ImmunoTools *special* Award 2014

Julie Jacobs, PhD-student

Supervisor: Prof. Dr. Patrick Pauwels

Faculteit Geneeskunde & Gezondheidswetenschappen, Laboratorium voor Kankeronderzoek en Klinische Oncologie, Universiteitsplein 1, CDE T3.13, B-2610 Wilrijk

Unraveling the role of CD27-CD70 signalling in different tumor types, resulting in the identification of new biomarkers

Cancer represents one of the largest unmet medical needs of western societies. This results partly from the aging of our populations as well as the therapeutic advances of the recent decades, which have modified the nature of most cancer indications from rapidly progressing illnesses to chronic, relapsing, rarely cured conditions. Immunological modulation of the host's anti-cancer response is a growing field in which targeted treatments lead to stimulation of the body's own immune response against tumors by taking the brakes off immune-inhibitory pathways. The therapeutic antibodies, Ipilimumab (Yervoy), blocking CTLA4 inhibitory pathway (recently approved for treatment of patients with late-stage melanoma) and BMS-636558, blocking the PD-1 immuno-inhibitory pathway, are in clinical development for a number of cancers. Both antibodies dramatically reduce tumor size in responding patients and Ipilimumab has been shown to dramatically enhance survival time. Clinicians indicate that in some cases complete cures from the cancer have been observed. However, response rates are still low, and side-effects in the form of auto-immunity of these immuno-stimulatory drugs have been very significant. Hence the need for more efficacious and safer cancer therapies remains urgent and very high.

ARGX-110 is a first in class, human antibody directed against the target CD70, involved in regulating the patient's anti-tumor immune response and the proliferation and survival of haematological tumors (leukaemias, lymphomas – both Hodgkin's and non-Hodgkin's - and myeloma) and certain solid tumors (i.e. cervical, renal, nasopharyngeal). ARGX-110 is designed to exhibit highly novel characteristics such that it strongly antagonizes CD70/CD27 signaling and also targets CD70-expressing tumor cells for destruction through Potelligent® enhanced ADCC properties

CD70 is chronically expressed on the tumor cells only, leading to a potentially large therapeutic index and excellent safety profile. In contrast to the broadly expressed CTLA-4, CD70 is only transiently expressed on activated B and T cells and mature dendritic cells. Whilst CTLA-4 is found on regulatory T cells, which are mediating

tumor induced immunosuppression, we postulate that CD70 modulates the activity of Tregs via the receptor CD27 expressed on this subset of cells. This is based on published data on tumor infiltrating lymphocytes (TILs) from a syngeneic mouse model as well as from lymphoma patient biopsies. Based on its triple mode of action ARGX-110 has the potential to become the drug of choice for future cancer treatments, overshadowing Ipilimumab and BMS-636558. This PhD project builds on the potential role of CD70 in tumor biology and intends to demonstrate that ARGX-110 will be the next generation cancer treatment having curative potential.

Only very few groups have studied the co-expression of CD27 and CD70 on tumours. Co-expression could theoretically result in signaling between tumor cells leading to proliferation and thus tumor growth. Therefore analysis of tumour biopsies and cell line for the (co)expression of both CD27 and CD70 with *ImmunoTools* antibodies will be an interesting way to gain more insight in the mechanism of tumor growth in different histologies.

Furthermore Yang and colleagues demonstrated the presence of increased numbers of activated regulatory T cells (Treg) in the biopsies taken from lymphoma patients. Whilst the lymphoma cells were shown to be CD70 positive, these could activate co-cultured Treg cells suggesting the presence of CD27 on this subset of T-cells. It is therefore considered of interest to study the number of Tregs with human conjugated *ImmunoTools* antibodies in different types of tumors and see if there is a link with CD27 and CD70 levels. In vitro co-culture experiments will allow us to further study the interaction between $CD70^+$ tumor cells and $CD27^+$ Tregs, and the effect of ARGX-110 mAb on this pathway tested by cytotoxicity assay with *ImmunoTools* conjugated antibodies.

This project has the exciting potential to create breakthrough insights into the tumor biology of CD70-CD27 signaling, expanding the field of cancer immunotherapy far beyond the current state of the art.

ImmunoTools *special* AWARD for **Julie Jacobs** includes 25 reagents

FITC - conjugated anti-human CD3, CD4, CD27, Control IgG2, Annexin V,

PE - conjugated anti-human CD8, CD4, CD44, CD105, CD27, Control IgG1, Annexine V,

APC - conjugated anti-human CD44,

human IL-4 ELISA-set for 96 wells, human TNFa ELISA-set for 96 wells (each 3 reagents),

recombinant human cytokines: rh EGF, rh FGF-2, rh beta NGF, rh MCP1, rh GM-CSF, rh TRAIL, rh IL-2, rh IFN-g, rh IL-4 DETAILS more AWARDS