CURALINK

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thecurafoundation.org

Welcome to CuraLink—a newsletter for innovators building a healthier future for all.

Dear Cura community,

I am thrilled to share the inaugural issue of CuraLink, a newsletter and interview series featuring the most pressing issues in human health, unmet medical needs and the emerging innovations and technologies directed to solve them.

Each month, we will invite some of the world's leading scientists, physicians, industry leaders, regulators and experts to share potential solutions and exciting breakthroughs with our global community. We'll also talk to industry veterans about ways to harness lessons learned to build a healthier future for all.

Ultimately, in line with our foundation's mission to #UniteToPrevent, #UniteToCure and improve human health worldwide, CuraLink will highlight voices that inform, enlighten and inspire action.

First up is a discussion with Dr. Martine Rothblatt, founder, chairperson and chief executive officer of United Therapeutics.

Robin L. Smith, MD
Founder, President and Chairman, Cura Foundation

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A conversation with Dr. Martine Rothblatt

Dr. Martine Rothblatt

Even when facing seemingly intractable problems, the visionary author, attorney, inventor and biotechnologist Dr. Martine Rothblatt has never taken no for an answer. She spent the early years of her career transforming human communication through satellite radio at Sirius XM. In 1994, her then-seven-year-old daughter, Jenesis, received a fatal lung disease diagnosis with a grim prognosis and Dr. Rothblatt immediately redirected her work toward a singular goal: create effective medications and ultimately, a cure for her child's disease.

What began as a quest to save her daughter's life has ballooned into a multi-pronged pharmaceutical and biotech company, United Therapeutics, the first publicly-traded company in the industry to take the form of a public benefit corporation. Dr. Rothblatt also created a regenerative medicine company, Revivicor, focused on applying leading-edge animal biotechnology platforms to provide a superior quality, high-volume, human-compatible, alternative tissue source for treatment of human degenerative disease.

Both endeavors have improved thousands of people's lives who are suffering from lung disease, including Jenesis's. Now, with three seminal xenotransplants having occurred in the past six months, Dr. Rothblatt's team is poised on the brink of revolutionizing the currently deficient organ transplant system. Dr. Rothblatt is closer than ever to building a world with a limitless supply of manufactured organs, in which she tells Cura, "what once was a death sentence becomes a second life."

This month, Dr. Rothblatt shares her team's tremendous progress in organ manufacturing, her personal motivations in biotech, and her ultimate hopes for humanity with the Cura Foundation.

Your journey in the medical field began as a parent. How did the life-altering diagnosis of your daughter Jenesis reorient your life and work over two decades ago?

Dr. Martine Rothblatt with her daughter, Jenesis.

It really did a complete realtering of my life's work. My passion was in the field of satellite communications, connecting people across the planet through its magic. And suddenly my daughter was diagnosed with a fatal illness, pulmonary arterial hypertension, and the doctor said she had two to three years to live—maybe a little bit longer—but that was the average. There were no medicines approved for her. The only thing they asked us to hope for was a lung transplant that was small enough for a young girl. At that moment, it was either I do something about changing that, or I am going to lose my youngest daughter.

I had no choice in my mind. I just said I'm going to pour my heart and soul into developing medicine that can save Jenesis, our daughter.

Throughout this more than two-decade journey—from researching pulmonary arterial hypertension to developing effective medications to working on organ transplant systems—you have faced seemingly insurmountable challenges. Obviously, you are working to save your daughter's life, but in addition to that, what keeps you motivated when you are up against these kinds of seemingly impossible problems?

What really keeps me motivated is my belief in science. With each problem so many people would say to me, "This is impossible, Martine, don't try it," I would ask myself: Is there a reason that it violated the laws of physics? Was there a reason that a new medicine could not be created? I would say to myself, well, thousands of medicines exist for all different types of illnesses. It is possible for me to do it. I realized the odds were long, but the alternative of not trying was to lose Jenesis. So, to me, even though the odds were long, as long as it was not impossible, I was going to go for it.

How did it feel when you heard the news that manufactured hearts and kidneys were successfully transplanted into living and brain-dead humans? How did you feel discussing these breakthroughs with your daughter, Jenesis?

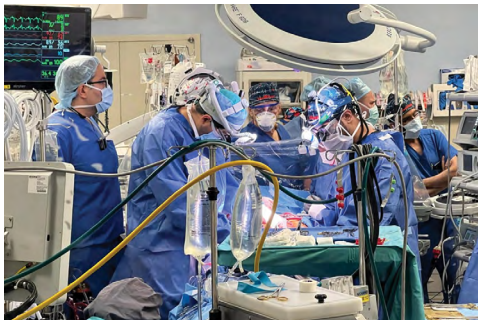
It was a tremendously gratifying experience because it was one of those things that many people thought was impossible. I knew that we could modify the genome of the pig so that its organs would not be rejected by humans. I knew that as a scientific matter, because genes are just molecules and molecules are tool kits for making things—whether they be medicines or modifications to pig organs that they won't be rejected. So, it just took a lot longer to develop the organs than to develop the medicines. Every time we modified the pig genome, we had to wait until the female pig birthed a litter of piglets, then we had to wait until that litter of piglets grew to a large enough size so that we could test to see if the organs were in fact humanized in the immunological sense. It was about a year per test of genetic modifications. And we didn't know, which were the right genes at the beginning—it was trial and error. So, it took over 10 years, but we saw that we were getting closer and closer. A year ago, we knew that we had reached the optimal number of genetic modifications. And then we asked the FDA to give us permission to begin saving people's lives.

"It's going to be a reinvention of medicine where what once was a death sentence becomes a second life."

Regarding my daughter, I could now say to her, "There are not just medicines to slow your disease. There is truly the hope of a cure on the horizon." And of course, she says, "I really would rather just stick with the medicine." Nobody wants to have a transplant surgery, and I pray to God that she can stick with the medicines. At the same time that we make these organs, we're also making our medicines better and better. We now have five different medicines approved by the FDA. But for some people, the medicines don't work and for many other lung diseases, and heart disease, kidney disease, or liver disease, medicines often don't work. So, for all of those, I've been told that our historic transplants are providing tremendous hope for literally thousands of kidney, liver and heart disease patients.

What is your ultimate vision for organ transplantation and manufacturing? What would the world look like if manufactured organs become regularly accessible?

I think it will be a whole new category of medicine. Instead of a person who ends up having liver disease, kidney disease, heart disease, or lung disease saying that they hope to get a transplant. Instead, they know they will get a transplant. I have a cousin who lost her kidney



Dr. Rothblatt (center, observing) and the University of Maryland Medical Center surgical team performing the first successful xeno-heart transplant into a living human, Mr. David Bennett.

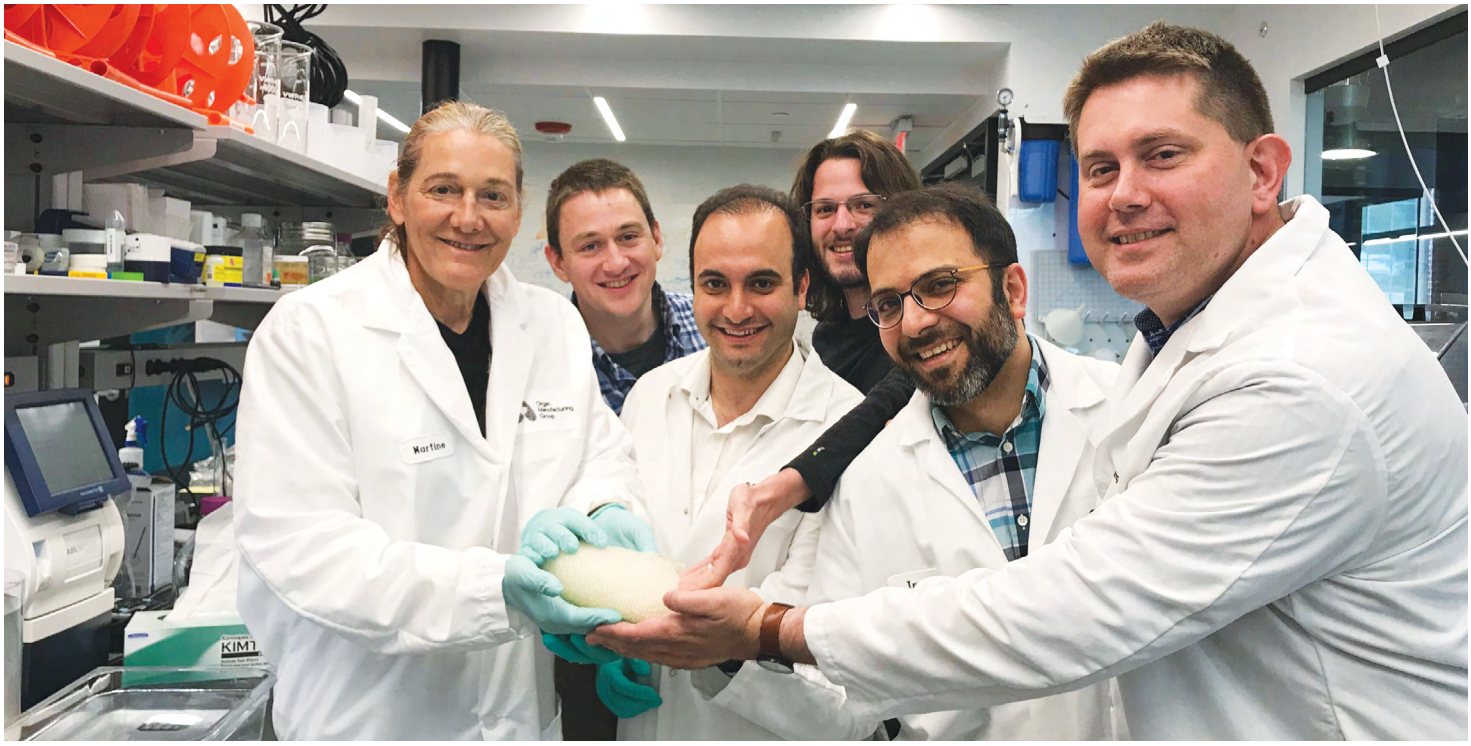
function in a terrible car accident. She has been told that because of the consequences of that car accident, she cannot be put on the kidney transplant list. But if I can just get these xeno-organs approved by the FDA, then she could have one of the xeno-kidneys, and it would be amazing for her. She has children and grandchildren, of course, like everybody else. It's going to be a reinvention of medicine where what once was a death sentence becomes a second life.

Thousands of scientists and innovators have been working on this problem for decades. Historically, why has the organ shortage been such a complex problem to solve, and what are the key ethical, financial, and medical factors involved?

It's a great question. It is such a tough problem to solve because you are working with two different black boxes or sets of unknown unknowns. One set of unknown unknowns is the human immune system. We know a lot about the human immune system, but I think most humble scientists would admit that mostly, we do not understand the human immune system. And you could see this with COVID-19 where people get vaccines, which activate antibodies, but the antibody system, which they call the humoral immune system, is only one of at least three branches and dozens of subbranches of the immune system. Vaccines don't directly affect T-cells yet people see now that we have some level of T-cell immunity against COVID-19. So, there's talking between the different arms of the immune system, which, really, we very poorly understand. So that's one black box—dealing with the human immune system.

"We are full of admiration and humility for the complexity and the elegant way everything works together in the human body."

The other black box is the pig, which believe it or not, has more genes than humans do. Pigs have a hundred thousand genes. You have to figure out which few genes out of a hundred thousand genes are the ones that allow you to make the puzzle fit together properly with the human immune system. So, you're taking one black box, the pig's genome, and you're merging it with another black box, the human immune system. That is something that could take centuries really, but we've tried to have a very disciplined, very scientific approach to do it. I provided all the funding that was necessary for it, and it is not cheap. We have spent well over a hundred million dollars on



Dr. Rothblatt and her team at United Therapeutics with the first 3D-printed collagen scaffold.

this effort to develop these transplantable kidneys and hearts, but we feel that it's our purpose to do it.

We feel very blessed that we have these wonderful medicines that have been approved by the FDA and patients who take our medicines. They're costly because they are rare diseases. We feel it's our obligation to use our revenues from providing these medicines for patients to developing a true organ cure for them. So, we have been absolutely devoted to doing this no matter how much money it took.

Your company is focused on taking three parallel approaches: xenotransplantation, regenerative medicine, and 3D bioprinting. Can you explain the key advantages and disadvantages of these different methods and how they are working together to revolutionize the way we conduct organ transplants?

We have a policy at United Therapeutics that we call "multiple shots on goal." We always try to take multiple shots on goal because we are full of admiration and humility for the complexity and the elegant way everything works together in the human body. And therefore, it would seem to us to be hubristic to think, "Oh, we definitely have the silver bullet for such and such a problem." Instead, we approach the human body with respect and humility.

To do that, we've developed three different approaches to provide an unlimited supply of transplantable organs. The first approach which we have been talking about already is modifying the pig's genome so that its organ will be no different when it is transplanted into a human than an organ donated from an unfortunate car accident victim or something like that. The patients will still need to take immunosuppressants with our xeno-organs because it is just like it is coming from another person.

Our second approach is to actually grow the organs in a laboratory and not involve the pigs at all. This approach is what we call regenerative medicine. In the laboratory, we create the shape of the organ or the scaffold. Then we grow billions of cells that will coat the organ. Every human organ has, to a rough approximation, typically around five billion cells. Right now, in our laboratories at United Therapeutics, we are growing over two trillion cells a year. That is enough for the many dozens of organs that we will use for clinical trials. When we grow the cells to then print them on top of the organ, the easier step is to grow cells in a handful of different types—sort of how there are blood types of O, A, B, AB, B+ and so on. So, there are also different immunological types for cells. It is easier for us to grow billions of cells when we are growing them of the same type over and over again. And so, with those organs that are covered with those cells or cellularized with those cells, the patient will be able to take a much lower dose of immunosuppression because it will be like they received an organ donation from a close relative.

The ultimate approach is autologous, which means it is from your own body. When a patient needs an organ, we will take a skin biopsy from the patient and in that skin biopsy, we will get a few million of their cells. We will turn those cells back to the stem cell stage in what is called making inducible pluripotent stem cells, which means we have forced it to become an all-powerful stem cell. And then we will re-differentiate that stem cell to be the particular type of organ cell that we are making. If we are making kidneys, it would become cells for the kidney, lung cells for the lungs, etc. Then using the same techniques that I talked about previously, we will make billions of those cells, but they will all be exactly that patient's DNA. So those organs will just be for one particular person—the cell-donating recipient of the organ. The benefit of that is that this person will not need to take any immunosuppression at all.

Each of these things fits into different categories. Let's say, for example, you are a soldier fighting in a war someplace trying to defend our country as our soldiers do. If there is a battle going on and soldiers are getting terribly injured, we can afford to send pig organs—xeno-hearts, xeno-kidneys and xeno-livers—every day into the battle zone. If a soldier receives a terrible bodily injury, they cannot wait months on the transplant list. They need to have a same-day transplant to save their life. So, we can send them organs every single day because they are as plentiful as pigs are. And you know, Americans eat a hundred million pigs a year.

On the other hand, if a patient has been diagnosed with a somewhat slowly progressing lung disease, something like pulmonary fibrosis or COPD (chronic obstructive pulmonary disease), and the doctor says, "Look, we can slow your disease a little, but in two years you're going to need an organ transplant." That is enough time for us to get a skin biopsy from the patient to create their stem cells and in less than a year, we could create for them

a personalized organ that can then be transplanted, and they would never need to take immunosuppressants. Regenerative medicine falls in between those two extremes.

If you did a transplant for a disease like idiopathic pulmonary fibrosis, would you still need to do something further so that the new lung wouldn't fibrose since the disease is progressive?

In my opinion, we should first get FDA approval for these personalized organs. This is often the case, for example, with liver disease, because a lot of liver diseases have a genetic component to them. Even if that liver or that lung is going to reacquire that person's genetic disease, it is usually going to take 10 to 20 years for that to happen. During that time, we can replace that organ that has fibrosed or otherwise been damaged by their genetic disease. After we accomplish FDA approval for xeno-organs, we could correct the individual's genetic defect before we make five billion copies of their cells. All of those cells would be their same DNA, except the genetic defect that was causing their disease would be corrected. Then they would not have to take immunosuppression, and they would also not redevelop that disease. We actually use our same team of people in San Diego that engineered the pig genome for us that allowed us to make the heart for Mr. Bennett and the kidneys for the patients to also engineer these genetic modifications starting with cystic fibrosis.

Dr. Martine Rothblatt with Dr. Bartley Griffith, the University of Maryland Medical Center surgeon who successfully transplanted a xeno-heart into patient David Bennett.

How far off is a future where some of these manufactured organs and this other technology are accessible and affordable to patients?

I would say it would be between the end of the twenties and the beginning of the thirties.

You've already saved thousands of people's lives through the medications you've developed and now you're doing the same with organ manufacturing. What do you hope your legacy will be in health care and biotech?

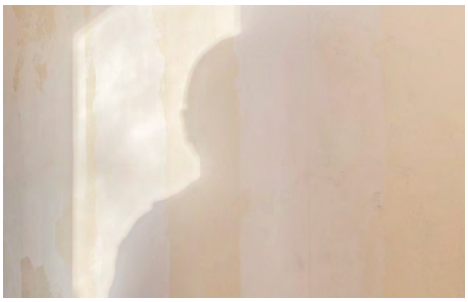
Honestly, I'm not really a legacy person. My philosophy is really to live each day at a time. I try, with whatever abilities I have, to help people live fulfilling, happy lives one day at a time. I love the saying, "The past is history, the future is a mystery, and today is a gift." So I really focus on one day at a time. I hardly think about my legacy at all.

Dr. Martine Rothblatt in the regenerative medicine laboratory.

I do not really think I'm separate from everybody else. We are all part of one fabric of humanity, and this is something that the Cura Foundation has been so beautiful about, in nurturing all of this new regenerative medicine from this incredible fountain of humanity, which is the Vatican. The Vatican has been able to communicate a message of human unity and human connectedness that goes deep back in time, literally back to the time of Jesus and the original apostles. There have been ups and downs, but that is the nature of humanity. We're not perfect. But there is a message of human unity that has come out of the Vatican for centuries on end. And to me, I feel that I, my friends, my coworkers, my colleagues, and the patients we help are all part of one team: humanity. Whatever legacy I have is just going to be part and parcel of the legacy of humanity.

This interview has been edited for length and clarity.

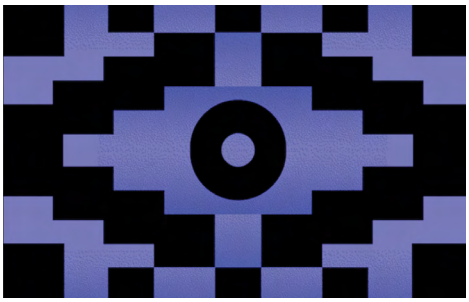
Insights, Perspectives & Ideas



The Millions of People Stuck in Pandemic Limbo

The Atlantic, February 2022

As some Americans relish in their restored freedoms, vulnerable populations navigate a tricky risk calculation. Science reporter, Ed Yong, asks the pressing question: What does society owe immunocompromised people?



The Artificial Intelligence Database

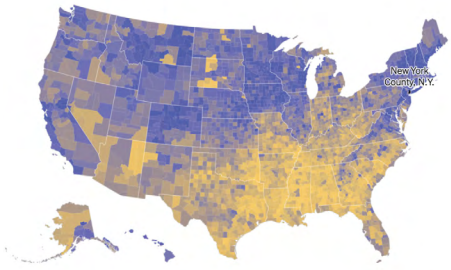
Wired, March 2021

Wired's digital hub collates their biggest stories about AI and filters them by sector, source data, end user, company and more. Recent stories highlight how AI regulations in China may shape global oversight of the technology, DeepMind's tool in modeling protein folding and the recent controversy over algorithms predicting teen pregnancy in Argentina.

COVID-19's Long Term Toll on the Heart

Nature Medicine, March 2021

In a large-scale analysis of over 11 million U.S. veterans' health records, scientists found that one year later, veterans infected with COVID-19 had increased risk of cardiovascular ailments, compared to without a COVID-19 infection. The results are "stunning ... worse than I expected, for sure," Dr. Eric Topol, a cardiologist at Scripps Research, told *Science*.



What We See in the Shameful Trends on U.S. Maternal Health

The New York Times, November 2021

Striking data from the Maternal Vulnerability Index shows that an American woman's chance of a healthy pregnancy varies greatly depending on where she lives and is based on factors such as whether she has a high school diploma, her exposure to poverty, and her access to OB-GYNs and midwives. A woman's risk of poor maternal health also varies significantly by race.

Neglected tropical diseases: ending the neglect of populations

The Lancet, January 2022

Neglected tropical diseases (NTDs) affect over 1 billion people, with most living in the world's poorest regions. In The Lancet, scientists review the progress made on the World Health Organization's decade-long effort to eliminate NTDs.

Here's How Religion Imprints Us—Even When We Walk Away

John Templeton Foundation, February 2022

Social psychologist Daryl Van Tongeren describes his research on what he calls religious "dones"—those who have de-identified with religion, and the residue their faith experience leaves behind.

Updates & Events

- Dr. Peter Libby, a leading cardiologist at Brigham and Women's Hospital, published the 12th edition of the essential medical textbook, *Braunwald's Heart Disease*.
- On February 21, the global health community lost the pioneer physician and public health expert, Dr. Paul Farmer. Through his organization Partners in Health (PIH), Dr. Farmer delivered quality health care to the world's most in-need communities.
- The Cura Foundation's and Sanford Health's #UniteToPrevent PSA Campaign was recognized as a Silver winner of Anthem Awards in Nonprofit Campaign (Health) and Best Influencer Endorsement (Health) categories. The campaign has been supported by three other entities: Aspire Capital, Alliance Global Partners and Akkad Holdings.
- From February 23-25, the Lake Nona Impact Forum hosted a conversation about building the well-being ecosystem of the future. Speakers included Dr. Noubar Afeyan, Dr. Nir Barzilai, Dr. Deepak Chopra, Dr. Richard Carmona, John Crowley, Dr. Robert Hariri, Goldie Hawn, Renée Fleming, Dr. Sanjay Gupta, Dr. Stephen Shaya, Dr. Michelle Williams, President Bill Clinton, to name a few. The conference featured especially salient conversations around mental health in the workplace, how science is transforming the aging process, and new ways of delivering potentially lifesaving vaccines.

The award-winning #UniteToPrevent PSA campaign has now reached over 535 million viewers, encouraging the public to stay positive and keep up public health practices. Learn more at UniteToPrevent.org.

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Get in Touch

Contact Us

(212) 584 4176

info@thecurafoundation.org

The Cura Foundation

PO Box 5298, New York, New York 10185

thecurafoundation.org

If you have any questions or feedback, please contact: curalink@thecurafoundation.com

Newsletter created by health and science reporter, Ali Pattillo and associate director at the Cura Foundation, Svetlana Izrailova.