Journal of Nuclear Medicine, published on February 1, 2018 as doi:10.2967/jnumed.118.208595

Response to "Molecular Imaging in Patients is an Attractive Fata Morgana, Not a Realistic Option"

Ismaheel Lawal[1], Alfred Ankrah[1,2], Mike Sathekge[1]

1. Department of Nuclear Medicine, Steve Biko Academic Hospital, University of Pretoria

2. Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen

In Response:

In their letter to the editor regarding our article titled "metabolic imaging of infection" *(1)*, Hess et al. disparaged our optimism for bacteria-targeted imaging and its potential for clinical application *(2)*. They speculated based on mathematical permutations that "…. bacterial concentrates in the body that are visible with bacterial PET tracers is more a rarity than a commonplace event."

Hess et al. submitted that the quantum of bacteria necessary to produce a detectable PET signal is not achievable in a human host. While it is true that a higher bacteria load will produce a stronger PET signal, a lower bacterial load, much less than 3.5×10^9 suggested by Hess et al. has been reported in different studies to produce detectable signal intensity. Pullambhatla et al. using ^{125}I-FIAU demonstrated detectable SPECT signal at a bacterial concentration of 1.4×10^9 CFU/ml *(3)*, a level where Hess et al. conjectured that PET signal will be barely detectable. Ordonez et al. reported a detectable PET signal with ^{18}F-FDS at a bacterial concentration of 1.1×10^6 CFU *(4),* two orders more sensitive than ^{18}F-FDG which also detected the infection at this concentration *(5)*. Bacterial load is not the only factor upon which signal intensity is dependent. A high target to background ratio provides good contrast resolution. Weinstein et al.

demonstrated almost a 1000-fold higher uptake of ^{18}F-FDS in bacteria compared with mammalian cells *(6)*. The minimum bacterial concentration Hess et al. estimated to be capable of producing a detectable signal was based on a PET volume resolution of 65mm^3 and medium-sized bacteria volume of 4.2µm^3. Their calculation failed to take into account that in human infection the bacteria would be present together with immune cells and fibroblast, easily making up that volume without having 3.5 x 10^9 CFU bacteria present.

The clinical utility of bacterial imaging with radiolabeled anti-microbial peptide Ubiquicidine has been shown *(1,7)*. This is already a clear indication that bacterial-specific imaging is a reality and not a mirage.

Again, Hess et al. argued that in infection bacteria are scattered and instantaneously attacked and removed by the immune system resulting in low numbers of bacteria. When bacteria are removed by immune system the patient is likely to recover and would not require imaging. It is when the immune system is unable to curtail the infection with proliferating organisms that the patient would come to clinical notice, moreover, very high bacteria concentrations have been reported in human infections *(8)*.

FDG remains the most commonly used PET tracer in clinical application. Its lack of specificity in differentiating sterile inflammation from infection however represent a significant limitation especially in the post-operative period *(9)*. An unmet need therefore remains in the clinical differentiation of inflammation from infection. Bacterial-specific imaging is a viable attempt to cater for this need, and efforts in this regard must be encouraged especially in view of the significant morbidity and mortality burden that infections continue to cause. Despite the prospects, there also remain challenges in the development of bacterial imaging including

identifying probes that have sensitivity for broader range of microbes rather than species-specific probes. This calls for more work to be done and not the pessimism expressed by Hess and colleagues.

References

1. Lawal I, Zeevaart J, Ebenhan T, et al. Metabolic imaging of infection. *J Nucl Med.* 2017;58:1727-1732.
2. Hess S, Alavi A, Werner T, Høilund-Carlsen PF. Molecular imaging of bacteria in patients is an attractive fata morgana, not a realistic option. *J Nucl Med.* Epub ahead of print on January 11, 2018. Doi: 10.2967/jnumed.117.207001.
3. Pullambhatla M, Tessier J, Beck G, Jedynbak B, Wurthner JU, Pomper P. [^{125}I]FIAU imaging in a preclinical model of lung infection: quantification of bacterial load. *Am J Nucl Med Mol Imaging.* 2012;2:260-270.
4. Ordonez AA, Weinstein EA, Bambarger LE, et al. A systematic approach for developing bacterial-specific imaging tracers. *J Nucl Med.* 2017;58:144-150.
5. Wang X, Murthy N. Bacterial imaging comes of age. *Sci Transl Med.* 2014;6:259fs43.
6. Weinstein EA, Ordonez AA, DeMarco VP, et al. Imaging Enterobacteriaceae infection in vivo with ^{18}F-fluorodeoxysorbitol positron emission tomography. *Sci Transl Med.* 2014;6:259ra146.
7. Sathekge M, Garcia-Perez O, Paez D, et al. Molecular imaging in musculoskeletal infections with ^{99m}Tc-UBI 29-41 SPECT/CT. *Ann Nucl Med.* 2018;32:54-59.
8. C. Konig, H.P. Simmen, J. Blaser. Bacterial concentrations in pus and infected peritoneal fluid—Implications for bactericidal activity of antibiotics. J Antimicrob Chemother. 1998;42:227-232
9. Lawal I, Sathekge M. F-18 FDG PET/CT imaging of cardiac and vascular inflammation and infection. Br Med Bull. 2016;120:55-74.