

Tracing biological pathways

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A new chemical process developed by a team of Harvard researchers greatly increases the utility of Positron Emission Tomography (PET) in creating real-time 3-D images of chemical process occurring inside the human body.

This new work by Tobias Ritter, Associate Professor of Chemistry and Chemical Biology, and colleagues holds out the tantalizing possibility of using PET scans to peer into any number of functions inside the bodies of living patients by simplifying the process of creating "tracer" molecules used to create the 3-D images.

For example, imagine a pharmaceutical company developing new treatments by studying the way "micro-doses" of drugs behave in the bodies of living humans. Imagine researchers using non-invasive tests to study the efficacy of drugs aimed at combatting disorders such as Alzheimer's disease, and identify the physiological differences in the brains of patients suffering from schizophrenia and bipolar disorder.

As described in the Nov. 4 issue of *Science*, the process is a never-before-achieved way of chemically transforming fluoride into an intermediate reagent, which can then be used to bind a fluorine isotope to <u>organic molecules</u>, creating the PET tracers. Often used in combination with CT scans, <u>PET imaging</u> works by detecting radiation emitted by tracer atoms, which can be incorporated into compounds used in the body or attached to other molecules.

"It's extremely exciting," Ritter said, of the breakthrough. "A lot of



people said we would never achieve this, but this allows us to now make tracers that would have been very challenging using conventional chemistry."

The new process builds on Ritter's earlier fluorination work, which reduced the risk of damage to the original molecules by reducing the amount of energy needed to create fluorinated compounds, and involved the development of a unique, "late-stage" process that allowed fluorination to take place at the end of a compound's synthesis, eliminating concerns about the extremely short, two-hour half-life of the fluorine isotope used as a tracer.

Ritter's process begins with fluoride, which is chemically altered to create an intermediate molecule, called an "electrophilic fluorination reagent." Armed with that <u>reagent</u>, and using the late-stage fluorination process developed in Ritter's lab, his team is then able to create fluorinated molecules for use in PET imaging.

The breakthrough opens the door to <u>pharmaceutical companies</u> using the relatively simple, non-invasive scans to track how "micro-doses" of drugs behave in living subjects, with the potential payoff coming in vastly more efficient and cheaper drug development.

"One of the most immediate applications of this is in using molecular imaging to give us an understanding of the bio-distribution of a drug," Ritter said. "If a pharmaceutical company is developing a drug to treat schizophrenia, they could use this test to see if it enters the brain. If early tests show it doesn't, they would be able to kill the project before spending a great deal of time and money on it."

The technique could even be used to unlock the physical traits of disorders that until now have been limited to phenomenological descriptions. Using biomarkers related to specific disorders, researchers



could use fluorination to identify biological differences between schizophrenia and bipolar disorder, and use that information to develop treatments for both.

"I don't know if we're ever going to reach that point," Ritter said. "But that's what this project may be able to deliver in the long term. The way my group works – we want to solve big problems, and we're willing to sacrifice to get there. This is one problem that is worth a little bit of sweat."

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