

EMBRACING DIVERSITY

Prof. Magda Konarska

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We talk to **Prof. Magda Konarska** from the Centre of New Technologies at the University of Warsaw about the “spliceosome,” the ongoing need for basic research and the importance of diversity in science.

ACADEMIA: You spent the majority of your professional life in the United States.

MAGDA KONARSKA: I completed my PhD at the laboratory of Prof. Witold Filipowicz at the PAS Institute of Biochemistry and Biophysics. In 1984, I got my dream post-doc position at MIT, at the biochemistry and molecular biology laboratory headed by Prof. Phillip A. Sharp. He won the Nobel Prize in physiology or medicine in 1993.

What impression did MIT make on you? You left Poland during a difficult time, after all...

People do not always understand what makes science great – they expect it to be all brand-new buildings and glass walls. When I first arrived at MIT, I saw cramped spaces, chaos and people having to fight for basic equipment. But real science is not just about giving people loads of money and space, or setting them up in huge offices – that’s simply how we imagine things in Poland.

The conditions at MIT may have been modest, but it’s still an institution filled with eminent researchers.

Certainly. I was exposed to the best of science – intense, fascinating, and creative. When I look at my colleagues of the time, I realize they are now all world-class professors at some of the finest universities around the world. The thing which marked MIT’s excellence when I worked there in the 1980s was the focused thinking and fantastic interpersonal relationships – so many conversations between colleagues about what we were all working on. That opened my mind to different directions in science, to different approaches and ways of thinking. Diversity drives creativity, and that’s something we really lack in Poland.

I think that the issue of low numbers of women working in science in Poland is one example of this issue.

Were there more women working in research in the US than Poland in the 1980s?

There were actually fewer women there than in Poland. I moved to the States as a freshly-baked PhD, and I left behind many women in professorial positions, but laboratories were run almost exclusively by men. After the war, women were routinely awarded PhDs and professorships, but they couldn’t progress much further. The situation is changing now but there is still space for improvement. I think it’s a question of mentality, and it takes a long time to change deep-rooted habits.

In the 1980s, there were just three women working at MIT’s Biology Department. When I joined the Rockefeller University in 1990, Titia de Lange, a professor of cellular biology and genetics originally from the Netherlands, and I were the only women in the institution’s hundred-year history to lead our own laboratories. But now the situation in the US is much better. For example, in 2012 Mark Zuckerberg – the CEO of Facebook – founded the Breakthrough Prize for life sciences, fundamental physics and mathematics. Each winner is awarded three million dollars. The award aims to compete with the Nobel Prize and presents a less rigid approach to selecting winners by stepping beyond the usual circles of well-known old white men. I rarely question the choices made by the Nobel Committee, but it’s worth noting that in the five years of the Breakthrough Prize one-sixth of the winners have been women, which is in stark contrast to the Nobel Prize. To encourage more women into science we can’t just leave the door open for them – we have to shift our entire way of thinking.

NEW FEMALE MEMBERS OF THE ACADEMY

How did your move to the Rockefeller University come about?

It turned out that I had nowhere to go back to, because my old laboratory had been closed after Prof. Filipowicz had also left Poland. I realized that I had to remain in the US, at least for the time being. That was a major challenge. I had to find a job as a woman, with a PhD from abroad – worse still, from the other side of the Iron Curtain – and with just a few years of experience

in the States. I wanted to practice science at the highest level. And yet I encountered no prejudices or stereotypes. I hope we will soon have more foreign scientists working in Poland, and we will treat them this way here.

I think it is important for us to accept diversity, to discover that even though other people may think differently, they still have valuable things to say. And the fact that they work differently from us is often a good thing. Our very attitude to science is mark-



edly different to that in the US. The biopharmaceutical industry there is flourishing, and universities and research institutes focus on basic research, which is regarded as fundamental. You have to make breakthrough discoveries before you can start thinking of their potential applications. In Poland we have it the other way around – I think we put too great emphasis on quickly implementing research results and this hinders our ability to make major discoveries.

What are the positive sides of Polish science?

I see so many talented young people, keen to work on fascinating projects. If only we could create working conditions to encourage them to set up laboratories here. I am in favor of people being trained abroad, but they should feel they have something to come back to. I also think we should encourage inviting talented researchers from abroad to work in Poland and lead their own teams here. We should support this, as this would stimulate our scientific community to help it

chaotic – everyone pops in to see everyone else and talks about their latest research. That is how inspiration and creative diversity work. But here everyone has their nose in their own project, which they have to complete and convert into points.

Has the Polish pathological obsession with points spread to the US?

I imagine it might in some places, but I have never heard about it there. The Polish obsession with calculating points is absurd, but it clearly doesn't bother enough people, if it still persists.

Polish researchers also receive very few ERC grants. Improving that record is one of the aims of the PAS Office of Scientific Excellence you founded last year. Have you considered applying for an ERC grant yourself? You are currently funded by a "Maestro" grant awarded by the National Science Centre.

Yes, I have been told that I should apply for an ERC grant. I may do it at some point, but before I apply for another grant here in Europe, I really want to achieve something first. I think that given the current funding of my team, we can make some significant progress.

Given what you said earlier about women in Polish science, I'm delighted to hear that your team includes women.

In fact it was a women-only lab until recently. But their gender isn't important. I came back to teach a handful of people to think and act scientifically; to get beyond the belief that mastering a few methods and techniques makes people into real scientists. Scientists should be intellectuals and be able to think about their results in a broader context.

Your research focuses on splicing. Tell us more about it.

This year marks forty years since splicing was first described. It is a process which occurs in the nuclei of all eukaryotic cells. Each gene is initially expressed to form a precursor RNA, from which certain fragments, so called introns, are removed through an unusual and highly complex process. It involves two simple consecutive chemical reactions, catalyzed by a very complex enzyme, resulting in the formation of mRNA, which serves as a template for the production of proteins. Just the very fact that the two reactions are catalyzed by a single enzyme, known as the spliceosome, has always fascinated me. It has since turned out that RNA itself, without the involvement of any proteins, can catalyze the same reactions. At the time of the discovery of this process this seemed incredible. Just like all catalytic reactions, splicing is driven by an enzyme, although in this case it isn't a single molecule but a complex of a few hundred proteins and five RNAs;

” For women to have it easier in science, it is important to accept that even though someone may think differently, they may still have valuable things to say.

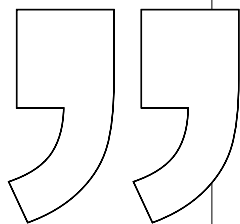
to adapt to higher standards in science. If we provide good overall management, support the best researchers and stimulate contacts with other countries, Polish science could make great strides. This is actually happening now, for example many initiatives of the Foundation for Polish Science address these issues. These are important new ideas that me very hopeful for the future.

Did you return to Poland because of a specific research project?

I came back hoping to make a contribution to the development of Polish science – not because I wanted to do something I couldn't do in the States, because it is far more difficult to work here. We have a real lack of lively scientific interaction and mutual inspiration.

Is it a question of mentality?

Absolutely. Here, at the Centre of New Technologies, more than a year after starting my lab, I still have not spoken to the majority of my colleagues – everyone is shut away in their own rooms. In contrast, laboratories in the States are so lively that they are almost



NEW FEMALE MEMBERS OF THE ACADEMY

the spliceosome is a complex biological machine. Recently, a major revolution took place, forty years after the discovery of splicing. Three laboratories around the world elucidated the spliceosome structure using cryo-electron microscopy – a microscopy technique incorporating extremely refined image analysis. The work of these laboratories allows us to visualize the enzyme structure at different stages of the reaction.

Where are those laboratories?

Kiyoshi Nagai works in England, Yigong Shi in China and Reinhardt Luhrmann in Germany. Today we have a far better understanding of the course of the splicing reaction, first described decades ago. To be able to see all these physical structures and compare them to what we once understood using genetics and biochemistry is fascinating. Even more so because we now understand that the entire spliceosome – the complex of proteins and RNA – is a relic of a very early retroelement, which infected early cells at the dawn of the evolution of eukaryotes. This past history is seen also in the structure of the central protein of the spliceosome, called Prp8 – a highly conserved protein that resembles a polyprotein of a retroelement. In other words, the origins of splicing are primordial. I suspect that most of the infected cells did not survive but those few that did, however, incorporated the retroelement into their own life cycle and gained an incredibly important functional element.

How do you envision your field developing in the next five or ten years?

We already have a solid understanding of the basic splicing reaction occurring in cells. The great majority of human genes contain introns – the non-coding sequences that surround exons, the coding sequences. In the coming years we will elucidate the mechanism of action of the spliceosome even more closely and gain a better understanding of how splicing interacts with other gene expression processes. In cells of higher eukaryotes – including humans – a single gene can be spliced in different ways, as shown through alternative splicing. It will be interesting to better understand the structural basis of the regulation of this process.

So your research studies the very foundations of life...

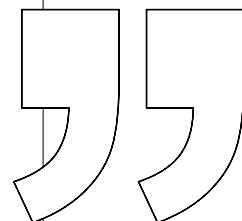
I was always drawn to basic questions in science, thinking that we need to first understand the essence of the studied problem and only then consider applying it for practical purposes. It is exciting to see now how many scientific questions can now be analyzed at a deeper level to help us really appreciate various biological processes. The spliceosome is an example of how other large complexes in cells actually work. It's a gigantic molecular machine, in a way not unlike the ribosome – another molecular machine producing

proteins. A clear look at the similarities and differences between them can be very revealing about the functioning of other structures.

You started off as a biochemist.

Initially I saw a great future in biochemistry. When I opened my first lab, I knew that biochemists always start by breaking something down to basic components, and then they work on putting them back together. But I understood that, because of its complexity, it would not be so easy with the spliceosome. To understand how such complex machines work, I decided to learn genetics. I work now on living cells where by introducing mutations, I tinker with the enzyme in a delicate and precise way at the atomic level. It may sound simple in theory, but the practice is far more complex. Until recently, imagining cells in dynamic life processes and formulating questions such that they could get meaningful answers remained the domain of an intellectual exercise.

I came back to Poland to teach a handful of people to think and act scientifically, to get beyond the belief that mastering a few techniques is what makes someone a scientist.

**What role is played by state-of-the-art technology in the latest genetic discoveries?**

The latest achievements are certainly driven by new technologies, a combination of improved techniques in electron microscopy with impressive advances in image processing. Yet this important new progress could have never happened without earlier conceptual breakthroughs. I have been a research scientist for over thirty years, and I have come to realize that great technological advances grow dated rather quickly. When I was a post-doc, researchers were being awarded PhDs for sequencing a fragment of the insulin gene. Now we send the whole gene off to one of myriad companies and we get the results the next day. And that's exactly how it should be! But we should remember that the most valuable skills in science are clear thinking, inspiration, taking a fresh look at the world and reaching far deeper than the existing knowledge. Without creative thinking, technology will remain a mere tool.

INTERVIEW BY ANNA KILLIAN

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