UNC HIV Cure Seminar

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9:00 - 10:00 a.m.
1131 Bioinformatics

'Therapeutic strategies for targeting the latent HIV reservoir'

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Abstract: Current HIV therapies do not cure HIV, as latent reservoirs persistent within infected CD4+ T cells. The induction of viral proteins in latently infected cells could facilitate their recognition and elimination by immune cells. High throughput screening has been used to identify novel compounds that induce viral expression in resting CD4 T cells isolated from cART-suppressed HIV infected donors. Pairwise combinations of latency reversal agents revealed that cyanotriazoles in combination with proteasome inhibitors synergistically reactivate latent virus without leading to proliferation or markers associated with T cell activation. Strategies for elevating expression of latent virus will likely need to be combined with interventions that lead to improved clearance of infected cells. Agonists of pattern recognition receptors may be able to facilitate both goals by activating latently infected T cells while at the same time stimulating innate and adaptive immune effectors. TLR7 agonists modestly increase HIV expression through a pathway that is dependent on type I IFNs. At the same time, they stimulate CD8 T cell cytolytic activity and antibody-mediated cytotoxicity. This is supported by preclinical models, which indicate that TLR7 can potentiate the antiviral immune response. Additional strategies that are being pursued to improve clearance of infected cells include Env-targeting strategies with broadly neutralizing antibodies and bispecific platforms. PGT121 was selected as the lead bNAb for engineering to enhance Fc-mediated killing of HIV infected cells and improve drug-like properties, while maintaining breadth of HIV Env recognition. These antibody-based approaches have the potential to specifically recognize and eliminate latently infected cells that are unmasked by latency reversal agents.