CURALINK

ISSUE 30
August-September 2024
thecurafoundation.org

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

Dear Cura Community,

Welcome back to 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 address them.

If you missed last month's conversation with the legendary Renée Fleming, we highly recommend reading it on bit.ly/CuraLink-29 as well as purchasing her groundbreaking new book, "Music and Mind: Harnessing the Arts for Health and Wellness." Ms. Fleming is bridging the worlds of arts and science and highlighting how creative arts shape humanity. You'll never listen to a song or look at a painting the same way again.

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

In this issue, we speak with the pioneering research scientist Dr. Jeffrey Bluestone on the ongoing immunology revolution unleashing powerful new therapies to fight diseases. Dr. Bluestone shared insights on his illustrious career of over 40 years in immune tolerance, his most exciting accomplishments and the hope for the future of immunology. Alongside his team at Sonoma Biotherapeutics, he is now working on mobilizing the body's natural defenses to protect against rheumatoid arthritis, Crohn's disease and other autoimmune conditions. Read on for an exciting journey into immunology.

To subscribe, click here

bit.ly/CuraLink-Subscribe

A conversation with Dr. Jeffrey Bluestone

Over the last two decades, new therapies that harness the power of the immune system have been developed to make cancers and debilitating autoimmune diseases more manageable and, in some cases, have led to cures. Dr. Jeffrey Bluestone is one of the pioneering scientists responsible for this shift, shaping the future of medicine through his relentless scientific curiosity and sharp focus on public impact. Pushing the boundaries of our understanding of immunology and immune tolerance for over 40 years, he has influenced the development of therapeutics for cancer and autoimmune diseases.

Dr. Bluestone has received numerous awards for his work and was elected as a member of the American Academy of Arts and Sciences in 2006, the National Academy of Medicine in 2013 and the National Academy of Sciences in 2023. In his lab and through various past initiatives like the Parker Institute for Cancer Immunotherapy and the Immune Tolerance Network, and now, through his current venture, Sonoma Biotherapeutics, he has been at the forefront of developing new insights to control the immune response and deliver new transformative therapies to reset the immune system. His groundbreaking work in developing engineered regulatory T cell (Treg) therapies holds the promise of a new era in medicine and treatments for autoimmune diseases like rheumatoid arthritis and inflammatory bowel disease.

Jeffrey Bluestone, PhD, CEO and Co-founder, Sonoma Biotherapeutics; A. W. and Mary Margaret Clausen Distinguished Emeritus Professor of Metabolism and Endocrinology, University of California San Francisco

What sparked your interest in biology and immunology?

I have always loved science, especially biology. As a child, I spent many afternoons in the Museum of Natural History in New York City, studied all kinds of creatures and even spent a summer on a farm working with large animals. At Rutgers University, I worked in Dr. Robert Cousins' lab at Cook College on a senior honors project studying the basic biology of nutrition. I was blown away by the ability of science to identify the fundamental processes of the body and, more so, by the possibility that our work may eventually affect people's lives.

I entered a master's program in virology at Rutgers, working on a polio-like virus found in mice. I enjoyed the research but wanted to paint on a bigger canvas. I had an opportunity to spend a summer in a cancer immunology lab at the Memorial Sloan Kettering Cancer Center (MSKCC). That experience was transformational. Dr. Robert Good, an immunologist who ran the Sloan Kettering Institute, was among the first U.S. researchers to test the idea that the immune system could be harnessed to attack cancer cells. It was not yet a mainstream idea. Then, most of the focus was on developing treatments that directly killed cancer cells, like radiation or chemotherapy. However, inspired by the immense power of the immune system, I decided to play in this sandbox, so I entered the MSKCC PhD program at Cornell Graduate School of Medical Science to focus on cancer immunology.

Dr. Good and others built on the anecdotal data from the studies by Dr. William B. Coley, a surgeon who operated on cancer patients in the late 1890s. Aseptic techniques weren't very good then, and some patients developed infections, which, surprisingly, led many of their cancers to melt away. Dr. Coley went on to intentionally infect cancer patients with bacteria—pretty scary—but quite effective in some patients. These observations foreshadowed the field of immunotherapy and the concept that boosting the immune system could fight cancers.

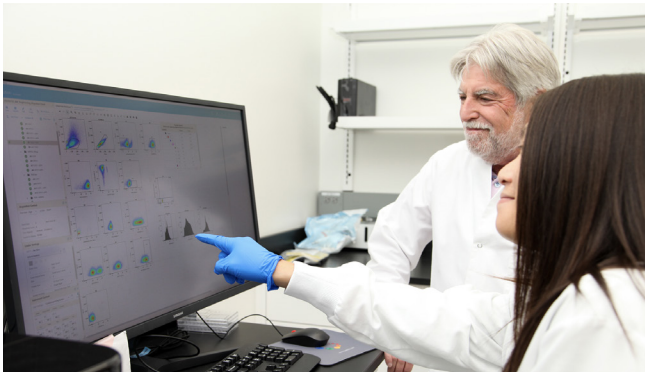
I was encouraged by the possibility of using the immune system to fight cancer but was struck by the hit-or-miss nature of the effects, with most cancers resistant to immune-mediated destruction. I focused my PhD on the idea that tumors might suppress the immune response by changing the microenvironment to inhibit tumor immunity. It took decades, but, finally, we and others showed that cancers were exceptional at shutting down the immune response by directly engaging the anti-tumor cells, known as checkpoints, and indirectly recruiting professional suppressor cells. These discoveries led to research on immune tolerance, where I have spent the rest of my career.

How did your research change the way we understand the immune system?

Immune tolerance is the ability of the immune system to respond to invaders while not attacking its own tissues—the fundamental cause of autoimmune diseases. My PhD work highlighted that the immune system had multiple mechanisms to block self-reactive immunity and that tumors were derived from one's own tissues. So, it seemed logical that if the immune system could control anti-tumor responses, the reverse must also be true: Autoimmunity resulted from the breakdown of immune tolerance.

"There are two sides to immune tolerance: inducing it and breaking it."

My PhD work was informative but lacked the molecular insights needed to understand how to induce or break tolerance. At the time, in the late 1970s, organ transplants from genetically distinct cadaveric donors were becoming a more routine treatment for kidney failure. Patients were treated life-long with immunosuppressive drugs to prevent rejection, and using the drugs led to infections or cancer. This drew me to study organ transplant rejection and immune tolerance in my postdoc at the National Institutes of Health. During eight years there, I began understanding the yin-yang of tolerance, inducing and breaking it. This work set the stage for the rest of my 40+ year career as I bounced back and forth between research in autoimmune diabetes (inducing it) and cancer (breaking it).



Dr. Bluestone's guiding philosophy of doing "kick-ass science" and collaborating with other scientists has pushed the boundaries of our understanding of immunology and immune tolerance and influenced the development of therapeutics for cancer and autoimmune diseases

The first inflection point in the field was the advent of a new technological toolkit in the 1980s: the ability to make monoclonal antibodies to detect proteins controlling the immune system and genetic engineering, a technology that allowed the identification and manipulation of individual genes in the genome. These tools allowed us to better understand the key players—the cells, pathways, proteins and cytokines involved—and what determines whether an immune response is turned on or off.

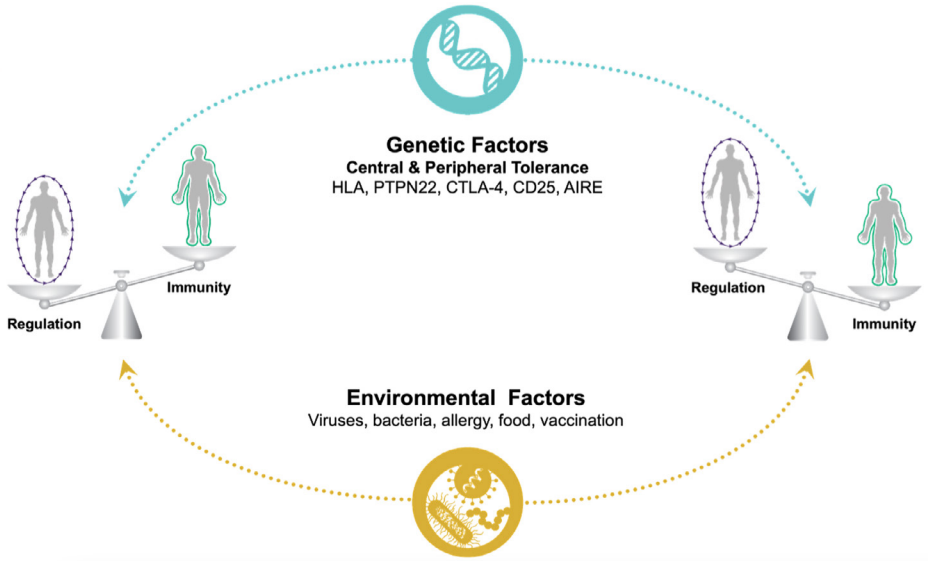
The second inflection point came with the knowledge that the immune system has sets of brakes and gas pedals designed to suppress and activate immune responses, respectively. We often imagine the immune system being composed of soldiers ready to look for and attack foreign threats. But, sometimes, these warriors make mistakes, attacking their own tissues and organs instead of foreign viruses, bacteria and other pathogens. In the 1990s, we realized that an entire arm of the immune system is designed to maintain tolerance, with some parts acting as policemen to prevent the warriors from inadvertently attacking their own tissue.

For me, this epiphany manifested in a series of studies conducted in my lab. We were studying the molecules on the surface of T cells that were critical in boosting the immune response. There was good evidence that CD28 (cluster of differentiation 28), a protein expressed on all T cells, was critical to generating a productive immune response. So, we speculated that another molecule, cytotoxic T-lymphocyte associated protein 4 (CTLA-4), expressed on activated T cells and 50% identical to CD28, likely played a similar role. So, we made an anti-CTLA-4 monoclonal antibody to block its activity, assuming it would "inhibit" T cell activation. But much to my surprise, adding anti-CTLA-4 monoclonal antibodies to cultures didn't prevent the immune response but enhanced it. This unexpected finding changed how we think about a class of molecules, including CTLA-4, expressed in the immune system that controls immune homeostasis. These checkpoints deter overzealous immune responses. This discovery established the checkpoint field and led to the development of checkpoint inhibitors that could block the off-signals and enhance tumor immunity. This discovery was an essential piece of the immune tolerance puzzle, resulting in the Nobel Prize-winning research by Drs. James Allison and Tasuku Honjo.

Perhaps as importantly, the discovery of CD28 as an "on" signal and CTLA-4 as an "off" signal broke another dogma: that all T cells performed the same role in maintaining tolerance. It became clear in the early 2000s that Tregs, a specialized cell population, expressed a high level of CTLA-4 and functioned as a major controller of immunity, seeking and shutting down unwanted immune responses. This seminal discovery was made by Drs. Fred Ramsdell and Alexander Rudensky, co-founders of Sonoma Bio, along with Japanese scientist Dr. Shimon Sakaguchi. This research changed the course of my career and led to further research on the use of engineered Tregs as therapeutics pioneered in my lab and now at Sonoma Bio.

Why are Tregs so critical, and what is their potential as therapeutics?

The immune system is engaged in a delicate balancing act, committed to seeking and eliminating infectious pathogens and, at the same time, creating a tolerogenic environment to avoid inadvertent self-reactivity. One example of an immune system gone awry is the consequence of the SARs-CoV-2 infection. The immune system is poised to recognize and destroy the virus, but, often, immune cells start producing factors that cause severe lung inflammation, resulting in COVID-19. Most people die of the consequences of dysregulated immunity rather than the viral infection itself. This



Immune regulation graphic (Bucktrout, Bluestone and Ramsdell, 2018) Immune health is a delicate balance between tolerance and immunity

dysregulation is likely partly due to the malfunction of Tregs, something seen in various autoimmune diseases.

Tregs are a key player in maintaining immune homeostasis and modulating immune function. Babies born without Tregs develop massive systemic autoimmunity, which can be lethal unless Tregs are replenished through a bone marrow transplant. Tregs are critical because they have multifaceted functions: They make several immunoregulatory factors and express proteins on their cell surfaces that shut down the immune response and educate other cells to suppress it. These proteins include several checkpoints like CTLA-4 and programmed cell death protein-1 (PD-1). Trying to replicate the polypharmaceutical activity of Tregs with a single drug is difficult unless sledgehammers like immunosuppressives are used, which can increase the risk of infection and cancer. Tregs not only shut down inflammation directly but also recruit other cells, turn them into regulatory cells and produce factors that can help regenerate and repair damaged tissues, thus amplifying their effect.

The first experiments on immune tolerance occurred in the 1950s, but the field lagged for decades after. What's it like watching progress accelerate recently?

There wasn't much progress for 30 years after Sir Peter Medawar's Nobel Prize-winning research on acquired immunological tolerance in newborn mice was published in 1951. The field was born, but many questions remained. The first major advance was the development of broad immunosuppressives to block the immune response. There was hope that tolerance would "evolve" over time. Some approaches were more successful than others. For example, bone marrow transplantation wipes out the entire immune system and lets the body rebuild it. But this broad therapeutic approach can often lead to graft-versus-host disease, where the "new" immune system attacks the body. Other treatments target the end-stage mediators of immunity. Broad immunosuppressives such as anti-TNF (tumor necrosis factor) or anti-CD20 monoclonal antibodies given for long periods of time can sometimes allow drug withdrawal. Most often, the disease requires life-long drug use, often at the expense of increased risk of infection or cancer.

I was fortunate to direct the Immune Tolerance Network where several new approaches to induce immune tolerance were pioneered including introducing peanuts during the first year of life to prevent peanut allergy. This work built on Dr. Medawar's research from the 1950s. Another example was the development of an anti-CD3 monoclonal antibody to prevent type 1 diabetes (T1D). The first monoclonal antibody drug, orthoclone OKT3, was FDA-approved in the 1980s to reverse kidney transplant rejection. The drug had some success but with significant side effects and was not durable. It took 30 years to understand all the complexities of achieving tolerance with drugs like OKT3. It led to the approval of a next-generation anti-CD3 monoclonal antibody, teplizumab, to treat at-risk individuals before they develop autoimmune T1D. It felt like vindication for the decades of hard work by so many people developing this potentially tolerogenic drug. So, are we there yet? No! Only a subset of individuals achieve life-long protection from developing T1D. Much work is left to harness the potential of immune tolerance—the holy grail for immunotherapy. We have ways to go to create scalpels instead of sledgehammers.

"Immune tolerance is the holy grail; we are not there yet."

For decades, cancer seemed like a death sentence. How has immunology changed the cancer-treatment landscape?

Cancer therapy has come a long way since the early days of radiation and chemotherapy, poisons that we hoped would kill more tumor cells than healthy tissues. We have new drugs that target cancers more specifically. Different approaches are used, too. Instead of putting chemo in the body systemically, drugs are being developed that arm tumor-specific antibodies that only kill the tumor and leave normal tissues unscathed. That's gigantic.

Turning cancers into chronic diseases is a race. You kill the cancer off with one drug, but a few of those cells mutate and come back, so you use another drug. Checkpoint inhibitors changed the game as unleashing the immune system meant that tumors "could run but could not hide." The mutations that allowed for an escape from the chemo- and targeted therapies that often beat up the immune system can be recognized by immune cells energized by the anti-PD-1, anti-CTLA-4 or other checkpoint inhibitors. These drugs were found to be even more effective when given as first-line therapies when there is a high tumor burden, the immune system is more intact, and the tumor is most immunogenic.

Cell therapy and immunotherapy could create living systems that fight cancer continuously. They rely on mutated proteins expressed by the tumor that can be recognized by the immune system, which sees them as foreign. Mutations are immunogenic and prime the immune system to recognize and kill cancer cells, generating a much more profound effect. This is where checkpoint inhibitors come in.

However, there are clear examples of failure where the immune system is not activated despite a significant mutational load. Much of this is due to the tumor microenvironment, where immunosuppressive factors and cells shut down local immunity. Tregs play a key role in this leading to new drugs to eliminate this population. In addition, more non-specific approaches like radiation and chemotherapy are now being repurposed to promote local immunogenic cell death to attract and activate the immune system.

Another approach uses killer T cells as immunotherapies. Researchers have developed novel killer cells with chimeric antigen receptors (CARs) to recognize tumor-expressed antigens in settings where mutational load is insufficient to promote tumor immunity. These engineered killer T cells are injected into patients to mediate tumor destruction. Dr. Carl June successfully treated the first pediatric patient in 2012 using genetically engineered T cells in a patient with blood cancer. It was a very gratifying moment in the field, giving hope for the future. The patient, Emily Whitehead, whom I have known since she was five, is still in remission 12 years later. However, even killer CAR T cell therapy is not a panacea, and there has been less success in other

tumors, often due to the same immunosuppressive tumor microenvironment usually associated with the inability of checkpoint inhibitors to be efficacious. Most excitingly, killer CAR T cell therapies are now being tested in autoimmune diseases to eliminate a subset of autoreactive B cells and the production of pathogenic autoantibodies, for example, in lupus nephritis patients.

How are we going beyond a single-disease, single-treatment approach?

The immune system is a fundamental platform organ in the body. It's liquid, exists in all tissues and spends all its time surveilling. Many diseases are caused by inflammation and the inability to effectively and consistently recalibrate the immune imbalance, resulting in the manifestation of autoimmune diseases, cancer or inflammatory diseases like Alzheimer's or amyotrophic lateral sclerosis (ALS).

"The immune system is a systemic and broad sentinel for tissue dysregulation."

The immune system has incredible plasticity and multifaceted activity. The same drug should work across multiple diseases if given to the right patients at the right time. We don't need to recreate the wheel but tailor our therapies to a particular disease based on a common mechanism of action. It's about tweaking the class of drugs to work specifically at disease sites while limiting off-target activity. With cancer, can we pinpoint which checkpoints the immune system is using to shut down anti-tumor immunity? Can we make the treatments work for prostate cancer versus melanoma, for instance, or will one drug work for all?

Diseases won't be defined by the tissue they target but by the biological pathways they use. In the future, we will likely develop drugs that target common pathways that affect multiple diseases and core activities throughout the immune system independent of the tissue affected. Autoimmune diabetes, rheumatoid arthritis and some neurological diseases, including multiple sclerosis, have common pathways. If we can develop a drug for those common pathways, the same drug should work in various settings.

What therapies or real-world solutions have emerged from your research that you're most proud of or excited about?

My career has followed a mantra with three philosophies, either by serendipity or intention.

"Do kick-ass science, collaborate like hell and make a difference."

The first example I mentioned was the development of a monoclonal antibody to delay and, in some cases, prevent the development of T1D. It's now given to people before they develop clinical disease and require insulin injections. Ten years out, some patients who received a single course of teplizumab still haven't developed T1D. This effort started in the 1980s. The trials and tribulations were frustrating, but we finally got over the finish line in 2022. It would not have been possible without the early science and great collaborative efforts with Dr. Kevan Herold and others. Hopefully, teplizumab will have a significant impact on T1D and other autoimmune diseases.

Another example of great science, collaboration and impact was our discovery of the first checkpoints and the development of the first antagonists to treat cancers. This work included efforts in both academia and industry. I was fortunate to be involved early and recently as CEO of the Parker Institute for Cancer Immunotherapy, a consortium of scientists who pioneered this field.

The latest example is the work that led to the founding of Sonoma Bio and its novel strategy for developing Treg-based cell therapies. The discovery by our co-founders of the key molecular switch that turned a small subset of T cells into Tregs has led to a new class of drugs that might be useful for multiple diseases and may lead to cures as long-lived drugs. Decades from now, I hope people look at cell therapy and recognize how transformative it is.

What progress have we made with autoimmune disease?

Immunotherapy in autoimmunity is further behind cancer because autoimmune diseases are generally not lethal. There is less focus on curing autoimmune diseases rather than dealing with their symptoms. In many conditions, while you are tackling an unhealthy and unhappy lifestyle, you'll be alive. Secondly, we have these sledgehammer-like drugs, including steroids, immunosuppressants and monoclonal antibodies like anti-TNF. Thirdly, the field has not been as organized, and there isn't the same sense of commonality in disease processes.

In the last five to ten years, we've realized we should treat autoimmunity like cancer. We need therapies that can profoundly change the patient's biology, give durable cures and tackle the fundamental processes responsible for the disease, not just its symptoms. The field is changing, and different stakeholders are coming together and recognizing the possibilities.

The science around autoimmunity has become more creative, and technology has helped us understand the core biology. We now have

Through his current venture, Sonoma Biotherapeutics, Dr. Bluestone has been at the forefront of developing new insights to control the immune response and create engineered regulatory T cell therapies to treat autoimmune diseases like rheumatoid arthritis and inflammatory bowel disease

some game-changing drugs that give durable treatments. We can develop drugs that weren't technically possible before, and we know which nodes to target. There's also more organizational alignment among philanthropic groups, the government and pharmaceutical companies.

What is unique about Sonoma Bio's approach and platform?

Sonoma was built on the premise that we can use genetic engineering to incorporate genes that encode CAR-Treg to enable selective targeting of immune regulatory cells to a particular protein at a certain site. In principle, the CAR-Tregs get activated at that inflamed site and focus on both increasing the specific activity of the natural Tregs and reducing the risk of systemic effects. Our goal is to create durable, safe and pathway-specific drugs.

What applications are in the pipeline?

The first indication for Sonoma Bio is rheumatoid arthritis, which affects 5 million people annually and is very difficult to control despite the wealth of approved drugs. The target we chose for the CAR is expressed in other inflammatory diseases, including certain lung and skin diseases. Thus, we initiated a second clinical trial in hidradenitis suppurativa (HS) patients. HS is a devastating and painful disease that creates abscesses and tunnels in the skin and, in turn, emotional and physical debilitation. Eighty percent of the patients are women, mostly women of color. Should we see a strong clinical response, our first product could be used in other diseases with similar causation.

Finally, we have partnered with Regeneron, a great company built on novel science and technology, to expand our disease portfolio. We are working on four more indications, including Crohn's disease and ulcerative colitis. It's been a monolithic endeavor requiring tremendous effort and collaboration.

What are the current limitations and risks of immunotherapy?

If the immune system had a simple on/off switch, it would be easy to develop drugs. But it is more like a thermostat. If you move too far to one side, you get autoimmunity. If you move too far to the other side, you get immune suppression and infections. The immune system must balance right in the middle. We must refine the therapies to ensure we don't go too far and induce other diseases while treating the primary ones. We are also working to engineer cells with receptors that allow for more specificity to activate at the disease site and shut down inflammation locally without systemic effects. Of course, one of the greatest challenges is accessibility. As a community of drug developers, we must find ways to make these therapies less expensive and logistically challenging to make them available to everyone in need.

What's next?

Next, immunotherapy will target non-immune-based diseases. We'll see an explosion of immunotherapy in functionally inflammatory diseases. Many diseases are affected by immune inflammation, including neurodegenerative diseases like Parkinson's, Alzheimer's, ALS, heart disease and stroke, for which there's an initial instigating event not necessarily involving the immune system. But the immune response to that event causes much of the damage. On the treatment side, some argue that statins reduce both cholesterol and inflammation. That may also be what drugs like Ozempic do, and we're seeing early evidence of their possible utility in autoimmunity with Crohn's or ulcerative colitis. The future is combining multiple treatments targeting distinct pathways to induce durable cures.

In Treg biology, we've learned that about half of Tregs are in circulation, and the other half sit in tissue. Fat and the intestine have more Tregs than anywhere else in the body. These Tregs control inflammation in the fat and the gut and make repair factors for damaged tissues. Excessive obesity, for instance, can cause cellular and transcriptional alterations in the Tregs, affecting their ability to modulate local and systemic inflammation and contributing to insulin resistance. The microbiome (bacteria in the gut) can alter Treg function to create susceptibility to inflammatory bowel syndrome. Treg and Treg-friendly cell therapies are potential treatments for these impacted tissues.

Is there anything people can do to support their immune tolerance or immune balance or even rebuild their immune system?

Everything I've talked about is fundamentally about inflammation. Unwanted inflammation causes immune system dysregulation. A healthy lifestyle with a reasonable diet and good exercise, combined with reduced stress, will lead to a more stable and reliable immune system. External forces constantly create imbalances in the immune system, but a more centered, balanced life will help center and balance it.

What is your ultimate vision for immunotherapy and cell therapy?

People say never to use the word cure because it sets the bar too high. But I expect cell therapies to become curative medicine. I would love for cell therapy to become so routine, effective and accessible that it is literally a pill in a bottle for people to rebuild and rebalance their immune systems. I hope it is transformational in how we treat diseases.

This interview has been edited for length and clarity.

Insights, Perspectives & Ideas

A Blood Test Accurately Diagnosed Alzheimer's 90% of the Time, Study Finds

The New York Times, July 2024

A new study in *JAMA* shows promising results for a blood test that can accurately diagnose Alzheimer's disease about 90% of the time in patients with memory problems. With over 32 million Alzheimer's cases globally, the test can become an affordable diagnostic for people with cognitive impairments. The test measured a form of the protein tau (ptau-217) and tracked amyloid, outperforming diagnostic methods used by memory specialists and primary care physicians, who were wrong 25% and 41% of the time. Experts cautioned that results of the Swedish study should be confirmed in more diverse populations and that the test should be administered after assessing memory and thinking abilities and be confirmed by gold-standard methods such as PET scans or spinal taps to measure amyloid.

Doctors Can Now Save Very Premature Babies. Most Hospitals Don't Try.

The Wall Street Journal, August 2024

Hospitals can now save increasingly younger premature newborns, with doctors agreeing on treatment for babies born at 25 weeks, while those 20 weeks or less are too small to save. Medical advances aiding lung development and protecting skin and organs allow newborns to survive at 22 weeks and, rarely, 21 weeks. Forty-five percent of U.S. neonatal intensive care units provide care to some of the 8,000 infants born at 22-24 weeks annually, with experienced hospitals reporting up to 67% survival rates. Most hospitals aren't equipped or choose not to offer care due to the likelihood of failure, high costs and risks of disability and offer comfort care instead. Parents often lack awareness of medical possibilities and nearby hospitals' capabilities, as no comprehensive list of hospitals treating 22-week babies exists.

Scientists May Have Finally Found a Cheap, Natural Cure for Baldness

BBC Science Focus Magazine, August 2024

Scientists have discovered 2-deoxy-D-ribose (2dDR), a naturally occurring sugar in the human body, as a potential treatment for male pattern baldness. A study published in *Frontiers in Pharmacology* found that 2dDR gel was 80-90% as effective as minoxidil, a component of Rogaine® and Theroxidil, in promoting hair regrowth in mice, with potentially fewer side effects than current FDA-approved solutions. 2dDR is inexpensive and stable, works by stimulating blood vessel growth and could potentially help with chemotherapy-induced hair loss. However, experts noted that the link between blood flow and hair growth has not been conclusively demonstrated. Research on human subjects is needed before 2dDR-based treatments become available.

The Summer Olympics Can't Keep Up This Speed

The Atlantic, August 2024

The 2021 Tokyo and 2024 Paris Olympics experienced extreme heat, with Los Angeles 2028 expected to face similar challenges. Heat can weigh down even the best-trained athletes, and it can negatively impact distance races in cycling and running if they are longer than 1.5-2 minutes, potentially limiting marathon times and record-breaking at the Summer Olympics. Climate change will also limit the roster of potential host cities for both Summer and Winter games and force the games to adapt. Summer games may have to be rescheduled to cooler seasons, and increased heat training would be necessary for athletes. Experts disagree on the long-term impact: While some believe records will continue to be broken due to adaptations and advancements, others suggest performance may decline if temperatures keep rising.

Long COVID Is a $1 Trillion Problem With No Cure. Experts Plead for Governments to Wake Up

Fortune Well., August 2024

A *Nature Medicine* review by Dr. Ziyad Al-Aly, Dr. Eric Topol and others highlighted that long COVID has affected around 400 million people worldwide. Its annual cost is $1 trillion of lost quality of life and economic output (or 1% of global economy) without factoring in the direct costs of health care. As COVID infection rates remain high and new variants continue to arise, more cases of long COVID are anticipated. More than 200 symptoms were identified, including memory problems, difficulty concentrating, fatigue, heart palpitations, chronic cough, shortness of breath and recurring headaches, with long COVID affecting multiple organ systems and potentially lasting years with low and inconsistent recovery rates. Awareness of the condition remains low, and researchers call for increased government action, including improved prevention measures, more research and large-scale drug trials.

Childhood Vaccines Aren't Just Saving Lives. They're Saving Money.

The New York Times, August 2024

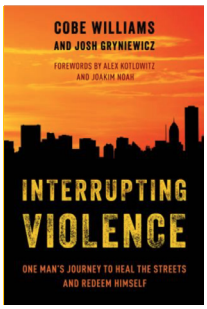
A new CDC report highlights the impact of childhood vaccines, including measles, tetanus and diphtheria in the U.S. Over 30 years, vaccines prevented 508 million illness cases, 32 million hospitalizations and 1.129 million deaths, saving $540 billion in healthcare costs and $2.7 trillion in indirect costs. Despite benefits, vaccine attitudes have shifted since 2001. According to Gallup, almost 70% of parents thought immunizations were "extremely important" or "very important," down from 94% in 2001. The shift is partly due to a lack of access to healthcare providers, rising misinformation on social media and COVID-19 vaccine skepticism that affected attitudes toward vaccines. Epidemiologist Dr. Jennifer Nuzzo is concerned that the decline in childhood vaccinations threatens not only to undo the health advances and economic benefits but also to cause larger societal instability.

Updates & Events

- Drs. Peter Libby, Eric Rubin, Marilyn Glassberg, Michael Farkouh and Robert Rosenson and Cura's President Dr. Robin Smith published "Inflammation Unites Diverse Acute and Chronic Diseases" in the *European Journal of Clinical Investigation*. The paper recounted the findings of the multidisciplinary think tank "Inflammation: Shared Pathways in Diverse Diseases" hosted by the Cura Foundation in September 2021, featuring inflammation specialists from leading global institutions. The paper demonstrates shared inflammatory mechanisms for various acute and chronic conditions spanning many specialties and calls for enhanced recognition of commonalities and cross-study to help recognize inflammation as a therapeutic target. Read it at doi.org/10.1111/eci.14280

- The Alliance for Regenerative Medicine (ARM) is hosting a 1.5-day workshop on cell-based immuno-oncology on September 5-6, 2024, in Philadelphia, PA. Free for ARM members attending in-person or virtually, this event will explore the current and future landscape of adoptive cell therapy, focusing on autologous and allogeneic cellular immunotherapies. Topics include patient access challenges for commercial autologous CAR-T products, allogeneic strategies, innate approaches and immuno-oncology techniques for solid tumors. Learn more and register at alliancerm.org/arm-event/workshops

- The Chopra Foundation is hosting its Sages & Scientists Symposium on September 13-15 at Harvard University. The event entitled "Conscious Collaboration for Global Transformation: Well-Being, Humanity, Cosmos" will feature entrepreneurs, philosophers, medical experts, scientists, celebrated musicians and influential artists to unlock innovative pathways to the most pressing global challenges. Speakers include Cura community members Drs. Deepak Chopra, Rudy Tanzi, Tyler VanderWeele, Mehmet Oz and Samarth Kulkarni as well as Salesforce CEO Marc Benioff. Cura's President Dr. Robin Smith will also participate and moderate a discussion on "The Aging Blueprint: Understanding Biomarkers for Health and Longevity." Learn more and buy tickets at sagesandscientists.org



- Congratulations to Cobe Williams and Josh Gryniewicz on publishing "Interrupting Violence: One Man's Journey to Heal the Streets and Redeem Himself." Cobe, a member of the Cura community, has been a violence interrupter for over a decade. He is trained in conflict resolution and has become an advocate for peace and safety. "Interrupting Violence" is a memoir that recounts Cobe's transformation from a gang leader to one of the leaders with a radically optimistic vision for addressing urban violence. Learn more at interruptingviolence.com and order the book at bit.ly/InterruptingViolenceBook

Join Us	Donate	Get in Touch
Become an Advocate	**Make a Contribution**	**Contact Us**
@CuraFdn	If you would like to help further our mission, we ask that you think of the Cura Foundation as you invest your time, energy and dollars.	(212) 584 4176
TheCuraFoundation		info@thecurafoundation.org
CuraFdn		**The Cura Foundation**
The Cura Foundation	thecurafoundation.org/donate	PO Box 5298, New York, New York 10185
CuraFdn		thecurafoundation.org

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

Newsletter created by health and science reporter and consulting producer for the Cura Foundation, Ali Pattillo, consulting editor, Catherine Tone and associate director at the Cura Foundation, Svetlana Izrailova.