Athletes' Use of Unproven Stem Cell Therapies: Adding to Inappropriate Media Hype?

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Few areas of research have received as much attention from the popular press as stem cells. And it is no wonder. Stem cell research is extraordinarily promising, with the potential to produce groundbreaking therapies for a range of ailments. In addition, it has generated an exceptional amount of public policy controversy, attracting attention from presidents, prime ministers, legislators, and religious leaders throughout the world. Combined, the representations of the promise and perils of this area of scientific inquiry have made stem cell research nothing short of a pop culture phenomenon. But many have speculated that this hype can be a less than constructive force,[1] contributing to numerous science policy challenges—including the growing market for unproven stem cell therapies.

Over the past few years, a new dimension of science hype has emerged: the well-publicized use of stem cell therapies by high-profile athletes. Starting with the 2011 story of New York Yankee pitcher Bartolo Colon receiving cell therapy for a chronic shoulder injury[2] and gaining momentum with the announcement of Peyton Manning's neck treatment in Germany,[3] stories of athletes using stem cell treatments as a recovery aid have become common.

This trend is problematic on a number of levels. As noted by numerous scholars, only a few stem cell therapies are currently supported by good scientific data.[4–6] However, despite this clinical reality, unproven stem cell therapies are being marketed to patients throughout the world. The clinics that offer these services often operate outside of ethical or regulatory oversight and exploit individuals at their most vulnerable by offering unproven treatments for incurable and debilitating diseases. Most professional athletes would try anything that promises a more speedy recovery after acute injury or the chance for "one more season" for those with chronic soft-tissue problems. This has given rise to an industry that has been roundly condemned by numerous scientific and professional organizations[7] yet profits from unsubstantiated claims of individual benefit. Media portrayals of athletes and public figures such as Bartolo Colon, Peyton Manning, and even Texas governor Rick Perry not only drive the market of stem cell therapies but also influence public opinion and science policy by implying the legitimacy of unproven and often unregulated treatments.

What are the media saying?

To get a sense of how the popular press is portraying this phenomenon, we did a search (using the Factiva database) for newspaper coverage of athletes who have used stem cell therapies. We found 88 original articles between 12 May 2011(the date of the first report, in the *New York Times*, of Bartolo Colon's procedure in the Dominican Republic) and 31 May 2012. The majority of articles (86%) were from the United States, but the trend also received coverage in Canada and the United Kingdom.

Most of the articles (73%) do not even touch on whether there was evidence of efficacy. Given that these stories are generally about the use of stem cells as a therapy or training aid, silence on the evidence could be viewed as implying potential efficacy. Although several articles note that the treatment was probably ineffective (or unproven), an equal number (10%) explicitly describe the treatment as being effective. A large number of the articles (42%) mention a specific benefit—again, implying efficacy—and several (13%) quote a stem cell provider in support of the treatment. Only five articles (6%) mention any possible risk or safety concern, such as tumor growth, with stem cell treatment.

In general, the use of stem cell therapies by athletes is portrayed in an uncritical manner and often as a cutting-edge therapy with career-changing potential (**Box 1**). Although there seems to be an increasing number of media reports that present a skeptical view of stem cell clinics and therapies, research has found that the popular press often present unproven therapies in a relatively positive light.[8] Given the role of the popular press in the dissemination of information about health and science,[9] this tendency raises a number of challenging policy issues.

Increased interest in the market for unproven therapies

The market for unproven stem cell therapies is substantial. Although it is difficult to obtain data on the exact size of the industry, some have estimated that it has already affected tens of thousands of patients throughout the world (including a large percentage of children) and is worth hundreds of millions of dollars.[10,11] In addition, it has been noted that, despite recent policy actions to address the problem—including steps by the US Food and Drug Administration[12] and international science organizations such as the International Society of Stem Cell Research[7]—the industry continues to thrive.

One of the reasons, of course, is patient demand. This demand may be facilitated by media representations that promise potential benefits, even if the science does not support such claims. Research has shown that "famous athletes can have an important influence on the [public's] health-related knowledge, attitudes, and behavioral intentions."[13] News coverage of baseball

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Box 1 Sample quotations from news media

"The resurgence of one previously out-of-work major league pitcher has increased demand for a controversial new procedure utilizing stem cells that could usher in advances in athletic-injury treatment so effective they seem to turn back the clock."

—Erik Malinowski, "Stem cells hold promise for injured athletes, but questions remain," *Wired*, 24 May 2011

"I know it worked for him, and maybe people will be motivated to bring it over here."

—Susan Slusser, "A's Colon is an entertaining set of contradictions," *San Francisco Chronicle*, 31 May 2012

"'A lot of National Football League players, and Olympic athletes as well, get the one-day procedure done so they can play the rest of the season and come back in the off-season to get the more mature stem cells,' Graves pointed out."

—Dwayne Erickson, "Graves earns special invite," *Calgary Herald*, 5 April 2012

"There have been comments that within two to three years there won't be any need for knee and hip replacements; that stem cell therapy will become a viable alternative."

—Dwayne Erickson, "Graves counts on stem cell therapy to repair ankle," *Calgary Herald*, 13 March 2012

"'I feel in my heart and my soul, his performance has been because of the treatment,' Liriano said. 'You see that his fastball is about 95 or 96 miles per hour. It is a miracle, no?'"

—Serge F. Kovaleski, "Pitcher's treatment draws scrutiny," *New York Times*, 12 May 2011 (first reported story of athlete getting stem cell therapy)

player Mark McGwire's use of steroids, for example, resulted in an increase in the stated interest in the substance.[13] Publicized use by well-known athletes can also influence perceptions of efficacy and safety.[14–16] Indeed, it is likely that the reported use of stem cell therapies by athletes adds to the allure of the technology, making it appear more innovative and currently useful. This seems particularly true given the absence of critical analysis in most of the recent stories.

Legitimization of unproven therapies

When athletes or professional sports teams work with clinics or suppliers, it may serve to legitimize unproven treatments in the eyes of the public. It can help to create the impression that these are efficacious treatments that, for a number of reasons (such as allegedly inappropriate regulatory hurdles), are available only to those with the resources to access them. This view is facilitated by commentary in the sports media[17] and the blogosphere. For example, the author of an editorial on a popular sports website, Bleacher Report, states that he has observed a number of athletes get "stem cell treatments and universally each one improved dramatically."[18] He also suggests, with a bit of conspiratorial flavor, that "thanks to a ban on stem cell research in the United States, American medicine is 10–15 years behind stem cell research in Europe" and that "in an effort to cut off athletes from embarrassing American medicine, doctors are questioning stem cell and other sports medicine procedures."

Such accusations are ridiculous, of course. But they serve to create a narrative that can be used by clinics to market unproven treatments. Clinic websites throughout the world often refer to the use of stem cell therapies by famous athletes. For example, one links to an example of "Professional Athletes Seeking Stem Cell Treatment Abroad,"[19] and another states that stem cell procedures allowed an injured player to return to the National Football League.[20] One company's website goes so far as to suggest that stem cell therapy will play a significant role in the performance of "American athletes vying for the gold."[21]

Conclusion

It is well known that professional athletes will do almost anything to keep a competitive edge or speed recovery from an injury. These characteristics make them an ideal market (and, one could argue, a vulnerable market) for unproven treatments such as those promoted by stem cell clinics throughout the world. Although use of these therapies creates a range of problems for the athletes in question (e.g., safety concerns), the trend has broader policy ramifications. The problems associated with the promotion of unproven stem cell therapies have been well documented.[5,6,22] Indeed, it has emerged as one of the most significant science policy issues in the realm of regenerative medicine and stem cell research. There seems little doubt that the publicized use of these therapies by famous athletes helps to promote use and legitimize both the procedures and the relevant clinics. This seems particularly worrisome at a time when public representations of efficacy have already been confused by ongoing public debates about how best to translate and regulate the use of emerging stem cell technologies.[23]

The scientific community needs to provide a clear and consistent message—as many are now doing[4]—about the actual, nascent state of stem cell research. In addition, we need independent and accurate information for both the public and health professionals about the risks and limitations associated with the services provided by stem cell clinics. And, given the uniquely influential position of high-profile athletes in this context, the scientific community should consider reaching out to professional sports teams and sport associations. Given that they have much to gain from proven and efficacious therapies, these organizations should be encouraged to support scientific research and to counter unjustified media hype by responsibly communicating to the public what we currently know and don't know about stem cells.

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A CRISPR Approach to Gene Targeting

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It is getting easier and easier to determine complete genome sequences—of model organisms, animals and plants of commercial importance, and humans: Craig Venter, Jim Watson, the 1000 Genome Project, soon you and me. Now that researchers have all this information at hand, the focus has shifted in many cases to manipulating particular sequences to determine their function or to alter their impact. A new study by Jinek *et al.*[1] proposes a new approach—based on the oldest of DNA recognition principles—to the design of reagents that can target specific genomic sequences.

Precision genome engineering has been enhanced substantially in recent years by the development of targetable DNA cleavage reagents.[2] A double-strand break (DSB) made at a specific genomic location by, for example, zinc-finger nucleases (ZFNs) will often be repaired inaccurately by nonhomologous end joining (NHEJ), creating a targeted mutation (**Figure 1**). When a modified donor DNA is also provided, repair by homologous recombination will lead to introduction of donor sequences at the target. These break-induced modifications can be very efficient, in the range of 10% or more of all targets in a single treatment. Gene-editing nucleases such as ZFNs, not only have been used for engineering precise genomic changes in experimental organisms but are being tested in current clinical trials.[3]

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ZFNs are hybrid proteins that have several favorable properties as targeting reagents.[2] The zinc-finger modules that comprise their DNA-binding domain can be assembled in many combinations to recognize a wide range of genomic sequences (**Figure 2**). The *Fok*I-derived cleavage domain is not active as a monomer, so the nuclease is assembled only when two ZFNs bind at the designed target. The binding and cleavage domains can be manipulated separately to alter recognition and cleavage properties independently.

A problem with ZFNs has been the unpredictability of their recognition capabilities. Some fingers apparently bind their corresponding DNA triplet (or quartet) reliably in different contexts, but others do not. Even procedures that select finger combinations explicitly for new targets are not always successful, and they can be dauntingly laborious.[4]

This design challenge has recently been addressed with the adoption of an alternative set of DNA-binding modules derived from *Xanthomonas*, a genus of proteobacteria.[5,6] Each transcription activator–like effector (TALE) module recognizes a single base pair, and standard modules for each of the four possibilities seem to behave well in essentially any sequence context. TALENs (TALE nucleases) (**Figure 2**) consist of multiple TALE domains fused to the *Fok*I cleavage domain, and they have outperformed ZFNs in many early trials.

Although TALE modules make design for new targets much easier and apparently more reliable, some questions about specificity remain. Ask any biochemist or molecular biologist what the gold standard is for DNA sequence recognition and the answer will be: Watson–Crick base pairing. This is the key to the proposal by Jinek *et al.*[1]