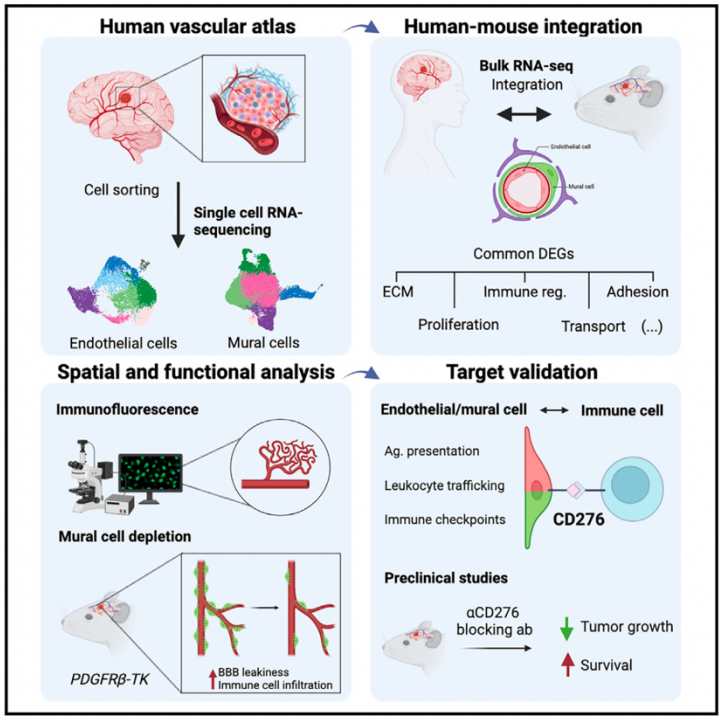
EVBO Paper-of-the-month - March 2024

Leire Bejarano, Annamaria Kauzlaric, Eleni Lamprou, Joao Lourenco, Nadine Fournier, Michelle Ballabio, Roberto Colotti, Roeltje Maas, Sabine Galland, Matteo Massara, Klara Soukup, Johanna Lilja, Jean-Philippe Brouland, Andreas F. Hottinger, Roy T. Daniel, Monika E. Hegi, and Johanna A. Joyce. Interrogation of endothelial and mural cells in brain metastasis reveals key immune-regulatory mechanisms. *Cancer Cell* 2024

The March 2024 EVBO Paper-of-the-month presents a study led by Prof. Johanna Joyce and Dr. Leire Bejarano from Ludwig Cancer Research Lausanne which interrogates the vascular component of the brain tumor microenvironment. The study focuses on brain metastasis from melanoma, lung and breast cancers, and unravels the heterogeneity of endothelial and mural cells in those clinically challenging tumors. It also develops a preclinical platform designed to evaluate potential therapeutic targets in brain metastasis mouse models.



Using a variety of techniques including single-cell and bulk RNA-seq analysis of FACS-sorted endothelial and mural cells, the team scrutinizes the cellular and molecular diversity of those cells in brain metastasis pointing to their altered transcriptomes as compared to non-tumor controls and high degree of heterogeneity. Moreover, the authors identify endothelial and mural cell clusters that are specifically associated with brain metastasis, while absent in the non-tumor controls. By creating a pre-clinical platform integrating human and mouse data, the authors show that the brain tumor metastasis-associated vascular alterations are conserved in brain metastasis mouse models, including pathways related to immune regulation, BBB dysfunction and cell adhesion.

Among the common vascular targets emerging from the interspecies analysis, is the immunomodulatory molecule CD276 (B7-H3), which was upregulated in both the human and mouse brain metastasis vasculature. As proof-of-concept, utilizing CD276 blocking antibodies decreased the tumor growth, increased the survival rate of mice bearing murine brain metastasis, moreover this was associated with increased expression of leukocyte adhesion molecules as *ICAM-1* and *VCAM-1*, and increased abundance of cytotoxic T-cells in the tumor microenvironment, highlighting the importance of the tumor vasculature in regulating the intra-tumor immune response. The insights garnered from this study emphasize the importance of integrated human-mouse analysis in identifying novel therapeutic strategies for brain tumors.