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Q&A with Dr. Corey A. Carter, President and CEO of EpicentRx Inc. developing "Smart" Oncolytic Virus Therapies in combining Immuno-oncology Agents that active the Human Immune System against Cancer with Minimally toxicity for Patients

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CEOCFO: ***Dr. Carter, what is the focus behind EpicentRx, Inc?***
Dr. Carter: The focus of the company is on immune-oncology, which involves strengthening the cancer patient's immune system to target and attack tumors. As a company of actively practicing oncologists we know what it means to sit in front of cancer patients and watch them deteriorate both from the cancer and from the toxicity of treatment, which provides powerful motivation to want to change the current paradigm of treatment; our philosophy in a nutshell is: maximal activity, minimal toxicity. Practically, what this slogan or tagline means to us is that to beat cancer you have to treat cancer in combination with minimal side effects.

Forget about "magic bullets" or single treatments that will cure cancer; they don't exist. Combination is the key. But unfortunately, combinations also add side effects. In general, the more anticancer agents that you combine the better the activity but the worse the side effects are for the patient.

Therefore, our goal is to combine immuno-oncology agents that are not only active against cancer but also minimally toxic for the patient, so quantity *and* quality of life are preserved. Quantity of life is very important obviously, and for some patients living longer is the top priority above all else, but our belief is that quantity and quality are inseparable, and both must be valued equally, which is what we hope and believe we are doing with our lead small molecule checkpoint inhibitor, RRx-001, and our "smart" oncolytic viruses.

"The goal of *next generation* immuno-oncology, as practiced at EpicentRx, is to improve response rates and break through this 20-30% ceiling with minimal toxicity. I think we're on track to do that with RRx-001 and the oncolytic viruses."- Dr. Corey A. Carter

CEOCFO: ***Before we talk about what you are working on, what does your still seeing patients bring to the table when you are in the development process? How does that make a difference?***
Dr. Carter: In drug development an important catchphrase is "important unmet need". A need is unmet in oncology insofar as it applies to patients. The best way to understand the degree and scope of unmet need is from the perspective of patients and their families, which is only possible when you're there caring for them and managing their problems. It's easy to lose sight of what matters in drug development, which is the patients, because of the incessant focus on the

bottom line; however, for me, because I'm a practicing oncologist rather than a sidelined oncologist who used to see cancer patients their plight always remains front and center and I'm very thankful for that.

CEOCFO: ***What do you understand about the subject that allows you to work on something that can make a difference, and can be, as shown on your site, 'next generation immuno-oncology? '***
Dr. Carter: First off, I'm a thoracic oncologist, which means I specialize in cancers of the lung, where immuno-oncology really started. The birth of immuno-oncology coincided with the start of my career at Walter Reed as a clinical trialist, so I've watched the field evolve, warts and all, to where it is now, and I've seen firsthand how it could be improved.

Secondly, I'm from the Navy so intrinsically the idea of marshaling immune forces to repel a malignant invader appeals to me. The military metaphor isn't for everyone, and I've even argued against its use at times, but I still find it helpful to explain to patients that the immune system is meant to continually transition between wartime and peacetime, between escalation and de-escalation depending on the context, much like a standing army. However, in cancer, this balance is disrupted, and the immune system 'stands down' and de-weaponizes; the result is similar to an army in peacetime where the soldiers, bored and idle, loiter around the barracks aimlessly in their skivvies, playing cards, gambling, smoking, drinking etc. instead of mustering up to go on the offensive against the tumor. Immuno-oncology is intended to stimulate the immune system to transform itself from a Nero-like fiddler, content to watch the fiery cancer blaze from the sidelines, into a *bona fide* anti-tumor war machine.

Problems remain, however: 1) immuno-oncology agents called checkpoint inhibitors only benefit 20-30% of patients in particular tumor types, which means 70-80% do not benefit and 2) checkpoint inhibitors are associated with some severe side effects, especially in combination.

The goal of *next generation* immuno-oncology, as practiced at EpicentRx, is to improve response rates and break through this 20-30% ceiling with minimal toxicity. I think we're on track to do that with RRx-001, the oncolytic viruses and the personalized viruses.

CEOCFO: ***Has this approach been tried previously? Is this a new way of looking at it? Where does this fit in the spectrum of what has been reviewed?***
Dr. Carter: To paraphrase Isaac Newton, if we've seen further, it's only because we've been standing on the shoulders of giants. That's not to meant to sound arrogant or boastful, by the way. Immunotherapy began at the start of the 20th century, with the surgeon William Coley, a giant on whose shoulders the rest of the immuno-oncology field has stood ever since, for having discovered that bacterial toxins—so-called Coley's toxins—could cure tumors. Nobody knew how or why it worked, including Coley, I might add, because at that time the immune system was undiscovered territory, and so his incredibly prescient observations were all but forgotten, relegated to history's dustbin, until the early 2000's when immune-oncology experienced a renaissance.

Currently the focus is on checkpoint inhibitors for T-cells, which are specialized white cells with the ability to recognize and eliminate cancer cells. However, T-cells make up only one part of the immune system called the adaptive immune system. The other half of the immune system is known as the innate immune system, which comprises cells such as the macrophages and neutrophils.

EpicentRx contains two minimally toxic platforms, which together stimulate both halves of the immune system: 1) RRx-001, which inhibits a checkpoint on macrophages called CD-47 and activates cells of the innate immune system 2) the oncolytic viruses, which stimulate the T-cells. It sounds completely obvious to say but both halves of the immune system are required to mount an effective anticancer response, just as the use of two arms are much better than one in a fistfight.

The minimal toxicity of these platforms is critically important. Cancer is an escape artist on par with Houdini in terms of how it manages to liberate itself from almost any therapeutic restraint. Block one pathway it escapes. Block two, three, four same result; it escapes. That in a nutshell is the problem with cancer. Whatever you do as an oncologist it escapes.

The good news is that the ability to escape isn't infinite. Block too many pathways, add too many therapeutic shackles and at some point, the cancer runs out of escape routes and molecular lock picks. The advantage of minimally toxic immuno-oncology agents is that they allow you to combine them with other immuno-oncology agents, like checkpoint inhibitors, and in this way by preventing the tumor from doing what it does best you stand a chance of really making a difference.

CEOCFO: ***Why does it work or does it matter as long as it works?***
Dr. Carter: Mechanism matters. In the past it would have been possible to develop an active drug with an unknown, "black box" mechanism but no longer. Today the key interrogatives are why and how, what and who. The why and the

how are the mechanism of action, the what is the cancer type and the who is the patient population. This is the essence of personalized medicine: right drug with the right mechanism for the right tumor type and the right patient population.

CEOCFO: ***Would you tell us about personalized, custom made viral vaccines?***
Dr. Carter: One of the first lessons anyone learns when they are shopping for clothes is that one size does not fit all. It's rare when shopper can walk into a store and buy clothes off the rack. The same lesson applies to tumors, only more so. Tumors are heterogeneous, which is a fancy word for different. No tumor is alike, just as no snowflake is alike and no fingerprint is alike. Therefore, it stands to reason that a potentially effective way to treat cancer is to individualize the therapy.

One way to personalize therapy is to manufacture an adenovirus, the agent of the common cold, which contains DNA from an individual patient's tumor. The advantage of a genetically engineered virus is that in tumors it makes copies of itself—thousands of copies, millions of copies—and the DNA that it contains. If the DNA is from the tumor itself and that DNA is mutated so that the immune system recognizes it as foreign, then the T-cells, the white cells of the adaptive arm of the immune system, will attack the protein in the tumor itself, resulting in cell death and tumor regression.

This isn't theoretical: to date we have manufactured three viruses, the only three in the world, for three patients that are currently undergoing treatment with them.

The best part is that we can manufacture the virus in-house over about 8 weeks, which means that when and if the tumor develops resistance, it is possible to custom-make another virus for the patient, which contains new DNA from their tumor and re-treat *ad infinitum*.

CEOCFO: ***Are there specific types of cancer that responds better to the newer concepts or is it case-by-case?***
Dr. Carter: Cancer is so complicated and so heterogenous that the approach is to design the viral vaccine separately for each patient on a case-by-case basis. To date, we've focused on solid tumors, in particular, microsatellite stable colon, pancreatic and checkpoint inhibitor resistant lung cancers on the premise that they are the most difficult to treat, but we are also able to use a different virus to treat hematological or so called liquid tumors. It's all about unmet need and what we can do to make a difference for the patients that we see in the clinic.

CEOCFO: ***How do you, personally and as a team, deal with some of the frustration of such a long and arduous process to figure something out, let alone get it to a point where people are going to benefit from your findings?***
Dr. Carter: I'd be lying if I didn't say that the bureaucracy of a corporate setting didn't sometimes put a damper on my naturally optimistic personality. However, in drug development, as in life, slow and steady wins the race. We want to treat patients as soon as possible but at the same time we need to do it the right way, which takes time. Pun intended, we recognize patients are a virtue, which is why we have patience.

CEOCFO: ***What is your timetable? What should we expect in the next year or two years?***
Dr. Carter: We are starting several Phase 3 trials with RRx-001 before the end of 2018 both in the US and Europe. Fingers crossed, the data is positive, and we receive an NDA in the US and/or marketing authorization in the EU in a year and half to two years. At the same time, we are entering the clinic with our oncolytic viruses by Q4 2018 so there's a lot of excitement and enthusiasm in the company as we approach the finish line in the case of RRx-001 and the start line with the viruses.

CEOCFO: ***Are you seeking funding, partnerships or investments?***
Dr. Carter: We are currently funded through venture capital an angel investors. One short-term goal is to make the company IPO-ready. We're also in the process of actively seeking partnerships in Europe and Asia.

CEOCFO: ***What has been the response from the medical community that is aware of what you are developing at EpicentRx?***
Dr. Carter: Before I was an oncologist, I worked on a submarine, where the operating principle was "run silent, run deep" and on that basis we've remained submerged and hidden from view until quite recently, when the need to present all the data we've generated with RRx-001 and the oncolytic viruses really compelled us to surface. It is early days but I would say the reaction of the oncology community as a whole has been one of surprise that we've managed to remain hidden for so long, but also one encouragement and enthusiasm. Frankly, there's been a lot of interest in the company from Big Pharma, Investment Bankers, and everything in between, which is not surprising, given that we're on leading edge of a very hot area, but it's still very gratifying to see.