Background NL-201 is a de novo IL-2 and IL-15 receptor agonist designed with enhanced affinity for IL-2Rβγ and no binding interface for IL-2Rα (CD25). Previously, we reported that NL-201 stimulates selective proliferation of CD8+ effector T cells and NK cells, leading to increased CD8:Treg and NK:Treg ratios in the tumor microenvironment. As a result, NL-201 treatment led to robust single-agent antitumor activity in syngeneic murine tumor models at well-tolerated doses. Methods Here, we evaluated the antitumor activity of NL-201 in combination with established and exploratory cancer immunotherapies, including tumor-targeting monoclonal antibodies and immune checkpoint inhibitors (CPIs). Specifically, we evaluated NL-201 in combination with an anti-gp75 antibody (TA99) in a murine melanoma model, or anti-PD-1 and anti-PD-L1 antibodies in a CPI-resistant murine colon cancer model. Results NL-201 synergizes with TA99, anti-PD-1, and anti-PD-L1 to inhibit tumor growth more effectively than either agent alone. The synergy of NL-201 with TA99 may result from enhanced NK-mediated antibody-dependent cellular cytotoxicity (ADCC), while the synergy with CPIs may result from CD8+ T cell stimulation, which can turn ‘cold’ tumor micro-environments ‘hot’. Conclusions The broad activity of NL-201 across diverse tumor models and its potential to be combined with a variety of established and exploratory cancer immunotherapies to achieve synergistic antitumor activity highlights the opportunity for NL-201 to become a critical component of future immunotherapy regimens.

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0576

577 ENGINEERED NON-PATHOGENIC SYNTHETIC BIOTIC PRODUCING L-ARGININE SYNERGIZE WITH PD-1-BASED CANCER IMMUNOTHERAPY

Fernando Canale, 1Camilla Basso, 2Ning Li, 2Anna Sokolovska, 1Michela Perotti, 2Michael James, 2Wenjie Jin, 2Jean-Philippe Theurillat, 2Daniel Leventhal, 2Kip West, 1Jose Lora, 1Federica Sallusto, 2Roger Geiger*. 1Institute for Research in Biomedicine, Bellinzona, Switzerland; 2Synlogic Inc., Boston, MA, USA; 3Institute for Oncology Research, Bellinzona, Switzerland

Background The availability of L-arginine in tumors is a key determinant of an efficient anti-tumor T cell response. Consequently, the elevation of typically low L-arginine levels within the tumor may greatly potentiate the anti-tumor responses of immune check point inhibitors, such as PD-L1 blocking antibodies. However, currently no means are available to locally increase intra-tumoral L-arginine levels. Methods We used a synthetic biology approach to develop an engineered probiotic Escherichia coli Nissle 1917 strain that colonizes tumors and continuously converts ammonia, a metabolic waste product that accumulates in tumors, into L-arginine. Results Colonization of tumors with these bacteria elevated intra-tumoral L-arginine concentrations, increased the amount of tumor-infiltrating T cells, and had striking synergistic effects with PD-L1 blocking antibodies in the clearance of tumors. The anti-tumor effect of the living therapeutic was mediated by L-arginine and was dependent on T cells. Conclusions These results show that engineered microbial therapies enable metabolic modulation of the tumor microenvironment leading to enhanced efficacy of immunotherapies.

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0577

578 TUMOR SELECTIVE IMMUNE RESPONSES OF STA551, A NOVEL ANTI-CD137 ANTAGONIST ANTIBODY ACTIVATED BY EXTRACELLULAR ATP

Yoshinori Naita*, Mika Kamata-Sakurai. Chugai Pharmaceutical Co., Ltd., Kamakura, Japan

Background Agonistic antibodies targeting CD137 in clinic have failed due to severe hepatotoxicity, leading to the development of bispecific approaches that must rely on high tumor-associated antigen expression to crosslink CD137. Here we report on STA551, a novel anti-CD137 agonist antibody which binds to CD137 only in the presence of ATP. Extracellular ATP concentration is well-known to be elevated in tumor tissue while remaining tightly regulated in non-tumor tissue, suggesting that STA551 can activate immune cells only in tumor tissue and not elsewhere. Thus, STA551 has great potential to overcome the limitations of conventional CD137-targeted antibodies.

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0578