Neuro-Oncology
XX(XX), 1–2, 2024 | https://doi.org/10.1093/neuonc/noae233 | Advance Access date 24 December 2024

Next step towards functional precision medicine in neuro-oncology

Tobias Weiss, Sohyon Lee, Berend Snijder, and Michael Weller

Department of Neurology, Clinical Neuroscience Center, University Hospital and University of Zurich, Zurich, Switzerland (T.W., M.W.); Institute of Molecular Systems Biology, ETH Zurich, Zurich, Switzerland (S.L., B.S.)

Corresponding Author: Tobias Weiss, MD, PhD, Department of Neurology, Clinical Neuroscience Center, University Hospital Zurich and University of Zurich, Frauenklinikstrasse 26, 8091 Zurich, Switzerland (tobias.weiss@usz.ch).

The concept of precision medicine aims to identify the optimal treatment for a given patient. There are essentially 2 main strategies that guide this approach: (1) Static *omics*-driven profiling to identify actionable molecular alterations for targeted therapy and (2) functional profiling,[1,2] where living cancer cells are directly exposed to drugs and the dynamic responses such as increased cell death, reduced proliferation, or decreased cancer cell numbers are measured to assess the anti-tumor activity of the drugs. In the context of glioblastoma, actionable mutations are rare, and therefore -*omics*-driven approaches lead to personalized treatments only in a minority of patients.[3] Therefore, functional precision medicine approaches are emerging as an attractive alternative. These functional platforms typically relied on patient-derived models, such as cell lines, patient-derived organoids (PDO),[4] or patient-derived xenografts.[5] However, generating these models can be time-consuming and success rates vary by tumor type, with more aggressive cancers generally having a higher chance of successful model establishment. An alternative approach is to use acute tumor samples directly, without the need for cultivation.

In the current study, Lee et al.[6] "High-throughput identification of repurposable neuroactive drugs with potent anti-glioblastoma activity" published in Nature Medicine, we employed an *ex vivo* drug testing platform using acutely dissociated glioblastoma patient samples. This platform integrates immunofluorescence with automated microscopy and computer vision and machine learning algorithms to examine drug effects within a brief *ex vivo* cultivation period of 48 h, which preserves cellular heterogeneity. The platform provides readouts on a single-cell level, enabling not only to quantify the anti-cancer efficacy of each drug, but also to evaluate its specificity for malignant versus nonmalignant cells. While this method has been applied to hematological malignancies,[7] this is the first study of its use with brain tumor samples.

In the study, we profiled dissociated tumor samples from 27 glioblastoma patients with confirmed *IDH*-wildtype status using a drug library of 132 compounds, 67 of which are repurposable neuroactive drugs typically used for neurological disorders like epilepsy, psychiatric disorders, or neurodegenerative diseases. We found that higher *ex vivo* responses to temozolomide, the standard chemotherapeutic drug for glioblastoma, were associated with longer progression-free survival and overall survival. Additionally, we identified several promising neuroactive drugs as candidates for repurposing, with the antidepressant vortioxetine showing the strongest selective reduction in cancer cells compared to nonmalignant cells. This promising anti-glioma activity was further validated in complementary *in vitro* experiments using glioma cell lines and *in vivo* studies involving 2 orthotopic xenograft glioma mouse models. In the mouse models, vortioxetine prolonged the survival as monotherapy and exhibited synergistic effects when combined with temozolomide and lomustine. Other neuroactive drugs, including the antidepressants paroxetine and fluoxetine and the antipsychotic brexpiprazole, showed more modest anti-glioma activity.

To elucidate the mode of action, we used a range of experimental approaches including transcriptomic and proteomic profiling after drug exposure, as well as machine learning algorithms to identify key genes that differentiate drugs with anti-glioma activity from those without. This revealed that the neuroactive drugs with anti-glioma activity triggered a rapid calcium influx, followed by an upregulation of genes associated with the activator protein-1—B cell translocation gene pathway.

This study represents significant progress toward the broader application of functional precision medicine in neuro-oncology. It demonstrates the feasibility of rapid, *ex vivo* drug testing platforms that work directly with acute patient samples, avoiding the need for time-consuming cultivation. Additionally, it may underscore the potential of drug repurposing, particularly when combined with standard-of-care treatments.

However, several limitations remain. One limitation is the short 48-h drug exposure duration, which primarily measures cytotoxic effects and may overlook drugs with cytostatic properties that inhibit tumor growth over a longer period.

Therefore, other functional precision platforms with longer treatment durations, such as PDO, are likely to provide complementary information. Moreover, modes of action like anti-angiogenesis can barely be assessed. Another limitation of such *ex vivo* platforms is the potential discrepancy between the drug concentrations tested *ex vivo* and the actual concentrations to which tumors are exposed in patients. Moreover, the platform depends on the sufficient amount and quality of tumor tissue, emphasizing the importance of standardized, nondestructive tissue extraction methods and tissue handling. Finally, the platform relies on markers and morphologies to distinguish cancer cells from nonmalignant cells. This means the results only provide a proxy of anti-tumor activity, particularly for cancers where no perfect marker exists, like glioblastoma.

Future directions are multifaceted. From the research perspective, such precision medicine platforms could be particularly useful for studying tumors that are difficult to culture, such as meningiomas or isocitrate dehydrogenase (*IDH*)-mutant gliomas. From a clinical standpoint, there is a clear need for further validation through rigorous clinical trials. The clinical utility of potential personalized, precision treatments based on such platforms should be thoroughly assessed in prospective, ideally randomized clinical trials, and some efforts in this direction are currently underway. Furthermore, we need a clinical trial to evaluate the anti-glioma activity of vortioxetine in glioblastoma patients and caution patients against using antidepressants like vortioxetine outside of clinical trials, as the current findings are based solely on preclinical studies. We envision a randomized trial investigating vortioxetine in combination with standard-of-care treatment versus standard care alone in newly diagnosed glioblastoma patients.

Conflict of interest statement

B.S. is scientific co-founder and shareholder of Prevision Medicine AG and Graph Therapeutics. T.W. has received honoraria from Philogen. M.W. has received research grants from Novartis, Quercis and Versameb and honoraria for lectures or advisory board participation or consulting from Anheart, Bayer, Curevac, Medac, Neurosense, Novartis, Novocure, Orbus, Pfizer, Philogen, Roche and Servier. S.L. declares no competing interests.

Funding

This project has received funding from the European Research Council under the European Union's Horizon 2020 Research and Innovation Program (grant agreement nos. 803063, to B.S., and 898549, to S.L.) and from the Personalized Health and Related Technologies (PHRT) strategic focus area of the ETH Domain (project nos. 2021-566, to B.S.). We acknowledge funding from the Swiss National Science Foundation (grant no. 310030_185155, to M.W.), the Swiss Cancer Research Foundation (KFS-5763-02-2023, to T.W.), the European Molecular Biology Organization (EMBO ALTF 956-2019, to S.L.), the Promedica Foundation (to T.W.), the Baasch-Medicus Foundation (to T.W.), the Sophien Foundation (to T.W.) and the Helmut Horten Foundation (to T.W.). The text is the sole product of the authors and no third party had input or gave support to its writing.

References

1. Letai AF. Precision cancer medicine-moving beyond pure genomics. *Nat Med*. 2017;23(9):1028–1035.
2. Letai A, Bhola P, Welm AL. Functional precision oncology: Testing tumors with drugs to identify vulnerabilities and novel combinations. *Cancer Cell*. 2022;40(1):26–35.
3. van den Bent MJ, Franceschi E, Touat M, et al. Updated EANO guideline on rational molecular testing of gliomas, glioneuronal, and neuronal tumors in adults for targeted therapy selection - Update 1 [published online ahead of print October 10, 2024]. *Neuro Oncol*. doi:10.1093/neuonc/noae213
4. Jacob F, Salinas RD, Zhang DY, et al. A patient-derived glioblastoma organoid model and biobank recapitulates inter- and intra-tumoral heterogeneity. *Cell*. 2020;180(1):188–204.e22.
5. Golebiewska A, Hau A-C, Oudin A, et al. Patient-derived organoids and orthotopic xenografts of primary and recurrent gliomas represent relevant patient avatars for precision oncology. *Acta Neuropathol*. 2020;140(6):919–949.
6. Lee S, Weiss T, Bühler M, et al. High-throughput identification of repurposable neuroactive drugs with potent anti-glioblastoma activity. *Nat Med*. 2024.
7. Snijder B, Vladimer GI, Krall N, et al. Image-based *ex-vivo* drug screening for patients with aggressive haematological malignancies: interim results from a single-arm, open-label, pilot study. *Lancet Haematol*. 2017;4(12):e595–e606.