Chapter 1
Short Peptide Vaccine Design and Development: Promises and Challenges

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Core Message There is a need for novel vaccine technologies where existing viral vaccine types (viruses, killed or inactivated viruses, and conjugate or subunits) are unsuitable against many viruses. Hence, short peptide (10–20 residues) vaccine candidates are considered promising solutions in recent years. These function on the principle of short epitopes developed through the binding of CD8+/CD4+-specific HLA alleles (12542 known so far). Thus, the specific binding of short peptide antigens to HLA alleles is rate limiting with high sensitivity in producing T-cell-mediated immune responses. Identification of HLA allele-specific antigen peptide binding is mathematically combinatorial and thus complex. Therefore, prediction of HLA allele-specific peptide binding is critical. Recent advancement in immune-informatics technologies with the aid of known X-ray-determined HLA-peptide structure data provides solutions for the accurate identification of short peptides as vaccine candidates for further consideration. Thus, we document the possibilities and challenges in the prediction, large-scale screening, development, and validation of short peptide vaccine candidates in this chapter.
1 Introduction

The types of approved viral vaccines include live attenuated viruses, killed/inactivated viruses, and conjugate/subunits. However, these types of vaccine technologies may prove unsuitable against some viruses. In some cases, there is interest in the development of short peptide vaccines to fill the gaps. For example, the use of live attenuated HIV-1/AIDS vaccines is not as yet approved due to safety concerns [1]. There are several subunit vaccines under consideration and evaluation. However, one of these, the NIAID and Merck Co.-sponsored 2004 STEP (HVTN 502 or Merck V520-023) trial using three recombinant adenovirus-5 (rAD5) vectors containing HIV-1 genes Ad5-gag, Ad5-pol, and Ad5-Nef, did not show promising results [2]. This has led to the development of a multifaceted strategy for HIV-1/AIDS vaccine development. However, encouraging results were observed with four priming injections of a recombinant canary pox vector (ALVAC-HIV) and two booster injections of gp120 subunit (AIDSVAX-B/E) in a community-based, randomized, multicenter, double-blind, placebo-controlled efficacy trial (NCT00223080) in Thailand [3]. The main concern following this study was that this vaccine did not affect the degree of viremia or the CD4 T-cell count in patients who later seroconverted. Further studies indicated that the challenges with the development of an HIV-1/AIDS vaccine are viral diversity and host-virus molecular mimicry [4–6]. Nonetheless, there is considerable amount of interest to develop gp160 (gp120-gp41 complex) TRIMER envelope (ENV) protein as a potential vaccine candidate [4].

The production of an HIV-1 ENV spike protein trimer complex is nontrivial due to protein size, protein type, sequence composition, and residue charge polarity. Therefore, the need for the consideration of alternative approaches for vaccine development such as T-cell-based HLA-specific short peptide vaccines is promising.
The LANL HIV molecular immunology database provides comprehensive information on all known T-cell epitopes in the literature. Thus, these resources in combination with other predictive advancements described in this chapter are collectively useful for the design, development, evaluation, and validation of short peptide vaccine candidates.

2 Methodology

2.1 Structural Data

A structural dataset of complexes for class I HLA-peptide (Table 1.1) and class II HLA-peptide (Table 1.2) is created from the protein databank (PDB). The characteristic features of the datasets are presented in Tables 1.1 and 1.2.

2.2 Structural Superposition of HLA Molecules

The peptide-binding grooves of both class I HLA (Fig. 1.1a) and class II HLA (Fig. 1.1c) molecules were superimposed using the molecular overlay option in the Discovery Studio software from Accelrys®.

2.3 Molecular Overlay of HLA-Bound Peptides

HLA-bound peptides in the groove of both class I HLA (Fig. 1.1b) and class II HLA (Fig. 1.1d) molecules were overlaid using the molecular overlay option in the Discovery Studio software from Accelrys®.

2.4 Accessible Surface Area Calculations

Accessible surface area (ASA) was calculated using the WINDOWS software Surface Racer with Lee and Richard implementation. A probe radius of 1.4 Å was used for ASA calculation.

2.5 Relative Binding Measure

Relative binding measure (RBM) is defined as the percentage ASA Å² of residues in the peptide at the corresponding positions buried as a result of binding with the HLA groove. This is the percentage change in ASA (ΔASA) of the position-specific peptide residues upon complex formation with the HLA groove (Fig. 1.2).
| S | Code  | Allele | Peptide sequence | L | Source           | RA  | Year | Group       | Country  | State     |
|---|-------|--------|------------------|---|------------------|-----|------|-------------|----------|-----------|
| 1 | 1W72  | A*0101 | EADPTGHSY        | 9 | Melanoma related | 2.15| 2004 | Ziegler A   | Germany  | Berlin    |
| 2 | 3BO8  | A*0101 | EADPTGHSY        | 9 | Melanoma related | 1.8 | 2008 | Ziegler UB  | Germany  | Berlin    |
| 3 | 3UTS  | A*0201 | ALWGPDDAAA       | 10| Insulin          | 2.71| 2012 | Andrew SK   | UK       | Cardiff   |
| 4 | 3UTT  | A*0201 | ALWGPDDAAA       | 10| Insulin          | 2.6 | 2012 | Sewell AK   | UK       | Cardiff   |
| 5 | 1H4F  | A*0201 | GVVYGREHTV       | 10| Melanoma related | 1.4 | 2001 | Mabbutt BC  | Australia| Sydney    |
| 6 | 1JHT  | A*0201 | ALGIGILTV        | 9 | Mart-1           | 2.15| 2001 | Wiley DC    | USA      | Cambridge |
| 7 | 1B0G  | A*0201 | ALWGFFFPVL       | 9 | Human-peptide    | 2.6 | 1998 | Collins EJ  | USA      | North Carolina |
| 8 | 1I7U  | A*0201 | ALWGFPVL         | 9 | Synthetic        | 1.8 | 2001 | Collins EJ  | USA      | North Carolina |
| 9 | 1I7T  | A*0201 | ALWGFPVL         | 9 | Synthetic        | 2.8 | 2001 | Collins EJ  | USA      | North Carolina |
| 10| 1I7R  | A*0201 | FAPGFFPYL        | 9 | Synthetic        | 2.2 | 2001 | Collins EJ  | USA      | North Carolina |
| 11| 1IIF  | A*0201 | FLKEPVHGV        | 9 | HIV RT           | 2.8 | 2000 | Collins EJ  | USA      | North Carolina |
| 12| 1HHI  | A*0201 | GILGFVFTL        | 9 | Synthetic        | 2.5 | 1993 | Wiley DC    | USA      | Massachusetts |
| 13| 1AKJ  | A*0201 | ILKEPVHGV        | 9 | HIV-1 RT         | 2.65| 1997 | Jakobsen BK | UK       | Oxford    |
| 14| 1HHJ  | A*0201 | ILKEPVHGV        | 9 | Synthetic        | 2.5 | 1993 | Wiley DC    | USA      | Massachusetts |
| 15| 1QRN  | A*0201 | LLFGAYAVV        | 9 | Tax peptide P6A  | 2.8 | 1999 | Wiley DC    | USA      | Massachusetts |
| 16| 1QSE  | A*0201 | LLFGYPYVV        | 9 | Tax peptide V7R  | 2.8 | 1999 | Wiley DC    | USA      | Massachusetts |
| 17| 1QSF  | A*0201 | LLFGYPYAV        | 9 | Tax peptide Y8A  | 2.8 | 1999 | Wiley DC    | USA      | Massachusetts |
| 18| 1AO7  | A*0201 | LLFGYPVVV        | 9 | HTLV-1 Tax       | 2.6 | 1997 | Wiley DC    | USA      | Massachusetts |
| 19| 1BD2  | A*0201 | LLFGYPVVV        | 9 | HTLV-1 Tax       | 2.5 | 1998 | Wiley DC    | USA      | Massachusetts |
| 20| 1DUZ  | A*0201 | LLFGYPVVV        | 9 | HTLV-1 Tax       | 1.8 | 2000 | Wiley DC    | USA      | Massachusetts |
| 21| 1HHK  | A*0201 | LLFGYPVVV        | 9 | Synthetic        | 2.5 | 1993 | Wiley DC    | USA      | Massachusetts |
| 22| 1IM3  | A*0201 | LLFGYPVVV        | 9 | HTLV-1 Tax       | 2.2 | 2001 | Wiley DC    | USA      | Boston    |
| 23| 1HHG  | A*0201 | TLTSCNTSV        | 9 | HIV-1 gp120      | 2.6 | 1993 | Wiley DC    | USA      | Massachusetts |
| 24| 1I1Y  | A*0201 | YLKEPVHGV        | 9 | HIV-1 RT         | 2.2 | 2000 | Collins EJ  | USA      | North Carolina |
| 25| 3FQN  | A*0201 | YLDSGIHSGA       | 10| Beta-catenin     | 1.65| 2009 | Purcell AW  | Australia| Victoria  |
| Entry | A*0201 | GLGSQVRA | 9 | Tyrosine-phosphatase | 1.8 | Australia | Victoria |
|-------|--------|-----------|---|---------------------|-----|-----------|---------|
| 26    | 3FOR   | A*0201    | GLGSQVRA | 9 | Tyrosine-phosphatase | 1.8 | Australia | Victoria |
| 27    | 3FOU   | A*0201    | GLGSQVRA | 9 | Tyrosine-phosphatase | 1.8 | Australia | Victoria |
| 28    | 3FOU   | A*0201    | GLGSQVRA | 9 | Tyrosine-phosphatase | 1.8 | Australia | Victoria |
| 29    | 3FOU   | A*0201    | GLGSQVRA | 9 | Tyrosine-phosphatase | 1.8 | Australia | Victoria |
| 30    | 3FOU   | A*0201    | GLGSQVRA | 9 | Tyrosine-phosphatase | 1.8 | Australia | Victoria |
| 31    | 3FOU   | A*0201    | GLGSQVRA | 9 | Tyrosine-phosphatase | 1.8 | Australia | Victoria |
| 32    | 3FOU   | A*0201    | GLGSQVRA | 9 | Tyrosine-phosphatase | 1.8 | Australia | Victoria |
| 33    | 3FOU   | A*0201    | GLGSQVRA | 9 | Tyrosine-phosphatase | 1.8 | Australia | Victoria |
| 34    | 3FOU   | A*0201    | GLGSQVRA | 9 | Tyrosine-phosphatase | 1.8 | Australia | Victoria |
| 35    | 3FOU   | A*0201    | GLGSQVRA | 9 | Tyrosine-phosphatase | 1.8 | Australia | Victoria |
| 36    | 3FOU   | A*0201    | GLGSQVRA | 9 | Tyrosine-phosphatase | 1.8 | Australia | Victoria |
| 37    | 3FOU   | A*0201    | GLGSQVRA | 9 | Tyrosine-phosphatase | 1.8 | Australia | Victoria |
| 38    | 3FOU   | A*0201    | GLGSQVRA | 9 | Tyrosine-phosphatase | 1.8 | Australia | Victoria |
| 39    | 3FOU   | A*0201    | GLGSQVRA | 9 | Tyrosine-phosphatase | 1.8 | Australia | Victoria |
| 40    | 3FOU   | A*0201    | GLGSQVRA | 9 | Tyrosine-phosphatase | 1.8 | Australia | Victoria |
| 41    | 3FOU   | A*0201    | GLGSQVRA | 9 | Tyrosine-phosphatase | 1.8 | Australia | Victoria |
| 42    | 3FOU   | A*0201    | GLGSQVRA | 9 | Tyrosine-phosphatase | 1.8 | Australia | Victoria |
| 43    | 3FOU   | A*0201    | GLGSQVRA | 9 | Tyrosine-phosphatase | 1.8 | Australia | Victoria |
| 44    | 3FOU   | A*0201    | GLGSQVRA | 9 | Tyrosine-phosphatase | 1.8 | Australia | Victoria |
| 45    | 3FOU   | A*0201    | GLGSQVRA | 9 | Tyrosine-phosphatase | 1.8 | Australia | Victoria |
| 46    | 3FOU   | A*0201    | GLGSQVRA | 9 | Tyrosine-phosphatase | 1.8 | Australia | Victoria |
| 47    | 3FOU   | A*0201    | GLGSQVRA | 9 | Tyrosine-phosphatase | 1.8 | Australia | Victoria |
| 48    | 3DXK   | A*0201    | GLGSQVRA | 9 | Tyrosine-phosphatase | 1.8 | Australia | Victoria |
| 49    | 3DXK   | A*0201    | GLGSQVRA | 9 | Tyrosine-phosphatase | 1.8 | Australia | Victoria |
| 50    | 3DXK   | A*0201    | GLGSQVRA | 9 | Tyrosine-phosphatase | 1.8 | Australia | Victoria |
| 51    | 3DXK   | A*0201    | GLGSQVRA | 9 | Tyrosine-phosphatase | 1.8 | Australia | Victoria |
| S  | Code   | Allele | Peptide sequence | L | Source            | RA | Year | Group      | Country | State  |
|----|--------|--------|------------------|---|-------------------|----|------|------------|---------|--------|
| 52 | 3DX8   | B*4405 | EENLLDFVRF       | 10| EBV decapeptide   | 2.1| 2009 | Rossjohn J | Australia| Victoria|
| 53 | 1E27   | B*5101 | LPPVVAKEI        | 9 | HIV-1 Kml         | 2.2| 2000 | Jones EY   | UK      | Oxford |
| 54 | 1A1M   | B*5301 | TPYDINQL         | 9 | HIV-2 gag         | 2.3| 1998 | Jones EY   | UK      | Oxford |
| 55 | 1A1O   | B*5301 | KPIVQYDNF        | 9 | HIV-1 Nef         | 2.3| 1998 | Jones EY   | UK      | Oxford |
| 56 | 3VRJ   | B*57:01| LTTKLTNTN        | 10| Cytochrome c Oxidase | 1.9| 2012 | McCluskey J | Australia| Victoria|
| 57 | 3UPR   | B*57:01| HSITYLLPV        | 9 | Synthetic construct | 2 | 2012 | Peters B   | USA     | Gainesville|
| 58 | 3VRI   | B*57:01| RVAQLEQVYI       | 10| SNRPD3            | 1.6| 2012 | McCluskey J | Australia| Victoria|
| 59 | 2RFX   | B*5701 | LSSPVTKSF        | 9 | Synthetic construct | 2.5| 2008 | McCluskey J | Australia| Victoria|
| 60 | 3VH8   | B*5701 | LSSPVTKSF        | 9 | Ig kappa chain C region | 1.8| 2011 | Rossjohn J | Australia| Victoria|
| 61 | 2DYP   | B27    | RIIPRLHQL        | 9 | Histone H2A.x     | 2.5| 2006 | Maenaka K  | Japan   | Fukuoka|
| 62 | 2D31   | B27    | RIIPRLHQL        | 9 | Histone H2A.x     | 3.2| 2006 | Maenaka K  | Japan   | Fukuoka|
| 63 | 1EFX   | Cw*0304| GAVDPLLAL        | 9 | Importin-2        | 3  | 2000 | Sun PD     | USA     | Maryland|
| 64 | 1IM9   | Cw*0401| QYDDAVYKL        | 9 | Synthetic         | 2.8| 2001 | Wiley DC   | USA     | Cambridge|
| 65 | 3CDG   | G      | VMAPRTLFL        | 9 | Synthetic construct | 3.1| 2008 | Rossjohn J | Australia| Victoria|
| 66 | 3KYN   | G      | KGPPAALTL        | 9 | Synthetic construct | 2.4| 2010 | Clements CS | Australia| Victoria|
| 67 | 3KYO   | G      | KLPAQFYIL        | 9 | Synthetic construct | 1.7| 2010 | Clements CS | Australia| Victoria|

S = Serial number; Code = PDB code; L = Length of peptide; R = Resolution
| S  | Code | Allele | Peptide sequence                  | L   | Source     | RÅ | Year | Group          | Country      | State      |
|----|------|--------|-----------------------------------|-----|------------|----|------|----------------|--------------|------------|
| 1  | 1UVQ | DC1    | EGRDSMNLPSKTKVSWAA VGGGSLVPREGS | 33  | Human Orexin | 1.8 | 2004 | Fugger L       | UK           | Oxford     |
| 2  | 1S9V | DQ1    | LQPFPQPELPHY                     | 11  | Synthetic  | 2.2 | 2004 | Sollid LM      | USA          | Stanford   |
| 3  | 2NNA | DQ8    | QQYPSEGSFQPQSQENPQ               | 18  | Gluten     | 2.1 | 2006 | Anderson RP    | Australia    | Victoria   |
| 4  | 1JK8 | DQ8    | LVEALYLVCGERGG                   | 14  | Human insulin | 2.4 | 2001 | Wiley DC       | USA          | Boston     |
| 5  | 4GG6 | DQ1    | QQYPSEGSFQPQSQENPQ               | 18  | MM1        | 3.2 | 2012 | Rossjohn J     | Australia    | Victoria   |
| 6  | 1KLG | DR1    | GELIGILNAAKVPAD                  | 15  | Synthetic  | 2.4 | 2001 | Mariuzza RA    | USA          | Maryland   |
| 7  | 1KLU | DR1    | GELIGTGLNAAKVPAD                 | 15  | Synthetic  | 1.9 | 2001 | Mariuzza RA    | USA          | Maryland   |
| 8  | 1T5W | DR1    | AAYSDQATPLLSPR                   | 15  | Synthetic  | 2.4 | 2004 | Stern LJ       | USA          | Massachusetts |
| 9  | 2IAN | DR1    | GELIGTGLNAAKVPAD                 | 15  | Human      | 2.8 | 2006 | Mariuzza RA    | USA          | Maryland   |
| 10 | 2FSE | DR1    | AGFKGEGQGPKGEG                   | 14  | Collagen   | 3.1 | 2006 | Park HW        | USA          | Memphis    |
| 11 | 1SJH | DR1    | PEVIPMSALSSEG                    | 13  | HIV1       | 2.2 | 2004 | Stern LJ       | USA          | Cambridge  |
| 12 | 2Q6W | DR1    | AWRSDALPGLS                      | 12  | Integrin   | 2.2 | 2007 | Stern LJ       | USA          | Cambridge  |
| 13 | 1ZGL | DR2    | VHFFKNVTPTPG                     | 15  | Myelin     | 2.8 | 2005 | Mariuzza RA    | USA          | Maryland   |
| 14 | 1H15 | DR2    | GGVYHFKVKKHVHES                  | 14  | EPV related | 3.1 | 2002 | Fugger L       | UK           | Oxford     |
| 15 | 1A6A | DR3    | PVSKRMATPLLMQA                   | 15  | Human CLIP | 2.7 | 1998 | Wiley DC       | USA          | Massachusetts |
| 16 | 2SEB | DR4    | AYMRADAAAGGA                     | 12  | Collagen   | 2.5 | 1997 | Wiley DC       | USA          | Massachusetts |

S = Serial number; Code = PDB code; L = Length of peptide; R = Resolution
Results and Discussion

3.1 HLA-Peptide Binding Prediction for T-Cell Epitope Design

The rate-limiting step in T-cell epitope design is allele-specific HLA-peptide binding prediction. The number of known HLA alleles is over 12542 in number as of March 2015 at the IMGT/HLA database [11]. Hence, a number of methods have been formulated so far and optimized for HLA-peptide binding prediction during the last two decades. Structural information on HLA-peptide complexes has increased our understanding of their binding patterns (Tables 1.1 and 1.2). The HLA-binding groove is structurally similar among class I (Fig. 1.1a) and class II (Fig. 1.1b) alleles. The class I (Fig. 1.1c) and class II (Fig. 1.1d) bound peptides do not show an identical binding pattern at the groove. A detailed illustration of peptide binding patterns (Fig. 1.2) at the groove of class I and class II alleles provides valuable insights using mean and deviation profiles (Fig. 1.3).
Fig. 1.2 The peptide binding pattern at the groove is illustrated as function of residue position for class I and class II alleles using a dataset (Tables 1.1 and 1.2) of HLA-peptide complexes (67 class I and 16 class II) retrieved from protein databank (PDB). This dataset is represented by several class I and class II alleles (see Tables 1.1 and 1.2). The peptide lengthwise distribution of the binding pattern is shown as relative binding measure using change in solvent-accessible surface area upon complex formation with the HLA groove.

A comprehensive description of HLA-peptide binding prediction is documented [14, 15]. Lee and McConnell [16] proposed a general model of invariant chain association with class II HLA using the side-chain packing technique on a known structural template complex with self-consistent ensemble optimization (SCEO) [17, 18] using the program CARA in the molecular visualization/modeling software LOOK (Molecular Application Group (1995), Palo Alto, CA) [16, 19]. This was an important development in the field and the approach was extended to a large dataset of known HLA-binding peptides. Kangueane et al. [20] collected over 126 class I peptides with known IC_{50} values from literature with defined HLA allele specificity. These peptides were modeled using available templates for a large-scale assessment of peptide binding to defined HLA alleles. Thus, a structural framework was estab-
The mean peptide binding pattern with standard deviation (SD) at the groove is illustrated as function of residue position for class I and class II alleles using a dataset (Tables 1.1 and 1.2) of HLA-peptide complexes (67 class I and 16 class II) retrieved from protein databank (PDB). This provides insight into the understanding of the nature of peptide binding at the groove towards the design of an effective T-cell epitope candidate.

An extended dataset of class 1 and class 2 complexes were manually created, curated, and analyzed for insights into HLA-peptide binding patterns at the groove [21]. These studies lead to a detailed analysis of the HLA-peptide interface at the groove and the importance of peptide side chain and backbone atomic interactions were realized [22]. Meanwhile, the amount of structural data on HLA-peptide complexes was increasing in size leading to the development of an online database [23]. Thus, information gleaned from HLA-peptide structural complexes helped to identify common pockets among alleles in the binding groove and provided insights into
functional overlap among them [24]. The need for a simple, robust, generic HLA-peptide binding prediction was evident. Therefore, a model was formulated by defining virtual pockets at the peptide-binding groove using information gleaned from a structural dataset of HLA-peptide complexes [25]. The model (average accuracy of 60%) was superior because of its application to any given class I allele whose sequence is clearly defined. The model (53% accuracy) was then extended for class II prediction using a class II-specific HLA-peptide structural dataset [26].

The techniques thus far established are highly promising towards short peptide vaccine design and development [27, 28]. Nonetheless, it was observed that alleles are covered within few HLA supertypes, where different members of a supertype bind similar peptides, yet exhibiting distinct repertoires [29]. These principles led to the development of frameworks to group alleles into HLA supertypes [30, 31], understand their structural basis [32], and cluster alleles based on electrostatic potential at the groove [33]. These observations should aid in the design of peptide vaccine candidates for viruses including HIV/AIDS [5, 6]. Further, for example, the importance of protein modifications to enhance HIV-1 ENV trimer spike protein vaccine across multiple clades, blood, and brain is discussed [4]. Currently available types of vaccine technology [34, 35], such as live virus, killed virus, and conjugate vaccines, have failed to produce a promising vaccine against several clinically important viruses, including HIV/AIDS [36]. Therefore, short peptide vaccines are promising solutions for viral vaccine development. It should be noted that there are many other viruses for which vaccines are needed. Examples of additional viruses for which there are no vaccines available, vaccines are still under development, vaccine failures occurred, or more effective vaccines are needed include RSV, measles, HBV, WNV, Coronaviruses, H5N1 influenza virus, HCV, Adenovirus, Hantavirus, and Filoviruses [37–47].

### 4 Conclusion

The design and development of short peptide cocktail vaccines is a possibility in the near future. This function on the principle of short epitopes developed through the binding of CD8+/CD4+-specific HLA alleles. HLA molecules are specific within ethnic populations and are polymorphic with more than 12542 known alleles as of March 2015. Thus, the binding of short peptide antigens to HLA alleles is rate limiting yet specific, with high sensitivity, while producing T-cell-mediated immune responses. Our understanding of this specific peptide binding to HLA alleles has improved using known HLA-peptide complexes. There is a search for superantigen peptides covering major HLA supertypes. Thus, peptide-binding predictions with large coverage, accuracy, sensitivity, and specificity are essential for vaccine candidate design and development. It should be noted that available HLA-peptide binding prediction methods are highly promising in these directions.
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