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Translational Research Institute (TRI)

Research Announcement

NNJ16ZSA001N-TRIRT

Research Topics

(Part 1)

Letters of Intent Due: April 10, 2017 11:59 pm ET
Pre-Proposal Virtual Meeting: March 23, 2017
Proposals Due: May 19, 2017 11:59 pm ET

This research solicitation NNJ16ZSA001N-TRIRT released by the Translational Research Institute is referenced by NASA as Appendix C of the NASA Human Exploration Research Opportunities (HERO) series of research calls. Together, Appendices C and D (the latter containing TRI proposal instructions) form the entire package of information necessary to respond to this TRI research solicitation. Non-TRI appendices refer to separate calls for proposals and are not pertinent to NNJ16ZSA001N-TRIRT.

A. TRI Mission and Goal

TRI's mission is to lead a national effort in applying cutting edge terrestrial research to spaceflight human risk mitigation strategies for long duration exploration missions. The goal of TRI's translational research is the production of a promising new approaches, treatments, countermeasures or technologies that have practical applications to spaceflight. TRI has identified several areas of promising cutting edge human health and performance research for translation to validated space flight human health and performance prediction, prevention, monitoring, detection, maintenance, and treatment capabilities for exploration missions.

In partnership with NASA's Human Research Program (HRP) management, TRI has chosen nine topics for solicitation whose solutions could reduce at least nine risks to human health on long duration spaceflight missions. Their solutions will require the efforts of a wide range of talented individuals, including medical professionals, engineers, and researchers covering a wide variety of specialties. TRI believes that diversity in each research team is likely to increase the team's success; proposers are therefore encouraged to include team members with a wide range of skills, backgrounds, professional training, and different ways of thinking, in additional to being open to diversity in sex, gender, ethnicity, and race.

Each topic description below includes a maximum project duration and a maximum annual budget. In the event that a complete solution cannot be provided within these boundaries, proposers should include a description of the completion state they would be able to reach within the stated boundaries, as opposed to planning for extensions or budgetary supplements.

All proposals should include controls appropriate for the experiments described, concentration-response data in experiments using pharmaceuticals, and validation of new methods or instrumentation to current medical or gold standard research methodologies or technologies. Proposers should consider the physiological and psychological adaptations previously described in humans during spaceflight missions and the effects of the spaceflight environment on consumables and instrumentation, as well as the limitations on resources (mass, power, volume, etc.) inherent in spaceflight travel.

Instructions for TRI proposal preparation and submission are provided in Appendix D.

B. Research Emphases

1. Omics capabilities for use during missions

DNA sequencing can now be performed in microgravity (https://www.nasa.gov/mission_pages/station/research/news/dna_sequencing). Ideally, this first series of sequencing in space experiments represent the beginning of omics

capabilities for research or even diagnosis during long duration deep space exploration missions. Advances in molecular biology, including a new sequencer on the International Space Station (ISS), may enable inflight detection of biomarkers of physiological or psychological stress. Metabolomics and proteomics technologies have recently identified many candidate biomarkers for a wide variety of medical conditions and could be used to research spaceflight-associated physiological changes or measure the efficacy of countermeasures. This project would permit a team of researchers and engineers to develop additional omics capabilities suitable for use in the spaceflight environment. The project should include validation against gold standard methods as well as proof of concept measurements of mission-relevant changes in a suitable analog environment. The omics assays may be complemented by concurrent physiological monitoring with wearables or other non-intrusive technologies for the assessment of physiological or psychological endpoints, however the testing and use of wearables should not be the main thrust of any proposed scope of work.

a. Challenge

This project should aim to provide validated biomarkers of mission-relevant physiological and/or psychological stress as well as instrumentation and methodology for inflight detection and measurement of these biomarkers.

b. TRI Core Research Project

It is likely (but not required) that the best solution to this topic will be developed by an interdisciplinary team of omics researchers, experts in biomarker assay development, clinicians, etc. working in a coordinated fashion. Therefore, this project will be considered for funding as a TRI Core Research Project (TCore), comprising a maximum of five individual science principal investigators (PIs) located at a maximum of four different institutions. One PI should be responsible for management of the entire project, specifically for integration, cooperation, and coordination among the individual research groups; this person should be designated as the TCore PI. Awards of up to four years in duration with annual budgets of up to $850,000 will be considered.

c. Examples of projects that could be considered:

- Proposals that use spaceflight mission or analog scenarios to induce relevant stressors and survey physiological fluids to identify candidate biomarkers along with development of analytical instrumentation and methodology for detection of biomarkers during a mission. Access to flight opportunities or analogs should be considered in feasibility and schedule.
- Proposals that include the use of wearables or other non-intrusive technologies for independent measurement of physiological and psychological endpoints.
- Multiple PI projects with clear plans for sharing resources and working together in a synergistic fashion.

d. Examples of projects that will not be considered:

- Proposals based on development of new drugs.
- Proposals whose primary focus is on meeting regulatory requirements (Food and Drug Administration (FDA) approvals).

- Solutions that would not be feasible in the limited resource, closed system of a long duration spaceflight mission.
- Multiple PI projects lacking adequate plans for integration and coordination among the individual component studies.
- Proposals reliant solely on return of samples to Earth for analysis.

2. Long lasting medications

Medications that remain safe and effective for five years or more will be required for long duration exploration missions. Most commercially-available medications, whether prescription or over-the-counter (OTC), have shelf lives of 36 months or less. Only about 10% of the current ISS medication kit would meet the five year requirement for exploration missions.

It is well documented that medications degrade over time and that each medication formulation undergoes unique changes over time; some show degradation of active ingredients into inactive ingredients, and become less effective over time. Others, however, undergo chemical reactions that produce toxic compounds, and thus become poisonous over time. It is not known to the public, pharmacists or physicians which medications fall into each of these categories, therefore all patients and pharmacists are advised to discard medications at their labeled expiration date.
Some of NASA's exploration mission designs last three years and will not include the opportunity for rendezvous with supply vehicles. Given that pre-launch preparations also require significant time, there is a need for medications to be safe and effective for at least five years.

a. Challenge
This project should aim to provide a medication supply that is both safe and effective at all times during a five year spaceflight mission with no opportunity for re-supply. For this challenge, amoxicillin, cetirizine, naproxen, promethazine, and zaleplon are required; other medications may also be studied, but these five must be included in each proposal. The safety and efficacy of medications should be validated against U.S. Pharmacopeia (USP) requirements using USP methodology. FDA approval of drug products is not required for successful completion of this project, however, proof of concept testing with validation to USP requirements is required.

b. TRI Core Research Project
It is unlikely that a single solution will work for all different types of medications, given the variety of dosage forms and formulations. This goal could be achieved by a variety of mechanisms or technologies. The best set of solutions may be developed by an interdisciplinary team of researchers, clinicians, engineers, pharmaceutical scientists, etc. working in a coordinated fashion. Therefore, this project will be considered for funding as a TRI Core Research Project (TCore), with a maximum of five individual PIs, but this team approach is not required. One PI should be responsible for management of the entire project, specifically for integration, cooperation, and coordination among

the individual research groups; this person should be designated as the TCore PI. Awards of up to four years in duration with annual budgets up to $850,000 will be considered.

c. Examples of projects that could be considered:

- Proposals that test novel materials and/or methods for the packaging and storage of medications.
- Proposals that develop *in situ* medication production from stored ingredients (such as 3D printing or additive manufacture) or other sources (such as purification from bioengineered microorganisms).
- Multiple PI projects with clear plans for sharing resources and working together in a synergistic fashion.

d. Examples of projects that will not be considered:

- Proposals based on development of new drugs.
- Proposals whose primary focus is meeting regulatory requirements (FDA approvals).
- Solutions that would not be feasible in the limited resource, closed system of a long duration spaceflight mission.
- Multiple PI projects lacking adequate plans for integration and coordination among the individual component studies.
- Proposals reliant on non-pharmacological countermeasures.

3. Human brain imaging

Imaging technologies—both structural and functional imaging—are advancing quickly. Brain imaging for spaceflight is a unique challenge, however, because clinical neuroimaging techniques (e.g., magnetic resonance imaging [MRI], computed tomography [CT], positron emission tomography [PET]) are too large, heavy and power-demanding for flight. Moreover, they often involve radiation exposures and/or contrast injections, both of which are problematic for exploration class space missions. While ultrasound has proved exceptionally useful for spaceflight imaging, it has difficulty penetrating the thick bones of the skull. However, new ultrasound techniques, as well as near-infrared imaging and even miniaturized MRI scanners are being developed. If made spaceflight-compatible, one or a combination of these approaches could provide important information about brain health during space flight and could potentially complement the ultrasound imaging capabilities available for other parts of the body. For example, while the etiology is unknown for microgravity ocular syndrome (MOS), also known as visual impairment – intracranial pressure (VIIP), there is now substantial evidence that vision changes in astronauts may involve fluid re-distribution within the central nervous system. Since no Earth-based analog provides a clear and unequivocal model of MOS symptoms, brain imaging of astronauts in spaceflight—including both structural components and fluid components—may prove necessary to make significant progress. Given a suitably general imaging approach, such technologies could provide important and currently unavailable medical imaging capabilities for other spaceflight conditions, as well as enable research during long duration space missions.

a. Challenge
Applicants will develop and demonstrate a spaceflight-compatible system for structural and/or functional brain imaging. Such systems should minimize mass, power, volume, and time required to use (or train on) the system, and provide information suitable for assessing conditions on NASA's Medical Conditions List (https://ntrs.nasa.gov/archive/nasa/casi.ntrs.nasa.gov/20110008645.pdf) and help guide appropriate medical decision making. Imaging contrast will ideally be intrinsic (i.e., not requiring an injection). Gels and other consumables should be minimized or eliminated. The required computing power and data storage should be modest. Data output should be provided in standard imaging formats that can be easily transferred and used with existing imaging viewers. Consideration should also be made for evaluating the data generated during the mission, without the need for communication with ground resources. Training and use of the system(s) by persons who are not medically-trained should be evaluated. This opportunity is for a single investigator, with a project duration of up to three years and a maximum funding level of up to $400,000 per year.

b. Examples of projects that could be considered:

- Demonstration of a system(s) capable of brain imaging, with sensitivities complementary to current inflight ultrasound based imaging capabilities.
- Validation of a spaceflight-compatible system against current clinical standards (e.g., MRI, CT, PET).
- Demonstration of feasibility of use in spaceflight analogs (e.g., parabolic flight, isolation, delayed communications with limited crew training).

c. Examples of projects that will not be considered:

- Proposals based on a technology that is not compatible with the resource restrictions of spaceflight.
- Technologies that deliver ionizing radiation to the subject.
- Invasive technologies (e.g., requiring contrast injection).

4. Inflight surgical capabilities

There are numerous challenges for performing surgery in spaceflight, including maintenance of sterile fields, fluid management, limited resource environment, operator guidance, and patient recovery time. Moreover, there is no guarantee that a crewmember needing to perform a surgical procedure will have surgical experience prior to flight, nor even significant medical expertise—particularly if it is the crew medical officer that requires a surgical procedure. There is thus a risk to the health of the crew and mission objectives if a surgical procedure is required but cannot be performed.

One approach that could substantially mitigate several of these challenges is to develop non- or minimally-invasive inflight surgical management capabilities, since this could broadly reduce both risks and recovery time. High-intensity focused ultrasound is one example technology that may enable users to perform non-invasive, image-guided surgical procedures on exploration missions. However, its capabilities—or those of

other non-invasive or even potentially invasive techniques—need to be further developed and demonstrated.

a. Challenge
Applicants should seek to develop and demonstrate proof-of-principle surgical capabilities that would be feasible for use in microgravity and in the resource limited environment of a spaceflight mission, with a primary capability of achieving hemostasis in the case of trauma, nose bleed, or surgical procedure. More advanced surgical capabilities could include appendectomy or cholecystectomy in cases of acute abdominal pain. Serious consideration must be given to the usability of the system on long-duration missions, including a lack of real-time guidance from ground-based experts, limited surgical expertise within the crew, and the availability of limited resources. Solutions should include validation of hardware and methods against current standard procedures for surgery and surgical training. This opportunity is for a single investigator, for a period of up to two years, and for a funding level of up to $300,000 per year.

b. Examples of projects that could be considered:

- Demonstrate a prototype non-invasive surgical device capable of key spaceflight surgical capabilities, (e.g., hemostasis, appendectomy, or cholecystectomy).
- Demonstrate just-in-time or image-guided training to support surgeries conducted by non-surgical personnel.

c. Examples of projects that will not be considered:

- Proposals that use gamma-knife or other technologies requiring ionizing radiation.
- Proposals that do not address the performance of surgical procedures by non-surgical personnel.
- Solutions that would not be feasible or safe in the closed, limited resource environment of a space flight mission.
- Solutions requiring real time communication from the crew in a spacecraft to ground.
- Solutions dependent upon the availability of a trained surgeon.

5. Increase an organism's resistance to radiation

Currently, exposure to space radiation is considered one of the primary risks to human spaceflight. Genetic methods now enable the direct targeting of specific therapies to particular genes or gene products for the treatment of human disease. Certain tardigrades (water bears) that are adapted to living in extreme environments have been found to be resistant to radiation, including space radiation. Genes unique to one species of hardy tardigrades have recently been isolated, and intriguingly, elevated resistance to x-irradiation was demonstrated by transference of those genes to human cells [Hashimoto, T. *et al.* Extremotolerant tardigrade genome and improved radiotolerance of human cultured cells by tardigrade-unique protein. *Nat. Commun*. 7:12808 doi: 10.1038/ncomms12808 (2016)].

This new understanding of how a species withstands high radiation exposures could potentially be used to develop a strategy to increase radiation-tolerance in humans. Validation of efficacy and safety must first be determined in model organisms.

a. Challenge

This project should aim to demonstrate decreased sensitivity to low-dose, chronic exposure, space-like radiation exposure, using for example a facility such as NASA's Space Radiation Laboratory (https://www.bnl.gov/nsrl/), located on the campus of Brookhaven National Laboratory. These space-like radiation exposures should occur in a standard non-mammalian animal model (such as Drosophila, fish, or amphibian), followed by testing in rodents, if warranted. This opportunity is for a single investigator, for a duration of up to three years, and a funding level of up to $400,000 per year.

b. Examples of projects that could be considered:

- Proposals that perform targeted genetic manipulation in human cultured cells or tissues or those derived from standard genetic model organisms (e.g., Drosophila, Zebra *danio*, Mus *musculus*).
- Proposals that perform targeted genetic manipulation *in vivo* in standard genetic model organisms (e.g., Drosophila, Zebra *danio*, Mus *musculus*).
- Proposals that employ temporary control strategies (such as, but not limited to, pharmaceuticals) to target biochemical pathways involved in Tardigrade resilience, in any model system.

c. Examples of projects that will not be considered:

- Proposals in model organisms that do not include long-term integrated health monitoring and multi-system physiological measures.
- Proposals whose primary focus is meeting regulatory requirements (FDA approvals).
- Solutions that would not be feasible in the limited resource, closed system of a long duration spaceflight mission.

6. Preserve muscle mass with pharmaceuticals

New medications, like selective androgen receptor modulators (SARMs) have been shown to maintain muscle mass and strength in healthy individuals, as well as in animal models of disuse, but clinical trials have been aimed almost exclusively at cancer cachexia patients. Spaceflight crewmembers, particularly those living and working during extended deep space exploration missions, will be at risk of disuse atrophy in skeletal muscles that are normally weight-bearing on Earth. The current ISS countermeasure of 1-2 hours exercise per day (30-60 minutes aerobic exercise, sometimes including high intensity intervals, and 60 minutes weight-bearing exercise) is effective for preserving muscle mass, but costs considerable crew time and can become repetitive. This topic aims to explore the feasibility of pharmaceutical use to minimize required exercise (in duration, frequency, or intensity) to allow for breaks in the work-out

schedule in the event of illness, injury, schedule difficulties, or failure of the exercise equipment.

This topic will enable a single PI to test the efficacy of pharmaceuticals to protect muscle mass and strength in healthy individuals in a disuse model, with the ultimate goal of reducing the length, intensity or frequency of required exercise sessions for crew. A successful proposal should include examination for any synergistic effects of medication plus some exercise, perhaps reduced in intensity, duration, or frequency.

a. Challenge
Develop and test a therapeutic protocol to act as a backup to existing exercise regimens for the maintenance of muscle strength while on spaceflight missions. Absence of significant side effects on muscle, and other organs systems should be evaluated. The impact of the solution on mood and behavioral health should also be evaluated. The best solutions will examine the combined effects of pharmaceutical use with exercise programs that are reduced in intensity or duration or frequency. This opportunity is for a single investigator, for a duration of up to three years, and for a funding amount of up to $400,000 per year.

b. Examples of projects that could be considered:

- Proposals that use a pharmaceutical(s) in an animal model of disuse, such as hind-limb unloading, to test efficacy in maintenance of muscle strength as well as screening for unexpected or untoward effects across multiple systems.
- Proposals that use a pharmaceutical(s) in a human model of disuse, using astronaut-like subjects to test efficacy in maintenance of muscle strength as well as screening for unexpected or untoward effects across multiple systems.

c. Examples of projects that will not be considered:

- Proposals that do not include integrated health monitoring and multi-system physiological and psychological measures.
- Proposals whose primary focus is meeting regulatory requirements (FDA approvals).
- Solutions that fail to collect the required data to support conclusions, including controls and concentration-response curves as appropriate for pharmacology studies.
- Solutions that would not be feasible in the limited resource, closed system of a long duration spaceflight mission.

7. Inflight production of fresh food

Lab-grown meat or dairy products are nearing commercial availability and may prove feasible for use in microgravity. Long duration exploration missions will likely last at least 2.5 years and will not include re-supply opportunities. Food will be stored for long durations, affecting texture and appearance as well as potentially decreasing nutrient content. The capability to produce fresh food, even occasionally, to supplement stored food items would provide welcome texture, aroma, flavor, and variety.

The closed long duration space mission environment will be limited in terms of volume for equipment, ingredients and other consumables. For a successful solution, the costs of food production must be carefully considered. Shelf lives of ingredients or other raw materials must be in excess of three years. Mass, volume and energy use must all be minimized. Off-gassing during all phases of production must be non-toxic and inoffensive.

a. Challenge

This topic would permit a single PI to determine if methods for laboratory production of fresh foods could be feasible for use in the spaceflight environment. Ideal solutions are those that result in nutrient dense foods that complement the stored food supply, have minimal footprint in terms of resource use, and use raw materials that have long shelf lives. Systems that provide the capability of producing multiple foods are desirable. Suggested protocols for use of food products by crew, including preparation or incorporation into recipes with stored food items, are also desirable. This opportunity is for a single investigator, for a duration of up to two years, and for a funding amount of up to $400,000 per year.

b. Examples of projects that could be considered:

- Proposals that use a cell culture system for the production of laboratory-grown meat or dairy products.
- Projects that determine a mission-feasible means to grow plants other than typical land green plants used for food like algae, mushrooms or seaweed.

c. Examples of projects that will not be considered:

- Proposals that fail to include evaluation of safety and palatability of food products.
- Proposals that require storage and maintenance of large equipment.
- Solutions that require refrigerated or frozen storage of ingredients.
- Proposals whose primary focus is development of a commercial product.
- Projects that overlap with NASA's existing efforts (e.g., Vegetable Production System [Veggie] https://www.nasa.gov/mission_pages/station/research/experiments/383.html)
- Solutions that would not be feasible in the limited resource, closed system of a long duration spaceflight mission.

8. Microbiome based therapies for improving health in spaceflight

Recent discovery of the important functions performed by the non-human cells of our microbiome has resulted in a new area of drug development. Microbiome involvement has now been demonstrated in regulation of the immune system, effects on the central nervous system (like mood) as well as gastrointestinal absorption. Sleep disturbances and immune system dysregulation have been documented on spaceflight missions; optimization of nutrient absorption could improve health while conserving mission food resources.

There are hundreds of clinical trials involving the microbiome; many aim to manipulate the diversity or community of the microbiome and some are developing therapies that act on the non-human cells of the microbiome, as opposed to acting on human cells as most pharmacotherapeutics do.

The closed mission environment will be limited in terms of volume for equipment, ingredients and other consumables. For a successful solution, the costs of food production must be carefully considered. Shelf lives of ingredients or other raw materials must be in excess of three years (ideally five years). Mass, volume and energy use must all be minimized. Off-gassing during all phases of production must be non-toxic and inoffensive.

a. Challenge

This opportunity would enable a single PI to investigate the utility of targeting the microbiome for any spaceflight-associated medical condition. For example, optimizing absorption of nutrients from the diet might maximize use of stored food supplies, or enhancement of microbiome immune functions could restore better immune regulation during missions or targeting CNS-microbiome interactions could result in better mood. This opportunity is for a single investigator, for a period of up to two years, and for a funding amount of up to $200,000 per year.

b. Examples of projects that could be considered:

- Projects that perform *in vitro* examinations of therapeutic regulation of the microbiome to produce outcomes consistent with downstream physiological consequences for a host. Examples include production of cytokines, interleukins, neurotransmitters, or other biochemical signaling molecules.
- Proposals that use an *in vivo* model to test pharmaceuticals that target commensal microbial cells to change in some fashion that affects health or well-being of the host.

c. Examples of projects that will not be considered:

- Proposals based on probiotic supplements similar to current commercially available products.
- Solutions that fail to include data to support health claims, including controls and concentration-response curves as appropriate for pharmacology studies.
- Proposals whose primary focus is development of a commercial product.
- Projects that examine the effects of spaceflight on the microbiome.
- Solutions that would not be feasible in the limited resource, closed system of a long duration spaceflight mission.

9. Lymphatic imaging in microgravity

New advances in understanding of the importance of the lymphatic system in fluid distribution under simulated microgravity conditions should be explored for potential application to spaceflight-associated medical conditions.

A microgravity ocular syndrome (MOS, also known as visual impairment – intracranial pressure or VIIP) has been described in astronauts related to exposure to microgravity. Ophthalmic changes in some astronauts, primarily the flattening of the back of the eye and optic nerve protrusion have suggested that there may be fluid shifts that occur in the brain and the eye and possibly changes in pressures. Given that lymphatic flow is a low-pressure system and sensitive to fluid shifts, it is possible that lymphatic flow is significantly altered or impaired in microgravity. This could contribute or be related to the ocular syndrome among other adaptations (such as immune system changes or sleep disturbances).

The lymphatic system has at least three cardinal functions: the maintenance of interstitial fluid balance, immune surveillance, and the absorption of fat. The lymphatic vessels play an important role in host defense by carrying antigens and immune cells from the tissues. The lymphatic system is a key component of tissue fluid homeostasis; but in contrast to the closed and high-pressure blood vascular system, the lymphatic vascular system transports lymph in an open and low-pressure network. Changes in pressure and flow are both causes and effects of adaptive processes of the lymphatic system. Hence, it is reasonable to assume that changes in gravitational forces experienced in microgravity not only affect lymph flow but may mediate adaptive changes of the lymphatics. Finally, regional lymph nodes in the head and neck region receive drainage of cerebrospinal fluid (CSF) and interstitial fluid from the central nervous system; hence, adequate lymphatic drainage may be important for CSF and interstitial fluid homeostasis in the brain. Given that lymphatic flow is a low-pressure system sensitive to fluid shifts, it is possible that lymphatic flow is impaired in microgravity.

a. Challenge

This topic would enable a single PI to develop methods to image the lymphatic system in simulated microgravity (e.g. bedrest) and to explore the possible involvement of the lymphatic system in spaceflight-associated conditions such as ocular changes or sleep difficulties. This opportunity is for a single investigator, for a duration of up to two years and for a funding amount of up to $400,000 per year.

b. Examples of projects that could be considered:

- Projects that image lymphatic system function in a spaceflight analog head down tilt bedrest, correlated with existing gold-standard measures of physiological change during bedrest.
- Projects that modify, adapt, or refine existing *in-vivo*, in real time lymphatic imaging capabilities for use in microgravity.

- Proposals that develop a systematic approach to evaluating the effects of gravitational forces on lymphatic flow and adaptive changes of the lymphatics system. Lymphatics should be studied throughout the body, but cervical lymphatics are of most interest and their possible involvement in microgravity ocular syndrome.
- Projects that demonstrate in real time cerebrospinal fluid drainage in larger animals (not rodents) or humans into the lymphatics and test the effects of changes in gravitational vectors on CSF drainage.
- Proposals that examine the role of lymphatics in the immune system adaptation in spaceflight.

c. Examples of projects that will not be considered:

- Proposals that image lymphatic function without associated outcomes measured by alternate means.
- Proposals whose primary focus is development of a commercial product.
- Solutions that would not be feasible in the limited resource, closed system of a long duration spaceflight mission.