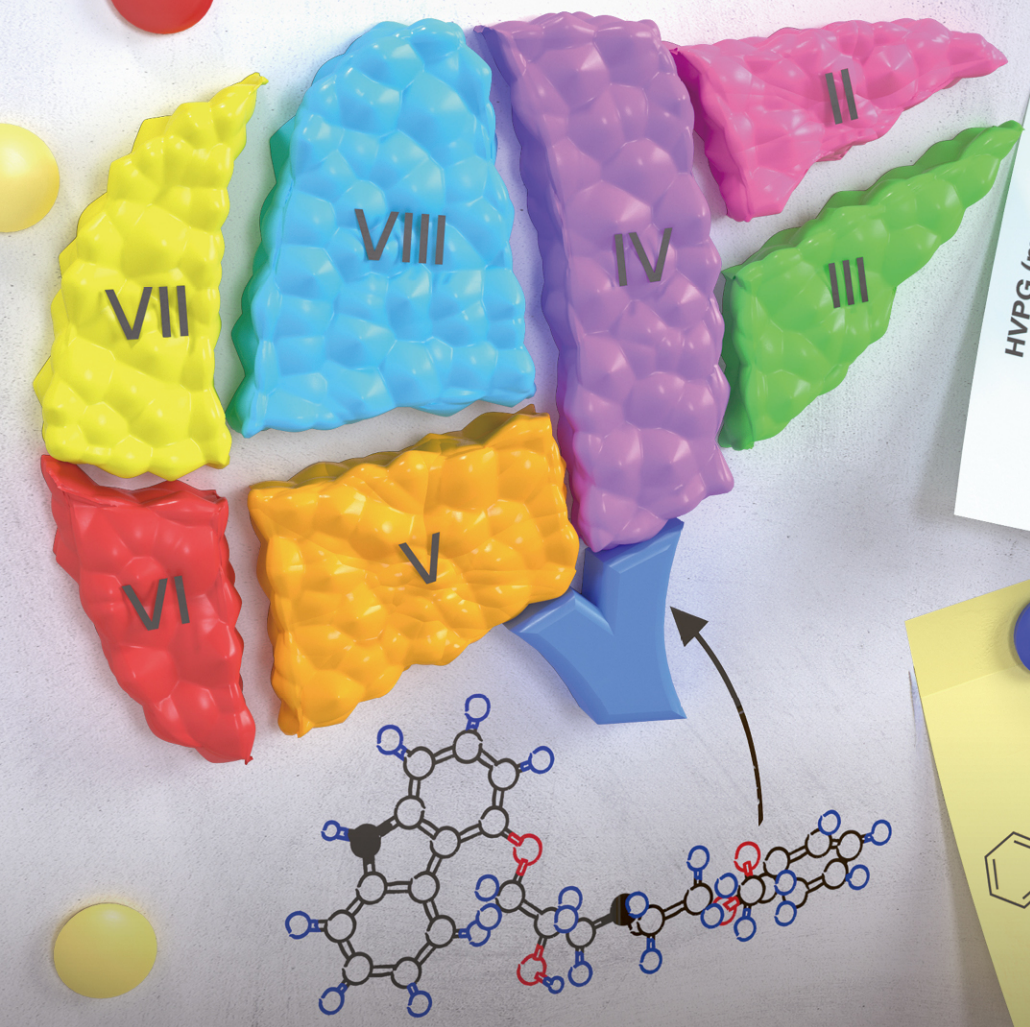
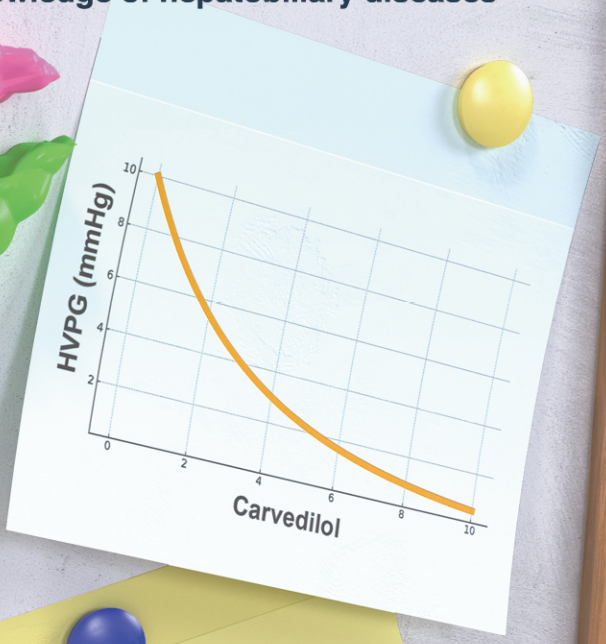
VOLUME 31 NUMBER 1 January 2025

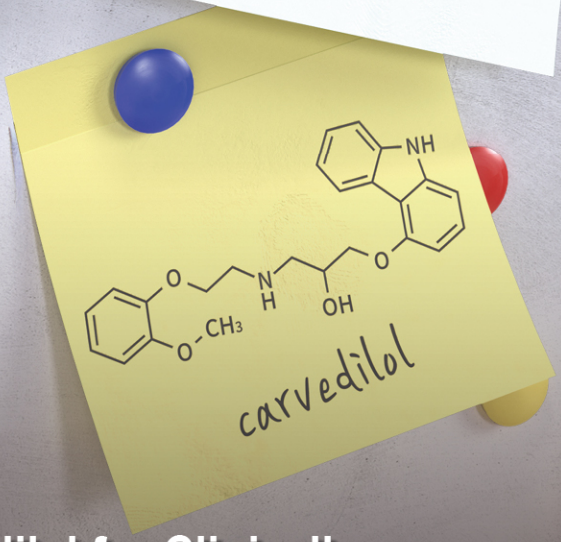
pISSN 2287-2728
eISSN 2387-285X

CLINICAL and MOLECULAR HEPATOLOGY

The forum for latest knowledge of hepatobiliary diseases







Non-invasive Model guiding Carvedilol for Clinically Significant Portal HTN

Intrapatient variability of tacrolimus on CKD in LT
HCV self-testing and disease burden reduction
MASLD and microbiota
Bariatric surgery for metabolic cirrhosis

KASL

pISSN 2287-2728
eISSN 2287-285X

CLINICAL and MOLECULAR HEPATOLOGY

https://doi.org/10.3350/cmh.2024.0781
Clinical and Molecular Hepatology 2025;31:e44-e47

Correspondence

Correspondence to editorial on "Genetically-modified, redirected T cells target hepatitis B surface antigen-positive hepatocytes and hepatocellular carcinoma lesions in a clinical setting"

Shunda Du[1], Karin Wisskirchen[2], Ke Zhang[2], and Ulrike Protzer[3]

[1]Department of Liver Surgery, Peking Union Medical College Hospital, PUMC, and Chinese Academy of Medical Sciences, Beijing, P. R. China; [2]SCG Cell Therapy Pte. Ltd., Singapore, Singapore; [3]Institute of Virology, School of Medicine, Technical University of Munich / Helmholtz Munich, Munich, Germany

Keywords: Hepatitis B virus; T cell therapy; RNA electroporation; lentivirus transduction; Hepatocellular carcinoma

Dear Editor,

We thank Dr. Antonio Bertoletti and Dr. Anthony T. Tan for their interests in our recent publication "Genetically redirected HBV-specific T cells target HBsAg-positive hepatocytes and primary lesions in HBV-associated HCC"[1] and their thoughtful commentary.[2] We welcome the opportunity to discuss the evolving field of T-cell receptor (TCR)-T cell therapy for hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) and the potential of different strategies in this complex clinical setting. In addressing this challenge, two distinct approaches have emerged: the use of RNA-electroporated T cells with a transient expression of the HBV-specific TCR, pioneered by Bertoletti and colleagues, and our approach involving lentiviral transduction to achieve stable TCR expression. Both strategies have been advanced in clinical settings through the biotech start-ups Lion TCR and SCG Cell Therapy, respectively. We want to take the opportunity to highlight key considerations as to why we chose stable TCR expression.

One of the key advantages of genetically modified TCR-T cell therapies, such as the lentivirally-transduced SCG101 used in our study, is their ability to establish memory T cells. This includes T memory stem cells, a rare subset of memory lymphocytes endowed with the stem cell-like ability to self-renew and the multipotent capacity to reconstitute the entire spectrum of memory and effector subsets. These memory cells are crucial for long-term immune surveillance

Corresponding author : **Shunda Du**
Department of Liver Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, 1 Shuaifuyuan, Wangfujing, Beijing 100730, P. R. China
Tel: +86-10-69152836, Fax: +86-10-69156043, E-mail: dushd@pumch.cn
https://orcid.org/0000-0002-9357-3259

Ulrike Protzer
Institute of Virology, Technical University of Munich/Helmholtz Munich, Trogerstrasse 30, 81675 Munich, Germany
Tel: +49-89-4140-6821, Fax: +49-89-4140-6823, E-mail: protzer@tum.de
https://orcid.org/0000-0002-9421-1911

Editor: Han Ah Lee, Chung-Ang University College of Medicine, Korea

Received : Sep. 23, 2024 / **Revised :** Oct. 12, 2024 / **Accepted :** Oct. 20, 2024

and control of viral infections and tumors - under physiological conditions and in cell therapy.[3,4] We demonstrated the presence of stem-cell-like memory T-cells carrying the TCR in our patient, indicating that these TCR-T cells persist and provide long-term immune memory. This allows for a robust, durable response that is not achievable with transiently expressed TCR-T cells.

Along that line, the persistence of infused T cells is a key factor in the success of adoptive cell therapies in hematologic malignancies, and chimeric antigen receptor (CAR)-T cells from complete-responding patients with chronic lymphocytic leukemia were shown to be enriched in memory-related genes.[5] In solid tumors, a lack of persistence of transferred cells has been identified as one of the major challenges, and a lot of research has focused on ways to support T-cell longevity.[6] All these efforts centered around stably genetically modified T cells as persistence cannot be achieved with RNA-electroporated cells.

Most convincingly, clinical studies that have analyzed T-cell persistence found a positive correlation with the response to T-cell therapy. In a trial in the early days of T-cell therapy, it was observed that neuroblastoma patients with cell persistence for more than six weeks had less progression of their tumors.[7] More recently, it was shown that clinical responses to treatment with claudin-6 (CLDN6)-specific CAR-T cells only occurred in patients with a sustained T-cell persistence over six weeks.[8] Similarly, the recent clinical data from Adaptimmune's TCR-T-cell product, the world´s first approved TCR-T therapy (Afamitresgene Autoleucel), demonstrated a correlation between exceptionally good T-cell persistence and overall survival in a phase II pivotal trial.[9] Our findings align with this perspective and suggest that TCR-T cells' durable persistence is associated with better clinical outcomes in HBV-associated HCC (unpublished results). In the following, we summarize the arguments that convinced us to use stably transduced TCR-T cells.

1. While stating T-cell persistence is indispensable, we acknowledge the discussion regarding T-cell exhaustion and the importance of maintaining functionality over time. However, it is at least possible to maintain functionality for stably transduced TCR-T cells while they persist. In contrast, mRNA-transfected T cells rapidly lose their TCR and thus cannot maintain their specificity and functionality. Although experimental data proving T-cell functionality are unavailable for the patient described, the observation of long-term tumor and virus control indicates the long-lasting functional activity of the TCR-engineered T cells, which is consistent with its capability of forming and maintaining memory T cells.
2. In their commentary, Bertoletti and Tan raised the point that neither RNA-electroporated nor stably transduced HBV surface antigen (HBsAg)-specific TCR-T cells may distinguish between HBV-infected non-tumor cells with integrated HBV-DNA, and HCC cells. This is certainly correct, and we appreciate that they have pioneered HBV-HCC T-cell therapy with the careful approach of using RNA-electroporated T cells. While RNA-electroporated T cells did not lead to any cytokine release syndrome (CRS) and only occasional liver function alterations, no sustained on-target activity was observed.[10] We hence concluded that another approach is required to increase target engagement and decided to exploit stable TCR expression. This indeed resulted in a fundamental reduction of HBsAg accompanied by alanine aminotransferase (ALT) flares proving the T cells' on-target activity. Safety considerations graded the elevation of liver enzymes within the range of benign flares,[11] most likely crucial for achieving long-term virus and tumor control. Targeting and eradicating hepatocytes carrying integrated HBV-DNA in tumors, non-tumor and premalignant cells is a vital component for improving overall treatment outcomes in HBV-HCC and preventing recurrence.[12]
3. An important consideration in the development of T-cell therapies is the development of an anti-drug immune response. Such an immune response may

Abbreviations:

ALT, alanine aminotransferase; CAR, chimeric antigen receptor; CLDN-6, claudin-6; CRS, cytokine release syndrome; DNA, deoxyribonucleic acid; HBsAg, hepatitis B virus surface antigen; HBV, hepatitis B virus; HBV-DNA, deoxyribonucleic acid of hepatitis B virus; HCC, hepatocellular carcinoma; RNA, ribonucleic acid; TCR, T-cell receptor; TCR-T, T-cell receptor T cells

arise after infusion of any kind of TCR-T cells as the TCR sequence is fully human but has been derived from another individual and is foreign to the recipient. Without prior lymphodepletion, a TCR-T-cell transfer can induce anti-TCR antibodies and anti-TCR-T-cell responses at least in a xenogeneic setting.[13] Repeated lymphodepletion, however, is not feasible and the chance of anti-drug immunity largely increases with multiple dosing, a concept widely applied in vaccination schemes. This is a particular concern for mRNA-containing products because mRNA is very potent in inducing immune responses.[14] Further human studies are needed to determine the extent to which these autoreactive immune responses occur after T-cell therapy and if anti-TCR antibodies can neutralize the infused cells, eliminate their effectiveness, or increase the risk of adverse reactions.

4. Treatment costs of T-cell therapies are a big issue. The persistence of lentivirally-transduced TCR-T cells and their capacity to amplify without losing their TCR requires only a single infusion, which largely reduces the time and costs for product fill and finish, storage, and administration, reduces hospital visits and thereby provides a better cost-benefit-ratio.

We believe that the data presented in our study provide a compelling argument for the suitability of lentiviral-transduced, stable TCR-expressing T cells for treating HBV-related HCC. The ability to form memory T cells, to avoid repeated infusions and potential immunogenicity of the TCR product, and to achieve lasting therapeutic effects makes stable grafting of T cells with TRCs the primary choice in most clinical trials. We are grateful for the opportunity to contribute to this important discussion on the evolving landscape of TCR-T-cell therapy for HBV-HCC. The development of effective, safe, and long-lasting treatments remains a priority, and we believe that diverse approaches, optimizing dose regimens, and exploring novel booster strategies, hold great promise.

We are looking forward to continued advancements in the field and collaborative efforts to improve the outcomes for the huge number of patients with HBV-related HCC.

Authors' contributions

KW wrote the initial draft, KZ and SD added important discussion points, and UP finalized the manuscript. All authors revised the final version.

Conflicts of Interest

KW and KZ are employees of SCG Cell Therapy; KW, KZ, and UP are shareholders and directors of SCG Cell Therapy Pte. Ltd.

REFERENCES

1. Wan X, Wisskirchen K, Jin T, Yang L, Wang X, Wu X, et al. Genetically-modified, redirected T cells target hepatitis B surface antigen-positive hepatocytes and hepatocellular carcinoma lesions in a clinical setting. Clin Mol Hepatol 2024;30:735-755.
2. Bertoletti A, Tan AT. Engineering HBV-specific T cells for the treatment of HBV-related HCC and HBV infection: past, present, and future. Editorial on "genetically-modified, redirected T cells target hepatitis B surface antigen-positive hepatocytes and hepatocellular carcinoma lesions in a clinical setting". Clin Mol Hepatol 2024;30:728-734.
3. Chi X, Luo S, Ye P, Hwang WL, Cha JH, Yan X, et al. T-cell exhaustion and stemness in antitumor immunity: characteristics, mechanisms, and implications. Front Immunol 2023;14:1104771.
4. Biasco L, Izotova N, Rivat C, Ghorashian S, Richardson R, Guvenel A, et al. Clonal expansion of T memory stem cells determines early anti-leukemic responses and long-term CAR T cell persistence in patients. Nat Cancer 2021;2:629-642.
5. Fraietta JA, Lacey SF, Orlando EJ, Pruteanu-Malinici I, Gohil M, Lundh S, et al. Determinants of response and resistance to CD19 chimeric antigen receptor (CAR) T cell therapy of chronic lymphocytic leukemia. Nat Med 2018;24:563-571.
6. Wittling MC, Cole AC, Brammer B, Diatikar KG, Schmitt NC, Paulos CM. Strategies for improving CAR T Cell persistence in solid tumors. Cancers (Basel) 2024;16:2858.
7. Louis CU, Savoldo B, Dotti G, Pule M, Yvon E, Myers GD, et al. Antitumor activity and long-term fate of chimeric antigen receptor-positive T cells in patients with neuroblastoma. Blood 2011;118:6050-6056.
8. Mackensen A, Haanen JBAG, Koenecke C, Alsdorf W, Wagner-Drouet E, Borchmann P, et al. CLDN6-specific CAR-T cells plus amplifying RNA vaccine in relapsed or refractory solid tumors: the phase 1 BNT211-01 trial. Nat Med 2023;29:2844-2853.

https://doi.org/10.3350/cmh.2024.0781

9. D'Angelo SP, Araujo DM, Abdul Razak AR, Agulnik M, Attia S, Blay JY, et al. Afamitresgene autoleucel for advanced synovial sarcoma and myxoid round cell liposarcoma (SPEARHEAD-1): an international, open-label, phase 2 trial. Lancet 2024;403:1460-1471.
10. Meng F, Zhao J, Tan AT, Hu W, Wang SY, Jin J, et al. Immunotherapy of HBV-related advanced hepatocellular carcinoma with short-term HBV-specific TCR expressed T cells: results of dose escalation, phase I trial. Hepatol Int 2021;15:1402-1412.
11. Liaw YF. Hepatitis B flare: the good, the bad and the ugly. Expert Rev Gastroenterol Hepatol 2022;16:1043-1051.
12. Yeh SH, Li CL, Lin YY, Ho MC, Wang YC, Tseng ST, et al. Hepatitis B virus DNA integration drives carcinogenesis and provides a new biomarker for HBV-related HCC. Cell Mol Gastroenterol Hepatol 2023;15:921-929.
13. Festag MM, Festag J, Fräßle SP, Asen T, Sacherl J, Schreiber S, et al. Evaluation of a fully human, hepatitis B virus-specific chimeric antigen receptor in an immunocompetent mouse model. Mol Ther 2019;27:947-959.
14. Drzeniek NM, Kahwaji N, Picht S, Dimitriou IM, Schlickeiser S, Moradian H, et al. In vitro transcribed mRNA immunogenicity induces chemokine-mediated lymphocyte recruitment and can be gradually tailored by uridine modification. Adv Sci (Weinh) 2024;11:e2308447.