

CAMB 546 – Seminar in Medical Virology

(revised 8/17/2010)

Spring Semester 2010

Thursday 3-5 pm

Room – 501 Johnson

First date: 1/13/2010

Last date: 4/22/2010

Holidays: 3/11/2010 (break)

14 classes total

A. Title - Seminar in Medical Virology: HIV Pathogenesis

B. Description: This course will introduce students to basic principles of viral pathogenesis, using HIV as a model. The focus will be on illustrating specific elements that relate to disease development, emphasizing (a) molecular virology, (b) pathogenesis, (c) immunology, (d) vaccine development. Offered spring semester

C. Course Directors (team-taught):

Drew Weissman	dreww@mail.med.upenn.edu	215-614-0291
Ron Collman	collmanr@mail.med.upenn.edu	215-898-0913
Rick Bushman	bushman@mail.med.upenn.edu	215-573-8732
Luis Montaner	montaner@wistar.upenn.edu	215-898-9143

D. Students:

E. Plan: One two-hour class weekly for the course of the semester. The first class will be an organizational class, where students select dates/seminars and reading material is distributed, and an introductory lecture. The seminars will begin in week 2.

For each class, one student will present a brief (~20 minute) background presentation of the topic chosen, followed by presentation and discussion of one to two related articles. The student should meet with the course director assigned to each topic in preparation for their session (likely several times), to provide additional papers for background, to assist in focusing the student's introductory presentation, and in helping analyze the articles. The articles should be distributed by the student via E-mail one week before they are to be discussed. The other students are expected to read the papers in advance and be prepared to participate in the discussion.

To aid in the understanding of the papers and to develop the ability to think beyond the papers, we ask that each student should prepare a short written description of the next hypothesis and experiments that is suggested by the paper. With this, we would like the students to develop the ability to synthesize the data and hypotheses within the paper and develop in their own mind the ability to look beyond the trees and see the forest. Students are encouraged to meet with the course directors if they are having problems reading and understanding the papers or developing what to do next ideas. Of note, if the discussion of the paper says, we will do these experiments *in vivo* next, we do not want you to simply repeat that back.

F. Prerequisites: A strong background in cell biology, immunology or virology is needed, but specific particular prerequisite courses are not necessarily required. This background could be provided by previous BGS courses for 1st year CAMB students or Module 1 of the medical school curriculum for combined degree students. Alternatively, a very strong undergraduate program could also provide sufficient background. BGS students from grad groups other than CAMB and any others not included in the above two groups need permission of the course director to enroll.

Students who need permission of the course director should contact him prior to the first class to determine if their background is appropriate. The course will be offered spring semester (a fall semester offering would not be suitable as first year students would likely not have sufficient background at that point).

G. Ensuring preparation and participation: Preparation and participation by all students is critical for the class to be interesting and successful. The grade is determined by both the presentation that each student does and the weekly participation by each student in the discussions. Students who feel they have difficulty talking in class or becoming part of a discussion are encouraged to talk to the course directors and will likely be approached by the course directors. The instructors will provide mid-course feedback to each student to help guide class participation in discussions.

H. Basis for grades: Grades will be based on (a) weekly preparation and participation in class discussions, (b) student seminar presentations, (c) weekly hypothesis write up, and (d) improvement over the course of the semester. The designated faculty member should meet with the student presenter after their presentation to provide feedback in real-time. In addition, mid-course feedback will be provided to each student regarding their preparation and participation in discussions.

I. Introductory handout topics:

- Viral entry
- HIV dynamics
- Reservoirs
- HIV integration & novel drug targets
- Vif & innate antiviral resistance
- Pathogenic & nonpathogenic infection
- Budding and maturation
- Reverse transcription

J. Schedule & Seminar Topics (3-5 pm on Thursdays):

Spring 2005	Topic	Instructor	Student
14-Jan	Organizational		
21-Jan	Intro lectures		
28-Jan	Entry and drug resistance	meg	
4-Feb	Reverse transcription	meg	
11-Feb	HIV integration		
18-Feb	Innate anti-viral response		
25-Feb	Humoral immunity		
5-Mar	Cellular immunity		
19-Mar	Transmission		
26-Mar	Pathogenic versus nonpathogenic infection	Mirko	
1-Apr	GALT and in vivo targets	Mirko	
8-Apr	Cell-cell transmission		
15-Apr	Vaccines		
22-Apr	Negative regulation of immune responses		

K. Topics and articles (subject to modification)

1. Entry and drug resistance Collman
 - a. Trkola A, Kuhmann SE, Strizki JM, Maxwell E, Ketas T, Morgan T, Pugach P, Xu S, Wojcik L, Tagat J, Palani A, Shapiro S, Clader JW, McCombie S, Reyes GR, Baroudy BM, Moore JP. HIV-1 escape from a small molecule, CCR5-specific entry inhibitor does not involve CXCR4 use. Proc Natl Acad Sci U S A. 2002 Jan 8;99(1):395-400.
 - b. Chan DC, Fass D, Berger JM, Kim PS. Core structure of gp41 from the HIV envelope glycoprotein. Cell. 1997 Apr 18;89(2):263-73.

2. Reverse transcription Bushman
 - a. Temin and Mizutani, 1970. Nature. RNA-dependent DNA polymerase in virions of Rous sarcoma virus. 226, p. 1211-1213.
 - b. Huang et al., 1998. Science. Structure of a Covalently Trapped Catalytic Complex of HIV-1 Reverse Transcriptase: Implications for Drug Resistance. 282, 1669-1675.

3. Humoral immunity Weissman
 - a. Hessel AJ, Hangartner L, Hunter M, Havenith CE, Beurskens FJ, Bakker JM, Lanigan CM, Landucci G, Forthal DN, Parren PW, Marx PA, Burton DR. Fc receptor but not complement binding is important in antibody protection against HIV. Nature. 2007 Sep 6;449(7158):29-30.
 - b. Decker JM, Bibollet-Ruche F, Wei X, Wang S, Levy DN, Wang W, Delaporte E, Peeters M, Derdeyn CA, Allen S, Hunter E, Saag MS, Hoxie JA, Hahn BH, Kwong PD, Robinson JE, Shaw GM. Antigenic conservation and immunogenicity of the HIV coreceptor binding site. J Exp Med. 2005 201:1407-19.

4. HIV integration Bushman
 - a. Schroder et al., 2002. Cell. HIV-1 integration in the human genome favors active genes and local hotspots. 110, 521-529.
 - b. Hazuda et al., 2004. PNAS. A naphthyridine carboxamide provides evidence for discordant resistance between mechanistically identical inhibitors of HIV integrase. 101, 11233-11238.

5. Innate anti-viral response Montaner

- a. Peng G, Lei KJ, Jin W, Greenwell-Wild T, Wahl SM. Induction of APOBEC3 family proteins, a defensive maneuver underlying interferon-induced anti-HIV-1 activity. *J Exp Med*. 2006 Jan 23;203:41-6.
- b. Alter G, Martin MP, Teigen N, Carr WH, Suscovich TJ, Schneidewind A, Streeck H, Waring M, Meier A, Brander C, Lifson JD, Allen TM, Carrington M, Altfeld M. Differential natural killer cell-mediated inhibition of HIV-1 replication based on distinct KIR/HLA subtypes. *J Exp Med*. 2007 204:3027-36.

6. Cellular immunity Weissman

- a. Goulder PJ, Brander C, Tang Y, Tremblay C, Colbert RA, Addo MM, Rosenberg ES, Nguyen T, Allen R, Trocha A, Altfeld M, He S, Bunce M, Funkhouser R, Pelton SI, Burchett SK, McIntosh K, Korber BT, Walker BD. Evolution and transmission of stable CTL escape mutations in HIV infection. *Nature*. 2001 Jul 19;412(6844):334-8.
- b. Jinghe Huang¹, James J. Goedert², Eric J. Sundberg³, Thai Duong Hong Cung¹, Patrick S. Burke¹, Maureen P. Martin⁴, Liliana Preiss⁶, Jeffrey Lifson⁵, Mathias Lichterfeld⁷, Mary Carrington⁴, and Xu G. Yu. HLA-B*35-Px-mediated acceleration of HIV-1 infection by increased inhibitory immunoregulatory impulses. 2009 *J Exp Med*.

7. Transmission Montaner

- a. Rong R, Bibollet-Ruche F, Mulenga J, Allen S, Blackwell JL, Derdeyn CA. Role of V1V2 and other human immunodeficiency virus type 1 envelope domains in resistance to autologous neutralization during clade C infection. *J Virol*. 2007 Feb;81(3):1350-9.
- b. Keele BF, Giorgi EE, Salazar-Gonzalez JF, Decker JM, Pham KT, Salazar MG, Sun C, Grayson T, Wang S, Li H, Wei X, Jiang C, Kirchherr JL, Gao F, Anderson JA, Ping LH, Swanstrom R, Tomaras GD, Blattner WA, Goepfert PA, Kilby JM, Saag MS, Delwart EL, Busch MP, Cohen MS, Montefiori DC, Haynes BF, Gaschen B, Athreya GS, Lee HY, Wood N, Seoighe C, Perelson AS, Bhattacharya T, Korber BT, Hahn BH, Shaw GM. Identification and characterization of transmitted and early founder virus envelopes in primary HIV-1 infection. *Proc Natl Acad Sci U S A*. 2008 May 27;105(21):7552-7.

8. GALT and in vivo targets Collman

- a. Brenchley JM, Price DA, Schacker TW, Asher TE, Silvestri G, Rao S, Kazzaz Z, Bornstein E, Lambotte O, Altmann D, Blazar BR, Rodriguez B, Teixeira-Johnson L, Landay A, Martin JN, Hecht FM, Picker LJ, Lederman MM, Deeks SG, Douek DC. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. *Nat Med.* 2006 12:1365-71.
 - b. Joseph J. Mattapallil, Daniel C. Douek, Brenna Hill, Yoshiaki Nishimura, Malcolm Martin and Mario Roederer. Massive infection and loss of memory CD4+ T cells in multiple tissues during acute SIV infection. 2005. *Nature* 434, 1093-1097
9. Pathogenic versus nonpathogenic infection Montaner
- a. Judith N Mandl, Ashley P Barry, Thomas H Vanderford, Natalia Kozyr, Rahul Chavan, Sara Klucking, Franck J Barrat, Robert L Coffman, Silvija I Staprans, Mark B Feinberg Divergent TLR7 and TLR9 signaling and type I interferon production distinguish pathogenic and nonpathogenic AIDS virus infections. *Nature Medicine* 14:1077-87.
 - b. Chakrabarti LA, Lewin SR, Zhang L, Gettie A, Luckay A, Martin LN, Skulsky E, Ho DD, Cheng-Mayer C, Marx PA. Age-dependent changes in T cell homeostasis and SIV load in sooty mangabeys. *J Med Primatol.* 2000 29:158-65.
10. Cell-cell transmission Collman
- a. Münch J, Rücker E, Ständker L, Adermann K, Goffinet C, Schindler M, Wildum S, Chinnadurai R, Rajan D, Specht A, Giménez-Gallego G, Sánchez PC, Fowler DM, Koulov A, Kelly JW, Mothes W, Grivel JC, Margolis L, Keppler OT, Forssmann WG, Kirchhoff F. Semen-derived amyloid fibrils drastically enhance HIV infection. *Cell.* 2007 131:1059-71.
 - b. Groot F, Welsch S, Sattentau QJ. Efficient HIV-1 transmission from macrophages to T cells across transient virological synapses. *Blood.* 2008 111:4660-3.
11. Negative regulation of immune responses Weissman
- a. Day CL, Kaufmann DE, Kiepiela P, Brown JA, Moodley ES, Reddy S, Mackey EW, Miller JD, Leslie AJ, DePierres C, Mncube Z, Duraiswamy J, Zhu B, Eichbaum Q, Altfeld M, Wherry EJ, Coovadia HM, Goulder PJ, Klenerman P, Ahmed R, Freeman GJ, Walker BD. PD-1 expression on HIV-specific T cells is associated with T-cell exhaustion and disease progression. *Nature.* 2006 443:350-4.

- b. Chase AJ, Sedaghat AR, German JR, Gama L, Zink MC, Clements JE, Siliciano RF. Severe depletion of CD4+ CD25+ regulatory T cells from the intestinal lamina propria but not peripheral blood or lymph nodes during acute simian immunodeficiency virus infection. *J Virol.* 2007 Dec;81(23):12748-57.

12. Vaccines

- a. Buchbinder SP, Mehrotra DV, Duerr A, Fitzgerald DW, Mogg R, Li D, Gilbert PB, Lama JR, Marmor M, Del Rio C, McElrath MJ, Casimiro DR, Gottesdiener KM, Chodakewitz JA, Corey L, Robertson MN; Step Study Protocol Team. Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial. *Lancet.* 2008 Nov 29;372(9653):1881-93.
- b. Supachai Rerks-Ngarm, M.D., Punnee Pitisuttithum, M.D., D.T.M.H., Sorachai Nitayaphan, M.D., Ph.D., Jaranit Kaewkungwal, Ph.D., Joseph Chiu, M.D., Robert Paris, M.D., Nakorn Premisri, M.D., Chawetsan Namwat, M.D., Mark de Souza, Ph.D., Elizabeth Adams, M.D., Michael Benenson, M.D., Sanjay Gurunathan, M.D., Jim Tartaglia, Ph.D., John G. McNeil, M.D., Donald P. Francis, M.D., D.Sc., Donald Stablein, Ph.D., Deborah L. Birx, M.D., Supamit Chunsuttiwat, M.D., Chirasak Khamboonruang, M.D., Prasert Thongcharoen, M.D., Ph.D., Merlin L. Robb, M.D., Nelson L. Michael, M.D., Ph.D., Prayura Kunasol, M.D., and Jerome H. Kim, M.D. 2009 Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand. *NEJM* 361:2209.