Unraveling the tangled threads of a stealthy disease

BY LEE SHERMAN

Last fall, the nation was riveted to the story of Brittany Maynard, a 29-year-old California woman afflicted with inoperable brain cancer. She captured the media spotlight when she moved to Oregon to access lethal drugs under Oregon’s death-with-dignity law. Maynard had chosen to die before the tumor took her autonomy. Her 100-watt smile, captured in photos from happier times, shone from every screen in America as we witnessed her struggle against glioblastoma, the same deadly disease that struck down Senator Edward Kennedy and kills some 13,000 U.S. residents yearly.

Maynard’s illness “reminded the world that science seems stuck in its bid to cure the most common type of brain cancer,” wrote journalist Bill Briggs of NBC News.com in November. Dr. Henry Friedman at Duke University’s brain tumor center observed, “We do not have enough weapons to deal with these tumors.”

But several potential new weapons are under the microscope at Oregon State University — next-generation approaches that could change the outlook for future patients like Maynard. Biomedical researchers at OSU, for example, are investigating the curative powers of a rare marine organism discovered on a Panamanian reef by natural-products chemist Kerry McPhail (see “Total Immersion,” Terra, spring 2014). In test tubes, this purple cyanobacterium clobbers glioblastoma cells with a supertoxic chemical it likely uses in its ocean ecosystem to ward off predators. To fund further studies, the American Brain Tumor Association recently awarded a $50,000 Discovery Grant to OSU pharmacology researcher Jane Ishmael, a McPhail collaborator.

Another team is working with Portland’s Oregon Health & Science University and Knight Cancer Institute on targeting tumors intravenously via nanoparticles loaded with drugs. Still others have spun off a company called Lasso Metrics to design a product for quick, easy, reliable cancer detection using “peripheral biomarkers” — substances in blood, urine or saliva that signal cancer in very early stages. In all, 60 scientists and social scientists at OSU are investigating some aspect of cancer.
“Cancer,” observes OSU biochemist Oleh Taratula, “is a very smart disease.”

To outwit this cunning foe is Taratula’s single-minded focus during countless late-night hours in his new lab on Portland’s South Waterfront. As he experiments with nanotechnologies for targeting deadly tumors, he holds memories of his Ukrainian grandfather who died of prostate cancer. As he investigates light and heat as treatment tools, he thinks of the nearly 600,000 people who succumb to cancer each year in the United States alone. His fierce drive to give hope to those who face devastating diagnoses fills his body with kinetic energy as he talks. “Every family has some history of cancer,” he says, poised restlessly on the edge of his swivel chair. “It is very difficult for families when there’s nothing that can be done. I want to change that.”

He came to the College of Pharmacy to be part of a new interdisciplinary team, four researchers whose collective expertise in nanomedicine and other next-generation technologies for drug delivery has been honed at Rutgers, MIT, Stanford, the University of Wisconsin, the University of Washington’s Department of Neurosurgery, Seattle Children’s Hospital and other academic settings around the country. The team’s mission: develop nanotechnologies for delivering anticancer drugs directly to a tumor, thus avoiding chemotherapy’s indiscriminate, whole-body barrage of chemicals.

Nano Zip Codes
“Those chemo drugs go to every organ, every tissue,” says Taratula. “They’re very toxic — they cause terrible side effects like nausea, weight loss, hair loss and even heart problems.”

He and his teammates Adam Alani, Gaurav Sahay and Conroy Sun — who were among the first researchers to set up labs in the $295 million Collaborative Life Sciences Building in Portland last summer — are in the early design stages of new nano-tools that can carry cancer-fighting drugs through the bloodstream right to the site of a tumor. Challenges abound. For instance, before the drugs can act against the tumor, they must first get to the tumor intact. The team is experimenting with nanomaterials such as organic polymers (chemically related to plastics, but water soluble and biodegradable) that can carry the drugs, as well as guide them, to their target.

To do this, the researchers encode the polymer carrier with specific chemicals that are drawn to the cancer cells, Adam Alani explains. This “active targeting” uses the cancer’s characteristic fingerprint against it by “decorating” the nanoparticles with “zip codes” — usually ligands (molecules that bind to other, usually larger, molecules) that have an affinity for compounds in the cancer cells.

Once it arrives at the tumor, the nano-packet needs to slip past the protective proteins that shield the cancer cells. In theory, the extreme tininess of the drug-loaded nanoparticles should let them pass through the defensive wall. That’s because the network of blood vessels feeding the cancer creates a mesh-like mass — a kind of leaky sieve — that is vulnerable to penetration by particles as big as 200 nanometers (the size of a small bacterium). But through a process called “endocytosis,” the cancer cells can engulf foreign invaders (such as nanoparticles loaded with drugs) inside fatty pouches called “lipid bubbles” and recycle them before they can enter the tumor. Gaurav Sahay dubs these pouches the “trash bags” of cancer cells.

So far, the secret to dodging the lipid bubbles has eluded scientists. “This is one of the huge challenges facing the field,” Sahay says. “There’s another huge challenge: finding and killing the stray cancer cells that surgeons inevitably leave behind after removing the visible mass. These “microtumors,” which form an invisible periphery of malignancy, often seed recurring cancers. Doctors can better detect the boundaries of tumors by using fluorescent dyes that cause errant cells to glow under optical imaging, says Conroy Sun, a bioengineer whose vita includes post-doctoral research in imaging technologies at Stanford’s Department of Radiation Oncology.

Sun veered from materials science to bioengineering when the urgency of cancer research touched him personally and emotionally. While he was doing graduate work at University of Washington, his father nearly died of a prostate cancer that went undiscovered until almost too late. Then there was the day at Seattle Children’s Hospital, where he was doing post-doctoral research. He ran into one of his mentors, a pediatric radiologist who was just leaving a family consultation over a child dying of medulloblastoma, an aggressive brain cancer. “He was very distraught, very emotional,” Sun recalls. “He was saying, ‘We just don’t have anything to help these people.’ It changed me. I realized I had to do something to help.”

“Is cancer’s end conceivable? Is it possible to eradicate this disease from our bodies and societies forever?”

— Siddhartha Mukherjee, The Emperor of Maladies: A Biography of Cancer
Sacred Flesh

Jane Ishmael’s uncle, a chemist from the north of England, had thrown himself into retirement with his characteristic gusto. An intrepid hiker and traveler who never set off without a book in his knapsack, he always seemed younger than his years to his admiring niece. But his active life took a sudden detour when he began to feel off-kilter, out of equilibrium. Something was wrong. Within seven months of learning he had a glioblastoma growing in his brain — a mass of rogue cells feeding on what journalist Bill Briggs calls “that most sacred of all human flesh, the organ that creates our identities” — he died.

“It was inoperable,” says Ishmael, her personal sorrow floating just beneath her scientist’s clinical language. “He was diagnosed in January 2006 and died in August.”

Losing her uncle to a disease that she characterizes as “cruel” altered her course as a researcher in the College of Pharmacy, focusing her knowledge of pharmacology (the study of how drugs work in the body) toward drug discovery (the active search for novel compounds that heal). “The progression of these cancers is often very rapid,” says Ishmael. “Really, the prognosis for these aggressive brain tumors hasn’t changed much at all. We’ve not improved patient outcomes.”

In 2008, when OSU medicinal chemist Kerry McPhail cracked the complex molecular structure of a rare marine organism she had discovered in Panama, Ishmael became captivated by its powerful cytotoxic (anticancer) action. So she teamed up with the university’s natural products team — scientists like McPhail and Taifo Mahmud, who brave some of the world’s hardest-to-get-to ecosystems in search of promising new drugs.
In 2014, Ishmael’s finding that “coibamide A” (the substance from the cyanobacteria McPhail had collected in Panama) induces death in human glioblastoma cells won her a $50,000 Discovery Grant from the American Brain Tumor Association. “The cellular machinery has to be working very well in a cancer cell because it’s got this massive demand to grow and proliferate at a faster rate than a normal cell,” she says. “We’re trying to target that aspect of its physiology. Coibamide A seems to be able to shut off some of the proteins that are required for the formation of new blood vessels via a potentially novel mechanism.”

At the Discovery Awards banquet, Ishmael met a top donor whose son had died of a glioblastoma. It was a poignant reminder of the stakes. “In pediatric medicine, if you radiate a child’s brain, it is really devastating to the child,” she says. “Despite all the advances in cancer medicine, this one remains just very, very difficult to treat.”

Fluid Clues
Could lung cancer someday be detected on someone’s breath?

Very possibly, asserts Dr. Christiane Löhr, a pathologist in the College of Veterinary Medicine. She’s part of a multidisciplinary team looking for “biomarkers” — biological molecules floating in blood, urine, saliva or even, as Löhr suggests, in airborne vapors from the lungs that indicate disease.

“Getting a diagnosis from such a biomarker instead of a biopsy is less expensive, less invasive and faster,” says Löhr, who collaborates with cancer researchers across campus, including Jane Ishmael. “This is the next big step in medicine — identifying diseases, especially cancer, earlier, identifying them more specifically, and monitoring their progression and therapeutic success.”

Biomarkers aren’t a new idea, Löhr says. Glucose in urine, for instance, is a familiar biomarker for diabetes. And salty skin has been noticed for decades on babies with cystic fibrosis. These more simple biomarkers, however, are just the precursors to a fast-emerging generation of super-sophisticated detection tools.

Animal research is where it starts. Löhr’s colleague Dr. Shay Bracha, a veterinary oncologist, explains the connection. “Many of the cancers we diagnose in veterinary medicine are essentially the same cancers we see in human medicine,” he says. “So we can translate findings from one to the other; it’s called comparative medicine.”

A clinician who has treated hundreds of cancer-stricken dogs at OSU, Bracha is a founding partner of Lasso Metrics, a spinoff launched in late 2014. The company’s goal: design a simple screening tool for use in the field or the clinic. Results are instant. He calls it “point-of-care” diagnostics. “For us as clinicians,” he says, “it will be extremely helpful to have something we can do quickly, cheaply and reliably without expensive instrumentation.”

That “something” could be as simple as a test strip with a drop of urine that can be read by a cell-phone app. Or it could be a molecule exhaled in a puff of air.
It’s a Library, Metaphorically Speaking

Robots help scientists screen chemicals for new drugs

Neither Jennifer Fox nor Robbie Allen is a poet. But when explaining their work to others, these scientists often rely on that pillar of poetry, the metaphor. That’s because for most people, picturing needles in haystacks, keys in locks, and spaceships in docks is a lot easier than getting a clear image of high-throughput screening, combinatorial chemistry, 3D virtual screening or other esoterica in the field of drug discovery.

In that spirit of clarity, Fox jumps in during a recent three-way interview about a highly specialized research facility called a “compound library.” When Allen tosses off terms like “assay,” she chips in with a more familiar synonym (“Assay just means experiment”). Same with the word “compound” (“Basically,” she says, “it’s a chemical substance.”). The library they run from their riverfront laboratory near downtown Portland has none of the visibility or familiarity of the stately, elm-shaded Multnomah County Library. But tucked away in its warren of office buildings and condos along Macadam Avenue, it draws researchers from universities and pharmaceutical firms all over Oregon in their search for lifesaving medicines.

“Basically, a compound library is a collection of chemicals that could be future drugs,” explains Fox, executive director of OTRADI, the Oregon Translational Research and Development Institute created by the Legislature in 2007 to speed up the quest to find new medicines and bring them to market.

Allen, OTRADI’s scientific director, elaborates. “The 300,000 compounds in our library have been preselected by chemists and biochemists for their potential to become drugs,” he says.

The word “library” is itself a metaphor of sorts; in your mind’s eye, you see books on shelves. Imagine, instead, plastic vials stacked in sub-zero freezers. And in place of Dewey Decimal numbers, think barcodes. The coded compounds are shipped in dry ice, usually from commercial suppliers like San Diego-based ChemBridge or Exquiron in Switzerland, at a cost of about $2 per 100 microliters (roughly four drops). If that sounds expensive, realize that thousands of experiments can be done with those few precious drops — a feat made possible by robots.

“No only do the robots work fast, they also work small,” says Allen. “They can pick up tiny volumes of liquid that a human with a handheld tool just cannot get.”

By using “high-throughput screening” (rapid-fire robotic testing of compounds in big batches), researchers greatly increase their odds of getting a “hit” — a reaction showing chemical activity that might stop a tumor or kill a virus. This is where the needle-in-a-haystack metaphor comes in — or, as Fox likes to say, a needle in lots and lots of haystacks. Researchers in fields as diverse as pharmaceutical science, veterinary medicine and environmental toxicology come here to screen compounds for treating melanoma and glioblastoma, identifying environmental carcinogens, inhibiting cancer cell growth and other urgent areas of investigation.

Unique to the OTRADI library is the Oregon Collection — compounds created by individual Oregon chemists. One of those chemists is OSU emeritus professor Jim White. “He was at Oregon State for 30-some years,” Fox reports. “We went to talk to him in his cold room, and there were thousands and thousands of chemicals he had made in his lab.” One of those frozen liquids might hold the building blocks of a new antibiotic or anticancer agent. With a bit of cataloging, White’s chemicals will one day join other OTRADI compounds, which include thousands from natural products discovered by OSU medicinal chemists in remote and exotic spots such as tropical reefs and “blackwater” ecosystems.