[CANCER RESEARCH 63, 2681–2687, May 15, 2003]

3′-[^{18}F]Fluoro-3′-Deoxythymidine ([^{18}F]-FLT) as Positron Emission Tomography Tracer for Imaging Proliferation in a Murine B-Cell Lymphoma Model and in the Human Disease

Martin Wagner,[2] Ulrike Seitz,[1,2] Andreas Buck, Bernd Neumaier, Stefan Schultheiß, Markus Bangerter,

murine model of B-cell lymphoma and in human malignant lymphoma. The human B-cell line DoHH2 expressed high levels of active thymidine kinase 1 (TK-1) as the key enzyme of [

^{18}F]-FLT metabolism. Immunostaining confirmed high levels of TK-1 in DoHH2 derived xenograft tumorsF]-FLT per gram of tumor tissue correlated with the tumor-prolifera tion index as evaluated in BrdUrd-labeling experiments. In a pilot study of 11 patients with both indolent and aggressive lymphoma, [

^{18}F]-FLT was suitable and comparable to [^{18}

Depicted in Fig. 2*B*

DNA and protein measurement, respectively (data not shown). [^{18}F]FLT-derived radioactivity associated time dependent with the perchloric acid insoluble fraction of $DoHH_2$ cells (Fig. 2*C*), but not with the perchloric acid insoluble fraction of HT1080 cells (data not shown). After 240 min, 1.05% □ 0.08% of the radioactivity applied to the medium was trapped in the acid insoluble fraction in DoHH2 cells (Fig. 2*C*

(33, 34). In this respect, inflammatory lesions show an increased uptake of FDG and are the most frequent cause of false-positive results (33–35). In contrast, the uptake of pyrimidine nucleosides and analogues such as [^{18}F]-FLT relates to the proliferative activity in the tissue as one of the key features of malignant disease. Recent advances in the labeling of FLT (28, 29), as used in this study, enable the synthesis of [^{18}F]-FLT in high radiochemical yield and with high radiochemical purity suitable for *in vitro* evaluation and PET imaging studies.

TK-1 represents the rate-limiting enzyme for the anabolism of several pyrimidine analogues, such as FLT through the salvage DNA synthesis pathway, and displays a complex S-phase regulated expression that is realized not only at the transcriptional level, but also the posttranscriptional level and posttranslational mechanisms (21, 36). The salvage pathway of DNA synthesis includes deoxycytidine kinase, TK-1, TK-2, and deoxyguanosine kinase; however, only TK-1 accepts FLT as a substrate (37). Here we show that TK-1 m-RNA is increased in DoHH2 cells. The DoHH2 cells originated from a patient with immunoblastic lymphoma (24), and DoHH2 derived xenograft tumors were used as a murine model of human malignant lymphoma in this study (26). Because a recent study reported a discrepancy of human TK-1 mRNA and enzymatic activity in patients with chronic lymphatic leukemia (38), we further confirmed active TK-1 in a fluorocytometric assay. Furthermore, high 48.4(.h)-293.234(a.7(in)-516.7(a)]T

ciently phosphorylated and incorporated into the perchloric acid insoluble cell fraction of DoHH2 cells *in vitro*. This intracellular trapping of [^{18}