

DRUG (RE) DISCOVERY

FROM BENCH TO SPORT SIDE

BY LOVRO ZIBERNA

Drug discovery makes our lives different. We can live longer and healthier lives, and moreover enhance normal physiology to perform better. But on the other hand, we are also exposed to adverse and toxic effects of drug compounds. Therefore, modern clinical pharmacology puts enormous emphasis on the risk versus benefit debate. The dilemma is well-defined when dealing with patients, as benefits in treating the disease usually overcome the risk of employing pharmacological treatment; however, when top athletes are involved, the benefit of going into a supra-physiological state endangers health and is morally wrong. At the same time, some might argue that allowing doping would induce an equal playing field. This idea is not only absurd, but plainly irresponsible if risks to health are considered.

In the age of fame and fortune, pharmacological compounds play an important role in professional sports. But – and this must be something common to human nature – athletes are not the only ones using performance enhancing substances: i) movie actors, singers, show business people, and college students use drug compounds to help them sculpt their bodies in a relatively short time; ii) classic musicians, who can use beta-blockers to improve their on-stage performance; iii) medical and law students, who use nootropics and amphetamines to enhance cognitive performance before important exams; iv) army soldiers, who are given special doping treatments to increase their endurance before engaging in battles; v) other professionals, who must meet tight deadlines and need to work beyond exhaustion. However, regulations – also called anti-doping rules – exist only in professional sports. One can look at these as specific rules of the game, and breaking those rules makes you a cheat. If caught, you are eliminated. The other doping-spoiled disciplines in modern

society don't have such rules. For instance, it's hard to imagine a college student undergoing a doping test before taking a written exam, even though if he has doped, he would have gained an unfair advantage over his peers. Top scores achieved in exams have an impact on future career opportunities of the students; similarly, winning sports competitions influences the future of top athletes.

DRUG DISCOVERY: HOPE FOR PATIENTS, BURDEN FOR ATHLETES

The role of scientists is to identify new molecular targets for existing pathologies, and to provide novel pharmacological solutions. However, such noble work can be misused for cheating purposes since the same drug therapy, used to treat diseases, can also have a performance-enhancing effect when used by healthy individuals. For example, gene therapy that effectively alleviates symptoms of patients with muscular dystrophy could also be used as gene doping for increasing the muscle strength of athletes. But, it is not the concern of scientists involved in the drug discovery process whether the athletes will abuse their findings. Research work must remain disease-oriented, and nothing should inhibit the time needed for a drug to reach the patients.

FROM DRUG DISCOVERY TO DOPING

On the other side, within the so-called doping society, one can only follow latest research developments and try to implement them before the anti-doping scientific community identify the risk and develop appropriate analytical methods to detect performance-enhancing compounds. By doing this, they remain undetected while training and competing in an enhanced state. This is the most crucial time window for doped athletes. As an example, erythropoietin

(EPO) was first introduced to the market in 1989, but the first analytical method appeared only as late as in the year 2000. An even more dramatic story is related to recombinant human growth hormone (hGH), which was developed in 1981, but its detection was introduced in 2004. However, further analytical improvements were needed, thus the first completed case involving an analytical finding for hGH happened only in 2010. Similarly, certain performance-enhancing compounds are currently either in clinical testing or on the market, but without proper analytical tests developed to detect them.

To try to bypass this time window, all collected samples are currently being stored for the period of 10 years, and can be re-tested later upon the discovery of new performance-enhancing compounds, or upon advances of analytical approaches.

Why is anti-doping one step behind the doping society? It can be speculated that information leaks out of pharmaceutical industry laboratories as early as drugs enter into pre-clinical testing. But even this is not necessarily true, since many ideas can be found using patent searching, reading research posters during scientific conferences, reading scientific papers, or by browsing through on-going worldwide clinical trials which are freely accessible online (at clinicaltrials.gov). It can be hypothesized, as shown by Figure 2, that the numbers of potential dopers increase as the clinical studies

advance into Phase II or Phase III. It is worth noticing that during the Phase III, tested drugs are sent to many clinical institutes worldwide. Tracking the drugs is difficult, and the potential abuse of athletes easier. Medical knowledge within the doping society is the key factor that enables athletic enhancement; thus, of course, considerable human resources are needed to run this efficiently. History has taught us that top-level athletes using performance-enhancing drugs usually have a strong interdisciplinary team around them, consisting of different professionals, such as medical doctors, pharmacists, nurses, endurance physiologists, coaches, team managers, and many others.

WHAT CAN ANTI-DOPING SOCIETY DO: IF YOU CAN'T BEAT THEM, JOIN THEM?

There are many approaches that can be employed in improving the fight against doping. The most obvious is to improve the analytical methods: faster analysis, higher sensitivity and stronger proof. In the same manner, tight collaboration with the pharmaceutical industry can help scientists develop early detection methods for drugs with performance-enhancing potential in sports. This has recently been put into practice as the drug company GlaxoSmithKline has signed a deal with the World Anti-Doping Agency (WADA) in July 2011. The company agreed to supply confidential information about medicines in early stages of development that may be abused by athletes once licensed. We

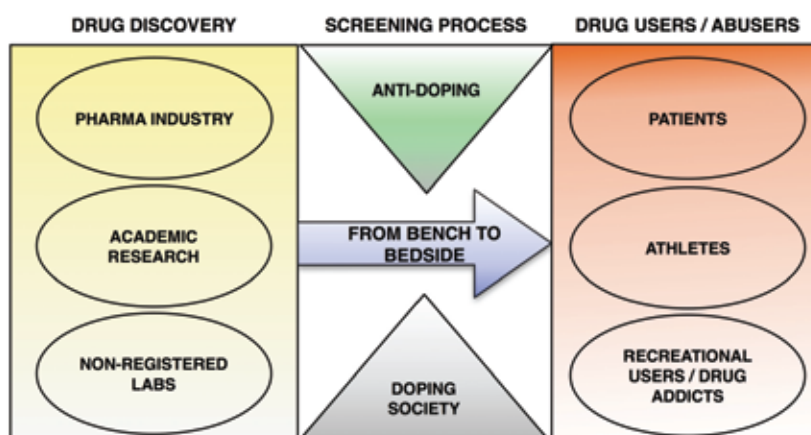


Figure 1. Scheme showing the parties involved in the drug discovery process. From the doping perspective, there are two options: a) Therapeutic pathway – from bench to bedside; b) Doping pathway – from bench to sport side.


can expect that WADA will try to sign similar deals with other big companies.

In addition, we must create a strong scientific team, as part of WADA’s department or even as an independent non-governmental organization, that would screen all the latest research in the pre-clinical and clinical spheres – similarly to how doping society is screening for new ideas. This approach – scientific guard watching – can identify so-called “hot spots”. Any new drugs found to have performance-enhancing potential would then be highlighted to WADA, which could coordinate the research activities of anti-doping research groups. Even more, such a scientific team could speculate on molecular mechanisms involved in athletic enhancement before the actual drug discovery – this could be a revolutionary transformation from “one step behind” to “one step ahead”.

Furthermore, intelligence gathered from everyone involved in sports, and elsewhere, can help anti-doping authorities to target drug testing of the athletes. It is important to get state-of-the-art knowledge from banned athletes, and others involved in the doping business. Similar approaches have been successfully employed in drug trafficking, as well as in gathering intelligence used by the military.

Lastly, much more emphasis must be put on education of young athletes. Many recently started educational programs have successfully raised doping awareness by highlighting negative health consequences, the cheating aspect, and the possibility of getting caught.

CONCLUSION

Nowadays, athletes believe that medically supervised doping is protecting them against serious adverse/toxic effects of drugs. But there is a catch: not all toxic effects appear acutely, and many serious ones must be considered in the mid- and long-term. Furthermore, participation of medical doctors in doping is against the basic principles of medicine, morally and legally. Pharmacology should be used to treat patients, and not to transform athletic competition into a competition between research teams, pharmaceutical companies, or even medical doctors. 

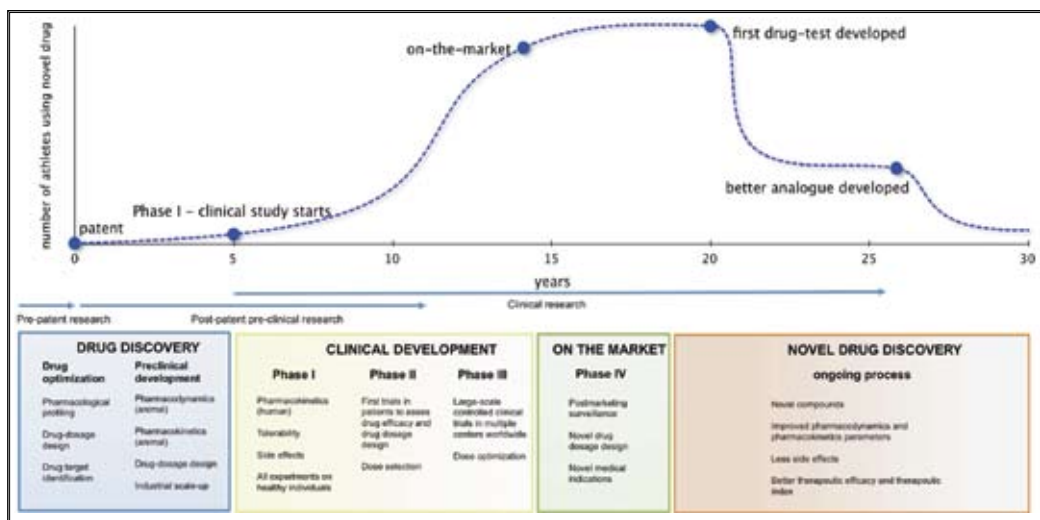


Figure 2. This hypothetical diagram shows the appearance of a novel compound, with performance-enhancing properties, from a drug discovery process into sports. Please note that this figure represents the author’s personal predictions, and therefore does not reflect the actual situation, since there is no data available for the exact evaluation.