Scientists solve mystery of a surprising drug response

Dana-Farber doctors treating Grace Silva for a lethal type of thyroid cancer were stunned when a drug they tried caused her tumor to “melt away” for 18 months. This was an unheard-of and mystifying reprieve in someone with anaplastic thyroid cancer.

The explanation came only after a team of scientists from Dana-Farber and the Broad Institute of MIT and Harvard made a thorough search of her tumor’s DNA.

Led by Jochen Lorch, MD, and Nikhil Wagle, MD, the researchers discovered the reason for Silva’s dramatic turnaround – a single DNA mutation in the tumor cells that made them highly vulnerable to the drug, known as everolimus or Afinitor. This previously unknown mutation – an error in the DNA code – made all the difference to Silva, who was 57 when diagnosed with the cancer in 2010, and who remains a survivor today.

The scientists reported in the Oct. 9 issue of the New England Journal of Medicine that in addition to the DNA mutation that prolonged her survival, they found another mutation that enabled the tumor to become resistant to the drug after 18 months and start to grow again.

The single case study illustrates how repeatedly sequencing a patient’s cancer DNA – first prior to treatment and again when the tumor shows signs of resistance – can identify unsuspected response and resistance mutations that may help guide treatment of other patients.

Mystery, page 4

Chemo day is dress-up day for resilient breast cancer patient

Cancer treatment is never fun, but Cheryl St. Onge figures if she has to go through it, she’s doing it with style – and smiles.

Each time the breast cancer patient arrives at Dana-Farber/Brigham and Women’s Cancer Center at Milford Regional Medical Center for her infusion visit, she wears a different themed outfit. One time she was a cowgirl with boots, hat, and a fringed vest; another time she came ready for a Hawaiian luau with the appropriate loud shirt and lei. Last month she was a nurse in scrubs.

The wardrobes are kept a secret from her caregivers and fellow patients, leading to much speculation as her visits near. Sometimes she dreams it up herself. In all cases, the ritual brings excitement and a lighter atmosphere to a place where both are welcomed.

“It started when I came in for my first infusion,” explains St. Onge, 58, a middle school assistant principal in Worcester, Mass. “I don’t want to make light of cancer, but I knew I couldn’t go through 17 infusions and not do something to change my attitude about them.”

That’s when St. Onge asked her nurse, Janet Rogers, RN, BSN, whether patients name their IV poles. Rogers said some do, and St. Onge dubbed her new IV pole “Rita.”

“I like to have a margarita now and then, so I figured this would be my margarita for the next year,” St. Onge says with a laugh.

Carrying this theme, St. Onge came in three weeks later with a margarita glass filled with Gatorade and a sombrero to honor Rita.

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So began the ritual. On “Cowboy Day,” there is a sea of pink took over the field at Gillette Stadium before the New England Patriots game against the Cincinnati Bengals on Oct. 5, when more than 100 breast cancer patients and survivors joined their caregivers for an emotional celebration of National Breast Cancer Awareness Month.

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This is like a coming out for me because I never wanted to say, “I have breast cancer,” said Julie Tympanick, an honoree who was diagnosed in 2011 and treated at the Susan F. Smith Center for Women’s Cancers at Dana-Farber. Adds Mary Gualterney, a single mom who called her daughter, Becca, her “rock” during treatment: “I am so proud to represent survivors tonight.” The women, decked out in pink Patriots t-shirts, formed a human awareness ribbon on the field.

Dress-up day, page 4
Matthew Meyerson receives American Cancer Society professorship

Matthew Meyerson, MD, PhD, of Medical Oncology, has been awarded an American Cancer Society (ACS) Research Professorship, the most prestigious national research grant given by the ACS. The grant, which runs for five years with the possibility of a five-year renewal, provides unrestricted funding to Meyerson’s group, supporting new and creative initiatives.

ACS Research Professorships provide flexible funding for full-time, mid-career cancer investigators who have made seminal contributions to cancer research and who will continue to provide leadership in their research area. Ordinarily, no more than two research professors are appointed in a year, and only 25 researchers nationwide hold the title at one time.

Danny Johnson honored with quarterly DAISY Award

Danny Johnson, RN, Adult Ambulatory Services on Tavkey 2, was recognized with a DAISY Award, a quarterly honor given to an extraordinary member of the nursing department.

“We’re the first ones many of the patients see as they come through the door at Dana-Farber,” says Johnson of his role drawing blood and inserting IVs for patients in laboratories. “This award is justification for doing what I genuinely love to do. It’s nice, and surprising, to be recognized.”

Dana-Farber is one of approximately 1,500 hospitals that participate in the DAISY Award program. The DAISY Foundation (Diseases Attacking the Immune System) established the award in memory of J. Patrick Barnes, whose parents created the foundation in Patrick’s memory after experiencing firsthand the skills, care, and compassion of nurses.

As health care changes, so does the job of assisting patients

If there is any trend in health care that Dana-Farber’s financial counselors, resource specialists, and pharmacy resource specialists haven’t encountered, it must be trivial indeed.

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Every change brings potential complications and questions about patients’ health insurance coverage, eligibility to be treated at Dana-Farber, qualifications for assistance programs, and more. As experts in guiding people through the health care maze, financial counselors and resource specialists have first-hand knowledge of how recent changes are affecting patients and their families.

“Insurance payers are redesigning their coverage plans – with networks that restrict where patients may receive care – and there have been changes in health care law at both the federal and state levels,” says Lisa Quashie, supervisor for financial counselors. “It’s our job to explain these changes to patients.”

As insurance rules change and costs rise, the demand for financial counselors’ services increases, says Raquel Gajonera, manager of Access Management. “In addition to helping patients apply for coverage and understand the provisions of their policies, counselors serve as referral specialists – helping patients identify and contact organizations that offer financial assistance.”

Of laws and markets

Some of these changes are the result of federal legislation, particularly the Affordable Care Act of 2010; others stem from state legislation, such as Massachusetts’ landmark health care reform law of 2006, and the creation of tiered and other restricted plans. Increased competition among health care providers and a push toward Accountable Care Organizations, which seek to improve care and lower costs by enrolling patients in networks of doctors and hospitals, also contribute.

Massachusetts recently instituted new rules guiding applications for state financial assistance. In the past, patients had to go into a hospital or community health center to apply, but the new rules allow patients to apply on their own. Though intended to make patients’ lives easier, the rules have often had the opposite effect. Gajonera explains: “Many of our patients are 65 or older and may not be computer-savvy. Some have difficulty navigating the site. The application process is lengthy and many find it stressful, but under the rules, we’re limited in what we can do for them.”

Lightening the load

Pharmacy resource specialists, who help patients find financial assistance for medication and other treatment-related expenses, have had to be especially agile. “We’ve seen health insurance plans become less comprehensive, resulting in higher deductibles and increased co-payments for patients,” says Darlene Holland, LSW, a senior pharmacy resource specialist. “This cost-shifting can have a major and unexpected impact on people’s ability to pay for their medications.”

“In addition to helping patients apply for coverage and understand the provisions of their policies, counselors serve as referral specialists.”

— Raquel Gajonera

Out-of-pocket expenses. We work closely with patients to identify groups and organizations that can provide assistance.

Perhaps the most disruptive recent event was the breakdown of the Massachusetts online health insurance site, the Health Connector, which affected thousands of residents who intended to sign up for insurance.

“If the site was taken down, people have had to enroll using paper applications,” explains Joe Chabot, pediatric resource program manager. “The processing of applications fell behind for tens of thousands of people.” In one sense, the failure of the website made matters easier in the short term: virtually all qualifying applicants were automatically enrolled in temporary insurance plans through MassHealth. Helping patients to complete these applications is just one of many areas where resource specialists and financial counselors can be of help to patients. Officials expect the refurbished Health Connector site to be up later this fall. Our counselors and specialists will be ready.

GIVE BLOOD OR PLATELETS IN OCTOBER

Get a treat (never a trick)

Donate blood or platelets at the Kraft Family Blood Donor Center any time in October and you’ll get a fun Halloween-themed T-shirt.

To schedule an appointment, please email BloodDonor@partners.org with two choices of appointment time or call the Kraft Center at 617-632-3206. Thank you for helping our patients in need.

Inside the Institute is published by the Dana-Farber Communications Department for staff members and friends of Dana-Farber Cancer Institute. The next issue is scheduled for November, 2014.

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The statistics on retinoblastoma – a cancer of the retina of the eye that often appears before age five – in Guatemala jarring Nitin Shrivastava while working in the country after college. In the region around the capital, Guatemala City, more than 60 percent of children diagnosed with the cancer survived it. In the rest of the country, less than 40 percent did.

The disparity has little to do with the availability of resources or medical know-how – the national pediatric cancer hospital has the expertise and technology to treat retinoblastoma successfully. Rather, he found, it results from inadequate early-diagnosis efforts outside the capital area, and a lack of coordination between rural doctors and specialists at the central hospital.

Shrivastava traveled to Guatemala seven times as a student at Tufts University and worked there full time the year following college, helping with public health projects for a non-governmental organization (NGO).

Early this year, he came across an online interview with Dana-Farber’s Paola Friedrich-Medina, MD, in which she discussed her research in pediatric sarcomas in Central America and the challenges of treating non-communicable diseases in developing countries. He sent her an email introducing himself and mentioning his interest in cancer-related work in Guatemala. They arranged to meet.

“Nitin was very calm, but very passionate about what he wanted to accomplish,” Friedrich-Medina recalls. Their discussions pointed Shrivastava toward a summer-long project on retinoblastoma. Working with two NGOs, he created a standard protocol for examining young children for early signs of the disease.

“An exam known as the red reflex test allows doctors to detect leukocoria, a white reflection on the retina that can be an early sign of retinoblastoma,” Shrivastava explains. “When retinoblastoma is caught early, it is almost always curable so we worked to disseminate information about the test – and the need to refer patients to test positive to specialists – throughout the country.” He made a video demonstrating the test and explaining how to interpret the results.

Shrivastava also worked to streamline the process by which children identified as having early stages of retinoblastoma are referred to specialists at the Unidad Nacional de Oncologia Peditraria (UNOP), the national children’s cancer hospital in Guatemala City. “The standard protocol is for such children to be referred to a regional hospital, then to a national hospital, and finally to the UNOP,” Shrivastava remarks. “At each step there can be a delay of weeks or months, during which the disease can progress and the prognosis worsen.” With help from the NGOs, he established a link between rural and suburban physicians and the UNOP. “Doctors now have a direct telephone line to the UNOP. They can schedule appointments for patients the next week.”

“Those of us who have worked in developing countries often talk about the barriers to better treatment for children with cancer,” Friedrich-Medina remarks. “Nitin knew from experience that those barriers are often cultural and societal. He focused on an issue – the need for faster referrals – that we had identified as crucial to improving outcomes for these patients.”

Research led by Carlos Rodriguez-Galindo, MD, Global Health Initiative Director at Dana-Farber/ Boston Children’s Cancer and Blood Disorders Center, had shown that referrals for retinoblastoma treatment were particularly rare in provinces with dense Mayan populations so these were the regions Shrivastava focused on.

“We have an opportunity to cure children of a disease that, if treatment is delayed, can be devastating,” Shrivastava remarks. “The project shows what can be achieved by partnering with local organizations that have the connections and local knowledge to get things done.”

Dana-Farber again named a leader in LGBT health care equality

Since 2010, Dana-Farber Cancer Institute has been recognized as a “Leader in LGBT Healthcare Equality” by the Human Rights Campaign (HRC) Foundation, the educational arm of the country’s largest lesbian, gay, bisexual, and transgender (LGBT) civil rights organization.

Anna Trask, senior director, Human Resources, notes, “We are proud of our commitment to provide high-quality care for all patients and in maintaining a progressive workplace that is welcoming to all.” Dana-Farber was one of a select group of 426 health care facilities nationwide to be named Leaders in LGBT Healthcare Equality, earning top marks again this year in meeting non-discrimination and training criteria that demonstrate its commitment to equitable, inclusive care for LGBT patients and their families, who can face significant challenges in securing the quality health care and respect they deserve.

Julianna Coricchio, administrative support associate for John Quackenbush, PhD, who led efforts to submit the application again this year, says, “We had been looking for years for a way to quantify LGBT health care issues. The HRC gave us the tools to offer a more culturally-balanced approach to health care here at DFCI!”

In an art studio in his Roslindale home, Bernard Manning, colored pencils in hand, sketched a baby penguin carrying a tree home on a winter day as snowflakes fell on their Santa hats. Bernard’s friends and family convinced him to submit the drawing for the Dana-Farber and the Jimmy-Fund 2014 Holiday Collection. He was hesitant, but sent the design in to be used for the holiday greeting cards collection. Even with four years of card designing experience, he is “his own worst critic.” When he received the news that it was accepted, he was surprised, but excited.

Bernard’s design is one of 15 in the card collection, all created by New England artists and photographers. The holiday collection also offers candles, ornaments, jewelry, and other locally-made gifts, including the limited-edition North Star bangle, designed exclusively for the Dana-Farber Holiday Collection by Alex and Ani.

For Bernard, Dana-Farber means more than a way to share his love for art. Diagnosed with a brain tumor at age 18, he had surgery to remove the tumor and received chemotherapy at the Jimmy Fund Clinic for two years. Now, the 29-year-old works with the Institute to promote skin cancer awareness, and also volunteers to help sell the card collections during the holiday season. He has been deemed one of the best salespeople by the volunteer program, and has become a familiar face to many doctors and nurses at the Institute. Bernard is the only patient to contribute to this year’s collection. “It’s nice to do something for a good cause, and reach a lot of people,” he says. “Hopefully people think, ‘Oh, that’s cute, I should send that out for Christmas.’”

The collection is available in the Friends’ Corner Gift Shop, online and in local stores, including The Paper Store, Stop & Shop, The Crafty Yankee, Cooper Jewelers, Christmas Dove, Lux Bond and Green locations in Massachusetts, Terrazza, Big Picture Framing, and photo cards by LookLoveSend. The North Star bangle is available through The Paper Store locations and in the Friends’ Corner Gift Shop. For more information, or to view the collection, visit www.dana-farberholiday.org.

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Four Dana-Farber win major NIH research awards

Four Dana-Farber scientists have received special funding awards from the National Institutes of Health (NIH) – three of them designed to support “High Risk – High Reward” research, and another award provided by NIH’s new “Big Data to Knowledge” program.

In an announcement made Monday, Oct. 6, Carl Novina, MD, PhD, was named one of 10 scientists chosen to receive a 2014 National Institutes of Health Pioneer Award, which funds “inherently risky” research “that could potentially create or challenge existing paradigms.” His award totals $4.9 million in total costs over five years. Novina’s proposal involves developing a “next-generation” form of gene modification aimed initially at treating sickle cell anemia. Novina believes the technique, called “epigenetic reprogramming,” may be “the next frontier” in gene therapy and could be used in cancer, neurological disorders, and autoimmune diseases.

Alexander Gimelbrant, PhD, of Cancer Biology, is one of eight recipients of a Transformative Research Award, which funds “inherently risky” research “that could potentially create or challenge existing paradigms.” His award totals $4.9 million in total costs over five years. Gimelbrant’s proposal focuses on a recently discovered epigenetic mechanism leading to differences between similar cells via independent regulation of the two copies of genes – one from the father and one from the mother. These differences are thought to contribute to tumor initiation and drug resistance. Gimelbrant and his group are building tools needed to control and eventually reverse these epigenetic changes.

Cigall Kadoch, PhD, of Pediatric Oncology, was selected for a New Innovator Award, supporting young investigators in pursuing “unusually innovative research.” Kadoch, who joined the DFCI faculty earlier this year, discovered that more than 20 percent of cancers have mutations in a group of genes that encode a “chromatin remodeling complex” and which appear to drive their growth. With the award of $2.5 million over five years, Kadoch and her research group will create tools to study how mutated complexes drive cancer and ultimately develop treatments that target these faulty complexes.

In a separate NIH announcement on Thursday, Oct. 9, Dan Landau, MD, PhD, was selected to receive a training award from NIH’s new Big Data to Knowledge (BD2K) initiative, which is supporting research in how to best use complex biomedical data sets produced by genomics technologies.

Landau, a member of the laboratory of Catherine Wu, MD, will receive more than $900,000 in funding to investigate the role of a mechanism called “disordered epigenetic patterning” in the evolution of more aggressive and drug-resistant forms of chronic lymphocytic leukemia.

Dress-up day, continued from page 1

were bandanas and sheriff’s badges for Rogers, Rita, and St. Onge’s oncologist, Natalie Sinclair, MD. When it was “Hawaiian Luau Day,” St. Onge wore the requisite loud shirt, attached a fake parrot to Rita, and everybody got leis. Rita, who has bandanas and sheriff’s badges for Rogers, Rita, and St. Onge’s oncologist, Natalie Sinclair, MD. When it was “Hawaiian Luau Day,” St. Onge wore the requisite loud shirt, attached a fake parrot to Rita, and everybody got leis. Rita

Novina, a member of the Department of Cancer Immunology and AIDS, will receive $4,325,000 in total costs over five years. His proposal involves developing a “next-generation” form of gene modification aimed initially at treating sickle cell anemia. Novina believes the technique, called “epigenetic reprogramming,” may be “the next frontier” in gene therapy and could be used in cancer, neurological disorders, and autoimmune diseases.

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Mystery, continued from page 1

“This is personalized, precision medicine at its best,” says Lorch, a thyroid cancer specialist at Dana-Farber/Brigham and Women’s Cancer Center’s Head and Neck Treatment Center and senior author of the report.

Having identified the mutation – in a gene called TSC2 – that caused Silva’s dramatic response to everolimus, researchers at Dana-Farber have opened a clinical trial to test the drug’s effectiveness in other cancer patients with TSC2 mutations. This type of trial, sometimes called a “basket” trial, is becoming more common as studies of patients who are “exceptional responders” are revealing previously unknown response mutations to a variety of drugs. A basket trial pools patients with a particular response mutation, regardless of the type of cancer they have.

“The study of patients with extraordinary responses can yield critically important insights,” explains Wagle, first author of the report. “These studies could help us develop methods for matching patients to drugs, highlight effective uses for otherwise ‘failed’ therapies, and design new therapeutic strategies to fight cancer.”

Wagle is an oncologist at Dana-Farber and is also affiliated with Brigham and Women’s Hospital.

Everolimus, sold as Afinitor, is approved to treat tumors associated with Tuberosis Sclerosis Complex (TSC), a rare genetic disorder caused by mutations in TSC1 and TSC2 genes. It is also approved for use in brain tumors, pancreatic cancer, kidney cancer and advanced breast cancer. Everolimus targets a protein kinase, mTOR, that is overactive in some cancers.

TSC2 normally suppresses mTOR activity; when it is mutated, mTOR is overactivated, making it a prime target for everolimus. None of the other anaplastic thyroid cancer patients who Lorch treated with everolimus in a small clinical trial had the same mutation as Silva, which explains why they didn’t benefit from the drug.

Specimens taken from Silva’s tumor after it grew again revealed a mutation in the TSC2 gene – that caused Silva’s dramatic response to everolimus, researchers at Dana-Farber have opened a clinical trial to test the drug’s effectiveness in other cancer patients with TSC2 mutations. This type of trial, sometimes called a “basket” trial, is becoming more common as studies of patients who are “exceptional responders” are revealing previously unknown response mutations to a variety of drugs. A basket trial pools patients with a particular response mutation, regardless of the type of cancer they have.

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Specimens taken from Silva’s tumor after it grew again revealed a mutation in the mTOR protein – a mutation that wasn’t present in the original tumor – that blocked everolimus from binding to it. This mutation explained how the cancer acquired resistance to the drug.

But that was not the end of the story. Laboratory experiments demonstrated that even the mutated, resistant cancer cells remained sensitive to a different type of mTOR inhibitor. A new drug of this type is about to enter clinical trials, and Silva is in line to receive the treatment, Lorch says.

Compliance Tip

Do you know how to report a compliance violation?

Compliance violations include violations or suspected violations of law, ethics, or DFC policy. Everyone working for, or representing, Dana-Farber is expected to report any concerns or violations. There are several ways to report a violation. Feel free to use the one you feel most comfortable with. A thorough investigation will occur.

• Talk to your supervisor.
• Call the compliance hotline at 800-451-0659. The hotline is managed by NAVEX Global and is available 24 hours a day. Reporters have the option to remain anonymous.
• Use the online reporting tool at www.dana-farber.alertline.com.
• Contact Dana-Farber’s compliance officer directly. Kelly Maxwell, Esq, can be reached at 617-632-5402 or via email at kelly_maxwell@dfci.harvard.edu.

Compliance is everyone’s responsibility. If you see something, say something!