BIOGRAPHICAL SKETCH

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NAME: Dressler, Gregory R.

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

POSITION TITLE: Collegiate Professor of Pathology Research

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
University of Pennsylvania, Philadelphia, PA	B.S.E.	05/1981	Bioengineering
University of Pennsylvania, Philadelphia, PA	Ph.D.	01/1987	Genetics
Max Planck Institute for Biophysical Chemistry Goettingen, Germany	Post-Doc	12/1990	Developmental Biology

A. Personal Statement

During my more than 30 years as a PI, my interests have bridged the fields of developmental biology, cancer, and renal disease. Over the years, my lab has made significant contributions to understanding cell signaling and gene regulation in the mammalian kidney. We have discovered multiple genes and pathways that are essential for kidney development and that also function in chronic and acute renal disease. We identified GDNF as the ligand for the c-Ret tyrosine kinase and demonstrated that activation of PI3K promotes chemotaxis during ureteric bud growth. I also discovered Pax2, one of the earliest genes expressed in the renal and urogenital epithelial lineage. Pax2 is essential for kidney development and has been linked to cancer in both kidney and uterine epithelia. More recently, we discovered PTIP, a protein that is essential for histone H3K4 methylation in development and stem cells. PTIP is an adaptor protein that links Pax2, and other serine phosphorylated proteins, to the histone H3K4 methylation machinery. This changed the model for how developmental DNA binding proteins may act to restrict cell lineage progression along certain pathways and unified the idea of developmental competence with epigenetic imprinting of the genome.

With respect to renal disease, my lab was the first to demonstrate the expression and necessity for Pax2 in adult and childhood renal cancers. That developmental regulatory proteins were reactivated in cancer and that their regulation was in part controlled by tumor suppressor genes are fundamental concepts developed in the lab. We are now using genetic and cell biological models to delineate the function of Pax genes in human cancers of the reproductive tract. The lab has also worked closely with the Center for Chemical Genomics to identify small molecules that can inhibit or enhance pathways important in renal cancer and development. In 25 years at Michigan, the lab has trained 17 post-doctoral and 6 pre-doctoral fellows. The lab has had undergraduates working either as honors students, work-study students, or for independent study credit. Of the four Clinical Fellows for whom I served as a K08 mentor (most recently Dr. Beamish who was supported by the Nephrology T32 and now has a K08), all are now in tenured faculty positions at major research universities. Currently, I am the director for Pathology 582, a literature based course in experimental Pathology, and have served on more than 23 thesis committees. Within the graduate program, I also serve on the curriculum committee, the preliminary exam committee, and on the executive committee for the Medical Scientist Training Program. I will continue to actively be involved in the UM-KUHR program and train scientists interested in developmental origins of kidney disease.

Ongoing and recently completed projects that I would like to highlight include:

R01 DK073722
Dressler (PI)
7/1/06 – 5/31/22
Epigenetic Regulation of Kidney Development.

R01 DK054740
Dressler (PI)
1/15/99 – 5/31/2025
Pax2 Interacting Proteins in Development and Disease.

R01-DK054740-16-S1
Dressler (PI)
3/1/2016 - 2/29/2020
Research Supplement to Promote Diversity in Health Related Research

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

1990-1995	Head of the Unit on Molecular Embryology, LMGD, NICHD, Bethesda, MD
1995-1998	Assistant Investigator, HHMI, University of Michigan, Ann Arbor, MI
1995-2000	Assistant Professor of Pathology, University of Michigan, Ann Arbor, MI
2000-2007	Associate Professor of Pathology, University of Michigan, Ann Arbor, MI
2007 - Present	Professor of Pathology, University of Michigan, Ann Arbor, MI
2008 - Present	Collegiate Professor of Pathology Research, University of Michigan, Ann Arbor, MI

Awards and Other Professional Activities

1987-1989	Received the Alexander von Humboldt Fellowship
2000-2004	NIH Study Section Member, General Medicine B
2003-2015	Editorial Board, *Developmental Dynamics*
2004-2009	Scientific Advisory Board, GUDMAP/NIDDK program project
2005-2009	American Society of Nephrology, Basic Science Committee
2007- Present	Editorial Board, *Journal of the American Society of Nephrology*
2007	Dean's Basic Science Award, University of Michigan Medical School
2008	Collegiate Professorship
2013	US Patent 8470599 “Renal progenitor cells from embryonic stem cells”
2014	Elected Fellow, American Association for the Advancement of Science
2017-	Editorial Board, *Journal of Biological Chemistry*
2017-2021	NIH Study Section Member, KMBD
2018	Chair, Organizing Committee for the International Workshop on Developmental Nephrology, Ein Gedi, Israel

C. Contributions to Science

1. The identification of the Pax gene family and their characterization as developmental control genes. How cells are specified during embryogenesis and the mechanisms of cell fate restriction have become clear through studies of developmental regulatory proteins and their interactions with epigenetic modifying complexes. Pax2 is a paradigm for intermediate mesoderm lineage specification. How Pax2 contributes to renal cancer and polycystic kidney disease has also been addressed.

    a. Kim, D. and **Dressler, G.R. (**2005) Nephrogenic factors promote differentiation of mouse embryonic stem cells into renal epithelia. *J. Am. Soc. Nephrol.* 16, 3527-3534.

b. Soofi, A., Levitan, I. and **Dressler, G.R.** (2012) Two novel EGFP insertion alleles reveal unique aspects of Pax2 function in embryonic and adult kidneys. *Dev. Biol*. 365, 241-250.
c. Ranghini, E. and **Dressler, G.R.** (2015) Evidence for Intermediate Mesoderm and Kidney Progenitor Cell Specification by Pax2 and PTIP Dependent Mechanisms. *Dev. Biol*., 399, 296-305.
d. Grimley, E., Liao, C., Ranghini, E.J., Nikolovska-Coleska, Z. and **Dressler, G.R.** (2017) Inhibition of Pax2 Transcription Activation with Small Molecules that Target the DNA Binding Paired Domain. *ACS Chemical Biol.* 12, 724-734.
e. Schaefer, S.A., Higashi, A.Y., Loomis, B., Schrepfer, T., Wan, G., Corfas, G., **Dressler, G.R.** and Duncan, R.K. (2018) From otic induction to hair cell production: $Pax2^{Egfp}$ cell line illuminates key stages of development in mouse inner ear organoid model. *Stem Cell Dev.* 27, 237-251.
f. Grimley, E. and **Dressler, G.R.** (2018) Are Pax proteins potential therapeutic targets in kidney disease and cancer? *Kidney Intern.* 94, 259-267.
g. Ihermann-Hella, A., Hirashima, T., Kupari, J., Kurtzeborn, K., Li, H., Kwon, H.N., Cebrian, C., Soofi, A., Dapkunas, A., Miinalainen, I., **Dressler, G.R**., Matsuda, M. and Kuure, S. (2018) Dynamic MAPK/ERK activity sustains nephron progenitors through niche regulation and primes precursors for differentiation. *Stem Cell Reports* 11, 912-928.

2. The discovery of PTIP and its characterization as an adaptor linking DNA binding proteins to MLL H3K4 methyltransferase complexes. This work defines a new mechanism for developmental regulatory proteins that can restrict cell lineages through epigenetic imprints and stabilize gene expression patterns.

a. Patel, S.R., Kim, D., Levitan, I. and **Dressler, G.R.** (2007) The BRCT-domain containing protein PTIP links Pax2 to a histone H3, lysine 4 methyltransferase complex. *Developmental Cell* 13, 580-592.
b. Fang, M., Ren, H,, Liu, J., Cadigan, K.M., Patel, S.R. and **Dressler, G.R.** (2009) *Drosophila* PTIP is essential for anterior/posterior patterning in development and interacts with the PcG and TrxG pathways. *Development* 136, 1929-1938.
c. Stein, A.B., Jones, T.A., Herron, T.J., Patel, S.R., Day, S.M., Noujaim, S., Milstein, M., Klos, M., Furspan, P.B., Jalife, J. and **Dressler, G.R.** (2011) H3K4 methylation stabilizes gene expression patterns and physiological function in adult cardiomyocytes. *J. Clin. Invest.* 121, 2641-2650.
d. Schwab, K.R., Patel, S. R. and **Dressler, G.R.** (2011) The role of PTIP in class switch recombination and long range chromatin interactions at the IgH locus. *Mol. Cell. Biol.* 31, 1503-1511
e. Sun, Y., Zhou, B., Mao, F., Xu, J., Miao, H., Zou, Z., Phuc Khao, L.T., Jang, Y., Cai, S., Witkin, W., Koche, R., Ge, K., **Dressler, G.R.,** Levine, R.L., Armstrong, S.A., Dou, Y., Hess, J.L. (2018) HoxA9 reprograms the enhancer landscape to promote leukemogenesis. *Cancer Cell* 34, 643-658.

3. The discovery of Kielin-Chordin like Protein (KCP) and its characterization as an enhancer of BMP signaling in fibrosis and metabolic disease. How BMP and TGF-beta signals are presented to receptors to enhance or suppress signaling is a critical issue that is relevant to human disease such as fibrosis and metabolic disease. Our work defines a new mechanism of BMP regulation through interaction with secreted cysteine- rich proteins that enhance receptor-ligand interactions.

a. Lin, J., Patel, S.R., Cheng, X., Cho, E. A., Levitan, I., Ullenbruch, M., Phan, S.H., Park, J.M. and **Dressler, G.R.** (2005) Kielin/Chordin-like protein (KCP), a novel enhancer of BMP signaling attenuates renal fibrotic disease. *Nature Medicine*, 11, 387-393
b. Lin, J., Patel, S. R., Wang, M. and **Dressler, G.R.** (2006) The cysteine rich domain protein KCP suppresses TGF-□/Activin signaling in renal epithelia. *Mol. Cell. Biol.* 26, 4577-4585.
c. Soofi, A., Zhang, P. and Dressler, G.R. (2013) Kielin/Chordin-like protein attenuates both acute and chronic renal injury. *J. Am. Soc. Nephrol.* 24, 897-905.
d. Soofi, A., Wolf, K.I., Ranghini, E.J., Amin, M.A., and **Dressler, G.R.** (2016) The Kielin/Chordin-like Protein KCP Attenuates Nonalcoholic Fatty Liver Disease in Mice. *Am. J. Physiol.* 311, G587-G598.

e. Soofi, A., Wolf, K.I., Emont, M.P., Qi, N., Martinez-Santibanez, G., Grimley, E., Ostwani, W. and **Dressler, G.R.** (2017) The Kielin/Chordin-like Protein (KCP) Attenuates High Fat Diet Induced Obesity and Metabolic Syndrome in Mice. *J. Biol. Chem.* 292, 9051-9062.
f. Higashi, A.Y., Aronow, B.J. and **Dressler, G.R.** (2019) Expression profiling of fibroblasts in chronic and acute disease models reveals novel pathways in kidney fibrosis. *J. Am. Soc. Nephrol.* 30, 80-94.
g. Bradford, S.T.J., Ranghini, E.J., Grimley, E., Lee, P.H. and **Dressler, G.R.** (2019) A high throughput screen for agonists of bone morphogenetic protein (BMP) signaling identifies potent benzoxazole compounds. *J. Biol. Chem.* in press.

4. The identification of GDNF as a ligand for the c-Ret receptor tyrosine kinase and the characterization of GDNF/Ret as a PI3-kinase activating chemotactic pathway. How GDNF activates the c-ret tyrosine kinase and promotes cell migration was first elucidated by my lab in the developing kidney. How epithelial cells migrate and undergo branching morphogenesis in response to c-Ret activation was studied in developing kidneys.

    a. Vega, Q.C., Worby, C.D., Lechner, M.S., Dixon, J.E. and **Dressler, G.R.** (1996) Glial derived neurotrophic factor is a ligand for RET and promotes kidney morphogenesis. *Proc. Natl. Acad. Sci. USA*.93, 10657- 10661
    b. Tang, M.J., Worley, D., Sanicola, M. and **Dressler, G.R.** (1998) The RET-Glial Cell-derived Neurotrophic Factor (GDNF) pathway stimulates migration and chemoattraction of epithelial cells. *J. Cell Biol.* 142, 1337-1345.
    c. Tang, M.J., Cai, Y., Tsai, S.J., Wang, Y.K. and **Dressler, G.R.** (2002) Ureteric Bud Outgrowth in Response to RET Activation is Mediated by Phosphatidylinositol-3 Kinase. *Dev. Biol.* 243, 128-136.
    d. Kim, D. and **Dressler, G. R.** (2007) PTEN modulates GDNF/RET mediated chemotaxis and branching morphogenesis in the developing kidney. *Dev. Biol.*, 307, 290-299.

5. The characterization of the molecular basis of Groucho mediated gene repression. How the Groucho/TLE family of repressors regulate gene expression and epigenetic imprints was determined and its relevance to Pax2 mediated gene regulation elucidated. We show that Groucho proteins can recruit a phosphatase that displaces PTIP from Pax2 and an arginine methyltransferase and the Polycomb repressor Complex 2 to imprint repressive epigenetic marks, thus turning Pax2 from an activator to a repressor.

    a. Cai, Y., Brophy, P., Levitan, I. and Stefano, S. and **Dressler, G.R.** (2003) Groucho suppresses Pax2 transactivation by inhibition of JNK mediated phosphorylation. *EMBO J*.22, 5522-5529
    b. Patel, S.R., Bhumbra, S.S., Paknikar, R.S. and **Dressler, G.R.** (2012) Epigenetic mechanisms of Groucho/Grg/Tle mediated transcriptional repression. *Molecular Cell* 45, 185-195.
    c. Zhang, P. and **Dressler, G.R.** (2013) The Groucho protein Grg4 suppresses Smad7 to activate BMP signaling. *Biochem. Biophys. Res. Comm.* 440, 454-459.
    d. Abraham, S., Paknikar, S., Bhumbra, S., Luan, D., Garg, R., **Dressler, G.R.,** and Patel, S.R. (2015) The Groucho Associated Phosphatase PPM1B Displaces Pax Transactivation Domain Interacting Protein (PTIP) to Switch the transcription factor Pax2 from a Transcriptional Activator to a Repressor. *J. Biol. Chem.* 290, 7185-94.