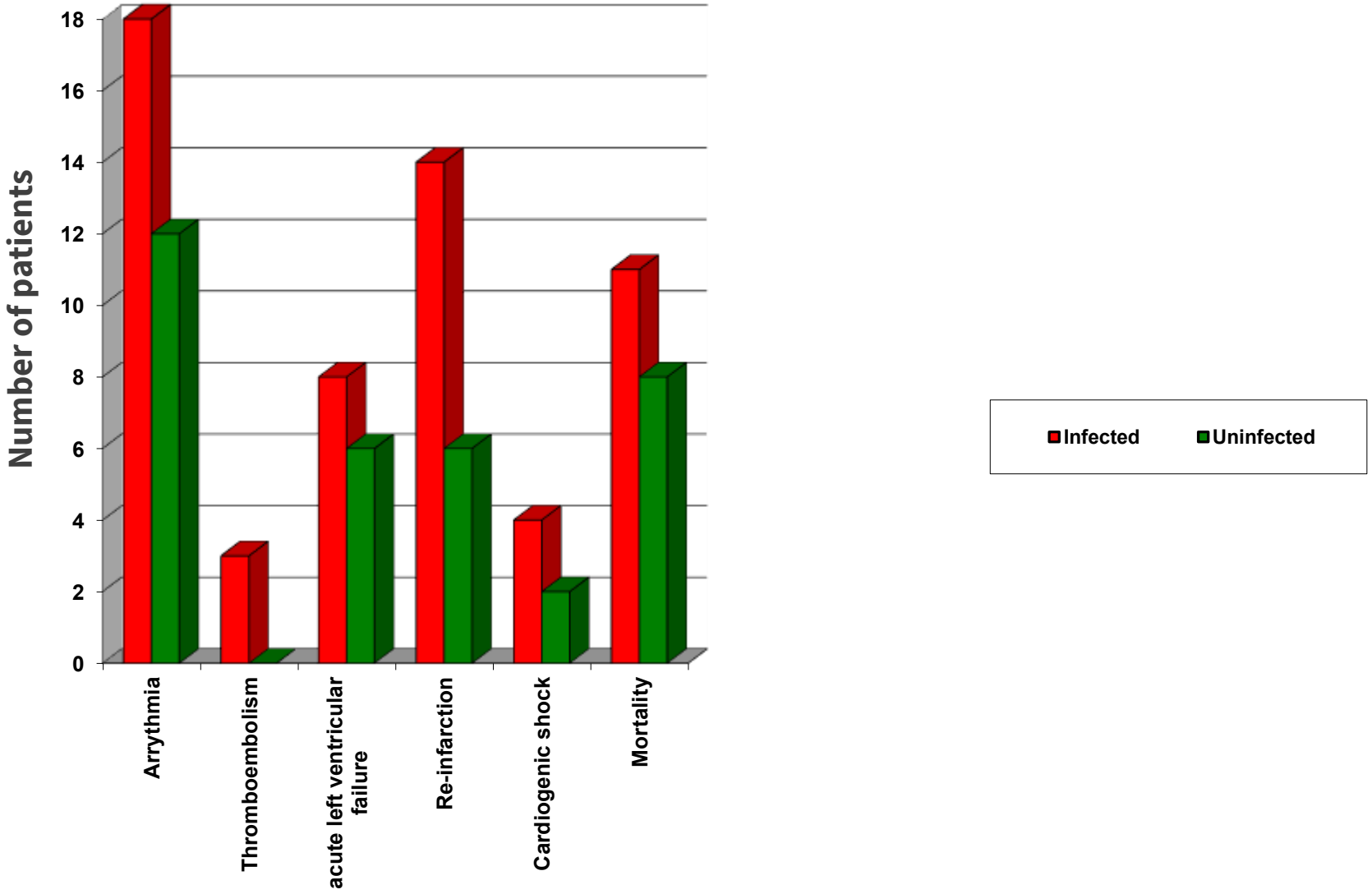


A visual image of atherosclerosis:



The plaques development with a complex structure inside a blood vessel, which lead to a narrowing in the clearance of the vessel and disruptions to the circulation.

Development of complications in the course of acute myocardial infarction in infected and uninfected Herpes virus patients



Detection of HSV and cytomegalovirus (CMV) antigen in patients who died

Group of patients who died:	Amount of Patients	CMV		HSV		CMV+ HSV	
	Amount	Amt	%	Amt	%	Amt	%
From CVS pathology	27	17	63	13	48,1	10	**47,0**
Control	19	5	26	2	7,4	1	**5,2**

AG- antigen
CVS- cardiovascular system
CMV - cytomegalovirus antigen
HSV - herpes simplex virus antigen
CMV + HSV-2 antigen detected - cytomegalovirus & herpes virus

Acknowledgements

- The research is a result of creative, dedicating and enthusiastic efforts of Noigel LLC.
- Scientists Team colleagues and partners. We thank our colleagues:

  Genrich Altshuller, Voluslav Mitrofanov, Boris Zlotin, Dr.Artur Martynov, Vadim Kaner, Dr. Ilya Kleyn , Ilya Gonta, Dr.Tatyana Osolodchenko, Dr.Yakov Duboshinsky, Dr.Tatyana Kabluchko, Dr.Leo Slusky, Dr. Yury Lisnyak,Dr.Tatyana Bomko, Dr.Tatyana Nosalskaya, Dr.Helen Romanova, Dr.Helen Grishina and many others, who provided insight and expertise that greatly assisted the research

“Coming together is a beginning; keeping together is progress; working together is success.”

Henry Ford

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“One flew over the Cuckoo's Nest”
Jack Nicolson

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