**Topical:**

# Use of Human Three-Dimensional Tissue and Organ Model Systems to Assess Radiation Risk and Develop Countermeasures

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**Abstract:**

With increased interest in long term space travel, it is critical to anticipate how exposure to radiation will affect human health. Human 3D tissue/organ models provide a state-of-the-art model to evaluate the effects of radiation damage and to assess mitigators of radiation damage. The use of physiologically active human avatars, like 3D tissue/organ models, to understand how human tissues and organs behave in the spaceflight environment will make a significant contribution to space radiation research and ultimately lead to discoveries that will ensure the safety and health of astronauts.

**Introduction:**

With increased interest in long term space travel, it is critical to anticipate how exposure to radiation will affect human health. There are significant knowledge gaps surrounding health risks related to long duration space travel and in the development of innovative countermeasures to reduce these risks. Cellular readouts that will assist in predicting organ and tissue responses to radiation are essential to closing these gaps and providing safe means for human space travel. The recent development and advancement of technology that has facilitated the establishment of ex vivo human 3D tissue model systems has **tremendous potential** to significantly advance the understanding tissue specific effects of radiation exposure. Additionally, these new models **provide the means** to develop and evaluate countermeasures that will prevent and protect against radiation induced damage that will be caused by space travel. This white paper highlights the valuable contributions 3D tissue model systems will make to the Space Biology Program in the area of the effects of long-term radiation exposure on astronaut health.

## *Gap in knowledge*

**There is limited information as to how human tissues and organs will respond to long duration space travel.**

Understanding the biological changes at the tissue and organ level that occur following exposure to ground based simulated space radiation will be predictive of changes that are expected to occur during long term space travel. There are major knowledge gaps as to how low dose/high LET radiation exposure effects human organs over long periods of time and there is serious concern that increased biological damage at the organ and tissue level is a significant risk to astronaut health (1;2). Traditionally rodent models have been used to examine the effects of radiation on human biology, including outcomes such as proliferation, transformation, and cell death (3). Although the complexity of in vivo rodent models has provided valuable basic biological insights to some effects of radiation damage, rodents have significant limitations in addressing the biology of human physiological responses (4;5). Thus, human tissue model systems that recapitulate in vivo biology, have been robustly characterized, and are amenable to assessment of biomarkers and outcomes of radiation damage are crucial to obtaining data to better predict human organ specific consequences of long-term space radiation exposure.

## *Advantages of 3D tissue culture models*

**Human 3D tissue culture models provide a better system than standard in vitro and in vivo models to evaluate the effects of radiation damage.**

Three-dimensional human tissue/organ models recapitulate key functional aspects of their in vivo counterparts that will be critical to evaluation of the effect of space radiation. These model systems incorporate many features of human organs including the three-dimensional architecture of the organ and the presence of multiple cell types that reflect a more accurate physiology of the native tissue by mimicking the organ microenvironment (6). Over the recent decade, a human 3D tissue culture model has been developed from almost every major human organ including brain, lung, liver, skin, intestine, and bone (7). Many of these models have been linked on platforms designed to investigate the contribution of inter organ signaling to the overall biological response to both internal and external stimuli and the results are predicted to more accurately reflect in vivo responses compared to more conventional tissue culture models (8;9). Their complexity can be increased by the inclusion of tissue-tissue interfaces, fluid flow, and mechanical cues (10). Clearly, 3D tissue models have become an important tool in the toolbox to predict human cellular responses to space radiation. Data will be derived from these model systems that is directly translatable to humans.

Previously, two approaches have been used to predict the effects of radiation damage on human organs. Rodents have been used extensively to study radiation induced damage; however, there are differences in physiological responses between rodents and humans that suggest that rodents do not necessarily accurately model human biology (4). It has long been known that there is frequent discordance between rodent and human studies (11). In many cases, preclinical animal testing do not accurately predict adverse outcomes in humans providing further evidence of the limitations of rodent models (12). Animal studies are labor-intensive, expensive, and lack genetic diversity, are not amenable to high throughput screening, and do not model human population-specific physiology and pathophysiology. In addition, there has been increasing pressure to limit the use of animals for research purposes (5;13). Most research using human cells are limited by the fact that traditional cell lines are cancer derived or otherwise immortalized, thereby losing their ability to capture the normal physiology of human cells (14). These cell lines generally consist of a single epithelial cell population and as such, they lack the cellular heterogeneity of most human tissues. As a result, these cell lines do not recapitulate much of the normal tissue architecture, functional specificity, biology, or molecular signaling of the human organ. This is particularly important in the area of the effects of space radiation, where the abnormal proliferation of cancer derived cells will yield meaningless data in respect to how tissues and organs respond to radiation damage. There is an unmet need for novel in vitro systems that better model human organs and tissues.

Human 3D tissue models have significant advantages over rodent and transformed cell lines in predicting how human tissues will respond to extended space radiation exposure. They bridge the gap between whole animal organs in vivo and transformed cell lines by providing the accessibility and ease of an in vitro platform while still maintaining features such as multiple cell types organized with realistic interactions and morphology (7;15). Direction of cellular architecture, chemical gradients, and mechanical forces allows for precision control in replicating the environment of the native organ. Genome editing of

these models is a powerful tool upon which molecular details of responses can be validated (15-18). Using genetic approaches to incorporate biosensors (19) can allow the biological responses of the tissue to be monitored and will result in data outcomes that can be mined for countermeasure targets. Most importantly, these models contain stem cells (20) which not only are the potential target of radiation damage but are crucial to regeneration of the organ following radiation damage. The importance of assessing the dynamics of stem cell responses to space radiation exposure within the context of their diverse cellular environment cannot be overstated. Human 3D tissue/organ models provide another advantage in that they have potential to provide personalized approaches to radiation risk. For example, organoid cultures derived from either pluripotent or somatic stem cells can be made from many donors and thus can be used to investigate the role of genetic variability on the response to space radiation (20;21). The influence of factors such as age, sex, and ethnicity on the cellular response to radiation can be interrogated at the cellular level in a way that animal and transformed cell-based models could never achieve. Human 3D tissue/organ models provide a gateway into developing personalized approaches to understanding the organ specific effects that will arise from radiation exposure during long duration space travel.

### *Development of countermeasures using 3D tissue culture models*

**The ability to assess mitigators of radiation damage is an important deliverable of the use of 3D tissue/organ cultures systems.**

Many of the well characterized human 3D tissue/organ models are amenable to evaluate the potential of preventive or therapeutic moieties to treat radiation damage. These models are amenable to high throughput screening for compounds (22) or treatments that might mitigate the damaging effects of space radiation. Results can be obtained rapidly and ultimately associated with the dissection of molecular mechanisms. Outcomes such as cell death, proliferation, survival, and regeneration are easily measurable and quantifiable in these models (23). Using 3D tissue models, novel, safe, and cost-effective countermeasure can be developed that have potential to protect tissues and organs from radiation damage. In addition, with the power to assess genetic variables, the 3D tissue and organ models facilitate the advancement of precision medicine-based tools that can be custom designed based on specific responses at the level of the individual.

## Conclusions

Three-dimensional human tissue and organ models replicate the complex cellularity and physiology of human organs. These model systems are developing and evolving rapidly. Within the last 10 years, the 3D tissue models have overcome the limitations of and surpassed the use of transformed cell lines and rodent models. The number of publications using human 3D tissue/organ models has exponentially increased over the last 10 years (**Fig. 1**). It is anticipated that over the next five years, increasing applications will emerge as the complexity of the models continues to expand. Clearly, 3D tissues and organ models provide a unique technology in which rapid accurate data can be collected while considering human individual variability in the biological analysis of damage and in the evaluation of mitigators. These insights will be critical to development of simple, cost-

effective, and safe countermeasures to prevent or treat radiation induced organ damage that has not been previously possible. The use of physiologically active human avatars to understand how human tissues and organs behave in the spaceflight environment will make a significant contribution to space radiation research and ultimately lead to discoveries that will ensure the safety and health of astronauts.

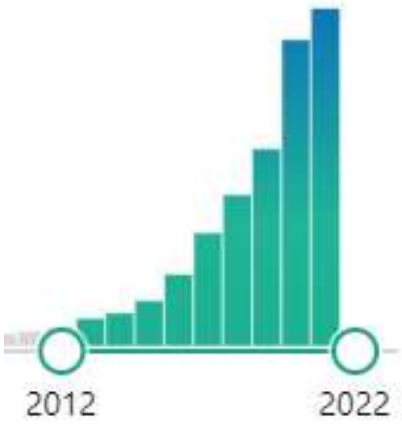


**Figure 1. Number of publications in PubMed from 2012 to 2022 upon searching the term "organoid"**

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