The Future

Think performance enhancers are a problem now? Welcome to the era of the genetically engineered superathlete

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By David Epstein

I am one of the most avid sports fans you'll find," Se-Jin Lee says. It's true. He'll watch anything. Basketball. Football. *Fútbol.* Billiards on channel seven-hundred-whatever. As a graduate student in the '80s Lee used to sit in his car in the driveway with the radio on to listen to the games of faraway baseball teams. Even now, in his lab at Johns Hopkins Medical School in Baltimore, he easily rattles off the NCAA basketball tournament winners in order from 1964 to 2007. And, like anyone who values fair competition these days, he's disturbed by the issue of performance-enhancing drugs in sports.

Why, then, is Lee working to usher in technology that will make even today's most inventive doping methods look primitive? A professor of molecular biology and genetics, the 49-year-old Lee studies genes that tell muscles what to do -- genes that he knows how to change. As clever as chemists are in altering steroid molecules to avoid detection (recall BALCO's THG, a.k.a. "the Clear"), those designer drugs can be spotted once antidoping agencies know what to look for. Even human growth hormone will be detectable soon, after a valid blood test becomes commercially available. But if athletes develop ways to alter their genes, the very blueprints for their own muscles, there may be no test of blood or urine that can pick that up.

Lee is pushing the frontier of genetic research into muscle building because the same breakthroughs that could boost performance in sports might also bring about a medical revolution. Advances could not only mitigate the effects of diseases like muscular dystrophy but also give senior citizens back their strength -- which, often, would amount to giving them back their lives.

In 1995 in his lab on North Wolfe Street, Lee and two colleagues identified the function of myostatin, a protein that tells muscles when to stop growing. It does so, scientists believe, by signaling "satellite cells," or stem cells that lie dormant around the muscle until they're needed to build or repair it. Experimenting on mice, Lee inactivated both copies of the gene in the animal that code for myostatin. The result: Over four to six weeks the rodents developed twice their normal muscle mass without a formal exercise regimen. After Lee's results were published in 1997, he was awash in e-mails from people with muscle-wasting disease (no surprise) offering themselves as subjects for human experiment. He got similar offers (surprise!) from

After discovering how myostatin affects muscle, Lee was flooded with inquiries from athletes.
Simon Bruty/SI

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bodybuilders and athletes. Imagine: double the muscle mass. Could he do to them what he had done on the mice?

Some of the athletes barely knew what they were inquiring about. They'd ask Lee where they could purchase some myostatin. "Of course, they didn't want myostatin," he says. "They wanted to block it." But if they could block it with a synthetic gene, the alteration would be a part of their DNA, and it would last for years at the center of their cells. The most straightforward way of detecting the new gene would be to remove a piece of the muscle and probe for it, a procedure most likely too invasive for widescale use. It would be enough to make one long for the simplicity of the steroid era.

The year after Lee's mice results went public, H. Lee Sweeney, a physiology professor at the University of Pennsylvania, published a paper detailing his own mighty mice, which he had injected with a gene engineered to produce a muscle builder called insulin-like growth factor (IGF-1). Sweeney, too, was inundated with inquiries from athletes. He says a high school football coach and a high school wrestling coach volunteered their entire teams as guinea pigs.

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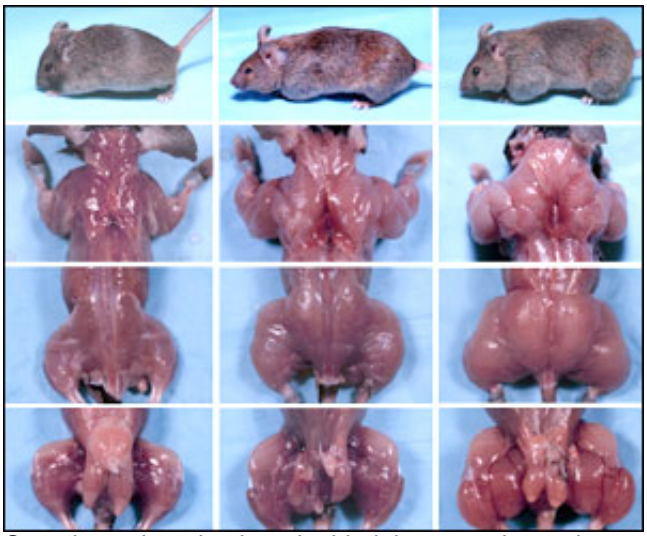
Since the gene genie escaped from the bottle a decade ago, researchers have discovered dozens more genes that appear to affect athletic performance. This is old news in the rodent community. Scientists have created mice whose bodies are flooded with oxygen-carrying red blood cells, creating greater endurance. Other mice have been engineered to produce extraordinary amounts of growth hormone, while still others metabolize fat and carbs in such a way that they can live like couch potatoes yet run like marathoners.



Genetic engineering has doubled the normal muscle mass in mice without the use of an exercise regimen. 2008 National Academy

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Significant safety hurdles remain before gene therapy is widespread for humans. The most efficient means of delivering a synthetic gene is by attaching it to a virus that shuttles it into human cells. Viruses are great at that. They can also trigger the immune system in a way that can lead to fatal results. In 1999 Jesse Gelsinger, an 18-year-old with a rare liver disease who had volunteered for a gene-therapy trial, died from a massive immune response to the virus used in the treatment. And the dangers extend beyond the immune system. In a gene-therapy trial in France, 12 boys were successfully treated for X-linked severe combined immunodeficiency, commonly known as Bubble Boy syndrome, but at least three of them developed leukemia.

One delivery method -- flushing the bloodstream with the desired gene -- is simple enough, says Sweeney, that it could be achieved by a clever undergrad in a molecular biology lab. The method is not very efficient and hasn't been thoroughly tested, but it hints at the possibilities for the spread of gene tampering in sports. Despite the unknowns and the dangers, chances are good that someone at the Beijing Olympics in August, someone willing to weigh his or her mortality in gold, will have undergone gene transfer in an attempt to enhance performance. "Even when I tell them it's not safe," Sweeney says, "some athletes are willing to try anything."

The signs are ominous. In January 2006, during German track coach Thomas Springstein's trial on charges of providing performance-enhancing drugs to minors, evidence emerged indicating that Springstein had attempted to procure Repoxygen, a gene-therapy drug developed to treat anemia by prompting cells to produce EPO and, in turn, red blood cells. (He was found guilty of giving illegal substance to minors and received a 16-month suspended sentence.) In addition, Mauro Di Pasquale, the 1976 world powerlifting champion and an Ontario physician who has written several books on sports doping, says he knows that athletes are experimenting with gene doping, with the help of Chinese doctors and researchers.

Human data relating to myostatin has been hard to come by. Soon after his discovery, Lee attempted to identify potential test subjects with natural mutations in their myostatin genes. He placed an ad in *Muscle and Fitness*, and close to 1,000 muscle-bound men and women responded. But after collecting samples from 150 of them, he has yet to find a single one with the myostatin mutation he had engineered in his mice.

From his study of Belgian Blue cattle, Lee knew the mutation could occur naturally. A cross between the Shorthorn and the Holstein, which have been bred for some 150 years, these massive animals look as if their skin has been stuffed with watermelons. Lee got in touch with Dee Garrels, owner of the Lakeview Belgian Blue Ranch in Stockton, Mo., who sent him samples for testing. Garrels knew Belgian Blues were strong -- her 2,500-pound bull once ripped a metal restraining gate off its hinges with its horns to get at a cow in heat -- and Lee found out why. He discovered that they had mutations in their myostatin genes.

Lee didn't see the power of a human myostatin mutation until Markus Schuelke contacted him in 2003. A pediatric neurologist in Berlin, Schuelke had been summoned three years earlier to examine a jittery baby in the nursery at Charité hospital in Berlin, where he was taken aback by the newborn's chiseled calves and sculpted quads. By the age of four the boy could hold up a pair of 6.6-pound dumbbells at arm's length. Schuelke had been monitoring the boy's development, and he got in touch with Lee, who confirmed the boy had mutations on both myostatin-coding genes, leaving no detectable amount of the protein in his body.

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Apparently it ran in the family. The boy's mother, who was 24 when she gave birth to the "superbaby," had a mutation on one of her two myostatin genes, presumably leaving her less of the protein than normal but not so little that she was as muscle-bound as her son. Nevertheless, she is a testament to the tantalizing temptation of gene-doping. Superbaby's mother, the only adult in the world with a documented myostatin mutation, was a professional sprinter.

The world anti-doping agency has banned gene tampering in athletes and spent millions attempting to develop tests to identify it. Such a procedure will require technology unlike any employed by antidoping scientists. The theory, according to Ted Friedmann, the scientist leading WADA's search for gene-doping countermeasures, is to fight genes with genes. If one medical breakthrough is revolutionizing doping, perhaps another can beat it back.

Thanks to the Human Genome Project, someday all of us could carry our entire genetic blueprint on a microchip, which we'd present to doctors during medical treatment. As that technology matures, Friedmann hopes athletes' genomes can be screened, and that gene-doping markers or signatures will emerge.

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As pharmaceutical companies race to turn genetic research into medicine, new gene-therapy drugs could come to market en masse over the coming years. In practical terms it will be impossible to develop specific tests for each of them. "We can keep buying instruments and keep building labs," says pharmacologist Don Catlin, founder of the UCLA Olympic Laboratory, "but [the antidoping] industry isn't like Exxon. There are certain limits."

Perhaps a time will come when there is no longer a need to define those limits -- not because of new artillery in the war on doping but because gene therapy will have become so widespread that it will be as controversial as Flintstone chewables. So far Sweeney has aided antidoping officials. "But I've often told WADA my position would change if [gene therapy] is proven to be safe," he says. "Then we're withholding something that would make the athletes healthier."

That would, in turn, raise a new series of questions: What is it we seek to gain from sport? Do we *want* to see larger-than-life behemoths swatting 600-foot home runs? Or do we prefer to see people more like us pressing the limits of their strength and skill? After all, with their legions of doctors and coaches and cutting-edge equipment, professional athletes, doped or not, are hardly us.

The gravest danger in the debate over gene transfer is not that athletes might taint sport by tampering with their genes. It's that by abusing such treatment, they'll create the same stigma for gene therapy that they have for steroids.

Pat Furlong has felt the effects of that stigma. She is the head of Parent Project Muscular Dystrophy. Her two sons began life happy and healthy, "and then over 10 to 15 years, you watch them go away, helpless," she says. Part of her job is to persuade parents of kids with

muscular dystrophy and their doctors that anabolic steroids are beneficial. "I get calls from parents nervous about steroids because of what they've heard," she says. "But the flip side is that steroids have benefits in people who are losing function. In Duchenne muscular dystrophy, it's all we have.

"We know there's no drug that will come without side effects, but steroids are an option to preserve and protect muscle for a few minutes longer, or a few months longer, or a few more years." The local newscasts, and Congress, rarely mention the part about how they can help kids with MD walk longer, which keeps their spines straighter and helps them breathe better.

As he stands at the edge, looking over the gene-doping precipice, Se-Jin Lee has similar concerns. The hysteria that will ensue when an athlete is caught gene-doping, Lee frets, will result in restrictions on gene-therapy drugs, making them hard to obtain by those who truly need them.

"If [an athlete] did cheat, it was his choice," Lee says. "If [the league] turned its back and allowed that to happen, it was their choice. Patients with debilitating diseases did not get there by choice."

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