The Use of the Immune Epitope Database to Study Autoimmune Epitope Data Related to Alopecia Areata

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The Immune Epitope Database (IEDB) is a repository of published epitope data for infectious diseases, allergy, transplantation and autoimmunity. Herein we provide an introduction to the IEDB search interface, focusing on data related to autoimmune diseases, including alopecia areata (AA). We demonstrate how common questions related can be answered, such as how to search for specific autoantigens, epitope sequences, response types (B- and/or T-cell assays), or host, as well as how to search for epitopes of known major histocompatibility complex restriction and for data related to a specific disease. Our survey of the data found that while as a whole Autoimmunity-specific records represent a significant portion (~30%); epitopes reported for AA are remarkably few, just 23 epitopes from six antigens. This reveals a significant knowledge gap for AA, and suggests that additional mapping of epitopes and identification of novel AA-associated autoantigens is warranted. Citing recently published examples, we show how bioinformatic, proteomic, and technological advances make it now increasingly feasible to identify epitopes and novel antigens in human disease. The goal herein was to increase awareness of the IEDB as a free resource for the scientific community and to demonstrate its use in finding (existing) and analyzing (prediction) epitope data.

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INTRODUCTION

The Immune Epitope Database and Analysis Resource (IEDB; IEDB.org) is an NIAID sponsored freely available resource that serves as a warehouse of published antibody and T-cell epitope data (Vita *et al.*, 2015). As of March 2015, it hosts >128,000 different sequences and structures, and nearly 800,000 curated experimental assays. As we will briefly discuss below, the IEDB's design allows for highly granular searches including, for example, the epitope structure, the epitope's derivative antigen (or autoantigen), host, disease associations, antibody, and/or T-cell assays of interest, references, as well as numerous other potential criteria.

The scope of the IEDB includes four broad disease categories: infectious disease; allergy; autoimmunity; and transplantation. In addition to the database as an epitope repository, the IEDB also houses a number of analysis tools with capability as diverse as epitope prediction, three-dimensional visualization, and population coverage. It is important to point out that the IEDB does not generate experimental data; it simply captures published epitope data and provides tools to predict and analyze epitopes.

THE IEDB ALLOWS FLEXIBLE QUERIES TO RETRIEVE EXPERIMENTAL DATA

The design of the database and associated query strategies allow the user to search the data using six main areas. These include, epitope, antigen, assay, major histocompatibility complex (MHC) restriction, host and disease. Figure 1 provides a screen shot of the IEDB's main search interface (IEDB.org) showing these six main ''search panes.'' From each main search pane the user can enter or select criteria for their query of interest. For example, in the epitope pane, the user can specify the nature of the epitope (linear, discontinuous, or non-peptidic), its sequence, whether to search for exact or homologous sequences, and so on. In the Antigen pane, one can enter a protein name or alternatively, search by its derivative organism. This can include pathogens (virus, bacteria), allergens, or even self, as would be the case with autoantigens. The antigen-specific search can be focused on a specific protein or set of proteins, specified by using a single branch on our protein tree menu.

The assay pane can be used to limit the search to specific ''assay types''. This is accomplished by selecting the response type of interest at the high level: T-cell assays, B-cell assays, or MHC ligand assays. Similarly, the MHC restriction and host panes allow the user to limit or specify search parameters related to MHC restriction as defined in the assay, and/or to specify a particular host, whether human or animal model. Lastly the disease pane allows the user to choose among the four main categories of disease, infectious, allergy, autoimmune (AI), and transplant-related, referring to the clinical manifestation of the host.

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Abbreviations: 2D, two dimensional; AA, alopecia areata; AI, autoimmune; DENV, dengue virus; IEDB, Immune Epitope Database; MC1R, melanocortin 1 receptor; MHC, major histocompatibilty complex; ORF, open reading frame; T1D, type I diabetes

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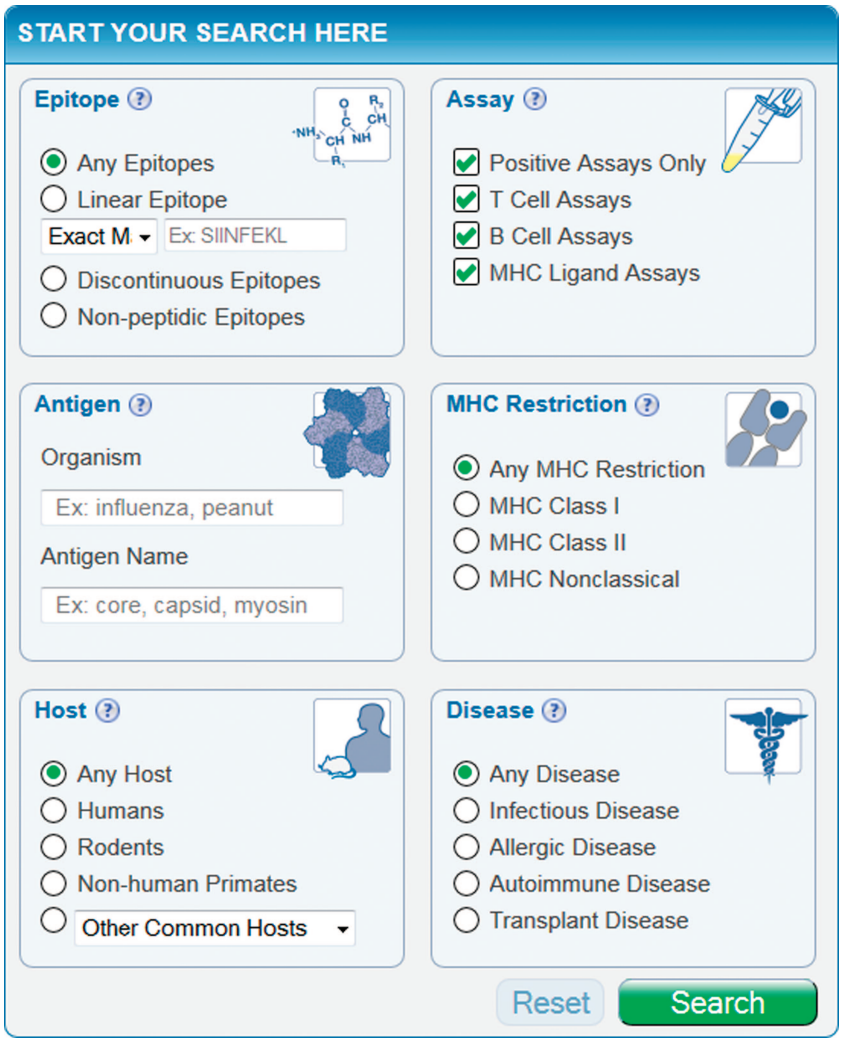

Figure 1. Immune Epitope Database (IEDB) Search Interface. A screen shot showing the main search interface on IEDB.org. The interface is comprised of six main ''search panes,'' epitope, antigen, assay, major histocompatibility complex (MHC) restriction, host and disease, which allow the user to select specific criteria pertaining to the nature of the epitope(s) of interest (e.g., linear T-cell epitopes from protein X) or to limit their query to certain subsets of the cumulative data (e.g., particular host with disease).

Once the initial query criteria are selected and the user hits ''search,'' a results page will be generated. The results page is organized with a central tab delineated summary table, as well as access to additional detailed search panes along left-hand side (Figure 2). On the Results table there are four tabs: (i) epitopes, (ii) antigens, (iii) assays, and (iv) references. Each tab shows in parentheses the total number of records from the latest query and can be clicked open to reveal data details (by row or column). Clicking on rows within a tab allows access to all details of the experiments captured within. Figure 3 show an example of the assays tab opened to show data content and organization. If the user chooses, the search can then be changed or further refined using the search panes along the left-hand side, specifying any number of additional parameters. Clicking the green ''search'' button updates the current query parameters and results. Search refinements performed at this level can include any field in the database. Current and pending search criteria ''filters'' are tracked along the top of the results page for quick reference.

SEARCHING THE IEDB FOR ALOPECIA RELATED DATA REVEALS A SIGNIFICANT GAP IN KNOWLEDGE

To specifically query for AI related records, the user can simply select on the home page from the disease pane, ''autoimmune disease.'' This search will return more than 10,000 epitopes that are associated with AI disease. Here, the results page tabs show: epitopes (9,741); antigens (1,951); assays (22,350); and references (2,465). As indicated above, the user can change or further refine this broad query using the specific search panes provided along the left side of this page. For example, the search may be limited to retrieve only human AI data specific, whereby the total is now 6,993 epitopes (data not shown).

In another example, the user might choose to restrict the search to a specific AI, such as diabetes mellitus (type I diabetes; T1D). This can be accomplished by scrolling down to the left-hand disease pane, clicking on specific disease and then typing ''diabetes mellitus'' into the free-text field. T1D is a good example, as it is a highly-studied AI disease and

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