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Commentary

A radiolabeled mAb 3BNC117 with copper-64: First round in favor for studying clearance of HIV reservoirs

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The article published by McMahon and colleagues [1] reports the first clinical trial in humans using a monoclonal neutralizing antibody (mAb) attached to a detection system with radioisotopes and measured by positron-emission tomography (PET) to assess the neutralizing effect of the mAb among the potential reservoirs of human immunodeficiency virus (HIV) in volunteers with and without HIV infection. The series of experiments implemented by the team shows the effort invested to obtain all measurements with the highest accuracy and precision crucial for this sort of studies. The most important similar study previously implemented used a poly(ethylene glycol)-modified, (64) Cu-labelled Simian Immunodeficiency Virus (SIV) Gp 120-specific antibody and was reported by Santangelo and his group [2]. They reported the dynamics of SIV in the whole body of viremic and under antiretroviral therapy (ART) treatment macaques using an antibody-targeted PET (immunoPET). An experiment, which until that time, was limited to biopsies and autopsies. These experiments showed detectable signals in important organs – higher signals among viremic macaques and lower in macaques under-ART. These results promised better approaches for the study of HIV pathogenesis, opening doors for the development of new drugs and vaccines.

In the initial stages of its development, immunotherapy against HIV was mostly inadequate, subsequent successes were achieved when cloning methods of antibodies based on single cells were further developed. These antibodies have a higher neutralizing effect, can prevent HIV infection and suppress the viremia in humanized mice and non-human primates, but until Santangelo's study we have not had indications of how to use this effect for immunotherapy. Caskey et al., reported the use of the mAb 3BNC117, a specific antibody directed against the CD4 receptor in a phase 1 clinical trial in humans [3], her work showed a reduction in viral load among persons living with HIV. This effect lasted for 28 days after injection in some cases. The same team years later, also showed that the use of combined 3BNC117 and 10–74 monoclonal antibodies could be a good choice for a successful pre-exposition prevention of HIV infection [4]. The immune response has apparently gained some strength against HIV-1 when the mAb 3BNC117 is used as a clinical therapy [5].

A critical barrier to achieving a HIV cure is to influence the viral reservoirs at organic and cellular levels. The persistence of these reservoirs can be explained by the low concentration of ART drugs. Therefore, characterizing the pharmacology of ART drugs is crucial, and can be more feasible with the abovementioned available tools to assess the dynamics of viral reservoirs *in vivo* [6,7].

There is a promising future, 40 years into the HIV pandemic we now have a better understanding of the pathogenesis of HIV infection, thanks to the development of monoclonal antibodies with enough neutralizing capacity to also prevent infection. By coupling image technology approaches such as PET with the use of better biomarkers, it is now feasible to identify the destination of these antibodies. In the near future perhaps, further developments will also allow detection of the neutralizing effect, decrease of the viral load in certain compartments and measure remnant virions in free cells and tissues.

There are still unanswered questions to be addressed in future studies. For example, the use of a different marker with a longer half-life, zirconium-89 as proposed by McMahon and colleagues. Will it improve the detection of HIV reservoirs in humans? There is a need to develop studies that do not result in increased radioactivity but allow comparable results to those found in non-human primates (NHP). Is it then possible to accurately reproduce experiments done in NHP in humans? Since there is low expression of the HIV surface viral protein gp 160 (*Env) in vivo*, we would need new recombinant antibodies with higher binding ability. Is it possible to develop antibodies with higher avidity than currently available antibodies? And if so, will it be possible to use combined methodologies to detect *Env* in single cells?

Limitations such as study sample size, which is usually very small, must be overcome in future trials. Additionally, the pharmacokinetics of 3BNC117 in patients undergoing PET, must be studied taking into consideration patients with different comorbidities and ethnic backgrounds.

McMahon et al. have performed the first study in humans and their data showed the safety of Cu-64 marked mAb. This opens up the possibility to study more precisely the effects of interventions for curing HIV in the near future.

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Declaration of Competing Interests

The author declares no conflicts of interest.

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