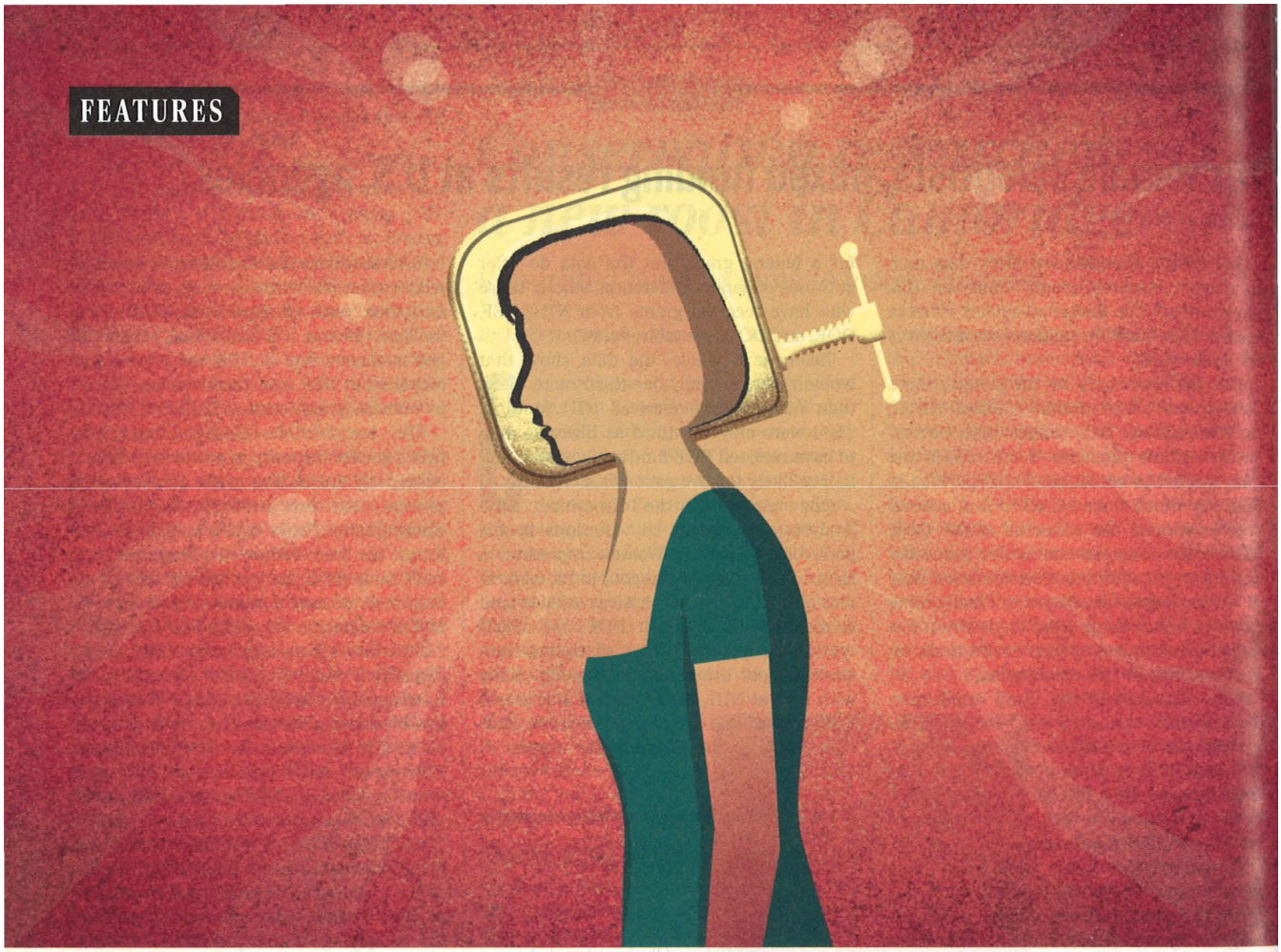


A SHOT AT MIGRAINE

Drug companies are racing to prove antibody treatments can prevent the debilitating headaches

By **Emily Underwood**

As long as she can remember, 53-year-old Rosa Sundquist has tallied the number of days per month when her head explodes with pain. The migraines started in childhood and have gotten worse as she's grown older. Since 2008, they have incapacitated her at least 15 days per month, year-round.

Head-splitting pain isn't the worst of Sundquist's symptoms. Nausea, vomiting, and an intense sensitivity to light, sound, and smell make it impossible for her to work—she used to be an office manager—or often even to leave her light-proofed home in Dumfries, Virginia. On the rare occasions when she does go out to dinner or a movie with her husband and two college-aged children, she wears sunglasses and noise-canceling headphones. A short trip to the grocery store can turn into a full-blown attack "or[illegible] dime," she says.

Every 10 weeks, Sundquist gets 32 bee sting–like injections of the nerve-numbing botulism toxin into her face and neck. She also visits a neurologist in Philadelphia, Pennsylvania, who gives her a continuous intravenous infusion of the anesthetic lidocaine over 7 days. The lidocaine makes Sundquist hallucinate, but it can reduce her attacks, she says—she recently counted 20 migraine days per month instead of 30. Sundquist sometimes ward off an attack with triptans, the only drugs specifically designed to interrupt migraines after they start.

Millions of others similarly dread the onset of a migraine,

To hear a podcast with author Emily Underwood, go to http://scim.ag/pod_6269

although many are not afflicted as severely as Sundquist. Worldwide, migraines strike roughly 12% of people at least once per year, with women roughly three times as likely as men to have an attack. The Migraine Research Foundation estimates that U.S. employees take 113 million sick days per year because of migraines, creating an annual loss of $13 billion. The toll underscores how little current treatments—not just drugs, but nerve-numbing injections, behavioral therapies, and special diets—can help many people.

On the horizon, however, is a new class of drugs that many scientists believe can stop migraines at their root. The drugs block the activity of a molecule called calcitonin gene-related peptide, or CGRP, which spikes during migraine attacks. CGRP is "the best validated target for migraine, ever," says David Dodick, a neurologist at the Mayo Clinic in Phoenix. It may also help finally solve the centuries-old puzzle of what triggers the complex events of a migraine attack, which can cause brain activity to be "completely disregulated" for several days, similar to epilepsy and other recurrent, seizurelike disorders, says Michel Ferrari, a neurologist at Leiden University in the Netherlands.

Four pharmaceutical companies are racing to complete advanced clinical trials of antibodies that either neutralize CGRP by binding to it, or block its receptor. So far, Dodick says, the data suggest the drugs work faster, for longer, and better than anything currently available. Most striking, he notes, is a subset of "superresponders," whose attacks appear to cease entirely for 6 months after a single injection of a CGRP-blocking antibody. "I've been in this field now for 21 years, and this is the most exciting thing we've seen so far," says Dodick, who has consulted for several of the companies developing CGRP blockers.

Others are more restrained. Given that the frequency of migraines can wax and wane, at least some people in these initial trials may simply be getting better on their own, Ferrari says. "For me, it's still too early to judge the efficacy."

GREEK PHYSICIAN HIPPOCRATES described migraines in detail in the 5th century B.C.E., including the shining, scintillating "auras" that roughly a fifth of sufferers see a few minutes before an attack. Because vomiting seemed to relieve some migraineurs' symptoms, Hippocrates believed that the headaches resulted from an excess of "yellow bile." But by the mid-20th century, most physicians thought that dilated arteries and veins in the head were key to the disorder. "Look at any portrait of a person having a migraine, and they are pressing their hands to their temples," says neurologist Marcelo Bigal at the Frazer, Pennsylvania, location of Israel-based Teva Pharmaceutical Industries, one of the companies developing a CGRP-blocking drug.

Many of the early remedies constricted blood vessels, adding to the misperception that abnormal blood flow was key to the disorder, Bigal says. The first such drugs, called ergotamines, were powerful vasoconstrictors derived from the ergot fungus, which grows on rye and other grains and led to mass poisonings in the Middle Ages. Large doses of the fungus can cause seizures, psychosis, and gangrene in the limbs—a syndrome some called St. Anthony's fire—but doctors found that small doses could help prevent women from hemorrhaging after childbirth, and they sometimes relieved migraines.

Yet even refined, synthetic versions of ergotamine can dangerously narrow blood vessels, so doctors and patients welcomed the triptans, which selectively constrict the blood vessels of the brain. Introduced in the 1990s and still the most widely prescribed migraine-specific drugs, triptans can head off a migraine attack in roughly 50% to 60% of people who take them. They don't work for everyone, however, and they share an unpleasant side effect with ergots and many pain medications: If a person takes them frequently, their headaches may become more frequent and severe.

Although both ergotamine and triptans act on blood vessels, studies that began in the 1990s "torpedoed" the idea that dilated vessels actually cause migraines, says neurologist Jes Olesen of the University of Copenhagen. Particularly important, he notes, have been a series of detailed functional magnetic resonance imaging (fMRI)-based blood vessel studies showing no relationship between abnormal blood flow in the brain and the pain of migraine attacks.

As the blood vessel theory of migraines unraveled, researchers looked to other potential triggers. One was a disruption of normal electrical activity in the brain: a seizurelike phenomenon called cortical spreading depression (CSD). Strongly associated with the aura many migraineurs get, this slow wave of abnormal neuronal excitation usually begins in the occipital lobe at

14%
Americans affected by migraine or severe headache

3:1
Ratio of women to men suffering migraine

$20 billion
Estimated annual U.S. cost of migraine in treatments and lost productivity

ute, says Michael Moskowitz, a migraine researcher at Harvard University. In its wake, neuronal activity is temporarily depressed.

Genetic studies of people with inherited forms of migraine and some animal studies suggest that CSD plays a central role in many, if not all, migraines, Moskowitz says. Of the 41 gene variants the studies have linked to migraine risk, many are in genes that modulate electrical activity in neurons and are thought to make carriers more susceptible to CSD.

Based on experiments in rodents, Moskowitz believes CSD can trigger migraines by irritating a network of neurons, the trigeminovascular system, which innervates cerebral blood vessels. Moskowitz's lab discovered the system at the Massachusetts Institute of Technology in Cambridge in the 1980s, when they traced a group of fine nerve fibers radiating from blood vessels in the meninges—delicate membranes that envelop the brain and spinal cord—to the trigeminal nerve, which innervates the face, head, and jaw. Moskowitz proposed that migraine pain arises when these fine nerves are irritated or stimulated by CSD or other factors. He also suggested that blocking the release of Substance P—the only pain-signaling neurotransmitter known at the time—in these nerves might ease migraineurs' symptoms.

Although many found the hypothesis compelling, multiple trials of drugs designed to block the activity of Substance P failed to head off acute attacks in migraine patients. Today, although most researchers agree that a hypersensitive trigeminovascular system is likely the source of pain in migraines, few would argue that CSD is the only or most important factor in inflaming it, Moskowitz says. For one thing, most people who get the headaches don't experience the visual aura thought to be a consequence of CSD. And only a handful of brain imaging studies have actually shown hints of CSD in human migraineurs. These experiments, however, are difficult to conduct because they require deliberately sparking a migraine right before putting a person in an fMRI scanner. In 2001, Moskowitz performed what many in the field describe as the most compelling demonstration of CSD's link to migraines, in an engineer who was able to trigger his own migraines through exercise—in this case, playing basketball for

THE FAILURE of the Substance P–blocking drugs opened the door for CGRP, an obscure, 37-amino acid peptide, discovered largely by accident by neuroscientists Susan Amara and Michael Rosenfeld of the University of California, San Diego. While studying a thyroid hormone called calcitonin, which helps regulate the body's sodium and calcium levels, Amara and Rosenfeld found that the same gene that encodes calcitonin in the thyroid gland produces a slightly different peptide in another part of the brain. As one of the earliest examples of alternative gene splicing, which enables a single gene to produce multiple proteins, the discovery made a splash when it was published in *Nature* in 1982.

After finding CGRP is plentiful in brain pathways that process pain and in brain regions that regulate blood flow, neurologist Lars Edvinsson, of Lund University in Sweden, wondered whether CGRP is involved in migraines. His group soon found that CGRP can trigger what was then considered a hallmark sign of migraines: When released from the trigeminovascular nerves, it is a powerful vasodilator of cerebral blood vessels. In 1990, he paired up with neurologist Peter Goadsby, now at King's College London, to further explore CGRP's role in migraine patients. After getting permission to take blood samples from the jugular veins of people who had come to the emergency room for a severe migraine, the researchers measured the amounts of a range of different peptides, including Substance P, during and after attacks. "The amazing thing was that CGRP was the only peptide that was significantly released," Edvinsson says.

At first, Edvinsson and others thought CGRP triggered migraines by expanding blood vessels in the brain. Instead, a growing pile of studies suggested that CGRP was not just a vasodilator, but a previously unknown, pain-signaling neurotransmitter. Other groups found that rising levels of CGRP in jugular blood—not patterns of abnormal blood flow—signaled a migraine attack. Then, in a pivotal 2002 study, Oleson and colleagues injected CGRP into the blood of migraineurs and found that they developed migrainelike headaches within hours, whereas

gested migraineurs are unusually sensitive to the peptide's effects, Oleson says.

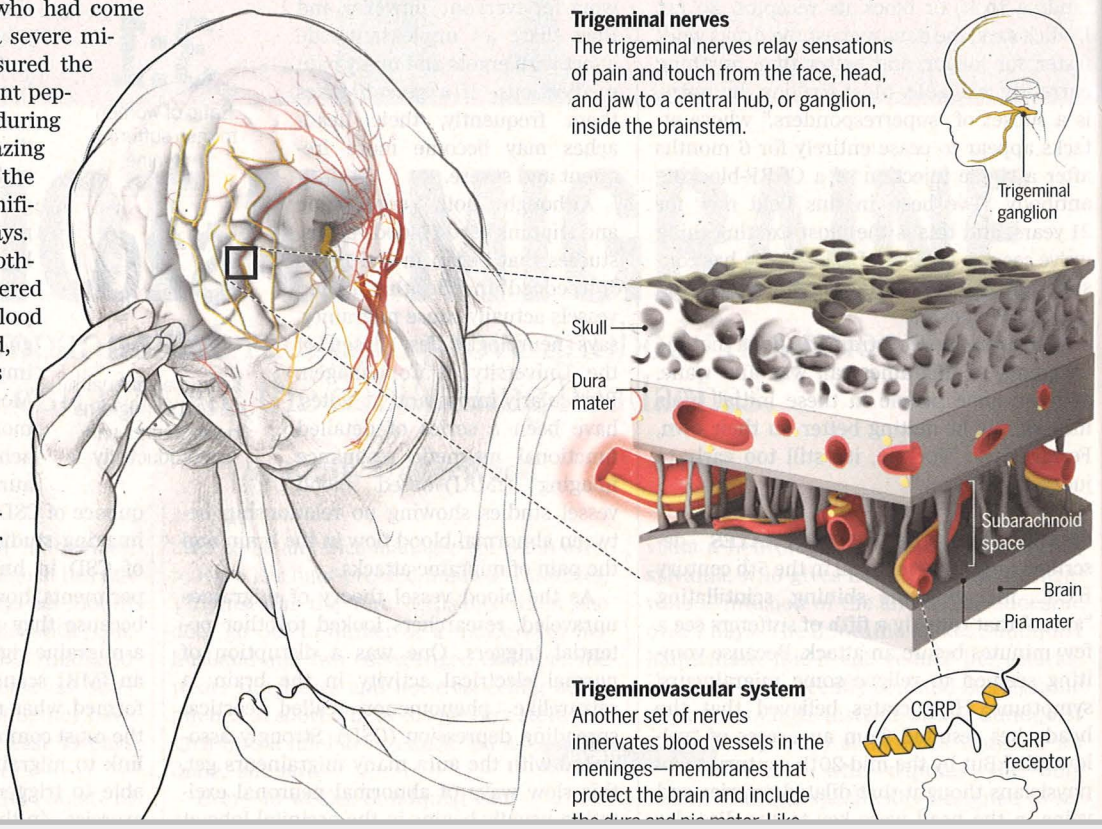
By the early 2000s, the biology around CGRP and migraine was strong enough to inspire a few companies to attempt drug development. German pharmaceutical company Boehringer Ingelheim designed a small molecule called bibn4096bs to block CGRP's receptor. The drug could stop acute migraine attacks in some people, but produced adverse side effects. Another company, Merck, tried to block the CGRP receptor with a different small compound. It, too, seemed to work modestly well, but its trial also had to stop because it showed signs of liver toxicity. But the glimmers of efficacy were encouraging, says Jaume Pons in San Francisco, California, who was at that time head of protein engineering at Rinat, a spinoff of Genentech that specialized in antibodies to treat cancer.

Pons and others began to explore other approaches. Perhaps antibodies were worth a shot, he thought, because they can last a long time in the body and can be exceptionally specific, reducing the frequency with which people need injections. But because most researchers thought it necessary to target migraines in the brain and antibodies are generally too large to pass through the blood-brain barrier, they tended to dismiss the option, Pons says. Back then, "most people were not considering the use of antibodies for pain," but Rinat had already begun clinical trials of a different antibody pain treatment with promising initial results, he says.

In 2004, Rinat launched an antibody program targeting CGRP. If it worked, the team reasoned, it would show that it was possible to treat migraines from outside the brain, by blocking CGRP only in the peripheral nervous system. That would lower the risk of the side effects often provoked by drugs that act in the brain, Pons says. In a few months, the firm developed the peptide-blocking antibody now being tested by Teva under the name TEV-48125. The antibody faced plenty of roadblocks. The Rinat team

Migraine's tangled roots

Once considered a disorder of blood vessels, neuroscientists have pinpointed a new mechanism for migraines: the release of a substance called calcitonin gene-related peptide (CGRP, below), which sensitizes nerves (yellow) in the face, head, and jaw, and alongside blood vessels (red) surrounding the brain. Antibodies that block interactions between CGRP and its receptors on cells could become the next generation of migraine drugs.



managed to launch a phase I study testing TEV-48125's safety, but Pfizer acquired the company in 2006, and by 2011, the firm "decided that migraine was not an area it wanted to pursue," Pons says.

Other big companies had made similar decisions at the time, Pons says. The Food and Drug Administration (FDA) has especially stringent safety standards for pain treatments, and estimates for the market value of a new migraine drug are uncertain, ranging wildly from roughly $200 million several years ago to $5 billion, making it hard for companies to commit a large amount of money to drug development.

Despite the risk, in 2013 a venture capital company called venBio bought the rights to TEV-48125 and launched a new company called Labrys Biologics and continued the antibody's clinical development. Neuroscientist Corey Goodman, a managing partner of venBio in San Francisco, California, had until 2009 been president of the biotherapeutics division at Pfizer, where he oversaw Rinat and Pons's team. Goodman remembered TEV-48125 was a "very good antibody," and after recruiting more investors, Labrys kicked off two phase II trials in people with frequent migraines. The trials produced "the most beautiful phase II data I've ever seen," Goodman says, with significant reductions in number of headache days over placebo, even for the most severe cases.

Teva bought Labrys in 2014 and is now racing with Alder Biopharmaceuticals, Eli Lilly, and Amgen to win FDA approval for the first migraine antibody drug. So far, the four phase II clinical trials, at least one from each firm, have produced similarly encouraging results, with up to 15% of participants experiencing complete relief, Goodman says: "I don't think it's too early to start talking about a cure for some patients suffering from this debilitating disease."

One of the superresponders is 26-year-old Julia Berner, who has been getting a migraine every day since she was a little girl. Over the years, she's tried epilepsy medications, Chinese remedies, and nerve blocks, among countless other treatments, with no success. Within a few days of receiving four shots of Teva's thick, viscous, antibody-containing solution in the back of her arms and the skin around her hips, however, the migraines disappeared.

The difference was "mind-blowing," she says. Berner usually spends her days avoiding any small disturbance that could make her constant, low-grade migraines more severe. After getting the antibody injections, that burden lifted. "I hadn't realized how tired they make me," she says.

DESPITE SUCH ANECDOTAL SUCCESSES, some migraine researchers don't think it's time to celebrate yet. If CGRP "really is a fundamental mechanism, you would expect a much higher proportion of patients to be completely free of attacks," Ferrari says. Safety also concerns him because of CGRP's natural role in dilating arteries and maintaining blood supply to the heart and brain. "Theoretically, if you block CGRP you could translate a minor stroke or cardiac ischemia ... into a full blown stroke or heart attack," he says. So far, the companies say they haven't seen that or other significant side effects in the several thousand people who have completed phase I and II trials, but the drugs have only been administered for up to 6 months—not long enough to judge long-term effects, Bigal says.

Still, the fact that CGRP antibodies can prevent migraines in some fraction of patients is a "really cool finding" from a research perspective, says Andrew Russo, a molecular physiologist and neurologist at the University of Iowa in Iowa City, who consults for Alder.

> ***"I've been in this field now for 21 years, and this is the most exciting thing we've seen so far."***
> **David Dodick**, Mayo Clinic

The trial results confirm that CGRP is a major new player in migraines—and perhaps even the fundamental trigger—even though the chain of events remains murky. "We don't really know what's going on, but we have some ideas," Russo says. One view is that the increased amounts of CGRP released at the start of a migraine sensitize the trigeminal nerve to what are normally innocuous signals, resulting in inflammation in the nerves that is relayed to the brain as a pain signal.

In that scenario, Dodick says, a migraineur's brain is like a car with a heightened alarm system that "goes off simply because you walked close to it." In the end, the brain reaches what Sigal describes as a "permissive" state, in which normal light becomes very bright, normal sounds very loud, "and you can smell a perfume two blocks away from Bloomingdale's." CGRP-binding antibodies help turn down the volume in the trigeminal nerve, by "mopping up" excess peptide or preventing it from binding to and activating cells, Dodick proposes.

But why are migraineurs more sensitive to CSD, which certain animal studies suggest can trigger a surge of CGRP, Russo says. In that case, genetic predisposition to the abnormal brain activity could lead to many migraines.

A growing number of studies point to another important factor: stress. Even minor insults, such as missing a few hours' sleep, can often "push the migraine brain over the line into having an attack," Sigal says. And experiments in rats and cultured cells show that corticotropin-releasing hormone, which the body releases in response to stress, also increases neuronal production of CGRP, Russo says. Strikingly, many migraine medications also boost CGRP in animal models, possibly explaining why people who use drugs like triptans too frequently end up with more severe migraines, he says.

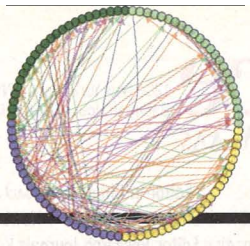
That the relatively large CGRP-blocking antibodies can prevent migraines in some people have convinced most in the field that it is indeed possible to stop the headache from outside the central nervous system, even though it is clearly a brain disorder, according to Moskowitz. "The evidence is favoring that [the drugs are] working somewhere on the trigeminal connections into the brain, not in the brain itself, unless there's some massive change" in the permeability of the blood-brain barrier during an attack, he says.

Some researchers, however, still argue that the CGRP-blocking antibodies must be getting past the blood-brain barrier into the brainstem—even in trace amounts—to be effective. Goadsby favors this view, and notes that some sections of the brainstem are not very well protected by the barrier.

Whatever the resolution to that debate, the discovery of CGRP's migraine connection underscores the value of carefully dissecting the neural pathways that lead to pain and searching for a linchpin molecule, Moskowitz says. If CGRP fulfills its promise as a blockbuster pain target, that success could signal to drug developers that effective treatments for other complex and seemingly intractable pain disorders, such as fibromyalgia, are also within reach, Moskowitz says. Eli Lilly is already testing its CGRP-antibody in people with cluster headaches, which occur in regular, cyclical patterns and can be even more painful than migraines.

As for Sundquist, she's well aware of the clinical trials for the various CGRP-related drugs, and she is hopeful. But the random assortment of failed remedies that fills her closet—antidepressants, nutritional supplements, a headband that transmits painful electric zaps to her scalp and "looks like something from *Star Trek*"—makes her wary as well. "I'm just waiting for more

180
Machinery to insert membrane proteins



158
Life after death

RESEARCH

IN BRIEF

REVIEW

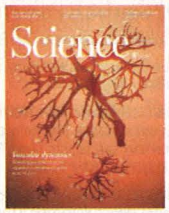
RESEARCH ARTICLES

REPORTS

198

DEPARTMENTS

ON THE COVER



Tree of portal blood vessels in the murine fetal liver at embryonic days 12 (bottom left), 13 (bottom right), and 14.5 (top), reconstructed in three dimensions from serial cryosections of portal vasculature. Branch surface area is scaled according to fractal geometries, together with the number of hematopoietic stem cells (HSCs; yellow spheres), suggesting that HSC niche expansion is related to portal vessel surface area. See pages 126, 139, and 176. *Data visualization: Valerie Altounian/* Science*; base meshes created by Jalal Khan (Icahn School of Medicine at Mount Sinai) using MeshLab*

SCIENCE (ISSN 0036-8075) is published weekly on Friday, except the last week in December, by the American Association for the Advancement of Science, 1200 New York Avenue, NW, Washington, DC 20005. Periodicals mail postage (publication No. 484460) paid at Washington, DC, and additional mailing offices.

Domestic individual membership and subscription (51 issues): $165 ($74 allocated to subscription). Domestic institutional subscription (51 issues): $1522; Foreign postage extra: Mexico, Caribbean (surface mail) $55; other countries (air assist delivery) $89. First class, airmail, student, and emeritus rates on request. Canadian rates with GST available upon request, GST #1254 88122. Publications Mail Agreement Number 1069624. **Printed in the U.S.A.**

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