CONTENT ***At the age of 44, Ivan Dikic can already look back on an impressive career. After obtaining an MD degree at the University of Zagreb in Croatia, he went on to gain his PhD in molecular biology. He worked at New York University, USA and at the Ludwig Institute for Cancer Research in Uppsala, Sweden, before moving to Germany. Prof. Dikic is now ready to mould the future of molecular life sciences at Frankfurt's largest university: he wants to form a new flagship institute at Goethe University. B.I.F. FUTURA met the dynamic scientist in his art-adorned office in Frankfurt.***

'My life is relatively simple'

Interview with Prof. Dr. Dr. Ivan Dikic, director of the Frankfurt Institute of Molecular Life Sciences (FMLS) at Johann Wolfgang-Goethe University in Frankfurt, Germany.

Ivan, you have been showered with prizes and grants of late, among them the Sir Hans Krebs Prize 2010, for your research on ubiquitin, not to mention the 2.5 million Euro grant from the European Research Council. Which award are you most proud of?

• Every award has its own merits and meaning. I consider prizes as an external recognition for the work I have been conducting with my colleagues, and we are certainly proud of our accomplishments. However, we also consider these awards as an obligation to continue carrying out good scientific research in the future. The ERC grant enables us to invest our energy and resources responsibly in novel and original ideas that will hopefully lead to important discoveries.

You were one of five scientists who has received the Boehringer Ingelheim Fonds Research Award, which no longer exists. How did this award shape your career?

• It was probably the most crucial financial support that I ever received. It came at a period in which I was keen to start my independent work, but asked myself how I would be able to manage financially with running my own lab. So the B.I.F. award came exactly at the time when I was starting to set up an independent lab in Sweden. I'm always happy and proud to acknowledge this, and to credit the foundation for this important investment in my scientific career.

You have been receiving a considerable amount of favourable coverage in the media. One article even claims in its headline that you have 'solved the Nobel mystery.'

• You'll often find simplified statements like that in the internet media, they are meant to attract the readers. As far as I am concerned, the most important thing is that my discoveries be correctly interpreted. I can only hope that anyone who reads the title will also read the content of the article, and make the right judgment. This particular article refers to something we were working on, and which had been enigmatic in the field of proteasomal regulation for many years. The Nobel Prize was awarded for the discovery that ubiquitin acts as a signal for the degradation of other proteins. One enigma that remained to be solved was the question of what receptors on the proteasome recognize ubiquitinated targets. We discovered that Rpn13 is the ubiquitin receptor on the proteasome, and explained its function, from the atomic details to the genetic level. This was an important contribution to the field, which is probably why the headline was added.

So, let's talk about ubiquitin. What's so fascinating about it anyway?

• One of the most exciting aspects of ubiquitin is that this relatively simple protein, which is expressed in all our cells, has the inherited ability to regulate a large spectrum of cellular

processes. At first sight there is nothing to suggest that this protein has the wherewithal to drive the complexity of life processes in the cell. A further fascinating aspect is that if you take ubiquitin from yeast, one of the most primitive eukaryotic cells, and transfer it to the human body, it will adopt the same functions as the endogenous human protein. It is a wonderful evolutionary conservation. Its structure and functions have remained the same through time. Many cellular functions – for example, gene transcription, receptor trafficking, budding of the HI virus, or autophagy – are also regulated directly or indirectly by ubiquitin. I find this extremely interesting to study. Now we need to understand why ubiquitin has so many divergent functions, and how it can regulate such a complexity despite being so simple, small, and globular.

How does ubiquitin regulate cellular processes?

• When our laboratory moved from Sweden to Frankfurt we asked ourselves the same question. We established a screening platform to identify novel interacting partners of ubiquitin. We used bioinformatics and biochemical methods to characterize several new folds or domains that bind to ubiquitin. We then used structure-function-analysis to prove in several instances that ubiquitin acts as a cellular signal decoded by these newly identified ubiquitin binding proteins. We also realized that, despite specialized methods of biochemistry and molecular biology, we were never going to be able to provide an answer to complex biological processes without the expertise of bioinformatics, structural biology, system biology and genetics.

What is the role of ubiquitin in the pathogenesis of diseases like cancer?

• When a cellular signal like ubiquitin is involved in the regulation of many physiological processes, it is liable to be affected in different disease states. Indeed, both the ubiquitin conjugation machinery and ubiquitin signaling networks are misregulated in many pathological diseases such as neurodegeneration, infection, and autoimmunity to cancer. One of the first projects we published after moving to Frankfurt was the work of Magda Bienko, a student from Poland, who discovered two ubiquitin-binding domains in an enzyme called translesion polymerase. By studying these on a biochemical level, she could explain a disease called *Xeroderma pigmentosum*. This disease has a genetic mutation in one of these enzymes which prevents the cells from repairing damage caused by ultraviolet light. The result is the appearance of multiple benign skin tumours.

Where is ubiquitin research taking us?

• Ubiquitin research is now heading towards understanding the complexity of all those processes in which it is involved. I would say that during the first twenty years of research, the focus was more on how ubiquitin is attached to a substrate, i.e. what proteins are ubiquitinated in cells? This research was so original that it was credited with the Nobel Prize in Chemistry in 2004. A new challenge arose once we realized that about 30% of cellular proteins are ubiquitinated at a certain time, but we don't know how they are linked to function. So this poses the next challenge in the field; how are ubiquitinated proteins recognized by other proteins, and how can they regulate the physiological processes in the cell? By asking such questions, we have opened other new issues such as regulation of DNA repair, immunity and inflammation, and, more recently, autophagy, which is a self-eating mechanism of a cell. In this way, a number of important contributions towards a better understanding of the pathogenesis of neurodegeneration and of cancer have been made.

How does the cell recognize variations of ubiquitination? How does it differentiate between them and translate them into different processes?

• That is yet another twist in evolution. I think we all need to learn more about biology by looking at how things have evolved in the past. Ubiquitin has inherited the ability to make chains of its own. And these chains are not identical. By creating a different kind of chain, the ubiquitin signal has evolved novel features that are functionally distinct. Our hypothesis is that ubiquitin signals are specifically recognized by receptor proteins. This results in a large network of interactions which we believe to be the basis of diversity in ubiquitin functions. At the moment, we are trying to incorporate more quantitative biology and system biology in our research, and I believe that these two disciplines will be invaluable in helping us understand how all these functions are incorporated in the fascinating life of the cell.

You found and characterized six new families of ubiquitin-binding domains. Any more around the corner?

• Up to now, more than 20 different families of ubiquitin-binding domains have been identified. These 20 families are present in approximately 200 proteins in our cells. Most of the domains were discovered on account of their binding to mono-ubiquitin or to some of the ubiquitin chains. So the new challenge would be to take all the different types of chains that can be made by ubiquitin and look for new domains, and I'm certain there are some more still waiting for us there.

How long did it take you to get the results you wanted?

• Science has got to the stage where you cannot have short projects that only run for a year or two. All our suc-

cessful projects took at least four years, and involved collaboration with several other laboratories. It takes long-term interdisciplinary research to obtain deep and comprehensive results. The message to younger scientists is that they should not try to conduct isolated projects, but should be open to interdisciplinary education and research projects.

Let's talk about molecular signaling in general. What are the hot-spots in this field, and where do you see the greatest challenges at present?

• Molecular characterization of the signaling pathway has been a very fruitful area in biomedical research in the last twenty years. We have learned a lot about many signaling pathways, and several successful drugs have been made available and are currently being used in clinics. Despite being happy with this progress, I'm also a little puzzled. Why? Because the more we learn about signaling complexity, the less we understand about the biology underlying it. It's a paradox; you see, we have this enormous amount of knowledge but cannot connect it yet. We do not understand how the life in a cell is coordinated. We need to incorporate more disciplines to help us apply our knowledge in a bid to understand the entire process. Perhaps we can then create the virtual life of a cell in the future.

What exactly do you plan to do with your ERC grant?

• The ERC funding is based on our proposal to examine a new type of ubiquitin chains, linear chains, and their role in the regulation of inflammation and cancer development. This will be a major focus of our work. The grant will finance the positions of six scientists and their independent subprojects in this vast theme. They will be provided with every possible modern technology from super-level microscopy to mass spectroscopy and bioinformatics – anything that will help them figure out how these processes are regulated. Any PhD student interested in this type of research can contact me directly.

If you were granted one wish for the advancement of your research projects, what would this be?

• Well, I've always valued and emphasized a creative atmosphere. It not only means being surrounded by intelligent people, but also having enough time to think. Not having countless administrative duties, committees, applying for funding, etc. Scientists need time to develop brilliant ideas that help address issues we normally would not have time to consider. So my wish would be that we scientists do not have to waste too much valuable time on administrative issues, but can dedicate ourselves to conducting research.

One of the articles about you describes you as 'a successful family man.' Looking at your workload and the fast pace of your research, how do you reconcile family and work?

• My life is relatively simple, it has two sides – one side is my family and the other is science.

Successful research is not any more important to me than having a family, walking at the banks of the Main river with my kids, or sharing moments of happiness with my wife. Despite all the awards and recognition, when you come home every evening, you are still the same person for your kids. I consider my job as my hobby; and since family and science obligations are intertwined during the day, I'm truly happy to have reached this ideal point. It was not always that easy though, but now here in Germany, we're really happy, and family and profession go well together.

Moving from the present to the future: What will biomedicine look like in a hundred years?

• Now, that's difficult to predict but I'll use my imagination. My feeling is that biology and biomedicine will not be as important as they are today. A hundred years ago, chemistry and physics were at the top of the field; since then, they have answered many important questions. Now biology and biomedicine are up-front. I can imagine that a hundred years from now we'll be more concerned with how we share the space on earth, and how we interact as individuals. We'll have to work with machines processing data that are incomprehensible to a human brain. Many of the tasks will be conducted by the machines rather than by us.

As the director of a new institute of biochemistry at the University of Frankfurt, what do you want to achieve?

• My decision to stay in Frankfurt was as important for the family as it was for me personally. That is why I accepted this new challenge of becoming scientific director at the FMLS. This decision was not an easy one because I really value having free time to spend with my students and postdoctoral fellows, and that will continue to be a high priority for me. However, I enjoy designing the scientific vision of something I believe will be the flagship of Frankfurt University. The institute will host eight full professors and about five junior groups that will collaborate in a truly interdisciplinary environment. The common philosophy is to have creative discussions on topics of science without a hierarchical structure of leadership. I prefer to consider my own position as that of a chairman who helps find a consensus and point to the best direction for the institute. I'm currently looking for the most brilliant young scientists from all over the world, who are ready to take on the challenge of moving to Frankfurt, working in the newly-furnished institute with interdisciplinary nature and helping us to be successful on a global level.

Best wishes for your institute, and thank you very much for this interview!