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Perspective

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Synthetic biology for space exploration

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Human space exploration faces different challenges. Topics like Bioregenerative Life Support Systems, In Situ Resource Utilization, and radiation protection, still require for more suitable solutions to be applied in long-term space exploration. Synthetic biology could be a powerful tool for enabling human exploration of space and planets. This paper explores key topics including resource utilization, life support systems, radiation protection, and human health, providing recommendations for short-, mid-, and long-term advancements in space exploration.

The Apollo 11 Moon landing encouraged humankind to consider and investigate life beyond Earth more than 50 years ago[1]. However, in contrast to its lightning-fast success in terms of the remarkable technology development of the Mercury, Gemini and Apollo programs, human space exploration has been confined in Low Earth Orbit (LEO) for the past 50 years. Nevertheless, other space agencies, such as the European Space Agency (ESA) and the Japan Aerospace Exploration Agency (JAXA), have joined the two main competitors, namely the U.S. National Aeronautics and Space Administration (NASA) and Roscosmos (the former Soviet space program). The major space agencies have mainly focused their efforts on crewed space missions in LEO (e.g., in the Space Shuttle, the Soyuz, the Salyut, International Space Station and Chinese space stations) or on uncrewed missions aimed at planetary exploration (e.g., NASA Mars 2020 Exploration and ESA ExoMars Programs). Nowadays, private space companies, such as SpaceX, Blue Origin, Virgin Galactic, are developing the next generation of spacecraft and testing a fully reusable transportation system (e.g., Starship) for crew and cargo, with the aim of sending humans into deep space in the next 5–10 years and for Mars colonization[2–4]. Even though significant progress is being made toward achieving the exploration of deep space and other planetary surfaces, more focus needs to be dedicated to how to sustain a stable settlement for a predetermined period of time on another celestial body. Indeed, two main mission scenarios have been hypothesized for the Martian exploration: a short-stay mission, which would take approximately 550 days, including the journey, and a long-stay mission with a total duration of around 900 to 1000 days[5].

Expeditions to the Moon are likely to range from 20 to 30 days[6,7].

The launch of NASA's Orion vehicles, designed to support a crew of four for 21 days, will be the first crew transfer to deep space in more than 40 years. Indeed, deep space and cis-lunar orbit will be the first destination of future human journey aboard the multi-national Lunar Gateway (NASA, ESA, JAXA, and the Canadian Space Agency), which will also act as a transfer point to the Moon and Mars[8]. A mission onboard the Lunar Gateway is expected to last roughly 30 days, during which crew members will be exposed to a radiative environment characterized by two main sources of radiation, primarily Galactic Cosmic Radiation (GCR) and Solar Particle Events (SPE)[9]. In addition to the exposure to space radiation, altered gravity, isolation, and confinement, can cause systemic and physiological effects, such as increased cancer risk, muscle degeneration, bone loss, cardiovascular and circadian rhythm dysregulations, and central nervous system impairments[10].

The longer missions and the farther humans will travel, the less reliant on Earth they will need to become. For example, astronauts need to carry or

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produce food and oxygen for long-term interplanetary travel lasting months or years[11,12].

For example, ~1.8 kg of food per day would need to be sent for each crew member if we were to provide astronauts with prepared food from Earth, similar to what occurs during missions to the ISS[13]. A crew of six members would require a 1000-day supply of food, which would increase the initial mass of the transit vehicle by more than 108 metric tons after accounting for the additional vehicle and fuel weight required to transport the food and assuming a 10:1 vehicle-to payload ratio[14]. Sending necessities from Earth on long-duration missions is therefore impractical given cost projections (e.g., on the order of $300,000 per kg sent to Mars[15]), as well as the fact that a diet entirely of packaged foods would prove to be inadequate in the long-term due to its nutritional deficiency.

Therefore, considering a 3-year mission to Mars and a crew of 6 astronauts, a total payload of 12 metric tons would be necessary as food and water[16], or[17] calculated for a long-duration mission of 30 months (assuming 30-day months), that one crew member requires 2250 kg of water and 1359 kg of food (i.e. about 26 metric tons for 6 crew members during 36 months).

For these reasons, it is necessary to become less dependent from Earth, considering that the lack of cargo resupply missions and communication delays can negatively impact human health and emergencies, emphasizing the need for crew members to be self-sufficient in preventing and managing emergencies and risks[18]. Moreover, costs can be dramatically decreased by recycling, using bioregenerative systems, using materials of lower mass, or using materials found at the destination, known as 'In Situ Resource Utilization (ISRU)'[19]. Synthetic biology has great potential to contribute crucially to these solutions for space exploration. Space synthetic biology, which straddles the lines of aerospace engineering and bioengineering, is a highly interesting field for long-duration space missions. For example, synthetic biology approaches may convert both astronaut waste resources and in situ destination planet resources into useful products while consisting of less mass (savings as much as 26–85% depending on the application) than conventional abiotic means[20]. For example, by naturally utilizing solar energy and only growing when activated using the available nutrients at the destination, biological technology can help reduce power demand and launch volume, two additional crucial space parameters.

Given the increasing importance of synthetic biology to support future deep space missions, in 2020, ESA brought together leading experts in the fields to define the main topics, carefully reviewed the scientific literature, with the goal of advancing the scientific community's knowledge in the field of space synthetic biology.

Figure 1 describes the main themes and key areas that have been recognized and agreed upon. They are divided into (A) In situ Resource Utilization for Human Outposts on Mars and Moon, (B) Bioregenerative Life Support and Food production, (C) Radiation and Stress Protection and (D) Human Health. Each key topic is described in more detail in the following sections.

Each key topic is strictly related and interconnected to the others in order to guarantee the success of long-term human mission exploration, as illustrated in Fig. 2.

Topic A: in situ resource utilization for human outposts on Mars and Moon

ISRU refers to the generation of materials needed for autonomous or human activities from materials found on locally, such as on the Moon or Mars. Utilizing these materials as resources can significantly reduce the costs and risks associated with human exploration of space as they do not need to be transported and are likely in greater supply. The trade-off may be that the infrastructure needed to access these materials may be greater than simply bringing new materials from Earth.

Biologically-driven technologies, employing organisms capable of thriving at least partially on available resources, including solar radiation, water, atmospheric gasses, and regolith, are collectively known as 'bio-

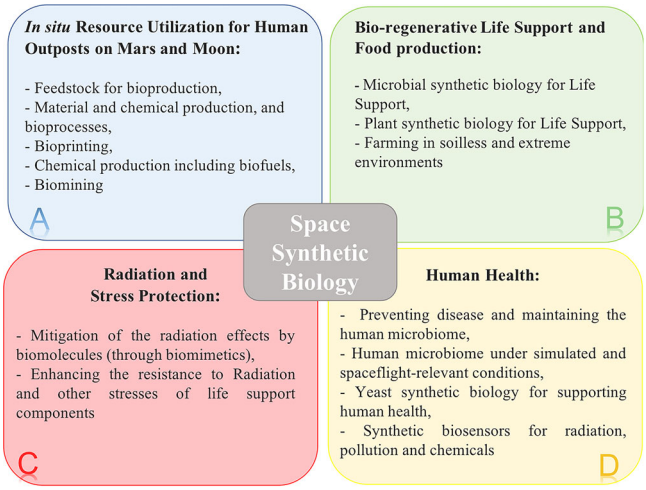

Fig. 1 | Key space synthetic biology topics. As identified in the 2023 ESA SciSpace Science Community WhitePaper, key space synthetic biology topics, are (**A**) In situ resource utilization for human outpost on Mars and Moon, (**B**) Bio-regenerative life support and foodproduction, (**C**) Radiation and stress protection and (**D**) Human healt.

ISRU'. This concept holds the potential to revolutionize the sustainability of human outposts on the Moon and Mars[21].

Bacteria, yeasts, fungi, algae, and plants, alone or combined, are widely used in transforming and recycling materials on Earth already, and as the technologies increase, are likely to have a transformative effect on off planet. They can be used for material production such as microbial cellulose, extraction of raw materials, and human life-support infrastructure, including bioremediation, waste recycling, and food production. In the development of bio-ISRU strategies, it is important to note it is likely that no single organism can serve all purposes[22]. This leaves two options: (1) using several complementary systems such as a consortium of organisms, or (2) employing synthetic biology to enhance the capabilities of these organisms to advance toward technological readiness for Bio-ISRU. In addition, among the factors that will determine the efficiency of ISRU is the physiology of the given microorganism. Liquid water is not stable on the surface of Mars under ambient conditions. However, a chassis organism engineered to operate as close as possible to ambient Martian conditions of atmospheric composition and temperature would reduce the need for infrastructure and power needed to maintain more Earth-like conditions. There are reports of organisms able to grow close to Martian atmospheric conditions, and certainly with composition of its atmosphere. For example, it was shown that the cyanobacterium Anabaena sp. PCC 7938 could be grown using a 96% N_2, 4% CO_2 gas mixture at a total pressure of 100 hPa[23].

Cyanobacteria and algae, due to their photosynthetic capabilities, represent typical primary autotrophic production organisms that could be used for feedstock production, including oxygen, organic carbon, chemical precursors, and molecules for radiation protection[24,25]. They can also serve as a source of food and other material, as can plants. Cyanobacteria and algae would be cultivated using materials available on site: water could be mined from subsurface reservoirs of water ice and minerals from regolith, whereas nitrogen diazotrophic cyanobacteria could use nitrogen present on the Martian atmosphere or more in general cyanobacteria could use human urine as a nitrogen source[26,27].

Anaerobic, acetogenic prokaryotes are of interest as they use mixtures of CO_2, CO and H_2 for the production of mostly acetate, formic acid, ethanol and methane[28]. These are products which could be further used as feedstock in coupled bioprocesses. Recent molecular insights into such carbon fixation mechanisms[29] will aid new strategies of energizing CO_2 fixation, such as

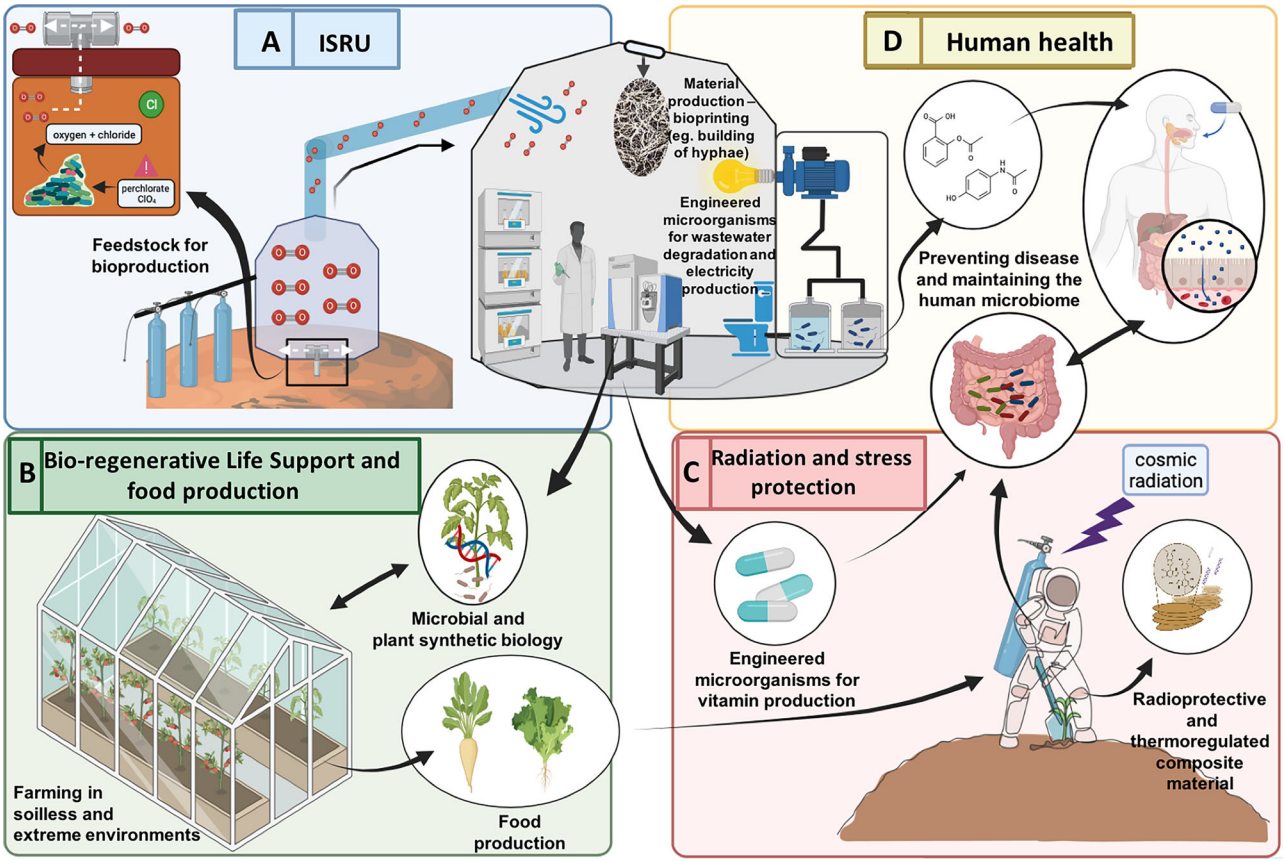

Fig. 2 | Illustrative guide to the four key topics of future human outposts on the Moon and on Mars that can be addressed by synthetic biology. By efficient use of local extraterrestrial resources and promotion of a more sustainable supply chain, synthetic biology can contribute significantly to human space exploration missions. This is done through incorporating the extraction, processing, and production of raw materials into consumables (**A**), enhancing recycling ranging from food production to waste management within life support systems (**B**), supporting radiation and stress protection strategies by producing stable biomolecules to mitigate harmful biological effects within life support systems (**C**), and engineering customized therapies, nutraceuticals, and biosensors to bolster astronauts' health (**D**). CREDIT: Midjourney software.

electricity. It will thereafter be determined whether this method is more efficient in terms of power, mass, volume compared to biological carbon fixation, or more reliable.

Yeasts and fungi could be employed to degrade crop and water waste, recycling them back into food or other products, and they can also be used for fermentation and food source themselves. Synthetic biology can be harnessed to biologically produce chemical substances off-planet, i.e., for microbial biomanufacturing in space[18,21].

The common soil bacterium, *Bacillus subtilis*, is particularly good chassis for production in space, as it is used commercially and has well-established genetic tools for manipulation. It is also generally recognized as safe (GRAS[30]), and importantly, it forms highly resistant spores that have been proven to withstand space conditions for nearly 6 years outside the Long Duration Exposure Facility (LDEF[31]). Extremotolerant cyanobacteria, such as desert strains of *Chroococcidiopsis*, could provide robust chassis organisms that can grow off the land and be exploited to produce compounds on-demand[32,33].

Other microorganisms, capable of deriving organic carbon from alternate sources, have the potential to produce various materials such as silk, wool, leather and bone[21].

Filamentous fungi have the capacity to produce food, convert waste, and excitingly, build large structures. The ability of polypore fungi to build materials and to feed on wood chips, and lunar and Martian regolith simulant supplemented with a nutrient solution, has led to the proposal that habitats, rover shells, and furniture could be produced this way off planet. A NASA team is now developing this technology in a Phase 3 project[32]. A structure grown on-site out of living materials has the capacity to conform to the environment and self-heal. Many fungi produce melanin which can protect from UV radiation and quite likely ionizing radiation as well[34,35], thus incorporating radiation attenuation into the biological composite material.

Among eukaryotic chassis, yeast, specifically *Saccharomyces cerevisiae*, provides a suitable expression platform for supplying protein-based drugs under space conditions[36], although *B. subtilis* retains the advantages enumerated above and thus is being used as the production organism in an astropharmacy being developed by NASA[37]. Microorganisms also play a role in bioprinting, a technique that involves the placement of living cells, DNA, proteins, or growth factors to create biologically active materials with a prescribed organization[38]. Synthetic biology offers numerous opportunities in this field, including the creation of 3D-printed multilayered structures with applications ranging from environmental detoxification and bioremediation to the biomedical field. For example, a hybrid biological photovoltaic device based on a 3D cooperative biofilm of cyanobacteria and heterotrophic bacteria demonstrated continuous bioelectricity generation from heterotrophic bacterial respiration, with organic biomass supplied by cyanobacterial photosynthesis[39].

Biologically produced chemicals, a key aspect of synthetic biology[40], can be harnessed to produce chemical substances off-planet. There is also potential to transform extraterrestrial organic material into useful products, such as asteroidal material, particularly carbonaceous material, which could be processed using organisms capable of fermentation or methane production with extraterrestrial organics. Some microorganisms are capable of breaking down recalcitrant macromolecular carbon found in carbonaceous chondritic material, for example, and could be engineered or produced to complete this task[41,42]. In fact, engineering microorganisms could increase carbon sequestration efficiency, such as by improving natural metabolic pathways[43–45].

Additionally, some organisms have the ability to create cement, using minerals found on the surface of Mars and the Moon. For instance, the bacterium *Sporosarcina pasteurii* can induce calcite precipitation, which has been used to make bricks through microbe-induced calcite precipitation (MICP[46,47]). These bricks could be used for building structures to protect astronauts, and the integration of bricks or other structures with mycelial fungi could offer radiation protection[32].

Microorganisms can be employed for biomining or bioleaching to extract useful elements. On Earth, around 20–25% of copper and 5% of gold are extracted using biomining processes[48]. This method offers environmental and economic advantages compared to traditional extraction methods[49]. Microorganisms can efficiently bind metals, requiring lower energy, cost, and mass to extract or separate metals from regolith, spent electronics, or e-waste[50]. These low-mass, renewable, and tunable extraction and separation methods hold great promise for metal acquisition and separation in extraterrestrial environments[51]. Filamentous fungi - either as in reference[52] or functionalized with specific peptides[53], show promise as microorganisms for biomining.

Topic B: bio-regenerative life support and food production

Basic requirements (oxygen, potable water, and nutritious food) are necessary for the crew to survive during space flight beyond LEO, and their supply must become more independent of Earth[54]. Long-term human missions to the Moon or further into the Solar System require Bioregenerative Life Support Systems (BLSSs) for the regeneration of primary resources, promoting autonomous management based on the use of in situ resources[55].

Furthermore, a BLSS must prevent cumulative pollution of the space habitat (e.g., by toxic CO_2 or volatile organics) and extra-terrestrial bodies by recycling waste[25,56]. Although extremely simplified, the BLSS can be considered an artificial closed ecosystem that functions similarly to an ecosystems on the surface of the Earth[57]. It has the same structure of producer (plants, microalgae, photosynthetic bacteria), consumer (humans/animals/fungi/microorganisms), and decomposer (microorganisms, insect)[56,58]. The selection of microorganisms within the system is tailored to specific tasks, and the system and bioprocess parameters are highly engineered towards the desired conversion efficiency and product quality[59–61]. One open question, particularly for systems to be used on Mars, is the atmospheric conditions under which such systems can operate. While the atmosphere of Mars is 95% CO_2, the total atmospheric pressure is <1% that of the Earth's. As liquid water, which is necessary for life, is not stable under these conditions, a human engineered increase in atmospheric pressure will be required to cultivate microorganisms. This will also increase the concentration of CO_2 to a level that will be suitable for photosynthesis. Low pressure is not necessarily incompatible with survival and metabolic activity of bacteria. A number of hypopiezotolerant bacteria have been described, including some that can grow at pressures as low as 0.7 kPa[20,62]. The use of bacteria at lower pressures would simplify the technical requirements and engineering of systems for space, Moon and Mars stations. A gas mixture extracted from the Martian atmosphere and compressed to about one-tenth of Earth's pressure at sea level would be suitable for growing cyanobacteria in photobioreactors[24]. Future research will have to show which atmospheric conditions offer the best compromise between technological concepts and biology. One of the key advancements enabled by synthetic biology is the modification of microorganisms to overcome limitations associated with wild-type organisms and to introduce new capabilities or even turn back time by reconstructing enzymes that were present in microorganisms of the ancient Earth, which had conditions more similar to those in space[63]. For example, it can enhance:

(1) Efficiency of metabolic pathways: by optimizing metabolic pathways in microbial life support processes and combining metabolic pathways for processes that are naturally carried out by multiple microorganisms, it is possible to increase conversion efficiency[64]. This ensures that available resources are used more effectively during space exploration.
(2) Bioproduction: synthetic biology allows us to introduce metabolic pathways in novel host organisms (e.g., in autotrophic organisms like cyanobacteria), enabling them to produce essential biomolecules from atmospheric CO_2 or to manufacture vitamins, antioxidants and other valuable biomolecules in microbial chassis suited to the available resources and stress conditions in space[65,66].
(3) Robustness: synthetic biology allows organisms to be modified or endowed with new functions to work robustly under the BLSS conditions, which may also include improved growth under low pressure conditions.

Plants are among the key organisms for BLSS, since they could (1) regenerate the space habitat air through photosynthesis, taking up CO_2 fixing carbon and producing O_2, (2) purify water through the transpiration process, (3) recycle nutrients from organic waste and (4) provide fresh nutritional food to sustain astronauts' diet[67]. Another important aspect concerns how plants contribute to recreate terrestrial eating habits and an Earth-like environment, thus helping to reduce the psychological pressure during the mission[68,69]. Synthetic biology makes it possible to overcome the challenges of agriculture in an extraterrestrial environment, in a dual way: fortifying the ability of species of interest to adapt to an extreme artificial environment and enhancing their nutraceutical properties. Indeed, it is possible to strengthen the defense against stress including radiation or orienting secondary metabolism[70,71]. The antioxidant metabolites are useful in counteracting the effects of oxidative stress, both in the plants as in the consumers when the plants producing them are introduced into the diet.

Furthermore, through metabolic engineering it is possible to obtain bacteria, yeasts, fungi, algae and plants that accumulate micronutrients (e.g., vitamins, folate, mineral salts) and immunostimulants to support the health of astronauts. From this point of view, a functional diet based on plant-derived, highly nutritious, fresh food can help counteract diseases induced by the space environment[72,73]. Indeed, it is largely reported that the pre-packaged food, used during short-term missions, tends to lose nutrients and vitamins over time[56,74].

Stresses imposed by the specific environment of space plant growth systems, such as hydroponic systems in microgravity and nutrient acquisition in space plant growth systems, as well as the utilization of in situ resources in planetary outposts, such as lunar or Martian regolith, are among the major challenges of plant growth. Plants live as holobionts in Earth habitats because their fitness, functions, and productivity are inextricably linked with their microbiome, which promotes plant growth through essential roles in nutrient acquisition and plant development, as well as maintenance of plant health and stress resilience.

A key point for advancing the BLSS and Food Production for space exploration is to transfer the terrestrial plant-microbiome holobiont concept to space and other planets for productive farming of plants in space plant growth systems[75]. Adjustments of the plant microbiome interactions will need to be tailored specifically to the plant and to the soil it will be grown in. It is here worthwhile to mention that plants grown beyond Earth could utilize regolith[76].

Topic C: radiation and stress protection

In the context of long-term space exploration, exposure to radiation, dust, and toxic compounds such as perchlorates presents significant challenges for the development of life support systems, human health, and spacecraft materials' stability. In particular, astronauts on multi-year space exploration missions face an increased risk of developing cancer and other harmful diseases due to radiation exposure[77]. The primary sources of radiation beyond LEO are GCR from outside the Solar System and SPE emitted by the Sun[78,79]. Secondary sources, such as low-energy metallic recoil ions, result from interactions between space protons and spacecraft materials[80]. Neutron radiation, a significant contributor to biological damage in space, represents ~30% of total exposure for those aboard the ISS[81–84]. To put this into perspective, while Earth's surface radiation exposure is limited to ~1 mSv/year, Mars surface has an exposure of ~267 mSv/year, and

interplanetary space exposes astronauts to ~600 mSv during a 180-day journey, assuming flight and shielding conditions similar to the Mars Science Lab (MSL)[85,86]. Ionizing radiation can directly interfere with DNA or indirectly produce radical species, that can lead to DNA damage, as well as a whole range of cellular responses such as apoptosis, senescence and cell cycle arrest[87,88].

To protect the astronauts, radiation protection measures and radiation damage mitigation strategies are being developed[89]. To address these challenges, the study of organisms that are able to survive high levels of radiation and their mechanisms of survival is crucial[90]. Investigating protective compounds produced by radioresistant microorganisms, as well as their activated mechanisms to recover from radiation damage, can help to identify stable biomolecules and genes that can be exploited to protect humans in space. The knowledge into biomolecule mitigation potential of, for example, antioxidant pigments like melanins, carotenoids, phycocyanins, or other proteins and antioxidants biomolecules, can then be leveraged in biotechnological applications through synthetic biology. It is largely reported that microorganisms (cyanobacteria, fungi, etc.) and their extracted biomolecules have astonishing abilities to withstand the space environment[91–94]. Such microorganism-based research is important for developing possible organic composite materials/medical and dietary supplements as supportive countermeasures in the overall radiation protection strategy for long-term manned space exploration missions[95]. Such nutritional radioprotective interventions can include vitamins, prebiotics, and probiotics. For example, vitamins E, A, C, B6, B9, and B12 have been reported as potent radioprotectors. Candidate radioprotective prebiotics are polyphenolic phyco- and phytochemicals, including anthocyanins, flavonoids, tannins, and lignins amongst others, which are highly enriched in cyanobacteria, algae and plants[96], but could also be added via synthetic biology to other (probiotic) strains or (fermented food) products. For example, soluble melanin has been demonstrated to mitigate effects of sublethal and lethal whole-body gamma irradiation in a mouse model[97]. Further, biologics produced by NASA's synthetic biology-based astropharmacy can be used as treatment in the case of radiation damage, such as the production of G-CSF to counteract the effects of a solar particle event[98].

In addition, microbes could be used for the production of hydrogen-rich organic composite materials that can be used in infrastructure to increase the radiation shielding and to help mitigate the space radiation hazard on future deep space missions. Low Z materials containing hydrogen are effective for shielding protons and heavy ions due to their high stopping power and large fragmentation cross section per unit mass[99]. Water is a very hydrogen-rich molecule that can absorb radiation, as well as polyethylene for example. Plastics such as high-density polyethylene and polycarbonate could be produced on Mars from locally available ethylene or methane[100]. But potentially also microbial resins and organic biopolymer (waste) products, with appropriate structural material properties, could be considered and biomanufactured via synthetic biology[101,102]. For example, brown-black pigment melanin is a poly-indolequinone biopolymer that has attracted attention for space material applications, including for radiation protection[101–105]. Composites with high mass attenuation coefficients based on fungal melanin's chelating activity with nanoparticles of bismuth, lead, and silver are explored as new radiation shielding coating materials[106]. Melanin is a redox active compound, contains a free organic radical with conductor capacity, and can absorb up to 20% of its own weight in water (roughly to ~2 water molecules to a monomer moiety), which all contributes to its specific properties[107]. Besides, the use of low-cost biomaterials in synthetic biology would allow for a reduction in mass/volume concerns that occur during launches as well as a reduction in dependence for supplies from Earth. Furthermore, in situ manufacturing will empower astronauts to address autonomously critical situations during space missions.

In addition to radiation concerns, settlers on Mars will encounter high levels of perchlorates, known to be toxic to terrestrial life, and strong oxidants that can compromise cell membrane integrity and disrupt the human hormonal system[108,109]. Perchlorate comprises ~0.5% of Martian regolith, a million times greater than in most terrestrial conditions[110]. Removing perchlorates from water is challenging as it consumes valuable resources that Mars lacks. An alternative approach is to utilize terrestrial microorganisms that have evolved genes capable of mitigating the toxic effects of perchlorates[107,111–113]. For instance, CO_2-utilizing bacteria could be engineered to express perchlorate reduction enzymes[114]. Alternatively, bacteria capable of complete perchlorate reduction could be engineered to achieve autotrophic carbon fixation[108,115]. This approach not only removes perchlorates but also releases water from hydrated perchlorate salts[116], facilitating plant life on Mars. In this context the relevance of the perchlorate tolerance of desiccation- and radiation-resistant desert cyanobacterium sp. 029 as 'PowerCell' in bio-ISRU technologies on the Moon and Mars was highlighted[117]. For example, this resistance, combined with the cyanobacterium's ability to convert CO_2 into organic compounds, could support ISRU technologies on Mars, which would otherwise be limited by the presence of perchlorates in the soil. Advanced research can transfer perchlorate-resistance-associated genes to polyextremophilic microorganisms, enabling human survival in high-perchlorate environments like Mars. A starting point to develop this research is the exploration and identification of the genes and molecular mechanisms involved in resistance to extreme conditions in extremophilic microorganisms, by combining traditional phenotyping and physiological data with omics-based analyses[111,112,118]. These genes will be used to modify, through synthetic biology, those microorganisms and plants involved in life support systems in space and planetary missions as well as in other processes such as biocementation, biomining, etc., with the aim of improving their resistance to the extreme conditions in these new environments (e.g., ionizing radiation and other oxidative stress-inducing conditions such as perchlorates on Mars). In addition, synthetic biology can be used to precisely enhance stress resistance or production of the compound of interest, without compromising fitness, for example through the controlled expression of (heterologous) expression of the responsible enzymes and genes.

Topic D: human health

Space represents an extreme environment for the human body, that during long-term flights is exposed to microgravity and high radiation levels that are considered as the major threats to the crew's health. Different effects of space environment have been reported on the human body, such as vestibular system impairment, sleep problems (6 h on average, but in some circumstances, values of less than 2 h/night were recorded[119]), motion sickness, impaired immune response, increased kidney stones formation, visual impairment, orthostatic intolerance, back aches, urinary tract infections, temporary anemia (decrease 15% red blood cells; decrease 22% blood volume), and bone and muscle loss (bone 2% loss per month and muscle 5% per week[120]). On top of this space flight conditions also pose new risks associated with microbiome health, and with viral and pathogen reactivation (e.g., due to weakened immune system) and transmission (e.g., due to aerosols in microgravity). The gut and skin are also important from a microbiome perspective. The gut microbiota is essential for preserving human health. The functions of gastrointestinal microorganisms span from metabolic regulation to immunological and neurological system development[121]. Alterations in gut microbiota composition and metabolite dynamics have been linked to a variety of clinical states, including metabolic disorders, immunological illnesses, cancer, neurological diseases, and behavioral problems[122]. Understanding how human microbiomes perform in spaceflight relevant conditions is a big challenge but could be addressed by the development of engineered biosensor-recorder bacteria that operate as 'sentients' in the microbiomes, detecting and recording changes in microbiome health that can be easily interpreted in-mission. The recently expanded CRISPR-Cas technologies, as well as systems-level insights into prokaryotic biology, have resulted in the development of synthetic bacterial cell-based sensors, able to detect specific disease biomarkers with functional in the gut[122–126]. Synthetic biology groups have already developed gut bacteria that record changes to the environment and bacterial diversity in the gut, and record these changes into the bacterial DNA in a way that allows this information to be quickly recovered from stool samples at low-cost (e.g.,

by paper-based DNA sensors or simple fluorescence measurements). Advancing these technologies for testing in astronauts offers a way to monitor microbiomes in near real-time in a small cohort of people[127]. Synthetic biology also offers novel technologies for continual disease prevention such as in situ regulated nutrient and drug release systems (e.g., patches) or implants containing sense-and-respond living cells that act to mitigate loss of homeostasis through 'prosthetic gene networks'[128]. These approaches have been demonstrated for treatment of diabetes, gout, and bacterial infections (e.g., urinary tract infections), and in theory work especially well at correcting diet/blood imbalances over months-long periods. This approach could be developed to mitigate spaceflight associated anemia and bone loss, since prolonged exposure to microgravity affects the musculoskeletal system[129]. Gut microbiome-based engineered bacteria can also correct metabolic diseases[130,131]. There are established *Escherichia coli*, yeasts and Bacteroides strains that can be engineered to work in the gut, and *Staphylococcus epidermidis* strains that act on skin[124].

Microorganisms are also engineered from a metabolic point of view to produce complex molecules such as antibiotics[39,132,133]. Genetic engineering of model microbes, especially yeasts, has now advanced to making entire synthetic chromosomes with foreign and synthetic genes. These turn cells into technologies, designed for flexible in situ biomanufacturing, and to sense and respond to desired external cues. Yeasts engineered with different biosynthesis and sensing modules would offer a broad technology for supporting health, acting as an 'astropharmacy'[134]. Such an astropharmacy system is currently being developed using *B. subtilis* as the chassis organism[37].

Engineered yeasts can make many therapeutics (opioids, antibodies, antivirals, vaccines, etc.) and is already an industrial source for nutraceuticals and food supplements. Engineered yeasts can be incorporated into material patches to release drugs on demand, or simply brewed to make a large amount of a desired protein. For example, the yeast *S. cerevisiae* can be modified to produce analgesic precursors such as morphine[135].

While many other model microbes (e.g., *E. coli*) are also used in synthetic biology, the breadth of uses of easy-to-grow, safe yeasts (*S. cerevisiae, Yarrowia lipolytica* and *Pichia pastoris*) should be prioritized. Establishing standard protocols and equipment to make use of engineered yeasts for bioproduction, therapeutic delivery and diet support in spaceflight situations should be a key goal, as should be getting a full understanding of their safety profiles and whether they change in space. Engineered microorganisms have also an established use as whole-cell environmental biosensors: with modified bacteria such as *E. coli* and *Bacillus sp.*[136], yeasts and even plants used to detect, record and report on environmental signals and the presence of certain molecules or pathogens in air, water, food or human samples. As well as this, biosensors are also possible without living organisms, by using cell-free transcription-translation (TX-TL) systems[137]. Cell-free synthetic biology can employ cell lysates to create inexpensive and user-friendly paper-based cell-free biosensors or simple on-site biosynthesis of proteins or drugs. Heavy metal detection (cadmium, arsenic, etc.) in water is a well-established application of synthetic biology[138]. More recently, biosensor cells (yeasts, *E. coli*) have demonstrated pre-clinical use in medical detection assay, for example, being able to detect pathogens (via their proteases), viruses, and toxins, as well as identifying abnormal levels of hormones, antibodies, and drugs. Small chemicals, complex compounds, and oligonucleotides (RNA and DNA fragments) are examples of ligands that bacteria can be developed to recognize. Biodosimetry and radiation damage detection is more complex, but recent work in cells with in vivo mutation recording (e.g., for directed evolution and cell lineage application) now offers new ways to detect, record and quantify radiation damage in cells, as an addon to the classical ex-vivo physicochemical radiation detections techniques. Biosensors are a mature application of synthetic biology but would greatly benefit from being directed into a standard framework, both for ease-of-use and for plug-and-play sensing.

Although several factors contributing to challenges faced by astronauts during spaceflight have been extensively investigated, certain aspects have not received enough research attention. There is increasing evidence that not only is the immune system dysregulated, but spaceflight conditions have a huge impact on the pathogens that infect the host. For example, spaceflight increases virulence of *Serratia marcescens* (strain Db11) in the Drosophila melanogaster infection model, compared to ground-based controls[139]. Additionally, *Salmonella typhimurium*, the bacterial pathogen cultured aboard Space Shuttle flight STS-115, had improved virulence in a murine infection model[140].

Space synthetic biology in the frame of future human exploration missions

The Moon and Mars are the next destinations for post-International-Space-Station human exploration, as stated in the Global Exploration Roadmap[141] (Fig. 3). The return of humans to the Moon through the NASA Artemis program includes the establishment and habitation of a Lunar Gateway, and a permanent base on the Moon's surface (not earlier than 2030). As human activity in space moves from LEO—where the ISS is orbiting, to deep space exploration, the crews will face different and new challenges. These include extended mission durations, increased distance from Earth, communication latency, limited or no re-supply possibility, a more complex space environment (low gravity, radiation, dust). It is evident that the Moon is a key passage to enable human exploration of Mars. The Moon can be used to investigate the biological effects of low gravity, the radiation environment beyond the Earth's magnetosphere, and the toxicity of lunar dust. Exposure experiments of organisms on the lunar surface would yield new insights into fundamental biological processes and the adaptation to, and evolution of, organisms in the space environment. This would feed into the implementation of bio-regenerative life-support systems, food production, and the mitigation of adverse consequences of low gravity and high radiation environments.

The Moon is ~360,000 km from the Earth, making resupply more difficult than for the ISS. Therefore, humans must learn to use the resources of the destination to produce oxygen, water, food and building materials to secure a long-term survival. In addition, to reduce launch costs and the total mass scale of launch vehicles, humans also need to learn how to use the resources of the Moon to produce propellants. In addition, living and working over a long period at the destination and to return to Earth from the destination, means the utilization of a significant volume of consumables. Representative volumes of consumables associated with a six-crew Lunar base is estimated at ~31 kg per day (0.83 kg/day oxygen, 0.62 kg/day oxygen, 3.56 kg/day drinking water, 26 kg/day clean water)[142]. In this context, the ISRU would benefit by the utilization of synthetic biology: the use of engineered microorganisms able to better grow in Lunar conditions could improve the production of feedstock, material and chemicals (including biofuel).

The crewed journey to Mars, including landing and safely returning to Earth, will take months and years and will require a strenuous effort on a completely new level. Many important issues are still to be solved: the duration of such a mission (~2 years total mission time), with no possibility of a premature return because the Earth-Mars transfer windows are open every 26 months, and the logistic problems of such a long trip (air, water, food, waste), the crew safety issues (radiation exposure in the first place but also microgravity, confinement and stress). In planning these undertakings, several challenges will need to be addressed in order to ensure the safety of astronauts during their space travels. One of the important challenges to overcome, that could be a major showstopper of the space endeavor, is the exposure to the space radiation environment. During deep space exploration, astronauts experience a chronic, low-dose-rate whole-body exposure to GCR, which can accrue to ~1 Sv during a 1000-day Mars mission[85,143,144]. Microorganism-based research is important for developing possible organic composite materials/medical and dietary supplements as supportive countermeasures in the overall radiation attenuation strategy for long-term manned space exploration missions. Newly identified resistance strategies could be used to improve the resistance of any component (plants and microorganisms) of life-support systems, as well as in other processes such as biocementation, biomining, etc. Human health (Topic D) would gain

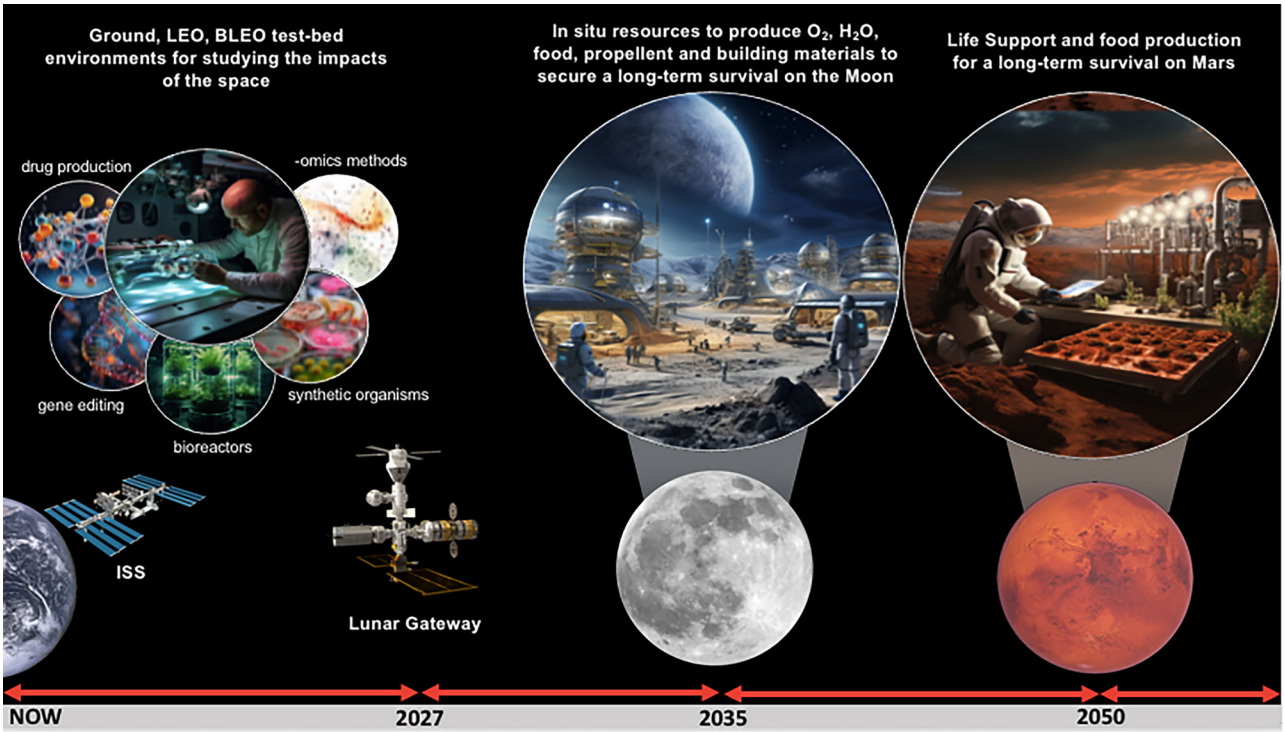

Fig. 3 | Timetable of future human space explorations. Illustrating how synthetic biology can be applied to support space exploration indeep space and beyond (BLEO Beyond Low Earth Orbit).

from synthetic biology as well: it may offer a new toolset to help in the prevention of diseases and maintaining microbiomes in astronauts, and be used for in situ biomanufacturing of drugs for diseases, for detecting radiation damage, and the effects of different gravity.

Recommendations

The main research questions and unresolved challenges identified in the introductory section can be answered through specific experiments in ground and in space. For each topic, we have identified several recommendations that could be implemented in the short (next 3 years), middle (next 6 years), and long term (>10 years) to advance the field of synthetic biology.

In the short and middle term for topic (A), 'In Situ Resource Utilization for Human Outposts on Mars and the Moon', we recommend testing the impacts of the space radiation environment and altered gravity on chassis robustness using -omics methods such as genomics, transcriptomics, proteomics, metabolomics, and lipidomics. Laboratory production techniques should also be extended to space-based production facilities such as the development of bioreactors for photosynthetic organisms and their cultivation in space.

In topic B, 'Bio-regenerative Life Support and Food Production', recommended experiments focus on the identification and optimization of synthetic organisms or microbial communities that can support life functions under space-relevant conditions, compared to their natural counterparts. Additionally, synthetic plant growth-promoting bacteria should be developed for plant growth in hydroponic and aeroponic systems, which could be used in farming. Within this topic, it is essential to consider generating new plant ideotypes capable of countering the deleterious effects of humans' presence in extraterrestrial environments. Techniques such as metabolic and protein engineering can be used to pursue the biofortification of plant species suitable for cultivation in planetary mission contexts. These biofortified plants may be used as fresh diet supplements (e.g., vegetables), for the production of bioactive molecules to support human health in space missions, or for bioremediation processes of extraterrestrial soil.

Topic C, 'Protection from Radiation and Stresses', focuses on using biomolecules and genes involved in resistance as protectors in the space environment. Studies (e.g., metagenomics and metatranscriptomics) aimed at identifying novel extremophilic organisms and their expressed genes involved in resistance and adaptation processes are of utmost importance. The newly identified microorganisms need to be tested after exposure to various space stressors (e.g., radiation, perchlorates) from molecular (genomics, transcriptomics, proteomics, and metabolomics) and morphological/physiological perspectives to assess their resistance and resilience under extreme conditions. Functional studies can identify stable molecules and genes in resistant microorganisms that can be used through synthetic biology to engineer microorganisms, plants, and model organisms to produce resistant biomolecules for large-scale biomanufacturing and improve their resistance and efficiency in life-support systems.

The recommendations of Topic D, 'Human Health', are to assess widely used bacterial strains (e.g., *E. coli, B. subtilis, Pseudomonas putida*) and yeasts (e.g., *S. cerevisiae, P. pastoris, Y. lipolytica*) to altered gravity and radiation environments on board the ISS and perform differential gene analysis, in order to compare gene expression levels among treated and control groups and highlighting the effects of these harsh conditions on microorganisms and on molecular pathways regulation.

By analyzing the overlap between health problems and health issues during spaceflight, leading issues can be identified, and engineered microorganisms can be utilized for disease treatment. In fact, from the fermentation of engineered bacteria or yeasts in controlled sterile bioreactors, small batches of clinical-grade therapeutics and nutraceuticals can be produced. It is worth considering the identification of a single yeast strain suitable to serve as a standard strain for an astropharmacy system, capable of robust growth and culture in space travel conditions and compatible with space bioreactor use. In addition to systems based on engineered microorganisms, cell-free systems should also be developed for daily measurements of astronauts. These systems could be initially developed through ground experiments designed for space utilization. They can also be used for the detection of key pollutants, chemicals, and radiation impact relevant to spaceflight conditions.

Benefits for Earth and industrial relevance

Overcoming the challenges of working in space has and continues to lead to many technological and scientific advances that have provided benefits on Earth in different areas including health and medicine, transportation, public safety, consumer goods, energy and environment, information technology, and industrial productivity. Topic (A) will contribute to implement water purification systems, to remediate environmental contamination, to sustainably produce bioenergy, drugs, and food and to reduce pollution by capturing carbon dioxide from industrial emissions. Topic (B) will lead to improvement in ground cultivation by ameliorating plant growth in hydroponic and aeroponic systems, but also by using the local regolith as a "soil", thus improving urban farming and obtaining a viable way to grow food[145,146].

In addition, space biology will contribute to the development of microorganism-based alternative concepts of nutrient production. Human health will also benefit from space synthetic biology of Topic (B) by identifying new plant ideotypes as a source of bioactive molecules. Synthetic biology, applied to space exploration will be an essential driver for opening up new domains in science and technology related to mitigation of radiation and other types of stress on organisms (Topic (C)). Implementation of new generation systems for enhancing radioprotection strategies by using biomaterials (edible molecules acting as antioxidants, or composite materials for skin care products, etc.) as well as improvement of crops resistance to high UV doses will be excellent returns of space synthetic biology. The fundamental benefits generated by Topic (D) concerns the unique opportunity to study the microbiome and the impact of interventions using synthetic biology (being conditions in space with high sterility and in-depth human monitoring). The study of the health of a small number of people would enhance human medicine. This could be beneficial in the development of tailored medical therapies, such as orphan medicines. Synthetic biology could also have the potential to modify current industrial biomanufacturing on Earth. Space biomanufacturing can help convert Earth's industrial model to low-impact local biomanufacturing by focusing on resource utilization rather than energy utilization (Topic (D)).

To conclude, synthetic biology has shown to have great promise for significant and practical uses in space exploration, but it also carries the risk of being abused to endanger human health or the environment. For example, gene editing may improve human health and food production, but it can also have serious unfavorable repercussions. Among the most significant effects are the unchecked spread of genetically engineered materials and the disturbance of ecologies[147]. These factors make the study of synthetic biology inextricably linked to the concept of biosafety.

Considering the many aspects of synthetic biology it is difficult to precisely define and establish laws on biosafety[148]. However, laws pertaining to synthetic biology are managed to be issued in accordance with the sectors of synthetic biology research and application in different countries. For instance, the government of the United States has established laws, rules, and policies relating to various biological products. Microorganisms are categorized, according to their degree of virulence, leading to the mandate of different levels of physical confinement. Regarding laboratory management, "Biosafety in Microbiology and Biomedical Laboratories," a handbook on suggestions for the physical containment of infections, was issued by the US Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) (for detailed information refers to[148]).

In terms of outer space, biosafety is referred to as "Planetary Protection"—"the practice of protecting Solar System bodies (i.e., planets, moons, comets, and asteroids) from contamination by Earth life, and protecting Earth from possible life forms that may be returned from other Solar System bodies"[149]. Despite the publication of an updated Planetary Protection paper by COSPAR[149], biosafety in synthetic biology is still a relatively unexplored area. Given this, we further suggest that, in the context of ongoing discussions regarding planetary protection, the concept of contamination of extraterrestrial bodies via the use of organisms in ISRU or BLSS should be evaluated.

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Competing interests

The authors declare no competing interests.

Additional information

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