PROLONGED VIRAL SUPPRESSION BY IMMUNOTHERAPY WITH ANTI-HIV ANTIBODIES 3BNC117 AND 10-1074

Christian Gaebler1, Lilian Nogueira1, Elina Stoffel1,2, Thiang Y. Oliveira1, Katrina G. Millard1, Martina Turroja1, Allison Butler1, Victor Ramos1, Michael S. Seaman3, Jacqueline D. Reeves4, Johannes F. Scheid5, Rajesh Gandhi5, Tae-Wook Chun5, Marina Caskey5, Michel C. Nussenzweig1,7

1 Laboratory of Molecular Immunology, The Rockefeller University, New York, NY, USA. 2 Columbia University Irving Medical Center, New York, NY, USA. 3 Center for Virology and Vaccine Research, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA. 4 Labcorp-Monogram Biosciences, LabCorp, San Francisco, California, USA. 5 Division of Infectious Diseases, Massachusetts General Hospital, Boston, MA, USA. 6 Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Bethesda, MD, USA. 7 Howard Hughes Medical Institute.

Background:
Broad and potent monoclonal anti-HIV-1 antibodies (bNabs) comprise a promising class of immunotherapeutics that have the potential to suppress HIV-1 infection, increase the rate of infected cell clearance and enhance anti-
HIV immunity. However, bNabs have only been tested in short term studies and their effects on the intact latent reservoir have not been investigated in depth. Here we report on a clinical study in which people living with HIV who started ART during chronic infection received 7 doses of a combination of two bNabs over a period of 20 weeks in the presence or absence of antiretroviral therapy (ART).

Methods:
We conducted a phase 1b, open label, randomized clinical trial of the combination of two bNabs, 3BNC117 and 10-1074, in the presence or absence of ART, including two study groups of people living with HIV on suppressive ART for at least 12 months prior to entry (NCT03526848). Study participants were enrolled without prior screening for proviral reservoir sensitivity to 3BNC117 or 10-1074. Participants in Group 1 discontinued ART 2 days after the first 3BNC117 and 10-1074 infusions, while participants in Group 2 remained on ART during the period of antibody infusions through week 26 (Fig. 1). Participants in both groups received up to seven infusions of 30 mg/kg each of antibody over the course of 20 weeks and were followed for a total of 48 weeks from enrollment.

Results:
Repeated antibody infusions over the course of 20 weeks were generally safe and well-tolerated by all participants. Serum concentrations of 3BNC117 and 10-
1074 were measured by a VNA-specific pseudovirus neutralization assay and showed average half-lives of 14.9 and 20.3 days, respectively (Fig.3). There was no significant difference in antibody half-lives in the absence (Group 1) or presence of ART (Group 2).

Envelopes (en) sequences were obtained from the reservoir by limiting dilution PCR and QPCR®. Env sequences were subsequently analyzed for known 10.1074 resistance mutations and categorized as sensitive or resistant. The samples were also analyzed for resistance to 10.1074 and 3BNC117 in the Phenosense Monoclonal Antibody (mAb) Assay (Labcorp-Monogram Biosciences) with an exploratory susceptibility threshold (IC50 10 µg/mL). In this small data set, both genotypic and phenotypic sensitivity analyses failed to predict clinical outcome and time to viral rebound.

To examine the effect of prolonged bNab therapy on the latent reservoir, we performed QPCR® in 3BNC117 samples obtained approximately 2-4 weeks before and 26 weeks after the first bNab infusion. In addition, we examined the reservoir in the parallel group of 10 participants that remained on suppressive ART without receiving antibody infusions at paired time points with a median interval of 12 weeks (range 24 to 58 weeks) between baseline and follow-up. Overall, we recovered and analyzed 6074 defective (NAI) Therapy mN=3865, ART alone n=2108) and 841 intact proviral (INAB Therapy combined n=842, ART alone n=209) sequences (Fig.7).

Conclusions:
• Prolonged viral suppression with repeated antibody infusions of 3BNC117 and 10-1074
• Post-treatment control (>48 weeks) in two study participants
• Viral rebound after one of the antibodies reached sub-therapeutic serum concentrations (below 10 µg/mL)
• Phenotypic and genotypic sensitivity analysis unable to predict time to viral rebound
• Immunotherapy with 3BNC117 and 10-1074 is associated with significant changes in the size and composition of the intact proviral reservoir without measurable effect on the defective reservoir
• Larger and longer studies are required to define the precise half-life of the intact reservoir during antibody therapy

References:

Contact:
Christian Gaebler, MD, cgaebler@rockefeller.edu