

REVIEW

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ABSTRACTS FROM THE MAY 2018 CLEVELAND IMMUNOPATHOGENESIS CONSORTIUM MEETING

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Below are selected abstracts from presentations at the annual Cleveland Immunopathogenesis Consortium meeting that was held on the campus of Case Western Reserve University in May 2018. The presentations covered a range of topics from HIV persistence/eradication to coinfection, inflammation and its determinants, and immunologic failure. These abstracts are provided by *Pathogens and Immunity* to inform interested readers about these findings. You are encouraged to contact the lead authors of these works to learn more. Their email addresses are at the end of each abstract.

RHEUMATOID FACTOR LEVELS REMAIN PERSISTENTLY ELEVATED 24 WEEKS (AND BEYOND) AFTER IFN-FREE HCV THERAPY IN THE MAJORITY OF RF+ HCV INFECTED PERSONS

Authors

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Summary

HCV Cryoglobulinemic vasculitis has been observed in some cases to linger long after Interferon free direct acting antiviral (DAA) HCV therapy induced sustained virologic response (SVR). Cryoglobulins are one pathogenic factor involved in this vasculitis. They are composed in part of Rheumatoid Factor (RF). Here we observed that RF remains positive (elevated) in the majority of RF+ HCV infected patients over 24 weeks after initiation of successful IFN free therapy. This variability in resolution of this immune derangement after successful treatment of HCV has implications for time to clinical improvement in HCV associated Cryoglobulinemic vasculitis, and provides support for a model where factors other than HCV itself participate in determining RF level during chronic active HCV infection, and during IFN free DAA therapy.

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**MAINTENANCE OF THE GUT INTEGRITY RATHER THAN THE CONTROL OF T CELL
ACTIVATION DRIVES CONTROL OF DISEASE PROGRESSION IN AFRICAN GREEN MONKEYS****Authors**

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Summary

We report here for the first time that natural hosts of SIVs (i.e., the African green monkeys) have the ability to maintain the integrity of the mucosal barrier throughout SIV infection. Furthermore, by dissociating T cell activation from mucosal and systemic inflammation, through regulatory T cell depletion, we showed that maintenance of mucosal integrity rather than the resolution of T cell activation at the transition from acute-to-chronic infection is the main factor behind the ability of natural hosts to avoid disease progression.

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HIV-ASSOCIATED CARDIOVASCULAR DISEASE IN THE GLOBAL CONTEXT: MOVING FROM CORONARY ARTERY TO THE MYOCARDIUM

Authors

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Summary

HIV associated cardiovascular disease (HIV-CVD) has been characterized by accentuated atherogenesis mediated, in part, by activation of innate immunity involving monocyte-macrophage pathways. Data describing this pathogenesis has been primarily ascertained in high-income countries, but with expanding antiretroviral coverage the burden of disease from HIV-CVD is also growing in low-to-middle-income countries. The phenotype of HIV-CVD is very likely to manifest differently in low-to-middle-income countries, due to differences in risk factor profiles, but may still involve activation of monocyte-macrophage pathways contributing to myocardial tissue inflammation, fibrosis, and ultimately dysfunction over time.

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ALTERED ENTERIC VIROME IN UNTREATED HIV INFECTION

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Summary

Advanced HIV infection was associated with a decrease in the abundance of plant viruses in stool samples and with an increase in the prevalence, abundance and diversity of human viruses. In particular, low peripheral CD4 T cell counts were associated with a striking expansion of viral sequences from the Anelloviridae family, commensal viruses recently suggested to reflect the overall state of immunosuppression. The expansion of human viruses might contribute to GI tract damage and persistent inflammation in immunocompromised HIV-infected individuals.

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**TRANSCRIPTOMIC APPROACHES TO IDENTIFYING POTENTIAL
MECHANISMS OF ELITE CONTROL IN HIV INFECTION****Authors**

Cheryl Cameron, Brian Richardson, Jackelyn Golden, Aarthi Talla, Remi Fromentin, Mary Ann Checkley, Ben Luttge, Krupa Subramanian, Peter Stock, Jean-Pierre Routy, Cecile Tremblay, Julie McElrath, Tim Henrich, Deanna Kulpa, Nicolas Chomont, Jonathan Karn, Steven Deeks, Mark Cameron, Rafick Sekaly

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Summary

We reported results from studies designed to identify potential therapeutic targets that could lead to or support a functional cure of HIV. We applied a comparative transcriptomic analysis of CD8 and NK cell subsets from elite controllers and cART suppressed subjects to identify potential mechanisms that allow elite controllers to maintain aviremic status in the absence of antiretroviral therapy. Newly identified pathways associated with innate aviremic status were validated and further dissected by immunological assays.

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**POTENT AND SELECTIVE KILLING OF LATENT HIV-INFECTED
MEMORY T CELLS BY NK CELL EXPANDED EX VIVO****Authors**

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Summary

We are pursuing a novel "kick and kill" HIV eradication strategy whereby treatment of patients with latency reversing agents would be followed by the adoptive transfer of autologous eNK cells, which are expanded and activated ex vivo prior to reinfusion. We find that eNK cells from HIV+ donors have a highly cytotoxic phenotype that is equal to eNK cells from HIV-negative donors. Using a primary HIV latent T cell model, we demonstrated that eNK cells displayed selective

killing of latently HIV-infected memory T cells after proviral reactivation. Finally, eNK cells from HIV+ participants efficiently kill autologous HIV+ Tm cells after proviral reactivation with vorinostat and IL-15 as detected by a progressive loss of inducible cell-associated HIV mRNA for up to at least seven days.

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COMBINING NON-INVASIVE IMAGING APPROACH AND TISSUE ANALYSES TO ASSESS LN DRAINING FUNCTION**Authors**

Claire Deleage, Baris Turkbey, Catherine Brands, David Morcock, Marcelino L. Bernardo, Hyun Jung, Yanling Liu, Gregory Q. Del Prete, Brandon F. Keele, Jeffrey D. Lifson, Jacob D. Estes

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Summary

We used longitudinal magnetic resonance imaging (MRI) to study uptake of a simulated particulate antigen by draining lymph nodes in SIV infected rhesus macaques and correlated these findings with histopathological analysis. We found that SIV infection is associated with a profound impairment of LN draining function as soon as 2 weeks post infection. We think that the relocation and persistence of DC and CD169+ cells within the subcapsular region, capturing the antigens, may affect the ability to mount effective immune responses.

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MACROPHAGE ACTIVATION: A POTENTIAL CONTRIBUTOR TO CVD RISK IN HIV INFECTION?**Authors**

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Summary

Monocytes can migrate from the bloodstream and into the blood vessel wall where they differentiate into macrophages and produce several inflammatory mediators. We have demonstrated previously that monocytes from people living with HIV (PLWH) are activated and express in-

creased vascular homing receptors compared to cells from HIV- individuals. We now report that monocyte derived macrophages from PLWH have altered gene expression profiles and produce increased levels of inflammatory cytokines, reactive oxygen species, and matrix metalloproteases compared to findings in cells from HIV- individuals.

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**THE LAST GIFT:
PERFORMING HIV CURE RESEARCH AT THE END OF LIFE****Authors**

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Summary

To cure HIV, we need a better understanding of the distribution of the HIV reservoirs throughout the body and how these reservoirs contribute to viral rebound after discontinuation of antiretroviral therapy (ART). Extensive investigations in humans have been unable to fully characterize the large and complex HIV reservoirs that must be eradicated to achieve a cure, because biological sampling is necessarily limited in life. To take the next steps in understanding and eradicating HIV reservoirs in tissues, we developed a “peri-mortem translational research model” (<http://last-gift.ucsd.edu/>), similar to existing models in cancer research. In this model, altruistic individuals living with HIV, with advanced non-AIDS related diseases and with six months or less to live, are participating in HIV cure research. These altruistic individuals will provide: (i) detailed clinical, risk and socio-demographic information before their death; (ii) weekly blood collections while they are alive and, (iii) their entire bodies after they die for a rapid autopsy (<6h from the time of death). In these volunteers, we will characterize cellular and tissue populations of HIV in blood (ante-mortem) and compare these populations in blood and anatomic compartments (at autopsy) while on and off ART to better understand dynamics of both viral rebound and populations in the blood and throughout the body. These altruistic individuals will provide a wealth of clinical information and biological specimens that can be used to answer important unanswered questions in the quest to cure HIV.

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**PATHOLOGICAL ROLE OF ANTI-CD4 ANTIBODIES IN HIV-INFECTED IMMUNOLOGIC
NONRESPONDERS RECEIVING VIRUS-SUPPRESSIVE ANTIRETROVIRAL THERAPY****Authors**

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Summary

Increased mortality and morbidity occur among human immunodeficiency virus (HIV)-infected patients in whom CD4+ T-cell counts do not increase despite viral suppression with antiretroviral therapy (ART). Here we identified an underlying mechanism. Significantly elevated plasma levels of anti-CD4 immunoglobulin G (IgG) were found in HIV-positive immunologic nonresponders (HIV-positive individuals with CD4+ T-cell counts of ≤ 350 cells/ μ L), compared with levels in HIV-positive immunologic responders (HIV-positive individuals with CD4+ T-cell counts of ≥ 500 cells/ μ L) and healthy controls. Higher plasma level of anti-CD4 IgG correlated with blunted CD4+ T-cell recovery. Furthermore, purified anti-CD4 IgG from HIV-positive immunologic nonresponders induced natural killer (NK) cell-dependent CD4+ T-cell cytolysis and apoptosis through antibody-dependent cell-mediated cytotoxicity (ADCC) in vitro. These data indicate that autoreactive anti-CD4 IgG may play an important role in blunted CD4+ T-cell reconstitution despite effective ART.

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RESERVOIR DOGGEREL**Authors**

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Summary

New assays to more accurately measure HIV reservoirs were developed using next generation sequencing technologies and digital droplet PCR. Intact proviral genomes were estimated using a two color ddPCR assay with primers targeting the gag and env regions of the genome. The EDITS assay measured inducible env RNA, a late gene product whose splicing pattern samples a large region of the genome. EDITS can detect single cells expressing HIV RNA and has an accuracy of plus minus 10%. The assay has been used to monitor induction of HIV following treatment of patients with ALT803 (an IL-15 derivative). It has also been adapted to measure replication competent virus at very early time points following proviral induction ex vivo.

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**HOW OFTEN CAN YOU GO TO THE WELL:
HIV COMPARTMENTALIZATION DURING OPPORTUNISTIC INFECTIONS:
PRE-ART CRYPTOCOCCAL MENINGITIS**

Authors

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Summary

Characterization of HIV populations in the CSF and blood compartments in HIV patients with cryptococcal meningitis pre-ART.

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A HIDDEN SYSTEM OF CELL-CELL COMMUNICATION

Authors

Wendy Fitzgerald, Michael L. Freeman, Michael M. Lederman, Elena Vasilieva, Roberto Romero, Leonid Margolis

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Summary

Cytokines that are considered to be soluble mediators of cell-cell interactions, have been found in various in vitro, ex vivo and in vivo systems to be associated with extracellular vesicles, both being presented on the vesicles' surface and encapsulated. Association with extracellular vesicles is a function of a biological system and is changed upon systems' activation.

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**IL-15 DRIVES THE GENERATION AND SURVIVAL OF
SENESCENT CD8 T CELLS IN HIV/CMV CO-INFECTION****Authors**

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Summary

We show that HIV/CMV co- infection and related inflammation can drive maturation of memory CD8 T cells toward an “inflammescent” phenotype that can localize to atherosclerotic plaques and has surface markers of senescence. Our in vitro data suggest that these ostensibly senescent CD57+ CX3CR1+ CD8 T cells can survive and proliferate in an Ag-independent manner, via IL-15 stimulation, which supported mitochondrial activity, as well as survival and proliferation signals.

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“BREAKING BAD”**Authors**

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Summary

The focus of this work was aimed at understanding the mechanisms of CD4 downregulation in African green monkeys, who are natural hosts of SIV infection. In genome-wide screening of AGM CD4 T cells induced to downregulate CD4, we found that the DNA methylation machinery is differentially regulated in these cells, and we can block CD4 downregulation with inhibitors of DNA methylating enzymes.

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**IL-10 LEVELS ARE INDUCED AFTER SIV INFECTION, NOT NORMALIZED BY ART,
AND REGULATE VIRAL PERSISTENCE IN SIV-INFECTED NONHUMAN PRIMATES****Authors**

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Summary

The mechanisms regulating the establishment and maintenance of the HIV reservoir are unknown, thus limiting the design of therapeutic strategies to limit it. We found that plasma interleukin-10 becomes elevated upon SIV-infection and correlates with measures of disease progression in chronic infection, such as CD4 counts and immune activation levels. Furthermore, plasma levels of IL-10 fails to normalize under suppressive ART and correlate with the frequency of CD4+ T follicular helper cells and SIV-DNA content in blood and lymph node during ART. Thus, IL-10 contributes to viral persistence in ART-treated, SIV-infected nonhuman primates.

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IMMUNE RECONSTITUTION AFTER INITIATION OF ANTIRETROVIRAL THERAPY**Authors**

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Summary

The longitudinal analysis of the gut microbiome of HIV-infected individuals starting their first antiretroviral treatment showed that certain gut bacteria become activated with significant increased fold-changes in the genus *Fusobacterium*, a known oral commensal/pathobiont and the genus *Succinivibrio* belonging to the Proteobacteria phylum. Notably, we found a decrease in *Enterobacteriaceae* family. No significant fold-change in Firmicutes was observed (both *Prevotella* and *Bacteroides* genera remain fairly constant). Bacterial diversity was also very dynamic within the first year of ART (gain and loss) but overall did not increase significantly after 1 year on ART.

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HIV, AGING, AND IMMUNE FAILURE**Authors**

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Summary

Plasma levels of IL-6 are strongly associated with age in healthy and treated, HIV-infected participants. Phenotypically naïve T cells (CD27+ CD45RA+) expressing exhaustion and senescent markers may be memory T cells with a naïve phenotype (T_{MNP}).

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UPDATES IN ICL PATHOGENESIS**Authors**

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Summary

An update on pathogenesis of ICL CD4 lymphopenia was presented with a focus on patients presenting with auto-antibodies and autoimmunity.

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IL-15 INDUCES MITOCHONDRIAL BIOGENESIS AND RESCUES IMMUNE EXHAUSTION OF CD4 T CELLS IN HIV-1 INFECTED IMMUNE FAILURE SUBJECTS**Authors**

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Summary

In this work we provide evidence that CD4 T cells of immune failure HIV-1 infected persons on ART have a mitochondrial defect linked to low CD4 T cell numbers. This mitochondrial dysfunction is correctible by exposure to IL-15 in vitro.

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FOOTNOTES

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