INDUSTRY NOTE

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PMCB: Intriguing Platform for Delivering Targeted Therapies

Thoughts Following Recent Meeting: We recently had the opportunity to speak with the Chief Operating Officer of PharmaCyte Biotech (PMCB, $0.12, Not Rated), Dr. Gerald Crabtree. PharmaCyte is a clinical stage biotechnology company focused on developing treatments for cancer and diabetes based upon a proprietary cellulose-based live cell encapsulation technology known as “Cell-in-a-Box”. Formerly known as Nuvilex, the company restructured its operations in 2013, acquiring the exclusive, worldwide licenses to use the Cell-in-a-Box technology for the development of treatments for all forms of cancer using certain types of cells, and to use the technology for the development of a treatment for diabetes. The company anticipates that it will initiate 3 separate clinical studies evaluating the use of its technology in treating pancreatic cancer in Q1 2016. Given the unique and proprietary nature of its technology, we believe that investor attention in the company’s progress with these initiatives is warranted.

Unique, Proprietary Platform Technology: The Cell-in-a-Box technology utilizes the formation of pinhead sized cellulose-based capsules in which genetically modified live cells can be encapsulated and maintained. The capsules are comprised of a natural bio-inert cellulose component of cotton, and are manufactured utilizing a proprietary process. The basic goal of this encapsulation technology is to enable the selected contained cells to survive in the human host and function like any other living cell in the body. This is facilitated by the presence of small pores on the surface of the capsules, which are large enough to allow small molecules, such as nutrients, oxygen and waste products, to pass through, but are able to block the passage of immune system cells, thus enabling the encapsulated therapeutic cells to ‘live’ in the body without any inflammatory response or rejection. Due to their flexibility and robustness, the spherical shaped cell-containing capsules can easily be injected through a needle or catheter without bursting into the targeted area.

Primary Focus is Pancreatic Cancer: The company believes that Cell-in-a-Box can be used as a platform for delivering more targeted treatments for several types of cancer, including advanced, inoperable pancreatic cancer, which is its primary focus today. In this application, the Cell-in-a-Box capsule will be filled with modified live cells that overexpress a cytochrome P450 enzyme, which are capable of converting the prodrug ifosfamide into its active or “cancer-killing” form. ifosfamide is a chemotherapeutic agent with a long established history of clinical use, which was approved some years ago for use in pancreatic cancer patients. However, serious toxicity-related side effects have precluded its use at therapeutic doses for pancreatic cancer. ifosfamide is a prodrug, which upon metabolization by cytochrome P450 enzymes (mainly those that are expressed in the liver), is converted into short-lived tumor toxic metabolites. However, this short half-life necessitates relatively high systemic levels of ifosfamide (and its unacceptable side effects) to achieve therapeutic levels, especially in the pancreas, which is located downstream from the liver. Using the Cell-in-a Box technology, the encapsulated live P450 cells are placed as close to the tumor as possible. Similarly, ifosfamide is delivered under angiography to the pancreas where the conversion of ifosfamide takes place (largely bypassing the conversion in the liver), which allows for a dose that is one third the normal dose, thus helping to eliminate its adverse side effects. PharmaCyte has received orphan drug designation from the FDA for its pancreatic cancer product.

Pancreatic cancer is the fourth leading cause of cancer death in the U.S., with a median survival of only six months and a five-year survival rate of only 3%–5%. The reason for this poor prognosis is that pancreatic cancer is seldom detected in its early stages. There are usually no symptoms in the disease's early stages, and symptoms that are specific enough to suspect pancreatic cancer typically do not develop until the disease has reached an advanced stage. By this time, pancreatic cancer has often spread to other parts of the body. Survival is better for those with malignant disease that is localized to the pancreas and is thus amenable to surgical resection. However, 80%–85% of patients present with advanced non-resectable tumors that respond only poorly to most chemotherapeutic agents. The introduction of gemcitabine in 1997, rapidly became the gold standard for the treatment of pancreatic cancer, supported by Phase 3 data that achieved a rather modest median survival of 5.7 months, while the percentage of one-year survivors was approximately 18%. In 2013, the FDA approved the combination of Abraxane plus gemcitabine, which was supported by Phase 3 data that increased median survival to 8.5 months, while the percentage of one-year survivors increased to approximately 35%, and is now the Gold standard.

PharmaCyte is attempting to combat pancreatic cancer both by treating the cancer itself, and also by treating the pain that accompanies this cancer's development, and the ascites fluid accumulation that is generated with this and other types of abdominal cancers.

The safety and efficacy of the company's approach has been evaluated in 27 pancreatic patients in two earlier clinical trials conducted in Europe in the late 1990s and early 2000s. These trials employed the combination of an earlier version of the cellulose-based live cell encapsulation technology with low doses of ifosfamide. The two trials differed primarily in the dosage of ifosfamide that was given. In the first study, the dose was 1 g/m2 (1/3 the normal dose), while in the second study, the dose of ifosfamide was increased to 2 g/m2 (2/3 the normal dose).

The first study was an open-label, single-arm study involving 14 patients treated at a single clinical center in Germany. 12 of the patients were diagnosed with Stage IV disease, while the other 2 had Stage III disease. These patients received two infusions of 1 g/m2 ifosfamide (on days 2-4, and days 23-25 post capsule administration). The size of the primary tumor was measured prior to starting the treatment and at Weeks 10 and 20 post-treatment. The tumor did not grow any further during this observation period in any of the treated patients, with 2 of the 14 patients showing a partial response (PR - characterized by a more than 50% reduction in tumor volume), while the remaining 12 patients showed stable disease (SD) with tumor sizes in the range of 50%–125% of the initial size. Median survival time of patients in this trial was 10 months, while the one-year survival rate was 36%.

The second study was an open-label, single-arm study involving 13 patients treated at treated at four clinical centers (three in Germany and one in Switzerland). 12 of the patients were diagnosed with Stage IV disease, while 1 had Stage III disease. These patients received two infusions of 2 g/m2 ifosfamide. In this study, there were no partial remissions were observed, but four patients did show tumor size reductions, whilst the other four patients showed tumor growth, and the remaining five patients were classified as having stable disease. Median survival time of patients in this trial was 9.5 months, while the one-year survival rate was 23%.

The results of the two studies, which have appeared in peer-reviewed scientific literature, support the notion that the delivery of these encapsulated cells is safe and well tolerated without evidence of inflammatory disease, like pancreatitis. The efficacy profile of this treatment was encouraging, achieving a median survival of 10 months, but which must be interpreted considering the small sample size and lack of randomized control. The increased dosage of chemotherapy in the second study did not bring any additional benefit with respect to parameters of efficacy, such as tumor reduction, improvement of median survival or quality of life, but did result in more severe side effects. Taken together, this data suggests that additional later stage clinical trials of this unique therapy, using the lower dose of 1 g/m2, are warranted.

The company is now preparing to conduct a Phase 2b study. This is expected to be a randomized controlled study that will compare the Cell-in-the-Box/ifosfamide treatment to the current standard of care of Abraxane plus gemcitabine. The study will be conducted in Australia and will enrolled between 80-100 patients with non-operable pancreatic cancer. The company anticipates commencing this study in Q1 2016, after its partner Austrianova's manufacturing facility in Bangkok, Thailand, which will produce the Cell-in-a-Box capsules that will be used in the human clinical trials, is deemed to be Good Manufacturing Practices (GMP) compliant by the relevant regulatory authorities. A possible end goal of this study is to demonstrate that the combination is effective in shrinking the tumors, which not only reduces the pain, but could be used as a pretreatment to bring inoperable patients to a point where they could undergo surgical removal of their primary tumors.

The company is also pursuing a parallel development of its Cell-in-the-Box/ifosfamide treatment, evaluating its ability to alleviate the pain and ascites fluid accumulation that occurs in patients with advanced pancreatic cancer. The company is working with Translational Drug Development (TD2), a premier oncology CRO in the U.S., which has been contracted to carry out preclinical and clinical studies in these areas. TD2 is led by Daniel D. Von Hoff, who is a preeminent medical oncologist and oncology drug developer who has conducted national clinical trials with more than 200 new antineoplastic and

biologic agents. Dr. Von Hoff was the principal investigator of the Phase 3 MPACT study that demonstrated the benefit of Abraxane plus gemcitabine in treating pancreatic cancer, which was the basis for its approval for this indication by the FDA in 2013. One of the goals of TD2 is to shorten the time that new therapies can become available to patients that need them. PharmaCyte established a formal working relationship with Dr. Von Hoff in 2014.

The accumulation of ascites fluid is problematic for patients with a number of solid tumor cancers including abdominal, pancreatic, liver, ovarian, uterine, and colon cancers. As fluid builds up, it causes dramatic swelling of the stomach, which can be very painful and can cause breathing and other serious problems. Once it gets to a certain stage, it must be removed on a regular basis, usually every four weeks, which involves placing trocar into the patient's stomach and slowly sucking this fluid out. This procedure in itself is very uncomfortable for patients as well as costly. TD2 is conducting a series of preclinical studies designed to show that the Cell-in-a-Box/ifosfamide combination could be effective in slowing the accumulation of malignant ascites fluid and thus reduce the number of withdrawals of the fluid that patients with abdominal cancers must endure over a given period of time. The goal of the preclinical studies is to optimize the treatment and to inform the design of the human clinical studies.

The company anticipates that it will initiate two Phase 1 studies that will be conducted by TD2 in the U.S. in Q1 2016. One study will evaluate the ability of the Cell-in-a-Box/ifosfamide combination to slow the accumulation of malignant ascites fluid in patients with solid tumor cancers. The overall goal will be to see if it can extend the time, between withdrawals of excess fluid. The second study will evaluate the effectiveness of the Cell-in-a-Box/ifosfamide combination in reducing the severe pain that accompanies advanced pancreatic cancer. Efficacy will be measured by changes in the use of analgesics to control pain and the effect on quality of life measurements. Both studies are expected to evaluate about 40 patients each.

The Company's Second Area of Focus is Diabetes: The company is also using the Cell-in-a-Box technology to develop a treatment for Type 1 diabetes and Type 2 insulin-dependent diabetes. This initiative will utilize the Cell-in-a-Box technology to encapsulate a human cell line which has been genetically engineered to produce, store, and secrete insulin on demand at levels in proportion to the levels of blood sugar in the human body. The goal is to provide insulin producing cells that remain viable for an extended time of several years, thus creating in effect a true bio-artificial pancreas. Since these capsules are composed largely of a bio-inert cellulose material they are exceedingly robust, which should allow them to remain intact for long periods of time in the body. Furthermore, it is hoped that the encapsulation will protect the enclosed living cells against immune system attack.

Type 1 diabetes is caused by the autoimmune destruction of insulin-producing pancreatic β-cells. Insulin is hormone, whose function is to transport glucose in the blood across the cell barrier where it can be used as a source of energy. This requires the diabetic to administer daily injections of insulin to control their blood glucose levels. There is a significant amount of research focused on the development of replacement β-cells that are capable of restoring this function. The idea of transplantation of insulin-secreting tissue in the diabetic has been explored, but has yet to overcome the key hurdle of rejection of the transplanted tissue by the patient's immune system, thus requiring the use of lifelong immunosuppression in order to keep the insulin-secreting tissue viable. In theory, artificial β-cells that are engineered from the patient's own cells could minimize the autoimmune responses. Liver cells are known to express enzymes which are key elements of the glucose sensing system that regulates insulin release from β-cells in response to changes in the external nutrient composition, and thus viewed as attractive candidates as non-β-cell precursors for the engineered β-cells. For an artificial β-cell line to be a realistic cure for diabetes, it would need to fulfill two criteria: first the ability to secrete insulin in response to glucose in the physiological range, and second to retain viability in the presence of cytokines secreted during proinflammatory immune responses that precipitate autoimmune diabetes.

The company has obtained the worldwide license from the University of Technology Sydney in Australia, to use their "Melligen" insulin-producing genetically modified cells for the development of a treatment for insulin-dependent diabetes. These Melligen cells can be readily grown in culture and hence are available

in unlimited supply. Further compared to native pancreatic beta islet cells, Melligen cells are much more resistant to the pro-inflammatory cytokines that have been shown to be involved in beta islet cell death.

The pre-clinical results for Melligen cells, while still at an early stage, look promising at this point. An article entitled "Reversal of diabetes following transplantation of an insulin-secreting human liver line: Melligen cells", published in the journal *Molecular Therapy - Methods and Clinical Development* in April 2015, described the ability of Melligen cells when transplanted into diabetic immunoincompetent mice to secrete insulin in response to glucose within the physiological range, restoring the presence of a normal concentration of glucose in the blood. Further, the exposure of Melligen cells to proinflammatory cytokines (TNF-α, IL-1β, and IFN-γ) affected neither their viability nor their ability to secrete insulin to glucose.

Going forward, much more research will be needed to demonstrate the effectiveness of the Cell-in-the-Box encapsulation technology in protecting the Melligen cells from destruction by the immune system, notably cytotoxic T cells, which mediate allograft and autoimmune reactions. Additionally, the encapsulated cells will still be exposed to immune mediators, such as proinflammatory cytokines, which played major roles in the initial autoimmune destruction of the native β-cell population. Finally, it must be demonstrated that the encapsulation can protect the recipient from the possible tumorigenic nature of the Melligen cells. As a result, human clinical trials for diabetes are still several years away.

To facilitate a more rapid development of its unique diabetes treatment, the company has established an international Diabetes Consortium that consists of 16 world-renowned physicians and scientists from several countries, all of whom share the same goal of developing a treatment for insulin-dependent diabetes. One of the members, the Institute of Virology at the University of Veterinary Medicine Vienna, has recently completed the first round of safety testing of the Melligen cells in mice. The company also has research agreements in place with consortium members, the University of Technology in Sydney, Australia, the Vorarlberg Institute for Vascular Investigation and Treatment in Feldkirch, Austria, the University of Barcelona in Barcelona, Spain and the University of Copenhagen in Denmark.

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