Nature Methods Publication Reveals Deep Insights into Functional Biology through First-of-its-Kind Quantification of Tau Proteoforms

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First large-scale, single-molecule analysis of the tau proteoform landscape reveals unique disease-associated modifications, a new source of potential biomarkers and drug targets, and a method Nautilus is now extending across disease areas

Key takeaways:

- Going beyond measurement of bulk tau to quantify each of the diverse proteoforms of tau is key to developing novel diagnostics and precision medicine for Alzheimer's disease and related tauopathies.
- Proteoforms – distinct forms of protein that are defined by ordered, non-random combinations of modifications – control biology and are uniquely quantifiable at scale on the Nautilus Voyager Platform.
- Iterative Mapping of tau resolved 130 tau proteoform groups at scale with precision, sensitivity, and reproducibility, quantifying proteoforms present at 0.1% of a sample, and delivering a median CV below 5.5%.
- The same validated approach used for tau is now being applied to α-synuclein in Parkinson's disease and to AKT1, Nautilus' first oncology proteoform assay, supporting a roadmap toward roughly 20 proteoform assays by mid-2028.

SEATTLE, Sept. 04, 2026 (GLOBE NEWSWIRE) -- Nautilus Biotechnology, Inc. (NASDAQ: NAUT), a company pioneering intact, single-molecule proteome analysis, today announced a peer-reviewed publication in *Nature Methods* demonstrating the power of Iterative Mapping to reveal the proteoforms underlying biology and disease. Measuring intact tau molecules at the single-molecule level, a view no other technology available today has been shown to produce, the study shows that combinations of disease-associated modifications accumulate on distinct proteoforms in ordered, non-random sequences. This insight is critical to determining function and may enable the development of a new class of therapeutics and diagnostics. The paper, "Large-scale single-molecule analysis of tau proteoforms," validates the performance and impact of Iterative Mapping, a methodology Nautilus is now planning to rapidly extend to other proteins and disease areas including Parkinson's disease and oncology.

"Proteoform identity determines protein structure and function, but until now we haven't had the ability to quantify proteoforms and connect them to specific functions at scale. Iterative Mapping changes that. This paper shows, for the first time, that tau proteoforms are non-random and closely tied to disease biology," said Parag Mallick, Ph.D., Co-Founder and Chief Scientist of Nautilus and corresponding author of the study. "Even in this small initial study, being able to quantify proteoforms is changing how we understand disease at the molecular level. Instead of just asking whether tau is present, we can now ask which specific proteoforms are driving disease. That's the starting point for finding new biomarkers and drug targets."

"With Iterative Mapping, we now have the unprecedented ability to analyze proteins at the level of distinct proteoforms and to see which variants drive disease. What surprised us most is how differently tau behaves across the model systems our field relies on every day. That has immediate consequences for how biomarker studies are designed and how drug programs choose their models," said Taylor Bertucci, Ph.D., Principal Investigator at the Neural Stem Cell Institute and a collaborator on the study.

"Understanding which forms of tau drive neurodegeneration has been one of the central unanswered questions in our field. Measuring combinatorial modifications on individual, full-length tau molecules at this scale opens a new path to accelerating the search for earlier diagnostics and more precise therapies that patients urgently need," said Joel Blanchard, Ph.D., Associate Professor at The Ronald M. Loeb Center for Alzheimer's Disease at Mount Sinai and a collaborator on the study.

About the Study Findings
Proteoforms arise from genetic differences, alternative splicing, and post-translational modifications. These subtle differences determine whether a protein supports healthy function or drives disease. Conventional proteomics tools fragment protein molecules or analyze them in bulk, obscuring this functional detail. Iterative Mapping of proteoforms addresses this challenge by measuring fully intact protein molecules with single-molecule resolution at scale, enabling researchers to measure up to billions of individual proteoform molecules in a single run.

The Nautilus Tau Proteoforms Assay used in the study employs 12 site-specific antibodies and leverages Iterative Mapping to resolve up to 768 proteoform groups of full-length tau. The assay was run across multiple model systems, including cell-derived and organoid models, mouse brain, and a small cohort of human brain samples spanning cognitively normal individuals and patients with Alzheimer's disease and related dementias (ADRD).

The results demonstrate the method's performance and power to potentially surface new biological insights:

- **Quantification of proteoforms at scale delivers novel insights into disease mechanisms:** Of up to 768 resolvable and biologically feasible tau proteoform groups, the assay quantified 130 across all samples measured in the study, some carrying as many as six phosphorylation modifications on a single molecule. Conventional methods don't have the resolution to discriminate among these disparate proteoforms. The assay reliably measured proteoforms at 0.1% of a sample, with a median coefficient of variation below 5.5% across a wide range of testing conditions.
- **Ordered modification across full-length molecules:** Specific combinations of tau modifications co-occurred far more often than predicted by chance. This suggests that tau is modified in a consistent, ordered sequence rather than through random accumulation, and it underscores the need for methods that can resolve proteoforms to identify novel biomarkers of disease.

- **A possible window into disease progression:** Across a small human cohort of five ADRD patients and two cognitively normal individuals, the assay resolved distinct tau proteoform profiles. The patient with the most severe pathology carried the most heavily phosphorylated tau, including 1N3R tau quadruply phosphorylated at pT181-pT217-pT231-pS396. Pathology-associated proteoforms like this one have the potential to become powerful biomarkers or drug targets and are uniquely discoverable with Iterative Mapping.

The Nautilus Tau Proteoforms Assay is currently available through the Nautilus Iterative Mapping Early Access Program (EAP). Beyond tau, Nautilus is applying Iterative Mapping to other disease targets, including α-synuclein in Parkinson's disease, and AKT1, which is expected to be the company's first oncology proteoform assay. The AKT1 assay is expected to enter the Iterative Mapping EAP in late 2026. Two additional oncology targets have cleared Nautilus' development criteria, highlighting that assay development is anticipated to be a repeatable process. Nautilus is targeting roughly 20 proteoform assays by the middle of 2028.

About the Nautilus Voyager™ Platform
The Nautilus Voyager™ Platform employs Nautilus' proprietary Iterative Mapping approach, which is designed to enable rapid measurement of intact, single-molecule proteins and proteoforms in a single, sample-to-answer workflow any lab can run. The platform's flow cells are designed to accommodate up to 10 billion intact protein molecules, enabling measurement across an exceptionally wide dynamic range. Iterative Mapping independently probes single protein molecules across tens to hundreds of cycles, recording unique binding patterns for each individual molecule. Machine learning algorithms then convert the resulting probe-binding patterns into confident protein and proteoform identifications, producing the structured, reproducible data required to train models on functional biology. Once analysis is complete, single-molecule counts are made available for download and further visualization. The Voyager instrument is designed for operational simplicity and standard lab benchtop placement, with a guided touchscreen user interface and minimal facility requirements, without need for bespoke gas or fluidic connections.

About Nautilus Biotechnology, Inc.
With its corporate headquarters in Seattle, Washington and its research and development headquarters in San Carlos, California, Nautilus is a development stage life sciences company advancing Voyager, a platform technology for quantifying and unlocking the complexity of the proteome. Nautilus' mission is to transform the field of proteomics by democratizing access to the proteome and enabling fundamental advancements across human health and medicine. To learn more about Nautilus, visit www.nautilus.bio.

Special Note Regarding Forward-Looking Statements
This press release contains forward-looking statements within the meaning of federal securities laws. Forward-looking statements in this press release include, but are not limited to, statements regarding Nautilus' expectations with respect to the potential of its platform technology, its future products, their functionality and performance or their applicability in biological research and in potentially enabling new diagnostics and therapies. These statements are based on numerous assumptions concerning the development of Nautilus' products, target markets, and other current and emerging proteomics technologies, and involve substantial risks, uncertainties and other factors that may cause actual results to be materially different from the information expressed or implied by these forward-looking statements. Risks and uncertainties that could materially affect the accuracy of Nautilus' assumptions and its ability to achieve the forward-looking statements set forth in this press release include (without limitation) the following: Nautilus' product platform is not yet commercially available and remains subject to scientific and technical development, which is inherently challenging and difficult to predict; we may experience material delays as a result of unanticipated events; we cannot provide any guarantee or assurance with respect to the outcome of our development, collaboration, and commercialization initiatives or with respect to their associated timelines. For a more detailed description of additional risks and uncertainties facing Nautilus and its development efforts, investors should refer to the information under the caption "Risk Factors" in our Annual Report on Form 10-K as well as in our Quarterly Report on Form 10-Q filed for the quarter ended June 30, 2026 and our other filings with the SEC. The forward-looking statements in this press release are as of the date of this press release. Except as otherwise required by applicable law, Nautilus disclaims any duty to update any forward-looking statements. You should, therefore, not rely on these forward-looking statements as representing our views as of any date subsequent to the date of this press release.

Disclosure Information
Nautilus uses filings with the Securities and Exchange Commission, its website (www.nautilus.bio), press releases, public conference calls, public webcasts, and its social media accounts as means of disclosing material non-public information and for complying with Regulation FD. Therefore, Nautilus encourages investors, the media, and others interested in Nautilus to review the information it makes public in these locations, as such information could be deemed to be material information.

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