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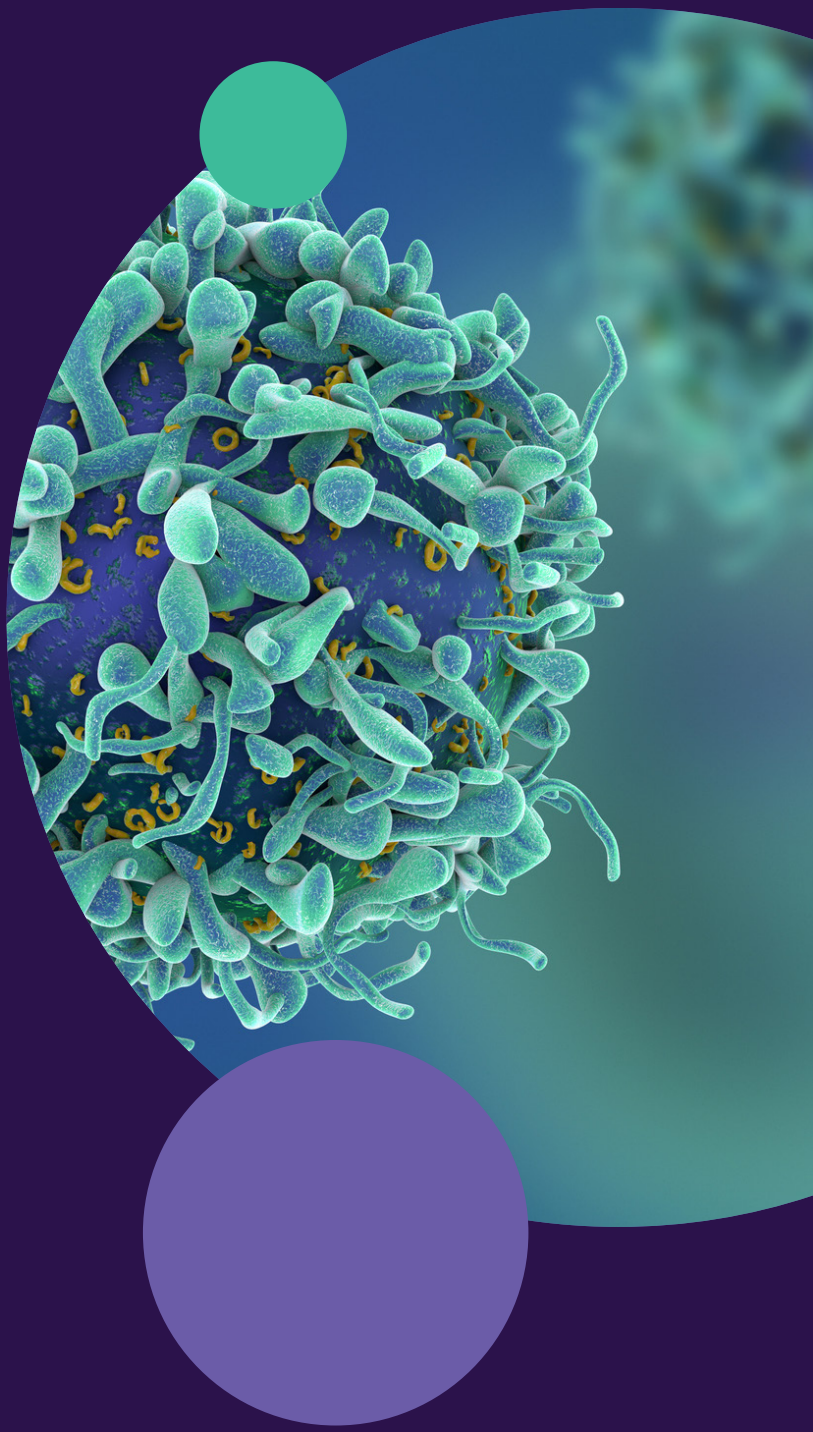


WHITEPAPER

Unlocking the Promise of Cell Therapies for Solid Tumors

Opportunities & Challenges

AUTHORED BY

Joseph Feingold, PhD, Partner, Boston
Head of Cell & Gene Therapy Center of Excellence
Portfolio, Licensing & Development Practice Lead

Jaideep V. Thottassery, PhD, Senior Director, New York

Reena Khurana, MSc MPhil, Senior Director, Delhi

RESEARCH CONTRIBUTORS

Rohit Mutneja, Analyst

Ruchi Ghildiyal, PhD, Project Manager

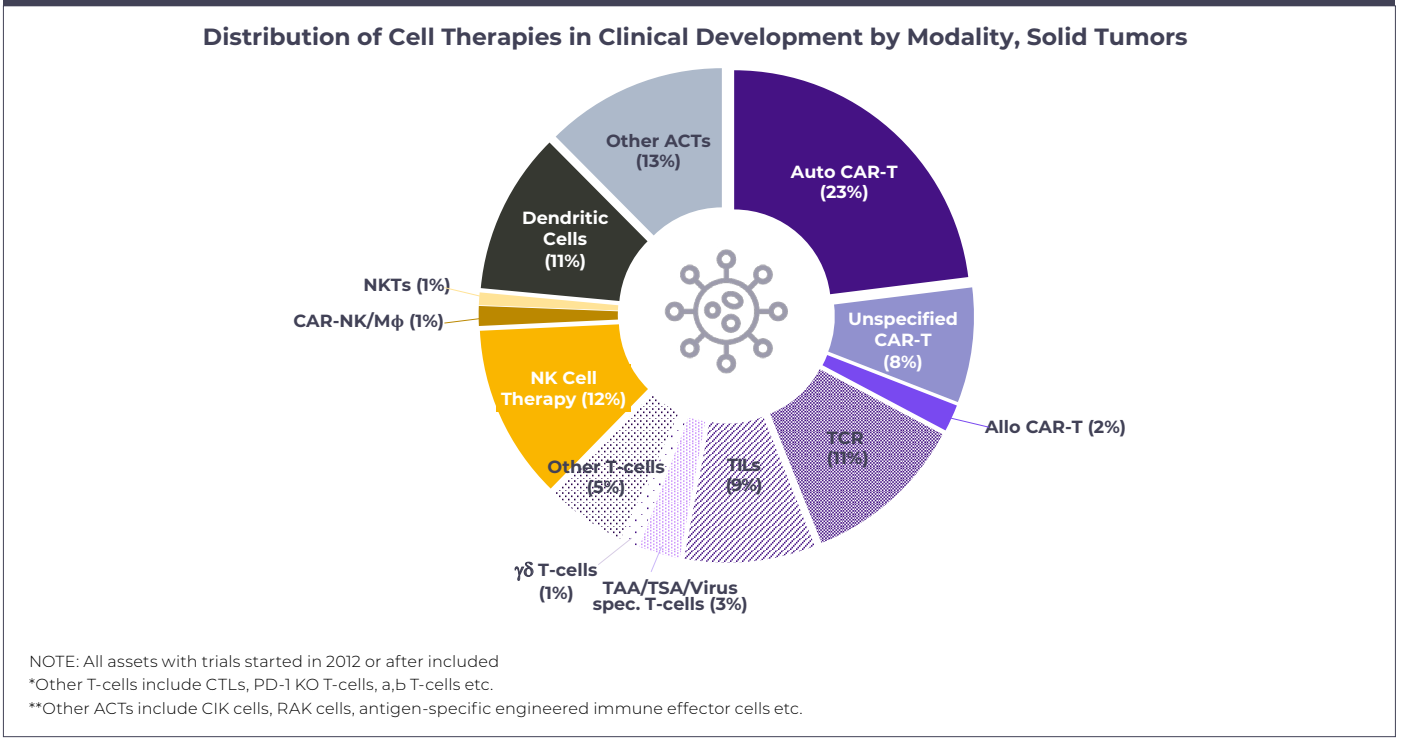
Introduction

The landscape of cell therapies for solid tumors has grown exponentially in recent years with several hundred in development worldwide. However, unlike hematologic malignancies, where several cell therapies have gained FDA approval, very few of the pipeline assets for solid tumors have reached pivotal trials, and those that have are for rare cancers. Proof-of-principle has yet to be established for cell therapies for more common epithelial cancers. Iterative studies are needed to continue to improve the potency and efficacy of cell therapies for such cancers, with the goal of demonstrating durable remissions in larger proportions of patients. This is easier said than done, as solid tumors present unique challenges to cell therapy, ranging from poor trafficking and infiltration and inadequate antigen recognition to lack of functional persistence. In this whitepaper we review the current state of solid tumor cell therapies and assess emerging approaches for expanding the target space with optimal antigens, combating resistance through multi-antigen targeting, and improving antigen recognition and signaling.

Extending the tried-and-true autologous CAR-T paradigm to solid tumors

Tumor-infiltrating lymphocyte (TIL) therapy is on track to becoming the first cell therapy modality for solid tumors with Iovance's lifileucel for melanoma expected to complete its rolling BLA submission in the first quarter of 2023[1]. Despite significant promise demonstrated in several melanoma trials, broad clinical applicability of TILs is unlikely due to lack of robust efficacy across various solid tumor types. The observed inefficacy is likely due to narrow antigen specificity. Unfractionated TIL products are primarily composed of T-cells, with multiple T-cell receptor (TCR) clones against both shared self-antigens as well as neoantigens, which in theory makes them more effective against tumor heterogeneity. However, studies have shown that only a small fraction of the intratumoral TCR repertoire is able to recognize autologous cancer cells[2]. TILs are further hindered by inadequate numbers of tumor reactive T-cells from sparse patient material, and their *ex vivo* expansion which can adversely affect functionality[3]. Given these challenges, TILs are unlikely to become the dominant cell therapy modality for solid tumors. Indeed, while T-cells are the most common effector cell type in the clinical-stage pipeline for solid tumors, accounting for more than 60% of the nearly 800 assets, only 15% of those are TILs (Fig 1).

FIGURE 1. CELL THERAPY MODALITIES IN DEVELOPMENT FOR SOLID TUMORS. A TOTAL OF 791 DIFFERENT CELL THERAPY ASSETS OF WORLDWIDE AS OF NOVEMBER 2022 THAT UTILIZE DIFFERENT EFFECTOR CELLS INCLUDING T-CELLS, NK CELLS, NKT, MΦ (MACROPHAGES), DENDRITIC CELLS AND OTHERS



NOTE: All assets with trials started in 2012 or after included
*Other T-cells include CTLs, PD-1 KO T-cells, a,b T-cells etc.
**Other ACTs include CIK cells, RAK cells, antigen-specific engineered immune effector cells etc.

The most common approach being investigated with T-cells involves redirecting them to tumor-specific targets using chimeric antigen receptors (CARs). CAR-T-cell therapies have demonstrated strong efficacy and even 'cures' in several hematological malignancies where they have become the first adoptive cell therapies to be marketed as approved oncology drugs[4,5]. Developers are now trying to translate these successes to solid tumors. Making up

a majority of T-cell assets being studied in solid tumors, CAR-Ts from autologous or allogeneic sources are likely to emerge as the predominant modality in the near future.

Similar to hematologic malignancies, sourcing T-cells for CAR-T therapies remains an issue for solid tumors, as patient bespoke autologous therapies are the current norm. Challenges with cell availability, viability, and scale-up from patient leukapheresis material have led developers to look toward renewable "off-the-shelf" allogeneic cell sources. The question for allogeneic CAR-Ts is whether they will continue to exhibit limited persistence *in vivo*, and the degree to which that will restrict their efficacy[6]. If they were to show sufficient efficacy and safety, allogeneic sources could offer several advantages, including improved quality control and the possibility of redosing, as well as the targeting of multiple antigens either sequentially or simultaneously[6]. Antigen escape and resistance could be overcome by using allogeneic T-cells to create multiple CAR-T-cell mixtures or universal modular CAR-T-cells that can target multiple tumor antigens[6]. Such off-the-shelf therapies using a 'universal' donor source could also reduce the cost per patient dose by distributing both direct and indirect costs of a single batch over hundreds of doses. To realize this cost benefit, however, large batches would need to be manufactured. Since many solid tumor antigens being targeted require patient selection with smaller eligible patient populations, such a strategy may not provide the usual economies of scale and may not be sustainable in all cases.

CAR-Ts are designed to specifically target known tumor antigens and are therefore customizable (unlike TILs), and likely to show better efficacy. However, for CARs to work, they must target cell surface antigens that are expressed differentially on tumor versus healthy cells. One key roadblock is the paucity of optimal target antigens in solid tumors that could apply to broad populations. In hematologic cancers, lineage-restricted antigens such as CD19 and BCMA are widely expressed on the surface of B-cell tumor cells, and patients can tolerate loss of normal B-cells. No such antigens have been found for solid tumors, and likely do not exist. Even if the antigen problem is solved for CARs, researchers would have to address resistance following antigen loss and heterogeneity as the cancer evolves.

Whereas the target space for CAR-Ts is severely limited because CARs only recognize cell surface antigens, T-cells transduced with high affinity TCRs (TCR-T) target antigens presented as peptide-MHC complexes, vastly extending the antigen space to include intracellular proteins. However, this advantage is outweighed by the need to select patients not only for the targeted antigen, but also for the corresponding antigen-restricting HLA allele. While such TCR-Ts typically can employ TCRs that are restricted to relatively common HLA alleles, such as HLA-A*02:01 (present in a large fraction of the US population), many antigen peptides may not bind to such common HLA types. In addition, the low frequency of neoantigen-specific T-cells plus the natural negative selection of autoreactive T-cells makes the discovery of optimal functional TCRs challenging independent of HLA binding[7]. For these and other reasons, TCR-Ts only account for 11% of the cell therapy assets in development for solid tumors (Fig 1).

The specific antigen-directed action of CAR or TCR modified T-cells is only one source of the antitumor effects of these modalities. The non-specific effects mediated by other immune effectors are increasingly recognized as important contributors to the overall response to cell therapies. This has spurred interest in evaluating other cell types, including natural killer (NK), natural killer T (NKT), gamma-delta (γδ) T, dendritic, and others (Fig 1). The proportion of NK cell therapies under development in solid tumors is second only to that of autologous CAR-Ts. NK cells are short-lived lymphocytes that have the potential to recognize cancer and induce cytotoxicity in an antigen-non-specific manner. Importantly, they can also be leveraged for allogeneic therapies, as they do not carry a risk of graft-versus-host disease (GvHD)[8]. These advantages are offset by NK cells' short half-life and naturally limited persistence, raising the question of whether to focus on extending their half-life or administering repeat infusions to achieve the desired activity.

"The *sine qua non* for successful antitumor activity is the ability to target a unique and critical feature of a tumor."

– CELL THERAPY EXPERT INSIGHT

Recent advances in γδ T-cell research have renewed interest in their potential use as cancer immunotherapy (9). γδ T-cells recognize broad signatures such as enrichment of phosphoantigen (PAg), an isoprenoid metabolite in tumors, and can kill PAg-enriched cells independently of HLA-antigen presentation. Early clinical studies investigating the therapeutic potential of such T-cells have shown acceptable safety, but limited overall efficacy, suggesting further work is needed. Also, it could take a long time to establish GMP for such relatively underexplored therapies and navigate them through the regulatory process. Initial studies with dendritic cells (DCs) have also been disappointing, and ongoing effort is driven by combination approaches which is needed to leverage genomic advances to target neoantigens. Other ACTs such as cytokine-induced killer cells (CIKs) and RetroNectin-activated killer cells (RAK cells)

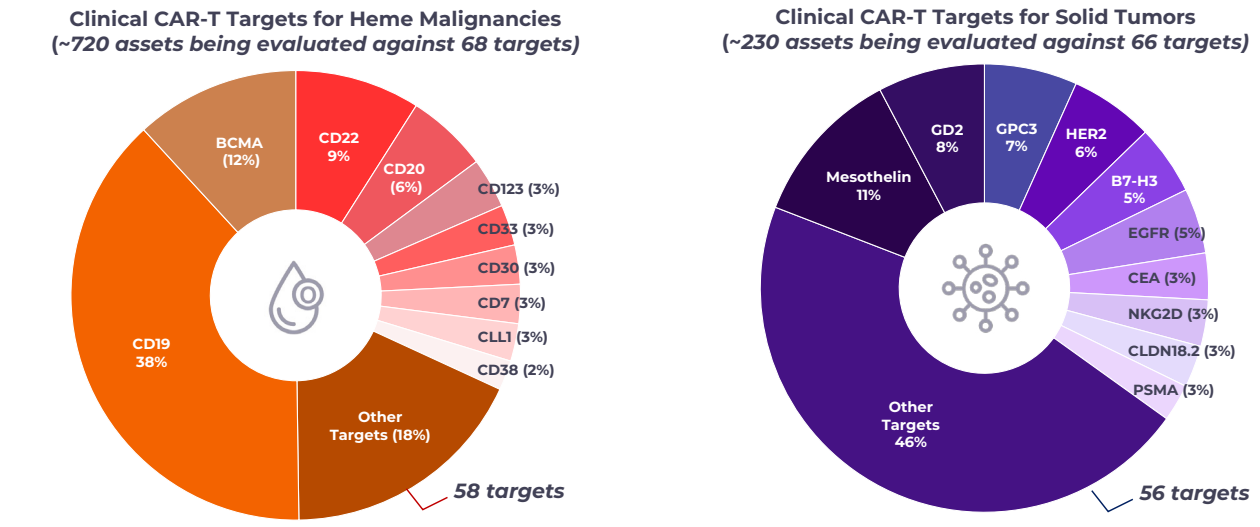
have been under evaluation for long and are yet to be optimized for safety and efficacy; at best these will be used in combination with other therapeutic modalities.

In sum, despite the seeming advantages of other modalities, including non-T-cells, it is likely that autologous CAR-T will remain the dominant approach in clinical development for solid tumors for the foreseeable future. However, unlike hematological cancers, where the CAR-T track record has been promising, solid tumors are unlikely to yield easily without critical modifications to the CAR-T approach. Below we describe the latest results seen with CAR-Ts and engineered TCR-T-cells in solid tumor trials. We then assess approaches for obtaining high confidence antigens, facilitating multi-antigen targeting, and improving antigen recognition and signaling.

Early trials targeting common solid tumor CAR and TCR antigens suggest target selection is a major challenge

Cell therapies targeting solid tumors face multiple and unique challenges related to their trafficking and infiltration into tumor nests, functional persistence *in vivo* over long periods, and an immune-suppressive micro-environment, to name a few. An essential prerequisite for successfully and safely eliminating tumors is the ability to target a feature (i.e., antigen) that is nearly unique to tumor cells. The ideal antigen would be exclusively expressed on the tumor cell surface, and preferably, encoded by a mutated gene. Such tumor-specific antigens (TSAs) would ensure safety when targeted with a specific cell therapy. Instead, most CAR-T targets are tumor-associated antigens (TAAs), which do not completely spare normal tissue and hence 'on-target, off-tumor' toxic effects are observed. For instance, CAR-Ts being developed for hematologic malignancies are predominantly against TAAs, with CD19 and BCMA encompassing 50% of all targets (Fig 2, left panel). The largest chunk of these assets is for B-cell malignancies and targets CD19, a B-cell lineage antigen. Unfortunately, this also causes normal B-cell aplasia, resulting in hypogammaglobulinemia, although this can be overcome in most patients.

FIGURE 2. ANTIGENS TARGETED BY CAR-TS IN HEMATOLOGIC MALIGNANCIES (LEFT) AND SOLID TUMORS (RIGHT).



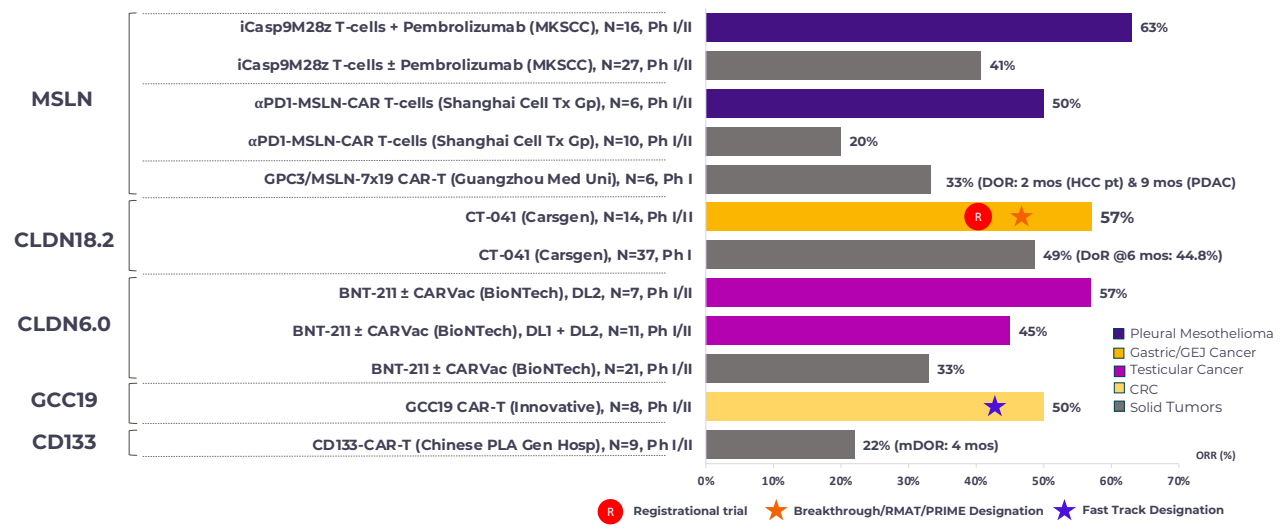
NOTE: All assets with trials started in 2012 or after included

In contrast, there are no broadly applicable lineage antigens for CAR-Ts in solid tumors, as shown in Fig 2 (right panel), which reveals a highly fragmented target landscape, with a diverse range of TAAs being evaluated. Mesothelin (MSLN) is one such TAA that is favored, but accounts for only 11% of pipeline assets. Conversely, 46% of the proteins are categorized as 'other targets', reflecting unspecified singletons or low frequency TAAs. Very few TSAs are targeted by CARs, with the EGFRvIII mutation in glioblastoma being one example.

Assets against currently targeted antigens in solid tumors are also not close to exhibiting the spectacular response rates of CAR-Ts in blood cancers. Indeed, there are only a few solid tumor CAR-T studies where response rates have exceeded 20% in a sample size of five or more patients (Fig 3), and within these, the duration of response (DOR) is far from promising. However, as shown in Fig 3, results from early ongoing trials utilizing some of these CAR antigens do provide reason for cautious optimism. For instance, three MSLN targeting CAR-Ts have early results that demonstrate the potential of such assets[11-13].

In particular, iCasp9 -M28z, a CAR-T against MSLN when combined with pembrolizumab demonstrated an overall response rate (ORR) of 63% in 16 evaluable patients with malignant pleural mesothelioma (MPM), with three investigator-assessed complete responses (CRs) and seven partial responses (PRs), and a 12-month overall survival of 80%[11]. Another enhanced MSLN CAR-T, aPD1-MSLN-CAR-T, that can secrete PD-1 nanobodies evaluated in a proof-of-concept trial in 6 MPM patients showed an ORR of 50%, with all responders being PD-L1 positive; one patient achieved CR and remained in CR for >15 mos[12]. Yet another CAR-T that secretes human IL-7 and CCL19 (7x19) and is targeted against MSLN in pancreatic cancer and ovarian cancer, and against GPC3 in hepatocellular carcinoma, demonstrated a combined ORR of 33% in a proof-of-concept trial that included the three cancer types[13].

FIGURE 3. EXAMPLE DATA OUTCOMES FROM EARLY CAR-T TRIALS IN SOLID TUMORS. SHOWN ARE DATA FROM CAR-TS TARGETING MSLN, CLAUDIN 18.2, CLAUDIN 6, GCC19 AND CD133, AND WITH ≥20% ORR IN ≥6 PATIENTS



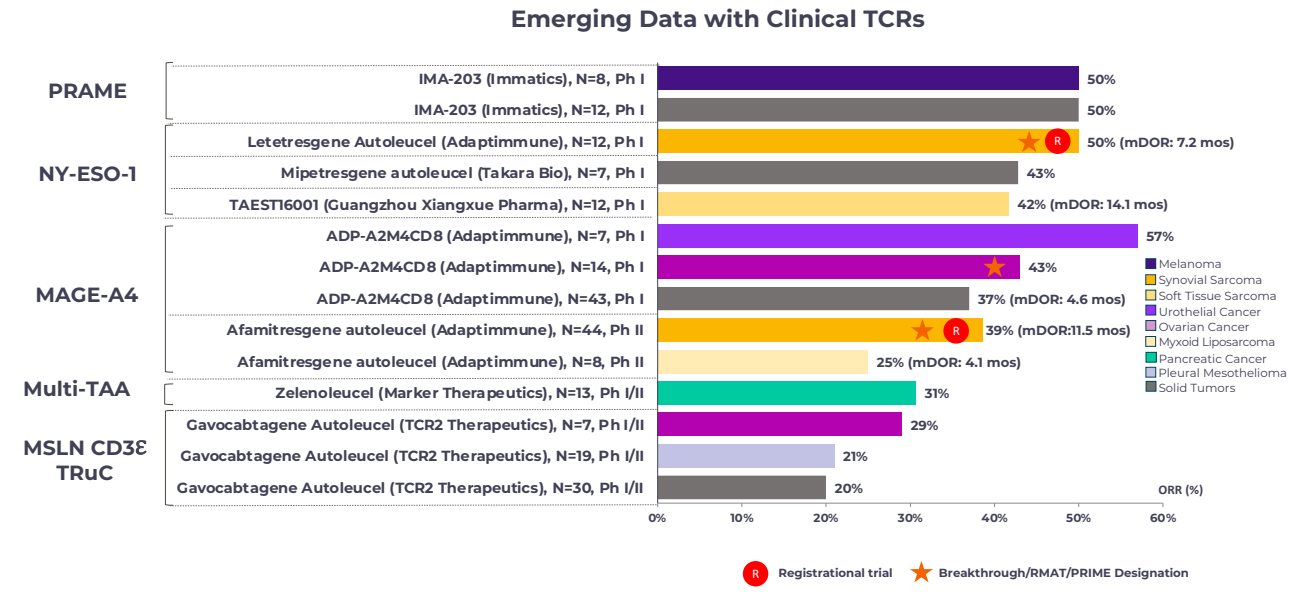
NOTE: Assets listed here have shown ≥20% ORR in ≥6 patients

Results from early phase trials evaluating CAR-Ts against members of the Claudin family CLDN18.2 and CLDN6.0 also provide reason for optimism (Fig 3). CT-041 (Carsgen), a CLDN18.2 CAR-T which is being studied in an open-label, single-arm, Ph 1 clinical trial in patients with previously treated digestive system cancers, showed an ORR of 48.6% (Fig 3), with a 6-month DOR at 44.8%[14]. In patients with gastric/gastric-esophageal junction cancer, the ORR reached 57.1% and the 6-month overall survival rate was 81.2%[14]. BNT211 (BioNTech), a therapy which comprises a synergistic combination of two of BioNTech's proprietary platforms – an autologous CAR-T-cell therapy targeting CLDN 6.0 and a CLDN 6.0-encoding CAR-T-cell amplifying RNA vaccine (CARVac) – showed an ORR of 33% in 21 evaluable patients, with one CR and six PRs (Fig 3)[15]. In a subset of 7 patients with testicular cancer, BNT211 demonstrated one CR and three partial responses (PRs), representing an ORR of 57%. Another CAR-T showing early promise is GCC19, which employs a coupled targeting strategy. This involves amplifying the proliferation of CAR-T-cells by targeting CD19 along with another tumor antigen, guanylate cyclase C (GCC). GCC is expressed in the metastatic lesions of 70-80% of patients with colorectal cancer. In an ongoing Ph I/II trial with a GCC19 CAR-T (Innovative) in China, the ORR was 50% (4/8) at the higher of the two doses tested, with all PRs; a Ph I trial is planned in the US.

One approach to targeting solid tumors is to utilize the ability of TCRs to recognize HLA-presented antigens derived from proteins that are not necessarily expressed on the cell surface. These TSAs include highly tumor-specific neoantigens, cancer germline antigens (CGAs), and viral antigens. Several TCR-T assets targeting CGAs, such as PRAME, NY-ESO-1, MAGE-A3 and MAGE-A4, have demonstrated therapeutic outcomes comparable to those achieved in CAR-T trials (Fig 4). These results highlight the fact that encouraging responses can be demonstrated even in cold tumors like sarcoma, if the target antigen is abundant, as is the case with NY-ESO1, MAGE-A4, and PRAME[16-18]. Much like for CAR-Ts, however, these results leave ample room for improvement. In particular, several studies have reported that CGAs are heterogeneously expressed within tumors, which could explain the limited therapeutic efficacy when targeting a single CGA. Recent high-profile announcements by GSK of discontinuation of the development of its partnered NY-ESO-1 TCR-T assets provide a lesson in the inadequacy of single antigen

targeting. Taken collectively, both the safety and efficacy characteristics of CAR-T and TCR-T assets directed against currently pursued targets reveal that more robust and selective antigens need to be identified and optimized.

FIGURE 4. EXAMPLE DATA OUTCOMES FROM EARLY TCR-T TRIALS IN SOLID TUMORS. SHOWN ARE DATA FROM ENGINEERED TCR-T CELLS TARGETING PRAME, NY-ESO-1, MAGE-A3 AND MAGE-A4, AND WITH ≥20% ORR IN ≥6 PATIENTS



NOTE: Assets listed here have shown ≥20% ORR in ≥6 patients

Expanding target space by identifying and selecting optimal antigens for cell therapies

Recent advances in both large-scale and high-throughput genomics and systems biology have facilitated the comprehensive identification, annotation, and prioritization of the cancer "surfaceome", which can provide reasonably cancer-specific membrane-localized antigens[19]. This analysis showed that of 3031 cell surface proteins that were found to be expressed in normal and tumor specimens from 33 different cancer types in The Cancer Genome Atlas (TCGA), 409 unique proteins were cancer-specific, using an expression specificity algorithm that compares their levels in each cancer to that in all normal tissues[19]. Several of these proteins are in current clinical development targeted by CAR-Ts. Such rich datasets, when combined with computational analysis of proteomics and genomics data from patient tumor tissue, will help identify many more optimized antigens, many of which could possibly be combined into two-antigen or three-antigen circuits or gates for more precise targeting.

"We have to solve the antigen problem first, or at least make a lot of headway, before we can start to understand the rest of the challenges of cell therapies."

– CELL THERAPY EXPERT INSIGHT

Proteins are not the only antigens that can be targeted with CARs. For instance, embryonal cancers can aberrantly express membrane-anchored gangliosides which are glycosphingolipids linked to sialic acids residues. The best-known example of such a molecule being targeted by CAR-Ts is the ganglioside GD2, which is expressed on the cell surface of neuroblastomas[20]. GD2-redirected CAR-T-cells have shown activity in clinical phase I/II trials in neuroblastoma and a Ph I for H3K27M-mutant glioma is ongoing[21]. Other carbohydrate targets for CAR-T-cells in preclinical development are O-acetyl-GD2, NeuGc-GM3 (N-glycolyl GM3), GD3, SSEA-4, and oncofetal glycosylation variants[22]. It makes sense to choose antigen targets that are not only expressed on the cell surface, but also play a distinct role in tumor signaling. Such targets are not likely to be easily shed or replaced by the tumor. Poseida, Minerva, and PGEN Therapeutics are developing CAR-Ts that target the unshed and tumor-specific forms of MUC1 and MUC16[23,24]

Using TCR-Ts could significantly expand the antigen space, and they are considerably more sensitive to low concentrations of target antigen compared to CARs, particularly in the case of affinity enhanced TCRs. In addition, unlike CAR-Ts, TCR-Ts do not drive ligand-independent tonic signaling, potentially making them better at maintaining

function *in vivo*. The source of most TCR antigens is the inherent genomic instability of tumors, which results in the accumulation of many tumor-specific mutations. Some of these mutations give rise to new proteins (neoantigens), which are expressed exclusively by cancer cells and would therefore be less risky in terms of on-target off-tumor toxicity. Unfortunately, most cancer mutations are so-called "bystander" mutations that do not drive progression. Such random, non-selected mutations typically reflect intratumor heterogeneity and thus may not be effective antigen targets for TCR-T therapies. Conversely, a small fraction of cancer mutations known as driver mutations directly promote cancer progression, and if immunogenic and restricted to a common HLA, these could be antigens against which new TCR-T therapies could be designed.

Multi-antigen targeting can combat antigen loss or heterogeneity, overcoming primary resistance and maintaining durable remissions

Even as the target space grows with further identification of optimized antigens with tumor-selective expression, single-antigen targeting strategies are likely to be inadequate for solid tumors. As has been shown in hematologic malignancies, despite impressive response rates with anti-CD19 or BCMA CAR-Ts, most responses are not durable, and antigen loss or down-modulation have been found in biopsies from relapses[25-27]. In addition to treatment-dependent antigen loss, inherent antigen heterogeneity within a tumor often causes primary resistance. This is further complicated by the fact that different metastatic lesions within a given patient may concurrently express different amounts of target antigens, and antigen expression can change as the tumors evolve. Therefore, characterizing the tumor based on primary early-stage cancers may not paint a full picture of antigen expression at late stages. Further biopsies may be required, but even they will not likely be representative of the entire tumor burden.

In the face of these challenges, developers are considering multi-antigen targeting for cell therapies, with the hope of exceeding the clinical promise of such strategies seen with bispecific and trispecific antibodies. Examples of these multi-targeting strategies include universal CARs (uCARs), bicistronic CARs, split, universal and programmable (SUPRA) CARs, tandem CARs, and logic-gated CARs, among others[28-33]. In uCARs, the targeting domain is disconnected from the CAR module with *in vivo* re-association taking place via different types of binding, using switch molecules. In uCARs based on the biotin-binding immune receptor (BBIR), for example, the CAR encodes an avidin motif, which can associate with high affinity with biotinylated targeting molecules[28]. In FcR-based CARs, an FcγRIII ectodomain can associate with the Fc-portion of IgG-type mAbs, resulting in an engineered form of antibody-dependent cellular cytotoxicity (ADCC)[29]. Other systems utilize classical CARs with an scFv that has specificity for an FITC-tag or a peptide tag on the targeting molecules[30]. SUPRA CARs have an extracellular leucine zipper that zips in with a complementary zipper on targeting molecules[31]. In convertible CARs (cCARs) the CAR incorporates the ectodomain of the NKG2D receptor that can associate with a ligand-derivative, which is conjugated to different TAA-targeting antibodies[32]. Another system from Prescient Therapeutics called SpyTag/SpyCatcher CARs relies on the formation of a covalent bond between the CAR and the adaptor molecule, via a chemical reaction[33]. These various approaches are interesting upgrades to the original CAR-T format, and while it's too early to pick a winner, their differentiation will be driven by their pharmacokinetic and pharmacodynamic properties.

Other multi-targeting strategies involve development of new molecular circuits in cells that can utilize Boolean logic for AND-, OR-, and NOT-gate possibilities[34]. OR-gate CARs are designed to reduce the risk of antigen escape and to tackle heterogeneous tumors, as they only require one targeted antigen to be expressed. AND-gate CARs are meant to provide increased specificity and safety, as they are active only against tumors expressing two or more targeted TAAs and spare healthy cells with a single TAA expression pattern. NOT-gate approaches are also intended to enhance safety, though they utilize a different approach wherein therapeutic cells express an activator CAR/TCR specific to a conventional TAA that is also present in normal tissue. However, the NOT-gate in the module blocks its activity in normal cells based on the presence of an inhibitory CAR/TCR (iCAR/iTCR) directed against HLA molecules that are frequently lost by many tumors. Other modules employ signaling elements derived from LIR-1 (Tmod) and PD-1 (NASCAR) inhibitory receptors[35]. One example of a NOT-gate strategy is the harnessing of loss of heterozygosity (LOH), arising out of large chromosomal deletions in cancer cells, which provides a means to distinguish tumor from normal tissue in a definitive manner[36]. In sum, multi-antigen targeting offers hope for overcoming

"Logic-gating is an interesting area…I like synNotch, and NOT-gate is a close second…these are some of the earliest and most well-studied, and in principle, fairly persuasive."

– CELL THERAPY EXPERT INSIGHT

tumor heterogeneity and building more precise, and hence safer, cell therapies, by using molecular circuits or gates to appropriately discriminate tumor cells from other cells. While still in the future, we believe these approaches, once optimized, will provide the breakthroughs for cell therapies to succeed in solid tumors, and hence need to be monitored closely.

Design considerations for improving antigen recognition and signaling function of CARs and TCRs

The discussion so far has focused on antigens, their ideal characteristics and expression and exploiting their heterogenous expression in tumors using combinatorial multi-targeting. However, this implies that the antigen recognition domain on the CAR needs to be optimized for triggering the signaling cascade[37]. The interactions between antigens and their CARs or TCRs need to be optimized not only vis-à-vis their affinity (which refers to the binding strength of individual interactions), but also their avidity (which is a function of receptor density and totality of interactions with antigen). For instance, studies have demonstrated that CARs have affinity ceilings, which, when exceeded, result in antigen-independent signaling[38]. Affinity tuning of the CAR scFv can therefore allow T-cells to dial affinity to levels sufficient to respond to antigens that are overexpressed on tumor cells, but not be triggered by lower levels on normal cells. For CARs targeting either CD[38] or EGFR it was found that scFvs with ~1000-fold reduced affinity conferred effective lysis of tumor cells, while sparing antigen-positive normal cells[39,40]. Another example is AffyImmune's ICAM-1-specific AIC100 CAR-T, derived by affinity tuning the I-domain of LFA-1 (ICAM-1 ligand), which is in Ph I trial against advanced thyroid cancer and has shown regression of tumor lesions at multiple sites[41]. Affinity tuning could however have the potential disadvantage of outgrowth of low-antigen-expressing tumor cells, leading to resistance.

The binding avidity of TCRs and CARs is determined by their expression levels and is thought to affect the persistence of engineered T-cells at the targeted tumor site[42]. High CAR density in CAR-Ts can result in clustering of molecules at the cell surface. This can cause antigen-independent tonic signaling, which can lead to activation-induced cell death (AICD). On the other hand, low levels of CAR expression can lead to impaired effector function. Therefore, fine tuning the avidity of CARs is needed to keep it below the threshold for exhaustion and death from tonic signaling, while maintaining high enough levels for robust antitumor efficacy. One example of tuning avidity is by directing expression of CARs to the T-cell receptor α constant (TRAC) locus, versus retroviral expression, which enhances T-cell potency[42]. As in the case of CARs, TCR avidity, which usually correlates with its affinity, also refers to the combined effect of multiple TCR-pMHC interactions, co-receptors (CD8), TCR density, and T-cell functional status[43]

Conclusion

Cell therapies have been very successful in hematological malignancies largely due to the fortuitous discovery of optimal antigens like CD19 and BCMA, which led to the validation of the design of CARs, including signaling and costimulatory domains. Understandably, developers are seeking to replicate these successes for solid tumors, though progress has been limited to date. Many different types of effector cells are being investigated for solid tumors, but autologous CAR-T is most likely to dominate in the near-term, given the experience, technical knowledge, and success achieved in hematologic cancers.

To be successful in solid tumors, research will have to focus not only on the discovery of optimized antigens, but also on the ability of engineered T-cells to interact with them. This will require tuning their affinity and avidity, as well as developing molecular circuits for combinatorial recognition of multiple antigens to optimize T-cell activation. CAR-based cell therapies can also harness the potential of other effector cells such as NK cells or γδ T-cells, which could be used for allogeneic therapies.

In conclusion, modified CAR-T approaches for solid tumors will likely be the primary focus for the foreseeable future. We encourage developers to prioritize identifying multi-antigen combinations to be targeted with universal CAR strategies or logic gating, by leveraging large-scale datasets plus newer bioinformatics tools. These advances will carry unknown risks with unnatural sequences, spacers, switching modules, and epitopes. How these will affect clinical trials, manufacturing, and regulatory strategies will need to be considered. Nevertheless, given the volume of patients affected by solid tumors and high level of unmet need, the impact of unlocking the promise of cell therapies for solid tumors would be substantial.

Author Bios

Joseph Feingold, PhD, Partner, Boston
Head of Cell & Gene Therapy Center of Excellence
Portfolio, Licensing & Development Practice Lead

A neuroscientist turned biotech strategy expert with deep experience navigating complex challenges in global markets, Joseph combines scientific and entrepreneurial skillsets to perform rigorous commercial analysis and deliver critical insights to biopharma, diagnostics, and medical device leaders. Joseph supports several large, established manufacturers, as well as many smaller biotechs and venture-backed startups, developing strategies for pipeline products and portfolios to guide BD, development, and commercialization. Joseph's clients span a wide range of therapeutic areas and modalities, with particular focus on hematology / oncology, neurology, and novel technologies, primarily cell and gene therapies and advanced protein / antibody approaches, requiring sophisticated hospital-based administration and new delivery, access, and reimbursement models.

Jaideep V. Thottassery, PhD, Senior Director, New York

As a strategic thinker with business instincts Dr. Thottassery has been a seasoned 'thought partner' to our clients to help advance impactful and innovative therapies. At Putnam Dr. Thottassery leads a team of data scientists and research managers guiding projects across multiple areas including commercial development, R&D, BD&L due diligence, forecasting, regulatory and IP, with a specific focus on disease area prioritization and scientific differentiation of assets in oncology and rare diseases. Jaideep was a Senior Scientist in the Drug Discovery Division at Southern Research Institute (SRI), Birmingham, AL for 17 years. At SRI, Dr. Thottassery's research interests dealt with exploring novel targets and drug discovery in several therapeutic areas including cancer, neuroscience and infectious diseases. Jaideep has a Ph.D. in Biochemistry from the University of Missouri-Kansas City and has performed postdoctoral research at the University of Tennessee Health Sciences Center, and at St. Jude Children's Research Hospital in Memphis, TN. Jaideep has authored numerous peer-reviewed articles and reviews across the areas of basic, clinical, and translational research.

Reena Khurana, MSc MPhil, Senior Director, Delhi

With over 20 years of experience in strategic consulting spanning complex business and scientific solutions, Reena has led 100+ projects for leading global pharma companies and biotechs in oncology, covering the breadth of solid tumors and hematological malignancies. Her main focus has been in mapping strategic solutions through scientific assessment of emerging technologies, targets and modalities, opportunity prioritization driven by disease area and asset strategy, due diligence for licensing/ acquisition propositions, developing and testing target product profiles, while closely tracking market innovation. She has also co-led portfolio optimization projects for both big pharma and biotechs. With an MS in Bioinformatics & Biotechnology and an M.Phil in Toxicology, she has core domain knowledge in oncology.

Contact us for more information.

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