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

I have been working in the field of cytokine cell signaling, cancer and immunology for 25 years. Overall, the aim of my work is to characterize the cell signaling pathways for T-cell derived pathologies in order to have an impact on human health worldwide. The research within my group has focused particularly on the molecular mechanisms that drive T-cell mediated diseases such as leukemia and lymphoma, graft versus host disease and autoimmune disorders so that new diagnostics and therapeutic strategies to effectively treat these conditions can be developed. I have a long standing interest, expertise and motivation to successfully carry out the proposed work in this application due to the many years of acquired skills. My extensive research efforts and laboratory experience that has spanned positions at the National Cancer Institute, University of Texas Houston Health Sciences, MD Anderson Cancer Center to UTEP will support the aims of this proposal.

My earlier first characterized a tyrosine kinase responsible for promoting IL-2 and other gamma common cytokines that is now known as 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 provided the first evidence that inhibitors that disrupt Jak3 and Stat5a/b signaling can protect against graft versus host disease. While many groups have focused on tyrosine kinase cell signaling and phosphoregulation of intracellular messengers, we have identified several novel serine and threonine phosphor-acceptor sites that play functional roles in promoting cell signaling, gene transcription and cellular proliferation. Their respective kinases and phosphatases have also been mapped for cytokines that include IL2, IL4, IL7, IL9 and IL5.

In addition to these activities I also serve as the PI for the NIH sponsored G12 grant. I have served as Director of this program for the past decade promoted the development of high-end research cores to facilitate research that spans genomics, proteomics, metabolomics, imaging and high throughput drug discovery.

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

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.

1. **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.
2. **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.
3. 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.
4. **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.* 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.

1. **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.
2. **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.
3. 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.
4. 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 protects against the rejection of transplanted organs.* 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.

1. 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
2. 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.
3. 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.
4. 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: in press, 3(2): 131-7, 2016.

4. *Mapped several novel regulatory Sites in Jak3 and Stat5.* Our group continues to examine the cross-talk via G-protein coupled receptors, regulation by serine and threonine kinases, and phosphatases that include receptor regulation.

1 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.
2 Rodriguez, G., Ross, J.A., Nagy, Z.S., and **Kirken, R.A**. Forskolin inducible cAMP pathway negatively regulates T-cell proliferation by uncoupling the Interleukin-2 receptor complex. J. Biol. Chem, 288: 7137-46, 2013.
3 Ruiz-Medina, Ross, JA, **Kirken, R.A**. Interleukin -2 Receptor Bea Thre-450 is a positive regulator for receptor complex stability and activation of signaling molecules. J. Biol. Chem. 290: 20972-83, 2015.
4 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.

Complete List of Published Work:
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 (PI) 07/01/14-3/31/19
Targeting Jak3 for certain types of leukemia
Investigates Jak3 as a molecular target for treating certain leukemias derived from minority populations.

Marsh Foundation (PI) 05/01/14-04/30/17
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 prevalent to the El Paso-ciudad-Juarez Mexico border region.

Completed Research Support *(selected)*

R01DK38016-15A1 (Co-Investigator) 09/01/01-08/31/05
NIDDK (NIH)
"Pharmacology of cyclosporine based immunosuppression"
This project addressed cyclosporine and other T cell inhibitors to induce immune suppression.

R01AI053566-01A1 (PI) 07/01/03-12/31/08
NIAID (NIH)

“T-cell growth factor pathways and immune modulation”
This project addresses T-cell growth factor signaling pathways and gene regulation.

1R03NS050774-01 (PI) 09/30/04-8/31/05
NIH
“Screening for small molecule inhibitors of Stat5”
This project sought to screen for peptide inhibitors of Stat5.

R21 AI051474 (Co-Investigator) 04/01/04-03/31/05
NIH/NIDDK
“The role of SOCS in regulation of transplantation tolerance”.
Determine the role of SOCS in T-cell activity and allograft rejection

Texas Ignite Grant (Principal Investigator) 7/21/08-7-20/09
“Targeting Jak3 for prevention of allograft rejection”
This projects seeks to commercialize a Jak3 inhibitor for protection against transplant rejection.