

CURRICULUM VITAE

NICOLAI STANISLAS CYRILLE VAN OERS

Department of Immunology
NA2.200, 6000 Harry Hines Blvd.
UT Southwestern Medical Center
Dallas, TX 75390-9093
nicolai.vanoers@utsouthwestern.edu
<http://www4.utsouthwestern.edu/vanoerslab/home/Welcome.html>
(214) 648-1236 (Business Phone)
(214) 648-7331 (FAX)

BIOGRAPHICAL DATA

Birth date: December 27, 1962
Marital Status: Married with 2 children
Citizenship: Canadian and Dutch, US permanent resident (green card)
Languages: English, French, Dutch, (Greek)

EDUCATION

1977-1980 Fort Richmond Collegiate, Winnipeg, Manitoba (High School)
1980-1984 University of Manitoba, Winnipeg, Manitoba (B.Sc.)
1984-1990 McGill University, Montreal, Quebec (Ph.D.)
1990-1992 University of British Columbia, Vancouver, British Columbia (Post-Doc)
1992-1997 Howard Hughes Medical Institute, University of California, San Francisco
(Post-Doctoral Fellowship)

DEGREES OBTAINED

B.Sc. 1984 University of Manitoba, Biochemistry
Ph.D. 1990 McGill University, Microbiology and Immunology, Montreal, PQ
Title: The biochemical and immunoregulatory properties of a distinct murine alpha-fetoprotein isoform (Supervisor: Dr. Robert A. Murgita)

AWARDS

1984 University of Manitoba Deans' Honor List (Science)
1984 Department of Microbiology Summer Fellowship (University of Manitoba)
1984-1985 Colin Inkster Memorial Award (Manitoba)
1984, 1986, 1989 F. C. Harrison Fellowship (McGill University)
1985 McGill University Summer Fellowship
1986-1989 Natural Sciences and Engineering Research Council of Canada
(NSERC)
Post-Graduate Scholarship
1988-1989 McGill Faculty of Medicine Internal Award
1990-1992 NSERC Post-doctoral Fellowship
1990 Fonds de la Recherche en Sante du Quebec Post-Doctoral Fellowship
(declined)

1990 Deans' Honor List (McGill)
1990-1991 Wilfred Yaphe Award (McGill)
1992-1994 National Cancer Institute of Canada Post-Doctoral Fellowship (declined)
1993-1995 Human Frontier Science Program Post-Doctoral Fellowship
1998 UT Southwestern Medical Center Packard Fellowship Nominee
2007-2009 J.Wayne Streilein MD Professorship

PROFESSIONAL POSITIONS

1990-1992 Post-doctoral fellow, The University of British Columbia, Vancouver, Canada
1992-1997 Post-doctoral fellow, The University of California, San Francisco
1997-2005 Assistant Professor, UT Southwestern Medical Center, Dallas, TX
2005-present Associate Professor, UT Southwestern Medical Center, Dallas, TX
2002-2005 Assistant Director, Program in Immunology
2005-2008 Director, Program in Immunology
2007-present Director, Integrated Immunology Training Grant
2009-present Associate Professor of Pediatrics, UT Southwestern Medical Center

PROFESSIONAL ASSOCIATIONS

American Association for the Advancement of Science
American Association of Immunologists

OTHER EXPERIENCE

1997-present Member of the Programs in Immunology and Molecular Microbiology, UT Southwestern Medical Center
2002-2003 National Cancer Institute Review Panel Site Visit, Ad hoc member
2002-present Ad hoc reviewer for the Natural Sciences and Engineering Research Council (Canada), the Canadian Red Cross, and the Israel Science Foundation
2002-present National Institutes of Health, Center for Scientific Review Panel, Immunobiology Study Section and CMIB, Ad hoc reviewer

RESEARCH GRANTS

Current

Grantor: High Impact/High Risk Grant UT Southwestern
Title of Project: The Function of Mycobacterium tuberculosis-encoded MicroRNAs during Human Infections
Role: Principal Investigator
Dates: 11/01/11-10/31/12

The goal of this project is to identify, characterize, and define the function of *M. tuberculosis* encoded microRNAs when they are expressed in human cells such as macrophages, dendritic cells, and epithelial cells. OVERLAP: None

Grantor: National Institutes of Allergy and Immunology (NIH)

Title of Project: Integrative Immunology Training grant
5 T32 AI005284-32

Role: Program Director

Dates: 9/01/08 - 8/31/13

The goal of this training grant is to provide students and post-doctoral fellows with advanced immunology training. OVERLAP: None

Pending

Grantor: National Institutes of Health

Title of Project: Characterization of Patients with Primary Immunodeficiency Diseases
R01 \$325,000/yr

Role: Principal Investigator

Dates: 10/01/12-09/30/17

Purpose: The goals of this project are to profile and characterize the microRNAs that are differentially expressed in the peripheral blood of pediatric patients with diverse primary immunodeficiency diseases. In addition, a total RNA profiling of thymic tissue from normal and DiGeorge syndrome patients will be undertaken.

Grantor: National Institutes of Health

Title of Project: Molecular Cause of the Thymic Hypoplasia in DiGeorge syndrome patients

R01 \$125,000/yr

Role: R21 Principal Investigator

Dates: 11/01/12-10/30/14

Purpose: The goals of this project are to define the roles of specific microRNAs and a long, non-coding RNA in the development of the thymic tissue. OVERLAP: 25% with the previously listed grant.

Grantor: National Institutes of Health

Title of Project: Characterization of Mycobacterium tuberculosis-encoded MicroRNAs in Infected Macrophages

R01 \$125,000/yr

Role: Principal Investigator

Dates: 11/01/12-10/31/13

The goal of this project is to identify, characterize, and define the function of *M. tuberculosis* encoded microRNAs when they are expressed in human cells such as macrophages, dendritic cells, and epithelial cells. OVERLAP: None

Completed

Grantor: National Institutes of Allergy and Immunology (NIH)

Title of Project: MicroRNA Profiling of Pediatric Immunodeficiency Patients
R21 AI083827-01

Role: Principal Investigator

Dates: 8/01/09 - 8/31/11

The goal of this project is to determine whether particular microRNAs, detected in the blood, can be used to diagnose primary immunodeficiency disorders. OVERLAP: None

Grantor: National Institutes of Allergy and Immunology (NIH)
Title of Project: T cell receptor signaling by phosphorylated forms of TCR
R01 AI 42953-11

Role: Principal Investigator
Dates: 7/1/04-6/30/11

The goals of this project are to characterize the functional contribution of the phosphorylated forms of CD3 zeta on T cell functions.

Grantor: National Institutes of Allergy and Immunology (NIH)
Title of Project: CD3 e functions in T cells
R56 AI071229-01A2

Role: Principal Investigator
Dates: 9/20/08 - 8/31/10

The goal of this project was to characterize the role of a phospholipid-binding motif in the CD3 e subunit. This motif, which we termed the basic-rich stretch, complexed to phosphoinositides such as PtdIns3P, PtdIns4P, and PtdIns5P

Grantor: National Institutes of Allergy and Immunology (NIH)
Title of Project: PTPN4 functions in lymphocytes
R21 AI69249-01

Role: Principal Investigator
Dates: 8/01/08 - 6/30/10

The goal of this project was to determine how a protein tyrosine phosphatase, PTPN4, regulates immune cell functions.

Grantor: High Impact/High Risk Grant UT Southwestern
Title of Project: Mycobacterium tuberculosis attenuation of immune cell function
Role: Principal Investigator

Dates: 1/01/07-12/31/07

The goal of this project was to identify genetic elements in the *M. tuberculosis* genome capable of suppressing innate inflammatory pathways in macrophages. We developed an innate inflammatory reporter cell line and generated a plasmid expression library containing segments of the *M. tuberculosis* genome.

Grantor: National Institutes of Allergy and Immunology (NIH)
Title of Project: IRAK-family function in bacterial infection
R01 AI50019-3

Role: Co-PI (Dr. J.A. Thomas, PI)
Dates: 5/1/02-4/30/07

Grantor: National Institutes of Allergy and Immunology (NIH)
Title of Project: The function of the immunological synapse
R03

Role: Co-PI (Dr. Christoph Wulfig: PI)
Dates: 7/1/04-6/30/06

Grantor: Alliance for Lupus research, Arthritis Foundation
Title of Project: Genes and Genetic Pathways that Suppress Lupus
Role: Co-PI (Dr. Edward Wakeland, PI)
Dates: 1/1/05-12/31/06

Additional Activities

Ad Hoc Reviewer

Immunity, Nature Immunology, Journal of Experimental Medicine, Molecular and Cellular Biology, The Journal of Immunology, The Journal of Biological Chemistry, Cellular Immunology, Leukemia, Science, Cellular Immunology, European Journal of Immunology

PUBLICATIONS

[1-52]

1. Evans, B., R. Harrop, D. Heywood, J. MacKintosh, R.W. Moore, B.D. Pate, T.J. Ruth, J.G. Rogers, C. Sayre, H.P. Sprenger, N. van Oers, and G. Y-X., *Engineering developments on the UBC-TRIUMF modified PET VI positron emission tomograph*. IEEE Trans. Nucl. Sci., 1983. **30**: p. 1-4.
2. Buschman, E., N. van Oers, M. Katz, and R.A. Murgita, *Experimental myasthenia gravis induced in mice by passive transfer of human myasthenic immunoglobulin. Evidence for an ameliorating effect by alpha-fetoprotein*. J Neuroimmunol, 1987. **13**(3): p. 315-30.
3. van Oers, N.S., B.L. Cohen, and R.A. Murgita, *Isolation and characterization of a distinct immunoregulatory isoform of alpha-fetoprotein produced by the normal fetus*. J Exp Med, 1989. **170**(3): p. 811-25.
4. van Oers, N.S.C., R. Boismenu, B.L. Cohen, and R.A. Murgita, *Analytical- and preparative-scale separation of molecular variants of a-fetoprotein by anion-exchange chromatography on Monobead resins*. J. Chromatogr., 1990. **525**: p. 59-69.
5. Carlow, D.A., S.J. Teh, N.S. van Oers, R.G. Miller, and H.S. Teh, *Peripheral tolerance through clonal deletion of mature CD4-CD8+ T cells*. Int Immunol, 1992. **4**(5): p. 599-610.
6. Carlow, D.A., N.S. van Oers, S.J. Teh, and H.S. Teh, *Deletion of antigen-specific immature thymocytes by dendritic cells requires LFA-1/ICAM interactions*. J Immunol, 1992. **148**(6): p. 1595-603.
7. Van Oers, N.S., A.M. Garvin, C.B. Davis, K.A. Forbush, D.A. Carlow, D.R. Littman, R.M. Perlmutter, and H.S. Teh, *Disruption of CD8-dependent negative and positive selection of thymocytes is correlated with a decreased association between CD8 and the protein tyrosine kinase, p56lck*. Eur J Immunol, 1992. **22**(3): p. 735-43.
8. van Oers, N.S.C., A.M. Garvin, M.P. Cooke, C.B. Davis, D.R. Littman, R.M Perlmutter, and H.-S. Teh, *Differential involvement of protein tyrosine kinases p56lck and p59fyn in T cell development*. Adv. Exp. Med. Biol, ed. S. Gupta. Vol. 323. 1992. 89-99.
9. van Oers, N.S., S.J. Teh, A.M. Garvin, K.A. Forbush, R.M. Perlmutter, and H.S. Teh, *CD8 inhibits signal transduction through the T cell receptor in CD4-CD8- thymocytes*

- form T cell receptor transgenic mice reconstituted with a transgenic CD8 alpha molecule.* J. Immunol., 1993. **151**: p. 777-790.
10. van Oers, N.S.C., W. Tao, J.D. Watts, P. Johnson, R. Aebersold, and H.-S. Teh, *Constitutive tyrosine phosphorylation of the T cell receptor (TCR) z subunit: Regulation of TCR-associated protein kinase activity by TCR z.* Mol. Cell. Bio., 1993. **13**: p. 5771-5780.
 11. Chan, A.C., N.S.C. van Oers, A. Tran, L. Turka, C.-L. Law, J.C. Ryan, E.A. Clark, and A. Weiss, *Differential expression of ZAP-70 and Syk protein tyrosine kinases, and the role of this family of protein tyrosine kinases in T cell antigen receptor signalling.* J. Immunol., 1994. **152**: p. 4758-4766.
 12. Iwashima, M., B.A. Irving, N.S.C. van Oers, A.C. Chan, and A. Weiss, *Sequential interactions of the TCR with two distinct cytoplasmic tyrosine kinases.* Science, 1994. **263**: p. 1136-1139.
 13. van Oers, N.S.C., N. Killeen, and A. Weiss, *ZAP-70 is constitutively associated with tyrosine phosphorylated TCR z in murine thymocytes and lymph node T cells.* Immunity, 1994. **1**: p. 675-685.
 14. van Oers, N.S.C., S.-J. Teh, B.A. Irving, J. Tiong, A. Weiss, and H.-S. Teh, *Production and characterization of monoclonal antibodies specific for the murine T cell receptor z chain.* J. Immunol. Meth., 1994. **170**: p. 261-268.
 15. Fagnoli, J., A.L. Burkhardt, M. Lavery, S.A. Kut, N.S.C. van Oers, A. Weiss, and J. Bolen, *Syk mutation in Jurkat E6-derived clones results in lack of p72^{Syk} expression.* J. Biol. Chem, 1995. **270**: p. 26533-26537.
 16. van Oers, N.S.C., H. von Boehmer, and A. Weiss, *The pre-TCR complex is functionally coupled to the TCR z subunit.* J. Exp. Med., 1995. **182**: p. 1585-1590.
 17. van Oers, N.S.C. and A. Weiss, *The Syk/ZAP-70 protein tyrosine kinase connection to antigen receptor signalling processes.* Sem. Immunol., 1995. **7**: p. 227-236.
 18. van Oers, N.S.C., N. Killeen, and A. Weiss, *Lck regulates the tyrosine phosphorylation of the TCR subunits and ZAP-70 in murine thymocytes.* J. Exp. Med., 1996. **183**: p. 1053-1062.
 19. van Oers, N.S.C., B. Lowin-Kropf, D. Finlay, K. Connolly, and A. Weiss, *ab T cell development is abolished in mice lacking both Lck and Fyn protein tyrosine kinases.* Immunity, 1996. **5**: p. 429-436.
 20. Page, S.T., N.S.C. van Oers, R.M. Perlmutter, A. Weiss, and A.M. Pullen, *Differential contribution of Lck and Fyn protein tyrosine kinases to intrapithelial lymphocyte development.* Eur. J. Immunol., 1997. **27**: p. 554-562.
 21. Qian, D., S. Lev, N.S.C. van Oers, J. Schlessinger, and A. Weiss, *Tyrosine phosphorylation of Pyk2 is selectively regulated by Fyn during TCR signaling.* J. Exp. Med., 1997. **185**: p. 1253-1259.
 22. Kadlecsek, T.A., N.S. van Oers, L. Lefrancois, S. Olson, D. Finlay, D.H. Chu, K. Connolly, N. Killeen, and A. Weiss, *Differential requirements for ZAP-70 in TCR signaling and T cell development.* J. Immunol., 1998. **161**(9): p. 4688-94.
 23. van Oers, N.S.C., P. Love, E.W. Shores, and A. Weiss, *Regulation of T cell receptor signal transduction in murine thymocytes by multiple TCR z-chain signaling motifs.* J. Immunol., 1998. **160**: p. 163-170.

24. Chu, D.H., N.S. van Oers, M. Malissen, J. Harris, M. Elder, and A. Weiss, *Pre-T cell receptor signals are responsible for the down-regulation of Syk protein tyrosine kinase expression*. J Immunol, 1999. **163**(5): p. 2610-20.
25. van Oers, N.S., *T cell receptor-mediated signs and signals governing T cell development*. Semin Immunol, 1999. **11**(4): p. 227-37.
26. van Oers, N.S.C., B. Tohlen, B. Malissen, C.R. Moomaw, S. Afendis, and C. Slaughter, *The 21- and 23- kDa forms of TCR z are generated by specific ITAM phosphorylations*. Nature Immunology, 2000. **1**: p. 322-328.
27. Witherden, D., N.S.C. van Oers, C. Waltzinger, A. Weiss, C. Benoist, and D. Mathis, *Tetracycline-controllable selection of CD4+ T cells: Half-life and survival signals in the absence of major histocompatibility complex class II molecules*. J. Exp. Med., 2000. **191**: p. 355-364.
28. Ito, Y., S. Arai, N.S.C. van Oers, I. Aifantis, H. von Boehmer, and T. Miyazaki, *Positive selection by the pre-TCR yields mature CD8+ T cells*. J. Immunol., 2002. **169**: p. 4913-4919.
29. Ren, H., A. Schmalstieg, N.S. van Oers, and R.B. Gaynor, *I-kappa B kinases alpha and beta have distinct roles in regulating murine T cell function*. J Immunol, 2002. **168**(8): p. 3721-31.
30. Pitcher, L.A., P.S. Ohashi, and N.S.C. van Oers, *T cell receptor antagonism is functionally uncoupled from the 21- and 23-kDa tyrosine phosphorylated TCR z subunits*. J. Immunol., 2003. **171**: p. 845-852.
31. Pitcher, L.A. and N.S.C. van Oers, *T cell receptor signal transmission: who gives an ITAM*. Trends in Immunology, 2003. **24**: p. 554-560.
32. Pitcher, L.A., J.A. Young, M.A. Mathis, P.C. Wrage, B. Bartok, and N.S.C. van Oers, *The formation and functions of the 21- and 23-kDa tyrosine phosphorylated TCR z subunits*. Immunol Rev, 2003. **191**: p. 47-61.
33. Sozio, M.S., M.A. Mathis, J.A. Young, S. Walchli, L.A. Pitcher, P.C. Wrage, B. Bartok, A. Campbell, J.D. Watts, R. Aebersold, R.H. Van Huijsduijnen, and N.S. van Oers, *PTPH1 is a predominant protein-tyrosine phosphatase capable of interacting with and dephosphorylating the T cell receptor zeta subunit*. J Biol Chem, 2004. **279**(9): p. 7760-9.
34. Mock, J.R., M. Vakevainen, K. Deng, J.L. Latimer, J.A. Young, N.S. van Oers, S. Greenberg, and E.J. Hansen, *Haemophilus ducreyi targets Src family protein tyrosine kinases to inhibit phagocytic signaling*. Infect Immun, 2005. **73**(12): p. 7808-16. PMC16299270
35. Pitcher, L.A., M.A. Mathis, S. Subramanian, J.A. Young, E.K. Wakeland, P.E. Love, and N.S. van Oers, *Selective Expression of the 21-Kilodalton Tyrosine-Phosphorylated Form of TCR {zeta} Promotes the Emergence of T Cells with Autoreactive Potential*. J Immunol, 2005. **174**(10): p. 6071-9. PMC15879101
36. Pitcher, L.A., M.A. Mathis, J.A. Young, L.M. Deford, B. Purtic, C. Wulfing, and N.S. van Oers, *The CD3 gammaepsilon/deltaepsilon signaling module provides normal T cell functions in the absence of the TCR zeta immunoreceptor tyrosine-based activation motifs*. Eur J Immunol, 2005. **35**(12): p. 3643-54. PMC16259006
37. Purtic, B., L.A. Pitcher, N.S. van Oers, and C. Wulfing, *T cell receptor (TCR) clustering in the immunological synapse integrates TCR and costimulatory signaling in selected T cells*. Proc Natl Acad Sci U S A, 2005. **102**(8): p. 2904-9. PMC15703298

38. van Oers, N.S. and Z.J. Chen, *Cell biology. Kinasing and clipping down the NF-kappa B trail*. Science, 2005. **308**(5718): p. 65-6. PMC15802594
39. Becker, A.M., L.M. Deford-Watts, C. Wuelfing, and N.S. van Oers, *The Constitutive Tyrosine Phosphorylation of CD3{zeta} Results from TCR-MHC Interactions That Are Independent of Thymic Selection*. J Immunol, 2007. **178**(7): p. 4120-8. PMC17371967
40. Deford-Watts, L.M., J.A. Young, L.A. Pitcher, and N.S. van Oers, *The Membrane-proximal Portion of CD3 {epsilon} Associates with the Serine/Threonine Kinase GRK2*. J Biol Chem, 2007. **282**(22): p. 16126-34. PMC17420248
41. Deng, K., J.R. Mock, S. Greenberg, N.S. van Oers, and E.J. Hansen, *Haemophilus ducreyi LspA proteins are tyrosine phosphorylated by macrophage-encoded protein tyrosine kinases*. Infect Immun, 2008. **76**(10): p. 4692-702. PMC2546853
42. Holst, J., H. Wang, K.D. Eder, C.J. Workman, K.L. Boyd, Z. Baquet, H. Singh, K. Forbes, A. Chruscinski, R. Smeyne, N.S. van Oers, P.J. Utz, and D.A. Vignali, *Scalable signaling mediated by T cell antigen receptor-CD3 ITAMs ensures effective negative selection and prevents autoimmunity*. Nat Immunol, 2008. **9**(6): p. 658-66. PMC18469818
43. Young, J.A., A.M. Becker, J.J. Medeiros, V.S. Shapiro, A. Wang, J.D. Farrar, T.A. Quill, R.H. van Huijsduijnen, and N.S. van Oers, *The protein tyrosine phosphatase PTPN4/PTP-MEG1, an enzyme capable of dephosphorylating the TCR ITAMs and regulating NF-kappaB, is dispensable for T cell development and/or T cell effector functions*. Mol Immunol, 2008. **45**(14): p. 3756-66. PMC2596642
44. Deford-Watts, L.M., T.C. Tassin, A.M. Becker, J.J. Medeiros, J.P. Albanesi, P.E. Love, C. Wulfing, and N.S. van Oers, *The Cytoplasmic Tail of the T Cell Receptor CD3 {epsilon} Subunit Contains a Phospholipid-Binding Motif that Regulates T Cell Functions*. J Immunol, 2009. **183**(2): p. 1055-64. PMC2954055
45. Singleton, K.L., K.T. Roybal, Y. Sun, G. Fu, N.R. Gascoigne, N.S. van Oers, and C. Wulfing, *Spatiotemporal patterning during T cell activation is highly diverse*. Sci Signal, 2009. **2**(65): p. ra15. PMC2694444
46. Becker, A.M., J.S. Blevins, F.L. Tomson, J.L. Eitson, J.J. Medeiros, F. Yarovinsky, M.V. Norgard, and N.S. van Oers, *Invariant NKT cell development requires a full complement of functional CD3 zeta immunoreceptor tyrosine-based activation motifs*. J Immunol, 2010. **184**(12): p. 6822-32. PMC2947369
47. Devora, G.A., L. Sun, Z. Chen, N.S. van Oers, E.P. Hanson, J.S. Orange, and M.T. de la Morena, *A Novel Missense Mutation in the Nuclear Factor-kappaB Essential Modulator (NEMO) Gene Resulting in Impaired Activation of the NF-kappaB Pathway and a Unique Clinical Phenotype Presenting as MRSA Subdural Empyema*. J Clin Immunol, 2010. **30**(6): p. 881-885. PMC 20652730
48. de la Cruz, J., T. Kruger, C.A. Parks, R.L. Silge, N.S. van Oers, I.F. Luescher, A.G. Schrum, and D. Gil, *Basal and antigen-induced exposure of the proline-rich sequence in CD3 (epsilon)*. Journal of immunology, 2011. **186**(4): p. 2282-90. PMC 21228347
49. de la Morena, M.T., J.L. Eitson, I. Dozmorov, S. Belkaya, A. Hoover, D. Moye, A. Winborn, and N.S. van Oers, *MicroRNA Profiling of Humans with 22q11.2 Deletion Syndrome Reveals MicroRNA Patterns with Clinical Relevance*. Submitted, 2012.
50. Deford-Watts, L.M., D.S. Dougall, S. Belkaya, B.A. Johnson, J.L. Eitson, K.T. Roybal, B. Barylko, J.P. Albanesi, C. Wulfing, and N.S. van Oers, *The CD3 {zeta} Subunit Contains a Phosphoinositide-Binding Motif That Is Required for the Stable*

- Accumulation of TCR-CD3 Complex at the Immunological Synapse*. Journal of immunology, 2011. **186**: p. 6839-6847. 21543646
51. Eitson, J., J.J. Medeiros, A.R. Hoover, S. Srivastava, K.T. Roybal, J.A. Ainsa, E.J. Hansen, T. Gumbo, and N.S. van Oers, *Mycobacterial Shuttle Vectors Designed for High Level Protein Expression in Infected Macrophages*. Submitted, 2011.
 52. Belkaya, S., R.L. Silge, A.R. Hoover, J.J. Medeiros, J.L. Eitson, A.M. Becker, M.T. de la Morena, R.S. Bassel-Duby, and N.S. van Oers, *Dynamic modulation of thymic microRNAs in response to stress*. PLoS ONE, 2011. **6**(11): p. e27580. 3217971

BOOK CHAPTERS

1. Weiss, A., T. Kadlecsek, M. Iwashima, A. Chan, and N.S.C. van Oers. 1995. Molecular and genetic insights into T cell antigen receptor signaling. In *Receptor Activation by Antigens, Cytokines, Hormones, and Growth Factors*. Eds. David Naor, Pierre De Meyts, Marc Feldman and Joseph Schlessinger, Ann. N.Y. Acad. Sci. 766, 149-154.
2. Weiss, A., M. Iwashima, B.A. Irving, N.S.C. van Oers, T.A. Kadlecsek, D. Straus, and A. Chan. 1994. Molecular and genetic insights into T cell antigen receptor signal transduction. In *Mechanisms of Lymphocyte Activation and Immune Regulation V: Molecular Basis of Signal Transduction* (Gupta, S., Paul, W.E., DeFranco, A., and Perlmutter, R.M. Ed.) Plenum Press, N.Y. pp53-62.
3. van Oers, N.S.C., and H-S. Teh. 1993. Intracellular signalling mechanisms required for T cell repertoire selection. In *Advances in Allergy and Immunology: Research Trends* (Ed. J. Menon).

RESEARCH TALKS (2010-2011)

Mayo Clinic, Rochester, MN, Department of Immunology 03/18/10
 UTSWMC, Division of Rheumatology 03/29/10
 UTSWMC, Immunology Retreat Speaker 05/07/10
 UTSWMC, Department of Internal Medicine 05/11/10
 Oxford University, England, Department of Pathology 06/15/10
 UTSWMC, Department of Immunology Excellence in Immunology, 03/16/11
 Children's Medical Center, Dallas, Allergy and Immunology, 04/14/2011
 University of British Columbia, Canada, Immunology Symposium, 06/13/11
 UTSWMC, Medical Scientist Training Program WIPS, 07/26/2011
 Children's Medical Center, Pediatric Infectious Diseases, 01/20/2012

Former/Current PhD Students

Dr. Lisa A. Pitcher- currently a post-doctoral fellow with Dr. Michael Carrol, Harvard University
 Dr. Jennifer A. Young-currently a post-doctoral fellow with Dr. Astar Winoto, UC Berkely
 Dr. Laura M. Deford-Watts- currently a post-doctoral fellow with Dr. Steven Kridel, UNC-Winstom Salem
 Dr. Amy Becker- post-doctoral at Washington University

Mr. Serkan Belkaya (third year graduate student)
Ms. Ashley Hoover (second year graduate student)

Former/Current Post-Doctoral/Medical Fellows

Dr. Teck-Chun Ayi-current researcher in Singapore
Dr. Laura DeFord-Watts (post-doctoral fellow at U. North Carolina, Winston-Salem)
Dr. Amy M. Becker (post-doctoral fellow at Washington University)
Dr. Robert L. Silge, MD (currently in medical practice)
Dr. David Dougall, PhD (currently in bioinformatics)

RESEARCH INTERESTS

Project 1: The antigen specific cells of the immune system, the T and B-lymphocytes, express multi-subunit cell surface receptors (TCR and BCR) that are essential for recognizing and responding to pathogens such as viruses, bacteria, and parasites. T cells have one intriguing feature in that each TCR recognizes a complex containing a small pathogen-derived peptide and a much larger self-protein termed the major histocompatibility complex (MHC). My laboratory has been elucidating how the TCR can discriminate between self-peptides versus foreign peptides bound to the MHC. Effective TCR signaling will elicit diverse biological outcomes such as lymphokine release and cytotoxic functions. Incomplete or attenuated signals may promote T cell death, and in the thymus, may be important for the development of the T cell repertoire. This has led us to an analysis of the intracellular signaling processes regulated by the different TCR subunits. We have been examining the functional roles of the cytoplasmic domains of the CD3 zeta and CD3 epsilon subunits of the TCR complex. The domains interact with families of kinases and phosphatases. We are pursuing several related questions.

1) The CD3 zeta subunit contains three copies of a signaling domain called the ITAM. These are tyrosine phosphorylated following TCR/ligand interactions. We have used transgenic and knockout mice to elucidate the functions of two phosphorylated forms of zeta termed p21 and p23. Our recent experiments have uncovered novel, phospholipid-binding domain in the CD3 zeta and CD3 epsilon subunits. Interestingly, the phospholipid-binding functions of CD3 zeta are required for the formation of a stable immunological synapse. Current experiments are designed to elucidate the functional contribution of these phospholipid-binding motifs using knock-in mice lacking the lipid-binding functions of CD3 zeta and epsilon.

2) The CD3 epsilon subunit contains several signaling domains including the ITAM and a proline-rich stretch. We have discovered recently a novel domain termed the basic rich stretch (BRS). This motif interacts with a serine/threonine kinase termed GRK2. We are addressing the role of this domain using transgenic and knockout mice. Our specific questions are whether this BRS-GRK2 interaction regulates T cell functions and T cell responses to chemokines.

Project 2: A second project in the laboratory pertains to tuberculosis. We are developing a large-scale screen to identify *M. tuberculosis*-encoded genes that suppress innate and/or adaptive immune responses. We developed a novel, high throughput screen to identify the *Mtb* gene products that suppress innate immune functions. There are two key aspects of this screen. First, a genomic expression library, derived from *Mtb*, will be introduced into the fast

growing, non-pathogenic Mycobacterium, *M. smegmatis*. The resulting *M. smegmatis* transformants will be used to assay for the presence of genetic regions that inhibit innate inflammatory responses. The second novel aspect of our approach is the design of a macrophage reporter cell line (innate cell) that fluoresces green once infected with *M. smegmatis*. The green emanates from an inflammatory response promoter, IL-6, linked to the green fluorescent protein. Thus, we will screen for recombinants that suppress GFP expression in the infected reporter cell line.

Project 3: We are developing a microRNA profiling system for children presenting with primary immunodeficiency disorders (PIDs). These disorders often result in life-threatening infections in children, and so far, mutations in over 150 genes have been linked to these immunodeficiencies. MicroRNAs are a recently discovered class of small RNAs that regulate diverse biological processes including immune cell development. We hypothesize that children presenting with PIDs will express microRNA signature profiles distinct from normal controls. MicroRNA array signature profiles will be developed for diverse DiGeorge and hyper-IgM patients. The particular types of microRNAs detected in different PIDs will also be used as a prognostic indicator for complications such as cancers or infections.

Project 4: Environmental stresses can dramatically alter immune cell functions. We have uncovered 17 distinct stress-responsive microRNAs in the murine thymus. We hypothesize that several of these stress-responsive microRNAs regulate critical steps during T cell development. A number of experiments are designed to address how such microRNAs control immune cell development in normal and stressed conditions. The future potential from these studies are to introduce stabilized microRNAs *in vivo* to correct immune system abnormalities.