Translation of $^{89}$Zr-VRC01 for PET/MR imaging of persistent HIV: First-in-human

Denis Beckford-Vera, Timothy Henrich, Cassandra Than, Enrique Martinez-Ortiz, Maya Aslam, Tony Huynh, Youngho Seo, Robert Flavell, Ramsey Badawi, Simon Cherry, Henry VanBrocklin

One of the biggest challenges to the successful design and implementation of HIV curative strategies is the limited ability to accurately quantify and characterize the whole-body burden of HIV infection. Despite the striking success of antiretroviral therapy (ART) in HIV patients, residual infected cells persists indefinitely. [1] These cells largely reside in anatomical and lymphoid compartments that are inaccessible to routine sampling. [2] Therefore, there is an urgent need for development and implementation of in vivo techniques to non-invasively identify and quantify persistent HIV. The objective of this work was to develop a Zr-89 labeled antibody (VRC01) for first-in-human PET/MR imaging of HIV infected individuals with the ultimate goal of characterizing persistent HIV. VRC01 is a broadly neutralizing monoclonal antibody that targets the CD4 binding sites of the HIV-1 external envelop protein (gp120) and have been safely applied in clinical studies. VRC01 was successfully modified with p-benzyl-isothiocyanate-deferoxamine and radiolabeled with Zr-89. The biological activity of $^{89}$Zr-VRC01 was assessed using a recombinant protein that contains the gp120 CD4 binding sites. In vitro binding saturation assay demonstrated that $^{89}$Zr-VRC01 binds with similar affinity ($5.21 \pm 0.84$ nM) to that reported for unmodified VRC01. Preclinical pharmacokinetics in healthy Balb/C mice and rhesus macaques was performed to estimate dosimetry in humans. (Fig 1A and B) The estimated effective dose for $^{89}$Zr-VRC01 was 0.3 mSv/MBq, similar to other Zr-89 radiolabeled antibodies that have been safely administered in clinical research studies. [3, 4] Following pre-clinical development, clinical batches of $^{89}$Zr-VRC01 were reproducibly prepared, under GMP, and an IND was submitted to the FDA.

After successful IND and IRB approval, PET/MR imaging was performed in HIV infected individuals and uninfected controls using $^{89}$Zr-VRC01. HIV infected individuals (4) and uninfected controls (4) were intravenously injected with $^{89}$Zr-VRC01 (37 MBq) and PET/MR scans were acquired 1, 4, 24 and 96h post-injection. Blood was also collected shortly before each imaging session. PET/MR imaging showed higher $^{89}$Zr-VRC01 uptake in inguinal lymph node, bowel and bone marrow (BM) on viremic individuals compared to controls (Fig 1C). $^{89}$Zr-VRC01 showed higher uptake in gut and BM in early treated individual on recent ART compared to uninfected control (Fig 1D and E). First-in-human PET/MR study using $^{89}$Zr-VRC01 in HIV infected individuals indicated that this technique has the potential to inform on whole-body anatomical localization and burden of persistent HIV infection.

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References