

## **Cancer Stem Cells: A New Frontier in the Treatment of Cancer**

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### **Introduction**

Despite tremendous advancements in fighting cancer, the prognosis for patients with advanced disease remains poor. Traditional therapies against cancer have limitations, such as, drug resistance and toxicity, which results in treatment failure and disease recurrence. However, today there is evidence that a subset of cancer cells, known as cancer stem cells (CSCs), could represent a fundamental gateway into improving cancer treatment.

CSCs are a small subset of cancer cells that have the ability to self-renew and initiate tumor growth. CSCs were first discovered in acute myeloid leukemia in the late 1990s. Since their discovery, CSCs have become the subject of intense research as a potential target for novel cancer therapeutics. CSCs share a number of properties with normal stem cells. Both typically make up a small percentage of the total number of cells in a tissue, they are largely quiescent, and most notably they are multipotent and can self-renew indefinitely.

The idea that CSCs are responsible for cancer growth and progression has important implications for the development of new therapeutics. Normally new anti-cancer therapies are assessed on their ability to shrink tumors, but if the therapies are not simultaneously eliminating CSCs, the tumor will return. Often the tumor will return with a resistance to the previously used therapy. CSCs also give rise to metastasis, the spread of cancer cells to new areas of the body, and can also serve as a reservoir of cancer cells that may cause relapse following treatment (surgery, radiation or chemotherapy) that has eliminated all observable signs of a cancer. Thus, innovative therapies must target and eliminate CSCs in order to prevent recurrence and improve patient survival.

The development of therapies against CSC targets is in its early stage, no CSC specific drug has yet to achieve FDA approval. This has not impeded multiple companies from entering this space and they have been rewarded with

both scientific and financial success. Several of the companies have achieved exits that could be valued in the billion dollars, providing record returns to investors and funding to advance treatments for patients suffering from diseases with limited therapeutic options.

### **Example of Companies Developing CSC Therapies**

#### **Boston Biomedical/Sumitomo Dainippon Pharma Co. Ltd.**

Boston Biomedical is developing novel compounds that target CSC pathways and has a product that is quickly approaching commercial launch. The company's lead product napabucasin is a small molecule inhibitor currently being tested in multiple clinical Phase III trials in combination with other cancer therapies for gastric/GEI adenocarcinoma, colorectal cancer, pancreatic cancer and non-squamous non-small-cell lung cancer. They have another compound, amcasertib, which is a small molecule currently being evaluated in multiple Phase II trials as monotherapy treatment for gastrointestinal stromal tumors, hepatobiliary cancer, urologic malignancies, ovarian cancer, and multiple solid tumors. The company has also developed a vast pipeline of additional CSC targeting therapeutics that includes both small molecule inhibitors and vaccine based therapies. In April 2012 Dainippon Sumitomo Pharma acquired Boston Biomedical in a deal that could be worth up to \$2.63 billion.

#### **Stemcentrx**

Stemcentrx's lead product is a targeted antibody drug conjugate Rova-T which is initially being developed for the treatment of small-cell lung cancer (SCLC). Stemcentrx determined that the protein, delta-like 3, was expressed on the surface of tumor cells but not in normal adult tissues. In preclinical studies, they demonstrated that Rova-T induced durable tumor regression across multiple models. They have since progressed into clinical testing for SCLC and are currently recruiting patients for a Phase I/II clinical trial. Rova-T is also being tested against several other cancers including ovarian cancer, medullary thyroid cancer, melanoma, and prostate cancer. Stemcentrx garnered major headlines in 2016 when it was acquired by Abbvie in a deal that could ultimately end up being worth over \$10 billion. The deal

represents the second-largest acquisition of a venture backed organization in history.

### **Oncomed**

Oncomed is discovering and developing monoclonal antibody therapeutics against novel CSC targets. Oncomed's platform technology has allowed it to rapidly develop a portfolio of seven antibodies that have advanced into clinical trials, and several others that are in preclinical development. The company's lead product is demcizumab, a monoclonal antibody. In preclinical and clinical studies, demcizumab demonstrated anti-tumor activity via multiple mechanisms, including inhibition of CSC growth. These results are being confirmed in an ongoing randomized Phase 2 trial. Another antibody in development by Oncomed is tarextumab, which is a novel anti-CSC antibody currently being studied in a randomized Phase 2 trial, in combination with differing chemotherapies in first-line for SCLC patients.

Oncomed went public in July 2013 and as of March 2017 had a market value of \$319 million. The company has also secured partnerships with Celgene, Bayer, and GlaxoSmithKline. Specifically, the Celgene deal is the company's most lucrative and could end up to be worth over \$3 billion. The deal involves OncoMed's lead drug, demcizumab, along with five preclinical candidates.

### **Agilvax**

A new entrant into the CSC scene is Agilvax, developing targeted cancer immunotherapies with its proprietary virus-like particle (VLP) platform technology. Agilvax's lead product, AX09, is being developed as an immunotherapy for triple-negative breast cancer (TNBC). Currently, no targeted therapy exists for TNBC, illustrating the critical need for the development of novel approaches and therapies for patients with this disease. Current preclinical studies conducted by Agilvax demonstrate that AX09 generates a robust response, reducing distal metastases and is well tolerated at all doses tested, with no toxicity observed after high dose administrations. Agilvax's immunotherapy candidate, AX09, is designed for use in combination with conventional and emerging treatments for TNBC.

Agilvax is currently raising its Series B round. At this point the company anticipates that AX09

will represent a significant licensing opportunity for the company.

To summarize, CSCs are thought to be the primary source of recurrence and metastasis; thus, therapeutics that target and eliminate CSCs have the potential to provide patients with durable and long-lasting relief from cancer. Investors and pharmaceutical communities have taken notice of this novel target, which is evident by the millions of dollars infused into CSC companies. Thus, these companies represent an investment opportunity that can provide outstanding return to investors. Of course, choosing the right investment needs great expertise and know-how that only specialists can provide. Evaluating biotech companies, especially in early stage, requires knowledge of the: 1. industry; 2. basic science; 3. translational medicine; 4. clinical execution; 5. competition; 6. legal (e.g. intellectual property); 7. company valuation and 8. the overall strategy. This is why all investors without in-depth knowledge of the industry should be careful and use professionals to drive their investment decisions.



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