Jeffrey Dorfman

Wernher & Beit Bldg South Rm S2.27
University of Cape Town
Anzio Road, Observatory,
Cape Town 7925
South Africa

Educational Background

1996 Ph.D. Molecular & Cell Biology, University of California, Berkeley, CA, USA
1990 A.B. Biochemistry, *cum laude*, Harvard College, Cambridge, MA, USA

Professional and Academic Experience

2009-present Group Leader, International Centre for Genetic Engineering and Biotechnology Cape Town, South Africa

2009-present Senior Lecturer, Immunology
University of Cape Town, Division of Immunology, Faculty of Health Sciences

Projects: antibody mediated neutralization of HIV-1; HIV-1 phylogeny; immunity to malaria

2006-2008 Research Associate with Dr. Patrick Duffy, Seattle Biomedical Research Institute, Malaria Vaccine Antigen Discovery Program, Seattle, WA, USA
Project: Human monoclonal antibodies for vaccine antigen discovery (malaria)

2005-2006 Research Associate with Dr. Grégoire Altan-Bonnet, Memorial Sloan Kettering Cancer Center, Department of Computational Biology, Sloan Kettering Institute, New York, NY, USA.
Project: Mechanism for setting T cell receptor sensitivity

2001-2004 Postdoctoral research under Professor Kevin Marsh, Wellcome Trust Research Laboratories, Kilifi, Kenya and University of Oxford, England
Project: B cell memory to *P. falciparum* antigens in exposed individuals

1997-2001 Postdoctoral research under Dr Ronald N. Germain, Laboratory of Immunology, National Institutes of Health, Bethesda, MD, USA
Project: Environmental TCR signaling in naive T cells: mechanism and biology

1997 Postdoctoral research under Professor David H. Raulet, Completion of projects initiated during PhD programme

1991-1996 PhD, Department of Molecular and Cell Biology, University of California, Berkeley, CA, USA, under Professor David H. Raulet
Project: self tolerance of and target recognition by natural killer cells

1988-1990 Research under Professor Bruce Demple, Department of Biochemistry and Molecular Biology, Harvard University, Cambridge, MA, USA
Project: Enzymology of DNA repair in *E. coli*

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Current Research Interests

My laboratory focuses upon HIV and malaria research, with projects on (1) antibody-mediated neutralization of HIV-1, (2) HIV-1 diversity and phylogeny and (3) immunity to malaria and the role of cytokines. Below is a summary of our current HIV-1 neutralization projects:

Shielding of the HIV-1 MPER from neutralizing antibody

The membrane-proximal external region (MPER) of the gp41 subunit of HIV-1 envelope is one of few attractive vaccine targets. It is highly conserved and MPER peptides bind most anti-MPER neutralizing antibodies, suggesting that immunogen modeling may be approachable. However, this apparent simplicity has not translated into viable vaccine approaches. We have found that some viruses appear unusually resistant to anti-MPER antibodies. Further study leads us to propose that this is best explained by steric shielding of MPER by gp120 or other parts of gp41, even in the post-CD4 conformation, in which the MPER is generally more exposed than in the envelope spike. Shielding may explain part of the difficulty in eliciting neutralizing anti-MPER antibodies with candidate vaccines.

Breadth of neutralization to key neutralizing antibody targets

We are mapping epitopes in a large cohort of chronically HIV-infected individuals in which we have measured neutralization breadth and potency. Epitope recognition associated with higher overall neutralization breadth may indicate which sites are attractive candidates for immunogen design. We find that MPER recognition and not PG9/16 site recognition is associated with higher neutralization breadth. We are studying PGT/2G12-like antibodies.

Preservation of CD4+ T cells positively correlates with anti-HIV neutralization capacity in HIV-infected children: the opposite effect from adults

Studies in HIV-1-infected adults suggest that breadth and potency of the anti-HIV-1 neutralization response is greater with lower CD4 counts. This is counterintuitive, as $CD4^+$ T cells are a critical component of the maturation of antibody responses and of the establishment of antibody memory. We have shown the opposite association in children. Children with fewer CD4+ T cells have *lower* anti-HIV-1 neutralizing antibody responses. Our preferred explanation is that children are still developing their CD4+ T cell populations. Even mild $CD4^+$ T cell depletion by HIV-1 may degrade children's ability to make proper antibody responses. In contrast, in adults, there may be a larger reservoir of $CD4^+$ T cells to help antibody responses, so this effect is not seen, and another, opposing effect predominates.

Probing which Envelope conformation is targeted by particular antibodies using rare MPER polymorphisms

We are generating mutant viruses that increase the lifetime of the post-CD4 intermediate conformation and are using these viruses to determine if neutralizing antibodies in serum samples preferentially target this conformation. We are using these viruses to understand why many antibodies to the PG9/16 site seem to be narrowly neutralizing.

Training and Teaching Experience

Training of postdoctoral fellows:

2011-2012	Dr. Rocio Laguna Goya
2011-2014	Dr. Mwanaidi Kafuye
2013-	Dr. Michelle van der Ventel Fisher

Formal mentoring of the following students:

2009-2013	Rajesh Abraham Jacob, PhD
2009-2014	René Ghislain Essomba, PhD
2012-	Emily N Tangie Visiting PhD student from University of Buea, Cameroon
2013-	Thandeka Moyo, MSc candidate

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2013	Isaline Goemaere BSc Honours, Infectious Disease and Immunology
2012	Trishana Nundallal BSc Honours, Infectious Disease and Immunology
2011	Jonathan Day BSc Honours, Infectious Disease and Immunology

Informal mentoring of the following students:

2006-2008	Kay Greeson, PhD 2009, University of Washington Patrick Duffy laboratory, Seattle, Washington, USA
2006-2007	Amber Randal, MS 2007, University of Washington Patrick Duffy laboratory, Seattle, Washington, USA
2002	Alice Nyakeriga, PhD 2005, University of Stockholm KEMRI Wellcome Trust Collaborative Programme, Kilifi, Kenya

Formal instruction**:**

2011, 2013	Convener, "Global Infectious Disease: an interdisciplinary course" International training course **(2015 planned)**
2011-present	Convener, Research Immunology semester course (MSc/PhD level) Division of Immunology, Faculty of Health Sciences University of Cape Town, Cape Town, South Africa
2010-2012	Instructor for the Immunology module Human Biology 2nd year students Department of Molecular and Cell Biology University of Cape Town, Cape Town, South Africa
2009-present	Instructor for the Immunology module Infectious Disease Immunology Honours BSc students University of Cape Town, Cape Town, South Africa
1997	Instructor, Introductory Biochemistry and Metabolism University of California Extension School, San Francisco, USA
1995	Instructor, Immunology of AIDS Department of Molecular and Cell Biology University of California, Berkeley, USA

Publications

Agthe M, Nemes E, Jacob RA, Abrahams F, Fainguem N, Ndiang Tetang SM, Cappelli G, Colizzi V, **Dorfman JR** (2014) Lower anti-HIV-1 neutralization in HIV-infected children with CD4+ T cell depletion: opposite correlation from adults. *AIDS*: in press

Jacob, RA, Abrahams F, Moyo T, **Dorfman JR**. (2013) Shielding of HIV-1 envelope membrane proximal external region from antibody. Manuscript submitted for publication

Jacob RA, Abrahams F, Tongo M, Schomaker M, Roux P, Mpoudi Ngole, E, Burgers WA, **Dorfman JR.** (2012) Refined identification of neutralization-resistant HIV-1 CRF02_AG viruses. *J Virol:* **86(14)**:7699-7703

Veiga J, Feinerman O, **Dorfman JR**, Germain RN, Altan-Bonnet, G (2008) Phenotypic variability of T cell signaling reveals flexibility in self/non-self discrimination. *Science*: **321(5892)**:1081-4

Oleinikov AV, Francis SE, **Dorfman JR**, Rossnagle E, Balcaitis S, Getz T, Avril M, Gose S, Smith JD, Fried M, Duffy PE. (2008) VAR2CSA domains expressed in E.coli induce cross-reactive antibodies to native protein. *Journal of Infectious Diseases* **197(8):**1119-23

Dorfman JR, Bejon P, Ndungu FM, Langhorne J, Kortok MM, Lowe BS, Mwangi TW, Williams, TN, Marsh K. (2005) B cell memory to three *P. falciparum* blood stage antigens in a malaria-endemic area. *Journal of Infectious Diseases* **191(10)**:1623-30

Nyakeriga AM, Troye-Blomberg M, **Dorfman JR**, Alexander ND, Bäck R, Kortok M, Chemtai AK, Marsh K, Williams TN. (2004) Iron deficiency and malaria in children living on the coast of Kenya. *Journal of Infectious Diseases*: **190(3)**:439-47.

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Jamieson AM, Isnard P, **Dorfman JR**, Coles MC, Raulet DH. (2004) Turnover and proliferation of NK cells in steady state and lymphopenic conditions. *Journal of Immunology* **172(2)**:864-70.

Stefanová I, **Dorfman JR**, Tsukamoto M, Germain RN. (2003) On the role of self-recognition in T cell responses to foreign antigen. *Immunological Reviews* **191**:97-106.

Stefanová, I., **Dorfman, J.R.** and Germain, R.N. (2002) Self-recognition promotes the foreign antigen sensitivity of naive T lymphocytes. *Nature* **420(6914)**: 429-34

Germain RN, Stefanova I and **Dorfman J.** (2002) Self-recognition and the regulation of $CD4^+$ T cell survival. *Adv Exp Med Biol*. **512**:97-105.

Dorfman J.R. and Germain R.N. (2002) MHC-dependent survival of naive T cells? A complicated answer to a simple question. *Microbes and Infection* **4(5)**:547-54.

Dorfman, J.R., Stefanova, I., Yasutomo, K. and Germain, R.N. (2000) $CD4^+$ T cell survival is not directly linked to self-MHC induced TCR signaling. *Nature Immunology* **1(4)**: 329-35

Chung, D.H., **Dorfman, J.**, Plaksin, D., Natarajan, K., Belyakov, I., Hunziker, R., Berzofsky, J.A., Yokoyama, W.M., Mage, M.G., and Margulies, D.H. (1999) NK and CTL recognition of a single chain H-$2D^d$ molecule: Distinct sites of H-$2D^d$ are involved in interactions with NK and T cell receptors. *Journal of Immunology* **163(7)**:3699-708

Porgador, A., **Dorfman, J.R.**, Corral, L., Strominger, J.L., Mandelboim, O. and Restifo, N.P. (1999) Tumor variability and sensitivity to T and NK cells: Implications for cancer immunotherapy. *Gann Monograph on Cancer Res* **48**:105-15

Dorfman, J.R. and Raulet D.H. (1998) Acquisition of Ly49 receptor expression by developing natural killer cells. *Journal of Experimental Medicine* **187(4)**:609-18

Dorfman, J.R., Zerrahn, J., Coles, M.C. and Raulet D.H. (1997) The basis for self tolerance of natural killer cells in $\beta 2m^-$ and TAP-1^- mice. *Journal of Immunology* **159(11)**:5219-25

Raulet, D.H., Held, W., Correa, I., **Dorfman, J.R.**, Wu, M-F. and Corral, L. (1997) Specificity, tolerance and developmental regulation of natural killer cells defined by expression of class I-specific Ly49 receptors *Immunological Reviews* **155**:41-52

Held, W., **Dorfman, J.R.**, Wu, M-F. and Raulet, D.H. (1996) Major histocompatibility complex class I-dependent skewing of the natural killer cell repertoire. *European Journal of Immunology* **26(10)**:2282-6

Dorfman, J.R., and Raulet D.H. (1996) Major histocompatibility complex genes determine natural killer cell tolerance. *European Journal of Immunology* **26(1)**:151-5

Yu, Y.Y.L., George, T., **Dorfman, J.R.**, Roland, J., Kumar, V. and Bennett, M. (1996) The role of Ly49A and 5E6 (Ly49C) molecules in hybrid resistance mediated by murine natural killer cells against normal T cell blasts. *Immunity* **4(1)**:67-76

Raulet, D., Correa, I., Corral, L., **Dorfman, J.** and Wu, M-F. (1995) Inhibitory effects of class I molecules on murine NK cells: Speculations on function, specificity and self-tolerance. *Seminars in Immunology* **7(2)**: 103-7