ĮVADAS
INTRODUCTION

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Is elite sport a driver for medical advance?

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Summary

In an era where the discovery and development of new medicine have hit its peak, areas of study that generate new thinking and related opportunity for medicine development are of great value. Society requires new medicine as an expanding ageing population in the developed world and the emergence of Western world diseases in the developing world place pressure on our global healthcare capability. Here we explore the possible meaning of elite sport to global, cutting edge medical advance. Why the elite sports industry might drive such advance?

We believe that there are two broad areas to do this:

1. Discovery of bioactive molecules with medicine development potential based upon the exploration of the molecular basis of responses to exercise and physical activity and area of research endeavor known as mechano-transduction. This area of study has revealed the incredible potential for a range of naturally occurring molecules to maintain musculoskeletal health and has identified some of the key cell types responsible for orchestrating the beneficial responses. In particular, the bone resident osteocyte has been transformed from a little studies quiescent cell type into the foreman in charge of bone shape, size, and strength and also distant kidney function.

2. The clinical need generated by sport injuries in the elite competing population. Injury in this professional group has greater meaning then in the amateur sports person in terms of both earnings and career progression. The generation of novel medicine and therapies is of great value and includes the emerging clinical specialty of regenerative medicine. This specialty includes the use of cell-based therapies and is emerging fast. At its best, a cell-based therapy will not just treat a clinical condition; rather, it will cure it. Instead of requiring multiple doses over extended periods to control a clinical condition, one dose will cure the condition through the establishment of live cells in the tissues of need.

The future holds medical promise and a little acknowledged role that elite sport plays important role in the realization of that promise might well represent a legitimate area for clinical therapy discovery.

Keywords: *sport, medicine, cell therapy, mechanotransduction, exercise is medicine, sports injury.*

Introduction

Medical advance is a fundamental enabler of society's advance. The ability to create a healthy society has allowed industrialisation, migration, and population growth. Throughout history, medicine has found itself advancing with dramatic leaps as new technologies became available.

Major historic leaps in medical technology include the introduction of anaesthetics, antibiotics, and organ transplantation. They were all what we might now call "game changers" or "disruptive technologies".

I believe that we are at the point of another of those game changing moments with respect to medical technologies. The advent of regenerative medicine, genetic engineering, and personalised medicine combine to create enormous opportunity for active extinction of number of clinical conditions including osteoarthritis and diabetes. This is an exciting time and one that is worthy of an analysis as for the drive of change.

While elite sport is globally visible and has for many years been acknowledged to be a catalyst for public health achieved through exercise and physical activity (the concept of "exercise is medicine") it might also be viewed as a driver of medical technology need.

The aim of this work is to examine the extent, to which a relatively unknowing elite sports industry plays a role in new medicine and therapy development and subsequent medical advance.

Exercise is medicine

The concept of "Exercise is Medicine" is not new. It has been existing from the times of Hippocrates (460-370 BC; translation by Jones in 1953) and Galen (129-

210 AD) when a shift from exercising positive impact on disease treatment turned to its influence on general health. More recently attention has shifted back to an understanding of the molecular mechanisms of action of physical activity in drug discovery.

One of the most influential organisations purporting the benefits of exercise on health has been the Olympic movement. However, much of their messaging has concentrated on performance, indeed their motto is *Citius-Altius-Fortius* meaning Faster, Higher, Stronger.

Early thinking was consolidated in 1705 when F. Fuller published "Medical Gymnastics: A Treatise Concerning the Power of Exercise". The clear connection between physical activity and health was built upon and continues in this basic form to this day.

More recently, two levels of thinking have risen to the fore:

1. the general health benefits of physical activity as driven by public health programmes and having an emphasis on heart health and controlling the obesity epidemic in the Western world. This area uses a basic understanding of human physiology to apply quasi-scientific principles to the use of physical activity for health;
2. specific learning from the modern specialty of mechano-transduction. The scientific reasons for any efficacious affects of physical activity have been sought. In particular, the molecular mechanisms, by which physical forces are translated into signals between cells and tissues in the body, have underpinned an era of drug discovery.

It is the second of these approaches that is of particular interest at a time when new drug discovery is at all time low (Arrowsmith, 2012). It is possible that the study of mechano-transduction will reap transformational benefits to the health of societies around the world and in clinical areas beyond those linked to a lack of physical activity. A very small number of more recent developments in drug discovery that have been initiated through more detailed understanding of the mechano-transduction that is engendered by physical activity is outlined here.

Osteocyte biology, micro damage and stress fractures

Much work has been undertaken to understand health meaning of the bone resident osteocyte. This cell has for many years been overlooked since it was considered as unresponsive and quiet cell in the body (Noble, 2008). Over recent years it has become clear that this is the primary cell sensing and transducing mechanical perturbations derived from physical activity and that it orchestrates the targeted formation and destruction of bone tissue. It is implicated in the development of osteoporosis (Noble et al., 1997; Compton, Lee, 2014) and both glucocorticoid (Weinstein, 2012) and amenorrhoea induced bone loss (Gibson et al., 2004) as well as the formation of microdamage that can result in overt stress fracture (Royer et al., 2012).

Microdamage (tiny fatigue cracks in bone that underlie the conditions sometimes referred to as shin splints and stress fractures) is targeted for removal by osteoclasts (bone destroying cells) through a previously unknown mechanism. In this way bone is not weakened through micro damage accumulation. Without this mechanism working bone is weakened during heavy physical exercise and fractures occur. An elite sport with specificity of microfractures is well established particularly with sports such as running, gymnastics, and rowing (DiFiori et al., 2014). The osteocyte has been shown to undergo apoptotic death at sites of microdamage in bones and to release particular signals for bone destruction at this time (Noble et al., 2003, Kogianni et al., 2008). These signals remain to be identified but are of obvious interest to those in drug discovery for bone health. The designs of molecules that are capable of enhancing repair or blocking bone destruction have clinical value. This is a clear example of elite sport driving medical advance.

Physical activity, bone health, and molecular pathways to health

An understanding, in molecular detail, of the way, in which physical activity exerts its positive effect on the musculoskeletal and other body systems, has tremendous potential for the discovery of new medicines. Increased muscle and bone bulk, heart health, diabetic changes, mental health, and anti-cancer activity represent a rich area for discovery. For many years these benefits have been associated with simple physical activity and the search for the reasons why had not been addressed. These times have changed and an exciting era of discovery has commenced.

Just a very few of the molecules associated with positive health of bone and cartilage include:

- parathyroid hormone (PTH) – a bone anabolic molecule;
- osteoprotegerin (OPG) – a naturally occurring inhibitor of the pro-bone resorptive (destroying) (RANKL);
- prostaglandin;
- bone morphogenic proteins (BMP);
- oestrogens;
- beta-catenin and the wnt pathways – inhibited by sclerostin a naturally occuring anti-anabolic molecule in bone;
- insulin-like growth factor 1 (IGF-1).

The production and activity of these important molecules are known to be controlled by physical activity. For example:

The **oestrogen pathway** is critical to the maintenance of bone mass. Not only oestrogen permissive function is known for the positive effects of mechanical stimulus, it has also been found that oestrogen alone activates molecular pathways used by physical activity (Galea et al., 2013). Cell membrane resident receptors play a role in this pathway and the inter-relationship between oestrogen and physical activity has been highlighted and driven forward by dietary restriction and extreme exercise engendered amenorrhea (associated with runners and gymnasts) (Gibson et al., 2004) and the reduced bone mineral density response (adaptation) in post-menopausal runners (Tomkinson et al., 2003). A more full understanding of the receptors and ligands involved in this pathway has led to important advances in medicine including the development of selective estrogen receptor modulators (SERMS) that provide all of the benefits of hormone replacement therapy without some of the unwanted side effects (Mirkin, Pickar, 2015).

The anti-anabolic molecule **sclerostin** is secreted by bone resident osteocytes and controlled by physical activity. Sclerostin is an inhibitor of the bone anabolic molecule wnt / beta-catenin (Yavropoulou et al., 2014). Mechanical stimulation of the skeletal system regulates sclerostin that allows bone forming osteoblasts to increase bone formation and overall bone density and strength (Moustafa et al., 2012). This molecule has been studied and monoclonal antibodies have been designed to neutralise it and allow bone formation in clinical trial (Recker et al., 2015).

Likewise, **PTH**, **OPG**, and **IGF-1** have all been shown to be regulated or implicated in the response to physical activity (Goldspink, Yang, 2001; Roberts et al., 2009, Bergstrom et al., 2011). The importance to musculoskeletal drug discovery of an improved understanding of the impact of exercise on cell and molecular activity is clear. The dramatic changes in tissue allometry engendered by elite sport cannot fail to pose questions as to the mechanism and possible clinical meaning of these changes.

Exercise demands medicine

Elite sport demands physical health and fitness. Performance lies at the core of the priorities of an elite athlete – male or female, and drives for continual improvement that eventually presents itself as performance plateau based upon biophysical limits, genetic barriers, and continued anabolism.

En route to the limits of performance possibility, there is estimated existence of traumatic injury risk points where physical strength of body structures is simply not scaling with the physical forces.

The balance between health benefits the potential injury associated with sport firmly swings towards health benefits (Khan et al., 2012). However, in the case of elite athlete, injury has far greater meaning with respect to career and financial stability for the individual or team.

What is the prevalence of injury in sport? This varies greatly between sports. London 2012 Olympics is an excellent indicator of injury prevalence in contemporary elite sport. In a study of 2012 Olympic games, 10,568 athletes were monitored over the 17 day period and it was found that there where 1361 injuries (11% of athletes had at least one injury) (Engebretsen et al., 2013). In the same study, there were 24 fractures and some 35% of injuries resulted in prevention of competition or training. For a general review see Joseph and Finch (2014).

Importantly, the debilitating effects of sports injury are not always immediate. While there is little definitive work on the link between injury and osteoarthritis later in life, the evidence is sufficient to cause concern. The study by Wittaker et al. (2015) points to the link between sport related knee injury and osteoarthritis, so called, post-traumatic osteoarthritis. Some 50 patients with sustained knee injury 3-10 years prior to the study were examined and it was found that knee scores (indicators of osteoarthritis) were poorer and that those with injury where 3.75 times more likely to be overweight or obese.

Injury of cartilage is particularly serious because this tissue has little, if any, capacity for self-repair (Heinagard et al., 2015). Post-traumatic osteoarthritis has no clinical solution other than the use of implants made of plastic and metal. These are susceptible to both wear and failure within the lifetime of patient with the result that multiple surgeries might be required (Pabinger, 2013).

In addition, in tissues that do have regenerative capacity, the ability to accelerate and improve repair has positive meaning in elite and professional sport. This would be true with bones where under most, but not all, circumstances it will repair. The case of footballers' metatarsal injuries has raised an issue of accelerated and improved repair value. Wayne Rooney, Steven Gerrard, David Beckham, Gary Neville, Roy Keane, Ashley Cole, Ledley King, David Nugent, and Michael Owen are United Kingdom footballers that have sustained metatarsal injury; and the financial impact of these injuries is high.

The emerging specialty of **regenerative medicine** is the newest hope for conditions where there is no current clinical solution. These new techniques are emerging fast and will address a number of unmet clinical needs. Regenerative medicine can be defined as **the creation of tissues that provide, repair, replace, or restore structures and functions absent or lost due to congenital defects, ageing, disease, or damage** (Segen's Medical Dictionary, 2012). While this area of medicine can involve the use of pharmaceutical agents it is unique in the utilisation of live cells in treatments called cell-based therapies.

There is much talk of the use of "stem cells" in regenerative medicine based therapies. Treatment with cells and the use of stem cells in those treatments have become synonymous. In fact, it will be rare that stem cells are used in a therapy. It will be much more common that stem cells will be used as a source of cells capable of becoming therapeutically useful cells for treatment. The reason for this is clear and is addressed here:

Stem cells are primitive cells found in some limited locations in the adult body and in large of early embryos. They have not become differentiated into specific functional cell types and have unique dual properties of being able to become any of multiple cell types (totipotent, pleuripotent, and multipotent - meaning all of the cells in the body plus extra-uterine cells, all of the cells in the body minus extra-uterine cells and some of the cells in the body, respectively) and being immortal (every time they divide, they leave behind at least one original stem cell type) (De Los Angeles et al., 2015). These unique characteristics hold great promise for producing large numbers of a range of cell types and tissues in the body but come with some drawbacks.

The stem cell itself is unlikely to be administered to the body to afford a repair since it is not differentiated and capable of mature cell function. It is much more likely that we will use stem cells immortality to produce large numbers of stem cells that can then be turned into useful differentiated cell types (capable of forming cartilage, tendon, or bone ASP appropriate to the clinical condition). One possible exception will be when stem cells are administered directly to dampen an inflammatory response since they have anti-inflammatory properties. In addition, some primitive stem cell types are capable of forming tumours if allowed to randomly differentiate in the body.

Currently, there a large number of cell-based therapies in the development stage and a small number available for use in the clinic (Mason et al., 2013). All of the current and incoming products might be viewed as first generation technologies. The exciting possibilities offered through the development of the second generation technologies capable of minimally invasive application and large-scale manufacture will be game changing.

Elite sport is one of the many drivers to the advancement of regenerative technologies. The primary reason is that tissues commonly injured during sports are those that have little, if any, innate regenerative capacity. These include cartilage, tendon, and spinal cord.

Conclusion

Some of the areas of medical advance in musculoskeletal medicine are being highlighted in the article. The drive that elite and professional sport gives to these mainstream technological advances is often underestimated. The same drivers exist in other areas, such as cancer, heart disease, and diabetes. Engagement of the sports industry with mainstream medicines research would provide a positive drive to advancement and to solving unmet clinical need in sport and general population.

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AR DIDELIO MEISTRIŠKUMO SPORTAS SKATINA MEDICINOS PAŽANGĄ?

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SANTRAUKA

Šiame medicinos pažangos ir atradimų proveržio amžiuje ypač didelę vertę turi naują požiūrį skatinantys tyrimai medicinos srityje. Daugėjant vyresnio amžiaus žmonių išsivysčiusiose šalyse, o besivystančiose šalyse vis labiau plintant Vakarų šalims būdingoms ligoms, kyla poreikis naujų medicinos atradimų, kurie savo ruožtu skatina ieškoti globalių sprendimų sveikatos priežiūros srityje. Šiame straipsnyje tirtas didelio meistriškumo sporto galimas poveikis globaliai, toli pažengusiai medicinai ir nagrinėtos jo priežastys.

Galima būtų išskirti dvi sritis, kuriose vyksta minėti procesai:

1. Medicininį potencialą turinčių bioaktyvių molekulių atradimas, grindžiamas molekuliniu atsaku į judėjimą bei fizinį aktyvumą, ir tyrimų sritis, žinoma kaip mechaninė transdukcija. Šioje mokslinėje srityje atskleista daug informacijos apie natūralias molekules, palaikančias gerą griaučių raumenų būklę. Taip pat nustatyti keli už teigiamų atsakų suaktyvinimą atsakingi ląstelių tipai, būtent kaulinio audinio ląstelė – osteocitas iš mažai tirtos, ramios būsenos ląstelės tapo aktyvia ląstele, atsakinga už kaulo formą, dydį ir stiprumą, taip pat iš dalies ir už inkstų funkciją.

2. Gydymo poreikis, atsiradęs dėl sporto traumų didelio meistriškumo sporte. Traumos sportininkams profesionalams turi didesnę reikšmę nei asmenims, vadinamiems sportuotojais, – tiek karjeros, tiek atlyginimo prasme. Naujų vaistų ir gydymo būdų atradimai yra ypač vertingi: atsirado nauja klinikinė specialybė – regeneracinė medicina. Šioje sparčiai besivystančioje šakoje taikomas vertingas, ląstelės tyrimais paremtas gydymas: užuot ilgą laiką klinikinei paciento būklei kontroliuoti vartojus didelėmis dozėmis vaistus, negalavimas gali būti pagydytas į atitinkamus audinius įkeldinus reikiamas gyvas ląsteles.

Dėl išvardytų priežasčių didelio meistriškumo sportas gali paskatinti medicinos vystymąsi darant naujus atradimus klinikinės terapijos srityje.

Raktažodžiai: sportas, medicina, ląstelės terapija, mechaninė transdukcija, judėjimas – vaistas, sporto traumos.

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