CREATION OF NEW MEDICAL DRUGS BASED ON TRIZ AND COMPUTER MATHEMATICAL MODELING

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In memory of Genrich Altshuller, creator of TRIZ philosophy and a Teacher, with whom we discussed the most significant of our trends and inventions.

TRIZ (the theory of inventive problem solving) is a new philosophy of thinking, created by Genrich Altshuller and further developed by his followers [1]. One of the authors of this article was fortunate enough to meet Genrich Altshuller many years ago through his father, an inventor. Based on the philosophy of TRIZ, we have created hundreds of technologies and inventions in various fields, some of which are widely used and have brought tremendous economic and social effects [2,3]. Some of our projects based on TRIZ were published in numerous books and articles. [4,5]. One example to highlight, is a new technology in logistics,that was developed with our involvement (situational methods of transportation planning) and created with the active participation of Academician Victor Glushkov. This technology was responsible for a large financial (several million USD) gain. We have developed and implemented hundreds of inventions in the following fields: automotive; construction; dynamic testing, agriculture, logistics, test methods; seismic exploration; training; electronics, applied optics; car industry, ignition systems, multi axis trucks, ergonomics, rheo magnetic fluid control, education, operators' control, sport, medicine, bioengineering, orthopedics, biomechanics, prosthetics, and bioelectrical control [6,7,8]. Additionally, we have inventions in medical systems, and vibrotactile receptor systems used not only on Earth, but also in spaceflights and orbital stations. We have even contributed to the field of education with a technique for teaching blind and deaf-mute students. [9].

A number of areas in bioengineering and subsequent inventions were discussed and approved by Genrich Altshuller himself, in the process of their creation. These include our first adaptive dynamic self-adjusting rational systems in bioengineering that are patented and commercially available in rocket and space complexes.

While TRIZ has been used widely, there is one field where it has not been thoroughly utilized [10,11]. This is an area which affects almost every family, and each and every one of us. Namely, the development of new effective drugs, [12].

To use TRIZ principles in drug development necessitates broad knowledge in several areas rooted in the molecular modeling method. This method includes the application of the laws of quantum physics and quantum chemistry. Additionally, it requires knowledge of the behavior of molecules in various situations and their interaction with each other at different temperatures, as well as in the presence of salts and other compounds.

Truly effective drugs can be developed only on the basis of a systematic approach and in-depth knowledge of the fields of medicine; pharmaceutical chemistry, medical chemistry, physical chemistry, analytical chemistry, pharmacognosy, chemistry of natural compounds; plant medicine technology; biochemistry, molecular biology; pharmacology; and many other disciplines.

Over the last 100 years the pharmaceutical sciences and industry have changed significantly. The approach to drug development has changed from banal screening (out of thousands of synthesized compounds, only one showed biological activity) to those obtained as a result of molecular modeling. The approach using molecular modeling led to the intensification of research - to the synthesis of drugs based on simulated inhibitor profiles. This increased the yield of drugs - out of every hundreds of the synthesized substances, one showed the expected activity. The cost of pharmaceutical development software is currently quite high and can reach tens of millions of dollars. However, this is a reasonable amount, which makes it possible to obtain the required pharmaceutical preparations, at least for known target proteins. However, for the design of drugs of new generations at all stages of development - from building a model of a target protein to creating a drug profile and its synthesis, TRIZ has not been used systematically. Pharmaceutical industry and pharmacology are huge niche for TRIZ [13].

Therefore, many years ago, we discussed the notion of using TRIZ in drug development with Genrich Altshuller. He approved this direction and we began to work in this field, while he wholeheartedly supported our research [14].

Ever since that discussion we have been intensively engaged in research. As a result, we first in the world applied TRIZ in drug development to develop synergistic combinations of existing drugs thereby creating new drugs with non-standard properties. We have created a revolutionary line of new dynamic, quasi-living, self-organizing drugs using the principles of TRIZ and computerized mathematical modeling. Let us illustrate 6 examples from our research and developments:

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Example 1. Novel directions to fight multidrug resistant microorganisms based on the TRIZ approach.

In the early twentieth century, Dr. Alexander Fleming accidentally discovered that fungi mold suppresses the growth of bacteria. This led to the discovery of the first antibiotic, penicillin, named in honor of the microscopic fungus that produced it - Penicillium. This was the beginning of the antibiotic era, and the entire scientific and medical world looked to the future with optimism, they hoped to overcome all infectious diseases with antibiotics.

Approximately 10 years later, it became clear that this was going to be a more difficult task than they had imagined. The phenomenon of bacterial resistance was soon discovered. Namely, bacteria quickly became "used to" antibiotics and developed resistance to them. The general mechanism for the resistance development became well understood and was quite similar for most bacteria, yet hard to overcome [15]. Scientists found that while placing an antibiotic into a culture of microorganisms, indeed most of the bacteria will die, but smaller amounts will survive and multiply. Specifically, the bacteria began to synthesize proteins, such as beta-lactamase, which destroy antibiotics. Additionally, the bacteria prevented antibiotic penetration through bacterial wall by producing biofilm.

This resistance was exacerbated, by the response to the defense from the immune system, and bacteria began to aggressively synthesize toxins, invasion factors, adhesion, increase iron uptake, and immunity resistance factors. (Fig 1). One could say, bacteria began to resist by all available means to host immune defense factors. Take for example, Corynebacterium diphtheria, this strain will only synthesize toxins when there are aggression factors displayed by the immune system [16]. Without the immune system aggression, the bacterium feels at ease, and does not produce toxins [17].

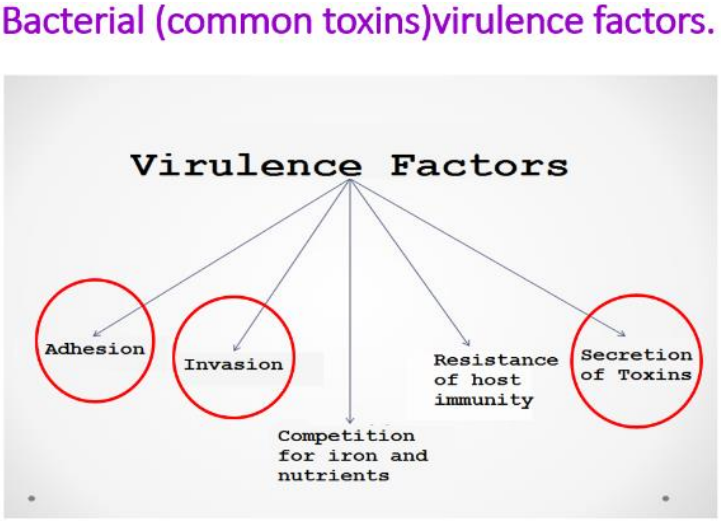

Fig 1. Main virulence factors of microorganisms

As mentioned earlier bacteria began to form biofilms and through this, biocenosis, antibacterial drugs cannot get into the bacterial cell [18]. The biopolymer frame consists of substances that do not allow organic compounds larger than amino acids and monosaccharides to pass the biofilm [19]. In fact, such biofilm is impermeable even for most antiseptics. It is very difficult to fight biofilms of nosocomial infections due to the impermeability of the framework. [20].

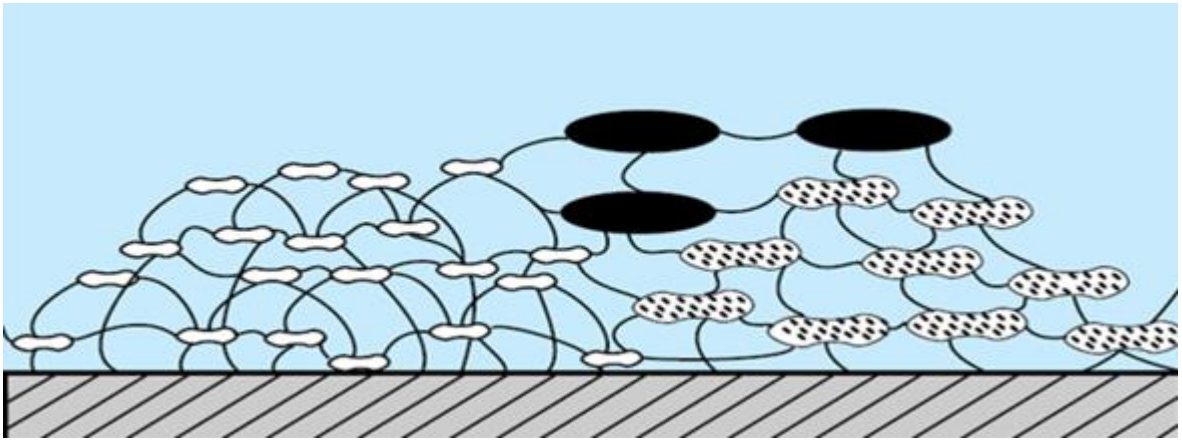

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Fig 2. Bacteria in biofilms bind together in a sticky web of tangled polysaccharide fibers which anchor them to surface and to each other

The more types of new antimicrobial drugs are synthesized, the faster the microorganisms will adapt. This large-scale resistance is due in large part, to the overuse of antibiotics in veterinary medicine, as well as the constant presence of antimicrobial drugs in drinking water, meat, and the environment [21,22].

As a result of this broad resistance, in many cases, large pharmaceutical companies gradually began to lose interest in the development of new antimicrobial drugs due to the inability to recoup the investment of development let alone make a profit [23].

Although bacteria of the same species live inside the biofilm, while in the process of growth and epigenetic changes they acquire significant differences from each other depending on the biofilm layer - upper and lower. These differences occur in their ability to adhesion and their ability to excrete the components of the biofilm framework **[24,25].**

It is not a fact that substances capable of penetrating the upper layer of the biofilm framework and killing bacteria close to the surface will affect the microorganisms of the lower biofilm layers [26].

TRIZ contradiction: from one side, in order to stop the production of virulence factors we should stop killing the microorganisms, however from another side, if they are not killed then the bacteria will persist in harming the patients. This contradiction was resolved by us using the principles of TRIZ and studying bacterial growth **[27].**

The major TRIZ principle used in this case is called "inversion" and belongs to the group of methods for resolving contradictions due to structural changes within the system.

The idea is to find a contrast alternative. After all, a burn can be attained not only from extreme heat, but also from extreme cold, and expansion process can occur not only by heating, but also by freezing water with the transition to ice. Overcoming psychological inertia allowing you to use the opposite action sometimes allows you to find novel solutions.

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.

Fig 3. TRIZ Principle 13 for new way of fighting infection

This TRIZ principle is based on "doing the opposite", this allows for resolution of contradictions related to the fact that a direct action dictated by the conditions of the problem is unacceptable, but the result is necessary to solve this problem [28]. *TRIZ principle: instead of the action dictated by the conditions of the task, we should carry out the reverse action***.**

It should be noted that, even if the application of reception does not give a solution, it will help you to better understand the system. In our case we asked, what will happen if the bacteria are not killed, but on the contrary, we stimulate its growth? How will bacterial aggressiveness change? How will this change virulence factors and toxins release? It is known that the bacteria secretes aggressive factors into the external environment to "clear out" the place of residence, to destroy other microbes and tissues with toxins [29]. If nothing needs to be "cleared out" the bacteria "feels" comfortable and it ceases to release toxins and begins growth [30].

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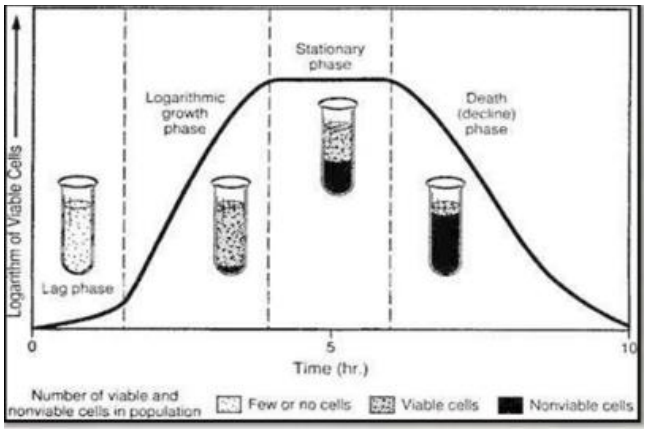

Fig 3. Phases of microorganisms growth: log phase – most perspective target for the action of antimicrobials

Using this idea, we have developed a pharmaceutical composition that prevents the bacteria from entering in to the phase of "clearing", and synchronizes them in to the phase of "reproduction" without toxins release [31]. In this phase bacteria becomes less-toxic and harmless to the host body. This bacteria does not secrete virulence factors and does not develop antibiotic resistance, on the contrary it loses them and becomes sensitive to the action of antibiotics.

In vitro experiments have shown the success of this approach for XMR strains of *P. aeruginosa*, *A. Baumannii*, *K. Pneumonii*. By the third passage on nutrient media with bacterial growth activators, in contrary to the background of rapid growth, all bacteria lost their resistance to antibiotics and ceased to release toxins into the nutrient medium.

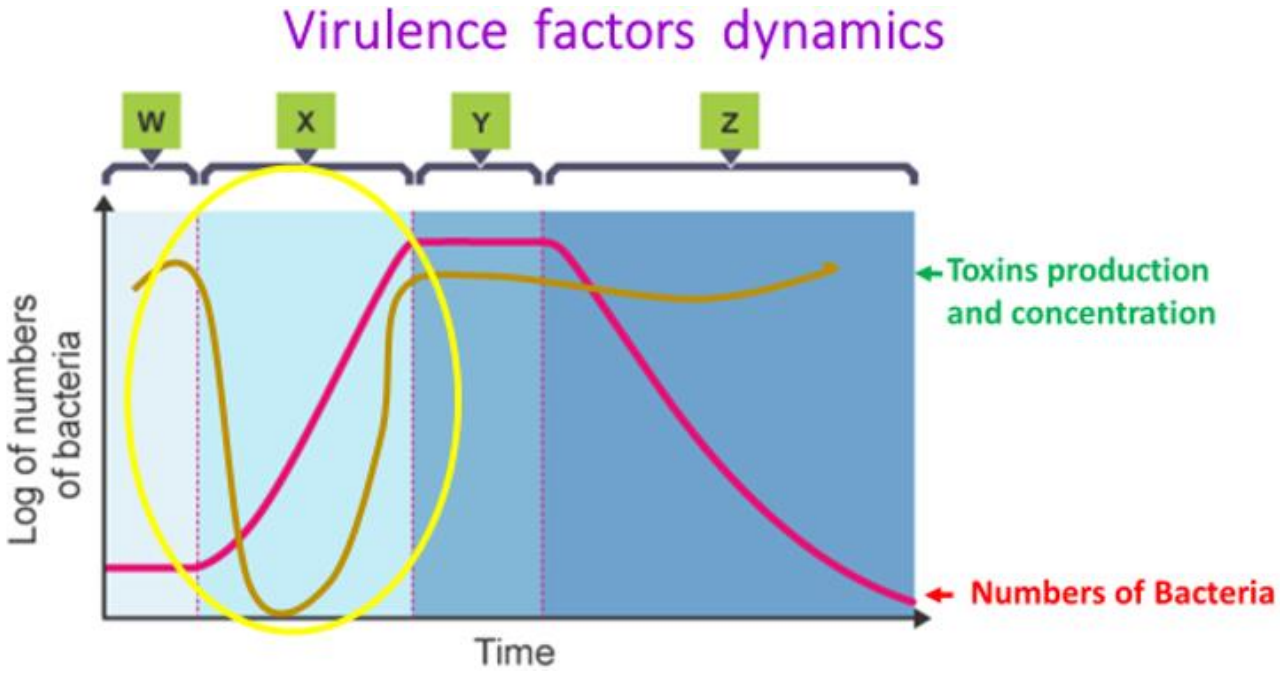

Fig4.Virulence factors dynamics in process of bacterial growth

The figure shows a graph of the inverse relationship between the rate of division of microbial cells and the release of toxin / virulence factors. The faster cells divide, the less they are able to resist external aggressive factors, namely to release toxins, antibiotic resistance factors and virulence enzymes. In fact, rapid growth is consistent with decreasing bacterial pathogenicity [32].

Therefore, we proposed a new scheme in which the bacterium synchronization would be altered, transferring them to the phase of rapid growth which would cause the ceased release of virulence factors. This step is a new direction in the fight against multidrug resistant bacteria. The proposed non-metabolic growth factors are a complex phosphodiesterase ligand and potentiate each other. In the presence of these substances in the nutrient medium, the

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bacteria became susceptible to antibiotics, although they did divide rapidly [33].

Example 2. Polymyxin with reduced nephrotoxicity

The issue of combating multi-resistant nosocomial infections, which we described above, also includes the problem of high toxicity found in the latest generations of peptide and amino peptide antibiotics [34]. Among of this group of antibiotics is drug polymyxin [35]. After intravenous polymyxin therapy, even for just a few days, nephrotoxicity and renal failure may occur in at least 50 percent of patients. [36].

TRIZ contradiction: from one side, in order to effectively treat infectious disease and save lives, we should use polymyxin however from another side, polymyxin causes kidney toxicity, preventing from it use in full therapeutic scale. This contradiction was resolved by us using TRIZ principle**s.**

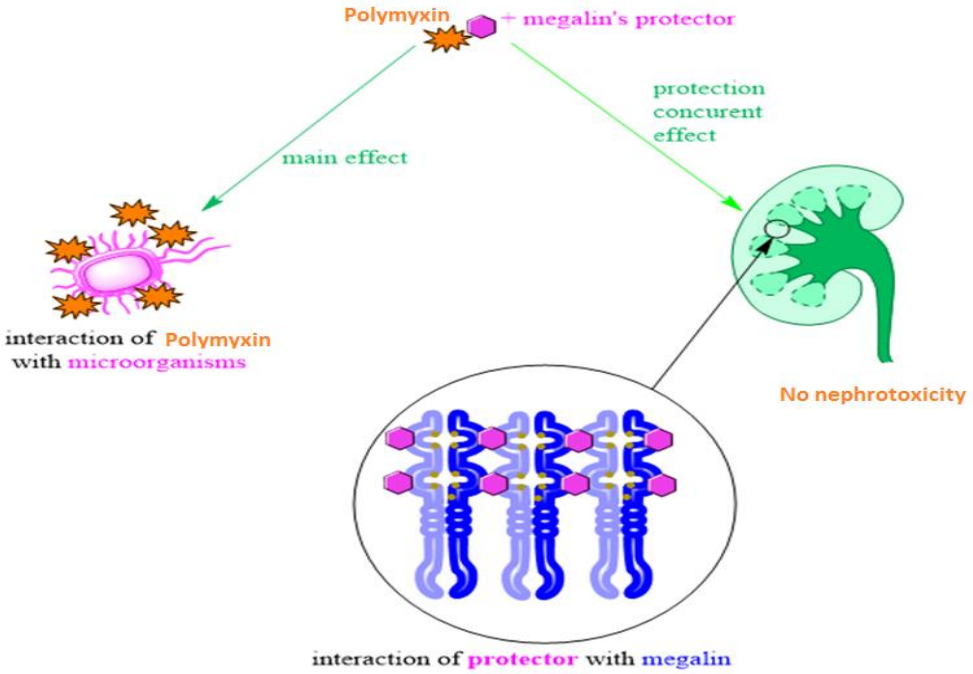
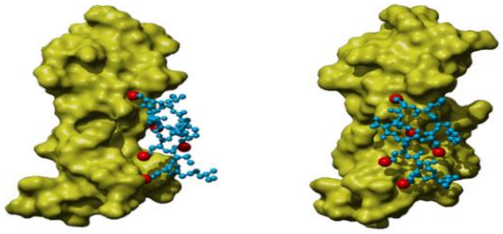


Fig 5. Mechanism of action of combined composition on base polymyxin and nephroprotectors

To solve this problem, we used the following principles of TRIZ [37,38]:

The principle of "pay harm in favor", the essence of which is as follows: a) We can use harmful factors (in particular, the harmful effects of the environment) to obtain a positive effect. b) Eliminate the harmful factor by adding it to another harmful factor. c) Reinforce the harmful factor to such an extent that it stops to be dangerous.



Polymyxin B complex with Megalin (in two projections): polymyxin B molecule (spherical-rod model of **blue color**) on the Megalin surface (**olive-colored**). The nitrogen atoms of the amino groups of the Dab of polymyxin residues are highlighted in red. Hydrogen atoms are not shown.

Fig. 6. Polymyxin B complex with Megalin (kindly provided by Dr. Lisnyak Yu.V.)

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The principle of imposition. Using this principle, we separate the "interfering" part from the object (the "interfering" property — in our case is nephrotoxicity) or, on the contrary, select the only necessary part (the desired property is to leave only the antimicrobial activity of polymyxin). The principle of local quality. a) To go from one object structure (or external environment, external influence) to a non-uniform (there was one polymyxin, now its combination with a nephroprotector) structure.
b) Different parts of the object should perform different functions (the main antimicrobial polymyxin and additional nephroprotector NGL022).
c) Each part of the object must be in the conditions most favorable for its work. *The principle of "pre-planted pillows." Compensate for the relatively low reliability of the facility by prepared emergency means.*

Using these principles, we created a pharmaceutical composition containing polymyxin and an additional harmless compound (as per principle of local quality — each component of the composition performs its function), in which the affinity (tropism) to renal megalin (a target protein in the kidney that is blocked by polymyxin, thus harming the function of the kidneys) is higher than polymyxin affinity, but which does not cause any toxic effects to the kidneys. This substance settles on the renal megalin and prevents polymyxin from connecting to it (the principle of repression) [39].

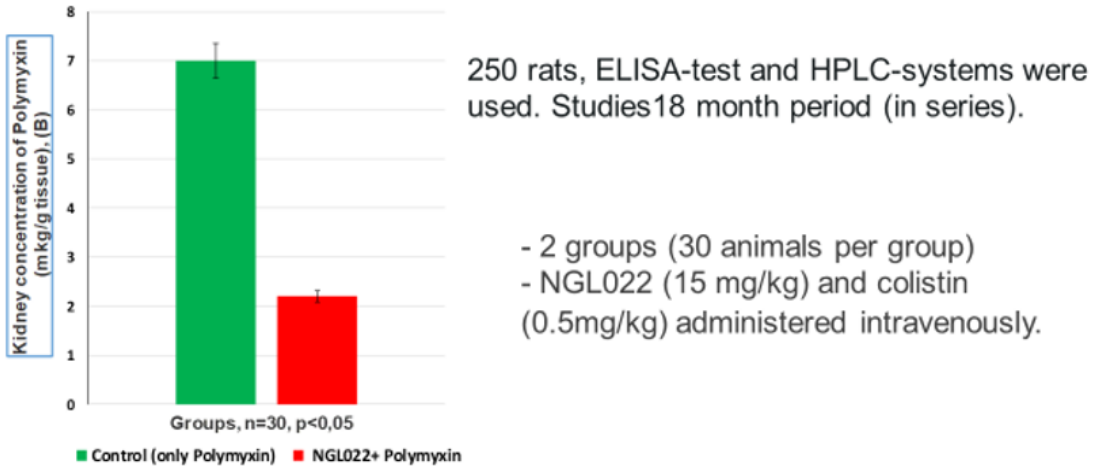

Fig 7. Polymyxin accumulation in the kidney

In fact, we use the principle of "pre-planted pillow" - blocking the target from the side effects of polymyxin and making renal megalin inaccessible for the toxic action of polymyxin.

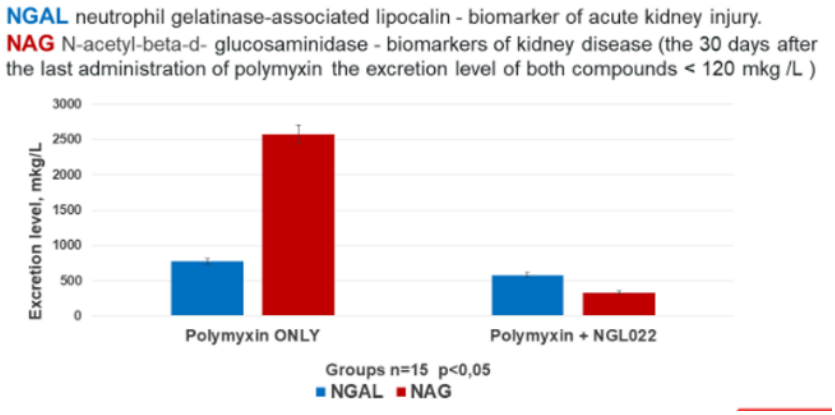

Fig 8. Level of the urine markers nephrotoxicity after using polymyxin only and polymyxin with nephroprotectors NGL022.

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This TRIZ principle of "pre-planted pillow" has made it possible to obtain several pharmaceutical compositions capable of almost completely eliminating the nephrotoxicity of amino peptide and aminoglycoside antibiotics during the course of intravenous therapy.

Example 3. Dynamic drugs: Dynamic insulin.

All modern medical products are unchanging static chemical structures. In this regard, the real efficacy of these static drugs in comparison with placebos has only shown slight statistical difference [40]. These current static substances are not working efficiently. Nearly 40% of people are not responding to these static substances. There are more than 40% of people currently taking classic insulin, which is completely ineffective **[41].**

This is due to the fact that human receptor sites are slightly different from person to person, but a static (classic) drug always has the same fixed structure [42]. Therefore, it will be effective only in some people, those people, whose receptor sites will be most suitable to this drug (analogous to a hand and glove). If the "glove" is smaller than the "hand", the drug will not match and will not work [43].

In this regard, take for example the current standard treatments of hypertension. To treat hypertension, we need a selection of a combination of complex drugs: antihypertensive, diuretic and antiarrhythmic drugs. Furthermore, a hypotensive agent that works successfully for some people is absolutely ineffective for others [44]. This process is extensive and not always successful. The same approach is observed in the treatment of diabetes.

Many patients with type 2 diabetes mellitus develop insulin resistance (even when a normal amount of insulin is in the blood, the tissues receptors are not sensitive to it) [45]. This insulin resistance is also partly due to the static nature of insulin: the insulin structure always remains the same, but receptor sites on the cells change over time. Insulin ceases to "fit in" to the insulin receptor, because the receptor size becomes smaller and insulin effects on the receptor are not achieved.

TRIZ contradiction: insulin, which is produced by drug manufacturers ideally should be the same to allow for mass production for all patients, but from another side each formulation must be different and adaptable to every patient and correspond to their receptor sites. Currently on the pharmacy shelves there is only insulin with a standard fixed structure, and it only work optimally for some people. What needs to be done to ensure that the same insulin fits the entire patient population? Insulin must become a dynamic structure, it must "be able" to adjust. Its structure should be able to "adjust" to the receptor of a particular patient.

According to the TRIZ Laws of technical systems evolution and increasing dynamism, systems are developed from being static to dynamic. This allows flexibility and maximum adaptability of the systems. In addition, to solve this contradiction, we utilized the principle of TRIZ known as "create dynamical" or increased dynamism, this facilitates transition from macro to micro level. When developing this composition, the TRIZ crushing principle of segmentation was also used.

To solve this we utilized the principle of TRIZ called "create dynamical" or increased dynamism. In addition, when developing this composition, the TRIZ crushing principle was also used. The crushing principle includes the following techniques: a) Divide the object into independent parts. b) Make the object collapsible. c) Increase the degree of fragmentation of the object. We suggested to split insulin in to fragments with proteolytic enzymes and partially replace the charges of amino group acid residues by carboxyl groups in these fragments.

Using these principles, we formed a mixture of thousands of insulin fragments, thereby causing only fragments that match the receptor to "settle" on that receptor in a particular patient [46]. In addition, these types of fragments can be easily absorbed by oral administration in the form of tablets. This is all possible because the insulin was divided in to fragments by proteolytic enzymes and these fragments were protected from further destruction by acylation due to alterations of charges on them. Chimeric insulin was chosen for this project. Using the oral administration normally used in rats with alloxan-induced diabetes. The results were quite impressive. The level of blood glucose in the rats was reduced from an average of 40 mmol / l to 9 mmol / l [47]. A single dose of such insulin maintained the glucose level in rats at the level of 9-11 mmol / l for 24 hours. By comparison in the control group the glucose level in rats was at the level of 38-42 mmol / l. Based on our research, it would be possible to create insulin tablets that can be taken once a day for patients with type 1 diabetes and patients with insulin resistance type 2 diabetes [48].

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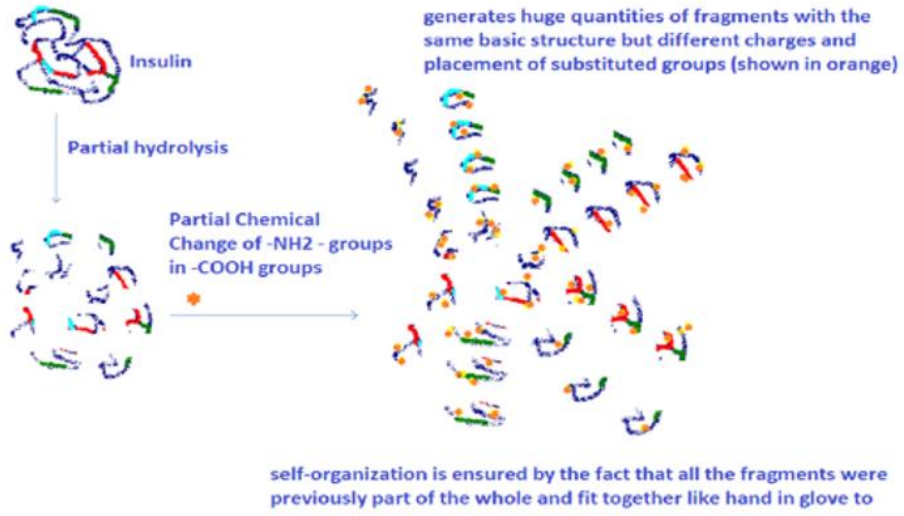

Fig 9. Mechanism of dynamization of insulin and forming chimeric dynamic self-assembled insulin.

Example 4. Dynamic drugs: The dynamic anticancer drug Target-R to treat different cancers.

The scourge of modern medicine is the incurability of most cancers. Despite the fact that in many cases much is known about the cancer including: the molecular mechanism, the etiology of it (in most cases viral), the pathogenesis of the disease, and the mechanisms of metastasis. Despite all this knowledge there are no effective means of dealing with this group of diseases [49].

There are a huge number of anticancer drugs on the market, including both direct cytotoxic agents (anticancer cytostatic) [50] and various types of immunomodulators [51]. The use of various combinations of these drugs usually does not lead to a complete cure for the most cancers.

Current anticancer drugs, despite of clinical efficacy, cause also numerous serious side effects. Anticancer cytostatic drugs side effects are – nausea, vomiting, hair loss, bone marrow suppression [52]. Very often the marked efficacy of chemotherapy in the initial stages of treatment, is reduced to ineffectiveness during long-term treatment. Especially distant cells of metastasis become practically insensitive to therapy due to the effect of "selection" of resistant cells [53].

This type selection effect is also typical for microorganisms and viruses. The more poisonous and toxic substances to the tumor are invented by scientists, the faster the cancer cells adapt to the therapy, sometimes it occurs even right after the first application.

TRIZ contradiction: from one side, in order to treat a patient from cancer, cancer cells must be killed, however from another side, to eliminate cancer cells adaptation to therapy, they should not be killed.

You can, of course, try to activate the host immune system to fight cancer as has been a trend in recent years. This strategy consists of activating the host immune system using immunotropic drugs. This approach has been tested against many oncological diseases, and has been developing by leaps and bounds and yielded positive results [54]. The correct activation of the immune system leads to the activation of the natural mechanisms to fight the tumors, but is not a complete solution. It is not possible to completely cure the cancer using only immunotropic drugs, but it is quite possible to prolong the life span and improve the "quality of life" [55]. Moreover, immunotropic drugs do not cause the adaptation of cancer cells to therapy, and the immune system also quickly adapts to changes in the tumor receptors.

From the point of view of TRIZ, we solved a contradiction proposing a solution to this most complex problem: we posited it in order to cure the patient we needed to place some of the cells in a dormant phase while killing others. Although it will be necessary to keep using the proposed drug constantly, the tumor growth will be suppressed, and the selection of resistant cancer cells will not be observed. At the same time the use of new classes of immunomodulators will allow "launching" immunity to fight against tumors more efficiently.

To solve the above problem, several difficulties had to be solved: It was necessary for the drug to be attracted and accumulate mainly in cancer cells, suppress cancer cell growth and the drug should not be toxic to healthy cells of the host body.

The ideal candidate for the anticancer drug should be chosen from existing drugs produced by pharmaceutical companies. We proposed to target the protein synthesis in cancer cells. It is well known that cancer cells have a unique

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ability to increase pinocytosis and phagocytosis, as well as selectively capture RNA and DNA oligonucleotides [56].

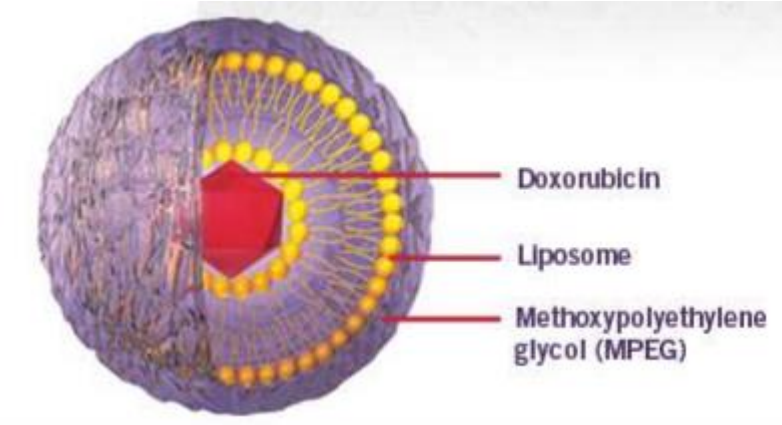

Fig 10. Liposomal doxorubicin with maximal tropism to cancer cells

Our research found that only macrophages in the human body have such properties. Thanks to pinocytosis it was possible to significantly increase the efficacy and reduce the toxicity of classical anticancer drugs by incorporating them inside or into the membranes of liposomes [57]. Liposomal drugs circulate in the blood stream for a longer period of time than pure drugs and are captured from there by cancer cells and macrophages. Doxyl liposomal doxorubicin and its analogues are considered one of the most effective liposomal anti-cancer drugs [58].

Practically for all existing chemotherapy drugs (cytostatic) liposomal dosage forms are used for prolonged action, and already exist on the market. Large-scale clinical studies have shown that such medicinal liposomal forms have virtually no toxicity to healthy cells and tissues of the host body, as long as they do not have pinocytosis properties [59]. In addition to liposomes, cancer cells are able also to ccapture oligonucleotides RNA and DNA from the environment [60].

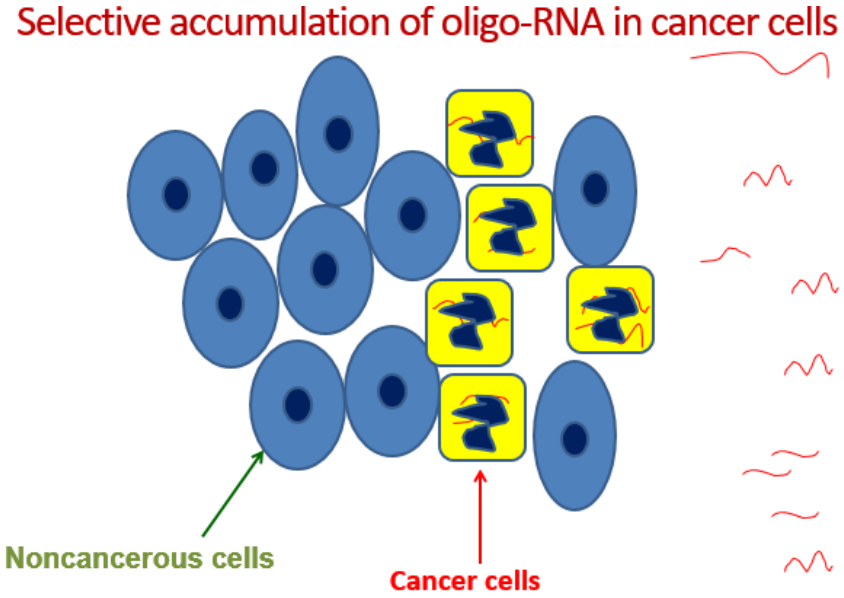

Fig 11. Selective accumulation of oligo-RNA in cancer cells

This property is necessary for them to provide a depot of nucleic acids for uncontrolled division. Due to this property, nucleoside antimetabolites work (for example, fluorouracil) - they are terminally inserted into RNA and stop the division of cancer cells [61]. Experimental studies have long tried to create oligonucleotides that hybridize with targets in cancer cells to "turn off" certain genes. These nucleotides were called “complementary” or antisense [62].

But they all used the natural principle of the formation of a double helix through hybridization - hydrogen

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bonds. Accordingly, the mechanism of DNA repair was originally highly active in cancer cells – for the restoration of damaged fragments. To do this, there are many enzymes in the cell (for example, helicase), which easily divide the double helix into separate chains, which are then repaired along a "healthy" DNA chain [63]. The same thing happened with antisense DNA - natural repair systems they were easily detected and divided into separate chains and replaced with the original fragment. Therefore, the cancer cell retained its genetic configuration and did not allow anti-cancer agents based on antisense DNA to interfere with it. To overcome cell repair systems, it was necessary to replace the principle of the formation of complementary bonds between DNA chains.

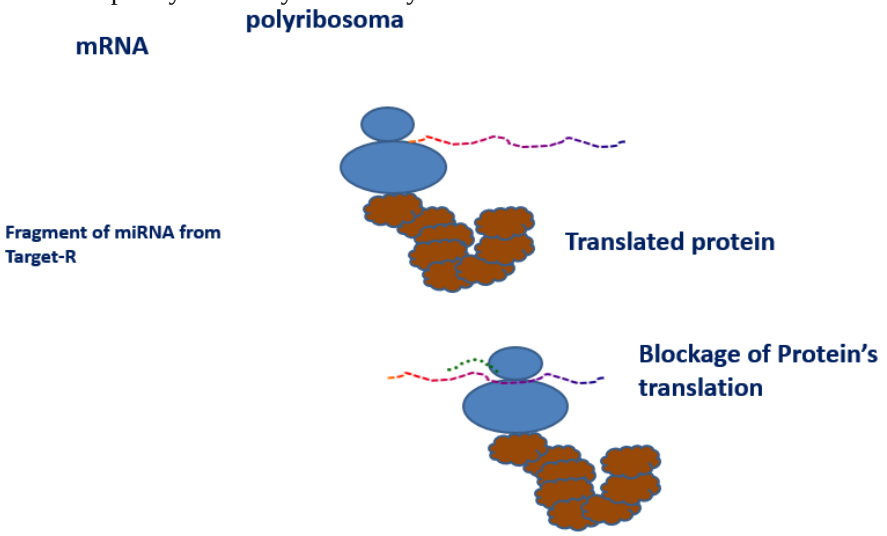

Fig 12. Molecular mechanism of action of antisense oligo-RNA

We have proposed to supplement complementary hydrogen bonds with ionic bonds, which are formed between amino groups in one DNA chain and carboxyl groups - in the other. Carboxyl groups can be introduced into the structure of RNA by a simple reaction to succinylation - the acylation of RNA with succinic anhydride [64]. Due to the lack of natural ability for the repair of such bonds in the cell, the double helix resulting from the action of new drugs will already be much more stable to helicases and nucleases than the helix based on hydrogen bonds.

But DNA in eukaryotic cells is located in the "strength" of the cell nucleus and is practically inaccessible for oligo and poly-nucleotides. Despite the fact that a cancer cell easily captures oligo-nucleotides into the cytoplasm, they practically cannot get from the cytoplasm into the nucleus.

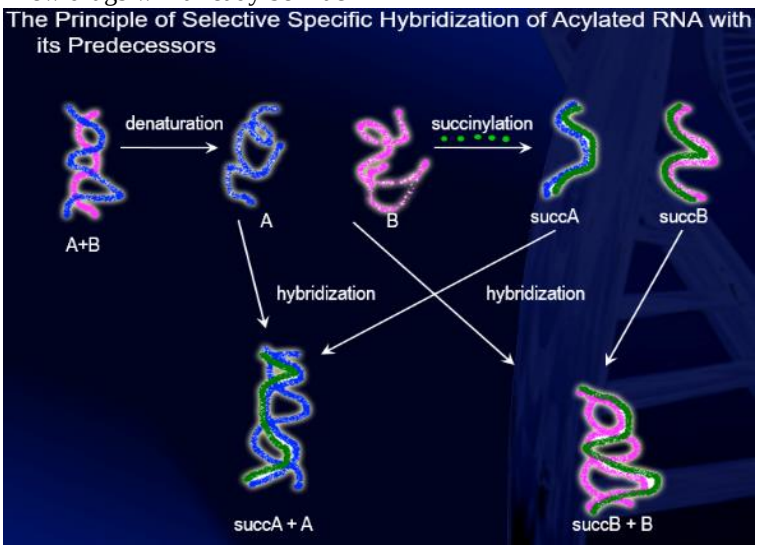

Fig 13. Molecular mechanism of inactivation cells RNA by AAR

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It is necessary to change the concept in principle: not only to change the very principle of formation of complementary bonds from hydrogen to hydrogen-ion, but also to change the targets themselves - not to try to "turn off" something in the DNA - cell nucleus, but to block more accessible cytoplasmic RNA. In the human cells the cytoplasm transport RNA is the most quantitatively represented. The function of this RNA is the delivery of individual amino acids to the polyribosome and their inclusion in the synthesized protein. We came up with an idea: if cancer cells will easily capture oligonucleotides, then eukaryotic RNA oligomeric fragments can be obtained if built on a different principle - ion-hydrogen complementarity. This would be complementary to similar fragments in the cytoplasmic RNA of cancer cells and not get destroyed by natural repair systems (helicases nucleases).

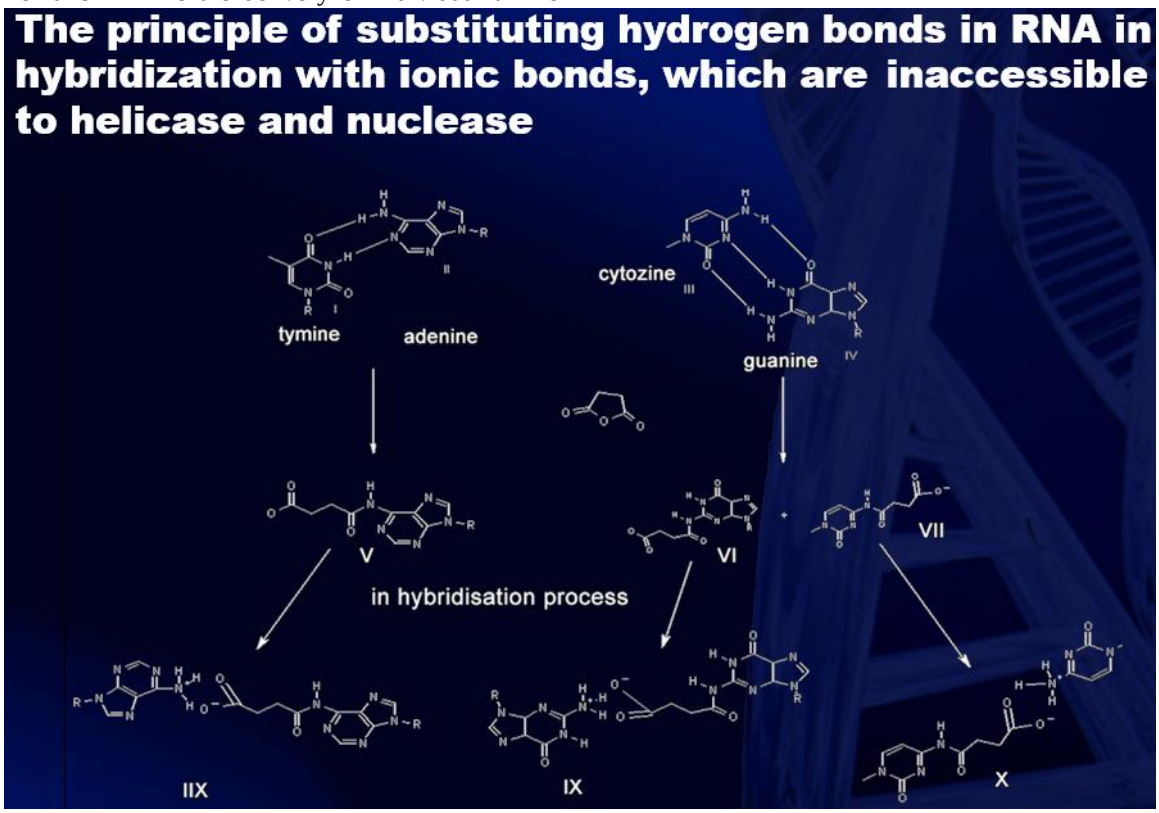

Fig 14. Principle of forming molecular bonds in hybridization process between modified and native mononucleotides

Selectivity of accumulation mostly in the tumors would be ensured by increased pinocytosis and phagocytosis of cancer cells, and by irreversible hybridization (subsidence of complementary fragments on the original t-RNA molecule and m-RNA). This would lead to inhibition or arrest of protein synthesis without killing the cancer cell itself. Moreover, if we can ensure the multiplicity of the original oligomeric complementary fragments, rather than selecting a single RNA molecule, we can prevent the selection of resistant cancer cells to therapy.

In fact, by using our approach, it is possible to block the growth of cancer cells for a prolonged period of time. Although this technique does not lead to a cancer cure, it prevents the cancer cells growth (division) for a prolonged period of time. At the same time, the toxicity of such antisense-RNA will be at a minimal level, and there will be no habituation or insensitivity of the tumor to subsequent therapy.

To overcome many of these contradictions, we used several principles of TRIZ [65]: Specifically, Principles #1 (fragmentation) and #50 (self-organization). In order to eliminate the addiction (adaptation) of cancer cells to the drug, we needed to create a mixture of similar oligonucleotides aimed at thousands of different targets (thousands of targets in t-RNA and m-RNA. it was necessary to choose a source of raw materials - it must be a eukaryotic organism. In eukaryotes, t-RNA differ slightly, since they perform a similar function - the delivery of amino acids to the polyribosome.

Yeast was chosen as a source of raw materials for our composition. To make whole RNA with a mixture of oligonucleotides capable of selectively accumulating in cancer cells, we fragmented (principle #1) the amount of

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yeast RNA into oligomeric fragments with a specific ribonuclease. In order to give all these fragments antisense properties, we replaced the amino groups in exocyclic nucleotides with carboxyl groups.

The oligonucleotides obtained had the property of specific self-organization on the target (#50) — its predecessor, whole RNA (t-RNA or m-RNA). The essence of the drug is that when it enters the human body due to excessive pinocytosis, the cancer cell selectively captures the drug. In the cytoplasm, these thousands of RNA fragments selectively settle on their targets, disrupting their functions (TRIZ principle No. 49 - first dissociation, then association on the target). At the same time, the repair systems are not able to destroy such complexes and RNA fail to function, thereby causing protein synthesis to be significantly inhibited, as well as inhibiting the division of cancer cells [66].

Example 5: Dynamic drugs: Dynamic antiviral drug Albuvir

Albuvir is composed of a mixture of 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) [67].

Currently Albuvir is on the market and widely used as a veterinary drug for the treatment of animals infected with viruses and for the prevention of animal mortality from excessive replication of vaccine viruses during vaccination [68]. The mechanism of action of Albuvir is based on the temporary inhibition of nuclear import peptides (alpha- and beta-importins) [69].

Carboxylated Albuvir peptides bind to the nuclear import peptide signal, and block both viral genome penetration into the cell nucleus and the release of viral particles of DNA from the nucleus. At the same time, on the target (imported), the active inhibitor self-assembles from various inactive Albuvir peptides [70].

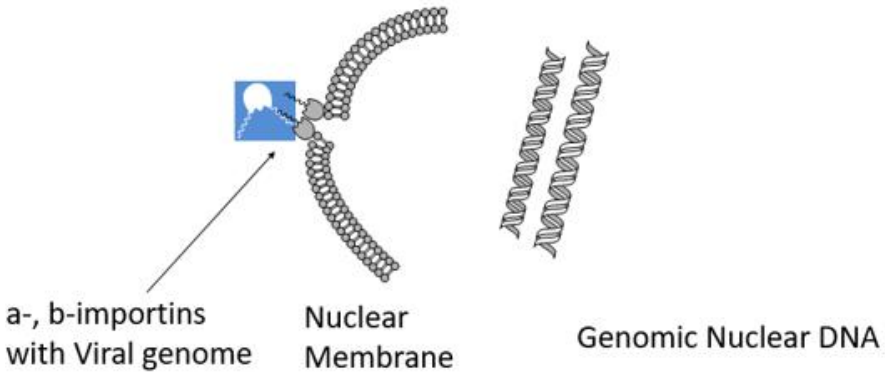

Fig 15. The mechanism of penetration of a viral genome through the nuclear membrane without Albuvir

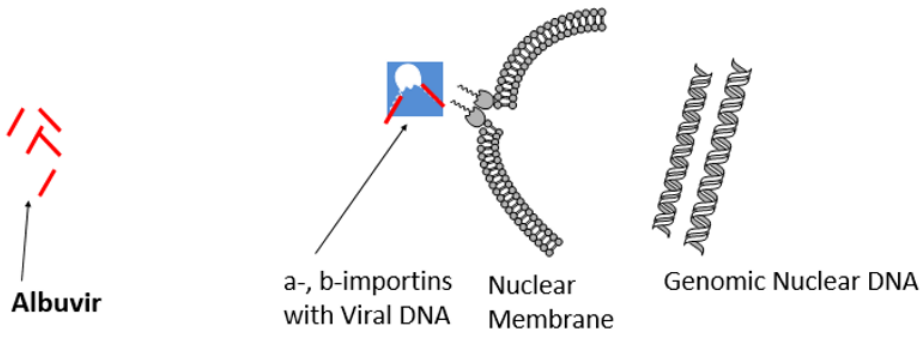

Fig 16. Albuvir's mechanism of action.

Albuvir pharmacological indicators: LD50 = 2880 mg / kg, ED50 = 25 mg / kg, Ti = 115.2, T1 / 2 = 29 min, application method: per oral. Albuvir virus, Influenza virus, Herpes Types 1 and 2, Cytomegalovirus Infection, Herpes Zoster virus, Epstein-Barr virus, Coronavirus virus.

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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. This contradiction was resolved by us using the principles of TRIZ.

The idea of creating Albuvir was based on 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 dynamism: the characteristics of the object should be changed so as to be optimal at each stage of work - for different viruses and different sequences of nuclear import peptide signals, a different sequence of inhibitor from a mixture of Albuvir peptides occurs;

b) to divide the object into parts capable of moving relatively to each other - fragmentation of proteins to Albuvir oligopeptides); 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 rejection and regeneration of parts (having fulfilled its purpose or become an unnecessary part of an object must be discarded (dissolved, evaporated, etc.)

d.) or modified directly during the work - complete biodegradation of "spent" and excessive concentrations of Albuvir peptides without toxic metabolites); the principle of dissociation-association ("Dissociation-association" is stronger than the "separation-association". It allows the substance to split apart when necessary, and when it is necessary to turn into one substance again — the Albuvir complementary peptides are associated with nuclear import peptides); 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) [71,72]

Example 6. Dynamic drugs: hemostatic Gemma

Since World War II till the present time, the main cause of death on the battlefield, surgical wards and other severe trauma is active bleeding. This accounts for up to 60% of the total number of soldiers' death during combat. As cited in "Military Times" [73], 90 percent of the deaths occurred before the injured soldiers reached a medical facility: of the 4,090 troops who suffered mortal wounds on the battlefield, 1,391 died instantly and 2,699 succumbed before arriving at a treatment center."

Modern hemostatic agents used in military and medical settings to treat bleeding are Celox, QuikClot and other drugs with similar chemical activity. Most of the hemostatic agents are based on natural polymers. For example, many are comprised of a composition of chitosan, alginic acid, kaolin, zeolite and other constituent components.

Current hemostatics, while somewhat effective have significant deficiencies. The set of complex wounds and injured body tissues cannot completely remove all the fragments of the known hemostatic agents after their application. Powdery forms source of non-absorbable granules which in turn irritate and delay wound healing. Additionally, the exothermic effect of the granules can cause second-degree burns and at times non-absorbable granules may lead to necrosis of the surrounding tissues.

In our opinion and through our research an ideal hemostatic should have a number of properties:

1. The new hemostatic substance should not be immunologically rejected by the body and have the capability of better resorption and metabolites safely eliminated from the human body.
2. We need to look beyond Biopolymers as they will degrade by 3 well-known mechanisms: a) Cleavage of crosslinks in water when using an insoluble form of biopolymers and transformation in water when using the soluble form without crosslinks; b) Transformation of side chains (for example: by oxidation in carboxylic group, they are more soluble in water than initial group);c) Cleavage of backbone between polymer repeat units (where each unit more soluble in water than polymer). With all these in mind we developed Gemma. Gemma has unique properties.
1. Biocompatibility with body tissues, thereby not causing necrosis and allergic reactions.
2. It does not cause burns during crystallization in the wound.
3. Biodegradable in the body and as such does not require complete removal from the wound.
4. Contains inexpensive raw materials based on natural semisynthetic polymers.
5. Absorbs 70 times the amount of blood compared to existing products.
6. Easy to manufacture and not affected by the process of sterilization.

First results of Gemma study show very interesting results.

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One of the most important indicators of hemostatic drugs is their biological inertness and complete controlled biodegradation. Accordingly, as a result of in vitro studies, the resorption rate of "K1" and "K2" was established. The materials for the study were haemostatic application means: a haemostatic collagen sponge, "Celox", "QuikClot ", as well as new materials on "K1" and "K2" The study of the degradation rate of haemostatic agents in an experiment in vitro showed that all the studied samples of materials underwent resorption. High resorptive activity was observed in the haemostatic composition "K2" - 100% (P≤0.001), resorption rate - 97.83% (P≤0.001), the maximum resorptive activity was observed in preparations K1 and K2. The minimal degradation rates were fixed in "QuikClot ", the resorption of which was 10 times smaller relative to the materials of "Celox" (42.3% (P≤0.05)) of 10.34% (P≤0.05). As a result of the study, the sorption properties of K1 and K2 were evaluated. In the experiment we established how much water K1 and K2 can absorb in comparison with control "Celox" and" QuikClot ".

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Table 1. Indicators healing of skin wounds in rats under influence of composition K2 (Gemma 2) and K1 (Gemma 1)

Sample	n	Wound area* (S) during the observation period, см^2 (M±m)				
		1-3 day	3-6 day	6-9 day	9-11 day	11-13 day
K2 (Gemma 2)	10	4,0±0,7	**1,1±0,4**	**0,2±0,1**	-	-
K1 (Gemma 1)	10	4,2±0,9	**2,0±0,4**	**0,7±0,2**	**0,4±0,1**	-
Celox	10	4,1±1,0	3,2±0,3	2,4±0,3	1,0±0,3	0,3±0,1
Control	8	4,0±0,6	3,6±0,6	2,6±0,6	1,5±0,5	0,5±0,2

* P≤0,05- As can be seen from table 1, in fact 2 times faster healing wounds in animals, the wound which had been treated with the K2-(6 to 13 days), whereas the control sample Celox efficiency did not differ from controls. Epithelization of wounds was initiated on the second day after application of the composition.

Thus, a relatively high sorptive activity was demonstrated by the haemostatic collagen sponge, having a hygroscopicity of 69.41 ± 1.65 ml / g and a sorption index of 15.1 ml × s / g. The results of the hygroscopicity of the materials K1 and K2 were - 70.31 ml / g (p≤0.05) and 49.1 ml / g (p≤0.05), and the sorption index was 17, 4 ml × s / g (p≤0.05) and 11.7 ml × s / g (p≤0.05), respectively. Minimal sorption properties were noted in the hemostatic substances "Celox" and "Celox", "QuikClot ", whose hygroscopicity was 5.63 ml / g and 6.11 ml / g, and the sorption index was 1.23 ml × s / g and 1.10 ml × s / g, respectively.

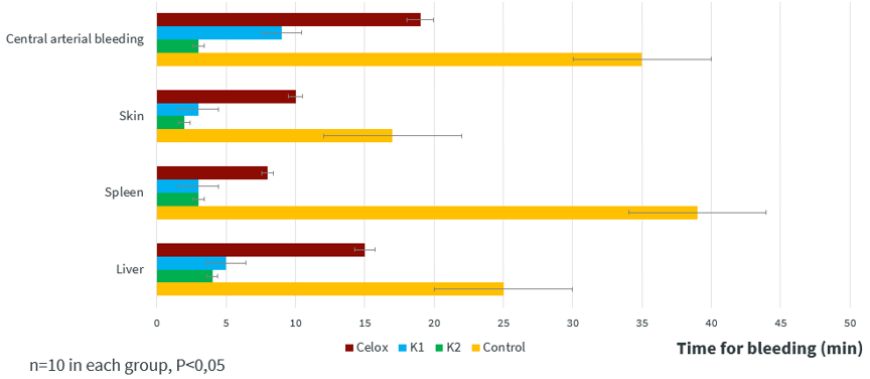

Fig 17. Effect of K1 and K2 on the blood coagulation time in rabbits

Wounds were made to each animal under anesthesia. In the control group wounds not closed. Animals

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with arterial and hepatic bleeding after 35-40 minutes died. In the experimental groups, no animals died. Gemma K1 and K2 stopped bleeding faster than Celox.

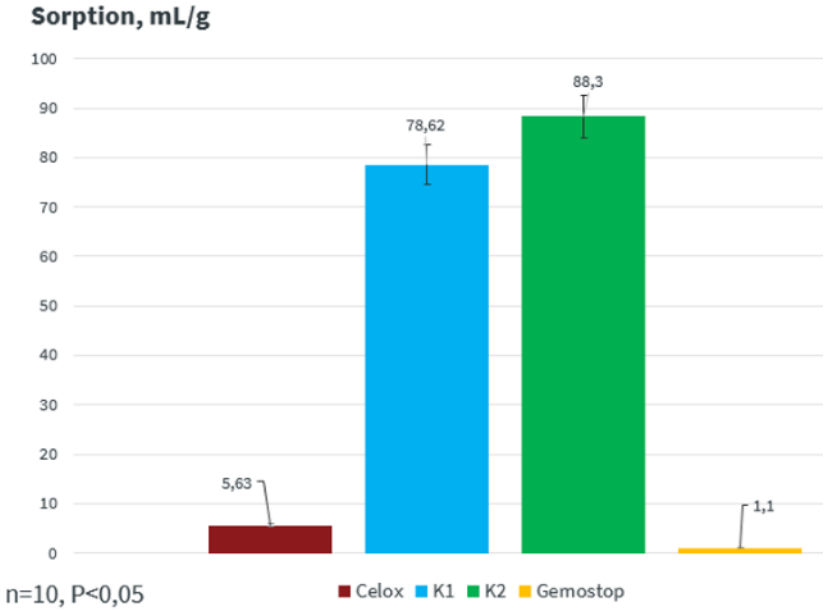

Fig 18. Absorption of water rate by K1, K2, Celox, Gemostop

The percentage of liquid absorption for Celox is 5.63 g of water for 1 g powder. The largest volume of absorbed liquid in 1 minute is observed in K1 and K2 agents, the smallest volume in Gemostop and the average value in Celox.

Hemorrhaging is responsible for about 40 percent of the deaths following traumatic injury, with 33 to 56 percent of those deaths occurring during the prehospital period (Kauvar, Lefering, & Wade, 2006). Early trauma care stresses the importance of minimizing blood loss in the prehospital environment.

New generation of hemostatic substances with a binary effect, can be used on the battlefield, in hospitals, and by surgeons in life threatening uncontrolled bleeding situations.

The first TRIZ contradiction: from one side, a new substance (Gemma) must quickly stop the bleeding and the tamponade must be tight and firm, on the other hand the rapid stop of the bleeding causes ischemia and necrosis of contacting compressed healthy tissues due to pressure and compression. Tamponade must be firm and must not be firm.

The second TRIZ contradiction: on the one hand, in order to stop severe bleeding from multiple injuries, you need to carry a whole bag of hemostatic, because the volume of the wound is equal to the volume of the powder brought in there; on the other hand, it is impossible to carry a lot of substance with you on the battlefield. Hemostatic substances should be a small amount and should be big enough amount for a wound at the same time. This contradiction is solved by us creating a dynamical self-adapting hemostatic substance.

When creating Gemma, we used several principles of TRIZ:

- the principle of dynamism: the characteristics of the object should be changed so as to be optimal at each stage of work - for different sizes of wounds the same dose of the drug should help, and only the percentage of absorbed blood will change dynamically [74,75];
- 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.). In this case, it means the complete biodegradation of an artificial thrombus or its parts after the function has been performed, even if then a fragment of an artificial thrombus will remain in the wound [76];
- the principle of self-organization is the self-assembly of the active substance from inactive precursors - a gel-like implant is formed from two dry components in the mixture in the presence of blood, the terminal fragments of which are firmly attached to the wound edges, tightening them and preventing bleeding [77].

Conclusion

1. Pharmaceutical industry and pharmacology are the most important areas to be fully analyzed using TRIZ. Drug development affects almost every one of us. As noted, nobody in the world has used TRIZ as a philosophy of

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problem solving in such important area as a pharmacology in research and development of new efficient medical drugs.

2. This is due to the high knowledge-intensiveness of developing new drugs based on the molecular modeling method. This method includes the application of the laws of quantum physics and quantum chemistry; additionally, knowledge of the behavior of molecules in different solutions and their interaction with each other at different temperatures, in the presence of salts and other compounds.

3. Effective drugs can be developed only based on systematic approach and in-depth knowledge of the team in the fields of medical, pharmaceutical, physical chemistry, analytical chemistry and pharmacognosy. Also, knowledge of such disciplines like chemistry of natural compounds, plant medicine technology, biochemistry, molecular biology and many other disciplines. It is despite changes in the concept of drug development: from drug screening (out of thousands of synthesized compounds, only one showed biological activity) to those obtained as a result of molecular modeling (another name is drug-design). The approach with the use of molecular modeling led to the intensification of research - to the synthesis of drugs based on simulated inhibitor profiles. This increased the yield of drugs - out of every hundreds of the synthesized substances, one showed the expected activity.

4. The cost of software development in pharmaceutical industry and pharmacology caries quite high expense and can reach millions of dollars. This amount makes it possible to obtain the required pharmaceutical preparations, at least for known target proteins. However, for the design of drugs of new generations at all stages of development - from building a model of a target protein to creating a drug profile and its synthesis, TRIZ could significantly decrease expenses, but has not been used systematically. Therefore, pharmaceutical industry and pharmacology are huge areas to explore by TRIZ.

5. Additionally there are significant difficulties in analyzing pharmaceutical patents based on Markush formula, which makes it difficult to analyze the system aspects of development in this important area.

6. The application of the principles of TRIZ in pharmaceutical industry and pharmacology opens up broad prospects in the creation of new classes of drugs that can independently adapt to the patient's body.

7. The combination of contradictions, laws of development systems, mathematical and ARIZ algorithms, Su-field analysis, and principles of TRIZ allows us to achieve extraordinary results and obtain significantly more effective drugs.

8. For the first time in the World we have developed dynamic self-organizing drugs based on the principles of TRIZ. These drugs are capable of adapting independently both to the human body and to molecular targets, including viruses, cancer cells and microorganisms.

9. One of our highly effective dynamic drugs is anticancer Target-R, which is based on antisense RNA oligonucleotides. The drug showed high anticancer activity both in vitro and in vivo without toxicity to host body, specifically in relation to healthy somatic cells.

10. Albuvir is another pioneer antiviral dynamic drug we have developed. It is widely used now in veterinary medicine for the treatment of animal diseases caused by viruses. Albuvir also showed no toxicity with a very wide range of effective pharmacological activity, and its use in the case of influenza was effective even in the later stages of infection.
The pharmacological effects of Albuvir begin very fast, from as little as 30 minutes to 2 hours. The effect becomes apparent in the form of lowering the fever, and reducing the signs of intoxication leading to full recovery. This our project is very important as well since currently, there is no really effective means of combating influenza in humans on the market

11. The proposed new paradigm of combating infectious diseases using TRIZ led to the creation of a pharmaceutical composition that does not kill microorganisms, but rather deprives them of virulence and pathogenicity factors.
This helps to stop antibiotic resistance factors. The absence of microbicidal and bacteriostatic effects within the framework of this concept is a positive sign and excludes the selection of resistant strains.

12. Using the principles of TRIZ will improve the traditional treatment of infectious pathologies using peptide and aminoglycoside antibiotics. As a result of using TRIZ, the nephrotoxicity of these antibiotics has been almost completely eliminated without affecting their direct antimicrobial activity.

13. Dynamic insulin made it possible to create a dosage formulation that was effective after a single oral administration and kept the glucose concentration low in rats with alloxan diabetes, which was previously not achieved.

14. We believe that the dynamization of drugs can overcome many problems from resistance to the slippage effect, to eliminate the side effects of drugs. This could save millions of lives.

15.Applying TRIZ, we created a new hemostatic Gemma, which is utilized in extreme bleeding situations and shows extremely successful results, working much faster than existing means without negative impact on wounded tissue, by saving people lives.

16. We are open and interested in cooperating with scientists from different fields of science to create new classes of drugs for the treatment of the most common human pathologies.

17. Our expertise of applying TRIZ and mathematical modeling in pharmaceuticals, produces new future R&D trends. We have been working on new TRIZ applications of

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these incredibly important and noble areas related to people's health.

CREATION OF NEW MEDICAL DRUGS BASED ON TRIZ AND COMPUTER MATHEMATICAL MODELING

Farber B.S., Martynov A.V., Kleyn I.R.

The article provides an overview of the current state of the use of TRIZ in the pharmaceutical industry and our R&D efforts in that area, based on TRIZ and computer mathematical modeling. Drug development is one of the most important research areas, which affects almost every family, and each one of us. However, nobody in the world has used TRIZ as a philosophy of solving problems in such important area as pharmaceutical research and development to develop new efficient medical drugs. The application of the principles of TRIZ in this arena opens up broad prospects in the creation of new classes of drugs that can independently adapt to the patient's body. The combination of contradictions, laws of development systems, algorithms, Su-field analysis, TRIZ principles, deep fundamentals of pharmaceutical industry and pharmacology, modern computer mathematical modeling, in the solution of each of the tasks at once, allows us to achieve extraordinary results and obtain significantly more effective novel drugs. For the first time in the World we have developed dynamic self-organizing, quasi live drugs, based on the principles of TRIZ and computerized mathematical modeling. These are drugs capable of adapting independently both to the human body and to molecular targets, including viruses, cancer cells and microorganisms. We have created 17 new projects, however, in this article we illustrate just 6 examples from our research and developments: 1. Novel directions to fight multidrug resistant microorganisms. 2. Polymyxin with reduced nephrotoxicity. 3. Dynamic drugs: Dynamic insulin. 4. Dynamic drugs: The dynamic anticancer drug Target-R to treat different cancers. 5. Dynamic drugs: Dynamic antiviral drug Albuvir. 6. Dynamic drugs: Hemostatic Gemma. Applying TRIZ and mathematical modeling in pharmaceutical industry, produces novel and future R&D trends. The proposed new paradigm of combating infectious diseases using TRIZ led to the creation of a unique pharmaceutical composition. The molecular modeling approach led to the intensification of research and for synthesis of drugs based on simulated inhibitor profiles. This increased the yield of novel dynamic drugs. The dynamic drugs can overcome many problems from resistance to the slippage effect, to eliminate the side effects of drugs. This will save millions of lives. We deeply integrated TRIZ and computer mathematical modeling in our R&D. In addition, our approach includes the application of the laws of quantum physics and quantum chemistry; additionally, knowledge of the behavior of molecules in different solutions and their interaction with each other at different temperatures, in the presence of salts and other compounds. Really effective drugs can be developed only on the basis of a systematic approach and in-depth knowledge in the fields of medical, pharmaceutical physical chemistry, analytical chemistry and pharmacognosy, chemistry of natural compounds, plant medicine technology, biochemistry and molecular biology, pharmacology and many other disciplines. Modeling these processes requires a large amount of not only computer time, but also knowledge in a number of broad areas: from quantum physics and chemistry to synthetic organic chemistry, in order to synthesize engineered substances. Despite changes in the concept of drug development: from banal screening (out of thousands of synthesized compounds, only one showed biological activity) to those obtained as a result of molecular modeling (another name is drug-design). (named as drug-design). The approach with the use of molecular modeling led to the intensification of research - to the synthesis of drugs based on simulated inhibitor profiles. This increased the yield of drugs - out of every hundreds of the synthesized substances, one showed the expected activity. The cost of pharmaceutical development software is currently quite high and can even reach tens of millions of dollars. But this is a reasonable amount, which makes it possible to obtain the required pharmaceutical preparations, at least for known target proteins. However, for the design of drugs of new generations at all stages of development - from building a model of a target protein to creating a drug profile and its synthesis, TRIZ has not been used systematically. Pharmaceutical industry is a huge area to be explored by TRIZ.

Keywords: TRIZ, theory of inventive problem solving, Altshuller, TRIZ in pharmaceutical industry and pharmacology, Laws of technical systems evolution, problem solving, Su-field analysis, drug-design, dynamic self-organizing, quasi live drugs, anti-cancer, antiviral, multidrug bacterial resistance, antibacterial, synergy.

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Photo. From left to right: TRIZ creator Genrich Altshuller and Dr. Boris Farber (Petrozavodsk city, USSR)

In memory of Genrich Altshuller, the editors publish a photo below. The photo was taken at Genrich Altshuller's apartment, enjoying a cup of tea and discussion of TRIZ application in pharmaceutical industry, pharmacology and bioengineering.

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