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The promise of organ and tissue preservation to transform medicine

Sebastian Giwa^{1,2,3,4,6}, Jedediah K Lewis^{1,4,6}, Luis Alvarez^{4,5,6}, Robert Langer⁷, Alvin E Roth⁸, George M Church⁹, James F Markmann¹⁰, David H Sachs¹¹, Anil Chandraker^{12,13}, Jason A Wertheim^{14,15}, Martine Rothblatt¹⁶, Edward S Boyden¹⁷, Elling Eidbo¹⁸, W P Andrew Lee¹⁹, Bohdan Pomahac²⁰, Gerald Brandacher¹⁹, David M Weinstock²¹, Gloria Elliott²², David Nelson²³, Jason P Acker^{24,25}, Korkut Uygun²⁶, Boris Schmalz^{1,27}, Brad P Weegman^{1,2}, Alessandro Tocchio^{1,28}, Greg M Fahy²⁹, Kenneth B Storey³⁰, Boris Rubinsky³¹, John Bischof³², Janet A W Elliott^{24,33}, Teresa K Woodruff³⁴, G John Morris³⁵, Utkan Demirci^{28,36}, Kelvin G M Brockbank³⁷, Erik J Woods^{3,25,38}, Robert N Ben³⁹, John G Baust⁴⁰, Dayong Gao^{25,41}, Barry Fuller⁴², Yoed Rabin⁴³, David C Kravitz⁴⁴, Michael J Taylor^{2,43,45}, and Mehmet Toner²⁶

¹Organ Preservation Alliance, NASA Research Park, Moffett Field, California, USA

²Sylvatica Biotech, Inc., Charleston, South Carolina, USA

³Ossium Health, San Francisco, California, USA

⁴Regenerative Biology Research Group, Cancer and Developmental Biology Laboratory, National Cancer Institute, Bethesda, Maryland, USA

⁵Walter Reed National Military Medical Center, Bethesda, Maryland, USA

⁶Department of Chemistry and Life Science, United States Military Academy, West Point, New York, USA

⁷Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA

⁸Department of Economics, Stanford University, Stanford, California, USA

⁹Department of Genetics, Harvard Medical School, Boston, Massachusetts, USA

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Correspondence should be addressed to J.K.L. (jedd@organpreservationalliance.org).

⁴⁶These authors contributed equally to this work.

AUTHOR CONTRIBUTIONS

S.G., J.K.L., and L.A. developed the main conclusions of the article. S.G. and J.K.L. developed the key points discussed with input from all other co-authors. S.G. developed the original concepts that led to the article's creation. J.K.L. developed the structure of the article and wrote the manuscript. S.G., J.K.L., L.A., R.L., A.E.R., G.M.C., J.F.M., D.H.S., A.C., J.A.W., M.R., E.S.B., E.E., B.P., W.P.A.L., G.B., D.M.W., G.E., D.N., J.P.A., K.U., B.S., B.P.W., A.T., G.M.F., K.B.S., B.R., J.B., J.A.W.E., T.K.W., G.J.M., U.D., K.G.M.B., E.J.W., R.N.B., J.G.B., D.G., B.F., Y.R., D.C.K., M.J.T., and M.T. added conclusions, content, and references, critically reviewed the manuscript, and provided input on structure, style and content. S.G., J.K.L., B.S., B.W., and A.T. created the figures and tables.

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- ¹⁰Division of Transplant Surgery, Department of Surgery, Massachusetts General Hospital, Boston, Massachusetts, USA
- ¹¹Columbia Center for Translational Immunology, Columbia University Medical Center, New York, New York, USA
- ¹²American Society of Transplantation, Mt. Laurel, New Jersey, USA
- ¹³Transplantation Research Center, Renal Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA
- ¹⁴American Society of Transplant Surgeons, Arlington Virginia, USA
- ¹⁵Comprehensive Transplant Center, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA
- ¹⁶United Therapeutics, Silver Spring, Maryland, USA
- ¹⁷MIT Media Lab and McGovern Institute, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA
- ¹⁸Association of Organ Procurement Organizations, Vienna, Virginia, USA
- ¹⁹Department of Plastic and Reconstructive Surgery, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
- ²⁰Department of Surgery, Division of Plastic Surgery, Brigham and Women's Hospital/Harvard Medical School, Boston, Massachusetts, USA
- ²¹Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts, USA
- ²²Department of Mechanical Engineering and Engineering Science, University of North Carolina at Charlotte, Charlotte, North Carolina, USA
- ²³Department of Transplant Medicine, Nazih Zuhdi Transplant Institute, Integris Baptist Medical Center, Oklahoma City, Oklahoma, USA
- ²⁴Department of Laboratory Medicine and Pathology, University of Alberta, Edmonton, Alberta, Canada
- ²⁵Society for Cryobiology, Baltimore, Maryland, USA
- ²⁶Department of Surgery, Center for Engineering in Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA
- ²⁷Max Planck Institute of Psychiatry, Munich, Germany
- ²⁸Department of Radiology, Stanford School of Medicine, Stanford, California, USA
- ²⁹21st Century Medicine, Fontana, California, USA
- ³⁰Institute of Biochemistry, Carleton University, Ottawa, Ontario, Canada
- ³¹Department of Mechanical Engineering, University of California Berkeley, Berkeley, California, USA
- ³²Department of Mechanical Engineering, University of Minnesota, Minneapolis, Minnesota, USA

³³Department of Chemical and Materials Engineering, University of Alberta, Edmonton, Alberta, Canada

³⁴Division of Obstetrics and Gynecology-Reproductive Science in Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

³⁵Asymptote Ltd., Cambridge, UK

³⁶Department of Electrical Engineering (by courtesy), Stanford, California, USA

³⁷Department of Bioengineering, Clemson University, Clemson, South Carolina, USA

³⁸Department of Microbiology and Immunology, Indiana University School of Medicine, Indianapolis, Indiana, USA

³⁹Department of Chemistry and Biomolecular Sciences, University of Ottawa, Ottawa, Ontario, Canada

⁴⁰Department of Biological Sciences, Binghamton University, State University of New York, Binghamton, New York, USA

⁴¹Department of Mechanical Engineering, University of Washington, Seattle, Washington, USA

⁴²Division of Surgery & Interventional Science, University College Medical School, Royal Free Hospital Campus, London, UK

⁴³Department of Mechanical Engineering, Carnegie Mellon University, Pittsburgh, Pennsylvania, USA

⁴⁴Organ Recovery Systems, Chicago, Illinois, USA

⁴⁵Department of Surgery, University of Arizona, Tucson, Arizona, USA

Abstract

The ability to replace organs and tissues on demand could save or improve millions of lives each year globally and create public health benefits on par with curing cancer. Unmet needs for organ and tissue preservation place enormous logistical limitations on transplantation, regenerative medicine, drug discovery, and a variety of rapidly advancing areas spanning biomedicine. A growing coalition of researchers, clinicians, advocacy organizations, academic institutions, and other stakeholders has assembled to address the unmet need for preservation advances, outlining remaining challenges and identifying areas of underinvestment and untapped opportunities. Meanwhile, recent discoveries provide proofs of principle for breakthroughs in a family of research areas surrounding biopreservation. These developments indicate that a new paradigm, integrating multiple existing preservation approaches and new technologies that have flourished in the past 10 years, could transform preservation research. Capitalizing on these opportunities will require engagement across many research areas and stakeholder groups. A coordinated effort is needed to expedite preservation advances that can transform several areas of medicine and medical science.

The global shortage of organs for transplantation has long been recognized as a major public health challenge, and the World Health Organization (Geneva) estimates that only 10% of

the worldwide need for organ transplantation is being met¹. The data suggest that the organ shortage is among the greatest crises facing biomedicine today. Although few estimates are available of the total number of patients who could benefit from organ transplantation if supply constraints were removed, the commonly cited transplant waiting lists clearly fail to capture the organ shortage's true magnitude. For example, the number of patients added to US transplant waiting lists each year—roughly 50,000—is dwarfed by the ~730,000 annual US deaths attributable to end-stage organ disease (Fig. 1)^{2,3}. As one example, the true need for heart transplantation in the United States has been estimated at more than ten times the heart transplant waiting list^{4,5}. It has been suggested that with all supply constraints removed, organ replacement could theoretically prevent >30% of all deaths in the United States—doubling the average person's likelihood of living to 80 years of age^{6–8}. Similarly, estimates based on incidence of diseases that are potentially addressable by on-demand organ replacement place the true need at millions of transplant organs per year in the United States and Europe combined⁹.

The organ shortage is markedly worse in many other countries. For instance, the continent of Africa holds 16% of the world's population but performs only 0.5% of its organ transplants (Fig. 2). Moreover, in some of the countries with the least access to transplantation, a substantial fraction of transplant procedures are actually instances of transplant tourism¹⁰. In Pakistan, for instance, up to two-thirds of kidney transplants in 2005 are estimated to have been performed on foreigners^{10,11}. The practice has widely been considered problematic because it creates opportunities for organ commodification and exploitation of vulnerable populations; the Declaration of Istanbul, signed by 157 representatives from countries across the globe, condemns the practice¹². Healthcare infrastructure, national wealth, and sometimes cultural factors can each play a major role in the disparities in access to transplantation internationally. Yet over time, easing logistical burdens and increasing supply can lower the barriers to development of transplantation infrastructure^{4,5}, and as discussed below, to equitable access to transplantation within countries.

The above considerations should place technologies that can substantially increase the availability of transplant organs at the top of our scientific priority list. Moreover, the need for these technologies is shared with many other major public health challenges. Banking of viable organs and tissues can transform cancer treatment for young patients and have a dramatic impact on precision medicine and research on diseases such as heart disease, cancer, and Alzheimer's disease. Ballooning costs in drug discovery are exacerbated by poor availability of human tissue models, which in many cases could provide more valuable data than the animal models currently used. Tissue transplantation faces enormous logistical barriers in emergency care because tissue is needed on such short notice. These challenges are magnified in contexts where large numbers of patients require care, such as the treatment of wounded service members and civilian victims of natural disasters or terrorist attacks. In these and many other areas, adequate techniques and treatments often already exist. However, their use is pervasively handicapped by the limited availability of organs and tissues, which are among the most precious resources in research and medicine. The aggregate toll on human health attributable to causes that could be addressed by increasing organ and tissue availability makes this problem one of the most important healthcare challenges of this era.

Developing an organ and tissue supply that can meet the healthcare demands of the twenty-first century requires the development of solutions to twin challenges: first, having enough of these lifesaving resources; and second, having the means to store and transport them for a variety of applications, each with distinct but overlapping logistical needs. Having enough organs and tissues to meet public health needs has been the subject of extensive efforts in science, medicine, and public policy aiming to increase organ donation^{13,14}, improve donor organ utilization^{15–18}, and gain the understanding needed to engineer laboratory-grown tissues¹⁹, bio-artificial organs^{20,21}, and ‘humanized’ animal donor organs for transplantation^{22,23}. The success of these efforts is intertwined with meeting the second challenge: preserving organs and tissues during procurement (or manufacturing), storage, transport, and other steps of the supply chain in order to meet logistical needs.

Despite its importance, the preservation challenge has received relatively little attention from funding agencies, the research community, and the general public. Taken together, preservation constraints place widespread burdens on efforts to use organs and tissues in transplantation, regenerative medicine, and research. Yet, although >80% of the budget of the US National Institutes of Health (NIH) goes to institutes with missions tied to unmet preservation needs²⁴, and numerous other science agencies and stakeholder groups stand to benefit from preservation advances, no funding body has been charged with overcoming the remaining technical challenges common to the preservation of organ and tissue systems. As a result, the past half-century has seen only incremental and relatively *ad hoc* investments to advance preservation technologies.

By overcoming these institutional barriers and facilitating coordinated and cross-disciplinary research, it is now possible to dramatically accelerate progress in organ and tissue preservation using existing knowledge from a diverse array of fields. The past decade of progress has allowed us to understand and intervene in human physiology at the tissue and organ level as never before, with breakthroughs in nanotechnology, sequencing, imaging, omics approaches, and other areas. These technologies can be used to build on proofs of principle for organ cryopreservation^{6,7,25–28}, discoveries from organisms that can enter ‘suspended animation’ at subzero temperatures^{29–32}, rapid advances in perfusion technologies^{33–41}, and other advances.

In light of these opportunities, a growing coalition of scientists, clinicians, policymakers, advocacy groups, academic institutions, and industry representatives is assembling to accelerate progress in organ and tissue preservation. This has led to an extensive dialog spanning more than a year, which has included the first global Organ Banking Summit at Stanford, NASA Research Park, and other locations⁷, a US National Science Foundation (NSF)-supported Roadmap to Organ Banking and Bioengineering Workshop⁶, a meeting hosted with the Defense Advanced Research Projects Agency (DARPA) leadership at the US Military Academy at West Point, New York, on a potential ‘Organs on Demand’ research program, a White House roundtable on organ banking and bioengineering, and a symposium and round-table on emerging organ preservation technologies on Capitol Hill. At these events, stakeholders have begun to outline the vast public health needs, remaining technological challenges, institutional and infrastructural barriers, and untapped research opportunities surrounding efforts to eliminate preservation constraints on the use of organs

and tissues in biomedicine²⁵. These efforts aim to facilitate the advancement of preservation platforms allowing us to transport, repair, assess, bank, and even enhance the health and function of organs and a variety of tissues used in research and medicine.

The diversity of authors of this article, with expertise spanning organ and tissue procurement and transplantation, preservation research, bioengineering, economics, trauma care, and regenerative medicine, reflects the breadth of need in this area—and the widespread concern that until preservation breakthroughs are pursued aggressively, many medical technologies will not come close to reaching their lifesaving potential. In the sections that follow, we describe how organ and tissue preservation can meet a variety of major public health needs. We also outline recent discoveries indicating that a revolution in organ and tissue preservation is now achievable, propose a novel paradigm for preservation involving convergence of a family of existing approaches, and describe how technologies have the potential to make a new generation of preservation technologies feasible. Finally, we suggest ways that the research community can overcome institutional barriers that hinder advances, and we highlight recent progress toward a coordinated research effort.

The unrealized potential of organ transplantation

Organ transplantation is one of the most impressive medical achievements of the past century. In the past 25 years, it has added over two million life-years to patients in the United States alone⁴². In the 60 years since its inception, researchers have made strides in drug-mediated immunosuppression⁴³, achieved increasingly complex transplant operations^{44–46}, and begun (recently) to move immune tolerance induction therapies into the clinic^{47–50}.

Yet access to transplantation and its efficacy are still fundamentally constrained. For the patients in need of organ replacement who are lucky enough to be placed on a transplant waiting list, morbidity and mortality are substantial^{51,52}; one in five waiting-list patients in the United States will die or become too sick for a transplant before receiving a new organ⁵². In part because of the rare conditions that must exist for organs to be suitable for recovery and transplantation, today only 0.3% of those who die in the United States become organ donors^{3,53}. Ideally, one organ donor can provide up to eight lifesaving organs to patients on transplant waiting lists, yet on average roughly only three are transplanted—despite decades of progress advancing organ procurement protocols and heroic efforts by organ procurement organizations^{2,53}. Although advances in immunosuppression have greatly increased transplant success rates and graft survival^{54–56}, half of these organs fail within 10 years of being transplanted, including as many as 75% of intestines and lungs (Fig. 3)⁵⁷. To delay rejection, transplant recipients must adhere to lifelong immunosuppressant drug regimes, the side effects of which put patients at increased risk for life-threatening infections as well as cancer and other major age-related diseases⁵⁸. Meanwhile, children, ethnic minorities, and other vulnerable patient populations have markedly reduced access to transplantation^{59–62}. The toll on the economy of the unmet need for transplantation is immense; for instance, the worldwide cost of treating end-stage renal disease totals over \$1 trillion in the course of a decade⁶³, with over \$40 billion spent by the United States in 2009 alone⁶⁴.

These problems are fueled by severe logistical constraints related to organ preservation limits. Although leaps forward in machine perfusion^{33–41,65–67}, organ cryopreservation^{26,27,68}, understanding scientific mechanisms of ischemic injury and metabolic regulation^{29–32,41}, and other areas have created a blueprint for transforming organ preservation, today maximum clinical organ preservation times are measured in hours, varying according to the organ transplanted, and necessitate transplantation almost immediately after the organ is recovered (<http://www.nedonation.org/donation-guide/organ/acceptable-ischemic-times>). Organs are rushed to their destinations, often by jet, or by helicopter flight straight to a landing pad on the transplant center rooftop. Speed is essential when arranging and performing the transplant surgery, leaving little room to adapt procedures to individual circumstances or deal with complications. Lengthy operations must be performed day or night with little advance warning. These factors contribute to high costs for organ transplantation, which in the United States can average well over \$1 million (e.g., heart, intestine, and double lung transplant)⁶⁹. During transplantation organs are exposed to a continuous barrage of inflammation and oxidative stress, both before and after organ procurement from the donor, contributing to immune rejection, delayed graft function, and other complications that harm transplant outcomes.

Donor organs and recipients must be matched over relatively short geographic distances and time periods, often resulting in the use of organs that are immunologically not well-matched to recipients. This puts patients at increased risk for organ rejection and contributes to the need for intensive immunosuppressive regimens⁷⁰. The increased rate and severity of rejection limits organ life span, further exacerbating the organ shortage; within several years of transplantation, many patients are in need of a new organ all over again⁵⁷. Limited matching distances leave waiting-list patients from different regions with unequal access to transplant organs as supply and need vary. These imbalances disproportionately affect patients with fewer resources, who cannot relocate to join more favorable waiting lists^{59,71}. Matching limitations often fall hardest on populations with small pools of potential matching donors, particularly among children and ethnic minorities^{60,61,72,73}.

Meanwhile, narrow windows of opportunity for organ assessment, allocation, and transplantation fuel organ discard. Organs are offered to individual patients on a waiting list, whose doctors must decide whether to recommend transplantation based on limited information about the organ's suitability for transplantation; with little information on the organ's functional status, some patients may turn it down when the donor's history or other indicators are dubious, waiting until a less risky organ is (hopefully) made available⁵². Even a functional, transplantable organ may be turned down by the transplant centers of one patient after another until the organ's preservation limits prevent further matching^{41,74}. Each year, this phenomenon contributes to thousands of abdominal organs being discarded^{74,75}, and the majority of thoracic organs from donors (~70% of heart and 80% of lung offers) going untransplanted^{2,76}. Most likely, many of these organs could have been successfully transplanted under the right circumstances^{41,77–79}. The resulting impact on waiting-list patients is profound. In the United States, if just 10% of the number of donor hearts currently left unused were transplanted, the number of additional hearts made available would equal the number of waiting-list patients who currently die or become too sick for a transplant before receiving one (Table 1)⁷⁵.

Organ transplantation without preservation constraints

A successful large-scale organ preservation research effort would create a very different world for organ transplantation, creating a breadth of new capabilities that could make more organs available, improve transplant outcomes and mitigate risks, decrease costs, and complement and accelerate the development of other biomedical technologies that can alter the landscape of transplantation in the coming years (Table 2). For instance, preservation advances can build on promising strategies that use perfusion circuits to mimic healthy physiological conditions^{38,80,81}. These platforms can allow the organ to recover from cellular stress and tissue injury during donor death and organ procurement, which can contribute to inflammation and organ rejection following transplantation^{80–83}, and also enable therapeutic intervention before transplantation^{83–87}. The advent of *ex vivo* organ perfusion shows promise to make larger pools of donor organs available by enabling rehabilitation of organs that would otherwise be unsuitable for transplantation^{38,41,82}.

Perfusion-based preservation could be harnessed as a platform to functionally enhance organs. Any of several existing techniques might be part of the process to condition organs for transplantation or subsequent steps of the preservation process⁸³; these include drug-mediated immunomodulation to apply treatments that block or alter sites recognized by the recipient's immune system to mitigate rejection^{84,85}; gene therapy^{86,87}; antisense, or RNA interference. Similar interventions could even be used to improve organs' health and function, making them in some ways healthier in the recipient than they were in the donor. For instance, perfusion platforms have allowed the 'defatting' of livers after removal in animal models of steatosis⁴¹, showing promise for mitigation or reversal of organ degeneration during the donor's lifetime that could otherwise affect both transplant outcomes and, later, the recipient's health^{15,88,89}.

Perfusion platforms can allow transplantation of many organs that would otherwise be deemed too risky to transplant by allowing their health and function to be assessed outside the body^{37,41,87,90,91}. For example, it has been proposed by the National Heart Lung and Blood Institute and found by other studies that many hearts that would provide substantial survival benefits to patients are going unused, largely owing to a lack of reliable methods to assess their suitability for transplantation^{79,92}. By allowing organ function to be observed after procurement, perfusion platforms are enabling the investigation of new biomarkers that predict organ health and transplantability^{93–96}.

A variety of preservation breakthroughs could enable transport of organs over longer distances^{7,40}, opening up many new possibilities for organ allocation and therapeutic intervention. With distance no longer a factor in donor–recipient matching, closer matches could be achieved. This could decrease rejection and the need for immunosuppression⁷⁰ and extend graft life span, while increasing access to transplantation for disadvantaged patient populations^{60,73}. Organs could also be routed through specialized facilities, which have been suggested by several groups as a way to make technically challenging assessment, repair, functional augmentation, or banking procedures a clinical reality^{7,87,91}. Thus, approaches that today would not be seriously considered could become practical and fruitful areas of innovation.

Preservation breakthroughs could allow organs to be banked in a state of suspended animation at subzero temperatures^{7,25–27,68}, protected from ischemic injury and the damaging environment of the deceased donor body, for periods long enough to perform any assay needed on patients or tissue samples. This would enable more thorough screening for malignancies and transmissible diseases, such as rabies^{97,98} and HIV⁹⁹. Currently, disease transmission rates in organ transplantation, although <1%, are estimated to be on the order of 10,000 times higher than in blood transfusion, where a maximum shelf life of 5–6 weeks enables the use of lengthy disease-screening assays¹⁰⁰. Organ banking could also provide many new opportunities for matching, by uncoupling organ allocation from the narrow windows of time that currently constrain it.

Importantly, organ banking could prevent unnecessary loss of life by allowing any organs not immediately matched to be saved until a match could be found. This would make transplantation available to more patients, not only by offering a complementary organ supply but also by shifting the risk–benefit balance for patients and their transplant centers away from refusing transplantable organs. Primary graft dysfunction is a major cause of morbidity and mortality following transplantation^{101–103}, and roughly 50–75% (depending on the organ transplanted) of all graft failure in the first year after transplantation occurs within the first 3 months⁵⁷. Banked organs could provide a ‘backup’ supply in the case of early failure of the initial transplant; in cases where multiple matching organs were available, often multiple successive transplants would be feasible if the initial transplant fails. Thus, even when an organ individually carries a risk of early graft failure, the alternative supply of banked organs could substantially de-risk the overall process of transplantation, allowing transplant centers to accept the organ with substantially decreased patient risk.

Organ banking could also make transplantation a lifesaving treatment for heart attack victims, trauma patients, victims of accidental poisoning, and others with acute vital organ failure. For these patients, matching transplant organs need to be available within extremely short time periods, necessitating off-the-shelf solutions. Banking the substantial fraction of organs that go unused in the current allocation system could be lifesaving for these patients. The public health benefits of banking organs for emergency surgery could be vast; traumatic injury accounts for more deaths among adolescents and children than all other causes combined¹⁰⁴. Similarly, an International Society of Heart and Lung Transplantation committee has estimated that a substantial proportion of heart attack victims could be saved if heart transplantation were available for these patients on demand⁴. This is a particularly attractive prospect given the large fraction of potentially transplantable hearts that currently cannot be matched^{79,92}, which could be used to establish a heart bank. Further advancement of banking, assessment, and repair capabilities could allow this approach to benefit ever-larger patient populations.

The ability to save organs not immediately matched could be useful in live donation as well. In the recent innovation of live-kidney-donor chains, in which a patient who has found a willing donor (e.g., a friend or relative) whose kidney is not compatible exchanges their donor kidney for a compatible one, transplants are arranged in long chains, so that each patient in the chain receives a compatible kidney. However, chains end when no appropriate

recipient can be immediately found for the last donor in the chain, who instead donates to an individual on the deceased-donor waiting list without a corresponding donor to continue the chain^{105,106}. The opportunity to delay transplantation could create wider opportunities to find a donor–recipient pair who can continue the chain, allowing longer chains to be assembled.

Moreover, the ability to bank organs can aid in the development of technologies that could be game-changers for transplantation. For instance, a diverse array of immune tolerance induction approaches could overcome graft rejection while largely eliminating the need for immune suppression. Currently, all successful clinical trials involve living donors, so that tolerance induction treatments can be initiated before transplantation^{47–50}. Temporary banking of donor organs could enable tolerance induction for deceased donor organs (the vast majority of transplants) as well, by allowing the required pretransplant preparative regimen to be administered to recipients before the organ transplant. This could give the patient’s immune system time to adapt to the donor’s antigens before transplantation, and it would also provide time to evaluate the success of tolerance induction protocols in a matched patient before transplantation.

Meanwhile, longer-term efforts to create lab-grown organs by tissue engineering or xenotransplantation of ‘humanized’ donor animal organs would be aided by the ability to bank inventories to make these approaches practical and cost effective at scale. With advances in immune tolerance induction²² and the advent of CRISPR–Cas9 gene editing methods that open the possibility of more complex genetic engineering of donor organs to make them less vulnerable to recipient immune rejection¹⁰⁷, xenotransplantation could potentially offer a vast new source of transplant organs. But attainment of an engineered organ capable of engraftment and survival remains years away, and the investments required for clinical xenotransplantation are tremendous; large, centralized facilities would be required to produce transplant organs at scale, making cost-effective manufacturing and distribution a major concern unless these organs can be banked²³. Similarly, shelf life has been widely recognized as a key bottleneck in the progress of tissue engineering^{6,108,109}.

Challenges in complex tissue preservation

The same technologies that promise to transform vital organ preservation also advance the preservation of a vast array of tissue systems and address a large breadth of public health needs. Inadequate tissue preservation capabilities are a constraint on basic and preclinical biomedical research aimed at addressing major illnesses, drug testing and drug development, trauma care, stockpiling of medical countermeasures for large-scale public health emergencies, fertility restoration, as well as the advancement of tissue engineering and regenerative medicine (Table 3).

Tissue engineering and regenerative medicine

Current preservation limits present major challenges for the clinical translation of tissue engineering breakthroughs. Without the ability to lengthen shelf life, any firm attempting to develop biomanufactured tissue products lacks capabilities for batch manufacturing and distribution, while also facing difficulties adjusting to changing demand^{8,19,24,110,111}. Short

product shelf life also prevents implementation of some methods for quality control for tissue and organ products, adding substantial cost and risk^{8,19,24,111}.

Opportunities abound to enhance banking capabilities for tissue engineering. For instance, successful cryopreservation of a 2.3 liter biomass consisting of encapsulated liver spheroids for use in a bioartificial liver device may stimulate research on other large-volume tissue-engineered products¹¹². These challenges have led the US Commerce Department, US Department of Defense (DoD), and the US government's Multi-Agency Tissue Engineering Sciences working group coordinating tissue engineering research support across the NIH, NSF, the US National Institute of Standards and Technology, the DoD, and other science agencies, to identify preservation as one of the key bottlenecks in tissue engineering efforts^{6,108,109}. For instance, a new Advanced Tissue Biofabrication Manufacturing Innovation Institute announced at the June 2016 White House Organ Summit has a major focus on advancing organ preservation¹¹³; the solicitation calls for preservation technologies to enable biomanufacturing to move from unscalable, just-in-time manufacturing to scalable models using off-the-shelf tissues¹⁰⁹. Likewise, potential future initiatives under the Defense Innovation Unit-Experimental (<http://www.diux.mil>) in the areas of biofabrication, tissue engineering, regenerative medicine, and tissue-based chip devices will all likely require capabilities emerging from organ and tissue preservation advances.

Protection of reproductive tissue in cancer patients

Organ and tissue banking could also become a staple of cancer care for children and young adults. Ovary, uterus, and testis banking could be used to restore fertility and hormone balance to the 140,000 childhood and young adult cancer survivors in the United States each year^{27,114–117} and hundreds of thousands more each year worldwide. Reproductive organs are highly sensitive to injury from chemotherapy and radiation, often leaving survivors of childhood and young adult cancer infertile and with altered endocrine function, resulting in lifelong sexual and psychological side effects^{27,117,118}. These complications could be prevented by saving and banking reproductive organs and tissue before treatment, then re-implanting them afterward^{27,28,119,120}.

Thus far, >60 healthy offspring have been born to women who banked ovarian tissue before their first sterilizing cancer treatment^{121–123}. Recently, whole sheep ovaries have been cryopreserved and reimplanted, and the sheep have gone on to produce healthy offspring²⁷. Additional research can make ovary banking clinically feasible and yield insights applicable to banking testicular tissue, whole testes, and larger organs. With >1 million survivors of childhood and young adult cancer living in the United States alone (spanning roughly two generations)^{118,124}, it is reasonable to estimate that reproductive organ and tissue banking could become the standard of care for millions of future cancer patients worldwide in the coming decades.

Countermeasures for public health emergencies

Advances in the preservation of many tissues are needed for trauma care, particularly to incorporate regenerative medicine therapies into strategic national stockpiles maintained by the United States' interagency Public Health Emergency Medical Countermeasures

Enterprise for natural disasters, nuclear accidents or attacks, chemical and biological weapons, and other large-scale public health threats. For instance, radiological threats stemming from nuclear accidents or attacks have led the US Biomedical Advanced Research and Development Authority (BARDA), charged with procuring medical countermeasures for the strategic national stockpile, to search for measures that can treat radiation injury¹²⁵. A 10-kiloton nuclear blast could cause acute radiation injury in >1 million people across a >10-mile radius. Large quantities of stockpiled bone marrow, cord blood, and other sources of hematopoietic stem cells could be used either to permanently replace irreparably damaged bone marrow or to serve as a 'bridge' until the recovery of autologous hematopoiesis¹²⁶. The blast from such an event could cause burns and/or trauma combined with radiation exposure in over 45,000 victims¹²⁷, necessitating skin grafts for severe burns^{128,129}, and blood vessel grafts for extremity injuries¹³⁰. Similar need for on-demand bone marrow and skin could also arise from the use of mustard gas or other exfoliants. Similarly, a large supply of banked human tissue—particularly liver, kidney, brain, or heart slices—could be a critical resource for the rapid study of novel bioagents and development of medical countermeasures for biological and chemical terrorism threats.

Tissue preservation and banking advances are needed to incorporate these and other treatments into strategic national stockpiles. For instance, precision-cut tissue slices can currently be cultured only for a matter of days, precluding standardization in preparation and on-demand use to address bioterrorism threats¹³¹. Shortages of skin for use on demand have led both BARDA and the US military to look for biomanufacturing solutions to stockpile large quantities of skin for combat or emergencies, yet for both groups short tissue shelf life has been cited as a limiting factor^{25,129,130}. Cryopreservation has enabled the banking and subsequent transplantation of both bone marrow and skin, but the current state of the art results in some loss of viability^{128,132}. In the case of bone marrow banking, improvements to cryopreservation methods can also reduce the incidence of complications after transfusion¹³². Thus, preservation advances would help address large public health needs for these tissues. For entities such as the DoD and BARDA to successfully leverage advances in regenerative medicine, preservation research is a necessity; the nature of emergency response dictates that banked tissues must be available for off-the-shelf use.

Transplantation for acute injuries

Preservation advances could also dramatically increase patient access to transplantation or recovery of vascularized composite tissues, such as limbs, hands, or faces after traumatic injury. For example, roughly 30,000 traumatic amputations occur per year in the United States, over two-thirds in children and young adults; it has been estimated that there will be >900,000 survivors of traumatic amputation living in the United States by 2020¹³³.

Extending preservation capabilities for recovered limbs can allow a greater number to be reattached, and in the past 15 years it has become possible to transplant hands, faces, and whole limbs from deceased donors^{44–46,134}. Although ample donor pools are already available, these procedures are still not routine—largely because matching must be done very quickly (for both cosmetic and immunological criteria) and patients face complications from immunosuppression¹³⁴. As discussed, preservation can address both of these

challenges, playing a pivotal role in providing access to hand, limb, and face transplantation for tens of thousands of new patients each year.

An integrated approach to preservation

A growing body of evidence indicates that a transformation in organ and tissue preservation is now achievable. Recent promising discoveries include organ cryopreservation and subzero cooling, perfusion, interventions before organ and tissue recovery, and adaptations that allow dozens of species in nature to enter suspended animation at subfreezing temperatures (Table 4). Together, these approaches form a blueprint for a leap forward in preservation capabilities, centered on a combination of two promising strategies:

1. Providing organ 'life support' by recapitulating aspects of the organ's healthy physiological environment.
2. Effectively controlling biological time by slowing or halting metabolism to decrease the rate of deterioration.

Progress on both fronts is needed because each preservation approach involves tradeoffs often requiring the application of combined strategies in the same organ or tissue. For instance, slowing organ deterioration for extended preservation periods can be achieved by lowering organ temperature and metabolic rates, but this also entails the loss of normal organ function and opportunities for beneficial interventions, such as organ assessment, repair, and functional augmentation (Table 2).

Thus, we must begin to think about the aim of preservation not as the pursuit of a singular 'best' environment to keep a particular organ or tissue healthy on its way to transplantation (or use in research), but as an 'integrated' process during which the organ or tissue traverses multiple preservation conditions and temperature ranges that are used synergistically (Fig. 4). To make an integrated approach to preservation successful, we must combine and advance a family of research areas that includes cryopreservation⁷, programmed metabolic suppression³¹, subzero preservation and supercooling¹³⁵, and perfusion and *ex vivo* maintenance at a variety of temperatures, ranging from hypothermia (refrigeration) to normothermia (body temperature)^{34,35,37,136}, and donor management before organ and tissue recovery^{137–139}. The discoveries noted in Table 4 have provided various proofs of principle for using these approaches in organ and tissue preservation. They have historically been relatively siloed, despite the fact that they are complementary and often synergistic^{6,7,26,31,40,87,91,137}.

Advancing organ and tissue preservation through an integrated approach has become an achievable goal, as the past decade has seen an explosion of technologies enabling us to understand and intervene in human physiology at the tissue and organ level. Advances in cellular and tissue imaging^{140–142}, organoids, organs on a chip and regenerative medicine¹³, high-throughput assays and sequencing readouts¹⁴³, miniaturization and microfluidics¹⁴⁴, nanotechnology^{145,146}, and molecular engineering and gene editing^{147–152} can all be harnessed to galvanize research into the fundamental biology of tissue and organ cryopreservation, discover novel cryoprotectants, and develop new preservation strategies. This creates exciting prospects for translating the 'suspended animation' programs of

animals, such as the arctic ground squirrel¹⁵³ and even tardigrade¹⁵⁴, into tools for organ and tissue preservation. This decade has also seen rapid advances in *ex vivo* perfusion platforms^{33,34,36–38,41,66}, which can be adapted to recapitulate aspects of an organ's *in vivo* environment, condition it for storage or transport in a hypometabolic state, or enhance recovery from stresses experienced during donor death or the preservation period^{40,155–158}. By building on, and combining, these innovations from different disciplines, we are now poised to create a new generation of organ and tissue preservation capabilities driven by both public and private sector funding (Box 1).

Catalyzing breakthroughs

So far, the very features that make preservation a foundational and high-impact research area have hindered its progress in the absence of coordinated support. The vast need to increase organ and tissue availability is spread across many areas of medicine and public health (Table 3)—and ultimately stakeholder groups. For instance, over 80% of NIH's budget goes to institutes with missions tied to unmet preservation needs, encompassing 15 different institutes²⁴. This makes organ and tissue preservation research a nearly universal concern, yet it is not the focus of any major funding body.

The research expertise needed is similarly dispersed. Organ and tissue preservation is quintessentially a 'convergence technology', integrating device engineering, applied mathematics, organic and inorganic chemistry, thermodynamics and biophysics, biochemistry and chemical biology, materials science, nanotechnology and molecular engineering, as well as molecular and cell biology^{6,143,159}. This creates special challenges, as the institutions supporting science and engineering research have historically been divided according to research discipline¹⁵⁹. For example, it can be inherently difficult to fund an ambitious preservation project because of the inability to assemble an NIH study section that can address all aspects of such a cross-disciplinary grant proposal—even if all the research expertise to propose such a project comes together in the first place. The nature of organ and tissue preservation demands coordination among a large number of actors spanning many research communities, science agencies, industries, and stakeholder organizations.

This coordination is beginning to take shape. For instance, the NSF-supported technology roadmapping process for organ banking and bioengineering, involving representatives from multiple agencies, including NIH, NSF, the US Food and Drug Administration, the DoD, and other agencies, along with dozens of academic institutions, identified >20 surrounding research areas that can be applied to accelerate progress on organ cryopreservation and recommended scientific and institutional strategies to enable organ banking⁶. Similarly, two US Health Resources and Services Administration-funded consensus conferences recently identified untapped opportunities for *in situ* preservation of organs through donor management¹⁶⁰. This set the stage for a National Academy of Medicine (Washington, DC, USA) study this year aiming to develop a national infrastructure that will foster donor management research in the United States (http://www.isHLT.org/ContentDocuments/2016DecLinks_Nelson.html). At the June 2016 White House Organ Summit¹¹³, the Organ Preservation Alliance (of which S.G. and J.K.L. are directors) announced that the alliance is leading a coalition of organizations to study the public health needs, scientific opportunities,

and institutional challenges in advancing organ and tissue preservation. The stakeholder groups, which to date include the Association of Organ Procurement Organizations (McLean, VA, USA), the American Society of Mechanical Engineers (New York), the Society for Cryobiology (Luton, UK), and others, will work together to craft a cohesive strategy to advance organ and tissue preservation on all fronts¹⁶¹. The need for a concerted effort to remove logistical barriers in organ and tissue replacement has also been emphasized in international efforts, for instance, in a recent strategic plan for organ and tissue donation in Canada developed by more than 140 stakeholder organizations¹⁶².

Initiatives aiming to encourage coordination have already borne fruit in the form of collaborative research efforts that have sprung up around them. In 2015, three DoD small business grant solicitations, targeted toward complex tissue preservation and banking^{163–165} (to the authors' knowledge, the first US grant solicitations on this topic), yielded applications from 35 teams consisting of >100 laboratories across industry and academia—a virtually unprecedented response for the funding mechanism used. The DoD increased its support with three more grant solicitations in 2016^{130,166,167}, largely as a result of the abundance of strong proposals during the previous year from cross-disciplinary teams.

Although this demonstrates the wealth of untapped opportunities in organ and tissue preservation research, active and centralized networking among research laboratories also played a substantial role in the strong response. Another successful effort to bolster research coordination is the Charlotte Banks research initiative at the University of North Carolina, Charlotte, which developed out of discussions at the first global Organ Banking Summit in 2015 in Washington, DC. The initiative aims to cryopreserve living thick tissues by coordinating research among almost a dozen laboratories in vascular biology, nanotechnology, materials science, machine perfusion, computational physics, thermodynamics, and other areas (<https://eng-resources.uncc.edu/charlottebanks/>). In response to the 2016 White House Organ Summit and Emerging Technologies in Organ Preservation roundtable on Capitol Hill, the American Society of Transplantation has launched a community of practice to advance organ and tissue preservation, in partnership with the Organ Preservation Alliance (<https://www.myast.org/about-ast/white-house-highlights-asts-new-initiative-organ-preservation-alliance>).

Beyond these promising first steps, several additional mechanisms could be used to accelerate progress. Ambitious but achievable preservation challenges, such as large tissue cryopreservation, may be a good fit for high-stakes, high-publicity incentive prize funding. A standing committee comprising experts and stakeholders from diverse fields is needed to coordinate organ and tissue preservation research. The broader challenge of increasing organ and tissue availability (which includes donation, preservation, manufacturing, and transplantation) is ideally suited for a national or international initiative on the scale of the NIH BRAIN Initiative or Human Genome Project, given the inherent complexity of the remaining scientific challenges and the coordination needed, the increasingly important role of regenerative medicine, and the enormous potential of organ and tissue replacement to improve human health.

Organ and tissue preservation has become fertile ground for the application of existing knowledge, talent and research tools. Opportunities abound for diverse (and often converging) fields to provide innovative solutions, but institutional challenges remain and mechanisms to facilitate wider collaboration are needed. If we meet these challenges and build on the scientific proofs of principle that already exist, we may enter a new era of organ and tissue preservation in the coming years—benefiting millions of patients globally and changing the course of many domains of public health.

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Box 1 Burgeoning public and private sector interest in preservation

The White House recently announced an upcoming Summit on Organ Banking through Converging Technologies to be held at the Harvard Medical School's Martin Conference Center in August (<http://obs2017.obs2017.org/en/>). This will be the first scientific consensus-building conference to map out how these and other technologies can be applied systematically to overcome remaining organ preservation challenges. Both basic and translational preservation research seems to be positioned to benefit from rapidly advancing platform technologies. Indeed, the past 3 years have seen a wave of new biotech companies in the organ and tissue preservation space, capitalizing on a small fraction of the opportunities that have emerged. Supported by multiple grant solicitations from the DoD and substantial funding from NIH, these firms are pursuing strategies such as programmed hypometabolism, biomimetic nanoscience, radiofrequency-based 'nanowarming,' isochoric preservation, subnormothermic perfusion, and high-subzero temperature preservation (<http://firstround.com/>; <http://x-therma.com/>; <https://www.sbir.gov/sbc/sylvatica-biotech-inc>)^{196–198}. Much of the current focus is on banking and subzero preservation; in this respect, the synergy between these technologies and *ex vivo* perfusion platforms (Tables 2 and 4)^{6,7,26,40,41,87,91} means they benefit from—and enhance the value of—the substantial investments made in *ex vivo* perfusion in recent years^{199–202}.

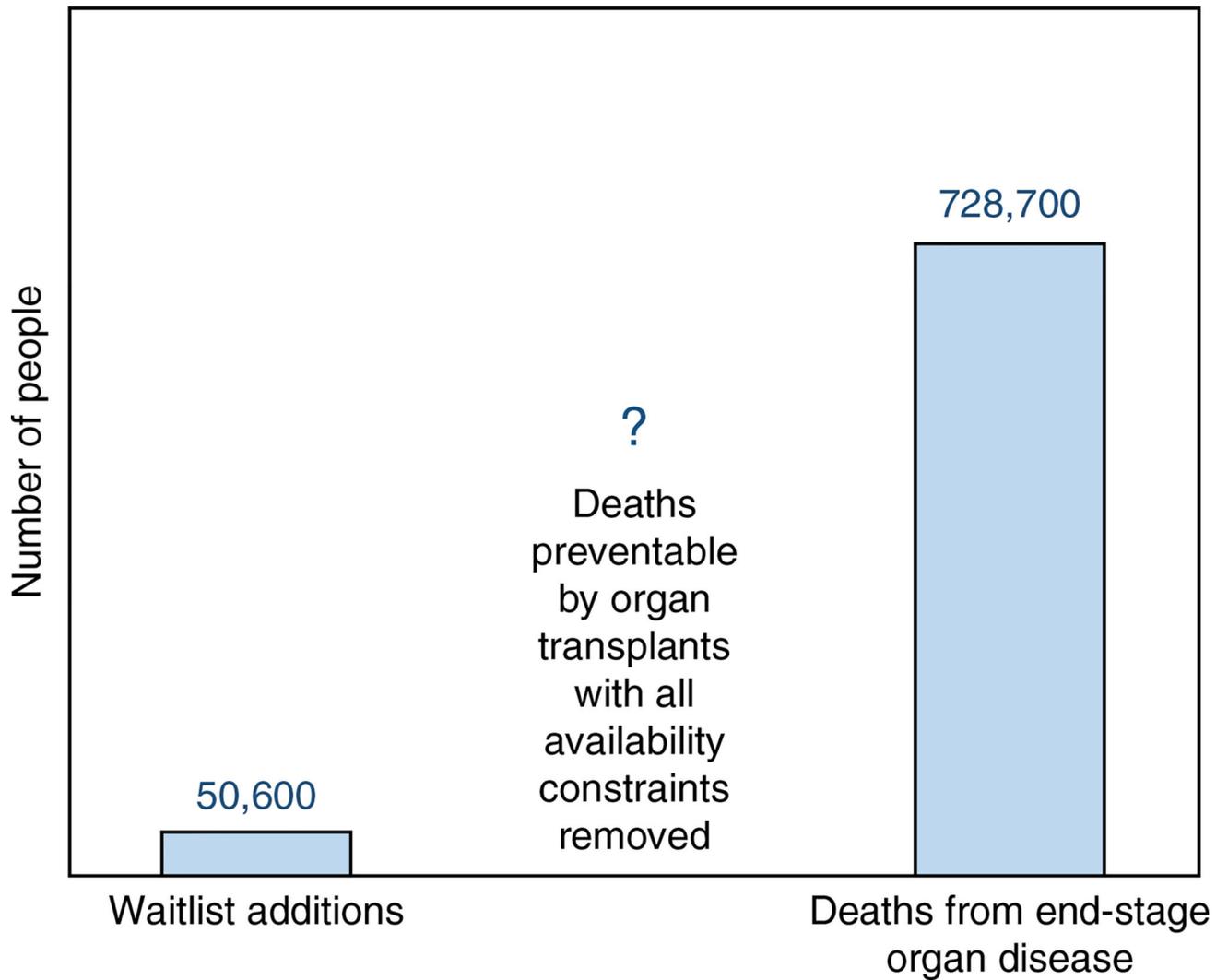


Figure 1.

The true lifesaving potential of organ transplantation. The roughly 50,000 US patients added to transplant waiting lists in 2011 were outnumbered over 14-fold by those who died from end-stage organ disease (<http://www.perfusix.com/impact-of-ex-vivo.html>), without counting cases where malignancies could have been treated with organ replacement¹⁶⁸. This suggests that the true size of the organ shortage could be many times larger than is reflected by transplant waiting lists (currently 120,000 US patients).

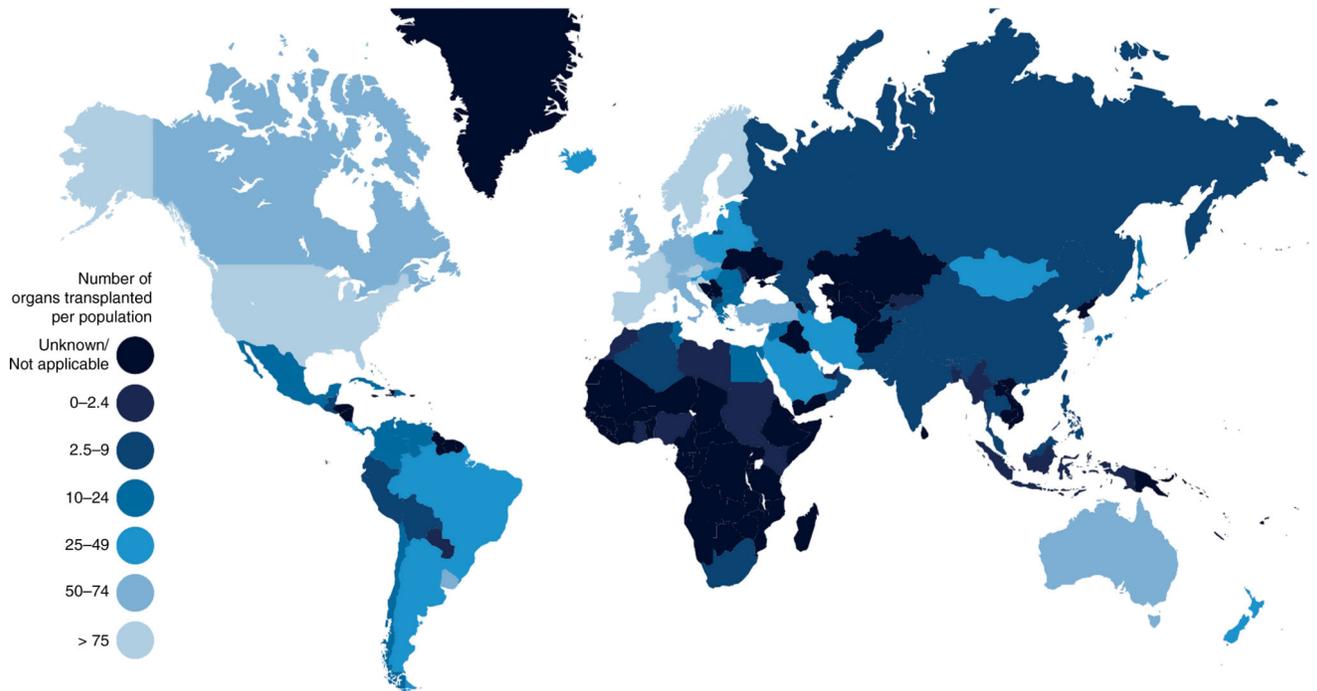


Figure 2.

The global unmet need for transplantation greatly exceeds that of the United States (see Fig. 1), which contains roughly 4% of the world's population but performs 25% of its organ transplants. By comparison, the continent of Africa contains roughly 16% of the world's population but performs fewer than 0.5% of its organ transplants (<http://www.transplant-observatory.org/summary/>; https://esa.un.org/unpd/wpp/publications/files/key_findings_wpp_2015.pdf).

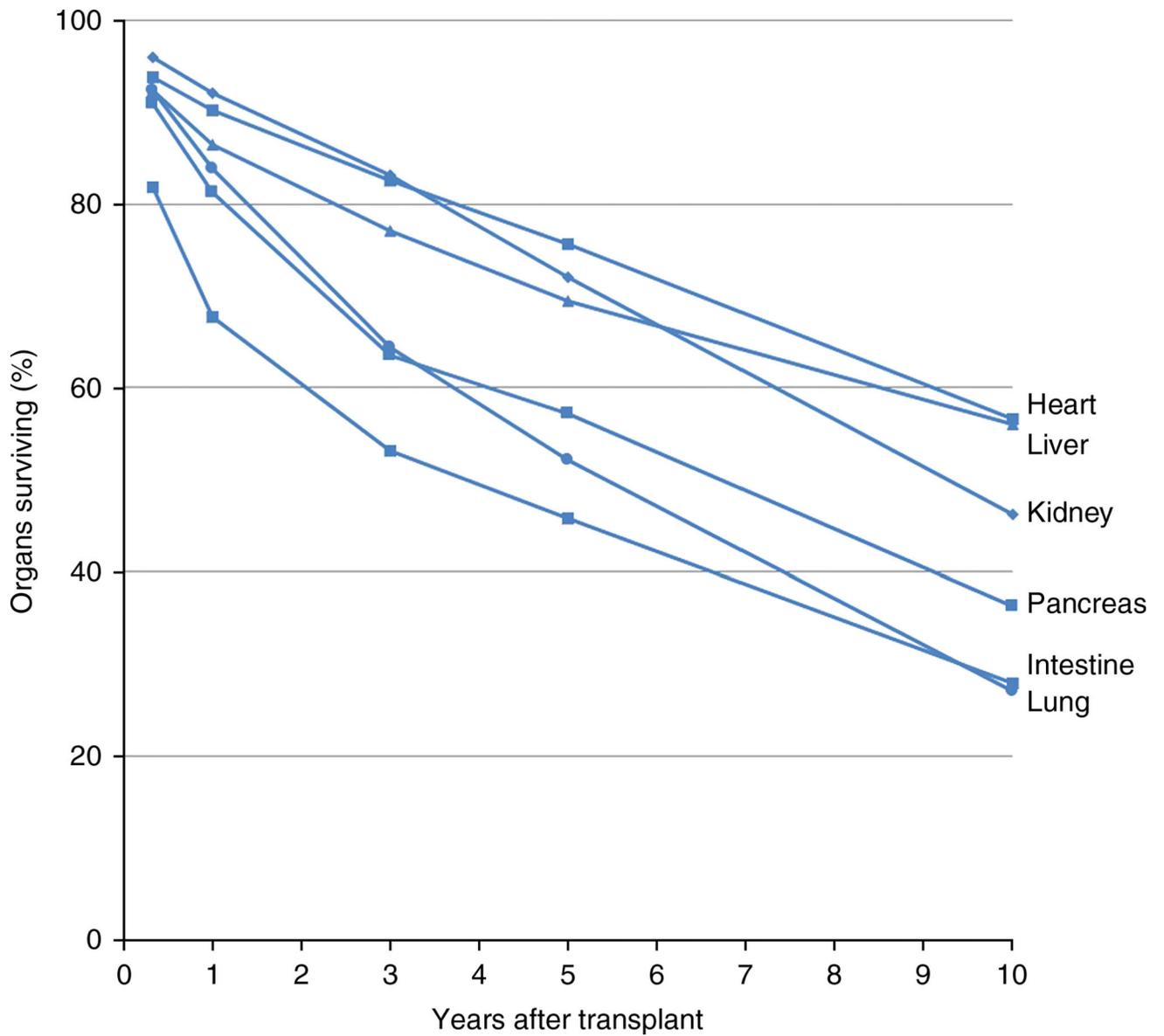


Figure 3.

10-year graft survival for each of the six vital organs currently transplanted (single-organ, deceased donor transplant)⁴⁹. 10-year survival rates for organs range from slightly over 50% (hearts and livers) to slightly over 25% (lungs and intestine). These data indicate that ensuring transplant organ quality and reducing susceptibility to chronic rejection are still major challenges in transplantation. Preservation advances present diverse opportunities to meet these challenges (Table 2).

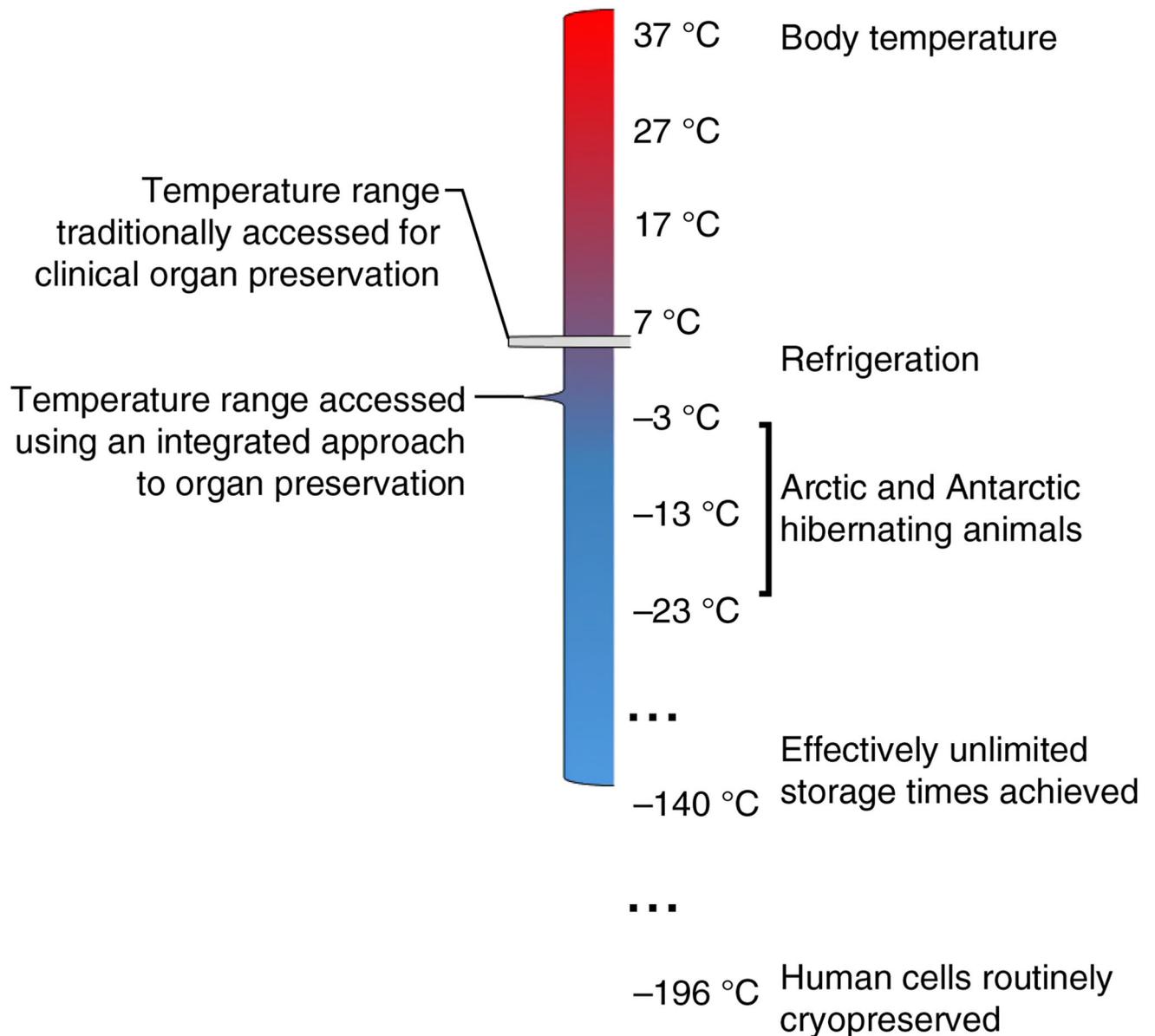


Figure 4.

An integrated approach to organ and tissue preservation would combine multiple preservation conditions and temperature ranges, drawing on the strategies found in Table 4. Thus, when called for, differing preservation modalities could be used during successive stages of the preservation process, accessing a much wider range of temperatures and conditions than are currently used in conventional organ preservation. For instance, transplant organs could be held at subnormothermic temperatures during pharmacological pre-conditioning for cryopreservation, then cooled to cryogenic temperatures for transport or banking, then returned to near-normothermic temperatures for functional assessment. Many combinations are conceivable based on the diverse proof-of-principle discoveries; the optimal preservation protocol will most likely vary according to tissue type and application.

Table 1

Summary picture for four vital organs from deceased donors

Vital organ	Number transplanted⁷⁵	Percentage of donor organs not transplanted⁷⁵	HLA compatibility used in matching algorithms?¹⁶⁹	Ratio of unused organs to waiting list patients removed for death or illness⁵³
Heart	2,421	70	No	10:1
Lung	3,019	81	No	32:1
Kidney	11,993	26	Yes	3:5
Liver	5,942	27	No	3:4

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Table 2

Preservation enables key transplant capabilities

Goal	Capabilities
Increasing pool of donor organs	Reducing organ discard
	Rescuing marginal organs
	Decreasing costs of transplantation
	New matching approaches in deceased donation
	Successive organ transplants in case of graft dysfunction
Enhancing transplant viability and function	Repairing organ injury during removal and transport
	Assessing organ function before transplant
	Enabling new immune-tolerance-induction strategies
	Transmissible disease screening for donors and organs
	Augmenting organs (e.g., gene therapy, immunomodulation)
	New donor-recipient compatibility assessment methods
	Preventing ischemic injury during transplant
Expanding transplantation access	Extending live kidney donation chains
	Enabling recipients with acute disease or trauma
	Flexible scheduling of transplant surgeries
Galvanizing research	Accelerating progress in cryobiology and preservation
	Accelerating progress in humanized xenotransplantation
	Accelerating progress toward lab-grown organs

Table 3

Unmet needs for organ preservation

Area of biomedicine	Example of public health need
Organ transplantation	Almost 70% of US donor hearts go untransplanted, largely due to preservation limits on assessment and matching ^{2,38,79,92,170}
Cancer treatment and fertility	Ovary banking can save fertility/hormone balance in 140,000 girls and young women diagnosed with cancer and potentially exposed to chemo- and radiotherapy in the United States each year ¹¹⁷
Emergency preparedness	Banked bone marrow and cord blood could benefit >10,000 patients after a nuclear accident or attack ^{130,171} as well as 14,000 US patients each year suffering acute injury who would benefit from a transplant ¹⁷²
Limb recovery and transplantation	30,000 traumatic amputations per year in the United States; two-thirds of victims are children and young adults ¹³³
Basic medical research	Human tissue would be a superior model to the 100 million mice and rats used in research each year ¹⁷³ ; tissue banking advances are critically needed to aid approaches seeking to treat malignancies ¹⁷⁴ , neurodegenerative diseases ¹⁷⁵ , and other disorders
Trauma care	30,000 patients admitted to specialized US burn units each year ¹⁷⁶ . After a nuclear accident/attack, and estimated ~3% of the skin grafts required would currently be available ¹⁷⁷
Tissue engineering and regenerative medicine Drug discovery	Shelf life of regenerative medicine products, a sector with a predicted >\$500-billion market by 2025 ¹⁷⁸ Banked human tissue would benefit pre-clinical drug testing and potentially improve low efficiency of drug development ^{179,180}

Table 4

Proofs of principle already exist for each pillar of organ and tissue preservation

Approach	Examples of proof-of-principle discoveries
<p><i>In situ</i> organ preservation</p> 	<ul style="list-style-type: none"> Mild hypothermia in deceased kidney donors shown to reduce delayed graft function¹³⁷ Hypothermic blood substitution protects from prolonged ischemia in trauma models^{181–183} Treatment of donor with dopamine decreases kidney rejection and improves graft survival¹³⁸ Cooperative donor management has been associated with more organs transplanted¹³⁹
<p><i>Ex vivo</i> organ life support</p> 	<ul style="list-style-type: none"> Hypothermic perfusion devices have improved kidney preservation outcomes^{33–35,37} Normothermic machine perfusion used in hundreds of heart³⁸ and lung transplants^{36,184,185} Subnormothermic machine perfusion used as platform for assessment⁹⁰, cooling⁴⁰ <i>Ex vivo</i> perfusion successfully used as platform to repair marginal organs⁶⁷
<p>High subzero preservation</p> 	<ul style="list-style-type: none"> At least 45 supercooling species (including mammals) tolerate temperatures as low as $-14\text{ }^{\circ}\text{C}$¹⁸⁶ Arctic wood frog can enter suspended animation as low as $-20\text{ }^{\circ}\text{C}$ for weeks to months²⁹ Rabbit kidneys successfully cooled to $-45\text{ }^{\circ}\text{C}$ before transplantation, sustaining life²⁶ Supercooling at $-6\text{ }^{\circ}\text{C}$ has extended liver preservation times three- to fourfold in rats^{40,65}
<p>Programmed metabolic suppression</p> 	<ul style="list-style-type: none"> Arctic wood frog, mammals, other species can initiate regulated metabolic arrest^{29,31} Genetic and biochemical studies have revealed mechanisms conserved in humans^{30–32} Pharmacologically induced 'suspended animation' has been demonstrated in mammals¹⁸⁷
<p>Cryopreservation</p> 	<ul style="list-style-type: none"> >60 healthy human offspring conceived from cryopreserved ovarian tissue^{188,189} Successful transplantation of whole rat hindlimbs¹⁹⁰ and replantation of partial rat hindlimbs¹⁹¹ following cryopreservation for weeks Cryopreserved whole sheep ovaries have been transplanted, producing healthy offspring²⁷ Rabbit kidney successfully cryopreserved at $-140\text{ }^{\circ}\text{C}$ and transplanted, supporting life⁶⁸ Human cells, embryos and some tissues have been cryopreserved for decades^{6,7} Ice-free cryopreservation has led to breakthroughs in banking of tissues for transplantation (e.g., blood vessels, cartilage and corneas)^{192–195} Research community has codified remaining sub-challenges for organ cryopreservation^{6,7}

Photo credits: "Programmed metabolic suppression": J.M. Storey, Carleton University; "Cryopreservation": G.M.F.