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MEETING REPORT

Advancing CIK cell immunotherapy: highlights from the second international conference on DC-CIK and CAR-CIK approaches

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Abstract

On April 7, 2025, the *2nd International CIK Cell Conference* was held in Monza, Italy, marking the establishment of the International Society for CIK Cells (ISCC). The conference, kindly supported by *Fondazione Tettamanti* (Italy), featured cutting-edge advancements in cytokine-induced killer (CIK) cell immunotherapy, used alone and in combination with dendritic cells (DC-CIK) and chimeric antigen receptors (CAR-CIK). The event also provided a valuable opportunity for young investigators to engage in insightful discussions and to network within experts in the field.

Keywords Cytokine-induced killer (CIK) cell immunotherapy · DC-CIK · CAR-CIK · International society for CIK cells · ISCC

Abbreviations

CIK cells	Cytokine-induced killer cells
NSCLC	Non-small-cell lung cancer
CRC	Colorectal cancer
ISCC	International society of CIK cells

Main text

Welcoming the attendees, **Prof. Schmidt-Wolf (Germany)** proudly announced the founding of the International Society for CIK Cells (ISCC, https://iscc-info.org/), which will now enable clinicians and researchers working in the field of immunotherapy to exchange ideas and achieve further progress in this area. Speaking about the ISCC, he emphasized that a stronger CIK cell network integrating preclinical research and up-to-date information on clinical trials is now foreseeable. The members of the ISCC Executive Board agreed on the importance of a standardized protocol for the production of CIK cells as the primary translational perspective of ISCC. In addition to sharing scientific content related to advances in CIK cells, cancer immunology, and immunotherapy from the ISCC community, the homepage and on the official LinkedIn page will also feature personal stories that are helping to reshape the cancer landscape. He explains that significant progress has been made over the past decade with advanced strategies aimed at increasing the cytotoxic activity and tumor specificity of CIK cells ($CD3^+CD56^+$ T cells). Some of these, outlined at the conference, include DC-CIK (dendritic cells combined with CIK) and chimeric

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antigen receptor (CAR)-modified cytokine-induced killer cells (CAR-CIK).

The event started with the keynote lecture by **Prof. Dario Sangiolo (Italy).** With the title of "CAR CIK as innovative strategy against chemoresistant solid tumors". He discussed his previous attempts to test CIK cells in a sarcoma tumor model, and how he gets into the advancements of CAR CIKs. Experimental evidence highlighted how CIK lymphocytes represent a promising platform for CAR-based strategies in solid tumors, leveraging their intrinsic antitumor activity to overcome the antigenic heterogeneity of many malignancies. The discussion also emphasized the importance of translational models, particularly 3D systems, to explore clinically relevant issues such as recruitment and penetration into matrix-rich and connective tissue–dense environments [1]. A specific focus was devoted to the opportunity offered by CAR-CIK cells to target the tumor fraction with stem-like and chemoresistant features, considered key drivers of clinical relapse [2, 3]. The session- *BASIC & PRECLINICAL RESEARCH* on CIK cells continued with the engaging talk from **Prof. Antonio Rosato (Italy)** entitled as CD19/CD20 mAb-engaged Cytokine Induced Killer (CIK) Cells can represent an effective alternative of CD19 CAR-T in adoptive immunotherapy of B-cell malignancies. Subsequently, **PD Dr. Amit Sharma (Germany)**, discussed about expanding the role of CIK cell therapy and its evolving applications in Glioblastoma (GBM). He discussed recent advances in understanding GBM—despite limited treatment options and issues related to the blood–brain barrier—and highlighted his team's efforts to characterize CIK cells and DC-CIK cells within the context of GBM. First, he presented the study on balancing CIK cell cancer immunotherapy and peroxisome proliferator-activated receptor (PPAR) ligands as a potential therapeutic application for malignant diseases of the central nervous system [4]. He then discussed the investigations of CIK and DC-CIK cells on glioblastoma cell lines, particularly those with the phenotype of stem-like cells (GSCs) and patient-derived GBM organoids (GBOs). From a molecular perspective he provided evidence that increased IFN-γ secretion (rather than TNF-α) could be a potential mechanism of attack by DC-CIK cells against GBM cell models [5]. And from a molecular perspective, increased IFN-γ secretion (rather than TNF-α) could be a targeting mechanism of DC-CIK cells against GBM cell models. With ongoing efforts by his team to expand more into CAR-CIK cells and the extracellular vesicle axis, new hope for GBM-related conditions was envisioned. During this event, he also proposed the idea of training and testing CIK cells (being a T/NKT cell mixture) for non-cancer CNS pathologies, including neurodegenerative diseases (NDDs), due to their molecular overlap and inverse correlation with cancer [6, 7].

While Dr. Sharma emphasis on the CAR-CIK axis in solid cancer (GBM), **Dr. Jingjing Pu (China)** demonstrated his success CAR-CIK in hematological cancer, in particular Multiple Myeloma. With the presentation entitled-Tandem CAR-CIK and Beyond: Optimizing Cell Therapy for Multiple Myeloma-, he demonstrated that BCMA targeted CAR-T cells show remarkable clinical success in multiple myeloma (MM). However, challenges such as antigen escape, immunosuppressive tumor microenvironment, complex manufacturing, and treatment-related toxicities make it clear that improved strategies are required. Therefore, his team seeks to combine CAR-CIK to test the advantages of allogeneic feasibility, lower risk of graft-versus-host disease, and strong anti-tumor activity. He revealed that in MM, dual-target CARs that recognize BCMA and CD38 represent a particularly promising approach due to the consistent expression of these markers on malignant plasma cells. With this approach, he hypothesized that tandem CAR-CIK cells that recognize both BCMA and CD38 simultaneously may enable better disease control by reducing the likelihood of antigen-negative relapse and increasing cytotoxicity. His preliminary results suggest that tandem CAR-CIK cells not only maintain robust proliferation and cytotoxic activity, but also exhibit improved tumor elimination and persistence compared to single-target counterparts. In particular, his initial data suggests a synergistic effect when both antigens are targeted, which could contribute to overcoming clonal heterogeneity and resistance mechanisms in advanced MM. For the future, his team plans to integrate tandem CAR-CIK cells with immunomodulatory agents, combination therapies, or gene editing approaches to further improve efficacy while ensuring safety.

Prof. Martino Introna (Italy), then mentioned about his experiences in Transposon mediated anti human tenascin C targeting solid tumors. Next, a much specified talk on the topic -Directing CAR-CIK cells homing to the acute myeloid leukemia bone marrow niche was presented by **Prof. Marta Serafini (Italy)**. She mentioned that the importance of rapid and effective homing of systemically infused effector cells to disease sites has emerged as a critical factor not only in the treatment of solid tumors, but also in leukemia. Current challenges associated with CAR-CIK cell therapy in acute myeloid leukemia patients may be partially addressed by promoting efficient redirection of these cells to the bone marrow (BM), the primary niche for leukemic cells. Indeed, effective trafficking of systematically infused CAR-CIK cells to the leukemic BM could enhance their antitumor activity and persistence, thereby offering clinical benefits such as reduced therapeutic cell dose, decreased toxicity, and lower manufacturing costs. Prof. Serafini presented a strategy to engineer CAR-CIK cells that co-express chemokine receptors that match chemokines produced by leukemia cells or leukemia-associated cells, with the goal to enhance their trafficking and persistence within the leukemia BM niche. In particular, her team demonstrated that overexpression

of CXCR4, the receptor for the chemokine CXCL12, in CD33.CAR-CIK cells significantly enhanced their accumulation in the BM, leading to improved elimination of BM-resident AML cells and extended survival in a preclinical AML mouse model. Prof. Serafini and her group are now investigating alternative chemokine axes to further optimize CAR-CIK cell homing to the AML BM niche. They are also developing advanced preclinical models combined with in vivo imaging systems to better characterize CAR-CIK cell kinetics and functionality. The session ends with the very informative Lecture from **Prof. Alessandro Rambaldi (Italy)** who signifies on the Donor-derived CIK cells for the treatment of leukemia relapse after allo-HSCT.

Another session, *NEXT to the CLINIC: HEMATOLOGIC MALIGNANCIES and SOLID CANCERS* starts with the talk from **Dr. Kevin A. Fenix (Australia).** He presented the work of his team about -CIK cell therapy for metastatic colorectal cancer treatment in South Australia. He focused on the use of G-REX-derived CIK cells as an adjunct therapy for metastatic colorectal cancer (mCRC), where his team recently completed the largest meta-analysis to date on CIK cell therapy for CRC, involving 6,743 patients from 70 clinical trials [8]. These results form the basis for a proposed clinical trial in Australia targeting treatment-naive mCRC patients who are eligible for first-line chemotherapy with FOLFOX6 with or without bevacizumab. He also pointed out critical developments in the production and administration of CIK cells for the study, as a comprehensive review of the literature revealed considerable heterogeneity in culture conditions and timing, as well as the lack of a standardized dosing regimen for CRC [9]. Nevertheless, Professor Schmidt-Wolf's original protocol remains the most widely used and has also been used. For a large-scale application, Dr. Fenix described the adaptation of this protocol using G-Rex bioreactors based on the methods currently also followed by Professor Antonio Rosato's team [10]. His group is currently validating this updated protocol using patient-derived tumor organoids and preparing a feasibility study on CIK cell therapy for metastatic CRC.

Next, **Prof. Xiubao Ren (China)** focused on the clinical aspects of CIK cells. He discussed randomized, multicenter, open-label phase II study to evaluate autologous CIK cell immunotherapy in combination with PD-1 inhibitor and chemotherapy as the first-line treatment of stage IV non-small cell lung cancer (NSCLC) (CCICC-002b). He described his team's efforts to integrate the clinical use of CIK cells at a time when PD-1 antibodies were not yet available and NSCLC was mainly treated with chemotherapy [11]. Using a combination of chemotherapy and CIK cells, they conducted an exclusive multicenter, prospective, randomized, controlled phase II clinical trial for the treatment of advanced squamous cell carcinoma of the lung [12]. The trial involved a total of 8 centers in China, and two groups were formed: the CIK-CT group (autologous CIK cells in combination with chemotherapy) and the CT group (chemotherapy alone), each with 45 patients. Since the advent of immune checkpoint inhibitors, the treatment strategy for NSCLC has changed a lot worldwide. So, they conducted a retrospective study to look at the combination strategy of CIK cells and PD-1 inhibitors in more than one second-line treatment and got promising clinical results. In their preliminary study, they examined the safety and efficacy of the PD-1 blockade antibodies pembrolizumab or nivolumab in combination with or without autologous CIK cell infusion in 18 patients with advanced NSCLC [13]. Based on the efficacy advantage demonstrated in retrospective studies and the safety results, they conducted a prospective single-arm Phase IB study with CIK cells in combination with PD-1 inhibitors and chemotherapy in stage IIIB-IV lung cancer [14]. Now, a large-sample, multicenter, randomized, controlled phase II clinical trial has completed recruitment in their clinical network, and the results will soon be announced to the scientific community.

The session was concluded by "**Dr.Sarah Tettamanti**" from the Tettamanti Center, Fondazione IRCCS San Gerardo dei Tintori, who presented the latest advances in the development of non-viral Sleeping Beauty-engineered Dual CARCIK cells for the treatment of acute myeloid leukemia (AML) [15]. Dr. Tettamanti outlined the challenges of CAR T-cell therapy in AML, including the lack of tumor-specific antigens, the complexity of the immunosuppressive microenvironment, and safety concerns. She highlighted the streamlined manufacturing process for CAR-CIK cells, now optimized through a feeder-free platform, the use of G-Rex bioreactors, and next-generation Sleeping Beauty plasmids (SB100X and pT4) [16]. The presentation also reviewed encouraging data from a Phase I/II clinical trial (NCT05869279) evaluating the safety of allogeneic CARCIK-CD19 cells in adult and pediatric patients with relapsed/refractory B-NHL, developed using the newly optimized feeder-free manufacturing platform. Focusing on AML, Dr. Tettamanti discussed the development of dual-targeting CARCIK cells (CD123/CD33), including the design of optimized scFv. Preclinical studies demonstrated robust anti-leukemic efficacy in vitro and in vivo, with a favorable safety profile supported by colony-forming assays. She also highlighted ongoing experiments in humanized in vivo models, designed to further evaluate hematotoxicity alongside anti-leukemic efficacy. Finally, she announced the initiation of a Phase I/II clinical trial to evaluate CD123/CD33 Dual CARCIK cells in patients with relapsed/refractory AML. The trial will feature a dose-escalation Phase Ia to establish the maximum tolerated dose (MTD), followed by a dose-expansion Phase II to evaluate efficacy as a bridge-to-transplant strategy.

Three presentations by young researchers were selected from several abstracts submitted to the ISCC review committee. In the end, **Dr. Marta Dossena**, representative of Biotechne Company, provided an overview about the technique of—How to simplify cytokine integration into an ATMPs manufacturing process. To conclude the conference, the organizers Prof. Marta Serafini, Dr. Sarah Tettamanti expressed their gratitude to thanked Prof. Schmidt-Wolf, widely regarded as the "father of CIK cells" on behalf of all researchers and clinicians in the field, acknowledging his outstanding and life-saving contributions. Prof. Schmidt-Wolf and Prof. Xiubao Ren thanked the audience for their continued support, which had also been evident at the previous conferences [17, 18], and announced that the next—*3rd International CIK Cell Conference*—will take place in Tianjin, China.

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