Welcome to a series of netcasts brought to you by Yale University.Thank you for joining us for this edition of Yale Cancer Answers where we provide you with up-to-date information on cancer care and research. Our host, Dr. Anees Chagpar is Associate Professor of Surgical Oncology. She is interviews some of the nations leading oncologists and cancer specialists who are on the forefront of the battle to fight cancer. If you are interested in past editions of Yale Cancer Answers, all of the shows are posted on the Yale Cancer Center Website at yalecancercenter.org. If you'd like to join the conversation, you can contact the doctors directly, the address is canceranswers@yale.edu. Here is Dr. Chagpar.Chagpar Welcome back to another episode of Yale Cancer Answers. This is Dr. Anees Chagpar and I am joined today by my guest, Dr. David Hafler. Dr. Hafler is the William S. and Lois Stiles Edgerly Professor of Neurology, Professor of Immunobiology, and a Neurologist-in-Chief at Yale New Haven Hospital. He is here with me to discuss the immunology behind glioblastoma. Thank you so much for joining me.Hafler Thank you for having me.Chagpar Maybe we should start off by talking a little bit of glioblastomas. What exactly are they?Hafler They are an interesting type of tumor unlike other tumors which often spread through the body, glioblastomas begin in the brain, in the central nervous system and generally stay there. They are very infiltrative. People ask why do not you just removed them and unlike metastatic tumors where you can just sometimes remove them, take them out, it is impossible to remove a glioblastoma because it just infiltrates into the brain.Chagpar How common are these?Hafler It is one of the most common tumors of the central nervous system. My father-in-law passed away from a glioblastoma.Chagpar I am so sorry.Hafler At the age of 63 and so it is something which has really struck our family and I have had a number of very close friends who have died from this tumor. So it is not an uncommon tumor at all.Chagpar And so because we cannot surgically remove it, how exactly do we treat this?2:40 into mp3 filehttps://ysm-websites-live-prod.azureedge.net/cancer/ybmc-1735_hafler_081116_285066_5_v1.mp3p3Hafler I am not a neuro-oncologist, I am a neuro-immunologist, but we generally use radiation therapy and drugs which inhibit the growth of the tumor, but I sort of left the field of neurology for about 25 years as I pursued my interest in immunology and immunology of the nervous system, then I came back to the field of clinical neurology when I became chair of neurology here at Yale and I was surprised at the advances in stroke, we can now remove the clots from the brain in realtime and dissolve the clots. In my own field of multiple sclerosis, we have had dramatic advances in understanding the disease and treating the disease very effectively. When I looked at brain tumors, the glioblastomas, I found that we really have not progressed much since I was a resident at Memorial Sloan-Kettering back in the late 70s and early 80s. We really have not changed the prognosis for brain tumors very much. It was a bit sad to see.Chagpar What have been the new advances, how did you marry your interest in immunology and the immune system, actually the nervous system, into treating brain cancers in a much more advanced way?Hafler Let me give a disclosure, in that, as an immunologist, who

studies the nervous system and autoimmunity, we felt that the immune system was important for autoimmune diseases and that turns out to be correct, which wasn't terribly surprising, but the big surprise, and I didn't see this, I think most of us didn't see this, was how important the immune system would be for dealing with cancer. When you have a viral infection or a cell becomes mutated, the immune system which recognizes that something has gone awry with itself or with a foreign infection and eliminates that cell that is infected or gets rid of that cancer cell and we just hadn't appreciated as a discipline how important that was and I will give credit to Jim Allison who is a very dear friend, who really championed the idea of immunotherapy for cancer, first for his brother who died from prostate cancer and then, Jim himself who is very public about this who developed prostate cancer and was instrumental in developing immune therapy as a treatment. The 5-year survival rate, if you had melanoma that spread throughout your body, used to be at 1%, now with these checkpoint inhibitors, the survival rate is well over 50%, maybe even higher. So the question is how are these drugs really working and it turns out that there is a cat and mouse game between the immune system and the tumor. It is in fact the same cat and mouse game that goes on with viruses and what the viruses want to do and what the cancers want to do is to evade the immune system and the way they do this, be it viruses or cancer, is to express the decoy molecules that turn off the immune system. So that is when you look at the response of immune cells to an infection or to vaccination, you want a response where the immune cells, you want them to expand to have memory and then you want them to turn off, they do not turn off and then you have unrestricted growth of immune cells and that is another form of cancer. So the way the immune system does this is that it expresses negative inhibitory receptors on the cell and when they are expressed the T cells have been signaled to 7:12 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/ybmc-1735_hafler_081116_285066_5_v1.mp3turn off and that is how the immune system works. You have signals which turn on the T cells and then you have signals which turn them off, the co-inhibitory signals. What the cancer does is very clever. It keeps mutating until it expresses an inhibitory receptor. So when the T cells, immune cells go to the tumor, they are expressing these inhibitory decoys which tell the immune system stop, turn off; when in fact, you want the immune system to kill the tumor cells and that is this cat and mouse game and what has happened in the immunotherapy is first the understanding of what these important molecules might be such as C1284 and PD1 which are the two now classic negative inhibitory receptors on T cells and what we now do is we block them, we take these proteins engineered in the laboratory called monoclonal antibodies, we inject them into the body and they bind to the T-cells, a part of T-cells involved in turning off immune responses and we fool the cancers and hence now the T-cells can kill the cancers and that is really what immune therapy is about.Chagpar So does that work in all cancers, it seems to me that some cancers respond really well to immunotherapies and other ones might not, is that true?Hafler Absolutely true and we talked about these 2 checkpoint inhibitors, C12A4 which was discovered many years

ago and PD1, but there are many other checkpoint inhibitors. As someone who studies autoimmunity, I am very interested in a molecule called TIGIT, another one called Tim3 and in fact, my dear colleague and friend, who is a colleague from Boston, discovered Tim3 and we have been partnering in understanding its function in human system and human cancers over the past few years. Every organ has its own set of inhibitory signals and the key I think is to understand what they are for in each cancer, each cancer will evade the immune system in a different way, so we are at just at very early stages with this checkpoint inhibitors. For example, a recent experiment we did was to compare glioblastomas to multiple sclerosis and ask, well in glioblastoma it is the T-cells, immune cells, going to the brain and they cannot kill the tumor whereas the multiple sclerosis T-cells go to the brain and they destroy the tumor, so it is the opposite, so we asked what is different between multiple sclerosis and glioblastomas in terms of the inhibitory receptors and we found that PD1 was not all that different, it was expressed in them as and it was expressing in glioblastoma, but this TIGIT was expressed on all of the immune cells infiltrating the glioblastoma, infiltrating the brain tumor, yet it was virtually absent on the T-cells going into the brain with MS. We are soon hopefully going to start a phase I trial with TIGIT in glioblastoma and we are studying it very deeply in MS. So I think we have to identify which tumors are evading the immune systems as a means of survival because maybe some tumors use other means of survival immunotherapy won't work point one and point two, which mechanism, which molecules each tumor uses to actually evade 11:18 into mp3 filehttps://ysm-websites-live-prod.azureedge.net/cancer/ybmc-1735_hafler_081116_285066_5_v1.mp3detection by the immune system and different tumors will be different. So we have these dramatic results in melanoma, a dramatic results in certain types of lung cancers and what about brain tumors, we do not know yet. We did a trial with anti-PD1 and anti-C12a4, a phase I trial here at Yale for glioblastomas and all I can say is I was intrigued enough with the results to move to a phase 3 clinical trial which has just begun last week where we are using anti-PD1 in a phase 3 trials in patients who are previously untreated with glioblastoma.Chagpar But if the PD1 is the same in glioblastoma as it is in MS, do we really think that there is going to be a positive outcome of that trial?Hafler Well, it is too early to say. But I think it is just the first effort and I think we clearly need to define other co-stimulatory molecules and TIGIT, Tim2, PD1, a host of coinhibitory receptors that have recently been identified as human immunologist which have potentials for being used and treating these diseases. So, we are at the very beginning of immunotherapy and the discovery of these molecules, and this is one of the strongest human immunobiology programs in the country if not the strongest and so we have this wonderful interphase between basic science discovery and very strong clinicians who are leading the clinical trials in the United States over these different immunotherapies.Chagpar Is it possible, when you biopsy a tumor, to see what are the immune checkpoints that are relevant in that tumor, so that you can say for this tumor, we should use an anti-PDI, but for this one, maybe anti-TIGIT.Hafler One would think so, but

in the recent clinical trial with antiPD1 where the PD1 ligand was measured in lung tumors it was not terribly predictive, so there may be other factors involved, but absolutely finding ways of using precision medicine to understand what mechanism the tumor is using for evasion, I think will be critical. For example, in an experiment that we are just beginning in my laboratory is to look at the T-cells, we have these new technologies where we can interrogate single T-cells at the tumor and out of the blood. We just recently published a paper in JCI Insight where we identified certain molecules expressed on the surface of cells that involve an exhaustion which we normally do not see but we do see them in the brain tumor and the notion is that the cells that we see in the blood which have these levels of exhaustion which we normally do not see, may be your T-cells are in the brain and we may have a liquid biopsy where we can identify these cells in the blood and have a sense of the functionality and mechanisms that the immune cells are using to evade the 15:22 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/ybmc-1735_hafler_081116_285066_5_v1.mp3tumor, so we just started that experiment, we are getting brain tissue and blood from the same patient and we are interrogating those tissues to see if indeed that is the case.Chagpar That is very cool. I guess the other question is that the brain is one of the specialized organs that has a way of keeping things out of it with the blood-brain barrier and that has always been an issue in terms of chemotherapy, for example. Are we thinking that the same thing is going to hold with immunotherapy or is that not the case?Hafler I do not think it is the case and just to take a step back, what is a blood-brain barrier, nature, in designing who we are as mammals and very careful about what it allows to get into the brain for obvious reasons, developed the blood-brain barrier, nature very carefully selects which molecules can cross into the brain, into the central nervous system. If you take a blue dye and inject it into the blood, skin turns blue, liver turns blue, everything turns blue except for the brain. The brain basically will not change color because the blue dye does not cross the blood-brain barrier, well that is the same for proteins. It turns out that cells go right in to the brain and it is the process where the cells just go through the blood-brain barrier and this is important for immune surveillance. If it did not happen when you had a viral infection in the brain, there would be no way of the immune system detecting it. In fact, the multiple sclerosis one of the main treatments we used a drug a called anti-VLA-4 antibody called natalizumab or Tysabri which blocks the T-cell traffic from the blood the brain but a side effect of that treatment in patients who have a virus called the JC virus, about 200 patients can develop growth of this virus in the brain because the immune system cannot do its immune surveillance and look for this virus and those patients may also have tumors that could potentially grow because again, the immune surveillance is absolutely critical. Our guess is that the antibiotics bind themselves in the periphery, then when they go in, they can do their functions. I am not sure the antibody needs get in, however, with chemotherapy, is indeed, it is a major issue.Chagpar So, maybe immunotherapy is particularly well suited to glioblastoma?Hafler Well, we got to do the experiment.Chagpar Yeah.Hafler

And we will see what the phase 3 trial shows, but again it is just the beginning and we are very excited about moving towards phase 1 clinical trials with different checkpoint inhibitors which we hopefully can do very soon.18:12 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/ybmc-1735_hafler_081116_285066_5_v1.mp3Chagpar Well that is just so exciting and it was so wonderful having you as my guest today on Yale Cancer Answers. This was a wonderful discussion about your research in glioblastomas and the promising potential of immunotherapy in this area. This is Dr. Anees Chagpar wishing everyone a happy and healthy tomorrow.This has been another edition of Yale Cancer Answers. We hope that you have learned something new and meaningful. If you have questions, go to YaleCancerCenter.org for more information about cancer and the resources available to you. We hope that you will join us again for another discussion on the progress being made here and around the world in the fight against cancer.