BIOGRAPHICAL SKETCH

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NAME: **Robert Kirken**

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

POSITION TITLE: **Professor of Biological Sciences and Dean College of Science**

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
Olivet College	BA	05/1986	Chemistry
Wright State University	PhD	12/1991	Biomedical Sciences
National Institutes of Health, NCI, MD	Postdoctoral	8/1998	Immunology-Cancer Cell Signaling

A. Personal Statement

Independent Research. As a research scientist I have been working in the field of cytokine cell signaling, cancer biology and immunology for nearly 30 years. I have trained numerous doctoral and masters students and greater than 50 undergraduate students that have gone on to have successful careers as medical doctors, dentists, pharmacists, technicians, staff scientists working in the biotechnology sector, or as productive university professors. I consider my research to have been impactful on many levels, especially the students I serve through my research. Overall, the aim of my research has been to characterize the cell signaling pathways responsible for immune-cell derived pathologies to better understand the mechanism by which certain diseases originate. The research within my group has focused particularly on the molecular mechanisms that promote uncontrolled proliferative growth of hematopoietic cancers such as leukemia and lymphoma so that new diagnostics and therapeutic strategies to effectively treat these conditions can be developed. My earlier work first characterized a tyrosine kinase responsible for promoting IL-2 and other gamma common cytokines signaling that we named “Jak3”. I also demonstrated that two key substrates, Stat5a and Stat5b are responsible for promoting T-cell proliferation and cell survival. Additional studies from my group have mapped a number of novel regulatory pathways and provided the first evidence that inhibitors that disrupt tyrosine kinases can have a positive impact on cancers and other disease conditions. In addition, our lab has generated unique Hispanic cancer biorepositories, utilize a host of nanotechnologies that allow for limited sample size characterization by high throughput drug sensitivity assays, monitor activated oncogenic signaling pathways via multiplex technologies for protein biomarkers, and utilize exome sequencing to assess genetic instability and oncogenic drivers. My extensive research efforts and laboratory experience since my doctoral degree have spanned positions at the National Cancer Institute, The University of Texas Houston Health Sciences, MD Anderson Cancer Center to my current position at UTEP. These skills will allow us to support the aims of this proposal.

Administrative Experience. Since 2013 I have served as Dean of the College of Science and helped to lead the research, teaching and various educational components of the many STEM initiatives being performed at UTEP. In addition to these activities, I have served as the PI-PD and architect for UTEPs RCMI grant for the past 13 years. Through the combined vision of the university president and UTEP scientists we have generated a host of core labs to promote biomedical research. Moreover, we have developed a number of contracts and MOUs with regional hospitals for the procurement patients and cancer tissues to support our clinical and

behavioral research within our Hispanic majority community. It is our combined vision, and the aim of this application to reduce cancer health disparities for Hispanic Americans where cancer is the #1 cause of disease related death. Prior to being Dean, I served as Chair of the department of Biological Sciences and ushered many new degree programs at the undergraduate and graduate level as they primarily relate to the biomedical sciences. UTEP has been consistently ranked in the Top 5 in the national for awarding degrees to Hispanic scientists. I have also chaired graduate student admissions for The University of Texas Houston and MD Anderson Cancer during his tenure in Houston as it has been a long-term mission. Presently, I serve administrative roles on multiple RCMI/RTRN committees, as an external advisor, as well as chair the Core Resources Subcommittee to facilitate access to key equipment and technologies across the RCMI schools. Undoubtedly these skills will support the successful completion of the many goals in this proposal in which I serve as PI.

B. Positions and Honors

Positions and Employment

1985-1986 Laboratory Instructor (Organic Chemistry & Biochemistry), Olivet College, Olivet, MI
1986-1991 Graduate Research Assistant, Wright State Univ., Dayton, OH
1992-1996 Intramural Research Training Assistantship, National Cancer Institute, Frederick, MD
1996-1998 IRSP, SAIC Scientist, NCI, Frederick, MD
1998-2004 Asst. Prof., UT-Houston Med. School, Integrative Biology & Pharmacology, Houston, TX
2001-2005 Joint Appointment, UT-Houston Med. School, Dept. of Surgery, Houston, TX
2002-2005 Joint Appointment, M.D. Anderson Cancer Center, Dept. of Bioimmunotherapy, Houston, TX
2004-2005 Associate Prof-Tenured, UT-Houston Med. School. Integrative Biology & Pharmacology, Houston, TX
2005-2013 Professor and Chair at UT El Paso, Dept. of Biological Sciences, El Paso, TX
2013-present Dean College of Science, UT El Paso, El Paso, TX

Honors and Awards (selected):

1982-'86 Presidential Scholar Award, Olivet College, Olivet, MI
1986 American Institute of Chemists Research and Recognition Award, Olivet College, Olivet, MI
1987 Sigma Xi Graduate Student Research Lecture Award, Wright State Univ., Dayton, OH
1992 Intramural Research Training Assistantship Award (IRTA), NIH
1993 Symposium Speaker VI International Prolactin Congress, Paris, France
1996 International Cytokine Society-Invited Member
1996 Chaired International Meeting on Standardization and Calibration of Cytokine Immunoassays, London, England
1999 Young Investigator Travel Award: American Soc. Transplant Surgeons
2000 Invited Membership into the Transplantation Society
2000 Invited Speaker for Transplantation Society Meeting, Rome, Italy
2001 Invited Membership into the American Association of Immunologists
2001 Plenary Lecture, Transplant Odyssey, Istanbul, Turkey
2002 Plenary Lecture, New Trends in Immune Regulation, Geneva, Switzerland
2002 American Society of Transplantation Membership.
2003 Plenary Lecture, Horizon in Transplantation, Amelia Island, FL.
2007-18 UTEP's Outstanding Research Performance and/or Leadership Awards

C. Contributions to Science

1. *Identified and Characterized Janus Tyrosine Kinase 3.* Earlier and continued work has focused on understanding how IL2 and other now recognized gamma common cytokine receptor families promote cell signaling. This novel work has characterized the activation of this tyrosine kinase, receptor recruitment domain requirements, activation profile, cytokine receptor domain recruitment and association for optimal cell signaling.

a. **Kirken, R.A.,** Rui, H., Evans, G.A., and Farrar, W.L.: Characterization of an interleukin-2 (IL-2) induced tyrosine phosphorylated 116-kDa protein associated with the IL-2 receptor β-subunit. J. Biol. Chem. 268:22765-22770, 1993.

b. **Kirken, R.A.,** Rui, H., Malabarba, M.G, and Farrar, W.L.: Identification of the IL2 receptor associated tyrosine kinase p116 as novel leukocyte specific Janus kinase, L-JAK. J. Biol. Chem. 269:19136-19141, 1994.
c. Johnston, J.A., Kawamura, M., **Kirken, R.A.,** Chen Y.Q., Blake, T.B., Subota, K., Ortaldo, J.R., McVicar, D.W., and O'Shea, J.J.: Phosphorylation and activation of the JAK3 Janus Kinase in response to interleukin-2. Nature. 370: 151-153, 1994.
d. **Kirken, R.A.,** Rui, H., Malabarba, M.G., Kawamura, M., O'Shea, J.J., and Farrar, W.L.: Activation of JAK3, but not JAK1, is critical for IL2-induced proliferation and STAT5 recruitment by a COOH-terminal region of the IL2 receptor β-chain. Cytokine. 7:789-800, 1995.

2. *Stat5a/b is a key regulator of T-cell survival and oncogenic signaling.* Provided original evidence of an IL2, gamma common cytokine receptor family members, and others growth factors such as including prolactin, employ multiple kinases (tyrosine and serine-threonine), that serve to regulate Stat5a/b activity. Disruption of this activation step, their protein expression, or drug inhibition resulted in a profound loss of cell survival.

a. **Kirken, R.A.,** Malabarba, M.G., Xu, J., Farrar, W.L., Liu, X., Hennighausen, L., Larner, A.C., Grimley, P.M. and Rui, H.: Prolactin **stimulates** serine/tyrosine phosphorylation and heterocomplexes of multiple STAT5 isoforms in Nb2 lymphocytes. J. Biol. Chem. 272:14098-14103, 1997.
b. **Kirken, R.A.,** Malabarba, M.G., Xu, J., DaSilva, L., Erwin, R.A., Liu, X., Hennighausen, L., Rui, H. and Farrar, W.L.: Two discrete regions of interleukin-2 (IL2) receptor-β independently mediate IL2 activation of a PD98059/rapamycin/wortmannin insensitive STAT5a/b serine kinase. J. Biol. Chem. 272:15459-15465, 1997.
c. Pericle, F., **Kirken, R.A.,** Bronte, V., Sconocchia, G., DaSilva, L., and Segal, D.M.: Immunocompromised tumor bearing mice show a selective loss of STAT5a/b expression in T and B lymphocytes. J. Immunol. 159:2580-2585, 1997.
d. Pericle, F., Pinto, L.A., Hicks, S., **Kirken, R.A.,** Sconocchia, G, Rusnak, J., Dolan, M.J., Shearer, G.M., and Segal, D.M.: HIV-1 infection induces a selective reduction in STAT5 protein expression. J. Immunol. 160:28-31, 1998.

3. *Disruption of Jak3-Stat5 signaling and therapeutic strategies and outcomes.* The lab continues to identify small molecules and other agents that can disrupt theJak3-Stat5 pathway. Our lab provided the first evidence that inhibition of this pathway by selective inhibitors promotes allograft survival due to the limited levels of Jak3 expression pattern and role of Stat5a/b as a substrate to regulate alloreactive T-cells.

a. Stepkowski, S.M., Erwin-Cohen, R.A., Behbod, F., Wang, M-E., Qu, X., Tejpal, N., Nagy, Z.S., Kahan, B.D., and **Kirken, R.A**.: A Selective Inhibitor of Janus Tyrosine Kinase (Jak) 3, PNU156804, prolongs allograft survival and acts synergistically with cyclosporine but additively with rapamycin. Blood. 99:600-609, 2002
b. Behbod, F., Nagy, Z.S., Stepkowski, S.M., Karras, J. , Johnson, C.R., Jarvis, W.D., and **Kirken, R.A.**: Specific inhibition of signal transducer and activator of transcription 5a and 5b (Stat5a/b) promotes apoptosis of IL2 responsive primary and human derive lymphoid cells. J. Immunol., 171: 3919-3927, 2003.
c. Stepkowski, S.M., Kao, J., Wang, M., Tejpal, N., Podder, H., Dimmock, J., Jha, A., Das, U., Kahan, B.D., **Kirken, R.A**. The Mannich base NC1153 promotes long-term allograft survival and spares the recipient from multiple toxicities. J. Immunol., 175: 4236-4246, 2005.
d. Martinez, G. Steven, Ross, J.A. **Kirken, R.A**. Transforming Mutations of Jak3 (A573 and M511) show differential sensitivity to selective Jak3 inhibitors. Clinical Cancer Drugs. 3(2): 131-7, 2016.

4. *Identify novel cancer regulatory proteins and phosphoregulatory sites as new therapeutic targets against hematopoietic tumors.* Our group continues to focus on oncogenic pathways and examines the cross-talk via G-protein coupled receptors, and role of serine/threonine kinases and phosphatases in this process.

a. Cheng, H., Ross, J.A. Frost, J.F., and **Kirken, R.A**. Phosphorylation of human Jak3 at tyrosines 904 and 939 positively regulates its activity. *Mol. Cell. Biol.* 28: 2271-2282, 2008.

b. Oaxaca, DM. Yang-Reid, S.A. Ross, J.A., Rodriguez, G. Staniswalis, J.G., **Kirken R.A**. Sensitivity of imatinib-resistant T315I BCR-ABL CML to a synergistic combination of ponatinib and forskolin treatment. Tumour Biol. 37(9):12643-12654, 2016.
c. Oaxaca, DM, Yang-Reid, SA, Ross, JA, Staniswalis, JG, **Kirken, RA**. Tyrosine Kinase Inhibitors and Phosphatases: Overcoming the BCR-ABL T315I Mutation in CML with a Synergistic Combination of Ponatinib and Forskolin J Clin Cell Immunol, 7:5, 206, 2016.
d. Ross, J.A., Robles-Escajeda, E., Eaxaca, D.M., Padilla, D.L., **Kirken, R.A.** The Prohibitin protein complex promotes mitochondrial stabilization and cell survival in hematologic malignancies. Oncotarget, 8(39): 65445-65456, 2017.

Complete List of Published Work (greater than 80):
http://www.ncbi.nlm.nih.gov/pubmed/?term=kirken

D. Research Support
Ongoing Research Support

2G12MD007592 (PI) 04/01/14-03/31/19
NIH RCMI Program
"Border Biomedical Research Center"
This program strives to enhance the capability for biomedical research relevant to the Border region.

Coldwell Foundation (investigator) 04/01/18-3/31/19
Targeting Jak3 for certain types of leukemia
Investigates Jak3 as a molecular target for treating certain leukemias derived from minority populations.

Completed Research Support *(selected)*

Marsh Foundation (PI) 05/01/14-10/30/17
Childhood leukemias and potential therapeutic targets
This application seeks to identify new molecular targets for therapeutic intervention.

1P20MD002287-01 (Co-Investigator) 09/30/08-06/30/16
NIH RCMI Program
"Hispanic Health Disparities Research Center" This program seeks to address health disparities issues

Coldwell Foundation (investigator) 07/01/14-3/31/18
Targeting Jak3 for certain types of leukemia
Investigates Jak3 as a molecular target for treating certain leukemias derived from minority populations.