Space Travel and Personalized Medicine: The Critical Value of the "Astronaut-on-a-Chip" Platform

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Ever since the first moon landing, space exploration has captivated both scientists and the public. The possibility of travel to distant planets awakens our curiosity, ignites our imagination, elicits innovation, and catalyzes technological development. However, we cannot accomplish—in fact, not even begin—these deep space human missions until we can protect astronauts from a barrage of insults from radiation to chronic stress. To fulfill our collective deep-space desires, we must understand the precise effects of these insults on human cells, tissues, and the body as a whole, and then learn to target them with equal precision. The magnitude of this challenge calls for multiple, non-overlapping, cutting-edge scientific strategies. Science tells us that these strategies must include examining "humans on a chip."

The last decade has shown tremendous scientific advancement via traditional cell culture and animal models. However, this work also highlighted these models' critical pitfalls. We have learned, for example, that rodent models—the most frequently used models for deciphering causes and pathology of disease as well as preclinical drug studies—simply cannot replicate certain uniquely human processes. Three examples:

- **Rodent models cannot replicate human genetic heterogeneity**. Unlike mice, humans are not inbred. We cannot understand or anticipate individual astronauts' responses to stressors associated with long space missions or develop effective countermeasures without taking human genetic diversity into account.

- **The human brain is far more complex than the mouse brain**. Human brain contains a wide variety of diverse cell types within the main classes of neurons and astrocytes. The magnitude of gene expression in these cells compared to the mouse one underscores human brain complexity with respect to function.

- **Human metabolism is unique**. This includes drug metabolism. For example, several drugs commonly used in people, like ibuprofen and warfarin, are toxic to rodents, and drugs' availability, distribution, efficiency, and excretion can widely vary between species. We see these differences in human clinical drug trials, where overall attrition rates from phase 1 through phase 4 remain well above 90%.

In sum, we cannot learn how to protect individual astronauts from many health risks and detriments associated with deep-space missions with rodent models alone. We need cutting-edge human models to safely explore other worlds.

It is rare that a technology awaiting an application aligns with a problem awaiting a solution. But this is the case with human-on-a-chip technology and human deep-space travel. Here's why:

- First, the **microfluidic devices** we started developing in the 1960s now allow for precise, automated fluid delivery, mixing, valve control, tissue separation, micro-molecule delivery, and *in situ* multi-sensors.

- Second, Shinya Yamanaka's discovery of induced pluripotent stem cells (iPSCs) in 2006, which earned him a Nobel Prize in 2012, has ushered in a new era of human disease models and corresponding breakthroughs in our understanding of human biology. iPSC models, which arose from simple human skin cell cultures derived directly from patients, have spurred the field to create person-specific, three-dimensional, self-organizing **organoid models** that are highly similar to—if not indistinguishable from—actual human organs. To date, we can grow almost all human organoids in a dish.

- Third, **human genome sequencing, 'omics sciences, and computational tools for analyzing big data** have exploded in recent years. In fact, these advances inspired President Obama to announce a new initiative to accelerate personalized and precision medicine in 2015.

Taken together, these advances have enabled scientists to develop and utilize the organs-on-a-chip platforms that let us conduct personalized studies on the many tissues vulnerable to insults in space while simultaneously creating precisely matched countermeasures to prevent, rescue, and repair these tissues in each astronaut.

These human models have received widespread attention among scientists precisely because they allow us to study multiple tissues at the same time *and* their interactions as in the human body as a whole. The organs-on-a-chip platform allows tissues to communicate with each other just as they do in the human body, via underlying vasculature that allows various soluble and insoluble factors like cytokines, nutrients, growth factors, and hormones to flow freely. Organs-on-a-chip have already proven profoundly useful in studies regarding bone repair and replacement and in lung, gut, liver, and heart pathology. They are rapidly evolving to include the brain and other organs.

Studying the risks associated with deep space missions—like radiation, hypoxia, and stress, to name a few—in these models will allow us to gather valuable information about the mechanisms underlying human organ reaction and repair to these conditions. These models are therefore hugely valuable not only to basic biological studies but to personalized drug testing and molecular medicine. Integrated, multiple organs on the single chip offer unique insight into drug absorption, distribution, metabolism,

excretion, and toxicity, and to our overall understanding of drug interactions in the human body. As such, they have great potential to better predict personalized drug efficacy and safety compared to traditional preclinical rodent models.

Science must constantly advance in order to serve society—it cannot remain stagnant. To protect astronauts' safety during long-term space missions, we have a responsibility to use every scientific tool currently available to tailor this protection to each individual. Organs-on-a-chip or, in this case, "astronauts-on-a-chip," represent the most advanced technology we have to mimic the human body. They afford the best chance for us to identify risk factors and develop countermeasures to prevent or repair damage in each individual crew member thereby providing their best chance of completing their deep-space mission. They are also the only complex models that account for the effects that ethnicity, race, sex, and other diverse characteristics may have on basic tissue biology. For all these reasons, organs-on-a-chip have compelling advantages compared to other *in vitro* and *in vivo* models and should not be dismissed.