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CAPRISA

CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA

Newsletter

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Majority of the replication-competent HIV-1 reservoir is established close to the time of treatment initiation

A collaboration between UCT, UNC and CAPRISA researchers has uncovered that the HIV-1 latent reservoir does not necessarily form continuously as previously thought, but rather that most latent viruses in individuals on long-term antiretroviral therapy (ART) are genetically most similar to those circulating in the blood shortly before therapy initiation.

The study in nine women from the CAPRISA 002 cohort, published this month in *Science Translational Medicine*, made use of phylogenetic analyses of next-generation sequencing data to identify the timing of the establishment of the reservoir. The reservoir is the source of ongoing viral replication if patients stop ART and it represents the greatest challenge to a cure for HIV.

On average, the 9 women were treatment naïve for 4.5 years and on ART for 4.9 years. Viruses were sequenced from the blood pre-treatment at 6-monthly intervals

and compared to sequences of viruses in the cellular reservoir after a viral outgrowth assay.

For each outgrowth virus, the most closely related variant in the blood pre-treatment was determined using genetic distance and placement probability methods.

The analysis revealed that ~71% of the replication-competent reservoir consists of viruses that are genetically most similar to strains circulating in the blood within a year of ART initiation (Figure 1).

Furthermore, these findings indicate a rapid turnover in latently infected cells over the course of untreated infection. This led the authors to hypothesise that ART indirectly creates an environment in which actively infected cells transition to a resting state, potentially due to lack of antigen stimulus.

This points to a window of opportunity to clear actively infected cells and/or prevent their transition to a latent state at the time of initiating therapy.

Melissa-Rose Abrahams

For further reading see:

Abrahams MR, et al. *The replication-competent HIV-1 latent reservoir is primarily established near the time of therapy initiation. Science Translational Medicine* 2019 October; 11(513): eaaw5589. doi: 10.1126/scitranslmed.aaw5589. <https://stm.sciencemag.org/content/11/513/>

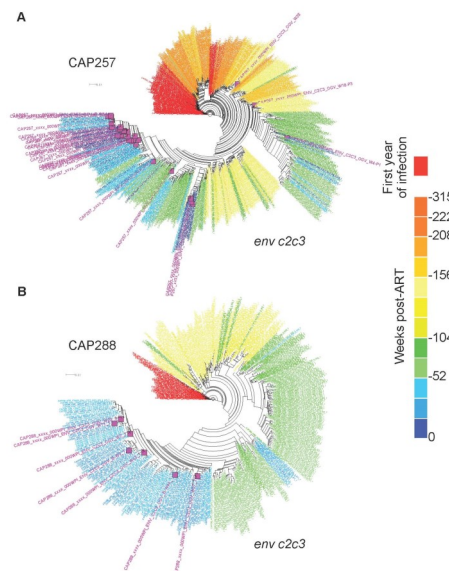


Figure 1. Maximum-likelihood-like phylogenetic tree of the c2 to c3 region of the viral env gene of CAP257 and CAP288. Pre-ART sequences are in red (within the first year after transmission) to blue (within the year before ART), and reservoir outgrowth viruses are in pink. Weeks pre-ART are indicated alongside the colour key.

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Professor Quarraisha Abdool Karim honoured for her pivotal role in HIV prevention research

Stellenbosch University (SU) will confer an honorary doctorate on Professor Quarraisha Abdool Karim, for her 'commitment to research and education in the field of women's health in Africa and globally, particularly her successful efforts in increasing the national and international focus on HIV, and her pivotal role in HIV prevention research'.

The press statement released by Stellenbosch University announcing the conferral of the 2019/2020 honorary degrees stated: 'The university's

honorary doctorates are a way of acknowledging the remarkable work of individuals who are regarded as role models and an inspiration to Stellenbosch graduates. Their contributions to society through education, activism and research also embody the values underpinning SU's Vision 2040 – compassion, respect, excellence, accountability and equity. Professor Abdool Karim's honorary doctorate will be conferred during SU's March/April 2020 graduation ceremony.



CAPRISA scientist receives Fogarty's 2019 Emerging Global Leader Award



We congratulate CAPRISA Scientist, Anushka Naidoo, PhD, who is a recipient of the National Institutes of Health (NIH) Fogarty's 2019 Emerging Global Leader Award of \$538,000 over five years, aimed at establishing independent careers in global health under the guidance of experienced mentors in the US and in developing countries.

Naidoo's proposal presented a five-year research career development program focused on clinical pharmacology that included training and mentorship and research activities aimed at sup-

porting the transition from an early stage to lead investigator. The research focus is in HIV-associated tuberculosis (TB) in South Africa. The World Health Organization recommends the antiretroviral drug dolutegravir as first-line treatment of HIV, however, dolutegravir is not recommended in patients with HIV-TB co-infection. Tuberculosis drug interactions may reduce dolutegravir efficacy.

"This study aims to fill this knowledge gap by understanding the impact of drug interactions with tuberculosis drugs on dolutegravir drug concentrations, adherence and treatment outcomes, said Naidoo.

The study will be conducted in a high HIV-TB burden setting in KwaZulu-Natal South Africa.

We wish Naidoo every success as she leaves her post in Pharmacy to embark on a career as an independent researcher.

EDCTP Fellowship awarded to scientist

CAPRISA congratulates Scientist Navisha Dookie, PhD on being awarded an European and Developing Countries Clinical Trials Partnership (EDCTP) Career Development Award aimed at providing individual training to talented early-career scientists to develop as independent researchers and team leaders at host institutions in sub-Saharan Africa for long-term continuity, networking and re-

search ownership in the region. Dookie was awarded the funding of €140 000 over a 3-year period.

The overall aim of the fellowship said Dookie was to 'optimise the clinical utility of whole genome sequencing for the detection of drug-resistant tuberculosis'.

She is being mentored by Prof Kogile Naidoo head of HIV-TB Treatment Research at CAPRISA.





Building momentum for global health and development



(L-R) Peter Singer, senior advisor to the WHO Director-General with Jerome Singh and Salim Abdool Karim from CAPRISA

CAPRISA participated in the 2019 Grand Challenges Annual Meeting co-hosted by Ethiopia’s Ministry of Health, Grand Challenges Canada, the United States Agency for International Development and the Bill & Melinda Gates Foundation, from 27 – 30 October held in Addis Ababa, Ethiopia.

The primary aim of the meeting was to build momentum for global health and development through innovation and scientific collaboration among international groups and researchers. The meeting convenes over 1,000 key leaders from across the global community to share best practices, encourage collaboration and seek solutions for common challenges.

Professor Salim Abdool Karim, CAPRISA’s Director, delivered a spotlight talk (akin to a [TED talk](#)) on the development of CAP256 bnAb for HIV prevention.

Professor Jerome Singh, head of Ethics and Law at CAPRISA participated in a plenary session on science advocacy and the official press conference to discuss gene drive - an approach to genetically modify mosquitoes for malaria control.

He also participated as a panellist in a Q&A session entitled: Innovation for Good, Innovation for Growth, held in the United Nations Conference Center and the Coalition for African Research and Innovation (CARI) Pharma Working Group meeting.

Diverted Antibody Evolution – implications for bnAbs

A recent study, published in *PLoS Pathogens* by NICD PhD student David Sacks, shows how somatic hypermutation to counter a globally rare viral sequence drove off-track antibodies in the CAP256-VRC26 bnAb lineage. bnAbs develop in only a few HIV infected individuals. Their development is complicated by complex evolutionary pathways that are characterized by extensive somatic hypermutation of antibodies.



Previous work by Jinal Bhiman showed that CAP256-VRC26 lineage includes both bnAbs and highly mutated “off-track” lineage members that share high sequence identity to broad members but lack breadth.

In this study, Sacks defined the specific mutations that limit breadth in two “off-track” members of the CAP256-VRC26 bnAb lineage, and showed that these occur with a relatively high probability. He also showed how a dominant virus within the CAP256 donor, that had a globally rare V2 sequence, selected for an off-track antibody, providing a mechanism for the development of this antibody during infection.

These data show that affinity maturation to counter globally rare viral immunotypes can drive antibodies within a broad lineage along multiple pathways towards strain-specificity. Defining developmental pathways towards and away from breadth will facilitate the selection of immunogens that elicit bnAbs and minimize off-track antibodies.

For further reading: Sacks D, et al. Somatic hypermutation to counter a globally rare viral immunotype drove off-track antibodies in the CAP256-VRC26 HIV-1 V2-directed bnAb lineage. *PLoS Pathogens*. 2019;15(9):e1008005. doi: 10.1371/journal.ppat.1008005. <https://www.ncbi.nlm.nih.gov/pubmed/31479499>

Dr Lenine Liebenberg invited to participate in CoMA



CAPRISA mucosal immunology scientist and FLAIR Fellow, Dr Lenine Liebenberg participated in the inaugural Connecting Minds Africa (CoMA) 2019 conference, hosted by the African Academy of Sciences, that was held on 25-27th September at the World Agroforestry Centre (ICRAF) in Nairobi, Kenya. Dr Liebenberg was invited to present her research, engage with other scholars and build mutually supportive networks to advance the develop-

ment of science, technology and innovation on the continent.

The meeting showcased innovative science from researchers including the African Academy of Science, the Royal Society, the Global Challenges Research Fund (GCRF), The World Academy of Science, the Next Einstein Forum, the Global Young Academy, and ASSAf.



Scientific papers published in 2019

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*continuation from previous newsletter

Prize for best 3 minute presentation at the 14th H3Africa meeting in Ghana



Holly Spencer, an MSc student at the NICD, won the prize for the best 3 minute presentation at the 14th H3Africa meeting in Accra, Ghana from 23 – 27 September.

Spencer's MSc project involves sequencing the germline of IGHG3 genes which encode IgG3 antibodies. She is also

making IgG3 versions of HIV-specific antibodies from CAPRISA donors, and testing the effect of the germline diversity on antibody function using effector function and neutralization assays.



CAPRISA hosts a DST-NRF Centre of Excellence in HIV Prevention



UNAIDS
CAPRISA is the UNAIDS Collaborating Centre for HIV Research and Policy



CAPRISA hosts a MRC HIV-TB Pathogenesis and Treatment Research Unit
CAPRISA hosts a DoH-MRC Special Initiative for HIV Prevention Technology



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