Cancer in the Wilderness

Elizabeth P. Murchison

A refreshing cool dampness draped the Tasmanian rainforest gully as I climbed out of the car that summer afternoon in January. We had just started the long drive back to Hobart, and my feet were aching from a week of walking in the remote central highlands, when I spotted the small black furry body by the road. I approached through a buzz of blowflies to see the distinctive white markings and thickset jaw: it was a Tasmanian devil. He was only recently killed, judging by the freshness of the impact wound on his neck that was still trickling blood onto the gravel roadside. He was a young male, probably not more than 2 years old, with a glossy coat and sleek black whiskers. As I stooped to turn him over, I saw what I was looking for: a firm pink pea-sized lump at the side of his nose. This devil had early signs of Tasmanian devil facial tumor disease, or DFTD, a transmissible cancer that is threatening Tasmanian devils with extinction. I didn't know it at the time, but as I prodded that tumor, with the black cockatoos screeching in the forest canopy above, I was at the beginning of a scientific journey that would take me around the world and thousands of years back in time, tracing the origins and evolution of transmissible cancers.

"I didn't know it at the time, but as I prodded that tumor, with the black cockatoos screeching in the forest canopy above, I was at the beginning of a scientific journey that would take me around the world…"

Cancer occurs when a somatic cell of the body acquires mutations that drive it toward an autonomous program of proliferation and survival. Although cancer often spreads to distant organs via a process of metastasis, it cannot usually survive beyond the body of the host that spawned it. DFTD is a cancer that has done just that. Indeed, as the comparison of my roadkill

Murchison in the Tasmanian rainforest.

The roadkill Tasmanian devil that Murchison found in 2006 with signs of Tasmanian devil facial tumor disease.

devil's tumor DNA with DNA from his normal tissues would later confirm, his tumor did not arise from his own cells but was, rather, composed of foreign cancer cells that originated in another devil and were implanted into his body by a bite. My devil, from a remote rainforest gully, was just one of tens of thousands of hosts for a cancer that is "metastazising" through the Tasmanian devil population.

"My devil, from a remote rainforest gully, was just one of tens of thousands of hosts for a cancer that is "metastasizing" through the Tasmanian devil population."

Having grown up in Tasmania, I was familiar with Tasmanian devils. Although they are shy nocturnal animals, their presence is evident in the Tasmanian landscape through their high-pitched nocturnal howls, their recognizable grayish scats, and their omnipresence on souvenir postcards and tea towels. Because of the demise of the thylacine, or Tasmanian tiger, Tasmanian devils are now the world's largest extant marsupial carnivore. However, since DFTD was first observed in 1996, the Tasmanian devil population has undergone such a rapid decline that the animals are now very rare in most areas.

In 2006, when I found my rainforest devil, I was in the final year of my PhD in molecular genetics at Cold Spring Harbor Laboratory. Like many young Tasmanians, I had fled the island after finishing high school; I was eager to set foot in a wider world and to explore the scientific possibilities let loose by the near completion of the Human Genome Project. During my undergraduate years at the University of Melbourne, I met Mary-Jane Gething, a kind and inspiring professor and alumna of Cold Spring Harbor Laboratory (CSHL). Mary-Jane told transfixing tales of CSHL scientific discoveries (identification of RNA splicing and transposons, the Hershey-Chase experiment) and showed dreamy photographs of scientists sailing on misty harbors. Within months, in August 2002, I was climbing out of a taxi on Bungtown Road as a new student at the CSHL graduate program.

Adjusting to American life was challenging at first. On my first day of classes I tried to wade across the harbor, only to sink into quicksand and retreat covered in mud. Later in the year, it became clear that my Australian polar fleece was not at all adequate for blisteringly cold New York winters. However, whereas in Australia Tasmanians are frequently regarded as dull and parochial, I quickly discovered that, in America, I was considered exotic. As "the Tasmanian girl" at CSHL, Tasmanian devils became (along with discussions of the spinning Loony Tunes character Taz) my main topic of conversation.

By the mid-2000s, by which time I was engrossed in my PhD focused on elucidating endogenous functions of the newly discovered RNA interference machinery, the devils' disease had spread widely and was raising fears for the species' survival. Although most of my colleagues at CSHL bar bet that a new oncogenic retrovirus was probably triggering the tumors in devils, I started to hear reports that this disease had a new and altogether unexpected etiology: that the extraordinary consistency in chromosomal rearrangements between tumors from different animals suggested that the disease might spread by the direct transmission of living allogeneic cancer cells by biting.

Coming face to face with a lump of these cancer cells in a rainforest gully a couple of months later changed the course of my career. The terrifying reality of contagious cancer cells and the bizarre predicament that threatened the devils spurred my interest, and encouraged by my extremely supportive PhD mentor, Professor Greg Hannon, I resolved to work on the devil. This was also the

Murchison holding a healthy Tasmanian devil during a field trip. Image courtesy of Maximilian Stammnitz.

time when the advent of next-generation sequencing technologies presented new possibilities for performing genome-scale analyses, and I thus jumped at the opportunity to understand the genetic changes underpinning DFTD. Indeed, the first devil that I ever sequenced was my Tasmanian roadkill.

"The Tasmanian devil may soon cease to be a feature of Tasmania's remote wilderness, having fallen victim to the runaway evolution of its own corrupted cells."

The Devil's DNA

In 2009, after spending some time back in Australia, I travelled to the Wellcome Trust Sanger Institute, near Cambridge, UK, with a box of devil DNA samples. Supported by a postdoctoral fellowship from the Australian Government, I had arrived to work with Professor Mike Stratton, a world leader in the burgeoning field of cancer genomics. Although Mike had not been to Tasmania, his shrewd attention had been caught by the devils' unusual quandary and the potential insights into cancer evolution that their disease could reveal. Together with a team of enthusiastic collaborators, we set about sequencing the DFTD genome. Our analysis indicated that the devil that first gave rise to DFTD, whose DNA is still contained within DFTD cells, was a female and that DFTD cells have acquired approximately 20,000 mutations during their spread through Tasmania. This number is similar to the number of mutations found in human cancers that exist within a single individual (most human cancers have between 1,000 and 30,000 mutations), consistent with a relatively recent origin for the disease. By analyzing patterns of mutations across the DFTD population, we were able to identify geographical features that have influenced tumor migration.

On a recent trip back to Tasmania, someone asked me whether it is possible that DFTD will eventually become so degraded by mutations that it will simply self-destruct. This is an interesting question, as DFTD, like other cancers, continuously accumulates irreversible mutations, some of which will be deleterious for the cell; but unlike other cancers, DFTD has a long-term evolutionary trajectory. However, another transmissible cancer that is much older than DFTD suggests that DFTD is unlikely to become inviable in this way—at least not soon.

Going to the Dogs

Canine transmissible venereal tumor, or CTVT, is the only other known naturally occurring transmissible cancer in mammals. It was a search for this tumor that took me to Sicily in the summer of 2009. Met at the airport by Gabriele Marino, an affable Sicilian vet, we drove up the Calabrian coast, passing through small towns huddled in valleys with sweeping Mediterranean vistas. As we drove, Gabriele talked excitedly about CTVT, a sexually transmitted cancer that

A healthy Tasmanian devil. Image courtesy of Maximilian Stammnitz.

causes tumors on the genitals of affected dogs. We arrived at the Lamezia municipal pound, and Gabriele produced a few vials of vincristine and hoisted a docile yellow-colored stray dog called Giallo onto the surgical table. Gabriele peeled back this dog's prepuce to reveal a nest of raspberry-sized bleeding masses at the base of the penis. ''I've already given him one dose of vincristine, and he has responded well,'' he explained as he inserted a catheter for chemotherapy infusion. Gabriele also cut me a small sliver of Giallo's tumor for genetic analysis. I have now collected CTVT tumors from around the world—and it is astonishing that the tumor that I found bulging from the vagina of a dog roaming one of the remote Cape Verde Islands off the coast of Africa and the tumor I collected from the flank of a farm dog in an Andean village are, in fact, the same cancer as the tumor on Giallo's penis, passed from dog to dog by the direct transfer of its living cancer cells.

Back in Cambridge, I embarked on sequencing the CTVT genome. Our analysis has shown that the animal that first gave rise to CTVT was a dog that may have most closely resembled a modern-day Alaskan malamute. Using one type of mutation as a ''molecular clock'' we estimated that the dog that gave rise to CTVT may have lived about 11,000 years ago. CTVT has acquired approximately two million mutations that have caused complete loss of at least 2% of dog genes and have potentially altered the protein composition of more than 10,000 genes. The CTVT genome has illustrated the robustness of the mammalian somatic cell to survive despite a vast mutation load.

In 2013 I started my own laboratory, the Transmissible Cancer Group, at the Department of Veterinary Medicine, University of Cambridge. Day by day, we piece together the events that underlie transmissible cancers. These lineages' histories are indelibly imprinted on the genomes that they have carried with them on their parasitic journeys, and reading these histories reveals fascinating stories of how evolution and chance allow such abnormal living entities to survive. Daily emails ping in from Tasmania, both from our dedicated team of collaborators and from my family, who have read of the latest devil research in the local news. The last year has yielded even more surprises, including our American colleagues' identification of transmissible cancers in clams and other bivalves, and, most recently, the appearance of what appears to be a second transmissible cancer in Tasmanian devils.

Earlier this year, I took two of my graduate students on a field trip in southern Tasmania. It is exciting to see them take possession of their scientific questions and leads me to reflect on the support, open-mindedness, and encouragement of the scientific mentors who gave me the confidence to follow an unusual path. I am indescribably lucky to have had the opportunities to make a difference in an important field that connects me to my island home and its unique wildlife and nature; it was also luck that I chanced upon the little roadkill animal that changed the course of

my career. When I reflect upon that encounter with the devil by the road 10 years ago, it is thrilling to know that we have now sequenced the entire genome of the parasitic cancer implanted under the skin of this devil's face. However, many of the basic biological mechanisms that cause and drive transmissible cancers remain unclear, and, unless we work quickly, the Tasmanian devil may soon cease to be a feature of Tasmania's remote wilderness, having fallen victim to the runaway evolution of its own corrupted cells.