Critical Reviews™ in Oncogenesis, 13(1):85–87 (2007)

New Doctorial Cancer Research

[^{18}F]Fluoroerythronitroimidazole, Tumor Hypoxia and Positron Emission Tomography/951-29-3265-2

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Ph.D. Dissertation date: January 12, 2007
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The growth of solid tumors depends on the formation of new blood vessels. Since the formation of new vessels in tumors is uncontrolled, it will result in a chaotic and heterogeneous tumor vascularization. Consequently, tumor blood flow is chaotic and variable and leads to irregular metabolic changes, particularly gradients in oxygen (O_2), and glucose concentrations.

Hypoxia, or a decreased level of O_2, is therefore a common feature in solid tumors. Even a small proportion of hypoxic cells can have important consequences for tumor progression. First, the effectiveness of radiation therapy is directly dependent on the O_2 tension in the tumor tissue. Second, the effect of certain chemotherapeutic drugs is decreased in hypoxic tumors. Finally, hypoxia may have an impact on the clinical aggressiveness of solid tumors.

As a consequence, significant effort is being made to find reliable methods to assess the tumor oxygenation status. At the moment, the most direct measurement of tumor oxygenation is with polarographic electrodes. A disadvantage of this method is that it is invasive and unable to distinguish between necrotic tissue and viable cells.

Noninvasive imaging of hypoxia utilizing the positron emission tomography (PET) method has received much attention. Nitroimidazoles are compounds that bind to cellular macromolecules under hypoxia, which renders them suitable for imaging of hypoxia when labeled with positron emitting isotopes. The most used tracer today, [^{18}F]fluoromisonidazole ([^{18}F]FMISO), has not completely fulfilled expectations in the clinical setting. For instance, [^{18}F]FMISO shows suboptimal metabolic properties and sometimes low hypoxia specific uptake.

This study evaluates the usefulness of an alternative nitroimidazole compound, [^{18}F]fluoroerythronitroimidazole ([^{18}F]FETNIM), as a hypoxia tracer for use with PET. Particular interest was focused on the pharmacokinetic properties and O_2 dependent uptake of this tracer. Oxygen dependent uptake of [^{18}F]FETNIM and [^{18}F]FMISO in experimental tumors of mice was compared

0278–940X/06/$35.00

using normal and elevated oxygen breathing atmospheres. Since hypoxia, blood flow, and glucose metabolism are closely linked to each other, one goal was to correlate PET findings describing these features with the expression of GLUT-1, Ki-67, p53, CD68, HIF-1α, $VEGF_{SC-152}$, CD31, and apoptosis in patients with squamous cell carcinoma of head and neck (HNSCC).

[^{18}F]FETNIM showed a lower nontarget uptake and was less metabolized than [^{18}F]FMISO in tissues. A similar oxygen dependent uptake of both tracers was seen in experimental tumors. PET findings showed a correlation between [^{18}F]FETNIM and blood flow in the early imaging phase, suggesting that uptake of [^{18}F]FETNIM is at least partly perfusion dependent. None of the hypoxia-linked biomarkers showed a correlation with [^{18}F]FETNIM uptake or blood flow as measured with [^{15}O]H_2O. In conclusion, [^{18}F]FETNIM showed some advantages over [^{18}F]FMISO in pharmacokinetic properties, but the uptake did not correlate with expression of biomarkers describing hypoxia or blood flow in HNSCC. The lack of correlation between PET findings and biomarkers most likely reflects the multiple mechanisms behind tracer uptake in heterogeneous tumor tissue. The quest for a tracer with superior hypoxia specificity is consequently still warranted. [^{18}F]EF5 is one potential tracer now being clinically evaluated in patients with HNSCC

Comment by Sydney M. Evans

The substance and topic of this thesis, "[^{18}F]FETNIM, Tumor Hypoxia and Positron Emission Tomography," is highly significant because hypoxia is known to be of substantial importance in many aspects of disease in both humans and animals. In terms of cancer, hypoxia has been shown to limit the response of cancer to radiation and chemotherapy, as well as to limit the effectiveness of other therapies such as photodynamic therapy and chemotherapy. Hypoxic tumors have been shown to be biologically more aggressive, with increased incidence of metastasis and invasion. The history of attempts to treat tumor hypoxia has demonstrated that there are substantial intertumoral heterogeneity levels in individual patient tumors. This observation suggests that in order to optimally treat each patient, therapy must be tailored to the individual tumor biology. This has lead to the extreme interest in noninvasive hypoxia imaging.

Positron emission tomography (PET) is an imaging methodology that reports the metabolic function of tissue. There have been extensive studies of the PET hypoxia-marking agent [^{18}F]FMISO in both humans and animals. However, these studies have shown this agent to have limitations, especially because of its unwanted metabolism. Therefore, studies on new agents are immensely important.

This thesis considers [^{18}F]FETNIM based on preliminary data published by DJ Yang, et al. This was a very good decision, both in terms of the importance of the topic and the available information. Because of the problems with the me-

tabolism of [18F]FMISO, the goal of this thesis was to study the metabolism of [18F]FETNIM in multiple species (mice, rats, dogs, and humans) and tumor types (implanted versus carcinogen induced). Unexpected findings regarding liver uptake and metabolism provide interesting and important questions regarding physiologic handling of some 2-nitroimidazole agents. Critical preclinical studies support that at least part of the [18F]FETNIM binding is hypoxia related. Additional studies of metabolism and molecular studies were carried out in tissues excised from human patients. Several of the expected relationships between hypoxia as measured by [18F]FETNIM imaging and immunohistochemical studies were negative and provide the basis for further study. This aspect of the thesis only scratches the surface of the biologically and clinically relevant questions that can be asked using banked or newly acquired tissues.

Although [18F]FETNIM was not shown to be an improved hypoxia PET agent compared to [18F]FMISO, these studies are important in order to move this field forward. Accepting or discarding any marker should be based on solid data, which this thesis provides for [18F]FETNIM. The biodistribution and pharmacokinetic studies are outstanding examples of how questions related to these parameters should be performed.