

'Quantification of lymphocyte dynamics' by Liset Westera PhD wins this year's NIVI thesis award. How long does a naive T cell or memory T cell actually live? And how many of these are produced by the thymus every day? These are apparently simple, basic textbook questions, but amazingly the answers were largely unknown. This is largely due to difficulties to experimentally address such questions, particularly in humans. Moreover, the translation of data into a lifespan or turnover rate is not straightforward. As a result, there is little consensus. Westera now figured out how to most reliably quantify lymphocyte dynamics in humans, and thus obtained a number of important biological insights into the maintenance of lymphocyte populations.

Liset Westera NIVI 2014 thesis award winner

## The importance of cell population quantification

Simple questions are no guarantee for simple methods. Large part of Westera's thesis investigates methodological aspects of *in vivo* deuterium-labelling techniques. With this method, a stable isotope of hydrogen, deuterium, is administered in the form of heavy water ( $^2\text{H}_2\text{O}$ ). Due to the presence of an additional neutron in the atom core, deuterium is twice as heavy as normal hydrogen. When cell division occurs in the presence of deuterium, newly synthesized DNA will incorporate deuterium. This can be measured and indicates cell lifespan.

"However", says Westera, "even with this technique there was still a tenfold variation between laboratories. A comparison of lifespans in literature revealed a curious pattern: the longer the period of deuterium labelling, the longer the estimated lifespan. We investigated this problem in mice and found that it was caused by the mathematical model used in our field: it could not correctly describe cell populations that contain multiple sub-populations with distinct turnover rates. An alternative model brought the solution. Not only does this finding explain controversy in literature; from now on this multi-exponential model can also be used to reliably quantify cell turnover from deuterium-labelling experiments."

### Biological outcomes

The work is not merely about calculation; these numbers actually tell us a lot about immune function. Hence the statement in the thesis: 'Quantification of biological processes often leads to important qualitative insights'. Westera mentions a few: "The main source of new naive T cells in mice and men is qualitatively different: while in mice the thymus is the major source of new T cells, in humans most naive T cells are produced by cell division in lymph nodes and spleen. Even though the human thymus shrinks with age and its output declines tenfold during adulthood, this has little impact on total production of naive T cells

Liset Westera:  
*"Quantification of biological processes often leads to important qualitative insights"*  
 (photo Liset Westera)



during aging, as the contribution of thymic output is already small in young adults."

This also explains why Westera found that T cells in elderly people do not divide more than T cells in young adults – there is no need for 'compensation'. As the source of naive T cells is fundamentally different in mice and men, it is not advisable to use a mouse model for human conditions where T-cell dynamics are disturbed.

Quantification of lymphocyte dynamics is also clinically relevant, says Westera: "To understand clinical conditions with disturbed lymphocyte dynamics, we need quantitative information from healthy people. This learns how lymphocyte dynamics is altered after stem cell transplantation, or establishes the effect of drugs on cell turnover."

### IBD

Westera now works as a post-doc in the group of professor Gijs van den Brink at the Amsterdam AMCTytgat Institute, where she studies Inflammatory Bowel Diseases (IBD). "This research is closer to the clinic and I like this translational angle. I use fresh human intestinal tissues to study the clonality of T cells in IBD. I do not exclude that, in the future, I will take the chance to apply deuterium labelling in this line of research."