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PROFILE

Integrated BioTherapeutics

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1. How and when did your company start, and where are you located?

Integrated Biotherapeutic (IBT) was founded by Dr. M. Javad Aman as a multi-program, multi-platform company focused on discovering and developing vaccines and immunotherapeutics for emerging infectious diseases. IBT's facilities are located in Rockville, MD, and include 12,000 SQF of laboratory space and a dedicated vivarium comprising 2000 SQF.

IBT was established based on non-dilutive funding from governmental agencies including National Institute of Allergy and Infectious diseases (NIAID) and the US Department of Defense (DoD), as well as seed funding from the State of Maryland Technology Development Company (TEDCO). IBT has developed a portfolio of patents for rationally designed vaccine candidates for *Staphylococcus aureus*, monoclonal antibody therapeutics for bacterial toxins and for treatment of Ebola virus hemorrhagic fever. Furthermore, IBT has developed a platform technology for directing anti-toxin antibodies to the site of bacterial infection (ISTAb technology) as well as a technology that redirects heterologous immune response to a new pathogen (InstaVax). In addition to IBT's internal research, we also have research services and a reagent business that helps fund the R&D programs.

2. How many employees do you have, and how do you find and attract them?

Currently IBT has 30 full time employees including 10 Ph.D. level scientists, 15 research associates, and 5 administrative personnel. We have recruited both from the industry and academia using a variety of outreach methods from word of mouth to posting the job on professional websites. The research-based nature of our business has helped us attract talented scientists who are excited about making a difference in people's lives. We retain them by providing competitive compensation, a nurturing work environment, and the opportunity to publish their work in prestigious scientific journals and be recognized as inventors on patent applications.

3. What are the main focus and platform technology (ies) of your company?

IBT's technology focus is on two areas:

a) Rationally designed vaccines: Our most advanced vaccine program focuses on a rationally designed toxoid vaccine for prevention of invasive diseases resulting from *Staphylococcus aureus* infection. These toxoids have been designed based on the crystal structures of the toxins in a manner to render the proteins non-toxic while maintaining immunogenicity. We have created numerous mutants in three classes of *S. aureus* toxins: alpha hemolysin, bi-component leukotoxins, and superantigens. These mutants have undergone an iterative selection process and a final vaccine composed of seven toxoids has been formulated with a breadth of neutralizing response that covers 12–15 toxins. Furthermore, in several highly collaborative projects, we work on rationally designed viral glycoprotein vaccines including Ebola, Marburg, and Zika. These technologies are at early stages of development. These programs are supported by CARB-X, NIAID and DoD.

b) Immunotherapeutics: Our most advanced immunotherapeutics program is a pan-ebolavirus cocktail of two broadly neutralizing antibodies. These antibodies have demonstrated full protective efficacy against all pathogenic ebolaviruses in nonhuman primates and ferret and are now ready for IND-enabling studies.

A growing arm of our R&D is focused on two technologies referred to as ISTAb and InstaVax. ISTAb is an engineered monoclonal anti-toxin antibody that carries a targeting domain to attach to the surface of bacteria and simultaneously clear the toxin and bacteria at the site of infection. InstaVax is a novel technology that targets a universal antigen to the surface of an invading pathogen, redirecting the antibody response to the antigen towards the heterologous pathogen. IBT is applying these two technologies to multiple bacterial pathogens.

4. Can you provide a short overview of your product pipeline?

IBT-V01 (STEBVax), is a monovalent staphylococcal enterotoxin B (SEB) vaccine intended as a product to prevent intoxication with the superantigen SEB as a biowarfare agent. IBT-V01 has recently completed a successful Phase I clinical trial in healthy volunteers.[1]

IBT-V02 is a heptavalent vaccine that consists of rationally designed toxoids for *S. aureus* alpha hemolysin,

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Panton-Valentine leukocidin F and S subunits (LukS and LukF), LukAB, Staphylococcal enterotoxins A and B as well as toxic shock toxin syndrome toxin 1 (TSST-1).[2,3] The vaccine is currently at the stage of process development and preclinical safety and efficacy testing. This vaccine is supported by NIAID and CARB-X through Phase I clinical trial that is planned for 2020. IBT-V02 is intended for prevention or mitigation of post-surgery MRSA infection in patients undergoing elective surgery. A second indication sought is prevention of recurrent *S. aureus* skin and soft tissue infections.

IBT-T02 is a monoclonal antibody cocktail for treatment of all pathogenic ebolaviruses.[4,5] The product has completed preclinical efficacy and cell line development.

ISTAb

A set of ISTAb candidates are being evaluated *in vitro* and *in vivo* for *C. difficille, B. Anthracis*, and *S. aureus*. This program is supported by NIAID.

Pneumococcal InstaVax

Using IBT's proprietory InstaVax technology and supported by NIAID we are developing a serotype-independent post exposure vaccine for treatment of infections with *Streptococcus pneumoniae*.

5. Who is your competition, and what advantage(s) do your products / technology offer?

Our primary competitors are companies developing vaccine for *S. aureus* infections. IBT is in a unique position in this field with the largest intellectual property portfolio on *S. aureus* toxins, and the only company with a fully toxoid based multivalent vaccine program. Over the past decade several vaccine and immunotherapeutics were developed that target the surface of *S. aureus*. However, all these approaches failed to protect against invasive disease in humans and some appeared to exacerbate the disease. The experimental vaccine V710, developed by Merck, was tested in patients undergoing thoracic surgery. Unfortunately, this trial ended with a significantly increased incidence of multiorgan failure and death in vaccines who developed *S. aureus* infection prompting Merck to terminate the trial. These concerns are further supported with reports of exacerbated disease and immunopathology in mice and rabbits when vaccinated with crude surface antigens of *S. aureus*. Further study indicates that a dysregulated immune response may have been responsible for the outcome of V710 trial. Our hypothesis is that toxins play a central role in this dysregulated immune response and by neutralizing the toxins the innate immunity against *S. aureus* can be directed towards a protective response. This is a novel approach supported by strong evidence in animal models[2,3,6] as well as epidemiological studies[7] prompting both NIAID and CARB-X to heavily invest in IBT-V02.

The engineering technologies for targeting immunological functions to site of infection appear to be unique and we are not aware of any competition. There are other companies with antibody therapeutics that protect against ebolaviruses. The competitive advantage of our antibodies is in the broad breath of protection and high potency (low dose).

6. What were the "highlights" in your recent product development?

The success of our Phase I clinical trial with STEBVax, one of the components of IBT-V02, was a major milestone as it demonstrated the safety of a superantigen toxoid in humans. Following this success, we were able to secure funding from CARB-X for up to $8.5M to manufacture the vaccine and conduct a phase I clinical trial. Another major advancement in our pipeline was completion of pre-clinical efficacy studies in nonhuman primates for our pan-ebolavirus antibody cocktail that positions the product for manufacturing and clinical development. Over the past few years we have been able to secure several funding streams from the government for our R&D program including SBIRs, STTRs, R01, and partnership R01 grants, a large contract with Defense Treat Reduction Agency (DTRA), as well as a recent CARB-X grant.

7. What have been the most critical problems in developing products in your field, and how can your company's technology help overcome these problems?

A major challenge in developing prophylactic and therapeutic countermeasures for emerging infectious diseases is the changing dynamics of outbreaks, the variability of the circulating strains across time and geography, and the multitude of virulence factors that pathogens, in particular bacteria like *S. aureus* have evolved to evade the immune response. Our approach has been to target highly conserved virulence factors and epitopes. This approach has been very successfull for ebolaviruses and we were able to generate broadly neutralizing antibodies that protect against all ebolaviruses. In case of *S. aureus*, the challenge is more in the variety of virulence factors. We have included rationally designed toxoids from various toxin groups and the antibody response against our vaccine covers up to 15 toxins by cross neutralization. Thus we expect that this breadth covers the current variety of circulating strains and possible those emerging or re-emerging in future.

8. What is your company's value proposition?

We consider IBT as a discovery engine. Concentrating on discovery to early stage development and myopic focus on certain infectious diseases, combined with a non-dilutive funding strategy has allowed us to take a deep dive into the underlying science. The government funding has been very crucial for our success as investor timelines can be hardly imposed on the science of discovery. We have developed a unique set of expertise in these specific areas that helped us make important discoveries and inventions as evidenced by more than 40 peer reviewed publications, numerous patents, and over 65M of grant funding since inception. Currently,

IBT has the largest patent portfolio in the space of *S. aureus* toxoids and filovirus monoclonal antibodies. Our ISTAb and InstaVax technnologies are very unique and have great potential.

9. What business development strategy do you pursue?

Our approach is to partner early on with academia and other biotech companies with complementary technologies and build a long term relationship focused on translational research. This consortium then seeks nondilutive funding from the government or through pharma partnership to work through discovery and complete proof of concept up to Phase I clinical trial. At the end of this process, it is our goal to either outlicense the graduating technologies or partner with large pharma for more advanced development and commercialization.

10. How does your company attract partners?

For early stage discovery, our track record in receiving government funding has been our strongest asset in attracting academic groups to work with us. To attract pharma partners we use primarily investor conferences, as well as scientific forums to reach out to the scientists in pharma companies who can be the internal champion for forging a strategic relationship.

11. Who are your most important partners?

Our most important partners are funding agencies such as NIAID, CARB-X, and DTRA that provide the initial resources for the discovery and development stages. Additionally, our academic and governmental research partners, US Army Medical Research Institute of Infectious Diseases, The Scripps Research Institute, Harvard University, and UCSF have been instrumental in providing expertise in moving these projects towards advanced development. Our partnership with pharma for advanced development is at its early stages and currently our most important partner is Emergent Biosolutions.

12. How do you balance performing work in-house vs out-sourcing?

We have a broad range of internal capabilities from bioanalytics, assay development, small scale production of proteins and antibodies, to over 15 animal models for infectious diseases. We have made a countious decision to perform nearly all discovery and proof of concept activities in house and outsource IND-enabling GLP/GMP work. This has helped us keep our overhead costs manageable.

13. What are your product development goals for the next 3 years?

We plan to complete the manufacturing of both IBT-V02 and IBT-T02 and initiate a Phase I clinical trial. Concurrently, we anticipate transitioning one ISTAb and one InstaVax candidate to advanced preclinical and IND-enabling stage.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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