UPWARD

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Mending a Broken Heart

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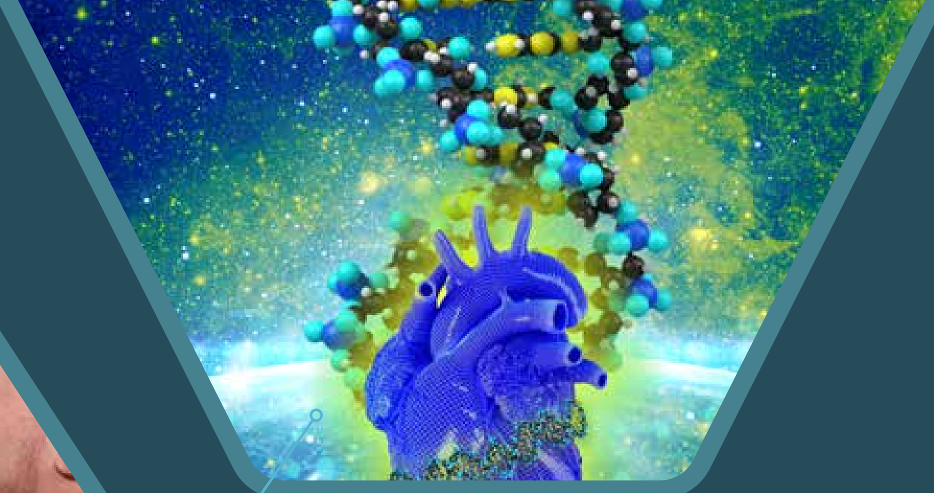
RETHINKING RODENT RESEARCH IN SPACE

ISS U.S. NATIONAL LABORATORY



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THE VIEW FROM THE CUPOLA

BY KIRT COSTELLO, NASA'S JOHNSON SPACE CENTER

Kirt Costello is the Chief Scientist of the ISS Program

I am pleased to provide the perspective to begin this issue of *Upward*, magazine of the International Space Station (ISS) U.S. National Laboratory. Some of you may wonder why the magazine was named *Upward* when in space, in the presence of microgravity, every direction can be upward. In the magazine's inaugural issue, ISS National Lab Deputy Chief Scientist Michael Roberts pointed out that the magazine's name is an embodiment of the spirit behind the ISS National Lab and that great discoveries await in the amazing space laboratory that is the International Space Station.

In honor of our orbiting laboratory, with its bewildering gravitational vector, I think it is important that we consider the downward objective of the ISS National Lab: its mission to return these discoveries to the planet for the benefit of everyone on Earth. The nearly 4,000 researchers who have sent more than 2,600 investigations to the ISS have envisioned the ultimate benefits to life on Earth resulting from their research.

On April 5th of this year, I was proud to announce that NASA and our International Partners released the 3rd edition of our *Benefits for Humanity*. This book details ISS research from NASA, the ISS National Lab, and many other organizations across the globe that has resulted in benefits for our Earthbound populations worldwide. In this new edition, we also included sections on the economic and scientific valuation of that research, showcasing not only the wide-ranging impact ISS research has on our scientific community but also the potential of the laboratory to foster a marketplace economy in low Earth orbit.

The ISS National Lab is an active, dynamic laboratory with continually exciting results. In this issue of *Upward*, we hear about research that should be close to all our hearts. A team of researchers from Loma Linda University leveraged the ISS National Lab to study human cardiovascular progenitor cells, young precursors to cardiovascular cells, in microgravity. Results from this research may open new avenues to develop cell-based regenerative therapies to combat heart disease and repair damaged cardiac tissue in patients on Earth.

Also in this issue, we learn how investigators are using the ISS National Lab for sustainability-related research aimed at finding new solutions to environmental challenges facing our planet today. From growing sustainable algae to studying the cohesiveness of sediment particles and improving membranes that separate contaminants from industrial air streams, ISS National Lab research is providing valuable insight for sustainable development to benefit Earth now and in the future.

Lastly, this issue highlights preliminary results of ISS National Lab projects from several innovative startups awarded through the MassChallenge accelerator program. MassChallenge financially supports, through competitive process of award, the development and testing of disruptive research and technology, and the ISS National Lab's partnership with Boeing to award grants to early-stage entrepreneurs through this program provides small businesses with access one of the most exotic environments on (or rather off of) Earth.

As you read this issue of *Upward*, remember that the old adage, "Everything that goes up must come down," is just a special condition. Our efforts at NASA have enabled astounding achievements—an orbiting National Lab, probes that continually travel outward into the cosmos, and technology to send humans to the moon (and eventually beyond!)—and it is the knowledge that returns to us on Earth that benefits us all. ■

MENDING A BROKEN HEART

USING MICROGRAVITY

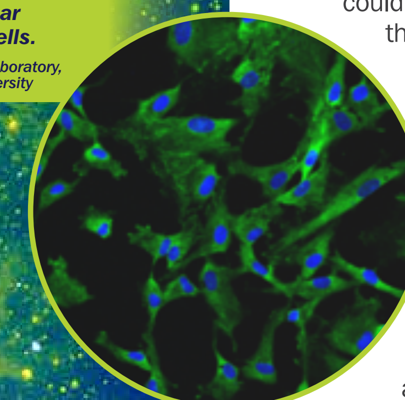
Cardiovascular Progenitor Cells Hold Promise for Regenerative Therapies

BY AMELIA WILLIAMSON SMITH, *Staff Writer*

The human heart is truly amazing. Each day, this small muscular organ beats approximately 100,000 times and pumps around 2,000 gallons of blood, bringing life-sustaining oxygen and nutrients to all parts of the body.

The heart continuously pumps blood—unless a coronary artery, which supplies blood to the heart, suddenly becomes blocked and the blood flow is severely restricted or stops. Without oxygen, the heart tissue rapidly begins to die. Even after blood flow is restored, the damaged tissue is unable to pump blood as well as healthy tissue. According to the Centers for Disease Control and Prevention, about 735,000 Americans have a heart attack and around 610,000 die from heart disease yearly, accounting for one out of every four deaths in the United States.

But what if there were a therapy that could regenerate heart tissue and help restore cardiac function? The microgravity environment of the ISS National Lab allows scientists to study cells in ways not possible on the ground, and research being conducted on the orbiting laboratory could help lead to the development of cell-based regenerative therapies for people with heart disease back on Earth.



Human neonatal cardiovascular progenitor cells.

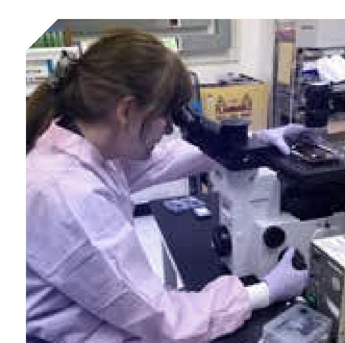
Kearns-Jonker Laboratory, Loma Linda University

One promising area of research into cell-based regenerative therapies is focused on human cardiovascular progenitor cells (CPCs). These cells are immature but in a beneficial way. CPCs are at a very early developmental stage along the path to becoming cardiovascular cells. This means they can differentiate into several different types of cells, such as heart muscle cells or the endothelial cells that line blood vessels.

On Earth, scientists are studying how CPCs might play a role in regenerative treatments for heart disease—and as unexpected as it may seem, knowledge gained from studying CPCs in space could accelerate their development as a therapeutic tool.

To examine the effects of spaceflight on CPCs, Loma Linda University researcher Mary Kearns-Jonker and her team sent cultures of CPCs to the ISS National Lab. The team looked at the effects of microgravity on both neonatal CPCs as well as adult CPCs, as the age of the person from whom the cells are derived affects how well the cells function.

"Our goal was to identify the functional effects of the CPCs after they've been flown in the spaceflight environment," Kearns-Jonker said. "We found that microgravity does cause some very distinct changes that are unique to neonatal cells when comparing them to adult cells."



Mary Kearns-Jonker examining CPCs as they are being prepared for launch at Kennedy Space Center.

Stefanie Countryman, BioServe Space Technologies

TAKING CELLS TO SPACE

Previous research using ground-based simulated microgravity—achieved by placing the CPCs in a 2D rotating culture device—yielded several indicators suggesting microgravity may hold promise for adaptation of CPCs for human therapies on Earth, said Jonathan Baio, who worked as a doctoral student in Kearns-Jonker's lab at the time of the team's ISS National Lab investigation.

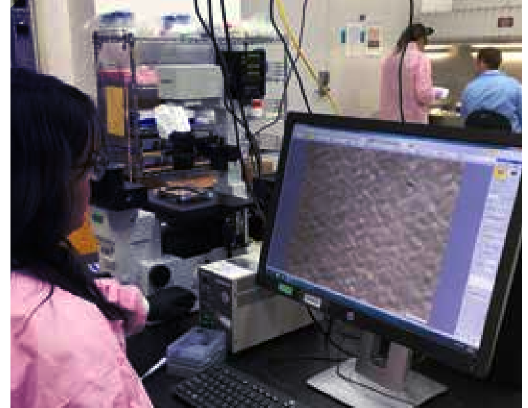
> ***"We looked at both neonatal and adult cells in microgravity to understand the differences that occur between the two and whether this information could ultimately be leveraged for regenerative therapies or to better understand how the heart develops," Baio said.***

The team worked with ISS National Lab commercial service provider BioServe Space Technologies and optimized conditions for the cells to grow in BioServe's BioCell cell culture system. Preflight optimization was challenging because Kearns-Jonker and her team had to find the ideal concentration of cells to put into the BioCell hardware. The team had to make sure the cell population was not too sparse initially but also did not become too crowded as the cells reproduced. Another challenge was to optimize the feeding schedules so that the neonatal and adult CPCs could be fed on the same day at the same time even though each type of cell grows at a slightly different rate.

Last-minute changes to the launch schedule also posed challenges, said Aida Martinez, a medical student at Frank H. Netter MD School of Medicine at Quinnipiac University, who worked as a research assistant in Kearns-Jonker's lab during the team's ISS National Lab investigation. The first launch date was cancelled due to bad weather, bumping the launch back by two days.

"This heightened the anticipation and excitement, but we had to go back and rethink part of it too, because our experiment had very specific timepoints," Martinez said. "The cells had to be under specific conditions for a certain amount of time with little wiggle room, so we had to brainstorm beforehand and in real time how we would deal with a change in the schedule."

In preparing an investigation for launch, preflight validation studies and activities involve contingency planning driven by the ISS National Lab Operations team and the commercial service provider to help prepare researchers for circumstances such as launch slips that could lead to setbacks. This allows the research team to think ahead and develop a detailed mitigation plan to help ensure the success of their investigation.



The Kearns-Jonker team prepared the CPCs live for launch on SpaceX CRS-11 in the laboratory at NASA's Kennedy Space Center.

Stefanie Countryman, BioServe Space Technologies

PREPARING THE CELL SAMPLES

Kearns-Jonker and her team used CPCs from four neonatal patients (ranging in age from birth to 4 weeks) and four adult patients (ages 57 to 72 years), looking both at individual patient samples and samples pooled according to age group. The cells from each patient were clonal populations, which means they were derived from a single cell and expanded, making the cells identical.

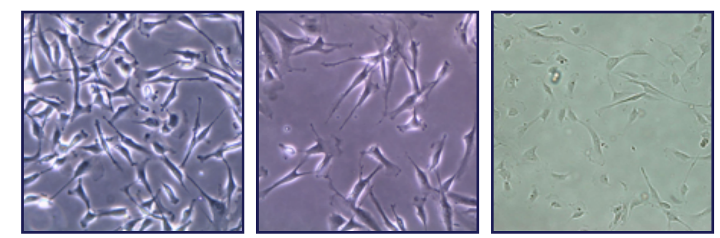
Aida Martinez and Jonathan Baio loading CPCs into the BioCell hardware at NASA's Kennedy Space Center in preparation for launch.

Stefanie Countryman, BioServe Space Technologies

The weather cooperated on the second launch date, and the team's investigation was launched on SpaceX's 11th commercial resupply services mission to the ISS, while the control cells, which were also grown in BioCell hardware, remained on the ground. After 12 days in space, some samples were placed in a fixative that stabilizes RNA, and the rest of the live cells were returned to Earth after 30 days in orbit.

> ***"We took the samples from splashdown, drove them straight to the lab, and were very happy to find that the cells had excellent viability," said Kearns-Jonker. "We didn't let the cells recover in the lab and did all of the functional studies right then to minimize the recovery time."***

In the lab, Kearns-Jonker and her team looked at the functional characteristics of the live cells—their ability to divide, move, and communicate via signaling. Such analyses had to be done immediately, before the cells had a chance to readapt to Earth's gravity. The team also analyzed the cells' gene expression and microRNA (noncoding RNA molecules that help regulate gene expression) profiles. The team compared results from the cells grown on Earth with those grown in microgravity, while also comparing differences between the neonatal and adult CPCs.



Neonatal CPCs cultured in the BioCell hardware.

Kearns-Jonker Laboratory, Loma Linda University

EXAMINING CHANGES FROM MICROGRAVITY

Kearns-Jonker and her team found that microgravity induced changes in the CPCs when compared with Earth-grown cells. Some changes were seen in both the neonatal and adult CPCs, while others were unique to the neonatal cells alone.

In the spaceflight samples, the team measured several markers of cardiac development. The neonatal CPCs were found to exhibit markers characteristic of a slightly earlier stage of development. This slight de-differentiation is associated with enhanced "stemness"—making the CPCs behave more like stem cells and enhancing their potential to develop into different types of cardiovascular cells. Interestingly, these changes were not found in the adult CPCs.

In the neonatal CPCs, calcium signaling and AKT signaling were both activated in response to spaceflight. This is significant because calcium signaling plays a prominent role in the early stages of heart development, Baio said. "Additionally, AKT is an important molecule in promoting pluripotency and stemness and the ability of a stem cell to continue to divide and expand and retain its stem-like state," he said.

The neonatal CPCs grown in microgravity were also found to have enhanced proliferation, meaning they were able to divide and increase in number more rapidly. In addition, both the neonatal and adult CPCs exposed to microgravity exhibited an enhanced ability to migrate. Migration is important, because once therapeutic cells are injected into the heart, you want them to be able to migrate and move to injured or damaged areas, Baio said.

Aida Martinez, Jonathan Baio, and Mary Kearns-Jonker at NASA's Kennedy Space Center.

Jonathan Baio

These spaceflight results are significant because researchers could use this knowledge to recapitulate the effects on the ground in the context of advancing cell-based regenerative therapies. "There are multiple examples in the literature where a slight de-differentiation and activation of the specific transcription factors that we see elevated here have been associated with improved outcomes in a cell transplant setting," said Kearns-Jonker.

__A transcription factor__ is a molecule that helps regulate gene expression by controlling whether a gene's DNA is transcribed into RNA.

COMPELLING RESULTS AWARD

Kearns-Jonker was presented with a 2018 ISS Compelling Results Award in Biology and Medicine at the annual ISS Research and Development Conference. The award was given in recognition of her compelling research into microgravity's effects on CPCs and the potential to leverage these results to advance the development of regenerative therapies for cardiac repair on Earth.

Loma Linda University

NASA astronaut Peggy Whitson exchanging the CPC growth media in the BioCell hardware onboard the ISS.
NASA

BRINGING BENEFITS BACK TO EARTH

Cells with markers of early stages of development and enhanced stemness could enable a more effective integration of therapeutic cells into heart tissue and improve tissue regeneration after an injury such as a heart attack, Baio said. Thus, the microgravity-induced changes in the neonatal CPCs may be helpful in developing cell-based therapies on Earth that can improve outcomes for patients with heart disease.

The next step would be to explore whether the microgravity-induced changes observed in neonatal CPCs produce beneficial effects *in vivo*, that is, in living organisms, Kearns-Jonker said. "What we don't know is: How do the gene expression and microRNA changes noted after exposure to microgravity translate into effects that we can see *in vivo*? We actually need to test that to see whether or not what appears to be something that could be very good for regeneration is, in fact, beneficial."

It is also important to continue to study CPCs to more fully understand the mechanisms behind the microgravity-induced changes. Although ground-based simulated microgravity is not a perfect model for true microgravity, scientists may be able to use simulated microgravity as a method to adapt CPCs for use in cell-based therapies.

> ***"If one finds that microgravity-induced benefits can be recapitulated in simulated microgravity models on Earth, it's very reasonable to envision pretreating the cells with simulated microgravity for prospective therapeutic applications," Kearns-Jonker said.***

Looking to the future, there is great potential in how microgravity or simulated microgravity could be used to directly affect cardiac repair on Earth, Baio said. "Being able to do space-based research is critical to being able to provide a unique perspective into cellular physiology and what the impacts could be for human health and, potentially, new therapeutics that we would never otherwise consider." ■

The third edition of NASA's "International Space Station Benefits for Humanity" book is now available. More than 3,000 researchers representing more than 100 countries have conducted experiments in microgravity onboard the orbiting laboratory, and that number continues to grow. This book is filled with stories illustrating the many benefits of conducting research on the orbiting microgravity laboratory, including examples of research accomplishments in the areas of economic development of space, innovative technology, human health, Earth observations and disaster response, and global education.

This edition includes new assessments of the economic and scientific value of the station, presenting some of the commercial products and realized benefits to date as well as providing greater detail about the scientific value of research activities on the International Space Station.

DOWNLOAD NOW:
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SPACEFLIGHT STUDIES FOR A SUSTAINABLE FUTURE

BY BRIAN GREENE, *Staff Writer*

European Space Agency astronaut Alex Gerst preparing to transfer algae from a fully grown culture to new media.
NASA

Humankind has made incredible technological advancements over the past two centuries. However, many of these advancements have come at a significant cost to the environment and risk to future generations. Globally, principal human impacts to the environment include accelerated changes to Earth's atmosphere and climate, rising sea levels and increasing ocean temperatures, desertification, shortages of natural resources such as water and food, loss of biological diversity, and widespread pollution.

Now more than ever, it is important to address these issues, and scientists are leveraging the ISS National Lab to gain new insights into global environmental challenges and develop new solutions to benefit Earth. Sustainability is a key focus area for research and development onboard the ISS National Lab, which currently has more than 30 sustainability projects in its portfolio.

ISS National Lab sustainability-related projects are diverse, including studies examining ecosystem production, sustainable land use, and water quality; remote sensing of our oceans and atmosphere for climate modeling; plant research to develop crops that require less water; and technology development designed to improve manufacturing methods and reduce harmful industrial emissions. Results from studies conducted onboard the ISS National Lab provide meaningful insights into materials and processes that drive sustainable development.

Three recent projects from the University of Florida; the University of California, Santa Barbara; and the Houston-based startup Cemsica showcase the diversity of sustainability research in the ISS National Lab portfolio.

ANALYZING ALGAE GROWTH IN SPACE

When people think of algae, they often imagine the green slimy substance that plagues aquarium tanks. However, algae are actually very useful. Algae can take carbon dioxide, water, and light and efficiently convert them into biomass, organic material that contains stored energy. Additionally, under certain types of stress, algae produce chemical compounds that have a variety of applications beneficial to humans, including medicine, fuel, and biodegradable plastics.

A research team from the University of Florida, led by Mark Settles, recently studied algae grown in microgravity onboard the ISS National Lab. Understanding how algae behaves in microgravity—and whether this stressor enhances production of certain compounds—could advance efforts to genetically engineer algae with an improved ability to produce biomass and valuable compounds.

An important first objective of the experiment was to domesticate algae for growth systems that would be practical in space.

> *"On Earth, the systems used to grow algae efficiently rely heavily on gravity," Settles said. "These methods are not applicable in a microgravity environment because you can't rely on convection or the mixing of gas and liquid to provide the appropriate conditions for the algae to grow."*

Settles admits he was not confident that their initial experiment would even maintain a healthy population of algae.

HOUSING THE ALGAE IN SPACE

The space algae grew onboard the ISS National Lab (and in ground controls) inside a photobioreactor, a device that houses and cultivates light-seeking microorganisms such as algae and bacteria. Algae use light and carbon dioxide to generate biomass within the walls of the photobioreactor. As the organisms grow, the excess biomass is harvested. A photobioreactor promotes greater biomass growth than natural systems.

Algae in the Veggie unit. *NASA*

Fortunately, when Settles and his team tested their algal growth system within the Veggie facility on the ISS, they found that it not only succeeded in maintaining a healthy population of algae but also resulted in production of more biomass than in ground controls. Settles posits that because algae do not settle into dense layers in space as they do on Earth, they were able to obtain greater access to the nutrients needed for growth.

These initial results are promising for two reasons. Firstly, the algae could possibly be cultivated as a space crop—both for nutritional use by humans and as a means to produce important compounds during long-term spaceflight. Secondly, results from the cultivation of algae with different genetic backgrounds in space could be used to advance efforts to grow a sustainable algae industry on Earth.

> ***"Right now, to produce high-value compounds, we use fermentation of* E. coli *or yeast," Settles said. "So, it's taking resources that originally came from plants and converting them into things that microbes can use, as opposed to directly using light to produce want you want."***

An algae bag floating in the ISS.

NASA

Having a viable algae industry would reduce demands on land use and offer other environmental and cost benefits.

Settles and his team are still analyzing data from the spaceflight algae, looking for genetic variants that thrived in the space environment and evaluating whether the biomass contains beneficial compounds. Settles says follow-on experiments could include looking at other species of algae or genetically modifying the algae to try and improve them for human use. "If we could get to the point where we're engineering algae to create custom compounds that are of high value, then these kinds of growth systems will be practical on Earth," he said.

WHAT GENES HELP ALGAE GROW WELL IN SPACE?

Settles exposed the algae to radiation to induce genetic mutations, and the postflight algae are undergoing whole-genome sequencing to evaluate which mutants were best suited for flight. "The cost of sequencing was too expensive even 5 years ago to even try and attempt this type of experiment we're doing now," said Settles. Luckily, gene sequencing technology has advanced to the point where its cost is significantly lower now, and Settles has already derived the whole-genome sequences from nearly all the samples obtained in this study.

STUDYING SEDIMENT COHESIVENESS

In another recent ISS National Lab investigation, a team of researchers at the University of California, Santa Barbara, led by Paolo Luzzatto-Fegiz and Eckart Meiburg, used microgravity to examine the cohesive forces between sediment particles. The process by which sediment particles stick together influences their mobility in the environment and plays a central role in sediment transport in rivers, lakes, and oceans, which can have significant impacts on ecosystems and fisheries. Sediment settling is also an important factor in global modeling of the carbon cycle, as sediment near the surface of the ocean absorbs carbon from the atmosphere. However, it is difficult to study cohesive forces on Earth because of the complex interactions of sediment particles with gravity.

Ideally, to measure sediment cohesiveness, one would place sediment in a vial and stir it to break up any particle aggregates. Then, one could evaluate cohesiveness by examining how the particles re-clump together. But compared with the force of gravity, cohesive forces are very weak. Additionally, gravity-driven sedimentation causes particles to quickly clump and settle.

ESA astronaut Alexander Gerst onboard the ISS sets up the University of California, Santa Barbara experiment to examine the cohesive forces between sediment particles in microgravity.

NASA

In the absence of gravity, particles aggregate much more slowly, allowing researchers to observe how they clump together and measure the cohesive forces involved.

> ***"The idea is if you take this experiment to microgravity, you can run it for a very long time and get much greater detail about the aggregation process," said Luzzatto-Fegiz. "Then you can figure out how cohesiveness depends on things like contaminants, salt content, and so on."***

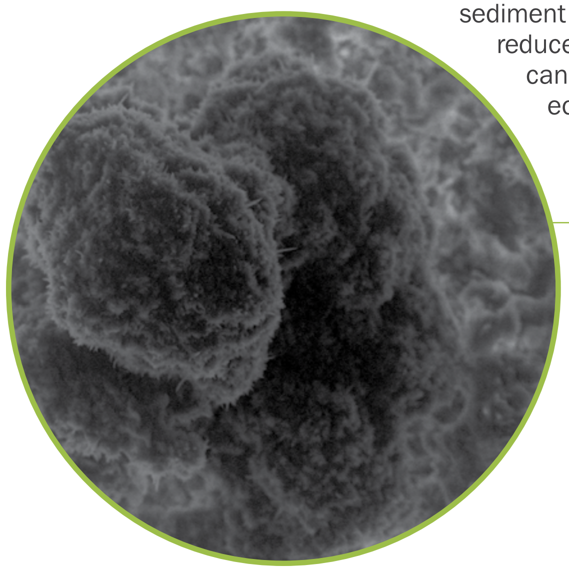
A better understanding of how particles aggregate and the properties that can affect aggregation could lead to better predictive models of environmental systems.

Onboard the ISS National Lab, the team was able to observe sediment aggregation for a whole class of different sediment types and soil compositions, Luzzatto-Fegiz said. Moreover, the researchers had expected the aggregation to last one or two weeks before the large size of the particles would preclude useful data collection; however, the aggregation occurred over a much longer timeframe, allowing the team to collect detailed data for almost 100 days.

These data newly identified that the salinity of water plays a key role in the process of sediment aggregation. "That was really a fundamental contribution that came out of these space station experiments that was not realized before," said Meiburg. Moreover, by comparing their spaceflight data with computer simulations, the research team produced numerical models of sediment transportation.

The team published their results in the *Journal of Fluid Mechanics* in January 2019. "We presented a first-of-its-kind numerical simulation of cohesive sediment particles as they clump," said Meiburg, "and we can demonstrate the mechanisms responsible for the fact that cohesive sediment settles out more rapidly than noncohesive sediment."

These findings provide valuable information for several sustainability applications. "In the ocean, how fast sediment settles impacts how much light you get into a water column," Luzzatto-Fegiz explained. "This in turn affects the ability of algae to bloom—and algae are the basis of the food chain in the ocean." A reduction in sediment settling could lead to reduced algae growth, which can negatively impact ecosystems and fisheries.



Clay aggregates viewed under an environment scanning electron microscope.

UC Santa Barbara

Sediment settling also plays a significant role in the carbon cycle. Carbon dioxide in the atmosphere is absorbed by sediment near the surface of the ocean, and it is important to understand how quickly this sediment forms into larger particles that then settle down into the ocean, leaving the surface layer free to absorb more carbon dioxide. Understanding this process could aid the development of methods to help temper detrimental effects of rising levels of carbon dioxide in the atmosphere, which contributes to global climate change.

CARBON CYCLE 101

Carbon compounds make up all living things, provide energy sources, and impact our climate. The global carbon cycle refers to the movement of carbon between the air, ground, water, and living matter. The oceans are the biggest reservoir of carbon on the Earth. Understanding the two-way exchange of carbon between the atmosphere and the ocean surface is particularly critical, as human-derived atmospheric carbon is on the rise.

NASA astronaut Serena Auñón-Chancellor working on Cemsica's investigation onboard the ISS.
NASA

SYNTHESIZING GAS SEPARATION MEMBRANES IN MICROGRAVITY

Despite many innovations in the energy industry, technology development has been lagging for the removal of gases, notably carbon dioxide, from waste air streams. The company Cemsica has been working on a potential breakthrough technology that addresses the critical need to reduce greenhouse gas emissions that result from industrial processes.

Cemsica is developing nanoporous membranes that can be tailored to remove specific contaminants, like carbon dioxide, from combustion exhaust gas streams, and the company recently conducted an investigation onboard the ISS National Lab aimed at improving synthesis of the membranes.

"The carbon dioxide footprint is one of the biggest problems in the energy industry," said Negar Rajabi, founder and chief executive officer of Cemsica.

However, carbon dioxide is not always a waste product. It can also be a commodity sold as a feedstock for manufacturing chemicals and beverages—if the carbon dioxide is pure and can be recovered economically.

Commercial methods for capturing carbon dioxide have been around for several years but are complex and very expensive. As such, they have not been successfully implemented on a large scale. Cemsica believes its nanoparticle membranes are a better solution that will reduce operational costs, increase efficiency, and accelerate technological innovations in the industry that benefit the world.

A critical feature of Cemsica's membranes are the nanopores—tiny holes that allow precise separation of carbon dioxide from other gas molecules. Because gravity significantly impacts how particles order themselves on the nanoscale, Rajabi hopes that synthesizing membranes onboard the ISS National Lab will allow Cemsica to overcome some remaining manufacturing challenges in the synthesis and assembly of the membranes—allowing them to produce even lower-cost membranes with improved properties.

Although nanomaterials are not new, Rajabi says there is still much to learn that can enhance nanomaterial properties. She and her team are still in the process of analyzing the data from their ISS National Lab investigation, but preliminary results have shown some improvements in the formation, shape, and size of the particles. Confirming these positive results would provide insights for improving manufacturing of the membranes on the ground and could also open the door for future in-orbit manufacturing in this sector, expanding industrial use of low Earth orbit.

NANOSCALE SCIENCE

One nanometer—one billionth of a meter—is tens of thousands of times smaller than the width of a human hair. A nanomaterial is a material made up of many nanoparticles, which are 1 to 100 nanometers in size. Nanomaterials can be naturally occurring (e.g., volcanic ash) or engineered by humans.

LOOKING AFTER OUR PLANET'S FUTURE

Achieving true sustainability has proven difficult and may require radical change, but novel approaches to sustainable living help preserve our Earth for future generations. Earth observations, life sciences investigations, and physical sciences studies onboard the ISS National Lab are each pushing the boundaries of innovation to help address many of our most pressing global environmental challenges. ■

ATTRACTING ENTREPRENEURS TO SPACE

MassChallenge Grantees Move Early-Stage Innovations Forward

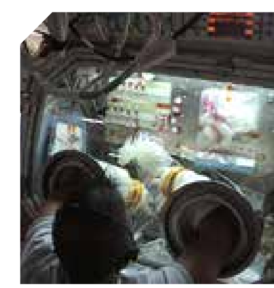
BY ANNE WAINSCOTT-SARGENT, *Contributing Author*

Imagine having the next revolutionary idea with the potential to improve disease treatment, to build better solar cells, or to detect nuclear radiation. What if that idea could benefit from evaluation on an off-the-planet test bed? Now imagine that you could test your idea in space onboard the International Space Station. Are such imaginings far-fetched? Incredibly, no.

Since 2013, the ISS National Lab has partnered with MassChallenge, the largest startup accelerator to award nondiluted funds to early-stage entrepreneurs. Founded in Boston, Massachusetts, MassChallenge has grown to become part of a movement to support entrepreneurs through grant competitions worldwide.

The ISS National Lab has also partnered with The Boeing Company since 2014 to award grants through a MassChallenge “Technology in Space Prize.” Annually, this prize is awarded to several promising companies to support projects to be conducted onboard the ISS National Lab. Together, Boeing and the ISS National Lab have allocated more than $4.5 million in funding toward this prize since its inception.

“The Technology in Space Prize is a great example of an ISS National Lab partnership that brings creativity to science in space,” said ISS National Lab Chief Operating Officer Kenneth Shields. “It helps us connect with the brightest minds in today’s entrepreneur community, and it allows us to mentor these nontraditional users and teach them how to develop ideas for space-based research and development.”



NASA astronaut Joe Acaba working on the LaunchPad Medical investigation onboard the ISS.
NASA

Boeing is an ideal partner for the MassChallenge Technology in Space Prize, given the company’s leadership in innovation and longstanding support of the orbiting laboratory. “Over the past 20 years, the ISS has proven to be a vital research and development platform for our nation and serves as an incubator for future commercial opportunities,” said Kevin Foley, Boeing’s global sales and marketing director for the ISS.

MassChallenge-funded projects conducted onboard the ISS have yielded promising results in the materials and life sciences, and upcoming projects span diverse innovations in areas such as drug delivery, diagnostics, optical materials for solar technology, and nanomaterials for radiation detection.

“The quality of proposals we receive continues to improve every year,” said Foley. “We are looking for projects that are feasible and will generate meaningful near-term impact, whether improving the time-to-market of a therapeutic or helping farmers know where to plant crops for best yields.”

NASA astronaut Peggy Whitson works on the Oncolinx investigation onboard the ISS.
NASA

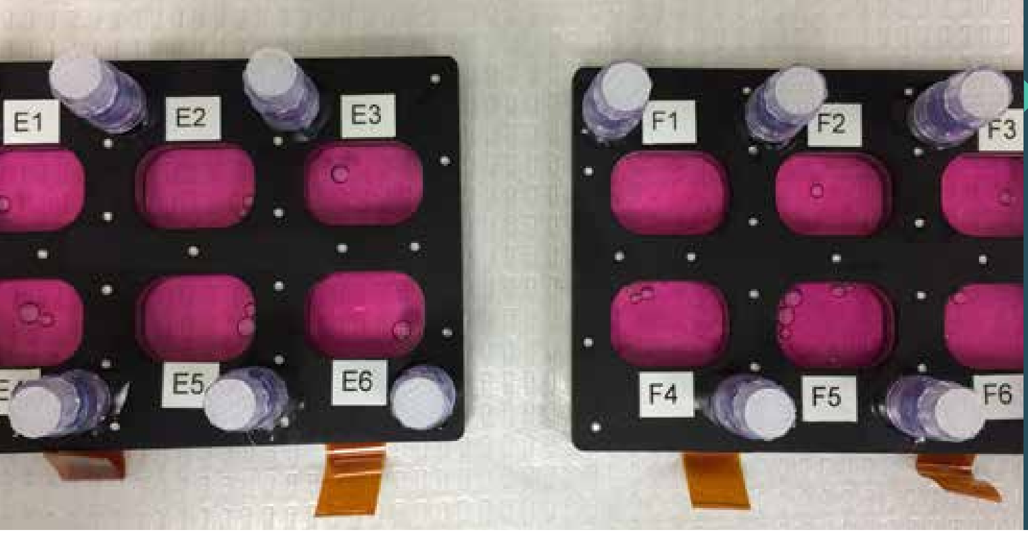
Ras Labs

MIMICKING REAL LIMBS IN FORM AND FUNCTION

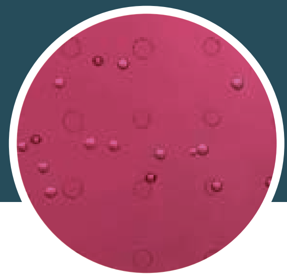
The first MassChallenge project conducted on the ISS focused on technology to create prosthetic limbs that look and feel like a human limb. The startup company, Ras Labs, had developed a new class of “smart” materials—electroactive polymers that drive the functionality of its Synthetic Muscle™ product. Their goal was to enable life-like dexterity for prosthetics, such as contracting and bending without mechanical aid.

In an ISS National Lab investigation, which launched on SpaceX CRS-6 in April 2015 and returned to Earth on SpaceX CRS-8 in May 2016, Ras Labs scientists examined how well Synthetic Muscle™ could function under stresses far beyond what any human being would ever endure. By exposing various polymer coatings and additives to the ISS environment, the experiment revealed the strengths and weaknesses of the materials—insights that will be applied to enhance the durability of prosthetics developed for both broad use and use in robotics.

Read more about this company’s successful experiment in “Bringing Motion to Life: Materials Science Research in Space” from volume 1, issue 2 of Upward.



The Oncolinx investigation used BioServe's 6-well BioCell hardware. Different films allow for distinct types of growth and gas permeability, while enabling microscopy and other types of data acquisition.
BioServe Space Technologies



USING THE BODY'S OWN IMMUNE SYSTEM TO FIGHT CANCER

Envision a therapy that delivers a cancer-fighting drug directly to a tumor without harming the healthy cells around it *and* activates the immune system to continue to hunt and destroy cancer cells. A MassChallenge-funded project conducted by Oncolinx Pharmaceuticals, a biotech company founded in Buffalo, New York, in 2014, used the ISS National Lab to test such a therapy.

Oncolinx scientists attached antibodies made from human immune cells to azonafide cytotoxin, a novel immune-activating cancer drug developed at the National Cancer Institute, to form antibody-drug conjugates (ADCs). The antibodies specifically target tumor cells, and upon attaching to the cancer cells, the azonafide cytotoxin is released.

Oncolinx founder and CEO Sourav Sinha at the Orbital ATK CRS-7 launch.
Oncolinx

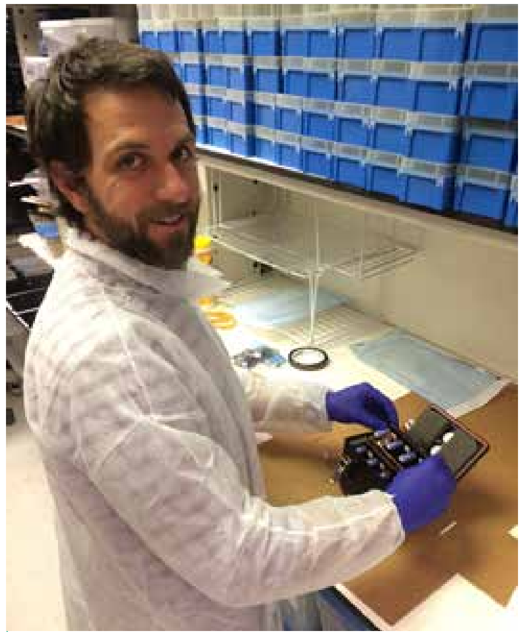
> *"Our technology leverages the body's own immune system to fight cancer," said Oncolinx CEO and co-founder Sourav Sinha, explaining that the drug causes only cancer cells to die, leaving healthy cells unharmed.*

By delivering the drug locally to the cancer cells, azonafide-based ADCs avoid the side effects associated with traditional types of chemotherapy. Preflight studies showed that the drug can destroy 98.2% of cancer cells.

Another powerful benefit of azonafide-based ADCs is that, in addition to destroying cancer cells, they also activate an anti-tumor immune response that could prevent cancer relapse. One of the reasons cancer cells grow in some people is that their immune system fails to recognize tumor cells as invaders. With azonafide-based ADCs, local immune cells are better able to recognize certain molecules secreted specifically by cancer cells, and that improved recognition can activate the immune system to identify and destroy cancer cells that previously were undetectable.

Oncolinx tested the efficacy and drug metabolism of azonafide-based ADCs on cells in microgravity as part of an investigation that launched to the ISS on Orbital ATK's 7th commercial resupply services (CRS) mission in April 2017 and returned on SpaceX CRS-12 in September 2017. To assess how well the azonafide-based ADCs were able to target and destroy cancer cells without harming healthy cells, the research team compared the effects of azonafide-based ADCs cultured with lung cancer cells and separately with noncancerous cells.

Performing these types of drug studies on the ISS National Lab is beneficial, because cells in microgravity (versus those in ground-based studies) may more realistically reflect how cancer behaves in the body.



BioServe Payload Engineer Matt Vellone preparing 6-well BioCells for the Onxolinx investigation inside a Plate Habitat, which provides further levels of containment while allowing for gas exchange and temperature data acquisition.
BioServe Space Technologies

In microgravity, the cancer cells arrange themselves into three-dimensional (3D) groups, or aggregates, that better resemble tumors in the body. This 3D structure permits improved cancer models that allow researchers to better test the performance of cancer drugs.

> *"The cool thing about microgravity is the cells float around and bind onto each other, forming these 3D spheres," Sinha said. "The spheres closely resemble solid tumors as they form in the human body, in contrast to how cells lay flat on the bottom of a petri dish."*

Sinha is still reviewing the spaceflight data. Preliminary results, however, indicate that Oncolinx's azonafide-based ADCs are particularly effective at treating solid tumors, including an aggressive, fast-moving form of lung cancer.

"It's very potent and very specific," Sinha said. "Activating the immune system allows us to leverage the body's natural defenses to target different cancers across the board."

To date, Oncolinx has partnered with more than 12 leading pharmaceutical companies to develop azonafide-based ADCs. These drugs have the potential to increase the effectiveness of cancer treatment and reduce side effects, and testing azonafide-based ADCs onboard the ISS was a once-in-a-lifetime opportunity, said Sinha. He credits the company's ISS experiment with helping Oncolinx accelerate their research and get closer to human trials, which he hopes will occur within the next two years.

GLUING BONES AND SPEEDING NEW BONE GROWTH

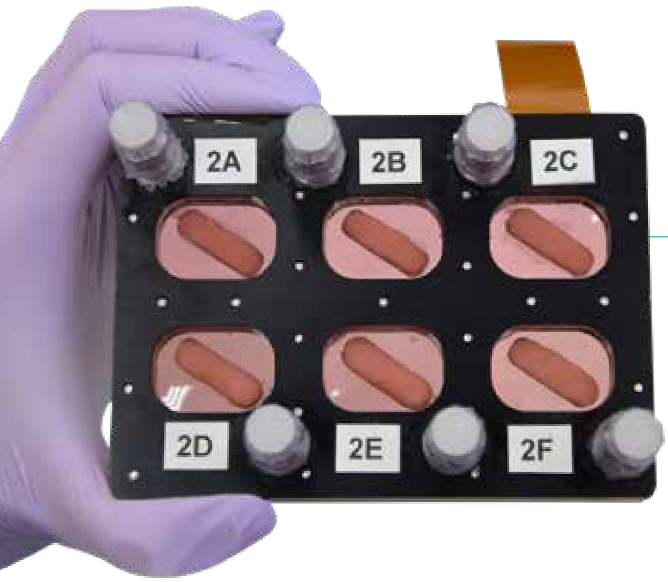
A MassChallenge-funded project from LaunchPad Medical used the ISS National Lab to test a new biomaterial that can glue bones together. The injectable glue, Tetranite®, has the potential to speed new bone growth while reducing the recovery time and pain of patients, particularly in the orthopedic world, said Brian Hess, LaunchPad Medical CEO and an engineer by trade. Located in Lowell, Massachusetts, LaunchPad Medical was founded in 2014 by Hess and a team of entrepreneurs with extensive expertise in startup medical device development and commercialization.

The company's experiment, which launched on SpaceX CRS-13 in December 2017 and returned with SpaceX CRS-13 in January 2018, examined how osteoblasts—the cells responsible for bone formation—reacted in the presence of Tetranite®.

> *"These cells typically slow down when in microgravity, because the space environment accelerates osteoporosis," Hess said, citing the well-known statistic that without intervention, astronauts can lose, on average, up to 2% of their bone mass for every month they spend in space.*

In LaunchPad Medical's ISS National Lab investigation, the research team examined how the osteoblasts responded to Tetranite® in comparison with osteoblasts alone and osteoblasts in the presence of an existing commercially available bone-graft product. ISS crew members captured photos of the cells to show their health and growth, while also collecting cell culture media every five days to study secreted molecules that relate to bone-cell behavior. Finally, cellular RNAs from the beginning and end of the experiment were compared to evaluate changes in the expression of genes related to bone growth.

LaunchPad Medical CEO Brian Hess (far right) and team at NASA's Kennedy Space Center before the SpaceX CRS-13 launch.
LaunchPad Medical



Osteoblasts growing around LaunchPad Medical's Tetranite® material.

LaunchPad Medical

Analyses revealed how the spaceflight osteoblasts responded to Tetranite® by growing and exhibiting bone-formation behaviors. "We saw favorable gene-expression changes marking bone growth that will help advance our studies," Hess said. "To see this response in the extreme and rapid osteoporosis-inducing space environment motivates us to study Tetranite® for use in patients with osteoporosis, who are susceptible to a bone injury because of their poor bone quality and whose recovery from injury is quite challenging."

Hess anticipates beginning human trials within the next year and will initially target the dental industry by providing glue to immediately stabilize tooth implants, as opposed to the current treatment plan, which often requires staged surgeries. However, Tetranite® has the most significant potential impact for older people who suffer from osteoporosis. According to the International Osteoporosis Foundation, more than half of the U.S. population ages 50 years and above have either osteoporosis or low bone density. Studies suggest that approximately one in two women and up to one in four men in this age range will break a bone because of osteoporosis.

"Our first program will focus on dentistry and then orthopedics, targeting specific parts of the body, including the spine, cranium, joints, and extremities," Hess said.

Having an injectable glue that naturally resorbs and is replaced with bone would eliminate or reduce the need to make large incisions in order to drill holes to implant metal screws or other hardware devices to repair damaged bone. Moreover, patients would not have to return for later surgeries to have hardware removed.

LaunchPad Medical CEO Brian Hess (third from left) and team in the lab at NASA's Kennedy Space Center in preparation for launch.

LaunchPad Medical

"Tetranite® could change the landscape of how clinicians treat bone problems and improve patients' experience by reducing pain and accelerating healing," Hess said. "It potentially could be a real revolution to the surgical field of orthopedics."

LOOKING AHEAD

As evidenced by these success stories, research and development in space is no longer just the domain of government agencies, academics, or big commercial companies. Small startups, too, can advance their technology or product line using the ISS National Lab.

Over the past year, two additional MassChallenge-funded projects have flown to the ISS National Lab, with results expected in the coming months. In an investigation that launched to the ISS on SpaceX CRS-15 in June 2018, the biotech startup Angiex, Inc., is testing a novel cancer therapeutic that targets both tumor cells and tumor blood vessels that potentially could be used to treat 90% of all cancers.

LambdaVision, Inc., a spinoff company from a University of Connecticut research group, launched an investigation on SpaceX CRS-16 in December 2018 that seeks to leverage the ISS National Lab to improve the manufacturing process for a protein-based retinal implant to restore vision to patients with retinal degeneration.

Thanks to MassChallenge and the ISS National Lab's partnership with Boeing, new innovators such as these are making their business case through diligent science in microgravity. They are taking critical steps to solve some of the world's toughest problems and are laying the foundation for a brighter, healthier world.

> ***"Boeing investment in innovation targets an untapped user community of startups through business accelerators like MassChallenge, with outcomes that benefit us here on Earth," Foley said, "and it holds the potential to expand our economic sphere well beyond 2028."***

SPOT LIGHT

Expanding Horizons for Microbiome Research on the ISS

BY HEATHER ANDERSON, *Contributing Author*

Microorganisms, whether fungi, archaea, bacteria, or viruses, are often disparaged as germs with nothing better to do but cause disease. However, scientific advances to better understand the form and function of the human microbiome (the collection of microorganisms that live in and on people) have revealed that the blind eradication of microorganisms is not the answer even if it were possible. In fact, each of us has a unique microbiome that is a vital part of human health, and healthy microbiomes play an active role in protecting us from disease. Healthy microbes (and their interactions with each other as part of the human microbiome) need to be identified and fostered to sustain health.

NASA astronaut Ricky Arnold swabbed surfaces in the ISS to collect microbe samples and then processed the microbial DNA using the Biomolecule Sequencer, a device that enables DNA sequencing in microgravity, to identify microbes able to survive in microgravity.

NASA

The ISS National Lab workshop "Exploring the Microbiome/Immunome and Disease on the International Space Station" focused on how the spaceflight environment might accelerate research to better understand the microbiome and its role in maintaining the balance between health and disease. The workshop brought together more than 40 thought leaders from academia, government, and the private sector to discuss ways in which they could work together to improve human health on Earth through spaceflight microbiome research.

Because the microbiome involves complex community interactions of numerous species, many of which are known only by their DNA signatures, it is difficult to fully characterize how the microbes on skin or in the gut contribute to health and disease or how the balance within microbial communities changes in response to the environment. However, research conducted on Earth has shown that our microbiome performs many functions essential to human health, such as making otherwise inaccessible nutrients digestible, providing essential vitamins and nutrients, and protecting us from pathogens.

For example, healthy microbiomes transplanted into individuals with recurrent gut infections are an effective clinical treatment. Moreover, the gut microbiomes of obese people are different from those of lean people, and the microbiomes of people with autism are different from those of people without autism. Because the microbiome may be involved in such diverse conditions, it is critical that researchers find ways to more fully understand its behavior and function—which is where the ISS National Lab may provide an advantage by offering an alternative platform for studying the microbiome.

Spaceflight induces sudden but persistent and profound effects on the human body. Studying the microbiomes of humans and animal models onboard the ISS provides a window into how microbial communities associated with different environments or locations on the body respond to stimuli such as stress, dietary changes, and immune dysfunction—all of which are known to impact the microbiome.

Thus, characterizing the microbiome's response to spaceflight may yield insights into the complex community interactions that underlie the microbiome's beneficial—or detrimental—effects on human health. Better understanding these interactions will help medical professionals devise new approaches to leverage those beneficial effects and combat detrimental effects here on Earth.

Participants of the ISS National Lab workshop provided recommendations aimed at maximizing the impact of microbiome research on the ISS, facilitating collaborations and public-private partnerships in support of such initiatives, and standardizing research approaches. These recommendations, which are detailed in a report released in July, are helping to define the path forward in developing a sustainable microbiome research program on the ISS National Lab.

> *"The workshop was a great opportunity to hear from a wide range of experts interested in using the ISS to study human health from a microbiology and immunology perspective," said Alexander Voorhies, staff scientist at the J. Craig Venter Institute who attended the workshop. "The ISS is a collaborative endeavor by its nature, and bringing diverse scientists together will hopefully inspire collaborative investigations into making space more habitable for humans."*

Rethinking Rodent Research in Space: Content & Design

SPOT LIGHT

BY AMY ELKAVICH, *Staff Writer*

Building on the scientific success of previous missions using animal models, the Rodent Research Reference (RRR) Missions adapt the standard rodent research format to maximize science return and resource utilization via tissue sharing—providing multiple investigators access to biospecimens from a single mission. Following the successful first RRR Mission, which launched to the ISS on SpaceX's 16th commercial resupply services mission in December 2018, the ISS National Lab recently announced its second RRR Mission for investigators seeking access to biological specimens to support fundamental biomedical inquiries.

NASA astronauts Scott Kelly and Terry Virts conduct rodent research investigations within the Microgravity Science Glovebox and the Rodent Habitat Module onboard the ISS.

NASA

The persistent microgravity environment on the ISS National Lab has profound effects on living organisms that can mimic the onset and progression of disease here on Earth, providing researchers with valuable information on the mechanisms behind diseases such as cancer and possible new methods of treatment. Mice and rats, which share many of the same genes and physiological characteristics as humans, have served as exceptional translational models in space-based research since the early 1980s.

The RRR Missions provide opportunities for investigators to obtain biospecimens from animal tissues that have been exposed to the spaceflight environment for a wide variety of research purposes. Insight gained from the RRR Missions may help advance research on diseases and aging effects involving muscle, bone, and other organ systems.

Each RRR Mission is a partnership between the ISS National Lab, NASA, and Taconic Biosciences. Taconic provides, at no cost to the mission, selectively bred and genetically engineered mice and rats for research use to advance our understanding of human disease. The objective of each mission is to generate data that validate the rodent research model in space for the benefit of medical science on Earth.

The significance of the RRR Missions rests in the adoption of an innovative and customizable mission concept using a standardized approach to operations and habitat configuration that both benefits researchers and maximizes ISS National Lab resources. Through the use of a simple and reproducible mission architecture based on use of the most commonly used genetic strains of mice, it is possible for RRR Missions to be quickly integrated for spaceflight to take advantage of missions of opportunity. In this way, the new RRR Mission concept has the potential to improve resource allocation by optimizing use of available space onboard flight vehicles.

Additionally, the RRR Mission concept significantly reduces the need for extensive feasibility assessment of individual rodent research investigations, enabling the ISS National Lab to rapidly implement RRR Missions, often reducing the time from mission concept to flight.

The RRR Missions join the existing Rodent Research Program Missions led by single investigators as a supplemental yet crucial element of a pathway for new partnerships across disciplines and industries. Partnerships with funders and investors, commercial service providers, and commercial suppliers introduced through this experimental design have the potential to expand access to invaluable biomedical research specimens, data, and knowledge. Additionally, cooperative partnerships such as these enable the costs of mission planning to be reduced while expanding access to specimens and data.

The introduction of the RRR Missions, conducted alongside the existing Rodent Research Program missions, may advance scientific knowledge to benefit human health here on Earth and reflects the ISS National Lab's commitment to delivering meaningful scientific advancement back to the U.S. taxpayer. ■

This content was abridged from an article that originally appeared on issnl.us/ISS360.

Chips in Space Improve Treatment Options for Osteoarthritis

SPOT LIGHT

BY EMILY TOMLIN, *Staff Writer*

In an era of escalating death and damage from the opioid epidemic, innovative solutions to prevent the more than 130 daily U.S. deaths from opioid overdose are a national priority. Within this context, a major focus area for the healthcare industry is to better understand the underlying causes of chronic pain and establish pain management strategies that avoid the risks of opioid addiction—and a research team from the Massachusetts Institute of Technology (MIT) recently took this quest to space.

Of the more than 50 million Americans living with chronic pain, nearly 6 million suffer from long-term osteoarthritis that results from a previous joint injury. Vehicle accidents, sports injuries, and other sources of joint trauma can lead to post-traumatic osteoarthritis (PTOA), even in young adults. Approximately 50% of individuals with knee injury develop PTOA within 10 years, and 30% of military personnel develop TOA from combat injuries.

Sadly, restoring joint stability via anterior cruciate ligament (ACL) reconstruction in the knee, for example, does not reduce the risk of developing PTOA. In fact, there is currently no approved therapy to prevent the lifelong pain and dysfunction of PTOA, which is a leading cause of disability worldwide. The MIT investigation, led by Alan Grodzinsky, launched to the ISS National Lab in May and seeks to develop a new approach to preventive care for PTOA.

Little is known about the molecular mechanisms underlying PTOA initiation and progression, but inflammation occurring immediately after joint injury appears to play a key role in the onset of chronic PTOA. The inflammation will resolve for some, but for others, the silent damage continues despite the absence of symptoms and apparent progress toward recovery. Previous PTOA research on trauma to cartilage has largely ignored the complex biomechanics involved in inflammation—some of which may be key to early medical intervention.

Canadian Space Agency astronaut David Saint-Jacques works on the MIT tissue chip experiment onboard the ISS

NASA

Grodzinsky's team is using a different approach: a tissue chip containing multiple cell types to mimic the fundamental biomechanics of how bone and cartilage move and interact with the synovial membrane (the joint-lining tissue that produces a lubricating fluid). The team's ISS National Lab experiment validated this tissue chip model both on the ground and in space, where bone and cartilage damage may be accelerated.

In orbit, the team exposed the tissue chip to pro-inflammatory molecules, simulated an impact injury, tested several therapeutics, and preserved samples of cells and secreted molecules at several experimental stages for postflight analysis. They used tissues from different donor individuals in these studies to characterize complex tissue chip responses to both "injury" and response to therapy.

The study holds the potential for new biomarker discovery that will enable early diagnosis and reveal the mechanisms that underlie individual variability in response to both injury and treatment. Successful preventive treatment following injury, during the 10 to 20 years of asymptomatic damage in at-risk individuals, could potentially drastically reduce the number of patients who develop chronic pain.

This type of early intervention is common in the management of diabetes, heart disease, and osteoporosis, but for those individuals suffering from chronic pain, preventive medicine is still beyond reach. Creative and advanced biomedical approaches to studying disease—on Earth and in space—can hopefully provide nonopioid relief to the military personnel, student athletes, and millions of others afflicted by PTOA or other causes of chronic pain. ■

Grodzinsky's ISS National Lab project is one of several tissue chip studies co-sponsored by the National Institutes of Health's National Center for Advancing Translational Sciences (NIH NCATS), complementing other spaceflight tissue chip experiments co-sponsored by NIH's National Institute of Biomedical Imaging and Bioengineering (NIBIB) and the National Science Foundation (NSF).

This content was abridged from an article that originally appeared on issnl.us/ISS360.

News & Notes
FROM THE ISS NATIONAL LAB

ISS
U.S. NATIONAL LABORATORY

NEW SCIENCE ON STATION

Two recent commercial resupply services (CRS) missions to the ISS carried more than two dozen ISS National Lab-sponsored payloads. Investigations on Northrop Grumman CRS-11, which launched in April, focused on materials and physical sciences, in-orbit manufacturing, drug development, and small satellite deployment. Many investigations on SpaceX CRS-17, which launched in May, were aimed at improving human health, with several focused on drug development and screening.

Additionally, SpaceX CRS-18, scheduled to launch to the ISS later this month, will deliver 25 ISS National Lab-sponsored payloads, ranging from advanced materials studies to biomedical research and education projects. This launch includes several investigations from well-known commercial entities, including pharmaceutical company AstraZeneca, brand apparel giant adidas, and the Goodyear Tire and Rubber Company. The ISS National Lab has seen a rapid increase in private-sector utilization of the orbiting laboratory—in fiscal year 2018, more than 70% of all payloads launched to the ISS National Lab represented private-sector research and development.

NEW STEM KIT WITH SPACE-THEMED ACTIVITIES

In April, the ISS National Lab education team released a new Space Station Explorers kit for students in grades 3–8 in both traditional classroom settings and nontraditional learning environments. The free kit includes hands-on space-themed activities that are engaging, use low-cost supplies, and align with national education standards for science, technology, education, and mathematics (STEM). The kit is now additionally being distributed as part JFK Space Labs, a STEM partnership with the John F. Kennedy Library Foundation.

WORLD CHANGING IDEAS: ISS COTTON SUSTAINABILITY CHALLENGE

The 2017 ISS Cotton Sustainability Challenge, sponsored by Target Corporation in partnership with the ISS National Lab, received an honorable mention in the 2019 World Changing Ideas awards from business magazine *Fast Company.* The Cotton Sustainability challenge sought to generate ideas on how the ISS could be leveraged to improve the use of natural resources such as water for sustainable cotton production on Earth. In April 2018, Target and the ISS National Lab awarded three projects through the challenge.

Read UPWARD online at **Upward.ISSNationalLab.org**