Overview
Boston Immune Technologies & Therapeutics, Inc. (BITT) (Boston, MA) is a first-in-class oncology company targeting the TNF superfamily with a novel class of antagonist antibodies. BITT’s lead candidate is a fully humanized monoclonal antibody that targets tumor necrosis factor receptor 2 (TNFR2), which is a surface oncogene expressed on the surface of cancer cells and on the most potent population of immunosuppressive cells in the tumor microenvironment, including Tregs and myeloid derived suppressor cells. The TNFR2 epitope is densely and exclusively expressed in the tumor microenvironment and has been shown to play a role in resistance to checkpoint inhibitors including anti-PD1 and CTLA4. BITT is a late-stage preclinical company with first-in-class TNFR2 antagonist antibodies for the clinic. BITT’s technology was developed at Massachusetts General Hospital/ Harvard Medical School.

TNFR2 and the Tumor Microenvironment
Multiple groups have recently confirmed the unique importance of TNFR2 in the tumor microenvironment. The TNFR2 protein has very limited natural expression in normal cells, but is highly expressed in the tumor microenvironment and on the surface of diverse cancer cells including renal cell carcinoma, colon cancer, non Hodgkins and Hodgkins lymphoma, and ovarian cancer. TNFR2 is not expressed on the majority of benefic T cells, but is highly expressed on the Tregs in the tumor microenvironment.

Overcoming Barriers to Immunotherapy
In cancer, Tregs and myeloid derived suppressor cells are highly enriched in the tumor microenvironment. They are considered among the greatest barriers to successful immunotherapy. This is because these cells have the ability to powerfully inhibit the body’s antitumor immune response when recruited or induced by growing tumors, which promotes peripheral tolerance of cancer cells, tumor angiogenesis and tumor progression. Increased numbers of Tregs are also associated with a poorer cancer prognosis. A particular type of Treg, the TNFR2 Treg, is the most dominant and most abundant Treg in and around malignant tumors.

Treg Inhibition
Treg inhibition is a strategy to stimulate and enhance the body’s antitumor immune response, particularly when combined with other immunotherapeutic approaches against cancer. For example, inhibiting Tregs prior to delivering an anti-cancer vaccine may significantly improve treatment efficacy by preventing Treg suppression of a robust immune response. Both murine and human data support the development of a TNFR2 Treg suppression approach to enhance various oncology treatments, including cancer immunotherapy and chemotherapy. Many cancer therapies that fail show large numbers of tumor-associated circulating TNFR2 Tregs.

Direct TNFR2 Oncogene Targeting
The growth-promoting properties of the TNFR2 receptor linked to NFkB are directly exploited by diverse forms of tumor types that express this receptor as an oncogene. Although many hard-to-target transcription factor oncogenes have been identified, TNFR2 is the first new, broadly expressed cell surface oncogene since HER2/EGFR. Unlike HER2, which is restricted to 20% of breast cancers, the TNFR2 oncogene has been identified across human tumor types. Tumor types known to express the TNFR2 oncogene range from cutaneous T cell lymphoma and renal cell carcinoma to colon cancer and ovarian cancer.

TNFRSF1B expression correlates with CD3E expression for multiple tumor types

**Similar data is seen using BITT antibodies in cutaneous T-cell lymphoma and colon cancer.**

Powerful Monotherapy and Combination Therapy
In multiple preclinical models (CT26, MC38, 4T1), TNFR2 antagonism has demonstrated superiority to anti-PD1 as monotherapy and significant cure rates when used in combination with anti-PD1 and other immunotherapies. In all models, in-vivo TNFR2 antagonism was able to kill Tregs and proliferate T effectors.

Struggles of Other PD1 Combination Agents
Agonist antibodies to TNF Superfamily Targets (OX40, GiTR, 41BB) have been proposed as potential combination agents with anti-PD1 and anti-PDL1. Agonist antibodies to the TNF superfamily have struggled in human clinical trials the last 3 years. Antagonists or blocking antibodies, however, work well in cancer (HER2, PD1, PDL1, CTLA4) but have never been successfully created for TNF Superfamily targets. BITT has a novel antibody approach, creating the first dominant antagonists to the TNF Superfamily through the use of anti-parallel dimers.

BITT’s Competitive Advantage
BITT’s approach has the following competitive advantages:

1. Reduced Systemic Toxicity: TNFR2 has limited distribution in human tissue, but is highly expressed in the tumor microenvironment.

2. Directly Targeting the TNFR2 Oncogene in Select Tumor Types: TNFR2 is directly expressed on cutaneous lymphomas, colon cancer, ovarian cancer and other cancers, similar to the way the HER2 target is directly expressed on certain breast cancers.

3. Simplified Manufacturing: BITT’s antibodies do not require crosslinking or ADCC.

4. Complementary: BITT’s antibodies can be used to boost efficacy of existing immunotherapies and other approaches. It is now appreciated that escape from checkpoint inhibitors such as anti-PD1 and CTLA4 is driven by a TNFR2 mechanism. BITT’s TNFR2 antibodies would make sense as combination therapy with checkpoint inhibitors.

5. Platform Technology: BITT offers a unique technology to make antagonistic antibodies to the TNF superfamily members, including TNFR2. This eliminates ADCC and crosslinking antibody requirements and expands the use of this technology to very broad indications.

6. Unique Patent Position: BITT’s patents cover the use of TNFR2 antagonistic antibodies for cancer therapeutics (see Intellectual Property). BITT’s technology also provides a platform for creating TNF superfamily antagonistic antibodies to diverse receptors such as lymphotixin, OX40, and CD40.

Market Opportunity and Unmet Need
The market for currently approved checkpoint inhibitors has been predicted to exceed $34 billion by 2022, despite well documented issues with low response rates, toxicity and the development of resistance. Currently between 10% and 30% of patients (depending on cancer) achieve objective non-toxic responses. BITT has the potential to provide the industry leading combination agent for checkpoint inhibitors. For potential combination partners, BITT antibodies provide a differentiator in a crowded checkpoint market. In cancer types that express the TNFR2 oncogene, BITT antibodies may also provide a novel method of direct killing of cancer cells as monotherapy.

Intellectual Property
BITT has an epitope-specific patent position unique in immuno-oncology. BITT has exclusive patent rights to the TNFR2 antibody platform to treat cancer. Claims include the method to treat subjects with cancer with TNFR2 antibodies, method to make, design and use TNFR2 antibodies that are antagonists that decrease Tregs, and methods to make, design and use TNFR2 antibodies that directly target the TNFR2 oncogene on the cancer themselves. In addition, BITT has composition of matter claims to make, design and use TNFR2 antibodies that are antagonists that bind to a select region of the TNFR2 receptor (sequences available) for cancer and Treg inhibited growth.

Development Status
BITT’s lead TNFR2 antibody (BITT1492) is fully humanized and moving through IND enabling studies. BITT1492 is the first dominant antagonist to the TNFR Superfamily ever developed and is confirmation of BITT’s novel approach to targeting the TNF Superfamily. BITT is completing cell line development and is currently raising funds to advance the clinical development of BITT1492.

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