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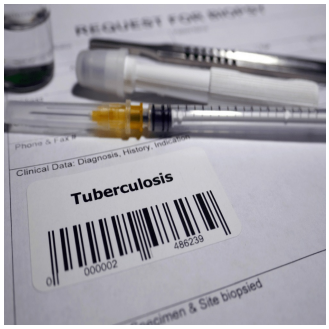
Tuberculosis Diagnostics: The Promise of [18F]FDT PET Imaging



Tuberculosis (TB) remains a critical global health challenge, with Mycobacterium tuberculosis (Mtb) causing approximately 1.3 million deaths worldwide in 2022. The rise in TB cases, with 7.5 million new diagnoses reported in the same year, highlights the urgent need for practical diagnostic tools and treatment monitoring strategies. Integrating positron emission tomography (PET) with computed tomography (CT) has significantly improved diagnostic imaging for various diseases, including cancer and inflammatory conditions. However, the lack of specificity in current PET tracers, such as 2-[18F]fluoro-2-deoxy-D-glucose ([18F]FDG), necessitates the development of more precise TB-specific tracers. Recent advancements in trehalose-based probes, particularly 2-[18F]fluoro-2-deoxy-trehalose ([18F]FDT), offer promising potential for enhancing TB diagnostics and monitoring, as researchers report in an article published in Nature Communications.

The Need for Specific and Sensitive TB Diagnostics

Effective TB control is contingent upon prompt and accurate diagnosis, as well as continuous monitoring of disease progression and treatment response. Traditional diagnostic methods, including sputum smear microscopy, culture, and molecular tests, are often time-consuming and lack sensitivity, leading to delays in treatment initiation and increased transmission risks. The World Health Organization (WHO) has emphasised the need for rapid and accurate TB diagnostics to improve public health outcomes and reduce the disease burden.

[18F]FDG PET/CT imaging has been widely used to visualise TB lesions by detecting elevated glucose uptake in inflamed cells. This technique has been beneficial in identifying active TB infections and monitoring treatment response. However, the lack of specificity of [18F]FDG, which is taken up by any metabolically active tissue, often results in false positives. This diagnostic ambiguity is further exacerbated by the emergence of lung pathology in COVID-19 patients, complicating the differentiation between TB and other inflammatory conditions. Consequently, there is a pressing need for more specific PET tracers that can accurately distinguish TB lesions from other inflammatory processes.

Trehalose-Based Probes: A Promising Alternative

Trehalose, a disaccharide uniquely metabolised by Mtb, has garnered significant interest as a highly specific and sensitive TB diagnostic agent. Trehalose is incorporated into the mycobacterial cell wall as trehalose monomycolate (TMM) and trehalose dimycolate (TDM), essential glycolipids for Mtb's structural integrity and pathogenicity. The enzyme family Antigen 85 (Ag85) catalyses the incorporation of exogenous trehalose into the mycobacterial cell wall, making it a potential target for TB-specific imaging probes.

Researchers have developed various trehalose-based fluorescent probes for in vitro TB detection, exploiting the unique metabolic pathway of trehalose in Mtb. The latest advancement in this field is the development of [18F]FDT, a radiolabelled trehalose analogue. [18F]FDT can be synthesised using a one-pot, automatable, chemoenzymatic process from [18F]FDG, ensuring that it can be produced without requiring specialised facilities. This method makes [18F]FDT accessible for widespread clinical use, particularly in resource-limited settings where TB is most prevalent.

Comparative Efficacy of [18F]FDT and [18F]FDG in TB Imaging

Studies have demonstrated that [18F]FDT offers superior specificity for TB compared to [18F]FDG. While [18F]FDG targets high glucose uptake in inflamed cells, leading to its accumulation in any metabolically active tissue, [18F]FDT targets the unique trehalose metabolism pathway in Mtb. This specificity reduces the incidence of false positives associated with [18F]FDG, which is particularly beneficial in differentiating TB from other inflammatory conditions, such as cancer and COVID-19-related lung pathology.

Preclinical studies in non-human primates (NHPs) have shown promising results for [18F]FDT. In these studies, [18F]FDT PET/CT imaging accurately visualised TB lesions and correlated significantly with bacterial burden. In one study, the uptake of [18F]FDT in TB lesions of marmosets correlated well with the number of culturable Mtb bacteria, demonstrating its potential as a reliable indicator of disease severity. Moreover, [18F]FDT showed low background signal in the lungs of uninfected animals, further emphasising its specificity for TB.

In comparison, [18F]FDG PET/CT imaging often results in false positives due to its uptake in any inflamed tissue. For instance, in patients with lung cancer or COVID-19, [18F]FDG PET/CT can misidentify inflammation as TB lesions, leading to diagnostic confusion. This limitation underscores the need for TB-specific tracers like [18F]FDT, which can provide more accurate and reliable diagnostic information.

Monitoring Treatment Response with [18F]FDT

One of the significant challenges in TB management is the prolonged treatment duration, which can span several months to years. Continuous monitoring of treatment response is crucial to ensure compliance and effectiveness, as well as to detect any potential relapse. Traditional methods, such as sputum culture and molecular tests, are often inadequate for real-time monitoring of disease progression and treatment response.

[18F]FDT PET/CT imaging offers a non-invasive and accurate method for monitoring treatment response in TB patients. In preclinical studies, [18F]FDT demonstrated the ability to track changes in TB lesions over time, correlating with reductions in bacterial load. For example, in marmosets treated with first-line TB therapy (isoniazid, rifampicin, pyrazinamide, and ethambutol), [18F]FDT PET/CT scans showed significant reductions in tracer uptake, consistent with the decline in bacterial burden. This ability to monitor treatment response in real-time provides invaluable feedback to clinicians and patients, helping to ensure adherence to treatment regimens and timely adjustments if necessary.

In contrast, [18F]FDG PET/CT imaging often shows persistent uptake in lesions even after successful treatment, reflecting ongoing inflammation rather than bacterial activity. This limitation can lead to misinterpretation of treatment effectiveness and unnecessary prolongation of therapy. The specificity of [18F]FDT for Mtb metabolism offers a more accurate reflection of bacterial viability, making it a superior tool for monitoring TB treatment.

Addressing Global Health Inequities with [18F]FDT

The global burden of TB disproportionately affects low- and middle-income countries, where access to advanced diagnostic tools is often limited. The scalable and automatable synthesis of [18F]FDT from [18F]FDG offers a practical solution to this challenge. By leveraging existing PET/CT infrastructure and the widespread availability of [18F]FDG, [18F]FDT can be produced and distributed in resource-limited settings, enhancing diagnostic capabilities and improving TB control efforts.

Integrating [18F]FDT PET/CT imaging into national healthcare systems can drive global equity in TB diagnostics, providing high-quality diagnostic services to underserved populations. Furthermore, the development of mobile PET/CT units and regional radiopharmacies can facilitate the dissemination of [18F]FDT to remote and rural areas, ensuring that even the most vulnerable populations have access to accurate and timely TB diagnostics.

The development of [18F]FDT marks a significant advancement in TB diagnostics and treatment monitoring. Its specificity and sensitivity address the limitations of current PET tracers like [18F]FDG, providing a more accurate tool for diagnosing and managing TB. The scalable, automated synthesis of [18F]FDT from [18F]FDG makes it a practical option for widespread clinical implementation, particularly in resource-limited settings where TB is most prevalent.

As TB continues to pose a global health challenge, innovative solutions like [18F]FDT are crucial for improving patient outcomes and controlling the spread of this disease. Future research and clinical trials will further establish [18F]FDT's efficacy and pave the way for its integration into standard TB diagnostic and monitoring protocols. By enhancing the accuracy and accessibility of TB diagnostics, [18F]FDT holds the potential to transform TB control efforts worldwide, ultimately contributing to the global goal of ending the TB epidemic.

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