Organ Bioengineering Research in Microgravity

PROGRAM GUIDE & ROUNDTABLE CONCEPTS

Roundtable discussion conducted in conjunction with the World Stem Cell Summit

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WSCS15 WORLD STEM CELL SUMMIT

REGENERATIVE MEDICINE FOUNDATION

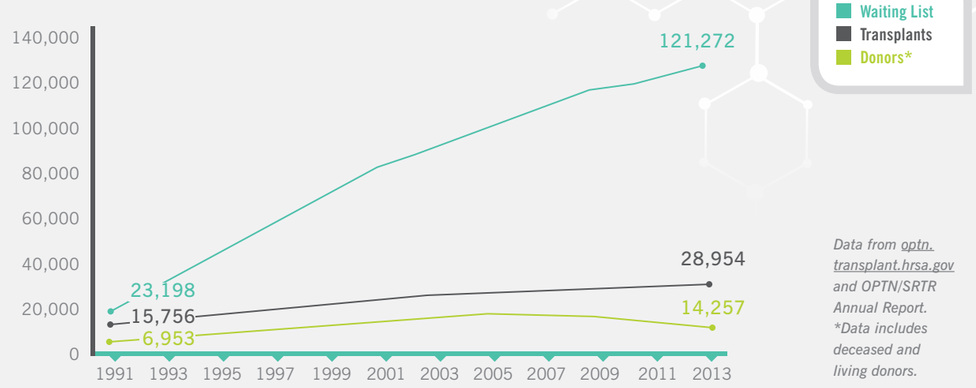
Contents

Report Introduction

THE NEED FOR ORGAN BIOENGINEERING

According to the U.S. Department of Health and Human Services, an average of 79 Americans receive a new organ each day; however, due to a shortage of donor organs, an average of 22 people die each day waiting for a transplant. The U.S. transplant waiting list currently contains more than 120,000 people, and the gap between donations and need continues to widen (see Figure 1).

FIGURE 1: *Gap between the need and supply of donor organs*



Efforts to increase organ donation through awareness campaigns and the use of living donors (for liver and kidney) have been somewhat effective; however, organ donation rates have stayed relatively flat while demand has soared. Two fields of work that stand to close the organ donation gap are organ banking (preserving and storing donor organs in order to shrink the number of donor organs deemed unsuitable for transport) and organ bioengineering (growing entirely new organs).

THE PATH TO GROWING NEW ORGANS

Regenerative medicine is a young field with much promise, but it has advanced more slowly than anticipated. One of the first successes in the field was Dermagraft®, the first fully human skin substitute for wound healing approved by the U.S. Food and Drug Administration (FDA) in 2001. In the years since the success of Dermagraft®, researchers have run clinical trials on many products, but few have made it to the market for patients. However, recent advances in regenerative medicine, precision medicine, and microfluidic-based platform technologies for *in vitro* cell and tissue culture are now starting to bring new products and therapies to the public.

Stem cell biology and microfluidic cell culture platforms such as microphysiological systems (MPS), also known as organs on chips, have recently provided researchers with new ways to study the human body. MPS platforms are structures made of polymers or other materials that act as a scaffold for growing cells, giving researchers a way to simulate how an organ such as the liver might respond to new drugs. As the field of MPS improves, so does the likelihood of creating replacement organs. Although this work brings the possibility of growing replacement organs closer to reality, there are technical challenges to overcome before organ systems can be reliably and repeatedly assembled. Many of these challenges are discussed in the roundtable session sections that follow.

USING MICROGRAVITY TO ACCELERATE RESEARCH

One potential avenue to accelerate research in stem cell biology and MPS platforms is exposure of cell cultures to reduced gravity conditions, which induces changes in cell growth and differentiation. Investigators from academic institutions, private organizations, or government agencies can utilize the microgravity environment onboard the International Space Station (ISS) U.S. National Laboratory to conduct stem cell research aimed at elucidating the fundamental biological mechanisms behind cell behavior, developing better scaffolding for growing cells, and studying cell clustering in an environment that better mimics *in vivo* conditions. The mission of the Center for the Advancement of Science in Space (CASIS) is to facilitate utilization of the ISS National Lab to benefit life on Earth—and improving human health through spaceflight cell-culture investigations is a significant pursuit within this mission.

The microgravity environment onboard the ISS affects biological functions—from the level of whole organisms down to intracellular and biomolecular processes. In cell cultures grown in microgravity, the physical properties of the space environment (e.g., the functional absence of buoyancy-driven convention, fluid shear, and sedimentation) induce improved aggregation of cells into a 3-D tissue-like architecture. Moreover, microgravity induces gene expression changes that result in phenotypic consequences that can include improved differentiation, proliferation, viability, and various other cell characteristics and functions.

> ***The ability of microgravity to alter the behavior of cell cultures may provide an exciting opportunity to augment traditional ground-based studies by providing new insights into cellular mechanisms and tissue behaviors. Organ bioengineering may thus directly benefit from near-term investment and participation in space-based tissue-growth research.***

ROUNDTABLE OBJECTIVES

CASIS organized the Organ Bioengineering Research in Microgravity Roundtable with two primary objectives:

1. *To identify key research questions and potential challenges for developing new technologies and platforms to enable next-generation regenerative medicine and organ bioengineering, and*
2. *To define and optimize a strategy to expand utilization of the unique environment of the ISS National Lab to advance the pace of such research for Earth benefit.*

In addition, roundtable participants considered collaborative funding opportunities and science, technology, engineering, and mathematics education initiatives related to organ bioengineering and microgravity.

The roundtable brought together thought leaders in stem cell biology, MPS platforms, and 3-D bioprinting from a variety of backgrounds and organizations, including academia, government, and private industry—some meeting face-to-face for the first time. These disciplines will all play a role in the future of bioengineering new organs; therefore, the facilitation of collaboration and communication is a critical factor for success. The ultimate intent of the roundtable was to define how these diverse organizations can come together to overcome the problem of organ shortages—perhaps through use of the ISS National Lab. Toward this end, this initial roundtable discussion specifically identified the first steps toward establishing a long-term organ bioengineering research program onboard the ISS National Lab.

Following the meeting, CASIS will establish a Science Definition Team to enable research on the ISS, with an eventual goal of creating an ISS National Lab initiative for microgravity-based bioengineering research that will accelerate regenerative medicine research efforts for government, private industry, and academia. The immediate objectives of this team will be to define the path to a sustainable sponsored research program or programs for fundamental and translational R&D on the ISS in areas identified by subject matter experts as critical to realizing the goals of regenerative medicine. The long-term aims of such a program are to help end the organ shortage and to spur future public-private investment in spaceflight research and educational opportunities that inspire scientists and truly benefit humanity.

CONCLUSION

The following sections contain information gathered during the roundtable discussion held at the 2015 World Stem Cell Summit in Atlanta, Georgia, as well as background information on the history and current state of organ bioengineering. This information highlights preliminary research questions, challenges faced in different facets of the field, and thoughts on the advantages of conducting organ bioengineering research in microgravity. Further work by the Organ Bioengineering Science Definition Team that will be assembled as a result of these preliminary discussions will rely on the foundation built during this roundtable discussion.

The enclosed recommendations are intended as a starting point on a path toward optimal use of the unique environment on the ISS National Lab to enable future cell-based technologies for improving human health on Earth. By identifying technical challenges and opportunities to utilize microgravity to advance organ bioengineering, this roundtable seeks to develop a science definition framework that will engage the interest of the research community and funding agencies to generate a sustainable sponsored research program in organ bioengineering. The points identified in this report will inform future bioengineering work, and the partnerships and collaborative research stemming from this meeting will continue to guide government-interagency, nonprofit, commercial, and academic organ bioengineering research.

Program Guide

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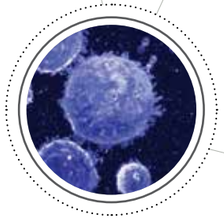

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Program Guide

ROUNDTABLE AGENDA

Hosted During the 2015 World Stem Cell Summit in Atlanta, Georgia
Friday, December 11, 2015

Welcome/Introduction
Jana Stoudemire/Warren Bates .....12:15 – 12:30P
- » *The importance of microgravity research*

Regenerative Medicine: Current Perspectives
Robert Nerem.....12:30 – 12:45P

Historical Perspective/Microgravity Fluid Dynamics
Michael Roberts.....12:45 – 1:00P

Break-Out Sessions
Jana Stoudemire/Break-Out Teams.....1:00 – 2:15P
- » *Each discussion group presents their requirement concepts*
- » *Note-taking/grouping of ideas*

Discussion Group I: Stem Cell Biology
Mahendra Rao (Discussion Lead)/Michael Roberts (CASIS Lead)

Discussion Group II: Microphysiological Systems (Organs-on-Chips)
Kevin Healy (Discussion Lead)/Bill McLamb (CASIS Lead)

Discussion Group III: Tissues to Organs
Anthony Atala (Discussion Lead)/Jana Stoudemire (CASIS Lead)

Consolidation of Requirements and Group Concurrence
Mahendra Rao, Keven Healy, Anthony Atala, Robert Nerem .....2:15 – 3:00P

Next Steps and Closing
Jana Stoudemire/Warren Bates .....3:00 – 3:30P

ABOUT THE ORGANIZERS

CASIS™

About CASIS: The Center for the Advancement of Science in Space (CASIS) was selected by NASA in July 2011 to maximize use of the International Space Station (ISS) U.S. National Laboratory through 2020. CASIS is dedicated to supporting and accelerating innovations and new discoveries that will enhance the health and wellbeing of people and our planet. For more information, visit www.iss-casis.org.

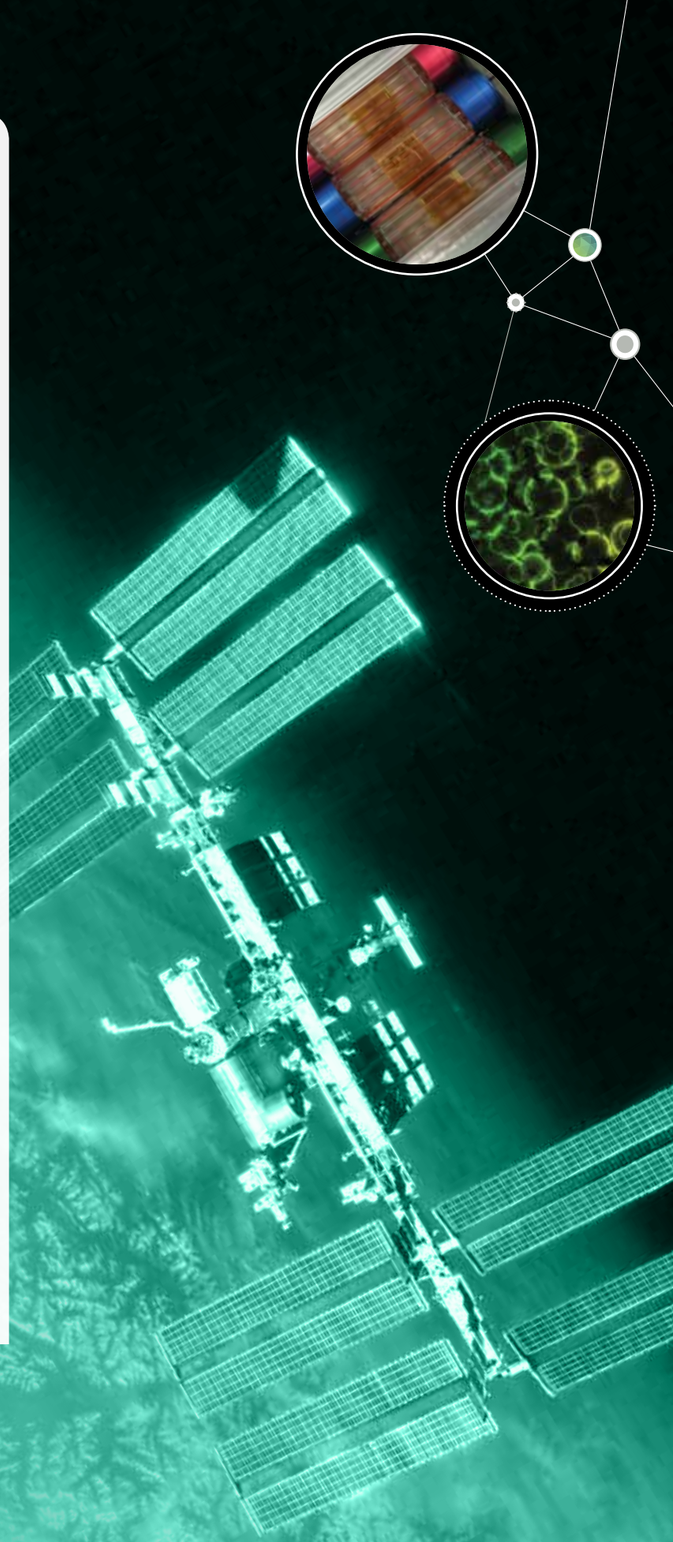
ISS U.S. NATIONAL LABORATORY

About the ISS National Lab: In 2005, Congress designated the U.S. portion of the International Space Station as the nation's newest national laboratory to maximize its use for improving life on Earth, promoting collaboration among diverse users, and advancing STEM education. This unique laboratory environment is available for use by other U.S. government agencies and by academic and private institutions, providing access to the permanent microgravity setting, vantage point in low Earth orbit, and varied environments of space.

ABOUT GOOD HEALTH

GOOD HEALTH

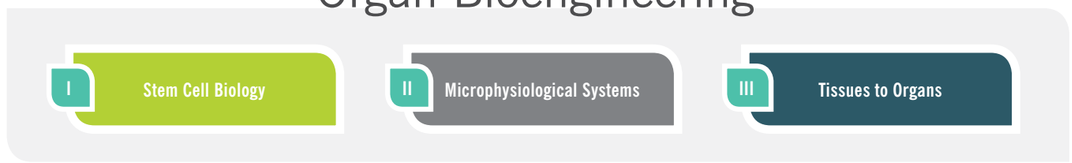
GOOD HEALTH is a CASIS research initiative in partnership with NASA to improve human health by enabling biomedical discovery in space for the benefit of life on Earth. Good Health capitalizes on the unique environment of the ISS National Lab to study, in humans and model organisms, transitions from health to disease that are accelerated by microgravity, including osteoporosis, muscle wasting, and immune dysfunction.



Roundtable Concepts

INTRODUCTION

With more than 120,000 Americans waiting for an organ transplant, the organ shortage is a modern health crisis. The growing gap between the need and supply of donor organs demonstrates that new and creative solutions are paramount. The field of organ bioengineering, together with organ banking, aims to address this critical issue.



Work in organ banking aims to shrink the number of donor organs deemed unsuitable for transport, thus preserving an extremely valuable resource. Advances in organ banking can also benefit work in organ bioengineering. For example, improved methods of cryopreservation in organ banking will not only minimize damage to tissue during storage and transport—it will also benefit regenerative medicine by improving preservation of bioengineered tissues and cells.

In addition to potentially accelerating capabilities for fully engineered organ replacements,

> *organ bioengineering research in microgravity aims to yield a better understanding of fundamental processes in regenerative medicine that could lead to additional improvements for human health and provide new and valuable commercial opportunities.*

For example, a better understanding of human physiology at the level of individual cells can help in the development of precision medicine—personalized drugs with better efficacy and fewer side effects for individual patients.

The Organ Bioengineering Research in Microgravity Roundtable sought to assess the trends in and future possibilities for regenerative medicine within the context of organ bioengineering and related fields, serving as a first step on the long road to solving the organ shortage crisis.

The results of this initial roundtable discussion provide the current state of various fields crucial to organ bioengineering, identify preliminary questions and challenges, and set the cornerstone for collaborative organ bioengineering research on the ISS National Lab.

PROCESS

CASIS held the Organ Bioengineering Roundtable to bring together thought leaders in the fields of regenerative medicine and stem cell biology to identify challenges and key research questions in organ bioengineering and ways that organ bioengineering research could benefit from the microgravity environment on the ISS. During the initial roundtable meeting, which was held during the 2015 World Stem Cell Summit in Atlanta, Georgia, participants broke into discussion groups focused on the topics of (i) stem cell biology, (ii) microphysiological systems, and (iii) creating tissues and organs.

Key findings from the three one-hour breakout discussions are presented in a condensed form in the following sections. These findings are meant to be a starting point for development of future organ bioengineering work on the ISS.

In addition, this roundtable served as the beginnings of a new interdisciplinary team aimed at further defining organ bioengineering research in microgravity and facilitating communication and collaboration among researchers. This Science Definition Team is currently being assembled.

I ROUNDTABLE DISCUSSION I: STEM CELL BIOLOGY

Stem cell biology is at the core of regenerative medicine. Fundamental research into stem cell biology elucidates critical details about cellular processes that are paramount to bioengineering efforts. Moreover, stem cells and progenitor cells from a variety of sources, including those derived from adult tissues (e.g., bone marrow, blood, skin, and fat), can produce the wide variety of different cell types that will be needed to grow replacement organs.

Roundtable Participants

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Key Findings

Advantages to Stem Cell Research in Space

- Allows study of the effects of gravity and the space environment.
- 3-D growth is easier to achieve.
- A reduction in shearing forces results in less stress on cells cultures.
- There may be better environmental controls (e.g., air content).
- The lack of buoyancy-driven convection could make protein solutions more stable.
- Spaceflight induces phenotypes that provide a model of aging (e.g., loss of bone and muscle mass, slowed healing).

Challenges to Stem Cell Research in Space

- There is a need for more information on how cells grow, age, and differentiate, particularly in microgravity.
- Currently, there are insufficient sources for the number of qualified cells needed.
- The field currently lacks consensus on growth factors, media, vendors, protocols, culture conditions, assays, etc.—all of which influence reproducibility of results.
- Initial experiments may likely be observational rather than hypothesis driven.
- There is limited space and crew time on the ISS, and astronauts may lack specialized skills for certain experiments.

Experimental Questions for Spaceflight

- How does spaceflight affect stem cell media and self-assembly?
- How should the community use what is learned from spaceflight cell culture to address health concerns in space and on Earth?
- How do bone marrow or peripheral blood counts change in space?
- How does spaceflight influence stem cell expansion? Should development of a bioreactor to accelerate cell growth be a goal?
- How does spaceflight influence continuity between cell types?
- Does cell energy metabolism improve in space? (Rationale: Cells on Earth are always “fighting” gravity.)
- Can cell migration research in space reveal new insights?
- What maintains “stemness” in spaceflight stem cells?

Roundtable Concepts

ROUNDTABLE DISCUSSION I: STEM CELL BIOLOGY (CONTINUED)

Abbreviated Discussion Minutes

Stem Cell Biology

Discussion Group I focused on issues related to human stem cells and their translation to regenerative medicine. A key initial discussion point was regarding which key cell type to focus on for translational research in this field: induced pluripotent stem cells (iPSCs) versus mesenchymal stem cells (MSCs). This discussion yielded a consensus that it is important to use all available cell types (e.g., iPSCs, MSCs, embryonic stem cells, and other progenitor cell types) and to determine on an individual basis which cell type is best suited for a particular experiment.

Subsequent discussion focused on the larger and more open-ended question of the "state of the field:" current challenges and focus areas for stem cell biology research. A major challenge currently facing the field is that there are still many things the community does not fully understand. For example, there is a need for additional data on mechanisms of cell aging, cell growth *in vivo* versus *in vitro*, and stem cell differentiation during tissue formation and organogenesis.

The challenge of reproducibility in experiments across various laboratories and approaches also remains an issue in today's investigations—and this may even be exacerbated in the future by new methodologies and the continued use of multiple cell types. The group concluded that for the success of translational initiatives, it will be necessary to identify and control the many variables that are at play during stem cell growth and differentiation, particularly for future experiments done in microgravity. To overcome the reproducibility hurdle, the stem cell research community will need to determine standards for cell sourcing, growth media, experimental protocols, and types of assays.

A final challenge that will need to be addressed early on is how to obtain the cells needed for large-scale research, as there are currently insufficient sources for the necessary quantities of qualified stem cells.

Research on the ISS

Discussion regarding the advantages of doing stem cell research in space began with acknowledgment that the ISS National Lab provides a unique opportunity to study how gravity affects stem cells and culture techniques. For example, the group discussed that the lack of buoyancy driven convection and sedimentation might affect nutrient and waste transport. Another advantage discussed was the ease of growing 3-D cell structures in microgravity. This is particularly beneficial toward enabling the translational applications of stem cell research and bioengineering, because developing organs will require us to grow complex, vascularized 3-D cell structures. Additionally, shear and other stress forces are significantly reduced in microgravity, which could help isolate the role stresses play in cell differentiation and tissue formation—and may even provide a superior model of *in vivo* environmental conditions.

Spaceflight has also shown the ability, in many ways, to serve as a model for accelerated aging. Some parts of the aging process—at the cellular and whole-organism level—happen at an accelerated rate in microgravity. When astronauts and model organisms spend time in microgravity, they experience loss of bone mass and muscle atrophy via mechanisms that in many cases appear to mimic age-related disease conditions on Earth. In addition, wounds take longer to heal in microgravity than on Earth, pointing to a possible role of gravity in the healing process.

Although microgravity provides these unique advantages to stem cell researchers, it also presents a number of challenges. For example, the availability of research space, crew time, and launch vehicles impose strict limits on how many experiments can be done on the ISS. The space inside the ISS is at a premium, particularly when discussing major initiatives, such as the addition of in-orbit equipment or bioreactors. In addition, astronauts on the ISS have a limited amount of time to devote to many varieties of science investigations, so they may not have the ability—let alone expertise—to conduct complex experiments. To develop a program of repeat stem cell experiments onboard the ISS, researchers would need to make simple experiments that rely on automation as much as possible. The group discussed the idea that automation and simple experimental designs have the added advantage of likely producing better consistency between experiments.

A second challenge that is somewhat distinctive to working in orbit is a lag in data analysis. In terrestrial studies, researchers can analyze and change parameters based on real-time indications during an experimental protocol. In spaceflight research, investigators traditionally must wait for experiments to return from the ISS before analyzing data, at which point they can change parameters and prepare a newly designed experiment to go back into space. Additionally, spaceflight experiments require 1g controls, effectively doubling the number of required cells, which are currently limited in supply.

The final challenge discussed by the group was that the types of experiments best done in space might likely be observational studies rather than hypothesis-driven inquiries. Spaceflight offers a radically different environment from conditions on Earth—not only with respect to the functional absence of gravity but also because of atmospheric pressure changes and exposure to space radiation. Additionally, delivery of experiments to the ISS (and return to Earth) involves a variety of physical forces that must be considered, including short periods of hyper-gravity. Observational studies under these unique conditions are likely to be powerful hypothesis-generating opportunities, but conversely, confounding factors may complicate results from hypothesis-driven inquiries.

With the likely observational nature of space-based stem cell studies in mind, the group concluded their discussion by brainstorming examples for future spaceflight experiments. The list of examples is long; however, one suggested experiment to note is a study of what maintains "stemness" in spaceflight stem cells (i.e., why do some stem cell types in microgravity show less differentiation than ground controls). Understanding what drives stemness (or the maintenance of pluripotency, the ability to differentiate into multiple cell types) may guide the development of better methods for growing large numbers of stem cells, which is critically needed for bioengineering tissues and organs on Earth.

II ROUNDTABLE DISCUSSION II: MICROPHYSIOLOGICAL SYSTEMS

Microphysiological systems (MPS) are a relatively new field of study in the regenerative medicine arena. MPS consist of cells grown on an artificial structure, commonly referred to as a chip, made of polymers or other materials. The chip acts as a scaffold (giving cells a structure to grow on and build tissue) and contains sensors and equipment used to monitor and manipulate the tissue as it grows. MPS, commonly referred to as tissues-on-a-chip or organs-on-a-chip, are giving researchers new ways to study human physiology and develop novel medications. The lessons learned and techniques developed in building MPS are serving as a basis for organ bioengineering research.

Roundtable Participants

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Key Findings

Main MPS Challenges	There is a need for more flexibility in seeding cells on MPS structures.
	There are insufficient sources for the needed cells.
	Cells are a valuable resource, thus there is an urgent need to develop a way to minimize cell loss when loading cells on a chip.
	Reproducibility (e.g., via reducing chip-to-chip variability) is lacking; there is a need for defined standards regarding methods, chip architectures, metrics, protocols, and techniques.
Challenges to MPS Research in Space	MPS scaffolds may not be useful for tissue assembly in microgravity.
	Should MPS be assembled on Earth and delivered frozen, or should they be assemble onboard the ISS?
	The lack of gravity and buoyancy-driven sedimentation will drive some restrictions on the cells that can be seeded on an MPS.
	Reproducibility, consistency, and limited ISS crew time are concerns (though, these could potentially be overcome through automation.
	The increased number of controls (e.g., +/- gravity, +/- radiation) requires additional cells, which are a limited resource.
	The limited onboard space and the cost of doing experiments on the ISS necessitates simplified experiments.

Roundtable Concepts

ROUNDTABLE DISCUSSION II: MICROPHYSIOLOGICAL SYSTEMS (CONTINUED)

Suggested ISS Experiments

- Observing self-assembly in absence of gravity.
- Using bone and bone marrow MPS to study microgravity-induced osteoporosis.
- Using ear-on-a-chip technology to study how gravity affects the inner ear.
- Study of various hormonal responses in microgravity.
- Study of aging of MPS created on Earth and in orbit; potentially also how MPS recover after returning to normal gravity.

Abbreviated Discussion Minutes

Microphysiological Systems

Discussion Group II focused on MPS, which are sometimes referred to as tissue-on-a-chip or organ-on-a-chip systems. This growing research field is a bridge between fundamental cell research and larger-scale bioengineering initiatives, such as bioprinting of organs.

At a basic level, MPS are a way to give a cell construct architecture and structure by seeding cells onto some kind of substrate (e.g., a polymer chip) and letting those cells grow and divide. For example, one could use stem cell-derived cardiomyocytes to artificially grow tissues that resemble cardiac muscle. In addition to giving a tissue its structure, MPS also provide ways to control physical forces and monitor the system using various types of instrumentation. For example, tissues in the body are subject to stretching and shearing forces and perfusion, and MPS provide a way to emulate these relevant biological forces.

Discussion Group II was tasked with identifying the main challenges and focus areas in the field of MPS as well as addressing the specific merit of single- versus multi-cellular systems. Early in the discussion, the group agreed that future studies should focus mainly on systems using multiple cell types. One of the critical goals of MPS research is how to best build systems that resemble native tissue, which can only be achieved with multi-cell systems. A related goal is integrating MPS with different tissue or organ types (e.g., liver and heart tissue) using a perfusion system. The hope is that an integrated multiple organ-on-chip system would yield new and better ways to model human physiology for multiple purposes, including disease studies and drug design.

The group subsequently discussed how the current challenges and focus areas of the MPS field relate to organ bioengineering. The primary challenge echoes the cell sourcing issue identified by Discussion Group I, because cell loss during the loading of MPS chips is a common difficulty. Stem cells are a valuable resource, so it is crucial to develop improved ways to load cells onto chips and thereby reduce cell loss as much as possible. Another challenge that echoes discussions from Discussion Group I is the need for reproducibility in studies, namely reducing chip-to-chip variation. Improving reproducibility will require standardized methods, chip architectures, and tissue monitoring techniques, as well as improved metrics and protocols.

Research on the ISS

With regard to taking advantage of the benefits of microgravity, the group had many suggestions for potential spaceflight experiments. In addition to fundamental studies to improve understanding of organ and tissue development, the group listed several areas of interest for spaceflight research. Examples are listed in the Suggested ISS Experiments table above and include interrogation of the effects of microgravity on the musculoskeletal system, the inner ear, aging, and hormonal activity.

The group's discussion regarding future MPS investigations onboard the ISS also identified several concerns or challenges—many akin to those identified by Discussion Group I. One important question unique to Discussion Group II, however, relates to tissue assembly: how does one load cells of different types onto a chip in microgravity? On Earth, this process relies on natural cell behavior—cells loaded onto an appropriate scaffold (or similar structure) self assemble via natural biological processes. The group questioned whether this self assembly would follow the same process in microgravity. As noted by the stem cell biology group, all living things on Earth have evolved in gravity, so it is logical to assume that gravity plays a critical role in biological processes even when that role has not yet been fully described or studied. Initial studies to observe how MPS self assemble in the absence of gravity could resolve some of these concerns and potentially improve understanding of the development process.

The group also discussed the logistics of where and when to assemble the chip for spaceflight MPS investigations (i.e., should it be pre-assembled and frozen for delivery or seeded with cells once onboard the ISS?). This in turn raises technical issues; for example, some cell-seeding techniques rely on the gravity-dependent phenomenon of heavier particles falling to the bottom of ports in the chip. In the absence of buoyancy-driven sedimentation onboard ISS, experimental protocols would need to be adjusted. Perhaps more critically, issues of technical consistency and availability of crew time are significant if it is decided that chips must be seeded in orbit. As mentioned in Discussion Group I, however, this issue could be partially overcome through automation.

Other challenges identified by Discussion Group II include the increased need for parallel control conditions, the space constraints onboard the ISS, and the importance of simple experimental designs (see Discussion Group I minutes for more detailed discussion). Discussion Group II also noted some concerns with the cost of executing spaceflight experiments.

III ROUNDTABLE DISCUSSION III: TISSUES TO ORGANS

Stem cell biology and MPS research are creating the building blocks of organ bioengineering, but making the leap from tissue-on-a-chip constructs to fully functioning organs presents additional challenges. The ability to bioengineer fully functioning organs capable of ameliorating the demand for donor tissues will require combining multiple tissue types and ensuring proper blood vessel and nerve connections. The lessons learned in stem cell biology and MPS studies must be augmented by advanced techniques and technologies such as 3-D bioprinting to truly reach future success in building various types of replacement organs.

Roundtable Participants

*Anthony Atala**	*Adam Feinberg*	*Gail Naughton*	*John Vellinger*	** Discussion lead*
Eugene Boland	*Robert Guldberg*	*Ricardo Solorzano*	*Stuart Williams*	*† CASIS representative*
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Key Findings

Tissues to Organs Challenges

- Vascularization is a major barrier—engineered vessels are not small enough and biological methods are limited to thin tissues.
- There is a need for better sources of stem cells and defined standards for growing, differentiating, and preserving cells.
- Questions remain regarding scaffold materials and potential patient immune response to polymers and bioinks.
- It is unclear how much complexity is needed for viable transplants (e.g., whether to generate fully constructed or less developed organs).
- The field needs to determine whether to work toward full replacement of damaged organs or focus on repair and restoration.

Roundtable Concepts

ROUNDTABLE DISCUSSION III: TISSUES TO ORGANS (CONTINUED)

Techniques and Technologies Needed	3-D printing and bioprinting.
	New polymers and bioinks.
	Improved 3-D imaging and software for organ "blueprints."
	Better microvascularization techniques; improved understanding of growth factors.
Comments about Spaceflight Research	There is a need to determine how to best use microgravity to advance regenerative medicine and benefit human health on Earth.
	Crew time and available space on the ISS are limited.
	Working in microgravity can be costly and complex.
	There is a need for automation and more standardized equipment/techniques.
	Observing differences in immune response and stem cell differentiation in microgravity could yield new biological insights.
	There is an ultimate goal of commercializing research coming from the ISS, and there is a need to determine how the community can best translate research into products for the patients in need.

Abbreviated Discussion Minutes

Tissues to Organs

Discussion Group III examined the translational path from tissue bioengineering, which is still in its early stages, to building new complex organs for transplant. The production of fully functioning organs requires insights from stem cell biology and MPS research as well as advances in techniques such as bioprinting.

Challenges discussed by the group spanned many stages of the organ bioengineering process, as there are many steps in the process of building tissues and organs. A major challenge discussed is the difficulty faced in vascularizing tissue; that is, the critical importance of blood vessel formation throughout tissue as a means to move nutrients and oxygen to cells and transport waste products away. One approach that has been somewhat successful in other areas of medicine is the use of polymers and other materials to engineer blood vessels. There is a limit, however, to the size of vessels that can be created through techniques like 3-D printing; it is possible to create large-diameter vascular structures, but smaller vessels have a tendency to clot. In addition, current bioengineering techniques are limited to building vessels larger than 200 microns. In contrast, some capillaries in the human body (e.g., capillaries in the retina) have diameters as small as 4 microns.

Fortunately, natural biological processes have been shown to perform some vascularization of artificially constricted tissues. Current studies show that some microvasculature can grow, but there is a limit to tissue thickness (approximately 0.3 mm maximum thickness). Thus, current research is capable of bioengineering large vessels, and natural processes can produce smaller ones, but getting microvasculature of the full appropriate size range on the scale needed for a whole organ remains a challenge. In addition, innervating new tissue will present a similar challenge.

Other challenges identified relate to the building blocks of bioengineered organs. The first of these challenges echoes the discussions of Discussion Groups I and II: cell sourcing. How can the community increase the availability of reliable, qualified cells—where should stem cells be procured and how can they best be grown, differentiated, and preserved?

Moving downstream in the process, the next challenge is determining which materials are best for creating the organ scaffolds—and how might these polymers and bioinks hamper eventual translational applications (e.g., how might the artificial materials influence patient immune responses). Finally, the building of a complete and functional organ will likely require new techniques and technologies, such as 3-D bioprinting—which pose their own challenges.

Growing a new organ from cells requires a scaffold to give the organ structure. Bioprinting techniques can help build some of the structures needed, and improving such techniques and technologies might make it possible to produce the detailed scaffold needed to build a solid organ. However, this will in turn require better 3-D imaging and software to evaluate and achieve the kinds of detailed "blueprints" needed.

Furthermore, it is unclear how much complexity is needed in the final organ for it to be medically useful. A key point the group noted is that although most work thus far has focused on growing mature organs, it might be possible to take a cue from embryology—that is, to start with basic structures and cell types and promote their development into a final, functional form. This approach could help address some previously discussed challenges; for example, some embryonic organs do not start out with capillaries but become vascularized later. Using this approach to organ bioengineering could be beneficial, but it is currently unclear at which stage to begin such a process.

With respect to such alternative approaches, a more radical question raised by the group is whether one truly needs to recapitulate natural organ structure—that is, could bioengineered organs use a novel design that provides similar function?

Organs on the ISS

Throughout the discussion, the group acknowledged the potential of utilizing the ISS as a microgravity platform to advance regenerative medicine in ways that may benefit human health on Earth and provide commercial opportunity. In particular, this group was interested in how differences in immune response and stem cell differentiation in microgravity could act as an accelerated model of aging and possibly yield novel insights into these processes. However, many of the same challenges outlined by this group with regard to spaceflight research echo those captured by Discussion Groups I and II. For example, cell sourcing, limits on crew time and space, and the cost and complexity of working in microgravity. They also posited similar ways to overcome some of these challenges, such as standardized equipment and techniques and the use of automation whenever possible.

One area of discussion more deeply explored by this group was the ultimate desire to commercialize organ bioengineering research enabled by the ISS—specifically, how to translate ISS research into improved patient outcomes. With respect to these translational goals, the group acknowledged that while full organ replacements are the ultimate objective, an intermediate goal of producing a "biological bandage" that can restore organ function would be a strong next step for the field of bioengineering. The path to organ failure in a patient typically occurs over a relatively long period, so such a product capable of regenerating parts of failing organs could substantially improve patient quality of life.

ROUNDTABLE KEY FINDINGS: A SUMMARY

The roundtable discussion groups focused on three separate but related areas of importance to organ bioengineering. Although each group had unique challenges, several common issues arose. These issues included cell sourcing, the limitations inherent to spaceflight research, and the need for standardization and automation. These common areas should serve as a starting point for further discussion by the organ bioengineering Science Definition Team.

Common Challenges to Address	Define and develop standards for cell sourcing, growth, assays, and protocols.
	Develop biomaterials and bioinks and methods to assemble biologically relevant cell-biomaterial constructs.
	Reduce variability and increase reproducibility.
	Mitigate space and cost constraints related to ISS research.
	Overcome limits to available ISS crew time and expertise.
	Optimize spaceflight experimental design.

The Path Forward

NEXT STEPS

The roundtable discussions outlined in this report are a first step in exploring new pathways for ending the organ shortage crisis via growth of replacement organs. Moving forward, a newly formed Science Definition Team will continue to define the key questions and challenges in this area of regenerative medicine and to identify opportunities for spaceflight organ bioengineering initiatives.

The Science Definition Team is currently being assembled and will meet on an ongoing basis to continue guiding a plan for future organ bioengineering research. In addition, the team will work toward an ISS National Lab initiative to promote organ bioengineering research in space for the benefit of people on Earth.

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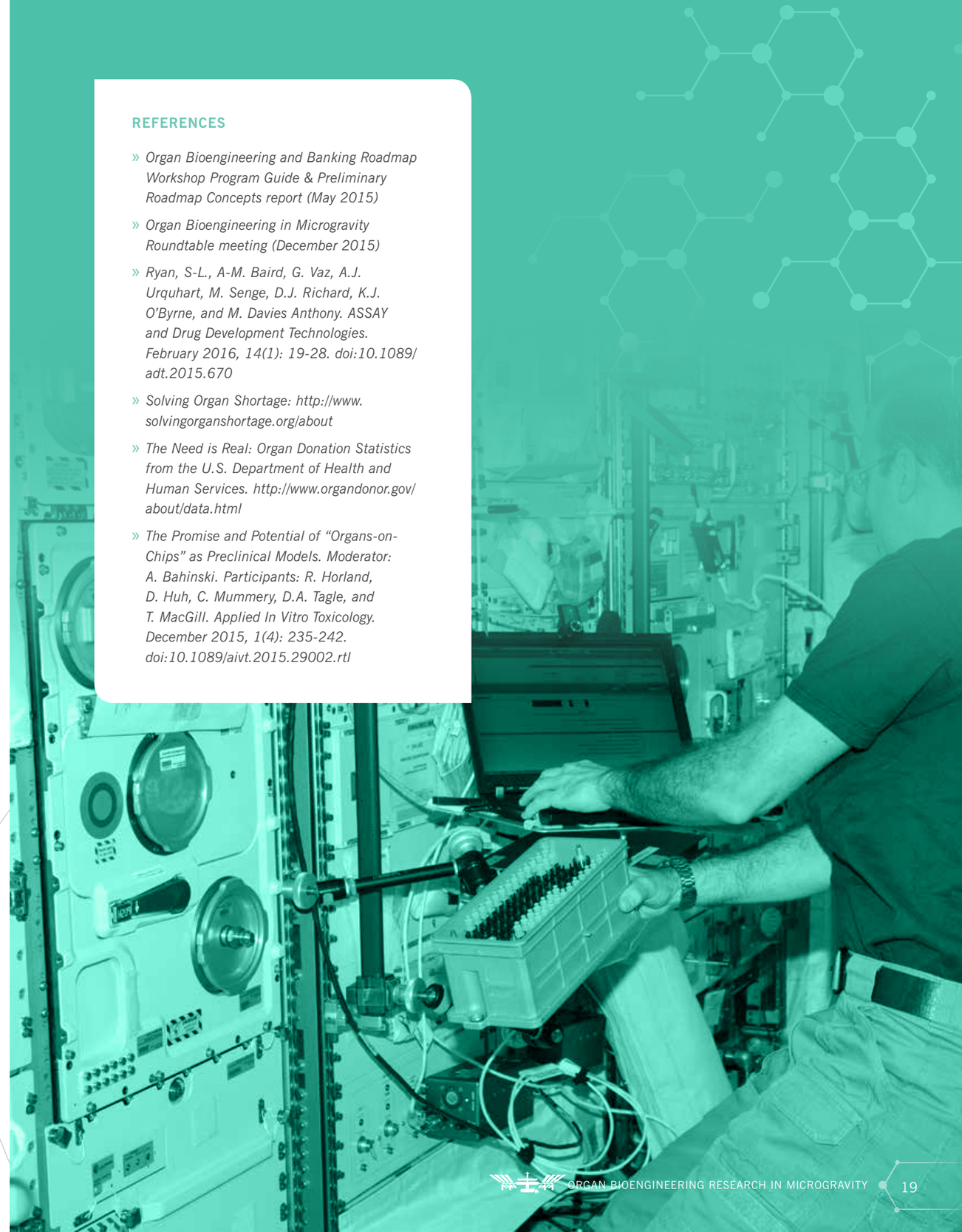

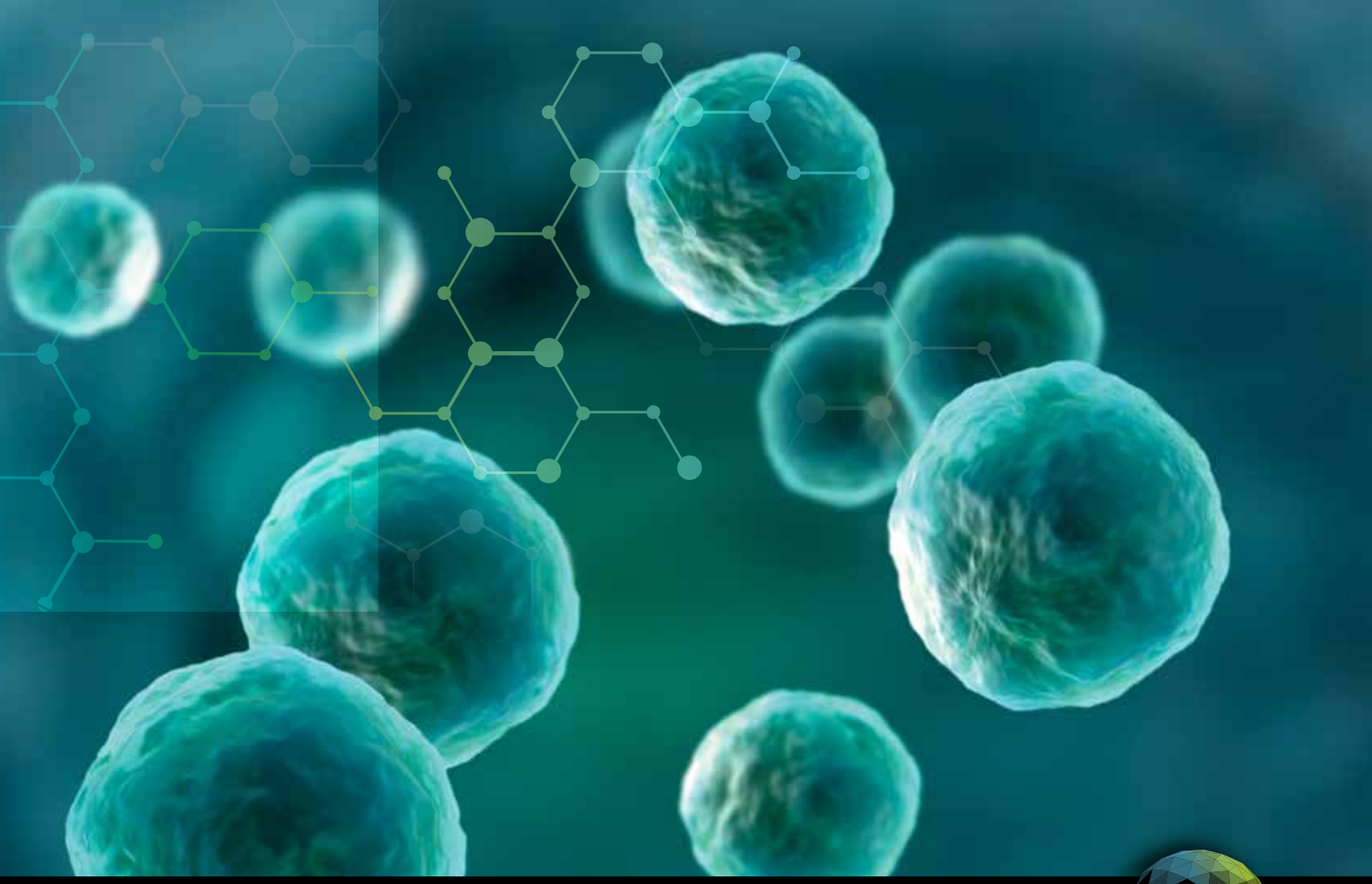

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