Melanie Cole (Host): Welcome to the podcast series from the specialists at Penn Medicine. I'm Melanie Cole and today, we're exploring glioblastoma multiforme. Joining me is Dr. Donald O'Rourke. He's a John Templeton Jr. MD Professor in Neurosurgery, the Director of the Human Brain Tumor Tissue Bank and the Director of the Glioblastoma Translational Center of Excellence at Penn Medicine. Dr. O'Rourke, thank you so much. This is such an interesting topic. And before we discuss the novel treatments that you're investigating, describe a little bit about why the microenvironment of glioblastoma is so challenging for immunotherapy.

Donald O'Rourke, MD (Guest): Thanks for the opportunity to go through this. This is a fascinating topic, the microenvironment from an intellectual point of view. Unfortunately, it's remarkably challenging from a therapeutic point of view, but in general, it's what we call a suppressive microenvironment. So, there's a lot of immunosuppression within the environment. The tumor is not alone. There's a lot of lymphocytes and other elements within the three-dimensional sphere of the tumor that cause immunosuppressive signals.

So, we've learned quite a bit about that over the last several years. And there are really two components to this immunosuppression. A baseline component—that is, in general, the brain is immunosuppressive. But there's also an adaptive component, that is, when you treat a brain tumor with cell therapy, as we've done, we see a real upregulation of even more immunosuppression, which is what we've called an adaptive wave after CAR T therapy, for example. So, we have really two elements of the immunosuppression to combat here if we're going to get therapeutic efficacy.

I think the reason, from an evolutionary point of view, of why this is there, is that the brain wants to limit inflammation. It's just not good to have inflammation in the brain. It's a highly eloquent organ contained within the skull, within a tight space, and any kind of inflammation or swelling, is going to make patients sick. So I think there's an evolutionary barrier that prevents inflammation, that we have to really figure out how to overcome, in a therapeutic orientation in order to impact this for cell therapy in the brain for brain tumors.

Host: Well, this is so fascinating. And you've described the recurrence of glioblastoma as an inevitable biological reality. That's so interesting to me. Do we know why this is?

Dr. O'Rourke: I mean, it seems like an easy, straight forward question, but it probably is the number one question right now in the field and there is

inevitable recurrence with glioblastoma. That's really a clinical observation. We see it in everyone. I mean, it's a fatal disease and we're trying to push out that time window and the time interval and keep people in remission for as long as we can.

And we've managed to improve in that regard, but inevitably we see recurrence. The biological basis of recurrence is really poorly understood. We're beginning to get clues. So, there are a number of genetic mutations that come up more in the recurrent setting than in the newly diagnosed setting, number one. Number two, we seem to see a shift of the cells to a more stem cell-like state, a less differentiated, more stem-like state in the recurrent glioblastoma setting. And lastly, these cells tend to exhibit what's known as a mesenchymal cell phenotype, which is a much more aggressive phenotype. So there are changes in the tumor cells that occur over time, making recurrent tumors more aggressive, and different and distinct from newly diagnosed tumors.

In addition to that, we recently just had a paper accepted in Cancer Immunology Research, where we show that the immune cells also change from the newly diagnosed setting to the recurrent setting. So, both the actual tumor cell population and its accompanying immune microenvironment are changing over time and evolving from the newly diagnosed type tumor to the recurrent tumor. So, it's really a dynamic flux that's occurring within the organ of the brain tumor, if you want to think of it in three-dimensional terms.

And the positive news is that we're beginning to get some clues into what those specific changes are. And if we do, we're obviously going to be in a better position to target them and alter that behavior.

Host: I can see why this is so complex and challenging for investigators. And you've been investigating gliomas in the context of chimeric antigen receptors T-cells or CAR T-cell therapy, for which Penn Medicine's Carl June is well-known. What were the outcomes in the studies of glioblastoma patients that were treated with CAR T, Dr. O'Rourke, and how have these findings altered the approach to chimeric antigen receptor therapy in the last investigations that you're conducting?

Dr. O'Rourke: I think that's one of the critical issues now that we're dealing with. It's always great to do novel clinical trials, but the most important thing about doing them is learning from them so that each generation or each iteration of the approach gets better. And I think that's what we're doing. We have learned several issues from the first two studies that we did. First of all, glioblastoma and any solid cancer is a lot more complicated, unfortunately, than

the hematologic tumors, where the major impacts have been with CD-19 CAR therapy and the approved product.

In liquid tumors as they're called, the hematologic leukemias, the genetic heterogeneity or the variance of mutations is just not as striking. In glioblastoma and other solid tumors, we have a major problem with heterogeneity, that is region A of the tumor is different from region B is different from region C. So, the whole three-dimensional structure is different and has different mutations in different spatial regions. So, one major finding in our first two studies was that the heterogeneity is maintained even after therapy.

And then if you reduce the amount of one mutated receptor, you still have other mutations to deal with. So that's number one. Number two, is as I said earlier, that the micro environment will adapt to CAR therapy—doesn't like it. After an initial wave of successful tumor killing, the brain really uses its intrinsic mechanisms to shut down that inflammation. Another factor that we've learned is that the CAR T-cells don't persist for longer than a month. And we have to deal with that problem. And lastly, we've learned that the recurrent patients, which is an interesting and somewhat counterintuitive finding, the recurrent patients seem to be more suited to CAR T therapy than the newly diagnosed patients.

And we're trying to learn why that is, but that serves as the basis for our next study, which we hope to have FDA approval by July 1st. And it perhaps could be June 1st, where we're targeting the recurrent patients with a CAR T approach, which has two surface binders rather than one. And these are like little claws on the surface of T-cells, which can bind to more than one target.

So we've made an improvement in the therapy and we've targeted a particular population, the recurrent patients, which we think are more well suited to this therapy. So we are hopeful for this next study, which will begin within the next couple of months.

Host: Absolutely fascinating. And Dr. O'Rourke, you're the Director of both the Abramson Cancer Center's GBM TCE, as well as the Human Brain Tumor Tissue Bank, a Penn Children's Hospital of Pennsylvania joint initiative. How have these entities advanced the research paradigm for glioblastoma?

Dr. O'Rourke: I think that the tissue bank has been critical as a core effort. It really supports all of the work we do and the work of a lot of our collaborators, both at Penn and across the country and even overseas. And why is it important? Well, we're studying human tissue. There's been sort of a paradigm

shift over the last, I would say 10, 15 years, where although mouse models for disease are very important, really the human tissue has become invaluable, in studying the disease.

So using the tissue bank as a central core of research has allowed us to develop better human models of glioblastoma. So, I believe a model with higher fidelity to the human disease. The access to the human tissue allows us to do correlative studies in our clinical trials, they refer to as window of opportunity trials, where we're actually looking at the human tissue earlier, and we're adapting our design of future efforts based on the study of the tissue. So, the human tissue allows us really a window into what's happening, that allows us to shift our focus into what we think is a greater and better representation of the disease.

Also, the tumor bank allows us new opportunities for drug discovery and target discovery, and a more accurate delineation of the molecular landscape of the tumor. So we just have a better, more accurate representation of the disease. So the tissue bank really has been central and the clinical engine that we have here really does drive the research engine in that way, because it allows us access to the tissue, which can then be studied by a variety of groups.

You have to keep in mind in the TCE center that we have here at Penn, we have over 10 departments represented. And we have 23 principal investigators and that number is growing. And many of these investigators were brought together just by the TCE mechanism. They had never studied glioblastoma before.

For example, people in Carl June's group and the Center of Cellular Immunotherapy of which I'm a part, many of the high level investigators have been studying immunology and immunobiology, but and its application to glioblastoma, but this mechanism of the TCE has allowed us to recruit in some of that expertise and rather than work in hematologic tumors or other tumors, they're now helping us with glioblastoma.

So, the sort of the intellectual sharing of ideas through this mechanism, I think is another major feature of how we've been able to accelerate the work.

Host: This is so interesting, Dr. O'Rourke, and I hope that you'll join us again to tell us as these studies continue and update other providers on the interesting research that you're doing at Penn Medicine. If a referring provider wants to learn more about clinical trials at Penn, what steps should they take? And give us your final thoughts, what you want the lasting message to be from this podcast today.

Dr. O'Rourke: I think in terms of clinical trials, they should just contact me directly. I will be able to triage any query to any member of our team. And I can give you my number or they can contact me through email, but I enjoy getting contacted for these studies because I think this is the only way we're going to be able to solve this problem.

The lasting message is I'm an optimistic person by nature, and I've been working in this field for 25 years, at least, on the research side, longer than that. And I believe that over the last few years there's been a gravitation towards immunotherapy and immuno-oncology approaches.

And I think that people in the field that are doing this, like our group feel hopeful, feel like we're working in an area that will allow us to make a significant impact. We have not figured out the best combination yet, but with this approach and the modification of cell therapy and the various combinations we can use, I think we're going to get there. And this is the first time I've felt this way, during the course of my career, which has been essentially dedicated to gliomas and in particular glioblastoma. So, the message here from Penn and from our group is one of hope. And then I think we will figure this out. I don't know the timeline, but I'm confident that we are going to make an impact, with this therapeutic approach.

Host: What an exciting time to be in your field, and you really are making such advancements in medicine. Thank you so much, Dr. O'Rourke, for joining us today and sharing your incredible expertise. To refer your patient to Dr. O'Rourke at Penn Medicine, please call our 24/7 provider only line at 877-937-7366.

Or you can submit your referral via our secure online referral form by visiting our website at pennmedicine.org/referyourpatient. That concludes this episode from the specialists at Penn Medicine. For updates on the latest medical advancements, breakthroughs and research, please follow us on your social channels. I'm Melanie Cole.