Relative Biodistribution and Tumor Uptake of ^{124}I–NM404, a.k.a. CLR1404, in Humans with Non–Small Cell Lung Cancer

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INTRODUCTION

NM404, a.k.a. CLR1404, is a refined, second–generation diapeutic phospholipid ether analogue that is characterized by preferential tumor uptake and prolonged tumor retention in 50/52 xenograft, spontaneous, and transgenic preclinical tumor models. Isosteric iodine substitution in NM404 affords either a diagnostic agent (*e.g.*, using ^{124}I for cancer–selective PET imaging) or a molecular radiotherapeutic agent (*e.g.*, using ^{131}I for cancer–selective cytotoxicity), both of which are in clinical development. NM404 and related alkylphospholipids enter malignant cells via membrane lipid rafts which are overexpressed in cancer cells. Together with Novelos Therapeutics, Inc., our lab is developing radioiodinated NM404 as a diagnostic and therapeutic ("diapeutic") agent for the detection and treatment of multiple solid tumors, including non–small cell lung cancer (NSCLC).

The aim of this study is to demonstrate the relative biodistribution and tumor uptake of ^{124}I–NM404 in humans with NSCLC–evaluated with PET/CT.

Subject 1: Metastatic NSCLC with previous history of sclerotic metastases to bone. These lesions were not ^{18}F–FDG or ^{124}I–NM404 avid (Figure 1).

Subject 2: NSCLC with diffuse patchy lesions through both lung fields. These lesions were ^{18}F–FDG and ^{124}I–NM404 avid (Figure 3).

Subject 3: Metastatic NSCLC with brain metastases. These lesions were ^{18}F–FDG and ^{124}I–NM404 avid.

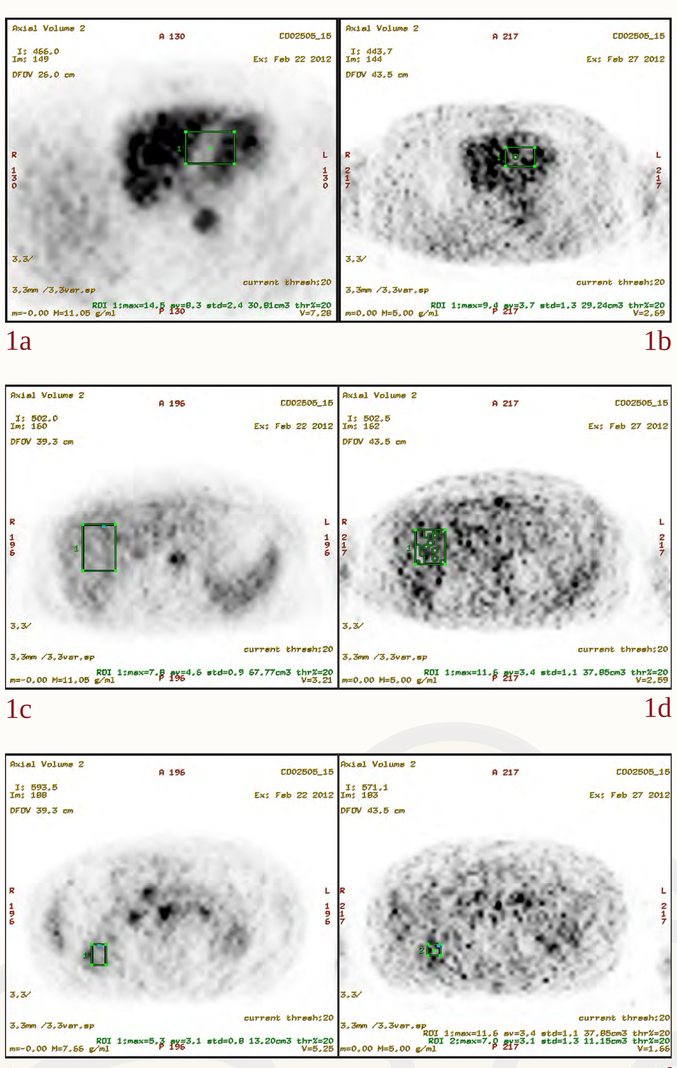
Subject 4: NSCLC with large metastasis in the liver that demonstrated intense ^{18}F–FDG uptake and mild ^{124}I–NM404 uptake.

METHODS

Three subjects with metastatic NSCLC were injected with 185 MBq and one subject with 111 MBq of ^{124}I–NM404. Whole–body PET/CT scans were obtained at five different time points over six days after injection: 1, 4, 24, 48, and 144 hours (6 days). ^{18}F–FDG PET/CT whole–body scans were obtained 24 hours prior to ^{124}I–NM404 intravenous administration. Qualitative (visual) and quantitative (SUV) analysis of major organs and malignant tumors (primary and metastatic lesions) was performed (Figure 1).

Figure 1

^{124}I–NM404 axial images of subject 1. Example of voxels measuring SUVav and SUVmax in the heart at (a) 1 hour and (b) 6 days, in the liver at (c) 1 hour and (d) 6 days, and right kidney at (e) 1 hour and (f) 6 days.



RESULTS & ANALYSIS

In the first 24 hours, initial uptake of NM404 was highest in the blood pool compared to other organs, but also, blood pool activity decreased most rapidly during the first 24 hours.

NM404 is known for high albumin binding in plasma and this persistent blood pool activity could be associated to this (Graph 1).

Liver uptake in 3 of the 4 subjects demonstrated the second highest initial uptake with mild clearance in the first 24 hours. By this time to 6 days, uptake becomes relatively stable. The spleen in these 3 subjects demonstrated very similar SUVmax and SUVav as well as a similar pattern of radiotracer clearance (Figure 2).

One subject had higher uptake in the liver that did not change significantly over 6 days (Figure 3). The etiology for this is not known and still too early to clarify with only one subject. There was normal hepatic ^{18}F–FDG uptake and no anatomical abnormalities seen on CT. Incidentally, this subject had a previous splenectomy, and thus this may have an effect on relative hepatobiliary uptake and/or retention. Uptake and excretion in the major organs and blood pool of all 4 subjects was very conistent (except for liver in 1 subject with a splenectomy). In all 4 subjects, the most constant uptake through time was seen in the kidneys.

NM404 does not have significant uptake in normal brain tissue (stable SUVmax and SUVav < 1), with the exception of 1 subject that, incidentally, had 4 brain metastases (images from this subject can be seen in a dedicated ^{124}I–NM404 brain tumor poster). From these lesions, the only one able to be seen on ^{18}F–FDG was a lesion in the left cerebellar lobe. This lesion was visualized not due to abnormal increased FDG uptake in comparison to the surrounding brain tissue, but because the lesion demonstrated a subtle hypermetabolic rim. On the other hand, the remaining brain lesions were not clearly identified, even after retrospective evaluation of the FDG PET/CT study. Three of the lesions were clearly seen on the ^{124}I–NM404 scans. A left subcentimeter lesion, which was identified on a diagnostic MRI was retrospectively seen on the study as a focus slightly more prominent than background.

Two subjects demonstrated both FDG and NM404 avid malignant lung lesions. One subject did not have evidence of malignancy on either FDG or NM404. Multiple FDG avid lung lesions were positive on NM404 PET 1 or 2 days post injection. A less than 1 cm FDG avid pulmonary lesion was not avid with NM404. There were 3 intensely NM404 avid brain metastases, only one was detectable with FDG. All of the NM404 avid malignant lesions increased uptake with time.

Graph 1

Physiologic organ ^{124}I–NM404 uptake average (SUVav) in relationship with tumor uptake (SUVmax). LL (left lung), RL (right lung), LUL (left upper lobe), RLL sup seg (superior segment of the right upper lobe), R (right), L (left). In general, lesion SUVmax increases with time, while SUVav average of the different organs decreases with time, with the exception of the kidneys where SUVav is relatively stable over time.

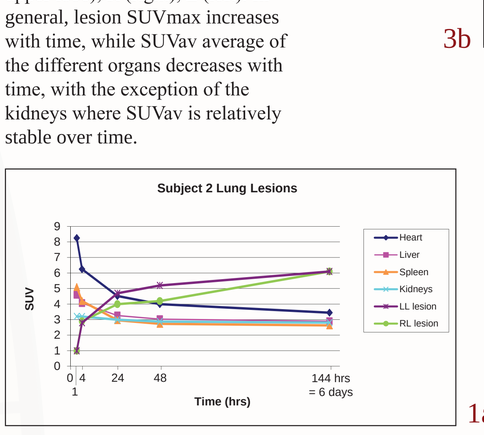
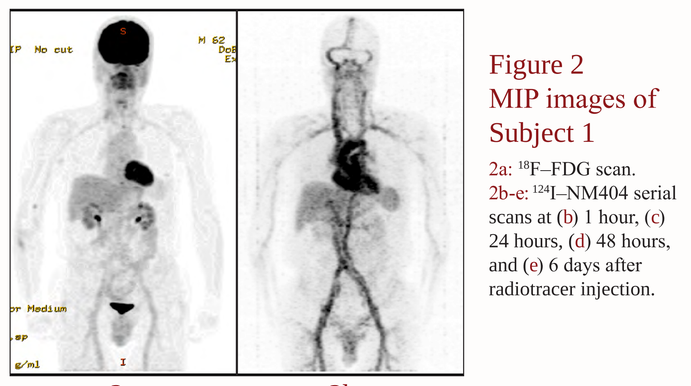


Figure 2
MIP images of Subject 1

2a: ^{18}F–FDG scan. 2b-e: ^{124}I–NM404 serial scans at (b) 1 hour, (c) 24 hours, (d) 48 hours, and (e) 6 days after radiotracer injection.



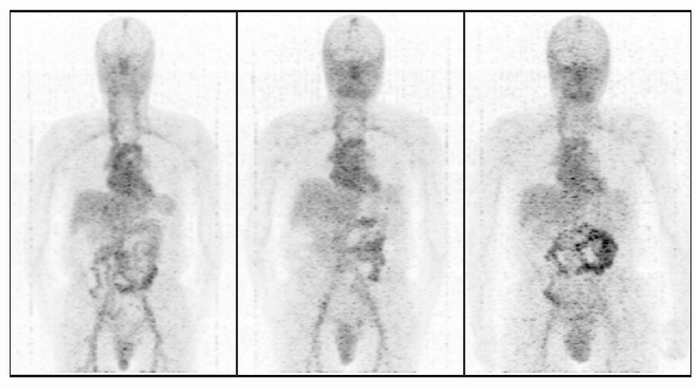
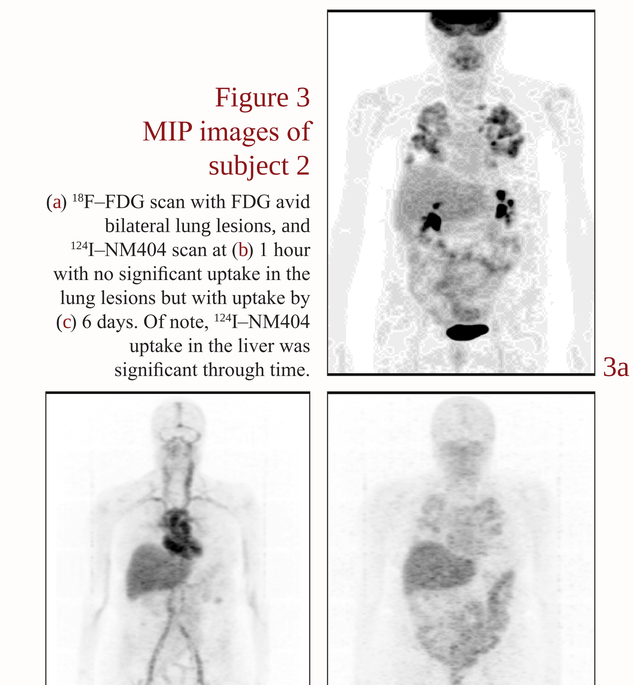


Figure 3
MIP images of subject 2

(a) ^{18}F–FDG scan with FDG avid bilateral lung lesions, and ^{124}I–NM404 scan at (b) 1 hour with no significant uptake in the lung lesions but with uptake by (c) 6 days. Of note, ^{124}I–NM404 uptake in the liver was significant through time.



^{124}I

Cyclotron produced positron emitter [^{124}Te(d,2n)^{124}I and ^{124}Te(p,n)^{124}I] with long physical half–life (4.18 days) and a positron abundance of approximately 23% (11.7% of a positron with Emax 1534.9 keV, and 10.8% of a positron with Emax 2137.6 keV). There are also several gamma photons emitted, being the most important a 602.7 kev photon corresponding to 63% of all the emitted gamma photons. This photon is emitted simultaneously with the 1534.9 positron (Figure 4).

Due to this gamma photon with an energy that falls within the energy window of our scanner (375 to 650), there is increased background due to spurious coincidences. The method we applied to improve target to background ratio was to scan patients in 2D mode and not 3D as we commonly do with ^{18}F tracers (Figure 4). Due to a significantly low dose of ^{124}I–NM404 (5 to 3 mCi) and delayed imaging up to 6 days after radiotracer injection, narrowing the energy window was not pursued.

Comparative spatial resolution measurements using different PET cameras:

	^{18}F	^{124}I
Gonalez Trotter et al.	8.71mm	9.74mm
Zhu and El Fakhri	5.56mm	6.06mm

Image resolution of ^{124}I is reported to be 0.5 to 1 mm inferior to that when using ^{18}F.

Figure 4

Reconstructed PET images of a ^{124}I–NM404 phantom in (a) 2–D and (b) 3–D acquisition. Although there is less noise with 3–D acquisition, there is a more homogeneous distribution of the radiotracer in 2–D acquisition.

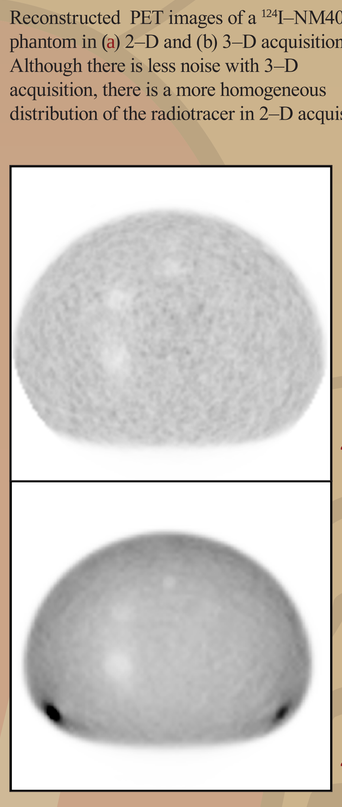
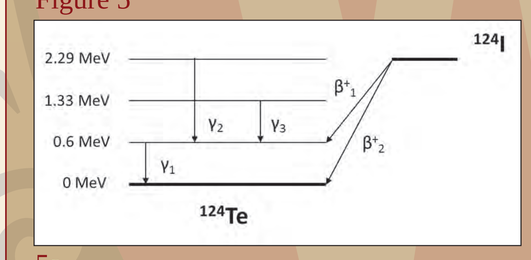


Figure 5



5a

	Energy (keV)	Abundance
β^+_1	1534.9	11.7
β^+_2	2137.6	10.8
γ_1	602.7	63
γ_2	1691	11
γ_3	722.8	10

5b

CONCLUSIONS

The relative normal organ biodistribution of ^{124}I–NM404 is reproducible and malignant tumor uptake has prolonged retention with increasing tumor to background uptake over time.

References:

1. M. Lubberink, H. Herzog. Quantitative imaging of ^{124}I and ^{86}Y with PET. Eur J Nucl Med Mol Imaging, 38 (suppl 1) (2011), pp. S10–S18
2. Nuclear Science Division LBNL http://ie.lbl.gov/

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