Paul Shapshak
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Global Virology I

Identifying and Investigating Viral Diseases

Springer

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Foreword

Viral diseases are spreading globally. Recent changes are accelerating due to concomitant human behaviors including war, violence, poverty, starvation, and contemporaneous vector transmission. Additional factors include global warming, international travel, and encroachment of the prior balance of nature, i.e., invasion of nonhuman ecological domains by humans.

This book for professionals, students, faculty, and the interested reader brings to bear a snapshot of where we are.

We acknowledge and thank Professor Francesco Chiappelli (UCLA, Los Angeles, CA) for help in initiating this book, and Ioanna Panos Morris and Rita Beck of Springer Science + Business Media for help and guidance through the steps leading to the production of this book.

Preface

Global warming, ever-increasing international travel, concomitant changes in human and animal behaviors, and vector transmission all influence and have had a huge impact on the spread of viral diseases. Many excellent and informative books review these topics. To reference a few, Wertheim et al. [1] published a human infectious disease atlas and Petersen et al. [2] published a geographic guide to infectious diseases. Geopolitics is also discussed in these books, as is the involvement of many diseases, including measles, influenza, poliomyelitis, yellow fever, dengue, malaria, smallpox, cholera, leprosy, typhoid, typhus, bubonic plague, tuberculosis, and diseases caused by parasites and protozoa. Historically, of 150 common infections, the most devastating have been 35 diseases caused by bacteria, 28 diseases caused by viruses, and 6 diseases caused by protozoa [3].

This book provides trajectories and illustrations of viruses that have catapulted into the global arena (linked to humans, animals, and vectors) due to human behaviors in recent years, as well as viruses that have already shown expansion among humans, animals, and vectors just a few decades ago. Topics in the current book include vaccines, environmental impact, emerging virus transmission, filoviruses (Ebola virus), hemorrhagic fevers, flaviviruses, dengue evasion, papillomaviruses, hepatitis C, giant viruses, bunyaviruses, encephalitides, West Nile virus, Zika virus, XMRV, henipaviruses, respiratory syncytial virus, influenza, and several aspects of HIV-1 infection.

It should also be noted that among many articles pertaining to public health, lack of hygiene is demonstrably an important element in the spread of disease. Moreover, public education is a key component of what is needed to combat the spread of disease (e.g., hepatitis A) [4, 5].

In conclusion, the eradication of war, human trafficking, drug abuse, and poverty should be major goals toward the suppression of such pestilence. Education is a pillar upon which such eradication is based.

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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.

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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

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[6, 7]. The LANL HIV molecular immunology database provides comprehensive information on all known T-cell epitopes in the literature [8]. 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) [9]. 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® [10].

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® [10].

2.4 Accessible Surface Area Calculations

Accessible surface area (ASA) was calculated using the WINDOWS software Surface Racer [12] with Lee and Richard implementation [13]. 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 $Å^2$ 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).

Table 1.1 Dataset of class 1 HLA-peptide structures downloaded from PDB

S	Code	Allele	Peptide sequence	L	Source	RÅ	Year	Group	Country	State
1	1 W72	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	ALWGPDPAAA	10	Insulin	2.71	2012	Andrew SK	UK	Cardiff
4	3UTT	A*0201	ALWGPDPAAA	10	Insulin	2.6	2012	Sewell AK	UK	Cardiff
5	1I4F	A*0201	GVYDGREHTV	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	ALWGFFPVL	9	Human-peptide	2.6	1998	Collins EJ	USA	North Carolina
8	1I7U	A*0201	ALWGFVPVL	9	Synthetic	1.8	2001	Collins EJ	USA	North Carolina
9	1I7T	A*0201	ALWGVFPVL	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	1I1F	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	LLFGYAVYV	9	Tax peptide P6A	2.8	1999	Wiley DC	USA	Massachusetts
16	1QSE	A*0201	LLFGYPRYV	9	Tax peptide V7R	2.8	1999	Wiley DC	USA	Massachusetts
17	1QSF	A*0201	LLFGYPVAV	9	Tax peptide Y8A	2.8	1999	Wiley DC	USA	Massachusetts
18	1AO7	A*0201	LLFGYPVYV	9	HTLV-1 Tax	2.6	1997	Wiley DC	USA	Massachusetts
19	1BD2	A*0201	LLFGYPVYV	9	HTLV-1 Tax	2.5	1998	Wiley DC	USA	Massachusetts
20	1DUZ	A*0201	LLFGYPVYV	9	HTLV-1 Tax	1.8	2000	Wiley DC	USA	Massachusetts
21	1HHK	A*0201	LLFGYPVYV	9	Synthetic	2.5	1993	Wiley DC	USA	Massachusetts
22	1IM3	A*0201	LLFGYPVYV	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

26	3FQR	A*0201	YLDGIHSGA	10	Beta-catenin	1.7	2009	Purcell AW	Australia	Victoria
27	3FQT	A*0201	GLLGSPVRA	9	Tyrosine-phosphatase	1.8	2009	Purcell AW	Australia	Victoria
28	3FQU	A*0201	GLLGSPVRA	9	Tyrosine-phosphatase	1.8	2009	Purcell AW	Australia	Victoria
29	3FQW	A*0201	RVASPTSGV	9	Insulin receptor	1.93	2009	Purcell AW	Australia	Victoria
30	3FQX	A*0201	RVASPTSGV	9	Insulin receptor	1.7	2009	Purcell AW	Australia	Victoria
31	1QQD	A*0201	QYDDAVYKL	9	HLA-CW4	2.7	1999	Wiley DC	USA	Massachusetts
32	1P7Q	A*0201	ILKEPVHGV	9	POL polyprotein	3.4	2003	Bjorkman PJ	USA	California
33	2HN7	A*1101	AIMPARFYPK	9	DNA polymerase	1.6	2006	Gajhede M	Denmark.	Copenhagen
34	1X7Q	A*1101	KTFPPTEPK	9	SARS nucleocapsid	1.45	2005	Gajhede M	Denmark.	Copenhagen
35	3BVN	B*1402	RRRWRRLTV	9	Latent membrane	2.55	2009	Ziegler A	Germany	Berlin
36	3BP4	B*2705	IRAAPPPLF	9	Lysosomal	1.85	2008	Ziegler A	Germany	Berlin
37	1HSA	B*2705	ARAAAAAAA	9	N/A	2.1	1992	Wiley DC	USA	Massachusetts
38	1JGE	B*2705	GRFAAAIAK	9	Synthetic (M9)	2.1	2002	Ziegler UB	Germany	Berlin
39	1OF2	B*2709	RRKWRRWHL	9	Intestinal	2.2	2004	Ziegler UB	Germany	Berlin
40	1JGD	B*2709	RRLLRGHNQY	10	s10R	1.9	2003	Ziegler A.	Germany	Berlin
41	1K5N	B*2709	GRFAAAIAK	9	Synthetic (M9)	1.09	2002	Ziegler UB	Germany	Berlin
42	3BP7	B*2709	IRAAPPPLF	9	Lysosomal	1.8	2008	Ziegler A.	Germany	Berlin
43	1ZSD	B*3501	EPLPQGQLTAY	11	BZLF1	1.7	2005	McCluskey J	Australia	Brisbane
44	1A9B	B*3501	LPPLDITPY	9	EBNA-3C	3.2	1998	Saenger W	Germany	Berlin
45	1A9E	B*3501	LPPLDITPY	9	EBV-Ebna3c	2.5	1998	Saenger W	Germany	Berlin
46	3LN4	B*4103	AEMYGSV TEHPSPSPL	16	Ribonucleo protein	1.3	2010	Blasczyk R	Germany	Hannover
47	3LN5	B*4104	HEEAVSVDRVL	11	Thioadenosine	1.9	2010	Blasczyk R	Germany	Hannover
48	3DX6	B*4402	EENLLDFVRF	10	EBV decapeptide	1.7	2009	Rossjohn J	Australia	Victoria
49	3DX7	B*4403	EENLLDFVRF	10	EBV decapeptide	1.6	2009	Rossjohn J	Australia	Victoria
50	1SYS	B*4403	EEPTVIKKY	9	Sorting nexin 5	2.4	2004	McCluskey J	Australia	Victoria
51	3DXA	B*4405	EENLLDFVRF	10	EBV decapeptide	3.5	2009	Rossjohn J	Australia	Victoria

(continued)

Table 1.1 (continued)

S	Code	Allele	Peptide sequence	L	Source	RÅ	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	TPYDINQML	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	RIIPRHLQL	9	Histone H2A.x	2.5	2006	Maenaka K	Japan	Fukuoka
62	2D31	B27	RIIPRHLQL	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

Table 1.2 Dataset of class 2 HLA-peptide structures downloaded from PDB

S	Code	Allele	Peptide sequence	L	Source	RÅ	Year	Group	Country	State
1	1UVQ	DC1	EGRDSMNLPSTKVSWAA VGGGGSLVPRGSGGGG	33	Human Orexin	1.8	2004	Fugger L	UK	Oxford
2	1S9V	DQ1	LQPFPQPELPY	11	Synthetic	2.2	2004	Sollid LM	USA	Stanford
3	2NNA	DQ8	QQYPSGEGSFQPSQENPQ	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	QQYPSGEGSFQPSQENPQ	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	GELIGTLNAAKVPAD	15	Synthetic	1.9	2001	Mariuzza RA	USA	Maryland
8	1T5W	DR1	AAYSDQATPLLLSPR	15	Synthetic	2.4	2004	Stern LJ	USA	Massachusetts
9	2IAN	DR1	GELIGTLNAAKVPAD	15	Human	2.8	2006	Mariuzza RA	USA	Maryland
10	2FSE	DR1	AGFKGEQGPKGEPG	14	Collagen	3.1	2006	Park HW	USA	Memphis
11	1SJH	DR1	PEVIPMFSALSEG	13	HIV1	2.2	2004	Stern LJ	USA	Cambridge
12	2Q6W	DR1	AWRSDEALPLGS	12	Integrin	2.2	2007	Stern LJ	USA	Cambridge
13	1ZGL	DR2	VHFFKNIVTPRTPGG	15	Myelin	2.8	2005	Mariuzza RA	USA	Maryland
14	1H15	DR2	GGVYHFVKKHVHES	14	EPV related	3.1	2002	Fugger L	UK	Oxford
15	1A6A	DR3	PVSKMRMATPLLMQA	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

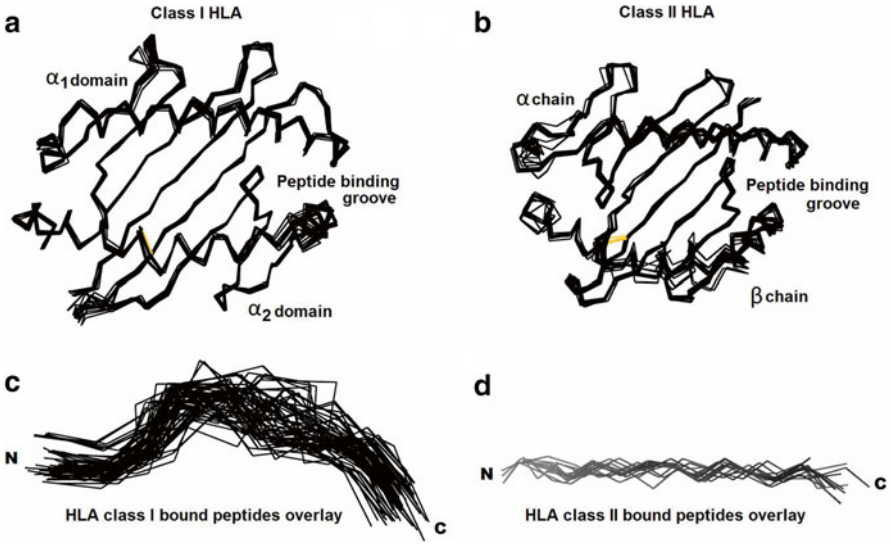

Fig. 1.1 The structural basis for short peptide vaccine design is illustrated. The allele-specific nomenclature defined, ethnicity profiled using known HLA sequences at the IMGT/HLA database [11], and the striking backbone structural similarity of antigen peptides at the HLA binding groove is the bottleneck. This is generated with 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) [9] using with Discovery Studio® (Accelrys Inc.) [10]. (**a**) The peptide-binding groove (superimposed) in class I HLA is structurally similar among known alleles and complexes. (**b**) The peptide-binding groove (superimposed) in class II HLA is structurally similar among known alleles and complexes; (**c**) class I HLA-bound peptides overlay showing structural constraints (bend peptides) at the groove; (**d**) class II bound peptides overlay showing extended conformation at the groove. This clearly suggests that class I (panel **c**) and class II (panel **d**) bound peptides do not have identical binding patterns at the groove

3 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).

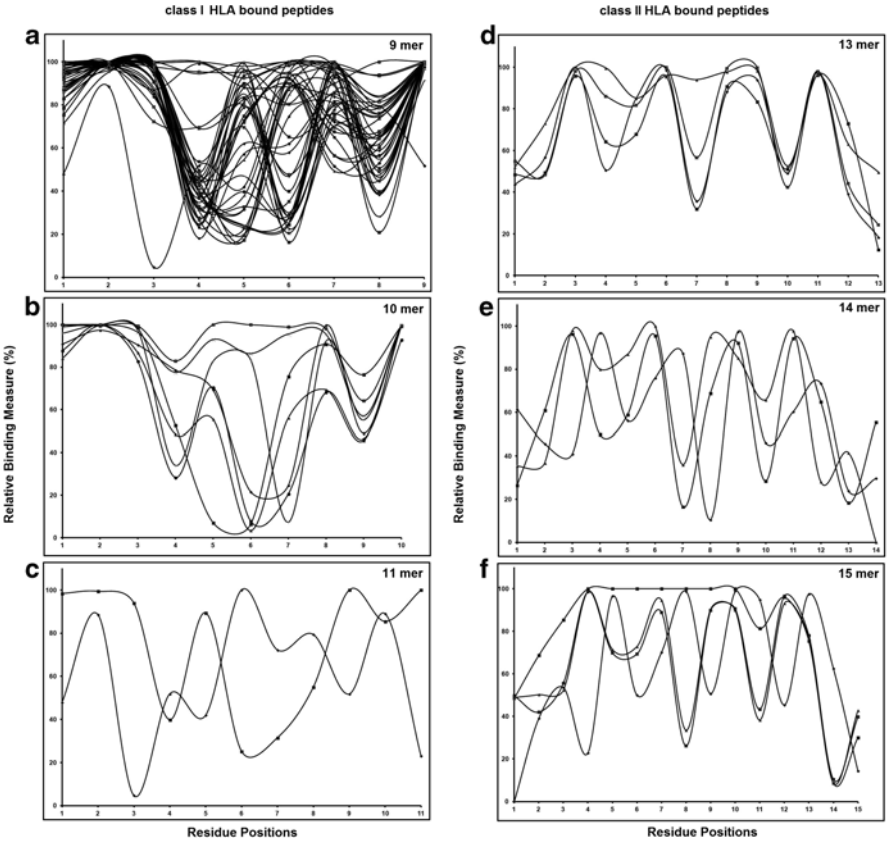

Fig. 1.2 The peptide binding pattern at the groove is illustrated as function of residue position for class I and class II alleles using a dataset (Tables 1.1 and 1.2) of HLA-peptide complexes (67 class I and 16 class II) retrieved from protein databank (PDB). This dataset is represented by several class 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-

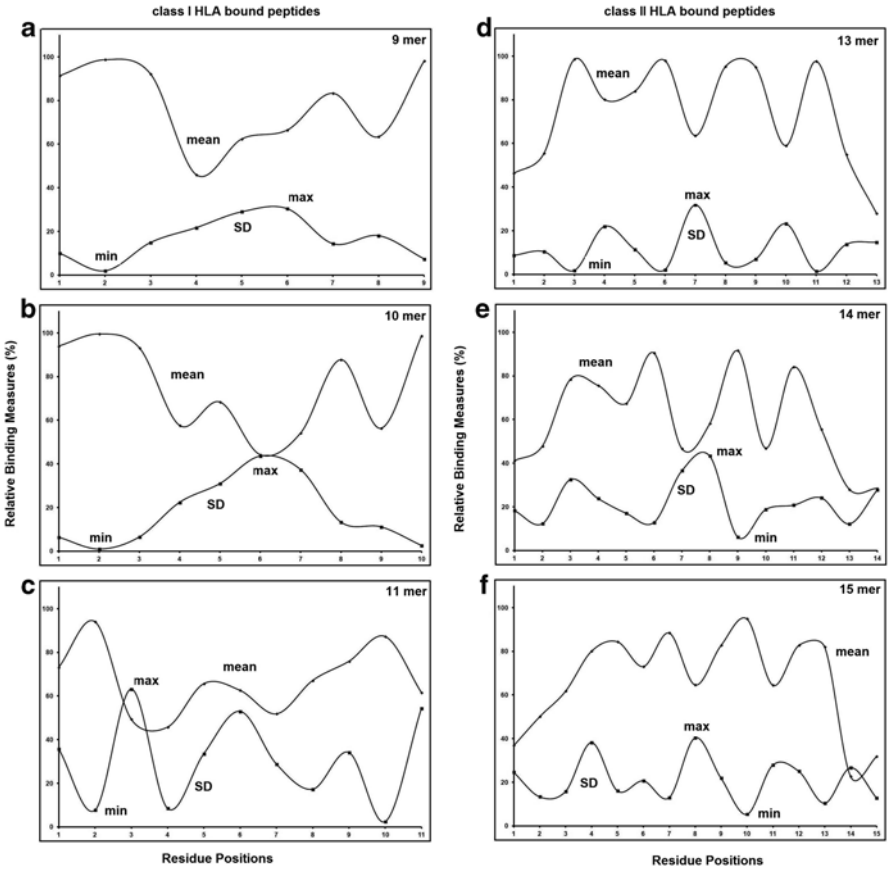

Fig. 1.3 The mean peptide binding pattern with standard deviation (SD) at the groove is illustrated as function of residue position for class I and class II alleles using a dataset (Tables 1.1 and 1.2) of HLA-peptide complexes (67 class I and 16 class II) retrieved from protein databank (PDB). This provides insight into the understanding of the nature of peptide binding at the groove towards the design of an effective T-cell epitope candidate

lished for discriminating allele-specific binders from non-binders using rules derived from a dataset of HLA-peptide complexes. This procedure was promising.

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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