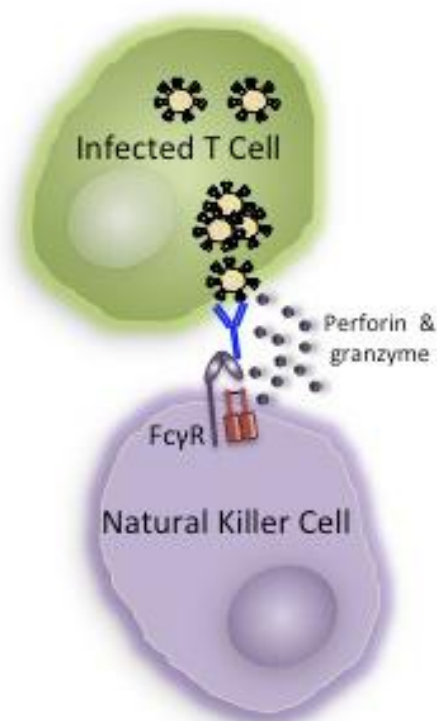


## Novel HIV-specific antibodies mediate ADCC

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Schematic of antibody-dependent cellular cytotoxicity (ADCC). An infected cell (green) displays antibodies on its surface that is recognized by an Fc receptor in Natural Killer cells (purple). The Natural Killer cells then secrete protein such as perforin and granzyme that cause the infected cell to lyse

*Image provided by Dr. Katherine Williams.*

The elusive search for an effective HIV vaccine continues in part due to incomplete understanding of what makes an effective HIV-protective antibody. Antibodies (Abs) are known to protect from infection either by directly neutralizing the virus or by targeting infected cells for destruction by a process known as antibody-dependent cellular cytotoxicity (ADCC). Much of the effort has been devoted to characterizing broadly neutralizing antibodies (bnAbs), but recent studies showing that infants with higher levels of ADCC activity may exhibit reduced viral loads & delayed disease progression and that Abs that when changed so they could no longer bind FcRs (& therefore could not mediate ADCC) demonstrated limited protective efficacy as compared to the fully intact Ab variant, suggest that further investigation of ADCC-mediating Abs is needed. However, because high-throughput approaches to isolate ADCC-mediating Abs have not been described, the epitope specificity and other defining features of ADCC immune responses remain poorly understood. A new study published in the journal *EBioMedicine* and led by Dr. Katherine Williams in the Fred Hutch Laboratory of Dr. Julie Overbaugh (Human Biology and Public Health Sciences Divisions), leveraged

a new method to isolate memory B cells from an HIV-infected individual to identify three antibodies that exhibited broad and potent ADCC activity. Said Dr. Williams: "The recently concluded RV144 vaccine trial demonstrated limited protective efficacy (~31.2%); one of the few correlates associated with this protection was ADCC-mediating antibody activity measured in vaccinees with low plasma IgA levels. Despite these observations, we know very little about which antibodies might mediate ADCC activity, which viral epitopes are targeted by these antibodies and how long it takes for these antibodies to develop after infection. This study investigates these questions – specifically we identified two ADCC-mediating antibodies which target a similar place on the virus surface and which develop from independent B cell lineages within the first 6 months of infection. When we looked at 9 other individuals from the same cohort study, we found that all of them made antibodies similar to the ones we identified – in 2 individuals, the majority of their ADCC activity could be attributed to the these types of antibodies".

The investigators began the study by obtaining peripheral blood mononuclear cells (PBMCs) from a study participant (QA255) 914 days post HIV infection. HIV viral-like particles (VLPs) expressing two different types of Envelope (Env) proteins were used to isolate memory B cells from total PBMCs. Antibody reconstruction using PCR of heavy and light chain regions obtained from 192-VLP-binding memory B cells resulted in 48 Abs that expressed detectable IgG. Three of these Abs (QA255.105, QA255.157 and QA255.253) exhibited ADCC activity as determined by the Rapid and Fluorometric ADCC assay, with potency comparable to well-described ADCC-mediating Abs (A32 and C11). Importantly, these three Abs exhibited activity towards not only the monomeric HIV Env protein but also to VLPs similar to the Env trimer found in infected cells. Epitope mapping studies revealed that QA255.105 targeted the V3 region of Env while QA255.157 and QA255.253 both targeted a CD4-induced conformational epitope, similar to the well-described C11 Ab. Due to the diversity of HIV Env proteins present in infected individuals, the researchers tested the breadth of their Abs by querying them against a panel of eleven Envs representing different HIV clades. Remarkably, the C11-like Abs (QA255.157 and QA255.253) showed ADCC activity against ten out of the eleven Envs tested. Experiments using versions of QA255.105, QA255.157 and QA255.253 that cannot bind to FcR markedly reduced their ADCC activity, showing that their ADCC activity develops within the first six months after infection. Finally, the authors examined whether these C11-like ADCC responses commonly occur in chronically infected individuals. To this end, they obtained plasma three years post-infection from ten women from the Mombasa cohort and found that nine of these exhibited significant ADCC activity. In summary, the investigators' novel strategy to isolate ADCC-mediating Abs from HIV-infected individuals that originated from unique B cells suggests that the C11-like epitopes should be considered in future vaccination strategies, and may pose fewer challenges than those associated with the development of broadly neutralizing Abs (bnAbs).

[Williams KL, Cortez V, Dingens AS, Gach JS, Rainwater S, Weis JF, Chen X, Spearman P, Forthal DN, Overbaugh J](#). 2015. HIV-specific CD4-induced antibodies mediate broad and potent antibody-dependent cellular cytotoxicity activity and are commonly detected in plasma from HIV-infected humans. *EBioMedicine*. 2(10):1464-77.

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