Zacks Small-Cap Research

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MabVax Therapeutics Holdings, Inc. (MBVX - OTC)

MBVX: Preclinical Data for HuMab 5B1 Shows the Versatility and Potential for Antibody Discovery Platform…

Current Recommendation	**Buy**
Prior Recommendation	N/A
Date of Last Change	07/13/2015
Current Price (11/16/15)	$0.97
Target Price	**$4.00**

UPDATE

On October 30, 2015, MabVax filed form 10-Q with financial results for the third quarter of 2015. The company recognized $0.1 million in income from a contract with the NIH and had a net loss of $5.3 million, or $0.20 per share. Subsequent to the close of the quarter, the company raised $2.75 million in gross proceeds from a public offering and we estimate the company will end 2015 with approximately $4.5 million in cash.

In this report, we examine the preclinical data that was recently presented on the company's lead antibody candidate, HuMab 5B1, at the World Molecular Imaging Conference, which shows both the versatility and potential of the company's antibody discovery platform.

SUMMARY DATA

52-Week High	**$4.62**
52-Week Low	**$0.84**
One-Year Return (%)	**-72.29**
Beta	**-0.26**
Average Daily Volume (sh)	**66,731**
Shares Outstanding (mil)	**28**
Market Capitalization ($mil)	**$28**
Short Interest Ratio (days)	**1.33**
Institutional Ownership (%)	**0**
Insider Ownership (%)	**7**
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	0.1 A	0.1 A	0.1 E	0.4 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	-$0.29 A	-$0.20 A	-$0.19 E	-$1.79 E
2016					-$0.57 E
2017					-$0.40 E

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WHAT'S NEW

Financial Update

On October 30, 2015, MabVax Therapeutics Holdings, Inc. (MBVX) filed form 10-Q with financial results for the third quarter of 2015. The company reported revenue of $0.14 million, which was recognized from the $1.5 million Phase II Small Business Innovation Research contract with the National Cancer Institute for developing HuMab 5B1 as an imaging agent in pancreatic cancer. The company recognizes the revenue from grants received from the National Institutes of Health (NIH) as expenses that directly relate to the grant are incurred.

Net loss for the third quarter of 2015 was $5.3 million, or $0.20 per share. R&D expenses for the current quarter were $3.1 million while G&A expenses were $2.3 million. Total cash burn for the quarter was approximately $2.6 million. The company exited the third quarter of 2015 with approximately $4.5 million. In October 2015, the company completed a public offering by selling 2.5 million shares of common stock at a price of $1.10 per share. Included in the offering were 1.25 million warrants with an exercise price of $1.32 per share that are immediately exercisable and expire in Sep. 2018. Gross proceeds to the company were $2.75 million, which combined with the company's current cash reserves should be enough to fund operations through the second quarter of 2016.

HuMab 5B1 Update

In September 2015, MabVax's lead antibody candidate, HuMab 5B1, was featured in five separate presentations at the World Molecular Imaging Congress (WIMC). Below we review three of the presentations and what they mean for future development of HuMab 5B1. For an overview of MabVax's antibody discovery platform and HuMab 5B1, we invite readers to review our previous report. The preclinical results presented at the WIMC all involved the use of HuMab 5B1 linked to a radionuclide, either as a positron emission tomography (PET) imaging agent or a radioimmunotherapy, and help to exhibit the incredible versatility and usefulness of antibody's discovered through the company's platform in a variety of applications.

Brief Background on Radionuclides

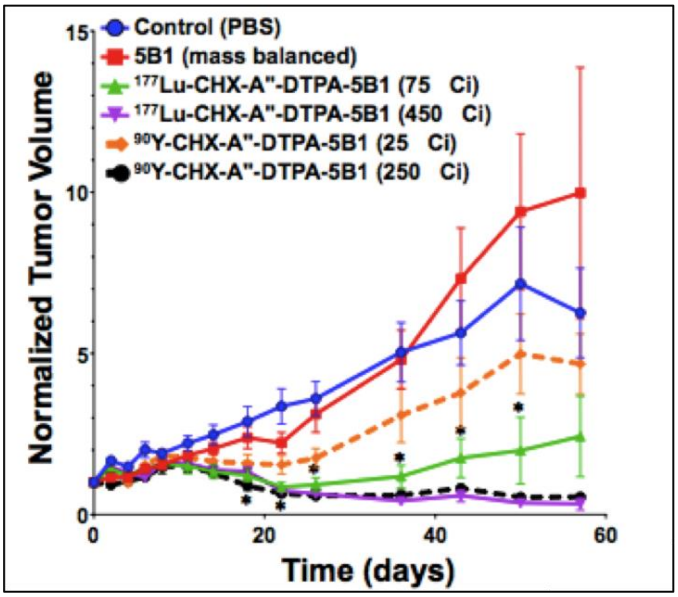
A radionuclide is an atom that contains excess nuclear energy, which results in it being unstable. The excess energy can be emitted in three forms: an alpha particle (a helium nuclei), a beta particle (an electron or positron), or gamma radiation. Most of the radionuclides used for therapeutic and imaging purposes emit beta particles.

For Positron Emission Tomography (PET) imaging, radionuclides that emit positrons are used. Positrons have the same mass as electrons but contain a positive charge. Positron-emitting radionuclides occur naturally but can also be produced through bombardment of natural targets with protons. When a positron is emitted it travels a short distance (~ 1 mm) while gradually losing energy. When most of the positron's kinetic energy has been lost, it reacts with an electron in a process called annihilation, which results in the release of two very high energy photons. It is these photons that are detected by PET imaging. Positron emitting radionuclides are not utilized for therapeutic purposes because the particle that is emitted is very low energy, and the resulting high energy photons can travel long distances (e.g., through the whole body) thus making them less than ideal for targeted therapy. In the development of HuMab 5B1 as a PET imaging agent, the radionuclide being used is ^{89}Zr. ^{89}Zr has a number of advantages compared to other radionuclides used in PET imaging such as a low energy requirement for producing the isotope, a half-life (3.3 days) that is compatible with the time needed to achieve optimal tumor to background ratios, and when an antibody is internalized (as is the case with HuMab 5B1) lysosomal proteolysis of the antibody leads to accumulation of metals such as ^{89}Zr (Zhang *et al*., 2011).

Radioimmunotherapy is the use of a radionuclide attached to a monoclonal antibody to deliver cytotoxic radiation to a target cell. Thus far, there have been two radioimmunotherapy treatments approved by the FDA: Zevalin® (anti-CD20 monoclonal antibody attached to ^{90}Y) and Bexxar® (anti-CD20 monoclonal antibody attached to ^{131}I). Both ^{90}Y and ^{131}I emit beta particles, which have a range of 2.7 and 0.8 mm, respectively. Thus, beta particles can deliver radiation not just to the target cell but the surrounding cells as well. This could offer the advantage of affecting tumor cells that may have lost expression of the target antigen.

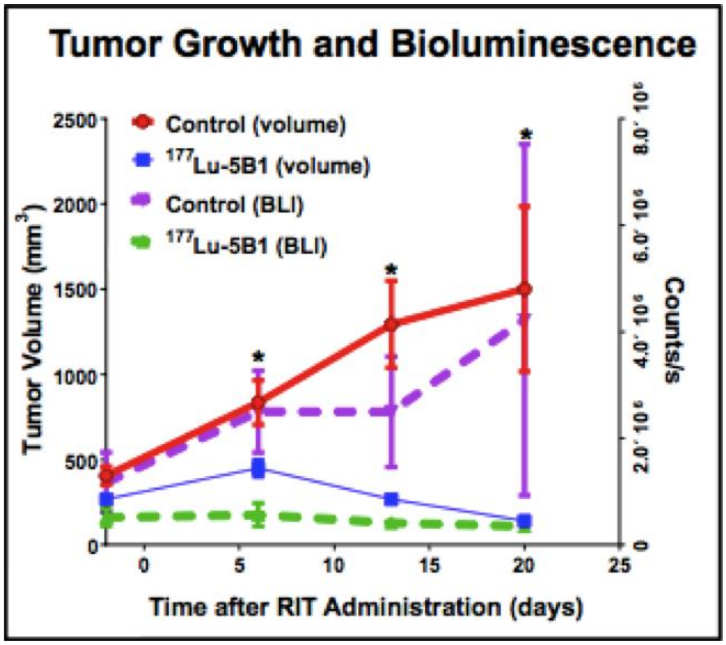
Presentation #1: Lanning* et al. - *Targeting CA19.9 For Radioimmunotherapy And Therapeutic Monitoring In Pancreatic Cancer;

HuMab 5B1 is being developed as both a therapeutic and a PET imaging agent. Since the antibody has shown such promising results as a PET agent through uptake of the antibody by tumor cells, Lanning *et al*. examined whether HuMab 5B1 could serve as a radioimmunotherapy construct. 5B1 was attached to both ^{90}Y and ^{177}Lu and used to treat mice bearing BxPC3 xenografts. The following figure shows the results of treating mice after tumors had reached approximately 100 mm^3 with either ^{90}Y-5B1 or ^{177}Lu-5B1. At the higher radiation dose, both ^{90}Y-5B1 and ^{177}Lu-5B1 showed tumor *regression*, not just inhibition or slowing of tumor growth.



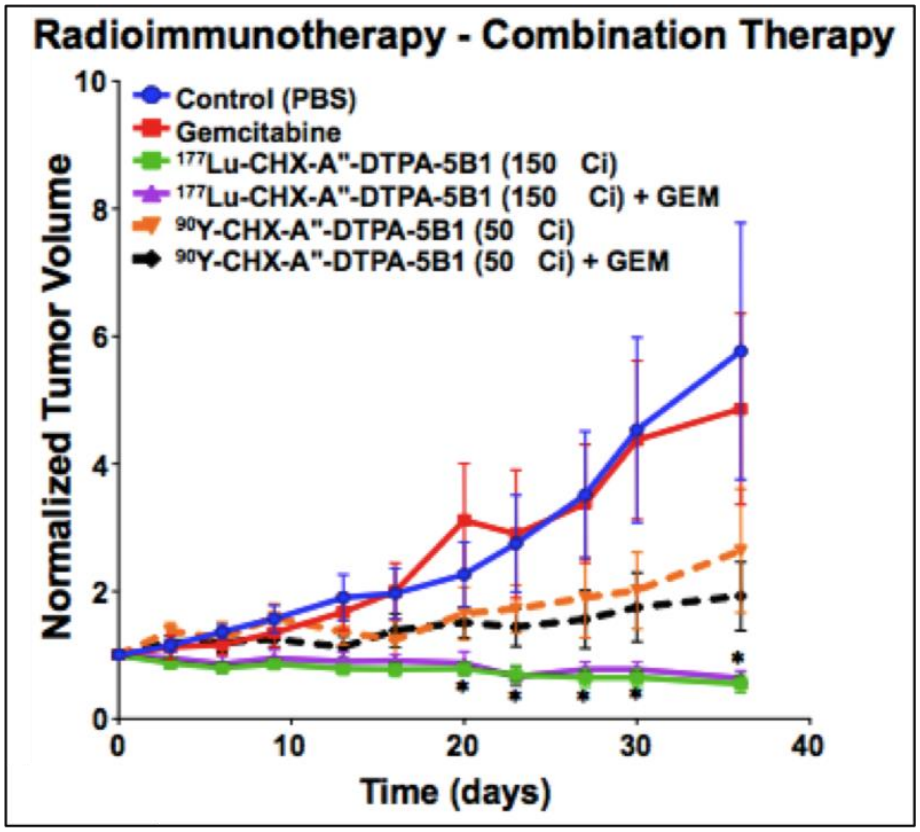
Source: Lanning *et al*., 2015

The 5B1 radioimmunotherapies were equally effective in an orthotopic pancreatic cancer model. As opposed to a xenograft, in which the cancer cells are injected subcutaneously, in an orthotopic model the cancer cells are injected into the tissue from which the tumor cells were derived. This has the advantage of being a more clinically relevant model. Lanning *et al*. utilized a luciferase expressing BxPC3 cell line that was implanted into the pancreas. The following graph shows how both the tumor volume and bioluminescence of the tumors decreases following administration of 300 µCi of ^{177}Lu-5B1.



Source: Lanning *et al*., 2015

Gemcitabine is the chemotherapy agent most commonly used to treat pancreatic cancer. The following graph shows survival of mice harboring BxPC3 xenografts treated with gemcitabine alone as well as in combination with ^{177}Lu-5B1 and ^{90}Y-5B1. Note that the amount of radioactivity utilized for ^{177}Lu-5B1 (150 µCi) and ^{90}Y-5B1 (50 µCi) is less than was used in the preceding two experiments. Combined therapy with gemcitabine and radioimmunotherapy did not show significant synergism at the selected doses. However, it is interesting that a 150 µCi dose of ^{177}Lu-5B1 was still able to cause tumor regression when used as a stand-alone therapy.



Source: Lanning *et al.*, 2015

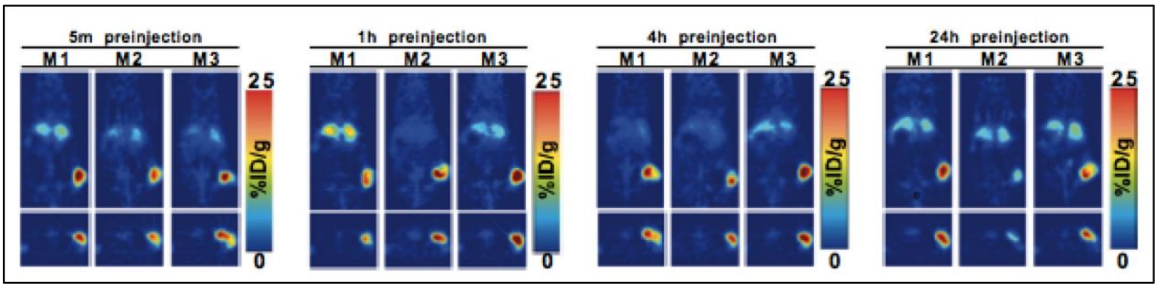
The preclinical results showing 5B1 as a radioimmunotherapy are very encouraging, particularly since the agents were successful against both a xenograft and an orthotopic model. The small error bars for mice showing regression of tumor means that all the mice showed tumor regression and it was not just a subset of those treated. This is important, as the combination of gemcitabine and nab-paclitaxel (Abraxane®) is only able to cause tumor regression in a subset of mice with human pancreatic cancer xenografts (Van Hoff *et al*., 2011). MabVax is hoping to quickly follow up on these successful preclinical results by filing an Investigational New Drug (IND) application with the FDA for a radioimmunotherapy product by the end of 2016.

Presentation #2: Houghton* et al*. - Preclinical optimization of anti-CA19.9 immunoPET in the context of shed antigen

One of the applications that HuMab 5B1 is being developed for is as a PET imaging agent. To create a PET imaging agent, 5B1 was coupled to the radionuclide ^{89}Zr using a clinically validated linking agent (DFO) to create ^{89}Zr-DFO-5B1. ^{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). The target of HuMAb 5B1 is the tumor associated carbohydrate antigen sialyl Lewis^a (sLe^a), otherwise known as CA19.9. One of the issues with targeting CA19.9 is that it is shed by tumor cells into the bloodstream, thus any radiolabeled antibody may bind to the circulating CA19.9, which could lead to a decrease in imaging sensitivity and increase radiation exposure in healthy tissues. To overcome these obstacles, scientists at Memorial Sloan Kettering Cancer Center (MSKCC) determined the optimal conditions for administration of "cold" 5B1 (e.g., not radiolabeled) prior to administration of ^{89}Zr-DFO-5B1 that would lead to enhanced imaging results. The study examined different time points for 5B1 preadministration, the optimal amount of antibody to preinject, as well as the proper time to perform the PET imaging after injection of ^{89}Zr-DFO-5B1. Subcutaneous and orthotopic Capan-2 xenografts were used, as the Capan-2 cell line (a human pancreatic adenocarcinoma) is known to shed clinically relevant amounts of CA19.9.

Optimal Time for 5B1 Preinjection

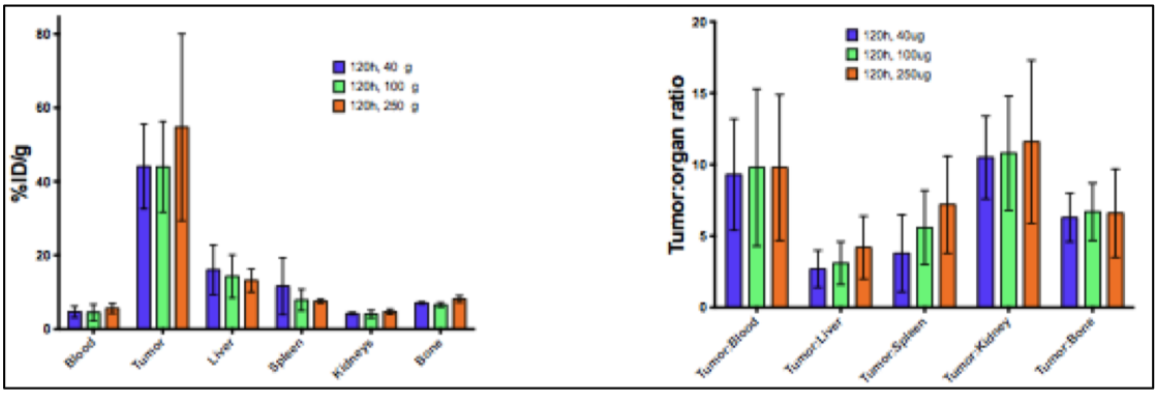
The following image shows the results of preinjecting mice harboring Capan-2 xenografts with 5B1 at either five minutes, one hour, four hours, or 24 hours before injecting ^{89}Zr-DFO-5B1. The data shows that preinjecting 5B1 four hours prior to ^{89}Zr-DFO-5B1 is optimal, as it results in the least amount of background compared to tumor uptake.



Source: Houghton *et al*., 2015

Optimal mass of 5B1 Preinjection

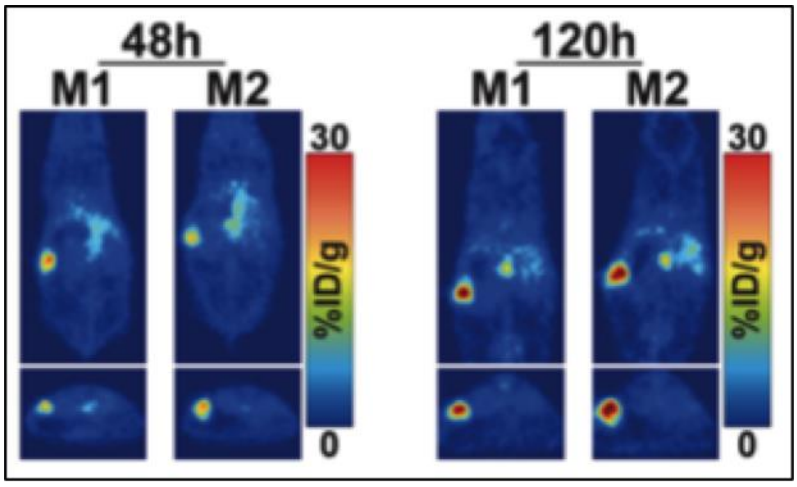
In addition to knowing *when* to preinject 5B1, it is also important to know *how much* 5B1 to inject to optimize imaging with ^{89}Zr-DFO-5B1. The following graphs show the amount of uptake of ^{89}Zr-DFO-5B1 for various tissues and tumor along with the ratio of tumor uptake to tissue uptake after preinjecting with 40 µg, 100 µg, or 200 µg of 5B1 four hours prior to administering ^{89}Zr-DFO-5B1. Based on these results, 100 µg was chosen as the optimal mass of 5B1 to be preinjected.



Source: Houghton *et al*., 2015

Optimal PET Imaging Protocol

The third parameter of 5B1 preinjection with ^{89}Zr-DFO-5B1 PET imaging had to do with the optimal time to perform the PET scan following radiotracer injection. Using 100 µg of 5B1 preinjected four hours prior to administering ^{89}Zr-DFO-5B1, the results show that a PET scan performed at 120 hours after ^{89}Zr-DFO-5B1 injection is superior to a scan performed 48 hours after ^{89}Zr-DFO-5B1 injection. This is shown in the following pictures, where the tumor uptake of ^{89}Zr-DFO-5B1 at 120 hours is superior with little to no increase in background compared to the scan at 48 hours.

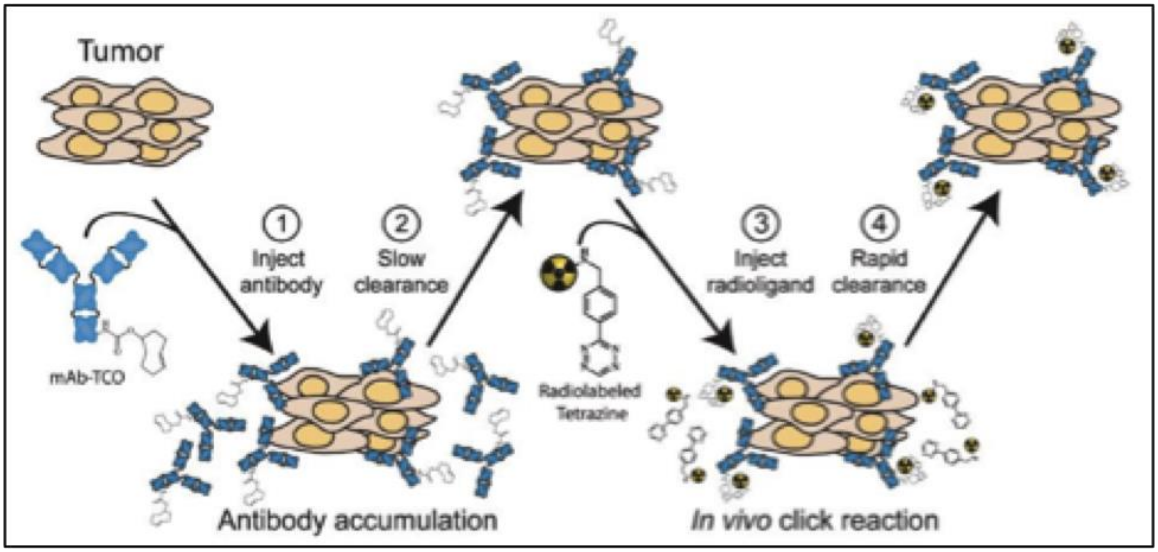


Source: Houghton *et al*., 2015

The conclusions from the preceding study are that injection of unmodified HuMab 5B1 improves PET contrast (through binding to shed antigen that is in the bloodstream), and that injection of 100 µg of unlabeled 5B1 four hours prior to administration of radiotracer was optimal in the murine model. These results will help to guide the design of MabVax's upcoming Phase 1 study of ^{89}Zr-DFO-5B1. Perhaps most importantly, regardless of when unmodified 5B1 was administered, ^{89}Zr-DFO-5B1 successfully illuminated the tumors in a consistent fashion.

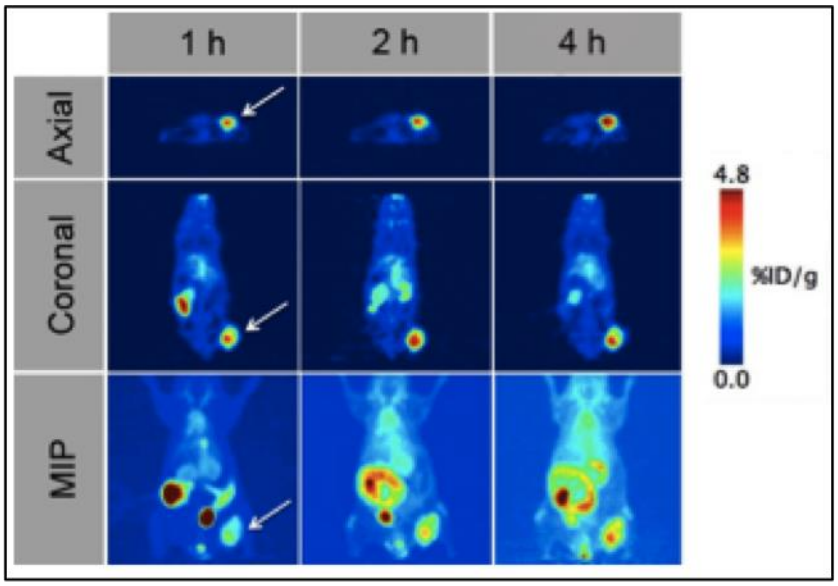
Presentation #3: Meyer* et al*. - Pretargeting CA19.9 in BxPC3 tumor xenografts for 18F-based PET Imaging using bioorthogonal Diels-Alder click chemistry

One of the drawbacks to using a radionuclide like ^{89}Zr for PET imaging is the relatively long half-life (3.3 days) compared to other short-lived radionuclides (e.g., ^{18}F, used in FDG-PET, has a half-life of only 109 minutes). ^{18}F cannot currently be used to label antibodies for PET imaging due to the time required for the antibody to fully bind the target antigen (which is typically on the order of 3-5 days). This was shown in the previous presentation, where the optimal PET image was obtained 120 hours after administering ^{89}Zr-DFO-5B1. The advantage of using a short-lived radionuclide like ^{18}F would be to limit the amount of time that the patient is exposed to the radionuclide. Researchers at MSKCC are developing a technology whereby a non-radiolabeled antibody containing a transcyclooctene moiety could be administered to a patient, allowed time to fully bind to the tumor, and then an ^{18}F-labeled compound would be administered that would chemically bind to transcyclooctene such that PET imaging could be performed in a relatively short time period (within 2-4 hours). An overview of the strategy is depicted in the following graphic:



Source: Meyer *et al*., 2015

The researchers chose HuMab 5B1 as the targeting antibody based on the positive preclinical results seen with PET imaging using ^{89}Zr-DFO-5B1, as HuMab 5B1 binds to pancreatic cancer cells with high affinity and specificity. While this technology is in the very early stages, the preliminary results look quite encouraging. The following PET images show a clear delineation of tumor to background just one hour after injecting an 18F-tetrazine molecule (which was injected 72 hours after injecting the chemically modified 5B1), with the signal in the tumor growing over time as the signal in the blood and intestines decreases over time. Admittedly, there is still radioactivity in the intestines at the 4 hr mark, which means that the compounds utilized in this method will likely need to be optimized. However, this is quite encouraging proof-of-concept data showing a method that could ultimately lead to decreasing the amount of radiation that a patient is exposed to during PET imaging while maintaining a good signal to noise ratio.



Source: Meyer *et al*., 2015

Conclusion and Recommendation

The preclinical data examined in this report shows the versatility that is possible with a high quality, robust, and highly tumor specific antibody such as HuMab 5B1. The reason that it is so versatile is due to its targeting of a highly specific tumor associated carbohydrate antigen that has very little expression on normal cells. Thus, the antibody can be used as a therapeutic, a radioimmunotherapy, an antibody-drug conjugate, and an imaging agent, something that is not possible with other antibodies that may target tumor associate antigens that are expressed to some degree on normal tissues.

The company is still planning to file an IND for HuMab 5B1 as a therapeutic and a PET imaging agent before the end of 2015 and initiate Phase 1 clinical trials in the first part of 2016. We are looking forward to analyzing the Phase 1 data next year, as all the preclinical data we have seen thus far has been very encouraging. The company will also be filing an IND for a HuMab 5B1 radioimmunotherapy before the end of 2016 and another IND for a HuMab 5B1 antibody-drug conjugate before the end of 2017. Thus, the company could have four different products in the clinic based on one antibody. Besides 5B1, the company has a library of over 100 other fully human antibodies that could be developed in a similar fashion to 5B1.

In late 2016 or early 2017 the company is also expecting topline overall survival data for the two cancer vaccine programs that are currently in Phase 2 clinical trials for treating ovarian cancer and sarcoma. We believe that positive news flow in 2016 will begin to lift the stock price as investors become more aware of the potential for 5B1 as both a therapeutic and imaging agent. We are maintaining a ‘Buy’ rating on the stock with a $4 price target.

PROJECTED FINANCIALS

MabVax Therapeutics, Inc.
Income Statement

MabVax Therapeutics, Inc.	2014 A	Q1 A	Q2 A	Q3 A	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	$0.1	$0.1	$0.2	$0.7	$1.0
YOY Growth	-	-	-	-	-	-	-
Total Revenues	**$0.3**	**$0.2**	**$0.1**	**$0.1**	**$0.2**	**$0.7**	**$1.0**
YOY Growth	-	-	-	-	-	-	-
Cost of Sales	$0	$0	$0	$0	$0	$0	$0
Product Gross Margin	-	-	-	-	-	-	-
Research & Development	$3.503	$1.726	$2.326	$3.127	$3.000	$10.179	$12.0
General & Administrative	$5.204	$0.981	$4.207	$2.286	$2.500	$7.861	$9.0
Other Expenses	$0	$0	$0	$0	$0	$0	$0
Operating Income	($8.393)	($2.467)	($6.396)	($5.280)	($5.3)	($17.3)	($20.0)
Operating Margin	-	-	-	-	-	-	-
Non-Operating Expenses (Net)	$0.475	$0.020	$0.000	($0.000)	$0.010	$0.030	$0.1
Pre-Tax Income	($7.918)	($2.4)	($6.4)	($5.3)	($5.3)	($17.3)	($19.9)
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)	$0.00	$0.00	$0.00	($0.09)	$0.00
Net Income	**($10.578)**	**($20.393)**	**($6.396)**	**($5.280)**	**($5.290)**	**($35.247)**	**($19.900)**
Net Margin	-	-	-	-	-	-	-
Reported EPS	**($9.51)**	**($6.25)**	**($0.29)**	**($0.20)**	**($0.19)**	**($1.79)**	**($0.57)**
YOY Growth	-	-	-	-	-	-	-
Basic Shares Outstanding	1.112	3.263	21.695	25.799	28.000	19.689	35.000

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

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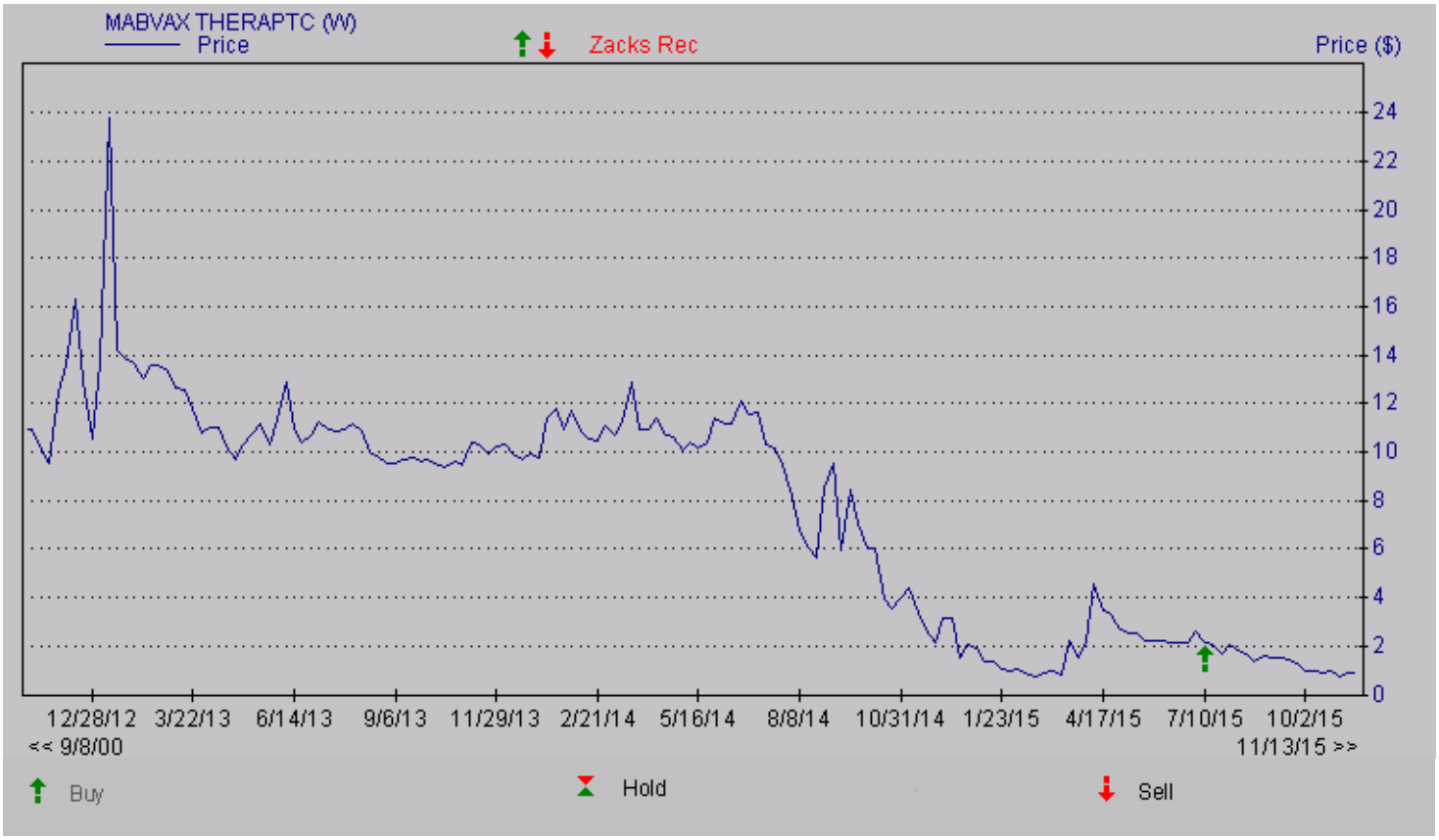

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Buy/Outperform: The analyst expects that the subject company will outperform the broader U.S. equity market over the next one to two quarters.
Hold/Neutral: The analyst expects that the company will perform in line with the broader U.S. equity market over the next one to two quarters.
Sell/Underperform: The analyst expects the company will underperform the broader U.S. Equity market over the next one to two quarters.

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