BIOGRAPHICAL SKETCH

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NAME: Bondada, Subbarao

eRA COMMONS USER NAME (credential, e.g., agency login): Subbarao.bondada

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Andhra Loyola College, Vijayawada, India	B.Sc.	5/1968	Math, Phys, Chem.
Indian Institute of Technology, Kanpur, India	M.Sc.	5/1970	Chemistry
Tata Institute of Fundamental Research, Mumbai, India	Ph.D.	5/1976	Molecular Biology
Laboratory of Immunology, Dr. W.E. Paul, NIH	Fogarty Visiting Fellow	2/1979	Immunology

Please refer to the Biographical Sketch sample in order to complete sections A, B, C, and D of the Biographical Sketch.

A. Personal Statement

I have extensive experience in B and T cell biology, B lymphoma growth regulation, B-cell dendritic cell interactions and immune senescence in the context of B-cell and macrophage function. This research has led to more than 130 peer reviewed publications including several invited articles. I have directed doctoral and Master's theses of 18 students and mentored ~15 postdoctoral fellows, many of whom have independent faculty positions in institutions such as CDC, Ohio State University, University of Arizona, FDA and in Pharmaceutical giants like Merck, Eli Lily etc. I have also served as an Associate Editor for the Journal of Immunology and was a member of the Editorial Board for Infection and Immunity. I am currently an Associate Editor for Frontiers in Immunology. I was a member of the Membership Committee for American Association of Immunologists. I had been a member of the Executive Council for the Autumn Immunology which held its 48th annual meeting in Chicago in November of 2018. At the University of Kentucky, I serve on advisory committees for several graduate students and was a member of the Faculty Council for the College of Medicine and the University Senate. I am the course director for the MI685 course on Immunobiology, Infection and Inflammation. My research has been funded by NIH continuously for the past 35 years. I have been the Director of an NCI funded Program Project Grant on Growth Regulation and Therapy of leukemias and lymphomas. Currently I am a member of the NCI SubCommittee F that focuses on training.

I am very focused on graduate student and postdoctoral training. I meet with each of my students once a week to discuss their progress, during which time I challenge them about the course of action to take after each series of experimental studies. A former student of mine is currently full Professor at the Ohio State University in the Department of Hematology with a vigorous research program that is well funded by NIH and foundations. Another former student is currently a tenured Associate Professor at the University of Arizona. One former postdoctoral fellow is Chief of the Malaria branch at CDC and two are scientists at the FDA. I am deeply committed to graduate student training and our department offers a rich training environment. I have trained over 40 graduate students, postdoctoral fellows, high school and undergraduate students in my laboratory. There have been several student trainees in my laboratory who were from under-represented groups, including my latest Ph.D. student who graduated last November and was from Eastern Kentucky. I have mentored Dr. Cheri Landers, a clinician in College of Medicine (COM) who is now a full Professor in the Dept. of Pediatrics

and I am a member of three mentorship committees for three junior investigators. Dr. Mosoka Faalh, one of my Ph.D. students was a member of the TIME person of the year for 2014 as an Ebola fighter.

My laboratory is very much interested in B-cell lymphoma and leukemia growth regulation as well as biomarkers of lymphoma. We have extensive experience in the study of B-lymphomas and leukemias. In the past my laboratory has shown that c-jun N-terminal kinase, a MAPkinase, and one of its transcription factor targets, Egr-1 (early growth response-1), are very important for the growth of B lymphomas. We were the first to demonstrate a requirement for constitutive B cell receptor (BCR) expression for the continued growth of already transformed B cells using B-lymphoma models. Recently, we have determined that Syk and Lyn, two protein tyrosine kinases, downstream targets of BCR signaling are constitutively active in B lymphomas. Inhibition of these two kinases inhibits growth of B lymphomas in vitro and in vivo. Recent studies in leukemia models confirmed our original findings and have led to development of several new small molecules that inhibit BCR signaling pathways. Clinical trials with Syk and SFK inhibitors are in progress showing some promise. Recently we have shown that withaferin A, a steroid lactone isolated from the plant, *Withania somnifera,* inhibits the growth of B lymphoma cells by targeting heat shock protein 90. We have extended our observations on the role of B cell receptor signaling to chronic lymphocytic leukemia (CLL). In fact Ibrutinib, an inhibitor of Btk downstream of BCR signaling, has been approved as a first line therapy for treating CLL patients. We made the novel observations that CLL B cells constitutively produce IL-10 and Par-4 which are regulated by tonic B cell receptor signaling and that splenic microenvironment is important for CLL growth. My laboratory has extensive experience in studying normal and malignant B cells, signal transduction mechanisms, macrophage function and regulation of immune response by IL-10.

1. Gururajan, M., Roger Chui, A. K. Karuppannan Jiyuan Ke, C. Darrell Jennings and **S. Bondada**. c-Jun N-terminal kinase (JNK) is required for survival and proliferation of B lymphoma. Blood 106: 1382-1391 (2005). PMCID: 1895189
2. McKenna M. K., S. K. Noothi, S. S. Alhakeem, K. Z. Oben, J.T. Greene, R. Mani, K. L. Perry, J. P. Collard, J. R. Rivas, G. Hildebrandt, R. A. Fleischman, E. B. Durbin, J. C. Byrd, C. Wang, N. Muthusamy, V. M. Rangnekar, **S. Bondada**. Novel role of prostate apoptosis response-4 tumor suppressor in B-cell chronic lymphocytic leukemia. Blood. 2018 131(26):2943-2954. doi: 10.1182/blood-2017-10-813931. PMCID: 6024641
3. McKenna, M, K., B. W. Gachuki, S. S. Alhakeem, K. N. Oben, V. R. Rangnekar, R. C. Gupta, and **S. Bondada**. Anti-cancer activity of withaferin A in B-cell lymphoma. Cancer Biology and Therapy 16: 1088; (2015) PMCID:4622669
4. Alhakeem, S., M. K. McKenna, K.Z. Oben, S.K. Noothi, J. R. Rivas, G.C. Hildebrandt, R.A. Fleischman, V. M. Rangnekar, N. Muthusamy, and **S. Bondada**. Chronic lymphocytic leukemia derived interleukin-10 suppresses anti-tumor immunity. J. Immunol. 200(12):4180-4189 (2018) PMID:29712773

B. Positions and Honors

Positions and Employment

1979-1983 Research Associate; The Institute for Cancer Research, Philadelphia, PA 19111
1981,1984 Visiting Fellow, Basel Inst Immunology, Basel, Switzerland,
1986-1989 Assist. Professor, Dept. of Microbio. and Immunol., Center on Aging, Univ. of Kentucky
1989-1995 Associate Professor, Dept. of Microbiology & Immunology, Center on Aging Univ. of Kentucky
1986-Present Member, Markey Cancer Center and Associate, Sanders Brown Center on Aging
1993-1994 Visiting Assoc. Professor, Howard Hughes Medical Institute, University of Washington, Seattle
1995-Present Professor, Dept. of Microbiology, Immunology and Molecular Genetics, University of Kentucky
1995-Present Professor, Graduate Program in Toxicology and Cancer Biology
1997-Present Professor, Graduate Center in Gerontology

Other Experience and Professional Memberships

1982-Present Member, American Association of Immunologists
1993 NIH Site Visit Teams. (Cancer Center and Program Project grants)
1993,1996 Ad hoc member of Study section, NIAID, NIH
1996-2001 Member, Allergy, Immunology and Transplantation Advisory Committee, NIAID, NIH
1997-2000 AAI Membership Committee;
1998-2003 Assoc. Editor, Journal of Immunology
1999-2002 Editorial Board, Infection and Immunity

1999-2008 Member, Molecular Immunology Study Section for National Arthritis Foundation
2001,2002 Chair and Member, Teleconference T32 Review Panels, AITRC, NIAID
2003 PO1, KO8 and Immunodeficiency Consortium &T32 Review Panels, NIAID; 2003
2004-2007 Ad hoc Member of Transplantation, Tolerance & Tumor Immunity Study Section, NIH.
2006 Innate Immunity & Aging SEP, NIH, Autoimmunity Cooperative Agreements SEP, NIH
2008 NIH, CSR, HAI Study Section ad hoc (2008)
2008-2009 DOD Lymphoma leukemia Research Panel (2008, 2009)
2008-2012 Regular member HAI Study Section, CSR, NIH
2012-Present Associate Editor, Frontiers in Immunology
2011-Present Associate Editor, Current Reviews in Immunology
2011-2019 American Cancer Society, LIB Review Panel
2013 Adhoc Member, HAI Study Section, CSR, NIH
2013 Ad hoc member, HAI Study Section Overflow Panel, CSR, NIH
2014 Ad hoc member, MIST Study Section, CSR, NIH
2014-2015 NSF – GSRF Panel
2015-2016 Ad hoc member, HAI and CMI Study Sections, CSR, NIH
2016-2020 Member, NCI Sub Committee F, Institutional Training and Education
2018 NIH Special Emphasis Panel ZCA1 RPRB-L (J2) S

Honors

1982, '84,'88 Teacher -, in the IUIS and ICRO Courses (Immunol.) in Bombay and Delhi, India;
1988–1991 Workshop Chairman, 17th Midwest Autumn Immunology Conference, St. Louis, MO.
1988 Invited speaker in ASM symposium; Dallas, TX 1990
1993 Visiting Professor ASM Minority Program
2006 Recipient of University Research Professor Award
2003 Invited Plenary Symposia Speaker – Autumn Immunology Conference, Chicago
2009 Chair, Block Symposium, American Association of Immunologists
2013-2018 Member, Executive Council, Autumn Immunology Conference

C. Contributions to Science

1. In addition to my experience in studying B lymphoma growth regulation, we have extensive track record in studying normal B cell function in the context of CD72 and other B cell surface markers. We were instrumental in defining Lyb5 and Lyb7 antigens before the era of monoclonal antibodies that defined B cell subsets and in defining CD22 and CD72 signaling molecules after the advent of hybridoma technology. CD22 is a well characterized negative regulator of B cell responses. CD72 has both positive and negative roles in B cell responses. Our work played a key role in defining the CD72 signaling pathway, especially the importance of protein tyrosine kinases such as btk, and its positive role in B cell activation. Our work was also important in demonstrating that CD72 was not the receptor/ligand for the CD5 molecule.

We have made seminal observations about the negative signaling role of CD5 in B cell receptor signaling in B-1 cells and the autoregulatory properties of B-1 cells in an IL-10 dependent manner. This research led me to question the importance of CD5 for T-reg function resulting in our novel finding that CD5 negatively regulates T-reg function presumably by affecting TCR signaling. More recently we showed that CLL cells from Emu-Tcl1 mice constitutively produce IL-10, which is dependent on constitutive signaling by BCR. CLL derived IL-10 inhibits the host immune response to CLL. We demonstrated that Par-4, a tumor suppressor gene has a novel role in CLL and that its expression is regulated by BCR signaling.

a. Bikah, G., J. Carey, J. Ciallella, A. Tarakhovsky and **S. Bondada**. CD5 Mediated Negative Regulation of Antigen Receptor-Induced Growth Signals in B-1 B cells. Science 274: 1906-1909 (1996). PMID: 8943203
b. Sindhava, V. and S. **Bondada.** Multiple regulatory mechanisms control B-1 B cell activation. Frontiers in Immunology 3: 372 (2012); PMCID: 3523257
c. Alhakeem, S.*, V. Sindhava*, B. Gachuki, K. McKenna, N. Muthusamy, J. Byrd and **S. Bondada.** Role for B cell receptor signaling pathway in constitutive secretion of IL-10 by normal and malignant B-1 cells. Annals of NY Academy of Sciences 1362: 239 (2015) (*co-first authors); PMCID: 4676736
d. McKenna M.K., S.K. Noothi, S.S. Alhakeem, K.Z. Oben, J.T Greene, R. Mani, K.L. Perry, J.P. Collard, J.R. Rivas, G. Hildebrandt, R. Fleischman, E.B. Durbin, J.C. Byrd, C. Wang, N. Muthusamy, V.M. Rangnekar and S. Bondada. Novel role of prostate apoptosis response-4 tumor suppressor in B-cell

chronic lymphocytic leukemia. Blood. 131:2943-2954 (2018). doi:10.1182/blood-2017-10-813931. t PMID:29695515

2. We have made a key observation about the importance of macrophages and B cells for antibody responses to T-independent antigens. We were the first ones to demonstrate a macrophage defect in both neonates and the aged that plays a key role in their defective immune responses to polysaccharide antigens from encapsulated bacteria. We showed that the spleen is required for anti-polysaccharide responses and that lymph node cells require additional macrophages to respond to pneumococcal polysaccharides. We demonstrated a dysregulation of cytokine production by spleen macrophages in response to a variety of TLR ligands in both neonates and the aged. We also identified two key pathways that have a role in this cytokine dysregulation, namely the p38 MAPkinase pathway and the PI3-kinase-Akt pathway. We have also worked with human B cell responses and the effect of age on such response.

a. Fallah, M. P., R. L. Chelvarajan, B.A. Garvy, **S. Bondada**. Role of Phosphoinositide 3-Kinase-AKT signaling pathway in the age-related cytokine dysregulation in splenic macrophages stimulated via TLR-2 or TLR-4 receptors. Mech Ageing Dev 132: 274-286 (2011). PMCID: 3155631
b. Chelvarajan, R. L., D. Popa, Y. Liu, T.V. Getchell, A.J. Stromberg and **S. Bondada**. Molecular mechanisms underlying anti-inflammatory phenotype of neonatal splenic macrophages. J. Leuk. Biol. 82:403-16. (2007) PMID: 17495050
c. Chelvarajan, R. L., Y. Liu, D. Popa, M.L. Getchell, T.V. Getchell, A.J. Stromberg and **S. Bondada**. Molecular basis of age-associated cytokine dysregulation in LPS-stimulated macrophages. J. Leuk. Bol. 79: 1314-1327 (2006). PMID: 16603589
d. Garg, M., A.M. Kaplan and **S. Bondada**. Cellular basis of differential responsiveness of lymph node and spleen to 23 valent Pnu-Imune vaccine. J. Immunol.152: 1589-1595 (1994).PMID:8120372

3. We became interested in understanding the regulatory properties of dendritic cells (DC). We were the first to demonstrate that immature DC and bone marrow resident DC suppress B cell responses to TLR and BCR signaling. This might have a role in presentation of soluble self-antigens to B cells in the bone marrow allowing their efficient inactivation. Also we have shown that DCs can regulate inflammatory responses in the colitis models and that this may depend on the PPAR-γ pathway.

a. Sindhava, V.J., H. Tuna, B. W. Gachuki, D. J. DiLillo, M. G. Avdiushko, T. M. Onami, T. F. Tedder, D. A. Cohen and **S. Bondada**. Bone marrow dendritic cell-mediated regulation of TLR and B cell receptor signaling in B cells. J. Immunology: 189(7):3355-67 (2012). PMCID: 3495978
b. Frantz, A. L., Bruno, M. E., Rogier, E. W., Tuna, H., Cohen, D. A., **Bondada, S.,** Chelvarajan, R. L., Brandon, J. A., Jennings, C. D. and Kaetzel, C. S. (2012), Multifactorial patterns of gene expression in colonic epithelial cells predict disease phenotypes in experimental colitis. Inflammatory Bowel Diseases 18(11):2138-48 (2012). PMCID: 3476470
c. Tuna, H., Rita G. Avdiushko, Vishal J. Sindhava, Leia Wedlund, Charlotte S. Kaetzel, Alan M. Kaplan, **S. Bondada** and Donald A. Cohen Regulation of the mucosal phenotype in dendritic cells by PPARγ: role of tissue microenvironment J Leukoc Biol. 95(3):471-85 (2014). PMCID: 3923081

4. More recently we are investigating the role of oxidative stress in hematologic malignancies. Our work shows that oxidative stress can affect normal and malignant bone marrow cells. A superoxide dismutase mimetic enhances bone marrow stem cell survival while increasing oxidative stress with the natural product withaferin A inhibits growth of myelodysplastic syndrome cells.

a. Zhao, Y., D. W. Carroll, Y. You, R. Wen, L. Chaiswing, **S. Bondada**, I. Batinic-Haberle, Y. Liang and D.K. St. Clair. A Novel Redox Regulator, MnTnBuOE-2-PyP5+, Enhances Normal Hematopoietic Stem/Progenitor Cell Function. Redox Biology 12:129-138. PMCID:5320058
b. Oben, K.Z., B.W. Gachuki, S. S. Alhakeem, M. K. McKenna, Y. Liang, D. K. St. Clair, V. M. Rangnekar, **S. Bondada**. Radiation Induced Apoptosis of Murine Bone Marrow Cells is Independent of Early Growth Response 1 (EGR1). PLoS One. 2017 Jan 12;12(1):e0169767. doi: 10.1371/journal.pone.0169767. eCollection 2017. PMCID:5230770
c. Oben, K. Z. S. S. Alhakeem, M. K. McKenna, J. A. Brandon, R. Mani, S. K. Noothi, L. J., S. Akunuru, S. K. Dhar, I. P. Singh, Y. Liang, C. Wang, A. Abdel-Latif, H. F. Stills, D. K. St Clair, H. Geiger, N. Muthusamy, K. Tohyama, R. C. Gupta, **S. Bondada** Oxidative stress-induced JNK/AP-1 signaling is a major pathway involved in selective apoptosis of myelodysplastic syndrome cells by Withaferin-A Oncotarget (2017) ;8(44):77436-77452. doi: 10.18632/oncotarget.20497. PMCID: 5652791

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/collections/mybibliography/

D. Research Support

Ongoing

R01 HL138179 (PI: Whiteheart, S) NIH 07/01/17-03/31/21
"Platelet Endocytosis in Innate Immunity"
Goals: To study the role of platelet endocytosis in TLR-based signaling.
Role: Co-Investigator

R01 CA217934 (MPI: St Clair, D [contact]) NIH 09/15/17-07/31/22
"A Redox-mediated Mechanism of Chemotherapy-induced Cognitive Impairment"
Goal: To define the role of redox pathway in chemotherapy induced impairment in cognition.
Role: MPI with St Clair, D [contact]; Bondada, S; Butterfield, DA

R01 CA217934 Supplement (MPI: St Clair, D [contact]) NIH 08/01/18-07/31/19
"A Redox-mediated Mechanism of Chemotherapy-induced Cognitive Impairment"
Goal: determine extracellular vesicles of biomarkers of cognition impairment in Alzheimer's disease patients that had cancer.
Role: MPI with St Clair, D [contact]; Bondada, S; Butterfield, DA

1R44CA221487-01 Subcontract
3P Biotechnologies and the University of Louisville (PI: Ramesh Gupta) 4/01/18 to 9/01/19
Exosomal delivery of anti-cancer drugs
Role: PI for the subcontract

UL1 TR001998 02 Center for clinical and translational science, University of Kentucky 3/15/18 – 9/14/19
Enhancement of anti-tumor responses by blocking inhibitory effects of chronic lymphocytic leukemia derived interlukin-10.
Role: Corresponding PI for multiple PI grant with Dr. M. Leggas

T32 CA165990-05 NCI/NIH 7/1/2017 to 7/1/2019
Interdisciplinary research training in cancer biology
PI: Vivek M. Rangnekar
Role: Mentor for Dr. Jackie Rivas

Pediatric Cancer Research Trust Fund
Chemotherapy induced cognition impairment – Mechanisms and Prevention 7/01/18 to 6/30/20
PI: Daret St. Clair
Role: Project Co-Leader

Completed Research Support:

PI of Consortium to study "Molecular Mechanisms and Therapies for Radiation-induced Myelodysplastic Syndrome (MDS**)"** from Edward P. Evans Foundation.
No overlap
Period: 4/01/2015-9/30/2015.
1R01CA139843-04 PI Name: St. Clair, Daret
Proposal Title: MnSOD in chemotherapeutic-induced cardiac injury – Goals are to determine how inhibition of free radicals by superoxide dismutase protects acts against chemotherapy induced cardiac injury.
No overlap
Period: 8/20/09-3/31/2015; Role: Co-Investigator

R01 CA165469 (MPI: Bondada S [contact]; NIH 02/07/13-01/31/19
"Role of Tcl1 and Par-4 in Regulation of Chronic Lymphocytic Leukemia"
Goals are to determine the interaction between Tcl1 and Par-4 in the survival of CLL cells.
Role: Contact MPI