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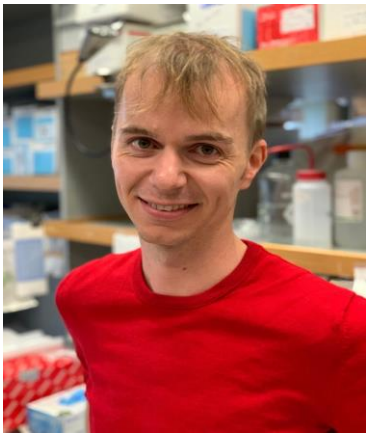
DUTCH SOCIETY FOR IMMUNOLOGY

NVVI Van Bekkum thesis award winner 2019: Vincent van Unen

From a tsunami of data to wealth of insight on mucosal immunology



Vincent van Unen was the first to use CyTOF in the Netherlands. It was no coincidence that this technology was used in the complex field of chronic intestinal disease. "It offered a tsunami of rich data, with the potential to chart intestinal immunology in unprecedented detail. Thanks to collaboration with bioinformaticians, we were able to unlock this potential."

"It took me a year before I could start working on the hypothesis for my thesis", says Van Unen, currently a postdoc at Stanford University. At the time he was working in the laboratory of Frits Koning at the LUMC. He refers to setting up CyTOF (mass cytometry) in close collaboration with TU Delft computer scientists from the group of Boudewijn Lelieveldt and Anna Vilanova. The time investment was worthwhile. There is only a limited supply of clinical biopsies available. These are costly. Flow cytometry only allows looking at one main branch at a time. CyTOF. However, enables charting all different immune cells in a sample, covering all five main branches of both the innate and adaptive immune system, including all subsets. Van Unen: "During the first study, we could unravel 132 subsets by using a set of 32 markers. The second study into the inflammatory bowel disease with an improved panel of 36 antibodies even led to finding 300 subsets."

Dizzying complexity

How does that improve insight? "The first conclusion was that the complexity of the immune system is – yet again – more complex than imagined. I must admit the complexity of the data made us dizzy at first. The information overload meant years of work for data analysis, but hidden in the data was a concise and detailed representation of the intestinal immune system, with valuable information on (refractory) celiac disease, Crohn's disease and Enteropathy-Associated T cell Lymphoma (EATL)."

Over time, patterns were discovered amidst complexity. "We saw how the composition of subsets differed between the various diseases. Diseases could be distinguished by their immune cell infiltrate. We obtained an integrated image of the immune reactions, including the interplay between innate and adaptive components."

Foetal intestines

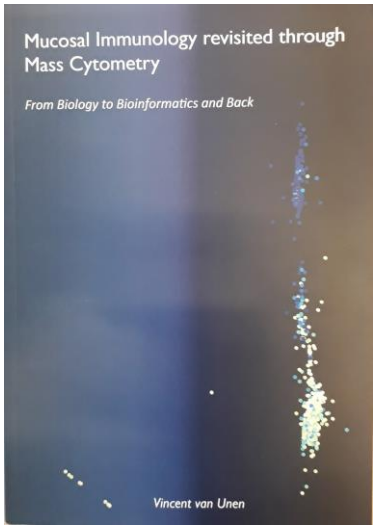
What's more, the complete picture provided unique insight into the riping process of the immune system, including which subsets could be associated with maturation. "That is why we decided to subsequently deploy CyTOF for research of the foetal intestine: the key to understanding chronic intestinal disease lies in the development of the immune system."

The dogma is that the foetal intestine is a sterile environment. "Recent research results, however, may suggest otherwise", says Van Unen. "Innate cells and T cells turn out to be very mature. For T cells, this implies that they have already encountered specific antigens. We don't know what process might explain this maturation, but it's clear that the unborn child comes prepared for the

myriads of bacteria it encounters during birth.”

Indispensable bio-informatics

Van Unen's experience underlines how bio-informatics becomes almost indispensable in immunology research. “Immunologists need approaches such as single-cell RNA sequencing, transcriptomics, proteomics and genetics. Just as with mucosal immunology, rheumatoid arthritis and cancer immunology prove to be likewise complex. Unraveling these complex diseases calls for complex technologies. A combination of technologies is necessary to first chart the complexity. In order to do that, you need to collaborate with bio-informaticians. Once the complexity is properly established, you can subsequently formulate immunology hypotheses and to go down the road of testing these.”



Leendert van der Ent, Bureau Loriënt

Thesis

Vincent van Unen, 'Mucosal Immunology revisited through Mass Cytometry: From Biology to Bioinformatics and Back', PhD Defence University of Leiden, Tuesday 27 November 2018