Title: CXCR4 signaling, hypoxia and breast cancer progression

Summary
Solid tumor masses include a microenvironment, which consists of multiple extracellular matrix molecules and of many different cell types beside tumor cells. Within any microenvironment, cross-talk communications is constant between cellular and non-cellular elements in part through receptor-ligand interactions. In non-diseased tissue, those communications allow tissues to carry their functions but also to repair altered components of the tissue. In contrast, in the presence of tumor cells, communications in particular through receptor ligand signaling are altered leading in part to the activation of alternate signaling pathways to different cell behaviors and ultimately to disruption of tissue homeostasis and promotion of cancer.

Chemokines are key small protein ligands involved in cell-cell signaling through binding to specific cell surface receptors. Chemokines are categorized into subfamilies based on their chemical structures. Importantly, chemokines bind receptors as either homo-dimers or hetero-dimers, which have different affinities depending on both the target receptor and the nature of the dimer. Chemokine signaling roles in inflammation and preventing infections have been extensively studied. In the cancer microenvironment, specific chemokines have been shown to promote the progression of cancers including breast cancer.

The effects of signaling through chemokine homo-dimers have been extensively investigated. In contrast, there is little data on effects of chemokine hetero-dimers that have been shown to impact biological activities. Recently, our lab demonstrated that the most abundant chemokines in human platelets, CXCL4 and CXCL12, were able to form hetero-multimers with many other chemokines.

Thus, the present research will define the effects of chemokine heterodimerization on breast cancer-related activities, specifically, the effects of CXCL4 and CXCL12 chemokine heterodimerization on tumor cell invasion. The two hypotheses investigated are: CXCL4 and CXCL12 chemokine heterodimerization differentially modulates breast cancer cell invasion (Hypothesis 1) and the CXCL4 and CXCL12 chemokine heterodimerization ratio correlates with alterations in breast cancer cell invasion (Hypothesis 2).

The data from these experiments will determine whether CXCL4-CXCL12 heterodimers affect breast cancer cell invasion activities. The long-term goal of the proposed research is the generation of effective cancer therapies that modulate local chemokine heterodimers to prevent cancer progression. This is proposed as an alternative to current cancer therapies that target chemokine receptors in part because of significant side effects. Furthering our understanding of chemokine heterodimerization and of the resulting alterations in biological activities will improve our knowledge of the role of chemokines in breast cancer progression and may also provide new anti-cancer therapeutic avenues.