Gene doping in sports entails challenges and dangers but may not be so dopey

At no time are we more aware about athletes doping than during an Olympiad. Training at altitude for several weeks leads to an increased capacity for one's blood to carry oxygen and it's a legitimate practice, but people sometimes look for shortcuts—like doping.

Traditional doping means blood doping, wherein an athlete is infused with oxygenated blood prior to competition. A more sophisticated tactic is EPO doping; the athlete is given erythropoietin (EPO), a hormone that normally the kidney produces to stimulate production of red blood cells (RBCs) in the bone marrow. In fact, the altitude training tactic works because EPO production is stimulated. Short of ascending to the mountains, however, injection provides the athlete with higher than normal levels of the hormone. This, in turn, leads to increase in the hematocrit, the ratio of blood cells to the liquid in blood. No matter what the method the end result is the same, the athlete's performance is increased beyond her or his normal abilities.

Modern methods allow for the detection of supplemental EPO in the blood and urine of athletes, so what does one do? One possibility is get gene therapy; the gene for EPO is introduced into the body, so many of the athlete's cells would have extra copies of the gene. Consequently, the athletes make extra RBCs, so their blood can carry extra oxygen, but the International Olympic Committee (IOC) announced recently that they'll soon be able to detect any extra copies of the EPO gene:

"We will store [athletes'] samples," said IOC medical chief Richard Budgett to reporters last week, and went on to explain the following:

> We can be very confident that an athlete who is cheating should be very scared. If someone thinks they have designer drugs eventually they will be found. The message for all those cheats out there is "beware you will be caught." I am confident we have the deterrents that should lead to the protection of clean athletes.

It's not clear how sensitive the emerging EPO gene test will actually be, and given how gene therapy can be directed to specific body tissues it's plausible that guaranteeing reliability would require tissue biopsies. This may be a problem in elite athletes, and moreover, EPO gene doping is only one of several genetic strategies that an athlete might employ. Potentially, one might also use gene therapy to increase muscle mass, to grow new blood vessels, or to modify muscle phenotype (the proportion of red [slow twitch] versus white [fast twitch] muscle fibers. Much less researched, but in the realm of possibilities, gene therapy also might be used to increase the pain threshold. If this sounds dangerous, that's because it is.

But the point of developing these techniques isn't to help athletes fake their way to a world record. The development of these gene therapies is potential boon to people with medical conditions ranging from muscular dystrophy to cancer cathexia, or for that matter elderly individuals with senile sarcopenia (muscle atrophy associated with old age).

Strategies for going faster, further, higher

Getting extra copies of the gene for EPO is one way to get more oxygen to tissues. another way is to introduce more genes for protein called vascular endothelia growth factor (VEGF), which stimulates growth of blood vessels in tissues where they're needed, such as muscle. One can also get specific to particular sports and in this case muscle fiber type is particularly important. In his 2001 book *Taboo: Why Black Athletes Dominate Sports And Why We're Afraid To Talk About It*, Genetic Literacy Project executive director Jon Entine made some points about muscle fiber types, to which he also alluded in a recent GLP article related to the Rio 2016 Olympics.

It's non-controversial and taught in any exercise physiology class that people with relatively high ratios of white fibers (cells), also called fast-twitch fibers, versus red, or slow-twitch, fibers in their muscles are well suited for power sports. The quintessential power sport is sprinting, short-distance running. That's where Jamaican runner Usain Bolt—also called 'the fastest man'—excels. There are optimal body dimensions that go a long with it too, but having a very large number of fast-twitch fibers enables the rapid use of energy to produce the needed bursts of physical power. At the opposite end of the spectrum is the endurance athlete, represented by the marathon runner, an area that is dominated by the Kalenjin tribe present in East Africa, specifically Kenya and Ethiopia.

Body dimensions, including lung dimensions, also come into play for distance, but distance runners have unusually high ratios of red to white fibers and the best way to have such a ratio is to be of Kalenjin descent. Similarly, the best way to have a high proportion of white fibers is to be of West African descent, like Bolt. Training comes into play too, not only for the cardiovascular system, but it can influence muscle fiber phenotype, because some fibers can be converted between fast and slower twitch. But short of being having the genetic background for fast- or slow-twitch-dominated muscles, one might be tempted to use gene therapy to do one of two things. Fast twitch (white) fibers are not only powerful (at the cost of fatiguing quickly), but they can also bulk up fairly easily compared with slow twitch fibers. But one can grow his or her muscle fibers by way of gene therapy to increase growth hormone, or to reduce activity of the enzyme myostatin. The latter is one strategy that the biotech company Bioviva has employed in its CEO/test subject Liz Parrish, who hopes this will lead to anti-aging therapies, along with therapies for people afflicted with muscle diseases, such as muscular dystrophy. In a sprinter, when the goal is to increase the ratio of white-to-red fibers, another potential approach would be to stimulate production or activation of a particular contractile protein within muscle cells called myosin 2b.

Possible benefit of all of these approaches is supported by studies in laboratory animals, but not clinical trials in humans (the single-subject Bioviva test that's in progress notwithstanding), so we're talking high risk. It might work, or it might not work. Moreover, given the mechanisms underlying such potential treatments, there also are dangers that could be life threatening.

Dangers of gene doping

It does not take much imagination to see how the various genetic strategies could harm an athlete, if enough genetic material is delivered to enough body cells to cause a physiological change. Whereas

VEGF grows new blood vessels, anti-VEGF agents are used in multiple clinical settings because new blood vessel growth, or neovascularization, is often part of a disease process. Since neovascularization occurs in various cancers, anti-VEGF agents are used as part of cancer therapies. The same agents are used against VEGF in certain eye diseases, in which blood vessels are trying to grow to compensate for low oxygen levels, but having such vessels grow would block out vision.

When it comes to making extra EPO because of an added gene, this could be extremely dangerous because an extra high hematocrit—too many RBCs—makes blood too thick. This could lead to strokes, or various other life-threatening situations. With myostatin inhibition, the situation is rather complicated. As with most genes in the body, you have two copies. Studies with laboratory animals show that when both myostatin copies, or alleles, are knocked out, the muscles do bulk up, but they become rigid and don't function well. Inhibiting myostatin makes muscles hypertrophy and get stronger when one of the two alleles is shut off, or knocked out, but the other remains functional. Thus with myostatin gene therapy, there's an optimal effect; you want to suppress myostatin, but not too much, and this could be really, really tricky to achieve in a clinical setting.

Benefits to the general population: Uses against disease

Considering effects of various gene doping strategies on physiology, it becomes clear that the athletes trying them could end up as population of human guinea pigs, a kind of phase 1 clinical trial that could highlight desired effects, but also safety issues, for potential treatments of human disease. People with chronic pulmonary disease would welcome novel treatments developed in athletes to deliver oxygen more efficiently to body tissues. People with muscular atrophy—from cancer cathexia to senile sarcopenia—could use a myostatin gene therapy to rebuild their muscle. If it works in the athletes it should work in the disease-afflited people too; in fact, risks might make more sense in the latter group. The list goes on an on with clinical applications that could change he world of medicine.

By no means will sports fans around the globe welcome the idea that more athletes will be able to get a way with cheating and for the athletes it may be entirely cost prohibited for most (at least). At present cost of gene therapy to treat blood diseases is anywhere in the neighborhood of $100,000-1,000,000 per case. From that perspective, a trip to Salt Lake City or Denver for a few weeks doesn't look so bad.

But if cheating is inevitable anyway, if development of the treatments is driven by the lucrative markets of elite sports, maybe the spinoffs in the clinic will constitute an acceptable silver lining to helping those who are suffering from a myriad of diseases.

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