THE GUY FOUNDATION

Quantum Biology and Space Health

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(Eds.)

Abstract proceedings of the 2023 Autumn Series

Driving innovation in medicine through quantum biology

Published December 2023

Contents

2023 AUTUMN SERIES:
QUANTUM BIOLOGY AND SPACE HEALTH

Introduction to the 2023 Autumn Series

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When living organisms, including human beings, travel to space they enter an alien environment that their biology has not evolved to deal with. Apart from the obvious risks, the launch involves being exposed to several minutes of excessive gravitational acceleration, but once in space, the complete opposite happens – microgravity. This is accompanied by increased exposure to various forms of radiation and high energy particles, as well as completely altered circadian stimuli. There are also changes in electromagnetic fields, both from the vehicle itself, but also regular shifts related to constantly moving through the Earth's magnetic field. Moreover, although in low Earth orbit the strength of Earth's magnetic field is not too dissimilar to that on the ground, beyond this there are almost no magnetic fields, which certainly from a quantum perspective, might be relevant to health.

What is clear at present is that the space environment causes health problems, which from a medical perspective appear to be associated with an accelerated ageing phenotype, not entirely dissimilar to the pattern seen on Earth when populations are exposed to a modern sedentary lifestyle, giving rise to the metabolic syndrome. One key biomarker they share are dramatic changes in mitochondrial function. Although this "space phenotype" can be "treated" to some degree by physical activity, much as it can on Earth, this treatment does not entirely compensate – indicating that astronauts are not living in optimal health. It does however hint at possible strategies, as exercise is well known to enhance mitochondrial function, as is a "healthy" diet, which supports the importance of nutrition; many plant compounds also stimulate a healthier mitochondrial population. Interestingly, it is possible that a species' ability to adapt to space may be dependent on its ability to evolve, implying that very short-lived organisms such as prokaryotes, may adapt very quickly, hinting that an astronaut's microbiome may evolve in unforeseen ways. Unfortunately, the difficulty in keeping humans healthy in space is perhaps compounded by the fact that we still don't fully understand some of our most basic biology, such as what ageing actually is, or even how life started. There are thus still some very "hard" questions in biology that we have not answered.

One approach to improve our understanding of how life works, and thus potentially how to tackle ageing and ill health, is to embrace the emerging awareness among many scientists that it is advantageous to incorporate the role that quantum mechanics and thermodynamics play in biology. This is not a new idea and many ranging from Niels Bohr to Erwin Schrödinger, to Albert Szent-Györgyi, to Ilya Prigogine and more recently, Roger Penrose, have suggested elements of it. Today, the field of quantum biology is rapidly expanding, with many scientists from multiple disciplines getting involved, as they are both developing and using new technologies to probe the inner workings of life. This includes accepting, as was said over 200 years ago by Luigi Galvani, that life is fundamentally electrical, one of the manifestations of which are bioelectric fields generated by ion distribution across membranes. Data is now emerging that shape, form and regeneration rely on this bioelectric field which seems to be integrated, with, for instance, epigenetics and mitochondrial function. Life can both generate and is sensitive to electromagnetic fields. It also seems to be able to detect lunar cycles in a way that is not dependent on photocycles. The concerns of quantum biology thus intersect with all of the questions pertinent to space health, but perhaps are also guiding us to new ways of thinking, for instance, how quantum mechanics can be integrated with gravity. The Guy Foundation's 2023 Autumn Series expanded on these ideas by inviting experts to speak about the different aspects of the space environment and what potential effects these may have on the human body and health.

The series began with a reminder that despite all our advances in technology, space travel is still very much a human pursuit. Retired NASA space surgeon and astronaut, Dr Tom Marshburn, gave a compelling description of what it is like to live and work in space. The presentation vividly communicated just how physically and mentally demanding space travel is, encompassing conditions at the extremes of what we are accustomed to across the spectrum of human experience: from acceleration to weightlessness; the roar of engines in the close confines of the shuttle to the silence and isolation of space; seconds of sheer terror and moments of euphoria.

What is less obvious, however, are the dramatic changes to the physical environment such as different levels of radiation and microgravity. It seems no wonder then that astronauts show distinct physiological changes. The rest of the series then took us through exactly what these changes involve and how they might be mitigated.

The first few sessions addressed the more high-profile aspects of space health research. These included the role of nutrition and exercise, as well as a focus on the physiological impact of microgravity and increased radiation. Mitochondria were central to the discussion, with evidence that their function is profoundly modulated by space travel and serves as a unifying factor for changes seen in disparate organs in the body. Mitochondria in space also offer insights into questions of accelerated ageing. In a way, mitochondria can be viewed as "canaries in the mine". Critically, they may be highly reliant on quantum processes, such as tunnelling, coherence and spin. Indeed, Nick Lane likes to call them "flux capacitors", which is actually a very good description of what they do – harnessing the movement of quantum particles to create enormous electric potentials (similar to a bolt of lightning). They therefore sit at the intersection of quantum biology and space health research. Mitochondrial function relies on electron and proton transport, hence REDOX, which is integrated with fundamental homeostasis and signalling molecules such as reactive oxygen species (ROS). Thus, as mitochondria are integrated with the cytoskeleton, one can see how changes in gravity will affect their function.

While the initial sessions focused on established avenues of research such as microgravity and radiation, the closing sessions sought to probe the horizons of space health research by investigating the possible effects of magnetic fields on biological systems. This included a detailed introduction to the quantum theory behind the radical pair mechanism as well as a demonstration of measurable outcomes of weak magnetic fields on stem cell dynamics and reactive oxygen species modulation. And finally, on a more speculative note, the experimental verification and possible biological relevance of quantum gravity was introduced and debated.

Introduction to The Guy Foundation

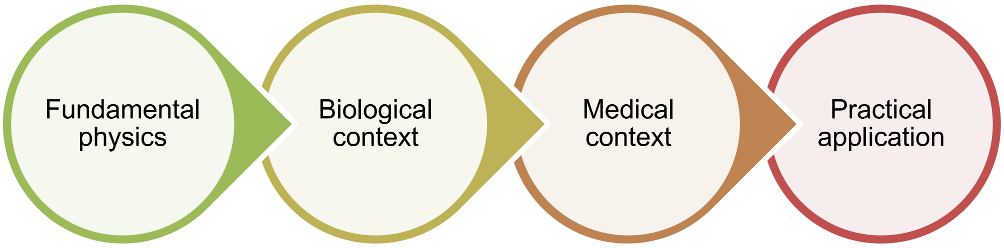
Professor Geoffrey Guy

Founder and Chairman, The Guy Foundation

The Guy Foundation aims to support and promote the investigation of quantum effects in biology, with the aim of improving our understanding of disease and thus medicine. Our belief is that significant quantum effects may well have been essential for life to get going, but also enabled it to grow in complexity by amplifying these effects both in space and time. All living systems depend on iron-sulphur compounds that display interesting tunnelling properties, which could be enhanced by the addition of proteins and chromophoric molecules. These molecules were all created by well understood geochemical/interstellar chemical processes long before life began, which coupled with established thermodynamic mathematical principles involving self-organisation of dissipative structures in energy gradients, do provide the basis of a starting point for life. In short, if significant quantum effects are part of life, the failure to maintain this state probably plays a role in disease and thus, the ageing process, and, of course, medicine.

The pioneers of thermodynamics and quantum physics, and – over the years – scientists, embracing many different disciplines, have discussed the possibility that biology could be using significant quantum effects. Some, such as Roger Penrose, have even gone as far as suggesting it could explain consciousness itself, which, even today in the 21st century, is still far from being understood. In fact, with time, despite the 20th century optimism that by the 21st century mankind would have found cures for cancer and many other diseases, and possibly even for ageing itself, a deeper understanding of life seems to be still out of reach. It could be even further away as emerging global obesity appears to be *shortening* both a healthy and absolute life expectancy, which is resulting in spiralling health care costs across the planet. Despite mankind's emerging technical mastery of nature, we still have a very long way to go in terms of truly understanding it.

The Guy Foundation thus leads, supports and contributes to quantum biological and related research with the ultimate aim of advancing the development of new medical diagnostics and therapeutics. The Foundation believes this advancement can be achieved in a number of ways, which is reflected by the research we fund as well as the cross-section of scientists invited to give presentations. Our approach is summarised as encompassing research from bench to bedside.



Our priorities encompass the spectrum of theoretical, experimental, and practical advances. Understanding the fundamental physics (e.g., quantum mechanics, electrodynamics, thermodynamics) is important. More specifically we aim to understand this physics within the biological and physiological contexts, with the emphasis on furthering the study of medicine. Overall, we would like to see this knowledge translated and applied in new diagnostics and therapeutics.

The Foundation therefore aims to provide a platform and a forum for upstream push through and downstream pull through of the understanding of the role of quantum effects in biology in health and disease. With an emphasis on building a research community to further investigate these interests, The Guy Foundation operates in a spirit of collaboration rather than straightforward grant funding, to advance the course of useful knowledge towards the mainstream and bring it to the attention of more conventional funders. We aim to do this in various ways. For instance, by curating a programme of scientific meetings and publications that incorporates the diverse aspects of the field and facilitates engagement from scientists across relevant disciplines; as well as by identifying what we see as research priorities and building a network of interested scientists through the funding of collaborative projects to accelerate relevant high-quality scientific research.

Abstract Proceedings

These are abstracts of a series of talks, hosted by The Guy Foundation, that were given online to an invited audience during the autumn of 2023.

They have been written by the presenters and have not been formally peer-reviewed. We hope you enjoy them; video recordings of the lectures are available on the Foundation's website **www.theguyfoundation.org**. To receive notifications about new videos, subscribe to our **YouTube channel**.

Session One: Day to day life of an astronaut and effects on health

Humans in Space: A Day in the Life

Dr Thomas H Marshburn

Sierra Space and retired NASA Flight Surgeon and Astronaut

View the video recording **here**

As an introduction to The Guy Foundation 2023 Autumn Series of symposia on space health, I was invited to give a firsthand account of what it is like to travel to space, focusing not only on the science, but also on the day-to-day life and health of an astronaut. In this talk, I presented a video and gave commentary on the experience of travelling to and living in space, as well as the perquisite training and preparation.

Space research and operations are by necessity highly technical and rigorously scientific. In terms of innovation, it is one of humankind's greatest achievements. The International Space Station (ISS), for example, is an astounding piece of engineering. As big as a five-bedroom house, it is the largest power station built and maintained in space. It houses a vibrant working laboratory with hundreds of experiments underway that include, among other things, a cold atom laboratory investigating matter at the level of individual atoms. However, it is important to be reminded of the humans this technology supports.

Life inside the ISS centers around a rigorous work schedule in its laboratories, yet retains a sense of play, with weightlessness adding novelty to everyday activities like eating and washing. However, crewmembers are constantly aware of the dangers inherent in space travel, and readiness to respond to emergencies responses, including executing a space-walk, quickly brings home exactly how much is at stake. Training for space is often aviation related to accustom astronauts to extreme physical conditions such as vibration and heat stress, as well as hone skills essential to working as a team in a confined space: mutual safety, communication, and rapid decision-making. In addition to this, astronauts are trained in novel environments such as underwater habitats.

Space travel is challenging, both physically and mentally. From the increased accelerations of take-off and re-entry to the disorientation of weightlessness, it takes at least weeks and sometimes months to fully acclimate physiologically, emotionally and mentally to living in space. Familiar tasks must be relearned in this completely novel environment. Hours of exercise are mandatory to maintain the health of different organ systems and prevent accelerated ageing. Despite this careful monitoring, astronauts still exhibit a number of physiological changes. These range from neurovestibular disorientation during transitions between one- and zero-g environments, to oedema, ocular problems, cardiovascular atrophy, bone density and lean body mass losses, and as yet unknown effects of ionizing space radiation. While some of these changes can be mitigated, some are more permanent. Vision changes and retinal anatomy can be altered, and bones remineralise and rebuild with different architectures.

Space remains a uniquely stressful environment, a profound reminder of the balance of nutrition, exercise, and rest that is essential to human survival. As astronauts, we know our life, indeed our survival, in space is underpinned by the research from many teams of scientists. I continue to be excited by the prospect of further research which continues to build on our present day understanding.

The role of nutrition

Dr Scott M Smith and Dr Sara R Zwart

Human Health and Performance Directorate, NASA Johnson Space Center
University of Texas Medical Branch, Galveston, Texas

View the video recording **here**

Space exploration is physically and physiologically challenging. Nutrition provides the underpinnings of health – on and off the planet (1). NASA's Nutritional Biochemistry Laboratory supports both operational and research protocols to help ensure astronaut health before, during, and after flight.

A nutritional assessment protocol includes pre- and postflight evaluation of a host of biochemical markers reflecting protein status, vitamin and mineral status, bone health and renal stone risk, hematology, lipids, and more. During flight, body mass and dietary intake are monitored, with real time feedback to the crew, and weekly reports provided to the Flight Surgeon. Like the ISS itself, this has been in place for more than 20 years, and there are many examples of how this helped astronauts meet mission objectives while maintaining health.

Research is conducted to better understand how physiology changes in weightlessness, and how to counteract any negative effects. Ground analog research is critical for expanding research opportunities. Analogs simulate elements of space flight, and while no one analog is perfect, they each provide unique advantages to model specific aspects of space flight. Examples of analogs include head-down tilt bed rest studies, studies of crews wintering over in Antarctica, multi-week hyperbaric exposures at the bottom of the ocean, and closed chamber studies evaluating crew behavior and performance. One key example is the ongoing Crew Health and Performance Exploration Analog (CHAPEA) mission, a 378-d stay in a 3-d printed habitat at the Johnson Space Center in Houston, where we are conducting a Mars surface mission simulation (https://www.nasa.gov/humans-in-space/chapea/).

Space flight research is often challenging and constrained for many reasons. Small numbers of astronauts participate in many competing experiments, limited crew time, limited up and down mass, limited conditioned storage, and the challenges of weightlessness itself. Nonetheless, we have managed to conduct several flight experiments over the past two decades, and have published findings on effects of spaceflight on vitamins, minerals (2-5), and hormones (6). We have documented dietary effects on bone health (7, 8), and effects of oral contraceptive use on hypoalbuminemia and venous thromboembolism risk (9). A key line of research has documented that the optic disc edema which affects approximately 20% of astronauts is genetically predisposed (10). Specifically, genetic differences in one carbon metabolism affect B vitamin requirements, and potentially affect the vascular and/or structural biochemistry leading to what NASA has dubbed SANS: Spaceflight-Associated Neuroocular Syndrome (11, 12). An experiment being conducted on the ISS right now is testing a B vitamin supplement countermeasure.

As humans move beyond low-Earth orbit and seek to establish extended, if not permanent presence on the Moon and Mars, nutrition will be critical for the maintenance of crew health and ultimately for mission success. As explorers on Earth often found, nutrition can make – or break – your expedition. Uniting the many disciplines which comprise the human system with the engineering of spacecraft will be a significant challenge, but daring to leave the planet demands this collaboration.

References

1. Smith SM, Zwart SR, Douglas GL, Heer M. Human adaptation to spaceflight: The role of food and nutrition. 2nd edition (NP-2021-03-003-JSC). Houston, TX: National Aeronautics and Space Administration Lyndon B. Johnson Space Center; 2021.

2. Smith SM, Zwart SR. Magnesium and Space Flight. Nutrients. 2015;7:10209-22.

3. Smith SM, Heer M, Shackelford LC, Sibonga JD, Spatz J, Pietrzyk RA, Hudson EK, Zwart SR. Bone metabolism and renal stone risk during International Space Station missions. Bone. 2015;81:712-20.

4. Smith SM, McCoy T, Gazda D, Morgan JLL, Heer M, Zwart SR. Space flight calcium: implications for astronaut health, spacecraft operations, and Earth. Nutrients. 2012;4:2047-68.

5. Zwart SR, Morgan JLL, Smith SM. Iron status and its relations with oxidative damage and bone loss during long-duration space flight on the International Space Station. Am J Clin Nutr. 2013;98:217-23.

6. Smith SM, Heer M, Wang Z, Huntoon CL, Zwart SR. Long-duration space flight and bed rest effects on testosterone and other steroids. J Clin Endocrinol Metab. 2012;97:270-8.

7. Zwart SR, Pierson D, Mehta S, Gonda S, Smith SM. Capacity of omega-3 fatty acids or eicosapentaenoic acid to counteract weightlessness-induced bone loss by inhibiting NF-kappaB activation: from cells to bed rest to astronauts. J Bone Miner Res. 2010;25:1049-57.

8. Zwart SR, Rice BL, Dlouhy H, Shackelford LC, Heer M, Koslovsky MD, Smith SM. Dietary acid load and bone turnover during long-duration spaceflight and bed rest. Am J Clin Nutr. 2018;107:834-44.

9. Zwart SR, Aunon-Chancellor SM, Heer M, Melin MM, Smith SM. Albumin, oral contraceptives, and venous thromboembolism risk in astronauts. J Appl Physiol (1985). 2022;132:1232-9.

10. Zwart SR, Gregory JF, Zeisel SH, Gibson CR, Mader TH, Kinchen JM, Ueland PM, Ploutz-Snyder R, Heer MA, Smith SM. Genotype, B-vitamin status, and androgens affect spaceflight-induced ophthalmic changes. FASEB J. 2016;30:141-8.

11. Zwart SR, Gibson CR, Gregory JF, Mader TH, Stover PJ, Zeisel SH, Smith SM. Astronaut ophthalmic syndrome. FASEB J. 2017;31:3746-56.

12. Zwart SR, Laurie SS, Chen JJ, Macias BR, Lee SMC, Stenger M, Grantham B, Carey K, Young M, Smith SM. Association of genetics and B vitamin status with the magnitude of optic disc edema during 30-day strict head-down tilt bed rest. JAMA Ophthalmol. 2019;137:1195-200

Session Two: Mitochondria in space

Maladaptive reversion: does living in space result in an accelerated ageing phenotype?

Professor Alistair Nunn

Director of Science, The Guy Foundation and Visiting Professor, University of Westminster

View the video recording **here**

Phenotypically, it seems that when humans spend time beyond the Earth's surface in space, they exhibit all the hallmarks of inflammaging, including mitochondrial dysfunction. Thus, astronauts could well be acting as an unfortunate model for an accelerated ageing phenotype often associated with a poor lifestyle on Earth. The question is which of the various "out of evolved environment" factors is the most important, and why.

Two of the key ones, long discussed, are a lack of gravity and increased levels of radiation, suggesting that spacecraft will need both heavy shielding and artificial gravity for long journeys, especially when outside of the Earth's magnetosphere. One of the ways to view this with regards the former, although it may also be affected by the latter, is that it seems that mild mitochondrial stress, called mitohormesis, which upregulates cellular robustness and maintenance of the ATP/reactive oxygen species (ROS) ratio is an evolved requirement to maintain optimal health. In short, the right kind of mild stress, for instance, physical activity, changes in oxygen, water and temperature, as well as many secondary plant stress compounds, are key. However, the stressors must remain within a metabolic flight envelope, or Goldilocks zone, which has been canalised by millions of years of evolution. In effect, mitochondria are a good canary in the system to indicate problems if the system is exposed to conditions outside of this – especially the *removal* of normal hormetins, which is a kind of "underload stress". Interestingly, exercise is still one of the most powerful ways of keeping astronauts healthy, stimulating both mitochondrial function and anti-inflammatory systems right throughout the body. Data do indeed suggest that hypergravity can induce many potential benefits, which is what would be expected, as humans have evolved putting a lot of stress on their systems, for instance, running, jumping, lifting and carrying things, but very rarely, if ever, did they ever experience something akin to continual reduced gravity, apart from when falling out of a tree, or off a cliff, which usually didn't end well. This ties in well with the concept of tensegrity and the integration of mitochondria with the cytoskeleton.

But what about radiation? Evidence is that small amounts of radiation, which are naturally occurring, can induce beneficial adaptive effects, and the pathways are similar to that invoked by many other stressors – but too much, as we know, induces damage. The commonality, both with adaptation and damage, is of course ROS. However, humans have never been exposed to very high energy particles, such as those ejected from the sun or as galactic cosmic rays, because we have been protected by the magnetosphere. One of the underlying signalling mechanisms in all of this is of course redox, and thus, ROS, which brings us to the role of quantum mechanics and thermodynamics, and a potential explanation derived from life as a far from equilibrium self-organising dissipating structure that as a group, act to equilibrate energy potential and thus fulfil entropy's arrow. Adaptive thermodynamics suggest that life will always get more complex, as this enhances dissipation of energy by retaining information and the ability to adapt leading to increased longevity. However, beyond a certain level of stress, these structures cannot survive, so there has to be a reversion to simpler, shorter-lived structures that can explore the "phase space" through natural selection. What this might suggest is that to a degree, ageing is adaptive, and may represent a failure to maintain, for instance, efficient electron transport, hinting at a breakdown of the proposed role of quantum tunnelling in this process. This could also be tied in with quantum spin, which is well known to be affected by magnetic fields, and for instance, the use of triplet states in normal homeostasis, which comes back to redox again. This programme is likely ancient, suggesting that inflammaging in complex organisms under the wrong kind of stress is a reversion to this.

The profound implication is that simpler organisms, especially prokaryotes, may well adapt through natural selection to space travel very quickly, but humans, alas will not. This would further suggest that the combination of increased levels of radiation, especially of types not previously encountered during evolution, with microgravity, and potentially, a lack of Earth's magnetic fields and circadian rhythms, which are also tied into these systems, will make matters worse as indicated by rising mitochondrial stress. In short, the accelerated ageing "space phenotype" represents the activation of an ancient programme that is trying to adapt to a new set of circumstances – the ROS signal is part of this but may fall outside the hormetic (biphasic) adaptive curve of the human metabolic flight envelope. However, it does hint at possible mitigation strategies, such as artificial gravity and shielding, as well as the use of drug- and EMF/photonic-based exercise mimetics.

Quantum mitochondria and space flight

Professor Douglas C Wallace

The Children's Hospital of Philadelphia (CHOP) Research Institute

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Long duration space flight perturbs mitochondrial function resulting in reduce oxidative phosphorylation (OXPHOS) energy production, increased reactive oxygen species production, elevated inflammation, and compensatory induction of mitochondrial DNA (mtDNA) transcription to varying extents in kidney, spleen, thymus, and eye. OXPHOS generates energy by the flow of electrons (S = ½) through complexes I, III, and IV of the electron transport chain (ETC) with pump protons (S = ½) into closed, confined, cristae lumens. Presumably this generates an intense electrostatic field since the cristae align in adjacent mitochondria. The mitochondrial cristae membrane potential oscillates as detected by the oscillating uptake of the cationic tetraphenylphosphonium (TPP^+) dye or by sensing electromagnetic field (EMF) oscillations using carbon nanotubes. These mitochondrial oscillations may result from the ETC pumping protons into the cristae lumen for which the maximal membrane potential is rheostated by the lipid-activated voltage-sensitive adenine nucleotide translocator (ANT) proton channel. Autism patient brains have altered magnetic field emanations and alterations in mitochondrial genes can manifest as autism phenotypes in both mice and humans with electroencephalograph alterations. Hence, mitochondrial oscillations are associated with brain magnetic field oscillations. Flavins are among the OXPHOS electron carriers. As single electrons travers flavins they can interact with the spin states of adjacent electrons in either singlet or triplet states. These quantum states favor either one or two electron transfer to O_2 to generate H_2O_2 versus $O_2^{\bullet-}$. Within the context of the Earth's 50 µT magnetic field, cells subjection to a 1.4 MHz EMF parallel or perpendicular to the magnetic field can bias energetics toward OXPHOS versus glycolysis (**PMID27995996**). Shielding Earth's magnetic field alters H_2O_2 production (**PMID21887222**). Therefore, mitochondrial quantum bioenergetics may be directly linked to exogenous and endogenous magnetic fields. Since magnetic fields are absent in deep space this might adversely affect astronaut bioenergetics.

Mitochondrial stress as a central biological hub for spaceflight impact

Dr Afshin Beheshti

Blue Marble Space Institute of Science

View the video recording **here**

Investigating the biological repercussions of spaceflight through innovative methodologies is imperative for minimizing health hazards faced by astronauts during extended space missions. The current established health risks due to spaceflight are only reflecting known symptomatic and physiologic responses and do not reflect early onset of other potential diseases. Numerous unidentified variables still demand identification to comprehensively grasp the health implications arising from the space environment. Our previous research highlighted the mitochondria as a central hub of dysregulation during spaceflight. We are now delving deeper into specific mitochondrial functions and genes experiencing dysregulation across various organs. This analysis encompasses both mice subjected to International Space Station (ISS) conditions and data from astronauts partaking in the Inspiration 4 mission and a Japan Aerospace Exploration Agency (JAXA) mission on the ISS. Our findings reveal inhibitory effects on genes and pathways linked to oxidative phosphorylation (OXPHOS) in the majority of organs in spaceflight mice. This inhibition triggers a cascade effect leading to upregulation of hypoxia (via the HIF1α pathway), increased stress responses (involving integrative stress response genes and suppression of innate immune activity), and pathways culminating in cell death. Additionally, we explore potential strategies for developing countermeasures, focusing on inhibiting key microRNAs (miRNAs) associated with spaceflight that impact mitochondrial function. Furthermore, we address how mitochondrial changes may specifically affect the female reproductive system. Of particular concern is investigating the potential amplification of health risks in future pregnancies due to spaceflight that may result in Small-for-Gestational-Age (SGA) fetuses with birth weights below the 10th percentile. We identified a common miRNA signature shared by SGA and the space environment. This signature, conserved between humans and mice, targets genes and pathways related to diseases, developmental issues, oxidative stress, and mitochondrial functions. To mitigate these risks, we utilize a machine learning framework to identify potential small molecule FDA-approved drugs targeting the SGA miRNA signature. Our analysis suggests that estrogen and progesterone receptor antagonists, vitamin D receptor antagonists, and DNA polymerase inhibitors may serve as countermeasures to address the impact of space travel on female health. Overall, our work underscores the profound effects of spaceflight on mitochondria and offers potential countermeasures to mitigate mitochondrial damage and associated health risks.

Session Three: Microgravity and radiation effects

Effects of Mars Mission-Equivalent Doses of SEP/GCR Radiation and Simulated Microgravity on the Human Hematopoietic System and Astronaut Cancer Risk

Professor Christopher D Porada and Professor Graça Almeida-Porada

Wake Forest Institute for Regenerative Medicine

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Future missions beyond LEO will expose astronauts to the poorly defined health risks of space radiation consisting of SEP and GCR that include HZE nuclei. While their flux intensity is fairly low, the RBE of HZE particles is not fully understood, complicating risk estimations. The hematopoietic system is extremely radiosensitive, and leukemias are a frequent radiogenic cancer - they also exhibit short enough latency to compromise a Mars mission. In ground-based studies at the NASA Space Radiation Laboratory, we used “humanized” mouse “avatars, whose hematopoietic/immune systems were repopulated with human hematopoietic stem cells (HSC) from healthy astronaut-age donors, to accurately define the risk of hematological malignancy following acute exposure to Mars mission-equivalent doses of SEP/GCR radiation. We reported the first-ever HZE ion-induced human leukemia [**PMID: 27881872**] and have found that the incidence and severity of splenomegaly (as a readout for abnormal proliferation of human hematopoietic lineages in vivo) increases in an LET-dependent manner. Histopathological analysis of enlarged spleens is ongoing to characterize possible radiation-induced malignancies. While radiation-induced cancer is NASA’s top “red risk” for prolonged missions in deep space, exposure to microgravity is known to produce myriad alterations in immunity, which led us to hypothesize that astronaut cancer risk may be greater than predicted by radiation exposure alone. We therefore performed studies to determine whether microgravity impacts the ability of the human immune system to recognize and eliminate hematological cancers. Our studies show that microgravity impairs the ability of HSC to repair DNA damage and to differentiate into dendritic cells, key immune sentinels that detect tumors and prime an effective immune response [**PMID: 29901426**]. We also showed that microgravity markedly impaired the cytotoxic activity of human NK cells, one of the body’s first defenses against cancer, against hematological tumors. Collectively, these data raise the possibility that astronaut cancer risk may, indeed, be further increased by conditions of microgravity present during spaceflight. We hope these ongoing efforts will better define, characterize, and ultimately lead to effective means of mitigating the damaging effects of space radiation and microgravity on the human hematopoietic system to enable safe long-duration missions beyond LEO. This work is supported by TRISH through Cooperative Agreement NNX16AO69A.

Leveraging gravitation and space biology to model immune aging and disease

Dr David Furman

Buck Institute for Research on Aging

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Dr. Furman discussed the importance of systemic chronic inflammation associated with aging in the development of chronic disease and the construction of the Inflammatory Age (iAge) aging clock, which predicts multimorbidity and mortality. Increased "inflammaging", altered immune responses and aging profiles previously reported in astronauts were confirmed in multi-omics analyses conducted on samples from the Space X Inspiration 4 mission. Using a microgravity simulation technology, the rotary wall vessel and, more recently, the random positioning machine/clinostat, Dr. Furman's group exposed peripheral blood mononuclear cells (PBMC) from healthy subjects and observed a substantial increase in the expression of aging-related genes such as MMP9 or CCL2, and a down-regulation of key genes that regulate the immune response against pathogens such as STAT1. At the single cell level, alterations in differentiation trajectories in innate immune cells, increased in the iAge metric and in aspects of cellular senescence, reactivation of latent viruses, elevated ligand-receptor interactions and cytoskeletal derangements were also discussed. Most of these changes were reversed by the pre-treatment of PBMC with compounds predicted to counteract the aging effects of simulated microgravity. Expanding on these results and with the aim of creating a model for age-related diseases, the researchers utilized a technology to derive human induced pluripotent stem cell (iPSC)-derived organoids and subjected these to simulated microgravity. Strikingly, cardiac organoids exposed to 24h of simulated microgravity showed a gene expression profile that resembled dilated cardiomyopathy and lamin A mutation signatures characteristic of progeria syndrome. Furthermore, using a transcriptomic clock of aging built on hundreds of post-mortem heart tissues from the Genotype-Tissue Expression (GTEx) database, Dr. Furman showed a 5-year biological age acceleration in organoids exposed to simulated microgravity. The application of the same technology on neural organoid cultures showed a significant enrichment for Parkinson's disease and other synucleinopathies and a 10-year biological age acceleration in a transcriptomic clock derived from brain cortex obtained from post-mortem tissues in the GTEx database. Current drug screening assays are being conducted on these disease models, which is expected will bring successful hits and lead candidates for the treatment of age-associated conditions.

Session Four: Potential effects of magnetic fields

An introduction to the radical pair mechanism

Professor Jonathan Woodward

The University of Tokyo

View the video recording **here**

There is increasing evidence for the ability of weak magnetic fields to influence biological processes and even for organisms to sense and respond to the geomagnetic field. Therefore, biological systems might exhibit unexpected behaviour in an environment devoid of magnetic fields, for example in outer space. For this response to take place, there must be an underpinning physical mechanism of interaction.

Molecules are magnetic if they contain unpaired electrons, but the strength of their interaction with external magnetic fields is negligible compared with the thermal energy at room temperature. Thus, thermodynamics predicts no molecular based mechanism by which chemical reactions might be influenced by such fields. However, there exists a very specific and well-studied mechanism involving short lived reaction intermediates that can render chemical reactions proceeding via their formation sensitive to weak magnetic fields. This mechanism is the radical pair mechanism (RPM). It relies upon the quantum coherent interconversion of long-lived correlated electron spin states and the selective chemical reactivity of these states.

In this presentation Prof. Woodward introduces the radical pair mechanism and explains how it allows for the magnetic field sensitivity of chemical and biological reactions by means of a clear visual narrative, avoiding the use of unfamiliar technical jargon and replacing mathematical equations with animations. The specific mechanistic steps and timescales of the mechanism and their interplay are key in understanding where radical pairs can and cannot play a role in biological magnetosensitivity, and the nature of their interaction with the magnetic field. Radical pairs exhibit a very non-linear response to magnetic fields with respect to the magnitude of the field. The reasons for this non-linear response are also simply delineated.

Manipulating tissue repair with weak magnetic fields

Professor Wendy Beane

Western Michigan University

View the video recording **here**

Organisms on Earth have evolved to live within its geomagnetic field, which averages 25-65 µT. The ability to sense and respond to changes in this field, for example as migration cues, has arisen in many species from bacteria to turtles to birds. As humans spend more time in space, understanding how our physiology interacts with magnetic fields will be essential. Between planets there is no magnetic field to protect astronauts from cosmic radiation, and scientists have long researched methods to provide spacecraft with artificial magnetic fields. However, comparatively little research has been done on the potential harm (or benefits) from the magnetic fields themselves. By exposing highly regenerative planarian flatworms to magnetic fields of different strengths, we have shown that dividing cells are able to respond to changes in magnetic field strength due to corresponding changes in reactive oxygen species (ROS). At certain strengths (such as 200 µT) we see increased ROS accumulation at the wound site after injury, which leads to gene expression changes that are required for stem cells to divide and produce new tissue [1]. Conversely, we also found other field strengths (such as 500 µT) that decreased ROS levels, inhibiting gene expression, stem cell expression, and regenerative growth [2]. Our data suggest that weak magnetic fields manipulate stem cell activities by changing endogenous levels of the superoxide radical, which alters cell signaling [2]. We are currently investigating the role of injury-induced membrane depolarization as an upstream regulator of ROS during new tissue growth. These data suggest that the ability to respond to quantum changes (such as those induced by magnetic fields) may be a more common cellular characteristic than previously thought. In addition, the data indicate that much more research needs to be done into the cellular effects from specific magnetic field strengths across a broad range of conditions.

[1] Van Huizen AV, Morton JM, Kinsey LJ, Von Kannon DG, Saad MA, Birkholz TR, Czajka JM, Cyrus J, Barnes FS, Beane WS. (2019) Weak magnetic fields alter stem cell–mediated growth. *Science Advances*, 5(1): eaau7201.

[2] Kinsey LJ, Van Huizen AV, Beane WS. (2023) Weak magnetic fields modulate superoxide to control planarian regeneration. *Frontiers in Physics.* Section: Biophysics. 10: 2022.

Session Five: Quantum gravity and inertial stresses

An overview of quantum gravity

Dr Nathan Babcock

Howard University

View the video recording **here**

In this introductory lecture, we explore the fundamental motivations for developing a unified theory of quantum gravity along with the theoretical and experimental challenges associated with it. As a homage to Lord Kelvin, we conceptualize these challenges as "clouds" obscuring the horizon of modern physics. For clarity, we consider the landscape of contemporary physics in the context of developments in physical principles dating back to Newton, Maxwell, and Einstein to reveal the "chasm of ignorance" that separates the two pillars of modern physics: quantum mechanics and general relativity. We elucidate the need for quantum gravity to fill the gap separating them.

The *Stanford Encyclopedia of Philosophy* defines quantum gravity broadly as the physical theory that includes both principles of general relativity and quantum theory. We discuss the various models of quantum gravity ranging from string theory to canonical approaches such as loop quantum gravity, as well as competing approaches that reject a unified theory in favor of a semiclassical approach. We delineate problems with the empirical validation of traditional approaches to quantum gravity, highlighting the need for new experimentally-motivated methods such as those being pioneered by Prof. Vlatko Vedral and colleagues. We sketch out an experimental test of quantum gravity proposed by Marletto and Vedral [1], emphasizing the need for a consistent theory that does not arbitrarily quantize only some forces.

In conclusion, we consider some fundamental principles at the intersection of quantum mechanics and gravitation, such as the enigmatic electron spin. Although quantum spin is often presented as a fundamentally quantum property for which there is no classical analogue, a foundational physical analysis reveals that spin arises in quantum theory as a direct consequence of considerations drawn from general relativity [2]. We summarize the necessity of a comprehensive theory of quantum gravity by reflecting on Einstein's "twin paradox" [3].

[1] Marletto & Vedral, "Witness gravity's quantum side in the lab." *Nature* **547**, 156-158 (2017).

[2] Ohanian, Hans C., "What is spin?" *American Journal of Physics* **54**, 500-505 (1986).

[3] Pesic, Peter, "Einstein and the twin paradox." *European Journal of Physics* **24**, 585 (2003).

Is quantum gravity a cloud on the physics horizon?

Professor Vlatko Vedral

The University of Oxford

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In my talk I will present what I believe to be the key features of quantum physics. Among them are the unification of the wave and the particle aspects of fields and matter as well as the abolition of the divide between observers and the observed. The latter is achieved through the concept of quantum entanglement which I will review in simple terms. Then I will shift focus onto gravity and argue that the basic tenets of general relativity are not in conflict with quantum physics. What's more relevant is the fact that some quantum aspects of gravity can already be tested with the current technology. I will outline the gist of such tests and comment on what versions of quantum gravity are compatible with which, different, possible, experimental outcomes. Will gravity prove to be a cloud on the current physics horizon? One can speculate here, but it is already exciting to be able to probe the intersection of our two best theories in physics.

Closing Note

Professor Geoffrey Guy

Founder and Chairman, The Guy Foundation

View the video recording presenting a recap of the series talks and the questions for roundtable discussion **here**

The 2023 Autumn Series concluded with a vigorous roundtable discussion. The various presentations ranged from more established research topics in space health, such as radiation and microgravity, to emerging research on magnetic fields and the speculative connections of quantum gravity. In the process, many questions were raised. The question of whether mitochondrial function is disrupted by space travel seems indisputable when faced with extensive data attesting to these changes across organ systems. A more nuanced question might then be: to what extent is mitochondrial function disrupted; what are the likely phenotypic presentations of longer-term mitochondrial dysfunction in space and upon return; and does this represent a morbidity or mortality concern. While the details remain to be worked out, the results of mitochondria studies in astronauts suggest that space travel may exacerbate or accelerate subclinical mitochondrial dysfunction into the pathological realm. Changes in morbidity and mortality, however, are a time concern as well as being environment dependent, with different outcomes expected for a temporary visit to the Moon and a lifetime on Mars.

The exact details of the environmental conditions that give rise to mitochondrial dysfunction also remain to be unravelled. While it is clear that microgravity and radiation can induce profound physiological effects, how other factors such as magnetic fields interact with these is still not understood. The combined effects seem likely to be synergistic. But in order to accurately determine this, we need a better understanding of the fundamental concerns relating to hypomagnetic fields, beyond their role in screening radiation. How might we go about testing this? While some astronaut data are available, the problem is standardisation. Despite there being nearly 700 subjects, the exact conditions of their exposure may differ dramatically, from a short trip to the Moon to a long stay on the International Space Station, with only an estimated 12 astronauts so far having ventured beyond low Earth orbit. In light of this, ground simulations may have to employ innovative experimental techniques or initiate novel interdisciplinary approaches. One example is the use of hypomagnetic environments developed for completely different contexts, such as magnetoencephalography.

Space health research would also benefit from investigation of the parallels it shows with other chronic conditions. Space flight appears to be associated with the reactivation of viruses, something it has in common with conditions such as long COVID. Understanding exactly how this is related to mitochondrial bioenergetic dysfunction and concomitant inflammatory and immune responses could help systematise the biomarkers used to measure the cumulative effects of space travel on health.

And finally, with a better understanding of the extent and scope of the problem, what mitigations might be considered? In the different presentations of the Autumn Series we heard about a number of molecules that appear to reverse some of the health conditions brought on by space travel. These include quercetin and curcumin, anti-inflammatory compounds that plants have developed to mitigate stress and that show medicinal properties in human use. Could plants grown in space and adapted to space conditions generate an anti-inflammatory profile of compounds appropriate to treating the stress of space travel in humans? Or could they at least offer insight through and analysis of the upregulation of relevant medicinal compounds?

While many of the questions raised in the discussion remain unanswered, their accumulated weight casts some doubt on the title of a recent report, 'Thriving in Space: Ensuring the Future of Biological and Physical Sciences Research: A Decadal Survey for 2023-2032' by the National Academies of Sciences, Engineering, and Medicine (NAS). What is without a doubt is that more research needs to be done in order to better understand the future of humans in space. The last expansion of humans across the globe was to a large degree facilitated or curtailed by matters of health and the discovery of new therapeutics, for example, of quinine to treat malaria. It is time the equivalent of this quinine effect is investigated in the context of space exploration and settlement.

December 2023

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