"Targeting the cancer stem-cell niche for novel cancer therapeutics"

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Abstract: Cancer stem cells are thought to be the ultimate arbiters of tumor maintenance and propagation, and the root cause of relapse of many cancers. A logical extension of the cancer stem-cell hypothesis is that cancer stem cells, like their normal counterparts, inhabit tissue-specific microenvironments termed "niches" that are requisite for their long term survival. Such niches have been best defined in the hematopoietic system, where osteoblasts are known to regulate the expansion of hematopoietic stem cells (HSCs). We observe that osteoblastic stromal cells also define a microenvironment for leukemia stem cells (LSCs).

We are interested in defining chemicals that perturb LSCs in the context of their microenvironment. We thus propose performing parallel high-throughput chemical screens on LSCs and HSCs co-cultured with osteoblastic stroma. Our goal is to leverage our combined experience in chemical biology and stem cell biology to define anti-leukemic or pro-stem cell therapies that target the cancer "microenvironment". To this end, we will:

1) Define small-molecule modulators of normal stem cell/niche interaction using primary stem and stromal cells to reconstruct the microenvironment ex vivo. Chemical "perturbagens" will be identified by high-content image-based screening and focused secondary screens.

2) Determine whether perturbagens of the niche/stem-cell interface can differentially affect LSCs in this ex vivo microenvironment. This will generate a highly cross-annotated data set of the effects on the normal and cancerous niche environment.

3) Evaluate the functional effects of a validated compound subset using primary AML samples in xenogeneic models of human leukemia.