INTRODUCTION: The Ethical, Legal & Policy Challenges of Stopping Biological Time

Susan M. Wolf[1], *Timothy L. Pruett*[1], *and Korkut Uygun*[2]

1. UNIVERSITY OF MINNESOTA, MINNEAPOLIS, MINNESOTA, USA.
2. HARVARD UNIVERSITY, BOSTON, MASSACHUSETTS, USA.

Keywords: Cryopreservation, Biopreservation, Biorepositories, Emerging Technology, ELSI

Human beings depend on biological materials for survival — everything from food to medical interventions such as organ transplantation, to the environments in which we live. So it is no surprise that techniques to avoid the deterioration of biological materials have been used since ancient times.[1] Cooling is one of the oldest techniques. Indeed, most of us now live with a cooling machine — a refrigerator — in our kitchens. But the function of those machines is primarily to retard the spoilage of materials that are already in the process of disintegrating: fruit that has already been harvested, meat from beef and chickens already slaughtered, and milk already derived from cows.

Beginning in the mid-20th century, scientists began to develop techniques for cryopreservation with more ambitious goals in mind. Instead of merely slowing the deterioration of biological materials, techniques could be developed to preserve living materials for prolonged periods of time and then allow their revival and use at a future time and place. An early application was cryopreservation of sperm (both human and animal), allowing sperm banking and later use.[2] Yet conventional cryopreservation had its limits. Prolonged preservation of solid organs for transplantation was among the applications that proved elusive.

Nature offered intriguing models, though, suggesting that prolonged preservation of biological materials followed by return to full function was possible. Both the Arctic ground squirrel and wood frog regularly undergo suspended animation to survive their frozen environment, followed by return to full function.[3] Understanding how these organisms survive extreme temperatures opened new avenues for exploration.

The 21st century is now seeing an explosion of interest in new techniques for biopreservation.[4] These techniques manipulate temperature, cryoprotective agents, infusion of nanoparticles to allow uniform rewarming, and the containers used in order to successfully control the entire process of cooling, storage, and rewarming to full function. Supercooling, partial freezing, vitrification, and nanowarming are among the techniques showing remarkable promise

Susan M. Wolf, J.D., *is Regents Professor; McKnight Presidential Professor of Law, Medicine & Public Policy; Faegre Drinker Professor of Law; and Professor of Medicine at the University of Minnesota. She serves as Lead for the Ethics & Public Policy component, NSF Engineering Research Center for Advanced Technologies for Preservation of Biological Systems (ATP-Bio).* **Timothy L. Pruett, M.D.,** *is Professor in the Department of Surgery's Division of Transplantation and Director of the Liver Transplantation Program at the University of Minnesota. He serves as Co-Lead for the Ethics & Public Policy component, NSF Engineering Research Center for Advanced Technologies for Preservation of Biological Systems (ATP-Bio).* **Korkut Uygun, Ph.D.,** *is Associate Professor of Surgery (Bioengineering), Harvard Medical School; Deputy Director of Research, Shriners Hospitals for Children; Director, Cell Resource Core, and Director, Organ Reengineering Lab, Center for Engineering in Medicine & Surgery, Massachusetts General Hospital; and Director of Research, NSF Engineering Research Center for Advanced Technologies for Preservation of Biological Systems (ATP-Bio).*

The Journal of Law, Medicine & Ethics, 52 (2024): 529-533. © The Author(s), 2024. Published by Cambridge University Press on behalf of American Society of Law, Medicine & Ethics. DOI: 10.1017/jme.2024.128

in a range of biological materials, from cells to tissues, whole organs, and even whole organisms.[5]

In 2020 the National Science Foundation (NSF) awarded major funding to create the Engineering Research Center (ERC) for Advanced Technologies for the Preservation of Biological Systems (ATP-Bio).[6] The ERC program began nearly 40 years ago and has funded scores of ERCs to conduct convergent and revolutionary research.[7] The ATP-Bio ERC crosses six core research institutions: the University of Minnesota (UMN), Massachusetts General Hospital (MGH), University of California Berkeley, University of California Riverside, Texas A&M University, and Carnegie Mellon University. Led by John Bischof, Ph.D. (UMN) and Mehmet Toner, Ph.D. (MGH), ATP-Bio is working to enable advanced biopreservation at multiple scales (from cells and tissues to whole organs and organisms). These flexible, enabling technologies will have a wide range of uses across three major spheres: biomedicine, food systems, and environmental conservation.

In funding ATP-Bio, NSF built a novel structure. For the first time, the agency embraced the need to ensure ethical, legal, and societal analysis of the revolutionary technology under development. ATP-Bio thus has a dedicated Ethics & Public Policy (EPP) component, directed by Susan M. Wolf, J.D., and co-led by Timothy Pruett, M.D.[8] Though some past ERCs had examined ethics, ATP-Bio is the first to our knowledge to build a dedicated component into the center's structure, though some other ERCs now have similar units. This reflects NSF's evolving ambitions for the ERC program, from the goal of successful translation and commercialization to the larger goal of achieving net societal benefit. In addition to ATP-Bio, NSF now funds other ERCs with dedicated attention to societal impact and community engagement. Indeed, NSF has now convened a Stakeholder Engagement & Impact Collaborative (SEIC) across the current ERCs to share methods and insights.[9]

The EPP component in ATP-Bio depends on the expert contributions of a 13-member Ethics & Public Policy Panel (EP3) (**Table 1**). From the start of our EPP work, this team has used multiple methods to analyze the ethical, legal, and societal implications of ATP-Bio research and technology development. These have included literature analysis; consultation with science, engineering, and biomedical experts inside the ERC and beyond; and consideration of multiple techniques for assessing the implications of emerging technologies. Those techniques include but are not limited to responsible innovation, anticipatory governance, horizon scanning, and a range of techniques associated with the National Institutes of Health's (NIH) ELSI program.[10] Helpful models have included those utilized by relevant study committees at the National Academies of Sciences, Engineering, and Medicine.[11]

This symposium grows out of EPP's efforts to map the landscape of ethical, legal, and policy challenges posed by the advanced biopreservation techniques that ATP-Bio scientists are developing. Analyzing these challenges has proven demanding. Advanced biopreservation is an evolving suite of techniques with an enormous range of potential applications spanning health, food, and environmental conservation. Anticipating impacts in these spheres is a predictive exercise with associated uncertainties. The one certainty is that the challenges will be profound. Advanced biopreservation —including vitrification — has the potential to suspend biological time. Cells, tissues, organs, and even whole organisms can be placed in a kind of suspended animation for an indefinite period of time, to be reanimated in a distant future and place. This has the potential to alter fundamentally the familiar rules governing biological life — life and then death in predictable geographical spaces. Advanced bio-

This symposium grows out of EPP's efforts to map the landscape of ethical, legal, and policy challenges posed by the advanced biopreservation techniques that ATP-Bio scientists are developing. Analyzing these challenges has proven demanding. Advanced biopreservation is an evolving suite of techniques with an enormous range of potential applications spanning health, food, and environmental conservation. Anticipating impacts in these spheres is a predictive exercise with associated uncertainties. The one certainty is that the challenges will be profound.

The Journal of Law, Medicine & Ethics, 52 (2024): 529-533.

preservation may enable indefinite organ banking for transplantation, aquaculture to bring protein to more of the world, preservation of endangered species and transport to new environments, and even prolonged space travel.

The articles in this symposium tackle all of those potential applications and more. In Section 1 of the symposium, four articles map the challenges of advanced biopreservation. The first article by Wolf et al. on "Anticipating Biopreservation Technologies that Pause Biological Time: Building Governance & Coordination Across Applications" canvasses the challenges across the major domains of potential application to analyze what governance innovations are needed and how to coordinate governance across disparate regulatory and oversight regimes. The second article by Maynard et al. on "Successfully Bridging Innovation and Application: Exploring the Utility of a Risk Innovation Approach in the NSF Engineering Research Center for Advanced Biopreservation Technologies (ATP-Bio)" reports the results of a novel workshop process inviting ATP-Bio Partners — the commercial, nonprofit, and government entities already engaged with the ERC — to systematically identify perceived areas of value and threats in translating advanced biopreservation methods to application. The third

Table 1

Members of the ATP-Bio Ethics & Public Policy Panel (EP3)
Evelyn Brister, PhD – Professor of Philosophy, Rochester Institute of Technology
Shawneequa L. Callier, JD, MA – Associate Professor of Clinical Research and Leadership, George Washington University School of Medicine and Health Sciences
Alexander Morgan Capron, LLB – University Professor Emeritus and Scott H. Bice Chair Emeritus in Healthcare Law, Policy and Ethics (Gould School of Law), and Professor Emeritus of Law and Medicine (Keck School of Medicine), University of Southern California
James F. Childress, PhD – Professor Emeritus of Religious Studies, University Professor Emeritus, and John Allen Hollingsworth Professor Emeritus of Ethics, University of Virginia
Barbara J. Evans, JD, PhD, LLM – Professor of Law and Stephen C. O'Connell Chair (Law School), and Professor of Engineering (Wertheim School of Engineering), University of Florida
Michele Bratcher Goodwin, JD, LLM, SJD – Linda D. & Timothy J. O'Neill Professor of Constitutional Law and Global Health Policy, and Co-Faculty Director, O'Neill Institute for National and Global Health Law, Georgetown University
Insoo Hyun, PhD – Director, Center for Life Sciences and Public Learning, Museum of Science Boston
Rosario Isasi, JD, MPH – Associate Professor of Human Genetics, University of Miami School of Medicine
Gary E. Marchant, PhD, JD, MPP – Regents Professor of Law and Faculty Director, Center for Law, Science and Innovation (Sandra Day O'Connor College of Law), and Lincoln Professor of Law, Ethics & Emerging Technologies (Lincoln Center for Applied Ethics), Arizona State University
Andrew D. Maynard, PhD – Professor, School for the Future of Innovation in Society, Arizona State University
Kenneth A. Oye, PhD – Professor of Political Science (School of Humanities, Arts and Social Sciences), Professor of Data Systems and Society (School of Engineering), and Director, Program on Emerging Technologies, Massachusetts Institute of Technology
Paul B. Thompson, PhD – Professor Emeritus & W.K. Kellogg Chair Emeritus in Agricultural, Food and Community Ethics, Michigan State University
Terrence R. Tiersch, PhD – Professor of Renewable Natural Resources and Director, Aquaculture Germplasm & Genetic Resources Center, Louisiana State University

The Journal of Law, Medicine & Ethics, 52 (2024): 529-533.

article by Childress et al. on "Ethical Issues in Emerging Technologies to Extend the Viability of Biological Materials Across Time and Space" applies an overarching ethical framework to consider the challenges posed in advanced biopreservation in three domains: organ and tissue transplantation and medical applications, food production, and environmental conservation. The fourth article by Hyun et al. on "The Need for Early Engagement with Interested Groups on Advanced Biopreservation" shows the importance of early engagement with all interested parties to guide development of this disruptive technology.

Section 2 then presents three articles focusing on biomedical applications. In "The Big Chill: Opportunities for, and Challenges to, Advanced Biopreservation of Organs for Transplantation," Capron et al. examine challenges looming even at this early preclinical stage and argue for broad dialogue to set the stage for later development of regulation and oversight processes. In "An 'Amazon of Living Things'? The History & Horror of Commodifying Life," Goodwin urges the importance of evaluating efforts to biopreserve, store, and potentially commercialize body parts, cells, and tissues in light of the history of human commodification both in the United States and globally. Then in "Biopreserving Pathogens: Promise & Peril," Jaskiewicz et al. consider the risks and benefits of biopreserving two important pathogens — *Cryptosporidium* and *Plasmodium* — the first of which is classified by the Centers for Disease Control and Prevention (CDC) as a Category B Bioterrorism Agent.[12]

Section 3 collects articles on applications in conservation biology and the food supply. In "Manipulating Time by Cryopreservation: Designing an Environmental Future by Maintaining a Portal to the Past," Brister et al. consider how the use of advanced biopreservation is framed in environmental conservation, including metaphors of "stopping" or "freezing" biological time. Feys et al. then analyze the potential development and use of suspended animation to allow deep space exploration in "Biopreservation Beyond the Biosphere: Exploring the Ethical, Legal & Social Implications of Suspended Animation in Space." Finally, in "Biopreservation in Agriculture and Food Systems: A Summary of Ethical Issues," Thompson et al. use ethical analysis to examine the application of advanced biopreservation in both agriculture and aquaculture.

This symposium is the first to map the ethical, legal, and societal challenges posed by emerging biopreservation technologies across the wide range of applications envisioned. The authors are drawn from across ATP-Bio, including EP3's experts in ethics and emerging technologies, the ERC's engineers and biomedical researchers, and additional colleagues with relevant expertise. Using multiple methods and disciplinary perspectives, we demonstrate the need for this kind of anticipatory analysis to inform research, development, oversight, and application. By embracing an examination of ethics and public policy as an intrinsic part of technology development and translation, ATP-Bio strives to integrate EPP considerations into ERC research, decisions, and progress.

Acknowledgments
Preparation of this article was supported by the National Science Foundation (NSF) Engineering Research Center for Advanced Technologies for the Preservation of Biological Systems (ATP-Bio), Award #1941543. Any opinions, findings, and conclusions or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of NSF.

Disclosures
K.U. has patent applications relevant to tissue and organ preservation and has a financial interest in and serves on the Scientific Advisory Board for Sylvatica Biotech Inc., a company focused on developing high subzero organ preservation technology. His competing interests are managed by the Massachusetts General Hospital and Mass General Brigham in accordance with their conflict-of-interest policies. The other authors have no relevant disclosures. All disclosure forms are on file with the Journal.

References
1. See, e.g., D. Knorr and M.A. Augustin, "Preserving the Food Preservation Legacy," *Critical Reviews in Food Science and Nutrition* 63, no. 28 (2023): 9519-9538, doi: https://doi.org/10.1080/10408398.2022.2065459.
2. See E.M. Walters et al., "The History of Sperm Cryopreservation," in A.A. Pacey and M.J. Tomlinson, eds., *Sperm Banking: Theory and Practice* (Cambridge: Cambridge University Press, 2009): 1-17, doi: https://doi.org/10.1017/CBO9781139193771.002.
3. See Y. Liu et al., "Genomic Analysis of miRNAs in an Extreme Mammalian Hibernator, the Arctic Ground Squirrel," *Physiological Genomics* 42A, no. 1 (2010): 39-51; D.J. Larson et al., "Wood Frog Adaptations to Overwintering in Alaska: New Limits to Freezing Tolerance," *Journal of Experimental Biology* 217, no. 12 (2014): 2193-2200; S. Giwa et al., "The Promise of Organ and Tissue Preservation to Transform Medicine," *Nature Biotechnology* 35, no. 6 (2017): 530-542.
4. See, e.g., Giwa et al., *supra* note 3.
5. See, e.g., *id.*
6. National Science Foundation Engineering Research Center for Advanced Technologies for the Preservation of Biological Systems, ATP-Bio, *available at* <https://www.atp-bio.org/> (last visited August 5, 2024).
7. National Science Foundation, Engineering Research Centers, *available at* <https://www.nsf.gov/eng/eec/erc.jsp> (last visited August 5, 2024).
8. See Consortium on Law and Values in Health, Environment & the Life Sciences, National Science Foundation Engineering Research Center for Advanced Technologies for the Preservation of Biological Systems (ATP-Bio), *available at* <https://consortium.umn.edu/research/bioengineering/nsf-engineering-research-center-advanced-technologies-preservation-biological-systems-atp/7226> (last visited August 5, 2024).
9. SEIC is co-chaired by Susan M. Wolf, J.D. (UMN) and Henning G. Schulzrinne, Ph.D. (Columbia University).
10. National Human Genome Research Institute, Ethical, Legal and Social Implications Research Program, *available at*

The Journal of Law, Medicine & Ethics, 52 (2024): 529-533. © The Author(s), 2024. Published by Cambridge University Press on behalf of American Society of Law, Medicine & Ethics.

<https://www.genome.gov/Funded-Programs-Projects/ELSI-Research-Program-ethical-legal-social-implications> (last visited August 5, 2024).

11. See, e.g., National Academies, Creating a Framework for Emerging Science, Technology, and Innovation in Health and Medicine, *available at* <https://www.nationalacademies.org/our-work/creating-a-framework-for-emerging-science-technology-and-innovation-in-health-and-medicine> (last visited August 5, 2024); National Academy of Medicine, Committee on Emerging Science, Technology, and Innovation in Health and Medicine, *available at* <https://nam.edu/programs/committee-on-emerging-science-technology-and-innovation-in-health-and-medicine/> (last visited August 5, 2024); National Academies, Future Biotechnology Products and Opportunities to Enhance Capabilities of the Biotechnology Regulatory System, *available at* <https://www.nationalacademies.org/our-work/future-biotechnology-products-and-opportunities-to-enhance-capabilities-of-the-biotechnology-regulatory-system> (last visited August 5, 2024).
12. Centers for Disease Control and Prevention (CDC), Bioterrorism Agents/Diseases, *available at* <https://emergency.cdc.gov/agent/agentlist-category.asp> (last reviewed Apr. 4, 2018) (last visited August 5, 2024).

The Journal of Law, Medicine & Ethics, 52 (2024): 529-533.