Materials and Methods To complete this work we used human cancer and non-malignant cell lines as well as primary human malignant liquid (leukaemia) and solid tumour samples. We also used human primary natural killer (NK) cells and TALL-104 cytotoxic T cell line. Western blot analysis, on-cell and in-cell Western analysis, ELISA, quantitative real-time PCR, flow cytometry (including imaging flow cytometry) and biochemical enzyme activity were used as research tools.

Results We found that galectin-9 is highly expressed in human liquid (acute myeloid leukaemia (AML) and solid (breast, colorectal, brain etc.) tumour cells. G protein-coupled receptors of latrophilin family and their natural ligand fibronectin leucine rich transmembrane protein 3 (FLRT3) trigger externalisation/exocytosis, and, in some cases (e. g. AML), biosynthesis of galectin-9 and its receptor and possible trafficker Tim-3. Galectin-9 can be used to suppress anti-cancer immune responses by impairing cytotoxic activity of NK cells and killing T cells.

Conclusions We report the Tim-3-galectin-9 secretory pathway as one of the biochemical mechanisms operated by human cancer cells to escape host immune surveillance. Differential activities based on cell type of origin are discussed.

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P01.21 VALIDATION OF ROMO1 INHIBITORS AS THE MITOCHONDRIAL ROS ENHANCER FOR ANTICANCER DRUG DEVELOPMENT

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Background Chemotherapy in conjunction with surgical operations have been commonly used for the treatment of many tumors. However, a significant number of tumors fail respond to radiation therapy and/or chemotherapy because many forms of tumors appear to become less sensitive or resistant to radiation and anticancer drugs after consecutive treatments. Although extensive studies on the molecular mechanisms of resistance to chemo- and/or radiation therapy have been carried out, problems related to overcoming this resistance remain to be solved. Romo1 is a nuclear-encoded small transmembrane protein located in mitochondrial inner membrane. It is known to induce mitochondrial reactive oxygen species (ROS) production in response to various cellular stresses. For a decade, Romo1 has been studied in the context of mitochondrial ROS production, cancer cell invasion, inflammation, replicative senescence, and mitochondrial dynamics.

Materials and Methods We identified a Romo1 antagonist and tried to its efficacy as chemotherapy sensitizer using cancer cells and animal models.

Results A Romo1 antagonist can enhance the cellular levels of ROS, leading to tumor cell death. Its treatment induced the elevation of chemotherapy-induced oxidative damage of cancer cells. We also treated the Romo1 antagonist in combination with various chemotherapeutic agents.

Conclusions We suggest that Romo1 antagonist can enhance the cellular levels of ROS, leading to elevation of chemotherapy-induced oxidative damage of cancer cells. We also suggest that Romo1 is the new target to identify effective substances for development of chemotherapy sensitizer.

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P01.22 EXTENDING CAR T CELL THERAPY APPLICATIONS VIA DRUG INDUCIBLE CONTROL OF TRANSGENE EXPRESSION

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Background Adoptive transfer of chimeric antigen receptor (CAR)-modified T cells has emerged as a promising treatment modality for a broad range of cancers highlighted by the approval of Kymriah™ and Yescarta™ for the treatment of B cell malignancies. However, lack of control of CAR T cell function and consequent excessive inflammation in patients can result in severe side effects especially when targeting tumor-associated rather than tumor-specific antigens. Thus, temporal and tunable control of CAR activity is of major importance for the clinical translation of innovative CAR designs. While the activation of suicide switches results in the apoptotic elimination of the transferred cells, other strategies, e.g. anti-tag CARs or small molecule-gated CARs, enable the reversible control of CAR-mediated function at the protein level but are restricted to a particular CAR design. Focusing on the control of expression rather than CAR signaling, transcriptional regulators represent a versatile tool facilitating a wide range of CAR T cell applications.

Materials and Methods To maintain control over the infused CAR T cell product and mitigate risks for the patient, we describe here the development of an inducible switch system for the transcriptional regulation of transgene expression in primary, human T cells. Chemically regulated synthetic transcription factors composed of a zinc finger DNA-binding domain, an inducible control domain and a transcription activation domain were designed, screened for functionality, and evaluated in T cells regarding their potential to control CAR expression both *in vitro* and *in vivo*.

Results By screening, we identified a synthetic transcription factor, which shows high transcriptional output in T cells in the presence of a clinically relevant inducer drug and absence of background activity in the non-induced state. Using this system we were able to control the expression of a CAR recognizing the CD20 antigen present on B cells and B cell leukemic blasts. The addition of the inducer drug resulted in rapid expression of the anti-CD20 CAR on the T cell surface. Moreover, inducible anti-CD20 CAR T cells executed cytolytic activity against CD20 positive target cells and secreted cytokines upon stimulation *in vitro*. Effectivity in co-cultures was thereby comparable to T cells expressing the anti-CD20 CAR under a conventional constitutive promoter. Furthermore, we could fine-tune CAR activity by titrating the inducer concentration. By defining the time-point of induction, modulation of the onset of therapy was achieved. Upon inducer drug discontinuation, inducible CD20 CAR T cells lost CAR expression and concurrently all CAR-related functions, indicating that the 'on' and 'off' status can be tightly controlled by the administration of the drug. After pausing of CAR T cell-mediated activity, we could re-induce CAR expression suggesting complete reversibility of effector function. Finally, we were able to show that inducible CD20 CAR T cells mediate a