AI-based solution for Identification of Immunopeptides with LC-MS

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Overview

Purpose: To develop an automated software suite to accelerate the identification of immunopeptides.
Methods: AI-based *de novo* sequencing and database search were integrated for peptide identification.
Results: A software suite, PEAKS X, was provided for immunopeptidomics with high sensitivity and accuracy.

Introduction

Personalized immunotherapy, in ideal cases, should depend on the neoantigens present on the cancer cell surface, of one person, one tumor, and one time. A few research groups reported direct identification of mutated peptides isolated from human leucocyte antigens (HLA) by LC-MS. Until recently, MS technologies were not sensitive enough to do this. The key challenges include diverse C-termini of HLA-peptides, lack of sequence library for spliced peptides, no peptide *de novo* sequencing algorithms for data independent acquisition (DIA) method, etc. We have introduced deep learning into peptide *de novo* sequencing [1]. Here, a new algorithm was proposed to combine *de novo* sequencing and database search for the identification of immnuopeptides from LC-MS data with both DDA and DIA approaches.

Methods

Since *de novo* sequencing is a completely unbiased peptide identification workflow, improvement of *de novo* sequencing is much more exploitable and useful for peptide identification. Deep learning technology was used for peptide *de novo* sequencing, yielding much higher accuracy and sensitivity [1].

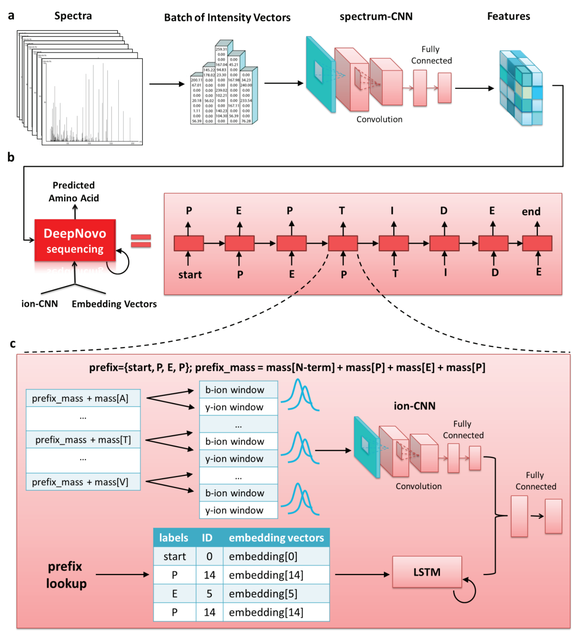


Figure 1. Deep learning system

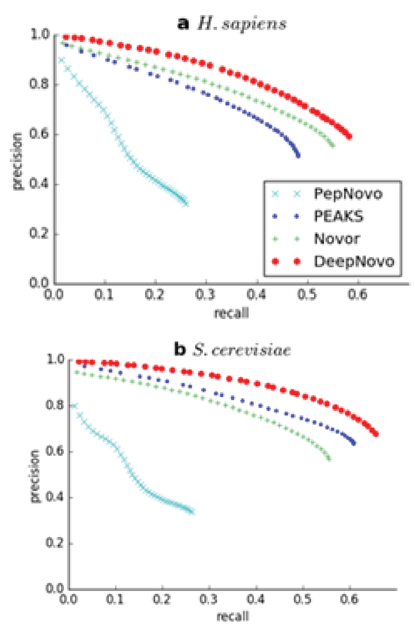


Figure 2. Performance of deep learning system

Results

1. Increased peptide identifications: By integrating the improved AI-based *de novo* sequencing into database search, PEAKS X gives higher peptide identification than current published methods. A comparison of peptide identification results for HLA peptidomes of glioblastoma multiforme (GBM) dataset (PXD008127 [2]) was conducted among the publication [2] and PEAKS X. PEAKS X identified a total of 3648 peptide sequences of soluble HLA-bound peptides in patient 11-002-V1* plasma sample, 73% more than analyzed with the method of the publication [2]. In addition, 87% peptides reported by the publication were present in PEAKS X results.

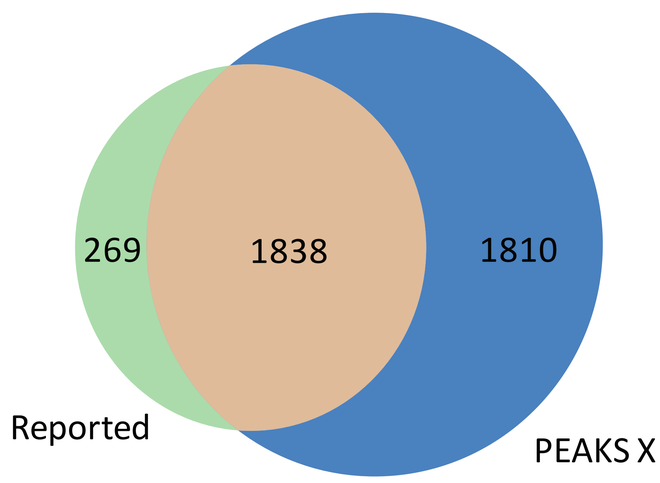
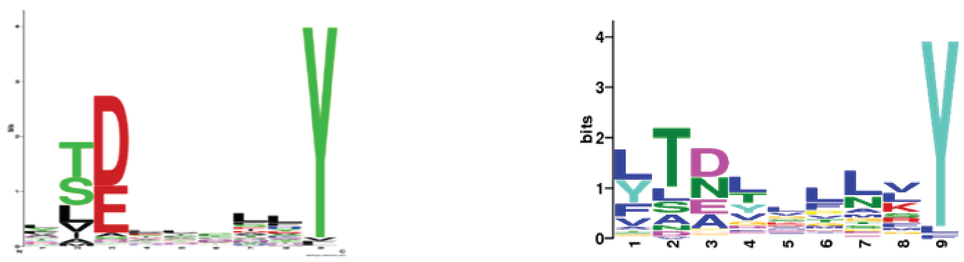


Figure 3. Venn diagram of identified peptides

2. Confident peptides found by *de novo* but not in the database: PEAKS X introduces an advanced AI-based *de novo* sequencing algorithm, which significantly improves the ability to identify peptides that are not included in current database. A test on the public DDA dataset (MSV000080527 [3]) shows that PEAKS X identified 454 peptide sequences by *de novo* only with 80% ALC for allele HLA-A*01:01. The sequence logos show that the peptides identified by *de novo* only and the peptides in IEDB database with strong binding have similar patterns.

ALC (%)	# peptides	# in IEDB
80	454	
90		4
95	33	2



2005 DB peptides with SB 454 *de novo* peptides

Figure 4. Motifs of peptides in IEDB and *de novo* peptides

3. DIA for HLA peptides: In addition to DDA data analysis, PEAKS X also supports *de novo* sequencing as well as direct database search without spectral library for the identification of immunopeptides from LC-MS data with DIA approach. A DIA dataset (PXD001904 [4]) was tested to compare the performance of PEAKS X against other methods. In total, PEAKS X identified 662 peptide sequences for Jurkat alleles (HLA-A03, -B07, -B35). Among those 304 high-confidence peptides, which were identified by at least two software tools, 90.1% (274/304) were reported by PEAKS X, 26% and 19.4% more than OpenSWATH (195/304) and a third party tool (215/304), respectively.

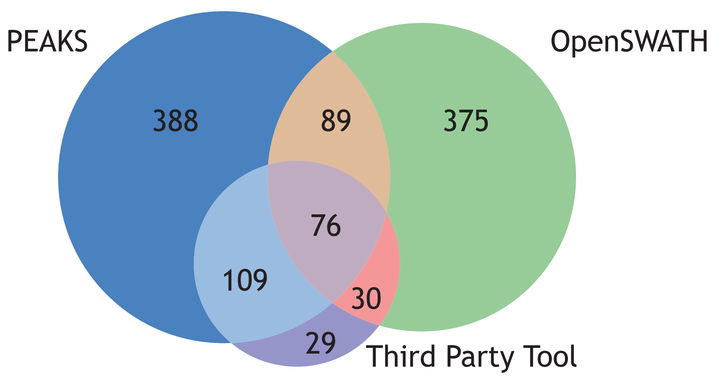


Figure 5. Comparison of identifications on PXD001904 dataset

4. Chimera spectra for DDA: Feature-based approach was implemented to handle chimeric tandem spectra for co-fragmented peptides, which significantly increases the efficiency of peptide identification. Figure 6 shows a chimeric scan with two features associated and both were identified with PEAKS X.

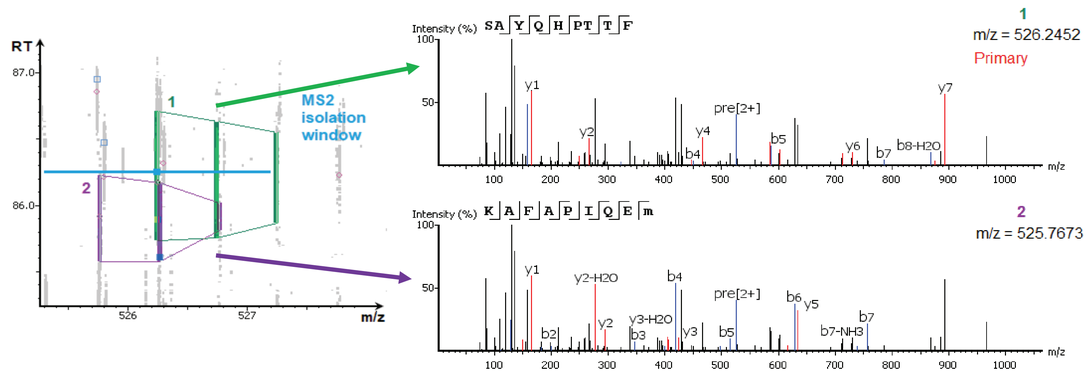


Figure 6. Peptide feature-spectrum matches for chimeric spectra

Conclusion

An AI-based data analysis workflow would provide a novel solution for immunopeptidomics with high sensitivity and accuracy.

Reference

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