Doctor Tran, maybe we can start off by you telling us a little bit about yourself and what you do.

Absolutely, I am a translational researcher at Yale Cancer Center. I did my residency and fellowship in heme/onc here and I’m happy to be involved in the Melanoma team treating patients with advanced malignancies and skin cancers.

I do a lot of translational research, which means that I am working at the bench but also take what we find out at the bench straight to the clinic.
so that we can effect real change in how we treat this disease. So tell us a little bit more about your research. I mean you work in the Melanoma team, how exactly does the translational research part fit in and what specifically are you looking at? I've been spending the past couple of years really looking at innate immunity in the brain and how we can really capitalize on stimulating those cells and in conjunction with our currently available therapies to try to improve disease outcomes for our patients. So just to give you an example. One of the projects that I'm highly involved with is trying to target the blood brain barrier. The blood brain barrier has been a really understudied but very clinically relevant and highly impactful way for cancers to really gain an advantage and to metastasize and grow in the brain and so really trying to focus on the blood brain barrier and try to get these drugs into the brain has been an area of ongoing interest.
So one of our currently active projects is looking at targeting Veg F, which stands for vascular endothelial growth factor. It’s a subtle kind that really stimulates blood vessel development, and sometimes these tumors and the immune cells surrounding them will secrete this cytokine to help stimulate tumor growth. How can we target this protein as well as maybe target the endothelial cells themselves to help decrease tumor growth in the brain.

And so we have a couple of interesting targets, one of which is currently an active clinical trial within our Melanoma group looking at Melanoma and lung cancer patients who have brain metastases. And so this clinical trial is a phase two study looking at the combination of bevacizumab, which is our anti Veg F drug, and the checkpoint inhibitor pembrolizumab, which targets another pathway to help stimulate our own bodies' immune system to help fight cancer.
second clinical trial of pembrolizumab or immune stimulating agent in combination with Lenvatinib, which instead of targeting the cytokine itself, targets the veg F receptors on the endothelial cells and hopefully we can get even a more dramatic immune response. So today I want to take a step back here and just kind of talk a little bit about the blood brain barrier itself. What exactly is it and how does it affect cancer cells? As we’re always learning more about the blood brain barrier, it’s not as simple as we first thought where it’s just comprised of the blood vessel and death elial cells, the blood brain barrier is actually much more complicated. It’s composed of not only the endothermal cells, but all these supportive cells adjacent to them, and so this includes parasites which control vasoconstriction or the ability of these blood vessels to contract and dilate. It also includes all the supportive astrocytes which have their little processes in and feet.
0:04:25.958 –> 0:04:27.746 on the endothelial cells.
0:04:27.75 –> 0:04:29.64 It includes interneurons,
0:04:29.64 –> 0:04:31.53 it includes microglia,
0:04:31.53 –> 0:04:32.592 microglia are considered,
0:04:32.592 –> 0:04:34.716 sort of the innate immune cells
0:04:34.716 –> 0:04:36.497 that reside within the brain.
0:04:37.27 –> 0:04:39.23 How come the cancer cells can get
0:04:39.23 –> 0:04:41.3 into the brain but the drugs can’t?
0:04:41.57 –> 0:04:44.456 You know the blood brain barrier
0:04:44.456 –> 0:04:47.042 in normal states without any
0:04:47.042 –> 0:04:49.855 pressure related to metastasis is
0:04:49.855 –> 0:04:52.43 a very intact endothelial layer,
0:04:52.43 –> 0:04:55.016 meaning that there are these specific
0:04:55.016 –> 0:04:56.74 interconnections within or
0:04:56.804 –> 0:04:58.552 between the endothelial cells
0:04:58.552 –> 0:05:00.737 that prevent any other molecules,
0:05:00.74 –> 0:05:04.732 such as drugs such as immune cells from
0:05:04.732 –> 0:05:07.639 infiltrating or getting beyond them.
0:05:07.64 –> 0:05:09.29 They typically are described
0:05:09.29 –> 0:05:10.94 as the soldiers.
0:05:10.94 –> 0:05:12.745 Remember the Roman soldiers
0:05:12.745 –> 0:05:15.308 if you ever watch one of those
0:05:15.308 –> 0:05:17.645 movies with all their Shields up
0:05:17.645 –> 0:05:20.107 so they form an impenetrable
0:05:20.107 –> 0:05:22.453 barrier to help prevent things
0:05:22.453 –> 0:05:24.889 from getting past that layer.
0:05:24.89 –> 0:05:26.198 And that’s what’s really
0:05:26.198 –> 0:05:27.833 caused a lot of issues.
0:05:27.84 –> 0:05:28.774 For example,
0:05:28.774 –> 0:05:31.109 in breast cancer therapy where
0:05:31.109 –> 0:05:32.51 chemotherapies that traditionally
work in breast cancers can’t penetrate into the brain, and so we’re seeing a lot more of late relapses in the brain because these cancer effective therapies are not able to penetrate and circulate there. So why can the cancer cells get through those Roman Shields? I mean, it sounds like that should really be, as you say, an impenetrable barrier. And yet, cancer cells can seem to sneak their way through. Cancer cells when they metastasize, they go through a very complex process, basically giving them the ability to invade through normal tissue and during that process they adopt a different shape, a different morphology. They become migratory. They get enter the bloodstream, and when they circulate, they essentially get into the brain. And either lodge at Branch points within those blood vessels in the brain and cancer cells have all sorts of different proteins and things that they up regulate or express to help them survive and proliferate during this process, and a few of those proteins include things like matrix metalloproteases.
where they can break apart different elements of the tumor stroma, or the tumor microenvironment, and this allows them essentially to break apart those tight junctions within this endothelial cells. Wedge themselves in between these cells and eventually be able to set up shop and grow there.

So I guess just to press the point further, my question is if the tumor cells can kind of finagle their way through this barrier, either they make holes in the barrier, they kind of distort and try to get through, then are those changes to the blood brain barrier that allow the cancer cells to get through, those don’t seem to be permanent enough to allow our drugs to get through. Or is there another thing at play? Are the drugs too large? Is it that they can’t squish through the little spaces? Or is this more than simply a mechanical problem? I think the answer is actually a little complicated to address and we don’t really at this point fully understand how our current effective therapies really penetrate to get into the brain.
So one hypothesis is that actually when we give immune therapy these immune stimulating drugs that help educate our own immune system to fight the cancer, we're doing that below the neck so peripherally, so these educated immune cells can then subsequently migrate through the circulation into the brain. They have a much easier ability to transmigrate through the endothelial layer and get into the tumor to where they can have antitumor effect, the other component of this is maybe the defects that lead to forming a tumor in the brain caused vessel leakiness and vessel damage, and such that you have this chronic adima or loss of vessel integrity and that therefore allows these large monoclonal antibodies which are essentially our immune checkpoint drugs, to actually access into the tumor because these vessels are already so leaky. That's really great news on the immunotherapy front, knowing that these therapies
can get into the brain, I guess the next question is, well, how come chemotherapy drugs can’t do that? I mean, we give them peripherally into a vein below the neck, right into a hand, they get into a blood vessel. How come they can’t follow the same kinds of path? Yeah, so our blood brain barrier through our development has upregulated a lot of drug efflux pumps and so these endothelial cells that constitute the blood brain barrier they have these specialized pumps that whenever drug does penetrate into the cells, they pump them right back out into the circulation. And so that’s what limits the effectiveness of standard chemotherapy and it’s really not a very good treatment option for patients with brain metastases. OK, I get all of that. So now let’s talk a little bit more about this. Veg F that you were mentioning just a moment ago, this vascular endothelial growth factor is that something that is present on particular
cancer cells that these therapies now are attacking?

Veg F is upregulated in a lot of different cell types, and one of those being Melanoma, where we have found that circulating veg F is actually a poor prognostic marker in patients, so they say essentially they have worse outcomes when they have elevated circulating levels of this protein.

It’s not necessarily on the tumor cells, or is it on both? It’s very ubiquitously expressed. It can be expressed by the tumor cells themselves and have a local effect in that increased regulation or increased expression of VEGF can also appear as circulating levels.

Tumor cells, in addition to immune cells, can also increase veg F levels too. So, for example, a specific type of immune cell which essentially gobble up a lot of tumor cells or cell debris. One of those is macrophages. So macrophages are able to secrete high levels of veg F as well.

And so that makes me think that these anti VEGF therapies that you’re
looking at in clinical trials,
they might be something not specific for particular patients that they might be more ubiquitously used rather than some of the therapies that come out where you really need to check the tumor cells to make sure that particular protein or that particular receptor is on the tumor cell. It sounds like this is something that could be used for most patients. Is that right?
That’s correct. So actually, even recently within the past couple weeks we’ve had another FDA approval for the combination of pembrolizumab and lenvatinib, being one of our veg F receptor targeting drugs in addition to other receptors that it does block as well. So that was actually just in advanced renal cell carcinoma.
The combination is already been also approved in advanced endometrial cancer, and then actually Merck, the company that produces pembrolizumab is currently investigating this combination in the first line and second line setting for Melanoma patients as well.
Wow, all really interesting developments which we will need to investigate more when we take a brief break for medical minute. Please stay tuned to learn more about Melanoma and brain metastases with my guest doctor Thuy Tran.

Funding for Yale Cancer Answers comes from AstraZeneca, dedicated to advancing options and providing hope for people living with cancer. More information at AstraZeneca Dash us.com.

The American Cancer Society estimates that more than 65,000 Americans will be diagnosed with head and neck cancer this year, making up about 4% of all cancers diagnosed. When detected early, however, head and neck cancers are easily treated and highly curable.

Clinical trials are currently underway at federally designated Comprehensive cancer centers such as Yale Cancer Center and at Smilow Cancer Hospital to test innovative new treatments for head and neck cancers. Yale Cancer Center was recently awarded grants from the National Institutes of Health to fund the Yale Head and neck Cancer Specialized program.
of Research Excellence or SPORE to address critical barriers to treatment of head and neck squamous cell carcinoma due to resistance to immune DNA damaging and targeted therapy. More information is available at yalecancercenter.org you're listening to Connecticut Public Radio.

Welcome back to Yale Cancer Answers. This is doctor Anees Chagpar and I'm joined tonight by my guest Doctor Thuy Tran. We're talking about the care of patients with Melanoma and brain metastases, and right before the break we were talking about some of the techniques, some of the new trials that are ongoing, especially looking at use of anti-veg F therapies and immunotherapy for patients with Melanoma, who had brain metastases.

So I thought we'd take a step back and talk a little bit more about patients with Melanoma who have brain metastases. So I think all of us know that Melanoma is one of the deadliest skin cancers. But how common is Melanoma? Many patients get Melanoma. What proportion of them will actually develop brain metastases?

Melanoma over the past couple decades it’s actually the incidence...
That’s increasing more recently about 75,000 new cases are diagnosed each year and it’s a malignancy that is driven by both genetic as well as environmental causes, some of which are related to non-UV exposure. Melanoma develops as we grow older in our fifth generation or fifth decade. And so it does have a higher dominance in men, and there are certain mutations associated with it. 50% of melanomas will contain a BRAF mutation that we can actually target with effective BRAF inhibiting drugs as well as MEC inhibiting drugs that also help boost that response. So just to pick up on the genetic element for a second. One of the things that you said, which I found really interesting is that there are a lot of melanomas that are not related to UV exposure. That may be genetic, so by that do you mean that we should know about our family history in terms of our risk of developing Melanoma? And when you talk about BRAF mutations, are you talking about germline
mutations or are these more somatic mutations that you’ll find in a tumor? The BRAF mutations are new mutations. Sometimes we actually see these mutations present but not associated with any malignancy. But when they do appear associated with advanced Melanoma, it is something that we can actually target. Now these BRAF mutations are not unique to Melanoma. They’re actually present in certain types of colon cancers. And as well as lung cancers. And so the same drugs apply they’re as effective in those other types as they are in Melanoma. And so some people, even if they wear sunscreen and they make sure that they’re not getting a lot of UV exposure and so on and so forth. They can still get Melanoma because of these genetic mutations. Is that right? Yes, in terms of the non sun exposed related melanomas, we typically think of those as a acral melanomas. Meaning they form between the hands, the webs of the hands and the feet on her extremities, and so these are typically places that you know aren’t basking
0:18:06.4 –> 0:18:09.992 in the Sun and other places
0:18:09.992 –> 0:18:12.474 that melanomas can evolve from,
0:18:12.474 –> 0:18:15.534 is the mucosal lining of
0:18:15.534 –> 0:18:18.32 our upper oral pharax
0:18:18.32 –> 0:18:20.854 as well as the anal rectal region.
0:18:20.86 –> 0:18:24.796 Vulvar melanomas from the reproductive tract,
0:18:24.8 –> 0:18:27.416 as well as uveal melanoma’s also
0:18:27.42 –> 0:18:29.149 from the pigmented layers of the eyes.
0:18:29.15 –> 0:18:30.502 So Melanoma, in essence,
0:18:30.502 –> 0:18:33.84 is a cancer of the melanocytes.
0:18:33.84 –> 0:18:36.48 These pigmented cells and so anywhere
0:18:36.48 –> 0:18:39.554 where we have pigment there are
0:18:39.554 –> 0:18:41.306 melanocytes associated with them.
0:18:42.18 –> 0:18:44.352 When you think
0:18:44.352 –> 0:18:45.8 about these genetic mutations,
0:18:45.8 –> 0:18:48.41 now that we know more and more about them,
0:18:48.41 –> 0:18:53.178 certainly you know people who have a
0:18:53.178 –> 0:18:56.26 genetic mutation who are at increased risk,
0:18:56.26 –> 0:18:58.724 they may want to take additional precautions.
0:18:58.73 –> 0:19:00.145 You know making sure that
0:19:00.145 –> 0:19:02.01 they’re really getting
0:19:02.01 –> 0:19:04.03 a good dermatologic exam,
0:19:04.03 –> 0:19:05.416 and staying out of the sun,
0:19:05.42 –> 0:19:07.19 and so on and so forth.
0:19:07.19 –> 0:19:08.954 But one of the questions that I
0:19:08.954 –> 0:19:11.07 have is for some genetic mutation,
0:19:11.07 –> 0:19:15.19 for example for the RET proto oncogene,
0:19:15.19 –> 0:19:18.32 which predisposes to thyroid cancers,
0:19:18.32 –> 0:19:20.66 these are things that newborn
0:19:20.66 –> 0:19:22.064 babies have tested,
0:19:22.07 –> 0:19:23.986 whereas other mutations like
BRCA for example is something that we don’t generally test until you know somebody comes up to us and says, you know I have a family history of breast cancer and so should I get tested. Where does BRAF kind of fit into the grand scheme of things? It’s less clear whether having a pre-existing BRAF mutation ultimately will induce cancer. A lot of the times it doesn’t, and it’s just something that we pick up that’s not prognostic or indicative of any future malignancy. It’s really something that we find later on once the cancer is developed that we can potentially target as an effective therapy. And you mentioned, BRCA mutations in a very small subset of patients can contribute to increased risk of Melanoma as well as pancreatic cancer. So really it depends on family history and it really depends on your personal history too. If you have a patient with multiple melanomas with a strong family history of multiple immediate kin with Melanoma cancers,
that’s when we typically flag and refer these patients to genetic counseling to see if there are indeed these generalized mutations that predispose these patients to developing Melanoma as well as other malignancies. And so it really has an impact on family members, particularly children. When we see patients in the clinic, we always counseled them about preventive measures that they can do to limit additional UV damage and sun exposure risk, but also, seeing the dermatologist regularly, making sure that they have full body skin exams and making sure that their family and their next of kin are also screened with full body skin exams as well. Sadly there isn’t anything that we can do that will kind of reverse that, but certainly taking additional precautions like all of us should be in terms of avoiding sun exposure and wearing sunscreen and avoiding tanning salons and things like that are really good ideas. I wanted to take us back to the whole concept of brain metastases so we know that Melanoma, as you said,
the incidence is increasing.
People are getting this as they get older.
But what proportion of patients with Melanoma actually will get brain metastases?
So about 40% of patients with advanced Melanoma at some point get a brain metastasis.
Now, as we’re using a lot of better imaging modalities, mainly MRI of the brain, we’re catching a lot of asymptomatic brain metastases, so these are very small metastases that are not associated with significant edema around them, and so we’re able to treat these smaller metastases earlier so that they don’t later become a larger issue. There’s a lot of toxicity related to symptomatic brain metastases because the brain itself is, encased in a very thick structural support system, which is the skull, and so there’s not a lot of room for any lesions to expand or any swelling to occur, and so you have a very finite window to address growing lesions in the brain and so that’s why we’ve come up with alternative and
adjunctive therapies to help achieve local control in the brain better. And that includes not in addition to immune therapy, but also adding radiation to that plan to help boost that immune response. I want to get to the treatments and what we can do about brain metastases in a minute. But that 40% number, that seemed high to me. So is that 40% of people who present with advanced Melanoma or any Melanoma? For example, let’s suppose you were going to your dermatologist and you know they happen to find a small Melanoma on the back of your hand. Would you automatically get a brain MRI and is your risk still 40% of getting a brain metastases? No, just to correct that number really only applies to those with advanced Melanoma, so Melanoma that has metastasized to other areas of the body, typically, for staging for Melanoma we really rely on tumor thickness and whether or not it’s gone to lymph nodes. When it’s gone to the lymph nodes,
that makes you a stage three Melanoma and at the initial visit we usually scan the brain to just make sure that it isn’t a stage four Melanoma that we aren’t catching, and under diagnosing what would have been metastatic disease. So that 40% really reflects those with advanced disease that spread beyond the lymph nodes to other distant sites. Got it and so if you do have a brain met it could be asymptomatic. It could be picked up on an MRI or it could be symptomatic at presentation. Tell us a little bit more about how exactly you treat these patients? So if you presented with symptoms are you likely to resolve those symptoms? How good are our treatments? The treatments themselves over the past five years have just magically improved. Not only do we have better systemic therapies that we know are effective in the brain, but we also are better at timing in terms of when to go in and resect symptomatic brain metastases or radiate them in conjunction with her systemic therapies. So, for example, if a patient presents to the emergency room with nausea, vomiting, some dizziness and balance issues,
they get a brain scan in the emergency room
are found to have new lesions in the brain,
if those lesions are large and associated
with significant edema, and that is
what’s contributing to the symptoms,
oftentimes we have to get our
neurosurgery colleagues involved to
rapidly address that lesion and
the most rapid way is via surgery.
You know, it's a morbid procedure,
but the outcomes are typically
very good and people have
a very fast recovery.
If, for example,
the lesion is amenable to what we
call stereotactic radiosurgery,
which is very high radiation but
very focused radiation to try to
spare the normal surrounding brain
and therefore limit the side
effects of radiation in the brain,
that itself is also a very effective therapy.
It’s considered definitive, however,
it can only really be treated
for lesions that are less than 3 centimeters,
if you have a lesion greater
than 3 centimeters,
surgery is the best option.
If you have multiple lesions,
basically multiple small lesions,
too many to be individually treated
with what we call stereotactic radiosurgery or gamma knife, then the next option is whole brain radiation which used to be very neurotoxic long term because these patients would develop cognitive decline later on. Memory issues very similar to dementia. Nowadays we have additional options where we can spare the hippocampus. This learning and memory center in our brain and so we can try to avoid some of these late chronic sequella of radiation therapy.

Other options are to actually use some of the drugs that have been known to be effective in treating Alzheimer’s patients while they get whole brain radiation to try to have a neuroprotective effect to spare the normal brain from receiving some of the detrimental long term side effects of radiation. I mean it sounds like there’s a lot of potential for therapies for brain metastases, but just in our last 30 seconds. So if you have a brain metastasis and it’s been treated, what’s your overall prognosis? So we’re finding with the combination of radiation and immune therapies, prognosis can be actually very good.
Before it was three to six months for anyone with brain metastases. Now we’re talking years out. If you have a tumor that responds to these treatments, the overall survival, the prognosis is much more bright than what it was ten years ago. Doctor Thuy Tran is an instructor of medicine in medical oncology at the Yale School of Medicine. If you have questions, the address is cancer answers at yale.edu and past editions of the program are available in audio and written form at yalecancercenter.org. We hope you’ll join us next week to learn more about the fight against cancer here on Connecticut Public radio funding for Yale Cancer Answers is provided by Smilow Cancer Hospital and AstraZeneca.