

Development of multispecific fusion proteins inducing targeted lysosomal degradation of receptors inhibiting the activity of immune system

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Despite significant advancements in oncology in recent years, cancer is still among the top death causes in highly developed countries. Development of immunotherapy gives hope to many suffering from cancer, who would have significantly lower survival chances when treated with chemotherapy. Unfortunately, not all patients respond equally to immunotherapy. The reason behind this is still not well understood, as individual differences between cancers of the same type can be significant. One of the approaches to overcome this problem is to create molecules with innovative mechanisms of action. An example of such molecules is Lysosome Targeting Chimeras (LYTAC) developed within the scope of the present dissertation. LYTACs are bispecific compounds that exhibit affinity for a selected molecular target (intended for degradation) and - at the same time - a receptor which induces lysosomal trafficking. Herein, IGF2R (CI-M6PR) has been selected as the lysosome-targeting receptor. In the course of the work, it was shown that the developed molecules are capable of inducing internalization of a selected immune checkpoint (PD-L1) in both soluble and transmembrane forms. The intensity of internalization depends on time and applied LYTAC concentration. A significant distinguishing feature of the molecules developed within this work is that they are completely genetically encoded (there is no need for chemical modifications) and they do not exhibit affinity for IGF1R. In principle, these molecules should induce a response analogous to the immune checkpoint blockade achieved with monoclonal antibodies. Engineered LYTACs induced significantly higher levels of tumor cell lysis in comparison with monoclonal antibodies approved for human use that are directed at the same molecular target. Targeted degradation technologies offer hope for the introduction of future therapies based on new mechanisms, targeting not only cancers but also other diseases for which finding an inhibitor using classical methods of rational drug design (such as Alzheimer's disease) is impossible.