TARGETING MARCO AND IL-37R ON ANTI-INFLAMMATORY MACROPHAGES IN LUNG CANCER BLOCKS REGULATORY T CELLS AND SHIFT BALANCE TO SUPPORT CYTOTOXIC LYMPHOCYTE FUNCTION

1Linnéa La Fleur, 2Johan Botling, 3Fei He, 1Catarina Pelciano, 1Giorgia Palano, 2Artur Medyheuski, 2Patrick Micke, 1Jeffrey Ravetch, 3Mikael Karlsson, 2Dhiaf Sarhan.
1Karolinska Institutet, Stockholm, Sweden; 2Uppsala University, Uppsala, Sweden; 3Rockefeller, New York, NY, USA

Background The progression and metastatic capacity of solid tumors are strongly influenced by immune cells in the tumor microenvironment (TME). In non-small cell lung cancer (NSCLC) accumulation of anti-inflammatory tumor-associated macrophages (TAMs) is associated with worse clinical outcome and resistance to therapy. Numerous clinical trials aiming to recover T cell anti-tumor activity have been failing due to the persistence immune suppression in TME. Thus, there is a clinical need for alternative treatments targeting the suppressive function of the TME. We have previously shown that antibodies targeting the scavenger receptor MARCO reprograms the pro-tumoral TAMs in murine cancer models. Here, we investigated the immune landscape of NSCLC in the presence of MARCO expressing TAMs. We tested targeting MARCO or the tumor mechanisms inducing MARCO on human TAMs and hypothesized that targeting these mechanisms will remodel the suppressive environment and relieve the anti-tumor responses to increase the efficacy of immunotherapy.

Methods To test our hypothesis, we first investigated the immune landscape of NSCLC in the presence of pro-tumoral MARCO+TAMs compared with tumors infiltrated by MARCO-TAMs. We next used RNAseq to analyze differential gene expression in NSCLC tumors infiltrated by MARCO positive or negative macrophages. In vitro, cytokine differentiated macrophages alternatively cultured with lung cancer cell lines were co-cultured with Natural Killer (NK) cells and T cells to mimic their interaction in the TME. Later, macrophages were treated with targeting antibodies and their phenotype and function were examined prior and following interaction with other immune cells.

Conclusions In summary, our data demonstrate a novel immune therapeutic approach targeting human TAM immune suppression of NK and T cell anti-tumor activities and remodel immune suppression.

REFERENCES

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AT1412, A PATIENT- DERIVED CD9 ANTIBODY IN PRECLINICAL DEVELOPMENT PROMOTING TUMOR IMMUNE INFILTRATION AND INDUCING TUMOR REJECTION

1Remko Schotte*, 1Julien Villaudy, 2Martijn Kedde, 1Wouter Pos, 1Daniel Go, 2Christien Fatmawati, 2Gemma Moiset, 2Etsuko Yasuda, 2Madalina Cercol, 2Esraa Frankin, 2Susan van Hal, 1Pauline van Helden, 2Els Verdegaa, 2Sjoerd van der Burg, 2Hergen Spits, 1Hans van Eenennaam. 1AIMM Therapeutics, Amsterdam, Netherlands; 2Leiden University Medical Center, Leiden, Netherlands

Background Adaptive immunity to cancer cells forms a crucial part of cancer immunotherapy. Recently, the importance of tumor B-cell signatures were shown to correlate with melanoma survival. We investigated whether tumor-targeting antibodies could be isolated from a patient that cured (now 13 years tumor-free) metastatic melanoma following adoptive transfer of ex vivo expanded autologous T cells.

Methods Patient’s peripheral blood B cells were isolated and tested for the presence of tumor-reactive B cells using A IMM’s immortabilisation technology. Antibody AT1412 was identified by virtue of its differential binding to melanoma cells as compared to healthy melanocytes. AT1412 binds the tetraspanin CD9, a broadly expressed protein involved in multiple cellular activities in cancer and induces ADCC and ADCP by effector cells.

Results Spontaneous immune rejection of tumors was observed in human immune system (HIS) mouse models implanted with CD9 genetically-disrupted A375 melanoma (A375-CD9KO) tumor cells, while A375wt cells were not cleared. Most notably, no tumor rejection of A375-CD9KO tumors was observed in NSG mice, indicating that blockade of CD9 makes tumor cells susceptible to immune rejection.CD9 has been described to regulate integrin signaling, e.g. LFA-1, VLA-4, VCAM-1 and ICAM-1. AT1412 was shown to modulate CD9 function...