Department of Applied and Computational Mathematics and Statistics Colloquium

Seth J. Corey
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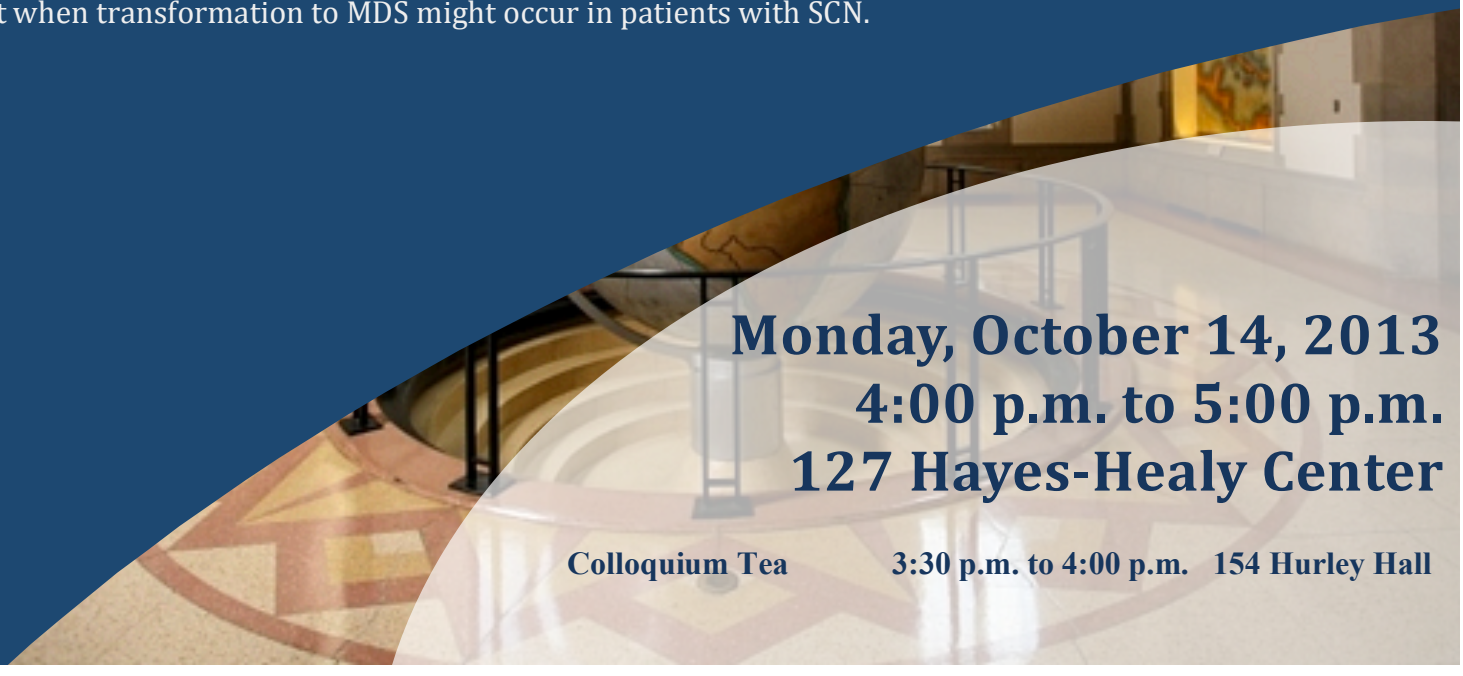
will give a lecture entitled:

A Game of Clones: Mathematical and Biochemical Mechanisms in Myelodysplasia

Abstract

How a blood stem cell develops into a highly specialized cell over several cell divisions is a profound question involving determinism and stochasticity and broadly applicable to human diseases and therapeutics. Hematopoiesis provides the best-characterized system for cell fate decision-making in both health and disease. Yet, the precise roles of external cues, intracellular signaling, gene regulatory networks, and homeostatic mechanisms have been elusive because of their complexity. The granulocyte is absolutely essential for our host defense and survival. Its pathophysiological importance is apparent in severe congenital neutropenia (SCN). Life-threatening infections in children with SCN can be avoided through the use of recombinant granulocyte colony-stimulating factor (GCSF). However, SCN often transforms into secondary myelodysplastic syndrome (sMDS) or acute myeloid leukemia (sAML). Multiple lines of evidence have demonstrated clonal evolution in cancer. Two thorny questions have emerged: how to account for the large number of mutations isolated in each tumor and how to identify which ones are "drivers" and which ones "passengers". Studying the SCN→sMDS→sAML model will simplify the complexity of clonal evolution. We hypothesize that clonal evolution of a sick hematopoietic progenitor cell in SCN involves perturbations in proximal and distal signaling networks triggered by a mutant GCSFR. We will employ a graph-theoretical model that will account for signaling effects of more fit verses less fit patient-derived GCSFR mutations and use existing and novel stochastic theories to estimate the number, timing, and fitness of driver mutations in granulocyte progenitors at the sMDS and sAML stages and build a stochastic model of normal and abnormal GCSFR-dependent pathways and validate it against experimental multivariate and network analysis of gene and protein expression, and develop a population genetics and population dynamics model for long-term transition from SCN to sMDS to sAML and validate it against existing data on time course of the disease. One insight emerging from our modeling is that we can predict when transformation to MDS might occur in patients with SCN.



Monday, October 14, 2013
4:00 p.m. to 5:00 p.m.
127 Hayes-Healy Center

Colloquium Tea **3:30 p.m. to 4:00 p.m.** **154 Hurley Hall**