PRESS RELEASE

Core2Edge: How tumor cells conquer the brain

Bonn research team develops fully human glioblastoma model offering insights into remote zones of tumor cell infiltration

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Bonn, July 28 – Glioblastoma is an aggressive brain tumor that infiltrates deep into the surrounding brain tissue. Even after surgery, tumor cells remain in the brain and the tumor recurs. Researchers at the University Hospital Bonn (UKB) and the University of Bonn have now developed *Core2Edge*, a model based entirely on human tissue that captures these hard-to-access infiltration zones at the tumor margin. The model enables investigation of the invasive front and direct assessment of new drug candidates in human tissue - without the need for animal testing. The study of the Brain Tumor Translational Research Group has now been published in Nature Protocols.

Glioblastoma is a malignant brain tumor and among the most aggressive cancers in humans. Despite multimodal therapy with surgery, radiation, and chemotherapy, there is still no cure. A major reason is the tumor's invasive behavior: glioblastoma cells migrate far beyond the visible tumor into healthy brain tissue. These infiltrating cells cannot be completely removed and seed tumor recurrence - often within just a few months. "To understand why glioblastoma keeps coming back, we need to look closely at the tumor cells that remain hidden in the brain after surgery," says Priv.-Doz. Dr. Matthias Schneider, Deputy Director of the Department of Neurosurgery at the UKB and Head of the Brain Tumor Translational Research Group at the UKB and the University of Bonn. "*Core2Edge* allows us to study these infiltrative tumor cells in a model based entirely on human tissue, closely mirroring what we see in patients."

Core2Edge combines glioblastoma organoids with human brain tissue in a single model

The research team from the Departments of Neurosurgery and Neuro-Oncology at the UKB combines glioblastoma organoids - miniature tumor tissues grown from freshly resected patient material - with organotypic human brain-slice cultures. The slices are prepared from brain tissue that is routinely removed during neurosurgical procedures to access deeper target regions and would otherwise be discarded. For *Core2Edge*, the organoids are implanted into the brain slices and co-cultured with the surrounding tissue. This allows tumor spread in human brain tissue to be tracked from the tumor core to individual infiltrating tumor cells, as they are found in brain regions distant from the solid tumor mass.

To visualize this process, the team uses high-resolution light-sheet fluorescence microscopy. After fixation, the tissue is first evenly expanded to improve light penetration and enhance the visibility of fine structures. The sample is then scanned layer by layer, creating three-dimensional images of the entire tumor-infiltrated brain volume –down to single-cell resolution. "This allows us not only to quantify tumor cell spread in three dimensions, but also trace

morphology down to individual infiltrating cells," explains first author Ahmad Melhem, who co-developed the *Core2Edge* model as part of his doctoral research. "This approach provides a detailed view of the earliest steps of invasion and the spatial organization of tumor cells infiltrating the human brain."

In addition to high-resolution microscopy, the team also applied spatial transcriptomics. This technology reveals which genes are active in individual tumor cells and where exactly these cells are located in the tissue. This is particularly important in glioblastoma, as glioblastoma cells differ markedly in their genetic activity states even within a single tumor. This so-called intratumoral heterogeneity is considered a key driver of therapy resistance: individual cell populations survive radiation and chemotherapy more effectively and give rise to renewed tumor growth. "We were able to show that *Core2Edge* recapitulates intratumoral heterogeneity. This provides further evidence that the model closely reflects the situation in patients", says Dr. Anna-Laura Potthoff, neurosurgeon and clinician scientist at the Brain Tumor Translational Research Group. *Core2Edge* thus lays the foundation for future research into which cellular programs are active in the infiltration zones and which therapeutic targets may emerge to delay or prevent tumor recurrence.

Beyond its contribution to glioblastoma research, the model reduces reliance on animal experiments. "As key aspects of glioblastoma biology - especially infiltration and intratumoral heterogeneity - can be studied directly in human tissue, *Core2Edge* offers a scientifically and ethically compelling alternative to animal models," Schneider says.

Scientists involved in Bonn:
The study of the Brain Tumor Translational Research Group from the Department of Neurosurgery (Director: Prof. Dr. Hartmut Vatter), the Department of Neuro-Oncology (Director: Prof. Dr. Ulrich Herrlinger) and the Department of Neuropathology (Director: Prof. Dr. Torsten Pietsch) was carried out in collaboration with Dr. Juan E. Rodriguez Gatica and Prof. Dr. Ulrich Kubitscheck (both Clausius Institute for Physical and Theoretical Chemistry, University of Bonn), Prof. Dr. Andreas Schlitzer (Life & Medical Sciences Institute (LIMES), University of Bonn), Dr. Martin Schwarz (Institute for Experimental Epileptology and Cognitive Research, UKB), and Prof. Dr. Michael Hölzel (Institute for Experimental Oncology (IEO), UKB).

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Further information on the Brain Tumor Translational Research Group is available at:
https://www.ukbonn.de/neurochirurgie/forschung/onkologische-forschung/

Publication: Ahmad Melhem, Barbara E. F. Pregler et al.: *Core2Edge*: A human glioblastoma organoid-brain slice model capturing infiltration and transcriptional heterogeneity from core to single-cell dispersion; *Nature Protocols*; DOI: https://doi.org/10.1038/s41596-026-01412-3

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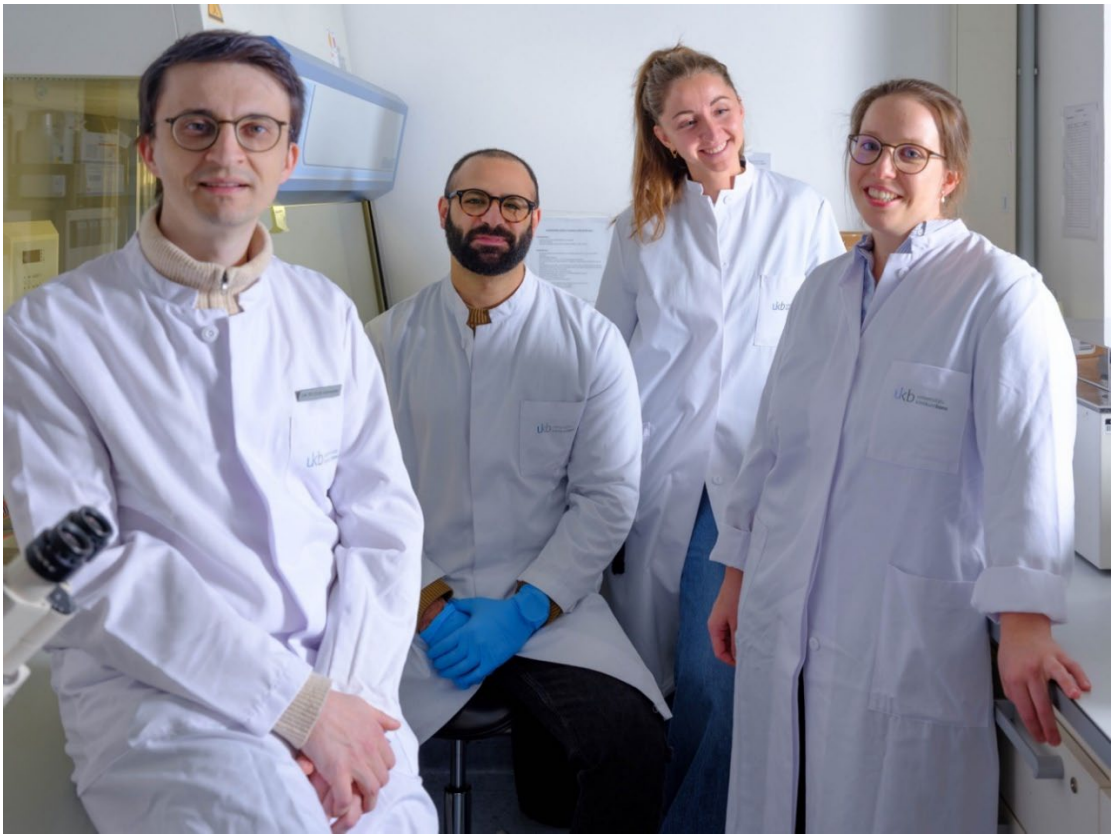
Image material:



Caption:
Tracking glioblastoma cell spread in human brain tissue: The *Core2Edge* model:
(from left to right) Priv.-Doz. Dr. Matthias Schneider, Ahmad Melhem, Barbara Pregler, and Dr. Anna-Laura Potthoff have developed a fully human glioblastoma model that replicates tumor cell infiltration into remote regions of the human brain.

Image credit: University Hospital Bonn / Aljoscha Mismas

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About the University Hospital Bonn: As one of Germany's leading university hospitals, Bonn University Hospital (UKB) combines excellence in medical care and research with high-quality teaching. Every year, UKB treats more than half a million outpatients and inpatients. Around 3,500 students are enrolled in medicine and dentistry, and over 600 individuals receive training in healthcare professions annually. With around 9,900 employees, UKB is the third-largest employer in the Bonn/Rhein-Sieg region. In the „*Focus* hospital rankings", UKB is rated the top university hospital in North Rhine-Westphalia and has the second-highest case mix index (an indicator of treatment complexity) of all university hospitals nationwide. In 2025, UKB secured nearly €100 million in third-party funding for research, transfer, and teaching. For the fourth consecutive year, the F.A.Z. Institute recognized UKB as both "Germany's Training Champion" and "Germany's Most Desirable Employer." For current figures and further information, please refer to the annual report at: geschaeftsbericht.ukbonn.de