Overview

Boston Immune Technologies & Therapeutics, Inc. (BITT) (Boston, MA) is a first in class oncology company targeting the tumor necrosis factor receptor 2 (TNFR2) oncosgene and the potent population of TNFR2 Tregs in the tumor microenvironment. The TNFR2 epitope is densely expressed on the immunosuppressive regulatory T cells (Tregs) in the tumor microenvironment that protect tumors and play a role in resistance to checkpoint inhibitors including PD1 and CTLA4. TNFR2 is also expressed on the surface of certain cancers as an NFkB-driven growth receptor oncogene. 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-Hodgkin and Hodgkin lymphoma, and ovarian cancer. TNFR2 is not expressed on the majority of beneficial T cells, but is highly expressed in the Tregs in the tumor microenvironment.

Barrier to Immunotherapy

In cancer, Tregs are highly enriched in the tumor microenvironment and are considered among the greatest barriers to successful immunotherapy. This is because Tregs 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.

Antagonist antibodies have specificity for the Tregs of the human tumor microenvironment

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. In particular, many cancer therapies that fail show large numbers of tumor associated circulating TNFR2 Tregs.

Direct TNFR2 Oncogene Targeting

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

T-NFRSF1B expression correlates with CD3E expression for multiple tumor types

Direct TNFR2 oncogene killing of human ovarian cancer cells (OVCAR3) with lead Ab candidate

Similar data using BITT antibodies in cutaneous t-cell lymphoma and colon cancer.
Shortcomings of Past Approaches
Numerous approaches have been proposed to deplete or inhibit Tregs. Most strategies to date have employed monoclonal antibodies or ligand-directed toxins targeted to cell-surface receptors. These strategies have included both non-specific targeting agents (e.g., anti-mitotic agents, Cox-2 inhibitors), as well as agents meant to specifically target all Tregs (e.g., anti-CD25 antibodies, CTLA-4 blockade). In clinical trials, Treg depletion has been shown to induce tumor regression by boosting CD8 T cell and other immune responses. However, overall efficacy has been relatively modest because these approaches failed to specifically deplete or inactivate the most potent Tregs of cancer, TNFR2 Tregs. In addition, other, desirable lymphocytes were concurrently eliminated. This has hampered efforts to combine Treg depletion with immunotherapy, since the immunotherapeutic approach relies on the stimulation of desirable immune cells.

BITT’s Competitive Advantage
1. **Reduced Systemic Toxicity:** TNFR2 has limited distribution in human tissue.

2. **Targeting the Most Potent Tregs in the Tumor Environment:** BITT’s antibodies selectively inactivate the most suppressive Tregs—TNFR2 Tregs—while preserving other T cells. BITT antibodies also have specificity for the tumor microenvironment.

3. **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.

4. **Simplified Manufacturing:** BITT’s antibodies do not require crosslinking or conjugation to toxin.

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

6. **Independent Validation in Murine Literature and Human Tumors:** Murine and human basic science data on TNFR2 Tregs match. Independent studies for three oncology indications confirm TNFR2 Treg potency in human cancer.

7. **Platform Technology:** BITT offers a unique technology to make antagonist 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.

8. **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 antagonist antibodies to diverse receptors such as: lymphotixin, OX40, and CD40.

Market Opportunity and Unmet Need
The potential value of immuno-oncology has been limited by toxicity and the development of resistance. BITT has the potential to be 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 provide a novel method of direct killing of cancer cells.

Intellectual Property
BITT has an epitope specific patent position unique in immune-oncology. BITT has exclusive patent rights to the its 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, 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 and composition of matter.

Financing and Partnering Goals
BITT has created first in class TNFR2 antagonist antibodies. BITT has an established investor base and is prepared to move into key IND enabling steps. BITT is also exploring the option of a partnership to quickly complete late stage preclinical and IND enabling activities.

Management Team
**Russell LaMontagne, Co-Founder, President & CEO.**
Senior advisor to biotechnology and pharmaceutical companies for over 20 years. Played a predominant roll in the development of several early stage companies, and has advised pharmaceutical companies regarding commercialization strategies. Russell is also co-founder of Enbiome, Inc.

**Sheila A. Mikhail, MBA, JD, Advisor and Board Member.**
Co-Founder and CEO of Bamboo Therapeutics (sold to Pfizer). Previous Co-Founder and CEO of Asklepios Biopharmaceutical, Inc. (which sold a subsidiary, Chatham Therapeutics, to Baxter), Co-Founder of InnerOptic Technology, Inc., and Co-Founder of NanoCor Therapeutics, Inc. (which partnered with Medtronic), Founder and Managing Member of Life Sciences Law. Significant experience structuring strategic partnership transactions and leveraging non-dilutive financing.

**Denise Faustman, MD, PhD, Co-Founder & Inventor.**
Director of Immunobiology, Massachusetts General Hospital; Associate Professor of Medicine, Harvard Medical School; NIH and National Library of Medicine Award, “Changing the Face of Medicine.”

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References