NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE

PRINCIPAL ACCOMPLISHMENTS

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INTRODUCTION

The National Space Biomedical Research Institute (NSBRI) has a distinguished and consistent record of high performance as a unique and critical biomedical component of the National Aeronautics and Space Administration (NASA).[1] Multiple assessments and reviews, including those for the NASA Chief Scientist, applaud the Institute's innovation, pathfinder role, focus on deliverables, agility, efficiency, academic excellence, leadership, and leveraging of the nation's investment in biomedical research.[2] As a non-governmental organization (NGO), the Institute adds core capabilities to NASA in reducing high-priority biomedical risks and solving problems associated with human space exploration. NSBRI also applies the advances to enhance life on Earth, and inspires and trains the next generation.

NSBRI attracts and actively engages a community of outstanding scientists, engineers, and physicians from across the nation, at top academic institutions and industry, to partner with NASA on seven interdisciplinary research teams.[3,4] Approximately half of the investigators drawn to NSBRI were not previously involved with NASA programs.

Institutions receiving NSBRI support bring unprecedented biomedical resources to NASA. They are required to cost share at a minimum rate of 10%, and companies cost share at a minimum rate of 50% in NSBRI's Industry Forum programs. Three hundred and fifty science and technology projects have been supported over 18 years, and abridged, albeit significant, results are reported herein.

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[1] NSBRI is supported by NASA through cooperative agreement NCC 9-58.

[2] Approximately $2.50 is leveraged for every $1.00 of NSBRI support for projects.

[3] NSBRI science and technology teams are in the following areas: Cardiovascular Alterations; Human Factors and Performance; Musculoskeletal Alterations; Neurobehavioral and Psychosocial Factors; Radiation Effects; Sensorimotor Adaptation; and Smart Medical Systems and Technology.

[4] Accolades among NSBRI community members include: the Nobel Prize; Congressional Gold Medal; National Medal of Science; election to the National Academy of Sciences, National Academy of Engineering, and Institute of Medicine; the NASA Distinguished (Public) Service Medal; appointment as the NASA Administrator, NASA Deputy Administrator, Undersecretary of the United States Department of Energy, University Chancellor, University President, and University Provost.

PRINCIPAL ACCOMPLISHMENTS

Scientific Advances for Space Operations

NSBRI supported groundbreaking fundamental and applied research demonstrating the effectiveness of blue-enriched light to entrain circadian rhythm.[5] Subsequent NSBRI-funded studies on sleep-wake alterations and performance using blue-enriched light as a potential operational countermeasure led to positive results that were paramount in NASA's decision to install **new solid state LED lighting with blue spectrum capabilities aboard the International Space Station** (ISS).[6]

Using state-of-the-art medical simulators and recruiting leading medical experts, NSBRI worked with NASA and industry to update post-spaceflight anesthesia protocols. Simulations were conducted using physiological data dependent on age, sex, and duration in space. **New anesthesia protocols** were delivered to NASA and immediately adopted for operational use by the agency.

NSBRI led research on the Psychomotor Vigilance Task (PVT), an **objective assessment tool of psychomotor performance**, which has become a cornerstone of NASA's behavioral health program. The Institute conducted studies in analog environments and aboard the ISS to characterize individual susceptibilities and differences, and inform countermeasure development and requirements.[7,8] The U.S. Department of Transportation relied on NSBRI-supported PVT research methods to set regulations improving truck driver health and safety, with the aim of reducing fatal tractor trailer accidents costing lives and more than $20 billion annually.

Scientific studies led NSBRI investigators to develop **improved guidance** for allocating procedure tasks to automation. They also **improved displays** for situational awareness during high dynamic operations in human spaceflight. These products were received favorably by NASA and have applications in other fields, such as commercial oil and gas drilling operations.

NSBRI **refined and improved astronaut training** for spaceflight robotics operation, and for sensorimotor adaptability. These improvements have been adopted by NASA for use in training. Advances in sensorimotor adaptability were also demonstrated by NSBRI to be effective in mitigating balance impairments in older adults, and in alleviating axial symptoms in Parkinson's disease (affecting 500,000 Americans).

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[5] *Curr Biol.* 2007;17(24):2122-2128. *Sci Transl Med.* 2010;2(31):31-33.

[6] Earth-based benefits relate to reducing accidents associated with excessive sleepiness, in which circadian shift work is a significant contributor. In addition to loss of life, the costs of such accidents are estimated to be $80 billion per annum.

[7] Analog studies included the Aquarius underwater habitat (NASA Extreme Environment Mission Operations) and a land-based isolation chamber for a 520-day simulated mission to Mars.

[8] Twenty-four astronauts have been studied using the PVT every fourth day during their six-month ISS missions. The data were used by NASA to inform the need for one-year ISS missions.

An NSBRI operational deliverable is replacing dated neurocognitive assessments of astronauts during flight. The **new cognitive test battery** was evaluated in space analogs and has been in use aboard the ISS since 2014. High levels of cognitive performance, and unobtrusive ways to rapidly assess metrics without interfering with a mission, are important for human space exploration and other critical job areas.

Research Deliverables to Mitigate High-Priority Risks

In 2013, NASA delegated authority to NSBRI for its acute radiation risk and select radiation-related degenerative tissue gaps associated with the heart and circulatory system. The confidence placed in NSBRI for risk mitigation of the **most important health threat beyond low-Earth orbit** is testament to the confidence NASA has in the quality, impact, ability to deliver, and mission relevance of the Institute.

NSBRI successfully developed and operated a six-year, $11 million **Center of Acute Radiation Research**, resulting in more than 50 peer-reviewed impactful publications elucidating mechanisms, informing NASA permissible exposure limits, testing promising countermeasures, and directing future research on space radiation. With a focus on protons simulating solar particle events, this large multi-institutional effort provided a thorough and systemic characterization of acute radiation effects.[9, 10]

NSBRI is following up on this seminal work with a recently funded **Center for Space Radiation Research**. The Center is investigating acute and degenerative effects of low-dose particle irradiation from both protons and heavy ions (characteristic of galactic cosmic rays). It is also blazing new trails in space radiation research with its emphasis on biomarkers, metabolic and epigenetic alterations, and the testing of targeted pharmacological countermeasures.[11]

Using protons and heavy ions to simulate space radiation, NSBRI scientists recently identified dopaminergic-related protein alterations in the central nervous system as a putative cause of radiation-induced neurobehavioral decrements. Dopaminergic agonists were then used to reverse the decrements in animals, offering promise as a **radioprotectant**.

Investigators at NSBRI have also shown the effectiveness of small molecules, such as arginase, to facilitate vasodilation and **block harmful effects of radiation** promoting endothelial cell senescence, accelerated aging, and atherosclerosis. Support by the NSBRI Industry Forum led to the formation of a company Arginetix, which became Corridor Pharma, and was recently acquired by AstraZeneca. Beyond use as a radio-protective, the research offers new treatment possibilities for pulmonary hypertension, a disorder primarily affecting young women.

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[9] Results included a dose-dependent decrease in white blood cell counts at > 0.5 Gy, inflammatory alterations in skin at > 2 Gy, reduced survival after a bacterial challenge, vomiting at > 1 Gy, and disseminated intravascular coagulation at > 2 Gy.

[10] As a result of this work, improvements in radiation oncology dosimetry models were made to better predict tumor and healthy tissue exposure in patients receiving radiotherapy.

[11] Findings from the Center of Acute Radiation Research and the Center for Space Radiation Research have relevance to radiation workers, cancer patients, pilots, and homeland security personnel.

NSBRI's space medicine physician-scientists were involved in the early recognition of what has recently been acknowledged as the **most important risk to astronaut health in low-Earth orbit**, namely the risk of spaceflight-induced intracranial hypertension/vision alterations. NSBRI plays a key role for NASA in rapidly engaging leading medical and scientific experts, holding interdisciplinary workshops, and funding research and development to better understand and find solutions to this important problem.

The Institute conducted the **first independent clinical test** of the Vittamed device for non-invasive assessment of intracranial pressure.[12] The results in normal subjects and patients were significant, and NSBRI worked with the manufacturer to make improvements to address NASA's needs. The device was accepted for use by NASA, and it also has applications in neurology and neurosurgery, where invasive measurement of intracranial pressure is one of the most commonly performed procedures.

NSBRI is **leading an international study** in Cologne to assess the effects of simulated spaceflight conditions – microgravity and elevated carbon dioxide levels - on intracranial pressure and vision. This ambitious analog study of conditions present aboard the ISS is unprecedented, strongly endorsed by NASA, and will yield new knowledge and potential countermeasures needed by the agency and its international partners.

NSBRI represented the United States in a **landmark 520-day high-fidelity simulation of a human mission to Mars** involving six crewmembers.[13] Institute investigators focused on high-priority risks of performance and behavioral health decrements, adverse cognitive and behavioral conditions, and psychosocial adaptation within a team. NSBRI results were the most widely cited from the entire MARS 500 project, and the investigators' findings on differential vulnerability highlight the importance of Earth's geophysical signals as a requirement for long-duration human space missions.[14]

NSBRI physician-scientists, at the request of NASA Space Medicine, rapidly developed and delivered a **novel critical tool to clinically assess the risk for cardiovascular events** in astronauts. The deliverable was promptly integrated into NASA flight medicine operations.

Enhanced Medical Capabilities for Space and Earth

The Institute collaborated with NASA and industry to advance ultrasound training and diagnostic medical imaging aboard the ISS. This resulted in the **first scientific research paper submitted from space**.[15] NSBRI subsequently supported the development of an ultrasound catalog for ISS autonomous medical care. The ability to clinically assess and treat conditions in space can

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[12] The Vittamed technology was developed in Europe. As an NGO, NSBRI used non-federal funds to facilitate trials that were not possible to conduct using NASA funds alone.

[13] Federal restrictions precluded NASA from participating in MARS 500, an international project in Moscow that included a 520-day study (June 2010 – November 2011). NSBRI raised non-federal dollars to support the international component of the project.

[14] *Proc Natl Acad Sci USA.* 2013;110(7):2635-2640.

[15] *Radiology* 2005;234:319-322.

obviate the need for an emergency egress from low-Earth orbit, estimated at more than $200 million.

An NSBRI-supported **intensive care unit ultrasound handbook**, stemming from methods designed for space, is in use around the world. It provides medical and non-medical health care workers the ability to conduct high-quality imaging and diagnostics, even in harsh remote environments. The techniques have been favorably adopted by the World Health Organization, the United Nations' Economic and Social Council, the United States Olympic Committee, professional sports teams, and numerous other organizations.

NSBRI developed spacesuit-compatible, FDA-cleared sensors using near-infrared spectroscopy for **non-invasive assessment of blood and tissue chemistry**. The devices are unobtrusive, operate in real time, obviate the need to draw specimens, and use proprietary algorithms that have led to product commercialization. The sensors have utility in acute settings (e.g., managing shock), as well as in chronic conditions, such as assessing vascular changes in diabetes mellitus, a disease affecting 29 million people (9.3% of the population) in the United States.

Diffuse optical tomography and near-infrared sensing have been adapted by NSBRI investigators for **portable functional brain imaging**. Devices have been tested and evaluated in space analog settings, including parabolic flight, and currently augment NASA's exploration medical capabilities. They have applications to pediatric neuro-monitoring and medical care in remote locations.

Scientists supported by NSBRI developed **scanning confocal pulsed ultrasound** to successfully assess and improve bone mineral density, structural integrity, and trabecular strength. They also showed that the technology can be made portable, enhance fracture healing, and reduce disuse-related bone loss. These advances are relevant to use in space, as well as on Earth, where there are an estimated 10 million Americans – 80 percent of them female – who have osteoporosis, and another 34 million who have significantly reduced bone mass (i.e., osteopenia).

NSBRI conducted the **first-in-human trial of non-invasively moving and clearing kidney stones**.[16, 17] The technology, developed by NSBRI-funded engineers, may transform urological practice. Astronauts are at increased risk of kidney stone formation, and 14 have experienced stones post-flight.[18, 19] The prevalence of kidney stones is 5% in the United States, and increasing worldwide, with associated rising costs – greater than $2 billion in health care and greater than $3 billion in workdays lost per annum in the United States.

Integrative Research for Space Exploration and Medicine

A collaboration across multiple NSBRI teams resulted in the **first multi-system study** targeted

[16] De novo, post-lithotripsy and operable stones were moved.

[17] NSBRI led and supported this project, with the majority of funding coming from non-NSBRI sources.

[18] The risk is due to bone demineralization and changes to urinary biochemistry in reduced gravity.

[19] The Russian space program experienced a suspected case of a kidney stone in-flight.

at cardiovascular, skeletal muscle, and bone deconditioning **using a single countermeasure strategy** (involving rowing exercise and nutrition). The findings were significant for space missions, and led to an effective intervention now used in clinical practice to treat postural orthostatic tachycardia syndrome affecting three million Americans.

NSBRI performed the first animal and human research to **evaluate whether partial gravity alone is protective of bone health**. Neither 1/3 G (Mars) nor 1/6 G (Moon) body weight loading prevents decrements in bone integrity.[20] The findings are relevant in determining exercise and loading countermeasures needed for planetary surface exploration.[21]

Scientists supported by NSBRI provided the **first evidence suggesting that fracture healing is different in microgravity**. They showed that unloading alters the expression of key genes involved in fracture healing, and that fracture sites have delayed healing, smaller calluses, and are more brittle. NSBRI has been at the forefront in addressing NASA's Human Research Roadmap risk of bone fracture due to spaceflight-induced changes in the musculoskeletal system.

A mathematical model of circadian rhythm, sleep, objective performance, and subjective alertness was developed by NSBRI scientists. The model was recently transitioned as a deliverable to NASA via an Institute-supported dashboard application. The product has utility in **optimizing and sustaining crew performance** and guiding countermeasures.[22] There are applications on Earth given that 29% of the American workforce works an alternative shift (i.e., not a regular day shift).

NSBRI developed and delivered to NASA software to maintain behavioral health in space using a suite of self-directed training and treatment **programs for interpersonal conflict and stress**. The programs are therapeutically effective, make use of multi-media, and provide stand-alone, easy-to-use training and treatment. Applications on Earth include high-stress job situations where anxiety and conflict compromise critical performance and health.

Team performance software was developed and deployed by NSBRI scientists for the first-ever collection of objective behavioral data on team cohesion at Concordia Station in Antarctica.[23] Operational feasibility and acceptability were established during three winter-over campaigns. The results provided fundamental scientific insights on team cohesion in multi-national crews over extended durations in extreme environments.

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[20] 1/3 G is only partially protective of cortical but not cancellous bone.

[21] NSBRI investigators have also shown that radiation exposure exacerbates bone loss but not muscle loss.

[22] NSBRI is a pioneer in new methods to treat disturbances of circadian rhythm. This particular deliverable is useful in planning effective crew work schedules and in deploying countermeasures (such as determining optimal light duration, timing, intensity, and color) to address nominal and off-nominal events (e.g., slam shifting for rendezvous and docking).

[23] Concordia Station is an analog setting used by NASA and other spacefaring nations given its harsh remote features.

Technology Advances

NSBRI has been at the forefront of technology that utilizes the **same platform for both diagnostic and therapeutic applications** for space medicine. Researchers at NSBRI invented and demonstrated a portable, image-guided, focused ultrasound device that detects and then stops internal bleeding (i.e., non-invasive surgery).[24] The Defense Advanced Projects Agency subsequently supported this effort at $75 million.[25]

A **next generation compact exercise device** was developed and tested by NSBRI, evaluated positively by NASA, and transitioned for use in a space analog environment. The prototype integrates endurance and resistance exercise, and is gravity independent. It is considerably smaller than equipment currently aboard the ISS and suitable for an exploration vehicle.

NSBRI supported research and development of gas and solid-state microdosimeters for flight, enabling astronauts to wear **miniature detectors determining radiation in real time**, with instant warning mechanisms. Conducted in partnership with the Department of Defense, the microdosimeters were tested and found to be effective regardless of radiation type or energy, and performed well in space.

NSBRI developed an **electronic database to aid NASA flight surgeons** to optimize medication use in space. The paradigm changed NASA's approach to the use of medications, especially those promoting sleep, to optimize their efficacy and safety.

The Institute partnered with industry leaders through the **NSBRI Vision for Mars** program to identify and support critical technologies addressing ocular pathology associated with spaceflight. A novel diagnostic capability using multispectral imaging, and a potentially disruptive countermeasure using pressure goggles, were accelerated. The technologies have clinical applications for patients with ocular pathologies, including glaucoma affecting more than three million Americans.

Pathfinder Role

NSBRI **elevated the caliber of scientific research** for NASA's Bioastronautics and Human Research Programs. The depth and breadth of its accomplished investigators, strong scientific leadership, team structure, focus on the Institute's mission, and resources brought by approximately 60 institutions at any given time add significantly to NASA's capabilities in space biomedical research. NSBRI's Board of Scientific Counselors was instrumental in moving NASA space life sciences away from *ad hoc* review panels and instilling peer-review panel leadership at a level comparable to that of the National Institutes of Health.

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[24] Demonstrations included transcutaneous hemostasis, lung pneumostasis, and non-invasive tissue emulsification.

[25] This high-risk high-payoff project by NSBRI was instrumental in the formation of the International Society for Therapeutic Ultrasound, and in positioning NASA space medicine to consider completely non-invasive therapeutics (as opposed to minimally-invasive ones) for space exploration.

To assist NSBRI with space operational considerations, including need and feasibility, the Institute formed a User Panel. It consists of current and former astronauts, flight surgeons, and flight directors.[26] The **User Panel retains NASA corporate memory**, and its members provide advice prior to research selection and throughout the maturation process of projects toward deliverables. The exceptional nature of the User Panel, and its helpful interactions with the Institute, have been noted repeatedly in reviews of NSBRI.

NSBRI has blazed new paths at the frontier of space and medicine. Most recently, NSBRI has been on the cutting edge of the new field of astro-omics, a discipline that brings human genomics, proteomics, metabolomics, and related fields to the forefront of space biomedical science and space medicine. NSBRI established the **first laboratory of astro-omics research**, and NASA relied on NSBRI to develop the scientific content for its twin astronaut study solicitation, which involved a significant omics component.[27]

The **NSBRI Industry Forum** commercializes biomedical discoveries made for space and challenges the private sector to develop space-compatible healthcare solutions. NASA has come to rely on the Industry Forum as a source of space biomedical deliverables that have Earth-based applications. Success of the Industry Forum partially rests with its private sector Steering Council and innovative strategies capitalizing on NASA's investment in NSBRI that benefit the American public.[28]

Legacy Achievements

In 2008, Baylor College of Medicine established the **first-ever academic department in space medicine** at a major university or medical school. This was the direct result of NSBRI's proven track record of success. The formation of a Center for Space Medicine elevated the stature of space medicine within America's scientific and medical communities, and provided NSBRI with new opportunities for research leveraging, education programs, clinical trials, and academic appointments.[29]

NSBRI and NASA collaborated to establish a 16,000 square feet, **state-of-the-art Consolidated Research Facility,** in the heart of the Texas Medical Center with close geographical proximity

[26] The User Panel is unique, with representation from Apollo, Skylab, Shuttle, and ISS programs. The spaceflight experience of astronauts on the User Panel exceeds 80 missions.

[27] The twin astronaut study involves Scott and Mark Kelly, the former participating in the first one-year mission aboard the ISS that began on March 27, 2015.

[28] Among the numerous success stories are: a gel-based formulation of wound dressings for space medicine that improves the efficacy of the product on Earth (ACell); a medical food that helps maintain hydration and restore normal gastrointestinal function during chemotherapy and radiation treatment, with the potential to serve as a space radiation countermeasure (Enterade); a non-invasive, portable monitor to assess changes in brain fluid levels in space with applications for early detection of cerebral bleeding and edema on Earth (Cerebrotech Medical Systems); and a multi-spectral ophthalmoscope to image the retina with unprecedented detail for a non-invasive device (Annidis Corporation).

[29] The Center for Space Medicine offers the first-ever, four-year Space Medicine Track for undergraduate medical students. Fifty-five percent of the first year medical school class chooses to take the Introduction to Human Space Exploration and Medicine course, making it among the most popular electives on campus.

to NASA Johnson Space Center. This award-winning physical asset has lasting value with laboratories augmenting those available to NASA, collaborative workspaces, meeting areas, conference rooms, and ready access to modern university and medical facilities.[30]

Training the Next Generation

NSBRI has evolved into the leader in space biomedical education. Award-winning national programs span middle school through undergraduate and postgraduate levels, and beyond. Over 50 outstanding graduate students and fellows have completed NSBRI mentored training programs, with 80% of First Award (post-doctoral) recipients acquiring jobs related to human space exploration in academia, industry, and government. Fellowships are competitive and successful recipients are integrated into NSBRI's science and technology research teams.

In 2009, NSBRI created the **Space Medicine Clinical Research Training Program**. Coordinating with NASA's Chief Health and Medical Officer, the Institute implements this program to elevate space medicine residency training in a manner that is consistent with research opportunities offered by other American medical and surgical specialty programs. The results have been impressive, with new findings and peer-reviewed publications appearing monthly, and an increase in the number of physician-scientists (M.D./Ph.D.) qualifying as board certified aerospace medicine specialists.

NASA relies on NSBRI to inspire and train the next generation of space biomedical researchers and leaders. Through career development and outreach, NSBRI provides internships, creates jobs, and helps sustain the scientific workforce. NSBRI retains connections among past and current trainees through its **NSBRI Society of Fellows**.

New Ways of Doing Business

NASA's cooperative agreement with NSBRI is held as a **model for how the government can effectively do business with a large, national academic consortium**. The partnership between NASA and NSBRI has matured to the benefit of both entities, as well as all other stakeholders.[31] The Institute has gained stature nationally and internationally, with a reputation of scientific excellence, collegiality, integrity, vision, ingenuity, and service.

Collaborations and synergies within and between NSBRI teams are abundant. Team leaders are both principal investigators for NSBRI and discipline experts for NASA. They work closely with NSBRI senior management and the Institute's External Advisory Council ensuring productivity

[30] The Consolidated Research Facility contains an Astro-Omics Laboratory, Biomedical Innovation Laboratory, Exploration Medicine Laboratory, and Advanced Technology Demonstration Laboratory.

[31] NSBRI and NASA interact on a daily basis. A formal Steering Committee, co-chaired by the NSBRI Director and the Manager of NASA's Human Research Program, meets monthly to coordinate activities and strategy between the two entities. The Committee is not mandated by the cooperative agreement, but has served the partnership well for more than a decade.

and programmatic excellence. Governance and oversight by a Board of Directors is highly cooperative, and there is stability in leadership and direction to achieve the Institute's mission.

Management costs are approximately 8% to 10% of expenditures. NSBRI leverages the business infrastructure of its academic constituents to keep operational costs low, and an NSBRI Executive Science and Medicine Committee meets weekly to address, in a timely manner, any scientific, budgetary, or programmatic issue that may arise. NSBRI has a **record of clean financial audits**.

Conclusion

NASA's effort to establish and support NSBRI has been tremendously successful. It is a formula that should be sustained and replicated in order to further benefit America's space program and the general public.