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Education:

- Postdoc., 1990-1994 Columbia University
- Ph.D., 1990 New York University
- B.A., 1985 SUNY College at Purchase

Research Interest:

Link to PubMed Articles: www.ncbi.nlm.nih.gov/pubmed

Signal transduction pathways converging on the tumor suppressor p53 are central in the regulation of cell growth and cell death. Conventional chemotherapeutics result in p53 checkpoint activation. However, when the p53 pathway is blocked, or mutated, a more targeted chemotherapeutic approach is required to result in cancer cell death. A focus on such targeted approaches are central to the research being carried out in the Bargonetti laboratory. The work focuses on the mutant p53, Mdm2, and MdmX molecular signal transduction pathways and we work to activate p53-independent cell death pathways that facilitate killing resistant cancer types. Presently this work is carried out using human cancer cell line models, xenograft models, and *C. elegans* nematode models. The Bargonetti research team is using genetically engineered tools to decrease expression of and/or mutate the three oncogenes (i.e. Mdm2, MdmX, and oncogenic mutant p53) because we hypothesize that these biomarkers are involved in the formation of different subtypes of breast cancer.

Project 1: Oncogenic Gain-of-function (GOF) Mutant p53.

The Bargonetti team recently defined a novel gain-of-function mutant p53 pathway that they termed the mtp53-PARP-MCM axis. This mtp53-PARP-MCM axis can be targeted using a PARP inhibitor that traps PARP on chromatin. We discovered of a set of interactions between mutant p53 (mtp53), PARP, and MCMs on chromatin that may elucidate at least one aspect of gain-of-function (GOF) mtp53. In addition, we observed that high mtp53 and PARP sensitize cells to PARP inhibitors (PARPi) plus DNA damage, suggesting a therapeutic targeting approach. In addition, we observed that high mtp53 and PARP sensitize cells to PARP inhibitors (PARPi) plus DNA damage, suggesting a therapeutic targeting approach. We are currently working on projects that address the mechanistic role of GOF mtp53 at replication forks and how mtp53 helps to recruit replication factors.

Project 2: MDM2 and MDMX p53-independent oncogenic roles in breast cancer..

We discovered that reducing the amount of Mdm2 in breast cancer cells reduces tumor growth and abnormal architecture in three-dimensional (3D) cell culture models. We identified that

estrogen receptor positive (ER+) breast cancer cells possess an Mdm2-associated growth activation pathway. Our work has been instrumental for introducing the concept of an estrogen driven signaling pathway that uses a non-canonical Mdm2 molecular mechanism. We are dissecting the relevant targets of Mdm2 and MdmX in different subtypes of breast cancer. We recently discovered that both Mdm2 and MdmX promote triple negative breast cancer metastasis (TNBC). We are currently addressing if blocking the Mdm2 and MdmX proteins with pharmacological agents can inhibit TNBC metastasis. The Bargonetti group also investigates alternative forms of MDM2, inclusing MDM2-FL and MDM2-C, that are expressed when a single nucleotide polymorphism (SNP) at position 309 in the mdm2 gene that causes increased Mdm2 overexpression. This overexpression can inhibit wild-type p53 activity but also causes p53-independent oncogenic functions in cells expressing mutant p53.

Project 3: The roles of Mutant C. *elegans* p53 1 (CEP1) in hyperproliferative germline and worm lifespan.

Undergraduate students are invited to register for Introduction to Experimental Biology to get college credits for working on this C. *elegans project*. This is a genetics and cell biology experimental cell biology project.

Jill Bargonetti received her B.A. from SUNY Purchase, her M.S. and Ph.D. from New York University and her postgraduate training from Columbia University. While in the Purchase Dance Corps she performed works by Sarah Stackhouse and Paul Taylor and then went on to became a member of Dianne McIntyre's Sounds in Motion from 1983-1985. In 1994 she became as an Assistant Professor at The City University of New York (CUNY) at Hunter College and The Graduate Center in the PhD Programs of Biology and Biochemistry and currently holds the title of Full Professor with tenure. Bargonetti was awarded the prestigious Presidential Early Career Award for Scientists and Engineers by President Bill Clinton in 1997, and has received research grants from the American Cancer Society, The Department of Defense, The National Science Foundation (NSF), The National Institutes of Health (NIH), and the Breast Cancer Research Foundation (BCRF). She was a member of the National Cancer Policy Board from 2002 until 2005 (a board of the Institution of Medicine and National Research Council of the National Academies) and served on the NIH Tumor Cell Biology study section from 2012-2018. She is currently a reviewer for American Association of Cancer Research grants and reviews manuscripts for numerous high impact journals.

Choreographing Genomics: Her understandings on the unifying principles of dance, genomics, and cancer inspire her work.

Bargonetti currently receives invitations to deliver lectures on both on research activities and on Choreographing Genomics into Understanding. See the PBS and TEDx/CUNY specials to get a closer view:

Selected Publications

- , G.K., Elshabassy, N., Lundine, D., Conde, D-G., Xiao, G., Ellison, V.,and Bargonetti, J., Frame-shift Mediated Reduction of Gain-of-function p53 R273H and Oligomerization of Mutant p53 R273H is Not Required for Gain-of-Function Chromatin Associated Activities Frontiers in Cell and Development Biology 2021 November 22: https://doi.org/10.3389/fcell.2021.772315

- Wilson, T. Pirovano, G., Xiao, G., Samuels, Z., Roberts,S., Viray, T., Guru, N., Zanzonico, P., Gollub, M., Reiner, T., and Bargonetti, J., PARP Targeted Auger Therapy in p53 Mutant Colon Cancer Xenograft Mouse Models. ACS Molecular Pharmaceutics 2021 July 28 online first PMID: 34318678.
- Ellison, V., Annor, G.K., Freedman, C., Xiao, G., Lundine, D., Freulich, E., Prives, C., and Bargonetti, J., Frame-shift Mediated Reduction of Gain-of-function p53 R273H and Deletion of the R273H C-terminus in Breast Cancer Cells Result in Replication-Stress Sensitivity.

Oncotarget 2021 June 8: 12 (12):1128-1146 PMID: 34136083

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