

TEN OPPORTUNITIES FOR BIOMEDICAL INNOVATION OVER THE NEXT TEN YEARS

Francis Collins, National Institutes of Health (NIH)

As the world's largest public funder of biomedical research, the National Institutes of Health (NIH) provides a unique vantage point from which to survey—and to shape—the rapidly evolving landscape of biomedical innovation. Over many decades, NIH's scientific vision has proven crucial to the health and economic well-being of those living in the United States of America (U.S.). But NIH is also a major supporter of global health that holds increasing promise for low- and middle-income countries, and medical research essentially knows no national boundaries.

Let us begin by recognizing that the future of biomedical innovation is built on fundamental knowledge—that the long arc of discovery begins with basic science. Experiments going on right now in basic laboratories around the globe contain the seeds of advances that will transform medicine and improve human health. We can already identify a great number of promising opportunities on the near horizon. This chapter will highlight 10 of the most exciting areas in which, given a sustained commitment of resources for biomedical research, we can expect to see striking progress 10 years from now. It will also examine scientific and public policy challenges that fall along the pathway to biomedical innovation, as well as explore a few examples of the many creative mechanisms being used by NIH and its partners to address such challenges.

Making big plans

The architect Daniel Burnham once said, "Make no little plans, they have no magic to stir men's blood and probably themselves will not be realized." While the source of the next major innovative breakthrough is hard to predict, the NIH has big plans—some might even say audacious plans—for biomedical innovation in the near future. Following is a high-level overview

of 10 of the many rapidly emerging fields of biomedicine in which we anticipate extraordinary advances over the next decade.

Single-cell analysis

Let us fast-forward to 2029 and what is likely to be among the first of these 10 breakthroughs: advances in the understanding of the exquisite complexity of the functions of individual human cells. Cells are to biology what atoms are to chemistry—the basic unit of understanding. Yet, during the long history of biomedical research, scientists have not possessed the technical ability to study individual cells in their normal environment. Instead, they have had to be content with low-resolution technologies that could only analyze millions, or maybe even billions, of cells as a group. With a variety of new technologies invented in the last few years, especially to ascertain what genes are turned on or off in an individual cell, this is all changing.¹ For example, using new approaches to single-cell analysis, we can now decode the process by which individual immune cells attack and destroy healthy tissue in autoimmune disorders. This promises to transform how healthcare professionals approach lupus, rheumatoid arthritis, multiple sclerosis, and many other autoimmune diseases. Likewise, single-cell analysis will likely prove valuable in understanding—and combating—the deadly process of cancer metastasis, in which malignant cells spread from their original location into other vital parts of the body, such as the brain, bone, lungs, and liver.

Mapping the brain

Improved understanding of basic science is also the aim of the NIH-led Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative.² With roughly 100 billion cells and 100 trillion connections, the human brain remains

one of science's most daunting frontiers and one of medicine's greatest challenges. In a decade, researchers will have used the tools and technologies developed through BRAIN to identify the hundreds of different types and subtypes of cells within our brain. Beyond that, BRAIN-supported research will also have mapped the key features of the circuits responsible for motor function, vision, memory, and emotion—all functioning at the speed of thought. As a result, we will have a much better grasp of the details of how the brain works in real time. This understanding will enable healthcare professionals to diagnose neurological conditions earlier and more precisely. We will also have uncovered new targets to explore for prevention and treatment of autism, epilepsy, traumatic brain injury, schizophrenia, Parkinson's disease, and many other disorders in urgent need of new approaches. Progress will even be made against formidable foes like Alzheimer's disease and spinal cord injuries.

Alzheimer's disease

Aided by new imaging techniques developed and optimized by the BRAIN Initiative, and biomarker discoveries made through NIH's partnership with private sector collaborators,³ we will be able in 10 years time to identify individuals at high risk for Alzheimer's disease even before symptoms appear. Right now, this fatal, neurodegenerative condition can only be conclusively diagnosed by examining the brain after death. With the arrival of ways to diagnose Alzheimer's much earlier, healthcare professionals may be able to provide at-risk people with effective therapies aimed at slowing or changing the course of the disease. Such innovation would delay or avert countless personal and family tragedies all around the world and translate into hundreds of billions of dollars of economic savings in the U.S. alone. Even the ability to delay the onset of cognitive decline by five years could provide profound human and economic benefit.

Spinal cord injuries

A decade from now, we will have developed effective treatments for spinal cord injuries. Already, groundbreaking research supported by NIH has enabled several young men, paralyzed from the waist down by a traumatic injury, to move their legs and walk through the use of surgically implanted electrical stimulators that bypass the severed cord.⁴ Other NIH-funded work has used a noninvasive spinal stimulation technique—electrodes strategically placed on the skin—to help people with lower body paralysis move their limbs again and those with upper body paralysis improve hand strength and dexterity.⁵ With additional follow-up studies, we may be able to give freedom of movement back to many more of the millions of people worldwide who are coping with spinal cord damage from traffic accidents, sports injuries, and other trauma.

Pain management

Ten years from now, researchers in the public and private sectors will have made tremendous progress toward developing effective, non-addictive, non-opioid approaches to pain management. Chronic pain is a serious and costly public health

problem, affecting tens of millions of people worldwide. NIH researchers recently showed that disability is just as likely for people suffering from chronic pain as it is for those with kidney failure, emphysema, or stroke. Unfortunately, current treatments used to manage chronic pain can be addictive, and that can lead to tragic outcomes. In the U.S., more than 130 people die every day from overdosing on opioids.

To help tackle this monumental challenge, the NIH recently launched the Helping to End Addiction Long-Term (HEAL) research initiative.⁶ A key part of this effort is developing non-addictive strategies for preventing and managing pain. Toward that end, NIH-supported researchers are utilizing the latest advances in genomics, neuroscience, and structural biology to better understand the biology of pain, and to uncover entirely new targets for treating this longtime scourge of humankind. For example, in a recent study of over 1,600 people injured in traffic accidents, researchers discovered that individuals with a specific variant in a stress-controlling gene, called *FKBP5*, were more likely to develop pain than those with other variants.⁷ The findings suggest that non-addictive small molecules that target the FKBP5 protein might reduce the pain response or prevent the transition from acute to chronic pain.

Regenerative medicine

The next decade will also witness large strides in regenerative medicine.⁸ For example, many are eagerly awaiting the introduction of a safe and effective bioartificial pancreas. For individuals with diabetes, such a system will continuously track changes in blood glucose levels and use that information to deliver more precise doses of insulin. Already approved are various "closed loop" systems,⁹ which typically use wireless technology to connect a monitor that continually measures the amount of glucose in a person's body with a small pump that, using real-time data from the monitor, infuses an appropriate dose of insulin subcutaneously. Such real-time monitoring and dose adjustment should significantly improve the management of diabetes, preventing countless complications like heart disease, amputations, and vision loss.

However, the ultimate achievement would be the creation of a completely biological replacement pancreas. To reach this goal, researchers might take advantage of bioengineering advances that enable reprogramming of a patient's own cells, ideally implanted within the portal circulation.¹⁰ The amazing innovation that makes this type of breakthrough a real possibility is induced pluripotent stem cell (iPS) technology. Derived from mature human skin or blood cells, iPS cells can be encouraged to differentiate into a wide variety of human tissues in the lab, including pancreatic islet cells that respond to blood glucose and make insulin. In fact, some researchers recently used iPS cells, in combination with other regenerative medicine techniques, to produce human pancreatic islets that not only secrete insulin, but also develop their own circulatory system to nourish the islets.¹¹ When transplanted into a mouse model of type 1 diabetes, these bioengineered islets successfully treated the animals' diabetes. Not only do iPS cells hold the potential to help people with diabetes, they may also make it possible to

make advances in many other areas of regenerative medicine. For example, it will likely be possible to rebuild damaged hearts, kidneys, and livers—rendering many organ transplants, organ waiting lists, and anti-rejection drugs a thing of the past.

Cancer immunotherapy

Cancer is another regrettably common disease poised for significant progress over the next decade, especially in the area of immunotherapy.¹² In the early 1970s, basic research, spearheaded in large part by NIH-funded scientists, led to the development of methods to splice fragments of DNA together, giving birth to the field of biotechnology. When merged with fundamental advances in molecular immunology, this set of technologies made it possible to pursue ideas for cancer immunotherapy—a radical new approach that involves enlisting a patient’s own immune system in the fight against cancer. In one promising strategy, immune cells are collected from patients and engineered to produce special cancer-fighting warriors, called chimeric antigen receptors. This work has already saved the lives of many children and adults with treatment-resistant leukemia, lymphoma, and other blood cancers.¹³

Now, cancer researchers in the public and private sectors are setting their sights on even tougher targets: breast, prostate, colon, ovarian, pancreatic, and other solid types of cancer, which have so far proven rather resistant to immunotherapy. Recent developments make us optimistic that a pathway forward is taking shape. In the last couple of years, an NIH team announced a novel modification of an immunotherapy approach, built upon a precise understanding of the driver mutations in a particular individual’s cancer. This strategy led to regression, most likely cure, of widely metastatic disease in individuals with breast cancer and bile duct cancer.¹⁴ Of course, this must be replicated in further studies, but without a doubt, these life-saving experiences represents hope for millions more. How phenomenal it would be if we could offer people with solid tumors that have metastasized to other parts of the body a chance of not just being treated, but actually being cured of their disease.

New vaccines

Important strides will also be made in the next 10 years in the prevention of influenza, HIV, and many other infectious diseases, thanks to the development of innovative vaccine strategies. Currently, a new flu vaccine must be produced each year to protect against the rapidly mutating influenza virus. Despite our best efforts, the vaccine isn’t always ideal and, in an average year in the U.S. alone, the flu kills nearly 50,000 people, at a cost to the economy of more than US\$87 billion. But it does not have to be that way. NIH is providing substantial resources to catalyze the arrival of a “universal” flu vaccine—strategically designed to target mutation-resistant parts of the influenza virus—that will provide long-lasting protection against a wide variety of flu strains. Not only will such a vaccine reduce the need for the annual flu shot, it will prepare us for the next overdue worldwide pandemic, potentially saving millions of lives. Human clinical trials of the first version of such vaccines

are now underway, through active collaboration between NIH and industry.¹⁵

We are also optimistic that a safe, effective vaccine for HIV/AIDS will finally be available, providing an opportunity to bring an end to this most frightening and costly global epidemic. One approach involves the assumption that a particular type of immune response would be protective against HIV infection. After all, some people living with HIV naturally produce broadly neutralizing antibodies (bNAbs), albeit too late after infection to clear the virus. Researchers have isolated— from people living with HIV—several varieties of bNAbs that have been shown in the laboratory to inhibit most HIV strains from infecting human cells. The challenge is to use that information to design a vaccine that will induce production of bNAbs in individuals who have never been exposed to HIV. Tests in animals have been encouraging, and a first-in-human trial is expected to begin within a year.¹⁶

Gene editing to cure disease

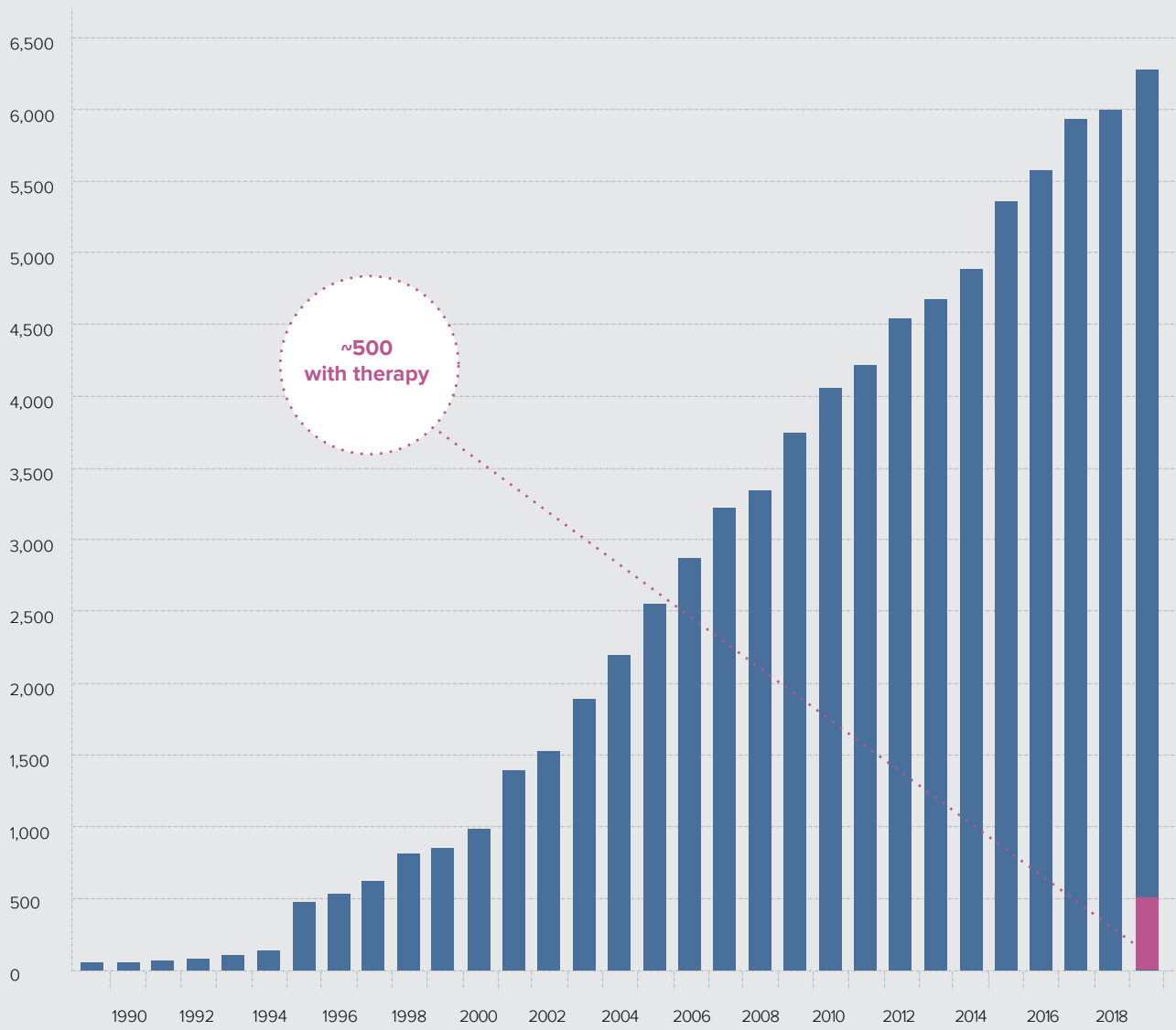
Within the next 10 years, biomedical research will also begin to realize the promise of new genetic technologies to treat or even cure diseases that once seemed out of reach. Scientists have identified the molecular causes of nearly 6,500 human diseases, yet treatments currently exist for only about 500 (Figure 4.1). Particularly exciting is the potential of Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR-Cas) technology for somatic cell gene editing—an approach that corrects gene mutations only in relevant tissues without the risk of passing those changes on to a future generation.

One of the first successful applications of gene editing will likely be for curing sickle cell disease (SCD), which affects over 20 million people worldwide, mostly in developing nations.¹⁷ SCD is the first “molecular disease,” with its genetic cause having been identified many decades ago. However, the need for a widespread cure for SCD has not been met. Since 1998, doctors have used a drug called hydroxyurea to reduce symptoms, but it can cause serious side effects. At present, the only way to cure SCD is through a bone marrow transplant, which is not an option for many patients due to a lack of matched donors, or possibly through experimental gene therapies delivered by viral vectors. CRISPR-Cas gene editing is offering a new strategy: remove blood precursor cells, called hematopoietic stem cells (HSCs), from a patient’s own bone marrow or bloodstream; use the magic of CRISPR-Cas to fix or offset the negative effects of the SCD-causing gene mutation in the HSCs; and then return the now-cured—no longer sickling—HSCs to the patient. Admittedly, that rather complicated process may not be practical for quite some time in places like sub-Saharan Africa. That is one reason why NIH recently launched a new effort to speed the development of safe, effective genome-editing approaches that could be delivered directly into a patient’s body (*in vivo*), perhaps by infusion of the CRISPR gene editing apparatus.¹⁸

As research moves forward in the fast-paced field of genetic therapy, it will be important that these endeavors remain ethical, but also remain bold, on behalf of the hundreds of millions

FIGURE 4.1

Disorders with known molecular basis



Source: Online Mendelian Inheritance in Man, available at <https://www.omim.org/statistics/geneMap>.

of people with genetic diseases who are still awaiting cures. Importantly, those therapeutic strategies can be pursued without altering the part of the genome that is inherited by future offspring. Over the next decade and beyond, scientific, economic, and thought leaders around the globe must continue to assess and address the very serious ethical concerns raised by *germline* gene editing of human embryos, which will irreversibly alter the DNA instruction book of future generations of humankind. NIH contends that our society is not ready to undertake such experiments in the foreseeable future.¹⁹

Precision medicine

Thanks to opportunities that span a wide range of biomedical disciplines, we also have the potential to develop a wide variety of tailored approaches to medicine that reflect the fact that not all individuals are the same. In the U.S., this opportunity will be enabled by the NIH-led *All of Us* Research Program.²⁰ This monumental undertaking is building a research cohort of 1 million or more volunteers from all across the nation, with roughly half of those participants coming from traditionally underrepresented racial and ethnic minorities. *All of Us* will capitalize on a broad array of innovations in a wide range of scientific fields. For example, it will apply the latest methods and approaches in data science, including advances in large-scale databases, computational tools, and “omics” methodologies of characterizing individuals. The aim is to pioneer efforts to merge, integrate, and analyze data from a wide variety of sources—biological, environmental, socioeconomic, and geospatial—that have implications for individualized disease prevention and treatment, and for understanding the causes and the solutions to health disparities.

NIH envisions that the willingness of the diverse array of *All of Us* participants to share a wide variety of their health-related information will establish a valuable research resource that will foster the emergence of important new insights—basic, translational, and clinical. Such insights will ensure that people from all walks of life, all around the world, will be healthier than ever.

Overcoming challenges together

This list of opportunities for biomedical innovation is ambitious. Not only will it take tremendous effort and ingenuity on the part of the worldwide research community to make these 10 advances happen in just 10 years, but it will also require some serious actions by other sectors of society. Perhaps the most significant action will be encouraging the next generation of researchers through a strong, sustained commitment to biomedical research by the public sector. The most important resource for the future of biomedical research is not buildings or technologically advanced equipment—it is the people that will have the dreams and do the work.

NIH leadership has recently taken several creative steps aimed at spurring biomedical innovation. These actions include: initiating special awards to encourage high-risk, high-reward research; encouraging the next generation of researchers; launching prize competitions aimed at finding innovative solutions

to major health challenges; and fostering the development of public-private partnerships to accelerate and transform current models for developing new diagnostics and treatments. However, NIH cannot do this alone. We need partners in the public policy and private sectors from all around the world to realize the full potential of biomedical innovation over the next decade and beyond. Among the areas in which we are calling our global partners to join us are measures aimed at facilitating data sharing, improving scientific rigor and reproducibility, and establishing oversight for emerging biotechnologies.

Data sharing

Opportunities to harness the power of big data and new technological breakthroughs in artificial intelligence (AI) and machine learning will depend on the development of infrastructure and policies that reflect the Findable, Accessible, Interoperable, and Reusable (FAIR) principles.²¹ This includes the establishment of field-appropriate data standards and interoperable, sustainable data resources. While protection of privacy and confidentiality of research participants is crucial, certain data protection policies and regulations may present obstacles to data sharing, especially through variable and conservative interpretation of such regulations in the absence of clear guidance from governmental entities and coalitions.²² We are working with our global counterparts across the public sector to find the balance between appropriate data protection and accessibility for research progress.

Rigor and reproducibility

Two of the related cornerstones of biomedical innovation are rigor in designing and performing research, along with the ability to reproduce research findings.²³ The application of rigor ensures robust and unbiased experimental design, methodology, analysis, interpretation, and reporting of results. When a result can be reproduced by multiple scientists, it validates the original results and indicates readiness to progress to the next phase of research. This is especially important for clinical trials in humans, which are built on studies that have demonstrated a particular effect or outcome. Research funders and journals are establishing policies to ensure rigorous methodology in all realms of research, including power analyses, validation/authentication of reagents or cell lines, justification of animal models, and consideration of sex as a biological variable.

Oversight of emerging biotechnologies

For new and emerging biotechnologies, it is appropriate to establish oversight systems commensurate with the risk and uncertainty related to the technology. However, such oversight systems need to be flexible enough to adjust as the technology, and the related risks, are better understood. For example, recombinant DNA merited intense scrutiny and oversight in the late 1970s, when the technology was new, the risks were unknown, and biosafety systems to contain the risk were in their infancy. Over time, our understanding of the risks has become highly sophisticated, the technology has become ubiquitous, and biosafety protocols have become well established, thus allowing a risk-based adjustment to the framework of oversight.²⁴

Compare that to a new technology such as gene editing. The use of CRISPR-Cas for creating gene-edited babies has already been highlighted above. But that is not the only application that raises ethical and societal concerns. Consider the use of CRISPR-based gene drives for control of disease vectors like mosquitoes, where the environmental risk is still uncertain and where high levels of precautionary oversight are still warranted.

In closing, it is imperative that we keep our minds open to the possibility that this vision of future opportunities—and future challenges—may change, perhaps even dramatically, over the next decade. There certainly is no guarantee that these 10 goals will be attained by 2029, but they are offered as examples in hope of inspiring the rapidly moving field of biomedical research to aim even higher for the benefit of all humankind. As has been the case so often in the past, the greatest biomedical innovations of tomorrow may very well come from directions that none of us could anticipate today.

Notes:

- 1 National Institutes of Health, 2018c.
- 2 National Institutes of Health, n.d.-b.
- 3 National Institutes of Health, n.d.-c.
- 4 National Institutes of Health, 2014.
- 5 Lu et al., 2016.
- 6 National Institutes of Health, 2019a.
- 7 Linnstaedt et al., 2018.
- 8 National Institutes of Health, n.d.-d.
- 9 Russell et al., 2014.
- 10 Yoshihara et al., 2016.
- 11 Takahshi et al., 2018.
- 12 National Institute of Health, 2018e.
- 13 Novartis, 2017.
- 14 Zacharakis et al., 2018.
- 15 National Institutes of Health, 2018a.
- 16 National Institutes of Health, 2018f.
- 17 Collins, 2018b.
- 18 National Institutes of Health, 2019b.
- 19 Collins, 2018a.
- 20 National Institutes of Health, n.d.-a.
- 21 National Institutes of Health, 2018b.
- 22 European Commission.
- 23 National Institutes of Health, 2018d.
- 24 Collins et al., 2018.

References:

- Collins, F. S. (2018a, November 28). Statement on Claim of First Gene-Edited Babies by a Chinese Researcher. Retrieved from <https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-claim-first-gene-edited-babies-chinese-researcher>
- . (2018b, December 11). Accelerating Cures in the Genomic Age: The Sickle Cell Example. Retrieved from <https://directorsblog.nih.gov/2018/12/11/accelerating-cures-in-the-genomic-age-the-sickle-cell-example/>
- Collins, F. S., & Gottlieb, S. (2018, August 15). The next phase of human gene therapy oversight. *N Engl J Med*. Retrieved from <https://www.nejm.org/doi/pdf/10.1056/NEJMp1810628>
- European Commission. (2018). 2018 reform of EU data protection rules. Retrieved from https://ec.europa.eu/commission/priorities/justice-and-fundamental-rights/data-protection/2018-reform-eu-data-protection-rules_en
- Linnstaedt, S. D., Riker, K. D., Rueckeis, C. A., Kutchko, K. M., Lackey, L. et al. (2018, August 27). A functional riboSNitch in the 3'UTR of FKBP5 alters microRNA-320a binding efficiency and mediates vulnerability to chronic posttraumatic pain. *J Neurosci*. Retrieved from <http://www.jneurosci.org/content/38/39/8407.long>
- Lu, D., Edgerton, R., Modaber, M., AuYong, N., Morikawa, E. et al. (2016, May 18). Engaging cervical spinal cord networks to reenable volitional control of hand function in tetraplegic patients. *Neurorehabilitation and Neural Repair*. Retrieved from <https://journals.sagepub.com/doi/full/10.1177/1545968316644344>
- National Institutes of Health, United States of America. (n.d.-a) *All of Us Research Program*. Retrieved from <https://allofus.nih.gov/>
- . (n.d.-b). *The BRAIN Initiative*®. Retrieved from <https://www.braininitiative.nih.gov/>
- . (n.d.-c). The Division of Neuroscience of the National Institute on Aging. *AMP – AD Biomarkers Project, Accelerating Medicines Partnership (AMP) for Alzheimers Disease*. Retrieved from <https://www.nia.nih.gov/research/dn/amp-ad-biomarkers-project>
- . (n.d.-d). *Regenerative Medicine Innovation Project*. Retrieved from <https://www.nih.gov/research-training/medical-research-initiatives/rmi>
- . (2014, April 8). The National Institute of Biomedical Imaging and Bioengineering. *Spinal stimulation helps four patients with paraplegia regain voluntary movement*. Retrieved from <https://www.nih.gov/news-events/news-releases/spinal-stimulation-helps-four-patients-paraplegia-regain-voluntary-movement>
- . (2018a, May 4). National Institute of Allergy and Infectious Diseases. *Universal Influenza Vaccine Research*. Retrieved from <https://www.niaid.nih.gov/diseases-conditions/universal-influenza-vaccine-research>
- . (2018b, July 24). Office of Strategic Coordination, The Common Fund. *New Models of Data Stewardship – Data Commons Pilot*. Retrieved from <https://commonfund.nih.gov/commons>
- . (2018c, August 1). Office of Strategic Coordination, The Common Fund. *Single-Cell Analysis*. Retrieved from <https://commonfund.nih.gov/singlecell>
- . (2018d, November 27). Office of Extramural Research. *Enhancing Reproducibility through Rigor and Transparency*. Retrieved from <https://grants.nih.gov/policy/reproducibility/index.htm>
- . (2018e, November 28). National Cancer Institute. *Immunotherapy to Treat Cancer*. Retrieved from <https://www.cancer.gov/about-cancer/treatment/types/immunotherapy>
- . (2018f, December 1). NIH Statement on World AIDS Day December 1, 2018 [News Release]. Retrieved from <https://www.nih.gov/news-events/news-releases/nih-statement-world-aids-day-december-1-2018>
- . (2019a, January). *NIH Health Initiative*. Retrieved from <https://www.nih.gov/research-training/medical-research-initiatives/heal-initiative>

———. (2019b, January 29). Office of Strategic Coordination, The Common Fund. Somatic Cell Genome Editing Program. Retrieved from <https://commonfund.nih.gov/editing>

Novartis (2017, August 30). Novartis receives first ever FDA approval for a CAR-T cell therapy, Kymriah(TM) (CTL019), for children and young adults with B-cell ALL that is refractory or has relapsed at least twice. Retrieved from <https://www.novartis.com/news/media-releases/novartis-receives-first-ever-fda-approval-car-t-cell-therapy-kymriahm-ctl019>

Russell, S. J., El-Khatib, F. H., Sinha, M., Magyar, K. L., McKeon, K. et al. (2014, June 15). Outpatient Glycemic Control with a Bionic Pancreas in Type 1 Diabetes. *N Engl J Med*. Retrieved from https://www.nejm.org/doi/10.1056/NEJMoa1314474?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dwww.ncbi.nlm.nih.gov

Takahshi, Y., Sekine, K., Kin, T., Takebe, T., & Taniguchi, H. (2018, May 8). Self-condensation culture enables vascularization of tissue fragments for efficient therapeutic transplantation. *Cell Reports*. Retrieved from <https://www.sciencedirect.com/science/article/pii/S221124718304996?via%3Dihub>

Yoshihara, E., Wei, Z., Lin, C. S., Fang, S., Ahmadian, M. et al. (2016, April 12). ERRγ is required for the metabolic maturation of therapeutically functional glucose-responsive β cells. *Cell Metab*. Retrieved from [https://www.cell.com/cell-metabolism/fulltext/S1550-4131\(16\)30108-5](https://www.cell.com/cell-metabolism/fulltext/S1550-4131(16)30108-5)

Zacharakis, N., Chinnasamy, H., Black, M., Xu, H., Lu, Y. C. et al. (2018, June 4). Immune recognition of somatic mutations leading to complete durable regression in metastatic breast cancer. *Nature Medicine*. Retrieved from <https://www.nature.com/articles/s41591-018-0040-8>