DOI:10.3872/j.issn.1007-385x.2025.09.011

·综 述·

CAR-T细胞治疗后复发机制及治疗新策略研究进展

Research progress in the mechanisms of recurrence following CAR-T cell therapy and novel treatment strategies

庞琼玉[1] 综述;孙慧生[2] 审阅(1. 河北医科大学研究生院,河北 石家庄 050017; 2. 衡水市人民医院 儿科,河北 衡水 053000)

[摘 要] 嵌合抗原受体基因修饰T淋巴细胞(CAR-T细胞)疗法作为肿瘤免疫治疗的重要突破,在血液系统恶性肿瘤中展现出显著疗效,但治疗后复发问题严重限制了其临床应用。本文系统总结了CAR-T细胞治疗后复发的关键机制,包括肿瘤抗原逃逸、CAR-T细胞功能耗竭、免疫抑制性肿瘤微环境、肿瘤异质性及克隆演化、肿瘤干细胞耐药性等,并基于此提出新型治疗策略,如多靶点CAR设计、联合表观遗传调控与代谢干预、重塑肿瘤微环境及人工智能辅助优化等。通过多学科交叉融合与技术创新,未来有望突破CAR-T细胞疗法在实体瘤及复发难治性肿瘤中的瓶颈,推动精准免疫治疗的发展。

[关键词] CAR-T细胞;肿瘤复发;免疫逃逸;肿瘤微环境;T细胞耗竭;表观遗传调控;治疗策略
[中图分类号] R730.5 [文献标识码] A [文章编号] 1007-385x(2025) 09-0975-08

嵌合抗原受体基因修饰T淋巴细胞(chimeric antigen receptor gene-modified-T lymphocyte, CAR-T细胞)制备采用离体基因工程策略,主要流程包括自体T细胞分选、体外活化、病毒载体介导的CAR基因转导、细胞扩增、冻存及最终产物回输[1]。CAR分子结构由3部分组成:(1)胞外抗原识别域(含scFv/纳米抗体及铰链区);(2)跨膜结构域;(3)胞内信号域(CD3ζ激活域协同CD28/4-1BB共刺激域),共同介导T细胞活化及肿瘤杀伤功能[2]。临床研究[3]显示,CAR-T细胞疗法在复发难治性血液肿瘤[如急性淋巴细胞白血病(acute lymphoblastic leukemia, ALL)、弥漫性大B细胞淋巴瘤(diffuse large B-cell lymphoma, DLBCL)]中可诱导持久缓解,但约50%的儿童/青年B细胞急性淋巴细胞白血病(B-cell acute lymphoblastic leukemia, B-ALL)患者在2年内出现复发。

1 主要复发机制

1.1 肿瘤细胞免疫逃逸机制

1.1.1 抗原逃逸

靶抗原丢失或表达下调:肿瘤细胞通过表观遗传改变或基因突变导致靶抗原[如CD19和B细胞成熟抗原(B cell maturation antigen, BCMA)等]表达下调或完全缺失[4]。KarMMa试验发现,1例ide-cel治疗后复发患者存在BCMA纯合缺失克隆逃逸机制[5]。研究[5]表明,治疗前存在BCMA杂合缺失(16p13.13)的骨髓瘤患者在接受BCMA靶向治疗后复发风险显著升高。BCMA靶向治疗后复发的多发性骨髓瘤患者常伴随del16p和del17p突变,提示TP53突变与耐药相关[6]。有研究[7]表明,在抗CD19 CAR-T细胞治疗后,多达一半的CD19阳性B-ALL患者发生CD19抗原阴性复发。CD19阴性复发在B-ALL患者中占比高达48%[8],机制包括谱系转分化、可变剪接、表观遗传沉默、溶酶体分选缺陷或预存抗原阴性克隆的选择性扩增[9-10]。

抗原掩蔽:肿瘤细胞通过分泌可溶性BCMA和膜蛋白(CD81)介导免疫逃逸机制,其中γ-分泌酶(γ-secretase, GS)调控的可溶性BCMA释放可竞争性遮蔽靶抗原表位,进而干扰CAR-T细胞特异性识别[11]。

1.1.2 免疫抑制信号激活

实体瘤肿瘤细胞上PD-L1、TIM-3和CTLA-4等免疫检查点分子,抑制T细胞的过度扩增[12]。MHC-Ⅰ分子缺失、IL-10/IL-6/TGF-β等免疫抑制因子分泌及IDO/Wnt通路激活,进一步加剧TME免疫抑制[13]。

1.1.3 抗原提呈缺陷

肿瘤细胞通过基因突变、缺失或表观遗传修饰(如DNA甲基化、组蛋白修饰)下调MHC-Ⅰ分子表达,逃避免疫监视,使细胞毒性T细胞无法识别和杀伤肿瘤细胞[14]。

1.2 CAR-T细胞功能受限

1.2.1 细胞持久性不足

自体CAR-T细胞易因终末分化或宿主T细胞耗竭导致功能受限[15]。CAR-T细胞在体内存活时间短,无法持续监控肿瘤,可能与细胞类型(如$CD8^+$效应T

[作者简介] 庞琼玉(1998—),女,硕士生,住院医师,主要从事肿瘤免疫治疗
[通信作者] 孙慧生(扫码获取作者联系方式)

细胞占比高）、共刺激域设计（如4-1BB比CD28更利于长效）或宿主免疫排斥（针对鼠源单链抗体scFv）有关[16]。CAR-T细胞疗法的临床试验[17]表明，体内输注T细胞的持久性较差，尤其是在实体瘤中。

1.2.2　T细胞耗竭

T细胞耗竭是慢性抗原暴露诱导的功能失调状态，其机制涉及多层级调控网络：（1）抗原持续刺激通过TCR信号异常活化，诱导代谢重编程及克隆扩增失调，阻碍效应T细胞向记忆表型分化，并触发PD-1/TIM-3/LAG-3等抑制性受体持续高表达[18]；（2）转录-表观遗传级联中，TCF1维持耗竭祖细胞自我更新能力，其表达衰减标志终末耗竭不可逆[18]，TOX/NR4A通过NFAT信号介导表观遗传重编程（如开放Pdcd1增强子区域），协同T-bet/EOMES失衡共同驱动终末分化[19-21]；（3）耗竭进程呈现阶段特异性特征，即可逆阶段耗竭祖细胞1/2并保留增殖潜能，中间阶段TCF1缺失启动不可逆转变，终末阶段则伴随TIM-3/LAG-3高表达及功能完全丧失，可通过CD38/CD101/CX3CR1等表面标志物及Ly108/CD69等转录特征进行分期鉴别[18, 20, 22]；（4）耗竭虽具有限制免疫过度激活的保护作用，但终末耗竭T细胞存活能力低下，显著削弱抗肿瘤/抗病毒免疫应答[23]。

1.2.3　CAR结构设计局限性

单靶点CAR-T细胞治疗易因靶抗原逃逸导致失效。CD28和4-1BB共刺激结构域通过PI3K/AKT与NF-κB等信号通路差异调控CAR-T细胞的增殖动力学、持久性及效应功能（包括IFN-γ、IL-2分泌和细胞毒性）[24]。scFv区诱发的宿主免疫应答可能限制CAR-T细胞的体内扩增持续性，增加白血病复发风险[13]。CAPPELL等[25]研究证实，CD28共刺激CAR-T细胞具有更强的体外细胞毒性，而4-1BB共刺激型则表现出更优的体内外增殖能力与持久性，凸显共刺激结构域对CAR-T功能的关键调控作用。

1.3　肿瘤微环境（TME）的免疫抑制

1.3.1　抑制免疫细胞浸润

TME通过多维度机制抑制CAR-T细胞功能。调节性T细胞（Treg细胞）、髓源性抑制细胞（MDSC）及肿瘤相关巨噬细胞（TAM）通过分泌TGF-β、IL-6等细胞因子，抑制T细胞活化并诱导耗竭表型[26-27]。肿瘤细胞通过双重调控机制抑制免疫细胞浸润：（1）分泌TGF-β/IL-10等免疫抑制因子抑制T细胞；（2）上调PD-1、CTLA-4、TIGIT和LAG-3等免疫检查点分子并下调MHC表达，干扰抗原提呈[28]。NF-κB/STAT3通路持续激活可诱导免疫抑制因子级联分泌，促进肿瘤免疫逃逸[26, 29]。PD-L1阻断通过$CD163^+$ M2巨噬细胞的IFN-γ调节恢复CAR-T细胞活性[30]。

1.3.2　物理屏障

异常血管构筑与细胞外基质（ECM）过度沉积构成CAR-T细胞浸润的关键物理屏障。研究[31]显示，HSPG等基质蛋白在维持肿瘤恶性表型中发挥重要作用。ZHOU等[32]开发的IL-21-CCL19共修饰NKP30 CAR-T细胞，通过降解ECM组分显著增强肿瘤浸润能力。该修饰策略同时诱导T细胞向中央记忆亚群（Tcm）分化，并抑制耗竭相关标志物表达，展现出物理屏障突破与免疫表型调控的双重效应。

1.3.3　代谢竞争

由于肿瘤脉管系统紊乱和肿瘤细胞糖酵解代谢（Warburg效应）的增强，TME中低氧、低葡萄糖及高乳酸环境抑制T细胞代谢活性，削弱CAR-T细胞扩增与存活[33]。

1.4　肿瘤异质性及克隆演化

1.4.1　肿瘤异质性

肿瘤靶抗原异质性制约CAR-T细胞特异性识别效能。治疗后抗原阳性细胞被清除，而阴性克隆通过表型转换（如$CD19^-$/$CD20^+$）介导的免疫逃逸选择性扩增，导致疾病复发[34]。实体瘤（尤其转移性病灶）与血液肿瘤的克隆特征显著不同：前者通过体细胞突变累积形成多克隆群体，促进基因组不稳定性及抗原异质性[35]。典型证据[36]显示，HER2阳性乳腺癌肿瘤微环境中免疫调控相关基因呈现显著空间异质性，而BCMA-CAR-T细胞治疗后复发机制与抗原阴性克隆选择性扩增直接相关[37]。这些发现提示肿瘤细胞可塑性及抗原动态演化是免疫治疗耐药的重要机制。

1.4.2　治疗压力下的克隆选择

CAR-T细胞疗法清除敏感克隆后，耐药亚克隆通过表型转换或基因组扩增形成复发主导克隆。实体肿瘤克隆演化可诱发双重免疫逃逸机制：靶抗原丢失（包括表位掩蔽/表达下调）或获得性耐药（如PD-L1上调伴随$CD8^+$ T细胞耗竭）[26]。多发性骨髓瘤（MM）临床研究[38]证实，BCMA靶向CAR-T治疗后残余肿瘤普遍存在BCMA抗原丢失/下调现象。该群体显著的肿瘤异质性使BCMA低表达/阴性亚克隆在治疗选择压力下获得增殖优势，进而导致治疗抵抗[39]。Ⅰ期研究数据显示，高肿瘤负荷复发/难治性MM患者接受CART-BCMA治疗后28 d即出现BCMA表达显著下调，但伴随持续性微小残留病灶，提示抗原逃逸是重要耐药机制[39]。

1.5　肿瘤干细胞（cancer stem cell, CSC）的存在

CSC具有干细胞静止态、多能性与自我更新等特性，驱动肿瘤异质性和恶性进展，其CAR-T细胞治疗抵抗机制涉及3个方面：（1）低靶抗原表达与Wnt/β

-catenin等耐药信号通路异常激活；(2)多重耐药机制，包括解毒酶表达上调、药物外排增强及DNA修复活性增加等内源性因素，以及TME低氧应激等外源性因素；(3)通过分泌免疫抑制因子及激活STAT3/PI3K/AKT存活通路，协同诱导免疫逃逸[40-41]。临床研究[42]数据显示，靶向CD123的单克隆抗体SL-401在母细胞性浆细胞样树突状细胞肿瘤(blastic plasmacytoid dendritic cell neoplasm, BPDCN)治疗中显现显著临床活性，7例受试者达到客观缓解(objective response rate，ORR)，占77.8%；其中，5例为完全缓解(complete response，CR)、2例为部分缓解(partial response, PR)。

1.6 CAR-T细胞毒性作用

细胞因子释放综合征(cytokine release syndrome, CRS)作为细胞免疫疗法的核心安全性问题，其发生机制与CAR-T细胞激活后级联释放的炎性介质密切相关。当CAR-T细胞识别肿瘤抗原后，通过释放IL-6、IFN-γ、TNF-α等关键细胞因子驱动CRS发生[43]。共刺激结构域的选择显著影响CRS表型：相较于CD28共刺激型CAR-T细胞，4-1BB共刺激型可延迟CRS发生时间并降低严重程度[44]。进一步研究[45]显示，CAR-T细胞活化后分泌的促炎因子谱(包括IL-8、IL-10、MCP-1等)不仅通过正反馈环路加剧炎症反应，更可能通过双重作用机制影响治疗效果：一方面直接抑制CAR-T细胞功能；另一方面通过募集Treg细胞和MDSC等免疫抑制细胞促进肿瘤微环境重塑。

1.7 表观遗传的调控

异常表观遗传修饰(如DNA甲基化、组蛋白修饰失调及lncRNA异常)通过调控CSC的恶性转化驱动肿瘤发生[46]。表观遗传调控可增强CAR-T细胞功能：通过修饰组蛋白/DNA甲基化促进记忆表型形成并逆转T细胞耗竭[41]；DNA甲基转移酶(DNA Methyltransferase, DNMT)/组蛋白去乙酰化酶(histone deacetylase, HDAC)抑制剂等表观遗传疗法在离体条件下能解除转录抑制，诱导新抗原/癌睾抗原表达以增强免疫识别，同时通过重塑T细胞表观遗传景观(染色质构象/DNA甲基化)恢复其趋化因子分泌与分化功能[47]。

2 新型治疗策略

2.1 针对抗原逃逸的优化策略

2.1.1 多靶点CAR-T细胞设计

双靶点/三靶点CAR-T细胞：靶向CD19/CD22或CD19/CD20可显著降低单一抗原丢失导致的复发风险[48]。临床试验[49]显示，CD19/CD20双靶点CAR-T细胞治疗复发/难治性非霍奇金淋巴瘤(relapsed/refractory non-hodgkin lymphoma, R/R NHL)的ORR达90%，CR达70%。体内基因表达谱[50]分析表明，CD70/CD33双靶点CAR-T细胞在持久性、激活状态和T细胞受体(TCR)信号通路相关基因的表达显著上调，提示其功能增强。

逻辑门控CAR(逻辑电路CAR)：SynNotch/AND-gate系统通过双抗原协同激活机制(仅当肿瘤表达初/次级抗原时触发CAR表达)，实现精准靶向，降低脱靶毒性(如CRS/神经毒性)，提升治疗安全性[51]。

分子开关设计：(1)可逆性激活系统：利用小分子药物(如雷帕霉素)或光控开关(光敏蛋白)调控CAR结构域的二聚化，实现CAR-T细胞的“开/关”控制[52]。(2)自杀基因系统：引入诱导型胱天蛋白酶9(inducible caspase 9, iCasp9)、截短表皮生长因子受体(truncated epidermal growth factor receptor, tEGFR)、单纯疱疹病毒胸苷激酶(herpes simplex virus thymidine kinase, HSV-TK)或CD20标记，通过药物(AP1903、西妥昔单抗、更昔洛韦或利妥昔单抗)快速清除过度激活的CAR-T细胞，防止细胞因子风暴[53]。

2.1.2 抗原表位扩展与通用型CAR-T细胞

靶向新型抗原：靶向肿瘤特异性抗原(tumor-specific antigen, TSA)及新抗原可有效降低脱靶风险并拓宽治疗适应症，其中病毒癌蛋白、癌症睾丸抗原(cancer-testis antigen, CTA)等胚胎相关抗原均为潜在的肿瘤治疗靶点[54]。

模块化/通用CAR-T细胞：“模块化”或“通用”CAR系统的开发通过可切换双特异性接头设计实现靶向适应性调控，进而提升对异质性肿瘤抗原的靶向精度[55-56]。例如，通用型嵌合抗原受体(universal chimeric antigen receptor, UniCAR)系统通过靶向模块介导与共刺激受体4-1BB交联，可激活NF-κB/MAPK信号通路轴，显著增强UniCAR-T细胞的扩增、持久性及效应功能(如细胞因子分泌与肿瘤杀伤活性)。

2.2 逆转CAR-T细胞耗竭的策略

2.2.1 优化CAR结构设计

替代靶向结构域：重链单抗可变区(variable domain of the heavy chain of heavy-chain-only antibody, VHH，亦称纳米抗体)因其独特的理化稳定性，可耐受高压、酸性等极端环境，同时维持抗原高亲和力。该特性使其在CAR-T细胞工程中的应用展现出显著优势，通过VHH结构域的整合可有效增强靶向受体识别能力[57]。

共刺激域创新：与CD28和4-1BB相比，新型共刺激分子（如ICOS、OX40、MYD88-CD40、KIR2DS2）能够在增强效应功能的同时减少T细胞耗竭，从而优化CAR-T细胞的抗肿瘤活性[58]。如，ICOS加4-1BB、TLR2（Toll样受体2的Toll/白细胞介素-1受体结构域）加CD28和4-1BB加OX40，所有这些组合在体内和数学模型中都表现出比CD28和4-1BB共模拟结构域的组合更好的性能[59-60]。

抑制性受体阻断：靶向PD-1/CTLA-4 scFv或通过CRISPR-Cas9技术调控T细胞耗竭相关基因（如敲除PD-1、TOX或增强TCF7表达），可有效改善CAR-T细胞耗竭状态并重塑TME免疫抑制特性，从而显著增强CAR-T细胞治疗的持久性和抗肿瘤效应[26, 61]。临床研究[62-63]显示，在复发/难治性B细胞非霍奇金淋巴瘤（relapsed/refractory b-cell non-hodgkin lymphoma, R/R B-NHL）中，CD19/22双靶向CAR-T细胞联合PD-1抑制剂治疗使ORR提升12%，其机制与T细胞耗竭标志物下调密切相关。

2.2.2　表观遗传调控与记忆表型增强

表观遗传药物联用：表观遗传调控药物（如地西他滨和伏立诺他）可通过不同机制逆转T细胞耗竭：DNA甲基转移酶抑制剂通过去甲基化恢复T细胞功能[61]，而HDAC抑制剂则通过增强染色质可及性解除PD-1、TOX等关键基因的沉默状态[64]。

靶向特异性T细胞亚群：中枢记忆T细胞（T central memory T cell, Tcm）与干细胞样记忆T细胞（T stem cell-like memory T cell, Tscm）因其长寿特性及强增殖潜能，在CAR-T细胞疗法中展现出优越的抗肿瘤潜力。研究[65]表明，基于这两种亚群构建的CAR-T细胞库可显著提升其扩增能力、持久性及抗肿瘤效应。SONG等[66]发现，电荷修饰的底物通过增强TCR信号转导促进T细胞活化，同时抑制初始T细胞向虚拟记忆T细胞（T virtual memory T cell, Tvm）转化，该调控机制可协同增强效应分子表达与T细胞增殖效能。

2.2.3 非病毒方法递送

非病毒方法递送有基于转座子的系统、mRNA电穿孔和脂质转染、CRISPR等。LNP递送CAR-mRNA较电穿孔体外疗效更持久，兼具低毒性、缓增殖、少耗竭优势[67]。CRISPR/Cas9编辑通过靶向敲除CAR-T细胞的抑制性受体（PD-1/CTLA-4）、表观调控因子（DNMT3A）及耗竭基因（TOX），提升功能持久性，同时规避病毒载体风险并优化精准安全性[54]。

2.3　重塑肿瘤微环境的联合治疗

2.3.1　靶向TME免疫抑制成分

清除抑制性细胞：抗CSF-1R抗体清除M2-TAMs，CCL5抑制剂阻断MDSC募集，可协同逆转免疫抑制微环境[68]。MUC1/TRAILR2.41BB CAR-T细胞，同时靶向肿瘤特异性抗原和MDSC，可以抵消CAR-T细胞耗竭并提高抗肿瘤疗效[69]。

细胞因子调控：共同表达IL-12、IL-15、IL-18和IL-36γ的CAR-T细胞可以提高CAR-T细胞的持久性，降低PD-1表达，并通过ATP-P2RX7/CCL20-CCR6双通路促进表位扩散及宿主免疫应答，显著提升肿瘤清除率[57]。

2.3.2　代谢干预

解除代谢竞争：通过抑制肿瘤糖酵解（如使用LDHA抑制剂）或补充代谢底物（如精氨酸、谷氨酰胺），改善CAR-T细胞的线粒体代谢功能，增强其抗肿瘤活性[70-71]。

缺氧调控：低氧诱导型CAR（hypoxia-inducible chimeric antigen receptor, HiCAR）整合氧依赖性降解结构域（oxygen-dependent degradation domain, ODD）和缺氧反应元件（hypoxia-response element, HRE），维持CAR-T细胞在低氧TME中的功能稳定性[72]。联用PX-478抑制HIF-1α活性，下调VEGF/GLUT1，阻断肿瘤血管生成、糖酵解重编程及EMT[68]。

2.3.3　协同联合疗法

低剂量化疗：抑制IL-10、TGF-β等免疫抑制因子及PD-1/CTLA-4检查点，改善TME，提升CAR-T细胞疗效与持久性[73]；放射疗法：促T细胞募集、重塑血管、增强浸润并逆转免疫抑制性TME，协同增效[74]；溶瘤病毒：裂解肿瘤释放抗原，重塑TME并激活Ⅰ型干扰素通路，优化CAR-T细胞治疗条件[75]；酪氨酸激酶抑制剂（tyrosine kinase inhibitor, TKI）：调控PI3K/AKT、JAK/STAT通路，增强CAR-T细胞在免疫抑制性TME中的持久性[76]。

2.4　应对肿瘤异质性的创新技术

2.4.1　单细胞技术与动态监测

单细胞多组学分析：通过单细胞RNA测序（single-cell RNA sequencing, scRNA-seq）和TCR克隆追踪揭示CAR-T细胞表型动态，结合基因表达与信号通路（如PI3K/AKT、NF-κB）特征优化工程化设计，指导抗肿瘤效能的精准调控，包括增强持久性、浸润能力和杀伤活性[77]。

人工智能（artificial intelligence, AI）预测模型：AI通过高通量数据优化CRISPR设计（如sgRNA筛选与脱靶预测），提升CAR-T细胞靶向性与安全性，并简化生产流程以降低成本。基于机器学习的脱靶效应预测模型进一步增强治疗特异性，推动CAR-T细胞适应症从血液瘤（白血病/淋巴瘤）向实体瘤（乳腺癌/肺癌）及自身免疫病扩展[78]。

2.4.2 原位CAR-T细胞激活与局部递送

原位CAR-T细胞激活：传统瞬时CAR-T细胞系统由于依赖非共价瞬时结合，存在稳定性差、靶标多样性有限等固有缺陷；基于共价生物偶联的改进系统通过设计合成生物材料（如共价偶联分子或功能性纳米材料），实现了更稳定、快速且可扩展的CAR-T细胞调控，为肿瘤免疫治疗提供了长效且可定制的解决方案[79]。

局部给药系统：CAR-T细胞局部递送通过瘤内注射实现靶向杀伤，降低全身毒性[80]。纳米载体保护CAR-T细胞并增强肿瘤迁移，通过可控释放提升疗效及持久性[81]。LI等[82]开发的空间分布式微针系统（spatially distributed microneedle system, SDMNS）结合空间递送与生物正交技术，解决实体瘤抗原异质性和CAR-T细胞浸润不足。

3 结 语

未来研究需聚焦多机制交叉调控网络解析，开发“CAR-T细胞 + 表观药物 + 代谢调节剂”联合方案，并通过纳米递送系统实现精准时空调控。临床转化需平衡安全性与可及性，推动通用型CAR-T细胞研发。随着机制理解与技术革新，CAR-T细胞疗法有望突破实体瘤治疗瓶颈，引领肿瘤免疫治疗进入新纪元。

利益冲突

作者声明无利益冲突。

[参 考 文 献]

[1] SINGH S, KHASBAGE S, KAUR R J, *et al*. Chimeric antigen receptor T cell: a cancer immunotherapy[J]. Indian J Pharmacol, 2022, 54(3): 226-233. DOI: 10.4103/ijp.ijp_531_20.

[2] DANIELS K G, WANG S Y, SIMIC M S, *et al*. Decoding CAR T cell phenotype using combinatorial signaling motif libraries and machine learning[J]. Science, 2022, 378(6625): 1194-1200. DOI: 10.1126/science.abq0225.

[3] FRIEDES B D, DINOFIA A M, IANNONE E, *et al*. Therapies and outcomes following extramedullary relapse of pediatric and young adult ALL after CD19 CAR T-cell therapy[J]. Blood Adv, 2025, 9 (2): 354-359. DOI: 10.1182/bloodadvances.2024014518.

[4] GARCÍA-GUERRERO E, SIERRO-MARTÍNEZ B, PÉREZ-SIMÓN J A. Overcoming chimeric antigen receptor (CAR) modified T-cell therapy limitations in multiple myeloma[J/OL]. Front Immunol, 2020, 11: 1128[2025-05-11]. https://pubmed.ncbi.nlm.nih.gov/32582204/. DOI: 10.3389/fimmu.2020.01128.

[5] DA VIÀ M C, DIETRICH O, TRUGER M, *et al*. Homozygous BCMA gene deletion in response to anti-BCMA CAR T cells in a patient with multiple myeloma[J]. Nat Med, 2021, 27(4): 616-619. DOI: 10.1038/s41591-021-01245-5.

[6] SAMUR M K, AKTAS-SAMUR A, LANNES R, *et al*. 16p deletion involving BCMA locus is frequent and predominantly observed with del17p[J/OL]. Blood, 2021, 138: 1590[2025-05-11]. http://dx.doi. org/10.1182/blood-2021-152286. DOI: 10.1182/blood-2021-152286.

[7] SCHULTZ L M, BAGGOTT C, PRABHU S, *et al*. Disease burden affects outcomes in pediatric and young adult B-cell lymphoblastic leukemia after commercial tisagenlecleucel: a pediatric real-world chimeric antigen receptor consortium report[J]. J Clin Oncol, 2022, 40(9): 945-955. DOI: 10.1200/JCO.20.03585.

[8] LAETSCH T W, MAUDE S L, RIVES S, *et al*. Three-year update of tisagenlecleucel in pediatric and young adult patients with relapsed/refractory acute lymphoblastic leukemia in the ELIANA trial[J]. J Clin Oncol, 2023, 41(9): 1664-1669. DOI: 10.1200/JCO.22.00642.

[9] RAFIQ S, HACKETT C S, BRENTJENS R J. Engineering strategies to overcome the current roadblocks in CAR T cell therapy [J]. Nat Rev Clin Oncol, 2020, 17(3): 147-167. DOI: 10.1038/s41571-019-0297-y.

[10] GARDNER R, WU D, CHERIAN S, *et al*. Acquisition of a CD19-negative myeloid phenotype allows immune escape of MLL-rearranged B-ALL from CD19 CAR-T-cell therapy[J]. Blood, 2016, 127(20): 2406-2410. DOI: 10.1182/blood-2015-08-665547.

[11] PONT M J, HILL T, COLE G O, *et al*. γ-Secretase inhibition increases efficacy of BCMA-specific chimeric antigen receptor T cells in multiple myeloma[J]. Blood, 2019, 134(19): 1585-1597. DOI: 10.1182/blood.2019000050.

[12] DABIRI H, SAFARZADEH KOZANI P, HABIBI ANBOUHI M, *et al*. Site-specific transgene integration in chimeric antigen receptor (CAR) T cell therapies[J/OL]. Biomark Res, 2023, 11(1): 67[2025-05-11]. https://pubmed.ncbi.nlm.nih.gov/37403182/. DOI: 10.1186/s40364-023-00509-1.

[13] LI X Q, CHEN W H. Mechanisms of failure of chimeric antigen receptor T-cell therapy[J]. Curr Opin Hematol, 2019, 26(6): 427-433. DOI: 10.1097/MOH.0000000000000548.

[14] GARRIDO F, APTSIAURI N, DOORDUIJN E M, *et al*. The urgent need to recover MHC class Ⅰ in cancers for effective immunotherapy [J]. Curr Opin Immunol, 2016, 39: 44-51. DOI: 10.1016/j.coi.2015.12.007.

[15] WATANABE N, MO F Y, MCKENNA M K. Impact of manufacturing procedures on CAR T cell functionality[J/OL]. Front Immunol, 2022, 13: 876339[2025-05-11]. https://pubmed.ncbi.nlm.nih.gov/35493513/. DOI: 10.3389/fimmu.2022.876339.

[16] SUZUKI H, OHISHI T, TANAKA T, *et al*. A cancer-specific monoclonal antibody against podocalyxin exerted antitumor activities in pancreatic cancer xenografts[J/OL]. Int J Mol Sci, 2023, 25(1): 161[2025-05-11]. https://pubmed. ncbi. nlm. nih. gov/38203331/. DOI: 10.3390/ijms25010161.

[17] GUEDAN S, RUELLA M, JUNE C H. Emerging cellular therapies for cancer[J]. Annu Rev Immunol, 2019, 37: 145-171. DOI: 10.1146/annurev-immunol-042718-041407.

[18] GUMBER D, WANG L D. Improving CAR-T immunotherapy: overcoming the challenges of T cell exhaustion[J/OL]. eBioMedicine, 2022, 77: 103941[2025-05-11]. http://dx. doi. org/10.1016/j.ebiom.2022.103941. DOI: 10.1016/j.ebiom.2022.103941.

[19] KHAN O, GILES J R, MCDONALD S, *et al*. TOX transcriptionally and epigenetically programs $CD8^+$ T cell exhaustion[J]. Nature, 2019, 571(7764): 211-218. DOI: 10.1038/s41586-019-1325-x.

[20] BELTRA J C, MANNE S, ABDEL-HAKEEM M S, *et al*. Developmental relationships of four exhausted $CD8^+$ T cell subsets reveals underlying transcriptional and epigenetic landscape control mechanisms[J]. Immunity, 2020, 52(5): 825-841. DOI: 10.1016/j.immuni.2020.04.014.

[21] MCLANE L M, NGIOW S F, CHEN Z Y, *et al*. Role of nuclear localization in the regulation and function of T-bet and Eomes in exhausted CD8 T cells[J/OL]. Cell Rep, 2021, 35(6): 109120[2025-05-11]. https://pubmed.ncbi.nlm.nih.gov/33979613/. DOI: 10.1016/j.celrep.2021.109120.

[22] HUDSON W H, GENSHEIMER J, HASHIMOTO M, *et al*. Proliferating transitory T cells with an effector-like transcriptional signature emerge from PD-1^+ stem-like $CD8^+$ T cells during chronic infection[J]. Immunity, 2019, 51(6): 1043-1058. DOI: 10.1016/j.immuni.2019.11.002.

[23] SCOTT A C, DÜNDAR F, ZUMBO P, et al. TOX is a critical regulator of tumour-specific T cell differentiation[J]. Nature, 2019, 571(7764): 270-274. DOI: 10.1038/s41586-019-1324-y.

[24] ZHANG G Z, JI G C, LIU L W, *et al*. The tumor microenvironment of hepatocellular carcinoma and its targeting strategy by CAR-T cell immunotherapy[J/OL]. Front Endocrinol (Lausanne), 2022, 13: 918869[2025-05-11]. https://pubmed.ncbi.nlm.nih.gov/36093115/. DOI: 10.3389/fendo.2022.918869.

[25] CAPPELL K M, KOCHENDERFER J N. A comparison of chimeric antigen receptors containing CD28 versus 4-1BB costimulatory domains[J]. Nat Rev Clin Oncol, 2021, 18(11): 715-727. DOI: 10.1038/s41571-021-00530-z.

[26] ALBARRÁN V, SAN ROMÁN M, POZAS J, *et al*. Adoptive T cell therapy for solid tumors: current landscape and future challenges[J/OL]. Front Immunol, 2024, 15: 1352805[2025-05-11]. https://pubmed.ncbi.nlm.nih.gov/38550594/. DOI: 10.3389/fimmu.2024.1352805.

[27] NAKASHIMA T, KAGOYA Y. Current progress of CAR-T-cell therapy for patients with multiple myeloma[J]. Int J Hematol, 2024, 120(1): 15-22. DOI: 10.1007/s12185-024-03794-0.

[28] QIN Y, XU G T. Enhancing CAR T-cell therapies against solid tumors: Mechanisms and reversion of resistance[J/OL]. Front Immunol, 2022, 13: 1053120[2025-05-11]. https://pubmed.ncbi.nlm.nih.gov/36569859/. DOI: 10.3389/fimmu.2022.1053120.

[29] CHO N W, GULDBERG S M, NABET B Y, *et al*. T cells instruct immune checkpoint inhibitor therapy resistance in tumors responsive to IL1 and TNFα inflammation[J]. Cancer Immunol Res, 2025, 13(2): 229-244. DOI: 10.1158/2326-6066.CIR-24-0416.

[30] YAMAGUCHI Y, GIBSON J, OU K, *et al*. PD-L1 blockade restores CAR T cell activity through IFN-γ-regulation of $CD163^+$ M2 macrophages[J/OL]. J Immunother Cancer, 2022, 10(6): e004400 [2025-05-11]. https://pubmed.ncbi.nlm.nih.gov/35738799/. DOI: 10.1136/jitc-2021-004400.

[31] ZHANG E H, GU J Y, XU H M. Prospects for chimeric antigen receptor-modified T cell therapy for solid tumors[J/OL]. Mol Cancer, 2018, 17(1): 7[2025-05-11]. https://pubmed.ncbi.nlm.nih.gov/29329591/. DOI: 10.1186/s12943-018-0759-3.

[32] ZHOU Z, LIU S, LI J, *et al*. Modification with IL-21 and CCL19 enhances killing efficiency and tumor infiltration of NKP30 CAR-T cells in lung cancer[J]. J South Med Univ, 2024, 44(10): 1926-1936. DOI: 10.12122/j.issn.1673-4254.2024.10.11.

[33] BO M D, DE MATTIA E, BABOCI L, *et al*. New insights into the pharmacological, immunological, and CAR-T-cell approaches in the treatment of hepatocellular carcinoma[J/OL]. Drug Resist Updat, 2020, 51: 100702[2025-05-11]. https://pubmed.ncbi.nlm.nih.gov/32371296/. DOI: 10.1016/j.drup.2020.100702.

[34] SCHUBERT M L, SCHMITT M, WANG L, *et al*. Side-effect management of chimeric antigen receptor (CAR) T-cell therapy[J]. Ann Oncol, 2021, 32(1): 34-48. DOI: 10.1016/j.annonc.2020.10.478.

[35] LOSIC B, CRAIG A J, VILLACORTA-MARTIN C, *et al*. Intratumoral heterogeneity and clonal evolution in liver cancer [J/OL]. Nat Commun, 2020, 11(1): 291[2025-05-11]. https://pubmed.ncbi.nlm.nih.gov/31941899/. DOI: 10.1038/s41467-019-14050-z.

[36] ANDERSSON A, LARSSON L, STENBECK L, *et al*. Spatial deconvolution of HER2-positive breast cancer delineates tumor-associated cell type interactions[J/OL]. Nat Commun, 2021, 12(1): 6012[2025-05-11]. https://pubmed.ncbi.nlm.nih.gov/34650042/. DOI: 10.1038/s41467-021-26271-2.

[37] SAMUR M K, FULCINITI M, AKTAS SAMUR A, *et al*. Biallelic loss of BCMA as a resistance mechanism to CAR T cell therapy in a patient with multiple myeloma[J/OL]. Nat Commun, 2021, 12(1): 868[2025-05-11]. https://pubmed.ncbi.nlm.nih.gov/33558511/. DOI: 10.1038/s41467-021-21177-5.

[38] ZHAO G X, WEI R H, FENG L, *et al*. Lenalidomide enhances the efficacy of anti-BCMA CAR-T treatment in relapsed/refractory multiple myeloma: a case report and revies of the literature[J]. Cancer Immunol Immunother, 2022, 71(1): 39-44. DOI: 10.1007/s00262-021-02959-8.

[39] GARFALL A L, COHEN A D, SUSANIBAR-ADANIYA S P, *et al*. Anti-BCMA/CD19 CAR T cells with early immunomodulatory maintenance for multiple myeloma responding to initial or later-line therapy[J]. Blood Cancer Discov, 2023, 4(2): 118-133. DOI: 10.1158/2643-3230.BCD-22-0074.

[40] DAKAL T C, BHUSHAN R, XU C M, *et al*. Intricate relationship between cancer stemness, metastasis, and drug resistance[J/OL]. MedComm (2020), 2024, 5(10): e710[2025-05-11]. https://pubmed.ncbi.nlm.nih.gov/39309691/. DOI: 10.1002/mco2.710.

[41] VESCHI V, TURDO A, STASSI G. Novel insights into cancer stem cells targeting: CAR-T therapy and epigenetic drugs as new pillars in cancer treatment[J/OL]. Front Mol Med, 2023, 3: 1120090[2025-05-11]. https://pubmed.ncbi.nlm.nih.gov/39086678/. DOI: 10.3389/fmmed.2023.1120090.

[42] FRANKEL A E, WOO J H, AHN C, *et al*. Activity of SL-401, a targeted therapy directed to interleukin-3 receptor, in blastic plasmacytoid dendritic cell neoplasm patients[J]. Blood, 2014, 124 (3): 385-392. DOI: 10.1182/blood-2014-04-566737.

[43] YU S N, YI M, QIN S, *et al*. Next generation chimeric antigen receptor T cells: safety strategies to overcome toxicity[J/OL]. Mol Cancer, 2019, 18(1): 125[2025-05-11]. DOI: 10.1186/s12943-019-1057-4.

[44] SIEGLER E L, KENDERIAN S S. Neurotoxicity and cytokine release syndrome after chimeric antigen receptor T cell therapy:

insights into mechanisms and novel therapies[J/OL]. Front Immunol, 2020, 11: 1973[2025-05-11]. https://pubmed.ncbi.nlm.nih.gov/32983132/. DOI: 10.3389/fimmu.2020.01973.

[45] PARIKH R H, LONIAL S. Chimeric antigen receptor T-cell therapy in multiple myeloma: a comprehensive review of current data and implications for clinical practice[J]. CA Cancer J Clin, 2023, 73(3): 275-285. DOI: 10.3322/caac.21771.

[46] VERONA F , PANTINA V D, MODICA C, *et al*. Targeting epigenetic alterations in cancer stem cells[J/OL]. Front Mol Med, 2022, 2: 1011882[2025-05-11]. https://pubmed. ncbi. nlm. nih. gov/39086963/. DOI: 10.3389/fmmed.2022.1011882.

[47] MOROTTI M, ALBUKHARI A, ALSAADI A, *et al*. Promises and challenges of adoptive T-cell therapies for solid tumours[J]. Br J Cancer, 2021, 124(11): 1759-1776. DOI: 10.1038/s41416-021-01353-6.

[48] HUANG R H, LI X P, HE Y D, *et al*. Recent advances in CAR-T cell engineering[J/OL]. J Hematol Oncol, 2020, 13(1): 86[2025-05-11]. https://pubmed. ncbi. nlm. nih. gov/32616000/. DOI: 10.1186/s13045-020-00910-5.

[49] LARSON S M, WALTHERS C M, JI B, *et al*. CD19/CD20 bispecific chimeric antigen receptor (CAR) in naive/memory T cells for the treatment of relapsed or refractory non-Hodgkin lymphoma [J]. Cancer Discov, 2023, 13(3): 580-597. DOI: 10.1158/2159-8290.CD-22-0964.

[50] SILVA H J, MARTIN G, BIROCCHI F, *et al*. CD70 CAR T cells secreting an anti-CD33/anti-CD3 dual-targeting antibody overcome antigen heterogeneity in AML[J]. Blood, 2025, 145(7): 720-731. DOI: 10.1182/blood.2023023210.

[51] HONG M H, CLUBB J D, CHEN Y Y. Engineering CAR-T cells for next-generation cancer therapy[J]. Cancer Cell, 2020, 38(4): 473-488. DOI: 10.1016/j.ccell.2020.07.005.

[52] GIORDANO ATTIANESE G M P, SHUI S L, CRIBIOLI E, *et al*. Dual ON/OFF-switch chimeric antigen receptor controlled by two clinically approved drugs[J/OL]. Proc Natl Acad Sci USA, 2024, 121(44): e2405085121[2025-05-11]. https://pubmed. ncbi. nlm. nih. gov/39453747/. DOI: 10.1073/pnas.2405085121.

[53] MOGHANLOO E, MOLLANOORI H, TALEBI M, *et al*. Remote controlling of CAR-T cells and toxicity management: Molecular switches and next generation CARs[J/OL]. Transl Oncol, 2021, 14(6): 101070[2025-05-11]. https://pubmed. ncbi. nlm. nih. gov/33789222/. DOI: 10.1016/j.tranon.2021.101070.

[54] ALI A, DIPERSIO J F. ReCARving the future: bridging CAR T-cell therapy gaps with synthetic biology, engineering, and economic insights[J/OL]. Front Immunol, 2024, 15: 1432799[2025-05-11]. https://pubmed. ncbi. nlm. nih. gov/39301026/. DOI: 10.3389/fimmu.2024.1432799.

[55] PESCHKE J C, BERGMANN R, MEHNERT M, *et al*. FLT3-directed UniCAR T-cell therapy of acute myeloid leukaemia[J]. Br J Haematol, 2023, 202(6): 1137-1150. DOI: 10.1111/bjh.18971.

[56] BOUTIER H, LOUREIRO L R, HOFFMANN L, *et al*. UniCAR T-cell potency-a matter of affinity between adaptor molecules and adaptor CAR T-cells? [J/OL]. Int J Mol Sci, 2024, 25(13): 7242 [2025-05-11]. https://pubmed. ncbi. nlm. nih. gov/39000348/. DOI: 10.3390/ijms25137242.

[57] WANG Z Y, ZHOU L, WU X Y. Influencing factors and solution strategies of chimeric antigen receptor T-cell therapy (CAR-T) cell immunotherapy[J]. Oncol Res, 2024, 32(9): 1479-1516. DOI: 10.32604/or.2024.048564.

[58] TIAN Y G, LI Y L, SHAO Y P, *et al*. Gene modification strategies for next-generation CAR T cells against solid cancers[J/OL]. J Hematol Oncol, 2020, 13(1): 54[2025-05-11]. https://pubmed. ncbi. nlm.nih.gov/32423475/. DOI: 10.1186/s13045-020-00890-6.

[59] GUEDAN S, POSEY A D Jr, SHAW C, *et al*. Enhancing CAR T cell persistence through ICOS and 4-1BB costimulation[J/OL]. JCI Insight, 2018, 3(1): e96976[2025-05-11]. https://pubmed. ncbi. nlm. nih.gov/29321369/. DOI: 10.1172/jci.insight.96976.

[60] KONSTORUM A, VELLA A T, ADLER A J, *et al*. A mathematical model of combined CD8 T cell costimulation by 4-1BB (CD137) and OX40 (CD134) receptors[J/OL]. Sci Rep, 2019, 9(1): 10862 [2025-05-11]. https://pubmed. ncbi. nlm. nih. gov/31350431/. DOI: 10.1038/s41598-019-47333-y.

[61] ZHOU S, YANG Y H, JING Y L, *et al*. Generating advanced CAR-based therapy for hematological malignancies in clinical practice: targets to cell sources to combinational strategies[J/OL]. Front Immunol, 2024, 15: 1435635[2025-05-11]. https://pubmed. ncbi. nlm.nih.gov/39372412/. DOI: 10.3389/fimmu.2024.1435635.

[62] ZHANG Y, GENG H Z, ZENG L Y, *et al*. Tislelizumab augment the efficacy of CD19/22 dual-targeted chimeric antigen receptor T cell in advanced stage relapsed or refractory B-cell non-Hodgkin lymphoma[J/OL]. Hematol Oncol, 2024, 42(1): e3227[2025-05-11]. https://pubmed. ncbi. nlm. nih. gov/37776326/. DOI: 10.1002/hon.3227.

[63] ZHANG Y, LI J Q, LOU X Y, *et al*. A prospective investigation of bispecific CD19/22 CAR T cell therapy in patients with relapsed or refractory B cell non-Hodgkin lymphoma[J/OL]. Front Oncol, 2021, 11: 664421[2025-05-11]. https://pubmed. ncbi. nlm. nih. gov/34113569/. DOI: 10.3389/fonc.2021.664421.

[64] ZHANG Z N, SU M Q, JIANG P R, *et al*. Unlocking apoptotic pathways: overcoming tumor resistance in CAR-T-cell therapy[J/OL]. Cancer Med, 2024, 13(19): e70283[2025-05-11]. https://pubmed.ncbi.nlm.nih.gov/39377542/. DOI: 10.1002/cam4.70283.

[65] ARCANGELI S, BOVE C, MEZZANOTTE C, *et al*. CAR T cell manufacturing from naive/stem memory T lymphocytes enhances antitumor responses while curtailing cytokine release syndrome[J/OL]. J Clin Invest, 2022, 132(12): e150807[2025-05-11]. https://pubmed.ncbi.nlm.nih.gov/35503659/. DOI: 10.1172/JCI150807.

[66] SONG J, LU Y H, LIU L L, *et al*. Charged substrate treatment enhances T cell mediated cancer immunotherapy[J/OL]. Nat Commun, 2025, 16(1): 1585[2025-05-11]. https://pubmed.ncbi.nlm.nih.gov/39939595/. DOI: 10.1038/s41467-025-56858-y.

[67] KHAWAR M B, AFZAL A, SI Y, *et al*. Steering the course of CAR T cell therapy with lipid nanoparticles[J/OL]. J Nanobiotechnology, 2024, 22(1): 380[2025-05-11]. https://pubmed. ncbi. nlm. nih. gov/38943167/. DOI: 10.1186/s12951-024-02630-1.

[68] GLAVIANO A, LAU H S, CARTER L M, *et al*. Harnessing the tumor microenvironment: targeted cancer therapies through modulation of epithelial-mesenchymal transition[J/OL]. J Hematol Oncol, 2025, 18(1): 6[2025-05-11]. https://pubmed. ncbi. nlm. nih. gov/39806516/. DOI: 10.1186/s13045-024-01634-6.

[69] NALAWADE S A, SHAFER P, BAJGAIN P, *et al*. Selectively

targeting myeloid-derived suppressor cells through TRAIL receptor 2 to enhance the efficacy of CAR T cell therapy for treatment of breast cancer[J/OL]. J Immunother Cancer, 2021, 9(11): e003237 [2025-05-11]. https://pubmed. ncbi. nlm. nih. gov/34815355/. DOI: 10.1136/jitc-2021-003237.

[70] CHANG C H, QIU J, O'SULLIVAN D, *et al*. Metabolic competition in the tumor microenvironment is a driver of cancer progression[J]. Cell, 2015, 162(6): 1229-1241. DOI: 10.1016/j.cell.2015.08.016.

[71] GEIGER R, RIECKMANN J C, WOLF T, *et al*. L-arginine modulates T cell metabolism and enhances survival and anti-tumor activity[J]. Cell, 2016, 167(3): 829-842. DOI: 10.1016/j.cell.2016.09.031.

[72] LIAO Q B, HE H, MAO Y Y, *et al*. Engineering T cells with hypoxia-inducible chimeric antigen receptor (HiCAR) for selective tumor killing[J/OL]. Biomark Res, 2020, 8(1): 56[2025-05-11]. https://pubmed.ncbi.nlm.nih.gov/33292642/. DOI: 10.1186/s40364-020-00238-9.

[73] KHALIULIN M, VALIULLINA A, PETUKHOV A, *et al*. Breaking the shield of solid tumors: a combined approach for enhanced efficacy of CAR-T cells[J/OL]. Cancer Immunol Immunother, 2024, 74(1): 3[2025-05-11]. https://pubmed. ncbi. nlm. nih. gov/39487875/. DOI: 10.1007/s00262-024-03817-z.

[74] QIN V M, HAYNES N M, D'SOUZA C, *et al*. CAR-T plus radiotherapy: a promising combination for immunosuppressive tumors[J/OL]. Front Immunol, 2022, 12: 813832[2025-05-11]. https://pubmed. ncbi. nlm. nih. gov/35095911/. DOI: 10.3389/fimmu.2021.813832.

[75] MAMOLA J A, CHEN C Y, CURRIER M A, *et al*. Opportunities and challenges of combining adoptive cellular therapy with oncolytic virotherapy[J]. Mol Ther Oncolytics, 2023, 29: 118-124. DOI: 10.1016/j.omto.2023.04.008.

[76] LIU J H, JIAO X F, MA D, *et al*. CAR-T therapy and targeted treatments: Emerging combination strategies in solid tumors[J]. Med, 2024, 5(6): 530-549. DOI: 10.1016/j.medj.2024.03.001.

[77] CHENG J L, ZHAO Y Y, HU H, *et al*. Revealing the impact of CD70 expression on the manufacture and functions of CAR-70 T-cells based on single-cell transcriptomics[J]. Cancer Immunol Immunother, 2023, 72(10): 3163-3174. DOI: 10.1007/s00262-023-03475-7.

[78] BORETTI A. The transformative potential of AI-driven CRISPR-Cas9 genome editing to enhance CAR T-cell therapy[J/OL]. Comput Biol Med, 2024, 182: 109137[2025-05-11]. https://pubmed.ncbi.nlm.nih.gov/39260044/. DOI: 10.1016/j.compbiomed.2024.109137.

[79] CARDLE I I, SCHERER D R, JENSEN M C, *et al*. *In situ* bioconjugation of synthetic peptides onto universal chimeric antigen receptor T cells for targeted cancer immunotherapies[J]. ACS Nano, 2025, 19(5): 5750-5768. DOI: 10.1021/acsnano.4c16824.

[80] BROWN C E, HIBBARD J C, ALIZADEH D, *et al*. Locoregional delivery of IL-13Rα2-targeting CAR-T cells in recurrent high-grade glioma: a phase 1 trial[J]. Nat Med, 2024, 30(4): 1001-1012. DOI: 10.1038/s41591-024-02875-1.

[81] GROSSKOPF A K, LABANIEH L, KLYSZ D D, *et al*. Delivery of CAR-T cells in a transient injectable stimulatory hydrogel niche improves treatment of solid tumors[J/OL]. Sci Adv, 2022, 8(14): eabn8264[2025-05-11]. https://pubmed. ncbi. nlm. nih. gov/35394838/. DOI: 10.1126/sciadv.abn8264.

[82] LI L Y, WANG F, MO S S, *et al*. A spatially distributed microneedle system for bioorthogonal T cell-guided cancer therapy[J/OL]. Adv Sci (Weinh), 2025, 12(13): e2416841[2025-05-11]. https://pubmed.ncbi.nlm.nih.gov/39921874/. DOI: 10.1002/advs.202416841.

［收稿日期］ 2025-05-12　　［修回日期］2025-08-15
［本文编辑］ 向正华