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The International Space Station U.S. National Lab – Tissue Engineering and Regenerative Medicine

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Abstract

The International Space Station (ISS) U.S. National Laboratory is an orbiting platform for research, technology development, and education that inspires innovation, provides opportunities for discovery that benefits life on Earth, and pushes scientific frontiers. The Center for the Advancement of Science in Space (CASIS) manages and provides access to the ISS National Laboratory, demonstrating to U.S. citizens and the world that space-based research is accessible, affordable, and capable of supporting research and development for far more than space exploration. CASIS has a congressionally mandated mission to maximize use of this unique laboratory to accelerate knowledge and commercial development for the benefit of humankind. In concert with this mission, the ISS National Laboratory's focus is to foster innovative research, inspire students, and stimulate demand for a sustained commercial economy in low Earth orbit. As described herein, a key area of focus for the ISS National Laboratory is to support efforts in the fields of tissue engineering and regenerative medicine.

Keywords: tissue chips, tissue engineering, biofabrication, organoids, regenerative medicine, stem cells

Acronyms/Abbreviations

BioFabrication Facility (BFF)
Centers for Disease Control and Prevention (CDC)
Center for the Advancement of Science in Space (CASIS)
Chemical, Bioengineering, Environmental and Transport Systems (CBET)
Civil, Mechanical and Manufacturing Innovation (CMMI)
European Space Agency (ESA)
International Space Station (ISS)
Japan Aerospace Exploration Agency (JAXA)
National Aeronautics and Space Administration (NASA)
National Center for Advancing Translational Sciences (NCATS)
National Institute of Biomedical Imaging and Bioengineering (NIBIB)
National Institutes of Health (NIH)
National Science Foundation (NSF)
National Stem Cell Foundation (NSCF)
New York Stem Cell Foundation (NYSCF)
Three-dimensional (3D)
Two-dimensional (2D)
U.S. Food and Drug Administration (FDA)

1. Introduction

Since taking over management of the ISS National Laboratory in 2011, CASIS has worked in partnership with NASA toward maximum utilization of the laboratory and promotion of nontraditional use by disruptive innovators. These collaborative efforts include the selection, preparation, launch, and return of experiments; the installation and use of hardware, software, and facilities; and the development of business relationships that have resulted from numerous partner and customer interactions and agreements.

One key area of focus for the ISS National Laboratory is to actively support research efforts that are germane to the tissue engineering and regenerative medicine communities. The ISS National Laboratory has engaged in these efforts in several ways, including conducting workshops and producing reports [1], issuing requests for proposals, and engaging other agencies to issue joint solicitations. This brief report will highlight the ISS National Laboratory's efforts in these areas, detail some early findings, and provide a perspective on future efforts. This report is not meant to provide an overview of all of the various efforts lead by NASA, ESA, JAXA, Roscosmos and others in utilizing the ISS (or other orbiting platform) as a platform for tissue engineering and regenerative medicine studies.

2. Stem Cells

Stem cells, which have the ability to differentiate into other cell types, are critically important in human development as well as in tissue repair and regeneration. Cell-cell interaction and cell mechanosensing are two cell properties that play an important role in stem cell proliferation and differentiation, and these properties are affected by microgravity. In 2013, the ISS National Laboratory issued a solicitation focused on examining the impact of microgravity on fundamental stem cell properties [2], and the solicitation resulted in seven awarded projects.

Fig. 1: NASA astronaut Kate Rubins images beating cardiomyocytes as part of the Effects of Microgravity on Stem Cell-Derived Heart Cells investigation. Image Credit: NASA

Several of these projects focused on cardiac stem cells, which are critically important to study from both a regenerative medicine and a disease modeling perspective [3,4]. A team of researchers from Stanford University led by Dr. Joseph Wu was the first to image beating cardiomyocytes in orbit (see Fig. 1). This project aims to understand how cardiomyocytes from a diverse patient population mature in the ISS environment. The ultimate goal of the project is to demonstrate that ISS-cultured cardiomyocytes could be utilized as a tool for disease modeling and/or drug screening (publication in development). Dr. Mary Kearns-Jonker from Loma Linda University was funded to study the effects of microgravity on adult and neonatal cardiac stem cells. Her work has leveraged both simulated microgravity as well as true microgravity on the ISS to discover pathways that transform adult cardiac stem cells into a more neonatal phenotype, thus making the cells more regenerative in nature [5-7]. Dr. Chunhui Xu from Emory University School of Medicine led a project that has shown microgravity can be utilized in conjunction with other techniques to facilitate greater maturation of cardiomyocytes [8,9]. Similarly, a project led by Dr. Robert Schwartz from the University of Houston also focused on how microgravity can be leveraged in the process of cardiomyocyte maturation (publication in development). Finally, Dr. Joshua Hare of the University of Miami School of Medicine showed how microgravity impairs cardiac autonomic neurogenesis, which has implications for human health both on Earth and on long-duration spaceflight missions [10].

Fig. 2: NASA astronaut Peggy Whitson examines the Microgravity Expanded Stem Cells investigation, which observes stem cell growth and morphological characteristics in microgravity and analyzes gene expression profiles of stem cells cultured in microgravity. Image Credit: NASA

In addition to the projects centered on cardiac stem cell, there were two other awards issued through the initial ISS National Laboratory stem cell solicitation. Dr. Abba Zubair from the Mayo Clinic was funded to study how the microgravity environment on the ISS may accelerate the expansion of stem cell populations (i.e., increase in cell density) for research and possibly therapeutic use (see Fig. 2). The study (publication in development) utilized mesenchymal, hematopoietic, and leukemia cancer stem cells. The last of these initial projects, led by Dr. Carl Gregory from the Texas A&M Health Science Center, demonstrated, among other

things, that a microgravity environment could be leveraged to develop a more relevant model for malignant bone disease [11], enabling novel quantitative insights into the disease not available through traditional cell culture or animal models.

3. Tissue Chips

Advancements in the fields of cell biology, bioengineering, microfluidics, data analytics, and materials science, coupled with the need for improvements in relevant models for studying disease pathology and generating preclinical efficacy and toxicity data, has led to the emergence of tissue chips (also known as organs-on-chips or microphysiological systems) [12]. In order to explore how tissue chip systems might be used on the ISS to exploit the unique microgravity environment, the ISS National Laboratory issued a request for information in 2015, followed by a request for proposals later that year. This effort resulted in the award of two projects, one from Dr. Siobhan Malany at Micro-gRx to study sarcopenia and the second to Dr. Rocky Tuan of the University of Pittsburg to develop a system for studying osteoporosis. Both projects utilize tissue chip platforms to take advantage of the accelerated aging effect that long-duration spaceflight has on human tissues, with the goal of expediting treatment options for populations here on Earth.

Building on these efforts with tissue chip platforms, in 2016, the ISS National Laboratory entered into a collaboration with the National Center for Advancing Translational Sciences (NCATS) to develop the Tissue Chips in Space initiative, and in 2018, the collaboration was expanded to include the National Institute of Biomedical Imaging and Bioengineering (NIBIB). Both NCATS and NIBIB are part of the National Institutes of Health (NIH). The goal of the Tissue Chips in Space initiative is to promote and fund ISS National Laboratory research into human physiology and disease that benefits patients on Earth. As a result of the collaboration, nine separate tissue chip projects have been funded through the Tissue Chips in Space initiative, five in 2017 through RFA-TR-16-019 [13] and four in 2018 through RFA-TR-18-001 [14]. Each of these projects is provided the opportunity to conduct two separate ISS experiments, as long as predefined milestones are met. In general, the first ISS experiment is designed for teams to validate their tissue chip model, while the second experiment will use the model to assess novel therapeutic options. Each of the funded teams works closely with Implementation Partners such as Bioserve Space Technologies, Techshot, Space Tango, and Space Technology and Advanced Research Systems to transform terrestrial systems into systems for use on the ISS. Each team is required to complete the payload development process and launch their first experiment within two years of award. The initial cohort of teams have all conducted their first ISS experiment and are in the process of postflight analysis. These projects include using microgravity as a model for studying immunological senescence and its impact on tissue stem cells and regeneration (launched on SpaceX-16) [15]; examining the effects of microgravity on healthy and diseased states of the blood-brain-barrier (launched on SpaceX-17) [16]; using a cartilage-bone-synovium model to study post-traumatic osteoarthritis and bone loss (launched on SpaceX-17) [17]; using a kidney chip model to study microgravity-induced kidney dysfunction, with the ultimate goal of identifying treatments for patients suffering from proteinuria, osteoporosis, and kidney stones on Earth (launched on SpaceX-17) [18,19] (see Fig. 3); and using a linked airway and bone marrow model to study immunological response to lung infections (launched on SpaceX-17) [20]. The teams are expected to launch their second experiments in 2020 or 2021.

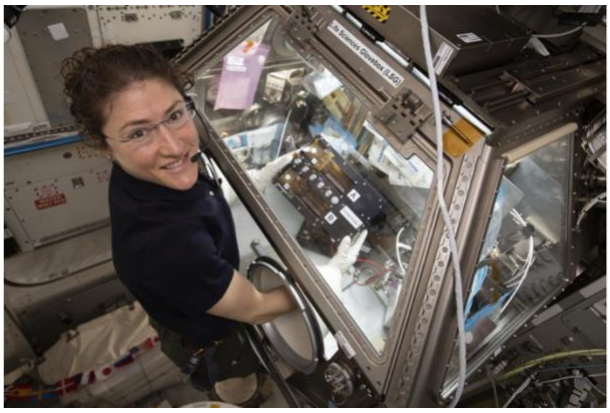

Fig. 3: NASA astronaut Christina Koch works inside the Life Sciences Glovebox with the Kidney Cells investigation. This NIH-sponsored Tissue Chips in Space investigation seeks innovative treatments for kidney stones, osteoporosis, and toxic chemical exposures. Image Credit: NASA

The cohort of projects awarded during the second round of funding is targeting launch of their first ISS experiments in 2020. This cohort includes two projects utilizing engineered heart tissue chips to study different aspects of microgravity-induced cardiomyopathy [21,22], a project using an electrically stimulated human myocyte model to evaluate novel therapeutic options to treat sarcopenia [23], and a project using a human intestine tissue chip platform to study the gut microbiome response to infection [24]. The teams involved in both cohorts of projects are also part of the larger NIH Tissue Chip Program [25], which works in partnership with multiple governmental agencies such as the U.S. Food and Drug Administration (FDA) to promote the development and validation of tissue chip

platforms, with the ultimate goal of expediting the process of providing safe and effective therapeutics to patients in need.

4. Tissue Engineering

In 2017, the ISS National Laboratory began a partnership with the National Science Foundation (NSF) in the area of tissue engineering. In collaboration with the Chemical, Bioengineering, Environmental and Transport Systems (CBET) division of NSF, the ISS National Laboratory issued a joint solicitation for fundamental and transformative research in biomedical engineering (NSF 18-514) [26]. The solicitation specifically sought proposals that could utilize the ISS environment in at least one of four main topic areas, including: development of models of pathological tissues and organ systems for the development and testing of therapeutics; design of systems that integrate living and nonliving components to improve diagnosis, monitoring, and treatment of disease or injury; advanced biomanufacturing of three-dimensional tissues and organs; and development of tools to investigate fundamental physiological and pathophysiological processes. All proposals were required to demonstrate a critical need for the ISS as well as a clear path to impacting life on Earth. Ultimately, the NSF and the ISS National Laboratory awarded two projects under this initial solicitation. One of the awarded projects is focused on developing a tissue-engineered muscle as a novel platform to study sarcopenia [27] and the other project is using the liver as a model organ to investigate how microgravity conditions onboard the ISS may facilitate the development of a large, vascularized tissue graft [28].

In 2018, the NSF collaboration was expanded to include the Civil, Mechanical and Manufacturing Innovation (CMMI) division of NSF, and the tissue engineering solicitation was reissued with the inclusion of studies focused on mechanobiology as an additional focus area (NSF 19-509) [29]. As a result of this solicitation, five projects were awarded the opportunity to conduct research on the ISS National Laboratory. These projects include: development of a platform to study the effects of aging as it relates to a tissue-engineered liver immune chip [30], use of a novel organ-on-a-chip model of the human cardiovascular system to study cardiovascular stiffness-related diseases [31], use of a three-dimensional cardiac organoid model to study changes in tissue function related to microgravity-induced atrophy [32], use of microgravity conditions to improve cardiomyocyte maturation [33], and development of a platform to monitor stiffness of osteoblasts that are subjected to mechanical compression while in microgravity [34]. The ISS National Laboratory and NSF released a third solicitation in this area during the 2019 calendar year (NSF 20-500) [35].

5. Biofabrication

The ability to manufacture patient-compatible tissues and organs has long been an aspiration of the medical industry. According to the Centers for Disease Control and Prevention (CDC), the waiting list for a donor organ contains about 75,000 people on any given day [36]. Advances in stem cell biology and tissue engineering have led to the development of specialized 3D bioprinters to construct viable tissue (tissue is defined as an ensemble of cells and their extracellular matrix from the same origin that together carry out a specific function) [37,38]. Generally, bioprinting is accomplished in a manner similar to the 3D printing used in additive manufacturing processes, but instead of extruding layers of melted plastic, biomaterials such as cells and growth factors are extruded in a low-viscosity bioink. However, printing the tiny, complex structures found inside human organs, such as capillary structures, has proven difficult in Earth's gravity. Due to the low viscosity of the bioink, scaffolding is required to prevent printed structures from collapsing, and the scaffolding material must be dissolved as the tissue matures. Microgravity could be a critical enabler for biomanufacturing to succeed, as it may mitigate the need for scaffolding.

At the time of this publication, four commercial entities are pursing 3D biomanufacturing in space, three through the ISS National Laboratory. One of these endeavors is the BioFabrication Facility (BFF), developed by Techshot, Inc. in partnership with nScrypt. This team modified a commercial off-the-shelf 3D-bioprinter developed by nScrypt to operate in microgravity and complement existing TechShot cell culture facilities on the ISS. The BFF launched on SpaceX-18 on July 25, 2019, and ISS crew members made their first and second prints using human cells on August 9, 2019 and August 12, 2019 (see Fig. 4). The printed tissues remained in the BFF for a short period of time before being transferred to a temperature-controlled incubator to continue maturation in microgravity. These first prints, which returned to Earth for analysis on SpaceX-18, are stepping-stones in a long-term plan to manufacture whole human organs in space. Additionally, the knowledge acquired along the way will create interim benefits related to cell regeneration in space and its application to humans on Earth.

Fig. 4: NASA astronaut Andrew Morgan works with the BioFabrication Facility investigating whether the microgravity environment in orbit may support the fabrication of human organs. Image Credit: NASA

6. Organoids

Organoids are miniature versions of an organ such as the brain, kidney, or pancreas. Unlike standard 2D cell culture, organoids are produced in such a manner that different cell types self-organize into 3D tissue cultures. This 3D aggregation is more similar to the ways in which cells aggregate in the body, compared with cell aggregation achieved through use of a 2D cell culture flask [39]. By organizing multiple cell types into a 3D shape, organoids can be generated such that they replicate much of the complexity and function of a whole organ [40]. Organoids are often derived from primary cells obtained directly from a patient's organ or from the patient's induced pluripotent stem cells. As such, organoids represent cellular models of disease that enable the study of human disease processes as well as drug interactions, potentially revolutionizing the field of drug discovery and opening new approaches to personalized medicine.

Organoids derived from patient cells were launched to the ISS National Laboratory and returned to Earth on SpaceX-18. This project from the National Stem Cell Foundation (NSCF) was a collaboration between research teams led by Dr. Valentina Fossati at the New York Stem Cell Foundation (NYSCF) Research Institute, Dr. Jeanne Loring from the Summit for Stem Cell Foundation, and Dr. Andres Bratt-Leal of Aspen Neuroscience. The project sought to study neurodegenerative diseases using organoids from induced pluripotent stem cells derived from patients with Parkinson's disease and Primary Progressive Multiple Sclerosis. Also on SpaceX-18, Drs. Alyyson Moutri and Erik Viirre from the University of California, San Diego, in partnership with Implementation Partner Space Tango, sent 100 brain organoids to the ISS to help answer fundamental questions about brain development. Insights from this research could also ultimately help researchers understand whether people can safely reproduce outside of Earth. Numerous additional organoid studies in microgravity are expected to follow to explore new methods of understanding organ development and treating diseases on Earth.

7. Future Direction

The ISS National Laboratory will continue to work with a variety of stakeholders to facilitate use of the ISS to benefit life on Earth. As results from current projects are disseminated and Implementation Partners continue to develop and validate novel spaceflight hardware, research focused on tissue engineering and regenerative medicine is expected to be a critical part of the experimental payloads supported through the ISS National Laboratory. To facilitate these activities and pave the way for commercial use of low Earth orbit platforms in the future, the ISS National Laboratory recently issued a request for proposals that is currently open targeting industrial biomedicine research and development onboard the ISS [41]. The ISS National Laboratory will also work with its stakeholder community to outline and publish a roadmap for the use of platforms in low Earth orbit in the area of industrial biomedicine.

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References

[1] https://www.issnationallab.org/research-on-the-iss/reports/bioengineering-report/ (accessed 30.08.19)

[2] https://www.issnationallab.org/press-releases/casis-issues-solicitation-for-proposals-titled-the-impact-of-microgravity-on-fundamental-stem-cell-properties-a-call-for-spaceflight-and-ground-based-experiments/ (accessed 30.08.19)

[3] Epstein JA. A Time to Press Reset and Regenerate Cardiac Stem Cell Biology. JAMA Cardiol. 2019 Feb 1;4(2):95-96.

[4] Tu C, Chao BS, Wu JC. Strategies for Improving the Maturity of Human Induced Pluripotent Stem Cell-Derived Cardiomyocytes. Circ Res. 2018 Aug 17;123(5):512-514.

[5] Fuentes TI, Appleby N, Raya M, Bailey L, Hasaniya N, Stodieck L, Kearns-Jonker M. Simulated microgravity exerts an age-dependent effect on the differentiation of cardiovascular progenitors isolated from the human heart. PLoS ONE. 2015 Jul 10;10(7):e0132378.

[6] Baio J, Martinez AF, Bailey L, Hasaniya N, Pecaut MJ, and Kearns-Jonker M. Spaceflight activates protein kinase C alpha signaling and modifies the

developmental stage of human neonatal cardiovascular progenitor cells. Stem Cells Dev. 2018 Jan 10.

[7] Camberos V, Baio J, Bailey L, Hasaniya N, Lopez LV, Kearns-Jonker M. Effects of Spaceflight and Simulated Microgravity on YAP1 Expression in Cardiovascular Progenitors: Implications for Cell-Based Repair. Int J Mol Sci. 2019 Jun 4;20(11).

[8] Yan L, Chunhui X & Teng M. In vitro organogenesis from pluripotent stem cells. Organogenesis. 2014;10(2):159-163

[9] Jha R, Wu Q, Singh M, Preininger MK, Han P, Ding G, Cho HC, Jo H, Maher KO, Wagner MB, Xu C. Simulated Microgravity and 3D Culture Enhance Induction, Viability, Proliferation and Differentiation of Cardiac Progenitors from Human Pluripotent Stem Cells. Sci Rep. 2016 Aug 5;6:30956.

[10] Hatzistergos KE, Jiang Z, Valasaki K, Takeuchi LM, Balkan W, Atluri P, Saur D, Seidler B, Tsinoremas N, DiFede DL, Hare JM. Simulated microgravity impairs cardiac autonomic neurogenesis from neural crest cells. Stem Cells Dev. 2018 Jun 15;27(12):819-830.

[11] McNeill EP, Reese RW, Tondon A, Clough BH, Pan S, Froese J, Palmer D, Krause U, Loeb DM, Kaunas R, Gregory CA. Three-dimensional in vitro modeling of malignant bone disease recapitulates experimentally accessible mechanisms of osteoinhibition. Cell Death Dis. 2018;9(12):1161.

[12] Low LA, Tagle DA. Tissue chips - innovative tools for drug development and disease modeling. Lab Chip. 2017 Sep 12;17(18):3026-3036.

[13] https://grants.nih.gov/grants/guide/rfa-files/RFA-TR-16-019.html (accessed 30.08.19)

[14] https://grants.nih.gov/grants/guide/rfa-files/rfa-tr-18-001.html (accessed 30.08.19)

[15] https://projectreporter.nih.gov/project_info_description.cfm?aid=9403001&icde=36136088&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball= (accessed 30.08.19)

[16] https://projectreporter.nih.gov/project_info_description.cfm?aid=9402972&icde=36136066&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball= (accessed 30.08.19)

[17] https://projectreporter.nih.gov/project_info_description.cfm?aid=9402868&icde=36136078&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball= (accessed 30.08.19)

[18] https://projectreporter.nih.gov/project_info_description.cfm?aid=9402456&icde=36136102&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball= (accessed 30.08.19)

[19] Yeung CK, Koenig P, Countryman S, Thummel KE, Himmelfarb J, Kelly EJ. Tissue Chips in Space-Challenges and Opportunities. Clin Transl Sci. 2019 Sep 16.

[20] https://projectreporter.nih.gov/project_info_description.cfm?aid=9403062&icde=36136027&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball= (accessed 30.08.19)

[21] https://projectreporter.nih.gov/project_info_description.cfm?aid=9644885&icde=41440096&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball= (accessed 30.08.19)

[22] https://projectreporter.nih.gov/project_info_description.cfm?aid=9644709&icde=41439964 (accessed 30.08.19)

[23] https://projectreporter.nih.gov/project_info_description.cfm?aid=9645400&icde=41440163&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball= (accessed 30.08.19)

[24] https://projectreporter.nih.gov/project_info_description.cfm?aid=9645490&icde=41440219&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball= (accessed 30.08.19)

[25] https://ncats.nih.gov/tissuechip/about/operations (accessed 30.08.19)

[26] https://www.nsf.gov/pubs/2018/nsf18514/nsf18514.htm (accessed 30.08.19)

[27] https://www.nsf.gov/awardsearch/showAward?AWD_ID=1829534&HistoricalAwards=false (accessed 30.08.19)

[28] https://www.nsf.gov/awardsearch/showAward?AWD_ID=1830768&HistoricalAwards=false (accessed 30.08.19)

[29] https://www.nsf.gov/pubs/2019/nsf19509/nsf19509.htm (accessed 30.08.19)

[30] https://www.nsf.gov/awardsearch/showAward?AWD_ID=1928095&HistoricalAwards=false (accessed 30.08.19)

[31] https://www.nsf.gov/awardsearch/showAward?AWD_ID=1929028&HistoricalAwards=false (accessed 30.08.19)

[32] https://www.nsf.gov/awardsearch/showAward?AWD_ID=1927628&HistoricalAwards=false (accessed 30.08.19)

[33] https://www.nsf.gov/awardsearch/showAward?AWD_ID=1926387&HistoricalAwards=false (accessed 30.08.19)

[34] https://www.nsf.gov/awardsearch/showAward?AWD_ID=1927803&HistoricalAwards=false (accessed 30.08.19)

[35] https://www.nsf.gov/funding/pgm_summ.jsp?pims_id=505735&org=NSF&from=home

[36] https://www.cdc.gov/transplantsafety/overview/key-facts.html (accessed 30.08.19)

[37] Prendergast ME, Burdick JA. Recent Advances in Enabling Technologies in 3D Printing for Precision Medicine. Adv Mater. 2019 Sep 12:e1902516.

[38] Moroni L, Boland T, Burdick JA, De Maria C, Derby B, Forgacs G, Groll J, Li Q, Malda J, Mironov VA, Mota C, Nakamura M, Shu W, Takeuchi S, Woodfield TBF, Xu T, Yoo JJ, Vozzi G. Biofabrication: A Guide to Technology and Terminology. Trends Biotechnol. 2018 Apr;36(4):384-402.

[39] Bartfeld S, Clevers H. Stem cell-derived organoids and their application for medical research and patient treatment. J Mol Med (Berl). 2017 Jul;95(7):729-738.

[40] Schutgens F, Clevers H. Human Organoids: Tools for Understanding Biology and Treating Diseases. Annu Rev Pathol. 2019 Sep 24.

[41] https://www.issnationallab.org/research-on-the-iss/solicitations/rfp2019-3/ (accessed 30.08.19)