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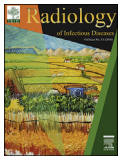

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Commentary

# Molecular imaging: Moving towards infectious diseases

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**Abstract**

Molecular imaging has been advanced into the field of infectious diseases, which provides not only new insights for basic science, but also new strategies for the effective management of infectious diseases in clinical practice.


*Keywords:* Molecular imaging; Infectious disease

Infectious diseases, including bacterial, viral, fungal and parasitic infections, remain an enormous public health problem in both the developing and the developed world. Populations that are particularly vulnerable to infections are children, the elderly people and immunocompromised patients. Despite the rapid advancement of *in vitro* laboratory diagnostic tests, such as polymerase chain reaction (PCR) with a high sensitivity and specificity in identifying infectious pathogens, *in vivo* imaging technologies are being developed at a slower pace. Among the currently available imaging techniques, molecular imaging has shown the greatest potential, permitting not only the fast and accurate diagnosis of infectious diseases, but also guidance and the monitoring of successful treatment.

Molecular imaging is designed to detect pathophysiological changes in living subjects at the molecular or cellular level. It has become a new and exciting frontier in modern medical imaging [1]. Several molecular imaging modalities have been successfully explored and implemented in diagnosing and treating various infectious diseases, which include magnetic resonance imaging (MRI), optical imaging, nuclear imaging, and radiographic-based imaging [2]. Among these modalities, MRI has several unique advantages: high-spatial resolution, multiplanar image capability, and functional assessment, all without the risk of ionizing radiation. A new member in the molecular imaging family is optical imaging, which includes fluorescent imaging and luminescent imaging. By detecting fluorescent or luminescent light emission from targeted tissues, optical imaging provides real-time and highly sensitive observations of superficially-sited targets. An additional molecular imaging modality is positron emission tomography/computed tomography (PET/CT). PET/CT constitutes a hybrid imaging mode to detect both anatomic and metabolic abnormalities with high specificity.

The essential elements of any infectious disease process are the pathogen, the host, and the interaction between the two. Control of an infectious disease would involve the following three primary objectives: 1) to identify, localize and eliminate infectious pathogens, including bacteria, viruses, fungi and parasites; 2) to assess the host reaction to an infection (e.g. local and systematic inflammatory changes, characterized by proliferation and accumulation of inflammatory cells and cytokines); and 3) to guide appropriate treatment strategies and monitor efficacy of treatment. According to these objectives, advances in molecular imaging for infectious diseases in the past few years can be summarized into the following three

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areas: 1) visualization of pathogens (organisms) for accurate diagnosis; 2) assessment of inflammation and tissue/organ damage; and 3) monitoring effectiveness of therapy and identifying complications secondary to an infection [3].

First, molecular imaging has been used to identify infectious pathogens. A typical example is labeling *Leishmania infantum* strains by fluorescence for optical imaging of visceral leishmaniasis, which may provide a robust model for better understanding of the pathogenesis of various infectious diseases [4]. Similarly, the luciferase gene from a firefly can be inserted into pathogenic stains, such as *Borreliaburgdorferi* and *Trypanosomacruzi*, which thus serve as ideal tools for basic science to investigate, *in vivo*, Lyme disease and Chagas disease [5,6]. However, clinical translation of optical imaging is restricted by difficulties in detecting pathogens in deep tissues. An attempt to solve this problem is by the use of a "red-shifted" luciferase to label different pathogenic strains. This modified luciferase emits light of a longer wavelength than standard bioluminescence-generating proteins, which can not only transport excitation and emission light into and from deep targets, but also reduce interference of auto-fluorescence from targeted tissues and organs of infections [7]. Similar to optical imaging, labeling of the influenza A/Udorn/307/1972 virus (H3N2) with the MRI agent, 5-fluorotryptophan, demonstrates the feasibility of using ($^{19}$F) MRI to directly visualize and quantify the helix−helix ED dimer interface of NS1A protein in *Influenza virus* infection [8].

Second, bacterial infection can cause inflammation, tissue damage, and ultimately disseminated septic shock [9]. Advanced technologies that enable the rapid detection and localization of bacterial infections in living subjects can address an unmet need for the diagnosis of certain infectious diseases [10]. Identification of host-pathogen interactions provides a great opportunity for the development of targeted molecular imaging as well as targeted therapies [11−13]. An example of this is the systemic administration of oligonucleotides that are chemically modified to resist mammalian serum nuclease digestion. The oligonucleotides are labeled with a fluorophore and a quencher. *Staphylococcus aureus* nucleases can specifically digest the oligonucleotides and thereby separate the fluorophore and quencher, which in turn generates fluorescent signals at the infection site for optical imaging [10]. Another example is to synthesize a dual-modality magneto-fluorescent nanoparticle-based probe, by combining an ultra small super paramagnetic iron oxide nanoparticle and Rhodamine B for both MRI and optical imaging. This dual-imaging probe can be used to specifically target monocyte-macrophages of myocardial inflammation [14]. In addition, administration of a near-infrared fluorescence (NIRF)-labeled anti-Siglec-F antibody allows for non-invasive optical imaging of eosinophils, a pathognomonic feature of parasitic infection [15].

Third, molecular imaging can be used to evaluate disease progression and to monitor treatment. For example, MRI with diffusion tensor imaging (DTI) has demonstrated the ability to assess white matter deficits in patients with human immunodeficiency virus (HIV) infection [16]. Another example is using optical imaging-based fluorescent angiography and spectral optical coherence tomography (OCT) to monitor acute ocular toxoplasmosis [17]. Furthermore, ($^{18}$F)-Fluorodeoxyglucose (FDG)-PET/CT has be recognized as a powerful tool in i) assessing the metabolic response to treatment in malignancies relating to viral infections, such as locally advanced cervical cancer due to high risk human papilloma virus (HPV) infection [18]; ii) detecting infections of central nervous system [19] and vascular prosthetic grafts [20]; and iii)evaluating drug efficacy in patients with tuberculosis [21,22].

Although still in its developmental phase, the clinical implementation of molecular imaging should focus on the three primary targets of infectious diseases: infectious pathogens, pathophysiological changes caused by infection, and the response to treatment of infection. While labeling various pathogen strains with different imaging dyes permits better understanding of the pathogenesis of various infectious diseases, further development of targeted and multi-modality imaging probes will allow for *in vivo* detection of pathogens, as well as evaluation of disease progression and therapeutic responses.

Overall, molecular imaging is becoming an exciting tool in infectious diseases, not only providing new insights for basic science, but also new strategies for the effective management of infectious diseases in clinical practice.

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## References

[1] Weissleder R, Mahmood U. Molecular imaging. Radiology 2001;219:316−33.
[2] Bocan TM, Panchal RG, Bavari S. Applications of in vivo imaging in the evaluation of the pathophysiology of viral and bacterial infections and in development of countermeasures to BSL3/4 pathogens. Mol Imaging Biol 2015;17(1):4−17.
[3] Warawa JM, Lawrenz MB. Bioluminescent imaging of bacteria during mouse infection. Methods Mol Biol 2014;1098:169−81.
[4] Calvo-Alvarez E, Stamatakis K, Punzon C, Alvarez-Velilla R, Tejeria A, Escudero-Martinez JM, et al. Infrared fluorescent imaging as a potent tool for in vitro, ex vivo and in vivo models of visceral leishmaniasis. PLoS Negl Trop Dis 2015;9(3):e0003666.
[5] Chan K, Alter L, Barthold SW, Parveen N. Disruption of *bbe02* by insertion of a luciferase gene increases transformation efficiency of *Borrelia burgdorferi* and allows live imaging in lyme disease susceptible C3H mice. PLoS One 2015;10(6):e0129532.
[6] Lewis MD, Fortes Francisco A, Taylor MC, Burrell-Saward H, McLatchie AP, Miles MA, et al. Bioluminescence imaging of chronic *Trypanosoma cruzi* infections reveals tissue-specific parasite dynamics and heart disease in the absence of locally persistent infection. Cell Microbiol 2014;16(9):1285−300.
[7] Taylor MC, Kelly JM. Optimizing bioluminescence imaging to study protozoan parasite infections. Trends Parasitol 2014;30(4):161−2.
[8] Aramini JM, Hamilton K, Ma LC, Swapna GV, Leonard PG, Ladbury JE, et al. (19)F NMR reveals multiple conformations at the dimer interface of the nonstructural protein 1 effector domain from influenza A virus. Structure 2014;22(4):515−25.
[9] Miller AH, Vayttaden SJ, Al-Khodor S, Fraser ID. Assay development for image-based quantification of intracellular bacterial replication and analysis of the innate immune response to infection. Assay Drug Dev Technol 2015;13(9):515−28.

[10] Hernandez FJ, Huang L, Olson ME, Powers KM, Hernandez LI, Meyerholz DK, et al. Noninvasive imaging of *Staphylococcus aureus* infections with a nuclease-activated probe. Nat Med 2014;20(3):301−6.
[11] Scales HE, Ierna M, Smith KM, Ross K, Meiklejohn GR, Patterson-Kane JC, et al. Assessment of murine collagen-induced arthritis by longitudinal non-invasive duplexed molecular optical imaging. Rheumatology (Oxford) 2015 Oct 16 [Epub ahead of print].
[12] Freise AC, Wu AM. In vivo imaging with antibodies and engineered fragments. Mol Immunol 2015;67(2 Pt A):142−52.
[13] Tree JA, Flick-Smith H, Elmore MJ, Rowland CA. The impact of "omic" and imaging technologies on assessing the host immune response to biodefence agents. J Immunol Res 2014;2014:237043.
[14] Chang D, Wang YC, Zhang SJ, Bai YY, Liu DF, Zang FC, et al. Visualizing myocardial inflammation in a rat model of type 4 cardiorenal syndrome by dual-modality molecular imaging. Biomaterials 2015;68:67−76.
[15] Markus MA, Dullin C, Mitkovski M, Prieschl-Grassauer E, Epstein MM, Alves F. Non-invasive optical imaging of eosinophilia during the course of an experimental allergic airways disease model and in response to therapy. PLoS One 2014;9(2):e90017.
[16] Tang VM, Lang DJ, Giesbrecht CJ, Panenka WJ, Willi T, Procyshyn RM, et al. White matter deficits assessed by diffusion tensor imaging and cognitive dysfunction in psychostimulant users with comorbid human immunodeficiency virus infection. BMC Res Notes 2015;8:515.
[17] Previato M, Frederico FB, Henrique Antunes Murata F, Siqueira RC, Barbosa AP, Silveira-Carvalho AP, et al. A Brazilian report using serological and molecular diagnosis to monitoring acute ocular toxoplasmosis. BMC Res Notes 2015;8:746.
[18] Siva S, Deb S, Young RJ, Hicks RJ, Callahan J, Bressel M, et al. (18)F-FDG PET/CT following chemoradiation of uterine cervix cancer provides powerful prognostic stratification independent of HPV status: a prospective cohort of 105 women with mature survival data. Eur J Nucl Med Mol Imaging 2015;42(12):1825−32.
[19] Tseng JR, Su YY, Lee MH, Chen KY, Tsai SF, Yen TC. Clinical usefulness of FDG PET/CT in the detection of unusual central nervous system infections. J Neurol Sci 2014;345(1−2):244−7.
[20] Saleem BR, Pol RA, Slart RH, Reijnen MM, Zeebregts CJ. 18F-Fluorodeoxyglucose positron emission tomography/CT scanning in diagnosing vascular prosthetic graft infection. Biomed Res Int 2014;2014:471971.
[21] Coleman MT, Chen RY, Lee M, Lin PL, Dodd LE, Maiello P, et al. PET/CT imaging reveals a therapeutic response to oxazolidinones in macaques and humans with tuberculosis. Sci Transl Med 2014;6(265):265ra167.
[22] Chen RY, Dodd LE, Lee M, Paripati P, Hammoud DA, Mountz JM, et al. PET/CT imaging correlates with treatment outcome in patients with multidrug-resistant tuberculosis. Sci Transl Med 2014;6(265):265ra166.