My goal? Effective linking of scientific disciplines for the benefit of the patient

Jan Mičan became one of the holders of this year's Dean's Award of the Faculty of Medicine, Masaryk University for the best undergraduate students of the faculty. He received it in the Category for outstanding scientific performance, where he took first place. The Dean's Award is given according to more selective criteria than in previous years - obtaining it is really a very prestigious matter. Jan Mičan is part of the Protein Engineering team of the International Clinical Research Center of St. Anne's University Hospital Brno (FNUSA-ICRC), where, according to the team leader prof. Damborsky was literally raised up. In the Loschmidt laboratories of the Faculty of Science, Masaryk University and the FNUSA-ICRC, he focuses, for example, on the development of new thrombolytics within the Stroke Brno platform.

Congratulations to the Dean's Award of the Faculty of Medicine, Masaryk University and the first place in the Category for excellent scientific performance. Was it a specific scientific performance or was it an award for a comprehensive work?

It is an award for the overall work, Professor Damborský and I have filled in a number of scientific publications in which I participated. These were, for example, publications from my very first research, which dealt with the development of enzymes for the decomposition of mustard gas. At that time, we developed more efficient enzymes to neutralize this war gas instead of using strong caustics or combustibles, which cannot be used, for example, after some expensive equipment or vehicles are hitted. A number of publications were also from research dealing with the development of new thrombolytics, ie drugs for dissolving blood clots, which we do in cooperation with Professor Mikulík within the Stroke Brno project.

You work in Loschmidt Laboratories of Faculty of Science, Masaryk University and FNUSA-ICRC. Was it your long-term career goal or is it a coincidence?

I would say that it was a coincidence… I met Loschmidt's laboratories at the grammar school, where I noticed a leaflet that attracted students to the Summer School of Protein Engineering event (this year, June 28-30 https://loschmidt.chemi.muni.cz/school/ ed. note). The scientific environment and science in general have always attracted me a lot, and the event promised to get acquainted with the issues of protein engineering directly in laboratories. I applied, I was selected and I was really interested. After high school, I got to FM MU, and that's where my hesitation between medicine and science began, which actually lasts to this day. I managed to get into biochemistry and medicine and I couldn't decide what would be better. Fortunately, I managed to get into the P-PooL program (Undergraduate Program for

motivated medical students with extended scientific training), in which I was able to do science from the first year of medicine. I was placed behind the 150th place on the receivers, which would normally close the door to P-PooL, but thanks to the saying " Nothing is lost for asking " and many emails, I was included in the selection procedure and fortunately I was selected later. When I had to choose a project in the first year, I remembered my stay in Loschmidt's laboratories and wrote prof. Damborsky and Dr. Bednar, if they don't have one. We agreed to start computational research - first these were the already mentioned enzymes for the decomposition of mustard gas. Although the project was not completed, because we were unable to create a better enzyme than those used now, I have learned the extreme number of different methods and procedures that I have used so far. I remember the beginning of the cooperation on the development of thrombolytics exactly, it was the day after the anatomy test, when I was able to attend the meeting of the team members, and I was offered if I did not want to work with the Stroke Research team and prof. Mikulík. So really a coincidence.

What do you plan after studying and what is the specific scope of your work?

When I graduate, I will be a general practitioner, I will specialize only in the attestation. I would very much like to work at a neurological clinic, where patients are treated and recovering after a stroke, but also with other neurological diseases, that is my goal. After I started doing stroke research, my grandmother died of it, so I have unresolved bills with the stroke… I'm still slightly hesitant to be a doctor and stay with research, but now the scales are inclined to work as a doctor, but certainly with research I will stay in the hospital.

When it comes to research, 98 percent of the time it's computer work. Either on mine or I use supercomputers everywhere in the country and around the world. I am a member of the Metacentrum organization, which enables this in the Czech Republic. There are times when I use, for example, a thousand computers at once, to calculate complex chemical reactions or to process statistical data on genetic or protein sequences from all possible animals and protein variants that exist in nature, when I try to find various useful connections between them. I also worked in the laboratory when I tested the enzymes I developed for the decomposition of mustard gas. I wanted to try it and learn techniques like protein purification, cultivation in bacteria, genetic modification of bacteria… I spent the whole summer and winter on it, but I wouldn't change it for computer work… There, if something goes wrong, then follow the steps you can find and fix a bug in the program, while in that lab you sometimes don't know what and why it went wrong. That life is simply unpredictable and even though we know a lot about it, it is still not enough… To do that, you have to sit it down, weld it, wash it off, dose it, stir it up. Computational biology and chemistry, on the other hand, are purely creative work, and if you don't like to do something a third time, you write a program and it will do it for you. And with an internet connection, you can do it, for example, from the Jeseníky Mountains.

Then I dealt with the issue of thrombolytics for a really long time, a number of new drug candidates emerged from the research. Now it is up to colleagues from the Veterinary Research Institute in Brno or the Institute of Biophysics of the AV CR to test them on animal and fluid models. Specifically, there are eleven new enzymes (so-called Ocean's eleven) with

different properties and approaches to the treatment of stroke and four thrombolytics based on staphylokinase, which I developed in Israel. Of course, I pay close attention to how the tests are evolving, but now I am fully committed to finding enzymes for more efficient degradation of plastics for industrial and environmental purposes. If successful, this would be a new way of recycling, which would help to make more and cheaper use of recycled plastics. I also now have several other strategies to further improve thrombolytics by analyzing coevolution or modeling the interaction with fibrin, so hopefully there will be time for them later, I'm looking forward to it.

Do staphylokinases have anything to do with the dreaded staphylococci?

Yes, we try to take advantage of the unique properties of these bacteria. Staphylokinase is a substance with which staphylococci literally make their way through the human body. The defenses that every person has try to stop their progress by using fibrin barriers that build around the bacteria. However, staphylococci can dissolve these clots with the enzyme staphylokinase, and this is exactly what we want to use in the treatment.

What are your other goals? What is the scientific holy grail you would like to achieve for you?

So this is probably the hardest question I've ever had… Of course, I would like to develop a new universal remedy for ischemic stroke, myocardial infarction and embolism in general - everything is caused by blood clots… But the Holy Grail is something else for me, I imagine it like it as an effective interconnection of various scientific disciplines and disciplines. For example, medicine, biochemistry, computer technology, data visualization… All this can be beautifully put together in medical practice and I am terribly fascinated by it. I would like to somehow blur the boundaries between these fields and find new uses for their interconnection. For example, using biochemical methods, develop a new drug, get it to the pediatric patient's bedside, and then compile an effective visually comprehensible treatment plan to understand what is happening to it and why doctors are doing what they are doing with it. And that will calm him down and allow him to manage his diagnosis and treatment well.

Another thing that I am very interested in is from the field of computational-chemical, it is the breaking of the so-called Anfinsen's dogma (This hypothesis states that, at least for small spherical proteins, the native structure of the proteins is determined only by the amino acid sequence. In the environmental conditions in which association occurs, the original structure is unique, stable and kinetically with minimal free energy. Three conditions apply to this: 1. Uniqueness - requires that the sequence has no other possibilities of comparable free energy, therefore the free energy must be unique. small changes in the environment cannot lead to changes in the model with the minimum possible free energy 3. Kinetic availability - means that the bond on the surface with free energy from uncoupled to associated must be sufficiently balanced. shape ed. note). It is a question of what those proteins actually look like, how we all de facto look on this microscopic scale. The standard protein has about 300 amino acids, of which there are twenty species. There are astronomical numbers of those combinations, here 20 to three hundred, which is a huge number, more than there are atoms

in the universe. But how and according to which laws is it put together? Google's AlphaFold2 project, which is now much talked about, is a great hope for solving this problem. It is based on machine learning, which is extremely complex in itself, machines sometimes learn completely on their own, combine different properties, so-called properties and metaproperties, but the weakness is the lack of intelligibility for humans - the project may tell us that some sequence amino acids fold into exactly this shape - a protein, which is extremely useful, but it does not create a theory that one can understand. And that's exactly what I want. Understanding how proteins are put together.

Now that we're interested in interdisciplinary collaboration - the media has recently said that physicists are on the verge of finding the fifth fundamental force in the universe - this also interests you, could it help in the field of biochemistry or machine learning and artificial intelligence?

This probably doesn't upset me, given that this force is so "strong" that we had to create a special accelerator in which we observe muons, particles smaller than atoms, and only then were we able to notice it… If it were to be a force that should have some significance in biochemistry, for example, would not escape us for so long. I don't think this will affect much in the medical world. Although the human body can perceive quantum effects with the basic senses - for example, you will know the difference between water and heavy water, which has a neutron more by taste, but this is extreme and this new force will probably have no effect. But I have heard that this discovery could fundamentally change communication between people and allow very fast transmission of information. And this could significantly improve the calculations and thus the machine learning.

Do you have any free time left in your work? If so, then how do you like to spend it the most?

Sometimes it's "just" walks or trips, I would like to invite you to the shores of Svitava, where we or our friends do such improvised guitar concerts. I also really like such more special walks, it's called urban exploration and it's a visit to old abandoned buildings created by human activity, which are somehow forgotten, unused, intended for demolition and at the same time interesting and beautiful. It's on the edge and I don't encourage anyone else to do it, but I don't do any destructive or harmful activities there, it's just about discovering places that are connected with the history of this or that place.

I will not report it anywhere and thank you for the interview!

Ing. Jiří Erlebach (FNUSA-ICRC)