ISSN: 2755-0168

Journal of Biotechnology & Bioinformatics Research

SCIENTIFIC Research and Community

Review Article

Open Access

The Art of Nano-CAR T Cells in Ovarian Cancer Management

Dito Anurogo

International PhD Program in Cell Therapy and Regeneration Medicine, College of Medicine, Taipei Medical University, Taipei 11031, Taiwan

Faculty of Medicine and Health Sciences, Universitas Muhammadiyah Makassar, Makassar 90221, Indonesia

ABSTRACT

The combination of nanotechnology and CAR T-cell therapeutics heralds a paradigm shift in the management of ovarian cancer, a disease characterized by substantial obstacles such as antigenic heterogeneity, an immunosuppressive tumor microenvironment, and physical barriers to treatment efficacy. This paper examines these obstacles critically and proposes innovative nano-engineered solutions, such as the development of nano-CAR T cells and nanoparticle-mediated delivery of CAR genes and immunomodulatory agents, as strategic approaches to improve CAR T-cell delivery, survival, and function within the hostile tumor microenvironment. The convergence of these two disciplines represents a promising strategy for overcoming these obstacles and optimizing the therapeutic potential of CAR T cells in solid malignancies. To translate this promising approach into a viable clinical reality in the fight against ovarian cancer, however, additional scientific research and rigorous clinical trials are required to ensure safety, optimize the design, and establish standardized production and application protocols.

***Corresponding author**

Dito Anurogo, International PhD Program in Cell Therapy and Regeneration Medicine, College of Medicine, Taipei Medical University, Taipei 11031, Taiwan and Faculty of Medicine and Health Sciences, Universitas Muhammadiyah Makassar, Makassar 90221, Indonesia.

Received: July 17, 2024; **Accepted:** July 24, 2024; **Published:** July 30, 2024

Keywords: Ovarian Cancer, CAR T-Cell Therapy, Nanotechnology, Nano-CAR T Cells, Tumor Microenvironment

Introduction

Due to late-stage diagnosis and the development of chemoresistance, ovarian cancer is the most fatal gynecological cancer [1]. CAR T-cell therapy is at the forefront of the battle against this fatal disease, thanks to recent advances in cancer immunotherapy [2]. Despite encouraging results in hematologic malignancies, CAR T-cell therapy for solid tumors such as ovarian cancer has been less effective [3]. This disparity is primarily attributable to obstacles such as the hostile tumor microenvironment and inefficient CAR T cell trafficking [4].

CAR T-Cell Therapy

CAR T-cell therapy is a type of Adoptive Cell Transfer (ACT) therapy in which the patient's T cells are re-engineered to express CARs, which are synthetic receptors that recognize specific antigens expressed by tumor cells [5]. The first generation of CAR T cells provided only activation signals; they were unifunctional [6]. The addition of co-stimulatory domains to subsequent generations enhanced T-cell activation, proliferation, and longevity [7].

Difficulties in using CAR T-Cell Therapy to Treat Ovarian Cancer

While CAR T-cell therapy has demonstrated significant promise in combating hematological malignancies, its efficacy in treating solid tumors such as ovarian cancer is significantly hampered by a number of distinct and complex obstacles [8-10]. These include antigenic heterogeneity of the cancer cells, an immunosuppressive tumor microenvironment, and the presence of physical barriers that inhibit the infiltration and function of CAR T-cells [4,11]. Each of these obstacles necessitates the creation of novel approaches to improve the delivery, survival, and efficacy of CAR T-cell therapy.

Antigen Heterogeneity

Ovarian tumors' inherent antigenic heterogeneity is one of the primary obstacles [12]. They frequently express multiple tumor-associated antigens (TAAs), and these expressions can vary between patients, tumors within the same patient, and even regions of the same tumor [13]. This antigenic landscape is extremely challenging for CAR T-cell therapy, which typically targets a specific antigen [14]. It increases the likelihood of antigen escape variants, in which subsets of cancer cells lacking the target antigen survive and proliferate, leading to relapse [15].

Moreover, certain subtypes of ovarian cancer, such as clear cell and mucinous carcinomas, express less of the commonly targeted antigens MUC16 and Mesothelin [16,17]. This further complicates the process of identifying effective and universal CAR targets [18].

Immunosuppressive Tumor Microenvironment

The Tumor Microenvironment (TME) in ovarian cancer epitomizes a remarkably inhospitable milieu for the propagation and efficacy of Chimeric Antigen Receptor (CAR) T cells [19]. This complex ecosystem is heavily infiltrated by a diverse array of immunosuppressive cell types, encompassing myeloid-derived suppressor cells (MDSCs), T-regulatory cells (Tregs), and tumor-associated macrophages (TAMs) [20]. These cellular constituents, through their effector functions, release a cocktail of immunosuppressive cytokines and modulators, including but not limited to, Transforming Growth Factor-beta (TGF-beta), Interleukin-10 (IL-10), and Prostaglandin E2 (PGE2) [21]. This

orchestrated interplay of inhibitory signals can precipitate a cascade of detrimental effects on T-cell dynamics, encompassing the attenuation of T-cell activation, instigation of T-cell exhaustion, and facilitation of immune escape mechanisms, thereby impeding the immunotherapeutic trajectory of CAR T-cell therapy [22-24].

In addition to this immunological impedance, the TME in ovarian cancer is marred by regions of hypoxia, a consequence of aberrant vascularization and rapid tumor cell proliferation outpacing oxygen supply [25]. Hypoxia is not merely a passive byproduct but actively subverts the anti-tumor immune response by skewing T-cell metabolism, driving T-cell apoptosis, and further perpetuating immunosuppression, all of which conspire to impair the function and longevity of CAR T cells [26,27].

The tumor stroma, an intricate network of extracellular matrix and non-malignant cells, further exacerbates the challenge [28,29]. This physical barricade imposes spatial constraints, obstructing the infiltration of CAR T cells and their subsequent direct interaction with cancer cells [30]. This stromal hindrance, along with the aforementioned immunosuppressive elements, coalesce to impose a multifaceted barrier, significantly curtailing the therapeutic efficacy of CAR T-cell therapy [31].

In light of this, a holistic understanding of these complex interrelationships in the ovarian TME, complemented by novel therapeutic strategies aimed at remodeling this hostile landscape, is indispensable for leveraging the full potential of CAR T-cell therapy in ovarian cancer. This necessitates an integrative, multi-disciplinary approach harnessing advanced molecular techniques and immunotherapeutic innovations to effectively target this intricate network of biological impediments [32].

Physical Limitations on CAR T-Cell Infiltration

In parallel with the intrinsic challenges posed by other solid neoplasms, ovarian malignancies epitomize a profound labyrinth of physical and anatomical constraints that can significantly stymie the trafficking and infiltration of Chimeric Antigen Receptor (CAR) T cells [33]. This composite fortress, erected by the tumor, entails an intricate, densely woven extracellular matrix, augmented interstitial fluid pressure, and a fundamentally dysregulated vasculature architecture [34].

The extracellular matrix (ECM) in ovarian tumors, laden with structural proteins like collagen and laminin, poses a physical impediment that can curtail the migratory capability of systemically infused CAR T cells [35]. This reticulated network, acting in concert with increased interstitial fluid pressure, can create a pathophysiological barrier, impeding the convective transport and spatial distribution of therapeutically administered CAR T cells [36].

Further, the aberrant vasculature, characterized by tortuous, disorganized, and hyperpermeable vessels, can disrupt the typical routes of T-cell homing and infiltration, thereby thwarting their access to the tumor locale [37]. These collective barriers can result in suboptimal tumor penetration and persistence of CAR T cells, culminating in a diminished anti-tumor efficacy [38].

The hostile topography and the physiological barricades presented by the ovarian tumor microenvironment necessitate the adoption of multidisciplinary modalities and state-of-the-art technologies [39]. Among these, nanotechnology stands out as a promising tool to fortify the delivery, survivability, and functional efficacy of CAR T cells [40]. The conception of efficacious therapeutic strategies pivots on an in-depth understanding of these multifaceted impediments, underpinned by rigorous, innovative scientific exploration [41].

The optimal orchestration of CAR T-cell therapy in ovarian cancer hinges upon a detailed understanding of this intricate biological maze [42]. By building on this knowledge through innovative research approaches, we can begin to decipher and dismantle these barriers, paving the way for transformative advancements in CAR T-cell therapy for solid tumors [14]. This endeavor demands an integrative and comprehensive approach, harnessing cutting-edge molecular techniques and immunotherapeutic innovations to effectively navigate this complex network of biological barricades [43].

The Convergence of Nanotechnology and CAR T-Cell Therapeutics: A New Approach to the Management of Ovarian Cancer

Nanotechnology is a sophisticated and potent field that provides cutting-edge strategies for overcoming obstacles associated with CAR T-cell therapy in the context of ovarian cancer [44]. By leveraging the unique properties of nanoparticles, we can engineer a variety of solutions that address critical issues associated with CAR T-cell delivery, their longevity within the hostile tumor microenvironment, and their functional performance in orchestrating a potent anti-tumor response [45].

Nanoparticles, at their core, are versatile entities that can be designed to carry a variety of cargoes, including pharmacological agents, genetic material, and even proteins [46]. This versatility enables them to function as vehicles for precision medicine, conveying cargoes to specific cell types or tissues in a targeted and regulated manner [47]. This provides opportunities to maximize therapeutic efficacy while minimizing collateral injury to healthy tissues in the context of CAR T-cell therapy [48].

In addition, the physical and chemical characteristics of nanoparticles, such as their size, charge, and surface properties, can be modified to optimize their pharmacokinetics and biodistribution [49,50]. This capacity is especially advantageous for augmenting the infiltration and retention of CAR T cells within the tumor microenvironment [51]. Nanoparticles can circumvent physical barriers presented by the dense stromal network of ovarian tumors due to their small size and flexibility, while their surface can be modified to resist immune clearance, ensure stability, and promote specific interaction with tumor and immune cells [52].

Moreover, nanoparticles can be engineered to respond to various stimuli in the tumor microenvironment, including pH, hypoxia, and specific enzymes [53]. This characteristic enables a responsive and sustained release of therapeutics, thereby preserving their potency and enhancing CAR T-cell survival and function over a prolonged period [54].

The incorporation of nanotechnology into CAR T-cell therapies represents an innovative and intriguing approach to ovarian cancer treatment. This fusion effectively capitalizes on the strengths of both disciplines, providing a promising path to overcome the current obstacles and maximize the therapeutic potential of CAR T cells in solid tumors [55].

Enhanced CAR T-Cell Therapy Utilization of Nanotechnology

The dynamic intersection of nanotechnology and CAR T-cell therapy has ushered in novel approaches for overcoming the

inherent difficulties of immunotherapy in the context of ovarian cancer [44]. Below, we delve into the specifics of these innovative strategies, each of which utilizes the unique properties of nanotechnology to enhance the efficacy of CAR T-cell therapy.

Preconditioning the Microenvironment of the Tumor

The immunosuppressive nature of the tumor microenvironment, which compromises the trafficking and function of CAR T cells, is a significant obstacle in ovarian cancer therapy [56]. As carriers of immunomodulatory agents that can reprogram this hostile environment, nanoparticles provide a strategic solution [57].

In preclinical studies, nanoparticles carrying toll-like receptor agonists or inhibitors of regulatory pathways (such as PD-1/PD-L1) have demonstrated their ability to recruit and activate immune cells while diminishing immunosuppressive factors [58]. This concerted modulation creates a more receptive environment for CAR T cells, enhancing their trafficking to the tumor site, enhancing their survivability, and enhancing their capacity to mount a robust antitumor response [59].

Innovations in CAR T-Cell Engineering: Nanoparticles can play a crucial role in the generation of CAR T cells by directly delivering the genetic materials required for CAR expression into T cells [41]. This method obviates the need for viral vectors, which are typically employed despite presenting challenges such as high cost, potential immunogenicity, and off-target integration.

Recent studies have emphasized the potential of nanocarriers that encapsulate the CAR-coding DNA or mRNA, such as lipid nanoparticles or gold nanoparticles [60]. These particles can be taken up by T cells, leading to the expression of CARs that are functionally equivalent to those produced by viral transduction [61]. Importantly, this nanoparticle-mediated transfection method could result in safer and more controlled production of CAR T-cells, reducing the risk of off-target effects and insertional mutagenesis [62-64].

Innovative Nano-CAR T Cells

The construction of nano-CAR T cells, in which nanoparticles are engineered to display CARs on their surface, mimicking the function of CAR T cells, is an emerging and promising strategy [40]. This paradigm shift eliminates the requirement for complex T-cell modification and expansion ex vivo and circumvents T-cell exhaustion and rejection issues [65].

Due to their compact size and flexibility, nano-CAR T cells have demonstrated superior tumor penetration in preclinical models [66]. In addition, by selectively targeting tumor cells and avoiding healthy tissue, these nano-CAR T cells reduce systemic toxicity, a significant concern in conventional CAR T-cell therapy [67].

Together, these novel approaches represent a daring new frontier in the application of CAR T-cell therapy to ovarian cancer, with nanotechnology providing the essential tools to improve therapeutic efficacy and safety [42]. Future research is required to validate these approaches in clinical settings and to investigate additional ways in which nanotechnology can be utilized to further optimize CAR T-cell therapy [68].

Future Prospects

While the advent of nano-CAR T cells has elicited considerable optimism in the context of preclinical models, the translation of this novel immunotherapeutic modality into clinical efficacy remains shrouded in scientific conjecture and hence, necessitates further elucidation [69]. This epoch-making advance in the realm of CAR T-cell therapeutics necessitates an investigational focus on several pivotal facets [70].

First, the conceptual refinement and optimization of nano-CAR T-cell design represent an imperative undertaking [71]. This includes a keen focus on the physicochemical properties of nanoparticles such as size, shape, charge, and surface modifications, all of which could influence nanoparticle interactions with biological systems, biodistribution, cellular uptake, and resultant therapeutic efficacy [72,73].

Second, escalating the targeting specificity of nano-CAR T cells is an essential endeavour [74]. The realization of this objective mandates the identification and validation of novel tumor-specific antigens and the construction of corresponding CARs that can elicit precise immune responses [75]. The nuanced manipulation of nanoscale engineering to generate bespoke nano-CAR T cells could reduce off-target toxicity, enhance tumor selectivity, and augment overall therapeutic index [76].

Finally, the establishment of standardized, scalable, and reproducible protocols for the manufacturing and clinical application of nano-CAR T cells is critical [77]. This incorporates considerations of good manufacturing practices (GMP), regulatory compliance, cost-effectiveness, and clinical scalability [78-80]. These protocols should ensure the consistent production of nano-CAR T cells with high quality, safety, and efficacy, thereby ensuring the smooth transition from bench to bedside [81].

Therefore, the future of nano-CAR T cells in the realm of ovarian cancer therapeutics pivots on a multidimensional, intricate interplay of several aspects of CAR T-cell design, nanoengineering, immunology, and clinical implementation [82]. This necessitates an integrated and collaborative research approach to explore, decode, and address these complex scientific conundrums, thereby pushing the frontiers of ovarian cancer therapeutics [83].

Conclusion

In the treatment of ovarian cancer, the convergence of nanotechnology and CAR T-cell therapies represents an intriguing new frontier. CAR T-cell therapy has not reached its maximum potential due to the unique challenges posed by ovarian cancer, such as antigen heterogeneity, an immunosuppressive tumor microenvironment, and physical barriers. However, strategic nanotechnology integration offers innovative solutions to these obstacles. Nano-CAR T cells, as well as nanoparticle-mediated delivery of CAR genes and immunomodulatory agents, are innovative strategies with the potential to revolutionize the treatment of ovarian cancer. As this field of study develops, it brings us closer to completely harnessing the power of CAR T-cell therapy in solid tumors, thereby transforming the prognosis for patients with ovarian cancer. However, continued research, including rigorous clinical trials, is necessary to assure the safety and efficacy of these approaches, bringing us one step closer to implementing this promising approach in clinical practice.

Conflict of Interests: None

References

1. Cabasag CJ, Paula J Fagan, Jacques Ferlay, Jerome Vignat, Mathieu Laversanne, et al. (2022) Ovarian cancer today and tomorrow: A global assessment by world region and Human Development Index using GLOBOCAN 2020. International Journal of Cancer 151: 1535-1541.
2. Hiltensperger M, Krackhardt AM (2023) Current and future concepts for the generation and application of genetically engineered CAR-T and TCR-T cells. Frontiers in Immunology 14: 1121030.
3. Domínguez-Prieto V, Siyuan Qian, Pedro Villarejo-Campos, Cecilia Meliga, Sara González-Soares, et al. (2023) Understanding CAR T cell therapy and its role in ovarian cancer and peritoneal carcinomatosis from ovarian cancer. Frontiers in Oncology 13: 1104547.
4. Kankeu Fonkoua LA, Olivia Sirpilla, Reona Sakemura Elizabeth L Siegler, Saad S Kenderian et al. (2022) CAR T cell therapy and the tumor microenvironment: Current challenges and opportunities. Mol Ther Oncolytics 25: 69-77.
5. Gao T A, Chen YY (2022) Engineering next-generation CAR-T cells: overcoming tumor hypoxia and metabolism. Annual Review of Chemical and Biomolecular Engineering 13: 193-216.
6. Bell M, Gottschalk S (2021) Engineered Cytokine Signaling to Improve CAR T Cell Effector Function. Front Immunol 12: 684642.
7. Goodman DB, Daniel B Goodman, Camillia S Azimi, Kendall Kearns, Alexis Talbot, et al. (2022) Pooled screening of CAR T cells identifies diverse immune signaling domains for next-generation immunotherapies. Sci Transl Med 14: 1463.
8. Knochelmann HM, Aubrey S Smith, Connor J Dwyer, Megan M Wyatt, Shikhar Mehrotra, et al. (2018) CAR T Cells in Solid Tumors: Blueprints for Building Effective Therapies. Front Immunol 9: 1740.
9. Li J, Wenwen Li, Kejia Huang, Yang Zhang, Gary Kupfer, et al. (2018) Chimeric antigen receptor T cell (CAR-T) immunotherapy for solid tumors: lessons learned and strategies for moving forward. Journal of Hematology & Oncology 11: 22.
10. Xia AL, Xiao-Chen Wang, Yi-Jun Lu, Xiao-Jie Lu, Beicheng Sun, et al. (2017) Chimeric-antigen receptor T (CAR-T) cell therapy for solid tumors: challenges and opportunities. Oncotarget 8: 90521-90531.
11. Liu Z, Zhaokai Zhou, Qin Dang, Hui Xu, Jinxiang Lv, et al. (2022) Immunosuppression in tumor immune microenvironment and its optimization from CAR-T cell therapy. Theranostics 12: 6273-6290.
12. Testa U, Eleonora Petrucci, Luca Pasquini, Germana Castelli, Elvira Pelosi (2018) Ovarian Cancers: Genetic Abnormalities, Tumor Heterogeneity and Progression, Clonal Evolution and Cancer Stem Cells. Medicines (Basel) 5: 16.
13. Leko V, Rosenberg SA (2020) Identifying and Targeting Human Tumor Antigens for T Cell-Based Immunotherapy of Solid Tumors. Cancer Cell 38: 454-472.
14. Daei Sorkhabi A, Leila Mohamed Khosroshahi, Aila Sarkesh, Amirhossein Mardi, Ali Aghebati-Maleki, et al. (2023) The current landscape of CAR T-cell therapy for solid tumors: Mechanisms, research progress, challenges, and counterstrategies. Front Immunol 14: 1113882.
15. Shah NN, TJ Fry (2019) Mechanisms of resistance to CAR T cell therapy. Nat Rev Clin Oncol 16: 372-385.
16. Schoutrop E, Lidia Moyano-Galceran, Stephanie Lheureux, Jonas Mattsson, Kaisa Lehti, et al. (2022) Molecular, cellular and systemic aspects of epithelial ovarian cancer and its tumor microenvironment. Seminars in Cancer Biology 86: 207-223.
17. Giordano G, Ferioli E, Tafuni A (2022) The Role of Mesothelin Expression in Serous Ovarian Carcinoma: Impacts on Diagnosis, Prognosis, and Therapeutic Targets. Cancers (Basel) 14: 2283.
18. Benard E, Nicholas P Casey, Else Marit Inderberg, Sébastien Wälchli (2020) SJI 2020 special issue: a catalogue of ovarian cancer targets for CAR therapy. Scandinavian journal of immunology 92: 12917.
19. Rodriguez-Garcia A, Asis Palazon, Estela Noguera-Ortega, Daniel J Powell Jr, Sonia Guedan (2020) CAR-T Cells Hit the Tumor Microenvironment: Strategies to Overcome Tumor Escape. Front Immunol 11: 1109.
20. Hofer F, Gianna Di Sario, Chiara Musiu, Silvia Sartoris, Francesco De Sanctis, et al. (2021) A Complex Metabolic Network Confers Immunosuppressive Functions to Myeloid-Derived Suppressor Cells (MDSCs) within the Tumour Microenvironment. Cells 10: 2700.
21. Komai T, Mariko Inoue, Tomohisa Okamura, Kaoru Morita, Yukiko Iwasaki, et al. (2018) Transforming Growth Factor-β and Interleukin-10 Synergistically Regulate Humoral Immunity via Modulating Metabolic Signals. Front Immunol 9: 1364.
22. Lamarche C, Kirsten Ward-Hartstonge, Tian Mi, David T S Lin, Qing Huang, et al. (2023) Tonic-signaling chimeric antigen receptors drive human regulatory T cell exhaustion. Proc Natl Acad Sci USA 120: 2219086120.
23. Chen C, Xin Liu, Che-Yu Chang, Helen Y Wang, Rong-Fu Wang, et al. (2023) The Interplay between T Cells and Cancer: The Basis of Immunotherapy. Genes 14: 1008.
24. Zhu X, Li Q, X Zhu (2022) Mechanisms of CAR T cell exhaustion and current counteraction strategies. Front Cell Dev Biol 10: 1034257.
25. Horst B, Shrikant Pradhan, Roohi Chaudhary, Eduardo Listik, Liz Quintero-Macias, et al. (2022) Hypoxia-induced inhibin promotes tumor growth and vascular permeability in ovarian cancers. Commun Biol 5: 536.
26. Phan AT, Goldrath AW, (2015) Hypoxia-inducible factors regulate T cell metabolism and function. Mol Immunol 68: 527-535.
27. Berahovich R, Xianghong Liu, Hua Zhou, Elias Tsadik, Shirley Xu, et al. (2019) Hypoxia Selectively Impairs CAR-T Cells In Vitro. Cancers (Basel) 11: 602.
28. Baghban R, Leila Roshangar, Rana Jahanban-Esfahlan, Khaled Seidi, Abbas Ebrahimi-Kalan, et al. (2020) Tumor microenvironment complexity and therapeutic implications at a glance. Cell Communication and Signaling 18: 59.
29. Henke E, Nandigama R, Ergün S (2019) Extracellular Matrix in the Tumor Microenvironment and Its Impact on Cancer Therapy. Front Mol Biosci 6: 160.
30. Sterner RC, Sterner RM, (2021) CAR-T cell therapy: current limitations and potential strategies. J Blood Cancer 11: 69.
31. Johnson A, Townsend M, Neill KO (2022) Tumor Microenvironment Immunosuppression: A Roadblock to CAR T-Cell Advancement in Solid Tumors. Cells 11: 3626.
32. Falzone L, Giuseppa Scandurra, Valentina Lombardo, Giuseppe Gattuso, Alessandro Lavoro, et al. (2021) A multidisciplinary approach remains the best strategy to improve and strengthen the management of ovarian cancer (Review). Int J Oncol 59: 53.
33. Rodriguez-Garcia A, Prannda Sharma, Mathilde Poussin, Alina C Boesteanu, Nicholas G Minutolo, et al. (2020) CAR T Cells Targeting MISIIR for the Treatment of Ovarian Cancer and Other Gynecologic Malignancies. Mol Ther 28: 548-560.

34. Dai H, Yao Wang, Xuechun Lu, Weidong Han (2016) Chimeric antigen receptors modified T-cells for cancer therapy. Journal of the National Cancer Institute 108: 439.
35. Cho A, Howell VM, Colvin EK (2015) The extracellular matrix in epithelial ovarian cancer–a piece of a puzzle. Frontiers in oncology 5: 245.
36. Zhang Q, Cheng Zu, Yongxian Hu, He Huang (2022) CAR-T cells for cancer immunotherapy-the barriers ahead and the paths through. Int Rev Immunol 41: 567-581.
37. Goel S, Dan G Duda, Lei Xu, Lance L Munn, Yves Boucher, et al. (2011) Normalization of the vasculature for treatment of cancer and other diseases. Physiol Rev 91: 1071-1121.
38. Stoiber S, Bruno L Cadilha, Mohamed-Reda Benmebarek, Stefanie Lesch, Stefan Endres, et al. (2019) Limitations in the Design of Chimeric Antigen Receptors for Cancer Therapy. Cells 8: 472.
39. Jordan KR, Matthew J Sikora, Jill E Slansky, Angela Minic, Jennifer K Richer, et al. (2020) The Capacity of the Ovarian Cancer Tumor Microenvironment to Integrate Inflammation Signaling Conveys a Shorter Disease-free Interval. Clin Cancer Res 26: 6362-6373.
40. Mi J, Ye Q, Min Y (2022) Advances in Nanotechnology Development to Overcome Current Roadblocks in CAR-T Therapy for Solid Tumors. Front Immunol 13: 849759.
41. Abdalla AME, Lin Xiao, Yu Miao, Lixia Huang, Gendeal MF, et al. (2020) Nanotechnology Promotes Genetic and Functional Modifications of Therapeutic T Cells Against Cancer. Adv Sci 7: 1903164.
42. Zhang XW, Wu YS, Xu TM, Cui MH (2023) CAR-T Cells in the Treatment of Ovarian Cancer: A Promising Cell Therapy. Biomolecules 13: 465.
43. Bonaguro L, Schulte-Schrepping J, Ulas T, Aschenbrenner AC, Beyer M, et al. (2022) A guide to systems-level immunomics. Nature Immunology 23: 1412-1423.
44. Corradetti B, Pisano S, Conlan RS, Ferrari M (2019) Nanotechnology and Immunotherapy in Ovarian Cancer: Tracing New Landscapes. J Pharmacol Exp Ther 370: 636-646.
45. Balakrishnan PB, Sweeney EE (2021) Nanoparticles for enhanced adoptive T cell therapies and future perspectives for CNS tumors. Frontiers in Immunology 12: 600659.
46. Spicer CD, Jumeaux C, Gupta B, Stevens MM (2018) Peptide and protein nanoparticle conjugates: versatile platforms for biomedical applications. Chemical society reviews 47: 3574-3620.
47. Waheed S, Li Z, Zhang F, Chiarini A, Armato U, et al. (2022) Engineering nano-drug biointerface to overcome biological barriers toward precision drug delivery. Journal of Nanobiotechnology 20: 395.
48. Hamieh M, Mansilla-Soto J, Rivière I, Sadelain M (2023) Programming CAR T cell tumor recognition: tuned antigen sensing and logic gating. Cancer Discovery 13: 829-843.
49. Sun T, Zhang YS, Pang B, Hyun DC, Yang M, et al. (2014) Engineered nanoparticles for drug delivery in cancer therapy. Angew Chem Int Ed Engl 53: 12320-12364.
50. Zhao Z, Ukidve A, Krishnan V, Mitragotri S (2019) Effect of physicochemical and surface properties on in vivo fate of drug nanocarriers. Advanced Drug Delivery Reviews 143: 3-21.
51. Martinez M, Moon EK (2019) CAR T Cells for Solid Tumors: New Strategies for Finding, Infiltrating, and Surviving in the Tumor Microenvironment. Frontiers in Immunology 10: 128.
52. Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA, et al. (2021) Engineering precision nanoparticles for drug delivery. Nature Reviews Drug Discovery 20: 101-124.
53. Dalir AE, Marziyeh F, Zahra P, Samira J, Mohammad S, et al. (2022) Strategies to improve drug penetration into tumor microenvironment by nanoparticles: Focus on nanozymes. OpenNano 8: 100100.
54. De Marco RC, Monzo HJ, Ojala PM (2023) CAR T Cell Therapy: A Versatile Living Drug. International Journal of Molecular Sciences 24: 6300.
55. Yan T, Zhu L, Chen J (2023) Current advances and challenges in CAR T-Cell therapy for solid tumors: tumor-associated antigens and the tumor microenvironment. Experimental Hematology & Oncology 12: 14.
56. Hou AJ, Chen LC, Chen YY (2021) Navigating CAR-T cells through the solid-tumour microenvironment. Nature Reviews Drug Discovery 20: 531-550.
57. Goldberg MS (2019) Improving cancer immunotherapy through nanotechnology. Nature Reviews Cancer 19: 587-602.
58. Saeed M, Gao J, Shi Y, Lammers T, Yu H (2019) Engineering nanoparticles to reprogram the tumor immune microenvironment for improved cancer immunotherapy. Theranostics 9: 7981.
59. Jo Y, Ali LA, Shim JA, Lee BH, Hong C (2020) Innovative CAR-T Cell Therapy for Solid Tumor; Current Duel between CAR-T Spear and Tumor Shield. Cancers (Basel) 12: 2087.
60. Tenchov R, Bird R, Curtze AE, Zhou Q (2021) Lipid Nanoparticles─From Liposomes to mRNA Vaccine Delivery, a Landscape of Research Diversity and Advancement. ACS Nano 15: 16982-17015.
61. Labbé RP, Vessillier S, Rafiq QA (2021) Lentiviral Vectors for T Cell Engineering: Clinical Applications, Bioprocessing and Future Perspectives. Viruses 13: 1528.
62. Wagner DL (2022) Review: Sustainable Clinical Development of CAR-T Cells - Switching from Viral Transduction Towards CRISPR-Cas Gene Editing. Front Immunol 13: p865424.
63. Lukjanov VI, Koutná, P Šimara (2021) CAR T-Cell Production Using Nonviral Approaches. J Immunol Res 2021: p6644685.
64. Pinto IS, RA Cordeiro, H Faneca (2023) Polymer- and lipid-based gene delivery technology for CAR T cell therapy. Journal of Controlled Release 353: 196-215.
65. Dai H, Yao Wang, Xuechun Lu, Weidong Han (2016) Chimeric Antigen Receptors Modified T-Cells for Cancer Therapy. J Natl Cancer Inst 108: 439.
66. Bao C, Quanli Gao, Lin-Lin Li, Lu Han, Bingxiang Zhang, et al. (2021) The Application of Nanobody in CAR-T Therapy. Biomolecules 11: 238.
67. Xin T (2022) In-Vivo Induced CAR-T Cell for the Potential Breakthrough to Overcome the Barriers of Current CAR-T Cell Therapy. Front Oncol 12: 809754.
68. Nawaz W (2020) Nanotechnology and immunoengineering: How nanotechnology can boost CAR-T therapy. Acta Biomater 109: 21-36.
69. Nguyen NT (2021) Nano-optogenetic engineering of CAR T cells for precision immunotherapy with enhanced safety. Nat Nanotechnol 16: 1424-1434.
70. Adachi K, K Tamada (2022) Paving the road to make chimeric antigen receptor-T-cell therapy effective against solid tumors. Cancer Sci 113: 4020-4029.
71. Srivastava S, SR Riddell (2015) Engineering CAR-T cells: Design concepts. Trends Immunol 36: 494-502.
72. Anastasiadis SH (2022) How the Physicochemical Properties of Manufactured Nanomaterials Affect Their Performance in Dispersion and Their Applications in Biomedicine: A Review. Nanomaterials 12: 552.
73. Albanese A, PS Tang, WC Chan (2012) The effect of

nanoparticle size, shape, and surface chemistry on biological systems. Annu Rev Biomed Eng 14: 1-16.

74. Kansagra AJ (2019) Clinical utilization of Chimeric Antigen Receptor T-cells (CAR-T) in B-cell acute lymphoblastic leukemia (ALL)–an expert opinion from the European Society for Blood and Marrow Transplantation (EBMT) and the American Society for Blood and Marrow Transplantation (ASBMT). Bone Marrow Transplantation 54: 1868-1880.
75. DeVette CI (2020) A pipeline for identification and validation of tumor-specific antigens in a mouse model of metastatic breast cancer. Oncoimmunology 9: 1685300.
76. Zhang F (2018) Nanoparticles That Reshape the Tumor Milieu Create a Therapeutic Window for Effective T-cell Therapy in Solid Malignancies. Cancer Res 78: 3718-3730.
77. Abou El Enein M (2021) Scalable Manufacturing of CAR T cells for Cancer Immunotherapy. Blood Cancer Discov 2: 408-422.
78. Wang X, I Rivière (2016) Clinical manufacturing of CAR T cells: foundation of a promising therapy. Molecular Therapy-Oncolytics 3: 16015.
79. Kaiser A (2015) Towards a commercial process for the manufacture of genetically modified T cells for therapy. Cancer gene therapy 22: 72-78.
80. Covarrubias CE (2022) Current GMP standards for the production of vaccines and antibodies: An overview. Frontiers in Public Health 10: 1021905.
81. Arcangeli S (2020) Next-Generation Manufacturing Protocols Enriching T(SCM) CAR T Cells Can Overcome Disease-Specific T Cell Defects in Cancer Patients. Front Immunol 11: 1217.
82. Chicaybam L (2020) Overhauling CAR T Cells to Improve Efficacy, Safety and Cost. Cancers 12: 2360.
83. Dressman HK (2007) An integrated genomic-based approach to individualized treatment of patients with advanced-stage ovarian cancer. J Clin Oncol 25: 517-25.