Zacks Small-Cap Research

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MabVax Therapeutics Holdings, Inc. (MBVX - OTC)

MBVX: MabVax Therapeutics Holdings, Inc. – Novel Vaccine and Antibody Discovery Platform – Transferring Analyst Coverage…

Current Recommendation	**Buy**
Prior Recommendation	N/A
Date of Last Change	07/13/2015
Current Price (07/29/15)	$1.64
Target Price	**$4.50**

INITIATION

We are transferring analyst coverage of MabVax Therapeutics Holdings, Inc. and continuing with a 'Buy' rating and a $4.50 price target.

MabVax is a clinical stage cancer immunotherapy company engaged in the discovery, development and commercialization of proprietary human monoclonal antibody products and vaccines for the diagnosis and treatment of a variety of cancers. The company has generated >100 fully human antibody leads from patients immunized with proprietary therapeutic vaccines.

The company will file an IND on its lead antibody candidate, HuMab-5B1 for the treatment of metastatic pancreatic and colon cancer in the fourth quarter of 2015, and anticipates receiving an FDA acceptance and go ahead to start human studies prior to the end of the year. The company will also file an IND and anticipates receiving FDA clearance for a pancreatic cancer diagnostic version of 5B1 in the fourth quarter of 2015. Data from the company's cancer vaccine program should be available in 2016.

SUMMARY DATA

52-Week High	**$15.00**
52-Week Low	**$0.85**
One-Year Return (%)	**-80.70**
Beta	**-0.34**
Average Daily Volume (sh)	**174,721**
Shares Outstanding (mil)	**24**
Market Capitalization ($mil)	**$38**
Short Interest Ratio (days)	**1.33**
Institutional Ownership (%)	**0**
Insider Ownership (%)	**36**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2013 Estimate	**N/A**
P/E using 2014 Estimate	**N/A**

Risk Level	**Above Average**
Type of Stock	**Small-Growth**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue

(In millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2014	0.1 A	0.1 A	0.1 A	0.1 A	0.3 A
2015	0.2 A	0.2 E	0.2 E	0.2 E	0.8 E
2016					1.0 E
2017					1.0 E

Earnings per Share

(EPS is operating earnings before non-recurring items)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2014	- A	- A	-$1.54 A	-$1.30 A	-$9.51 A
2015	-$6.25 A	-$0.12 E	-$0.11 E	-$0.11 E	-$1.66 E
2016					-$0.48 E
2017					-$0.40 E

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WHAT'S NEW

Initiating Coverage

We are initiating coverage of MabVax Therapeutics Holdings, Inc. (MBVX) with a Buy rating and a $4.50 price target. MabVax is a clinical-stage cancer immunotherapy company engaged in the discovery, development, and commercialization of proprietary human monoclonal antibody products and vaccines for the diagnosis and treatment of cancer.

The company utilizes a novel antibody discovery platform whereby lead antibody candidates are derived from patients immunized with the company's proprietary therapeutic vaccines. MabVax is the only company we know of to be developing fully human antibodies targeting cancer from immunized humans, which has a number of advantages over other antibody discovery platforms.

1) There is no need to genetically modify a murine derived antibody or perform any type of *in vitro* affinity maturation, as the patient's immune system has already performed that work.
2) The self-censoring mechanism of the human immune system prevents the production of "self-harming" antibodies. Thus, any antibody derived from a vaccinated patient that responds well to the vaccine is unlikely to result in unwanted side effects.
3) A "proof-of-concept" experiment has already been performed; a source patient who had a positive clinical outcome provides anecdotal evidence for clinical activity of any derived antibodies.

MabVax's lead antibody candidate, originally known as HuMab-5B1, is being developed as both a therapeutic and a diagnostic agent. These products are now designated as MVT-5873 for the therapeutic product and MVT-2163 for the diagnostic product. The antibody targets the carbohydrate antigen sialyl Lewis^{a} (sLe^{a}), which is overexpressed on a number of epithelial tumor types and has limited and restricted expression in normal tissue. As a therapeutic, MabVax will be developing MVT-5873 as a treatment for metastatic pancreatic and colorectal cancer, two diseases with very grim prognoses. For use as a diagnostic agent, HuMab-5B1 will be coupled to the radionuclide ^{89}Zr using a clinically validated linking agent (DFO). The resulting ^{89}Zr-DFO-HuMab-5B1 (MVT-2163) is planned for evaluation in pancreatic cancer patients for use in PET imaging. Pre-clinical data for the HuMab-5B1 therapeutic and diagnostic programs show the antibody to be highly effective. The company will file an IND for MVT-5873 for the treatment of metastatic pancreatic and colorectal cancer in the fourth quarter of 2015 and anticipates receiving FDA clearance prior to the end of the year. The company will also file an IND and anticipates receiving FDA clearance for MVT-2163 as a pancreatic cancer diagnostic product in the fourth quarter of 2015.

In addition to monoclonal antibodies, MabVax has licensed a series of cancer treatment vaccines, two of which are currently in Phase 2 clinical trials as adjuvant treatments for recurrent sarcoma and ovarian cancer. Data readouts for these two trials are expected in 2016. A third vaccine for treating recurrent neuroblastoma has finished Phase 1 clinical testing with good clinical activity noted, and a Phase 2 trial is expected to begin in 2016.

We would expect a company with multiple Phase 2 cancer treatment assets and a novel antibody discovery platform to be trading at least on par with similar companies, if not for a slight premium. However, MabVax has a current market cap of only $50 million, most likely representing the fact that investors are not familiar enough with the company's story. We believe that the combination of increased investor awareness and multiple upcoming milestones will offer investors the chance for sizeable returns.

INVESTMENT THESIS

Monoclonal Antibodies

Biological therapeutics, or biopharmaceuticals, have been a huge success for the biotechnology industry, both in terms of the number of patients that have been treated and the revenues generated from their sale. Examples of biopharmaceuticals include vaccines, gene therapies, tissues, and recombinant proteins. Monoclonal antibodies are a particular type of recombinant protein and comprise many of the top-selling therapeutics in the world. The following chart lists the top five selling monoclonal antibodies in 2014 along with their indications. Combined global sales of all approved monoclonal antibodies were approximately $78 billion in 2014.

Name	Indication	2014 Sales ($ Billions)
Humira® (adalimumab)	Autoimmunity	$12.7
Remicade® (infliximab)	Autoimmunity	$9.8
Rituxan® (rituximab)	Cancer	$7.6
Avastin® (bevacizumab)	Cancer	$7.0
Herceptin® (trastuzumab)	Cancer	$6.8

Source: Company documents / Zacks SCR

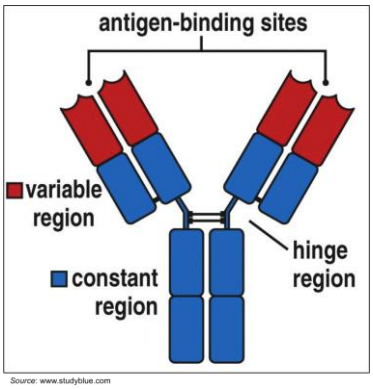
Since 1986, the U.S. Food and Drug Administration (FDA) and/or the European Medicines Agency (EMA) have approved 44 monoclonal antibodies (The Antibody Society). Of these, five are murine, eight are chimeric, 18 are humanized, and 13 are fully human. The origin of a monoclonal antibody is indicated by its name, as the following substems are used before the stem 'mab' (which indicates it's a monoclonal antibody):

-o- murine
-xi- chimeric
-zu- humanized
-u- human

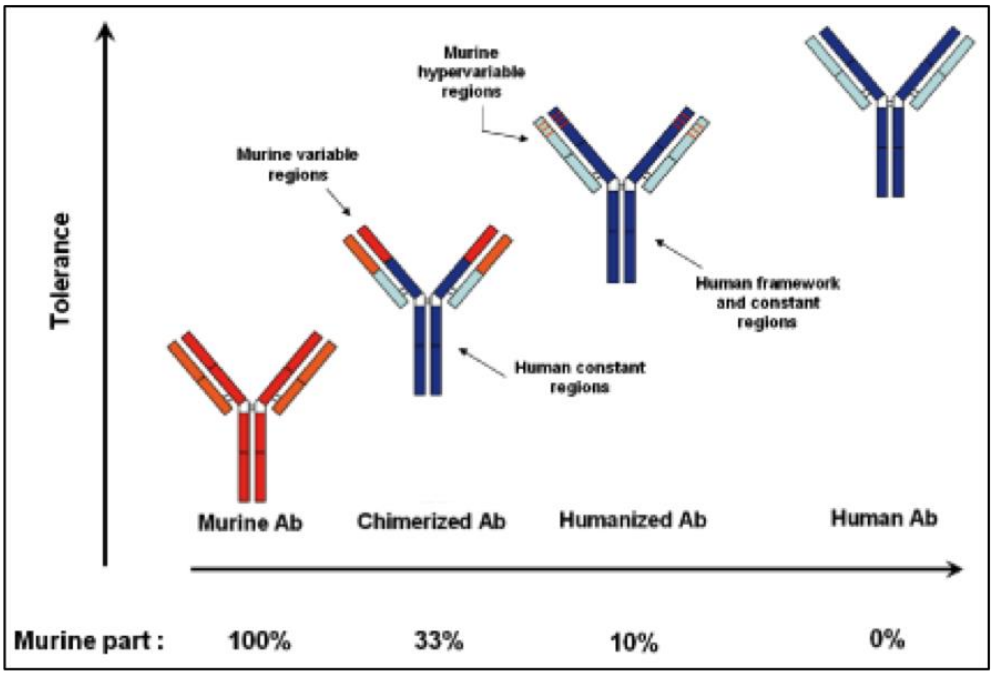
For example, adalim**u**mab is a fully human monoclonal antibody, infli**xi**mab is chimeric, and bevaci**zu**mab is humanized. The differences in origin can have a significant effect on the efficacy and immunogenicity of the antibody.

…Differences Between Types of Monoclonal Antibodies…

Antibodies are produced by specialized cells of the immune system called B-cells and their purpose is to bind to a foreign substance such that it can be neutralized or eliminated. Monoclonal antibodies are monospecific (meaning they bind only one target) and are derived from a single B-cell. They are large, complex proteins composed of two heavy chains and two light chains. Each heavy and light chain is composed of a constant and a variable region. The amino acid sequence of the constant region is the same for all antibodies of the same isotype, while the amino acid sequence of the variable region is unique for each antibody. The binding specificity is due to the unique amino acid sequences of the antigen-binding sites (complementary determining regions or CDRs), which are composed of certain amino acids of the variable regions of both the heavy and light chains.



While all share the same basic structure, the four different types of antibodies currently in clinical use differ in the origin of the constant and variable regions of the antibody (Imai *et al*., 2006).



Source: Pelat *et al*., 2011

Murine antibody: This is a monoclonal antibody derived from a mouse B-cell through hybridoma technology. B-cells are isolated from an immunized mouse and fused with myeloma cells to immortalize the B-cells. Single B-cells are then tested for high-affinity antibodies against the target antigen. The B-cell producing the optimal antibody can then be propagated *ad infinitum* in order to collect enough of the desired antibody for its intended purpose. These antibodies are rarely developed for therapeutic purposes anymore because repeated administration of murine antibodies results in the generation of human anti-mouse antibodies (HAMA), which can lead to decreased efficacy and the potential for anaphylactic shock. Orthoclone Okt3, the first monoclonal antibody approved by the FDA, is a murine monoclonal antibody.

Chimeric antibody: This is a monoclonal antibody where the variable domains are derived from a murine antibody and then genetically linked to the constant domains of a human antibody. The genetic sequence of a chimeric antibody is then inserted into a cell line (typically chinese hamster ovary (CHO) cells) to allow for expression of the antibody. A chimeric antibody is approximately 65% human origin and thus has decreased immunogenicity and a longer half-life than a murine antibody. Rituxan® (rituximab) is an example of a chimeric antibody.

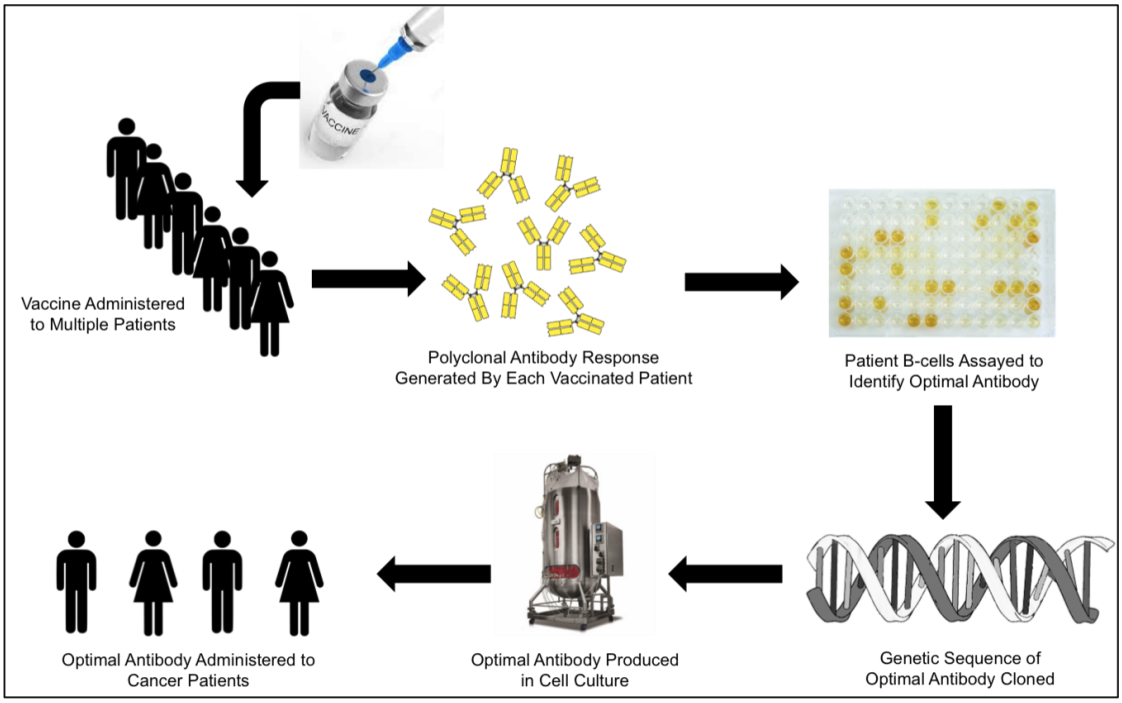
Humanized antibody: This is a monoclonal antibody where the specific amino acids that come into contact with the target antigen (from a murine antibody) are inserted into a human monoclonal antibody sequence. The result is an antibody that is approximately 90-95% human origin and thus is less immunogenic than a chimeric antibody. Creating humanized antibodies is highly complex and requires a significant expertise. If not done properly, humanized antibodies will typically bind with less affinity to the target antigen than the original mouse antibody from which the antigen-binding amino acids were derived. Avastin® (bevacizumab) is an example of a successfully developed humanized antibody.

Human antibody: This is a monoclonal antibody that is 100% human origin. It is created through the use of transgenic mice that have human immunoglobulin genes inserted into their genome or through the use of phage display, in which human immunoglobulin genetic sequences are manipulated *in vitro* to identify an antigen-binding domain of interest. Humira® (adalimumab) is an example of a human antibody discovered through phage display while Opdivo® (nivolumab) is an example of a human monoclonal antibody discovered through the use of transgenic mice.

…MabVax's Novel Antibody Discovery Platform…

MabVax has generated >100 fully human antibody leads from the use of a novel antibody discovery platform. Instead of using transgenic mice or phage display, MabVax generates fully human antibodies from B-cells extracted from patients immunized with proprietary cancer vaccines. This is the only example we know of where fully human monoclonal antibodies targeting cancer are generated from immunized patients.

1) The vaccine (containing a target antigen/s) is delivered to the patients multiple times, which aids in driving a specific and high-affinity antibody response. In addition, this technique takes advantage of the natural mechanisms unique to the human immune system to produce highly useful and protective antibodies.
2) Each patient produces a polyclonal antibody response to the antigen.
3) B-cells are harvested from small volumes of blood samples obtained from the immunized patients and assayed to identify high-affinity antibodies to the target antigen. Importantly, patient outcomes can be utilized in antibody selection, thus if a patient has a positive clinical outcome due to the vaccine (i.e., becomes cancer free), an antibody from that patient is more likely to result in a favorable clinical outcome upon use of that antibody in other patients.
4) The genetic sequence from the optimal antibody is then cloned into an expression vector and the antibody is produced as a monoclonal through standard cell culture techniques.
5) The monoclonal antibody is purified for use as a cancer therapeutic.



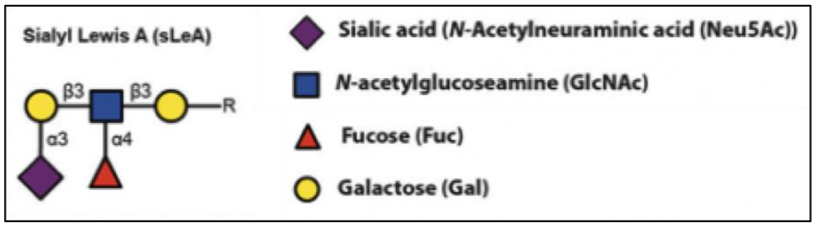
Source: Zacks SCR

Deriving fully human monoclonal antibodies from vaccinated patients is a novel approach to generating therapeutic antibody candidates and comes with a number of advantages over traditional antibody discovery programs. These advantages include:

1) There is no need to genetically modify a murine derived antibody or perform any type of *in vitro* affinity maturation, as the patient's immune system has already performed that work.
2) The self-censoring mechanism of the human immune system prevents that production of "self-harming" antibodies. Thus, any antibodies derived from a vaccinated patient that responds well to the vaccine are less likely to result in unwanted side effects.
3) A "proof-of-concept" experiment has already been performed; a source patient who had a positive clinical outcome provides anecdotal evidence for clinical activity of any derived antibodies.

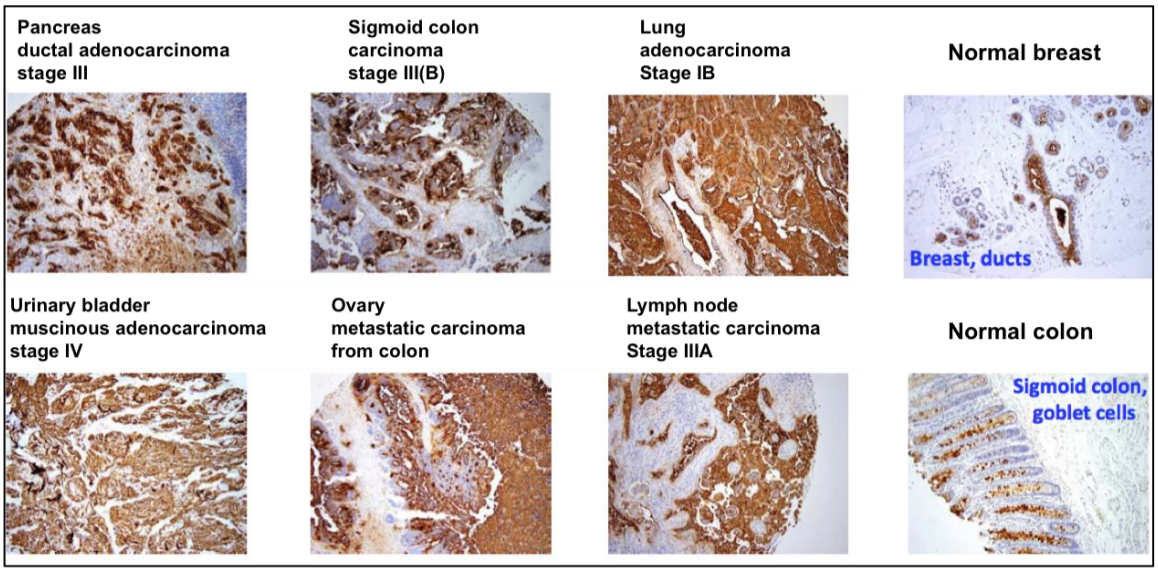
…MabVax's Lead Antibody Candidate Targets Sialyl Lewis^a Antigen…

MabVax has focused its initial antibody discovery work against tumor associated carbohydrate antigens (TACAs), as they are consistently over-expressed across a wide range of cancer types while being less expressed on normal tissue (Dabelsteen, 1996). The TACA sialyl Lewis^a (sLe^a) was discovered in the early 1980's and a diagnostic assay using an antibody (CA19-9) raised to sLe^a is used worldwide to aid in the management of pancreatic cancer (Magnani *et al*., 2004). The American Society of Clinical Oncology discourages the use of CA19-9 as a screening test for cancer due to a high number of both false positives and false negatives (Locker *et al*., 2006), however CA19-9 is useful in determining whether a pancreatic tumor is secreting sLe^a and if so, how the tumor is responding to treatment through the rise and fall of sLe^a serum levels.



Source: Glycopedia.eu

sLe^a is over-expressed on a number of different epithelial tumor types including pancreatic, colon, stomach, ovarian, breast, and small-cell lung cancers. The following figure shows significant homogeneity and staining intensity of sLe^a on different types of cancer cells along with limited staining of normal tissue. The expression of sLe^a on normal breast, colon, and pancreatic tissue is restricted to cells of the secretory ducts and lumen, which are inaccessible to the immune effector mechanisms.



Source: MabVax Therapeutics, Inc. / MSKCC

Circulating cells from those tumors typically over-express sLe^a, and as a ligand for E selectin (a protein expressed in the inner lining of blood vessels) this antigen facilitates interactions between tumor cells and tissues that are key events for tumor metastasis. Colorectal cancer cells that express high levels of sLe^a metastasize more efficiently than cells that express low levels of sLe^a (Ben-David *et al*., 2008). In addition, the loss of sLe^a expression was shown to inhibit metastasis of human gastrointestinal tract cancer cells (Kawamura *et al*., 2005). Due to the overexpression of the antigen on the surface of cancer cells and its role in metastatic disease, **WE CONCLUDE** that the sLe^a antigen is an attractive target for therapeutic intervention.

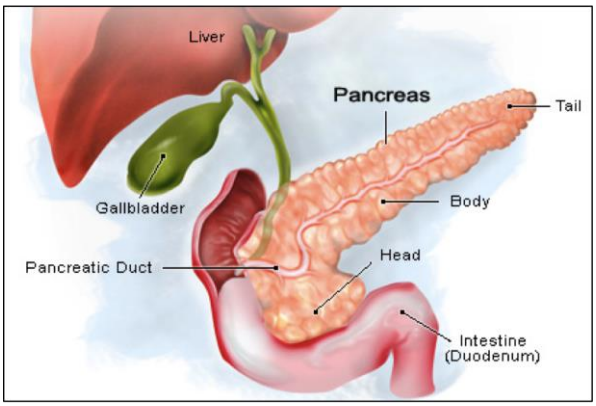
Monoclonal Antibody Indication I: Metastatic Cancer

The lead antibody in MabVax's pipeline is HuMab-5B1, which has demonstrated exceptionally high affinity (Kd = 140 pM) and specificity for sLe^a. HuMab-5B1 was derived from a patient with Stage IV breast cancer who was originally vaccinated with a sLe^a vaccine at the end of 2008. A total of seven patients were vaccinated at that time with the sLe^a vaccine and six of them are still alive today. The patient from whom 5B1 was derived remains disease free to this day. MabVax is targeting HuMab-5B1 for the treatment of metastatic pancreatic and colorectal cancer, as these two diseases have very low 5-year survival rates and improved therapeutic options are clearly warranted.

…Pancreatic Cancer…

Pancreatic cancer is responsible for 7% of all cancer deaths in both men and women, making it the fourth leading cause of cancer death in the U.S. (American Cancer Society). Estimates indicate that 40% of pancreatic cancer cases are sporadic in nature, 30% are related to smoking, 20% may be associated with dietary factors, and only 5-10% are hereditary in nature (Raimondi *et al*., 2009).

Pancreatic cancer is notoriously difficult to diagnose in early stages. The reason for this is because initial symptoms of the disease are often nonspecific and subtle in nature, and include anorexia, malaise, nausea, fatigue, and back pain. Approximately 75% of all pancreatic carcinomas occur within the head or neck of the pancreas, 15-20% occur in the body of the pancreas, and 5-10% occur in the tail.



Source: medicinenet.com

The only potential curative therapy for pancreatic cancer is complete surgical resection. Unfortunately, this is only possible for approximately 20% of cases, and even of those patient's whose cancer is surgically resected, 80% will develop metastatic disease within two to three years following surgery (Daniel *et al*., 2008). Patients with unresectable pancreatic cancer have a median overall survival of 10 to 14 months while patients diagnosed with Stage IV disease (indicative of metastases) have a 5-year overall survival of just 1%.

…Current Treatment Options for Pancreatic Cancer…

Surgery remains the primary mode of treatment for patients with pancreatic cancer. However, there is an important role for chemotherapy and/or radiation in an adjuvant (given to prevent recurrence) or neoadjuvant (given before surgery to shrink the tumor to make complete resection more probable) setting as well as in patients with unresectable disease.

Since its approval in 1996, gemcitabine has been partnered with approximately 30 different agents in late-stage clinical trials in an attempt to improve upon the effectiveness of gemcitabine alone in treating patients with metastatic pancreatic cancer. Only two of these trials have led to an FDA approval – erlotinib (Tarceva®) and nab-paclitaxel (Abraxane®).

In patients with metastatic disease, the use of erlotinib with gemcitabine led to a significantly higher 1-year survival rate than with the use of gemcitabine alone (23% vs. 17%, $P = 0.023$) as well as an increased median overall survival (6.24 months vs. 5.91 months, $P = 0.038$) (Moore *et al*., 2007). A more recent study showed that the addition of nanoparticle albumin-bound (nab)-paclitaxel to gemcitabine significantly improved overall survival in treatment naïve patients with metastatic cancer, as overall survival was approximately two months longer in patients treated with combination therapy (8.5 vs. 6.7 months) (von Hoff *et al*., 2013).

The FOLFIRINOX (leucovorin + 5-fluorouracil + oxaliplatin + irinotecan) regimen was shown to significantly improve overall survival compared to treatment with gemcitabine (11.1 months vs. 6.8 months) (Conroy *et al*., 2011). While dramatically improving overall survival, the FOLFIRINOX treatment was accompanied by serious adverse events and thus is only recommended for patients with good performance status.

Other combinations of gemcitabine with cisplatin, oxaliplatin, irinotecan, or docetaxel tested in Phase 3 trials have not been of superior benefit to gemcitabine alone. The combination therapy nab-Paclitaxel and gemcitabine was recently approved by the FDA as an additional standard of care for the treatment of patients with untreated pancreatic adenocarcinoma. However, the improvements were modest, and treatment of pancreatic cancer remains an intense area of research with 92 products in all stages of clinical development with 14 of them in Phase 3 at this time.

…Pancreatic Cancer Market Analysis…

It is estimated that in 2015 approximately 49,000 people will be diagnosed with pancreatic cancer in the U.S. More than half of these patients will be diagnosed with metastatic disease. The 5-year survival rates for patients with pancreatic cancer are dismal (<14%) and are particularly bad for those with metastatic disease (~1%).

The current standard of care for patients with metastatic pancreatic cancer includes gemcitabine combined with either erlotinib or nab-paclitaxel. Gemzar® (gemcitabine) is now available as a generic, however prior to losing patent protection the drug generated peak revenues of approximately $700 million in the U.S. for Eli Lilly. Tarceva® (erlotinib), which is approved for the treatment of metastatic non-small cell lung cancer and metastatic pancreatic cancer, is marketed by Roche and Astellas and sales of the drug generated $1.4 billion in revenue in 2014. Abraxane® (nab-paclitaxel), which was approved for the treatment of breast cancer in 2005 and non-small cell lung cancer in 2012, was approved by the FDA in 2013 for the treatment of metastatic pancreatic cancer. Sales of Abraxane® totaled $848 million in 2014 for all indications.

…Background on Colorectal Cancer…

Colorectal cancer (CRC) is the second leading cause of cancer death in the U.S. and the most common type of gastrointestinal cancer. It is also a preventable disease through the use of widely available screening programs that aid in early detection, most notably colonoscopy. This has resulted in decreasing the death rate from CRC for the past 20 years, mostly from finding and removing polyps before they develop into cancers and diagnosing the disease at earlier stages.

CRC is a genetically complex disease that typically contains a number of genetic alterations associated with the progression of the disease from an adenoma to an invasive adenocarcinoma. This sequence of mutations involves the activation of an oncogene (a gene that promotes tumor growth) coupled with the loss of activity in several genes that suppress tumor formation (Vogelstein *et al*., 1988). The vast majority of CRC's arise spontaneously (>90%) with a small percentage of cases due to heritable diseases such as Lynch syndrome.

Overall survival is inversely proportional to the stage at which the disease is diagnosed. While 5-year survival rates for all CRC patients is 65%, when broken down by stage the survival rates are: 95% for Stage I, 60% for Stage III, and <10% for Stage IV (National Cancer Institute). CRC typically metastasizes to the liver, and surgery is considered the standard of care for metastatic disease. Approximately 33% of patients undergoing surgery for colorectal liver metastases will survive five years, with half of those patients surviving 10 years and thus being cured of the disease (Chua *et al*., 2011).

…Current Treatment Options for CRC…

Surgery is the only curative therapy for patients with Stage I-III disease, and can be used for patients with limited metastatic disease in the liver or lungs. However, 50% of CRC patients will have relapse of disease even after complete macroscopic tumor removal, including 25% of patients with Stage I and II disease (Young *et al*., 2014).

Chemotherapy is standard of care for patients with Stage III (in the adjuvant setting) or Stage IV disease (in the neoadjuvant or adjuvant setting) and a wide number of agents are currently used in the treatment of CRC, including oxaliplatin, leucovorin, 5-fluorouracil, capecitabine, and irinotecan. Those agents are typically used in various dosages and combinations. Chemotherapeutic agents may also be combined with agents that target specific cell surface receptors such as the epidermal growth factor receptor (EGFR) with panitumumab (Vectibix®) or cetuximab (Erbitux®) and the vascular endothelial growth factor (VEGF) with bevacizumab (Avastin®) or ziv-aflibercept (Zaltrap®). Regorafenib (Stivarga®) is an oral multi-kinase inhibitor that targets VEGFR2 and TIE2.

…CRC Market Analysis…

Approximately 140,000 new cases of CRC will be diagnosed in the U.S. in 2015 (American Cancer Society). Approximately 40% of new CRC cases are diagnosed at Stage I or II, 36% at Stage 3, and 20% at Stage IV. While rates of CRC in those over the age of 50 have been declining, rates in those younger than 50 have been increasing.

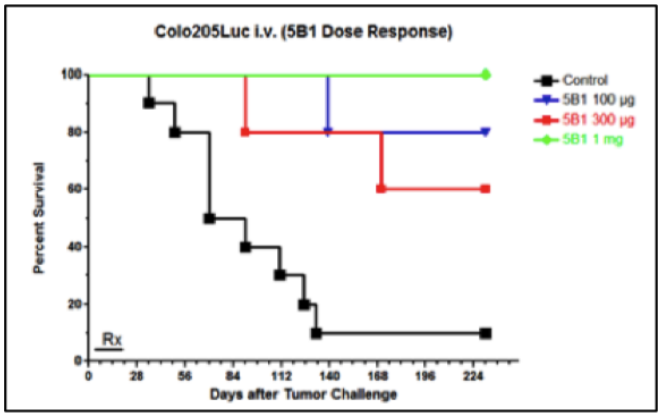
As mentioned previously, surgery remains the standard of care for early stage CRC patients. For patients with advanced disease and those ineligible for surgery, systemic treatment with chemotherapeutic agents (discussed previously) and/or targeted agents is considered first line treatment with more treatment options available for those who fail first line treatment. The following table lists available targeted treatments along with sales of each of those drugs in 2014.

Name	Target	Company	Indications	2014 Sales ($ Millions)
Vectibix® (panitumumab)	EGFR	Amgen	CRC	$500
Erbitux® (cetuximab	EGFR	BMY/ Merck KGaA	CRC Head and Neck	$1,900
Avastin® (bevacizumab)	VEGF	Roche	CRC NSCLC Glioblastoma Ovarian Cervical	$7,000
Zaltrap® (ziv-aflibercept)	VEGF	Sanofi/ Regeneron	CRC	$91
Stivarga® (regorafenib)	VEGFR2-TIE2	Bayer	CRC GIST	$250

Source: Company documents / Zacks SCR

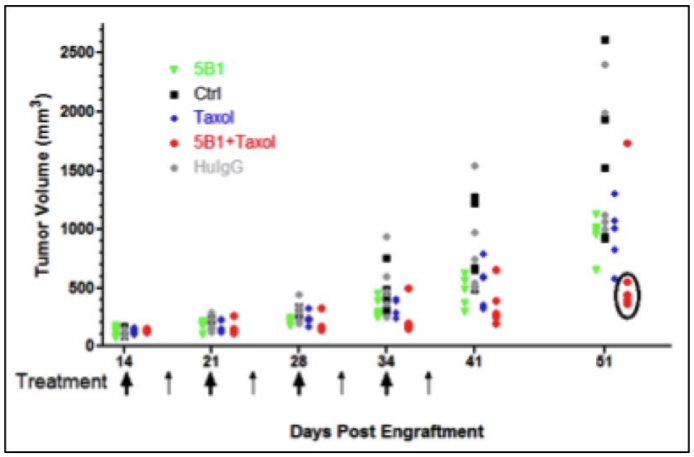
…MVT-5873 is Effective in Pre-Clinical Cancer Models…

MabVax has tested MVT-5873 (Hu-Mab-5B1) in multiple pre-clinical tumor xenograft models. The first model involved the use of colo205 cells, which are a human colorectal cancer cell line. The following figure shows the effect of treating mice inoculated with colo205-luc cells with MVT-5873 (5B1) at varying concentrations. Mice were treated twice a week for the first two weeks and then once a week for the next 7 weeks. All mice treated with MVT-5873 at 1 mg per injection survived the experiment.



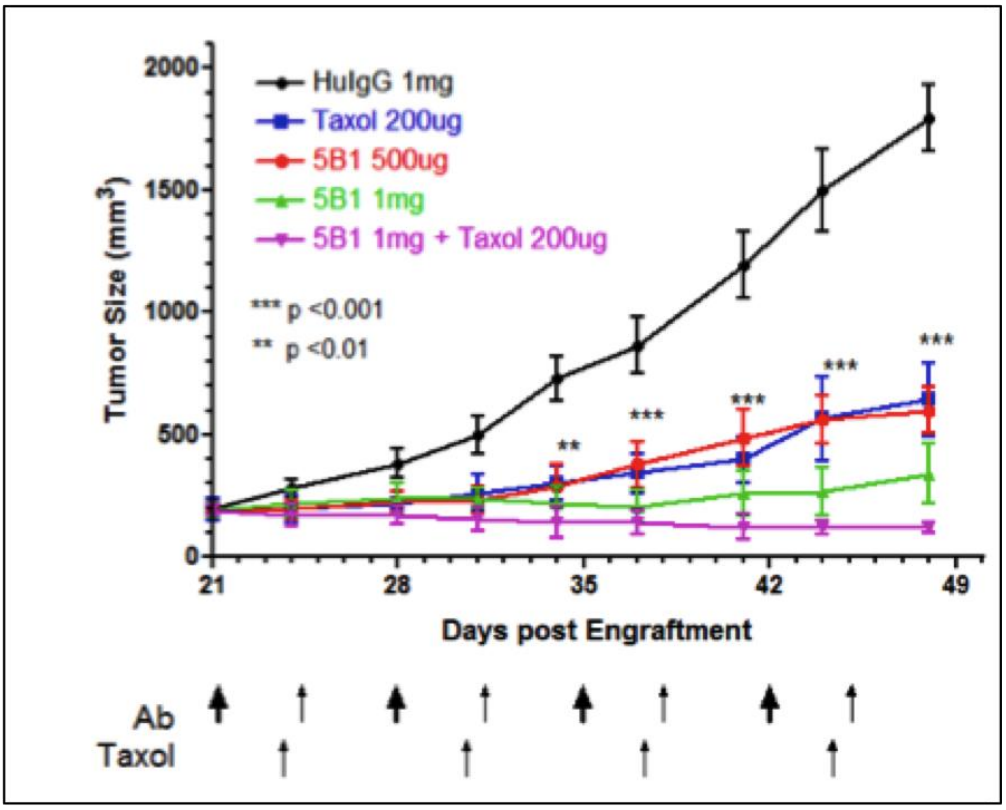
Source: MabVax Therapeutics, Inc.

Another experiment was performed with BxPC3 cell line, which is a human pancreatic cancer cell line. BxPC3 cells were injected into mice and the tumors were allowed to grow for 14 days (>100 mm^3) before commencing treatment. Mice were treated twice per week with either MVT-5873 or control human IgG and taxol was administered once a week for four weeks. Results show that either MVT-5873 or taxol reduced tumor growth over control and the combination of MVT-5873 and taxol significantly reduced tumor growth compared to either treatment alone.



Source: MabVax Therapeutics, Inc.

MVT-5873 has also been tested in a human small-cell lung cancer model using the DMS79 cell line. After allowing the tumors to grow for three weeks, treatment was begun with MVT-5873 and taxol either alone or in combination. Results showed that MVT-5873 treatment coupled with taxol inhibited tumor growth while MVT-5873 treatment alone resulted in only modest tumor growth.



Source: MabVax Therapeutics, Inc.

In summary, MVT-5873 has shown activity in pre-clinical models using human colorectal, pancreatic, and small-cell lung cancer xenografts, exactly as would be predicted based on the expression of sLe[a] on those tumor types. In addition, the data support the use of MVT-5873 in combination with chemotherapeutic agents since MVT-5873 was able to increase the effectiveness of taxol in two separate models.

… MVT-5873 Development Plan in Metastatic Cancer…

MabVax is planning to file an investigational new drug (IND) application with the FDA for MVT-5873 before the end of 2015 and initiate a Phase 1 clinical trial to examine the safety and pharmacokinetics in a group of patients with different cancer types shortly thereafter. We anticipate preliminary results from this study being available in the first half of 2016 with full results available later in the year.

Following the Phase 1 study, MabVax is planning to initiate a Phase 2 clinical trial that will enroll approximately 150 patients and require two to three years to complete. The program will likely be eligible for Orphan Drug Designation since pancreatic cancer only affects approximately 50,000 individuals each year. The Phase 2 study would likely require $10 million to complete, however the MVT-5873 program has garnered the interest of several larger biopharmaceutical companies based on the positive pre-clinical testing, xenographic animal model experiments, and toxicology results generated thus far and the company would consider partnering after the Phase 1 study is complete if acceptable terms can be established. The robust pipeline of follow-on antibodies already generated means the company can partner MVT-5873 early on as a means of generating non-dilutive capital.

Monoclonal Antibody Indication II: Diagnostic Imaging

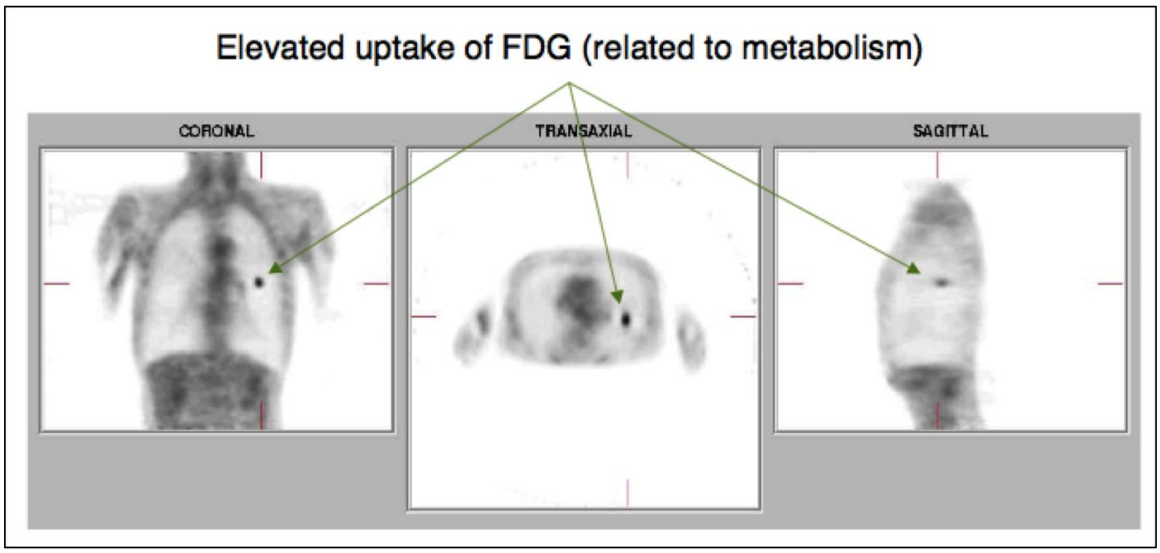
A number of cancer biomarkers have been identified that aid in early detection and diagnosis as well as for monitoring of therapeutic progress and tumor recurrence. These include prostate specific antigen (PSA), a protease over-expressed by prostate cancer cells, and CA125, a peptide cleaved from the transmembrane protein MUC16 that is over-expressed by ovarian cancer cells. While PSA is useful for detecting residual tumor burden or recurrence after radical prostatectomy, a number of benign pathologies of the prostate (e.g., prostatitis) also cause an increase in PSA, thus limiting its value in the context of early diagnosis of aggressive cancer (Ulmert *et al*., 2009). Likewise, CA125 level typically changes due to hormonally triggered fluctuations (e.g., menstruation, pregnancy) that limits the use of serum CA125 levels as a primary screening tool (Nossov *et al*., 2008).

To overcome the limitations of serum based markers, a new methodology was developed to target a cancer biomarker at its tissue of origin using an antibody-based radiotracer (combined antibody and radiolabel) in positron emission tomography (PET).

…PET Imaging…

PET scans are utilized to examine for the presence and severity of cancer and can give information on the location of tumors, the size of tumors, differentiate between benign and malignant growths, monitor the success of therapy, and detect any recurrent tumors.

The procedure works by using a scanning device to detect positrons, which is the antiparticle of an electron. A positron is produced during positron emission radioactive decay, whereby a proton inside a nucleus is converted into a neutron while releasing a positron and an electron neutrino. For cancer, the most commonly used imaging agent is 2-deoxy-2-(^{18}F)-fluoro-D-glucose, or FDG, which is a glucose analog that is used based on cancer cells increased metabolic activity and uptake of glucose compared to normal cells. Once taken up, FDG is phosphorylated and "trapped" inside the cell. Since FDG is not a substrate for glucose-6-phosphate isomerase it does not enter the glycolytic pathway and reaches a near steady-state equilibrium inside the cancer cells approximately 60 minutes after being injected into the patient (Seam *et al*., 2007). The following figure shows a PET image of a patient with lung cancer and the very obvious signal from the tumor.



Source: courses.washington.edu/bioen508/Lecture5-B-PET.pdf

While effective in imaging cancers that are fast growing with high metabolic activity, FDG PET is known to lack sensitivity and specificity in pancreatic and other slow growing cancers. False-negative results can occur when the lesions are small (<7mm), in the presence of cytostatic treatments that may decrease FDG uptake, and when there is improper patient preparation in those with glucose intolerance or diabetes. In addition, high FDG uptake by the brain and urinary tract can inhibit detection in those regions. False-positives can also occur since FDG is rapidly taken up by activated macrophages, fibroblasts, and neutrophils that may be present at the site of chronic sites of inflammation or areas of healing (such as after surgery). Given the limitations of FDG, **WE CONCLUDE** that a PET tracer targeting a cancer biomarker at the tissue of origin could theoretically overcome these challenges and allow for more specific and accurate tumor imaging.

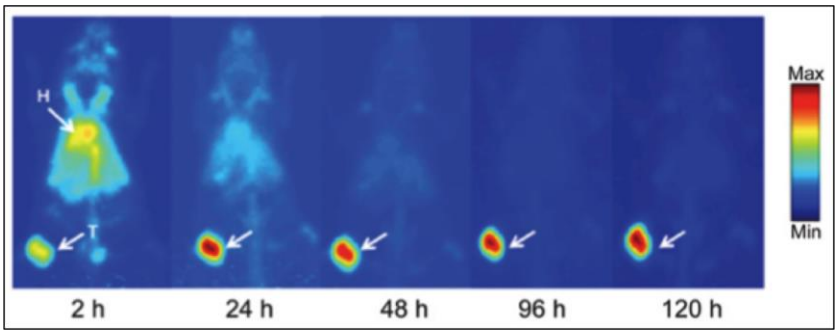
…Unique Challenges to Pancreatic Cancer Imaging…

Patients with pancreatic cancer have such dismal survival rates, at least in part, due to an inability to accurately diagnose the disease in its early stages. The symptoms associated with the disease are often vague and attributed to other more benign etiologies, which could be overcome if an accurate screening test was available. The end result is that the majority of pancreatic cancers are diagnosed at a late stage of disease, which makes it much more difficult to provide curative therapy.

Currently, pancreatic cancer is diagnosed by a combination of patient history and physical examination, coupled with computed tomography (CT), ultrasound, and PET imaging. In patients deemed to be at high risk for metastasis or for whom the staging is indeterminate, the diagnosis is confirmed by fine needle aspiration or laparoscopy along with FDG PET. Accurate staging, particularly identification of distant metastases, is of paramount importance in order to properly select patients who are the most likely to benefit from surgery. Differential diagnosis between pancreatic cancer and pancreatitis (non-cancerous inflammation of the liver) is a common problem with imaging modalities (Sendler *et al*., 2000). Lastly, while FDG PET is able to accurately detect metastases, it is unsuitable for determining resectability of the primary tumor in the pancreas (Strobel *et al*., 2008).

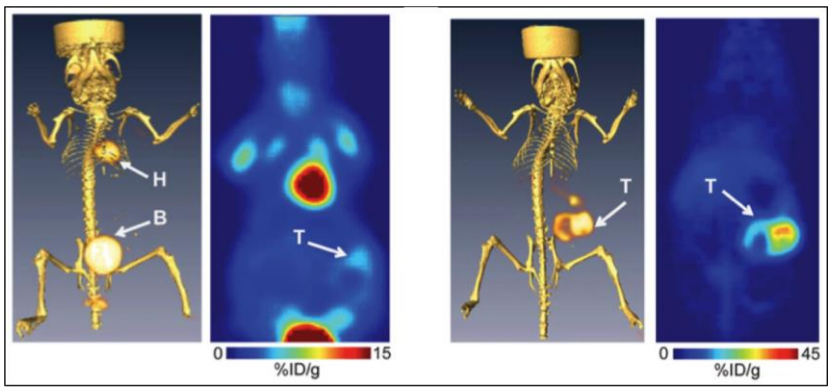
…HuMab-5B1 (MVT-2163) as a PET Tracer in Pancreatic Cancer Imaging…

In order to test the hypothesis that targeting sLe^a would be a useful imaging tool, HuMAb-5B1 (MVT-5873) was coupled to the radionuclide ^{89}Zr using a clinically validated linking agent (DFO). ^{89}Zr is known to offer good quality imaging data based on previous pre-clinical and clinical data (Ulmert *et al*., 2012; Holland *et al*., 2010). A small imaging study was then performed with ^{89}Zr-DFO-HuMab-5B1 (MVT-2163) in mice bearing a subcutaneous BxPC3 pancreatic cancer xenograft on the left hind leg. PET imaging showed impressive delineation of the tumor by MVT-2163 with normal tissue binding activity disappearing at 24 hours post injection (Viola-Villegas *et al*., 2013). The following figure shows high tumor localization at 24 hours, which increases up to 120 hours post injection.



Source: Viola-Villegas *et al*., 2013

Next, MVT-2163 was tested in a more clinically relevant tissue microenvironment. BxPC3-luc cells (which express the luciferase gene allowing for monitoring of tumor growth by bioluminescence) were injected directly into the pancreas of immuno-deficient mice. After the tumors had grown for two weeks, all mice received FDG PET and a subset of mice then received MVT-2163. The following figure shows combined PET/CT analysis for a representative mouse that received FDG PET (left) and MVT-2163 PET (right). The images show that FDG PET has a high degree of background as shown by the intense signal at the heart and bladder and minimal uptake by the tumor. In contrast, the MVT-2163 PET image shows very little background and clear uptake by the tumor.



Source: Viola-Villegas *et al*., 2013

…Opportunity and Development Plan for MVT-2163…

We believe that MVT-2163 is the only human derived imaging agent currently in development for improving imaging of pancreatic cancer and if proven effective would be welcome by patients and physicians. The opportunity for MVT-2163 is significant in a number of ways since accurately diagnosing, staging, and assessing treatment outcomes in pancreatic cancer, along with accurate determinations on the extent of disease and resectability, are essential to improving care for patients with the disease.

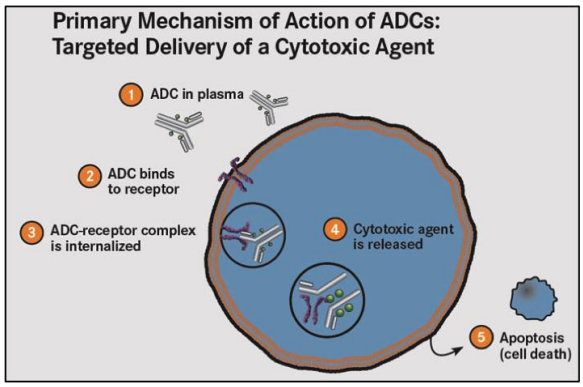
The regulatory pathway for a diagnostic agent is considerably less expensive and time consuming than for a therapeutic agent as it requires less intensive clinical trials. New diagnostic agents must be compared to validated standard diagnostic testing techniques. Initial work is performed in limited Phase 1 and 2 studies with a portion of the validation work coming from comparing published data from the standard technologies to the new product data. This approach can allow for more rapid development and approval of a new diagnostic agent. MabVax is planning to file an IND prior to the end of 2015 and initiate a Phase 1a clinical trial shortly thereafter. We estimate a total of 50 patients will be necessary to get MVT-2163 through Phase 2 trials at a total cost of approximately $5 million.

Additional Antibody Products

Results from various pre-clinical studies with MVT-5873 showed that certain cancer types, particularly pancreatic cancer cells, internalized the antibody. Based upon this characteristic, MabVax believes that MVT-5873 could be useful as an antibody-drug conjugate (ADC). In addition, the company has two other antibodies in development that target the antigen GD2, which is over-expressed on sarcoma, melanoma, and neuroblastoma.

…HuMab-5B1 as an Antibody-Drug Conjugate…

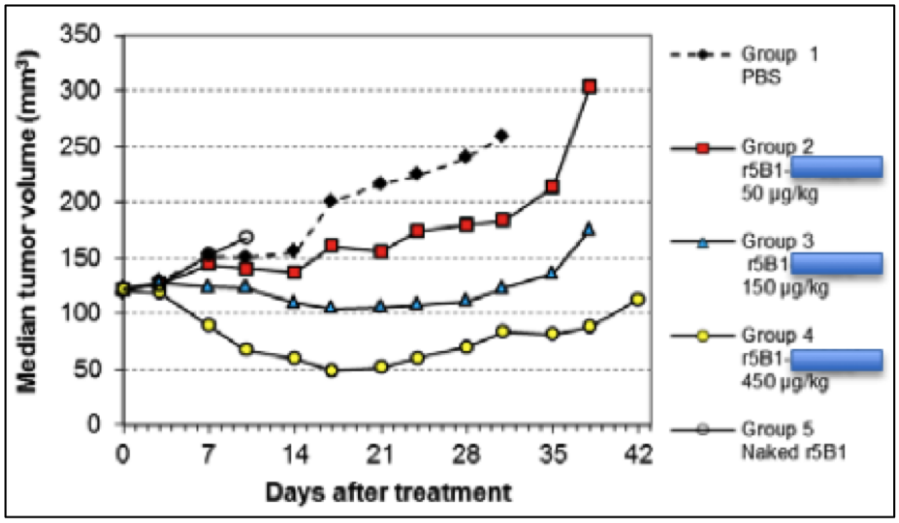
ADC's are monoclonal antibodies that are conjugated to a cytotoxic agent through a stable, chemical linker (Ducry *et al*., 2010). The compounds work through the ability of a monoclonal antibody to delivery a cytotoxic payload to a cancer cell through its specific binding of a tumor antigen (such as sLe^a for MVT-5873). Binding between the monoclonal antibody and the cell causes the internalization of the antibody along with the attached cytotoxic agent. Once inside the cell, the cytotoxic agent is released and the cancer cell is killed.



Source: onclive.com

There are currently two ADC products approved by the FDA: brentuximab vedotin (Adcetris®), for the treatment of Hodgkin lymphoma and systemic anaplastic large cell lymphoma, and trastuzumab emtansine (Kadcyla®), for the treatment of HER2 positive metastatic breast cancer.

The largest challenge in developing additional ADC products is the production of viable linkers that prevent premature off-loading of the cytotoxic agent before the antibody reaches the cancer cell. MabVax has entered into collaboration with Heidelberg Pharm, a company with its own proprietary linker and toxin technology, and as part of the collaboration Heidelberg has performed initial pre-clinical experiments utilizing HuMab-5B1-toxin ADC candidates. Results show the ability to successfully conjugate a linker and toxin to HuMab-5B1 with no apparent loss of binding specificity or affinity between HuMab-5B1 and sLe^a. This HuMab-5B1-toxin ADC shows potent *in vitro* and *in vivo* activity, as shown by the following figure where a single dose of HuMab-5B1-toxin ADC at varying concentrations limits the growth of BxPC3 xenografts.



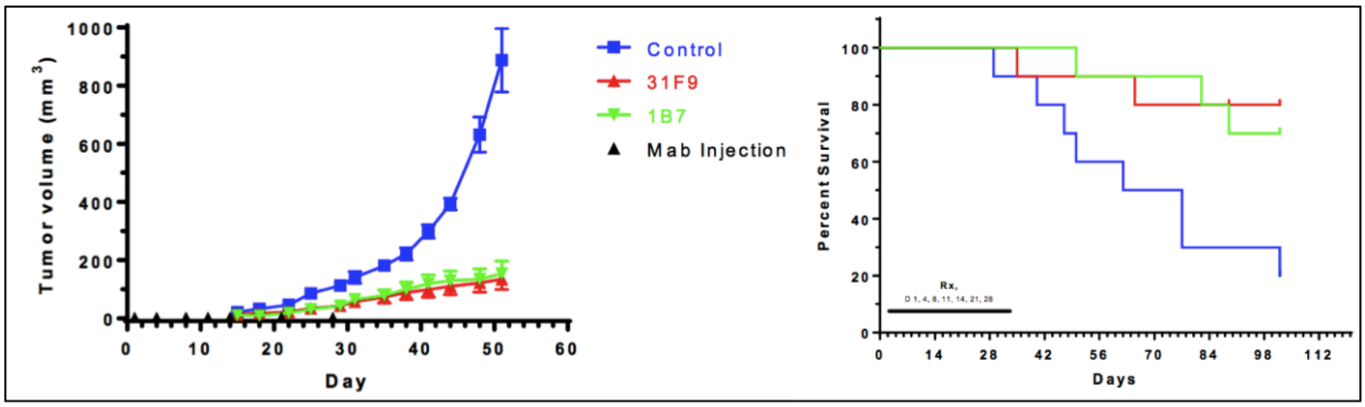
Source: MabVax Therapeutics, Inc.

The company plans to continue preclinical testing and select the optimal linker by the end of 2016. In 2017, the company will perform GMP manufacturing of HuMab-5B1-toxin ADC and file an IND such that Phase 1 studies can be initiated.

…Anti-GD2 Antibody Candidates…

GD2 is a sialic-acid containing glycosphingolipid expressed primarily on the cell surface. The function of GD2 is not completely understood, although it is thought to play a role in the attachment of tumor cells to extracellular matrix proteins (Cheresh *et al*., 1986). It is expressed on the surface of neuroblastomas, melanomas, and sarcomas (Mujoo *et al*., 1987; Chang *et al*., 1992; Tsuchida *et al*., 1987). Due to its relatively tumor-specific expression, GD2 is an attractive target for tumor-specific therapy. Treatment of children with neuroblastoma with a chimeric anti-GD2 antibody (ch14.18) resulted in a statistically significant improvement in time to progression of disease as well as overall survival (Yu *et al*., 2010). Based on these results, the FDA recently approved dinutuximab (Unituxin®) for the treatment of neuroblastoma, thus validating GD2 as an effective therapeutic target.

MabVax has identified two lead anti-GD2 candidates (HuMab-31F9, HuMab-1B7) by examining the immune response from more than 60 patients who participated in a sarcoma vaccine trial over the last three years. Preclinical studies performed with these antibodies showed them to be effective against Ewing's sarcoma (TC71, below left) and osteosarcoma (SaOS2, below right) xenograft models.



Source: MabVax Therapeutics, Inc.

Since each antibody has a unique set of characteristics, MabVax will be conducting further *in vitro* and *in vivo* testing in multiple disease models in order to determine which candidate to move forward into clinical testing. Following pre-clinical evaluation, MabVax will finalize candidate selection by the end of 2015 such that an IND can be filed in 2016 and a Phase 1 study commenced shortly thereafter. The company is planning to target sarcoma as the primary indication for the anti-GD2 antibody candidate.

Vaccine Program

Dr. Philip Livingston, who is the company's Chief Scientific Officer and former Head of the Laboratory of Tumor Vaccinology at Memorial Sloan-Kettering Cancer Center (MSKCC), has been developing a series of monovalent (targeting a single tumor antigen) cancer vaccines for the last 30 years that target carbohydrate antigens on neuroectodermal and epithelial cancers. MabVax has licensed exclusive rights to vaccines that cover 11 validated target antigens from MSKCC. The license agreement calls for MSKCC to complete all preclinical and Phase 1 clinical trial work at MSKCC's expense at which point the IND would be transferred to MabVax for continued development.

…Carbohydrate Antigens as Cancer Vaccines…

Carbohydrate antigens have proven to be surprisingly potent immunogens. This is exemplified by the fact that the majority of monoclonal antibodies derived from mice immunized with human cancer cells are targeted against carbohydrate antigens expressed on the cell surface (Feizi, 1985). The majority of carbohydrate antigens are recognized exclusively by B-cells and antibodies, thus in order to augment the antibody response it is necessary to link the antigens to a highly immunogenic carrier protein. This method is widely used to induce antibody production in pre-clinical models and is the methodology used in the cancer vaccines developed at MSKCC.

Over the past 30 years, a number of studies have been performed that examined various ways to induce an antibody response to carbohydrate antigens including the use of autologous or allogeneic tumor cell lines, multiple different immunological adjuvants, chemical modification of antigens to render them more immunogenic, conjugation to different immunological carrier proteins, and adherence of antigens to a variety of vehicles. Based on these studies the optimal approach was determined to be the use of an immunogenic carrier protein along with a potent immunological adjuvant. The optimal carrier protein is keyhole limpet hemocyanin (KLH), a large metalloprotein isolated from the hemolymph of the giant keyhole limpet *Megathura crenulata*, while the optimal adjuvants were saponins such as QS-2134 or GPI-010035 obtained from the bark of *Quillaja saponaria*.

Instead of using a monovalent vaccine, the vaccines under development utilize a combination of various monovalent antigens to create polyvalent vaccines. The reasons for this include the heterogeneity of antigen expression from one patient to another, the heterogeneity of the immune response due to previous immunological exposure and genetic background, and because the anti-tumor effector mechanisms are proportional to the amount of antibody bound to the cell surface, which will in turn be proportional to the number of different antigens in the vaccine.

…MabVax Vaccine Program…

MabVax has three cancer vaccines under active development targeting recurrent sarcoma, ovarian cancer, and neuroblastoma. The vaccines targeting recurrent sarcoma and ovarian cancer are currently in proof of concept Phase 2 clinical trials, while the neuroblastoma vaccine has completed an initial Phase 1 trial at MSKCC and a Phase 2 trial should commence in 2016.

Sarcoma Vaccine

Sarcomas comprise a diverse group of malignant tumors that develop from fat, muscles, nerves, joints, blood vessels, and bone. They are relative rare, with approximately 13,000 people diagnosed with sarcoma each year in the U.S. Eighty percent of those cases are due to soft-tissue sarcoma and the rest arise from bone (National Cancer Institute). Five-year survival rates for localized, regional (spread to nearby lymph nodes only), and distant (metastasized) sarcomas are 83%, 54%, and 16%, respectively.

Like other cancers, recurrence and metastasis are common with sarcoma. Approximately 20% of patients with extremity sarcoma will have lung metastases at some point during the disease course. For patients who are diagnosed with metastatic disease, approximately 30% will recur following initial therapy. When sarcomas do recur the prognosis is poor and gets worse with each subsequent recurrence.

The standard of care for sarcoma is surgery, which may or may not be coupled with radiation or chemotherapy. Multi-agent chemotherapy with doxorubicin, cyclophosphamide, and methotrexate following surgery improved disease-free survival rates for patients with high-grade extremity sarcomas; however, the toxicity associated with treatment was substantial (Chang *et al*., 1988). Following successful treatment where the patient is diagnosed as being free of disease the current standard of care is watchful waiting, where the patient is closely monitored to determine if recurrence occurs, however no treatment is given during this time.

MabVax has designed its cancer vaccines to be utilized during the watchful waiting portion of treatment to determine the effect on time to recurrence and overall survival. A randomized, multi-center, double blind Phase 2 clinical trial was initiated in July 2010 with 136 patients who had Stage IV metastatic sarcoma but were cleared by surgery (NCT01141491). The patients received 10 vaccinations over an 84-week period. The study was powered to show a statistical improvement in both progression free survival (measured at the mid-point of the study) and overall survival. In October of 2013, MabVax presented the mid-point results to the independent Drug Safety Monitoring Board (DSMB). The DSMB concluded that there were no unanticipated or clinically worrisome safety concerns and that investigators and patients should remain blinded as to treatment assignment and the patients should continue to be followed to assess overall survival.

The company reported that the sarcoma vaccine elicited an antibody response intended to kill circulating tumor cells and micrometastases in all but one of the vaccinated patients. However, the DSMB concluded that the study did not reach statistical significance for its primary efficacy endpoint of a 50% improvement in progression free survival. The study has not yet accumulated a sufficient number of events to evaluate the secondary endpoint of overall survival. Prior to initiating the study, the FDA indicated that the overall survival endpoint would be considered the primary endpoint for the measurement of efficacy. Thus, patients will be followed until sufficient numbers of events (deaths) have occurred to allow analysis of the overall survival endpoint. We anticipate results from this study to be reported in 2016.

Ovarian Cancer Vaccine

Ovarian tumors are the most common cause of death from gynecological cancers in the U.S. Approximately 21,000 women will be diagnosed while approximately 14,000 will die with the disease in 2015 (American Cancer Society). Almost half of the women diagnosed will be over the age of 63. As with all other cancers, five-year survival rates are dependent on when the disease is diagnosed and range from >90% for Stage I disease to 17% for Stage IV disease.

Most ovarian cancers are diagnosed at later stages due to the fact that patients with early disease have very few symptoms, which are often vague and nonspecific. Symptoms associated with later-stage disease include gastrointestinal symptoms such as nausea and vomiting, constipation, and diarrhea. Approximately 20%, 5%, 58%, and 17% of women present with stage I, II, III, and IV, respectively (Medscape). A large percentage of patients (70%) will have recurrence of disease, with prognosis worsening for each successive recurrence.

Surgery is the initial treatment option provided patients are in a good enough condition and includes aggressive cytoreduction where as much of the cancer is removed as possible. Following surgery, patients are given taxane- or platinum-based chemotherapy. Patients with recurrent ovarian cancer that is resistant to platinum-based chemotherapy may be treated with bevacizumab (Avastin®) and another chemotherapeutic agent.

Just as with the sarcoma vaccine, the ovarian cancer vaccine was administered to patients who have been cleared of the disease in the hopes it can prevent recurrence. A randomized, multi-center, double blind Phase 2 clinical trial was initiated in July of 2010. Importantly, a NIH grant award co-authored by Dr. Philip Livingston is fully funding the trial, which is being managed by the Gynecologic Oncology Group (GOG). MabVax has contributed to the development of the IND and provided financial support for the manufacture of the clinical material.

A total of 164 patients with Stage IV ovarian cancer were enrolled. They had been treated with cytoreductive surgery and chemotherapy and were in complete clinical remission as defined by CA-125 levels in the normal range, negative physical examination, and no evidence of disease by CT scan. Patients were vaccinated 10 times over 84 weeks and monitored throughout the study period. The study was powered to show a statistical improvement in both progression free survival (measured at the mid-point of the study) and overall survival. The study has not achieved a sufficient number of events to trigger the mid-point analysis. We anticipate results from the overall survival endpoint will be announced in 2016.

Neuroblastoma Vaccine

Neuroblastoma is the most common extra-cranial solid tumor in children with approximately 700 diagnoses annually in the U.S. (American Cancer Society). It accounts for 7% of all childhood malignancies but 10% of all childhood cancer-related deaths each year (Irwin *et al*., 2015). The vast majority of cases arise sporadically, with only 1-2% thought to be inherited.

More than 50% of children who are diagnosed with neuroblastomas have metastatic disease. Staging of neuroblastomas is done using a risk-group staging system known as the International Neuroblastoma Risk Group Staging System (INRGSS) (Monclair *et al*., 2009). The INRGSS uses image-defined risk factors (IDRFs), which are factors seen on imaging tests that might make it harder to remove the tumor. The INRGSS classifies tumors into four stages:

- **L1:** A localized tumor that does not involve vital structures as defined by the list of IDRFs. It is confined to one body compartment, such as the neck, chest, or abdomen.
- **L2:** A locoregional tumor (for example, it may have grown from the left side of the abdomen into the left side of the chest) that has at least one IDRF.
- **M:** A tumor that has metastasized to a distant part of the body (except tumors that are stage MS).
- **MS:** Metastatic disease in children younger than 18 months with the cancer confined to the skin, liver, and/or bone marrow, in which less than 10% of marrow cells are cancerous. In addition, MIBG scintigraphy must be negative in bone and bone marrow.

A number of prognostic markers exist that help determine a child's prognosis, including age (children younger than 18 months are more likely to be cured), tumor histology (the more normal looking the tumor cells are microscopically the better the prognosis), DNA ploidy (how much DNA a cell contains compared to a normal cell; cells that are hyperdiploid tend to respond better to treatment), and *MYCN* gene amplification (*MYCN* is an oncogene; tumors with multiple copies of *MYCN* tend to grow faster and lead to a worse prognosis).

Current standard of care calls for surgical resection of low stage tumors with multi-agent chemotherapy used for more advanced stage disease. Interestingly, infants with disseminated neuroblastoma have favorable outcomes with combined chemotherapy and surgery, while children older than 1 year with high-stage neuroblastoma have very poor survival rates despite intensive multimodal therapy (Gains *et al*., 2012). Additional treatment options include myeloablative consolidation chemotherapy with stem cell support, radiation doses intended to eliminate the immune system of the patient followed by stem cell reconstitution of the system, focal radiation (precise pin-point radiation doses), post-consolidation treatment (chemotherapy treatment post surgical resection), and the recently approved dinutuximab (Unituxin®).

Based on increased expression of GD2 and GD3 on the surface of neuroblastoma cells, a vaccine composed of these two carbohydrate antigens was tested in a Phase 1 clinical trial at MSKCC along with the immunostimulant β-glucan (Kushner *et al*., 2014). The study was conducted in high-risk patients who were in second (or later) complete, very good partial, or partial remission. Subjects received seven subcutaneous injections over 52 weeks. Thirteen of 15 subjects received the entire 12-month treatment protocol. No dose limiting toxicity was noted in any of the subjects and most subjects had detectable anti-GD2 or anti-GD3 antibodies. Twelve remain relapse-free at 29-40 (median 36) months post-treatment. One patient had a focal relapse (recurrence of the cancer at a specific spot) at 21 months while two other subjects had early focal relapses (2.3 and 4.6 months). Progression free survival (PFS) was 87±9% at 12 months and 78±11% at 24 months. Overall survival is 100% with a follow-up of >22months. These data are particularly encouraging given an expected relapse rate at 12 months of 50% to 60% (Maris *et al*., 2010).

MabVax was awarded a Phase I Small Business Innovation Research (SBIR) grant from the NIH to support manufacturing of clinical material for a Phase 2 study of the neuroblastoma vaccine. In addition, the company has entered into a relationship with a consortium of 13 academic hospital based neuroblastoma treatment programs called New Advances in Neuroblastoma Therapy (NANT). The NANT Scientific Review Committee has reviewed the Phase 2 clinical protocol, which involves enrolling 125-150 patients and which we estimate will take two years to enroll and an additional two years to complete. The trial will likely cost $7.5 million, however the company will likely seek outside sources of funding from the NIH or non-profit entities to help defray the costs.

…Vaccine Market Analysis…

The only cancer treatment vaccine to be approved by the FDA is sipuleucel-T (Provenge®), which is approved for the treatment for metastatic prostate cancer. Provenge® was shown to extend median overall survival of patients for approximately 4 months. The treatment was developed by Dendreon and when approved it cost $93,000 for a standard course of treatment. Due in part to a lack of sales and manufacturing issues, Dendreon filed for bankruptcy and Provenge® was subsequently acquired by Valeant Pharmaceuticals. Amgen has filed for approval of its cancer vaccine talimogene laherparepvec (T-Vec®) for the treatment of melanoma. In April 2015, the drug received a positive recommendation from an FDA advisory panel, which voted 22-1 in favor of approval.

Initially, each of the vaccines under development by MabVax would be implemented during the time of treatment known as 'watchful waiting', where a patient is closely monitored for recurrence but when no treatment is given. Thus, the vaccines would not necessarily take the place of any currently administered therapeutics but would instead be integrated into the patient's overall clinical program.

For sarcoma, the total number of patients in the U.S. who currently have the disease is approximately 100,000 and approximately 30-50% of patients will have recurrence of disease. The current standard of care for these patients is surgery, which may be combined with radiation or chemotherapy depending upon the severity of the disease. There are no 'targeted' therapies approved to treat sarcoma.

Based on data from the National Cancer Institute, there are approximately 192,000 patients currently living with ovarian cancer in the U.S. Approximately 70% of advanced ovarian cancer patients will have recurrence of disease and even for patients with Stage I or II disease the relapse rate is approximately 25%. Standard of care treatment is surgery coupled with chemotherapy, with the only approved 'targeted' agent being Avastin®.

Neuroblastoma is an incredibly rare disease as only 700 children are diagnosed each year in the U.S. Surgery followed by heavy-dose chemotherapy is the standard of care for patients with advanced disease. Unituxin® was recently approved by the FDA for the treatment of high-risk neuroblastoma based on the results of a Phase 3 clinical trial that showed treatment with Unituxin® resulted in an increase in event-free survival (66±5% vs. 46±5% at 2 years, *P*=0.01) and overall survival (86±4% vs. 75±5% at 2 years, *P*=0.02). The drug is being marketed by United Therapeutics and consensus estimates call for sales of approximately $75 million by 2019.

Juno Therapeutics Option Agreement

Juno Therapeutics (JUNO) is a biotechnology company that is developing cell-based cancer immunotherapies based on its chimeric antigen receptor (CAR) and high-affinity T cells to recognize and kill cancer cells. Part of the CAR is the antigen-binding region from an antibody that directs T-cells to a specific cellular target. MabVax has granted Juno the option to obtain an exclusive, worldwide, royalty-bearing license with regards to fully human antibodies against human GD2 or sLe^a. Juno has until June 30, 2016 to exercise the option to purchase the license, at which time MabVax expects to negotiate for license fees, milestone payments, and royalty-based compensation.

Financials and Capital Structure

As of March 31, 2015, the company had $4.7 million in cash and cash equivalents. On April 6, 2015, the company announced the closing of a private placement that generated gross proceeds of approximately $11.6 million, which was led by OPKO Health, Inc. (NYSE:OPKO) and Dr. Phillip Frost, the CEO and Chairman of OPKO Health.

As of May 19, 2015, there were 23.7 million shares of common stock outstanding. In addition, there were 213,851 shares of Series D Preferred Stock and 33,333 shares of Series E Preferred Stock. Both the Series E and Series D Preferred Stock are convertible into common shares at a ratio of 1:100, thus representing 24.7 million common shares. The company also has 1.9 million warrants outstanding with a cashless exercise feature based on a closing price of $2.20. The number of warrants varies proportionally with a change in share price. This results in a current fully diluted share count of 50.3 million shares.

Intellectual Property

MabVax is the exclusive licensee, sole assignee, or co-assignee of 20 granted U.S. patents, 16 pending U.S. patent applications and 41 international patents covering the monovalent vaccines that make up the polyvalent vaccine products. The major claims of these patents cover composition of the vaccine, methods of treatment, chemical modification of antigens, and synthesis. The company also owns or has rights to two patent applications in the U.S. and six in other geographic areas currently pending, covering aspects of ovarian cancer and breast cancer. The company also has 21 granted U.S. patents, 12 pending U.S. patent applications, 99 international patents, and 88 international patent applications that are being maintained by the company from prior to the merger with Telik, Inc.

MANAGEMENT PROFILES

David Hanson – President and Chief Executive Officer
Mr. Hansen is a senior corporate executive with diverse and in-depth experience in the biopharmaceutical business. He has proven leadership abilities in creating, building, and directing small start-up operations and key departments in both large and small biopharmaceutical companies along with broad therapeutic area expertise including oncology and immunology. Mr. Hanson has had direct responsibility for corporate and commercial development functions including in and out licensing, product acquisition, strategic planning, and new product planning. Most recently, Mr. Hansen was Senior Vice President of Corporate Development at AVANIR Pharmaceuticals, a company focused on developing and commercializing novel therapeutic products for the treatment of chronic diseases. Prior to that he was a founder, President, and COO of Xenerex Biosciences, a monoclonal antibody company focusing on development of fully human antibody products.

Philip Livingston, MD – Chief Science Officer
Dr. Livingston has recently retired as member and Attending Physician, Melanoma and Sarcoma Service, Department of Medicine at Memorial Sloan-Kettering Cancer Center (MSKCC). He was the Head of the Laboratory of Tumor Vaccinology at MSKCC where Dr. Livingston has treated cancer patients and conducted research for the past 31 years. He held the position of Professor of Medicine at the Weill Graduate School of Medical Sciences of Cornell University. It is Dr. Livingston's patents and associated intellectual property that MabVax has licensed from MSKCC. Dr. Livingston has led the development of multiple cancer vaccine therapies and has extensively published in the subject area. His work continues to be supported by grants from the National Institutes of Health, MSKCC, the US Army, and the Breast Cancer Research Foundation.

Wolfgang W. Scholz, PhD – Vice President of Antibody Discovery
Dr. Scholz is a co-founder of MabVax and has been Vice President of Antibody Discovery of MabVax since 2008. He has extensive drug discovery experience in multiple therapeutic categories and has collaborated with major pharmaceuticals companies in several projects. Dr. Scholz earned his Ph.D. in Microbiology/Immunology from the University of Kiel, Germany in 1985 and completed his postdoctoral training at the Research Institute of Scripps Clinic, La Jolla. He held positions with increasing responsibilities at Tanabe Research Laboratories from 1990 to 1994 and most recently he was Senior Director at Avanir Pharmaceuticals from 2000 to 2008, where he led research and development efforts for 8 years. He was a cofounder of Xenerex Biosciences, a subsidiary owned by Avanir Pharmaceuticals, and under his leadership, the antibody discovery group developed monoclonal antibodies to multiple infectious disease targets using in vitro and SCID mouse antibody generation technologies. Dr. Scholz's work has been supported by multiple grants from the National Institute for Allergy and Infectious Diseases. Dr. Scholz has been principal investigator on multiple grants received by MabVax totaling more than $4 million. Dr. Scholz is an inventor on three pending and two granted antibody patents, three issued small molecule patents, and author on 35 peer-reviewed publications.

Gregory P. Hanson, CMA, MBA – Chief Financial Officer
Mr. Hanson joined MabVax in February 2014 as Chief Financial Officer. Mr. Hanson is an experienced CFO and was a Managing Director of First Cornerstone, starting in 2008 until February 2014, a board and management advisor to companies and executives in the areas of international corporate development, financing strategies, commercialization of technologies and products, and M&A advisory services. Since November 2009, Mr. Hanson has served as Advisory Board Member of Menon International, Inc. in an international capacity developing renewable products partnering and licensing arrangements, financings, and in commercializing technologies involving biosensor devices and assays. Since October 2011, Mr. Hanson has served on the Life Sciences Advisory Board of Brinson Patrick Securities, a boutique investment bank, and continues to serve as a confidential advisor to several other tech and life sciences companies. Mr. Hanson is the 2012-2013 President and 6-year Board Member of San Diego Financial Executives International (FEI), and has served on the Capital Formation Committee at BIOCOM since 2011. Mr. Hanson is a Certified Management Accountant and has an MBA with distinction from the University of Michigan, a BS in Mechanical Engineering from Kansas State University, and Series 7 & Series 63 securities licenses.

Paul W. Maffuid, PhD – VP Product Development and Operations
Dr. Maffuid joined MabVax in July of 2014 as Vice President Product Development and Operations. He has extensive experience in both preclinical and clinical product development, product manufacturing, regulatory submissions and the commercial launch of novel products. Prior to joining MabVax, Dr. Maffuid held the position of Executive Vice President, Pharma Operations for AAIPharma Services Corporation. He was a member of the Executive Team and was responsible for integrating, streamlining, and managing multiple functional service divisions within AAIPharma and successful transaction of AAIPharma from Water Street Healthcare Partners to American Capital. Prior to his AAIPharma experience, Dr. Maffuid founded Biopharmalogics, Inc., a successful consulting firm focused on Chemistry, Manufacturing and Controls (CMC) and Drug Metabolism-Pharmacokinetics (DMPK) services expediting the development of multiple pharmaceutical products for clients. Dr. Maffuid was Vice President of Pharmaceutical Development for Arena Pharmaceuticals and as a member of the executive management team, was responsible for all CMC and DMPK activities in support of discovery and development operations. Earlier in his career Dr. Maffuid was the Director of Pharmaceutical Development at Amylin Pharmaceuticals and as Research Investigator, Structural Chemistry at Glaxo Research Institute supporting CMC packages for IND and NDA filings.

VALUATION AND RECOMMENDATION

We are initiating coverage of MabVax Therapeutics, Inc. (OTC: MBVX) with a Buy rating and a price target of $4.50. MabVax is a biopharmaceutical company developing vaccine and monoclonal antibody based therapeutics for the diagnosis and treatment of cancer. The company's novel antibody discovery platform and multiple upcoming catalysts make it a compelling investment opportunity.

…MabVax's Antibody Discovery Platform the First of its Kind…

Monoclonal antibodies have proved to be highly successful therapeutics. The combined global sales of all approved monoclonal antibodies were approximately $78 billion in 2014. Traditionally, monoclonal antibodies have been discovered through immunizing mice with a target antigen and altering the antibody in some way to make it more "human" (i.e., more of the antibody is derived from human sources). Fully human antibodies are now available either from genetically engineered mice (where the mouse antibody genes have been replaced in the genome with human antibody genes) or phage display (where a human antibody sequence is genetically manipulated in an *in vitro* system).

MabVax has developed a unique antibody discovery platform where patients are immunized with the company's cancer treatment vaccines and then the patient's B-cells are analyzed to identify high affinity antibodies against the target antigen. The optimal antibody is then produced on a large scale and used as a cancer therapeutic. Fully human antibodies developed from this means have a number of advantages, including:

1) There is no need to genetically modify a murine derived antibody or perform any type of *in vitro* affinity maturation, as the patient's immune system has already performed that work.
2) The self-censoring mechanism of the human immune system prevents that production of "self-harming" antibodies. Thus, any antibodies derived from a vaccinated patient that responds well to the vaccine are unlikely to result in unwanted side effects.
3) A "proof-of-concept" experiment has already been performed; a source patient who had a positive clinical outcome provides anecdotal evidence for clinical activity of any derived antibodies.

We believe MabVax's antibody discovery platform sets it apart from other antibody discovery companies and gives the company a competitive advantage that should help the company enter into potential collaborations or partnerships. In addition, the company is targeting tumor-associated carbohydrate antigens (TACA), which are present in very high copy numbers on the surface of tumor cells but have limited and restricted expression on normal tissues, thus making them attractive anti-cancer targets.

…Lead Antibody Candidate Targeting Three Separate Applications…

MabVax's lead antibody candidate, HuMab-5B1, is targeted against the carbohydrate antigen sialyl Lewis^{a} (sLe^{a}), which has been shown to be over-expressed on the surface of pancreatic, colon, small-cell lung, and breast cancers. HuMab-5B1 was shown to bind selectively and with high affinity to cancer cells and the antibody does not cross-react with related carbohydrates. HuMab-5B1 (designated MVT-5873 for therapeutic and MVT-2163 for diagnostic purposes) has shown utility in the following applications:

- As a **therapeutic agent**, MVT-5873 has shown efficacy in pre-clinical models of pancreatic, colon, and small-cell lung cancers. MabVax is planning to initially target metastatic pancreatic and colorectal cancer and file a first in human Phase 1 IND before the end of 2015 and begin clinical trials shortly thereafter.

- As a **diagnostic agent**, MVT-2163 (^{89}Zr-DFO-HuMab-5B1) showed very little background and clear uptake by the tumor. MabVax is planning to utilize MVT-2163 as a diagnostic agent for pancreatic cancer and file a first in human Phase 1 IND before the end of 2015 and begin clinical trials shortly thereafter.

- As an **antibody-drug conjugate** (ADC), HuMab-5B1 showed potent *in vitro* and *in vivo* activity including limiting the growth of BxPC3 xenografts. Pre-clinical studies are on-going to select a lead candidate ADC with the company likely to initiate clinical trials in 2017.

We believe that utilizing HuMab-5B1 in multiple formats is a smart way to capitalize on an important asset, and given the supportive pre-clinical data we feel there is a high likelihood that the antibody could be effective in all three indications.

…Multiple Clinical Milestones in the Next 12 Months…

MabVax has compiled a considerable amount of pre-clinical data on HuMab-5B1 as a therapeutic and diagnostic agent. The company is planning to file an IND for each indication before the end of 2015 and subsequently initiate Phase 1 clinical trials. The Phase 1 trial for the therapeutic indication will likely be a safety and pharmacokinetic study involving late-stage cancer patients with multiple types of solid tumors. Data from this study should begin to be available by mid-2016, and will be used to guide optimal dosing for a Phase 1b clinical trial later in 2016. The Phase 1 trial for the diagnostic indication will likely enroll up to 30 patients in both the dose escalation and expansion arms of the trial. We estimate it will take approximately one year to fully enroll the trial and obtain all results, however important safety and targeting specificity readouts are likely to come much sooner, perhaps by mid-2016. We believe the cost of the trial will be approximately $2 million.

The company is currently investigating two cancer treatment vaccines in Phase 2 clinical trials for preventing recurrence of sarcoma and ovarian cancer. Both trials are fully enrolled and overall survival data from each of the studies should be available in 2016. In addition, an IND will be filed for the neuroblastoma vaccine in the first half of 2016 with a Phase 2 trial likely to begin shortly thereafter.

…A Couple of Issues To Note…

While the antibody discovery platform is something we are quite excited about, there are some risks to consider in making an investment in the company at this point:

- Cancer vaccines have had limited success in the clinic and we are unsure of the likelihood of success in the on-going Phase 2 clinical trials, particularly given that the sarcoma vaccine did not show an effect on progression-free survival compared to placebo. If both vaccine trials report negative results in 2016 the company may have a hard time overcoming the negative perception even with a promising candidate in HuMab-5B1.
- In addition, we are uncertain about the company developing a therapeutic for neuroblastoma, which has an extremely limited patient population (~700/yr in the U.S.) and may not offer a sizeable enough market to justify the expenses necessary to gain approval. This uncertainty could be overcome by the company obtaining non-dilutive funding to conduct the neuroblastoma Phase 2 clinical trial.
- There are 213,851 shares of series D Preferred Stock outstanding, which are convertible into 21.385 million shares of common stock. The company currently has approximately 23.6 million shares outstanding, thus representing approximately 90% dilution to current shareholders when those shares are converted. Anyone looking to exit their position after the Preferred shares are converted could put significant downward pressure on the stock.

…Valuation Methodology…

We value MabVax using a probability-adjusted discounted cash flow model that takes into account potential future revenues from MVT-5873 as a therapeutic in pancreatic and colorectal cancer, MVT-2163 as a diagnostic in pancreatic cancer, and the cancer treatment vaccines for sarcoma, ovarian cancer, and neuroblastoma. The following table summarizes our valuation model.

Compound	Indication	Approval	Peak Sales U.S. ($millions)	Peak Sales E.U. ($millions)	Discount Rate	Probability	**NPV $millions**
MVT-5873	Pancreatic Cancer	2021	$800	$900	20%	20%	**$48**
MVT-5873	Colorectal Cancer	2021	$1,900	$1,800	20%	20%	**$77**
MVT-2163	Pancreatic Cancer	2020	$60	$60	20%	25%	**$29**
Trivalent Vaccine	Sarcoma	2020	$125	$180	20%	15%	**$20**
Pentavalent Vaccine	Ovarian Cancer	2020	$300	$500	20%	15%	**$50**
Bivalent Vaccine	Neuroblastoma	2021	$45	$30	20%	10%	**$3**
						Total	**$227**

Source: Zacks SCR

Combining the total sum of parts with the company's current cash position, the cash that could be brought in from warrants, and estimate capital expenditures gives a net present value for the company of $225 million. Dividing this by the company's fully diluted share count of 50.3 million shares leads to a fair value of approximately $4.50 and we are assigning a 'Buy' rating to the stock.

PROJECTED FINANCIALS

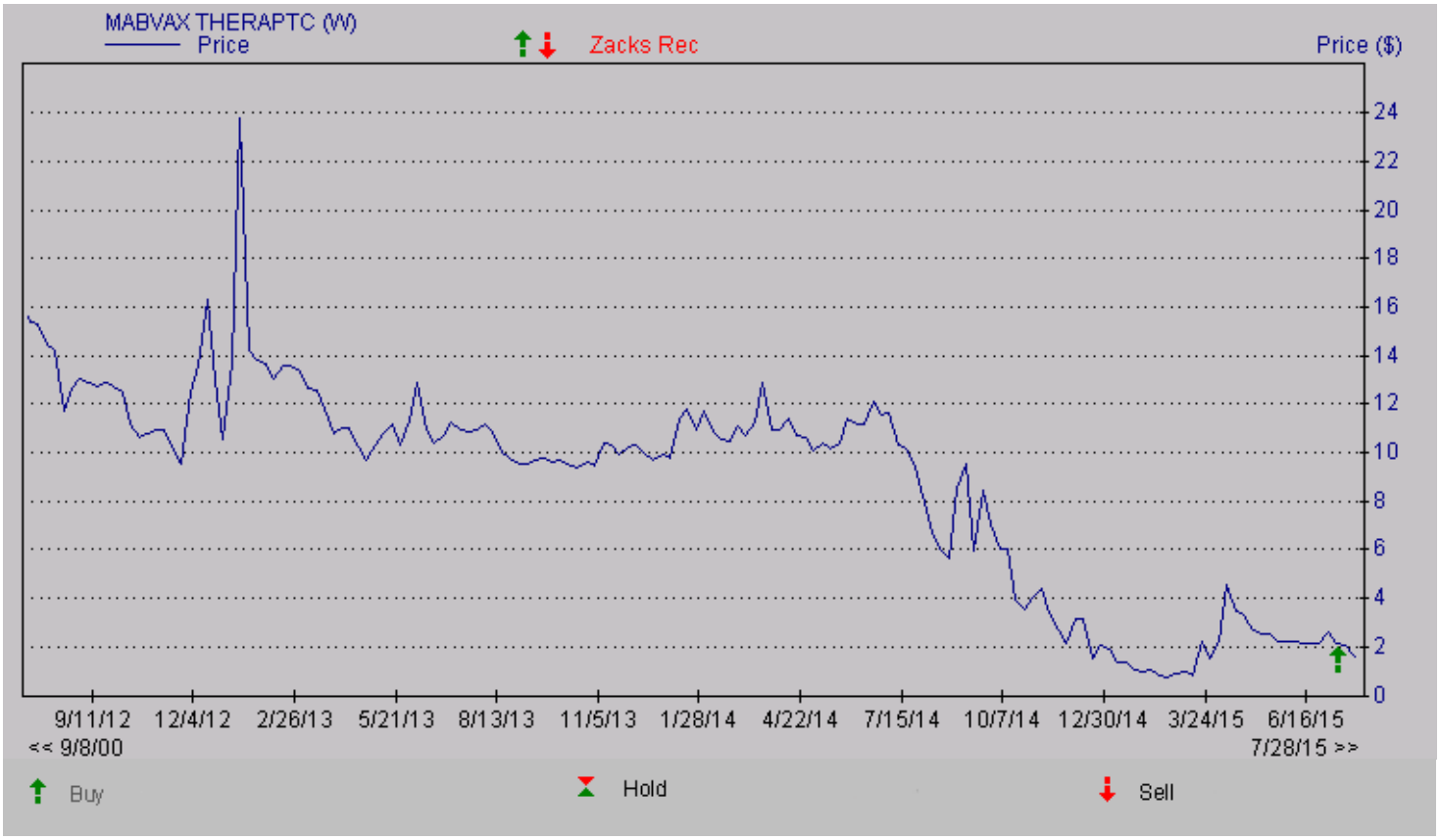
MabVax Therapeutics, Inc.
Income Statement

MabVax Therapeutics, Inc.	2014 A	Q1 A	Q2E	Q3 E	Q4 E	2015 E	2016 E
MVT-5873	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
YOY Growth	-	-	-	-	-	-	-
MVT-2163	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
YOY Growth	-	-	-	-	-	-	-
HuMab - ADC	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
YOY Growth	-	-	-	-	-	-	-
Trivalent Vaccine - Sarcoma	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
YOY Growth	-	-	-	-	-	-	-
Pentavalent Vaccine - Ovarian Cancer	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
YOY Growth	-	-	-	-	-	-	-
Bivalent Vaccine - Neuroblastoma	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
YOY Growth	-	-	-	-	-	-	-
Grants & Collaborative Revenue	$0.3	$0.2	$0.2	$0.2	$0.2	$0.8	$1.0
YOY Growth	-	-	-	-	-	-	-
Total Revenues	**$0.3**	**$0.2**	**$0.2**	**$0.2**	**$0.2**	**$0.8**	**$1.0**
YOY Growth	-	-	-	-	-	-	-
Cost of Sales	$0	$0	$0	$0	$0	$0	$0
Product Gross Margin	-	-	-	-	-	-	-
Research & Development	$3.503	$1.726	$1.800	$1.800	$1.900	$7.226	$9.5
General & Administrative	$5.204	$0.981	$1.000	$1.000	$1.200	$7.861	$8.5
Other Expenses	$0	$0	$0	$0	$0	$0	$0
Operating Income	($8.393)	($2.467)	($2.600)	($2.600)	($2.9)	($14.2)	($17.0)
Operating Margin	-	-	-	-	-	-	-
Non-Operating Expenses (Net)	$0.475	$0.020	$0.010	$0.010	$0.010	$0.050	$0.1
Pre-Tax Income	($7.918)	($2.4)	($2.6)	($2.6)	($2.9)	($14.2)	($16.9)
Income Taxes Paid	$0	$0	$0	$0	$0	$0	$0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Deemed Dividends	($2.21)	($17.85)	$0.00	$0.00	$0.00	($17.85)	$0.00
Accretion of Preferred Stock Dividends	($0.44)	($0.09)	($0.10)	($0.10)	($0.10)	($0.39)	$0.00
Net Income	**($10.578)**	**($20.393)**	**($2.690)**	**($2.690)**	**($2.990)**	**($32.444)**	**($16.900)**
Net Margin	-	-	-	-	-	-	-
Reported EPS	**($9.51)**	**($6.25)**	**($0.12)**	**($0.11)**	**($0.11)**	**($1.66)**	**($0.48)**
YOY Growth	-	-	-	-	-	-	-
Basic Shares Outstanding	1.112	3.263	22.000	25.000	28.000	19.566	35.000

Source: Zacks Investment Research, Inc. *David Bautz, PhD*

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