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With their Oral Small Molecule Drug in Human Trails in the US, Copenhagen, Denmark the Toronto, Karyopharm Therapeutics Inc. is focused on Bringing the First Nuclear Export Inhibitor to Approval in the US and Europe for Treatment of Various Cancers

Healthcare
Nuclear Transport Modulators

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Michael Kauffman
CEO

BIO:
Dr. Kauffman cofounded Karyopharm with Dr. Sharon Shacham at the inception of the Company. Prior to joining Karyopharm, he was the chief medical officer at Proteolix Inc., which was acquired by Onyx Pharmaceuticals Inc., where he lead the development of carfilzomib, a novel proteasome inhibitor approved in refractory myeloma as Kyprolis® by Onyx in July, 2012. Dr. Kauffman was President and Chief Executive Officer of EPIX Pharmaceuticals, Inc. (previously Predix Pharmaceuticals, Inc.) from 2002 to 2008. He was the leader of the Velcade® Development Program at Millennium Pharmaceuticals, and held a number of senior positions at Millennium Predictive Medicine and Biogen. Dr. Kauffman received his MD and Ph.D. from Johns Hopkins Medical School and is board certified in internal medicine. He currently serves on the Boards of Verastem (VSTM), Zalicus (ZLCS), and Metamark Genetics Inc.

About Karyopharm Therapeutics Inc.:
Karyopharm Therapeutics is a pharmaceutical company focusing on discovery and development of novel drugs for the treatment of cancer, inflammation and other diseases related to cell proliferation. Karyopharm Therapeutics is developing small molecule drugs that modulate the activity of critical pathways in cancer, inflammation, and other diseases of cell proliferation by targeting nuclear pore complex pathways, which control the transport of key regulatory, tumor suppressor, anti-inflammatory, and viral proteins between the nucleus and cytoplasm.

Interview conducted by:
Lynn Fosse, Senior Editor
CEOCFO Magazine

CEOCFO: Dr. Kauffman, what is the vision for Karyopharm Therapeutics?
Dr. Kauffman: Our goal is to bring the first nuclear export inhibitor to approval in the US and Europe for treatment of various cancers.

CEOCFO: What is a nuclear transport inhibitor?
Dr. Kauffman: I think we are all aware that the "brain center" of the cell is called the nucleus. The cytoplasm does the "work" and the "brain" or the nucleus directs it. One of the fundamental differences, if not "the" fundamental difference, between cancer and normal cells is that the DNA that is in the nucleus in cancer cells has been altered in a way that leads to cancer. The only similarity between all cancers, as many different kinds of cancers that there are, is that their DNA is always substantially altered and abnormal. Now, our bodies have actually evolved a whole set of proteins whose job it is to look at the DNA and sort of do an "audit", just like the IRS does an audit. These proteins are actually called "tumor suppressor proteins", or TSP's. When these proteins detect that the DNA has been damaged, they set off one of two possibilities. One is that the cell tries to repair the damage. The second one is that if the TSPs have determined that the damage is too great, then the cell has to die: the TSPs send it to commit suicide. These systems work very, very well, which is why the majority of us do not get cancer. There are at least ten or fifteen of these major systems in our bodies that we already know about. What is interesting is that in cancer, when it does develop, it actually has to turn off, essentially, all of these ten or fifteen systems; these tumor suppressor proteins. One of the ways it does it is to carry these proteins out of the nucleus where they do their job and put them in the cytoplasm. I know this is a long winded story, but here comes the punch line. Getting out from the nucleus to the cytoplasm requires an escort or a chaperone. The chaperone, in this case, is very interesting. That is because there are seven known chaperones that carry proteins from the nucleus to the cytoplasm. Our founder, Dr. Shacham, realized that only one of these nuclear export proteins is actually responsible for handling these tumor suppressor proteins. There-

fore, if you block this particular chaperone, which is called Exportin 1 or XPO1, because it exports things, if you block it, then you end up with these tumor suppressor proteins staying in the nucleus where they belong. If they do that then they can detect cancer, and if they can detect cancer they can tell the cell to commit suicide. Very simply then, what our drugs do -- and these are oral anti-cancer drugs -- is that they very, very specifically block XPO1 and turn off the nuclear export of these tumor suppressor proteins. Therefore, the tumor suppressor proteins build up in the nucleus. And if the cell's DNA looks like cancer, then the TSPs will tell the cell to commit suicide. If the cell is normal, then they will just tell the cell to wait until the drug goes away and then the cell can go on and do its business.

CEOCFO: Have people been actively looking for a way to do this?
Dr. Kauffman: The target, Exportin 1, has been in the literature now. When Dr. Shacham had the idea to start the company back in 2009, there were actually seven hundred publications in the medical databases that are available to everyone, but no one had been able to find a way to make a nice oral drug that could block this Exportin 1, and do it in a way that would not be toxic to other parts of the cell. We were successful in doing that, at least so far, and we now have our compound that has gone through all of the animal testing required. It is almost nine months into its Phase I studies in humans with cancer.

CEOCFO: What is your drug doing, or how is it working where others have not been able to learn how to do it?
Dr. Kauffman: There is a term in the pharmaceutical industry called "drug-like". That means that a particular compound or chemical looks like other drugs look; that its chemical structure has certain characteristics. It is very much as if you could look at a building and tell that this is a building and not a football field. There are just certain characteristics of a building: four walls, a roof, and a floor; literally that. Nearly all drugs have similarities to a trained eye, to a chemist; that is, they just look like drugs. That is different than what natural products -- things that you isolate from the earth, or from trees, or from plants -- look like chemically. Our founder, Dr Sharon Shacham who started the company, has expertise in computer-aided drug design. Based on the known structure of this particular protein, Exportin 1, she was able to, initially on the computer, create a molecule that looked like a drug, fit only into this particular protein. That means it did not bind to other proteins. She predicted that it would work out, and ultimately it did. She eventually made these compounds in the laboratory. We tested them on cells and we made sure that they only bound to Exportin 1; and they do. Unlike others who have tried to use natural products block this target, or use related drugs that were not designed specifically for Exportin 1, we were able to do that based on Dr Shacham's ground breaking in silico design technology; computer aided design technology.

CEOCFO: Has the medical community been paying attention, or is it too early?
Dr. Kauffman: We are conducting our trials in humans in the US in a number of centers, in Copenhagen, Denmark, and in Toronto, Canada. There is an increasing amount of attention to this. We have had a large showing in all of the medical meetings. At the last American Society of Hematology meeting, I believe we had eight different presentations. Five of them were oral presentations and three of them were posters. Therefore, there is an increasing interest in this area. We have a number of publications that have come out and we are even getting calls, occasionally, for doctors who want to study the compound in our lab, or get involved in the clinical trial. Given the stage of this program which is, as I said, the first phase in humans, Phase I, we have had a lot of interest.

CEOCFO: Will you be looking for funding? Will you be looking to partner? What is the strategy going forward?
Dr. Kauffman: The goal in the company is to take this drug to approval in the United States and Europe, largely on our own. We have my background as the lead clinical developer for Velcade® and more recently on Kyprolis®, and Dr Shacham's background as Senior Vice President of Product Development at Epix Pharmaceuticals. We feel comfortable that between this small company that we have and the excellent collaborators and consultants and contractors that we use, that we can bring these drugs to regulatory approval in the US and Europe. That said, we do want to partner this in Asia. We are looking at that immediately, because we cannot carry out simultaneous development in all of Asia. We will eventually partner in the US and Europe for marketing and sales.

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- Michael Kauffman

CEOCFO: What are the most important things that you have learned in previous ventures that you are able to

bring to the table that you anticipate to be most helpful, or have been helpful so far in getting everything the way it should be?

Dr. Kauffman: I think one of the things is that we have stayed very lean and focused. The company is only about eighteen people. We use a lot of folks from the outside. We use many good contractors and consultants. However, the nice thing is that when we have done the good work we need to do with them and it is time to move ahead in the project, that they go and see other clients; that we do not have to keep them occupied. I think that is extremely important in the company. The goal here is to keep the management and the product leadership; and I would stress leadership rather than just managing, inside the company; and the technical expertise outside of the company to some extent. Secondly, I would say that we have been relentless in our push to move things forward. We are really quite focused on timelines. We remind the company all of the time that cancer patients are waiting, and that the cancer cells have not stopped dividing; that they will continue to progress unless we do something about it. We really try to use that mantra to keep people focused and keep things moving. Even loosing a few days here and there; we fight about that in the company. We fight for the patients and we fight to move things forward, because a few days, when you start to add them up, really can make a big difference. Our Board has been very supportive and helpful. We have kept them very well informed on the company's progress, and they have been very supportive. We did have a "trip up" in toxicology, I do not mind admitting it. Everyone does in this business. The Board was very helpful in getting us to look at another compound, which is the compound that is now in the clinic, and that has gone very well. With all of those things I said, I think that those are the main things that has helped us get to where we are in a relatively short time with relatively little capital.

CEOCFO: Are you aware of competitive research that is getting anywhere in the same area?

Dr. Kauffman: No. There were a couple of early attempts that did not really move. A company called Kosan, which was acquired by Bristol-Myers Squibb, had an early program in this field. It was, again, using natural product inhibitors of Exportin 1. And then there is a small company in Japan called CanBas Ltd, which is a microcap company on the Tokyo exchange, which again, has an early program in this area. We are not sure that it is going anywhere. Other than that, we are the only people working on this in terms of drug development. As far as we know we are the only that have ever put an oral drug like this in the clinic and have moved it forward.

CEOCFO: How do you deal, personally and as a company, with the fact that it takes so long to get drugs approved and reviewed and studied?

Dr. Kauffman: That is a great question. We always say this is kind of a marathon. When you are a small company you have to be running at a sprints pace, because time is your enemy in a small company. I actually think that any company should develop drugs with the same urgency that a small company has to. That is because it does cost a lot. Much of that cost is time. The way we try to deal with it is to learn as much about the drug as quickly as you possibly can. There is one track in drug development where you do things very methodically and rationally and linearly. Our belief is that human biology and human pharmacology is just too complex, and we are not nearly smart enough to know what the right linear path is for any of these problems. Therefore, before we even get into humans, we looked at this drug in mice, rats, monkeys and dogs, as well as cats, just to look at the different effects it would have and be on the lookout. We are actually developing a companion compound for Dogs with Lymphoma. This project has moved into a pivotal study now, and we have agreement with FDA on a track to approval for Dog Lymphoma, so we believe this is a way to shorten the path to learning about whether a drug can really work in a significant cancer. Dog Lymphoma turns out to be extremely similar to Human Lymphoma. That is one thing that helps. Secondly, when we got into the clinic we initiated both a solid tumor study, so patients with tumors like colon cancer and ovarian, and head and neck, and lung cancers, at the same time as we initiated a study in the hematologic malignancies, which are the leukemia's, and lymphomas, and myeloma, so that we could learn as much as we possibly could as quickly as possible; both on the safety side and on the potential efficacy side. Again, none of us are smart enough to really know how drugs are going to work in the end. When we started Velcade we believed it would have broad activity across a number of different tumors, and instead it showed extremely good, much better activity than we anticipated, in myeloma in particular, and activity in mantle cell lymphoma. Therefore, you make your best guess, but I think you have to be honest with yourself and the system, that we do not understand a lot of this and we need to go carefully, but expeditiously, into studying it in a way that can potentially help people as quickly as possible.

CEOCFO: Why should investors and people in the business community pay attention to Karyopharm Therapeutics?

Dr. Kauffman: We raised thirty two million dollars in a Series A in late 2010. We closed in October. That money brings us nearly to the completion of Phase I, which we anticipate occurring in the next six months or so. We will be raising an additional large chunk of Series B money, from our current investors with additional wealthy private investors, which was similar to our current investors. However, I think it is rare to see, in this business, to see a company take a completely novel target, develop an oral drug and, on thirty two million dollars, be able to bring it through two Phase I studies. We think that we have used the money carefully and judiciously, but also efficiently, in a way that has generated an awful lot of value. We see a path to approval if the drug continues to behave the way it is currently. We see paths to approval in the next several years in at

least two or three different cancers, which should create additional value for investors. We have a very targeted approach to approvals. We have used the money very efficiently to date, and we think those are good reasons to look to invest in us in the future.

CEOCFO: Final thoughts?

Dr. Kauffman: From the biology perspective, and as a physician who is licensed to practice medicine and still holds his board certification and his license, it has been extremely exciting working on this compound; more than anything else in my life. Both the biology and the medicine are turning out to be very gratifying and quite exciting. We hope to open up an entirely new field that gives many cancer patients a new shot at better quality and longer life.

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