NAUTILUS™

BIOTECHNOLOGY

Delivering on the Promise of the Proteome

NOVEMBER 13, 2024

Safe harbor

This presentation and the accompanying oral presentation contain forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, including, among others, statements regarding the size and growth of the protein analysis market; Nautilus Biotechnology's anticipated total addressable market; the performance, value and enabling nature of Nautilus Biotechnology's proteomics and proteoform analysis technology platform; statements regarding Nautilus Biotechnology's future development milestones and timing; statements regarding the timing and nature of Nautilus Biotechnology's potential engagements with partners in proteoform analysis; Nautilus Biotechnology's business and operational strategy and financial targets; Nautilus Biotechnology's prospective products; Nautilus Biotechnology's business development plans and opportunities; Nautilus Biotechnology's anticipated customer mix and collaborations plans; and objectives of management for future operations are forward looking statements. Forward-looking statements are neither historical facts nor assurances of future performance. Instead, they are based on our current expectations and projections about future events and financial trends that we believe may affect our financial condition, results of operations, business strategy, and financial needs. All statements other than statements of historical facts contained in this presentation, including, without limitation, statements regarding our future performance and our market opportunity, could be deemed forward-looking statements. The words "may," "will," "expect," "anticipate," "aim," "estimate," "intend," "plan," "believe," "is/are likely to," "potential," "continue" and other similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

Forward-looking statements are subject to numerous risks and uncertainties that could cause actual results to differ materially from currently anticipated results, including but not limited to risks relating to the development and commercialization of our Nautilus platform; macroeconomic conditions; regional conflicts; Nautilus Biotechnology's dependence on certain sole and single source suppliers; competition; market acceptance of Nautilus Biotechnology's current and potential products; Nautilus Biotechnology's ability to manage the growth and complexity of its organization; Nautilus Biotechnology's ability to maintain, protect and enhance its intellectual property; and Nautilus Biotechnology's ability to continue to stay in compliance with its material contractual obligations, applicable laws and regulations. Information on these and additional risks and uncertainties and other information affecting Nautilus Biotechnology's business and operating results is contained in Nautilus Biotechnology's Annual Report for the year ending December 31, 2023, filed February 28, 2024, and in its other filings with the Securities and Exchange Commission. These forward-looking statements speak only as of the date hereof. Except as required by applicable law, Nautilus Biotechnology does not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise. No representations or warranties (expressed or implied) are made about the accuracy of any such forward-looking statements.

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Nautilus seeks to revolutionize biomedicine

Single-molecule proteome analysis platform

with integrated machine learning designed to enable unprecedented **sensitivity and scale**

Potential to unlock a massive market

$55+ Billion opportunity across proteomics and adjacent markets by 2027
(Source: BCC Research)

Research collaborations

Genentech
A Member of the Roche Group
AMGEN
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
tgen part of City of Hope

Defining a new gold standard for single-molecule protein analysis

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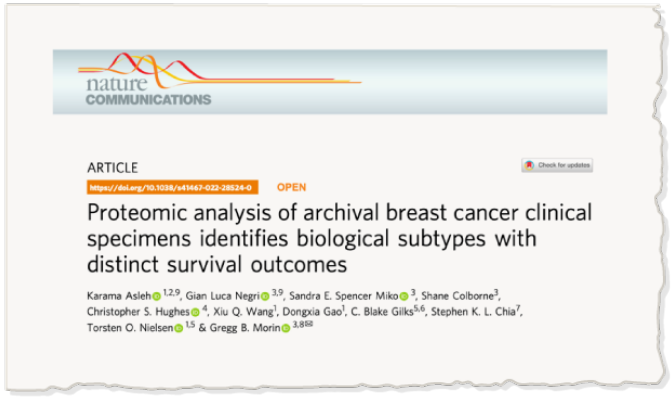
Proteins are key drivers of biology

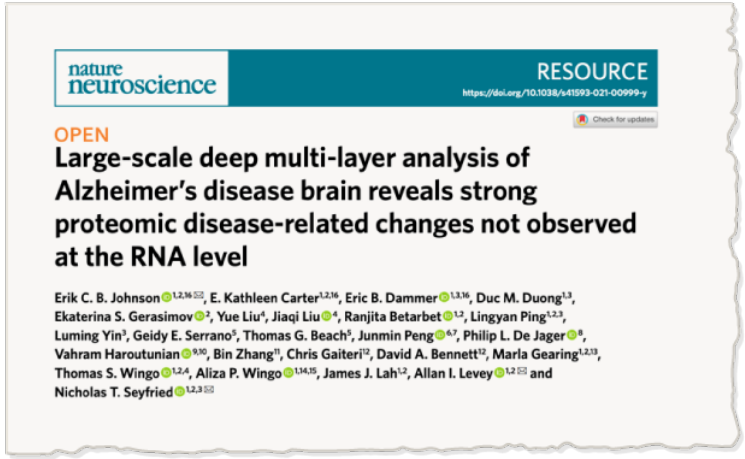

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-022-28524-0 OPEN

Proteomic analysis of archival breast cancer clinical specimens identifies biological subtypes with distinct survival outcomes

Karama Asleh, Gian Luca Negri, Sandra E. Spencer Miko, Shane Colborne, Christopher S. Hughes, Xiu Q. Wang, Dongxia Gao, C. Blake Gilks, Stephen K. L. Chia, Torsten O. Nielsen & Gregg B. Morin


nature neuroscience

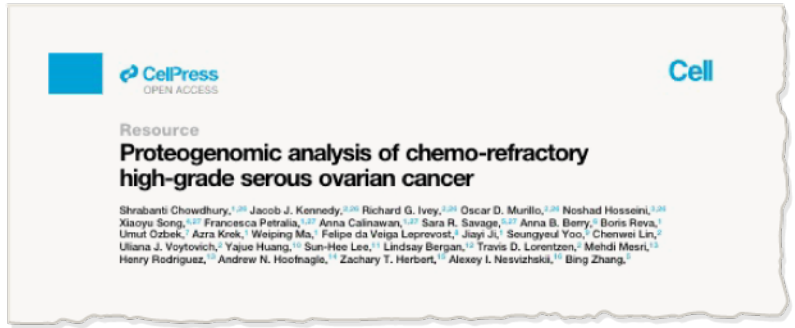
RESOURCE

https://doi.org/10.1038/s41593-021-00999-y

OPEN

Large-scale deep multi-layer analysis of Alzheimer's disease brain reveals strong proteomic disease-related changes not observed at the RNA level

Erik C. B. Johnson, E. Kathleen Carter, Eric B. Dammer, Duc M. Duong, Ekaterina S. Gerasimov, Yue Liu, Jiaqi Liu, Ranjita Betarbet, Lingyan Ping, Luming Yin, Geidy E. Serrano, Thomas G. Beach, Junmin Peng, Philip L. De Jager, Vahram Haroutunian, Bin Zhang, Chris Gaiteri, David A. Bennett, Marla Gearing, Thomas S. Wingo, Aliza P. Wingo, James J. Lah, Allan I. Levey and Nicholas T. Seyfried

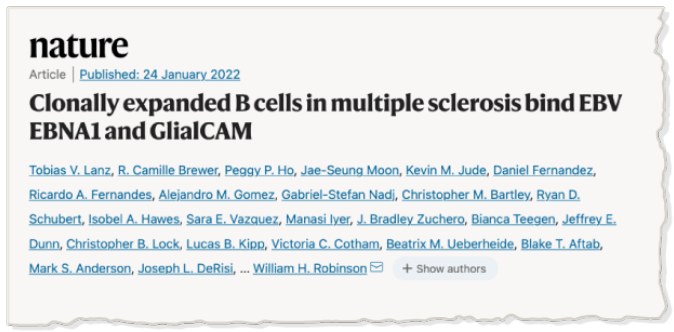

CellPress OPEN ACCESS

Cell

Resource

Proteogenomic analysis of chemo-refractory high-grade serous ovarian cancer

Shrabanti Chowdhury, Jacob J. Kennedy, Richard G. Ivey, Oscar D. Murillo, Noshad Hosseini, Xiaoyu Song, Francesca Petralia, Anna Calinawan, Sara R. Savage, Anna B. Berry, Boris Reva, Umut Özbek, Azra Krek, Weiping Ma, Felipe da Veiga Leprevost, Jiayi Ji, Seungyeul Yoo, Chenwei Lin, Uliana J. Voytovich, Yajue Huang, Sun-Hee Lee, Lindsay Bergan, Travis D. Lorentzen, Mehdi Mesri, Henry Rodriguez, Andrew N. Hoofnagle, Zachary T. Herbert, Alexey I. Nesvizhskii, Bing Zhang


nature

Article | Published: 24 January 2022

Clonally expanded B cells in multiple sclerosis bind EBV EBNA1 and GlialCAM

Tobias V. Lanz, R. Camille Brewer, Peggy P. Ho, Jae-Seung Moon, Kevin M. Jude, Daniel Fernandez, Ricardo A. Fernandes, Alejandro M. Gomez, Gabriel-Stefan Nadi, Christopher M. Bartley, Ryan D. Schubert, Isobel A. Hawes, Sara E. Vazquez, Manasi Iyer, J. Bradley Zuchero, Bianca Teegen, Jeffrey E. Dunn, Christopher B. Lock, Lucas B. Kipp, Victoria C. Cotham, Beatrix M. Ueberheide, Blake T. Aftab, Mark S. Anderson, Joseph L. DeRisi, ... William H. Robinson + Show authors


Proteogenomic Analysis of Human Colon Cancer Reveals New Therapeutic Opportunities

Cell

Suhas Vasaikar, Chen Huang, Xiaojing Wang, Vladislav A. Petyuk, Sara R. Savage, Bo Wen, Yongchao Dou, Yun Zhang, Zhiao Shi, Osama A. Arshad, Marina A. Gritsenko, Lisa J. Zimmerman, Jason E. McDermott, Therese R. Clauss, Ronald J. Moore, Rui Zhao, Matthew E. Monroe, Yi-Ting Wang, Matthew C. Chambers, Robbert J.C. Slebos, Ken S. Lau, Qianxing Mo, Li Ding, Matthew Ellis, Mathangi Thiagarajan, Christopher R. Kinsinger, Henry Rodriguez, Richard D. Smith, Karin D. Rodland, Daniel C. Liebler, Tao Liu, Bing Zhang, and Clinical Proteomic Tumor Analysis Consortium


nature neuroscience

Resource | Published: 08 July 2021

Genomic atlas of the proteome from brain, CSF and plasma prioritizes proteins implicated in neurological disorders

Chengran Yang, Fabiana H. G. Farias, Laura Ibanez, Adam Suhy, Brooke Sadler, Maria Victoria Fernandez, Fengxian Wang, Joseph L. Bradley, Brett Eiffert, Jorge A. Bahena, John P. Budde, Zeran Li, Umber Dube, Yun Ju Sung, Kathie A. Mihindukulasuriya, John C. Morris, Anne M. Fagan, Richard J. Perrin, Bruno A. Benitez, Herve Rhinn, Oscar Harari & Carlos Cruchaga

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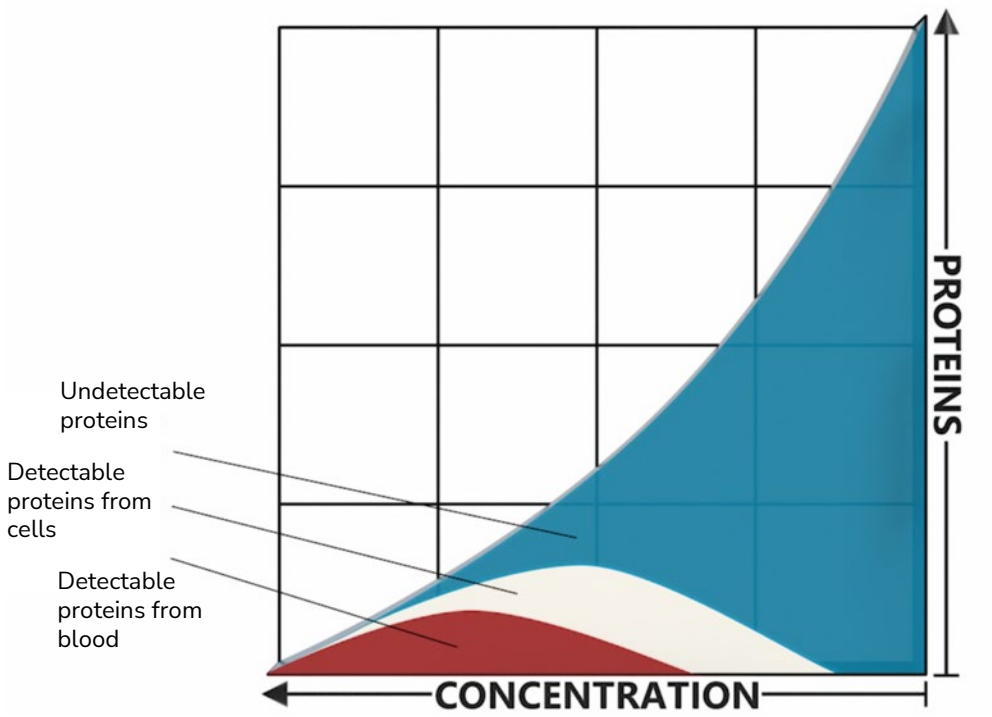
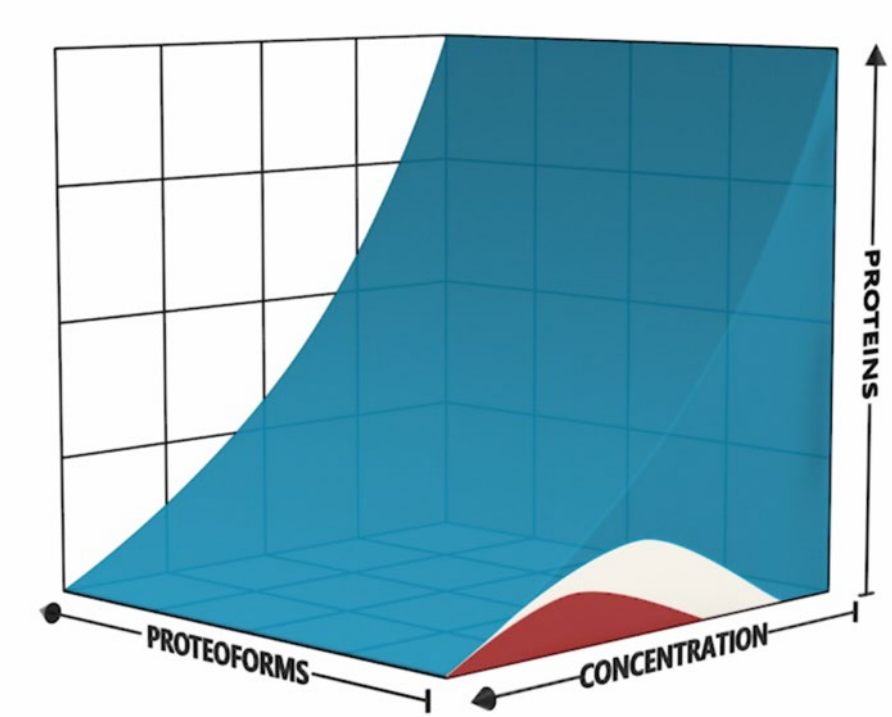
Current analysis methods can't see most proteins and proteoforms



Mass spec solutions today only capture a fraction of the proteome from blood or cells



There is no solution today to measure and quantify intact proteoforms

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Nautilus is reinventing proteomics from the ground up

What is necessary to identify and quantify the proteome and proteoforms?

Comprehensive	→	Measure substantively all the proteins and proteoforms in a sample
Sensitive	→	Single-molecule detection
Wide dynamic range	→	Match the scale of the proteome
Reproducible and robust	→	Path to clinical translation of discoveries
Rapid run time	→	Process a large number of samples
Easy to use	→	Any lab can run it

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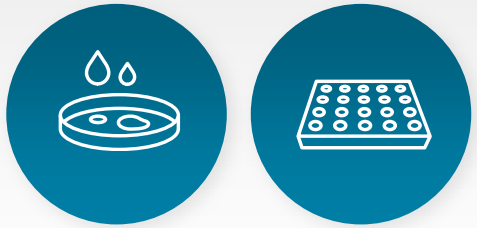
Core platform components

Sample Preparation & Single-Molecule Protein Deposition



HYPER-DENSE SINGLE MOLECULE ARRAY

Instrumentation and Reagents for Iterative Affinity Reagent Hybridization and Imaging

DIGITAL PROTEOMIC DATA

Machine Learning-Based Analysis

PROTEIN DECODING ANALYTICS

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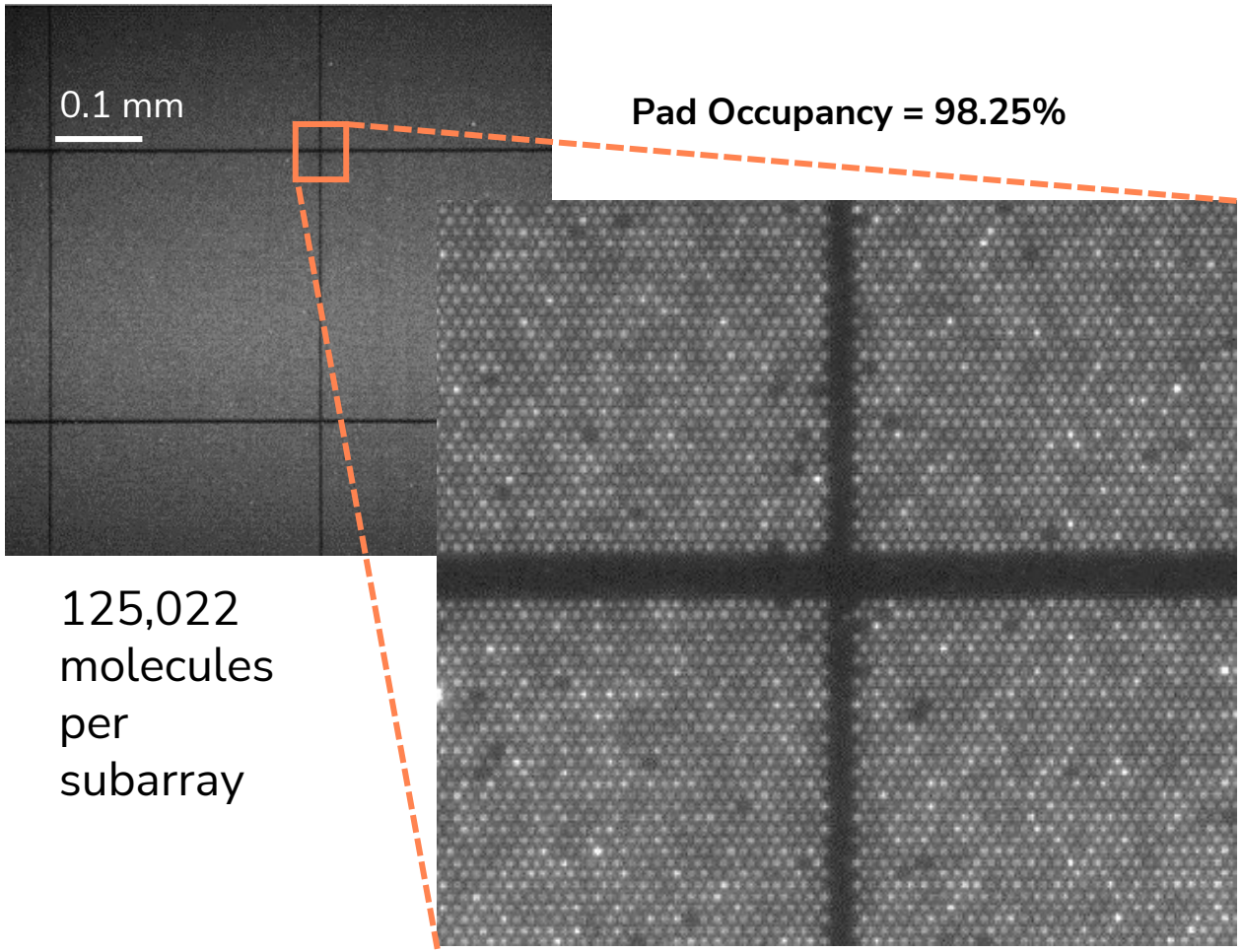
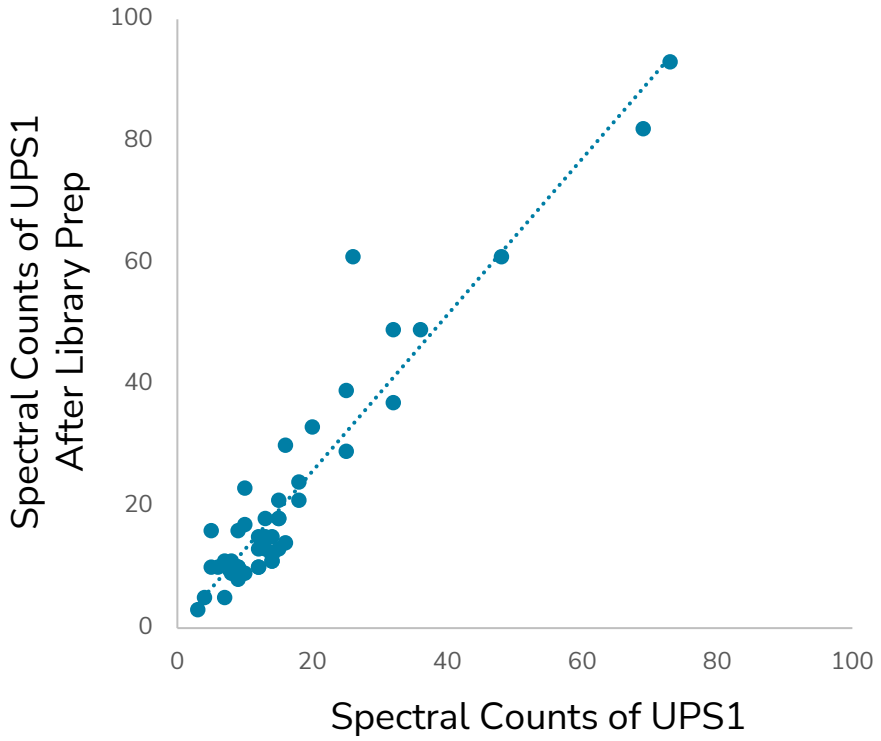
High-density rapid measurement of billions of single protein molecules for wide dynamic range while minimizing bias





Aksel, et al (2022), BioRxiv

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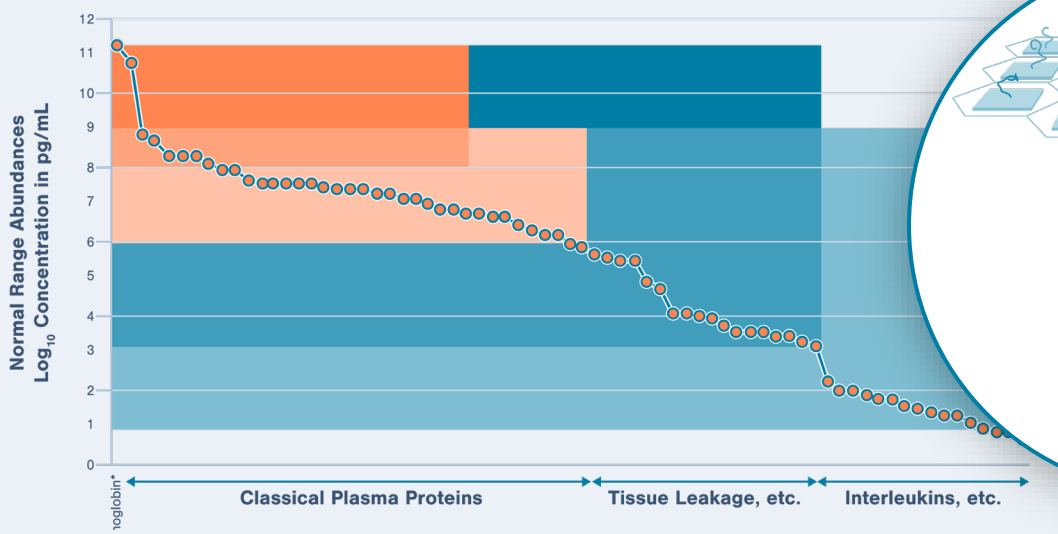
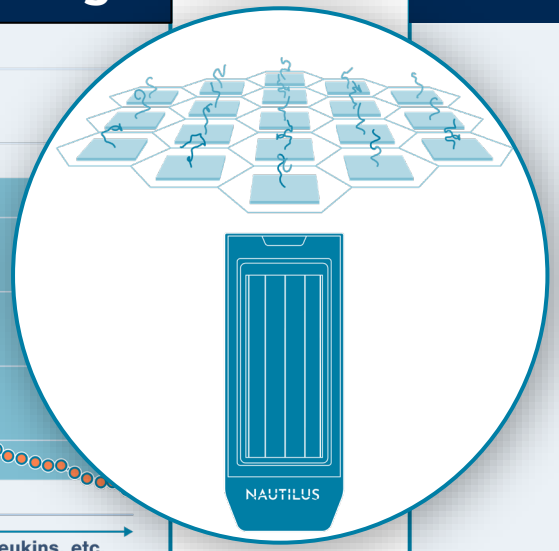
Multiple applications from the same core platform

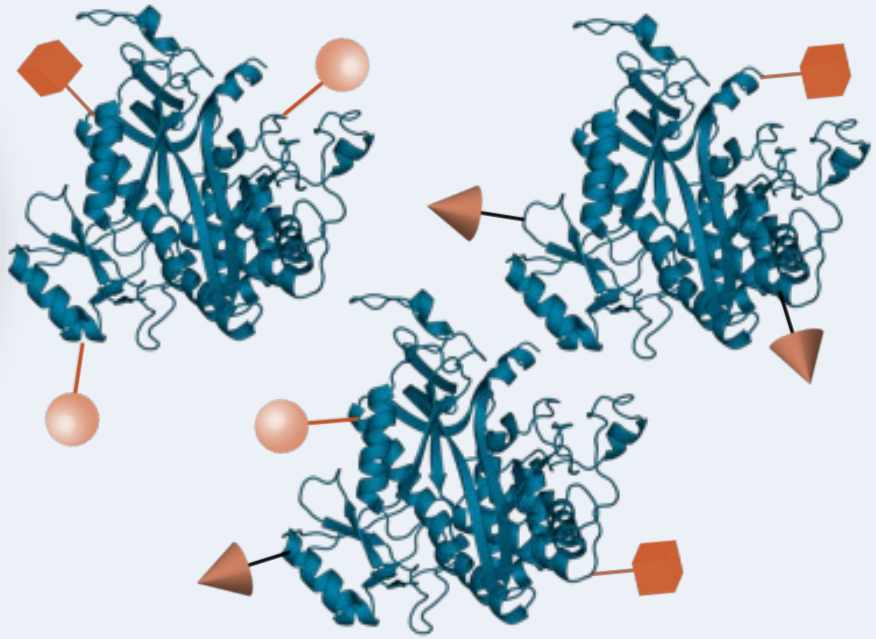
Broadscale
Proteome coverage with wide dynamic range





Protein Identification by Short-epitope Mapping:
Nautilus proprietary reagents designed for comprehensive proteome analysis

Targeted Proteoform
High resolution for targets of interest



Off-the-shelf reagents validated for targeted proteoform analysis

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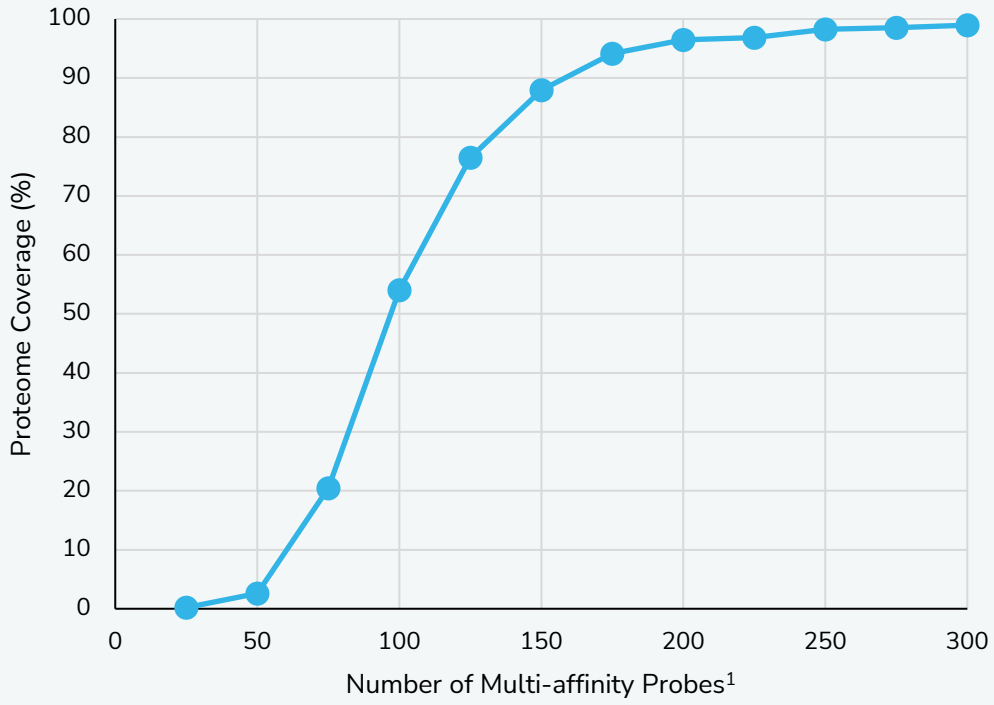
Designed to comprehensively quantify the proteome

Human Proteome Coverage Across 300 Unique Multi-affinity Probes



Capable of Achieving

>95% Proteome Coverage

[1]Estimates based on Nautilus computational analysis projecting the number of Nautilus designed short epitope probe binding events necessary to identify the SwissProt reference proteome.

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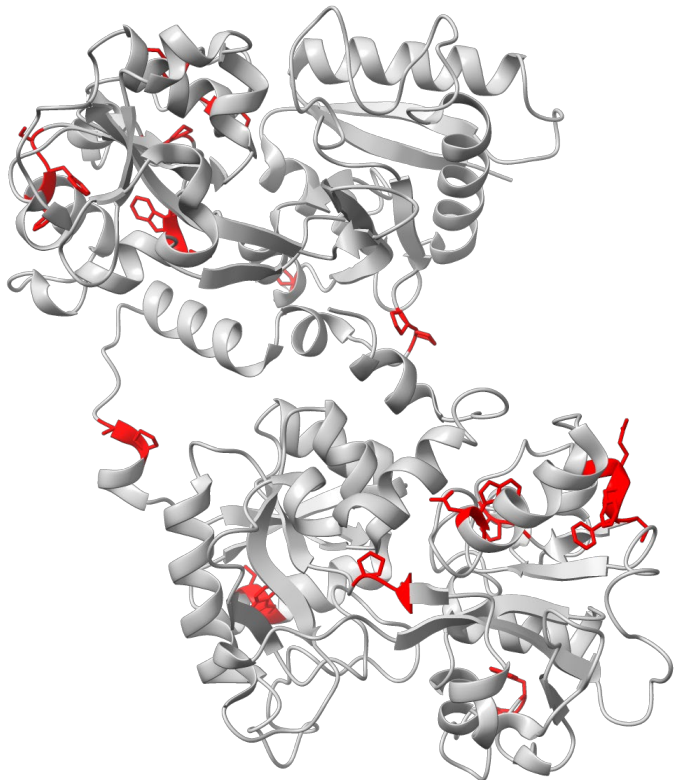
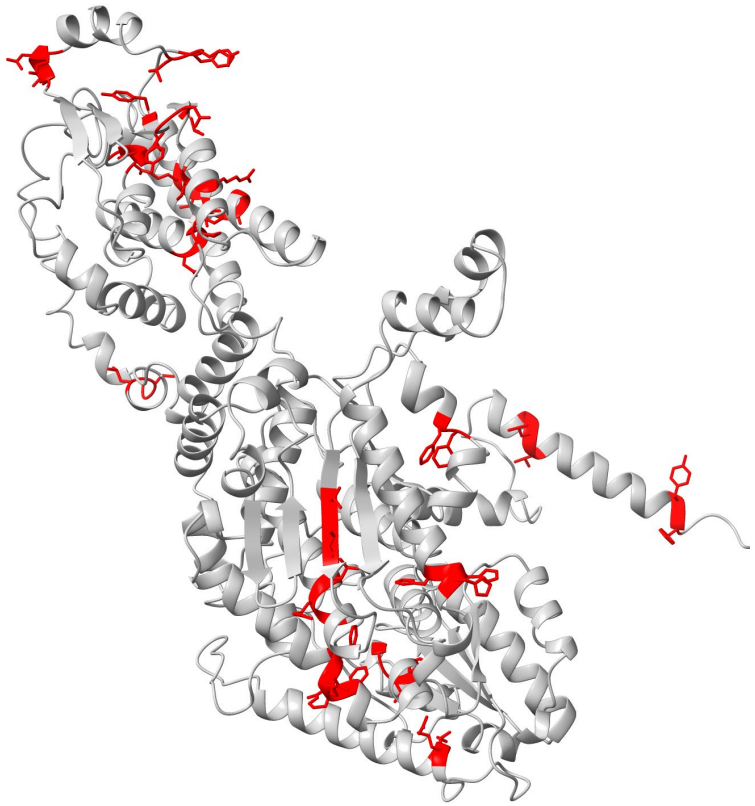
Multi-affinity probes bind to buried/structured regions in denatured proteins

- Binding of a multi-affinity probe to its intended peptide target is required
- Multi-affinity probes must also be able to bind to short epitopes in denatured, full-length proteins
- We have demonstrated binding to short epitopes in internal portions of denatured, but full-length proteins (red) using both aptamer- and antibody-based multi-affinity probes



Transferrin



G6PI

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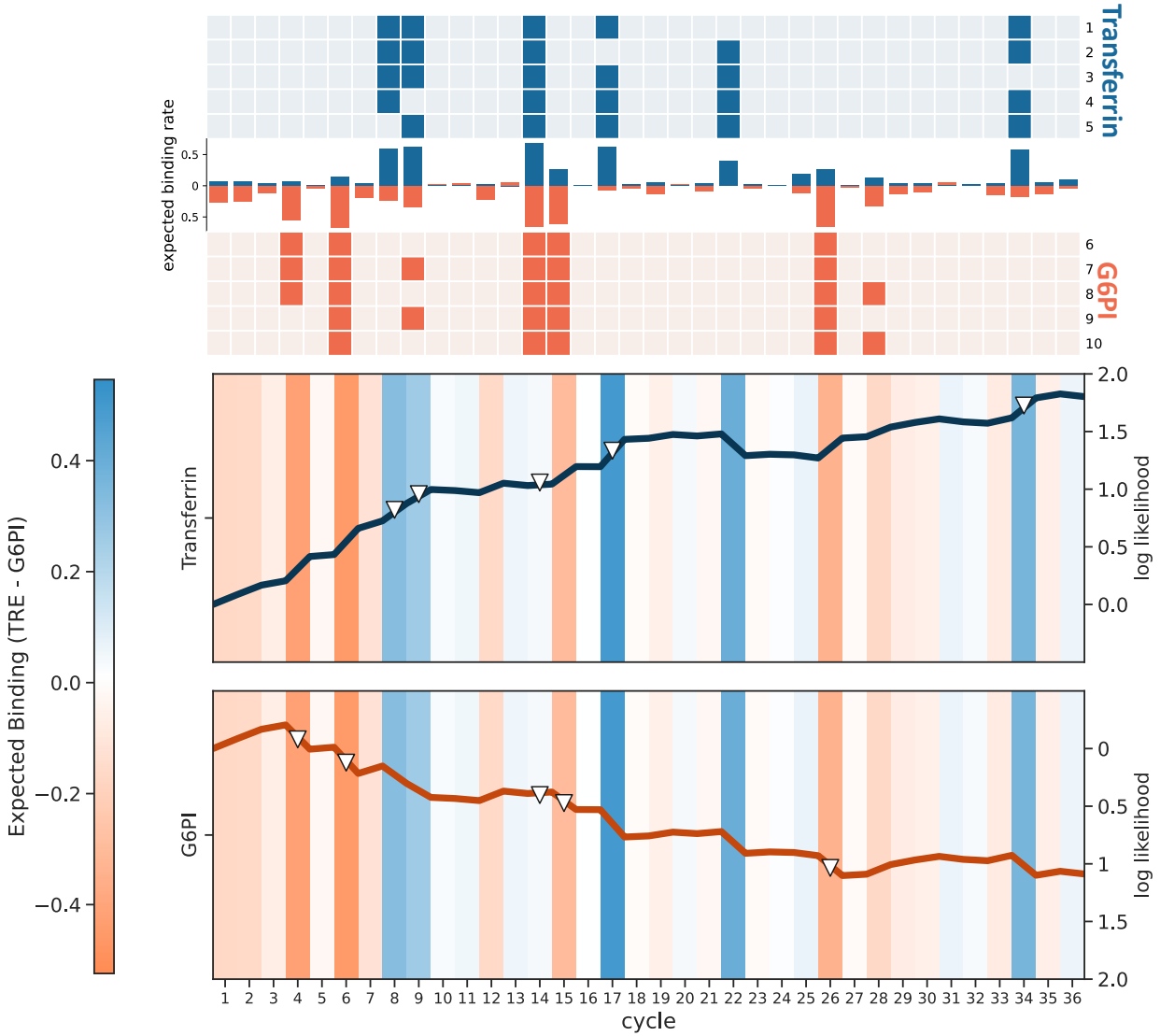
Binding patterns to transferrin and G6PI at single-molecule resolution

Samples consisting of transferrin (TRFE), glucose 6 phosphate (G6PI), pyruvate kinase M2 (PKM2), a model protein, no protein (negative control) or mixtures thereof were deposited into flowcell lanes for PrISM analysis.

Shown top are the 5 most prevalent binding patterns from these experiments for transferrin and G6PI.

From these binding patterns, machine learning tools identify each molecule. Each additional cycle builds additional information about protein identity as transferrin and G6PI have different binding patterns, indicated by the triangles.

The resulting difference in probability between the best-matching protein, and the next best protein in the database leads to confident protein identifications.



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Ultra-sensitive quantification of transferrin

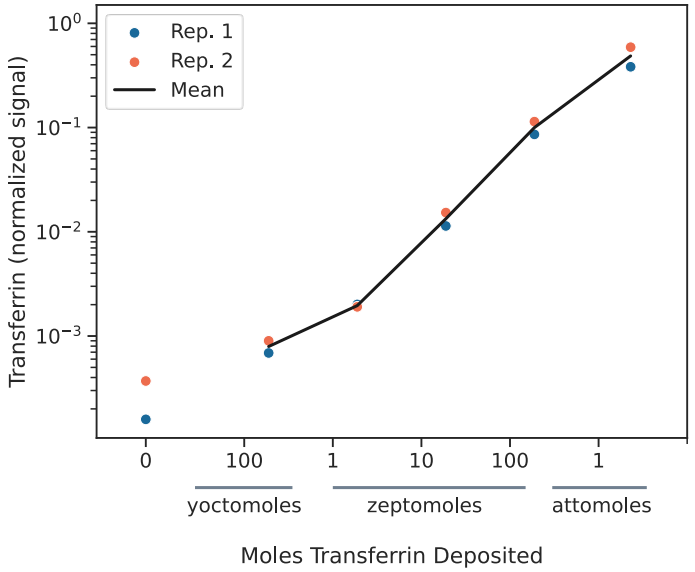
(LEFT) Sensitive single-molecule measurements: Lower limit of detection in the high-yocto to low-zeptomole range

Reproducible single-molecule measurements: The highest abundance Transferrin measurement (2 attomoles) was repeated 7 times across 4 days and 7 flow cells with a CV of **7.7%**

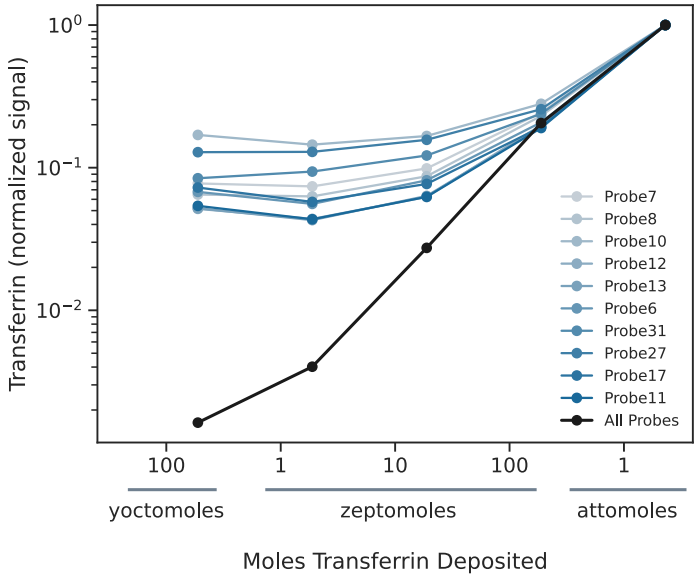
(RIGHT) High fidelity quantification: Multi-cycle decoding data is significantly more sensitive and error tolerant than achievable with any one multi-affinity probe alone

This improvement arises from the ability of the machine learning software to better identify proteins whose identifications were derived from either false positive or false negative bindings

Transferrin dilution series in a background of alternate protein, or null scaffolds



Multi-probe decode vs single-probe



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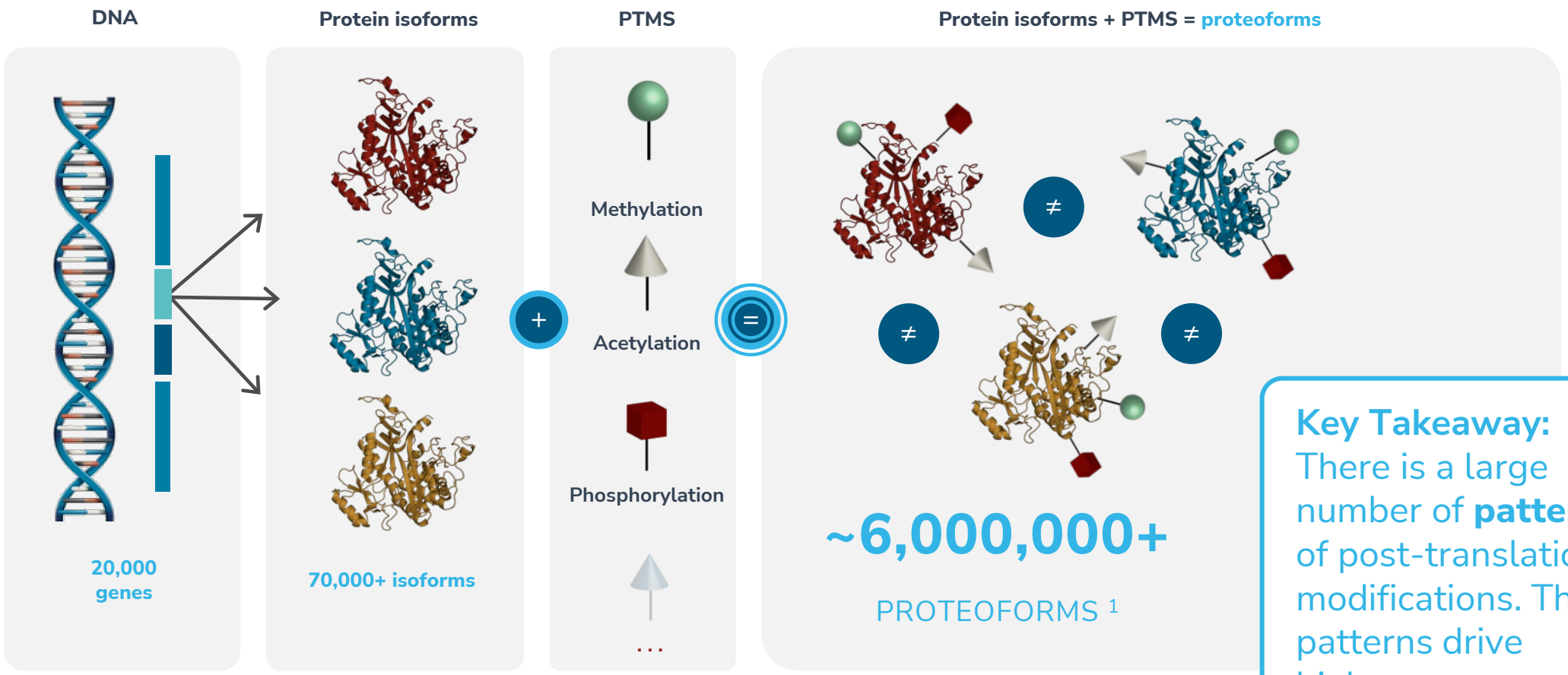
Nautilus: Revealing unseen proteoforms



Key Takeaway:
There is a large number of **patterns** of post-translational modifications. These patterns drive biology.

[1]International Journal of Analytical Chemistry. 2016; 2016: 7436849. The Size of the Human Proteome: The Width and Depth, Elena A. Ponomarenko et al.

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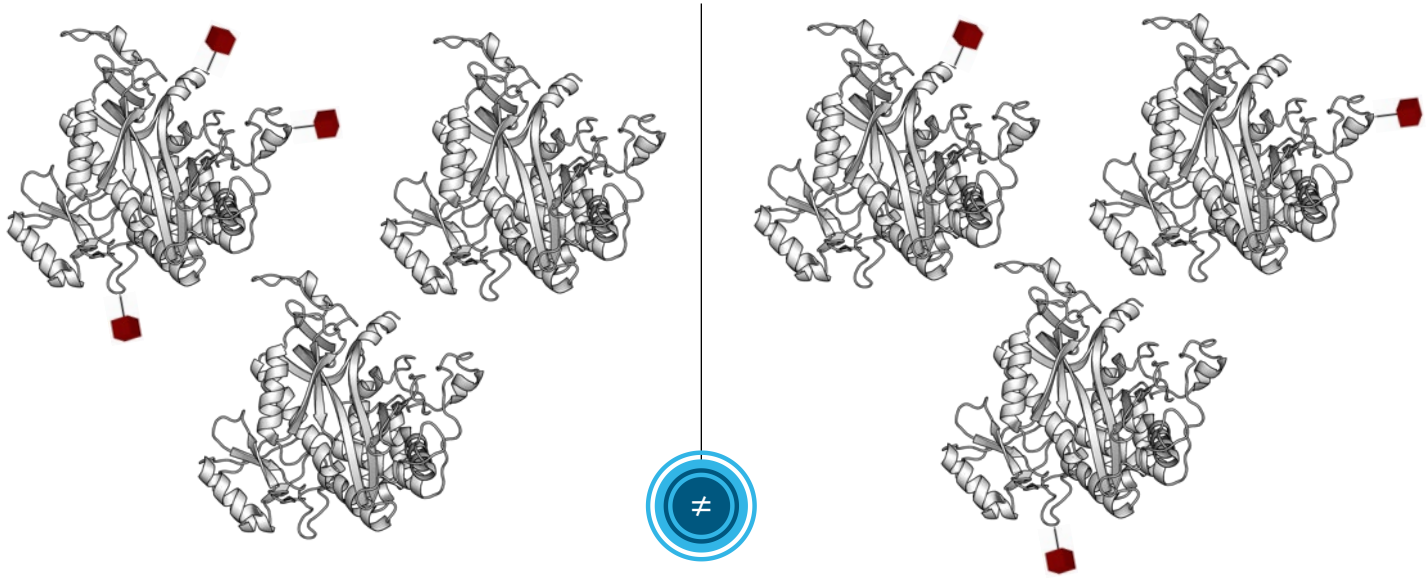
High-resolution proteoform quantitation: a core application of Nautilus' platform

Peptide-centric proteomics methods are unable to differentiate mixtures of proteoforms



> "Which drugs work and to what extent is defined not by just the total amount of PTMs and splice forms, but instead by how combinations of specific alterations operate together. Creating a technology to see these PTM patterns, and measure their relationship to one another, has the potential to hugely advance precision medicine."
>
> **Dr. Ruedi Aebersold, Head of IMSB, Swiss Federal Institute of Technology (ETH) and Nautilus Scientific Advisory Board Member**

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Research collaborations

Genentech
A Member of the Roche Group

- Signed a pilot study Research Collaboration Agreement in **December 2020.**
- Collaborating with Genentech using the Nautilus platform **to analyze and map the proteoform landscape** of a Genentech protein target of interest.

AMGEN

- Signed a pilot study Research Collaboration Agreement in **October 2021.**
- Collaborating with Amgen using the Nautilus platform across **a number of projects to investigate proteins and proteoforms of interest to the company.**

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

- Signed a Research Agreement in **October 2021.**
- Collaborating with MD Anderson using the Nautilus platform to measure the quantity and patterns of post-translational modifications on **specific oncology protein targets of interest** across different settings.

tgen
part of City of Hope

- Signed a Research Agreement in **January 2023.**
- Collaborating with TGen using the Nautilus platform to analyze specific protein targets **in diffuse intrinsic pontine glioma (DIPG), a rare and often fatal childhood cancer.**

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Expanded panel for tau proteoform quantification

11 reagents enables measurement of 2,048 proteoform groups of tau

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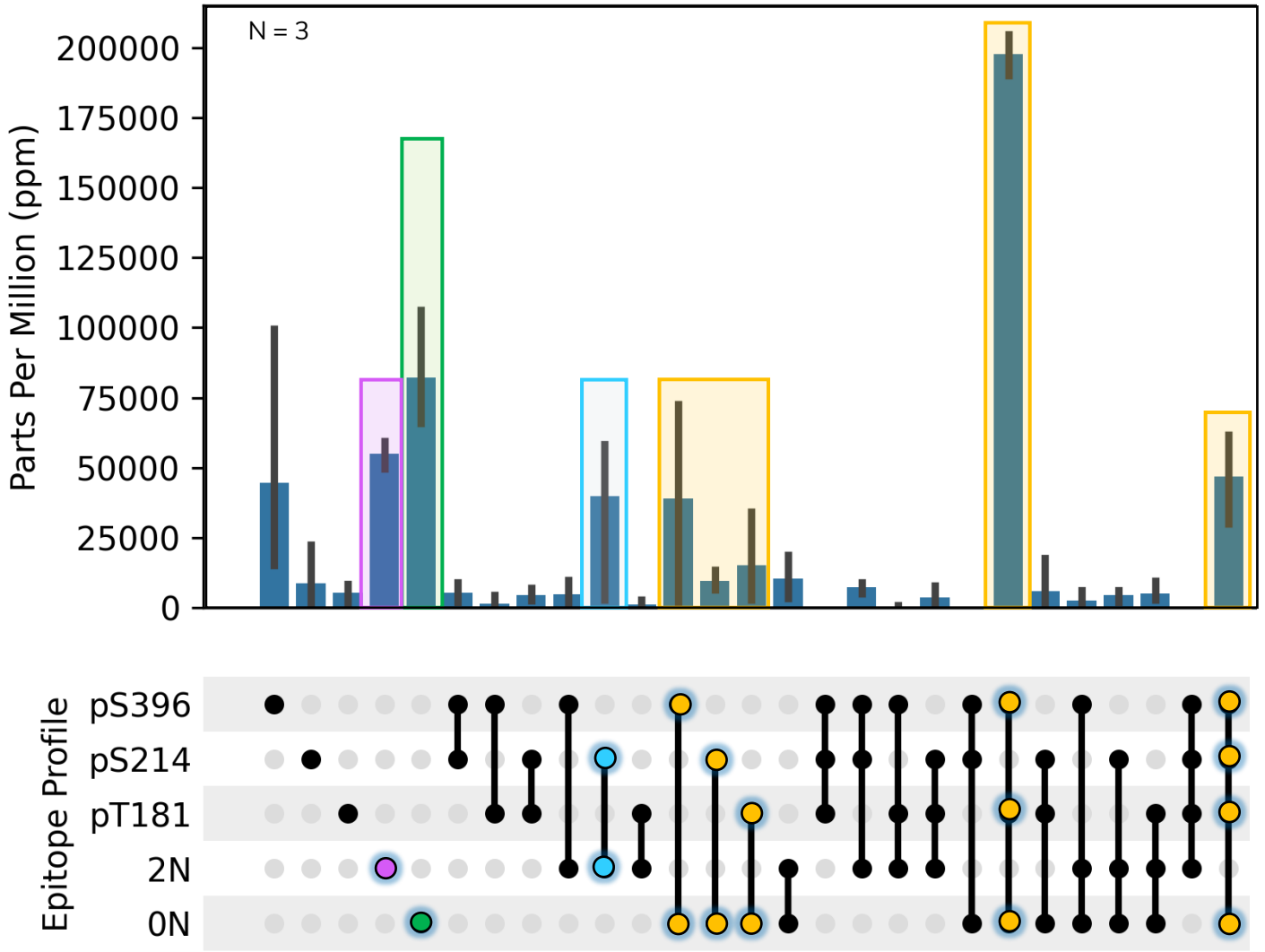
Quantification of mixtures of proteoforms



Tau proteoforms	Molar ratio
0N	25
0N ERK (181 & 396)	50
2N	12.5
2N PKA (214)	12.5

Exploiting the massively parallel nature of our platform, the relative abundances of seven Tau proteoforms were accurately quantified. This measurement is intractable on both traditional and emerging peptide-based platforms.

We additionally showed how the platform can be applied to measure Tau proteoforms.

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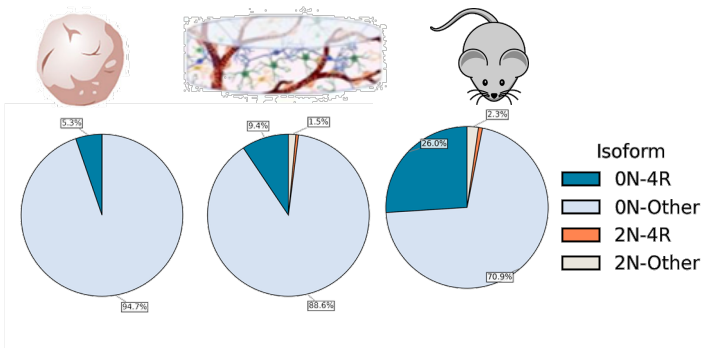
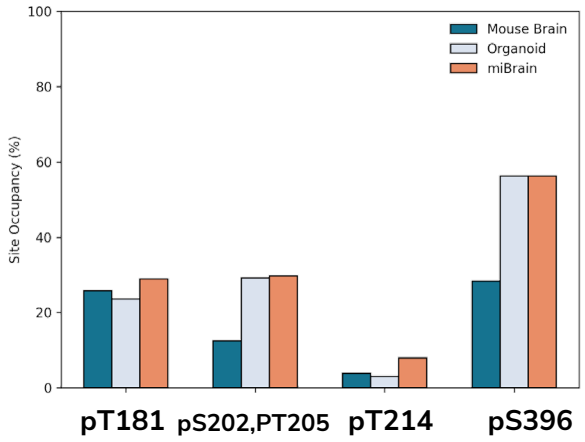
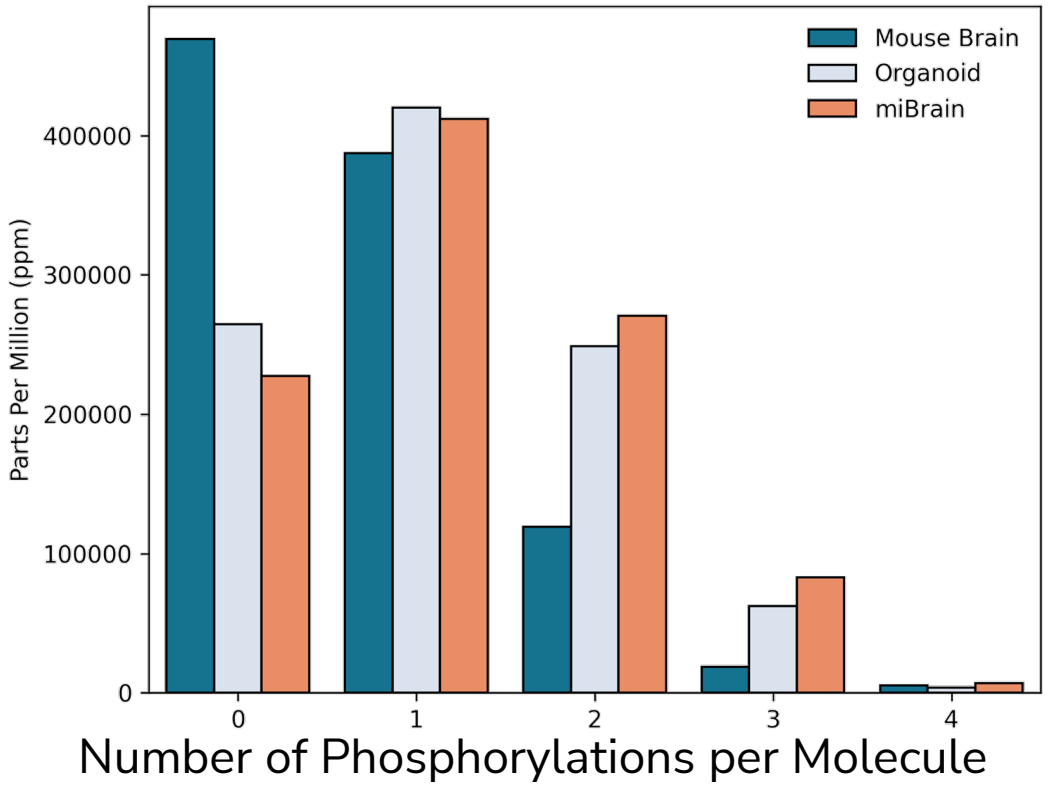
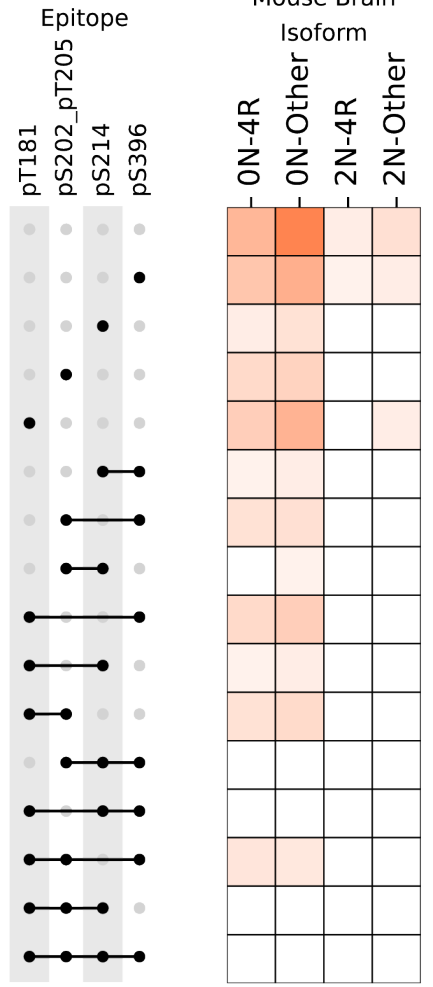
New additional detail into the proteoform landscape of model systems enabled by Nautilus Platform









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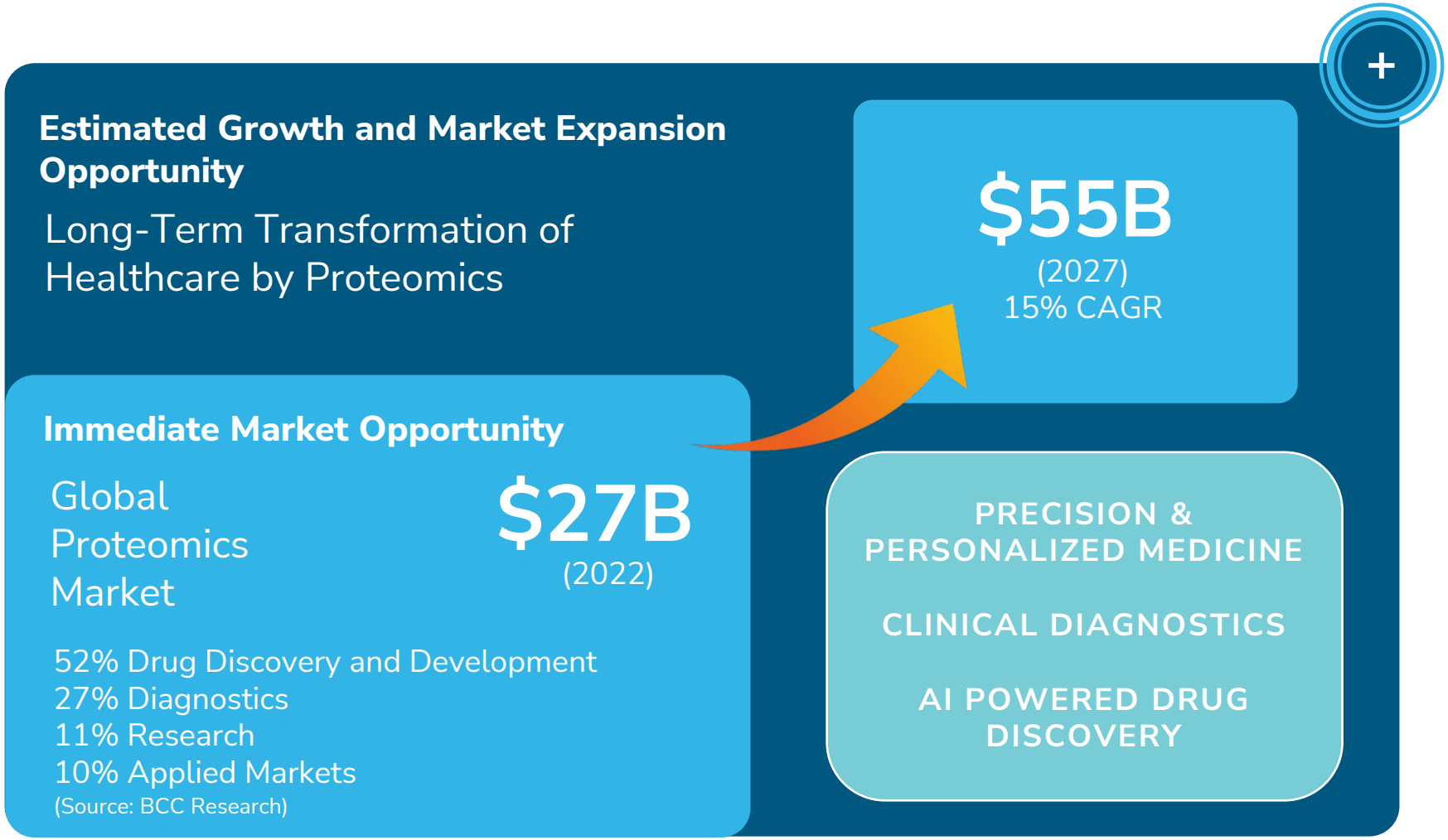
Large market opportunity ready for disruption



Phases leading to commercial launch planned for 2025

Every step represents a fundamentally new and unprecedented use of our technology

Today → 2025

Note: timeline not to scale

3. Launch of Proteome Analysis Platform (Expected in late 2025)

Shipment of First Instruments & Consumables

Early Access Beta Testing, and Full Commercial Launch

2.b. First Broadscale Proteome Decoding Data

Early Access Program for High-Output Discovery Proteomics

Launch in-house data production facility, support customer proof of concept studies

2.a. Tau Proteoform Data

Collaborations and Partnerships

Accelerate engagements with pharma partners and key academic collaborators using Tau as our first biomarker

1. Leveraging Single-Molecule Multi-Cycle Data Read-out

Continue to Establish Collaborations & Partnerships Focused on Targeted Proteomics

Engage early through research collaborations, build a foundation of publications

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Financial Overview

	Q3 2024
CASH BALANCE	$221.2M
CASH BURN	$11.7M
OPERATING EXPENSE	$19.1M (+0% YoY)
HEADCOUNT	161 (+0% YoY)
CASH RUNWAY	INTO 2027

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Why Nautilus?

We believe that humanity needs a dramatic acceleration of drug development and that a bold scientific leap is required to make possible a new world of precision and personalized medicine.

To deliver, we need to radically reinvent proteomics, a large untapped opportunity in biological science today.

Potential for revolutionizing biomedicine

Proven team, driven to win

Significant new potential market opportunity

Designed to address what the market wants – the proteome at single molecule resolution, enabling unprecedented sensitivity and scale

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Corporate Headquarters
2701 Eastlake Avenue, Suite 300
Seattle, WA 98102

Research Headquarters
835 Industrial Rd, Suite 200
San Carlos, CA 94070

(206) 333-2001 info@nautilus.bio

www.nautilus.bio