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SPECIAL REPORT

Diffusion Pharmaceuticals Takes Aim at Brain Cancer: CEO David Kalergis

Source: George S. Mack of *The Life Sciences Report* (3/30/16)

It takes extraordinary dexterity to execute a strategic merger, and then to take first steps toward positioning a new molecular entity for a Phase 3 drug trial and potential partnership with a big pharma. That's exactly the inflection point at which Diffusion Pharmaceuticals Inc. finds itself, says CEO David Kalergis. In this interview with ***The Life Sciences Report*** ***(https://www.thelifesciencesreport.com/)***, Kalergis lays out Diffusion's plan for pivotal development of its treatment for primary brain cancer, which could drive the company's market cap to valuations that would bring huge upside to investors if successful.

MANAGEMENT Q&A: VIEW FROM THE TOP

***The Life Sciences Report*: Diffusion Pharmaceuticals Inc. (DFFN:OTCQX) (https://www.thelifesciencesreport.com/pub/co/7556)** was a privately held company. In January 2016, you completed a reverse merger with RestorGenex Corp., and got a new ticker that fits your company's name quite well. Can you describe that process?

David Kalergis: RestorGenex was an active, forward-moving biotech company that had made a strategic decision to get involved with a company with a more advanced pipeline—a company like us. Its board of directors decided to enhance shareholder value with later-stage assets. In the end, we, the private company, acquired RestorGenex, the public company, hence a reverse merger. Right after the merger, we at Diffusion controlled about 86% of the company, and the former RestorGenex shareholders controlled about 14%.

TLSR: What led up to this reverse merger?

DK: It started last July, when we had a positive readout of data in a Phase 2 clinical trial (**NCT01465347 (https://clinicaltrials.gov/ct2/show/NCT01465347?spons=Diffusion&rank=1)**) in newly diagnosed patients with high-grade primary brain cancer, glioblastoma multiforme (GBM). The data supported our hypothesis that our drug, trans sodium crocetinate (TSC), could safely extend survival in these patients. We

went to the FDA for an end-of-Phase 2 meeting in August 2015, presented the data and got a positive response. We agreed on a single-study design that would support registration of TSC. That was a milestone: After that, we saw life science investors taking another look at us.

Shortly after that meeting with the FDA, we got a call from an investment banker who had been following Diffusion. He had not moved forward because he wanted to see the Phase 2 data and hear what the FDA had to say about it. Upon hearing the data looked good and that we had a successful FDA meeting, he proposed a deal by which we could very quickly become public by acquiring another biotech company through a reverse merger.

The merger brought about $8.5 million ($8.5M) in cash to our balance sheet, and also brought in several interesting drug candidate assets. We—the original Diffusion shareholders—have taken over the board of directors and management of the company.

TLSR: Investment bankers can make going public easier because they can match parties for this kind of transaction. Did that make this reverse merger an easier process than doing an initial public offering (IPO)?

DK: I don't think you can ever characterize going public with a merger as easy, but I do think that it was more streamlined than the alternative methods for us, and it certainly was faster. In this case, the investment banker was out there keeping his ear to the ground and his eyes open, and he saw the opportunity to make a match. Just a few months later, we became a publicly traded company.

"The FDA took a look at the 36% increase in overall survival at two years, combined with the lack of adverse events attributable to our drug, and agreed to allow us to enter Phase 3."

One more positive thing about this reverse merger: We didn't have to worry as much about the state of the market to get our deal done and to get shares public. Market conditions were depressed at the beginning of January, and we would have been dependent on what the stock market would be doing on any given day if we had gone the traditional IPO route.

TLSR: While anything you found interesting in the RestorGenex pipeline will probably take a back seat to your current lead candidate, TSC, is there anything you like from that acquisition?

DK: Yes, there is. I hate to use the expression "back seat," but our focus does need to be on our more advanced programs. I wish we had all the resources in the world to develop some of the other interesting things we now own.

There is a preclinical drug in the RestorGenex pipeline called RES-529. It is a very interesting molecule that targets the Pi3K/Akt/mTOR signaling pathway, and it too is targeted at brain cancer, which is a happy coincidence. RES-529 is early stage, but we think it could have synergies with our brain cancer platform. Like TSC, RES-529 can penetrate the blood-brain barrier. It's just a question of amassing the resources to advance this program.

TLSR: David, let's talk about your clinical program. The Diffusion platform is designed to oxygenate tumor tissues with TSC prior to conventional therapies. The hypothesis is that oxygenation of the tissues makes tumor cells more vulnerable to radiation and chemotherapy. Does this premise rest on the theory that

tumor cells are a) more aggressive in a hypoxic environment, or b) that rapidly proliferating tumor cells are outrunning their blood supply, therefore making them less capable of receiving therapeutic agents via bloodstream?

DK: What we think is it's "b," which leads to "a." The inherent hypoxic nature of the tumor tissue outgrowing its blood supply then begins to select for more aggressive cells that have evolved to thrive in what would otherwise be an oxygen-deprived, hostile environment. That low-oxygen environment confers treatment resistance on these cancer cells. When you do not have a sufficient amount of free oxygen in the cell to support the killing power of radiation and chemo, those cells that have survived begin to thrive, and they evolve toward a more proliferative, metastatic cancer phenotype than what originally arose in the tissues.

TLSR: Your approach is to administer TSC via intravenous infusion prior to radiation sessions to sensitize the tumor cells. You did that for six weeks in your 59-patient Phase 2 trial. You are attempting to potentiate the standard of care for GBM, which is conventional radiation and temozolomide, a cytotoxic agent. This study was open-label, so every patient got the experimental agent. The primary endpoint of the study was overall survival. What comparator did you use?

DK: We were matching our data up against the historical standard-of-care therapy for newly diagnosed GBM patients, which was established by what's known as the Stupp study, published in *The New England Journal of Medicine* in March 2005. Dr. Roger Stupp's data supported approval of the first-ever chemotherapy—temozolomide—for newly diagnosed brain cancer. We are using temozolomide in our studies, including the upcoming Phase 3, where the experimental arm will be TSC + the standard-of-care therapy in frontline use.

TLSR: How did the TSC arm compare to the Stupp historical control?

DK: We dosed 59 patients, and then compared the results to the historical standard after 24 months. We felt that if we saw data to support our hypothesis of improved survival with no degradation in quality of life or increase in toxicity, that would be the signal we needed.

"We argued that TSC belonged on the frontline. Fortunately, the clinical community and the FDA understood and agreed."

What we found was that 70% of patients who received TSC + standard of care had survived to one year, versus 62% of people in the historical control group. After two years, 37% of patients receiving TSC + standard of care had survived, versus 27% in the historical control arm. Although you can't determine statistical significance in an open-label trial using a historical control, the clinical community seemed to think we moved the needle. The FDA took a look at that overall 36% increase—37% versus 27% in overall survival at two years—combined it with the complete lack of any adverse events attributable to our drug, and then agreed to allow us to enter Phase 3 with a single trial to support registration.

This Phase 3 will be designed for statistical significance with 400 patients—200 on TSC + standard of care and 200 in the control arm, meaning standard of care alone. This Phase 3 trial will tell us whether what we saw in the Phase 2 is reproducible. We think it will be. Diffusion and the FDA have also agreed that we have the opportunity to double the number of dosing exposures, which we think will help get an even better result.

TLSR: David, the $8.5M you received in the RestorGenex reverse merger is obviously not going to carry you very far in this Phase 3. Do you anticipate partnering before you begin this trial?

DK: We're considering all options. We are not planning to dose the first patient until we have the resources on hand.

TLSR: I've heard you say that you want to position TSC as a frontline therapy in GBM. From an investor's perspective, pursuing a frontline label adds another hurdle to successful development. Is that correct?

DK: In terms of the market, frontline is always the best place to be because it is the most inclusive of the patient population. Front line means you use the drug first, and not as a fallback when something else fails.

The question is, do you have the efficacy and safety data to make your drug frontline worthy? That's a clinical question answered with data, and also—very importantly—by an FDA decision. When we first looked at TSC as a radiation and chemotherapy sensitizer, a lot of people advised that we would, by necessity, enter the market as a second- or third-line treatment because the drug is new and unknown. But we made the argument to the agency that with TSC's demonstrated safety profile and mechanism of action, it would not be right to relegate the drug to second- or third-line status where patients are more advanced, with treatment-resistant tumors, and often in the last stage of disease. We argued that TSC belonged on the frontline. Fortunately, the clinical community and the FDA understood and agreed.

TLSR: A veritable industry has arisen around the advent of angiogenesis inhibitors, the most notable of which is Genentech/Roche Holding AG's (RHHBY:OTCQX) humanized monoclonal antibody, bevacizumab (Avastin), which is a blockbuster. Bevacizumab essentially strangles blood vessels nourishing solid tumors. Your hypothesis appears to be the opposite of the angiogenesis-inhibitor approach. How do both theories coexist in the real world of solid-tumor oncology?

DK: It's a great question. I think there is a consensus that the angiogenesis inhibitors tend to buy time. I don't know that they have been demonstrated to completely strangle the blood vessels nourishing solid tumors, thereby eradicating them. If angiogenesis inhibition was perfected to the point where you could strangle every cancer, we would know that by now.

Avastin and other angiogenesis inhibitors definitely have a place in the treatment paradigms for various cancers. But let's look at this antibody in the cancer indication of newly diagnosed GBM. It was tested in two very large studies in recent years as a possible addition to the first-line standard of care in newly diagnosed primary brain cancer patients—the same initial patient population that we are targeting. In both trials, Avastin did not improve on the overall survival of the Stupp study. It may have allowed a longer period of progression-free survival (PFS), but ultimately, since it did not selectively strangle all the blood supply and kill the entire tumor, the cancer won out.

"We also have orphan disease designation for TSC in the pancreatic disease indication, as well as in metastatic brain cancer."

The angiogenesis-inhibitor approach is a very different way to attack the problem, and it did not work any better in the same patient population that we are addressing. Avastin did not get approved as a first-line GBM therapy—and we at Diffusion don't believe we are competing with Avastin directly.

Another thing to remember is that Avastin is being used as a chemotherapy, whereas our drug, TSC, is being used to promote the efficacy of the existing standard-of-care therapies. Genentech and Diffusion are both dealing with oxygenation of the tumor microenvironment, but our applications are very different, and there is a place for both of them in treatment paradigms.

TLSR: Oncologists would also like to get non-angiogenesis inhibitors—both antibodies and small molecules—deep into tumor tissues, especially in those situations that are inoperable. Do you see TSC as an agent that could improve many different therapies, even some that have not even been thought of yet?

DK: Yes, we do. We think the literature is clear that tumor hypoxia generally confers treatment resistance to radiation and to cytotoxic chemotherapies. At least in theory, and to some extent what we've seen in our laboratory animal models, mitigating the hypoxia generally improves the activity of cytotoxic chemotherapies. We are definitely interested in potentiating other chemotherapeutic agents.

TLSR: Diffusion is planning a pancreatic cancer trial with TSC at some point. Tell me about that.

DK: We are working with key opinion leaders to design a Phase 2/3 clinical trial that would test the hypothesis that TSC would enhance the tumor-killing power, or mitigate the treatment resistance, to Gemzar (gemcitabine; Eli Lilly and Co. [LLY:NYSE]) and Abraxane (nab-paclitaxel; Celgene Corp. [CELG:NASDAQ]) in pancreatic cancer. TSC does not hurt, and there's a good chance it will help. We want to try it. That argument seems to have won favor, but of course the FDA will have the last word.

TLSR: David, Diffusion completed a Phase 1/2 trial with TSC in peripheral artery disease back in 2010. That seems like a terrific indication for an agent that oxygenates hypoxic tissues. Have you thought of TSC as an agent that might be helpful in cardiovascular disease, where patients might have hypoxic or failing ischemic hearts?

DK: We started off as a cardiovascular company. TSC was invented by my partner and cofounder, Professor John Gainer, as a cardiovascular agent designed to promote the reoxygenation of hypoxic tissues, with a primary focus unrelated to cancer. If you look at the preclinical and clinical work, you'll see some fascinating data in stroke, heart attack and in hemorrhagic shock, the latter of which the military financed.

TLSR: Why did you shift your focus to oncology?

DK: A couple of things happened. One is that cardiovascular indication studies are very expensive, the trials are huge, and a lot of standard of care must be integrated into the platform and into the studies. It became clear to us that, all things considered, cardiovascular indications might not be the most efficient way to develop this drug. But that option is open for the future.

Why are we focusing on oncology now? Some investigators raised the issue that hypoxia confers treatment resistance in cancer, and asked if they could use TSC in some cancer models in their labs. We started getting results from rat studies that showed TSC could reoxygenate hypoxic tissue in cancers, and then improve the efficacy of radiation and chemo. The preclinical data from collaborators brought Diffusion to a tipping point, and that's when we went to the FDA to demonstrate how safe the drug was and its prospects in cancer. That was the starting point for Diffusion as a cancer-focused company.

TLSR: Diffusion has FDA orphan-disease designation in GBM, right?

DK: Yes. We also have orphan disease designation for TSC in the pancreatic disease indication, as well as in metastatic brain cancer—not primary brain cancer, but cancer that arose elsewhere and metastasized to the brain.

TLSR: Given the recent reverse merger, investors don't yet have a clear idea of what Diffusion's capital structure looks like. The company got $8.5M in the merger. Do you anticipate that you will have the capital to start the Phase 3 trial in GBM? Do you believe you can raise capital this year?

DK: We definitely are going to need to raise capital to start that Phase 3 trial. It might take a little longer because the markets are so unsettled, but there is interest and enthusiasm in the Diffusion story. We are different, we have data, and we believe we have prospects. Right now, external factors in the capital markets are difficult, but we will find a way.

We anticipate starting Phase 3 in GBM within 12 months, assuming financing is available. We also anticipate beginning the Phase 2/3 in pancreatic cancer, subject to the same assumption.

TLSR: Thank you for your time.

David G. Kalergis (http://www.thelifesciencesreport.com/pub/htdocs/expert.html?id=13668) *is the cofounder of Diffusion Pharmaceuticals Inc., and has served as the company's Chief Executive Officer since 2004. Under his leadership, Diffusion has grown into a publicly traded clinical-stage drug development company commercializing a novel proprietary pharmaceutical technology. Before attending graduate school, Kalergis worked as an intelligence analyst for the U.S. government. In 1982, after receiving MBA and JD degrees from the University of Virginia, he was associated with the New York City law firm of Dewey, Ballantine, Bushby, Palmer & Wood, practicing in the areas of corporate finance, public offerings and mergers and acquisitions. In 1991, Kalergis became the first private investor in Pharmaceutical Research Associates Inc. (PRA), a contract research organization providing clinical trials services to international pharmaceutical and biotechnology companies. PRA went public in 2004 and is now among the world's largest CROs. Kalergis served on PRA's Board of Directors, and from 1991 to 1994 first as head of business development and then as general counsel. After leaving PRA, Kalergis became associated with the University of Virginia in an initiative to more closely link high-technology industry with research. He met Professor John Gainer and the two launched Diffusion Pharmaceuticals shortly thereafter. Kalergis has remained involved with the University's efforts to encourage the spinout of new high technology companies. Kalergis is a founding director of publicly traded Virginia National Bank, and served on its board until May 2012. Other past board service includes the Virginia Biotechnology Association. Kalergis graduated from the University of Virginia College of Arts and Sciences with a bachelor's degree in psychology. In 1982 he graduated from the Combined Program of the Colgate Darden Graduate School of Business Administration and the University of Virginia School of Law, receiving both JD and MBA degrees. He is also a graduate of the Harvard Business School's Leadership and Strategy in the Pharmaceutical and Biotechnology Industry program.*

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