Pathogen specific antibody-based molecular imaging of Invasive Aspergillosis with the newly developed PET tracer [64Cu]DOTA-JF5 and its humanized variant [64Cu]NODAGA-hJF5

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ABSTRACT BODY:
Abstract Body: Humans with impaired immunity, e.g. those with haematological malignancies or bone marrow transplant recipients are at an elevated risk of severe *Aspergillus fumigatus* infection known as invasive aspergillosis (IA). Currently IA is diagnosed based on clinical symptoms, radiology, laboratory tests and microscopy or relies on invasive biopsy, which is not always feasible in very sick patients. Most of these methods are unspecific and time consuming, which impedes an early and accurate diagnosis leading to fatalities of up to 80% in certain patient groups. Consequently, there is the potential to increase the survival rates of IA patients, if a definite diagnosis of IA could be obtained early and its response to treatment monitored and adjusted accordingly. The highly *A. fumigatus* specific monoclonal antibody (mAb) JF5 and its humanized variant hJF5 were radiolabeled with ^{64}Cu, tested in an experimental setup and compared to the standard PET tracer [^{18}F]FDG in various infection models.

In vivo biodistribution studies were performed with neutropenic *A. fumigatus* infected C57BL/6 mice after the injection of 13 MBq of [^{64}Cu]DOTA-JF5, the isotype control [^{64}Cu]DOTA-MG 3-35, [^{64}Cu]NODAGA-hJF5 or [^{18}F]FDG and compared to the distribution of the respective tracers in control infections (*S. pneumoniae* and *Y. enterocolitica*). The Gr-1 antibody RB6-8C5 was administered 24h prior to the intratracheal infection of the mice with *A. fumigatus* to mimic impaired immunity by the depletion of neutrophil granulocytes. 3, 24 and 48h after the injection of the ^{64}Cu labeled antibodies or [^{18}F]FDG, PET/MRI images of the respective infection groups were acquired and compared to PBS treated controls. Additionally, blocking studies, e*x vivo* biodistribution, autoradiography and plating of various organs for the detection of the pathogen were performed.

[^{18}F]FDG-PET showed similar results in *A. fumigatus* infected animals (%ID/cc lungs: 14.67±0.53), PBS treated control animals (%ID/cc lungs: 10.47±2.77) as well as in *S. pneumoniae* control infections with 13.05±2.80 and 12.37±1.19 %ID/cc in the respective PBS treated control group. Quantification of the PET images showed a significantly higher binding of the *A. fumigatus* specific JF5 mAb in neutropenic, *A. fumigatus* infected animals (%ID/cc lungs: 11.08±2.28) compared to PBS treated animals (%ID/cc lungs: 7.51±1.50). All control infections revealed a reduced uptake of JF5 in the lungs. Blocking experiments and studies with the unspecific isotype control antibody demonstrated the high specificity of JF5. Biodistribution studies with the newly developed humanized [^{64}Cu]NODAGA-hJF5 displayed similar uptake characteristics as the mouse mAb JF5 with 22.73±6.77 %ID/g in infected animals compared to 10.14±3.68 %ID/g in PBS treated animals.

[^{18}F]FDG-PET revealed to be highly unspecific and is therefore not suitable for monitoring

disease progression and therapeutic success in IA. In contrast to that, [^{64}Cu]DOTA-JF5 and especially the humanized variant [^{64}Cu]NODAGA-JF5 have been developed and show great potential as novel timely and accurate diagnostic and therapeutic strategy for IA to improve the survival rates of patients.

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