MICHELLE MONJE | LUDWIG STANFORD

The inspired neuro-oncologist

David T. Lees | The Studio Deux

Michelle Monje has by any measure had quite a year. In September, she was named a MacArthur Fellow—an honor colloquially known as the "genius grant"—the same month that she was named an Investigator of the Howard Hughes Medical Institute. The following month, she was elected to the U.S. National Academy of Medicine.

True to form, Michelle capped those accolades with more groundbreaking science: a landmark publication in *Nature* in February reporting the preliminary results of a phase 1 trial she led with Ludwig Stanford Colleague Crystal Mackall examining a CAR-T cell therapy they devised in four patients with H3K27M-mutated diffuse midline gliomas. Three of the four patients diagnosed with these invariably lethal pediatric brain cancers exhibited radiological and clinical benefits from the therapy,

including such things as a renewed ability to walk and chew food. Its side effects, which, due to the nature of the therapy, included inflammation in the parts of the brain involved by tumor and a potentially deadly brain fluid build-up known as hydrocephalus, proved to be reversible with prompt and intensive care. The ongoing trial is the culmination of some two decades of pioneering work led by Michelle—much of which is described in our profile of her—that has brought new hope to the families affected by these intractable cancers. Michelle, Crystal and their colleagues presented an update on these results at the AACR Annual Meeting, reporting that a trial delivering repeated infusions of a new dosage of CAR-T cells, both intravenously and through a catheter directly into the brain, resulted in dramatic tumor regressions and clinical improvements in another set of patients with these cancers. And this is just one of several recent groundbreaking studies to come out of her lab.

Ludwig Link caught up with Michelle to ask her about all this and more.

Congratulations on receiving the MacArthur Award and being named a Howard Hughes investigator, not to mention your election to the National Academy of Medicine. How has all this affected your life and work?
I feel so supported. I'm already in such a fortunate position here at Stanford and with Ludwig's support. But this makes me feel like we can really expand the research program, take on high-risk, high-reward endeavors in the lab. And there's a degree of validation that people think we're doing the right kind of work. I feel a great deal of gratitude.

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Could you tell us what the results coming out of these ongoing clinical trials of CAR-T cell therapy for H3K27M-mutant gliomas have meant to you?
I have been dedicated to improving outcomes for children and young adults affected by this horrific cancer of the brainstem and spinal cord since, as a medical student, I first encountered this disease, first watched a child—who we could not help—die from her brainstem cancer. I knew that it was going to be a long and very difficult road filled with many obstacles, but I have always maintained a glimmer of hope that we might really be able to change the cruel course of this disease, to give children and

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their families more, good quality time, to someday even cure the cancer. The results of this trial have been the first indication that may be possible, the first time in my career I have been able to give good news to a patient with an H3K27M-mutant glioma. Finally, the path we are on appears to be the right one, and while the road is still long, I now believe with much more than a glimmer of hope that this cancer can be defeated. That said, and perhaps because I am now truly hopeful that each patient I care for might be the first one to truly beat this cancer, the losses have been that much more devastating.

You work a lot with children and their families. How does that influence your research?

My patients are just incredible individuals, each with loving and giving families. There's a lot of beauty and a lot of hope and humanity that I have the privilege to see. With DIPG, there's a point at which it becomes clear that, while we might be delaying things, we're ultimately going to lose the battle against this tumor. And the degree of altruism, the degree of worrying about other kids with this disease is such a strong sentiment in most of the patients and in their families. It's pretty amazing. My patients inspire the work that I do in the lab.

You recently had a preprint on COVID brain fog, which you showed is very similar to the cognitive impairment often called "chemo-fog," a phenomenon you have studied extensively. Could you tell us about that study?

I've been studying the neurobiology of cancer therapy-related cognitive impairment for about 20 years now and, again and again, for cancer therapy-related cognitive impairment, the central mechanism is an inflammatory one. When I saw how very inflammogenic the SARS-CoV-2 infection was, even in relatively mild cases, I worried that we were going to start to see the kind of cognitive impairment that we see in some cancer patients. And, indeed, within months of the pandemic, it was clear this was happening. The syndrome is nearly identical to what is commonly called "chemo-fog"—impaired attention, concentration, speed of information processing, memory, executive function. My lab doesn't work with infectious agents, so I reached out to people I had never met and was able to connect with

Akiko Iwasaki, who is a thought leader in the virology and immunology of COVID and other respiratory infections. She's been a wonderful collaborator. What we found supported exactly what we had hypothesized: a particular pattern of reactivity in microglia (resident immune cells in the brain) associated with white matter, and consequent effects that lead to the loss of myelinated axons in the subcortical white matter, even after very mild COVID (in experimental models and in line with what we are seeing in the human disease). I am hoping that we will find that the same kinds of therapeutic interventions that are useful for cancer therapy-associated cognitive impairment will prove to be useful in the cognitive impairment that occurs with long COVID.

Alison Yin | Howard Hughes Medical Institute

Your work on neural firing and glioma growth has really proceded apace. Could you tell us a little about this work?

We have found that neuronal activity regulates both low- and high-grade glioma growth and progression in powerful ways. This occurs both through paracrine factors (neuronal activity-regulated release of molecules that signal as growth factors to the cancer) as well as through bona fide electrical communication via neuron to glioma synapses. Beyond brain cancers, it is becoming clear now that the nervous system plays a critical role in many cancers. We are also exploring how we might best target this therapeutically. Which existing drugs that target neurotransmitter receptors and ion channels might affect cancer growth? And we're finding some powerful modulators of tumor progression in drugs that we use all the time. Certain drugs, anti-epileptic drugs for example, powerfully inhibit glioma progression and, disturbingly, we are finding that some commonly used drugs—in specific tumor contexts—may accelerate growth. There is a clinical trial open that I'm leading within the Pediatric Brain Tumor Consortium targeting an enzyme, ADAM10, that is involved neuronal activity-regulated glioma growth and in establishing neuron-glioma synapses through its cleavage of a factor called neuroligin-3.

The neuroscientist Kathleen Susman, whom you met as a freshman in Vassar College, was an early mentor of yours. How did she influence your life and career?
Oh, she changed my life because she put me on the path in science. I had always been interested in science and in becoming a physician, since I think I was in kindergarten. But I had a really discouraging experience in high school, a teacher who quite literally said to me, "It's a rare woman who has a mind for science. Don't worry about it, sweetheart," which I took to mean, "Don't even try." When I went to Vassar, Kate Susman was assigned to me as my pre-major advisor. And I said to her, "Gosh, I wish I could be a doctor, but I don't have a mind for science." I've known Kate for nearly 30 years, and I've never seen her look angry except in that one moment, when she learned where I got that phrase from. She looked at me, and she composed herself, and she said, "Well, you had a bad teacher, and we're good here, so we're going to fix this. I want you to sign up for my biology class … let's give this a go." And that was it. I ended up doing research in her neuroscience laboratory, and everything clicked from there. She was an incredibly important pivot point in my life.

Having had that experience, what would you say to your younger self or to somebody who had a similar experience?
Follow what you love, and don't listen to the noise. That principle came up again later in my career when I was an MD PhD student and when I was a resident: I got a lot of unsolicited advice that there was no way to have family and a big career in science or medicine, that one has to choose. That did not prove to be the case for me, and I am grateful I had the chance to do both. I think the advice I would give to women is to just believe in yourself and do what you care about. Other people are often wrong about your capabilities.

And your mom was also successful professionally. Was she an inspiration to you? Did she have a big influence?
Oh, absolutely. I was and am so close to my mother. She's always been my biggest

cheerleader and supporter. She started as a computer programmer in the sixties and made her way through the ranks at IBM. She's really quite impressive, and raised me on her own for most of my life, since I was about three years old. She's a great mom and showed me that it is possible to balance career and family well.

We've seen a lot of reports about this pandemic taking a disproportionate toll on young scientists. Have you noticed anything like this?

I am deeply worried that we are going to lose a generation of young parents in science, both men and women, but especially women. A couple of my former trainees were in the process of starting their own labs at the beginning of the pandemic, and that is one of the hardest things that a scientist ever does. To have a pandemic hit at that moment, it could have been a fatal blow. I think it will take many years for many junior faculty to recover. I'm very worried that despite the Band-aids applied to the problem by institutions, we're going to lose people from science.

What can be done, do you think—not a Band-aid—that could help these early career researchers?

We really have to give these young scientists financial support to recover, to lengthen the runway for them, because it's all just so incredibly difficult and expensive to launch a research program. We have to give them almost a do-over. We need to help them recover from this incredible blow at a very vulnerable time.

Taking a step back then, what do you think are the biggest societal and professional barriers for women in science?

Something that is incredibly important and that affects all new parents, but women disproportionately to men, is how difficult it is to become a new parent during training or during early faculty years. I have four children, and I feel like I got through that not because of the rules, but despite them. When I was a postdoctoral fellow, I had the benefit of a mentor—who was invested in me and my success—providing funding for a research assistant so that my project could continue while I was on maternity leave, and so I could still mentor the research assistant and direct the project while my hands were full at home. In general, we don't give people sufficient maternity leave, we don't give people sufficient time for things like lactation, or provide affordable childcare to graduate students, postdocs and young faculty. Something I do for everybody in my lab, in addition to the expectation that mothers will work from home until babies are on solids, is to pair new parents, men and women, with a research assistant. It is good for the research assistant to have an opportunity to do more science before going off to graduate school or whatever their next phase may be, it's great for the scientist who needs a pair of hands at the bench and to practice mentoring, and it's good for science because it keeps the projects moving forward. That kind of support can make a really big difference. We need to make that not an exception, but more the norm.