

regrowth, suggesting the development of immunological memory in hetIL-15 treated mice. hetIL-15 promoted tumor accumulation of proliferating and cytotoxic CD8+ T and NK cells. Additionally, peritumoral hetIL-15 administration resulted in an increased tumor infiltration of both conventional type 1 dendritic cells (cDC1s) and of a novel DC population found only in the hetIL-15 treated animals. Phenotypic profile analysis confirmed the expression of several cDC1 specific markers, including CD103 and IRF8 on this DC population. Transcriptomics and flow analysis of intratumoral dendritic cells indicate that the new hetIL-15 induced cells reside preferentially in the tumors and are distinct from cDC1 and cDC2 populations. Both cDC1s and the novel DC population were inversely correlated with the tumor size.

Conclusions Locoregional administration of hetIL-15 results in complete eradication of EO771 and significant reduction of 4T1 primary breast cancer tumors, prolonged survival and long-lasting specific anti-tumor immunity. hetIL-15 increases the tumor infiltration of activated T and NK cells and intensifies the tumor infiltration of conventional type 1 dendritic cells (cDC1) and a new population of dendritic cells. We propose that the anti-cancer activity of hetIL-15 in primary EO771 tumors is orchestrated by the interplay of NK, CD8+T cells, cDC1 and a novel subset of DCs with a distinct phenotypic profile. These findings suggest a role for hetIL-15 in the treatment of breast cancer.

Ethics Approval The study was approved by the National Cancer Institute-Frederick Animal Care and Use Committee, approval number 19-324 and was conducted in accordance with the ACUC guidelines and the NIH Guide for the Care and Use of Laboratory Animals.

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576 NL-201, A DE NOVO IL-2 AND IL-15 AGONIST, DEMONSTRATES ENHANCED IN VIVO ANTITUMOR ACTIVITY IN COMBINATION WITH MULTIPLE CANCER IMMUNOTHERAPIES

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Background NL-201 is a de novo IL-2 and IL-15 receptor agonist designed with enhanced affinity for IL-2R $\beta\gamma$ and no binding interface for IL-2R α (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 microenvironments '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.

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

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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.

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

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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.