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ImmunoCellular: The Potential For A Cancer Vaccine

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A discussion with Dr. John S. Yu M.D., Chairman and Chief Scientific Officer of ImmunoCellular Therapeutics, Ltd. ([IMUC.OB](#)) in Woodland Hills, CA.

JE: How did you come to be involved first as chief scientific officer, then as director, and now as chairman at IMUC?

Dr. Yu: Well, the company that I founded with a colleague of mine -- I was originally attracted toward commercializing our therapy because of some of the frustrations I felt as an academic investigator in terms of being able to develop therapies for our patients, and that was essentially a therapy did not have a strong commercial backing and a clear pathway toward commercialization. It was something that was very difficult to take past the phase one clinical trial, meaning the small clinical trial testing a few patients. If you wanted to develop a therapy that would be applicable to the population of patients out there, it had to be strategically developed with an eye toward commercialization from the start. Let me give you an example of this.

One of the therapies that we had developed was a vaccine that could not be patented because it used similar types of strategies that were developed elsewhere. Well, you know, this might be fine for an academic trial that we'd do in a small number of patients, but because of the inability to patent it, it was something that no pharmaceutical company would take past a small phase one trial. Even if we wanted to test whether that therapy had legs and whether it would be something that could make an impact in patients with brain cancer, it was something that we really could not take any further. So understanding that type of frustration and what it would take to overcome that type of frustration, we were careful from the get go to patent our technology and then to develop a commercialization strategy in which we would have a significant intellectual input into the company, so that it could be developed right, so that the trials could be done correctly. For the development of the drug to be done correctly with an eye toward regulatory approval, for all of these sort of factors from the intellectual property to the regulatory approval to the generation of a therapy to be commercialized and be relevant for the treatment of our patients, it really had to be done right from the start. And in order to be able to do it right we felt that starting a small start up in which we could control how the trial was done, and how the drug was developed would be the most favorable way to go.

JE: I'd like to talk about ICT107, your cancer vaccine treatment for Glioblastoma multiforme (GBM). That is the most common, most aggressive brain tumor, the primary brain tumor at this point in humans.

Dr. Yu: Yes. Glioblastoma is the most common. It accounts for about half of all primary gliomas, and also the most malignant with the survival measured in months, and at this point in the history measured in 14.6 months is the median survival. So clearly a novel way of treating this therapy is really needed for this disease. So we developed ICT107, (as a vaccine 201) that from our experience really targeted some of those Achilles heel of the cancer. We used several peptides or antigens that we knew were relevant on glioblastoma that were highly expressed on the cancer cells. And we used several of them together knowing that by targeting several at once we could really make an impact on the tumor before the tumor has a chance to make variants that have lost a single or two antigens, and so by virtue of targeting several antigens we got several shots at our goal and prevented an escape variant which would no longer make the antigen that was targeted.

JE: And these are dendritic cell-based. The therapy is the dendritic cell-based?

Dr Yu: Yes, Dendritic cell-based therapies. We chose the dendritic cells because these are the most potent antigen presenting cells in the immune system. So what that means is that the antigen presenting cells are the first responders in an immune response. They're the cells that take up the abnormal proteins that have infected a cell through a virus, or a cell that is abnormal because it's a cancer cell, and it takes up those proteins from dead tumor cells, processes it, and cuts them up into small pieces, namely nine amino-acid pieces, and places them on MHC molecules or major histocompatibility molecules on their cell surface. Then they present these pieces of protein to T-cells which can then recognize these proteins and will target cancer cells that bear these proteins on their cell surface in association with their MHC molecules.

JE: And these are the most potent first responders for an immune system?

Dr Yu: Yes, the dendritic cells are the most potent first responders to an immune response so we put together dendritic cells with antigens that are known to target cancer cells. We later found out that these antigens are highly expressed or highly made on cancer stem cells, and we were one of the first groups to identify cancer stem cells in glioblastoma, -- the most virulent or most aggressive cells of the cancer.

You see, before cancer researchers thought that all cancer cells were similar to each other, but more recently we've found that cancers are very heterogeneous with very different types of cancer cells within them. And only a few of them, between one to five percent, have the sole ability to self-renew or to make perfect copies of themselves and to make more differentiated cells which are astrocytes, oligodendrocytes and neurons in the brain. This is very parallel to normal stem cells that make these cells even through adulthood in the brain. But cancer stem cells no longer have the ability to regulate their growth, and so instead of stopping when they should, they continue to grow

and they continue to make more cancer cells. So we and others have found that in order to kill the cancer you have to really get at its root. You have to really target the cancer stem cells. What we subsequently found were that the antigens that we're targeting with ICT107, made a lot more of the cancer stem cells than our normal cells, and so this provided an avenue to target the cancer stem cells of the tumor preferentially.

JE: And GBM when treated conventionally with chemotherapy and radiation -- it doesn't seem to be affected with that type of brain cancer. It's resistant?

Dr. Yu: Yes. And that's really because cancer stem cells have the ability to be resistant to radiation and chemotherapy, and this is very much parallel with normal stem cells. Normal stem cells in order to be able to withstand all the toxins that we face in life, and still be able to regenerate the cells and neurons that we need to retain our memory, have the ability to withstand radiation like that from the atmosphere, and withstand toxins like chemotherapies with genes that allow them to be resistant to these drugs. Well, the cancer stem cells are resistant to all of these types of therapies including radiation, and chemotherapy, and so whereas the daughter cells can die off, the root of these cancers remained and then will cause a recurrence of the tumor. So the idea is to really target the cancer stem cells so the tumor no longer has the ability to re-grow after treatment.

JE: So with other therapies, immunotherapies under development for cancer, how is ICT107, how is it distinguished or how does it differ from other?

Dr Yu: Okay. So for one thing, we have the only drug that's targeting the cancer stem cells immunologically and preferentially trying to kill the cancer stem cell which is the root of cancer. Number two, by using several antigens we're preventing antigen escape variants from growing out from the tumor so that we can really kill off the tumor before it has the potential of growing back again, and by using dendritic cells which are the most potent and professional antigen presenting cells in the body and using the body's own dendritic cells at that, we hope to generate the most potent immune response possible. So that combination, together with the strategies that we've learned historically from our previous trials using our previous generation of vaccines, we feel like we can make the biggest impact on patients with cancer.

JE: So the phase one data that's available indicates there was significant progress in survival improvement by more than a 150 percent, and that seems to be very encouraging. Do you expect validation of that result as you move into further trials?

Dr. Yu: Well, so, our initial indications are that the survival that we've seen is not a fluke when we look at the patients that we've treated so far. So we think it's a real phenomenon, but really the only way to test it is within a randomized trial. When we look at other patients on other vaccine trials that are not ICT107, that were done concurrently at the same time, we find that the survival of patients on ICT107, is significantly longer than those patients on the other trials, suggesting that it's not the choice of the patients on the trial, but rather the therapy itself. And so we feel confident that the improvement in survival that we've seen will be carried through in larger trials at different institutions.

JE: And the next trial is a phase two upcoming?

Dr Yu: Yes. So the current trial is a multi-institutional randomized phase two trial which is blinded both to investigators as well as to patients; however, the patients have a two to one likelihood of getting the real vaccine rather than the placebo vaccine, and so we've seen enrollment numbers that are quite robust, and you know, patients seem to want to get on this trial with the hopes of getting a vaccine that will improve their outcome.

JE: IMUC has recently formed an agreement with Progenitor Cell Therapy (PCT) a cell therapy services company to qualify the cGMP manufacturing process for ICT-107

Dr. Yu: Yes.

JE: Why PCT? What value do they bring to the table for IMUC? How are they going to help IMUC in this situation?

Dr Yu: Well, they're a company that's well-versed at commercialization of cell therapies, and that's wherein their expertise lies. By working with PCT it'll improve any potential bottle neck that may occur in terms of patient enrollment by having a site of manufacturing besides the U. Penn. site where it's presently being manufactured. Also, because they're a facility that commercializes their cell products, we feel we can move quickly into commercialization if and when we achieve FDA approval for this treatment.

JE: They worked with Dendreon Corp. ([DNDN](#)) on multiple phases of their products, which actually brought a therapy to market.

Dr Yu: Yes, absolutely. They're quite professional and quite good at generating these products in a very efficient manner. We've searched high and low and clearly they were the front runner for this type of cell therapy.

JE: So with the next stage that you're going into with the clinical trials, what would you say are the biggest milestones that you're looking for there?

Dr. Yu: Well, we'd like to see a survival benefit with our randomized phase two trial. Clearly we've shown that we can handle the complexity of the technical manufacturing of the cells, the complexity of randomization, and of managing clinical sites. With our CRO (Clinical Research Organization) we've been rolling this out to more than 20 academic medical centers throughout the United States. We've been enrolling ahead of schedule, and so what we consider to be our greatest technical challenges, I believe we've overcome already. I think our next challenge is to get our data and to analyze and report it well, and then based on the data to efficiently make our next steps in terms of how we'll develop this technology.

JE: And enrollment for the phase two trial has already begun?

Dr Yu: We've already begun enrollment, and we've enrolled more than 65 patients already.

JE: Okay. I want to go back to phase one for a moment. The data and the results from the phase one trial, is that viewed in the scientific community and maybe in the investment community as valid data, a controlled setting?

Dr Yu: Well, it's a one center, phase one clinical trial with limited numbers. I think what we were surprised with and what I believe a lot of investors are surprised with is how well the patients are doing. You know, for the highly educated investor, they were always critical of whether we tried to load the patients on the trial with, you know, patients that have potentially good outcomes, but we really enrolled all comers in which we could surgically resect the tumor, and so we've shown our pre- and post- operative MRI's to some people that were wondering whether these were all patients with tiny tumors, and they were really surprised to see the dramatic nature of the size of some of these tumors. So clearly, you know, there's no loading of the trial in one way or another. So I think what we're seeing is really some pretty amazing outcomes, and we've tried to compare the patients with other patients on historic trials, but the only way you'll convince people is with a large randomized clinical trial - which essentially we're starting to do now.

JE: So, this cancer vaccine, what value does this represent? Let's say if this is successful, these trials come out with positive data and you move into the next phase, when the best case situation happens, what value is this going to bring - in your mind - to the company, to the industry? Does this, its success, does this have the potential to become a mainstream therapy?

Dr Yu: Well, absolutely. So the idea is to bring this to mainstream therapy. I think the idea of cancer vaccines being part of the armor for mainstream therapy is really grabbing hold recently with the approval of Provenge and recent large trials with melanoma and lymphoma, so that the clinical efficacy of vaccines is becoming more and more of a reality. We think that for brain cancers this will represent the biggest impact in being able to affect the patient's outcome, and so clearly there's commercial aspects of an efficacious agent, but what I think we as investigators in this field would be most proud of is the ability to impact the patient's outcome with a low degree of morbidity, unlike the poisons that we normally give patients right now with radiation, chemotherapy. This is really a therapy that capitalizes on the patient's own immune system and ability to mount their own immune response against a cancer, so by doing that I think we'll make a paradigm shift in how brain cancer is treated and hopefully make a dramatic impact on patients' lives and their families' lives.

JE: And as this would become a mainstream therapy and subsequently this would represent a revenue streams, would this be done via licensing of this therapy by other firms?

Dr Yu: Well, I would defer to the future in how we develop this therapy so I wouldn't hazard a guess on how we'll strategically develop this, but certainly that's one of several possibilities.

JE: Are you looking for any of the pharmaceutical companies to joint venture with this or invest in ICT107?

Dr Yu: Not necessarily, but certainly from a business standpoint I'm sure we would entertain any offers, but we're really focused right now in developing this therapy and really rolling out this clinical trial which appears to be successful so far.

JE: If these therapies are successful, and in particular this one, if we could move ahead, how will these therapies be prescribed? How will they be delivered and administered to a patient?

Dr Yu: Well, essentially in a very similar way that a patient would receive a prescription to receive this therapy. Clearly it's more than receiving the prescription for antibiotics. I mean, it's an involved therapy that they'll have to go to a large medical center in order to get their blood cells out, and then to generate a vaccine at one of our vaccine centers, but it's something I believe that patients will be very willing to do if we show a significant improvement in their outcome.

JE: So if you are diagnosed with let's say GBM, the process is or will be that you would go to a center; you would have your stem cells extracted.

Dr Yu: Your white blood cells would be removed. Mainly monocytes removed. They would be sent to a cell therapy center where we would generate the vaccine. It would be mailed back within a week or two, and then the patients would start getting their vaccine doses.

JE: And how long right now, based on the first trial data, how long after you receive the vaccine can you tell that there's progress?

Dr Yu: Well, I mean, no news is good news. If we see the vaccine and the patient has no progression then that's good news. The bad news is if and when a patient has a recurrence of the tumor. So we follow quite closely every two months with MRIs, and then we follow any evidence of toxicity with blood tests and other exams.

JE: So stopping the advancement of the cancer once it's diagnosed is essentially the proving ground.

Dr Yu: Yes. Exactly.

JE: So with IMUC's therapies in development and there are several other companies that are working on various types of development, when is the day when this is common day treatment, when this is the standard of care?

Dr Yu: Well, you know, if and when we finish our phase three trial and we receive the BLA (Biologics License Application) or approval from the FDA is when we'll be able to roll it out to all patients.

JE: On the business side, IMUC in terms of number of people is actually very small. Correct?

Dr Yu: Yes. In fact basically all of the officers (5) in addition to our CFO David Fractor.

JE: Is this one of the reasons why it's so efficient to do this, that your investment and so, say, the burn rate is lower, and the efficiency that these trials are carried out in.

Dr Yu: Yes. Manish Singh (CEO) has been able to run this company as a bare bones company very, very efficiently with only the talent that we need, but the talent that we have is really second to none in terms of meeting all the requirements to execute a very efficient trial.

JE: What kind of funding does it take to bring a therapy -- to get through phase two, phase three, where you have a sustainable inflection point?

Dr Yu: Well, the funding that we would need to finish a phase two trial is somewhere on the order of ten million or so.

JE: Okay. So we're in phase two with ICT107, is there anything that you see that could be extremely problematic coming up with the development of this particular therapy?

Dr Yu: Well, I think we've overcome all the technical hurdles that we can imagine. We've shown that we can do it efficiently. We've shown that we've done it cost effectively, that we've overcome the technical barriers to generate a viable clinical product. So, I don't really see any barriers to developing this therapy. I think the main hurdle that we have to overcome is to show its efficacy, which is exactly what we're doing.

JE: In our pre discussion, we were speaking of the human side of the disease (GBM).

Dr Yu: Yes, to add one more point to humanize this disease. The reason that I was really drawn towards a career in the treatment and research of brain cancer is that, unlike other cancers where the cancer can be separated from yourself, really the brain cancer has the ability to take over all of that which makes us human, and that's from our intellect to our ability to have emotions, to speak and to move. So it's a cancer that not only takes our ability to be conscious of our own cancer, but it also takes away our ability to be conscious of ourselves. Really it's a very debilitating and devastating disorder that really hits at the heart of our humanness, and the patients that have this disease are beyond brave in being able to fight off this disease as it eats away at their humanity, and so whatever impact that we can make as an investigator, as a company, and as fellow human beings to really make an impact in this disease will all be a life well spent.

JE: That's very clear. When you read some of the impacts that the therapies developed so far have had, it's very moving. To even extend someone's life by several months seems to be a heroic feat.

Dr Yu: Yes, and when you're looking at 14 months of survival ahead of you, I tell you, even two or three months makes a big difference. That can be a whole lifetime in somebody's life, and so, I certainly don't downgrade any improvement in survival by any type of medication, but certainly we'd like to make a more significant impact than what's been made in the past.

JE: Well, it seems as though if this is successful, that because of the less amount of toxins being injected into the body - in this case the brain as well - the quality of life once you undergo treatment is going to be much more improved as well.

Dr Yu: Absolutely, and that's really the beauty of this therapy is that it uses your own drug, your own cells. You're just helping yourself fight off your own cancer. You're not adding any poisons or any kinds of toxins to your body. You're just helping the body fight off the cancer, so that's really a big paradigm shift in cancer therapy which I think will be attractive to more physicians and patients in the future.

Disclosure: I have no positions in any stocks mentioned, and no plans to initiate any positions within the next 72 hours.