United Therapeutics
A PUBLIC BENEFIT CORPORATION

Addressing the Organ Shortage: United Therapeutics Corporation's Organ Manufacturing Program

Achieving a new annual record, more than 46,000 organ transplants were performed in the United States in 2023, according to the Organ Procurement and Transplant Network (**OPTN**),[1] and more than 800,000 patients have benefited from organ transplantation since the OPTN began tracking them in 1998.[2] This is the great news!

Here's the challenging news. Despite the almost 9% year-over-year growth in the number of organ transplants performed in 2023 compared to 2022, more than 100,000 people in the United States are on the national transplant waiting list today. What's more, one new person joins the list about every 10 minutes.[3]

But getting on the organ recipient list does not mean a person is guaranteed a transplantable organ. Organs must be matched to recipients based on blood type, body size, distance between the donor's and patient's hospital, whether the patient is ready for the transplant, and more. These are just some of the reasons why many people can remain on an organ transplant list for years, and why 17 people die each day waiting for a suitable transplant.[4]

These facts also highlight the need for and promise of a steadier supply of tolerable transplantable organs.

A (Very) Brief History of Organ Transplantation

The history of organ transplantation is older than you might think. **Dr. Jacques-Louis Reverdin**, a Swiss surgeon, completed the first verifiably documented skin transplant in 1869. But it wasn't until the 1950s that scientific research into organ transplants – and specifically for kidneys since early research focused on living donors who could survive on a single kidney – that **Dr. Joseph Murray** completed the first successful kidney transplant into **Richard Herrick**. With a kidney from his twin brother, Herrick lived another eight years after the surgery. Fast-forward, a decade of research and scientific breakthroughs in immunosuppression helped advance transplantation work of kidneys and other organs from brain-dead donors into living recipients, and ultimately to the creation of the National Organ Transplant Act of 1984.

The work the UT teams are doing today builds on these early achievements and seeks to accelerate this life saving science to make sure that **no patient gets left behind**. Ever.

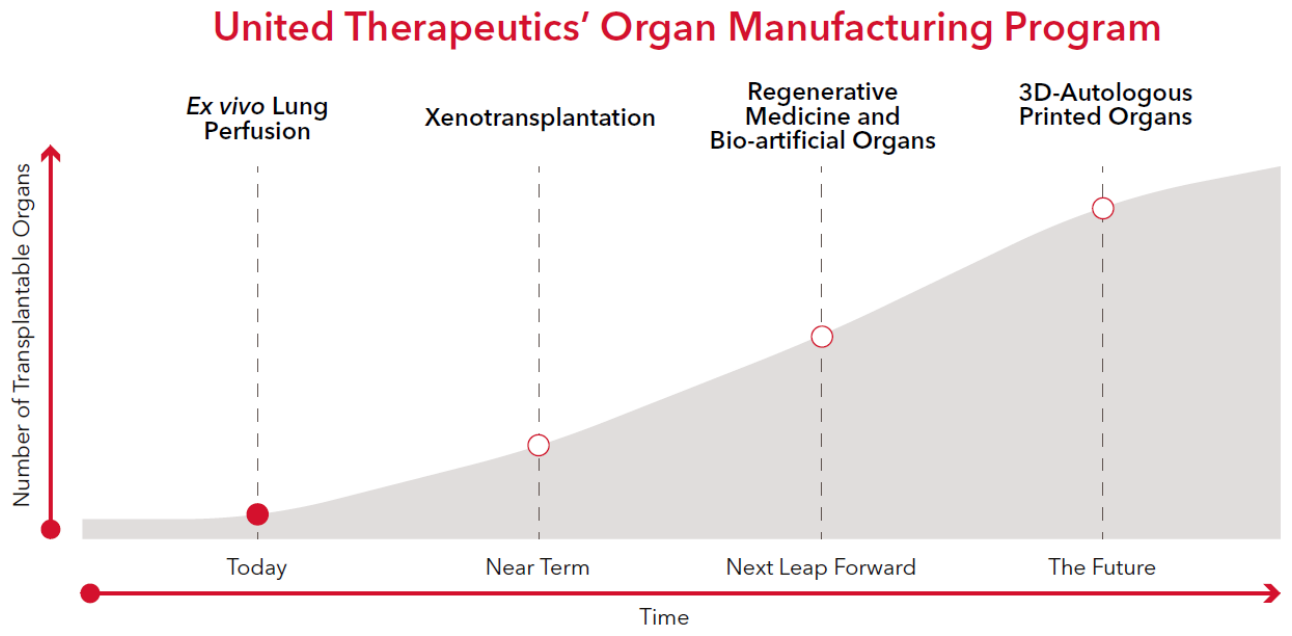
At United Therapeutics Corporation (**UT**), we strive to help address the gap between the need and the availability of suitable organs for transplant. Our founding focus—to disrupt the devastating course of a rare, terminal lung disease called pulmonary arterial hypertension (**PAH**)—led us here. The only known cure for PAH and many other end-stage organ diseases is an organ transplant. This is why **our public benefit purpose** has two parts: **to create a brighter future for patients through the development of novel pharmaceutical therapies and technologies that expand the**

[1] *Continued increase in organ donation drives records in 2023; New milestones exceeded*. (2024, January 10). OPTN.https://optn.transplant.hrsa.gov/news/continued-increase-in-organ-donation-drives-new-records-in-2023-new-milestones-exceeded/. Accessed March 26, 2024.
[2] Nordham KD, Ninokawa S. The history of organ transplantation. *Proceedings* (Baylor University Medical Center). 35(1), 124–128. https://doi.org/10.1080/08998280.2021.1985889 Accessed March 26, 2024.
[3] *National data*. (2024 March 26). OPTN. https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/#. Accessed March 26, 2024.
[4] Organ Donation Statistics. HRSA. https://www.organdonor.gov/learn/organ-donation-statistics. Accessed March 26, 2024.

availability of transplantable organs. Our first purpose helps delay or avoid the need for a transplant, while the second purpose enables a patient to have a transplant when they need one.

Turning the Improbable into Reality

The pace of innovation in the life sciences industry is fast. Successful biotechnology companies often use a portfolio approach to development. This approach increases the number of "**shots on goal**", a concept borrowed from sports to track the number of times a player or team shoots the ball or puck toward the opponent's net to score a goal. The idea works best when multiple technological approaches are focused on a single overarching goal and, through their progress, each approach enhances the potential for success of the others. This informs how we advance our organ manufacturing work.



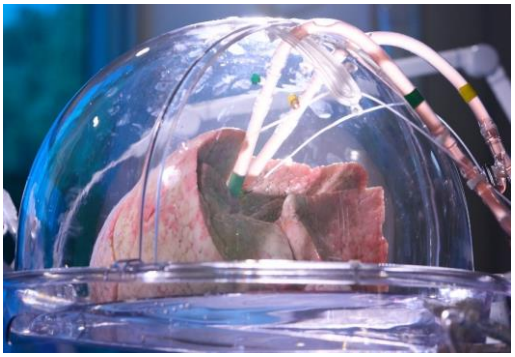
This chart is a qualitative depiction and should not be interpreted as reflecting real-world data

Through our ex vivo lung perfusion (**EVLP**) service, we are increasing the number of organs available for transplant today. We are innovating solutions that we believe will soon help save even more people's lives through our xenotransplantation and regenerative medicine efforts. We are progressing the science of manufactured organs through our bio-artificial liver and kidney organ work under way at our Miromatrix Medical (**Miromatrix**) and IVIVA Medical (**IVIVA**) subsidiaries. And we are building toward a longer-term vision to be able to supply 3D-printed organs for all who need them.

At the same time, to help support the overall organ transplant ecosystem, we are investing in new services to help ease the administrative burden associated with organ procurement and transportation and engaging with academic centers and researchers at the forefront of transplant science.

This is how we will make what seems improbable today a reality.

EVLP – Increasing the Number of Organs Available for Transplant Today



Human donor lungs under analysis at one of UT's Lung Bioengineering labs

Highlights

- More than 400 patients have received lung transplants following use of our centralized EVLP service, including more than 100 in 2023 alone.
- Our expert team of Lung Bioengineering (**LBE**) Clinical Specialists use the XVIVO Perfusion System (**XPS™**) with STEEN Solution™, the first FDA-approved EVLP device on the market.
- We developed the first centralized EVLP service model in the United States providing 24/7 year-round support services from organ procurement to transplant.

Improving the Existing Human Donor Transplant System

A record setting number of human donor lung transplants—over 3,000—were performed in the United States in 2023, according to the OPTN. Nonetheless, the OPTN notes that only about 20% of donor lungs in the U.S. are used for transplant. The reason? Among other factors, lungs are fragile and how a person lived or died affects the suitability of any organ for transplantation into a recipient and whether a transplant surgeon will accept the lung for their patient-recipient.

The Journey of an Organ

The human donor organ transplant system is complex, involving interactions between several stakeholders: patients, family members, healthcare professionals, organ procurement and transplant coordinators, the hospital where the donation occurs, the organ procurement organization (**OPO**) that facilities the acquisition and distribution of organs, and the transplant center. Our EVLP process helps increase the number of lungs used for transplant by allowing physicians to gather more data on lungs that would otherwise not be used so that a "no" can become a "yes." Our LBE team also helps OPOs and transplant centers by facilitating movement of organs from donor to recipients.

Sustainable aviation for organ delivery: The safe and efficient transportation of organs is not easy. Flight or ground transportation delays can close a precious window of viability in which a recipient waits for a life-saving organ to arrive.

Since its inception in 2017, **Unither Bioelectronics** has reached several groundbreaking milestones. For example, the team completed the world's first successful **drone** delivery of donor lungs between two hospitals in Toronto in September 2021. In 2022, the team performed the first **all-electric** cross-country helicopter flight. Most recently, in 2024, the team announced the development of **hydrogen**-powered aircraft.

In recognition for its groundbreaking and deeply humanitarian efforts, **Mikaël Cardinal**, VP of Program Management, Organ Delivery Systems, and team accepted the inaugural Aéro Montréal Enterprise Innovation award at the 2024 International Aerospace Innovation Forum.

Unither Bioelectronics team accepts the 2024 Aéro Montréal Enterprise Innovation Award

Since 2014, we have been developing technologies and services with the goal of increasing the number of human donor lungs for transplantation specifically, by enabling advanced assessment of those organs that would not have been used for transplant without the use of EVLP technology. We have two facilities dedicated to EVLP: one in Silver Spring, Md., and one in a site-net zero energy facility constructed on the campus of the

Mayo Clinic in Jacksonville, Fla. Each has dedicated surgical suites with specialized EVLP expertise, equipment, and advanced software and communication technologies enabling physicians to do remote monitoring.

Our **OrganVue™** software enables practitioners to engage remotely with LBE Clinical Specialists and make in-depth clinical evaluations of donor lung viability in real-time, at any time.

Xenotransplantation – Expanding the Number of Organs for Transplant in the Near Term

Highlights

- In January 2022, University of Maryland Medicine surgeons successfully transplanted our experimental, gene-edited **UHeart™** into a living human under an expanded access authorization by the FDA. The patient survived for two months following the UHeart transplant. In June 2022, data from this procedure were published in the *New England Journal of Medicine*. In September 2023, the same surgeons successfully transplanted a second UHeart into another living human, with 40-day survival.
- Surgeons at New York University (**NYU**) successfully tested **UThymoKidneys™** and University of Alabama Birmingham (**UAB**) successfully tested **UKidneys™** from our gene-edited pigs in recently deceased human donors maintained on artificial life support. This work provided preclinical evidence that gene edited pig organs could transcend the most proximate immunological barriers to xenotransplantation. Results of the UAB study were published in the *American Journal of Transplantation* in January 2022, and results of the NYU experiments were published in the *New England Journal of Medicine* in May 2022. In 2023, researchers at NYU conducted a 61-day UThymoKidney study in a brain-dead recipient.
- We opened the world's first clinical-scale designated pathogen free (**DPF**) facility in February 2024 and expect the facility to supply **cGMP**-compliant[5] xenografts for human clinical trials, with an initial capacity of up to 125 organs per year.
- In April 2024, surgeons at NYU Langone Health successfully transplanted a UThymoKidney and the first ever left ventricular assist device (**LVAD**) into a living person.

Drawing on Nature's Work

As with the history of human-to-human organ transplantation, the concept of xenotransplantation is not new. Between the 17th and 20th centuries, there have been numerous attempts at blood transfusion from animals to humans. [6]

Organs are more complex. Composed of two components—an extracellular matrix that provides the scaffolding and structure of the organ and differentiated cells which enable the needed function—they are challenging to manufacture. So, the fastest next path forward to provide organs to those who need them today is to source them from other animals.

Pigs are being raised for this purpose for several reasons, including their short gestation periods and large litters, the fact that their organs are close in size to humans, and their tissues have been successfully transplanted into humans for years.[7]

Acquired by United Therapeutics in 2011, **Revivicor** was the first organization to clone pigs successfully. The company received FDA approval in 2020 for use of **GalSafe™** pig as a source for food and human therapeutics. These pigs contain a single gene-edit to disrupt the gene responsible for the production of the galactose-α-1,3-galactose carbohydrate, called "alpha-gal,"

[5] cGMP = current Good Manufacturing Practices
[6] Cooper, D. K. C., Ekser, B., & Tector, A. J. (2015). A brief history of clinical xenotransplantation. International Journal of Surgery (London, England), 23(Pt B), 205–210. https://doi.org/10.1016/j.ijsu.2015.06.060. Accessed March 26, 2024.
[7] Boyle, Patrick. How pig organs made their way into humans: The slow advance to transplant kidneys and hearts. (2022 February 23). AAMCNEWS. https://www.aamc.org/news/how-pig-organs-made-their-way-humans-slow-advance-transplant-kidneys-and-hearts. Accessed March 26, 2024.

on the surface of cells. The presence of alpha-gal causes an immune response in humans and is an important cause of organ transplant rejection.[8] GalSafe pigs are the source of our UThymokidneys that have been used in recent xenotransplant studies. The UHeart and the UKidney are from pigs with ten genetic edits to support organ functioning in the human body.

We are committed to animal welfare in our operations. See our **Animal Welfare Policy**.

Regenerative Medicine and Bio-artificial Organs – The Next Leap Forward

Highlights

- In 2024, UT's Miromatrix team was granted FDA clearance for the first ever clinical trial of a bioengineered organ—**miroliverELAP®**, an investigational-stage external liver assist product (**ELAP**) designed to provide liver support in critical care settings.
- In 2023, our Regenerative Medicine Laboratory in Research Triangle Park, N.C., produced 450 decellularized lung scaffolds, 220 recellularized lungs, and 1.7 trillion human cells for use in recellularization.

Bioengineering for Humans

Through our regenerative medicine and bio-artificial bioengineering programs, we seek to engineer organs using porcine organ scaffolds combined with human donor (allogeneic) cells to produce a human-like organ. **ULobe™** is a development-stage, engineered lung for transplantation, generated from pig lungs that undergo a process of decellularization to remove porcine cells and DNA leaving an acellular, pathogen-free protein scaffold which is then recellularized with primary human-derived lung cells. Our goal is to manufacture engineered lungs to help increase the supply of lungs for transplant.

UT's Miromatrix and IVIVA teams are developing bioengineered kidney and liver technologies. As noted above, in January, Miromatrix was granted FDA clearance for the first-ever clinical trial of a bioengineered organ, miroliver*ELAP*. Acute liver failure is a devastating condition with no approved therapies. A liver transplant is often the only way to save these patients. The miroliver*ELAP* is intended to give the patient's liver a chance to heal itself, possibly reducing the need for liver transplant and improving patient outcomes. Miromatrix is also working on other approaches—**miroliver®** and **mirokidney®**—that combine the use of human cells with porcine organ scaffolds. UT's IVIVA team is developing an implantable biologic graft to augment or replace vital kidney function in patients with end stage renal disease.

3D-Autologous Printed (3DAP) – The Future

Highlights

- Our 3D printed lung scaffold remains the most detailed 3D printed object in the world today, composed of about 44 trillion voxels (voxels are 3D pixels).
- A single 3D-printed lung lobe scaffold includes 200 million alveoli—about 67% of those in an average human lung today; and approximately 4,000 km of pulmonary capillaries (about 2,500 miles, roughly the distance between New York City, N.Y. and Las Vegas, Nev.).

Making to Fit

Lungs are among the most complex and delicate organs in the human body. A single lung is composed of more than 40 cell types that provide its unique structure and enable its primary function: efficient gas

[8] Li, Q., Lan, P. (2023). Activation of immune signals during organ transplantation. Signal Transduction and Targeted Therapy. 8, 110 https://doi.org/10.1038/s41392-023-01377-9. Accessed July 8, 2024.

exchange.[9] Each lung contains approximately 300 million alveoli—tiny air sacs within the lungs where oxygen and carbon dioxide exchange happens. If spread out, the alveoli alone would cover a tennis court, while the length of the capillaries on the lungs could stretch across most of the continental United States.

Our bodies' immune systems have evolved to protect us from substances or objects they recognize as "foreign" and reject them. Except for rare transplants between identical twins, organ transplantation (whether allotransplantation or xenotransplantation) has historically required recipients to take immunosuppressive drugs to prevent rejection of the transplanted organ by the recipient's body.

Our **3DAP Lung™** is a development-stage product made of high-resolution lung scaffolds that are 3D-printed with bioinks and then cellularized with a patient's *own cells* to create tolerable, transplantable, personalized organs that should not require immunosuppression to prevent rejection. In collaboration with **3D Systems Corporation**, which launched the 3D printing industry in 1986, our team co-developed a process they call **Print to Perfusion™**. Through this process, we successfully printed lung scaffolds—organ-sized objects with production accuracy at the micron scale.

3D printed lung scaffold

Improving the Organ Transplant System

As severe as the shortage of tolerable transplantable organs is today, we know that even if we could snap our fingers and magically solve the challenges associated with the supply of tolerable transplantable organs for all who need them, we would not be able to close the gap between supply and need. The fact is this: the ecosystem of organ donation is not yet ready to receive an unlimited supply of organs. There are not enough transplant centers and transplant surgeons everywhere there is a need. In addition, while the organ transplantation system is composed of many dedicated professionals, it is a system like others steeped in a culture that does not foster equity everywhere. Our companion challenge is addressing this fact identified in a recent report by the **National Research Council**: "an individual's chance of being referred for a transplant evaluation, being added to the waiting list, and receiving a transplant varies greatly based on race and ethnicity, gender, geographic location, socioeconomic status, disability status, and immigration status."[10]

Among our public benefit corporation objectives is a commitment to making sure **no patient gets left behind**. We are looking forward to continued collaboration with those who seek to enhance the trustworthiness of the organ transplant system, who are working on ways to enhance equity, and evolving ways to measure and improve overall system performance.

[9] Cunniff, B., Druso, J. E., & van der Velden, J. L. (2021). Lung organoids: advances in generation and 3D-visualization. Histochemistry and cell biology. 155(2), 301–308. https://doi.org/10.1007/s00418-020-01955-w. Accessed March 28, 2024.
[10] National Research Council. 2022. *Realizing the Promise of Equity in the Organ Transplantation System*. Washington, DC: The National Academies Press. https://doi.org/10.17226/26364. Accessed April 9, 2024.

References

- See the latest Corporate Responsibility and Public Benefit Report for additional details about our public benefit goals, objectives, and targets, and our sustainability and ESG progress: https://corporateresponsibility.unither.com/
- About our Lung Bioengineering Services: https://www.lungbioengineering.com/
- About our Revivicor subsidiary: https://www.revivicor.com/
- About our Miromatrix subsidiary: https://www.miromatrix.com/
- About our IVIVA subsidiary: https://ivivamedical.com/
- About Unither Bioelectronics: https://unither.aero/

External Resources

- **Donate to Life America**, a U.S.-based nonprofit organization that seeks to motivate the public to register as organ, eye, and tissue donors: https://donatelife.net/
- **UNOS** living organ donor information: https://unos.org/transplant/living-donation/

UN Sustainable Development Goals

Our organ work aligns most closely with UN Sustainable Development Goal 3 – Good Health and Wellbeing

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XPS and STEEN SOLUTION are registered trademarks of XVIVO Perfusion AB.

United Therapeutics Corporation rechartered as a public benefit corporation (**PBC**) in 2021—the first publicly-traded biopharmaceutical company to do so. Our **PBC purpose** has two parts: ***to create a brighter future for patients through the development of novel pharmaceutical therapies and technologies that expand the availability of transplantable organs.*** Our first purpose helps delay or avoid the need for a transplant, while the second purpose enables a patient to have a transplant when they need one.

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