Three-dimensional structures of protein molecules

The Cogs That Make Life Tick

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We talk to Dr. Marcin Nowotny, the head of the Laboratory of Protein Structure at the International Institute of Molecular and Cellular Biology, about the role of microcrystals, his scientific dreams, and his team

Academia: Why is research into the three-dimensional structure of protein molecules so important?

Dr. Marcin Nowotny: *There are two main aspects of such studies: cognitive and applied. In cognitive terms, studying spatial structures of proteins and other molecules essential for life is like the job of a watchmaker - an attempt to understand all the tiny cogs making a living organism tick. Organisms resemble mechanical devices, with chemical molecules - proteins and nucleic acids - acting as wheels, catches, and springs. Knowing their spatial arrangement helps us understand how these cogs are responsible for driving life. In terms of practical aspects, there are many* *chemical substances with medicinal properties which frequently block these wheels, catches, and springs. They are small molecules which adhere to specific biological macromolecules - such as enzymes - whose function is essential, for example in infection. Knowing the exact shape of the biological molecules we want to block means we are able to design far more effective drugs.*

How do you do such research?

It's important to remember that protein and amino acid molecules are incredibly small. If we were to enlarge the proteins that comprise the human body to the size of a few centimeters, then the scaled-up body would stretch to 20,000 kilometers - half the circumference of the Earth. At the same time, proteins are incredibly complex, comprising thousands of atoms, each of which has a precisely defined location.

There are several ways of elucidating their structures. I think the most powerful is protein crystallography, or more precisely biocrystallography. Using the ever-popular experimental method of trial and error, we create conditions - temperature, chemical solution, additives - that cause our protein to form tiny crystals. They look like crystals of salt or sugar, but they are tenths of a millimeter in size. They are also very unstable outside water solutions.

How do you start working with them?

First of all, we need to obtain the protein. We can't simply isolate it from tissue, because the quantities we need are far too great. The most popular and effective method is to genetically modify bacteria so that they synthesize vast volumes of the required protein on demand.

Once we have obtained our microcrystals, we place them in an X-ray beam. By recording the pattern of X-ray diffraction in a given crystal, we are able to use mathematical methods and computer programs to calculate the positions of individual atoms. It's a highly complicated process; elucidating a single structure takes a minimum of six months, often running into several years - and often it is not possible at all.

You are also running other projects at the Laboratory.

Our 15-strong team is currently involved in over twenty projects. The majority involve determining specific structures of enzymes, proteins, and nucleic acids in order to learn how they work.

We are focusing on two main processes in living cells. The first is repair of DNA - deoxynucleic acid, the main carrier of genetic information. DNA is an incredibly long molecule whose structure encodes information and can be described as the "template" for every living organism. It can be modified in various ways, either spontaneously or as a result of external factors. The modifications disrupt the code and how it is read, which can lead to immediate cell death, or to the formation of tumors. Cells defend themselves using very effective methods of finding and repairing the damage. And this repair system and maintenance of the stability of genetic material is also fascinating.

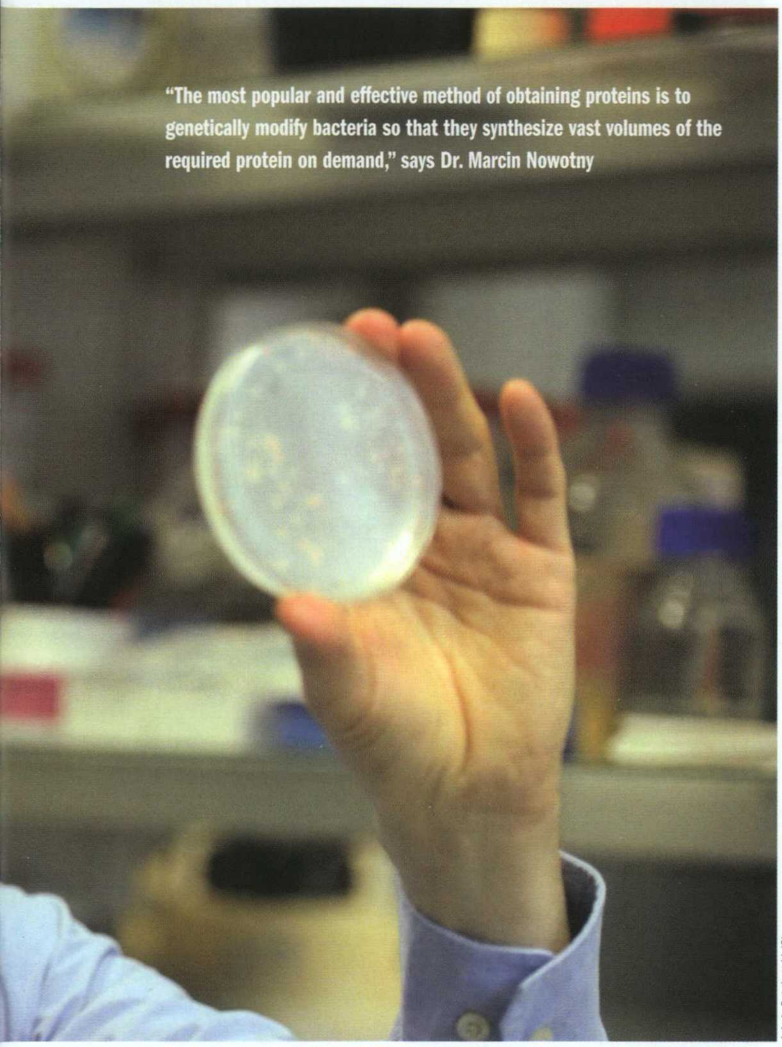
Another important topic for us is reverse transcription. Each living organism contains two types of nucleic acid: DNA, which encodes genetic information, and RNA, which mediates the translation of genetic information into the construction of the organism. Certain enzymes are able to reverse this flow of information, using RNA to synthesize the corresponding DNA molecule. Some viruses carry genetic information encoded in RNA,

which must be transcribed into DNA before they can infect cells. One such virus, which we are trying to better understand, is HIV.

Do you work alongside the pharmaceutical industry?

Of course! We have been working with the Polish pharmaceutical company Adamed for many years. We also have very close ties with OncoArendi - a new, dynamic and very promising company founded in Warsaw and developing cancer treatments.

We are able to provide industry with information about molecular structures, which is essential in designing new generations of drugs. Or, more precisely, chemical substances that have potential to become medicines - it takes many *years to take a substance through the development process before it becomes a drug, and clinical trials are very lengthy and costly. Our project with OncoArendi and labs from Warsaw's "Ochota Campus" - in particular Prof. Andrzej Dziembowski's laboratory - has generated fascinating substances which may be used to treat multiple myeloma in the future. Of course it's far too early to talk about a success, but*



"The most popular and effective method of obtaining proteins is to genetically modify bacteria so that they synthesize vast volumes of the required protein on demand," says Dr. Marcin Nowotny

Jakub Ostałowski (2)

it's encouraging that we have obtained substances with the desired properties, and that we can continue studying them.

What's your greatest scientific dream?

My first would be making a groundbreaking scientific achievement which would help us understand a significant process occurring in the human body or living organisms in general. The second is making a contribution to developing a new, effective drug. Such research is difficult and fraught with risk, so there aren't many such opportunities. Participating in a project which culminates in bringing a drug to market is almost as good as being awarded the Nobel Prize.

Perhaps a simpler ambition is to create a center for electron microscopy in Poland. The technique is currently experiencing a major revival. In many cases it surpasses crystallography, because it does not require crystals. Unfortunately, no institutions in Poland currently have the right equipment. I would like to raise funds to buy state-of-the-art electron microscopes and open a national center. I think it would be a major boon for the entire country, and it would help us catch up with other countries, which are some way ahead.

Do you think we're still lagging behind?

Oh, undoubtedly, although it's also fair to say that Polish scientific research has progressed by leaps and bounds in recent years. I can see it clearly; after I completed my PhD, I spent a few years working in the US and since my return to Poland seven years ago, the progress has been very impressive. But the rest of the world isn't standing still, either, and we have a long way to catch up in terms of technologies, skills and even scientific vision.

When you were in the US, you worked at the National Institutes of Health (NIH). What made you come back to Poland?

One major reason was the foundation of the International Institute of Molecular and Cellular Biology in Warsaw; I don't hesitate to call it a miracle. It's something to be proud of that even without major financial support from state funds an institute was created from scratch which is among the finest of its kind in Poland. And the institute is mainly supported by grants awarded to researchers who work there. I think Poland is now a land of opportunity. Ambitious scientists, frequently very young, who have the right knowledge and skills to conduct significant research can make real changes in the country. Personally, I'm interested in building a strong research team, able to create a synergy with the groups working on our campus.

You have received many research grants. Which one do you value the most?

It's difficult to pick a favorite. We are working on projects financed by grants from three prestigious institutions: the European Research Council, the Howard Hughes Medical Institute in the US, and the Wellcome Trust in the UK - the latter has awarded us two grants. I've also received non-financial awards for our achievements: the Prime Minister's Award, the Order of Polonia Restituta, and the award of the Polish Biochemical Society. But I'm delighted that members of our team are also very successful. Marcin Jaciuk, Małgorzata Figiel and Mirosław Śmietański have all received prestigious START grants from the Foundation for Polish Science, and Dr. Elżbieta Nowak was recently awarded a Women in Science grant from L'Oreal. It makes me happy, and it motivates my team. It's hugely encouraging to see them grow and mature as independent researchers. ■

Interview by **Anna Zawadzka** and **Agnieszka Pollo**