BIOGRAPHICAL SKETCH

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NAME: Kent L. Rossman, Ph.D.

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POSITION TITLE: Assistant 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
The State University of New York-Plattsburgh	B.S.	05/88	Biochem. & Biophys.
The University of North Carolina at Chapel Hill	Ph.D.	12/02	Biochem. & Biophys.
The University of North Carolina at Chapel Hill	Postdoctoral	09/09	Cancer Biology

A. Personal Statement

I am an Assistant Professor in the Department of Surgery at UNC Chapel Hill where I investigate the mechanisms regulating the signaling of RAS family GTPases at the structural, biochemical and cell biological levels. RAS proteins are binary switches that cycle between ON and OFF states to control signal transduction. This switching mechanism is normally tightly regulated in cells, but in RAS-related diseases (such as cancer, RASopathies, and many psychiatric disorders) mutations in RAS proteins render them constitutively active. There is an emerging appreciation that different mutations in RAS cause distinct biochemical alterations that rewire signal transduction and cell biology. Therefore, these mutation-specific alterations in RAS activity necessitate mutation-specific therapeutic strategies. Thus, a major goal of my current work is to define the novel biochemical and structural properties of mutant RAS that can be leveraged to design chemical probes specific for these proteins, and hopefully one day, new therapies that target them in cancer and other diseases.

B. Positions and Honors

Positions and Employment

1988-1992 Research Technician. I & II, Dept. of Pharmacology, Albany Medical College, Albany, NY
1992-1993 Assistant Chemist, Glaxo Inc., Zebulon, NC
1993-1995 Senior Scientist, Glaxo Inc., Zebulon, NC
1995-2002 Graduate Student, Dept. of Biochemistry and Biophysics, UNC Chapel Hill
2002-2009 Postdoctoral Fellow, Lineberger Comprehensive Cancer Center, UNC Chapel Hill
2009- 2018 Assistant Professor, Dept. of Pharmacology and Lineberger Cancer Center, UNC Chapel Hill
2018- Assistant Professor, Dept. of Surgery and Lineberger Cancer Center, UNC Chapel Hill

Honors

1994 Special Recognition Award, Glaxo Inc., RTP, NC
1996-1998 Cancer Cell Biology Training Program Predoctoral Fellowship, UNC Chapel Hill
2001 Lineberger Comprehensive Cancer Center Graduate Fellow Award, UNC Chapel Hill
2002-2004 Lineberger Comprehensive Cancer Center NIH Postdoctoral Fellowship
2005-2007 American Cancer Society Postdoctoral Fellowship
2009-2011 NCI GI Cancer SPORE Developmental Research Award.

C. Contribution to Science

1. A major theme of my research investigates the mechanisms by which the binding and hydrolysis of guanine nucleotides by Ras superfamily GTPases controls their activity. This work has focused on the contributions of deregulated Ras family GTPases to cancer progression. This commonly occurs through direct mutation of RAS or through deregulation of their guanine nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAPs). My early structural and biochemical studies were some of the first to show the mechanism of GEF catalyzed activation of Ras GTPases. This work led to key insights into how GEFs act to disrupt interactions between guanine nucleotides and Ras-related GTPases, giving us clues on the design of small molecule drugs to modulate nucleotide binding, and hence Ras activity.
    a. Worthylake, D. K., **Rossman, K.L.**, and Sondek, J. (2000). Crystal structure of Rac1 in complex with the guanine nucleotide exchange region of Tiam1. Nature 408, 682-8.
    b. **Rossman, K.L.**, Worthylake, D.K., Snyder, J.T., Siderovski, D.P., Campbell S.L. and Sondek, J. (2002). A crystallographic view of interactions between Dbs and Cdc42: PH domain-assisted guanine nucleotide exchange. EMBO J. 21, 1315-26.
    c. Snyder, J. T., Worthylake, D. K., **Rossman, K. L.**, Betts, L., Pruitt, W. M., Siderovski, D. P., Der, C. J., and Sondek, J. (2002). Structural basis for the selective activation of Rho GTPases by Dbl exchange factors. Nat. Struct. Biol. 9, 468-475.
    d. **Rossman, K.L.**, Cheng, L., Mahon, G.M., Rojas, R.J., Snyder, J.T., Whitehead, I.P. and Sondek, J. (2003). Multifunctional roles for the PH domain of Dbs in regulating Rho GTPase activation. J. Biol. Chem. 278, 18393-400.

2. A second major theme of my research has been the determination of how large, multidomain GEFs are auto-regulated and how their deregulation can act to promote cancer. One example from this work determined how the GEF, ASEF (for APC stimulated exchange factor) is auto-inhibited through interactions between its GEF domain and SH3 domain, which is relieved when bound to the tumor suppressor APC. We examined this interaction in colorectal cancer cell models and determined ASEF activates the Ras-related GTPase, Cdc42 in certain cellular compartments when bound to APC. Several other studies of ours revealed multiple auto-regulatory mechanisms utilized by GEFs to control diverse cellular processes.
    a. Lu, M., Kinchen, J.M., **Rossman, K.L.**, Grimsley C., Hall, M., Sondek, J., Hengartner, M.O., Yajnik, V., and Ravichandran, K.S. (2005). A Steric-inhibition model for regulation of nucleotide exchange via the Dock180 family of GEFs. Curr Biol. 15, 371-7.
    b. Yohe, M.E., **Rossman, K.L.**, Gardner, O.S., Karnoub, A.E., Snyder, J.T., Gershburg, S., Graves, L.M., Der, C.J. and Sondek, J. (2007). Auto-inhibition of the Dbl Family protein Tim by an N-terminal helical motif. J. Biol. Chem. 282, 13813-23.
    c. Mitin, N., Betts, L., Yohe, M.E., Der, C.J., Sondek, J. and **Rossman, K.L.** (2007). Release of auto-inhibition of Asef by APC leads to Cdc42 activation and tumor suppression. Nat. Struct. Mol. Biol. 9, 814-23.

3. The ultimate goal of our work is to couple our structural and biochemical insights with cellular biology to give a detailed, mechanistic picture of the biology controlled by RAS-related GTPases in normal vs cancer cells. We have several ongoing studies that aim to assess the functional roles of GEFs, GAPs and Ras superfamily GTPases using this combined approach. Overall, these studies emphasize the host of cellular processes that involve signaling through one or more Ras-related GTPase.
    a. Neel N.F., **Rossman K.L.**, Martin T.D., Hayes T.K., Yeh J.J. and Der C.J. (2012). The RalB small GTPase mediates formation of invadopodia through a GTPase-activating protein-independent function of the RalBP1/RLIP76 effector. Mol. Cell. Bio., 32(8):1374-86.
    b. Mitin, N., **Rossman, K.L.**, Currin, R., Anne, S., Marshall, T.W., Bear, J.E., Bautch, V.L. and Der, C.J. (2013). The RhoGEF TEM4 Regulates Endothelial Cell Migration by Suppressing Actomyosin Contractility. PLoS ONE, 6: e66260.
    c. Damoulakis, G., Gambardella, **Rossman, K.L.**, L., Lawson C.D., Anderson, K.E., Fukui, Y., Welch, H., Der, C.J., Stephens, L.R. and Hawkins, P.T. (2014) P-Rex1 directly activates RhoG to regulate GPCR-driven Rac signalling and actin polarity in neutrophils. J. Cell Sci.;127(Pt 11):2589-600.

d. Lawson, C.D., Fan, C., Mitin, N., Baker, N.M., George, S.D., Graham, D.M., Perou, C.M., Burridge, K., Der, C.J. and **Rossman K.L.** (2016) Rho GTPase Transcriptome Analysis Reveals Oncogenic Roles for Rho GTPase-Activating Proteins in Basal-like Breast Cancers. Cancer Res.; 76(13):3826-37.

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/1x5wQTrwwbg/bibliography/41109398/public/?sort=date&direction=descending

D. Research Support

Ongoing Research Support

R01CA223495-01A1 Rossman (PI) 09/2018 - 08/2022
NIH/NCI
A HTS Approach to Discover Guanine Nucleotide-Competitive Inhibitors of Oncogenic KRAS
The goal of this proposal is to utilize HTS assays with diverse small molecule libraries, and virtual screens that leverage our recently solved x-ray structures of KRAS mutants to discover mutation-selective inhibitors of KRAS oncoproteins.

Role: PI

Completed Research Support

University Cancer Research Fund Innovation Grant Rossman (PI) 07/2014 - 12/2017
UNC-Chapel Hill, Lineberger Cancer Center
DEVELOPMENT OF AN HTS ASSAY FOR ONCOGENIC KRAS
The goal of this proposal is to develop and validate screens to discover small molecule inhibitors of KRAS that act to inhibit oncogenic signaling in relevant cancer models.

Role: PI