Background: Clonal hematopoiesis of indeterminate potential (CHIP) is a recently recognized disorder defined by presence of circulating blood cell clones with mutations in genes associated with myeloid cancers (*JAK2*, *DNMT3A, TET2, SF3B1, ASXL1, TP53,* and others, Xie et al., *Nat Med* 2014). CHIP is prevalent in older patients (10% in persons >65 years old), and associated with increased risk of myelodysplasia, leukemia, cardiovascular disease, and death (Jaiswal et al, *NEJM* 2014). Recent reports strongly suggest that CHIP precedes therapy-related acute myeloid leukemia (t-AML; Wong et al, *Nature* 2015: *TP53* mutations detected 3-6 years prior to t-AML), and it precedes secondary myeloid neoplasms among recipients of stem cell transplantation (Gibson et al., *J Clin Oncol* 2017: 14% incidence with, and 4% without CHIP detectable before transplantation). About 1% of recipients of adjuvant chemotherapy for early-stage solid tumors develop secondary AML or myelodysplasia (3-7 years after treatment), which is often resistant to treatment and fatal in outcome. So far, it is not known if the prevalence of CHIP increases after administration of adjuvant chemotherapy for solid tumors, and whether CHIP is associated with subsequent t-AML among such patients.

Research Aims: Our *long-term research goal* is to study acquired genetic defects in hematopoietic stem cells, elucidating pathology of myeloid cancers. CHIP is an excellent model of an "initiating" mutation which leads to subsequent myeloid cancer by acquisition of additional mutations over time. The ***overall objective*** of this pilot research project is to determine if patients who received adjuvant chemotherapy as part of therapy for a solid tumor have increased prevalence of CHIP several years later, compared with those who had similar cancers, but did not require adjuvant chemotherapy. The ***central hypothesis*** is that CHIP appears within a few years after completion of chemotherapy as a result of DNA damage and failed immune surveillance. This hypothesis relies on strong preliminary data from the above reports indicating a relationship between asymptomatic CHIP and secondary myeloid cancers.

To achieve our objective, we formed a collaboration between clinicians with expertise in epidemiology research and cancer management (*PI*, Olszewski), molecular analysis of hematopoietic stem cells (Co-*PI*, Dubielecka), and stem cell biology (*Mentor*, Quesenberry). We will also collaborate with researchers at Dana Farber Cancer Institute (DFCI, *Collaborators*, Kuo & Scholl), using their clinically validated Next Generation Sequencing (NGS) platform which can detect the low-level (2%) variant allele frequency (VAF) that characterizes CHIP. This pilot project will consist of a single Aim:

- **Aim 1**: To compare prevalence of CHIP in solid tumor survivors who had received adjuvant chemotherapy as part of their cancer treatment (with an alkylating agent and an anthracycline), with matched controls who had the same solid tumors, but did not receive chemotherapy.

Strategy: We will conduct a case-control study drawing on the large population of cancer survivors receiving care at Rhode Island Hospital Comprehensive Cancer Center. We will enroll 80 survivors of solid tumors diagnosed within 1-7 years earlier, matching cases and controls 1:1 by age, sex, tumor type, and time from diagnosis. After providing informed consent, subjects will donate 10 mL of blood during a routine medical visit at the Cancer Center. We will extract DNA from circulating CD45+ leukocytes, and perform NGS on the extracted DNA using the DFCI Rapid Heme Panel technology. We will then calculate the odds ratio for presence of CHIP (outcome) based on receipt of adjuvant chemotherapy (exposure), in a conditional logistic model. A power analysis indicates that 80 subjects will provide adequate statistical power for this pilot project.

Significance: Defining the population of patients who are commonly encountered in oncology practice as at high risk of chemotherapy-related secondary myeloid cancers will provide an opportunity to alter their management, minimize further bone marrow damage, and ultimately t-AML-related death. An easily identifiable risk factor (post-chemotherapy CHIP) will enable further translational research studying the process of mutation acquisition, additional risk factors for progression, and preventive interventions. This project is thus an ideal ***fit for the Advance-CTR pilot award***, as it involves application of complex genomic technology to a population of cancer survivors derived from a Rhode Island community-based oncology center, and carries a potential to develop genomically-driven preventive or therapeutic interventions. The *expected outcome* of this pilot project will be the first piece of evidence that adjuvant chemotherapy is associated with increased risk of CHIP, and characterization of detected mutations. Completing the project will allow us to competitively obtain funding for a larger study on a prospective cohort of patients receiving cytotoxic chemotherapy, with longitudinal clinical and molecular analysis, assessment of risk of CHIP and secondary t-AML. Achieving the goal of the project will position our group at the forefront of a novel research field with a rapidly increasing importance and general interest, as it has a potential to substantially alter the future of cancer therapy.