OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 09/30/2024)

BIOGRAPHICAL SKETCH

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NAME: Jean J. Latimer, Ph.D.

eRA COMMONS USERNAME (credential, e.g., agency login): LATIMER_J

POSITION TITLE: Associate Professor of Pharmaceutical Sciences and Director, NSU AutoNation Institute of Breast Cancer Research and Care

EDUCATION/TRAINING:

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Cornell University	B.A.	05/1982	Cell Biology
SUNY at Buffalo, Roswell Park Cancer Institute Division	Ph.D.	04/1989	Molecular and Cellular Biology
Laboratory of Radiobiology and Environmental Health, University of California, San Francisco	Postdoctoral	08/1993	Developmental Biology

A. Personal Statement

My laboratory performs functional assays of DNA repair based on my postdoctoral training at the Department of Energy funded Laboratory of Radiobiology at UCSF under Dr. James Cleaver. I have extended this work into the molecular analysis of individual gene expression of the Nucleotide Excision Repair pathway using the model systems established in my own laboratory at the University of Pittsburgh Medical Center. Together with Dr. Stephen Grant, I have also performed functional analyses of DNA repair and somatic mutation on some rare human DNA repair disorders.

My laboratory has developed a number of important *in vitro* models related to the human breast and breast cancer. My background in developmental biology and murine embryonic stem cells has allowed my laboratory to establish a tissue engineering system that involves multiple cell types from the non-diseased breast without the use of transforming agents or gene constructs. We have established 48/48 reduction mammoplasty (non-diseased) extended explants/cell lines,12 of which are from African American patients. This system culminates in an organotypic breast epithelial/myoepithelial ductal system in vitro, after one month, over a field of stromal fibroblasts.

We have established 60 breast tumor cell lines stages 0-IV (at an 85% success rate) about half of which have matching adjacent isogenic counterparts. We have RNA sequencing data on many of these lines. We have established the intrinsic role of Nucleotide Excision Repair in early stage sporadic breast cancer in *PNAS* and shown the use of our cell lines in *Experimental Cell Research*, *Cell and Tissue Research* and *Stem Cells*. Using Nanostring analyses on RNA from these cell lines that we established, we were able to identify "miRRA", a microRNA that reduces functional Nucleotide Excision Repair.

We have a assembled a team for this grant proposal that includes Dr. Stephen Grant a geneticist and molecular toxicologist who has spent 25 years studying environmental mutagenesis and who serves on Environmental Protection Agency and NIEHS expert panels several times a year for his expertise in environmental carcinogens. We have just completed a Department of Defense grant studying Gulf War Illness from the perspective of DNA repair and somatic mutation issues that have occurred in bone marrow stem cells. Dr. Grant and I have published 14 papers together on breast, breast cancer, stem cells and leukemia. Dr. Hardigan is a long time colleagues at NSU who performs biostatistical analyses for several of our projects. Dr. Yates is a board-certified plastic surgeon who operates on local women in Broward County and performs among other procedures, breast reduction mammoplasties. Working with her team we have been consenting these patients with African ancestry, European white ancestry and most recently, Hispanic/Latina ancestry to

procure tissue for our primary, explant and cell line cultures. Historically we have worked with Drs. Temple and Tranakas are dedicated cancer physicians who are motivated to help their patients by collaborating with researchers. Dr. Temple is an orthopedic surgeon who works on sarcomas and is currently at the University of Miami. He sometimes discovers advanced breast cancers in his bone surgeries which he can provide to our laboratory. Dr. Tranakas is a breast cancer oncologic surgeon who has many patients that reflect our local demographics for example patients of African origin such as the Caribbean diaspora and Haiti as well has Latino and Hispanic patients. The samples we have received are under IRBs and consented. They have helped to build our RNA sequence databases as we establish explants and cell lines from them.

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

Florida Breast Cancer Foundation
Latimer, PI
7/1/22-6/30/23
$100,000
"Impact of S. Florida Chemicals on Breast Cells Derived from Women of Different Ancestries"

USA MED Research
W81XWH-16-1-0678
Latimer, Co-I
09/30/16–09/29/22
"Persistently Elevated Somatic Mutation as a Biomarker for Clinically Relevant Exposures in Gulf War Illness"

AutoNation Research Project
Latimer, PI
7/1/16-1/31/2022
$150,000)
"Modulation of Nucleotide Excision Repair in Advanced Breast Cancer to Create a Window of Genotoxic Vulnerability"

Citations:

1. **Latimer, J.J**., Alhamed, A., Sveiven, S., Almutairy, A., Klimas, N.G., Abreu, M., Sullivan, K., and Grant, S.G. (2020) Preliminary evidence for a hormetic effect on DNA nucleotide excision repair in veterans with Gulf War Illness. *Military Medicine* **185**: e47–e52. PMCID: PMC7353836

2. Grant, S.G., Ibrahim, O.M., Jin, X.-L., Klimas, N.G., Sullivan, K., and **Latimer, J.J**. Elevated somatic mutation and evidence of genomic instability in veterans with Gulf War illness. (2021) *Life Sciences* **281**: 119746, doi: 10.1016/j.lfs.2021.119746

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2016-present **Director**, NSU AutoNation Institute for Breast Cancer Research and Care, Nova Southeastern University, Fort Lauderdale, FL
2011-present **Adjunct Faculty**, Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh, Pittsburgh, PA
2011-present **Director**, Cancer Research Laboratory, College of Pharmacy, Nova Southeastern University, Fort Lauderdale, FL
2011-present **Associate Professor**, Department of Pharmaceutical Sciences, Nova Southeastern University, Fort Lauderdale, FL
1993-2011 **Investigator**, Magee-Women's Research Institute, Magee-Women's Hospital, Pittsburgh, PA
1993-2011 **Assistant Professor**, Departments of Obstetrics, Gynecology and Reproductive Sciences and Human Genetics, University of Pittsburgh, Pittsburgh, PA

Federal Advisory Committees
2009 NIH/NCI: RC1 Challenge Grant Program Basic and Translational Oncology SEP

2003 NASA: Radiation Biology
2001-2021 DOD Breast Cancer CDMRP: member of **25 study sections**, **Chairperson of 3**

2001-2010 DOD Prostate Cancer CDMRP: **3 study sections**
2001 NASA: Cellular Biotechnology and Tissue Engineering
1999-2001 Institute of Medicine/National Cancer Policy Board Committee to Study Technologies for the Early Detection of Breast Cancer

Other Experience and Professional Memberships

2020 **Member**, Florida Komen Foundation Breast Cancer Research Program
2015-2022 **Chairperson (7 years)**, American Institute for Biological Sciences, NYSTEM Rowley Breast Cancer Grant Proposal Committees
2009 **Member**, Expert Panel: Chemicals Policy and Breast Cancer Project, California Breast Cancer Research Program
2007 **Member**, Process Revision Taskforce, Susan G. Komen For the Cure
2006–2008 **Member**, Special Research Initiatives Strategy Team, California Breast Cancer Research Fund
2006-2011 **Member**, Cellular and Molecular Pathology Graduate Faculty, Interdisciplinary Biomedical Graduate Program, University of Pittsburgh
2006-2011 **Member**, Cancer Stem Cells Program, University of Pittsburgh Cancer Institute
2005-2011 **Member**, Center for Environmental Oncology, University of Pittsburgh Cancer Institute
Member, McGowan Institute for Regenerative Medicine, University of Pittsburgh
2004, 2005 **Member,** Research Funding Priorities Taskforce, Susan G. Komen Breast Cancer Foundation
1999–2001 **Member**, Committee to Study Technologies for the Early Detection of Breast Cancer U.S. Institute of Medicine/National Cancer Policy Board
1999–2000 **Member**, Advisory Panel on Interactive Health Communication (IHC) Environmental Scan for Allegheny County, Allegheny County Department of Health
1999-2011 **Member**, Molecular Genetics and Biochemistry Graduate Faculty, Interdisciplinary Biomedical Graduate Program, University of Pittsburgh
1994-2011 **Member**, Molecular and Cellular Carcinogenesis Program, University of Pittsburgh Cancer Institute

C. Contributions to Science

1. My Ph.D. training involved transcriptional regulation of mammalian genes and utilized classical cloning, transient transfection, in situ hybridization, and nuclear run on and liver culture techniques. My work demonstrated the presence of a novel tissue specific element that changed the transcriptional regulation of Alpha1 antitrypsin (alpha-1-protease inhibitor) from liver specific to liver and kidney expression in the wild mouse species, *Mus caroli*.

    1. **Latimer**, **J.J**., Berger, F.G., and Baumann, H. (1987) Developmental expression, cellular localization, and testosterone regulation of alpha$_1$-antitrypsin in *Mus caroli* kidney. *J. Biol. Chem. 262*: 12641–12646.

    2. **Latimer**, **J.J**., Berger, F.G., and Baumann, H. (1990) Highly conserved upstream regions of the alpha$_1$-antitrypsin gene in two mouse species govern liver-specific expression by different mechanisms. *Mol. Cell. Biol.* **10**: 760–769.

    3. Rheaume, C., Goodwin, R.L., **Latimer**, **J.J**., Baumann, H., and Berger, F.G. (1994). Evolution of murine alpha$_1$-proteinase inhibitors: gene amplification and reactive center divergence. *Journal of Molecular Evolution* **38**: 121–131.

    4. Baumann, H., Isseroff, H., **Latimer**, **J.J**., and Jahreis, G.P. (1988). Phorbol ester modulates interleukin-6 and interleukin-1 regulated expression of acute phase plasma proteins in hepatoma cells. *Journal of Biological Chemistry* **263**: 17390–17396.

2. Demonstration of functional tissue-specificity of DNA nucleotide excision repair in human and mouse applying the unscheduled DNA synthesis assay, as performed in the laboratory of my post-doctoral mentors, Dr. James Cleaver and Roger Pedersen at UCSF. This is an aspect of epigenetic gene regulation. For the first time in the scientific literature, we demonstrated functional differences in DNA repair capacity among various normal tissue and cell types.

    1. **Latimer**, **J**.**J**., Hultner, M.L., Cleaver, J.E. and Pedersen, R.A. (1996) Elevated DNA excision repair capacity in the extraembryonic mesoderm of the mid-gestation mouse embryo. *Exptl. Cell Res.* **228**: 19–28.

    2. **Latimer**, **J**.**J**., Nazir, T., Flowers, L.C., Forlenza, M.J., Beaudry-Rodgers, Kelly, C.M., Conte, J.A., Shestak, K., Kanbour-Shakir, A., and Grant, S.G. (2003) Unique tissue-specific level of DNA nucleotide excision repair in primary human mammary epithelial cultures. *Exptl. Cell Res.* **291**: 111–121.

    3. Alanazi, J.S., and **Latimer, J.J.** (2020). Host cell reactivation: Assay for actively transcribed DNA nucleotide excision repair using luciferase family expression vectors. *Meth. Mol. Biol.* 2102:509-528. doi: 10.1007/978-1-0716-0223-2_28.

    4. Pimpley, M.R., Foley, M.L., **Latimer, J.J**. (2020) New perspectives on unscheduled DNA synthesis: Functional assay for global genomic DNA nucleotide excision repair. *Meth. Mol. Biol.* 2102:483-507. doi: 10.1007/978-1-0716-0223-2_27

3. Our group was the first to establish that Nucleotide Excision Repair has an important role in the sporadic breast cancer. In addition, we discovered that there are significant differences in functional DNA repair in early stage tumors vs. late stage breast tumors and in recurrent vs non-recurrent acute lymphoblastic leukemia that could play a significant role in chemotherapy sensitivity and resistance.

    1. **Latimer**, **J**.**J**., Johnson, J.M., Kelly, C.M., Miles, T.D., Beaudry-Rodgers, K.A., Lalanne, N.A., Vogel, V.G., Kanbour-Shakir, A., Kelley, J.L., Johnson, R.R., and Grant, S.G. (2010) Nucleotide excision repair deficiency is intrinsic in sporadic stage I breast cancer. *Proc. Natl. Acad. Sci. USA* **107**: 21725–21730.

    2. **Latimer**, **J**.**J**., Majekwana, V.J., Pobón-Padín, Y.R., Pimpley, M.R., and Grant, S.G. (2015) Regulation and disregulation of mammalian nucleotide excision repair. *Photochem. Photobiol.* **91**: 493–500.

    3. Ibrahim, O., As Sobeai, H., Grant, S.G., and **Latimer**, **J**.**J**. (2018) Nucleotide excision repair is a predictor of early relapse in acute lymphoblastic leukemia. *BMC Med. Genom.* **11**: 95.

4. We were the first to show that Nucleotide Excision Repair is upregulated in Gulf War Illness (in bone marrow stem cells) and is also impacted by psychological stress.

    1. Forlenza, M., **Latimer**, **J**., and Baum, A. (2000). The effects of stress on DNA repair capacity. *Psychology and Health* **15**: 881–891. doi: 10.1080/08870440008405589

    2. **Latimer, J.J**., Alhamed, A., Sveiven, S., Almutairy, A., Klimas, N.G., Abreu, M., Sullivan, K., and Grant, S.G. (2020) Preliminary evidence for a hormetic effect on DNA nucleotide excision repair in veterans with Gulf War Illness. *Military Medicine* **185**: e47–e52.

    3. Grant, S.G., Ibrahim, O.M., Jin, X.L., Klimas, N.G., Sullivan, K., and **Latimer, J.J**. (2021) Elevated somatic mutation and evidence of genomic instability in veterans with Gulf war illness. *Life Sciences* **281**:119746

5. We have established over 100 novel breast epithelium and breast tumor derived cell lines without the use of telomerase or traditional immortalizing/transforming agents such as viruses (60 tumor cell lines + adjacent, 48 non diseased explants/cell lines) [Latimer, J.J. (2002) Methods Related to Primary HMEC.

U.S. Patent #6,383,805]. Applying the skills and knowledge gained from my experience in creating mouse embryonic stem cells in Dr. Roger Pedersen's laboratory, my laboratory was able to reliably grow cells in culture from both normal breast epithelium (100% success rate) and stages 0-IV of breast cancer (85% success rate). These cells were provided to collaborators who used them to study stem cells in breast cancer, immunological and molecular biological characterization of breast cancer:

1. Sajithlal, G.S., Rothermund, K., Zhang, F., Dabbs, D.J., **Latimer**, **J.J**., Grant, S.G., and Prochownik, E.V. (2010) Permanently blocked stem cells derived from breast cancer cell lines. *Stem Cells* **28**: 1008–1018.

2. Viscus, C., Ito, D., Dhir, R., Szczepanski, M.J., Chang, Y.J., **Latimer, J.J**., Grant, S.G. and Deleo, A.B. (2011) Identification of Hydroxysteriod (17B) dehydrogenase type 12 (HSD17B12) as a CD8+ T-cell-defined human tumor antigen of human carcinomas. *Cancer Immunol. Immunother.* **60**(7): 919–29.

3. Wend, P., Runke, S., Wend, K., Anchondo, B., Yesayan, M., Jardan, M., Hardie, N., Loddenkemper, C., Ulasov, I., Lesniak, M.S., Wolsky, R., Bentolila, L.A., Grant, S.G., Elashoof, D., Lehr, S., **Latimer**, **J.J**., Bose, S., Sattar, H., Krum, S.A., and Miranda-Carboni, G.A. (2013) WNT10B/β-catenin signaling induces HMGA2 and proliferation in metastatic triple-negative breast cancer. *EMBO Mol. Med.* **5**: 1–16.

4. Dodda, B., Corry, D., Bondi, C.D., Hasan, M., Clafshenkel, W.P., Gallagher, K.M., Kotlarczyk, M.P., Sethi, S., Buszko, E., **Latimer, J.J**., Cline, J.M, Witt-Enderby, P.A. and Davis, V.L. (2019). Co-administering Melatonin with an Estradiol-Progesterone Menopausal Hormone Therapy Represses Mammary Cancer Development in a Mouse Model of HER2-positive Breast Cancer, *Frontiers in Oncology* 9: 525 doi: 10.3389/fonc.2019.00525

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/16AbQxr2orWk7/bibliography/40740488/public/?sort=date&direction=ascending