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Cytokinetics CEO Robert Blum: An Interview With "The Pink Sheet" DAILY

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During the BIO InvestorForum in San Francisco, Cytokinetics Ceo Robert Blum, along with Corporate Development Director Scott Jordan, sat down with "The Pink Sheet" DAILY to talk about plans for Cytokinetics' lead candidates, the oncologic ispinesib and heart failure drug CK-1827452, partnering with GSK and Amgen, and the biotech's eventual commercialization strategy.

Blum joined Cytokinetics in 1998, working initially as exec VP-corporate development and finance and as CFO. He was appointed president in January 2006 and added the CEO title in January 2007.

"The Pink Sheet" DAILY: Let's start out talking about your cancer portfolio, particularly ispinesib. Do you want to talk about the mechanism of action of this class of mitotic kinesin spindle protein inhibitors, how they work and potential benefits over earlier generation drugs like Taxol?

Robert Blum: Ispinesib is an inhibitor of KSP. KSP is a target that's involved essentially in mitotic progression. There are existing anti-mitotics, Taxol and Taxotere, that have demonstrated that this class of anti-mitotics is very important to the treatment of certain cancers, and [are] first-line mainstay in breast, ovarian, lung, prostate and other cancer, but the use of those drugs is severely limited by side effects and cumulative toxicities, the most important of which is peripheral neuropathy... KSP is not expressed in peripheral neurons, so at minimum, the hypothesis is that ispinesib may be a better tolerated form of anti-mitotic because it would not have the peripheral neuropathy.

As it has turned out, because with the benefit of [GlaxoSmithKline] and [the National Cancer Institute], we have hundreds of patients that have received ispinesib therapy, we've seen an even more remarkably clean tolerability profile. Not only have we not seen peripheral neuropathy, but we've also not seen the other standard side effects you see with chemotherapies, no alopecia, no thrombocytopenia, no other gut toxicities. There's an exquisitely specific effect on one side effect, neutropenia, which can be very easily and well managed by the use of growth factor support.

We've also established that its highly combinable, meaning it can be used with other standard

chemotherapies, especially capecitabine and carboplatin, and we've also seen across nine phase II clinical trials that GSK or the NCI has done, that it also looks to have clinical activity in some very important tumor types as monotherapy, in particular in breast cancer, but also in ovarian and platinum sensitive non small cell lung cancer. We've seen clinical activity that we think can be amplified as we might now optimize the dosing schedule and evaluate the activity of the drug in less chemo-refractory populations.

"The Pink Sheet" DAILY: Is that why you're initiating a Phase I/II study in breast cancer, and what is the timeline for that trial?

Blum: That will happen before the end of this year, Phase I, which will look in a dose escalation way at a new treatment schedule for ispinesib, then to roll into a Phase II study in metastatic breast in front-line chemotherapy patients who would not have already received a Taxol.

"The Pink Sheet" DAILY: Why did you amend the deal with GSK to take the reigns on breast cancer?

Blum: So we can do this work. We think that the drug warrants further investigation. This way we have the resources, financially and operationally, and we have the real focus now to be able to do this work, still subject to our GSK collaboration. We came to them and said we'd like to do this, we can pay for it. If we're right then you can repay us the cost plus the cost of capital for having done it and the program continues under our then same collaboration. We thought this was something important to do and we can make it a priority.

[Cytokinetics announced plans to initiate a Phase I/II trial of ispinesib in the second half of the year in June after amending its deal with GSK ("The Pink Sheet" DAILY, July 2, 2007).]

"The Pink Sheet" DAILY: What do you envision being the best path forward for registration for this drug?

Blum: In doing this ...we are actually borrowing a page from [GSK's] playbook. They have a product called lapatinib that had demonstrated about a 4 percent response rate in a similar chemo-refractory population. They went into a more chemo naive population, and they were able to, in HER-2 positive breast cancer patients, amplify that to 35 percent. So, from the same page from their playbook, we're looking to go to the similar type of design to see if we can optimize, amplify. If we're right, then I think this would be very much a product that then could be developed probably in combination with capecitabine in a registration study probably then in second-line metastatic breast.

But before we would invest the many tens of millions of dollars to do that study, we think this is a prudent thing to do first. Can we get an amplification of the response rate? If you look at Tykerb, if you look at [Bristol-Myers Squibb's] ixabepilone, if you look at Taxol, any of those products in second- or third-line metastatic breast cancer as monotherapy will produce about a 5 percent to 15 percent response rate. So we're in the game, but before we can invest our more precious risk capital in a registration path, we thought we should see if we can amplify that

response by going into less heavily pre-treated patients.

"The Pink Sheet" DAILY: What is the timeline for that? How long will it take to complete?

Blum: We'll start the phase I/II study this year, and we'll have the Phase II data next year to inform the path.

"The Pink Sheet" DAILY: Let's turn to SB-743921. Can you talk further about that follow up program?

Blum: '921 is a second KSP inhibitor. This was originally conceived as a back up to ispinesib, but it has some very different pharmaceutical properties. It has more potency, a different volume of distribution, different pharmacokinetic properties, so it lends itself to evaluation possibly in hematologic cancers. We embarked already on a Phase I/II study of that drug candidate in non-Hodgkin's lymphoma. That's in the Phase I portion of a Phase I/II trial, and that might allow us to see whether this mechanism translates also into activity in hematologic cancers, where we saw some very good preclinical activity. That's ongoing. Some data was presented at ASCO this year. We think that again, with a preferred more dose dense dosing schedule, we might be able to see some activity there.

"The Pink Sheet" DAILY: You have a third candidate that has entered the clinic through your research collaboration with GSK?

Blum: Also arising out of our research, there's a compound called GSK-923295 that's an inhibitor of another mitotic kinesin involved in cancer cell division. That's one that GSK is taking forward itself subject to our option. So we have this parallelism in our clinical trials, where GSK is taking forward one compound subject to our option [and] we're taking forward two subject to their option. They're all three under the umbrella of our collaboration. That compound is a first-in-class compound that showed some very remarkable broad preclinical activity. It's now in a Phase I dose escalation safety and tolerability and pharmacokinetics trial. It may be producing data in 2008 and going into Phase II in 2008 and that's something that we would be interested in developing with GlaxoSmithKline if it moves into later stage development, so three cancer compounds all of which arose from our research in this area of mitotic kinesin biology.

"The Pink Sheet" DAILY: Is the goal then to eventually have your own candidates that you develop independently?

Blum: We're building a business that eventually we would think about partnering differently as we evolve. But very much in our interest right now, these three candidates, to have this relationship with GSK...it's been very fruitful. Three products to come out of one research relationship is unusual. The deal is structured in a way that would be very attractive to us were it to continue because we can continue to participate in clinical trials with our partner footing the bill and commercialization with them reimbursing a lot of our costs so that it helps finance the forward migration of the company into some very expensive late-stage clinical activities and commercial activities. So the deal was structured seven years ago, but still very much is unusual

in that way.

"The Pink Sheet" DAILY: Let's discuss your selective cardiac myosin activator, CK-1827452, which is partnered with Amgen. How are the development responsibilities divided between Cytokinetics and Amgen?

Robert Blum: We're doing the Phase II work, and as the product may move into Phase IIb, they are required to exercise their option.

"The Pink Sheet" DAILY: How is that program progressing?

Blum: This is an activator of cardiac myosin for the potential treatment of heart failure. It has both an IV form and an oral form. We presented data last year in Phase I in healthy volunteers for the IV form showing that this drug has an unusual activity in terms of inotrophy, increasing cardiac muscle contractility. It does so by a unique signature of mechanism that was provocative in its result. We also showed in Phase I last year in a separate study it's essentially 100 percent orally bioavailable. So those two results combined, I think, attracted Amgen.

We ended up doing a deal that we signed in December '06 in which they paid us \$75 million to take an option on CK-452 as we continue to advance it under our leadership and sponsorship through Phase IIa. We had really not intended to partner it so soon, but this deal has advantages to Amgen and advantages to us. It brings us cash, but it also allows us to control the movement of the program through proof of concept, and I think a company like ours with an evolving development capability is in the best position to manage development through proof of concept, at which time then a pharmaceutical partner can bring its muscle and mass to the late stage development.

We began these studies this year. They'll continue in 2008, and I expect sometime in 2008 we'll be in a position where we'll have satisfied the requirements of our contract to give them data from a subset of these studies to inform their interest in exercising their option. If they do so, prior to our movement into Phase IIb clinical trials, they then would pay us \$50 million, in addition to up to \$600 million in milestone payments ... When the program was partnered, it was in Phase I, but the deal terms we think were favorable, not unlike late stage partnering, and we can then buy into the program and escalate our royalty even higher. And that affords us co-promotion rights, where our sales force, together with their sales force, would be promoting the product in North America ... Again, like the GSK deal, it has an optionality that allows us to flexibly dial-in our level of financial risk and exposure as we can afford to and continue to mature our business towards the marketplace where ultimately we would hope to be in a position where we could commercialize these assets ourselves in a very profitable way. So it's a way of evolving into that state.

"The Pink Sheet" DAILY: Does Cytokinetics have anything else in the earlier stage pipeline that looks particularly promising?

Blum: The majority of our research right now is focused to muscle biology. We still do other research in other areas including some very interesting things in early oncology, but we spend

about 38 percent of our R&D [budget] on research, and that research is primarily focused on muscle biology. The activators of cardiac muscle for the potential treatment of heart failure in the clinic have provided a guiding light to other ways of modulating muscle contractility so we can also be now focused to inhibitors of smooth muscle contractility. We already have good in vitro and in vivo evidence that an inhibitor of smooth muscle contractility has good potential for the treatment of bronchoconstriction or reactive airways disease, pulmonary arterial hypertension, systemic hypertension, so there is a whole body of clinical trials that can arise from compounds moving out of that program, and we hope to be in IND enabling studies next year there. Similarly, we have activators of skeletal muscle at a similar level of maturity, moving towards IND enabling studies, and that would be even more pioneering in that these activators of skeletal muscle could be useful for diseases associated with geriatric conditions of muscle wasting, so there is a whole pharmacology there to be opened up in terms of healthy aging about providing more muscle mass, strength and utility.

Those are the two most mature research programs and they borrow very synergistically from our cardiac muscle program. Right now if you think about the company from 30,000 feet ... [we have] four products in clinical trials and two others that are coming in behind towards a portfolio of what would be then six, where each of them has relevance to many indications, and for a young company and still a relatively small company, that's an unusual level of productivity and yield for drug discovery. All of these are first in class; all of these are next generation. Scott [Jordan], who leads our commercial development business and our corporate development, then has an opportunity to be thinking about this from really a pioneering way, setting new standards, but in each case, walking in the footsteps of an already validated commercially successful therapeutic area but with a new mechanism designed to engineer away liabilities of drugs on the market, Taxol with its neuropathies, inotropes with their limitations, so it makes for a very nice business strategy.

"The Pink Sheet" DAILY: Scott, can you talk for a moment about the commercial structure and eventual plans?

Director-Corporate Development Scott Jordan: We've been on a plan that has been in place for 10 years and consistently go back and ensure that we're still building the organization in the right direction. The partnerships that we have with GSK and Amgen from a commercial standpoint allow us to build out an organization and build capabilities while in step with major pharmaceutical companies.

"The Pink Sheet" DAILY: What size commercial organization do you envision as you are starting out?

Jordan: It depends on how we build out with certain partners, but the way we look at this is the best approach is to build out a commercial organization that is focused in the acute hospital type of settings, a place where we can be competitive with major pharmaceutical companies where the number of sales reps is not the key to success in terms of blanketing. We could never compete with Pfizer in a GP market that way. The key for us to be successful is to find a place where we've got good products, good science and can compete very effectively in concentrated

markets.

Blum: And we do deals ... where we can preserve the key upside for ourselves and for shareholders without becoming what all too often companies do, which is become fee-for-service ... systems for pharma. It tells us what kinds of deals we can afford to do, which ones we should do. We only selectively partner. We're not in the business of trying to have pharma companies basically sponsor us to do research so we take a passive royalty interest. That's not a particularly compelling business model. We now know, with focus to the commercial markets we can afford to penetrate, how to build out a company that can affordably get there.

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- Jessica Merrill (j.merrill@elsevier.com)