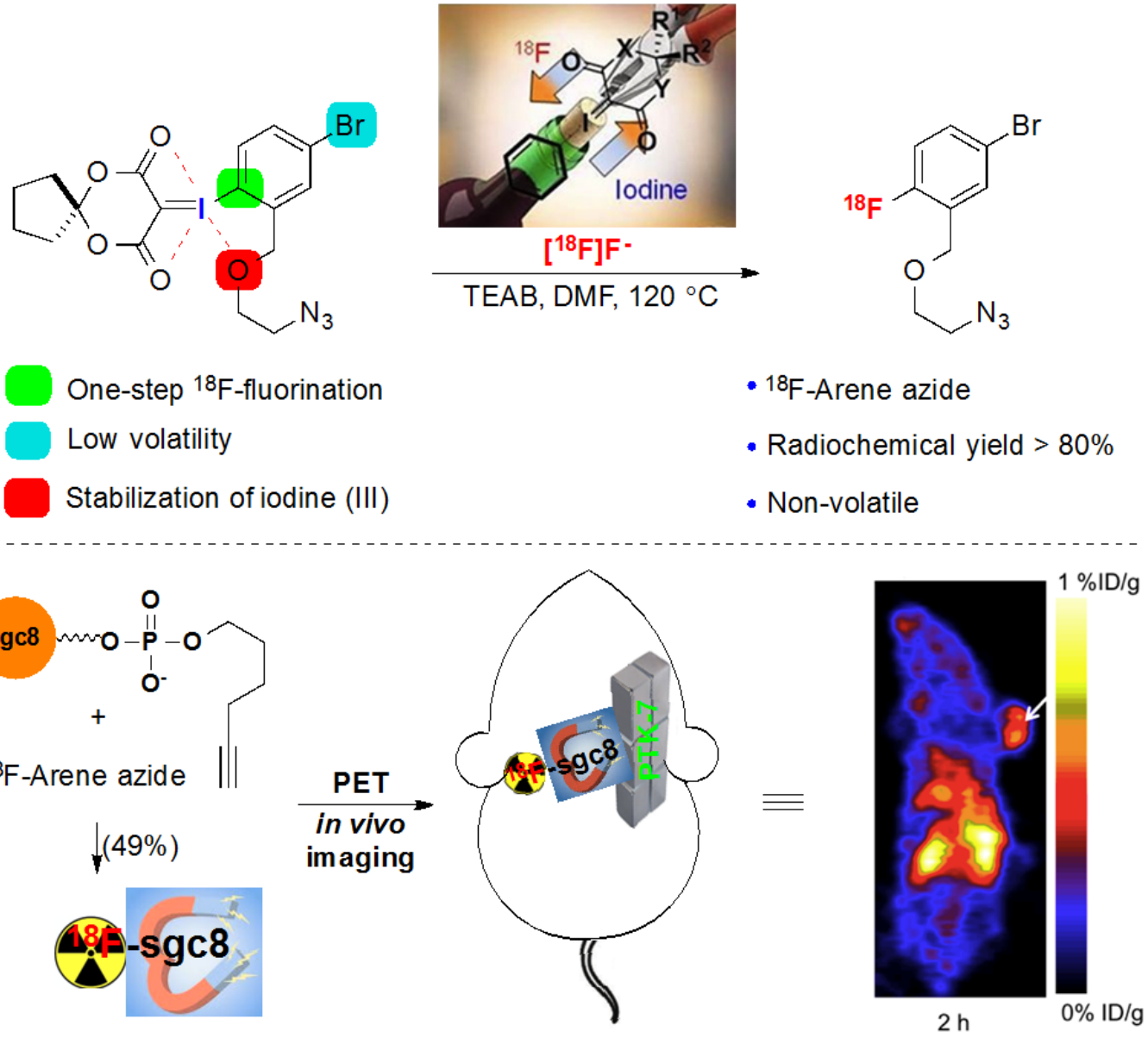
A novel 18F-azido click agent and their applications in PET imaging

Positron-emission tomography (PET) is a non-invasive molecular imaging technique that is used to study and visualize in vivo physiology by the detection of positron-emitting (radiolabeled) compounds. Fluorine-18, represented by symbol ^{18}F, is the most widely used element in PET study due to its relatively long half-life time ($t_{1/2}$ = 109.7 min). The introduction of fluorine-18 in clickable reagent and the subsequent utilization in bioconjugation, including Huisgen reactions, is the most routinely-used strategy to “tag” biologics, such as nucleic acids, peptides, and proteins with radioisotopes for PET imaging studies. The radiolabeling process imaging necessitates the need of fast, high yielding and position-selective bioconjugation methods under mild conditions. But only limited ^{18}F-labeled azides are attractive for routine production for PET radiochemistry. Although ^{18}F-arene based azides are generally preferred, existing methods to produce azido ^{18}F-arene click agents are inefficient, multistep consuming and/or need special equipment, and the generated ^{18}F-azides suffer from UV-undetectability and low volatility, which is fatal for the following click reactions with biologics. Thus, there is an unmet need for a convenient and highly efficient radiofluorination method to provide a practical ^{18}F-arene azido agent for bioconjugation via robust click chemistry.



Our group developed a first-in-kind, thermally-stable and highly reactive labeling precursors, and provided ^{18}F-azido click agents in a one-step high-yield high-purity [^{18}F]fluorination. For the first time, we utilized ortho-effect and secondary bonding interaction in hypervalent iodine (III) chemistry to design oxygen ortho-stabilized iodonium derivatives (OIDs). Click reactive ^{18}F click agent from OID chemistry provided a convenient and highly efficient way of labeling biomolecules compared with traditional amide bond coupling method. The production of 18F click agent can be automated on a commercial radiosynthesis unit. As proof for concept, a ^{18}F-tagged ssDNA aptamer sgc8, labeled by this method, provided a unique and unprecedented in vivo imaging tool to visualize and track aptamer in PTK-7 expressing cancer models. This agent would enable us to utilize PET

imaging to understand this new target in cancer biology and to develop targeted therapy with precision medicine. We expect this OID based strategy to be widely utilized in ^{18}F-labeling and tracking of biologics for tumor-targeting PET imaging applications.

Publication

Ortho-Stabilized (18) F-Azido Click Agents and their Application in PET Imaging with Single-Stranded DNA Aptamers.
Wang L, Jacobson O, Avdic D, Rotstein BH, Weiss ID, Collier L, Chen X, Vasdev N, Liang SH
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