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An investigation into Fluorine-18 and its recent contributions to the field of oncological chemistry

Nearly four in every ten adults will be diagnosed with cancer in their lifetime (ACS 2020). Cancerous tumors, or atypical masses of rapidly-reproducing cancer cells, grow at alarming rates and are often fatal. Likewise, detecting cancer at its earliest stage is integral to limiting its profound impact on the body. Understanding the science behind tumors and tumor imaging is crucial to progressing cancer treatment. Advancements in chemical tracers are vital to the future of chemical oncology. More efficient tracer molecules can detect cancers and malignant tumors more quickly, improving the chances of successful treatment and saving lives. “Development of Novel 18F‑PET Agents for Tumor Hypoxia Imaging” is an investigation into the effectiveness of various molecules housing 18-F as a Positron Emission Tomography (PET) agent for tumor hypoxia imaging. Chemicals housing 18-F were synthesized and injected into mice carrying malignant tumors (Li et al. 2021). The investigation found that the laboratory-synthesized compound [18-F]-23 has the potential for efficient uptake into cancerous tumors and could further expand the field of PET imaging (Li et al. 2021). While previous studies have examined imaging techniques of similar molecules, the substances described in “Development of Novel 18F‑PET Agents for Tumor Hypoxia Imaging” showed outstanding levels of 18-F uptake/absorption and imaging effectiveness.

Commonly known by its acronym “PET,” positron emission tomography is a medical imaging examination method that reveals the biochemical activity of an individual's tissues (Tong et al. 2016) PET scans are often used as an imaging tool for internal organs and are capable of locating tumors (concentrations of cancerous cells), such as the mice tumors studied in “Development of Novel 18F‑PET Agents for Tumor Hypoxia Imaging” (Li et al. 2021). PET scans rely on positron emission, a form of radioactive decay wherein a radioactive molecule sheds a subatomic particle known as a positron (Tong et al. 2016). Further, the ability of the radiopharmaceutical to uptake, or absorb, into an organ depends on the tissue’s tendency to absorb a molecule of specific chemical characteristics. For instance, in order for uptake to occur, the molecule must have an affinity for blood.

The process of a PET scan begins with an injection of a radiopharmaceutical (a molecule capable of positron emission, such as 18-F) to a patient. After a designated wait time, which varies depending on the radioactive element, the radiopharmaceutical travels through the patient’s blood and is absorbed by the patient’s tissues, such as their lungs, or perhaps a malignant tumor. After being absorbed by the targeted biological tissue, the positron, emitted by the radiopharmaceutical, then travels and collides with an electron generated by the PET machine. This collision is captured by the PET machine’s sensor and displays the radionuclide on the machine’s interface. This display allows medical professionals to analyze images of the radionuclides by positron emission in order to see possible problems such as tumors (Tong et al. 2016).

Fluorine-18 (F-18 or 18-F) is a radiopharmaceutical commonly used in PET imaging of cancers, such as those in lung and thyroid cancer (Blau et al. 1972), is the primary radioactive nuclide studied in “Development of Novel 18F‑PET Agents for Tumor Hypoxia Imaging” (Li et al. 2021). 18-F was one of the first tracers used in PET scans and has been utilized in radiology and nuclear medicine since the 1960s. Its importance to PET stems from the release of positrons in high volume during radio-nuclear decay, making it a particularly common tracer in recent years. 18-F is used extensively in health and medicine, including PET as a tracer to image vital organs such as the heart, brain, and thyroid. Further, its significance in recent years lies in finding malignancies that have spread from other parts of the body, and in radiation therapy to treat malignant tumors (Blau et al. 1972).

The uptake of 18F is due to hypoxia, which is a process wherein cells are starved of oxygen and more uptake of more minerals occurs as a result of the lost nutrients to carry out vital functions (Horsman et al. 2012). This concept can be applied extensively to uptake of 18-F, as desired tissues are deprived of oxygen, said tissues would, in theory, absorb a significant portion of the radiopharmaceutical and display a high concentration on a PET scan (Tong et al. 2016).

The researchers involved in “Development of Novel 18F‑PET Agents for Tumor Hypoxia Imaging” derived motivation from the need to make advancements in oncology and, more specifically, to develop more effective hypoxia PET agents (Wilson and Hay 2011). The supporting information built upon in this experiment involves prior research regarding hypoxia and its relationship to tumor progression (Horsman et al. 2012), and information on previous PET cancer tracers. After many previous experiments have investigated the impacts of various radioactive tracers on cancer imaging, the recent investigations stem from 18-F (Tong et al. 2016). While other radioactive tracers are available, such as Copper-64 and Gallium-68, neither are proven to be as effective ad 18-F (Tong et al. 2016). Furthermore, this investigation aims to synthesize new 18-F-bearing compounds to address the “great need to develop new hypoxia PET agents” (Li et al. 2021).

The research process began with experimental synthesis of 18-F-bearing (probe) compounds. After facing problems with low product yield, the researchers redesigned the probes, taking into account the properties of specific molecule groups that influence the absorption into blood. This proved successful, yielding four, 18-F-bearing probes, denoted as [18-F]-20, [18-F]-21, [18-F]-22, and [18-F]-23. These newly-formed compounds are an improvement from previous 18-F compounds, as they are more efficient in the uptake process relative to their predecessor 18-F-bearing probes (Li et al. 2021).

The four aforementioned 18-F samples were then prepared and injected into mice with FaDu tumors, which are tumors with cancerous cells, highly-used in medicine for oncology and immunology research After 0.5 hours, the concentration of each 18-F material in the tumor, liver, muscle, and kidney cells in their respective mice was gathered by PET imaging. After discovering that [18-F]-20 and [18-F]-23 had the greatest uptake potential, the two compounds were studied independently in FaDu tumor-bearing mice and UPPL (cancerous cells, highly-used in oncology because of resistance to certain cancer treatments and reduced growth) tumor-bearing mice with similar data collection as the previous samples. After realizing potential for additional manipulation of the probe molecules, 2 additional 18-F-bearing probes were created, denoted as [18-F]-24, and [18-F]-25. Lastly, [18-F]-23, [18-F]-24, and [18-F]-25 compounds were injected into mice with UPPL tumors and imaged using a PET machine at 0.5, 1, and 2 hours post-injection. Still, [18-F]-23 proved to be the most efficient in terms of uptake by the malignant tumors (Li et al. 2021).

While there seems to be no instance of discussion of improvements or flaws to the study, limitations of the chemical compounds created were discussed in-depth. For instance, the decomposition of 18-F bearing compounds was heavily-discussed as a problem that the researchers faced, increasing the need for the synthesis of new 18-F compounds. Furthermore, each reaction step in the synthesis of each 18-F probe is discussed in full, along with reasoning or theories as to why specific 18-F probes were producing low-yield. In my opinion, the flaws of this investigation come mostly in the lack of an overarching experimental design. There is a significant amount of variability in how certain 18-F compounds were prepared/synthesized, which could have impacted the final result and possible clinical trials. Secondly, most of these 18-F compounds seem to have been discovered and synthesized solely by this lab and during this particular investigation, which means that there is little or no replication of this experiment.

In order to further verify the conclusion that the [18-F]-23 probe is the most effective, more testing should be done on animals bearing a variety of different tumors, perhaps in a wider variety of animals. Thirdly, the combination of the discovery and synthesis of 18-F probes and the subsequent testing makes the article more confusing, since the experimental design changes as a result of the discovery of potentially more effective 18-F probes. Perhaps a hypothesis should have been developed after the synthesis of the many 18-F compounds and a separate investigation should have been done independent of the synthesis itself.

While the limitations of this investigation highlight that there is need for additional testing to ensure accuracy in the results, the information presented in “Development of Novel 18F‑PET Agents for Tumor Hypoxia Imaging” is, nevertheless, extremely important to 18-F PET imaging. The researchers practically invented new 18-F probes tumor imaging and proceeded to demonstrate their effectiveness by showing their outstanding ability to be imaged in mice. The demonstrated effectiveness of [18-F]-23 in tumor-bearing mice proves hopeful that these tests could move to human clinical testing in the near future. As more patients are willing to accept this novel imaging technique, perhaps cancerous tumors will be caught more frequently in earlier stages, causing fewer people to suffer the serious or fatal consequences of cancer.

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