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Rational Design of Membrane Peptides for Cancer Targeting

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Several pathological processes including inflammation, ischemic infarction, and tumor formation result in acidification of the extracellular milieu. A significant opportunity exists to develop therapeutic technologies that target extracellular acidosis. The pHLIP peptide takes advantage of acidosis to insert into membranes of cancer cells for tumor imaging and drug delivery applications. The pHLIP can be found in three states: it is soluble (state I), and at neutral pH it binds to the surface of lipid membranes in an unstructured conformation (state II). Finally, at neutral pH, pHLIP contorts into the membrane to form a transmembrane domain. We have discovered that the membrane insertion of pHLIP is affected by the exposure of negatively charged lipids, which are altered in cancer cells. Despite the relevance of pHLIP, a number of drawbacks might limit its applicability. These include only moderate aqueous solubility and a low p*K*. We hypothesize that designing new peptides with the characteristics of pHLIP but without its limitations is the most effective strategy to overcome this barrier and allow further progress. To this end, we have developed the **a**cidity-**t**riggered **ra**tional **m**embrane (ATRAM) peptides. The ATRAM peptides not only have the three characteristic states of pHLIP, but also are endowed with properties that enhance its potential for drug delivery in cancer cells. Finally, I will discuss about the evolution of the ATRAM concept into a new peptide (TYPE7) with the three states that are able to establish interactions with a human receptor and modulate its action. TYPE7 targets the EphA2 receptor, which is responsible for cancer metastasis. We used super-resolution microscopy, Western blot, immunoprecipitation, cell migration assay and fluorescence correlation spectroscopy to show that TYPE7 binds to and activates EphA2. TYPE7 inhibits cell migration through Akt de-phosphorylation similarly to cross-linked eprhinA1, the natural ligand of EphA2. However, significant differences in the activation mechanism were found: specifically, no JM phosphorylation was induced, and instead of formation of large clusters, smaller oligomers were formed. The differences in the activation mechanism between TYPE7 and the cross-linked version of ephrinA1 allows gaining new mechanistic insights on how EphA2 is activated.

Date: Wed, Sept. 5, 2018
Time: 4:30-5:30 pm
Location: 208 Clark Hall

Students, meet the speaker over coffee and cookies in the Bennett Conference room at 3:30 pm