

Beneficial Efficacy of Histone Deacetylase Inhibitor Butyrate and Histone Crotonylation to Human Immunodeficiency Virus-Infected Subjects

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ABSTRACT

The mechanism of how gut microbiota is involved in the host inflammatory processes that influence human immunodeficiency virus (HIV) replication and disease progression in HIV is elucidated in present review.

Key words: Histone butyrylation and crotonylation; Beneficial efficacy; Human immunodeficiency virus; HIV-1 latency

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INTRODUCTION

Canadian human immunodeficiency virus (HIV) Trial Network (Montaner *et al*^[1]) assessed the safety and surrogate marker's effect of acemannan (ACM) in aloe vera gel fraction as an adjunctive to anti-retroviral therapy among patients with advanced HIV disease receiving zidovudine (ZDV) in a randomized double-blind, placebo-controlled trial of ACM (400mg orally 4 times daily). The results demonstrated that ACM at an oral daily dose of 1.6 g does not prevent the decline in CD4 count characteristic of progressive HIV disease. While ACM showed no significant effect on p24 antigen and quantitative virology, ACM was well tolerated and showed no significant pharmacokinetic interaction with ZDV, and moderated the side effect. Oral administration of ACM may not be directly efficacious to HIV disease, but inhibits viral replication. The ability is important to the effectiveness of a vaccine, as antigens alone sometimes fail to produce an immune response. This immunostimulant and vaccine adjuvant ability would be extremely important in the fight against acquired immunodeficiency syndrome. In our early review^[2] we discussed importance of ACM as an immune stimulant and an adjuvant for HIV, and importance of diet and host-microbial cross talk to ensure maintenance of homeostasis. ACM was approved by United States Department Agriculture for use as a vaccine adjuvant in chickens, cats and dogs.

Alterations in the gut microbiota have been associated with age-related phenotypes, and proper maintenance of microbiota with epigenetic modifiers, like probiotics has shown to be effective in managing chronic disease progression. Histone acylation which is one of the key epigenetic modification processes controlling gene expression is known to be involved in lifespan determination. There is substantial evidence that indicates the geroprotective potential of histone deacetylase inhibitor, such as butyrate. The ability of human immunodeficiency virus-1(HIV-1) to establish latent infection and its re-activation is considered critical for progression of HIV-1 infection. Imai *et al*^[3] investigated the effect of butyric acid on HIV-1 gene

expression. The authors suggested that butyric acid stimulates HIV-1 promoter through inhibition of the transcription factor Sp1-associated HDAC activity and recruitment of cAMP response element-binding protein to the HIV-1 viral long terminal repeat (LTR). The transcription factor Sp1 is a target of acetylation at K703 and is known to be associated with HDAC1. Sp1 binding site is essential for butyric acid-induced transactivation of HIV-1LTR. The findings suggest that SP1 binding sites within the HIV-1 promoter are primarily involved in butyric acid-mediated HIV-1 activation. Sp1 should be considered as one of therapeutic targets in anti-viral therapy against HIV-1 infection aggravated by butyric acid-producing bacteria.

Targeting the microbiome for HIV cure

The components of the human gut microbiome have been found to influence a broad array of pathologic conditions ranging from heart disease to diabetes, cognitive impairment and even to cancer. HIV infection upsets the delicate balance in the normal host-microbe interaction both through alterations in the taxonomic composition of gut microbial communities as well as through disruption of the normal host response mechanisms. Koay *et al.*^[4] discussed the interaction between HIV infection, the gut microbiome, inflammation and immune activation, and HIV reservoirs, along with interventions to target the microbiome and their implications for HIV remission and cure. Understanding the association of HIV with the microbiome, metabolome, and metaproteome may lead to novel therapies to decrease inflammation and immune activation, and impact HIV reservoir size and vaccine responses.

Butyrate-producing bacteria live in the colon and are primarily utilized by colon cells as a major energy sources in HIV-infected subjects

In the mitochondria of colon cells, 70% to 90% of butyrate is oxidized into acetyl-CoA, which is subsequently processed through the TCA cycle to generate a large quantity of ATP. Histone deacetylase inhibitors (HDACi) are studied in HIV-infected adults as latency reversing agents as a way to eradicate the latent HIV reservoir. HDACi have been shown to upregulate HIV transcription but have not led to reductions in HIV reservoirs when added to standard antiretroviral therapy. Rasmussen *et al.*^[5] provided an overview of the initial experiences with the use of latency-reversing agents in clinical trials in HIV and discussed and contrasted results arising from these studies.

Serrano-Villar *et al.*^[6] studied that a deeper understanding of how nutritional interventions could ameliorate gut dysbiosis in the pilot blindly randomized study. Increases in the abundance of *Faecalibacterium* and *Lachnospira* strongly correlated with moderate but significant increases of butyrate production and amelioration of the inflammatory biomarkers soluble CD14 and high-sensitivity C-reactive protein, especially among HIV-viremic untreated patients. The bacterial butyrate synthesis pathway holds promise as a viable target for interventions.

A cross-sectional study by Dillon *et al.*^[7] was performed to compare the relative abundance of butyrate-producing bacterial species in colonic biopsies and stool of untreated, chronic HIV-1-infected ($n = 18$) and HIV-1-uninfected ($n = 14$) study participants. Relative abundance of total butyrate-producing bacteria and specifically of *Roseburia intestinalis*, were lower in colon mucosa of HIV-1-infected versus HIV-1-uninfected individuals. In HIV-1-infected study participants, *R. intestinalis* relative abundance inversely correlated with systemic indicators of microbial translocation, immune activation, and vascular inflammation. The effect of

exogenously added butyrate on gut T-cell activation and HIV-1 infection was evaluated using an ex-vivo human intestinal cell culture model. Reductions in mucosal butyrate from diminished colonic butyrate-producing bacteria may exacerbate pathobiont-driven gut T-cell activation and HIV replication, thereby contributing to HIV-associated mucosal pathogenesis.

HIV infection upsets the delicate balance in the normal host-microbe interaction both through alteration in the taxonomic composition of gut microbial communities as well as through disruption of the normal host response mechanisms. Liu *et al.*^[8] described some of the important biomolecules produced by gut microbiota and the role that they may play in maintaining host immune homeostasis with and without HIV infection. Alterations in the fecal microbiota and intestinal epithelial damage involved in the gastrointestinal disorder associated with HIV-1 infection result in microbial translocation that leads to disease progression and virus-related comorbidities. Notably via production of SCFAs, bacteria migrating from the lumen to the intestinal mucosa could influence HIV-1 replication by epigenetic regulatory mechanisms, such as histone acylation.

Noguera-Julian *et al.*^[9] indicated that initial cross-sectional studies provided contradictory associations between microbial richness and HIV serostatus and suggested shifts from *Bacteroides* to *Prevotella* predominance following HIV-1 infection which have not been found in animal models or in studies matched for HIV-1 transmission groups. The findings indicated that HIV gut microbiome studies must control for HIV risk factors and suggest interventions on gut bacterial richness as possible novel avenues to improve HIV-1-associated immune dysfunction.

Bolduc *et al.*^[10] investigated the effect of acetate on the susceptibility of primary human CD4⁺ T cells to HIV-1 infection and demonstrated that HIV-1 replication is increased in CD3/CD28-costimulated CD4⁺ T cell upon acetate treatment. Acetate enhances virus production in primary human CD4⁺ T cells. Moreover, the authors reported that acetate impairs class I/II histone deacetylase activity and increases integration of HIV-1 DNA into the host genome. Therefore, it can be postulated that bacterial metabolites such as acetate modulate HIV-1-mediated disease progression.

HIV-1 infection causes severe gut and system immune damage, but its effects on the gut microbiome remain unclear. Shotgun metagenomics studies in HIV-negative subjects linked low-microbial gene counts (LGC) to gut dysbiosis in diseases featuring intestinal inflammation. Using a similar approach in 156 subjects with different HIV-1 phenotypes, Guillen *et al.*^[11] found a strong, independent, dose-effect association between nadir CD4⁺ T-cell counts and LGC. Low nadir CD4⁺ T-cell counts, rather than HIV serostatus per se, predict the presence of gut dysbiosis in HIV-1 infected subjects. Such dysbiosis does not display obvious HIV-specific features; instead, it shares many similarities with other diseases featuring gut inflammation. Gonzalez-Hernandez LA *et al.*^[12] compared the composition of fecal microbiota, SCFAs, and systemic biomarkers between elderly HIV-positive and HIV-negative subjects. An increase in the *Firmicutes/Bacteroides* ration, coupled with a significant increase in the proteobacteria phylum was detected in HIV-positive subjects. In contrast, a decrease in the *Clostridium leptum* group was observed. Nevertheless, these elderly HIV-positive patients showed higher levels of total SCFAs mainly by an augmented propionic acid values, compared to HIV-negative subjects. Whereas high levels of hs-CRP were positively correlated with sCD14 in the HIV-positive group. Alterations in bacterial communities reveal a dysbiotic state related to an unbalance of fecal SCFAs. Therefore, these intestinal

conditions might drive an increase of poor prognostic biomarkers in elderly HIV-positive subjects.

Qing *et al.*^[13] reported a cross-sectional comparison of 15 asymptomatic HIV-infected men who have sex with men treated with non-nucleoside reverse transcriptase inhibitors-based combination antiretroviral therapy with 10 non-matched HIV-negative heterosexual male controls. The authors found that *Rikenellaceae*, *Microbacteriaceae*, *Roseburia*, *Lachnospiraceae*, *Alistipes*, and *Ruminococaceae* were decreased, while *Maraxellaceae* and *Psychrobacter* were increased in HIV-positive patients. Butyric acid and valeric acid were reduced in HIV-positive patients. The differences in the distribution of intestinal flora between HIV-infected and healthy individuals, especially some SCFAs, suggest that there is already a predisposition to intestinal mucosa damage in HIV-infected individuals. In a cross-sectional study of older people living with HIV (PLWH), median age 61.5 years, N = 14, and uninfected controls (median 58 years, N = 22), Liu *et al.*^[14] compared stool microbiota, levels of microbial metabolites (SCFAs) and systemic inflammatory biomarkers by HIV serostatus and age. The authors found that stool SCFAs levels were similar between the two groups yet patterns of associations between individual microbial taxa and SCFAs levels differed. Abundance of various genera including *Escherichia* and *Bifidobacterium* positively associated with inflammatory biomarkers among PLWH, but not among control. The age effect on the gut microbiome and associations between microbiota and microbial metabolites or systemic inflammation differed based on HIV serostatus, raising important implications for the impact of therapeutic interventions, dependent on HIV serostatus or age.

The microbiota profile of rectal swabs from 26 HIV-infected individuals and 20 HIV-uninfected controls were examined by Lee *et al.*^[15]. Patients were classified as suboptimal responders ($n = 10$, CD4⁺T-cell < 359 cells/ μ l) and optimal responders ($n = 16$, CD4⁺T-cell > 500 cells/ μ l) after a minimum of 2 years on suppressive antiretroviral therapy (ART). The authors found that *Fusobacterium* was significantly enriched among the HIV-infected and suboptimal responders. Enrichment of *Fusobacterium*, butyric acid-producing bacteria, was associated with reduced immune recovery following ART. Modulating the abundance of the bacterial taxa in the gut may be a viable intervention to improve immune reconstitution in the setting. To understand the longitudinal effects of HIV-1 infection on the human gut microbiota, Rocafort *et al.*^[16] prospectively followed 49 Mozambican subjects diagnosed with recent HIV-1 infection (RHI), and 54 HIV-1-negative controls for 9-18 months and compared them with 98 chronically HIV-1-infected subjects treated with antiretrovirals ($n = 27$) or not ($n = 71$). Despite early resilience to change, an HIV-1-specific signature in the gut bacteriome-featuring depletion of *Akkermanisia*, *Anaerovibrio*, *Bifidobacterium*, and *Clostridium*-previously associated with chronic inflammation, CD8⁺T cell anergy, and metabolic disorders, can be eventually identified in chronically HIV-1-infected subjects. Recent HIV-1 infection is associated with increased fecal shedding of eukaryotic viruses, transient loss of bacterial taxonomic richness, and long-term reduction in microbial gene richness. An HIV-1-associated microbiome signature only becomes evident in chronically HIV-1-infected subjects. Longitudinal studies addressing the ability of ART to prevent and/or recover such changes are needed.

Short chain fatty acid, essential for a newly discovered epigenomic modification: histone crotonylation

Lysine is an amphipathic residue with a hydrophobic side chain. Acylation of lysine neutralizes the positive charge of the amino group

and may change the conformation of proteins. According to the difference in hydrocarbon chain length, hydrophobicity and charge, the short chain lysine acylation include the well-studied lysine acylation; acetylation, propionylation, butyrylation, 2-hydroxyisobutyrylation, succinylation, malonylation, glutarylation, crotonylation and β -hydroxybutyrylation. Various chain acylation of histone have been characterized, including butyrylation, 2-hydroxybutyrylation, and crotonylation. These acylation has been linked to cellular metabolism, because they reflect the availability of the SCFAs and their coenzyme A adducts in the cells.

Follows *et al.*^[17] characterized histone crotonylation in intestinal epithelial and found that histone H3 crotonylation at lysine 18 is a surprisingly abundant modification in the small intestine crypt and colon, and is linked to gene regulation. Furthermore, the authors showed that known histone deacetylase (HDAC) inhibitors, including the gut microbiota-derived butyrate, affect histone decrotonylation. The authors suggested that depletion of the gut microbiota leads to a global change in histone crotonylation in the colon and histone crotonylation connects chromatin to the gut microbiota, at least in part, via SCFAs and HDACs.

Regulation of HIV latency with histone deacetylase inhibitor

Although the clinical administration of histone deacetylase inhibitors to HIV-infected individuals to antiretroviral therapy significantly increased cell-associated HIV RNA in CD4⁺ T cells and some cases plasma HIV RNA, this did not reduce the frequency of latently infected cells in blood. Potential reasons for this include insufficient potency in latency reversal, lack of virus or immune-mediated cytolysis of virus-expressing cells and/or a high frequency of immune escape mutations in the recently activated virus. More effective latency-reserving interventions and additional strategies to eliminate virus-expressing cells are needed.

Eradication of HIV-1 (HIV) is hindered by stable viral reservoirs. Viral latency is epigenetically regulated. Jiang *et al.*^[18] discovered that histone crotonylation involved in HIV replication and decrotonylation of histone tails at HIV long terminal repeats may be linked to the establishment of HIV latency. Reactivation of latent HIV was achieved following the induction of histone crotonylation through increased expression of the crotonyl-CoA-producing enzyme; acyl-CoA synthetase short-chain-family member 2 (ACSS2). ACSS2 induction was highly synergistic in combination with either a protein kinase C agonist or a histone deacetylase inhibitor in reactivating latent HIV. The present study links the HIV/simian immune deficiency virus (SIV) infection-induced fatty acid enzyme ACSS2 to HIV latency and identifies histone lysine crotonylation as a novel epigenetic regulator for HIV transcription that can be targeted for HIV eradication. This epigenetic modification mechanism and its reversal open new avenues for HIV cure approaches.

Crakes and Jiang^[19] review that the current understanding of gut microbial signatures across various stages of HIV versus SIV infection, with an emphasis on the impact of microbiome-based therapies in restoring gut mucosal immunity as well as their translational potential to supplement current-HIV cure efforts. Lysine crotonylation is a newly discovered post-translational modification, which is structurally and functionally different from the widely studied lysine acylation. Wan *et al.*^[20] summarized the writers, erasers and readers of lysine crotonylation, and their physiological functions, including gene transcription, acute kidney injury, spermatogenesis, depression, telomere maintenance, HIV latency and cancer process. Lysine crotonylation facilitates telomere maintenance and enhances chemically induced reprogramming to pluripotency.

SUMMARY

Currently there are no data directly linking the gut microbiome in HIV patients, via any sampling methodology, to later clinical outcomes. Detailed dietary information may explain changes in microbial composition and metabolism. More throughout investigation of colonic mucosa tissue samples may identify HIV-associated defects. Multiple sampling points such as stool, rectal swab, colonic mucosal biopsy, and small bowel aspiration or biopsy will need to be concurrently evaluated to determine which is most relevant to systemic disease in HIV.

Studies in non-human primates have contributed greatly working knowledge of viral transmission, gut-associated inflammation and early immune responses. Recent findings indicate the signaling pathways critical for HIV disease progression and gut mucosal damage, which require the development of powerful computation tools, such as bacterial transcriptome and epigenetic analyses in combination with host genetic and metabolomics analyses. The mechanisms of how metabolic function in the gut is altered in HIV and SIV infection and how this can be targeted therapeutically to promote both gut and brain health is under active investigation. Harnessing the SIV model to study host-microbial interactions at the molecular level could provide great insight in restoring gut mucosal immunity in HIV infection. Current strategies of gut microbial alterations to restore mucosal damage, suppress viral replication, and reduce reservoir size in patients are the key to the success of HIV cure efforts.

REFERENCE

1. Montaner JS, Singer J, Raboud J, Arseneau R, McLean BD, Schchter MT, Ruedy J. Double-blind placebo-controlled pilot trial of acemannan in advanced human immunodeficiency virus disease *J. Acquir Immune Defic Syndr Hum Retrovirol.* 1996; **12**: 153-157. [PMID: 8680886]
2. Yagi A and Yu BP. Immune modulation of aloe vera: acemannan and gut microbiota modulator *J. of GHR* 2015; **4(8)**: 1707-1721. [DOI: 10.17554/j.issn.2224-3992.2015.04.525]
3. Imai K, Okamoto T, Ochiai K. Involvement of SP1 in butyric acid-induced HIV-1 gene expression *Cell Physiol Biochem.* 2015; **37(3)**: 853-865. [PMID: 26383101]; [DOI: 10.1159/000430213]
4. Koay WLA, Siems LV, Persaud D. The microbiome and HIV persistence: implications for viral remission and cure *Curr Opin HIV AIDS.* 2018; **13(1)**: 61-68. [PMID: 29135490]; [DOI: 10.1097/COH.0000000000000434]
5. Rasmussen T, Lewin S. Shocking HIV out of hiding: where are we with clinical trials of latency reversing agents? *Curr Opinion HIV* 2016; **11(4)**:394-401. [PMID: 26974532];[DOI: 10.1097/COH.0000000000000279]
6. Serrano-Villar S, Vazquez-Castellanose JF, Vallejo A, Latorre A, Sainz T, Feeando-Martinez S, Rolo D, Martinez-Botas J, Del Romero J, Madrid N, Leal M, Mosele JI, Motilva MJ, Barbas C, Ferrer M, Moya A, Moreno S, Gosalbes MJ, Estrada V. The effects of prebiotics on microbial dysbiosis, butyrate production and immunity in HIV-infected subjects *Mucosal Immunology* 2017; **10**: 1279-1293. [PMID: 28000678]; [DOI: 10.1038/mi.2016.122]
7. Dillon SM, Kibble J, Lee EJ, Guo K, Santiago ML, Austin GL, Gianella S, Landay AL, Donovan AM, Frank DN, McCarter MD, Wilson CC. Low abundance of colonic butyrate-producing bacteria in HIV infection is associated with microbial translocation and immune activation *AIDS* 2017; **31(4)**: 511-521. [PMID: 28002063]; [DOI: 10.1097/QAD.0000000000001366]
8. Liu J, Williams B, Frank D, Dillon SM, Wilson CC, Landay AL. Inside Out: HIV, the gut microbiome, and the mucosal immune system. *The J. of Immunology* 2017; **198**: 605-614 . [PMID: 28069756]; [DOI: 10.4049/jimmunol.1601355]
9. Noguera-Julian M, Rocafort M, Guillen Y, Rivera J, Casadella M, Nowak P, Hildebrand F, Zeller G, Parera M, Bellido R, Rodriguez C, Carrillo J, Mothe B, Coll J, Bravo I, Estany C, Herrero C, Saz J, Siera G, Torrela A, Novarro J, Crespo M, Brander C, Negro E, Blanco J, Guarner F, Calle ML, Bork P, Sonnerborg A, Clotet B, Paredes R. Gut microbiota linked to sexual preference and HIV infection *EBioMedicine.* 2016; **5**: 135-146. [PMID: 27077120]; [DOI: 10.1016/j.ebiom.2016.01.032]
10. Bolduc JF, Hany L, Barat C, Ouellet M, Tremblay MJ. Epigenetic metabolite acetate inhibits class I/II histone deacetylases, promotes histone acetylation, and increases HIV-1 integration in CD⁺ T cells. *J. Virol.* 2017; **91(16)**: pii. e 01943-16. [PMID: 28539453]; [DOI: 10.1128/JVI.01943-16]
11. Guillen Y, Noguera-Julian M, Rivea J, Casadella M, Zevin AS, Rocafort M, Parera M, Rodriguez C, Arumi M, Carrillo J, Mothe B, Estaany C, Coll J, Bravo I, Herrero C, Saz J, Siera G, Torrella A, Navarro J, Crespo M, Negro E, Brander C, Blanco J, Calle ML, Klatt NR, Clotet B, Paredes R. Low nadir CD4⁺ T-cell counts predict gut dysbiosis in HIV-1 infection *Mucosal Immunology* 2019; **12**: 232-246. [DOI: 10.1038/s41385-018-0083-7]
12. Gonzalez-Hernandez LA, Ruiz-Briseno MDR, Sanchez-Reyes K, Alvarez-Zavala M, Vega-Magana N, Lopez-Iniguez A, Diaz-Ramos JA, Martinez-Ayala P, Soria-Rodriguez RA, Ramos-Solano M, Andrade-Villanueva JF. Alterations in bacterial communities, SCFA and biomarkers in an elderly HIV-positive and HIV-negative population in western Mexico *BMC Infect Dis.* 2019; **19(1)**: 234. [PMID: 30845929]; [DOI: 10.1186/s12879-019-3867-9]
13. Qing Y, Xie H, Su C, Wang Y, Yu Q, Pang Q. Gut microbiome, short-chain fatty acids, and mucosa injury in young adults with HIV infection. *Digestive Diseases and Sciences* 2019; **64(7)**: 1830-1843. [PMID: 30560340]; [DOI: 10.1007/s10620-018-5428-2]
14. Liu J, Johnson R, Dillon S, Kroehl M, Frank DN, Tuncil YE, Zhang X, Ir D, Robertson CE, Seifert S, Higgins J, Hamaker B, Wilson CC, Erlandson KM. Among older adults, age-related changes in the stool microbiome differ by HIV-1 serostatus. *EBioMedicine* 2019; **40**: 583-594. [PMID: 30685386]; [DOI: 10.1016/j.ebiom.2019.01.033]
15. Lee SC, Chua LL, Yap SH, Khang TF, Leng CY, Raja Azwa RI, Lewin SR, Kamarulzaman A, Woo YL, Lim YAL, Loke P, Rajasuriar R. Enrichment of gut-derived *Fusobacterium* is associated with suboptimal immune recovery in HIV-infected individuals *Sci Rep.* 2018; **8(1)**: 14277. [PMID: 30250162]; [DOI: 10.1038/s41598-018-32585-x]
16. Rocafort M, Noguera-Julian M, Rivera J, Pastor L, Guillen Y, Langhorst J, Parera M, Mandomando I, Carrillo J, Urrea V, Rodriguez C, Casadella M, Calle ML, Clotet B, Blanco J, Naniche D, Paredes R. Evolution of the gut microbiome following acute HIV-1 infection *Microbiome.* 2019; **7(1)**: 73. [PMID: 31078141]; [DOI: 10.1186/s40168-019-0687-5]
17. Fellows R, Denizot J, Stellato C, Cuomo A, Jain P, Stoyanova E, Balazsi S, Hajnady Z, Liebert A, Kazakevych J, Blackburn H, Correa RO, Fachi JL, Sato FT, Ribeiro WR, Ferreira CM, Peree H, Spagnuolo M, Mattiuz R, Matolcsi C, Guedes J, Clark J, Veldhoen M, Bonaldi T, Vinolo MAR, Varga-Weisz P. Microbiota derived short chain fatty acids promote histone crotonylation in the colon through histone deacetylases *Nat Commun.* 2018; **9(1)**: 105. [PMID: 29317660]; [DOI: 10.1038/s41467-017-02651-5]
18. Jiang G, Nguyen D, Archin NM, Yukl SA, Mendez-Lagares G, Tang Y, Eiseikh MM, Thompson GR 3rd, Hartigan-O'Connor DJ, Margolis DM, Wong JK, Dandekar S. HIV latency is reversed by ACSS2-driven histone crotonylation *J Clin Invest.* 2018; **128(3)**: 1190-1198. [PMID: 29457784]; [DOI: 10.1172/JCI98071]
19. Crakes KR, Jiang G. Gut microbiome alterations during HIV/SIV infection: Implications for HIV cure *Front Microbiol.* 2019; **10**:

Yagi A *et al.* Gut microbial functions in HIV infections

1104 [PMID: 31191468]; [DOI: 10.3389/fmicb.2019.01104]

20. Wan J, Liu H, Chi J, Zhang H. Functions and mechanisms of

lysine crotonylation *J Cell Mol Med.* 2019; **23(11)**: 7163-7169.

[PMID: 31475443]; [DOI: 10.1111/jcmm.14650]