Development of novel anti-cancer immunotherapy against mesothelioma comprising of oncolytic adenovirus vectors armed with ICOS and CD40 ligands in combination with checkpoint inhibitors anti-PD-1 and anti-CTLA-4

The proposed research project seeks to develop a new treatment regime in mesothelioma therapy. Therefore, to continue a new research front within the field of immuno-oncology utilizing oncolytic adenoviruses in Poland. Despite major advances in cancer treatments by surgery, chemotherapy, radiotherapy, immunotherapy and their combination, the outcome remains partially ineffective against numerous cancer types like mesothelioma. Furthermore, due to resistance factors and the subsequent loss of response, which may occur rapidly during the conventional treatment regimes, new anti-cancer agents, presenting new mechanisms of action and lacking cross-resistance to commonly used therapies, are in high demand. Malignant mesothelioma (MM) is a treatment-resistant cancer to standard therapies with no effective curative options for advanced cancer patients.

Until recently, the only approved treatment was combination chemotherapy with cisplatin and pemetrexed, with carboplatin and pemetrexed an alternative. In 2020 combination immunotherapy was approved in mesothelioma, after ipilimumab plus nivolumab demonstrated improved overall survival (OS) as compared with cisplatin and pemetrexed. An OS benefit has been reported in patients treated with combination immunotherapy (anti-PD-1 (nivolumab) anti-CTLA-4 (ipilimumamb)) compared to chemotherapy [4]. Nevertheless, the objective response rate in the nivolumab plus ipilimumab arm was only 40% versus 44% in the chemotherapy, suggesting that there is an unmet medical need for mesothelioma therapy.

Oncolytic virotherapy is a promising anti-cancer strategy, and the approval of the first oncolytic virus, Imlygic (T-Vec, talimogene laherparepvec), in Western world by US Food and Drug Administration (FDA) and European Medicines Agency (EMA) has opened new perspectives for improved treatment of cancer. Recently also in Japan oncolytic virotherapy Delytact (G47Δ; teserpaturev) was approved for the treatment of malignant glioma.

In this project it has been hypothesized that by combining unique oncolytic adenovirus expressing ICOS ligand (ICOSL) and CD40 ligand (CD40L) with checkpoint inhibitors (CPIs) we could improve anti-cancer efficacy through synergistic anti-cancer effect.

This research project offers challenges in the field of drug delivery for targeted cancer therapy. The investigated treatment strategy will have a wide positive impact in academic and healthcare field. The expected outcome of this research will bring possibility to improve mesothelioma treatment. Oncolytic adenoviruses have been used for a long time, and although they have been tested in different clinical scenarios, the results have thus far been modest. Recently, oncolytic viruses have substantially increased interest because the real potential of viruses as vaccine platforms (rather than as simple cytolytic agents) has finally been demonstrated. However, their use as oncolytic vaccines is limited due to low efficacy. This project aims to overcome this limitation by combining immunogenic AdV-D24-ICOSL-CD40L with anti-PD-1 and anti-CTLA-4 toward synergistic anti-cancer interactions. This feature renders this approach for development of patient's oncolytic vaccines. If successful, this project can be tested in a Phase I clinical trial. Moreover, the findings will provide important information to basic tumour immunology and immunotherapy, including knowledge on mechanism of action, comprehensive immunogenomic profile of the tumour and its microenvironment (broad immunogenomic characterization).