BIOGRAPHICAL SKETCH

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NAME: Stephen G. Grant, Ph.D.

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

POSITION TITLE: 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
University of Toronto, Canada	B.Sc. (Hons)	06/1979	Biochemistry and Chemistry, Zoology
Hospital for Sick Children Research Institute, University of Toronto, Canada	Ph.D.	12/1985	Medical Genetics
Roswell Park Cancer Institute, Buffalo, NY	Post-Doctoral Fellowship	10/1988	Molecular Genetics
University of California, San Francisco, CA	Clinical Fellowship	06/1993	Medical Genetics

A. Personal Statement

I am a Ph.D. in Medical Genetics with broad training in dosimetry, radiation health and toxicology. My laboratory studies human diseases that occur as a consequence of environmental exposures as mediated by host effects, particularly variation in DNA repair. My work on environmental, occupational and medical exposures and genetic predisposition to cancer has generated almost 18.7 million dollars in funding and led to over 100 published scientific papers and almost 300 abstracts and presentations. I have studied populations exposed to radiation at Hiroshima and Chernobyl, environmental exposures related to leukemia, breast and prostate cancer, as well as autism and Gulf War Illness. I have been the Program Director for Project SEAMIST, a training program for hazardous chemical safety since 2013, and I have successfully expanded the program into other aspects of worker training and safety, including disaster response. Since 1986, I have hosted 1 visiting scientist, 5 postdoctoral fellows, 4 clinical fellows and residents, 17 graduate students, 5 professional students, 25 undergraduate students, 5 high school students and 2 high school teachers in my laboratory. These trainees have been funded off of my research grants from the NIH and DOD, foundations like Komen for the Cure and the American Cancer Society, by institutional funds and consortiums such as the Associated Western Universities Summer Research Program. Students in my lab learn molecular toxicology, which can entail assaying samples or simply analyzing archived data from secondary sources. Ten interns have contributed to 15 publications from my laboratory; 23 interns have contributed to (and gained authorship on) 62 abstracts of presentations at local, national and international meetings. These students have won 10 awards for their work from their host institutions and academic meetings.

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

W81XWH-16-1-0678
Grant (PI)
09/30/16–09/29/21
Persistently Elevated Somatic Mutation as a Biomarker for Clinically Relevant Exposures in GWI

2U45ES019350
Grant (co-PI)
08/11/20–05/31/25
Project SEAMIST (South East Area Maritime Industry Safety Training)

Florida Breast Cancer Foundation
Grant (co-I)
07/01/22–6/30/23
Impact of South Florida Environmental Chemicals on Breast Cells Derived from Women of Different Ancestries

Research Products/Publications:

1. U.S. Patent **10**,**684**,**293** "Associating somatic gene mutations in glycophorin A with complex multifactorial diseases" 6-16-20.
2. **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. PMID: 34181965.

B. Positions, Scientific Appointments, and Honors

Positions

2019–present	**Professor**, Department of Public Health, Dr. Kiran C. Patel College of Osteopathic Medicine, Nova Southeastern University, Fort Lauderdale, FL
2016–present	**Investigator**, AutoNation Institute for Breast Cancer Research and Care, Nova Southeastern University, Fort Lauderdale, FL
2013–2019	**Associate Professor**, Department of Public Health, Dr. Kiran C. Patel College of Osteopathic Medicine, Nova Southeastern University, Fort Lauderdale, FL
2011–2013	**Visiting Associate Professor**, Department of Pharmaceutical Sciences, College of Pharmacy, Nova Southeastern University, Fort Lauderdale, FL
2006–2007	**Associate Director**, Center for Environmental Oncology, University of Pittsburgh Cancer Institute, Pittsburgh, PA
2001–2010	**Associate Professor**, Departments of Environmental and Occupational Health and Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh, PA
1997–2010	**Director**, Cancer Toxicology Satellite Facility, Molecular Cytogenetics Laboratory, University of Pittsburgh Cancer Institute, Pittsburgh, PA
1995–2010	**Member**, Magee-Womens Research Institute, Magee-Womens Hospital, Pittsburgh, PA
1994–2010	**Member**, Molecular Carcinogenesis/Molecular Epidemiology Programs, University of Pittsburgh Cancer Institute, Pittsburgh, PA
1993–2001	**Assistant Professor**, Departments of Environmental and Occupational Health and Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh, PA
1992–1993	**Assistant Research Scientist**, Departments of Radiology and Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco, CA
1988–1992	**Senior Biomedical Scientist**, Biomedical Sciences Division, Lawrence Livermore National Laboratory, Livermore, CA

Scientific Appointments

2023	**Associate Editor**, Environmental Health and the Exposome, *Frontiers in Public Health*
2022, 2023	**Chair**, **Peer Review Panel**, U.S. National Institutes of Health
2011, 2021–23	**Peer Reviewer**, U.S. National Institutes of Health
2018–21	**Member**, Scientific Advisory Committees, U.S. Environmental Protection Agency (X 6)
2015	**Chair**, **Peer Review Panel**, U.S. Army Medical Research and Material Command (Breast Cancer Program)
2007	**Peer Reviewer**, National Sciences and Engineering Research Council of Canada (*ad hoc*)
2006–12	**Peer Reviewer**, French National Research Agency (X 3)
2005–23	**Peer Reviewer**, U.S. Army Medical Research and Material Command (Breast Cancer Program, X 20, Toxic Exposure Program)

2005–present **Editorial Board**, *Toxicology In Vitro*
2005, 2014 **Editor**, **Molecular Toxicology Protocols**, *Methods in Molecular Biology*
2003, 2005 **Peer Reviewer**, U.S. National Aeronautics and Space Administration
2001 **Peer Reviewer**, U.S. Environmental Protection Agency

Board Certification
1993 Clinical Molecular Genetics (renewed 2002, 2007, 2009)

C. Contributions to Science

1. Development of the *GPA* assay, a cumulative biomarker of human genotoxicity

My thesis work was based on a somatic hybridization model of mutagenesis, with the delineation of a number of novel mechanisms such as epigenetic gene inactivation contributing to clones selected for drug resistance. At Lawrence Livermore Laboratory we developed a blood-based version of this assay, based on the antigenic determinant of the MN blood group, glycophorin A (GPA). Besides applying this assay to exposed populations and hereditary DNA repair deficiency disorders (resulting in elevated cancer incidence or premature aging), we continue to explore what the assay can tell us about normal populations, including evidence of genomic instability in aging populations. Total mutation frequency as delineated by the GPA assay has been shown to be associated with cancer incidence in the normal population.

a. **Grant**, **S**.**G**., Bigbee, W.L., Langlois, R.G., and Jensen, R.H. (1991) Allele loss at the human *GPA* locus: a model for recessive oncogenesis with potential clinical application. *Clinical Biotechnology* **3**: 177-185.
b. **Grant**, **S**.**G**., and Bigbee, W.L. (1993) *In vivo* somatic mutation and segregation at the human glycophorin A (*GPA*) locus: phenotypic variation encompassing both gene-specific and chromosomal mechanisms. *Mutation Research – Fundamental and Molecular Mechanisms of Mutagenesis* **288**: 163-172.
c. **Grant**, **S**.**G**. (2001) Molecular epidemiology of human cancer: biomarkers of genotoxic exposure and susceptibility. *Journal of Environmental Pathology, Toxicology and Oncology* **20**: 245-261.
d. Myers, N.T., and **Grant**, **S**.**G**. (2014) The blood-based glycophorin A human *in vivo* somatic mutation assay. *In:* Molecular Toxicology Protocols, 2nd Edition (Keohavong, P., and **Grant**, **S**.**G**., ed.). Humana Press, New York, New York. *Methods in Molecular Biology* **1105**: 223–244.

2. Detection and quantification of genotoxicity of ionizing radiation

The *GPA* assay was developed at the Lawrence Livermore National Laboratory as a detector of biological effects of exposure to ionizing radiation. The assay has been applied in a number of studies involving such exposures, such as Hiroshima and Chernobyl and to detect the effects of medical use of radiation.

a. **Grant**, **S**.**G**., and Bigbee, W.L. (1994) Bone marrow somatic mutation after genotoxic cancer therapy. *Lancet* **343**: 1507-1508.
b. Jensen, R.H., Langlois, R.G., Bigbee, W.L., **Grant**, **S**.**G**., Moore, D., II, Pilinskaya, M., Vorobtsova, I., and Pleshanov, P. (1995) Elevated frequency of glycophorin A mutations in erythrocytes from Chernobyl accident victims. *Radiation Research* **141**: 129-135.
c. Jensen, R.H., Reynolds, J.C., Robbins, J., Bigbee, W.L., **Grant**, **S**.**G**., Langlois, R.G., Pineda, J.D., Lee, T., and Barker, W.C. (1997) Glycophorin A as a biological dosimeter for radiation dose to the bone marrow from iodine-131. *Radiation Research* **147**: 747-752.
d. Livingston, G.K., Jensen, R.H., Silberstein, E.B., Hinnefeld, J.D., Pratt, G., Bigbee, W.L., Langlois, R.G., **Grant**, **S**.**G**., and Shukla, R. (1997) Radiobiological evaluation of immigrants from the vicinity of Chernobyl. *International Journal of Radiation Biology* **72**: 703-713.

3. Detection and quantification of genotoxicity of environmental tobacco smoke *in utero*

As a detector of biological effects of exposure, the *GPA* assay has been applied in a number of studies confirming known effects, such as Hiroshima, Chernobyl and medical use of radiation (above). In an important demonstration of its sensitivity, however, it was applied in a pair of studies of cord bloods, where it not only detected the effects of an actively smoking mother, but also a smoking father, demonstrating the transplacental effects of environmental tobacco smoke. These studies have been used to support legislation to ban

occupational and environmental smoking around “women who are pregnant or might become pregnant” in the U.S. and around the world.

a. Bigbee, W.L., Day, R.D., **Grant**, **S**.**G**., Keohavong, P., *Xi*, *L*., *Zhang*, *L*., and Ness, R.B. (1999) Impact of maternal lifestyle factors on newborn *HPRT* mutant frequencies and molecular spectrum—Initial results from the Prenatal Exposures and Preeclampsia Prevention (PEPP) study. *Mutation Research – Fundamental and Molecular Mechanisms of Mutagenesis* **431**: 279-289.
b. Keohavong, P., Xi, L., Day, R.D., *Zhang*, *L*., **Grant**, **S**.**G**., Day, B.W., Ness, R.B., and Bigbee, W.L. (2005) *HPRT* gene alterations in umbilical cord blood T-lymphocytes in newborns of mothers exposed to tobacco smoke during pregnancy. *Mutation Research – Genetic Toxicology and Environmental Mutagenesis* **572**: 156-166.
c. **Grant**, **S**.**G**. (2005) Qualitatively and quantitatively similar effects of active and passive maternal tobacco smoke exposure on *in utero* mutagenesis at the *HPRT* locus. *BMC Pediatrics* **5**: 20. PMCID: PMC1185547
d. **Grant**, **S**.**G**. (2010) Tobacco smoke exposure and somatic mutation in newborns. *Open Pediatric Medical Journal* **4**: 10-13.

4. Characterization and diagnosis of human DNA repair deficiency diseases

Human DNA repair deficiency diseases usually result in premature disease and death, either with symptoms of precocious carcinogenesis or aging. They are not, however, either screened for, nor obviously evident at birth. We have applied a suite of genotoxicological measures, including the GPA assay, to a number of these diseases and demonstrated increased sensitivity to normal environmental exposures in bone marrow cells. Indeed, the GPA assay has been used to aid in diagnosis of two such diseases, ataxia telangiectasia and Fanconi anemia, including in otherwise asymptomatic individuals. We also documented previously undetectable effects in heterozygotes for Werner syndrome and Fanconi anemia, and showed that BRCA carriers exhibit a phenotype consistent with other heterozygotes for Fanconi anemia.

a. Moser, M.J., Oshima, J., Bigbee, W.L., **Grant**, **S**.**G**., Langlois, R.G., Jensen, R.H., and Monnat, R.J., Jr. (2000) Genetic instability and hematologic disease risk in Werner syndrome patients and heterozygotes. *Cancer Research* **60**: 2492-2496.
b. **Grant**, **S**.**G**., Wenger, S.L., Latimer, J.J., Thull, D., and Burke, L.W. (2000) Analysis of genomic instability using multiple assays in a patient with Rothmund-Thomson syndrome. *Clinical Genetics* **58**: 209-215. PMCID: PMC4712958
c. Evdokimova, V.E., McLoughlin, R.K., Wenger, S.L., and **Grant**, **S**.**G**. (2005) Use of the glycophorin A bone marrow somatic mutation assay for rapid, unambiguous identification of Fanconi anemia homozygotes regardless of *GPA* genotype. *American Journal of Medical Genetics* **135A**: 59-65. PMCID: PMC4849896
d. **Grant**, **S**.**G**., Das, R., Cerceo, C.M., Rubinstein, W.S., and Latimer, J.J. (2007) Elevated levels of somatic mutation in a manifesting *BRCA1* mutation carrier. *Pathology and Oncology Research* **13**: 276-283. PMCID: PMC4301730

5. Demonstration of tissue- and cancer-specific regulation of nucleotide excision repair

In collaboration with Dr. Jean Latimer, we have performed a long-term study of the regulation of the nucleotide excision repair pathway in humans and mice. When we began, it was essentially assumed that DNA repair was an essential metabolic function, and as such, would be fully expressed in all cells (although skin was always prioritized, due to the inherent sensitivity to sunlight). Dr. Latimer first showed functional tissue-specificity in this type of DNA repair in embryonic tissues, and together, we extended this observation to various adult tissues. We demonstrated relatively low repair in epithelial cells, but exceptionally low repair in brain, whereas heart muscle had very high repair. We also demonstrated a consistent loss of repair in early stage breast tumors. Many of these results have been explained by showing coordinate epigenetic regulation of the canonical genes in the pathway, and we are presently using this observation to find ways to modulate expression to optimize genotoxic chemotherapy.

a. Latimer, J.J., Johnson, J.M., Miles, T.D., Dimsdale, J.M., Edwards, R.P., Kelley, J.L., and **Grant**, **S**.**G**. (2008) Cell-type-specific level of DNA nucleotide excision repair in primary human mammary and ovarian epithelial cell cultures. *Cell and Tissue Research* **333**: 461-467. PMCID: PMC4301738
b. 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. *Proceedings of the National Academy of Sciences USA* **107**: 21725–21730. PMCID: PMC3003008

c. Ibrahim, O., As Sobeai, H.M., **Grant**, **S**.**G**., and Latimer, J.J. (2018) Nucleotide excision repair is a predictor of early relapse in pediatric acute lymphoblastic leukemia. *BMC Medical Genomics* **11**: 95. wwwPMCID: 6208034

d. 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

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/stephen.grant.1/bibliography/49860140/public/?sort=date&direction=ascending