

THE CURE CHRONICLES

June 2022 ISSUE

Enabling affordable and accessible advanced medicines

Greetings,

In our latest issue we review the news we are most excited about, spotlight **Dr. Umut Gurkan** of Case Western Reserve University, and share links to exciting presentations that are freely accessible to all.

Of note, the link in our “**Community**” section highlights a seminar series focused on Cell and Gene Therapy for the patient advocate and supporter community, sponsored by DARE (Delaney AIDS Research Enterprise, anchored at UCSF).

News

Here is the latest on what we are excited about:

- ➔ [Bluebird Bio's gene therapy for neurological disorder gets FDA panel backing](#)
- ➔ [FDA advisory committee unanimous in support of Bluebird Bio's two gene therapies](#)
- ➔ [FDA panel backs Bluebird gene therapy despite safety risks](#)

It was a big month for the cell and gene therapy community, as Bluebird Bio presented their lentiviral gene vector-based curative approaches for beta-thalassemia (transfusion dependent beta thalassemia, or Cooley's anemia, product name,

betibeglogene autotemecel or beti-cel, marketed in Europe as Zynteglo) and CALD (cerebral leukodystrophy, product name, eli-cel or elivaldogene autotemecel, marketed as Skysona in Europe) to the US FDA Cell, Tissue and Gene Therapies Advisory Committee.

For CALD, despite the occurrence of myelodysplastic syndrome (MDS) in 3 of 67 patients, the benefits far outweighed the risk for this rare, yet progressive and fatal storage disease, for patients who did not have a bone marrow donor. There were no reported transformational events for beti-cel, which had extremely impressive clinical results reported.

The review panel was stocked with experts, and the clinical and lab-based data presented by Bluebird made for an impressive and educational hearing, with a true depth to the debate. For upcoming presentations, we anticipate that addressing concerns of the committee for transformational events (that is induction of leukemia or pre-leukemic expansion of precursor cells, called “clonal expansion”) will be a key to future successful approvals. In-depth vector insertion-site analysis and monitoring for oligo-clonality are ripe for development as a service for central labs or commercial entities seeking to support new developments in gene therapy. The endorsement of both products by the Advisory Committee is great news for patients and inspires the field to keep the advances coming.

[→ PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer](#)

[→ PD-1 blockade alone for mismatch repair deficient \(dMMR\) locally advanced rectal cancer.](#)

We were also impressed by the data reported at ASCO 2022 (American Society for Clinical Oncology) for the small number of patients with mismatch repair deficient (dMMR) rectal tumors (stage II and III locally advanced). Treatment with PD-1 blockade therapy resulted in phenomenal responses, 100% of the 12 patients reported in the literature, had complete responses with no additional surgery or chemotherapy. We feature this report because it shows that the marshalling the immune system to combat solid cancers is just beginning.

[→ Safety and antiviral activity of triple combination broadly neutralizing monoclonal antibody therapy against HIV-1: a phase 1 clinical trial](#)

Our final reports feature the impact of broadly neutralizing antibodies (bNAb) on HIV infection, and the possibility of engineering B cells directly in vivo to produce them.

Senior author Dan Baruch presented data from a large group of investigators who clinically tested two broadly neutralizing antibodies in the setting of anti-retroviral therapy interruption. For as long as the antibodies were present (infused antibody half-life is generally in the neighborhood of 30 days), viral levels remained suppressed. It's an important step forward, and although an entirely passive therapy (not a vaccine), it begins to define what could be expected if such responses could be induced.

— Combination anti-HIV antibodies provide sustained virological suppression

In a similar manner, Tae-Wook Chun reported potent HIV suppression in a clinical study with two broadly neutralizing antibodies administered by direct infusion. We are encouraged by these recent advances.

— In vivo engineered B cells secrete high titers of broadly neutralizing anti-HIV antibodies in mice

While vaccination is the traditional manner by which antibodies are induced in the body, HIV appears uniquely able to evade vaccine strategies that have been tested over decades of research. Given that bNAbs can be identified (the 2 references above), researchers are now looking to directly engineer cells to produce these antibodies in the body. Senior author Adi Barzel reported the ability to do just that in mice. B cells were engineered with two AAV (adeno-associated virus vectors) -one encoding Cas9 and the other an anti-HIV bNAb, that were injected directly in vivo. These reports are each important advances on their own. Taken together, it appears the field of gene therapy may leap-frog traditional vaccine approaches by hotwiring B cells to produce bNAb directly in vivo. The key challenge will be not only in identifying the right bNAbs, but durable expression of these antibodies from the vector-transduced cells in a manner that is safe, non-genotoxic, and durable.

Community Advocate Spotlight

Umut Gurkan, PhD

Professor of Mechanical and Aerospace Engineering

Case Western Reserve University

Member of the Cancer Prevention Control & Population Research Program at Case Comprehensive Cancer Center, Case School of Medicine.



Tell us about your background and how you came to be in your current position.

I was born and raised in Turkey, the crossroads of eastern and western civilizations. My family were immigrants from Europe (Balkans) to Turkey. While in college, I discovered a passion for research and teaching, and I realized that I am good at making and inventing new things. I had no desire to work in the manufacturing or petrochemical industry, which was the traditional pathway for engineering graduates in Turkey at the time. I wanted to make a difference and help humanity. I decided to move to the US to pursue a Ph.D. degree in Biomedical Engineering at Purdue University in Indiana. After my PhD, I completed my

postdoctoral training at Harvard-MIT Health Sciences and Technology and Harvard Medical School, before joining Case Western Reserve University as a tenure-track Assistant Professor in 2013. I am the director of Case Biomanufacturing and Microfabrication Laboratory at Case Western Reserve University.

My group is at the forefront of red blood cell and microcirculation research, translational microfluidics, and point-of-care diagnostics for underserved populations. Our research has led to 90+ publications, 12 US Patents, and four biotechnology companies with products all over the world. Our inventions have turned into medical products, many of which have received FDA and regulatory approvals in the US, Europe, India, and Africa. More than 200,000 lives have been touched by our life-saving biomedical inventions to date.

The impact of my research on the welfare of the society has been recognized and highlighted by numerous honors, awards, and my induction to the National Academy of Inventors (NAI) as a Senior Elite Member, my induction to the American Institute for Medical and Biological Engineering (AIMBE) as a Fellow, and a member of the New Voices of the National Academies of Sciences, Engineering, and Medicine (NASEM).

Tell us what the focus of your efforts at the present time is and what motivates you.

Growing up in Turkey with a European heritage and spending almost half of my life in the US as a middle easterner and working in many countries in Africa and Asia for my research on sickle cell disease, I learned many critical life lessons. My life experiences define my thinking and decisions every day. For example, as a scientist, engineer, and academic entrepreneur, I find myself extraordinarily lucky to be working on improving access to personalized diagnostics, effective treatments, and definitive cures for all, regardless of where they are from or where they live ensuring equity and ethics.

For example, every year, millions of babies are born with severe hemoglobin mutations, such as sickle cell disease (SCD) and thalassemia. >99% of people living with severe hemoglobin disorders reside in resource-limited underserved communities. The World Health Organization designated SCD a global public health priority in 2006. It was reported that >70% of under-five SCD-related mortalities could have been prevented by implementing affordable, accessible screening followed by available cost-effective treatments. My group's fundamental research on human red blood cells and hemoglobin has led to discoveries and biomedical technologies for the improved diagnosis and monitoring of SCD. My team invented a portable, low-cost, point-of-care diagnostic device (the commercial name is Gazelle Hb Variant by Hemex Health Inc., <https://hemexhealth.com/>) that

can quickly detect the presence of hemoglobin variants and SCD in newborns and babies. Gazelle combines a micro-engineered lab-on-a-chip technology with artificial intelligence and wireless connectivity. We optimized Gazelle for the world's underserved and low- and middle-income regions. Gazelle is now available globally, and it has been used to screen hundreds of thousands of newborns and babies, helping save thousands of young lives.

What is your vision for the future and how would you overcome any challenges?

We are entering a new era in diagnosing, preventing, treating, and curing major diseases with rapid advances in personalized diagnostics, novel therapeutics, mRNA vaccines, cell therapies, and genome-editing-based cures. Despite the success of cell and gene therapies for certain genetic diseases, a massive gap exists between the academic labs, researchers, and companies developing these new curative genetic therapies and their availability to the patients who need them. The unfortunate reality is a geographic and demographic exclusion of underserved populations, resource-limited clinics, and low- and middle-income countries in gene therapy research, and ultimately, the availability of gene therapies to patients who need them the most. This is particularly relevant for gene therapies to treat inherited hemoglobin disorders, such as sickle cell disease that impacts millions of people in underserved communities. More than 99% of people who need gene therapy cures live in low- and middle-income countries. Bridging this divide will require inclusive basic and translational research, capacity-building, diverse workforce development, and community adoption for success and sustainable affordability. My goal is to achieve equity via promoting inclusivity and diversity in gene therapy research for sickle cell disease. My current research is focused on understanding the underlying barriers to the lack of representation and involvement of underserved populations and resource-limited regions in gene therapy research and development, specifically for sickle cell disease. We work on developing new strategies, technologies, workforce, and the necessary infrastructure to address these pressing challenges.

If there is one thing that would make a difference to your efforts, what would it be?

I am proud to say that I have established and maintain a remarkably diverse and inclusive research team. Women and underrepresented minorities in STEM comprise the 'majority' of my group. My team members are from countries including the USA, Italy, Turkey, China, India, Korea, Uganda, Nigeria, Jordan, and Bangladesh. Diversity of ideas and inclusion of everyone regardless of their race or ethnicity is the key to our group's success. All members of my lab are involved in the search, interview, and recruitment of new team members, which has remarkably maintained and enhanced the diversity of my group over the years.

Finding the right team members with shared goals and values takes time and effort. We often do highly targeted recruitment to find the right person for the right position. One thing that would make a difference to our efforts is to have motivated and interested researchers find out about us and reach out to us directly to meet and talk, and apply to join our team.

What is a fun fact about yourself that you would like to share?

I like to read history fiction novels and I am a fan of World War I and II literature, museums, and movies.

Whitepapers

Interested in learning more? Read our latest whitepapers on the Caring Cross website. Click below to access them.

→ [Centralized vs Decentralized Manufacturing of Personalized Cell Therapies: How to Implement Local Manufacturing of CAR T-Cells](#)

→ [Regulatory Considerations for Decentralized Manufacturing of Personalized Cell Therapies: A Path Forward for Commercialization of Decentralized Manufacturing of CAR-T Cell Therapies](#)

→ [Centralized vs Decentralized Manufacturing of Personalized Cell Therapies: CAR-T cell Product Manufacture, Quality and Release](#)

→ [Centralized vs Decentralized Manufacturing of Personalized Cell Therapies: Overview and Logistics](#)

→ [Introduction to Chimeric Antigen Receptor \(CAR\) engineered immune cells](#)

Upcoming Events

On the first Friday of every month, we feature a **Technology Education** seminar series. We just completed a 9-part series describing in-depth the current concepts and the development of new approaches for CAR-T therapy. This coming month we change gears entirely. We will now present a multi-part series on how to manufacture CAR-T cells and other gene therapy products in a place-of-care setting. This month we will feature introductions to the series by **Jane Resse-Koc, MBA**, and **Marcos de Lima, MD**, who together led the charge to create a high-impact clinical program at Case Western Reserve University/University Hospitals. In subsequent months you will see a step-by-step series with direct hands-on demonstrations as to how they did it.

Place-of-care manufacturing of CAR-T cells, a practical guide

[!\[\]\(3d8c13c92b853674f749aac6fa869926_img.jpg\) **Register for the event**](#)

Date: Jul 1, 2022

Time: 3:00pm EST / 12:00pm PT

Location: Zoom (link provided upon registration)

This event will last approximately 30-40 minutes and will consist of a presentation and Q&A session following.

On the third Friday of every month, we feature an international expert in cell and gene therapy. This July please register to hear **Dr. de Lima** present,

Local manufacture of anti CD19 CAR T cells to treat non-Hodgkin's lymphoma

[!\[\]\(e1c624d4757f08486e89482c18364c17_img.jpg\) **Register for the event**](#)

Date: Jul 15, 2022

Time: 3:00pm EST / 12:00pm PT

Location: Zoom (link provided upon registration)

This event will last approximately 30-40 minutes and will consist of a presentation and Q&A session following.

All our events are on Fridays at 3pm EST and require registration to access the live webinar. A recorded replay will be available to Caring Cross Community members only (**Membership is free**).

Recent Events

If you missed these recent events, click on the links below to view them.

- [Surface modification of gene transfer vectors to facilitate entry into cellular targets of gene therapy](#)
- [Molecular switches and logic gates for CAR-T \(series 9/9\)](#)
- [Point-of-Care Bispecific CAR T-cells for B-cell Malignancies](#)
- [CAR-T cells specific for multiple targets \(series 8/9\)](#)

If you are not a member, you can [become a member](#) and view all our past events.

Caring Cross Community

Please follow the link below to be enrolled for an in-depth seminar series designed to educate our community about cell and gene therapy. This series was designed by patient advocates, with a general audience in mind. Don't miss this unique opportunity to hear from international leaders in the field, designed just for you.

the DARE Community Cell and Gene Therapy webinar series

- **Register:** <https://bit.ly/3kapavg>

We are creating a membership community to connect healthcare professionals, scientists and engineers, community advocates and business leaders that are on a mission to develop new advanced medicinal cures - and help make them affordable to all who need them.

Join us to collaborate in a group, learn from seminars and training, and gain access to job opportunities or internships.

[→ Become a member](#)

What else would you like to hear about in this newsletter?

Reply to let us know.

Thank you for being here, look out for another update every other month!

- Caring Cross

P.S. Are you following along with us on social media? Be the first to know about our progress and share in the conversation!

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