574 ONM-400, A NOVEL APPROACH FOR INTERLEUKIN-2 THERAPY USING A PH-ACTIVATED NANOPARTICLE TARGETING METABOLIC ACIDOSIS IN SOLID CANCERS

[1]Xinliang Ding, [1]Jason Miller, [1]Qingtai Su*, [1]Stephen Gutowski, [1]Ashley Campbell, [1]Drew Robinson, [2]Tian Zhao. *[1]OncoNano Medicine, Inc., Fort Worth, TX, USA; [2]OncoNano Medicine, Inc, Southlake, Texas, USA*

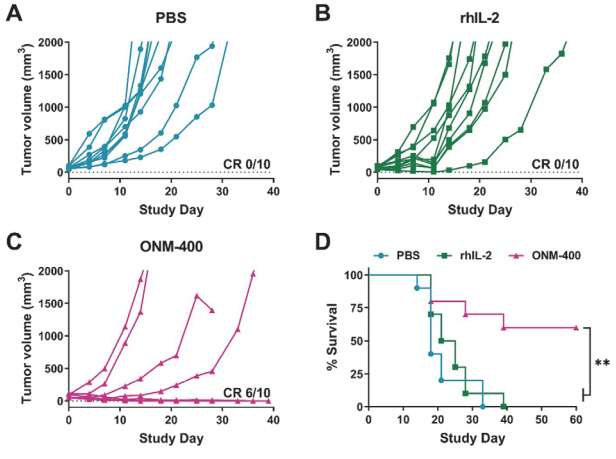
Background Interleukin-2 (IL-2) is a potent immunotherapy for treatment of metastatic melanoma and renal cell cancers. However, the clinical application has been hindered by immunosuppressive stimulation and unfavorable pharmacological properties that can induce life-threatening toxicities.[1] Although strategies including 'no-alpha' muteins have been developed to provide target specificity at the molecular level,[2] little has been done to improve tumor specificity and accumulation at tissue level. We developed ONM-400, a novel IL-2 encapsulating pH-activated nanoparticle that targets metabolic acidosis of cancer to improve the therapeutic index of IL-2 therapy. During circulation, IL-2 activity is sequestered within the nanoparticles. Upon entering the tumor microenvironment, IL-2 release is precisely and instantly triggered by acidic tumor pH, resulting in the selective deposition of active IL-2 at the site of disease.

Methods A tumor-agnostic pH-activated nanoparticle with pH responsiveness similar to ONM-100, a cancer imaging agent currently in a Phase 2 clinical trial,[3] has been developed for cytokine delivery. IL-2 was encapsulated within the nanoparticle using a proprietary method to produce ONM-400 and the physical properties were characterized. Activity of IL-2 in ONM-400 was evaluated using a bioluminescent cell-based assay for both its encapsulated (inactive) state and activated format. Tumor accumulation and biodistribution following intravenous injection (I.V.) of ONM-400 were evaluated in mice bearing head and neck tumors using fluorescent imaging. In vivo antitumor efficacy of ONM-400 after I.V. injection was studied in MC38 colon cancer-bearing mice and compared with unencapsulated IL-2 at the same dose.

Results Quantitative analysis shows high encapsulation efficiency and drug loading density of IL-2 in ONM-400. At neutral pH, IL-2 bioactivity is effectively sequestered in ONM-400 through encapsulation which avoids IL-2 toxicity in normal tissue. Upon acid-triggered release, IL-2 bioactivity is rescued without compromise compared to unencapsulated IL-2 control. Significantly higher tumor accumulation and lower renal elimination were observed with ONM-400 in biodistribution studies as compared to free IL-2 control suggesting an alteration of pharmacokinetics of IL-2 after encapsulation. ONM-400 induced strong antitumor efficacy as a monotherapy in MC38 colon cancer-bearing mice (figure 1). After ONM-400 treatment 60% of the animals showed complete tumor regression and remained tumor free 60 days. Following a secondary MC38 challenge, 5/6 animals resisted tumor growth.

Conclusions Tumor acidosis-driven accumulation and activation of ONM-400 provide a high local concentration of IL-2 within tumors resulting in strong antitumor response as a monotherapy. Tumor metabolic targeting pH-activatable nanoparticles provides a novel strategy to deliver immunomodulators for cancer treatment.

Ethics Approval All animal experiments were reviewed and approved, and performed in accordance with, by Pennsylvania State College of Medicine Institutional Animal Care and Use Committee under Animal Protocol Number: 47682.



Abstract 574 Figure 1 Anti-tumor efficacy of ONM-400
ONM-400 induces strong antitumor response in MC38 tumor bearing mice as a monotherapy. Mice received I.V. injections of PBS, 50 ug of rhIL-2 or ONM-400 with 50 ug of encapsulated rhIL-2 on Day 0, 2, 4 and 6. A-C, individual tumor growth curve of animals treated with PBS (A), rhIL-2 (B) or ONM-400 (C); CR = complete response. D. Kaplan-Meier curves of animals after the treatment. Statistical significance was analyzed by Log-rank test. **P<0.01

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575 REGRESSION BY HETIL-15 MONOTHERAPY IN DIFFERENT MOUSE BREAST CANCER MODELS CORRELATES WITH INTRATUMORAL INFILTRATION OF A NOVEL POPULATION OF DENDRITIC CELLS

Sevasti Karaliota, Dimitris Stellas, Vasiliki Stravokefalou, Bethany Nagy, Cristina Bergamaschi, Barbara Felber, George Pavlakis*. *National Cancer Institute at Frederick, Frederick, MD, USA*

Background IL-15 is a cytokine which stimulates the proliferation and cytotoxic function of CD8+ T and NK cells. We have produced and applied the native heterodimeric IL-15 (hetIL-15) on several preclinical models, which have supported the anti-tumor activity of hetIL-15. Based on these results, hetIL-15 has advanced to clinical trials. The objectives of this study were to explore how hetIL-15 shapes the tumor microenviroment and to characterize the interactions between tumor-infiltrating lymphoid and myeloid cells.

Methods We studied the efficacy of locoregional administration of heterodimeric IL-15 (hetIL-15) in two different orthotopic triple-negative breast cancer (TNBC) mouse models, syngeneic for C57BL/6 and Balb/c, respectively. The effects of hetIL-15 on immune cells were analyzed by flow cytometry, immunohistochemistry (IHC) and gene expression profiling. The profile of the novel infiltrated dendritic cell populations was further explored by bulk and single cell RNAseq.

Results hetIL-15 resulted in tumor eradication in 40% of treated mice and reduction of metastasis. Subsequent rechallenges with the same cell line failed to generate tumor

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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

Carl Walkey*, Ryan Swanson, Umut Ulge, Daniel Adriano Silva Manzano, Jonathan Drachman. *Neoleukin Therapeutics, Seattle, WA, USA*

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 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

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

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

Yoshinori Narita*, 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.

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