PhD defence Pieter Pannus

Predictive biomarkers of a functional cure for HIV

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Dit is de omschrijving

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Abstract:

Although combination antiretroviral therapy (cART) is very effective at suppressing viral replication and preventing disease progression, it is not curative due to the existence of a latent viral reservoir in resting memory CD4+ T cells. As a result, HIV infected patients need to take life-long antiretroviral therapy. Besides the high economic cost, it is proving to be very challenging to get all HIV positive people on treatment, especially in low -and middle income countries. In addition, although the pill burden has been reduced to one pill per day, daily treatment continues to affect quality of life and may still have a long-term impact on the patients' health. Therefore, a cure for HIV is needed.

It is becoming increasingly clear that achieving a 'sterilizing cure', where a patient becomes completely virus-free, will be very difficult. In contrast, achieving a 'functional cure', where a patient is still infected but suppresses the virus without the need for drugs after a period of therapy, might be more realistic. This state of "post-treatment control" has been observed in a small proportion of patients and has become an important focus of HIV cure research. The main goal of this doctoral thesis was to find immunologic and/or viral biomarkers which are predictive of functional cure with the help of three clinical trials.

In the first trial we hypothesized that virally suppressed patients on cART who have a very small viral reservoir (measured as the amount of proviruses) and very little proviral transcriptional activity (measured as the amount of cell-associated viral RNA), would be more likely to have delayed viral rebound after treatment interruption as compared to the general HIV positive population on cART. Sixteen such patients interrupted therapy but all experienced rapid viral rebound within two to eight weeks. This observation is consistent with the findings from other recent trials and affirms that it is unlikely that post-treatment control can be achieved by merely reducing the size of the reservoir, and that an immune intervention is required.

In the second trial we set up a sensitive and specific assay to measure the *in vitro* viral inhibitory activity (VIA) of CD8+ T cells, which was to be used in the third (therapeutic vaccination) trial. In addition, we explored associations between VIA and clinical, viral and immune parameters. Interestingly, we found positive associations of VIA with expression of immune exhaustion markers PD1 and CD160, as well as with CD57, a marker of replicative senescence, and HLA-DR, a marker of immune activation, on terminally differentiated memory CD8+ T cells. While we did not show that these cells are responsible for the VIA we measured, it indicates that a distinct activation state of fully differentiated memory cells might play an important role in suppressing viral replication.

In the third and last trial, we assessed the immunogenicity of an innovative therapeutic vaccination strategy and its capacity to induce delayed viral rebound after treatment interruption in virally suppressed patients on cART. Study participants received three intra-nodal injections of a naked mRNA vaccine. The mRNA construct coded for a set of rationally selected, conserved, immune subdominant HIV peptides (vaccine) and three dendritic cell activation stimuli (adjuvant). Unfortunately, the construct was found to contain an error which likely compromised the translation of the mRNA, thereby invalidating the findings of the trial.

In conclusion, the findings from this doctoral work contribute to the growing consensus that the induction of a functional cure will require an immune intervention (e.g. therapeutic vaccination) on top of a sufficiently reduced viral reservoir. Unfortunately, we were not able to verify the potential of our own

therapeutic vaccine due to a serious error in the mRNA construct which was produced by one of our private partners.