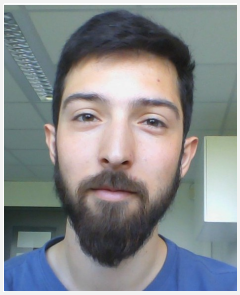
ImmunoTools *special* Award 2018



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Combined targeting of the epidermal growth factor receptor and the innate immune system: a novel therapeutic approach for the treatment of head and neck cancer

Head and neck squamous cell carcinoma (HNSCC) is a cancer type that has mostly been associated with tobacco and alcohol use and, more recently, with infection with high-risk types of human papillomavirus (HPV). Although advances in conventional anti-cancer treatments have increased the overall 5-year relative survival proportion above 50%, they are still limited in their effectiveness due to their toxic profiles. Our increasing knowledge regarding the molecular biology of different cancers has therefore led to the development of several new therapeutic strategies. Namely, the targeted inhibition of oncogenic signalling pathways, and the modulation of a patient's immune system towards the cancer are now at the forefront of personalized medicine in cancer treatment. Until recently, the monoclonal antibody (mAb) cetuximab has long been the only FDA-approved targeted therapy for HNSCC. This changed with the approval of the anti-programmed death protein 1 (PD1) immune-inhibitory antibodies pembrolizumab and nivolumab as second line treatment for recurrent and metastatic HNSCC. However, although both targeted and immunotherapies have shown great promise, either of these approaches have yet to result in a durable success in most patients. The lack of effectiveness has been attributed mainly to the heterogeneous nature of HNSCCs and molecular resistance mechanisms that bypass the signalling blockade to provide tumours with the potential for uncontrolled growth and, mediate escape from the immune system.

The epidermal growth factor receptor (EGFR) plays a fundamental role in the tumorigenesis of many cancer types, including HNSCC. In addition, EGFR is overexpressed in 90% of HNSCC, making it a compelling drug target. Interestingly, besides the direct receptor blocking effects of cetuximab, it can bind to specific membranous Fc receptors (CD16) present on immune cells, such as natural killer (NK) cells. This interaction is established with the FC portion of the antibody and induces an antibody-dependent cellular cytotoxicity (ADCC).

Furthermore, there is increasing evidence that NK cells, aside from their innate tumour cytolytic capabilities, may influence the adaptive immunity [12], making it a key effector of antitumor immunity. Importantly, the ability of NK cells to kill tumour targets has been studied extensively in various haematological malignancies, whereas NK cell-based therapy directed against solid tumours is still in early development. Therefore, in

our project, blockade of NK cell checkpoint receptors with agents targeting NK cell inhibitory receptors, such as KIR, will be investigated.

We are convinced that personalized medicine using combinations of targeted therapies with immunotherapy may achieve the much-needed progress in HNSCC treatment. Combination of targeted therapies with immunotherapies is a relatively new concept that hasn't been studied extensively. Importantly, in comparison to other immune infiltrated tumor types, HNSCC tumors are marked by the highest levels of NK cell infiltration. Thus, we are convinced that our rationale to strengthen NK cell immunotherapy through a combination with cetuximab can synergistically generate an immune mediated elimination of HNSCC cells that are resistant to treatment with cetuximab alone.

Since cetuximab has been shown to alter the expression of PD-L1 through IFN-γ, we will assess the expression of other immune checkpoint ligands, known to bind to checkpoint receptors on NK cells, on a panel of HNSCC cell lines. Therefore, analysis of these ligands with ImmunoTools antibodies will be an interesting way to gain more insight regarding the influence of cetuximab treatment on the expression of the immune checkpoint ligands.

In addition, we will generate an "immune checkpoint profile", by investigating the expression of several immune checkpoints that are expressed by subpopulations of NK cells identified using ImmunoTools antibodies.

This project has the exciting potential to provide more insight into the use of immune checkpoint inhibitors targeting the innate immune system, expanding the field of cancer immunotherapy beyond the current state of the art.

ImmunoTools *special* AWARD for **Hasan Baysal** includes 25 reagents

FITC – conjugated anti-human CD3, CD4, CD27, Control IgG2a, Annexin V
PE – conjugated anti-human CD4, CD8, CD27, CD44, CD105, Control IgG1, Annexin V
APC – conjugated anti-human CD44

recombinant human cytokines:
rh EGF, rh FGF-2, rh beta NGF, rh MCP1, rh GM-CSF, rh TRAIL, rh IL-2, rh IFN-γ

human ELISA-set (for one 96 plate): human TNF-a

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