Dedication Brings Success

We talk to **Prof. Bożena Kamińska-Kaczmarek** from the Nencki Institute of Experimental Biology about treating cancer, obvious and impossible discoveries, and academic courage and strength.

Prof. Bożena Kamińska-Kaczmarek is director of the Department of Molecular Neurobiology, Centre of Neurobiology, Nencki Institute of Experimental Biology. She studies the molecular processes guiding gene expression and underlying brain pathologies. Her research focuses on the mechanisms of neoplastic transformation, the role of the environment in the development of brain tumors and searching for novel targeted therapies for gliomas using siRNA and inhibitors of epigenetic enzymes. Since 2009 she has been leading the Postgraduate School of Molecular Medicine at the Medical University of Warsaw.

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ACADEMIA: **Tell us about the research at the Department of Molecular Neurobiology, set up in 2013.**

BOŻENA KAMIŃSKA-KACZMAREK: Today the Department has a staff of 25, with 60% of the salaries financed with grants from the Polish National Science Centre, the Polish National Centre of Research and Development and the Foundation for Polish Science. To some extent, those sources drive the direction of the department's development. It means that we are increasingly engaged in applied and translational research aiming to develop novel cancer treatments and discover new diagnostics for brain tumors and other neurological disorders. We are developing new cellular models, such as cells with specific genetic modifications for targeted therapies, and animal models for testing new compounds with anti-cancer properties. One of our major achievements to date is the introduction of next-generation sequencing methods following the acquisition of the Illumina 1500 sequencer with funds from the Foundation for Polish Science. It allows us to test hundreds of genes at once, or even whole genomes, to look for genetic mutations which could become new diagnostic factors. These kinds of wide-scale studies should lead to improved diagnostics, and enable us to select cancer patients best suited to targeted therapies. We have also founded a laboratory for other researchers and we conduct next-generation sequencing for other institutions in Poland and abroad.

You analyze pathological processes in the brain. It's a wide research field. Do you also study processes leading to the formation of tumors?

We try to elucidate neoplasia, examining processes taking part in cancer cells and their interactions with their environment. We are especially interested in brain tumors; although they are relatively rare, they remain extremely difficult to treat, posing a major challenge to researches and medical professionals. We have also recently expanded our research to childhood brain tumors, the second most lethal childhood form of cancer after leukemia. Our results show that malignant tumors send signals which switch and actively block the immune response. The tumor "pretends to be" a cell requiring help, and attracts innate immune response cells known as macrophages, which it converts into "slaves" to help the cancer cells spread through the body, and "soldiers". Macrophages modified this way secrete proteins inhibiting the anti-tumor response. Scientists working in the nineteenth century referred to tumors as "non-healing wounds"; this turns out to have been rather prescient, since cancer cells pretend they need assistance from their surroundings. My team was one of the first to explain the mechanism of action of a type of malignant brain tumors known as gliomas. They produce certain proteins which change how macrophages work in the brain and convert them into cells supporting tumor growth. Identifying these proteins forms the basis of a new therapeutic strategy targeting the direct surroundings of the cancer rather than the tumor itself. Brain tumors are fascinating, because the nervous system has its own macrophages known as microglia, which are the first cells to come into contact with the tumor and attract macrophages from the bloodstream and bone marrow.

How important is it to discover all the functions of the human microglia?

Microglia account for between 10 and 15% of all cells within the brain, and their glia are in contact with all types of cells in the nervous system. For many years researchers believed that microglia are simply sensors of pathological changes, infections or damage, and that

their role was to eliminate damaged cells and initiate inflammation, which in turn deals with and eliminates the threat. We have since learned that microglia play an important role in the development of neuron connections in early development, and affect learning and memory processes. They are also activated in almost all pathologies of the brain and neurological disorders; additionally, any problems in their function affect the course of strokes, Alzheimer's and Parkinson's, as well as mental disorders such as depression, schizophrenia and autism. In brain tumors, infiltrating microglia show highly increased protective function and behave as cells which repair their surrounding and support tumor growth. This makes it all the more important to isolate them from the brain in various pathological states to investigate which functions are more active and which one are damaged. Everything suggests that microglia have a positive and negative side, so understanding their function and action should help us restore their original physiological state in which they support and protect the nervous system.

Four years ago you had trouble raising funds for pre-clinical studies into gliomas. Did you manage to resolve the problem?

Yes, I did. We were able to raise funds to finance four projects working on different treatments for malignant gliomas from the National Centre for Research and Development. It has allowed us to join forces with biotech companies to conduct pre-clinical studies into novel cancer treatments. As part of our collaboration with Selvita, we are looking into genetic changes which may confirm damage as part of neoplastic processes. We focus on changes whose effects can be adjusted pharmacologically, so we are using glioma cell cultures to test novel cancer inhibitors. Our collaborations with Glia and Oncoarendi are at the stage of testing leading compounds which elicit anti-cancer response in animal glioma models, rather than affecting cancer cells directly. The pre-clinical studies are on track to conclude by the end of the year, and since the compounds were shown to be non-toxic, we will seek partners and sponsors for clinical trials. We have no experience conducting clinical trials ourselves, and we are seeking partners at home and abroad.

We have also initiated research into finding genetic changes and developing novel diagnostic methods. For example, we are aiming to develop tests based on next-generation sequencing to improve diagnostics of tumor types, predict their aggressiveness and select patients for specific targeted therapy. We are already receiving requests from doctors and patients to investigate the degree of methylation of the MGMT gene promoter, which is helpful in predicting the response to DNA-damaging drugs. The gene is involved with DNA repair, and the level of its methylation indicates its activity. We are also working with the Medical University of Silesia on a genetic test to be conducted on trace amounts of cancer DNA found in the patient's blood, which would make diagnosis simpler and make it possible to monitor the course of therapy non-invasively.

Will we ever be able to cure neurodegenerative diseases?

We are making significant progress and increasingly focusing on early detection, since it is essential to intervene before any loss of function of major parts of the brain due to cellular death. Since we currently have no means of returning lost function to cells and

their connections, and all repair mechanisms become less effective with age, we cannot recover information lost when cells die. Our understanding of the mechanisms of cellular death and processes taking place during chronic inflammation is improving, so there is a good chance that we will learn to direct those processes, although early detection of disease is critical. Additionally, some of us are genetically predisposed to develop certain types of cancer or disorders such as Alzheimer's at an unusually early age. Unfortunately, despite extensive research using animal models we still don't have a good understanding of neurological disorders, making them highly difficult to treat.

Which genes do you see as the most significant for the continuing development of medicine?

It would be almost impossible to talk about specific genes, since none of them exist or work in isolation and switching off or disrupting the function of any genes controlling important cellular pathways often results in the same effect, such as neoplasia. That said, the discovery of groups of genes known as oncogenes, largely responsible for tumor formation, and tumor suppressor genes which counter their effect, has been momentous. Switching off the latter is followed by an avalanche of changes. Using next-generation sequencing to analyze genomes of cancer cells reveals that there are between tens and thousands of genetic mutations in each tumor, since frequently the original change affects a gene whose products control DNA repair processes or which is responsible for the elimination of cells with unrepaired DNA.

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Our health isn't just the result of our genes, though. What can we do ourselves to help our brains stay healthy?

It's true that although all the information needed to build a specific organism is recorded in its DNA, the genetic information can be interpreted in different ways. One of the mechanisms controlling this are epigenetic processes, which in turn are sensitive to external stimuli. Scientists have been debating the relative importance of genes and their environment ever since the discovery of genes as carriers of information and their significance in shaping the organism's growth and development. This is a molecular version of the evergreen debate of nature vs. nurture. At the risk of attracting criticism from scientific circles, I think that many disorders are driven by hereditary disease predispositions, or simple bad luck which means our DNA accumulates genetic mutations leading to disease. This means that some people should be genetically tested to find out whether they are carriers of damaged genes, or have regular health checks to detect any early stages of illness. Early detection makes even serious disorders such as cancers easier to treat. But it's not just about the genotype. There are cases where a disease progresses very differently in patients with the same harmful genetic mutations because their immune systems respond to them differently. Even identical twins with identical genotypes can exhibit significant differences if they live in different environments, since those environments affect epigenetic processes and how genetic information is interpreted. Research indicates that a healthy diet and regular physical and mental activity all contribute to delaying ageing of the brain and the onset of Alzheimer's disease, and slow down neoplastic processes. They cannot replace treatment, but they can support it.

We are seeing great progress being made in neurobiology. Where do you see the discipline in ten years' time? What can we realistically expect, and what's likely to remain a dream?

Recent years have seen the development of novel methods of studying the mode of action of individual neurons and synapses, so we can expect our understanding of neurons, neural networks and the brain to improve rapidly; we are also hoping to elucidate the mechanisms underlying emotions and thoughts. We are also aiming to explain the basis of mental disorders and improve how they are diagnosed. We are already able to culture nerve cells and even organoids – miniaturized, simplified in vitro versions of the brain – from individual patients. Next-generation sequencing should allow us to assess pathological changes in DNA and use cell cultures to test the effectiveness of various drugs, and even discover how we can use pharmaceuticals to enhance the speed of neural networks to improve processes underlying thinking and memory.

What projects are you currently working on?

Our two main projects are NCN Maestro and Bio4Med, which aim to explain how malignant tumors affect their environments to block anti-cancer responses. I am also interested in pinpointing the function of microglia in different physiological and pathological states, such as stroke, to gain an understanding of how various programs are switched on and controlled. Another major, interdisciplinary project

is Symfonia 3 NCN, implemented jointly with a team of computer scientists and mathematicians from the University of Warsaw and the PAS Institute of Computer Science, aiming to create a map of all the DNA regions in the brain which don't encode proteins but are significant because they control how genetic information is interpreted. We believe it is the site of numerous genetic changes which decide whether neighboring genes should be interpreted and how. Studies of whole genomes also frequently reveal changes associated with disorders which are not found in genes encoding proteins but which are nevertheless significant. We believe this is because they are found in regulatory regions and sites of epigenetic changes. In July 2017 we stared the TEAM TECH CORE Facility FNP project, aiming to launch a platform for diagnosing genetic changes in gliomas, in particular less-well understood childhood gliomas, using next-generation sequencing. We also participate in three projects of the National Centre for Research and Development, aiming to develop novel therapies reversing epigenetic changes (EPTHREON), develop novel immunotherapeutic drugs restoring the anti-cancer response (DIMUO), and test short peptides inhibiting negative interactions between gliomas and cells of the immune system (PBS GLIA-TOR). The next project aims to develop a liquid biopsy method for diagnosing gliomas on the basis of DNA isolated from blood.

Does your team include researchers from outside Poland?

I have been striving to engage as many scientists as possible from abroad for many years, and as a result English has gradually become the basic language of our seminars. Foreign researchers generally find their way to my team because of our participation in EU projects, which recommend engaging people from different countries. In any case I select team members on their qualifications rather than nationality, and it's often simply easier to find experts from abroad. I believe that it is very important and beneficial for Polish science that laboratories employ researchers from all over the globe, and I welcome anyone with open arms. The free movement of people and ideas is absolutely essential to the development of science. But of course they have to be outstanding and ambitious scientists. Our problem is that Poland isn't sufficiently attractive in research terms, and it isn't widely recognized for having centers of excellence. Creating laboratories on the scale of the Max Planck Institute or the EMBL would significantly improve the situation. I have been running the prestigious Brain Tumors conference for the last few years, attracting eminent researchers from around the globe so that we can show them and their junior colleagues the laboratories at our institute and convince them that they are up to the highest international standards.

Are there many women working in neurobiology research in Poland?

Not only are there many women working in neurobiology and biology in general, I think women are in the majority on the PhD level. I don't know whether there are many women working in other scientific fields, and that's not really important – what's important is that there are plenty of good researchers. Unfortunately, once they reach the PhD and post-doc level, not many women tend to focus sufficiently on their careers to quickly reach independence. Not many decide to take post-doc positions abroad or even in different cities, even though it's clear that this is an essential step in a research career. Until very recently, research salaries were low and this was more widely accepted by women than men. It is only in recent years that programs allowing young scientists to earn reasonable incomes have been created. I'm afraid that the situation is more difficult for women because of the strong social pressure – now stronger than ever, since it's sanctioned by governmental policy – to start families and have children. And combining family duties with a research career is difficult, so not many women are able to find the right balance. A few of my team members had children while working towards their PhDs, which undoubtedly made it difficult for them to continue their research and – sadly – even marked the end of their careers. I get the impression that in other countries women tend to establish their research careers before starting families. Perhaps women are less ambitious, or taught by society not to fight for their own views or professional independence.

Are women working in science in Poland given equal opportunities at all stages of their careers?

I think they are. There are plenty of women working in science in Poland and most of them understand the difficulties of combining a research career and having a family. In my experience, if someone is talented, works hard and is able to dedicate themselves to research, they have no problems in becoming successful regardless of gender. But being a scientist is demanding; it requires a lot of time and attention and full engagement. It's also stressful, because experiments frequently don't work and genuine discoveries bringing major satisfaction are rare. So you really to be highly driven and set yourself high standards, rather than simply hoping for a comfortable, undemanding position. Not everyone has sufficient courage and mental strength to take up this challenge.

Interview by **Anna Kilian**
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This is the English translation of an interview that was approved by the author in the original Polish version.