THE NOVEL STRATEGY TO FIGHT MULTIDRUG RESISTANCE BASED ON TRIZ, DOCKING DRUG DESIGN THROUGH DRUGS SYNERGY.

Dr. Boris Farber CEO

NOIGEL, LLC

- Noigel LLC is a startup company that was established in 2010 by a group of scientists to study and develop new substances in medical field, based on **TRIZ and modern technologies.**

- **Inversion of “NOIGEL” is “LEGION”**

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NOIGEL,LLC:
SCIENCE WITHOUT BORDERS

- NOIGEL is composed of several groups of scientists from different fields of science and expertise all over the world:

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Solving problems in Pharmaceutical R &D.

1. TRADITIONAL APPROACH:

R & D BASED ON MODERN TECHNOLOGIES

2. NON TRADITIONAL APPROACH:

Creating new HEURISTIC METHOD of research and

ONLY AFTER THAT,

Based on this new HEURISTIC METHOD, apply Classical approach

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What Methods our Research is based on?

- **Noigel LLC based on principles of multiple synergisms, TRIZ (theory of inventive problem solving) , modern design and technologies in different fields.**

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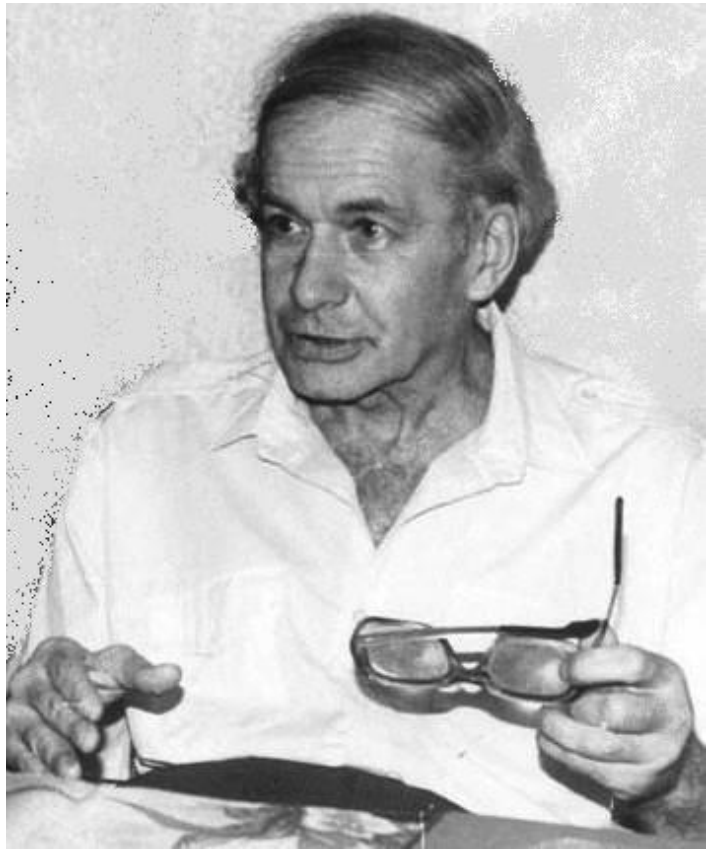
The father of TRIZ

(TRIZ IS theory of inventive problem solving)



TRIZ was developed by Genrich Altshuller and his colleagues, beginning 1946, generalizing patterns in the nature of inventive solutions and the distinguishing characteristics of the problems.

(1926-1998)

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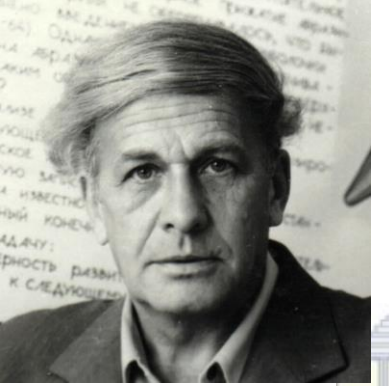

OVER 70 YEARS OF DEVELOPMENT INITIATED AND LED BY G. ALTSHULLER AND INVOLVING HUNDREDS OF SCIENTISTS AND INVENTORS

More than 3.000.000 world- wide patents

Practical experience of thousands of scientists, inventors, engineers, managers, businessmen, etc.

Eureka!

Theory of Inventive Problem Solving

TRIZ

History of evolution in different areas of technology and science, social systems, business, management, art, languages, etc.

Feedback from solving with TRIZ thousands of problems.

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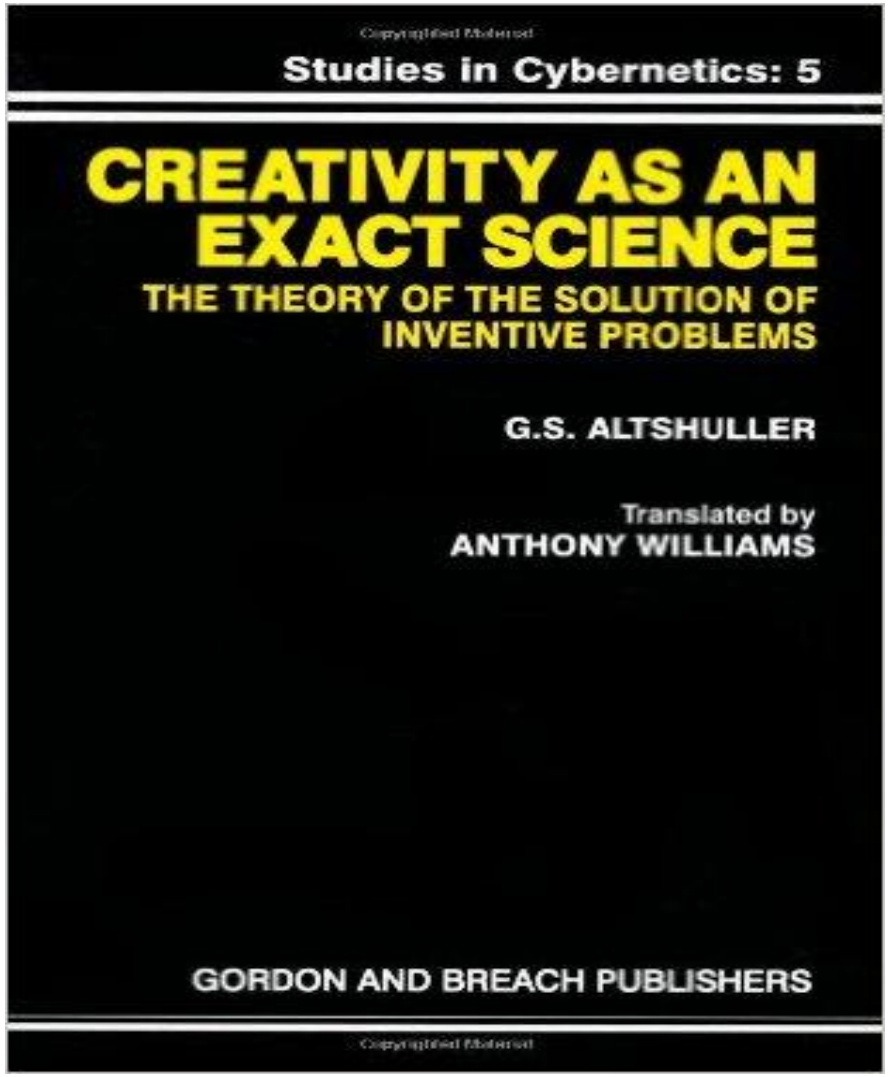
Genrich Altshuller's Book



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ISBN-13: 978-0677212302

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TRIZ - theory of inventive problem solving

- TRIZ is based on patterns of evolution
- Systematic, structured way of thinking supported by numerous tools.
- Set of applications, in particular:
  - Inventive Problem Solving
  - Research (scientific) Problem Solving
  - Directed Evolution- systematic process for purposeful management system evolution
  - Failure Analysis
  - Failure Prediction
  - Enhancement and Protection of intellectual Property

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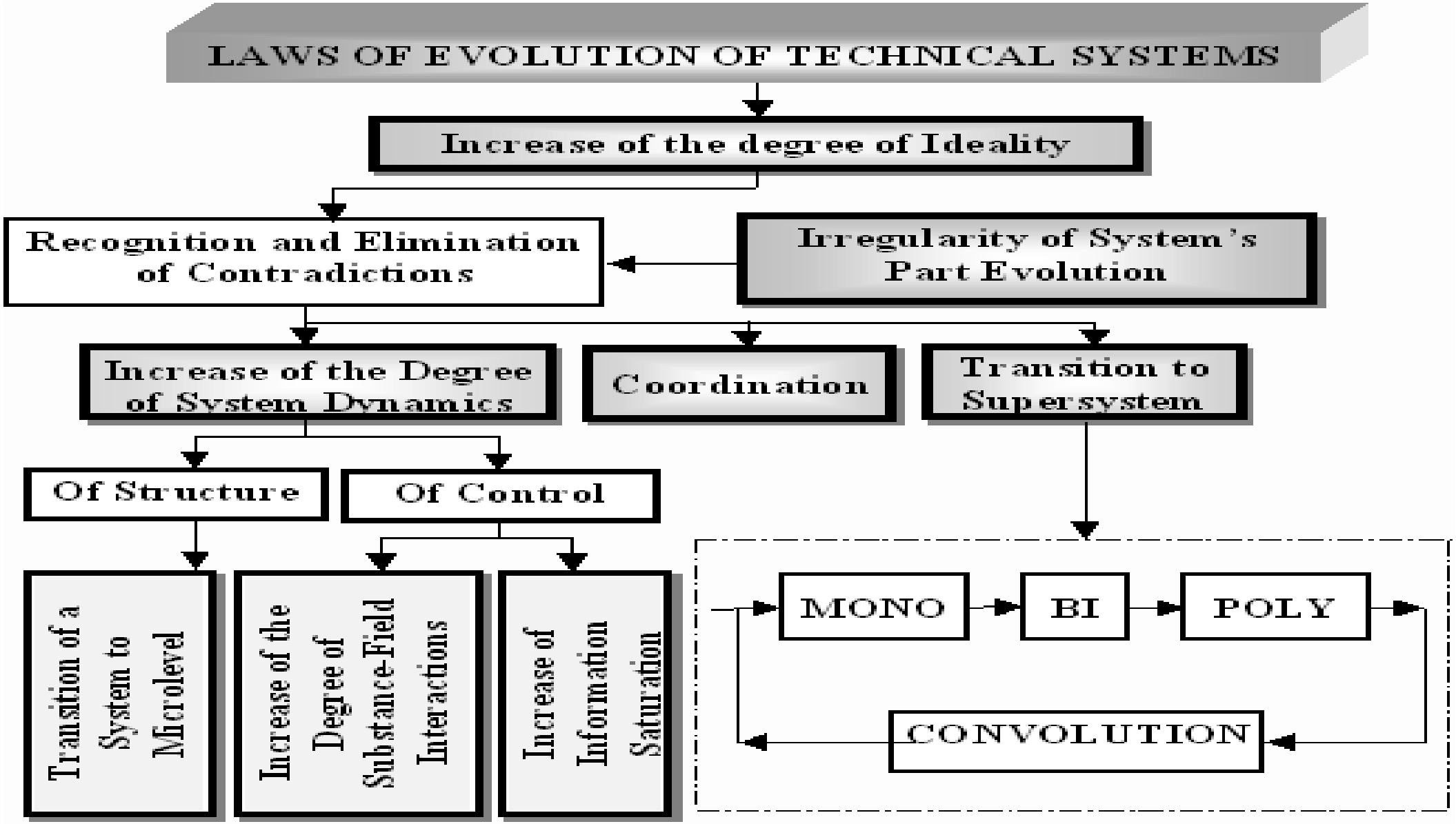
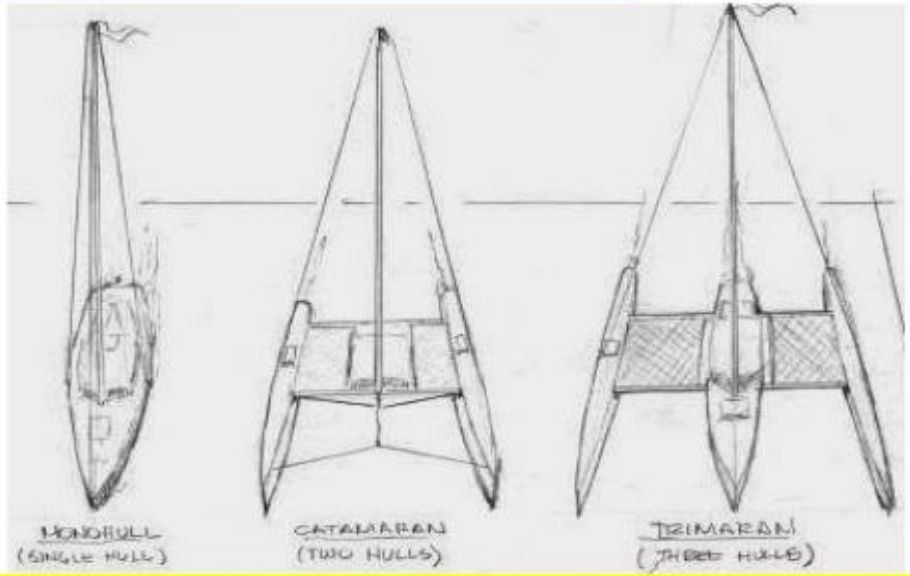


Example 1: Mono-Bi-Poly-Hull

Monohull, Catamaran, Trimaran



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Example 2: Two materials combination synergy: STEEL+ CONCRETE

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TRIZ – 40 Principles

item combinations (red) can be used by TRIZ algorithms to solve MDR problem

1 Segmentation
2 Taking out
3 Local quality
4 Asymmetry
5 Merging
6 Universality
7 Russian dolls
8 Anti-weight
9 Preliminary anti-action
10 Preliminary action
11 Beforehand cushioning
12 Equipotentiality
13 "The other way round"
14 Spheroidality - Curvature
15 Dynamics
16 Partial or excessive actions
17 Another dimension
18 Mechanical vibration
19 Periodic action
20 Continuity of useful action
21 Skipping
22 Blessing in disguise
23 Feedback
24 Intermediary
25 Self-service
26 Copying
27 Cheap short-lived objects
28 Mechanics substitution
29 Pneumatics and hydraulics
30 Flexible shells and thin films
31 Porous materials
32 Colour changes
33 Homogeneity
34 Discarding and recovering
35 Parameter changes
36 Phase transitions
37 Thermal expansion
38 Strong oxidants
39 Inert atmosphere
40 Composite materials

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OUR TRIZ EXPERTISE:

- **Developing and implementing TRIZ in diverse R&D in different fields, for instance: Bioengineering and Rocket Space Industry.**

- **Solving inventive problems and sharing success of hundreds of companies and individuals worldwide.**

- **A few of them are: (see the next slide)**

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OUR EXPERTISE - SOME OF OUR TRIZ CLIENTS:

Aurigin Systems Inc.
Bank of Montreal
Boeing
BP Amoco
BTU Cottbus
Chrysler Corporation
CTI Cryogenics
Dana Corporation
DTM Corporation
Emerson Electric Company
Ford Motor Company
General Motors Corporation
George Mason University
Goodyear
Hewlett Packard Company
Honeywell, Inc.
LABEIN Centro Tecnológico
Liverpool John Moores University
Massachusetts Institute of Technology
Motorola
NASA
National Semiconductor Corporation
Navistar International Corporation
Nordak Innovatikk AS
Nortel (Northern Telecom)
North Carolina State University
Nupro (Swagelok Company)
Pratt & Whitney
Rockwell International
Solarex Corporation
Technion-Israel Institute of Technology
Tel Aviv University
Unisys
United States Air Force
United States Army
University of Colorado

"I predict that TRIZ will become a standard practice worldwide "— Daniel Burrus, leading technology forecaster, author of *Technotrends*
One of our TRIZ Client

An Open Letter to Colleagues

”I would appreciate feedback from anyone who wants to participate in bringing new ideas to the table of treating and improving health, or has a suggestion or comments.”

Dr. Boris Farber: Director of Science Central Research Institute of Prosthetics and Prosthetics Design.

Vice President of the Russian Biomechanical Society

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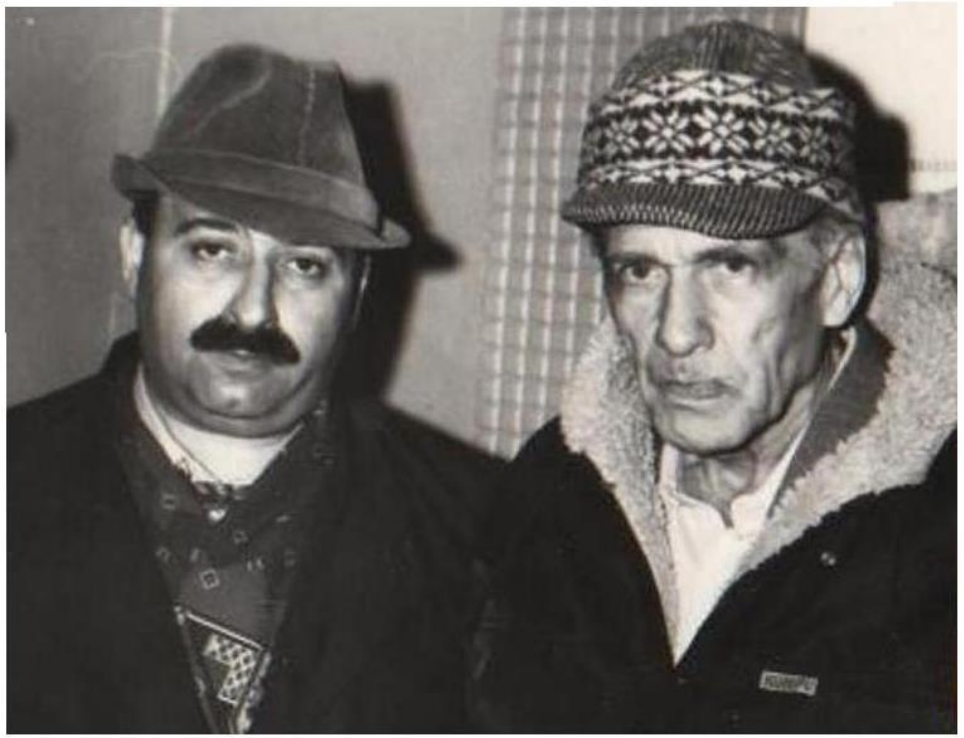
Together with my teacher Genrich Altshuller

after discussing TRIZ application for future drug design (STARTING POINT of our research)



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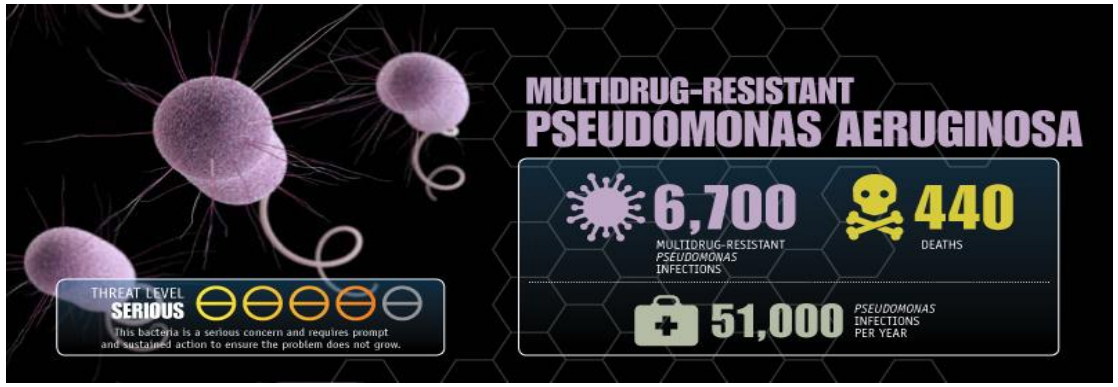
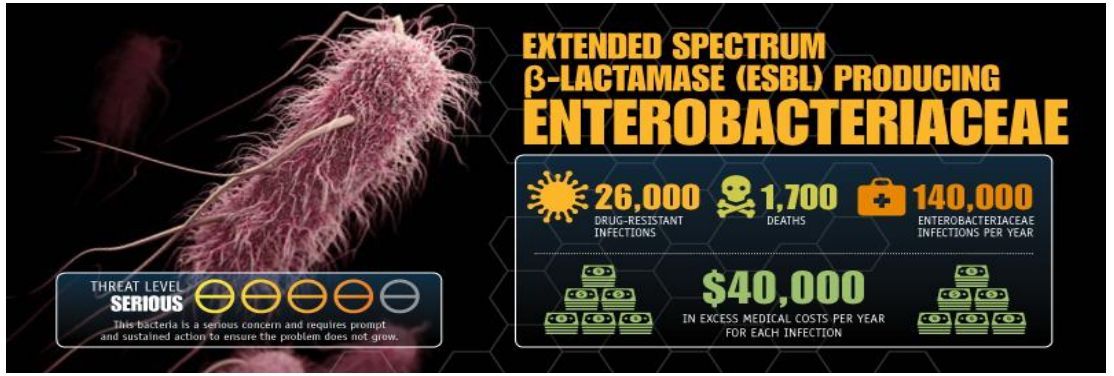
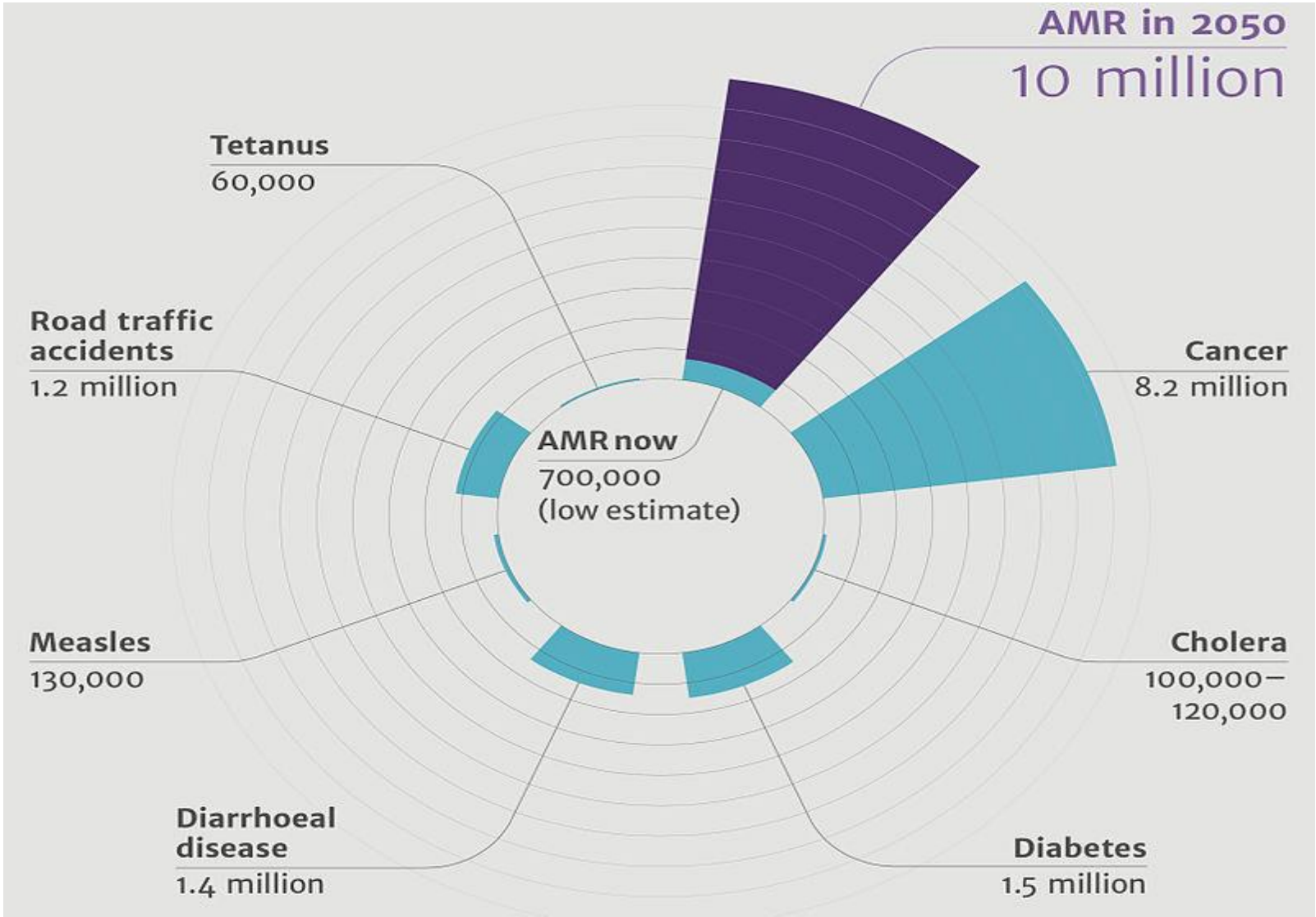
CDC Statistics





Major Causes of Deaths in the USA Compared to Antimicrobial Resistance Death



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To survive, rate of bacteria's "innovations" faster than rate of new antibacterial drugs development.
This is time to find another, NON traditional way to fight MDR Bacteria.

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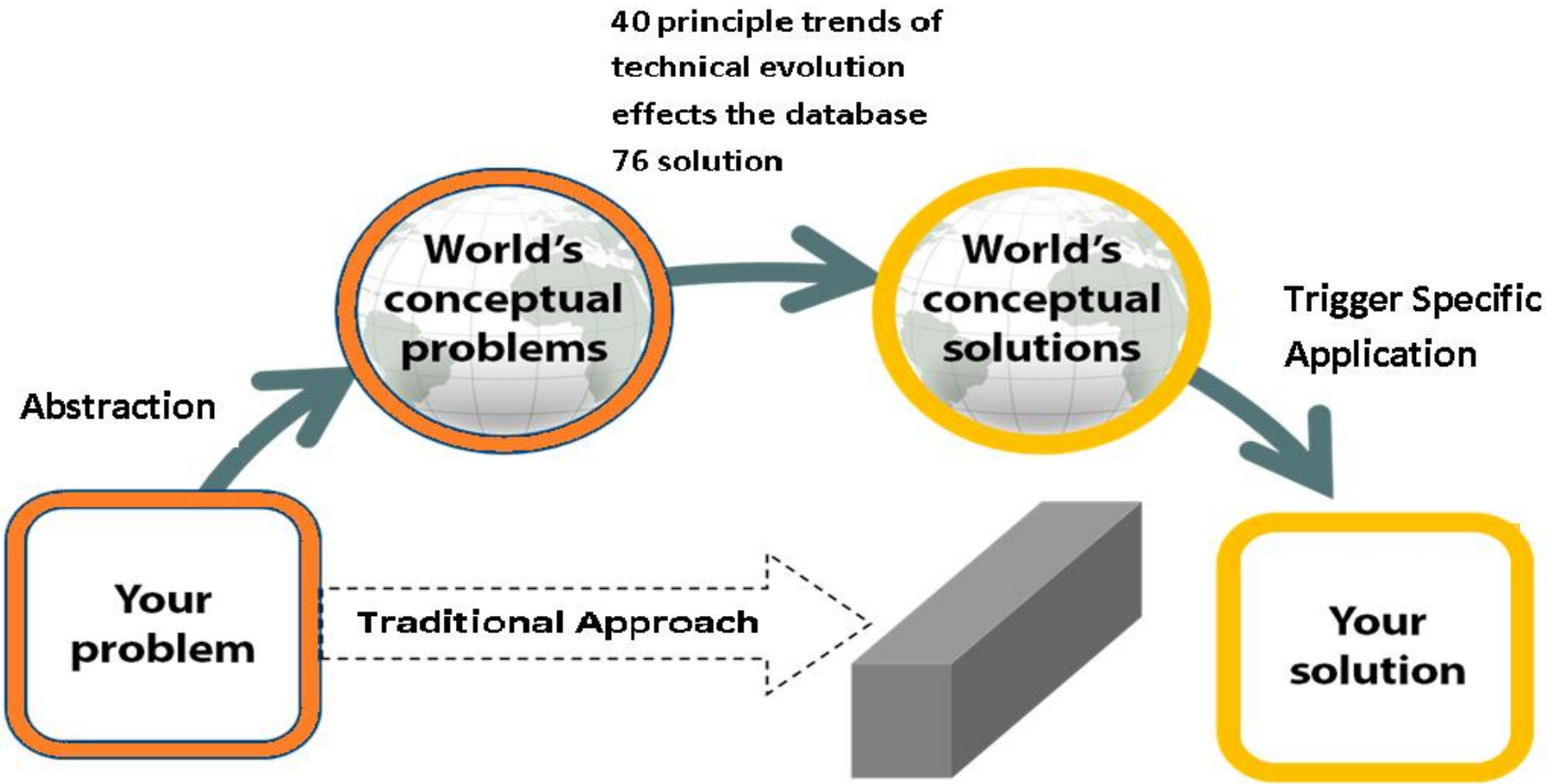
PRISM OF TRIZ

TRIZ is theory of inventive problem solving



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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
- 10 Preliminary action
- 13 "The other way round"
- 15 Dynamics
- 21 Skipping
- 24 Intermediary
- 25 Self-service
- 35 Parameter changes
- 36 Phase transitions

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Innovative Approach to MDR Research

Using TRIZ Example:

• Inventive Principle # 13 “Inversion” or do the opposite” or **"The other way round":**

• Instead of killing bacteria provide comfortable conditions reducing their resistance to harmful factors.

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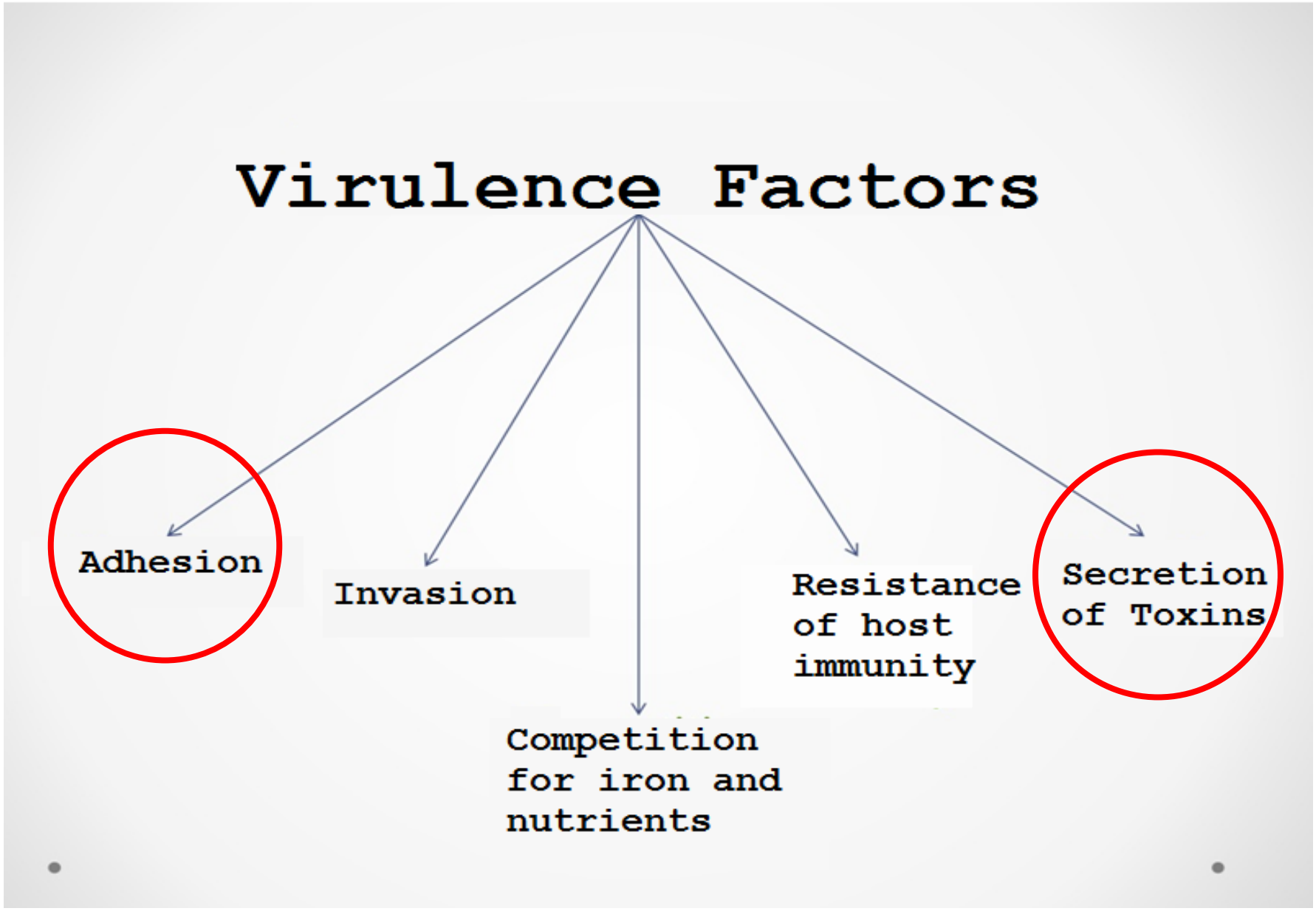
Hypothesis

- 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.



Biofilms are one of the most aggressive virulence factor

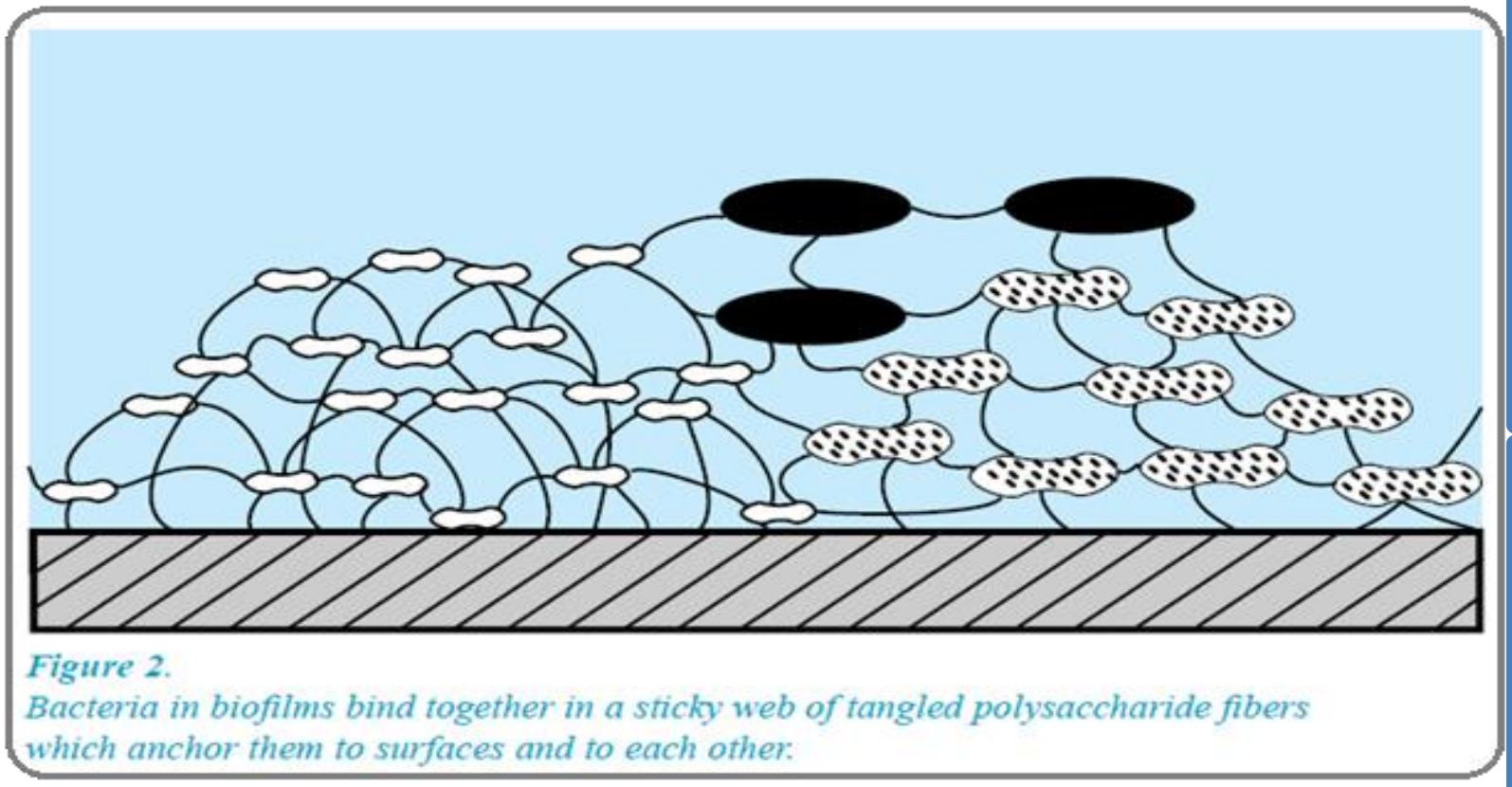
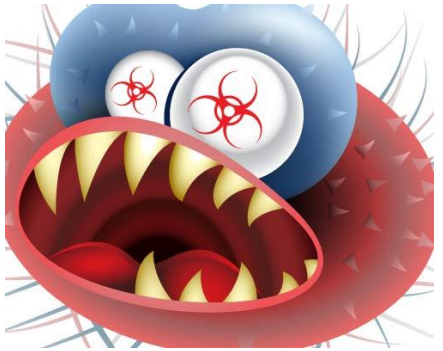


Figure 2.
Bacteria in biofilms bind together in a sticky web of tangled polysaccharide fibers which anchor them to surfaces and to each other.



Biofilms formation medium has presence the exogenic aggressive factors: (blood, lymphocytes, Imunoglobulins, some antibacterials etc.)

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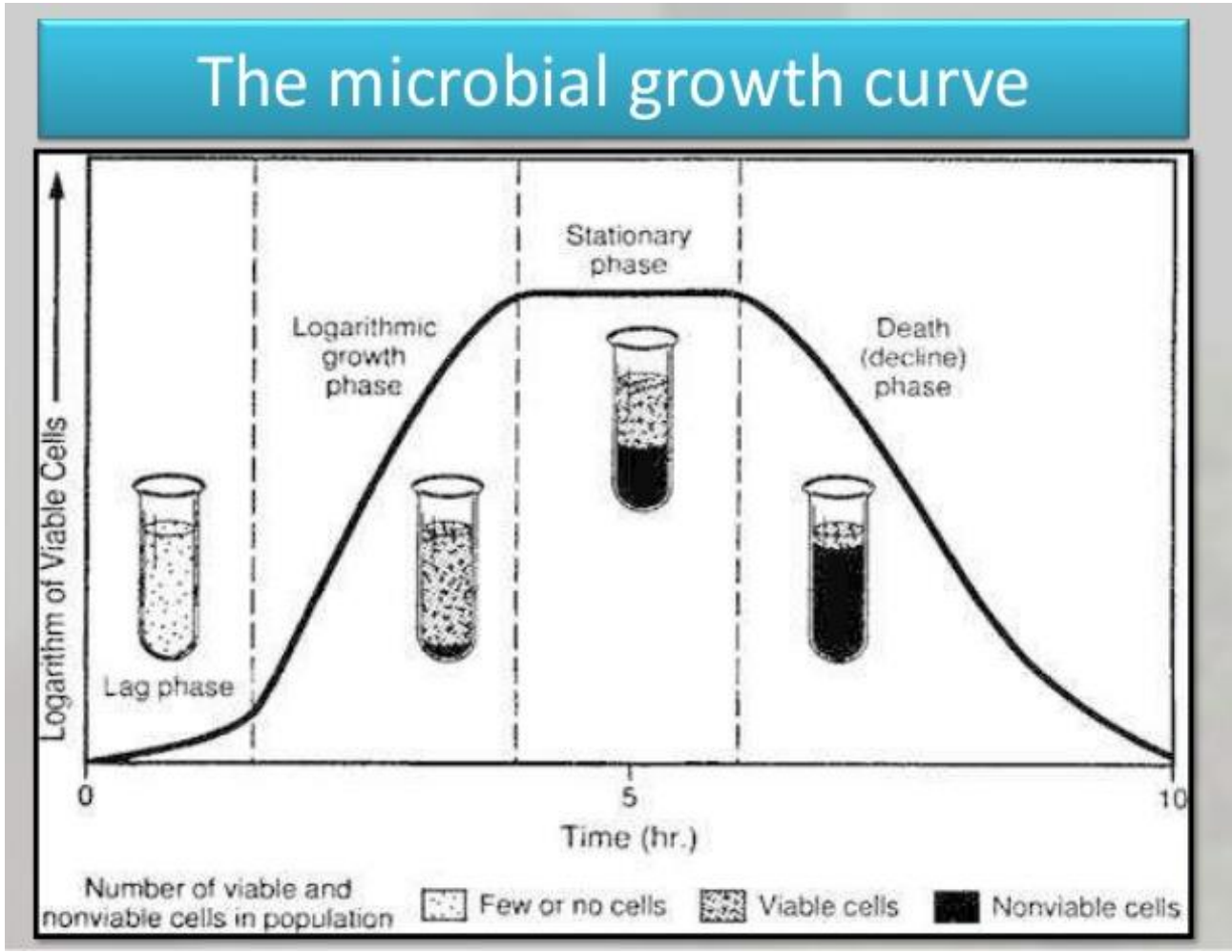
The most interesting is the phase of logarithmic growth, when the bacteria are completely provided with nutrients and absence competition with each other, they are not struggling with any external aggressive factors. In this case, they "dump" the majority, if not all, of virulence factors (including factors of acquired antibiotic resistance), toxin formation, and spend all their resources only on the division and reproduction.

- **Log phase is the most perspective target for the action of 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.

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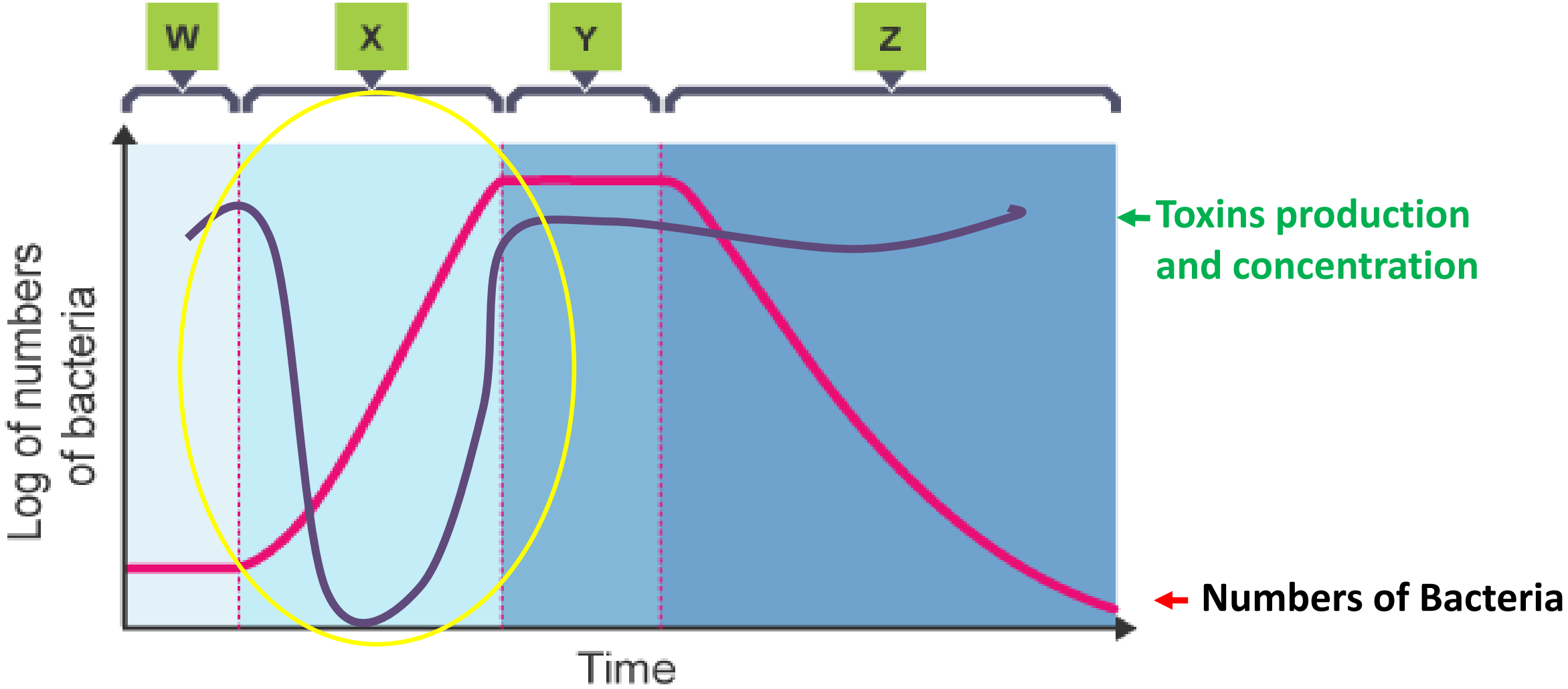
Virulence factors dynamics



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.

Criteria for virulence factors and synthesis by bacteria.

It is well known fact that in a nutrient starvation medium and in the presence of aggression inducers (erythrocytes, human serum and different types of animal products like: brain and liver extracts) growth bacteria not such active.

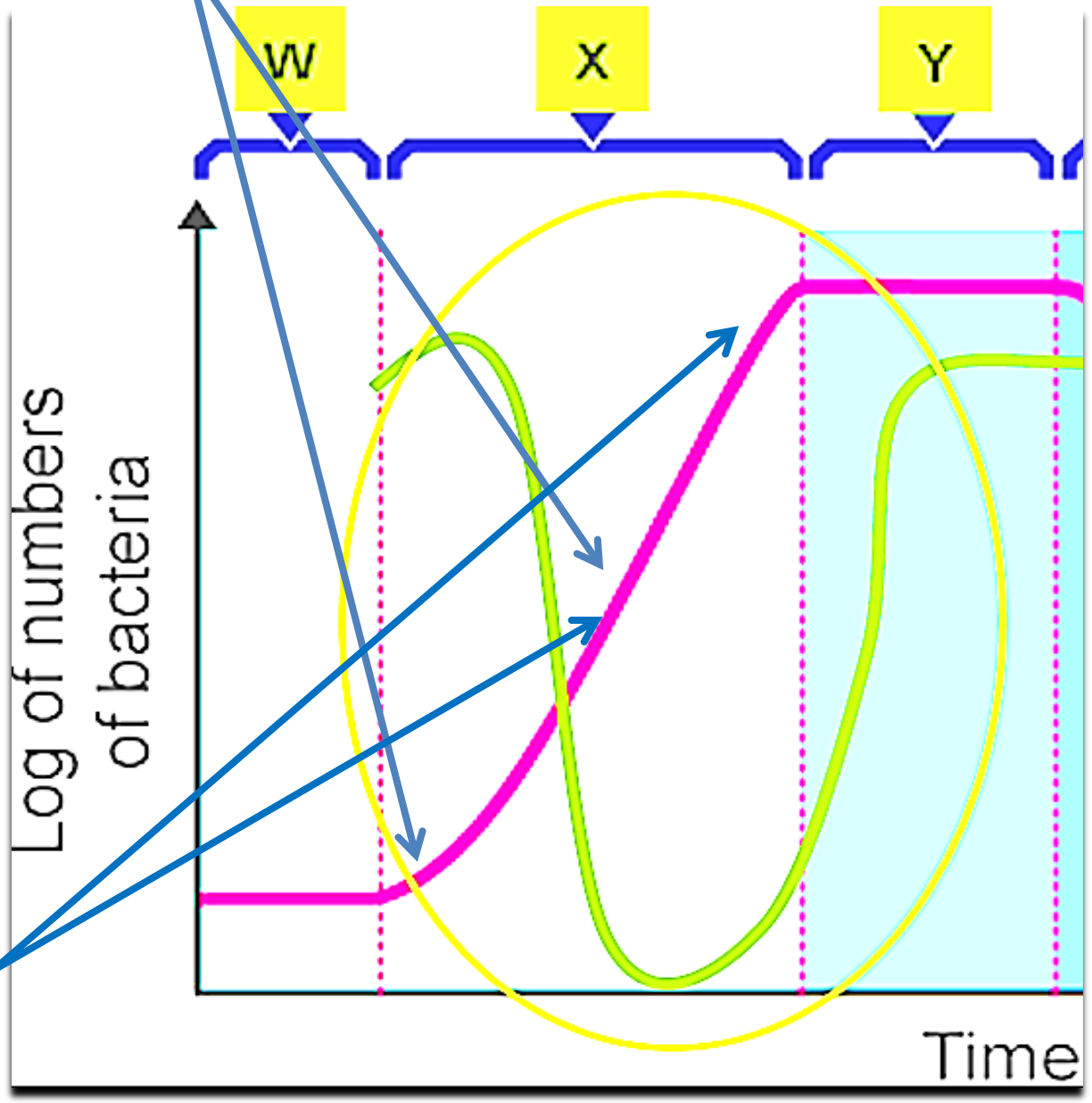
Most of these biofilms are impermeable for antibiotics and resistant to heat and antiseptic solutions.

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 antimicrobials

Impact of growth enhancers on the suppressing adhesive properties of Pseudomonas Aeruginosa

Enhancers	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)*

Enhancers influence on the microbial growth

Nutrient media - packed red blood cells			
Enhancer, 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**

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

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

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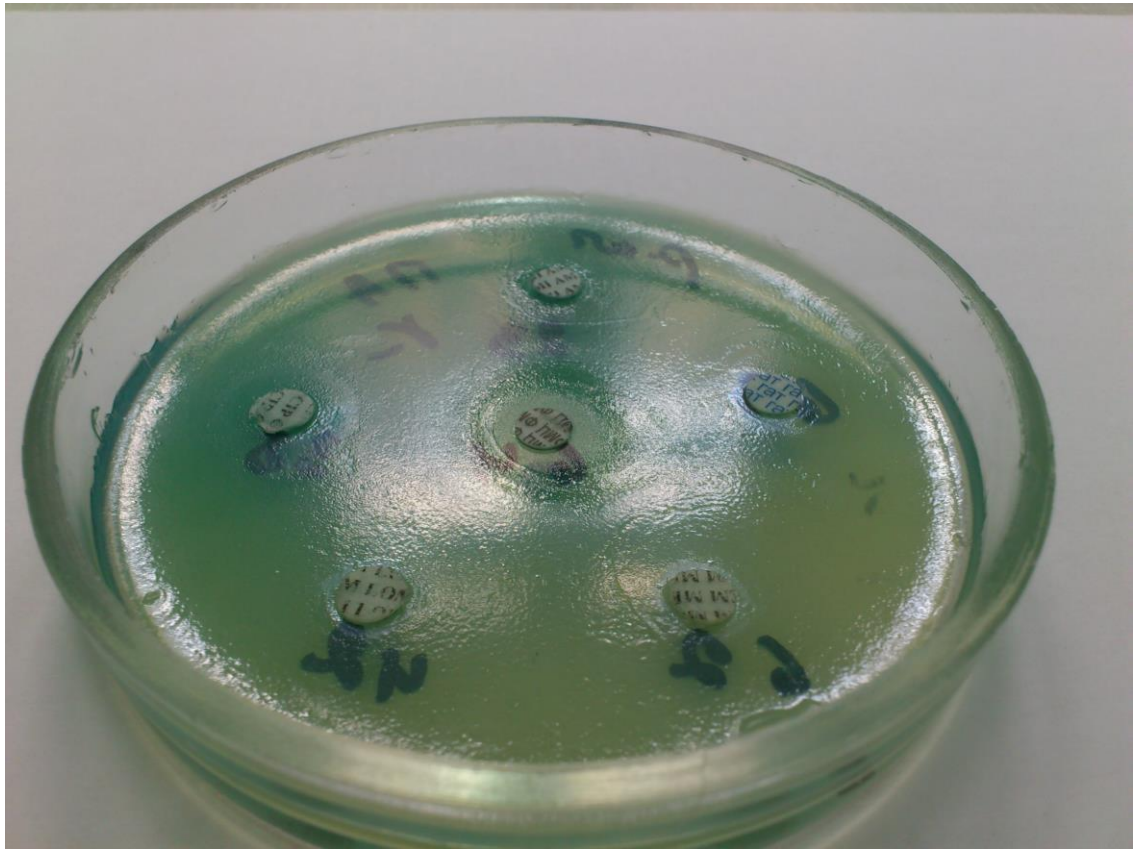
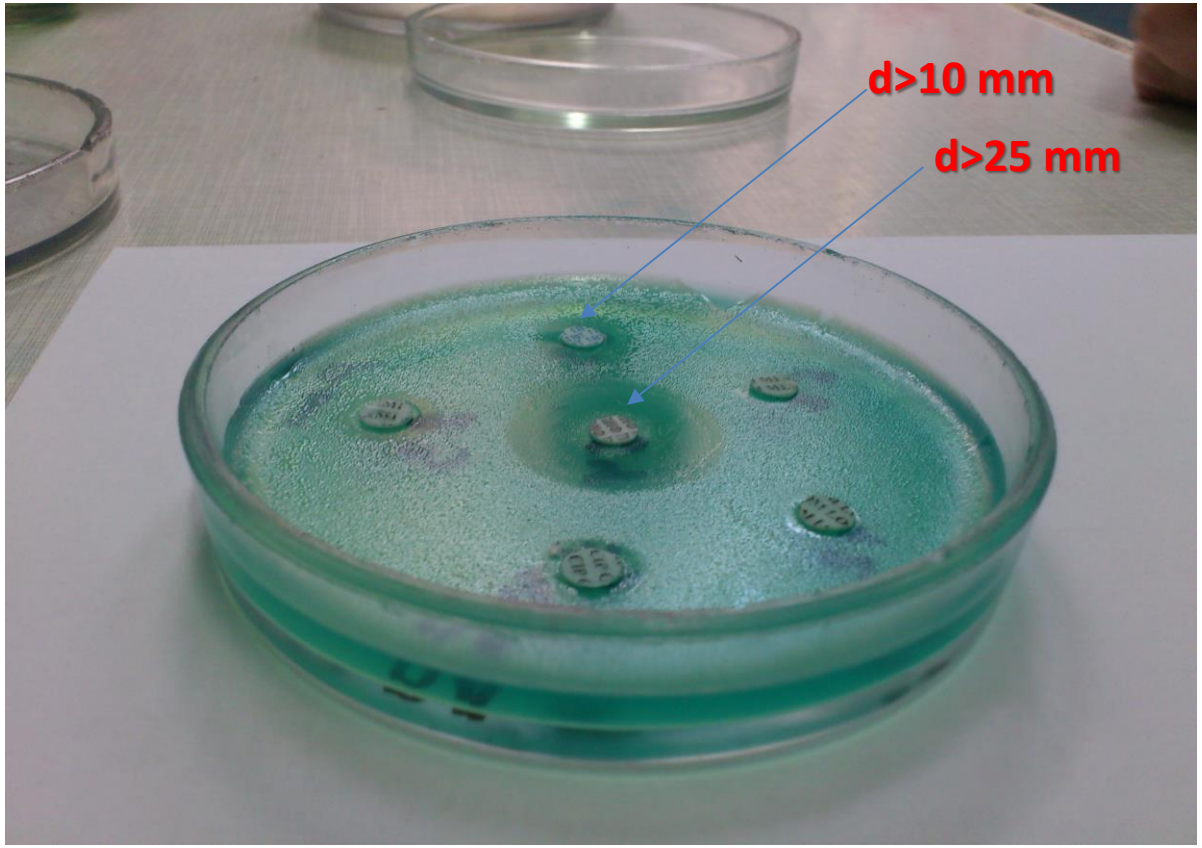
Effects in vitro Pseudomonas Aeruginosa



Multiresistant *P.aeruginosa*
(central disc – polymyxin d=10 mm)
Growth without enhancers: 3 day growth,1st passage



Multiresistant *P.aeruginosa*
(central disc – polymyxin, upper disc – amikacin)
Growth with enhancers: 3 day growth, 1st passage

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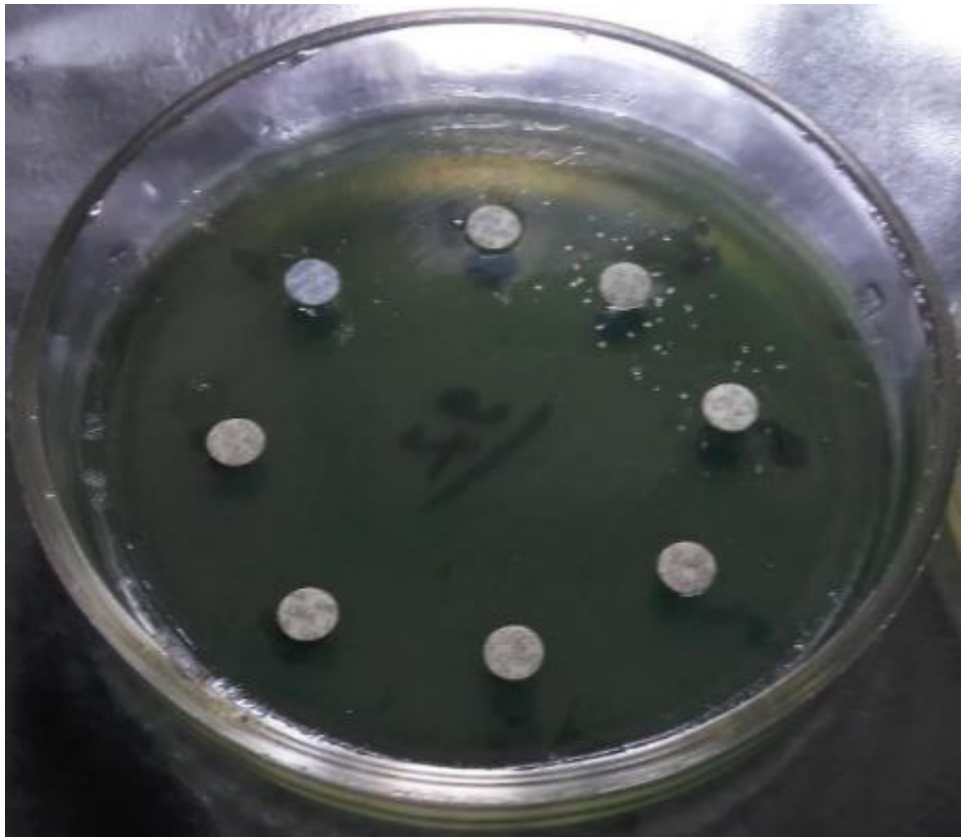
Effects in vitro Pseudomonas Aeruginosa

Multiresistant *P.aeruginosa*
Growth with enhancers: 6 day growth,
2nd passage (lost of virulence factor – pyocyanine)



Multiresistant *P.aeruginosa*
Growth with enhancers: 9 day growth,3rd passage (Loss of bacteria's viability)

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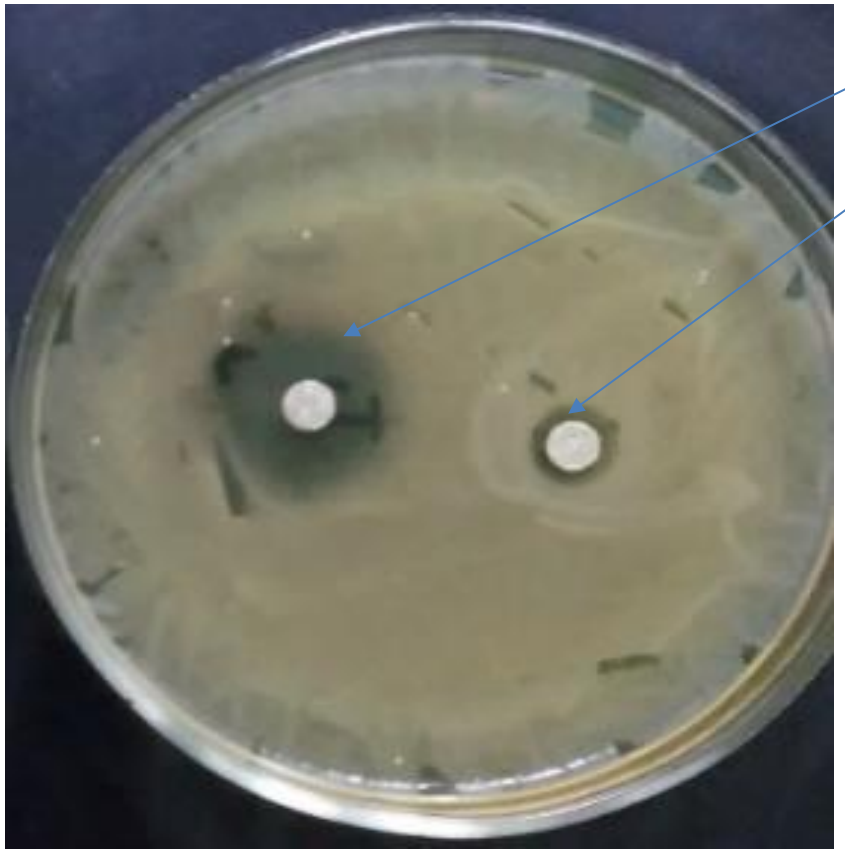
Effects in vitro Acinetobacter Baumannii

Multiresistant *Acinetobacter baumannii*
(full resistance for all antibacterials)
Growth without enhancers: 6 day growth,2nd passage



Multiresistant *A.baumannii* (central disc – polymyxin, upper disc – amikacin)
Growth with enhancers: 6 day growth, 2nd passage

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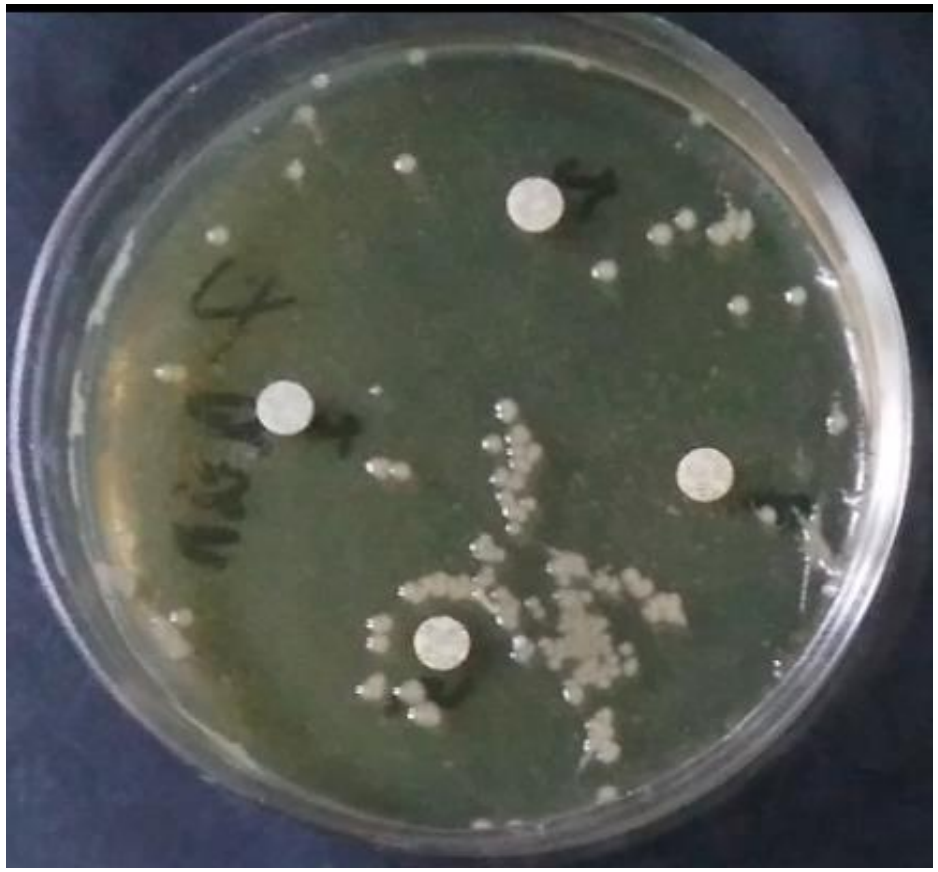
Effects in vitro Acinetobacter Baumannii

Multiresistant *Acinetobacter baumannii*
(full resistance for all antibacterials)
Growth with enhancers: 9 day growth,3rd passage



Multiresistant *A.baumannii* (first disc – polymyxin, second disc – amikacin)
Growth with enhancers: 12 day growth, 4th passage.
Loss of bacteria's viability.

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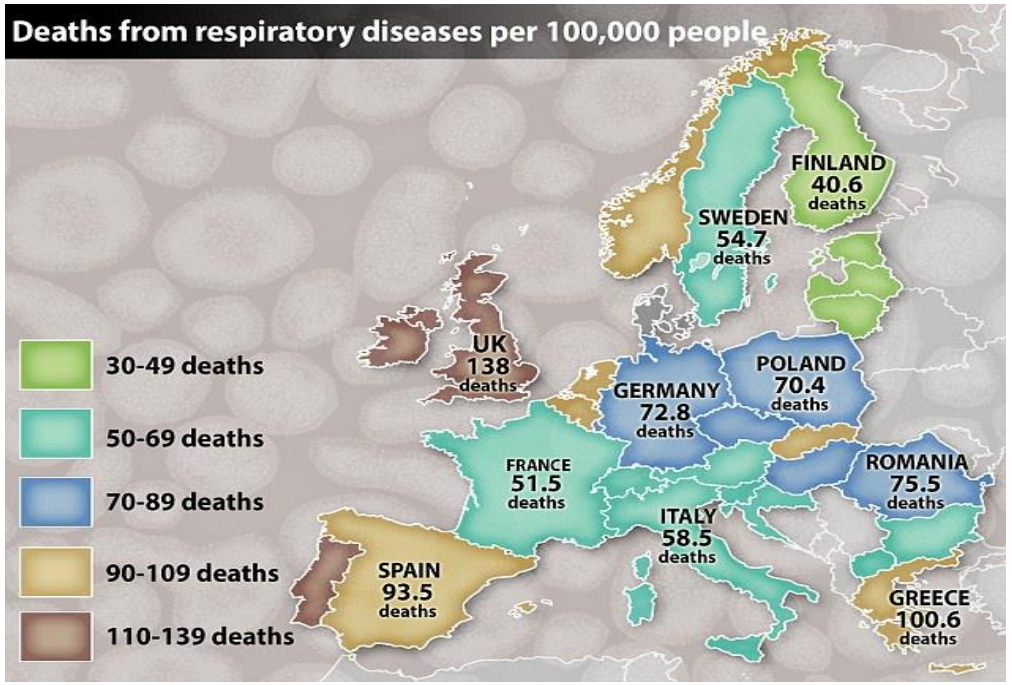
Respiratory disease and death as result of superbugs resistance

Pneumonia can strike anyone, from presidential candidates to famous people. And the number-one cause of death from infectious disease is all too frequently a race against time. (Medscape Internal Medicine Oct 19, 2016)

Henry Edward "Ed" Roberts “the father of the personal computer".

Died April 1, 2010 after a months-long bout with pneumonia at the age of 68.



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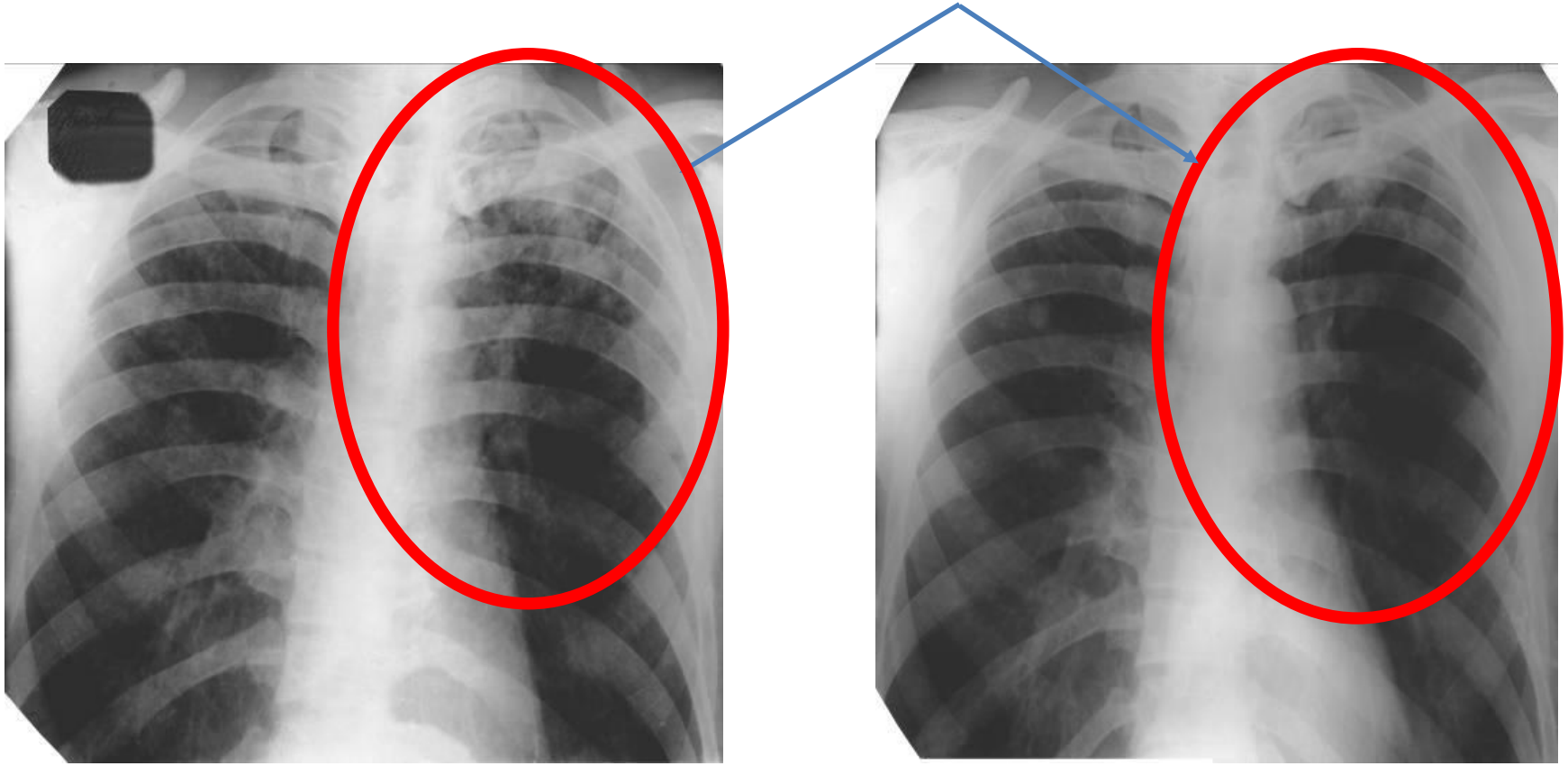
Clinical case of active MDR pulmonary TB



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.

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.

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We are looking for partners and investors for our startup company

1.For implementing our MDR new platform:
“To win, Stop fighting." Objective the platform – inhibition of bacterial resistance factors without killing microorganisms. This will prevent the selection new dangerous multi-resistance virulence strains.
2.For implementing our ongoing researches and findings, based on principle multiple synergisms, TRIZ (theory of inventive problem solving), modern Design and Technologies in different fields not only for MDR but also for many other applications.

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Advantage for pharmaceutical industry producing Antimicrobials

Our approach could help industry to increase market in well known and new upcoming antimicrobials.

1. Using antimicrobials in synergistic combination with enhancers will make MDR bacteria more sensitive to current and to older antibiotic generations.
2. The pharmaceutical companies with our approach will recommence decreased use of antibiotics affected by MDR bacteria.
3. Pharmaceuticals based on our approach will be able to decrease MDR bacteria to new generation of antibiotics.

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Advantage for pharmaceutical industry producing enhancers

Our approach could help industry to increase market in well known and new upcoming enhancers.

1. Using enhancers in synergistic combination with antimicrobials will make MDR bacteria more sensitive to current and to older antibiotic generations.
2. Enhancers are medications approved by FDA for other conditions.

With our approach enhancers in synergy with antibiotics acquires new properties to fight MDR bacteria.

3. Enhancers and other substances may have additional and newer applications in pharmaceutical and medical industry.
4. Our approach using different synergistic combinations of enhancers and antimicrobials may generate new medications beneficial in medical, pharmaceutical and financial industries.

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Advantage for pharmaceutical, medical and financial industry

1. Using our approach in synergy of different components, **industry** can achieve not only benefits in medical and pharmaceuticals and also in financial sector.
2. By minimizing expenses for FDA approving well known and approved components, **pharmaceuticals** will accelerate production of new drugs based on financial benefits.
3. Our approach could help **industry** to increase market in well known and new upcoming antibiotics.
4. Increased sensitivity MDR bacteria to current antibiotics, will decrease **patient's** hospital length of stay and will bring to faster recovery.
5. **Pharmaceutical** companies can resume inpatient and outpatient antibiotics use, which was decreased due to MDR bacteria.

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Proposal for forms of collaboration

1.We invite **pharmaceutical companies** for collaboration to research and developing innovative medicines based on combination antimicrobials and enhancers in the new dosage forms.
2.We understand the value of **investors and partnership**, and we are looking for creative, mutually beneficial pharmaceutical collaborations that will provide the best medicines for patients.
3.Collaboration with partners in **scientific research** for new enhancers groups and new antimicrobial combinations based on our approach.
4.We would share and disclosure our **trade secrets (know-how)** with potential Investor / Partner.
5.Collaboration with pharmaceuticals by **TRIZ consulting** in upcoming MDR and ongoing R&D.

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Proposal for solving problems by using TRIZ

1. Our team has a proven track record for helping companies of solving problems by using TRIZ.
2. Our staff is fortified by a team of scientists and engineers, who specialize in a wide range of disciplines. This diversity in technical excellence and expertise allows us to help our partners, customers and investors manage and control the innovation process.
3. We could become partners in a strategic alliance through which complex challenges become opportunities for success.

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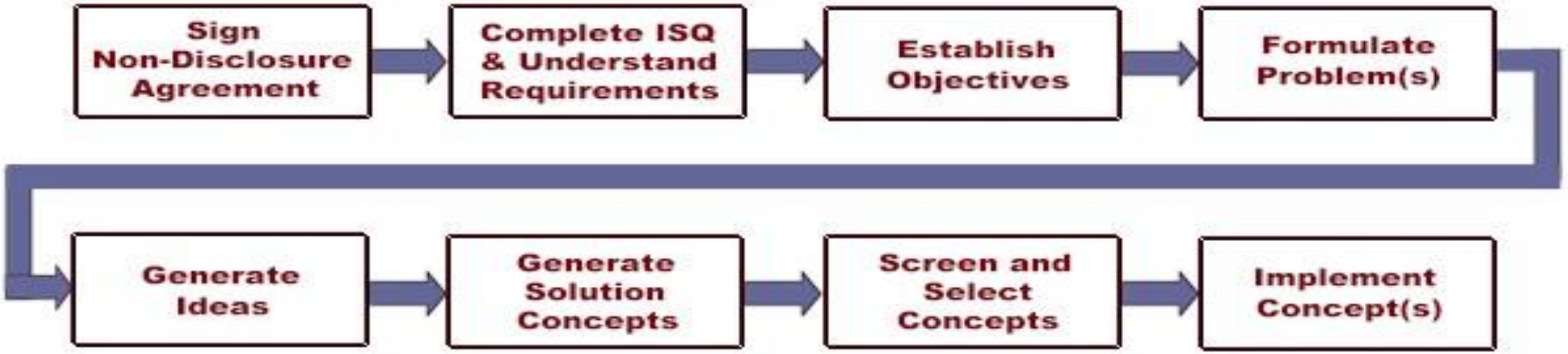
We could participate in collaboration in several ways:

CONSULTING SERVICES – you provide the details and direction, we solve the problem.

FACILITATION – we form a partnership, combining our joint expertise, using TRIZ Methodology, and our software tools to systematically analyze and resolve the problem.

COACHING – Our TRIZ team specialists provide post-training assistance to your subject matter experts, ensuring that their work stays focused, success criteria are met, and maximum benefits of TRIZ Methodology and its tools are realized.



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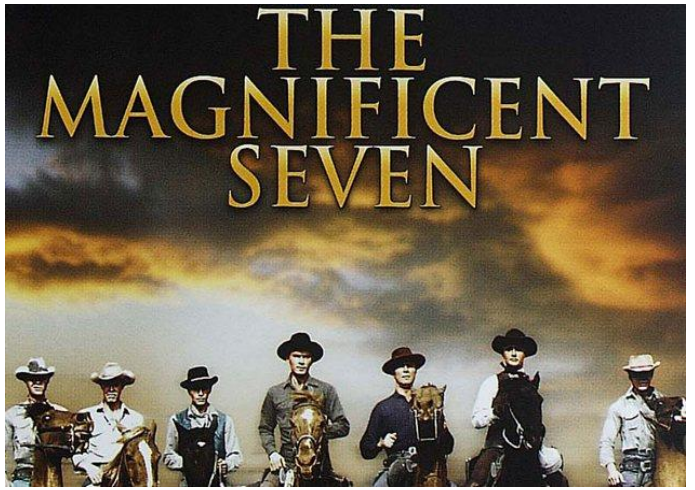

“Coming together is a beginning; keeping together is progress; working together is success.”

Henry Ford

TRIZBioInnovation

Optimistic vision of a new approach for design and synthesis synergistic drugs

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