

## **Gene Transfer for Pain: A tool to cope with the intractable, or an unethical endurance- enhancing technology?**

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### **Introduction**

In this paper we consider two plausible scenarios in which an individual is seeking treatment with gene transfer tools to cope better with pain. In the first scenario the individual is a patient; in the second an athlete. The general question explored is whether it is ethically justifiable for the individual to seek an experimental gene transfer treatment in order to raise his/her tolerance to pain. We employ here a comparative strategy to highlight the similarities and dissimilarities between the ethical frameworks used to evaluate the two scenarios, and to reach conclusions regarding the justifiability of the potential practice.

### **Gene transfer for pain**

Untreatable pain represents an enormous problem to society. As estimated by current statistics, approximately 20 per cent of the adult population suffers from chronic pain, and the financial cost to society is estimated at more than €200 billion per annum in Europe, and \$150 billion per annum in the USA<sup>3</sup>. Treatment options are limited, with many patients either not responding to them or having incomplete pain reduction.<sup>4</sup>

In the last decade, several translational clinical trials have been carried out that employed gene transfer tools to try to overcome this medical need. Gene transfer trials certainly qualify as translational trials, as they are designed to bring to the bedside the tools developed at the bench of a molecular biology laboratory. We performed a search with keywords 'gene transfer' and 'pain' on the National Health Institutes clinical trials directory, which revealed 20 clinical trials that are either completed or in recruitment.<sup>5</sup> To date nine clinical trials have been completed.<sup>6</sup> Some of these trials are aimed at treating intractable cancer pain, some at treating pain associated with angina pectoris, others at epidermolysis bullosa (a heritable condition where connective tissue disease causes painful blisters in the skin and mucosal membranes), and others to treat the pain associated with peripheral arterial occlusion (a mini-stroke in the leg which causes the necrosis of muscular tissue leading to impaired functionality and chronic pain). This last kind of pain, and the related clinical trial, serves as a case study for our comparative evaluation between a medical context and a sports context, where the former is a traditionally conceived therapeutic intervention, and the latter is one where the intervention rests in the grey zone between therapy and enhancement – or as it has been labelled, therapeutic enhancement.<sup>7</sup> We set out the two scenarios below and evaluate them ethically according to two different frameworks.

### Scenario a): The medical context (the patient)

In scenario a), in the US TV series *House MD* the protagonist, Dr Gregory House, has suffered from peripheral ischemia to a leg, which has left him limping and with intractable chronic pain, due to the extensive necrotic muscular tissue in his thigh muscles. He is seeking an alternative solution in a gene transfer clinical trial. Dr House can perhaps be seen as a contemporary instance of the archetypical mythological figure of the “wounded healer” Chiron, who is able to heal others but unable to heal himself. After having tried many standard and less standard treatments unsuccessfully, our protagonist is now seeking experimental treatments, i.e. treatments that are currently being tested in clinical trials and not yet approved by national regulatory bodies such as the US Food & Drug Administration (FDA) or the European Medicines Agency (EMA), and are unavailable on the market. Among the gene transfer trials currently active or recruiting, one study stands out as the perfect match for a patient like Gregory House.

The trial (Identifier # NCT00304837)<sup>8</sup> is a Phase 1 study that seeks to transfer the DNA codifying for the Vascular Endothelial Growth Factor (VEGF) protein into the legs of patients with peripheral artery disease (PAD). PAD encompasses a range of conditions presenting with blockages in the arteries in the limbs. The nature of the disease is progressive, so that it frequently leads to patients presenting with claudication or critical limb ischemia (CLI).<sup>9</sup> It is this former manifestation of PAD that we are interested to discuss. Most Phase 1 studies are aimed at testing the safety of a new pharmaceutical or treatment in a restricted number of patients, after the treatment has proved efficacious in laboratory testing and animal models, but some – like this one - may also test the efficacy of the agent under study. According to the trial protocol, the DNA codifying for the VEGF protein is injected into the affected legs of the trial subjects on three separate occasions, each two weeks apart. The DNA codifier then directs the cells of the artery wall to increase production of VEGF, which has been shown to cause new blood vessels to grow around the blockages in the leg arteries.<sup>10</sup> It has also been demonstrated that increased VEGF expression through gene transfer techniques improves microcirculation in muscle, and hence increased oxygen and nutrient supply, as well as removal of waste products.<sup>11</sup> Kim et al have observed evidence of growth of new collateral vessels, relief of ischemic pain and ulcer healing in patients with CLI.<sup>12</sup> The trial we are analysing aims not only to test the safety of VEGF-gene transfer, but also to relieve pain and/or heal the ulcers caused by PAD.<sup>13</sup>

Generally speaking, safety concerns about gene transfer are related both to the kind of carrier/vector being used (usually a modified virus) and to the encoded transgene. In our case study, the former are eliminated by injecting the DNA coding for the VEGF protein directly into the patients’ leg muscles, without any viral or non-viral carrier, thus eliminating the risks inherent in the vectors and common to many other gene transfer trials. As to the latter risks, it has been shown that overexpression of VEGF causes haemangiomas (benign tumours characterised by an increased number of normal or abnormal vessels filled with blood) in skeletal muscle in mouse animal models.<sup>14</sup> In addition, angiogenesis, can have detrimental consequences in non-target

tissues. In particular, the theoretical risk of facilitation of tumour vascularization (and therefore, increased growth) or plaque angiogenesis in non-target tissues must not be ignored.<sup>15</sup> Transient peripheral edema (swelling) due to increased local perfusion is a relatively common and mild side effect.

More serious adverse effects have been rarely observed and are mostly related to the use of viral vectors, therefore are not pertinent to the trial we are discussing which injects DNA in the form of a plasmid (a circular molecule of DNA).<sup>16</sup> A recent study conducted by Muona et al and aimed at assessing the long-term side effects (10+ years) of local VEGF gene transfer to ischemic lower limbs found that adenovirus or plasmid (our case) or liposome mediated intravascular *local* gene transfer does not increase the risk of malignancies, diabetes or any other disease in the long term. The authors also identified as a key element to safe gene transfer the local delivery to the treatment side (as in our case), which reduced the risk of systematic spread of the vector, as well of adverse side-effects to other organs. This suggests that the technique described here could be safely applied both in trial subjects and in healthy individuals (which is pertinent to Scenario b), below).<sup>17</sup>

As noted by Mughal et al,<sup>18</sup> PAD cannot be attributed to one specific genetic cause, and greater therapeutic efficacy could be obtained by targeted gene transfer using multiple growth factors. Indeed, angiogenic gene transfer strategies such as VEGF-gene transfer are by no means the only ones being explored in the treatment of chronic pain<sup>19</sup> but appear to be among the most advanced at the clinical level, while other strategies are still at the level of animal studies. As a general remark, while we are aware that a certain degree of speculation is necessary when applying our case study to the second scenario (the elite sports context), we think there is sufficient scientific and medical evidence to argue that gene transfer for pain has very plausible applications for enhancing athletic performances.

### **Scenario b): The sports context (the elite athlete)**

In scenario b), the would-be protagonist is an elite athlete competing in an endurance event, such as cross-country skiing, marathon running, tour cycling, triathlon, or an event of similar extended duration, seeking VEGF-gene transfer in order to cope better with the pain inherent in the event as a primary outcome, and as a secondary outcome to perform better as a result. The growth of blood vessels in the limbs, as demonstrated by the clinical trial described above, is likely to aid the athlete in his/her performance by increasing the oxygen-carrying capacity to the limbs (nutrient supply) and the removal of waste products.

It is also obvious that an athlete feeling less pain could perform better, *ceteribus paribus*, than other athletes experiencing a greater degree of pain.

### **Comparing the scenarios**

How are we to understand the similarities and differences these contexts present, and to what extent will the context determine whether it is ethically justifiable for an individual to seek an experimental gene transfer treatment better to cope with pain?

To what extent is the ethical permissibility of the practice dependent upon or independent of the context of gene transfer? We respond to these questions by spelling out two ethical frameworks that might be adopted in order to analyse the two scenarios.

### **Framework a): Ethics of translational research**

With a few relevant exclusions,<sup>20</sup> we do not normally regard pain as an essential or valuable part of our lives. On the contrary, we take measures to diminish or even eliminate pain from our daily lives, and from the lives of those who are dear to us. Even in illnesses where pain is present, we try to eliminate it, although it may not be possible to cure the patient of the underlying cause. Palliative care, which we consider an essential part of treating a sick human being with dignity, is predicated on such an understanding.

The first framework we use to analyse the scenarios is the ‘ethics of translational research’ approach recently developed by Kimmelman.<sup>21</sup> Kimmelman develops the new concept of ‘translational distance’, which refers to the space created between cutting-edge biomedical research and clinical applications. It may not be possible in the first in-human studies to apply the concept of ‘clinical equipoise’, defined by Friedman as “a state of honest, professional disagreement in the community of experts about the preferred treatment”.<sup>22</sup> The level of uncertainty is so high in first-in-human research employing gene transfer techniques that robust epistemic thresholds required for clinical equipoise cannot be secured. In its place, the concept of translational distance is a useful and insightful kind of ‘epistemic heuristics’ to understand the bidirectional flow of knowledge between the bench and the bedside.

While traditionally the value of early clinical trials has been regarded only in terms of their ‘progressive value’ towards later Phase 2 and Phase 3 studies, such a framework is not applicable when evaluating the social value of first-in-human research as in our case study. In Kimmelman’s model, Phase 1 translational studies in between the ‘bench and the bedside’ are loaded with value if they stimulate preclinical research or if they stimulate further clinical development. In addition, adopting a translational distance model with a non-progressive epistemic value for these trials would help to dispel the ‘therapeutic misconception’<sup>23</sup> widespread among (often desperate) first-in clinical trials volunteers. Therapeutic misconception arises where subjects misinterpret the primary purpose of a clinical trial as therapeutic, and conflate the goals of research with the goals of clinical care. As shown in a study of consent documents of gene transfer clinical trials, 20 per cent of consent documents for gene transfer trials fail to explain their purpose as establishing safety and dosage, while only 41 per cent of oncology trials identify palliative care as an alternative to participation. Moreover, the term gene therapy is used with twice the frequency of the term gene transfer.<sup>24</sup>

As defined by Kimmelman, the concept of translational distance “is intended to prompt researchers, review committees, and policy-makers to contemplate the size of the ‘inferential gap’ separating completed preclinical studies and projected human

trial results”,<sup>25</sup> and should inform both the design of the studies (that need to incorporate endpoints that make it possible for the knowledge produced to have an impact in terms of further research), and the ethical approval of the trial, that needs to take into account the concept of translational distance rather than that of clinical equipoise. We agree with Kimmelman that the translational research model better captures the reality of how information flows in translational research. As for the individual seeking to be enrolled in such an experimental trial, we recommend that researchers spell out the potential risks and benefits of the experimental procedure to the would-be volunteer; researchers should evaluate the severity of the pre-existing condition in the subject and its refractoriness to other standard treatment; and they should evaluate the subject’s decisional autonomy, which will be predicated on reasonable comprehension (and voluntariness) in relation to the foregoing.

Returning to our fictional protagonist, we can see that in this particular case the risks inherent in gene transfer trials due to the viral vectors are eliminated by injecting VEGF directly into the leg muscles of the patients, and therefore the translational distance between the bench and the bedside can also be considered a modest ‘inferential gap’. In addition, the pre-existing condition of chronic pain caused by peripheral artery ischemia is severe and refractory to standard treatment. And finally, Dr Gregory House seems to be in a position to make an autonomous decision, one not clouded by therapeutic misconception. As autonomy plays a fundamental role in the ethical framework describing the medical context, there would need to be strong reasons to justify interference with the patient’s self-regarding and autonomous choice to participate in the trial, even recognising as we do that the patient may have no available option (apart from palliative care) other than participating in the trial, due to the severity of his condition and the unavailability of therapeutic options. Provided all the above conditions were met, we might reasonably reach the conclusion that his informed consent to participating in the VEGF-clinical trial would be valid.

### **Framework b): Ethics of sports enhancement**

How should we frame the request of an athlete seeking VEGF-gene transfer for the purposes of better coping with pain during a competition? In the first instance, his participation might look like a case of what we could call ‘physician-assisted doping’.

The World Anti-Doping Agency (WADA) sets out three criteria used in the decision to call a product or process ‘doping’.<sup>26</sup> These pertain to (i) the (potential) performance-enhancing effects; (ii) the potential harm to health; the (potential) health risks. Only two criteria need apply for a product or process to be prohibited. The Anti-Doping Code recognises the rights of athletes to secure healthcare and that this right supersedes anti-doping regulations. This does not, however, allow the patient-athlete *carte blanche*. Prior to utilising banned products or processes athletes on a registered testing pool (who are on notice that they may be randomly tested) must submit a Therapeutic Use Exemption (TUE) Certificate signed by a relevant medical authority. This certifies that the therapy is necessary for the athlete’s condition and that no non-doping alternative is available. Clearly, the process is open to abuse. Moreover, in

Paralympic sport, where elite athletes have at least one disabling condition, the problem is even more complex.<sup>27</sup>

Leaving aside for the present the added complexities of unethical behaviour, let us assume that the athlete is asking for a TUE from the relevant authority. In addition to the World Anti-Doping Agency, this might be an International Federation, such as the International Association of Athletics Federations (IAAF), or the Union Cycliste International, or the International Triathlon Union, or an event organiser such as the International Olympic Committee (IOC) or the International Paralympic Committee, who (interestingly) take exclusive charge of in-competition testing during the Olympic and Paralympic Games. There is very little to suggest that a TUE would be achievable in this scenario. Despite TUE precedents for beta-blockers in relation to cardiac patient-athletes in target-accuracy events (such as archery), it is highly unlikely that it would be given for mere pain relief where that pain is simply a marker for injury (and where there may be performance enhancement side effects). The deputy director of the World Anti Doping Laboratory in Cologne, widely recognised as one of the premier testing laboratories, recently remarked upon the practice of using analgesics as analogous to doping:

"It is a grey zone. In my opinion pain killers fulfil all requirements of a doping substance because normally pain is a protection mechanism of the body and with pain killers you switch off this protection system."<sup>28</sup>

Given the longstanding routine use and abuse of painkillers in elite sport<sup>29, 30, 31</sup> it might be argued that the introduction of VEGF would represent merely an extension of everyday practice. In both the first and also in this second scenario, consideration would have to be given to the autonomy of the decision-making of the individual in arriving at ethically justifiable interventions. In the second scenario this would be thought necessary, while in the first scenario this might be thought both necessary and sufficient, provided that the conditions for a modest translational distance were met, as they are in our case-study. Why then is it insufficient in the context of elite sports? Well, in addition to determining the conditions of consent, additional factors regarding the ethical permissibility of VEGF-gene transfer in an athletic context must be considered,

In contrast to scenario a), pain can be seen as an essential, integral part of endurance sports. Performing at an elite level in endurance sport and not experiencing pain are mutually exclusive. Indeed, an athlete's ability to tolerate pain is one of the fundamental characteristics that determine athletic performance and provide competitive advantage. Five-times Tour de France winner Lance Armstrong called the event "an exercise in pointless suffering".<sup>32</sup> He and others have talked insightfully about wanting to take opponents (metaphorically) to places that they could not endure. The capacity to endure high levels of pain over significant time (ie suffering) is a highly prized trait in multi-day/week Tour event cycling.<sup>33</sup> Indeed one may refer to them as "communities of suffering".<sup>34</sup>

Not only is it the case that we must distinguish the experience of pain from suffering<sup>35</sup> in sports<sup>36</sup> but in addition there are, of course, different kinds of pain an athlete can experience in competition.<sup>37</sup> One is the acute kind that can be defined as an intense and specific pain that occurs suddenly, often a result of injury, often experienced by athletes competing in football or other contact sports. Moreover, one can experience such pain in endurance events too – the cycle crash, the herniated disc in running, and so on. VEGF-gene transfer treatment would be meaningless for this kind of pain so it is irrelevant to this discussion. Rather, we wish to discuss the kind of pain that occurs with endurance exercise. This may include muscle soreness or a burning sensation in the lungs, the feeling that one's heart will explode if the same level of intense effort is maintained much longer, and so forth. The strength of these sensations can range from unpleasant to what is typically thought of as unbearable pain. This second kind of pain is typical of endurance sports such as marathons, triathlon, long distance swimming and cycling, cross-country skiing, and so on. Among athletes, the former kind of pain is often referred to as a 'bad' kind, as it impairs the ability of the athlete to continue playing or competing, while the latter is referred to as a 'good' kind of pain, as it pushes the athlete to compete and perform at a higher level. Indeed, many athletes regard this second or 'good kind' of pain as an achievement and as an essential part of their life and identity as elite athletes.<sup>38</sup>

The level of physical training of an athlete can raise the level of pain that he/she is able to endure, and make a difference in his/her performance. Athletes also report that the level of their 'mental toughness'<sup>39</sup> makes a difference in their ability to cope with pain. Different individuals, though, start from very different baselines in their abilities to endure pain,<sup>40</sup> and this is one of the factors, among many other biological and environmental factors, that affect an athlete's performance. Among these are: their birth place (contrast pre-athletic life at altitude and how this affects phenotypic factors with competitors born at or near sea level); wealth and other non-athletic factors that can enhance the possibilities of success (contrast athletes or teams with and without sports psychological services, or sponsorships that improve equipment access), genetic conditions that may confer an advantage over fellow athletes by increasing the amount of erythrocytes and oxygen supply to muscle cells (consider for example the case of Finnish skier Eero Mäntyranta who won two gold medals in cross-country skiing at the 1964 Winter Olympics. It was later discovered that he had primary familial and congenital polycythemia (PFCP), which causes an increase in red blood cell mass and haemoglobin due to a mutation in the erythropoietin receptor (EPOR) gene).<sup>41</sup>

There is no absolutely agreed upon standard or trigger as to when sports administrators or regulatory bodies like WADA try to even out genetic and biological differences to reach a sufficiently 'level playing field' for all athletes: some inequalities are systematically excluded, while others are ignored.<sup>42</sup> What happens in practice is that we do not usually try to level biological and genetic factors affecting athletic performance, even where we know those factors confer an advantage (as with Mäntyranta), although there is currently a controversy about new IAAF and IOC rules which exclude women athletes with hyperandrogenism from competing in women's events on the basis of a supposed unfair advantage derived from increased levels of

testosterone.<sup>43</sup> Typically, philosophers generally agree that the question centres around notions of fairness and equal opportunity, or what Loland calls Fair Opportunity.<sup>44</sup>

Let us think counter-factually here: if we were to try to equalise all the starting conditions (of which tolerance to pain is, again, merely one example) we would move in the direction of having all athletes crossing the finish line at the same point, and then what would be left of the meaning of sport and athletic performance? After all we are precisely interested in distinguishing among excellent performers and performances. Only in certain circumstances, such as horse racing, do sports institutions initiate handicapping systems. And this, it might reasonably be argued, is to keep the competition tight and promote gambling interests. In other scenarios, where a league system – heavily underwritten by commercial media interests – has an incentive to prolong interests and more broadly spread opportunities to win, we find systems like the lower teams gaining access to the best new potential players in a draft system (such as in American Football). But in the main, we would not normally level out the effects of the genetic lottery in sports. If an athlete is 1 metre 40 we steer them away from high jump. If they are 2 metres tall, we do not encourage them to pursue a career as a professional jockey, and so on. Furthermore, a few US companies have started to sell online direct-to-consumer (DTC) genetic tests<sup>45</sup> that aim to exploit the genetic lottery as early as possible, channelling children towards the most ‘profitable’ athletic future as predicted by the results of the tests.

As mentioned above, different athletes have different baselines and different abilities to cope with pain. While we do try to give people tools better to cope with pain in everyday life, where pain is not – with certain noted exceptions - seen to be an essential or meaningful part of the activity we are performing, in the elite-sports context we do not give people those tools, because pain, as described above, is a fundamental part of practising and competing at an elite level.

Pain can be distinguished from non-relevant inequalities, as for example the kind of shoes or swimsuits or bikes the athletes run, swim or cycle with, which do not impact upon the mental and physical qualities that are the source of our admiration for athletes and which are instrumental to the securing of victory. For these sorts of products, however, we can and do insist upon degrees of standardisation. Thus, in baseball, cricket, or tennis there are regulations regarding the size and composition of the striking implement and the ball. Curiously, in Formula 1 racing there are prizes for both the best driver *and* the best constructors: the best supporting team of engineers and technologists. But even here there are strict rules about engineering variations. In European football, there are even suggestions that there should be financial fair play, so that team owners cannot “buy” victory by purchasing sufficiently large numbers of the talent pool.

We cannot, however, ‘level-out’ the capacity for enduring pain in endurance events without usurping or compromising a key psychological variable inherent within the test. By levelling the ability to endure pain, we would also diminish a substantial part of the meaning of athletic performance, which can be understood as trying to break

one's own limits given the starting conditions one has. That is why the toleration of pain qualifies as a relevant inequality that serves *inter alia* to demarcate athletic merit, and we consider that genetically based therapy for pain should not be permitted as it undermines the meaning of sport by interfering significantly with the relationship between natural talents, their virtuous perfection, and athletic success".<sup>46</sup> In other words, our view of the athlete's capacity for pain tolerance could be seen a relevant inequality and essential for the meaning of competition. In the model developed by Loland and Hoppeler that combines a biologically based approach with a Fair Opportunity principle, the use of VEGF transfer could be understood as a way to go beyond human phenotypic plasticity<sup>47</sup>, and thus to go against the Fair Opportunity principle and the idea of the virtuous development of talent.<sup>48</sup>

## Conclusions

The differences between the two scenarios we have presented are many and varied. We have focused only on the existence of a fundamental difference between a medical and an elite athletic context of VEGF-gene transfer to tolerate pain. In the latter the choice is fundamentally a self-regarding one, predicated on individual autonomy together with a risk/benefits calculation as the principal factor determining the ethics of that decision. A cautionary note must be struck here. One must be mindful of the areas of uncertainty, the limited evidential base in relation to the experiment<sup>49</sup> and its hoped-for outcomes in scientific and clinical terms. Nevertheless, in elite endurance sports contexts individual autonomy ceases to play the decisive role in the ethical analysis. Sports have traditionally incorporated paternalistic practices regarding the health of competitors but also the fairness of the structuring of competition in order to produce admirable victors. The context of gene-transfer matters for the evaluation of the ethical desirability or permissibility of the experimental practice we are analysing: while in an everyday life scenario, pain does not play a meaningful role (with some noted exceptions), pain does play a meaningful and constitutive role in endurance athletic competition, along with a range of other anatomical, physiological and psychological factors. By increasing the capacity for pain-tolerance, or even subtracting it altogether from the sports picture, we would inevitably subtract also a fundamental part of the meaning of that picture.

We conclude, therefore, that while we would not interfere with the decision of Dr House to be enrolled in a trial for VEGF-gene transfer, we could not justify the request of the athlete seeking VEGF-gene transfer to increase his/her tolerance to pain. As a tool to cope with the intractable pain that visits afflicted patients, VEGF-gene transfer is ethically justifiable and desirable. In endurance sports, the use of VEGF-gene transfer as an endurance enhancement technology is not merely ethically unjustifiable; it compromises an element essential to the activity itself.

What does this comparison tell us about the relationship between the ethics of clinical research (scenario a) and the ethics of sports medicine (scenario b)? We might note that, while the field of clinical research ethics is more established and has a longer history, the field of ethics of sports medicine is a relatively young one, and reflects the underlying tension between the goals of medicine (health) and elite sports (athletic

excellence).<sup>50</sup> But the ethics of first-in- human studies, including gene transfer studies, are still largely under-explored. Indeed, Kimmelman's analysis of translational distance is the first and only attempt, to the best of our knowledge, to fill in the void left by the impossibility of applying the concept of clinical equipoise in first-in human gene transfer studies, which are characterised by a level of uncertainty that is simply too high (as we have shown above). Both fields are young and relatively under-explored, and a comparison between the two may highlight insightful similarities, and shed light on problematic aspects of each.<sup>51</sup>

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- <sup>33</sup> See most recently the biography of Armstrong's one-time team mate Tyler Hamilton who notes that he was almost singled for a professional contract out by the capacity of suffer. T. Hamilton & D. Coyle 2012. *The secret race*, London: Bantam Press. Armstrong's own capacity for suffering is the stuff of legend.
- <sup>34</sup> M.J. McNamee. 2008. *Sports, virtues and vices*. Abingdon. Routledge.
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- <sup>43</sup> K. Karkazis, R. Jordan-Young R, S. Camporesi, et al. Out of bounds? A critique of the new policies on hyperandrogenism in elite female athletes. *Am Journal Bioethics* 2012; 12(7): 3-16.
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175-204. In a notable and carefully articulated review of the essays of the book, Murray argues *inter alia* against the Rawlsian understanding that Loland offers of the fair opportunity principle. The precise details are beyond the scope of the present essay. See, however, T. H. Murray. 2009. Ethics and Endurance–Enhancing Technologies in Sport. In *Performance enhancing technologies in sports*. T.H Murray, KJ Maschke and AA Wasunna, eds. Baltimore. Johns Hopkins University Press: 141-159.

<sup>45</sup> Among these, Atlas Sports Genetics based in Boulder, CO (<http://www.atlasgene.com/>) and ‘Sports X Factor’ (<http://www.sportsexfactor.com/>) (accessed October 12, 2012)

<sup>46</sup> Murray, op cit. Note 42, pp. 141-159.

<sup>47</sup> Defined as the capacity of a single genotype to exhibit variable phenotypes in different environments, and therefore as the capacity to adapt to different environments.

<sup>48</sup> S. Loland & H. Hoppeler, Justifying anti-doping: the fair opportunity principle and the biology of performance enhancement. *European Journal of Sports Science* 2012; 12(4): 347-353.

<sup>49</sup> Kimmelman, op. cit. note 21.

<sup>50</sup> M. B. Mathias, The competing demands of sport and health: an essay on the history of ethics in sports medicine. *Clinics in Sports Medicine* 2004; 23:195–214.

<sup>51</sup> See further: S. Camporesi & M.J. McNamee. High risk-acceptance in professional guinea pigs: a comparison between the clinical trial and the doping context. In *Proceedings of the 40<sup>th</sup> Annual conference of the International Association for the Philosophy of Sport* T Lacerda, J Lima, J. Ilundain, S Soares, eds Porto. Universidade de Evora Press, 61-2.