Boston Immune
Technologies & Therapeutics

Platform for Infectious Disease Immunotherapy

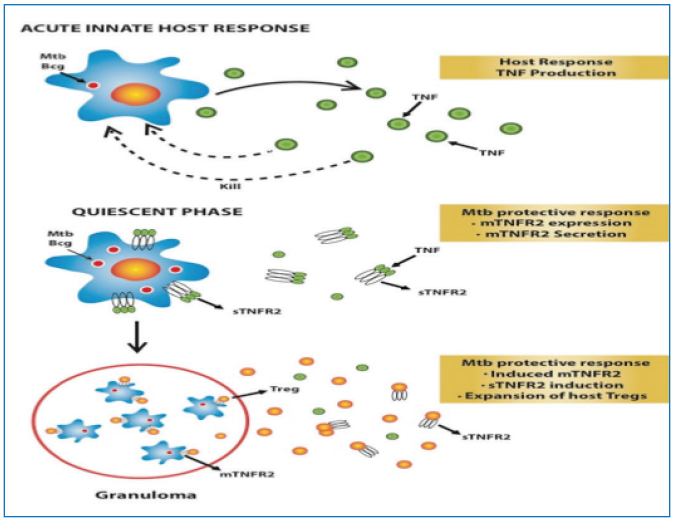
Overview

Boston Immune Technologies & Therapeutics, ID, LLC (BITT-ID) (Boston, MA) is a biotechnology company developing novel immunotherapy for chronic infectious diseases. Chronic infections, as well as some acute infections, can become disguised once inside the host, inducing suppression of the host response through regulatory T cells (Tregs, formerly known as suppressor T cells). BITT-ID is developing an approach to infectious disease that targets the host Tregs, not the microorganism, through tumor necrosis factor receptor 2 (TNFR2) antagonism. This platform approach has two advantages:

- No antibiotic resistance
- One platform for all infections

BITT-ID has built a broad portfolio of intellectual property around targeting TNFR2 in infectious disease, has identified lead monoclonal antibody candidates, and is exploring treatment models in human and animal health. BITT-ID's technology was developed at Massachusetts General Hospital and Harvard Medical School.

TNFR2 Expressing Tregs in Infectious Disease



BITT-ID's Approach: Selectively Destroy Tregs

BITT-ID's approach to infectious diseases is to use TNFR2 antibody antagonism to selectively destroy Tregs that protect infectious organisms, while preserving beneficial T cells. Pathogenic viruses (e.g., HIV, hepatitis C, HPV), antibiotic resistant bacteria (Acinetobacter, Campylobacter, Salmonella, Shigella, Streptococcus, *S. aureus*), parasites, yeast and tuberculosis all induce host Tregs to prevent immune detection. TNFR2^{hi} Tregs are the most potent Tregs identified to date in mouse and human systems. Furthermore, in select infectious diseases, TNFR2 (TNFRp75) Tregs drive the hampered host response.*

Treg Overview: Tregs are a subpopulation of host T lymphocytes that play a critical role in regulation of the immune response. Tregs act as the negative surveillance system of the immune system. When faced with pathogens, the immune system summons a swarm of cells made up of killer T cells and Tregs. The Tregs, as peacekeepers, instruct the killer T cells to stop fighting after the pathogens are cleared. In infectious diseases, however, the Treg function can sometimes become "hijacked," impeding infection immunosurveillance and effective immunity. Two major disease categories are now known to produce too many suppressive Tregs: cancer and chronic infectious diseases.

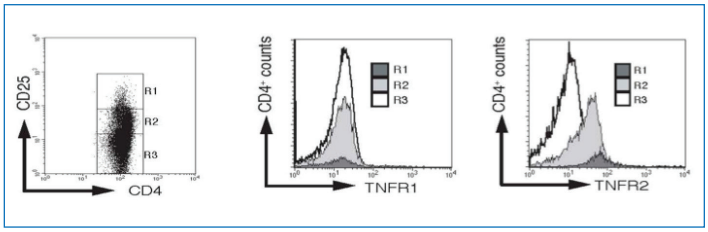
Barrier to Infectious Disease Therapy: Over the past 10 years, considerable knowledge has been gained on how infections induce host Tregs to prevent recognition. Tregs, which are highly enriched in the infection microenvironment, promote infection progression by limiting host immune responses, promoting peripheral tolerance, and promoting antibiotic resistance. A particular type of Treg, the TNFR2^{hi} Treg, is found at very high levels in and around sites of infection. In some cases, such as tuberculosis, it is even known how the pathogen induces Tregs, which is mainly through the ligand for the TNFR2 receptor. In infectious diseases, it is now recognized that Tregs are among the barriers to successful therapy because of their ability to powerfully inhibit the body's anti-infection immune response.

Treg Inhibition: Treg inhibition is a strategy to stimulate and enhance the body's antitumor immune response, particularly when combined with other treatments directed against infection. Both murine data and human data support the development of a Treg suppression approach to enhance various infection treatments, but it has been hampered by difficulty in identifying a selective Treg drug target confined to the cells that need to be eliminated.

Shortcomings of Past Approaches: Numerous approaches have been proposed to deplete or inhibit Tregs, often in the setting of cancer where immunotherapy trials are advanced. BITT-ID proposes to be the first platform immunotherapy for infections and is an antibody-based therapy predicted to have remarkably targeted approach. Most Treg inhibition/depletion 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 Tregs (e.g., anti-CD25 antibodies, CTLA-4 blockade). However, overall efficacy has been relatively modest and balanced by high toxicity because these approaches failed to specifically deplete or inactivate the most potent Tregs, TNFR2^{hi} Tregs. In addition, other, desirable lymphocytes were concurrently eliminated, since many of the targets used in these strategies are expressed broadly, causing toxicity that might be permissible in oncology but not in infectious disease. This has hampered efforts to combine Treg depletion with immunotherapy, since the immunotherapeutic approach relies on the stimulation of desirable immune cells.

BITT-ID's Solution: BITT-ID's novel Treg inhibition technology has the potential to boost the efficacy of anti-infection therapies by selectively and safely inactivating the most potent suppressive Tregs, TNFR2^{hi} Tregs. The restricted tissue distribution of TNFR2 makes it possible to specifically inactivate undesirable Tregs *in vivo*, while preserving desirable T cells.

TNFR2 is preferentially expressed on Treg cells: CD4+/CD25 T



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BITT-ID's Advantage

BITT-ID's approach has the following competitive advantages:

1. **Lead Antibodies Identified:** BITT-ID has identified lead antibodies for applications in infectious disease.
2. **Reduced Systemic Toxicity:** TNFR2 has limited distribution in human tissue and high expression on suppressive Tregs.
3. **Targeting the Most Potent Tregs:** BITT-ID's antibodies selectively inactivate the most suppressive Tregs— TNFR2^{hi} Tregs—while preserving other T cells.
4. **Simplified Manufacturing:** BITT-ID's antibodies do not require crosslinking or conjugation to toxin.
5. **Complementary:** BITT-ID's antibodies can be used to boost efficacy of existing antibiotics and thwart antibiotic resistance through combination therapies.
6. **Independent Validation in Murine Literature and Human Tumors:** Murine and human basic science data on TNFR2 Tregs match and confirm that TNFR2^{hi} Tregs are the most potent Tregs and are involved in chronic infectious diseases.
7. **Platform Technology:** BITT-ID offers a unique technology to make antagonistic antibodies to TNF superfamily members, including TNFR2. This eliminates ADCC and crosslinking antibody requirements and expands the use of this technology to very broad indications. This antibody technology can broadly target most chronic infectious diseases by selectively eliminating suppressive host responses.
8. **Unique Patent Position:** The BITT-ID technology covers the use of TNFR2 antagonistic antibodies for infectious disease therapeutics to remove host Tregs.

Intellectual Property

BITT-ID has an epitope specific patent position unique in infectious disease. BITT-ID has exclusive patent rights to the its TNFR2 antibody platform to treat infectious disease. Claims include the method to treat human and animal subjects with infectious diseases with TNFR2 antibodies, method to make, design and use TNFR2 antibodies that are antagonists that decrease Tregs. In addition, BITT-ID 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 infectious disease and Treg inhibited growth and composition of matter.

Competition

BITT-ID has first-mover advantage in developing TNFR2 antagonism for the treatment of infectious diseases, and has procured broad patent protection for this approach. Unlike other therapeutic approaches based on TNF superfamily targets, BITT-ID's antibodies do not require any complex crosslinking, enjoys a unique patent position and has a unique target—TNFR2. BITT-ID's antibodies can be used alone or with other infectious disease therapies to augment their effectiveness and prevent drug resistance.

Unmet Need

There is a significant unmet need for new antibiotic treatments, and especially antibiotic treatments that work on chronic infectious diseases. Antibiotic/antiviral resistance is on the rise and it has become more difficult to develop pathogen-directed drugs. BITT-ID provides a platform immunotherapy approach that is host directed and antibody based.

Market Opportunity

The market for infectious disease immunotherapy is extremely large, and an opportunity to be the first-to-market with a platform immunotherapy for infectious disease indications is valuable. To date the major technologies to fight infections are antibiotics and vaccines. These technologies are pathogen specific and pathogen directed. With the high proliferative rate of diverse microorganisms, antibiotic resistance is common and also the design of new vaccine evolves rapidly. Research efforts to identify new antibiotics have been very difficult with antibiotic resistance winning in many global arenas and for many kinds of infections. BITT-ID's approach ignores the unique traits of pathogens and capitalizes on a common evolutionary trait for escape from host detection, the induction of host Tregs. BITT-ID's antibodies technology can be used to increase the effectiveness of antibiotic, antiviral and other therapeutics and expand the number of patients for which they are effective.

Financing

Development Plans: BITT-ID seeks a pharma partner to rapidly bring TNFR2 antagonistic therapies to clinical testing in infectious diseases.

Prior Funding: BITT-ID has secured seed funding from several angel investors, which has been used primarily for patent expenses, licensing fees, and initial development work.

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."

Contact

Russell LaMontagne
Co-Founder, President & CEO
Boston Immune Technologies & Therapeutics
Email: russell@bostonimmunetech.com
Tel: 917-744-7957

*Keeton R et al TNFR2p75 regulates host protective immunity against Mycobacterium tuberculosis. JCI 2014;124,1537.