Rao: None. B. van de Wiel: None. A.J. Spillane: None. R.A. Scolyer: F. Consultant/Advisory Board; Modest; MSD, Nera-care, Myriad, Novartis. A.M. Menzies: F. Consultant/Advisory Board; Modest; BMS, MSD Oncology, Novartis, Pierre Fabre, Roche. A.C.J. van Akkooi: B. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received); Modest; Amgen, BMS, Novartis. F. Consultant/Advisory Board; Modest; Amgen, BMS, Novartis, MSD, Merck, Merck-Pfizer, 4SC. G.V. Long: F. Consultant/Advisory Board; Modest; Aduro, Amgen, BMS, Mass-Array, Pierre-Fabre, Novartis, Merck MSD, Roche. C.U. Blank: B. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received); Modest; BMS, Novartis, Nanostring. F. Consultant/Advisory Board; Modest; BMS, MSD, Roche, Novartis, GSK, AZ, Pfizer, Lilly, Genmab, Pierre Fabre.

P01.16 EFFECTS OF THE STAT3 INHIBITORS ON SENESCENT TUMOUR CELLS

¹O Sapega*, ¹R Mikyskova, ²K Musilek, ¹J Bieblova, ³Z Hodny, ¹M Reinis. ¹Laboratory of Immunological and Tumour Models, Institute of Molecular Genetics of the ASCR, v. v. i., Prague, Czech Republic; ²Department of Chemistry, Faculty of Science, University of Hradec Kralove, Hradec Kralove, Czech Republic; ³Department of Genome Integrity, Institute of Molecular Genetics of the ASCR, v. v. i., Prague, Czech Republic

10.1136/jitc-2020-ITOC7.29

Background Cellular senescence is the process of cell proliferation arrest. Premature cellular senescence can be induced by chemotherapy, irradiation and, under certain circumstances, by cytokines. Senescent cells produce a number of secreted proteins and growth factors that may either stimulate or inhibit cell proliferation. One of the major cytokines that play role in regulation of cellular senescence is IL-6. IL-6/STAT3 signaling pathway represent decisive regulatory factors in cellular senescence. The objective of this study was to compare the effects of the STAT3 inhibitors on senescent and proliferative tumour cells. Further, the therapeutic potential of the STAT3 inhibitors was evaluated using murine tumour models.

Materials and Methods *In vitro*, as well as *in vivo* experiments were performed using TC-1 (model for HPV16-associated tumours) TRAMP-C2 (prostate cancer) cell lines. C57BL/6Ncrl mice, 7–8 weeks old, were obtained from Velaz (Prague, Czech Republic). Experimental protocols were approved by the Institutional Animal Care Committee of the Institute of Molecular Genetics (Prague, Czech Republic). STAT3 inhibitors, namely STATTIC, BP-102 (synthesised at the University of Hradec Kralove) and their derivatives were tested for their effects on tumour cells, such as cytotoxicity, ability to inhibit STAT3 phosphorylation, cell proliferation and tumour growth in syngeneic mice.

Results We have previously demonstrated that docetaxel-induced senescence in the TC-1 and TRAMP-C2 murine tumour cell lines, which was proved by *in vitro* (detection of increased p21 expression, positive beta-galactosidase staining, and the typical SASP capable to induce 'bystander' senescence), and *in vivo* experiments, using C57BL/6 mice [1]. Both TC-1 and TRAMP-C2 cells displayed elevated IL-6 secretion and activated STAT3 signaling pathway. Therefore, we tested efficacy of the STAT3 inhibitors on these cell lines. Cytotoxic and STAT3 phosphorylation inhibitory effects of the

inhibitors were observed in both proliferating and senescent cells. Antitumor effects of selected inhibitors were evaluated.

Conclusions Collectively, STAT3 is an attractive target for therapeutic approaches in cancer treatment and we can assume that inhibition of the STAT3 pathway can be used for elimination of the pernicious effects of the senescent cells.

REFERENCE

1. Simova J, Sapega O, Imrichova T, Stepanek I, Kyjaccova L, Mikyskova R, Indrova M, Bieblova J, Bubenik J, Bartek J, et al: Tumor growth accelerated by chemotherapy-induced senescent cells is suppressed by treatment with IL-12 producing cellular vaccines. *Oncotarget* 7: 54952-54964, 2016. This work was supported by the research grant No. NV18-05-00562 provided by the Grant Agency of the Ministry of Health of the Czech Republic.

Disclosure Information O. Sapega: None. R. Mikyskova: None. K. Musilek: None. J. Bieblova: None. Z. Hodny: None. M. Reinis: None.

P01.17 TIM-3/GALECTIN-9 PATHWAY CONTROLS THE ABILITY OF MALIGNANT CELLS TO ESCAPE HOST IMMUNE SURVEILLANCE. REGULATORY MECHANISMS AND THERAPEUTIC TARGETS

¹VV Sumbayev*, ¹IM Yasinska, ¹SS Sakhnevych, ²E Fasler-Kan, ³BF Gibbs. ¹University of Kent and Greenwich, Chatham Maritime, UK; ²Department of Pediatric Surgery, Department of Biomedical Research, Children's Hospital, Inselspital, University of Bern, Bern, Switzerland; ³Division of Experimental Allergology and Immunodermatology, University of Oldenburg, Oldenburg, Germany

10.1136/jitc-2020-ITOC7.30

Background Human cancer cells implement a variety of biochemical mechanisms which allow them to escape host immune surveillance resulting in disease progression. We have reported that the immune receptor Tim-3 and its natural ligand and possible trafficker galectin-9 determine the capability of human acute myeloid leukemia (AML) cells to evade cytotoxic immune attack.¹ Our further studies demonstrated that breast, colorectal and other human solid malignant tumour cells display high activity of this pathway² which can also be used for immune evasion. It is, however, important to understand the mechanisms which regulate the biochemical activity of Tim-3/galectin-9 pathway and expression of its components as well as the molecular basis of its capability to impair anti-cancer activity of cytotoxic lymphoid cells.

Materials and Methods In this study we used human cancer and non-malignant cell lines as well as primary human malignant tumour samples. We also used primary human T cells and natural killer (NK) cells. Western blot analysis, ELISA, quantitative real-time PCR, on-cell Western, immunohistochemistry, flow cytometry and biochemical assays were used as key instrumentals to conduct measurements.

Results We found that galectin-9 is used by human cancer cells to escape host immune surveillance. Cancer cells use various biochemical pathways to overexpress galectin-9. Regardless the biochemical background, transforming growth factor-beta (TGF-β) and transcription factor Smad-3 play crucial role in galectin-9 expression in human cancer cells. We identified the key receptors through which galectin-9 can then trigger killing of cytotoxic T lymphocytes and impairing of anti-cancer activity of natural killer cells.

Conclusions In this work, we report the biochemical mechanisms underlying overexpression of galectin-9 in human