



Project Title: The DNA Replication Stress Response		Code: CMRI2
Host School / Institute: Children's Medical Research Institute		Address: 214 Hawkesbury Road, Westmead.
Certificates & Clearances required: No		
Primary Supervisor: Dr Anthony Cesare		
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Co-Supervisor/team: Research team includes post-doctoral scientists in the Cesare laboratory		
Project Type: Laboratory based		
Project Category: Molecular biology; Cancer		
Skills / Attributes of a successful student: Highly motivated and talented student to work on our projects related to the replication stress response. Ideally the candidate will have some laboratory experience. We will provide all training related to experimentation and research topic. Projects will be developed relative to the candidate's interests and strengths. Individuals interested in pursuing a Ph.D. will be given priority.		
Project Keywords: DNA Replication; DNA Damage Response; Cell Biology; Molecular Biology; Microscopy		
<p>Project Description: Genome instability is a hallmark of nearly all solid tumors and adult-onset leukemias. It is now apparent that in the early stages of cancer development, genome instability is primarily caused by DNA "replication stress". Replication stress is broadly defined as perturbations in the dynamics of the replication machinery, characterized by slow progression of DNA replication forks, replication fork collapse, and activation of additional origins of DNA replication. Replication is frequently challenged through stresses originating exogenously (e.g. low nutrient environment, genotoxic agents) or endogenously (e.g. oncogene expression). In healthy cells, replication stress activates the DNA damage response (DDR) to induce growth arrest and tumor suppression. However, in the absence of functional tumor suppressor pathways, the DDR does not activate senescence and cells continue to proliferate despite replication difficulties. For this reason, tumour cells typically display high levels of endogenous replication stress. This presents an opportunitstic target to induce cancer cell death by exploiting and endogenous weakness in the cancer cell.</p> <p>Replication stress has been associated with "mitotic catastrophe". Another broad descriptor that is used to explain mitotic cell death of an unexplained mechanism. Our laboratory has recently elucidated a mechanism of mitotic catastrophe in reponse to replication stress. Additionally, we identified a novel pathway where DNA replication stress alters nuclear architecture to efficiently propagate repair.</p> <p>We are looking to expand on these discoveries in three directions: 1) Further elucidate how replication stress translates to mitotic cell death; 2) probe if mechanisms of cell death induced by chemotherapeutic replication stress inducing drugs are conserved; 3) understand how nuclear architecture is changed to enable repair of DNA replication stress in health cells. Opportunities are available in all three trajectories and projects will be tailored to applicant's interests and strengths on an individual basis.</p>		