



# Space Life Sciences Research Highlights

## Research on Muscle Atrophy in Space Points Way to Clinical Applications

*What does space flight have in common with the aging process here on Earth? Both lead to significant muscle wasting. Herman Vandenburg's basic research began as an attempt to understand why muscle wastes when humans and animals are sent into space. Potential spinoffs from this basic research offer potentially promising treatments for chronic muscle wasting in elderly people, AIDS patients, and others with muscle-wasting disorders.*

When it comes to muscles, "use it or lose it" is an inescapable fact of life. It is well known that if muscles are not regularly used, they weaken and atrophy.

Muscle forms as a result of mechanical forces on the body's muscle fibers. These forces include not only the stresses and tensions imposed by body movement but also gravity: every time we stand, walk, raise an arm, or nod our head, the body and its muscles are working against gravity. Numerous experiments conducted in space, as well as ground-based simulations, have shown that removing the force of gravity leads to rapid muscle atrophy.

Muscles also atrophy as humans and animals age. In part this is because as we get older the body makes less human growth hormone (hGH), which is a potent growth factor for both muscle and bone. People have about a fifth as much hGH in their bloodstream at age 65 as they did at puberty. Levels of hGH in the bloodstream also diminish when humans and animals go into space.

Both disuse and diminished levels of hGH contribute to muscle wasting, but the underlying mechanisms of this process have not been well understood. Because muscle atrophy is likely to be a serious problem for long-duration space flight, NASA wants to understand these mechanisms and develop countermeasures.

Herman Vandenburg and his colleagues, with research support from NASA's Life Sciences Division, have developed techniques for removing muscle cells from the body and sustaining them for as long as 45 days in a culture chamber, an artificial system that provides all the nutrients, vitamins, and growth factors that the muscles need to remain healthy and viable. Most of these experiments have used bird and rodent muscle cells.



The cells are embedded in a gelatin-like matrix that allows them to be subjected to mechanical tension. The goal of this work is to understand the chemical signals that interact with tension and gravity to regulate muscle growth at the cellular and molecular level. The culture chamber was developed by the Walter Reed Army Institute of Research for NASA.

This experimental system was flown on the space shuttle for a series of experiments between 1994 and 1998. These experiments showed that the muscle cells wasted because of a slowing-down of the rate at which new proteins were being made in the muscle cells. They also showed for the first time that muscle fibers themselves are directly responsive to the effects of space flight.

"Proteins in cells are turning over constantly," says Vandenburg, Professor of Pathology at Brown University School of Medicine in Providence. "Atrophy of muscle cells can occur either because cellular proteins are broken down at a faster rate than normal or because new proteins are made at a slower rate. In the shuttle experiments, we found no change in the

rate at which cellular proteins were broken down, but we did find a significantly slower rate of protein synthesis—the process of making new proteins.”

“We now know that what happens to animals and humans in space flight is very similar to what happens in the aging process—there is a decrease in the rate at which new proteins are made in the muscle. The next step is to test potential compounds that might speed up the rate at which new proteins are made in the muscle cells.”

In the next experiment—scheduled to be conducted on the shuttle in December 2000—muscle cells in the culture chamber will be treated with insulin-like growth factor 1 (IGF-1). In experiments on the ground, IGF-1 has been shown to be a potent stimulator of protein synthesis in muscle cells. “We think that by adding IGF-1 we might be able to slow down or prevent muscle atrophy,” says Vandenburg.

Measures that prevent muscle wasting during space flight may also prevent aging- or disease-related muscle atrophy, notes Vandenburg. However, before proteins such as IGF-1 can be therapeutically useful in people, more effective ways must be found to deliver them in the body. They cannot be taken by mouth because they are immediately broken down by stomach acids.

Nearly all therapeutic proteins are currently given by injection, which is costly and unpleasant for patients. Additionally, injected proteins are of limited effectiveness because the body still breaks them down fairly quickly. Vandenburg’s research team is using the techniques of gene therapy and tissue engineering to develop an alternative approach to delivering therapeutic proteins.

“We envision being able to remove some of a patient’s muscle cells and insert into them the gene for the protein that we want to deliver. We would then use the methods that we developed for the space flight studies to grow the cells outside the body, keeping them healthy and viable until they are ready to be put back into the patient.”

The genetically altered cells would continuously deliver a low level of the therapeutic protein into the patient’s bloodstream. Vandenburg calls this system an “implantable protein factory.”

He and his colleagues have successfully used this technique in mice. They first removed muscle cells from the mice, inserted into them the gene for hGH—which (like IGF-1) is a potent stimulator of muscle growth and implanted the cells into the animals. They then induced hind-leg muscle atrophy in the mice by suspending their rear legs. (“Hindlimb unloading” is one of the techniques used on Earth to simulate the gravity-free conditions encountered in space.)

“We showed that by implanting these genetically engineered cells to deliver growth hormone, we could reduce the muscle wasting caused by hindlimb disuse,” says Vandenburg.

“We confirmed that giving the animals daily injections of growth hormone doesn’t reduce muscle wasting, but that a cell-based gene therapy approach does.”

There are many potential clinical applications for this technology. The U.S. Food and Drug Administration has approved hGH as a treatment for dwarfism in children, adult-onset growth hormone deficiency, and muscle wasting in people with AIDS. Clinical trials have shown that giving hGH to patients with congestive heart failure can strengthen the heart muscle, causing the heart to pump blood more effectively. Many frail elderly people could potentially benefit from treatment with hGH.

However, hGH injections in humans are not very effective. Doses large enough to have a therapeutic effect cause side effects such as water retention and carpal tunnel syndrome in as many as half of the patients treated. A more effective approach to delivering hGH that avoids these side effects would be highly desirable.

“Right now this technology is highly experimental, but if it is successful it could have profound effects on how we treat a lot of chronic disorders that are not effectively treated now,” says Vandenburg.

#### References

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