



DUTCH SOCIETY FOR IMMUNOLOGY

## Van Loghem laureate Jan de Vries:

*So much for career planning. Jan de Vries' labor experience has been far from a straight line from his study to heading big pharma research activities. But his inquisitiveness and love for knowledge of immunology brought him there anyway. This eventually resulted in a string of medicines, some of which are only entering the market nearly three decades after discovery. This background might explain his keen eye for the coincidence factor and, subsequently, his warm plea for nurturing research talent on a not-to-tight leash.*

“It was my biology teacher who ignited the spark of scientific curiosity in me. Some of his lectures and practical lessons were truly inspirational. I thought: this is my world, I want to learn more about this.” De Vries recounts his experience of attending of the Tweede Christelijk Lyceum in Zeist, in the region where he grew up. “Later on I took interest in the work of 1960 Australian Nobel-Prize winner MacFarlane Burnet. His work on immune surveillance, the distinction between self and not-self and other basic mechanisms of the immune system, at the time still mainly only theoretically explained, was truly impressive. During my study of Biology in Utrecht, however, I didn't follow any lectures on immunology. These were simply non-existent at the time. Only in microbiology there was some notion of antibodies and bacterial infections.”

De Vries' career in immunology therefore didn't follow a premeditated plan. “Far from it. At several points, it could have taken an altogether different turn. At 22 I was Dutch champion in decathlon. This led to a tempting offer from Oregon University, which I only turned down because I did not want to do a second master's degree.” So instead of moving to the American West coast, De Vries went looking for a job in Holland. He found one at Poviet, a small pharmaceutical subsidiary of the Amstel Brewery at the Nassaukade in Amsterdam. “They made ready-for-use infusions of dextrans, a bacterial product grown in a medium containing yeast extract. This product was in high demand by various armies in the world because it saves lives as a surrogate for blood transfusions. I remember that for example the Israelian army was a good customer during the six days war in 1967.

### **Immunology experience**

The year after witnessed the takeover of the Amstel Brewery by Heineken. “One of the issues during the procedure was the question: How does the beer yeast used by Amstel compare to that of Heineken? “Answering this question actually was my first step in immunology”, De Vries smiles. “I was asked to develop an answer to the question and used an immunological method to provide one. Rabbits were injected with the two different yeasts. By measuring the type of antibodies these animals produced against the yeast, it could be defined how different the yeasts were. It turned out they were actually very similar.”

This little experiment, however, proved to be vital for De Vries' next career move. At the time, the Antoni Van Leeuwenhoek Huis was located at the Sarphatistraat, on the other side of the Nassaukade. A job opening emerged at the immunology department where Philip Rümke was setting up a human tumor immunology department. De Vries recalls: “I applied and had a job interview with Philip. I was pleasantly surprised that he hired me out of nine applicants because of 'my immunological experience' – based on the beer yeast experiment”

## **From scratch**

At the Antoni Van Leeuwenhoek Huis the entire human immunology research activity had to be set up from scratch. “Rümke gave me total freedom to realize this. He also had a great idea for my first research project, including the necessary funding to get me started and to learn immunological techniques, says De Vries. “It was to study the immune status of pairs of identical twins of whom one was a heavy smoker and the other half was a non-smoker.

A pretty good idea, except for a tiny detail: identical twins stand out for the similarity in their behavior, regardless of the circumstances of their upbringing. “So”, De Vries recounts, “we ended up with n=4. The whole initiative had to be canceled.” It is fun to tell about this lemon, because it allowed me, with Philip’s support to initiate my own research project based on the observation that a relatively high proportion of melanoma patients undergo spontaneous remissions.”

There was the notion this recovery occurred thanks to the immune system. De Vries started to culture melanoma cell lines and isolated lymphocytes from melanoma patients to find out if they could kill their tumor cells in vitro. “Given the primitive ways lymphocytes were separated in those days, the early research went surprisingly well. We made two important observations: we were among the very first to describe that patients who recovered, had lymphocytes that were able to kill their tumor cells in a selective fashion. Apart from that, a proportion of melanoma patients also made antibodies against their tumors.”

## **SLAM DUNK**

In 1985 De Vries switched from academic research to big pharma research, a switch that was even more rare then as it is now. Together with Hergen Spits – another Van Loghem laureate – he moved to the Schering-Plough Institute for Immunological Research in Lyon a biotechnology research center focused on human immunology. The French adventure was productive, but short lived. Corporate rearrangements led De Vries to the DNAX Research Institute in Palo Alto, the scene of ‘The golden helix’ where Arthur Kornberg, Paul Berg, Charles Yanofsky and Alex Zaffaroni had worked their magic.

“My Focus there was on human T- and B-cells, and cytokines and their receptors. We cloned human IL-4, IL-10 and IL-13 and published the first biological characterizations of these cytokines, Both IL-4 and IL-13 proved to be important for allergic responses”, says De Vries. “Just very recently, these original findings have eventually made it into a successful launch in the clinic for the treatment of asthma and atopic dermatitis. We were also the first to determine that IL-10 is an important immune regulatory molecule which down regulates immune responses including pathological responses in models of inflammatory- and autoimmune diseases.”

Another activity was the cloning and functional characterization of the Signaling Lymphocytic Activation Molecule (SLAM), CD150. “It proved to be a self-aggregating molecule, while we initially anticipated that it would have its own receptor. That was a pity as I, as a basketball fan, had already thought up that the name for this receptor should be DUNK. Unfortunately the SLAM-DUNK didn't work out.” Recently the SLAM-family molecules are, however, recognized as unique checkpoint regulators.

## **Life-changing**

Back in Europe, De Vries headed Novartis research activities in Vienna and Basel respectively. He led the discovery and early development stages of several immunology based drugs that have become blockbusters. These include Elidel® for treatment of atopic dermatitis, Cosentyx®, an IL-17A antibody for treatment of psoriasis, psoriatic arthritis and ankylosing spondylitis, Ilaris® which is used for treatment of periodic fever syndromes, juvenile arthritis and gout and Maizent® for a progressive form of MS.

“A special case is Gilenya®”, De Vries tells. “We got a license from a Japanese firm for a drug originally meant as transplantation medication. Unfortunately, this eventually turned out to be toxic in use for that purpose. But in our models for multiple sclerosis it showed spectacular effects. Rats that were completely paralyzed recovered within two days of treatment. We discovered that it blocked the migration of disease causing T cells to the central nervous system. It was quite a battle to get this important drug candidate to MS patients, because Novartis was initially not interested to develop it. Fortunately, it was eventually launched in 2010. It was incredibly rewarding to read the blogs of patients who used this drug and how it changed their lives for the better.”

After his retirement, De Vries remained involved in a number of biotech start-ups, notably as CEO of Amsterdam based AIMM Therapeutics until the end 2017. This company was founded by Hergen Spits and aims at discovering antibodies against cancer that are isolated from individuals who have overcome the disease. Most recently De Vries returned to his old love for IL-10 and founded Tr1X, a biotech company that utilizes IL-10 transduced T-cells for the treatment of Graft-versus-Host Disease and severe autoimmune diseases.

### **Cherishing talent**

With research experience spanning The Netherlands, France, Austria, Switzerland and the USA it is De Vries' observation that research practices are reasonably comparable everywhere nowadays. “There is an international competition for talent. That is why I plead wholeheartedly for Centers of Excellence against mere regional distribution of funds. Talent attracts talent and mutual stimulation brings these talents to ever higher levels of achievement. It is in centers of excellence where the biggest steps forward are made. I think, by the way, that The Netherlands do well in that respect.”

De Vries is grateful for the opportunities and freedom he received early on in his career. “It is very important to give researchers the freedom for in depth exploration of a certain topic – as long as they remain within the guidelines of a broader program.” He also pleads for reasonably paid post-doc tenures, for an extended period of time. “Scientists shouldn't have to live a nomadic existence due to underpaid short term contracts. In fact this is the first step in the quest for talent: research & science should provide an attractive career perspective. This is one of the reasons that smart young people presently are less interested in a career in basic science, to the detriment of science.”

### **Linking the chain**

His career in academia as well as big Pharma gives De Vries rare oversight of the research chain in drug discovery and development. “Academia needs a vision on bringing its discoveries to the next phase. It may be in academia's own best interest not to leave this translation from the bench to the bedside just to biotech and big pharma companies. Although the situation has already improved, there still is a gap between academia and the next phase for drug development in pharma. We need for example physician-scientists who understand the underlying principles of the diseases and who can translate academic discoveries to clinical proof of concept studies to bridge that gap. Important discoveries still remain on the shelf due to imperfect fit of the links in the chain.”

Since the modest beginnings of immunology in cancer research, immunotherapy has now become the hottest topic in cancer treatment. The checkpoint modulators have led to a breakthrough in cancer treatment. Progress in the immunology field in general is still very promising and exciting.”

Leendert van der Ent [Bureau Loriënt]

### **Concise CV**

Msc. Biology, University of Utrecht

Ph.D. Immunology University of Amsterdam.

Post doctoral studies Dept Hematology/Oncology University of California San Diego

Head of Department Immunology, Netherlands Cancer Institute

Co-Director of the Institute for Immunological Research, Schering-Plough, Lyon, France

Director of the Immunology Department, DNAX Research Institute for Molecular Biological Research, Palo Alto, California

Head of the Novartis Research Institute, Vienna, Austria.

Novartis : VP and Global Head Therapeutic Area Autoimmunity, Inflammatory diseases and Transplantation, Vienna, Basel

Head of the Novartis Research Institutes for BioMedical Research in Basel, Switzerland

Currently involved in various roles in AIMM Therapeutics (NL), AnaptysBio (USA), Cassiopea SpA (I), and Tr1X bio (USA)