Neurologist Michelle Monje harnesses passion and purpose as she works to cure a devastating childhood cancer.

Brains and Heart

By Kelli Anderson

The girl was an only child, with wavy dark hair, big eyes with long lashes, and a dazzling smile to match a radiant spirit. She loved Disney characters and dotted the *i* in her name with a little heart, as 9-year-old girls sometimes do. Michelle Monje, a Stanford MD/PhD student when she met the girl in 2002, was smitten. Twenty years later, Monje remembers how she sat alongside the girl's mother in the family's kitchen after the funeral as the grandmother, in tears, cooked for guests.

The girl was the first patient that Monje, MD '04, PhD '04, had ever seen with the rare pediatric brain cancer called diffuse intrinsic pontine glioma (DIPG). Perhaps because it strikes a few hundred children a year in the United States—usually between the ages of 4 and 11—and does its lethal work swiftly, DIPG is far less notorious than it deserves to be. It's the leading cause of death from pediatric brain cancer. Otherwise healthy children suddenly have some clumsiness, weakness on one side or one eye that turns inward. As the tumor weaves itself around healthy tissue in a deep part of the brainstem, foreclosing the possibility of surgery, the nerves that control the head, neck and face start to fail. The typical therapy is six weeks of radiation, which might shrink the tumor, buying kids some time and

Photographs by Timothy Archibald

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giving them some function back. But the disease always returns and leads to a death of increasing paralysis, with patients unable to move, communicate, swallow, control secretions or, eventually, breathe—but still perfectly aware of everything that is happening. Patients with glioblastoma, the most common adult brain cancer, face a five-year survival rate of just 7 percent. The outlook for DIPG patients is even grimmer: The five-year survival rate is less than 1 percent. Most patients die within a year of diagnosis.

As her young patient followed DIPG's predictably cruel trajectory, her beautiful smile fading to sadness, Monje felt grief, frustration and what would become unshakable purpose. "I had never seen anything as horrible as this disease," she says. "I was stunned that we knew so little about it." No one knew what mutations drove the disease or what developmental process went awry. There were no animal models, such as mice implanted with the tumor, to study. "It was a black box with no tools," says Monje.

In the two decades since that girl died, Monje, now a professor of neurology at Stanford, has devoted herself to ripping open that box. She has done far more than that: By shedding light on the dark secrets of DIPG and other high-grade gliomas—the deadliest of the cancers that arise from glia, the brain cells that support and surround neurons—and highlighting the role of neurodevelopmental biology in pediatric brain cancer, she has upended the whole field of brain tumor research.

Tracy Batchelor, neurologist-in-chief at Brigham and Women's Hospital in Boston, says Monje has shown scientists "what we had been ignoring for too long: that the brain's micro-environment is critical to brain tumors." By revealing how tumors exploit that environment, Monje has "opened up a whole new axis of biology, and that's opened up a new therapeutic opportunity," Batchelor says. "We can now begin to think about how we might manipulate that interaction to better treat gliomas."

That achievement alone "would have been a success story for any investigator over a lifetime," says David Gutmann, a pediatric neurologist at Washington University in St. Louis and a frequent Monje collaborator.

But Monje's research interests don't end with disease states. Her lab also studies the way that the nervous system develops and remains plastic throughout adulthood and how cancer treatments like chemotherapy disrupt that plasticity, leading to the mental fog known as chemo brain. Tying all those threads together, Monje has spearheaded the emergence of a new field of research (which she named): cancer neuroscience, the study of cancer and nervous system interactions.

In September, Monje was awarded a MacArthur Foundation "genius" grant of $625,000 and named a Howard Hughes Medical Institute investigator, an honor that comes with $9 million in funding over seven years. As a physician-scientist—that is, a researcher who treats patients who have the disease she studies—Monje says the support couldn't have come at a better time. "It really is wind at my back because now that we have a foundation for understanding these diseases, there are some really exciting new directions I want to immediately go."

Monje goes in a lot of directions already. On a recent holiday plane trip with her family—Monje and her husband, the prominent Stanford neuroscientist Karl Deisseroth, MD '98, PhD '00, have four children between the ages of 6 and 13 and a son, Cole, '19, from Deisseroth's previous marriage—she picked up a breakthrough case of COVID-19. Sweating out a fever in bed, she took the opportunity to write a report, based on research by her team and another lab, that even mild cases of COVID-19 can have cognitive impacts similar to chemo brain.

Deisseroth, who met Monje more than 20 years ago on a neurology rotation at Stanford—where he was "blown away by how good she was at everything"—says Monje is defined, in part, by two seemingly contradictory personality traits. "She is a warm, empathic person who always has great relationships with patients and families, and she has a relentless, have-to-solve-it, this-is-what-needs-to-be-done drive. That combination is very rare."

Stanford professor of psychiatry and behavioral sciences Rob Malenka, PhD '82, MD '83, was Deisseroth's postdoctoral adviser and is now a family friend and occasional Monje collaborator. He says Monje shares a number of qualities with Deisseroth, a psychiatrist-bioengineer who is famed for developing optogenetics, the groundbreaking research technique that controls neurons using light-sensitive microbial proteins. Malenka, who calls the couple "the Pierre and Marie Curie of the neurosciences," says both are visionary—and fearless. "In their own ways, they took major risks early on in their careers to try to do something really new and impactful. They both have a fire of *I'm gonna make this happen*, but you don't see it. If they ever get stressed out, it's really hard to tell."

Monje has been achieving uncommon equilibrium and making difficult things look easy since her days as a competitive figure skater in Indiana and later Danville, Calif. She spent so many hours on the ice, practicing at 5 a.m. and competing in regional events on weekends, that her mom finally asked her, when she was in junior high, "Are you going to do anything that helps other people, or is it just going to be you practicing your figure eights all the time?"

Monje had a friend with Down syndrome, so she decided to start a program teaching kids with neurological disabilities how to skate. "I loved that," she says. "It felt so much more rewarding than trying to get a gold medal."

Fascinated by how her skating pupils' nervous systems developed in ways that created challenges but also often led to strengths like emotional intelligence, Monje envisioned a future in biology and medicine. But a high school biology teacher stuck a pin in that plan. When she asked him about a subpar test result one day, he told her, "Don't worry, sweetheart. It's a rare woman who has a mind for science."

Convinced she wasn't smart enough for biology, Monje entered Vassar in 1994 intending to study English and possibly law beyond that. But her assigned adviser, biology professor Kathleen Susman, talked her into giving biology another try. Monje quickly became a star of the department, eventually first-authoring a paper with Susman on the roles vitamins E and C play in mitigating free radical damage in the aftermath of stroke, a research direction that was Monje's idea and a pivot for Susman. "That was the first time I decided to follow the instincts of a student on a research project," says Susman.

Monje has continued to have a strong sense of the right path forward, the right thing to do next—even when that thing is unheard of. As a PhD student between her third and fourth years in medical school at Stanford, Monje was studying neural development and what goes wrong after cranial radiation. She wanted to know whether what she was seeing in rats was happening in patients. To do that, she'd need human tissue.

Paul Fisher, a Stanford neuro-oncologist and chief of the division of child neurology, remembers the day Monje approached him and colleague Gary Dahl with a previously unthinkable request. Could they get some postmortem tissue from leukemia or brain cancer patients who had had radiation? "You can imagine: This poor family just lost their child to a horrible cancer, and I'm going to come in like a vulture and ask for their child's brain?" says Fisher, '85.

To Fisher's surprise, families were willing to donate tissue if it would lead to advances in treatment. "Suddenly, there was a window to do real science," he says. Monje and her PhD adviser, professor of neurosurgery Theo Palmer, subsequently found that cranial radiation therapy can cause cognitive deficits in the hippocampus, the area of the brain central to memory formation. Their research laid the groundwork for a shift in the way radiation is delivered.

It was about this time Monje met that first DIPG patient. Something Fisher had pointed out in clinic one day had really struck her: DIPG and other pediatric brain tumors happen in a predictable spatial-temporal pattern. "If you tell me the age of the patient, I'll tell you where their brain tumor is," Fisher had said. Unlike most adult cancers, which tend to be diseases of exposure accumulation, brain tumors showed up in kids at the same place and same developmental stage over and over. It seemed obvious to Monje that DIPG and similar cancers appear because of something gone awry in brain development. But that's not how the disease was being approached.

It was something Monje thought of often during her residency in adult neurology at Harvard through Brigham and Women's Hospital and Massachusetts General Hospital. The program, which focuses on neurological issues of adulthood but has a strong pediatric/developmental component, gave Monje perspective on the full life span of the brain and nervous system, and it

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trained her in a range of clinical skills. But she kept thinking about DIPG and that young girl she had met during medical school.

In 2008, she returned to Stanford for a pediatric neuro-oncology fellowship with Fisher and a postdoc with Stanford developmental biologist Phil Beachy. "I really thought developmental neurobiology was the way to approach DIPG," she says.

There was one big—and familiar—problem. Because DIPG tumors entwine around healthy cells in the pons, a part of the brain stem that controls vital functions like breathing and heartbeat, biopsies were all but impossible. No one had ever cultured DIPG cells or developed a mouse model for it. Several people warned Monje that DIPG was a research dead end because without tissue, there was no way to study it.

In late 2008, Monje met the DIPG patient who would change that. Dylan Jewett was a bright 5-year-old who loved superheroes and his Thomas the Tank Engine toy. But he was suffering from a tumor so aggressive it didn't even make sense to complete the course of radiation. When his family asked if they could donate his organs after he passed, Monje asked if they would donate his tumor. They agreed. From Dylan's donation, Monje produced the first-ever cell culture and mouse model of DIPG.

Inspired by a story about Dylan's gift in *Stanford Medicine* magazine, parents of other DIPG patients reached out to arrange for donations. The autopsy program Monje created has been logistically challenging—tissue donation requires time-sensitive collaboration with physicians and pathologists around the country—but transformative. Monje has shared the DIPG cell lines with hundreds of labs around the world. She is still shattered by every DIPG loss, usually waiting until her kids are in bed before weeping over another young life cut short. "I don't care who finds the answer," she says. "I just want someone to."

Myelination is the process that gives the brain's white matter its color and, more important, wraps nerves in an insulating sheath to ensure speedy and efficient signaling. Distinctly timed and located waves of myelination occur throughout infancy, childhood and well into young adulthood, starting with the brain stem, then the spinal cord and proceeding throughout the brain. Those waves, Monje would discover as a postdoc, are key to the spatial-temporal pattern of childhood brain cancers.

Studying healthy pons tissue samples, Monje had found that oligodendrocyte precursor cells (OPCs)—which become oligodendrocytes, which make myelin—showed up in increased numbers right at the peak of the myelination wave that happens at the location (ventral pons) and age range (6 to 8 years) in which DIPG tends to show up. That's also the age when kids tend to step up their motor-skills game by learning to skip or ride a bike. Monje suspected that dysfunctional OPCs were the genesis of DIPG, a suspicion that her lab and others later confirmed. She also found that the peaks of other waves corresponded with the timing and locations of other childhood high-grade gliomas.

By the time she opened her own lab in 2011, Monje had collected a few other clues about DIPG. One of the striking aspects of all glial malignancies is that patients have minimal symptoms to begin with—maybe a bit of slurred speech or an eye turning inward—but imaging shows large areas of their brain, brain stem or spinal cord occupied by the tumor. "We think about cancer as a space-occupying and destructive process," says Monje. "But if it were, in this case, that whole part of the brain wouldn't work. So something else is going on." Moreover, looking at DIPG samples under a microscope, she was struck by an observation that was first made decades ago: Glioma cells cluster around neurons like a halo, which suggested to her a strong relationship between the two. Although gliomas can enter the bloodstream, they almost never grow anywhere but the nervous system. They seem to need the brain's environment to thrive. She had a hunch that the thing that drives brain development and plasticity, which is the activity of the nervous system itself, might also be driving the cancer. It was a radical idea. "People didn't expect neurons to have a role in cancer, but it made so much sense," she says.

To explore her hypothesis, Monje first looked at what happens in the circuit of a healthy brain. Using optogenetics—which many researchers do, but "conveniently, I have the great benefit of living with a great innovator of tools to study the nervous system," Monje says—she and her team found that light-induced nerve activity led to the production and remodeling of myelin in the activated circuit. Moreover, that myelin modulation improved function in that circuit—in this case, the limb of a mouse. The upshot of the findings, published in *Science* in 2014: Myelination, once considered a process that ended in young adulthood, continues, triggered by nerve activity, throughout adulthood and contributes to ongoing neural circuit "tuning" that's critical for brain function.

In a follow-up study, Monje found that nerve activity likewise drove the growth of gliomas. Her research also identified a growth factor, the neural protein neuroligin-3, that helped drive cancer cell proliferation and could be a target for drug therapy. That paper, published in *Cell* in 2015, made a splash even beyond the neuroscience community.

Monje's game-changer paper, as she calls it, came out in *Nature* in 2019. It contained even bigger news about gliomas: They form synapses and electrically integrate and communicate with neurons. In other words, the tumors hijack the brain's normal process and become part of it.

Another lab had discovered the same thing, so the two labs submitted their papers together. A third paper in the same issue showed that when breast cancer metastasizes to the brain, it also gleans electrical signals from the brain, albeit in a different way.

"So all of a sudden, it was like, brain cancers need brain physiology," says Monje. "It makes so much sense that these cancers that grow in the brain take advantage of the signals in the brain. But that was not recognized before those three papers came out in *Nature*."

Monje has the cover of that issue framed and hanging on a wall at home. The cover illustration, which she conceptualized, shows a flower with a root system in the shape of a brain next to a weed whose root system has intertwined with the flower's. A garden-gloved hand is poised to pluck the weed. "We have to pluck out the weed, and we have to take its root system with it," she says. "That's a whole other way to think about cancer, and it really changes the way we need to start approaching it. In addition to the traditional ways of fighting cancer, we have to disintegrate it from the nervous system and target the way it's communicating with the nervous system." Some drugs developed for psychiatric disease, epilepsy and migraine do exactly that and are already showing promise in mouse models, says Monje. "We just hadn't been thinking of these things as cancer therapies."

In the wake of the 2019 *Nature* paper, Monje has become something of a rock star in the neuroscience community. Stanford pediatric neuro-oncology colleague Cynthia Campen, MS '11, recalls planning to meet Monje for tea after the latter's keynote at the Society of Neuro-Oncologists meeting in Phoenix in 2019. The crowd of scientists wanting to talk with Monje afterward was so big that tea had to be postponed. The scene reminded Campen of a quote from a 2015 *New Yorker* article about Deisseroth. Upon seeing neuroscience conference attendees crowd around her husband in the wake of his optogenetics breakthrough, Monje said she realized she was "married to a Beatle, the *nerdy* Beatle." Now it was her turn. Says Campen, laughing, "Michelle was having a moment. It was fun to see."

If Monje were the admonishing type, she could say her success stands as a rebuke to that sexist high school biology teacher and to those along the way who said her novel ideas would ruin her career. And let's not forget those who told her motherhood and science wouldn't mix. "When I was a young trainee, people told me not to have kids," she says. "When I started having my kids, they said, 'Oh, I guess you're choosing not to do big science.' And I thought, I'm not choosing that. I'm choosing to have a slower year. And to make a person, you know?"

Both Monje and Deisseroth make their kids their top priority, outsourcing some housecleaning and grocery delivery but mostly handling drop-offs and pickups themselves. Monje bakes a loaf of sourdough every night as she makes dinner for her family, topping many with cut-out shapes like hearts to please her 6-year-old daughter. She also drops off gifts of freshly baked bread on her colleagues' porches, much to their delight. "Sometimes I think she has one of those devices that stops time," says assistant professor of psychiatry and behavioral sciences Erin Gibson.

Monje says her ability to make it all work stems, in part, from crucial but unusual support she got as a new parent. It's a big soapbox issue for her. She cites a study published in the *Proceedings of the National Academy of Sciences* that found that nearly half of women and nearly a quarter of men leave science fields after their first child is born—a terrible waste of trained talent, she says. "It makes no sense that our system doesn't support young parents," says Monje, who serves on a task force to expand lactation spaces at Stanford Medicine. "I was in the system, but I got exceptions. I was able to demand time to pump, to demand more than six weeks off after having my first child. Paul Fisher hired a technician for me when I was a postdoc to help me keep hands at the bench. All of those exceptions should be the rule for everybody, because it's only reasonable."

They are the rule in her lab. Every new parent gets six months to work from home, with flexible hours and access to a dedicated research assistant. "Michelle had given me the time off, but I wanted to come in at times, and she made it easy for me. I could bring my kid, and someone would watch her," says Gibson, who had her two daughters when she was a postdoctoral fellow in Monje's lab. "If I didn't work for a week, there was no pressure. That flexibility with parenthood is part

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of the reason for her and her lab’s success—and for my success.”

In addition to feeling supported, anyone working in Monje’s lab will learn a lot about unfamiliar methodologies and the fruits of collaboration. Chimeric antigen receptor (CAR) T-cell therapy involves taking T cells, a type of immune cell, from a patient’s blood, engineering them to attack specific molecular targets, and then returning them to the patient. It’s not a specialty of Monje’s lab. But in 2016, after attending one too many meetings where researchers hypothesized which molecules on DIPG might make good immunotherapy targets—instead of actually looking at the DIPG cells she offered them—Monje had her lab do the looking. “And,” she says, “we found GD-2.”

GD-2 is a sugar molecule, and it was abundant on the surface of DIPG tumor cells that Monje’s lab examined. Results in hand, Monje walked down the hall from her lab in the Lorry I. Lokey Stem Cell Research Building and knocked on the door of cancer immunotherapy expert Crystal Mackall, who had already engineered CAR-T cells to target GD-2 on the cells of another pediatric brain cancer, neuroblastoma. “That started a perfect collaboration,” says Mackall, who also leads Stanford’s efforts to translate research into immune therapies for cancer.

Mackall compares CAR-T cells to bloodhounds that go after a scent. “We had the bloodhounds, and Michelle gave us the scent. She had found us an almost perfect target.” When given to mice with DIPG tumors, the CAR-T cells sniffed out the GD-2 on the DIPG cells and all but obliterated the tumors, leaving only a few cancer cells.

After that study came out in *Nature Medicine* in 2018, Monje and Mackall moved swiftly to their first clinical trial, the results of which were published in *Nature* in February. All four of the initial patients eventually died from DIPG or its complications, but three experienced significant tumor shrinkage and symptom improvement after getting the CAR-T cells. When he joined the trial in September 2020, Jace Ward, a 21-year-old University of Kansas student, had double vision, a stiff jaw, and weakness on the left side of his face and right side of his body. His intravenous first dose provided impressive but temporary symptom reversals. When his symptoms returned, Ward went back to Stanford in January of 2021 for a second dose. This time, he arrived in a wheelchair, unable to walk or open his mouth much. For the second dose, patients received the CAR-T cells directly into the cerebrospinal fluid through an intracranial port. Monje leveraged her extensive training in the neuro-critical care unit during her residency in Boston to anticipate and manage subsequent tumor inflammation.

The results were stunning. Two weeks after his infusion, “Jace walked out of the hospital and got a big hamburger,” says his mom, Lisa. Not long after, he was able to walk four miles a day and attend the 2021 Super Bowl. Ward had three more infusions before he succumbed, on July 3, 2021, to a tumor bleed unrelated to the trial. “Throughout the trial, Dr. Monje was so compassionate, so accessible, so engaged, and, really, so brave,” says Lisa. “She has given the DIPG community so much hope.”

Deisseroth says this trial—one of a handful Monje has run—might be the most mind-blowing thing his wife has accomplished to date. Its success depended on “a convergence of four threads that I don’t think are unified in another human being on the planet”—her compassion, her relentlessness, her deep knowledge of molecular biology and her neuro-ICU training. “It’s not typical for a neuro-oncologist to have years of neuro-ICU training,” he says. “Who knew that would turn out to be essential?”

Monje cautions that the trial team still has much to learn and that effective treatment of DIPG and other high-grade gliomas will require more than one type of therapy, including drugs to disrupt neuron-glioma communication. But the CAR-T cell trial has given her hope for real progress against an unyielding disease. “We’re seeing some incredible responses,” she says. “In some ways, it’s almost more devastating when I lose a patient now, because I start out thinking maybe we’re going to cure it this time. It feels that close.” ■

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