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Report: Micromet, Inc. (MITI)
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Author: Eric Sharps, Ph.D.

In May 2006, Munich, Germany-based Micromet listed on the Nasdaq exchange after its reverse merger with San Diego-based CancerVax. Micromet primarily focuses in oncology. This summer, the Company plans to initiate the first pivotal clinical trial in its history. Micromet will test blinatumomab, a novel single-chain antibody, to treat acute lymphocytic leukemia (ALL) in adults. Yesterday, the stock closed at $6.73 with 80.8 million shares outstanding giving the Company a market capitalization of $544 million. Cash and equivalents at March end were $183 million. Both the cash and stock count include results from a secondary offering completed in mid-March that netted about $75 million from the sale of 11.5 million shares at $7.00 each.

Conclusion

Despite clinical development weaknesses and limited progress over the past seventeen years, I am optimistic about the outcome of the single phase 3 trial in adult B-cell ALL and propose a long thesis in the Company. The trial is scheduled to begin this summer and is predicated on the data from an open-label, single-arm phase 2 study in which 16 of the 20 patients achieved molecular complete remission (mCR) of their bone-marrow based disease within 28 days. Although based on a small German study, this outcome is extraordinary and predicts sustained clinical benefit. Spontaneous mCR is rare and half these patients would have been expected to relapse within . 18 weeks of entering the trial. Given the merits and risks described in this report, a long investment in Micromet based on blinatumomab's clinical outcome is an example of betting more on the horse (the antibody) and less on the jockey (the Company). Like many investments in the biotechnology arena, the risk in Micromet is high, commensurate with the reward or penalty.

Company Background

In 1993, the Institute for Immunology at Munich University spun off Micromet AG. After the reverse acquisition of CancerVax by Micromet, Micromet's shareholders owned 67.5 percent of the combined company. At year-end 2006, Micromet's reported accumulated deficit was $111 million. Today, over 90 percent of its 130 employees are based in Munich and approximately a dozen, including the CFO Barclay Phillips (joined September 2008), are located in Bethesda, Maryland. Christian Itin, Ph.D., joined the Company in 1999 as VP Business Development and was named President and CEO in March 2004. Chief Scientific Officer, Patrick Baeuerle, Ph.D., joined Micromet in October 1998 and Chief Medical Officer, Jan Fagerberg, MD/Ph.D. joined in November 2009.

Micromet's Technology

Micromet refers to its novel antibody constructs as BiTEs, Bispecific, T-cell Engagers. However, single-chain antibodies (SCAs) of a more conventional design were originally developed in the mid-1980s at Genex Corporation. Enzon, Inc. (now Enzon Pharmaceuticals, Inc.) acquired Genex in June 1991 for less than $25 million. Originally, Enzon intended to license SCA technology rather than develop it internally. However, in April 2002, Micromet and Enzon established a 30-month collaboration, based in Munich, to develop at least two SCA-based therapeutics, one in inflammatory disease and the other, using anti-GM-CSF, in autoimmune disease. In November 2005, the collaboration ended, although the Companies' cross-license and marketing agreements for the combined intellectual property estate for SCA remain intact.

Despite 25 years of development, SCAs have earned only a modest reputation. Among the hopeful was Alexion's pexelizumab, a C5 complement inhibitor, which was abandoned in late 2005 after nine years in clinical development including several failed phase 3 trials. Other companies that have pursued SCAs include Aventis, Bristol-Myers Squibb, Eli Lilly and Merck. Currently, Roche/Genentech's Lucentis, an SCA to treat adult macular degeneration, is perhaps the best-known commercial SCA.

The next few sections provide background information on antibodies, SCAs, T-cells and leukemia/lymphoma for readers interested in a more complete understanding of Micromet's underlying technology and clinical focus. Those already well informed on these topics may skip ahead to page 4. And, for readers with a background in biochemistry, a technically advanced discussion about Micromet's BiTE antibodies is at the end of this report, as an addendum.

Antibody Structure

Secreted into the blood by immune cells, an antibody is a protein that can bind, with great specificity, to a foreign molecule. The foreign molecule (called an *antigen*) can be a protein, a carbohydrate or almost any molecule that is not recognized as "self." For example, the blood types, A, B and AB reflect the presence of specific antigens on red blood cells that are recognized by antibodies, specifically isoantibodies against non-self blood group antigens. For example, if you have type O blood, you have neither A or B antigens on the surface of your red blood cells but you have both A and B antibodies in your blood. And, vaccines are injected antigens that can elicit the formation of antibodies that provide protective immunity. Typically, phagocytes ("immune cells that eat bacteria and viruses") e.g., in the liver, degrade the antigen:antibody complex. Certain white blood cells are also phagocytic. Antibodies that form against the individual's own proteins (self) result in what's called autoimmune disease. Multiple sclerosis, arthritis and psoriasis are examples.

In the antibody-secreting cell - it's called a B-cell - the protein is assembled from four separate protein chains. That is, antibodies are tetrameric ("four parts") incorporating two "heavy" chains and two "light" chains. Heavy and light refer to the relative molecular masses of the proteins, with heavy chains weighing 53,000 Daltons[1] and light chains at 22,500 Daltons. Thus, on average, an antibody has a molecular mass of ≈ 150,000 Daltons. For perspective, a carbon atom has a mass of 12; aspirin has a mass of 180 while the anticholesterol drug, Lipitor (atorvastatin), has a mass of 1,209. Thus, antibodies are comparatively big, chemically complex molecules. Please see Figure A (next page) for a concise lesson in antibody structure and, importantly, how that structure relates to its antigen-binding capability.

Single-Chain Antibodies

Antibodies are far more complex structures than described above. Further, it is easier for a molecular biologist to construct the single gene needed to encode a single protein than the four genes required to make a tetrameric protein. In fact, one only needs the gene segment encoding the variable region (Figure A) of a heavy chain and a light chain (from the same antibody) to generate an antigen-binding protein. Linking those two gene segments, end-to-end into a single protein creates a single-chain antibody.

[1] The Dalton unofficially indicates a unit of mass of one-twelfth the mass of a carbon-12 atom. In practice, when discussing molecular masses (once called molecular weights), no terms are used at all. But enough Chemistry 101.

The SCA described above will bind to one antigenic site. Micromet has gone one step further and combined, into one SCA, *two* antigenic binding sites, with each site specific for a different molecule. This is where Micromet's terminology, bispecific originates. For a cancer target, one of the antigen-binding sites is specific for the cancer cell. It is the second antigen-binding site that constitutes Micromet's "secret sauce."

The T-cell

There are two principal arms of immunity in all vertebrates. As described above, the *B-cell* produces and secretes an antibody that can attach to a foreign molecule. A specialized cell, the T-cell, constitutes the second arm of immunity. T-cells are effective against invading *cells* (not just molecules) and, for example, are what account for organ rejection in organ transplants (kidney, heart, etc.). There are multiple subtypes of B- and T-cells, distinguished by their activity. The second binding site in all of Micromet's SCA constructs is specific for binding the T-cell. Micromet refers to this element of its SCA as a T-cell engager. Thus, the Company's BiTE SCAs are bispecific, T-cell Engager molecules. Micromet's scientists have proposed that the SCA can provide a transient, serially active ("catalytic," not stoichiometric) tether between a T-cell and a tumor cell. After the T-cell digests the tumor cell, it moves on to another tumor cell with the help of the SCA, which also moves on. Beyond that, the T-cells specifically targeting the tumor will proliferate. One piece of evidence supporting a BiTE's multiple, vs. single, engagement of the tumor cell and the T-cell is the remarkably low concentration of drug required for anti-tumor activity. For example, in test tube experiments, Micromet's blinatumomab has shown activity at one hundred thousandth (five orders of magnitude) the concentration of another, conventional antibody-based drug, Roche/Genentech-Biogen/Idec's Rituxan (rituximab).

Leukemia and Lymphoma

Micromet's primary focus has been in hematologic rather than solid tumor cancers. New blood cells originate either in the bone marrow or in tissues of the lymphatic system that includes the lymph nodes and the spleen. Leukemias and lymphomas are blood-borne cancers frequently caused by an activating mutation in an oncogene in a single stem cell. The dysfunctional, mutant stem cell proliferates uncontrollably, crowding out normal, functional blood cell production. Leukemia is a general term covering at least four major types of leukemias, but is most simply described as the proliferation of immature (i.e., nonfunctional) precursor cells *originating* in the bone marrow. In contrast, lymphomas are solid tumors typically *originating* in the lymph nodes or spleen. The two most recognizable lymphomas are Hodgkin's (85-95 percent five-year survival, affecting . 8,500 new patients each year in the US) and Non-Hodgkin lymphoma (. 70 percent five-year survival, affecting 66,000 new patients each year in the US). ALL is one type of leukemia and is discussed in more detail below. For an excellent, non-technical introduction to leukemia and lymphoma and the diseases' statistics, see http://www.leukemia-lymphoma.org/all_mat_req_index.adp?b_type=1&item_id=11198.]

Almost 90 percent of all leukemias fall into one of four types with just under 45,000 new cases diagnosed each year in the US. The four are named by 1) the tissue where the cancerous cells originate and 2) those cells' maturity (functionality). Acute disease results in an excess of *immature*, nonfunctional cells. Also, acute disease progresses (worsens) rapidly and, if untreated, can be fatal over months. Chronic disease results in an excess of *mature*, functional cells. Further, chronic disease progresses slowly, and, if untreated, is fatal over a period of years. If the cancerous cells originate in the *bone marrow*, the disease is classified as myelogenous. If the cancer cells originate in the *lymph glands or spleen*, for example, the disease is lymphocytic. Both forms of chronic disease (CLL, CML) and AML predominantly affect elderly adults (median age . 66 years). The most common leukemia in children (# 14 years old) is ALL and they account for . 60 percent of the 6,000 new ALL diagnoses each year in the US. Finally, ALL is further refined into B-cell lineage (80 percent) and T-cell lineage (20%) diseases. Micromet's most advanced molecule is blinatumomab, which is designed to treat B-cell lineage cancers. It will be tested against ALL first and possibly NHL and CLL later.

Over the past fifty years, the improvement in five-year survival for pediatric ALL has been spectacular. It has risen from three percent in 1964 to over 95 percent in children under five years old (and . 80 percent in adults) today. Sadly, five-year survival does not translate to "cure" for everyone and problems remain, primarily due to disease relapse. Over 50 drugs have been FDA-approved to treat hematologic cancers and many of these cancers are treated with combinations of two or more chemotherapeutics.

The goal in treating first line ALL patients is complete remission (CR), meaning there are no cancer cells detected in the circulation and less than five percent of the immature cells (called blasts) in the marrow are cancerous. The 95 percent CR noted above refers to these first-line successes. While worrisome, disease relapse is generally well treated and can result in up to 85 percent CR in children but only 35 percent CR in adults. Further, second remissions tend to be brief. Five-year survival in adults after first relapse is seven percent. For all patients, bone-marrow transplant from matched donors provides the best chance for lasting remission, but also the highest risks, especially for adults. Further, it's been known for 20 years that the higher the percentage of cancerous blast cells remaining in the marrow and the longer they are there after remission, the higher the likelihood of relapse and death. Microscopic examination of blood or bone marrow samples can only detect approximately five percent residual disease (five leukemic cells per 100 normal marrow cells). More sensitive biochemical tests developed over the past 15 years (e.g., qPCR of specific genetic aberrations, flow cytometry) can detect these cells, referred to as minimal residual disease (MRD), down to one leukemic cell per 10,000 normal cells. Based on several prospective studies, bone marrow-based MRD (magnitude and timing) is widely recognized as an independent prognostic for subsequent relapse. Micromet's clinical trials for blinatumomab will target adults after their first remission but with detectable MRD (i.e., < five percent).

Blinatumomab for ALL

Micromet's most clinically advanced project, a BiTE SCA, is the primary driver of the long thesis. For completeness, the other BiTE-based projects and the 200 series antibodies are reviewed too. Micromet develops both its sophisticated BiTE SCAs (named as 100 series molecules) and conventional human or humanized monoclonal antibodies (200 series). While members in the 200 series have mostly been partnered out, the Company retains full ownership of its BiTE SCAs.

Originally described in March 2000, Micromet's '103 has since been assigned the formal name, *blinatumomab*. The tumor-specific portion of this construct targets a cell surface protein called CD19. CD19 is found on virtually all B-lineage cells, except the earliest stage stem cells and the terminal stage plasma cells, but not on other cell types in the marrow. Roughly 80 percent of ALL patients suffer from this B-lineage variety of the disease. The other 20 percent suffer from a T-cell version.

Micromet has completed several clinical studies of blinatumomab monotherapy in NHL patients since 2006. Early results were published in August 2008 in Science (Bargou et al., Vol. 321, pages 974-977) and work continues for this indication. However, the Company has decided to pursue ALL as the first indication for regulatory approval. Spread over six clinical sites in Germany, Micromet began a phase 2 study of blinatumomab in ALL in mid-2008. All patients were in complete remission and all had MRD. Interim data have been presented at several medical meetings since the trial began.

The most current results are from a single arm, open-label study in which 21 adults were treated with blinatumomab monotherapy starting at 15µg/M²/day. The dosage could be increased to 30- or, if necessary and tolerated, 60µg/M²/day, delivered as a continuous infusion over 28 days. After a two-week rest, patients could begin another cycle of therapy for up to ten cycles. The primary clinical endpoint was no detectable disease, mCR, in bone marrow biopsies at 24 weeks (see http://www.clinicaltrials.gov/ct2/show/NCT00560794?term=blinatumomab&rank=1).

Results were reported at the American Society of Hematology (ASH) conference in December 2009 for 20 evaluable patients of the 21 enrolled. The single dropout was due to an (reversible) epileptic seizure. In other studies with blinatumomab (e.g., in NHL patients), the risk of seizure has been a recurring problem; however, titrating patients up to the final dosage may mitigate this risk in future studies. Remarkably, 16 of 20 patients (80 percent) achieved mCR after the first four-week course of therapy. Micromet's December 8, 2009 press release was less informative than the abstract (#840), which had been submitted at least four months earlier. From the abstract, 19 patients had been enrolled, 16 were evaluable and there were 13 mCRs (81 percent). The other three patients had stable disease. One of these three experienced a relapse of disease in their bone marrow. Among the 13 mCRs, there were two who relapsed, but the disease was found at sites external to the marrow. Acknowledging that this was a very small, open-label, single arm study, greater transparency of the results should have included a nominal calculation of relapse-free survival. Secondary endpoints included time to molecular and hematological relapse, but these were not disclosed either. Still, as disclosed, the top-line data appear encouraging.

Clinical Development Plans for Blinatumomab

This year, Micromet plans to initiate two clinical trials of blinatumomab in ALL. The first, a pivotal phase 3 based in Europe, will enroll 130 *adult ALL* patients with MRD after their first CR. Scheduled to begin in mid-2010, the study is a single arm, open-label trial exactly as described for the phase 2 above; however, the trial will allow up to four, 28-day courses of continuous infusion dosed at 15µg/M²/day with two weeks rest between each course. The primary endpoint is mCR with relapse-free survival as a secondary endpoint. Since some patients will be suitable for a bone-marrow transplant from matched donors ("transplantable"), the secondary endpoint will include survival at 100 days post the transplant. For non-transplantable patients, the secondary endpoint includes the relapse-free survival rate at one year.

The second trial, a phase 2 also scheduled to begin this summer is similar to the first except that the adult ALL patients will have *relapsed* or will be *refractory* to chemotherapy. This single-arm study will enroll 20 patients, some possibly from the US, and the primary endpoint will be hematological CR. In other words, this trial will more closely mirror conventional chemotherapeutic studies. Micromet has not disclosed other details of the trial design.

The Company also plans to initiate a phase 2 trial of blinatumomab in CLL and will have other early-stage clinical trials in progress. And, as noted earlier, Micromet has several corporate partners with active clinical development programs. However, blinatumomab in adult ALL is likely to remain the most advanced project and therefore, in the absence of external events, most likely to affect Micromet's stock performance over the next year or two.

<u>Other Products in Development – The MT100 Series</u>

Micromet's second BiTE antibody is '110 which targets the epithelial cell adhesion molecule (EpCAM) found on the surface of many solid tumors including breast, prostate, pancreatic and lung cancers. In April 2008, Micromet initiated a phase 1 dose-ranging study of '110, primarily designed to identify the antibody's maximum tolerated dose (MTD). The MTD is that dose at which adverse events or side effects are unacceptable. Initial data from 18 patients were presented in September 2009 at a European cancer conference. Three patients each were tested with '110 at increasing dosages, beginning at 1µg/day up to 12µg/day, as a continuous infusion lasting 28 days. Of 18 evaluable patients, seven had stable disease. This means only that their cancers had not grown, not that any tumors had shrunk. The cohort included nine patients with colorectal cancer, three with gastric cancer and one each with small cell and non-small cell lung cancer. Four patients with other solid tumors were also treated. Although some elevation of liver enzymes was found, suggesting biological activity, no dose-limiting toxicity (DLT) was seen. Therefore, testing continues with dosages higher than 12µg/day.

Micromet has not reported any clinical data for its third BiTE construct, '111, an antibody targeting CEA (carcinoembryonic antigen). Originally described in 1965 as one of the first tumor specific antigens (for colorectal cancer), CEA turns out not to be very specific at all. CEA is used diagnostically to monitor patients on chemotherapy, but over the years, immunotherapeutics developed against CEA have not panned out and the FDA has not approved any.

The MT200 Series

Micromet's best-studied conventional monoclonal antibody is MT201 ('201), a human monoclonal antibody which like '110 above, also targets EpCAM. The formal name assigned to '201 is adecatumumab. Partnered with Merck Serono since December 2004, the deal was revised in December 2006 after modest results were reported in October 2006 in breast and prostate cancer. For example, in the breast cancer study of 109 patients split into four arms (two dosages split between patients with high and low level EpCAM expression), the clinical benefit rate did not exceed 25 percent in any cohort. Clinical benefit was defined as complete or partial response or stable disease using RECIST criteria[2]. This suggests that in each of the four groups, not even seven patients out of 27 met the minimum criterion for stable disease, let alone demonstrating partial or complete responses.

In March 2009, Micromet initiated a new phase 2 trial of '201, this in colorectal cancer. The Company plans to enroll 90 patients into one of three arms: 1) a multi-drug chemotherapy regimen using oxaliplatin or 2) '201 monotherapy or 3) the two approaches combined. As of January 2010, only three of the sixteen European sites were actively enrolling patients. The primary completion date is planned for June 2011 (see http://www.clinicaltrials.gov/ct2/show/NCT00866944?term=MT201&rank=1) for additional details. And, although it was approved in 1995 in Germany, (Johnson & Johnson's) Centocor dropped its US efforts to develop Panorex, an anti-EpCAM antibody, in 2002. Given the data thus far, it is difficult to be optimistic that '201 will become a successful drug.

Micromet has described at least four other 200 series antibodies, three of which have been out-licensed and are in development by the licensees, two private firms and one Japanese company. There is limited data available for these molecules, but all three are in early stage clinical development. The fact that Micromet licensed most of its 200-series antibodies clearly suggests that its clinical development plans do not contemplate conventional antibodies.

Briefly, '203 is a human monoclonal antibody that targets GM-CSF, a naturally occurring protein. The drug GM-CSF (sargramostim, granulocyte-macrophage colony stimulating factor) is currently marketed as Bayer Schering's Leukine and is used to expand the white blood cell population in leukemia patients who have received a bone marrow transplant. However, an excess of GM-CSF may be involved in autoimmune diseases such as multiple sclerosis, rheumatoid arthritis and psoriasis. In May 2007, Micromet received $7 million (€ 5 million) up-front in a $167 million deal for '203 from privately held Nycomed, based in Denmark. Nycomed initiated a phase 1 clinical trial in June 2009.

[2] Solid tumors are typically evaluated using standardized methods to measure tumor size (shrinkage). Published in February 2000, RECIST (*Re*sponse *C*riteria *I*n *S*olid *T*umors) updated and simplified the measurement criteria originally published in 1979. A complete response was still defined as 100 percent tumor regression (disappearance); however, a partial response was defined as ≥ 30 percent regression (previously 50 percent) and stable disease was defined as < 30 percent shrinkage and less than a 20 percent increase. Disease progression is defined as more than a 20 percent increase in tumor size. For more technical details, see JNCI, 92, 205-216 (2000).

Micromet's '228 is also a human monoclonal antibody (technically an IgM subtype vs. the more typical IgG subtype). It targets a glycolipid that is found on the surface of melanoma cells. In February 2007, Micromet licensed worldwide rights to '228 to Morphotek, a privately held firm in Pennsylvania that was acquired by Japanese pharmaceutical giant Eisai two months later. There is no mention of a clinical development program for '228 at Morphotek's web site.

The last is '293, a humanized monoclonal antibody specific for cleaved collagen that is found in the extracellular matrix surrounding tumor cells, especially melanoma, breast and pancreatic cancers. In March 2007, it was licensed to privately held, San Diego-based Tracon Pharmaceuticals, where it is now named TRC093. In July 2007, Tracon initiated a phase 1 trial of '293 in solid tumors. Initial safety data were reported in October 2008 for 16 patients (no option, open-label, solid tumors) at four dosages (at least three patients at each) up to 12mg/Kg and in one patient tested at 24mg/Kg. Dose-escalation continues.

Investment Merits

- *Clinical Data* – By any measure, the top-line phase 2 data for blinatumomab in adult B-type ALL are impressive, if incomplete. While surrogate markers of clinical success are common endpoints in the treatment of second- or third line therapy, it remains to be seen if the FDA and US-based clinical trial sites will accept mCR as a primary endpoint in a single-arm pivotal trial. Since half of the enrolled patient population would be expected to relapse in . 18 weeks, relapse-free survival is a superior primary endpoint of genuine clinical value. In addition, many single-arm studies have to cross a higher statistical threshold (e.g., p # 0.01 instead of the standard $p < 0.05$) when comparing against historical controls. Micromet's pivotal trial is expected to begin this summer, so the Company has yet to disclose numerous details about the study. Hopefully, (see "Translucency" in Investment Risks) the Company will do so when the study begins.

- *Acquisition* – If Micromet's blinatumomab proves successful in treating ALL (even worldwide, the patient population is small) the Company will not be independent for long. Nothing validates a potential platform technology better than clinical success. The first monoclonal antibody pure play was Hybritech, acquired by Lilly in 1986 for ≈ $350 million, then sold to Beckman Coulter in 1995 for about $10 million. Subsequent antibody-centric acquisitions have fared better, including Abgenix (by Amgen for $2.2 billion in April 2006), Medarex (by Bristol-Myers Squibb for $2.4 billion in September 2009) and Facet (by Abbott for $720 million, announced March 2010). Although not sufficient, having a product in sight, if not on the market, clearly helps.

Investment Risks

- *Clinical Leap* - Every clinical trial conducted or sponsored by Micromet has been single-arm, open label and, therefore, uncontrolled. The Company's press releases provide no historical context with which to judge, even superficially, a clinical study's results. And yet, Micromet plans to enter a pivotal clinical trial based on the results from 21 patients. A clinical development program like this is at high risk of failure. Remarkably, there is precedent for embarking on a single-arm, open-label pivotal trial in ALL. In 1992, the FDA cleared Bristol-Myers Squibb's Vumon (teniposide) for first and second line use in pediatric ALL based on testing in 25 children. Similarly, Genzyme's Clolar (clofarabine) was FDA approved in late 2004 to treat third line pediatric ALL patients based on testing in 58 patients. There is less data to support testing in adult ALL patients and, as noted, no drugs have been FDA-approved based on a mCR endpoint.

- *Big R, Little D* - After 17 years, Micromet has intriguing science, an abundance of publications in well-respected, peer-reviewed journals (Science, PNAS, Blood) but limited clinical progress to show for its efforts. In 1993, Micromet AG was formed from a research group spun from the Institute for Immunology at Munich University. In the university environment, especially in a research institute, success is primarily measured by establishing a robust publication record. The company raised its first venture round in 1996 from well-regarded institutional venture investors including 3i, Abingworth, Advent Ventures and The Wellcome Trust, among others. Nevertheless, after 13 years as a private firm, the Company could come public only by reverse merging into Nasdaq listed CancerVax whose sole clinical program had failed in October 2005. With increased investor interest, Micromet will need to refocus its efforts towards clinical development.

- *Translucency* - The Company needs to improve its transparency with investors. For example, February's R&D Day in New York City was rich in science -- more than 160 slides -- but light on specifics and not always clearly presented. Similarly, when the Company has issued a press release to complement an abstract presented at a medical conference, the content has been incomplete and, at times, murky.

- *Platform Hypothesis* – Until one of Micromet's antibodies succeeds in the clinic and passes regulatory muster, the BiTE platform remains hypothetical. For now, Micromet simply owns a cleverly designed single-chain antibody construct. Historically, platforms have made for a better story than the reality they've delivered (remember combinatorial chemistry, high-throughput screening). The challenge, as always, will be whether Micromet can bring a molecule to market.

- *Target Choices* - Micromet is testing several targets that have been tested previously by others. Many molecular targets suitable for treating disease have some level of biological rationale behind them. For example, inhibiting HMG-CoA reductase to lower LDL synthesis has worked splendidly to treat hypercholesterolemia. That is why eight statins have been FDA approved in the US. Micromet has developed antibodies against CEA, EpCAM and CD33. CD33 provides a valuable lesson in the vagaries of drug development. Wyeth's Mylotarg (gemtuzumab ozogamicin) was FDA approved in May 2000 to treat second line AML in patients older than 60 years. Mylotarg has not become a blockbuster drug. However, PDL Biopharma (Protein Design Labs then, later Facet, currently being acquired by Abbott), which ironically was earning a royalty on Mylotarg, tried to develop its own anti-CD33 mAb, called Smart M195 or Zamyl, beginning in the early nineties. Disappointing phase 3 results in December 2001 and again in May 2002 put an end to that project. Same target, different outcomes. Targeting CD33 may still be viable, but Micromet needs some fresh ideas.

Based on the merits and risks described above, a long investment in Micromet based on blinatumomab's clinical outcome is an example of betting more on the horse (the antibody) and less on the jockey (the Company). As with many investments in the biotechnology arena, the risk is high, commensurate with the reward or penalty.

A technically advanced discussion about Micromet's BiTE antibodies appears as an addendum on the following page.

Addendum

BiTE Antibodies

This technically advanced section about Micromet's BiTE antibodies is included for those with a background in biochemistry, but it is not materially germane to the long thesis for blinatumomab in ALL.

All BiTE constructs[3] are entirely murine, manufactured in CHO cells and have an average molecular mass of ≈ 55-60kDa. The V_L and V_H domains are cloned from the relevant hybridomas using standard PCR methods. Protein purification is facilitated by adding a histioline tag (His_6) to the C-terminus of each construct and purifying the protein on a metal-chelate affinity column (e.g., zinc or nickel-nitrilotriacetate). Elution employs 200-500 millimolar imidazole, which is removed in subsequent purification steps. T-cell specificity is conferred by an anti-CD3 binding site, which is common to all BiTE constructs and typically at the C-terminus of the molecule. The cell targeting domain (e.g., anti-CD19 in blinatumomab) is at the N-terminus of the construct and a Gly_4-Ser_1 pentapeptide linker (a $[Gly_4\text{-}Ser_1]_3$ 15-mer has also been used) sits between the two binding domains. Thus, a prototype construct may be drawn schematically as shown below (single-letter amino acid code):

$$V_{L1}\text{-}V_{H1}\text{--G-G-G-G-S--}V_{H2}\text{-}V_{L2}\text{--H-H-H-H-H-H}$$

Note that the order of variable light and heavy domains are reversed (N → C) between the two binding domains. Also, each of the four canonical domains would be expected to have at least one intra-domain disulfide bond; however, expression in CHO cells apparently produces correctly folded, soluble protein so that solubilization and disulfide refolding are not necessary during purification. Periplasmic expression in E. coli results in a nonfunctional protein. Finally, in a natural antibody, all four variable domains are at the free amino terminus of each full-length protein. Clearly, that is not the case with an SCA. While it is surprising -- and not at all intuitively obvious -- that the construct illustrated above would retain full binding activities for *both* domains, in vitro and in vivo data trump intuitions and bear out the sophistication (or at least good fortune) of this design[4].

Encouraging clinical data for blinatumomab in ALL has been based on dosing the SCA as a continuous infusion at 15μg/M²/day for a 28-day course of therapy. Like other SCAs, this molecule has a short half-life (hours) in blood, therefore the continuous infusion. Conventional antibodies have a half-life measured in weeks. Although Micromet has not disclosed details of the infusion system, a reasonable guess includes the use of a small portable infusion pump (reservoir refilled weekly) delivering blinatumomab mixed in human serum albumin, which is stable at room temperature. For an average adult of ≈ two meters surface area, the total antibody dosage is only 840 micrograms per month. This helps explain why such a foreign molecule avoids immunologic detection. Even four courses of this regimen expose an individual to less than four milligrams of a foreign protein. By comparison, a *single* infusion of rituximab (for NHL) is dosed at 375mg/M², almost 200 times the protein exposure generated by a four-month course of therapy with blinatumomab.

[3] See Mack et al. in PNAS, 92, 7021-7025, 1995.

[4] For a fascinating discussion of the possibilities, see US patent 7,635,472 issued to Micromet December 22, 2009. This is the most recent of 14 US patents issued to the Company since its first in November 2002.