

## Symposium Report

The second meeting in the series titled “Current Status of Cell and Gene Therapy Products in Hematological Malignancies” organized by the Scientific Subcommittee on Cell and Gene Therapies of the Turkish Hematology Association, titled “Manufacturing and Application Challenges in CAR T Cell Therapies,” was held as an international symposium on October 7, 2023, at the Radisson Blu Hotel in Şişli, İstanbul, with the support of the Turkish Society of Hematology.

Participants from various disciplines across Türkiye (e.g., hematologists, immunologists, physiologists, biochemists, molecular biologists, engineers), international speakers, and representatives from public institutions including TÜSEB, TÜBİTAK, TİTCK, and the Tissue, Organ, and Dialysis Center of the General Directorate of Health Services (SHGM) were invited. The meeting consisted of four main sessions.

In the first session, under the heading “Solutions for CAR T-cell therapies, for which demand is rising worldwide,” Prof. Jürgen Kuball from Utrecht University in the Netherlands presented data on commercial CAR-T products, typically produced at high scale under standardized conditions on a centralized production line by major biotechnology firms and used in various clinics, as well as sharing academic CAR-T data generated at different centers across Europe within the scope of phase 1/2 studies. He also shared the challenges encountered by the bone marrow transplantation community (EBMT GoCART Consortium) during real-world implementation processes. Discussing the centralized production model that is typically overseen by major biotechnology firms in the industry and the decentralized approach of on-site production (point-of-care manufacturing), aimed at facilitating/accelerating patient access and reducing costs, he presented the advantages and disadvantages of both approaches, the potential for industry support in the widespread distribution of academically produced products, and key considerations when selecting production centers during the initial transition to these therapies. In response to questions, he noted that in a country like Türkiye, starting academic CAR-T production at selected centers supported by other institutions and establishing a network that includes application centers could be an effective model. Prof. Michael Hudecek from the University of Würzburg in Germany shared data from the T2Evolve project and other ongoing European Union-funded CAR-T cell therapy research projects. He then presented a comparison of autologous and allogeneic CAR-T therapies from the perspectives of production and application as a solution to the rapidly increasing demand and scope of CAR-T cell therapies worldwide. Finally, Dr. Marta Espanole Rego from the University of Barcelona in Spain shared real-world experiences from the academic CAR-T process developed in Spain, the application of which was expanded after successful phase 1/2 trials and the obtaining of a special license. In the same presentation, she discussed the establishment, design, and minimum requirements of the facilities used for CAR-T production. During the discussion following that presentation, emphasis was placed on the inevitable need for industry support in the distribution phase if on-site production (decentralized or point-of-care) is chosen.

During the second session, presentations were given on the latest developments in automated closed-system cell processing platforms used in CAR-T cell production. Prof. Hans Vrieling from the Netherlands discussed the leukapheresis method used to obtain the highest-quality T cells, a critical step in CAR-T cell production, while Dr. Christina Conforti Andreoni from the R&D Department at Miltenyi Biotec in Germany highlighted Miltenyi’s technology and expertise in automated closed-system cell processing. Dr. Leticia Alserawan from the University of Barcelona in Spain shared her experiences in CAR-T cell production using various closed-automated systems in the academic CAR-T production process, while Dr. Layka Abbasi from Terumo BCT in Belgium introduced Terumo’s technology and experience in automated closed systems. During the final discussions of the session, it was noted that automated closed systems enable standardized, faster production, reducing the total process from 3-4 weeks to as little as 1 week, and quality control can be documented at every stage. It was emphasized that these systems will become the standard production technique in the future, and that even if the equipment and production costs are higher, a cost-effectiveness balance will be achieved through faster and more efficient production in both autologous and allogeneic applications.

During the third session, titled “Current Challenges in Advanced Cell and Gene Therapies in Turkey,” Prof. Kaan Kavaklı from Ege University in İzmir discussed his experiences with phase III gene therapy trials for hemophilia and the challenges encountered during the process. Prof. Mete Hüsemoglu from the Association of Research-Based Pharmaceutical Companies discussed current health policies and operations in Türkiye, the budget allocated to pharmaceuticals and healthcare, comparisons with similar countries and Europe, and regulations in Türkiye regarding advanced therapy medicinal products (ATMPs). The scarcity of centers conducting clinical trials, difficulties in evaluating efficacy, gaps in regulations, reimbursement issues (particularly the cost of ATMPs far exceeding the budget), logistical challenges, and inadequate hospital infrastructure were highlighted. Following this, Abdi İbrahim CEO Prof. Aydın Ali Özür shared his firsthand experience of the entire CAR-T process from start to finish after working in the field abroad for an extended period, and he described how this process has evolved internationally based on his own experiences. He discussed the critical importance of establishing an ecosystem that addresses the gaps between medical and non-medical disciplines and the industry, specifically focusing on how and over what timeframe these gaps were bridged and the essential connections required to initiate the process. During the discussion, the inevitability and importance of collaboration among medicine, basic sciences, reimbursement agencies, patient associations, and industry were emphasized, along with the need to set aside personal and institutional rivalries and work together with a shared vision and division of labor.

The final session was dedicated to representatives of the health authority responsible for the regulation and oversight of the development, application, and monitoring of advanced cell and gene therapies in Türkiye. Information was shared regarding the updating of regulations at TİTCK to prepare for future cellular and gene therapies, as well as how to apply for and obtain approvals for such studies. The current status of Türkiye's institutions, organizations, and regulations was outlined. Representatives from TÜBİTAK and TÜSEB discussed the current forms of grant, budget, and funding allocations, as well as the payment options available for various types of projects. Legal regulations and penalties regarding payments were also addressed. Finally, a representative from the SHGM Organ, Tissue Transplantation, and Dialysis Unit shared updates and insights regarding the application stages for clinical research and studies involving cellular and gene therapy products classified as ATMPs, as well as future projections. The discussion particularly addressed ongoing clinical trials, funding challenges, and the anticipated difficulties that similar complex processes may pose for CAR-T production in the future.

In the closing discussion, future goals and plans were discussed as follows:

- i. CAR-T cells and other cellular and gene therapy products are becoming an indispensable form of treatment.
- ii. Globally, there is a shift from manual production under conventional, GMP-compliant conditions, which have limited production capacity, toward closed-system, automated, and scaled-up production, as well as a transition from autologous to allogeneic production.
- iii. CAR-T cell and other cell/gene therapies are high-cost treatments in terms of production, distribution, and administration. New models for cost-sharing among relevant stakeholders could be developed.
- iv. It is crucial to develop, produce, and bring CAR-T cell therapies to clinical practice in our country and using our own resources, in accordance with international standards. To initiate this process and accelerate the current progress, it is of great importance to secure adequate research budgets and to establish and maintain productive collaborations among relevant research groups, industry representatives, and clinicians.
- v. While R&D efforts in this field continue, until processes are developed and optimized to expand the production and clinical use of selected academic CAR-T products, which will be prioritized for various hematological cancers at designated centers, another alternative to address the current need involves sitting down with health authorities, relevant stakeholders, and major biotechnology firms currently engaged in the commercial production and distribution of CAR-T cells to develop realistic and feasible solutions regarding patient access to these products and clinical trials.