The design and synthesis of novel PET radioligands for non-invasive imaging

The process of discovering and developing of a new pharmaceutical is a long, difficult and risky process which requires numerous resources. Molecular imaging techniques such as positron emission tomography (PET) have recently become a useful tool for making decisions along a drug candidate’s development timeline. PET is a translational, non-invasive imaging technique that provides quantitative information about a potential drug candidate and its target at the molecular level. Using this technique provides decisional information to ensure that the right drug candidate is being chosen, for the right target, at the right dose within the right patient population. PET provides key information about a drug candidate’s pharmacokinetics (PK) and pharmacodynamic (PD) properties in both pre-clinical and clinical studies. PET is being used in all phases of the drug discovery and development process and the goal of these studies are to accelerate the process in which drugs are developed. One important target in the area of immuno-oncology is the programmed death protein (PD-1) and its ligand programmed death-ligand 1 (PD-L1). This pathway plays a critical role in a major checkpoint pathway in which cancer cells can evade detection by the immune system. A same-day PET imaging agent capable of measuring PD-L1 status in both primary and metastatic lesions simultaneously could be an important tool for optimizing PD-L1 treatments in mono- and combination therapies. The purpose of this work is to evaluate the tumor targeting potential of an anti-PD-L1 Adnectin (derived from the 10th type III domain of human fibronectin (10Fn3); ~ 10 kDa) after 18F-fluorine labeling with a novel prosthetic group and characterize its properties as a PET radioligand for the PD-L1 receptor. BMS-986192, an anti-PD-L1 Adnectin bound to human and cynomolgus monkey PD-L1 with Kd in the picomolar range (10-13 pm) and autoradiography studies show this tracer has specific and saturable binding to human NSCLC tissues. In vivo PET imaging using this agent clearly visualized PD-L1 expression in xenografted mice and co-administration of 3 mg/kg unlabeled anti-human PD-L1 Adnectin reduced the tumor uptake at 2 h post-injection by more than 70% demonstrating PD-L1 specific binding. PET studies in cynomolgus monkeys confirmed binding to PD-L1(+) tissue (e.g. spleen) with minimal nonspecific background signal exclusive of primary clearance organs. BMS-986192 demonstrated the feasibility of non-invasively imaging the PD-L1 status of tumors by micro-PET studies. Clinical studies with 18F-BMS-986192 are underway to measure PD-L1 expression in human tumors.

Friday, June 1, 2018
1:30 – Meet the Speaker in room 328 Havemeyer
3:00 – Tea & Cookies in room 328 Havemeyer
3:30 – Seminars in room 209 Havemeyer

Please note special day and times