CEO CFO

Minerva Biotechnologies

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Having Completed Pre-clinical Studies for their Anticancer Drug based on Stem Cell Research showing that they can interfere with the Mechanism of Self Replication, Minerva Biotechnologies is well positioned for Growth

Healthcare
Cancer/Stem Cell

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Dr. Cynthia Bamdad
CEO

BIO:
While a student at Harvard, Dr. Cynthia Bamdad invented the first electronic DNA chip, now an FDA-approved handheld diagnostic instrument, which formed the cornerstone of a startup company, Clinical Micro Sensors, which sold within two years to Motorola for $300 million. Dr. Bamdad is lead or sole inventor of over 100 patent applications in the United States and abroad for technologies, therapeutics and diagnostics.

Dr. Bamdad founded Minerva in 1999 to develop nanotechnology to better understand the mechanism of cancers. In the course of these studies, Bamdad discovered that stem cells grow by the same mechanism that drives the growth of 75% of cancers. This discovery provided critical insight into how to stop cancers from growing. Importantly, it also showed how to use the tricks of cancer cells to override the stem cell's natural SHUT-OFF mechanism to make stem cells grow in the pluripotent state indefinitely and without maturing until the override signal is withdrawn. Recent experiments show that this single growth factor method for growing human stem cells solves many of the problems that have plagued stem cell research. Both the stem cell growth media and surfaces that Minerva developed are chemically defined and animal-free, which should expedite FDA approval for therapeutic use of stem cells grown this way.

Dr. Bamdad was previously the Chief Scientific Officer of Clinical Micro Sensors. Cynthia also served on the Board of Directors of Pharmacyclics(**NASDAQ: PCYC**) during their turn-around.

About Minerva Biotechnologies:
Minerva is focused on the space between stem cells and cancer cells. Minerva discovered that a clipped form of the transmembrane glycoprotein MUC1, that we call MUC1* (pronounced muk 1 star), is a powerful growth factor receptor that mediates the growth of both stem cells and cancer cells. We hypothesized that cancer cells and stem cells were the same except that cancer cells had learned to override some unknown mechanism that limited a stem cell's ability to self-replicate. By studying stem cells and cancer cells in parallel, we elucidated a feedback loop by which the MUC1* ligand, NM23 (NME1), regulates self-replication; we saw how cancer cells learned to short circuit this feedback loop to keep self-replicating indefinitely. We adopted the cancer cell tricks to make stem cells grow without spontaneous differentiation, but can interrupt this process at any time to initiate differentiation. Minerva recently reported that, for the first time, genetically unmodified human stem cells were converted to, and maintained in, the "naïve" state by culturing the cells in the dimeric form of NM23. Interestingly, subsequent exposure of the naïve cells to bFGF, the standard growth factor used in all human stem cell culture, reversed the process and caused the cells to enter the "primed" state. As predicted by comparison to mouse naive cells, the NM23 cultured stem cells have a much higher cloning efficiency than the same cells cultured in FGF-containing media and differentiate in ways that are far superior to current technology.

Interview conducted by:
Lynn Fosse, Senior Editor
CEOCFO Magazine

CEOCFO: Dr. Bamdad, would you tell us the vision and plan behind the founding of Minerva Biotechnologies and where is Minerva Biotechnologies today?
Dr. Bamdad: The plan when I founded the company was to make nano-

particles with a chip surface which would be a next-generation biochip and the next logical step after I invented and commercialized the DNA chip that was sold to Motorola for $300 million. In the process of testing of this new chip-derivatized nanoparticle, we, quite by accident saw something that showed us how cancer cells were replicating. With that critical insight, we made the decision to shift our business strategy and chase down developing a whole new kind of anticancer drug that interferes with their mechanism for self-replicating.

CEOCFO: How has that developed so far?

Dr. Bamdad: We are the first to learn how this protein works. For some 25 or 26 years it was known that the pattern of the MUC1 protein was very different on healthy cells than on cancerous cells. For 25 years nearly every drug company spent tens if not hundreds of millions trying to figure out if the difference in the MUC1 pattern was an artifact of cancer or if it was somehow causing the cancer. Minerva discovered that, without knowing, people were looking at two different things. The full length molecule, MUC1, does nothing; it's in the "off" or quiescent state, as it's supposed to be on healthy adult cells. On cancerous cells most MUC1 has been clipped by an enzyme to a shortened form, and it was that shortened form, that we call MUC1*, that is a powerful growth factor receptor driving the growth of 75% of all cancers.

CEOCFO: How has Minerva Biotechnologies been able to apply this knowledge?

Dr. Bamdad: The MUC1* protein works by ligand-induced dimerization, meaning some growth factor binds to the outside of the receptor and sends a signal to the inside of the cell, telling it to self-replicate. Once we knew how that worked, it was fairly simple to see how we could disrupt it - how we could block that growth factor from binding to the MUC1* receptor. The drugs we are developing will not affect healthy cells because we showed that that MUC1 receptor looks very different on healthy cells than the way it looks on cancerous cells. In an important twist, we found out that stem cells grow exactly the same way as cancer cells. This was a big shift in the way people have been thinking about cancer--that a cancer cell is really a healthy cell that is reprogramming itself to revert to being a stem cell. Then the question became, well, stem cells regulate themselves. They self-replicate but then they mature into cells that do not keep self-replicating, so what happened in cancer cells? They have lost that ability to limit or control their self-replication. By studying human stem cells right next to human cancer cells, we learned the link: how stem cells control their self-replication but cancer cells do not. That became yet another feature of how we are blocking cancer cell growth in a patient by reinstating the natural, default shut-off mechanism that stem cells have. It was a complicated process learning how that works, but at this point it is very straightforward and we are on the path to humanizing antibody-based drugs that will treat 75% of all cancers. The humanizing of the drug is done so that the human body does not see it as anything foreign. We should start human trials in about 3 to 4 years from now.

"What I have learned from my past experiences is to always keep your eye on the prize and do not be encumbered by conventional wisdom – it is usually not all that wise."- Cynthia Bamdad

CEOCFO: Has the medical community been paying attention, or is it too early?

Dr. Bamdad: Recently, the medical community has been paying much attention. When we first proposed this idea, that cancer cells were just healthy cells that were becoming reprogrammed to act like stem cells, we had grant proposals into the National Institute of Health that were all rejected, saying that it was a crazy idea. Now, it is largely accepted that cancer cells have many of the same molecules that stem cells have and in some methods of blocking cancer cell growth they are actually being induced to differentiate or mature the same way a stem cell would. In fact, that is what the anti-cancer drugs that we are developing do. They induce the stem cells to mature and stop the self-replicating. They show all the molecular markers of a stem cell maturing.

CEOCFO: Would you tell us what happens a year or two from now?

Dr. Bamdad: Most of the scientific risk is gone. For the anticancer treatment, we are at the stage that we have completed pre-clinical studies, including showing dramatic anti-tumor effect in animals. As soon as we humanize our antibodies, we'll be starting the FDA approval process so we can start testing in humans. The near term potential, which we are now realizing, is that by looking at stem cells and cancer cells in parallel and seeing how stem cells self-regulate but cancer cells do not, we discovered how to use the tricks of cancer cells to make stem cells grow without spontaneously differentiating and in what is called the "naïve" state. We have published a paper about that in the peer-reviewed journal PLOS ONE. We discovered the natural growth factor, NM23, that makes human stem cells grow in the truly pluripotent naïve state. Having human stem cells in the naïve state is extremely important. There has been news in the press about researchers taking stem cells and turning them into cardiomyocytes, which can be used for heart repair. This can be routinely done using mouse stem cells because the growth factor that makes mouse stem cells grow in the naïve state is known. As soon as one tries to do anything with a human stem cell the efficiency is so low that it is commercially unfeasible. Until we published our paper, the natural growth factor that makes human stem cells grow in the naïve state was unknown. People were using a growth factor called FGF, or fibroblast growth factor, that researchers like Rudy Jaenisch at MIT and Jennifer Nichols in England already showed produced human stem cells that were not naïve. Jaenisch showed, and we recently confirmed, that if one adds FGF to naïve human stem cells they progress to a more differentiated state called

"primed" and are no longer truly pluripotent, or able to become any cell in the human body. They go to a somewhat differentiated state where they do not function the right way--one cannot make a whole group of them become cardiomyocytes, for example. So by bringing stem cells back to the naïve state, we are now showing in our lab that they act like the mouse stem cells. They have very high efficiency in becoming cardiomyocytes, high efficiency in becoming neurons, and other types of cells that would be therapeutically useful. We have reagents to sell to the R&D community and we are negotiating with other companies for commercial applications of our stem cell growth factors and growth-promoting surfaces. We are talking to companies interested in using our naïve human stem cells to differentiate into cardiomyocytes, both for drug and toxicology screening. Drug companies are very interested in testing the effects of drugs on real human heart cells rather than on mouse heart cells. Eventually, we would like to take this technology into the clinic to treat patients with cardiomyocytes derived from their own cells to repair damaged heart tissue.

CEOCFO: Will Minerva Biotechnologies be seeking funding?
Dr. Bamdad: As a small start-up company we are always looking for funding. We have recently opened an equity raise. We had been waiting for our paper to come out. In addition, we are now receiving offers from rather large companies wanting to invest in Minerva.

CEOCFO: What challenges do you foresee for Minerva Biotechnologies?
Dr. Bamdad: One challenge is that the big distribution companies selling stem cell reagents are already locked into selling products based on using FGF (fibroblast growth factor) as the growth factor. Millions of dollars have been spent developing and promoting something that we just showed does not work. It will be a challenge to turn that ship around. However, we think that once the end-user tries our product, NM23 and our related stem cell products, they will rapidly have a change of heart. It is just easier and produces a better stem cell that is easier to work with, in the end – higher cloning efficiency, higher efficiency of differentiation, etc. Some researchers we collaborate with were working with iPS cells that were not optimal. But, when they used our growth factor, NM23, they starting seeing an improvement in their stem cells and in their final product when they differentiated them. We are currently collaborating with a company that has been making cardiomyocytes that they sell to drug companies for drug screening and toxicity testing -- it took about 4 weeks to turn their ship around. They went from a very low efficiency of making cardiomyocytes to an incredibly high efficiency and a higher quality of cardiomyocytes. We believe that once people start using our growth factor and our stem cell surfaces it will not be hard to convince them.

CEOCFO: What has been most valuable from your previous experiences as you have been working on and developing Minerva Biotechnologies?
Dr. Bamdad: What I have learned from my past experiences is to always keep your eye on the prize and do not be encumbered by conventional wisdom – it is usually not all that wise. I have known from that first experience when we saw how cancer cells grow that I was right, and I knew that eventually we would get there. It is like putting together the pieces of a puzzle; when you get enough of the pieces in place, then everyone can see it. Suddenly everything flips, everybody wants to use it, and everybody wants to get on board. I believe we are now bringing that picture into sharp focus.

CEOCFO: During this long process of development, how do you handle frustration when dealing with a technology so potentially game-changing and life-saving?
Dr. Bamdad: It *is* a long process. But success is invigorating and we've had a series of breakthroughs that clearly show that this is the right path we're on. This is not a "dot com" business. We are talking about unraveling the mysteries of life itself. We do not want to *treat* cancer – we aim to *cure* it. In science, it is a very exciting area and the challenge of doing it is almost as exciting as when one actually makes a breakthrough. I feel like we have been clipping along at a fast pace, so I have not found it that frustrating. However, there are two things about being in this business that I do find frustrating: one is there is a bias toward male CEOs and it is frustrating when people look at the company that I have built and have kept afloat when many companies have gone under and they only want to invest if we get a "real" CEO. To them, the definition of a "real" CEO is a young, aggressive male. Interestingly, this is much less of a problem with the younger generation. The other frustrating part of this business is that while investors are all well-meaning, science is a complicated area, and there is often confusion between hype and reality. In this business we repeatedly hear hype like, "This is the greatest thing, it is going to revolutionize science, it is going to be the next Genentech…" Then the company fails or fades away. Then a company comes along that really does have revolutionary science and investors are confused. We stick to what we've actually done and what we're going to do. That speaks for itself. We solved the technical problems that stood between the benchtop science of stem cells and being able to repair a person's heart using stem cell therapy. We discovered a completely new mechanism that regulates the growth of over 75% of all human cancers and figured out how to stop it. This is a paradigm shift in how we treat cancers that could actually *cure* cancer, not just hold it off until an eventual recurrence.

CEOCFO: How does Minerva Biotechnologies stand out to the business and investment communities?
Dr. Bamdad: Well, we figured the detailed molecular mechanism of how cancer cells and stem cells grow. We figured out how stem cells limit their self-replication, and how cancer cells short circuit the feedback loop so they just keep self-replicating indefinitely. In short, we figured out the primal growth mechanism; we can turn it off, to treat cancers, or turn it on to grow stem cells. We have the only technology that enables the growth of geneti-

cally unmodified human stem cells in the "naïve" state. Scientists widely believe that the inability to grow human stem cells in the naïve state has been one of the biggest obstacles preventing stem cell therapies from getting into the clinic. In this business, the value of your company is the value of your patent portfolio. Minerva has an extensive patent portfolio, that we believe constitutes a virtual franchise for the MUC1* receptor and its activating ligand, for the treatment of cancers or the manipulation of stem cells. We have already demonstrated in vitro and in vivo efficacy of our anti-cancer agents in animals. We are in the process of applying for IND which is the first step toward FDA approval. The good news is that this will be a drug that treats 75% of all cancers. It could be the largest and most effective blockbuster drug for cancer.

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