Speaker: Jeffrey W. Keillor

Title: “Targeted Covalent Inhibition of Transglutaminase in Cancer Stem Cells”

Abstract:
Tissue transglutaminase (TG2) is a complex multifunctional protein that exists in two dramatically different conformations. In its open, extended conformation, it catalyses a transamidation reaction resulting in the cross-linking of proteins, predominantly in the extracellular matrix. In its closed, compact conformation, it functions as a G-protein in intracellular signalling. The latter role is critical for the survival and propagation of certain cancer stem cells, and is the target of our medicinal chemistry program.
We have designed irreversible inhibitors on a peptidomimetic scaffold that lock TG2 in its open conformation, thereby abolishing both its catalytic and G-protein activities, killing cancer stem cells and reducing tumour growth in vivo. We have also derived chemical biology tools from this scaffold, and have applied them to confirm the permeability of our inhibitors and to validate intracellular TG2 as the phenotypical target. Finally, we have recently confirmed the potency of a different class of small molecule inhibitors, and their surprising ability to also lock TG2 in an open conformation and block GTP binding. These results point the way to the development of new targeted covalent inhibitors with superior drug-like properties.