De *novo* mass spectrometry peptide sequencing with a transformer model

Melih Yilmaz, Will Fondrie, Wout Bittremieux, Sewoong Oh, William Noble

Mass spectrometry provides a high-throughput framework for identifying proteins

- Proteins are digested into ~15-20 amino acid long peptides
- Peptides are analyzed in the mass spectrometer

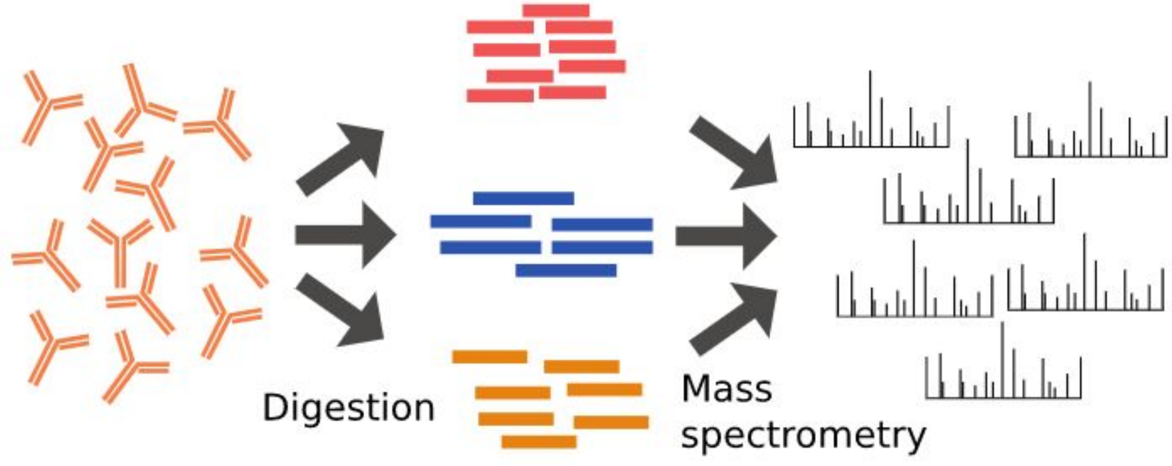
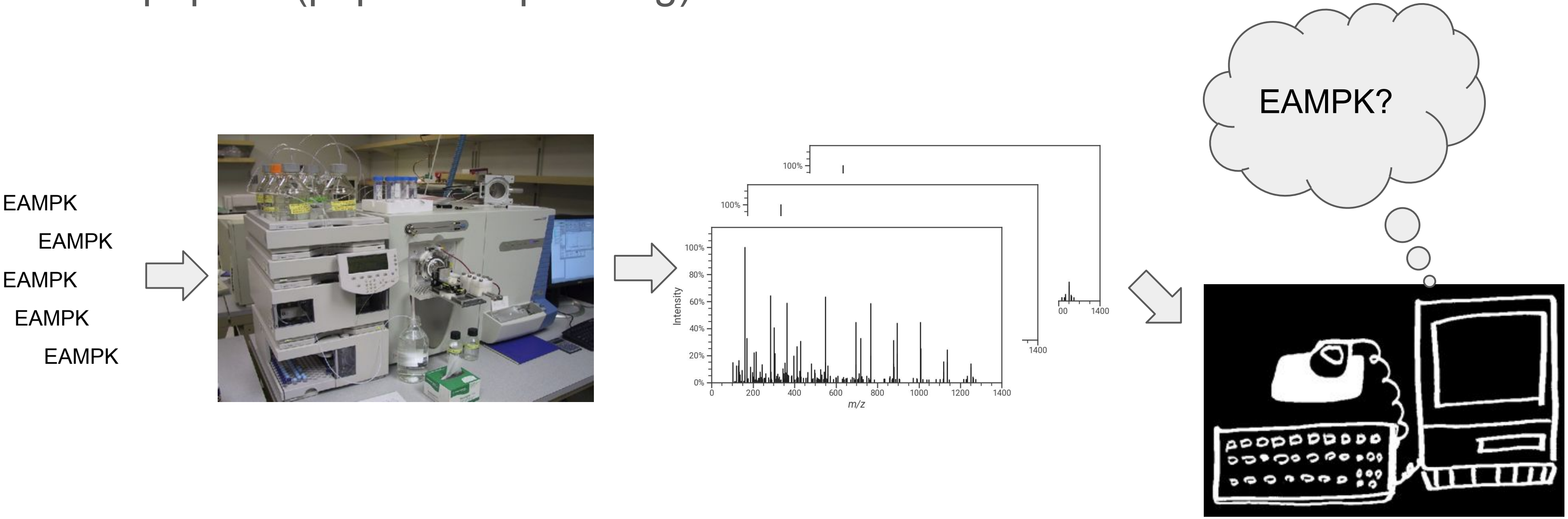


Image https://abterrabio.com/2018/08/06/de-novo-antibody-sequencing-an-overview/

The goal: assign a generating peptide to each spectrum

- Given a spectrum, computationally identify the amino acid sequence of its peptide (peptide sequencing)



EAMPK

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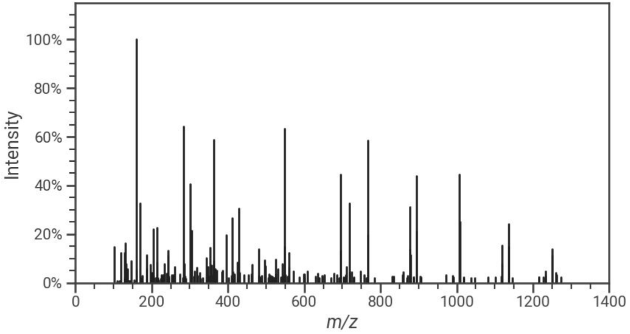
EAMPK?

De novo sequencing infers peptide directly from spectrum

Observed mass spectrum



Generating peptide

DNTIEINVEPK

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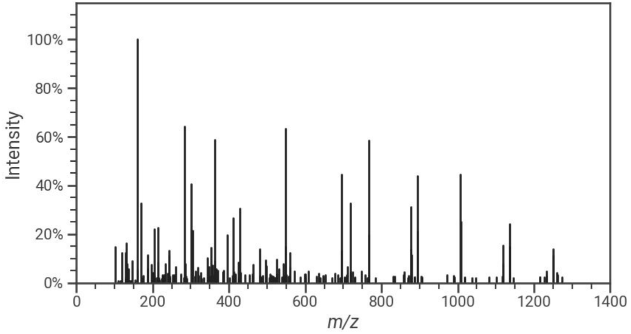

Generating peptide

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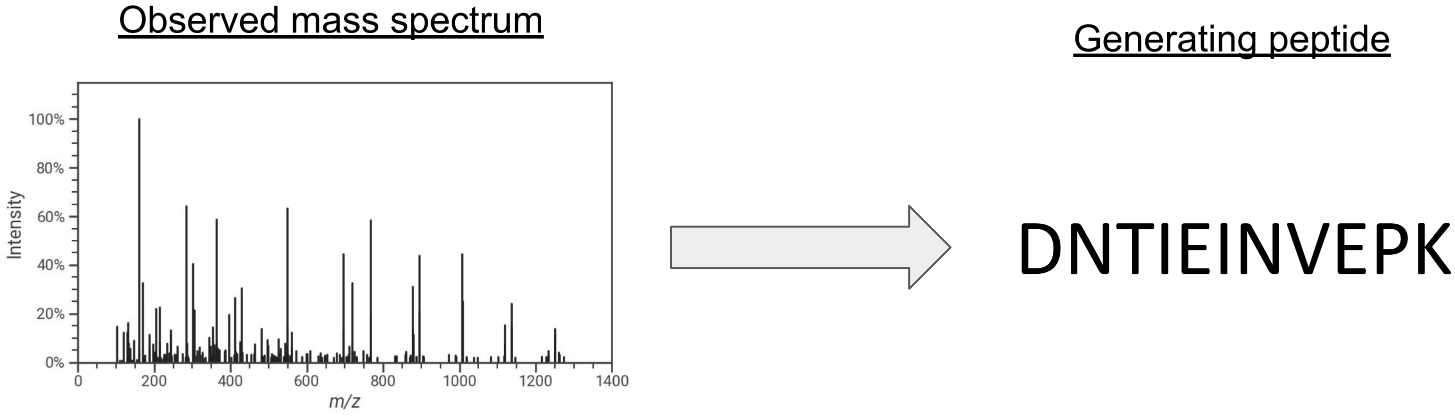
De novo sequencing infers peptide directly from spectrum

- In addition, we also observe precursor mass, i.e. full mass of the peptide, and charge
- Hard to *de novo* sequence accurately



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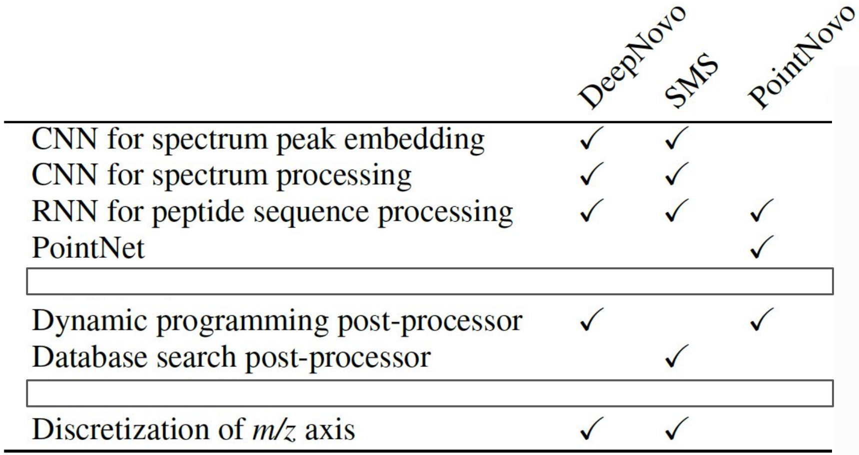
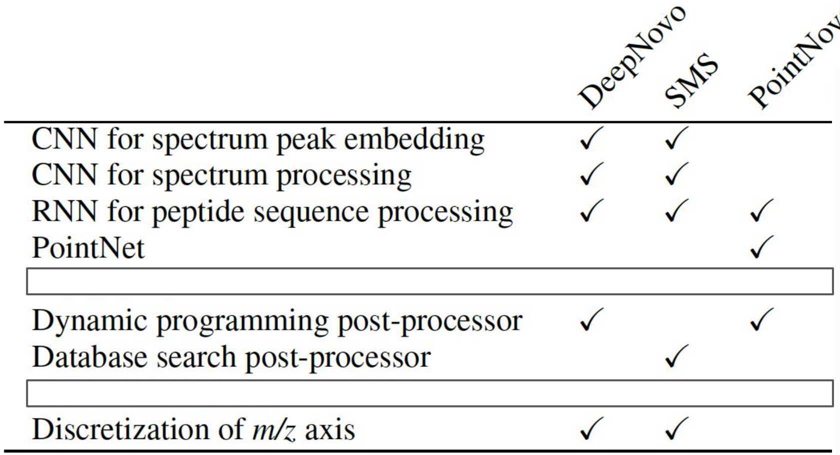


	DeepNovo	SMS	PointNovo
CNN for spectrum peak embedding	✓	✓	
CNN for spectrum processing	✓	✓	
RNN for peptide sequence processing	✓	✓	✓
PointNet			✓
Dynamic programming post-processor	✓		✓
Database search post-processor		✓	
Discretization of *m/z* axis	✓	✓	

Table: Comparison of existing deep learning methods for de novo peptide sequencing.

Shortcomings of existing methods

- **Accuracy is still low:** correctly assigns peptides to 40-60% of spectra
- **Complex models:** combines multiple neural nets and post-processing steps
  - → higher # of parameters and slow inference
- ***m/z* axis discretization:** presents a tradeoff between low binning resolution and higher model complexity



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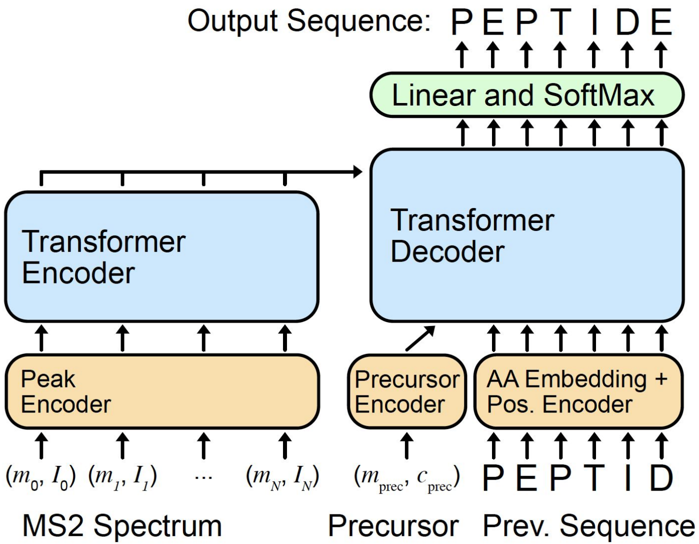
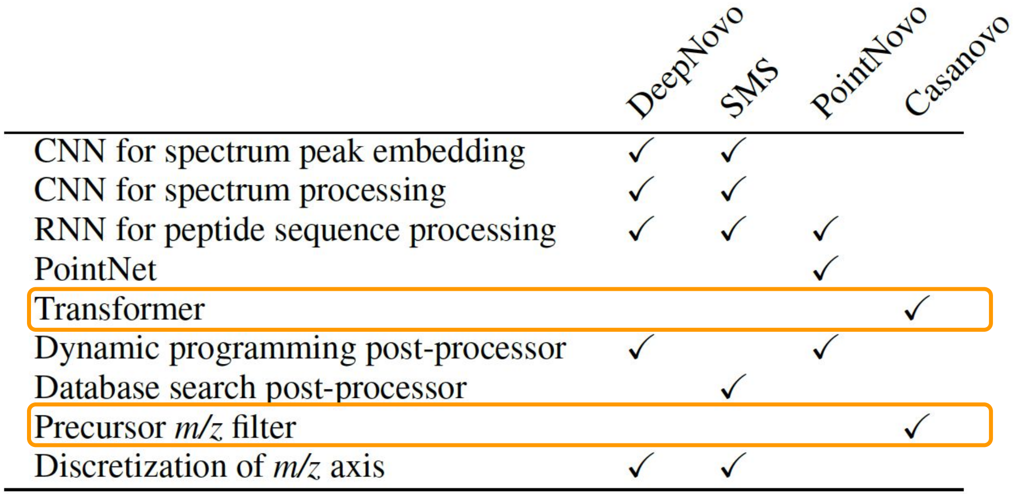
And learned with a transformer model



Output Sequence: P E P T I D E
Linear and SoftMax
Transformer Decoder
Transformer Encoder
Peak Encoder
Precursor Encoder
AA Embedding + Pos. Encoder
(m_0, I_0) (m_1, I_1) ··· (m_N, I_N)
$(m_{\text{prec}}, c_{\text{prec}})$
P E P T I D
MS2 Spectrum
Precursor
Prev. Sequence

Casanovo: a *de novo* peptide sequencing transformer

- We propose a **unified** solution to sequencing sub-tasks



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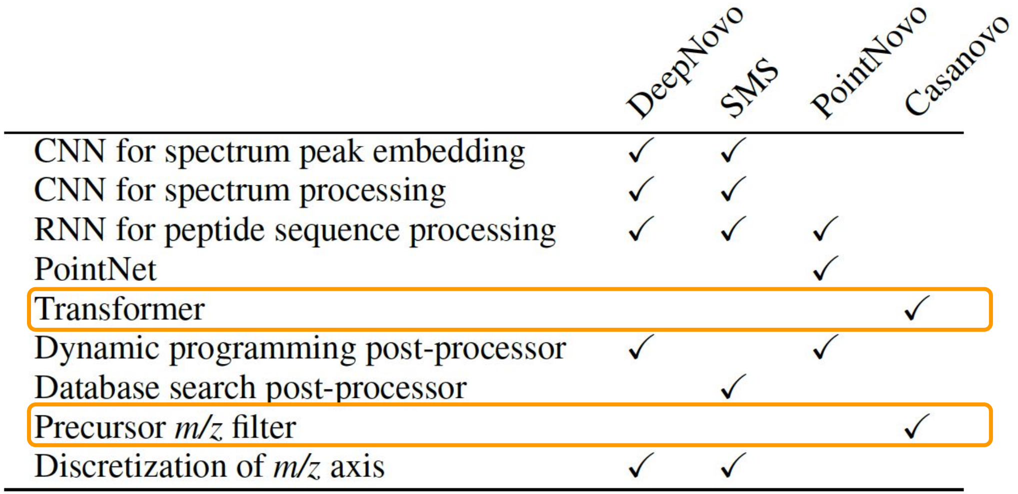

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Casanovo: a *de novo* peptide sequencing transformer

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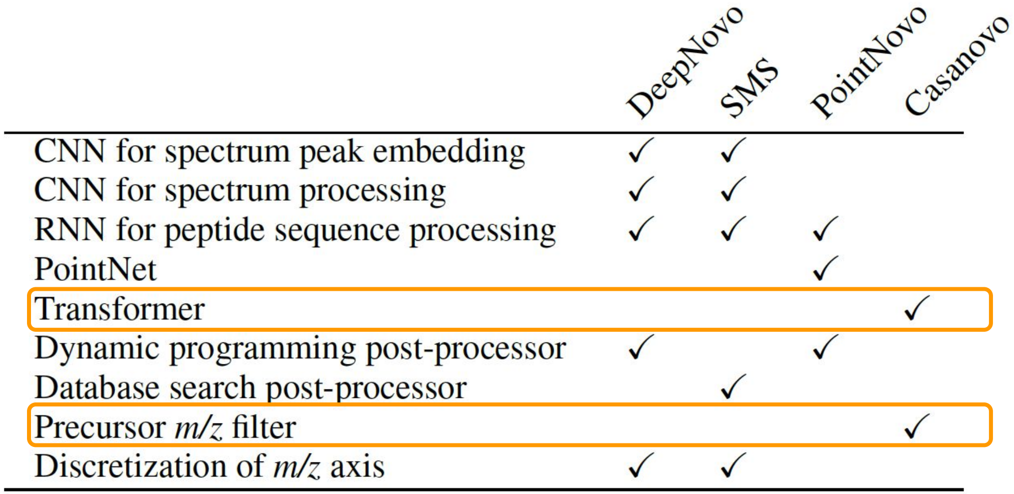
- Casanovo directly models spectrum peaks
  - No need for m/z discretization!
- Filters out implausible de novo sequences based on precursor m/z



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Cross-species evaluation framework

- Benchmark dataset with **~1.5M peptide-spectra matches** from **9 species** was used

8 species

- Train/Validation
  - 90/10
  - ~1.4M spectra

1 species (e.g. yeast)

- Test
  - ~100k spectra

Cross-species evaluation framework

- Benchmark dataset with **~1.5M peptide-spectra matches** from **9 species** was used
- Test set peptides are mostly unique, i.e. not seen in the training set

8 species

- Train/Validation
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  - ~1.4M spectra

1 species (e.g. yeast)

- Test
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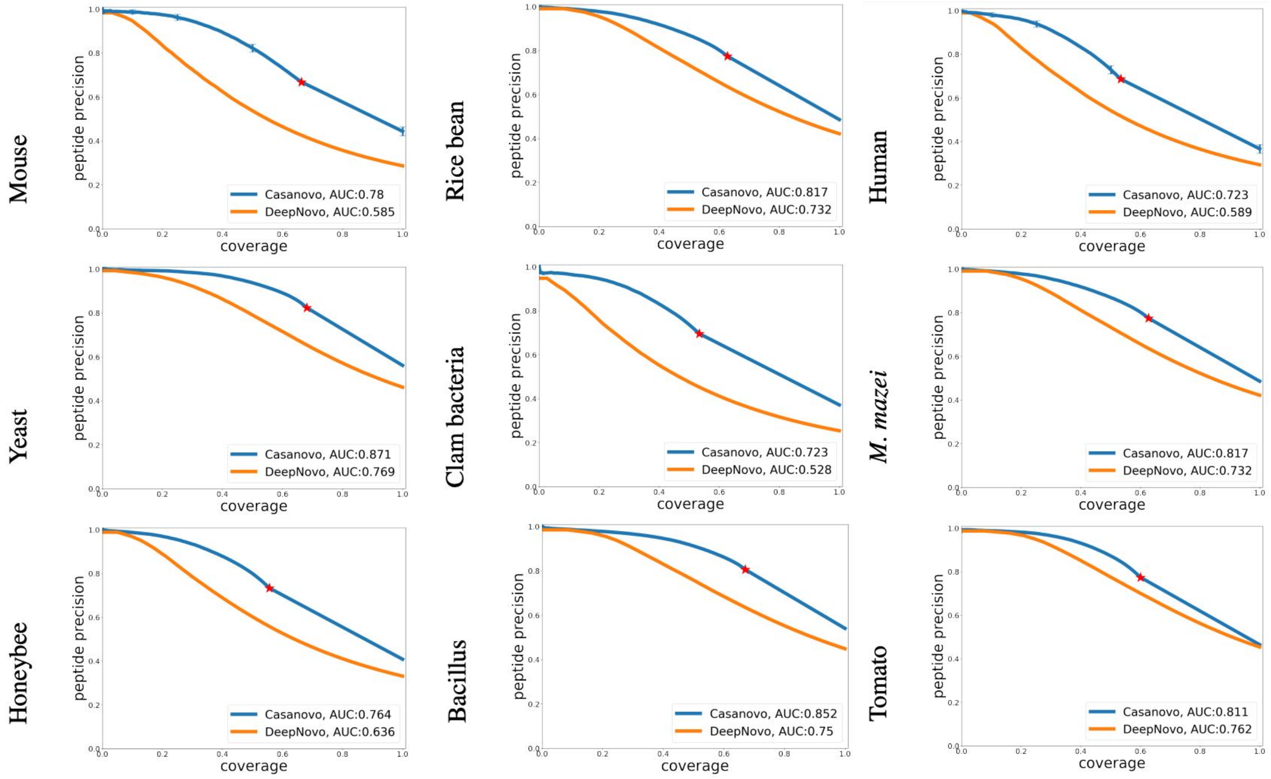
Casanovo achieves higher peptide precision in all species

- Consistently better precision at the same coverage
- Higher overall precision in all
- Mean AUC improvement of **0.13**

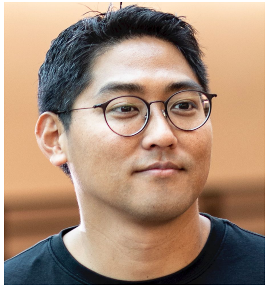


Thanks!

Code @ github.com/Noble-Lab/casanovo

Bill Noble

Will Fondrie


Sewoong Oh

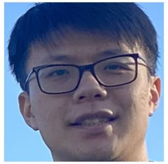
Wout Bittremieux

Noble Lab

Dejun

Kris

Bobby


Gang

Ran

Gesine

Ayse

Anu

Kianna

Lincoln

Alan

Mu

Robin

Yang

Melih

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Genome Sciences
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