ImmunoTools *special* Award 2014

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The prognostic and predictive value of the cMET-signalisation pathway and preclinical research to HGF-and cMET inhibition through mono-and combinational therapy in lung cancer treatment

Lung cancer is the second most prevalent and the deadliest cancer worldwide (5-year survival of 10%). Lung cancer mostly consists of predominantly malignant epithelial tumours; these can be divided in two main categories: small cell lung cancer (SCLC) and non small cell lung cancer (NSCLC). The treatment of lung cancer consists of surgery, chemotherapy, radiotherapy and targeted molecular therapies (EGFR and ALK inhibitors). A good selection of patients for a given therapy is crucial, not only to provide the correct treatment to patients who will benefit from it, but also for the economy. A second problem is the acquired resistance to chronic treatment.

In this project we want to study the role of the cMET (hepatocyte growth factor receptor) pathway in SCLC and NSCLC. Research has indicated that a disturbed cMET signalisation plays an important role in cancer cell migration and metastasis. A disturbed cMET activation is also a known resistance mechanism against EGFR inhibitors. By gaining more insight in the cMET pathway we want to achieve better and novel treatment options.

The first part of the project will evaluate the potential of the cMET pathway as a prognostic and predictive marker in lung cancer. The extent of a dysregulated cMET pathway will be determined in the different subtypes of lung cancer. The amount of clonal selection in metastasis will be studied; next to the predictive value of cMET activation for metastasis. The connection between the cMET pathway and the MDM2/p53 pathway will be studied. Finally we will try to link miRNAs with cMET activation and develop methods to trace these miRNAs in serum samples, so they can be used for an earlier detection of metastasis in lung cancer.

In the second part of the project we will take a look at the inhibition of the cMET pathway as a treatment in lung tumours. Hereby the influence of cMET and HGF inhibitors will be tested on lung cancer cell lines, under normoxia and hypoxia, and in the presence of different concentrations of rhHGF from ImmunoTools. Next the synergistic effects of these inhibitors will be evaluated in combination with other therapies (chemo, radiotherapy, EGFR-inhibitors, anti-apoptotic inhibitors and

angiogenesis inhibitors). Finally the activation of NK cells by the selected antibody-based inhibitors will be tested by co-culturing the tumour cells with NK cells and peripheral blood monocytes. NK-cells will be isolated by flow cytometry with use of ImmunoTools conjugated antibodies. The cytotoxicity of these inhibitors will be tested by the flow cytometry cytotoxicity assay with ImmunoTools conjugated antibodies. To confirm the results of the above mentioned assays on stable cell lines, we will also test these inhibitors on primary cell lines that will be isolated from freshly resected lung tumours. These cells will be cultured in serum-free media supplied with a mixture of ImmunoTools growth factors. From these tests the most beneficial cMET status criteria for a given treatment can be determined, so a good patient selection can follow. Finally we will try to identify and overcome the resistance mechanism against cMET and HGF inhibitors.