DELINEATING THE ONTOGENY OF AN N332-DIRECTED ANTI-HIV-1 BROADLY NEUTRALISING ANTIBODY LINEAGE.

Thamara

Naidoo

1317469

Supervisors: Dr Dale Kitchin (Senior Medical Scientist, Antibody Immunity Research Unit (AIRU), National Institute for Communicable Diseases (NICD)) and Professor Penny Moore (Head of AIRU, NICD and Full Research Professor, University of the Witwatersrand)

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Abstract

Broadly neutralising antibodies (bNAbs) develop in chronically HIV-1 infected individuals and can neutralise a variety of HIV-1 Env strains, making them an important element contributing to the design of HIV-1 vaccines. By understanding and delineating the long affinity maturation pathways that bNAb lineages follow against evolving viruses, it is hoped that this process will be able to be replicated in uninfected people with a series of vaccine immunogens. Investigating the ontogeny of a N332-directed bNAb lineage will provide insights into the key somatic hypermutations necessary for the development of neutralisation breadth. CAP255.G3 is an N332-directed bNAb isolated from CAP255, a participant in the CAPRISA 002 cohort, at 149 weeks post-infection (wpi). Six key antibody intermediates were selected from the CAP255.G3 lineage arm between 17 and 47 wpi, based on their position on a phylogenetic tree and because they contained mutations that were present in broad members of the lineage. We hypothesized that these intermediates would exhibit breadth similar to CAP255.G3. The intermediates were tested against a panel of eight autologous and six heterologous pseudoviruses using a TZM-bl neutralisation assay. The sequence identity of the first heavy chain complementarity-determining region (CDRH1) of CAP255.G3 differed from the closest intermediate and therefore, a CDRH1 chimera was constructed to determine if the CDRH1 from CAP255.G3 affected neutralisation activity. Later intermediates from 39 and 47 wpi, had moderate neutralisation activity against the autologous pseudoviruses, but only the intermediate closest to CAP255.G3 had limited neutralising activity against the heterologous pseudoviruses. Although the CDRH1 chimera had increased neutralisation activity against the heterologous viruses relative to the intermediates, it was less broad and potent than CAP255.G3. This indicates that additional affinity maturation between 47 and 149 wpi, at sites outside of the CDRH1, was required for the development of neutralisation breadth in the CAP255.G3 lineage arm.