RESEARCH ON TAP

Working Towards an HIV Cure

September 24, 2019

bu.edu/research/events

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Boston University Office of Research

Andrew Henderson

Professor of Medicine and Microbiology
Associate Director Prov/Bos CFAR
Boston University School of Medicine

MISSION: Reduce burden of HIV infection world-wide by supporting multidisciplinary basic, translational and clinical research.

APPROACH: Collaborative effort between Brown University/Lifespan and BU/BMC to provide services to support on-going HIV research and to encourage new investigators to explore questions relevant to HIV/AIDS with funding opportunities, services and collaboration

PROV / BOS CFAR
CENTER FOR AIDS RESEARCH
Lifespan • Brown • Boston University • Boston Medical Center

ORGANIZATION AND SERVICES

Cores, Scientific Working Groups, Research Interest Groups

CORES

- Admin
- Develop-mental
- Bio-Behavioral Sciences
- Basic Sciences
- Substance Use Research
- BioStats

SWG

- HIV/TB

RIG

- Oral Health & HIV
- Disrupt HIV Infection
- -omics and HIV Pops

HENDERSON LAB

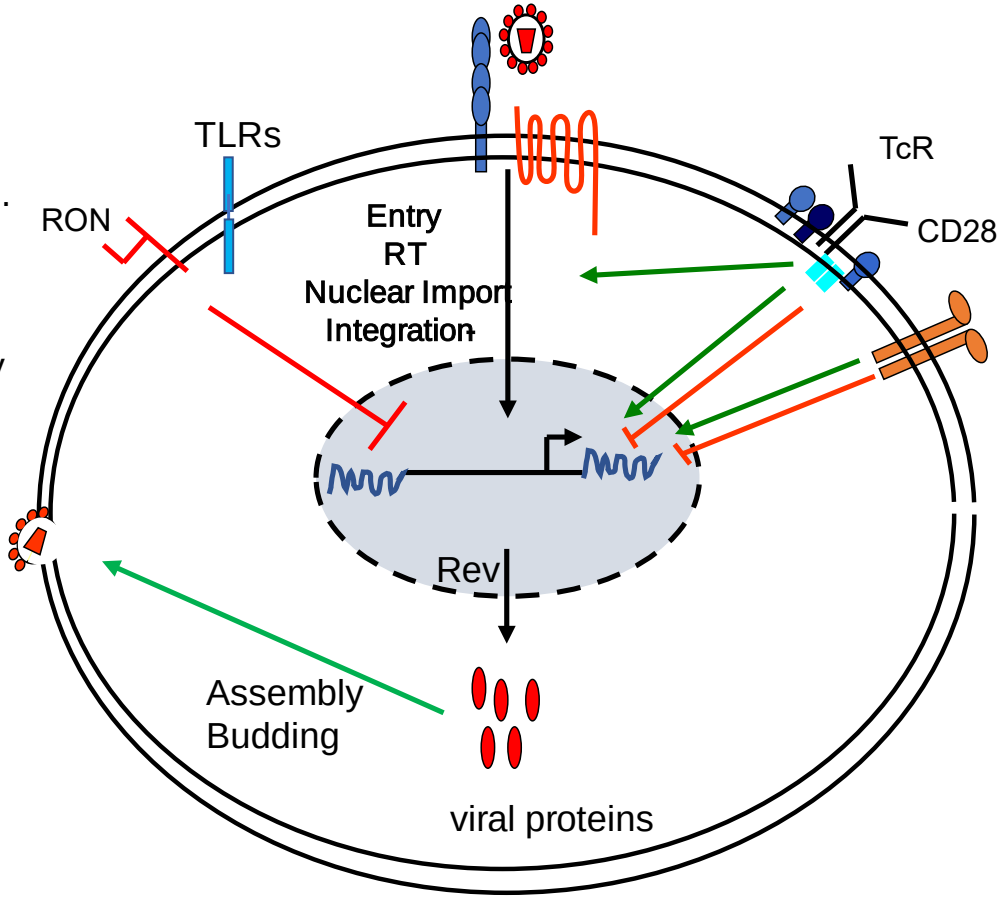
CELLULAR MECHANISMS THAT REGULATE HIV LATE

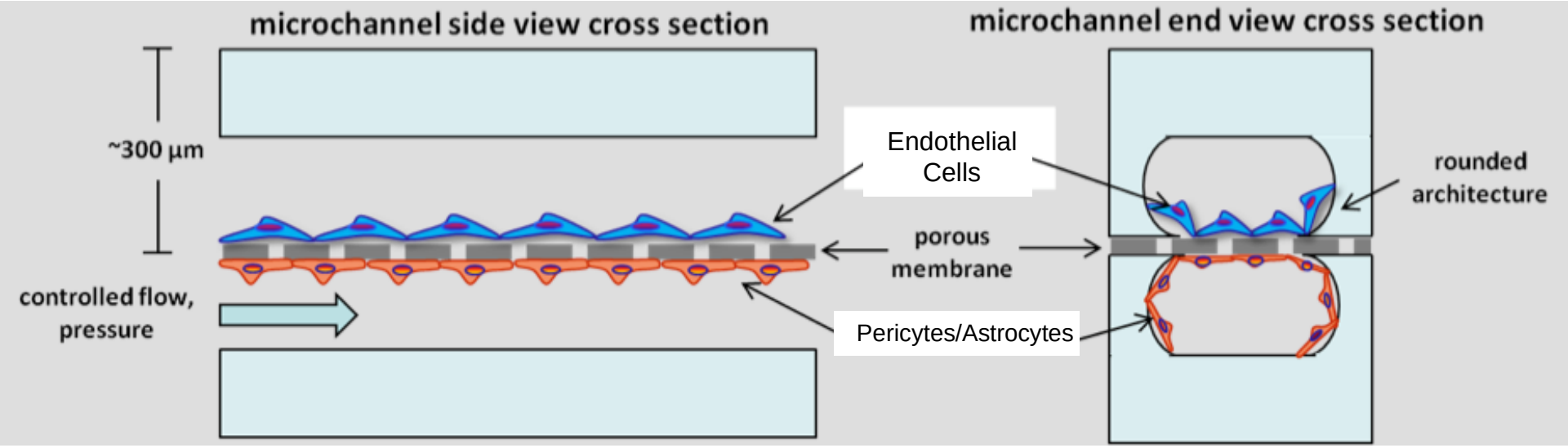
We want to understand what cells get latently infected.
Resting cells, T memory cells, myeloid cells?
(Agosto et al. 2018. Cell Reports)

We want to know the mechanisms that lead to latency
Chromatin? Host-Transcription Factors?
Specific signaling pathways?

We want to understand at a mechanistic level of the interplay of HIV infection, inflammation and pathogenesis.

We want to identify druggable targets for HIV and associated comorbidities (Graci et al. 2017. PLoS One)





Brain Microenvironment Models for HIV Research

Tyrone Porter, PhD, Engineering
Suryaram Gummuluru, Microbiology
Boston University

A Gap in Life Expectancy Remains Between HIV+ Infected and HIV- uninfected Individuals

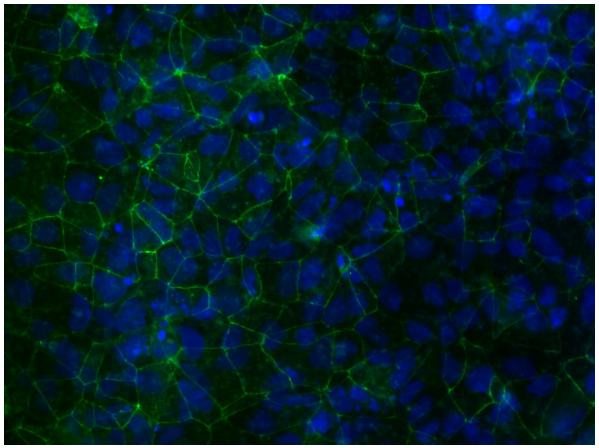
- Chronic immune activation in the central nervous system (CNS) is observed in cART-suppressed HIV+ patients
- BBB breakdown and progressive neurocognitive disorders have shown a correlation with chronic immune activation
- How does HIV evade cART in the brain, what are the mechanisms of chronic immune activation, and what strategies/therapeutics may be employed to more effectively treat and/or manage HIV infection in the brain?

Hypothesis

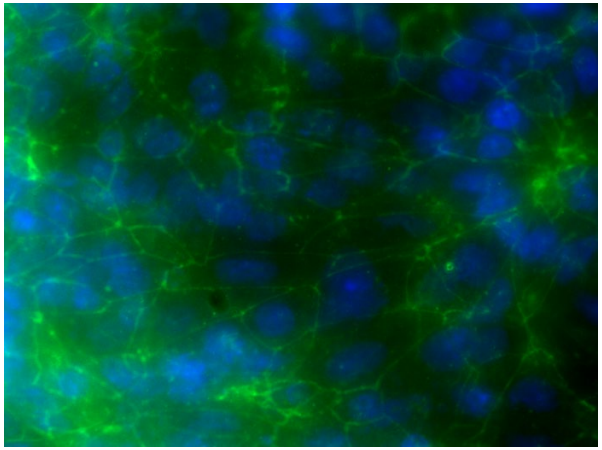
Persistent de novo expression of HIV-1 RNA induces innate immune activation in microglia, which contributes to neurotoxicity

Characterizing human BBB model (established in Transwells)

VE-cadherin



ZO-1



(3x cm^2)

Verdinexor Penetrated Co-BBB and Inhibited HIV-1 Production

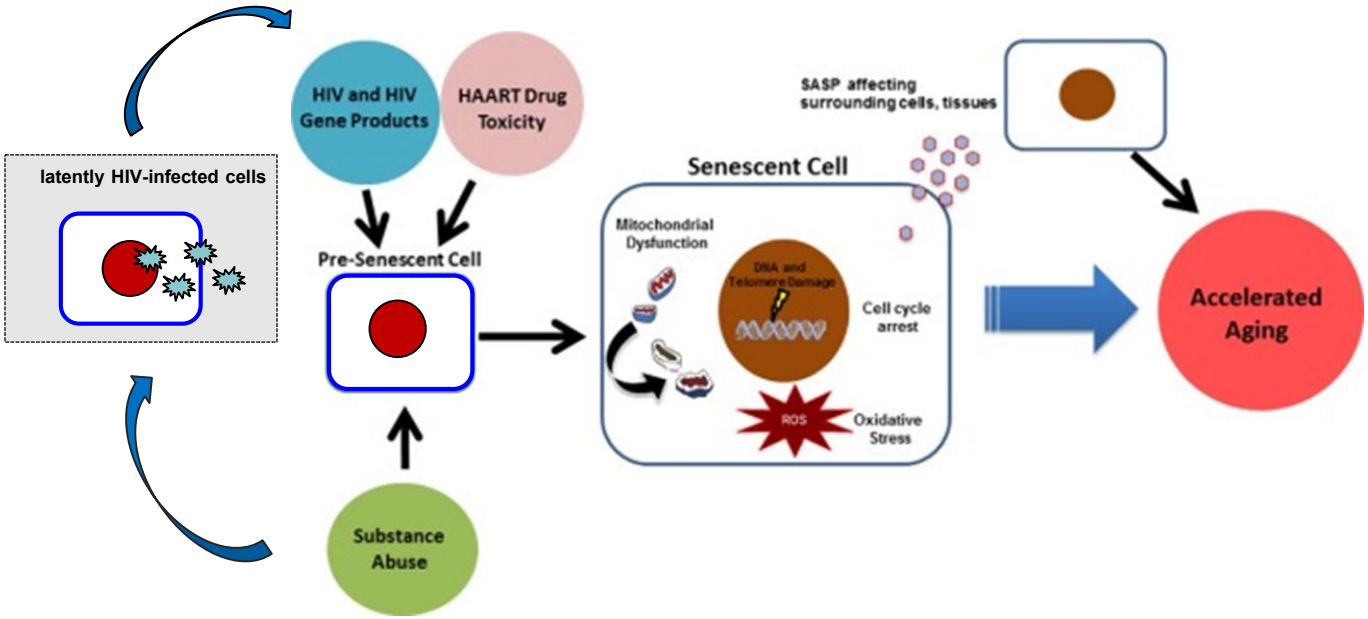
- Co-incubation of infected MDMG with CRM-1 inhibitor verdinexor significantly reduced HIV-1 production
- Verdinexor inhibitory activity was dose-dependent
- Verdinexor penetrated Co-BBB model and suppressed HIV-1 production by infected MDMG
- Findings suggest that less than 5% of verdinexor added to luminal chamber penetrated the BBB. Additional studies are required to test this estimate and quantify P_{app}

Translational Approach to Understand HIV-Associated Diseases and Barriers to Cure

Nina Lin, MD

Assistant Professor of Medicine
Director of ID Clinical Research Unit (CRU)
Boston University School of Medicine

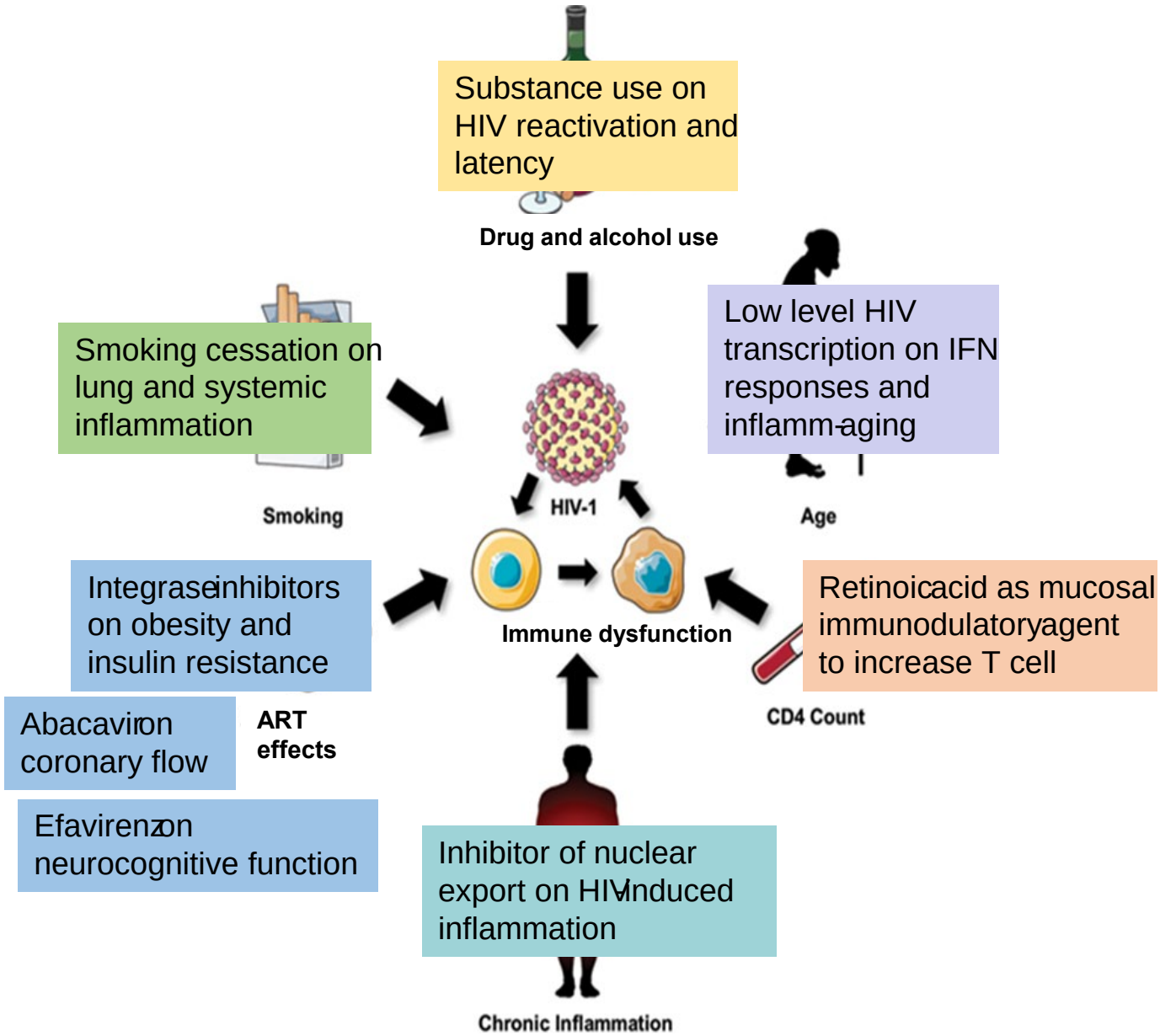
Inflammation is central in HIV pathogenesis



Multidisciplinary approach to identify factors influencing:

1) HIV residual viremia and latency
2) its effect on aging = end-organ disease

HIV translational research: Using our patients to inform us



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A Causal Inference Approach to HIV Research

Sara Lodi

Assistant Professor
Department of Biostatistics
BU School of Public Health

Clinical practice requires decision making

- Example: switching to integrase inhibitors: Who? When? What to switch to? Frequency of monitoring?

Randomized experiments estimate causal effects, but:

- can be expensive, untimely or even unethical

Can use observational data to explicitly emulate a **target trial**:

- The (hypothetical) randomized trial that we would like to conduct to answer a causal question

Step 1 : Specify Target Trial protocol

- Eligibility criteria
- Treatment strategies
- Outcomes
- Randomized assignment
- Analysis plan

Step 2 : Emulate Target Trial protocol

- Eligibility criteria
- Treatment strategies
- Outcomes
- Identify confounders
- Analysis plan – adjusting for confounding (standard methods or g-methods)

Examples

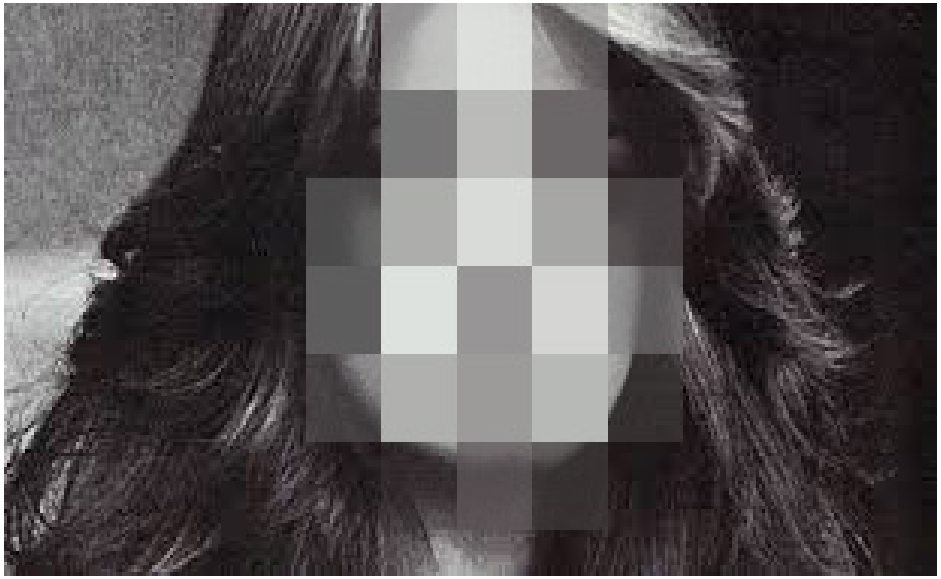
- Effect of early ART initiation on mortality (Lodi et al Lancet HIV 2015) and on development of drug resistance (AIDS 2018)
- Frequency of monitoring for CD4 count and viral load (Caniglia et al JAIDS 2016)

Healthcare in Russia for HIV+ People Who Use Drugs: Role of HIV and Substance Use Stigma

Marina Vetrova, MD

General Internal Medicine
Boston University Medical Campus

Stigma and Health



- ¾Labeling
- ¾Exclusion
- ¾Avoidance

Addressing Stigma

- Public education
- Provider training
- Personal empowerment:

Acceptance and commitment training

HIV-positive person

Person with substance use disorder

Addressing Tuberculosis In High HIV-Burden Settings

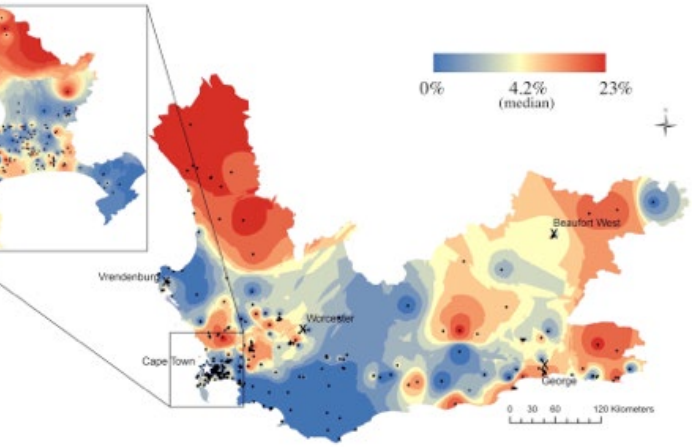
Helen Jenkins

Assistant Professor
Department of Biostatistics
Boston University School of Public Health

Defining the care cascade for rifampin-resistant TB patients in South Africa, geographically and by HIV/non-HIV

With Jacob Bor and Karen Jacobson

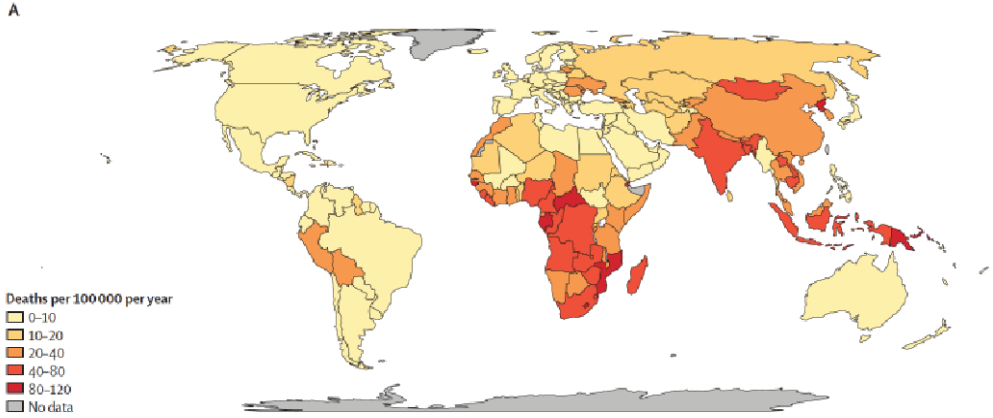
- 60% of TB cases in HIV positive patients in South Africa, no database to monitor these spatially and longitudinally
- We will combine longitudinal TB and HIV laboratory test data to identify hot-spots, track patient movement and define the care cascade



Counting kids: Detection of Pediatric TB in Ukraine

With Natasha Rybak

- Pediatric TB presents differently in children and is harder to diagnose
- Only 45% of 1 million annual incident cases are diagnosed and treated. ~250,000 annual deaths
- One third of European TB/HIV patients are in Ukraine, pediatric TB is under-diagnosed
- We aim to review autopsy records (mandatory autopsy policy in Ukraine), and clinical data to assess pediatric burden



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the ANCHOR study.org

ANal Cancer/ HSIL Outcomes Research Study
ANCHOR

Elizabeth Stier, MD
Associate Professor, Obstetrics and Gynecology
Boston University School of Medicine
Boston Medical Center

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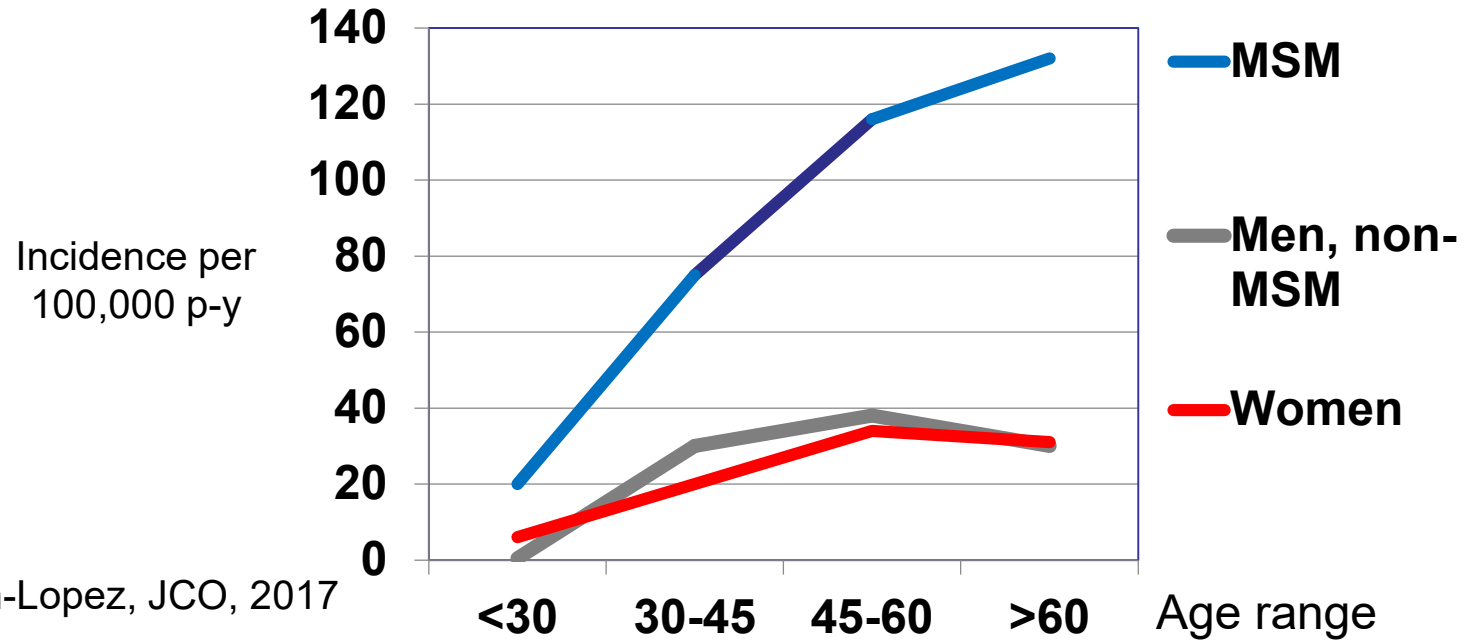
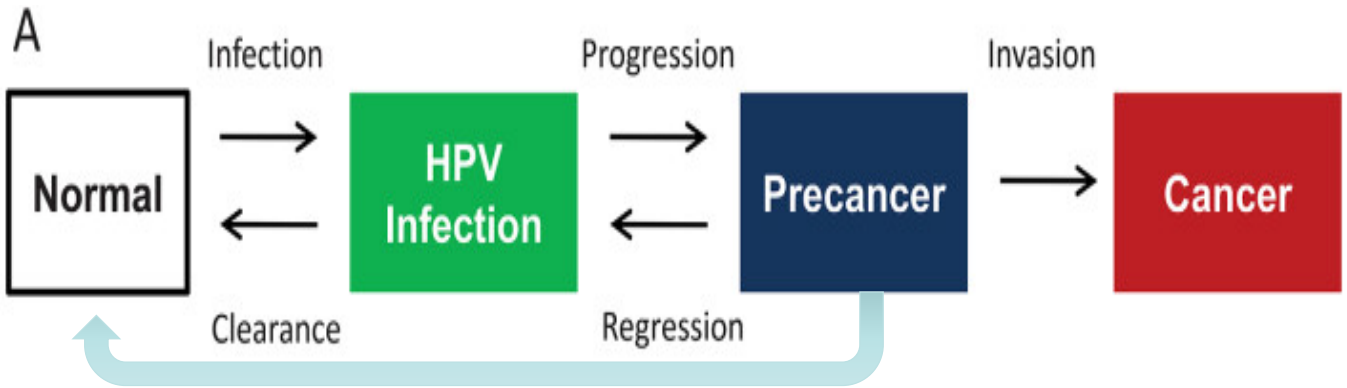
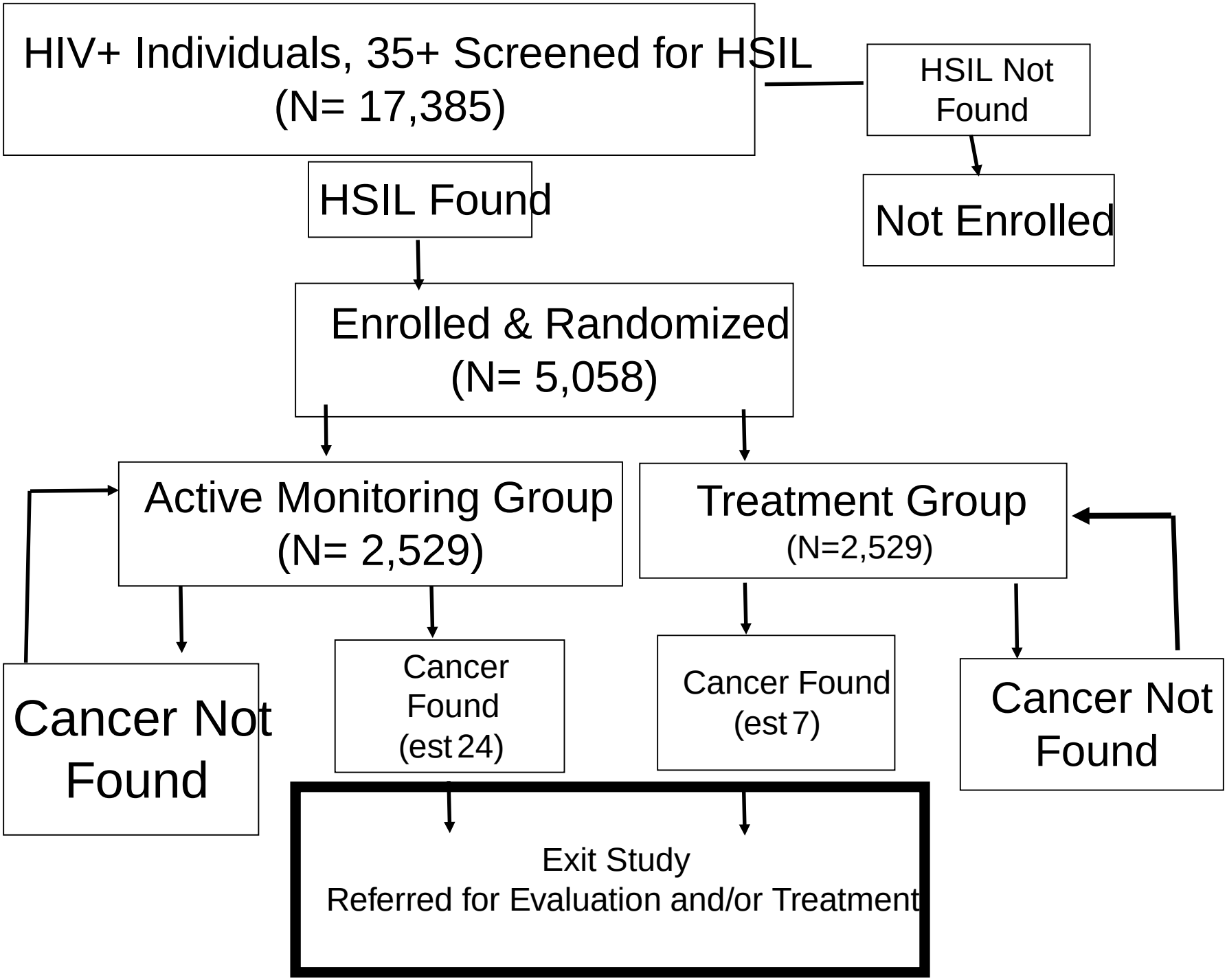
Anal cancer incidence in HIV+ persons by age, HIV/AIDS Cancer Match Study (1996-2012)



Colon-Lopez, JCO, 2017




HIV+ Individuals, 35+ Screened for HSIL
(N= 17,385)
HSIL Not Found
Not Enrolled
HSIL Found
Enrolled & Randomized
(N= 5,058)
Active Monitoring Group
(N= 2,529)
Treatment Group
(N=2,529)
Cancer Not Found
Cancer Found
(est 24)
Cancer Found
(est 7)
Cancer Not Found
Exit Study
Referred for Evaluation and/or Treatment

HIV & Oral Health in the Post-cART Era

Matthew Mara, DMD

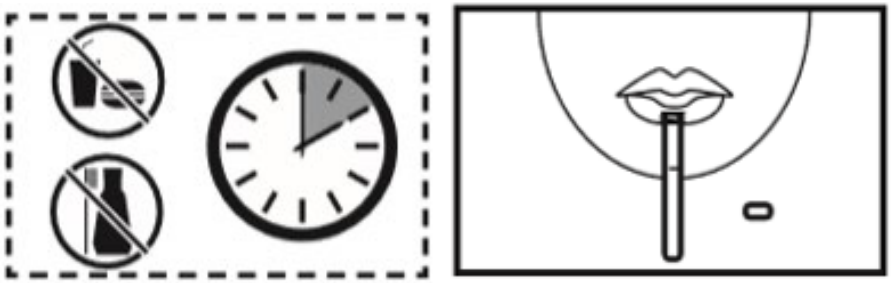
Clinical Instructor
General Dentistry, Henry M. Goldman School of Dental Medicine

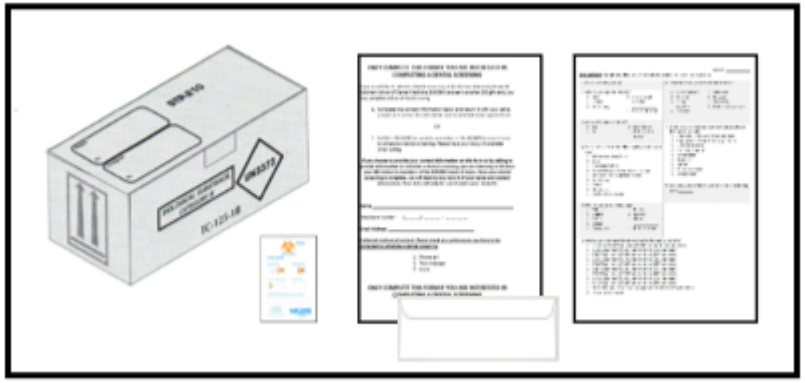
Specific Aims

Aim 1. Validate self-reported measures of periodontal disease.

Aim 2. Characterize the oral health status (tooth count, dental caries, periodontal disease, oral lesions) of PLWH residing in the Greater Boston area.

Aim 3. Establish the feasibility of participant self-collection, packing and mailing of saliva samples in a cohort of PLWH.





Determining Immune Cell Drivers of Inflammation in Art-Suppressed HIV and Aging Using Systems-Level Approaches

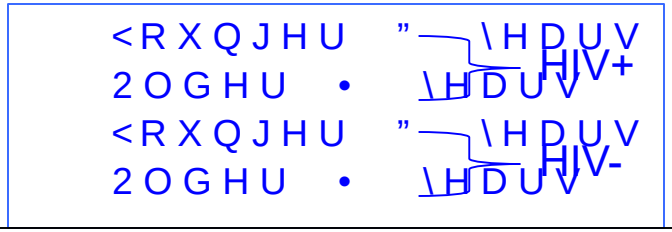
Jennifer Snyder-Cappione

Assistant Professor, Department of Microbiology
Director, Flow Cytometry Core Facility
Boston University School of Medicine

Premature ‘inflamm-aging’ with aviremic HIV infection?

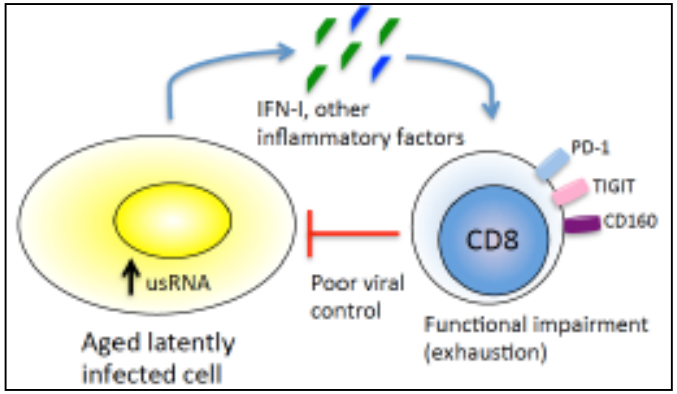
Despite successful viral suppression,
↑ ‘older age’ co-morbidities in HIV+ persons

Nina Lin, M.D.



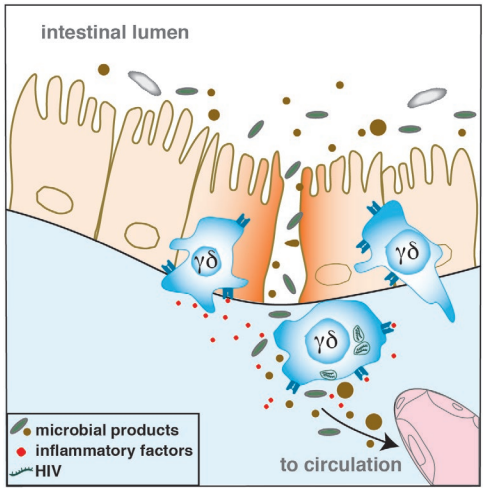
Projects

(1) Determine links between CD8+ T cell exhaustion, macrophage activation, and inflammation



Rahm Gummuluru Ph.D.
Nina Lin M.D.,
Manish Sagar M.D.

(2) Investigate role of γδ cells in intestinal permeability



Anna Belkina, M.D., Ph.D.
Nina Lin, M.D.,
Luis Agosto, Ph.D.,
Irina Vonovoy, M.D.

Readouts

(1) 33-color flow cytometry (blood lymphocytes)

(2) 20+ markers of inflammation (plasma)

(3) 30+ parameter tissue analysis via Imaging Mass Cytometry (gut biopsies)

How can we analyze these enormous datasets?

Data Analyses: Multivariate Algorithmic Approach

Anna Belkina, M.D., Ph.D.

Bioinformatic analysis tools:

opt-SNE*
Citrus
SPADE
PLSR
PLS-DA…

Enable:

(1) Unbiased, comprehensive analysis of all collected data
(2) Determination of how different parameters co-vary to better understand biological systems as a whole
(3) Measurement of what happens when conditions collide (HIV and Aging)

*Belkina et al, Nature Communications, in press

(1) Citrus

TIGIT

(2) PLS-DA

LV2 = age

LV1 = HIV infection

placed subjects into correct groups (+/- HIV) with 89% accuracy

γδ cell, plasma markers used to train model

Belkina et al, Front Immuno, Dec. 2018

Conclusions:

(1) γδ cells involved in/impacted by inflammaging

(2) **Age, HIV infection distinctly impact immune/inflammatory signatures in blood**

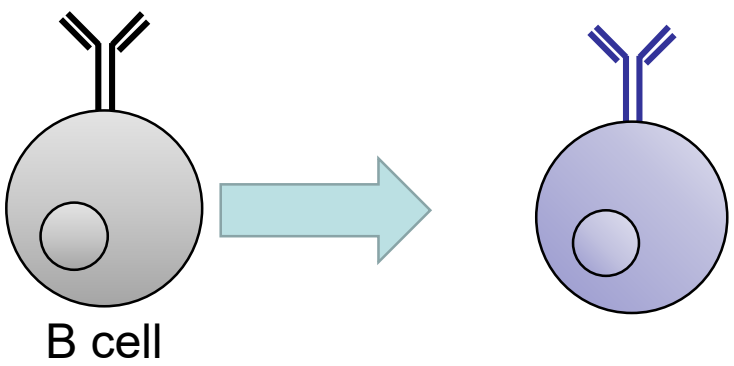
Humoral Immunity, Cell by Cell

Fumi Aihara

Kepler Lab
Boston University

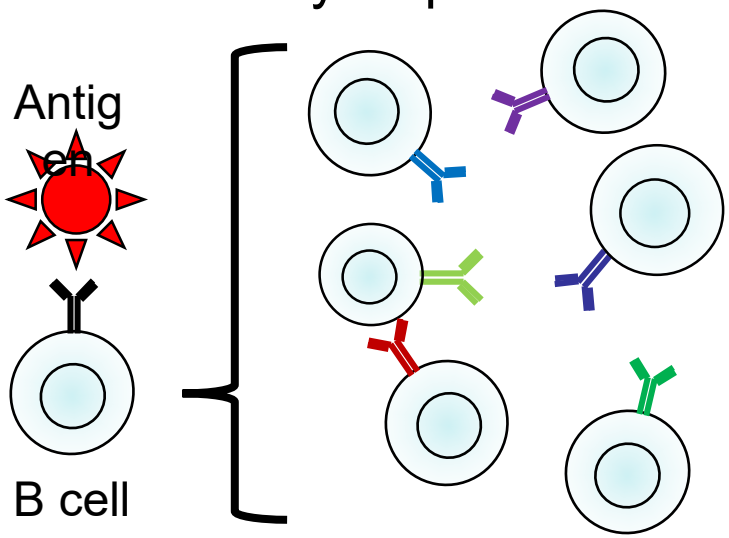
What We're Interested In

Affinity Maturation



How do antibodies improve?

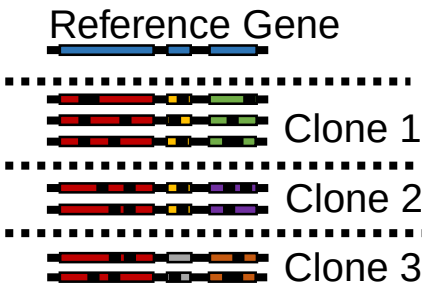
Antibody Repertoire



How diverse are a pool of antibodies?

Techniques

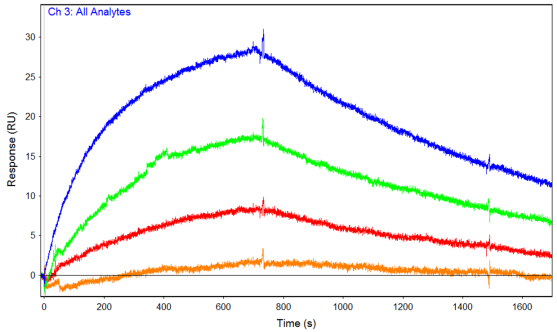
RNA Sequencing



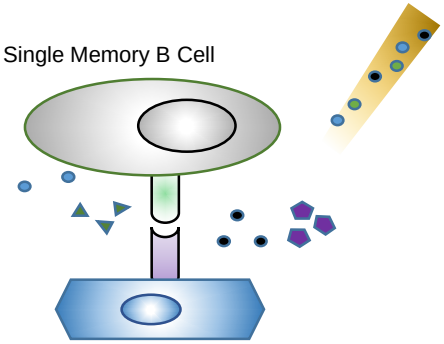
Analysis and Modeling

https://www.google.com/search?rlz=1C1GCEU_enUS847US848&tbm=isch&q=Computer&chips=q:computer,g_1:desktop:p9fvRxODGhw%3D&usg=AI4_kRIbhK8EMb9OFXqxkOwgzV9FprlOw&sa=X&ved=0ahUKEwiXxv3p1OfkAhXMUt8KHSmnDhgQ4IYILCgA&biw=1413&bih=703&dpr=1#imgrc=cATv2HQQLM:

Surface Plasmon Resonance



Single Cell B Cell Culture



Affinity Maturation From a Single B Cell Clone

Kd measured imM

- ½= - â Ù Ù / - â á

6.7

23 aa diff

2.9

22

3.0

5.7

36

4.2

Clone founder

10

17

29

670

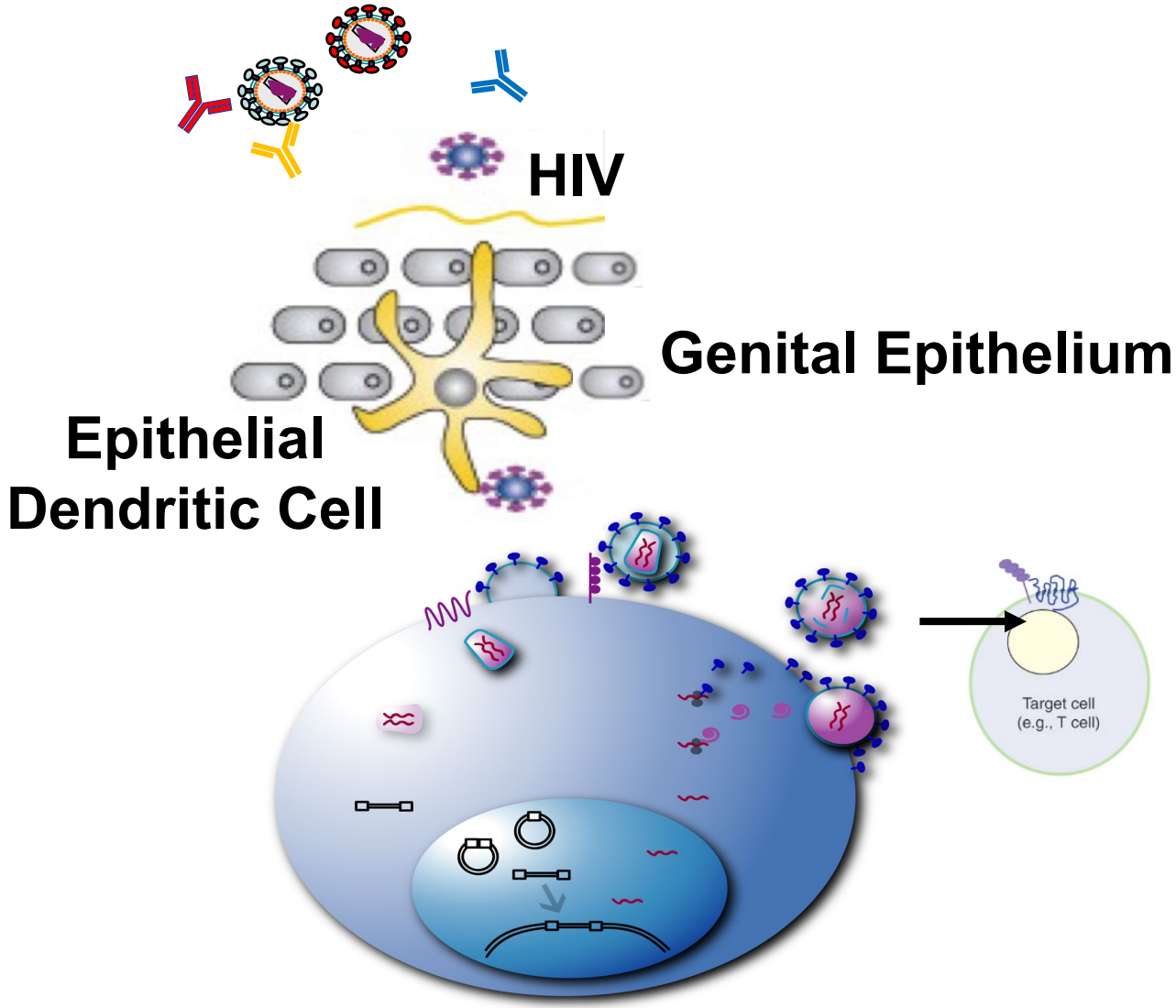
: vaccine 4.
All others, vaccine 3

Antibodies and HIV-1 Mucosal Transmission

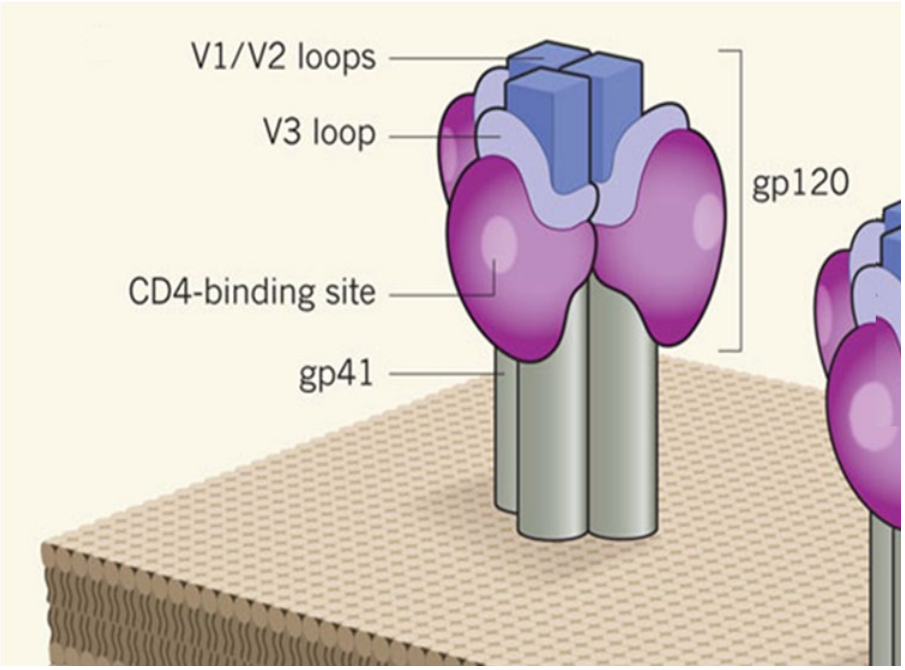
Manish Sagar, MD

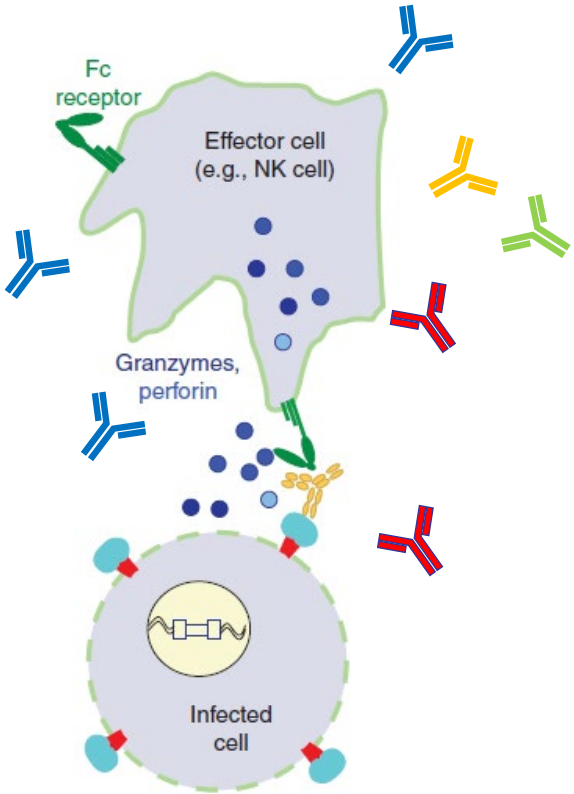
Associate Professor
Department of Medicine
Boston University School of Medicine

Selection of HIV-1 variants during mucosal transmission



Role of antibodies in preventing transmission and eliminating infected cells



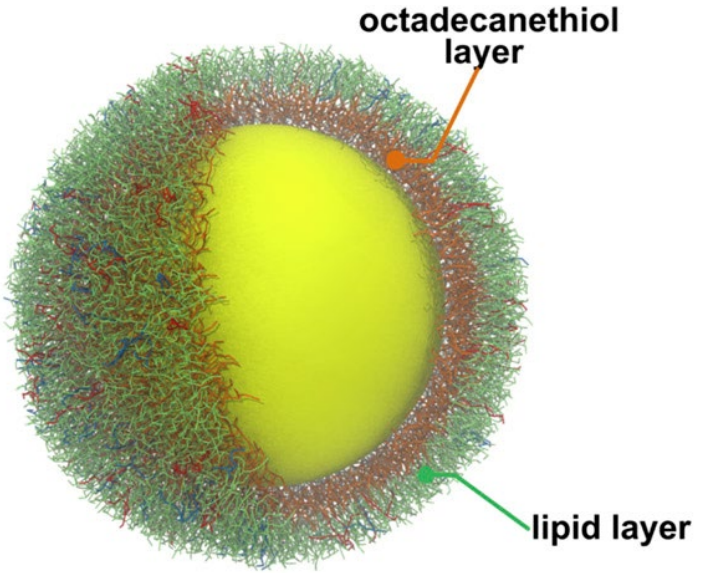


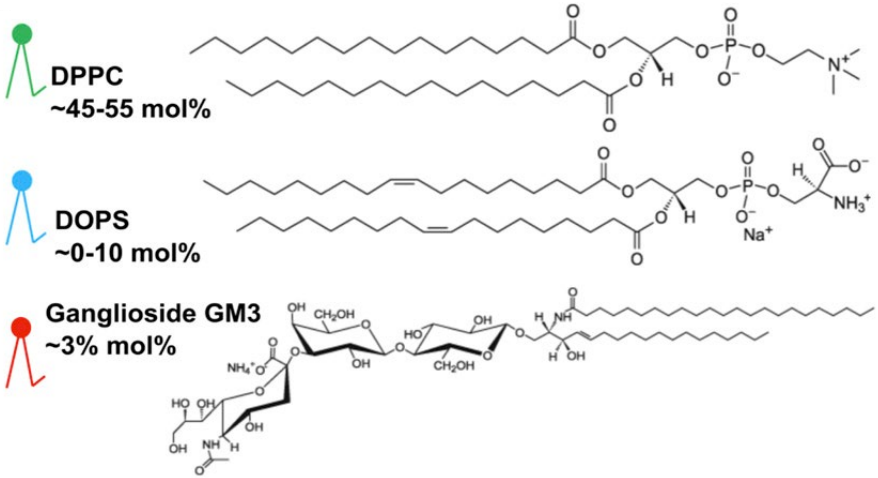
Antiretroviral Strategies Based on Artificial Virus Nanoparticles

Björn Reinhard

Professor
Chemistry, College of Arts and Sciences

Artificial Virus Nanoparticles Target Glycoprotein-Independent, Lipid-Mediated Virus Recognition





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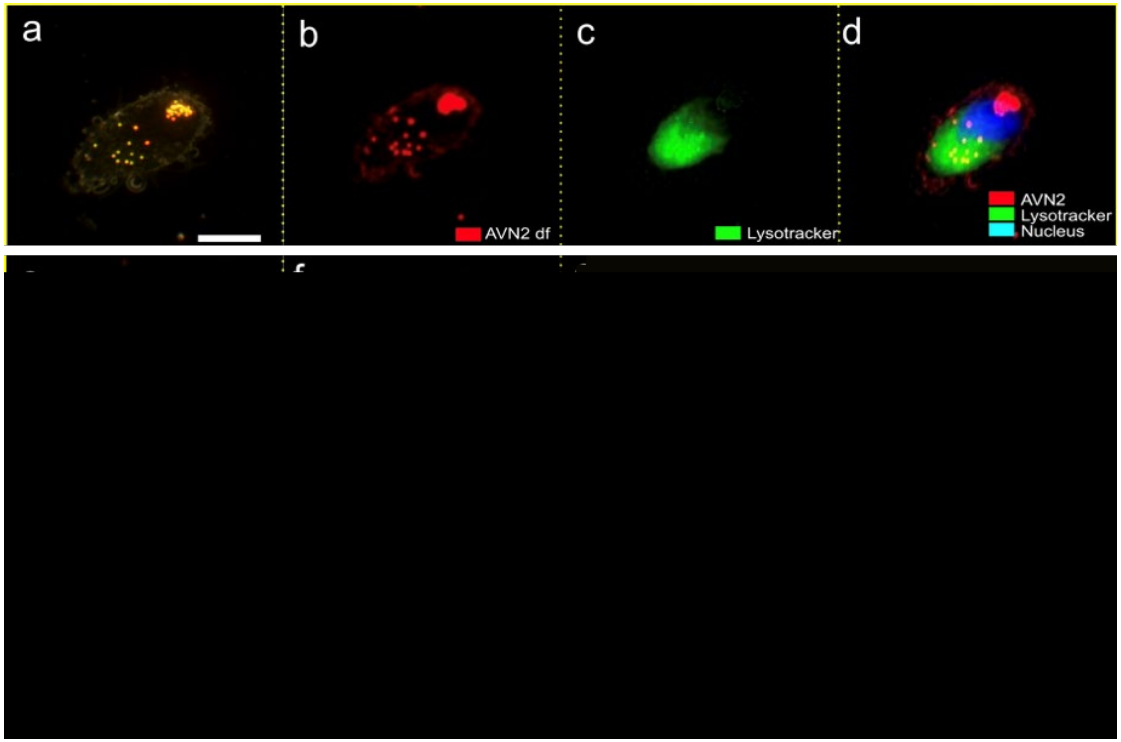
W.B. Puryear et al. PNAS 109, 7475 (2012).
X. Yu et al., Nat. Commun. 5, 4136 (2014).
F. Xu et al, PNAS 115, E9041 (2018).

Artificial Virus Nanoparticles Recapitulate CD169-dependent HIV-1 Uptake and Trafficking

Nanoparticles Escape Endocytosis and Co-localize with Virus Like Particles in Non-Endolysosomal Compartments



Targeting of CD169-expressing myeloid cells in Mouse Lymph Node

Nanoparticle CD169

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X. Yu et al., Nat. Commun. 5, 4136 (2014).
F. Xu et al, ACS Nano 10, 1189 (2016).