Interview: Professor Dr. Susan M. Gasser â?? Director, Friedrich Miescher Institute for Biomedical Research (FMI), Switzerland

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Professor Dr. Susan M. Gasser of the Friedrich Miescher Institute for Biomedical Research describes FMIâ??s fundamental connection between academia and industry in Switzerland, the effects of the foundationâ??s research, notably on Novartis, and future projects in the making.

Could you begin by introducing both yourself and your institute to our readers?

I am a molecular biologist with a background mostly in basic sciences. I studied biophysics and biochemistry and then completed a postdoc in Geneva on chromosome structure and chromatin genetics. I was at the Swiss Institute for Experimental Cancer Research for 15 years in Lausanne where I set up my own research program on genome stability and nuclear organization. I was a professor at the University of Geneva, studying questions of genome organization, gene expression, and gene silencing, when I was asked to run FMI, the Friedrich Miescher Institute for Biomedical Research, in Basel, in 2004.

The Friedrich Miescher institute has a lively community of tremendously talented researchers. It has grown from 70 to 350 people since its founding in 1970. 70 percent of our funding is generously provided by Novartis, which provides our core funding. We are focused on topics in epigenetics, neurobiology, and quantitative biology. Our mission is two-fold. It is to train young scientists and researchers in scientific research in areas that are of interest to the pharmaceutical industry, and

secondly, to conduct forefront fundamental biological, and biomedical research.

Could you tell us more about your relationship to Novartis?

We bring ideas to Novartis that cannot be read in the literature. We approach biomedical problems creatively, sometimes with a different perspective, and can take greater risks in our research efforts. We try to explore areas where the pharmaceutical industry should be in five to ten years from now. We are under an intellectual agreement with Novartis where everything we do is to be shared with them, but our research is what we call â??D zeroâ?•, the step before drug development. On average, Novartis in-licenses two patents a year out of total of eight to ten that we register.

What are some of the specific contributions that you have made to Novartis?

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There are three areas where FMI has made particularly significant contributions. The first one is regarding Gleevec. In the 1990s FMI was the first to suggest to Ciba Geigy (which later merged with Sandoz to form Novartis) that one could target specifically a growth controlling receptor tyrosine kinase. The company went on to develop a kinase specific inhibitor, which was a major breakthrough at the time. Novartis invested in its development, even though originally there was only a small target market for the product. It has since proven to have other uses that go beyond CML (Chronic Myeloid Leukemia), to become a blockbuster treatment.

Another FMI contribution was to suggest the application of TOR inhibitors in cancer. In 2001, one of our researchers was looking at growth control by S6 kinase and was conducting a screen in *Drosophila* monitoring fly size. He found that a TOR mutant suppressed the effects of S6 kinase hyperactivity, which is correlated with cancer cell proliferation. Thus he argued that an inhibitor of TOR, which already existed, could be used to stop cancer cell growth. The company has now exploited this idea and Affinitor is a big selling cancer therapy, which also has other applications.

The third area we are working on is targeted gene therapy for adult onset blindness, with a therapeutic model that is currently still in development. Blindness is an increasing problem due to the aging population. We have a therapeutic model that has been patented and is being tested on primates. It delivers light sensitive channels to the cone cells that have lost their photoreceptors due to degeneration. Adult blindness is often caused by this loss of light-sensitivity in photoreceptor cells. The signalling infrastructure to the brain is intact, but the receptors cells are no longer light responsive. One of the FMI group leaders had the idea to restore this sensitivity by using light-sensitive channels from algae expressed from cell-type specific promoters. Even if it does not restore full vision, sensing light can be an enormous advance for someone who becomes blind as an adult.

These are three notable contributions; alongside numerous smaller ones. We aim to achieve interesting basic scientific progress while remaining aware of the biomedical application of our work.

What kind of outreach initiatives do you have with the research and life sciences community?

I see our foundation as the middle ground between academia and industry. We collaborate closely with Novartis, where we have 120 ongoing projects, and we are affiliated to the University of Basel, where we have over 100 graduate students enrolled. This type of outreach is our duty. We also have programs that reach out to educate the community and have outstanding core platforms that contribute to the technological education of students and postdocs.

What are your most important objectives for next five years?

At the FMI, we are convinced that there is great potential in solving structures by cryoelectron microscopy. Until a few years ago you could not study large macromolecular complexes at atomic resolution, but with new improvements in cryoEM, this is a reality. It allows us to study large multicomponent complexes that cannot be readily crystallized. These molecular machines are responsible for most cellular functions, and are important even if one is developing small molecular inhibitors to specific domains. Often small ligands act by modulating the conformation of the overall complex.

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The second concept that the FMI promotes is that neuronal circuits are at the root of neurological disease. The pharmaceutical industry is very interested in this field, but are still far from effectively treating such diseases. Most of the drugs used are not targeted towards circuits within the brain or certain subsets of cells, but instead are pan nerve cell treatments, with only a fraction of the drug acting on the specific cell network that is at the root of the disease. We need to identify the neuronal circuits, i.e., the cell networks, that determine normal or abnormal behavior within a given disease model. Targeting these specifically is a long way off, but it is progressing in areas such as retina research. Our neurobiology groups are at the forefront of this research.

The third objective I have is to change the mindset towards model organisms. The world is turning away from this type of research, believing that progress can only be made using human cell models. I believe that this mindset is wrong, although I am a minority saying this. Genome sequencing has given us a vast resource to explore the genetic basis of disease. However, it is not sufficient to use this information to scan human genes and find the mutations and SNPs that correlate with dysfunction across the human population. Rather we should exploit genome sequence and mutant information across many species, from archaea to whales, and learn from natureâ??s greatest experiment, i.e. evolution. There is a vast amount of information that can be obtained quickly and efficiently from the compilation and in depth analysis of gene variation across species. I refer to these two approaches as horizontal (across the human populations) and vertical (pan species). When it comes to the development of a drug, one of course needs human models. However, when it comes to understanding tissue function, that is, the context within which an inhibitor, a protein or pathway functions, the effect of the environment or its role in development, we must study species other than humans.

Nature has often exaggerated the importance of a set of molecules or a pathway in a specific species, due to its peculiar environment or lifestyle. One example is *C. elegans*, the simple threadworm. In this worm, there are hundreds of small peptides that are used to signal between cells, much like neurotransmitters or peptide hormones in humans. It will be far easier to identify the receptors and modes of action in worms than in a more complex organism or in vitro. I am not against in vitro differentiation systems based on human cells, as these are useful to study human cell fate decisions, but I am a strong defender of the speed, power and insight gained from simple model organisms. We must exploit the wide diversity in biology to understand human disease. Some national agencies only fund research on mammalian cells, and those countries will lose the expertise they need, and the advances they could make, from doing what I call vertical research.

What do you see as some the characteristics that make Switzerland a leading environment for scientific research?

The Swiss would rather be modest and influential than pushy and overstated. Sometimes this can be frustrating, because they tend to undersell their discoveries, but it is really a great place to do science. It is said that 70 percent of the people in Basel either work for or support the pharmaceutical industry or its medical application (including university research faculties and local hospitals). It is a fantastic environment for pharmaceuticals, as demonstrated by the fact that two of the leading

companies in the world, Novartis and Roche, have their headquarters in this city.

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