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# Robust, scalable virus-host proteomics with AI-generative library of life kingdoms and iterative search of zoological space

Mingqi Liu[1], Duo Xu[1], **Quanqing Zhang**[2]*, Rong Hai[1]*

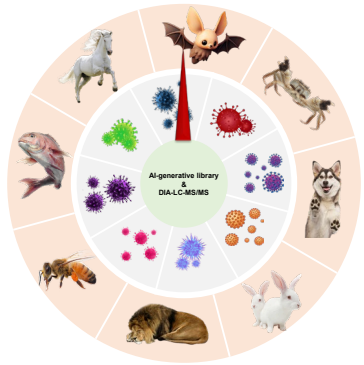
1. Department of Microbiology and Plant-pathology, University of California, Riverside, Riverside, CA, United States
2. Institute for Integrative Genome Biology, Proteomics Core, University of California, Riverside, Riverside, CA, United States

## Abstract

The surveillance of environmental viral pathogens is crucial for public health.[1,2] Ideally, the detection information should include both virus's identity and the host. However, current nucleic acid-based detection is better suited for identifying the former. An innovative approach that combines advanced liquid chromatography-mass spectrometry (MS) proteomics with artificial intelligence (AI) and iterative search was developed. AI/MS-proteomics identified diverse viruses in environmental samples and revealed the correct host information for exotic samples such as bat-origin virions. This framework of proteome-based surveillance presents a potent tool for studying viral dynamics, informing public health responses, enhancing ecological understanding, and mitigating emerging viral threats.

## Introduction

The presence of viruses in waste water has been shown to precede their prevalence in humans. The surveillance of viral pathogens in waste water, therefore, becomes a critical need in public health, particularly for proactively responding to emerging zoonotic viruses. Monitoring viral pathogens in waste water allows for early detection and identification of potentially harmful viruses before they can cause widespread outbreaks. Ideally, waste water surveillance requires monitoring a population's qualitative and quantitative health status within a specific area by detecting the concentration of target chemical or biological markers in waste water, in conjunction with human metabolism, water inflow volume, and population information. We propose to develop a tandem hydrophilic size-exclusion chromatography system for concentrating viruses in residential environment waste water and a protein-based detection that combines advanced liquid chromatography-mass spectrometry (LC-MS) proteomics with artificial intelligence (AI).




## Results

**Robust, scalable AI-generative library of proteome of life kingdoms**

We developed a scalable AI-generative library pipeline capable of handling proteomes of any size, achieving over a 20-fold performance boost across ultra-large search spaces (Figure 1a-1e). This pipeline leverages open-source deep learning models to generate in-silico LC-MS libraries from proteome databases, enabling efficient identification and quantification of DIA-LC-MS data. To enhance adaptability, we applied transfer learning to fine-tune models for various LC-MS signal types. Notably, the pipeline maintained performance across different samples and instruments, with no signs of overfitting. DIA-based transfer learning consistently outperformed DDA-based approaches in our datasets. We benchmarked our pipeline against conventional sample-specific methods using public datasets.

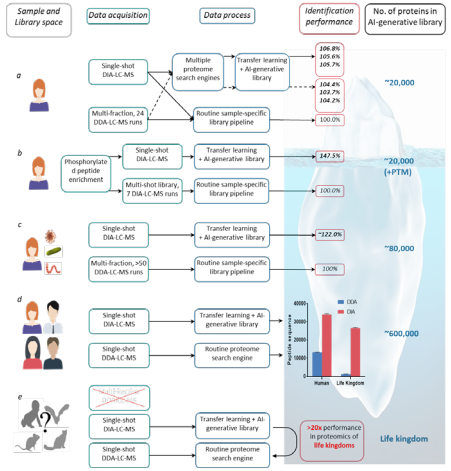



Figure 1. Robust, scalable AI-generative library of proteome of life kingdoms. (A) Performance evaluation of AI-generative library with routine sample-specific library pipeline on public proteomic dataset. (B) Performance evaluation of AI-generative library with routine sample-specific library pipeline on public phosphoproteomic dataset. (C) Performance evaluation of AI-generative library with routine sample-specific library pipeline on public proteomic dataset with multiple species. (D) Performance comparison of DDA/DIA-LC-MS in different search spaces. (E) Necessity of AI-generative library in analysis of small sample volume with unknown species information.

**Framework of fast, sensitive LC-MS based virus-host proteomics**

We developed a fast and sensitive virus-host proteomics workflow that completes within half a day, combining optimized virion sample preparation, DIA-LC-MS, and an AI-generative library (Figure 2a-1c). Removing detergents improved digestion efficiency, and complex DIA samples enhanced transfer learning. Using a serial dilution of influenza A PR8 virions (1-512 ng), our pipeline identified strain-specific viral peptides and over 3,600 host proteins-exceeding DDA-based methods by over 10×. This scalable approach enables high-depth, accurate analysis across diverse proteomes with minimal sample input.

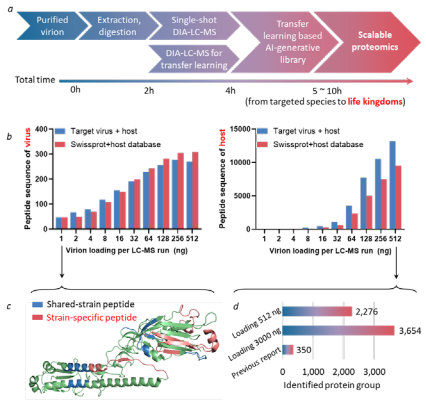



Figure 2. Fast, sensitive LC-MS based virus-host proteomics. (A) Workflow of virus-host proteomics with LC-MS and AI-generative library. (B) Peptide sequence identification of virus and host under different conditions. (C) HA protein coverage under 1 ng virion loading. (D) Performance comparison of existing virion proteomic study.

**Framework of fast, sensitive LC-MS based virus-host proteomics**

Building on the strength of our AI-generative library with large proteomes (Figure 2B), we developed a three-step iterative search framework for unbiased virus-host identification from unknown sources (Figure 3a). A direct one-step search across all known and unknown proteomes (>250 million proteins) is currently infeasible, so we implemented a decision-tree approach using DIA-LC-MS data. Step 1 screens all Swiss-Prot proteomes to narrow down top virus and host candidates. Step 2 refines identification using UniProt databases of these candidates. Step 3 confirms identities using focused virus-host proteomes.

We demonstrated this approach on PR8 virions and extended it to additional viruses (WSN, ZIKA) from various sources, successfully identifying virus-host pairs in each case (Figure 3b). Functional analysis of host proteomes revealed consistent biological themes-such as enrichment in protein synthesis and degradation pathways-regardless of the culturing system (Figure 3c), suggesting selective incorporation of host proteins into virions. In summary, our iterative, AI-assisted workflow enables accurate, scalable virus-host profiling from unknown samples, validated across multiple viruses and host systems.

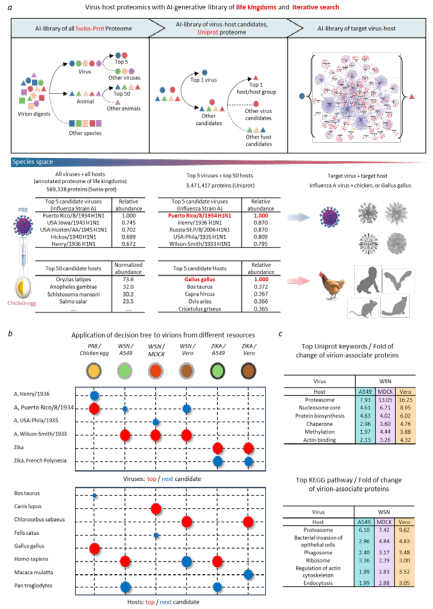



Figure 3. dedicated iterative search and AI-generative library reveals virus-host resources. (A) Workflow and example of iterative search for virus-host proteomics, in the form of decision-tree. (B) Application of proposed iterative search to virions from different resources. (C) Bioinformatic analysis of virion-associated proteins from different resources.

## Conclusions

In summary, we designed a dedicated experiment with comparison between double-spike in mixtures before and after virion enrichment processes. The mixture consists of a known quantity of virions and environmental bacteria. We observed dozens of folds of increase in host protein intensity after virion enrichment, confirming the source of the identified host proteins is the viral particle. Additionally, consistent host protein signals were observed in different virus-host combinations.

## References (if necessary)

1. Bruderer R, Bernhardt O M, Gandhi T, et al. Optimization of experimental parameters in data-independent mass spectrometry significantly increases depth and reproducibility of results[J]. Molecular & Cellular Proteomics, 2017, 16(12): 2296-2309.

2. Chi H, Liu C, Yang H, et al. Comprehensive identification of peptides in tandem mass spectra using an efficient open search engine[J]. Nature biotechnology, 2018, 36(11): 1059-1061.

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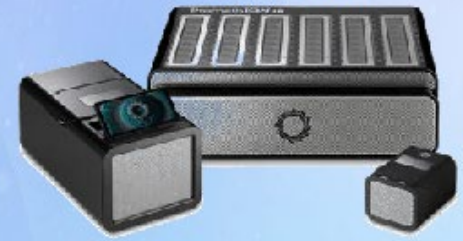

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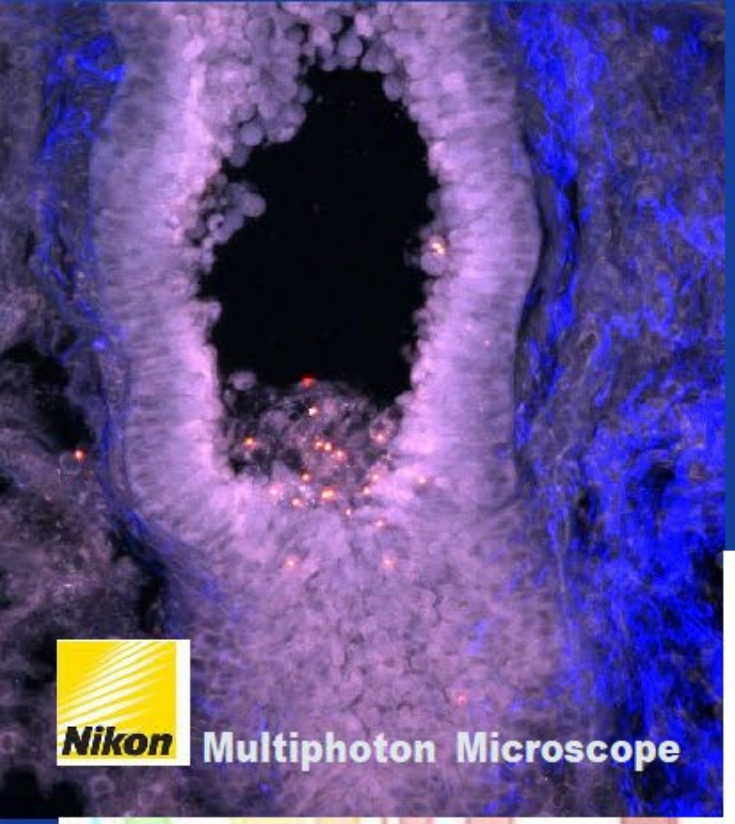




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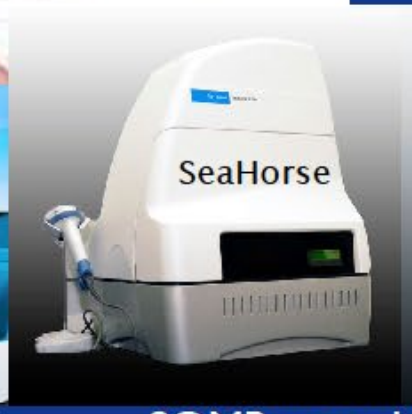



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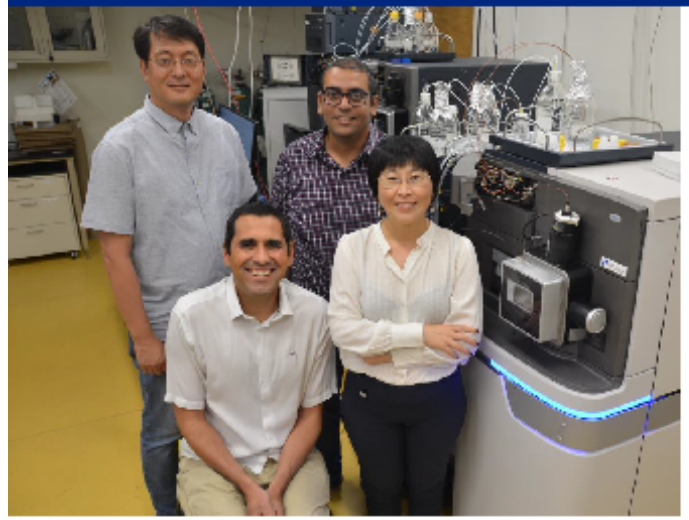

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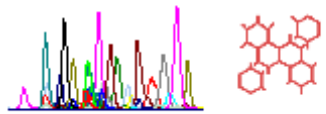

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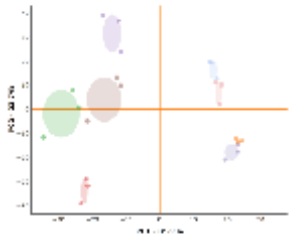

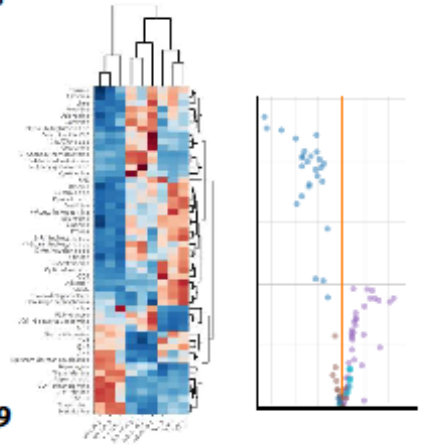



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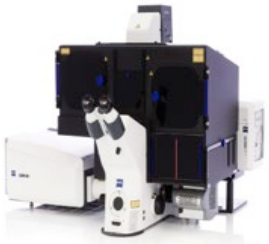

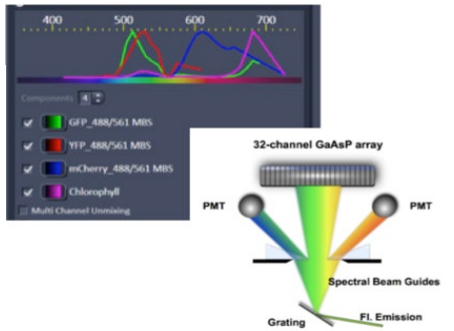


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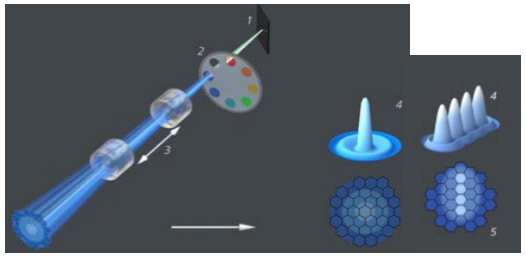

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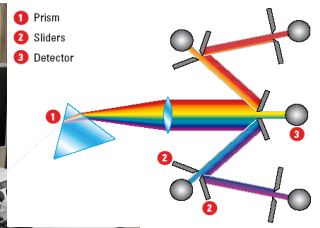


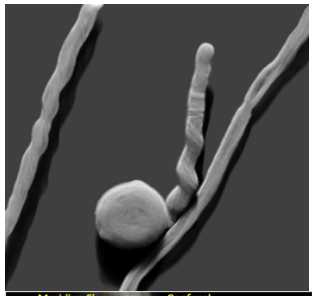

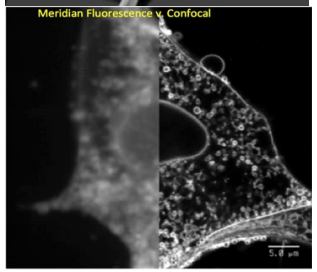


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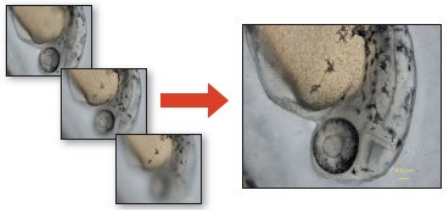

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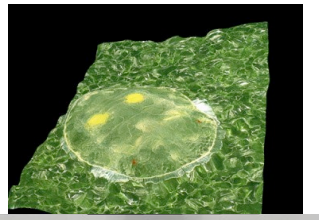

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