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Signal transduction to- and from- wild-type p53, mutant p53, and MDM2 isoforms in cancer.

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 an outcome of 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 molecular signal transduction pathways activated by various chemotherapeutic drugs to bring about differential activation of p53 target genes as well as to activate alternative p53-independent cell death pathways that facilitate killing resistant cancer types. Presently this work is carried out using human cancer cell line models as well as with a C. elegans nematode model system. 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.

The Bargonetti research team is using genetically engineered tools to decrease the expression of 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. They discovered that reducing the amount of Mdm2 or mutant p53 protein 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. Their work has been instrumental for introducing the concept of an estrogen driven signaling pathway that uses a non-canonical Mdm2 molecular mechanism. They are delineating the molecular targets of estrogen driven Mdm2 isoforms by using genetically engineered human breast cancer cell lines to selectively rid the cancer cells of either Mdm2, MdmX, or oncogenic mutant p53 in order to dissect the critical targets that promote tumorigenesis. Estrogen receptor positive (ER+) breast cancers often have high levels of Mdm2 and ER negative (ER-) breast cancers often have mutant p53. They are dissecting the relevant targets of Mdm2, MdmX, and oncogenic mutant p53 in different subtypes of breast cancer.

Many cancer cells have high levels of the oncogenic Mdm2 protein due to either increased expression or amplification of the mdm2 gene. The Bargonetti group 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.

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 and the National Institutes of Health. She is currently funded by the Breast Cancer Research Foundation. She won a Young Investigator Award, given by the mayor of New York City, the New York Voice Award, given to those who have made a significant improvement to the quality of life in New York City, and the Kathy Keeton Mountain Top Award from the New York branch of the NAACP. 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: