T cell control of HIV:
A tale in six brief chapters

New England Cytometry Meeting
October 25, 2018
Chapter 1.
A New Disease
Learning from patients: 1981

• 19 year old male transferred to MGH
  Previously well
    – Profound weight loss
    – TB in sputum, on Rx
    – Acute change in mental status

• Presumptive diagnosis on transfer:
  – Pulmonary TB with TB meningitis
Diagnoses

• Brain:
  – No TB
  – Mass lesion: lymphoma

• Lung:
  – No TB
  – Multiple mass lesions: Kaposi’s sarcoma and pneumocystis pneumonia

• Abdomen:
  – No TB
  – Multiple masses: Kaposi’s sarcoma
  – Disseminated CMV infection of the colon
Chip Schooley and Marty Hirsch, ca. 1984
The life expectancy of Americans with HIV is higher than it was 15 years ago, thanks specifically to the funding of AIDS research.

The National Cancer Institute (NCI) researcher Robert Gallo discovered HIV in 1984, almost reaching the life expectancy of Americans with HIV.

The Montagnier lab -- but not Gallo's. Still, 35 million people have lived with HIV.

It turns out to be an adventitious contaminant of a cell line used by the Montagnier lab.
HIV is an infection of the immune system
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE

INDIVIDUAL NATIONAL RESEARCH SERVICE
AWARD APPLICATION

FOLLOW INSTRUCTIONS CAREFULLY

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☐ PREDOCTORAL  ☑ POSTDOCTORAL  ☐ OTHER:

1. TITLE OF TRAINING PROPOSAL (Do not exceed 56 typewriter spaces)
   CELL MEDIATED IMMUNE RESPONSE TO HTLV-III

2. PROGRAM ANNOUNCEMENT AREA
   NATIONAL INSTITUTES OF HEALTH

3. APPLICANT

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PART 1 (Pages 1 to 5)

OMB NO. 0938-0005
HIV-specific CD8\(^+\) T cells

HIV-specific cytotoxic T lymphocytes in seropositive individuals

Bruce D. Walker*, Sekhar Chakrabarti†,
Bernard Moss†, Timothy J. Paradis*, Theresa Flynn*,
Amy G. Durno*, Richard S. Blumberg*,
Joan C. Kaplan*, Martin S. Hirsch* & Robert T. Schooley*

AIDS virus-specific cytotoxic T lymphocytes in lung disorders

Fernando Plata*, Brigitte Autran†,
Livia Pedroza Martins*, Simon Wain-Hobson*,
Martine Raphaël†, Charles Mayaud‡,
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‡ Service de Pneumologie, Hôpital Tenon, 75010 Paris, France

Nature 328:345, 1987
Nature 328:348, 1987
Chapter 2.
Outliers
1978 2wk pre Thanksgiving

Sex hard to describe

Sudden onset very severe flu
Doing something at death

Sudden feeling of extreme fatigue

"Frozen in mud"

Happened 2-3 times → over 1-2d.

Called NY Hosp → ? must hemorrhage

To hosp not infirm

CT scan → R/l

Infusing factor
Worsening

Ha

7-10 d in hosp.

Samples

Long diagnostic process

? Temps.

? Swollen glands
tion in Si(100) has intriguing consequenc-
es. Besides providing a logical pathway
from adatom adsorption and diffusion to
growth of islands, these chain structures
and their prevalence suggest that the
smallest and most obvious stable structure
on the surface, the ad-dimer residing on
top of the dimer rows, does not participate
to a full extent, but instead may be a part of
metastable structures that may have a va-
riety of sizes.

REFERENCES AND NOTES

1. For a review and an extended list of references, see
Z. Zhang and M. G. Lagally, Science 276, 377
(1997).
2. Y.-W. Mo and M. G. Lagally, Surf. Sci. 248, 313
(1991); Y.-W. Mo, J. Kleiser, M. F. Webb, M. G.
T-helper cells

Cytotoxic T-cells

Infected cell

HAART
HIV-Specific CD4+ T cell Responses following treatment in acute infection
Immune control:
Early treatment of acute HIV infection followed by treatment interruption

Weeks after first treatment interruption

Viral load (copies RNA/mL)
Immune control of HIV-1 after early treatment of acute infection


Partners AIDS Research Center and Infectious Disease Division,
Massachusetts General Hospital and Harvard Medical School, Boston,
Massachusetts 02114, USA

Nature 2000
Immune control of HIV-1 after early treatment of acute infection


Partners AIDS Research Center and Infectious Disease Division, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02114, USA

Nature 2000

Limited Durability of Viral Control following Treated Acute HIV Infection


1 Partners AIDS Research Center, Infectious Disease Unit, Massachusetts General Hospital and Division of AIDS, Harvard Medical School, Boston, Massachusetts, United States of America. 2 Howard Hughes Medical Institute, Massachusetts General Hospital and Division of AIDS, Harvard Medical School, Boston, Massachusetts, United States of America

PLoS Medicine 2004
Chapter 3.
Insights from a raging epidemic
Emerging evidence from Africa of the importance of HIV-specific CTL

- Transmission of CTL escape variants to neonates
- Impact of HLA-B alleles on immune control
- PD-1 expression and HIV-specific T cell exhaustion
- Importance of Gag-specific T cell responses and control
The breadth of the Gag-specific CD8 response is associated with lower viral load.

The breadth of the Env-specific CD8 response is associated with higher viral load

Chapter 4.
A late night conversation
RNA particles/ml plasma

CD4 Cell Count

Viral Load

30 years
The International HIV Controllers Study

Are you HIV positive with a low viral load, without medications? You could help us better understand HIV. Consider enrolling in our study.

The goal of the International HIV Controllers Study is to help scientists understand why some people are able to control HIV infection without the need to take any medications. These findings could assist in the development of vaccines and new therapies.

www.hivcontrollers.org
Genome-Wide Association Study: HIV control is associated with chromosome 6 polymorphisms

- 313 SNPs in HLA reach $p<5\times10^{-8}$
- 974 controllers and 2648 progressors

The Major Genetic Determinants of HIV-1 Control Affect HLA Class I Peptide Presentation

The International HIV Controllers Study*†

Chapter 5.
Science and Social Good
Female HIV Prevalence by Age: KwaZulu Natal

Annual Incidence: 9.1%

Kharsany AB, et al. JAIDS 2015; 70(3): 289–95
FRESH Study (2012-Present):
Females Rising through Education, Support and Health

Goals:  1. HIV prevention and poverty reduction
2. Immunology of hyperacute infection

http://www.ragoninstitute.org/international/fresh/
Learning from patients: Hyperacute HIV Infection

Set point viremia predicts disease outcome
Video linked in this article:

https://www.massgeneral.org/News/pressrelease.aspx?id=2290
FRESH Study

• Subjects:
  – Uninfected 18-23 year old women at high risk of HIV infection in an impoverished township

• Methods:
  – Provide a twice weekly empowerment, life skills, job readiness and HIV prevention education with the goal of employment after one year
  – Test twice weekly for HIV RNA by finger prick
K-RITH: KwaZulu Natal Research Institute for TB and HIV
Kinetics of Hyperacute HIV Infection

Ndhlovu et al, *Immunity* 2015
Dong et al, *Lancet HIV* 2017
Massive HIV-specific T cell activation in acute HIV infection

Days following onset of plasma viremia (DFOPV)

Percent CD38+HLA DR+

Days: 0 20 40 60 80 100

Percentages: 0 36 186 102 039 267 309 093 271 198 268 208
Hyperacute HIV Infection

No Treatment

Atripla

Ndhlovu et al, *Immunity* 2015
Dong et al, *Lancet HIV* 2017
Ndung’u et al, *Science Immunology* 2018
Early treatment leads to enhanced HIV-specific CD8$^+$ T cell function

Untreated

Tetramer

Tetramer

Treated

CD127

3.8

85.9
Robust CD4^{+} T cell responses in treated acute HIV infection

Ndhlovu et al, unpublished
HIV Gagp24 staining of a LN tissue from an early treated subject
Chapter 6.
Stock Markets and Social Networks
“A successful vaccine must do better than natural immunity to HIV”
“A successful vaccine must do as well as the best natural immunity to HIV”
Measures of conservation: Sequence analysis

- Based on available sequence data
- Measures mutability of single amino acids
- Does not incorporate amino acid interactions or protein structure
- Does not correlate with fitness
Can we identify a subset of conserved residues that incur a maximal viral fitness cost?
Can we identify a subset of conserved residues that incur a maximal viral fitness cost?
Measures of conservation:
Fitness Landscapes

- Based on available sequence data
- Employs analysis tools used in the stock market
- Measures interdependence of amino acid mutations
- Suggests structural features are linked to fitness (Gag Capsid)

Dahriel et al, *PNAS* 2011
Ferguson et al, *Immunity* 2013
What can we learn from protein structure?

Structure-based Network Analysis (Think social networks)
Gaurav Gaiha, MD, PhD

Elizabeth Rossin, MD, PhD
Amino acid properties affect protein folding

Glycine

\[
\begin{align*}
\text{H} & \\
+\text{H}_3\text{N} \text{--C--COO}^- & \\
\text{H} & 
\end{align*}
\]

\[G\]

Tryptophan

\[
\begin{align*}
\text{HN} & \\
+\text{H}_3\text{N} \text{--C--COO}^- & \\
\text{CH}_2 & \\
\text{H} & 
\end{align*}
\]

\[W\]
Amino acid side chains influence structure

Covalent bonds

Intermolecular bonds
Proteins act as networks

Provides **LOCAL** and **GLOBAL** insight by transforming the system to **NODES** and **EDGES**

**NODE** = Amino Acid
**EDGE** = Intermolecular Interaction
Structure-based Network Analysis

INPUT: 3-dimensional atomic level data from PDB file
Concepts from Network Theory
– Degree Centrality

A measure of **LOCAL** Importance – # of Connections

Greater size = greater magnitude
Concepts from Network Theory—Betweenness Centrality
A measure of GLOBAL Importance – Involvement in Bridges

Greater size = greater magnitude
The purpose of this Funding Opportunity Announcement (FOA) is to solicit grant applications that propose to establish Consortia for HIV/AIDS Vaccine Development (CHAVD) to support a coordinated, multidisciplinary team(s) of researchers focused on iterative approaches to accelerate HIV vaccine development by addressing key immunogen design roadblocks to the discovery and development of a safe and effective antibody-mediated preventive HIV vaccine.

The following activities will NOT be supported by this FOA:

- Vaccine protection where the major mechanism of protection is not antibody-mediated
T cell-directed therapy in Melanoma
Conclusions

• Durable natural immune control and possibly cure of HIV is achievable

• Durable immune control is mediated by CTL targeting of highly networked epitopes, providing a rational approach for HIV immunogen design

• Immediate treatment of hyperacute infection leads to induction of HIV-specific CD4 and CD8 T cells with enhanced function, and provides an ideal model for iterative immunotherapeutic intervention studies