Interview with Dr. Agnieszka Żmieńko from the PAS Institute of Bioorganic Chemistry

All's Working Out for the Best

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Dr. Agnieszka Żmieńko tells *Academia* both about her intriguing scientific work, and about how she combines it with her personal life

I work in functional genomics, which involves studying and describing the products of the genome - meaning RNA and proteins. For a few years now I've been studying the transcriptome - the set of all RNA molecules produced by a cell in a given state and under given conditions and circumstances. Researchers used to have to analyze the activity of each gene individually, which was a very onerous task.

That was until the arrival of microarrays, which you work with.

Yes, this technology allows us to study many RNAs simultaneously. The chip - similar to a microscope slide - is coated with oligonucleotide probes; each one is used to detect a specific RNA molecule in the sample. The number of RNA molecules under analysis is only limited by the number of probes that fit on the chip. Using the state-of-the-art techniques, this number can run into the hundreds of thousands. The analysis is based on hybridization; the material of interest must be isolated, qualified for detection with a fluorescent marker, attached to the base, and hybridized. If the given RNA is found in the original sample, it will bind to the corresponding probe. The intensity of the signal allows us to estimate its content within the cell.

So you can study the whole RNA content - not just those molecules coding for proteins, but also regulatory ones.

Yes. We are only limited by what's on the chip. I can't study RNA which isn't represented by microarray probes. Fortunately there is now a new method allowing us to go a step further: we can study the entire transcriptome without having any prior knowledge of it. This is high-throughput, next-generation sequencing. Techniques for mass analysis of transcripts have been changing, evolving, and I've used them all as they have become available. My PhD involved analyzing fragments of numerous RNAs using classical sequencing. Expressed sequence tags (EST) are used as a basis to guess the transcript they represent. Soon after, we opened a microarray laboratory at the PAS Institute of Bioorganic Chemistry. We worked and still work with DNA microarrays, but we have also started next-generation sequencing. We have set up all the methods from scratch.

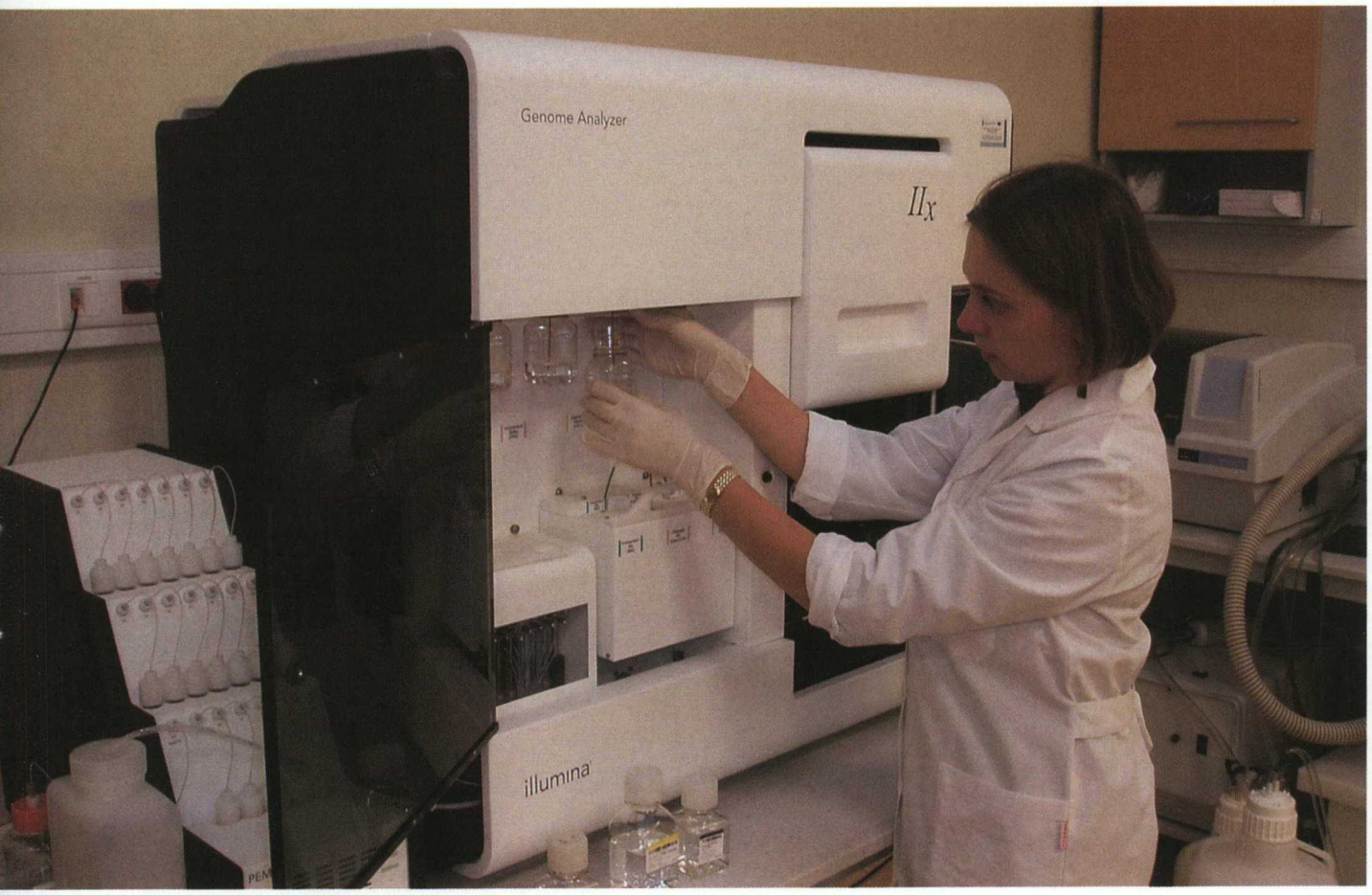
That's pioneering work. Who do you work with?

We have numerous associates throughout the country. We are learning from foreign institutes; our researchers travel abroad to train and gain new skills. When we were forming Poland's first workshop with full microarray equipment, the method was already almost a decade old elsewhere. In terms of next-generation sequencing, the technology is only a few years old, yet we are already using it in Poland. It allows us to sequence millions of samples simultaneously. We prepare a sample from the transcriptome; sequencing it allows us to gain new understanding of RNA sequences about which we previously had no knowledge. In comparison with traditional sequencing, the sequences are very short: between 35-150 bases in a single readout. Sophisticated computer tools are used to compile the short sequences into transcripts and read the actual RNA sequence. Online databases can be used, although they are not essential. We can assemble the sequences from scratch, which gives us unlimited potential to discover completely new transcripts; new isoforms, products of alternative folding or transcription. This is something we were not able to obtain using microarrays. However, now we have a new problem: too much information. The state-of-the-art, high-throughput HiSeq 2000 sequencer is able to produce 600 billion nucleotides during a single analysis cycle lasting a few days. That is equivalent to millions of concurrently read sequences. They cannot be analyzed without bioinformatics tools.

We've unlocked all this information, so now we need to find the tools to deal with it.

The European Centre for Bioinformatics and Genomics opened earlier this year in Poznań. It is a joint venture between the Poznań University of Technology and the PAS Institute of Bioorganic Chemistry, which I represent. The Centre's task is to bring together biologists and IT specialists; we have extremely well equipped laboratories, and we work side by side. We biologists know exactly what we want to extract from this wealth of information; we just don't know how. The IT specialists, on the other hand, don't know which information is important from the biological point of view, but they are able to deal with the massive volumes of data.

So you work from overview down to the details?



Agnieszka Żmieńko's private archives

Dr. Żmieńko in her laboratory at the European Centre for Bioinformatics and Genomics

If it's our own project (we also analyze data for other centers in Poland), then yes. Additionally, following years spent working on transcriptomes, I decided to take a closer look at the structures of genomes, and how they affect the entre organism. I used to study various aspects of plant response to stress at an RNA level; now I'm trying to find out how stress affects genomic structure. I'm not interested in what the genome is producing at any given time, but whether genomic structure itself is undergoing changes, and, if so, whether they are permanent. I use next-generation sequencing and several other techniques in the model plant Arabidopsis thaliana *to look for physical changes in genomes, such as lost sequences generated as a result of stress. They may possibly signal the plant's adaptation. I'm interested in seeing whether those changes become permanent in future generations -whether subjecting the plant to a certain type of stress causes directional changes.*

Perhaps Lysenko wasn't completely wrong after all?

[Laughs] Changes in the number of copies of genome fragments have been studied in the human genome for several years. Many of them are responsible for various disorders. In humans, we can observe a powerful phenotypic effect, although studying how this is inherited or how it's affected by the environment is difficult. For example, Arabidopsis is a plant with a small genome and a short reproductive cycle. We can produce a cycle of generations from an individual plant to study how a given trait changes.

How do you combine such intensive research with being a mother of three?

Both family and professional life have their ways of completely absorbing you. I manage by trying to structure both into a fixed timetable - I divide my day into different parts. I start off by being a scientist; later I get in the car, collect my daughters, and turn into a full-time mother. After 10pm I get a bit of time to myself, but I feel a bit guilty, so I either sit at my computer to catch up with work or try to catch up on housework. Leisure activity generally tends to get put off. It's an incredibly busy and challenging time of my life - I'm building a family and a professional career at the same time.

Have you ever felt that your colleagues are moving on and leaving you behind?

Those who haven't taken maternity leave or raised small children, undoubtedly so. But I've never felt I'm missing out; I actually think things are working out for the best for me. It's a long-term investment. I want to have everything; I won't give anything up if at all possible. But I do try to keep a balance. Science is my passion, but my family brings me happiness and helps me make sense of everything I do. They are not mutually exclusive - they complement one another perfectly. ■