**Abstract:** Performance of bioinformatic approaches to discover HLA-II binding epitopes is still far from best. HLA-II polymorphism lead to the creation of the so-called pan-specific tools, which are able to predict binding epitopes for MHC alleles without previous affinity data. In fact, this kind of tools do perform slightly worse than tools focused on HLA-I molecules. The aim of this review is to perform a presentation of the forms as well as the limitations in the latest pan-specific tools in order to give some enlightenment for the progress in the field.

**Results:**

- **General schematic introduction into bioinformatic tools for the prediction of MHC-II binding epitopes.**
- **Pseudosequence generation:**
  - From NetMHCII, NetMHCIIpan’s database updates reflect the growth of data available.
  - Predivac, which is called PredivacDB and, in fact, contains 2695 to epitope promiscuity and immunodominance.
- **Epitope binding prediction:**
  - For known alleles, NetMHCIIpan’s PSSMs, Predivac assigns values to peptides.
  - In order to consider different epitope lengths, $K_{\text{d}}(\alpha) = \left( \frac{K_{\text{d}}(\alpha)}{n} \right)^{\frac{1}{n}}$.
  - Data from: Héctor Puigdomènech Gómez|Bachelor’s Degree in Genetics 2013-2017

**Discussion:**

- **Database dynamics:**
  - The aim of this review is to analyse important features which represent some of the latest pan-specific bioinformatic tools relevant to determine non-binders and binders.
- **Pseudosequence generation:**
  - There are four main tools presented in this review that use the same rule to create their pseudosequences, which is based on the distance between some peptide-bound MHC-II structures which were analysed. The fact is that some of these structures were obtained from a variety of sources, for example, proteins whose structures were determined by cryo-electron microscopy.
- **Promiscuity evaluation:**
  - All of these tools are able to make predictions for new alleles at once.
  - AUC of 0.5 random assignments.

**Key references:**

- Predivac, which is called PredivacDB and, in fact, contains 2695 to epitope promiscuity and immunodominance.

**Final remarks:**

- One of the most important conclusions of this review is the fact that there is a need of bioinformatic approaches that use semi-supervised learning techniques. This way, the field of bioinformatics can be expanded to include more complex and diverse data sets that can provide insights into the mechanisms underlying MHC-II binding epitopes.