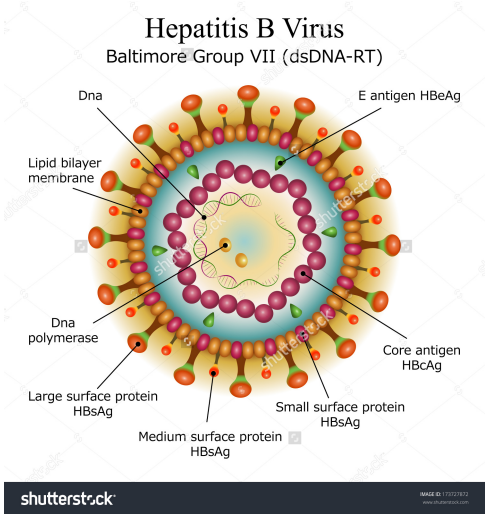
SIAM Dynamical Systems, Snowbird, UT
May 19, 2019



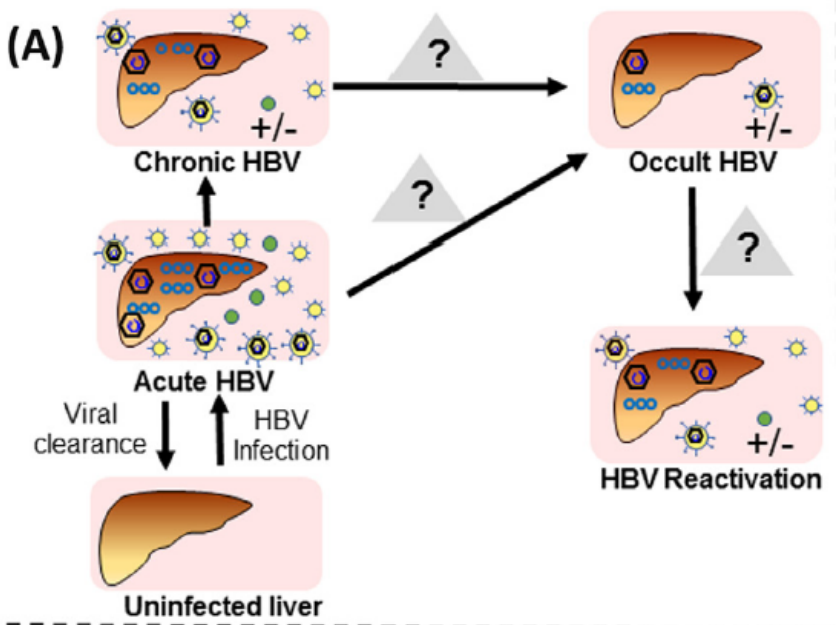
Early events during hepatitis B virus infection

Stanca Ciupe
Virginia Tech

Department of Mathematics

Types of hepatitis B infections

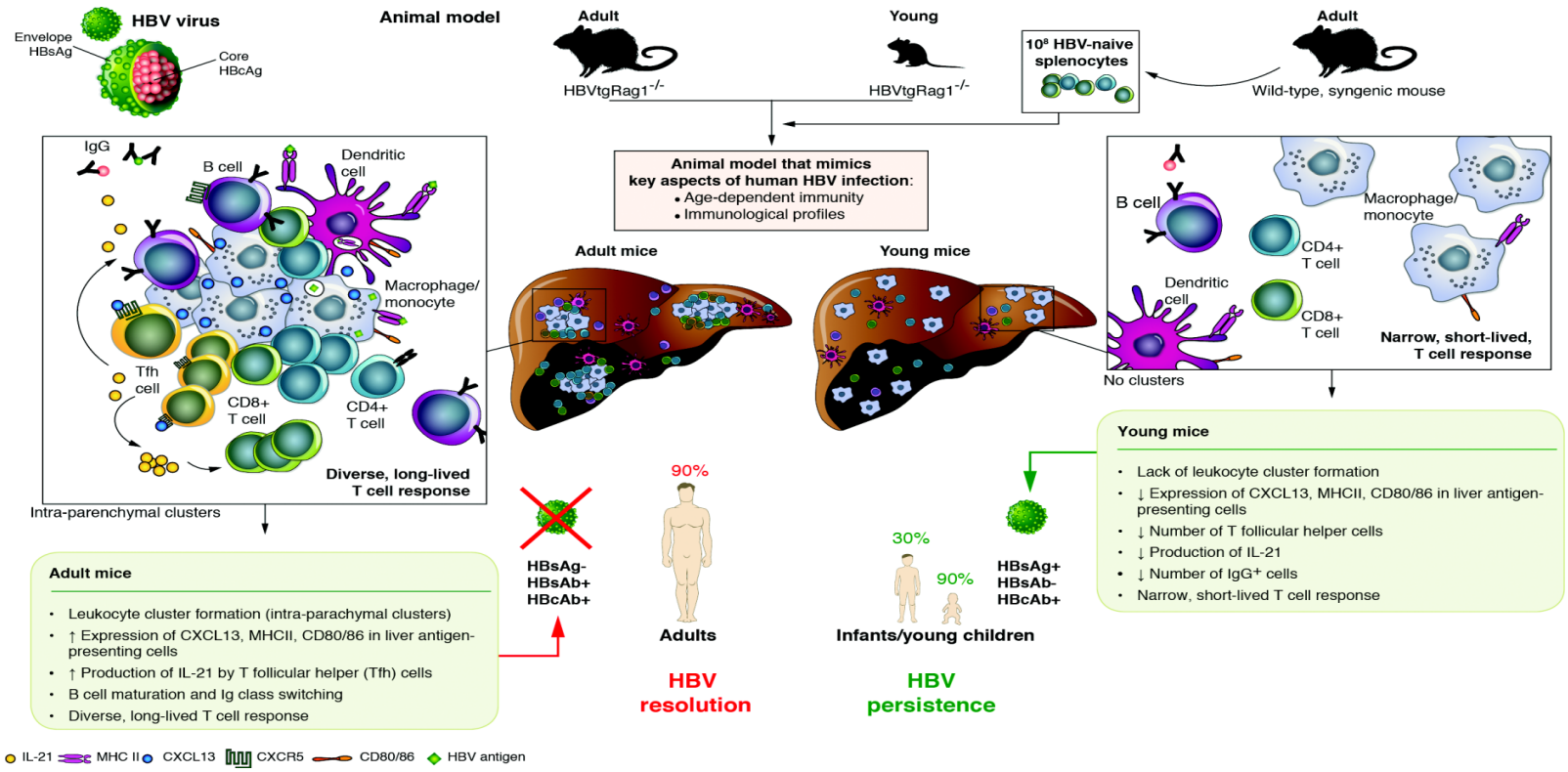
- pdsDNA virus that infects the liver
- Acute infections
  - Occurs in 85-90% of adult infections
  - High virus load that is cleared in less than a year
  - Results in long lasting immunity
- Chronic infections
  - 95% of prenatal transmissions
  - 50% in young children infections
  - leads to cirrhosis and hepatocellular carcinoma



Goyal, JTB 2018

- It is believed that the difference between acute and chronic disease is host mediated with immune responses being responsible for liver disease

Age-influenced immune priming determines disease outcome



Baron, J Clin Invest 2011, 2013, Hepat 2016

Are early virological and immunological events important in disease resolution?

- Is initial immune priming relevant for protection?
- Is the initial virus more or less fit?
- Virus kinetics versus immune kinetics?
- Virus magnitude versus immune response magnitude?

Relationship between virus stages of infection (and inoculum size) and disease outcome: HIV/SIV

Journal of Virology

High Specific Infectivity of Plasma Virus from the Pre-Ramp-Up and Ramp-Up Stages of Acute Simian Immunodeficiency Virus Infection

Zhong-Min Ma, Mars Stone, Mike Piatak Jr., Becky Schweighardt, Nancy L. Haigwood, David Montefiori, Jeffrey D. Lifson, Michael P. Busch and Christopher J. Miller

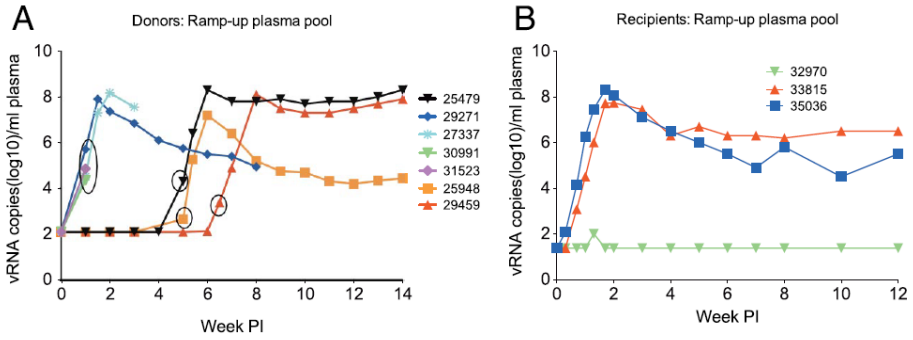
J. Virol. 2009, 83(7):3288. DOI: 10.1128/JVI.02423-08. Published Ahead of Print 7 January 2009.

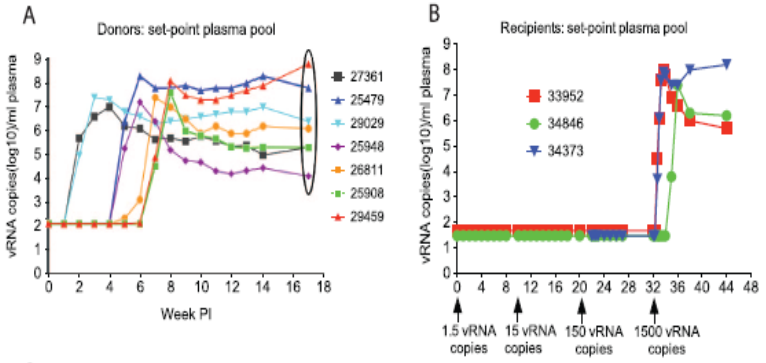
frontiers in Microbiology

ORIGINAL RESEARCH
published: 06 June 2018
doi: 10.3389/fmicb.2018.01216

A Bistable Switch in Virus Dynamics Can Explain the Differences in Disease Outcome Following SIV Infections in Rhesus Macaques

Stanca M. Ciupe[1], Christopher J. Miller[2] and Jonathan E. Forde[3]*





- Later virus is less infectious due to the presence of immune modulators.

Relationship between virus stages of infection (and inoculum size) and disease outcome: HBV

PNAS

Genomic analysis of the host response to hepatitis B virus infection

Stefan Wieland*, Robert Thimme*†, Robert H. Purcell‡, and Francis V. Chisari*§

*Department of Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, CA 92037; and ‡Hepatitis Viruses Section, Laboratory of Infectious Diseases, National Institutes of Health, Bethesda, MD 20892-8009

Contributed by Francis V. Chisari, March 12, 2004

Journal of Medical Virology 80:2064–2068 (2008)

Titration of Hepatitis B Virus Infectivity in the Sera of Pre-Acute and Late Acute Phases of HBV Infection: Transmission Experiments to Chimeric Mice With Human Liver Repopulated Hepatocytes

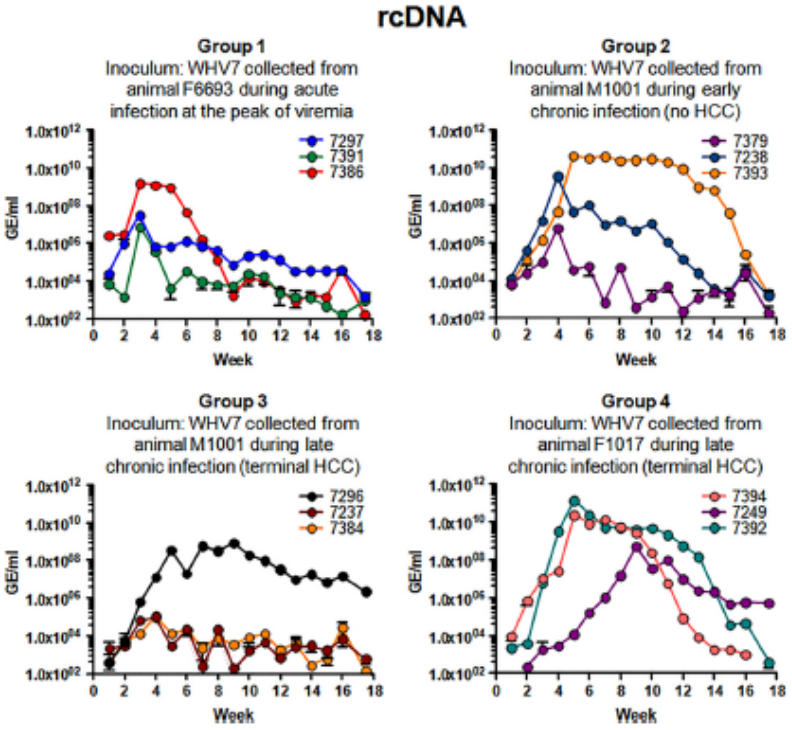
Ayako Tabuchi,[1] Junko Tanaka,[1]* Keiko Katayama,[1] Masaaki Mizui,[2] Harumichi Matsukura,[3] Hisao Yugi,[4] Takashi Shimada,[5] Yuzo Miyakawa,[6] and Hiroshi Yoshizawa[1]

JVI Journals.ASM.org

Infection Patterns Induced in Naive Adult Woodchucks by Virions of Woodchuck Hepatitis Virus Collected during either the Acute or Chronic Phase of Infection

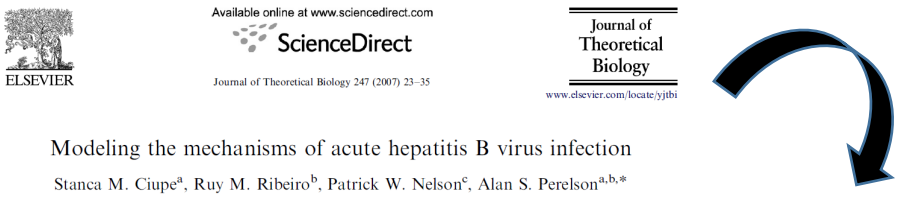
Natalia Freitas,[a] Tetyana Lukash,[a] Louise Rodrigues,[a] Sam Litwin,[b] Bhaskar V. Kallakury,[c] Stephan Menne,[d] Severin O. Gudima[a]

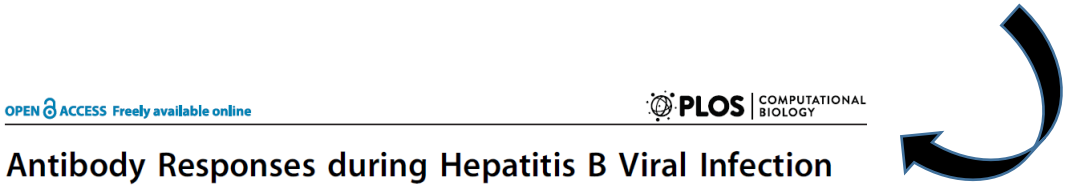
Department of Microbiology, Molecular Genetics and Immunology, University of Kansas Medical Center, Kansas City, Kansas, USA[a]; Biostatistics and Bioinformatics Facility, Fox Chase Cancer Center, Philadelphia, Pennsylvania, USA[b]; Department of Pathology, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC, USA[c]; Department of Microbiology and Immunology, Georgetown University Medical Center, Washington, DC, USA[d]



- No decrease in virus infectivity during later stages.
- Consistent results for high virus inoculation regardless of age, size, sex and monkey
- genetics (stealth virus early on).

Immune responses essential in resolution of adult infections





While stages of infection do not mater, inoculum size does!

JOURNAL OF VIROLOGY, Oct. 2009, p. 9652–9662
0022-538X/09/$08.00+0 doi:10.1128/JVI.00867-09

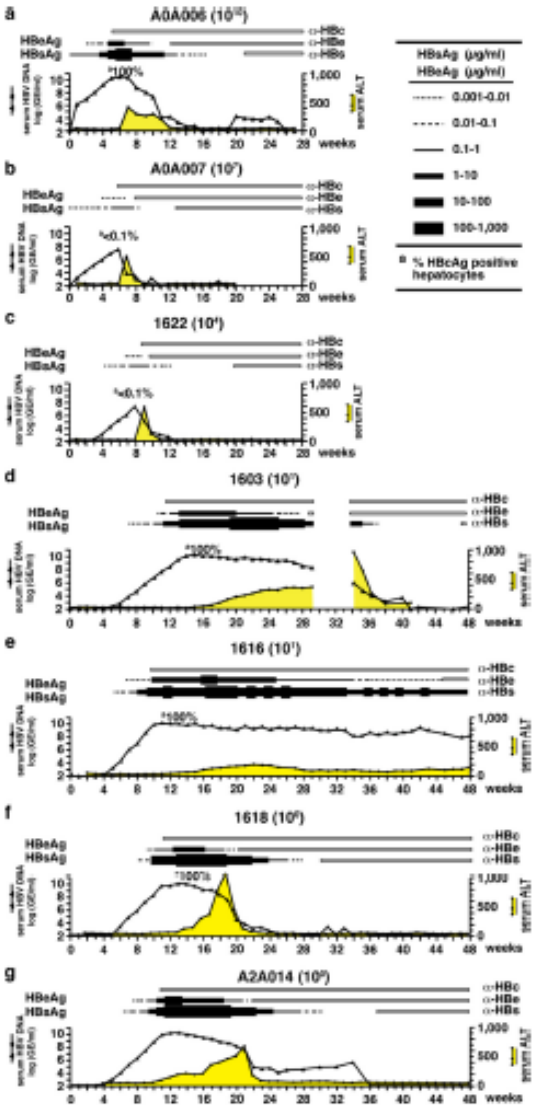
Vol. 83, No. 19

The Size of the Viral Inoculum Contributes to the Outcome of Hepatitis B Virus Infection▽†

Shinichi Asabe,[1] Stefan F. Wieland,[1] Pratip K. Chattopadhyay,[2] Mario Roederer,[2] Ronald E. Engle,[3] Robert H. Purcell,[3] and Francis V. Chisari[1]*

Department of Immunology and Microbial Science, The Scripps Research Institute, La Jolla, California 92037[1]; Immuno Technology Section, Laboratory of Immunology, Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892[2]; and Hepatitis Viruses Section, Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892[3]

Received 30 April 2009/Accepted 13 July 2009



- Seven HBV negative chimps were inoculated with serial dilutions of monoclonal HBV isolates: 10^{10}, 10^{7}, 10^{4}, 10^{1} (two), 10^{0} (two) GE.
- High and low dose infected 100% of the liver.
- Intremediate dose 10^{7} and 10^{4} infected 0.1% of the liver.
- CD 4 T cell priming similar for 10^{10} and 10^{0} GE.
- CD4 T cell priming delayed for 10^{1} GE.

Role of CD4 T cell in CD8 T cell priming is controversial

➢Not needed in acute infections, needed for memory activation?

European Journal of Immunology Antigen processing

CD4 T cell help is required for primary CD8 T cell responses to vesicular antigen delivered to dendritic cells *in vivo*

Karine Serre[1,2,3], *Laurent Giraudo*[1,2,3], *Carole Siret*[1,2,3], *Lee Leserman*[1,2,3,4] *and Patrick Machy*[1,2,3]

$CD4^+$ T cells are required for secondary expansion and memory in $CD8^+$ T lymphocytes

Edith M. Janssen*, Edward E. Lemmens*, Tom Wolfe†, Urs Christen†, Matthias G. von Herrath† & Stephen P. Schoenberger*

** Division of Cellular Immunology and † Division of Developmental Immunology, La Jolla Institute for Allergy and Immunology, 10355 Science Center Drive, San Diego, California 92121, USA*

Outcome of Acute Hepatitis C Is Related to Virus-Specific CD4 Function and Maturation of Antiviral Memory CD8 Responses

Simona Urbani, Barbara Amadei, Paola Fisicaro, Daniela Tola, Alessandra Orlandini, Luca Sacchelli, Cristina Mori, Gabriele Missale, and Carlo Ferrari

The Journal of Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America hivma hiv medicine association OXFORD

$CD4^+$ T Cells Are Not Required for Suppression of Hepatitis B Virus Replication in the Liver of Vaccinated Chimpanzees

Jolanta Rybczynska,[1,2] Katherine Campbell,[3] Saleem Kamili,[2] Stephen Locarnini,[5] Krzysztof Krawczynski,[2] and Christopher M. Walker[3,4]

[1]Department of Pathology, Medical University of Warsaw, Poland; [2]Division of Viral Hepatitis, Centers for Disease Control and Prevention, Atlanta, Georgia; [3]Center for Vaccines and Immunity, Nationwide Children's Hospital, [4]Department of Pediatrics, College of Medicine, The Ohio State University, Columbus; and [5]Victorian Infectious Disease Reference Laboratory, North Melbourne, Australia

What is the role of CD8 T cell in HBV and ALT kinetics? Does it correlate with CD4 T cell data?

$$\frac{dT}{dt} = rT(1-\frac{T+I}{K}) - \beta TV$$

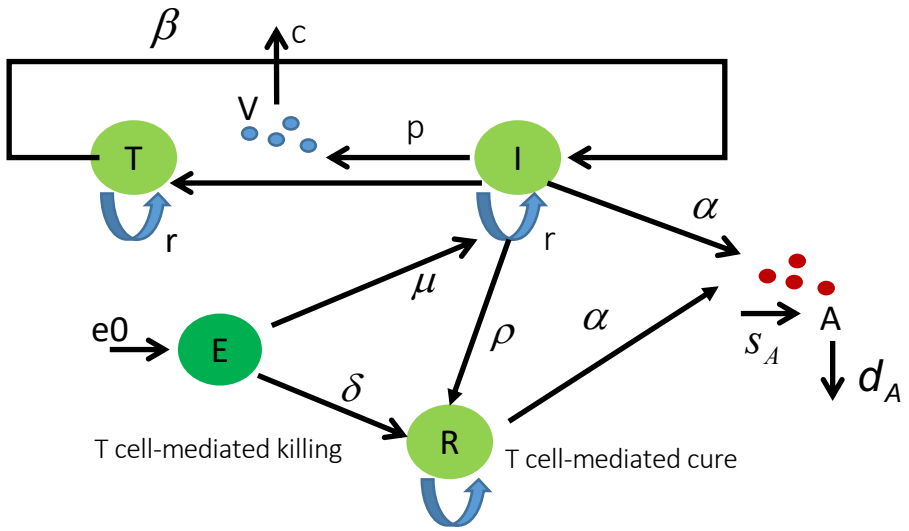
$$\frac{dI}{dt} = rI(1-\frac{T+I}{K}) + \beta TV - \mu E_8 I - \rho E_8 I$$

$$\frac{dV}{dt} = pI - cV$$

$$\frac{dA}{dt} = s_A + \alpha\mu IE_8 + \alpha\delta R - d_A A$$

$$\frac{dR}{dr} = rR(1-\frac{T+I+R}{K}) + \rho E_8 I - \delta E_8 R$$

$$E_8 = e_0 + \alpha_E \frac{t^n}{t^n + \tau_4^n}$$



T	Uninfected liver cells
I	Infected liver cells
V	HBV
A	ALT
E8	CD8 T cells
R	Cells refractory to reinfection

Ciupe et al., in preparation

Fitting procedure

- Functional we want to minimize

$$J = \sum_{i=1}^{n} \frac{\log(V_{data}(t_i)) - \log(V(t_i))}{\max \log V_{data}} + \sum_{i=1^n} \frac{\log(A_{data}(t_i)) - \log(A(t_i))}{\max \log A_{data}} + (\frac{I}{T_m} - L_{tot})$$

- Parameter space:

$0 < p < 5000$

$10^{-11} < \beta < 10^{-9}$

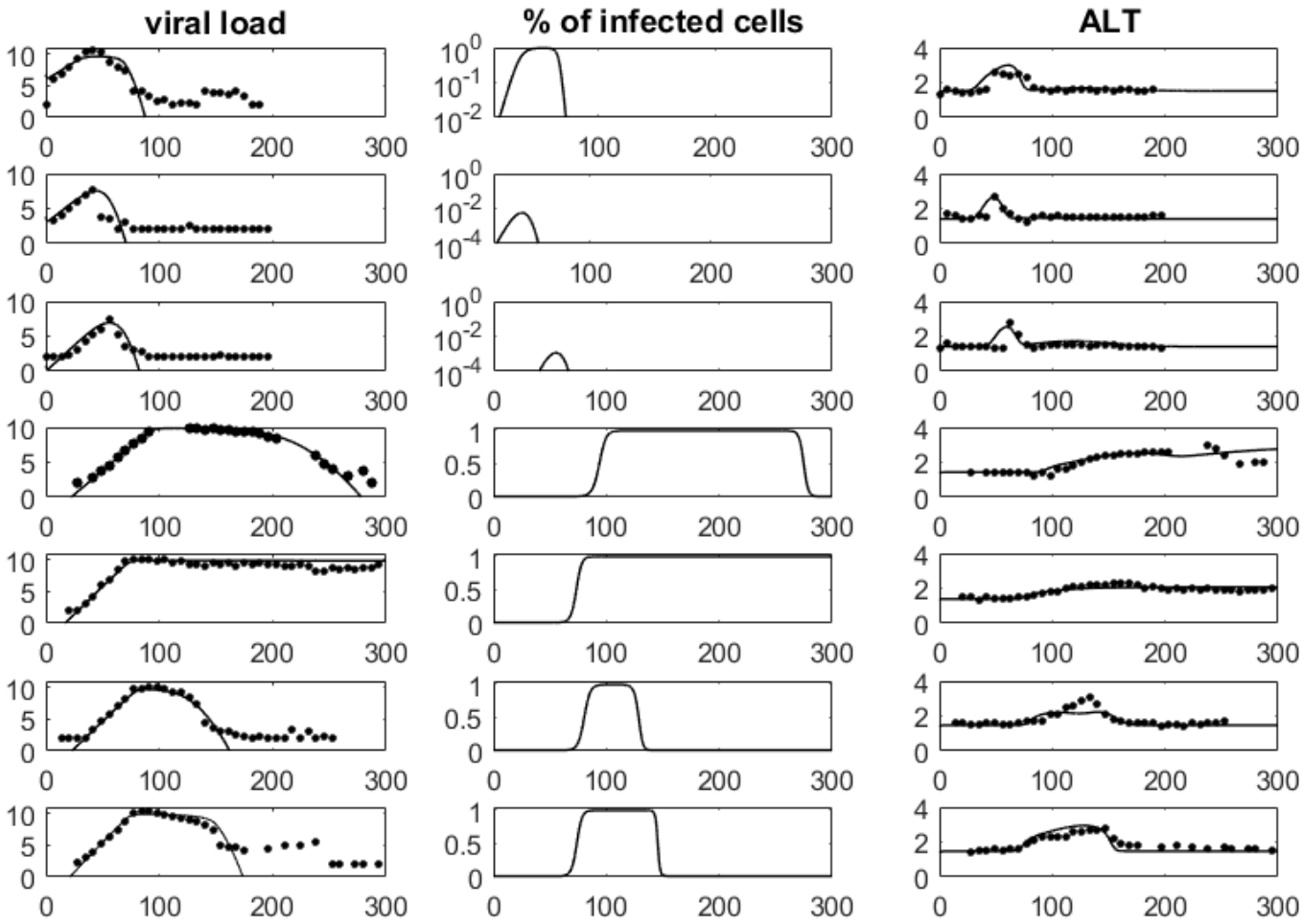
$0 < \alpha_A < 1$

$0 < E_4 < 1000$

$0 < \mu < 1$

- Procedure: fminsearch and fminbnd in MATLAB.

Results


viral load
% of infected cells
ALT
V(0)=10^{10} GE
V(0)= 10^{7} GE
V(0)= 10^{4} GE
V(0)= 10 GE
V(0)=0.1 GE

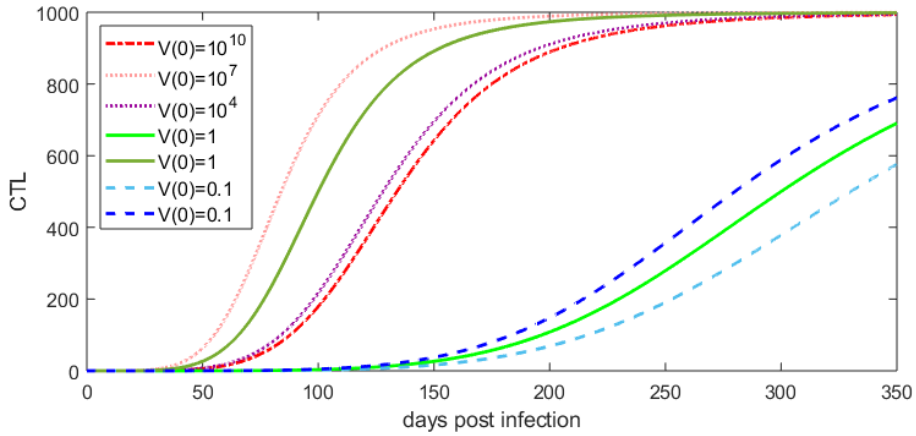
Parameter estimates

Monkey	p	$\alpha \times 10^{-4}$	μ	$\beta \times 10^{-11}$	E_4	s_A	ρ	δ
ChA006	600	2	0.031	6.2	134	22	4×10^{-4}	6×10^{-5}
ChA1007	778	100	0.010	5.3	84	17	4×10^{-4}	6×10^{-5}
ChA1622	933	450	0.022	5.4	128	17	10^{-2}	6×10^{-5}
ChA1603	912	6	0.0009	5	300	18	4×10^{-4}	6×10^{-5}
ChA1616	980	0.5	0.0009	6.2	100	16	10^{-6}	6×10^{-5}
ChA1618	800	1	0.052	7.5	330	20	2×10^{-2}	10^{-2}
ChA0014	990	1.5	0.0126	6.7	280	20	4×10^{-4}	6×10^{-5}

- Delayed CD8 T cell expansion for super low inoculum of 1 GE.
- CD8 T cell **exhaustion** for low inoculum of 10 GE.
- Similarity in the strength of CD8 T cell response between super low and high dose.
- Strong non-cytolytic response for one subject on low inoculum, similar to 10^4 GE.

- **No synchrony between CD4 T cell results and CD8 T cell dynamics!**

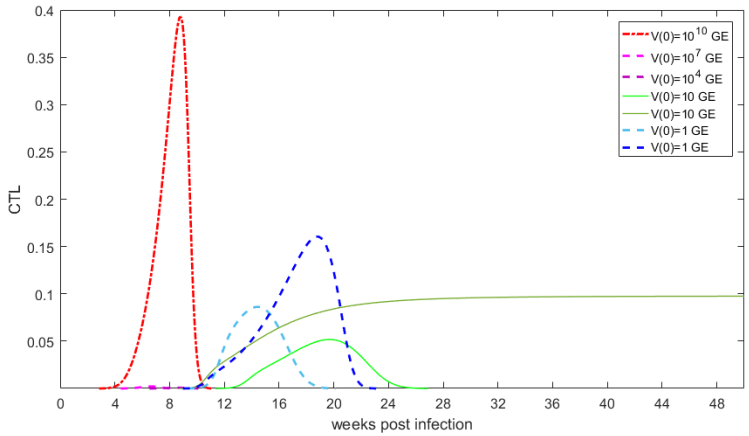
Half-maximal CD8 T cell expansion does not correlate with CD4 T cell priming.

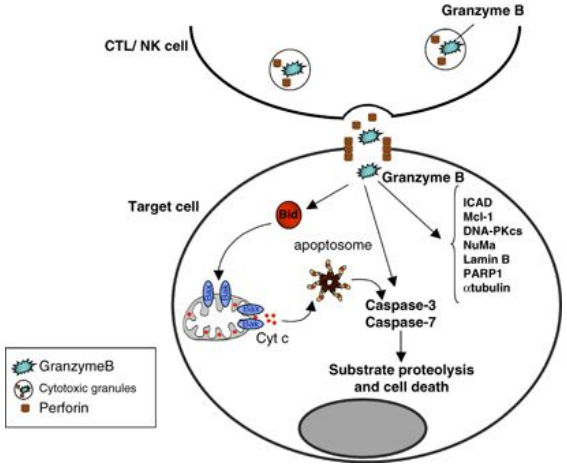


Dose	τ_4 from simulations	CD4 T cell priming from experiment
10^{10} GE	Week 19	Week 3
10^{7} GE	Week 12	Week 1
10^{4} GE	Week 18	Week 3
10 GE	Week 42	Week 13
10 GE	Week 14	Week 13
1 GE	Week 47	Week 7
1 GE	Week 40	Week 7

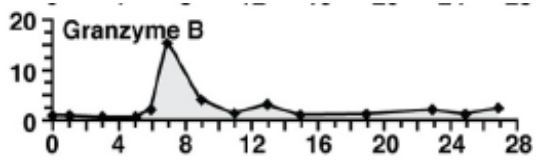
Timing of the combined cytolytic and non-cytolytic effects is similar with the timing of cytokine production.

$$\text{Percent CTL effect} = \frac{\mu I(t)E_8(t) + \rho I(t)E_8(t)}{T(t) + I(t) + R(t)}$$

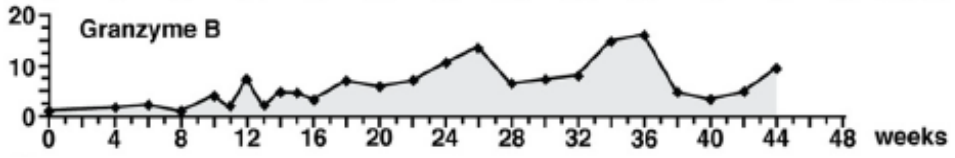




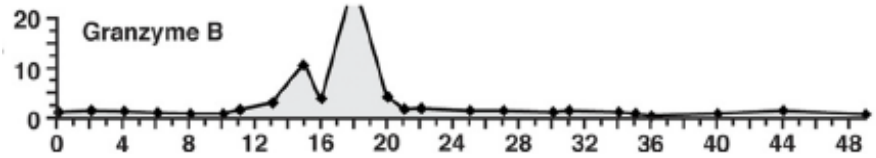
Cell Death & Differentiation
ISSN 1476-5403 (online)



Ch A006



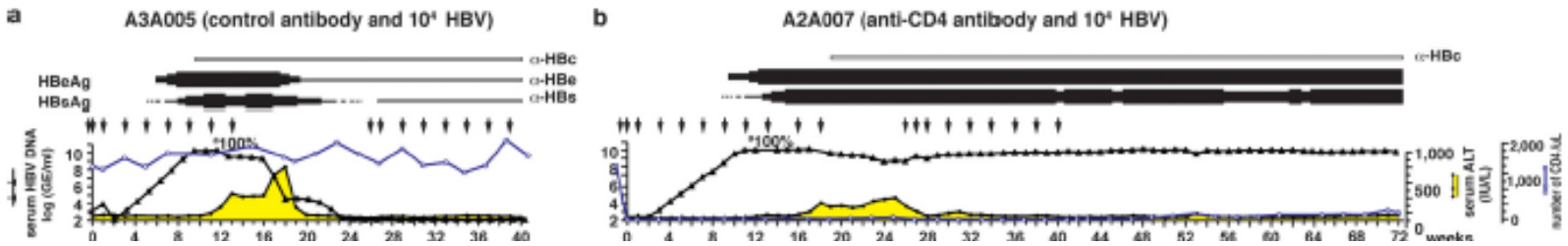
Ch 1616



Ch 1618

How do CD8 T cell dynamics (half-maximum stimulations τ_4) change when CD4 T cells are knocked out?

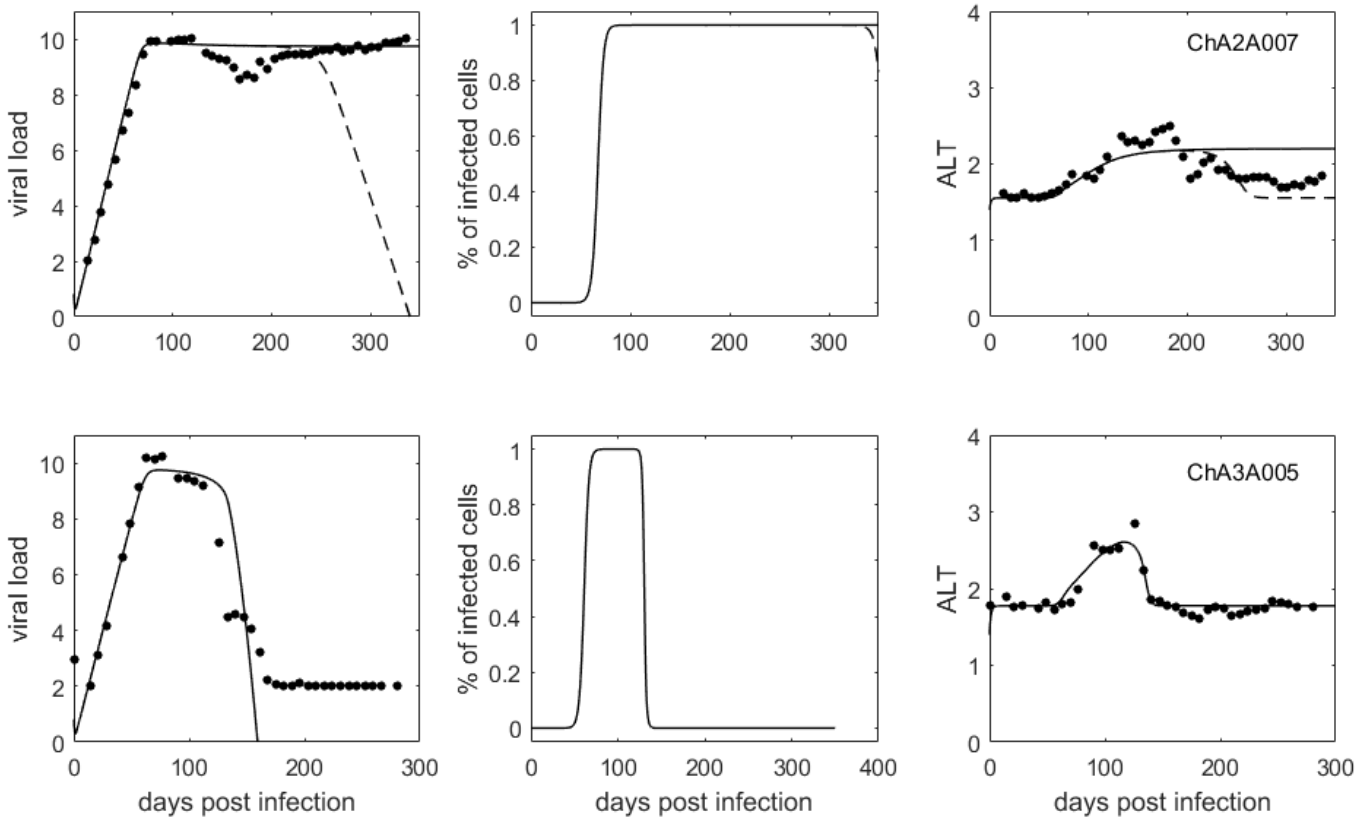
- Two additional monkeys were infected with 10^4 GE.
  - One was treated with an anti-CD4 antibody;
  - The other was treated with a control antibody;



- Both led to 100% liver infection;

- First had chronic disease;
- The second had acute disease.

Data fitting results



Results

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ChA006	600	2	0.031	6.2	134	22	4×10^{-4}	6×10^{-5}
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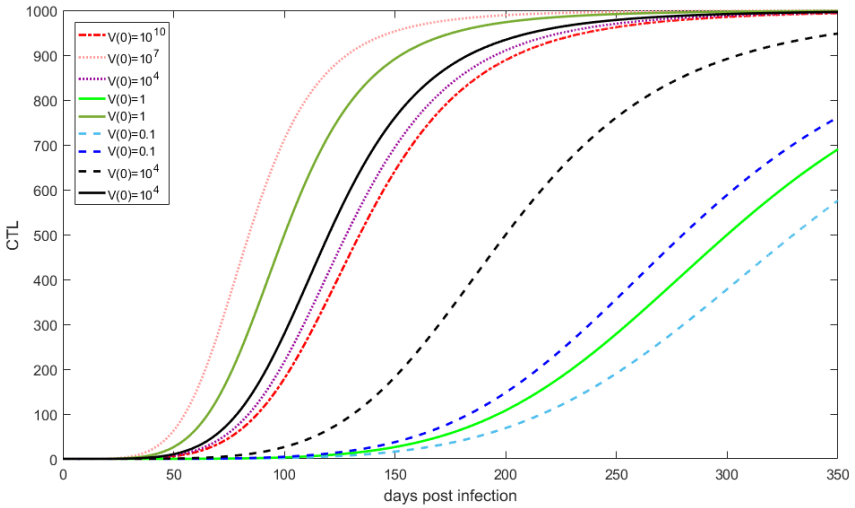
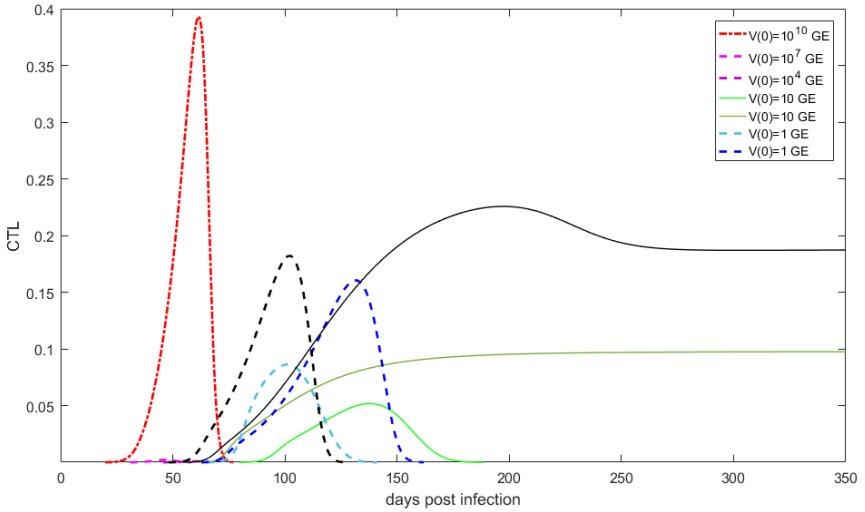
ChA0014	990	1.5	0.0126	6.7	280	20	4×10^{-4}	6×10^{-5}
ChA2007	891	0.34	0.00024	5.5	120	24	10^{-8}	6×10^{-5}
ChA3005	723	0.6	0.009	7	200	40	4×10^{-4}	6×10^{-5}

- The CD4 T cell immunocompromised monkey has **exhausted** CD8 T cell function.
- ChA3 005 has intermediate CD8 T cell function.

Tradeoff between inoculum size and CTL strength





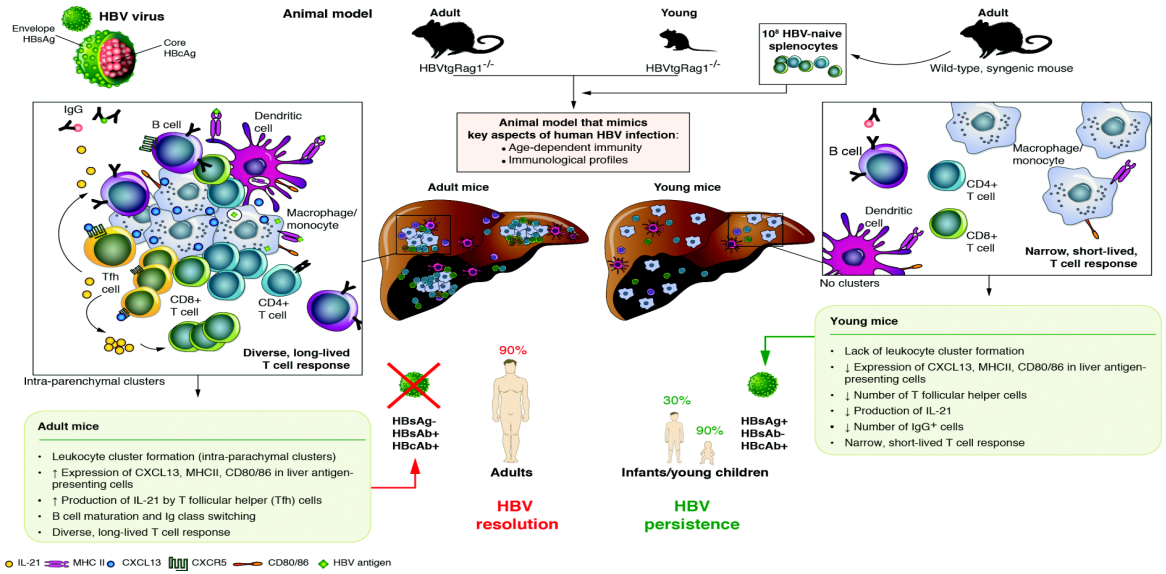
Conclusions

- Early CD4 T cell priming synchronizes with potent CD8 T cell response, rather than CD8 T cell expansion.
- Delayed CD4 T cell priming correlates with **CD8 T cell exhaustion.**

- Correlation between the CD4 T cell priming , percentage of infected liver cells and persistence.
- Correlation between peak immune response and CTL markers (granzyme B, perforin, PD-1, FAS-L).

- Why does medium inoculum dose lead to 100% liver infection?
- Need a better definition for the cut-off between high, intermediate and low doses.

Are CD4 T cells needed for CD8 T cell responses? What is their role in protection? How can this inform management of chronic infection?



➢Our results suggest that CD4 T cell priming prevents CD8 T cell exhaustion: **quality rather than quantity** important for protection.

Acknowledgements

- Jonathan Forde, Hobart and William Smith Colleges
- Naveen Vaidya, San Diego State University
- Frank Wieland, The Scripps Research Institute