Delivery department.
The magnetic field will spread the drugs to the diseased cells.

Any medicine brings not only benefits, but also harm. How can we minimize the harm, treat a specific organ, vessel, cell? It is important not only to organize the "targeted delivery of the drug" to the lesion, without stuffing the whole body with it, but also to take the drug out of the container where it is needed and when it is needed. Medical nanotechnology can help in solving this problem.

A group of scientists from the Department of Chemical Enzymology of the Chemical Faculty of Moscow State University is engaged in one of the topics in this area. The researchers are led by the Deputy Director of the Scientific and Educational Professor Natalia Klyatschko. She is a well-known scientist in the field of nanotechnology, biochemistry and biocatalysis, specializing in the study of enzymes. Natalia Lvovna heads the research carried out under the grant of the Russian National Science Foundation, with the complex title "Remote control using an ultra-low-frequency magnetic field of the functions of biopolymers and other macromolecules immobilized on magnetic nanoparticles".

The group under her leadership developed and experimentally confirmed a fundamentally new approach to changing the functional properties of proteins (enzymes), biological membranes and other biomolecules using magnetic nanoparticles and an alternating magnetic field.

The essence of the process consists in the mechanical breaking of the bond between, for example, the molecules of the drug-enzyme and the molecules of its blocker-inhibitor under the influence of a magnetic field or in changing the permeability of the lipid bilayer of the biological membrane of the cell.

Given the small scale of the system, this method was called nanomechanical. The research of N.Klyachko's group belongs to the category of technological breakthroughs in the field of medical technologies and medicines. The work is already in its third year, as a result, the basic laws of the influence of the alternating magnetic field (AMF) on the structure and biochemical properties of nanoaggregates should be revealed. This will make it possible to purposefully create new molecular biomedical technologies that allow not only to deliver drugs directly to the diseased cell, but also to turn them on/off their work.

-Natalia Lvovna, what exactly do you do under a grant from the Russian Humanitarian Science Foundation?

- We are engaged in fundamental scientific research, - Natalia Klitschko smiles, - meaning the further application of our developments in the field of medicine. The

effect of the magnetic field (MF) on biological processes has been known for a long time.
Research is conducted all over the world in a variety of aspects and directions. Such a direction as hyperthermia is very common.

-What is it?

- For example, a large number of magnetic particles are loaded into a cancer cell, and then they are exposed to a high-frequency magnetic field. This was accepted as the norm until recently. There is a local heating of the particles and the cell and it dies. We once also started with this with a professor of Moscow State University and the University of North Carolina (at that time he worked at the University's Medical Center Nebraska) Alexander Kabanov and his colleague Marina Sokolsky. But we, enzymologists, wanted to understand the mechanisms of action, how MF affects enzymes - biological catalysts, protein structure and a catalyzed reaction, as far as it is possible to control something at all.

- Who are we?

- I have very good colleagues! This is the Doctor of Physical and Mathematical Sciences, Professor Yuri Golovin. He has been lecturing at MSU physics of nanostructures and nanomaterials for students on the for many years, serving as the director of the Center for Nanomaterials and Nanotechnology at Tambov State University at the same time. Alexander Kabanov is a young doctor of Sciences and also very passionate about this work.

Alexander Mazhuga, who bears the “burden” of obtaining magnetic nanomaterials themselves and studying their properties. And students, graduate students, of course, - there is no other way. Now I have 15 people. The composition is changing: new people are coming, tasks are expanding. So, we began to understand and realized: the observed effects do not fit into the concept of local heating – something else is working!

Our colleagues from Tambov made a simple installation on which we were able to create not a high-frequency, but a low-frequency magnetic field (50 hertz and below). It is now a museum exhibit. Such a field does not warm up the system. And there is an effect! The effect of MF can be seen both by changes in the structure of the protein (the circular dichroism method - different absorption of light by the substance depending on the polarization of the latter), and by the catalytic activity of the enzyme. And we had a hypothesis: it's not about warming up, but the effect of MF is due to some kind of mechanical effect on the structure of the protein.

- And due to what can such a mechanical effect occur?

- We found out, for example, that we can fix a protein molecule of several nanometers in size between magnetic nanoparticles (also small, 30 nanometers).

Under the influence of MF, these particles begin to “hang out” and pull the protein molecule with them. Thus, we can change the conformation of the protein, that is, the spatial arrangement of atoms in the molecule.

This largely determines its chemical, physico-chemical and biological properties. This was one aspect from which, in fact, we started and continue these studies. Then they began to try different systems, including for drug delivery. After all, the task is to first send the medicine to the cell in a certain container, and then somehow take it out. This is a big problem, and there can be a lot of options.

For example, how to get a substance out of a polymer container or how to deliver an enzyme to a cell and then pull it out? We started messing with that too. We tried a variety of variants of magnetic particles, differently functionalized depending on the task. There were enough questions: which molecules to use for functionalization, long “tails” or short, “charged” molecules or not, etc.

- Tails?

- For example, a long “tail” is a natural polymer made of polyaminoacids, polyvisin having many, many positive charges. The protein (the medicine in this case) is negatively charged, the “tail” is positively charged and fairly strong complex of protein and polymer is formed on a magnetic particle. Under the action of MF, the “tails” begin to move and ... throw off the protein. Voila, the delivery is complete.

- Straight wings, legs and tails are obtained.

- Well, yes, - Natalia Lvovna smiles. - “Tails”,but we thought and tried to influence the cell membrane. We took a “container” on the surface of which there is a bilayer of lipids (like a cell membrane). It can be a liposome or an exosome-type vesicle (exosomes are microscopic extracellular vesicles (vesicles) with a diameter of 30-100 nanometers secreted into the intercellular space by cells of various tissues and organs. - A.S.).

Magnetic nanoparticles were used. They were grown in the form of long sticks. And we got again an interesting result: under the influence of a magnetic field, such a wand “walks” and pulls these same lipids from the biological membrane. At the same time, the membrane itself is disordered, in other words, its integrity is violated. And if so, then you can inject the medicine from the outside into the container or unload it into the cells from the delivery container. We were able to load a high-molecular protein into the cell by disordering the membrane under the action of MF.

Another important point is working with enzymes that destroy cells of various pathogens. They are isolated from bacteriophages - viruses-bacteria. It is possible to isolate an enzyme that will kill only a pathogenic cell. Usually bacteriophages infect a cell and produce an enzyme from the inside, which leaving the cell, kills it.

And we want to force the enzyme to kill a given cell from the outside. And here, too, a low-frequency MF turned out to be useful, which can force the enzyme to "crawl" through the membrane to the peptidoglycan of the cell, which this enzyme is able to destroy. We already have a fairly large line of devices that create magnetic fields of various frequencies.

- Are the devices domestic?

- Yes, developed and made by our colleagues from Tambov (the company "Nanodiagnostics") - "Astra" and "Tor" and another one that allows you to measure the spectra and kinetics of absorption and fluorescence directly in MF.

- In December, the work on the grant will end. What results will you report? What's next?

- We want to apply for an extension. We have many ideas for continuing this work, including not only with an alternating magnetic field, but also with a constant one.

Our colleagues are currently developing for us a universal device with variable and constant MF of low and high frequency (within the grant). And there is something to report. For example, we were able to show that with the help of a field and magnetic rods, it is possible to change the actual ordering of lipids in the biological membrane both in the containers of liposomes and exosomes, and in the cells themselves. These studies have great prospects.

- Who else in the world, in the country deals with this problem?

- There are several groups in the world that study the influence of MF on certain processes. Although they continue to exploit the idea of hyperthermia, many scientists already use the term "magneto-mechanical action" . They noticed us, they read our publications.

- Are you the discoverers?

- In fact, yes. We understand what we are dealing with at the molecular level. We work with a homogeneous MF and no one knows how to do this and does not do it: we use a strictly homogeneous field in experiments with specified frequency and intensity parameters.

- Have your works been noticed at scientific conferences or through publications?

- And so and so. Publications read well.

- And how many publications have already been made on the project?

Probably twelve pieces, even a little more than necessary. Although we don't have time for everything , it also takes time.

Was the application for a grant from the Russian State Foundation conditioned by the need to find money for new research or in order to continue the ones already started?

- You know, before we had a megagrant of the first wave of 2010 from the Ministry of Education and Science, Alexander Kabanov led the work on it. There were many directions related to enzymes in polymer nanoparticles. And a small piece concerned our topic today.
Even then we tried to understand these fields. And the developments required continued research. And some works on this topic have already begun to appear in the world. I wanted to figure it out further. And the money is never small scholarships.
In general, after a megagrant from the Ministry of Education and Science with a huge number of papers to fill out, it seemed to me just manna from heaven: the report is simple, there are few papers.

- What hinders?

- We have to work within the framework of what we have. And this is much longer. A lot of papers. The delivery time is several months. I periodically work in the USA, in Europe. I ordered a reagent there and after two days it was brought to you.

- Did the economic situation in the country also affect the research?

- According to the grant, we receive about 5 million rubles a year. Salaries have been paid and we are paying, and purchases, of course, have become more expensive. It has become more difficult to send an employee to a scientific conference abroad.

- If there was no grant, research in this area would not have taken place either?

- We live in such a country... We are altruists, we love science. In many cases, we solve scientific problems regardless of funding. The lack of money will not stop research, but it can slow down a lot.

- Why did you choose this profession, Natalia Lvovna?

- I've always liked chemistry. Back in the fifth grade, my mother told me very simply about the periodic table. It's so simple that when chemistry lessons started, everything was easy for me. I liked it.
At one time I thought of going to criminology, I was fond of detectives and even now I like to read. But I went to the chemical faculty anyway.
And I was interested in biology too. We had a Czech professor Karel Martinek, who was my teacher. Then the Department of Chemical Enzymology was just formed. Martinek didn't take girls in the group. But after some hesitation, he suggested to me: “Would you like to deal with enzymes in reversed micelles?” Without understanding a word, I answered undoubtedly : “Yes!”... Then I defended my doctorate early, became a professor early. I managed to work in the USA. Most of scientists left Russia at that time. And I came back: there is devastation in the

country, but there are a lot of students with burning eyes at the department. Where will you go?! Worked, created new directions.

Recently, we have another direction at the Faculty of Chemistry - the chemistry of living systems. There are a lot of people who are interested in, but we can only take 24 people.

- Do you have enough time for scientific research?

- The responsibility is great: at the department I am responsible for the entire educational process, I am also busy at the Faculty of Materials Sciences, the Faculty of Biotechnology, a lot of papers, again... But I try to keep up.

- How soon will it be possible to implement grant research in the applied field?

I think it's not a very distant future. We try to offer maximum efforts in this direction. We will soon move on to experiments on mice. We expect that the experiments carried out will become the basis for the development of a new direction in targeted drug delivery, in particular, cancer therapy, which will lead to the creation of a commercially available therapeutic drug and give patients with currently incurable diseases hope for recovery.