27 July, 2023

National Science Foundation
2415 Eisenhower Ave
Alexandria, VA 22314

Re: Request for Information (RFI) on Developing a Roadmap for the Directorate for Technology, Innovation, and Partnerships at the National Science Foundation

Submitted electronically to: https://www.federalregister.gov/documents/2023/04/28/2023-08995/request-for-information-rfi-on-developing-a-roadmap-for-the-directorate-for-technology-innovation#open-comment

The International Society for Stem Cell Research (ISSCR) appreciates the opportunity to provide recommendations to the National Science Foundation (NSF) on how to develop a roadmap for the newly established Directorate for Technology, Innovation, and Partnerships (TIP). Founded in 2002, the ISSCR is an independent, global, nonprofit organization that promotes excellence in stem cell science and applications to human health. The ISSCR represents 4,500 scientists, educators, ethicists, and business leaders across 80 countries. Our vision is a world where stem cell science is encouraged, ethics are prioritized, and discovery improves understanding and advances human health.

Stem cell research holds immense potential for medicine and scientific advancement, and the field is growing rapidly. Stem cell-based systems are in large-scale use in academia and industry because they have the unique ability to reproduce features of human disorders, as well as the potential for discovering and testing therapeutics under development to ensure that they are safe and effective on human cells, negating the use of cells from animals whose responses only poorly predict those of patients. As investigators seek to move their research from the bench to the clinic, novel challenges are being discovered in the translational process for developing these transformative therapies. These challenges include laborious cell culturing techniques, analysis of large and complex datasets, quality control issues, safety concerns with scalability, and cost-effective manufacturing.

To overcome these challenges, researchers, funders, and regulators will need to embrace an interdisciplinary approach that utilizes modern tools like artificial intelligence (AI) and machine learning (ML), robotics, high throughput automated imaging, and advanced manufacturing to simplify and accelerate the development of cellular therapies and facilitate other uses of cells derived from patients with serious diseases. Other governments, most notably China, have invested heavily in accelerating growth in stem cell-related technologies and are already at the forefront in advanced cellular manufacturing. With a congressional mandate to focus on use-inspired and translational research, the TIP directorate can nurture the development and adoption of these new tools that will contribute to the U.S.’s leadership in this critical scientific field.

Here, the ISSCR submits comments in support of prioritization of the following Key Technology Focus Areas: artificial intelligence (1), robotics, automation, and advanced manufacturing (4), biotechnology, medical technology, genomics, and synthetic biology (7), and advanced materials science, including composite 2D materials, other next-generation materials, and related manufacturing technologies (10).
Focus Area 1: Using AI/ML to accelerate stem cell-based biological discovery across space, time, and human diversity.

Advances in genomics and imaging bring unprecedented opportunities for insights into fundamental biological processes like development, homeostasis, aging, and disease. They also bring opportunities to understand how variation in our genomes contributes to these processes, providing the “natural experiments” for cause-and-effect biological relationships. With this increased capacity to generate comprehensive datasets that include space, time, and genetic diversity, investigators now struggle with a bottleneck of understanding—how to discern meaning when data exceed the ability of human minds to comprehend them. Fortunately, recent breakthroughs in AI/ML offer the ability to discern patterns and causal relationships from such datasets, generating testable hypotheses that can be tested experimentally in high throughput.

Images, whether from climate-monitoring satellites or electron microscopes, are intrinsically data-dense. Imaging becomes particularly powerful when used in multimodal applications. For example, overlaying microscopic anatomy with the local transcriptome gives unprecedented ability to answer biological questions like how tissues regenerate, how cancer invades and metastasizes, or how transplants are rejected. These multimodal applications yield simultaneous data on dozens of cell types and thousands of transcripts over ~10^8 pixels, generating terabytes of data from just a few images. AI/ML allows us to begin deconvolving these datasets, calling patterns and inferring potential causal connections.

Temporal dynamics are one of the most widely used approaches in science to understand cause and effect. Longitudinal imaging, where the same experimental subjects are studied sequentially, is particularly powerful, because it rapidly narrows the possible mechanistic solutions. Experience from the Allen Institute for Cell Science (AICS) is illustrative here. The AICS aims to define the cell “state” by tracking the spatial relationships among ~25 cellular organelles during fundamental stem cell processes like colony formation, cell division, and differentiation. Their study of pluripotent stem cells in interphase and mitosis, recently published in Nature, curated 200,000+ live cell images in 3D. Through a complex use of AI/ML and statistical dynamics, they discerned key spatial relationships of organelles in the cell (the “wiring”), showing how the cell is “rewired” as it goes through mitosis.

Human diversity. Medicine has long assumed that patients who are medically similar are likely respond to the same treatments. Unfortunately, common diseases, such as cardiovascular, cancer, and neuropsychiatric, are complicated, and patients display obvious variability in their symptomology. This variability stems from genetics, from environmental/behavioral sources, and from their place in the disease’s temporal trajectory. As an example of how stem cells and AI/ML can move the needle on a common chronic illness, consider Parkinson’s disease (PD). While classified as a movement disorder, PD is genetically heterogeneous and frequently involves cells other than those in the movement control center of the brain. Some patients suffer from depression and/or loss of cognitive ability, meaning that neurons in other parts of the brain also deteriorate. Moreover, tissues outside the brain such as the gastrointestinal tract often malfunction in PD. In many cases, changes in peripheral tissues are observed years before movement disturbances become apparent, presenting, under appropriate conditions, the possibility of pre-diagnosing the eventual onset of CNS degeneration. Imagine a scenario where an AI algorithm scours
electronic health records, permitting grouping of many patients from different institutions by clinical phenotype, thereby reducing variability due to disease trajectory and disease subtype. Researchers then could prepare stem cell banks and gather genomic data from highly informative subgroups. These cell banks and genomic datasets, in turn, could be used with AI-augmented experiments for understanding disease mechanisms and for use in drug discovery.

Finally, while groundbreaking studies have demonstrated the capacity of AI/ML to facilitate breakthrough discoveries, access to these technologies is available to only a select few institutions with sufficient human and financial capital. It is essential that access to AI/ML is democratized, reaching an order of magnitude more researchers than is currently possible. Democratizing access to AI/ML will accelerate scientific discovery as much as the mass production of semiconductors.

**Focus Area 4: Robotics, automation, and advanced manufacturing for stem cell derivatives.**

Growth of cells in culture is the basis for virtually all biomanufacturing and is foundational to medical advancement. Despite this, techniques for cell culture have advanced little over the last 50 years, relying on intensely manual processes of liquid transfer through pipettes. This brings forth a conundrum: on the one hand, the cells we culture, our biochemical reagent library, and our experimental designs have become increasingly more sophisticated. On the other hand, despite the ever-increasing need for precision, the execution of these experiments involves mind-numbingly rote maneuvers that lead to imprecision, too often causing repetitive motion injury in our best bench scientists. The results are predictably biphasic. We now can generate nearly any cell type in the human body and do so at pharmaceutical grade and clinical scale. Yet, our reproducibility is poor, with far too many batch failures. Moreover, the variability in our products masks subtle-but-critical clues to understanding disease and gives variable treatment outcomes. If the U.S. is to compete for the best minds and generate the best products in the nascent revolution in regenerative medicine, we need to bring robotic automation into stem cell manufacturing.

ISSCR members have toured manufacturing facilities around the world, both in the academic and private sectors. We have seen the power of bringing automation to bear on stem cell-based biomanufacturing. Currently, the two most advanced countries in the world for automated biomanufacturing are China and Japan, with Germany following as a close third and the U.S. as a distant fourth. However, it is still the early days for this technology and increasing the U.S.’s competitive stance is principally a matter of will. While the above-referenced robotic systems have advanced manufacturing, there is considerable room for improvement. Their image recognition systems and onboarded AI are not sufficiently sophisticated to allow them to produce cells with equal quality from many individual patients, since the cells grow and mature at different rates. We propose to evolve the state of pattern recognition so that the treatment of each individual set of cells is set according to its own state of differentiation, as determined by cell morphology and other measurable cell features. Development of a system capable of producing patient-specific, disease-relevant differentiated cells from large numbers of patients would be highly valuable. Similar systems could be used to optimize large-scale cell manufacturing methods as well. In that case, each run will be optimized by a self-contained system that would modify the manufacturing conditions depending on the particular cells in each production chamber.
Ultimately, cell purification could also be accomplished using automated separation of labeled cells.

Finally, it is worth noting that areas of biomanufacturing excellence do exist in multiple areas within the U.S., principally in biopharma and in non-profit agencies like the Advanced Regenerative Manufacturing Institute. An investment in this domain could leverage knowhow from these entities and democratize access, ideally bringing biomanufacturing into the academic sector where engineers and life scientists could accelerate discoveries, develop next-generation innovations, and begin training a new workforce in this critical area of home-grown infrastructure.

**Focus Area 7: Biotechnology, medical technology, genomics, and synthetic biology.**

Advances in stem cell science are one of the major breakthroughs of the 21st century. With the development of human pluripotent stem cells, we now can generate nearly any of the 240+ cell types of the human body and do so at pharmaceutical quality and clinical scale. Stem cells provide a versatile platform for pairing with other technologies, including genome editing, synthetic biology, and analytical genomics. Applications of stem cells are protean, but here we will consider three: cell replacement therapy, disease modeling, and drug discovery.

**Cell Replacement Therapy.** Many of society’s most burdensome diseases result from deficiency of a critical population of cells that the body cannot replace. These include heart failure (#1 cause of death), osteoarthritis (#1 cause of pain/suffering), type 1 diabetes, stroke, Parkinson’s disease, spinal cord injury, chronic obstructive pulmonary disease, kidney failure, retinal blindness, deafness, and so on. We now can make all of these missing cell types in the laboratory, and for most examples, have approaches to delivering the cell to rebuild damaged tissues. When coupled with genomic engineering or synthetic biology, these cells can be imbued with properties beyond their natural phenotypes, for example, neurons that secrete pro-survival molecules to halt neurodegeneration, cardiac muscle cells that augment contractile function of the host heart muscle, cartilage cells that sense inflammation and secrete anti-inflammatory molecules within the joint, and T cells that are programmed to kill specific cancer types. American scientists have been leaders in cell replacement therapy, but governmental policies in Japan and China have created favorable funding opportunities as well as regulatory pathways to accelerate stem cell therapeutics. Cellular replacement therapies are proven concepts in many therapeutic areas. A large-scale governmental initiative in cell replacement therapy would leverage advances in multiple technological platforms and galvanize the research community toward a common effort to eliminate chronic diseases.

**Disease Modeling and Drug Discovery.** Our ability to generate pluripotent stem cells by reprogramming skin or blood cells from patients creates tremendous opportunities for understanding and treating diseases. Consider patients who have a genetically based disease that causes death or dysfunction of a critical cell type (e.g., motor neurons in spinal muscular atrophy or cardiomyocytes in cardiomyopathy). These diseases have traditionally been difficult to study, because obtaining these critical cell types from patients is virtually impossible, and animal models do not reproduce essential features of human disease. The ability to generate reprogrammed pluripotent stem cells from patients carrying a genetic disease (or to induce the disease-causing mutation via gene editing) creates a theoretically
unlimited supply of critical cells. Such cells can be studied to understand mechanisms of disease, e.g. in microphysiological systems/on-chip devices, or used in drug screens to identify and test new compounds for therapeutic development.

Focus Area 10: Advanced materials science, including composite 2D materials, other next-generation materials, and related manufacturing technologies.

Materials science plays a critical role in stem cell biology. By engineering a stem cell’s extracellular environment, it is possible to tune its intracellular signaling pathways to control critical properties such as survival, proliferation, differentiation, and maturation. Similarly, biomaterials offer the ability to control a patient’s response to a stem cell transplant, e.g., by controlling inflammation, vascularization, and fibrosis, as well as permitting transfer of genetic material into host cells, e.g., the lipid-based carriers to the mRNA COVID-19 vaccines. Advanced manufacturing breakthroughs now allow precise control of biophysical properties such as stiffness (with Young’s moduli ranging from brain to bone), topography, porosity, and electrical conductivity. Biochemical signals, e.g., growth factors, anti-inflammatory molecules, angiogenic molecules and so on can be incorporated into synthetic materials through covalent bonding or bulk-incorporation. No longer restricted to the static state of replacement joints, modern biomaterials can be modulated dynamically, e.g., by hydrolytic release of ligands, degradation of cross-links to soften substrates, or temporal control with small molecule inducers or photochemistry. Originally restricted to 2-dimensional interfaces, biomaterials have moved into 3D, including synthetic or protein hydrogels that provide niches for stem cells and their derivatives.

Despite this promise, moving advanced biomaterials into stem cell science has been difficult. There are only a few institutions with the requisite scientific prowess in both domains. Synthesis of bulk materials and their fabrication into formats useful for cell biology is outside the expertise of most biologically based laboratories. Conversely, the ability to generate stem cells and differentiated cell types exceeds the expertise of most researchers in materials science. An NSF investment to support this interface will accelerate research in this space markedly by making advanced materials more widely available and bringing stem cell expertise into engineering and manufacturing.

Stem cell-based medicine has already reached the clinical trial stage in the US and around the world, and this heralds a coming revolution. The US is a leader in this effort, but there are many countries in Asia, Europe, and Australia that are investing heavily and already ahead in some domains. In this brief letter we have emphasized how advancing research in AI/ML, Robotics/Manufacturing, Biotechnology, and Materials Science will foster US competitiveness in this next-generation technology. If you have any questions regarding this response, please contact ISSCR’s Director of Policy, Tyler Lamb, at tlamb@isscr.org. On behalf of the ISSCR, we thank you for your efforts to improve American research infrastructure.

Respectfully Submitted,

Charles Murry, MD, PhD, University of Washington, Seattle, WA
Lee Rubin, PhD, Harvard University, Cambridge, MA
Kristen Brennand, PhD, Yale University, New Haven, CT
Tyler Lamb, JD, International Society for Stem Cell Research