



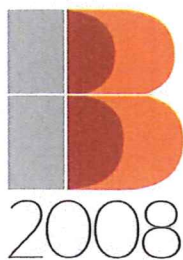
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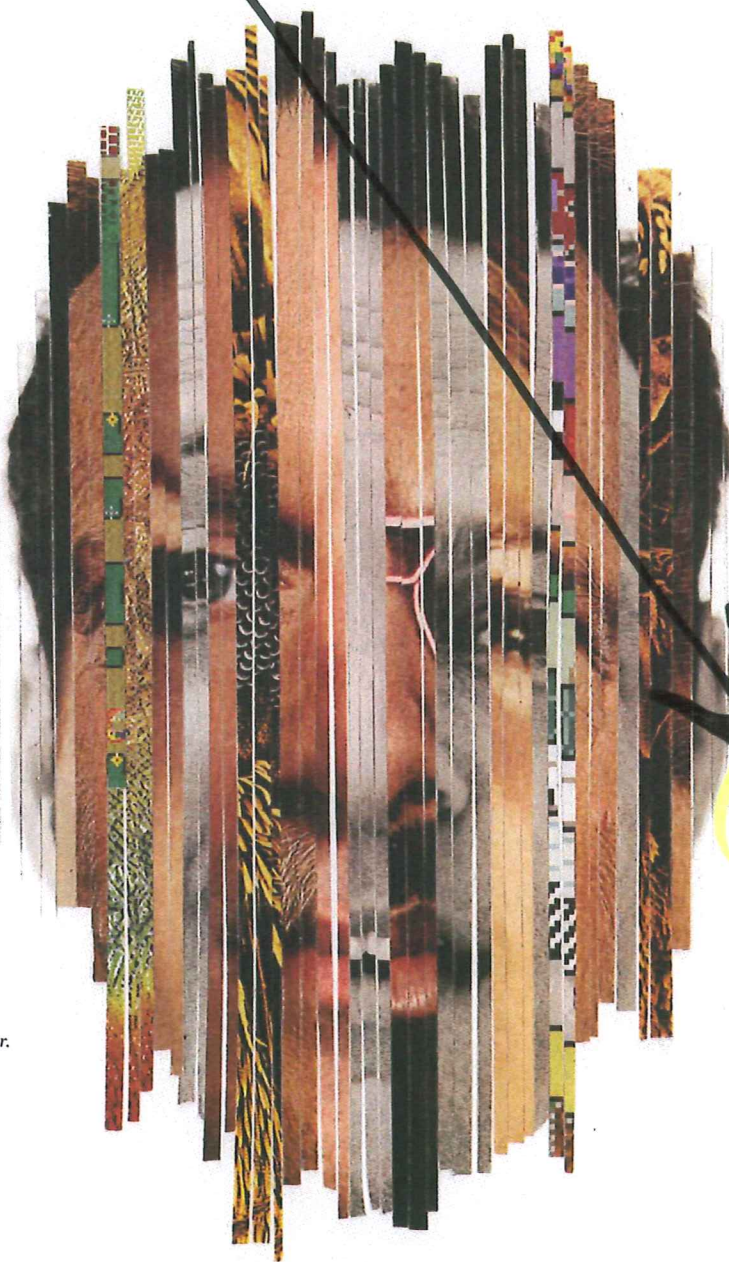
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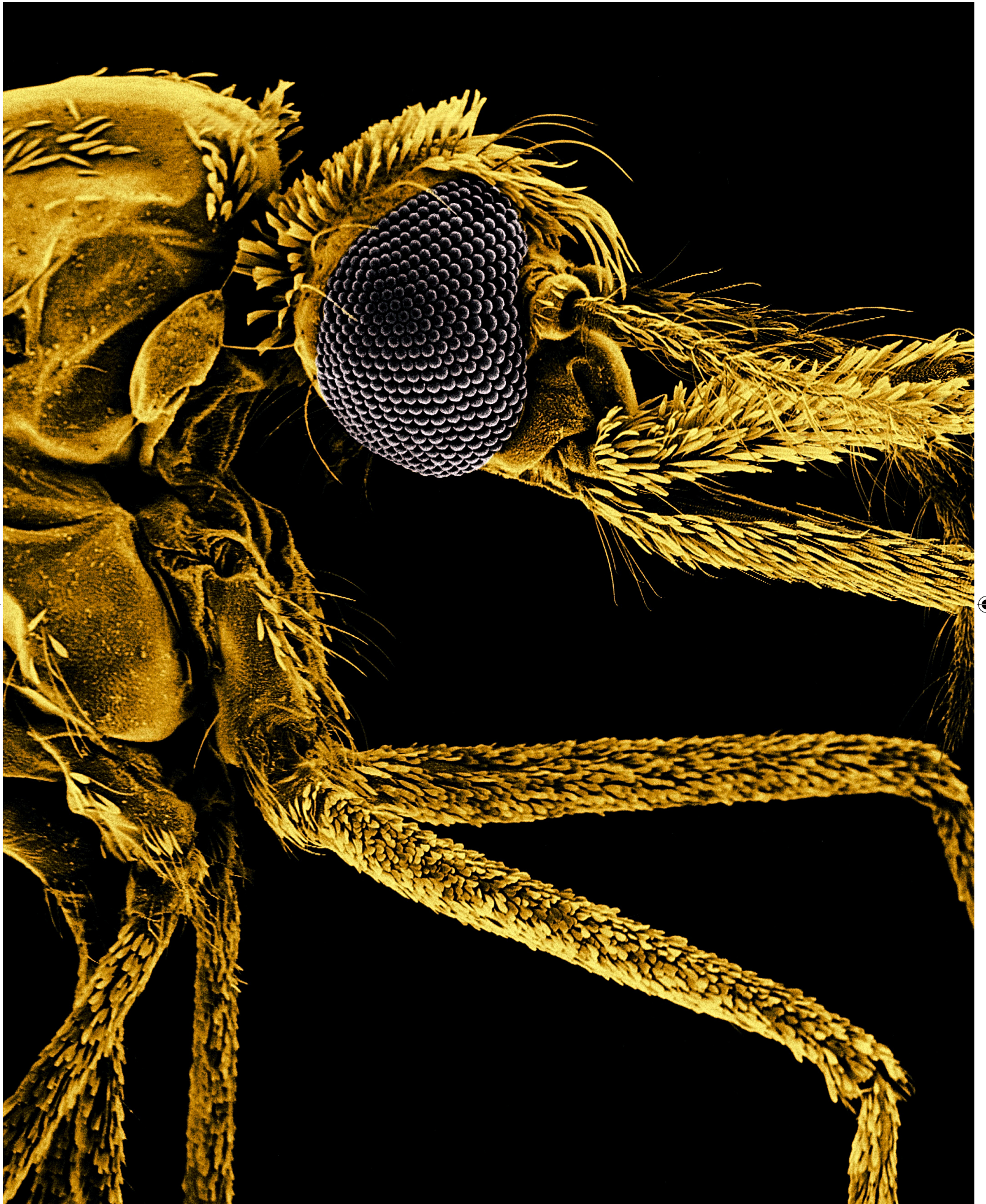
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Web advertising that is actually useful.

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The Persistent Primitive Dream of an Implacable Scientist and His Army of Mosquitoes

For decades scientists have been chasing a genetically engineered vaccine that would prevent the one million deaths that occur from malaria every year.

Stephen Hoffman thinks he's found a better one—in the mosquitoes themselves. By **JASON FAGONE**



SO YOU LIVE IN A HOT PLACE. It swarms with *Anopheles* mosquitoes. Indonesia. Venezuela. Ghana. Florida, thirty years from now, after global warming has pushed the mosquitoes north. You work outdoors in construction. Water pools in the dirt and mosquitoes breed in the stagnant water. Today the job's running late, after dusk. This is when the mosquitoes feed. A female pricks your arm, draws a blood meal. In exchange, she sends a dozen or so comma-shaped parasites down her salivary glands and into your body.

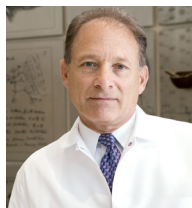
These parasites are genetic heirs to bugs as old as the primordial ooze. When they enter the body, they are immature little parasites: sporozoites. They have already had sex inside the mosquito; they need only to divide. For this, they find a warm, meaty place—your liver—and penetrate the liver cells they find there. Over the course of a week, each single sporozoite becomes an army of thirty thousand. Then the army hatches into the bloodstream, expanding exponentially. Your blood is now frothing with a billion copies of *Plasmodium falciparum*. If you don't take an antimalarial compound, all bets are off. Fever, chills, delirium, coma, death.

It turns out, though, that there is a way to disrupt the life cycle of the parasite. If a scientist zaps one of these mosquitoes with gamma radiation, the parasites inside it become weakened. If this irradiated mosquito bites you, the parasites travel to your liver, same as before. But now they just sit there. They don't cause you any harm, because they never multiply into an army or hatch into your blood. And yet the parasites—as the scientist can't help but notice—are still *alive*, meaning that, in theory, they're capable of priming an immune response. Which is how vaccines have worked for more than two hundred years, going all the way back to Edward Jenner's discovery that when he scraped some fluid from a cowpox blister into a cut on a little boy's arm, that boy was protected against smallpox.

But how can the scientist be sure that the things inside this live mosquito—these shocked, “attenuated” parasites—could truly provide protection against malaria?

If the scientist is Stephen Hoffman, he takes a small can and fills it with three hundred irradiated mosquitoes. He inverts the can, placing the mesh lid against his bare forearm, and a cloth over his arm to simulate night. He begins to feel a tickling sensation. Three thousand bites later, he withdraws the can. He has “vaccinated” himself. Then, two weeks later, he repeats the process, only with *infectious* mosquitoes instead of benign ones, and . . . waits.

IN HIS THIRTY-YEAR CAREER in tropical medicine, twenty-one of those in crisp Navy whites, Hoffman, sixty, has always been a dreamer. He trudged through the Colombian jungle while in medical school in search of a witch doctor and indigenous salves. Years later he traveled to the remote Indonesian island of Flores, rigging up a twelve-volt battery to a field incubator so he could test the native strains of malaria for resistance to drugs. He escaped death twice: first when a bout of typhoid fever in Ecuador roasted his body for days like a self-basting



Once the mosquitoes are irradiated, they are placed in petri dishes and sent to another room, where workers pull off their heads to reach the parasites—the vaccine.

turkey, then again, fifteen years later, when he and his wife walked away from a plane crash in rural Kenya, where they had been studying malaria in indigenous people. Yet he didn't put the can to his arm out of some sense of romance or dare. He did it because he had already tried to make and test a vaccine using more mainstream methods, and he had failed.

During the eighties at the Naval Medical Research Institute in Bethesda, Maryland, Hoffman's job was to make a malaria vaccine for marines deployed abroad. The era of genetic engineering was dawning, and Hoffman and his colleagues spliced and cloned loops of DNA. Once they had created a “recombinant” vaccine they liked, they shot it into their bodies, then used the can and the mesh and the cloth to give themselves a chaser full of parasites.

Two weeks later, Hoffman was speaking at a medical conference when, in midsentence, he felt a wave of coldness snap through his limbs, deep and sharp, and he lost control of his body. He staggered to a chair and sat down, his teeth chattering uncontrollably. This was a malarial “rigor,” his body's vain attempt to boil away the parasite now bursting his red blood cells.

For years afterward, Hoffman kept trying to refine the recombinant vaccine. As part of his efforts he also began experimenting with irradiated parasites. Scientists had known since the seventies that irradiated parasites were good at juicing the immune system to go on the attack. You could use them in the lab as tools to learn about the human body's response to infection. But what you couldn't do was use the parasites themselves to make a vaccine. Too impractical. Too primitive.

At least that was the scientific consensus. But Hoffman had chafed against consensus before. Back in the early eighties, when an alarming number of his patients in a Jakarta, Indonesia, hospital began dying from severe typhoid fever, Hoffman came up with a new cure—one that seemed foolish to most. But he and his colleagues went forward with it anyway, designed a study and got the data published; the treatment went on to become the new standard, virtually eliminating mortality for a disease that killed tens of thousands of people every year in Indonesia.

Now, years later, Hoffman was on the verge of another heresy. From 1989 to 1999, he had repeatedly dragged out the can and the mesh and the irradiated mosquitoes for ten military volunteers and himself. And of the eleven test subjects “vaccinated” with irradiated parasites, ten were completely protected from malaria. Hoffman included.

Hoffman looked over his data. It had been more than a decade since he'd begun work on the military vaccine, and it still

seemed years away. Yet the success rate from the irradiated mosquitoes was more than 90 percent. Was it crazy to think that the missing vaccine had been there all along?

IN A WORD, YES. There were so many potential pitfalls that it was hard to know where to start. For one thing, it was a question of money. Any funding for Hoffman's radical idea would have to be diverted from the grant stream of someone else's experimental vaccine, and it wasn't at all clear if that would be wise. As even Hoffman admitted, the genetically engineered vaccines did show some protective effects; the next generation of the old military vaccine, the one that had failed to protect Hoffman, has since proven to be between 35 and 66 percent effective in tests and could be on the market by 2011.

But this was merely the prologue to the case against Hoffman. Because even if you granted his two key arguments—one, that his approach was quick and could therefore get a vaccine to market in years and not decades, and two, that his approach could achieve unheard-of effectiveness—there were huge practical obstacles.

Vaccines are made inside gleaming sterile facilities manned by robots and computers. Hoffman's vaccine would have to be made inside mosquitoes. It would be like baking a pie in a cow. How would you extract it? By hand? With a little needle, one by one, mosquito by mosquito? And how would you separate the parasites from the surrounding mosquito goo—the “contaminating material”? (“All these irradiated mosquitoes that I was bitten by, and others, they were loaded with bacteria and fungi,” Hoffman says.) And even assuming you could do all that, how could you do it fast enough to make the one hundred million doses per year it would take to blanket Asia and Africa with a cure? Hoffman, for all these reasons and more, was a doubter himself, at first. He used to say, “You'd need an insectary the size of Texas.”

Yet Hoffman began to see the obstacles as a goad. He retired in 2001 and joined Craig Venter, one of the pioneers of the human genome, at his company, Celera Genomics. It didn't last long, as Venter was soon forced out of his own company, but it was long enough to gain an appreciation for the value of staking out a bold claim and holding yourself to getting it done. By 2002, when Hoffman presented his study on irradiated parasites at a scientific conference and received a less than enthusiastic response—“You could have heard a pin drop”—he was ready.

The irradiated parasites worked. That was the good news. Now he just had to prove he could manufacture them—in bulk.

SANARIA'S CORPORATE headquarters is on the second floor of a glassy office building in Rockville, Maryland. The reception area is astonishingly bare, the carpet dotted with forlorn stains; a sticker on the copier says *MALARIA SUCKS*. “As you can see,” Hoffman jokes, “we didn't put much money into the decor.”

Instead, the money—the bulk of a \$29.3 million grant from the Bill & Melinda Gates Foundation via the PATH Malaria Vaccine Initiative—has gone into a suite of twenty-two rooms behind a whitish keypad door just down the hall from the reception area. As you walk down the hospital-bright corridor and peer right and left into the rooms, you can see exactly what the money has bought: a ton of little blue booties for the Sanaria factory workers and white lab coats and lunch-lady hairnets and giant silver chemical hoods and boxy silver portals that connect each room and pass the factory's “product”—the vaccine-in-progress—from one room to the next.

The process is balletic, a dance of precision movements choreographed by Kim Lee Sim, Sanaria's [continued on page 189]

JON FAVREAU, 27. SPEECHWRITER

Fresh out of college, just in time to make history

On the night of the New Hampshire primary in January, a young man of twenty-six stood at the back of the crowd in the Nashua High gym and watched his boss deliver a speech conceding defeat to Hillary Clinton in the day's election. And even though his boss, Barack Obama, had lost, Jon Favreau couldn't help but smile. Obama had won big in Iowa just five days before, sending the Clinton campaign into a death spiral, but Hillary's surprising comeback meant that any notions of putting her away quickly were now dispelled. This would be a long, bloody fight for the nomination. Yet they all smiled. Had there ever been a more triumphal concession speech, ever?

And then the senator got to the emotional heart of the speech, the part when he recognized that nothing this big is easy. “For when we have faced down impossible odds, when we've been told we're not ready or that we shouldn't try or that we can't, generations of Americans have responded with a simple creed that sums up the spirit of a people: Yes, we can....”

Speeches claiming victory are never as interesting as those conceding defeat, because people are never more interesting than when they lose. In any case, neither Favreau nor his co-writers Adam Frankel and Ben Rhodes had been expecting to have to concede anything that evening. But things change quickly. After consulting with Obama for about half an hour—Obama talked, Favreau typed notes—they decided to reprise the hopeful refrain of “Yes, we can....” which had been the slogan of Obama's 2004 senate race in Illinois. And at that moment, a mere presidential campaign was transformed into a movement, coalesced around three simple words.

He is too busy to read much. “I'm embarrassed to say that since college”—



Favreau graduated from Holy Cross in 2003—“I've been so busy speechwriting for Kerry and then Barack that I haven't been reading all the good literary stuff I used to read back in the day.” As for speechcraft, while he says the speeches of Bobby Kennedy are his favorites, he also says Peggy Noonan is his all-time favorite speechwriter. He cites Ronald Reagan's Pointe du Hoc speech marking the fortieth anniversary of D-day as his favorite of hers, and in Noonan's sugary epic, you can hear the faint echo of Barack Obama talking about his grandfather.

Favreau also says he has greatly admired the writing of Michael Gerson, who was President Bush's main speechwriter for five years, especially his address to the joint session of Congress after the September 11 attacks. Gerson returns the admiration. One night in New Hampshire, he sought out Favreau at a campaign rally and introduced himself to talk shop.

And Favreau is right, Gerson's speech for Bush that September 20 was one of the great speeches in American history. But it must be noted here that with that speech the discord between speech and speaker has never been more pronounced, for we have come to know that Gerson's boss never fully grasped the power of words. With an exalting script, Gerson could make George W. Bush sound like Winston Churchill for an hour. But it is Jon Favreau's task and his gift that he is able to make his boss—a fellow who has been known to write a sentence or two on his own—sound like Barack Obama.

—MARK WARREN

Malaria Vaccine

[continued from page 177] vice-president and Hoffman's wife, whom he met twenty-six years ago at a tropical-medicine conference in her native Malaysia. Sim's team breeds mosquitoes by the thousands, feeds them human blood infected with *Plasmodium falciparum*, then irradiates them. A technician pushes a button on a giant blue kiln, which fills the kiln's hearth with invisible gamma rays that singe something within the cells of the parasites. The parasites are now in limbo, alive but unable to divide. Then it's harvesting time. Workers kill the mosquitoes with an alcohol bath, quick and easy, and then, one by one, they separate the male mosquitoes from the females (males don't transmit malaria), arrange the females on microscope slides, and use needles and tweezers to pull their heads ever so delicately from their bodies. Then they isolate the salivary glands full of the zombie parasites and dissolve away the contaminating mosquito material (How? "I could tell you," says Hoffman, "but then I'd have to kill you"), leaving only the zombies, irradiated and perfect and pure. In a small plastic vial less than an inch high, they appear as a clear, odorless liquid. Like water. Then the vial's placed into vaporized nitrogen for storage.

It's all so low-tech that it's easy to miss the engineering breakthroughs; many of the steps had to be invented by Hoffman's team from scratch. (For instance, because the parasites are so big relative to bacteria, Hoffman had to hire one of the world's foremost supercooling experts to build a customized cooling system.) Yet Hoffman won't apologize if it seems kind of primitive. That's the point: speed. It doesn't have to be elegant; it just has to be safe. "Anything that was not on the main path, we put on blinders for," Hoffman says. He can refine it later. After. After the first key test. The one he's been dreaming about for six years.

"Is it going to work or not?" says Dr. Christian Loucq, head of the PATH Malaria Vaccine Initiative and Hoffman's partner. "That's the big question."

This is what it means to make a vaccine nobody has ever made before, using methods everybody assumed would be unworkable. It means acknowledging the risks and the probabilities of failure and the unanswered questions, even as you try to show people how you've already beaten the odds. It means standing up at scientific meetings and answering the pointed questions of the Glaxo guys. ("Well, what about the contaminating material? Well, we've solved that. 'But what about the potency?' We've solved that. 'What about the quantity?' They kept trying to shoot us down.") It means trying not to squirm in your chair as a reporter from *The New York Times* presents you with a nasty quote from a competing vaccine maker in Paris: "Even calling it a vaccine is a compliment. . . . It is like Captain Ahab in the movie trying to kill Moby Dick with his knife." It

means that at any point, Hoffman "may encounter insurmountable hurdles," according to Dr. Myron Levine, director of the Center for Vaccine Development at the University of Maryland School of Medicine and an admirer of Hoffman's progress to date. "One by one, he has addressed those hurdles so far, and in fact has been able to overcome them," Levine says. It means that before Hoffman can sell the vaccine to First World tourists and Third World governments and global public-health agencies and replenish the grant money he has burned through—before he can give the vaccine a chance to prove its worth in human tests scheduled for the United States and Africa—he has to sit around and wait. The FDA has asked for additional safety tests, which should be completed by January. Safety studies are necessary but expensive. "You have to be so assiduous," says Hoffman. "And it's really good. We cannot do harm. The Hippocratic oath and all that. But it is mind-boggling."

Sanaria is almost broke. Hoffman is dipping into his own personal funds to keep the company afloat. He still has to make payroll every month for his forty-five employees, some of whom relocated to Rockville from foreign countries, seduced by the chance to work on the vaccine. In down moments it can get to Hoffman. There have been "extraordinary setbacks" in the past year; all six production runs have gone "perfectly," but before that there were major hitches, unforeseen expenses, dead parasites in the vials.

"It takes a toll," Hoffman says. "Personally."

"But it makes us better," Sim says.

Hoffman nods, seeming to draw strength from her. "But every time we do it, we get better and better."

This is what's so hard for Hoffman. His major creative leap as a scientist was to take this massive open-ended search for a malaria vaccine and redefine it as a basic engineering problem. And now he's in a position in which all his creativity has to be funneled into waking up every day and putting out a series of tiny fires before they have a chance to form a giant blaze.

And at the same time that he's struggling to veer away from worst-case scenarios, he has to plan for the best case—for human tests. In August, with funding from the National Institutes of Health, Hoffman put one of his employees on a plane to Accra, Ghana. On a separate plane, Hoffman shipped a vial of "research material"—Sanaria's irradiated parasites. The parasites were packed in a white box about the size of a minifridge, full of liquid nitrogen. When the employee landed, he retrieved the vials and checked to see if the parasites were still potent. They were. Then he took another plane and a 4x4 truck to a remote, heavily malarious region in the north of Ghana and checked the parasites a second time. Then he turned around and flew home. The vials arrived in Maryland, and Hoffman's employees tested the parasites again to make sure they were still okay, this vaccine that was never supposed to exist but exists, but exists. **■**



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