Interview: Prof. Dr. med. Adriano Aguzzi – Director, Institute of Neuropathology, Switzerland

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Prof. Dr. med. Adriano Aguzzi provides insight on the past, present, and future of prion and antibody therapy research in Switzerland. The Institute of Neuropathology works closely with the University Hospital of Zurich to conduct their research. He also touches on translating research to industry and his spinoff ImmunoQure, which screens patients for protective antibodies.

You have been leading the Institute of Neuropathology for nearly two decades now. How would you characterize the Institute's mission today?

The Institute of Neuropathology's mission is to better understand the basic mechanisms and causes of neurological diseases. In addition, the institute has clinical duties; we work with patients and conduct biopsies, all in relation to our scientific mission.

We are focused on protein aggregation diseases, specifically prions. We started working on prions before they acquired notoriety because of the mad cow disease crisis. People knew very little about prions in those days. About that time Charles Weissmann, a Hungarian-Swiss molecular biologist, proved the hypothesis that infectious proteins are the agents of prion diseases – and not a virus or bacteria as many had believed. He did this by removing the prion protein from the mouse genome; prionless mice became resistant to prion infections.

This was a scientific breakthrough, but it also led to more questions. Mad cow disease suggested that cows and humans could acquire prion infections by eating prions – hence we wondered how

simple protein aggregates could make their way to the brain and how the infection could spread to people who consumed the meat. We spent about 10 years on this research topic, and we identified most of the cells and molecules that transport the prions to the brain.

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This was a successful endeavor, but led to the question: why do why have this protein if it can become so dangerous? At first the mice without the gene were healthy, but we noticed that after an extended period of time they suffered from a peripheral demyelinating neuropathy – a disease of the Schwann cells that unsheathes the axons. We then performed genetic experiments in which we removed the prion protein only from the neurons, and the mice still developed the disease in Schwann cells. How was it possible that, after taking out the proteins from the neurons, the disease was found in another cell type? One idea was that maybe there was a receptor with the Schwan cells. We spent the following years looking for such a receptor, and we eventually found it. It was a G protein-coupled receptor called GPR126. We published its discovery in Nature in August 2016. This information is particularly exciting because GPCRs are mostly “druggable” receptors, meaning that the beneficial anti-neuropathy effects of PrP might in principle be mimicked by low-molecular weight drug-like compounds.

What are some of the other areas of interest to the Institute?

I have a longstanding interest in antibody therapies, and I have been working for two decades with anti-prion antibodies. My lab has shown in 2001 (and published in Science) that certain antiprion antibodies can block the passage of prions from extracerebral sites of inoculation to the brain. I was also the coordinator of a large European Union collaborative group making immunotherapeutics against aggregated proteins – not only against prions but also against Alzheimer’s and Parkinson’s disease.

We discovered three years ago that the precise epitopes targeted by the antibodies are crucially important. With the prion proteins there is a fine line between a protective antibody and a terribly toxic one. This necessitates structural studies (crystallography, nuclear-magnetic resonance spectroscopy) and molecular dynamics modeling to assure that the correct antibody is used.

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We are currently investigating whether antibodies may also be naturally protective. Many people with genetic predisposition to prion diseases develop clinical signs in their mid-50s, but we found that there are some people who live a happy and healthy live for much longer – despite the

presence of prion mutations. Now, when the prion protein becomes misfolded and aggregated, it creates neo-epitopes. I am currently suspecting that such neoepitopes may be recognized as “dangerous” by the immune system, and antibodies may arise against it. We discovered that indeed some people actually carry antibodies that seem to serve as an autoimmunity against these aggregated proteins. We still know little about these anti-prion antibodies, and whether they are protective, but we are studying this and my greatest hope is that one might be able to develop an antiprion drug starting with such antibodies as templates.

What work are you conducting to enable the development of such a drug?

If you are able to screen a very large number of people, you can find people with antibody against pretty much anything in the general population, even if this is a very rare occurrence. Our university hospital draws blood from over 100,000 people each year and I have proposed to screen all of them in order to find people with potentially useful antibodies. We only investigate patients who give an informed consent to their residual blood (whatever is left after diagnostic tests were performed) being used for research – but it turned out that almost everybody is happy to help advancing medical science. Once we find an antibody carrier, we can isolate the immunoglobulin genes from his memory B-lymphocytes which are also present in the residual blood.

The biggest problem with all investigational new drugs is that they can be rather dangerous – and that applies to therapeutic antibodies as well. The first time a human is injected with an entirely new drug, nobody knows what is going to happen, and bad things have indeed happened in the past. If, conversely, the therapeutic antibody was derived from a human who was healthy despite carrying a high concentration of the antibody in question, this provides strong confidence that that antibody will be well-tolerated also by others.

The importance of safety aspects cannot be overestimated. Yet it is not only the intrinsic safety that drives the use of human-derived antibodies. The current process of “humanizing” the antibodies from animals or from synthetic libraries creates structures which, over time, are recognized as non-self by the immune system and lead to the generation of anti-idiotypic antibodies. This, in turn, generates immune complexes which reduce the therapeutic effectiveness. Antibody therapy today makes up more than 50 percent of the revenues of the largest Swiss pharmaceutical companies, and it is widely predicted that this number will only increase – yet one-third of patients treated chronically with antibodies develop anti-idiotypic resistance which mandates that the therapy be discontinued. The solution, in my opinion, is to take antibodies that were already created by the human immune system. The human body is much less reactive to human produced antibodies because they are not recognized as foreign.

In this context, I co-founded an academic spinoff company called ImmunoQure Research, whose very mission is the development of such human antibodies. The University of Zurich is a shareholder of the company, and we have access to the blood that is drawn from patients (pending of course the patients' permission). Through its unique access to rare patient populations, ImmunoQure is able to identify patients harboring naturally optimized antibodies against key drug targets that are involved in preventing a number of human diseases.

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The Institute also participates in knowledge transfers from research to patients. Are there any particular initiatives that the institute has to engage both the public and industry?

I consider ImmunoQure a prime example of technology transfer from academia to industry. In addition, I have served on the Scientific Advisory Board of large pharmaceutical companies (including Novartis, Roche, and Lilly) over many years. I continue to serve on the board of the Friedrich Miescher Institute, which receives 70 percent of its funding from Novartis.

In terms of public awareness and outreach we do conduct numerous activities. We hold open-house days where citizens can come to the hospital to inform themselves on our activities. We realize the importance of keeping the public aware of what we do, so that they understand the importance of our research. This is particularly important since the taxpaying public foots the majority of our bills. As a long-term goal, my vision is for the public to be as proud of their scientists as they are of their athletes. Also, science needs to be international, and indeed has been global for hundreds of years – long before the business world discovered globalization. We need to explain this to people.

Indeed, there has been concern over the immigration referendum of 2014 and that Switzerland will become less open as a consequence. What is your perspective on this?

The concerns of the Swiss people cannot be ignored. On the other hand, the immigrants coming to Switzerland are almost exclusively well-educated scientists, medical doctors, and highly qualified workers. As a result, Switzerland trains less than half of the medical doctors that it actually needs – which saves the country a lot of money while ensuring that we are exposed to the most modern technologies. What people see, however, is that their doctors are foreign and might not speak the Swiss German dialect. This can lead to friction. Also, the highly-educated (and highly-paid)

foreigners drive gentrification in the cities, and this creates resentment. These are understandable concerns, and any solutions must be reasonable and respectful for both sides. But one thing is clear: blocking the immigration of scientists and highly qualified workers may destroy the technological and scientific ecosystem upon which much of the Swiss economy is based.

It is sometimes said that the Swiss biotech environment suffers from being overly conservative. Is this an accurate characterization?

The innovative power of Switzerland should not be underestimated. The biotech scene is doing incredibly well here. In Schlieren, a suburb of Zurich, there are over 100 companies (including ImmunoQure) and enormous international investments taking place. I am particularly impressed by the long-term horizon that is envisaged by many Swiss investors. Real breakthroughs in biotech may take a long time to come to fruition, and not all venture capitalists are prepared for this kind of lifecycle. Also, the proximity between University, ETH, and University Hospital has generated an academic-medical-entrepreneurial triangle whose technological and innovative potential is similar to what you would find in Boston or in the Bay Area. In short, we are very ambitious country, and when it comes to biotech we are reaching for the stars.

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What do you want the Institute of Neuropathology to be remembered for?

If you had asked me this question 10 years ago I would have said that I wanted to find the fundamentals of at least one disease, most likely prion disease. Also, I would have told you that the institute’s mission was squarely on the basic science and pathogenic mechanisms rather than translational medicine. Today, however, we are doing far more. Also my personal goals have evolved after 30 years in basic medical science. I have developed the ambition to go the next step, which is translation of fundamental research findings into bedside medicine. With our expertise in both academia and industry, we feel that if anybody is positioned to do this in the realm of neurodegenerative diseases, it is going to be us.

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