Beta Roadmap Report

SOLVING ORGAN SHORTAGE THROUGH ORGAN BANKING AND BIOENGINEERING

from the December 2014 - July 2015 Roadmapping Process
including the the NSF-Funded Washington D.C. Workshop
and White House Roundtable

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new organ

ORGAN PRESERVATION ALLIANCE

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INTRODUCTION

INTRODUCTION

Ending the organ shortage in the United States has the potential to transform public health as we know it and recent scientific advances suggest that this goal is now within reach. In order to help streamline the development of new technologies, systems, and research approaches that can systematically combat organ disease, injury, and scarcity, this Beta Roadmap for Organ Banking and Bioengineering has been developed through a landmark workshop funded by the National Science Foundation (NSF) in Washington, D.C. on May 27, 21015 and a subsequent Roundtable held at the White House Office of Science and Technology Policy on May 28.

Under the title "**Building a Roadmap for Solving Organ Disease and Impairment,**" the Washington D.C Workshop and the subsequent White House Roundtable brought together top researchers in the fields of tissue engineering and organ banking, along with representatives from the National Institutes of Health (NIH), the Department of Defense (DoD), BARDA/Project Bioshield, NASA, the NSF, and numerous private-sector organizations. The gatherings built on recent momentum toward organ banking and bio-engineering, including an interagency meeting on "incentivized innovation" hosted by the Department of Health and Human Services (DHHS) in July, 2014; the first global Organ Banking Summit held in February, 2015 at Stanford University; and three new federal grant programs issued by the DoD in January, 2015 for organ and tissue banking R&D.

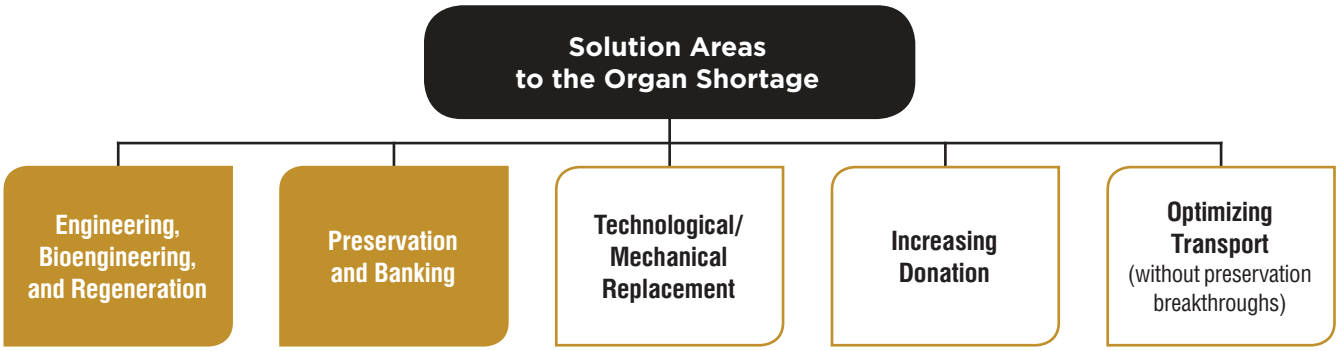
At the Roadmap Workshop, key challenges, milestones, and associated metrics were identified that can provide focal points for a national cross-disciplinary research effort to generate technological solutions to the organ shortage. The result of these discussions has been turned into this Beta Roadmap, a document that is intended to help inform the creation of actionable next steps to produce the most viable, beneficial, efficient, and sustainable responses to the challenges before us.

The roadmapping effort has been coordinated by two nonprofits – New Organ and the Organ Preservation Alliance – who gathered an Organizing Committee of leading scientists, government agency representatives, and other stakeholders. Together, they surveyed numerous experts in the field and synthesized their findings into an *alpha* report that served as the basis for the Washington D.C. Rodmap Workshop and White House Roundtable meeting which in turn served as the basis for this *beta* report. While this Beta Report represents hours of research, the challenges in Organ Banking and Bioengineering are complex; therefore these Beta Maps will continue to be updated as more experts are able to contribute their expertise.

INTRODUCTION

THE SYNERGY OF ORGAN BANKING AND BIOENGINEERING

While many policies and research efforts may help close the gap between need and supply (e.g. increasing organ donation rates or mechanical organ replacement), **organ bioengineering and organ banking both present unique and scalable opportunities.** Organ banking and bioengineering are highly synergistic research areas; pursued in parallel, they have the potential to eliminate the organ shortage altogether. Moreover, there exists a gaping asymmetry between federal research funding for these areas and their potential public health impact, which far exceeds even the current organ shortage. Indeed, innovation in these areas has the distinct potential to open up broad new ranges of possibility for health care.



The research conducted, spanning many different scientific fields, suggested that **the twin goals of organ banking and organ bioengineering should be considered a scientific Grand Challenge with the potential to save millions of lives** by enabling on-demand, off-the-shelf, universal organs and tissues.

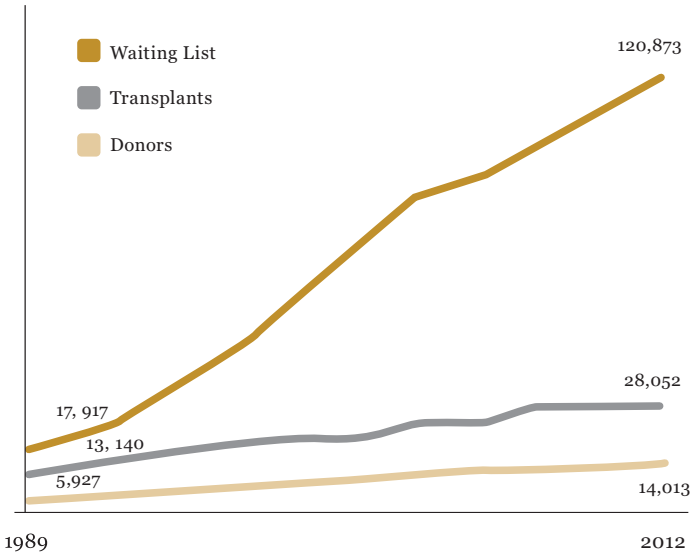
Organ banking and bioengineering also **directly impact the goals of key federal agencies** such as NIH, NSF, DoD, BARDA/Project Bioshield, and NASA, and they provide significant benefits outside transplantation itself. For example, advances in these research areas are likely to give rise to many commercial products that will **spur private investment**. If the United States leads the world in the development of bioengineering and banking industries for complex tissues and organs, it will simultaneously **spur U.S. economic competitiveness**, lead to new high-technology jobs, present significant federal cost savings, and **benefit millions of citizens** affected by organ failure and shortages.

THE GRAND CHALLENGE

This Beta Roadmap for Organ Banking and Bioengineering is based on the recognition that **ending the organ shortage in the United States** is not only an achievable target, but a ripening focal point for a coordinated national grand challenge.

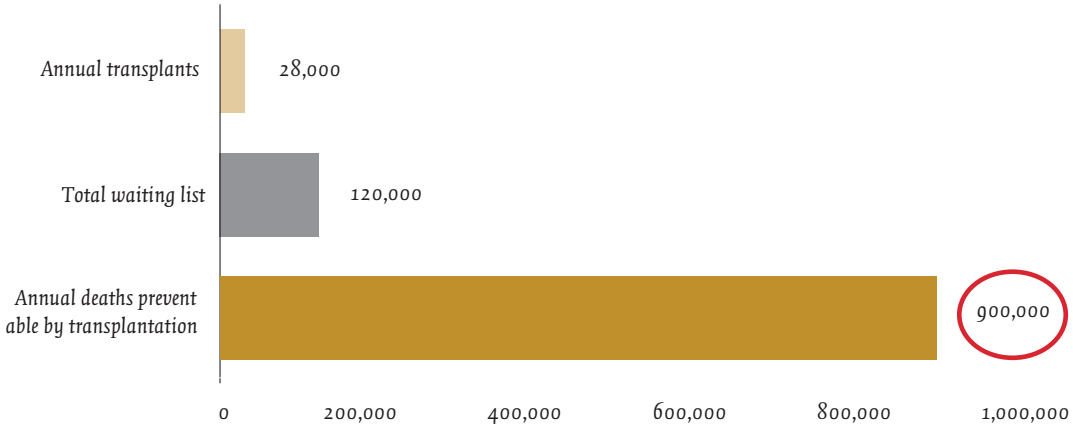
The existing need is clear: Organ bioengineering and banking have the potential to save millions of lives, but are currently limited by **acute shortages** of donor organs and tissues, **exorbitant costs**, difficulties with **intermediate- and long-term storage**, and complications due to **sub-optimal matching** and necessary **immunosuppression** [1]. Currently, the demand for organ transplants in the U.S. outweighs the supply by a factor of 5 to 1, and the gap continues to grow [2].

THE GROWING ORGAN SHORTAGE[2]



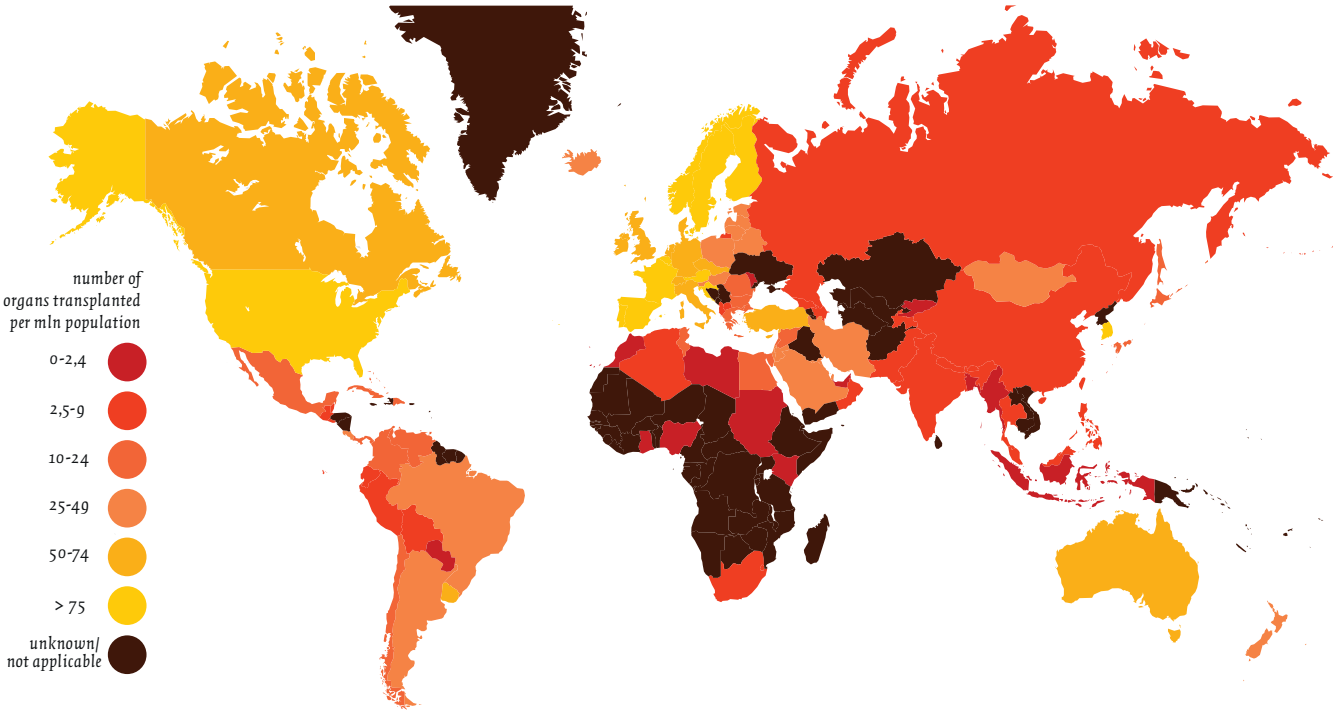
However, the official organ waiting list represents **just a fraction of a much bigger problem**: an estimated **35% of all annual U.S. deaths** could be prevented or substantially delayed by organ transplantation and more through full-blown tissue engineering [3, 4].

AN ESTIMATED 35% OF ALL U.S. DEATHS COULD BE PREVENTABLE BY ORGAN TRANSPLANTATION [3, 4]



The organ shortage is even worse for many ethnic minorities, who face significantly lower likelihoods of obtaining suitable matching organs. [13, 14] Worldwide, the World Health Organization (WHO) estimates that organ transplants currently meet less than 10% of demand.[25]

GLOBALLY THE PROBLEM IS EVEN MORE SEVERE [15, 25]



ACCORDING TO THE WORLD HEALTH ORGANIZATION, ORGAN TRANSPLANTS ARE CURRENTLY MEETING LESS THAN 10% OF THE GLOBAL NEED

In many developing countries, transplantations per capita are less than 1% of those performed in the U.S. and Western Europe [15]. At the same time, many organs potentially fit for donation are discarded, mostly because of prohibitively short preservation times (4-12 hours for most vital organs)[16]. At present, we discard nearly two thirds of potential donor hearts and one fourth of potential donor kidneys. [18,19]. If just half of all unused hearts and lungs could be utilized, it is estimated that transplantation waitlists for these organs would disappear in 2-3 years [17].

All told, **more people die in the U.S. from organ impairment than die from cancer** [5], yet organ bioengineering **research remains significantly underfunded**, and organ banking research even more so. Recent calls for grant applications by the Department of Defense, for example, represent the first federal funding in history to be targeted specifically toward the banking of organs and large tissues.[24] Similarly, U.S. research institutes have yet to prioritize organ banking in their research agendas.

There are **strong commercial and competitiveness reasons** for the US to invest in these areas. The HHS-led report Vision 2020: A Future for Regenerative Medicine estimates that the world market for replacement organ therapies alone is over $350 billion. In addition, the Alliance for Regenerative Medicine's 2013

annual report states that "potential savings from regenerative medicine treatments – for the U.S. ... have been estimated at approximately $250 billion a year." The economic cost of treating end-stage renal disease has been estimated at over $1 trillion over the course of a decade [20]. $34.3 billion of the U.S. Medicare budget was spent on dialysis in 2010 alone [22]. In addition to the financial burdens, dialysis patients typically experience a poor quality of life compared with transplantation [21].

By eliminating logistical burdens, organ banking can bring down the costs of transplantation, which for some procedures have skyrocketed to more than $1 million [23]. Increasing transplantation effectiveness, reducing complications, and minimizing rejection can help avoid the need for many costly treatments in the first place. Furthermore, innovation in organ banking and bioengineering will give rise to **new industries and economic opportunities**, creating jobs, spurring collaboration between the public and private sectors, encouraging substantial private investment, and generating national wealth.

Perhaps most significantly, the systemic medical innovations required to end the organ shortage promise **far-reaching benefits beyond the organ disease crisis** itself, with the potential to revolutionize human health care through enabling **cryobanked, on-demand, off-the-shelf, bioengineered organs and tissues** with a vast array of medical applications. These breakthroughs will be relevant not just for vital organ disease but for other forms of organ impairment and regenerative medicine, and they will extend past normal civilian medical organ needs to areas including:

- **Trauma damage and wound healing**: In addition to the lack of vital organs for transplant, there is a huge shortage of vascularized composite tissues to be used for trauma, reconstructive, and regenerative medicine. Approximately 1,600 wounded service members sustained amputations during the wars in Iraq and Afghanistan; close to 500 of those suffered amputations of more than one limb, and 4,000 service members sustained facial injuries.[6] While these numbers of catastrophic combat injuries to the face and limbs are unacceptably high, the number of civilians who suffer similar injuries is even greater. Two million people are living with limb loss in the U.S.; 185,000 amputations are conducted each year (almost half caused by trauma, and thus disproportionally affecting young people).[7,8] Three million facial injuries are treated in emergency rooms in the US each year.[9] By conservative estimates, if even 0.5% of those are catastrophic injuries, then 15,000 patients each year suffer life-changing facial disfigurement and disability and would be potential candidates for a face transplant.

- **Medical countermeasures for mass casualty events**: To guard against a nuclear power plant accident, war, terrorist attack, or other emergency healthcare surge, stockpiling bioengineered and/or deceased donor tissues (skin, blood vessels, bone marrow etc.) would bolster the U.S. Strategic National Stockpile and provide the U.S. Department of Health and Human Services (via agencies such as the Biomedical Advanced Research and Development Authority (BARDA) and Project Bioshield) with critical resources for use in emergency response.

- **Better and safer immune tolerance induction protocols**: Developments in organ bioengineering and banking and bioengineering could enable immune tolerance induction treatment to be given prior to transplantation, reducing immune system reactivity for transplantees and minimizing the need for costly and dangerous immunosuppression.

- **Protecting and restoring hormone balance and fertility after cancer treatment**: In the U.S. alone, there are an estimated 379,000 survivors of childhood and adolescent cancer (diagnosed at ages 0-19) [12] and an estimated 630,000 young cancer survivors (age 20-39) [10], many of whose fertility, hormonal balance, and psychological health could have been improved if their ovary or testes had been preserved via better banking technologies prior to radiation or chemotherapy, and later re-transplanted. Up to two-thirds of male pediatric cancer survivors will face germ cell dysfunction [11]. According to the National Cancer Institute, 1 out of every 250 adults will be a survivor of childhood cancer by 2015 [10]; an estimated 175,000 annual cases of cancer in children younger than 15 years of age are diagnosed worldwide [12].

- **Skin and vascular grafts**: Advances in skin and vascular production and/or banking would significantly improve treatment for the two most common complications of lifestyle diseases, diabetic ulcers and coronary artery bypass, in addition to other skin and vascular injury resulting from accidents, fires, or combat trauma. [24]

- **Minimizing animal use in scientific research and drug discovery**: Advancements in tissue engineering and organs-on-a-chip, as well as successful cryopreservation of more and larger human tissue, tissue systems, and organ types, will allow more in-depth longitudinal studies to be done on human tissues, increasing productivity per sample while reducing dependence on often less representative/predictive animal models. This should also cut out costs, set-up time-lags, etc.

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PROCESS

The development process for the Beta Roadmap for Banking and Bioengineering has been jointly coordinated by New Organ, the Organ Preservation Alliance, and an Organizing Committee of leading scientists and institutional leaders.

In order to identify and gather relevant expertise in the fields of organ bioengineering and organ banking, from both public and private sectors, the coordinators conducted literature reviews, interviewed dozens of stakeholders, and drafted an Alpha Roadmap Report outlining the challenges and milestones towards addressing organ disease and injury. This Alpha Roadmap Report served as the basis for the "**Building a Roadmap for Organ Disease**" workshop held in Washington, D.C. on May 27th, 2015. The following day, May 28th, 2015, the White House gathered the workshop participants for a Roundtable entitled the "**White House Meeting on Regenerative Medicine**" focused on organ banking and bioengineering. Following these two events, the coordinators synthesized the results from the discussions, conducted follow-up interviews, meetings and research, and created this Beta Roadmap Report.

The Roadmap Workshop and the White House Roundtable were attended by more than 70 participants from both public and private sectors across government agencies, leading academic institutions, industry and stakeholder organizations.

In addition to the detailed information that the coordinators gathered, these roadmap documents have also been built upon **recent groundswells of activity** charged with spurring American innovation, including the White House Office of Science and Technology Policy (OSTP), the DoD, several of the National Institutes of Health (NIH), and the Biomedical Advanced Research and Development Authority (BARDA). These recent developments include:

- An inter-agency meeting, "**Using Incentivized Innovation to Advance Tissue Engineering**," hosted in Washington, D.C. by the DHHS on July 29, 2014. Participants included representatives from HHS, NIH, NSF, OSTP, BARDA, GSA, the Harvard Stem Cell Institute, Massachusetts General Hospital, the National Institute of Standards and Technology, the Alliance for Regenerative Medicine, New Organ, the Institite of Competition Sciences, the Organ Preservation Alliance, and the Methuselah Foundation.

- Three new **multi-million dollar federal SBIR grant programs** issued by the DoD as part of its Tissue Injury and Regenerative Medicine program on January 15, 2015, all focused on organ and tissue banking R&D. Aimed at supporting U.S. commercialization of science while achieving both military and civilian health goals, these business innovation programs together will fund research for many leading American research teams.

- The first global **Organ Banking Summit** held from February 26-28, 2015 at Stanford University (and with sessions at Lawrence Berkeley National Lab and NASA Research Park in Moffett Field, CA). This summit brought together world leading scientists in regenerative medicine, cryobiology, and transplantation with representatives from biotech, venture capital, and organ procurement organizations to explore scientific paths toward organ and tissue banking.

- An RFI launched by NASA in May 2015 to explore the development of a **Tissue Engineering Prize** that would benefit both NASA and the national health care industry. This is the first time NASA's Centennial Challenges program has explored how tissue engineering and regenerative medicine could benefit the future of space exploration. According to NASA, this program "would challenge competitors to create a thick tissue construct with cells performing functions of one of the four major solid organs (heart, lung, liver, kidney) and remaining alive long enough to advance scientific research capabilities."

COORDINATORS

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Dr. Erik J. Woods
President of the Society for Cryobiology and Senior VP and Lead Scientist at Cook Regentec.

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COORDINATING ORGANIZATIONS

New Organ is a collaborative philanthropic initiative tackling organ scarcity and injury through challenge prizes and partnerships that advance specific targets in tissue and organ regeneration, bioengineering, and preservation. New Organ is underwritten by the Methuselah Foundation and managed by the Institute of Competition Sciences.

To advance breakthroughs in bioengineering, banking and regeneration, we have established the New Organ Alliance, a growing group of leaders with overlapping interests and missions. The purpose of the New Organ Alliance is to better leverage resources and further shared goals. The Alliance includes TERMIS, the Harvard Stem Cell Institute, the Organ Preservation Alliance, Organovo, and 30 individual scientific advisors.

In addition to building the Alliance, New Organ creates and launches incentive prizes that spur innovation in organ regeneration, bioengineering, and preservation. This year, New Organ (via its sponsor, the Methuselah Foundation) entered into an MOU with NASA to develop rules for a potential NASA tissue engineering challenge focused on thick tissue vascularization. In 2013, New Organ launched the inaugural New Organ Liver Prize at the 2013 World Stem Cell Summit with $1 million in initial funding from the Methuselah Foundation. To date, 10 labs have committed to pursue this challenge.

ORGAN PRESERVATION ALLIANCE

The **Organ Preservation Alliance** is a non-profit incubated at SU Labs at NASA Research Park in Silicon Valley, which is working to catalyze breakthroughs on the remaining obstacles towards the long-term storage of organs by building on recent advances in cryobiology and relevant fields.

These breakthroughs will save and enrich the lives of millions; they will also accelerate progress towards breakthroughs in organ tissue engineering. Innovation in these technologies will enable cryobanked, tissue-engineered organs to be available off-the-shelf and on-demand, eventually revolutionizing human health.

In February of 2015, we convened leading scientists and transplant surgeons from around the world to the first global Organ Banking Summit at Stanford (and with sessions at the Lawrence Berkley National Lab and at SU Labs at NASA Research Park). The next Organ Banking Summit will be held in June 2016 at Harvard and other venues in Cambridge and Boston, MA.

The Organ Preservation Alliance is a Founding Partner of New Organ.

SOURCES

The following list includes all sources that have been used in defining the scientific challenges, milestones, and metrics for these Beta Roadmaps on Organ Bioengineering and Organ Banking. Much of this information has been derived from live interviews with experts and organizational leaders, in concert with background material from published research.

INTERVIEWS

The following stakeholders were interviewed by New Organ and the Organ Preservation Alliance:

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President
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OTHER KEY SOURCES

- 22 conference calls, meetings and/or lab visits conducted by the Organ Preservation Alliance and Lt. Col. Luis Alvarez from June to September 2014 when drafting a NextGenCryo proposal for DARPA.
- 19 conferences calls and/or meetings conducted by the Organ Preservation Alliance when putting together an alpha concept for an Organ Banking Grand Challenge Prize.
- 30 Scientific Advisors interviewed by the New Organ team in development of the Liver Prize, Kidney Prize, and Vascular Prize rules.

LITERATURE REVIEWED

- 2020: A New Vision – A Future for Regenerative Medicine
- 3D Bioprinting of Vascularized, Heterogeneous Cell-Laden Tissue Constructs
- ARM National Strategy White Paper
- ARM Challenging Regeneration to Transform Medicine White Paper
- Challenge Regeneration to Transform Medicine (Confidential)
- Compendium of Organ and Tissue Banking Concepts
- Engineered Whole Organs and Complex Tissues
- Human Organ Project Presentation
- MATES: Advancing Tissue Science and Strategic Report
- MATES Strategic Plan Primer, Prepared by Rosemarie Hunziker (Director, Tissue Engineering and Regnerative Medicine, National Institute of Biomedical Imaging and Bioengineering (NIBIB)
- Perspectives on Whole-Organ Assembly
- Mayo Clinic Regenerative Medicine Primer
- Nanotechnology: Emerging Tools for Biology and Medicine
- Potential of the Combination of CRISPR/Cas9 and PSCs to Provide Human Organs from Chimaeric Pigs
- Regenerative Medicine Applications in Organ Transplantation
- Revisiting the Flight of Icarus: Making Human Organs from PSCs with Large Animal Chimeras
- Solving Organ Shortage Infographic
- Vascularized and Complex Organ Buds from Diverse Tissues via Mesenchymal Cell-Driven Condensation
- Whole-Organ Bioengineering: Current Tales of Modern Alchemy
- Will Regenerative Medicine Replace Transplantation?
- The Xi'an Papers

ROADMAPS

ORGAN BANKING ROADMAPS

INTRODUCTION: THE CHALLENGE AND PROMISE OF ORGAN BANKING

The landscape of tissue preservation science is rapidly shifting, and many recent developments indicate that significant breakthroughs in the cryopreservation of complex tissues may be possible within the next 5 years. The consensus among the world experts surveyed is that with high levels of collaboration within the scientific community and adequate institutional support, **it should be possible to bank whole human organs and other complex tissues within a decade.**

HUGE NEED AND VALUE. Organ transplantation has seen miraculous advances over the last 50 years, but the vast and growing shortage of donor organs limits patients' access to these lifesaving treatments. Patients who are fortunate enough to receive a transplant face a lifelong battle with immune rejection of the transplanted organ. Technologies to preserve donor organs and other complex tissues during transplantation can impact these problems in many ways, with **the potential to transform organ transplantation and many other areas of public health**.

WHAT IF ORGANS COULD BE RELIABLY PRESERVED?

Advances in complex tissue preservation can impact organ transplantation by allowing for increasing donor utilization, limiting organ discard, allowing for matching for more organs and across large regions (ideally globally), reducing costs such as the short-notice plane and helicopter transportation often currently needed to arrange transplants within short preservation windows, making possible new immune tolerance induction therapies, enabling techniques for organ rehabilitation and conditioning for transplantation, reducing health disparities, and more.

The **benefits of banking organs and other complex tissues also extend far beyond organ transplantation**, affecting many broad areas of public health. As is clear from the strategic plan of the Multi-Agency Tissue Engineering Science (MATES) Interagency Working Group (see http://tissueengineering.gov), preservation and banking is a key bottleneck in bioengineering and is needed to enable a shelf-life for logistics, inventory, on-demand access and quality control. This was re-iterated by the Chair of MATES, Dr Richard McFarland, at the White House Roundtable on May 28, 2015. Banked tissues can be stockpiled for national emergencies, military conflicts, and mass casualty events. Complex tissue preservation could greatly enhance the success of limb salvage, improve research and drug discovery, reduce the reliance on use of animals in scientific experiments, and protect the fertility of patients undergoing chemo and radiation therapy.

Descriptions of the public health benefits are provided in the appendix "*Organ and Complex Tissue Preservation: The Need and Value*" provided at the end of this roadmap.

ORGAN BANKING APPEARS TO BE WITHIN REACH

Nature has already overcome many key organ banking challenges, with many species able to survive long periods of time in a state of hibernation or even suspended animation. During these periods the entire animal, including every single organ, is "banked" through depressed metabolism and at depressed temperature - without injury to any of the vital organs upon rewarming and revival. Our understanding of these mechanisms (that to a large extent are conserved across species) has radically increased over the last 5-10 years.

Clinically, stem cells, sperm, and embryos have been banked for decades through cryopreservation, and progress in cryobiology has also made it possible to bank arteries, heart valves, corneas, organ slices and more. We have **seen progress in the preservation of whole animal organs, including rat hearts, pig livers, sheep ovaries, pig uteri, rodent limbs, and the cryopreservation and successful transplantation of a rabbit kidney.** [1]

Building on these successes to make organ banking routine medicine is still a large challenge. To discuss how to overcome it, **leading scientists from around the world convened at the first global Organ Banking Summit** in Palo Alto, CA (with events at Stanford University, NASA Research Park and Lawrence Berkeley National Lab) in February 2015. The consensus of the Organ Banking Summit was that this grand challenge can be broken into six remaining sub-challenges. Because of the body's own regenerative capabilities, total tissue stress during preservation and banking need only to be kept under threshold levels to allow for survival and healthy function post-thaw. Thus none of the six remaining sub-challenges represent an absolute barrier to organ banking. Progress on any sub-challenge reduces tissue injury, in turn reducing the burden to make breakthroughs on other challenges. Moreover, progress in many of these subchallenges is interconnected, with advances in one challenge providing valuable understanding that can lead to breakthroughs in the others.

As never before, valuable knowledge and tools in surrounding (and often radically accelerating) areas of science, technology and innovation can empower researchers to make breakthroughs on the six subchallenges.

At the same time, there are several key bottlenecks limiting progress in this field. These include need for steady, multi-center research funding focused on long-term goals and applications, the incorporation of more high-risk high-reward research projects into the funding portfolio, improved coordination between funding organizations and among other stakeholders in complex tissue banking research, and vibrant involvement from industry and venture investment to realize the tremendous long-term market potential of organ and complex tissue banking.

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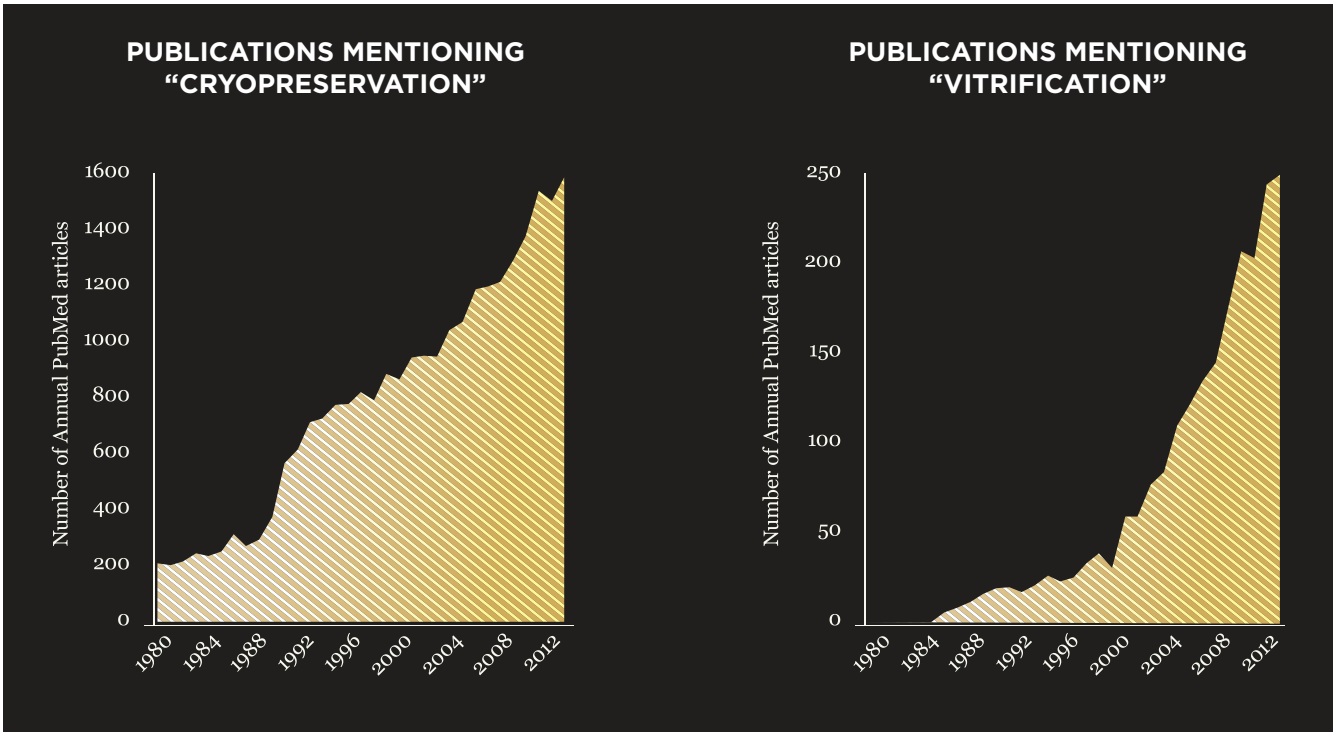
[1] Gavish, Z., et al,. 2008. "Cryopreservation of whole murine and porcine livers", Rejuvenation Res, 11, 765-72, Armitage WJ, Pegg DE., "The contribution of the cryoprotectant to total injury in rabbit hearts frozen with ethylene glycol", Cryobiology. 1979, G. Amir et al., "Improved viability and reduced apoptosis in sub-zero 21-hour preservation of transplanted rat hearts using anti-freeze proteins," J Heart Lung Transplant, 24:1915-29, 2005., G. Fahy et al, "Physical and biological aspects of renal vitrification ", Organogenesis. 2009 Jul-Sep; 5(3): 167–175 and Xu H, et al, "An experimental research on cryopreserving rabbit trachea by vitrification", Cryobiology. 2009, Arav A., et. al, Oocyte recovery, embryo development and ovarian function after cryopreservation and transplantation of whole sheep ovary.Hum Reprod. 2005 Dec;20(12):3554-9. Epub 2005 Sep 20.

ORGAN PRESERVATION AND BANKING CHALLENGES

While from a small base, there has been significant progress in this field as discussed in the section above and the rate of increase in understanding is in some ways exponential:



Traditionally used to bank cells, the field of cryopreservation has seen accelerating growth recently - both in the study of cryopreservation itself and its use for research and medicine. Along with many recent advances in tissue banking, this growth can be harnessed to lead to powerful organ banking breakthroughs. Biological systems can be stored at extreme low temperatures (i.e. -196ºC) with no significant tissue degradation over periods of months or years, as significant molecular motion is arrested and insufficient internal energy exists for chemical reactions. To cryopreserve a tissue is effectively to stop biological time.

Biological systems can be stored at low temperatures with no significant tissue degradation over periods of months or years, as significant molecular motion is arrested and insufficient internal energy exists for chemical reactions. To cryopreserve a tissue is effectively to control biological time.

The challenge of cryopreservation stems from injury occurring as tissues traverse the temperature ranges between body temperature and storage temperatures during the cooling and rewarming process. One of the primary sources of injury is ice crystal formation, which damages cell membranes and other structures. Ice formation can be controlled, mitigated or prevented by controlling cooling and rewarming conditions and by addition of cryoprotectants. Cryo-injury can also occur as a result of direct "chilling injury" to tissue and cellular structures, mechanical and thermodynamic stress caused by uneven heat transfer throughout the tissue, and toxicity of the added cryoprotectants. Ischemia during the cryopreservation process also contributes to organ injury.

In recent years, significant progress has been made in understanding these sources of injury and devising strategies to prevent them. Moreover, new paradigms have emerged involving the conditioning of tissues to resist cryo-injury, largely inspired by studies of vertebrates that tolerate sub-freezing temperatures with no harmful effects.

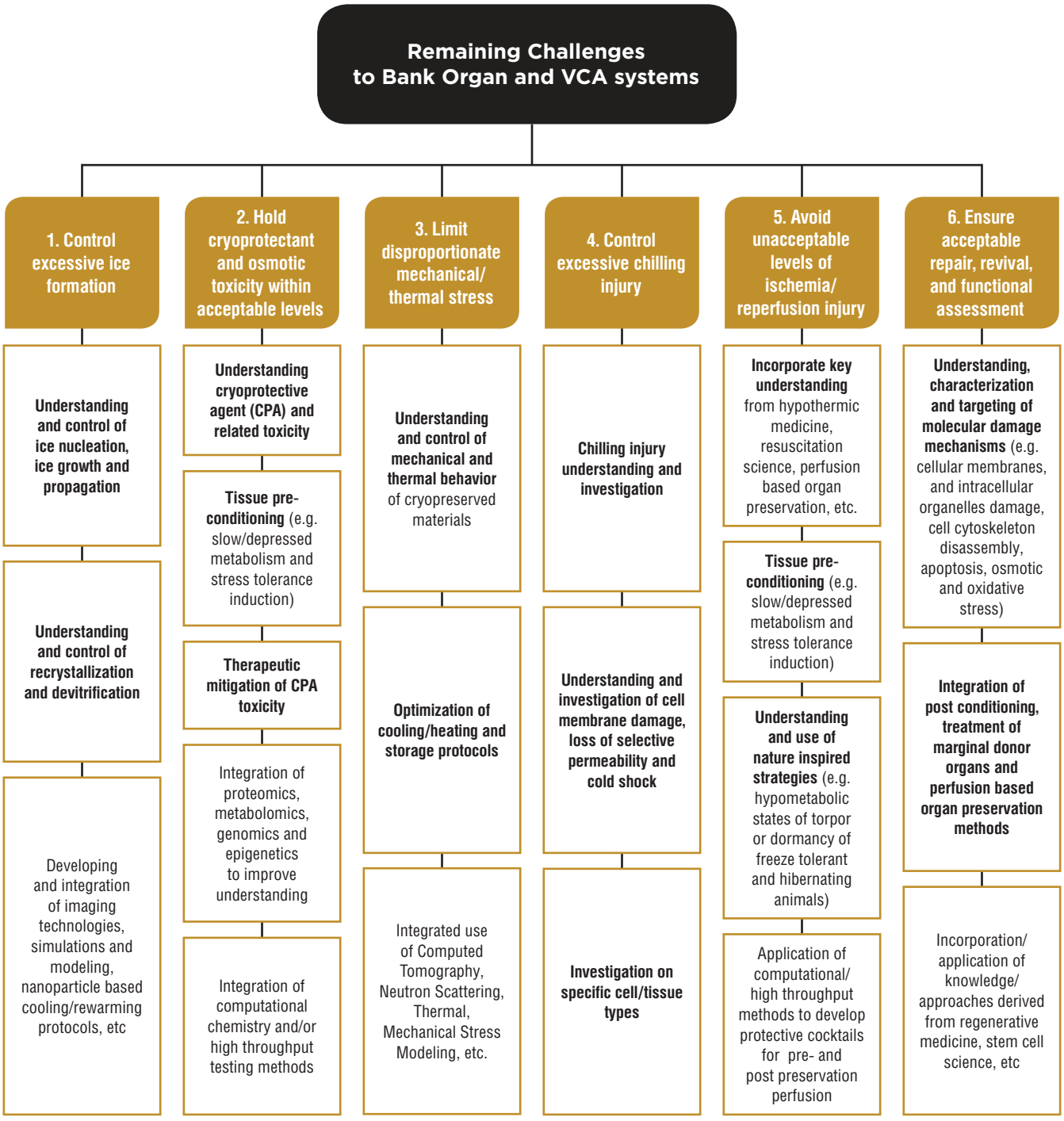
ORGAN BANKING ROADMAPS

The challenge of complex tissue and organ banking can be divided into six tractable sub-challenges:

1. Control excessive ice formation
2. Above threshold level of cryoprotectant and/or osmotic toxicity
3. Limit disproportionate mechanical/thermodynamic stress
4. Control excessive chilling injury
5. Avoid unacceptable levels of ischemic injury
6. Develop methods for revival, repair, and functional assessment

Because aggregate tissue injury needs "only" to be kept to acceptable minimum levels to ensure post-storage health of tissues, many combinations of advances on the different sub-challenges may ultimately enable organ banking. Numerous opportunities exist for large breakthroughs that can enable organ banking, but small incremental advances in several of these areas may also be sufficient to minimize cryo-injury to acc banking, but instead constitute interdependent, and sometimes synergistic, areas of opportunity to limit organ injury and enable organ cryopreservation. eptable levels. Thus the sub-challenges do not represent necessary conditions for the realization of organ banking, but instead constitute interdependent, and sometimes synergistic, areas of opportunity to limit organ injury and enable organ cryopreservation.

ORGAN BANKING ROADMAPS



Please also see appendix 6 for a more in depth discussion of *Individual Organ & Tissue Systems – Progress, Challenges and Key Questions.*

TOOLS TO ADDRESS THE SIX SUB-CHALLENGES: INTEGRATING NEW TECHNOLOGIES AND APPROACHES

Researchers pursuing low-temperature preservation strategies have made significant progress on each of the six sub-challenges, but the historical fragmentation of expertise and scarcity of resources in the field have prevented the integration of tools, technologies, and knowledge gained in outside fields.

The large gap between decades-old, simple, and widely effective "one-size-fits-all" cellular cryopreservation methods and the multi-faceted, cross-disciplinary research needed to achieve complex tissue cryopreservation has left much of cryobiology in a scientific "no man's land." Compared with other fields (and since the early cryopreservation breakthroughs decades ago), there have been few opportunities for incremental advances that carry immediate high-impact applications or broad scientific interest. As a result, many other fields and approaches that are highly applicable to cryobiology have advanced around it, and they have yet to be integrated into the study of cryopreservation to a meaningful extent.

This knowledge surplus in surrounding fields presents unique opportunities for organ banking research. **An impressive array of state-of-the-art technologies, scientific know-how, tools and talent from outside fields now exist that may be leveraged to solve organ banking challenges**. Similarly, many innovative techniques show promise or have achieved experimental success, but their wider application depends on increased support for cryopreservation research. Some of these are listed below:

UNDERUTILIZED APPROACH	EXAMPLES OF APPLICATIONS
Broad, Revolutionary Approaches	
1. Systems biology ("omics" technologies)	Combine "-omics" approaches (proteomics, metabolomics, etc.) to characterize injury, cryoprotectant toxicity, and cellular responses that can be harnessed for cryotolerance
2. Bioengineered 3-D tissue models and organ-on-a-chip devices	To study effects of cooling, rewarming, perfusion, cryoprotectant toxicity, etc. while manipulating spatial and organizational aspects of tissues
3. High Throughput Screening Platforms	High throughput chemical screens have yet to be utilized to find effective, non-toxic compounds with cryoprotective properties; genetic screens for cryotolerance pathways
4. Computational Modeling	Modeling of ice crystal growth, heat transfer, cryoprotectant diffusion, etc.
5. Nanotechnology	Use of nanoparticles to heat tissues uniformly via radiofrequency microwaves, nanoparticle delivery of cryoprotectants
6. Imaging technologies	A diverse array of imaging technologies may be widely utilized to investigate cryoprotectant perfusion, ice crystal growth, cryoinjury lesions, and many other topics

ORGAN BANKING ROADMAPS

Research Fields

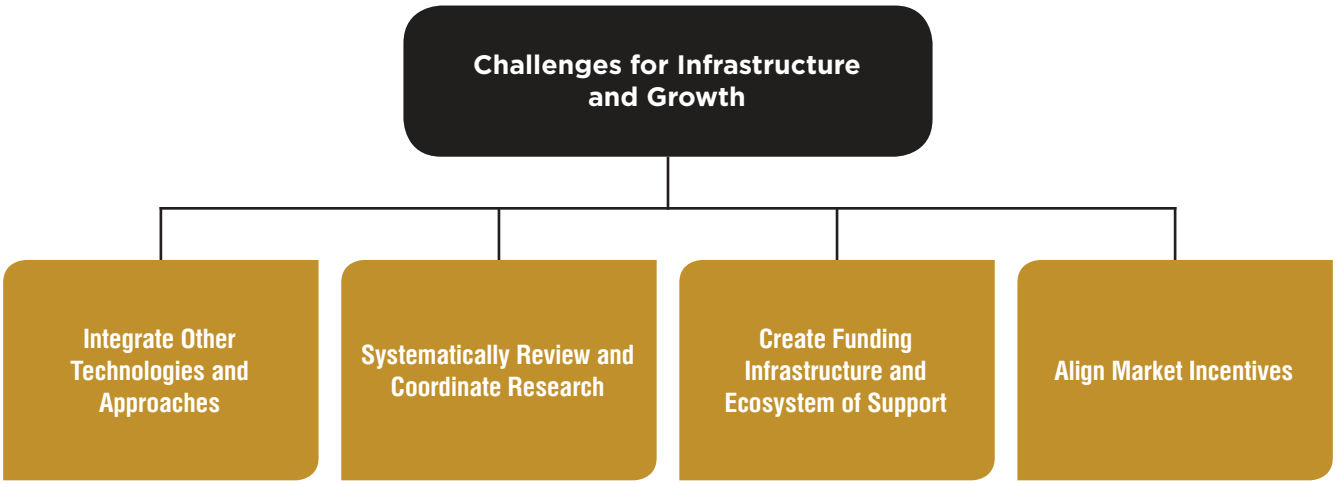
7. Cellular Injury and Cell Death	Direct intervention in injury mechanisms via conditioning, repair, and blocking apoptotic cell death; knowledge from many fields, i.e. Cancer biology, biogerontology, toxicology
8. Cellular Stress Responses	Cellular responses to protein denaturation, damage to outer membranes, organelles, and cytoskeletal structures, oxidative stress, hypoxia, metabolic dysregulation, etc.
9. Tissue Organization	Effects of extracellular ice formation on ecm; osmosis and ionic solution effects on cell junctions and tissue deformation
10. Metabolism	Programmed metabolic depression is a key aspect of cryotolerance in nature, and many widely conserved mechanisms have been uncovered. Yet little investigation of metabolic dysregulation as an injury mechanism and therapeutic target
11. Thermodynamics	To understand and model the effects of temperature changes on biological systems
12. Modern Organic and Synthetic Chemistry	Greatly needed for development of next-generation cryoprotectants to limit cryoinjury without toxic side-effects
13. Cryoenzymology	To study the effect of extreme low temperatures on enzyme-catalyzed reactions in order to understand how cellular pathway regulation is affected by cryopreservation

Innovative Techniques

14. Normo-, sub-normo- and hypothermic Perfusion Technologies	Allow for pre- and post-conditioning of tissues for long-term storage, as well as pre-transplantation repair and evaluation
15. Hypothermic surgery	Hypothermia and hypometabolic treatments to induce suspended animation, preconditioning for cold storage
16. Hyperbaric and Isochoric Systems	Pressure manipulation to avoid or limit ice growth and limit thermal and mechanical stress
17. Gas Persufflation	Rapid cooling by venous persufflation with helium or other gases
18. Electro-Magnetic and Microwave Radiofrequency	Uniform penetration of tissues with high temperature conductance conductance, enabling rapid, uniform rewarming (ice growth is a larger risk during re-warming than during cooling)
19. Liquidous Tracking	Temporal control of cryoprotectant delivery to minimize cryoprotectant toxicity across all temperature ranges
20. Wireless Micro- and Nano-Sensors	Widely applicable, for real-time readouts of multiple tissue parameters during cryopreservation

CHALLENGES FOR INFRASTRUCTURE AND GROWTH

Almost all scientists that were interviewed stressed how the historical "orphan, neglected and under-supported" nature of organ preservation means that, **today in 2015, "institutional" challenges are at least as significant road blocks/rate limiters as the actual remaining scientific challenges**. Many mentioned how the size of the list of institutional challenges can actually be seen as a positive and is partially why they are optimistic about future progress in organ banking: Each of these historical challenges is also a future opportunity. Several scientists stated that it may in fact be the case that the ability to facilitate, support and accelerate scientific and technological breakthroughs in this historically under-focused area is significantly larger than in many/most other areas of medical need.



1. INTEGRATE RESEARCH AND TECHNOLOGIES

- Much of the needed expertise exists across individual labs, but multi-center collaborative efforts that bring together those different pieces are required.
- Field is still highly fragmented, "orphan" and "almost forgotten and neglected." But the response to this year's Department of Defense calls for SBIR applications on complex tissue and organ banking[2], as well as by the strong presence of top researchers at the first global Organ Banking Summit, suggest that there exists a significant pool of talent with an untapped supply of promising ideas, research approaches and early experimental results that could lead to the needed breakthroughs.
- Lack of collaboration with and by transplant surgeons and others clinicians, as well as with organ procurement organizations and hospital systems.
- Much valuable knowledge, understanding and tools now exist in domains outside of cryobiology that could help solve remaining problems - mechanisms to bring in such expertise and tools via interdisciplinary collaboration and integration are needed.
- Investigational focus tends to be on physical stabilization and modeling (ice control), with little incorporation of modern molecular biology techniques to study cellular and molecular responses to cryopreservation.
- Insufficient focus on true system viability and function. Assessment endpoints and definitions of success are restricted to immediately post thaw vs. longer term; more precise methods employed in transplantation as well as tissue engineering fields may be adapted to evaluate cryopreservation outcomes.
- Lack of development of and/or incorporation from other fields of needed platform technologies (scanning, screening, modeling and other tools).

[2] ~~According to Lt Col Alvarez, the Program Manager for 2015 DoD~~ Tissue and Organ Banking SBIRs, the number and strength of proposing teams for the three DoD Tissue and Organ banking SBIR calls was almost unprecedented - with many extremely strong multi-lab teams forming, including from Harvard/MIT, Stanford and Lawrence Berkeley National Labs.

2. REVIEW AND COORDINATE RESEARCH

- Organ and complex tissue banking impacts critical goals of many federal funding agencies (numerous NIH institutes, Department of Defense, BARDA/Project Bioshield, NASA, Veterans Affairs), but its benefits are spread out over many applications and do not fall squarely within the purview of a single agency. A study is needed to identify overlapping areas of interest in organ banking research among these organizations, including direct and indirect shared benefits and spillover effects.

- The widespread applications and cross-disciplinary nature of organ and complex tissue banking may make it poorly suited for institutional support through traditional channels. A study is needed to identify potential sources of funding gaps in organ banking research and propose solutions.

- Similarly, the impact of organ preservation on critical goals of multiple federal agencies, necessitates interagency initiatives in organ and tissue preservation (interagency workshops, joint reviews, joint grant efforts, etc.).

- There is a general lack of understanding of the full impact of organ banking on transplantation and trauma medicine. Studies are needed to understand the effects of banking of specific diseases and for specific purposes, in order to prioritize research objectives

- Likewise, studies are needed to gain a detailed understanding of organ and tissue banking for tissue engineering industries, in order to identify critical near-term supply chain bottlenecks and prioritize research objectives accordingly

- There is also a need to gain a comprehensive understanding of recent progress in organ banking, myriad unexplored potential solutions to each of the sub-challenges, and the resources and technical knowledge within cryobiology and, importantly, surrounding domains that have not yet been applied to solving these challenges.

- The field lacks a complete inventory of challenges, clear milestones, and a roadmap and priorities. This workshop and roadmapping process and the beta roadmap are excellent first steps, additional in-depth investigation is needed by the National Institutes of Health and other agencies.

- The field would benefit greatly from coordination and standardization of model systems. The society for Cryobiology could form a working group to identify the most productive models for organ banking research, and such standardization can then be incorporated into future organ banking efforts.

- Regular scientific conferences, workshops and gatherings are needed focusing on complex tissue cryopreservation and other organ preservation topics. Follow-up global Organ Banking Summits have been requested by many scientists, and the second summit is scheduled for June 2016 at Harvard and other locations in Cambridge and Boston, in conjunction to the Transplant Congress.

3. FUNDING AND ECOSYSTEM OF SUPPORT

- While organ and complex tissue banking impacts critical goals of multiple NIH institutes (NIDDK (kidney, liver, bioengineered tissues), NHLBI (heart, lung, bioengineered tissues), NIBIB, NCI (ovaries/testes for onco-fertility, all types of tissue for cancer treatment testing/research, and others), this field does not fall directly within the responsibility of any one institute. Many researchers have expressed the view that the field lacks focused initiatives and collaborative, longer-term term grants from the NIH.

- Likewise NSF, BARDA, NASA and the Department of Defense have critical goals that organ and tissue banking can help meet.

- The field lacks large-scale research projects with long-term objectives. Cryopreservation research mostly done in "bits and pieces," on small budgets, over short time frames, and primarily with immediate applications in mind. No cooperative NIH grants, no single institution, no research network, nor any consortia exist that coordinate multi-center, long-term research projects.

- Preservation capabilities should be explicitly stated as a preferred component of bioengineered tissues in federal grant calls. A powerful way to enable preservation of an engineered construct is to design it to be "preservation-friendly."

- There is a need for further clarification by the Food and Drug Administration as to how new organ and tissue banking solutions will be treated.

- The enormous public health impact of organ banking means that if improvements in the research funding infrastructure and scientific ecosystem accelerate organ banking efforts by even a few months, a huge number of lives may be saved. This increases the need for high-risk, high-reward research and for multi-center cooperation on research projects. A large, coordinated research program by one agency could serve as a scaffold around which further research efforts may be organized.

4. ALIGN MARKET INCENTIVES

While studies providing detailed estimates of the market potential of organ banking are needed, preliminary research makes it clear that the aggregate value of complex tissue and organ preservation applications are vast.

Yet the field suffers from:

- A lack of corporate/industry involvement
- Scarcity of venture capital and other early stage investment funding
- Limited coordination between academic and industry researchers. The field would benefit greatly from workshops and conferences that highlight basic cryobiology research advances in biology, engineering, and other disciplines but with a product-driven focus that facilitates the identification of translational research opportunities.
- Little collaboration and integration with tissue engineering research, despite that tissue engineering creates arguably the largest emerging needs for complex tissue preservation. Bioengineered tissue constructs often face problems of preservation and storage that may be avoided if a knowledge base can be established for the engineering of cryotolerant tissues.

ORGAN BANKING ROADMAPS

ORGAN BANKING MILESTONES:

NEAR TERM (0-3 YEARS)

The consensus among scientists at the workshop, as well as dozens of tissue preservation experts surveyed, is that a highly focused research program could achieve banking of human organs within 8-10 years.

Below we have synthesized the key suggestions and recommendations from scientific experts for **near-term (next 0-3 years)** milestones towards this goal, along with examples and metrics for progress. These examples are not exhaustive, and more detail can be obtained by contacting the Organ Preservation Alliance.

Goal/Milestone	*Example Sub-Objectives and Metrics*
1 Adapt important **platform technologies**	Combined use of "**-omics" technologies** to characterize response to cryoinjury Develop/adapt **perfusion platforms** for pre- and post-conditioning **High throughput screening** platforms for cryoprotectants
2. **Translational research** on vast array of targets already provided by basic research	Use of **hyperbaric and isochoric systems** to limit ice growth and thermal/mechanical stress Apply **solutions from nature**, i.e. metabolic depression and stress preconditioning **Liquidous tracking** to calibrate cryoprotectant release and minimize toxicity
3. Further develop prototypes to control **heat transfer, ice nucleation, and devitrification** during cooling/rewarming	**Nanoparticle approaches** for rapid, uniform heat transfer Use of **radio-frequency waves** for heat generation **Gas persufflation** systems to accelerate cooling
4. Integrate advances to enable better **simple tissue cryopreservation** and stepping stones towards more complex systems	Viable, functional cryopreserved **skin** for transplantation Viable, functional cryopreserved **blood vessels** for transplantation Viable, functional cryopreserved **muscle flaps** for transplantation
5. **Improved, non-toxic cryoprotectants** to increase effectiveness/reduce complications from **bone marrow and stem cell therapies**	Bone marrow transplants for leukemias, blood disorders, many other diseases Hematopoietic stem cell transplants for leukemias, immune disorders, etc. Mesenchymal stem cell transplants for tissue injury, immune disorders, etc.

MID-TERM (3-6 YEARS)

The consensus among scientists at the workshop, as well as dozens of tissue preservation experts surveyed, is that a highly focused research program could achieve banking of human organs within 8-10 years.

Below we have synthesized the most prominent suggestions and recommendations from scientific experts for **mid-term (next 3-6 years)** milestones towards this goal, along with examples and metrics for progress. These examples are not exhaustive, and more detail can be obtained by contacting the Organ Preservation Alliance:

Goal/Milestone	*Example Sub-Objectives and Metrics*
1. Continue pursuing leads from **platform technologies, translational research,** and prototype systems developed in years 1-3	Outline cryoinjury response pathways, pursue **novel preconditioning targets** Optimize promising **heat transfer systems** (i.e. nanoparticles, persufflation) Optimize promising **cryoprotectant delivery systems**
2. Extended preservation of **small mammalian organs** with post-thaw functionality	Increase preservation times of small mammalian vital organs several-fold Successful vitrification of small mammalian vital organs Development of gold-standard cryopreservation methods, while continuing optimization and additional research on cryoinjury sources and solutions
3. Extended preservation of **human-composite tissues** with post-thaw functionality	**Cryopreservation** for banking and transplantation of **human faces** **Extend limb preservation times** several-fold (supercooling, metabolic conditioning)
4. Enable banking of **whole human ovaries and testes**	Gonad removal and reimplantation to **protect endoncrine function and fertility during radiation and/or chemotherapy – demonstrated in sheep ovaries already with healthy babies**
5. Enable **short-term banking of human sized organs** and bioengineered tissues at high subzero temperatures (-10/20C to -80C)	Storage of **transplantable human sized hearts, livers, and other organs for 1 month to 2 years**
6. Establish **next-generation skin banks** for burn and wound treatment with viable banked skin	Stockpiling of viable skin for burn treatment in **mass casualty events** Banking of **cryopreserved donor skin** comparably healthy to fresh skin grafts Banking of viable, functional **skin substitutes**
7. **Optimize prototype systems** for rapid, uniform cooling and rewarming	Increase **uniform heat transfer** during cooling by a factor of 4-fold or greater Continued development of **rewarming units** that eliminates variability in rewarming outcomes Optimize perfusion technology for pre- and post-conditioning and organ assessment
8. **Develop cryopreservation strategy** forhuman organs and large tissues	Preliminary protocols for transplantable human limb cryopreservation Preliminary protocols for transplantable human vital organ cryopreservation

LONG TERM (6-10 YEARS)

The consensus among scientists at the workshop, as well as dozens of tissue preservation experts surveyed, is that a highly focused research program could achieve banking of human organs within 8-10 years.

Below we have synthesized the most prominent suggestions and recommendations from scientific experts for **Long Term (within 6-10 years)** milestones towards this goal, along with examples and metrics for progress. These examples are not exhaustive, and more detail can be obtained by contacting the Organ Preservation Alliance:

Goal/Milestone	*Example Sub-Objectives and Metrics*
1. Cryopreserve organs and limbs from **large mammals** (including humanized porcine organs)	Reliably vitrify **large mammalian vital organs** with healthy pre-transplant functionality Vitrify **humanized pig hearts** with healthy post-thaw pre-transplant functionality
2. Development of next generation **bioengineered tissues with enhanced preservation capabilities**	Cryotolerant bioengineered skin, blood vessels, etc. for **on-demand injury treatment** The **first bioengineered experimental vital organs incorporate cryotolerance modifications** Target well-established cryotolerance pathways, i.e. heat shock response
3. **Last development phase** of human organ cryopreservation protocols and devices with pre-transplant functional evaluation	Improved, cost-effective **cooling/rewarming devices and protocols** Improved, cost-effective **perfusion devices and protocols** Devices and protocols for rapid post-thaw**, pre-transplant organ assessment**
4. **Successful clinical cryopreservation of human organs and limbs for transplantation**	First successful transplantation of banked **human kidney** First successful transplantation of banked **human heart** First successful transplantation of banked **human liver** First successful transplantation of cryopreserved **human limb**

CONCLUSIONS:

MEETING THE CHALLENGE OF ORGAN BANKING

The emerging consensus among leading scientists is that in the past decade breakthroughs in cryopreservation, along with revolutions in related fields, have brought the goal of banking human organs within reach. **With the right focus and support the world could achieve organ banking within the next 8-10 years.**

Achieving this goal will require focused institutional support as well as high levels of coordination within the scientific community. Organ and complex tissue banking is an exceptionally interdisciplinary undertaking. Even incremental progress often requires the integration of expertise in cell biology, mechanical engineering, physical chemistry, structural biology, thermodynamics, materials science, and many other fields. **Because of the scope and complexity of this challenge, it cannot be accomplished efficiently through research focused only on immediate and near-term applications.**

With a detailed scientific vision and focused research program, what would otherwise take decades may be accomplished in years. This workshop and resulting roadmap are a major step in the development of that vision.

Organ banking may be achieved **by building on numerous proofs of concept** from the decades of cryopreserving cells, cryotolerance and metabolic stasis in nature, breakthroughs in tissue and organ cryopreservation, and currently fragmented research from a variety of disciplines applicable to the study of low-temperature biology.

Organ banking may be achieved **by leveraging technologies and research fields that have advanced rapidly** but have yet to been brought in or not yet effectively applied for organ banking solutions, such as tissue engineering, systems biology, nanotechnology, computational modeling, and high throughput chemical screening. And it will require applying a wealth of basic research knowledge in cellular injury and death, stress responses, tissue organization and metabolism that are underexplored in the context of cryopreservation.

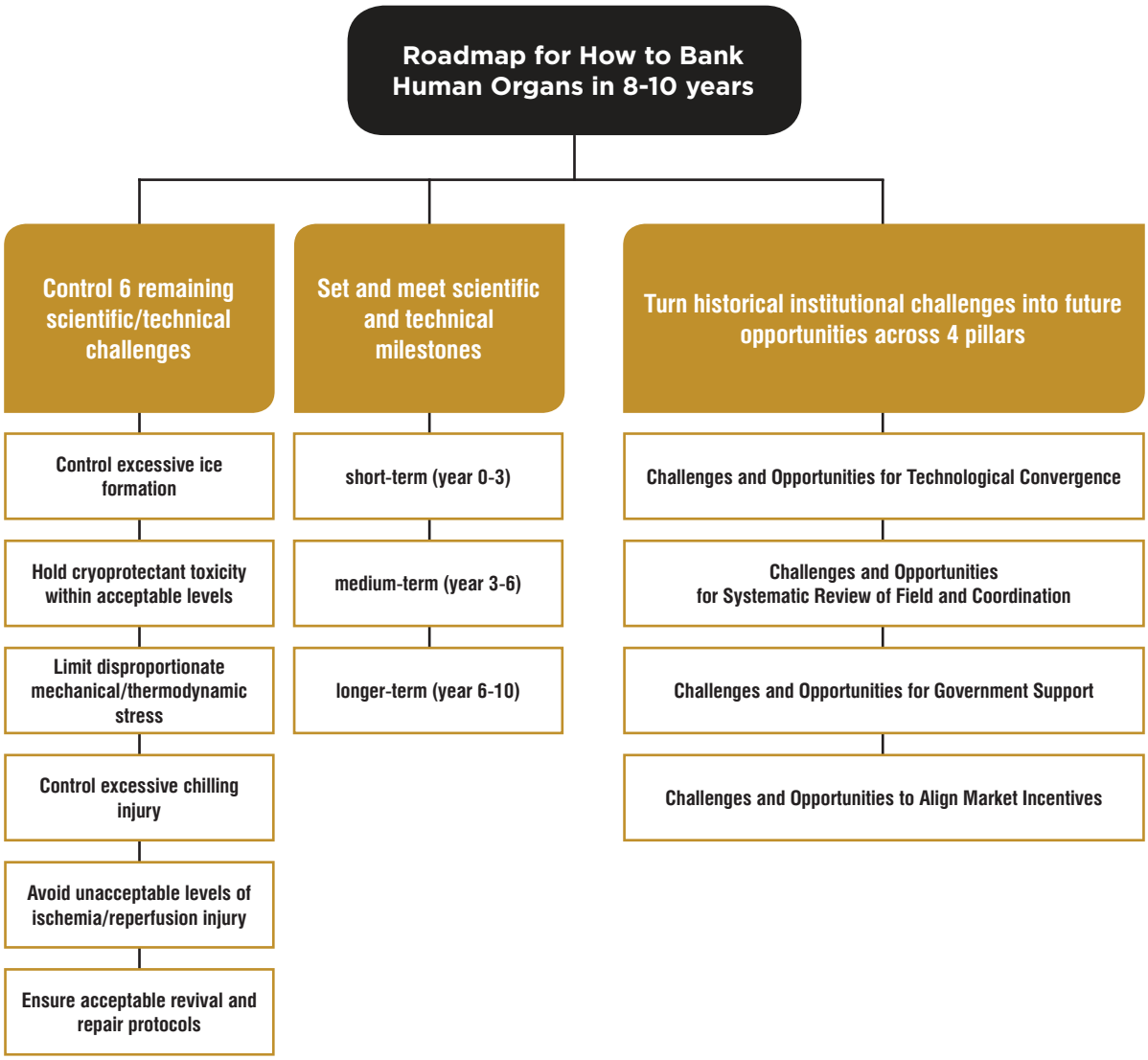
Organ banking may be achieved **by developing a scientific ecosystem and funding infrastructure** that can support the grand scientific challenge of organ banking. This includes the involvement of numerous governmental agencies whose goals are directly furthered by organ banking breakthroughs, as well as by the many spillover benefits from organ banking research. It also includes systematic review and oversight by these agencies and by leaders in the field, which can support large, multi-center collaborative efforts with the goal of organ and complex tissue banking. And includes regulatory transparency and the alignment of market incentives to promote translational research and commercialization of organ banking technologies.

Organ banking may be achieved **by conquering a handful of tractable scientific sub-challenges**, each of which draws from and benefit numerous fields outside of tissue preservation research, as well as the other sub-challenges. Because aggregate injury during tissue preservation needs only to be kept below threshold levels, these sub-challenges are not absolute barriers but instead present multiple independent opportunities to address complex tissue cryopreservation. Many combinations of advances on the different sub-challenges,

whether key breakthroughs or the aggregation of small discoveries, may ultimately enable organ banking. **Most likely there are many scientific paths to organ banking.**

If these sub-challenges are pursued in parallel, progress on organ banking may be accelerated many-fold. The historical fragmentation of expertise among scientific disciplines, the scarcity of resources in the field, the unmet need to apply cutting edge technologies and basic research advances that are highly synergistic with tissue preservation, and the lack of a unifying scientific vision have thus far slowed progress toward organ and complex tissue banking. These are institutional problems with straightforward solutions.

The tissue preservation field has already begun to organize around the goal of organ and complex tissue banking. But many challenges remain, and focused support from government and integration and collaboration with a wider scientific community is needed. With the involvement of key governmental bodies, stakeholders and the scientific community at large, we can revolutionize transplant, trauma and regenerative medicine and save millions of lives.



BIOENGINEERING ROADMAPS

BIOENGINEERING ROADMAPS INTRODUCTION

Bioengineering solutions to repair or replace organ functionality include at least four defined pathways. Pathways are an overarching solution-space to provide the required function. Each pathway has multiple high-level challenges that need to be overcome before providing a viable solution for patients. Each challenge also has many milestones to be reached along the way. In this report we are not yet identifying specific milestones to be reached in solving these challenges, but expect to provide greater definition in future iterations.

There are many ways of defining these pathways, and many more ways to articulate the specific challenges that need to be overcome along each pathway. Through research, interviews, and discussions during the NSF Roadmapping Workshop and White House Round Table, there was some general consensus about the high-level pathways and challenges, but much more discussion is required to identify all the tactical milestones to be achieved along the way.

In this section we take an overarching look at some of the possible definitions for these items, and we examine the relationship between the challenges and the pathways. We envision that additional detail and quantitative milestones leading to solutions to each challenge will be identified in future versions of this report.

It is our goal that this roadmap help better define specific areas of support and interest on the pathways to ending the organ shortage. By better understanding critical milestones and challenges in these pathways, we will be able to improve the placement of our funding opportunities.

BIOENGINEERING ROADMAPS

Cross Cutting Bioengineering Challenges

Pathways to ending the organ shortage through bioengineering.

Layer-by-Layer Building of Organs and Tissues	De-cell / Re-cell scaffolding	Cellular Repair or Regeneration	Transgenic Animal Organ Replacements
Top level biologic challenges associated with each pathway			
Cell Mapping	Cell Mapping	Cell Mapping	
Manufacturing / Cell Sourcing	Manufacturing / Cell Sourcing	Manufacturing / Cell Sourcing	
Immune Tolerance	Immune Tolerance	Immune Tolerance	Immune Tolerance
Integration	Integration	Integration	Integration
Preservation / Banking	Preservation / Banking		Preservation / Banking
Vascularization	Vascularization		

BIOENGINEERING ROADMAPS

BIOENGINEERING PATHWAYS

1. **Layer-by-layer building of new organs or tissues:** a process in which cells and intercellular materials are laid out (e.g., 3D bioprinting or biofabrication) to create a functioning tissue or organ. This living construct would then be implanted into the patient to replace lost organ functionality.

2. **De-cell/re-cell scaffolding:** the use of existing tissue scaffolds from other organs or biologic material. These scaffolds first have their previous cells removed, and replaced with new cells forming the organ functionality required. The re-cellularized scaffolds would then be implanted into the patient.

3. **Cellular repair/regeneration of damaged tissues:** In-vivo repair/regeneration of damaged organs via delivery of growth factors, genome editing technology or new cells into existing organs in a patient. It is expected that the new cells integrating with the existing tissues may increase tissue functionality through a paracrine effect, as well as by directly supplementing functional cells. Additionally, growth factors or genome editing techniques could boost organ functionality or stimulate regeneration. Genome editing techniques such as the clustered, regularly interspaced, short palindromic repeat (CRISPR) technology are showing promise in this area. This approach generates RNA-guided nucleases with customizable specificities. Genome editing mediated by these nucleases has been used to rapidly, easily and efficiently modify endogenous genes in a wide variety of biomedically important cell types. It is expected that advances to CRISPR or other genetic modification systems could repair damaged tissues caused by cancers or disease and remove the need for replacement organs in some patients.

4. **Transgenic animals:** the use of genome editing of animals to alter immune recognition and prevent organ rejection. Animal organs would then be implanted into the human patient. Much complexity remains in understanding the appropriate functional and genetic modifications that would be required for Transgenic animal organ replacement.

BIOENGINEERING CHALLENGES

1. **Mapping:** it is important to improve our understanding of the detailed structures and organization of cells within each organ to accurately bioengineer tissues to replace lost functionality. Specific maps of cell placement, cell types, functions, organization, and interactions have not been created in enough detail to be able to reliably repair or replace the functions of existing organs. Some organs and tissues are understood better than others. For example, relatively simple organs such as the skin are fairly well understood, while complex, thick-tissue organs such as the heart, lung, liver, and kidneys are much more complex. The generation of a comprehensive "cellular atlas" for each of these organs would provide great benefit to reconstruction and repair of organ functionality.

   In many solution pathways, bioengineered organs will likely not be perfect mimics of real organs, but nonetheless will deliver the functions needed For example, Islet transplants into the liver can function, but they don't replicate the pancreas map. Additionally, Liver "buds" placed in lymph nodes have been shown to demonstrate liver functions but do not follow the traditional Liver structure. It remains to be determined if these approaches will be successful for long-duration, patient viability with impairment to these organs. Therefore, it can be argued that successful bioengineering techniques to replacing lost organ function may not require the exact replication of existing organ structures. However, understanding the detailed placement of cell types, their functions, and interactions within existing organs is likely to prove valuable when developing other functional support structures.

2. **Cell Manufacturing & Sourcing:** creating better, more reliable sources of different types of cells that are required to produce each desired organ function. We do not yet have enough reliable, replicable sources of key cell types that can be provided at economical costs and scale. The purity and quality of existing cell sources also needs to be improved to better prepare bioengineered tissues and organs. Autologous cell sourcing techniques are preferred to banking of non-autologous sources to mitigate rejection and immunosuppression requirements.

3. **Immune Tolerance:** when cells or tissues are implanted into new patients, immune suppression requirements can greatly hamper the quality of life, or ability of the tissue to produce the functionality required. Immunosuppressive therapies must be improved, or the need for such therapies must be eliminated. This may be addressed by using autologous cell sources, the genetic modification of cells and tissues, and possibly by methods we haven't yet conceived.

4. **Integration:** connecting new tissues and organs to a patient's biological functions, such as innervation, vascular systems, bile, lymphatic, etc. remain challenges. Improvements in biologic integration for patients is important when creating long-term solutions to lost organ functionality. The challenge is complex and varies from one organ to the next. Solutions will also vary with the pathways being pursued. Connecting thick-tissues to an existing host's vasculature will require different techniques than integrating new skin tissues, or other thin-walled tissues.

5. **Preservation / Banking:** The ability to preserve or bank bionengineered tissues is an important part of bionengineering as the storage of cells, tissues, and organs is needed to give tissue engineered products a shelf-life that allows for logistics, inventory, on-demand access and quality control. See pages 19 -33 for a holistic review of preservation technologies. See also the strategic plan of the Multi-Agency Tissue Engineering Science (MATES) Interagency Working Group (at http://tissueengineering.gov).

6. **Vascularization:** engineering thick tissues in-vivo or ex-vivo requires the ability to create an internal vascular system that provides the required nutrients to all cells. This has not yet been achieved for tissues thicker than several millimeters. In order to engineer thick-tissue organs such as the heart, liver, lung, or kidney, this challenge must be overcome.

RECOMMENDATIONS AND SUGGESTIONS

RECOMMENDATIONS AND SUGGESTIONS

We hope that these roadmaps that will help identify specific targets for new RFAs, prizes, SBIRs, and other support mechanisms to help achieve the milestones. The list below notes several specific potential action items that we hope will result from this effort.

NEAR TERM

- **Enable Continued Engagement:** Ensure that there's a system of top-level coordination for ongoing engagement between organizations and agencies interested in pursuing solutions to the grand challenge of ending the U.S. organ shortage, building upon the workshop, roadmap report, and the Alliance for Regenerative Medicine's "Challenging Regeneration to Transform Medicine" framework. Use overlapping interests identified in the roadmap report to help coordinate collaboration between organizations and agencies interested in specific challenges or milestones.

- **Enhance Roadmap Development:** Convert the roadmapping workshop process results into a beta version of the roadmap and secure support to conduct required follow on meta-level research to fully understand the step-by-step advances that can lead to solutions to achieving universal tissues and organs and ending the organ shortage.

- **Generate New RFAs, SBIRs, Non-Funded PAs and Other Research Support Opportunities:** Expand upon existing RFAs and create new ones to support solutions to specific milestones and challenges identified in the roadmaps.

- **Create New Challenges and Prizes:** Develop new prizes and incentivized innovation mechanisms for key milestones noted in the roadmaps that will support grants and create a dual push-pull mechanism toward the milestones.

- **Institutional Support of Organ Banking:** NIH center(s), consortia for multi-lab-center collaborative projects, and a research network are all non-existent but needed for the organ preservation field.

OTHER IDEAS THAT HAVE BEEN PROPOSED / LONGER TERM FOCUS

- **National Grand Challenge - On-Demand, Off-the-Shelf Universal Tissues and Organs:** New Organ, Organ Preservation Alliance, and many of the stakeholders interviewed for this collection of suggestions see a large need for and significant value of a U.S. Grand Challenge to "End the Organ Shortage." This is congruent with the Alliance for Regenerative Medicine's "Challenging Regeneration to Transform Medicine" white paper as an inclusive framework for enabling a public-private partnership with the shared mandate of eliminating the U.S. organ shortage and reducing U.S. government medical expenditures (e.g. the American Society of Nephrology estimates that the combined kidney-care cost for end-stage renal disease and chronic kidney disease is $79 billion annually).

RECOMMENDATIONS AND SUGGESTIONS

- **US National Strategy:** Supporting and advancing the development of a multi-faceted US national strategy for regenerative medicine, including organ bioengineering, regeneration, and banking to achieve on-demand, universal tissues and organs for ending the organ shortage, obviating chronic disease, injury, reducing the government's medical expenditures, etc. Japan show's a powerful example of this.
- **Identify Cross-Cutting Standards:** Advance an in-depth look at establishing greater standards in this space, such as an international registry of artificial organ transplants, building consensus on key areas (e.g. decellularization algorithms and standardizing assays), and the prospect of an Open Standards bio-equivalent of IEEE.
- **In-depth look at the scientific, societal and economic value/opportunity** of catalyzing industries for organ banking, bioengineering, and regeneration, including the healthcare-cost savings to the U.S. government.
- **Regulatory Landscape and Transparency:** Greater regulatory clarity is needed to entice greater academic and private investment and development. The FDA process for the BRAIN Initiative with a paper, workshop, and post workshop provides a good framework.

APPENDIX

APPENDIX 1

ORGAN AND COMPLEX TISSUE PRESERVATION: THE NEED AND VALUE

Organ transplantation has seen miraculous advances over the last 50 years, but the benefits to patients are limited by a large and growing shortage of organs as well as the key problems of poor donor/recipient matching and recipient immune suppression. Improved organ and tissue preservation would have a tremendous impact on both these problems, and it would also enable many other broad public health benefits. These are listed here and expanded on in the sections below.

BREAKTHROUGHS IN ORGAN PRESERVATION CAN ADVANCE TRANSPLANTATION BY...

- Improving **donor utilization**
- Reducing **discard** of otherwise viable organs
- Improving **organ matching** between donors and recipients
- Preventing **organ injury** and resulting **graft rejection**, increasing transplant success rates
- Decreasing the **cost and logistical burdens** of transplantation
- Enabling testing that can **prevent disease transmission** from donors to recipients
- Enabling options for **immune tolerance induction** strategies
- Allowing for **post-conditioning, repair, and quality assessment** of marginal organs, increasing their use and effectiveness in transplantation
- Increasing **organ lifespan**
- Decreasing the need for **costly and dangerous immunosuppression**
- Alleviating **national health disparities** by increasing access of ethnic minority patients to well-matched organs
- Alleviating **global health disparities** by increasing access of patients in geographically isolated regions and developing countries to donor organs

APPENDIX 1

OTHER BROAD PUBLIC HEALTH BENEFITS OF COMPLEX TISSUE PRESERVATION INCLUDE...

- Giving **tissue engineering** constructs a shelf-life and removing major supply chain bottlenecks
- Enabling tissue stockpiling for **emergency preparedness, military conflicts and mass casualty events**
- Enabling successful **limb salvage** in many more cases
- Providing on-demand tissues for **trauma care**
- Bolstering **national defense** capabilities
- Enabling more cost-effective and accurate **research and drug discovery**
- Reducing reliance on use of **animals in research**
- Enabling **fertility protection** for cancer patients who undergo chemotherapy

APPENDIX 1

ADVANCING ORGAN TRANSPLANTATION THROUGH PRESERVATION BREAKTHROUGHS

- **Donor Utilization:** Currently less than 1% of deceased persons' organs are considered for transplant in the US. While the vast majority of these deceased individuals would never be suitable donors, it has been suggested by many that by limiting ischemic injury during transplantation, allowing time to condition and rehabilitate organs, enabling new methods for quality evaluation, it should be possible to use many organs from more donors, particularly Donors after Cardiac Death.

  Moreover, many more organs from each eligible donor could be used. While a single cadaveric donor can provide up to 8 vital organs and over 50 distinct transplantable tissues, currently on average between 3 and 4 vital organs per donor are transplanted. For some vital organs, such as the heart and lungs, the majority are not transplanted.

  Many transplant surgeons have identified limited preservation capabilities and ischemic damage during storage and transportation as frequent and prominent factors in the decision not to use a vital organ for transplantation.

- **Organ Discard:** Among the multifold benefits to donor utilization, organ preservation capabilities have a direct impact on donor organ discard. For instance, almost 20% of kidneys removed for transplantation are discarded, and a substantial fraction of those are discarded simply because they expire before a suitable matching recipient can be found.

  Greatly extended preservation times, combined with the potential to rehabilitate and optimally screen organs for transplantation, have the potential to encourage a "No Organ Left Behind" mentality, saving many more lives using organs that would be discarded today.

- **Better Matching:** The matching of specific surface antigens (human leukocyte antigens, HLAs) between donor and recipient is common in kidney transplantation as a method to decrease rejection, HLA matching is not used for organs with shorter preservation times, such as the heart and lungs. Additionally, Queuing Theory shows that if organ banks can be established, much better matches could obtained (HLA, size, age, gender, etc) without extending wait list time. Ideally donors and recipients could be matched globally, rather than in over the small geographic regions used for matching today.

APPENDIX 1

- **Organ Injury and Graft Rejection:** Ischemic damage that occurring during storage and transport has been shown to contribute to graft rejection, lowering transplant success rates. If this injury can be prevented by metabolic conditioning of organs, ex-vivo perfusion, or cryogenic storage, the contribution of ischemia/reperfusion injury to rejection can be minimized or eliminated.

- **Costs and Logistical Burdens:** An organ transplantation is very costly procedure in large part because of the complex logistical demands imposed by short preservation times. Jet and helicopter flights must often be arranged with no notice, and longer preservation times have the potential to make these obsolete. Increased availability and predictability of transplantation procedures would limit costly hospitalizations for patients awaiting a transplant. Lengthy and complex transplant procedures could be performed within regular working hours, with careful planning and with personalization for patient needs. These changes would make transplantation much more cost-effective, and they may significantly improve outcomes.

- **Conditioning, Repair, and Quality Assessment:** Importantly, extended organ preservation would lay the groundwork for an entirely new class of interventions during transplantation: ones that focus on rehabilitating organs and conditioning them to be more suitable for transplantation. Even in the ideal organ donor, brain death initiates a wide spectrum of physiological derangements that can damage organs, in turn worsening transplantation outcomes or contributing to graft rejection. Rather than reversing this injury, current hypothermic organ preservation protocols only compound it by exposing the organs to additional ischemia/reperfusion injury.

  Moreover, lengthy or complex protocols that could reduce the immunogenicity of donor organs are impossible with current preservation times. The same is valuable for lengthy quality assessment protocols, which could not only allow for procedures and post-operative treatments to be tailored to individual circumstances but could also enable more informed, selective use of organs from extended criteria donors - saving lives without compromising on safety or transplantation success rates.

  Companies such as such as Transmedics, Perfusix and Xvivo have demonstrated the potential of ex vivo perfusion systems not only to extend preservation times, but to increase of donor organ quality.

- **Disease Transmission:** While rare, disease transmission does occur between donors and recipients, for instance rabies and HIV. Recipients report that this is a prominent psychological burden and source of anxiety ahead of their transplant. Improved preservation can enable better disease screening prior to transplantation, saving lives, reducing complications, and providing peace of mind.

APPENDIX 1

- **Immune Tolerance Induction:** Tolerance induction is widely considered the "holy grail" of transplantation, with the potential to reduce or eliminate immunosuppression while preventing graft rejection. So far, some tolerance induction protocols (thymic inoculation) that have demonstrated success have required weeks to months of preconditioning prior to the transplantation; tolerance induction becomes more difficult when initiated after the immune system has already responded to foreign tissue.

  Clinical trials in immune tolerance induction are showing success in living donor organ donation, but these protocols are not widely applicable to cadaveric transplantation: because recipient tolerance is specific to donor antigens, doctors must identify and have access to the donor and recipient to initiate tolerance induction therapies.

  If cadaveric donor organs could be preserved after removal and matching of donors to recipients, sophisticated tolerance induction strategies could be initiated well before transplantation. This would open up many more possibilities, and it would make strategies that have already been proposed more likely to be successful.

- **Organ Lifespan:** Transplant organ injury during storage and transport has been linked with chronic rejection, limiting organ lifespan. As a result, patients can often outlive their transplanted organs, requiring a second or sometimes even third transplant. Preservation technologies hold the promise of limiting this injury and in turn, potentially increasing transplant organ lifespan.

  It can also enable many other approaches that can decrease chronic rejection and organ lifespan (discussed above), such as rehabilitation organs and assess their quality, more stringent matching between donors and recipients, more careful planning and personalization of transplant procedures, and new tolerance induction protocols.

  Not only can extending organ lifespan improve quality of life for patients post-transplant, but it can increase the effective supply of organs by reducing or eliminating the need for additional transplants.

- **Immunosuppression:** If reliance on immunosuppressants could be reduced or eliminated, in part through the many other benefits of improved preservation, this could decrease post-transplant mortality and dramatically improve recipients' quality of life and decrease risk of cancer and infections due to suppressed immune system. The reduction in complications from immunosuppression, as well as the reduction in need for the immunosuppressants themselves, would further add to cost savings.

APPENDIX 1

- **National Health Disparities:** For some organs, ethnic minority patients typically experience far worse shortages than Caucasian waitlist patients. In large part, this has been attributed to the fact that HLA frequencies used for matching vary by ethnicity, making it more likely to match patients of the same ethnicity. Because there are fewer ethnic minority donors and recipients, it can be much more difficult to find a well matched organ for a minority waitlist patient within suitable proximity.

  By dramatically extending the time and distance over which organs can be matched, extended organ preservation can give ethnic minority patients and those with rare HLA types a much better chance of receiving a well matched organ. In this way, health disparities in transplantation can be alleviated – without sacrificing donor utilization.

- **Global Health Disparities:** The U.S. has one of the highest per capita organ transplantation rates in the world, and in many countries transplantation rates are less than 1% of those in the U.S. In developing countries, organ transplantation is often non-existent (even though more suitable donors exist due to higher frequency of traffic, construction related and other deaths due to accidents that lead to brain death). Even when perfectly matched to an organ donor in a developed country, patients in developing countries have no hope of receiving a transplant.

  By enabling global matching between donors and recipients, extended organ preservation eliminates many barriers to establishing systems that would give patients in the developing world access to transplantation. If carefully and equitably conducted, cross-border organ donation has the potential to improve transplantation outcomes worldwide, increase access to donor organs and tissues for patients in the developing world, and greatly accelerate the development of transplantation infrastructures worldwide.

- **Savings to the Healthcare System:** Preservation technologies can alleviate the economic burdens of the healthcare system by reducing the costs of transplantation procedures, adding productive years to patients' lives (by enabling more transplants and more effective transplants), and reducing the costs of treating post-operative complications.

  Moreover, the additional transplants that are enabled through improved preservation eliminate the need for costly alternative treatments. For instance kidney transplantation, widely considered the best treatment for end stage renal disease, avoids costly and grueling dialysis treatments: while patients report much lower quality of life on dialysis than after transplantation, $34.3 billion of the U.S. Medicare budget was spent on dialysis in 2010 alone - over 6% of the total Medicare budget The global economic cost of treating end-stage renal disease has been estimated at over $1 trillion over the course of a decade.

APPENDIX 1

- **Tissue Engineering:** Preservation and banking capabilities are needed to give tissue engineered products a shelf-life. Banking can enable storage, transport, and quality control of engineered complex tissues, becoming a vital part of the tissue engineering supply chain. With a sufficient understanding of tissue preservation, bioengineered products can be optimized for long-term storage at both the design and manufacture stages. If preservation issues are not addressed, storage constraints are likely to become the limiting factor in the public health benefits of many engineered tissues.

  Many in the tissue engineering field are already feeling this need. The Multi-Agency Tissue Engineering Sciences (MATES) intra-agency working group, comprising members from multiple NIH institutes, NSF, the U.S. Army, DOE, HHS, NASA, the Armed Forces Institute for Regenerative Medicine (AFIRM), and others have identified tissue preservation as a key unmet need in the tissue engineering field.

- **Tissue Stockpiling for Mass Casualty Events:** Banked tissues such as skin, blood vessels, and bone marrow could be used to treat burns, limb trauma, radiation poisoning and other life-threatening injuries. Having stockpiles of these tissues on hand could greatly reduce loss of life in natural disasters, terrorist attacks, military conflicts, and other mass casualty events.

- **Limb Salvage and Trauma Care:** In addition to providing skin, blood vessels, bone marrow, and other tissues for emergency surgery, complex tissue preservation can enable the salvage of limbs lost by civilians during accidents or soldiers in conflict. Preservation technologies could allow crucial time for evacuation to advanced medical facilities, diagnostics and preparation for surgery, making limb reattachment more effective and achievable under a wider range of circumstances.

  Moreover, much of the knowledge gained from tissue preservation research may be applicable to induced hypothermia and suspended animation treatments, buying time for trauma victims to receive lifesaving care.

- **National Defense:** Tissue stockpiling for mass casualty events, the use of on-demand tissues (natural, and bioengineered) for trauma care, and improved limb salvage are all tied to key military capabilities. They also greatly enhance preparedness for threats to the homeland, particularly terrorist attacks. Complex tissue banking has the potential to make regenerative medicine a key component of national defense, protecting service members as well as civilian populations.

- **Research and Drug Discovery, Without the Use of Animals:** Successful banking of complex human tissues will increase the cost-effectiveness and productivity of human tissue research, enable more in-depth longitudinal studies, and decrease reliance on animal testing. In many cases human tissues are less expensive and more accurate than animal models, and they avoid the ethical dilemmas inherent to animal research. Having tissues off-the-shelf, on-demand also takes away large lead-lag times in executing experiments as desired.

- **Fertility Protection:** Ovary and testes banking would markedly improve treatment and quality of life

for people with treatable cancer but in need of chemo and/or radiation therapy. In fact each year there are 12,400 children and adolescents (younger than 19 years) diagnosed with cancer in the US, for whom ability to bank ovaries or testes could enable a normal transition through puberty and hormonal health in addition to fertility in later life and the NCI reports that 1 out of every 250 adults will be a survivor of childhood cancer by 2015. In the U.S. alone there are an estimated 380,000 survivors of childhood cancer and 630,000 survivors of cancer contracted as young adults (ages 21-40). This means that over two young generations there are over 1 million cancer survivors in the U.S. alone, each of whom could potentially have had their lives changed by protective ex-vivo storage of their reproductive organs during treatment. Worldwide an estimated 175,000 annual cases of cancer in children younger than 15 years of age are diagnosed.

APPENDIX 2

MAXIMUM THEORETICAL SUPPLY OF DONOR ORGANS AND ADDITIONAL ELIGIBLE ORGANS WITHIN NEAR-TERM REACH (US)

Removing technological constraints, the number of potentially transplantable donors far exceeds the number currently donated to. Even if one only considers organs from donors who have deaths resulting from traumatic brain injury in the controlled environment of a trauma center (comprising only 2% of all US deaths) and then only assuming that a fraction of them lead to eligible donors the number of additional eligible organs within near term reach is vast. Even with stringent donor eligibility criteria, removing technological constraints to donor utilization can dramatically increase organ supply.

Affected Organ	Current cadaveric donor organs transplanted (yearly)[3]	% of organs that are **unused** from eligible donors[4]	Additional eligible organs within near term reach [7,8]			Theoretical high-case additional number of eligible organs[5,6]		
			Number	% of current available organs	% of organs available from all deaths	Number	% of current available organs	% of organs from all deaths
Heart	2,421	70%	5,500	227%	0.2%	180,000	Orders of magnitude more	7%
Lung	3,019	63%	5,500	182%	0.2%	222,000	Orders of magnitude more	9%
Kidney	11,993	26%	19,800	165%	0.4%	888,000	Orders of magnitude more	18%
Liver	5,942	27%	9,900	167%	0.2%	438,000	Orders of magnitude more	18%
Pancreas	1,042	87%	2,200	211%	0.04%	78,000	Orders of magnitude more	3%
Intestines	106	98%	550	519%	0.01%	588,000	Orders of magnitude more	24%
Total/Other	24,591	57%	2,394,000	Orders of magnitude more	14%	2,394,000	Orders of magnitude more	14%

[3] Total number of organs transplanted in the US in 2012. Source: http://srtr.transplant.hrsa.gov/annual_reports/2012/Default.aspx

[4] Rate of unused organs based on all organs of all available donors - all transplanted organs

[5] This estimate is the thoretical number of potentially available organs calculated by all deaths meeting official UNOS/OPTN donor eligibility criteria from all deaths reported in the US (An eligible death is any hospital-reported death or imminent death that is evaluated and meets organ donor eligibility requirements: age 70 years or younger, death by neurological criteria (based on the American Academy of Neurology practice parameter for determining brain death), and with none of the following indications: tuberculosis, human immunodeficiency virus (HIV) infection with specified conditions, Creutzfeldt-Jacob Disease, herpetic septicemia, rabies, reactive hepatitis B surface antigen, any retrovirus infection, active malignant neoplasms (except primary central nervous system tumors and skin cancers), Hodgkin disease, multiple myeloma, leukemia, miscellaneous carcinomas, aplastic anemia, agranulocytosis, fungal and viral encephalitis, gangrene of bowel, extreme immaturity, or positive serological or viral culture findings for HIV.). Sources: http://www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_06.pdf and Israni et al.: OPTN/SRTR 2013 Annual Data Report: deceased organ donation, American Journal of Transplantation, 2015

[6] With optimal salvage, preservation, reconditioning and assessment (after adjusting for organ disease, age and pre-retrieval ischemia)

[7] Only looking at deaths resulting from traumatic brain injury in the controlled environment of a trauma center and then only assuming a fraction of them lead to eligible donors.

[8] This conservative estimate only takes into account the 53,000 deaths (2% of all deaths) in the US that occur as a result of traumatic brain injury in the controlled environment of a trauma center. It then assumes that only 20% of those deaths could lead to suitable organ donors and then assumes that of those donors 50% can donate hearts and lungs, 90% kidneys and livers, 20% pacreas and 5% intenstines. Raw data from http://www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_06.pdf. See also www.perfusix.com/impact-of-ex-vivo.html for similar estimates.

APPENDIX 3

NEED AND POTENTIAL FOR BETTER MATCHING

Organ	Summary	HLA-matching prioritized?	Advanced antibody testing	Other valuable criteria	10 year graft survival rate	Median time on waitlist (months)
Heart	Based on urgency of transplant and short possible ischemia time HLA-matching and prospective cross-matching falls short.	no	no	better size, age matching	57%	9
Lung	Similar to heart: high urgency and short ischemia time prevent from better graft assessment and no HLA matching or anti-body / cross matching is typically conducted.	no	no	better size, age matching	27%	4
Kidney	Require most precise testing to prevent allograft deterioration. Even when HLA typing is taking into account most transplants are not optimally HLA matched and mismatches are particularly more severe for minority groups.	yes	Cross-match		46%	60
Liver	No HLA matching is conducted although it would be valuable (especially outside of autoimmune liver disease cases)	no	N/A*	better size, age matching	56%	20
Pancreas	Require precise testing to prevent allograft deterioration	yes	Cross-match		36%	19
Intestines	High rejection rate shortly after transplant (median 2.5 weeks)	yes	Cross-match		28%	15
Hand/limb	Skin is highly immunogenic. Small donor pool and short ischemia times prevent from prioritizing HLA-matching	no	Cross-match	better size, age, skin tone	N/A*	N/A*
Face	Skin is highly immunogenic. Small donor pool and short ischemia times prevent from prioritizing HLA-matching	no	Cross-match	better size, age, skin tone, texture	N/A*	N/A*

* Data not available.

APPENDIX 4

LARGE COST AND MARKET SIZE OF ORGAN TRANSPLANTATION (US)

Organ	Costs per transplant (Millions of Dollars) [1]	Current number of organ transplants from deceased donors	Potential number of organ transplants from deceased donors when including organ donors within near term reach with better preservation and assessment technologies (see table above for calc) [2, 3]	Current transplant market from deceased donor organs (Billions of Dollars) [4]	Potential near term tranplant market from deceased donor organs (Billions of Dollars)
Heart	$ 1.00	2,421	7,921	2.4	7.9
Lung	$ 0.80	3,019	8,519	2.4	6.8
Kidney	$ 0.26	11,993	31,793	3.2	8.4
Liver	$ 0.58	5,942	15,842	3.4	9.1
Pancreas	$ 0.29	1,042	3,242	0.3	0.9
Intestines	$ 1.21	106	656	0.1	0.8
Hand/limb**	$ 0.53	7	4,110	0.0	2.2
Face***	$ 0.77	5	822	0.0	0.6
Average	$ 0.68				
Total		24,535	72,905	12	37

[1] http://transplantliving.org/before-the-transplant/financing-a-transplant/the-costs/

[2] Assuming about half the recovery rates as for hearts and lugns (note that ptential demand by far exceedes this supply - there 2 million Americans living with limb loss (i) and 185 000 new amputation per year [i, ii]. [i] Ziegler-Graham, K., MacKenzie, E. J., Ephraim, P. L., Travison, T. G. & Brookmeyer, R. Estimating the Prevalence of Limb Loss in the United States: 2005 to 2050. Arch. Phys. Med. Rehabil. 89, 422–429 (2008). [ii] Owings, M. F. & Kozak, L. J. Ambulatory and inpatient procedures in the United States, 1996. Vital Health Stat. 13. 1–119 (1998).

[3] Assuming a low recovery rate of 10% (note that potential demand by far exceedes this supply - Three million facial injuries are treated in emergency rooms in the US each year [iii] if even 0.5% of those are catastrophic injuries, then 15,000 patients each year suffer dramatically life-changing facial disfigurement and disability and would be potential candidates for a face transplant. [iii] Daniel D. Sutphin. Facial Soft Tissue Trauma, http://emedicine.medscape.com/article/882081-overview. Medscape (2013).

[4] Calculated as cost per transplant x number of performed transplants.

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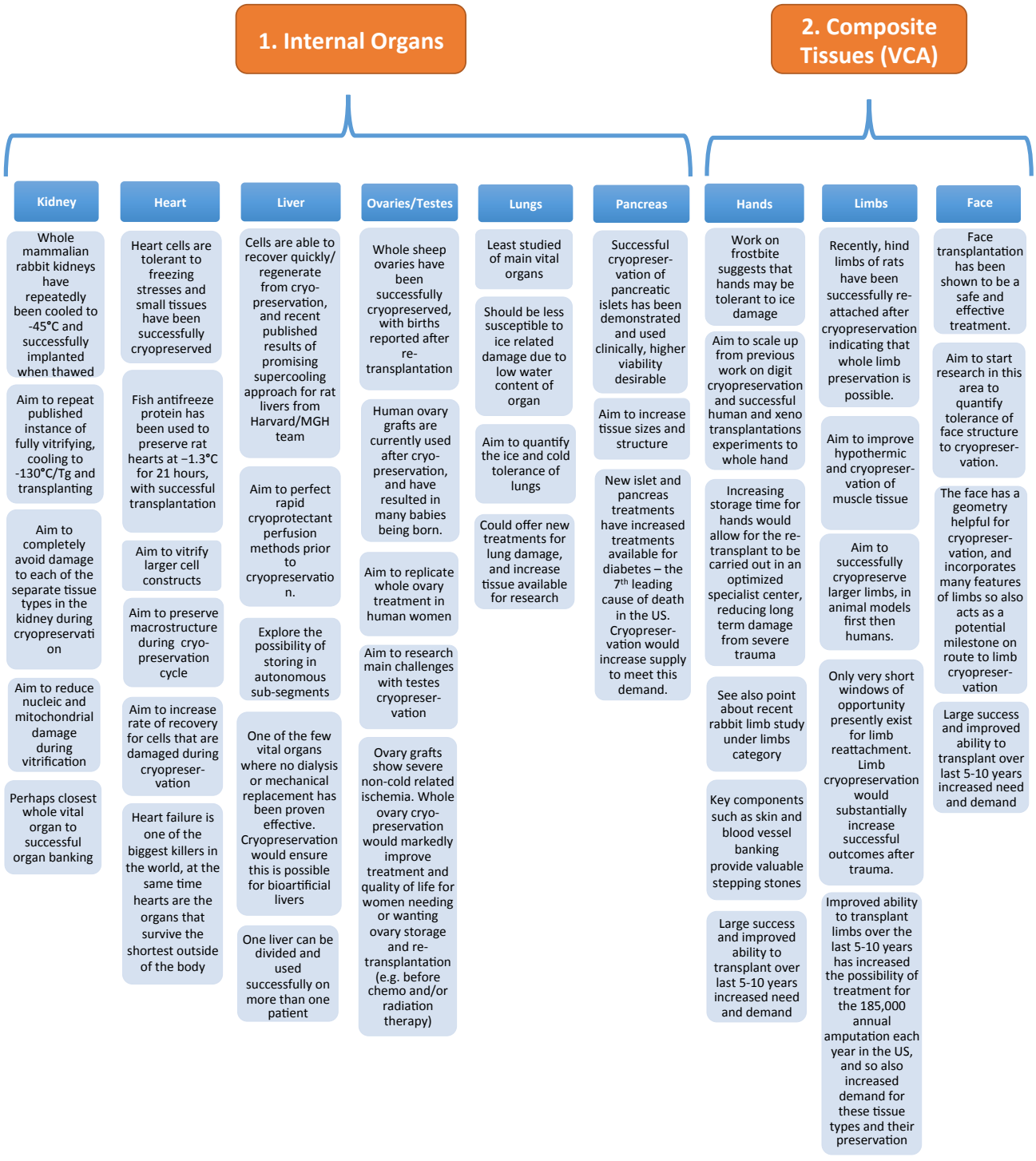
APPENDIX 5

INDIVIDUAL ORGAN & TISSUE SYSTEMS: PROGRESS, CHALLENGES AND KEY QUESTIONS

While little to very little cryopreservation work has been conducted on the majority of the systems below, there is an emerging picture of progress, challenges and key questions:



APPENDIX 5

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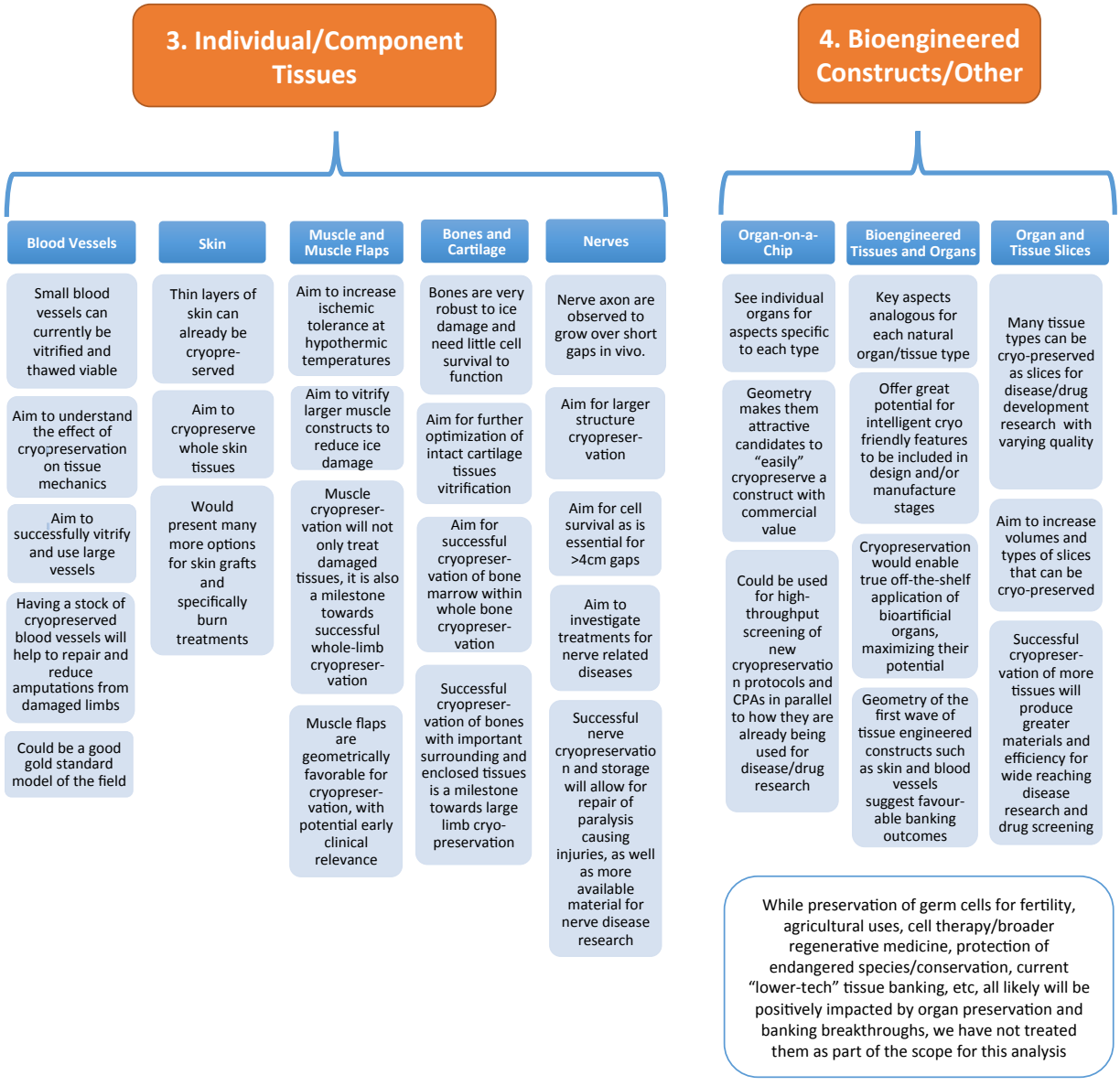

APPENDIX 5

SUMMARIES OF INDIVIDUAL ORGANS AND TISSUE SYSTEMS

1. **The Kidney.** Published papers show that the kidney has been cooled ice-free to -45°C and re-transplanted to rabbits successfully multiple times [1], with one published instance of successful vitrification. The primary challenge is to replicate the success at a stable storage temperature below -130°C. Rabbit kidneys appear more sensitive to cryopreservation than those of more robust mammals like pigs and humans, so parallel work on such systems may now be called for. Current clinical preservation time is **ideally < 24 hours**, up to 48 hours with simple cold storage in preservation solutions [2].

2. **The Heart.** While heart cells (cardiomyocytes) are tolerant to cryopreservation stresses, they recover slowly from any damage that they do exhibit [3]. Perfusion is simpler to achieve than in most other internal organs, but current clinical preservation time is **ideally < 3 hours** with a 6 hour upper limit with hypothermic preservation, however this may be increased with new heart-in-a-box technology [2].

3. **The Liver.** Liver cells (hepatocytes) can be easily damaged in the cryopreservation cycle, however due to their rapid regeneration characteristics recovery can be quick. Promising results from a recent supercooling approach for a whole rat liver from a Harvard/MGH team have been published [4]. The liver also contains a lot of capacity, as one healthy liver can treat up to 3 people, so large potential impact is available here, as well as the possibility of cryopreserving the liver in smaller segments [5]. Challenges for the liver include managing large thermal gradients, effective perfusion techniques due to its large size, and determining what steps may be necessary to reduce cooling injury. Ice is also particularly damaging to cells and must be avoided. Current clinical preservation time is between only **12 hours** and18 hours [2] with hypothermic storage in University of Wisconsin (Viaspan) solution.

4. **Ovaries and testes.** Recently, whole sheep ovaries have been banked by several teams with live births after re-transplantation [6][7]. Human ovary slices can also be cryopreserved and re-grafted, which has resulted in around 50 births worldwide. The majority of tissue damage in this procedure is from the grafting not the preservation [6][7]. Whole ovaries would overcome this problem, and so scaling up to whole human ovary cryopreservation is a next step. Testes cryopreservation research is limited, though would be applicable for pre-pubescent boys who have treatment for medical conditions that destroys or damages their testes. Pre-pubescent treatment that damages reproductive organs affects 15,000 boys and girls in the US alone.

5. **The Lungs.** The least amount of research of the major organs has been directed at the lungs, though the lower water content of lungs suggests that they may be less susceptible to freezing damage. Current clinical preservation time is **only 2 hours**, with a 4 hour upper limit chilled [2].

6. **The Pancreas.** Pancreas islet transplantation is a promising treatment for diabetes mellitus, the 7th leading cause of death in the US, and islets have been successfully cryopreserved [8][9]. Cryopreservation of whole pancreas has received little attention, despite clear applications. Current clinical preservation time is **ideally < 12 hours** up to 18 hours under hypothermic conditions [2].

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7. **Hands**. Single index fingers have been successfully cryopreserved in China recently, and great improvements in hand transplantation have been made. Frostbite research suggests that hands may be less susceptible to cold damage compared to other tissues, and the short timeframe in which hands can currently be preserved highlights the need for increased preservation times . Research here will compliment face and limb cryopreservation. Current clinical preservation time is **2-3 days** when stored at 4°C [10].

8. **Limbs.** This is one of the least studied areas in the West despite clear medical applications. Limb transplantation has had improved success in the last 5-10 years, increasing both demand and need for limb transplants, and is a natural progression of hand and face cryopreservation. Recently a Chinese team cryopreserved rat hind limbs successfully [11]. Increasing investment here will reduce amputations and allow the West to regain its technological edge. Current clinical preservation time is **less than 4 hours** optimally, up to around 6 hours under hypothermic conditions, though wide variations in studied material exist. In general the larger the amputated limb, the shorter the acceptable preservation time [12] [13][23][24].

9. **Face.** Thanks to successful face transplant technology in the past 5-10 years, the demand for and usefulness of face cryopreservation is huge, despite lack of research. The face shares many cryopreservation challenges and opportunities with the hand and limbs, but due to its flat geometry and small muscles, should be easier to cryopreserve and act as an important milestone on the way to limb cryopreservation.

10. **Skin.** Skin cryopreservation opens up the possibility of greater options and more complete recovery for victims of burns through more effective use of graft therapy. Currently only layers of skin can be preserved. Preserving the whole tissue affords greater flexibility through off-the-shelf tissues being available for treatments [14][15].

11. **Blood Vessels.** Smaller vessels can already be cryopreserved through vitrification, and artificial blood vessels are a developing field. Perfecting warming techniques to prevent cracking with larger vessels would allow greater treatments for limb damage, and substantially reduce trauma-related amputations. This is a potential good model system for the field [16][17].

12. **Muscle and muscle flaps.** Fingers and hands can be preserved by refrigeration at 4°C for several days, [10]. This is not currently possible with limbs due to the short ischemic window of muscle tissues [18]. Increasing muscle ischemic tolerance will enable improved short-term limb preservation, and their geometry makes them attractive models with potential early clinical relevance.

13. **Bones and Cartilage.** Bones are generally robust and their structure survives cryopreservation well. Cartilage cryopreservation is much less developed, but necessary for successful limb cryopreservation. While chondrocytes have been cryopreserved in suspension for many years, cryopreservation in situ has proved more difficult but with recent success, with vitrification considered the most promising approach for intact cartilage [19][20][21][22].

14. **Nerves.** For small tissues such as fingers, nerves may re-grow, however the rate of growth is too slow for larger limbs, so effective cryopreservation methods must be developed.

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15. **Organ-on-a-chip.** Geometry makes them attractive candidates to bank, adding to the commercial value. Organs-on-a-chip can help disease research and drug screening. They could also prove very valuable for cryoprotectant screening and cryopreservation protocol development. See also individual organs for specifics of each type of chip.

16. **Bioengineered tissues.** Key aspects analogous to each natural organ/tissue type listed above. For true 'off-the-shelf' bioengineered tissues, cryobanking is essential as manufacture on demand is often not feasible, neither with regards to time, logistics, nor economy [1]. Tissues could be designed to be "cryo friendly", allowing easier perfusion of cryoprotectants, incorporating cells that are more tolerant to freezing, or with small gaps to relieve thermal stresses for example. Thin geometry of the first wave of tissue engineered constructs - skin, blood vessels, etc., favors successful cryopreservation requirements.

17. **Organ and Tissue Slices.** Many thin tissue segments are currently cryopreserved for research into different diseases and conditions. Successful cryopreservation of more and larger human tissues, tissue systems and organ slices will allow more in-depth longitudinal studies, increasing productivity and research into these conditions per sample while decreasing needs for animal testing and the associated costs and limitations.

APPENDIX 5

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APPENDIX 6

AGENDA FROM THE ORGAN BIOENGINEERING AND BANKING ROADMAP WORKSHOP, WASHINGTON D.C. MAY 27, 2015

NETWORKING BREAKFAST (8:15 – 9:00AM)

WELCOME & INTRODUCTION (9:00AM – 9:15AM)

Welcome: Goals for the Day	• *Joshua Neubert*, CEO Institute of Competition Sciences, New Organ Managing Partner, NSF Workshop PI • *Robin Farmanfarmaian*, Executive Director, the Organ Preservation Alliance
Intro Organizing Committee	• *David Gobel*, Founder, New Organ
Intro National Science Foundation	• *Dr. Athanassios Sambanis*, Program Director, Division of Chemical, Bioengineering, Environmental, and Transport Systems, National Science Foundation (NSF)

SETTING THE STAGE: BIOENGINEERING & BANKING NEED AND POTENTIAL (9:15AM – 10:30AM)

Big Picture Context	**White House Perspective** • *Dr Robbie Barbero*, Assistant Director for Biological Innovation, White House Office of Science and Technology Policy (OSTP) - Invited **The Enormous Need and Value** • *Dr. Sebastian Giwa*, President and CEO, Organ Preservation Alliance **A National Strategy and Grand Challenge Vision** • *Michael Werner*, Executive Director, Alliance for Regenerative Medicine
State of the Art Technologies	**Organ Preservation and Banking** • *Dr. Erik Woods*, President, The International Society for Cryobiology • *Dr. Ken Storey*, Canada Research Chair in Molecular Physiology and Professor in Biochemistry at Carleton University **Bioengineering** • *Dr. Jennifer Lewis*, Hansjorg Wyss Professor of Biologically Inspired Engineering, Harvard
Roadmap Introduction	• *Lt Col Alvarez*, PhD, Academy Professor and Director of the Center for Molecular Science, US Military Academy, Author of the DoD's Organ Banking Grant Programs and Former co-founding Deputy Director of the DoD's Tissue Injury and Regenerative Medicine Program

20 MINUTE BREAK (10:30AM- 10:50AM)

APPENDIX 6

CRITICAL CHALLENGES (10:50AM – 12:10PM)

Discussion: Top Level Challenges	Discussion groups on top challenges (scientific, technology and other) towards ending the organ shortage **Introduction to Ecosystem Challenges** • *Bernard Siegel*, Executive Director, Genetics Policy Institute (GPI)/World Stem Cell Summit (WSCS) **Introduction to Bioengineering Challenges** • *Dr. Jason Wertheim*, Assistant Professor in Surgery-Organ Transplantation, Northwestern **Introduction to Banking Challenges** • *Dr. Gregory Fahy*, Chief Science Officer, 21st Century Medicine and Fellow of the Society for Cryobiology

HOSTED LUNCH (12:10PM – 1:15PM)

MILESTONES, METRICS AND PRIORITIZING SUPPORT (1:15PM-3:30PM)

Discussion: Scientific Milestones and Metrics	Discussion groups on the top scientific milestones towards solving the challenges and what metrics are required to measure/evaluate such milestones. **Introductions** • *Lt Col Alvarez*, PhD, Academy Professor and Director of the Center for Molecular Science, US Military Academy • *Dr. Martha Lundberg*, Program Director, Advanced Technologies and Surgery Branch, National Heart, Lung, and Blood Institute (NHLBI)
Panel: Ideas on Prioritizing and De-Prioritizing Research Areas	NSF, NIH, DoD, and ARM explore existing and new mechanisms to better prioritize or de-prioritize research areas. **Presenters** • *Dr. Athanassios Sambanis*, Program Director, Division of Chemical, Bioengineering, Environmental, and Transport Systems, National Science Foundation (NSF) • *Dr. Deborah Hoshizaki*, Program Director, Division of Kidney, Urologic, and Hematologic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) • *Dr. Kristy Pottol*, Director, Armed Forces Institute for Regenerative Medicine, US Army Medical Research and Materiel Command (USAMRMC) • *Dr. Claudia Zylberberg*, President/CEO, Akron Biotech/Alliance for Regenerative Medicine (ARM)

20 MINUTE BREAK (3:30 – 3:50)

APPENDIX 6

PATH FORWARD & NEXT STEPS (3:50 PM - 6:00PM)

Discussion: Government and Institutional Support	Discussion on how government and institutional support could be improved and leveraged through cross-organizational collaboration. **Introductions** • *Dr. Mehmet Toner*, Helen Andrus Benedict Professor of Surgery, Harvard Medical School • *Dr. Jeffrey Morgan*, Director of Biomedical Engineering, Brown • *Dr. Teresa Woodruff*, Director of Oncofertility Consortium, Professor and Chief of the Division of Reproductive Science in Medicine, Northwestern
Discussion: Public-Private Partnerships, Open Innovation and Prizes	Discussion groups on how public and private collaboration and open innovation and prizes can support more traditional models of support to help achieve milestones. **Introductions** • *Dr. Sandeep Patel*, Open Innovation Manager, DHHS. • *Sam Ortega*, Program Manager, Centennial Challenges, NASA • *Jennifer Gustetic*, Assistant Director, Open Innovation, White House Office of Science and Technology Policy (OSTP) • *Kelly Olson*, Senior Innovation Advisor & Director, Challenge.gov, US General Services Adminstration (GSA) - Invited
Discussion: The Roadmap and Path Forward	Discussion on next steps and framework for continued dialog and coordination between stakeholder organizations, private-sector, and government. **Moderators** • *Mr. Joshua Neubert*, CEO Institute of Competition Sciences, New Organ Managing Partner, NSF Workshop PI • *Dr. Sebastian Giwa*, President/CEO, Organ Preservation Alliance

HOSTED RECEPTION (6:00 – 8:00PM)

APPENDIX 7

PROGRAM FFROM THE WHITE HOUSE CONVENED AND HOSTED ROUNDTABLE ON ORGAN BANKING AND BIOENGINEERING WASHINGTON, D.C. MAY 28, 2015

8:30	**Check-In and Networking**	
9:00	**Welcome and White House OSTP Introduction**	Tom Kalil, Senior Advisor for Science, Technology and Innovation for the United States National Economic Council / Deputy Director for Technology and Innovation, White House, Executive Office of the President
9:10	**Organ Banking and Bioengineering**	
	Addressing the Challenge of Organ Scarcity & Impairment	Sebastian Giwa, President and CEO, Organ Preservation Alliance
	Key Remaining Obstacles and Milestones Identified in Roadmap Process and Workshop – Organ Banking	Erik Woods, President, Society for Cryobiology
	Key Remaining Obstacles and Milestones Identified in Roadmap Process and Workshop – Bioengineering	Alejandro Soto-Gutiérrez, Assistant Professor, UPitt
9:35	**Break**	
9:45	**Industry Perspective and Vision** Opportunity for Cross-Sector Coordinated Strategy Industry's Grand Challenge Vision Initial Key Priorities Benefits and Resources of Public-Private Partnerships	Michael Werner, Executive Director, ARM; Dr. Jason Wertheim, Assistant Professor in Surgery-Organ Transplantation , Northwestern University and Dr. Stewart Abbot, Executive Director, Integrative Research, Celgene Cellular Therapeutics
10:35	**Discussion on the Grand Challenge Vision, and How the Roadmap Obstacles and Milestones Tie into It**	Robbie Barbero, Assistant Director, Biological Innovation, White House Office of Science and Technology Policy, Executive Office of the President
10:45	**Break**	
10:55	**The Administration's Perspective on Manufacturing:** Remarks Q&A	JJ Raynor, Senior Policy Advisor, National Economic Council, Executive Office of the President
11:05	**MATES Perspective on Promising Future Activities or Opportunities**	Richard McFarland, Chair of Multi-Agency Tissue Engineering Science (MATES) Interagency Working Group
11:10	**Government Program Examples**	Luis Alvarez, Academy Professor, US Military Academy Sheng Lin-Gibson, Deputy Chief, Biosystems and Biomaterials, NIST Thanassis Sambanis, Program Director, NSF
11:35	**Power and Role of Prizes**	Sandeep Patel, Open Innovation Manager, HHS Sam Ortega, Centennial Challengers Program Manager, NASA Joshua Neubert, CEO, ICS, New Organ Managing Partner
11:50	**Break**	
12:00	**Tactical Next Steps and Actionable Items from Discussions**	Robbie Barbero, Assistant Director, Biological Innovation, White House Office of Science and Technology Policy, Executive Office of the President
12:30	**Break and Networking**