

BIOGRAPHICAL SKETCH

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NAME Ruth M. Ruprecht		POSITION TITLE Professor of Medicine	
eRA COMMONS USER NAME (credential, e.g., agency login) RRUPRECHT			
EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)			
INSTITUTION AND LOCATION	DEGREE (if applicable)	MM/YY	FIELD OF STUDY
University of Zürich, Switzerland	2 nd Prediploma	1970	Organic Chemistry
Columbia University, New York	Ph.D.	1973	Human Genetics
University of Miami School of medicine, Florida	M.D.	1977	Medicine

A. Personal Statement

I have a longstanding track record on my work on lentiviral pathogenesis and AIDS vaccine development, areas in which I made important contributions. My group has provided proof-of-concept that neutralizing antibodies (nAbs) can provide complete protection, including sterilizing immunity, from oral challenge with simian-human immunodeficiency viruses (SHIVs), even when given as post-exposure prophylaxis. Over the past years, we sought to develop a bimodal vaccine against HIV clade C (HIV-C) and thus generated a panel of SHIVs that encode *env* genes of recently transmitted HIV-C strains isolated from infants with perinatal infection. The new clade C SHIVs (termed SHIV-Cs) are exclusively R5 tropic and caused gradual disease progression in rhesus monkeys, including AIDS. Our SHIV-C panel includes strains with tier 1 as well as tier 2 neutralization sensitivity profiles.

The goal of our bimodal AIDS vaccine strategy is to induce balanced immune responses consisting of cellular as well as humoral immune defenses. Our initial vaccine strategy involved trimeric HIV-C gp160 and other recombinant immunogens and has yielded significant protection against mucosal SHIV-C challenges, including prevention of infection against upfront heterologous challenge, whereby the Env immunogens and the *env* gene encoded by the challenge virus were mismatched (Rasmussen et al., 2007; 2010). Several vaccinated monkeys developed high-titer nAbs.

In a complementary approach, my group has developed a novel immunofocusing strategy with the goal to induce nAbs while avoiding generating binding antibodies against immunodominant regions on HIV-C Env. Essentially, we have “deconstructed” HIV-C Env and isolated a panel of ~500 mimotopes by biopanning with recombinant phages encoding random peptide libraries; positive selection involved sera from monkeys with high-titer, broadly reactive nAbs resulting from chronic SHIV-C infection or vaccination with HIV-C Env immunogens. Because the region represented by a peptide mimotope is smaller than the antibody paratope, we sought to provide the immune system with a “blueprint” of the correct 3D HIV-C Env structure by priming with a DNA vector encoding the entire HIV-C gp160. This DNA priming *per se* did not induce antibody production, but after repeated boosts with phages bearing HIV-C Env mimotopes fused to protein III, cross-neutralizing antibodies were induced (Humbert et al., 2008).

B. Positions and Honors

Positions and Employment

1973 – 1975 Staff Associate, Institute of Cancer Research, Columbia University, New York, NY
 1977 – 1980 Intern & Resident in Medicine, University of California, Los Angeles
 1980 – 1981 Fellow in Hematology-Oncology, University of California, Los Angeles
 1981 – 1983 Fellow in Hematology-Oncology, Memorial-Sloan Kettering Cancer Center, New York, NY
 1983 – 1984 Assistant Professor of Medicine, Mount Sinai Medical Center, New York, NY
 1984 – 1991 Assist. Professor of Medicine, Harvard Medical School & Dana-Farber Cancer Institute, Boston

Program Director/Principal Investigator (Last, First, Middle): Ruprecht, RM

- 1987 – 1996 Assistant Physician, Dana-Farber Cancer Institute, Boston, MA
1991 – 1997 Laboratory Chief, Laboratory of Viral Pathogenesis, Dana-Farber Cancer Institute, Boston, MA
1991 – 1999 Associate Professor of Medicine, Harvard Medical School & Dana-Farber Cancer Institute
1997 – Collaborative Scientist, Division of Microbiology & Immunology, Yerkes National Primate Research Center, Emory University, Atlanta, GA
1999 – Professor of Medicine, Harvard Medical School & Dana-Farber Cancer Institute, Boston, MA

Awards and Honors (selected)

- 1986 Governor's Award in Recognition of Outstanding Contributions to AIDS Research
1994 Howard Temin Prize: Best Basic Science Contribution – *J Acqd Immunodef Syndr*, 1993
2001 – Honorary Professor, Institute of Medical Biology, Chinese Academy of Medical Science, Peking Union Medical College, Kunming, People's Republic of China
2003 – 2012 NIH Merit Award
2004 World AIDS Day: recognized by amfAR for pioneering efforts of research in the field HIV/AIDS among women: *Women and HIV/AIDS: The Research Frontier*
2004 Fellow, American Association for the Advancement of Science (AAAS)
2008 – Member, Association for American Physicians (AAP)

Government Committees (selected)

- 1990 Member, National Institute of Allergy & Infectious Diseases Special Review Committee
1993 – 1997 Member, NIH, AIDS & Related Research Study Section 3
1997 Member, Ad Hoc Panel on AIDS Research, NIH, National Institute of Dental Research
2000 Panel Member, Military Infectious Diseases Research Program Review for Fiscal Year 2002
2002 Chair, National Institute of Dental and Craniofacial Research, Special Emphasis Panel
2003 – 2007 Member, National Advisory Allergy and Infectious Disease Council of the NIH
2007 Member, NIH Search Committee for Director of DAIDS
2010 – US Chair, US-Japan Panel on AIDS

C. Selected Peer-reviewed Publications

1. Grisson RD, Chenine A-L, Yeh L-Y, He J, Wood C, Bhat GJ, Xu W, Kankasa C, Ruprecht RM. Infectious molecular clone of a recently transmitted pediatric HIV clade C isolate from Africa: evidence of intra-clade recombination. *J Virol* 2004; 78:14066-9. PMID: 15564517
2. Song RJ, Chenine A-L, Rasmussen RA, Ruprecht CR, Mirshahidi S, Grisson RD, Xu W, Whitney JB, Goins LM, Ong H, Li P-L, Shai-Kobiler E, Wang T, Mc Cann CM, Zhang H, Wood C, Kankasa C, Secor WE, McClure HM, Strobert E, Else JG, Ruprecht RM. Molecularly cloned SHIV-1157ipd3N4: a highly replication competent, mucosally transmissible R5 simian-human-immunodeficiency virus encoding HIV clade C *env*. *J Virol* 2006; 80:8729-38. PMID: 16912320
3. Rasmussen RA, Ong H, Song R, Chenine A-L, Ayash-Rashkovsky M, Hu S-L, Polacino P, Else JG, Novembre FJ, and Ruprecht RM for the Clade C Program Project. Efficacy of a multigenic protein vaccine containing multimeric HIV gp160 against heterologous SHIV clade C challenges. *AIDS* 2007; 21:1841-8. PMID: 17721091
4. Humbert M, Rasmussen RA, Song R, Ong H, Sharma P, Chenine AL, Kramer VG, Siddappa NB, Xu W, Else JG, Novembre FJ, Strobert E, O'Neil SP, Ruprecht RM. SHIV-1157i and passaged progeny viruses encoding R5 HIV-1 clade C *env* cause AIDS in rhesus monkeys. *Retrovirology* 2008; 5:94. PMID: 18928523
5. Humbert M, Rasmussen RA, Ong H, Kaiser FMP, Hu S-L, Ruprecht RM. Inducing cross-clade neutralizing antibodies against HIV-1 by immunofocusing. *PLoS One* 2008; 3:e3937. PMID: 19081789
6. Siddappa NB, Song R, Kramer VG, Chenine A-L, Velu V, Ong H, Rasmussen RA, Grisson RD, Wood C, Zhang H, Kankasa C, Rao R, Else JG, Novembre FJ, Montefiori DC, Ruprecht RM. Neutralization-sensitive R5-tropic simian-human immunodeficiency virus SHIV-2873Nip, which carries *env* isolated from an infant with a recent HIV clade C infection. *J Virol* 2009; 83:1422-32. PMID: 19019970
7. Rasmussen RA, Lakhashe SK, Ruprecht RM. Bimodal AIDS vaccine approach: induction of cellular as well as humoral immunity can protect from systemic infection. *Vaccine* 2010; 28S:B25-31. PMID: 20510739
8. Siddappa NB, Watkins JD, Wassermann KJ, Song R, Wang W, Kramer VG, Lakhashe S, Santosuosso M,

Program Director/Principal Investigator (Last, First, Middle): Ruprecht, RM

- Poznansky MC, Novembre FJ, Villinger F, Else JG, Montefiori DC, Rasmussen RA, Ruprecht RM. R5 clade C SHIV strains with tier 1 or 2 neutralization sensitivity: tools to dissect Env evolution and to develop AIDS vaccines in primate models. *PLoS One* 2010; 5(7):e11689. PMID: 20657739
9. Baba TW, Liska V, Hofmann-Lehmann R, Vlasak J, Xu W, Ayehunie S, Cavacini LA, Posner MR, Katinger H, Stiegler G, Bernacky BJ, Rizvi TA, Schmidt R, Hill LR, Keeling ME, Lu Y, Wright JE, Chou T-C, Ruprecht RM. Human neutralizing monoclonal antibodies of the IgG1 subtype protect against mucosal simian/human immunodeficiency virus infection. *Nat Med* 2000; 6:200-6. PMID: 10655110.
 10. Hofmann-Lehmann R, Vlasak J, Rasmussen RA, Smith BA, Baba TW, Liska V, Ferrantelli F, Montefiori DC, McClure HM, Anderson DC, Bernacky BJ, Rizvi TA, Schmidt R, Hill LR, Keeling ME, Katinger H, Stiegler G, Cavacini LA, Posner MR, Chou T-C, Andersen J, Ruprecht RM. Postnatal passive immunization of neonatal macaques with a triple combination of human monoclonal antibodies against oral simian-human immunodeficiency virus challenge. *J Virol* 2001; 75:7470-80. PMID: 11462019
 11. Ferrantelli F, Hofmann-Lehmann R, Rasmussen RA, Wang T, Xu W, Li P-L, Montefiori DC, Cavacini LA, Katinger H, Stiegler G, Anderson DC, McClure HM, Ruprecht RM. Post-exposure prophylaxis with human monoclonal antibodies prevented SHIV89.6P infection or disease in neonatal macaques. *AIDS* 2003; 17:301-9. PMID: 12556683
 12. Ferrantelli F, Rasmussen RA, Buckley KA, Li P-L, Wang T, Montefiori DC, Katinger H, Stiegler G, Anderson DC, McClure HM, Ruprecht RM. Complete protection of neonatal rhesus macaques against oral challenge with pathogenic SHIV by human anti-HIV monoclonal antibodies. *J Infect Dis* 2004; 189: 2167-73. PMID: 15181562
 13. Chenine A-L, Shai-Kobiler E, Steele LN, Ong H, Augostini P, Song R, Lee SJ, Autissier P, Ruprecht RM, Secor WE. Acute *Schistosoma mansoni* infection increases susceptibility to systemic SHIV clade C infection in rhesus macaques after mucosal virus exposure. *PLoS Negl Trop Dis* 2008; e:265. PMID: 18648516
 14. Chenine AL, Siddappa NB, Kramer VG, Sciaranghella G, Rasmussen RA, Lee SJ, Santosuosso M, Poznansky MC, Velu V, Amara RR, Souder C, Anderson DC, Villinger F, Else JG, Novembre FJ, Strobert E, O'Neil SP, Secor WE, Ruprecht RM. Relative transmissibility of an R5 clade C simian-human immunodeficiency virus across different mucosae in rhesus macaques parallels the relative risks of sexual HIV-1 transmission via different routes. *J Infect Dis* 2010; 201:1155-63. PMID: 20214475
 15. Garcia AP, Siddappa NB, Li Q, Haase AT, Paul K, Stroud F, Zhang X, Fountain JA, Villinger F, Novembre FJ, Else JG, Secor WE, Ruprecht RM. AIDS and optic neuritis in a rhesus monkey infected with the R5 clade C SHIV-1157ipd3N4. *J Med Primatol* 2010; Apr 13 [Epub ahead of print]. PMID: 20412378

D. Research Support

Ongoing Research Support

5P01 AI048240-07 Ruprecht (PI) 08/01/2007 – 07/31/2012

Vaccination against mucosal HIV clade C transmission

The goal of this Program Project is to develop a safe, effective vaccine against mucosal transmission of HIV clade C. Primate efficacy studies will use newly created R5 clade C SHIV strains.

Role: PI and Leader, Project 2 and Core D

R37 AI034266-12 Ruprecht (PI) 12/01/97 – 12/28/13

Infant immunoprophylaxis against a primate lentivirus

This Merit Award seeks to develop passive immunization against maternal HIV transmission during birth and via breast milk. We will evaluate the efficacy of human nmAbs against mucosal virus exposure.

Role: PI

3R37 AI034266-14 Ruprecht (PI) 07/14/2009 – 06/30/2011

Infant immunoprophylaxis against a primate lentivirus

The goal of this administrative supplement is to provide support for summer student research experience.

Role: PI

R01 RR14180-09 Ruprecht (PI) 04/01/1999 – 06/30/2010 (NCE)

Molecular evolution of multiply deleted SIV in vivo

We seek the efficacy of Rev-independent, nef SIV in monkeys infected for various time periods against low-dose mucosal challenges with pathogenic SIV.

Role: PI

R21 NS063877-02 Ruprecht (PI) 09/30/08 – 08/31/10

HIV-1 Env microglial tropism and neurovirulence

The goal of this project is to use our new hybrid virus as a research tool to study the role that the HIV-1 envelope gene plays in causing neurological damage in primate models.

Role: PI

P30 AI060354-06 Walker (PI) 07/01/04 – 07/31/14

Harvard University Center for AIDS Research (CFAR)

Site B will provide the use of an animal facility in which the spread of contagious agents is prevented between animals. Training will be provided for safe handling of potential human pathogens in small animal models.

Access to technical support will be provided for performing HIV-1 inoculations into chimeric BLT or NOG mice reconstituted with CD34+ human hematopoietic stem cells.

Role: Leader, Core H, Site B

P01 AI048240-08 Ruprecht (PI) 09/30/00 – 07/31/12

Vaccination against mucosal HIV clade C transmission

The goal of this Program Project is to develop a safe, effective vaccine against mucosal transmission of HIV clade C. Primate efficacy studies will use newly created R5 clade C SHIV strains.

Role: PI

3P01 AI048240-08S1 Ruprecht (PI) 09/01/09 – 08/31/11

Vaccination against mucosal HIV clade C transmission

Each of the three Projects proposes to extend important findings made to date, and the research aims are based upon the ground work we have laid – with the support of all four Cores – in our highly productive HIVRAD Program Project.

Role: PI

P01 AI082282-0 Ertl (PI) 09/01/09 – 08/31/11

Bimodal vaccine strategy with broader anti-HIV clade C neutralizing antibodies

Project 2

Project 2 seeks to demonstrate that bimodal vaccine strategies that mobilize cellular as well as humoral immunity have improved levels of protection compared to one alone; this will be shown in R5 SHIV/primate models using passive immunization with high-titer anti-SHIV immunoglobulins isolated from rhesus monkeys.

Role: Leader, Project 2

RC2 CA148462-01 Wood (PI) 09/29/09 – 08/31/11

Immunofocusing on KSHV neutralizing epitopes

We will perform phage display experiments to isolate mimotopes representing subdomains of the KSHV envelope glycoprotein or other viral components.

Role: Leader, Consortium

Bill & Melinda Gates Foundation 53074 Ruprecht (PI) 04/01/09 – 10/31/10 (NCE)

Novel HIV-1 Env immunogens for immunofocusing

We seek to focus humoral immunity onto HIV Env regions that are linked to broadly neutralizing antibodies.

Role: PI

Completed Research Support.

A number of R01/P01 projects have been completed but cannot be listed because of space constraints.