# Exploring the role of neutrophils in brain metastasis

## Summary of the project

*Prof. Johanna Joyce*

The development of metastases unfortunately remains the leading cause of death in cancer patients. Of all metastatic cancers, those invading the brain represent a particularly difficult challenge to treat. Brain metastases (BrM) frequently arise from melanoma, lung and breast cancers. Although considerable advances have been made in treating these cancers at the primary site, a steep increase in mortality is observed in patients who develop BrM. This is partly due to our limited knowledge about the BrM tumour microenvironment (TME), which directly translates into a lack of clinical treatment options.

While the importance of immune and stromal cells in the TME in shaping a favourable environment for tumour growth is well-established, much less is known about the complexity of these interactions during metastasis. This is particularly true for BrMs, where the unique properties of the brain create an environment that is very different to other organs. By comprehensively analysing the TME in diverse brain tumour patient samples, we recently identified neutrophils, the most numerous circulating white blood cell population in humans, as among the most abundant immune cells infiltrating BrM specifically.

The aim of this project led by Prof. Johanna Joyce (Department of oncology, UNIL, Ludwig Institute for Cancer Research Lausanne), is to unravel how neutrophils may functionally contribute to the colonisation and metastatic outgrowth of cancer cells in the brain. It represents the first in-depth study of neutrophil phenotypes and functions in BrM patients and preclinical models.

The rigorous and integrated experimental strategy devised by the Joyce lab, including both mouse models and human tissue analyses, will provide the first comprehensive view of how neutrophils may regulate metastatic progression to the brain. Neutrophils have generally been associated with poor prognosis in cancer patients, but have also been found to serve opposing functions in other metastatic settings, specifically breast-to-lung metastasis, in a context-dependent manner. By contrast, the role of neutrophils in the context of BrM remains virtually unexplored. Thus, a rigorous analysis of their functions in BrM is urgently needed. The combination of functionally analysing neutrophils in human BrMs and utilising state-of-the-art murine BrM models represents a comprehensive strategy to explore neutrophil education by brain-colonising cancer cells. Critically, these data will reveal how neutrophils in the periphery and the brain TME evolve with, and contribute to, the progression of metastatic cancers. Regardless of whether we discover neutrophils to be tumour-supporting or tumour-suppressing in BrM, this is an essential question to answer, which we are uniquely capable to address.

This project will significantly enhance our understanding of neutrophil functions in metastasis and may have important implications for devising therapeutics to target the BrM TME in the future. The cancer immune-microenvironmental perspective of this project additionally addresses a topic of intense focus at present, as different immunotherapies are rapidly advancing to first-line treatments for many cancer types. However, patients presenting BrMs have been largely excluded from clinical trials, resulting in a critical lack of knowledge for how

novel treatment modalities might specifically affect or benefit intracranial metastases. Thus, the advance in knowledge that we expect to achieve through this ISREC-funded project will provide the necessary bridge linking fundamental research on BrM tumour immunity to answering essential clinical questions.