Scientists create imaging 'toolkit' to help identify new brain tumor drug targets

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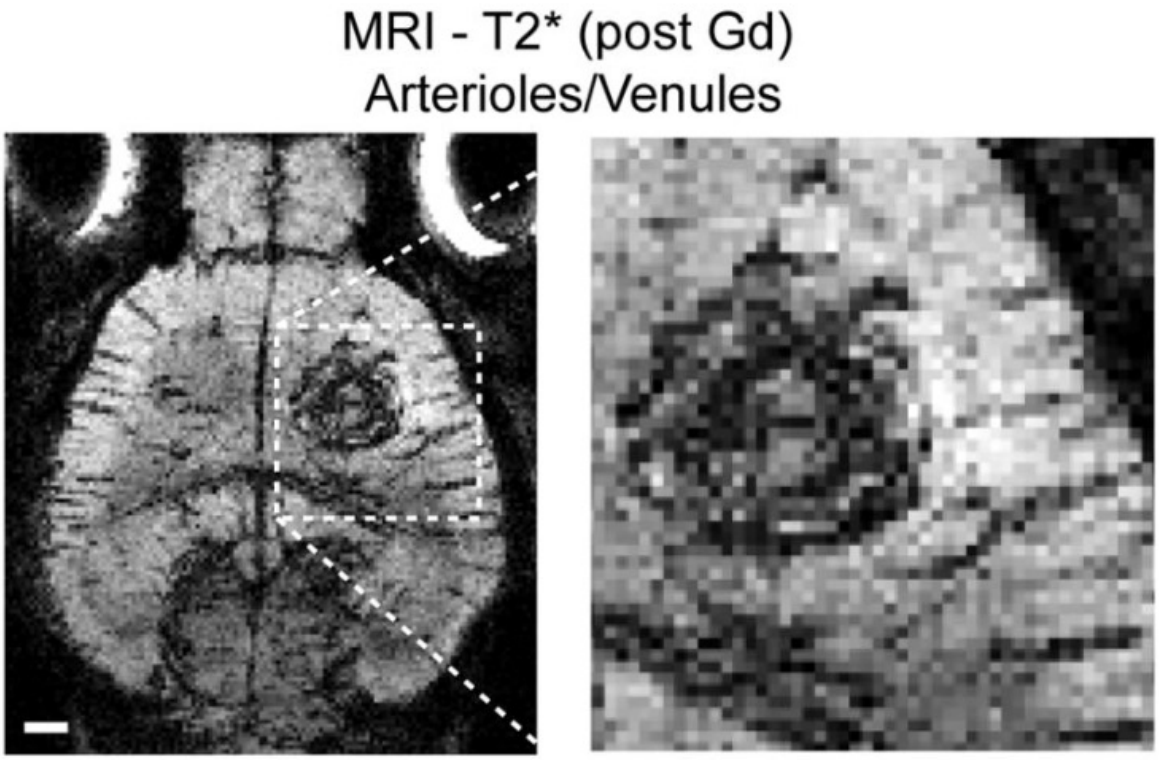


Brain tumor vascularisation is visualized using T2*-weighted magnetic resonance imaging. Credit: Breckwoldt, Bode et al.

Stopping the growth of blood vessels in tumours is a key target for glioblastoma therapies, and imaging methods are essential for initial

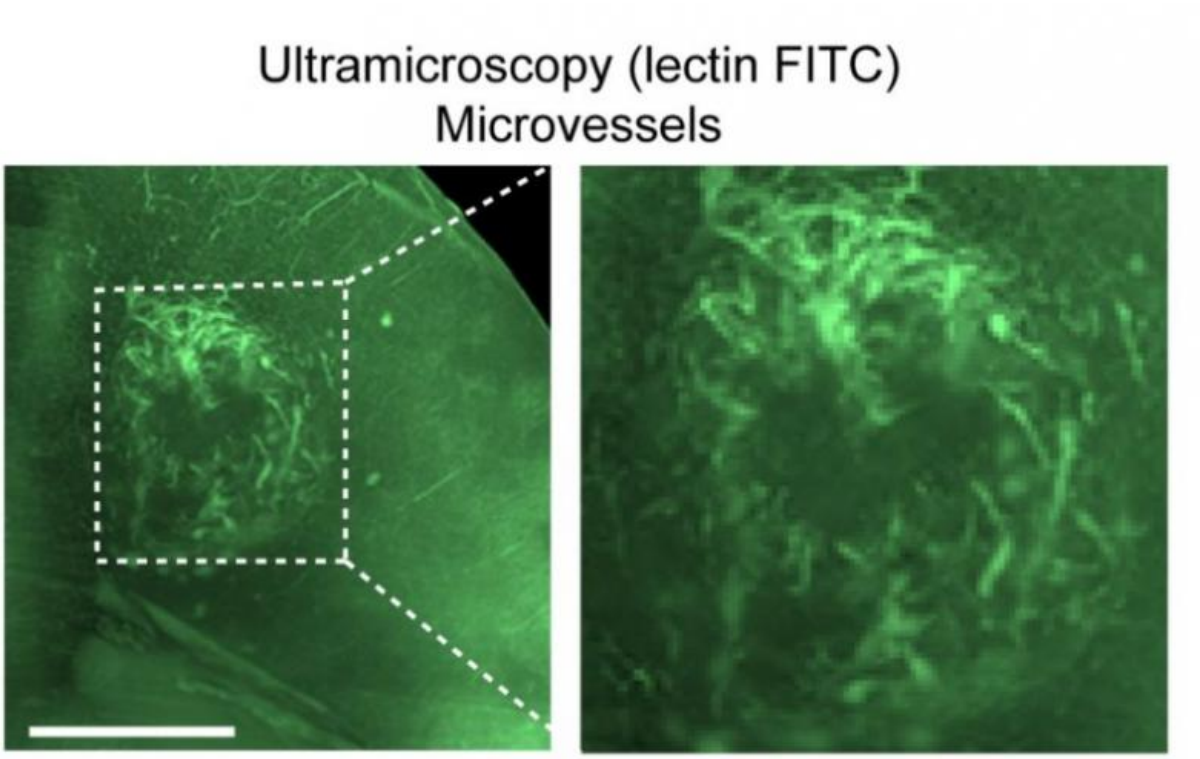
diagnosis and monitoring the effects of treatments. While mapping vessels in tumours has proven a challenge, researchers have now developed a combined magnetic resonance imaging (MRI) and ultramicroscopy 'toolkit' to study vessel growth in glioma models in more detail than previously possible. Their study is to be published in the journal *eLife*.

"Gliomas are highly malignant brain tumours with poor prognosis," says Michael Breckwoldt, a physician-scientist and one of the lead authors of the paper from the University of Heidelberg.

"Many efforts have been made to develop therapies against the growth of blood vessels and therefore 'starve' tumours of their resources, but they are not entirely effective. Improved imaging techniques that faithfully show the vessel architecture, including their growth, structure and density, and the effects of treatments in a non-invasive way are therefore needed to inform the development of future clinical trials."

In their study in mice, the team combined an MRI approach in vivo with ultramicroscopy of ex vivo whole brains cleared for imaging.

The technique is based on T2*-weighted (T2*-w) MRI images, one of the basic pulse sequences in MRI, with high resolution to allow for substantially more detail than conventional T2*-w imaging. Pre- and post-contrast MR scans were performed to define the growth of vessels during glioma development in two different glioma models.



Brain tumor microvessels are visualized using dual-color ultramicroscopy. Credit: Breckwoldt, Bode et al.

The team further mapped the development of vessels by dual-colour ultramicroscopy of whole, cleared brains. Using fluorescent labelling of microvessels, they collected complementary 3D MR and ultramicroscopy data sets (dubbed the 'MR-UM'), which could be compared side-by-side.

"MR-UM can be used as a platform for three-dimensional mapping of single vessels and detailed measurements of the growth of newly formed vessels over time," Dr. Breckwoldt explains.

"This provides a better understanding of the underlying mechanisms of

existing treatment and could help identify novel targets for future drug development," adds Dr. Julia Bode, co-lead author from the German Cancer Research Centre.

The team also used the toolkit to assess the effects of existing anti-vascular endothelial growth factor (anti-VEGF) treatments or radiation therapy on the vessel compartment within the glioma models. They found that such treatments are insufficient to halt tumour growth in mice, which mirrors current human studies.

"Dual inhibitors of vessel growth are now being developed and our toolkit could also help assess their therapeutic effects in detail," says Bode.

The T2*-weighted imaging sequence and UM studies in ex vivo brains are at present only suitable for mapping tumour vessels in a preclinical setting. The team anticipates, however, that future studies using high-field clinical MR systems should enable possible translation of the MRI approach to the clinical arena. Furthermore, specimens taken for clinical diagnosis could be studied using ultramicroscopy, making the full MR-UM toolkit a potential player in a clinical setting.

More information: Michael O Breckwoldt et al. Correlated magnetic resonance imaging and ultramicroscopy (MR-UM) is a tool kit to assess the dynamics of glioma angiogenesis, *eLife* (2016). DOI: 10.7554/eLife.11712

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