B CELL EPITOPES AND PREDICTIONS
OUTLINE

• What is a B-cell epitope?
• How can you predict B-cell epitopes?
WHAT IS A B-CELL EPITOPE?

- B-cell epitopes:
  - Accessible structural feature of a pathogen molecule.
  - Antibodies are developed to bind the epitope specifically using the complementary determining regions (CDRs).
THE BINDING INTERACTIONS

- Salt bridges
- Hydrogen bonds
- Hydrophobic interactions
- Van der Waals forces

Binding strength
**B-CELL EPITOPE CLASSIFICATION**

B-cell epitope: **structural feature of a molecule or pathogen, accessible and recognizable by B-cell receptors and antibodies**

- **Linear epitopes**
  - One segment of the amino acid chain
- **Discontinuous epitope (with linear determinant)**
- **Discontinuous epitope**
  - Several small segments brought into proximity by the protein fold

Technical University of Denmark - DTU
Department of systems biology

ECCB/ISMB-2009 - Immunological Bioinformatics Tutorial

Thursday, 11 June 2009
BINDING OF A DISCONTINUOUS EPITOPE

Antibody FAB fragment complexed with Guinea Fowl Lysozyme (1FBI).

Black: Light chain, Blue: Heavy chain, Yellow: Residues with atoms distanced < 5Å from FAB antibody fragments.

Guinea Fowl Lysozyme

KVFGRCELAAAAMKRHGLDNYRGYSGLGNWVCAAKFESNFNSQNRNTDGS
DYGVLNSRWYNDGRTPGSRNLCPNCSALSQSDITANCAKKIVSDG
GMNAWVAWRKCKGTDRVWIKGCRL
B-CELL EPITOPE ANNOTATION

• Linear epitopes:
  • Chop sequence into small pieces and measure binding to antibody

• Discontinuous epitopes:
  • Measure binding of whole protein to antibody

• The best annotation method: X-ray crystal structure of the antibody-epitope complex
B-CELL EPITOPE DATA BASES

- Databases:
  - IEDB, Los Alamos HIV database, Protein Data Bank, Antijen, BciPep

- Large amount of data available for linear epitopes

- Few data available for discontinuous
B CELL EPITOLPE PREDICTION
SEQUENCE-BASED METHODS FOR PREDICTION OF LINEAR EPITOPES

- **Protein hydrophobicity – hydrophilicity algorithms**
  - Parker, Fauchere, Janin, Kyte and Doolittle, Manavalan
  - Sweet and Eisenberg, Goldman, Engelman and Steitz (GES), von Heijne

- **Protein flexibility prediction algorithm**
  - Karplus and Schulz

- **Protein secondary structure prediction algorithms**
  - PsiPred (D. Jones)

- **Protein “antigenicity” prediction**:
  - Hopp and Woods, Welling

TSQDLSVFPLASCCKDNIASTSVTLGCLVTGYLP
MSTTVTWDTGSLNKNVTTFPTTFHETYGLHSIVS
QVTASGKWAKQRFTCSVAHAESTAINKTSACAL
NFIPPTVKLFHSSCNPVGDHTTTIQLCLISGYV
PGDMEVIWLVDGQKATNIFPYTAPGTKENGVTST
HSELNITQGEWVSQKTYTCQVYTQGFTKDEARK
CSESDPRGVTSYLSPPSPL
**PROPENSITY SCALES: THE PRINCIPLE**

- The Parker hydrophilicity scale

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<tr>
<th>Amino Acid</th>
<th>Hydrophilicity</th>
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<tr>
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<tr>
<td>W</td>
<td>-3.00</td>
</tr>
</tbody>
</table>

**Hydrophilicity**

Friday, 11 June 2009
PROPENSITY SCALES: THE PRINCIPLE

\[ \frac{(-2.78 + -1.27 + 2.46 + 1.86 + 1.26 + 0.87 + 0.3)}{7} = 0.39 \]

Prediction scores:

\[
\begin{align*}
0.38 & 0.1 & 0.6 & 0.9 & 1.0 & 1.2 & 2.6 & 1.0 & 0.9 & 0.5 & -0.5 \\
\end{align*}
\]

Epitope
EVALUATION OF PERFORMANCE

1 - specificity

- reference line
- HADS-Dep.
- HADS-Anx.
- HADS-Total
Pellequer found that 50% of the epitopes in a data set of 11 proteins were located in turns.

Turn propensity scales for each position in the turn were used for epitope prediction.

Pellequer et al., Immunology letters, 1993
• Extensive evaluation of propensity scales for epitope prediction

• Conclusion:
  – Basically all the classical scales perform close to random!
  – Other methods must be used for epitope prediction
BEPIPRED

- Parker hydrophilicity scale
- PSSM
- PSSM based on linear epitopes extracted from the Antijen database
- Combination of the Parker prediction scores and PSSM leads to prediction score
- Tested on the Pellequer dataset and epitopes in the HIV Los Alamos database
# PSSM

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<tr>
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<td>5.2</td>
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<tr>
<td>5</td>
<td>7.9</td>
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</table>

**Sequence:**

```
.....LISTFVEDEKRPGSDIVEDLILKDENKTTVI....
```

**Prediction Value:**

\[2.46 + 1.86 + 1.26 + 0.87 + 0.3 = 6.75\]
ROC EVALUATION

Evaluation on HIV Los Alamos data set

ROC curve for BepiPred, Parker, Levitt, and random predictions.
# BEPIPRED PERFORMANCE

- **Pellequerr data set:**
  - Levitt \( \text{AROC} = 0.66 \)
  - Parker \( \text{AROC} = 0.65 \)
  - BepiPred \( \text{AROC} = 0.68 \)

- **HIV Los Alamos data set**
  - Levitt \( \text{AROC} = 0.57 \)
  - Parker \( \text{AROC} = 0.59 \)
  - BepiPred \( \text{AROC} = 0.60 \)
BEPIPRED

• BepiPred conclusion:
  • On both of the evaluation data sets, Bepipred was shown to perform better
  • Still the AROC value is low compared to T-cell epitope prediction tools!

• Bepipred is available as a webserver:
  • www.cbs.dtu.dk/services/BepiPred
# Prediction of Linear Epitopes

<table>
<thead>
<tr>
<th><strong>Pro</strong></th>
<th><strong>Con</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- easily predicted computationally</td>
<td>- only ~10% of epitopes can be classified as “linear”</td>
</tr>
<tr>
<td>- easily identified experimentally</td>
<td>- weakly immunogenic in most cases</td>
</tr>
<tr>
<td>- immunodominant epitopes in many cases</td>
<td>- most epitope peptides do not provide antigen-neutralizing immunity</td>
</tr>
<tr>
<td>- do not need 3D structural information</td>
<td>- in many cases represent hypervariable regions</td>
</tr>
<tr>
<td>- easy to produce and check binding activity experimentally</td>
<td></td>
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</table>
SEQUENCE BASED PREDICTION METHODS

• Linear methods for prediction of B cell epitopes have low performances
• The problem is analogous to the problems of representing the surface of the earth on a two-dimensional map
• Reduction of the dimensions leads to distortions of scales, directions, distances
• The world of B-cell epitopes is 3 dimensional and therefore more sophisticated methods must be developed

Regenmortel 1996, Meth. of Enzym. 9.
SO WHAT IS MORE SOPHISTICATED?

- Use of the three dimensional structure of the pathogen protein
- Analyze the structure to find surface exposed regions
- Additional use of information about conformational changes, glycosylation and trans-membrane helices
SOURCES OF THREE-DIMENSIONAL STRUCTURES

- Experimental determination
  - X-ray crystallography
  - NMR spectroscopy

- Structure prediction
  - Homology modeling
  - Fold recognition

- Both methods are time consuming and not easily done in a larger scale
- Less time consuming, but there is a possibility of incorrect predictions, specially in loop regions
PROTEIN STRUCTURE PREDICTION METHODS

• Homology/comparative modeling
  >25% sequence identity (seq 2 seq alignment)

• Fold-recognition
  <25% sequence identity (Psi-blast search/ PSSM 2 seq alignment)

• Ab initio structure prediction
  0% sequence identity
WHAT DOES ANTIBODIES RECOGNIZE IN A PROTEIN?

A: Everything accessible to a 10 Å probe on a protein surface

Novotny J. A static accessibility model of protein antigenicity.
THE CEP SERVER

- Conformational epitope server
  http://202.41.70.74:8080/cgi-bin/cep.pl
- Uses protein structure as input
- Finds stretches in sequences which are surface exposed
THE DISCOTOPE SERVER

• CBS server for prediction of discontinuous epitopes

• Uses protein structure as input

• Combines propensity scale values of amino acids in discontinuous epitopes with surface exposure

• [http://www.cbs.dtu.dk/services/DiscoTope](http://www.cbs.dtu.dk/services/DiscoTope)
DISCOTOPE

• Prediction of residues in discontinuous B cell epitopes using protein 3D structures

Pernille Haste Andersen, Morten Nielsen and Ole Lund, Protein Science 2006
A DATA SET OF DISCONTINUOUS B CELL EPITOPE

- Structures of antibodies/antigen protein complexes in the Protein DataBank

- Dr. Andrew Martin's SACS database (available at http://www.bioinf.org.uk/abs/sacs) was used to get an overview of PDB entries

- Epitopes in the data set were identified by finding residues within 4Å from heavy or light chains in the Abs

- We used homology grouping and cross-validation for the training and testing of the method to avoid biasing towards specific antigens

- The 5 sets used for cross-validated training/testing are available at: http://www.cbs.dtu.dk/suppl/immunology/DiscoTope.php

An example: The epitope of the outer surface protein A from Borrelia Burgdorferi (1OSP)
LOG-ODDS RATIOS OF AMINO ACIDS IN DISCONTINUOUS EPITOPES

Frequencies of amino acids in epitope residues compared to frequencies of non-epitope residues

Several discrepancies compared to the Parker hydrophilicity scale

Predictive performance (AUC) of B cell epitopes:
- Parker: 0.614
- Epitope log–odds: 0.634

<table>
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<tr>
<th>Amino acid</th>
<th>Parker</th>
<th>Log-odds Ratios</th>
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<tr>
<td>D</td>
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<td>0.691</td>
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<td>Q</td>
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<td>W</td>
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<td>-0.064</td>
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</table>

*Amino acids are listed with descending hydrophilicity using the values of the Parker scale.
DISCOTOPE: A PREDICTION METHOD USING 3D STRUCTURES

A combination method:

- Addition of epitope log-odds values of residues in spatial proximity
- Contact numbers

LIST..FVDEKRPGS DiVEd......ALILKDENKTTVI.

Contact number: 7

Sum of log-odds values

DiscoTope prediction value

-0.145 +0.691+0.346+1.136+1.180+1.164

Contact number: 7

Sum of log-odds values

DiscoTope prediction value

Technical University of Denmark - DTU
Department of systems biology

Thursday, 11 June 2009
DISCOTOPE: PREDICTION OF DISCONTINUOUS EPITOPES

- Receiver Operator Characteristics (ROC) curves were used for performance measures

- The reported performance is an average of the AUC values of the non-homologous groups of antigens:
  - Parker 0.614 Seq.-based
  - Epitope log–odds 0.634 Seq.-based
  - Contact numbers 0.647 Str.-based
  - Naccess 0.673 Str.-based
  - DiscoTope 0.711 Seq./Str.-based
EVALUATION EXAMPLE AMAI

• Apical membrane antigen 1 from *Plasmodium falciparum* (not used for training/testing)

• Two epitopes were identified using phage-display, sequence variance analysis and point-mutation

  (green backbone)

• Most residues identified as epitopes were successfully predicted by DiscoTope

  (black side chains)

**DiscoTope is available as webserver:**

[http://www.cbs.dtu.dk/services/DiscoTope/](http://www.cbs.dtu.dk/services/DiscoTope/)
Recent Developments

BIOINFORMATICS APPLICATIONS NOTE

Structural bioinformatics

PEPITO: improved discontinuous B-cell epitope prediction using multiple distance thresholds and half sphere exposure

Michael J. Sweredoski\textsuperscript{1,2} and Pierre Baldi\textsuperscript{1,2,*}

\textsuperscript{1}Department of Computer Science and \textsuperscript{2}Institute for Genomics and Bioinformatics, University of California, Irvine, 92697-3435, California, USA

Software

ElliPro: a new structure-based tool for the prediction of antibody epitopes

Julia Ponomarenko*\textsuperscript{1,2}, Huynh-Hoa Bui\textsuperscript{3}, Wei Li, Nicholas Fusseder, Philip E Bourne\textsuperscript{1,2}, Alessandro Sette\textsuperscript{4} and Bjoern Peters\textsuperscript{4}

Address: \textsuperscript{1}San Diego Supercomputer Center, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093, USA, \textsuperscript{2}Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093, USA, \textsuperscript{3}Isis Pharmaceuticals, Inc., 1896 Rutherford Road, Carlsbad, California 92008, USA and \textsuperscript{4}La Jolla Institute for Allergy and Immunology, 9420 Athena Circle, La Jolla, California 92037, USA
SECONDARY STRUCTURE IN EPITOPES

Sec struct:  H  T  B  E  S  G  I  .

Log odds ratio:  -0.19  0.30  0.21  -0.27  0.24  -0.04  0.00  0.17

H:  Alpha-helix (hydrogen bond from residue i to residue i+4)
G:  310-helix (hydrogen bond from residue i to residue i+3)
I:  Pi helix (hydrogen bond from residue i to residue i+5)
E:  Extended strand
B:  Beta bridge (one residue short strand)
S:  Bend (five-residue bend centered at residue i)
T:  H-bonded turn (3-turn, 4-turn or 5-turn)
:  Coil

Guillermo Carbajosa
Thursday, 11 June 2009
# Amino Acids in Epitopes

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<th>Amino Acid</th>
<th>G</th>
<th>A</th>
<th>V</th>
<th>L</th>
<th>I</th>
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<td>0.04</td>
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**DIHEDRAL ANGLES IN EPITOPES**

**Z-scores for number of dihedral angle combinations in epitopes vs. non epitopes**

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<td>0.83</td>
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<td>1.68</td>
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<td>0.00</td>
<td>1.03</td>
<td>-0.21</td>
<td>-0.79</td>
<td>0.83</td>
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RATIONAL VACCINE DESIGN

Rational Vaccine Design

>PATHOGEN PROTEIN
KVFGRCCELAAAMKRHGLDNYRGY
SLGNWVCAAKFESNF
RATIONAL B-CELL EPITOPE DESIGN

• Protein target choice

• Structural analysis of antigen

- Known structure or homology model
- Precise domain structure
- Physical annotation (flexibility, electrostatics, hydrophobicity)
- Functional annotation (sequence variations, active sites, binding sites, glycosylation sites, etc.)
RATIONAL B-CELL EPITOPE DESIGN

• Protein target choice
• Structural annotation
• Epitope prediction and ranking

- Surface accessibility
- Protrusion index
- Conserved sequence
- Glycosylation status
RATIONAL B-CELL EPITOPE DESIGN

• Protein target choice
• Structural annotation
• Epitope prediction and ranking

• Optimal Epitope presentation

- Fold minimization, or
- Design of structural mimics
- Choice of carrier (conjugates, DNA plasmids, virus like particles)
- Multiple chain protein engineering
Rational optimization of epitope-VLP chimeric proteins:

- Design a library of possible linkers (<10 aa)
- Perform global energy optimization in VLP (virus-like particle) context
- Rank according to estimated energy strain
CONCLUSIONS

• Rational vaccines can be designed to induce strong and epitope-specific B-cell responses

• Selection of protective B-cell epitopes involves structural, functional and immunogenic analysis of the pathogenic proteins

• When you can: Use protein structure for prediction

• Structural modeling tools are helpful in prediction of epitopes, design of epitope mimics and optimal epitope presentation