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Guiding Antiviral Cell Therapy Approaches with an Online Resource of Clinically Scored Epitopes, T-Cell Receptors, and B-Cell Receptors

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Keywords

Adoptive T-cell transfer · Antibodies · Antigens · B-cell receptor · Epitope · Immune response · Infections · MHC · T cells · T-cell receptor

Abstract

Introduction: The clinical application of cell-based immunotherapies is a rapidly emerging field, and recent advances in gene therapy have opened up a new era of innovative treatment approaches. Introducing a specific T-cell receptor (TCR) against viral epitopes or chimeric antigen receptor (CAR) into T cells and effector cells allows reprogramming of their specificity and utilization for advanced therapeutic applications in infectious diseases and virus-induced malignancies. Many technologies have been developed to genetically engineer T cells, and existing databases in silico predict or describe identified viral epitopes, TCRs, or B-cell receptors (BCRs). However, their therapeutic application is still hampered by limited knowledge on their clinical impact. ***Methods:*** An open-access online resource was developed, integrating a data-mining algorithm scoring the epitopes, TCRs, and BCRs (ETB database) according to clinical evidence. ***Results:*** We hereby present a new level of clinical evidence-based knowledge transfer for

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selecting individual protective TCRs or BCRs for therapeutic application. The database is publicly available at https://app.bitcare.de/epitopeFrontend/. ***Conclusion:*** Redirecting T-cell specificity by genetic engineering using clinically protective TCR or CAR sequences will not only bring significant progress to the field of adoptive T-cell therapies but also lay the groundwork for broader applications such as off-the-shelf approaches.

Introduction

Advances in hematopoietic stem cell transplantation (HSCT) and solid organ transplantation have yielded improved survival benefits for patients suffering from (malignant) hematopoietic diseases, inborn errors of immunity, or end-stage organ failure. On the downside of delayed immune reconstitution and medical immunosuppression viral infections from persistent or newly acquired viruses pose a significant risk for severe or life-threatening complications [1–4]. For patients resistant to antiviral therapy, the transfer of virus-specific T cells (VSTs) has emerged as a promising new treatment approach for many viral entities [5, 6]. In addition, a relevant subset of patients suffers from therapy-limiting side effects of antiviral treatments and is therefore eligible for antiviral T-cell therapies. Various techniques of cell product manufacturing from either stem cell donor or (partially) HLA-matched third party donors have been developed using in vitro cell expansion after antigenic stimulation or direct isolation following cognate antigen recognition [7–11]. All strategies have in common that potential donors must have been previously exposed to the virus to form a memory T-cell response (usually referred as "seropositive" donors). So far, strategies aiming at producing therapeutic VSTs from naïve donors have been laborious and of limited efficacy. To circumvent the need of seropositive donors, strategies have been developed to identify [12–15] and introduce specific T-cell receptor (TCR) sequences recognizing viral peptide epitopes in the context of HLA molecules or chimeric antigen receptors (CARs) binding to surface protein structures of infected cells using various techniques of genetic modification [16–21].

All strategies are based on the knowledge of protective TCR or B-cell receptor (BCR) sequences to be used to target effector cells to virus-infected patient cells. The knowledge of viral epitopes has increased dramatically in recent years, leading to difficulties in data overview for the individual researcher and/or clinician. Several databases have been developed recently to (1) identify immunogenic T-cell epitopes in silico, (2) share cognate TCR sequences, and (3) summarize knowledge on neutralizing antibodies and BCR sequences. While the existing databases are comprehensive and highly useful, they do not categorize epitope or immunoreceptor information based on information about clinical aspects such as control of infection in vivo, remission or protection from infection after immunotherapy. For example, TCRdb contains a large number of TCR sequences from a variety of clinical samples and offers flexible search and comparison options, but clinically relevant information on function and specificity of individual TCRs is limited [22]. VDJdb is a curated resource focused on specific TCRs, but it also lacks detailed information on features relevant for clinical application [23, 24]. Currently, the Immune Epitope Database and Tools (IEDB) is the most comprehensive source of T- and B-cell epitopes, 3D structures, TCRs and BCRs, their in vitro characterization and it also links epitopes to TCRs and BCRs (IEDB; www.iedb.org) [25, 26]. Epitopes and immunoreceptors are provided with descriptions of assays used to characterize them, with a binary evaluation of positive or negative outcome of these assays, and to literature references. However, linking the published knowledge on epitopes, TCR, and BCR sequences to clinically meaningful data on in vivo immunogenicity, effectiveness, or protection remains challenging.

Therefore, we set out to develop an open-source database that links viral proteins, virus-derived epitopes, cognate TCR and BCR sequences with information on clinical context and therapeutic relevance. Based on information on how the effectiveness was demonstrated (in vitro, in vivo model, in vivo human [natural], or in vivo human [clinical trial]), an algorithm was developed to provide the user with a score reflecting stages of clinical evidence and development as well as protective capacity. We expect application in future orthotopic TCR and CAR-T-cell development and facilitate the design of individual personal antiviral T-cell therapeutics.

Methods

Database Programming

We implemented a robust and scalable architecture utilizing various technologies for the web application. The front end was developed using Angular, a framework for building dynamic and responsive user interfaces. On the backend, we implemented a Java-based solution to provide RESTful services to communicate between the client and server. Apache Tomcat was the application server, providing the environment for running the backend application. For Object-Relational Mapping (ORM), we used Hibernate, which facilitates interaction between the Java objects and the underlying MySQL database. Authentication and authorization were managed using the

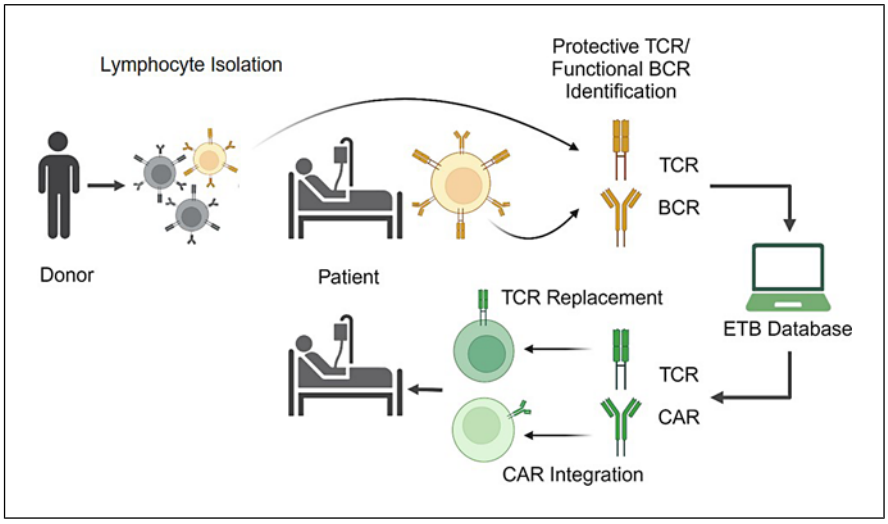

Fig. 1. Scheme of redirecting T-cell specificities for therapeutic application. The ETB database harbors T-cell receptor (TCR) and B-cell receptor (BCR) sequences identified in patients after successful clearance of the infection or in protected healthy donors. From those, TCR sequences can be selected to reprogram T cells for adoptive transfer into a patient. Therapeutic chimeric antigen receptor (CAR) T cells can be generated from protective B-cell receptor sequences (BCRs) (created with BioRender).

Shiro framework, ensuring secure access control. To enhance portability and consistency across different environments, the entire application was packaged and deployed using Docker containers.

Analyses of Database Content

Data were extracted from the database and analyzed via Microsoft Excel (Microsoft Corporation, Redmond, Washington, USA). Frequencies were determined by dividing the absolute number of all epitopes, TCRs, or BCRs with the respective information available. Results were graphically illustrated via GraphPad Prism (GraphPad Inc., San Diego, California, USA).

Results

Redirecting T-Cell Specificities for Therapeutic Application

Novel developments in site-directed genetic engineering technologies and large-scale identification of T-cell antigens circumvent the need for virus-experienced donors and allow for adoptive T-cell transfer approaches in naïve donors. Therefore, in the first step, protective TCR or BCR sequences can either be isolated from expanding immune cell populations correlating with a patient's clearance of infection or from protected healthy individuals' memory T-cell populations (Fig. 1). Recent progress in single-cell sequencing technologies and large-scale T-cell antigen decoding allow the setup of comprehensive epitope, TCR, and BCR databases. From those, either protective BCR sequences can be used to generate CARs or protective TCRs can be selected, both to be introduced into a T cell to redirect its specificity (Fig. 1). Thereby, antigen-specific T-cell products for therapeutic application can be manufactured by redirecting naïve donors' T cells.

Database Structure

The ETB database has been set up to harbor epitopes, TCR, and BCR sequences linked to the respective clinical data relevant for selection for adoptive T-cell therapy (ACT), such as HLA restrictions or evidence levels. The ETB database web page provides users with two options: the home page and the search page. The home page summarizes background information on the database, scientific background, and information on the calculation of the clinical score. The search interface has been pretested to be clear and intuitive and allows searching by the basic elements pathogen, MHC molecule or antigenic protein (Fig. 2a, c). Additionally, the search can be further refined by specific epitope, TCR, or specific BCR sequences. A "finder" feature automatically assists in selecting the respective elements from a drop-down list in order to unify the highly variable nomenclature of the search elements. Ticking the additional box "Show only clinically confirmed results" allows further filtering of the results for human clinical application from patients with a treatment response.

The results interface is updated simultaneously during entry and contains four tabs: the epitope, TCR, BCR, and studies tab (Fig. 2b, c). The fields displayed in the epitope tab include the sequence and the source of the respective epitope in terms of virus and viral protein, the presenting MHC molecule, the score of the epitope, and a link to the epitope-related studies of the studies tab. The TCR tab displays the fields α chain and β chain sequences of the TCRs fulfilling the search criteria, the related epitope, the presenting MHC molecule, the score, and a link to the specific TCR-related studies of the studies tab. Similarly, the BCR section includes the antibody name, heavy chain and light chain sequences, the related epitope, the score, and the link to the BCR-related studies of the studies tab. Users can sort the results list by score by clicking the column header. Entering the list of studies via a specific

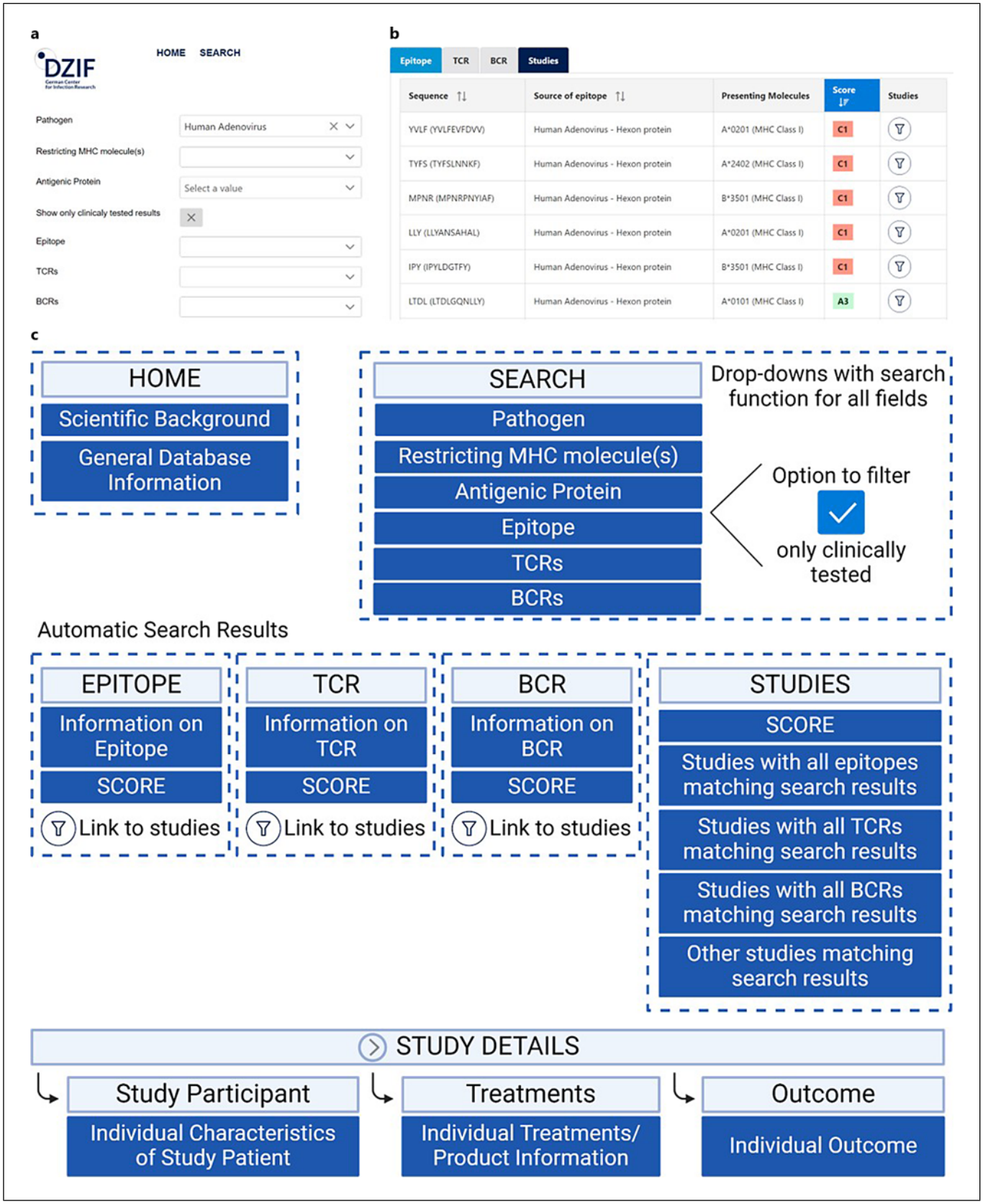

Fig. 2. ETB database user interface and database structure. User interface: search page (**a**) and results page (**b**). **c** Schematic overview of database programming structure.

epitope, TCR, or BCR link enables additional filters for the studies related to this specific epitope, TCR, or BCR. Entering the list of studies via the studies tab directly results in a complete list of studies fulfilling the search criteria from the search interface. The studies tab displays the title, the PMID, and the Clinical Trials registry identifier, the year, the authors, the score, and the type of the study.

In order to browse details from a clinical study, users can click on the arrow icon, which will open a drop-down menu with general information on the study, such as clinical phase and endpoints. Figure 2c depicts the programming structure: for each individual or treatment group, three field groups can be opened separately in hierarchical order: (1) a field group with general patient characteristics on biological sex, age, indication for HSCT, HSCT donor type, HLA type of patient, HLA match with HSCT donor and indication for cell transfer; (2) a field group with the T-cell transfer details T-cell depletion, T-cell donor type, HLA type of T-cell donor, days of T-cell transfer post-HSCT, the dosage of T cells, production technique of T cells; (3) a field group with the outcome details severity of symptoms before and after the transfer, viral load outcome, infusional toxicities, side effects, as well as GvHD before and after T-cell transfer. In case the publication does not provide an element, the respective fields are not displayed for the user to keep the interface simple.

Database Content

The ETB database captures data from systematic literature searches as well as data from direct submissions by partners of the epitope identification project consortium. To date (February 2, 2025), 538 epitopes, 141 TCRs, and 36 BCRs are included (Fig. 3a), but the database is continuously extended.

The database's epitopes cover a broad range of MHC class I and MHC class II HLA allotypes (Fig. 3b, c). Most frequent HLA restrictions of the database's epitopes are A*02:01 (12%), B*08:01 (9%), B*07:02, DRB1*13:01 (5% each), A*03:01, B*35:01, and DRB1*0101 (each 4% of all database's epitopes), making up nearly half of all epitopes (Fig. 3b). Of the database's TCR sequences, 29% also cover A*02:01 restrictions, but TCR sequences most frequently cover B*35:01 (31%). Further, each 16% of the database's TCR sequences are restricted to B*07:02 and A*01:01 and 1.4% to B*08:01 (Fig. 3b).

The database covers Epstein-Barr virus (EBV), adenovirus (AdV), human herpesvirus 6 (HHV-6), cytomegalovirus (CMV), severe acute respiratory syndrome coronavirus-2, and JC virus epitopes, TCRs, or BCRs. Of epitopes, 61% were identified from EBV, 18% from CMV, 8% each from AdV and HHV-6, 3% from severe acute respiratory syndrome coronavirus, and 2% from JC virus antigens (Fig. 3d, left). Most of the database's TCRs target CMV (85%), followed by EBV (12%), AdV and HHV-6 (each 1%; Fig. 3d, middle). All BCRs included in the database target CMV (Fig. 3d, right).

Scoring Algorithm

To select the most suitable TCR or BCR candidate for a patient's individual ACT product, the immune receptor, and epitope sequences are not only linked to the clinically relevant data but also clinically scored. Therefore, a default epitope and receptor scoring algorithm has been designed to guide the user to the clinically relevant and valid data. According to the availability and evidence level of clinical data, the epitopes, TCRs, or BCRs are scored in A 1–4, B or C 1–3 (Fig. 4a): An epitope, TCR, or BCR is scored C after identification with or without in vitro data available. Thereby, C1 stands for a descriptive report on the identification of its sequence only, and C2 for additional in vitro data demonstrating the binding of the isolated TCR/BCR to its epitope in an assay system independent of the assay for identification. C3 stands for additional availability of functional activity, such as cytokine release or cytotoxicity. An epitope, TCR, or BCR is scored B as soon as it has been reported in a nonhuman individual responding to viral infection in vivo. An A score stands for the identification in a human individual responding to viral infection in the context of immunotherapy or remission of acute disease. Depending on being reported in a case report, phase I clinical study, phase II clinical study, or phase III clinical study, it is classified as A1 to A4, respectively (Fig. 4a).

Applying the algorithm to the epitopes results in 54% with high clinical evidence level scores, 29% A1, 6% A2, and 19% A3 score. Of the epitopes, 44% show C1 and 2% show C3 in vitro evidence level (Fig. 4b). Of TCR sequences, 98% show in vitro confirmation scores, whereas 2% have been confirmed in clinical trials (Fig. 4c). BCRs consist of two-thirds (67%) C2 scored and one-third C1 scored BCR sequences (Fig. 4d). Neither of the database's epitopes, TCRs, or BCRs were functionally confirmed in nonhuman in vivo studies (score B). Consequently, the studies are scored A1–A3 (22, 19, and 20%, respectively) and C1–C3 (26, 7, and 6%, respectively, Fig. 4e).

Discussion

ACT with VSTs after allogeneic HSCT represents a rare clinical indication that emerged to routine application of advanced pathogen-specific cell therapy [5, 6]. Recent developments in site-directed genetic engineering technologies opened a new era of reprogramming T cells from naïve donors for therapeutic application [15–19, 21]. The complex nature of an antigen-specific T-cell therapy makes it cumbersome to identify clinically

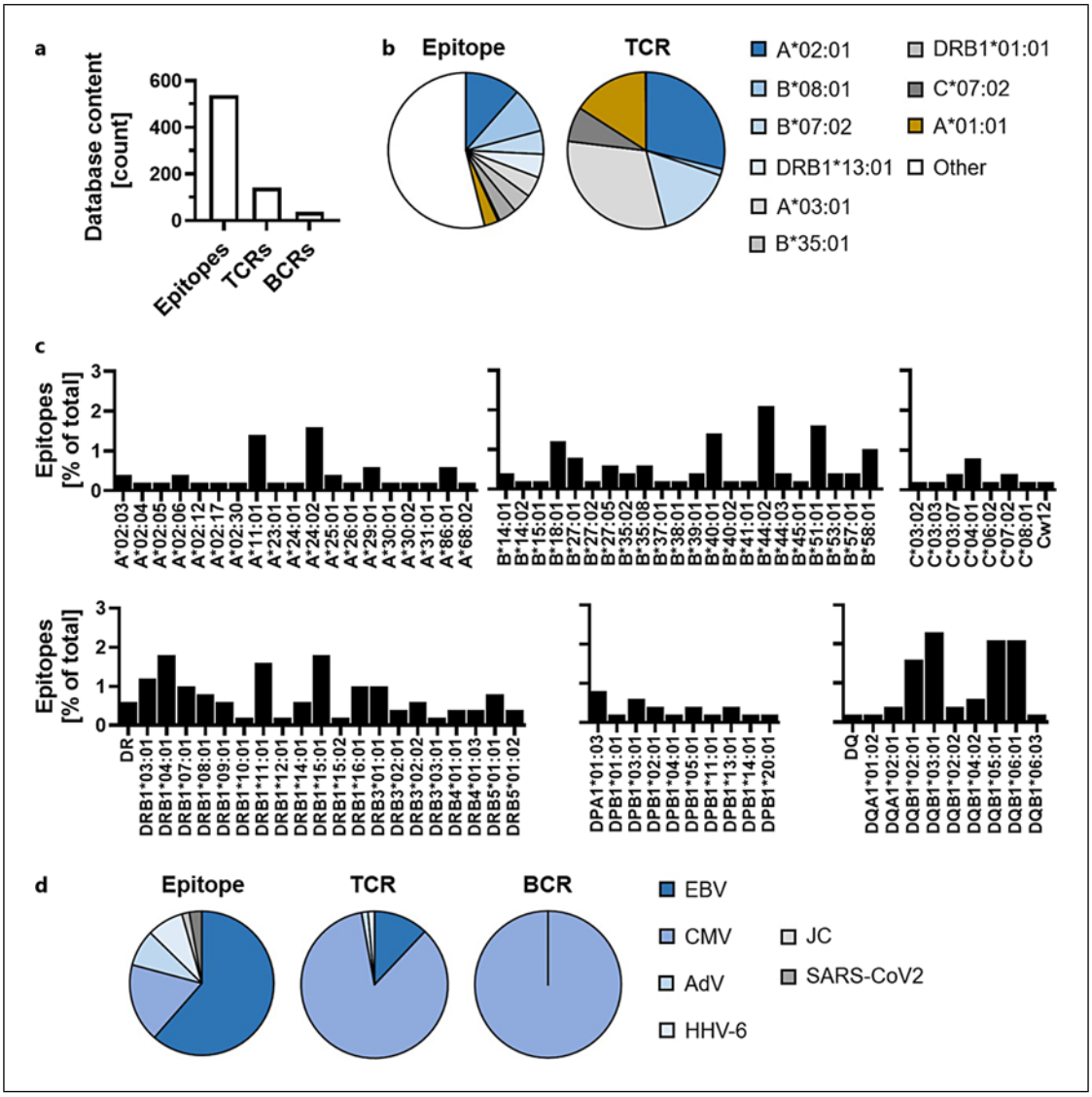

Fig. 3. Database content. **a** Absolute number of epitopes, TCR, and BCR sequences captured in the database. **b** Frequency of epitopes restricted by the respective HLAs among all database's epitopes in %. **c** "Other" HLA restrictions within HLA-A, HLA-B, HLA-C, DR, DP, and DQ of the database's epitopes. Frequency among all database's epitopes in %. **d** Frequency of viral epitopes (left) identified from the respective virus antigens. Frequency of TCRs (middle) and BCRs (right) targeting the respective virus antigens. Frequency among all database's epitopes/TCRs/BCRs in %.

relevant specificities. Nevertheless, the intentional specificity of cell-based immunotherapies is essential for efficiency, specificity, long-term maintenance of protection, and low risk of side effects.

For various viruses, decades of research have established a body of knowledge about major epitopes in a number of antigens and TCRs targeting them in specific HLA-I context [22–26]. However, typically, this information is most extensive for HLA allotypes that are of high frequency in Western countries and for viral proteins that contain immunodominant epitopes presented by such HLAs. In addition, available data are focused on viral types and strains that are most prevalent or have historically been designated as representative laboratory strains. Studies on virus-specific TCR repertoires and identification of epitope-specific TCR sequences have mostly been limited to a subset of those epitopes that fulfill abovementioned conditions. Therefore, major challenges in this field are (1) the characterization of epitopes for additional relevant antigens, HLA restrictions, and pathogens and the immunoreceptors targeting them, (2) identification of those epitopes and epitope-specific TCRs or BCRs that promise to confer the best protection in the absence of toxicity, and (3) organization of this ever enlarging body of knowledge in a form that makes it readily applicable for disease prediction, immunomonitoring, and cellular therapy. Ultimately, clinically meaningful spontaneous

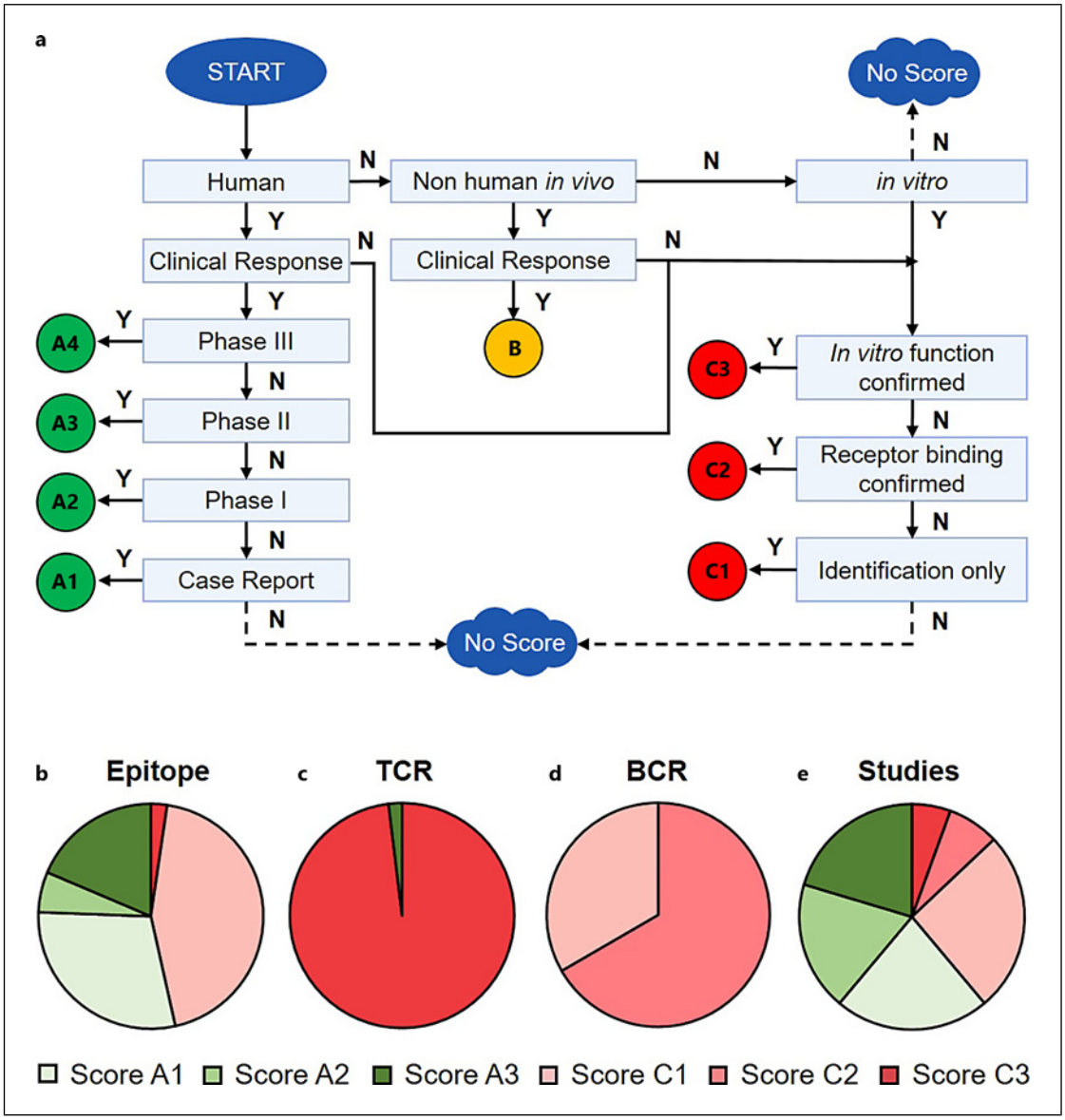

Fig. 4. ETB database score. **a** Schematic overview of score algorithm programming. Frequency of epitopes (**b**), TCRs (**c**), BCRs (**d**), studies (**e**) among all epitopes/TCRs/BCRs/studies in the database scored in the respective group according to the algorithm described above.

or therapeutic immune responses via TCRs and BCRs should be readily available to clinicians needing diagnostic and/or therapeutic decisions. A simple use case is the adoptive transfer of VSTs for immunocompromised patients with viral reactivations post-stem cell transplantation. In the high-risk setting of seronegative stem cell donors, a virus-specific T-cell product can be generated by integration of a highly potent virus-specific TCR by genetic engineering. The ETB database could support preselection of TCRs with high clinical relevance and data validity based on the viral infection and HLA allotype.

While the human cellular immune response to pathogens is highly individualized, it nonetheless shows characteristic, largely conserved patterns for epitopes and corresponding TCRs. For example, many of the well-characterized CMV $CD8^+$ and $CD4^+$ T-cell epitopes produce a lifelong T-cell response in a majority of CMV carriers of the appropriate HLA type [27–29], and even the sequence of TCRs specific for a given epitope is often entirely or largely conserved among a majority of carriers [30–33], giving rise to a considerable degree of "publicness" of the specific T-cell response. It has not been possible to date to predict the epitope specificity of TCRs in the absence of prior empiric information about specific epitope/TCR sequence correlations [34], but progress in this area might be anticipated in the near future, especially if the state of information on specific

TCRs is becoming available in comprehensive, quality-checked, scored datasets.

While existing databases are expanding, comprehensive and highly useful, they do not categorize epitope or immunoreceptor information based on information about clinical aspects such as control of infection in vivo, or remission or protection from infection after immunotherapy [22–26]. The ETB database presented here is designed and intended to facilitate this information derived from clinical translation and applicability. It introduces a scoring method that places particular emphasis on two aspects: first, the context of epitope, TCR, or BCR identification (in vitro, nonhuman primates, in humans); second, the degree of evidence for functional and/or protective relevance according to the respective context. In this respect, epitopes verified in clinical trials to be immunogenic and protective reach the highest scores in this database.

Taken together, our present categorization and scoring system represents a clear and simple framework for evaluating epitopes and immunoreceptors and estimating their effectiveness in clinical application. Thereby, it fills an important gap in available databases. Within a pilot testing phase, feedback from early test users – including clinicians and researchers in the field – was implemented to enhance usability and user experience. Improvements include a color-coded score display (ranging from red for low to green for high clinical relevance and validity), with entries lacking a score automatically moved to the bottom of the table. Further, each entry in the epitopes or receptors tab now provides a quick reference button to the respective citation details in the Studies tab. Moreover, a filter option has been added to display only clinically validated entries, allowing users to focus on translationally relevant data. Additionally, a background tab was introduced to offer broader context and background, supporting users with varying levels of expertise. We intend to refine and enhance our evaluation approach in further versions of our database. Further improvements will include specific evaluation and scoring of the degree of quantitative and temporal association of particular epitope-specific responses and immunoreceptors with remission and long-term suppression of infection in the context of immunotherapy and immune reconstitution in patients after transplantation and patients with other types of immunodeficiencies.

In the future, automated and artificial intelligence-based data extraction and evaluation will compete with manual curation in collecting and evaluating such complex data. In this regard, a combination of automated data collection, manual curation, and expert evaluation will help make the best clinical use of the increasing amount of information in this expanding field. Interfaces with other specialized databases may broadly expand and enhance the available knowledge on clinically meaningful immune responses in viral infection.

Acknowledgment

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Statement of Ethics

Publicly available datasets were used in this project. Thus, additional ethics approval was not required. An ethics statement was not required for this study type as it is based exclusively on data extracted from https://pubmed.ncbi.nlm.nih.gov/.

Conflict of Interest Statement

F.Ko. is the director and A.M. is an employee of Bitcare GmbH. B.E.-V. was a member of the journal's Editorial Board at the time of submission. All other authors declare that they have no conflicts of interest.

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Author Contributions

The project concept was set up by T.K., B.E.-V., U.B., D.H.B., B.M.-K., and T.F. Design of database was set up by T.K., B.E.-V., U.B., L.G., D.A., B.M.-K., and T.F. Scoring algorithm was set up by T.K., B.E.-V., A.M., B.M.-K., and T.F. Database and algorithms were programmed by F.Ko. and A.Me. M.D., L.G., and M.R. filled and tested the database. J.M., A.Mo., F.Kl., C.K., D.H.B., and E.I. contributed with large datasets. T.K., B.E.-V., A.M., M.R., F.Ko., A.Me., S.W., and B.M.-K. designed and drafted the manuscript. The manuscript was reviewed by all authors.

Data Availability Statement

The ETB database can be freely accessed at https://app.bitcare.de/epitopeFrontend/. The contents of the database were summarized by the author's best knowledge. We can be held liable only by general laws for our own contents. As a provider of online data, we can be held liable for external contents only once we have knowledge of a concrete infringement of law. However, we cannot guarantee that the content is correct, complete, or up-to-date. Any medical or genetic information present in the database is provided for research, educational, and informational purposes only. It is not in any way intended to be used as a substitute for professional medical advice, diagnosis, treatment, or care.

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