

## Review article

## Biomaterials for human space exploration: A review of their untapped potential

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## ABSTRACT

As biomaterial advances make headway into lightweight radiation protection, wound healing dressings, and microbe resistant surfaces, a relevance to human space exploration manifests itself. To address the needs of the human in space, a knowledge of the space environment becomes necessary. Both an understanding of the environment itself and an understanding of the physiological adaptations to that environment must inform design parameters. The space environment permits the fabrication of novel biomaterials that cannot be produced on Earth, but benefit Earth. Similarly, designing a biomaterial to address a space-based challenge may lead to novel biomaterials that will ultimately benefit Earth. This review describes several persistent challenges to human space exploration, a variety of biomaterials that might mitigate those challenges, and considers a special category of space biomaterial.

## Statement of significance

This work is a review of the major human and environmental challenges facing human spaceflight, and where biomaterials may mitigate some of those challenges. The work is significant because a broad range of biomaterials are applicable to the human space program, but the overlap is not widely known amongst biomaterials researchers who are unfamiliar with the challenges to human spaceflight. Additionally, there are adaptations to microgravity that mimic the pathology of certain disease states ("terrestrial analogs") where treatments that help the overwhelmingly healthy astronauts can be applied to help those with the disease. Advances in space technology have furthered the technology in that field on Earth. By outlining ways that biomaterials can promote human space exploration, space-driven advances in biomaterials will further biomaterials technology.

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## 1. Introduction

Biomaterials and human space exploration are both relatively new fields with the potential to mutually benefit one another's advancement. Human space exploration is arguably one of the most daunting engineering challenges ever undertaken. Sustained human presence in space requires knowledge and resources that promote human health on Earth. In addition, it demands the creation of life-sustaining habitats in singularly inhospitable environments

with incompletely characterized threats to health and well-being that do not exist on Earth.

Every item launched into space—equipment, supplies, or crew—must meet specifications for weight, durability, resilience, and multi-functionality, among a host of others. These stringent requirements push the design parameters of materials used for space, whether they are materials used in systems to promote spacecraft function or systems to promote human health. Physiological adaptation to the space environment can resemble pathological states on Earth, the latter of which have benefitted from biomaterials. The evolving capabilities to design biomaterials with specific properties offers important opportunities to address some of the more intractable problems in human spaceflight.

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The purpose herein is to consider how biomaterials can support current and future human space exploration, specifically, biomaterial characteristics, function, and impact on mission success. To date, the majority of biomaterials used in space have been to enable research investigations (e.g., 3D cell culture), rather than to support crew health. There are only a handful of emerging biomaterials that have been tested in space, none of which have been used for their eventual function. Therefore, the review aims to:

- 1) Delineate areas in current and future space exploration where biomaterials could provide substantial, unique benefits;
- 2) Review existing biomaterials and investigations that could be applied for space exploration;
- 3) Offer a framework for identifying and advancing key characteristics of biomaterials that both mitigate certain risks incurred by human space exploration and optimize human health; and
- 4) Propose a new definition, “space biomaterials,” to capture the intersection of biologically-derived materials and biomedical materials, and their under-utilized potential in supporting human space exploration.

### 1.1. Defining space biomaterials

At just over 50 years old, biomaterials science is a broad field that defines biomaterials as biocompatible materials—any material whether synthetic or natural in origin that is designed to be used in close contact with biological systems, tissues, and fluids—that serve a medical purpose such as evaluating, treating, augmenting, or replacing any tissue, organ, or bodily function. In contrast, when the Space Studies Board of the National Academies first convened a workshop in 1997 to identify biology-based technology to enhance human well-being in space, they defined biomaterials as *biologically-derived materials*, and their focus was materials for habitats that could be grown on an off-planetary site [1]. At the most recent 2020 workshop of NASA's Human Research Program (HRP), there were no biomaterials sessions, and only one presentation explicitly describing a biomaterial [2]. Addressing this divergence of definitions between those working on biomedical materials for use on Earth and the investigators seeking to exploit biologically-derived materials for space missions is crucial if both materials are to be fully employed in space exploration.

Due to the enormous cost and vast amount of fuel consumed in launching each pound into space [3], any component that eliminates the cost of launching additional components is considered extremely desirable. Thus, any component that can fulfill more than one function, can be re-purposed or recycled, or used to generate new materials once on site are sought [4]. In many ways, biological systems have such flexibility. While this explains the interest in biological materials, it does not address the divergence in terminology.

The primary source for this divergence in defining biomaterials is in the way missions are conceptualized. For the most part, space missions are designed, built, analyzed, and implemented using a distinctive aerospace engineering systems approach that models the human crew (and any other biology) as one of the mission's many component systems. In the recently released 2020 NASA Technology Taxonomy [5], the human system, TX06 Human Health Life Support and Habitation Systems, is just one of seventeen systems that must be accounted for in any current or future mission. This human system has six subsystems: radiation protection, nutrition, portable life support systems, waste management, therapeutic and preventative medical care, and shelter. The crew also interfaces with the other mission systems. Further, for space applications, equipment, materials, or supplies may be divided into types—components that must be launched or supplies that can be generated during the mission.

For these reasons space systems designers must consider all potential applications of both biologically-derived materials and biomedical materials, particularly where they overlap. While for Earth-based applications a material is a biomaterial or it is not, during human space exploration one material may or may not be a biomaterial depending on the context. Hence, while the focus is biomedical materials to facilitate human space exploration, this review will make a case for a new definition that encompasses both biologically-derived materials and biomedical materials and captures the need for their overlap in space, “space biomaterials.”

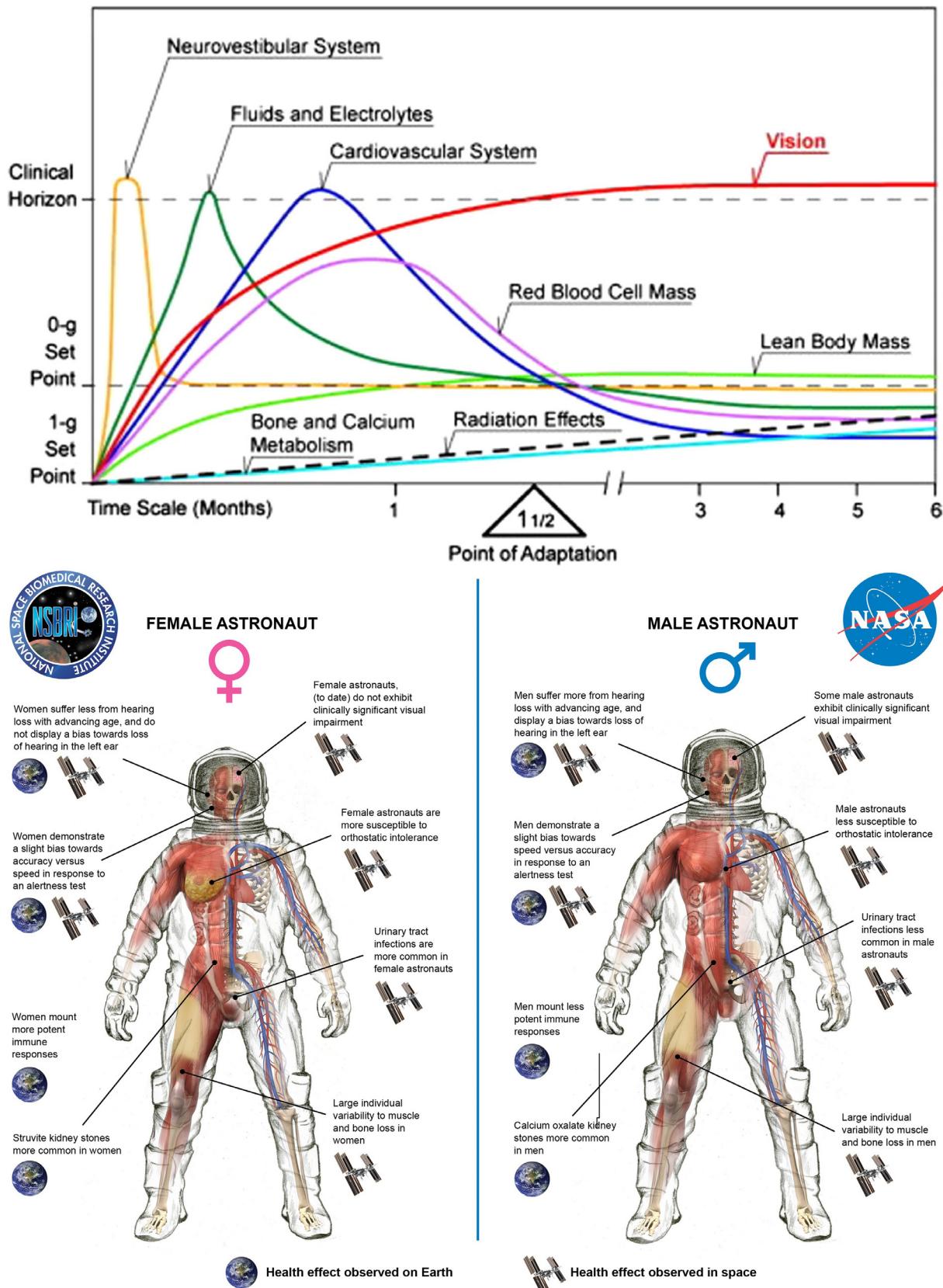
### 1.2. The Space Environment

Space environments are inhospitable to human life. Therefore, a life-sustaining habitat must be created for the duration of any mission with humans or other higher biological systems on board. Notable characteristics of space environments that must be accounted for include: 1) gravitational variability, 2) temperature extremes, 3) particle contamination, and 4) cosmic radiation [6], as well as 5) toxic or no atmosphere, and 6) isolated and confined environments. In particular, gravity can range from 0 G (microgravity) on the International Space Station (ISS) to a fraction of Earth's gravity as on the Moon (16.7% G) or Mars (37.6% G) to many multiples of Earth's gravity as experienced during spacecraft acceleration and deceleration. Any biomaterial must be designed to function in or tolerate the entire mission acceleration/gravity profile. Temperature extremes ranging from very hot to very cold can be experienced on other celestial bodies or during extravehicular activity (EVA) when in full view of the Sun (121°C) or in the Earth's shadow (-157°C). Any atmosphere must be provided—both for respiration and to generate atmospheric pressure. The provided atmosphere, whether in the confines of an EVA suit or the larger spacecraft, is generally within a closed environment that may be composed of gasses and pressures that differ from Earth's atmosphere and may entrap toxins from off-gassing equipment or respiratory waste metabolism, such as CO<sub>2</sub>. These gasses must be scrubbed from the environment, therefore, the majority of materials used in the habitable compartment are selected because, among other criteria, they have minimal toxic off-gassing. The lower gravity also means dust and particles remain suspended. Whether from crew activities, normal shedding of hair and skin, or lunar soil, these suspended particles must be addressed because in the atmosphere they can be inhaled by crew and clog filtration systems. Finally, cosmic radiation has never been fully shielded by any spacecraft, exposing both crew and supplies to radiation. Therefore, resistance to cosmic radiation is also a desired attribute in any biomaterials for space.

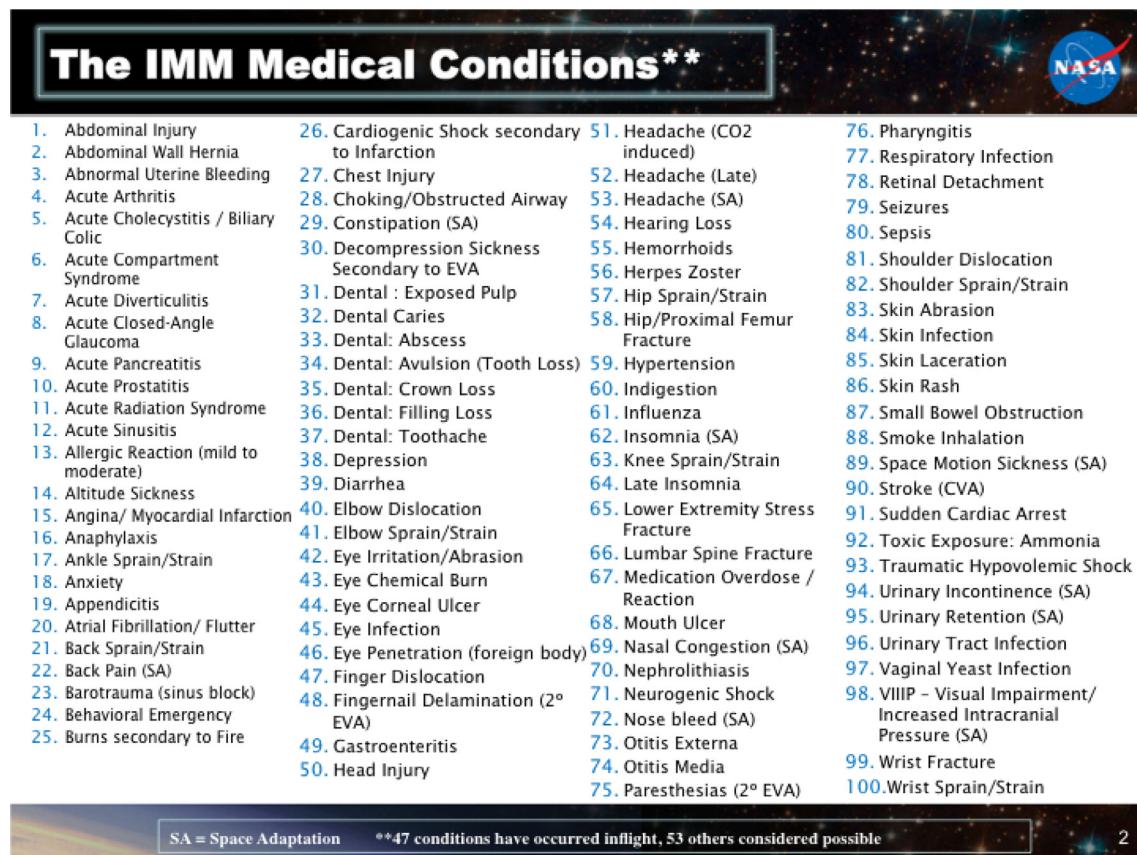
Importantly, the majority of a space mission's payloads are produced and frequently stored months prior to launch, making a long shelf life an important criterion. As is being nonflammable in a 30% oxygen environment [7,8]. While not immediately obvious, the number of nonmetallic materials that can pass NASA spacecraft flammability tests falls off rapidly at 30% O<sub>2</sub>; for instance, polystyrene is not flammable in air, but it is at 30% oxygen [9]. Such constraints also apply to biomaterials.

### 1.3. Impacts of space on human health: observed and projected

The space environment affects every organ system in the body (Fig. 1) [10]. Microgravity leads to: 1) disuse atrophy of muscles, including the heart; 2) resorption of weight-bearing bones, which can lead to increased fracture risk and kidney stones due to the excess calcium excretion; 3) a headward shift or redistribution of fluid that can lead to visual changes and also triggers baroreceptors to excrete excess fluid, which in turn leads to a reduction in blood volume, further cardiovascular changes, and orthostatic intolerance



**Fig. 1.** Time course and location of physiological shifts in response to microgravity. Images courtesy of NASA, NSBRI.



**Fig. 2.** One hundred potential medical conditions during space exploration, as identified by NASA's Integrated Medical Model (IMM). Image from Ref [11], courtesy of NASA.

upon return to Earth. Additional changes include alterations in: 4) circadian, 5) sensorimotor, 6) reproductive, 7) immunological, 8) reproductive, and 9) wound healing systems. Although some of these adaptations may be well tolerated in a weightless environment, they become problematic during reentry to gravity environments, such as landing on Mars after travel from Earth or returning to Earth from the ISS. Not all adaptations happen immediately, some stabilize to a zero G set point while others continue to progress throughout the duration spent in zero G. As space travel becomes accessible to the general public, the typical assumptions of normal physiology in an abnormal environment may no longer hold. There will likely be greater variation in the physiological health and fitness of travelers with the attendant need to monitor and treat pre-existing conditions.

The Integrated Medical Model (IMM) was developed by NASA researchers to inform mission planning, research investments, and medical kit optimization (Fig. 2). The IMM provides insight into the 100 most likely medical conditions that could occur during various space mission scenarios. Based on data gathered from the Apollo, Skylab, Mir, Space Shuttle, and ISS missions, as well as terrestrial space mission analogs, the IMM provides medical condition incidence rates and treatment requirements. Approximately 40% of IMM conditions have actually occurred during the Apollo, Mir, Space Shuttle, and ISS missions [11].

Current therapeutic options for crew health management aboard the ISS includes a limited pharmacy, equipment to deliver fluids or drugs intravenously and intraosseously, diagnostic equipment like sphygmomanometers, ultrasound equipment, an optical coherence tomography device, an emergency defibrillator, and dental equipment [12]. For major medical emergencies aboard the ISS, the option to return the astronaut to Earth exists but may not be possible if the patient has a compound leg fracture, is intubated

with an oxygen tank, or has an injury that prohibits the individual from being placed in a flight suit in the crouched position required in the Soyuz, or even the more expansive (but still confined) crew compartment of the SpaceX Dragon vehicle. The option does not exist at all for deep space or missions to Mars. A final consideration that will influence biomaterial selection is the delicate balance between acceptable negative short- and long-term health effects against mission success.

## 2. Biomaterials in human space exploration – existing and potential

The requirements set forth by the IMM and the 2020 TX06 Human Health Life Support and Habitation Systems combined with general space flight operational constraints provide a launch pad for biomaterial researchers to identify biomaterials needed for human space exploration. These considerations guide this review's focus on which biomaterials might be suitable in space to support and optimize human health, well-being, and performance as well as to treat potential illnesses or medical emergencies. This article highlights uses for biomaterials that may in some way be unique to or beneficial for human space exploration. Once identified, the potential for new avenues of research, new collaborations, new inventions, new discoveries, and new funding sources will be vast.

### 2.1. Radiation protection

Radiation exposure has long been considered a major challenge for long duration human space missions. The Earth's magnetosphere and atmosphere are powerful shields against a steady flux of cosmic radiation from protons and high atomic number high energy particles. At sea level, cosmic radiation is attenuated to a

global average of 0.22 mGy per year [13]. At high altitudes, where the protection of the magnetosphere is intact but there is less atmosphere present to act as a shield, the incidence of cancer increases for those exposed to altitude for prolonged periods, such as commercial airline pilots [14–15] and denizens of high altitude cities [16,17]. The ISS is entirely outside of Earth's atmosphere but still receives a measure of protection from the magnetosphere. On the ISS, the dose has been calculated to be 675.4 µGy per day [18], or 246.7 mGy per year, over 1,000 times the yearly sea level dose on Earth. In deep space, beyond the protection of Earth's magnetosphere, the cosmic radiation dose is 104 Gy per year, nearly 500,000 times Earth's yearly sea level dose [13]. These radiation values are influenced by: an interaction with the shielding and atmosphere of a spacecraft or planetary surface such as Mars, which can offer both some measure of protection and the creation of secondary particles (e.g., neutrons, light ions, etc.); and the Sun's 11-year solar cycle, which can increase or decrease cosmic radiation values [18].

Contrary to popular belief, the solution is not merely lining the spacecraft with lead, which is only effective for a certain range of high energy particles. For instance, lead is highly effective at blocking gamma or X-ray radiation but generates secondary X-rays when beta radiation passes through it, while acrylic effectively blocks beta radiation. Furthermore, although existing shielding provides some measure of protection against cosmic radiation, it greatly increases a spacecraft's weight and cost to launch, but most importantly, it does not completely protect astronauts against radiation—shields 5–7 cm thick can only block 30–35% of cosmic radiation [19]. This has led NASA to investigate the use of pharmacological and dietary supplements to mitigate the effects of ionizing radiation [19].

Here, biomaterials may offer a unique solution. When compared to radioprotective geologic materials such as lead, biological materials such as melanin are both lighter and more flexible in their potential application. A group of heterogeneous biopolymers, melanins act as pigments and/or provide radiation protection and are ubiquitously found throughout plant, fungal, bacterial, and animal kingdoms [20]. Melanin-coated nanoparticles were investigated for their ability to protect bone marrow during radiation therapy for cancer. Schweitzer et al. coated 20 nm plain silica nanoparticles with a 15-nm-thick layer of melanin via enzymatic polymerization of 3,4-hydroxyphenylalanine and/or 5-S-cysteinyl-3,4-hydroxyphenylalanine [21]. Following intravenous injection with the melanin-nanoparticles, they irradiated healthy or tumor-bearing mice at 125 cGy and found reduced hematologic toxicity in mice receiving nanoparticles and no tumor protection. Noting that silica nanoparticles persist in tissue and therefore may not be optimal for human therapy [22], Ju et al. circumvented this issue by developing melanin nanoparticles through simple oxidation of dopamine under basic conditions, resulting in nanoparticles that were excellent free radical scavengers that showed high dispersion stability in aqueous solutions such as biological media [22,23]. Rageh et al. tested melanin nanoparticles in irradiated mice exposed to a dose of 7 Gy  $\gamma$ -irradiation [22]. They assessed the impact of the intraperitoneally delivered nanoparticles on radiation damage to peripheral blood, spleen, and DNA by evaluating the blood count, spleen histopathology, and the comet assay to measure cellular DNA damage in the bone marrow at 1, 4, 8, and 12 days following irradiation. They found that treatment with melanin nanoparticles protected hematopoietic tissues against radiation damage, thereby enhancing the survival of mice in treated groups (40 % survival) compared to controls (10 % survival) and concluded that melanin nanoparticles provide significant radioprotection to hematopoietic tissues.

Rather than coat nanoparticles with melanin, Cao et al. developed a novel melanin that they envision being used on the

skin as a melanin-based sunscreen [20,24]. While five multifunctional varieties of melanins are known, (allomelanin, eumelanin, neuromelanin, pheomelanin, and pyomelanin), their structure and biosynthesis remain incompletely understood. The authors noted that despite a strong focus on allomelanin and eumelanin in radiation protection research, pheomelanin's X-ray absorption coefficient may be better than eumelanin's. Further, since selenium has a higher atomic number (Z) than sulfur, the researchers hypothesized that melanin enriched with selenium would provide better X-ray protection than the sulfur-containing pheomelanin because the X-ray absorption coefficient is proportional to  $Z^4$  [20]. The group noted the importance of selenium as an essential micronutrient, particularly since the amino acid selenocysteine is genetically encoded in 25 human proteins. These observations led the authors to hypothesize the existence of an undiscovered selenomelanin in nature, where it provides organisms with protection from ionizing radiation superior to that of the known melanins. Utilizing a combination of chemical and biosynthetic protocols, they then developed a novel selenomelanin by using selenocystine to develop a selenium analogue of pheomelanin. They found that selenomelanin formed perinuclear caps (that they dubbed "microparasols") in neonatal human epidermal keratinocytes, and when subjected to high-dose X-ray irradiation the microparasols effectively prevented the cells from G2/M phase arrest compared to control keratinocytes without the selenomelanin. Samples of melanin are currently on orbit on the ISS to determine their reaction to cosmic radiation exposure [25].

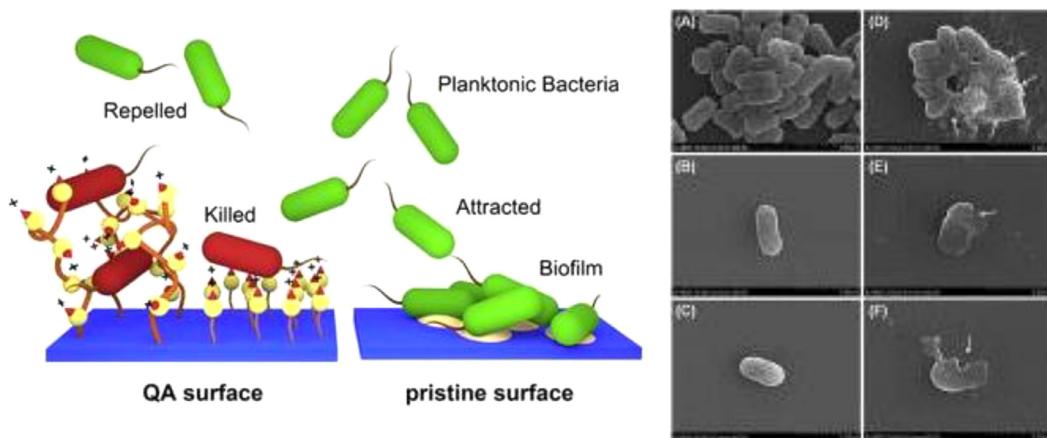
## 2.2. Microbe resistant surfaces

Contact killing surfaces are a current biomaterial research area that would have far reaching benefits in space. Habitat maintenance consumes significant amounts of an astronaut's time on orbit. Biofilms pose problems for all systems within the crew habitat [26]. Cleaning supplies are constrained due to storage, weight, and potential toxicities. Space stations—both Mir and ISS—have significant bacterial and fungal colonization [27]. Microbial infestation has been detected on panels, exercise equipment, and even in drinking water. Surfaces that could abrogate microbial contamination without requiring cleaning by the crew might reduce payload (e.g., less cleaning supplies) and could be beneficial for both crew health and productivity [28].

Contact-killing surfaces hold the potential to greatly reduce the level of contamination of space habitat equipment. Biomaterial approaches to creating these surfaces generally include biomimicry of topological features or chemical coatings. Surface coatings of selenium or silver, which limit microbial contamination and are used in contact lenses and urinary catheters, respectively [29], immobilized quaternary ammonium compounds, and mechano-bactericidal surfaces have all been shown to kill a wide variety of microorganisms.

### 2.2.1. Surface coatings

For centuries, the antimicrobial properties of silver have been known; ancient civilizations applied silver to open wounds and mariners put silver coins into drinking water to keep it fresh. However, only recently has its mechanism of action been elucidated. Gugala et al. mapped all 225 genes that contributed to either silver resistance or toxicity in *Escherichia coli* (*E. coli*) [30]. Their study confirmed other work demonstrating that the antimicrobial activity of silver involves disruption of iron-sulfur cluster containing proteins and the disabling of certain cellular redox enzymes. The work also described a more complex mechanism of silver bactericidal activity, including genes involved in cell wall maintenance, quinone metabolism, and sulfur assimilation. Antibiotics that have lost function due to antibiotic resistance regain their efficacy when



**Fig. 3.** Quaternary ammonium (QA) bactericidal activity. Left: Surfaces with immobilized quaternary ammonium compounds. Right: *E. coli* incubated with and without quaternary ammonium functionalized quantum dots ]. Reproduced with permission from American Chemical Society and The Royal Society of Chemistry. From Refs. [285,286].

silver is added [31,32]. Recently, silver nanolayer coatings (40 nm thick Ag/Al<sub>2</sub>O<sub>3</sub> nanocomposite layers) were applied to stainless steel surgical and microsurgical instruments using radio frequency reactive magnetron sputtering [33]. Following coating, the instruments were incubated for 24 and 48 hours in a growth medium containing *E. coli* or *Staphylococcus aureus* (*S. aureus*, 13 × 10<sup>6</sup> cells each), two common hospital-acquired infections, termed nosocomial infections [34]. By 48 hours, the bacteria were completely inactive.

In addition to silver, quaternary ammonium compounds are cationic surfactants that exhibit a wide range of biocidal activity (Fig. 3) [35,36]. Jiao et al.'s comprehensive review [35] describes in depth many of the benefits and drawbacks of these materials, which are briefly discussed here. Although the exact mechanism for their antimicrobial activity has not fully been described, quaternary ammonium compounds are understood to act through disruption of the cell membrane [35,37]. In this way, quaternary ammonium compounds are lethal to a broad spectrum of organisms, including bacteria (both gram-positive and gram-negative), fungi, parasites, and lipophilic (enveloped) viruses [35,38–39], though they have not demonstrated an ability to destroy hydrophilic (non-enveloped viruses), and they are not sporicidal, nor are they tuberculocidal [35,40].

Surface-immobilized quaternary ammonium compounds are currently being explored for orthopedic and dental related materials, sutures, and wound dressings [35]. A recent randomized, double-blind clinical trial investigating quaternary ammonium compounds in orthodontic materials demonstrated *in vivo* efficacy of these materials [35,41]. Thirty-two human subjects wore custom-made retainers designed to create 48-hour multi-species biofilms [41]. One side of the retainer was fabricated with 5% wt. quaternary ammonium methacryloxy silicate while the other side was not. The trial demonstrated effective biocidal activity of the quaternary ammonium compounds without harm to the oral mucosa or systemic health of the subjects.

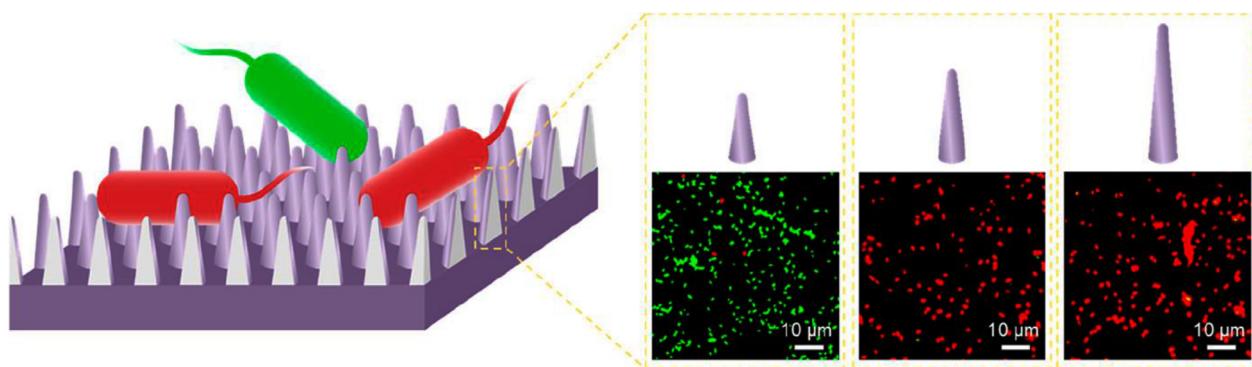
Despite the promise and advances of quaternary ammonium compounds in providing anti-microbial surfaces, its biocidal activities that extend beyond the microbial must be addressed before its widespread use. Recent reports demonstrate their toxicity and genotoxicity in water fleas [42] and genotoxicity in mammalian and plant cells *in vitro* [43] at levels found in commercial nasal sprays [44], which may potentially harm the ecosystem and human health. Recently it has been demonstrated in several mammalian cell lines that the cytotoxicity of quaternary ammonium compounds is not due to membrane disintegration or cell lysis as previously thought, but rather they induce disruption of

intracellular biochemical processes [35,45,46]. Further, low concentrations of quaternary ammonium compounds induce oxidative stresses and oxidative DNA damage, cause mitochondrial dysfunction, perturb cellular energetic mechanisms, and trigger apoptotic signals [35,42,47–48].

Quaternary ammonium compounds may accumulate in soil over time and when combined with other contaminants may alter soil environments and in turn result in bioaccumulation in soil organisms, which may ultimately lead to biological risks to other organisms [35,49]. Such risks may be compounded in the closed environment of a spacecraft. For instance, quaternary ammonium compounds and their degradation products have been detected in surface water, sediment, and sludge-amended soil, which is concerning because in addition to microbes, quaternary ammonium compounds by themselves are toxic to aquatic organisms [35,50–51], soil organisms [52], animals [42,53–54], and humans [50]. Additional toxicity data are needed to fully assess the possible biological and environmental risks of quaternary ammonium compounds and whether certain formulations are more specific in their microbial activity [35,55]. Theoretically, quaternary ammonium compounds cannot be released from quaternary ammonium-based materials; therefore, further characterization of the mechanisms of quaternary ammonium-related toxicity may permit the safe use of these materials [35]. For instance, antioxidants (e.g., N-acetyl cysteine) have been used to scavenge reactive oxygen species towards reducing the oxidative stress-induced cytotoxicity of quaternary ammonium compounds [56,57]. Another strategy to combat the toxicity of quaternary ammonium compounds has been to modify their molecular structures. For instance, PEGylating (covalently attaching polyethylene glycol, PEG) quaternary ammonium compounds fully prevents their hemolysis of human red blood cells [58,59].

#### 2.2.2. Surface topography

Biomaterial approaches that alter surface topography to create mechano-bactericidal properties may be advantageous for long-term use in both space exploration and on Earth. While selenium, silver, and quaternary ammonium compounds all have effective antimicrobial properties, they all pose the risk of environmental accumulation and contamination. Following the discovery that cicada and dragonfly wing surfaces contain nanopillar structures capable of physically killing bacteria [60–61], biomaterials with nanopatterned surfaces that exhibit bactericidal properties have been increasingly researched and refined in recent years (Fig. 4) [62,63,64–65].



**Fig. 4.** Fluorescence live (green)/dead (red) images of *E. coli* on varying nanopillar heights. Ref. [64]. Reproduced with permission from American Chemical Society.

A recent review article by Wu et al. describes recent advances using surface topography to inhibit microbial growth [66]. They highlighted the importance of microscale surface topographical features that either inhibit or promote biofilm formation. While anti-adhesion surfaces prevent microbes from attaching, bactericidal surfaces have special structures capable of destroying cell membranes. Surface properties that influence the ability to inhibit growth include surface charge, surface free energy, (e.g., superhydrophobicity), and surface roughness (e.g., nanopillars or other nanostructural shapes, or number of these per unit area). Biomimetic approaches that borrow from plants and animals capable of resisting biofilms, such as cicada and dragonfly wings, shark skin, and lotus leaves, have guided recent investigations. Methods to construct these surfaces included a variety of techniques to induce severe plastic deformation, grinding with abrasive particles, using lithography to construct patterns, nanoprinting, hot embossing, reactive ion etching, or laser ablation. These nanosstructured surfaces have been fabricated on aluminum and its alloys [67], gold [68,69], polycarbonate [64], polyethylene terephthalate [70], polymethyl methacrylate [71], quartz [72], black silicon [62,73,74,75,65], silicon wafer [76,77], titanium [63,78,79,80,81,82], and titanium alloy [83], which have all been extensively investigated for antibacterial purposes and hold the potential to transform contact-killing biomaterial surfaces. The range of microbes killed by naturally occurring mechano-bactericidal surface topographies and biomimetic surfaces include both gram positive (e.g., *S. aureus*) and gram negative (e.g., *Pseudomonas aeruginosa* and *E. coli*). The authors further noted that a major concern is to avoid adversely impacting the overall properties of the surface material while changing its topography, a critical consideration for use in space.

### 2.2.3. Wearable equipment

Though not considered a biomaterial on Earth, in the context of space exploration garments and equipment that have intimate and sustained contact with the skin may be an important area of investigation for biomaterials researchers, in keeping with the notion that any material the crew comes into constant contact with should serve multiple purposes, i.e., be biocompatible and promote crew health. For instance, garments and other materials have prolonged contact with the skin in space as there is no capability to launder garments and bedding in space. Clean clothes are brought up with a supply ship; dirty laundry is ejected into Earth's atmosphere to burn up [84]. A crew of 6 goes through 900 lbs. of clothing per year. Clothing resupply will not be an option for long duration missions. As it stands, clothes may be worn for weeks to months at a time. In some areas on the body, the prolonged contact can in many ways resemble that of a patch, and similar design criteria must be considered that might not typically be of concern

on Earth, e.g., comfortable clothing on Earth may become skin sensitizers in space.

EVA suits pose a particular challenge as they are complex individual mobile spacecraft that at present can only receive minimal service and repair while on orbit. In addition, suit components may be exchanged to accommodate multiple astronauts. Abrasions from extravehicular activity (EVA) suits and gloves are not uncommon (Fig. 5); crew may wear such gloves for up to eight hours or more. Throughout EVA tasks, crew wear maximum absorbency garments (adult diapers) to manage waste. Male crewmembers may wear condom catheters to direct urine. Worn over these are the form-fitting EVA coolant and pressure garments that include tubing routed throughout. The suit also has filters that scrub and revitalize the respiratory gases and must provide liquid hydration and nutrition for the crew during the hours-long excursions. The choice of such materials in these circumstances are particularly important as 1) the wearer has little ability to make adjustments to garments inside the suit during an EVA and 2) normal skin flora changes in space and pathogens become more virulent [85–86].

Another nontraditional opportunity to apply biomaterials towards supporting human space exploration is in minimizing the impact of maintaining clean or sterilized garments or bedding. The resources to launder clothing are minimal and carrying sufficient clean garments for a long duration mission that cannot be resupplied is not feasible. In addition, astronauts are constantly in contact with the surfaces of exercise equipment. Although these are not life and death concerns, advances in biomaterials could optimize such system components, significantly decrease payload launch weights, and increase crew function and effectiveness. One potential approach is through superhydrophobic surfaces.

Superhydrophobic surfaces, defined as surfaces displaying contact angles  $>150^\circ$  and contact angle hysteresis  $<5^\circ$  for water, are found in lotus leaves, geckos' feet [87,88], the legs of water striders [89–90], and are increasingly being used as biomaterials to control protein adsorption, cellular interaction, bacterial growth, drug delivery, and diagnostics [91,92]. Beyond biomedical applications, superhydrophobic surfaces have the potential to create stain-free clothing, which would not need to be washed.

Similarly, wearable health and performance monitoring instrumentation is critical for supporting astronaut health, but the duration of contact of these devices may exceed typical times on Earth. Additionally, the microbial environment in which they must operate is altered. Such devices should ideally be made of materials that are flexible, non-restrictive, can be securely attached to the body for an extended time without initiating abrasions, sensitizations, infections, nor deteriorations in functionality [5]. In conjunction with wearables, minimally invasive indwelling devices may provide more detailed physiological data without the potential complications and time required for blood, saliva, urine, or fecal collection, which are the current means for monitoring astro-



**Fig. 5.** Astronauts donning EVA suits and subsequent skin abrasions following an extended EVA. From Ref [255], courtesy of NASA.

naut health. In addition to long-term biocompatibility, durability, and small size, such devices should also be easily removed and replaced under the conditions of space exploration. Such capabilities would both support identification of individual crewmember health / performance issues and contribute to better understanding of human health, physiology and performance in space. Such an application was recently developed. In 2017 the FDA approved the first “smart pill” [93,94]. In combination with a wearable sensor on the patient’s abdomen, the pill digitally tracks whether patients have taken their medicine. These pills work for approximately a week at a time. Such technology could be adapted to monitoring astronaut health.

### 2.3. Intravascular access, hemodynamic support, and therapeutics

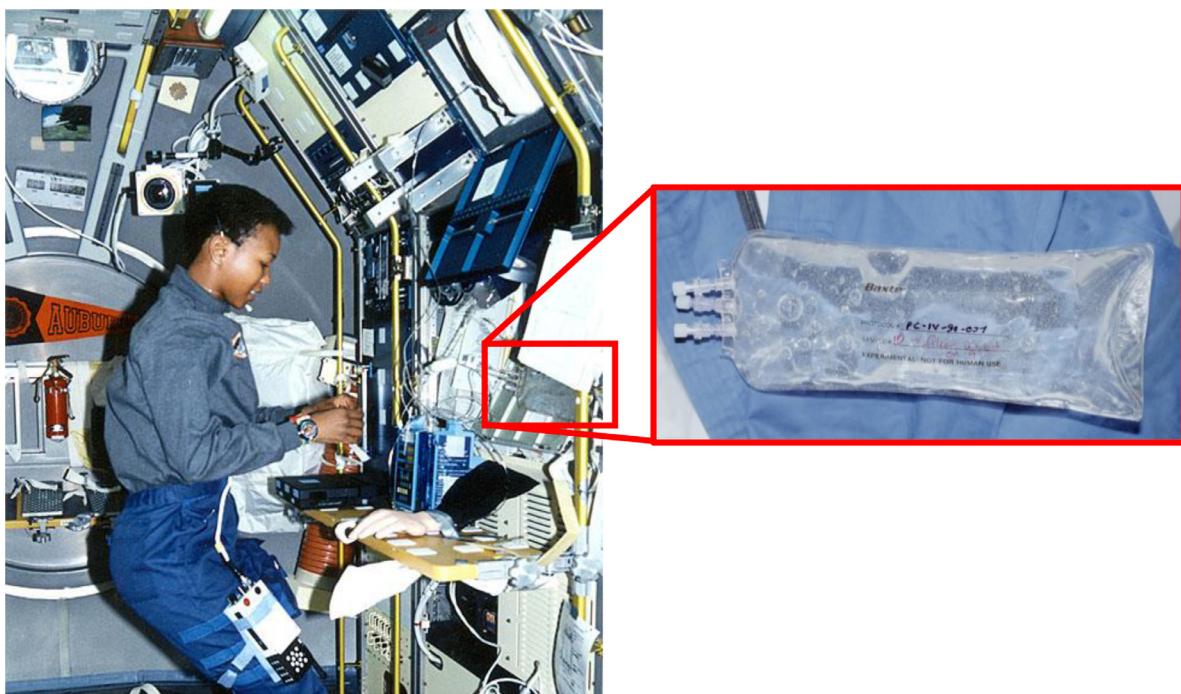
Intravascular volume loss or collapse can be the result of massive external or internal hemorrhage, dehydration (e.g., diarrhea, sweating), “third spacing” of fluid into body tissue or potential spaces (e.g., ascites in the peritoneum or swelling with limb crush injuries), and even sepsis. All of which impact hemodynamics, can be life threatening, and must be addressed quickly. In the space environment, the urgency is more pressing as microgravity significantly affects the circulatory system. Continuous human presence in space, especially as the distance from Earth and time required for return increases, requires robust, immediate access to therapies delivered through intravenous (IV) systems.

#### 2.3.1. Intravenous fluids and drugs

Delivering blood or fluids intravenously on Earth relies on gravity. Bubbles harmlessly float to the top of IV bags while gravity

drives fluid flow. In space, a pump is required to drive IV fluid flow but any bubbles present persist in solution, increasing the risk for air emboli. Beyond the difficulties with delivery, there remains the problem of launching and storing different IV solutions produced on Earth for months to years in space.

The first experiment to produce and test IV administration in space was the Fluid Therapy System (FTS) flown aboard the space shuttle STS – 47 Spacelab J (Fig. 6). The objective was to demonstrate the feasibility of generating a variety of safe, sterile IV solutions while on orbit and executing procedures to administer them. The Intravenous Fluid Generation (IVGEN) experiment onboard the ISS, Increment 23/24, during May 2010 also assessed a means to generate IV fluids on orbit. In both experiments, water was sourced from the crew water supply, which was a byproduct of the shuttle’s hydrogen-oxygen fuel cells that generated the vehicle’s electricity. Iodine is routinely added to crew water to inhibit bacterial growth. This potable water was next filtered and then introduced into IV bags containing specific dry chemical components to reconstitute mixtures into various IV solutions: 1) FTS chemicals generated Ringer’s Lactate, normal saline, or Dextrose 5% in Water (D5W) solutions, and 2) IVGEN normal saline. In testing the FTS, the crew inserted an intravenous catheter into a dummy arm and used an electric pump to deliver the reconstituted IV fluids. Upon return to Earth, the IV fluids from both FTS and IVGEN were demonstrated to be sterile. While the feasibility of generating IV solutions on orbit are bolstered by these studies, additional investigations must focus on removing air bubbles, ensuring desired chemical composition, and removing trace organic contaminants [95]. Remaining questions that biomaterials researchers could ad-



**Fig. 6.** Testing of the Fluid Therapy System showing the dummy arm for injection and the reconstituted fluids (inset) containing bubbles. Images courtesy of NASA.

dress is the integrity of the IV bags and catheters after sustained exposure to radiation and whether they begin to degrade and diminish their biocompatibility over time.

### 2.3.2. Hemorrhage in space

There are critical differences in the therapeutic needs and endpoints between intravascular volume expansion in the case of hemorrhage and dehydration. With dehydration, IV fluid administration as described above is often sufficient—rehydration or expansion of the intravascular volume is the primary therapeutic endpoint. With major blood loss, the remaining blood's oxygen carrying capacity as well as its clotting capacity may be severely compromised and both must be replaced, generally requiring infusion of blood or a blood substitute.

Adaptation to microgravity results in astronauts having significantly decreased total circulating blood volume compared to their levels on Earth in addition to altered cardiovascular vasoconstriction and vasodilation dynamics. Thus, what is a normal, healthy adaptation for microgravity results in a cardiovascular system that responds as if it has already suffered a large blood volume loss. Uncontrolled bleeding at a rate more than 100 mL/min in space is considered not survivable [96]. Hemostasis and blood volume replacement is critical in space.

**2.3.2.1. Hemostasis.** For externally accessible injuries, robust research in a variety of natural and synthetic biomaterials have led to hemostatic technologies including glues, bandages, tamponades, tourniquets, dressings, and procoagulant powders [97]. Any number of these would be suitable for human space exploration in an off-the-shelf manner. Hickman et al. recently reviewed hemostatic biomaterials and agreed with previous reports that hemostatic dressing technology had reached a plateau in efficacy [97,98]. The authors noted that most studies focused on the short-term effects of such dressings and called upon biomaterials researchers to evaluate such technologies for long-term *in vivo* effects, with a focus on biodegradation/resorption/removal pathways. They further noted that while various clinically approved options

existed for achieving hemostasis in externally accessible injuries, there were far fewer options for internal non-compressible hemorrhage, the management of which is often achieved by whole blood and/or blood's hemostatic components such as platelets, fibrinogen, and/or coagulation factors. On Earth, there are numerous challenges associated with transfusing platelets, including limited availability, high cost, contamination risks, short shelf-life, low portability, performance variability, and immunological side effects; however, using fibrinogen or coagulation factors, which have less challenges, provides only partial mechanisms for hemostasis [97]. These various challenges are magnified and perhaps insurmountable for space exploration. Whole blood can be stored at 2–6°C for 35 days [99], packed red blood cells for 42 days [100]; platelets for 5 days at 20–24°C [101]; and plasma for 3 years at temperatures below -40°C [102]. The operational costs and the energy required to refrigerate platelets and blood limit their potential use on current and anticipated space missions. Even if selecting crew with the same blood type was feasible, the possibility for adverse reactions arising from direct donor transfusions remain.

**2.3.2.2. Blood substitutes.** For these reasons, blood substitutes that can expand blood volume, carry oxygen and support respiratory gas exchange in the tissues may be a crucial for deep space human space exploration. Worthy of an independent review article specifically for their applications in human space flight, blood substitutes as used on Earth have many categories, successes, challenges, and requirements. Herein we highlight these to better inform and direct biomaterials research and development for these blood substitutes in support of human health in space.

Research aimed at developing blood substitutes has spanned 7 decades, yet to date there are no FDA approved oxygen-carrying blood substitutes [103]. Interest in blood substitutes has historically varied with perceived need. Research peaked in the 1980s with concerns over transfusion-transmitted infectious diseases [103,104] and decreased with reports of inferior performance and toxicity when compared to red blood cells. Rekindled research interest has focused on scenarios when red blood cell infusion is

not a viable option [104]. For instance, the majority of battlefield deaths are due to hemorrhage in locations far from blood banks [104,105]; blood substitutes would benefit patients with medical conditions such as myelodysplastic syndrome and aplastic anemia, which necessitate long-term blood transfusions [103]; patients who refuse transfusions for religious reasons; those who live in the developing world or are otherwise far from hospitals with blood banks; individuals who have rare blood types; persons who are in isolated and confined environments, such as arctic researchers, submarine crews, or astronauts. In any of these populations, an injury requiring both hemostasis and oxygen transport augmentation to survive would benefit from blood substitutes.

Prioritizing the desired characteristics of blood substitutes depends upon the therapeutic intent, e.g., volume expansion, hemostasis, immune system support, oxygenation. In general, beyond a minimal requirement to serve as a temporizing measure until transfusion with red blood cells is possible, the key considerations for the ideal blood substitute on Earth are remarkably similar to those for space flight. For space these are: 1) shelf stability, can be stored more than two years at ambient or room temperatures; 2) rehydratable, can be reconstituted with fluids on board; 3) not antigenic, does not require blood type matching; 4) sterilizable; 5) ease of administration; 6) metabolism and excretion do not damage the liver, kidneys, or the immune system and degradation products do not accumulate in body; 7) normal osmolarity; 8) minimal alteration to clotting mechanisms; and 9) a hemoglobin dissociation curve similar to whole blood under normal O<sub>2</sub> conditions. However, since the ideal substitute does not exist, there may be existing products that are sufficient when whole blood is unavailable. In addition to requirements for blood substitutes on Earth, such as a robust physiologically relevant oxygen carrying profile and an effective blood volume expansion, for use in space a blood substitute must be capable of being reconstituted in microgravity, have long-term shelf stability, minimal side effects, and simplicity of administration.

Oxygen must be maintained in sufficient quantities until it reaches the capillary network where it is most needed. Physiologically, oxygen dissociation curves represent the relationship between the oxygen tension and the oxygen saturation, where p50 is the oxygen tension when the substance of interest (e.g., hemoglobin) is 50 % saturated with oxygen. Inside red blood cells hemoglobin binds 2,3-bisphosphoglycerate (2,3-BPG; also referred to as 2,3-diphosphoglycerate, 2,3-DPG), facilitating release of oxygen through an allosteric effect. Hemoglobin has a sigmoidal oxygen dissociation curve [106–107]. Hemoglobin in red blood cells has a p50 of 26.7 mm Hg (3.5 kPa) [103], while tissues typically have a partial pressure of oxygen of 22.8 mm Hg (3 kPa) [108]. In short, hemoglobin still has oxygen to deliver when it reaches the tissues. The oxygen dissociation curve reflects how oxygen carriers deliver oxygen and is key to selecting effective blood substitutes (Fig. 7).

**2.3.2.2.1. Perfluorochemicals.** Liquid perfluorochemicals are synthetic, bioinert, hydrophobic, highly flexible and efficient carriers of most gases, including respiratory gases (O<sub>2</sub> and CO<sub>2</sub>) [106]. They have a low surface tension, are eliminated by evaporation, and an oxygen-carrying capacity three times greater than whole blood, enabling liquid breathing in humans and animals [109]. Also referred to as perfluorocarbons, they are fluorine-substituted analogues of saturated aliphatic hydrocarbons with linear, cyclic, or polycyclic molecules [106,109]. Because perfluorochemicals are immiscible in aqueous solutions, for use as a blood substitute they must be delivered as an emulsion [103,110]. When delivered intravenously, emulsion droplets are taken up and broken down by the reticuloendothelial system, transported to blood where they are bound to lipids, then eliminated through metabolism or exhalation following transport to the lungs [103].

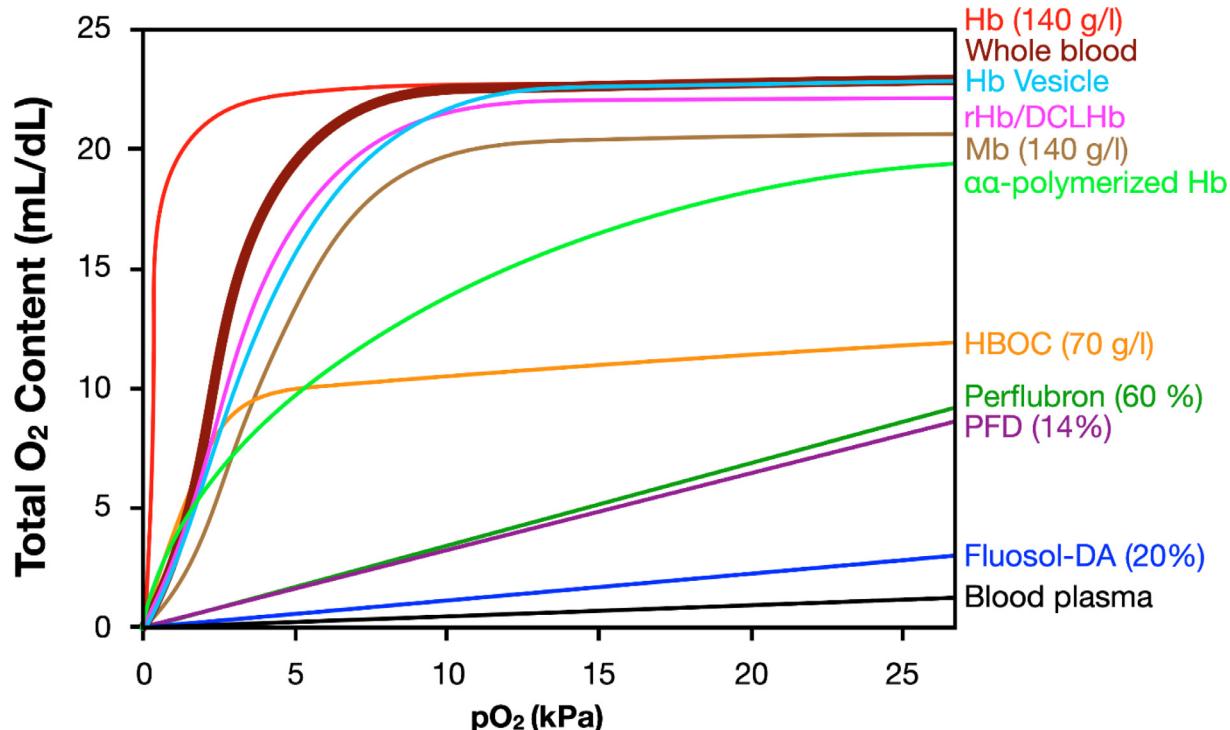
Perfluorochemicals do not reversibly bind to oxygen as hemoglobin does. Rather, oxygen is physically dissolved in perfluorochemical solutions, resulting in a linear oxygen dissociation relationship that corresponds to enhanced oxygen transport where partial pressures of oxygen are greater, such as in arteries, resulting in the release of most of the oxygen prior to arrival in the capillary network, where partial pressures of oxygen are the lowest and the tissue need for oxygen is the greatest [103].

In the 1980s, the first perfluorochemical marketed as a blood substitute, Fluosol-DA, comprised a 20% solution containing a 7:3 ratio of perfluorodecalin (PFD) and perfluorotripropylamine emulsified using Pluronic F-68 (poloxamer 188) [103,109]. When compared to whole blood it was found to be marginally effective, had a short effective half life, required frozen storage as it was unstable at room temperature, and was in general difficult to use [103,109,111]. Adverse effects such as acute complement activation and disruption of pulmonary surfactant limited the dose that could be delivered [103,109]. Second generation perfluorochemicals like Perflubron (C<sub>8</sub>F<sub>17</sub>Br) were investigated for use as a blood substitute. Oxygenet, an egg yolk phospholipid-stabilized perflubron emulsion, was FDA-approved in 1993 for use as a contrast agent in magnetic resonance, computed tomography, and ultrasound [109]. Despite a level of success in phase II and phase III clinical trials for cardiac and orthopedic patients wherein large blood loss was anticipated [112–113], ultimately significant problems were revealed for routine use in normovolemic applications including limited shelf life, post-surgical ileus, increased frequency of stroke and extended organ retention [112]; transient decline in platelet count [109,114,115]; reticuloendothelial system uptake with decreased phagocytosis until the perfluorochemical was excreted [109,116], of particular concern with the prevalence of hospital-acquired infections, and potential for oxygen toxicity in the lungs and other organs due to the elevated inspired oxygen concentrations needed for a therapeutic effect [109,117].

Despite these numerous setbacks, perfluorochemicals may yet have potential applications in space exploration. Within the last decade, researchers transitioned from emulsifications to techniques that nanoencapsulate perfluorochemicals into amphiphilic biopolymers [112]. The thin capsule wall lends the perfluorocarbon biocompatibility with the blood while allowing easy release or absorption of respiratory gases [118]. These perfluorochemical nanocapsules have been formed from poly(n-butyl-cyanoacrylate) or albumin and have shown promising results for use as both artificial oxygen carriers and as a treatment for decompression illness [112,118–119].

Sudden changes in pressure resulting from rapid ascent from underwater or during aerospace related events can lead to decompression illness, “the bends.” Although the pathophysiology of decompression sickness is not fully understood, it is generally accepted that a rapid reduction of pressure releases the dissolved nitrogen in the blood and tissues, resulting in the formation of gas bubbles that cause damage. Perfluorochemicals can scavenge and dissolve these gas bubbles and transport them to the lungs, reducing the morbidity and mortality of decompression illness [120]. When delivered intravenously in a high oxygen environment shortly after rapid ascent from depth in a swine model of decompression sickness, Oxycyte, a second generation perfluorochemical, reduced spinal cord injury over pigs receiving saline [109,121]. Nanoencapsulated perfluorochemicals are less toxic and more stable than these second generation emulsions [112,118–119], and their use as a decompression illness treatment is more feasible for treating potential decompression illness in space than is engineering the launch of a hyperbaric chamber.

An additional proposed use of perfluorochemicals for spaceflight is fully immersing the astronaut in the perfluorochemical to support pressurization of the EVA suit, or to enable astronauts

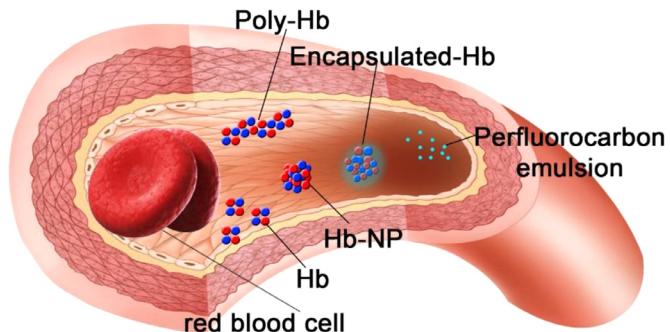


**Fig. 7.** Comparison of oxygen-carrying capacity of the blood substitutes hemoglobin based oxygen carriers (HBOCs), recombinant hemoglobin (rHb), bis-(3,5 dibromosalicyl)-fumarate (also known as Diaspirin) cross-linked hemoglobin (DCLHb), and emulsions of perflubron, perfluorodecalin (PFD), and Fluosol-DA against whole blood, blood plasma, stroma-free hemoglobin (Hb), or myoglobin (Mb). Image created based on data from Refs. [106,260–264].

to sustain greater external pressures and accelerations beyond the current 24 G limit without discomfort, since humans can tolerate higher accelerations when immersed in an incompressible liquid [122]. However, there remain significant challenges to using perfluorochemicals as an immersion liquid in space. For instance, 1) perfluorochemicals are too dense to breathe normally and require continuous mechanical ventilation, which is more challenging than gas ventilation [123]; 2) they must be oxygenated and scrubbed of carbon dioxide 4 times per minute [124]; 3) the pressures and flow must be precisely regulated to avoid mechanical damage to lung tissues [122]; and 4) they increase radiation sensitivity in tissues because oxygen is necessary for radiation-induced cell damage and perfluorochemicals increase local oxygen levels [125].

Nevertheless, perfluorocarbons may be useful as a blood substitute in space. A case series of 186 patients for whom blood transfusion was not an option reported that the drug Fluosol-DA [126] was well tolerated with stable hemodynamics [109,127] and with significantly increased arterial oxygen content for recipients of supplemental oxygen. Though compared to the gold standard of red blood cell transfusions, the success of perfluorochemicals was limited. When there is no other alternative, perfluorochemicals are better than no treatment.

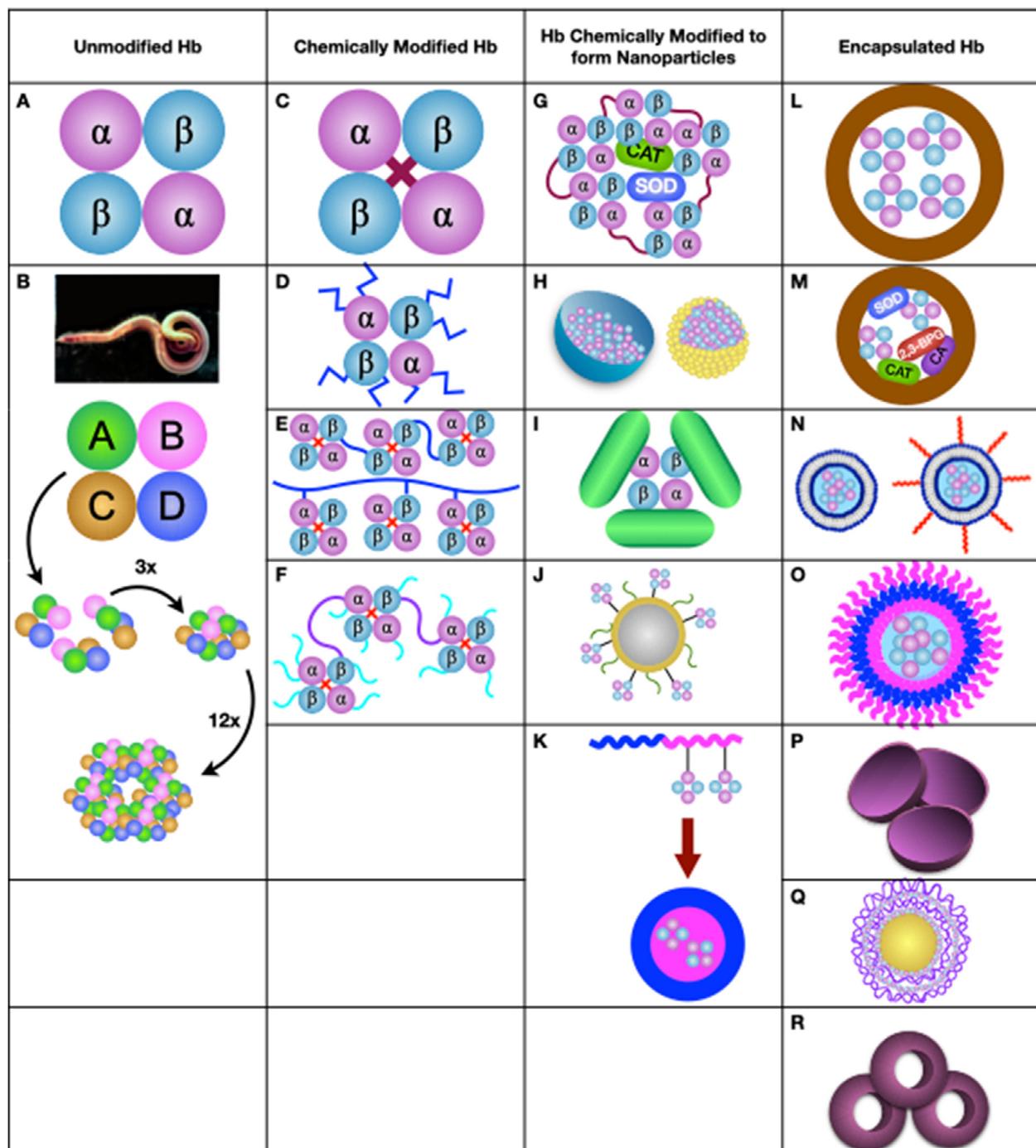
**2.3.2.2.2. Hemoglobin-Based Oxygen Carriers.** The majority of blood substitutes that have made it to advanced-phase clinical trials are all some form of hemoglobin-based oxygen carrier (HBOCs) [103,104]. HBOC research seeks to mimic the ability of hemoglobin in red blood cells to hold oxygen in sufficient quantities until it reaches the capillary network where it is most needed, while not requiring cells to be too hypoxic to release its oxygen. HBOCs are biological-synthetic hybrid systems that employ hemoglobin as the oxygen carrier. Generally, HBOCs are either chemically modified cell-free hemoglobin suspensions, hemoglobin that is conjugated and crosslinked with polymers and protective enzymes, or hemoglobin encapsulated into micro- or nanoparticle carriers [128–129].



**Fig. 8.** Blood substitutes sizes in comparison to red blood cells. Shown are stroma-free hemoglobin (Hb), unmodified, recombinant, or with crosslinked intramolecular subunits. Also shown are polymerized hemoglobin (Poly-Hb), encapsulated hemoglobin (Encapsulated-Hb), hemoglobin crosslinked to form nanoparticles (Hb-NP), and perfluorocarbon emulsions.

HBOCs have sigmoidal oxygen dissociation curves more similar to the oxygen-binding globular proteins such as hemoglobin (Hb) in blood, or myoglobin (Mb) in muscle [106–107,130]. Gupta et al. recently released a comprehensive review of available and emerging hemoglobin-based oxygen carriers [128] that are compared in Fig. 8 and summarized in Fig. 9. Here we provide a brief overview of the categories of HBOCs and their current and future potential to support human space exploration.

Stroma-free hemoglobin, also referred to as cell-free hemoglobin, is hemoglobin separated from red blood cells. It is not antigenic, does not require blood type matching, can be sterilized, and has a room temperature shelf-life of approximately 2 years, [131,132] all qualities that make stroma-free hemoglobin a promising candidate for space exploration. However adverse effects confound its use as a blood substitute including renal dysfunction, cardiovascular complications, hypertension, and coagulopathy



**Fig. 9.** Representative approaches and design schematics for hemoglobin-based oxygen carriers that are stroma-free (A-B), based on chemical modification (C-F; cross-linking, surface modification, polymerization, etc.), modification designed to form nanoparticles (G-K), or encapsulation (L-R). A. Stroma-free hemoglobin sourced from human, bovine, salmon, or recombinant blood. B. Giant extracellular hemoglobin (3,600 kDa) sourced from marine annelid blood. Image of annelid courtesy of NOAA. C. Stroma-free hemoglobin crosslinked between subunits (intramolecular crosslinking) using, for example, glycine, glutaraldehyde, O-raffinose, 3,5-dibromosalicyl fumarate, pyridoxal-5-phosphate, e.g., HemAsist, Hemopure, Optro, Hemolink. D. Stroma-free hemoglobin surface conjugated with maleimide-activated polyethylene glycol (Hb-Mal-PEG), e.g., Hemospan. E. Stroma-free hemoglobin intra- and intermolecularly crosslinked like a string of pearls or as pendants from polymer chains by crosslinkers such as glutaraldehyde, polyoxy ethylene, O-raffinose, e.g., PolyHeme, pyridoxylated hemoglobin. F. Bovine hemoglobin intramolecularly crosslinked with adenosine triphosphate, intermolecularly with adenosine, and finally with glutathione. G. Stroma-free hemoglobin intermolecularly crosslinked or polymer-bound with enzymes like superoxide dismutase (SOD), catalase (CAT), etc. that can promote efficient hemoglobin activity by maintaining redox activity. H. Hemoglobin coprecipitated with  $\text{CaCO}_3$  or  $\text{MnCO}_3$ , stabilized with crosslinking agents, then bound to anionic proteins (e.g., human serum albumin) to form clustered nano- or microparticles. I. Core-shell structured protein clusters of bovine hemoglobin (Hb) and human serum albumin (HSA) by linking Hb surface lysines to HSA cysteine-34 using  $\alpha$ -succinimidyl- $\epsilon$ -maleimide crosslinker. J. Hemoglobin conjugated to the surface of block copolymer-based core-shell nanoparticle structures. K. D. Hemoglobin conjugated to the hydrophobic region of a block copolymer followed by the formation of micelles from the polymer molecules to form hemoglobin-encapsulated micelle nanoparticles. L. Hemoglobin encapsulated within polymer membrane micro- or nanoparticles. M. Hemoglobin encapsulated with various redox enzymes (e.g., SOD, CAT, carbonic anhydrase CA, 2,3-BPG) within polymer micro- or nanoparticles. N. Hemoglobin encapsulated within sub-micron sized lipid vesicles (liposomes), bare or PEGylated. O. Hemoglobin encapsulated within sub-micron sized polymer vesicles (liposomes) made from amphiphilic block copolymers (e.g., PEG-PLA, PEG-PBD, PEG-PCL, etc.). P. Mechanobiologic mimicry of red blood cell morphology and are formed by lithographic or template-induced printing techniques. Q. Template-induced layer-by-layer assembly of cationic hemoglobin with anionic polymers (e.g., dialdehyde heparin), followed by dissolution of the template core. R. Nanobialys particles produced by conjugating the hydrophobic tail of amphiphilic polyethylene imine (PEI) molecules following self-assembly with recombinant hemoglobin, 2,3-BPG, and antioxidants in a reverse-micelle process. Images inspired by images and text in Refs. [128] and [287].

[103,104,128]; a propensity to split into immunoglobin-binding monomers that undergo rapid clearance by the reticuloendothelial system into the spleen and liver, leading to hemoglobin-induced toxicity; [128,133,134] a tendency towards irreversible oxidation into methemoglobin, thus permanently losing its oxygen transport capability [128]; and a very short circulation residence time. Removing hemoglobin from red blood cells also removes 2,3-BPG, increases its oxygen affinity, shifting its oxygen dissociation curve to the left relative to RBCs [103], rendering it ineffective at oxygenating tissues.

Efforts to address the issues with stroma free hemoglobin can generally be categorized into how the hemoglobin is modified. There are chemically modified, encapsulated or recombinant hemoglobin (rHb) HBOCs, [128,129,135–136]. The first rHb product (rHb 1.1) was a human hemoglobin variant genetically engineered to reduce its high oxygen affinity. rHb 1.1 had an increased shelf-life over red blood cells (refrigerated, 18 months vs 42 days) [103], but refrigeration requirement limits its usefulness for space exploration. Clinical trials of rHb 1.1 and a successor, rHb 2.0 were discontinued due to numerous adverse effects, including vasoconstriction, GI distress, fever, and backache [103]. The optimal combination of mutations to improve shelf-life and reduce adverse events has yet to be identified [128,137–138].

Sourced from human or bovine blood, chemically modified hemoglobins are altered through a variety of mechanisms, such as polymerization, cross-linking, macromeric surface conjugations, or adding organic phosphate to stand in for 2,3-BPG and adenosine triphosphate to stabilize the tetramer structures and reduce vascular endothelial extravasation [103,128]. Such formulations included products such as PolyHeme, Hemospan, HemoLink, Hemopure, and HemAssist, the last of which was invested heavily in by the US Army but adverse events such as increased risk of mortality and myocardial infarction in all five products stymied their further development and use [139]. However, Hemopure has been commercially available in South Africa for acutely anemic surgical patients since 2006, in Russia for anemia for any reason, and in the US for investigational or expanded access (formerly known as compassionate use) [126]. In space with no other option for a hemorrhaging astronaut, Hemopure might be sufficient as an interim measure.

Another approach in chemically modifying hemoglobin is to cause the hemoglobin molecules to form micro- and nanoparticles. Core-shell cluster structures were formed by conjugating hemoglobin to human serum albumin [140], calcium and manganese carbonates were used to coprecipitate hemoglobin into microparticles [128], and self-assembled hemoglobin-loaded micelles were formed by covalently conjugating hemoglobin onto block-copolymers [141,142]. The resulting nanoparticles have improved oxygen-binding capacity, redox properties, stability, reduced rates of clearance and extravasation, and improved intravascular half-lives [140,143].

Since the pioneering research in the 1950s where Chang et al. first encapsulated hemoglobin (then dubbed “hemoglobin corpuscles”) into cellulose nitrate and then polyethylene glycol-polylactic acid (PEG-PLA) [144,145], a variety of other polymers have since been used to encapsulate hemoglobin, including poly( $\epsilon$ -caprolactone)/poly(L-lactic acid) (PCL/PLA), poly(L-lysine) (PLL), poly(lactic-co-glycolic acid) (PLGA)/PEG, and amphiphilic block-copolymers [146,147]. Current approaches coencapsulate 2,3-BPG, reduce capsule sizes, and add lipid or polysaccharide surface modification in efforts to improve both polymer and lipid based vesicles to achieve uniform hemoglobin encapsulation concentrations and vesicle sizes, vesicle stability both in terms of shelf-life and intravascular half-life, pharmacokinetics, and complement-mediated immune responses *in vivo* [128], all while approaching oxygen transport properties analogous to whole blood [148–149]. Vesicles

with fully phospholipid and cholesterol membranes further improved upon polymer vesicles [150–151]; the encapsulation of hemoglobin into liposomal vesicles demonstrated high stability, increased intravascular half-life, and could withstand freeze-thawing, freeze-drying, and rehydration processes [128].

The most recent encapsulation approaches use biomimicry, creating biomechanical mimics of red blood cells in terms of size, shape, flexibility, and surface charge [128,152,153]. A variety of techniques have now demonstrated the formation of nanoparticles capable of mimicking the shape and/or size of red blood cells; that enhance the oxygen carrying capacity, redox properties [128,154], stability, and intravascular half-life of blood substitute candidates [128,155,156]; and have elastic moduli and elastic deformation *in vitro* that allow them to navigate narrow channels [128], although detailed *in vivo* oxygen transport properties have not yet been described.

#### 2.4. Wounds and wound healing

Alterations in tissue repair have been long documented in space [157,158] and may present complications to healing following the common abrasions reported during an EVA [159,160], other cutaneous injuries, or a surgery [161]. Microgravity affects wound healing both directly and indirectly, by changing the behavior of the cells that orchestrate wound healing and by decreasing the ability of the organism to withstand injuries in the first place due to tissue degeneration caused by microgravity-induced functional alterations of many organs and systems [162,163].

The delayed wound healing induced by microgravity differs in etiology from that of chronic wounds on Earth. Normal wound healing progresses through inflammatory, proliferative, epithelialization, and maturation/remodeling phases, while chronic wounds are arrested in the inflammatory phase, with immune cells continually degrading collagen and extracellular matrix as it is laid down. Microgravity-delayed wound healing is caused by impairment in individual components in the wound healing process. Specifically, microgravity impairs tissue repair mechanisms such as matrix formation, proliferation and migration of cells into wounds, collagen production, revascularization, and keratinocyte migration [164].

Using both actual and simulated weightlessness, researchers have demonstrated microgravity-induced alterations in fibroblast [162,165,166] and endothelial cell [167–168] production and behavior, differences in the cells involved in inflammation [164], altered extracellular matrix remodeling [162,169], and dysregulation in apoptosis [162]. In a sutured wound healing model in leeches, Cialdi et al. demonstrated that simulated microgravity caused a healing delay and structural alterations in the repair tissue, which were counteracted by platelet rich plasma treatment [170]. When the group also examined the effects of microgravity and platelet rich plasma on an *in vitro* wound healing model in fibroblasts, they showed that platelet rich plasma counteracted the microgravity-induced impairment in fibroblast migration. Platelet rich plasma is also effective in accelerating chronic wound healing [171].

While platelet rich plasma may successfully accelerate microgravity-delayed wound healing, the 3–7 day shelf-life of platelets [97] excludes its use as a healing agent for long term missions in space. The success of platelet rich plasma at treating microgravity-delayed wounds may suggest factors in platelet rich plasma may stimulate the individual components of wound healing affected by microgravity. Further, the success of platelet rich plasma at treating both chronic wounds and microgravity-delayed wounds suggests that other treatments effective in healing chronic wounds may also be effective in accelerating microgravity wound healing.

Ranging from natural, composite, to fully synthetic, there are a variety of clinically approved wound healing biomaterials that

may have both the long shelf life for space exploration and the capacity to reverse microgravity-induced healing delays. Some are more appropriate for burns, others for diabetic wounds, and others for chronic wounds. Each has its strengths and weaknesses; there is no single dressing that has been definitively identified as the best for any particular wound. Some wound healing biomaterials are formed through relatively simple polymerization techniques, paving the way for their potential fabrication to replenish expired stocks during a space mission. Because natural biomaterials may degrade over time, synthetic polymers are increasingly being explored. A NASA-patented electroactive wound healing device uses polyvinylidene difluoride (PVDF) fibers, poled to exhibit pyroelectric and/or piezoelectric properties such that when external stimuli such as body heat or increased pressure due to cell growth are applied, the fibers deliver an electric output to the wound [172].

It has been proposed that the ideal wound dressing would be able to [173–174]: 1) absorb wound exudate, 2) maintain a moist wound environment, 3) allow gas exchange, 4) provide thermal insulation, 5) prevent bacterial infiltration, 6) avoid harming the host, 7) stay in place, 8) be removed easily, 9) have good handleability, 10) be robust/resistant to wear, 11) have good conformability, 12) be easy to sterilize, 13) be non-immunogenic, 14) modulate proteolytic activity to reset chronic wounds to an acute state, 15) provide a bioresorbable scaffold that facilitates cellular migration and promotes cellular proliferation and matrix deposition, 16) recruit angiogenic and fibroblast cell types to synthesize granulation tissue, and 17) absorb and neutralize free radicals. For space, wound healing materials must also: 18) have a long shelf life, 19) be resistant to cosmic radiation, 20) not require gravity to function, and 21) be nonflammable in a 30% oxygen environment [7,8].

Hydrogels, which are formed by crosslinked networks of polymers that electrostatically or physically retain water, fulfill many of the criteria for ideal wound healing materials [175,176–177]. Hydrogels' water content is ideal for maintaining a moist wound environment; they permit gaseous exchange; they can be functionalized to prevent or signal bacterial infiltration; they can be designed to serve as a tissue scaffold; they are often used in burns and ulcers; and beyond not harming the host they are often described as relieving patient pain due to the cooling from their high water content and ease of removal due to their nonadherent nature [177].

Although hydrogels are resistant to radiation damage due to the dissipation of radiation energy by the comprising water and the polymer frame [178], this phenomenon has only been described for hydrated hydrogels. Therefore, although dried hydrogel dressings may not add unnecessary weight to the cargo that would be added by hydrated polymerized hydrogels, without water hydrating them, molecular bonds crosslinking the hydrogel into a network might be compromised during storage by cosmic radiation. A potential solution would be polymerizing the hydrogels as needed in space.

Uncrosslinked reagents generally have longer shelf lives than crosslinked hydrogels, though their stability under cosmic radiation remains unknown. Hydrogels can be formed into desired shapes a variety of ways, including 3D bioprinting or polymerization into molds. There are 3D bioprinters currently installed on the ISS and a growing number of researchers are investigating bioprinting in space [179–180]. Ahlfeld et al. demonstrated that personalized hydrogel bioinks could be formed from human blood plasma and biopolymers like alginate and methylcellulose [181]. In an assessment for the suitability of 3D bioprinting for space exploration, the group offered a scenario in which an astronaut donates 450–500 mL of their own blood to produce ~250 mL of plasma through centrifugation, thereby generating enough raw materials with ISS equipment to bioprint 1.103 cm<sup>2</sup> of artificial skin appropriate for wound healing using their system [179,182]. Although their system has only been evaluated *in vitro* as tissue engineering scaf-

folds for mineralized tissues, the constructs showed high viability of bioprinted mesenchymal stem cells.

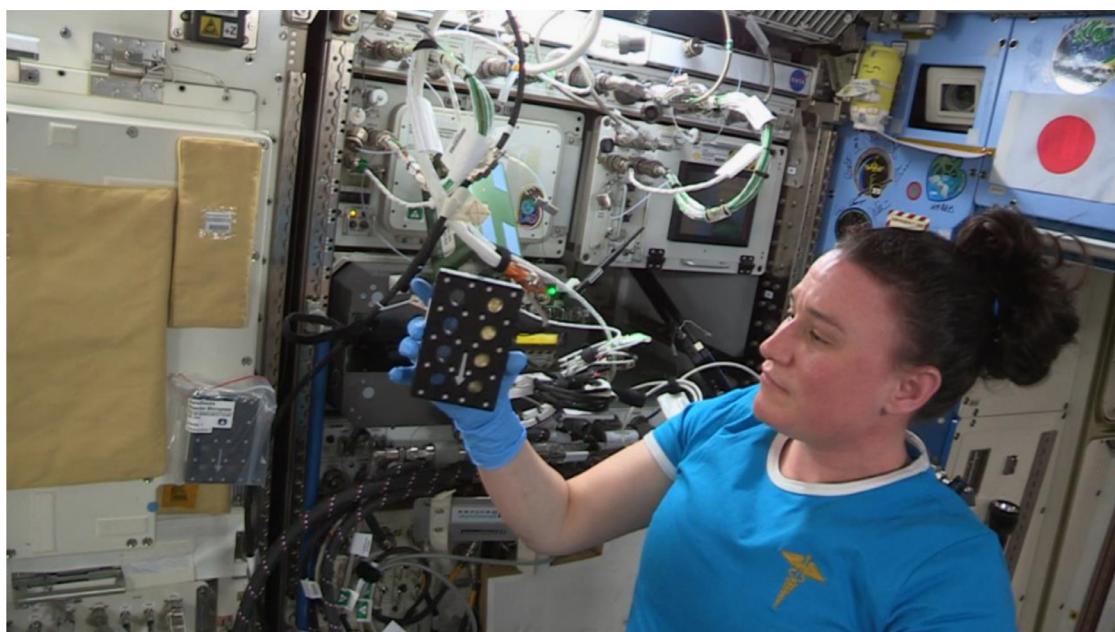
At the 100 Year Starship 2015 Public Symposium, Finding Earth 2.0, Magin et al. described a bilayered biodegradable hydrogel appropriate for space travel that mimics the topology of shark skin [183,184]. Their hydrogel dressing uses microarchitecture to guide re-epithelialization and revascularization, two key steps in the proliferative phase of wound healing. They evaluated the dressing *in vitro* in a cell migration assay and *in vivo* in a bipedicle ischemic rat wound model and found increased artificial wound coverage by up to 64% *in vitro* and significantly enhanced overall healing outcomes compared to untreated wounds. The benefit of their system for space applications is that the wound healing promotion relies on topography rather than pharmacological agents, which may degrade over time. Further, the dressings can be formed on demand and to fit any particular wound.

Rubinstein et al. described a hydrogel patch for the repair of perforated tympanic membranes [185]. Composed of photocrosslinked hyaluronic acid and modified chitosan, the hydrogels were reported to have inherent antimicrobial properties. *In vivo* evaluations in chinchillas demonstrated an 81% healing rate of perforated tympanic membranes, which they attributed in part to tensile forces exerted by the slightly dehydrating hydrogels. Following this success, they evaluated the hydrogels' suitability for wound healing in space [186]. The hydrogels were loaded with antibiotics and their rate of drug release was evaluated and correlated to the structural and mechanical properties of the hydrogel. By performing these analyses in space, the researchers were able to evaluate material properties without the confounding influence of gravity-driven phenomena (e.g., diffusion is influenced by density and buoyancy only in gravity). When compared to ground-formed hydrogels, the investigators found that hydrogels polymerized in space in general had similar mechanical properties. However, they detected differences in pore size and the structure (of the polymer network. In addition, they showed that diffusion of any size molecule progressed more slowly in the absence of gravity. The group is positioned to evaluate the hydrogel for *in vivo* studies in microgravity and is the only wound healing material as yet evaluated on the ISS (Fig. 10) [186].

## 2.5. Bone Repair

Bone remodels itself in response to its environment, and in the microgravity environment the decreased load bearing causes bone to be resorbed at a rate of ~1–3% per month [187]. Astronauts on long duration missions to the ISS have developed spaceflight osteopenia and osteoporosis. By reducing salt intake, preventing weight loss, and increasing resistance training, the loss can be reduced, but not eliminated [188]. As a result, astronauts on long duration missions are at increased risk of pathological bone fractures upon arrival to higher gravity environments, whether returning to Earth or arriving at other destination planets such as Mars. In addition, it is anticipated that fracture healing in microgravity environments will be impaired. Thus, fracture repair materials are of interest for human spaceflight.

Fracture repair has also long been an interest for the Department of Defense (DoD). Compound bone fractures occur frequently on the battlefield and are so difficult to repair that they often require multiple surgical attempts with extensive healing and rehabilitation times [189]. Standard treatments often lead to further complications and do not stabilize the fracture, delaying patient transport. As a result, in 2008, the DoD's Defense Advanced Research Projects Agency (DARPA) sought to develop a nontoxic, putty-like material that could be applied on the battlefield to immediately stabilize compound bone fractures and pro-



**Fig. 10.** NASA astronaut Serena Maria Auñón-Chancellor conducting wound healing experiments onboard the ISS. Image courtesy of NASA.

mote the rapid growth of new bone [190]. The goal was a “Fracture Putty” that would give wounded soldiers full load-bearing capabilities within days, create an osteoconductive bone-like internal structure, and degrade over time to harmless resorbable by-products as normal bone regenerates. DARPA gave three awards to: 1) the company Smith & Nephew, a global medical technology business, specializing in Orthopaedics, including Reconstruction, Trauma and Clinical Therapies, Endoscopy and Advanced Wound Management; 2) a team led by doctors Mauro Ferrari and Ennio Tasciotti of the Methodist Hospital Research institute in Houston that included researchers from Rice University, Northwestern University, and Harvard University; and 3) a team led by bone biologist Elizabeth Olmsted-Davis (Baylor College of Medicine), bio-engineer Jennifer West (Rice University), and orthopedic surgeon Michael Heggeness (Baylor College of Medicine) that included researchers at the University of Texas Health Science Center at Houston and the University of Georgia. In 2008, Smith & Nephew filed a patent for an epoxy-like “fracture putty” system that comprised a porous and hand moldable putty consisting of a polyurethane resin and a hydroxyapatite filler with particle sizes ranging from 5 – 4000  $\mu\text{m}$  that could contain BMP2 and antibiotics. The Ferrari-Tasciotti team developed an implantable scaffold designed to restore weight-bearing to a fracture while simultaneously promoting bone regeneration [191,192]. These scaffolds comprised collagen bioactive sponges with platelet rich plasma, polylactic-co-glycolic acid silicon-based nanoparticles, BMP2 peptide amphiphiles, and mesenchymal stem cells within a load-bearing, biodegradable, and biocompatible polymeric shell of poly(propylene-fumarate), a rigid polyester they used to stabilize the fracture while the other components repaired it [193]. When the implants were placed subcutaneously on the rear flanks of rats for 4 weeks, they generated new bone [194]. Rather than develop a cement that could stabilize the bone while it healed, the Davis-West-Heggeness team’s approach was to rapidly stabilize fractures by rapidly repairing the bone. By genetically modifying cells to release bone morphogenetic protein type 2 (BMP2), encapsulating them into polyethylene glycol diacrylate hydrogel microspheres, then injecting them into desired locations via syringe, the team was able to induce heterotopic ossification [195,196], fuse spines [197], and repair critical size defects in fibulas [198] and femurs [199] in as little as 1 week in mice, rats,

and sheep. In 2015, the technology was patented. Although none of the endeavors resulted in a putty that upon injection permitted immediate load-bearing as envisioned by DARPA, the program involved over 60 investigators and has since sparked a great deal of research in the area. The capacity to accelerate fracture repair during space missions remains one of the major technology gaps identified by NASA.

## 2.6. Surgery

Appendicitis, acute cholecystitis, and small bowel obstruction are all on the IMM list of 100 probable spaceflight medical conditions and all may require immediate surgery to resolve. In the weightlessness of space, open surgery would lead to floating blood droplets and fluids in the cabin, therefore laparoscopic surgery would be preferred. Without gravity, blood can pool around an incision like a dome, interfering with the ability to visualize the incision [96]. To address this problem, Hayden et al. developed a transparent, hermetically sealed, fluid-filled, self-healing surgical enclosure for microgravity through which laparoscopic devices might be inserted, preventing blood from pooling in domes at the site [200].

In anticipation of an emergency in space requiring surgery, researchers at NASA and the University of Lincoln-Nebraska have designed a miniaturized surgical robot to be inserted entirely inside a patient’s abdomen requiring only a single surgical incision or port (Fig. 11) [201].

Having a minimally invasive surgical robot to assist medical personnel on a space mission could prove beneficial, with communication delays factoring into whether procedures would be telesurgery or telemonitoring as 0.8 – 1 second delays are considered difficult for telesurgery and telemonitoring of a procedure is recommended instead [202] (e.g., ISS < 1 second delay [203], Moon 1.25 second delay [204], Mars 3–24 minutes one-way, depending on planetary positions [205]). However, one of the drawbacks of such surgical robots is that they are notoriously difficult to clean [206,207]. As described in the section on antimicrobial surfaces, this is where biomaterials may contribute.

Despite an increased use of biomaterial implants and the high complication rate involving implant-associated infections, very few



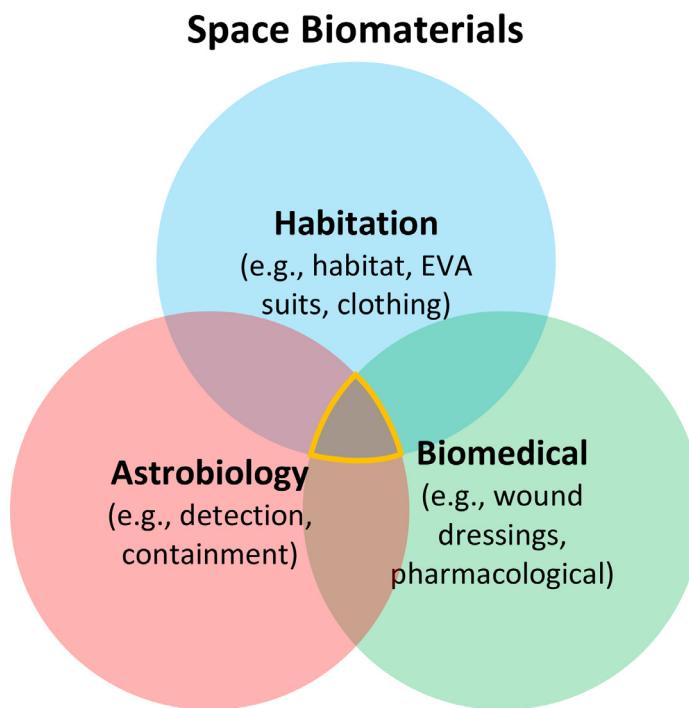
**Fig. 11.** Miniaturized surgical robot from Ref. [201], reprinted with permission from Elsevier.

biomaterials have been designed that effectively reduce the incidence of these infections [29]. In addition, implants are the most frequent targets for applying biomaterial surface coatings to reduce infection rather than applying them to surgical instruments and devices. Generally, surgical tools are autoclaved to sterilize them and tools used with robotic surgical procedures are disposable, neither of which are optimal for space exploration due to energy and storage constraints. Surgical site infections are not uncommon as the operating room is not sterile, and bacteria in the environment can fall directly into the patient or onto the tools as they are being used on Earth; in microgravity, bacteria may drift into what should be aseptic fields. Nosocomial infections are difficult to treat and lead to significant morbidity and mortality, and prophylactic postoperative antibiotics have been the standard of care in averting these infections. In the wake of antibiotic-resistant bacterial strains, the development of surgical tools that kill bacteria on contact may reduce recovery dependence on antibiotics, improve morbidity and mortality on Earth, as well as provide a viable means to provide shelf-stable sterile surgical tools for astronauts. The development of an antimicrobial coating for surgical tools and instruments could enable reuse without the need for an autoclave, potentially reducing the duration required for heat sterilization or replacing it altogether with simpler cleaning methods. An antimicrobial surface might prolong the shelf-life of autoclaved instruments, which remain sterile for 3 days – 24 months, depending on the method in which they are wrapped for sterilization [208,209]. Projected durations for missions to Mars range from 12–36 months [210].

### 3. Earth benefits of continued biomaterials research for space

Human space exploration has resulted in a myriad of discoveries and inventions that transformed technology so profoundly that our current era is commonly referred to as the Space Age. The communication satellites, contoured boots, filtration systems, and cordless drills that were developed to support the Apollo astronauts have directly enabled satellite radio and television [211], cell phones [212], GPS systems [213], the first shoe insoles [211], water filters [214], and cordless tools [215]. Scratch resistant and UV coated extravehicular activity (EVA) suit visors led to scratch resistant glasses and sunglasses [211,214–216], while clear protective TPA coatings for antenna led to invisible braces [211,217]. From improved radial tires [218] to enriched baby food [219] to ear thermometers [220], the products of space exploration have impacted every aspect of our lives while their origins have largely gone unnoticed.

Some innovations were directly translated—for instance, the invention of cordless drills for Apollo astronauts to drill Moon rocks led to consumer cordless drills. Other innovations have been serendipitous—a process for purifying and recycling water for Apollo astronauts led to sorbent dialysis for kidney patients requiring hemodialysis [221]. Common among the majority of these innovations is their benefit to life on Earth. The few innovations that did not immediately benefit society at large, such as advances in telehealth, benefitted workers in isolated environments such as Antarctic research stations, submarines, oil rigs, deployed soldiers, or many other remote locations throughout the world [222]. As the



**Fig. 12.** Space biomaterials are materials that are either biological in origin or biomedical in nature, but ideally can serve multiple functions critical for mission success. For instance, infection-detecting hydrogels that can also detect microbial life on off-planetary bodies or bacterial cellulose that can serve as clothing [233], habitation materials [234], and wound dressings [235]. Optimal materials would fall in the yellow triangle, fulfilling needs from each subcategory.

COVID-19 pandemic drives the need for more remote healthcare, that benefit expanded to society at large. Telemedicine and tele-health have exploded with faster and more data-dense transmission connections alongside improved imaging capabilities.

Biomaterials here on Earth have tremendous potential to benefit greatly from and contribute to the success of human space exploration. Yet, clarity around the definition of biomaterials in human space exploration is needed to fully exploit the potential and optimize collaboration among researchers concerned primarily with biomaterials on Earth and space researchers designing from the perspective of biologically derived materials and overall mission success.

Herein we have made the case that in the context of space exploration, the scope and purpose of biomaterials should be broadened. As demonstrated throughout the varied topics shared in this review, in space any biological material interfacing with the crew must be biocompatible (e.g., cannot off-gas toxic compounds) and ideally may be used to support life, thereby pushing the boundaries of Earth-based biomaterials. In other words, on Earth, biomaterials are biocompatible materials that interface with human tissue systems to serve a medical purpose, while in space, Space Biomaterials are the range of biologically derived and biocompatible materials that interface with human systems to help keep the crew alive, the ultimate medical purpose. And because every component of a space mission incurs significant resource costs – fuel, volume, energy and money – when designers consider using biological systems and materials derived from them in space, it is essential to exploit all the potential uses of such materials.

In addition, while biomaterials on Earth are biocompatible materials designed to be used in close contact with biological systems, tissues, and fluids to serve a medical purpose, this review aimed to demonstrate that in the context of space exploration, the environments are radically different and the needs multifaceted such that many nontraditional biomaterials serve a medical purpose. For space missions, biomaterials possess such a range of potential properties to exploit—flexibility, multi-functionality, ability to build

complex products from simple generic components, recyclability—that this makes them particularly compelling for addressing needs in space. Biomaterial substrates combined with other components available from other mission systems or *in situ* resources in a planetary environment could be used to produce not only medications and medical devices, but also shelter, energy, or food, while also supporting safety and mental health. The truly transdisciplinary insight, resources, and methodologies gained from using biomaterials in space would benefit not just space exploration but has the potential to advance biomaterials on Earth.

Importantly, beyond the notion that the space environment expands the categories to include clothing as a biomaterial, is the premise that biomaterials may have the capacity to serve multiple purposes in space. For instance, it is not difficult to imagine that wound healing hydrogels that are capable of detecting infection in wounds might be repurposed to detect microbial life on off-planetary sites, thereby minimizing the amount of cargo that must be launched.

Hence, for human space exploration, biomaterials researchers and researchers investigating biological materials for habitat structures may both benefit by expanding their definitions for biomaterials when referring to biomaterials used in space. We offer the term “Space Biomaterials.” For the biomaterials researcher, that would include bio-based habitats. For the bio-based space materials researcher, that would include synthetic biomedical materials. Any definition of Space Biomaterials should encompass the full range and multiple functions of such materials for space. In summary, we propose a definition (Fig. 12) that includes the traditional biomedical biomaterials, as well as materials intended to support crew living environments (such as habitats and clothing) and materials intended to detect microbial life on off-planetary sites in conjunction with materials intended to contain hitchhiking microbes from Earth that may confound results.

Space exploration and biomaterials science can benefit from purposeful targeting of biomaterials to solve unmet needs in space technology. Biomaterial innovations derived from space

are generally serendipitous or are a result of using microgravity as part of the manufacturing process. For example, Parylene ( $H_2C=C_6H_4=CH_2$ )<sub>n</sub>, a stable polymer that off-gasses virtually no volatile compounds, was developed as an ultrathin coating to protect circuit boards and other equipment in space [223,224]. These properties have rendered Parylene an excellent biomaterial to coat pacemakers, coronary stents, and surgical needles [225,226]. Conversely, retinal implants were not the incidental result of another application. Retinal implants require extremely thin and extremely even layers to protect the vision of the patient. On Earth, gravity creates a settling effect during the bonding process that makes the coating uneven; space is the only place these implants could be successfully produced [227]. Therefore, companies producing such implants sought partnerships with NASA, not the other way around. Thus, while there are incidental biomaterial advances resulting from space exploration, there are no such advances resulting from an identified need. In other words, the need for cordless tools to drill Moon rock was identified, developed, and now cordless power tools exist. This has not happened with biomaterials.

The microgravity of space provides a unique platform for investigating biomaterials, human physiology and other biological processes. Microgravity-induced alterations in the body's physiological mechanisms elucidate normal physiology and biochemistry on Earth. The Frog Embryology Experiment in 1992 highlighted areas for research with unexpected outcomes on embryogenesis in microgravity [228]. In another experiment, free flow electrophoresis in microgravity was used in a novel way to separate large, complex organic molecules and cells [229]. Certain proteins can only be crystallized in space [230]. And tissue engineered cartilage in space [231] may reveal the importance of gravity while multicellular spheroids [232] may pose a new platform for examining the impact of radiation.

Those designing and building space missions and systems may improve mission outcomes by recognizing the remarkable potential of biomaterials and integrating into the biomaterials an understanding, research methodology, and product capabilities from the beginning of any crew mission design process. Biomaterials offer a number of significant capabilities for space exploration that can be exploited including the following: 1) the ability to manipulate "blank slate" substrates to produce multifunctional materials; 2) the use of 3D printing to construct biomaterial implants, wound healing dressings, or other therapeutics or wearables could decrease the need to stock multiples of supplies that would deteriorate over time; and 3) biomaterials can be designed to be reusable, biodegradable, recyclable, or able to be repurposed for other processes in the resource-poor, need intense environment of space habitats.

#### 4. Conclusions

Although this is by no means an exhaustive review of all biomaterials that would be beneficial for spaceflight, the objectives were to: 1) consider how biomaterials' capabilities could support spaceflights of varying durations; 2) highlight characteristics of biomaterials needed to support space exploration; 3) show how biomaterials might overcome some of the primary obstacles to long duration spaceflight; 4) illustrate how biomaterials might be used to mitigate risks to human health that have no readily available solutions or ideal countermeasures; and 5) suggest an updated perspective from which to consider biomaterial investigations and their use in the context of space exploration.

For biomaterials to be successful in space, when specifying design criteria for the biomaterials' performance, five key characteristics of the space environment must also be considered: radiation, microgravity, microbes, fire resistance, and weight to launch. Several areas identified have made exciting new discoveries. Even

beyond use for surgical tools, contact-killing surfaces throughout the spacecraft would benefit long duration missions as throughout the ISS exist surfaces colonized with bacteria and fungi, which have a tendency to become more virulent in space [86]. While the prospect for a clinically approved blood replacement may be decades away, a suitable candidate for emergency use in space may already exist among the products currently approved for investigational and expanded use. However, none of these products have been evaluated in space. Similarly, there are no wound healing devices that have been evaluated on mammals in the space environment. The biomaterials researcher who does not typically investigate cosmic radiation may still have the tools to address ionizing radiation if their research involves nanoparticles. The ability of selenomelanin and melanin-nanoparticles to block ionizing radiation is a promising candidate for protection from cosmic radiation, though further research is needed to assess their ability to protect against other radiation besides X-rays. Colonization of the lunar surface and other planets will require autonomy and crew facilities unlike any on Earth and an ability to meet challenges that will evolve over time. As this review has aimed to demonstrate, the field of biomaterials has promising resources to meaningfully contribute to achieving deep space exploration, while improving health technologies on Earth.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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