MICHAL BASSANI-STERNBERG

Explorer of the immunopeptidome

Michal's pioneering work on the recognition of cancer antigens is being applied to the design of novel immunotherapies

Michal Bassani-Sternberg's group at Ludwig Lausanne, the immunopeptidomics unit, has become a key participant in the Branch's ambitious efforts to develop, optimize and streamline the delivery of personalized immunotherapies to cancer patients. Michal is uniquely qualified for the role. As a postdoc in Germany, she helped pioneer the field of immunopeptidomics—the use of mass spectrometry and computational analysis to predict which antigens out of the thousands proffered to the immune system's T cells are most likely to provoke effective immune responses. Her high-throughput technologies are today integral to the development and clinical evaluation of individualized cancer vaccines and adoptive T cell therapies at the Branch and the Center of Experimental Therapeutics at the University of Lausanne. On the basic research front, her laboratory is making invaluable contributions to our understanding of the rules that govern antigen presentation and recognition. Ludwig Link recently caught up with Michal for an interview about her life, work and more. Here is an excerpt of our conversation.

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Where were you born and raised?

I was born and raised in Israel, in Haifa, a city in the north, close to the sea. And I grew up there in a very normal family. I have an older sister, younger brother, and they're all still living there in Israel. My father worked as a chemist in the paint industry and my mother worked as a secretary in the hospital.

Where and what did you study from college onward?

I attended the Technion, which is the Technical University of Israel, and studied biology there as an undergraduate and got my master's degree and PhD there as well. My master's was in plant physiology and it was in a very nice laboratory. I learned a lot of scientific techniques and became independent as a researcher early on, but the topic was not very interesting for me. After two years of that I said, okay, I need to change direction. So I transitioned into cancer immunology, in which I got my PhD, getting involved in immunopeptidomics in the early years of the field. I just moved from one floor to the other in our faculty building, but I had to learn so many new things about cancer and immunology and become familiar with a completely different technology, which was mass spectrometry. This is when I started to explore HLA-bound peptides and measure them with mass spec.

What are HLA-bound peptides?

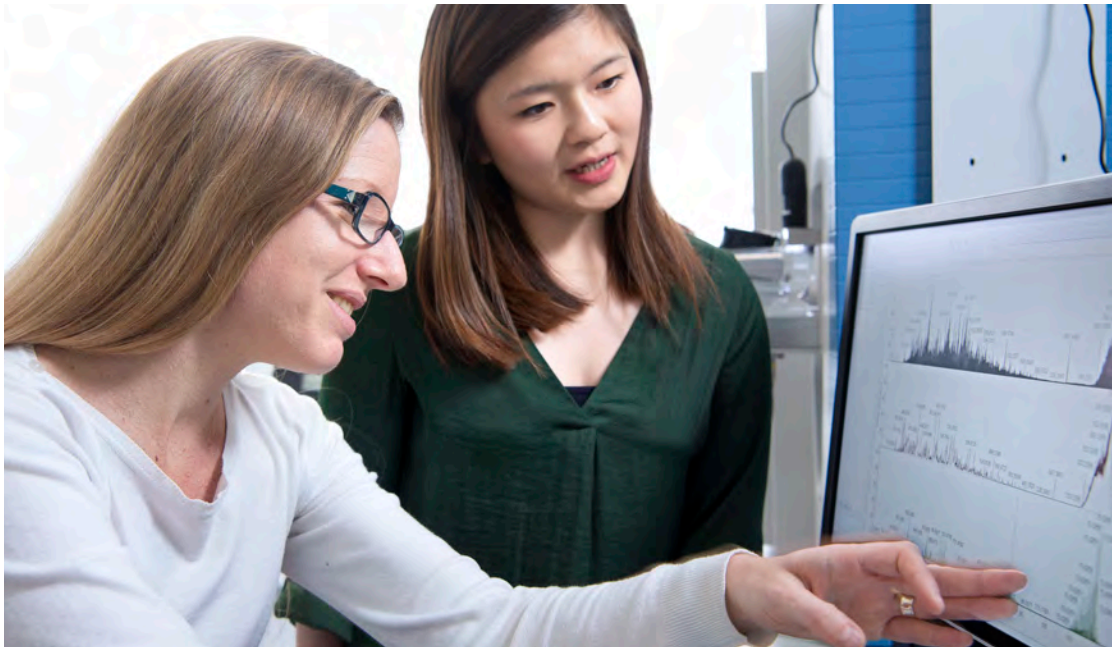
Normally, cells present cellular proteins to the immune system as short peptides bound to human leukocyte antigen (HLA) molecules on the cell surface. When cells become diseased by cancerous transformation or infection, they present altered, new or non-self peptides that can be recognized by T cells and induce a T cell response. The one line of work that really picked up and developed eventually into my thesis was after we realized that we could identify HLA-bound peptides from plasma samples of cancer patients. This was a completely new discovery and application, and it was really at the very early stages when the technology was not yet ready for this crazy idea. But we saw it as a proof of concept.

What did you do next?

During my PhD I got married, I had my two kids and then we moved the family to Munich, Germany, where my husband was going to do his postdoc. I also did my postdoc there, in a department that remains a world leader in mass spectrometry and proteomics. I continued work in immunopeptidomics, but now in the best place in the world to do mass spec and proteomics. It was very inspiring to be at the first line of innovation in this domain and to apply it to my scientific questions. People were working on many applications of proteomics, while I was the only one doing immunopeptidomics there at that time.

Could you tell us what immunopeptidomics is?

Immunopeptidomics is a technique by



Aside from its practical applications, Michal's work is elucidating important principles of antigen presentation and recognition, which are early steps in the initiation of adaptive immune responses.

which we isolate, identify and analyze large numbers of HLA-bound peptides. Most of the peptides that are presented derive from normal proteins, but we are looking for the very few that are specific to disease, in our case, cancer. We are looking for the very few peptides that are unique to a cancer and are not presented anywhere else in the body. Once we identify those peptides, we can develop immunotherapies to target them and induce anti-cancer immune responses in patients—for example, by vaccination.

So you must coordinate with T cell biologists in this work.

Exactly. We ask, what are the relevant targets in any given tumor? It's a personalized approach. And we are trying to collect as much information as we can. We do genome sequencing, RNA sequencing and peptidomics—analyzing the full repertoire of peptides that are presented by cancer cells—and we try to find all the abnormalities within the cells that could lead to the presentation of cancer specific targets. We aggregate all this information and come up with the most likely immunogenic antigens, and then we work with our colleagues here in Lausanne, for example, Alex Harari's group, who are experts on T cell recognition assays. They test whether the antigenic peptides we propose are recognized by autologous T cells of the patient and which of them are immunogenic. We work very, very closely with them.

What scientific challenges does your work address?

Well, there are different challenges. There's the more conceptual challenge—to understand which classes of antigens we should target or explore further. These could be mutations or different flavors of mutations; they could be abnormally translated regions in our genome, or

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posttranslational modifications made to proteins. For every source of antigens, we need to collect different data or develop different computational tools for their robust identification. So we analyze these patient by patient and then try to go as deeply as possible and characterize as many different types of antigens of interest as we can. And yeah, it's growing quickly. Every few months we come up with a different source of antigens we need to explore, and we have to adapt our pipelines and algorithms for their analysis. We are trying to understand the rules of what makes an antigen immunogenic. And we are trying to understand this now more and more in the context of the immune microenvironment of the tumor, and how that affects the immune responses provoked by antigens.

Then there are practical challenges related to the tissue samples that we receive, which are sometimes very, very small. We are developing new methods to analyze them by mass spec. And, of course, there are challenges related to the fact that every tumor comes from a different individual. The patient may have received prior treatment that could change the tumor and there is not a lot of information about how different treatments affect the antigenic landscape in cancer. This is a topic we are very interested in exploring.

How is this work contributing to medicine?

We have put together in recent years a very complex, high throughput proteogenomics pipeline that is quite exceptional, which can identify in a patient's tumor the various antigens that are presented and are likely to elicit immune responses. We have applied it to research in the lab, but also to ongoing clinical trials in Lausanne. So we can now explore the antigenic landscape at a level where we can propose relevant targets for the development of immunotherapies. And I think immunopeptidomics is a field still in its early days, in terms of its potential impact on immunotherapy. But the technology is incredibly better today than it was even a few years ago, in terms of its sensitivity and speed and robustness as well as the computational tools that support it.

What trials are utilizing this technology right now?

We're involved in cancer vaccine trials and adoptive T cell therapy trials. For cancer vaccine trials, we propose the most relevant mutations in tumors for use in personalized cancer vaccines. The antigens these mutant genes encode are produced and loaded on dendritic cells from the patient, which are then offered as a vaccine to the patient with the expectation that they will induce immune responses against the cancer cells that present these antigens. We are also involved

in the NeoTIL trial, which involves adoptive T cell transfer. In this trial, we again propose the neoantigenic peptides that might be most relevant and they are produced and used in the selective, *in vitro* expansion of neoantigen-specific T cells obtained from patients. Those T cells are then infused into the patient from which they were isolated as a personalized immunotherapy.

What cancers are you trying to treat using these techniques?

We have vaccine trials in pancreatic and lung cancers and we just started one for ovarian cancer. The NeoTIL program is in various solid tumors.

How has the environment in Lausanne enabled you to do things that maybe you couldn't have done otherwise?

It was George's vision, when he recruited me here in 2015, to establish the immunopeptidomics lab and develop our proteogenomics approaches within the oncology department. So this is quite a translational environment. To bring such technology into a clinical environment is quite unique. We are being challenged to do things very robustly, to do things in a very, very careful way, but also to innovate and challenge ourselves with scientific questions that are linked to the burning questions and needs of the clinic.

Congratulations on the Swiss Bridge Award. Could you tell us about the project you proposed?

The project supported by the Swiss Bridge Award will bridge two distinct domains—infectious disease and cancer. A lot is known about cancers that are induced by viral infection, like HPV for example. There is already information about which targets could be immunogenic and we realized that we have now an opportunity in the lab to explore with our pipelines what are really the peptides that are naturally processed and presented in tumors or model cell lines of these cancers. We will also try to understand how different drugs change the peptidome, applying high throughput methods and screening approaches to try to see how different drugs and their combinations alter the expression and presentation of viral peptides with the hope of developing immunotherapies that target those antigens.

You said your husband is also a researcher, what does he study?

He studied astrophysics, but in recent years he has transitioned more into data science in oncology and other life sciences.

What global issues concern you the most?

What has really kind of shocked me is climate change. We feel its effects every day here in Switzerland. You would assume the kind of changes people anticipate will take tens of years to happen. But no, we feel them every day, and every year it's getting worse and worse.

What are your main interests and hobbies?

We hike a lot on the mountains here in the summer and in winter we ski with the family and friends. I would say the normal hobbies in Switzerland. Also, I have been doing hot yoga for the past two years or so, and I really enjoy it. It's 90 minutes in a very hot room, so you sweat a lot. Funnily, it's exactly like the weather on a normal summer day in my hometown in Israel. It's very demanding on the body but it's quite excellent. It's good for the soul and for the body as well. It's a good meditation while you do a very intense sport.