Orbital Oncology

3D Cell Cultures in Space Reveal the Secret to Killing Cancer Cells on Earth

By Amelia Williamson Smith,
Managing Editor

At a fundamental level, science and magic are about as far apart as you can get. Science is focused on systematically studying the structure and behavior of the physical world through observation and experimentation. It is rooted in figuring out the rules of nature—how things work and why—and being able to make predictions based on those rules. Magic, on the other hand, is quite the opposite. Magic is the apparent ability to alter the world, not through the natural laws of science, but through supernatural forces that break those rules. Magic is unpredictable, and it evokes a sense of wonder and awe.

But, sometimes, science reveals something so unexpected and wonderous that it almost feels magical. Research in space that uncovers a way to treat all types of cancer, killing cancer cells without harming healthy cells, sounds like magic—except it's not. Biotech startup MicroQuin leveraged the International Space Station (ISS) National Laboratory to grow 3D cultures of breast and prostate cancer cells to identify mechanisms behind the transformation of healthy cells into cancerous ones.

In labs on Earth, cancer cells grow in a single layer due to gravity. However, on the ISS, where gravity is significantly reduced, cells grow into 3D structures that more accurately represent how tumors grow and behave in the human body. Microgravity also causes changes in cancer cell signaling and gene expression, which dictates how cancer cells respond to their environment and communicate with other cells. By studying 3D cancer cell cultures in space, MicroQuin hoped to uncover critical pathways involved in the formation and growth of breast and prostate cancers. However, the company's space station investigation revealed much more than that.

Results led to what MicroQuin founder and CEO Scott Robinson says is a "massive paradigm shift" in the way scientists think about treatments not just for certain types of cancer but for all cancers. And it doesn't end there. The results apply to many other conditions as well—from neurodegenerative diseases like Alzheimer's and Parkinson's to traumatic brain injuries and even viral infection. It all comes down to changes in the environment inside cells caused by disease or injury and how these changes are regulated.

Representatives from the ISS National Lab and Boeing pose for a photo with the MicroQuin team, which was awarded a 2018 Technology in Space Prize for two investigations.

MassChallenge

"One of the best things about science is that you can start off looking in one direction, and then your data starts to show you something really magical in a different direction," Robinson said. "What was so magical about our findings is that they don't just apply to cancer. The new theories we came up with because of our ISS research allowed us to pivot to understand how our findings could be applied across many other disease areas as well."

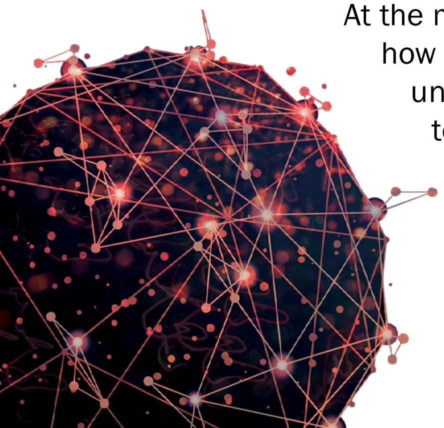
The Path to Space Scientist

When Robinson was young, he dreamed of being an artist one day—possibly a cartoonist working for Disney. But, in high school, the wonder of space changed his life's direction and led him to his career as a scientist.

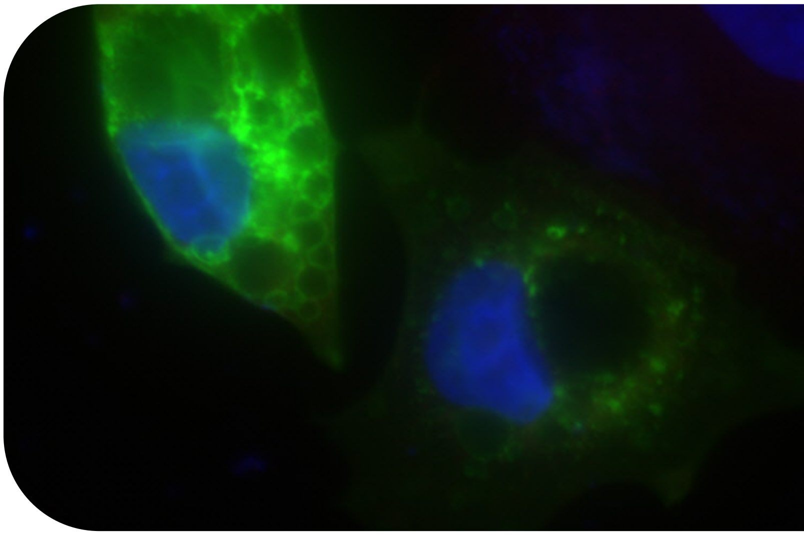
"It was space that showed me how fascinating science is," he said. "As soon as I had that first science lesson on space in high school, I was just enamored, and there was nothing else I wanted to do."

However, it wasn't until 2018 that Robinson found himself with an opportunity to work on research that brought him back to his inspiration. At the time, MicroQuin was participating in the MassChallenge startup accelerator program, and Robinson received an unexpected message. MassChallenge contacted him to say MicroQuin was identified as a startup whose research could benefit from leveraging the ISS National Lab.

Intrigued, Robinson attended a meeting on the Technology in Space Prize, which provides startups with grant funding and access to the space station for innovative research and technology development (R&D). Since its inception, the prize—funded by the Center for the Advancement of Science in Space™, which manages the ISS National Lab, and Boeing—has provided more than $10 million to startups identified through MassChallenge.



At the meeting, Robinson learned how other startups utilized the unique space environment to advance their R&D. He had never considered how microgravity could benefit his research, and his eyes were opened to exciting possibilities.



Immunofluorescence image of breast cancer cells (MCF-7) treated with a MicroQuin therapeutic taken at 100x magnification.

MicroQuin/Scott Robinson

"Honestly, I think I walked out of that meeting with seven ideas immediately," he said. "I was blown away and knew I wanted to do this."

MicroQuin applied for the 2018 Technology in Space Prize and received awards for two spaceflight projects: one to crystallize TMBIM6, a protein that plays a key role in cancer development and growth, and the other to study 3D cell culture models of human breast and prostate tumors.

Untangling Cancer Cell Signaling Pathways

To defeat an enemy army, you must first understand how its members communicate and coordinate operations. Similarly, to find a way to kill cancer cells, scientists must first understand how the cells communicate and coordinate actions that ensure their survival.

Cell behavior is governed by complex cell signaling. Signals from within a cell, the cell's environment, or other cells trigger cascades of actions in the cell. These chains of actions, called signaling pathways, serve many purposes, including regulating gene expression.

When specific genes are expressed, the cell produces proteins that carry out different tasks. For example, proteins can initiate cell growth or the production of other molecules necessary for cell survival. When cells become cancerous, these signaling pathways change, and genes are expressed differently to carry out actions that benefit cancer growth.

If researchers could determine the pathways essential to cancer development and their role in cell survival, they could design drugs that target these pathways. However, this is difficult because cancer cells have many signaling pathways that play different roles in cancer development and growth.

So, what does space have to do with it? When you take cancer cells to space, microgravity acts as a unique stressor that triggers changes in cell signaling to keep the cells alive. Researchers have found that for many cancers, cell signaling pathways activated on Earth are suppressed in microgravity. The suppressed pathways are clearly not essential to cancer cell survival. So, the activated pathways must be critical, and researchers can focus on those.

"There are a lot of benefits you can get by doing work on the space station that really allow us to understand what the key pathways for cancer are," Robinson said. "We can then start to look at how to target the pathways to kill the cancer and how to manipulate the cancer microenvironment to enable life-saving technologies like immunotherapy to come through."

Launching to Space

To translate MicroQuin's research into spaceflight-ready investigations, the company worked with ISS National Lab Commercial Service Provider BioServe Space Technologies.

BioServe's Brian Medaugh (forefront) and Luis Zea (background) preparing the cells for integration into the flight hardware ahead of the NG-17 launch.

Ivan Castro

"BioServe did a phenomenal job making sure we got our research launched," Robinson said. "I told them exactly what I wanted to do, and there were things we couldn't do and things we had to compromise on, but they came up with new ideas we could try."

The BioServe team on console communicating with ISS crew members during in-orbit operations for MicroQuin's 3D cell culture experiment (right to left: Shela Nielsen, Shakini Doraisingam, and Matt Vellone).

BioServe Space Technologies

BioServe provided support throughout the process—helping the team design investigations to operate in microgravity, conducting experiment verification testing before launch, and even communicating with the astronauts doing the research.

"We were present in real time on the console, talking to the crew, answering questions, and giving them cues," said BioServe research associate Sheila Nielsen. "It's really important that we know as much as possible about the science so we can understand how best to operate the experiment on station."

The team's first investigation to crystallize TMBIM6, a protein involved in cancer development, launched to the ISS on SpaceX's 18th Commercial Resupply Services mission. TMBIM6 is difficult to purify and crystallize on Earth, and scientists had been unable to produce high-quality crystals to determine its structure. In microgravity, crystals often grow larger and more well-ordered, resulting in higher-quality crystals than those made on Earth. Robinson and his team hoped to leverage the space station to produce crystals of TMBIM6 with a high enough quality for structural analysis.

(Above) A BioCell Return Bag from the ISS containing plates used to grow cells. The cells are being analyzed to identify differences between cancer cells cultured in space versus those cultured on Earth.

MicroQuin/Scott Robinson

(Below) MicroQuin founder and CSO Scott Robinson, holding a specialized 12-well tissue culture plate containing breast cancer cells grown on the ISS.

MicroQuin/Scott Robinson

MicroQuin's second investigation to grow 3D cultures of breast and prostate cancer cells flew on Northrop Grumman's 17th Commercial Resupply Services mission. The team used BioServe's BioCell hardware for the cultures, and the cells were launched live. Once on the ISS, the cell cultures were allowed to acclimate to the microgravity environment for a week. Then, half the cultures were treated with a peptide-based drug developed by MicroQuin, and the cells were left to grow for another week, with the astronauts periodically checking on their progress. The cultures were then fixed, frozen, and returned to Earth for analysis.

When Wei Luo, MicroQuin investor and long-time advisor to the company, first heard about MicroQuin's opportunity to send research to space, he didn't know what to make of it. Was it realistic? Could it really be beneficial? He wasn't sure. But as the team worked with the ISS National Lab and BioServe to design the experiments and prepare them for flight, any doubt he had turned to excitement.

"Seeing the rocket go up on the livestream was incredible—even though I knew it was happening, it didn't feel real," he said. "I never imagined that some of MicroQuin's research would go into space and then come back with amazing results, so it has been a fantastic journey."

It All Boils Down to ICE

When MicroQuin examined the 3D cancer cell cultures from space, the team made a remarkable discovery. "We identified some key pathways that are essential in what seems to be all cancers," Robinson said. "Although we've looked at two cancer types on the ISS, we have taken that research and started to test more on Earth."

These pathways are related to the intracellular environment, or ICE, and the proteins that regulate it, like TMBIM6. The team knew TMBIM6 was important in cancer growth and that its functions were related to the intracellular environment. But they didn't realize the critical role ICE regulators like TMBIM6 play in cancer cell survival, drug resistance, and cancer spread.

By its nature, cancer produces a toxic environment within tumor cells. Cancer begins when key genes that regulate cell growth mutate, causing cells to replicate uncontrollably, which puts a lot of stress on the cells, Robinson explained.

NASA astronaut Christina Koch working on MicroQuin's protein crystallization investigation on the ISS.

NASA

"Imagine you were working 24 hours a day and were pushing really hard and had to constantly eat and drink and run on a treadmill—you would find that ridiculously stressful," he said.

These stressful conditions lead to problems within the cells. For example, for cancer to grow continuously, cells must constantly work to reproduce, which requires a significant increase in metabolism. A byproduct of metabolism is lactic acid, so the increased metabolism causes a buildup of acid within the cell. Acidification is detrimental to cellular function, and if the cell doesn't do something about the toxic environment, it will die.

This is where a family of proteins called ICE regulators come in. These proteins perform functions to correct a toxic intracellular environment, such as pushing excess acid out of the cell. The genes that produce ICE regulators aren't activated unless the cell's environment becomes so toxic the cell cannot survive.

"ICE regulators are like the military," Robinson said. "On a day-to-day basis, you may need the police to help keep things in check, but you shouldn't really need the military unless things get extreme, like in a disease or injured state."

MicroQuin found that when you take cancer cells to space, microgravity causes significant changes in the intracellular environment, which triggers a massive upregulation of genes that produce ICE regulators. The ICE regulators then perform whatever functions are necessary to keep the cells alive. So, if you can design a drug that binds to ICE regulators and changes how they function, you can kill the cancer cells, Robinson explained.

"It was our discoveries on the space station that really led us to identifying these key pathways and understanding why they are so important," he said. "This is a very poorly characterized form of cell death, but it's one of the most fascinating, and our work on the ISS will hopefully allow us to enrich an area that we really don't know much about on Earth."

Applying Discovery to Drug Development

MicroQuin's ISS National Lab-sponsored research led to another exciting result—albeit with a twist. The team determined the structure of TMBIM6, but not from the space-grown crystals. Due to a series of unfortunate issues, the ISS experiment did not return crystals that could be used for structural analysis. However, sometimes the journey is more important than the destination.

In preparing for their spaceflight investigation, Robinson and the team worked hard to optimize their protein generation and purification methods for the highest chance of successful crystallization. When they analyzed the crystals produced on Earth as the ground control for their spaceflight experiment, they were thrilled to find several high-quality crystals. Analysis of these crystals provided valuable data on TMBIM6's structure and revealed several binding sites for drug design.

Knowing What to do When

Through MicroQuin's ISS National Lab-sponsored research, the team gained valuable insight into how ICE regulators work to balance changes in the intracellular environment.

"TMBIM6 has 15 or 20 functions in the cell, and that's always bugged me," Robinson said. "It's great to do so many things, and they're all so important, but how do you know what to do and when to do it?"

As part of MicroQuin's first investigation, the team crystallized the TMBIM6 protein in several different growth conditions. The team found that the environment around the protein triggers a change in its conformation, or 3D shape, which determines its function. So, if the intracellular environment is too acidic, the high acidity changes the shape of TMBIM6 so it performs an action to regulate the amount of acid in the cell.

Equipped with the new knowledge of TMBIM6 as a critical ICE regulator and its structure, MicroQuin was able to improve its current therapeutic and develop a new small molecule drug. The drug binds with TMBIM6 inside cancer cells and alters how it regulates the intracellular environment.

"We refocused our efforts on small molecules and have had phenomenal results; if you know the structure of the protein and how to interact with it, you know how to get the effect you want," Robinson said.

In the case of cancer, the therapeutic directs TMBIM6 to carry out actions that recruit enzymes to the cells' endoplasmic reticulum. The enzymes eat away at the endoplasmic reticulum, eventually causing the cells to die. Because ICE regulators are only activated in diseased cells, the therapeutic can target and kill only cancer cells, leaving healthy cells unharmed.

"It didn't matter which cancer cell line we tested," Robinson said. "It didn't matter if it was breast, lung, prostate, or ovarian cancer—using our therapeutic, by 24 hours, we would literally get floating dead cancer cells."

It all comes back to MicroQuin's theory around ICE regulation, uncovered through its space station research. And even more amazing—the theory is not limited to cancer. The company now has a large portfolio of disease areas and new therapeutics it is working on.

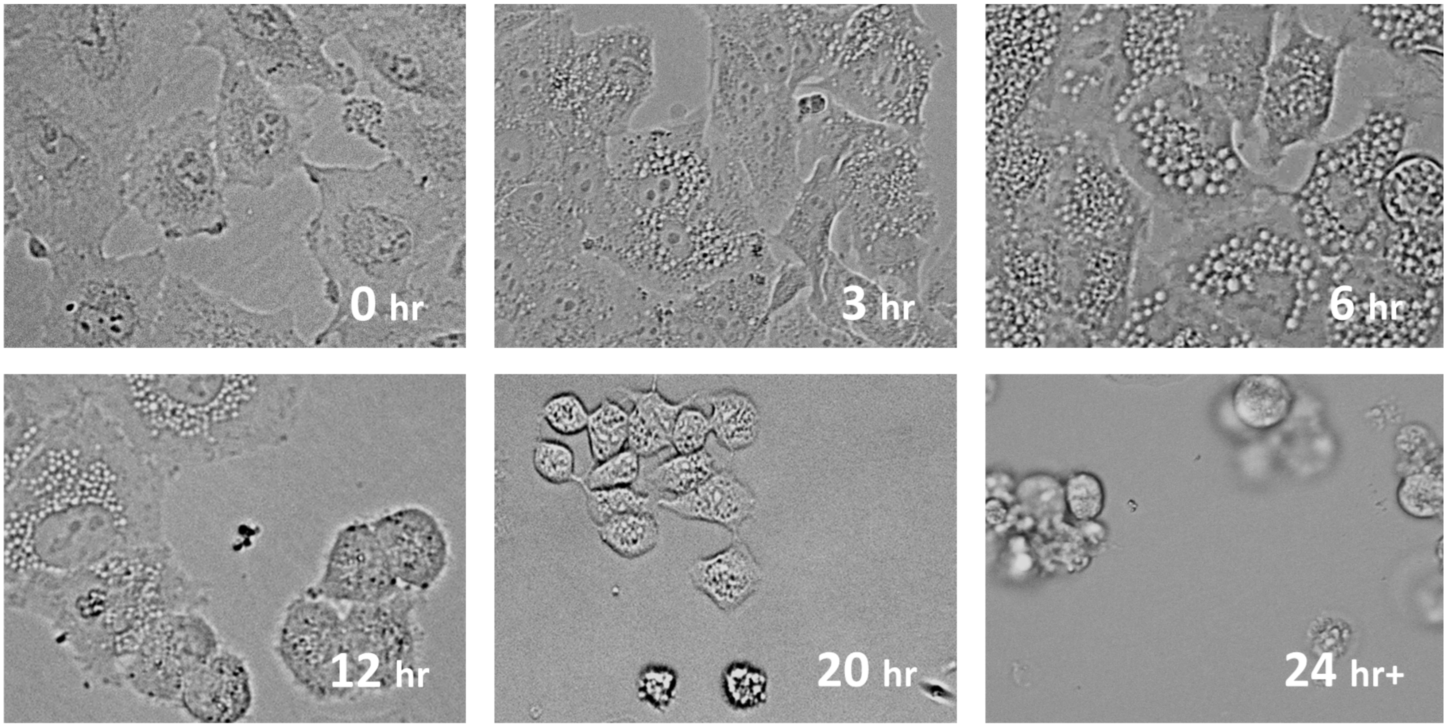
"What we're seeing is that at the heart of every disease or injury, you have an intracellular environment change," Robinson said. "And if you can alter how a disease changes the cell's intracellular environment, you can either fully stop the disease or slow its progression."

Cleaning Up the Microenvironment

While MicroQuin's small molecule therapeutic is highly effective at killing cancer cells, it may not provide a complete cure for all cancers, Robinson said. However, the therapeutic could be revolutionary in complementing immunotherapy drugs. A key obstacle for immunotherapies is the toxic microenvironment around tumors.

Everything that gets pushed out of cancer cells to enable their survival pollutes the environment immediately surrounding the tumor, killing healthy cells in that area. Immunotherapies rely on immune cells to attack tumors, but the immune cells cannot penetrate the toxic microenvironment.

If MicroQuin's therapeutic can alter the way intracellular changes are regulated in cancer cells, limiting the toxic pollutants that are pushed out into the microenvironment, it will be easier for immunotherapies to get through and successfully kill the cancer.



This 24-hour time progression of lung cancer cells treated with MicroQuin's small molecule drug shows holes forming in the endoplasmic reticulum of the cells, with floating dead cancer cells in the final frame.

MicroQuin

From Space to the Future

Following its ISS National Lab-sponsored research, MicroQuin has been awarded several grants to continue research on ICE regulators and therapeutic development, including multiple grants from the U.S. Department of Defense.

"The work we've done on the ISS has been instrumental in the grant application process to showcase what we have achieved that nobody else has to be able to achieve," Luo said. "In addition to the funding we received to do our experiments on the ISS, the validation it provided is paramount for startups and really opens doors."

MicroQuin's vision is to eventually work with a larger pharmaceutical company to take its therapeutics to market. "We want to make an impact, and we're hoping this will be a revolutionary treatment to help people with cancer," Luo said.

As Robinson looks to the future, he is excited by the idea of MicroQuin's therapeutics one day helping people find hope in the face of a devastating cancer diagnosis. Now, he is inspired not only by the wonder of space but also by the power of space-based R&D to enable breakthroughs that benefit people on Earth.

"I think it's such a strange concept for people that you can do something on the space station and that it has any applicability to your life," he said. "But the results from research in space can be transforming—it transformed our company for sure."