Development of a novel B cell-based vaccine for metastatic solid cancers

Project

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It is now well established that the immune system plays a very important role in controlling tumor growth; in fact, the remarkable results achieved in the past few years with the arrival of cancer immunotherapies and checkpoint inhibitors have clearly revolutionized the field of oncology and have dramatically changed the therapeutic scenario in many tumor types. Among the different cancer immunotherapies now available, cancer vaccines focus on the therapeutic use of a special type of immune cells called antigen-presenting cells (APCs). The main physiological role of these cells is to intercept and recognize pathogen-associated and foreign material (called antigens), and to subsequently initiate an immune response aimed at clearing the original antigen-containing threat from the host. Given the pivotal role played by APCs in orchestrating an immune response, it comes as no surprise that this type of cells has been employed since the infancy of modern cancer immunotherapy in the fight against cancer. Canonical approaches have so far relied on the use of a special type of APCs called dendritic cells (DCs), which have long been considered the most potent type of APCs in the human body. However, despite proving generally safe and being associated with very mild collateral effects, DC-based therapeutic vaccines have so far demonstrated limited therapeutic efficacy. Mounting evidence now suggests that a second type of APCs called B cells present a valid alternative with several advantages. First of all, B cells can be obtained and expanded in large quantities from the human body, while cell availability often constitutes a limiting factor with DC-based vaccines. Contrary to DCs, B cells are also resistant to functional inhibition induced by tumor-produced factors, another aspect often limiting DC therapeutic efficacy. Several previous studies have also shown that B cells are indeed able to induce a potent and cancer-specific immune response.

Based on this collective evidence, our project focuses on developing a novel therapeutic vaccine against cancer, based on B cells. One of the first project goals is to manipulate and engineer B cells to express special receptors that increase their accumulation at the tumor site after infusion into the patient. This aspect is obviously crucial in improving their efficacy against their tumor targets and in limiting off-side and systemic effects. In a second phase, we will test our B cell vaccine formulation in combination with checkpoint blockade inhibitors, another promising immunotherapy with a different and complementary mode of action. Checkpoint blockade refers to specific pathways normally developed by tumors that inhibit T cell activities, exerting a sort of “break” on the function of the immune system and anti-cancer properties. Thus, combining these two therapies constitutes an interesting potential therapeutic option, in which B cells would activate the immune system (more specifically T cells) against tumor targets, whilst checkpoint blockade inhibition would remove inhibitory

“breaks” on T cell function and unleash these cells’ true anti-cancer potential.

In the last part of this project and thanks to the infrastructure for translational studies available at the University Hospital of Lausanne and at the Ludwig Institute (Lausanne Branch), we will also develop protocols and tests for an efficient production of our B cell final formulation in a good manufacturing practices (GMP) context, so as to enable its future application in clinical studies and patient tests. The requirements for testing cellular therapies in patients (usually referred to as GMP conditions) are obviously very different and stricter than laboratory bench and animal research settings, and a great deal of work is usually needed to adapt therapy production in order to meet such requirements. Thus, the validation of the findings of this project in a GMP context will pave the way for future translational studies in cancer patients, and will potentially help advance both the therapeutic scenario and clinical outcomes.