7th Annual
Patricia Durbin Memorial Lecture

"Radiometals in PET: How Chelate Chemistry Informs *in vivo* Imaging of Disease"

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Wednesday, May 4, 2016
Refreshments at 3:30 pm
Seminar 4:00 - 5:00 pm
Bldg. 50 Auditorium

Positron Imaging Tomography (PET) is a state-of-the-art diagnostic imaging modality that images biochemistry and physiology with radiopharmaceuticals labeled with positron emitters. The traditional PET radionuclides have half-lives from 2 to 110 min, and include O-15, N-13, C-11 and F-18. Over the past two decades, there have been major advances towards radiometal-labeled PET tracers, particularly agents labeled with Ga-68 ($T_{1/2}$ = 68 min), Cu-64 ($T_{1/2}$ = 12.7 h) and Zr-89($T_{1/2}$ = 3.3 d). The kinetics of in vivo clearance of the tracer dictate the physical half-life required for optimal target imaging and target:background ratios. Clearance through the blood and normal organs is highly dependent on radiometal chelate stability, with kinetic stability being more important than thermodynamic stability. Cu(II), Ga(III) and Zr(IV) have distinctly different coordination chemistries and require very different chelation strategies to keep the radiometals attached to their biological targeting agents. Our lab has been at the forefront of investigating how charge, lipophilicity and kinetic stability of radiometal-chelates dictate biological behavior, particularly for Cu-64. Together with our collaborators, Edward Wong and Gary Weisman, we pioneered the use of cross-bridged (CB) macrocycles functionalized with carboxylate and phosphonate groups that form neutral and negatively charged 64Cu(II) complexes that favor renal clearance. The CB macrocycles have been been conjugated to receptor-targeted peptides and peptidomimetics that are specific for various types of tumors and immune cells for PET imaging with Cu-64 in mouse models of cancer, inflammation and tuberculosis. We are also investigating different chelators for Ga-68, which due to the ease of production as a daughter of long-lived Ge-68 ($T_{1/2}$ = 271 d), is highly attractive for widely available clinical PET imaging. We are currently focusing on ^{68}Ga- and ^{64}Cu-labeled LLP2A, a peptidomimetic with picomolar affinity for very late antigen 4 (also called integrin $\alpha4\beta_1$), which is involved in tumor and immune cell adhesion and migration. Through a systematic study, we have found optimal chelator conjugates of LLP2A for Ga-68 and Cu-64, and are now investigating PET imaging of metastatic melanoma and monitoring the response to targeted radiotherapy with beta emitting Lu-177-labeled LLP2A in mouse models.

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