Acceptance Speech by Kai Simons

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[Address]

I feel greatly honored by being included among the distinguished recipients of this award.
What a privilege to work as a scientist in a life-long pursuit of insight and discovery! I started off in Helsinki, Finland. It all goes back to a discussion that I had with my father in the last year of school when he asked me what my plans were. My father was a physicist and I had seen many famous physicists in our home and also during a sabbatical in Princeton when I as a kid took a photo of Albert Einstein, carrying his umbrella. So my answer was that also I wanted to become a physicist. My father looked at me a little worried. He was a farmer's son: a practical and pragmatic man. Kai, are you sure? I am not sure you have the makings of a physicist.
WHAT A RELIEF! A huge burden fell off my back. I knew deep down that my mathematical skills were not brilliant. Kai, why don't you study medicine. If you want to do research, then do. But if not, you can become a practicing doctor. I followed his advice and studied medicine and then moved into research. My PhD thesis was in a classical subject in Finland: pernicious anemia. The broad tapeworm was endemic in eastern Finland and caused pernicious anemia because the worm, which infested the gut sucked up vitamin B12 from the food so that the infested person suffered vitamin B12 deficiency after some years and this vitamin deficiency was the cause of the pernicious anemia. My task was to purify intrinsic factor from human gastric juice. This protein is the only essential ingredient in our gastric juice and is required for the absorption for vitamin B12 from the intestine. We calculated that we needed 30 liters of gastric juice to be successful. This is a huge amount! My PhD supervisor, Ralph Gräsbeck was like my father a practical man and hired a very beautiful nurse. She organized sessions in different locations in Helsinki and usually found a long queue of volunteers waiting to be intubated by her. Without her, we would never have managed to collect the amount that I needed to finish my PhD! Fortunately, I also managed to purify the protein and characterize it. The tapeworm was soon eradicated in Finland and pernicious anemia disappeared.

Then I left Helsinki to spend my postdoc in New York at the Rockefeller University. I worked on human blood proteins. I learned a lot and got a group leader position at my home university. But the real breakthrough for me came after I had returned to Helsinki and spent a month in the famous

Laboratory of Molecular Biology in Cambridge. There I was learning new methods of protein chemistry in the lab of Brian Hartley. He amazingly spent quite some time with me, an unknown Finn. We of course discussed what my research plans were. When I started describing my rather dull work on blood proteins, Brian interrupted me and asked bluntly: “That's rather boring what you are doing. Don't you have anything more interesting to offer?” Luckily I had. I had met a Finnish virologist Leevi Kääriäinen in New York who worked on Semliki Forest virus. This virus was enveloped by a membrane that the virus acquired by stealing a patch from the plasma membrane when it budded out from the host cell. This was the world's simplest membrane and had only one membrane protein. I wanted to know how this virus membrane was assembled in the cell. The idea was to use it as an experimental model for how cell membranes are assembled. Brian told me: “Go for it, Kai” And I did.

Again I got the kick that I needed. We formed a troika with Kääriäinen, and with Ossi Renkonen, a lipid chemist in Helsinki and started characterizing the virus together. This was a unique team at that time, analyzing a biological membrane from all aspects, including cell biology, RNA, protein and lipid chemistry. Our research caught the attention elsewhere and gave me a ticket to Heidelberg. There Sir John Kendrew had started the European Molecular Biology Laboratory in 1974 and he offered me a group leader position. I managed to persuade Henrik Garoff and Ari Helenius, two PhD students in my lab to join me as staff scientists at EMBL, a lucky break for my career as a scientist. There we continued to use Semliki Forest virus but our attention turned away from the virus itself. We started to use it as a tool to study how proteins are sorted and moved around in the host cell. We demonstrated how the virus gets into its host cell and how it delivers its RNA to reprogram the cell to become a virus factory. We showed how the virus uses the host cell to produce new viruses and how they exit from the cell. The most important discovery was the revelation that the virus uses endocytosis to get into the cell. For the first time endosomes were identified as functional compartments on the route towards the lysosome. We showed how Semliki Forest virus manages to fool the cell to allow the virus to inject its RNA into the cytosol. In the endosome the virus triggers its own membrane to fuse with the membrane of the endosome. With this trick the virus escapes from being destroyed in the lysosome and can start the infection.

We also managed to construct a subunit vaccine for Semliki Forest virus that was far ahead of its time. This was 1978. The industry did not care about vaccines then because of the simple fact that there was no money in producing vaccines. Furthermore, Semliki Forest virus caused disease in mice, not an interesting model for vaccine producers. But the principles that we discovered were generally valid.

At that time I got an offer for a professorship at the University of Helsinki but there was little funding for research in Finland then. John Kendrew offered me a tenured position at EMBL and this was an offer that I could not resist. I became the head of the Cell Biology Program and I also took up a new research area: How do epithelial cells polarize? Again, I relied on viruses as tools to simplify the analysis. Most importantly, we included not only proteins but also lipids in the analysis. We wanted to find out how proteins and lipids are delivered to their correct address in the polarized cell surface membrane. We could trace the routes that they take from the sites of synthesis and in the end also show how this was accomplished. But most exciting was a side-track: the discovery of a new way to sub-compartmentalize cell membranes, the concept of lipid rafts. Cell membranes are 5 nanometers thin, two-dimensional liquids, consisting of a bilayer of lipids in which the membrane proteins swim around. The lipid rafts are dynamic nanoscale assemblies of specific lipids and proteins in the membrane. Imagine a thin fluid, in which small platforms arise - tiny reaction centers in which many membrane functions take place. They form and disappear again. This dynamic sub-compartmentalization principle allows multi-parallel processing and in this way enhances the organisational efficiency in the cellular nano-world. This concept was long controversial but then came the breakthrough: phase separation. Take a well-stirred homogeneous emulsion of vinegar and oil, let it stand and two liquid phases form. This is what happens in a constrained way when the raft platforms phase separate. Cell membranes are the products of evolution - an oily fluid with remarkable material properties that incorporate inbuilt sub-compartmentalization. Presently in cell and tissue organisation physical principles such as phase separation are entering into research repertoire. In the era of the DNA revolution that reigned until recently, biological research became dominated by fairly straightforward experimental procedures. Now this homogenization of biology is giving way to more multi-disciplinary approaches.

In 2001 I moved from Heidelberg to Dresden to start a new venture, the founding of the Max Planck Institute of Molecular Cell Biology and Genetics. The challenge was to establish a center of excellence in this area of research in the east of unified Germany. However, it was from the beginning obvious that it would not be sufficient to build up one ivory tower. We had to include the neighboring university in the equation as well and this we did. Today you need a cluster of activities to be able to sustain a functioning research environment. Today there are several new research institutes on our campus that work together to enhance impact. The success of what we accomplished is perhaps best judged by the fact that TU Dresden became an elite university with excellence in biological research as a driving force. This was quite astonishing because before the wall came down in 1989, there was no modern

molecular life science research in Dresden. This achievement was only possible by teamwork. Our team was international: Ivan Baines, Joe Howard, Wieland Huttner, Tony Hyman and Marino Zerial with generous support of the government of Saxony under the leadership of Kurt Biedenkopf. The alliance of biologists, physicists, computer scientists and medical researchers has now catapulted Dresden into the global elite in an area, which we call The Physics of Life. For me, it is a most satisfactory turnaround.

One more challenge is awaiting me as a scientist. I have founded a startup company, Lipotype, deriving from my research on lipids and cell membranes. Together with Andrej Shevchenko, we developed a new technology platform, shotgun lipidomics, based on mass spectrometry. We are introducing a new way to measure blood lipids efficiently, absolutely quantified in high throughput with broad coverage. Until now cholesterol and triglycerides were the only lipids in clinical diagnostics. We can measure more than 250 others. With personalized LPOTYPEs, we hope to stratify health and disease to live up to our slogan for Lipotype, lipidomics for a better life. My life remains exciting.

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