HIV感染与肠道菌群

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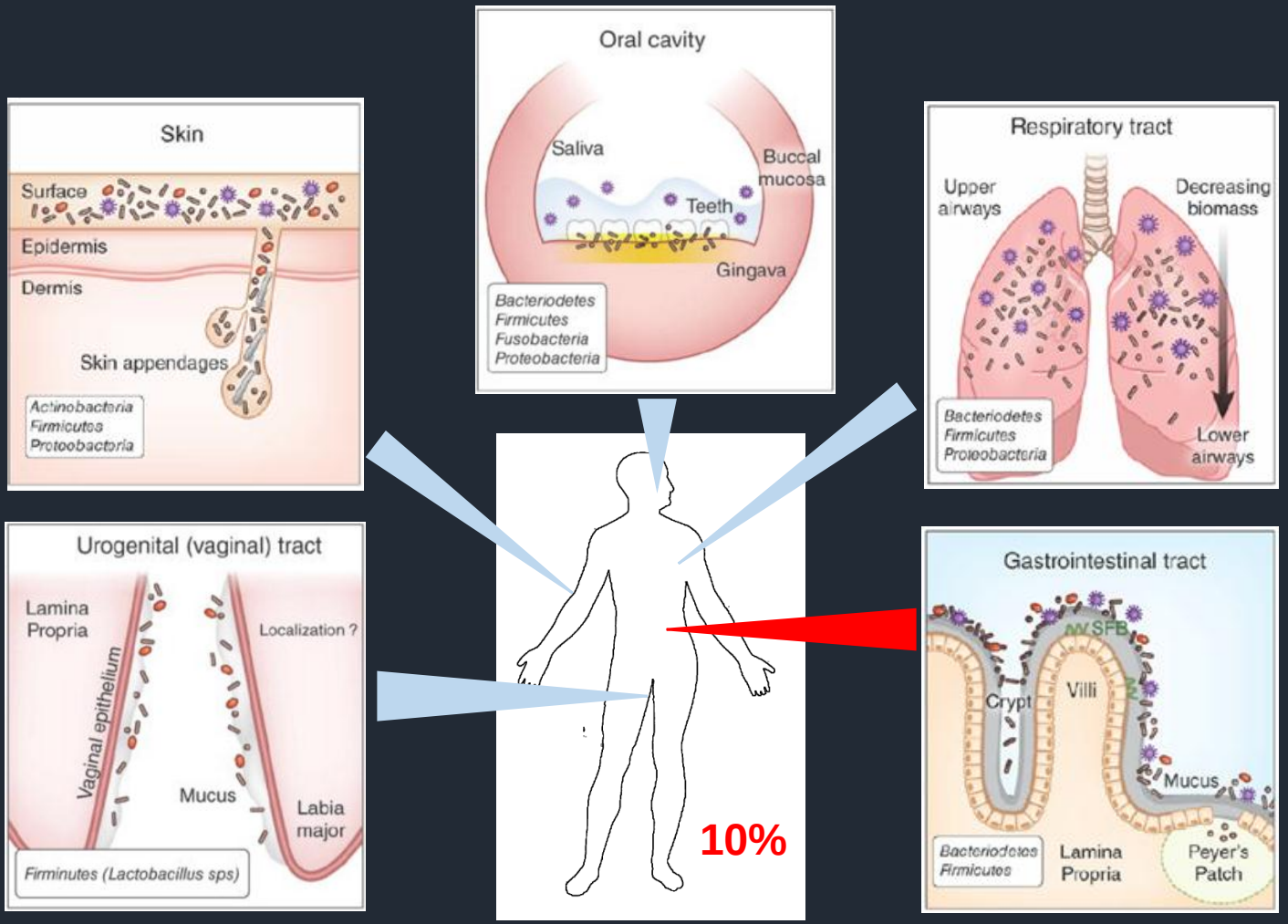
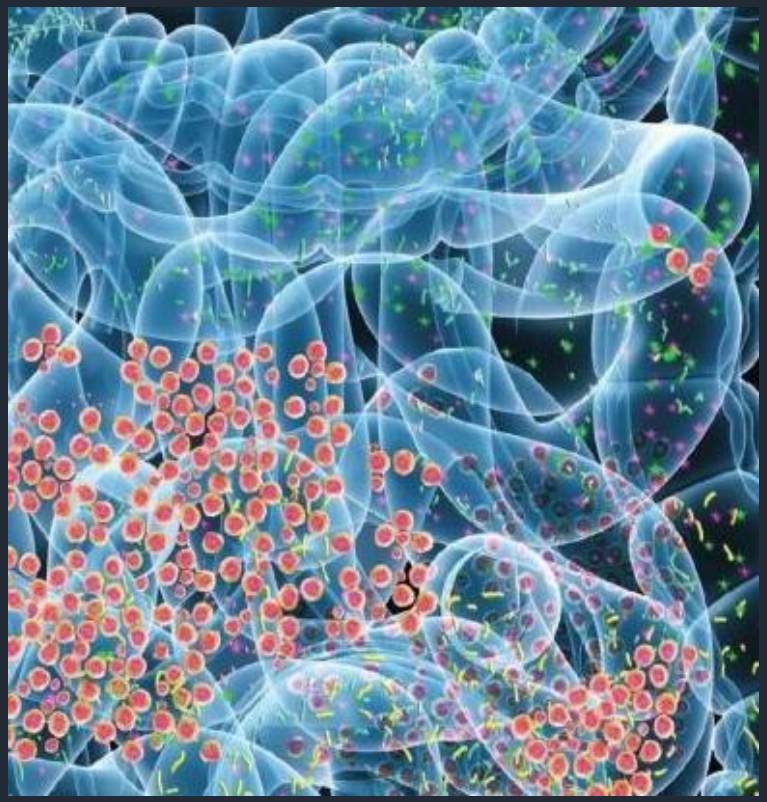
广州市肝病医院
广州市传染病研究所

不同部位具有各自独特微生态



Belkaid Y et al, Nat Immunol, 2013

人体肠道微生态

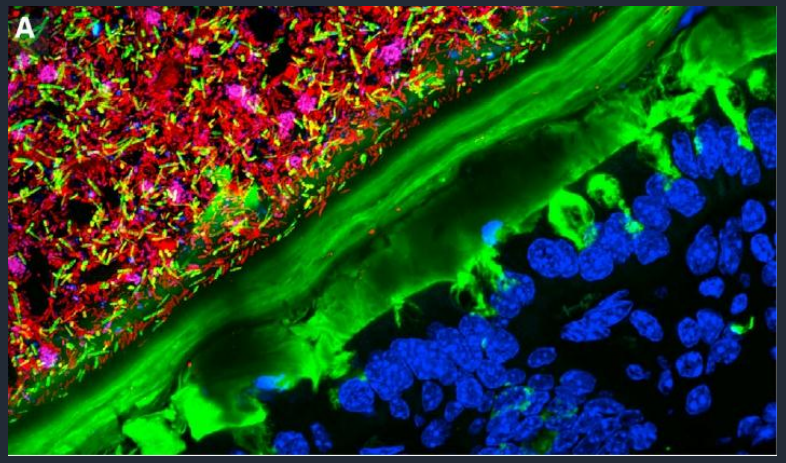


Penn Medicine Magazine Spring 2014

- 肠道内寄住的微生物群种类超过1000种，数量超过10^{14}，约10倍于人体细胞
- 肠道微生态与肠道免疫系统共同抗击病原体入侵并保持肠内稳态
- 对于肠道免疫系统发育非常重要

人体肠道微生态与疾病

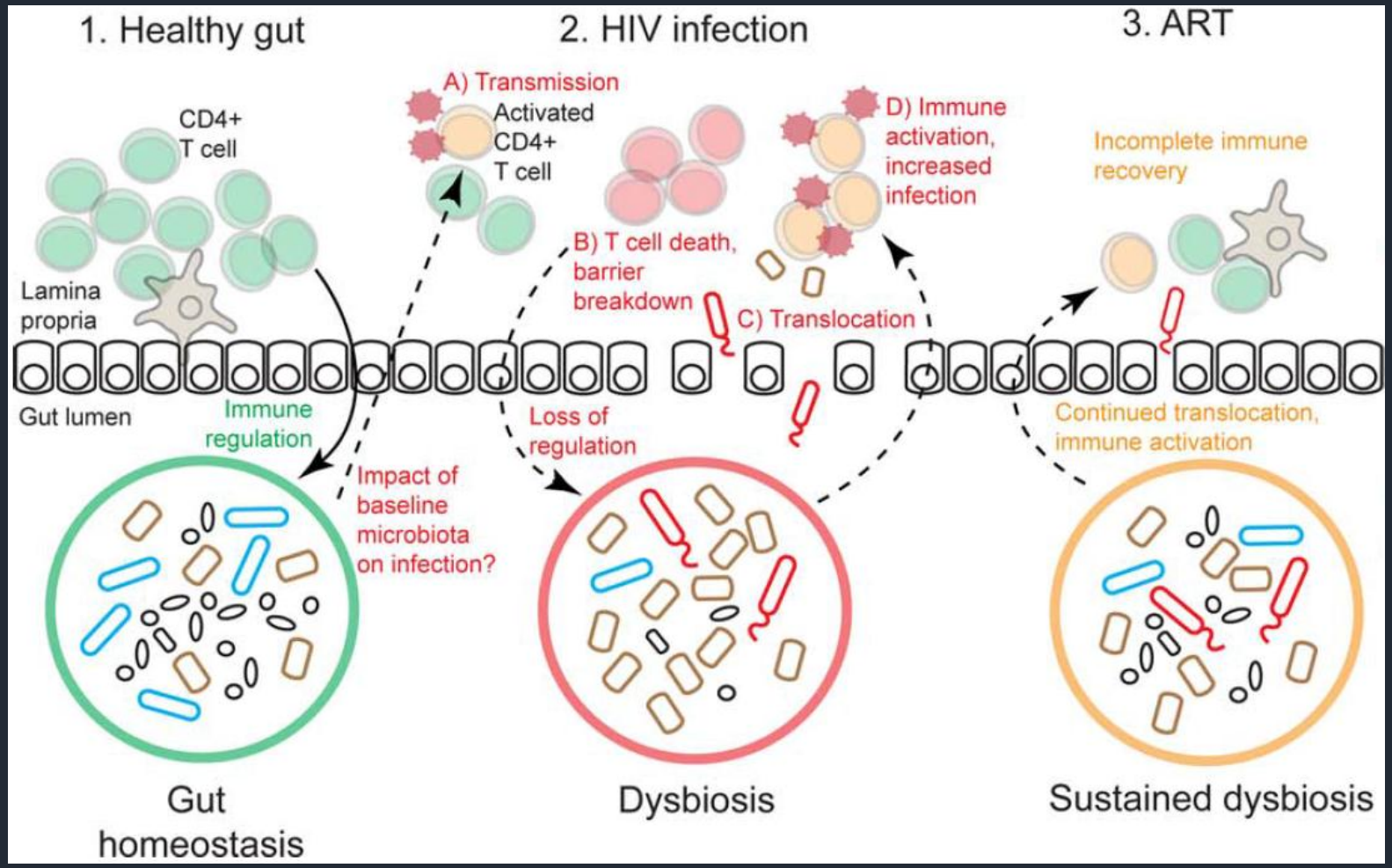
- 肠道菌群组成发生改变常见于:
  - 炎症性肠病
  - 肿瘤
  - 糖尿病
  - 肥胖
  - 感染性疾病



- 肠道菌群紊乱与疾病之间的因果关系尚未阐明

Tropini C, et al, Cell Host Microbe, 2017

HIV感染过程肠道变化

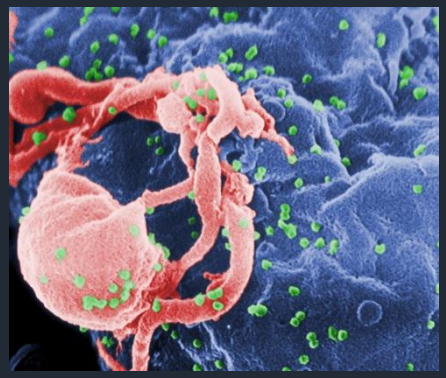


无论何种感染途径，HIV/AIDS患者肠道菌群组成均发生改变

Li SX et al, Clin Pharmacol Ther, 2016

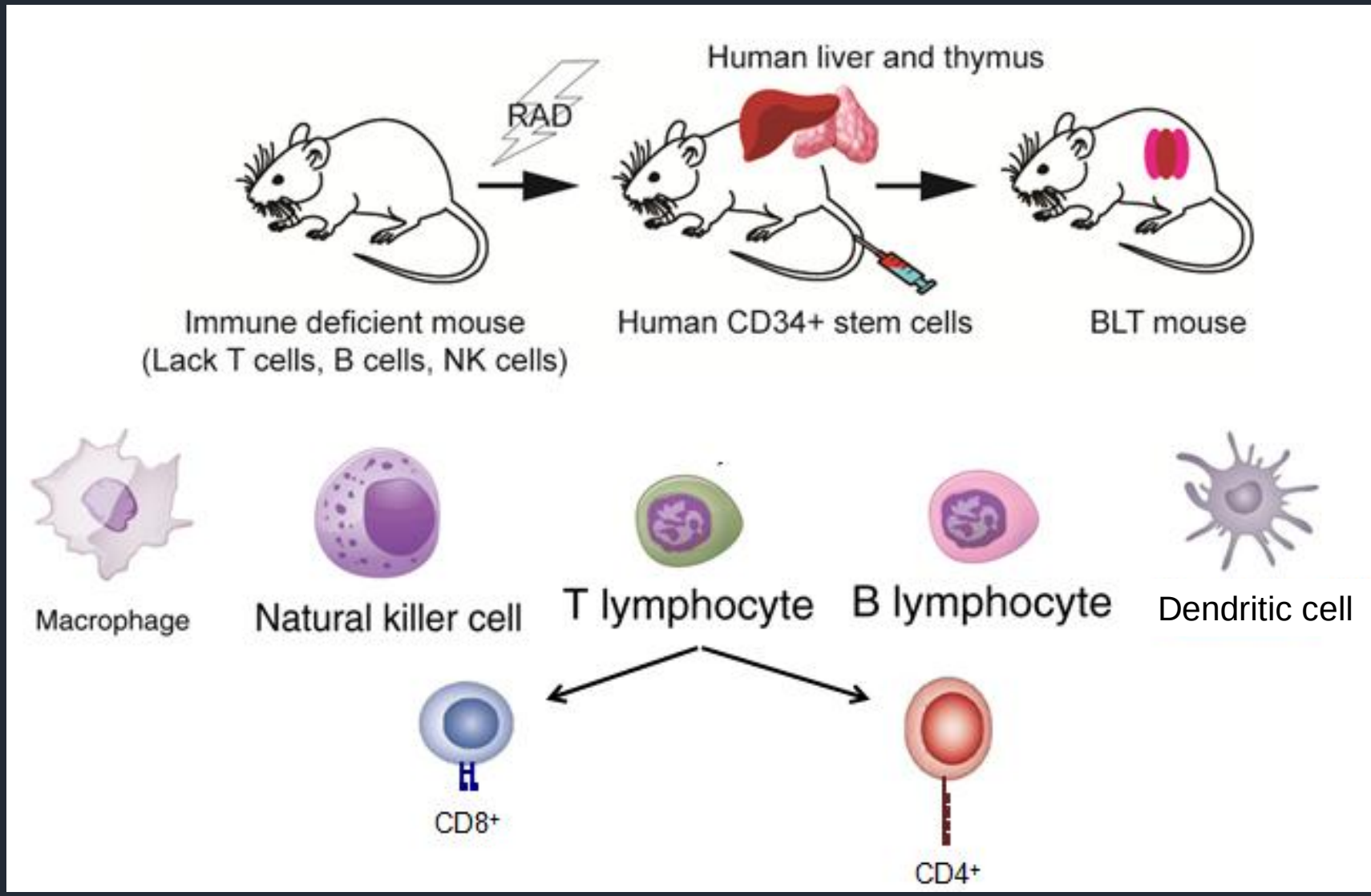
人体肠道菌群与HIV感染

- HIV/AIDS患者肠道菌群紊乱可能导致：
  - 肠道细菌移位
  - 系统免疫活化
  - 心血管疾病
  - 脂肪代谢障碍
  - 消耗综合征



- 肠道菌群紊乱与HIV感染之间的相互影响机制尚未阐明
- 目前亦尚不清楚肠道菌群紊乱发生在急性HIV感染期，还是随着疾病慢性进展而出现

骨髓/肝脏/胸腺(BLT)人源化小鼠



BLT小鼠广泛用于HIV体内研究


Journal of Virology

APOBEC3G and APOBEC3F Act in Concert To Extinguish HIV-1 Replication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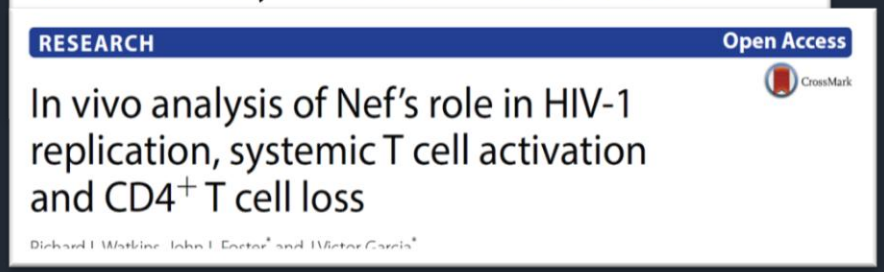
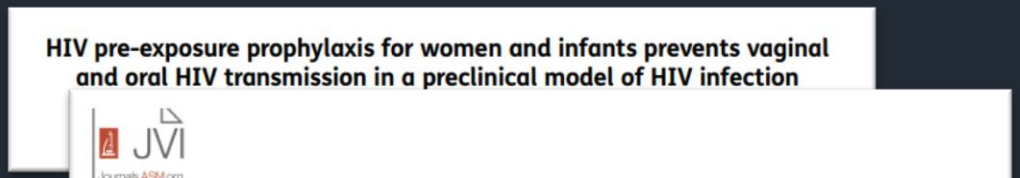
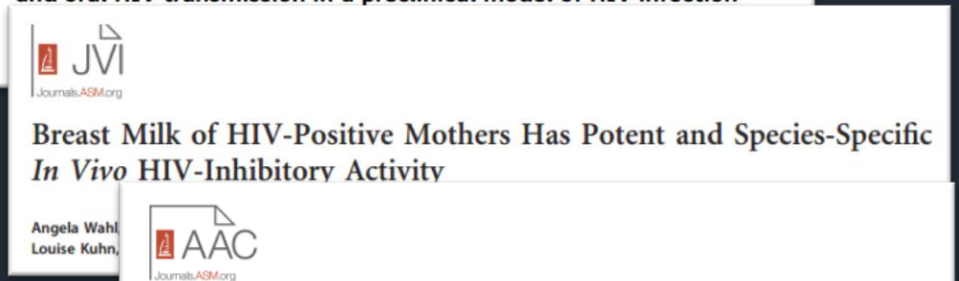
HIV Restriction by APOBEC3 in Humanized Mice


RESEARCH

Open Access

In vivo analysis of Nef's role in HIV-1 replication, systemic T cell activation and CD4+ T cell loss


HIV pre-exposure prophylaxis for women and infants prevents vaginal and oral HIV transmission in a preclinical model of HIV infection


JVI

Journals.ASM.org

Breast Milk of HIV-Positive Mothers Has Potent and Species-Specific *In Vivo* HIV-Inhibitory Activity

Angela Wahl

Louise Kuhn,

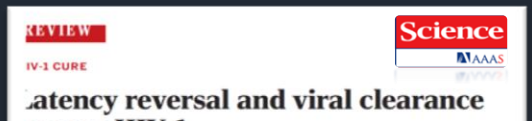

AAC

Journals.ASM.org

Role of Semen on Vaginal HIV-1 Transmission and Maraviroc Protection

Olivia D. Council, Michael D. Swanson, Rae Ann Spagnuolo, Angela Wahl, J. Victor Garcia

Division of Infectious Diseases, Center for AIDS Research, University of North Carolina at Chapel Hill, School of Medicine, Chapel Hill, North Carolina, USA

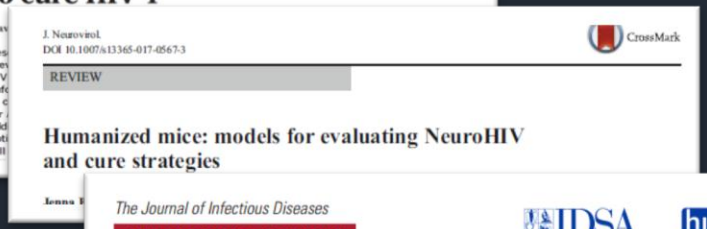

REVIEW

IV-1 CURE

Science

AAAS

atency reversal and viral clearance o cure HIV-1


J. Neurovirol.

DOI 10.1007/s13365-017-0567-3

CrossMark

REVIEW

Humanized mice: models for evaluating NeuroHIV and cure strategies


The Journal of Infectious Diseases

SUPPLEMENT ARTICLE

IDSA Infectious Diseases Society of America

hivma hiv medicine association

In Vivo Models of Human Immunodeficiency Virus Persistence and Cure Strategies

Christopher C. Nixon,[1] Maud Mavigner,[2] Guido Silvestri,[3] and J. Victor Garcia[1]

[1]Division of Infectious Diseases, Center for AIDS Research, University of North Carolina at Chapel Hill School of Medicine; [2]Department of Pediatrics, Emory University School of Medicine, and [3]Emory Vaccine Center and Yerkes National Primate Research Center, Emory University, Atlanta, Georgia


ART influences HIV persistence in the female reproductive tract and cervicovaginal secretions

RESEARCH ARTICLE

Efficient Inhibition of HIV Replication in the Gastrointestinal and Female Reproductive Tracts of Humanized BLT Mice by EFdA

Uma Shanmug

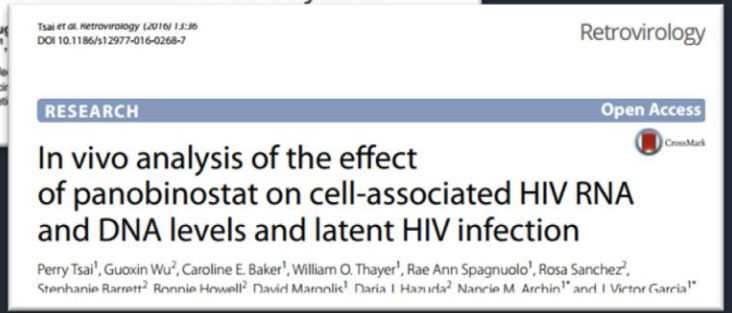
Angela Wahl[1],

1 Division of Infe

School of Medici

Molecular Genet

America


Tsai et al. Retrovirology (2016) 13:36

DOI 10.1186/s12977-016-0268-7

Retrovirology

RESEARCH

Open Access

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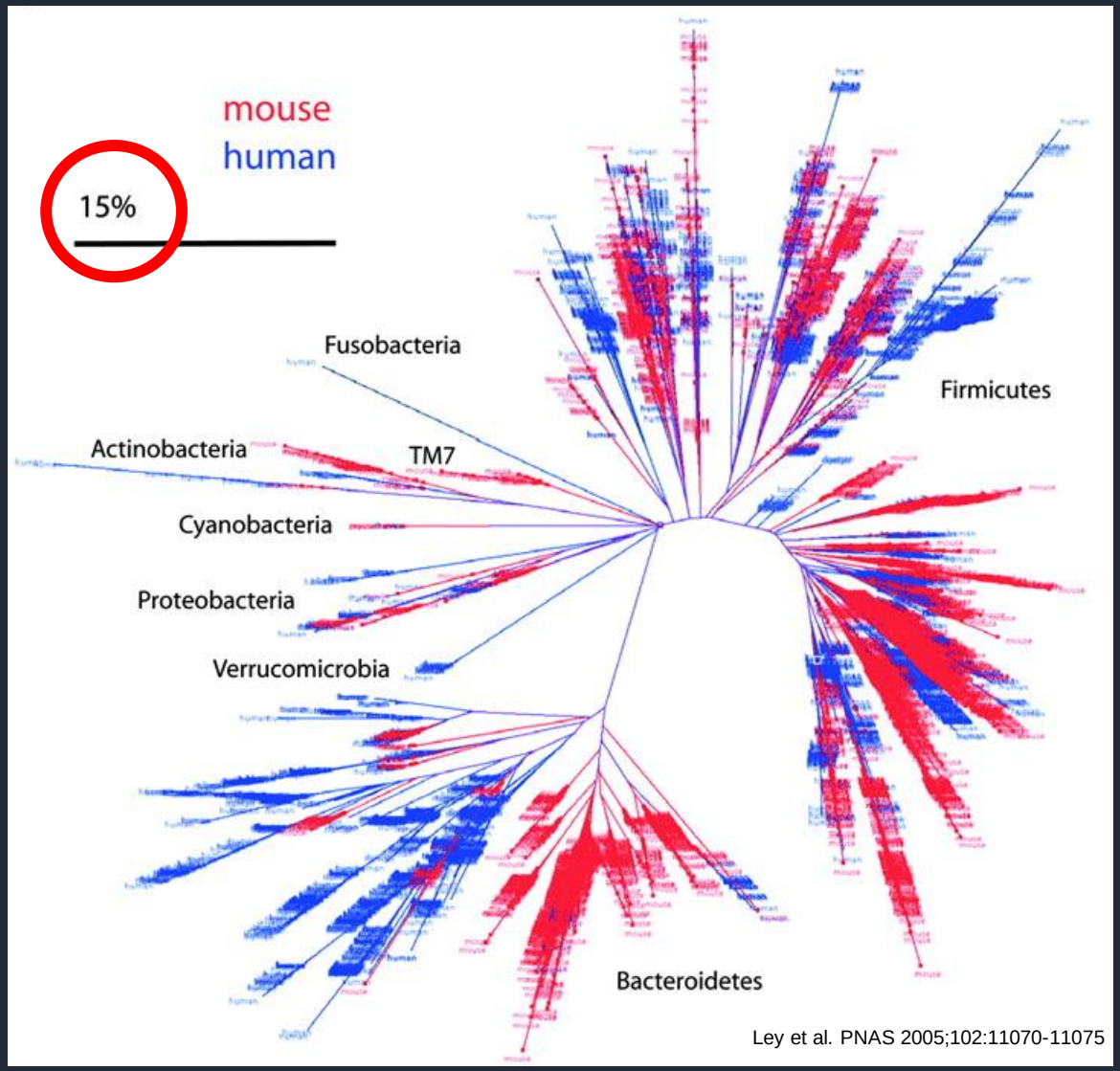
In vivo analysis of the effect of panobinostat on cell-associated HIV RNA and DNA levels and latent HIV infection

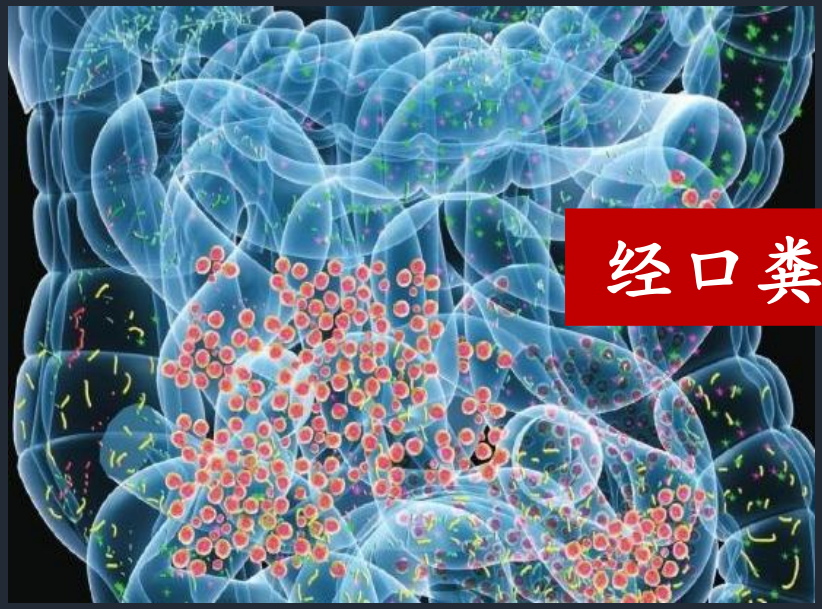
Perry Tsai[1], Guoxin Wu[2], Caroline E. Baker[1], William O. Thayer[1], Rae Ann Spagnuolo[1], Rosa Sanchez[2], Stephanie Barrett[2], Bonnie Howell[2], David Margolis[1], Daria J. Hazuda[2], Nancie M. Archin[1*] and J. Victor Garcia[1*]

小鼠与人类肠道菌群相似率低



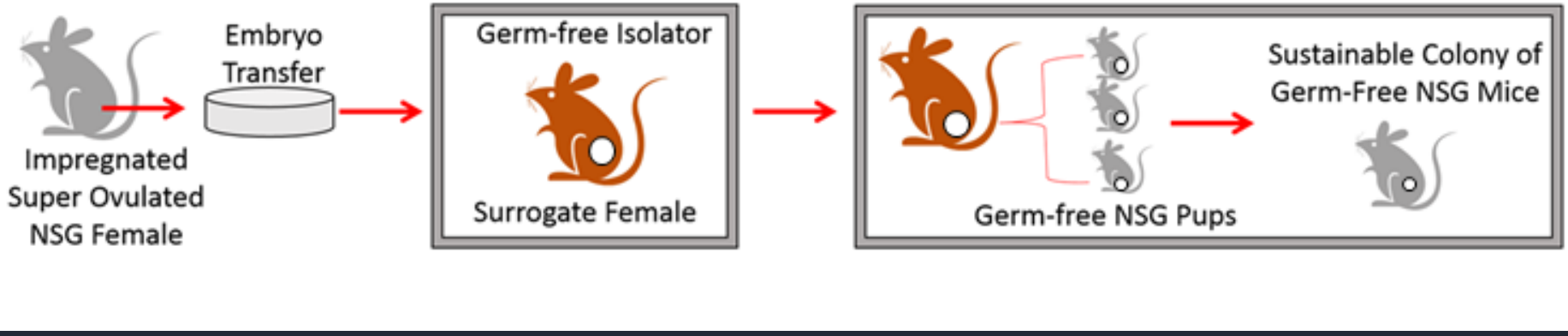
Ley et al. PNAS 2005;102:11070-11075

具有人类肠道菌群的BLT小鼠
Human Microbiome (HuM)-BLT



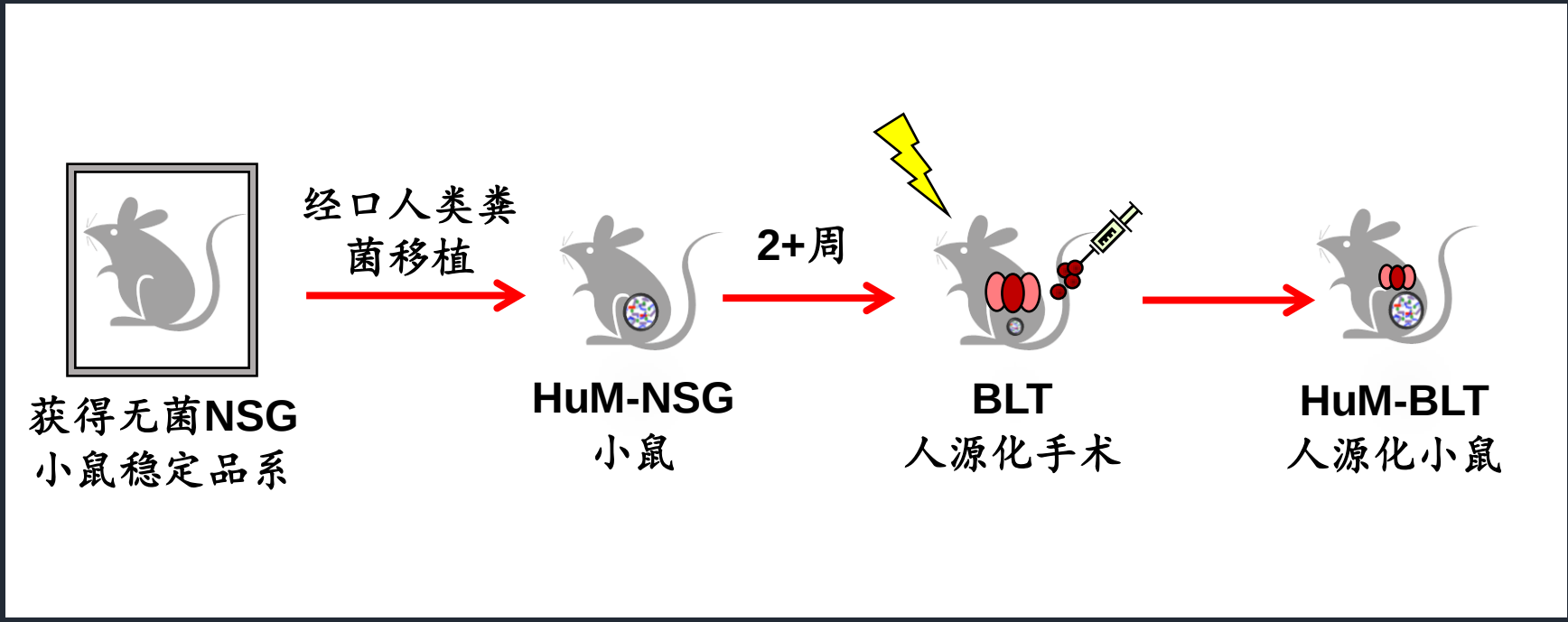
经口粪菌移植

无菌免疫缺陷小鼠

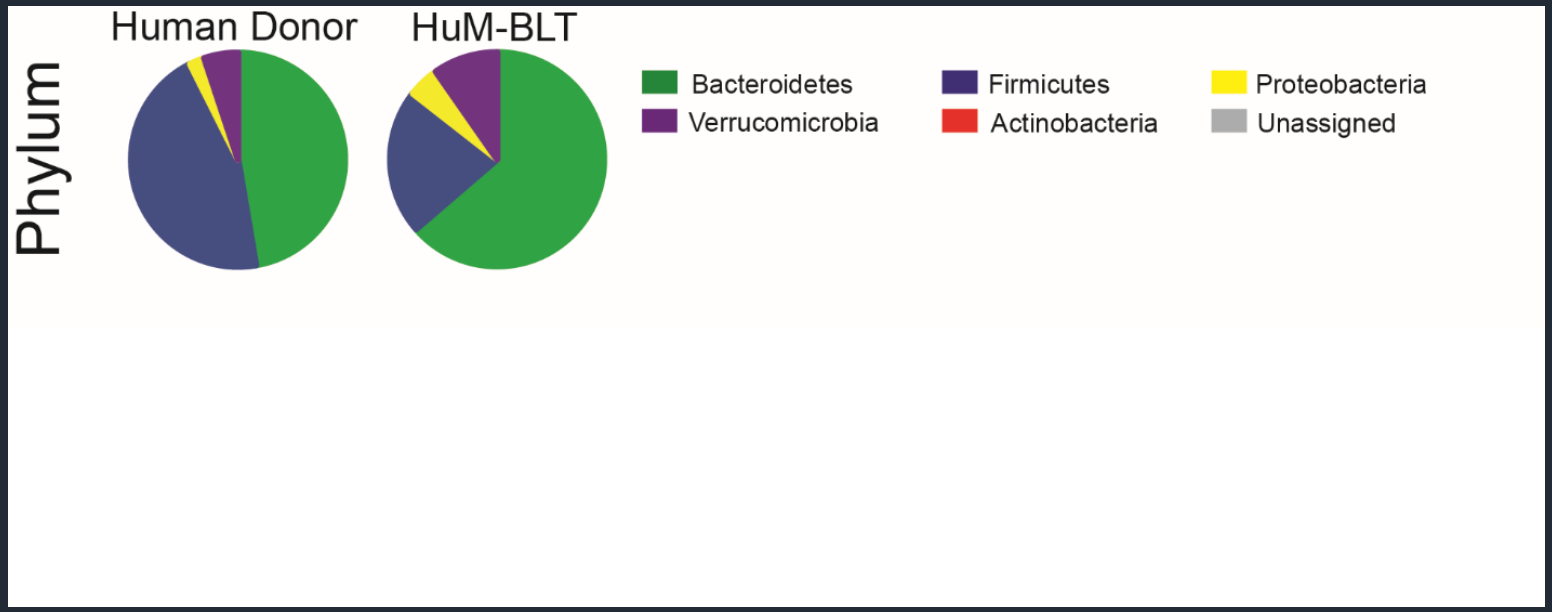


通过PCR、染色和细菌培养三种方法确保无菌NSG小鼠的无菌状态

HuM-BLT人源化小鼠

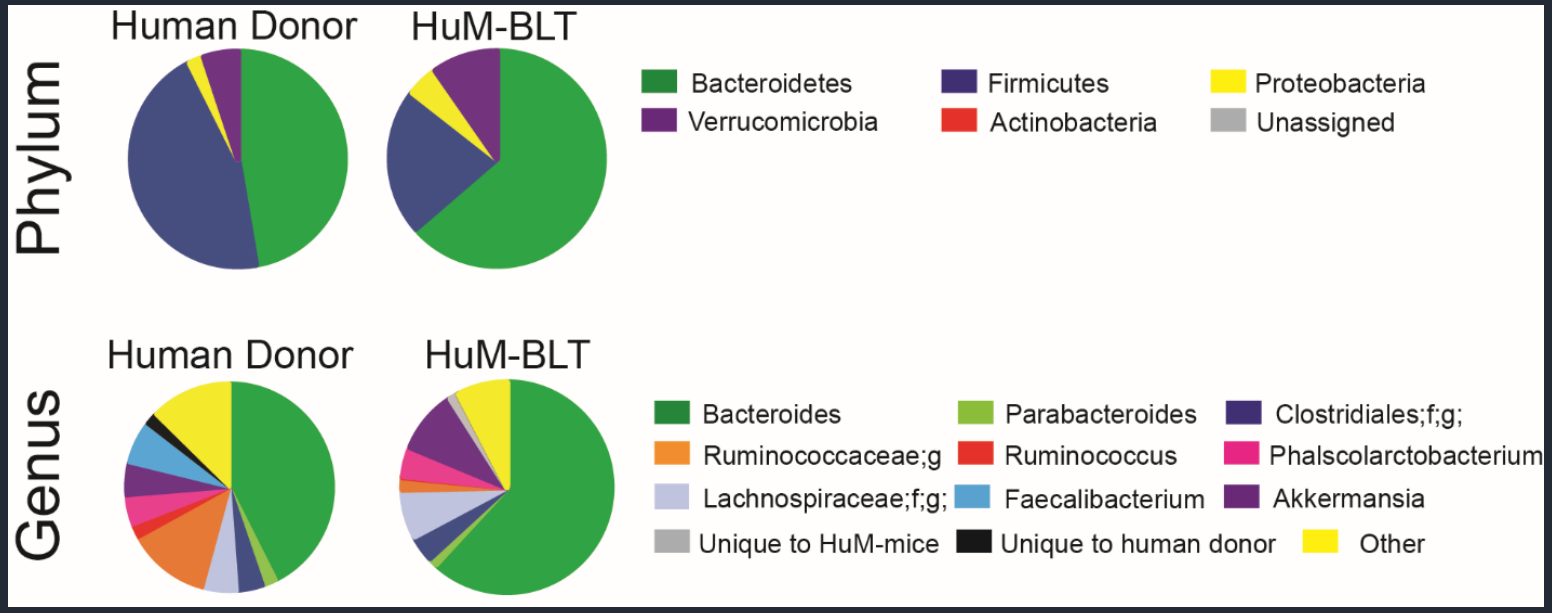


HuM-BLT小鼠肠道
成功移植人类肠道菌群



采集接受人类粪菌移植14周后的HuM-BLT小鼠粪便（n=4）
进行16S rRNA基因测序分析

HuM-BLT小鼠肠道
成功移植人类肠道菌群

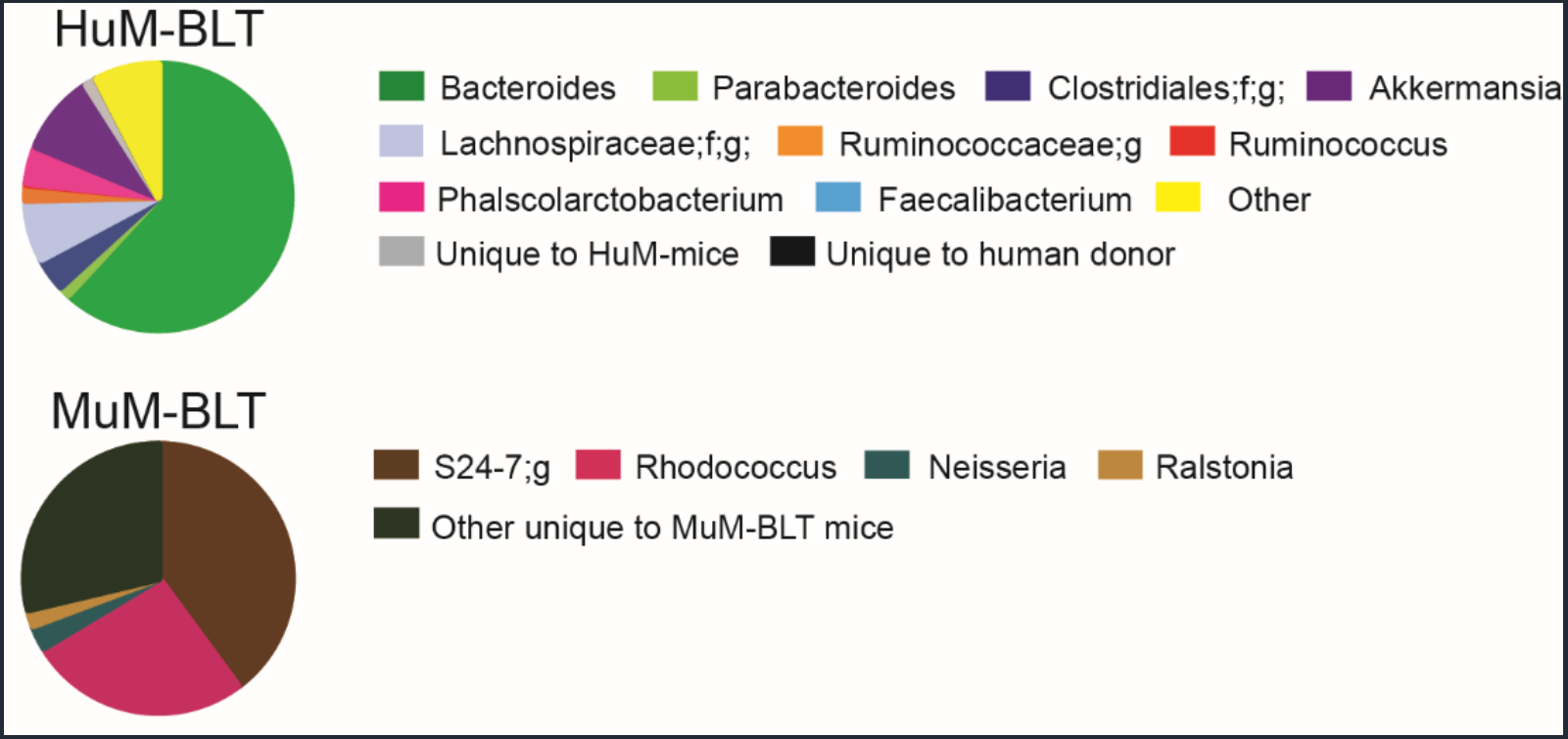


接受人类粪菌移植14周后的HuM-BLT小鼠（n=4）粪便进行16S rRNA基因测序分析

- 健康供者人类肠道菌群共检测出23个肠道菌属，当中19个肠道菌属可在HuM-BLT小鼠肠道菌群中检测出现
- 与健康供者人类肠道菌群对比，HuM-BLT小鼠肠道菌群中2个属（Rikenellaceae和Oscillospira）水平显著下降

Mann-Whitney Test

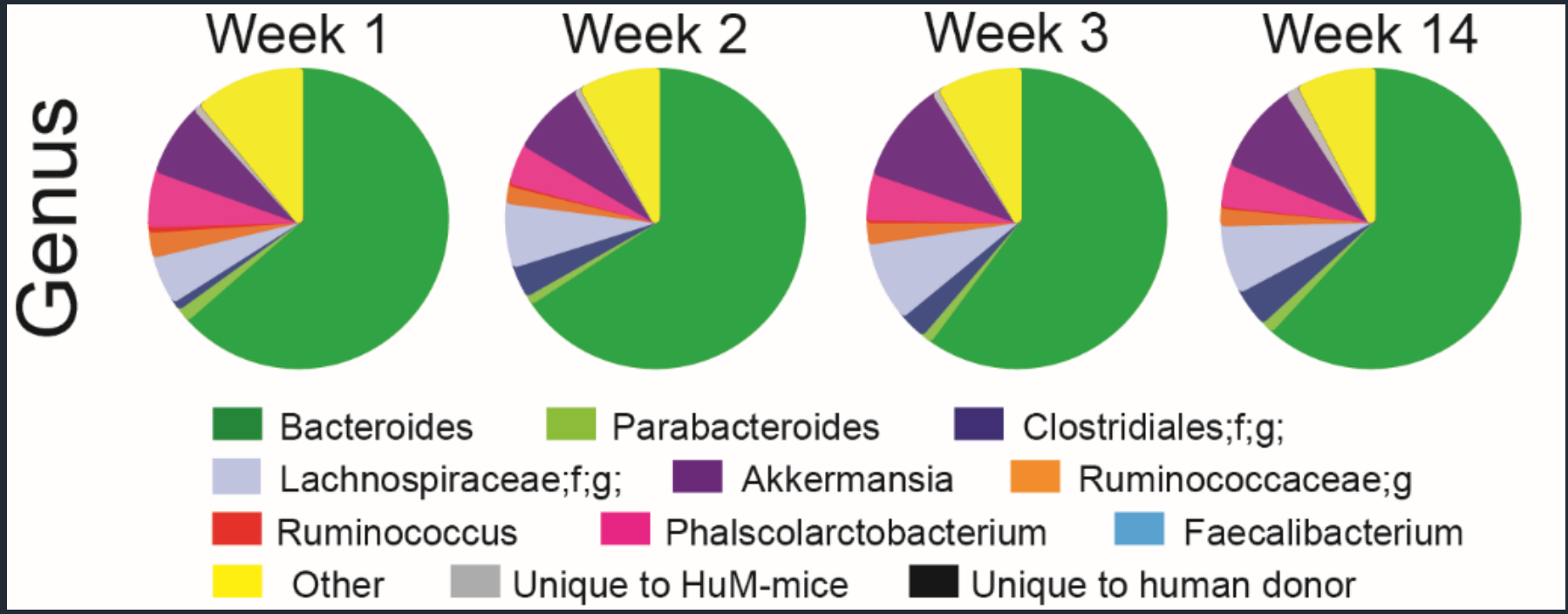
HuM-BLT与伴鼠类肠道微生态的BLT小鼠(MuM-BLT)肠道菌群组成差异显著



16S rRNA基因测序分析肠道菌群（HuM-BLT [n=4]和MuM-BLT[n=6]）

- <4% 重叠

人类肠道菌群可在HuM-BLT小鼠肠内长时间保持稳定

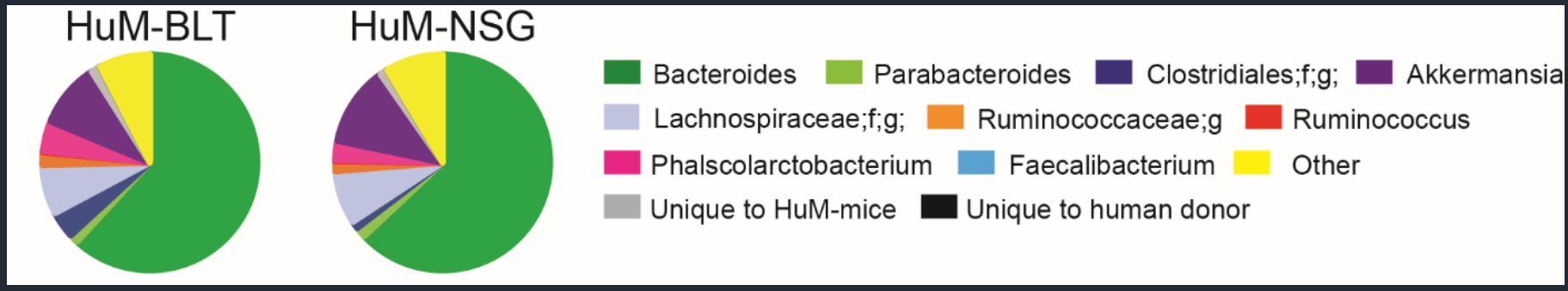


16S rRNA基因测序分析HuM-BLT小鼠肠道菌群（n=4）

- 在粪菌移植术后第3周和第14周采集粪便样本并分析，结果显示两个时间点之间的肠道菌群组成无显著差异

Repeated measures ANOVA test with Bonferroni's correction

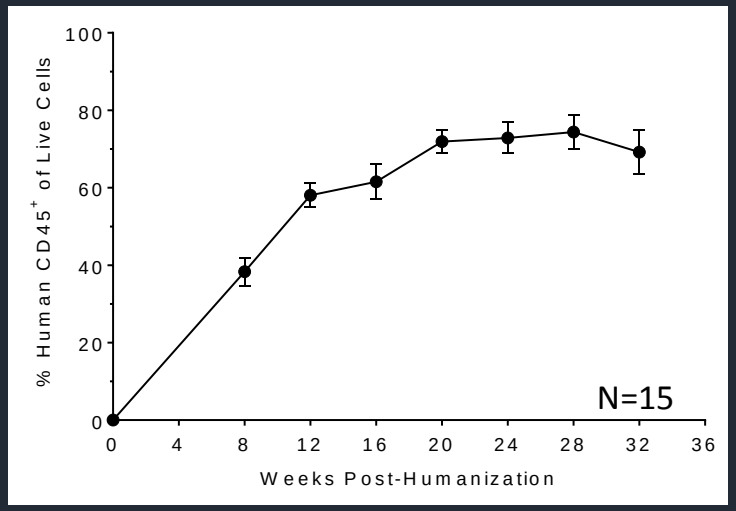
BLT人源化手术过程不影响肠道菌群组成



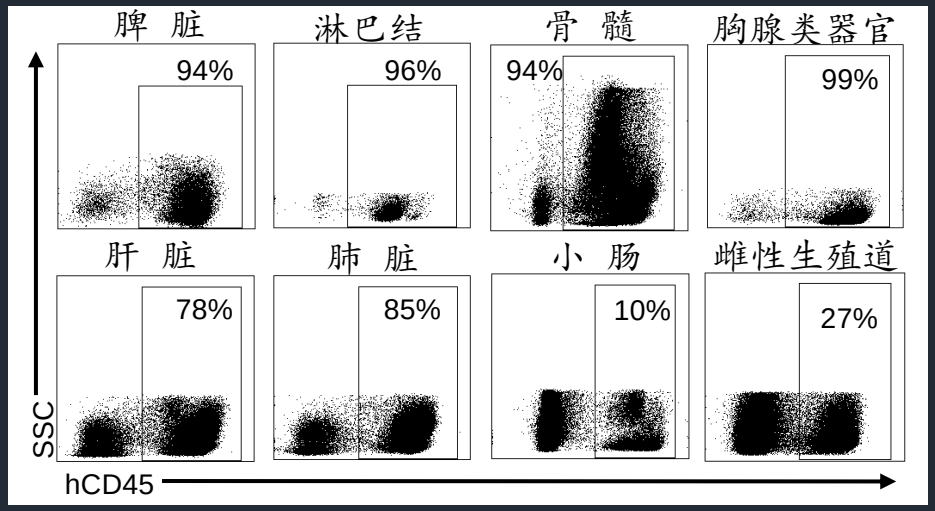
16S rRNA基因测序分析(n=4 HuM-BLT and 4 HuM-NSG小鼠)

HuM-BLT小鼠
体内系统重建人类造血细胞

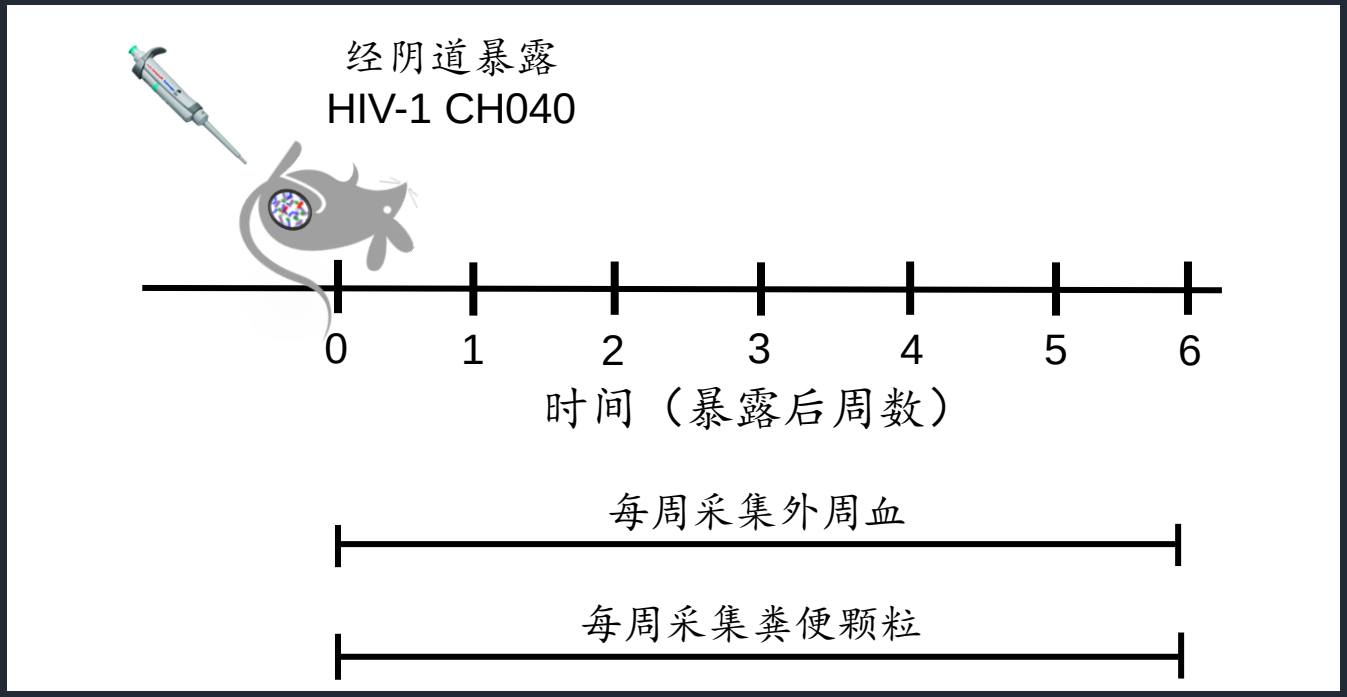
外周血



器官组织



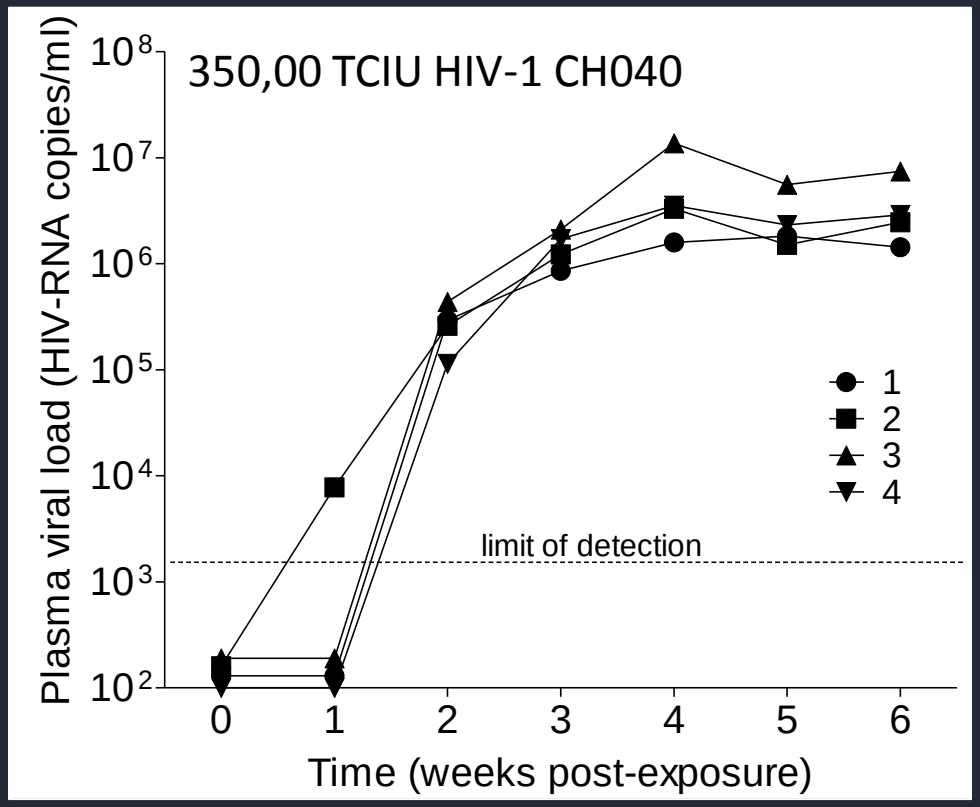
急性HIV感染与人类肠道菌群变化



外周血：血浆HIV-RNA水平
CD4⁺T细胞和活化CD8⁺T细胞水平

粪便颗粒： 16S rRNA基因测序分析（Illumina MiSeq）

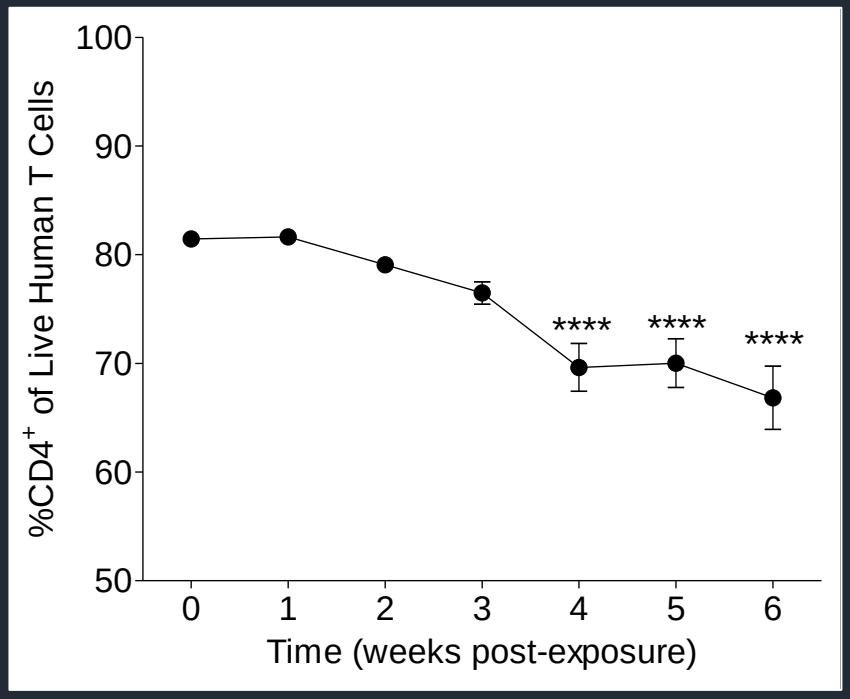
HuM-BLT小鼠对经阴道暴露HIV-1易感



(n=4 HuM-BLT)

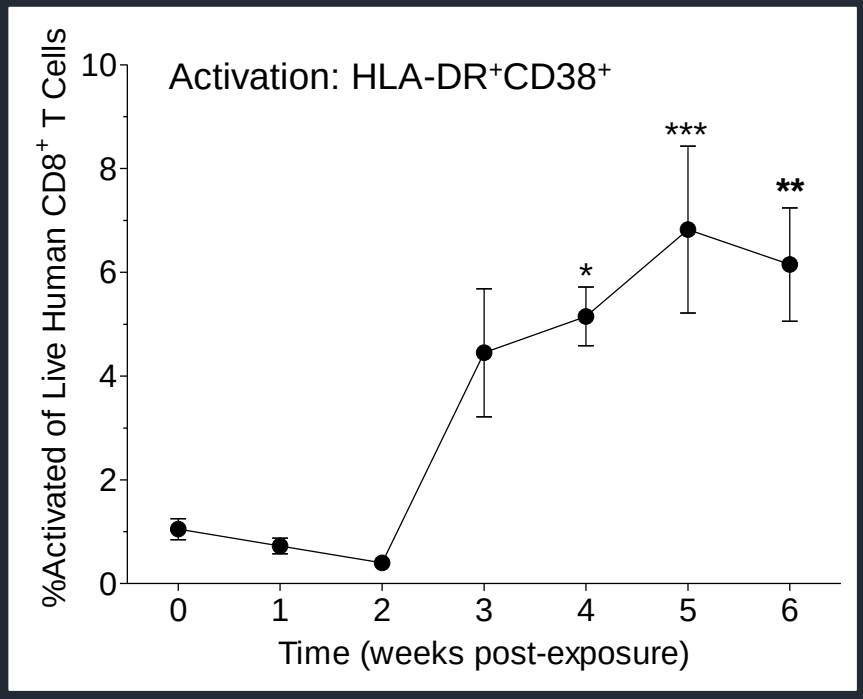
HuM-BLT小鼠感染HIV后
高度模拟急性期患者免疫变化

CD4⁺T细胞水平



(n=4 HuM-BLT)

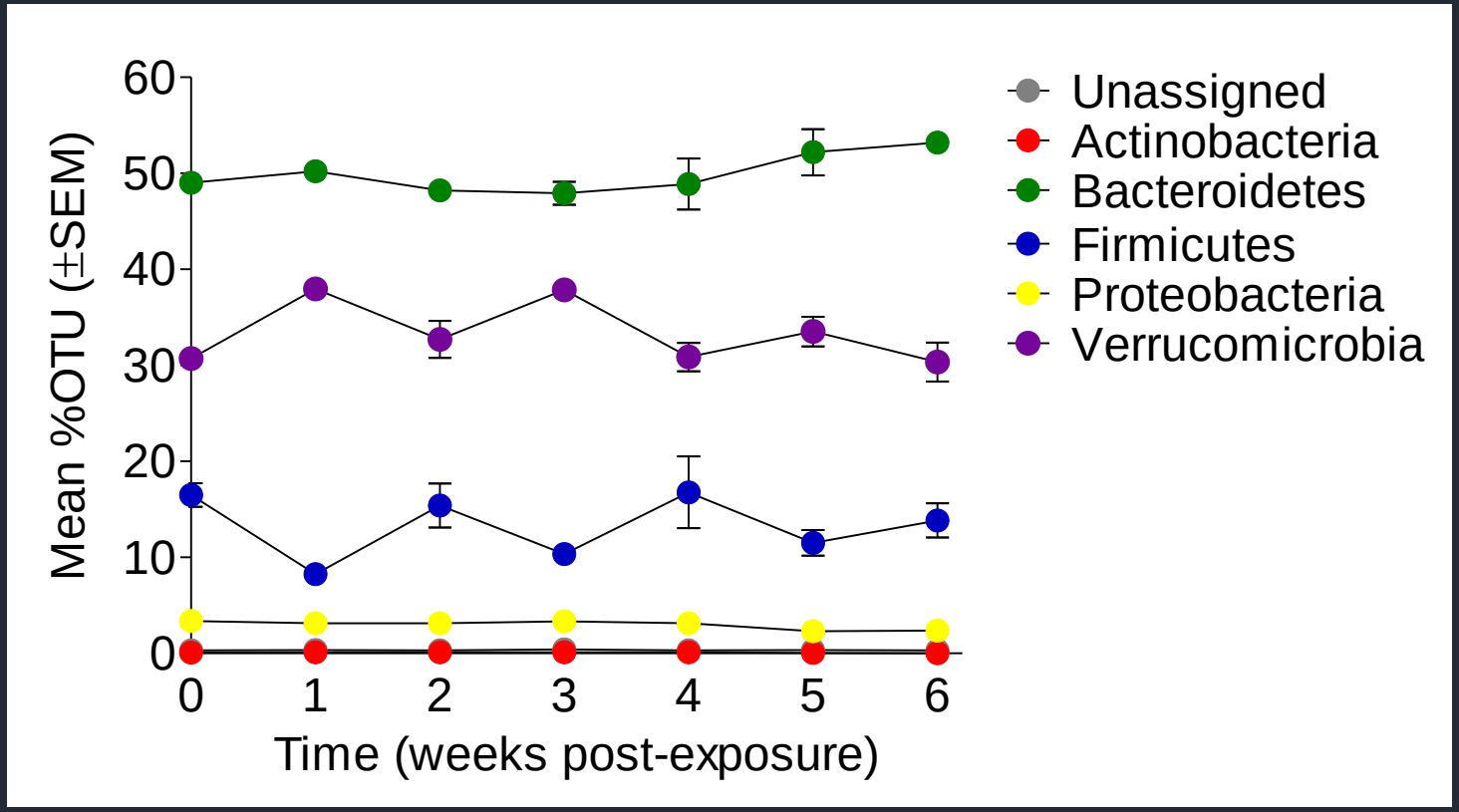
活化CD8⁺ T细胞水平



(n=4 HuM-BLT)

Repeated measures ANOVA test with Bonferroni's correction

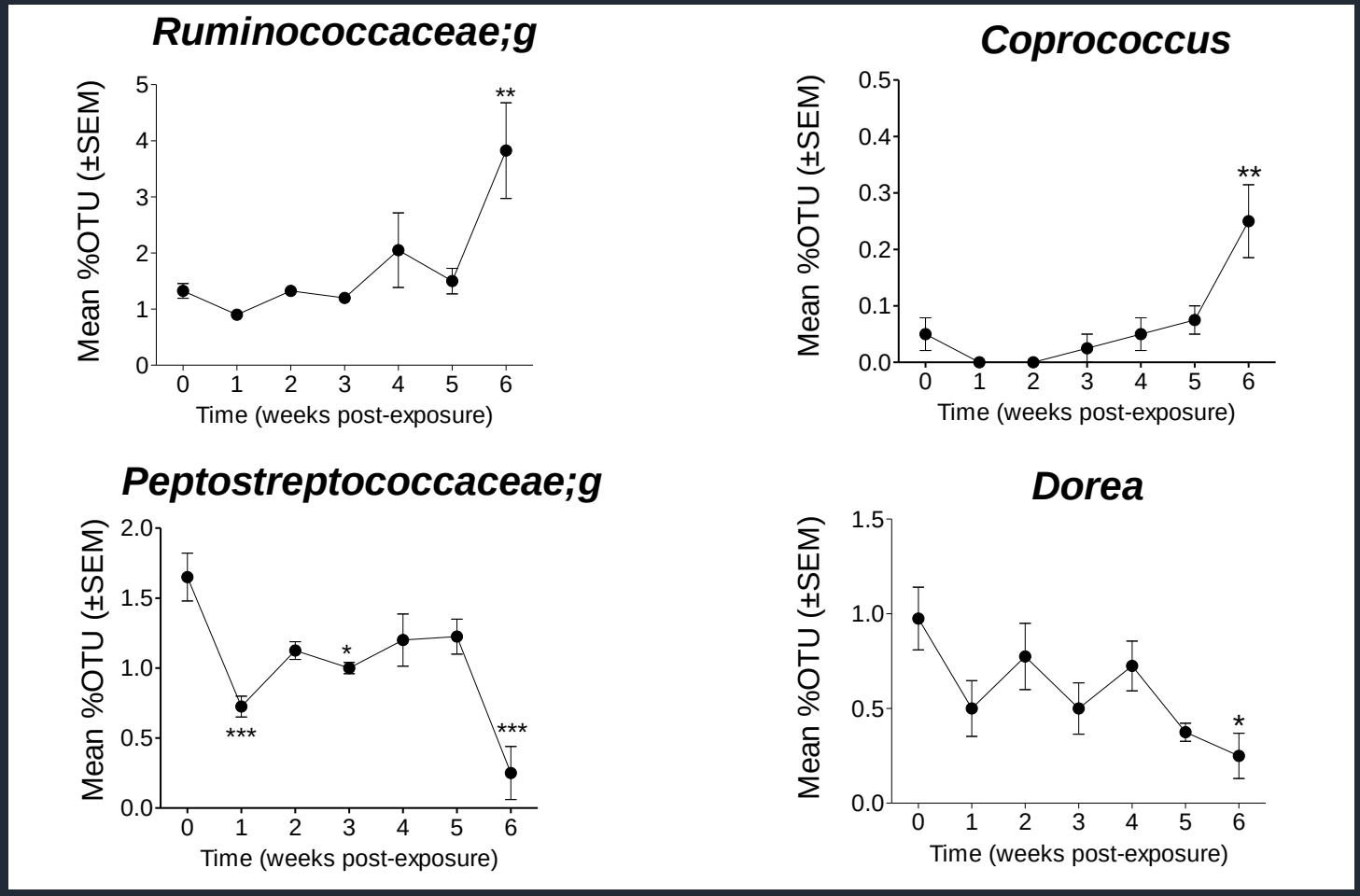
急性HIV感染期肠道微生态在门水平无显著变化



(n=4 HuM-BLT小鼠)

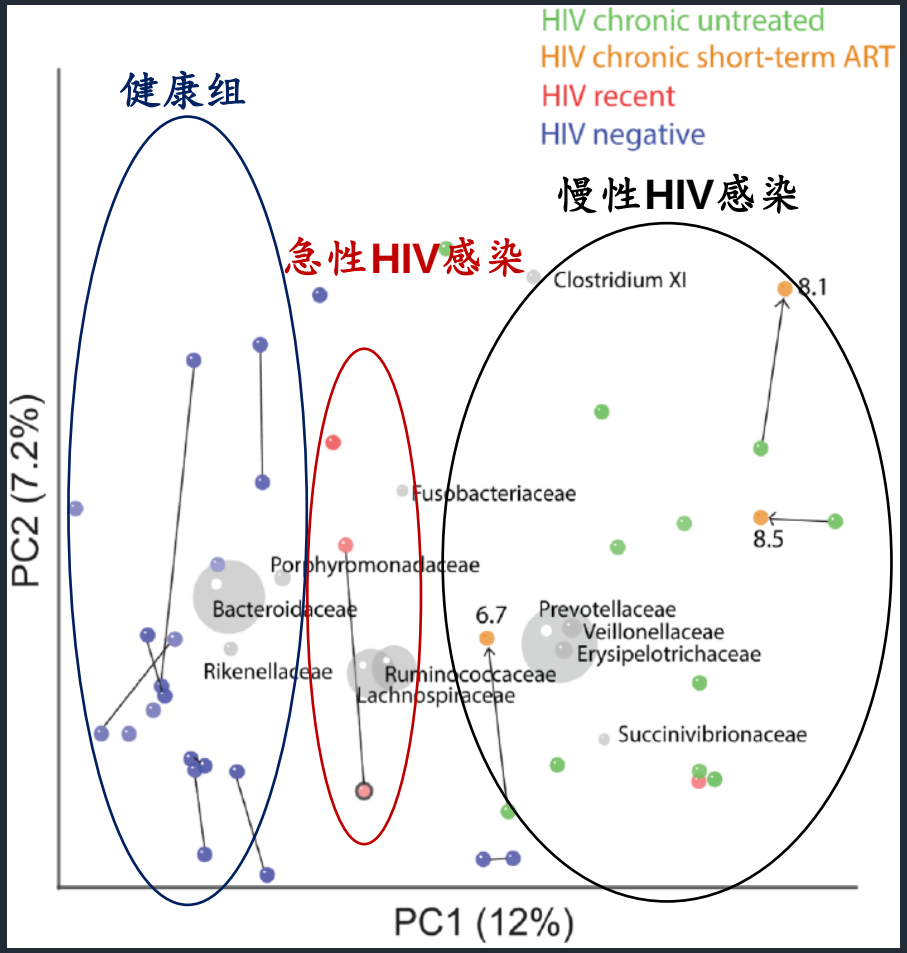
Repeated measures ANOVA test with Bonferroni's correction

急性HIV感染导致梭菌类肠道菌属显著改变



Repeated measures ANOVA test with Bonferroni's correction

急性HIV感染者肠道微生态与健康人群差异不大



Lozupone et al, Cell Host & Microbe, 2013

总　结

- HuM-BLT人源化小鼠肠道成功移植人类肠道菌群，且人类肠道微生态可长期稳定保持
- HuM-BLT人源化小鼠体内系统重建人类造血细胞
- HIV感染6周后，肠道微生态梭菌类中4个肠道菌属水平发生显著改变

致　谢

广州市第八人民医院感染病中心

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UNC-Chapel Hill

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- J. Victor Garcia博士
- Morgan Chateau博士
- Cara Richardson
- 所有Garcia实验室成员