BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
Ralph C. Budd	Professor of Medicine
eRA COMMONS USER NAME (credential, e.g., agency login) Ralph_Budd	

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
M.I.T., Cambridge, MA			
Cornell University, Ithaca, NY	B.A.	05/1973	Biology
Cornell University Medical College, New York, NY	M.D.	05/1977	Medicine

A. Personal Statement

Dr. Budd is a well-established investigator and leader in the areas of death receptors, such as Fas (CD95), and the activation of downstream caspases in apoptosis and regulation of the immune response. Fas-deficient humans and mice develop an autoimmune disease resembling lupus, as well as profound enlargement of lymph nodes. Dr. Budd is studying the origin of the lymphocytes that accumulate in the absence of Fas-induced death. His group is also examining the Fas signal pathway and has made the paradoxical discovery that caspase-8 is required not only for cell death by Fas, but also to initiate proliferation of T lymphocytes. The switch between cell death and growth appears to be regulated by the caspase-8 paralogue, c-FLIP. Current studies are focused on determining how and where in a cell caspase activity is controlled during cell growth versus cell death. As caspase-8 and c-FLIP are ubiquitously expressed, they are likely to regulate cell growth and death in many cell types.

Dr. Budd's group is also investigating the function of an unusual subset of T lymphocytes known as $\gamma\delta$ T cells in Lyme arthritis. These T cells accumulate in the synovial fluid in patients with various types of inflammatory arthritis, as well as in inflammatory conditions of other organs. These $\gamma\delta$ T cells are activated indirectly by lipopeptides from *Borrelia burgdorferi* via Toll-like Receptor (TLR)2 on dendritic cells. Current studies are producing a soluble $\gamma\delta$ T cell receptor to determine what antigen(s) is recognized by the $\gamma\delta$ T cells.

Dr. Budd has directed the Immunobiology Program at UVM for the past 18 years, and more recently the Vermont Center for Immunology and Infectious Diseases (VCIID) for the past 7 years. He directed the Cell and Molecular Biology Graduate Program and is currently PI for a T32 grant for Immunology and Infectious DIseases. He is a former Pew scholar in the Biological Sciences and was a 2009 UVM University Scholar. He has served on numerous NIH study sections, and chaired four of them.

B. Positions and Honors

1977-1980 Resident in Medicine, Dartmouth-Hitchcock Medical Center, Hanover, NH
1980-1982 Fellow in Rheumatology, Dartmouth-Hitchcock Medical Center, Hanover, NH
1982-1984 Fellow in Immunology/Rheumatology, Dartmouth-Hitchcock Medical Center, Hanover, NH (
1984-1987 Postdoctoral Research Fellow, Ludwig Institute for Cancer Research, Lausanne Branch, Epalinges, Switzerland.
1987-1988 Postdoctoral Research Fellow, Department of Medicine, Division of Immunology, Stanford University School of Medicine, Stanford, CA
1988-1989 Scientist, Division of Molecular Immunology, Genentech, Inc.
Clinical Assistant Professor of Medicine, Stanford University School of Medicine, Stanford CA.

1989-1992 Assistant Professor of Medicine, Department of Medicine, The University of Vermont College of Medicine, Burlington, VT.
1992-1997 Associate Professor of Medicine, Department of Medicine, The University of Vermont College of Medicine, Burlington, VT
1995-present Director, Immunobiology Program; Associate Chair of Medicine for Research
1997-present Professor of Medicine, Department of Medicine, The University of Vermont College of Medicine, Burlington, VT
2006-present Director, Vermont Center for Immunology and Infectious Diseases, The University of Vermont

HONORS (SELECTED)

1983-1986 Arthritis Foundation Postdoctoral Fellow.
1989-1992 RJR Nabisco Research Scholars Award in Immunology.
1990-1994 Pew Scholars Program Award in the Biomedical Sciences.
1994 Member, American Society for Clinical Investigation
2009-2010 University Scholar (The University of Vermont)
2011 Member, Association of American Physicians
2013 Senior Researcher of the Year Award (University of Vermont Medical Group)

C. Selected Peer-reviewed Publications (from over 80)

1. Vincent, M., Roessner, K., Lynch, D., Cooper, S.M., Sigal, L.H., and **Budd, R.C.** Apoptosis of Fas^{high} $CD4^+$ synovial T cells by *Borrelia*-reactive $Fas\text{-}ligand^{high}$ γδ T cells in Lyme arthritis. *J. Exp Med.* 184:2109-2117, 1996. PMID: 8976167
2. Vincent, M.S., Roessner, K., Sellati, T., Huston, C.D., Sigal, L.H., Behar, S.M, Radolf, J.D, and **Budd, R.C**. Lyme arthritis synovial γδ T Cells respond to *Borrelia burgdorferi* lipoproteins and lipidated hexapeptides. *J. Immunol.* 161:5762-5771, 1998. PMID: 9820558
3. Kennedy, N.J., Kataoka, T., Tschopp, J., and **Budd, R.C**. Caspase activation is required for T cell proliferation. *J. Exp. Med.* 190:1891-1895, 1999. PMID: 10601363 PMCID: PMC2195711
4. Kataoka, T., **Budd, R.C**., Holler, N., Thome, M., Martinon, F., Irmler, M., Burns, K., Hahne, M., Kennedy, N.J., and Tschopp, J. The caspase-8 inhibitor FLIP promotes activation of NF-kB and ERK signaling pathways. *Curr. Biol*. 10:640-648, 2000. PMID: 10837247
5. Huber, S., Shi, C., and **Budd, R.C.** γδ T cells promote a Th1 response during infection by selective Fas-dependent killing of Th2 cells. *J. Virol*. 76:6487-6494, 2002. PMID: 12050361 PMCID: PMC136276
6. Roessner, K., Wolfe, J., Shi, C., Sigal, L.H., Huber, S.A., and **Budd, R.C.** High Expression of Fas-Ligand by Synovial Fluid-Derived γδ T cells in Lyme Arthritis *J. Immunol.* 170:2702-2710, 2003. PMID: 12594300
7. Dohrman, A., Kataoka, T., Cuenin, S., Russell, J.Q., Tschopp, J., and **Budd, R.C**. c-$FLIP_L$ regulates $CD8^+$ T cell activation through caspase-8-dependent NF-κB activation. *J. Immunol.* 174:5270-5278 2005. PMID: 15843523
8. Collins, C., Wolfe, J., Roessner, K., Shi, C., Sigal, L.H., and **Budd, R.C.** Lyme arthritis synovial γδ T cells instruct dendritic cells via Fas-ligand. *J. Immunol*. 175:5656-5665, 2005. PMID: 16237055
9. Shi, C., Wolfe, J., Russell, J.Q., Hardin, N., Collilns, C., Anguita, J., and **Budd, R.C.** Fas-Ligand deficiency impairs host inflammatory response against infection with the spirochete, *Borrelia burgdorferi. Infect. Immun.* 74:1156-1160, 2006. PMID: 16428764 PMCID: PMC1360353
10. **Budd, R.C.,** Yeh, W-C, and Tschopp, J. cFLIP regulation of lymphocyte activation and development. *Nature Rev. Immunol.* 6:196-204, 2006. PMID: 16498450
11. Misra, R., Russell, J.Q., Hinshaw-Makepeace, J., Wen, R., Wang, D., Huo, H., Littman, D., Thome, M., and **Budd, R.C**. c-$FLIP_L$ and Caspase-8 Associate in Lipid Rafts to Activate NF-κB During T Cell Activation. *J. Biol. Chem*. 282:19365-74, 2007. PMID: 17462996
12. Anathy, V., Aesif, S.W., Guala, A.S., Havermans, M., Reyneart, N.L., Ho, Y-S., **Budd, R.C.,** and Janssen-Heininger, Y.M.W. Redox amplification of apoptosis by caspase-dependent cleavage of glutaredoxin 1 and S-glutathionylation of Fas. *J. Cell Biol.* 184:241-252, 2009. PMID: 19171757 PMCID: PMC2654302

13. Collins, C., Shi, C., Russell, J.Q., Fortner, K.A., and **Budd, R.C.** Activation of γδ T cells by *Borrelia burgdorferi* is indirect via a TLR and caspase-dependent pathway. *J. Immunol.* 181:2392-2398, 2008. PMID: 18684928 PMCID: PMC2832482
14. Shi, C., Sahay, B., Russell, J.Q., Fortner, K.A., Hardin, N., Sellati, T.J., and **Budd, R.C**. Reduced Immune Response to *Borrelia burgdorferi* in the Absence of γδ T cells. *Infect. Immun.* 2011 Oct; 79(10):3940-6. Epub 2011 Jul 18 PMID: 21768278 PMCID: PMC3187251
15. Thai, P.T., Collins, C.C., Fortner, K.A., Koenig, A., Hayes, S.M., and **Budd, R.C.** Greater caspase activity in human γδ T cells versus αβ T cells primes γδ T cells for increased proliferation and death. *Human Immunol.* 72:1168-75, 2011 [epub]. PMID: 21983117 PMCID: PMC3224150
16. Koenig, A., Fortner, K. A., King, B. R., Madden, J., Buskiewicz, I. A., **Budd, R. C.** Proliferating gamma delta T cells manifest high and spatially confined caspase-3 activity. *Immunology* 135:276-86, 2012. PMID: 22117649 PMCID: PMC3372744
17. Koenig, A., Buskiewicz, I.A., Fortner, K.A., Russell, J.Q., Asaoka, T., He, Y-W., Hakem, R., Erikssom, J.E., and **Budd, R.C.** The c-FLIP$_L$ cleavage product p43FLIP promotes activation of ERK, NF-κB, caspase-8, and T cell survival. *J. Biol. Chem.* In press.
18. Saligrama, P.T., Fortner, K.A., Collins, C.C.,. Russell, J.Q., and **Budd, R.C.** IL-15 maintains T cell survival via S-nitrosylation-mediated inhibition of caspase-3. *Cell Death and Diff.* In press.
19. Buskiewicz, I.A., Koenig, A., Moussawi, M., Roberts, B., Russell, J.Q., Shi, C., Lee, S-W, Jung, J., Huber, A., and **Budd, R.C**. Cellular FLIP-Short Increases Susceptibility to Myocarditis from Coxsackievirus B3. Submitted.

D. Research Support

ONGOING RESEARCH SUPPORT

R01 AR 43520 Budd (PI) **γδ T cells in Lyme Arthritis**
07/01/95-7/14/14
The goals of this project are:
1. *B. burgdorferi:* does it activate synovial Vδ1 T cells directly, or indirectly through Toll-like Receptor 2 (TLR2)-induced upregulation of recognition determinants as well as costimulatory molecules?
2. Synovial γδ T cells: how do they maintain prolonged high expression of FasL
3. Dendritic Cells (DC): does their high expression of the Fas inhibitor FLIP result in Fas signals being diverted from death pathways toward positive differentiation signals that include upregulation of stimulatory molecules for synovial γδ T cells?

T32 AI 055402 Budd (PI) **Immunology / Infectious Diseases Training Grant**
09/01/05-07/31/16
This is a training grant for two graduate students studying in the area of Immunology and Infectious Diseases

P20 GM103496-07 Budd (PI) **Vermont Immunobiology / Infectious Diseases Center** (COBRE)
08/01/2006-06/30/16
The goal of this project is to establish a Vermont Immunobiology / Infectious Diseases Center that will serve to nurture and mentor new faculty, support needed core facilities and seminars, and foster translational research toward a better understanding of the immune response to infectious diseases.

COMPLETED RESEARCH SUPPORT (PAST THREE YEARS)
R21 AI079712 Budd (PI) **A caspase-8 substrate in T cell activation**
07/01/2008-06/30/2010
The goal of this project was to determine whether c-FLIP$_L$ is the substrate for caspase-8 in T cell activation, and that cleaved p43FLIP functions to recruit adaptor proteins important for NF-κB activation.

P01 AI 45666 Budd (PI) **Regulation of CD4 Effector T Cells During Infection**
09/30/99-08/31/11

The goals of this program project were to examine the effects on development and survival of effector CD4 T cells by: (1) histamine receptor polymorphisms (Project 1, PI: C. Teuscher), (2) $\gamma\delta$ T cells Project 2, PI: R. Budd), and (3) IL-6 (Project 3, PI: M. Rincon).

R01 AI 36333 Budd (PI) **Role of Fas in T Cell Development and Function**

09/01/96 - 06/01/12

The goals of this project were:

1. Determine whether $CD8^+$ T cells that make low avidity/affinity TCR interactions with peptide/MHC preferentially give rise to $CD4^-8^-$ TCR$\alpha\beta^+$ T cells.
2. Does the loss of Fas increase the proportion of T cells bearing low affinity TCR interactions with a fixed MHC/H-Y self-peptide?
3. Is Fas expression by host non-T cells important for homeostatic proliferation?
4. Does homeostatic proliferation enhance the frequency and function of self-reactive T cells?