Robert Koch Preis 2023

Laudatio on Francisco Sanchez-Madrid und Timothy Springer

Dear friends and supporters of the Robert Koch foundation,

Today we are honoring two eminent scientists for their seminal work and discovery of cell adhesion molecules. They introduced the concept that cells use distinct adhesion molecules to make contact to defined other cells and the extracellular matrix. That is to move to and stay in defined places of the body. Thgey introduced this concept into cell biology and demonstrated the key relevance of adhesion molecules in particular for positioning and function of cells of the immune system. Their discoveries have paved the way to treat immune-mediated diseases by interfering with the positioning of immune cells and thus with their promotion of the disease.

The story dates back to the days when monoclonal antibodies were first described in 1976 by George Köhler and Cesar Milstein. Monoclonal antibodies proved to be great tools for scientific discovery and later on, also for the therapy of diseases. The aera of biologicals had begun. Immunologists and cell biologists quickly began to exploit the new opportunities. Two of them will receive the Robert Koch prize this year.

Francisco Sanchez-Madrid was born in 1954 in the small Spanish community of Anora. He studied Biology at the Universidad de Sevilla and obtained his PhD in Biochemistry from the Universidad Autonoma de Madrid in 1980. From 1980 to 1983 he joined the research group of Tim Springer at Harvard Medical School in Boston. It was probably one of the best decisions of his life and a most productive one. in 1984, Francisco returned to Madrid became an assistant professor and in 1990 full professor for immunology at the Universidad Autonomia de Madrid, a position that he still holds. Apart from that, since 2009 he holds positions at the Hospital de la Princesa and as Scientific Director of the Instituto de Investigacion Sanitaria Princesa. His list of awards is long, to long to read it here, It includes the Ramon y Cajal Award in 2020.

Timothy Alan Springer was born in Fort Benning in Georgia in 1948. He studied Biochemistry at Berkeley and finished his PhD with Jack Strominger at Harvard in 1976. He then briefly visited Cesar Milsteins lab in Cambridge UK, in 1977, to learn the new monclonal antibody technology. Then he returned to Harvard Medical School and essentially stayed there, moving up from the ranks of assistant to full professor, holding the Latham Family professorship since 1989. He also holds or did held positions at the Dana-Farber Cancer Institute, the Center for Blood Research, and Boston´s children hospital. He is founder of the very successful start-up company LeukoSite and the Institute for Protein Innovation, a key player in Open Science. He also has acted as a business angel and investor for other start-ups, among them Moderna. The list of honours he has received is extensive, with just two to mention here, the Crawfoord prize in 2004 by the Swedish Academy of Science, and the Lasker Basic Medical Research Award in 2022.

Francisco Sanchez-Madrid and Tim Springer initially described the cell adhesion molecules LFA-1, -2 and -3 in 1982 and 1983. They were the first representatives of the integrin gene family. To understand the relevance of the discovery of integrins, we have to zoom back in time to the 1980s, when immunologists were fascinated by antibodies and putative T cell antigen receptors. Common belief was that lymphocytes would use these receptors to find their targets and interact with them. Not much more required. The work of Francisco and Tim challenged this view. They produced monoclonal antibodies against T lymphocytes, and identified antibodies that would block cytotoxic T lymphocytes from killing their target cells, irrespective of the antigens involved. Then they used these monoclonal antibodies to identify and characterize the molecules they recognize. They called them “lymphocyte-function associated antigens” or LFA´s, with the first ones being LFA-1, -2 and -3. Today we know that they were the first of a large family of adhesion molecules, the integrins. Integrins form heterodimers and the repertoire of integrins a cell expresses defines where the cell can adhere to, somehow like a postal address code. The Springer team also identified some of their ligands, so ICAM-1 for LFA-1 and CD-2 for LFA-3. This discovery of cell-recognition molecules was the first ever, not only in immunology but in cell biology. It was a revolution! It completely changed the view of the scientific community on how cells interact with other cells. It also immediately became clear, that this would open new ways to treat diseases which are driven by

cellular interactions, namely by interfering with the positioning of disease-promoting cells.

However, when it comes to immunology, it still was not clear, why lymphocytes do function in an antigen-specific way, nevertheless. They only act on target cells for which they have a specific antigen-receptor. Again, the team of Tim Springer could solve this conundrum. They could show that activation of the T cell receptor is required to activate the integrins. It induces their unfolding, and thus allows them to bind to their ligands. Today we are talking of “immunological synapses”, complex structures involving antigen receptors, receptors for cytokines and chemokines and adhesion molecules. Their characterization has been driven by Francisco Sanchez-Madrid and his research group, focussing on the signal integration in the cells triggered by activation and adhesion, and how this controls their behaviour. Francisco ´s group also identified and characterized other molecules controlling cellular trafficking and positioning, among them CD69. As we know today, CD69 expression of activated and memory lymphocytes is essential for their continued participation in immune reactions, when activated, and for their continued survival as memory cells in the tissues. It is a key molecule of adaptive immunity.

As are the integrins. Essentially, integrins are involved whenever cells touch upon other cells to adhere and interact. The classical textbook scheme of integrin-mediated extravasation of leukocytes from the blood stream by initial tethering, rolling on and adhering to endothelial cells, to then leave the blood and enter the tissue is based on Tim Springers work. Integrins can signal through the phosphoinositide 3-kinase (PI3K) pathway with all its downstream ramifications, to impact on function, metabolism and survival of immune cells. My own research group has shown lately that integrins are also keeping immunological memory cells alive in adherence to bone marrow stromal cells. Thus they are key to provide us with immunity for a lifetime against pathogens once encountered, including the SARS-CoV-2 virus. Just a personal remark from my side. Likewise, the work of hundreds of scientists has been and still is building up on the seminal discovery of Francisco Sanchez-Madrid and Tim Springer.

The discovery that the integrin-code of a leukocyte is key to leave the blood and enter a specific tissue also offers a unique option to interfere with the immigration of leukocytes into inflamed tissues, and thus ameliorate chronic inflammatory diseases. The first example was Natalizumab with the brand name Tysabri, a humanized monoclonal antibody against alpha 4 – integrin. This antibody is blocking trafficking of leukocytes expressing alpha 4 – integrin into the gut and into the brain. It is used to treat Multiple Sclerosis, a chronic inflammation of the brain. In 1992 Tim Springer founded the start-up LeukoSite, which then developed among other drugs the drug Vedolizumab with the brand name Entyvio, a monoclonal antibody recognizing alpha 4 / beta 7- integrin, the key to enter the gut tissue. This one is used to treat chronic inflammatory diseases of the gut, Morbus Crohn and Ulcerative Colitis. These are just two examples of drugs based on the concept to interfere with trafficking and positioning of cells of the immune system to treat chronic immune-mediated diseases. A concept based on the key discoveries of Francisco Sanchez-Madrid and Timothy Alan Springer, which today receive the Robert-Koch Prize 2023.