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Findings

inside

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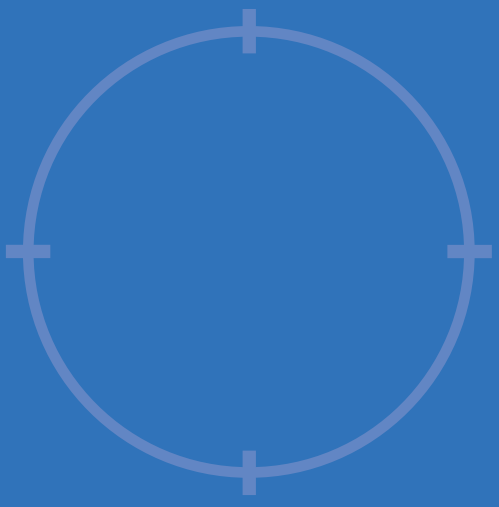


Editor's Note

Twice a year, *Findings* takes you inside the labs of scientists working on lots of different topics that advance what we know about health.

Honeybee behavior. Viruses. Glow-in-the-dark bacteria. Wound healing. Sleep.

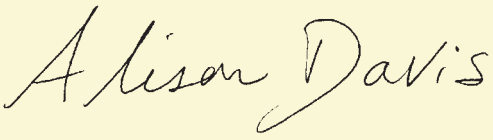
We try to bring all kinds of cutting-edge science to life on these pages, and now *Findings* is going one step further.

We want *you* to do some of the finding, too.

Listen to scientists talk about their work. Watch a hilarious video poking fun at life in the lab. Do a bioinformatics experiment—using your own computer!

As for what's in this issue, turn the page to read about researchers Atul Butte and Peggy Goodell, who are doing some of the hottest science around, on the role of computers in medicine and stem cells.

After that, grab your computer and get clicking. Check out *Findings* online to see and hear why Goodell and Butte are so hooked on science.



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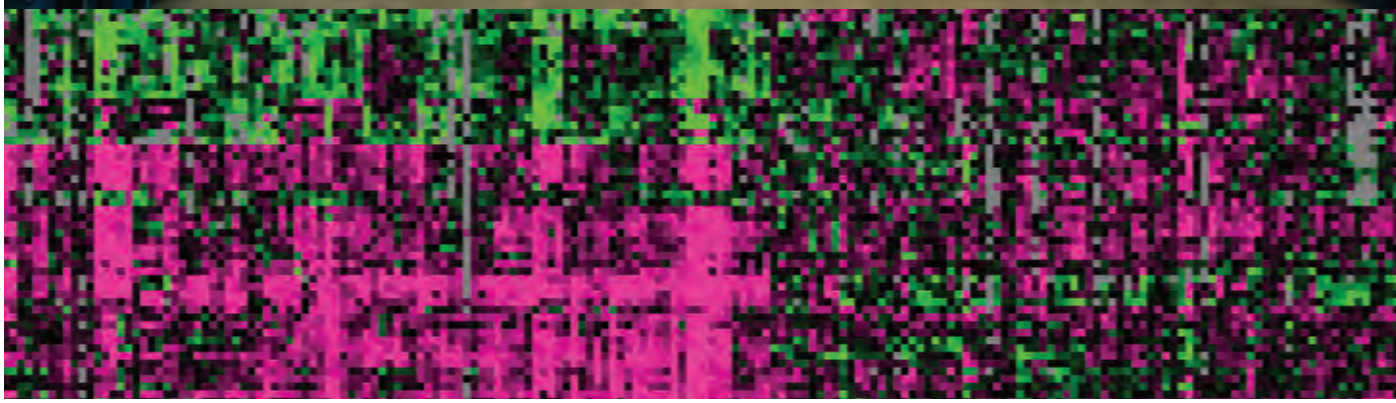
Dr. Data



TOP: STEVE GLADFELTER
BOTTOM: GEO, NCBI, NLM

BY ALISA ZAPP MACHALEK

Atul Butte is one of those people who thinks big. Really big.

Trained as both a doctor and a researcher, he's always busy with something—he does gene experiments on his computer one day and sees patients another. But Butte isn't satisfied with studying just one disease or a single gene.

Instead, he throws his net over all of them. Then he reels in tantalizing patterns that take shape in the vast sea of data.

Butte, 38 (whose name is pronounced Byoot), is both a pediatrician and a bioinformatics researcher at Stanford University in California. He is using computers to analyze the activity of all 20,000-plus genes in the human genome.

Specifically, Butte is examining which genes rev up and which stall in diabetes, heart disease, muscular

dystrophy, or other conditions. That, he hopes, will lead to a new understanding of diseases and new ways of treating them.

"The overall goal of my work is to redefine our entire knowledge about all diseases and to predict new uses for all existing drugs," he says.

That may seem like an incredibly ambitious dream, but if you met Butte, you'd understand. His energy, zeal—and lots of coffee—keep him in nearly constant motion.

Career Crisis

Butte has always had twin passions—medicine and computers. Although he didn't realize it until he was nearly done with his schooling, feeding both of his passions was the perfect preparation for his eventual career.

He has wanted to be a doctor as long as he can remember. After high school, Butte enrolled in a program at Brown University in Providence, Rhode Island, that allows college students to major in virtually anything—and guarantees that they get into Brown's medical school.

But rather than most pre-med students, who pick majors like biochemistry in college, Butte chose computer science. He got summer jobs in computer programming, working at Apple, Microsoft, and other computer firms.

"We still don't even know why people get diabetes."

When he graduated in 1991, the computer science field was exploding. Many of his classmates had already gotten high-paying jobs at places like Apple, Microsoft, Oracle, and Silicon Graphics.

Meanwhile, Butte had 4 years of medical school ahead of him, and then even more years after that if he wanted to become a specialist.

"I had a bit of crisis," Butte admits. "I didn't know whether to just bail and go into the computer industry."

Ultimately, medicine won. Butte decided he'd rather care for patients and advance the field of medicine than build tools to let other people do it.

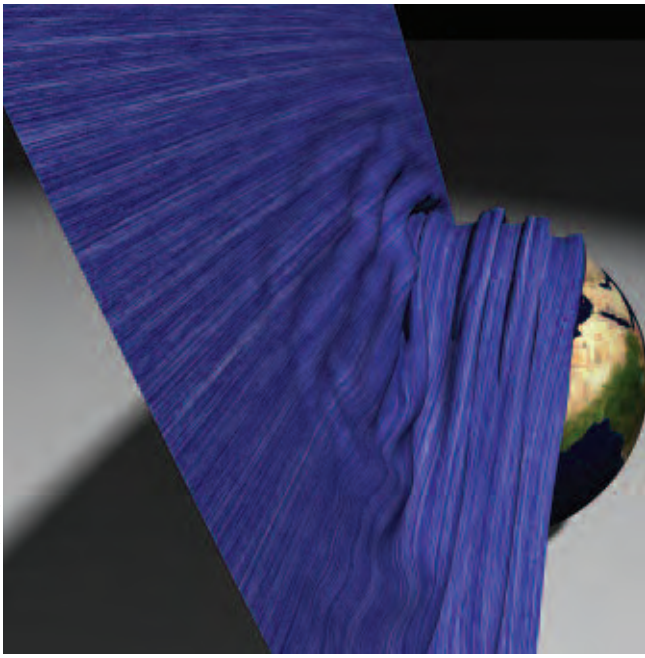
Focus Found

While Butte was in medical school, he saw the chance to ride another wave of excitement. Now, it was the life sciences that were taking off, thanks to the Human Genome Project and other technological wonders just coming online.

He was lucky to find an opportunity to see first-hand what all of the hubbub was about. He got a spot in a year-long program sponsored by the Howard Hughes Medical Institute. The program allows medical students to work side by side with laboratory researchers at the National Institutes of Health in Bethesda, Maryland.

What Butte learned that year steered the rest of his career. He discovered that, although biological questions fascinated him, he wasn't suited for bench research ("I was terrible in the lab," he claims).

Even more significant, he was introduced to a topic that completely captivated him and cemented his interest in one disease in particular: diabetes.



ATUL BUTTE, NASA (EARTH)

▲ Butte created this tapestry image using 8.4 million measurements of human gene activity (light/dark lines).

"I hadn't even thought about diabetes before," Butte says, although "this disease affects more than 10 percent of the world's population."

Butte explains that while thousands of researchers are working hard on the problem, much remains a mystery.

"We still don't even know why people get diabetes," Butte says.

Butte decided to go into pediatric endocrinology. Doctors in this specialty deal with the body's production and use of insulin and other hormones. Butte treats children with diabetes and growth problems.

He says he chose pediatrics "because it's the field of medicine that's closest to genetics." That's because many serious childhood diseases can result from genetic, rather than environmental, causes.

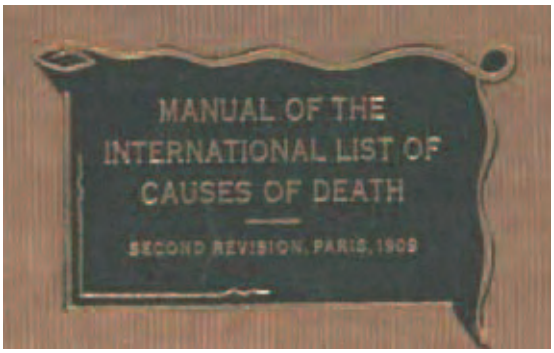
All the pieces came together when Butte met Isaac ("Zak") Kohane, a scientist at Harvard Medical School in Boston, Massachusetts, and began working with him. Kohane was a perfect mentor for Butte: Like Butte, Kohane is a pediatric endocrinologist with an interest (and a Ph.D.) in computer science.

Spending time in Kohane's lab, Butte learned to balance medicine and computation in an integrated and synergistic way. He also earned master's and doctoral degrees in medical informatics, a field that blends information science with the analysis of medical data.

The experience landed Butte a dream job at Stanford, where he now combines his two passions in a cutting-edge career.

Dusting Off Disease Definitions

According to Butte, the way we think about diseases is antiquated. And he's become a bit of an expert on the subject.



▲ Inspired by old books like this one, Butte wants to modernize the way we think about diseases.

DAVE MANGHAM

▲ Surprise! Gene studies suggest that the hyrax is the closest living relative to an elephant. Butte expects to uncover genomic surprises about health and disease.

Thanks to Google™ Book Search, Butte developed an interest in history—especially in the history of disease classification, or nosology. One of the books he uncovered provides code numbers for each of the commonly recognized causes of death in 1909.

Cancers are listed as code numbers 39 to 45 and include cancer of the oral cavity, stomach, liver, peritoneum, intestines, rectum, female genital organs, breast, skin, and "other organs."

"Imagine!" he exclaims. "Lung cancer, which now kills more Americans than any other cancer, was lumped in with 'other organs.' And that was less than 100 years ago!"

Butte thinks that the way we classify diseases is horribly obsolete and that the way we treat them is too. What he wants to do is modernize nosology by replacing our current, anatomy- and symptoms-based system with one based on information from genes.

According to Kohane, if anyone can pull this off, Butte can.

"He's absolutely meticulous and exhaustive."

A Genomic Surprise

Can old medicines learn new tricks? Butte thinks so.

His ultimate goal in creating a genome-based disease classification system is to come up with new uses for existing medicines. And Butte may already have almost succeeded by finding a surprising connection between heart attacks and muscular dystrophy.

The two diseases could hardly look more different, Butte says.

Heart attacks typically affect older people after decades of accumulated damage to blood vessels. Muscular dystrophy, on the other hand, appears in the toddler years as progressive muscle weakness. The disease is incurable, and patients die in their teens or early 20s.

Yet, according to Butte, heart attacks and muscular dystrophy are pretty similar at the genomic level. In other words, both diseases alter the activity of the same group of genes.

So, could the same medicines treat both diseases? Butte hopes so.

Currently, there are more than 40 medicines used to treat heart attacks but only one for muscular dystrophy, and it's not a cure.

If existing heart-attack drugs turn out to work against muscular dystrophy, not only would this provide immediate benefits for the thousands of children with the disease, it would also be a huge savings in time and money.

That's because a pharmaceutical company typically spends close to $1 billion and more than 10 years to develop a new medicine from scratch.

The Power of GEO

Much of the data that Butte taps into is in the form of microarrays, which are also called gene chips or DNA chips. That's because they are often manufactured like computer chips.

The thumbnail-sized devices are microscopic grids that have pieces of DNA representing every gene in the human genome stuck on them. Scientists use them to measure the activity of our 20,000-plus genes at the same time.

By using multiple microarrays, scientists can compare how patterns of gene activity change under different conditions, like in different diseases.

"Isn't this an amazing world?"

Butte compared the patterns of gene activity in people with muscular dystrophy to those of people who survived a heart attack.

This approach—analyzing mountains of data simultaneously to find meaningful patterns and tantalizing surprises—is a radical departure from the way most medical research has been done for the past 20 or so years, with an intense focus on one gene, one protein, or one biological process.

Researchers like Butte who want to publish scientific studies using microarrays are required to deposit their data into databases like GEO, the Gene Expression Omnibus. The data is coming hard and fast: Scientists are submitting more than 1,000 files each week.

That means that by the time this article is published, GEO will contain the digitized microarray results from more than 200,000 samples.

All the data in GEO is freely available online, enabling anyone with a reasonably good personal computer and an Internet connection to do bioinformatics experiments (see "How You Can Be a Bioinformatician," page 7).

"So any high school student who wants to do an experiment for a science-fair project can start with some 200,000 microarrays—and that number is doubling or tripling each year," says Butte.

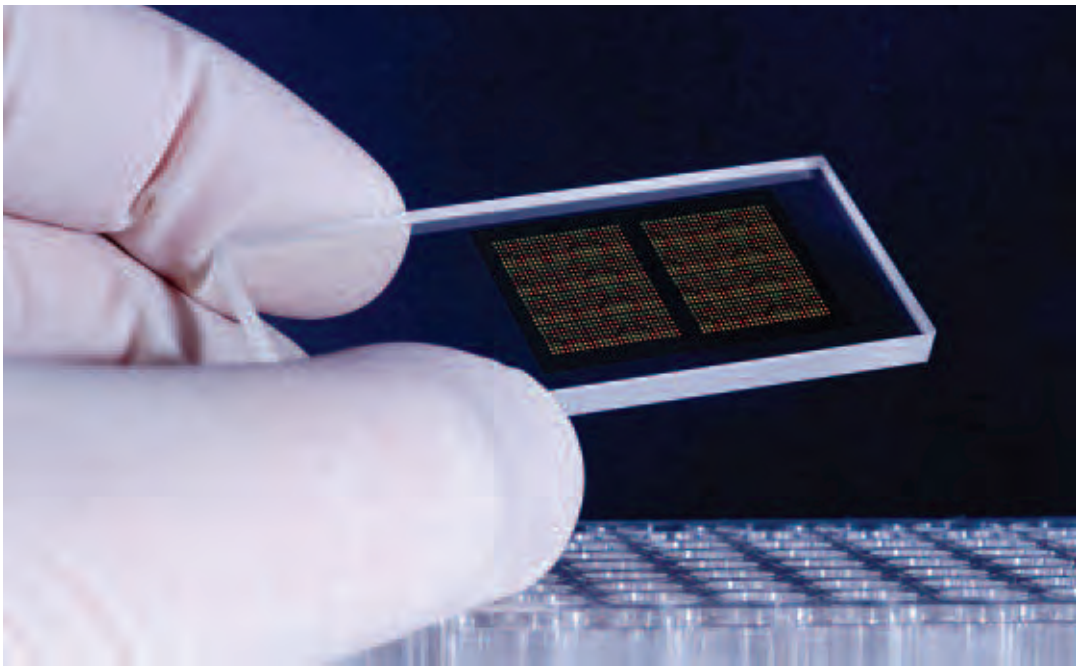
"Isn't this an amazing world?"

But there's a downside to this wealth of information: Butte and other scientists are drowning in data.

"Life-science data is growing faster than computational power," he says. "It's outpacing what hard drives and processors can do."

As a result, Butte can't simply use brute force to tackle the research topics that interest him—he has to choose his questions very wisely.

To do that, Butte focuses on "big" questions about health—questions



▲ Scientists use DNA chips like this one to measure gene activity.

Butte fuels his enthusiasm with lattes and other coffee drinks.

that can only be answered by analyzing hundreds of diseases and tens of thousands of genes simultaneously.

Like these:

What are the molecular similarities and differences across all diseases that plague us?

Which genes are affected in every single human disease?

Can we find biological markers that predict diseases before symptoms show up?

Can we use the molecular similarity between diseases to help us apply drugs for one disease to another?

"Those are the kind of cool questions that no one could answer before," Butte says.

The Good Things in Life

Although intensely committed to science and medicine, Butte's job is not the only driving force in his life.

"Before he got married," Kohane says, "he used to work all the time at the hospital—all hours of the day and night."

Now, Butte tries to get home in time for dinner and loves to talk about the latest amusing or impressive things that his daughter is doing.

"He's a family man, and I really respect that," Kohane says.

Butte is also well-known for being a coffee connoisseur.

Because of their WiFi connections (and caffeine), Butte was an early fan of Starbucks® coffee shops. He even had his first date with his wife there.

Butte is one of those people who orders incredibly complex coffee drinks. "He has completely mastered the idiosyncratic language Starbucks uses to describe their coffees," Kohane laughs.

Butte's favorite is an iced grande, non-fat, no-whip, raspberry mocha.

Butte also loves good food. "Whenever I'd meet him in any part of the world," Kohane says, "he'd always know where all the best restaurants were in detail, including their closing times and ratings."

Could it be that Butte is getting a bit of help from technology? Indeed.

During a recent meeting in Vienna, Austria, for example, Butte and a coworker had a digital duel to find directions to a restaurant.

Each whipped out his electronic sharpshooter—Butte has an HTC TyTN smartphone with a 3G UMTS/HSDPA wireless connection. His friend had an iPhone with a 2.5 G EDGE wireless connection.

Butte won. By a lot.

Of course, as a bioinformatician, Butte also uses gadgets professionally.

In his research lab, he uses a networked cluster of 64 hyper-threaded CPUs to crank away at staggeringly complicated computational problems.

And for nearly a decade, he has downloaded and indexed on his laptop every research article relevant to his scientific interests.

"When attending seminars, he'll ask questions quoting these papers as if out of an infinite knowledge base," says Kohane.

"Life-science data is growing faster than computational power."

Passion Level High, Prognosis Good

For Butte, though, gadgets will never be enough by themselves. He wants his computational findings to reach the people who need them—real kids and real adults with real diseases.

"When I first met [Atul], he was very impatient with the current state of medicine, and that really made him stand out," remembers Kohane. "It was clear that he wanted to help cure the diseases that affect lots of people and that he was going to use all his energies to make it happen."

Butte's enthusiasm is infectious, says Kohane. "He draws many people towards him. He's always smiling and genuinely excited. He's energized by the potential opportunity to improve the system."

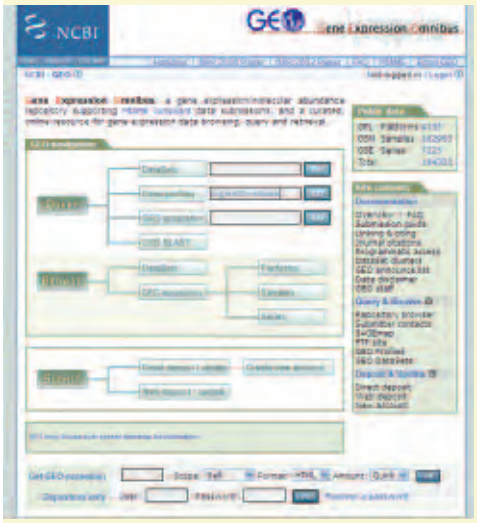
As things look now, the prognosis is good that Butte will improve many lives, as he develops a recipe for health that perfectly combines computers and compassion. ■

To learn more about microarrays, visit the National Library of Medicine's online fact sheet at http://www.ncbi.nlm.nih.gov/About/primer/microarrays.html.

How You Can Be a Bioinformatician

Try your own bioinformatics experiment! To explore links between cigarette smoking and lung cancer, go to http://www.ncbi.nlm.nih.gov/geo.

Type "cigarette smoke" into the second empty box, which is next to the "Gene profiles" label, and click GO. You'll get information on thousands of genes. Look for the experiment (numbered row) that says "UBE2D3: ubiquitin-conjugating enzyme E2D 3."



GEO/NCBI/NIH

In this experiment, the researchers studied human lung cells grown in the lab. Some of the cells were exposed to 15 minutes of cigarette smoke, and others (the controls) were kept in a smoke-free environment.

Click on the chart to the right to see an enlarged version. The left half of the chart shows the activity of the UBE2D3 gene in control cells. The right half shows the gene's activity in cells exposed to smoke. The height of the red bars shows how active this gene is. As you can see, UBE2D3 activity increases noticeably in response to cigarette smoke.

To get a list of other genes that also activate in response to cigarette smoke, go back one page and click on "Profile Neighbors" above the chart. Then scroll down to see the charts of UBE2D3's "neighbors." You'll see that the patterns in all the charts look much the same, with mostly red bars on the right side of the graph.

Because these genes ramp up when exposed to cigarette smoke, some may be linked to lung cancer. Genes that are activated whether or not smoke is present are probably unrelated to lung cancer, and these do not show up as "neighbors" to the UBE2D3 gene.

In this simple search, you uncovered several genes that could help researchers learn more about how lung cancer develops and how to design drugs against the disease.

To see a bioinformatics tutorial, go to http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=coffeebrk.box.666 and click on the presentation called "Aging and the Human Brain."

—A.Z.M.

Mastering Stem

AGAPITO SANCHEZ, JR.

BY EMILY CARLSON

Like many people turning 40, Peggy Goodell had hoped the monumental day would come and go quietly.

Goodell treated it like any other Wednesday: She got up, rallied her girls to school, and headed to work.

Laying low didn't last. Later that day, a man wearing a gold suit studded with rhinestones sashayed into her office, took her by the hands, and crooned, "Don't Be Cruel."

Turns out the singing Elvis was a "gift" from her dad, and Goodell, now 42, wasn't all that surprised. Her father, she laughs, has a knack for teasing her and her sisters.

That sense of humor must run in the family, because Goodell always enjoys a practical joke, even if it's on her.

Cells

"I encourage people to poke a little fun at things," she says.

Her job, though, is no laughing matter. A molecular biologist at Baylor College of Medicine in Houston, Texas, Goodell works in one of the hottest areas of science: stem cell biology.

She's studying how cells that all start out alike can turn into any of about a dozen different types of blood cells. Her findings could help improve treatments for leukemia, lead to new insights about aging, and advance a field in which so much remains unknown.

All-Purpose Cells

Stem cell scientists have worked with two types of cells: embryonic stem cells and adult stem cells. Both varieties seem to live forever, dividing indefinitely to give birth to even more cells just like themselves. Some of them will mature, or differentiate, into a specific type of cell.

Embryonic stem cells are particularly talented since they have the potential to become just about anything—cells of the heart, brain, stomach, you name it.

Adult stem cells, on the other hand, have already specialized and don't change careers.

"Adult stem cells from the skin can make skin cells, but they can't make blood cells," Goodell explains.

If you want to know the latest on stem cells, you'd better pay attention to the news. Scientists report new developments and discoveries about them all the time.

In fact, researchers recently announced that they had reprogrammed ordinary skin cells to function just like embryonic ones. The advance could offer a way to study stem cells without using human embryos, which have been the only source for isolating the embryonic master cells.

Goodell works mostly with adult blood stem cells called hematopoietic stem cells. (Their abbreviated name, HSC, is much easier to say!)

Scientists have been researching these cells for more than 40 years. Found mainly in the spongy marrow filling the hollows of our bones, HSC manufacture all our blood cells—from the red ones that carry oxygen to the white ones that fight infection.

HSC are extremely important since they constantly replenish sick or dying blood cells.

When people with leukemia or other blood cancers receive bone marrow transplants, what they're really getting is a supply of HSC that can produce healthy blood cells inside the body.

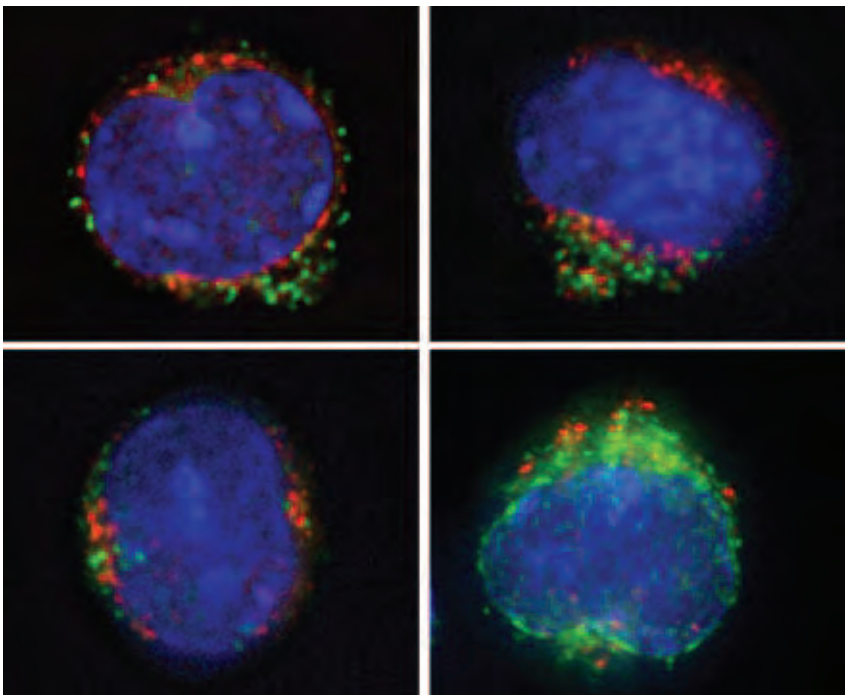
But HSC make up less than 1 percent of the cells in a quart of bone marrow—the amount typically donated.

While bone marrow transplants are life-saving therapies, they carry significant risks. Giving a higher proportion of stem cells in the transplanted cell mixture would help make this a safer procedure, Goodell explains.

To up the dose of the blood-making stem cells, Goodell is trying to coax HSC to make more of themselves in a lab dish.

Describing this process, Goodell conjures up an image of strawberry jam. Like the jam, bone marrow is a thick, jelly-like concoction stocked with seeds—stem cells.

"What I'd like to do is find a way to select out the 'seeds' from just a teaspoon [of marrow] and grow them," Goodell says.



KUAN LIN

▲ Hematopoietic stem cells (HSC, shown in this photo from a microscope) manufacture all our blood cells. A huge nucleus (blue) nearly fills each of these four HSC.

Major Players

Goodell and her lab group have figured out how to isolate HSC from bone marrow, and now they're looking for methods to grow them in a controlled way. One tactic is to study the mechanisms involved in the constant division of HSC and their decision to specialize.

The researchers have identified a handful of genes that they think play a role. Now, they're trying to figure out what each one does. In time, they're hoping to see the big picture of how hundreds of genes work together to instruct a cell to stay young, or to grow up.

Each person in Goodell's lab works on a small piece of the puzzle. Graduate student David Weksberg, for instance, is examining an HSC gene that helps the cells divide but also plays a role in triggering immune responses to bacteria.

Weksberg, who's finishing a combined M.D.-Ph.D. program (see "Dual Doctors," page 13), had tried out many labs before he settled on working in Goodell's.

"It was the best fit," says Weksberg, who attributes the lab's hard-working but laid-back vibe to its boss.

"The lab's personality comes from Peggy," he says.

Levity in the Lab

Goodell might not have experience hiring Elvis impersonators, but she does know how to mix work with fun. Like her dad, Goodell endorses humor as a key part of life. Laughter helps Goodell's lab members stay close while they work on the serious business of figuring out stem cells.

For example, when Weksberg was away at a scientific meeting, his lab friends neatly wrapped everything in his work area—notebooks, storage trays, canisters—in foil.

Another time, jokesters stuffed shredded paper in the ceiling and created a trapdoor so the confetti rained down on one of Weksberg's unsuspecting friends.

One Halloween, Goodell's students surprised her by each showing up in "Pregnant Peggy" costumes complete with black wigs, scarves, and bulging bellies. Undeterred, the boss—who was pregnant with her third daughter—joined her look-alikes for group photos.

GOODELL LAB, DAVID WEKSBERG

▲ Lab pranks and costume fun lighten the mood of doing serious lab work.

DAVID WEKSBERG

▲ Watch a Goodell lab video featuring the department chairman-superhero "Super-Art": http://video.google.com/videoplay?docid=-8512151439908280785.

Other lab Halloween themes have included the "Ballad of Peggy Bobby" race car costumes and the Simpsons (Goodell was Marge).

With Goodell's encouragement, Weksberg directs video skits about lab life for an annual competition sponsored by the Baylor genetics department. The top prize nets up to $3,000—enough to cover lunch for all the lab members at weekly meetings for 3 months.

The videos make working in the lab seem like a day at *The Office*, full of the characters and crazy situations familiar to fans of this TV show.

The 2007 entry tackles the topic of lab space—and spoofs the constant need for more of it. When the next-door neighbor of the Goodell lab

moves out in the fictional video, her students claim the vacated area for their research—and relaxation between experiments!

They turn blank walls into movie screens, abandoned desks into ping-pong tables, and an empty room into a dance club booming with hip hop by the rapper 50 Cent. Goodell, looking cool in red leather and black sunglasses, waits for the bouncer to let her in.

Alas, any permanent plans are thwarted when a new professor gets the space.

An earlier flick shows the department chairman as a fast-changing superhero flying through the sky with his laptop, ready to help students zero in on important data or simply get to hard-to-reach lab equipment.

Students typically spend a weekend filming the parodies, which they brainstormed earlier over pizza provided by Goodell.

Although hands-off with the production, Goodell herself was the mastermind behind the whole video competition. She got the idea from some British colleagues, who performed skits poking fun at lab life during their holiday parties.

She admits that she loved the British researchers' ability to laugh at themselves. She volunteered to set up the Baylor competition, establish the ground rules, and run the audience-voting system. So far, Goodell's lab has won about $8,000 in prize money.

"I love it because not only are the skits funny, they are a good team-building exercise," says Goodell, who has cameo appearances in almost all of the videos.

"The students really have a great time and are very proud," she says.

Making Connections

Along the way to studying the genes controlling HSC function, the Goodell lab has discovered many interesting things about the role of the stem cells in other biological processes.

For example, stem cells grow old.

Goodell says this shouldn't be too much of a surprise.

"As you age, most aspects of your body simply stop working as effectively as they did when you were younger," she says.

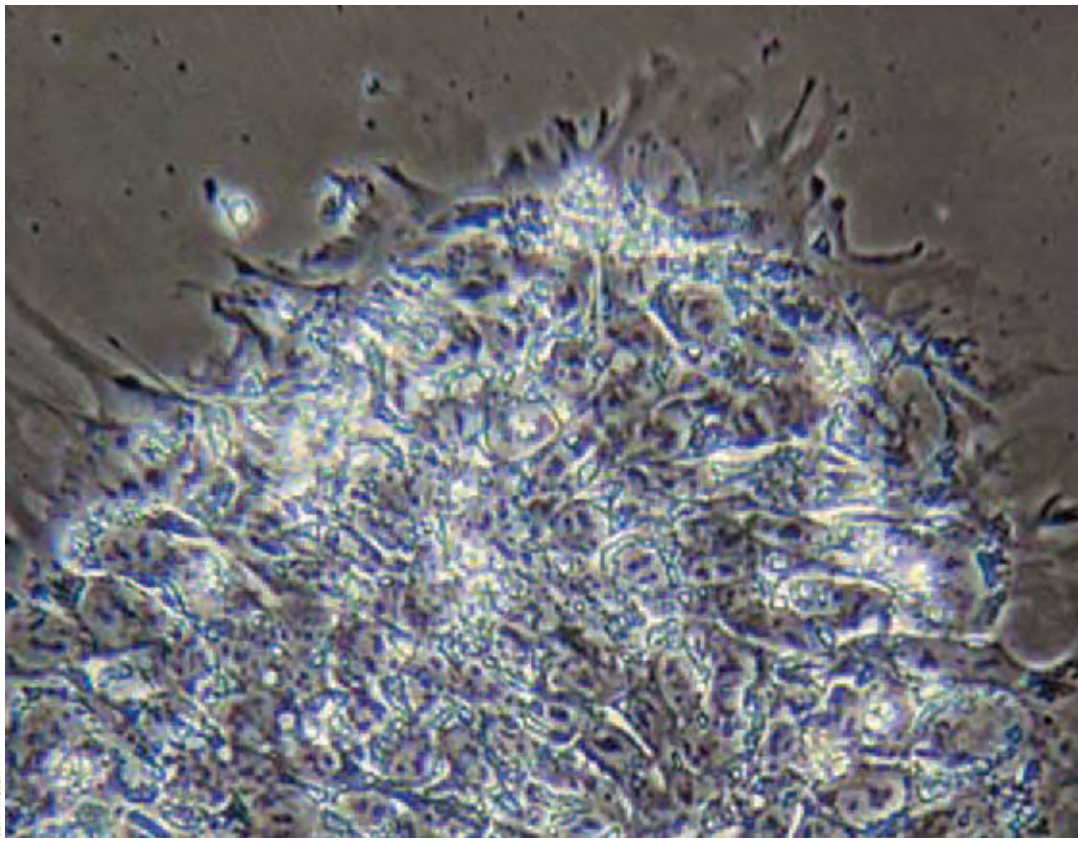
"If your blood stem cells are really just as good when they're old, then your immune system should be just as good. Obviously, we know that's not the case," Goodell adds.

But determining stem cell age isn't simple. And, it's not as exact as carbon dating or counting tree rings.

To show that HSC age, Goodell transplanted mice with stem cells from either young or old relatives. She found that the aged stem cells made fewer new blood cells, suggesting that they didn't work as well.

"Now what we're interested in," says Goodell, "is how we could improve stem cell function with age." Doing so could rev up immune function in older adults and lower their chances of developing blood cancers, for example.

Goodell has also found that stem cells and cancer cells have similar patterns of gene activity. This may explain why



JEFF MILLER

▲ These human embryonic stem cells are "blank slate" cells that can differentiate into any of the 220 cell types in the human body.

they share something else—their ability to divide endlessly.

Finding the genes that can control how stem cells grow could help other scientists find ways to *stop* cancer cells from growing.

Following Suit

Getting HSC to make more of themselves would be one way to produce a hardy supply of the blood-making stem cells for transplants.

Another way draws on the innate talent of human embryonic stem cells. Since these cells can make any kind of cell, Goodell is trying to cajole them into becoming HSC.

Goodell and other researchers don't yet have a good handle on how to tell embryonic stem cells to turn into nerve cells or skin or bone, for example. That's partly because the field is so young: Scientists first learned to isolate and cultivate the cells less than 10 years ago—not very long in the world of medical research.

"I love the work, and it's really important for health."

While some researchers are trying to guide the stem cells' differentiation by changing the environment in which they grow, Goodell is changing their genes.

All the cells in our bodies contain the same genes, but the genes differ widely in their activity. For example, skin cells sense heat, cold, and pain, whereas heart cells beat. That's because different genes are switched on and off in different cells, triggering a range of outcomes.

The same goes for stem cells: The genes in embryonic and adult stem cells differ in their activity. Goodell knows which ones are "on" in HSC, and she wonders if turning on those genes in embryonic stem cells could change the cells from wild cards that can be anything to cards that have to follow a particular suit.

"We still have a long way to go," admits Goodell. "But I love the work, and it's really important for health."

One More Hour…

The possibility of a breakthrough on the horizon keeps Goodell going—just like it did when she joined her sister Maryellen in Tanzania to hike Mt. Kilimanjaro.

At the time, Goodell had plenty else to do and many reasons not to go. She had just started her job at Baylor and still needed to set up her lab. Plus, she didn't even like to hike.

None of that mattered.

"Family is very important to me," says Goodell, who saw the trip as an adventure to share with her sister.

Just after midnight on the fourth morning of the 20,000-foot mountain climb, the guides woke up the Goodell sisters and the other hikers. They needed to reach the top before sunrise, otherwise clouds could block the panoramic views… and, more problematically, the path back down the mountain!

PEGGY GOODELL

▲ Peggy Goodell (left) and her sister Maryellen climbed to the peak of Mt. Kilimanjaro in Tanzania.

The group trudged on, clambering over giant rocks, scaling steep slopes, and growing even more exhausted.

"I wanted to quit," Goodell recalls. "But I thought, 'There's only one more hour of this. I can make it.' That's become a metaphor for my life."

Reaching that summit helped Goodell sustain her stamina when she returned to Texas to start and run a research lab.

As a student, she had learned how to do science, but now she had to basically manage a business. She had to hire people, fill out forms, get lab equipment, and apply for grants to fund her research.

"It's like you've never been taught to juggle and someone hands you 10 balls and says you have to get them all up in the air!" says Goodell.

Unlimited Potential

Now operating at full speed, the Goodell lab in its quest to grow HSC offers just one example of how scientists can use human embryonic stem cells. Goodell says that others could use them to study normal human cells, understand the causes of birth defects, and test the safety and effectiveness of medicines.

Scientists also see the cells as a potential source of replacements for diseased or injured cells in people.

Imagine curing diabetes by coaxing the master cells to produce insulin.

Or getting them to make the neurotransmitter dopamine to fix the brains of people with Parkinson's disease.

But a lot more progress needs to happen, says Goodell. Currently, only adult stem cells—mainly HSC and skin stem cells—are used to treat illnesses in people.

To teach more researchers how to work with human embryonic stem cells, which are notoriously finicky, Goodell has set up a training facility. There, researchers can explore the best conditions in which to grow and study the cells, ultimately advancing our understanding of the cells and realizing their potential.

"I think these cells are an important technology, and we want to encourage other scientists to learn how to work with them," says Goodell.

As for her own research, Goodell is still looking for the answers. She knows that she might find the key to growing HSC tomorrow, or she may spend the next 10 years looking.

"You never really know with science!" she says. ■

Dual Doctors

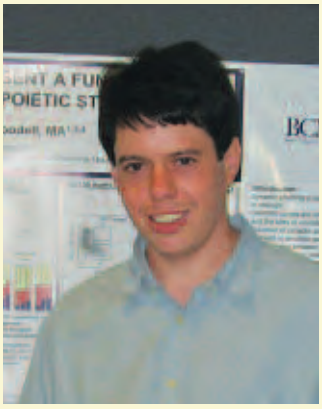
Want to be a doctor? What kind? One who sees patients (an M.D.), or one who does lab research (a Ph.D.)?

How about doing both?

Today, more than 40 medical schools offer joint degree programs that train students to treat patients *and* do research.

David Weksberg is one of them. In college, Weksberg liked asking questions and testing different ideas through experiments. But during his senior year, he realized that he also was interested in how that research could help people.

Physician-scientists bring special skills to research. They ask medically related questions that can help turn basic experiments into improved patient therapies.



ALLAN WEKSBERG

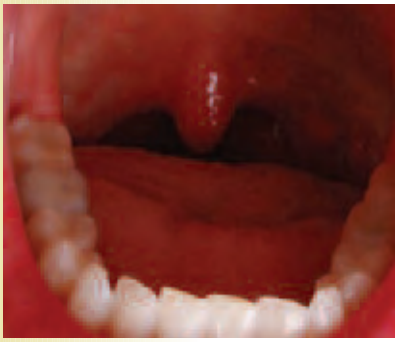
Dual doctors spend about 8 years completing both advanced degrees. They are in short supply and high demand.

Many types of financial support are available for this kind of training. Some programs pay tuition and offer stipends for living expenses. Loan repayment programs can offset debt if a student does research after he or she graduates.

Most M.D.-Ph.D.s work for universities or hospitals and split their time between the lab and clinic (see "Dr. Data," page 2). They do many different kinds of research: biochemistry, neuroscience, pharmacology, computer science, epidemiology, and bioethics.

Weksberg, who in his spare time shoots videos about lab life (see main story), is searching for genes that control how stem cells grow and divide. When he graduates in 2009 with both degrees, he plans to do a medical residency in radiation oncology. His career goal, he says, is to use stem cells to boost radiation-based cancer treatments.—*E.C.*

Just Found



Researchers use a miniature machine to get more information about mouth bacteria.

What's in Your Mouth?

You might feel the urge to brush your teeth after reading this story.

That's because there are more than 700 different species of bacteria living in your mouth! Most of them are good, helping with digestion and other normal functions. But some cause problems like tooth decay.

Scientists already knew that our mouths are teeming with microbes, but until now they didn't know much more. That's because it's been impossible to grow most types of mouth bacteria in petri dishes, where researchers can look closely at them under a microscope.

Now, a microbiologist-physicist team from Stanford University has invented a clever way to identify and analyze these bacteria without culturing them.

David Relman and **Stephen Quake** built a miniature machine that retrieves and examines a single bacterium in a scraping from unbrushed teeth.

The device pumps tiny volumes of chemicals that burst the microbe, push its contents through a series of chambers, and then read the microbe's genetic material. This information identifies the bacterium and helps explain its role in maintaining health or causing illness. —*Alison Davis*

Chemists figure out how microbes create the smell of dirt.

Chemists Smell Dirt

The smell of freshly plowed soil can signal that winter's frozen grip is finally giving way to spring.

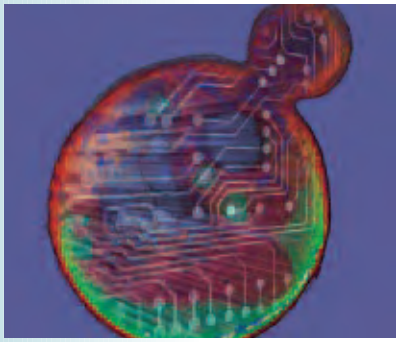
Like any odor, the smell of dirt is a volatile, or gaseous, molecule. After attaching itself inside the nose, an odor molecule sends an electrical signal to the brain, telling us what the smell is.

Scientists know that the odor of dirt is a molecule called geosmin (Greek for "earth odor") and that our noses are exquisitely sensitive to it. We can detect as few as five molecules of geosmin out of a trillion other molecules.

Researchers also know that bacteria and algae make geosmin in a two-step chemical reaction that breaks apart a larger molecule called a terpenoid.

Health researchers like Brown University chemist **David Cane** are interested in the chemistry of terpenoids because many of these substances are hormones, antibiotics, or other medically relevant molecules.

Cane recently discovered how bacteria and algae make geosmin. His findings should be useful to environmental and food chemists too, since geosmin can give drinking water, fish, and some vegetables a bad taste. —*A.D.*



CAROLYN LABABELL

A precisely controlled protein circuit in a yeast cell creates a simple form of "memory."

Molecule Memories

What if an organ could, by itself, "remember" what to do in an emergency? Could a lab-grown heart instantly repair damage to its cells after a heart attack?

This is still science fiction, but basic researchers are working to bring it closer to reality. As a first step, synthetic biologist **Pamela Silver** used an engineering approach to build a simple memory circuit in yeast cells.

Working with other Harvard University scientists, Silver constructed two genes from scratch—using bits of DNA that she stitched together with enzymes. Each of the genes contained instructions for making a type of protein called a transcription factor.

Transcription factors control gene activity—regulating how much or how little protein a gene makes. Silver created a feedback loop in which one protein switched on the other—and the cycle repeated—but only when very specific conditions were met.

By precisely setting the protein amounts, Silver created cellular "memory"—a system of working parts that behaved reliably and predictably in a particular situation. —*A.D.*

Scientists suspect that the flu virus vacations in the tropics.

Does Flu Fly South?

During flu season, we all know where the influenza virus spends its days and nights: hopping among unwashed hands and clinging to doorknobs, keyboards, and cell phones.

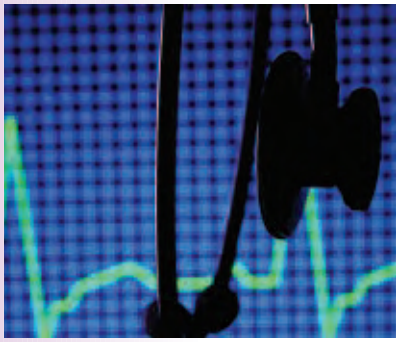
But where does the flu virus go in the off-season, during a North American summer? Does it lay low, "resting," waiting for warm temperatures or increased sunlight?

Or does it travel across the equator, visiting the tropics where it is warm year-round?

Biologist **Edward Holmes** of Penn State University tested the migration idea by comparing the DNA of flu viruses from New Zealand, Australia, and New York.

He discovered that the viruses were all pretty similar in their genetic makeup, suggesting that they spend time in the same place and trade bits of their genes.

Holmes thinks that place might be in the tropics—probably Southeast Asia—where animals and people live close to each other. The "vacation" likely allows viruses to mingle and exchange genetic material before heading off for new attacks on the human immune system the next winter. —*A.D.*



Gene-activity readouts may help determine an intensive-care patient's infection risk.

Rapid "Ribo" Readout

At the turn of the 20th century, doctors learned how to record electrical activity in the heart of a living person. Tracking this information over time led to electrocardiograms, now known as EKGs.

Fast-forward 100 years. Now, researchers have created a prototype of a "riboleukogram," which in a similar fashion tracks gene activity over time in a sick person's white blood cells, or leukocytes.

If the prototype's effectiveness can be confirmed in larger studies, riboleukograms may accurately signal infection changes in a critically ill patient just like EKGs indicate changes in heart function.

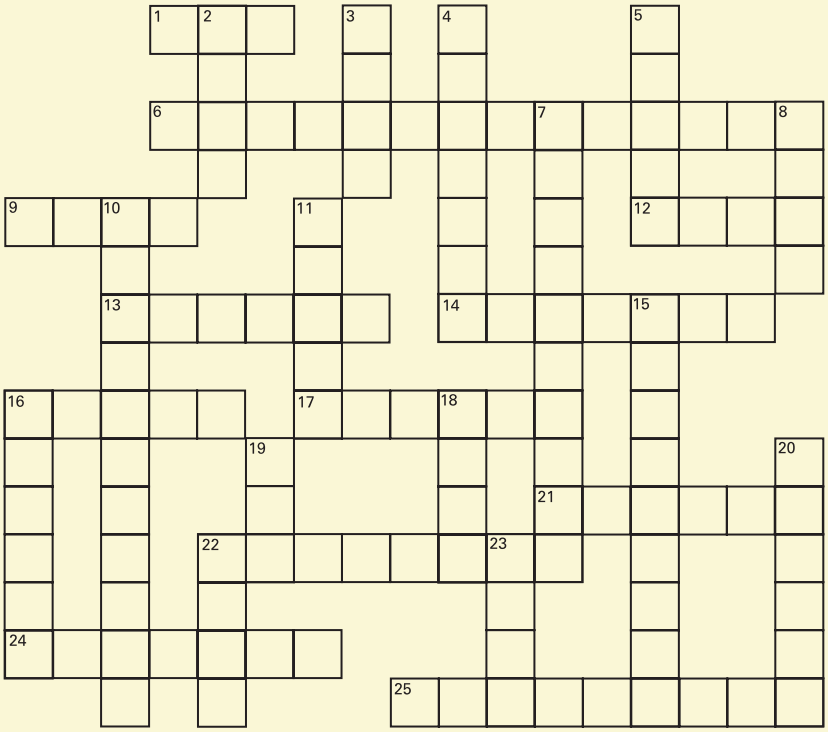
Intensivist **J. Perren Cobb** of Washington University in St. Louis and his team developed the new technology by collecting blood from intensive-care patients and measuring the activity of certain genes in their leukocytes.

A computer program then sorted the information into patterns that helped indicate a patient's likelihood of getting a severe type of pneumonia.

Rapid riboleukogram readout could be a powerful health tool for helping doctors intervene early, Cobb explains. That's because typical infection tests can take days—too long for many critically ill patients. —*A.D.*

These stories describe NIGMS-funded medical research projects. Although only the lead scientists are named, they work together in teams to do this research.

The Last Word



ACROSS

1. blood cell-makers
6. science of using computers to study biology
9. every one
12. otherwise
13. blood cell birthplace
14. stem cell scientist Peggy
16. career-committed stem cell
17. physician
21. any person
22. disease classification
24. dirt smell
25. white blood cell

Puzzle answers can be found at
http://www.nigms.nih.gov/findings

DOWN

2. short, funny play
3. skeleton piece
4. maturing
5. computational biologist Atul
7. DNA chip
8. master cell
10. calculation
11. red body liquid
15. these stem cells can become any cell
16. as in a play
18. group of three
19. bioinformatics program, for short
20. all the genes in an organism
22. what you're called
23. expert teacher

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