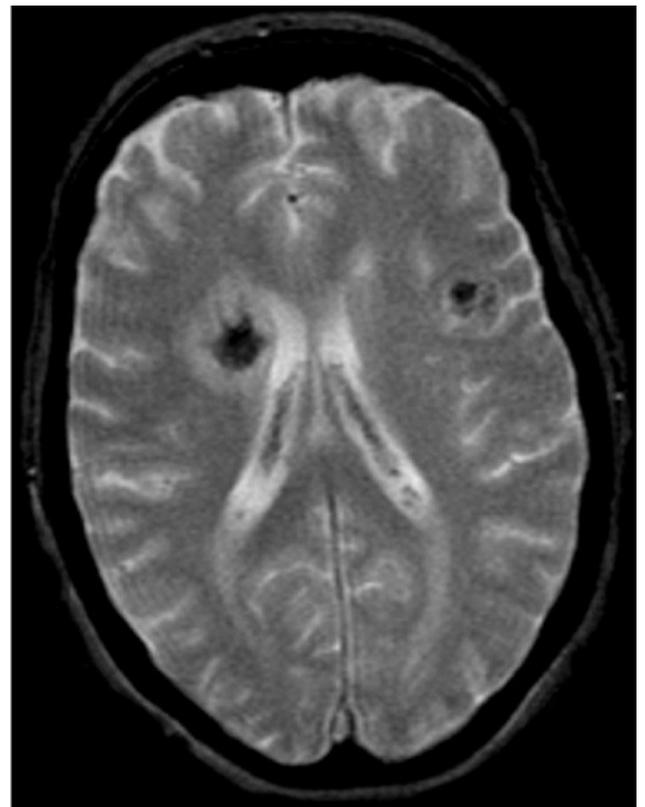
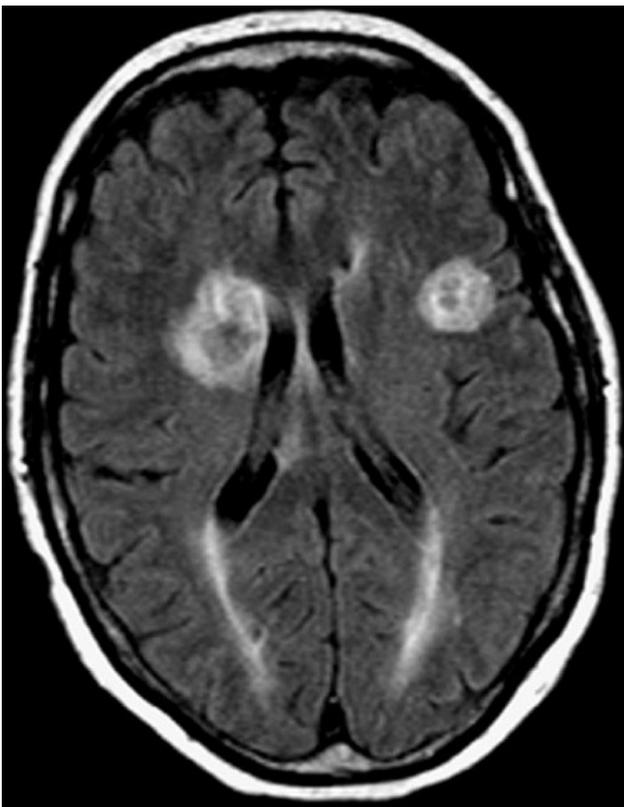


## Fungal infections of the lungs – antibody-based imaging improves diagnosis

**Cancer was the first area of diagnostics in which antibody-based PET/MRI imaging was used. The diagnosis of fungal infections will be the next. The innovative method is being developed by a European research consortium coordinated by researchers in Tübingen.**



MR images of a patient with cerebral aspergillosis, a disease where the fungus has managed to infect the brain. The two spherical regions in the upper half of the photo (right: light; left: dark) show the areas that have been infected by the fungus. © with the courtesy of Prof. Dr. Thomas Nägele, Neuroradiology, University Hospital Tübingen

The Werner Siemens Imaging Center at the University Hospital in Tübingen is making a considerable contribution to shaping the future of medical imaging. Prof. Dr. Bernd Pichler, who holds a chair endowed by the Werner Siemens Foundation, has been developing innovative imaging methods since 2008. Last year, Pichler was one of ten experts who prepared a position paper on the future of imaging on behalf of the National Academy of Sciences Leopoldina. Pichler is also a member (since autumn 2015) of the German Academy of Science and Engineering (acatech) as well as various other

bodies that are involved in this important branch of medical technology.

Pichler's team's most recent success is a new method for diagnosing invasive pulmonary aspergillosis, one of the most dangerous and frequently fatal infectious lung diseases. It is caused by the fungus *Aspergillus fumigatus*. The fungus does not affect healthy people with intact immune systems. However, it can disseminate in the lungs of people with deficient immune systems, such as cancer or AIDS patients, causing widespread damage that can lead to death.

Although the fungus can be treated with anti-fungal drugs, an early and rapid diagnosis is crucial for successful treatment outcome. However, this is still a pipe dream. "At present, patients suspected of having aspergillosis undergo a lung biopsy, and laboratory cultures are established with the small piece of tissue removed. The results are available around a week after the intervention," says Dr. Stefan Wiehr, a biologist in Pichler's team. "Apart from the loss of time before treatment can be started, biopsies are also stressful for immunocompromised patients," adds Anne-Marie Rolle. Anne-Marie Rolle is a biosystems engineer in Pichler's team and is also involved in developing the new diagnostic method. The large-scale EU-funded project called MATHIAS (New Molecular-Functional Imaging Technologies and Therapeutic Strategies for Theranostic of Invasive Aspergillosis) also involves Prof. Dr. Matthias Gunzer and his team from the University Hospital in Essen, scientists from Prof. Roger Schibli's team at the Paul Scherrer Institute and the ETH in Switzerland, a company called ISCA Diagnostics, a spin-off from Exeter University in the UK, as well as a number of researchers from France and Denmark.

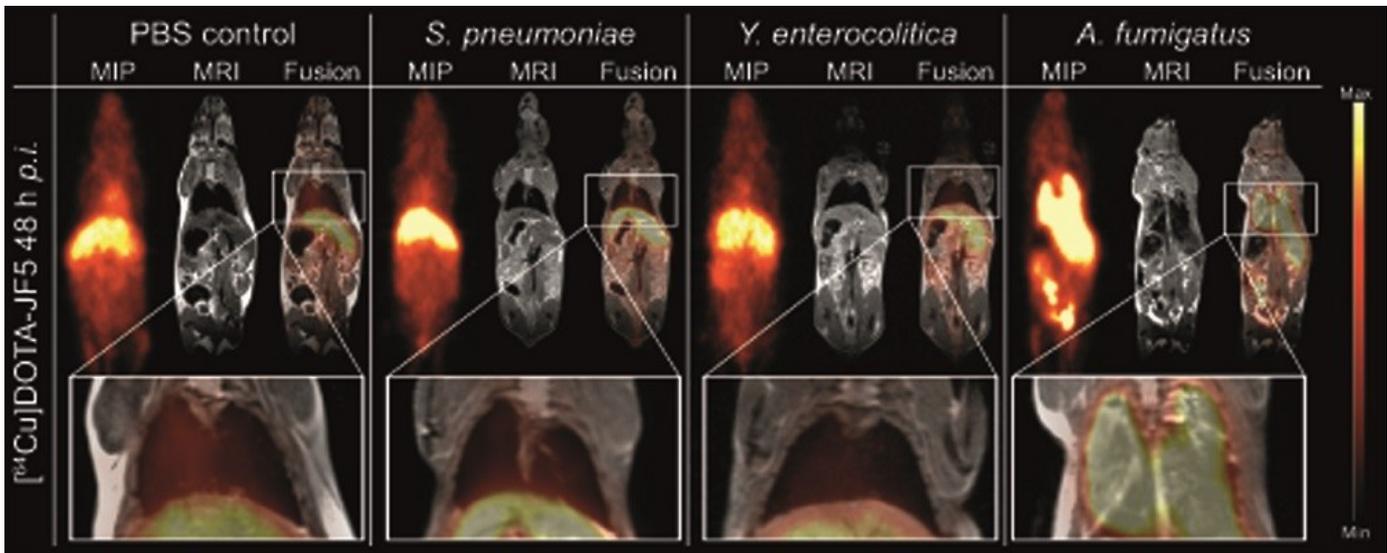
## Successful treatment depends on early diagnosis

MATHIAS researches the use of radioactively labelled antibodies that are able to highly specifically recognise and bind to a structure on the surface of fungal hyphae. The antibodies are injected into a patient's bloodstream and the patient is ready for examination within a few hours. Examination involves a combination of PET/MRI. Pichler's team works at the forefront of science in the further development of the method. PET/MRI allows completely new imaging dimensions because it combines the advantages of both methods. While magnetic resonance imaging comes with a particularly high morphological resolution, positron emission tomography (PET) has an outstanding detection sensitivity (down to the picomolar range). The signal-emitting tracer molecules contain the  $^{64}\text{Cu}$  copper isotope, but other labels can also be used and will be tested in the future.

The use of antibody-coupled imaging in the diagnostics field is fairly new and is currently mainly used in cancer diagnosis. Some years ago, Wiehr gave a lecture on the subject in Berlin where he met Prof. Gunzer from the University of Magdeburg who was working on *Aspergillus*. They exchanged information, became interested in each other's research, developed the idea of the MATHIAS project and went on to look for other experts across Europe in order to get the project off the ground. The EU project finally started in October 2013. Gunzer had since moved to Essen where he developed the first animal model for the tests. A French company provides the chelator, a compound that links the actual antibody with the radionuclide. The experts from the Paul Scherrer Institute ensure that the components bind effectively together. The antibody is adapted to the project's specific requirements and produced by the English company ISCA Diagnostics. Colleagues from Denmark are focused on optimised production of innovative radioactive isotopes. The threads are all brought together in Tübingen where Pichler, the project coordinator, has established the method for use on the aforementioned animal model, which he had further developed before the project began.

## The researchers are already planning clinical trials and regulatory approval

Meanwhile, the joint efforts are bearing fruit: in early 2016, the project partners published a paper on



The images show the highly specific diagnosis of disease using antibody-based imaging in mice infected with *Aspergillus fumigatus* fungi. The figure shows a PET image, an MR image and a PET/MRI image. 48 hours after infection with *Aspergillus fumigatus* (on the far right), the animals emit a very strong signal (uptake of large tracer amounts) in the lung. As regards infections with *Yersinia enterocolitica* (2nd from the right) and with *Streptococcus pneumoniae* (3rd from the right), the animals' lungs did not show any sign of the tracer. The control group (on the far left) was injected with PBS, purely for irritating the lungs. No tracer accumulated. All this is proof of the high specificity of the *Aspergillus*-specific antibody.

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the successful and specific detection of *Aspergillus* in the mouse model. "We can reliably demonstrate that the fungus is indeed *Aspergillus fumigatus*, rather than a bacterial or viral pathogen," says Wiehr. The method is now being further developed for human application. "We hope to obtain the first patient data next year, and are already in contact with a company that will carry out the toxicological tests for us. Clinical imaging will then be performed in Essen and Tübingen," says Pichler. The researchers still have some work to do. Amongst other things, they need to optimise the imaging process and find out how much time needs to elapse after injection of the antibodies for the best possible results.

However, the scientists from Tübingen are already thinking ahead. Wiehr outlines their vision: "We are further developing antibody-based imaging so that it can be used for therapeutic as well as diagnostic purposes. This would bring a significant cost advantage. Antifungal therapies cost between 250,000 and 400,000 euros per patient, making aspergillosis treatment very expensive. We want to find a company with a certified GMP facility, and intend to advertise in order to find a company that can inexpensively produce customised specific therapeutic antibodies in the entire EU."

The University of Tübingen, the University of Stuttgart, the University Hospital in Tübingen and local research institutions are planning to establish a national centre for imaging techniques in order to extend the development of innovative imaging methods and better use local expertise. "We are modelling this on the large American centres and are looking to establish a globally competitive institute that can do everything from developing imaging probes to clinical phase I and II trials," says Pichler.

## Article

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Dr. Heike Lehmann

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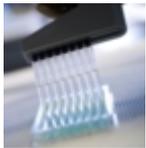
## Further information

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- ▶ University Hospital Tübingen Department of Preclinical Imaging and Radiopharmacy
- ▶ Original publication

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Disease prevention through better diagnostics



Respiratory disease - congestion in the respiratory system



diagnostics

infectious diseases

lungs

imaging  
methods

clinical  
trial

fungi

antibody

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