T-Cell Therapy: Options for Infectious Diseases

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The emergence of drug-resistant tuberculosis is challenging tuberculosis control worldwide. In the absence of an effective vaccine to prevent primary infection with *Mycobacterium tuberculosis* and tuberculosis disease, host-directed therapies may offer therapeutic options, particularly for patients with multidrug-resistant and extensively drug-resistant tuberculosis where prognosis is often limited. $CD8^+$ and $CD4^+$ T cells mediate antigen-specific adaptive cellular immune responses. Their use in precision immunotherapy in clinical conditions, especially in treating cancer as well as for prevention of life-threatening viral infections in allogeneic transplant recipients, demonstrated safety and clinical efficacy. We review key achievements in T-cell therapy, including the use of recombinant immune recognition molecules (eg, T-cell receptors and CD19 chimeric antigen receptors), and discuss its potential in the clinical management of patients with drug-resistant and refractory tuberculosis failing conventional therapy.

Keywords. T-cells; adoptive cell therapy; *Mtb*; CAR; host-directed therapy.

Although the global incidence of tuberculosis has been steadily declining over the past decades, the absolute number of patients with tuberculosis is increasing worldwide. There has been a dramatic rise in the numbers of notified patients with multidrug-resistant (MDR) tuberculosis, from 47 897 in the year 2009 to 136 412 in the year 2013 globally [1]. These patients have a poor prognosis; cure rates for patients with MDR tuberculosis and extensively drug-resistant (XDR) tuberculosis globally have been reported to be 48% and 22%, respectively [1]. The emergence of deadly drug-resistant strains resistant to all 12 antituberculosis drugs tested reveals another challenging task to the global tuberculosis problem [2]. Although novel drugs are being developed for the treatment against tuberculosis [3, 4], drug-resistant strains of *Mycobacterium tuberculosis* (*Mtb*) rapidly emerge once antituberculosis drugs are marketed. In the absence of a vaccine that is superior to the *Mycobacterium bovis* BCG vaccine to prevent primary infection with *Mtb* and progression to active disease, future tuberculosis control will depend on novel therapeutic strategies beyond antimicrobial drug treatment. In the preantibiotic era, approximately 30% of patients with smear-positive pulmonary tuberculosis were able to achieve natural cure by their immune defense mechanisms alone [5]. Augmenting the *Mtb*-specific immune response could substantially improve the prognosis for patients with MDR and XDR tuberculosis. Recent clinically relevant advances aid in understanding the regulatory mechanisms of adaptive immune responses in cancer, infectious diseases, and T-cell therapies. We review here developments and current concepts in adoptive T-cell therapy, and discuss whether such concepts may aid to offer tailored T-cell–based therapy for patients with refractory MDR and XDR tuberculosis, who may have limited or no other treatment options.

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Clinical Infectious Diseases® 2015;61(S3):S217–24

DOI: 10.1093/cid/civ615

Table 1. Effector T-Cell Subsets in Immunopathogenesis of Human Tuberculosis

Cell Subset	Functions (Production, Cytotoxic, Regulatory)	Infection: Acute/Early/Chronic Inflammation: Too Little/Right Balance/Too Much	Ref
CD4 T cells	IFN-γ, IL-2; TNF-α produced by CD4, responsible for establishment and maintenance of TB granulomas	Early/acute/chronic phases; Multifunctional (IFN-γ, IL-2, and TNF-α) CD4 cells associated with active TB correlated with bacterial load	[6–11]
CD8 T cells	Cytolytic functions to kill *Mtb*-infected cells via granule-mediated function (via perforin, granzymes, and granulysin); Classical (HLA-I restricted) and nonclassical (CD1d and HLA-E restricted): ESAT6-specific $CD8^+$ T cells have a role in protection against TB	Early/acute/chronic phases Protective T-cell subsets (T_{EM}: $CCR7^-$, $CD45RA^-$) and T_{EMRA}: $CCR7^-$, $CD45RA^+$)	[12–14]
γδ T cells	Innate protective response IFN-γ; IL-17 and cytotoxic activity; Human alveolar macrophages and monocytes serve as APCs for γδ T cells; predominance of Vγ9Vδ2T cells in TB disease	Early and acute phases Restricted to CD1b/c with cytolytic activity; recognize "phosphoantigens" of host or bacterial origin (mycolic acid of *Mtb*)	[15]
Dendritic cells	Most potent APC, cross-presentation of extracellular and endogenous *Mtb* antigen	Acute and in chronic phases Play a crucial role in the outcome of granuloma and protective immune responses	[16]
T-regulatory cells	$CD4^+CD25^+Foxp3^+$ Treg $CD127^-$; produce IL-10 and TGF-β interfering with productive and protective inflammation	Acute/chronic phases; Impairment of *Mtb*-specific $CD4^+$ and $CD8^+$ T-cell activation and proliferation	[17]
NK T cells (CD18/DN)	PD-1 preferentially induces apoptosis of IFN-γ–producing NK T cells while sparing NK T cells that produce IL-4	Acute/chronic phases; Higher percentages of PD-1 + NK T cells correlating with sputum bacillary load in active TB patients	[18]
NK cells	LAG3 expression in active *Mtb* infections within granulomatous lesions of the lungs; interaction of $CD8\alpha^+$ DCs with iNK T cells during presentation result in NK cell transactivation with Th2 α-galcer agonist activity following PDL upregulation inhibiting IFN-γ response or with Th1 α-galcer agonist activity following CD70 upregulation stimulating IFN-γ response	Acute/chronic phases Critical role in proinflammatory or anti-inflammatory outcome following interactions within DCs, iNK, and NK cells through glycolipid antigens	[19]
Mucosal-associated invariant T cells (MAIT)	Innate-like CD8T cells capable of recognizing pathogens via MHC-I–related MR1; contain and control *Mtb* upon initial exposure in the airways; produce IFN-γ, TNF-α, and granzymes in vitro when used *Mtb*-infected human airway epithelial cells as APCs	Early and chronic phases	[20]
iNK T cells	Interacts with $CD8a^+DEC\text{-}205^+$ DCs as key APCs for a range of structurally different glycolipid antigens and modulate outcome through costimulatory and coinhibitory molecules on these DCs: early producers of IFN-γ; suppressing intracellular bacterial growth	Early innate response	[19]
Regulatory CD8 T cells	Not yet been fully defined; but include the following: $CD8^+LAG3^-FoxP3^+CTLA\text{-}4^+$, $CD8^+LAB\text{-}3^-CCL4^+$, and $CD8^+CD39^+$	Function and relevance yet to be defined	[21]

We do not cover here the immune effector functions, including cytokine production in B cells and nonimmune cells (eg, fat cells, fibroblasts), as well as monocytes, macrophages, and dendritic cells.

Abbreviations: APC, antigen-presenting cell; DC, dendritic cell; HLA, human leukocyte antigen; IFN-γ, interferon gamma; IL, interleukin; iNK, invariant natural killer; *Mtb*, *Mycobacterium tuberculosis*; NK, natural killer; PD-1, programmed cell death-1; PDL, programmed cell death-1 ligand; TB, tuberculosis; T_{EM}, effective memory T cells; T_{EMRA}, terminally differentiated effector memory T cells; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis factor alpha.

ROLE OF T CELLS IN IMMUNOPATHOLOGY AND IMMUNOPROTECTION

The goal of immune responses in infectious diseases is to eliminate pathogens through inflammatory reactions without collateral damage. T cells are not only the key mediators of adaptive immune responses, but they also orchestrate the delicate balance of immune responses between nonproductive and exaggerated inflammation. $CD4^+$ antigen-specific responses are found in humans 3–8 weeks following infection with *Mtb* [6], corroborated by the tuberculin skin test or interferon gamma (IFN-γ) release assay (IGRA) in humans. The role of $CD4^+$ cells, as well as interleukin (IL) 12 and IFN-γ, have been well documented by studies of the syndrome of Mendelian susceptibility to mycobacterial diseases, defined by a selective vulnerability to weakly virulent mycobacterial species (BCG and environmental

mycobacteria) due to mutations in the IL-12 and IFN-γ receptors [7–10] (Table 1). Reactivation of latent infection with *Mtb* to clinical disease during TNF-α antagonist therapy in the first year of treatment suggests that TNF-α contributes to contain *Mtb* infection, which had been observed previously in murine models [11, 22]; TNF-α antagonist therapy also removes terminally differentiated TNF-α^+ ($CD45RA^+$ $CCR7^-$) immune effector $CD8^+$ T cells [12], which underlines the role of *Mtb*-specific $CD8^+$ T cells in clinical tuberculosis, along with the observation that $CD8^+$ immune effector functions, including cytokine production and cytotoxic abilities [13], may be impaired (Table 1). Concepts in targeted cellular therapy that are already used in clinical trials for viral targets or malignant cells may cross-fertilize directed cellular therapy for the treatment of tuberculosis.

THE NATURE OF IMMUNE EFFECTOR T CELLS

The nature and specificity of the T-cell receptor (TCR), as well as the phenotype and function of the recipient effector cell population, appear to be crucial for clinically relevant responses. Immunopathogenesis of human tuberculosis is orchestrated by multiple players (Table 1) in dynamic cascades, and the outcome depends on these balances between several subsets of immune cells as well as a number of cytokines and chemokines. Too little inflammation or too much inflammation can lead to detrimental effects by allowing *Mtb* to multiply and thrive or exaggerated immune response to be pathogenic to the host, respectively, whereas the right balance determines the immune response to win the race. For instance, terminally differentiated T cells may be used for immediate immune effector functions, yet long-term memory responses (usually defined by the cell surface markers CD45RA, CCR7, and CD62L) are required to contain pathogens or transformed cells.

Early differentiating stem-cell memory T cells (T_{SCM}), precursors of other memory cells including central memory T cells (T_{CM}), have enhanced self-renewal capacity and multipotency. Human T_{SCM} express high levels of CD95, CXCR3, CD122, and LFA-1 and are distinct from central T_{CM} in terms of surface markers, tissue localization, cytokine production, and in vivo turnover. This antigen-specific subset is preferentially localized to lymph nodes and virtually absent from mucosal surface; it is generated in the acute phase of viral infection and persists beyond removal of the antigen contributing in supporting long-term cellular immunity in vivo [23]. Therefore, the induction or adoptive transfer of these T-cell populations may be beneficial in anti-*Mtb*–directed immune responses. T_{SCM} have been demonstrated to persist, while preserving their precursor potential in bone marrow–transplanted patients for up to 12 years after infusion of gene-corrected hematopoietic stem cells, or mature lymphocytes that were tracked concerning their fate and activity [24]. Antigen-specific T_{SCM} can differentiate directly from naive precursors [25], correlating with IL-7 serum levels. T_{SCM} may be achieved by pharmacological activation of the WNT (wingless type, signaling molecule) pathway [26]. Alternate ways are being explored to achieve such a phenotype, for instance, using signaling inhibitors, for example, with inhibition of the AKT-1 signaling pathway [27]. The nature of antigen-specific immune cells, the anatomical localization, and homing patterns are crucial to mediate clinically relevant effects: T cells infused for adoptive therapies are trapped in the lungs where they encounter first a microcapillary network; inflammatory signals in case of tuberculosis would make intravenous application simple as T-cells are directly delivered to the lung, the first passage site. This also has an inherent risk of a "cytokine storm" once T cells encounter their nominal target antigen(s) [28].

CYTOKINES FOR THERAPY

Cytokines have been used with success to treat infections in primary immunodeficiencies; granulocyte colony stimulating factor in various infections such as *M. bovis* BCGosis in severe combined immunodeficiency as well as for the treatment of osteomyelitis due to *Aspergillus nidulans* in X-linked chronic granulomatous disease (X-CGD). Other interleukins include IL-2 for the treatment of chronic nontuberculous mycobacteria (NTM) pulmonary disease due to *Mycobacterium avium* complex (MAC) and *Mycobacterium chelonae* in patients with idiopathic $CD4^+$ lymphocytopenia (ICL). IL-7 has clinically been used for patients with progressive multifocal leukoencephalopathy resulting from infection by the John Cunningham virus with ICL. Other cytokine-based approaches include IFN-α to treat disseminated NTM disease (MAC) with autosomal recessive (AR) IFN-γR1 deficiency and disseminated Epstein-Barr virus (EBV) common variable immunodeficiency, as well as IFN-γ to treat hepatic abscess formation due to *Staphylococcus aureus* in the background of X-CGD, as well as disseminated NTM (with ICL or with AR IL12RB1 deficiency), BCGosis, or multifocal NTM with autosomal dominant partial IFN-γR1 deficiency (reviewed in [29]).

CELLULAR THERAPY: FROM DONOR LYMPHOCYTE INFUSION TO SPECIFIC-TARGETED T-CELL THERAPY FOR INFECTIOUS DISEASE PATHOGENS

Donor lymphocyte infusion (DLI) is a clinical procedure used after hematopoietic stem cell transplant (HSCT) to treat disease relapse by inducing the process of graft-vs-leukemia effect with the nonselective transfer of T cells from the original stem cell donor. At the same time, the DLI also contains antigen-experienced

T cells directed against viral pathogens. This is clinically relevant in the case of EBV or cytomegalovirus (CMV) nonmatched donors and stem cell recipients with increased risks of CMV or EBV disease associated with (CMV/EBV) seronegative transplanted immune cells and/or drug-induced immunosuppression associated with HSCT. The DLI contains the desired specificity against infectious (usually viral) targets [30, 31], which has been successfully used in the case of EBV^+ posttransplant lymphoproliferative disorder [32]. The T cells, contained in the DLI, may be derived from different sources—that is, matched sibling donor [30], matched unrelated donor (reviewed in [33]), or mismatched unrelated donor [34].

It became evident in the 1990s that the DLI is helpful not only to treat residual malignant disease, but also to treat infections, as it contains pathogen-specific T cells [35]; CMV, one of the major complications after HSCT, was the first target in cellular therapy, and T-cell transfer technologies soon become more refined (Supplementary Data).

The protective role of antiviral T cells infused to patients with allogeneic HSCT does only show the efficacy of antipathogen-directed T-cell therapy, yet also underlines the biology of immunosuppression in anti-*Mtb* immune responses. A retrospective study examining 2040 patients undergoing HSCT between 1997 and 2006 demonstrated an increased risk for tuberculosis in the immunocompromised population (3.52%) compared with the control group (0.38%); HSCT recipients with tuberculosis exhibited a higher rate of mortality compared with the nontuberculosis cases [36]. Compared with other populations of immunocompromised hosts, HSCT recipients exhibited the lowest frequency of *Mtb*-specific immune adaptive T-cell responses defined by the tuberculin skin test and IGRA [37].

The last decade has witnessed milestone developments in adoptive T-cell therapy to produce and consistently expand antigen-specific clinically relevant T-cell products. Technologies include adenoviral vectors, IFN-γ capture T-cell technology, and magnetic bead–mediated selection, generating specific T-cell clones, artificial antigen-presenting cells, and viral systems to transfect specific TCR (Supplementary Data). Cross-reactivity of TCR targeting pathogens and nonrelated target structures needs to be explored, as anti-*Mtb*–directed T-cell clones have been shown to cross-react to human central nervous system targets [38]. The immune effector role of B cells in anti-*Mtb* immune responses is discussed by Rao et al elsewhere in this supplement.

CHIMERIC ANTIGEN RECEPTORS

To confer novel antigen specificity, T cells can be manipulated genetically for clinical use by introducing novel synthetic chimeric antigen receptor (CAR) through various approaches to redirect these cells toward the target. It is important to note that (*i*) antigen specificity is linked with (*ii*) a signaling molecule and (*iii*) that it can be transferred to recipient effector cells (eg, T cells, γδ T cells, natural killer [NK] cells) with (*iv*) different vectors. CAR can also be engineered to be expressed transiently with choice of safety-check mechanism. One such option may be to separate the antigen for specificity of CAR T cells with the chimeric costimulatory receptor engaging a separate antigen.

CAR-modified T cells were first tested clinically in the human immunodeficiency virus (HIV) setting with the extracellular and transmembrane portions of the CD4 receptor for HIV envelope protein, fused to TCR-ζ signaling molecule (CD4ζ CAR). Autologous CD4ζ modified $CD4^+$ and $CD8^+$ T cells were given to HIV-infected patients with CD4 counts >50 μL and viral loads of at least 1000 copies/mL with or without IL-2 [39]. In addition to establishing safety and concept of the approach, the data from the study allowed to study trafficking of gene-modified T cells to mucosal sites, as well as their persistence after infusion. A modest effect on viremia was observed in a subsequent phase 2 trial with CD4ζ-CAR as adjunctive therapy along with highly active antiretroviral therapy [40]. The US Food and Drug Administration mandated long-term follow-up of 3 clinical trials revealed persistence of CAR T cells for at least 11 years after infusion at frequencies that exceeded average T-cell levels after most vaccine approaches [41], showing that passive transfer of transgenic target specific T cells can lead to establishment of long-term T-cell memory directed against the nominal target, a situation that may also be desirable in chronic infections or with multiple exposures. The best clinical results have been observed in chronic lymphocytic leukemia patients with CARs targeting the CD19 molecule containing the CD3ζ signaling module together with 4-1BB: CD19-specific CAR demonstrated high levels of antileukemia activity, ex vivo expansion, and high levels of T-cell persistence [42]. Polyclonal CAR^+ γδ T cells have been successfully generated retaining the expression of receptors displaying inherent antitumor activity [43, 44]. CAR technology has been translated into opportunistic fungal infections with *Aspergillus* to render cytotoxic T cells specific against fungi using the antibody directed against the pattern-recognition receptor Dectin-1 of the *Aspergillus* cell wall to activate T cells via chimeric CD28 and CD3-ζ (designated D-CAR) molecules, upon binding with the nominal carbohydrate antigen present on *Aspergillus*. The $D\text{-}CAR^+$ T cells exhibited specificity for β-glycan, which led to damage and inhibition of hyphal growth of *Aspergillus* in vitro and in vivo [45]. It is possible that anti-*Mtb* CARs could also be developed if a distinct target antigen could be identified that would qualify for (*i*) specificity of *Mtb*, (*ii*) frequently expressed by infected cells, and (*iii*) low or absent mutations in the target sequence.

A different approach to passively transfer antigen specificity is the transfer of T-cell receptors directed to the nominal *Mtb* target antigens displayed by major histocompatibility complex (MHC) class I or class II molecules. In short, TCRs directed

against a specific epitope (in this case: *Mtb* epitope) and displayed by a distinct MHC molecule are cloned and transferred into an appropriate vector system. The cloned epitope-MHC molecule can be used safely and effectively to transfer TCR reactivity to recipient immune cells, similar to the CAR approach. Retroviral, lentiviral [46], RNA-based systems (for short-term expression), [47], as well as newer, nonretroviral systems (eg, the "sleeping beauty system" [48]) may be used to effectively transfer T-cell specificity.

This approach would have certain advantages. First, the use of transgenic TCRs may be beneficial as *Mtb* is an intracellular pathogen and a number of *Mtb*-specific CD8 and CD4 epitopes have been described [49]. Second, the use of transgenic TCRs would remedy the situation that clinically relevant TCR specificities may not be available in the patient's TCR repertoire. Third, a number of studies using antiviral (eg, hepatitis, CMV) or antitumor target-associated antigen) specific and MHC class I [50] or class II [51] restricted TCRs have undergone phase 1 safety studies and have been successfully implemented in clinical trials with promising clinical responses. Fourth, the recipient effector cells can be manipulated ex vivo to actively produce the cytokine profile desired for intracellular infections (eg, a multifunctional Th1 profile). This antigen-specific transfer could also have downsides. First, such therapies are cost-intensive and need a Good Manufacturing Practices set-up. Second, off-target toxicity (in this case cross-reactivity to vital "self" target antigens) may not be predictable for each case [52]. Third, current studies with lentiviral vectors have been shown to be safe, yet nevertheless integrate into the genome. Fourth, such TCR reagents need to be matched for the patients' genetic makeup (which could be remedied by targeting the most frequent MHC class I/II molecules in the treatment group). Fifth, there is a risk for mutation in *Mtb* epitopes [53] that may lead to aberrant T-cell responses or defective recognition of the mutant target antigen. Sixth, the *Mtb* antigen would need to be expressed on the cell surface that may be impaired by immunosuppressive cytokines that downregulate either *Mtb* target gene expression and/or MHC class I/II on infected cells [54].

However, less diverse recognition structures may help to provide a more universal TCR arsenal—for instance, TCRαβ TCRs restricted by CD1 molecules, presenting *Mtb* targets [55], for example, TCRγδ T cells detecting *Mtb* antigens (see below), or more recently identified T cells (mucosal-associated invariant T cells) cells that are restricted by MR1 [56]. The latter cellular population could be interesting for adoptive T-cell programs as well as the use of more commonly MHC class II molecules, such as HLA-DP*04:01, which is shared among 60% of humans [57]. This fact has been used to create TCR against cancer target antigens that are restricted by HLA-DP*04 and therefore applicable for larger cohorts of patients [58]. Soluble TCRs against target antigens had been developed previously with very limited success due to the intrinsic low avidity of the TCR (with the proper CD3 assembly), yet newer developments in grafting proteins to therapeutically and clinically acceptable scaffolds to improve antigen binding, while avoiding cross-reactivity, may revitalize this field [59].

TIMING OF INTERVENTION

Adoptive T-cell therapy using tumor-infiltrating lymphocytes (TILs) has been best studied in metastatic cancers. The most promising results with TIL therapy has so far been shown in patients with metastatic malignant melanoma, where a response rate >50% has been consistently reported [60]. Vital lessons were learned from the clinical success of TIL. More recent data showed that the clinical success of TIL in mediating long-term and effective tumor regression is related to the recognition of "private" mutant target antigens [61]. This may be due to a selection process—that is, that commonly shared targets, expressed by transformed cells, may have already been removed. It shows also that targeting mutant epitopes appears to be safe as the non-mutated target epitopes, displayed by nontransformed cells, are not recognized: Targeting mutant epitopes bears less risk for collateral damage by cross-reactive T-cell responses. Differential recognition of wild-type vs mutant target *Mtb* epitopes have been described [62]; the prevalence of different *Mtb* strains, their mutation pattern [42], and the impact of mutant *Mtb* epitopes on the breadth and efficacy of a functional T-cell response has to be explored. Second, T-cell therapy has been so successful because the patients are "conditioned" with a nonmyeloablative therapy, mostly using cyclophosphamide and fludarabine. Cyclophosphamide decreased regulatory T cells by decreasing intracellular cAMP [63]. Cyclophosphamide reduces in concert with fludarabine T lymphocytes, without affecting the patients' stem cells. This has certain advantages, as (*i*) the newly infused T cells will not have to compete for cytokines, such as IL-7 or IL-15; (*ii*) there is more "space" for proliferation of clinically relevant T-cell clones (expansion of T cells is limited by the "setpoint" of the absolute number of T cells for each (healthy) individual; and (*iii*) these drugs may also decrease the production of immunosuppressive factors. A similar situation—that is, decreasing the number of T cells in the peripheral circulation without inducing clinically relevant immunosuppression—may be beneficial for patients with tuberculosis, as some tuberculosis patients exhibit lymphocytosis [64], which may inhibit expansion of newly triggered T-cells of *Mtb* specificities.

REDUCING ANTIGEN LOAD

There would be a theoretical advantage in administrating TIL in the adjuvant setting for resectable cancers that have very high recurrence rates [65]. Addressing minimal residual disease

that is not detectable by current imaging methods would provide TIL with a potentially more favorable (Th1) environment, and less antigenic burden. The immunomodulatory tumor microenvironment (particularly those with abundant tumor stroma that would restrict the immune cells from reaching the target cancer cells) can be inhibitory to infiltrating immune cells. Instead, targeting remaining cancer cells might provide patients with a chance of cure. Application of TIL to large tumor burdens, similar to large *Mtb* antigen burden, may lead to tissue destruction, an overt proinflammatory reaction, and a tumor-lysis syndrome [66]. More preclinical studies may be needed to address the timing of cell-based therapeutic interventions—for example, in a treatment setting, where the immune system is confronted with a large antigen (tumor or *Mtb*) burden, or in an adjuvant setting, where antigen load has been reduced (eg, after removing tuberculosis-positive lesions in XDR tuberculosis with surgical intervention) and where immune cells would encounter a more favorable environment to mediate long-term immune protection.

γδ T CELLS IN THERAPY OF INFECTIOUS DISEASES AND CANCER

The γδ T cells, representing <5% of total T cells, can be grouped in 2 populations depending on their TCR: Vδ1 γδ T cells, present in mucosal epithelium site (ie, skin, intestine), and Vδ2 and Vγ9 γδ T cells circulating in the peripheral blood [67]. Vγ1 and Vδ3 γδ T cells (also called Vδ2neg γδ T cells) were described [68] to drastically expand following a CMV infection in kidney recipients during the lymphopenic period. γδ T cells have been shown to contribute to relevant and effective immune responses to EBV-positive B cells and [69] or to *Mtb* infections in nonhuman primates. In a macaque model, γδ T cells contributed to *Mtb*–directed immune responses by the production of cytokines, IFN-γ, and perforin [70]. Clinical applications of γδ T cells were performed using the Vγ9Vδ2 γδ T-cell subset, which is the most abundant in the peripheral blood, activated by aminobisphosphonates in combination with IL-2: Most clinical trials using γδ T cells did not show promising results [71], with some striking responses in individual cases [72]. However, anti-*Mtb*–directed cytolytic TCRγδ T-cell responses have been described to be restricted to CD1c [15]; such TCRs may be candidates for T-cell–driven expansion and/or *Mtb* antigen–driven TCRγδ-transfer into recipient cells if shared *Mtb* targets would represent the nominal antigens, avoiding the challenge of matching the diverse MHC class I or class II background in the human population in adoptive therapies.

OUTLOOK

At present, our understanding of the complexity of human immune defenses in tuberculosis is still limited to design individually tailored immunotherapies. However, T-cell–based interventions could tip the balance to augment *Mtb*-specific immune responses to achieve relapse-free cure, especially when the effect of antituberculosis drug treatment does not deliver, as in MDR tuberculosis and XDR tuberculosis. The use of T-cell therapy in cancer as well as for prophylaxis and treatment of infectious diseases following HSCT in selected centers around the globe is rapidly expanding, and immunotherapy was highlighted as the breakthrough for cancer in 2013. Similar tools available for precision medicine may now be taken forward for drug-resistant and refractory tuberculosis patients to generate antigen-specific protective immune response with the hope for cure of a significant number of failed treatment cases in high-prevalence drug-resistant-tuberculosis settings. The cost per patient of treating XDR tuberculosis is approximately US$30 000 in South Africa [73] and approximately US$200 000 in Europe [74]. The costs of consumables for cell therapy for failed drug-resistant tuberculosis cases may be in the range of US$5 000, which would be rather limited in comparison to the current MDR/XDR tuberculosis treatment costs. Host-directed therapies may provide hope for cure for individual patients, associated with an economic return from the patient's productive life, as well as curtailed costly second-line therapy and tuberculosis healthcare costs.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Financial support. A. Z. receives funding from the UK Medical Research Council; European Union FW7 Rid-RTI; European Developing Countries Clinical Trials Partnership; UBS Optimus Foundation, Switzerland; and the National Institute of Health Research Biomedical Research Centre, University College Hospitals, London, UK. M. M. receives funding from Hjärt-lungfonden (Swedish Heart and Lung Foundation); Vinnova; Vetenskåpsrådet (Swedish Research Council); and the European Developing Countries Clinical Trials Partnership.

Supplement sponsorship. This article appears as part of the supplement "Advances in Tuberculosis Research: A Blueprint for Opportunities." This article was sponsored by the Karolinska Institutet.

Potential conflicts of interest. All authors: No potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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