HHS Public Access

Author manuscript

Crit Rev Immunol. Author manuscript; available in PMC 2024 July 17.

Published in final edited form as:

Crit Rev Immunol. 2019 ; 39(2): 105–122. doi:10.1615/CritRevImmunol.2019030788.

T Cell Receptors for Gene Transfer in Adoptive T Cell Therapy

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Abstract

The past decade has seen enormous progress in cancer immunotherapy. Checkpoint inhibitors are a class of immunotherapy that act to recruit endogenous T cells of a patient's immune system against cancer-associated peptide-MHC antigens. In this process, mutated antigenic peptides referred to as neoantigens often serve as the target on cancer cells that are recognized by the T cell receptor (TCR) on endogenous T cells. Another successful immunotherapy has involved adoptive T cell therapy, where therapeutic doses of T cells expressing a gene for an anti-cancer receptor are delivered to a patient. This approach has been used primarily against hematopoietic cancers using synthetic receptors called chimeric antigen receptors (CARs). CARs typically contain an antibody fragment (single-chain Fv, scFv) against a cancer cell surface antigen such as the B cell molecule CD19. While therapeutic CARs (and full antibodies) target antigens expressed on cell surfaces, TCRs can target a much larger array of intracellular proteins by binding to any cellular peptide associated with an MHC product. These cancer targets include self-peptides from aberrantly expressed/overexpressed proteins or neoantigens. In this review, we discuss the use of TCRs in adoptive T cell therapy and their target antigens. We focus on two properties that impact sensitivity, potency, and possible toxic cross-reactivity of TCR-mediated therapy: (1) the affinity of the TCR for the target antigen, and (2) the density of the target antigen. Finally, we provide a comprehensive listing of the current clinical trials that involve TCRs in adoptive T cell cancer therapy.

Keywords

T cell receptor; cancer; adoptive T cell therapy; clinical trials

I. INTRODUCTION

Cancer immunotherapy offers the potential for greater efficacy with fewer side effects than conventional chemotherapies. The hallmark of immunotherapies, in line with the era of precision medicine, is the targeting of cancer-associated antigens that are not expressed on normal cells. In some forms, ongoing immunotherapeutic approaches are extensions of therapies with monoclonal antibodies in which a cancer-associated cell surface antigen is targeted with an antibody (typically an IgG), leading to either direct effects on the cancer cell or recruitment of immune cells through Fc-mediated effects. For example, use of antibody fragments (single-chain Fv, scFv) as components of synthetic chimeric antigen

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receptors (CARs) are used to directly mediate T cell activity against cancer cells.[1–3] This treatment requires personalized treatment: *ex vivo* expansion of peripheral blood T cells, followed by gene transfer of the CAR, and reinfusion of the T cell product; this process is termed adoptive T cell therapy (ACT) (Fig. 1).

The class of immunotherapies known as checkpoint inhibitors operate quite distinctly by enhancing the activity of a patient's own T cells against potentially many different antigens (often mutated peptides, called neoantigens), presented as complexes of a cancer peptide bound to a major histocompatibility complex (MHC) product, or pepMHC.[4] While checkpoint inhibitors offer great promise in some cancer types, they have been less successful in cancers with fewer mutations and in cases where the tumor microenvironment is immunosuppressive (i.e., noninflamed, or "cold").[5] *Ex vivo* expansion of tumor-infiltrating lymphocytes (TILs) provide yet another alternative immunotherapy that attempts to harness the power of therapeutic doses of T cells and the potential for targeting multiple cancer antigens as pepMHC products.[6,7] However, TILs are difficult to isolate from most patients, and their expansion can be time consuming.

Combining the potency of T cells with the vast array of possible cancer antigens as pepMHC complexes is a form of adoptive T cell therapy in which T cells are endowed with cancer-antigen specific T cell receptors (TCRs) (Fig. 1). In this review, we focus on ACT with such TCR-transduced T cells. By way of background, T cells express an αβ-TCR that recognizes peptides only when they are bound to a product of the MHC complex.[8] The recognition of self-peptide/MHC antigens by T cells plays an important role during thymic development. TCRs mediate negative selection (deletion of the T cell) when they bind to a self-peptide/MHC with too high an affinity. This process is termed central tolerance and it is key to avoiding autoimmune reactivities.[9] However, TCRs also must bind to self-peptide/MHC with some minimal affinity in order to drive positive selection, whereby T cells and the TCR are required to recognize peptides only when they are bound ("restricted") by the MHC. This intricate process positions TCRs to drive T cell activity when a foreign peptide, as an MHC complex, binds with even a small increase in binding affinity. However, this narrow affinity window underlies the critical nature of identifying TCRs that are optimally active against a cancer antigen but not cross-reactive with self-peptides.

Nevertheless, because TCRs can recognize potentially any peptide antigen bound to MHC, they can target virtually any peptide arising from protein degradation inside the cancer cell. These antigens include peptides arising from viral proteins, mutated proteins, or aberrantly expressed self-proteins that are associated with cancer. Over 400 cancer-associated peptide antigens have been described in the cancer antigenic peptide database.[10] Hence, TCR-mediated adoptive T cell therapy remains an attractive area but so far has not had significant success compared to its counterpart, CAR-mediated therapy. However, given their exquisite potency, a number of pharmaceutical companies and academic labs have TCR campaigns to determine the appropriate parameters for effective use of TCRs in therapeutic settings.

Although many cancer-associated antigens have been identified over the past several decades, selection of an antigen that is truly cancer-specific and that is not expressed

on normal tissue remains a challenge in the field of TCR-mediated ACT.[11,12] Although there is excitement in targeting cancer neoantigens as pepMHC because of their cancer specificity, these antigens typically differ from patient to patient, requiring personalized treatment strategies.[6,13] On the other hand, cancer-associated self-antigens that are either aberrantly expressed or highly overexpressed in cancerous (compared to normal) tissue offer an advantage, as these are shared among patient populations. These include differentiation antigens (e.g., melanoma antigens: MART-1, gp100, tyrosinase), overexpressed antigens [e.g., Wilms' tumor antigen (WT1)], and cancer testis antigens (e.g., NY-ESO-1, the MAGE family of antigens) that can be overexpressed in cancer, but are expressed normally in restricted and sometimes dispensable tissues. Antigens from these categories have been studied in TCR ACT clinical trials over the past 15 years (Table 1), and modest responses have been obtained with low-affinity TCRs (high micromolar affinities) used to target shared or overexpressed antigens. On the other hand, targeting antigens like NY-ESO-1 with an engineered, higher-affinity TCR (affinity in the low micromolar to high nanomolar range) appears to show more promise. However, targeting overexpressed antigens with higher-affinity TCRs has been challenging because of recognition of lower-density antigens on normal tissue or because of recognition of structure-related antigen(s). Overall, studies with TCRs have shown significant potential in cancer immunotherapy, but they have also taught important lessons about harnessing their power in an "optimal therapeutic window." Here, we discuss the potential targets for TCRs in ACT and two parameters that must be considered in identifying this optimal window for ACT with TCRs: the density of the pepMHC antigen complex on cancer cells and the affinity of the TCR for the pepMHC antigen. We end with a review of ACT clinical trials to date that involve TCR transfer.

II. CANCER-ASSOCIATED ANTIGENS AS TARGETS FOR TCR-MEDIATED ADOPTIVE T CELL THERAPY

Just over ten years ago, the National Cancer Institute (NCI) sponsored a workshop of experts who generated a prioritization list of 75 cancer-associated peptides that could potentially serve as targets for vaccines or T cell therapies.[14] That report described the properties of peptides that could be considered in their "targetability" as complexes with MHC products. Here, rather than focusing on specific peptides, we discuss the advantages and disadvantages of targeting such self-antigens in comparison with targeting neoantigens, a rapidly emerging class of interest with significant potential. A recent study discussed some aspects of this topic.[15] From a mechanistic standpoint, self-peptides and neoantigenic peptides share some features. Peptides from upregulated proteins are expressed at higher levels as a pepMHC complex than at the normal levels that operate during tolerance induction. Similarly, a mutation in a neoantigen that increases the binding of the peptide to MHC is also present at higher levels than the normal (wild-type) pepMHC. So long as the mutation does not also alter the structure of the peptide "seen" by the TCR, this scenario yields the same outcome for the upregulated pepMHC and the mutated pepMHC: a higher level of specific pepMHC on the tumor than on normal cells. Accordingly, what really matters from a quantitative perspective in this comparison is the extent of upregulation (e.g., 10-fold), or the increase in affinity of the neoantigenic peptide for the MHC. Because some mutations can yield a 100-fold or greater increase in MHC binding (e.g., determined as stability or affinity),[16] it

can be difficult to achieve a comparable increase in upregulation of protein levels. Despite this argument, upregulated proteins have the distinct advantage that they are often shared among cancers of many different patients, whereas individual neoantigens are typically unique and thus require personalized TCR identification for each patient. However, there are recent examples of several shared neoantigens which may provide opportunities.[17–20] In addition, it could be argued that with new and more rapid TCR discovery platforms, it will ultimately be possible to deploy neoantigen-specific TCRs on a personalized basis.[13,21–24]

Another scenario for neoantigens is mutations that could impact binding to the TCR, either because they are in exposed residues or they alter the conformation of the peptide or MHC in regions that contact the TCR.[25] Here, the neoantigen peptide might be viewed as an advantage over self-peptides as there could be neoantigen-reactive T cells that have not undergone tolerance against the wild-type peptide. However, it is also possible that T cells against self-peptide/MHC expressed at higher levels, as on cancer cells, have not been deleted through negative selection.[26–28] At issue in all of these scenarios is identifying TCRs that mediate activity with the level of the pepMHC on the cancer cell but not with the level of the self-peptide MHC on normal cells.

The window that exists to achieve therapeutic effects without side effects due to reaction with normal tissue is key to the success of a TCR. This window must consider the density of the cancer pepMHC complex on the cancer cell versus normal cells, and it must consider the affinity of the TCR and the thresholds for mediating CD4 and CD8 activity.

III. DENSITY OF ANTIGENIC pepMHC COMPLEXES

The density of antigenic pepMHC complexes refers to the number of antigenic pepMHC complexes expressed on a target cell surface. Immune responses to a pepMHC cancer antigen depends on the surface density of the antigen,[29] and a minimum threshold is required for T cell activation. As described below, the coreceptors CD4 and CD8 act to synergize with the TCR, lowering the number of required pepMHC complexes to one or just a few.[30–33] The affinity of the TCR also impacts this density threshold.[34] Accordingly, pepMHC complexes from upregulated self-antigens could activate T cells if their overexpression exceeded the threshold at which TCRs are “tolerized” during selection in the thymus. As described above, neoantigens with mutations that yield enhanced binding to MHC could activate T cells because the density of the pepMHC may greatly exceed this threshold.

The density of a specific pepMHC complex is dependent on various factors, including the level of the intracellular protein, the efficiency with which the peptide is processed from the protein, and the binding affinity of the peptide for the MHC product.[35] The antigen-processing and presentation pathway has several steps, and hence each participant of the pathway can potentially impact peptide loading and hence pepMHC density on the cell surface. It is hence not surprising that cancer cells can hijack the cellular machinery to downregulate pepMHC expression to “hide” from naturally existing low-affinity T cells.[36,37] For example, genes encoding the MHC heavy-chain or beta-2 microglobulin can be downregulated. Similarly, proteins involved in generation of peptides (i.e., components

of the immunoproteasome), peptide loading, and folding and transport of MHC molecules (e.g., TAP, calnexin, calreticulin, tapasin) can be downregulated by cancer cells to directly impact pepMHC density. In such scenarios, T cells transduced with affinity-enhanced TCRs can enable recognition of the low-density cancer antigen but often require an optimal affinity window to ensure a cancer-specific response without reactivity to self-antigens (explained below).

In addition to the antigen presentation pathway, the intrinsic ability of a peptide to bind to the peptide-binding groove of the MHC also directly impacts the number of pepMHC complexes exported to the cell surface. Therefore, peptides with optimal anchor residues are expected to be present at higher densities as pepMHC complexes compared to those with suboptimal anchors.[38] Accordingly, neoantigens that arise because of mutations in anchor residues leading to improved MHC binding are expressed at higher levels, similar to aberrantly upregulated cancer-associated self-antigens.[39] On the other hand, mutations that destabilize peptide–MHC interaction limit stable expression of such pepMHC complexes on the cell surface and result in reduced T cell responses.[40] In a neoantigen trial for melanoma, peptides were prioritized for vaccination based on mutations that resulted in anchor-residue changes (among other criteria that resulted in class I MHC binding epitopes), indicating the importance of pepMHC stability and density in initiating immune response.[41] This approach led to the induction of T cell responses in all patients, with 4/6 patients showing no recurrence of disease after 25 months. Other studies have also indicated that the presence of neoantigens that have higher binding affinity for class I MHC (compared to wild-type antigens) correlate with survival in certain cancer types.[42]

While TCR-mediated recognition of neoantigens results in cancer-specific responses, targeting upregulated cancer-associated antigens with TCRs is more challenging because of their normal levels of expression on non-cancerous tissues. In several clinical trials, targeting an upregulated (i.e., higher-density) cancer-associated self-antigen resulted in activity against their normal (i.e., lower-density) expression on normal tissues.[43,44] Accordingly, such “shared” cancer-associated antigens need to be carefully targeted with TCRs, especially when using higher-affinity receptors because of their lower threshold requirements (see below). Recent observations from clinical trials have suggested thorough examination not only of target antigen expression profiles in normal and cancer tissues but also of TCR reactivity to panels of normal human cell lines and tissues prior to adoptive T cell therapy in humans.

IV. TCR AFFINITY REQUIRED FOR CD4 AND CD8 T CELL RESPONSES

TCR affinity for pepMHC is known to determine the sensitivity of the T cell. In the context used here, sensitivity refers to how many specific pepMHC complexes per target cell are required to induce T cell signaling. Remarkably, while the affinity of many TCRs for “foreign” peptides in complex with an MHC molecule is low (micromolar), especially compared to most antibodies (nanomolar), these TCRs are able to mediate activity, as noted above, when induced by only a few pepMHC molecules per target cell.[30–33] This exquisite sensitivity comes in part from the TCR/CD3 machinery itself and in part from synergy with the coreceptors CD4 and CD8.[45, 46] The coreceptors facilitate T cell activity through binding

of the ligands as the TCR and class I and class II MHC (although binding of class I by CD8 appears to be more effective than class II binding by CD4).[32,34] Sensitivity is also enhanced by signaling mechanisms achieved through recruitment of the coreceptor-associated kinase Lck.[47]

While CD8-dependent signaling through the TCR enables such sensitivity, it also impacts potential cross-reactivity with noncognate self-peptides because of the low-affinity threshold required. TCR affinities against cancer self-peptides are generally lower than TCR affinities against foreign pepMHC,[48] probably because of negative selection. However, it is possible to use various screening or engineering approaches to raise the affinity of these TCRs.[49] This strategy can yield greater TCR sensitivity (i.e., recognition of lower levels of the specific pepMHC) and can even obviate the requirement for CD8.[34,50] TCRs with higher affinity (e.g., K_D values of ≤ 1 μM) can thus drive activity of CD4 T cells,[51] a feature that is especially valuable in elimination of cancers through direct lytic action of CD4 T cells and through recruitment of other immune cells through CD4 T cell polyfunctional activities.[52,53]

The risk of using higher-affinity TCRs against cancer-associated pepMHC antigens is that they have not been through a stringent negative selection process and so they may cross-react with structurally similar self-peptides.[54] This has in fact led to two different clinical trials with lethal toxicities.[55,56] The use of non-natural TCRs can be mitigated to some extent by careful screening of normal tissues and by *in silico* screens of possible MHC-binding structurally similar self-peptides.[57–59] It is possible to use natural TCRs isolated against neoantigen pepMHC complexes in autologous T cell transfers, but this process requires personalized workup of the antigens and the TCRs for each individual.[13,15,22,60,61] Regardless of the preclinical workup and safety screens done for human TCR gene therapies, clinical trials are required to fully ascertain possible detrimental cross-reactivity and safety issues.

V. CLINICAL TRIALS WITH TCR GENE TRANSFER

TCRs used clinically in an ACT format have been identified by isolation of a T cell clone that recognizes a specific cancer-associated pepMHC complex. These TCRs are subjected to thorough *in vitro* analysis to understand sensitivity and specificity prior to use in autologous T cells isolated from patients (Fig. 1). In 2004, Rosenberg and colleagues at the NCI enrolled metastatic melanoma patients for treatment by adoptive transfer of autologous lymphocytes that were genetically modified to express the TCR called DMF4 against the melanoma antigen MART-1/HLA-A2 complex (Table 1). The results of their “first in human” trial demonstrated the therapeutic potential of using TCRs to genetically engineer cells for cancer.[62] While they noted objective regression of melanoma lesions in only 2 out of 15 patients, their study provided the groundwork for further efforts on the optimization of TCRs and other parameters. Since then the number of TCR trials initiated worldwide for cancer treatment has been increasing (Fig. 2).

As DMF4 had a lower affinity to MART-1 (K_D = 170 μM), the efficacy of an affinity-enhanced TCR, DMF5 (K_D = 40 μM),[63] was subsequently examined in melanoma patients to determine if higher-affinity TCRs could mediate higher antitumor reactivity owing to

recognition of lower amounts of antigen.[43] While the objective responses increased to 30% in this trial, patients also experienced uveitis and hearing loss due to recognition of normal cells expressing MART-1 in the eye and ear. Similarly, targeting carcinoembryonic antigen (CEA) in metastatic colorectal cancer patients with an affinity-enhanced TCR resulted in 33% objective response but also in development of colitis in all patients due to recognition of normal levels of CEA on the colon mucosa.[44] Results from these trials demonstrate that, while higher-affinity TCRs can yield improved efficacy, the enhanced sensitivity may also elicit on-target reactivity with normal tissues that are normally nonreactive with lower-affinity TCRs. These results also prompted pursuit of alternative targets such as cancer testis antigens that can be more exclusively associated with expression in cancerous tissue (e.g., NY-ESO-1, LAGE-1, MAGE family of antigens).

Results from NY-ESO-1 clinical trials have been promising, with objective responses ranging from 45 to 70% (Table 1).[64–66] It is therefore not surprising that TCR trials for a variety of cancers are targeting this antigen with an affinity-enhanced TCR, NY-ESO-1^{c259} (K_D = 730 nM).[66] In contrast, two TCRs that each targeted a different MAGE antigen resulted in patient fatalities due to unexpected off-target cross-reactivities. In one case, targeting MAGE-A3/HLA-A2 antigen with an affinity-enhanced TCR resulted in neurotoxicity due to unexpected expression of a related antigen, MAGE-A12, in the brain.[55] In the second case, targeting the MAGE-A3 antigen (HLA-A1–restricted) with an affinity-enhanced TCR (a3a, K_D = 2.3 μM) resulted in cardiotoxicity due to unexpected cross-reactivity with the cardiac peptide from the titin protein that shared 5 out of 9 residues with the targeted antigen.[56,57] Following these reports of lethal off-target cross-reactivity, safety screens with TCRs now include reactivity with (1) all variants of the targeted peptide, (2) structurally similar self-peptides identified by *in silico* screens of the proteome,[59] and (3) panels of normal human cell lines and tissues in preclinical assays.[67] With these key lessons, the use of TCRs in ACT is expanding to safely pursue additional cancer-associated antigens.

Trials are now underway for targeting MAGE-A4, A6, A10, WT-1, Tyrosinase, PRAME, AFP, and KRAS antigens among many others (Table 1). Based on our analysis, there are currently 74 clinical trials that involve either affinity-enhanced TCRs or wild-type TCRs in ACT. For example, Adaptimmmune's panel of engineered TCRs for ACT have enhanced affinity [these are termed specific peptide-enhanced affinity receptor (SPEAR) T cells] and have been assessed for optimal affinity and cross-reactivity. In contrast, Immatics conducts high-throughput screening of natural human T cell repertoires to isolate therapeutic TCRs with optimal affinity.

Although not addressed in detail here, mispairing of exogenous TCRs with endogenous TCRs can present a challenge in ACT by impacting TCR transduction efficiencies or possibly creating unknown specificities. The addition of cysteines in the constant domains[68] or the use of murine constant domains[69] has allowed preferential assembly of exogenous TCRs. With the advent of CRISPR/Cas9, engineered T cells can have their endogenous TCR α and β loci disrupted.[70,71] TCRs against the NY-ESO-1 antigen with CRISPR-disrupted endogenous TCR chains (NYCE) and/or PD-1 are now in clinical trials for multiple indications (NCT03399448).

Since tumor microenvironment is often immunosuppressive,[9,72] combination treatments with checkpoint inhibitors are being assessed in clinical trials—for example, to prevent engineered T cells from inhibitory interactions with PD-L-1 on cancer cells among other cell types (e.g., NCT03709706, NCT03168438, NCT02070406). In addition, in order to achieve durable responses in patients, there is also significant interest in TCR engineering of memory subsets of T cells to achieve durable anticancer response (e.g., NCT02408016, NCT02770820[73]).

VI. CONCLUDING REMARKS

TCR gene transfer into T cells has tremendous potential as an effective cancer therapeutic because of the potency of T cells and the opportunities to identify novel targets (pepMHC). Continued understanding of T cell and cancer biology, in addition to the discovery of unique targets matched with specific T cell receptors, will allow safer targeting of diverse types of cancers. The field has realized the importance of affinity thresholds of TCRs, in both CD4 and CD8 T cells, when treating patients with genetically modified T cells. In addition, the basic principles of dependence of T cell activation not only on TCR affinity but also on ligand density, coreceptors, CD3 subunits, costimulatory or inhibitory molecules, and downstream signaling mechanisms have guided the expanding array of clinical studies in progress.

ACKNOWLEDGMENTS

We thank past and present members of the Kranz lab for their contributions over the years. This work was supported by NIH grant R01 CA178844 (D.M.K).

ABBREVIATIONS:

ACT	adoptive T cell therapy
CAR	chimeric antigen receptor
HLA	human leukocyte antigen (refers to human MHC alleles)
K_D	dissociation constant
MHC	major histocompatibility complex
pepMHC	peptide-major histocompatibility complex antigen
TCR	T cell receptor

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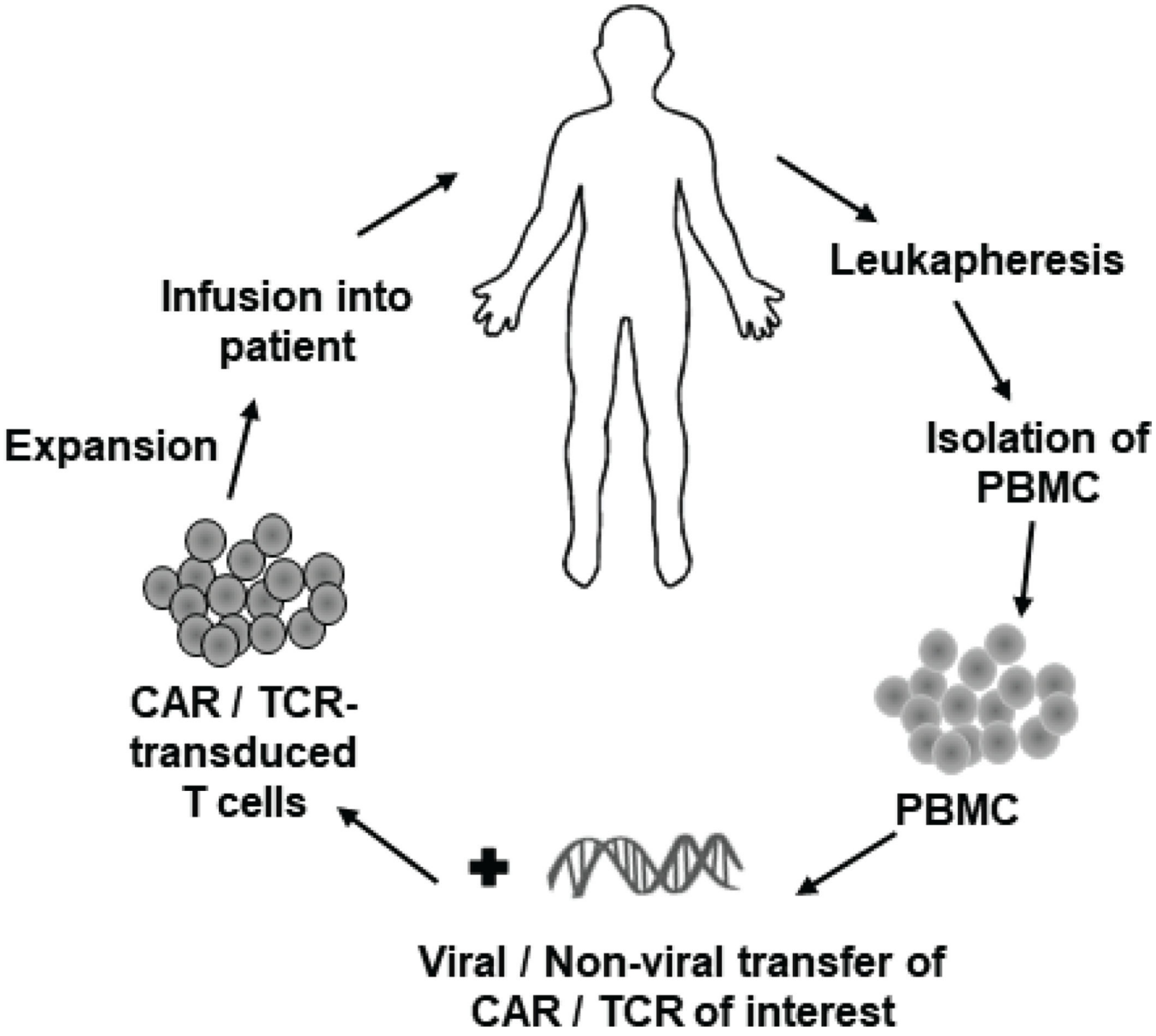

FIG. 1:
Schematic of ACT using genetically modified (CAR- or TCR-) transduced T cells.

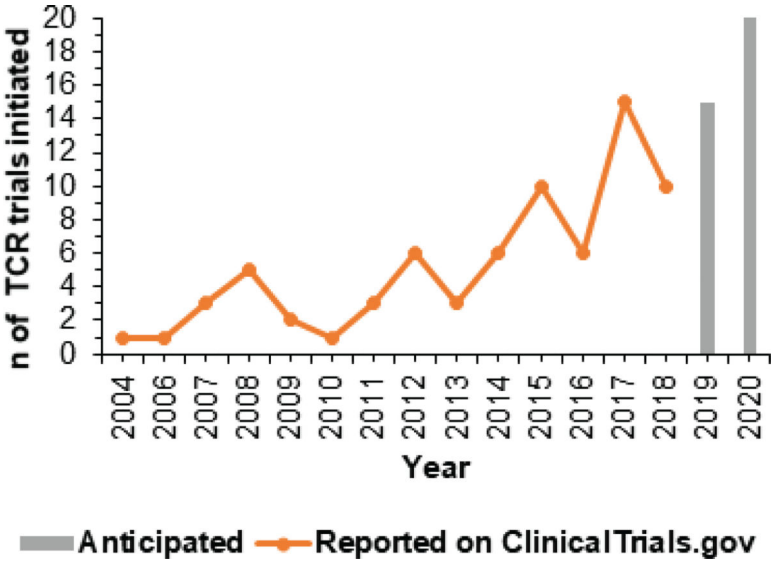

FIG. 2:

Number of cancer clinical trials in the ClinicalTrials.gov database that use TCR-transduced T cells for ACT. The database was searched for TCR trials on January 9, 2019. The search was delimited by “T cell receptors” and “Cancer” as key words.

TABLE 1:

Selected clinical trials using TCR ACT for cancer[a]

	Target, sequence[b]	HLA	TCR; affinity-matured (yes/no/not specified); K_D (if known)	Cancer(s)[c]	No. of patients[d]	Trial phase	Response[e]; trial status	Sponsor,[f] country	Trial ID, start date
1	p53:264–272; LLGRNSFEV	HLA-A*02:01	p53 TCR; no[74,75]	Metastatic melanoma and other metastatic cancers	12	II	No information	NCI, USA	NCT00393029, Oct 2006
2	p53	HLA-A*02:01	p53 TCR; not specified	Progressive or recurrent metastatic cancer	3	II	Terminated (withdrawal of collaborators' support)	NCI, USA	NCT00704938, June 2008
3	MART-1, AAGIGILTV	HLA-A*02:01	DMF4; no; K_D = 170 μM[63]	Metastatic melanoma	15	—	13% OR (2/15)	NCI, USA	See ref. 62
4	MART-1, AAGIGILTV	HLA-A*02:01	DMF5; yes; K_D = 40 μM[63]	Metastatic melanoma	20	II	30% OR (6/20); 55% uveitis (11/20); 50% hearing loss (10/20)	NCI, USA	NCI-07-C-0175, NCT00509288, June 2007[43]
5	MART-1, AAGIGILTV	HLA-A*02:01	DMF5; yes; K_D = 40 μM[63]	Metastatic melanoma	1	I, II	Terminated (low accrual)	NCI, USA	NCT00924001, Aug 2007
6	MART-1, AAGIGILTV	HLA-A*02:01	DMF5; yes; K_D = 40 μM[63]	Metastatic melanoma	4	II	Terminated (low accrual)	NCI, USA	NCT00612222, Jan 2008
7	MART-1	HLA-A*02:01	DMF5; yes; K_D = 40 μM[63]	Melanoma	50	II	Terminated (low enrollment)	NCI, USA	NCT00706992, June 2008
8	MART-1	HLA-A*02:01	DMF5; yes; K_D = 40 μM[63]	Metastatic melanoma	13	II	69% tumor regression (9/13); 38% progressive disease (5/13); 54% stable disease (7/13)	JCCC (UCLA), USA	NCT00910650, Oct 2009[76,77]
9	MART-1:26–35, EAAGIGILTV	HLA-A*02:01	1D3 HM CysTCR; no[78]	Stage IV skin melanoma, eye melanoma	12	I, II	Active, not recruiting, no results posted	Netherlands Cancer Institute, Netherlands	NCT02654821, Mar 2012[79]
10	gp100, KTWGQYWQV	HLA-A*02:01	gp100154 mouse TCR; no	Metastatic melanoma	16	II	19% OR (3/16); 25% uveitis (4/16); 31% mild hearing loss (5/16); Terminated	NCI, USA	NCI-07-C-0174, NCT00509496, June 2007[43]
11	NY-ESO-1: 157–165, SLLMWITQC	HLA-A*02:01	1G4-α95:LY; yes; K_D = 730 nM[80]	Metastatic SCS, metastatic	Metastatic SCS: 6;	II	Metastatic SCS: 66% OR (4/6);	NCI, USA	NCT00670748, April 2008[64];

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	Target, sequence[b]	HLA	TCR; affinity-matured (yes/no/not specified); K_D (if known)	Cancer(s)[c]	No. of patients[d]	Trial phase	Response[e]; trial status	Sponsor,[f] country	Trial ID, start date
				melanoma, metastatic SCS, metastatic melanoma	metastatic melanoma: 11; metastatic SCS: 18; metastatic melanoma: 20		metastatic melanoma: 16% PR (1/6); metastatic SCS: 45% OR (5/11); metastatic melanoma: 18% CR (2/11), 61% OR (11/18), 55% OR (11/20)		NCT00670748, April 2008[65]
12	NY-ESO-1/LAGE-1: SLLMWITQC	HLA-A*02:01	NY-ESO-1^{c259}; yes; K_D = 730 nM[81]	Multiple Myeloma	20	I, II	70% nCR/CR (14/20); 10% VGPR (2/20); 10% PR (2/20); active, not recruiting	GSK, USA	NCT01352286, May 2011[66]
13	NY-ESO-1	HLA-A*02:01	NY-ESO-1^{c259}; yes; K_D = 730 nM[81]	Melanoma	4	I, II	Terminated (lack of enrollment)	Adaptimmune, USA	NCT01350401, June 2011
14	NY-ESO-1/ LAGE-1,SLLMWITQC	HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06	NY-ESO-1^{c259}; yes; K_D = 730 nM[81]	Metastatic SCS	12	I	50% OR (6/12); 42% PR (5/12); 8% CR (1/12); Recruiting	GSK, USA	NCT01343043, Sep 2012[82,83]
15	NY-ESO-1:157–165, SLLMWITQC	HLA-A*02:01	NY-ESO-1 TCR; not specified	Malignant neoplasm	22 (est.)	II	Recruiting	JCCC (UCLA), USA	NCT01697527, Nov 2012
16	NY-ESO-1:157–165, SLLMWITQC	HLA A*02:01, HLA-A*02:05, and/or HLA-A*02:06	NY-ESO-1^{c259}; yes; K_D = 730 nM[81]	Ovarian	6	II	0% response (not recruiting)	Adaptimmune, USA	NCT01567891, Jul 2013
17	NY-ESO-1 and/or LAGE-1	HLA-A*02:01	NY-ESO-1^{c259}; yes; K_D = 730 nM[81]	Multiple myeloma	6	I, II	Terminated (sponsor decision)	Adaptimmune, USA	NCT01892293, Oct 2013
18	NY-ESO-1	HLA-A*02:01	NY-ESO-1 TCR with murine chains; no[84]	Melanoma, meningioma, breast cancer, NSCLC, HCC	43	II	Recruiting	NCI, USA	NCT01967823, Oct 2013
19	NY-ESO-1	HLA-A*02:01	NY-ESO-1 TCR; not specified	Metastatic melanoma	2	II	Terminated (low accrual)	NCI, USA	NCT02062359, Feb 2014
20	NY-ESO-1:157–165	HLA-A*02:01	NY-ESO-1 TCR; not specified	Solid cancers	4	I	Terminated (low accrual)	JCCC (UCLA), USA	NCT02070406, Jul 2014

	Target, sequence[b]	HLA	TCR; affinity-matured (yes/no/not specified); K_D (if known)	Cancer(s)[c]	No. of patients[d]	Trial phase	Response[e]; trial status	Sponsor,[f] country	Trial ID, start date
21	NY-ESO-1	HLA-A*02:01 or HLA-A*02:06	NY-ESO-1 TCR (TBI-1301); not specified	Solid cancers	9	I	Active, not recruiting	Mie University, Japan	NCT02366546, Mar 2015
22	NY-ESO-1	HLA-A* 02	NY-ESO-1 TCR; not specified	Solid cancers	36 (est.)	1	Recruiting	Shenzhen Second People's Hospital, China	NCT02457650, Apr 2015
23	NY-ESO-1	HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06	NY-ESO-1^{c259}; yes; K_D = 730 nM[81]	Advanced (stage IIIb or IV) NSCLC	10 (est.)	I	Recruiting	GSK, USA	NCT02588612, Feb 2016[85]
24	NY-ESO-1	HLA-A*02:01	NY-ESO-1 TCR with murine chains; no[84]	Metastatic cancers	10 (est.)	—	Recruiting	Albert Einstein College of Medicine, USA	NCT02774291, Aug 2016
25	NY-ESO-1	Not specified	NY-ESO-1 TCR; not specified	Advanced malignant solid tumors	15 (est)	—	Recruitment status unknown	Fudan University, China	NCT03047811, Aug 2016
26	NY-ESO-1	HLA-A*02:01, HLA-A*02:06	NY-ESO-1 TCR (TBI-1301); not specified	Solid cancers	15 (est.)	I	Recruiting	University Health Network, Canada	NCT02869217, Sep 2016
27	NY-ESO-1	HLA-A*02:01, HLA-A*02:05, or HLA-A*02:06	NY-ESO-1^{c259}; yes; K_D = 730 nM[81]	Advanced MRCLS	10 (est.)	II	Recruiting	GSK, USA	NCT02992743, Dec 2016
28	NY-ESO-1:157–165	HLA-A*02:01	NY-ESO-1 TCR; not specified	Stage IV or locally advanced solid tumors	12 (est.)	I	Recruiting	JCCC (UCLA), USA	NCT02775292, Jan 2017
29	NY-ESO-1	HLA-A2*02:01	NY-ESO-1 TCR TAEST16001; yes	Advanced NSCLC	20 (est.)	I	Recruiting	Guangzhou Institute of Respiratory Disease, China	NCT03029273, Mar 2017
30	NY-ESO-1	HLA-A2*02:01	NY-ESO-1 TCR TAEST16001; yes	Solid tumors	20 (est.)	I	Recruiting	Zhujiang Hospital, China	NCT03159585, Apr 2017
31	NY-ESO-1	HLA-A*02:01	NY-ESO-1 TCR; not specified	Stage IV or locally advanced unresectable cancers	12 (est.)	I	Recruiting	JCCC (UCLA), USA	NCT03240861, July 2017
32	NY-ESO-1 /LAGE-1	HLA-A*02:01, HLA-A*02:05,	NY-ESO-1^{c259}; yes; K_D = 730 nM[81]	Multiple myeloma	24 (est)	II	Recruiting	GSK, USA	NCT03168438,Aug 2017 (Follow-up; see ref. 83)

	Target, sequence[b]	HLA	TCR; affinity-matured (yes/no/not specified); K_D (if known)	Cancer(s)[c]	No. of patients[d]	Trial phase	Response[e]; trial status	Sponsor,[f] country	Trial ID, start date
		and/or HLA-A*02:06							
33	NY-ESO-1:157–165, SLLMWITQC	HLA-A*02:01 and HLA-A*02:06	NY-ESO-1 TCR; not specified	SCS	8 (est.)	I, II	Recruiting	Takara Bio Inc., Japan	NCT03250325, Sep 2017
34	NY-ESO-1	HLA-A*02:01	NY-ESO-1 TCR with murine chains; no[84]	Recurrent or refractory ovarian, primary peritoneal, or fallopian tube carcinoma	12 (est.)	I	Recruiting	Roswell Park Cancer Institute, USA	NCT03017131, Dec 2017
35	NY-ESO-1	Not specified	NY-ESO-1^{c259}(GSK3377794); yes; K_D = 730 nM[81]	—	200 (est.)	I	Recruiting	GSK, USA	NCT03391778, Apr 2018 (long-term follow-up of subjects exposed to NY-ESO-1^{c259} T cells)
36	NY-ESO-1	HLA-A2*02:01	NY-ESO-1 TCR TAEST; yes	Sarcoma	20 (est.)	I	Recruiting	Sun Yat-sen University, China	NCT03462316, May 2018
37	NY-ESO-1	HLA-A*02:01	NY-ESO-1 TCR (NYCE T cells); not specified	Multiple myeloma, melanoma, SCS, MRCLS	18 (est.)	I	Recruiting	UPenn, USA	NCT03399448, Sep 2018
38	NY-ESO-1/LAGE-la	HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06	NY-ESO-1^{c259}(GSK3377794); yes; K_D = 730 nM[81]	NSCLC	44 (est.)	II	Recruiting	MSD, USA	NCT03709706, Dec 2018
39	NY-ESO-1	HLA-A*02:01 and HLA-DP*04	NY-ESO-1 TCR; not specified	Recurrent or refractory ovarian, fallopian tube, or primary peritoneal cancers	15 (est.)	I	Recruiting	Roswell Park Cancer Institute, USA	NCT03691376, Jan 2019
40	CEA, IMIGVLVGV	HLA-A*02:01	PG13-CEA mouse TCR; yes[86]	Metastatic CRC	3	I	33% OR (1/3); 100% colitis (3/3) (CEA on normal colon mucosa); Terminated	NCI, USA	NCT00923806, Dec 2008[44]
41	TRAIL/DR4	HLA-independent	2G-1 TCR; no[87]	Metastatic renal cancer	5	I, II	Terminated	NCI, USA	NCT00923390, Mar 2009
42	MAGE-A3, KVAELVHFL, MAGE-A12, KMVELVHFL	HLA-A*02:01	PG13-MAGE-A3 TCR9W11; yes[88]	Metastatic melanoma, SCS, esophageal cancer	9	I, II	11% CR (1/9); 44% PR (4/9); 22%	NCI, USA	NCT01273181, Dec 2010[55]

	Target, sequence[b]	HLA	TCR; affinity-matured (yes/no/not specified); K_D (if known)	Cancer(s)[c]	No. of patients[d]	Trial phase	Response[e]; trial status	Sponsor,[f] country	Trial ID, start date
							neurotoxicity (2/9) (MAGEA12 in brain); Terminated		
43	MAGE-A3, EVDPIGHLY	HLA-A*01	a3a TCR; yes; K_D = 2.3 μM[57]	Melanoma, high-risk or relapsed myeloma	2	III, IV	2/2 deaths (cardiovascular toxicity to titin peptide: ESDPIVAQY in heart); Terminated	UPenn, Adaptimmune, USA	Dec 2011 (see refs. 56,57)
44	MAGE-A3	HLA-A*01	MAGE-A3 TCR; not specified	Breast, cervical, renal, bladder cancers; melanoma	3	I, II	Terminated	NCI, USA	NCT02153905, Jul 2014
45	MAGE-A3:248–258, QHFVQENYLEY	HLA-DP0401	MAGE-A3-DP4 TCR; no[89]	Cervical, renal, urothelial, breast cancers; melanoma	107 (est.)	I, II	Recruiting	NCI, USA	NCT02111850, Feb 2014
46	MAGE-A3 and/or MAGE-A6	HLA-DPB1*04:01	MAGE-A3/A6 TCR (KITE-718); not specified	Solid tumors	75 (est.)	I	Recruiting	Kite (Gilead), USA	NCT03139370, May 2017[90]
47	MAGE-A4:143–151, NYKRCFPVI	HLA-A*24:02	MAGE-A4 TCR (TBI-1201); no[91]	Solid cancers	12 (est.)	I	Persistence of TCR-transduced T cells in 50% of patients (5/10); Recruiting	Mie University, Japan	UMIN00000239, NCT02096614, Apr 2014[92]
48	MAGE-A4:230–239, GVYDGREHTV	HLA-A*02	MAGE-A4^{c1032} TCR; yes; not specified	Urinary bladder, head and neck, ovarian, esophageal, gastric cancers; SCS, NSCLC, MRCLS, melanoma	42 (est.)	I	Recruiting	Adaptimmune, USA, Canada	NCT03132922, May 2017
49	MAGE A10:254–262, GLYDGMEHL	HLA-A*02:01 and/or HLA-A*02:06	MAGEA10^{c796}; yes; K_D = 370 nM[93]	Advanced NSCLC	28 (est.)	I	Recruiting	Adaptimmune, USA, Canada, Spain, LTK	NCT02592577, Nov 2015[85]
50	MAGE-A10	HLA-A*02:01 and/or HLA-A*02:06	MAGEA10^{c796}; yes; K_D = 370 nM[93]	Urothelial carcinoma, bladder urothelial carcinoma, head and neck cancer; melanoma	22 (est.)	I	Recruiting	Adaptimmune, USA, Canada, Spain	NCT02989064, Oct 2016[94]

	Target, sequence[b]	HLA	TCR; affinity-matured (yes/no/not specified); K_D (if known)	Cancer(s)[c]	No. of patients[d]	Trial phase	Response[e]; trial status	Sponsor,[f] country	Trial ID, start date
51	MAGE-A4:230–239 GVYDGREHTV, MAGE-A10:254–262, GLYDGMEHL	HLA-A*02, HLA-A*02:01, HLA-A*02:06	MAGE-A4^{c1032}; yes; not specified; MAGEA10^{c796}; yes; K_D = 370 nM[93]	Solid and hematological malignancies	300 (est.)	—	Enrolling by invitation	Adaptimmune, USA, Canada	NCT03391791, Feb 2018 (long-term follow-up of subjects exposed to genetically engineered TCRs)
52	WT1: 126–134 RMFPNAPYL	HLA-A*02:01	Cys1 WT1 TCR; no[95]	AML, CML	7	I, II	No results posted	Cell Medica Ltd., UK	NCT01621724, April 2012
53	WT1: 126–134 RMFPNAPYL	HLA-A*02:01	WT1 TCRc4; no[11]	High-risk AML, MDS, CML	45	I, II	Active, not recruiting, no results posted	Fred Hutch, USA	NCT01640301, Jul 2012
54	WT1:126–134 RMFPNAPYL	HLA-A*02:01	WT1 TCRc4 (JTCR016: Celgene); no[11]	Stage III–IV NSCLC or mesothelioma	20 (est.)	I, II	Active, not recruiting, no results posted	Fred Hutch, USA	NCT02408016, May 2015
55	WT1	HLA-A*02:01	WT1 TCR (CMD-602); not specified	MDS, AML	3	I, II	No results posted	Cell Medica Ltd., Belgium, Germany, UK	NCT02550535, Sep 2015
56	WT1:126–134 RMFPNAPYL	HLA-A*02:01	WT1 TCRc4; no[11]	AML	9	I, II	Active, not recruiting	Fred Hutch, USA	NCT02770820, Nov 2017
57	Tyrosinase:368–376, 370D:YMDGTMSQV, 370N:YMNGTMSQV	HLA-A*02:01	1383I TCR; no; K_D = 10 μM[96,97]	Melanoma	14	I	33% tumor shrinkage (1/3); 66% vitiligo (2/3)	Loyola University, USA	NCT01586403, July 2012[97]
58	Tyrosinase 368–376 370D:YMDGTMSQV, 370N:YMNGTMSQV	HLA-A*02:01	1383I TCR; no; K_D = 10 μM[96,97]	Melanoma	18 (est.)	I	Recruiting	NCI, USA	NCT02870244, Feb 2015
59	E6:29–38 TIHDIILECV	HLA-A*02:01	HPV-16 E6 TCR; no[98]	HPV-associated cancers	12	I, II	1 CR; 1 PR	NCI, USA	NCT02280811, Oct 2014[99]
60	E6:29–38 TIHDIILECV	HLA-A*02:01	HPV-16 E6 TCR; no[98]	High-grade squamous intraepithelial lesion	200 (est.)	I	Recruiting	NCI, USA	NCT03197025, Jan 2018
61	E7:11–19 epitope of HPV E7 protein	HLA-A*02:01	E7 TCR; not specified[100]	HPV-associated cancers	180 (est.)	I, II	Recruiting	NCI, USA	NCT02858310, Jan 2017
62	HBV antigen	Not specified	HBV antigen-specific TCR; not specified	HCC	10 (est.)	I	Recruiting	Lion TCR Pte. Ltd., China	NCT02686372, Dec 2015
63	HERV-E–derived antigen: ATWLGSKTWK	HLA-A* 11:01	HERV-E TCR; not specified	Metastatic ccRCC	24 (est.)	I	Recruiting	NHLBI, USA	NCT03354390, July 2018
64	Human thyroglobulin (hTG)	HLA-A*02:01	hTG mouse TCR; not specified	Metastatic thyroid cancer	0	I, II	Withdrawn	NCI, USA	NCT02390739, Mar 2015

	Target, sequence[b]	HLA	TCR; affinity-matured (yes/no/not specified); K_D (if known)	Cancer(s)[c]	No. of patients[d]	Trial phase	Response[e]; trial status	Sponsor,[f] country	Trial ID, start date
65	PRAME	HLA-A*02:01	PRAME TCR (BPX-701); not specified[101]	AML, MDS, uveal melanoma	116 (est.)	I, II	Recruiting	Bellicum Pharmaceuticals, USA	NCT02743611, Apr 2017
66	PRAME	HLA-A2*02:01	MDG1011; not specified	High-risk myeloid and lymphoid neoplasms	92 (est.)	I, II	Recruiting	Medigene AG, Germany	NCT03503968, Mar 2018
67	AFP:158–166 FMNKFIYEI	HLA-A*02:01 or HLA-A*02:642	AFP^{c332} TCR; yes; K_D = 10.6 μM[102]	HCC	24 (est.)	I	Recruiting	Adaptimmune, USA, Spain, UK	NCT03132792, May 2017
68	KRAS G12V: (V) VVGAVGVGK, NRAS G12V, HRAS G12V	HLA-A*11:01	KRAS G12V mouse TCR; no[103]	Pancreatic, gastric, gastrointestinal, colon, rectal cancers	110 (est.)	I, II	Recruiting	NCI, USA	NCT03190941, Sep 2017
69	G12D variant of mutated RAS	HLA-A*11:01	KRAS G12D mouse TCR; no[103]	Gastrointestinal, pancreatic, gastric, colon, rectal cancers	70 (est.)	I, II	Recruiting	NCI, USA	NCT03745326, Apr 2019
70	Not specified	HLA-A*02:01	IMA201; no	Solid tumors; HNSCC, NSCLC	16 (est.)	I	Recruiting	Immatics US, Inc., USA	NCT03247309, Sep 2017
71	Not specified	Not specified	IMA202; no	Solid tumors, including NSCLC and HCC	16 (est.)	I	Recruiting	Immatics US, Inc., USA	NCT03441100, Apr 2019
72	Not specified	Not specified	IMA203; no	Refractory/ recurrent solid tumors	16 (est.)	I	Recruiting	Immatics US, Inc., USA	NCT03686124, Mar 2019
73	HA-1: VLHDDLLEA	HLA-A*02:01	HA-1 TCR; no[104]	Relapsed or refractory acute Leukemia	24 (est.)	I	Recruiting	Fred Hutch, USA	NCT03326921, Feb 2018
74	TGFβII	HLA-A*02	Not specified; no	CRC	5 (est.)	I, II	Recruiting	Oslo University Hospital, Norway	NCT03431311, Mar 2018

[a] Previous or combination treatments are not listed.

[b] AFP: Alpha-fetoprotein; CEA: carcinoembryonic antigen; HA-1: minor histocompatibility (H) antigen; HBV: hepatitis B virus; HPV: human papilloma virus; HERV-E–derived antigen: human endogenous retrovirus–derived antigen; MART-1: melanoma antigen recognized by T cells 1; NY-ESO-1: New York esophageal squamous cell carcinoma 1 [LAGE-1: cancer testis antigen homologous to NY-ESO-1 containing 157–165 peptide (SLLMWITQC)]; PRAME: preferentially expressed antigen in melanoma; TGFβII: transforming growth factor beta receptor type II; TRAIL/DR4: TNF-related apoptosis–inducing ligand bound to its receptor DR4; WT1: Wilms' tumor antigen

[c] AML: acute myeloid leukemia; ccRCC: clear cell renal cell carcinoma; CML: chronic myeloid leukemia; CRC: colorectal cancer; HCC: hepatocellular cancer; HNSCC: head and neck squamous cell carcinoma; MDS: myelodysplastic syndrome; MRCLS: myxoid/round cell liposarcoma; NSCLC: non-small-cell lung cancer; SCS: synovial cell sarcoma.

[d] est.: estimated patient enrollment

[e] CR: complete regression; nCR: near complete response; OR: objective regression; PR: partial response; VGPR: very good partial response

[f] Fred Hutch: Fred Hutchinson Cancer Research Center; GSK: GlaxoSmithKline; JCCC (UCLA): Jonsson Comprehensive Cancer Center at the University of California, Los Angeles; MSD: Merck Sharp and Dohme Corp.; NCI: National Cancer Institute; NHLBI: National Heart, Lung, and Blood Institute; UPenn: University of Pennsylvania