ImmunoTools *special* Award 2018

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The potential and underlying mechanisms of therapeutic activation of p53 with immunotherapy to stimulate an innate immune response in non-small cell lung cancer

Non-small cell lung cancer (NSCLC) accounts for more than 80% of all lung cancer cases and is responsible for over 1 million deaths each year. At present, platinum-based doublet chemotherapy remains the backbone of advanced NSCLC therapy, but this is often associated with severe side-effects and poor response due to therapy failure and resistance. Therefore, the discovery of new treatment strategies for NSCLC is imperative.

In recent years, there is a shift from more general non-specific treatments to targeted treatments, depending on the molecular background of individual tumors. Almost half of all NSCLC patients carry a genetic abnormality in their *TP53* tumor suppressor gene, which contributes to NSCLC development, chemoresistance and unfavorable prognosis. This makes p53 an interesting therapeutic target with compounds that restore both wild type and mutant p53 function already used in clinical trials.

In addition, an arising field in cancer research that opens new perspectives for NSCLC treatments is immunotherapy, designed to boost the body's natural defenses to fight cancer. Immunotherapy has already proven its value in a specific subset of NSCLC patients, leaving room for improvement to help more patients and to increase survival rate.

My PhD project aims to combine targeted p53- and immunotherapy to improve the outcome for NSCLC patients. I want to explore the link between p53 and innate immunity, based on literature that suggests a critical function for p53 in human cancer cells in stimulating natural killer (NK) cells. The majority of (novel) immunotherapeutic strategies focuses on activating T cells. However, innate immune cells, especially NK cells, are less sensitive to suppression by current chemotherapeutic treatments and are shown to be attractive effectors in immunotherapeutic treatments. In addition, most

therapeutics investigated to promote innate immune responses against cancer can be used ‘off the shelf’ and do not require complex, patient-specific, ex vivo cellular or molecular creation of compounds.

I will perform *in vitro* experiments, including allogeneic and autologous co-cultures of tumor cells and immune cells, to test the possibility of anti-tumor immunity after therapeutic reactivation of p53. Recruitment of NK cells to the tumor cells is an important hallmark in the activation of an innate immune response, which can be established by the secretion of chemokines in the tumor microenvironment. Several studies implicate that the genetic reactivation of p53 induces a senescent state of the tumor cells, characterized by the secretion of soluble factors, which includes numerous proinflammatory chemo- and cytokines that regulate immune responses. Secretion of these soluble factors will be determined by ELISA-set from ImmunoTools (IFN-γ, IL-15, CXCL10, TNFa). NK cells can kill cancer cells via the expression or secretion of death ligands (TRAIL, FAS, TNFa) which trigger apoptosis pathways in the target cell. We will determine the therapy induced expression of the CD95 (Fas) receptor on the target cells using the CD95-PE antibody, and the potential antitumoral effect of TRAIL and TNFa using the corresponding recombinant human cytokines from ImmunoTools. The CD3-FITC and CD56-PE antibodies will be used to determine NK-cell purity.

Together, this project will create novel fundamental insights on newly designed combination strategies of p53-targeted therapies and immunotherapy in NSCLC. Reagents of ImmunoTools will be valuable assets to perform this study.

ImmunoTools *special* AWARD for **Laurie Freire Boullosa**

includes 25 reagents

FITC - conjugated anti-human CD3, Annexin V

PE - conjugated anti-human CD56, CD95, CD66adecb (CEACAM1/3/5/6/8)

recombinant human cytokines: rh TRAIL, rh TNFa

human ELISA-set (for one 96 plate), human IFN-gamma, human IL-15, human IP-10, human TNF-a

DETAILS more AWARDS