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Immunomics: discovering new targets for vaccines and therapeutics

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T-cell-epitope mapping has emerged as one of the most powerful new drug discovery tools for a range of biomedical applications. Initially, T-cell-epitope discovery was applied to the development of vaccines for infectious diseases and cancer. T-cell-epitope-mapping applications have now expanded to include reengineering of protein therapeutics (a process now called deimmunization), as well as the fields of autoimmunity, endocrinology, allergy, transplantation and diagnostics. Research employing T-cell-epitope mapping falls within the realm of immunomics, a new field that addresses the interface between host and (pathogen) proteome, bridging informatics, genomics, proteomics, immunology and clinical medicine. This review highlights aspects of recent immunomics research that are related to the discovery of the T-cell immunome.

Immunomics: a brave new science

The marriage of a new technology with almost any field of inquiry is guaranteed to result in exciting new discoveries. For example, the marriage of bioinformatics (computational biology) with molecular biology and the emergence of their progeny, genomics, have radically transformed science in the past two decades. Bioinformatics tools that identify putative genes, aligning and comparing gene sequences and seeking out proteins of particular types, are now considered requisite tools for the 'sea chest' of a savvy scientist.

Genomics has successfully emerged as an area of research, distinct from other fields of scientific inquiry. However, the same cannot yet be said about immunomics – the field of inquiry related to the interface between the host immune system and proteins derived from pathogens or from self. Scientific investigation of that interface usually involves searching for the antigens and mapping the epitopes that stimulate an immune response. In the past, scientists isolated proteins from whole cells and then digested the proteins (antigens) to find smaller fragments, known as epitopes, that stimulated the T-cell and B-cell response.

By contrast, immunomics tools, such as T-cell- and B-cell-epitope-mapping algorithms, are only slowly being integrated into the mainstream of scientific inquiry. Is this because the internal workings of these algorithms are obscure? In fact, most T-cell-epitope-mapping algorithms are based on straightforward mathematical analyses of the patterns of amino acids that occur in peptides bound to (and presented in the context of) human leukocyte antigen (HLA) by antigen-presenting cells (Box 1). Because the epitope peptide is bound in a linear form to HLA, the interface between ligand and T cell can be modeled with breathtaking accuracy. Several T-cell-epitope-mapping algorithms have already been developed, and the T-cell-epitope-mapping approach, outlined in Figure 1, has been successfully integrated into the field of drug discovery in several research laboratories, allowing these groups to accelerate their discovery programs dramatically. However, not all epitope-mapping tools are equivalent. For reviews of T-cell-epitope-mapping tools, see De Groot and Berzofsky [1], the accompanying issue of Methods [2] and the list of independently developed, validated tools in Table 1.

B-cell-epitope-mapping algorithms have lagged behind T-cell-epitope-mapping algorithms. Recent examples of B-cell-epitope-mapping algorithms include 3DEX [3] and CEP [4]. Many such algorithms have been created and used to analyze existing datasets *in silico* [5] but only a handful of these tools have been used in prospective research studies, and validated using *in vitro* and/or *in vivo* methods. Few B-cell-epitope-mapping algorithms are in current use. Consequently, this article will focus on the applications of T-cell-epitope-mapping tools in the discovery of the T-cell immunome.

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BOX 1

Immunomics terminology

Antigen: usually a protein (sometimes a glycolipid or carbohydrate) that causes the immune system to produce antibodies or a T-cell response targeted against it. This is caused by the presence of epitopes that engage T cells or B-cell receptors.
Epitope: the defined group of amino acids derived from a protein antigen that interacts with the B-cell receptor (immunoglobulin) or the T-cell receptor, thereby activating an immune response.
HLA: proteins on the surface of leukocytes involved in the body's response to foreign substances. In humans, these MHC proteins present T-cell epitopes to T cells.
Immunomics: the field of inquiry related to the interface between the host immune system and proteins derived from pathogens or from self.
Immunomics tools: comprising immunoinformatics (*in silico* analysis) and also bench-based immunology techniques, such as HLA binding assays, ELISpot assays and MHC-tetramers.
Immunome: the set of epitopes derived from a proteome (human or pathogen) that are presented to the host immune system in the context of MHC class I and class II molecules or that engage antibodies, engendering a protective immune response.
Immunodominant protein: a protein that has been identified as the dominant antigen in terms of the number of T cells that respond to the antigen or the number of individual responses.
MHC: two classes of molecules on cell surfaces (class I for cytotoxic T lymphocytes and class II for T helper cells) primarily responsible for the graft versus host rejection, also involved in signaling between lymphocytes and antigen-presenting cells.

Perhaps immunomics is to immunology as the spherical shape of the earth was to early cartographers – something that could not be fully conceived at first. Indeed, despite decades of experience with T-cell-epitope-mapping algorithms and the publication of >2000 articles on the topic, many immunologists appear to prefer traditional approaches to mapping T-cell epitopes, believing that epitopes identified using 'hands on' peptide-by-peptide *in vitro* assays are somehow more substantive than epitopes selected by *in silico* methods. And yet, epitope mapping is not, as some would have it, unsubstantiated. Instead, T-cell-epitope-mapping research is uncovering dogma and revealing new truths, as will be illustrated in examples given herein.

Positive confirmation of the predictive accuracy of epitope-mapping algorithms and their utility in drug development has come from a range of disciplines. Initially, T-cell-epitope discovery focused on the development of vaccines for infectious diseases [2]. More recently, the number of epitope-mapping applications expanded to include reengineering of protein therapeutics [6], autoimmunity [7,8], endocrinology [9], allergy [10,11], transplantation [12] and diagnostics [13]. Even more-potent applications await the scientific adventurer.

Beyond the horizon: new applications

T-cell-epitope-mapping algorithms can be applied to a wide range of protein datasets, yielding exciting new discoveries. For example, if scientists were to apply an epitope mapping analysis to the entire proteome of a pathogen, thereby uncovering peptides that stimulate responses in the human host, the resulting data could be used to develop new diagnostic tests (such as the ELISpot assay kit, which differentiates tuberculosis infection from Bacille Calmette–Guerin, BCG, vaccination [14]), new vaccines (based on the antigens that are discovered [15]), and new means of comparing a pathogen under examination with other pathogens (by comparing genes that stimulate immune responses). If it is possible to examine the human immunome (i.e. the set of peptides that interacts with the human immune system) and to compare these peptides with those presented by pathogens or by allergens, then it should also be possible to reveal new truths about autoimmunity [7]. A few of the many scientific questions that could be answered using T-cell-epitope-mapping tools are listed in Box 2 and discussed in more detail in the next sections.

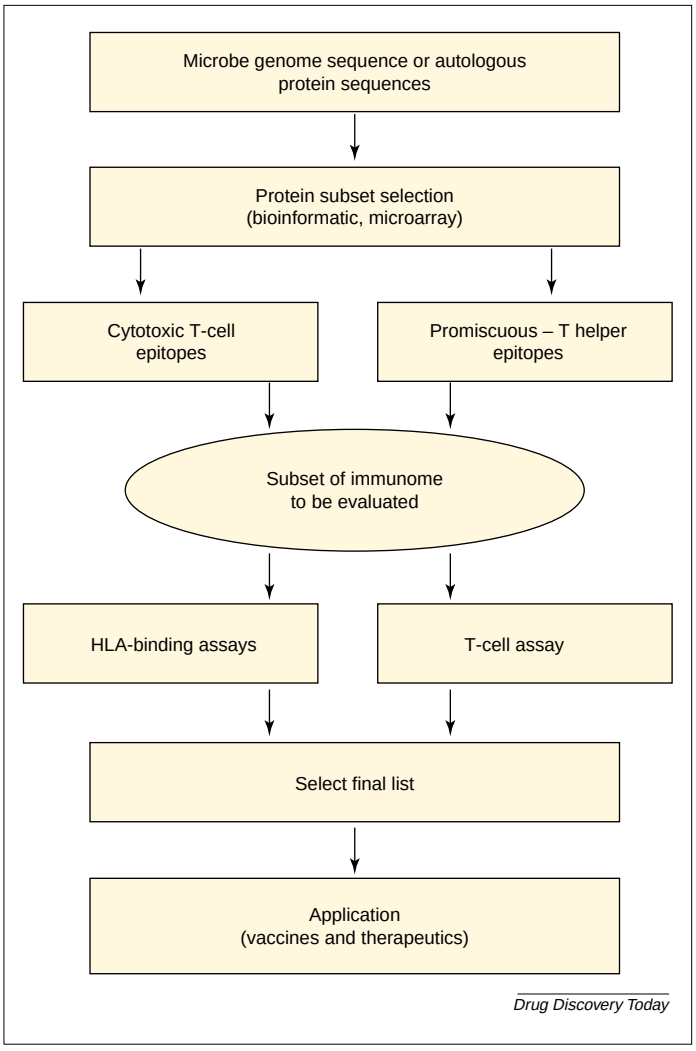

FIGURE 1

T-cell-immunome-discovery flow chart. Bioinformatics tools for selecting protein subsets (by searching for motifs corresponding to secretion signals or transmembrane domains) combined with molecular tools, such as microarrays, allow the selection of a subset of genes from genomic sequences for further *in silico* screening. Epitope-mapping tools allow the selection of the ensemble of epitopes within these proteins that could interact with the host cellular immune system. Confirmation of the immunogenicity of these epitopes can be obtained *in vitro* (using HLA binding assays and/or T-cell assays) or *in vivo*, in HLA transgenic mice.

Measuring the dimensions of the human T-cell response to pathogens

One application of T-cell-epitope mapping might be to measure the dimensions of the human immune response or, more specifically,