



Scientific Abstract

SU2C Multiple Myeloma Dream Team:

“Screening and Interception of Precursor Myeloma”



[This abstract was provided by the scientists when their application was accepted.]

Multiple Myeloma (MM) is a fatal plasma cell dyscrasia that almost always progresses from precursor states of monoclonal gammopathy of undetermined significance (MGUS)/smoldering multiple myeloma (SMM). The incidence of MGUS is about 3% of the general population aged 50 years. African Americans (AA) have a 3-fold increased prevalence compared with Whites. Although many patients are diagnosed with earlier phases of disease, most patients do not receive treatment until their disease progresses, at which time they have overt end-organ damage.

This concept of initiating therapy at the time of symptomatic disease is analogous to initiating therapy in patients with solid tumors only after the development of measurable metastatic disease. It is therefore not surprising that cure is not achieved for most patients with MM. However, not all patients with MGUS/SMM progress to myeloma; thus, screening is not standard despite being a simple blood test.

Our overarching hypothesis is that early detection of MGUS/SMM in a high-risk population, along with comprehensive characterization of genomic/epigenomic and microenvironmental/immune regulators of disease progression will lead to effective strategies that intercept disease progression and improve survival.

In Specific Aim 1, we will establish a screen-detected prospective cohort study of MGUS/SMM patients by screening a high-risk population (defined as a population with a higher prevalence of MGUS/SMM including AAs and individuals with first degree relative with a plasma cell dyscrasia, with an age ≥ 45 years), **the PROMISE study**. We expect to screen 50,000 individuals to obtain 3,000 MGUS/SMM cases who will be followed over time.

In Aim 2, we dissect genomic characteristics of clonal evolution from MGUS/SMM to MM and germline variants of high-risk individuals.

In Specific Aim 3, we evaluate the role of race, obesity, and health-related comorbidities on progression from MGUS to MM.

Specific Aim 4 defines the role of the tumor microenvironment in being permissive for tumor progression. We use integrative genomic platforms to identify genes present in the bone marrow niche at the single-cell level and alter immune evasion during disease progression. We will further characterize the T cell receptor clonal dynamics and mutation associated neoantigen recognition in these samples.





Finally, in Aim 5, we will develop novel imaging and therapeutic approaches to detect and intercept disease progression at the precursor stages of the disease including the first neoantigen personalized vaccine study.

By performing the first screening study for myeloma and by focusing on high-risk populations especially AA, we will change the landscape of diagnosis/screening and early prevention and interception of this myeloma. These studies will not only lead to better molecular markers to define progression but also define therapeutic options that will make MM a preventable or possibly curable disease.