Crafting tumor-killing viruses

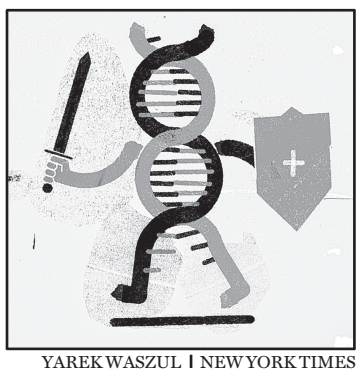
Researchers close to achieving new cancer weapon

The Hypothesis

Viruses can be designed to attack tumors.

The Investigators

Dr. Robert Martuza, Harvard Medical School; Dr. Bernard Roizman, University of Chicago; Dr. Ian Mohr, New York University.



YAREK WASZUL | NEW YORK TIMES

Rachel Nuwer
New York Times

In 1951, a 4-year-old boy with leukemia contracted chickenpox. His liver and spleen, swollen by the cancer, soon returned to normal, and his elevated blood cell count fell to that of a healthy child.

His doctors at the Laboratory of Experimental Oncology in San Francisco were thrilled by his sudden remission, but the blessing was short-lived. After one month, his leukemia returned and progressed rapidly until the child's death.

In the early 1900s, not much could be done for cancer patients. Unless surgeons could excise a tumor, the disease typically spelled a swift and inevitable end. But in dozens of published cases over the years, doctors noticed a peculiar trend: Struggling cancer patients sometimes enjoyed a brief reprieve from their malignancies when they caught a viral infection.

It was not a coincidence. Common viruses sometimes attack tumor cells, researchers discovered. For decades, they tried to harness this phenomenon, to transform it into a cancer treatment. Now, after a long string of failures, they are nearing success with viruses engineered to kill cancer.

"It's a very exciting time," said Dr. Robert Martuza, chief neurosurgeon at the Massachusetts General Hospital and professor of neuroscience at Harvard Medical School. "I think it will work out in some tumor, with some virus." Candidates are already in advanced trials, he noted.

Cancer cells are able to replicate wildly, but there's a trade-off: They cannot ward off infection as effectively as healthy cells. So scientists have been looking for ways to create viruses that are too weak to damage healthy cells yet strong enough to invade and destroy tumor cells. It has been a long, difficult challenge.

Researchers started down this road in 1904, when they discovered that women with cervical cancer temporarily recovered when given a rabies vaccination.

By midcentury, physicians were administering live viruses to cancer patients. They tried infecting terminally ill children with polio and adenovirus. They injected patients with concoctions from the feces of normal children, from sick chickens, and from "feline spleen suspension" of rural kittens infected with "cat plague."

These experiments proved ill-fated. The cancer returned, or — in the worst cases — the injections themselves caused "the development of lethal infection in the host," according to a 1964 American Journal of Pathology report.

The field was abandoned for a time. But in 1991, Martuza seized upon the idea of using the herpes simplex virus, or HSV-1, as a cancer-fighter.

The genome of HSV-1 is comparatively large and can accommodate a number of mutations and deletions. Martuza weakened the virus by removing some of its genes. The modified virus was injected into mice with brain cancer, and it did bring about remission. But most of the mice died of encephalitis.

In 1990, Bernard Roizman, a virologist at the University of Chicago, found a "master gene" in the herpes virus. When this gene is removed, the virus no longer has the strength to overcome healthy cells' defenses. As it turned out, the modified virus was so crippled that it could only slow tumor growth.

Then, in 1996, Dr. Ian Mohr, a virologist at New York University, stumbled on a way of further altering Roizman's crippled virus. He exposed it repeatedly to cancer cells until a new viral mutant evolved with the ability to replicate in those cells.

An engineered form of vaccinia — the viral agent that helped eradicate smallpox — is being tested against advanced liver cancer, the third leading cause of cancer deaths globally. In a recent trial, survival for patients treated with high doses of the virus, called JX-594, doubled to 14 months from 7, compared with that of patients treated with low doses.

"To see that kind of response in a randomized trial is simply unheard of," said Tony Reid, the director of clinical investigation at the Moores Cancer Center of the University of California, San Diego, who has no financial ties to the virus's manufacturer.

A herpes virus based on Mohr's original discovery is in advanced trials against melanoma; initial data showed a 26 percent response rate in patient regression and survival. A reovirus is being tested against head and neck cancers, often difficult to treat.

According to the researchers, the side effects of treatment with these viruses are minimal, and include nausea, fatigue and aches. "In comparison to what happens with standard chemotherapy, flu-like symptoms are very manageable," said Reid, who has treated hundreds of patients with oncolytic viruses.

NOISE

from E1

Healing power of quiet

On the ninth floor, a pre- and post-op floor for transplant patients, noise-reduction efforts consisted of adding a TV channel that plays white-noise tracks.

Vidal and her staff also passed out comfort kits containing earplugs and eye masks to help battle the "unavoidable noise," a practice that has since gained popularity throughout UH, says Kimberly Kotora, director of critical care.

In 2011, the fifth floor ranked in the bottom 1 percent of over 1,700 hospitals surveyed nationwide for noise in the Hospital Consumer Assessment of Healthcare Providers and Systems, or HCAHPS, a standardized government survey.

"Here we were providing this level of care and [the patients' surveys were] telling us they're not feeling that care," says Vidal.

The Centers for Medicare & Medicaid Services looks at hospitals' HCAHPS survey scores as part of an equation to determine the hospitals' Medicare reimbursement, says Adam Beach, a senior clinical data analyst at UH.

If scores did not improve, Vidal says, UH risked losing millions of dollars.

"We couldn't afford not to do it," says Vidal, who credits the HCAHPS survey for making patient comfort a priority and thus encouraging UH to provide more funding to improve the patient environment.

Lerner Tower, like many hospitals, was built before awareness about noise in hospitals began to affect the facilities' designs, says Vidal. The cardiac-care floors have the added challenge of housing patients whose conditions require noisy machines to monitor their health.

"Whenever you have people and equipment moving, it's going to be impossible to eliminate all noise," says Vidal. "We needed to give our patients these amenities to help with that."

Installing the noise-reduction tiles on the fifth and seventh floors cost just under $10,000. The change, says Vidal, was "night and day."

"I expected there to be a difference, but I think I was surprised by how much of a difference," says Vidal. "I was surprised to see how much the staff has responded and actually changed their behaviors with lowering their voices. Nurses say they don't feel as though they're competing with the noise anymore."

The decrease in noise was measurable after the tiles were installed, says Melissa Braskie, a safety supervisor at UH.

Braskie analyzed the noise levels on the seventh floor on two separate occasions, before and after the tiles were installed. She had a noise dosimeter placed near the main nurses station — considered one of the loudest areas — over a period of several workdays.

"It's going from the sound of a vacuum cleaner to somebody just talking," says Braskie, who was asked by Vidal to monitor noise levels, after conducting a similar study at UH's Lakeside Hospital for a master's project at the University of Toledo.

After the noise-reduction efforts, 56 percent of patients on the fifth floor — almost twice as many as before — rated the area around their room as "always" quiet at night.

The floor has shown a significant improvement in patients' perception of noise and now ranks in the 43rd percentile in the HCAHPS survey of hospitals.

Kotora says they recognize, "There's still a lot more work to do."

In a 2005 study, James West, a professor at Johns Hopkins University's Whiting School of Engineering, and a team of acoustical engineers brought to light the challenges hospitals face in controlling noise. That study showed that, internationally, noise levels have grown steadily over the past five decades.

"A hospital is just a big bathroom, a room without absorbing materials," says West, who believes hospitals often shy away from addressing the problem of noise because of the cost.

"You have metal clanking on metal, motors running, you have support systems for medical equipment and each one of these contributes to noise, and it keeps building and building and building. Some nurses tell me if they have anything to think about that they just go to the bathroom because it's quieter than the ward."

Increasingly, others are proving that noise is not just a nuisance, but a risk to patients' health.

In 2011, UMass Memorial Medical Center made headlines when, for the second time in four years, reports surfaced that a patient may have died due to what is referred to as alarm fatigue. The Massachusetts Department of Public Health cited various violations by the hospital, including failure to respond to alarms "in a timely manner" in the case of a 60-year-old male patient who, according to state investigators, showed signs of potential respiratory failure and a fast heart rate before his death in August 2010.

A recent study out of the University of Illinois at Chicago showed that millions of prescription errors were made each year because of similar-sounding names of medications being confused in a noisy environment.

Another study from the University of Minnesota in 1976 found that it took patients significantly longer to recover from cataract surgery when construction noise was present.

Wendy Miano, chief nursing officer at UH Seidman Cancer Center, says because Vidal was able to improve patient-satisfaction scores in a cost-effective manner, hospital committees may look to implement her initiatives campus-wide.

"She's taking the space that we have to work with, and hopefully with some very simple interventions, is going to change the standard of practice across campus. I think it is extremely influential work," says Miano. "Just by virtue of that leadership, she is reminding staff to create a more healing space."

Ultimately, Vidal says, she wants to see patient satisfaction on all floors in Lerner Tower ranking in the top 50 percent nationwide. The tiles, she says, can cover only so much; the culture around noise must change as well.

"We can't say, 'It's a hospital — of course it's noisy,' " says Vidal. "Nobody would ever make noise in a library and say, 'Oh, it's a library.' "

"We need to get to that level where everybody walks into a hospital and uses their hospital voice."

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FAMILY

from E1

Health center plans to open third office

Patients will have the option of using the new location or Neighborhood Family Practice's other offices, a few miles away, at 3569 Ridge Road and 2358 Professor Ave.

"We are thrilled to provide additional access to high–quality primary care on the West Side," said Jean Polster, executive director of Neighborhood Family Practice.

"We really believe people should have health care near where they live. And transportation is a big issue for many of our patients."

All three locations are accepting new patients and all types of insurance, including Medicaid and Medicare. Those without insurance pay on a sliding scale, based on income.

The health center provides primary care for people of all ages as well as family planning, discounted prescription drugs, lab testing, mental health services for existing patients and other services including management of diabetes, heart disease and asthma.

The center strives to be a medical home for its patients, providing regular and accessible primary health care as well as same-day appointments. It expects to serve more than 14,000 people this year.

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HEALTH LETTERS

The culprits behind cavities

I am responding to the article "New tools to make your dentist smile," (July 31). I assist the dentists in a pediatric practice. In the last few years, I have seen a trend of more decay in children. Some of these children have been coming to us for years.

I started asking the parents what they have been eating. Many have stated that the children do not eat much candy, no pop, and watered-down fruit juices. The culprit in all these cases was "hot chips"! The way the flavoring stays on the potato chips is [with] corn syrup, and [an] ingredient used to make them hot is an acid! Put those together and you have a cavity waiting to happen

Patricia Forkapa
Cleveland

I drank very little pop, but still had a problem with cavities, in my late 40s. My dentist recommended using xylitol instead of sugar to sweeten foods and beverages. It can be purchased in packets or bags, just like sugar. It might also be effective to use gum or mints sweetened with xylitol. It works by "jamming" the bacteria in your mouth, and preventing them from excreting acid onto your teeth.

cantrmmbr64
posted on cleveland.com

Bad teeth and expanding waistlines.

Get with it parents, dental repairs are costly.

weezel
posted on cleveland.com

Stem cells and brain disease

Thank you for the article about iPSC (induced pluripotent stem cells) that are being used for research in studies for brain diseases such as Parkinson's and Huntington's ("Stem cells key in brain-disease studies," July 24). Your article helps the public to know that this type of stem cells from adult skin or blood has indeed brought great hope and answers for numerous diseases, not only Parkinson's and Huntington's.

And, as the article stated, they are not "controversial" because no one had to lose their life so someone else could live.

Carolee Zentkovich
Columbia Station

Letters regarding stories in the Health section can be sent to healthletters@plaind.com or mailed to: Health Editor, The Plain Dealer, 1801 Superior Ave., Cleveland, OH 44114. Letters may be edited for length and clarity.

TOWNSEND

from E1

Weighing clues to women's health

As far as the heart-disease risk, previous findings suggested that genetics affected the uterus and the type of environment it provides a growing fetus.

But rather than genetics, in the case of small babies, the researchers in the latest study think that the mother's placenta was deficient in growth factors related to the development of blood vessels and the repair of coronary circulation. Those deficiencies, they think, could negatively affect a woman's cardiovascular system and increase her chance of developing heart disease decades later.

The issues surrounding cancer risk might not be as complex. Lowering the risk might be as simple as a woman figuring out the best way to control her weight.

The most common reason that a woman has a big baby is because she happens to be a big person, said Dr. Patrick Catalano, who heads the department of obstetrics and gynecology at MetroHealth Medical Center.

Previous studies have established that obese women produce more estrogen than do women who weigh less. In 2002, the National Institute of Environmental Health Sciences added estrogen, in the form of hormone-replacement therapy and oral contraceptives, to its list of "known" human carcinogens.

But the role of estrogen as either a risk factor or as an aid in preventing various types of cancer continues to be studied.

"For an obese woman, it's certainly in her good health to try and get her weight down through good lifestyle intervention," he said.

An average-weight woman who eats too little or two much during pregnancy can certainly increase her risk of a smaller or larger baby, respectively, he said.

In commenting on the research on elevated breast cancer risk, Catalano said certain factors such as breast-feeding (a nursing woman burns twice as many calories when she is breast-feeding than when she isn't), and eating more fresh fruits and vegetables, may help lower a woman's risk of breast cancer by assisting in weight loss.

"There's a lot more dots that [the researchers] need to connect," said Catalano, adding, "This brings up a very interesting question that needs more study. We need to look at more of the factors related to the [elevated risk]."

New research, which the team has already begun, is trying to answer the question of whether using the information about the weight of her firstborn will improve physicians' ability to predict a woman's risk of future disease.

"We think it's possible, maybe likely," Bukowski said. "But until it's tested, we won't know." Results of that research are several months away, he said.

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STRETCH

from E1

Cycling around the velodrome

When I arrived, workers were still painting the blue, nearly flat rim at the bottom of the track. One day soon, the facility in Cleveland's North Broadway neighborhood could also receive a dome, enabling it to be used year-round. Beyond that, if the long-term plan comes to fruition, the site off East 55th Street would include an athletic field and numerous other amenities.

Adding to the fear factor as I went around the track was the nature of the bike itself. For track bikes aren't like the road, mountain or even time-trial bikes I'm used to riding.

First off, they're fixed-gear, meaning there are no gears to switch. The crank stem, the piece that connects the pedal to the bike, is also shorter, to prevent scraping the ground as you climb a bank or lean into a turn.

More daunting, though, is the bike's lack of brakes. To stop, your only options are to mash down hard on the pedals, using the your strength and body weight to physically stop the pedals from turning, or somehow get a foot on the ground. But that can be tricky or impossible if your shoes are strapped tightly into toe cages or clipped to the pedals.

Still, in my experience, confidence came quickly. Moments after my nervous beginning, I was blissfully blazing around the track, loving the lack of hills and gaining senses of when and how to apply speed, how to hew to the most efficient route, and when to start braking for a smooth descent and stop. My first time down, I very nearly ran out of space and almost ran right back up the track.

Have I mentioned yet what great exercise all this was? I have no idea how many calories I burned or how far I traveled, but I know for sure my heart rate spiked and my legs were in near constant overdrive through bouts of pure anaerobic intensity. It was like every sprint I've ever done compressed into a single ride.

Not that it needed to be so furious. Plenty of track cycling events require aerobic endurance, as competitors seek to sustain a pace over a certain number of laps or a given distance.

Just my thing, in other words. I don't know if I have what it takes to be a track racer, but I've definitely got the drive to be a track rider. Now, happily, the rest of Northeast Ohio and I also have the means.

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WHAT NEXT?

Have a suggestion for an activity you think I should try? Call me at 216-999-4632 or send me an e-mail.