6″-^{18}F-Fluoromaltotriose PET Evaluation in *Escherichia Coli*–Induced Myositis: Is There Uptake Saturation in Control?

TO THE EDITOR: In a recent paper, Dr. Gowrishankar and colleagues have demonstrated that 6″-^{18}F-fluoromaltotriose, which targets the bacterial maltodextrin transporter, is taken up by a variety of pathogenic bacterial strains in vitro and in vivo (*1*). This new tracer might thus play a major role in diagnosis and, potentially, in assessing response to antibiotic therapy. In particular, in a simple *Escherichia coli*–induced myositis model, the authors compared two 1-h dynamic PET time–activity curves that were obtained in mice bearing both viable and heat-inactivated bacteria injected in left and right thigh muscle, respectively (Fig. 2A in Gowrishankar et al. (*1*)). These decay-corrected time–activity curves showed 2 remote peaks at about peak time (t_{peak}) = 4.5 and 27.5 min after injection, respectively, thereby indicating that tracer trapping was reversible in each muscle (*2*).

We thought of interest to further investigate the comparison between these 2 time–activity curves, focusing on their common input function (IF), for which the time constant α can be assessed from their peak time. Previous studies have shown that in each time–activity curve, tracer release rate constant k_B can be obtained from a monoexponentially decaying fit of its decreasing part, and when t_{peak} and k_B are known, the value of α can be obtained from the equation $t_{peak} = \text{Ln}\,[\alpha/k_B]/[\alpha - k_B]$ (assuming IF decay correction and monoexponential decay) (*3,4*). Fitting the last 5 data points in each time–activity curve provided the following k_B values 0.011 and 0.018 min^{-1} and $R = 0.996$ and 0.991, hence leading to an IF time constant estimate of $\alpha = 0.883$ versus 0.085 min^{-1} for control versus infected muscle (using solver in Microsoft Excel software), respectively. This 10-fold discrepancy in α does not make sense because the tracer IF must be exactly the same for any tissue in a mouse and, more specifically, whereas the value of α in infected muscle may be plausible that in control muscle is just not realistic. In an attempt to explain this major discrepancy, we would like to suggest that the issue of a time-decaying uptake rate constant for the control muscle, in other words, an uptake saturation, may be considered. Indeed, it has been previously shown that a time decay of the tracer uptake rate is equivalent to an apparent increase in the IF time constant α, leading to a peak time of the tissue time–activity curve earlier than without saturation (Appendix in Laffon et al. (*5*)). In this connection, the uptake rate constant of the control muscle could be written as: $\text{Ki}(t) = \text{Ki} \times \exp(-0.798 \times t)$ where 0.798 min^{-1} is the difference between the 2 α values "0.883–0.085." That is, the number of tracer molecules that could be potentially trapped in control muscle was very likely too small in comparison with that of injected ones. We therefore suggest that the lower the expected number of injected tracer molecules to be trapped in a tissue of interest, the lower the activity to be injected. Otherwise, the so-called tracer dose assumption usually made in molecular PET imaging, that is, radiotracer is injected in a small amount that does not affect its own kinetics, may be ruled out. Because of a too large amount of injected tracer molecules leading to a saturation situation, tracer uptake may be hard to quantify because of its time-varying nature. Furthermore, we suggest that the above-proposed reasoning for identifying a saturation situation might apply to the framework of the radiopharmaceutical use for therapeutic purpose, in an effort to limit adverse effects and to optimize costs.

To conclude, Dr. Gowrishankar and colleagues have convincingly demonstrated that 6″-^{18}F-fluoromaltotriose is able to image bacterial infections in preclinical models and have shown that the pharmacokinetic properties of this novel tracer make it suitable for future clinical studies. On the basis of their results (illustrated in Fig. 2A of Gowrishankar et al. (*1*)), we suggest that uptake saturation might occur in PET imaging, as assessed by using the above-proposed rationale.

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REPLY: We thank Laffon et al. for their comments on our paper on a new bacterial imaging PET tracer (*1*). In their Letter to the Editor, they took keen interest in the different shapes of the time–activity curves of 6″-^{18}F-fluoromaltotriose in an *Escherichia coli*–infected mouse muscle and its contralateral noninfected control muscle. By incorporating the peak times of the 2 curves and calculating the tracer release rate constant k_B using a method with several underlying assumptions (*2*), they estimated the input function (IF) time constant α after its peak. They found an approximate 10-fold difference in α for the control and bacteria-infected muscle curves. They reasoned that while the value of α for the infected muscle was plausible, the value of α for the control muscle was not realistic. To explain this discrepancy, they suggested an exponentially time-decaying uptake rate constant for the control muscle. They claimed that a time decay of the tracer uptake rate is equivalent to an apparent increase in the IF time constant α, leading to a peak time of the tissue time–activity curve earlier than without saturation (*3*).

Although we appreciate the explanation offered by Laffon et al., we respectfully disagree with their proposed argument. We do not think an uptake saturation is occurring in the control muscle. When we convolve the image-derived IF from the left-ventricle blood pool to a 2-tissue-compartment model (something which Laffon et al. could not do because they did not have access to the actual IF), the fitted result is very much like that of the time–activity curve of the control tissue (Fig. 1). This, by itself, indicates that there is likely no saturation in uptake (the speculation made by Laffon et al.). If there was truly tissue uptake saturation, one would not likely be able to fit the control muscle time–activity curve with a *linear* model (i.e., a compartmental model).

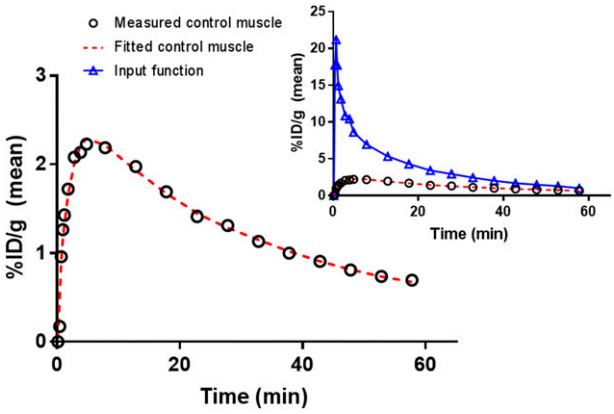

FIGURE 1. Plots of the image-derived IF, the average measured control muscle time–activity curve, and the compartmental model fitted curve. The influx rate constant Ki for the control muscle was estimated to be 0.001084 ± 4.475E−5 mL/min/g (very low as expected for noninfected muscle). If there was tissue uptake saturation, one would not likely be able to fit the control muscle time–activity curve with a linear tracer kinetic model.

To better explain the different shapes of the 2 curves, we believe the issue is more related to the time–activity curve of the active bacteria muscle site. For example, what was the state of the bacteria in tissue 24 h after injection? Was the vascular supply or perfusion to the infected tissue changed? Was the first-pass extraction fraction of the tracer in the infected tissue close to 100%? There are many different but more plausible reasons that could explain the different shapes of the 2 time–activity curves, and would certainly need to be investigated further.

Nevertheless, we and Laffon et al. all agree that 6″-^{18}F-fluoromaltotriose is an exciting new PET tracer that could potentially play an important role in the diagnosis of infectious diseases of bacterial origin as well as in the assessment of antibiotic therapy. Indeed, this new molecular imaging tracer will help us to better understand bacterial biology in living subjects.

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Does PET Reconstruction Method Affect Deauville Scoring in Lymphoma Patients?

TO THE EDITOR: Advances in PET/CT technology, such as the development of digital PET detectors, extended axial fields of view (total-body PET), and the use of resolution modeling during reconstruction, improve image quality, for example, by affecting sensitivity and spatial resolution. This results in enhanced lesion detectability and changes both visual and quantitative reads. These developments, however, pose challenges for multicenter studies and the application of previously validated interpretation criteria, such as the Deauville score (DS) in the clinical management of patients with lymphoma (*1*,*2*). These criteria are derived from studies performed on previous generations of PET/CT systems and do not necessarily translate 1-to-1 with data generated using the latest systems.

Recently, a shift toward more positive reads for ^{18}F-FDG PET/CT studies in patients with Hodgkin lymphoma with clinical consequences was reported by Barrington et al. (*3*) This shift was found to coincide with the introduction of a new generation of PET/CT systems that incorporate resolution modeling during reconstruction (also called point-spread function [PSF] reconstructions). Such reconstructions are associated with increased SUV in (small) lesions, but not in large uniform organs such as the liver and blood pool (*4*). This nonuniform change in apparent ^{18}F-FDG uptake may affect reads when based on comparing lesion ^{18}F-FDG uptake with that of liver and mediastinal blood pool, as is the case when using the DS. PSF reconstructions have also been found to overestimate SUV in lung cancer patients (*4*,*5*). This upward bias seems also to depend on the size of the lesion or sphere, being the largest (sometimes up to 60%) for spheres and lesion of about 1.0–1.5 cm in diameter (i.e., the upward bias seems to be largest for this particular size). PSF reconstructions also introduce image artifacts, as illustrated in Figure 1 showing reduced uptake at the center of a

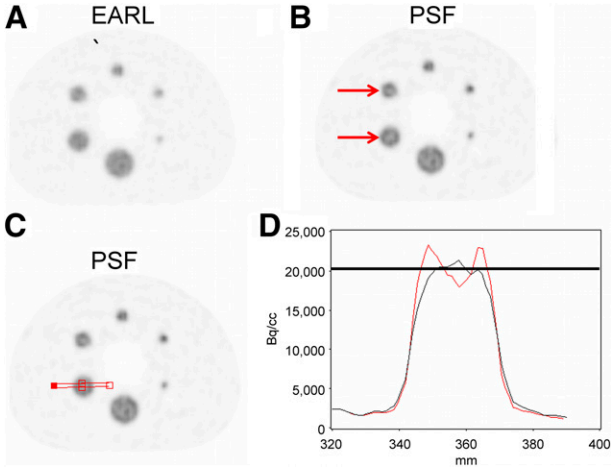

FIGURE 1. PET images (axial slice) of NEMA Image Quality phantom filled conforming with EARL instructions. (A) PET image reconstructed with EARL-compliant settings. (B) PET image reconstructed using resolution modeling (PSF). Red arrows point to typical PSF artifact showing increased uptake at edge of a sphere and reduced uptake at center of the sphere, which appear most strongly for 1- to 1.5-cm-diameter spheres. (C) Image illustrating location of activity profile (red line) as plotted in D. Red line in D indicates activity profile seen in PSF-reconstructed PET image, and black line indicates that of EARL-compliant reconstruction.