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The role of small studies in advancing the development of cell therapies

An interview with:

Renier Brentjens, Medical Oncologist, **Memorial Sloan-Kettering Cancer Center**

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Dr. Renier Brentjens is a medical oncologist at Memorial Sloan-Kettering Cancer Center. He has been quoted in several articles in scientific journals and newspapers, such as *Science Translational Medicine,* the *New York Times* and the *Wall Street Journal.*

He is the first author of a study for a treatment which genetically alters a patient's own immune cells to fight various types of acute lymphocytic leukemia (ALL), through a T-cell therapy.

In this interview, we speak more about the role of small studies in advancing the development of cell therapies.

Enjoy!

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About Renier

Dr Brentjens obtained an MD/PhD (microbiology) from SUNY Buffalo, completed residency in medicine at Yale New Haven Hospital, and a medical oncology fellowship at Memorial Sloan Kettering Cancer Center (MSKCC). Currently, Dr Brentjens is an associate member on the faculty at MSKCC and an attending physician on the leukemia service. As a medical oncology fellow during his training at MSKCC, Dr Brentjens initiated the initial pre-clinical studies demonstrating the potential clinical application of autologous T cells genetically modified to target the CD19 antigen through the retroviral gene transfer of artificial T cell receptors termed chimeric antigen receptors (CARs). Following completion of his medical oncology training, Dr Brentjens became the principle investigator of his own laboratory. As a PI, Dr Brentjens successfully translated these studies to the clinical setting treating patients with relapsed $CD19^{+}$ tumors including chronic lymphocytic leukemia (CLL) and B cell acute lymphoblastic leukemia (B-ALL). Ongoing pre-clinical research in the laboratory is focused on the further development of CAR modified T cells designed to overcome the hostile immunosuppressive tumor microenvironment through the generation of “armored CAR T cells” currently being translated to the clinical setting as second generation CAR modified T cell clinical trials. Additionally, work in the Brentjens’ lab has expanded this CAR technology to target additional tumor antigens expressed on other tumors including targeting the MUC-16 antigen expressed on ovarian carcinomas as well as the more ubiquitous WT-1 tumor associated antigen. These latter projects are similarly in the process of translation to the clinical setting.

In your opinion, what is the role and real value of small studies in advancing cell therapies' research and development?

I believe that even though studies such as ours are not as powered as Phase III studies, strong data from planned Phase II trials will hopefully be convincingly good enough to get an FDA approval for this technology. Its value relies on illustrating the potential of the technology. Because of the cost of running later stage trials is high, these studies help spur the interest of industry, investors and other research institutions. These *boutique trials* are also a way to keep the development pipelines robust by trying different development pathways that have not yet been explored.

Is the FDA too stringent when evaluating these experimental approaches, or is it just a matter of adapting these small studies to comply with the current framework for biologics?

Yes and no. Our experience with the FDA has been extremely positive, but we have also been very well behaved. The positive side of it is that the FDA has not complained about our single patient use and reinfusion cases so far. On the negative side, when you're looking at these experimental approaches, these small studies require additional replicated Quality Assurance/Quality Control testing, which end up almost doubling the cost of production. The financial cost to complete regulation requirements, thus bringing therapies to patients faster or at all, limits us.

We always tell potential investors that the actual cost will definitely go down with automation and with the potential of more relaxed standards of safety testing.

Was this recent study experimental to showcase better and faster results when stakeholders in the cell therapy space collaborate? What is missing?

In truth, you can point to 8 pivotal patients that have really motivated and moved this field forward. The first 3 patients were treated at the University of Pennsylvania with Chronic Lymphocytic Leukemia and the other 5 patients were treated here with B-cell Acute Lymphocytic Leukemia.

Since UPENN got together with Novartis, the pharmaceutical industry has gotten a lot more responsive to this type of technology, when previously they would say, “It’s not feasible because it is a different type of model; it’s a cell therapy, it’s not a drug, it’s individualized, it’s too burdensome and it probably doesn’t work anyway”. Now they can’t really say that anymore. The fact is that scientific work has been producing such dramatic and positive responses which spurred greater interest from investors, venture capitalists and the pharmaceutical industry.

What are the next steps for this trial/experimental therapy? What challenges do you foresee?

There are multiple next steps. The first is most reasonable and which we are currently in the process of doing is designing the phase II trials for patients with relapsed B-cell ALL. The two other directions that this field is going are: to make T-cells more potent to overcome the tumor micro-environment and to drive this technology towards discovering different tumors antigens to target this way on other tumor types apart from focusing on CD-19 targeted cells.

There's actually one more important next step in developing this therapy which is to better control the adverse reactions to treatment such as cytokine related fevers and hypotension. It is necessary that we become better at predicting how the patients will react to the therapy and also to have better control over the T-cells in order to avoid side effects such as the suicide factor.

Where will funding to continue the development of the therapy come from? Do you think strong clinical data, even from an experimental study, is a "sign of validation" to big pharma and other investors?

Because of its complexity and cost, our approach must demonstrate clear anti-tumor responses. And that's probably fair because why would you want to get into all this technology and production for a clinical drug that is no better than the next phase I drug coming out from big pharmaceutical companies? We have to report small numbers and those smaller numbers have to be supported by larger ones in phase II trials. Our outcome can't be a slightly longer survival, but a "9 out of 10 patients being cured" type of result. When you use this "C" word, things become easier. And this I believe would serve as a real sign of validation.

How difficult has it been for research institutions and academia to attract capital for regenerative medicine development?

I think this is a matter of experience and expertise. We had to learn all about VC, Intellectual Property and all these terms about licensing and funding, which we don't learn in medical school. Here, we learn as we go along. My suspicion is that institutions, such as UPENN, have better well-oiled machines to deal with venture capitalists and investors. However, technologies such as this force institutions to pay closer attention to capital formation and to try to recruit investors. Once we are able to secure the needed investors, everyone involved with these efforts will do so much better the next time.

Are you aware of other promising experimental studies? If so, which are they and what makes them promising?

I think that immunotherapy as a whole has really been coming into its own. That can be illustrated by the PD1 antibody that has received a lot of attention recently and as we are learning more about how the immune system recognizes and can potentially kill off cancer, I think we have a far wider range of approaches that we can use to target tumors. Just like what happened with chemotherapy, the future of immunotherapy will rely on a combination of different approaches. Everyone working in this field is probably on the right track.

Is there anything you would like to tell researchers and scientists concerning continuous efforts of developing a cure?

I found it striking that when our clinical studies was published in the New York Times, that all at once validated the study for a lot of people; when this actually didn't come out of the blue. Industry took notice of it at that point as well, when they should have access to the same journals where this was reported in the first place. Had we not received the attention through that article, we would still have the scientific translational medicine paper, but the industry and academia would have probably paid less attention.

You would think that publications in a high end journal of striking clinical results would suffice, but they don't. Sometimes it's not the data, but the hype that gives it most legitimacy. Therefore, it's not all about publishing in a renowned journal, but making everyone know about it, especially in this media frenzy era.

We'd love to meet you too…

This is just a preview of what Dr. Brentjens will be talking about at Stem Cells & Regenerative Medicine Congress 2013.

You will also hear insights from the FDA, industry and academia and how each stakeholder will contribute to the advancement of cell therapies.

Hear from pharma, biotechs, academia and government as they discuss:

- How to optimize clinical development of stem cell therapies
- How to overcome strategic and regulatory challenges
- How to negotiate reimbursement
- How to navigate funding and partnership opportunities
- How to implement stem cell platforms into drug discovery

Interested in attending or sponsoring? Contact me, Andre, at +1 646 619 1797 or email me at andre.singer@terrapinn.com for more information .

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