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The Optimization of Helper T Lymphocyte (HTL) Function in Vaccine Development

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Abstract

Helper T lymphocyte (HTL) responses play an important role in the induction of both humoral and cellular immune responses. Therefore, HTL epitopes are likely to be a crucial component of prophylactic and immunotherapeutic vaccines. For this reason, Pan DR helper T cell epitopes (PADRE), engineered to bind most common HLA-DR molecules with high affinity and act as powerful immunogens, were developed. Short linear peptide constructs comprising PADRE and *Plasmodium*-derived B cell epitopes induced antibody responses comparable to more complex multiple antigen peptides (MAP) constructs in mice. These antibody responses were composed mostly of the IgG subclass, reactive against intact sporozoites, inhibitory of schizont formation in liver invasion assays, and protective against sporozoite challenge in vivo. The PADRE HTL epitope has also been shown to augment the potency of vaccines designed to stimulate a cellular immune response. Using a HBV transgenic murine model, it was found that CTL tolerance was broken by PADRE-CTL epitope lipopeptide, but not by a similar construct containing a conventional HTL epitope. There are a number of prophylactic vaccines that are of limited efficacy, require

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multiple boosts, and/or confer protection to only a fraction of the immunized population. Also, in the case of virally infected or cancerous cells, new immunotherapeutic vaccines that induce strong cellular immune responses are desirable. Therefore, optimization of HTL function by use of synthetic epitopes such as PADRE or pathogen-derived, broadly crossreactive epitopes holds promise for a new generation of highly efficacious vaccines.

Introduction: The Role of HTL Responses in General Immunity

Helper T lymphocytes (HTL) play several functions that are key in establishing the immune capacity to fight pathogens. Firstly, they support the induction of both CTL and antibody responses. By both direct contact and by secretion of lymphokines, such as IL-2 and IL-4, HTL promote and support the expansion and differentiation of CTL and B cell precursors into effector cells. In addition, in the case of tumors, and viral, bacterial, parasitic, and fungal infections *(1–23)*, HTL can be effectors in their own right, an activity also mediated by direct cell contact and lymphokine secretion (e.g., IFN-γ and TNF-α).

HTL recognize a complex formed by antigenic peptides bound to Class II MHC molecules. Antigenic peptides recognized in the context of Class II molecules are usually between 10 and 20 residues in length, with sizes between 13 and 16 amino acids being the most frequently observed *(24–30)*. Peptide-Class II interactions have been analzyed in detail, both at the structural *(31–34)* and functional level *(35–37)*, and peptide-binding motifs have been proposed for various human and mouse Class II specifities *(35,38–52)*. Predictions based on these motifs appear, however, to be less accurate relative to the peptide binding motifs defined for Class I molecules. This situation may be the result of the peptide binding groove of Class II molecules being "open" at both ends *(24–34)*, and thus allowing a given peptide to potentially bind in several different registers.

In the last few years, epitope-based approaches have been proposed as a possible strategy to develop novel prophylactic and immunotherapeutic vaccines (53-58). Selection of appropriate T and B cell epitopes should allow the immune system to be focused on conserved epitopes of pathogens whose proteins are characterized by high sequence variability (such as HIV, HCV, and *Plasmodium Falciparum*) *(13,59–66)*. Focusing the immune response toward selected determinants could be of specific value in the case of those chronic viral diseases and cancers where T cells directed against the immunodominant epitopes might have been inactivated, while T cells specific for subdominant epitopes might have escaped T cell tolerance *(67–77)*. The use of epitope-based vaccines also might allow the circumvention of "suppressive" T cell determinants, which might induce TH2 responses, in conditions where a TH1 responses is desirable, or vice versa *(20,78,79)*.

Epitope-based vaccines also offer the opportunity to include in the vaccine construct epitopes that have been engineered to modulate potency, either by increasing MHC binding affinity, or by alteration of their TCR contact residues, or both *(80–82)*. In this context, we have recently described the engineering of the nonnatural T helper epitope called (PADRE) *(80)*. The use of completely syn-

thetic, nonnatural epitopes, or epitopes genetically unrelated to the pathogen of interest *(80,83–85)*, also represents a possible means of modulating the HTL response toward a TH1 or TH_2 phenotype.

Once appropriate epitope determinants have been defined, they can be assorted and delivered by various means, including lipopeptides *(86)*, viral delivery vectors *(87–92)*, particles of viral or synthetic origin *(93–95)*, adjuvants *(96,97)*, liposomes *(98,99)*, and naked or particle-absorbed cDNA *(100–102)* (for reviews, *see* refs. *13* and *94*).

Development of High Potency, Universal DR Restricted Helper Epitopes (PADRE)

PanDR-binding peptides were originally developed by introducing the main DR anchor residues necessary for binding to a representative set of common DR molecules, into a polyalanine backbone. In addition, empirical screening of the binding capacity of single amino acid analogs of the initial construct maximized binding affinity, perhaps by ensuring that residues that may negatively affect binding capacity because of steric hindrance and disruption of backbone hydrogen bonding were not included in the Pan DR binding sequence *(80)*.

PanDR peptides bound 10 of 10 DR molecules tested, with affinities in most instances in the nanomolar range, and in several instances significantly higher than known naturally occurring broad DR binding peptides, such as the Ii chain derived CLIP, or the HA 307-319 or TT830-843 immunodominant epitopes. In PanDR peptides only, the small methyl groups of the polyalanine backbone are exposed for T cell recognition. Accordingly, when tested for biological activity, these peptides were indeed shown to be extremely powerful competitive blockers of DR-restricted antigen presentation *(80)*.

To engineer powerful immunogens, we started from the observation that if bulky and/or charged side chains are present at crucial peptide positions, pointing up and away from the DR-peptide complex, they are often recognized as main determinants of immunodominant peptides, both in mouse and human systems. Introduction of bulky and charged residues at these positions, accessible for T cell recognition, indeed yielded extremely powerful immunogens, denoted PADRE. Table 1 illustrates the broad specificity pattern and the high binding affinity of PADRE, as compared to TT830-843 and CLIP peptides.

These peptides were highly immunogenic in vitro for human PBMC, and several orders of magnitude more active than the control TT830-843 epitope *(80)*. Because PADRE peptides also bind certain mouse Class II molecules, the in vivo activity of these peptides could also be analyzed. It was found that PADRE peptides were up to 1000-fold more powerful than natural T cell epitopes in their capacity to deliver help during induction of antigen-specific CTL responses *(80)*.

It is currently assumed that elicitation of specific antibody responses against protein antigen requires that two independent signals be delivered to B cells. According to this commonly held view simple, monovalent synthetic peptides cannot be effective immunogens, since they would not be anticipated to effectively crosslink surface Ig and thus generate the necessary signals *(103,104)*. For this reason, single antigens are routinely conjugated to complex carrier systems.

In a recently published series of experiments *(105)*, the immunogenicity of short linear peptide constructs comprising *Plasmodium vivax* (*P. vivax*) B cell epitopes (PVB) and nonnatural Pan-DR T helper cell epitopes (PADRE) was assessed in mice and compared to other types of antigen constructs. A 33-residue long PADRE-PVB linear construct was

Table 1. PADRE Binding Affinity

Antigen	Cytel assay	Tet Tox 830-843[a]	PADRE, 965.10[a]	Invariant chain[a]
DR1	(DRB1*0101)	23[b]	1.2	0.89
DR2w2 ß1	(DRB1*1501)	22,750	40	14
DR2w2 ß2	(DRB5*0101)	20	5.6	31
DR3	(DRB1*0301)	3261	214	118
DR4w4	(DRB1*0401)	8036	2.8	141
DR4w14	(DRB1*0404)	—[c]	12	12
DR4w15	(DRB1*0405)	1462	58	200
DR5w11	(DRB1*1101)	20	11	444
DR5w12	(DRB1*1201)	39,211	—[c]	392
DR6w19	(DRB1*1302)	4.4	206	0.66
DR7	(DRB1*0701)	25	147	40
DR8w2	(DRB1*0802)	49	96	258
DR8w3	(DRB1*0803)	1600	762	889
DR9	(DRB1*0901)	74	168	53
DR52a	(DRB3*0101)	15,667	979	16,786
DRw53	(DRB4*0101)	17,576	87	8.2
Alleles bound	(16 alleles)	7	15	15
Hit rate		0.438	0.938	0.938

[a]Sequences: Tet Tox 830-843, QYIKANSKFIGITE; PADRE (965.10), aK(14)VAAWTLKAAa, 14 indicates cyclohexylalanine; Invariant chain, LPKPPKPVSKMRMATPLLMQALPM.

[b]Significant binding is defined as IC50 n$M \leq 1000$.

[c]Indicates no significant binding.

found to be highly immunogenic. This construct could induce responses comparable to those obtained with the multiple-antigen peptides (MAP) constructs, in terms of absolute immunoglobulin titers, isotype distribution, dose–response, and overall duration of the response. The anti-PVB antibody responses lasted for several months and were composed mostly of IgG subclass. These results were also generalized to B-cell epitopes from *P. falciparum*. In terms of biological significance, the antibody response was shown to be reactive with intact sporozoites. Finally, the PADRE-PVB constructs were also shown to be immunogenic when formulated in various different adjuvants, including Alum and Montanide ISA 51, thus underlining the relevance of these findings for human vaccine development *(105)*.

Induction of Protective Responses Against the *Plasmodium yoelii* Circumsporozoite Protein by Immunization with Peptides Containing B Cell and Universal T Helper Epitopes

To further evaluate the biological relevance of PADRE B cell epitope constructs, we analyzed the capacity of antibody responses elicited by this type of construct to inhibit schizont formation *(106)* in a liver cell invasion assay.

Sera from mice immunized with PADRE constructs containing a *P. yoelli* B cell epitope inhibited invasion by *P. yoelli* sporozoite of

mouse liver cells. Sera from mice immunized with similar epitopes from *P. falciparum* had no inhibitory effect. Conversely, in the case of infection of human hepatoma cells by *P. falciparum* sporozoites, the sera from mice immunized with PADRE constructs incorporating the *P. yoelli* B cell epitope was ineffective, whereas sera from mice immunized with *P. falciparum* B cell epitope-PADRE constructs was highly inhibitory. These results underlined the potency and specificity of antibody responses induced by the linear monovalent PADRE constructs (Franke et al., Vaccine, in press).

Next, encouraged by these results, we investigated whether this type of construct could protect against mouse challenge with *P. yoelli* sporozoites. Previously, protection against challenge with sporozoites of *Plasmodium yoelii* had been achieved by immunization with a multiple antigen peptide (MAP) vaccine designed to induce the production of antibodies to the PyCSP repeat region *(107)*. The PyCSP MAP vaccine contains the B-cell epitope of the *P. yoelii* circumsporozoite protein (CSP) and two universal T-helper epitopes (p2 and p30) from tetanus toxin *(107)*. Which have also been shown to induce lymphocyte proliferation in H-2^b, H-2^d, and H-2^k mice *(108)*. In the experiments described herein, we compared the protective efficacy and antibody responses in C57BL/6 mice immunized with linear peptides or a MAP that was composed of the B cell epitope of the *P. yoelii* CSP and either p2p30, PADRE, or no T-cell helper epitope.

Protective efficacy and antibody titers were highest in the group that was immunized with PADRE-PyB, followed by the group that was immunized with the much more complex MAP(QGPGAP)p2p30 construct. These studies demonstrated that immunization with a single monovalent construct containing the B cell epitope of the *P. yoelii* CS protein and a PADRE induces high levels of protective efficacy, correlated with high antibody titers. Protection and antibody levels were higher in the mice immunized with PADRE-PyB compared to mice immunized with either a linear peptide containing the B cell only or a MAP containing the B cell epitope and the universal T helper epitopes from tetanus toxin. Notably, the linear PADRE construct was more effective than cDNA immunization with the whole CSP antigen, both in terms of antibody titers and protective capacity.

The Need for HTL Optimization in Vaccine Development: Prophylactic Vaccines

In most cases, prophylactic subunit vaccines and vaccines based on killed and/or inactivated pathogens act by inducing vigorous antibody responses. Circulating antibodies can clear the infectious agent before clinical signs of infection become apparent. In other instances, especially in the case of "attenuated" vaccines, significant contributions from cellular immunity might also come into play in protection from disease.

Prophylactic vaccines save millions of lives annually, and without doubt represent the most dramatic contribution of immunology to medicine *(109,110)*. However, many of the existing vaccines could still be significantly improved, and several diseases of worldwide concern go unchecked because of the lack of suitable vaccines *(109,110)*. Vaccines for which improvements are desirable fall into diverse categories. Certain vaccines are of limited efficacy, conferring protection to only a fraction of the immunized population, and/or require multiple boosts to achieve the level of immunity associated with protection from disease.

Familiar examples include the current HBV vaccines, which are not effective in a significant fraction (approximately 10%) of the general population, and require three to four repeat

immunizations. Another example is flu vaccines, which provide variable protection in the adult population, and are less effective in the elderly, the patient population where unfortunately the most serious morbidity occurs. In both cases, it is reasonable to hypothesize that potentiation and/or optimization of HTL function might be of significant benefit.

Specifically, in the case of the HBV-S subunit vaccine, it has been shown that laboratory mice can be classified as responders and nonresponders, as a function of their genetic background at the MHC Class II locus *(111,112)*. The exact nature of the defect has been pinpointed to deficient HTL function of these mice in recognition of the HBV-s antigen *(113)*.

Several studies have also pointed out that in humans, the nonresponder phenotype appears to be linked to the DR3 HLA Class II molecule, although controversy still exists over the strength and role of this linkage *(114,115)*. In conclusion, it is likely that increased HTL function would increase the immunogenicity of the current HBV-S vaccine and, consequently, increase the percentage of the population that would respond to the vaccine. It is also possible that a vaccine containing more potent T helper activity might decrease the number of immunizations required to achieve protection from infection.

In the case of decreased helper responses of the elderly population, it is also hoped that potentiation of the HTL response would lead to increase in responsiveness, since it has shown that decrease in HTL responsiveness is one of the earliest alterations associated with an aging immune system *(116)*.

In addition, an optimized HTL function might be crucial for development of vaccines for a significant number of new indications. In particular, development of efficacious and cost-effective vaccines against meningococcal and streptococcal infections have been hampered by the carbohydrate (CHO) nature of the well-characterized protective antigens *(109,110)*. This is because it is commonly observed that CHO antigens elicit mostly IgM responses, which are poorly boostable and often T cell-independent, resulting in less than the optimal vaccine performance. It is anticipated that linkage of these antigens to HTL-inducing protein antigens would be significant benefit, increasing the absolute titers achieved, facilitating the IgM to IgG switch, and facilitating boosting of the responses. In fact, the currently available vaccines for *Haemophilus influenza* (Hib) is a conjugate between *Tetanus toxoid* and various specific CHO antigens *(117)*.

Large carrier proteins are a powerful source of helper epitopes, but suffer from several disadvantages, such as relatively high production costs and poor batch-to-batch reproducibility because of the cumbersome conjugation process. Carrier suppression effects can also raise doubts concerning whether the optimal potency has indeed been reached and exploited. Other examples of important diseases for which potentially protective CHO antigens have been identified that could benefit from linkage with strong HTL-inducing epitopes are *Salmonella typhi*, Cholera, and Group B Strep *(118–120)*. In conclusion, in all these cases, use of high-potency, well-defined HTL epitopes, such as PADRE, might offer significant potency, safety, and cost advantages.

HTL Activity and Therapeutic Vaccines: The Case of Chronic HBV Infection

As described in the preceding sections, antibody responses can, to a large extent, allow prevention of the disease process. By contrast, therapeutic intervention, after the disease process is established, is often likely to require induction of CTL responses, specifically to recognize and eliminate infected or cancerous cells. A significant degree of controversy existed regarding whether induction of CTL responses required concomitant induction of

HTL responses, to support the expansion of CTL precursors, and facilitate their conversion into mature effector or memory cells.

Our first target in development of therapeutic immunomodulators has been chronic HBV infection. This choice was based on evidence suggesting that individuals that are acutely infected with HBV and successfully clear the infection develop a vigorous HBV-specific, HLA Class I-restricted CTL response. By contrast, spontaneous CTL responses are weak or absent in chronically infected individuals, and reactivation of such responses is associated with clearance of HBV infection either spontaneously or in response to IFN-α treatment *(10)*. Finally, using HBV transgenic mice, it has been directly shown that transfer of activated CTL can lead to clearance of expression of HBV antigens by a nonlytic mechanism *(121,122)*.

Based on data obtained using mouse model Class I and Class II epitopes, we constructed a potential HBV immunomodulator (Theradigm-HBV) by covalently linking an immunodominant, A2-restricted CTL epitope, with the broadly restricted HLA DR epitope TT830-843. We opted to utilize a non-HBV-derived T helper epitope, for two reasons. First, we postulated that the crucial therapeutic variable was induction of HBV-specific CTL response. Second, potential T cell tolerance at the level of Class II HBV epitopes could be circumvented by the use of a non-HBV-derived HTL epitope. Vaccination of healthy normal volunteers indeed demonstrated that Theradigm-HBV could induce powerful CTL responses *(86,123)*. Furthermore, simultaneous induction of good HTL activity was highly correlated ($p = 0.001$) with successful induction of CTL activity, and HTL responses also appeared to be crucial for development of long-term memory CTL. When chronically infected HBV patients were immunized, significant CTL responses were also observed but their overall magnitude was lower relative to the normal volunteers, and not yet sufficient to clear the infection. In addition, a dysfunctional helper response was observed, even against the non-HBV-derived TT830-843 epitope, suggesting that a generalized defect in the HTL function may be associated with chronic HBV infection.

Overall, these data suggest that successful therapeutic intervention in chronic HBV infection may be feasible, but is likely to require further optimization of HTL responses. It should be noted that the PADRE epitope was not utilized in Theradigm-HBV, simply because at the time the clinical trials were originally planned, PADRE had not yet been discovered.

Based on the data available to date, we would anticipate that PADRE might be a much more effective inducer of HTL activity and thereby potentially associated with effective clearance of HBV chronic infection. This notion is also corroborated by data recently obtained in the HBV transgenic mouse model, where Theradigm lipopeptide constructs incorporating either PADRE or conventional Class II HTL epitopes were utilized. It was observed that tolerance at the CTL level was broken by a PADRE-CTL epitope lipopeptide, but not by a similar construct containing a conventional HTL epitope (Livingston et al., submitted).

Identification of Pathogen-Derived, Broadly Crossreactive HTL Epitopes

The preceding section illustrates the use of broadly reactive HTL epitopes, unrelated to the disease causing antigen, to increase the potency of therapeutic and prophylactic vaccines.

In certain situations, optimization of HTL function is likely to also require the identification of disease-related HTL epitopes. This type of situation is best exemplified by chronic HIV and HCV infection where positive clini-

cal outcomes have been associated with recognition of particular HTL epitopes. Recognition of the NS3.1748 has been to associated with resolution of HCV infection *(3)*. Similarly, in the case of HIV, recognition of certain epitopes has been associated with long-term nonprogression to AIDS *(125)*. Finally, in the case of cancer, elegant data presented by Riddell, Greenberg, and associates have demonstrated that adoptive transfer of T cell lines is dependent not only on the antitumor cytotoxic activity, but also on the presence of HTL activity, potentially implicated in allowing persistence of the CTL themselves *(126)*. Data supporting these concepts have also been produced in the Ras feline leukemia model *(127)*.

However, one major obstacle to the practical feasibility of the epitope approach has to be overcome: the extremely high degree of polymorphism of human MHC molecules. Hundreds of different types of HLA Class I and Class II molecules have already been identified *(128,129)*. Previous studies demonstrated that peptides capable of binding several different HLA Class I molecules can indeed be identified, and in fact, a majority of the known HLA Class I molecules can be grouped into four broad HLA supertypes characterized by similar overlapping peptide binding specificities (HLA supermotifs) *(130–135)*. Furthermore, we have also shown that humans naturally present such peptides in the course of natural infections *(136–138)*.

There are also HLA, Class II peptides, which bind and are immunogenic in the context of different HLA molecules *(46,47,80, 84,85,139–144)*. It has been hypothesized that such antigenic peptides could be identified through the use of allele-specific motifs *(38–48)*. In fact, in a recent report *(145)*, we have described the development and validation of specific motifs and assay systems for various DR molecules. The subset of DR molecules studies was chosen to be representative of the worldwide population, and it was shown how a relatively simple strategy can be applied to the identification of broadly degenerate HLA Class II binding peptides.

More specifically, the study initially analyzed the peptide binding specificity of three common DR types (HLA DRB1*0401, DRB1*0101, and DRB*0701). Nearly all peptides binding to these DR molecules carried a motif characterized by a large aromatic or hydrophobic residue in position 1 (Y, F, W, L, I, V, M) and a small, noncharged residue in position 6 (S, T, C, A, P, V, I, L, M). On definition of allele-specific secondary effects and secondary anchors, allele-specific algorithms were derived and utilized to identify peptides binding DRB1*0101, DRB1*0401, and DRB*0701. Further experiments identified a large set of DR molecules, which includes at least the DRB1*0101, DRB1*0401, and DRB*0701, DRB1*1501, DRB1*0901, and DRB1*1302 allelic products, and is characterized by largely overlapping peptide binding repertoires. In addition to their implications for understanding the molecular interactions involved in peptide-DR binding, these results also have obvious potential practical implications for the development of epitope-based prophylactic and therapeutic vaccines, as described in the preceding sections.

Conclusions

A large set of data, reviewed herein, underlines the crucial importance of HTL in development of antibody and CTL responses, as well as the potential direct effector role of HTL in control of infectious diseases and cancer.

Development of high-potency, nonnatural, synthetic epitopes, such as PADRE, offers an opportunity to optimize and potentiate both CTL and antibody responses. Consequently, it may allow development of novel prophylactic and therapeutic vaccine applications, as well as improvement of existing vaccines

without the drawbacks, in terms of potency, manufacturing challenges, and safety concerns of more conventional vaccine carriers.

Herein we have also reviewed development of experimental strategies that allow the identification of broadly reactive, pathogen, or tumor antigen-derived, Class II epitopes. These epitopes could be utilized above or in conjunction with PADRE peptides, this offering a complementary approach to optimization of HTL function in the context of vaccine development.

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