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Future space missions and human enhancement: Medical and ethical challenges

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ABSTRACT

Future human space missions to Mars and beyond may be realized for different research, economic, political or survival reasons. Since space remains a hazardous environment for humans, space exploration and exploitation requires the development and deployment of effective countermeasures. In this paper, we discuss prospects for human enhancement by gene editing, synthetic biology, or implants, for the purposes of future space missions. We argue that there are good reasons to consider such options, and that ethical arguments can be made in favor of human enhancement to enable long-term space exploration.

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1. Introduction

1.1. Advantages of human enhancements in space

There is a high likelihood that human space missions to the Moon, Mars and possibly beyond will become a reality within the next century. Humans have good reasons to go to space, which include economic incentives, research programs, and opportunities for building and establishing permanent space settlements. While some critics may argue against the concept of human space missions in general and the idea of a space refuge in particular, many authors agree that in the long term colonizing new environments in space either within or beyond our solar system may support the long-term future of humanity (Mason, 2021).

In this paper, we discuss the application of human enhancement and its potential role for enabling a future human presence in space. The idea of human enhancement to better permit living and working in space is simple: because the space environment is hazardous and humans are not adapted by evolution to live there, it makes sense to artificially increase human adaption to space by biomedical means. However, the precise nature of enhancement, which may be more or less invasive, reversible or irreversible, and heritable or non-heritable, requires very careful thought and might well be driven by scientific and ethical considerations on Earth. Genetic engineering, particularly germ-line gene editing, is one of the most controversial forms of bioenhancement, at least on Earth. However, there are good reasons to assume that in the context of space, there is a stronger rationale for human enhancement than in the terrestrial context, in which case the ethical analysis should also differ. Our paper has several important ramifications for space science and technology on the one hand, and bioethics and futures studies on the other. Most analyses of living off-Earth focus on the required technologies or practical considerations; social and cultural implications have received less consideration. The emergent field of “space ethics” (or “astrobioethics” or “astroethics” or “environmental ethics in space”; cf. Chon-Torres, 2018; Owe, 2019; Wanjet, 2020; Peters, 2002, 2013, 2019a, 2021) is developing rapidly, following the progress made in the last two decades in astrobiology and space science, and also in molecular biology and biotechnology.

In our paper we do not consider arguments for or against various types of space missions, including the concept of space refuge, nor do we analyse the superiority of humans over robots in space, or vice versa. We focus on the medical and biological risks that humans may encounter in space, current and future protective measures, and related ethical and bioethical issues. Some of the proposals and concepts considered can be seen in terms of a thought experiment today, and a plausible development for the future of our species in space.

1.2. Should we use human enhancements for Mars settlements?

Humankind has always sought to extend itself. For much of our history, such developments came about through migration, trade, and improved methods of communication. Over the course of time, such enhancements have increasingly relied on technology – such as boats to carry us across the sea and the development of writing to make communication records more permanent. Usually, that kind of enhancement is not considered to have ethical implications, but in the past century, enhancements have increasingly become possible through the intersection of medicine and technology (e.g., many of us increasingly rely on spectacles, hearing aids, pacemakers, dialysis, and insulin injections). But even these technological enhancements were not necessarily ethically controversial until humanity had the capacity to change our own genetic material. Thus far, genetic manipulation has been used solely for therapeutic reasons (e.g., the treatment of certain immune disorders, a type of heart disease and a type of blindness), but gene therapy paves the way for a whole new level of genetic modification which may include enhancement. To date, much of the literature on genetic enhancement focuses on non-therapeutic applications for attractiveness, intelligence, sporting prowess and the like (Agar, 2014; Savulescu, ter Meulen, & Kahane, 2011; Savulescu & Bostrom, 2011).

The public has been ambivalent about the use of genetic engineering in general, although support is slowly increasing (CGS Staff, 2018). Advocates of the technology were not helped by the fact that its initial uses seemed to suggest few immediate benefits of real importance for humans (Reiss and Straughan, 1996) – for example, one early proposal was to enable Christmas trees to glow. A relevant distinction can be made between somatic and germ-line genetic engineering. Somatic cells make up most of our body (muscles, skin, nerves, bone, etc.) and are responsible for everything *except* producing our gamete, while germ-line cells are directly responsible for producing our eggs and sperm. At present, most countries with the available technology do not allow germ-line gene editing, though somatic gene editing is becoming increasingly widespread, whether for research or therapeutic purposes (Mason, 2021). If genetic engineering is to be used for Mars astronauts, it may be that germ-line genetic engineering will be needed. Any long-term colony will need to exist for multiple generations, which means any single generation’s genetic manipulation would have to be repeated on site. This is a theoretical assumption, but one that needs to be made for any concept of a self-sustaining extraterrestrial colony that must be able to reproduce under conditions of altered gravity and increased exposure to cosmic radiation. It is not possible at this time to be certain which human genes we might want to alter but we already know enough to have pinpointed genes for such valuable features as radiation resistance, extra-strong bones, toleration of lower oxygen levels, enhanced memory and reduced incidence of a range of diseases and medical conditions including atherosclerosis and various cancers (Church, 2019; Pontin, 2018). It may be argued that a new generation of ‘Martians’ receive preventive medicine rather than enhancement, since the purpose is to enable survival in this harsh environment. If this argument is accepted, it weakens ethical objections to the use of genetic engineering to facilitate human missions to Mars. However, such a strong justification – arguably the strongest possible justification, since the survival of our species is ultimately at stake – does not remove the serious bioethical problem that lies at the beginning of this journey, namely the possible necessity of human in vivo experimentation to effectively apply genetic modification procedures in a situation where non-human animal testing may at some point prove inadequate.

Previous analyses of ethical issues raised by genetic engineering have focused on two main areas: safety and moral acceptability (Tachibana, 2019). As genetic engineering has been available for several decades, safety concerns, while still in existence, have abated as predicted disasters have failed to materialize. This is not to minimize the importance of safety considerations but rather to conclude that standard procedures for determining the efficacy and safety of any new technology should continue to be implemented. Moral acceptability can be examined from two angles. First, is there anything intrinsic about genetic engineering that should prohibit it; secondly, how do people feel about it? Intrinsic objections have mostly concentrated on issues to do with moving genes between species (Reiss, 2000) but have abated somewhat given the increasing realization that such horizontal gene transfer happens in nature. How people feel about genetic engineering is of central importance as people's autonomy needs to be respected. However, this is more an argument for practices such as the labelling of genetically engineered food than an argument in favor of forbidding the genetic enhancement of space travelers.

It is difficult to predict where genetic enhancement of space travelers might lead. All of today's humans belong to the one species, *Homo sapiens*. But we can envisage a future where this is not the case – as predicted by H G Wells (1895) where humanity evolved over some 800,000 years into the Eloi and the Morlocks. If genetic engineering really does result in individuals whose genetic constitution, over time, is very different, it is possible that on the standard criteria used to characterize new species (interbreeding and morphological similarity) astronauts and their descendants could eventually belong to a different species from *Homo sapiens*.[1] It is also possible, for instance, that astronauts heading to Mars might be given an additional chromosome, so that their 'normal' (diploid) cells would have 48 chromosomes and their eggs or sperm 24. This additional chromosome would be a convenient way of hosting large numbers of genes for additional human capacities – such as the ability to synthesize all essential amino acids rather than requiring a particular diet containing them.

Even without artificial genetic manipulation, natural selection and drift could mean that, should Martian colonies survive for generations, the individuals in such colonies will start to diverge genetically from their terrestrial counterparts since there will presumably be strong selection pressure for variants better able to deal with high levels of radiation, low gravitational force and so on.[2]

1.3. Ethical challenges of various human enhancement applications for space missions

There is no doubt that genetic modification of humans living in space will open the field for multiple beneficial applications. It will also instigate ethical debate and controversy, perhaps even greater than those discussed on Earth, and we will address some of these areas in the following sections.

1.3.1. The potential impact of modifications designed for space missions on humans living on earth

This section will describe both the technology and the practice of modifying humans primarily for space exploration, but also the possible impact and interaction of modified inhabitants of the space base or colony on the unmodified inhabitants of Earth. We see no overriding ethical problem in either scenario. In the case of the first scenario, a modification carried out only for space missions thus acquires a special moral justification. It is not seen as something trivial, or universally applicable, but as a procedure with a special application, exclusively for the needs of an exceptionally demanding environment. For the second scenario, assuming that the substantially modified inhabitants of the space colony, for example, would return to Earth and thus interact with the unmodified inhabitants of Earth, we see no ethical problems on the grounds that the modifications we are discussing, if they were to be applied at all, involve only health-related functions such as prevention and treatment. Thus, we are not talking about the forms of enhancement often discussed by philosophers in the form of somewhat unrealistic speculation who theorize on enhancing intelligence or morality.

1.3.2. Military use of human enhancement

The use of human modification technology for military purposes is a procedure, currently in practice. The same will likely apply to possible human enhancement technologies applied for the purposes of space exploration. Military missions in the broad sense will probably be a fairly routine form of political-economic missions. Astronaut-soldiers will be fully-fledged, and one of many participants in space missions, alongside scientists or colonizers. Like others, they have every right to benefit from modification technologies aimed at protecting health and life in space. The negative side of such applications may be the provision of a unique military advantage to one state over others, but this is unfortunately inevitable as long as states are the primary decision makers, regulators, and financiers in the combined space and biomedical industries.

1.3.3. The ethics of modification for reproduction in space

We assume that one possible future scenario is that only gene-editing interventions in human reproductive biology will enable effective human adaptation to life in space. This is a hypothetical option for which the only alternative is to abandon the project motivated by a morally conservative desire to avoid using an ethically controversial procedure. Thus, if we assume that only germ-cell genetic modification or preimplantation genetic diagnosis or other procedures are able to produce healthy and adapted offspring in space, this provides a strong justification in favor of using these procedures. However, its ultimate moral justification should depend on

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[1] Of course, there are various ways of defining species, so even colonists with very different genetic composition from their Earth counterparts might still count as members of *H. sapiens*.

[2] Genetic drift is the phenomenon whereby isolated small populations (humans or otherwise) gradually diverge genetically as random forces lead to the disappearance of certain genetic variants in one population whereas in another population the same variants come to predominate.

the justification for the mission itself. We assume that the more trivial the mission, the less justification there is for using morally controversial biomedical procedures.

On the other hand, if we assume that humanity should colonize space in order to find refuge and to enable the continuation of its own species, then, under certain conditions, the demand to modify future offspring in space may even become a moral obligation, growing out of the knowledge we possess. But this is possible only under certain conditions, namely, when such a colony is necessary, as well as when we know that the lack of modification would lead to the birth of diseased or deficient offspring and a significant deterioration in their quality of life. Then we would be faced with an ethical situation where, by omission, we have brought worse or even catastrophic living conditions upon future generations.

1.3.4. The ethics of designing children in space

All objections to the concept of child design currently being discussed can be applied to the space environment. However, this environment potentially offers a strong rationale for such a modification, assuming that germline gene editing (GGE) is the only option and that the projected effects of abandoning GGE are unequivocally worse on the quality of life of the child – and thus the entire space colony population – than its use. We thus see the ethical rationale in favor of such modifications, provided they are indeed necessary and safe. Thus, an ethic of concern for future humans, a desire to preserve intergenerational justice – so that future generations are not called into existence under worse conditions than those currently living (assuming that earlier generations can realistically shape the quality of life of future generations) – as well as consequence-maximizing principles like beneficence and non-maleficence may justify the concept of designing children in space.

We see greater moral difficulties in the situation of re-adaptation to earthly conditions of persons born in space with a significant modification applied – a scenario that meets the following conditions: (a) There is a colony in space, for example on Mars, where reproduction is possible, (b) Humans (at least some part of the human population) continue to live on Earth, (c) Economically and temporally reasonably comfortable transports between the space colony and Earth are possible, (d) Earth can still be seen as a reasonably attractive or simply habitable place, e) Some or even all children born in space are subjected to significant genetic interventions during their embryonic life in order to adapt them to life in space, f) The applied changes are irreversible and make re-adaptation to the terrestrial environment impossible, which is morally unacceptable. There is no doubt that every human being born in a future space colony should have the right to make the decision to return to Earth, and previous generations without their knowledge and consent cannot establish irreversible obstacles to this. Another moral issue is the presence of temporary obstacles, but genetic modification of an embryo could lead to the permanent exclusion of the possibility of returning to Earth.

These are important moral issues, also related to our responsibilities to future people and their rights. The concept of intergenerational justice is also an important issue here, requiring that the living conditions of future generations be no worse than those of earlier generations, and that important opportunities for future people to develop, act, and decide are not eliminated. Finally, there is the issue of the ethics of quality of life. In this paper, we merely signal these important issues that should undoubtedly be taken into account when considering the concept of long-term space exploration and the application of modification.

1.3.5. The ethics of adult modification versus the right to return to earth

Similar to the design of children in a space colony, the main moral issue regarding adult modifications for space exploration, while meeting the criteria of indispensability and safety of such modifications, is the possibility of re-adaptation to Earth conditions. In a situation where the individual is expected to return to Earth after completing a time-defined mission, or in a situation where the individual has the option of remaining in the space colony but can express a desire to return to Earth at any time, no modification should prevent or impede the individual from doing so. The alternatives then remain automated missions where possible, or abandonment of the mission type. If the conditions listed in the section above are met, the right to re-adaptation, and the possible prevention of it by the modifications introduced, is a serious moral challenge. Perhaps it is even the type of obstacle that should preclude the possibility of such missions until the difficulty of re-adaptation to earthly conditions is eliminated.

2. Types of human challenges and enhancements as potential solutions

2.1. New eyes and inner ears for Mars

There will continue to be skeptics concerning human space missions in general – independently of enhancement – and also those with a conservative approach to human enhancement in general. But we still have strong reasons to assume that at least some enhancements may be necessary, or at least desirable, for human missions to Mars. What body modifications, intentional changes or artificial enhancements, would be most likely to help Mars explorers and settlers? This is a broad area for investigation and conjecture. There are challenges arising from living in an enclosed artificial environment, as well as those from potentially toxic or abrasive soil (Khan-Mayberry, James, Tyl & Lam, 2011, Liu & Taylor, 2011). We discuss here a few ideas for body modifications and enhancements to address some of these hazards, limiting the discussion to techniques that are within the realm of current or foreseeable technology.

One of the most obvious and realistic body modifications has to do with the human balance system: the vestibular organs of the inner ear and their interactions with other senses to maintain spatial orientation and compensatory reflex responses (Goldberg et al., 2012). The role of the vestibular system in space exploration has been recognized since the dawn of the aerospace age. It has a central role since one part of the vestibular apparatus is dedicated to measuring linear acceleration and gravity. When gravity is altered, there are consequences: disorientation, nausea, ataxia, and motion sickness (Reschke, Bloomberg, Harm & Paloski, 1994). Travelers in space and on planets with different gravity levels will be faced with challenges related to these factors. Most critical might be problems with manual-control tasks such as piloting, while reduced performance in general can result from the associated malaise. Vestibular adaptation does occur, but body function can be dangerously deficient in the initial phases of the transition to a new gravity level. However, Earth patients with some types of vestibular pathology face similar issues, and implantable vestibular prostheses are under development which can replace some of the lost function (Golub et al., 2014). This is an area of current research, but certainly this type of body enhancement seems feasible.

Extended spaceflight does not appear to have direct detrimental effects on the visual system (notwithstanding visual impairment due to fluid shift as mentioned below). With reduced gravity, however, there is an increased risk of eye damage due to debris that floats or is not drawn to the floor as rapidly as normal. A corneal implant or protective membrane might be useful in such a circumstance (Scheuring et al., 2008). However, there might be an increased incidence of cataracts from radiation, which could be mitigated through genetic intervention or artificial lens implants. More expansively, safety and performance might be improved if the visual system were to be enhanced so as to respond to a wider range of wavelengths: infrared, ultraviolet, radio, microwave, and X-ray. This would allow direct perception of things such as heat signatures, permit vision through darkness and dust storms, and provide visual indications of high radiation areas. Specialized retinal implants (Bloch, Luo & da Cruz, 2019; Luo & Da Cruz, 2014), though still in the early stages of development, might provide this capability.

For a variety of reasons associated with the multiple interacting stressors of space flight, the gut microbiome (fungus, bacteria, and other intestinal microorganisms) can be altered (Siddiqui, Akbar & Khan, 2021; Voorhies & Lorenzi, 2016). This can cause widespread disruptions because of interactions of the microbiome with many other body systems, including cognition (Gareau, 2014; Shreiner, Kao & Young, 2015). Adding to the problem is the fact that in space there will be less regular turnover of the biome as normally results from contact with a wide variety of other organisms. To remedy this, an implantable pump might be used to provide a regular infusion of new microbiome components, similar in principle to probiotic supplements or fecal transplants (Turroni et al., 2020). While there may be simpler ways to introduce such compounds into the body, a permanent pump could allow for administration of a wider variety of substances, and permit constant monitoring and adjustment as needed in order to maintain physiological fitness.

2.2. *Human challenges in space travel: microgravity, radiation, and isolation*

The human species is not well adapted to live and work in space for long periods of time, which introduces many challenges for human physical and psychological health, including the need to develop and deploy new medications for maladies unique to space (Braddock, 2017). Although the benefits of a microgravity environment may provide unique opportunities for scientific advancement, including drug discovery and development (Ryder & Braddock, 2020), the obstacles that will need to be overcome for a colony on the Moon or Mars are daunting. Yet several potential options present themselves. The first proposes that colonization of new worlds, at least in the first instance, will not involve humans and instead be fully automated (Campa, Szocik, & Braddock, 2019). It could well be that the timeframe for adapting human astronauts to space is too long to allow for commercially viable asteroid mining and other activities that might motivate the establishment of a colony, which shows that an ethical assessment of human enhancement in space missions should take into account, at least to some extent, pragmatic parameters like time and cost-effectiveness. A second option accepts that, in parallel with the development of automated technologies, the human judgement needed to manage and direct complex operations (particularly in times of crisis) is an essential part of colonisation. In that case, genetic enhancement may have a key role to play, by modifying human psychology to become better adapted to the space environment. Psychological modifications might even allow colonists to manage their lives and productivity significantly better[3] than on Earth. As such, psychological human enhancement differs from behavioral molding and training. Critics of the latter option emphasize that teleoperations and telerobotics eliminate the need for human presence in the field. They also point to the need to wait and believe in the leapfrogging development of AI, which may replace the need for human cognition where it seems necessary today. We do not know this yet and probably we are not able to predict it today.

There are three major challenges for human existence in space, even for periods as short as six months: (1) the physical and psychological effects of exposure to radiation, (2) the effects of reduced gravity, (3) the demands of working in an isolated environment. Before we discuss the potential for human enhancement, we should recognize that humans already have an innate ability to manage, adapt, and cope with extreme environments (Bartone et al., 2019; Illardo & Nielsen, 2018) and that astronauts go through a careful selection process which will likely magnify these attributes.

First, the radiation encountered in space is of several kinds, but commonly referred to as particle nuclei of high energy and charge (HZE) (Cucinotta and Durante, 2006, Guo et al., 2015). Radiation can induce carcinogenesis in several ways. It can cause direct DNA damage and mutation, alter cell signaling (Barcellos-Hoff and Cucinotta, 2014), and increase the capacity of the immune system to induce inflammation that causes cellular damage which leads to carcinogenesis. This process has been well-documented in patients exposed to the atomic bomb in Hiroshima (Hayashi et al., 2012). Radiation can also directly damage DNA and transform normal cells to cancer cells (Bielefeldt-Ohmann, Genik, Fallgren, Ullrich, & Weil, 2012, Rivina & Schiestl, 2013). The risk of significant visual impairment from radiation cataract (Cucinotta et al., 2001) and changes to cognition and memory are also during mission concerns (Tachibana, 2019).

Second, microgravity during space travel causes bone and muscle loss, which inadvertently affect the cardiovascular system overall. Most of the interventions to tackle bone and muscle loss are through exercise and pharmacological intervention (Cavanagh,

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[3] That human existence in space might be immensely better than the one on Earth in terms of both quantity and quality of life was suggested by many early space-age pioneers and visionaries, including Tsiolkovsky, Goddard, Buckminster Fuller, and O'Neill (e.g., O'Neill, 1977).

Licata & Rice, 2005; Diao, Chen, Wei & Wang, 2018; Kast, Yu, Seubert, Wotring & Derendorf, 2017). In the zero gravity of deep space, and on planets such as Mars where the gravity level is one third that on Earth, the reduced gravity might no longer provide sufficient loading to maintain bone and muscle integrity, and optimal cardiovascular function (Hackney et al., 2015). There are also disturbances attributable to the head-ward shift of body fluids (Lee, Mader, Gibson, Brunstetter & Tarver, 2018); this is of most concern in zero gravity and will not be discussed further.

Third, isolation and confinement, especially as experienced by the first sets of explorers and settlers, will be dramatic; these have not only direct psychological consequences (depression, anxiety, interpersonal conflict), but can also contribute to degradation in physiological functions such as immunity and cardiovascular functioning (Palinkas, 2007).

2.3. Synthetic biology and genetic engineering solutions to radiation and microgravity challenges

The synthetic biology pioneer Craig Venter has already suggested, with some controversy, that NASA select astronauts based on genetic strengths in regard to their resistance to hazardous factors in space and consider actively engineering the human genome to maximize their suitability for these new environments (Gage, 2010). It may be far easier to “Marsaform” terrestrial life to fit Mars than it is to “terraform Mars.”

Indeed, candidates for useful genetic enhancement have recently been described (Braddock, 2020). To manage the effects of radiation, a multi-disciplinary team led by the NASA Ames Research Centre has published a roadmap which includes proposed mechanisms for conferring radiation resistance upon astronauts (Cortese et al., 2018). This team also outlined future research directions which include gene therapy with genes known to confer radio-resistance on lower organisms, upregulation of endogenous DNA repair and, outside of the theme of human enhancement, isotopic substitution of organic molecules as a further potential radio-protective mechanism. To avoid the effects of low gravity on human physiology, NASA and many international partners have reviewed current and future research activities to determine the requirements for implementing artificial gravity on board exploration-class space vehicles. Some molecular targets for human enhancement, such as genes known to play major roles in the development and maintenance of hard tissue, have been reviewed (Author, 2020).

Despite early and appropriate concerns regarding the potential misuse of gene editing (Cyranoski, 2019), the potential for this technology is considerable, especially in the context of corrective intervention where the benefits and risks can first be assessed in terrestrial applications. Recently, it has been reported (Allegan & Editas Medicine press release, 2020; Clinical trials, 2020) that an experimental medicine (AGN-151587 or EDIT-101), delivered via sub-retinal injection, is being tested in patients for the treatment of Leber congenital amaurosis 10 (LCA10), an inherited form of blindness caused by mutations in the CEP290 gene. The phase 1/2 clinical single ascending dose study will assess the safety, tolerability, and efficacy of AGN-151587 in approximately 18 patients with LCA10. Today, this example serves to illustrate where future decisions may need to be taken. This case refers to testing and refining the technology for an indication in patients on Earth for where the return exceeds the risk. However, in future space dwellers, the proposition is different. In the first instance, gene editing is augmentative and not corrective, and secondly it will be performed on healthy individuals, and the balance of risk needs to be considered as procedures would be performed well before the ability to test whether the enhancement confers benefit.

The most promising gene-editing platform of our day is called CRISPR gene editing. CRISPR gene editing is the simplest yet most versatile genetic engineering tool to-date. The original CRISPR/Cas9 editing system works by reprogramming bacterial defense mechanisms against viruses to our advantage (Gouw, 2020). Scientists have been able to reorient this system to target any gene of interest for editing, insertion, or deletion. CRISPR has been used to create more efficient agricultural plants, anti-malaria mosquitoes, biofuel producing microorganisms, and dozens if not hundreds of other genetically modified organisms (GMOs) (Gouw, 2018). This allows CRISPR to be used as therapy for thousands of human genetic diseases as well as for enhancement purposes (Tachibana, 2019).

Nevertheless, a cautious approach should be called for. A new and well-regarded study (Kosicki, Tomberg & Bradley, 2018) shows that, far from being specific in its application, the CRISPR deletion technology, for example, often resolves into deletions found over many thousands of bases. Crossover events and lesions distal to the cut site seem common as well. This genomic damage may also lead to cancer and other pathogenic consequences.

While CRISPR provides *internal* biological modifications, 3D bioprinting (the application of 3D printing for biological substrates) provides an *external* source of biological modifications and the role of tissue engineering and 3D bioprinting in space exploration has recently been reviewed (Tachibana, 2019). In general, 3D bioprinters introduce new challenges due to the demands of printing live cells, but we have been able to bioprint cells, tissues, and organs (Thayer, Martinez & Gatenholm, 2020) including tissues that will not cause immune rejection (Alonzo, AnilKumar, Roman, Tasnim & Joddar, 2019; Crook & Tomaskovic-Crook, 2020).

When it comes to the problem of radiation exposure on, for example a mission to Mars or during deep space travel, one of the most natural defenses against radiation may be hibernation or the induction of torpor as demonstrated in animal studies (Puspitasari et al., 2021; Tinganelli et al., 2019). Hibernation is an ordered process of reduced metabolism (Cerri et al., 2016; Heldmaier, Ortmann & Elvert, 2004). Since scientists are now beginning to understand the neuroendocrine as well as genetic mechanisms behind hibernation (Dugbartey, Bouma, et al., 2015; Dugbartey, Talaei, et al., 2015); it may be possible to create an induced hibernation process where synthetic torpor may provide an internal mechanism for radioprotection.

Another reason for caution comes from an alternative, non-medical approach to the radiation problem (Frazier, 2017). During the trip to Mars, existing technology may prevent radiation damage from solar flares. The real danger comes from cosmic rays, which are protons, helium and other particles travelling close to the speed of light. The radiation they produce when hitting the walls of the spacecraft can, nonetheless, be stopped by the hydrogen in water and in plastics such as polyethylene. We may then protect the crew by placing the spacecraft’s water supplies in polyethylene containers attached to the outer walls. In addition, NASA is developing hydrogenated boron nitride nanotubes (hydrogenated BNNTs), the ideal shield against radiation, both for spaceships but also for dwellings and vehicles on Mars. Moreover, this material can be made into yarn that will clothe the explorers themselves. More prosaically, NASA has also demonstrated the ability to use electrochemical methods to create “bricks” from the lunar or Martian regolith (Savage, 2017), or even from dormant fungi (Tavares, 2020), which could readily provide a radiation-resistant shell for any habitat. The success of these technologies would reduce the motivation for biological enhancements.

Another main concern regards bone loss due to microgravity. Several genetic factors involved in the process of bone loss and muscle loss have been identified (Bao, Zheng & Wu, 2012; Li et al., 2005). This gives the possibility for CRISPR or other techniques to be used to enable better bone and muscle regeneration (Carmeliet, Nys, Stockmans & Bouillon, 1998; Xix Congresso Nazionale S.I.C.O.O.P. Societa’ Italiana Chirurghi Ortopedici Dell’Ospedalita’ Privata et al., 2019; Yuan et al., 2019). Since severe bone loss leads to fractures, 3D printing has been widely applied to help with treating fractures by printing exoskeleton systems to provide structural stability, internal replacement with Titanium skeletal parts, and skeletal scaffolds for stem cells to regrow and mend the break (Maroulakos, Kamperos, Tayebi, Halazonetis & Ren, 2019, Ou, Wang, Chang & Chen, 2020, Yang, Grottkau, He & Ye, 2017).

The synthetic biological forms of human enhancement that extend beyond genetic modification may include the development of 3D bioprinting, prosthetic limbs and tissue-engineered organs, which could be accompanied by the production of an exoskeletal structure (Awad et al., 2017). There is also progress in the generation of brain-computer interface communication systems in patients who are either unable to have full movement (Hotson et al., 2016) or are unable to communicate after trauma (Chaudhary, Xia, Silvoni, Cohen & Birmbauer, 2017) or as a consequence of degenerative disease (McCane et al., 2013). Very recently, remarkable progress has been made in developing algorithms to transfer brain patterns into sentences in real-time speech with word error rates as low as 3 % (Makin, Moses & Chang, 2020). Although the speech was limited to 30–50 sentences, this study represents a substantial improvement in decoding neural activity. Some of these examples may be untestable as enhancements for healthy individuals on Earth and it is hard to conceive how such enhancements could be considered in a new space colony even if justified. Nevertheless, the possibility exists for studying and understanding the possibilities for human enhancement in individuals on Earth for which there is very little to lose with respect to restoration of even partial patient quality of life. To ensure an objective assessment of risk, we will need to develop a strict set of regulatory and ethical guidelines to reduce the potential for gratuitous self-enhancement (Gaspar, Rohide & Giger, 2019) and to maximize the safe translation of terrestrial enhancements for the purpose of colonization of other bodies in the solar system.

Again, as with the issue of radiation, we may wish to ponder a different technological approach to the problem of reduced gravity. Non-medical solutions have been discussed for over a century (O’Neill, 1977, Tsiolkovsky, 1911) in scientific and popular writings: artificial gravity created by rotating structures. Consider a spaceship in which the different components (rocket, supply compartment, and human compartment) instead of being stacked up (with the rocket in the bottom) are assembled side by side. The rocket would be in the middle and the other two compartments connected to the rocket by a cable or thin structure, at least 200 m apart from each other, and made to rotate. Astronauts, inside their compartment as it rotates, are subjected to acceleration comparable to Earth’s. Of course, this may only provide a partial solution to the problem, for we would still need to determine how the lower gravitational attraction of Mars may adversely affect human physiology. If it does so, biological enhancements may offer a variety of solutions.

2.4. *Making Homo sapiens Homo galacticus*

There has begun a discussion of how humans might be modified by the likely near-term establishment of lunar and Martian colonies. Indeed, one very recent discussion addresses this concept (Starr, 2020). We may use this “*Homo galacticus*” definition of future humans modified to fit their environment. Visionary people already understand that humans will be modified by their new environments. For example, as we discussed above, settlements on both the Moon and Mars will be subject to high radiation environments. Over many generations selective genetic pressure would result in higher radiation resistance. On Mars, settlers will also be subjected to high levels of perchlorates which are particularly toxic to early development in humans as perchlorate inhibits thyroid function key in early growth (Niziński, Błażewicz, Kończyk & Michalski, 2020). Perchlorate on Mars composes roughly 0.5 % of the Martian regolith, a million times more than in most terrestrial environments. Standard remediation techniques will not be effective in removing this much toxic material for human settlement (Davila, Willson, Coates & McKay, 2013). Some terrestrial micro-organisms have evolved genes capable of mitigating perchlorates (Lamprecht-Grandío et al., 2020). With further research and development, it might be possible to add these mitigating genes to higher organisms including humans. Such modifications would make possible survival in high-perchlorate environments such as Mars in combination with more conventional mitigation approaches.

However, there are good reasons to assume that even the most substantial and invasive ways of biomedical enhancement may be far from enough to provide safe and effective interstellar travels for humans. The only way we can imagine is to provide tailored genomes and then only sending a small “boot-up” payload to the new star system. It is worth keeping in mind that long-term perspective, and to evaluate reasonable prospects for the future. There are a number of significant threats to life on earth, and even in the solar system that would justify establishing human settlements on nearby stars. In 2017 Stephen Hawking made a video presentation in Beijing where he postulated that human population expansion and increased energy usage could make the earth uninhabitable in 600 years. He proposed interstellar expansion as a solution (Cooper, 2017). Conversely, possible solar superflares could do the same (Karoff et al., 2016).

One of our biggest challenges with expanding into the solar system is the requirement to physically transport people and other organisms (plants and animals) needed to set up a viable colony. Craig Venter suggests “faxing” just the genome and recreating the organism with a 3-D genetic printer (David, 2014).[4] Once we have established a small outpost on another world such as Mars and established a working in-situ-resource-utilization system this may well be the way most things are transferred, including life – not by physical transfer but electronic.

In 2018 and 2019, Breakthrough Initiatives held a series of seminars and discussions on how life might be transferred at interstellar distances (Breakthrough Initiatives, 2019).[5] One of the most intriguing ideas is that life here could have been planted by an alien entity billions of years ago. This is called "Directed Panspermia" and was proposed by Nobel Laureate and DNA co-discoverer Francis Crick and Leslie Orgel, a chemist, in 1973 (Crick & Orgel, 1973). In December 2018 at one of these conferences, noted Harvard geneticist George Church suggested we will soon have the capability of those, probably purely hypothetical aliens. Concepts such as Breakthrough Starshot should later in the century give us the ability to directly access nearby star systems (Starshot, 2021). Other technologies, such as fusion propulsion that now appears more feasible in the future[6] could enable us, possibly within a century, to place a small research station on an alien world light years away that could receive tailored genetic information to enable us to "boot-up" a new Earth tailored for that environment. Once established, information could be sent from Earth at the speed of light – including perhaps the entire information content of a human brain – to begin our interstellar expansion.

To be sure there are significant ethics issues with these scenarios. It's essential that we consider the key philosophical issues to go hand-in-hand with the technology development. For example, if we try to remotely settle an alien world light years away, what do we do with any life that's already there – or could we even recognize it? While these topics are already discussed in space ethics and SETI and METI literature (Author, 2016; 2019, Brin, 2019; Cockell, 2016; Haramia & DeMarines, 2019; Traphagan, 2019; Wilks, 2016), it is likely that far-future human missions, which will go beyond the Solar System, will increase our chances for contact with other forms of life including possibly an extraterrestrial intelligent life. The concept of "*Homo galacticus*" also offers some fairly obvious advantages when adopting a distant time frame directed at the survival of the human species at any cost and in any form.

3. Social assessments of human enhancements

One of the main threats caused by human enhancements, from a public viewpoint, is associated with their mixed legacy of benefits and hazards. The same human enhancement technology aimed at benefits for humans may also be used and result in dangerous side effects. Such side effects may include, in the case of genetic editing, unintended on-target and off-target effects, but also possible long-term social and economic consequences such as social inequality (Peters, 2002, 2019a).

Our view is that society should have a right to require from policy makers the means to be involved in future policy regarding human enhancements, in order to make them context-sensitive and responsive to both human and environmental concerns. Therefore, societies should develop cogent rationales for using human enhancement. Humans have a rightful expectation of progress, fairness, and appropriate care in medical treatment, which will make human lives longer and healthier. This social expectation is guided partly by the medical directive to "cause no harm" and minimize negative side effects. While human enhancement technologies theoretically offer benefits such as saving time, in some cases they may be the only available solution, especially for space missions. There are still too many risks and ethical considerations involved to accept human enhancement technologies without an informed societal and social debate. Human enhancements for space exploration have a greater chance of being socially accepted if there are honest and organized efforts to minimize risk to space crew.

4. Conclusions

As we have shown in this and other papers (Szocik et al., 2020), discussion of the future of humanity in space, including missions to Mars and elsewhere, evokes long-term ethical challenges which go far beyond current medical and technological debates. One such challenge is the idea of human enhancement for space. It is worth mentioning that the time needed to develop the science can be very long-term since space programs take decades to develop. The idea of human enhancement, as well as human space missions in general, has both advocates and opponents and we argue that human enhancement may be inseparably connected with a future human presence in space. This means that every mission planner should consider an enhancement strategy. Some ethical considerations are relevant for issues discussed on Earth, but differ markedly when applied to the context of space missions. We hope that our paper will help inspire debate on crucial questions such as: Is human enhancement justified for purposes of future human space missions? Should we enhance future astronauts to make them better adapted to the challenging space environment? If effective space missions require human enhancement, should we realize such a mission? All these possibilities for human-enhancement technologies raise the question: is it worthwhile going to such lengths for people to settle other planets (Gibson, 2006)? This is a discussion that should take place among various sectors of the spaceflight community, and society and governments more generally. While these and other ethical questions are often addressed by personal moral intuitions, we have attempted to outline more objective ethical principles as well.

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[4] See also (Gibson, Hutchison, Smith & Venter, 2018; Venter, 2016).

[5] For more on the specifics, challenges and opportunities regarding interstellar missions, see for example (Millis, Greason & Stevenson, 2018).

[6] As for interstellar transport with light-sails stopping at the other end there are serious efforts underway. Rene Heller and Michael Hippke published a paper in 2017 detailing how this can be done using existing technology and the destination star's light (Heller & Hippke, 2017). There are well-funded efforts underway to develop both light-sail concepts and other concepts including high-Isp fusion engines to enable humans to travel inter-stellar distances (https://www.helicityspace.com/). Many are being funded by the US Government. This author is a member of the board of a major privately-funded effort by the Limitless Space Institute in Houston, Texas (https://www.limitlessspace.org/).

There is an emerging wave of activity in the field (though as yet it lacks a standard label), which may one day develop into a truly enlightened vision of the cosmic future of humanity.

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References

Agar, N. (2014). *Truly human enhancement. A philosophical defense of limits*. Massachusetts London, England: MIT Press Cambridge.

Allegan and Editas Medicine press release. (2020). *Allegan and Editas Medicine press release*. https://ir.editasmedicine.com/news-releases/news-release-details/allergan-and-editas-medicine-announce-dosing-first-patient.

Alonzo, M., AnilKumar, S., Roman, B., Tasnim, N., & Joddar, B. (2019). 3D Bioprinting of cardiac tissue and cardiac stem cell therapy. *Translational Research, 211*, 64–83. https://doi.org/10.1016/j.trsl.2019.04.004.

Author. (2016). The curious case of the martian microbes: Mariomania, intrinsic value and the prime directive, 195–208. In J. S. S. Schwartz, & T. Milligan (Eds.), *The ethics of space exploration*. Springer.

Awad, L. N., Bae, J., O'Donnell, K., De Rossi, S. M. M., Hendron, K., Sloot, L. H., et al. (2017). A soft robotic exosuit improves walking in patients after stroke. *Science Translational Medicine, 9*, eaai9084.

Bao, J., Zheng, J. J., & Wu, D. (2012). The structural basis of DKK-mediated inhibition of Wnt/LRP signaling. *Science Signaling, 5*(224). https://doi.org/10.1126/scisignal.2003028. pe22.

Barcellos-Hoff, M. H., & Cucinotta, F. A. (2014). New tricks for an old fox: Impact of TGFβ on the DNA damage response and genomic stability. *Science Signaling, 7*, 341–345. https://doi.org/10.1126/scisignal.2005474.

Bartone, P. T., Roland, R. R., Bartone, J. V., Krueger, G. P., Sciarretta, A. A., & Johnsen, B. H. (2019). Human adaptability for deep space missions: An exploratory study. *Journal of Human Performance in Extreme Environments, 15*. Article 5.

Braddock, M. (2017). Ergonomic challenges for astronauts during space travel and the need for space medicine. *Journal of Ergonomics, 7*, 1–10.

Braddock, M. (2020). Limitations for extra-terrestrial colonisation and civilization build and the potential for human enhancements. In K. Szocik (Ed.), *Human Enhancements for Space Missions. Lunar, Martian, and Future Missions to the Outer Planets*. Cham: Springer.

Bielefeldt-Ohmann, H., Genik, P. C., Fallgren, C. M., Ullrich, R. L., & Weil, M. M. (2012). Animal studies of charged particle-induced carcinogenesis. *Health Physics, 103*(5), 568–576. https://doi.org/10.1097/HP.0b013e318265a257.

Bloch, E., Luo, Y., & da Cruz, L. (2019). Advances in retinal prosthesis systems. *Therapeutic Advances in Ophthalmology, 11*, 1–16.

Breakthrough Initiatives. (2019). *Breakthrough discuss 2019*. https://breakthroughinitiatives.org/events/discussconference2019.

Brin, D. (2019). The "Barn door" argument, the precautionary principle, and METI as "Prayer"—An appraisal of the top three rationalizations for "Active SETI.". *Theology and Science, 17*(1), 16–28.

Campa, R., Szocik, K., & Braddock, M. (2019). Why space colonisation will be fully automated. *Technological Forecasting and Social Change*. https://doi.org/10.1016/j.techfore.2019.03.021.

Carmeliet, G., Nys, G., Stockmans, I., & Bouillon, R. (1998). Gene expression related to the differentiation of osteoblastic cells is altered by microgravity. *Bone, 22*(5 Suppl), 139S–143S. https://doi.org/10.1016/s8756-3282(98)00007-6.

Cavanagh, P. R., Licata, A. A., & Rice, A. J. (2005). Exercise and pharmacological countermeasures for bone loss during long-duration space flight. *Gravitational and Space Biology Bulletin, 18*(2), 39–58.

Cerri, M., Tinganelli, W., Negrini, M., Helm, A., Scifoni, E., Tommasino, F., et al. (2016). Hibernation for space travel: Impact on radioprotection. *Life Sciences in Space Research, 11*, 1–9. https://doi.org/10.1016/j.lssr.2016.09.001.

CGS Staff. (2018). *CGS summary of public opinion polls*. https://www.geneticsandsociety.org/internal-content/cgs-summary-public-opinion-polls.

Chaudhary, U., Xia, B., Silvoni, S., Cohen, L. G., & Birmbauer, N. (2017). Brain-computer interface-based communication in the completely locked-in state. *PLoS Biology, 15*, Article e1002593.

Chon-Torres, O. A. (2018). Astrobioethics. *International Journal of Astrobiology, 17*, 51–56.

Church, G. M. 2019. [No title] http://arep.med.harvard.edu/gmc/protect.html.

Clinical trials. (2020). *Single ascending dose study in participants with LCA10 NCT#03872479*. https://clinicaltrials.gov/ct2/show/NCT03872479.

Cockell, C. S. (2016). The ethical Status of microbial life on earth and elsewhere: In defence of intrinsic value, 167–179. In J. S. S. Schwartz, & T. Milligan (Eds.), *The ethics of space exploration*. Springer.

Cooper, G. F. (2017). *Stephen Hawking: Earth could be 'ball of fire' in 600 years*. Cnet. https://www.cnet.com/news/stephen-hawking-earth-ball-of-fire-600-years-tencent-we-summit-beijing/.

Cortese, F., Klokov, D., Osipov, A., Stefaniak, J., Moskalev, A., Schastnaya, J., et al. (2018). Vive la radioresistance!: Converging research in radiobiology and biogerontology to enhance human radioresistance for deep space exploration and colonisation. *Oncotarget, 9*. https://doi.org/10.18632/oncotarget24461.

Crick, F. H., & Orgel, L. E. (1973). Directed panspermia. *Icarus, 19*(3), 341–346.

Crook, J. M., & Tomaskovic-Crook, E. (2020). Bioprinting 3D human induced pluripotent stem cell constructs for multilineage tissue engineering and modeling. *Methods in Molecular Biology, 2140*, 251–258. https://doi.org/10.1007/978-1-0716-0520-2_17.

Cucinotta, F. A., & Durante, M. (2006). Cancer risk from exposure to galactic cosmic rays: implications for space exploration by human beings. *The Lancet Oncology, 7*, 431–435.

Cucinotta, F. A., Manuel, F., Jones, J., Izsard, G., Murray, J., Djojonegoro, B., & Wear, M. (2001). Space radiation and cataracts in astronauts. *Radiation Research, 156*, 460–466.

Cyranoski, D. (2019). The CRISPR-baby scandal: What's next for human gene editing. *Nature, 566*, 440–442.

David, L. (2014). 'Faxing' life from Mars: Craig Venter's wild. *Digital Space Exploration Idea*. https://www.space.com/24923-faxing-life-from-mars-craig-venter.html.

Davila, A. F., Willson, D., Coates, J. D., & McKay, C. P. (2013). Perchlorate on Mars: A chemical hazard and a resource for humans. *International Journal of Astrobiology, 12*(4), 321–325.

Diao, Y., Chen, B., Wei, L., & Wang, Z. (2018). Polyphenols (S3) isolated from cone scales of Pinus Koraiensis alleviate decreased bone formation in rat under simulated microgravity. *Scientific Reports, 8*(1), 12719. https://doi.org/10.1038/s41598-018-30992-8.

Dugbartey, G. J., Bouma, H. R., Strijkstra, A. M., Boerema, A. S., & Henning, R. H. (2015). Induction of a torpor-like state by 5'-AMP does not depend on H2S production. *PloS One, 10*(8), Article e0136113. https://doi.org/10.1371/journal.pone.0136113.

Dugbartey, G. J., Talaei, F., Houwertjes, M. C., Goris, M., Epema, A. H., Bouma, H. R., & Henning, R. H. (2015). Dopamine treatment attenuates acute kidney injury in a rat model of deep hypothermia and rewarming - the role of renal H2S-producing enzymes. *European Journal of Pharmacology, 769*, 225–233. https://doi.org/10.1016/j.ejphar.2015.11.022.

Frazier, S. (2017). Real martians: How to protect astronauts from space radiation on mars. *NASA's goddard space flight center publication. Sept. 30, 2015. Updated: Aug. 7, 2017*.

Gage, D. (2010). *Craig Venter to NASA: Think about engineering your astronauts*. https://xconomy.com/san-francisco/2010/11/03/craig-venter-to-nasa-think-about-engineering-your-astronauts/.

Gareau, M. G. (2014). Microbiota-gut-brain axis and cognitive function. *Microbial endocrinology: The microbiota-gut-Brain Axis in health and disease* (pp. 357–371). Springer.

Gibson, T. M. (2006). The bioethics of enhancing human performance for spaceflight. *Journal of Medical Ethics, 32*, 129–132.

Gibson, D. G., Hutchison, C. A., III, Smith, H. O., & Venter, J. C. (2018). Synthetic cells and minimal life. *Handbook of Astrobiology* (pp. 75–90).

Goldberg, J. M., Wilson, V. J., Angelaki, D. E., Cullen, K. E., Buttner-Ennever, J., & Fukushima, K. (2012). *The vestibular system: A sixth sense*. Oxford University Press.

Golub, J. S., Ling, L., Nie, K., Nowack, A., Shepherd, S. J., Bierer, S. M., et al. (2014). Prosthetic implantation of the human vestibular system. *Otology & Neurotology, 35*, 136–147.

Gouw, A. (2018). Challenging the therapy/enhancement distinction in CRISPR gene editing. In David Boonin (Ed.), *The Palgrave Handbook of Philosophy and Public Policy* (pp. 493–508). New York, NY: Palgrave Macmillan.

Gouw, A. (2020). Introducing the Brave New CRISPR World. *Zygon, 55*(2), 421–429.

Guo, J., Zeitlin, C., Wimmer-Schweingruber, R. F., Hassler, D. M., Ehresmann, B., Kohler, J., et al. (2015). MSL-RAD radiation environment measurements. *Radiation Protection Dosimetry, 166*(1-4), 290–294. https://doi.org/10.1093/rpd/ncv297.

Hackney, K. J., Scott, J. M., Hanson, A. M., English, K. L., Downs, M. E., & Ploutz-Snyder, L. L. (2015). The astronaut-athlete: Optimizing human performance in space. *Journal of Strength and Conditioning Research, 29*, 3531–3545.

Haramia, C., & DeMarines, J. (2019). The imperative to develop an ethically-informed METI analysis. *Theology and Science, 17*(1), 38–48.

Hayashi, T., Morishita, Y., Khattree, R., Misumi, M., Sasaki, K., Hayashi, I., et al. (2012). Evaluation of systemic markers of inflammation in atomic-bomb survivors with special reference to radiation and age effects. *FASEB Journal, 26*(11), 4765–4773. https://doi.org/10.1096/fj.12-215228.

Heldmaier, G., Ortmann, S., & Elvert, R. (2004). Natural hypometabolism during hibernation and daily torpor in mammals. *Respiratory Physiology & Neurobiology, 141* (3), 317–329. https://doi.org/10.1016/j.resp.2004.03.014.

Heller, R., & Hippke, M. (2017). Deceleration of high-velocity interstellar photon sails into bound orbits at a centauri. *ApJ Letters, 835*. https://doi.org/10.3847/2041-8213/835/2/L32.

Hotson, G., McMullen, D. P., Fifer, M. S., Johannes, M. S., Katyal, K. D., Para, M. P., et al. (2016). Individual finger control of a modular prosthetic limb using high-density electrocorticography in a human subject. *Journal of Neural Engineering, 13*, Article 026017.

Illardo, M., & Nielsen, R. (2018). Human adaptation to extreme environmental conditions. *Current Opinion in Genetics and Development, 53*, 77–82.

Karoff, C., Knudsen, M., De Cat, P., Bonanno, A., Fogtmann-Schulz, A., Fu, J., et al. (2016). Observational evidence for enhanced magnetic activity of superflare stars. *Nature Communications, 7*, 11058.

Kast, J., Yu, Y., Seubert, C. N., Wotring, V. E., & Derendorf, H. (2017). Drugs in space: Pharmacokinetics and pharmacodynamics in astronauts. *European Journal of Pharmaceutical Sciences, 109S*, S2–S8. https://doi.org/10.1016/j.ejps.2017.05.025.

Khan-Mayberry, N., James, J. T., Tyl, R., & Lam, C. W. (2011). Space toxicology: Protecting human health during space operations. *International Journal of Toxicology, 30*, 3–18.

Kosicki, M., Tomberg, K., & Bradley, A. (2018). Repair of double-strand breaks induced by CRISPR–Cas9 leads to large deletions and complex rearrangements. *Nature Biotechnology, 36*, 765–771.

Lamprecht-Grandío, M., Marta, C., Salvador, M., de la Cmaraámara Macarena, B., de Figueras Carolina, G., Danilo, P.-P., et al. (2020). Novel genes involved in resistance to both ultraviolet radiation and perchlorate from the metagenomes of hypersaline environments. *Frontiers in Microbiology*, 11.

Lee, A. G., Mader, T. H., Gibson, C. R., Brunstetter, T. J., & Tarver, W. J. (2018). Space flight-associated neuro-ocular syndrome (SANS). *Eye, 32*, 1164–1167.

Li, X., Zhang, Y., Kang, H., Liu, W., Liu, P., Zhang, J., et al. (2005). Sclerostin binds to LRP5/6 and antagonizes canonical Wnt signaling. *The Journal of Biological Chemistry, 280*(20), 19883–19887. https://doi.org/10.1074/jbc.M413274200.

Liu, Y., & Taylor, L. A. (2011). Characterization of lunar dust and a synopsis of available lunar simulants. *Planetary and Space Science, 59*, 1769–1783.

Luo, Y. H., & Da Cruz, L. (2014). A review and update on the current status of retinal prostheses (bionic eye). *British Medical Bulletin, 109*, 31–44.

Makin, J. G., Moses, D. A., & Chang, E. F. (2020). Machine translation of cortical activity to text with an encoder–decoder framework. *Nature Neuroscience*. https://doi.org/10.1038/s41593-020-0608-8.

Maroulakos, M., Kamperos, G., Tayebi, L., Halazonetis, D., & Ren, Y. (2019). Applications of 3D printing on craniofacial bone repair: A systematic review. *Journal of Dentistry, 80*, 1–14. https://doi.org/10.1016/j.jdent.2018.11.004.

Mason, C.h. E. (2021). *The next 500 years*. MIT Press.

McCane, L. M., Sellers, E. E., McFarland, D. J., McFarland, D. J., Mak, J. N., Carmack, C. S., et al. (2013). Brain-computer interface (BCI) evaluation in people with amyotrophic lateral sclerosis. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 15*, 207–215.

Millis, M. G., Greason, J., & Stevenson, R. (2018). *Breakthrough propulsion study assessing interstellar flight challenges and prospects, NASA grant No. NNX17AE81G first year report*.

Niziński, P., Błażewicz, A., Kończyk, J., & Michalski, R. (2020). Perchlorate - properties, toxicity and human health effects: An updated review. *Reviews on Environmental Health*. https://doi.org/10.1515/reveh-2020-0006. Epub ahead of print. PMID: 32887207.

O'Neill, G. K. (1977). *The high frontier: Human colonies in space*. New York: William Morrow & Company.

Ou, Y. K., Wang, Y. L., Chang, H. C., & Chen, C. C. (2020). Design and Development of a Wearable Exoskeleton System for Stroke Rehabilitation. *Healthcare (Basel, Switzerland), 8*(1). https://doi.org/10.3390/healthcare8010018.

Owe, A. (2019). *Environmental Ethics in Outer Space: A macrostrategic space journey through cosmism, posthumanism and moral enhancement*. Master's Thesis in Development, Environment and Cultural Change, University of Oslo (https://www.duo.uio.no/bitstream/handle/10852/69331/1/Owe-Andrea-15-05-2019-Environmental-Ethics-in-Outer-Space-MAthesis-.pdf).

Palinkas, L. A. (2007). Psychosocial issues in long-term space flight: Overview. *Gravitational and Space Research, 14*, 25–33.

Peters, T. (2002). *Playing god? Genetic determinism and human freedom* (2nd ed.). London and New York: Routledge.

Peters, T. (2013). In Chris Impey, Anna Spitz, & William Stoeger (Eds.), *Astroethics: Engaging Extraterrestrial Intelligent Life-Forms, Encountering Life in the Universe*.

Peters, T. (2019a). Flashing the yellow traffic light: Choices forced upon us by CRISPR gene editing technologies. *Theology and Science, 17*(1), 79–89.

Peters, T. (2019b). Should we send messages to extraterrestrials? *Theology and Science, 17*(1), 6–8.

Peters, T. (2021). Astroethics for earthlings: Our responsibility to the galactic commons. In Octavio A. Chon-Torres, Ted Peters, Joseph Seckbach, & Russell Gordon (Eds.), *Astrobiology: Science, Ethics, and Public Policy* (pp. 17–56). Singapore: Wiley Scrivener.

Pontin, J. (2018). *The genetics (and ethics) of making humans fit for Mars*. Wired, 7 August. Available at https://www.wired.com/story/ideas-jason-pontin-genetic-engineering-for-mars/.

Puspitasari, A., Cerri, M., Takahashi, A., Yoshida, Y., Hanamura, K., & Tinganelli, W. (2021). Hibernation as a tool for radiation protection in space exploration. *Life, 11*, 54.

Reiss, M. J. (2000). The ethics of xenotransplantation. *Journal of Applied Philosophy, 17*, 253–262.

Reiss, M. J., & Straughan, R. (1996). *Improving nature? The science and ethics of genetic engineering*. Cambridge: Cambridge University Press.

Reschke, M. F., Bloomberg, J. J., Harm, D. L., & Paloski, W. H. (1994). Space flight and neurovestibular adaptation. *Journal of Clinical Pharmacology, 34*, 609–617.

Rivina, L., & Schiestl, R. (2013). Mouse models of radiation-induced cancers. *Advances in Genetics, 84*, 83–122. https://doi.org/10.1016/B978-0-12-407703-4.00003-7.

Ryder, P., & Braddock, M. (2020). Harnessing the space environment for the discovery and development of new medicines. In Y. Pathak, M. Araújo dos Santos, & L. Zea (Eds.), *Handbook of space pharmaceuticals*. Cham: Springer.

Savage, N. (2017). *To build settlements on Mars, we'll need materials chemistry*. retrieved from: Chemical & Engineering News https://cen.acs.org/articles/96/i1/build-settlements-Mars-ll-need.html.

Savulescu, J., ter Meulen, R., & Kahane, G. (Eds.). (2011). *Enhancing human capacities*. Wiley-Blackwell.

Savulescu, J., & Bostrom, N. (Eds.). (2011). *Human enhancement*. Oxford, UK: Oxford University Press.

Scheuring, R. A., Jones, J. A., Novak, J. D., Polk, J. D., Gillis, D. B., Schmid, J., et al. (2008). The Apollo Medical Operations Project: Recommendations to improve crew health and performance for future exploration missions and lunar surface operations. *Acta Astronautica, 63*, 980–987.

Shreiner, A. B., Kao, J. Y., & Young, V. B. (2015). The gut microbiome in health and in disease. *Current Opinion in Gastroenterology, 31*, 69–75.

Siddiqui, R., Akbar, N., & Khan, N. A. (2021). Gut microbiome and human health under the space environment. *Applied and Environmental Microbiology, 130*, 14–24.

Starr, M. (2020). *Homo Galacticus: How space will shape the humans of the future. Science alert*. https://www.sciencealert.com/homo-galacticus-how-space-will-shape-the-humans-of-the-future.

Starshot. 2021 n.d. https://breakthroughinitiatives.org/initiative/3.

Szocik, K., Abood, S., Impey, C., Shelhamer, M., Haqq-Misra, J., Persson, E., Oviedo, L., Capova, K. A., Braddock, M., Rappaport, M. B., & Corbally, C. (2020). Visions of a Martian Future. *Futures, 117*, 102514.

Tachibana, K. (2019). A Hobbesian qualm with space settlement. *Futures, 110*, 28–30.

Tavares, F. (2020). *Could future homes on the moon and mars be made of fungi?*. retrieved from: NASA Ames https://www.nasa.gov/feature/ames/myco-architecture.

Thayer, P., Martinez, H., & Gatenholm, E. (2020). History and trends of 3D bioprinting. *Methods in Molecular Biology, 2140*, 3–18. https://doi.org/10.1007/978-1-0716-0520-2_1.

Tinganelli, W., Hitrec, T., Romani, F., Simoniello, P., Squarcio, F., Stanzani, A., et al. (2019). Hibernation and radioprotection: Gene expression in the liver and testicle of rats irradiated under synthetic torpor. *International Journal of Molecular Sciences, 20*, 352.

Traphagan, J. W. (2019). Active SETI and the problem of research ethics. *Theology and Science, 17*(1), 69–78.

Tsiolkovsky, K. (1911). Investigation of outer space rocket devices. *Science Review*.

Turroni, S., Magnani, M., Kc, P., Lesnik, P., Vidal, H., & Heer, M. (2020). Gut microbiome and space travelers' health: State of the art and possible pro/prebiotic strategies for long-term space missions. *Frontiers Physiology, 11*, Article 553929. https://doi.org/10.3389/fphys.2020.553929.

Venter, J. C. (2016). A conversation with J. Craig Venter, PhD. *Industrial Biotechnology, 12*(3), 134–136.

Voorhies, A. A., & Lorenzi, H. A. (2016). The challenge of maintaining a healthy microbiome during long-duration space missions. *Frontiers in Astronomy and Space Sciences, 3*, 23.

Wanjet, C.h. (2020). *Spacefarers: How humans will settle the moon, Mars, and beyond*. Cambridge MA: Harvard University Press.

Wells, H. G. (1895). *The time machine*. London: Heinemann.

Wilks, A. F. (2016). Kantian foundations for a cosmocentric ethic, 181–194. In J. S. S. Schwartz, & T. Milligan (Eds.), *The ethics of space exploration*. Springer.

Xix Congresso Nazionale S.I.C.O.O.P. Societa' Italiana Chirurghi Ortopedici Dell'Ospedalita' Privata, Accreditata, Aicale, R., Tarantino, D., Maccauro, G., Peretti, G. M., & Maffulli, N. (2019). Genetics in orthopaedic practice. *Journal of Biological Regulators and Homeostatic Agents, 33*(2 Suppl. 1), 103–117.

Yang, L., Grottkau, B., He, Z., & Ye, C. (2017). Three dimensional printing technology and materials for treatment of elbow fractures. *International Orthopaedics, 41* (11), 2381–2387. https://doi.org/10.1007/s00264-017-3627-7.

Yuan, J., Tickner, J., Mullin, B. H., Zhao, J., Zeng, Z., Morahan, G., & Xu, J. (2019). Advanced genetic approaches in discovery and characterization of genes involved with osteoporosis in mouse and human. *Frontiers in Genetics, 10*, 288. https://doi.org/10.3389/fgene.2019.00288.