BIOGRAPHICAL SKETCH

NAME: REYLAND, Mary E.

eRA COMMONS USER NAME: REYLANDM

POSITION TITLE: Professor

EDUCATION/TRAINING:

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
George Mason University, Fairfax, VA	BS	1977	Biology
Medical College of Virginia/Virginia Commonwealth University, Richmond, VA	PhD	1983	Pathology
University of Washington, Seattle, WA	Postdoc	1987	Biochemistry

A. Personal Statement

As a result of my broad training in biochemistry and cancer biology, I am poised to address complex biological problems from a mechanistic perspective. My lab has a long-standing interests in biological functions of the protein kinase C (PKC) family of lipid-regulated kinases and in salivary gland biology. I have had continuous funding from NIH since 1998. We have explored the contribution of PKC isoforms to many biological functions including cell death, cell survival and tumorigenesis. Our studies have elucidated an essential role for PKCδ in genotoxin-induced apoptosis in epithelial cells, and in irradiation induced apoptosis *in vivo*. We have identified nuclear translocation of PKCδ as a critical regulatory event in response to apoptotic agents and have probed the molecular mechanisms underlying this regulated translocation. Our recent studies suggest that PKCδ regulates cell death through modulation of DNA repair and chromatin structure. Understanding how the pro-apoptotic function of PKCδ is regulated has led to the identification of key steps in this pathway that can be targeted therapeutically. Based on these studies we are currently investigating the use of tyrosine kinase inhibitors for radioprotection of salivary gland function.

My contributions to biomedical research training and education at the university and national levels are evidence of my longstanding commitment to predoc and postdoc training. I have trained 11 graduate students and 7 post-doctoral fellows, many of whom have gone on to successful careers in research or research-related fields. In addition, I have trained 35 undergraduate, dental and high school students in summer programs. I have served in multiple leadership positions in the UC Anschutz Graduate School and am currently the program director for the Cancer Biology Graduate Training Program. I am co-PI of a T32 in Cancer Biology that provides funding for pre and postdoc trainees, and an R25 that provides funding for the UCCC summer fellowship program (CREU). Nationally, as a member of the board of the Cancer Biology Training Consortium (CABTRAC), I contribute developing and setting guidelines for pre and postdoctoral training, particularly in the context of cancer biology. I serve on numerous external review panels for both graduate programs and T32 grants. I have had the pleasure of reviewing the proposed application for the University of Virginia T32 NCI cancer training grant and I am fully committed to participating as a member of the External Advisory Board. I look forward to serving as a mentor on the NCI R25 START Program.

Ongoing projects that I would like to highlight include:

1R01DE027517-04 (REYLAND) 07/01/2018-05/31/2023
NIH/NIDCR
PKCdelta and salivary gland radioprotection

Goal: In this proposal, we will explore the hypothesis that inhibition of PKCδ suppresses apoptosis and protects against the initial, or "early" effects of IR damage to the salivary gland through regulation of the DNA damage response and increased DNA repair. Our studies will define the mechanism(s) underlying radioprotection of the salivary gland by inhibition of PKCδ and TKIs, and may lead to the identification of new "rational" strategies for radioprotection for oral tissues.

2R01DE015648-13 (REYLAND) 12/01/2003 – 12/31/2021
NIH/NIDCR
Regulation of Salivary Cell Apoptosis by PKCδ
Goal: We will explore the hypothesis that tyrosine kinase inhibitors can be used prophylactically to suppress apoptosis and loss of salivary gland function in response to irradiation. Our studies will also explore downstream targets of PKCδ in the context of irradiation damage and address the hypothesis that PKCδ regulates activation of the Extra-cellular-Regulated-Kinase (MEK/ERK) signaling pathway in the context of apoptosis. TKIs and radioprotection.

T32CA160216-04 (REYLAND, CRAMER) 07/07/2016 – 06/30/2021
NIH/NCI $360,462
Training Program in Cancer Biology
Goal: Training devoted to understanding molecular and cellular mechanisms of cancer is vital to the development of novel treatments and therapies for patients.

R25CA240122-01 (REYLAND) 09/01/20-08/31/25
Cancer Research Experiences for Undergraduates (CREU)
Goal: This award funds a summer research program through the University of Colorado Cancer Center.

B. Positions, Scientific Appointments and Honors

Professional Employment

09/16-01/17	Visiting Professor, Peter MacCallum Cancer Center, Melbourne, Australia
10/10-Pres	Director, Cancer Biology Graduate Program, University of Colorado Denver, Aurora, CO
07/07-Pres	Professor, with tenure, Dept. of Craniofacial Biology, School of Dentistry, University of Colorado Denver (formerly UCHSC), Aurora, CO
09/01-08/02	Visiting Professor. Cancer Research UK, Protein Phosphorylation lab (PJ Parker)
07/00-07/07	Associate Professor with tenure, Dept. of Craniofacial Biology, School of Dentistry, UCHSC
09/95-06/00	Assistant Professor, Dept. of Craniofacial Biology, School of Dentistry, UCHSC
05/94-08/95	Assistant Professor, Division of Endocrinology, Department of Medicine, University of Colorado Health Sciences Center (UCHSC), Denver, CO
01/90-11/93	Research Assistant Professor, Department of Pharmacological Sciences, State University of New York at Stony Brook
09/87-12/89	Instructor, Dept. of Pharmacological Sciences, State University of New York at Stony Brook

Other Selected Professional Activities

Patent application # PCT/US14/61038 "Tyrosine Kinase Inhibitor" filed October 17, 2014. Approved May, 4, 2018
Board of Directors, Cancer Biology Training Consortium (CABTRAC), 2017-
Chair (with Peter Parker), FASEB SRC: Lipids and Lipid Regulated Kinases in Cancer, 2014
Co-Chair (with Alan Fields, Peter Parker), FASEB SRC: Lipids and Lipid Regulated Kinases in Cancer, 2012
Chair (with David Yule), Gordon Research Conference on Salivary Glands and Exocrine Secretions, 2009
Chartered member, NCI Subcommittee F Study Section, 2017-2022
Ad Hoc Reviewer, NIH/NCI, 2014-Present
Chartered member, NIH Oral, Dental and Craniofacial Sciences Study Section, 2009-2012
Ad Hoc Reviewer, NIH/NIDCR, 2003-present
President, Salivary Gland Research Group, International Association of Dental Research, 2006-2008
Vice- President, Salivary Gland Research Group, International Association of Dental Res., 2004-2006
Grant Reviewer, American Heart Association Regional and National Consortiums, 1997-2002
Board of Directors, American Heart Association of Metro Denver, 1998-2000

Cancer League of Colorado Scientific Advisory Board, 1998-2000

C. Contributions to Science

1. **Fidelity of DNA replication.** My research as a postdoc with Dr. Larry Loeb explored the fidelity of DNA replication by DNA polymerase-α. Faithful DNA replication is critical for maintaining genetic integrity and processes that maintain fidelity are often abrogated in cancer cells. Our studies contributed to understanding how the fidelity of DNA replication is regulated and were foundational for later work that explored how such processes are altered in disease. Specifically, we identified a DNA polymerase-primase complex and showed that primase association with polymerase-α increased the accuracy of DNA replication. Additional studies helped to define how specificity in proofreading is achieved in during DNA replication, and laid the foundation for studies from other laboratories that identified DNA polymerase-α as a major proof-reading polymerase in eukaryotic cells. More recent studies have shown that alterations in error-prone DNA polymerases and proof reading exonucleases can contribute to tumorigenesis in humans.

a. **Reyland ME**, Loeb LA. On the fidelity of DNA replication. Isolation of high fidelity DNA polymerase-primase complexes by immunoaffinity chromatography. *J Biol Chem* 1987; 262:10824-30. PMID: 3038898
b. Cotterill SM, **Reyland ME**, Loeb LA, Lehman IR. A cryptic proofreading 3'----5' exonuclease associated with the polymerase subunit of the DNA polymerase-primase from Drosophila melanogaster. *Proc Natl Acad Sci U S A* 1987; 84:5635-9. PMID: 3112771, PMC298917
c. **Reyland ME**, Lehman IR, Loeb LA. Specificity of proofreading by the 3'----5' exonuclease of the DNA polymerase-primase of Drosophila melanogaster. *J Biol Chem* 1988; 263:6518-24. PMID: 3129427

2. **Regulation of corticosteroid synthesis.** As a Research Assistant Professor in Dr. David William's lab, and later in my lab at the University of Colorado, I studied the regulation of enzymes involved in corticosteroid synthesis. We defined novel signaling pathways for regulation of adrenal steroidogenesis and identified the biosynthetic enzymes targeted by these signaling pathways. These studies laid the foundation for understanding how adrenal corticosteroid synthesis is regulated by protein kinase C, and identified novel mechanisms by which cholesterol can regulate adrenal steroidogenesis. Our work also has implications for understanding alterations in cholesterol biosynthesis, and potentially lipid storage, in a variety of disease states. Notably, as a junior scientist I was awarded both a New York Regional and a National American Heart Association Grant-in-Aid to pursue this research.

a. **Reyland ME**, Gwynne JT, Forgez P, Prack MM, Williams DL. Expression of the human apolipoprotein E gene suppresses steroidogenesis in mouse Y1 adrenal cells. *Proc Natl Acad Sci U S A* 1991; 88:2375-9. PMID: 1848701, PMC51234
b. **Reyland ME**, Prack MM, Williams DL. Elevated levels of protein kinase C in Y1 cells which express apolipoprotein E decrease basal steroidogenesis by inhibiting expression of P450-cholesterol side chain cleavage mRNA. *J Biol Chem* 1992; 267:17933-8. PMID: 1517229
c. **Reyland ME**. Protein kinase C is a tonic negative regulator of steroidogenesis and steroid hydroxylase gene expression in Y1 adrenal cells and functions independently of protein kinase A. *Mol Endocrinol* 1993; 7:1021-30. PMID: 7694083
d. **Reyland ME**, Evans RM, White EK. Lipoproteins regulate expression of the steroidogenic acute regulatory protein (StAR) in mouse adrenocortical cells. *J Biol Chem* 2000; 275:36637-44. PMID: 10960482

3. **Protein kinase C (PKC) function in apoptosis**. After relocating to the University of Colorado Health Sciences Center (now Anschutz Medical Campus) as an Assistant Professor I began to explore the function of PKC isoforms in apoptosis. At that time very little was known about the biological functions of specific isoforms of PKC, and there were no studies linking PKCδ to apoptosis. Our studies identified PKCδ as a critical regulator of apoptosis induced by DNA damaging agents and in the context of mammary gland development. Further studies defined a series of events that regulate the pro-apoptotic function of this ubiquitous kinase. We identified a C-terminal nuclear localization signal on PKCδ, and showed that phosphorylation on specific tyrosine residues and nuclear translocation was critical for the pro-apoptotic function of PKCδ. We went on to show that nuclear translocation of PKCδ is initiated by sequential tyrosine phosphorylation at Y155 and Y64 by Abl and Src, respectively, which results in a conformational change that facilitates importin-α binding. Our research was foundational to understanding how apoptotic signaling is regulated in response to DNA damaging agents and

enabled the development of rational strategies to regulate the function of PKCδ to enhance or suppress the apoptotic response (see #5 below).

a. Matassa AA, Carpenter L, Biden TJ, Humphries MJ, **Reyland ME**. PKCδ is required for mitochondrial-dependent apoptosis in salivary epithelial cells. *J Biol Chem* 2001; 276:29719-28. PMID: 11369761
b. DeVries TA, Neville MC, **Reyland ME**. Nuclear import of PKCδ is required for apoptosis: identification of a novel nuclear import sequence. *EMBO J* 2002; 21:6050-60. PMID: 12426377, PMC137198
c. DeVries-Seimon TA, Ohm AM, Humphries MJ, **Reyland ME**. Induction of apoptosis is driven by nuclear retention of protein kinase δ. *J Biol Chem* 2007; 282:22307-14. PMID: 17562707
d. Adwan TS, Ohm AM, Jones DN, Humphries MJ, **Reyland ME**. Regulated binding of importin-α to protein kinase Cδ in response to apoptotic signals facilitates nuclear import. *J Biol Chem* 2011; 286:35716-24. PMID: 21865164, PMC3195609
e. Ohm AM, Affandi, T, **Reyland, ME**. EGF receptor and PKCδ kinase activate DNA damage-induced pro-survival and pro-apoptotic signaling via biphasic activation of ERK and MSK1 kinases. *J Biol Chem* 2019; 294(12):4488-4497. doi: 10.1074/jbc.RA118.006944

4. Development of strategies to inhibit radio-toxicity in the oral cavity. Damage to the salivary gland resulting in salivary gland hypofunction is a frequent complication of irradiation for head and neck cancer and diminishes the effectiveness of anti-cancer therapies and the quality of life for affected patients. Using our knowledge of PKCδ structure/function, we are exploring strategies to protect salivary gland function and limit damage to other oral tissues in this vulnerable patient population. Specifically, we have shown that tyrosine kinase inhibitors (TKIs) can protect against loss of salivary gland function in a mouse model of head and neck irradiation without impacting treatment of the tumor. Our proposed use of TKIs represents a novel application of these drugs which are already in use for cancer therapy. A patent application for use of tyrosine kinase inhibitors as radio-protectors has been filed. We are also exploring the utility of small molecule inhibitors (SMIs) of PKCδ for protection of salivary gland function through collaborations with industry and chemists who have developed such agents. Both TKIs and PKCδ SMIs are potentially widely useful for limiting toxicity in patients who receive irradiation and chemotherapy for many types of cancer.

a. Humphries MJ, Limesand KH, Schneider JC, Nakayama KI, Anderson SM, **Reyland ME**. Suppression of apoptosis in the protein kinase Cdelta null mouse in vivo. *J Biol Chem* 2006; 281:9728-37. PMID: 16452485,
b. Wie SM, Adwan TS, DeGregori J, Anderson SM, **Reyland ME**. Inhibiting tyrosine phosphorylation of protein kinase Cdelta (PKCdelta) protects the salivary gland from radiation damage. *J Biol Chem* 2014; 289:10900-8. PMID: 24569990, PMC4036201
c. Wie SM, Wellberg, E, Karam, S.D. and **Reyland ME**. Tyrosine Kinase Inhibitors Protect the Salivary Gland from Radiation Damage by Inhibiting Activation of Protein Kinase C-δ. *Mol Cancer Ther* 2017 Sep;16(9):1989-1998. doi: 10.1158/1535-7163
d. Affandi, T, Ohm, AM, Gaillard, D, Haas, A, **Reyland, ME.** Tyrosine kinase inhibitors protect the salivary gland from radiation damage by increasing DNA double stranded break repair. *J Biol Chem 2021;Feb 8 in press*

5. Protein kinase C function in cancer. In contrast to the pro-apoptotic function of PKCδ in non-transformed cells, we were the first to show that PKCδ can function as a tumor promoter in some oncogenic contexts. Studies from our lab have shown that PKCδ is required for tumorigenesis driven by oncogenic K-ras and that PKCδ regulates proliferation of Her2/neu driven tumors *in vivo* and in human breast cancer cells *in vitro*. Our studies demonstrate a very high correlation between K-ras and PKCδ dependency (R=0.8) in lung cancer cells and show that PKCδ is required for survival signaling through the MEK/ERK pathway and for invasion/migration of lung cancer cells dependent on oncogenic K-Ras. Our studies support exploration of PKCδ as a drug target in lung cancer and suggest that dependency on this pathway may define the subset of *KRAS* mutant tumors most amenable to targeting of the K-ras pathway.

a. Symonds JM, Ohm AM, Carter CJ, Heasley LE, Boyle TA, Franklin WA, **Reyland ME**. Protein kinase Cδ is a downstream effector of oncogenic K-ras in lung tumors. *Cancer Res* 2011; 71:2087-97. PMID: 21335545, PMC3271733
b. Allen-Petersen BL, Carter CJ, Ohm AM, **Reyland ME**. Protein kinase Cdelta is required for ErbB2-driven mammary gland tumorigenesis and negatively correlates with prognosis in human breast cancer. *Oncogene* 2014; 33:1306-15. PMID: 23474764, PMC4292929

c. Symonds JM, Ohm AM, Tan AC, **Reyland ME**. PKCδ regulates integrin $\alpha_V\beta_3$ expression and transformed growth of K-ras dependent lung cancer cells. *Oncotarget* 2016; PMID: 26918447
d. Ohm, A.M., Tan, A-K, Heasley, L.E., **Reyland, M.E.** 2017. Co-dependency of PKCδ and KRAS: Inverse association with cytotoxic drug sensitivity in KRAS mutant lung cancer, *Oncogene* 2017; Jul 27;36(30):4370-4378. doi: 10.1038/onc.2017.27

Complete list of published works in MyBibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/mary.reyland.1/bibliography/40725856/public/?sort=date&direction=ascending