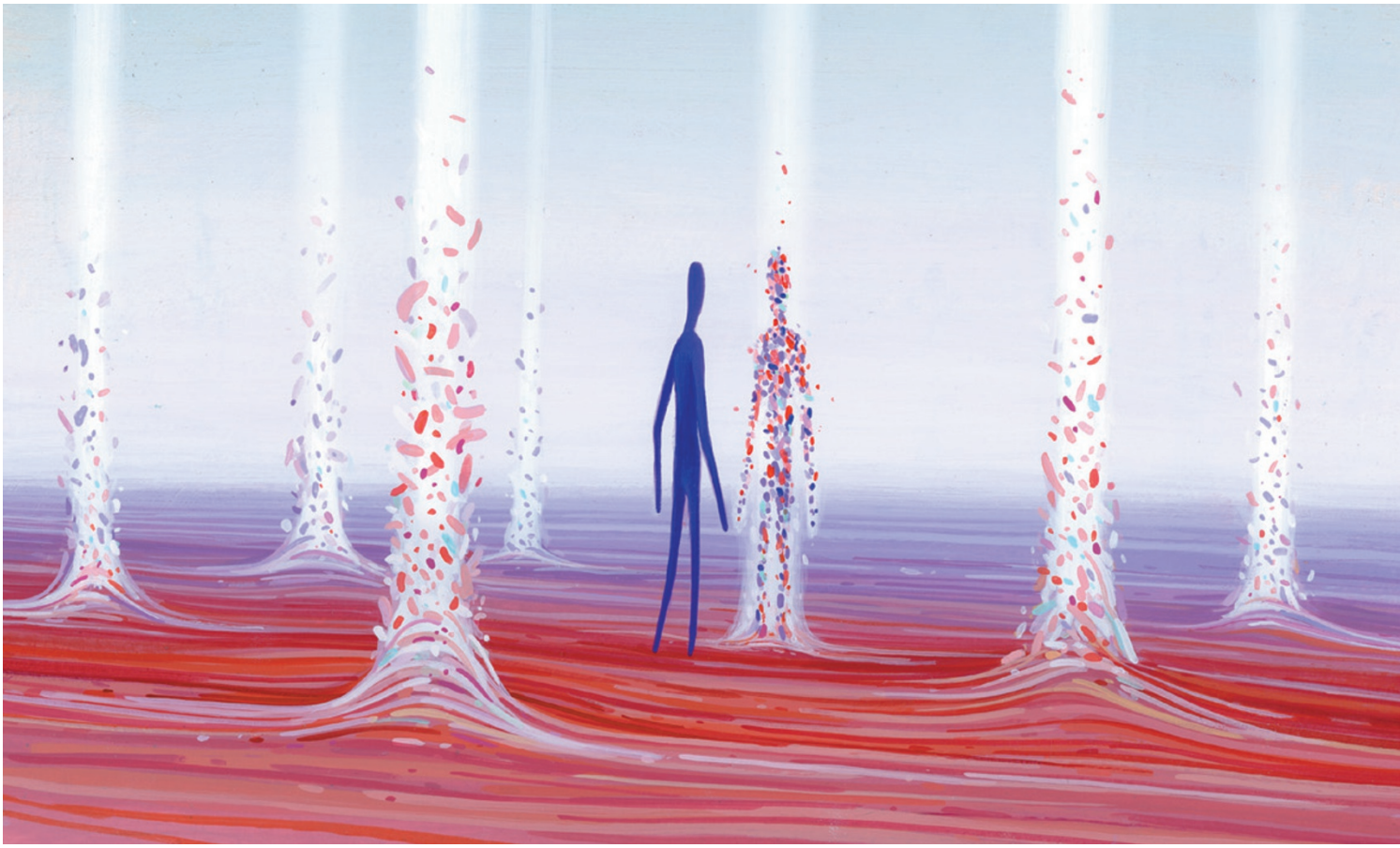


BRENDAN MONROE

THERAPY

This time it's personal

Tailoring cancer treatment to individual and evolving tumours is the way of the future, but scientists are still hashing out the details.

BY LAUREN GRAVITZ

Elaine Mardis and her colleagues first encountered 39-year-old Lucy (not her real name) in 2010 at the Genome Institute at Washington University in St Louis, Missouri. Lucy had been referred there after a confusing leukaemia diagnosis. Her doctors thought she had a subtype of the disease called acute promyelocytic leukaemia (APL) — one of the most treatable forms — which usually occurs when parts of chromosomes 15 and 17 get mixed up, or translocated, triggering overproduction of blood-forming cells. But other features of her chromosomes suggested that she might have a much more dangerous form of the disease and therefore need a bone-marrow transplant.

Mardis, co-director of the Genome Institute, is involved in a university initiative to use whole-genome sequencing and other analyses to launch precision attacks against difficult cancers. While her medical colleagues treated Lucy, Mardis sequenced Lucy's genome and that of her cancer and discovered that the leukaemia was indeed caused by a piece of chromosome 15 inserting itself into chromosome 17 (ref. 1). "Our chromosomal analysis indicated that she would respond well to traditional APL therapy," Mardis says. In other words, the treatment she had already received should hold her cancer at bay — and no risky transplant would be needed.

Personalized, 'precision' medicine for cancer is in a difficult time of transition. There are promising stories like Lucy's, wherein the DNA typing of tumours suggests clear approaches to therapy, with improved results for patients. But the field is still limited by many complexities and constraints.

Researchers have learned enough about cancer to know that the way it has been tackled for decades — with cocktails of chemotherapeutic drugs that indiscriminately hit populations of rapidly growing cells — is effective only up to a point. They believe that if they can find the key genetic mutations that drive a particular cancer's growth, they will be able to target the tumour more selectively and with fewer toxic side effects. But they don't yet know enough about which genetic mutations drive a given cancer, let alone how to interrupt the aberrant cellular pathways that result.

MAKE ME A MATCH

Every cancer has a weak spot — a genetic vulnerability that could be exploited by the right drug — and many envision a day when the genome of every cancer will be sequenced, in full or in part, and then paired with an appropriate therapy.

Researchers point to the effectiveness of imatinib (marketed as Gleevec and Glivec) against chronic myelogenous leukaemia (CML) — a rare blood cancer — as perhaps the greatest success in the personalized cancer field so far. CML is most often caused by an abnormal gene rearrangement in which pieces of two chromosomes switch places with each other. Assessing whether a patient is a candidate for the drug requires the analysis of a small group of genes in what is referred to as a gene panel.

"In the 1980s, unless you got a bone-marrow transplant, the disease was an absolute death sentence in four to six years," says Razelle Kurzrock, director of the Center for Personalized Cancer Therapy at the University of California, San Diego. "Today, average survival is more than 20 years. And because the average age at diagnosis is 60, it's almost a normal life expectancy." That success comes at a price: in 2012, a year's worth of the therapy cost US$92,000.

Imatinib's success has not been easy to duplicate. Every tumour has a unique set of genetic mutations — tumours are commonly likened to snowflakes, each is slightly different from the next. And this heterogeneity, which is found even between cells in a single tumour, means that matching a patient with the appropriate therapy can be a complex proposition.

Vulnerabilities such as the one that imatinib capitalizes on are known as driver oncogenes, genetic changes that generate the proteins driving a cancer's growth. Disabling these proteins should, at least in theory, beat back the disease. The number of driver oncogenes seems to be limited — perhaps as few as 200–300 common ones, says Robert Nussbaum, a medical geneticist at the University of California, San Francisco. Understanding how to disable the common driver oncogenes should therefore enable the treatment of a large number of cancers. "First, we have to know what the genes are and how are they mutating. Then, the second challenge is developing drugs that target these abnormally activated proteins," Nussbaum says.

Such an approach means that oncologists are no longer limited to treating cancer on the basis of the organ in which it first appeared. "The whole idea of starting to classify tumours by their mutations and expression profile as opposed to the way they look under the microscope is another branch of this precision oncology that's developing," Nussbaum adds. A case in point: imatinib is not only good at keeping CML in check, it works for certain gastrointestinal cancers and other tumours as well.

"For the first time, we have a landscape of all the frequent mutations that occur in every single major cancer type," says José Baselga, a cancer biologist at the Memorial Sloan-Kettering Cancer Center in New York. "We know which are the frequent mutations that occur in breast cancer, we know which occur in all forms of thyroid cancer, leukaemia, lymphoma, CML — you name it."

Baselga and his colleagues are using this information to design clinical trials that group patients by genotype rather than by a cancer's organ of origin. For example, mutations in the gene *BRAF* can cause the protein it encodes to become oncogenic. The team has been testing a drug called vemurafenib (Zelboraf), which is effective against melanomas that contain a mutation in the BRAF protein known as BRAF(V600E), in patients with other types of cancer who test positive for the same mutation.

"We are beginning to see responses in tumour types that we would have never guessed," Baselga says. "We have very high responses in histiocytosis, hairy-cell leukaemia and some forms of thyroid cancer."

CATCH 22

Drugs with precise molecular targets such as the one that Baselga is testing can be dazzlingly effective in the short term. But that brilliance is dimmed by a massive cloud: because cancer is a continually evolving disease, such therapies rarely retain potency in the long term. Adapting mutations eventually allow cancer cells to grow back in treatment-resistant forms. "Tumours evolve for a living," Nussbaum says. "When you treat them with a targeted therapy, it's a perfect Darwinian system for selecting exactly the cells you don't want."

Because cancer cells evolve ways to survive when one oncogenic pathway is blocked, researchers are seeking to identify not just one but all of the potentially malignant pathways so as to hit them simultaneously — and curtail the ability of tumours to evolve resistance. "Mutations are occurring all the time," Kurzrock says. "Targeting just one abnormality means you're constantly chasing your tail."

Kurzrock ran into this problem in a study in which her group used a gene panel from a company in Cambridge, Massachusetts, called Foundation Medicine (see 'Testing times') to test 75 women with advanced breast cancer. Although the patients each had, on average, five or six malignancy-linked mutations, none had the same combination.

"Not only do we have next-generation sequencing-based methods, we also have this incredible growth in our general knowledge."

Why is it, then, Kurzrock asks, that we have been trying to fit these differently shaped pegs into the same round hole? Instead, she says, "we should take a patient and ask: 'What cocktail of drugs does this particular patient need based on their particular profile?'".

Another problem with the targeted approach is that therapies are typically tested only on patients with advanced cancers, which are much harder to treat than those in their early stages. Trying out drugs earlier in the course of a disease, when the cancer is more likely to be driven by just one or two key mutations, would require a major shift in the clinical trial system (see page S55).

But perhaps the biggest obstacle in targeting the products of mutated genes is that so many of the causative mutations result not in something's presence but in its absence. Most of the driver oncogenes have what is known as loss-of-function mutations — changes that disable the genes or proteins normally

TESTING TIMES

Biotechnology companies are developing sophisticated ways to match patients to therapies — and even determine whether therapy is necessary. Here are some of the most prominent.

Company	Goal	Technology	Developmental stage
Genomic Health, Redwood City, California	Risk assessment	Assesses molecular markers in tumours. Predicts whether chemotherapy will be beneficial, as well as likelihood of recurrence.	Launched onco*type* DX test for breast cancer in 2004. Tests now also available for colon and prostate cancers.
Epic Sciences, San Diego, California	Diagnosis and monitoring	Isolates tumour cells circulating in blood, and tests them for receptors and enzymes that indicate effectiveness of therapeutics.	Partnering with pharmaceutical and biotechnology companies and cancer centres. Tests are currently in clinical trials and not yet commercially available.
Foundation Medicine, Cambridge, Massachusetts	Match tumour to drug	Screens biopsies for alterations in 236 cancer-related genes for solid tumours and 405 genes for haematological cancers. Then matches mutations to drugs that are either approved by the US Food and Drug Administration or in clinical trials.	Two clinical products are available to oncologists: FoundationOne for solid tumours, launched in 2012; and FoundationOne Heme for haematological cancers, launched in 2013.
Qiagen, Hillden, Germany	Targeting appropriate patient subgroups	Uses the polymerase chain reaction analysis to detect mutations in epidermal growth factor receptor and determine whether the drug afatinib is the appropriate treatment.	Approved by US Food and Drug Administration for testing in conjunction with afatinib to select metastatic non-small-cell lung cancer patients for first-line treatment with afatinib.
Trovagene, San Diego, California	Monitoring	Analyses cell-free cancer DNA in urine to detect mutations and monitor disease progression, recurrence and therapeutic response.	Urine testing available for *KRAS* and *BRAF* mutations, which are predictive of response to colon cancer and melanoma therapies.

responsible for preventing cancerous cells from growing out of control. "It's one thing to develop a drug that blocks an activated protein. It's quite another to develop a method to compensate for the loss of a tumour-suppressor protein," Nussbaum says. Attacking these kinds of cancers will require a more nuanced approach — one that tinkers with the DNA itself rather than the proteins for which it codes.

TIME IT RIGHT

Beyond matching tumour to drug, precision medicine also depends on providing the drugs at the right time — something that requires knowing not only which mutations got a tumour started, but also how the tumour is likely to change. To ensure that therapies that start out personalized remain that way, a doctor needs to know when new oncogenic pathways pop up and when it is time to change course. But repeated biopsies are difficult, and often impossible.

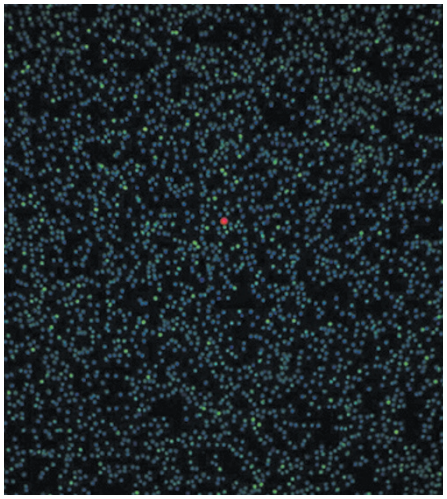
Researchers have therefore been working on non-invasive ways to monitor mutations. Technology is getting good enough to separate out tumour cells or sequenceable scraps of DNA from blood samples, making it possible to do 'fluid' biopsies that provide accurate biomarkers for assessing the disease over time[2]. For instance, Epic Sciences in San Diego, California, in collaboration with cell biologist Peter Kuhn at the nearby Scripps Research Institute, has developed a way to separate tumour cells from blood and assess them for mutations and abnormal protein expression. Others are focusing on bits of DNA that have leaked from dying cells and can be analysed for cancer-driving mutations.

Such methods could one day allow real-time assessment of a patient's tumour make-up. Sarah-Jane Dawson, a molecular biologist and oncologist at the Peter MacCallum Cancer Centre in Melbourne, Australia, studies cell-free DNA — DNA that has escaped from dying cells and is circulating in the blood. She and her colleagues have found that changes in cell-free tumour DNA are detectable, on average, five months before any changes to a patient's cancer are seen in computed tomography (CT) or other scans. "That's not an insignificant amount of time for someone to remain on a therapy they're growing resistant to," Dawson says.

Researchers are also beginning to understand more about how the body fights cancer, and how to take advantage of that. Certain types of immunotherapy — treatments that prompt the body's immune system to detect and attack a tumour — seem to work better if the disease is slightly more advanced: the more mutations a cancer has, the more foreign proteins there are for immune cells to detect.

NATURE.COM
For more on immunotherapy approaches, see:
go.nature.com/vdnyet

Tumour cells can be adept at exhausting, or simply turning off, the body's immune response. The best approach to treatment, therefore, might be to combine precision therapy with immunotherapy. First, prune back the cancer with molecularly targeted drugs. Next, use immunotherapy to help the patient's immune system recognize and attack the mutant cells at the first sign of danger[3]. "The vast majority of patients respond to genomically targeted therapies, but with short durability," says James Allison, a cancer immunologist at the University of Texas MD Anderson Cancer Center in Houston. Immunotherapy, he says, is the opposite. "A fraction of patients respond, but with long durability." Combining the approaches, he says, should dramatically improve outcomes.



EPIC SCIENCES

Using just a blood sample, Epic Sciences can detect a single cancer cell (red) among a field of white blood cells (blue and green).

ATTACK FROM WITHIN

Allison has pioneered a class of immunotherapy drugs called checkpoint inhibitors, which can set loose an otherwise-blocked immune system and allow it to break through the defences of certain cancers. Most notably, drugs that inhibit the a protein found on the surface of T cells called PD1, or the PDL1 protein to which it binds, have been shown in numerous clinical trials to be effective against various types of advanced cancers[4]. And Allison's colleague, oncologist and immunologist Padmanee Sharma, is seeking markers that could indicate whether a patient is responding to another checkpoint inhibitor that works against a T-cell surface receptor, CTLA4. One of the markers she has found — inducible co-stimulator (ICOS) — seems to increase when someone is responding to treatment that targets that receptor[5].

Another, still-more personalized form of immunotherapy genetically engineers a patient's immune cells (or those from a matched donor) so that they can recognize and attack cancer cells. The approach, called chimaeric antigen receptor (CAR) T-cell therapy, has produced encouraging results in several small unpublished clinical trials for advanced blood cancers: some patients achieved complete remission.

Ideally, a treatment should be personalized and hit multiple pathways simultaneously. Chemical engineer Mark Davis from the California Institute of Technology in Pasadena and cancer biologist Frank McCormick from the University of California, San Francisco, believe that the answer lies in RNA interference, a technique that uses double-stranded sequences of 'short interfering' RNA (siRNA) to mute specific genes.

Davis has created a way to encapsulate cancer drugs in nanoparticles that have the right size and surface properties to be taken up by tumour cells (see page S58). He is now working with McCormick to infuse these nanoparticles with siRNA. Until now, delivering these fragile molecules to cancer cells had proved nearly impossible, but Davis's nanoparticles provided an elegant solution. The approach has been tested in a phase I clinical trial in solid cancers[6], and the results are now being assessed.

The siRNA method could disable cancer at its very origin by silencing the genes responsible. "In a dream situation, you find a set of genes that affect your tumour, load them up and go," McCormick says. As a patient's tumour evolves, an oncologist can simply swap old siRNAs for new ones. "Once the delivery system works, you could just plug and play different payloads."

Combining a single delivery system with pluggable siRNAs would make drug development faster, cheaper and more routine, and also present less risk to the patient, McCormick says. The multi-siRNA technique has been tested successfully in mice, but human trials using a combination of siRNAs may still be a few years off — such fast-turnaround, individualized therapies pose a challenge for regulatory bodies such as the US Food and Drug Administration.

Cancer is a wily enemy and protects its secrets well. Precision approaches, such as the one Lucy received, are not yet available for most patients. But the rush of research suggests that it is only a matter of time before they are. "Not only do we have next-generation sequencing-based methods," Mardis says, "we also have this incredible growth in our general knowledge."

For Lucy, at least, that knowledge is everything. Four years on, she is still cancer free. ■

Lauren Gravitz *is a freelance science writer based in Los Angeles, California.*

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