BIOGRAPHICAL SKETCH

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NAME: Cross, Janet V.

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POSITION TITLE: Associate Dean for Graduate and Medical Scientist Programs, Harrison Distinguished Associate Professor of Medical Education and Pathology

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
State University of New York College at Fredonia; Fredonia, NY	B.S.	05/1992	Recombinant Gene Technology, Medical Technology
Case Western Reserve University; Cleveland, OH	Ph.D.	05/2000	Molecular Biology and Microbiology
Case Western Reserve University; Cleveland, OH	Postdoctoral	02/2002	Pathology

A. Personal Statement

The central objective of my research program has been to understand how the host immune response is reprogrammed by tumors to promote growth and metastasis, focused on the study of mechanisms that contribute to tumor development. Early on, my work centered on the regulation of cell signaling pathways and the aberrations in these networks that promote cell growth, prevent cell death, or otherwise contribute to cancer. We identified an inflammatory cytokine, the Macrophage Migration Inhibitory Factor (MIF), as the major target of the isothiocyanate chemopreventives, a discovery that ultimately led to our published study demonstrating the critical importance of MIF in tumor growth and metastasis through regulation of myeloid derived suppressor cells (MDSCs) and our subsequent study demonstrating the role of MIF in preventing Immunogenic Cell Death (ICD) at the very early stages of tumor growth. This further advanced our understanding of the role of MIF in mediating tumor/ immune interactions. Our findings provide foundations for efforts to dissect the role of MIF in the tumor microenvironment and evaluate MIF inhibition as an approach for prevention of cancer progression.

My interest in and passion for training the next generation of scientists is evidenced through my mentoring of individual trainees in my research lab, my extensive participation in the teaching mission of the institution, my directorship of the Molecular and Cellular Basis of Disease/Experimental Pathology graduate program, my term as Director of the Summer Research Internship Program, my leadership roles in the Biomedical Sciences curriculum development, admissions and recruiting process in positions as the Assistant Dean for Graduate Research and Training and, currently, Associate Dean for Graduate and Medical Scientist Programs. Through all of these different roles, I have developed substantial expertise in nearly every facet of graduate education, as well as embracing every opportunity to enhance the training environment for our trainees to equip them for ultimate success. Over my last several years in leadership of the BIMS program, a major focus of my efforts has been on advancing the recruitment and retention of underrepresented students into our programs. These efforts have correlated with substantial advances in the recruitment of underrepresented students, as well as improvements to the environment that I believe foster their success, including a faculty-student alliance centered around diversity, equity and inclusion/belonging in our program. In my current position as Associate Dean, I am now responsible for strategic decision-making for the graduate and summer programs administered through our office, as well as oversight of the substantial budget of the graduate program and the Medical Scientist Training Program. I also directly or indirectly supervise a staff of 12 dedicated individuals who ensure the smooth operations of our PhD programs. All of these experiences combined make me uniquely positioned to provide advice to the leadership team of the proposed Genomic Instability in Human Disease Training Program and I am happy to serve as a member of their Advisory Committee.

B. Positions and Honors

Positions and Employment

2002 - 2003	Research Associate, Dept. of Pathology, University of Virginia
2003 - 2004	Senior Scientist, Department of Pathology, University of Virginia
2004 - 2007	Assistant Professor of Research, Department of Pathology, University of Virginia
2008 - 2014	Assistant Professor, Department of Pathology, University of Virginia
2010 -	Director, Molecular and Cellular Basis of Disease Graduate Program, University of Virginia
2014 -	Associate Professor, Department of Pathology, University of Virginia
2015 - 2016	Interim Assistant Dean for Graduate Research and Training
2016 - 2020	Assistant Dean for Graduate Research and Training
2020 -	Associate Dean of Graduate and Medical Scientist Programs
2020 -	Harrison Distinguished Associate Professor

Other Experience and Professional Memberships

2012	NIH/NCCAM Special Emphasis Panel
2013 -	Member, American Association for the Advancement of Science
2013 -	Member, American Association for Cancer Research
2014	DOD BRCP Study Section
2015	DOD BRCP Study Section
2016	NIH (NHLBI) R25 Training Grant Study Section
2017	NIH F09CY(20)L Fellowship F30, F31, F32 SEP (Acting Chair)
2017	NIH (NCI) F09 Fellowship F30, F31, F32 Study Section (June)
2018	NIH (NCI) F09 Fellowship F30, F31, F32 Study Section (March)
2018 -	Chair of Enhancing Diversity Committee for Cancer Biology Training Consortium
2018	NIH (NCI) F09 Fellowship F30, F31, F32 Study Section (November)
2019	NIH (NCI) F09 Fellowship F30, F31, F32 Study Section (March)
2020	NIH (NCI) F09 Fellowship F30, F31, F32 Study Section (March)
2021	NIH (NCI) F09 Fellowship F30, F31, F32 Study Section (March)
2021 -	Board Member, Cancer Biology Training Consortium (CABTRAC)

Honors

2011	University of Virginia Dean's Excellence in Teaching Award
2011	Appointed to the University of Virginia Academy of Distinguished Educators

C. Contributions to Science

1. Identification of the Macrophage Migration Inhibitory Factor (MIF) as an important mediator of metastasis through influence over the immune response. MIF is overexpressed in many cancers, and the degree of overexpression correlates with tumor aggressiveness and metastatic potential. This observation, along with our identification of MIF as a target of the cancer chemopreventive isothiocyanates (see point 2 below), supported our efforts to determine how MIF might contribute to cancer. We established that MIF promotes tumor growth and is required for tumor metastasis and demonstrated that MIF carries out its pro-tumor effects through influence over the host immune system, rather than by altering an intrinsic property of the tumor cells. Specifically, we discovered that MIF regulates the abundance of a class of immunosuppressive cells within the tumor microenvironment—monocytic Myeloid Derived Suppressor Cells (Mo-MDSCs)—that suppress T cell mediated immune responses, protecting the tumor from immune destruction. We showed that our MIF inhibitory drug reduces the abundance of Mo-MDSCs in the tumors, suggesting that we may be able to target MIF therapeutically to inhibit tumor progression through manipulation of the host immune response. In follow up studies, we demonstrated that MIF is responsible for preventing immunogenic cell death and that, in its absence, the tumor becomes susceptible to an enhanced T cell mediated immune response. Our hope is that this work will form the foundation for future efforts to further explore the mechanism(s) behind this significant finding, as well as to further evaluate whether MIF inhibition may represent a clinically translatable approach to overcome the immunosuppressive tumor microenvironment to promote tumor control, either alone or in combination with immunotherapy approaches.

a. Simpson K., D.J. Templeton, and J.V. Cross (2012) Macrophage Migration Inhibitory Factor (MIF) promotes tumor growth and metastasis through induction of MDSCs in the tumor microenvironment. *J. Immunol.* 189:5533-40 [NIHMS414813]

b. Simpson, K.D. and J.V. Cross (2013) MIF: Metastasis/MDSC Inducing Factor. Oncoimmunology 2(3):e23337.

c. Balogh, K.N., D.J. Templeton and J.V. Cross (2018) Macrophage Migration Inhibitory Factor protects cancer cells from immunogenic cell death and impairs anti-tumor immune responses. PLoS One. 13(6):e0197702. PMC5986154

2. Understanding the molecular mechanisms by which chemopreventives exert their anti-cancer effects. Decades of research established that the isothiocyanate (ITC) class of compounds prevalent in cruciferous vegetables protect against cancer in animal models of carcinogenesis, as well as in xenograft and genetic models of cancer. However, the underlying molecular mechanism(s) through which they mediate these effects remained elusive, with available models insufficient to explain all of the observed anti-cancer activities. My early studies on the MEKK1 protein kinase confirmed that these electrophilic chemicals could covalently modify protein targets and alter their activity. The inhibition of MEKK1 by ITCs led to our hypothesis that the anti-cancer effects may be mediated through modification of significant protein targets, leading to alterations of cell signaling responses. This motivated my effort to develop an affinity reagent to probe these interactions. My validation of this reagent led to a novel proteomics screen and identification of the second covalent target of modification, the inflammatory cytokine MIF. I further demonstrated that ITC modification of MIF inhibited an enzymatic activity of the protein with an IC50 within the physiologically attainable concentration range observed in the plasma of human subject who consumed a broccoli sprout meal. We continue to pursue the significance of MIF in the chemoprevention phenomenon and examine the potential utility of the ITCs as anti-cancer and anti-inflammatory agents by virtue of their ability to inhibit this important inflammatory mediator. This work provided the foundation for our effort to characterize the tumor promoting effects of MIF mediated by its influence over the immune response, with the ITCs playing a significant role.

a. Zhang, D.D., S.-C. Lo, J.V. Cross, D.J. Templeton, and M. Hannink (2004) Keap is a redox-regulated substrate adaptor proteins for a Cul3-dependent ubiquitin ligase complex. *Mol Cell Biol*. **24**:10941-53.

b. Cross J.V., F.W. Foss Jr, J.M. Rady, T.L. Macdonald, and D.J. Templeton (2007) The isothiocyanate class of bioactive nutrients covalently inhibit the MEKK1 protein kinase. *BMC Cancer* 7:183. PMCID: PMC2071920

c. Cross J.V., J.M. Rady, F.W. Foss, C.E. Lyons, T.L. Macdonald, D.J. Templeton (2009) Nutrient isothiocyanates covalently modify and inhibit the inflammatory cytokine macrophage migration inhibitory factor (MIF). *Biochem J* 423:315. PMCID: PMC2858637.

d. Zhou J., D.G. Joplin, J.V. Cross, D.J. Templeton (2012) Sulforaphane Inhibits Prostaglandin E2 Synthesis by Suppressing Microsomal Prostaglandin E Synthase 1. *PLOSOne* 7(11):e49744.

3. Dissection of the molecular mechanisms by which oxidative stress events impact cell signaling. Cell signaling responses are fine-tuned through a number of post-translational modifications on signaling proteins. The prototype of this is protein phosphorylation, which has been studied for decades as an essential mediator. One other significant means of regulation involves oxidative modification of proteins on cysteine residues mediated by reactive oxygen species, which are generated during many cell signaling responses. The study of these modifications has lagged behind, due to the difficulties inherent in studying these unstable modifications in an oxygen environment. In addition to characterizing specific protein targets that are regulated by these modifications, we also tackled one of the major technical hurdles in the field, developing a protocol (PROP – purification of reversibly oxidized proteins) that supports identification of targets of redox modification. We have applied this approach to characterizing specific targets, as well as to proteomics-based approaches to uncover novel targets in an unbiased manner.

a. Cross, J.V. and D.J. Templeton (2004) Oxidative stress inhibits MEKK1 by site-specific glutathionylation in the ATP binding domain. *Biochem. J.* **381**:675-83.

b. Cross J.V. and D.J. Templeton (2006) Regulation of signal transduction through protein cysteine oxidation. *Antioxid Redox Signal*. 8:1819-27.

c. Templeton D.J., M.-S. Aye, J.M. Rady, F. Xu, and J.V. Cross (2010) Purification of Reversibly Oxidized Proteins (PROP) Reveals a Redox Switch Controlling p38 MAP Kinase Activity. PLOSOne 5:e15012. PMCID: PMC2981573

d. Victor KG, JM Rady, J.V. Cross, D.J. Templeton Proteomic profile of reversible protein oxidation using PROP, purification of reversibly oxidized proteins. *PLoS One*. 2012;7(2):e32527.

4. Furthering our understanding of the regulation of the MEKK1 protein kinase. We contributed significant advances to our understanding of how this central MAPK3K in this stress signaling pathway is regulated. Specifically, our work uncovered a novel means of regulating the MEKK1 protein kinase through caspase-mediated proteolytic cleavage at a specific site in the N terminus. This cleavage frees the C terminal catalytic domain from the N terminal regulatory domain, leading to altered subcellular localization of the protein and concomitant effects on downstream signaling responses. In an effort to further understand these signaling responses, we collaborated with Kevan Shokat to develop a MEKK1 mutant that would accept his synthetic "bumped" ATP analogs. The ultimate goal of these studies was to search for additional substrates for this protein kinase. In the process, we discovered that it was necessary to mutate an additional site in MEKK1, beyond that predicted by the original sequence analysis. This allowed us to contribute to a collaborative paper on these second site mutations. Moreover, the necessary second site of mutation proved to be a cysteine residue, which serendipitously led us to discover the redox regulation of MEKK1 discussed in section 3 above. Finally, in a yeast two hybrid screen, we identified the NADPH quinone oxidoreductase (NQO1) as an interacting partner of MEKK1. Using a number of inhibitors of NQO1, we demonstrated a role for these enzymes in regulating stress signaling pathways, with downstream impacts on stress signaling and NF-kappaB pathways.

   a. Deak, J.C., J.V. Cross, M. Lewis, Y. Qian, L.A. Parrott, C.W. Distelhorst, and D.J. Templeton (1998). Fas-induced proteolytic activation and intracellular redistribution of the stress-signaling kinase MEKK1. *Proc Natl Acad Sci U S A* **95:** 5595-600.

   b. Cross, J.V., J.C. Deak, E.A. Rich, Y. Qian, M. Lewis, L.A. Parrott, K. Mochida, D. Gustafson, S. Vande Pol, and D.J. Templeton (1999). Quinone reductase inhibitors block SAPK/JNK and NFkappaB pathways and potentiate apoptosis. J Biol Chem 274: 31150-4.

   c. Zhang, C., D.M. Kenski, J.L. Paulson, A. Bonshtien, G. Sessa, J.V. Cross, D.J. Templeton and K.M. Shokat (2005) A second-site suppressor strategy for chemical genetic analysis of diverse protein kinases. *Nature Methods* **2:** 435-41.

5. Characterization of the role of SAPK/JNK stress signaling pathway in cell cycle regulation. Stress signaling pathways have been implicated in controlling cellular responses ranging from proliferation to differentiation to death. Central among this pathway is the SAPK protein kinase, which is also known as JNK. Work in my early career focused on dissecting how these pathways are regulated, as well as how they contribute to significant outcomes for the cells. In the course of these studies, we determined that SAPK plays a significant role in cell cycle progression, through its ability to directly phosphorylate a specific residue in the cell cycle phosphatase cdc25c. The expertise and reagents that we developed allowed us to contribute to subsequent collaborative work that further dissected the role of this signaling event and implicated SAPK/JNK in regulation of the DNA damage response.

   a. Goss, V.L., J.V. Cross, K. Ma, Y. Qian, P.W. Mola, and D.J. Templeton. (2003) SAPK/JNK regulates cdc2/cyclinB kinase through phosphorylation and inhibition of cdc25c. Cell Signal. 15:709-18.

   b. Gutierrez G.J., T. Tsuji, J.V. Cross, R.J. Davis, D.J. Templeton, W. Jiang, Z.A. Ronai (2010) JNK-mediated phosphorylation of Cdc25C regulates cell cycle entry and G2/M DNA damage checkpoint. J Biol Chem 285(19):14217-28. PMCID: PMC2863176.

Complete List of Published Work

https://pubmed.ncbi.nlm.nih.gov/collections/59542511/?sort=pubdate

D. Research Support

Ongoing Support

R25 CA206972 Bouton/Cross (MPI) 03/01/2017 – 02/28/2024
Summer Research Experience in Cancer (SuRE-C)
Provides support for 15 undergraduates and 5 medical students to participate in the summer research programs.

T35 AI060528 Petri/Cross (MPI) 06/01/2019 – 05/31/2024
Biodefense & Infectious Diseases Short-Term Training to Increase Diversity in Biomedical Research
Provides support for 10 medical students to participate in the summer research programs in the UVA School of Medicine.