Interrogating the Microbiome
A Systems Biological Approach

Frederic Bushman
Department of Microbiology
University of Pennsylvania
• HIV or SIV infection and the gut bacterial microbiome
• HIV and the virome
• HIV and the lung microbiome
• HIV and the vaginal microbiome
• HIV, the microbiome, and the metabolome
• Future research directions
No detectable effects of SIV infection on gut microbiota in macaques

The Macaque Gut Microbiome in Health, Lentiviral Infection, and Chronic Enterocolitis

Philip McKenna¹, Christian Hoffmann¹, Nana Minkah¹, Pyone Pyone Aye², Andrew Lackner², Zongzhi Liu³, Catherine A. Lozupone⁴, Micah Hamady⁵, Rob Knight⁶, Frederic D. Bushman⁷

¹ Department of Microbiology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, United States of America, ² Tulane National Primate Research Center, Tulane University Health Science Center, Covington, Louisiana, United States of America, ³ Department of Chemistry and Biochemistry, University of Colorado at Boulder, Boulder, Colorado, United States of America, ⁴ Department of Molecular, Cellular and Developmental Biology, University of Colorado at Boulder, Boulder, Colorado, United States of America, ⁵ Department of Computer Science, University of Colorado at Boulder, Boulder, Colorado, United States of America

Pathogenic Simian Immunodeficiency Virus Infection Is Associated with Expansion of the Enteric Virome

Scott A. Handley¹,¹,¹,¹ Larissa B. Thackray¹,¹,¹,¹ Guoyan Zhao¹,¹,¹,¹ Rachel Prestl³, Andrew D. Miller⁴, Lindsay Droit¹,¹,¹ Peter Abbink², Lori F. Maxfield², Amal Kambal¹, Eming Duan¹, Kelly Stanley³, Joshua Kramer⁴, Sheilla C. Maori⁴, Sallie R. Permar⁴, Joern E. Schmitz⁴, Keith Mansfield⁴, Jason M. Brenchley⁴, Ronald S. Veazey⁵, Thaddeus S. Stappenbeck¹, David Wang¹,¹,¹ Dan H. Barouch⁶,⁷,⁷ and Herbert W. Virgin¹,¹,¹

Effects are detectable in animals put down for colitis, but this was not SIV specific
Going the other way: numerous papers suggesting influence of HIV infection on the human gut microbiome

Vujovic-Cvijin et al., 2013; McHardy et al., 2013; Lozupone et al., 2013, Mutlu et al., 2014; Lozupone et al., 2014; Dillion et al., 2014; Dinh et al., 2015, Vasquez-Castellanos et al., 2015

Partially consistent results: enrichment of Prevotella, depletion of Bacteroides, increase in Enterobacteriaceae.

Parallels strong trend in gut microbiota: urban dwellers in developed world high in Bacteroides, rural dwellers living traditional live styles high in Prevotella
Compare wild chimps: not much effect of SIV infection except near death

Destabilization of the gut microbiome marks the end-stage of simian immunodeficiency virus infection in wild chimpanzees.

HANNAH J. BARBIAN, YINGYING LI, MIGUEL RAMIREZ, ZACHARY KLASE, IDDI LIPENDE, DEUS MJUNGU, MICHAEL L. WILSON, ANNE E. PUSEY, ELIZABETH V. LONSDORF, FREDERIC D. BUSHMAN and BEATRICE H. HAHN, 2015 AJP

2015

- Large population of wild chimps
- SIV status carefully monitored
- No strong dysbiosis in SIV+ animals
- No detectable alterations in virome
- Some alterations in the bacterial microbiota of SIV+ animals shortly before death

Maybe sick animals killed efficiently by predators, so they are not sampled?
Remarkable twist: high Prevotella found in MSM regardless of HIV infection

Gut Microbiota Linked to Sexual Preference and HIV Infection

Marc Noguera-Julian a,b,c,1, Muntsa Rocafort a,c, Yolanda Guillén a,c, Javier Rivera a,b, Maria Casadellà a,c, Piotr Nowak d, Falk Hildebrand e, Georg Zeller e, Mariona Parera a, Rocío Bellido a, Cristina Rodríguez a, Jorge Carrillo a,c,g, Beatriz Mothe a,b,c,f, Josep Coll a,f, Isabel Bravo f, Carla Estany f, Cristina Herrero f, Jorge Saz h, Guillem Sirera f, Ariadna Torrelà i, Jordi Navarro i, Manel Crespo i, Christian Brander a,b,c,i, Eugènia Negredo b,c,f, Julià Blanco a,b,c, Francisco Guarner k, Maria Luz Calle b, Peer Bork e,i,m, Anders Sönnerborg d, Bonaventura Clotet a,b,c,f, Roger Paredes a,b,c,f,*

2015

• Little or no association of HIV+ and gut microbiome changes
Possibly more evident effects of HIV on microbiome in a sicker developing world cohort?

Altered Virome and Bacterial Microbiome in Human Immunodeficiency Virus-Associated Acquired Immunodeficiency Syndrome

Conclusions:
• High Prevotella associated with MSM, not HIV+
• Other reported associations uncertain; possibly more evident in sicker HIV+
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Potentially more pronounced effects of HIV or SIV infection on the virome

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Several positive studies, though no detectable effect in Gombe Chimps

Destabilization of the gut microbiome marks the end-stage of simian immunodeficiency virus infection in wild chimpanzees.
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Lung HIV Microbiome Project

- Multi-center study
- Focused on HIV+ subjects and healthy controls
- Very challenging to sample lung (low microbial biomass compartment; mouth has high microbial biomass)
- Patterns of colonization not notably different HIV+ versus HIV-
- Tropheryma whippelii more common in HIV+ lung
- T. whippelii colonization diminished with effective HIV therapy

Widespread Colonization of the Lung by Tropheryma whippelii in HIV Infection

Catherine Lozupone\textsuperscript{1}, Adela Cota-Gomez\textsuperscript{2}, Brent E. Palmer\textsuperscript{2}, Derek J. Linderman\textsuperscript{2}, Emily S. Charlson\textsuperscript{3}, Erica Sodergren\textsuperscript{4}, Makedonka Mitreva\textsuperscript{4}, Sahar Abubucker\textsuperscript{4}, John Martin\textsuperscript{4}, Guohui Yao\textsuperscript{4}, Thomas B. Campbell\textsuperscript{2}, Sonia C. Flores\textsuperscript{5}, Gail Ackerman\textsuperscript{1}, Jesse Stombaugh\textsuperscript{1}, Luke Ursell\textsuperscript{1}, James M. Beck\textsuperscript{2,5}, Jeffrey L. Curtis\textsuperscript{5}, Vincent B. Young\textsuperscript{6}, Susan V. Lynch\textsuperscript{6}, Laurence Huang\textsuperscript{6}, George M. Weinstock\textsuperscript{4}, Kenneth S. Knox\textsuperscript{7}, Homer Twigg\textsuperscript{8}, Alison Morris\textsuperscript{9}, Elodie Ghedin\textsuperscript{9}, Frederic D. Bushman\textsuperscript{1}, Ronald G. Collman\textsuperscript{3}, Rob Knight\textsuperscript{1,10}, and Andrew P. Fontenot\textsuperscript{2}; for the Lung HIV Microbiome Project

2013
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HIV and the vaginal microbiome

Search "HIV, vaginal, microbiome" yields 121 papers. Closely studied area.

In vagina, low diversity (high Lactobacillus) associated with health (probably)
Bacterial vaginosis (BV) associated with high diversity, often but not always associated with symptoms
BV is more common among African American women
BV risk factor for HIV transmission
Acting via inflammation?
Association of HIV infection and microbiota community structure have differed among studies

Vaginal bacteria may act directly to degrade antivirals, influencing efficacy of PREP

Associations of the vaginal microbiota with HIV infection, bacterial vaginosis, and demographic factors

Christel Chehouda, Daniel J. Stiehb, Aubrey G. Baileya, Alice L. Laughlinb, Shannon A. Allenc, Kerrie L. McCotterc, Scott A. Sherrill-Mixa, Thomas J. Hopeb and Frederic D. Bushmana

2017

HIV+ associated with BV, even though ladies sampled many years after infection

Persistent state associated with increased transmission risk?
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Search for effectors produced by the microbiota
A few studies associating the three published (lung: Cribbs et al., 2016; brain Cassol et al., 2015, Dickens et al., 2015, Cassol et al., 2014; plasma: Cassol et al., 2013).
Specific proposals for effects of TMA, TMAO in CV disease (Srinivasa et al., 2015; Haissman et al., 2015)
Comprehensive survey under way at Penn. Food and Resulting Microbial Metabolites FARMM. Large consortium within CCFA.

- Direct read out of metabolites synthesized or modified by microbiota
- Next step: array purified metabolites, screen in numerous assays, including HIV related
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Possible future directions for research on HIV and the human microbiome

Studies of the microbiome and HIV infection in global populations
  Address issue of gut microbiome and MSM
  Sicker populations will likely show more pronounced alterations

Lung microbiome, HIV and T. whipplei

The microbiome and drug metabolism

The vaginal microbiome and HIV transmission

The microbiome, inflammation, and HIV disease progression

The microbiome, inflammation, HIV and CV disease.

Role of the microbiome in shaping immune responses to lentivirus infection

HIV infection and the virome

HIV infection, alterations in the microbiome, and alterations in the metabolome.
  Maybe support follow-up organic synthesis to figure out mass spec data?
Acknowledgements

Bushman Lab

Erik Clarke
Laurie Zimmerman
Arwa Abbas
Grant Eilers
John Everett
John Gregg
Scott Sherrill-Mix
Aoife Doto
Young Hwang

Brendan Kelly
Abigail Lauder
Frances Male
Chris Nobles
Shantan Reddy
Aurea Simon Soros
Louis Taylor
Sesh Sundararaman
John Everett

Gary Wu
Bob Baldassano
Ron Collman
Beatrice Hahn
James Lewis
Kyle Bittinger
Hannah Barbian
Ceylan Tanes
Casey Hofstaedter
Dorothy Kim

Boston Children’s Hospital SCID
Luigi Notarangelo
Sung-Yun Pai
David Williams

European SCID
Emmanuelle Six
Marina Cavazzana
Alain Fischer
Adrian Thrasher
Bobby Gaspar

Funding: NIAID, NHLBI, Human Microbiome Project
END
Opportunistic infections associated with HIV infection and AIDS

- **Brain**: Cryptococcal meningitis, Toxoplasmosis
- **Eyes**: CMV infection
- **Mouth and Throat**: Herpes virus infection, Thrush (Candidiasis)
- **Lungs**: Histoplasmosis, PCP pneumonia, Tuberculosis
- **Gut**: CMV infection, Cryptosporidiosis, Mycobacterium avium complex, Adenovirus
- **Liver**: Hepatitis C infection
- **Reproductive system**: Genital ulcers, Human papilloma virus infection, Urinary tract infections, Candidiasis

Coinfections associated with HIV studied from the beginning