Preclinical *in vivo* imaging of multiple myeloma with [^{18}F]fluorohomoleucine (FHL) PET/CT

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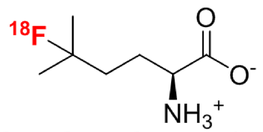
INTRODUCTION

Multiple myeloma (MM) is the second most prevalent hematological malignancy, accounting for 1-2% of all neoplasms.(1–3) Current diagnostic methods, such as whole-body X-ray, whole-body CT, and MRI, rely on the detection of anatomical lesions,(4) and fail to give accurate information on disease activity and treatment response. The LAT1 amino acid transporter has long been recognized as a biomarker of malignant cancers, and its overexpression is significantly associated with high proliferation and poor prognosis in newly diagnosed MM patients.(5) Herein we explore the use of a LAT1-targetting radiopharmaceutical to provide molecular insights into diagnostic and therapeutic strategies for MM.



***S*-[^{18}F]Fluorohomoleucine (FHL)**

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METHODS

L-[^{18}F]Fluorohomoleucine (FHL) was synthesized according to the previously published procedure.(6,7) LAT1 expression in multiple myeloma (MM) cell lines was confirmed by flow cytometry. Cell uptake assays were conducted using luciferase-transfected MM1S, L363, NCI H929 and AMO1 MM cells, and 2-amino-bicyclo[2.2.1]heptanes-2-carboxylic acid (BCH) was used as a blocking agent. For *in vivo* studies, male NRG mice were injected either with 1 x 10^6 MM cells intravenously (i.v.) *via* the caudal vein or subcutaneously (SQ) with 1 x 10^7 cells. Tumor engraftment was monitored weekly on an *in vivo* bioluminescence imager Perkin Elmer's IVIS Ilumina 5, starting at 2 weeks post-injection (p.i.). Biodistribution and PET/CT imaging studies were conducted at 4-6 weeks p.i.

Multiple Myeloma Cells Exhibit LAT1-specific FHL uptake

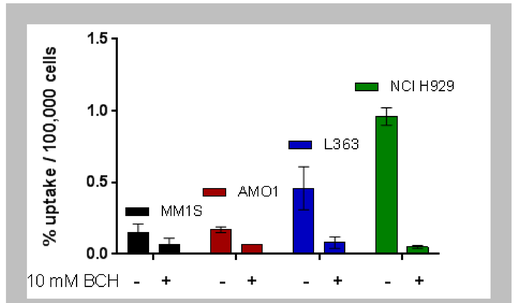

Figure 1. *In vitro* uptake of (*S*)-5-^{18}F-FHL in an array of multiple myeloma (MM) cell lines. Uptake was measure in the presence and absence of system L inhibitor = 2-amino[2.2.1]heptane-2-carboxylic acid (BCH).

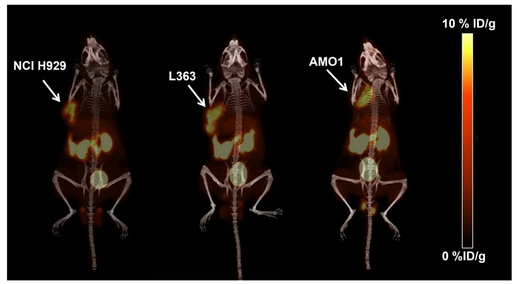

Figure 2. μPET/CT images of [^{18}F]fluorohomoleucine (FHL) at 1 hr post-injection in multiple myeloma xenograft-bearing mice.

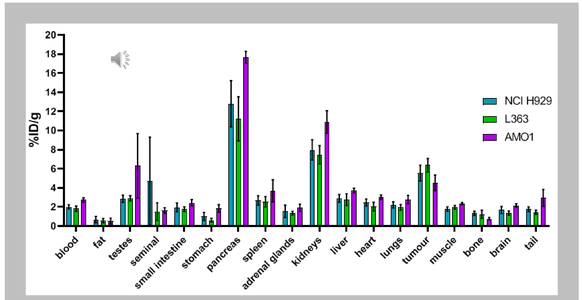

Figure 3. Biodistribution of [^{18}F]fluorohomoleucine (FHL) at 1 hr post-injection in multiple myeloma xenograft-bearing mice.

CONCLUSION

We have demonstrated the ability of FHL for *in vivo* imaging of three human multiple myeloma tumors in SQ murine models, with the tumor uptake ranging from 4.53±0.82 %ID/g in AMO1 xenografts to 6.37±0.70 %ID/g in L363 tumors (Figures 2 and 3). Work is underway to establish the utility of this tracer in detecting disease dissemination in the orthotopic murine models of multiple myeloma, with promising preliminary results presented herein (Figures 4 and 5).

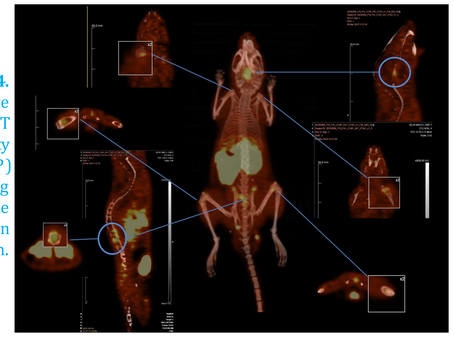

Figure 4. Representative [^{18}F]FHL PET/CT maximal intensity projection (MIP) highlighting numerous bone lesions evident on the scan.

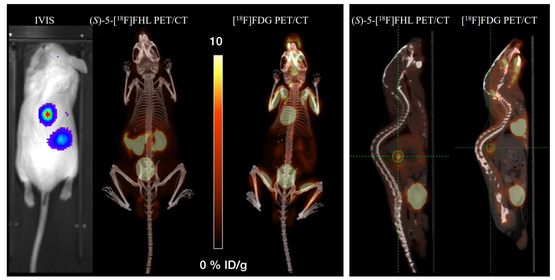

Figure 5. (a) IVIS image of a mouse intravenously inoculated with L363 cells at 34 days post-inoculation; (b) [^{18}F]Fluorohomoleucine (FHL) PET/CT MIP of the same mouse at day 34 p.i.; (c) [^{18}F]Fluorodeoxyglucose PET/CT MIP of the same mouse at day 36 post inoculation.

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