Transcript of Cerebrum Podcast—Fire in the Smoke: Battling Brain Tumors

Guest: Michael Lim, M.D., is director of the Brain Tumor Immunotherapy Program and a professor of neurosurgery, oncology, otolaryngology, and radiation oncology at Johns Hopkins. Lim's research laboratory is focused on understanding the mechanisms of immune evasion by primary brain tumors. Lim obtained his M.D. from the Johns Hopkins University School of Medicine and completed his residency in neurosurgery at Stanford University Hospital. In addition to running a laboratory, he also directs the immunotherapy clinical trials program at Johns Hopkins. He currently serves as the principal investigator of several large brain tumor immunotherapy clinical trials based on findings from his laboratory.

Host: Bill Glovin serves as editor of *Cerebrum* and the *Cerebrum Anthology: Emerging Issues in Brain Science*. He is also executive editor of the Dana Press and *Brain in the News*. Prior to joining the Dana Foundation, Mr. Glovin was senior editor of *Rutgers Magazine* and editor of *Rutgers Focus*. He has served as managing editor of *New Jersey Success*, editor of *New Jersey Business* magazine, and as a staff writer at *The Record* newspaper in Hackensack, NJ. Mr. Glovin has won 20 writing awards from the Society of Professional Journalists of New Jersey and the Council for Advancement and Support of Education. He has a B.A. in Journalism from George Washington University.

Bill Glovin: Senator John McCain has been diagnosed with glioblastoma. A fast growing, aggressive type of central nervous system brain tumor that killed Senator Edward Kennedy and Beau Biden, the son of former Vice President Joe Biden.

Welcome to the *Cerebrum* podcast. Hi, I'm *Cerebrum* editor Bill Glovin and on the phone with us today is Dr. Michael Lim, director of the Brain Tumor Immunotherapy Program at Johns Hopkins University School of Medicine in Baltimore. He is also a professor of neurosurgery and a bunch of other stuff too numerous to mention.

Dr. Lim is kind enough to co-write our latest *Cerebrum* article, "Fire in the Smoke: Battling Brain Tumors", which you can read at dana.org. The article focuses mainly on glioblastoma which is the most common grade four brain cancer.

Dr. Lim let's start with you can explain immunotherapy, what that means?

Michael Lim: Immunotherapy is a concept where we try to use one's own immune system to kill cancer cells. Our body's immune system is very potent to fighting off infections. It turns out that our body naturally fights off cancer cells throughout our lifetime. For example, we've learned this from watching people who developed severe immunosuppression with diseases such as HIV. When you develop severe immunosuppression you actually are more susceptible to cancer. The whole concept with immunotherapy is that we are trying to program the immune system to target and to kill the cancer cells.

Bill Glovin: Viruses have showed some success in killing cancer cells in glioblastoma. Can you tell us about what you know or do you believe that has a future in trying to concur this terrible problem?

Michael Lim: I think the concept of using viruses to kill cancer is very exciting. What I think has been going on is that in the past we've been trying to use viruses to directly kill the cancer cells. We hope that the viruses would be just directly killing the cancer cells. When we had done that approach we had gotten some killing of the cancers, but the results were disappointing. I think today with some of the viral therapy, the concept is to try to, in essence, use the viruses as kindling to mount a systemic immune response. The thought is that as viruses kill the cancer cells they release antigens and they induce a very vigorous immune response so that the body then starts to know what the cancer cells look like and hopefully, effectively wipe out the cancer.

Bill Glovin: Have there been any clinical trials with this type of strategy?

Michael Lim: Sure, there've been numerous clinical trials with the strategy. The results are still early, but they have been promising. There have been viruses such as what they call the Tocagen virus and they presented their data a few months ago showing some patients doing very well with this therapy. There's been studies, places in MD Anderson and Brigham who have also used viruses and again showed that they were able to illicit an immune response. I think recently there was a ... I'm sure you've seen the publication ... with using the polio virus where they were thinking that they were able to start an immune response.

Bill Glovin: Have we made much progress in the last five years?

Michael Lim: Are you saying much progress in the past five years with immunotherapy or with viruses?

Bill Glovin: Well with just fighting glioblastoma in general.

Michael Lim: Sure, I think we've made some progress. Progress isn't always defined by just improved survival. I think that progress is also defined by us learning a lot more about glioblastoma. I think each year out we're learning more and more about the glioblastomas. We understand the genetics behind glioblastoma. We understand better the way that glioblastomas spread and we better understand that they glioblastomas evade the immune system. I think as we learn more about these cancers our clinical trials today are a lot more sophisticated and more rationally based.

Bill Glovin: Where on the brain is glioblastoma or where is it most likely to occur? Does that make a difference in treatment?

Michael Lim: Glioblastomas can appear anywhere in the brain and even in the spinal cord. Most people say it's both common in what they call the supratentorial space,

which is above the cerebellum, but that's also my problem with statistics, they make type of probably in statistics in the stuff that has the biggest volume of brain matter.

In terms of prognosis in general, if you have a tumor that arises in what they call a non-eloquent area, which is a place that, for example, does not contain speech, or arm and leg movement, or specific sensory functions. You can often be more aggressive in removing those tumors and we know that if you're more aggressive in removing these tumors people do better. If your tumor arises in more eloquent tissue you're less apt to get a gross total resection. People sometimes do poorly, a person who has a tumor in the eloquent area.

Bill Glovin: In the article you use an example of a fictional character named Harry who learns he has a glioblastoma, but survives beyond the median mortality rate of 20 months. Do we know why someone like him survives while so many others don't?

Michael Lim: Well I guess at the end of the day we still don't know. We think that there is an association with infections, with infections of people living a longer period of time.

Bill Glovin: In the article you talk about glia and infection, how do both of these things relate to glioblastoma?

Michael Lim: I think in the article I think we're focused on the fact that this patient had an infection. Many of us who have taken care of patients with brain tumors have seen people who are long-term survivors after developing a brain infection. We think that these infections have someone turned on the immune system to kill the cancer cells. These infections are thought to just ... We think it somehow unlocks or unleashes the immune system. This concept of new, historically people have used, for example, Dr. Coley started introducing bacteria into patients with cancer almost a century ago and had reports of people being cured.

Bill Glovin: In the article you discuss a growth factor receptor that you call a promising target for immunotherapy. It's called EGFR I guess VIII in Roman numerals. Can you explain what that is?

Michael Kim: Sure. That's EGFRvIII target which is basically a mutated form of something called the epidermal growth factor receptor. This mutated protein appears to be uniquely expressed cancer cells, but not in the body. If you have a target that seems to be uniquely expressed on a cancer cell we are able to develop therapies that specifically target anything that expresses that unique antigen. There have been vaccines. They have developed what they CAR T cells against this peptide in hopes of generating a very targeted therapy against this, a targeted immune therapy. This is an area under intense investigation because

it's not just the epidermal growth factor variant III or the EGFRvIII, but many people are looking for unique antigens, tumor expressed antigens right now.

Bill Glovin: You mentioned that some patients have had remarkable response to something called PD-1 blockade. Is that our best hope going forward?

Michael Lim: Well I think that PD-1 has is part of class of checkpoint inhibitors that I think is a resolution in terms of cancer care for patients with tumors in general. I think that with a PD-1 it's made a huge difference in patients with, for example, melanoma, kidney cell cancer, and lung cancer. The trials so far have been negative in glioblastoma, but we are looking actively at trying to combine PD-1 with other agents and other modalities at this point in time. Many people are still trying to look for ways to get the PD-1 to work in glioblastoma.

Bill Glovin: You write that you and others are attacking immunosuppression in glioblastoma on multiple fronts. You mentioned immunotherapy obviously, viruses, are there some others that we haven't touched on?

Michael Lim: I think that's a great point. I think that what we've understood and what we've learned is that immune system or the ways that the glioblastoma suppresses an immune response is different then, for example, what lung cancer, or melanoma, or kidney cancer does. We've learned that the brain tumor induced suppression in individuals not just only in the brain, but also systemically. Because of that, we have better understanding of this as a suppression and have come to realize that it's not just recruiting the T cells to kill cancer cells, but we made need to also recruit another class of cells called myeloid cells which are things such as macrophages to try to fight cancer. With that, people are looking at other therapies to try to turn on myeloid cells. They're trying things like dendritic excel vaccines and they're trying agents that directly target myeloid cells. That's one area that's being very actively studied in glioblastoma in addition to the other studies. There are a lot of other great approaches, such as CAR T cells that are currently being employed. I think that where we are today is really amazing and I think where we're going to be in the next 5 to 10 years with the technologies that we have available to us will be even I think more potent.

Bill Glovin: In some other types of cancer, most obviously being lung cancer, we all know that nicotine and cigarette smoking is a cause. Is there anything that someone could do to help prevent glioblastoma or brain cancer in general? The second part of that would be are there certain symptoms that someone should be aware of, perhaps maybe early detection would be advantageous?

Michael Lim: Those are great question. Glioblastoma is still a very rare tumor. It affects everyone in all walks of life in terms of education, social class, smokers, nonsmokers. I think there really isn't a known carcinogen that we can directly point to that says this will cause glioblastoma. Besides some of the familial syndromes or some genetic mutations that have predisposed somebody to glioblastoma we really don't know and can't predict.

In terms of symptoms, most people they can be very nonspecific. Some people can present with headaches, but oftentimes, they will present with a very focal neurologic deficit when they present with a brain tumor. They can present with speech problems, vision problems. They could have a seizure. They could have weakness. Almost any of those symptoms would then immediately result in the patient getting imaging and that's how the diagnosis is at least made, or at least started. Ultimately, the diagnosis is made with surgery of course, but it's usually a symptom that makes people present for a workup.

In terms of screening it's really hard to do as I alluded to earlier because only 13,000 people have glioblastoma per year in the United States. Getting an MRI on everybody as a baseline may not be the best screening method.

Bill Glovin: So there are many different types of brain cancers. Obviously I think there's at least 100 and glioblastoma is rare. Are brain cancers rare in general?

Michael Lim: Yes, in general, brain cancers are rare. I think the latest statistics I've seen, I think worldwide there's still less than a million. To answer your question, yes, it's still pretty rare.

Bill Glovin: Finally, you say we need a "call to action" for a more intense focus. Are you alluding to funding or something else? What do you mean by that?

Michael Lim: I'm just reinforcing the fact that I think that glioblastoma is a very tough disease, it's a very aggressive disease. I think it's one of the most aggressive tumors that we know of. Because of that, it's been a tough fight in the sense that probably only a handful of drugs and devices have been approved by the FDA for glioblastoma over the past 30-40 years. It's just a thing that we still have to keep chipping away at this, keep chipping away at this is really what I'm getting at.

Bill Glovin: Is there enough funding or enough people working on this around the country? Are there a lot more people working on this than let's say there were 10 years ago?

Michael Lim: I do think that there are more people working on this. I think that funding is always an issue in terms of resources. I think the more resources we have the better. I think we can have better bandwidth to better understand the tumors and run bigger trials, and come up with novel therapy. I certainly think that it's imperative to get more funding and more resources to fight this.

Bill Glovin: I think it's important to get the word out as well, I would think. That's one of the reasons someone as busy as you decided to co-author the article and do this podcast when you have very limited time. The more people who are aware, the better.

Michael Lim: I absolutely agree. I think the more people we can recruit to help fight this disease in terms of scientists and advocates, the better.

Bill Glovin: I think that's a good place to end. Thanks again to Dr. Michael Lim, one of the country's foremost experts on brain cancer.

Just as a short aside, Dr. Lim was telling me that when he was an undergraduate at the University of New Hampshire he studied starfish and clams in trying to understand cell pathways, leukemia, and cell division. As co-writing on this *Cerebrum* article, Dr. Chris Jackson, a chief resident, majored in English. Now they are both in the glioblastoma world.

Anyway, you can find the article at dana.org. As always, thanks for listening.

I'm *Cerebrum* Editor Bill Glovin at the Dana Foundation. Have a great day.