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HARNESSING THE POWER OF SPACE BUBBLES

NEW BIOSENSING METHOD COULD DETECT CANCER MARKERS AND MICROPLASTICS

ON PAGE 2

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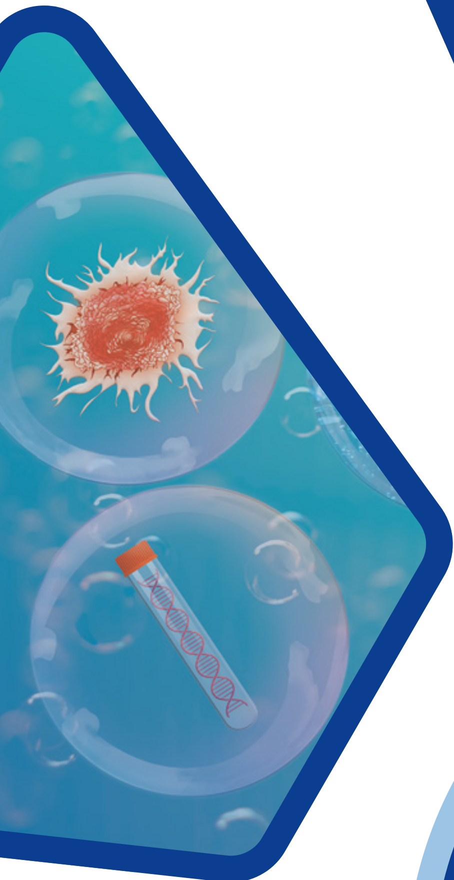

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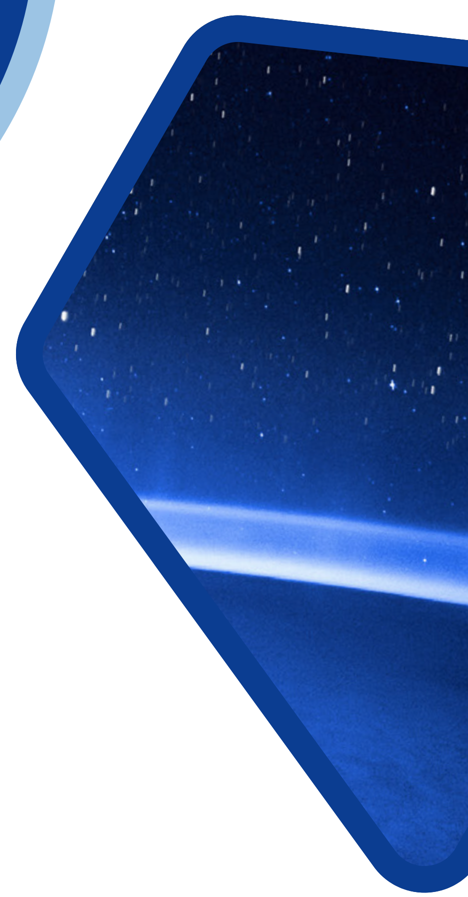

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VIEW FROM THE CUPOLA

By Twyman Clements, Space Tango President and Co-Founder

Twyman Clements is the president and co-founder of Space Tango, where he leads the organization's engineering, science, and business teams to deliver automated products that return usable results to customers looking to leverage the microgravity environment of low Earth orbit.

The possibilities that lie ahead are inspiring, as we explore space to find solutions to some of Earth's most pressing problems. The Space Tango team is at the forefront of discovering how microgravity can unlock new frontiers in research. Our journey isn't just about science—it's about transforming bold ideas into reality through the automated solutions we've meticulously designed.

Fundamental science is the bedrock of innovation. It's the starting point where curiosity meets experimentation, and from this foundation, groundbreaking discoveries emerge. By understanding the basic principles of how things work in microgravity, we pave the way for applications that could change industries and improve lives. This is why we're so committed to delivering publishable, impactful science that pushes the boundaries of what we know and can achieve.

This is possible thanks to the vibrant and collaborative community of low Earth orbit (LEO) users and providers, including the International Space Station (ISS) National Laboratory. These dynamic partnerships advance fundamental science and help lay the groundwork for a thriving space economy. As you dive into this edition of *Upward*, you'll see how these collaborations continue to evolve and inspire us all.

Highlighted on the cover of *Upward* is research from the University of Notre Dame, which sent two investigations utilizing Space Tango hardware to the space station to study how bubbles form and behave in microgravity. Microgravity is the only environment where buoyancy is eliminated, allowing thermal bubbles to remain suspended for an extended period for observation. Findings revealed that bubbles grow larger and faster in the space environment. This crucial result provides a pathway to advance biosensors that could detect early cancer biomarkers. After a successful launch on Northrop Grumman's 21st Commercial Resupply Services mission, Space Tango is excited to have begun a third investigation with this Notre Dame team.

This edition also features research from the University of Florida, a long-term partner of Space Tango, which used our CubeLab hardware for three tissue chip investigations to study age-related muscle loss, a condition referred to as sarcopenia. Microgravity allowed the research team to study muscle loss at an accelerated rate, and results could lead to new treatments for patients with sarcopenia on Earth. The CubeLab for this research was custom-made—the first and only of its kind, and we were able to image muscle cells as they contracted space. While the initial results were inspiring, we were dedicated to getting the science right. This was possible with continued iteration over multiple missions, which resulted in a standardized CubeLab design for valuable tissue chip research on age-related muscle loss in space.

The issue also highlights an investigation from Clemson University that utilized the orbiting laboratory to find sustainable solutions for the cotton industry. The project was sponsored by the ISS National Lab, funded by the Target Corporation, and supported by Techshot, which Redwire Corporation has since acquired. The Clemson University team examined gene expression in cotton plants to explore the genetics behind regenerating whole plants from single plant cells. The experiment found that microgravity may reveal genes that control this process, allowing researchers to effectively alter plants to add traits such as disease resistance and drought tolerance, benefiting agriculture both on and off Earth.

These investigations highlight the power of public-private partnerships in advancing fundamental science and, in the long-term, laying the groundwork for a commercial economy in LEO. The work described is a testament to the collaboration between industry, nonprofit, and government teams. My sincere thanks go to our flight partners, the ISS National Lab, and the space research community for pushing the boundaries of fundamental science. The investigations featured in this edition of *Upward* showcase just a few of the exciting ways we are leveraging microgravity to unearth answers for humanity and our greatest challenges.

Harnessing the Power of Space Bubbles

New Biosensing Method Could Detect Cancer Markers and Microplastics

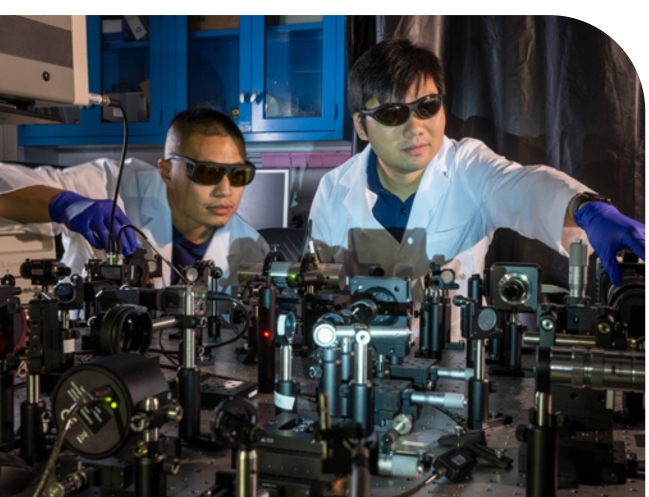
By Stephenie Livingston, *Staff Writer*

Imagine a sensor so sensitive it can detect early cancer in a single drop of blood, enabling diagnosis and treatment before the first symptoms—possibly before a tumor even forms.

Next, picture a device capable of identifying trace amounts of even the smallest plastic pollutants in ocean water, empowering scientists to mitigate the environmental impact of dangerous microscopic toxic waste like nanoplastics, a subgroup of microplastics between 1 and 1,000 nanometers in size.

The catch? Blood samples and vials of contaminated water undergo screening in space, where the absence of gravity leads to an unexpected occurrence: the formation of unusually large bubbles that more efficiently concentrate substances like cancer biomarkers for detection.

This is the futuristic vision of Tengfei Luo, a researcher at the University of Notre Dame who studies mass and energy transport at the molecular level. His concept is simple but has profound applications. By harnessing the unique properties of heat, fluid, and light and their interaction with bubbles, Luo seeks to create sensing technology that's useful on Earth but performs significantly better in the microgravity environment of space. These sensors measure biological or chemical content by generating signals proportional to the concentration of a substance.



Tengfei Luo works in his lab with graduate student Qiushi Zhang (left).

University of Notre Dame

Luo's technology uses bubbles to concentrate and extract the tiniest substances submerged in liquid samples, promising to achieve sensitivity and accuracy in detection several orders of magnitude better than what's currently possible. The key to this technology is freeing the bubbles from the constraints of gravity-induced forces, allowing them to act as the concentrator of targeted microscopic substances for a larger spatial extent and longer duration, making the substances easier to detect and analyze.

Luo says this biosensing method could ultimately improve the efficiency of cancer diagnostic tools reliant on highly concentrated sample extraction from liquids.

"The technology currently available to screen for early, asymptomatic cancer before a tumor is visible during imaging is very limited to just a few cancers," Luo said. "If cancer screening using our bubble technology in space is democratized and made inexpensive, many more cancers can be screened, and everyone can benefit. It's something we may be able to integrate into annual exams. It sounds far-fetched, but it's achievable."

The first in a series of International Space Station (ISS) Laboratory-sponsored experiments flew to space on SpaceX's 22nd Commercial Resupply Services (CRS) mission, contracted by NASA. The investigation aimed to study how bubbles form and grow on surfaces of different roughness when water boils in space compared with the process on Earth. The initial experiment examined bubble behavior on one surface, and a second iteration that flew on Northrop Grumman's 17th CRS mission studied four different surfaces. This research was funded by the U.S. National Science Foundation.

A high-speed camera inside the flight hardware, provided by ISS National Lab Commercial Service Provider Space Tango, captured the bubble growth process, and then Luo's team analyzed the videos together with computer simulations. The experiment focused on two fundamental factors affecting bubble formation: the surface's texture and the surrounding liquid's movement. According to Luo, the results are promising, showing that the bubbles grew larger and faster in space than on Earth.

Understanding the mechanisms behind bubble growth in space will help Luo advance his technology to extract extremely low concentrations of substances from liquids, which he says is the next step in detecting cancer in blood samples or minute traces of pollutants in water. Beyond Earth applications, the technology could bolster the low Earth orbit economy and potentially accompany astronauts during deep space exploration to assess onboard water sources for contamination or monitor crew member health.

Unraveling the Physics of Bubbles in Space

Originally from China, Luo joined Notre Dame after completing a postdoc at the Massachusetts Institute of Technology and started the MONSTER (Molecular/Nano-Scale Transport and Energy Research) Lab in 2012 to study molecular-level energy and mass transport.

For a 2020 study published in *Advanced Materials Interfaces*, Luo and his research team used a laser to heat a solution containing nanoparticles coated with DNA biomarkers. They successfully lured the nanoparticles to the bubbles generated by the laser and deposited them on the substrate, creating what Luo calls a "high-density concentrated island."

Thanks to a phenomenon called the Marangoni flow, nanoparticles are transported to the surface of bubbles. The bigger the bubble and the longer it is maintained in a liquid without detaching from the surface, the more concentrated the substances attracted to it become. The biomarkers migrate along the bubble to the solid surface, where they bunch together and collect, ready to study. At that point, Luo uses microscopy to examine the bubbles and determine what's deposited on the surface.

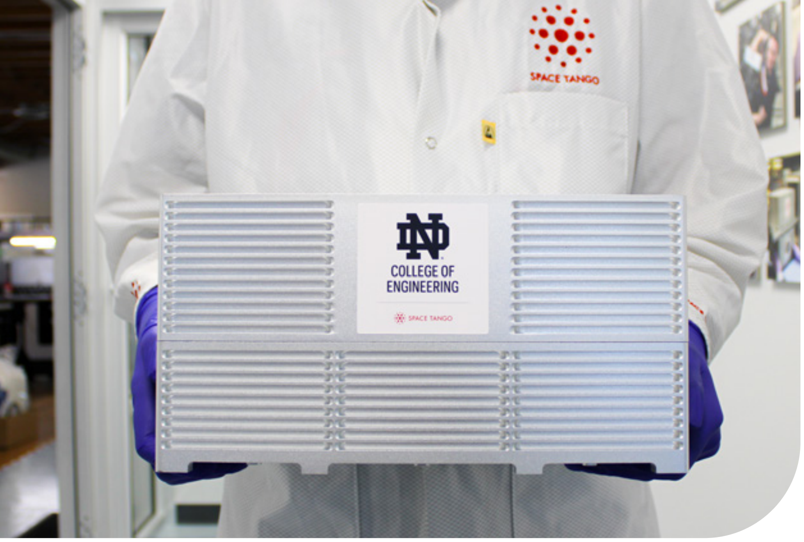
To grow "larger bubbles that last longer on the surface" and make his biosensors more sensitive, Luo turned to the space station's unique microgravity environment and enlisted the help of Space Tango.

(Left) Bubble formation during experimentation on Earth.

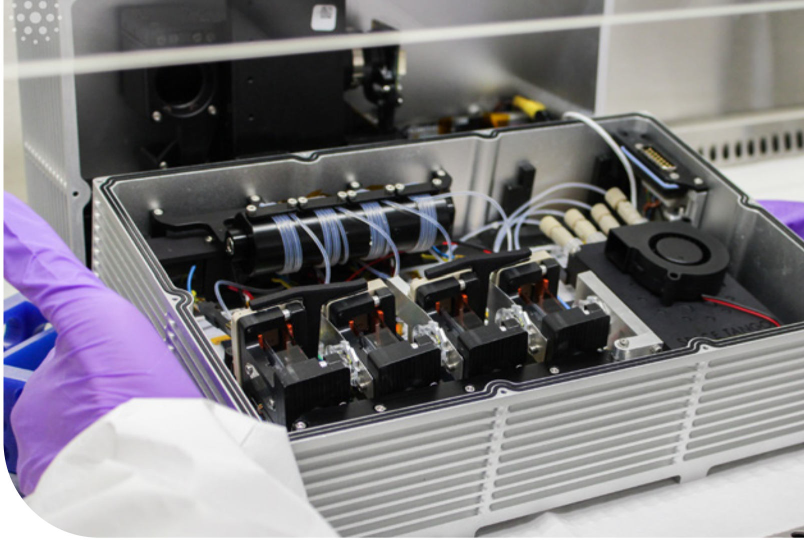
Tengfei Luo

(Right) Bubble formation in the Space Tango CubeLab on the space station.

Tengfei Luo



(Above) The CubeLab designed by Space Tango.
Space Tango



(Above) Inside the CubeLab designed by Space Tango.
Space Tango

“Microgravity provides an ideal environment to explore physics fundamentals by removing one of our universe’s fundamental forces,” explained Twyman Clements, president and co-founder of Space Tango. “On Earth, bubbles are influenced by competing forces such as surface tension and buoyancy, but in low Earth orbit, these forces are removed.”

Space Tango partnered with Luo’s team to develop customized hardware to ensure the success of the spaceflight project.

“For this study, the team designed an automated experiment, from fluid containment systems to high-speed imaging tools, that function under microgravity conditions and heat the liquids under study safely on the space station,” Clements said. “As we continue to improve our technologies, this effort underscores our commitment to pushing the boundaries of fluid dynamics research for applications that benefit humanity on Earth and beyond.”

The experiment was housed in a novel CubeLab, an automated platform the size of a shoebox, developed by Space Tango. The hardware includes four specialized fluid chambers and high-resolution imaging systems specifically designed to observe and analyze bubble formation in microgravity. The experiment involved the controlled introduction of various fluids into the chambers, allowing researchers to study bubble formation, growth, and coalescence under microgravity conditions.

“We found that bubbles form much quicker in space than on Earth. For instance, in one experiment, bubbles formed after 4 minutes and 35 seconds in space, but it took twice as long on Earth due to the movement of liquid cooling the area known as thermal convection,” Luo said.

In space, without the presence of buoyancy and convective flow, the dynamics of bubble growth change drastically. On Earth, buoyancy—the tendency of objects to rise or fall in a fluid due to gravity—plays a significant role in bubble formation and growth. Additionally, convective flow, caused by the movement of hot liquid around the heating area, helps regulate temperature and slows bubble growth.

There’s hardly any buoyancy in microgravity. This means bubbles aren’t pulled away from the surface, allowing them to grow larger without being disturbed. Additionally, without convective flow, there’s nothing to cool down the heating area. As a result, the heat energy is concentrated in a smaller area, leading to much faster and larger bubble growth than on Earth, Luo says.

The results from his space experiments successfully illustrated these concepts. The bubbles did not detach from the surface but burst at the end when they grew too big. “We still don’t understand why,” says Luo.

Turning Dreams Into Tangible Tech

After analyzing and quantifying the bubble volume, Luo and his team determined that space bubbles can be orders of magnitude larger than terrestrial bubbles. They published their results earlier this year in *Nature Microgravity*.

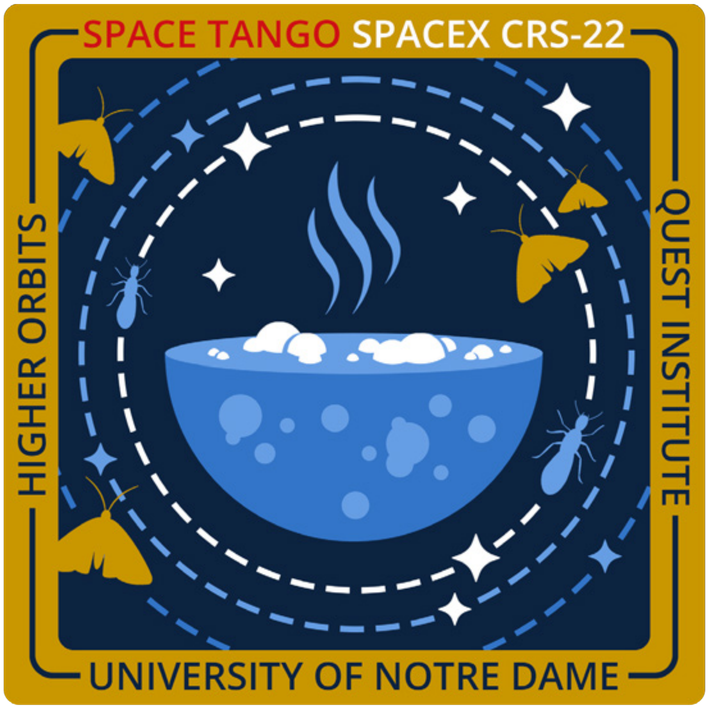
On Earth, Luo used his technique to find nanoplastics—including those from disposable coffee cups, water bottles, and fish nets—in a vile of ocean water he collected off the coast of the United States, which he describes in another recent paper published in *Science Advances*.

“We find some kinds of particles 300 meters deep in the Gulf of Mexico in very, very low concentrations, but this gives us a look at what nanoplastic looks like in our ocean environment,” says Luo.

Luo and his team will continue their research in an upcoming ISS National Lab-sponsored experiment scheduled for launch in August. This time, the team will conduct particle disposition to confirm that the larger bubbles do indeed increase the density of concentrated nanoparticles collected.

The Space Tango CubeLab will also undergo some changes. Luo is working with Space Tango to implement a safe, inexpensive laser to heat the liquid; the nanoparticles absorb the laser light and convert it into heat. Heating the nanoparticle suspension with a laser allows better control of the Marangoni flow to improve biomarker concentration and collection.

"If the concentration ratio is proportional to the bubble size, we should be able to increase the sensitivity of our biosensors by another three orders of magnitude," says Luo. "So that would allow us to, theoretically, screen early cancer."



Space Tango's mission patch for SpaceX's 22nd Commercial Resupply Services (CRS) Mission.

Space Tango

Luo is starting to think about how to make this dream a reality. He estimates that sending around 10,000 blood samples to the space station costs a few hundred dollars. Of course, that doesn't cover the cost of flying a spacecraft. He hopes vehicles like Boeing's Starliner and future commercial space destinations may help reduce the cost of screening for diseases in space and further democratize access.

Still, scaling up this process to make space screening available to everyone is a significant hurdle to overcome. In the meantime, these experiments are improving our understanding of the physics of fluid around surface bubbles in complex environments. Validating this technology at the extremes of particle concentration, bubble size, and bubble growth rate could benefit all sorts of terrestrial screening. This translates to mapping out the scientific limits of cancer biomarkers or environmental pollutant detection.

And Luo says it's not just people on Earth who could benefit. Monitoring astronauts' health is crucial for prolonged space missions, where early detection of changes in health can ensure their well-being. Enhancing biosensor technology in space can lead to more accurate and reliable health monitoring, contributing to safer space exploration.
Dual-use applications, such as Luo's biosensing, have transformative potential, benefiting both space exploration and technology on Earth, says Jonathan Volk, business development director for Voyager Space, a commercial space company focused on advancing deep space missions, encompassing lunar and Mars exploration programs, and developing Starlab, a commercial space station.

"Increasing accessibility to space is pivotal to encourage more projects like Tengfei's," Volk said, underscoring the ISS National Lab's role in translating visionary concepts into practical realities.

"To do science in the space environment, whether in physics or biology, innovative thinking is essential, and it's easy for an idea to sound like a pipe dream," says Volk. "But once we grasp the possibilities within the space environment, what may seem impossible can become possible."

Cotton Revolution

Unlocking New Cotton Varieties for a Sustainable Future

By Stephenie Livingston,
Staff Writer

Clemson University researchers Chris Saski and Sonika Kumar examine cotton plants.
Clemson University

Since the first viral cotton disease was observed in Nigeria in 1912, quickly spreading from Africa to North America and Asia, we've known cotton is vulnerable. Over the decades, scientists and farmers have worked to protect the billion-dollar industry. With diverse applications spanning clothing, household essentials like bed sheets and towels, medical supplies, and even renewable biofuels, cotton remains an invaluable global crop.

New cotton diseases have appeared in recent decades, adding to the industry's challenges. Climate change and limited resources compound these threats. Meanwhile, the global population continues to grow, further straining the supply chain for a plant that has been woven into our daily lives for the last 3,000 years. The result is rising prices to produce premium cotton.

Breeding new, disease-resistant, and affordable cotton varieties using traditional techniques to crossbreed plants with desired traits has been slow, sometimes taking more than a decade. However, genetic modification could significantly expedite this process, says Chris Saski, a plant geneticist with Clemson University, whose research explores the genetic architecture of cotton's fiber-related traits.

"Right now, there are some major disease threats to cotton in the Cotton Belt. Sure, you can use classical breeding that requires extensive experimentation with crossing different plants to release a line with the right combination of traits to address those, but it can take up to a decade or more," Saski said. "Our work could help shorten this timeline to just two breeding cycles, or about a year."

The goal is to develop these premium cotton varieties with tailored characteristics achieved through precise genetic modifications using biotechnology and gene editing tools. New lines could be designed to produce cotton plants instilled with disease or drought-resistant properties or engineered to produce high yields—the possibilities are endless, says Saski.

"With genetic modification, we can design cotton that's high quality and more resistant to pests and other threats while remaining affordable," he said.

Perfecting the science of gene editing could revolutionize cotton production and lend knowledge to other essential crops; however, a fundamental problem stands in the way: delivering the gene-editing cassettes (small segments of DNA) and successfully regenerating modified plants from single cells. This genetic program of regeneration, called somatic embryogenesis, is written in the DNA of all crops but is silenced by various factors influencing it on Earth. To improve his system for genetic modification, Saski needs to turn these silenced genes on.

All life on Earth is subject to gravity, a critical factor in plant development. Gravity influences specific genetic signals and processes within plant cells that guide the development of plant shoots upward toward the sun and roots downward in the soil. But plant cells behave differently in space, where gravity is much weaker, potentially leading to a new understanding of the genetics underlying regeneration.

Chris Saski in a research greenhouse at Clemson University.
Clemson University

Scientists can revert plant cells into a stem cell-like form, similar to human stem cells. The cells can then be genetically modified and reprogrammed into a new plant. Studying the genetic architecture of plant stem cells in tissue culture, both on Earth and in microgravity, can help identify which genes need to be expressed during somatic regeneration—a key step in genetic modification.

Saski and colleagues proposed sending a plant tissue culture experiment to the International Space Station (ISS) to explore whether microgravity can trigger plant stem cells to regenerate into whole plants from a single cell. The project was selected through the ISS National Lab Cotton Sustainability Challenge, which Target Corporation funded.

Results from this spaceflight research could help unlock the underlying molecular mechanisms of plant regeneration and remove a significant bottleneck in gene editing cotton and other crops on Earth. Saski envisions a future where gene editing becomes more accessible and efficient, addressing global food, fuel, and fiber supply challenges.

Cotton plants grown in Saski's lab.
Clemson University

High-Flying Cotton

Saski's method for precise genetic modification involves introducing foreign genes into a plant's genome to produce desirable traits, such as pest resistance or improved yield. However, the success of genetic transformation often relies on the plant's ability to regenerate transformed cells into whole plants. If regeneration is suppressed, it becomes challenging to achieve stable genetic modification, and the new plant fails to perform.

Scientists can potentially manipulate these processes to enhance regeneration efficiency by identifying the specific mechanisms suppressing the regeneration process, which Saski hoped to do in space.

He teamed up with Techshot, which has since been acquired by Redwire Corporation, to develop hardware for cultivating plant tissue cultures in microgravity. Saski said there were many challenges to overcome because experimenting with plant tissue cultures in space hadn't been done since NASA's Space Shuttle Program ended. These challenges mainly involved keeping contamination out of the hardware and simplifying the experiments.

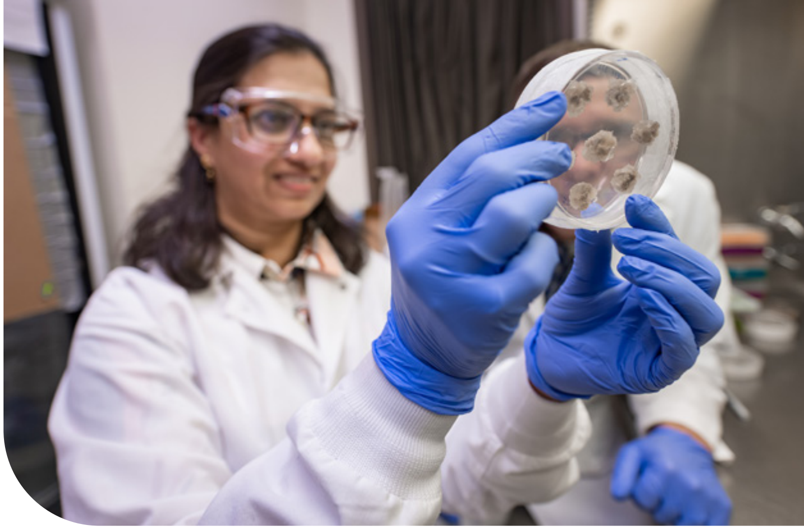
"When students come to my lab to learn how to do tissue culture, the main concern is contamination, for example, having some sort of microbe or fungus contaminate your plates," Saski said. "So, you can imagine our concern, sending our sterile tissue culture plates to the space station and having astronauts who are likely nontrained tissue culturists work on it."

The team worked with Techshot to design several small, round Petri dishes with growth media and samples of stems from a cotton plant grown on Earth. "The cut stems respond to hormones in the media that initiate cellular de-differentiation into stem cells," Saski says. On the ISS, the Petri dishes were put into a plant habitat the size of a large microwave that provided controlled light, temperature, and humidity levels for growing the cells.

The flight hardware was adorned with Clemson stickers, symbolizing the university's contribution to cutting-edge space research. In 2021, the experiment was launched to the space station onboard SpaceX's 24th Commercial Resupply Services (CRS) mission.

The experiment took place over about 90 days, "and long story short, there was no contamination, the astronauts did an amazing job, and the experiment was a success," says Saski. "We do believe that we were able to visualize some interesting morphological changes in the stem cells because of the lack of gravity."

Chris Saski removed cotton samples from storage in his lab.
Clemson University



Sonika Kumar examines cotton samples similar to those used for the experiment in space.
Clemson University

Now, co-principal investigator Jeremy Schmutz, a geneticist at HudsonAlpha Institute for Biotechnology, and his team are analyzing the space-flown cotton samples. As analysis continues over the next few months, data from the space cotton should begin flooding in.

Based on preliminary results, Saski expects the space experiments will reveal key genes involved in regeneration and how the genes are regulated. The research team can translate this information into a system that enables regeneration in virtually any cotton line that does not currently regenerate, which is typical of most cotton lines, Saski said.

With this ability, researchers can edit commercially grown elite cotton lines with genetic traits tailored for growing in specific environments.

“So, when we need to engineer drought resistance or resistance to a pathogen, we can use our new system from this project to directly modify an elite line, saving decades,” he said.

Cotton samples similar to those used for experimentation in space.
Clemson University

Over the past few years, Saski’s research team has also performed many experiments back on Earth related to the ISS National Lab-sponsored project. For example, Sonika Kumar, a senior scientist in the department of plant and environmental sciences under Saski’s direction, has identified several key morphogenic genes that facilitate the rapid generation of genetically engineered Coker 312, an upland cotton line with traditionally poor agronomic and fiber traits compared with commercial lines.

She developed a system that makes Coker 312 regeneration faster and more efficient and allows her to manipulate plant traits, including drought and disease resilience. This initial research led to new findings related to plant regeneration for upland cotton, which were published in the National Institute of Health journal *Plants (Basel)*. Importantly, the outcomes allow Kumar to establish regeneration systems for direct gene editing of commercially available lines. Saski says these findings have already significantly improved his gene editing system, and the team is excited to see what more is revealed in the space-flown cotton.

“It was fascinating to watch the callus, or stem samples, float in microgravity during subculturing by the astronauts,” says Kumar. “I enjoyed configuring plant tissue compatible with flight hardware and developing protocols for the astronauts to conduct our experiment and to capture high-resolution image data. Now, we’ve completed all our space and ground experiments and are working with the genomic data to advance our project to the next stages.”

The team plans to use what they’ve learned to regenerate elite lines of cotton, such as Pima cotton, more efficiently and rapidly—saving time and money.

Space Solutions for Earth's Cotton

Saski's project was partly funded by Cotton Incorporated, a national program for upland cotton, the most widely planted species of cotton. The program supports hundreds of research projects to improve profitability for both growers and retailers. Don Jones, director of breeding, genetics, and biotechnology at Cotton Incorporated, says that upland cotton falls behind much larger acreage crops such as corn and soybean when it comes to investment devoted to crop improvement. Not only are there fewer research investments, but cotton is also further hindered by its basic biology: poor somatic embryogenesis.

"This, in turn, has slowed gene editing techniques such as CRISPR Cas9 in cotton," says Jones. "Dr. Saski's space station project aims to significantly improve embryogenesis, allowing for greater deployment of the latest gene editing techniques to increase yield and sustainably improve fiber quality."

Already, agricultural companies have approached Saski about licensing his technology, but the benefits continue beyond that. Gene banks that store plant diversity in various forms, like seeds, living plants, or cells, could benefit from Saski's work. If researchers understand genetic programs well enough to store and regenerate cells, we could streamline how we maintain plant diversity on Earth and explore options for space colonization and deep space exploration, Saski says.

"Imagine storing plant species as single cells, providing astronauts with a diverse array of plants for research or even sustenance during long-duration space missions," he said.

Saski's primary focus, though, is growing more crops with less land and water to feed a growing population amidst climate change. As he moves closer to removing the plant regeneration barrier, Saski has become interested in understanding and engineering genetics from weeds into crops, an idea that could help meet the needs of 10 billion people on Earth by 2050.

"What resilient traits can we translate from indigenous weeds that might help our crops grow more plentiful and resistant to threats?" he said. "We're trying to develop pathways to do that, which would significantly benefit people worldwide."

The Beauty of Accelerated Aging

Using Tissue Chips to Explore Age-Related Muscle Loss in Microgravity

By Amelia Williamson Smith,
Managing Editor

Contrary to Bob Dylan's famous song, it's not possible to "stay forever young," and aging is inevitable. As we get older, many things change, and while we may gain wisdom, we often lose muscle.

At age 30, people begin to lose three to five percent of their muscle mass per decade, and the loss speeds up in a person's 60s. The World Health Organization estimates that more than 50 million people worldwide have sarcopenia, an age-related condition causing loss of muscle mass, strength, and function, and the condition will affect more than 200 million people within the next 40 years.

But sarcopenia isn't just about weakened muscles. People with sarcopenia have a higher risk of falling, which can lead to fractured bones, loss of mobility, long hospital stays, and significant healthcare costs. A study published in the *Journal of Frailty and Aging* in 2019 found that the total annual cost of hospitalization for Americans with sarcopenia is more than $40 billion.

Right now, there are no treatments for sarcopenia other than exercise. To find new therapies, researchers need a better understanding of how muscles change at the tissue level as we age. However, studying age-related change is difficult because studies must last decades, and it can be hard to see changes that occur slowly over time.

But what if there were a way to accelerate the muscle aging process? A University of Florida research team led by Siobhan Malany found a place where this is possible: the International Space Station (ISS).

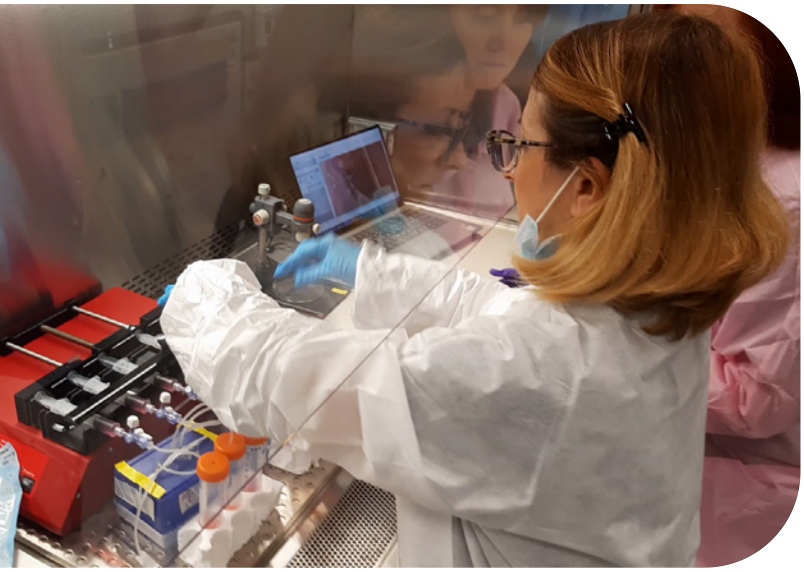
In an investigation funded by the National Institutes of Health (NIH) and sponsored by the ISS National Laboratory®, Malany and her team sent skeletal muscle tissue chips to space to help people with muscle loss on Earth. The team created a tissue chip system that grows bundles of human skeletal muscle called myobundles. By sending the tissue chips to the microgravity environment of the ISS, where muscle loss is accelerated, the researchers hoped to study age-related muscle deterioration in ways not possible in ground-based labs.

"Our system can study human muscle responses under disease conditions for which there are not a lot of therapeutics, mainly because there hasn't been a way to look at what's happening at the tissue level," said Malany, an associate professor in the College of Pharmacy at the University of Florida. "There are mechanisms you don't pick up on in studies in the whole animal, but you can see at the human tissue level."

Malany and her team knew that microgravity induces muscle loss, but does it mimic muscle loss specifically related to aging? To answer that question, the team launched three experiments to the space station, each using tissue chips created using skeletal muscle cells from two groups of donors: young active adults and older sedentary adults.

Upon return to Earth, gene expression analysis of the space-flown tissue chips revealed several microgravity-induced gene changes that mimic aspects of muscle aging and stress, including changes in muscle differentiation, decreased muscle contraction, a shift in muscle fiber type, and metabolic alterations. The team also found differences in gene expression between the young and old age groups and published the initial findings in *npj Microgravity*.

"Through insight we gather from microgravity, we can understand not just the end result of the disease, but really look at the progressive change in young and old cells to see what happens as cells age," Malany said. "We don't get that on the ground because aging occurs over so many years, but in space, we can see the snapshots of how these cells are changing by monitoring tissue structure, contraction magnitude, and gene expression."



(Above) Maddalena Parafati at Kennedy Space Center preparing the programmable syringe pumps that dispense the culture media at fixed reproducible flow rates into the tissue chips.

University of Florida

Maddalena Parafati viewing a skeletal muscle tissue chip with electrodes attached at Kennedy Space Center before launch.

University of Florida

Building a Microgravity Muscle Tissue Model

To better understand the mechanisms behind age-related muscle loss, Malany and her team created a microfluidic device that grows three-dimensional muscle tissue and circulates fluids through the tissue, recapitulating the growth and function of muscle tissue in the body. The goal is for these tissue chips to replace animal models to more accurately test potential new drugs for treating sarcopenia.

On Earth, muscles constantly work against gravity, but in space, where gravity is removed, muscles don't have to work as hard and weaken quickly. Malany and her team hypothesized that microgravity would speed up age-related changes to muscle physiology, making it possible to study muscle cell aging on a much quicker timescale.

The team collaborated with AdventHealth, Micro-gRx, Micro Aerospace Solutions, and Space Tango for the investigation. To develop the tissue chips, AdventHealth provided donor cells from two groups: people younger than 40 who exercise several times a week and people older than 60 who are sedentary.

"A unique aspect of this work is the use of human muscle cells derived from muscle biopsies performed on our study volunteers," said Paul Coen, associate investigator at the AdventHealth Translational Research Institute. "Results from these experiments are highly relevant to skeletal muscle health, and our participants get a kick out of knowing their muscle cells may take a trip to the ISS."

The muscle cells for each group were acquired from six to eight donors and pooled to create "young" and "old" sets of tissue chips. The cells retain their age-related characteristics in culture as they mature into muscle tissue on the chips, explained Maddalena Parafati, a pharmacodynamics research assistant professor at the University of Florida.

"We have a micro-engineered chip, and we model the muscle tissue in our body at the smallest acceptable biological scale," Parafati said. "Donor-derived younger and older myoblasts are seeded on the chips and then proliferate, migrate, align, and fuse to form a functional construct."

Going From Ground to Space

Creating the tissue chips was only half the puzzle—the team also had to design the experiments to work in space, a process Malany said was done in partnership with the ISS National Lab and Commercial Service Provider Space Tango.

"The ISS National Lab is beneficial because it already has the implementation processes and the technology to tap into," she said. "There is a framework in place that has continually become more efficient and less expensive to take your research to space and bring it back."

The team at Kennedy Space Center preparing the first experiment for launch on SpaceX CRS-21 in December 2020 (left to right: Siobhan Malany and Shelby Giza, of the University of Florida; Lee Malany, Mario Garcia, and Austin Hinkle of Micro-gRx; and Don Platt of Micro Aerospace Solutions).

Space Tango

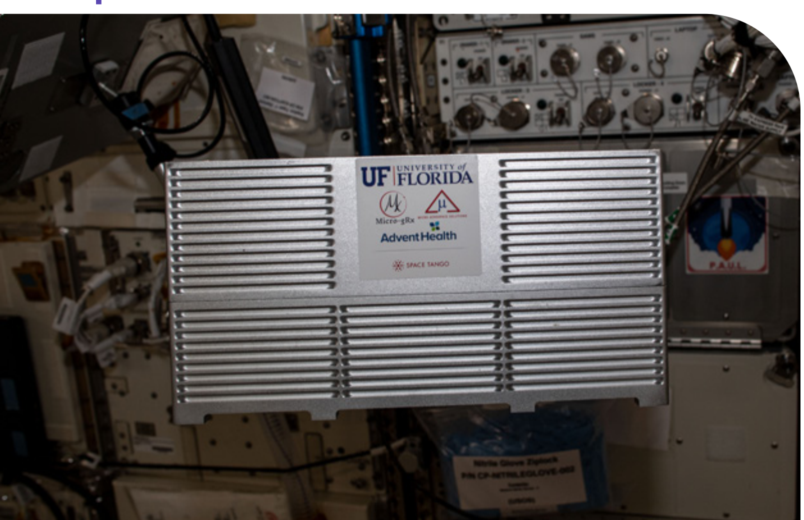
Space Tango worked closely with Malany and her team on the experiments, said Shelby Giza, director of scientific business strategy at Space Tango. Before joining Space Tango, Giza was a researcher on Malany's team at the University of Florida, giving her a unique perspective on both sides of the process.

"From the beginning, Space Tango works with investigators on their science requirements and translates those needs into a hardware solution to make sure their research is successful," Giza said. "As a Commercial Service Provider, we can see around corners because we have so much experience with microgravity research and can help ensure success."

The team's experiments were hosted in a novel Space Tango CubeLab, a standardized, modular system that can house a variety of payloads on the ISS. With a ground control CubeLab remaining on Earth, a flight CubeLab would be installed into a Space Tango Powered Ascent Utility Locker (PAUL) facility

The team's first experiment in a CubeLab on the ISS.

NASA



that provides power and environmental control during all phases of flight. Designed specifically to host the team's tissue chips, the CubeLab is equipped with a camera and microscope system to record muscle movement, and data could be sent to the research team in near real time, allowing the team to check on the experiment and make adjustments if needed. Lastly, a key feature of the platform is that it runs autonomously.

"Automation is really important for reliability and reproducibility, and being able to run experiments autonomously in space enables better data and research," Giza said.

For Malany, having the old and young sets of tissue chips together in the same automated platform was crucial because it allowed the team to compare the two age groups directly.

"Because the tissue chips were all in the same CubeLab with the same spaceflight conditions and the same automated flow rate, any changes we see should be directly comparable," Malany said. "So, we can gain insight into the process by which the muscle cells are responding to microgravity, and then we can look at potential countermeasures."

Iteration on Station

The team's first experiment launched on SpaceX's 21st Commercial Resupply Services (CRS) mission in December 2020. Knowing that doing automated experiments in space is challenging, the main goal of this mission was to validate the tissue chip system. The team sent 16 tissue chips to the ISS, half created using young cells and half using older cells. In space, myobundles grew on the chips for 15 days and then were preserved, frozen, and returned to Earth for analysis. While there were operational issues, the overall mission was a success in demonstrating the technology, and the team learned a lot about the system's camera operation, temperature control, and fluid flow and how to improve them.

"The key things that came out of that first flight were the generation of myobundles and demonstrating the end-to-end processing with the tissue chips in an autonomous closed system," Malany said. "It was complex biology and a complex system, and even though we had some operational issues, the 3D-engineered tissue was robust. We obtained good-quality RNA for gene expression studies, and that was a big accomplishment for the team."

Building on lessons learned, Malany and her team worked with Space Tango to overcome the challenges from the first flight and improve the integrated system for its second flight on SpaceX CRS-25 in 2022. This time, when the tissue chips were returned to Earth, gene expression analysis revealed something big: in microgravity, the cells from the young active adults had many more gene expression changes than those from the older sedentary adults.

The team also compared the differences between the young and old cells grown in space to the differences between the young and old cells grown in the same CubeLab on the ground. When they looked specifically at 957 muscle tissue genes associated with human aging, Malany and her team found something really exciting. Several genes upregulated in aging muscle cells on Earth were upregulated in the young muscle cells in space.

"We have lacked the data to prove the concept of accelerated aging in microgravity, and I think our data starts to speak to that," Malany said. "We found that microgravity induces changes in the expression of specific aging genes in muscle tissue chips in space, and that is an exciting result."

Additionally, this time, the team embedded electrodes in half the tissue chips to examine contraction in the myobundles. Understanding contraction is important because it can be used to assess muscle performance. The CubeLab delivered electrical stimulation to the chips through the electrodes and captured video of the muscle bundle contraction.

"I think this was probably the first time muscle cells have been electrically stimulated in space in a tissue engineering product, so that's a big takeaway," Malany said.

To analyze myobundle contraction, the researchers use "digital image correlation." With the help of software, the team can identify small changes in the myobundles based on the movement of pixels in the video, and this data can be converted into micrometers of contraction, Parafati explained. Although the team is still analyzing the data, there appears to be less contraction in the spaceflight tissue chips than in ground controls, indicating decreased muscle function in microgravity.

The University of Florida and Space Tango teams at Kennedy Space Center before the launch of Malany's second experiment on SpaceX CRS-25.

University of Florida

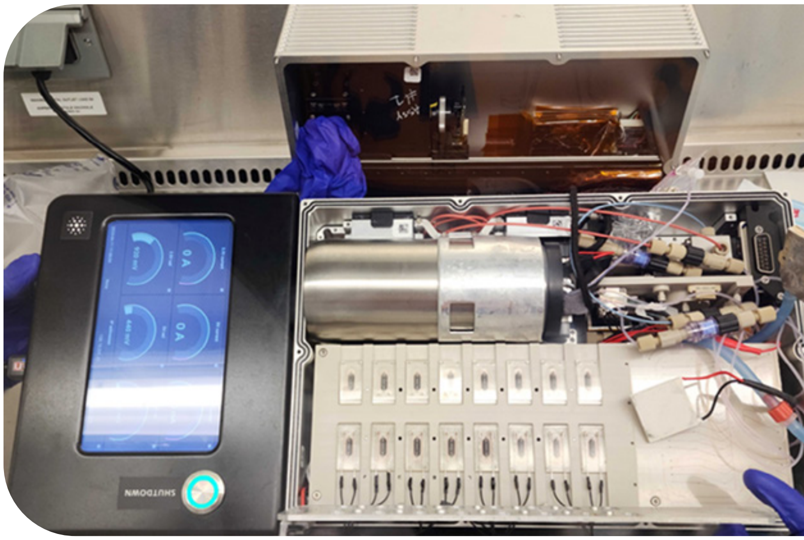
The team's third flight, which launched on SpaceX CRS-26 later in 2022, took the experiment one step further and used the tissue chips to test a potential muscle loss drug—an anti-atrophy compound derived from the skin of green tomatoes. This analysis is also ongoing, but initial results show differences in contraction response between young and old tissue chips treated with the drug in space versus those on the ground and those untreated, which is promising.

Gene Expression

Genes contain instructions to produce proteins that carry out certain tasks in the body. For example, some proteins act on muscle cells to promote muscle growth and other proteins act to limit muscle growth.

During gene expression, the instructions from a gene are copied to make an RNA molecule in a process called transcription. The instructions in the RNA are then decoded to produce a specific string of amino acids in a process called translation. The specific string of amino acids forms a protein, and the order of the amino acids determines the protein's function.

The level of gene expression can change as people age, and certain genes could be upregulated (expressed more) or downregulated (expressed less). This leads to changes in the processes controlled by the proteins. For example, upregulated genes that produce proteins that limit muscle growth would lead to weaker muscles.

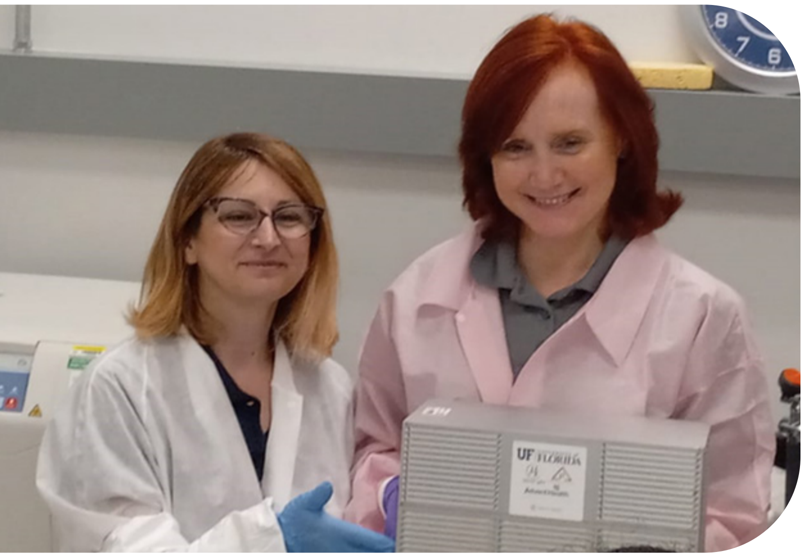


The 16 human skeletal muscle tissue cihps integrated into a CubeLab for the team's second experiment on the ISS. Half of the tissue chips contain electrodes to deliver electrical stimulation to induce contraction in the myobundles.

University of Florida

Making the Leap From Concept to Commercialization

The success of these experiments underscores the value of conducting fundamental research in microgravity, said Danilo Tagle, director of the Office of Special Initiatives at NIH's National Center for Advancing Translational Sciences (NCATS). "Studies through the ISS National Lab that leverage the unique stressor of microgravity have provided opportunities for NCATS-funded research to identify some of the hallmarks of accelerated aging," he said. "Dr. Malany's findings will provide crucial clues toward developing new treatments for patients on Earth with muscle loss."



Maddalena Parafati (left) and Siobhan Malany (right) at Kennedy Space Center preparing the team's second experiment for launch on SpaceX CRS-25.

University of Florida

According to Malany, the priority now is getting the team's results out to the scientific community, and her team is planning to submit multiple papers for publication. Malany also started a consortium of faculty labs across multiple disciplines for space-based research at the University of Florida, called the In-Space Biomanufacturing Innovation Hub, which received a $1.5 million investment from the university.

"We have made substantial progress from the exposure and the experience we've gained through our ISS National Lab research," she said. "Now that we have validated this technology, we can continue to improve both the tissue chip and CubeLab integration to make the system more standardized, higher throughput, and adaptable to operate over several months in orbit, which will be important to test potential therapeutics."

Continued research on the ISS is critical for the team's work, she says. Validation studies are needed to gather enough statistical data to advance the tissue chips beyond proof of concept and entice pharmaceutical companies to invest in them over animal models to study disease progression and test drugs.

Parafati says she feels many emotions when she thinks about the opportunity to take her research to space and what it could one day mean for sarcopenia patients on Earth.

"Conducting research on the ISS is exciting because it allows us to do experiments that are not possible anywhere else," she said. "It enables innovative research that, hopefully at the end of the day, can help us identify biomarkers to treat different types of muscle disease." ▮

University of Florida researcher Siobhan Malany received an International Space Station Award for Compelling Results at the 2024 ISS Research and Development Conference.

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