BIOGRAPHICAL SKETCH

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NAME: Kavitha Yaddanapudi

eRA COMMONS USER NAME: K0YADD01

POSITION TITLE: Associate Professor of Surgery

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	COMPLETION DATE	FIELD OF STUDY
Osmania University, Hyderabad, India	BSc	1994	Chemistry, Microbiology & Botany
Madurai Kamaraj University, Madurai, India	MSc	1996	Biotechnology
Indian Institute of Science, Bangalore, India	PhD	2004	Immunology
Columbia University, New York, NY	Post-Doc	2009	Immunology

A. Personal Statement

My role will be that of a Project Co-PI for Research Project # 2 in this U54 Program. I am an Associate Professor of Medicine at the University of Louisville. I have over 15 years of experience in functional immune cell assessment, design and development of immune monitoring techniques and flow cytometry. I hold a PhD in viral immunology from the Indian Institute of Science, India. I continued my research in viral immunology as a post-doctoral fellow with Dr. Ian Lipkin at Center for Infection and Immunity at Columbia University in New York. During this time, I studied the cross-talk between innate and adaptive immune responses generated during the course of viral and bacterial infections in mouse models. Since arriving here at the University of Louisville and establishing my own laboratory in the JG Brown Cancer Center, I have fully acquainted myself with the field of tumor immunology. During this period, I have published over 20 manuscripts in the field of Onco-Immunology. I have successfully administered and directed two NCI-funded R21 grants as the PI. I have successfully coordinated projects and collaborated with other researchers and have demonstrated a record of productive research. The current U54 project proposal builds logically on my expertise in flow cytometry and murine models which makes me uniquely suited to carry out the proposed work. The goal of the proposed U54 project is to test the hypothesis that poor clinical outcomes from SARS-CoV-2 in cancer patients receiving therapy are caused by the amplification of the PD-1^{+}CXCR3^{+} T effector cell/CXCR3 ligand-mediated cognate responses to SARS-CoV-2. As the Co-PI of this proposal, I will oversee the processing and analyses of murine and melanoma patient samples using CyTOF and functional studies to characterize the effects of SARS-CoV-2 infection on circulating and intra-tumoral immune cell mediators' phenotype and function. All immune monitoring measurements and ICI therapy outcome correlations will be analyzed in collaboration with all the project investigators Drs. Jason Chesney (Project PI and Co-PI on this U54 grant), Jun Yan (Project Co-I and Co-PI on this U54 grant) and Melissa Smith (Project Co-I). My lab uses comprehensive technologies for the preclinical and clinical assessment of immune cell phenotype and function in samples collected from various disease-bearing animals and humans. These include preclinical and clinical specimen processing, banking, developing cell culture tools for *in vitro* stimulation, flow cytometry, and measurement of anti-tumor T-cell function using cytokine and ELISPOT assays. Data from these studies can be used as metrics for measuring active responses to immunotherapies. I am confident that my expertise in immunology/flow cytometry along with Dr. Chesney's expertise with melanoma clinical trials and immune checkpoint inhibitors will ensure a productive and successful collaboration.

B. Positions and Honors

2009–2010 *Associate Research Scientist*, Center for Infection and Immunity, Columbia University, NY
2010–2012 *Instructor*, Department of Medicine (Hematology/Oncology), University of Louisville
2010–2012 *Assistant Scientist*, James Graham Brown Cancer Center, University of Louisville

2012– *Assistant Professor*, Department of Medicine (Hematology/Oncology), University of Louisville
2012– *Associate Scientist*, James Graham Brown Cancer Center, University of Louisville
2013– *Faculty Member*, Graduate School of Department of Medicine, University of Louisville
2014– *Associate Faculty*, Department of Microbiology & Immunology, University of Louisville
2019–2020 Assistant Professor, Department of Surgery, Division of Immunotherapy, University of Louisville
2020– Associate Professor, Department of Surgery, Division of Immunotherapy, University of Louisville

Honors

1994–1996 *Student Fellowship*, Department of Biotechnology, Government of India
1996–2002 *Junior and Senior Research Fellowship*, Council of Scientific and Industrial Research, Government of India
1996–2002 *Junior and Senior Research Fellowship*, IISc, Bangalore India
2005–2007 *Young Investigator Award*, National Alliance for Research on Schizophrenia and Depression (NARSAD)
2011 *Roger Herzig Junior Faculty Research Award*, University of Louisville
2014 *Roger Herzig Junior Faculty Research Award*, University of Louisville

C. Contribution to Science

1. I completed my graduate studies in the laboratory of Dr. R. Manjunath at Indian Institute of Science, India. My initial studies evaluated the induction of protective immunity against neurotropic viral infections (Japanese Encephalitis and West-Nile viruses). These studies provided important insights into alterations induced in the host thymic function and in the host lymphocyte response towards specific viral antigens and other recall antigens during the course of an acute viral infection in the brain.

A. **Kavitha Y**, Manjunath R. (**2004**) Induction of MHC 1 and thymic depletion due to replication of JEV in mouse brain. *Arch Virol* 149:2079-93. PMID: 15503198

B. **Kavitha Y**, Manjunath R. (**2007**) Replication of JEV in mouse brain induces alterations in lymphocyte response. *Acta Virol* 51:179-87. PMID: 18076308

C. Abraham S, **Yaddanapudi K**, Thomas S, Damodaran A, Ramireddy B, Manjunath R. (**2008**) Nonclassical MHC-I and Japanese encephalitis virus infection: induction of H-2Q4, H-2T23 and H-2T10. *Virus Res* 133:239-49. PMID: 18314211

2. I conducted my post-doctoral studies with Dr. Ian Lipkin at the Center for Infection and Immunity (CII), Columbia University, NY. At CII, I worked on several multi-disciplinary projects that focused on delineating the effects of a peripheral immune challenge on the nervous system. My initial work at CII clearly established the link between the triggering of neuropsychiatric syndrome and strep throat infection. PANDAS is an abbreviation for Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal (Strep) Infections. Using an autoimmune-disease susceptible strain of mice, we showed for the first time that exposure to strep triggered OCD-like repetitive behaviors and auto-antibodies that attacked specific molecules in the mouse brain (A). PANDAS-like behaviors also emerged in naïve mice after they received antibodies passively from such PANDAS mice (A). The mouse model findings support the view that PANDAS is a distinct disorder and represent a key advance in tracing the path leading from an ordinary infection in childhood to the surfacing of a psychiatric syndrome. These compelling findings opened up several new treatment options for the disease. NIMH (NIH) post cited this work as one of the key research finding in the field of PANDAS (*http://www.nimh.nih.gov/about/director/2010/microbes-and-mental-illness.shtml*). Based on our findings (A) and a related study conducted by investigators at Yale University, NIMH (with support from a NIH Clinical Center *"Bench to Bedside"* award) launched a new clinical trial of intravenous immunoglobulin (IVIG) treatment for children with PANDAS. I also contributed to projects examining the potential role of viruses and innate immune responses on prenatal brain development and in the genesis of schizophrenia (B–D).

A. **Yaddanapudi K**, Hornig M, Serge R, De Miranda J, Baghban A, Villar G, Lipkin WI. (**2010**) Passive transfer of streptococcus-induced antibodies reproduces behavioral disturbances in a mouse model of Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus (PANDAS). *Mol Psychiatry (Nature Publishing Group)* 15:712-27. PMID: 19668249 **(*Cover Article*)**.

B. De Miranda J, **Yaddanapudi K**, Hornig M, Lipkin WI. (**2009**) Astrocytes recognize intracellular polyinosinic-polycytidylic acid via MDA-5. *FASEB J* 23:1064-71. PMID: 19036857 **(*Cover Article*).**

C. De Miranda J*****, **Yaddanapudi K***, Hornig M, Villar G, Serge R, Lipkin WI. (**2010**) Gestational induction of TLR3-mediated immunity inhibits cortical neurogenesis and causes behavioral disturbances. *MBio*. Oct 5;1(4). pii: e00176-10. PMID: 20941330 ****Contributed Equally***.

D. **Yaddanapudi K**, De Miranda J, Hornig M, Lipkin WI. (**2011**) Toll-like receptor 3 regulates neural stem cell proliferation by modulating the Sonic Hedgehog pathway. *PLoS One.* Oct 25; 6(10):e26766. PMID: 22046349

3. At CII, I was part of a team that was actively developing vaccines for the treatment of Filoviral infections, such as those caused by Marburg and Ebola. The Ebola virus infection is characterized by immune suppression and a systemic inflammatory response that eventually leads to multi-organ failure and shock. Using a variety of molecular/immunological techniques, we were the first to demonstrate that the Filoviruses disarm their hosts by means of a glycopeptide wherein the primary functional domain is a 17-mer amino acid peptide (A). In collaboration with Drs. Jonathan Towner and Stuart Nichol at the CDC, we deciphered precisely how filoviral glycopeptides disarm the immune system (A). This study opened up an appealing avenue towards the development of a treatment strategy for Ebola viral infections that focuses on targeting these amino acids and disrupting their interactions, hence, reviving the immune response.

A. **Yaddanapudi K**, Palacios G, Towner JS, Nichol ST, Chen I, Sariol CA, Lipkin WI. (**2006**) Implication of a retrovirus-like glycoprotein peptide in Ebola virus and Marburg virus immunopathogenesis. *FASEB J* 20:2519-30. PMID: 17023517 ***(cover article)***.

4. My current research efforts at UofL are focused on developing novel immunotherapeutic strategies for the treatment of different solid tumors, including lung and melanoma (A–C). We are evaluating the use of an embryonic stem cell-based vaccine (ES cell vaccine) as a potential immunotherapeutic agent for treating lung cancer. Our initial observations have shown that ES cell vaccination effectively prevents both implantable and carcinogen-induced lung adenocarcinoma development (A, B). Recent data from our lab have indicated, for the first time, that ES cell-based vaccination strategy can generate an immunologic reaction against cancer-initiating stem cells (CICs). Lung CICs are resistant to systemic therapies, such as chemotherapy, targeted agents or radiation therapy, and contribute to cancer relapse in patients. By evaluating the lung CICs as targets for our stem cell vaccination strategy, our studies will provide important insights towards developing a 'first-of-its-kind' immunotherapeutic approach for the prevention of lung cancer recurrence. We are currently testing the translational potential of ES cell-derived exosomes (ES-exo) as a novel cell-free vaccine for lung cancer. This technique of using ES-exo based vaccine in which ES cell derived exosomes can exploit the anti-tumor immunity generating capabilities of ES cells while bypassing the risk of teratoma formation holds great promise in lung cancer immunotherapy.

A. **Yaddanapudi K**, Mitchell RA, Putty K, Willer S, Sharma RK, Yan J, Bodduluri H and Eaton JW. (**2012**) Vaccination with Embryonic Stem Cells Protects against Lung Cancer: Is a Broad-Spectrum Prophylactic Vaccine against Cancer Possible? *Plos One*; (7):e42289. PMID: 22860107

B. **Yaddanapudi K**, Mitchell RA and Eaton JW. **(2013)** Cancer vaccines: Looking to the future. *Oncoimmunol.* 2 (3); Mar. 2013; eLocation ID: e23403. PMID: 23802081

C. Shidal C, Al-Rayyan N, **Yaddanapudi K***, Davis KR*****. (**2016)**. Lunasin is a novel therapeutic agent for targeting melanoma cancer stem cells. *Oncotarget* Dec 20;7(51):84128-84141. PMID: 27566591. ***Corresponding authors.**

D. **Yaddanapudi,** K*., Meng, S., Whitt, A.G., Al Rayyan, N., Richie, J., Tu, A., Eaton, J.W., Li, C. **(2019)** Exosomes from GM-CSF expressing embryonic stem cells are an effective prophylactic vaccine for cancer prevention. *OncoImmunology*. 8:3. 2162402X.2018.1561119 (PMID: 30723593). ***Corresponding author.**

5. The second major focus of my current research is to investigate the role of soluble cytokines, in modulating the functions of immunosuppressive myeloid cells within the cancer microenvironment, both in mice and in cancer patients. Working with Dr. Robert A. Mitchell's and Dr. Howard Donninger's group here at the JGBCC, we recently showed that stromal myeloid-derived cytokines (MIF and IL-6) contributes to the immunosuppressive and pro-angiogenic microenvironment that constitutes cancer lesions. We further showed that small molecule targeting of cytokines is sufficient to induce pro-inflammatory, immunocompetent, and reduced angiogenic phenotypes within malignant cancer lesions (A, B). Our more recent findings indicate that small molecule

inhibitors of MIF activity dramatically attenuate the suppressive properties of circulating monocytic myeloid-derived suppressor cells (MDSCs) isolated from late stage metastatic melanoma patients, thereby, confirming MIF as a critical mediator of MDSC-dependent immune suppression in patients with advanced stage melanoma. Furthermore, inhibition of MIF activity effectively induces differentiation of MDSCs into immunostimulatory dendritic Cells (DCs) with concomitant improvement in antigen-specific T-cell-mediated immune responses (C). These results provide strong support to the rationale that therapeutic inhibition of human melanoma MDSCs represents a clinically viable approach to enhancing anti-tumor T cell immunity in advanced cancer patients receiving immunotherapy (D).

A. **Yaddanapudi K***, Putty K, Rendon BE, Lamont GL, Faughn JD, Satoskar A, Lasnik A, Eaton JW and Mitchell RA*. **(2013)** Control of tumor-associated macrophage alternative activation by MIF. J. Immunol. Mar 15; 190 (6). PMID: 23390297 ***Corresponding authors**

B. R.A. Mitchell and **Yaddanapudi K (2014)** Stromal-dependent tumor promotion by MIF family members. Cell Signal. 26(12):2969-2978. PMID: 25277536

C. **Yaddanapudi K*,** B.E. Rendon, G. Lamont, E.J. Kim, N. Al Rayyan, J. Richie, S. Albeituni, S. Waigel, A. Wise and R.A. Mitchell* **(2016)** MIF is necessary for late-stage melanoma patient MDSC immune suppression and differentiation. *Cancer Immunol. Res.* (*AACR*) PMID: 26603621. ***Corresponding authors**

D. Chesney, J, Mitchell RA, and **Yaddanapudi K**. **(2017)** Myeloid-derived suppressor cells—a new therapeutic target to overcome resistance to cancer immunotherapy. *J Leukoc Biol.* 2017 May 25. pii: jlb.5VMR1116-458RRR. doi: 10.1189/jlb.5VMR1116-458RRR. [Epub ahead of print]

Complete List of Published Work in My Bibliography:

https://www.ncbi.nlm.nih.gov/sites/myncbi/kavitha.yaddanapudi.1/bibliography/48208006/public/?sort=date&direction=descending

D. Additional Information: Research Support and/or Scholastic Performance

Agency: NIH/NCI R21 **(PI)** 12/07/19 – 12/06/21
Title: "Overcoming resistance to cancer immunotherapy by targeting MDSC-derived adenosine"
Description: The major goal of the proposed project is to test the hypothesis that in lung cancer patients, aberrant accumulation of CD73-expressing myeloid derived suppressor cells (MDSCs) leads to an increase in the generation of adenosine in the tumor microenvironment that further enhances MDSC-mediated suppressive activities on T cells that leads to immunotherapeutic resistance.

Agency: NIH/NCI P20GM135004 **(Project PI)** 02/01/20 – 1/31/2023
Title: "Targeting CD73 signaling in MDSCs to enhance the efficacy of cancer immunotherapy"
Description: The major goal of the proposed project is to test the hypothesis that in lung cancer patients, cAMP/CREB is also required and acts in tandem with STAT3 to regulate PGE_2-induced CD73 expression in M-MDSCs.

Agency: NIH/1U01AA026225 (**Co-I**, PI: Sirish Barve) 09/22/17 – 08/31/22
Title: "Alcohol Associated Comorbidities and Microbiome Evaluation in HIV (ACME HIV 1/2)"
Description: The goal of the proposed U01 research program is to assess longitudinal qualitative and quantitative changes in the gut microbiome (dysbiosis) associated with very heavy alcohol consumption and to determine the impact of HIV infection and alcohol abuse induced gut dysbiosis on intestinal permeability, microbial translocation (MT), and resultant peripheral endotoxemia, immune activation and inflammation.

Agency: Hyundai Foundation (**Co-PI,** PI: Ashok Raj) 01/1/18 – 12/30/20
Title: "Enhancing Tumor Antigen Specific T cell Responses following Autologous SCT"
The goal of this project is to test feasibility of expanding cytotoxic T lymphocytes (CTL) specific for the cancer testis (CT) antigens MAGE-A1, MAGE-A3, and NY-ESO-1 from blood specimens derived from previously treated neuroblastoma and sarcoma patients.

Agency: Kentucky Lung Cancer Research Program (**Co-PI,** PI: Howard Donninger) 07/1/18 – 12/31/21
Title: “Overcoming lung cancer MDSC suppressive function by targeting IL-6”
Description: The major goal of this study is to establish a mouse model to test the in vivo efficacy of novel IL-6 small molecule inhibitors at blocking melanoma MDSC induction and function.

Agency: Kentucky Lung Cancer Research Program (**PI**) 07/1/18 – 08/31/20
Title: “Adenosine Deaminase as a novel immunotherapeutic agent for the treatment of cancer”
Description: The goal of this project is to evaluate the clinical feasibility of PEG-ADA as a cancer immunotherapy that can be used as monotherapy or in combination with immune checkpoint inhibitors in melanoma.

Agency: Department of Defense Lung Cancer Research Program **(Co-I)** 08/15/19 – 08/14/21
Title: “Identifying and characterizing neoantigens of an embryonic stem cell-based lung cancer vaccine”
Description: The major goal of this project is to identify and characterize the neoantigens of a lung cancer vaccine consisting of murine embryonic stem cells along with murine fibroblasts expressing immunostimulatory adjuvant GM-CSF.

Agency: NSF 1827521 (**Co-I**, PIs: Paula Bates and Jonathan Kopechek) 09/01/18-08/31/21
PFI-RP: “High Precision Sonoporation System for Cell Transfection and Preservation”
Description: This Partnership for Innovation-Research Partnership grant will partner with industry to further develop a REACH-funded platform technology that has potential applications in cell transfection and preservation.