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CAR T cells redirected to B7-H3 for pediatric solid tumors: Current status and future perspectives

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Abstract

Despite intensive therapies, pediatric patients with relapsed or refractory solid tumors have poor outcomes and need novel treatments. Immune therapies offer an alternative to conventional treatment options but require the identification of differentially expressed antigens to direct antitumor activity to sites of disease. B7-H3 (CD276) is an immune regulatory protein that is expressed in a range of malignancies and has limited expression in normal tissues. B7-H3 is highly expressed in pediatric solid tumors including osteosarcoma, rhabdomyosarcoma, Ewing sarcoma, Wilms tumor, neuroblastoma, and many rare tumors. In this article we review B7-H3-targeted chimeric antigen receptor (B7-H3-CAR) T cell therapies for pediatric solid tumors, reporting preclinical development strategies and outlining the landscape of active pediatric clinical trials. We identify challenges to the success of CAR T cell therapy for solid tumors including localizing to and penetrating solid tumor sites, evading the hostile tumor microenvironment, supporting T cell expansion and persistence, and avoiding intrinsic tumor resistance. We highlight strategies to overcome these challenges and enhance the effect of B7-H3-CAR T cells, including advanced CAR T cell design and incorporation of combination therapies.

Keywords

B7-H3; CAR T cell therapy; Chimeric antigen receptor; Solid tumor; Immunotherapy; Pediatric cancer

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CRediT authorship contribution statement

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests. R. E., S.G. and C.D. have patent applications in the field of CAR T cell therapy, including B7-H3-specific CAR T cells. S.G. is a member of the Scientific Advisory Board of Be Biopharma and CARGO, and the Data and Safety Monitoring Board (DSMB) of Immatics and has received honoraria from TESSA Therapeutics within the last year.

1. Introduction

Pediatric patients with relapsed/refractory solid tumors have dismal outcomes despite attempts at intensive multimodal therapies including chemotherapy, radiation therapy, and surgical resection [1–5]. These patients are urgently in need of novel therapies to improve outcomes. Chimeric antigen receptor (CAR) T cell therapy represents a promising potential strategy for treating pediatric patients with solid tumors. In contrast to CD19-CAR T cell therapy which has produced dramatic responses for pediatric B-ALL [6–10], initial attempts to translate CAR T cell therapy for pediatric solid tumors have demonstrated limited clinical activity [11–16]. However, a recent study with GD2-CAR T cells has demonstrated significant antitumor activity in pediatric patients with neuroblastoma and low disease burden [17]. Identifying target antigens that are differentially expressed in a broad range of pediatric tumors and not in healthy tissues remains a significant challenge. Likewise, for individual pediatric solid tumor types, there may be heterogeneity in antigen expression among individual patients, between metastatic and primary sites, and within an individual tumor [18].

B7-H3 (CD276) is an immunomodulatory protein that has emerged as an attractive target for immunotherapy, due to its expression on a range of malignancies including pediatric solid tumors [4,19–21]. Beyond antigen expression, CAR T cell therapy approaches for pediatric solid tumors must also overcome the challenges of localizing to and penetrating tumor sites, evading a hostile immune microenvironment, optimizing T cell dynamics, and avoiding antigen escape [11,12]. In this review we detail the expression of B7-H3 in pediatric solid tumors and brain tumors, discuss efforts in preclinical B7-H3-targeted CAR (B7-H3-CAR) T cell development, describe the current landscape of pediatric B7-H3-CAR T cell clinical trials, and explore strategies to improve B7-H3-CAR T cell approaches.

2. B7-H3 as an antigen for CAR T cell therapy

2.1. Physiologic role of B7-H3

B7-H3 is a surface glycoprotein encoded on chromosome 15 which can exist in two isoforms: containing either two or four immunoglobulin-like (Ig) regions, with the four Ig isoform predominating in humans [22–24]. The receptors of B7-H3 have not been definitively described, with conflicting reports existing on the role of potential candidates including TLT-2, IL-20Rα, and PLA2R1 [24–30]. Physiologically, B7-H3 plays a role in immunomodulation [30,31]. While initial reports proposed a costimulatory effect [32], subsequent studies have identified associated B7-H3 expression with inhibition of T cell activation and suppression of T cell-mediated antitumor responses [24,27,33]. Proposed mechanisms of immune inhibition include decreased signaling through the PI3K/AKT/mTOR pathway [34], restriction of antigen-presenting cells [35], M2 macrophage polarization [36,37], and inhibition of natural killer cell-mediated lysis [38]. Beyond immune regulation, B7-H3 is proposed to directly support cancer cell invasion, proliferation, angiogenesis, and metabolism [30]. Through both immunologic and non-immunologic roles, B7-H3 has the potential to support tumor progression and immune evasion, while having antitumor effects under some circumstances [31].

Minimal healthy tissue B7-H3 expression has been detected at the protein level by immunohistochemistry (IHC) and at the RNA level in sequencing-based assays [21,39,40]. Low-level expression has been reported in normal stomach [19,40,41], colon [41], salivary gland [40], skin [42], pancreas [19] and liver [19], with variable expression in normal adrenal tissue [19,21,40]. Importantly, initial clinical studies targeting B7-H3 with monoclonal antibodies did not identify concerns for significant on-target off-tumor toxicities [43–45]. Because of this favorable expression profile, a number of B7-H3-targeting therapeutic strategies are being explored, including bispecific antibodies, antibody-drug conjugates, radioimmunotherapy, and cellular therapy [42,45–51]. As B7-H3 continues to be explored as an immunotherapy target, it will be necessary to continue monitoring for off-tumor toxicities and further defining its physiologic role as we seek to understand potential mechanisms of treatment resistance.

2.2. B7-H3 expression in pediatric solid tumors

In contrast with low-level normal tissue expression, B7-H3 is highly expressed in pediatric solid tumors [4,11,19,21,39,40]. Pediatric sarcomas have particularly high B7-H3 expression, including osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, and non-rhabdomyosarcoma soft tissue sarcomas [19,21,39,40]. This includes >95% expression reported in samples from patients with osteosarcoma, coinciding with expression in a range of preclinical osteosarcoma models including in vitro assays and in vivo murine and spontaneously-occurring canine models [52–57]. In rhabdomyosarcoma, B7-H3 expression was identified in both alveolar and embryonal histologic subtypes, encompassing *FOXO1* fusion-negative and fusion-positive disease, with a relationship identified between *PAX3--FOXO1* and *B7-H3* expression in functional studies [21,39,58,59].

Likewise in neuroblastoma, B7-H3 was identified in samples from patients with both localized and metastatic disease, with higher levels of B7-H3 identified through IHC or mRNA expression associated with poor prognosis [60,61]. This clinicopathologic observation is supported by preclinical studies demonstrating that knockdown of B7-H3 in neuroblastoma models is associated with tumor cell proliferation [62], and overexpression of B7-H3 can confer chemotherapy resistance [60,63]. Importantly, B7-H3 expression can be retained in patients with GD2-low or negative disease after receipt of prior GD2-targeted immunotherapy [64]. In addition to the extended analyses in neuroblastoma and sarcomas, additional pediatric solid tumors with reported B7-H3 expression include Wilms tumor, malignant peripheral nerve sheath tumor, hepatoblastoma, melanoma, and desmoplastic small round cell tumor [19, 21,39].

2.3. B7-H3 as a pan-cancer antigen

Beyond extracranial pediatric solid tumors, B7-H3 is also highly expressed in a range of other malignancies. The majority of pediatric brain tumor samples evaluated express B7-H3 across all subtypes including medulloblastoma, high-grade glioma, diffuse midline glioma (formerly diffuse intrinsic pontine glioma [DIPG]), ependymoma, and atypical teratoid rhabdoid tumor (ATRT) [19,65]. B7-H3 expression exceeds or is comparable to that of other immunotherapy targets of interest in pediatric brain tumors [65]. Increased intensity of B7-H3 IHC has been associated with high-grade features, and increased mRNA expression

associated with shorter overall survival [66]. B7-H3 expression is also noted in adult brain tumors including glioblastoma and anaplastic meningioma [67–69].

Like pediatric solid tumors, adult solid tumors also have marked B7-H3 expression [70]. B7-H3 has been extensively evaluated in prostate, breast, and ovarian cancers, where increased expression is associated with increased risk of recurrence, decreased survival, and treatment resistance [30,71–76]. Notably, in prostate cancer increased B7-H3 expression is associated with biochemical recurrence after radiation therapy and increased androgen receptor activation [72,73]. In non-small cell lung cancer, B7-H3 is associated with advanced stage and metastatic disease [77,78]. Across a range of gastrointestinal cancers including hepatocellular, gastric, pancreatic, esophageal, and colorectal, B7-H3 is expressed and often associated with poor prognosis [40, 70,79–82]. In pancreatic cancer models, increased intensity of B7-H3 expression is seen in metastatic disease and associated with increased pathological stage [80]. In addition to solid tumors, B7-H3 is being explored as a target for hematologic malignancies including acute myeloid leukemia [83,84], anaplastic large cell lymphoma [85], and NK/T cell lymphoma [86]. The spectrum of malignancies which express B7-H3, overall differential expression from healthy tissues, and association with high-risk disease features, support the role of B7-H3 as a pan-cancer antigen and attractive immunotherapeutic target. This potentially broad impact further supports developing B7-H3-targeting therapies for individually rare pediatric tumor types.

3. B7-H3-CAR T cell preclinical development

The efficacy of a CAR T cell construct is dependent on the interaction between each component of the CAR design, including antigen recognition domains, structural elements, and costimulatory molecules (Fig. 1). Variations of B7-H3-CAR T cells are undergoing translational development, with many groups exploring additional enhancements to improve CAR T cell function [48].

3.1. CAR design

Traditional CAR T cell antigen recognition domains are based on the single chain variable fragment (scFv) of a monoclonal antibody. For B7-H3, initial products proceeding in clinical development include those based on MGA271 [21,39,41,87] and mAb376.96 [40,88] scFvs. To evaluate the properties of B7-H3-CAR T cells with variable antigen recognition properties, single-chain antibody libraries have been produced to generate additional scFvs for preclinical evaluation [89]. As an alternative to traditional scFvs, nanobody-based libraries have also been explored to generate high-affinity recognition domains [90]. Beyond the antigen recognition domain, key components of the hinge and transmembrane can affect structure and activity of the CAR T cell construct [21,87]. While first generation CAR T cells consisted of antigen recognition and intracellular signaling domains, second generation CAR T cells include the addition of costimulatory molecules. Costimulatory molecules of the immunoglobulin superfamily including CD28 are associated with potent initial antitumor activity, while costimulatory molecules of the tumor necrosis factor receptor superfamily including 4–1BB and OX40 are associated with improved CAR T cell persistence [91]. Both classes of costimulatory molecules are being evaluated in B7-H3-CAR T cell constructs, in

addition to third generation CARs which incorporate multiple costimulatory domains [48]. When incorporating multiple costimulatory domains, the route of costimulation can affect function [21,91].

3.2. Functional safety studies

In addition to screening healthy tissue libraries for B7-H3 expression [21], functional preclinical studies support the safety of pursuing B7-H3-CAR T cell therapy. While several preclinical murine studies evaluating human B7-H3-CAR T cell constructs have not identified any unexpected toxicities [21,39,40], models are potentially limited by a lack of cross-reactivity between human and murine B7-H3. While there is 88% homology between human and murine B7-H3 at the amino acid level, many human B7-H3-directed antibodies do not specifically cross react with murine B7-H3 [22,92,93]. Thus, cross-reactivity must be considered both in functional assessment of on-target off-tumor effects and in screening methods. To overcome this barrier, studies evaluating murine CAR T cells in immune competent models have also been performed, and have not unveiled any additional toxicity concerns [65,92]. Beyond murine studies, the MGA271 monoclonal antibody, from which the scFv in several B7-H3-CAR T cell constructs is derived, has been evaluated in a non-human primate model [41] and B7-H3-CAR T cells have been evaluated in naturally occurring spontaneous canine sarcoma. [53,57]. B7-H3-targeted therapies have demonstrated safety in these non-human primate and canine models.

3.3. Enhancing function

Due to challenges associated with initial attempts to translate CAR T cell therapy for solid tumors, many groups are developing next-generation B7-H3-CAR T cell constructs with additional enhancements (Fig. 2). A variety of gene editing techniques have been explored to enhance CAR T cell function, safety, and persistence across CAR T cell targets [94]. Hairpin RNA strategies have been explored to knockdown a panel of inhibitory molecules including PD-1, TIM-3, TIGIT, TGFβR, IL-10R, and IL-6R to improve antitumor activity of B7-H3-CAR T cells in a cholangiocarcinoma model [95]. B7-H3-CAR T cells engineered to include a PD-1 decoy receptor demonstrated improved persistence in a panel of solid tumor models [96]. An alternative strategy aimed at improving T cell persistence is the inclusion of STAT3- and STAT5-related activation motifs to generate less differentiated B7-H3-CAR T cells, which showed superior activity in breast and ovarian cancer models [97]. In addition, expressing chimeric cytokine receptors to activate STAT-signaling pathways in B7-H3-CAR T cells has improved their effector function in xenograft models [98]. Beyond T cell persistence, CAR T cell design can be enhanced to improve CAR T cell trafficking and direct activity to tumor sites. In brain metastases models, overexpression of CCR2 in B7-H3-CAR T cells improves migration across the blood brain barrier through the CCL2/CCR2 chemokine axis [99]. In an attempt to localize antitumor activity of B7-H3-CAR T cells to tumor sites, a microenvironment regulated system (MRS) was also developed to promote B7-H3-CAR T cell proliferation in the tumor microenvironment in an esophageal carcinoma model [100]. To further enhance targeting specificity for improved safety and expanded applications, B7-H3-targeted CAR T cells have been generated which use alternative intracellular domains such as ZAP-70 in a logic-gated platform, rather than traditional CD3ζ sequences [101]. The incorporation of a PDZ binding motif has also been

shown to improve effector cell functionality by enhancing synapse formation [102]. B7-H3 has also been targeted in osteosarcoma models using a switchable CAR T cell system, which offers potential for broad translational efforts [55].

4. Pediatric B7-H3-CAR T cell clinical trials

Based on the encouraging preclinical data and safety profile, B7-H3 CAR T cells are now being evaluated in early phase clinical studies. Table 1 outlines “active” and “active, not recruiting” clinical B7-H3 CAR T cell studies for pediatric patients.

4.1. Pediatric solid tumor clinical studies

Systemic CAR T cell infusion is being studied for pediatric solid tumors (Table 1). In general, these studies are designed as basket trials, which enroll patients across a range of tumor types. Enrollment criteria vary regarding requirements for confirming B7-H3 antigen positivity and whether there is a focus on specific tumor types. The CAR T cell constructs being translated vary in the method and route of costimulation. They include plans for both single- and multiple-antigen targeting strategies, including the co-expression of CD19-CARs in B7-H3-CAR T cells with the goal of improving their expansion and persistence. In general, these studies evaluate a systemic infusion of B7-H3-CAR T cells after administration of lymphodepleting chemotherapy (i. e. fludarabine and cyclophosphamide) (Fig. 1). These first-in-human studies are ongoing, and current data available in abstract form notes a tolerable safety profile with limited antitumor activity [103].

4.2. Pediatric primary central nervous system (CNS) clinical studies

For primary central nervous system (CNS) tumors, preclinical data favors locoregional CAR T cell administration [65,104,105]. This approach is being translated in active clinical studies, where B7-H3-CAR T cells are injected into the ventricular space or tumor resection cavity [106,107]. In contrast to systemic infusion with preceding lymphodepleting chemotherapy, these local approaches are administered as serial infusions without lymphodepleting chemotherapy (Table 1). Recently, three patients with DIPG were reported who had received intracranial B7-H3-CAR T cells, which were tolerated without dose limiting toxicity at the first dose level and associated with evidence of local immune activation [87]. One participant demonstrated clinical and radiographic response.

4.3. Lessons from adult B7-H3-CAR T cell clinical experience

Parallel studies in adult solid and CNS tumors have the potential to generate important safety and efficacy data regarding B7-H3-CAR T cell therapy [20]. Early evidence includes a report of partial response after intratumoral B7-H3-CAR T cell injection for a single patient with basal cell carcinoma [108]. Transient clinical activity has also been reported in an adult patient with glioblastoma multiforme after local B7-H3-CAR T cell administration [68]. Beyond brain tumors, adult studies are evaluating local administration for other solid tumors, including intraperitoneal delivery for ovarian tumors [40]. While data in adults can provide proof of principle for clinical activity, pediatric patients have unique physiologic considerations and tumor biology. Due to the urgent need to improve treatments for

pediatric patients with relapsed/refractory tumors, it is imperative that novel products be simultaneously studied directly in the pediatric population.

5. Strategies to improve B7-H3-CAR T cell therapy

Beyond antigen selection, there are several hurdles to establishing effective CAR T cell therapy for pediatric patients with solid tumors. These include CAR T cell homing to and penetrating tumor sites, overcoming the hostile tumor microenvironment, and having adequate T cell expansion and persistence [5,12]. As described above, investigators are pursuing enhanced CAR T cell design [94] and exploring locoregional delivery methods [68,87,104] to begin addressing these hurdles. Moving forward, additional strategies seek to evaluate B7-H3 CAR T cells in combination therapies, as part of multi-antigen targeting approaches, and through alternative immune effector cells (Fig. 2).

5.1. Combination therapies for immune and antigen modulation

Given the challenges of effectively targeting solid tumors with CAR T cells, combined immune therapy approaches have the potential to enhance T cell activity and improve penetration to a hostile tumor microenvironment. One approach is the combination of B7-H3-CAR T cells with oncolytic adenovirus (ADV) to deliver immune regulators. In a glioblastoma model, CXCL11-armed oncolytic ADV injected to the tumor site improves infiltration of B7-H3-CAR T cells and decreases proportions of inhibitory immune cells [109]. Also in glioblastoma models, interleukin-7-loaded oncolytic ADV has been co-administered with B7-H3-CAR T cells, demonstrating improved T cell proliferation [110]. B7-H3-CAR T cell therapy can also be enhanced by modulating surface B7-H3 expression in tumor targets. The combination of a pan-histone deacetylase inhibitor (SAHA) has been shown to upregulate B7-H3 expression on solid tumors, in addition to downregulating CTLA-4 and TET2, leading to improved B7-H3 CAR T cells in preclinical models [111]. In a drug library screen, ingenol-3-angelate was also identified to increase B7-H3 expression through PKCα activation, which enhanced B7-H3-CAR T cell function [112]. Screening efforts have also identified small molecules which enhance B7-H3-CAR T cell activity through direct antitumor mechanisms. For example, the hedgehog signaling inhibitor JK184 directly induced tumor apoptosis and had synergistic antitumor effects in combination with B7-H3-CAR T cells [113]. A recent study has highlighted that local treatment of solid tumors in xenograft models simulates robust immunogenic cell death, enhancing B7-H3-CAR T cell expansion, persistence, and antitumor activity [114]. Local radiation by itself has also been shown to increase B7-H3 expression and promote a more favorable immune microenvironment [115,116].

5.2. Multi-antigen targeting

Targeting multiple antigens with CAR T cells has the potential to overcome key resistance mechanisms. Strategies which are dependent on the presence of both antigens for CAR T cell activation (AND gates) can improve specificity, overcome low antigen density, and help discern between tumor and normal tissues [117]. Strategies that allow for activation in the presence of either one or both antigens (OR gates) aim to address antigen heterogeneity and prevent resistance through development of, or selection for, antigen-loss variants. For

neuroblastoma, B7-H3 has been combined with other common antigens. GD2/B7-H3 CAR T cells developed in a SynNotch system sought to improve specificity [118], and ALK/B7-H3-CAR T cells overcame low antigen density [119]. An OR gated strategy targeting GPC2 or B7H3 retained activity despite heterogeneous antigen expression [120]. Beyond neuroblastoma, CAR T cells targeting both CD70 and B7-H3 had activity against a range of solid tumors [121] and GPC3-CARs also secreting B7-H3-specific T cell engagers had activity in hepatocellular carcinoma [122]. In an osteosarcoma model, dual B7-H3- and CXCR2-specific CAR T cells had enhanced antitumor activity [57]. The inclusion of B7-H3 or EpCAM targeting in a ROR1-CAR T cell construct focused antitumor activity to tumor sites, avoiding bone marrow toxicity observed with single-targeting ROR1 CAR T cells [123]. While multi-antigen targeting holds promise to improve CAR T cell activity and limit toxicity, there is significant complexity to the design of these constructs. Comprehensive preclinical and correlative studies will be necessary to establish the best methods of dual targeting, which may vary by antigen and tumor type.

5.3. Alternative immune effector cell sources

Because of the challenges of T cell expansion and persistence in the tumor environment, efforts are underway to identify ideal subsets of T cells for adoptive cellular therapy and explore alternative immune effector cell sources. Both γδ T cells and natural killer (NK) cells are subsets that exist at the intersection between the innate and adaptive arms of the immune system [124]. Benefits of these cell sources include natural tropism for tumor tissues, potential for intrinsic antitumor activity, and lack of alloreactivity supporting potential allogeneic approaches [124]. Engineering these immune cells to express B7-H3-CARs can add an additional layer of specificity. The antitumor effect of Vγ9 Vδ2 T cells was enhanced with the addition of a B7-H3-CAR in glioma models [125]. Similarly, B7-H3-CAR NK cells generated from the NK-92 line have demonstrated activity in melanoma and non-small cell lung cancer models [126,127]. Activity of B7-H3-CAR NK cells evaluated in a glioblastoma model were more resilient in a hostile immune environment through the addition of a TGF-β dominant negative receptor [128]. These examples highlight the potential benefits of exploring alternative immune effector cell sources for engineered cell therapy.

6. Conclusions

Targeting B7-H3 with CAR T cells presents a promising strategy for treating pediatric patients with solid tumors. B7-H3 represents an ideal target antigen due to diffuse tumor expression including a range of pediatric solid tumors and limited healthy tissue expression. Several B7-H3-CAR T cell products have demonstrated preclinical activity. Early phase clinical studies in pediatric patients are underway, evaluating systemic administration for extracranial solid tumors and locoregional administration for primary CNS tumors. Despite encouraging preclinical data, CAR T cell therapy for solid tumors, including for B7-H3, still faces significant barriers including localizing T cells to tumor sites, overcoming the immune suppressive microenvironment, avoiding intrinsic tumor resistance mechanisms, and promoting functional T cell persistence. Thus, producing safe and effective B7-H3-CAR T cell therapy to target pediatric solid tumors will likely require enhanced CAR T cell

design and thoughtful combinatorial approaches. Insights gained from correlative analyses on early phase clinical studies will be key in prioritizing next steps to advance this treatment approach.

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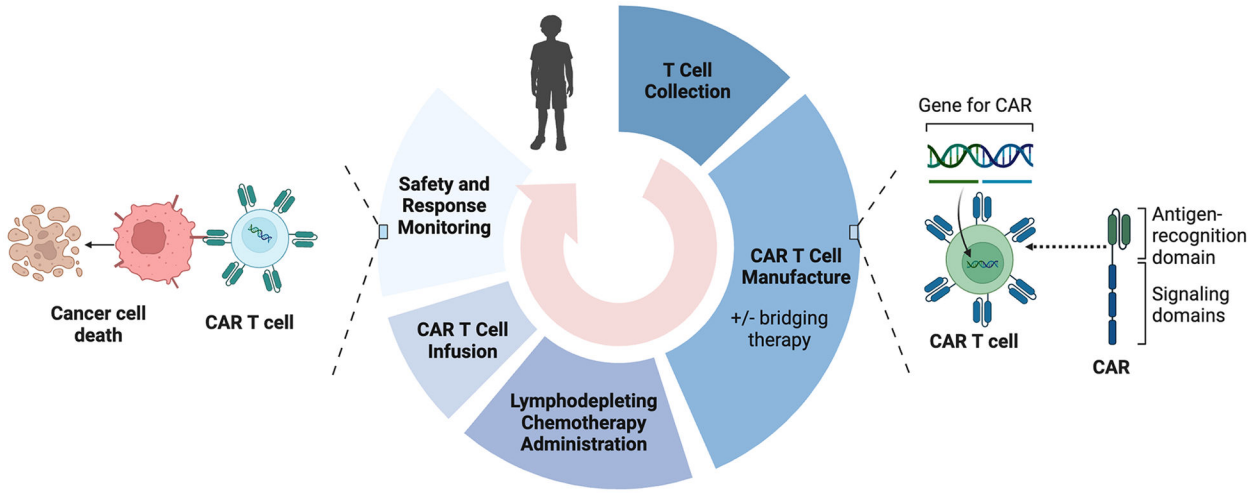

Fig. 1.

CAR T cell therapy strategy for pediatric patients with solid tumors. Inserts highlight CAR T cell generation and CAR T cell tumor cell killing. For additional details see text.

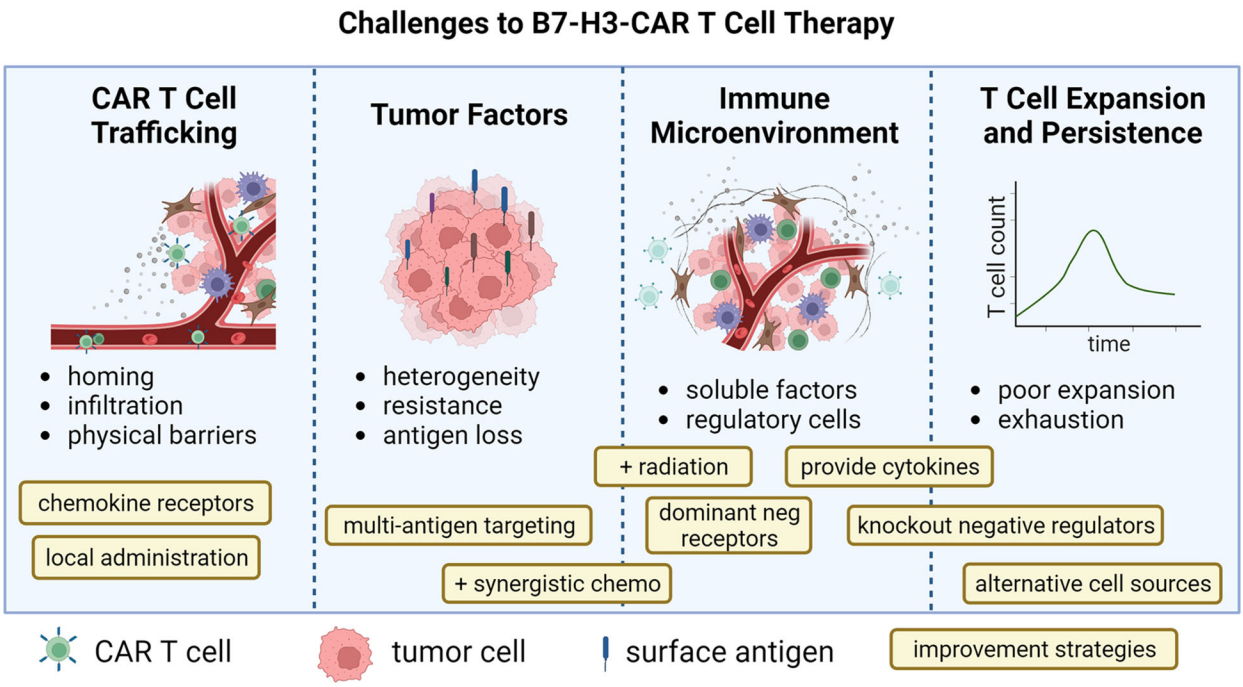

Fig. 2.

Strategies to Enhance B7-H3-CAR T Cell Therapy. Primary challenges facing chimeric antigen receptor (CAR) T cell therapy for solid tumors; Neg: negative; +: combination therapy. For additional details see text.

Table 1

Pediatric B7-H3 CAR T Cell Clinical Trials.

NCT/status	Institution/Sponsor	CAR Design	Indication	Age*	Administration
Extracranial Solid Tumors					
NCT04483778 STRIvE-02 *Active, not recruiting*	Seattle Children's Hospital	*Arm* A: B7-H3.4–1BBζ *Arm B*: B7-H3.4–1BBζ + CD19.4–1BBζ	Recurrent/refractory non-primary CNS solid tumor	≤ 26	Systemic infusion
NCT04897321 3CAR *Recruiting*	St. Jude Children's Research Hospital	B7-H3.CD28ζ+41BBL	Relapsed/refractory B7-H3 positive solid tumor	≤21	Systemic infusion
NCT04433221*Recruiting*	Shenzhen Geno-Immune Medical Institute	multi-antigen specific	Stage III/IV or recurrent sarcomas	1–75	CAR T cells in combination therapy
NCT04637503 4SCAR-T *Recruiting*	Shenzhen Geno-Immune Medical Institute	B7-H3, GD2, and/or PSMA-targeted	Relapsed/refractory neuroblastoma	1–65	Systemic infusion
NCT05562024*Recruiting*	PersonGen BioTherapeutics (Suzhou)	B7-H3 (TAA-06)	B7-H3 positive recurrent/ refractory neuroblastoma	≥1	Systemic infusion
Primary Central Nervous System tumors					
NCT04185038 BrainChild-03 *Recruiting*	Seattle Children's Hospital	B7-H3.4–1BBζ/EGFRt	Recurrent/ refractory CNS tumors, DIPG, or DMG	1–26	-Local administration *Arm A*: tumor resection cavity (supratentorial) *Arms B and C*: ventricular -repeat weekly infusions
NCT05768880 BrainChild-04 *Recruiting*	Seattle Children's Hospital	B7-H3, EGFR806, HER2, and IL13-zetakine	Recurrent/ refractory CNS tumors, DIPG, or DMG	1–26	-Local administration -repeat weekly infusions
NCT05835687 Loc3CAR *Recruiting*	St. Jude Children's Research Hospital	B7-H3.CD28ζ+41BBL	*Arm* A: B7-H3 positive relapsed/ refractory non-brainstem primary CNS tumors *Arm B*: brainstem high-grade neoplasms	≤ 21	-Local administration -repeat weekly infusions

Child (birth-17), and Recruiting OR Active, not recruiting, as of September 25, 2023

*years; DIPG = diffuse intrinsic pontine glioma; DMG = diffuse midline glioma