*Studia Humana*
Volume 11:1 (2022), pp. 1—16
DOI: 10.2478/sh-2022-0001

# Sustaining Resources for *Homo Martis*: The Potential Application of Synthetic Biology for the Settlement of Mars

*Rauf Sharpe*

Rosliston Astronomy Group, Rosliston Forestry Centre
Burton Road, Rosliston, Swadlincote
DE12 8JX, England, United Kingdom

*e-mail:* raufsharpe@outlook.com

*Martin Braddock*

Sherwood Observatory, Mansfield and Sutton Astronomical Society
Coxmoor Road, Sutton-in-Ashfield, Nottinghamshire, NG17 5LF
England, United Kingdom

Science4U.co.uk, Radcliffe-on-Trent
Nottinghamshire, NG12 2LA, England, United Kingdom
https://orcid.org/0000-0001-8152-3580

*e-mail:* martinbraddock@rocketmail.com

*Abstract*:
The recent success of the Mars 2020 project and the high quality images relayed back to Earth have provided further impetus and expectations for human missions to Mars. To support space agency and private enterprise plans to establish a sustainable colony on Mars in the 2030s, synthetic biology may play a vital role to enable astronaut self-sufficiency. In this review, we describe some aspects of where synthetic biology may inform and guide *in situ* resource utilisation strategies. We address the nature of Martian regolith and describe methods by which it may be rendered fit for purpose to support growth and yield of bioengineered crops. Lastly, we illustrate some examples of innate human adaptation which may confer characteristics desirable in the selection of colonists and with a future looking lens, offer potential targets for human enhancement.

*Keywords*: Mars colonisation, *in situ* resource utilisation, synthetic biology, bioengineered crops, human enhancement.

## 1. Introduction

The concept of establishing semi-permanent or permanent colonies on Mars is receiving much attention. Private enterprise and space agencies have plans to establish a sustainable colony on Mars in the late 2020s or 2030s [1] – [3] and much will be learnt from both past and future unmanned missions to Mars and terrestrial analogue studies of confinement and self-sufficiency. Advances for the conservation of resources on Earth necessary to support an increasing global population will have positive collateral effects on space exploration. It is recognised that there are many challenges for human travel to Mars let alone permanent colonisation and the establishment of '*Homo martis'*. A recent crowd-sourcing study illustrated physiological and psychological obstacles which must be overcome [4]. The study used socio-technical systems models which included cognitive work analysis methodology [5] which was employed to build a nine step abstraction hierarchy supporting a work domain analysis [6]. The top-ranking sub-category from the 387 responders who provided input was the provision of an adequate food and water supply chain [4].

It is possible to estimate how much food may be required for a mission to Mars. We will assume that a return mission would include a 9 month travel period to Mars, a residence time of 18 months and a 9 month return trip. We will also assume that the amount of food, and packaging required for each of six astronauts is equivalent to the amount currently allowed for on the International Space Station (ISS) which is 1.8 kg per day [7], [8]. A 9 month journey requires an upfront cargo weight of approximately 3,000 kilograms (kg) which potentially could be catered for. An 18 month stay and 9 month return trip adds approximately an additional 9,000 kg. Launch windows are timed to coincide with the closest distance between Earth and Mars and are typically every 2-3 years where the inter-planetary distance at opposition is between 58 – 92 million kilometres (km) [9], [10] although the actually journey follows a least energy Hohmann transfer orbit, which is an elliptical orbit used to transfer between the two circular planet orbits using the lowest possible amount of propellant [11]. In the Hohmann transfer the spacecraft uses an elliptical orbit to transfer between two circular orbits of different radii around a central body in the same plane. The overall distance travelled is much further than the direct distance, for example the Mars 2020 mission has travelled over 234 million km from Earth to Mars. Transporting a large weight of food this distance would be logistically very challenging using technology available today.

The cost of space launch has been dramatically reduced over the years [12] and it is possible to estimate the costs involved for carrying the cargo alone [13]. Assuming that a medium-lift vehicle would be required (a cargo range of 2,000 – 20,000 kg), we can estimate a cost of between \$1700 and \$15,000 to launch 1 kg of material into low Earth orbit. Costs do not stop there and using current technology, transport to Mars requires approximately 9 times the weight of propellant per kg of cargo for launch, so it would appear that regular launches from Earth may not be financially viable to transport large masses of food such a great distance, especially given that inter-planetary launch windows are every 2-3 years. Therefore, it seems a reasonable planning assumption that as human beings begin to look further to living and existing as an interplanetary species, we cannot simply rely on Earth to supply the whole of the Martian population and as this population expands there will be an increasing demand for food and resources to be produced *in situ.*

This situation provides scientists and engineers with technical challenges and opportunities and drives the current set of planning assumptions that laying the foundations to rapidly develop sustainable agriculture ahead of any permanent human presence on Mars will be critical to the success of inhabitation and the future build of a colony. We propose the use of synthetic biology to provide solutions to some of these tasks. First, we will address the problem statements.

## 2. Problem Statements

The challenges we will address in the review have applications not only for the colonisation of Mars but for the optimisation, reclamation and utilisation of resources and land on Earth. With the population of Earth expected to reach 10 billion (bn) people by the mid to late 2050s [14], an increase of 20-25% from today, it is clear that radical changes in farming practice, sustainability of both food stuffs and drinkable water and conservation of the Earth's ecosystems will be required to meet the demand of an expanding population. Three problem statements may be defined which will be addressed in the next sections.

- the composition of the Martian regolith *in situ* may not support crop growth
- the conditions on the surface of Mars are inhospitable to life
- expansion of Earth's population requires further inventive ways to sustain all inhabitants with an acceptable quality of life.

## 3. Surface Martian Conditions

Mars is generally an arid, frigid, lifeless, desert receiving approximately half the level of sunlight on the surface when compared with Earth. The common average temperature reported is −63 °C (210 K; −81 °F) [15]. Surface temperatures may reach a high of approximately 20 °C (293 K; 68 °F) at noon at the equator and a low of about −153 °C (120 K; −243 °F) at the poles [16], [17]. The radiation environment at the Martian surface is, apart from occasional solar energetic particle events, dominated by galactic cosmic radiation (GCR), secondary particles produced in their interaction with the Martian atmosphere and albedo particles from the Martian soil, termed regolith. The highly energetic primary cosmic radiation consists mainly of fully ionized nuclei creating a complex radiation field at the Martian surface [18], [19]. Mitigating the risk of exposure to harmful levels of GCR will likely require the construction of one or more underground shelters and candidates could include modification of existing lava tubes which are located in low lying regions of the planet and which receive reduced levels of GCR. This is important as a previous study of analogue lava tubes on Earth showed that the amount of radiation in the interior of the tubes is 82% lower than on the surface of the planet [20]. These surface conditions set the scene for where synthetic biology may be able to help, which is likely in a sub-terranean environment using Martian regolith.

## 4. Nature of Soils

An average composition of Earth soil and Martian regolith is shown in Figure 1.

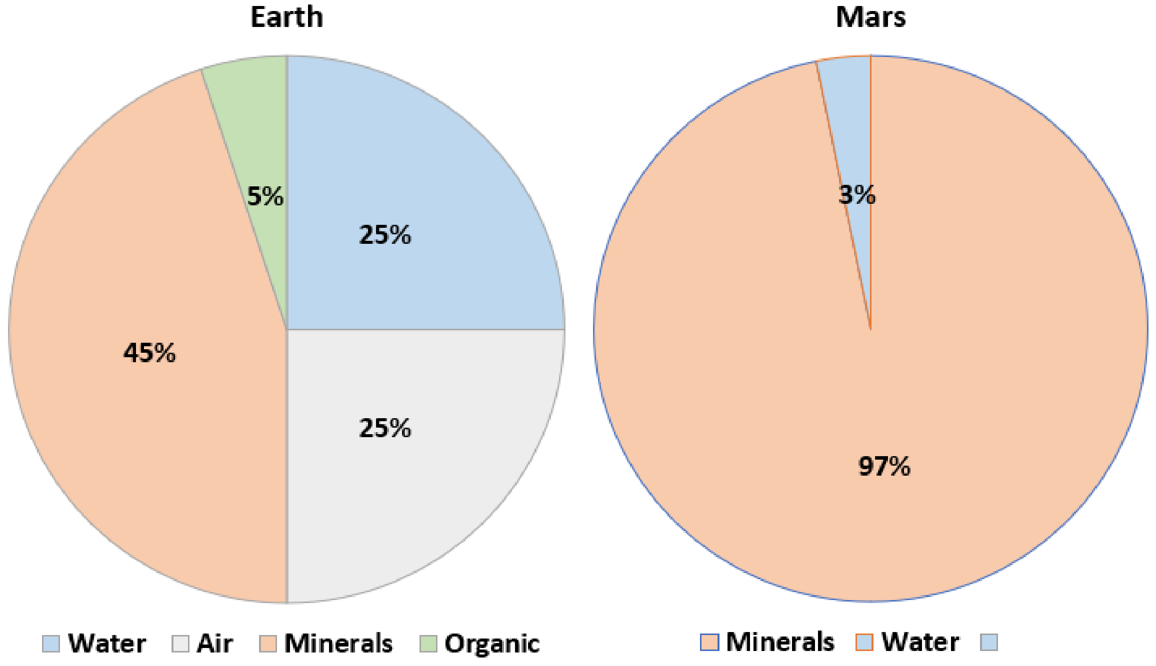


Figure 1. Approximate composition of Earth soil and Martian regolith [21 – 23].

As of May 2021, the composition of Martian regolith is believed to be devoid of organic matter due to the absence of either living or extant carbon-based lifeforms and the recent Mars 2020 mission will seek astro-biological signatures of life at sites within the Jezero crater. Unlike Martian regolith, soils on Earth comprise approximately 25% water, 25% air, 45% minerals of varying compositions and textures and 5% of organic matter derived from living or dead organisms [21] – [23].

Martian regolith is a dusty, pulverised rock layer which has been produced by the impact of asteroid and meteorite collisions with the planet's surface together with the erosion of iron-rich igneous rock by physical weathering over billions of years. The mineral matter in Martian soil is derived from weathered volcanic rock [24]. It has clay and silt-sized particles, a thin surface layer of very small sized dust particles and a reddish colour due to the presence of iron oxides. Overall, Martian regolith is of a sandy texture [25], [26] and has evolved over time [27]. Previous expeditions to Mars such as the Viking, Pathfinder, Spirit, Opportunity and Curiosity landers have analysed the chemical composition of regolith and found it to be made up mainly of silicon, iron, aluminium, magnesium and calcium oxides and these studies have permitted the sourcing of Mars regolith simulants (MRS) [28], [29] with a comparable elemental composition.

However, MRS have not included the presence of perchlorate which is present in Martian regolith as a salt of both magnesium, sodium and calcium. NASA's Phoenix Lander discovered the presence of perchlorate anions at a concentration of 0.4–0.6 weight % [30], [31] which was confirmed by the Sample Analysis at Mars instrument onboard the Curiosity rover [32]. In September 2015, the Mars Reconnaissance Orbiter detected hydrated salts of $NaClO_4$, $Mg(ClO_4)_2$ and $Mg(ClO_3)_2$ in locations thought to be brine seeps.

Perchlorates are powerful oxidising agents and toxic to both humans [33] and to plant growth [34] and a study showed that perchlorates, at concentrations similar to those detected in Martian surface regolith, become bacteriocidal when irradiated with a simulated Martian UV flux which caused vegetative cells of *Bacillus subtilis* to rapidly lose viability within minutes [35]. Moreover, two additional components of the Martian surface, iron oxides and hydrogen peroxide, were shown to act in synergy with irradiated perchlorates to cause a 10.8-fold increase in cell death when compared with cells exposed to UV radiation for 60 seconds. Interestingly, the distribution of perchlorates in the Martian regolith may be driven by the distribution of chlorine and the photocatalytic ability of silicon dioxide and other metal oxides, suggesting that areas may exist where the perchlorate concentration may vary [36].

## 5. Addressing the Problem Statements with Synthetic Biology

Synthetic biology, popularly known as SynBio is a multi-disciplinary area of research which aims to create new biological entities or to re-engineer systems existing in the natural world. It is a cross-disciplinary science which integrates multiple specialities including biology, systems biology and bioinformatics, biotechnology, machine-based learning, engineering, manufacturing and safety assessment. The scientific and ethical potential of synthetic biology for space exploration has been extensively reviewed [8], [37] – [41] and may in some instances be able to ameliorate the risks perceived for travelling to and living on Mars [42].

This section will review some selected candidates, provide an update on their status and illustrate examples under the most relevant category proposed [38], namely resource utilisation to permit life support. The mind map in Figure 2 illustrates the areas under consideration for this review. Other themes such as medicine, manufacturing, cybernetics and terra-formation are out of scope here and have been covered elsewhere, e.g. [8] and will be the subject of an additional future review when more data becomes available over the next several years.

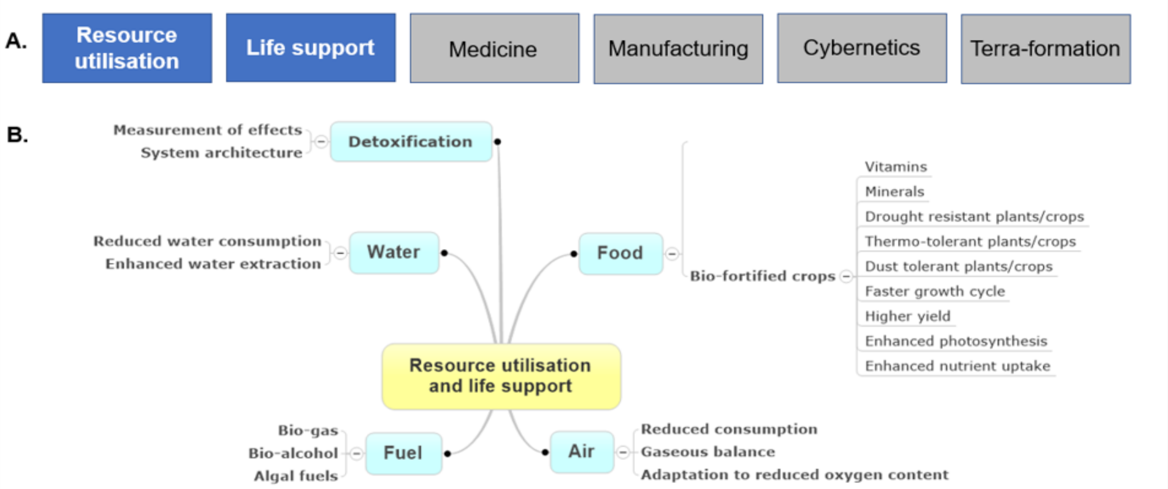


**Figure 2. Mind-map of some potential targets for synthetic biology. A. Themes are denoted and those in blue colour B. form the subject of review.**

## a) Detoxification

The presence of perchlorate on Mars presents one immediate challenge which must be overcome to permit the growth of crops if Martian regolith is to be a substrate for establishment of a food supply chain. A terrestrial study with four wetland plants showed plant growth in soil in the presence of 0.5% perchlorate was associated with a decline in leaf chlorophyll content, a reduction in the oxidising power of root systems, a reduction in plant size above and below ground, and an accumulation of perchlorates in the leaves [34]. This study illustrates that for plants to grow in Martian regolith, the regolith needs to be processed to remove perchlorate and other toxic impurities. Moreover, findings suggest that the combined effects of irradiated perchlorates, iron oxide and hydrogen peroxide on the Martian surface, may demonstrate the low probability of survival of organisms introduced to Mars not adapted or engineered to grow in such conditions [35].

Perchlorate contamination on Earth is an issue of increasing global concern as it has a deleterious effect on ecosystems, with a concomitant loss of environmental quality and diversity [43]. Perchlorate is a ubiquitous contaminant produced from both natural and anthropogenic sources [44] and is present in areas associated with the use and manufacture of rockets and ammunition. In humans, perchlorate is a potent endocrine hormone attenuator affecting iodine fixation by the thyroid gland which is responsible for regulating metabolism, growth, and development [45] and may be considered harmful to the development of infants and children throughout their growing period [46]. Acute, short-term exposure has been shown to affect the nervous, respiratory, immune, and reproductive systems [47], [48] and it has also been related to thyroid cancer and teratogenesis during the first trimester of pregnancy [49]. The main direct routes of exposure of astronauts to perchlorate on Mars would be through direct inhalation of dust into the lungs, ingestion of contaminated water and ingestion of foods grown in the presence of perchlorate. Exposure to perchlorate through inhalation is not a general serious problem on Earth and concentrations are typically low in drinking water [50]. Most naturally occurring sources of perchlorate of potential health concern appear to be geographically limited to arid environments where deposits tend to be low in concentration, except for the relatively high natural concentrations found in Chilean caliches and some potash ore deposits containing perchlorate ranging from 0.03 to 0.1% [43]. Potash ore is mined and milled in Saskatchewan, Canada (silvite mineral), United States (New Mexico, hankite mineral from California), and Playa crusts from Bolivia [51]. The potassium chloride in these deposits originated in briny sea beds, similar to those of Chilean deposits where the concentrations of perchlorate range from 0.0025 to 0.27 %.

Given that perchlorate poses a threat to human health in some regions on Earth, various approaches have been identified which have both terrestrial utility and may be transferable to Mars, albeit in a limited environment in the first instance. It has been known since the 1920s that bacteria exist which can use chlorate and perchlorate as a terminal electron acceptor for anaerobic energy production and dissimilatory perchlorate reducing bacteria (DPRB) use a highly conserved perchlorate reductase (PcrABC), to reduce perchlorate to chlorate and subsequently chlorite. Chlorite is then rapidly removed by another highly conserved enzyme, chlorite dismutase (Cld), to produce molecular oxygen and chloride. One recent study described DPRB isolated from soil samples from hypersaline deposits in the Colombian Caribbean [45]. Capable of growing in salt concentration of 30% sodium chloride, bacteria related to *Vibrio, Bacillus, Staphylococcus* and *Nesiotobacter genera* were shown to reduce perchlorate concentrations from between 10 – 25% when grown in culture medium containing potassium perchlorate at various concentrations between 100 and 10,000 mg/L. DRPB may also have a secondary effect, particularly relevant to the concept of a closed biosphere, which is a unique ability to generate molecular oxygen as a transient intermediate of the central pathway of perchlorate respiration [52]. Constructing an ecosystem with such a population of bacteria may both protect colonists from serious health problems while also bolstering their breathable air supply.

Wherein lies the opportunity for synthetic biology? One proposition is that proposed by NASA [53] which is the construction of a synthetic biology system architecture capable of detoxifying perchlorate and enrichment Martian regolith in *one* entity. This is an example of using synthetic biology towards building organisms with a repertoire of individual functions [54]. In this case, the two system processes of perchlorate reduction and nitrogen fixation are proposed to be *combined* and be permissive for regolith-based agriculture on Mars. Research is underway to investigate two strains of a diverse clade of *Pseudomonas* organisms, which are technically more amenable to laboratory experimentation and include a perchlorate reducer and a nitrogen fixer. The concept is part of a broader field of study which includes the design, incorporation of engineered organisms and operationalisation of the Crucible open source bioreactor to emulate the Martian environment [55].

## b) Engineered Plants

### i) Drought Resistant Plants

Over the last decade it is now become clear that not only did water exist on the surface of Mars in the past to shape the landscape, but that it exists on the planet today in both liquid and frozen forms [56] – [59]. All plants require water, even if grown hydroponically and as of the time of writing, it is believed that considerable effort and energy will be required to abstract water and establish a supply chain even on a small scale. Water storage and retention in a form that can be made available to support plant and crop growth on demand is a significant hurdle which needs to be overcome. We should, therefore, regard water as a valuable commodity. Indeed, the predicted need to produce more terrestrial based food for human consumption and the demand for additional water to support crop irrigation and growth [60], [61], has warranted research efforts which have recently been reviewed [62]. In brief, synthetic biology has demonstrated that the amount of water lost through plant stomata can be reduced by modulation of Photosystem II (PSII). In 2018, a study investigated the effects of increased expression of PSII subunit S (*PsbS*), a chloroplast-derived signal for stomatal opening in response to light [63]. Transgenic tobacco plants were generated with a range of *PsbS* expression up to approximately 4 times that of the wild-type plant. Plants with increased *PsbS* expression showed reduced stomatal opening in response to light which resulted in a 25% reduction in water loss per $CO_2$ molecule imported. This study may have widespread benefit if findings can be transferred to higher plant species and food crops given that PsbS is a protein universally expressed amongst plants which photosynthesise.

A second example of the application of synthetic biology illustrates the reprogramming of plants to consume less water when they are exposed to an agrochemical [64]. In dry conditions, plants naturally produce abscisic acid (ABA), which is a stress hormone that slows plant growth and reduces water consumption by closing stomata. Using the model plant *Arabidopsis* and the tomato plant, ABA receptors were re-engineered to be activated by the much lower cost mandipropamid instead of the more expensive ABA. When the reengineered plants were exposed to mandipropamid, the plants survived drought conditions by activating the abscisic acid pathway, which subsequently closed the leaf stomata and reduced water loss.

Any plants which currently grow in a dry arid climate or could grow in such an environment may benefit if their water loss was reduced and in turn they would consume less water. Moreover, crops on the verge of viability in dry climates may become a better value proposition if their water consumption was more closely aligned with the regional supply chain. In addition to modulation of the stomatal opening and the potential application to higher plants and arable crops on Earth, these advances may offer an opportunity for growing crops on other planets such as Mars and perhaps over time, drive plant evolution to regulate stomatal opening in synchronicity with conditions. Further studies will be required to understand the extent to which these findings can be replicated in other plants and to explore any potential deleterious effects on plant growth including germination, flower and seed production and overall biomass and in the case of mandipropamid, the potential environmental risk posed by this agrochemical.

### ii) Thermo-tolerant Plants

The next example concerns the bio-engineering of crops to withstand temperature extremes. As discussed above the surface of Mars experiences extremes of temperature [15-17], and today it does not appear possible that plants could be engineered to withstand such temperature extremes. However, any incremental level of tolerance, for example to cold, may reduce the need for heating and permit the constraints of temperature regulation to be more flexible. This is important as at low temperatures, ice crystals are formed in the extracellular matrix which ultimately causes dehydration in cytoplasm, shrinkage of the cell membrane and cellular rupture on elevated temperature. Engineering cold stress tolerance in crop plants and cold hardiness in trees has been reviewed elsewhere [65-67] and for heat tolerance via heat shock proteins [68]. In the case of low temperatures, our understanding of the biochemical pathways suggests that common pathways are involved in regulating both cold hardiness and plant growth, where inducer of CBF expression (ICE) and C-repeat binding factor (CBF) transcription factors play a key role in determining cold-induced gene expression [69], [70]. Molecular targets where modulation of gene expression may have utility in generation of transgenic crops tolerant to cold have been previously described [65], and one example is the production of frost tolerant tomatoes using the gene for an anti-freeze protein (AFP) isolated from carrots. Expression of AFP under the control of constitutive cauliflower mosaic virus (CaMV) 35S promoter when transformed into tomato var. PKM1, showed a significant decrease in membrane injury index upon exposure to chilling stress (4 °C) in the AFP transgenic tomato plants when compared with the wild type [71].

In summary, synthetic biology has the potential to meet increasing global food demand in the first instance and as a consequence, a collateral benefit is that our better understanding may benefit space exploration and push the envelope of genetic engineering to produce plants capable of surviving extremes. CRISPR gene editing technology, which will be referred to in a later section opens new opportunities to engineer thermo-tolerant and also disease resistance traits; current knowledge gaps and potential concerns have been reviewed elsewhere [72]. Although not addressed in detail here, the potential for plants to be engineered to dust tolerance and to photosynthesise using restricted wavelengths of light is also an area of current research.

### iii) Bio-fortification of Food Stuffs

As with the previous sections on drought resistant and thermotolerant plants, the concept of bio-fortification is directed at alleviating a shortage of high quality food on Earth [73] and the first example is that of engineered rice [74]. Golden rice is a variety of rice (*Oryza sativa*) designed to produce β-carotene, a precursor of vitamin A, in the edible parts of the crop [75]. Primarily intended as a food for consumption by children in areas of the world where dietary insufficiency is prevalent, it is a product of synthetic biology which may provide an effective route to ensure a healthy complement of this vitamin in space settlers. The bio-engineered variety differs from the parental strain as it harbours three additional β-carotene genes capable of producing β-carotene in the endosperm and a further improved strain termed Golden Rice 2, was able to produce approximately 20 fold greater levels of β-carotene when compared with the original golden rice [76]. Golden rice has been demonstrated to be an effective source of vitamin A for humans [77], [78] and has received regulatory approval as a food in Australia, New Zealand, Canada and the United States [79], [80].

Other crops synthetically bio-engineered to produce increased β-carotene content include potato, canola, tomato, carrot, and cauliflower [81], [82]. Further examples of bio-fortification include tomatoes to produce a higher level of the B-vitamin folate, producing up to a 25-fold increase when compared with wildtype [83], rice and field-grown cassava to produce a higher iron content by over-expression of the iron storage protein ferritin from French bean and soybean [84].

### iv) Bio-fuels

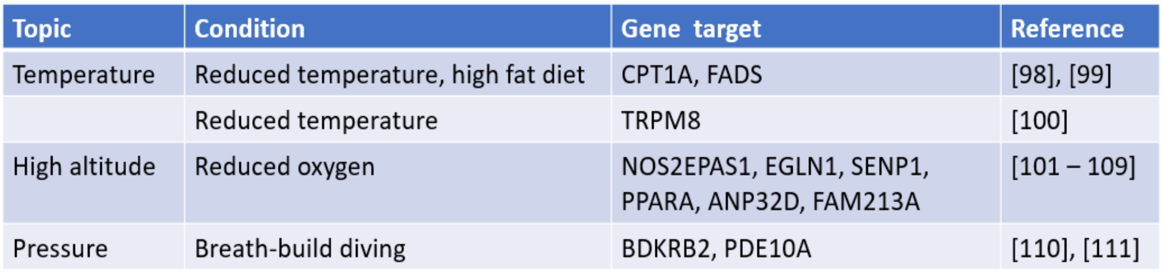
There has been great interest in the generation of bio-fuels for example, bio-gas, bio-alcohol and algal fuels over recent years, largely based on the desire and increasing requirement to develop alternative replacements for fossil fuels for terrestrial use, with a secondary consideration for provision of fuel on other worlds, e.g. [8], [85] – [89]. One of the major limiting factors for travel to and return from Mars is the limitation of propellant mass and the ability to produce propellant *in situ* rather than transporting it from Earth would dramatically reduce one of the largest contributors towards the cost of space missions. There are numerous methods for producing bio-fuels on Earth such as ethanol, hydrogen, methane, butanol and hydrazine and the production of bio-fuel on Mars would have utilisation for colony maintenance in addition to providing fuel to return spacecraft to Earth. Of particular note is a recent study [89] which aims to test the hypothesis whether cyanobacteria supported from Martian regolith and atmosphere could serve as a basis for biological life-support systems reliant purely on local materials. The investigators developed a low-pressure photobioreactor providing regulated atmospheric conditions to cultivation chambers to study the growth of cyanobacteria. The study concluded that growth of the cyanobacteria *Anabaena* was supported from the Martian regolith Mars Global Simulant-1 (MGS-1) and that cyanobacterial biomass could be used for feeding the secondary bacterium, *Escherichia coli*. This study, albeit using unmodified bacterial strains is important, because it suggests that a simulated atmospheric complement of gases at a pressure of approximately one tenth that of the Earth at sea level, may be capable of supporting photobioreactor constructs of cyanobacteria-based life support systems. It proposes the concept for future research that energy production may be made more effective by a combination of individual strain attributes in an architecture-based design system.

### c) Next Steps: SynBio to SynEnhancement (SynEnh)

In the same way that synthetic biology has been popularised as SynBio, we may wish to coin the term ‘SynEnhancement’ or ‘SynEnh’, which conceptually starts to explore the potential of human synthetic biology to adapt performance to environment. The potential for SynEnh may come from many areas and one area to consider are those innate adaptations which have been identified in extremophiles. Extremophiles are organisms, generally bacteria which can live and propagate in environmental extremes including temperature, pressure, salinity, alkalinity/acidity and high radiation levels, e.g. [90], [91]. The ability of organisms to withstand such extremes may support the concept of panspermia where primitive life forms have migrated between worlds [90], [92]. A previous study has demonstrated that the *Bacillus subtilis* strain MW01 can tolerate exposure to low-earth orbit and simulated Martian conditions [93] and more recently an investigation conducted on the ISS studied the survival of three different bacteria; *Sphingomonas desiccabilis, Bacillus subtilis, and Cupriavidus metallidurans* placed in an environment which simulated the gravity of Mars [94]. The study found no significant differences in final cell count after experiencing Martian gravity. This suggested that the effects of reduced gravity change on the bacteria was overcome by the end of the experiment which may support the notion that microbial-supported bio-production and life support systems can be effectively constructed on Mars. A logical extension of this observation is that synthetic biology can be used to harness the characteristics of extremophiles harbouring pre-designed modifications as described previously in section a).

A further extension relates to the possibility of SynEnh for human enhancement [95] which proposes that the genetic component of a healthy human individual, in this case an astronaut or new-world colonist, may be modified by gene editing to confer adaptation to such an environment. Further research is needed to identify potential target genes and to ensure that the technology is both reliable and safe and this topic is out of scope for further discussion in this review. However, understanding the potential to engineer accommodation of extreme environments may be greatly assisted by understanding innate adaptation to, for example, temperature, altitude and atmospheric pressure [96], [97].

Table 1 summarises some examples of human adaptation to extreme environments which include high fat diet and cold, high altitude and reduced oxygen and increased atmospheric pressure. Human adaptation to high fat diet in populations is indicative of strong selection of the *CPT1A* allele in natives of Northeast Siberia [98] and a similar finding was made in the FADS genes in the Inuit population from Greenland [99]. Positive selection may have influenced cold adaptation where allele frequency variant increase in the TRMP8 gene may have played a role in thermoregulation [100].



| Topic | Condition | Gene target | Reference |
|---|---|---|---|
| Temperature | Reduced temperature, high fat diet | CPT1A, FADS | [98], [99] |
| | Reduced temperature | TRPM8 | [100] |
| High altitude | Reduced oxygen | NOS2EPAS1, EGLN1, SENP1,<br>PPARA, ANP32D, FAM213A | [101 – 109] |
| Pressure | Breath-build diving | BDKRB2, PDE10A | [110], [111] |

**Table 1. Selected examples of gene targets implicated in human adaptation to extreme environments.**

There are numerous examples of human extremophiles showing adaptation to reduced oxygen levels, such that are present at high altitude which is generally defined as greater than 2,500 m on Earth. Some Tibetans, Andeans and Ethiopians possess genetic determinants that have evolved at different times and which confer advantages for gaseous exchange in the respiratory system. Genes harbouring mutations in NOS2, EPAS1, EGLN1, SENP1, PPARA, ANP32D and FAM213A [101-109] have all been shown to play roles in adaptation to high altitude.

Lastly, some studies have shown that members of the Bajua Indonesian population have acquired adaptations to hypoxia by developing large spleens, possibly as a result of the practice of breath-hold diving performed for several minutes permitting dives to a depth of 30 m or greater [110], [111]. The study identified physiological and genetic adaptations to diving where the development of larger spleens in individuals were associated with a gene involved in regulating thyroid hormone levels which enables additional storage for oxygenated red blood cells.

These examples illustrate two things. First, it may be possible to include in astronaut or colonist selection criteria innate genetic predisposition to adaptation to extreme environments where the genotype confers a phenotypic advantage to, for example atmospheric conditions which may require less energy to maintain. Secondly, an understanding of genetic adaptation may profer candidates for gene editing strategies supporting the concept of SynEnhanced humans, specifically engineered to cope better with the Martian environment than their wild type counterparts.

In summary, Figure 3 presents an overview of the inter-disciplinary components contributing to both SynBio and SynEnh. At the heart of the principal disciplines, manipulation of DNA is a core activity which may lead to the generation of modified plants and other organisms or the construction of multi-architecture pathways within an organism.

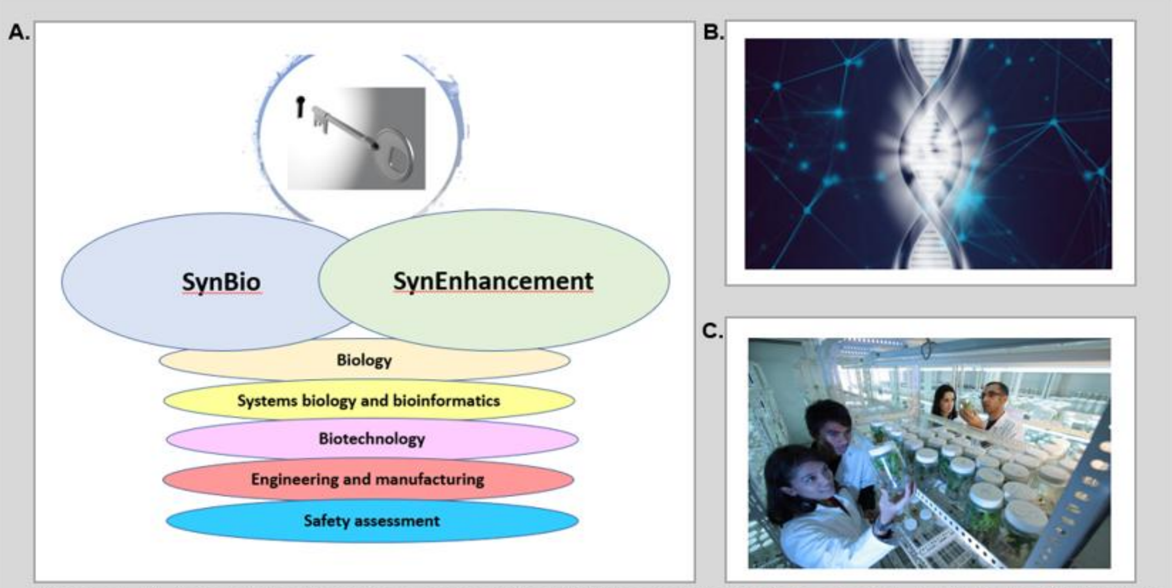


**Figure 3. A. Some key disciplines supporting SynBio and SynEnhancement, B. DNA manipulation is integral and C. scientists study potential SynBio engineered plants (Images credit PIXABAY).**

## 6. Conclusion

In this review we defined three problem statements where synthetic biology may play a role to better the future of mankind for life on Earth and to permit the exploration of space and other worlds. The first relates to the nature of Martian regolith; the requirement to detoxify perchlorates and the need to bio-augment with bacteria which fix nitrogen.

The second challenge refers to the conditions on Mars where extremes of surface temperature, the lack of flowing liquid water, the propensity for dust storms and the presence of GCR will prevent anything but short term residence of human beings and the growth of colonies. Clearly humans will need to be sheltered in a biosphere which may either be on the surface, semi or completely subterranean and the atmosphere in the biosphere must be conducive to supporting life. Thus the application of synthetic biology is as appropriate to supporting life in a closed environment on Mars in much the same way that it may support life on Earth, except on a much smaller scale and where the interdependencies of feedback control systems are absolute and where there may be little margin for error.

The third problem statement is illustrative of where developments in synthetic biology may greatly benefit life on Earth. Figure 4 shows the actual and projected increase in the total global population of the human species over the decades and sets both a challenge and an opportunity for humanity. In meeting the needs of a population which appears to be increasing linearly by approximately 0.5 to 1 bn people per decade, with no apparent sign of the rate decreasing and predicted to reach 10 bn by 2050 [112], it appears obvious that a food and supply chain will need to ever increase in efficiency while reducing the carbon footprint needed for maintenance and future growth. Crop modifications such that have been described in this review include biofortification, reduced use of water to produce faster life-cycle times and higher yield in more extreme environments. These are some prime targets for the development and deployment of synthetic biology strategies.

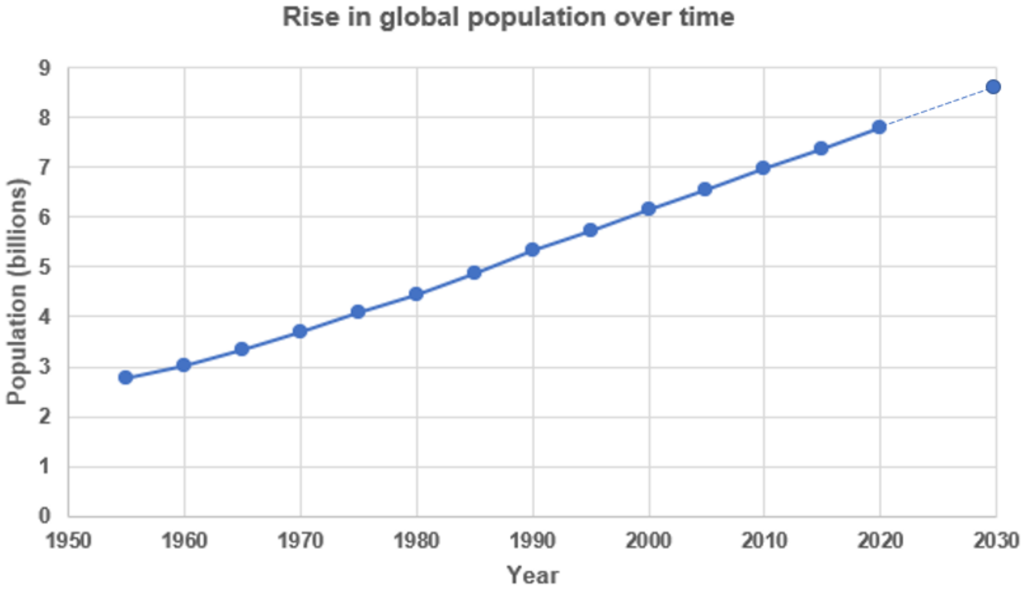


**Figure 4. Graph showing the global rise in population over time. Dotted line represents the extrapolation to 2030. Redrawn from data table [14].**

The potential implications of these studies are clear for sustaining an expanding human population on Earth. Likely driven out of necessity and in part to meet the challenges of climate change, the application of any discoveries provide realizable benefit for human settlements living in isolated environments on Earth, during prolonged space travel, or in the establishment and maintenance of colonies on other worlds. Synthetic biology has already changed how humans live today, e.g. [113], [114] and may have a role to play in the preservation of biodiversity, e.g. [115] and in a new generation of biosensors, e.g. [116]. There would seem to be no limit on how synthetic biology can be developed and exploited and the duty falls on us as human beings to ensure ethical and responsible use for the whole of humankind [117] – [119].

It would appear that today in 2021, that the potential benefits of synthetic biology outweigh the perceived and known risks and with the judicious and considered use of our knowledge in molecular biology, engineering science and agriculture, our species may not only be able to live and thrive on Earth, but also to expand our presence within our solar system. With the stated aim of Mars colonization by the early 2030s timeframe, this promises to be an exciting decade ahead!

## References

1. Duffy, D. Elon Musk says SpaceX will get humans to Mars in 2026. https://www.businessinsider.co.za/elon-musk-spacex-starship-humans-mars-mission-2026-experts-question-2021-2. Accessed 11th May 2021.
2. Mars One Roadmap. https://www.mars-one.com/mission/roadmap. Accessed 11th May 2021.
3. How Investing in the Moon Prepares NASA for First Human Mission to Mars. https://www.nasa.gov/sites/default/files/atoms/files/moon-investments-prepare-us-for-mars.pdf. Accessed 1th May 2021.

4. Braddock, M, Wilhelm, CP, Romain, A, Bale L, Szocik, K. Application of socio-technical systems models to Martian colonisation and society build. *Theoret. Issues Ergonomics Sci.* 21, 2019, pp.131-152.

5. Vincente, K.J. *Cognitive work analysis: towards safe, productive and health computer-based work.* CRC press, 1999.

6. Naikar, N. *Work domain analysis: concepts, guidelines and cases.* CRC press, 2013.

7. Cooper, M., Douglas, D. & Perchonok, M. Developing the NASA food system for long-duration missions. *J. Food Sci.* 76, 2011, R40- R48.

8. Verseux, C., Lima, I.G.P., Baque, M., Rothschild, M. Synthetic Biology for Space Exploration: Promises and Societal Implications. In: *Ambivalences of Creating Life. Societal and Philosophical Dimensions of Synthetic Biology*. Hagen, K., Engelhard, M., Toepfer (eds.), Springer-Verlag publishers, 2016, pp. 73-100.

9. Ishimatsu, T., Grogan, P., de Weck, O. Interplanetary Trajectory Analysis and Logistical Considerations of Human Mars Exploration *J. Cosmol.* 12, 2010, pp, 3588-3600.

10. Ogawa, N., Haruki, M., Kondoh, Y. et al. Orbit plan and mission design for Mars EDL and surface exploration technologies demonstrator. *Trans. JSASS Aerospace Tech*. 14, 2016, pp. 9-15.

11. Hohmann, W. The Attainability of Heavenly Bodies. In: *NASA Technical Translation,* F-44, 1960.

12. Jones, H.W. The recent large reduction in space launch cost. In: *48th International Conference on Environmental Systems*, 2018, CES-2018-81, pp. 1-10.

13. Roberts, T.G. Space Launch to Low Earth Orbit: How Much Does It Cost? *Civil and Commercial Space Space Security,* 2020 https://aerospace.csis.org/data/space-launch-to-low-earth-orbit-how-much-does-it-cost/, accessed 28th April 2021.

14. World population projections. https://www.worldometers.info/world-population/world-population-projections/. Accessed 11th May 2021.

15. Eydelman, A. Temperature on the surface of Mars. *The Physics Factbook.* Elert, G. (ed.), 2001.

16. Mars facts, NASA (2013). https://web.archive.org/web/20130607140708/http:/quest.nasa.gov/aero/planetary/mars.html. Accessed April 28th 2021.

17. Mars fact sheet, NASA (2018). https://nssdc.gsfc.nasa.gov/planetary/factsheet/marsfact.html. Accessed May 10th 2021.

18. Matthiä, D. et al. The radiation environment on the surface of Mars – Summary of model calculations and comparison to RAD data. *Life Sci. Space Res.*, 14, 2017, pp. 18-28.

19. Bloshenko, A.D., Robinson, J.M., Colon, R.A., Anchordoqui, L.A. Health threat from cosmic radiation during manned missions to Mars. *arXiv:*2012.09604v1.

20. Paris, J., Davis, E.T., Tognetti, L., Zahniser, C. Prospective Lava Tubes at Hellas Planitia, *J. Wash. Acad. Sci.* 2004.13156, 2019.

21. Voroney, R.P., Heck, R. J. The soil habitat. In: *Soil microbiology, ecology and biochemistry (3rd ed.).* Eldor, P.A. (ed.). Amsterdam, the Netherlands: Elsevier publishers. 2007, pp. 25–49.

22. Needelman, B. A. What Are Soils? *Nature Education Knowledge* 4, 2013, 2.

23. Kalev, S.D., Toor, G.S. Chapter 3.9 - The Composition of soils and sediments. In: *Green Chemistry*. Torok, B., Dransfield, T. (eds.) Elsevier publishers, 2018, pp. 339-357.

24. McSween, H.Y., Taylor, G.J., Wyatt, M.B. Elemental Composition of the Martian Crust. *Science*, 324, 2009, pp. 736-739.

25. Cousin, A., Meslin, P.Y., Wiens, R.C. et al. Compositions of coarse and fine particles in martian soils at gale: A window into the production of soils. *Icarus*, 249, 2015, pp.22-42.

26. Ming, D. W., Morris, R. V. Dust in the Atmosphere of Mars and Its Impact on Human Exploration. In: *Proceedings of the LPI,* contribution No. 1966, 2017, id.6027.

27. Bohle, S., Montaño, H.S.P., Bille, M., Turnbull, D. Evolution of soil on Mars. *Astron. & Geophys.*, 57, 2016, pp. 2.18–2.23.

28. Ramkissoon, N.K., Pearson, V.K., Schwenzer, S.P. et al. New simulants for Martian regolith: Controlling iron variability. *Planetary Space. Sci*., 179, 2019, 104722.
29. Braddock, M. Mission to Mars: Countdown to Building a Brave New World – Laying the Foundations. In: *Yearbook of Astronomy*. Jones, B. (ed.), White Owl publishers 2022, In press.
30. Hecht, M. H., Kounaves, S.P., Quinn, R.C. et al. Detection of perchlorate and the soluble chemistry of Martian soil at the Phoenix Lander Site. *Science* 325, 2009, pp. 64–67.
31. Davila, A.F., Willson, D., Coates, J.D. & McKay, C.P. Perchlorate on Mars: a chemical hazard and a resource for humans. *Int. J. Astrobiol*. 12, 2013, pp 321-325.
32. Glavin, D., Grotzinger, J.P. Evidence for perchlorates and the origin of chlorinated hydrocarbons detected by SAM at the Rocknest aeolian deposit in Gale Crater. *J. Geophys. Res. Planets* 118, 2013, pp.1955–1973.
33. Niziński P, Błażewicz A, Kończyk J, Michalski R. Perchlorate - properties, toxicity and human health effects: an updated review. *Rev. Environ. Health.* 2020, doi: 10.1515/reveh-2020-0006.
34. He, H., Gao, H. Chen, G. et al. Effects of perchlorate on growth of four wetland plants and its accumulation in plant tissues. *Environ. Sci. Poll. Res. Int.* 20, 2013, pp. 7301-7308.
35. Wadsworth, J., Cockell, C.S. Perchlorates on Mars enhance the bacteriocidal effects of UV light. *Sci. Rep.* 7, 2017, 4662.
36. Carrier, B.L. Kounaves, S.P. The origins of perchlorate in the Martian soil. *Geophys. Res. Lett.* 42, 2015, pp. 3739–3745.
37. Race, M.S., Moses, J., McKay, C., Venkateswaran, K.J. Synthetic biology in space: considering the broad societal and ethical implications. *Int. J. Astrobiol*. 11, 2012, pp. 133-139.
38. Menezes, A.A., Montague, M.G., Cumbers, J., Hogan, J.A., Arkin, A.P. Grand challenges in space synthetic biology. *J. R. Soc. Interface* 12, 2015, 20150803.
39. Llorente, B., Williams, T.C., Goold, H.D. The multiplanetary future of plant synthetic biology. *Genes*, 9, 2018, 348.
40. McNulty, M.J., Xiong, Y., Yates, K. et al. Molecular pharming to support human life on the moon, Mars, and beyond. *Preprints* 2020, 2020090086.
41. Nangle, S.N., Wolfson, M.Y., Hartsough, L. et al. The case for biotech on Mars. *Nat. Biotechnol.* 38, 2020, pp. 401–407.
42. Patel, Z.S., Brunstetter, T.J., Tarver, W.J. Red risks for a journey to the red planet: the highest priority human health risks for a mission to Mars. *npj Microgravity* 6, 2020, 33.
43. Duncan, P.B., Morrison, R.D., Vavricka, E. Forensic identification of anthropogenic and naturally occurring sources of perchlorate. *Environ. Forensics.* 6, 2005, pp.205–215.
44. Cole-Dai, J., Peterson, K.M., Kennedy, J.A., Cox, T.S., Ferris, D.G. Evidence of influence of human activities and volcanic eruptions on environmental perchlorate from a 300-year Greenland ice core record. *Environmental Science & Technology,* 52, 2018, pp. 8373–8380.
45. Acevedo-Barrios, R., Sabater-Marco, C., Olivero-Verbel, J. Ecotoxicological assessment of perchlorate using in vitro and in vivo assays. *Environmental Science and Pollution Research*, 25, 2018, pp. 13697–13708.
46. Maffini, M.V., Trasande, L., Neltner, T.G. Perchlorate and diet: human exposures, risks, and mitigation strategies. *Current Environmental Health Reports*, 3, 2016 pp. 107–117.
47. Smith, P.N. In: *The Ecotoxicology of Perchlorate in the Environment BT-Perchlorate: Environmental Occurrence, Interactions and Treatment*, Gu, B and Coates, J.D. (eds.), Boston, USA, Springer publishers 2006.
48. Knight, B.A., Shields, B.M., He, X. et al. Effect of perchlorate and thiocyanate exposure on thyroid function of pregnant women from South-West England: a cohort study. *Thyroid Res.*, 11, 2018, 9.
49. Steinmaus, C., Pearl, M., Kharrazi, M. et al. Thyroid hormones and moderate exposure to perchlorate during pregnancy in women in southern California. *Environ. Health Perspect.*, 124, 2016, pp. 861–867.
50. Srinivasan, A., Viraraghavan, T. Perchlorate: health effects and technologies for its removal from water resources. *Int. J. Environ. Res. Public Health* 6, 2009, pp 1418-1442.

51. Orris, G.J., Harvey, G.J., Tsui, D.T., Eldrige, J.E. Preliminary analyses for perchlorate in selected natural materials and their derivative products. *USGS*, 2003. https://www.fws.gov/uploadedFiles/AR%200025%202003%20Preliminary%20analyses%20for%20perchlorate%20in%20selected%20natural%20materials%20and%20their%20derivative%20products.pdf accessed on 10th May 2021.
52. Wang, O., Coates, J.D. Biotechnological Applications of Microbial (Per)chlorate Reduction. *Microorganisms*. 5, 2017, pp, 76.
53. Arkin, A. A Synthetic Biology Architecture to Detoxify and Enrich Mars Soil for Agriculture, 2017. https://www.nasa.gov/directorates/spacetech/niac/2017_Phase_I_Phase_II/Mars_Soil_Agriculture/. Accessed on April 27th 2021.
54. Venturelli, O S; Egbert, R G; Arkin, A P. Towards engineering biological systems in a broader context. *J. Mol. Biol.*, 428, 2016, pp. 928–944.
55. Enrichment of Martian regolith to useful agricultural soil. https://cubes.space/divisions/mmfd. Accessed May 11th 2021.
56. Orosei, R., Lauro, S.E., Pettinelli, E. et al. Radar evidence for subglacial liquid water on Mars. *Science*, 361, 2018, pp. 490-493.
57. Nazari-Sharavian, M., Aghababaei, M., Karakouzian, M., Karami, M. Water on Mars – a literature review. *Galaxies* 8, 2020, 40.
58. Joseph, R., Gibson, C.H., Schild, R. Water, ice, mud in the Gale crater: implications for life on Mars. *J. Cosmol.* 29, 2020, pp. 1-33.
59. Scheller, E.L., Ehlmann, B.L., Hu, R., Adams, D.J., Yung, Y.L. Long-term drying of Mars by sequestration of ocean-scale volumes of water in the crust. *Science*, 372, 2021, pp. 56-62.
60. Rosa, L. et al. Global agricultural economic water scarcity. *Science Advances* 6, 2020, eaaz6031.
61. Mekonnen, M.M., Gerbens-Leenes, W. The water footprint of global food production. *Water* 12, 2020, 2696.
62. Yang, X., Cushman, J.C., Borland, A.M., Liu, Q. Editorial: Systems Biology and Synthetic Biology in Relation to Drought Tolerance or Avoidance in Plants. *Front. Plant Sci.* 11, 2020, 394.
63. Głowacka, K., Kromdijk, J., Kucera, K. et al. Photosystem II Subunit S overexpression increases the efficiency of water use in a field-grown crop. *Nat. Commun.* 9, 2018, 868.
64. Park, S.-Y. et al. Agrochemical control of plant water use using engineered abscisic acid receptors. *Nature*, 520, 2015, pp. 545-548.
65. Sanghera, G.S., Wani, S.H., Hussain, W., Singh, N.N. Engineering cold stress tolerance in crop plants. *Curr. Genomics* 12, 2011, pp. 30-43.
66. Wisniewski, M., Nassuth, A., Arora, R. (2018). Cold hardiness in trees: a mini-review. *Front. Plant Sci.* 9, 2018, 1394.
67. Joshi R., Singh, B., Chinnusamy, V. Genetically Engineering Cold Stress-Tolerant Crops: Approaches and Challenges. In: *Cold Tolerance in Plants*, Wani S., Herath V. (eds). Springer, Cham. 2020, pp. 179-195.
68. Singh, A,, Grover, A. Genetic engineering for heat tolerance in plants. *Physiol. Mol. Biol. Plants*. 14, 2008, pp. 155-166.
69. Jia, Y., Ding, Y., Shi Y. et al. The cbfs triple mutants reveal the essential functions of CBFs in cold acclimation and allow the definition of CBF regulons in *Arabidopsis*. *New Phytol.* 212, 2016, pp. 345–353.
70. Zhao C., Zhang Z., Xie S., Si T., Li Y., Zhu J. K. Mutational evidence for the critical role of CBF transcription factors in cold acclimation in *Arabidopsis*. *Plant Physiol.* 171, 2016, pp. 2744–2759.
71. Kumar SR, Kiruba R, Balamurugan S, Cardoso HG, Birgit A-S, et al. Carrot antifreeze protein enhances chilling tolerance in transgenic tomato. *Acta Physiologiae Plantarum*, 36, 2014, pp. 21-27.

72. Zaidi, S.SeA., Mahas, A., Vanderschuren, H. et al. Engineering crops of the future: CRISPR approaches to develop climate-resilient and disease-resistant plants. *Genome Biol.* 21, 2020, 289.
73. Bouis, H. E., Saltzman, A. Improving nutrition through biofortification: A review of evidence from HarvestPlus, 2003 through 2016. *Glob. Food Sec.*12, 2017, pp.49-58.
74. Bhullar, N.K. Gruissem, W. Nutritional enhancement of rice for human health: the contribution of biotechnology. *Biotechnol. Adv*. 31, 2013, pp. 50-57.
75. Ye, X., Al-Babili, S., Klöti, A. et al. Engineering the provitamin A (beta-carotene) biosynthetic pathway into (carotenoid-free) rice endosperm. *Science* 287, 2000, pp. 303–305.
76. Paine, J.A., Shipton, C.A., Chaggar, S. et al. Improving the nutritional value of Golden Rice through increased pro-vitamin A content. *Nat. Biotechnol.* 23, 2005, pp. 482–487.
77. Datta, S.K., Datta, K., Parkhi, V. et al. Golden rice: introgression, breeding, and field evaluation. *Euphytica,* 154, 2007, pp. 271–278.
78. Tang, G., Qin, J., Dolnikowski, G.G., Russell, R.M., Grusak, M.A. Golden rice is an effective source of vitamin A. *Am. J. Clin. Nutr.* 89, 2009, pp. 1776–1783.
79. New Plant Variety Consultation: FDA (2018). https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=NewPlantVarietyConsultations. Accessed December 12th 2020.
80. Provitamin A Biofortified Rice Event GR2E (Golden Rice): Health Canada (2018).https://www.canada.ca/en/health-canada/services/food-nutrition/genetically-modified-foods-other-novel-foods/approved-products/golden-rice-gr2e.html. Accessed 28th April 2021.
81. Sautter, C., Poletti, S., Zhang, P., Gruissem, W. Biofortification of essential nutritional compounds and trace elements in rice and cassava. *Proc. Nutr. Soc.* 65, 2006, pp. 153–159.
82. Diretto G, Al-Babili S, Tavazza R. et al. Metabolic engineering of potato carotenoid content through tuber-specific overexpression of a bacterial mini-pathway. *PLoS ONE* 2, 2007, e350.
83. Díaz de la Garza, R.I., Gregory III, G.F., Hanson, A.D. Folate biofortification of tomato fruit. *Proc. Natl. Acad. Sci. USA,* 104, 2007, pp. 4218-4222.
84. Narayanan, N., Beyene, G., Chauhan R.,D. et al. Biofortification of field-grown cassava by engineering expression of an iron transporter and ferritin. *Nat. Biotechnol.* 37, 2019, pp. 144-151.
85. Connor, M.R., Atsumi, S. Synthetic biology guide biofuel production. *BioMed Res. Int.* 2010, 2010, 541698
86. Khatib, S.E., Yassine, N.A. Advances in Synthetic Biology and Metabolic Engineering in the Production of Biofuel. *Int. J. Curr. Microbiol. App. Sci.,* 8, 2019, pp. 1762-1772.
87. Mortimer JC. Plant synthetic biology could drive a revolution in biofuels and medicine. *Experimental Biology and Medicine*. 244, 2019, pp,323-331.
88. Verseux, C. et al. Sustainable life support on Mars – the potential roles of cyanobacteria. *Int. J. Astrobiol.* 15, 2016, pp. 65-92.
89. Getting there and back. In: *Human missions to Mars*. Springer Praxis Books. Springer, Berlin, Heidelberg, 2008.
90. Merino, N., Aronson, H.S., Bojanova, D.P. Living at the Extremes: Extremophiles and the Limits of Life in a Planetary Context. *Front. Microbiol.,* 10, 2019, 780.
91. Schröder, C., Burkhardt, C. & Antranikian, G. What we learn from extremophiles. *ChemTexts* 2020, 6, 8.
92. Ginsburg, I., Lingam, M., Loeb, A. Galactic panspermia. *Astrophys. J. Lett.,* 868, 2018, L12.
93. Wassmann, M., Moeller, R., Rabbow, E. et al. Survival of spores of the UV-resistant Bacillus subtilis strain MW01 after exposure to low-earth orbit and simulated Martian conditions: data from the space experiment ADAPT on EXPOSE-E. *Astrobiology, 12,* 2012, pp. 498-507.
94. Santomartino, R., Waajen, A.C., de Wit, W. No effect of microgravity and simulated Mars gravity on final bacterial cell concentrations on the International Space Station: applications to space bioproduction. *Front. Microbiol.* 11, 2020, 579156.
95. Braddock, M. Limitations for colonisation and civilisation build and the potential for human enhancements. In*: Human Enhancements for Space Missions*. *Space and Society*. Szocik K. (eds) Springer, Cham. publishers 2020, pp. 71-93.

96. Ilardo M, Nielsen R. Human adaptation to extreme environmental conditions. *Curr. Opin. Genet. Dev*. 53, 2018, pp. 77-82.

97. Burtscher, M., Gatterer, H., Burtscher, J., Mairbäurl, H. Extreme terrestrial environments: life in thermal stress and hypoxia. A narrative review. *Front. Physiol.* 9, 2018, 572.

98. Clemente F.J. et al. A selective sweep on a deleterious mutation in CPT1A in Arctic populations. *Am. J. Hum. Genet.* 95, 2014, pp.584–589.

99. Fumagalli, M. et al.: Greenlandic Inuit show genetic signatures of diet and climate adaptation. *Science,* 349, 2015, pp.1343–1347.

100. Key F.M. et al. Human local adaptation of the TRPM8 cold receptor along a latitudinal cline. *PLoS Genet.* 14, 2018, e1007298.

101. Bigham A.W. Identifying positive selection candidate loci for high-altitude adaptation in Andean populations. *Hum. Genomics* 4, 2009, pp.79–90.

102. Simonson, T.S, et al. Genetic evidence for high-altitude adaptation in Tibet. *Science*. 2010 329, 2010, pp. 72-75.

103. Simonson, T.S., McClain, D.A., Jorde, L.B., Prchal, J.T. Genetic determinants of Tibetan high-altitude adaptation. *Hum. Genet.* 2012,131, pp.527-533.

104. Hanaoka M. et al. Genetic variants in EPAS1 contribute to adaptation to high-altitude hypoxia in Sherpas. *PLoS One.* 7, 2012, 50566.

105. MacInnis MJ, Wang P, Koehle MS, Rupert JL. The genetics of altitude tolerance: the evidence for inherited susceptibility to acute mountain sickness. *J. Occup. Environ. Med.* 53, 2011, pp.159-168.

106. Peng Y, et al. Genetic variations in Tibetan populations and high-altitude adaptation at the Himalayas. *Mol. Biol. Evol.* 28, 2011, pp, 1075-1081.

107. van Patot MC, Gassmann M. Hypoxia: adapting to high altitude by mutating EPAS-1, the gene encoding HIF-2α. *High Alt. Med. Biol.* 2011 12, 2011, pp.157-167.

108. Zhou D. et al. Whole-genome sequencing uncovers the genetic basis of chronic mountain sickness in Andean highlanders. *Am. J. Hum. Genet.* 93, 2013, pp. 452-62.

109. Valverde G. et al. A novel candidate region for genetic adaptation to high altitude in Andean populations. *PLoS One* 10, 2015, 0125444.

110. Angelin-Duclos, C. et al. Thyroid hormone T3 acting through the thyroid hormone α receptor is necessary for implementation of erythropoiesis in the neonatal spleen environment in the mouse. *Development* 132, 2005, pp. 925–934.

111. Ilardo, M.A. et al. Physiological and genetic adaptations to diving in sea nomads. *Cell,* 173, 2018, pp. 569–580.

112. Hickey, L.T., Hafeez, A.N., Robinson, H. et al. Breeding crops to feed 10 billion. *Nat. Biotechnol.* 37, 2019, pp. 744–754.

113. Voigt, C.A. Synthetic biology 2020-2030: six commercially-available products that are changing the world. *Nat Commun*. 11, 2020, article 6379.

114. Brooks, S.M., Alper, H.S. Applications, challenges, and needs for employing synthetic biology beyond the lab. *Nat. Commun.* 2021, 12, 1390.

115. Reynolds, J.L. Engineering biological diversity: the international governance of synthetic biology, gene drives and de-extinction for conservation. *Curr. Op. Environ. Sust*. 49, 2021, pp. 1-6.

116. Del Valle, I., Fulk, E.M., Kalvapalle, P. et al. Translating new synthetic biology advances for biosensing into the Earth and environmental sciences. *Front. Microbiol*. 11, 2021, article 618373.

117.Douglas, T., Savulescu, J. Synthetic biology and the ethics of knowledge. *J. Med. Ethics*. 36, 2010, pp. 687-694.

118.Wang, F., Zhang, W. Synthetic biology: recent progress, biosafety and biosecurity concerns, and possible solutions. *J. Biosafety & Biosecurity* 1, 2019, pp. 22-30.

119. Conde-Pueyo N, Vidiella B, Sardanyés J, et al. Synthetic biology for terraformation lessons from Mars, Earth, and the microbiome. *Life 10,* 2020:14.