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by Michael Behar

NATURAL INTELLIGENCE

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In 2007, molecular biologist Ron Evans flipped a genetic switch on test mice and turned them into super-athletes. Headlines ensued, as did nervous references to human applications and “exercise in a pill.” Evans is still toiling away in the lab, and guess what? The day is coming.

BACK IN THE EARLY 1960s, when the architect Louis Kahn designed the airy layout of the Salk Institute—a collection of stark concrete towers aligned like teetering dominoes on a Pacific Ocean bluff in La Jolla, California—he oriented the buildings so that robust sea breezes would waft through the upper floors. But as I descend four flights of stairs to enter a sprawling subterranean lab, the sweet ocean air turns sour. Researchers at Salk are conducting cutting-edge experiments in genetics, biology, neuroscience, and human physiology. At the core of this futuristic work are 6,000 old-fashioned, defecating rodents, stacked in shoebox-size plastic cages, creating an odor far too potent for Kahn’s ingenious ventilation scheme to handle.

Despite the funk, the facility is meticulous. Wearing powder-blue scrubs, a surgical mask, a bouffant cap, and cloth shoe covers, I enter through a sterile clean room closed off between double doors. A whitewashed hallway adjoins various smaller labs, where mice are being injected with performance-enhancing compounds and forced to sprint on tiny treadmills. Others have had bits of their DNA reprogrammed to make them better runners. There are paunchy mice gorging on high-fat diets and svelte mice getting low-cal meals. Hunched over a metal table, a technician sorts through a squirming posse, plucking out prime studs for breeding and banishing aggressive males to solitary con-

finement. Mice are sacrificed and their muscles examined. Blood is sampled, hearts are inspected, kidneys and livers prodded.

This busy little world is the multi-million-dollar endeavor of Ron Evans, a 61-year-old molecular and developmental biologist who’s trying to crack the code of human endurance. With help from a team of 35 scientists, Evans has an ambitious goal: to develop the first-ever performance-enhancing drug that can radically boost physical endurance in humans.

The “exercise in a pill” project began during the summer of 2007, when Evans made a stunning announcement. While investigating obesity, he stumbled upon a genetic switch that unexpectedly turned his lab rodents into super-athletes. In August 2008, Evans published the findings in *Cell*, a prestigious scientific journal, claiming that in some cases his augmented mice could run 90 percent farther than ordinary critters. By comparison, it’s considered extraordinary when a human athlete’s performance jumps by only 3 percent. Evans’s breakthrough would be like transforming a dawdling weekend jogger into an Ironman contender overnight. And, as Evans assures me, “This wouldn’t require you to actually exercise muscle to gain a benefit.”

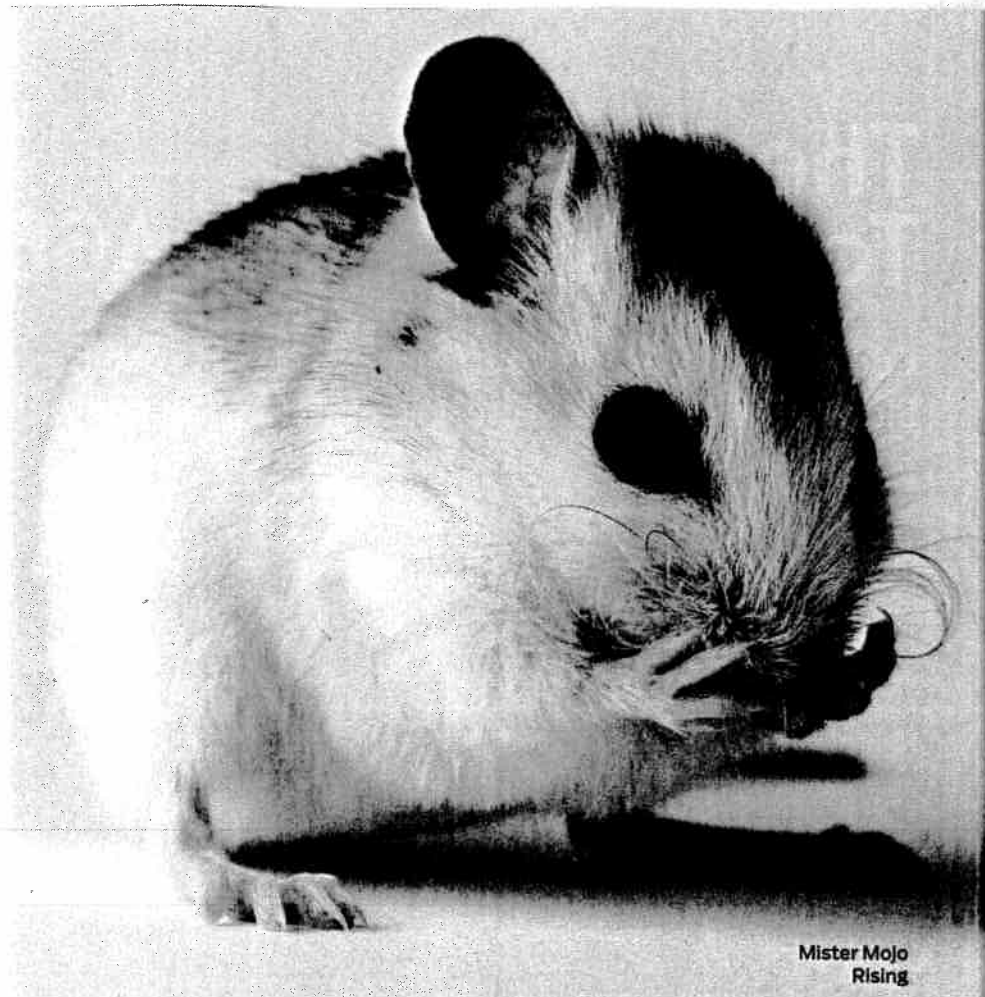
In the now famous *Cell* paper, Evans and his co-authors—a collaborative multinational team based at research institutes in California, Massachusetts, and South

Korea—confidently announced that they had found a way “to enhance training adaptation or even to increase endurance without exercise.” Physiologists who’d spent their careers deconstructing the sophisticated mechanics of exercise and its numerous benefits were skeptical, dismissing the notion of pill-popping your daily workout as ludicrous.

But that didn’t stop every major media outlet—including the big four networks, cable news channels, *The New York Times*, and *The Wall Street Journal*—from declaring the breakthrough a “couch potato’s dream.” *Nova scienceNow*, a PBS program, interviewed Evans, who said that “the benefit of exercise alone and the benefit of the drug [are] almost exact” and predicted that athletes would be the earliest adopters.

Though it may be years before doctors are writing prescriptions that turbocharge your training, serious people are aimed at that goal. Evans’s group is a front-runner in the race, but there are others: independent teams around the world developing naturally derived and synthetically engineered compounds that in preliminary animal experiments—and a few human tests—have measurably increased overall fitness.

Obviously, there will be hurdles. One is convincing biotech firms to back the costly studies required to create a marketable drug. Another is the U.S. Food and Drug Administration, which won’t green-light a new treat-



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ment that exists solely to help people run farther. (Scientists would first have to show that the drug can cure a real disease.) Even so, Evans believes that we're heading toward an inevitable day in which a pill will supplement and, in many cases, entirely replace exercise.

I FIRST HEARD ABOUT EVANS on the *NBC Nightly News*, shortly after slogging through a 40-minute treadmill run at my gym. When a smirking Brian Williams flashed the on-screen headline EXERCISE IN A PILL, my bullshit meter redlined. So I phoned Evans, who amiably assured me that his research was legit and invited me to visit his lab, where I could see his supermice firsthand.

Now, over the course of an introductory two-hour chat in his oak-paneled fifth-floor office, Evans, a SoCal native who's tan and slim and looks far younger than his age, does his best to simplify the science. When it comes to genetics and pharmacology—subjects I've covered for more than a decade—I'm usually a quick study. Not so today. Listening

to Evans delve into the complexities of cellular nutrient transfer makes my brain hurt.

Evans is goateed and wears frameless specs, designer jeans, a crisp blue oxford shirt, and black retro sneakers. On the windows, across the glass, he's scribbled elaborate equations that almost completely obscure the ocean view. Academic honors in elegant frames crowd the walls, with overflow awards aligned neatly along baseboards. On a shelf are three bobbleheads—one of Evans beside James Watson and Francis Crick, the legendary scientists who in 1962 shared a Nobel Prize with Maurice Wilkins for mapping the structure of DNA. There's a stainless-steel yo-yo on his desk and a half-empty bottle of Jose Cuervo on a coffee table. I ask about the tequila, but Evans, a wicked tennis player and avid swimmer, can't remember how it got there and would rather talk about Lance Armstrong's quads.

To be an endurance athlete like Armstrong, Evans explains, your leg muscles need lots of slow-twitch fibers. "Energy is stored in the

chemical form of ATP, adenosine triphosphate," he says. "The mitochondria, the powerhouses of the cells, break down sugar and fat to create ATP." Every endurance athlete knows what comes next: when ATP stores run dry, you bonk, hit the wall—kablooney.

Exercise creates more slow-twitch fibers and fuels a process known as "mitochondrial biogenesis." Put simply, train hard and your mitochondria multiply like microbes. More mitochondria equals more ATP and, whoosh, you're running sub-three-hour marathons. Among exercise physiologists, the consensus has always been that the only way to increase mitochondria was through intense, prolonged physical activity.

"Endurance is a matter of real-time generation of ATP, and it was thought that exercise was the only way to get the system to work better," says Evans, who accepted this idea until 1998. That's when he began exploring the role of genes in obesity, homing in on a genetic switch called peroxisome proliferator-activated receptor delta, or PPAR-delta,



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a protein known to regulate metabolism and fat burning. When your body demands fuel, PPAR-delta can influence whether it chooses glucose (sugar) or lipids (fats).

At rest, PPAR-delta is dormant. But during exercise it awakens to sustain a metabolic chain reaction that produces muscle fibers with slow-twitch properties, which feed on body fat. Vigorous exercise isn't an option if you're morbidly obese, though. So Evans wondered: what if we exercised the gene and not the muscle? Activate PPAR-delta, his thinking went, and fat-eating slow-twitch fibers would materialize like blades of grass sprouting from a freshly watered lawn.

In his first experiment, Evans coded the PPAR-delta gene to activate only in fat cells, where he thought it would have the most impact on weight loss. "We reengineered PPAR-delta in mice to be permanently on, like a light switch," he says. "What happened was a bit of a miracle. The animals slimmed down and were resistant to weight gain even on a high-fat diet." Fat cells in the mice had become more oxidative, similar to what happens when you blow air over smoldering coals and they erupt into flames. The cells could, quite literally, vaporize excess blubber.

Impressive results, but Evans wasn't satisfied. By 2004 he'd figured out how to tweak the PPAR-delta gene to fire in muscle cells. If the muscle became oxidative, like in the fat-cell experiment, it would cultivate the growth of mitochondria-rich slow-twitch fibers, essential for endurance.

Recalling all this, Evans grins broadly, eager to reveal the outcome. "We got marathon mice—an entire strain of animals that had become long-distance runners without ever having had to run," he says. "We proved that endurance could be genetically engineered through this particular switch. And the switch stayed on, and could be passed on as a genetic trait. You could have a whole lineage of long-distance-running mice."

WHILE WE TALK, Evans sits cross-legged in a sage-colored lounge chair, fiddling with pencil-thin paper wands that resemble giant chopsticks. He makes them by rolling together discarded Post-its. "Humans and spotted hyenas are endurance predators. They wear their prey out," he says, delving into a tangential discussion of fast-twitch muscle fibers in primates. I nudge him back on topic. "So we wanted to find a drug that could activate the PPAR-delta switch by injection or pill," he says, "because genetic

engineering is impractical."

At this point Evans leaps from his chair and starts pacing in front of a large whiteboard. He grabs a red marker and draws a box. Inside, he writes "GW1516." "This is a Glaxo compound," he says, referring to the pharmaceutical giant GlaxoSmithKline, which, Evans learned, had created GW1516 more than a decade ago, later making it publicly available for biotech researchers. "They were developing it to trigger the PPAR-delta switch, because they had observed that in obese primates it tripled HDL levels, the good cholesterol." Glaxo test subjects had been receiving GW1516 in intermittent doses—enough to increase HDL but not a lot else. GW1516 was available commercially, so Evans ordered up a batch and fed it to his mice every day for five weeks, a dose that far exceeded amounts given in any previous experiments. "The effect was huge!" he says.

It sure was. Couch-potato mice could eke

winner was a chemical compound called AICAR (pronounced *aye-car*), which had been around since the 1980s and was being used in clinical trials for the treatment of ischemic reperfusion, a rare complication of coronary bypass surgery that occurs when blood flow restored to previously damaged arteries causes inflammation and damage to heart tissue.

"We knew AICAR could stimulate a more oxidative metabolism," Evans says. "There were reports that it had been given to people, and activity in muscle had been measured. But these studies were all based on single injections. They weren't giving it once a day for 30 days. When we did that, the results were beautiful!"

Once again, here was an experimental compound readily available to scientists—but one that nobody had thought to test in a high-dose way. Mice that hadn't done any

"We got marathon mice," Ron Evans says of his genetically tweaked lab rodents. "An entire strain of animals that had become long-distance runners without ever having had to run."

out a lame two-thirds of a mile. The same was true for mice given GW1516 that didn't train. Mice that didn't get GW1516 but did ten-minute daily stints on a treadmill eventually hit 1.1 miles. But mice that had both—training and GW1516—easily hit 2.3 miles.

In short, the drug had doubled the normal performance-enhancing effect of regular endurance training. Unlike mice with genetically altered PPAR-delta, GW1516 had no impact on sedentary animals. Exercise, it seemed, was an essential part of the equation, though Evans didn't know why.

He submitted the results to *Cell* in 2007. But the editors wanted more and initially refused to publish his paper. "We had ended the story with a drug working in the context of exercise, and the *Cell* reviewers said, 'Look, you can't leave us hanging, because if what you're saying is correct, then the real breakthrough would be to completely replace exercise! They wanted us to take it to the next level, to find a drug that could enhance performance without any exercise. That was something nobody had done before, and we didn't think it was possible."

Evans persisted, searching for another substance to flip the PPAR-delta switch. The

exercise but were given AICAR could run 23 percent longer and 44 percent farther than sedentary mice that didn't get the drug.

Sure, it wasn't the doubling of endurance seen with GW1516. But the AICAR mice hadn't trained at all. They'd become remarkably fit by doing nothing.

ONCE WORD GOT OUT about AICAR and GW1516, Evans figured that human athletes would jump the gun and start ingesting the stuff. Before Evans published his *Cell* paper, he tipped off the World Anti-Doping Agency (WADA), the Montreal-headquartered outfit that sets drug-testing and enforcement policies adopted by every Olympic and many non-Olympic sports. WADA asked him to devise a test to detect the drugs in urine and blood and added both compounds to its list of banned substances. It didn't take long for the drug to make news: the French Anti-Doping Agency alleged that AICAR had been used by riders in the 2009 Tour de France, though it never came forward with specific allegations or named names.

Meanwhile, on supplements-oriented Web forums like RxMuscle.com, the buzz grew quickly. "I can't wait!" one poster

declared. "Give me some of that GW1516!" Another wrote: "AICAR is already available on the grey market." There's also an online clearinghouse, aicar.co.uk, which provides AICAR data and calls the compound "a new dawn in dieting and fitness ... the revolutionary AICAR and GW1516 are the newest buddies of athletes."

Other studies have shown that a healthy abundance of mitochondria can mitigate aging and make it easier to lose weight, factors that will likely extend AICAR and GW1516 use well beyond a handful of zealous endurance athletes. And as Evans points out, "These compounds are easy to make or obtain." He shows me a Web site where a licensed research institute can buy GW1516 online; AICAR is also available from biotech suppliers. "Type 'purchase AICAR' into a search engine," Evans suggests. I quickly find some, though it's not cheap: a thousand bucks for ten grams, about 20 times the street price of cocaine.

Though AICAR is easy to buy, that doesn't

mean it's safe. "The big problem with AICAR is the side effects," says Laurie Goodyear, an associate professor of medicine at Harvard Medical School and senior investigator at the Joslin Diabetes Center. "Athletes would get a huge increase in lactic acid. There's also a molecular mutation in the heart that can lead to sudden death. Certainly there's a possibility that drugs could be developed to increase endurance. But I don't believe AICAR would improve performance in humans." In 2008, Goodyear wrote an article for *The New England Journal of Medicine* that examined Evans's claims. Her parting advice: "Don't get too comfortable on that couch just yet."

In addition, Evans's mice were couch potatoes that had never exercised. With a fitness baseline of zero, there's plenty of room to improve. "If you have a highly trained athlete that already has high levels of mitochondria," Goodyear says, "it's possible they may get some benefit, but I don't think it would be really huge."

Mark Davis, who directs the Exercise Bio-

chemistry Laboratory at the University of South Carolina, believes that in elite athletes mitochondria hit a ceiling at some point, in part because "too many of them can actually be toxic to the cells."

EVANS ISN'T DISSUADED, but he's also aware that the FDA won't approve any drug unless it has a specific disease application. So his team is focusing its resources and funding on identifying legitimate therapeutic uses for AICAR and GW1516. He's been talking with biotech firms about funding clinical trials that "target frailty, or people in wheelchairs who can't exercise, or who've gone through surgery and are bedridden." There's also potential for treating diabetes, high cholesterol, obesity, metabolic disorders, and muscular dystrophy. Still, Evans isn't bashful about admitting where the real money will be made.

"If approved, this can be prescribed by doctors for anything you want," he says. "And very few people in this **continued on page 91**

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DROPPING IN **continued from page 27**

country get the recommended minimum of 40 minutes a day of exercise. So when you ask me who would want a drug that confers some of the benefits of exercise without actually exercising, it would be the majority of the population."


That's the kind of market pharma love—and it's why Evans isn't the only one dreaming of riches. "We're doing the same thing with resveratrol as Evans did with AICAR," says Johan Auwerx, a professor of energy metabolism at École Polytechnique Fédérale de Lausanne, in Switzerland. "There is a healthy competition going on between us." Resveratrol, in case you missed it being touted on *Oprah*, *60 Minutes*, and *Good Morning America*, is a potent antioxidant found in the skins of red grapes. In mice given colossal doses—to match them, you'd have to chug something like 50,000 bottles of wine a day—it curbed aging, lowered blood sugar, slowed the spread of cancer, and spawned mitochondria.

"Our mice ran longer when we gave them resveratrol," says Auwerx, who is now trying to identify other natural compounds more potent still, to be taken as an over-the-counter supplement.

Evans is one of only a few scientists targeting endurance through genes—and that, he believes, gives him an edge. "A lot of people study the end result [of exercise] or study hormones," he says. "But what controls everything is the genome. It's the heart of the entire system, and it's what I'm interested in changing." First, though, he must test hordes of mice for every conceivable side effect, inject them with varying dosages of AICAR at different intervals to establish an optimal treatment program, and demonstrate that his compounds can do something other than just endow rodents (and ultimately humans) with superlative endurance. There's also that minor little discrepancy between rodent and human physiology: after all, the list of prototype miracle drugs that performed spectacularly in mice, and then failed catastrophically during human clinical trials, is long and sordid.

IN THE BASEMENT LAB at the Salk Institute, my escort—a bespectacled postdoc with a boyish smile, named Vihang Narkar—raises another concern. Athletes rely on mental stamina as much as they do physical fortitude to push through pain, a phenomenon that could make it tricky to accurately assess the potency of AICAR or GW1516 in people. Our tendency to either persevere or succumb is inextricably tied to both brain and brawn. But according to Narkar, mice bonk for only one reason: their muscles are simply depleted of every last bit of ATP.

While chatting with Narkar, I sort of forget



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about the "wild" mice we've left on the treadmill, which he'd set up earlier to demonstrate a typical training session. Neither has been tainted with the magic jock-juice, and they appear identical—just two ordinary plump and furry rodents with no discerning features that might hint at physical prowess. They've been plodding along for 20 minutes or so without much fuss.

Then Narkar ups the belt speed to 18 meters per minute (roughly two-thirds of a mile per hour) and the mice burst into a gallop. He pushes it higher, to 22 meters per minute, and the mouse closest to me takes the lead—a born athlete, for sure—while the slower mouse languishes. Suddenly, the speedy mouse dashes right off the end of the belt,

springs from the treadmill, plummets four feet onto the floor, and is headed in a blind sprint for the door when Narkar nabs it with a lightning-fast lunge-and-swipe combo that he's definitely performed more than once.

I insist that Narkar mistakenly grabbed an AICAR mouse for this demonstration. "Some wild mice are just inherently better runners," he says. It's apropos that he recognizes its natural athleticism—often the game-changing wild card integral to competitive sports—since he's part of a team developing drugs that could give any beer-bellied schlub a fast-track ticket to the peloton. ○

BOULDER-BASED MICHAEL BEHAR IS A FREQUENT CONTRIBUTOR TO *OUTSIDE*.