Modeling and Investigating the Tumor Microenvironment of Non-Small Cell Lung Cancer Brain Metastasis

MD-PhD project summary – September 2021

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Lung cancer, including the most common type, non-small cell lung cancer, is the leading cause of cancer-related deaths worldwide. Metastasis represents the final stage of lung cancer progression, when cancer cells have successfully spread to a new organ and colonized it. Critically, 20-40% of lung cancer patients develop brain metastasis over the course of the disease progression. We urgently need to devise novel therapies for lung cancer brain metastasis because, first, more than 50% of the patients die in the year following diagnosis, and second, these metastases cause deaths in patients in which the disease in the lung and other sites of metastasis is under control. However, the lack of animal models that faithfully represent human lung cancer brain metastasis impedes our current understanding of the underlying molecular mechanisms. Yet this information is urgently required for the identification of the unique vulnerabilities of these mechanisms for future therapeutic targeting.

In this project, we will take advantage of our collaborations with pathologists, surgeons and scientists within the Swiss Cancer Center Léman and overseas, to reveal novel therapeutic combinations that target the non-cancerous cells in the tumors (the tumor microenvironment), including the immune cells. We will generate a first of its kind mouse model of lung cancer that recapitulates all the steps of lung cancer brain metastasis. Since these mice will have an intact immune system (which is not the case in many current models), we will be able to determine how the body's defenses react to lung cancer metastasis in the brain, and identify therapies that can boost this response. In parallel, we will leverage novel technologies that describe the cellular interactions that determine how the non-cancerous cells react to the cancer cells and where these interactions occur in the tumor. By performing these analyses in patient samples and in our animal model, we aim to identify yet unappreciated vulnerabilities in the non-cancerous cells of lung cancer brain metastasis, which we will target in our novel mouse model. We hope that this will ultimately lead to a personalized management of non-small cell lung cancer brain metastasis, whereby rationally designed treatments will target distinct molecular subtypes.