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EDITORIALS

Germ line genome editing and the emerging struggle for supremacy in the Chemical, Biological and Radiological (CBR) balance of power

David J Heslop[1] & Chandini Raina Macintyre[2]

[1]School of Public Health and Community Medicine, University of New South Wales, Sydney, Australia
[2]Kirby Institute, University of New South Wales, Sydney, Australia

Abstract

The promise of genetic engineering to reduce the burden of disease on the human population, alleviate suffering and provide new avenues for mastering disease has recently been overshadowed by the announcement by He Jiankui of successful germ line modification of two human embryos and their subsequent successful birth. The use of gene editing technologies enabled by CRISPR-Cas9 and related systems to successfully modify the germ line of humans has now been demonstrated. The ramifications of this event are significant for medical research, but also in diverse other areas of human society. Such technologies can now be considered as a possible route to achieve military, economic and social advantage compared to rivals. In this article, the possible emergence of a genetic warfare escalation is described and some simple avenues for military use of gene editing to enhance and augment friendly forces, or target enemy forces, are identified. We suggest that He's work, conducted clandestinely and apparently outside of regulatory frameworks, possibly represents the Trinity Test of genetic warfare, and momentum driving an emerging genetic warfare arms race may be beginning to gather.

Introduction

He Jiankui's recently announced germ line modification of two embryos which were carried to term and born has raised significant concerns about scientific misconduct, lack of ethical oversight, and the scientific merit of the methods used in the experiment (1). However, significant concerns over the broader ramifications to human genetic diversity and unintended or unexpected outcomes have also been raised by the announcement by He of the first modified human embryos carried to term and resulting in live births (2). Since 2016, several researchers published work on editing of human embryos, but the research had not resulted in live births (3). Whilst the ethics of human germline editing has been debated (4), and mechanisms for governance proposed (5), there are broader future ramifications to human society and survival, which must be explored.

Since 2013, gene editing has been greatly enabled by CRISPR Cas9 (a relatively new method for conducting precision editing of genetic information), which has broad application across all of life sciences, including agriculture, food production and medical therapies (6). The benefits to treatment and prevention of human disease are substantial (7), including the potential to cure monogenic diseases and alter the clinical impact of polygenic diseases (8). Clinical trials are currently underway to edit human cells for the treatment of cancer (9). Other studies of human germline editing for prevention of hereditary diseases have also been conducted (3). It should be noted that alternatives to editing of human genes are also available for the treatment of genetic diseases, such as gene silencing (10). The first gene silencing drug to get US FDA approval in 2018 was patisiran, which causes RNA interference to block the harmful effects of hereditary transthyretin amyloidosis on cardiac and nerve function (11). The purpose of He's work, however, was neither treatment of existing disease nor prevention of genetic disease, but design of a human being to be resistant to a potential health threat which they may or may not ever be exposed to (10). The allegedly engineered infants were born to HIV positive fathers, but vertical transmission of HIV is from mother (not father) to infant, so even the purported justification is flawed. He's university (from where he was on unpaid leave to pursue his private enterprise) and the Chinese government have denounced the experiment, so it appears the work was conducted in the private sector without appropriate ethical oversight (12). This highlights how easy it is to conduct such work outside of the regulated academic sector.

An emerging genetic warfare arms race

The potential advantages and drawbacks of germ woperations has not yet been rigorously explored. Nevertheless, genome editing opens the door to the deliberate conception and selective modification of

cohorts of individuals for the express purpose of building superior military capability. Certain countries prohibit such an enterprise from being undertaken. However, as seen in the case of He in Shenzhen, this activity can be undertaken through to completion in jurisdictions with intact regulatory frameworks (2). He's work has signalled a successful "proof of concept" to industry, military organisations and government agencies, and has opened a vista of Genetic Warfare to allies and enemies alike. Irrespective of the social and moral fallout of this momentous announcement, this technique is now a potential pathway to achieving future military or strategic aims that could result in irrevocable change to humanity. Historically, similar situations – the Battleship arms race in Europe in the late 1800s and the missile gap between US and USSR during the cold war - have resulted in great power arms races, destabilised the balance of power, and led to conflict and suffering (13-16). One example of the willingness to exploit available biotechnology for gain is the illicit use of erythropoietin and other stimulating agents (to induce biological changes in the human body) and other performance-enhancing drugs to enhance performance in competitive sport, which appears to occur in all countries despite being banned (17). The governance requirement around this has necessitated a World Anti-doping Authority, with very little effect on the competitive race to enhance performance (18). It seems likely that once the gates are open to create enhanced human beings, a race will begin, either covertly or overtly. The He experiment also raises questions about whether the engineered babies or other similarly designed babies will then be tested for their resistance to the disease they were designed to overcome, and the ethics of using human infants for such experimentation. If an arms race occurs, in the drive for rapid progress, this is very likely to be a consequence.

The concept of genetic modification for population goals is not new. More broadly, it has featured regularly in narratives and philosophical discourse on the future of humanity – adapt and evolve to survive – and recent discourse about risks of and accelerating evolution towards *homo superior* (19). However, the temptation to use He's now proven techniques to achieve *homo superior* immediately, in the context of great power rivalry and realpolitik, may be too great and now is likely unavoidable. Historical parallels abound – most concerningly that started by the development of the atomic bomb and demonstrated by the Trinity test series, and subsequent arms races and real or perceived capability gaps marking the cold war (20). Is He's work the Trinity Test of genetic warfare, and will an arms race evolve to address perceptions of a genetic warfare capability gap?

Genetic engineering offers numerous potential military capability advantages but its use would require significant distortions to the historical and ethical norms of the raising, training and sustainment of armed forces (21, 22), and provide a new source of combatants to armed conflict with parallels to the use of paid mercenaries by great powers in recent centuries (23). Germ line modification for military purposes would necessitate the selective raising of genetically modified cohorts of individuals destined to fill the ranks of future armed forces from birth – the creation of a genetically modified military caste within the unmodified mass of humanity. This has been attempted earlier through selective breeding programs, such as the Lebensborn program of the Nazi SS (24-26) that attempted to increase the numbers of Aryan offspring. Prior to He's work the possibility of this transpiring was theoretical – considered to be at least a number of major advances distant, undesirable as more acceptable genetic therapeutic options were available, and ethically proscribed. It is instructive, now that the pathway to germ line modification has been opened, to explore what military capabilities could be achieved through this methodology.

Targets for germ line modification for friendly forces

Germ line modification for military purposes would likely be turned towards addressing factors that would offer advantages in conflict where human personnel currently introduce limitations. Alteration or augmentation of the pseudocholinesterase gene (27), which is important for protection against exposure to organophosphate compounds such as nerve agents, could be germ line modified to augment expression or improve performance, thus rendering individuals highly resistant or invulnerable to intoxication. Similar modifications could be made to the target proteins of various plant and bacterial toxins (e.g. ricin, abrin, staphylococcal enterotoxin B, botulinum neurotoxin), or manipulation of the vulnerabilities or protective capacities of the resilience and adaptability of individuals in dimensions bypassing historical evolutionary pressures (28). Strength, resilience to environmental stressors such as acute radiation exposure, reduced need for nutrition, and physical stamina could be optimised. For example, germ line modification could be used to selectively introduce high performance haemoglobin or upstream modulators of haematological system parameters. Introduced prior to conception from sequences taken from superior examples of human resilience and strength, such changes would then become part of the individuals' genome indistinguishable to the discarded wild-type sequences (29). Cognition, attention, tolerance to pain, creativity and potentially more desirable personality traits are all possible future targets for engineering (30, 31). Finally, the creation of human-other hybrids or introduction of non-natural sequences for technological purposes (e.g. integrated Mind-Machine interface) are potential future avenues for capability exploitation (32, 33).

Targets for germ line modification against enemy forces

The potential for this technology to also be used for harm against enemies must not be neglected. It is possible through this technology to insert "sleeper" mechanisms within the genome of a target population, activated through exposure to otherwise innocuous events and causing deleterious effects. This might include subtle modifications of populations for resilience to environmental stressors, decreased resistance to infection or disturbances to immunity, and cognitive or behavioural effects. Equally, this could include development of novel characteristics in organisms or humans, or exploitation of characteristics of both materiel and unmodified personnel, to achieve military aims (34). In the strategic domain, ecological weaknesses could be introduced to a population - caused by gradual reductions in genetic diversity or introduction of lower performance genes, into a population leading to changed ability to adapt to environmental change, stress, changed fertility and survival - risks already identified in human and non-human modification alike (35). The primary concern is the almost limitless ability of actors to interfere with others using methods and techniques difficult to identify, prove or counter. Given that human ambition, greed and competition remains strongly conserved in the population, it would appear inevitable that most of the negative scenarios possible with genomic editing are likely, or have already, begun to play out.

Implications

The recent calls for a moratorium (35, 36) highlight the significant concern in the scientific, security and wider community that germ line editing has stimulated. However, we are already in the post-editing era where not only are the practical techniques for achieving germ line modification now clear, but new research horizons will open. In all domains of society – commercial, military, social – this technology opens up areas of individual and population competitions and tensions that have been recognised as at best destabilising, and at worst likely to result in mass suffering and destruction that is unpredictable. Furthermore, CRISPR Cas9 technology still has problems, with unintended DNA changes that can lead to unexpected consequences including cancer and other diseases (36).

In the military domain, the logic of strategic balance of power dictates likely emergence of genetic warfare arms race, with some form of involvement of all major powers (37). This situation further complicates an already sensitive global balance of power, introducing uncertainties into strategic calculus with possible severe negative implications. He Jiankui's work could be seen as the "Trinity Test" of an era of Genetic Warfare, and not only of germ line modification. However, the implications of this may be more profound, far reaching, and impactful than the recent nuclear escalations for humanity.

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