**Case Study:** NSF/SBIR IA2011-003

**Company:** 0848952 Stellar Biotechnologies, Inc.

**Technology Segment:** Biotechnology

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### 1. PREAMBLE:

#### 1.1 TECHNOLOGY AND MARKET DESCRIPTION

This project will develop methods for the reliable control of settlement and metamorphosis of larval stages of *Megathura crenulata* (the giant keyhole limpet) to support the production of commercial quantities of Keyhole Limpet Hemocyanin (KLH), a unique and medically valuable marine natural product. Unlike many other prospective medical products from marine organisms, KLH is already in extensive use as an immuno-stimulant in over 20 KLH-based clinical trials of therapeutic vaccines. KLH is commonly produced from animals harvested from the finite and fragile natural populations of California and Northern Baja California. With the potential success of one or more of these KLH-based cancer vaccines, the commercial market for KLH could exceed $50M and place extreme pressure on the species. Prior National Science Foundation (NSF) Small Business Innovation Research (SBIR) funded research successfully identified a critical “cue” for settlement of *M. crenulata* larvae and demonstrated the feasibility of achieving the long-term commercial objectives of this research. Current efforts involve translating the results of current work into prototype designs for testing and optimization of systems, diets and aquaculture methods for cultivation of the age-specific developmental
phases, from metamorphosis to fully developed juveniles that are capable of being transitioned onto adult diets and cultured for KLH production.

*Megathura* presents unique challenges for control of larval settlement, metamorphosis and cultivation. Unlike *Haliotis* and other cultivated herbivorous molluscan species, *Megathura* is an opportunistic carnivore, and predisposed to cannibalism. Elucidating the underlying biochemical factors that promote settlement, metamorphosis and early postlarval survival will add significantly to the body of scientific knowledge in this field. This knowledge is critical for controlling production of *Megathura* and other commercially important carnivorous gastropods with biomedical potential such as *Concholepas concholepas*. The ultimate objective of this research is to provide sustainable commercial supplies of KLH for new, life-saving therapeutic vaccines for cancer, arthritis, hypertension, addiction, and other debilitating diseases. The therapeutic vaccine industry urgently requires a viable commercial KLH supply other than the fragile natural population of *M. crenulata*. By providing a commercial alternative to the current dependence on the limited and threatened fishery, this research will provide fishery regulators and resource managers the opportunity to formulate management policies to protect the wild population without imposing limitations on KLH or the important KLH-based vaccines under development. By making GMP-grade KLH more broadly available this research will stimulate new vaccine research, and facilitate the translation of basic research into clinical studies of new therapeutic vaccines.

Currently, Stellar markets two GMP KLH products to the biopharmaceutical and vaccine development markets. Supply agreements for the company’s KLH products are in place with two vaccine developers. All of the company’s KLH product manufacturing procedures, from aquaculture animal husbandry to final protein purification, have been developed for GMP compliance. Stellar’s marketing strategy is to sell to vaccine developers as early as possible during the development cycle, under long-term supply agreements that offer assured scalability and continuity of supply. Stellar markets KLH products directly to biopharmaceutical customers. The company has established strategic relationships and engaged potential customers without the use of distributors or advertising. Stellar’s management has formed relationships with many of the major customers in the cancer vaccine market. The company is also negotiating a co-marketing relationship with a leading Contract Manufacturing Organization (CMO) partner to help promote Stellar’s GMP KLH for new conjugate vaccines. Stellar’s prospective CMO partner is an established provider of GMP conjugation services and can act as a conduit for new biopharm customers for GMP KLH conjugates. Stellar’s other points of entry for this market will be the institutional vaccine researchers at academic, medical, military, and other institutions. By 2014 the total vaccine market will have a value of $21B of which $3.5B will be KLH-based. Several kilograms of KLH will be required to meet this demand with a KLH value of approximately $35M.

### 1.2 Value Proposition

Stellar Biotechnologies is a product-stage company that was formed in 1999 to develop manufacturing methods for a critical component of the new class of medicines known as therapeutic vaccines. The company’s products are formulations of a marine natural product, Keyhole Limpet Hemocyanin (KLH), a highly immunogenic carrier protein used in the production
of conjugate vaccines for cancer, hypertension, infectious disease, drug addiction, and other serious diseases. Stellar’s growth plan is built upon its demonstrated ability to win customers for its KLH products by promoting the sustainable supply advantages offered by the company’s unique aquaculture technology for cultivation of the source animal. Although all commercially available sources of KLH are currently produced from animals collected by wild-harvest from the very limited fishery, Stellar’s products are further distinguished by the fact that they are produced by repeated, periodic non-lethal extraction from captive colonies grown in a controlled, GMP-compliant aquaculture system. An important component of Stellar’s competitive strategy is developing KLH deemed by regulatory authorities to be bioequivalent to that already being studied in clinical trials. The ability to show bioequivalence is a critical success factor for Stellar’s ability to displace competing KLH products and to be qualified as a source of supply for existing vaccine products. Stellar is also pursuing customers that are in the early (preclinical) stages of vaccine development which do not require bioequivalence testing, and therefore have lower barriers to product acceptance. To conserve financial resources during product development, the company has utilized a commercial CMO for GMP purification services to manufacture Stellar’s subunit product. As demand increases the company plans to construct and qualify its own GMP manufacturing facility in order to lower manufacturing costs and increase competitiveness. Stellar’s forecasted revenues are predominantly from the sale of KLH products. Stellar is currently selling KLH intermediates produced from captive colonies of limpets held in controlled aquaculture systems and in January 2008 introduced to the market a fully purified GMP subunit KLH product for vaccine customers.

The company’s competitive advantages are its sustainable and proprietary methods for commercially scalable production of the previously resource-limited natural KLH protein. KLH supplies for the vaccine market cannot be sustained by the limited natural population of Megathura. With the imminent potential approval of KLH-based vaccines, it may not be possible for a bona fide commercial fishery for M. crenulata to be instituted in time to mitigate the unsustainable harvesting pressure that will result from increasing KLH demand. Stellar’s solution to this supply problem, i.e. aquaculture production of M. crenulata, will ensure the continuity of supply to meet the growing pharmaceutical demand. The strategic advantages offered by Stellar are sustainability, control of supply, and consistent high quality; advantages that are readily acknowledged in the marketplace for the company’s aquaculture-derived, GMP-grade KLH. Interviews with the company’s existing and potential customers have identified the improved lot-to-lot consistency and reduced regulatory risk of KLH from a controlled aquaculture source (versus uncontrolled ocean sources which are potentially subject to environmental contamination) as key factors in choosing Stellar as a KLH supplier. Most KLH products used in preclinical and early clinical research are supplied by established research reagent vendors such as Pierce Chemical Company and Sigma-Aldrich Fine Chemicals (SAFC). GMP-grade KLH products are supplied principally by Stellar and its main competitors, Biosyn and SAFC. Stellar’s competitors rely on limpets caught from the ocean as their source of KLH; the animals are typically bled to death to obtain the KLH-containing hemolymph. Stellar’s primary competitor in the Subunit KLH market, Biosyn Arzneimittel (Germany), has filed a Drug Master File (DMF) with the U.S. Food and Drug Administration (FDA) for its subunit product. Biosyn has secured at least two supply agreements with cancer vaccine developers. SAFC also is planning to enter the subunit KLH market. Stellar has manufactured and produced four commercial lots of this...
product to date and has initiated long-term stability studies. The chemistry, manufacturing, and controls (CMC) data from these lots will be used by Stellar for its own DMF filing with the FDA in 2008. At that point, Stellar will be one of only three manufacturers worldwide capable of supplying GMP Subunit KLH. Unlike its competitors, Stellar will have a unique and patent-protected ability to manufacture consistent, sustainable supplies of KLH from the only source of the molecule, the *M. crenulata* limpet, from a controlled aquaculture environment. To compete effectively with Biosyn and SAFC for KLH supply agreements, Stellar has developed its own proprietary process for GMP-grade KLH subunit purification. The company now is one of only three manufacturers worldwide that has successfully developed a GMP purification process for Subunit KLH. Stellar’s patent (U.S. No.6,852,338) on the non-lethal method for extraction of hemolymph is the only other relevant published intellectual property (IP) that claims methods pertaining to the production or formulation of KLH products. Patents in this field include method and composition-of-matter patents held by Intracel Corporation, a former customer for Stellar’s KLH intermediates. The patents claim a HMW formulation by molecular weight for use in the treatment of bladder cancer. The methods and formulations claimed are not practiced or produced by Stellar. Due to the highly complex nature of KLH molecules, it is extremely unlikely that a cloned KLH fragment will reproduce the glycosylation patterns and immunogenicity of the native molecules, and thus Stellar does not consider these patents to be threats to its business.

### 1.3 Team

Stellar has assembled a team that combines eminent scientists, medical researchers with others possessing deep experience in developing and financing biotech and pharmaceutical companies. Backgrounds include those with former senior positions at successful public companies, large and small, and academic institutions like Genentech, Harvard, Abbott Labs, Scripps Research, Sunesis Pharmaceuticals, Johnson & Johnson, Praecis Pharmaceuticals and MIT. Through significant shareholdings and stock options, these professionals are motivated by aligning themselves with shareholder interests and value. The company currently has sixteen full time employees, three in management, one in sales and marketing, one in administration, one in Quality Assurance, three in manufacturing, three in aquaculture production and two dedicated to product R&D. All management and administrative personnel perform technical functions within the organization in addition to managerial responsibilities. The project leader is Frank Oakes, a company founder with eleven years dedicated to building the business. Frank has a 35-year history in the aquaculture industry including 19 years as founder and CEO of the Abalone Farm, Inc., which he built into the largest U.S. abalone producer. The aquaculture research team for this project includes Brandon Lincicum the company’s Aquaculture Production manager. Studies of KLH quality and developmental expression patterns are led by Dr. John Sundsmo, the company’s Chief Operating Officer. Dr. Sundsmo gained impressive experience in business, intellectual property and research experience at Triton Biosciences/Royal Dutch Shell, Viagene, TransCell Therapeutics and PrimeGen Biotech, and at law firms Christensen, O’Connor (WA) and Weiss, Jensen (WA). He is a Patent Agent and co-founder of biopharmaceutical companies. Dr. Sundsmo earned his Ph. D. in Microbiology/Immunology at the University of Washington with post-doctoral studies in Molecular Oncology at Fred Hutchinson Cancer Research (Seattle) and Molecular Immunology at Scripps Research (La Jolla). Daniel E. Morse, Ph.D., is a Director and Executive Vice President of Science and Technology. Dr. Morse is Professor of Molecular Genetics and Biochemistry at the University of California, Santa Barbara,
and Director of the UCSB-MIT-Caltech Institute of Collaborative Biotechnologies. He is an internationally recognized expert in protein chemistry, molecular biology, molluscan reproductive biology, and aquaculture.

1.4 **Innovation Accelerator (IA) Role**

Stellar Biotechnologies engaged with the Innovation Accelerator during the summer of 2009 as they were exploring the opportunity to go public on the Toronto Stock Exchange via a reverse IPO. The IA introduced Frank Oakes (President and CEO, Stellar) to Mike Zarriello (Executive Director, Capstone Advisory Group) to act as an advisor during this process. The value of Zarriello’s advice throughout this process was recognized by Oakes in the form of an invitation to sit on Stellar’s Board of Directors; Zarriello declined. Additionally, IA introduced John Sundsmo as an “at-large” advisor to the company in early 2010; Sundsmo is now the Vice President of Research and IP. IA continues to monitor Stellar’s growth and offers assistance and responds to requests from the Company as needed.

1.5 **Key Relations**

In May 2010 the Company engaged the services of the public relations services of Maximus Strategic Consulting Inc. (“Maximus”), the owner of PinnacleDigest.com (“Pinnacle”), an online investor information portal with content providers from across North America, Europe and Australia. Pinnacle advertises press releases of public companies, custom flash advertisements and provides marketing for public companies in its newsletter which summarizes their development and press releases in a report format. Maximus will manage the company’s public and investor media relations under the guidance of Darrell Brookstein, EVP, Finance, Business Development and Investor Relations. In August 2009 the company entered into a research collaboration agreement with Bayer Innovation GmbH (BIG) for the development of biopharmaceuticals. Bayer’s personalized idiotype vaccine for the treatment of Non-Hodgkin’s-Lymphoma (NHL) is currently in Phase I clinical trials, and the cooperation is related to the development of a personalized Non-Hodgkin’s-Lymphoma vaccine. The vaccine antigen is produced in tobacco plants based on Bayer’s proprietary magniCON® technology. Under terms of the agreement, Stellar Biotechnologies supplies Keyhole Limpet Hemocyanin (KLH) which is coupled to the idiotype protein produced in tobacco plants. KLH is a highly potent immunostimulatory protein, which stimulates the lymphocytes to recognize even familiar proteins attached to it as foreign. During the immune response that ensues, the lymphocytes mainly focus on the peptide sequence of the attached tumor idiotype. This so-called immunogenic carrier molecule comes solely from the rare keyhole limpet, and Stellar has proprietary technology for the maintenance of the animal, the non-lethal extraction of the critical molecule and a profitable refinement process for the purification of KLH. Stellar received a scheduled milestone payment from BIG in September 2010, and the co-development agreement is being expanded and continued to achieve important new endpoints that may prove critical to Bayer’s interest in therapeutic vaccines based on its plant-based protein expression system, the magniCON®-technology.

1.6 **Execution and Growth Strategy**

- Rapid growth via infusion of venture capital/private equity funds
- Sales-driven steady and slow growth
- Merger; Acquisition; Spin-off
1.7 **Supplemental Reading Material:**
   a. IPVision intellectual property (IP) analysis
   b. NSF SBIR documents

2. **Workshop Block 1: Introduce the Case Study**

Participants: Moderator + NSF Program Director (PD) + Founder/CEO

Discussion Items
   1. Assess commercial opportunity/potential and value proposition
   2. Technology strategy/roadmap – prototype/beta-version development
   3. Business strategy/business model to adopt?
   4. How best to fund this endeavor?

Course Content
   1. Participants discuss items identified for Block 1
   2. Founder/CEO explains Company approach/path; why NSF SBIR Program? SBIR route constraints; technical risk elements & mitigation; market factors – non-existent (create one); existing (carve out niche); NSF/SBIR panel reviews/summary implications; team building/dynamics
   3. NSF PD viewpoint: Decision-making process/considerations; technology pull-push issues; rationale for funding

3. **Workshop Block 2: Assess Where the Company is Now**

Participants: Moderator + IA+ Founder/CEO + NSF PD

Discussion Items
   1. Identify risk elements (technical, team, market, finance); how to manage/mitigate them?
   2. Additional funding strategy
   3. Barriers to entry
   4. Right business model?
   5. Identify areas where Company needs help

Course Content
   1. Participants discuss items identified for Block 2
   2. Company’s efforts to obtain additional funding; developing business plan elements
   3. NSF/SBIR PD: Next-round funding decision process/considerations; PD-Company relations; why introduce Company to IA
   4. IA-Company relationship: building trust; identifying areas to provide assistance
   5. How did IA help? Fill-out management team; mentoring; potential customer/partner/investor introductions; Board (Directors; Advisors) formation; business/IP/market strategy; valuation/negotiations
4. **Workshop Block 3: Determine Where to Go Next**

Participants: Moderator + IA+ Founder/CEO + “Partner” + NSF PD

**Discussion Items for Block 3**
1. IA approach right?
2. Timing market entry; go-to-market strategy
3. Growth strategy
4. Startup valuation exercise
5. Potential risk elements

**Course Content**

*Note:* “Partner”, a potential customer/strategic partner (larger company)/investor

1. Participants discuss items identified for Block 3
2. Regulatory issues
3. Company valuation; partner negotiations
4. Partner relations – communications/clarity; expectations alignment
5. Additional resources/funding
6. Adversity: problem mitigation/resolution; mistakes/lessons learned
7. Growth; exit strategy

5. **Wrap Up**

Take away; final thoughts

6. **Course Evaluation Questionnaire**