UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 6-K

REPORT OF FOREIGN PRIVATE ISSUER PURSUANT TO RULE 13a-16 OR 15d-16
UNDER THE SECURITIES EXCHANGE ACT OF 1934

FOR THE MONTH OF OCTOBER 2025

COMMISSION FILE NUMBER 001-39081

BioNTech SE
(Translation of registrant's name into English)

An der Goldgrube 12
D-55131 Mainz
Germany
+49 6131-9084-0
(Address of principal executive offices)

Indicate by check mark whether the registrant files or will file annual reports under cover Form 20-F or Form 40-F: Form 20-F ☒ Form 40-F ☐

Indicate by check mark if the registrant is submitting the Form 6-K in paper as permitted by Regulation S-T Rule 101(b)(1): ☐

Indicate by check mark if the registrant is submitting the Form 6-K in paper as permitted by Regulation S-T Rule 101(b)(7): ☐

DOCUMENTS INCLUDED AS PART OF THIS FORM 6-K

On October 1, 2025, BioNTech SE (“BioNTech”), alongside its artificial intelligence (“AI”) company InstaDeep Ltd., hosted its second AI Day, an edition of BioNTech’s “Innovation Series”, providing an overview of BioNTech’s AI strategy and capabilities and the application of AI in BioNTech’s pipeline and internal processes. The presentation is attached hereto as Exhibit 99.1.

SIGNATURE

Pursuant to the requirements of the Exchange Act, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

BioNTech SE

By:	/s/ Ramon Zapata-Gomez	By:	/s/ Dr. Sierk Poetting
	Name: Ramon Zapata-Gomez		Name: Dr. Sierk Poetting
	Title: Chief Financial Officer		Title: Chief Operating Officer

Date: October 1, 2025

EXHIBIT INDEX

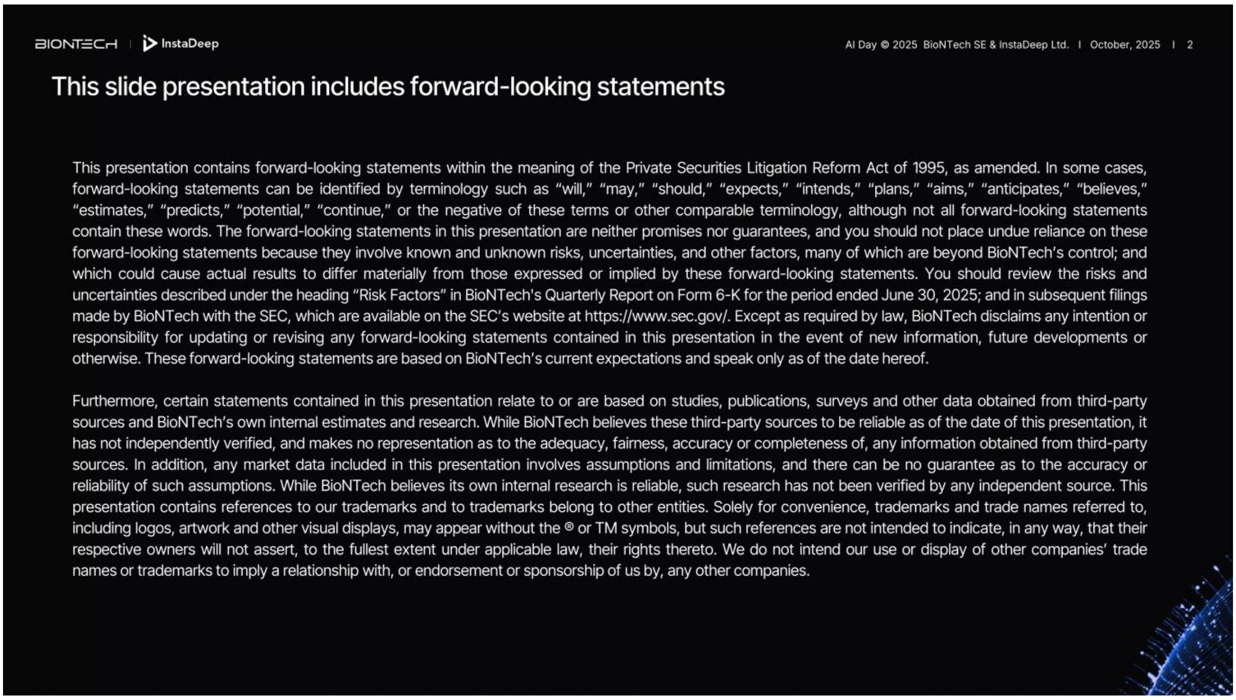
Exhibit	Description of Exhibit
99.1	Presentation

Exhibit 99.1

BIONTECH | InstaDeep

AI Day

October 1, 2025



This slide presentation includes forward-looking statements

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended. In some cases, forward-looking statements can be identified by terminology such as “will,” “may,” “should,” “expects,” “intends,” “plans,” “aims,” “anticipates,” “believes,” “estimates,” “predicts,” “potential,” “continue,” or the negative of these terms or other comparable terminology, although not all forward-looking statements contain these words. The forward-looking statements in this presentation are neither promises nor guarantees, and you should not place undue reliance on these forward-looking statements because they involve known and unknown risks, uncertainties, and other factors, many of which are beyond BioNTech’s control; and which could cause actual results to differ materially from those expressed or implied by these forward-looking statements. You should review the risks and uncertainties described under the heading “Risk Factors” in BioNTech's Quarterly Report on Form 6-K for the period ended June 30, 2025; and in subsequent filings made by BioNTech with the SEC, which are available on the SEC’s website at https://www.sec.gov/. Except as required by law, BioNTech disclaims any intention or responsibility for updating or revising any forward-looking statements contained in this presentation in the event of new information, future developments or otherwise. These forward-looking statements are based on BioNTech’s current expectations and speak only as of the date hereof.

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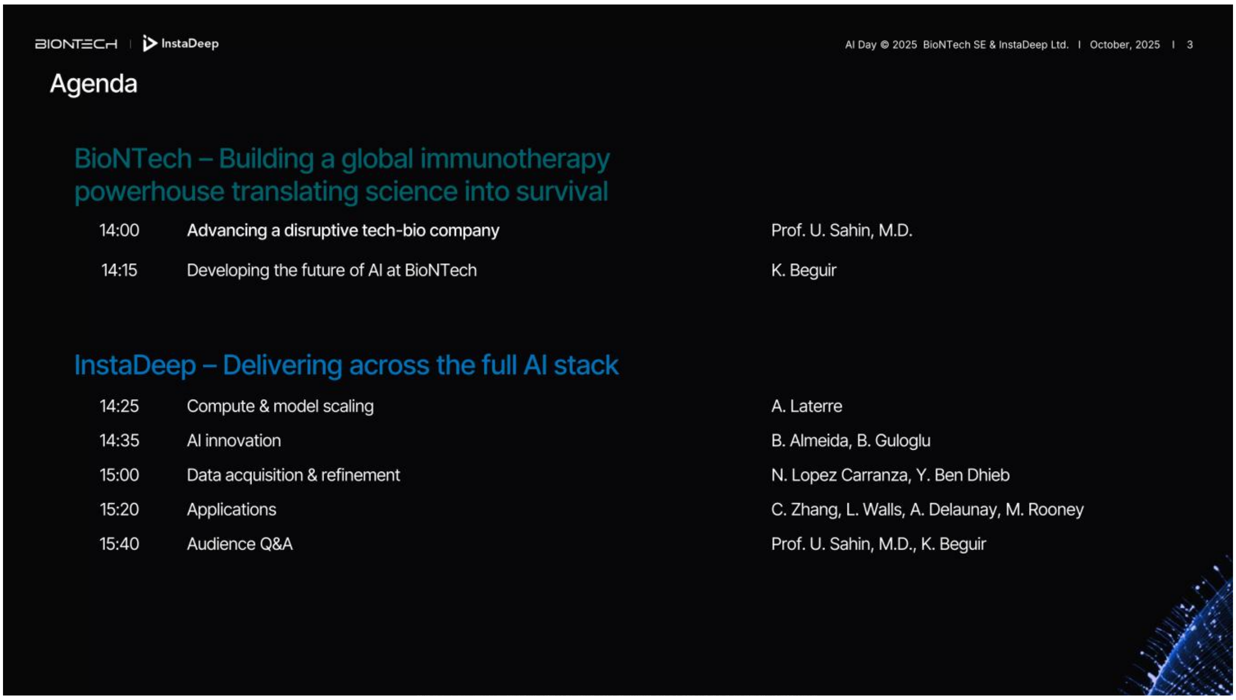


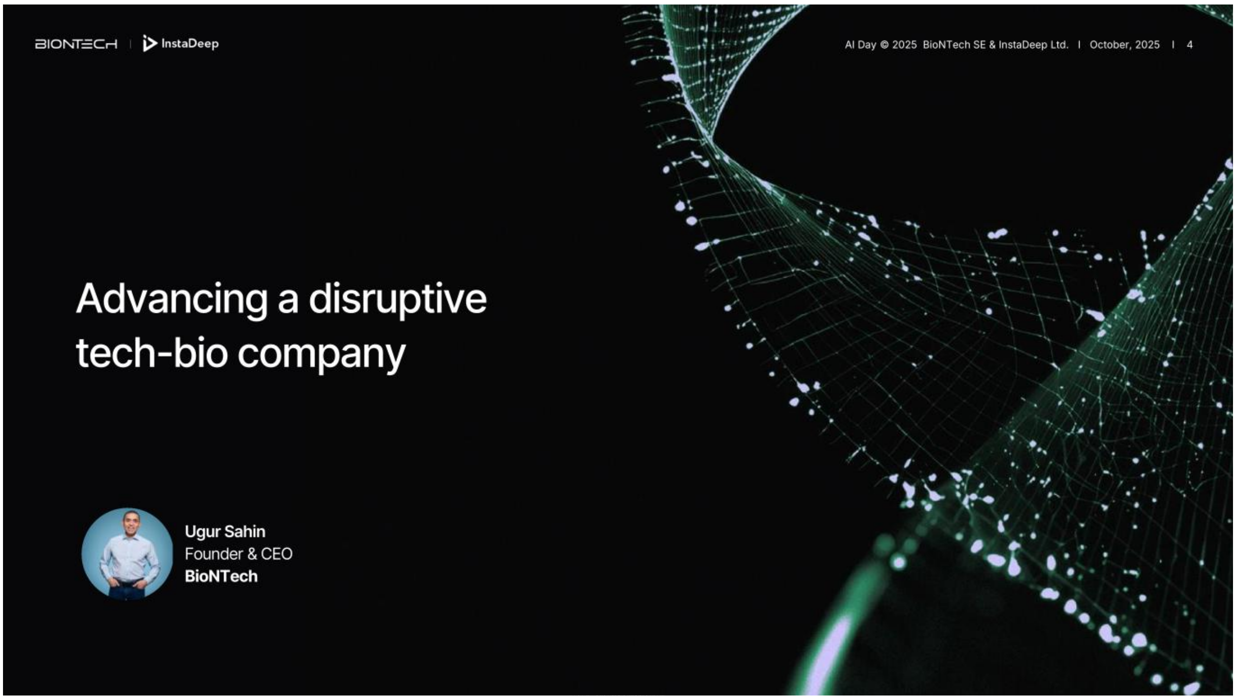
Agenda

BioNTech – Building a global immunotherapy powerhouse translating science into survival

14:00	**Advancing a disruptive tech-bio company**	Prof. U. Sahin, M.D.
14:15	Developing the future of AI at BioNTech	K. Beguir

InstaDeep – Delivering across the full AI stack

14:25	Compute & model scaling	A. Laterre
14:35	AI innovation	B. Almeida, B. Guloglu
15:00	Data acquisition & refinement	N. Lopez Carranza, Y. Ben Dhieb
15:20	Applications	C. Zhang, L. Walls, A. Delaunay, M. Rooney
15:40	Audience Q&A	Prof. U. Sahin, M.D., K. Beguir



Advancing a disruptive tech-bio company

Ugur Sahin
Founder & CEO
BioNTech

BIONTECH | InstaDeep

Margaret Keenan Dec. 8, 2020

London Science Museum

BioNTech's AI capabilities with worldwide reach

United Kingdom
London

U.S.
Cambridge
Gaithersburg

Germany (HQ + 6 sites)

France
Paris

Austria
Vienna

Tunis
Tunisia

South Africa
Cape Town

Rwanda
Kigali

UAE
Dubai

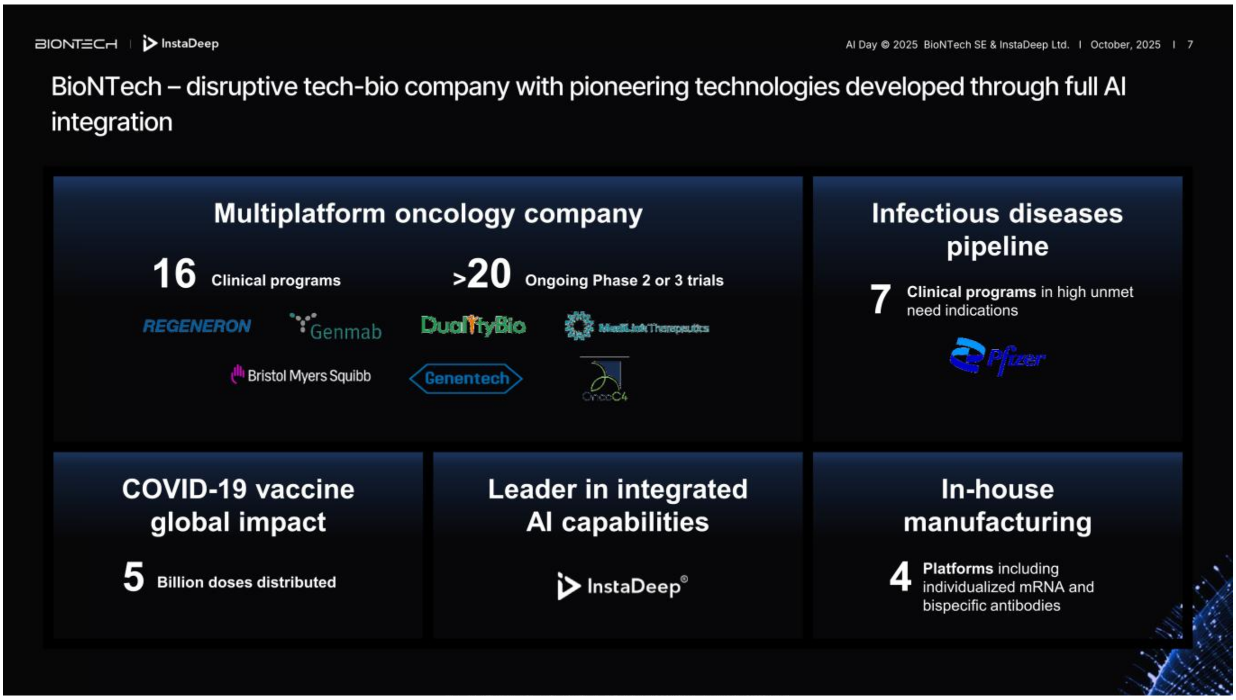
Turkey
Istanbul

China
Shanghai

Singapore

Australia
Victoria

○ BioNTech locations
● BioNTech AI centers



BioNTech – disruptive tech-bio company with pioneering technologies developed through full AI integration

Multiplatform oncology company

16 **Clinical programs**

>20 **Ongoing Phase 2 or 3 trials**

REGENERON
Genmab
DualityBio
MediLink Therapeutics
Bristol Myers Squibb
Genentech
OncoC4

Infectious diseases pipeline

7 **Clinical programs** in high unmet need indications

Pfizer

COVID-19 vaccine global impact

5 **Billion doses distributed**

Leader in integrated AI capabilities

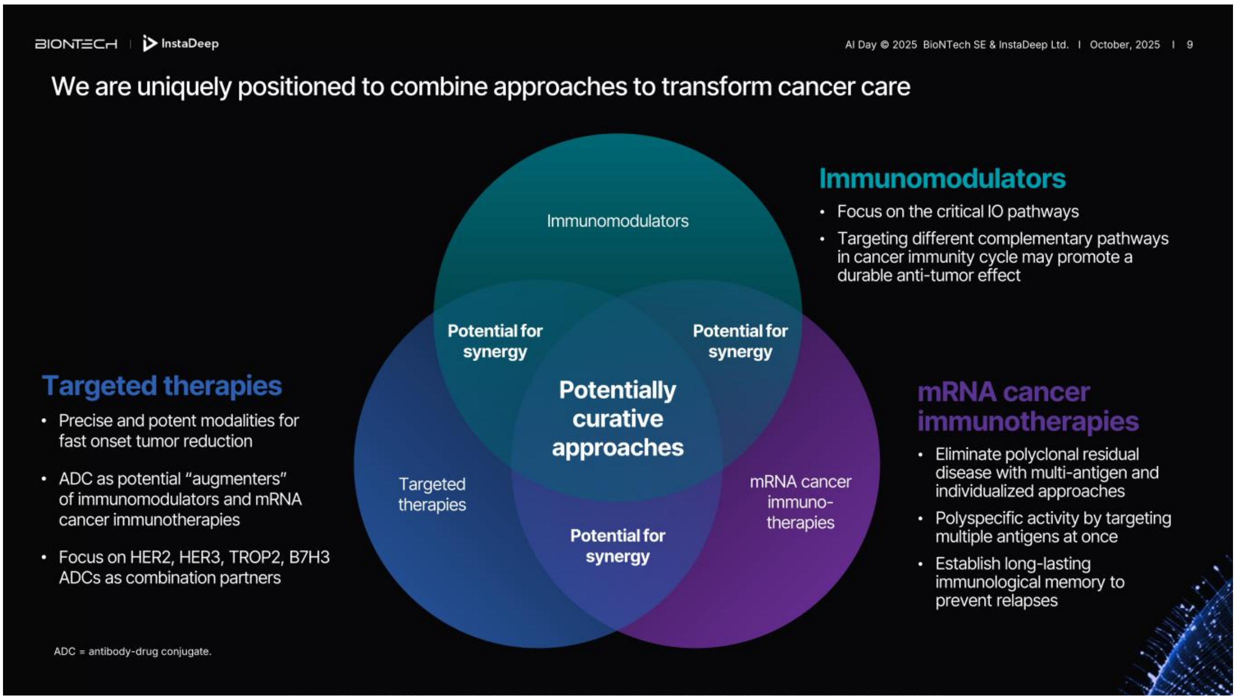
InstaDeep®

In-house manufacturing

4 **Platforms** including individualized mRNA and bispecific antibodies

Vision

Building a global
immunotherapy powerhouse
translating science into survival



We are uniquely positioned to combine approaches to transform cancer care

Immunomodulators

Potential for synergy

Potential for synergy

Potentially curative approaches

Targeted therapies

mRNA cancer immuno-therapies

Potential for synergy

Immunomodulators

- Focus on the critical IO pathways
- Targeting different complementary pathways in cancer immunity cycle may promote a durable anti-tumor effect

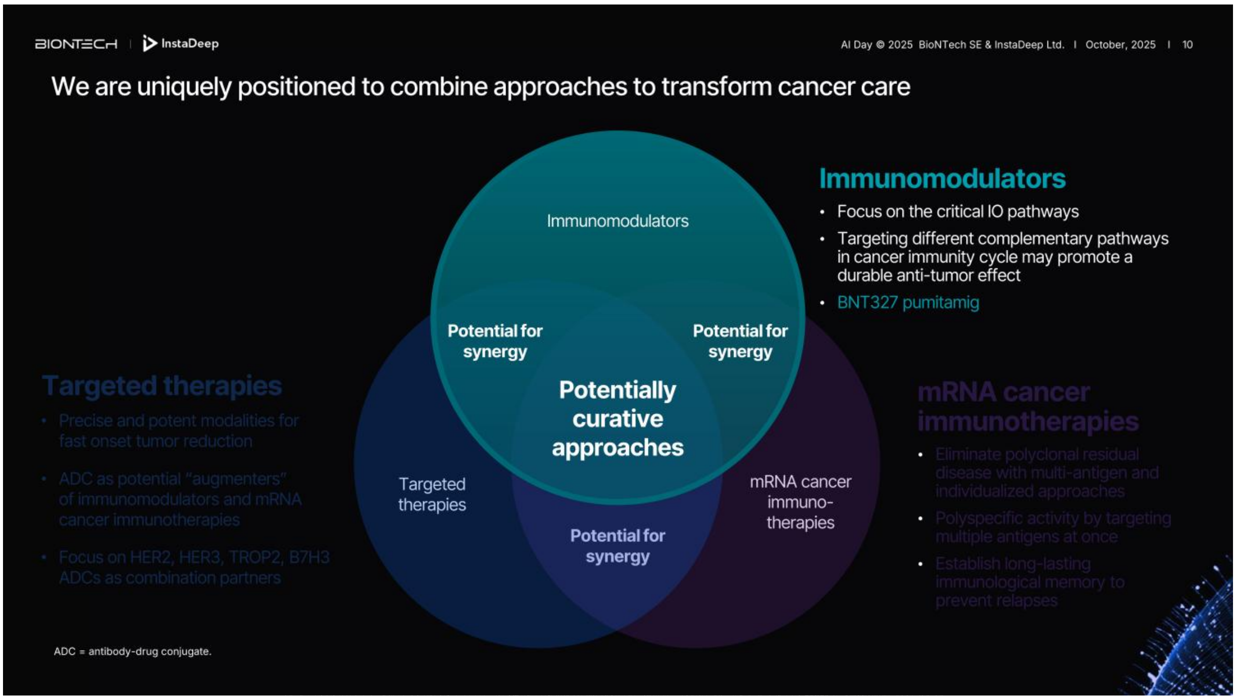
Targeted therapies

- Precise and potent modalities for fast onset tumor reduction
- ADC as potential "augmenters" of immunomodulators and mRNA cancer immunotherapies
- Focus on HER2, HER3, TROP2, B7H3 ADCs as combination partners

mRNA cancer immunotherapies

- Eliminate polyclonal residual disease with multi-antigen and individualized approaches
- Polyspecific activity by targeting multiple antigens at once
- Establish long-lasting immunological memory to prevent relapses

ADC = antibody-drug conjugate.



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- BNT327 pumitamig

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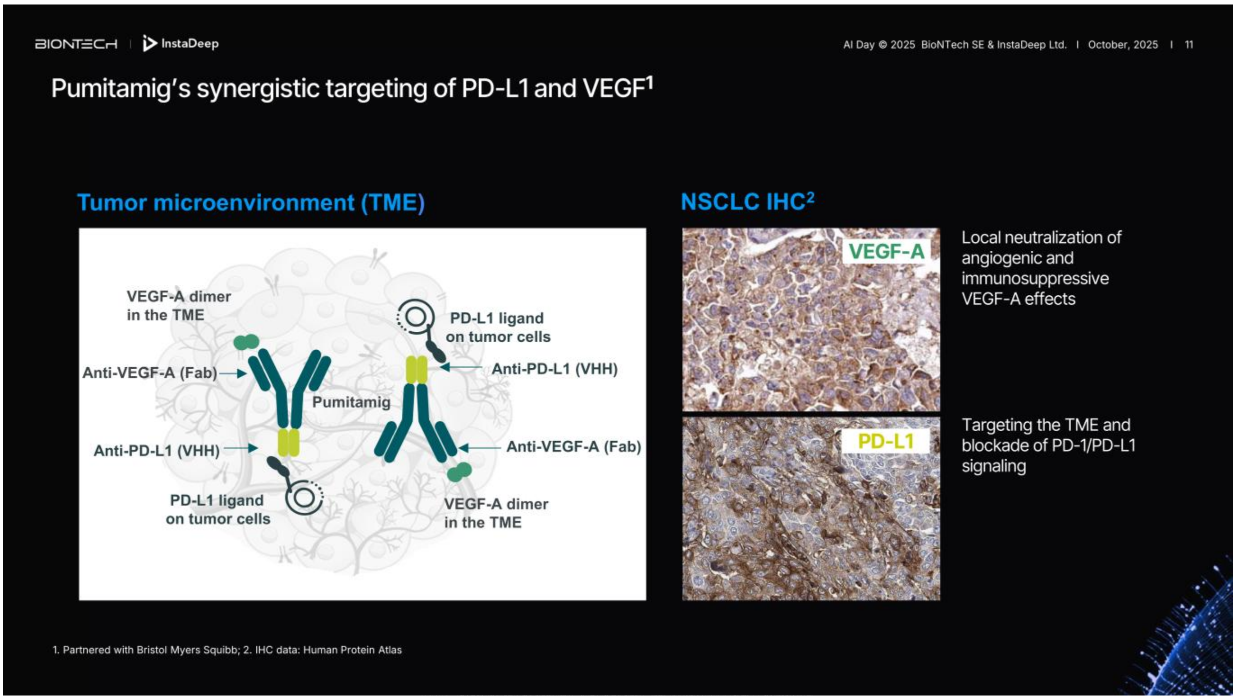


Pumitamig's synergistic targeting of PD-L1 and VEGF[1]

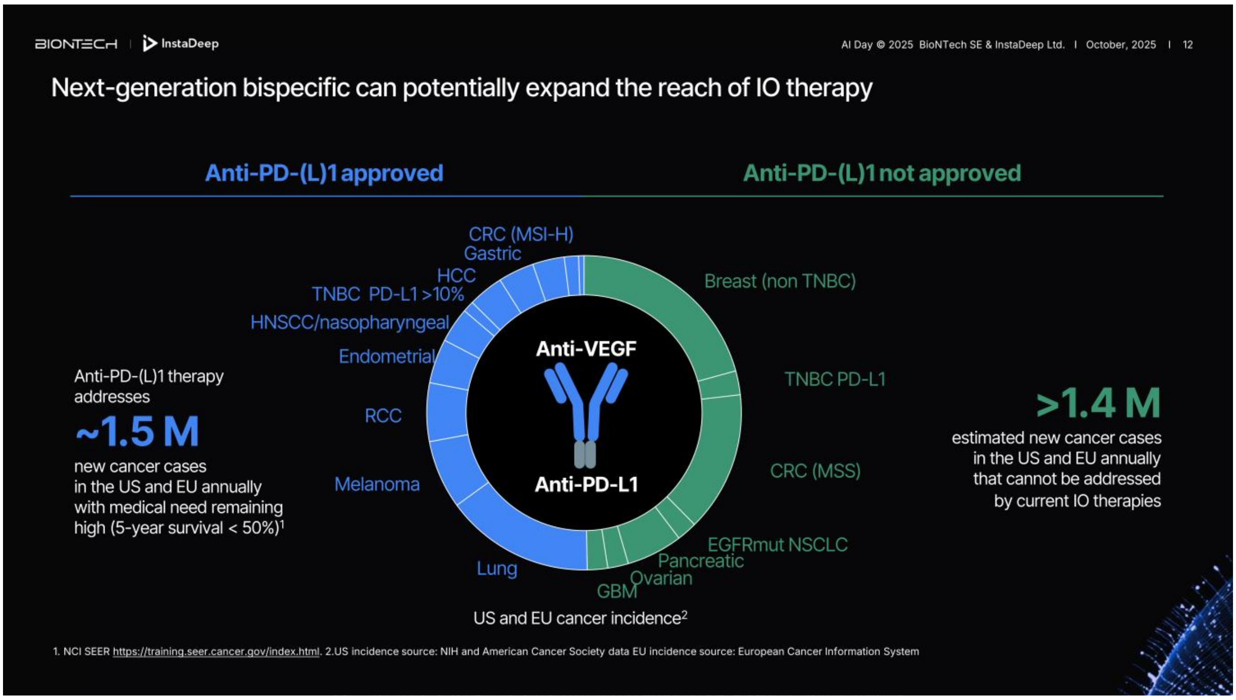
Tumor microenvironment (TME)

NSCLC IHC[2]

Local neutralization of angiogenic and immunosuppressive VEGF-A effects

Targeting the TME and blockade of PD-1/PD-L1 signaling

1. Partnered with Bristol Myers Squibb; 2. IHC data: Human Protein Atlas



Next-generation bispecific can potentially expand the reach of IO therapy

Anti-PD-(L)1 approved

Anti-PD-(L)1 not approved

Anti-PD-(L)1 therapy addresses

~1.5 M

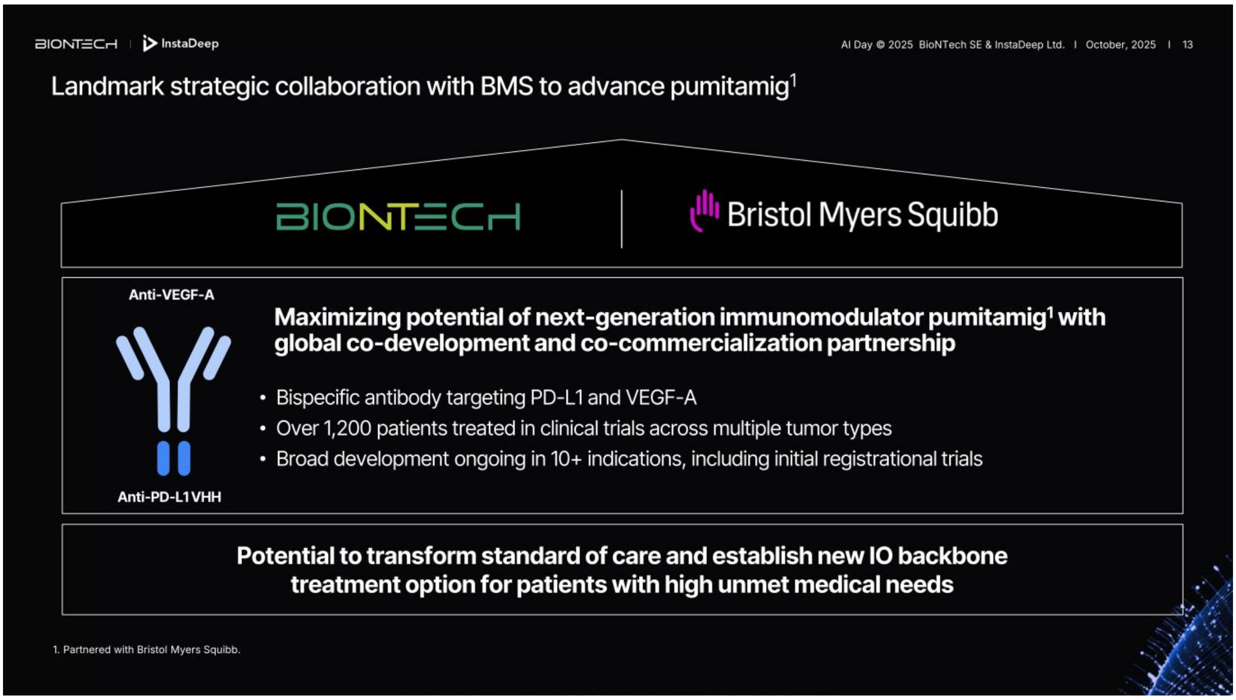
new cancer cases
in the US and EU annually
with medical need remaining
high (5-year survival < 50%)[1]

US and EU cancer incidence[2]

>1.4 M

estimated new cancer cases
in the US and EU annually
that cannot be addressed
by current IO therapies

1. NCI SEER https://training.seer.cancer.gov/index.html. 2.US incidence source: NIH and American Cancer Society data EU incidence source: European Cancer Information System



Landmark strategic collaboration with BMS to advance pumitamig[1]

BIONTECH | Bristol Myers Squibb

Anti-VEGF-A

Anti-PD-L1 VHH

Maximizing potential of next-generation immunomodulator pumitamig[1] with global co-development and co-commercialization partnership

- Bispecific antibody targeting PD-L1 and VEGF-A
- Over 1,200 patients treated in clinical trials across multiple tumor types
- Broad development ongoing in 10+ indications, including initial registrational trials

Potential to transform standard of care and establish new IO backbone treatment option for patients with high unmet medical needs

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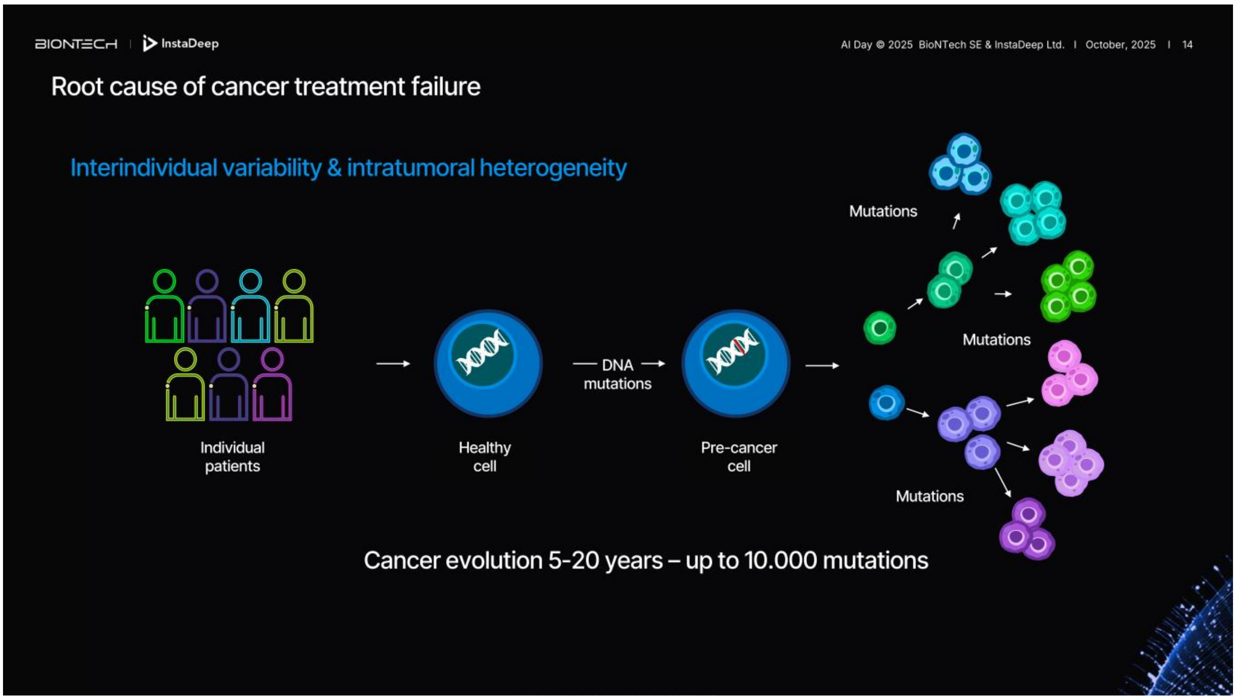
[1] Partnered with Bristol Myers Squibb.



Root cause of cancer treatment failure

Interindividual variability & intratumoral heterogeneity

Individual patients

Healthy cell

DNA mutations

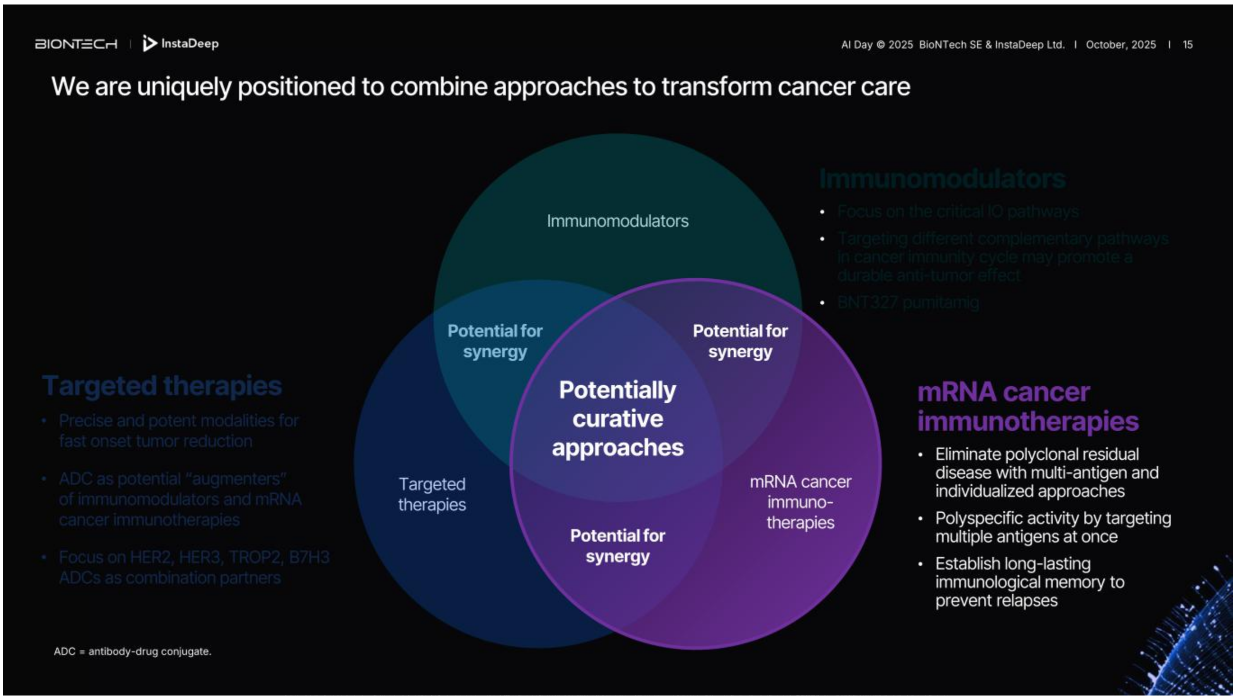
Pre-cancer cell

Mutations

Mutations

Mutations

Cancer evolution 5-20 years – up to 10.000 mutations



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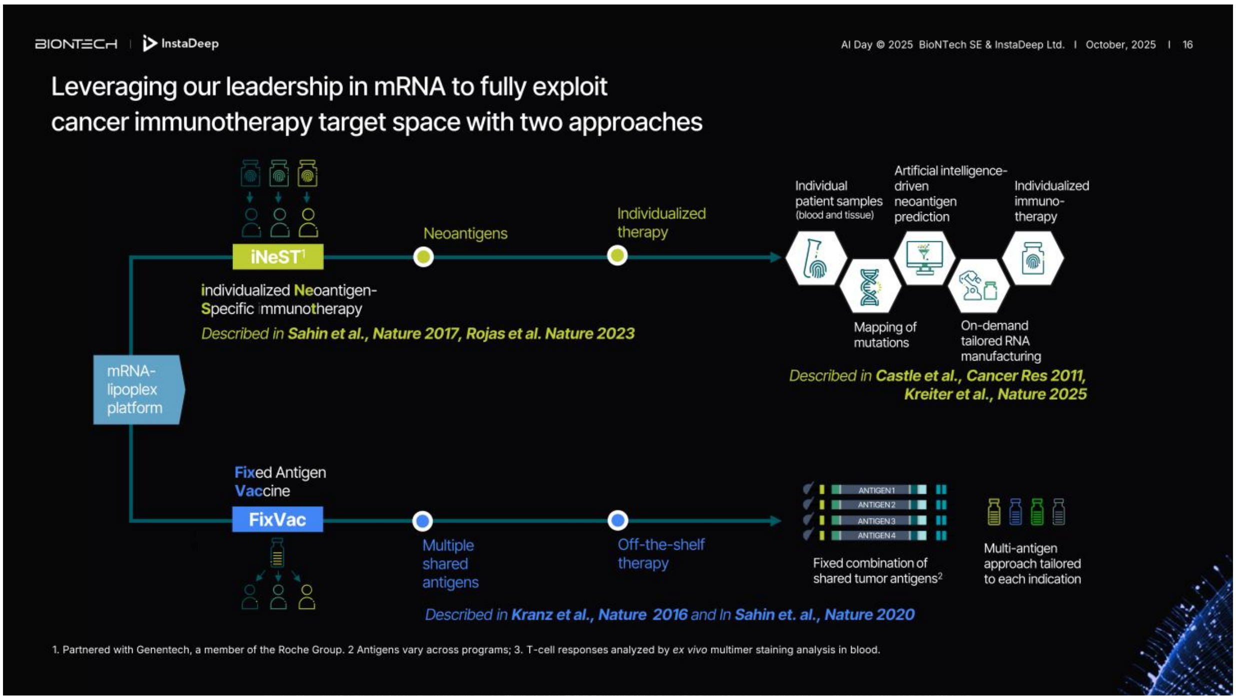


Leveraging our leadership in mRNA to fully exploit cancer immunotherapy target space with two approaches

mRNA-
lipoplex
platform

iNeST[1]

individualized **Ne**oantigen-
Specific **i**mmuno**t**herapy

Neoantigens

Individualized
therapy

Described in ***Sahin et al., Nature 2017, Rojas et al. Nature 2023***

Individual
patient samples
(blood and tissue)

Mapping of
mutations

Artificial intelligence-
driven
neoantigen
prediction

On-demand
tailored RNA
manufacturing

Individualized
immuno-
therapy

Described in ***Castle et al., Cancer Res 2011, Kreiter et al., Nature 2025***

Fixed Antigen
Vaccine

FixVac

Multiple
shared
antigens

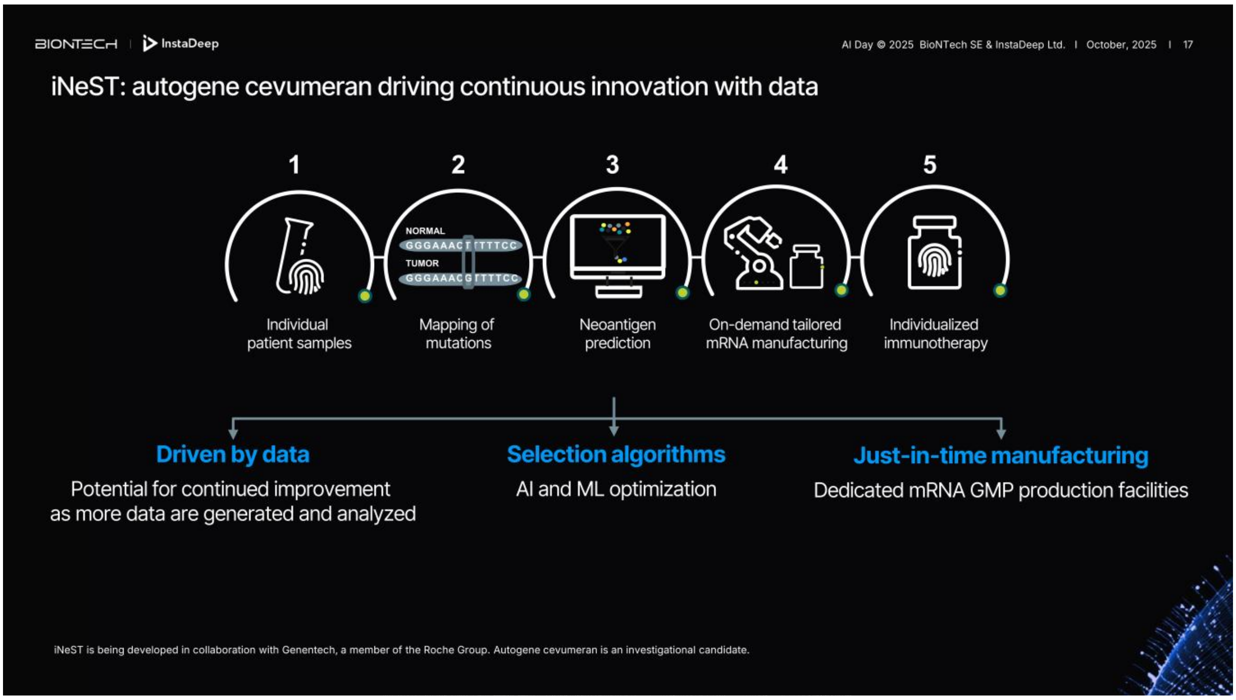
Off-the-shelf
therapy

Fixed combination of
shared tumor antigens[2]

Multi-antigen
approach tailored
to each indication

Described in ***Kranz et al., Nature 2016*** *and In* ***Sahin et. al., Nature 2020***

1. Partnered with Genentech, a member of the Roche Group. 2 Antigens vary across programs; 3. T-cell responses analyzed by *ex vivo* multimer staining analysis in blood.



iNeST: autogene cevumeran driving continuous innovation with data

1. Individual patient samples
2. Mapping of mutations
3. Neoantigen prediction
4. On-demand tailored mRNA manufacturing
5. Individualized immunotherapy

Driven by data

Potential for continued improvement as more data are generated and analyzed

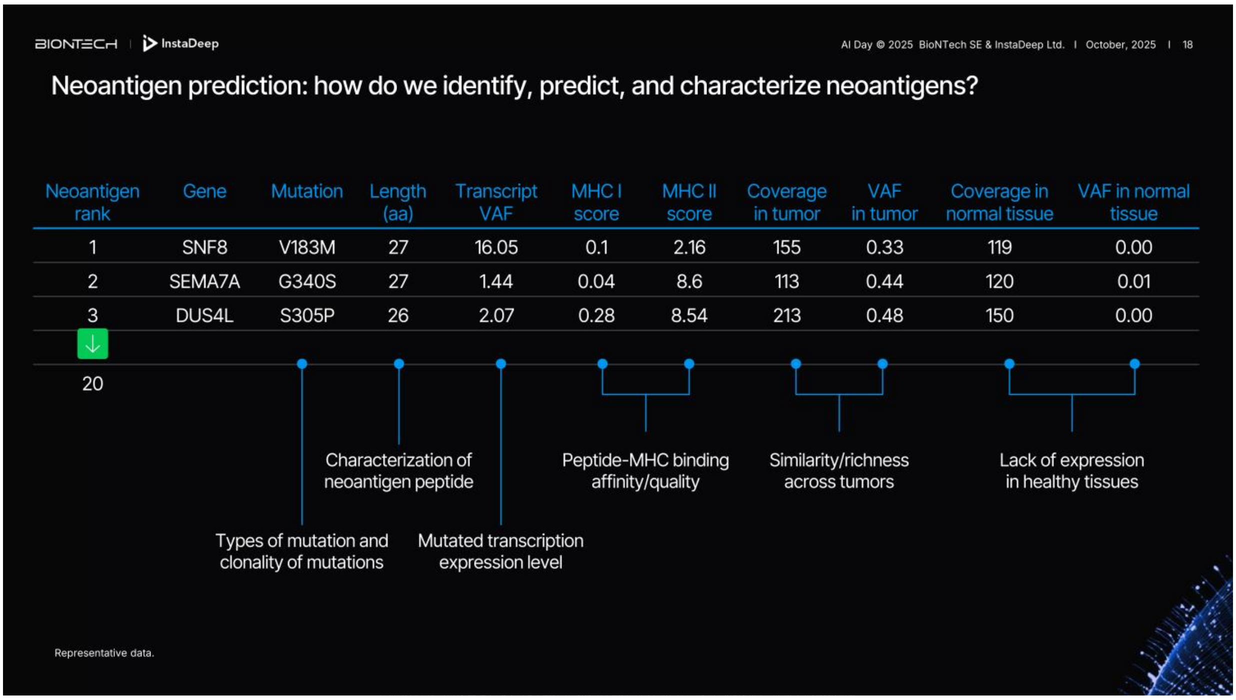
Selection algorithms

AI and ML optimization

Just-in-time manufacturing

Dedicated mRNA GMP production facilities

iNeST is being developed in collaboration with Genentech, a member of the Roche Group. Autogene cevumeran is an investigational candidate.



Neoantigen prediction: how do we identify, predict, and characterize neoantigens?

Neoantigen rank	Gene	Mutation	Length (aa)	Transcript VAF	MHC I score	MHC II score	Coverage in tumor	VAF in tumor	Coverage in normal tissue	VAF in normal tissue
1	SNF8	V183M	27	16.05	0.1	2.16	155	0.33	119	0.00
2	SEMA7A	G340S	27	1.44	0.04	8.6	113	0.44	120	0.01
3	DUS4L	S305P	26	2.07	0.28	8.54	213	0.48	150	0.00
↓										
20										

Characterization of neoantigen peptide

Peptide-MHC binding affinity/quality

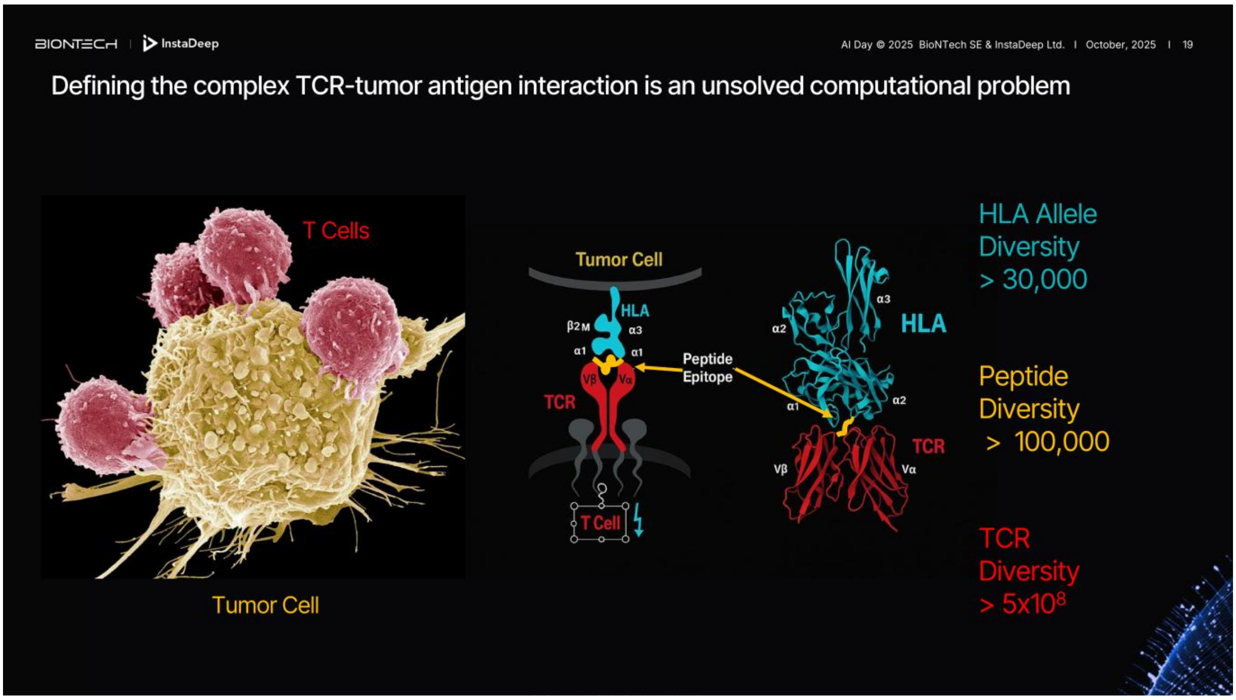
Similarity/richness across tumors

Lack of expression in healthy tissues

Types of mutation and clonality of mutations

Mutated transcription expression level

Representative data.

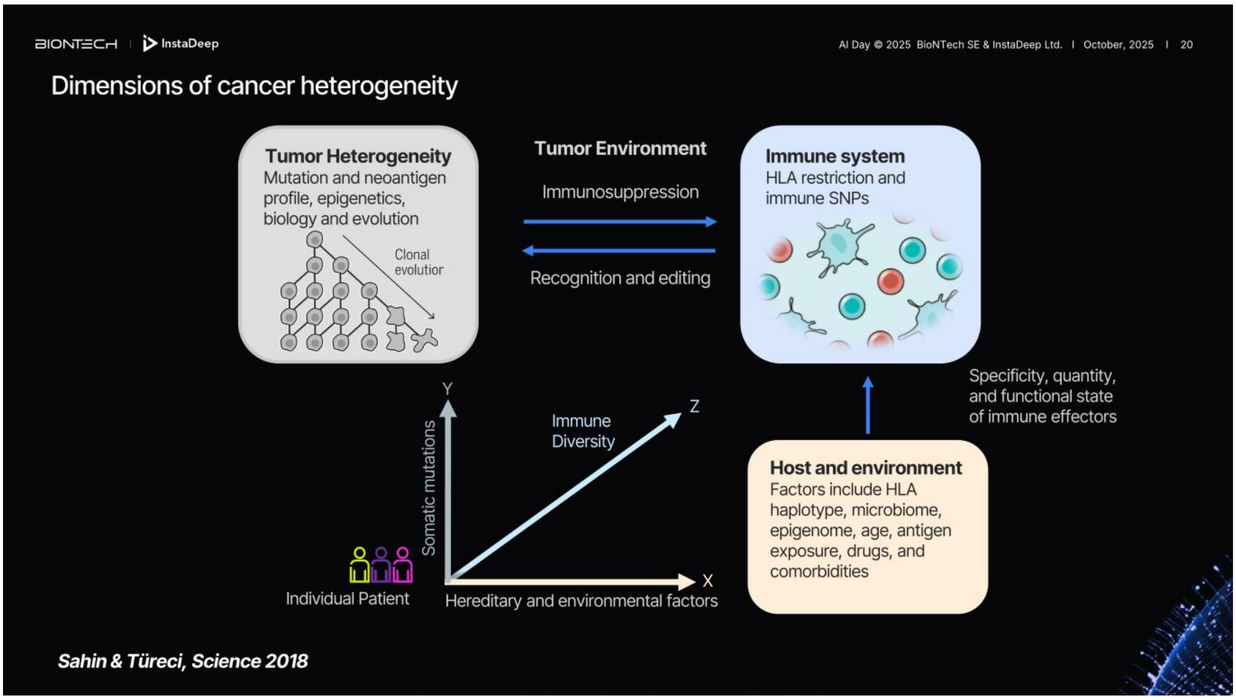


Defining the complex TCR-tumor antigen interaction is an unsolved computational problem

HLA Allele Diversity > 30,000

Peptide Diversity > 100,000

TCR Diversity > 5×10^8



Dimensions of cancer heterogeneity

Tumor Heterogeneity
Mutation and neoantigen profile, epigenetics, biology and evolution

Clonal evolution

Tumor Environment

Immunosuppression

Recognition and editing

Immune system
HLA restriction and immune SNPs

Specificity, quantity, and functional state of immune effectors

Host and environment
Factors include HLA haplotype, microbiome, epigenome, age, antigen exposure, drugs, and comorbidities

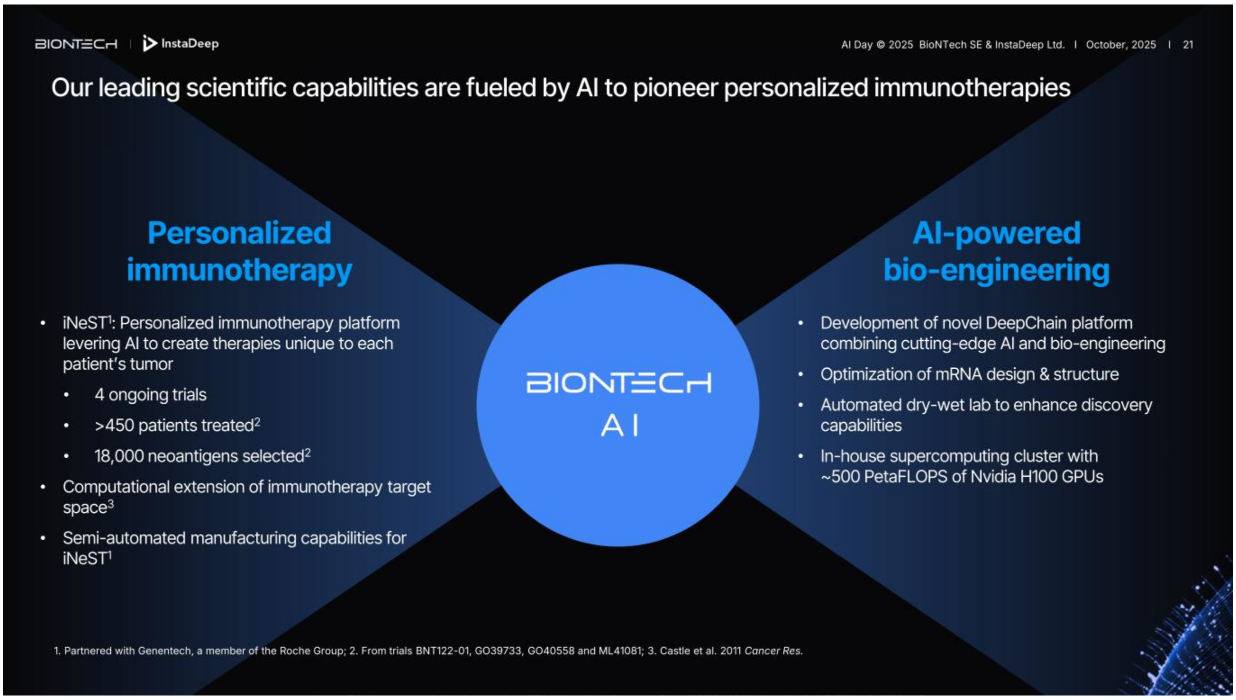
Y
Somatic mutations

Z
Immune Diversity

X
Hereditary and environmental factors

Individual Patient

Sahin & Türeci, Science 2018



Our leading scientific capabilities are fueled by AI to pioneer personalized immunotherapies

Personalized immunotherapy

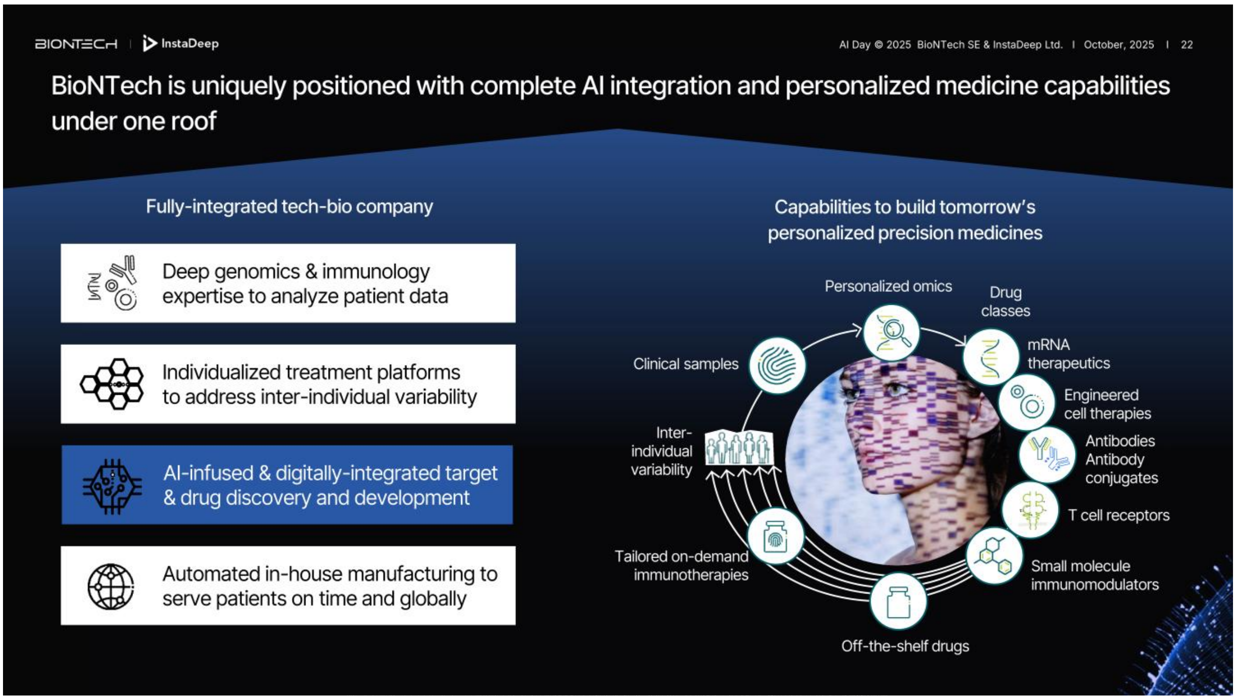
- iNeST[1]: Personalized immunotherapy platform levering AI to create therapies unique to each patient's tumor
  - 4 ongoing trials
  - >450 patients treated[2]
  - 18,000 neoantigens selected[2]
- Computational extension of immunotherapy target space[3]
- Semi-automated manufacturing capabilities for iNeST[1]

BIONTECH AI

AI-powered bio-engineering

- Development of novel DeepChain platform combining cutting-edge AI and bio-engineering
- Optimization of mRNA design & structure
- Automated dry-wet lab to enhance discovery capabilities
- In-house supercomputing cluster with ~500 PetaFLOPS of Nvidia H100 GPUs

1. Partnered with Genentech, a member of the Roche Group; 2. From trials BNT122-01, GO39733, GO40558 and ML41081; 3. Castle et al. 2011 *Cancer Res.*



BioNTech is uniquely positioned with complete AI integration and personalized medicine capabilities under one roof

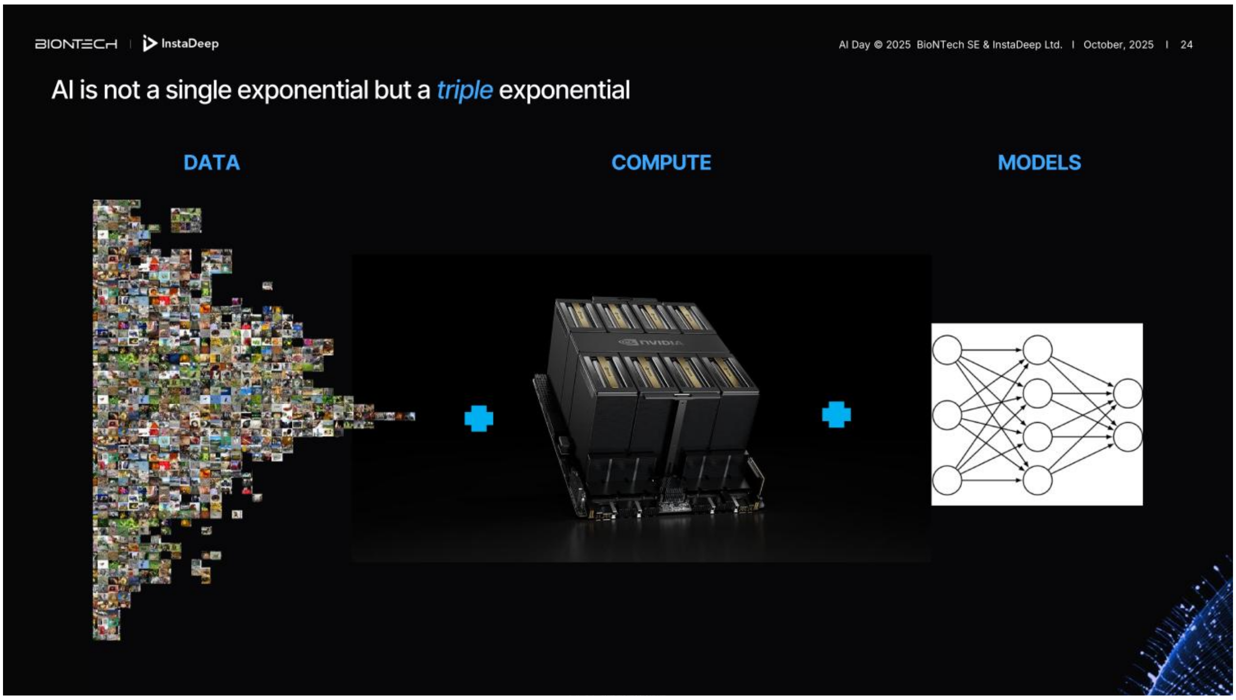
Fully-integrated tech-bio company

- Deep genomics & immunology expertise to analyze patient data
- Individualized treatment platforms to address inter-individual variability
- AI-infused & digitally-integrated target & drug discovery and development
- Automated in-house manufacturing to serve patients on time and globally

Capabilities to build tomorrow's personalized precision medicines

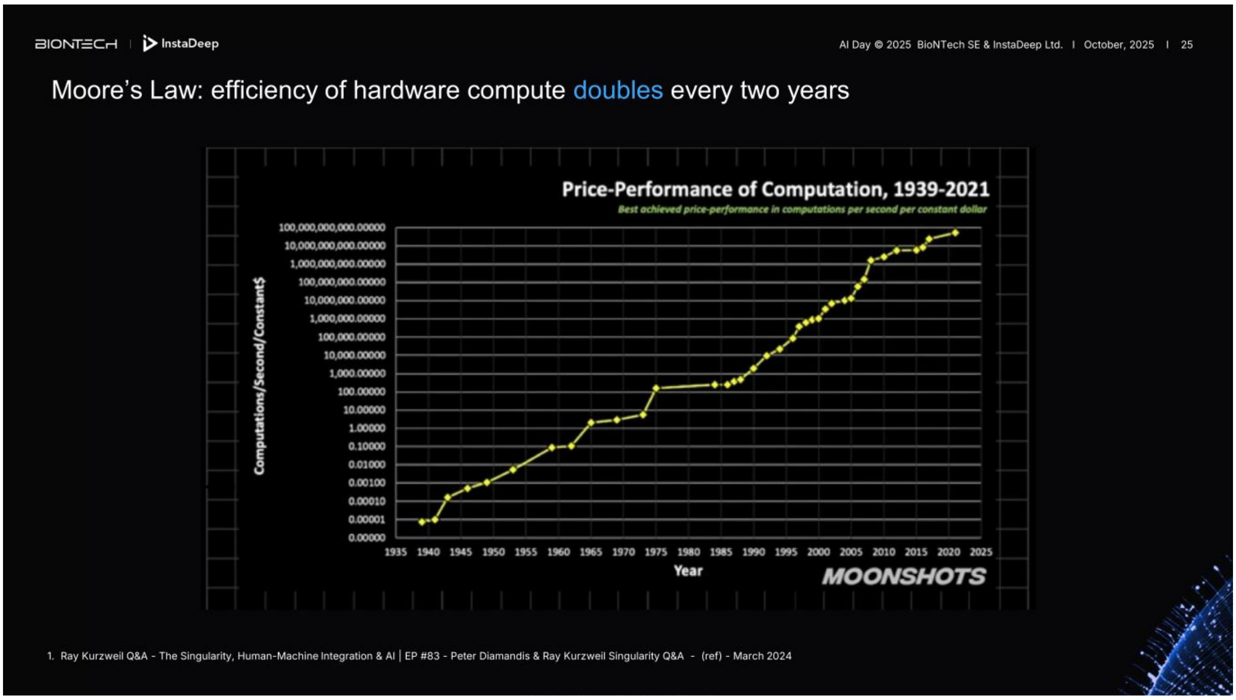
Developing the future of AI at BioNTech

Karim Beguir
Co-Founder & CEO
InstaDeep



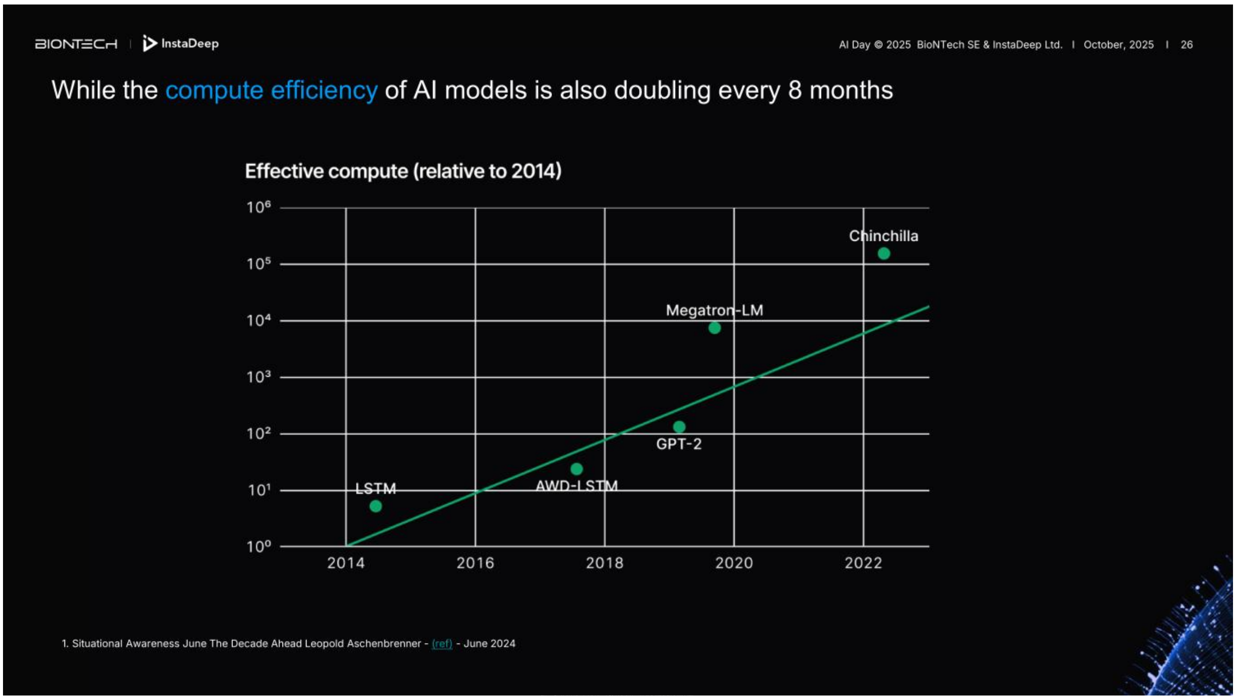
AI is not a single exponential but a *triple* exponential

DATA + **COMPUTE** + **MODELS**



Moore's Law: efficiency of hardware compute doubles every two years

1. Ray Kurzweil Q&A - The Singularity, Human-Machine Integration & AI | EP #83 - Peter Diamandis & Ray Kurzweil Singularity Q&A - (ref) - March 2024

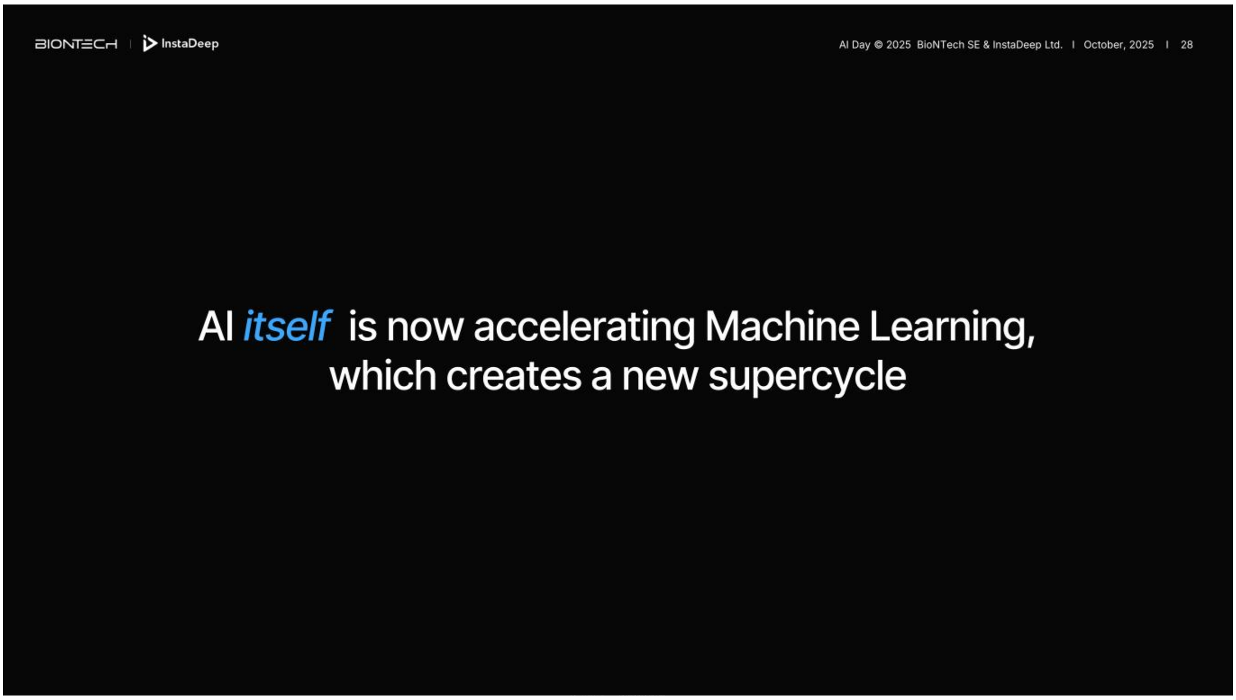


While the compute efficiency of AI models is also doubling every 8 months

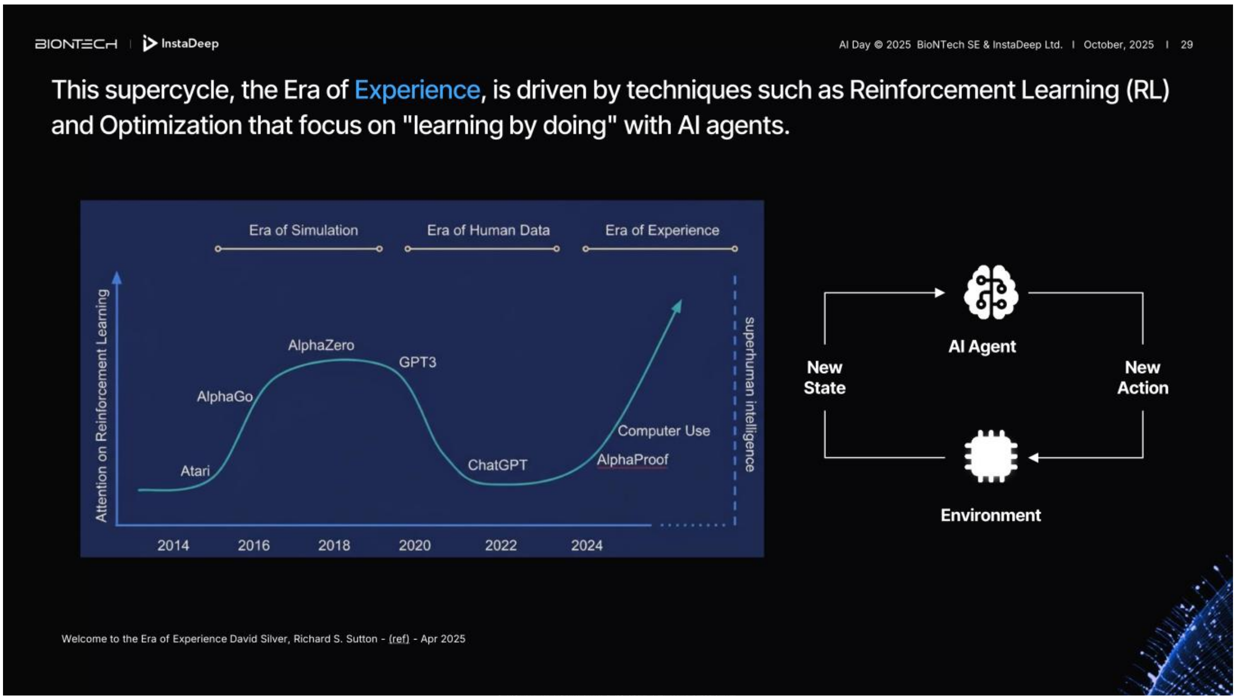
1. Situational Awareness June The Decade Ahead Leopold Aschenbrenner - (ref) - June 2024

Is AI likely to expand even further?

The AI Revolution: The Road to Superintelligence - By Tim Urban -January 22, 2015



AI *itself* is now accelerating Machine Learning, which creates a new supercycle



This supercycle, the Era of Experience, is driven by techniques such as Reinforcement Learning (RL) and Optimization that focus on "learning by doing" with AI agents.

Welcome to the Era of Experience David Silver, Richard S. Sutton - (ref) - Apr 2025

InstaDeep is active in Reinforcement Learning research

Oryx: a Performant and Scalable Algorithm for Many-Agent Coordination in Offline MARL

Claude Formanek[1,2,*] Omayma Mahjoub[1] Louay Ben Nessir[1] Sasha Abramowitz[1] Ruan de Kock[1] Wiem Khlifi[1] Simon Du Toit[1] Felix Chalumeau[1] Daniel Rajaonarivonivelomanantsoa[1,3] Arnol Fokam[1] Siddarth Singh[1] Ulrich Mbou Sob[1] Arnu Pretorius[1,3]

[1]InstaDeep
[2]University of Cape Town
[3]Stellenbosch University

Abstract

A key challenge in offline multi-agent reinforcement learning (MARL) is achieving effective many-agent multi-step coordination in complex environments. In this work, we propose **Oryx**, a novel algorithm for offline cooperative MARL to directly address this challenge. Oryx adapts the recently proposed retention-based architecture Sable (Mahjoub et al., 2025) and combines it with a sequential form of implicit constraint Q-learning (ICQ) (Yang et al., 2021), to develop a novel offline auto-regressive policy update scheme. This allows Oryx to solve complex coordination challenges while maintaining temporal coherence over lengthy trajectories. We evaluate Oryx across a diverse set of benchmarks from prior works—SMAC, RWARE, and Multi-Agent MuJoCo—covering tasks of both discrete and continuous control, varying in scale and difficulty. **Oryx achieves state-of-the-art performance on more than 80% of the 65 tested datasets**, outperforming prior offline MARL methods and demonstrating robust generalisation across domains with many agents and long horizons. Finally, we introduce new datasets to push the limits of many-agent coordination in offline MARL, and demonstrate Oryx's superior ability to scale effectively in such settings. We will make all of our datasets, experimental data, and code available upon publication.

Oryx: a Performant and Scalable Algorithm for Many-Agent Coordination in Offline MARL

NeurIPS Conference 2025

MEMORY-ENHANCED NEURAL SOLVERS FOR EFFICIENT ADAPTATION IN COMBINATORIAL OPTIMIZATION

Felix Chalumeau*[1] Refiloe Shabe[1] Noah De Nicola*[1,2] Arnu Pretorius[1] Thomas D. Barrett[1] Nathan Grinsztajn[1]
[1]InstaDeep [2]University of Cape Town

ABSTRACT

Combinatorial Optimization is crucial to numerous real-world applications, yet still presents challenges due to its (NP-)hard nature. Amongst existing approaches, heuristics often offer the best trade-off between quality and scalability, making them suitable for industrial use. While Reinforcement Learning (RL) offers a flexible framework for designing heuristics, its adoption over handcrafted heuristics remains incomplete within industrial solvers. Existing learned methods still lack the ability to adapt to specific instances and fully leverage the available computational budget. The current best methods either rely on a collection of pre-trained policies, or on data-inefficient fine-tuning; hence failing to fully utilize newly available information within the constraints of the budget. In response, we present MEMENTO, an approach that leverages memory to improve the adaptation of neural solvers at inference time. MEMENTO enables updating the action distribution dynamically based on the outcome of previous decisions. We validate its effectiveness on benchmark problems, in particular Traveling Salesman and Capacitated Vehicle Routing, demonstrating its superiority over tree-search and policy-gradient fine-tuning; and showing it can be zero-shot combined with diversity-based solvers. We successfully train all RL auto-regressive solvers on large instances, and show that MEMENTO can scale and is data-efficient. Overall, MEMENTO enables to push the state-of-the-art on 11 out of 12 evaluated tasks.

1 INTRODUCTION

Combinatorial Optimization (CO) encompasses a vast range of real-world applications, ranging from transportation (J-F Audy & Rousseau, 2011) and logistics (Dischas et al., 1992) to energy management (Froger et al., 2016). These problems involve finding optimal orderings, labels, or subsets of discrete sets to optimize given objective functions. Real-world CO problems are typically NP-hard with a solution space growing exponentially with the problem size, making it intractable to find the optimal solution. Hence, industrial solvers rely on sophisticated heuristic approaches to solve them in practice. Reinforcement Learning (RL) provides a versatile framework for learning such heuristics and has demonstrated remarkable success in tackling CO tasks (Maryavkina et al., 2021).

Memory-Enhanced Neural Solvers for Efficient Adaptation in Combinatorial Optimization

NeurIPS Conference 2025 Spotlight

Breaking the Performance Ceiling in Complex Reinforcement Learning requires Inference Strategies

Felix Chalumeau*[1] Daniel Rajaonarivonivelomanantsoa*[1,2] Ruan de Kock*[1] Claude Formanek[1] Sasha Abramowitz[1] Omayma Mahjoub[1] Wiem Khlifi[1] Simon Du Toit[1] Louay Ben Nessir[1] Refiloe Shabe[1] Arnol Fokam[1] Siddarth Singh[1] Ulrich Mbou Sob[1] Arnu Pretorius[1,2]

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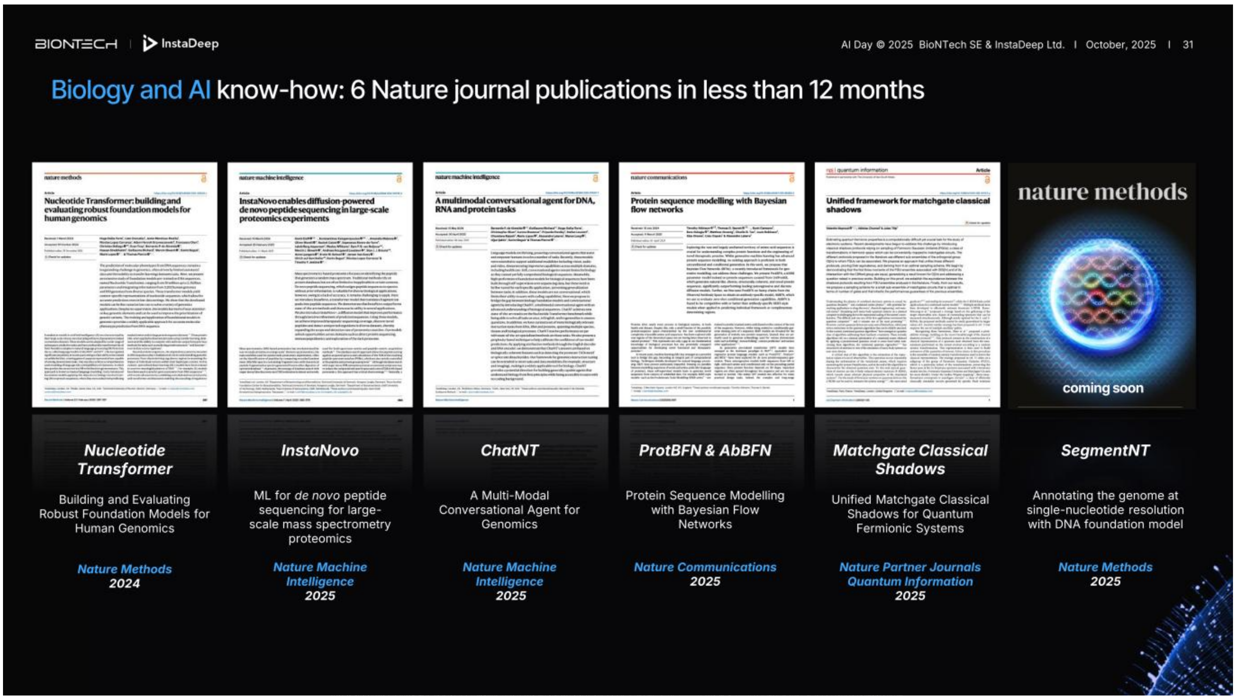
[2]Stellenbosch University

Abstract

Reinforcement learning (RL) systems have countless applications, from energy-grid management to protein design. However, such real-world scenarios are often extremely difficult, combinatorial in nature, and require complex coordination between multiple agents. This level of complexity can cause even state-of-the-art RL systems, trained until convergence, to hit a performance ceiling which they are unable to break out of with zero-shot inference. Meanwhile, many digital or simulation-based applications allow for an inference phase that utilises a specific time and compute budget to explore multiple attempts before outputting a final solution. In this work, we show that such an inference phase employed at execution time, and the choice of a corresponding inference strategy, are key to breaking the performance ceiling observed in complex multi-agent RL problems. Our main result is striking: **we can obtain up to a 126% and, on average, a 45% improvement over the previous state-of-the-art across 17 tasks, using only a couple seconds of extra wall-clock time during execution.** We also demonstrate promising compute scaling properties, supported by over 60k experiments, making it the largest study on inference strategies for complex RL to date. **Our experimental data and code are available at** `https://sites.google.com/view/inf-marl`[1].

Breaking the Performance Ceiling in Complex Reinforcement Learning requires Inference Strategies

NeurIPS Conference 2025 Oral



Biology and AI know-how: 6 Nature journal publications in less than 12 months

Nucleotide Transformer

Building and Evaluating Robust Foundation Models for Human Genomics

Nature Methods
2024

InstaNovo

ML for *de novo* peptide sequencing for large-scale mass spectrometry proteomics

Nature Machine Intelligence
2025

ChatNT

A Multi-Modal Conversational Agent for Genomics

Nature Machine Intelligence
2025

ProtBFN & AbBFN

Protein Sequence Modelling with Bayesian Flow Networks

Nature Communications
2025

Matchgate Classical Shadows

Unified Matchgate Classical Shadows for Quantum Fermionic Systems

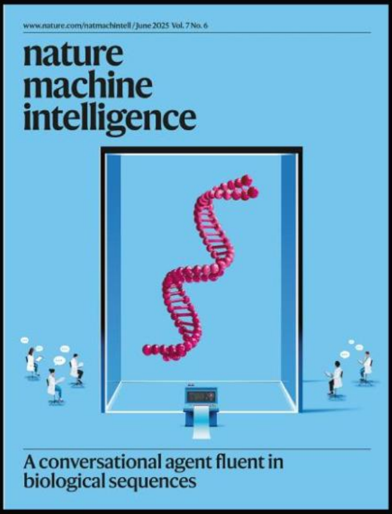
Nature Partner Journals Quantum Information
2025

SegmentNT

Annotating the genome at single-nucleotide resolution with DNA foundation model

Nature Methods
2025

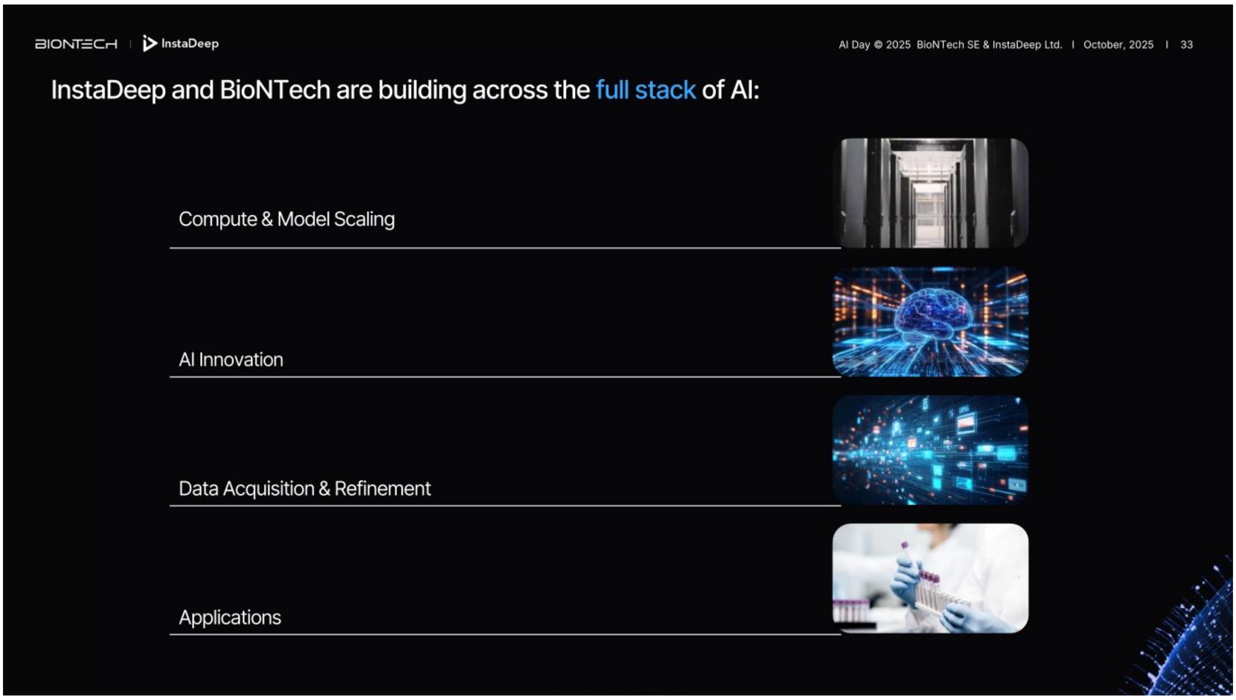
ChatNT, our conversational agent for Genomics, made the cover of Nature Machine Intelligence



www.nature.com/natmachintell / June 2025 Vol. 7 No. 6

nature
machine
intelligence

A conversational agent fluent in
biological sequences



InstaDeep and BioNTech are building across the full stack of AI:

Compute & Model Scaling

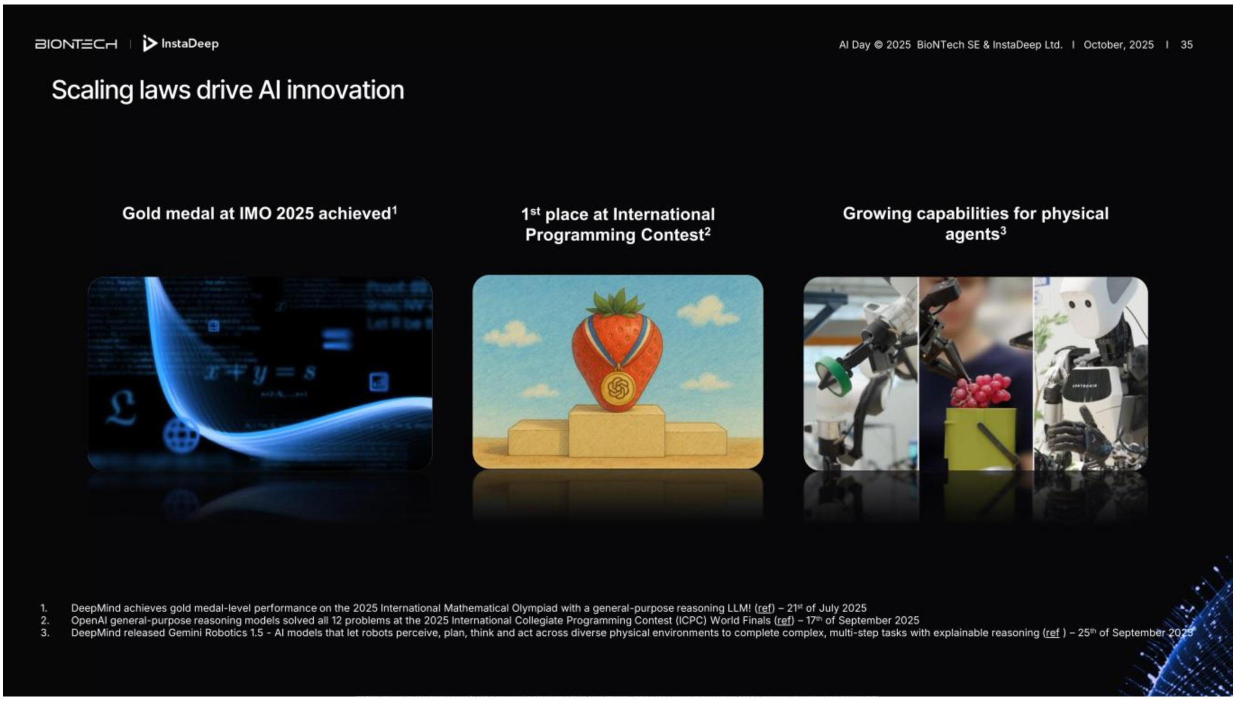
AI Innovation

Data Acquisition & Refinement

Applications

Compute & Model Scaling

Alex Laterre
Head of AI Research
InstaDeep



Scaling laws drive AI innovation

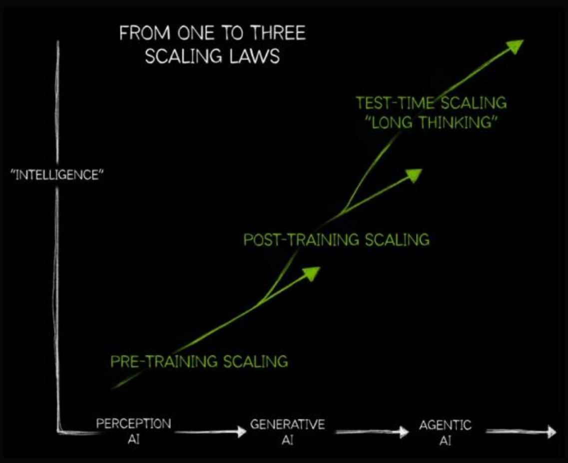
Gold medal at IMO 2025 achieved[1]

1st place at International Programming Contest[2]

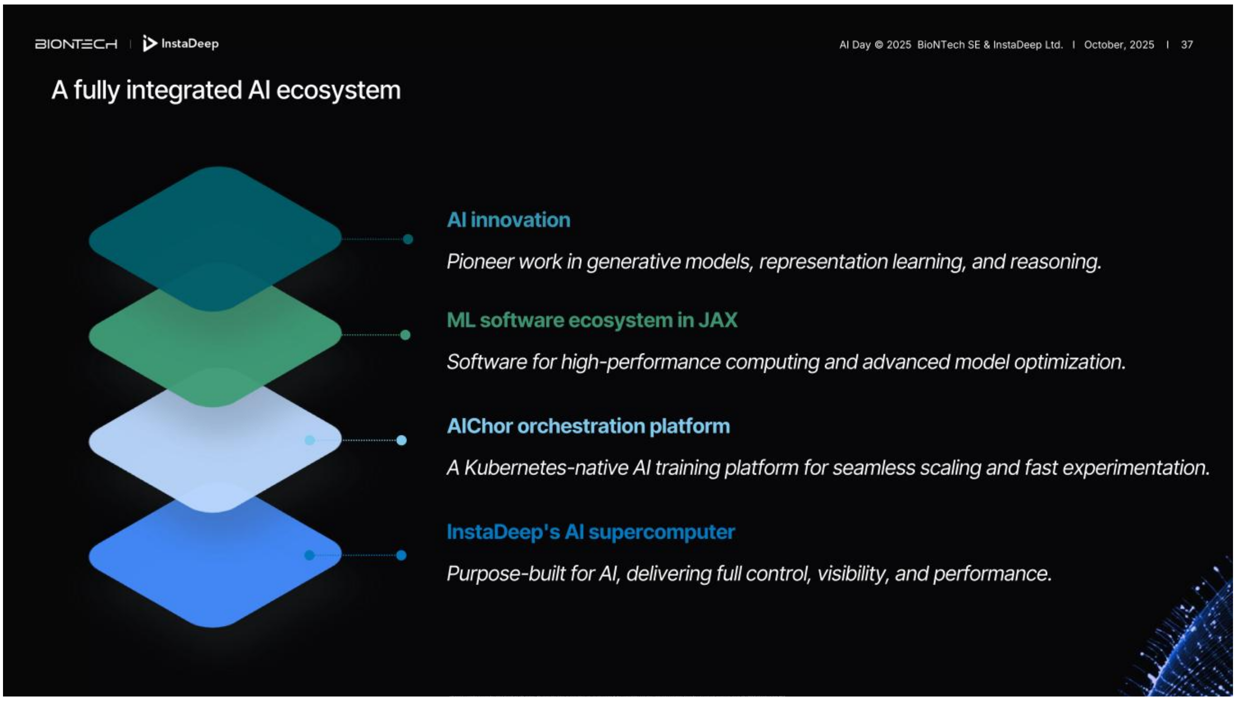
Growing capabilities for physical agents[3]

1. DeepMind achieves gold medal-level performance on the 2025 International Mathematical Olympiad with a general-purpose reasoning LLM! (ref) – 21st of July 2025
2. OpenAI general-purpose reasoning models solved all 12 problems at the 2025 International Collegiate Programming Contest (ICPC) World Finals (ref) – 17th of September 2025
3. DeepMind released Gemini Robotics 1.5 - AI models that let robots perceive, plan, think and act across diverse physical environments to complete complex, multi-step tasks with explainable reasoning (ref) – 25th of September 2025

Compounding intelligence



Jensen Keynote that Nvidia GTC 2025



A fully integrated AI ecosystem

AI innovation

Pioneer work in generative models, representation learning, and reasoning.

ML software ecosystem in JAX

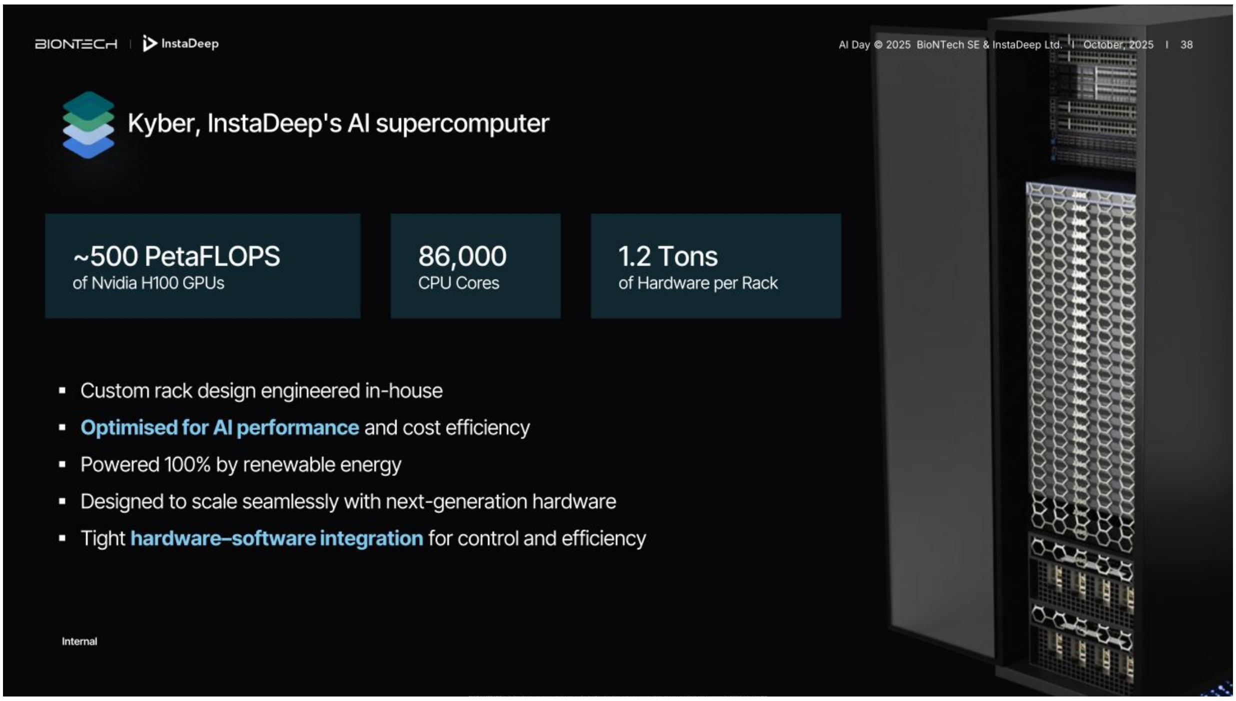
Software for high-performance computing and advanced model optimization.

AIChor orchestration platform

A Kubernetes-native AI training platform for seamless scaling and fast experimentation.

InstaDeep's AI supercomputer

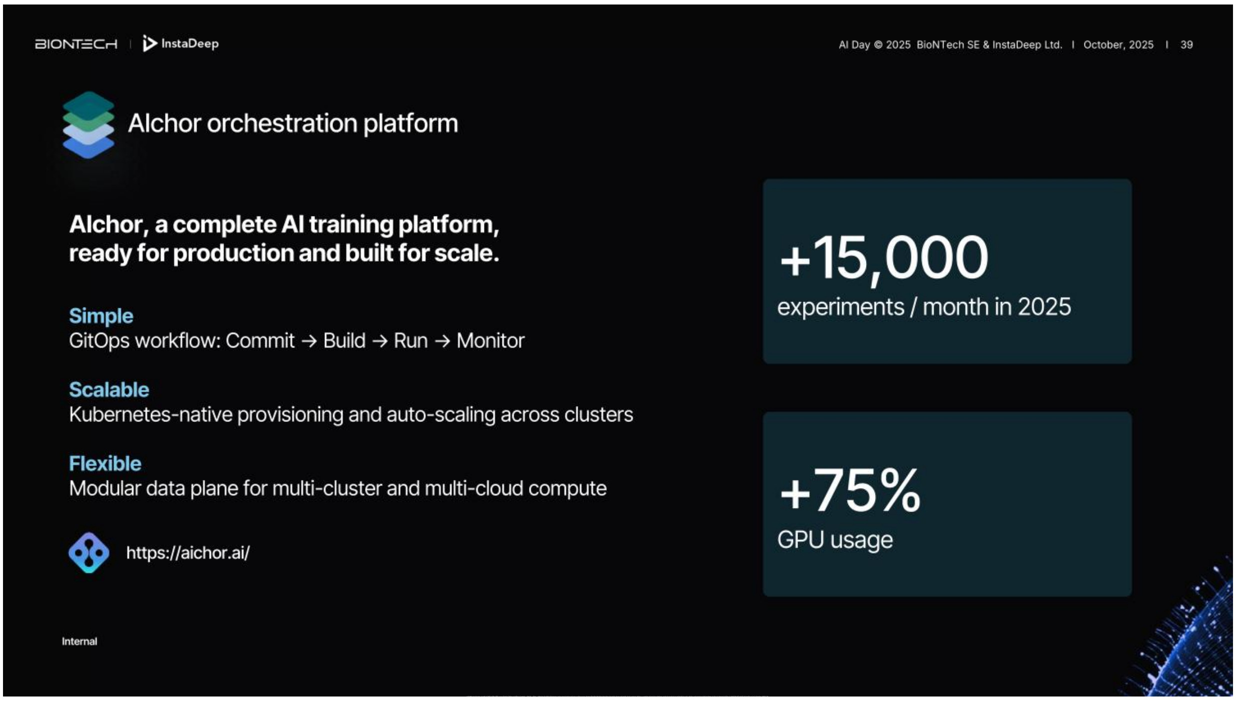
Purpose-built for AI, delivering full control, visibility, and performance.



Kyber, InstaDeep's AI supercomputer

~500 PetaFLOPS of Nvidia H100 GPUs	86,000 CPU Cores	1.2 Tons of Hardware per Rack

- Custom rack design engineered in-house
- **Optimised for AI performance** and cost efficiency
- Powered 100% by renewable energy
- Designed to scale seamlessly with next-generation hardware
- Tight **hardware–software integration** for control and efficiency



AIchor orchestration platform

AIchor, a complete AI training platform, ready for production and built for scale.

Simple
GitOps workflow: Commit → Build → Run → Monitor

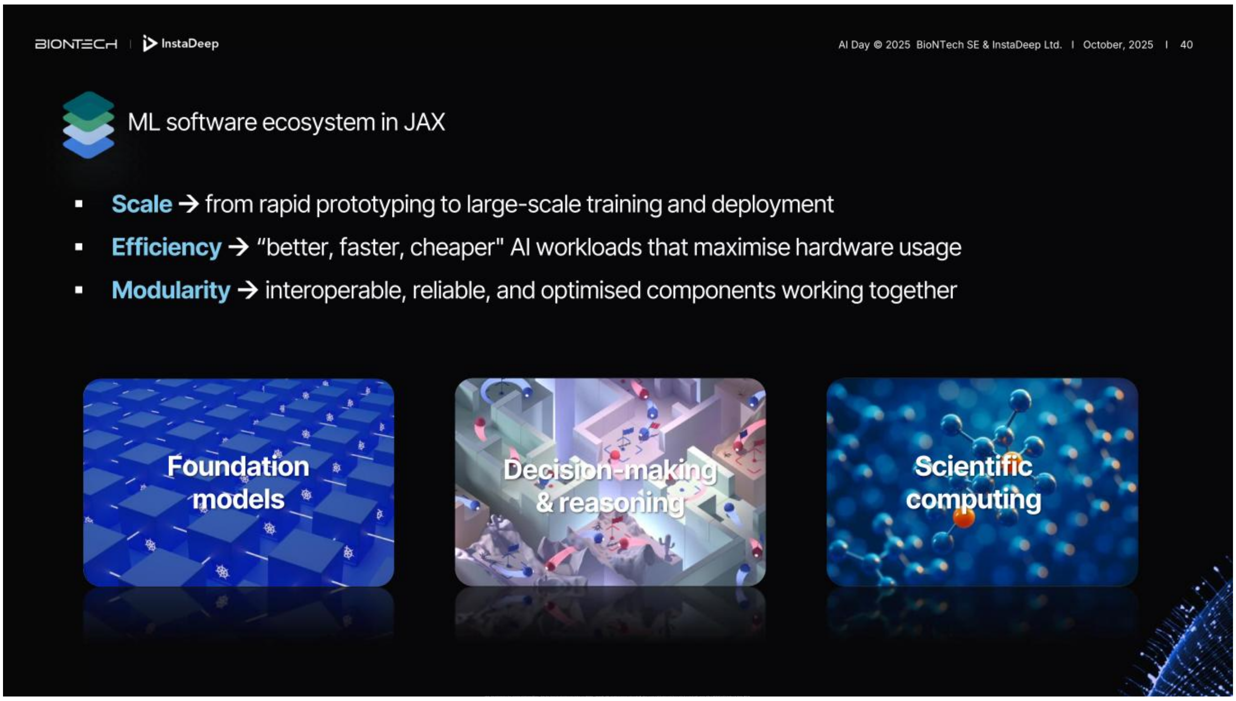
Scalable
Kubernetes-native provisioning and auto-scaling across clusters

Flexible
Modular data plane for multi-cluster and multi-cloud compute

https://aichor.ai/

+15,000
experiments / month in 2025

+75%
GPU usage



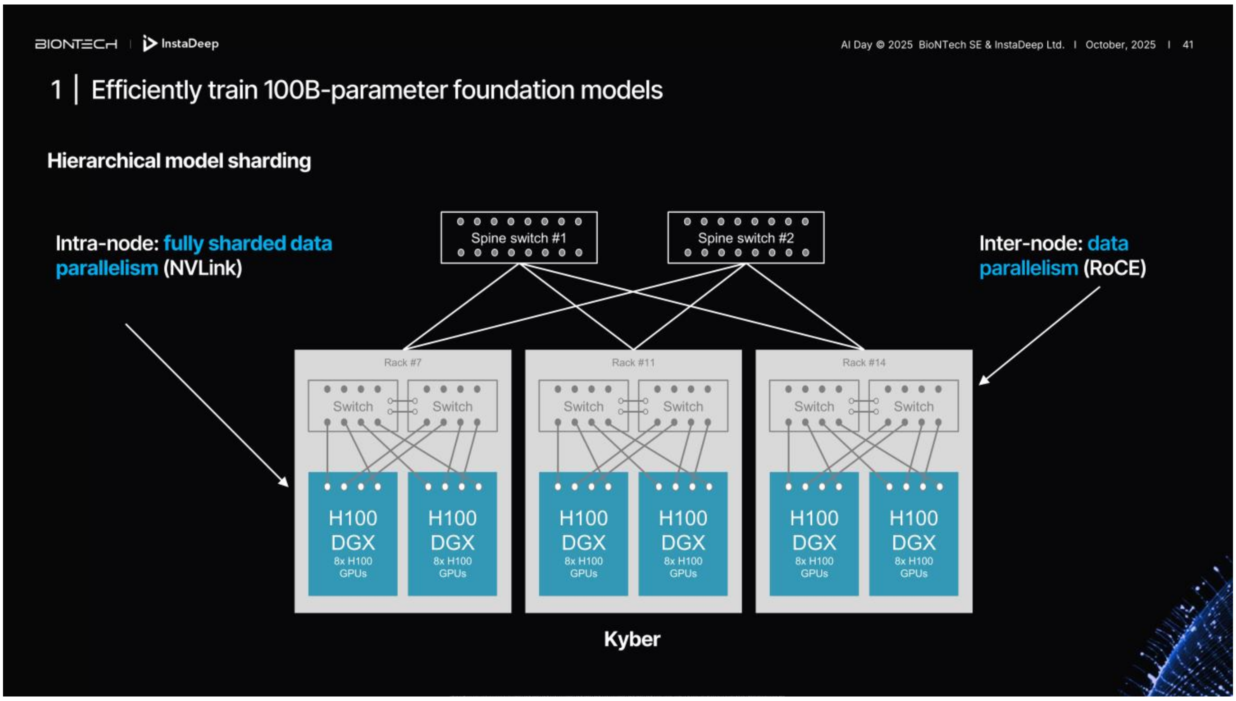
ML software ecosystem in JAX

- **Scale** → from rapid prototyping to large-scale training and deployment
- **Efficiency** → "better, faster, cheaper" AI workloads that maximise hardware usage
- **Modularity** → interoperable, reliable, and optimised components working together

Foundation models

Decision-making & reasoning

Scientific computing



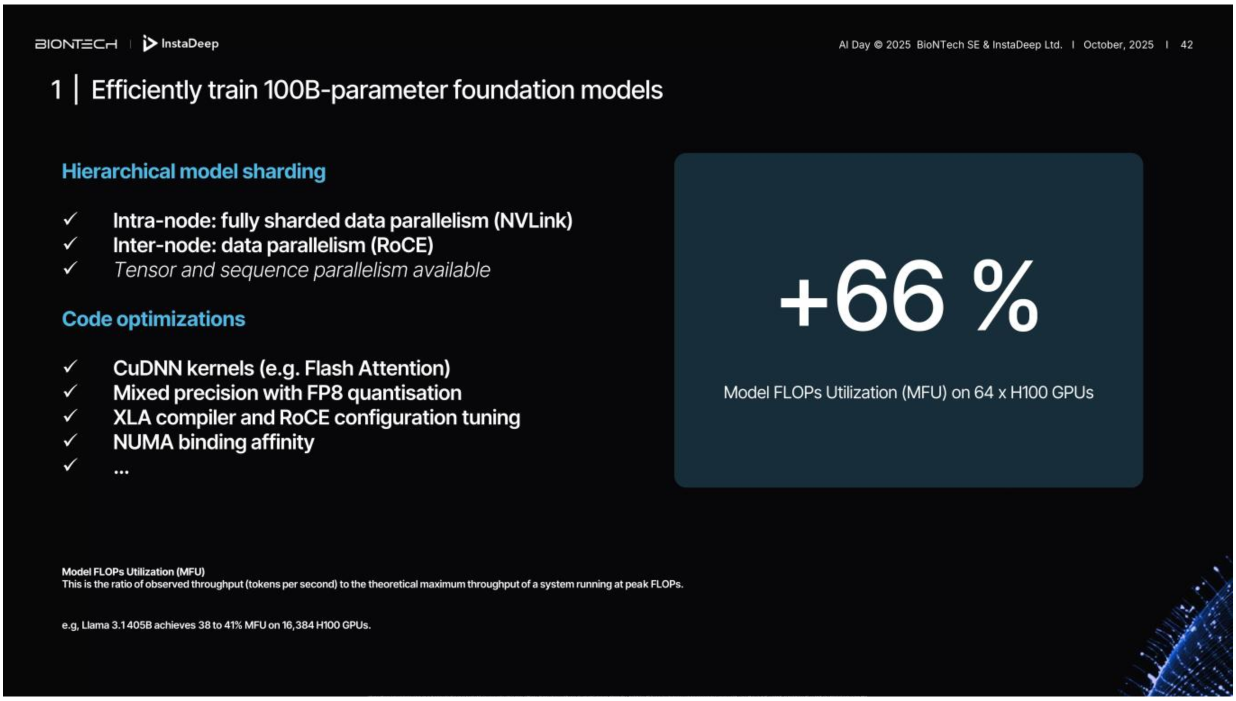
1 | Efficiently train 100B-parameter foundation models

Hierarchical model sharding

Intra-node: fully sharded data parallelism (NVLink)

Inter-node: data parallelism (RoCE)

Kyber



1 | Efficiently train 100B-parameter foundation models

Hierarchical model sharding

- ✓ **Intra-node: fully sharded data parallelism (NVLink)**
- ✓ **Inter-node: data parallelism (RoCE)**
- ✓ *Tensor and sequence parallelism available*

Code optimizations

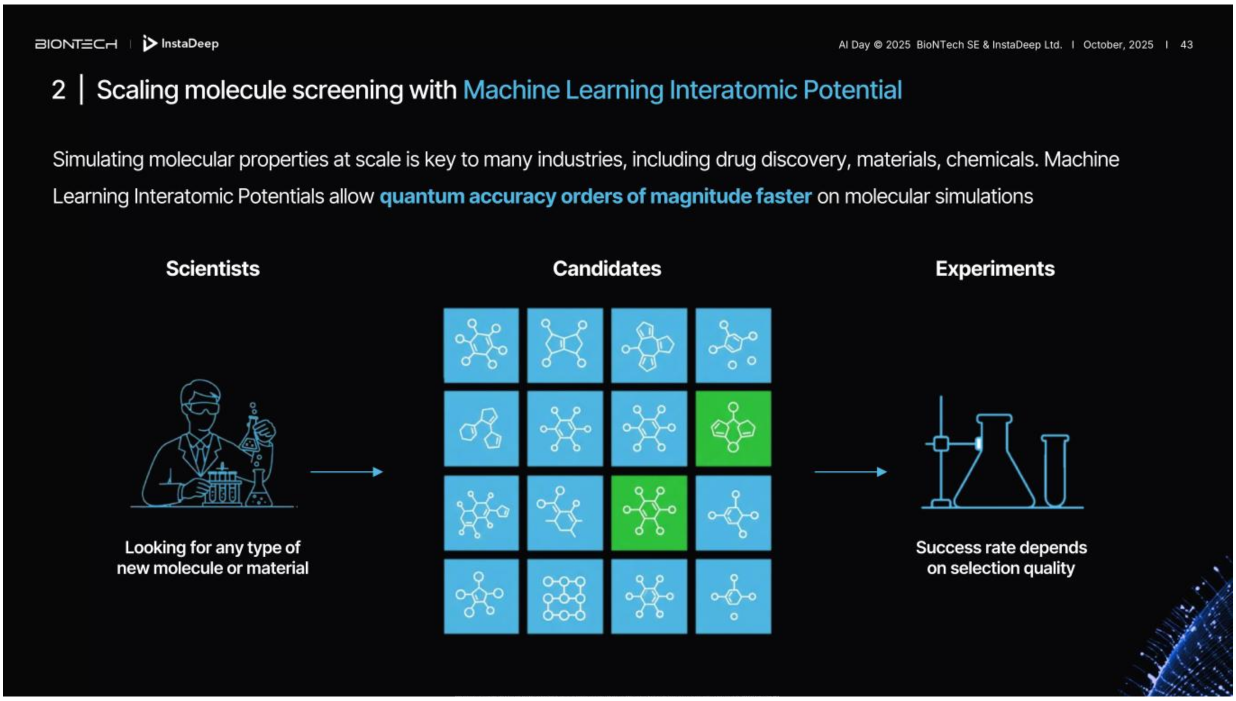
- ✓ **CuDNN kernels (e.g. Flash Attention)**
- ✓ **Mixed precision with FP8 quantisation**
- ✓ **XLA compiler and RoCE configuration tuning**
- ✓ **NUMA binding affinity**
- ✓ **...**

+66 %

Model FLOPs Utilization (MFU) on 64 x H100 GPUs

Model FLOPs Utilization (MFU)
This is the ratio of observed throughput (tokens per second) to the theoretical maximum throughput of a system running at peak FLOPs.

e.g, Llama 3.1 405B achieves 38 to 41% MFU on 16,384 H100 GPUs.



2 | Scaling molecule screening with Machine Learning Interatomic Potential

Simulating molecular properties at scale is key to many industries, including drug discovery, materials, chemicals. Machine Learning Interatomic Potentials allow **quantum accuracy orders of magnitude faster** on molecular simulations

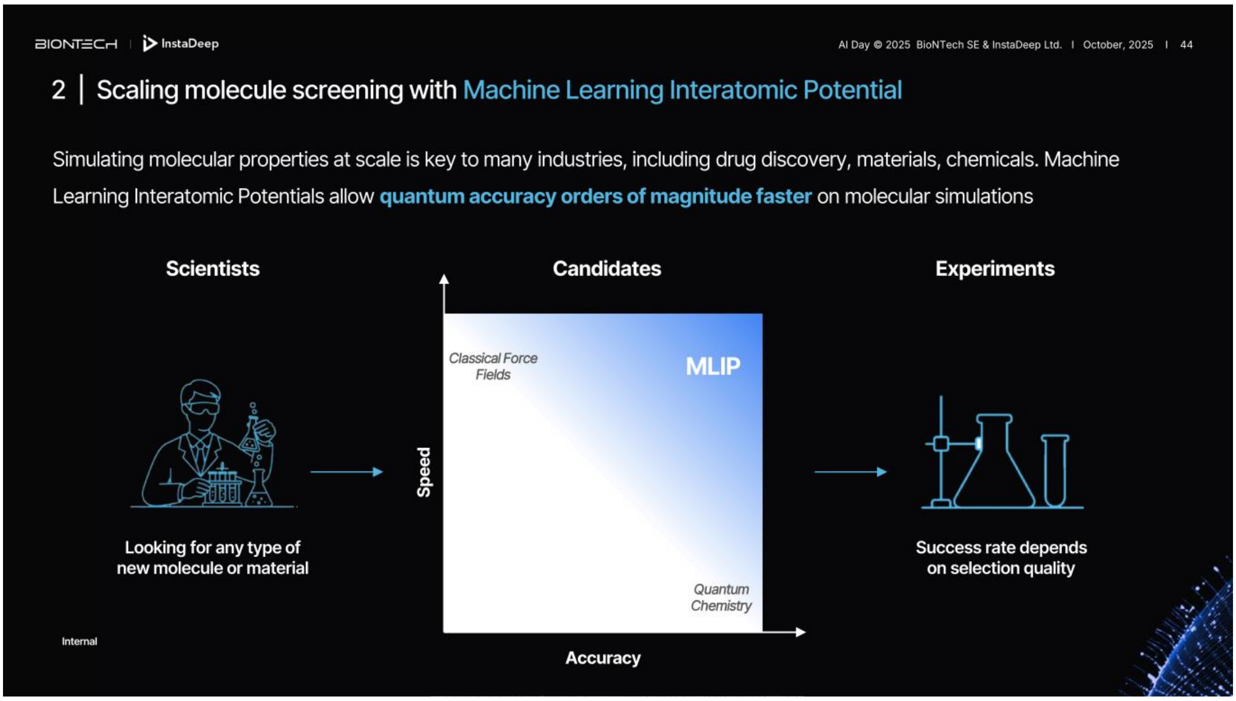
Scientists

Looking for any type of new molecule or material

Candidates

Experiments

Success rate depends on selection quality



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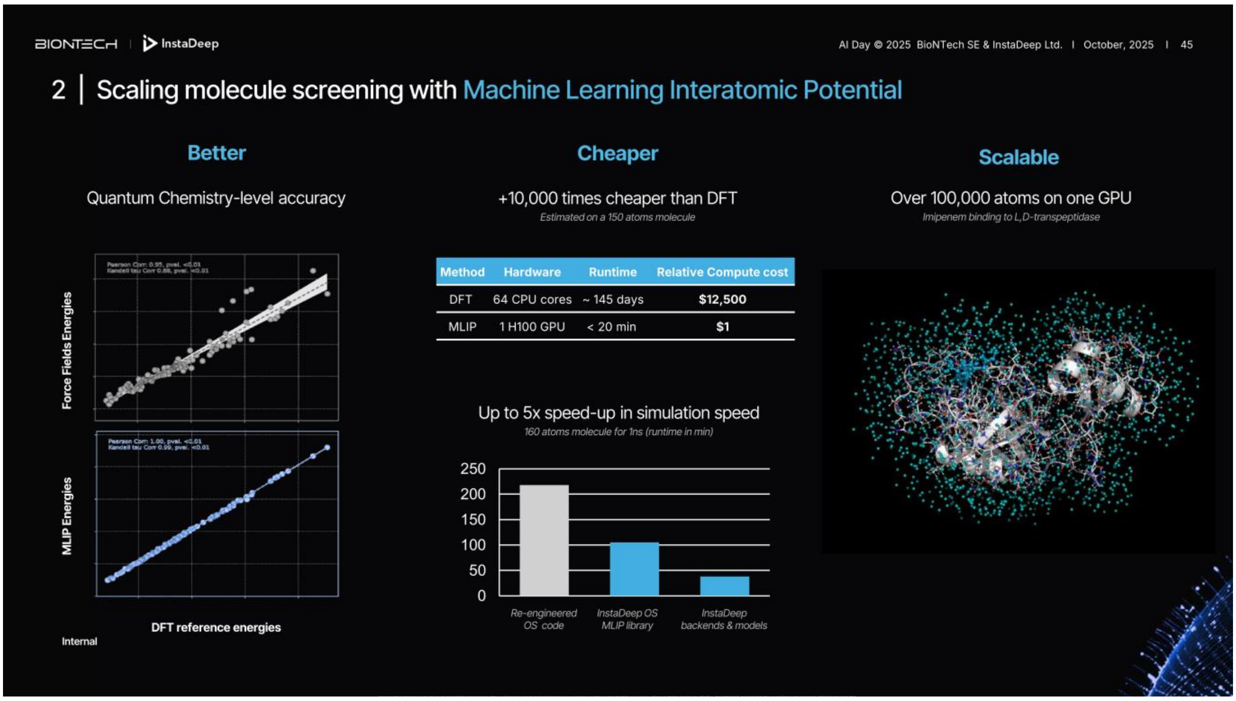


2 | Scaling molecule screening with Machine Learning Interatomic Potential

Better

Quantum Chemistry-level accuracy

Internal

Cheaper

+10,000 times cheaper than DFT

Estimated on a 150 atoms molecule

Method	Hardware	Runtime	Relative Compute cost
DFT	64 CPU cores	~ 145 days	**$12,500**
MLIP	1 H100 GPU	< 20 min	**$1**

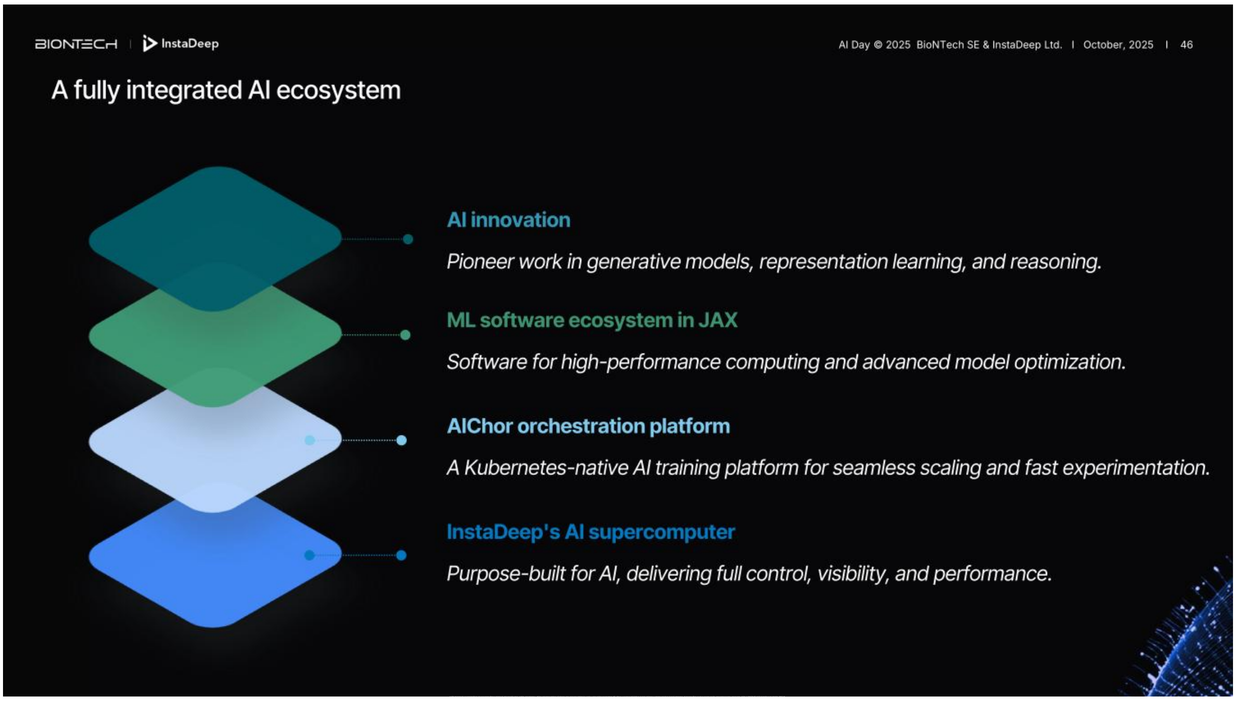
Up to 5x speed-up in simulation speed

160 atoms molecule for 1ns (runtime in min)

Scalable

Over 100,000 atoms on one GPU

Imipenem binding to L,D-transpeptidase



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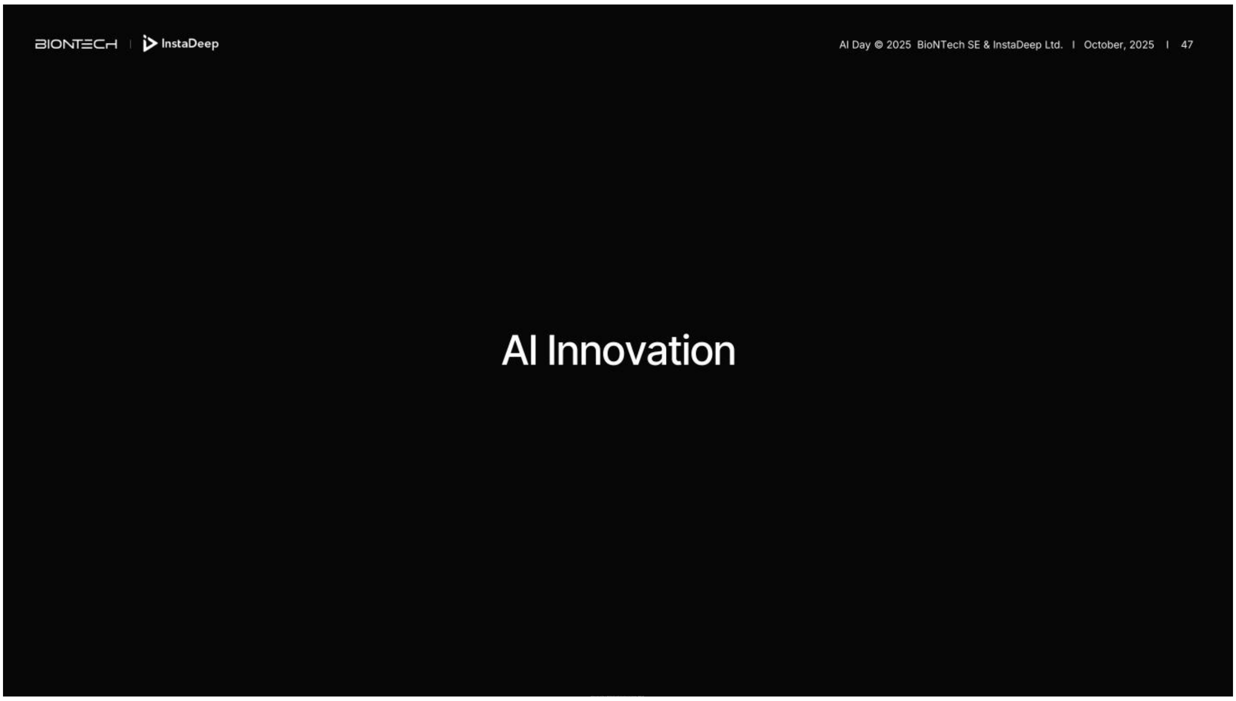
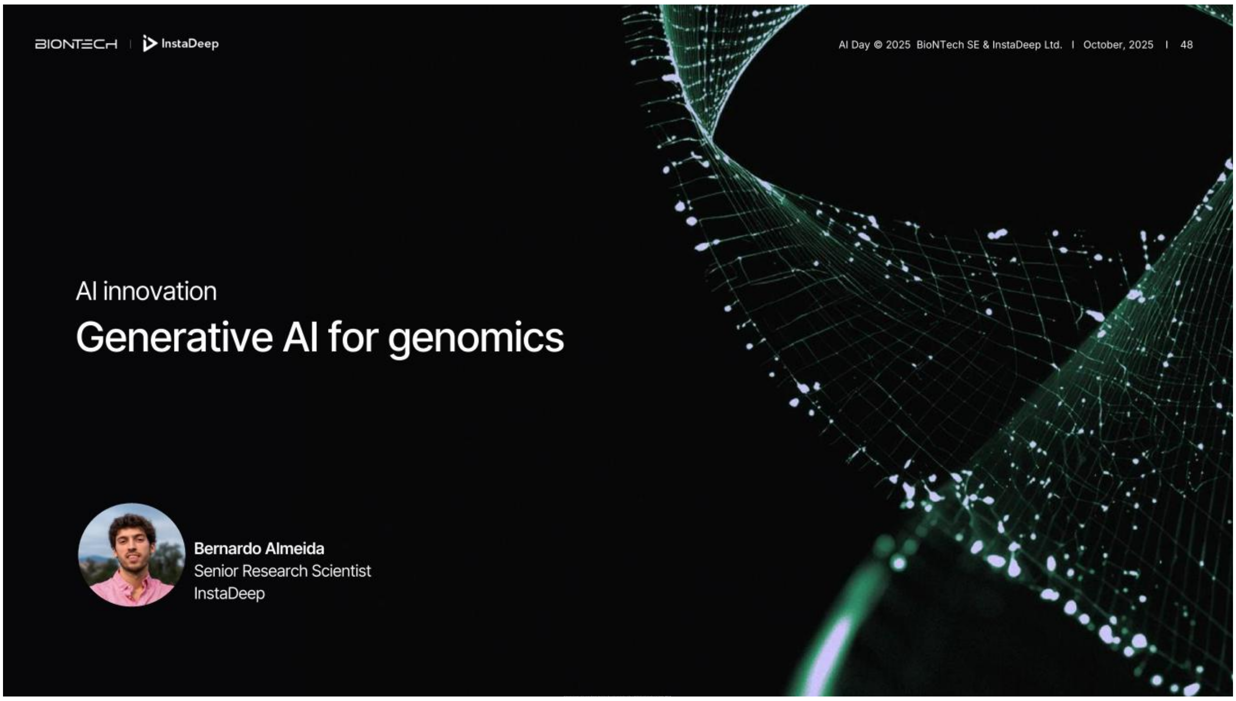


AI Innovation

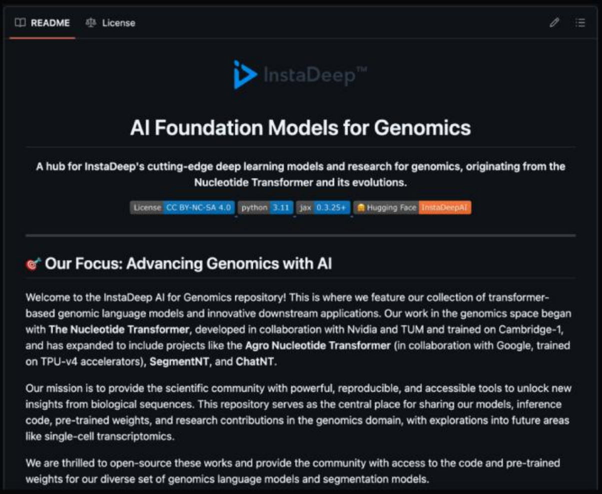


AI innovation

Generative AI for genomics

Bernardo Almeida
Senior Research Scientist
InstaDeep

Nucleotide Transformer: one of the most popular genomics AI models on Hugging Face



InstaDeep™

AI Foundation Models for Genomics

A hub for InstaDeep's cutting-edge deep learning models and research for genomics, originating from the Nucleotide Transformer and its evolutions.

License CC BY-NC-SA 4.0 | python 3.11 | jax 0.3.25+ | Hugging Face InstaDeepAI

🎯 Our Focus: Advancing Genomics with AI

Welcome to the InstaDeep AI for Genomics repository! This is where we feature our collection of transformer-based genomic language models and innovative downstream applications. Our work in the genomics space began with **The Nucleotide Transformer**, developed in collaboration with Nvidia and TUM and trained on Cambridge-1, and has expanded to include projects like the **Agro Nucleotide Transformer** (in collaboration with Google, trained on TPU-v4 accelerators), **SegmentNT**, and **ChatNT**.

Our mission is to provide the scientific community with powerful, reproducible, and accessible tools to unlock new insights from biological sequences. This repository serves as the central place for sharing our models, inference code, pre-trained weights, and research contributions in the genomics domain, with explorations into future areas like single-cell transcriptomics.

We are thrilled to open-source these works and provide the community with access to the code and pre-trained weights for our diverse set of genomics language models and segmentation models.

+1 Million Downloads

Across model sizes[1]

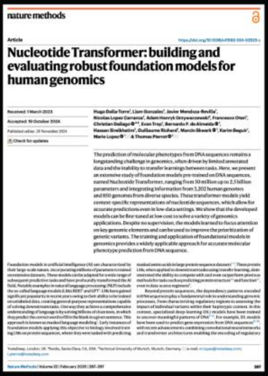
+500 Citations

Across model types[2]

---

1. Hugging Face Statistics.
2. Google Scholar.

Generative AI for genomics – publications in top-tier journals



nature methods

Nucleotide Transformer: building and evaluating robust foundation models for human genomics

Annotating the genome at single-nucleotide resolution with DNA foundation models

Multi-modal Transfer Learning between Biological Foundation Models

nature machine intelligence

A multimodal conversational agent for DNA, RNA and protein tasks

Nucleotide Transformer

Building and Evaluating Robust **Foundation Models** for Human Genomics

Nature Methods, 2024

SegmentNT

Segmenting the Genome at **Single-Nucleotide Resolution** with DNA Foundational Models

Nature Methods, 2025

Isoformer

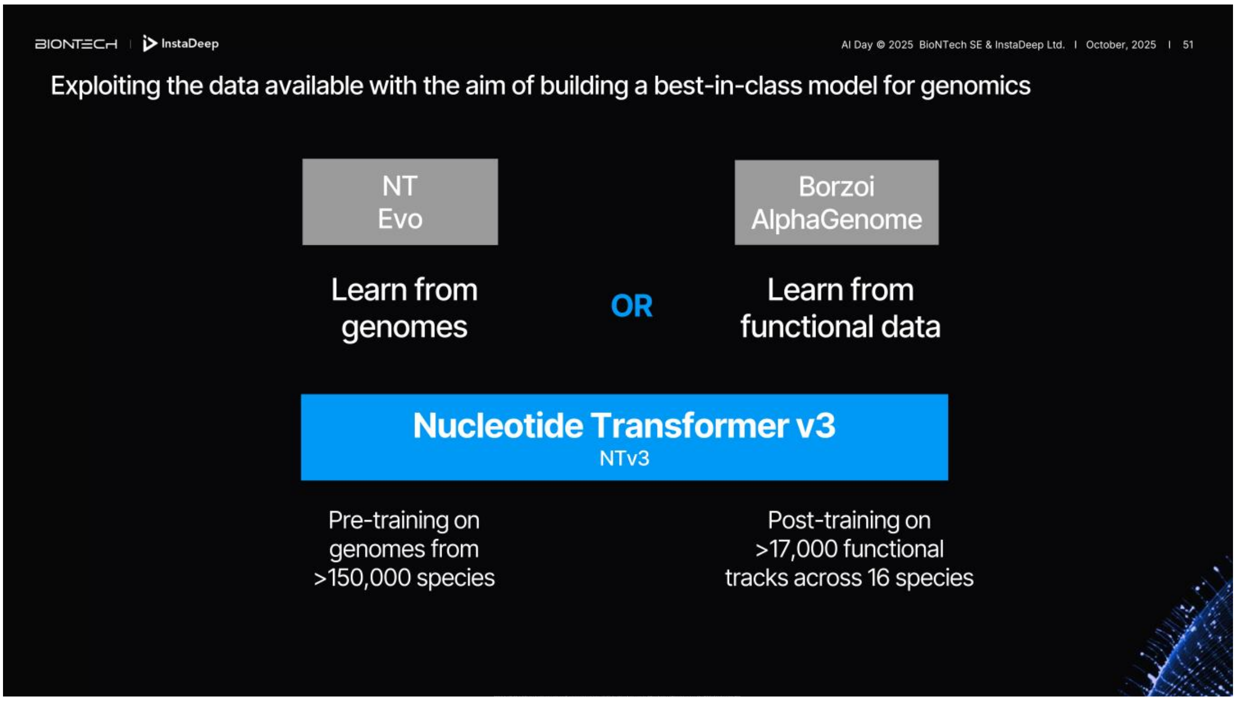
Multi-modal Transfer Learning between Biological Foundation Models

NeurIPS Conference, 2024

ChatNT

A Multi-Modal Conversational Agent for Genomics

Nature Machine Intelligence, 2025



Exploiting the data available with the aim of building a best-in-class model for genomics

NT
Evo

Learn from genomes

OR

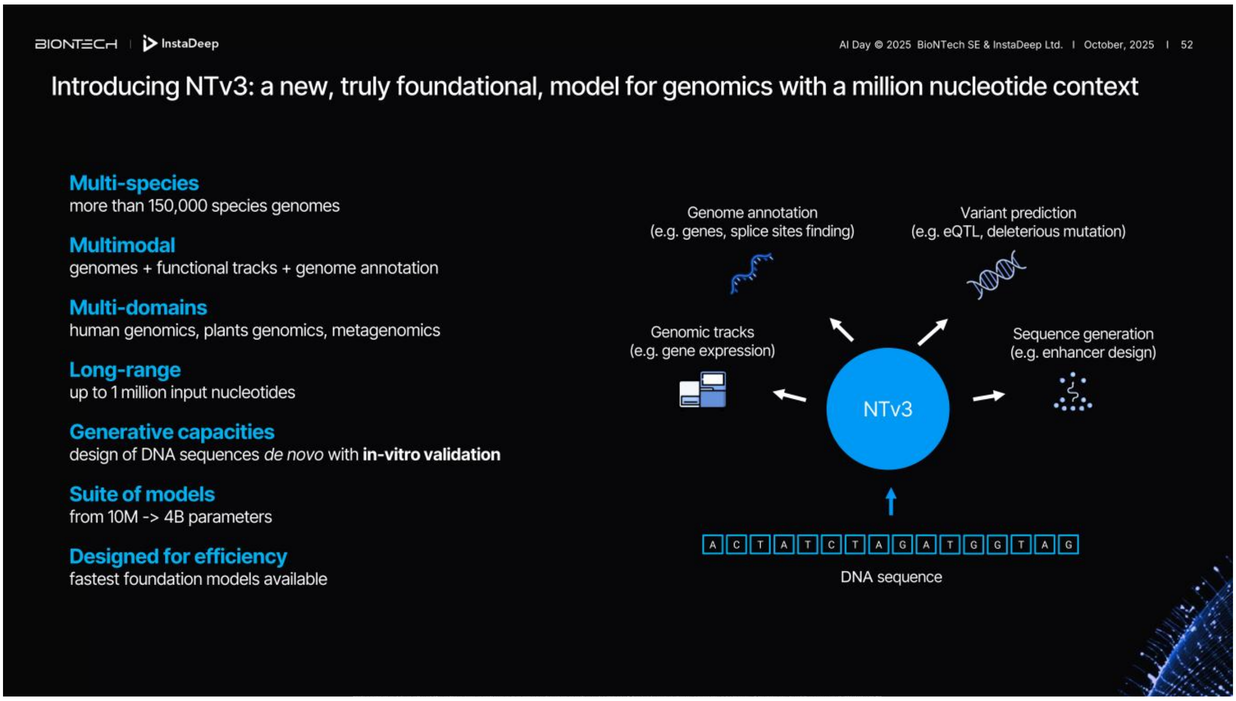
Borzoi
AlphaGenome

Learn from functional data

Nucleotide Transformer v3
NTv3

Pre-training on genomes from >150,000 species

Post-training on >17,000 functional tracks across 16 species



Introducing NTv3: a new, truly foundational, model for genomics with a million nucleotide context

Multi-species
more than 150,000 species genomes

Multimodal
genomes + functional tracks + genome annotation

Multi-domains
human genomics, plants genomics, metagenomics

Long-range
up to 1 million input nucleotides

Generative capacities
design of DNA sequences *de novo* with **in-vitro validation**

Suite of models
from 10M -> 4B parameters

Designed for efficiency
fastest foundation models available

Genome annotation
(e.g. genes, splice sites finding)

Variant prediction
(e.g. eQTL, deleterious mutation)

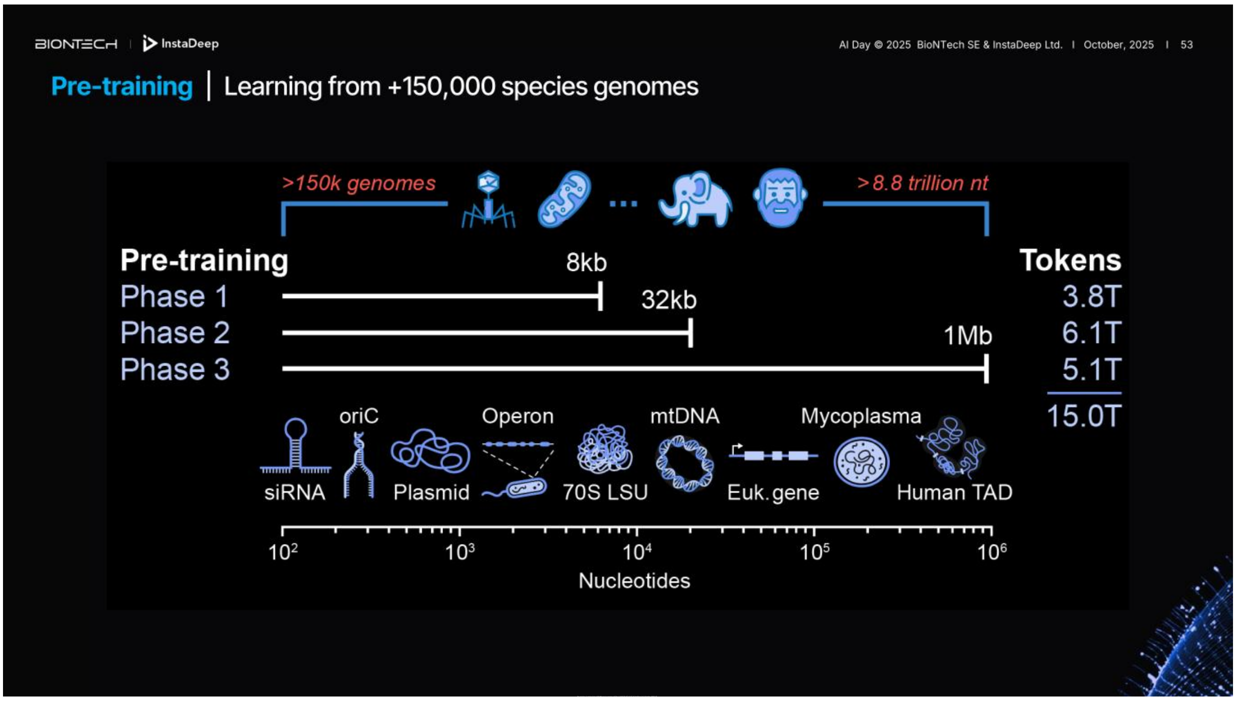
Genomic tracks
(e.g. gene expression)

NTv3

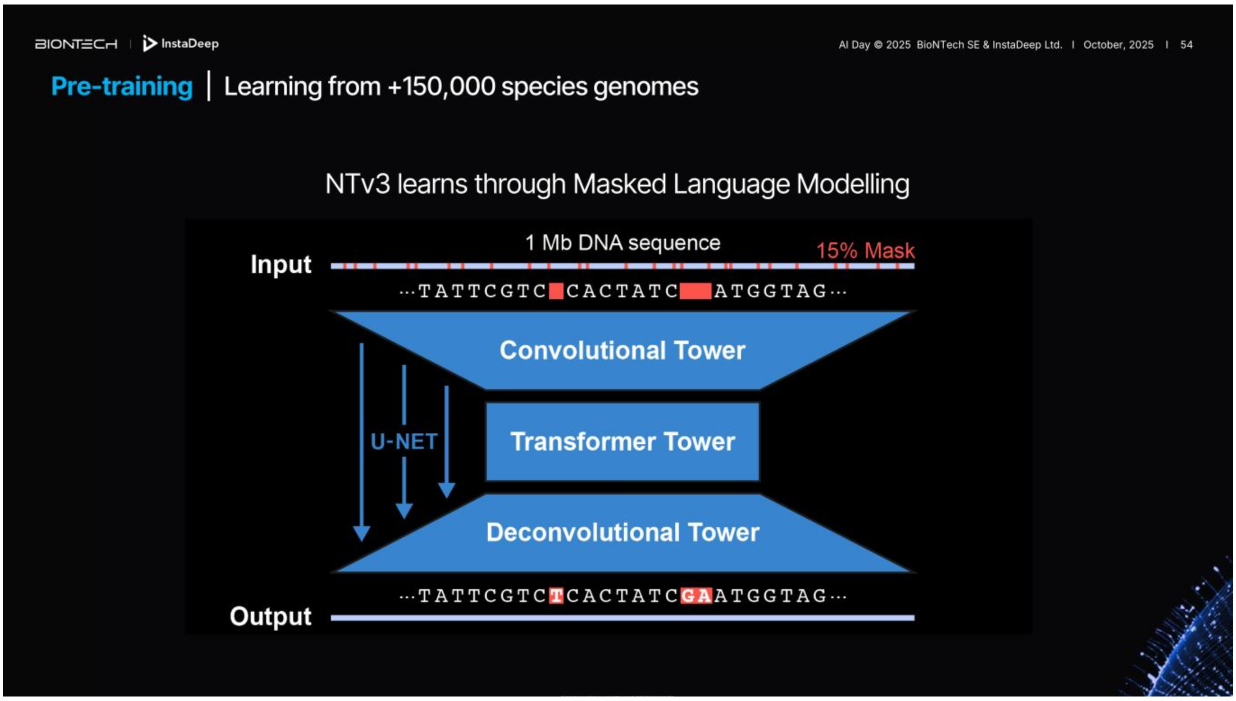
Sequence generation
(e.g. enhancer design)

A C T A T C T A G A T G G T A G

DNA sequence



Pre-training | Learning from +150,000 species genomes



Pre-training | Learning from +150,000 species genomes

NTv3 learns through Masked Language Modelling

Input

1 Mb DNA sequence

15% Mask

···TATTCGTC🟥CACTATC🟥🟥ATGGTAG···

Convolutional Tower

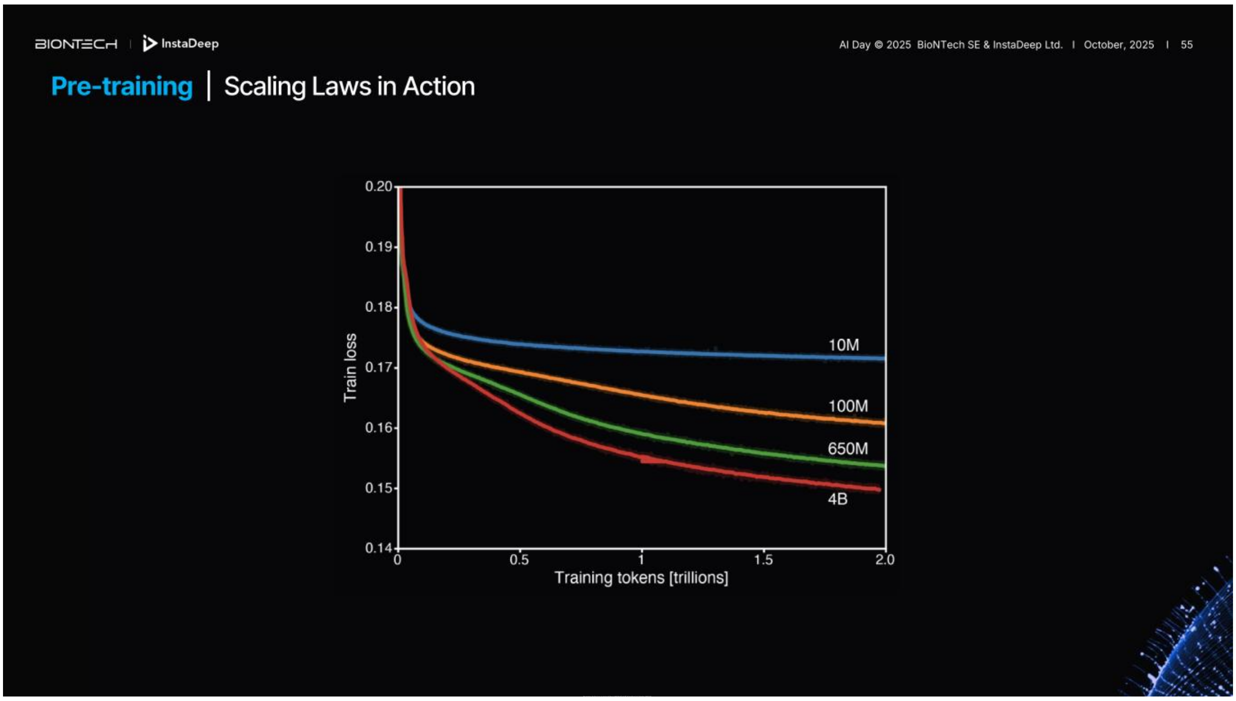
U-NET

Transformer Tower

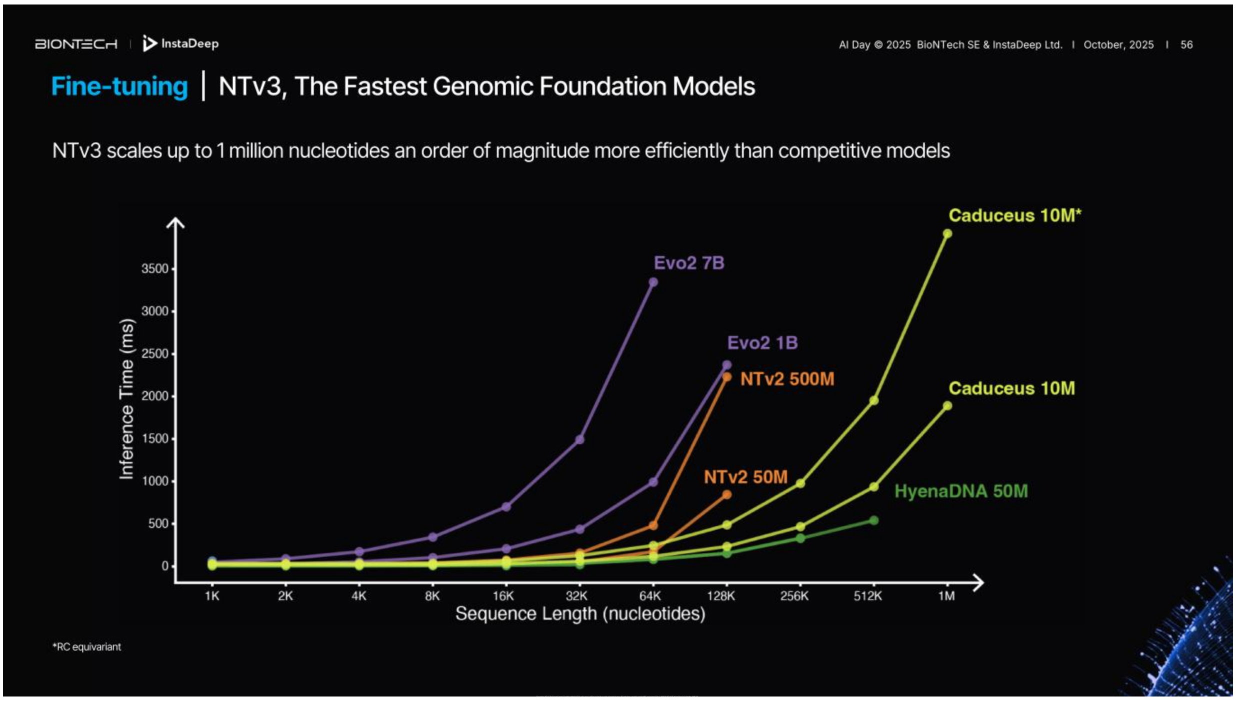
Deconvolutional Tower

···TATTCGTCTCACTATCGAATGGTAG···

Output



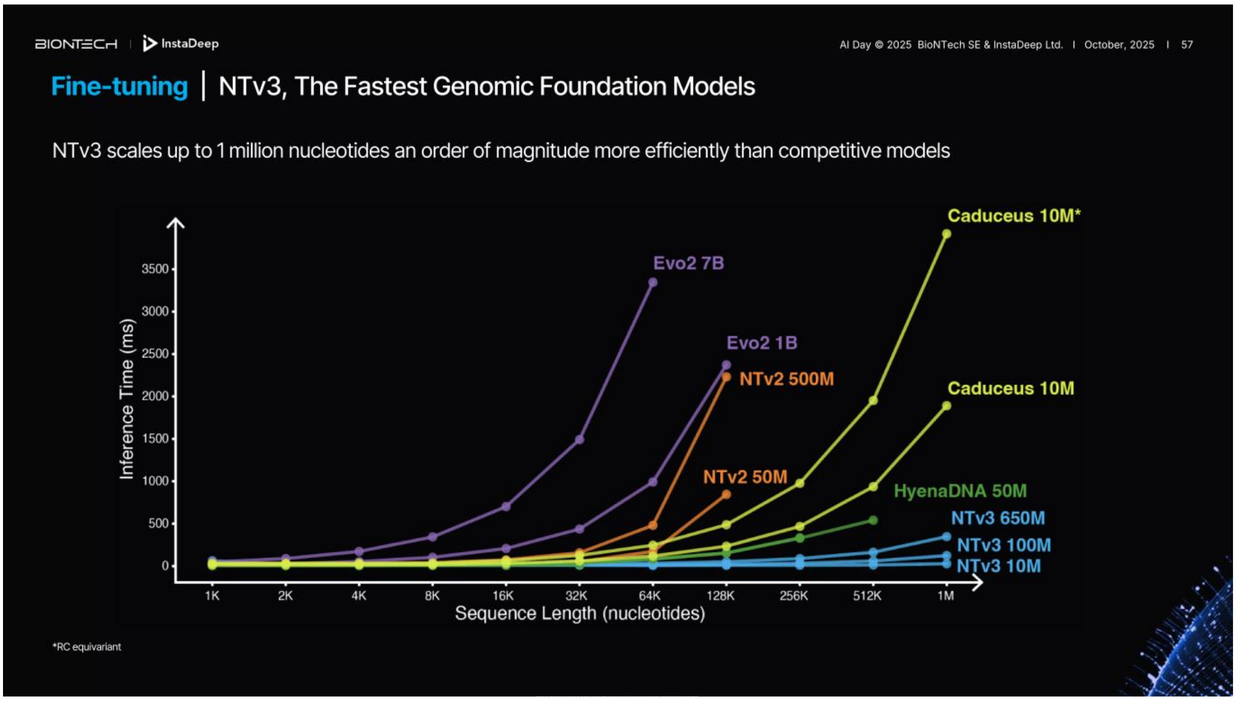
Pre-training | Scaling Laws in Action



Fine-tuning | NTv3, The Fastest Genomic Foundation Models

NTv3 scales up to 1 million nucleotides an order of magnitude more efficiently than competitive models

*RC equivariant



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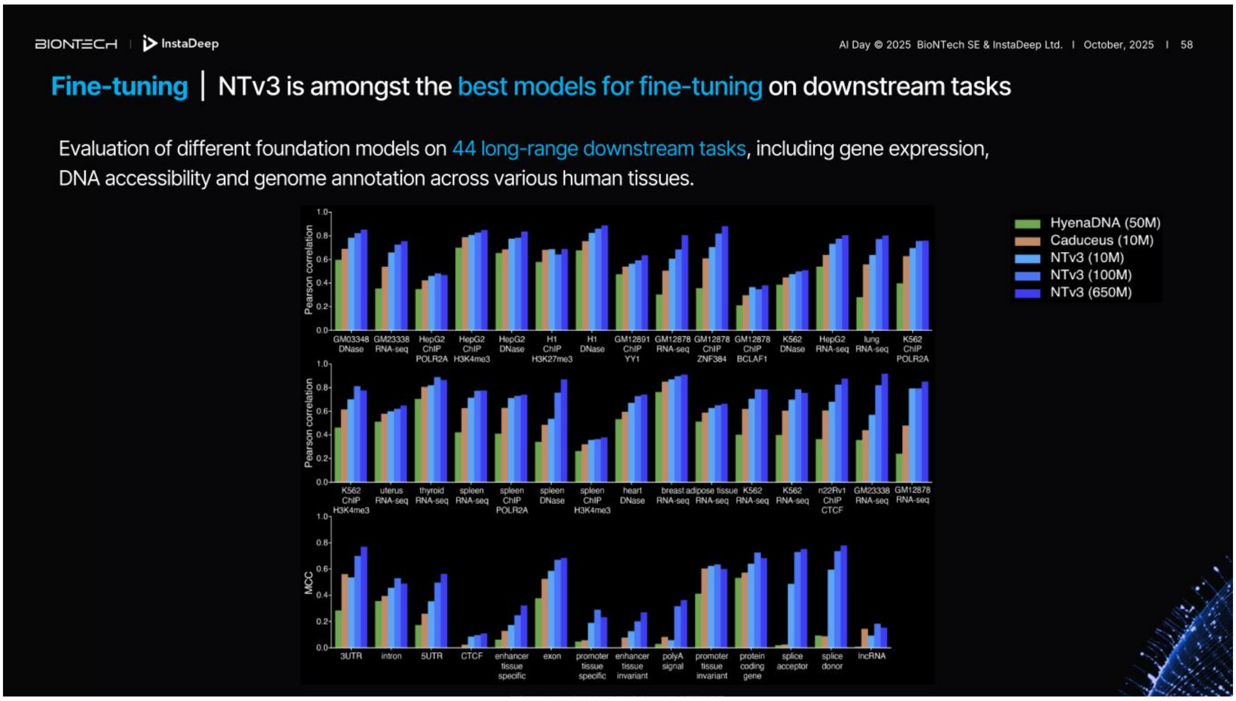
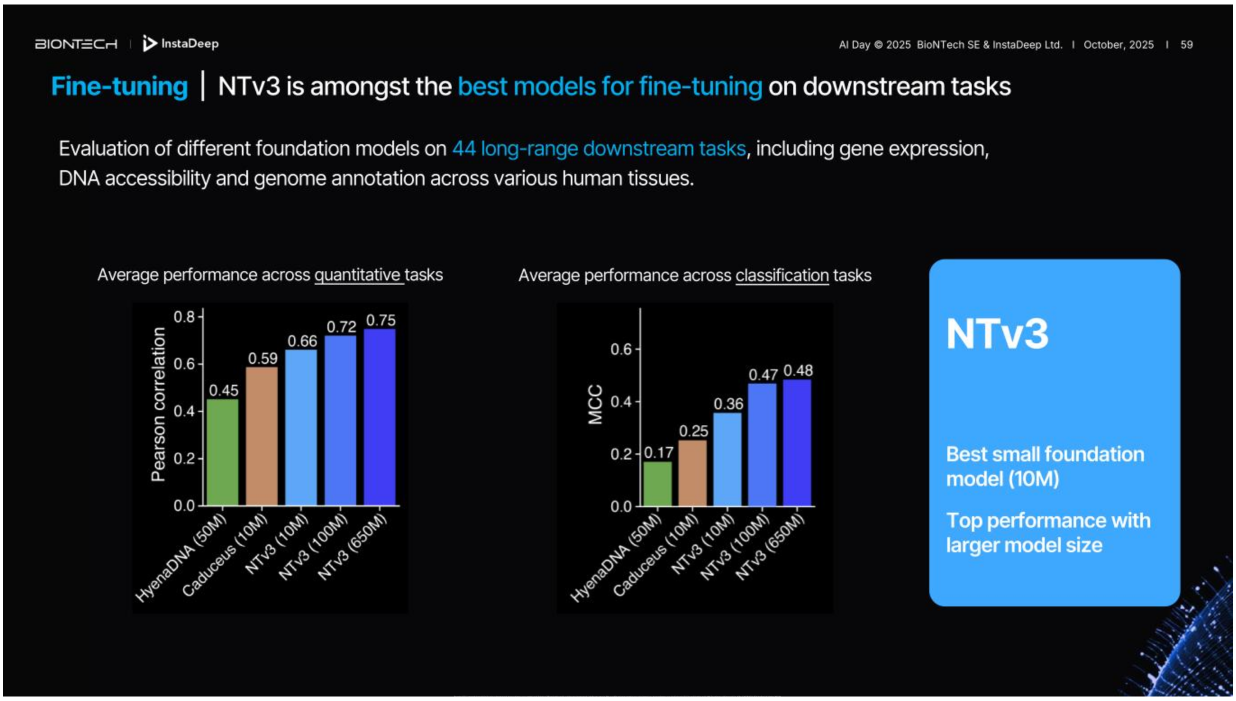


Fine-tuning | NTv3 is amongst the best models for fine-tuning on downstream tasks

Evaluation of different foundation models on 44 long-range downstream tasks, including gene expression, DNA accessibility and genome annotation across various human tissues.



Fine-tuning | NTv3 is amongst the best models for fine-tuning on downstream tasks

Evaluation of different foundation models on 44 long-range downstream tasks, including gene expression, DNA accessibility and genome annotation across various human tissues.

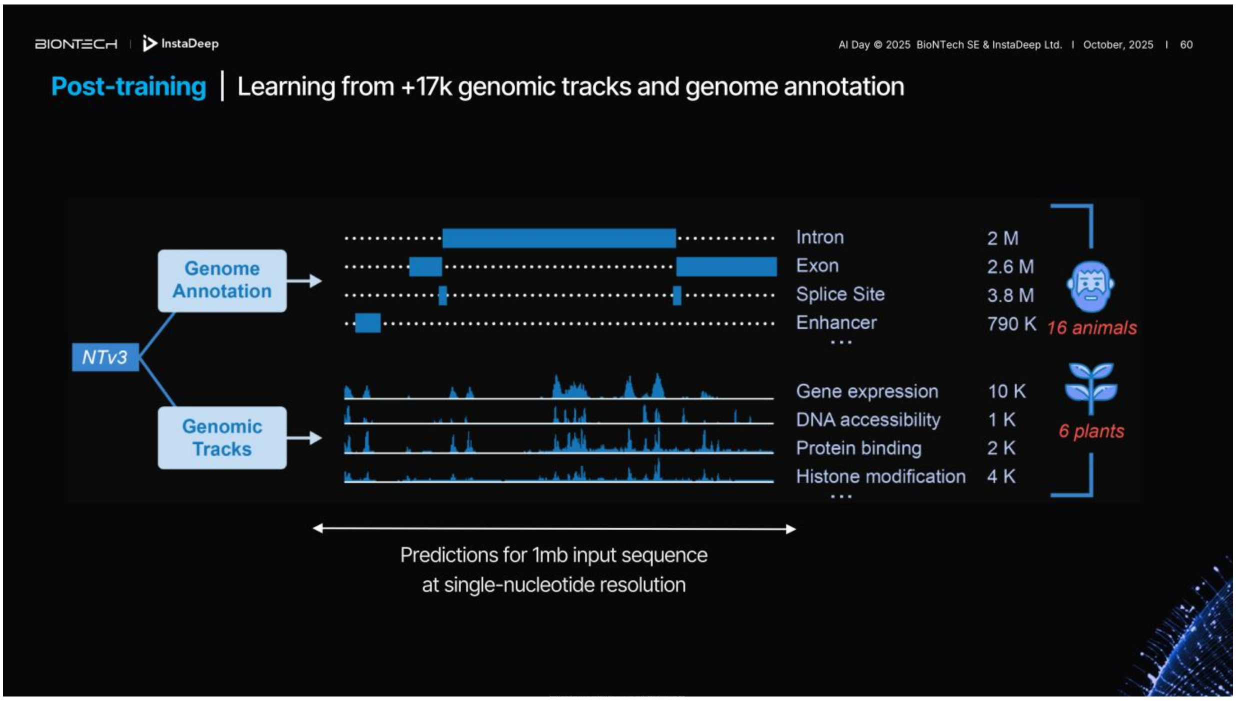
Average performance across quantitative tasks

Average performance across classification tasks

NTv3

Best small foundation model (10M)

Top performance with larger model size



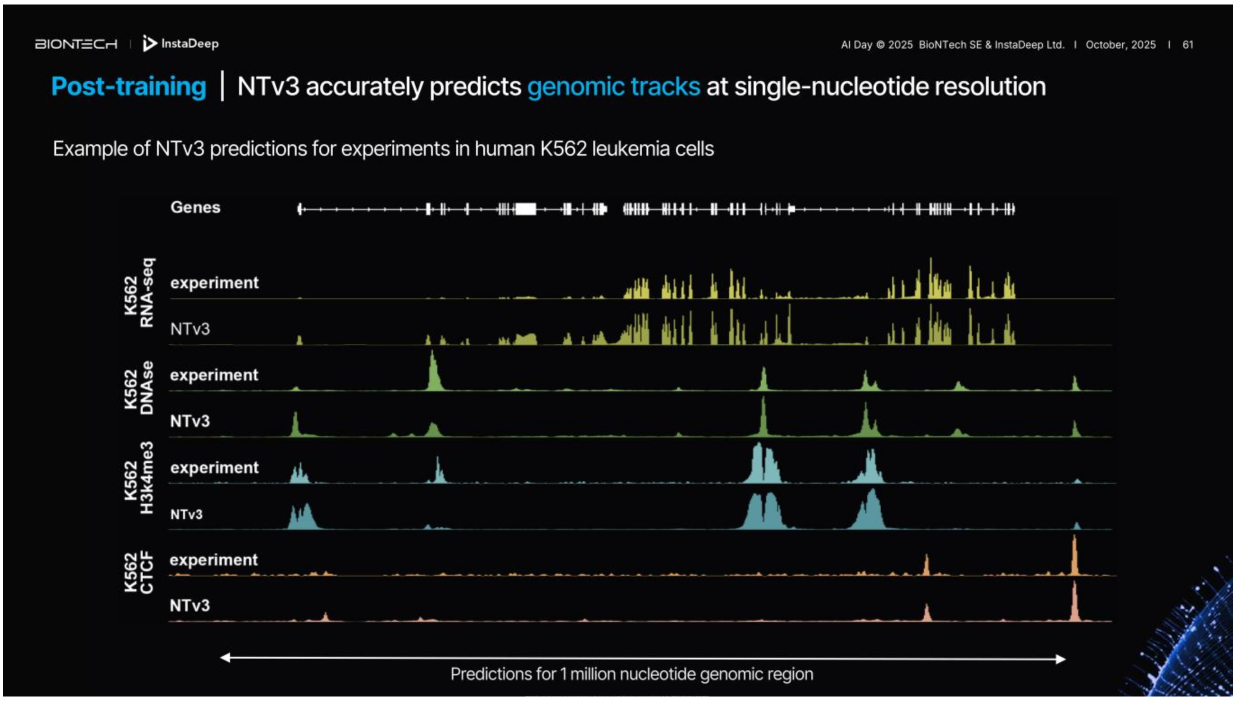
Post-training | Learning from +17k genomic tracks and genome annotation

Intron	2 M
Exon	2.6 M
Splice Site	3.8 M
Enhancer	790 K
...	
Gene expression	10 K
DNA accessibility	1 K
Protein binding	2 K
Histone modification	4 K
...	

16 animals

6 plants

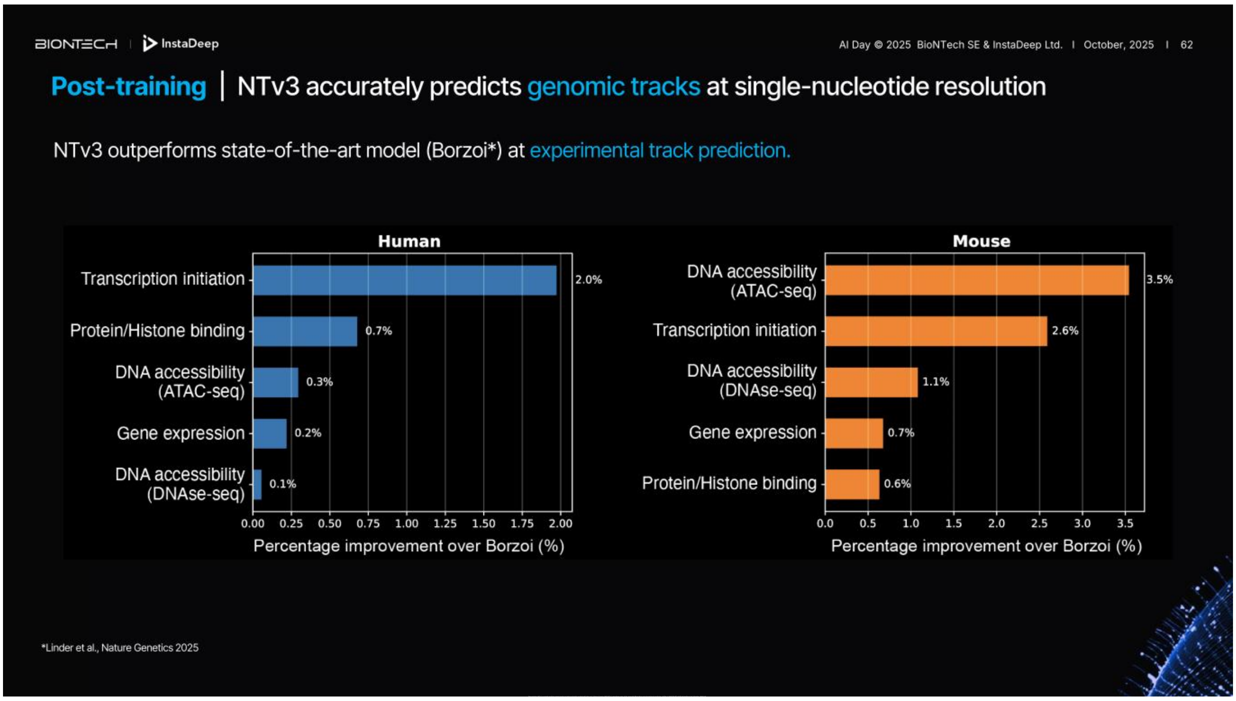
Predictions for 1mb input sequence
at single-nucleotide resolution



Post-training | NTv3 accurately predicts genomic tracks at single-nucleotide resolution

Example of NTv3 predictions for experiments in human K562 leukemia cells

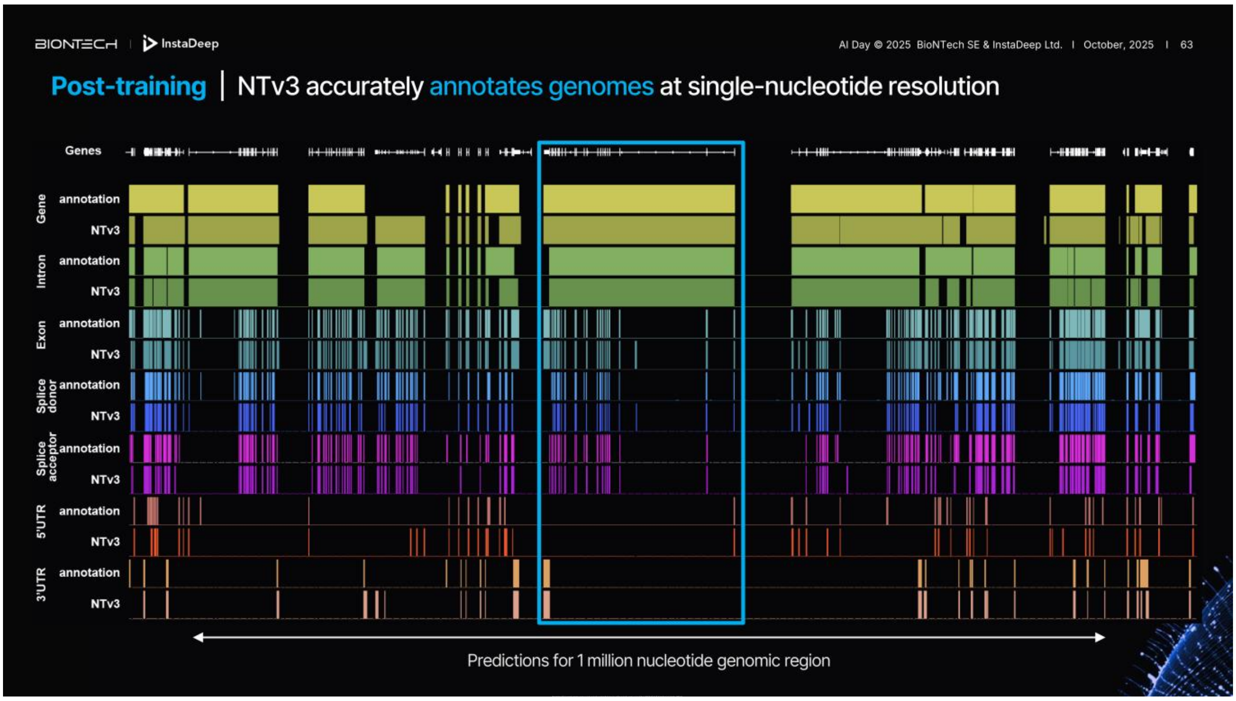
Predictions for 1 million nucleotide genomic region



Post-training | NTv3 accurately predicts genomic tracks at single-nucleotide resolution

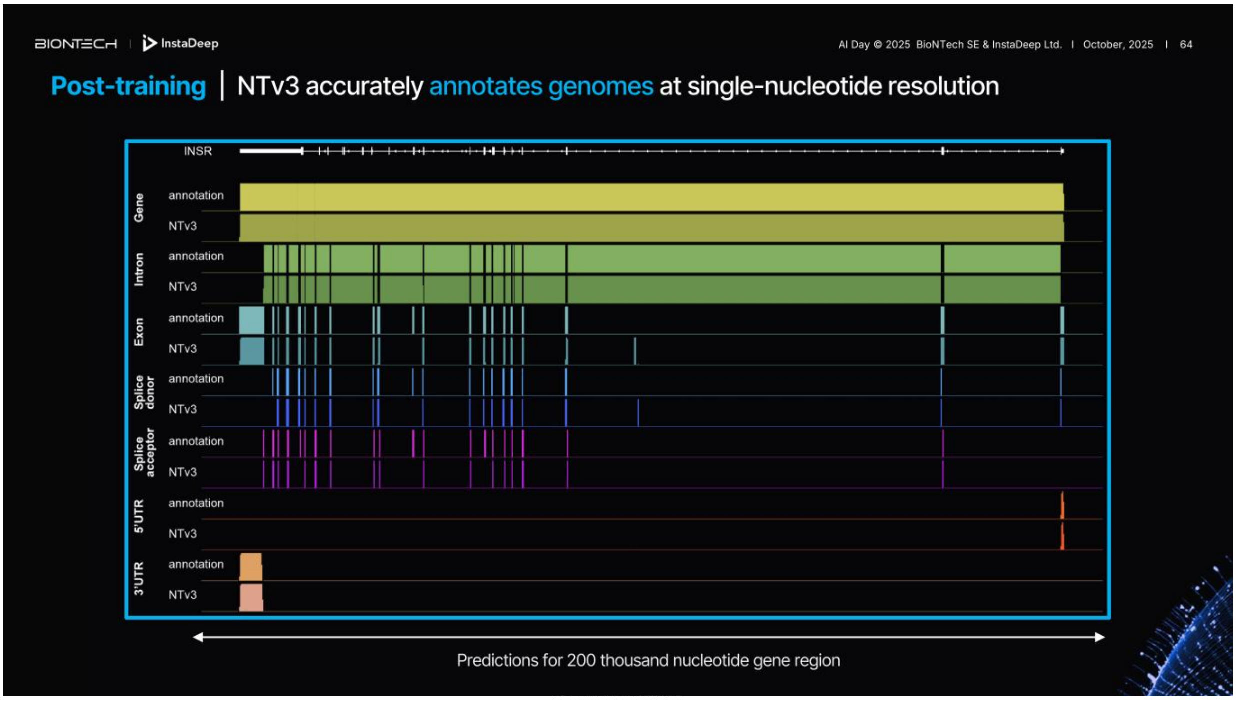
NTv3 outperforms state-of-the-art model (Borzoi*) at experimental track prediction.

*Linder et al., Nature Genetics 2025



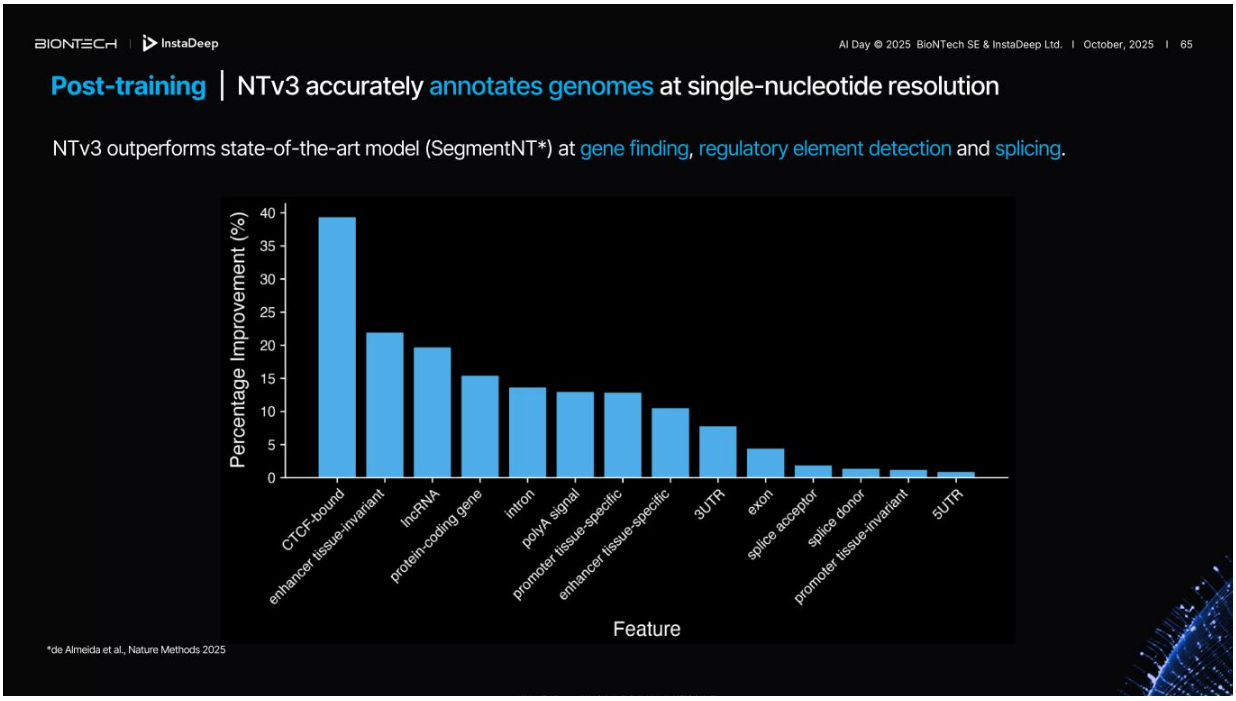
Post-training | NTv3 accurately annotates genomes at single-nucleotide resolution

Predictions for 1 million nucleotide genomic region



Post-training | NTv3 accurately annotates genomes at single-nucleotide resolution

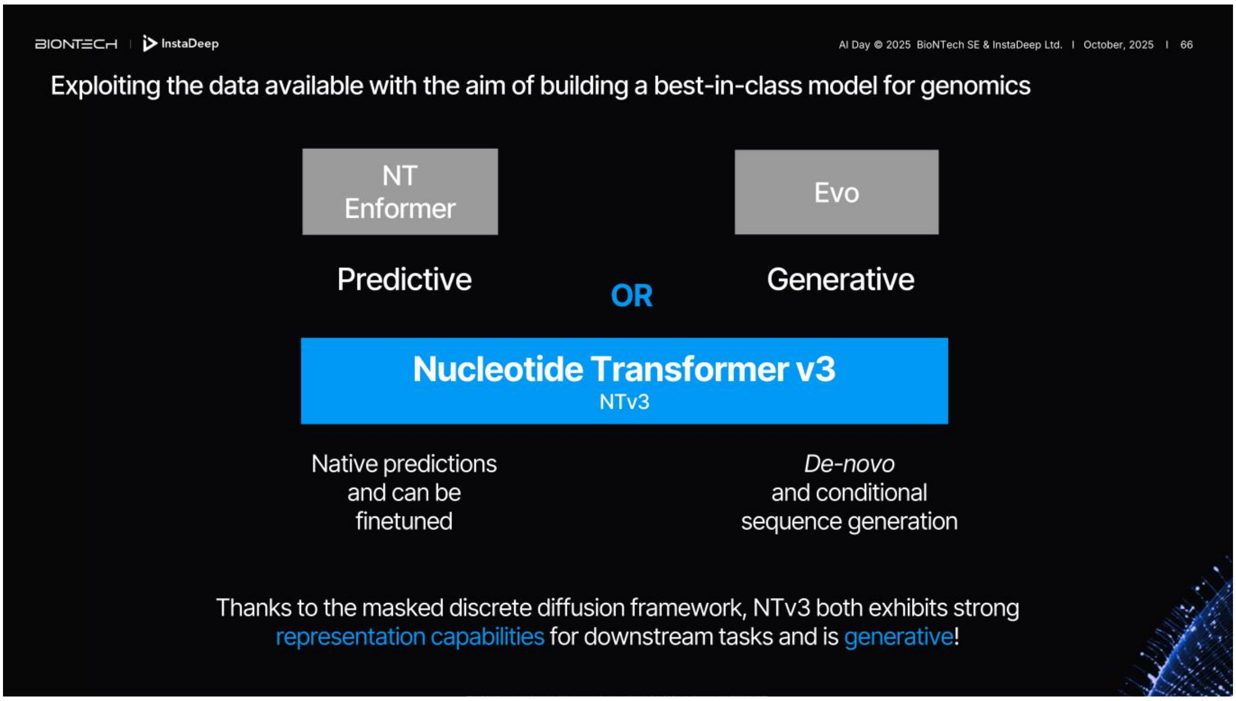
Predictions for 200 thousand nucleotide gene region



Post-training | NTv3 accurately annotates genomes at single-nucleotide resolution

NTv3 outperforms state-of-the-art model (SegmentNT*) at gene finding, regulatory element detection and splicing.

*de Almeida et al., Nature Methods 2025



Exploiting the data available with the aim of building a best-in-class model for genomics

NT
Enformer

Predictive

Evo

Generative

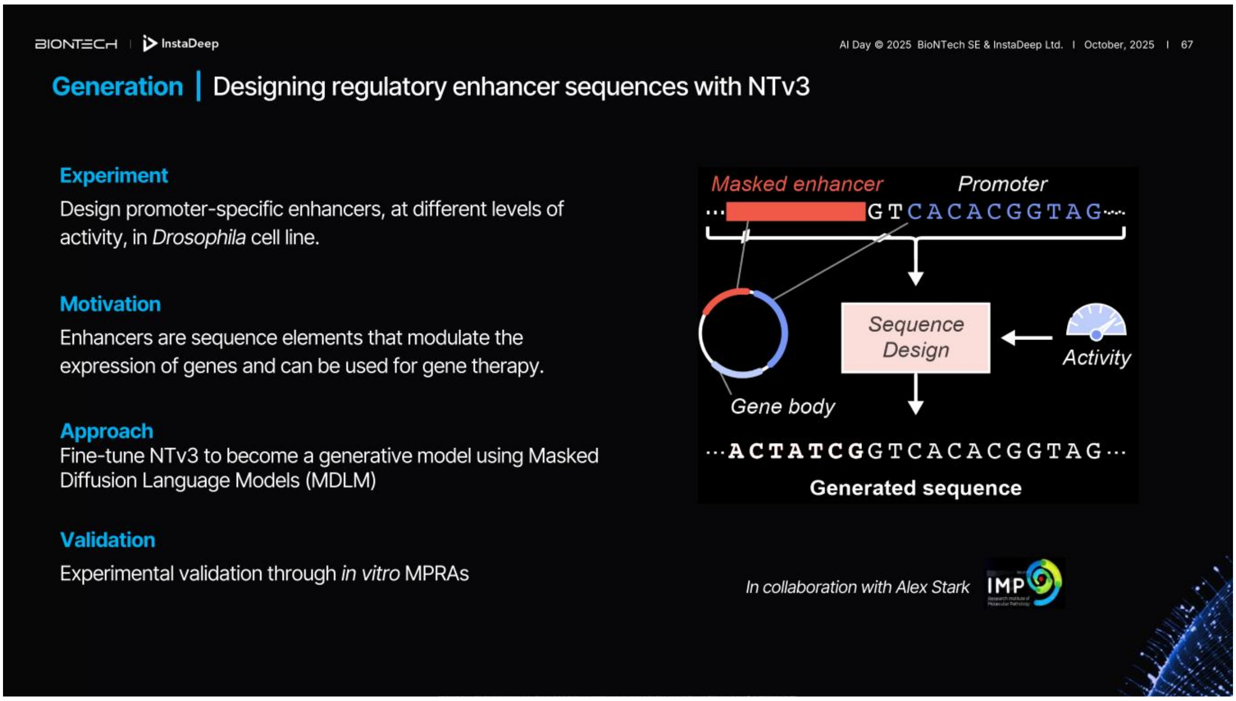
OR

Nucleotide Transformer v3
NTv3

Native predictions
and can be
finetuned

De-novo
and conditional
sequence generation

Thanks to the masked discrete diffusion framework, NTv3 both exhibits strong representation capabilities for downstream tasks and is generative!



Generation | Designing regulatory enhancer sequences with NTv3

Experiment

Design promoter-specific enhancers, at different levels of activity, in *Drosophila* cell line.

Motivation

Enhancers are sequence elements that modulate the expression of genes and can be used for gene therapy.

Approach

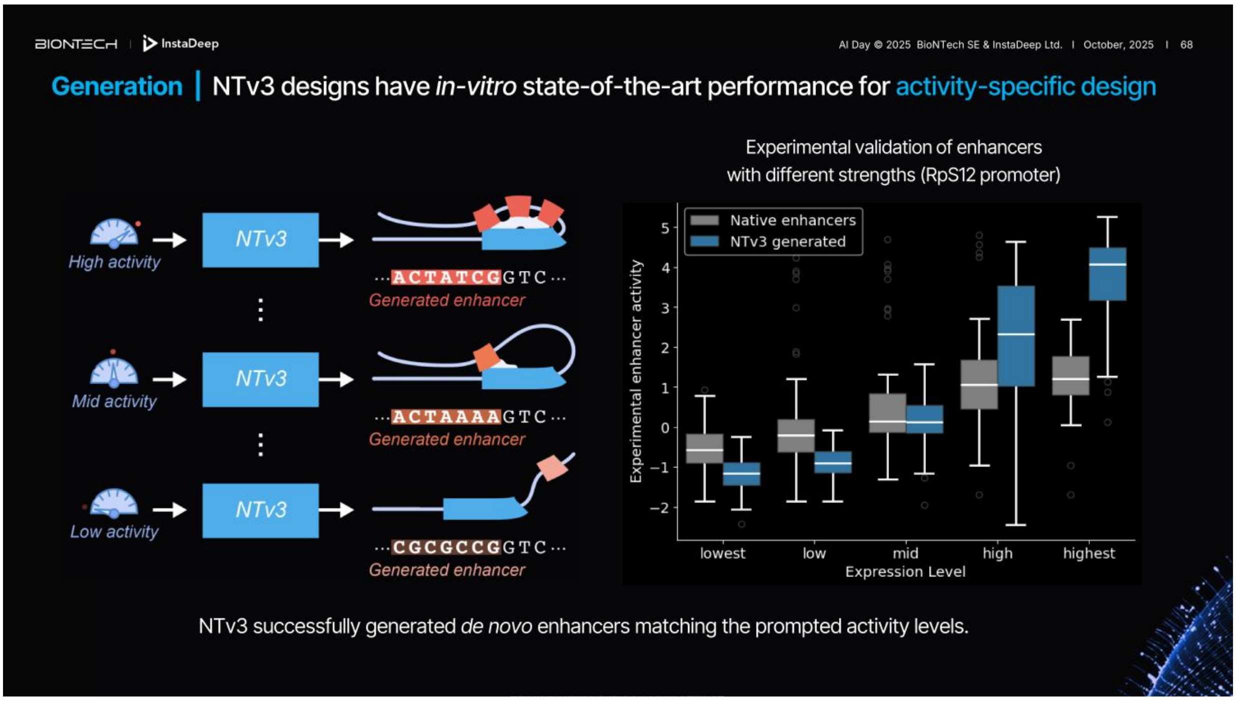
Fine-tune NTv3 to become a generative model using Masked Diffusion Language Models (MDLM)

Validation

Experimental validation through *in vitro* MPRAs

In collaboration with Alex Stark

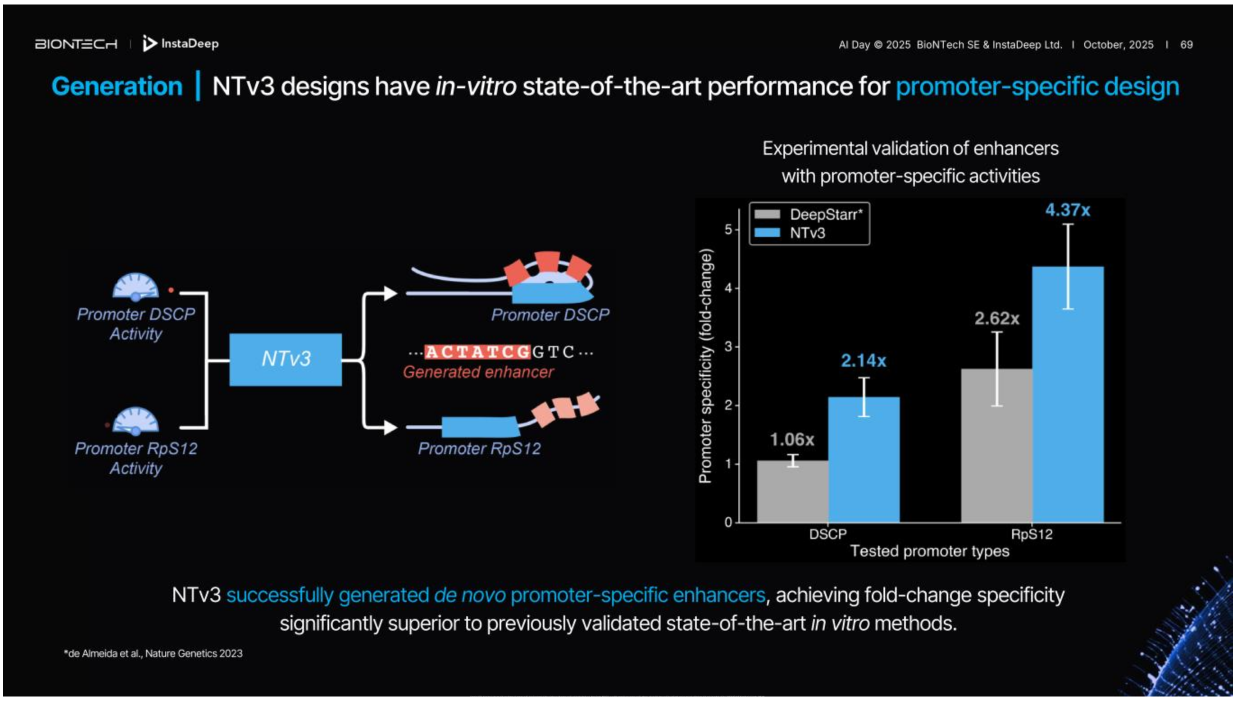
Generation | NTv3 designs have *in-vitro* state-of-the-art performance for activity-specific design



Experimental validation of enhancers
with different strengths (RpS12 promoter)

NTv3 successfully generated *de novo* enhancers matching the prompted activity levels.

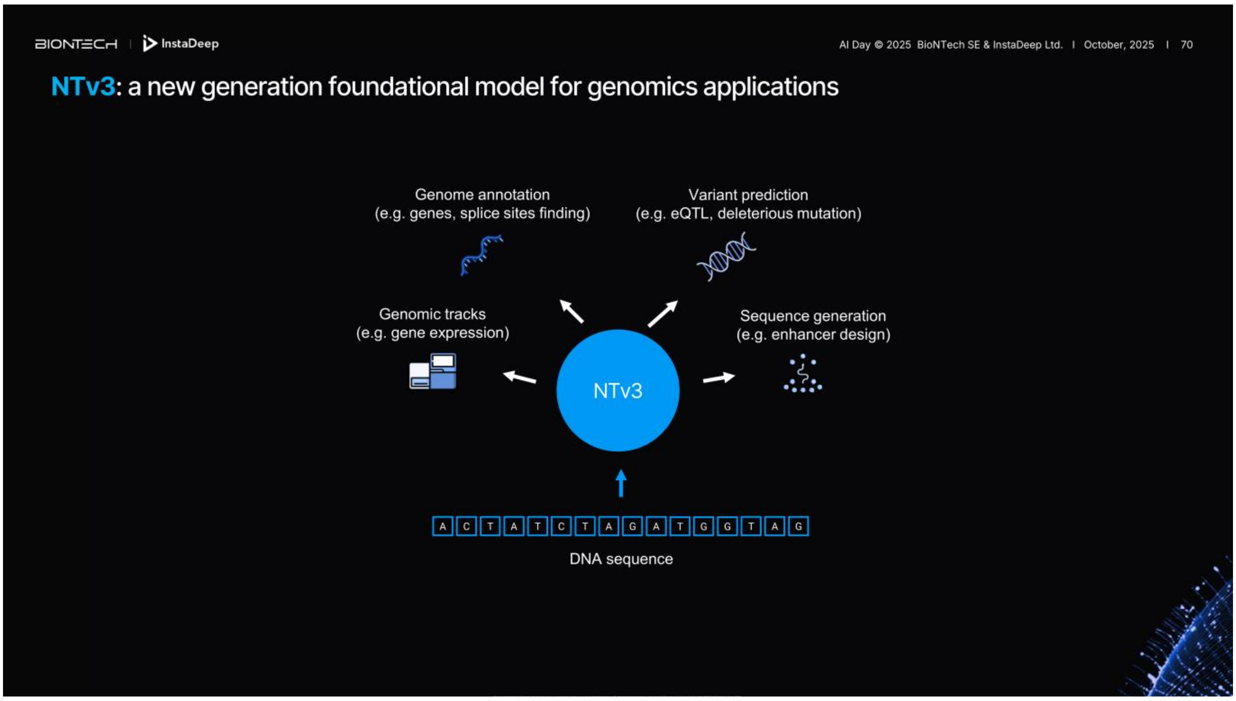
Generation | NTv3 designs have *in-vitro* state-of-the-art performance for promoter-specific design



Experimental validation of enhancers with promoter-specific activities

NTv3 successfully generated *de novo* promoter-specific enhancers, achieving fold-change specificity significantly superior to previously validated state-of-the-art *in vitro* methods.

*de Almeida et al., Nature Genetics 2023



NTv3: a new generation foundational model for genomics applications

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(e.g. genes, splice sites finding)

Variant prediction
(e.g. eQTL, deleterious mutation)

Genomic tracks
(e.g. gene expression)

NTv3

Sequence generation
(e.g. enhancer design)

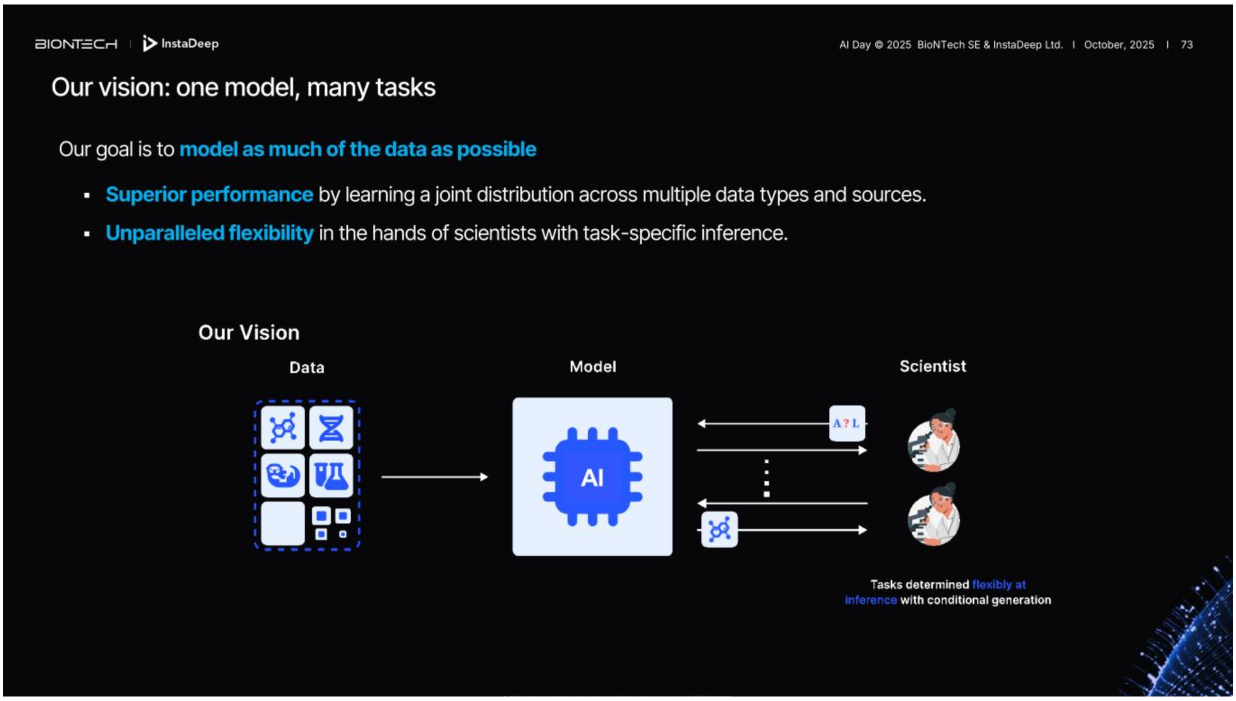
A C T A T C T A G A T G G T A G

DNA sequence

AI Innovation

Generative AI for protein and antibody engineering

Bora Guloglu
Senior Research Scientist



Our vision: one model, many tasks

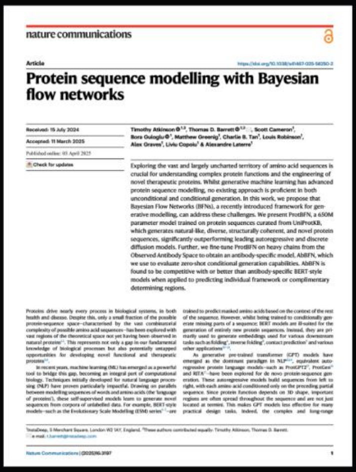
Our goal is to **model as much of the data as possible**

- **Superior performance** by learning a joint distribution across multiple data types and sources.
- **Unparalleled flexibility** in the hands of scientists with task-specific inference.

Our Vision

Tasks determined flexibly at inference with conditional generation

Laying the Groundwork



nature communications

Article

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Protein sequence modelling with Bayesian flow networks

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Timothy Atkinson[1,2], Thomas D. Barrett[1,2] ✉, Scott Cameron[1], Bora Guloglu[1], Matthew Greenig[1], Charlie B. Tan[1], Louis Robinson[1], Alex Graves[1], Liviu Copoiu[1] & Alexandre Laterre[1]

Exploring the vast and largely uncharted territory of amino acid sequences is crucial for understanding complex protein functions and the engineering of novel therapeutic proteins. Whilst generative machine learning has advanced protein sequence modelling, no existing approach is proficient in both unconditional and conditional generation. In this work, we propose that Bayesian Flow Networks (BFNs), a recently introduced framework for generative modelling, can address these challenges. We present ProtBFN, a 650M parameter model trained on protein sequences curated from UniProtKB, which generates natural-like, diverse, structurally coherent, and novel protein sequences, significantly outperforming leading autoregressive and discrete diffusion models. Further, we fine-tune ProtBFN on heavy chains from the Observed Antibody Space to obtain an antibody-specific model, AbBFN, which we use to evaluate zero-shot conditional generation capabilities. AbBFN is found to be competitive with or better than antibody-specific BERT-style models when applied to predicting individual framework or complimentary determining regions.

Proteins drive nearly every process in biological systems, in both health and disease. Despite this, only a small fraction of the possible protein-sequence space—characterised by the vast combinatorial complexity of possible amino acid sequences—has been explored with vast regions of the theoretical space not yet having been observed in natural proteins. This represents not only a gap in our fundamental knowledge of biological processes but also potentially untapped opportunities for developing novel functional and therapeutic proteins.

In recent years, machine learning (ML) has emerged as a powerful tool to bridge this gap, becoming an integral part of computational biology. Techniques initially developed for natural language processing (NLP) have proven particularly impactful. Drawing on parallels between modelling sequences of words and amino acids (the 'language of proteins'), these self-supervised models learn to generate novel sequences from corpora of unlabelled data. For example, BERT-style models—such as the Evolutionary Scale Modelling (ESM) series—are trained to predict masked amino acids based on the context of the rest of the sequence. However, whilst being trained to conditionally generate missing parts of a sequence, BERT models are ill-suited for the generation of entirely new protein sequences. Instead, they are primarily used to generate embeddings used for various downstream tasks such as folding, inverse folding, contact prediction and various other applications.

As generative pre-trained transformer (GPT) models have emerged as the dominant paradigm in NLP, equivalent autoregressive protein language models—such as ProtGPT2, ProGen and RITA—have been explored for de novo protein sequence generation. These autoregressive models build sequences from left to right, with each amino acid conditioned only on the preceding partial sequence. Since protein function depends on 3D shape, important regions are often spread throughout the sequence and are not just located at termini. This makes GPT models less effective for many practical design tasks. Indeed, the complex and long-range

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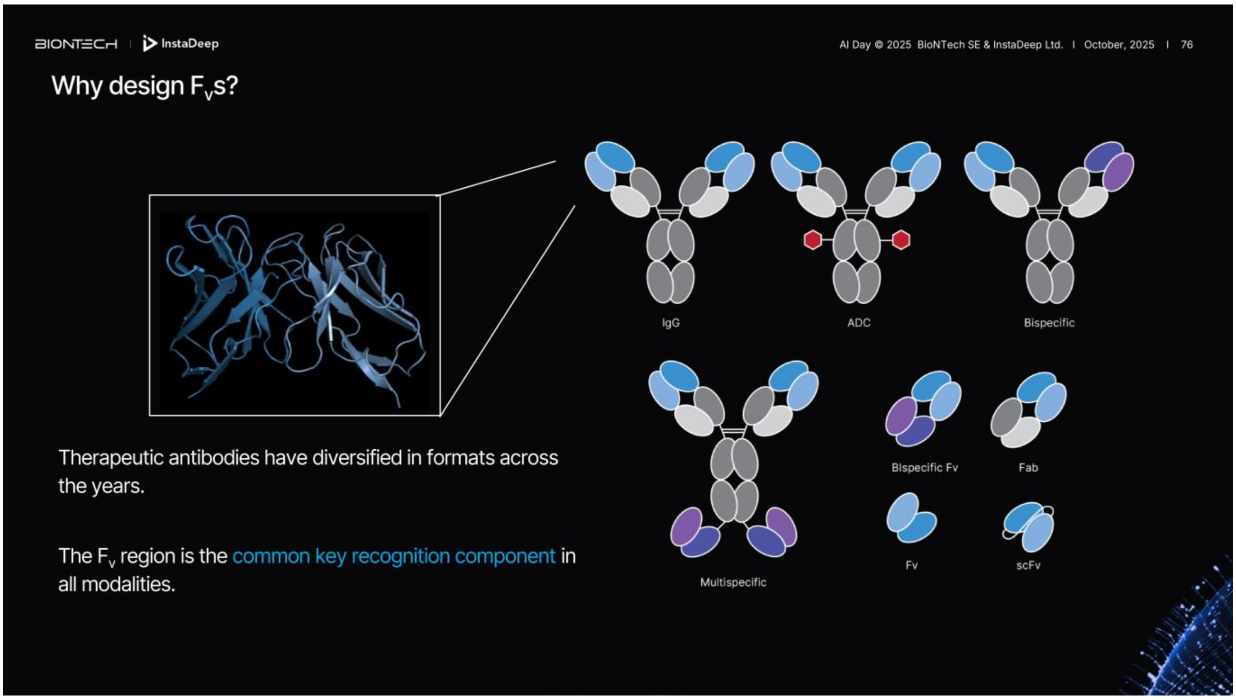
1. Atkinson, T., Barrett, T.D., Cameron, S. *et al.* Protein sequence modelling with Bayesian flow networks. *Nat Commun* **16**, 3197 (2025)

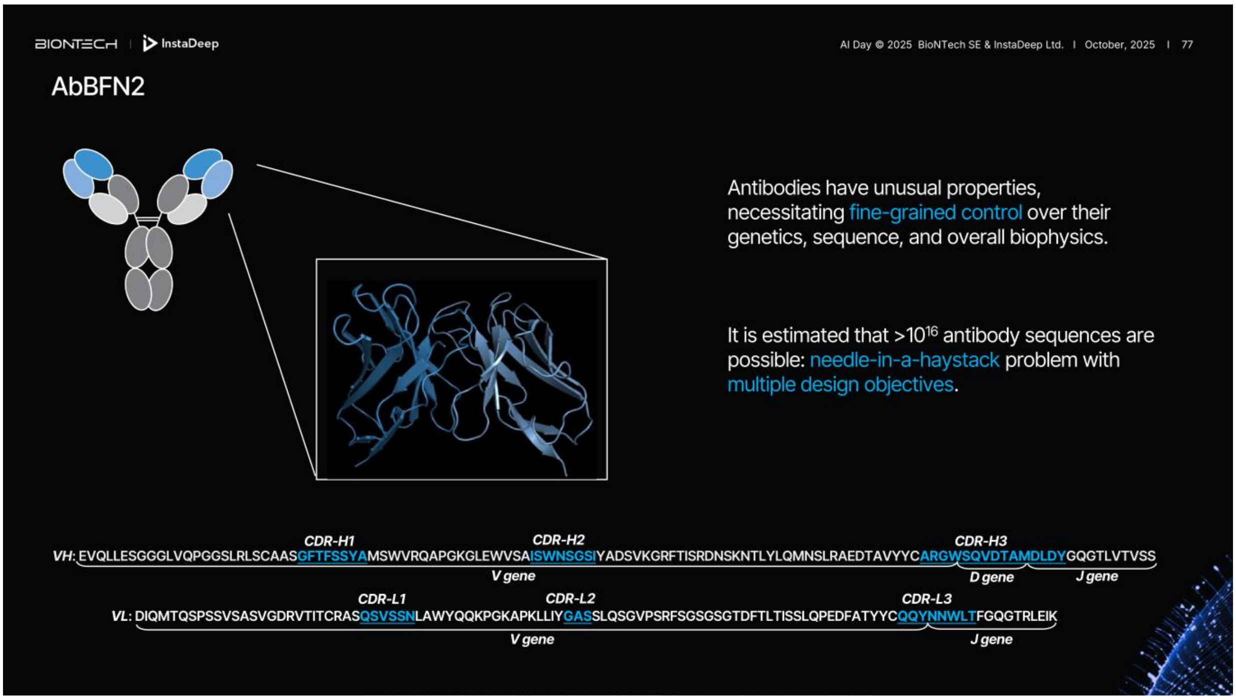
AbBFN2



Why design F_vs?

Therapeutic antibodies have diversified in formats across the years.

The F_v region is the common key recognition component in all modalities.



AbBFN2

Antibodies have unusual properties, necessitating fine-grained control over their genetics, sequence, and overall biophysics.

It is estimated that >10^{16} antibody sequences are possible: needle-in-a-haystack problem with multiple design objectives.

CDR-H1 *CDR-H2* *CDR-H3*

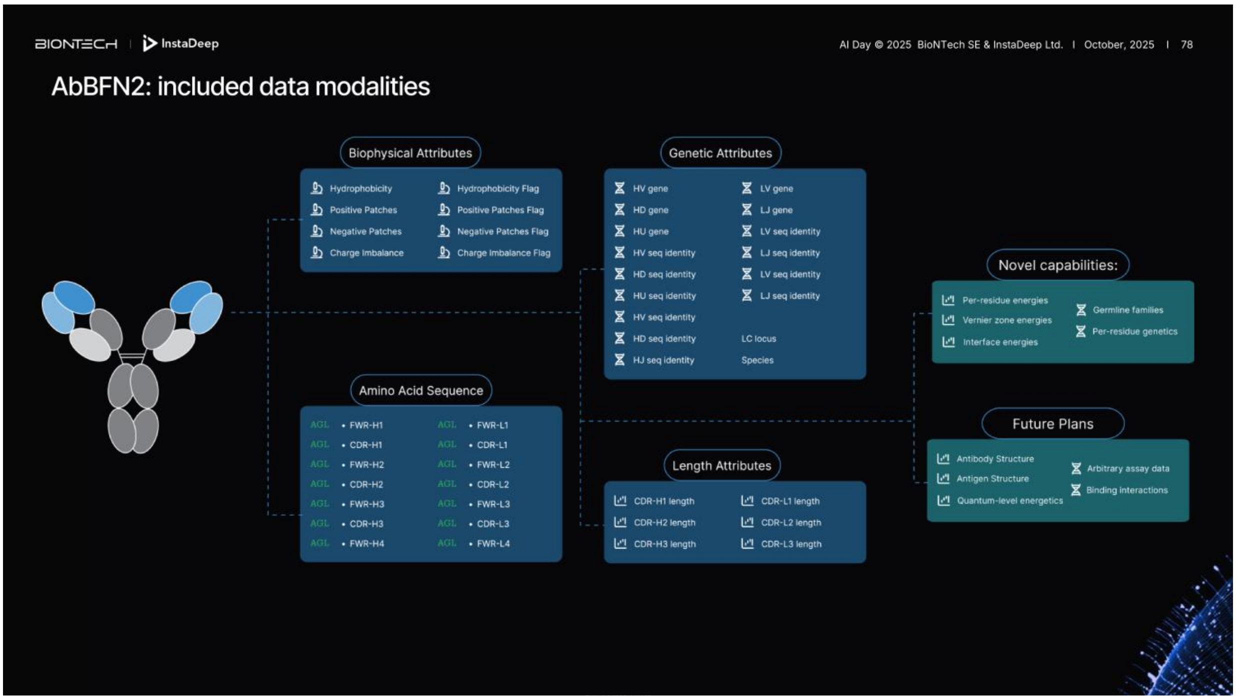
VH: EVQLLESGGGLVQPGGSLRLSCAAS<u>GFTFSSYA</u>MSWVRQAPGKGLEWVSA<u>ISWNSGSI</u>YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC<u>ARGWSQVDTAMDLDY</u>GQGTLVTVSS

V gene *D gene* *J gene*

CDR-L1 *CDR-L2* *CDR-L3*

VL: DIQMTQSPSSVSASVGDRVTITCRAS<u>QSVSSN</u>LAWYQQKPGKAPKLLIY<u>GAS</u>SLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC<u>QQYNNWLT</u>FGQGTRLEIK

V gene *J gene*



AbBFN2: included data modalities

Biophysical Attributes

- Hydrophobicity
- Positive Patches
- Negative Patches
- Charge Imbalance
- Hydrophobicity Flag
- Positive Patches Flag
- Negative Patches Flag
- Charge Imbalance Flag

Amino Acid Sequence

AGL • FWR-H1
AGL • CDR-H1
AGL • FWR-H2
AGL • CDR-H2
AGL • FWR-H3
AGL • CDR-H3
AGL • FWR-H4
AGL • FWR-L1
AGL • CDR-L1
AGL • FWR-L2
AGL • CDR-L2
AGL • FWR-L3
AGL • CDR-L3
AGL • FWR-L4

Genetic Attributes

- HV gene
- HD gene
- HU gene
- HV seq identity
- HD seq identity
- HU seq identity
- HV seq identity
- HD seq identity
- HJ seq identity
- LV gene
- LJ gene
- LV seq identity
- LJ seq identity
- LV seq identity
- LJ seq identity
- LC locus
- Species

Length Attributes

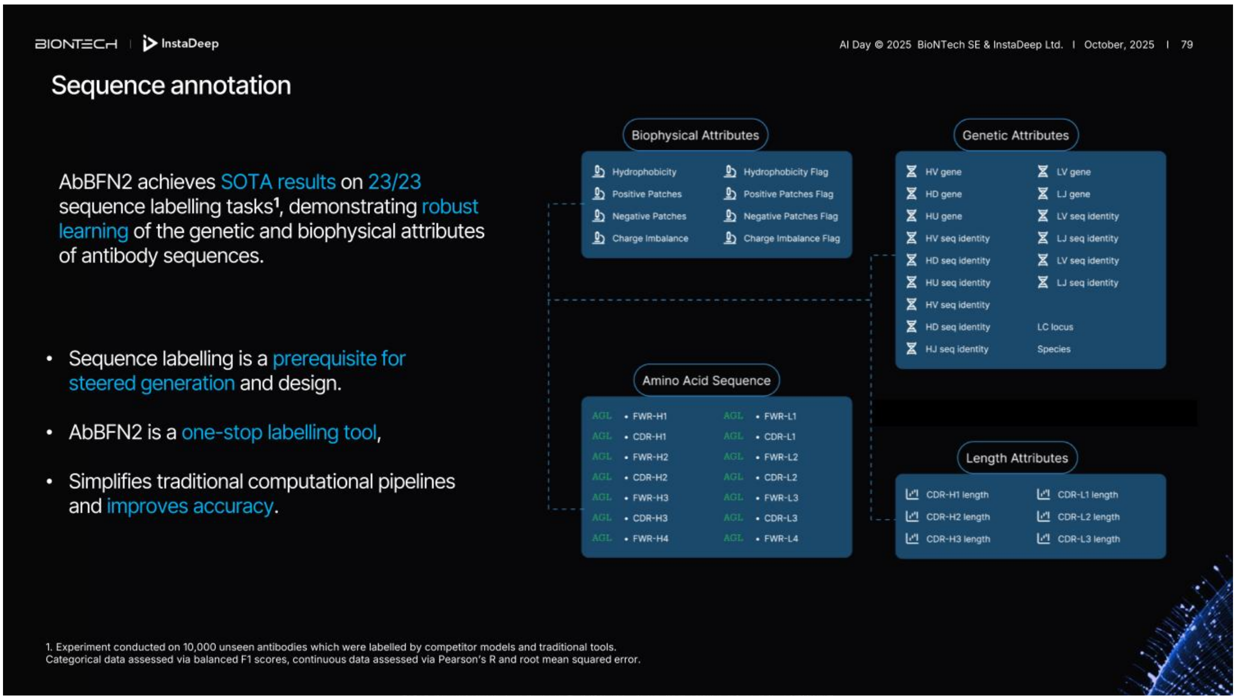
- CDR-H1 length
- CDR-H2 length
- CDR-H3 length
- CDR-L1 length
- CDR-L2 length
- CDR-L3 length

Novel capabilities:

- Per-residue energies
- Vernier zone energies
- Interface energies
- Germline families
- Per-residue genetics

Future Plans

- Antibody Structure
- Antigen Structure
- Quantum-level energetics
- Arbitrary assay data
- Binding interactions



Sequence annotation

AbBFN2 achieves SOTA results on 23/23 sequence labelling tasks[1], demonstrating robust learning of the genetic and biophysical attributes of antibody sequences.

- Sequence labelling is a prerequisite for steered generation and design.
- AbBFN2 is a one-stop labelling tool,
- Simplifies traditional computational pipelines and improves accuracy.

Biophysical Attributes

- Hydrophobicity
- Positive Patches
- Negative Patches
- Charge Imbalance
- Hydrophobicity Flag
- Positive Patches Flag
- Negative Patches Flag
- Charge Imbalance Flag

Genetic Attributes

- HV gene
- HD gene
- HU gene
- HV seq identity
- HD seq identity
- HU seq identity
- HV seq identity
- HD seq identity
- HJ seq identity
- LV gene
- LJ gene
- LV seq identity
- LJ seq identity
- LV seq identity
- LJ seq identity
- LC locus
- Species

Amino Acid Sequence

- AGL • FWR-H1
- AGL • CDR-H1
- AGL • FWR-H2
- AGL • CDR-H2
- AGL • FWR-H3
- AGL • CDR-H3
- AGL • FWR-H4
- AGL • FWR-L1
- AGL • CDR-L1
- AGL • FWR-L2
- AGL • CDR-L2
- AGL • FWR-L3
- AGL • CDR-L3
- AGL • FWR-L4

Length Attributes

- CDR-H1 length
- CDR-H2 length
- CDR-H3 length
- CDR-L1 length
- CDR-L2 length
- CDR-L3 length

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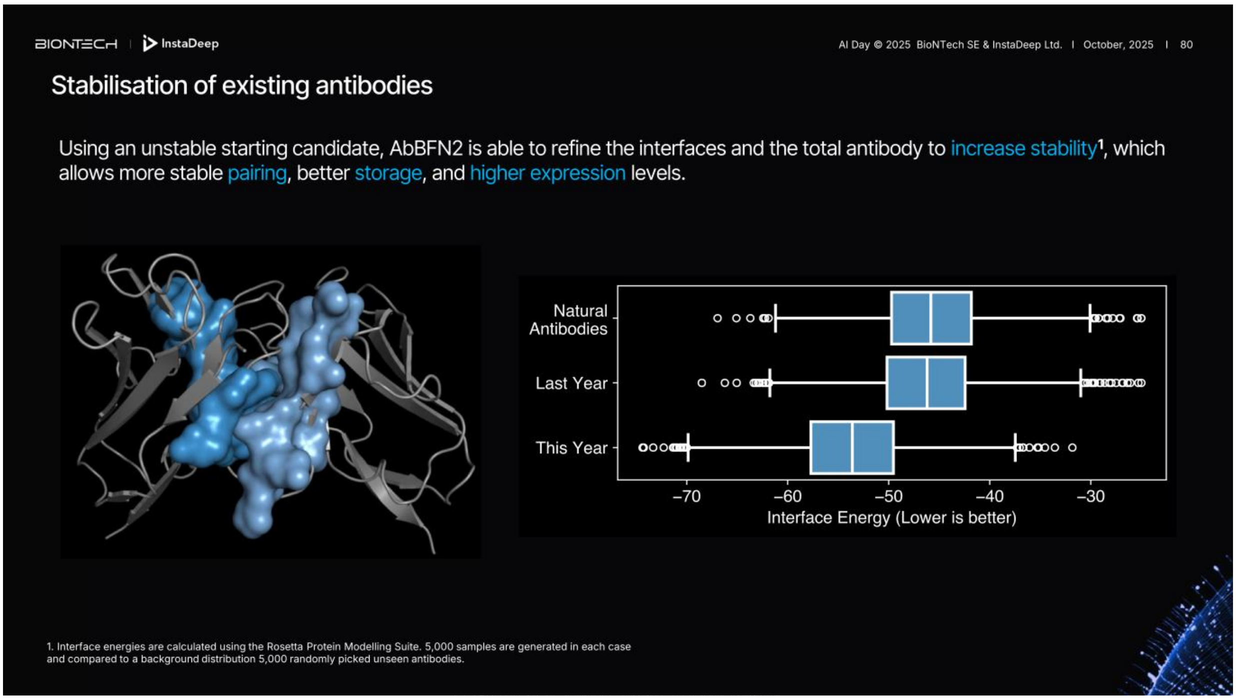
[1] Experiment conducted on 10,000 unseen antibodies which were labelled by competitor models and traditional tools. Categorical data assessed via balanced F1 scores, continuous data assessed via Pearson's R and root mean squared error.



Stabilisation of existing antibodies

Using an unstable starting candidate, AbBFN2 is able to refine the interfaces and the total antibody to increase stability[1], which allows more stable pairing, better storage, and higher expression levels.

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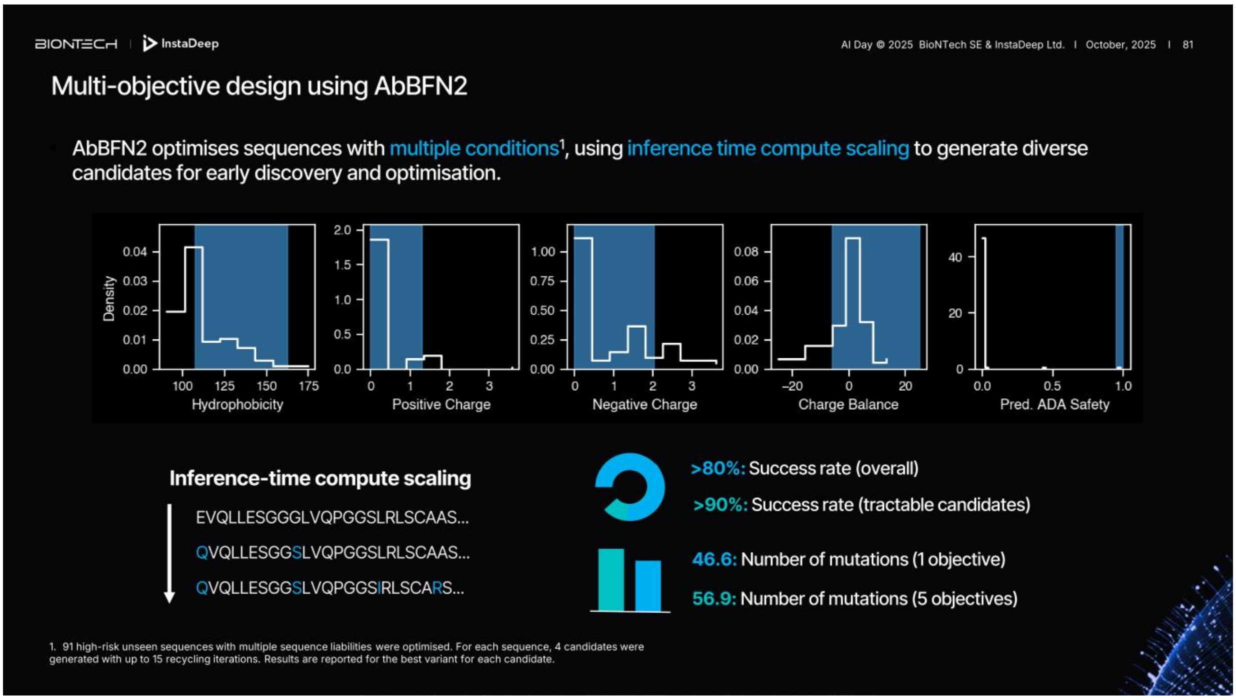
[1] Interface energies are calculated using the Rosetta Protein Modelling Suite. 5,000 samples are generated in each case and compared to a background distribution 5,000 randomly picked unseen antibodies.



Multi-objective design using AbBFN2

- AbBFN2 optimises sequences with multiple conditions[1], using inference time compute scaling to generate diverse candidates for early discovery and optimisation.

Inference-time compute scaling

EVQLLESGGGLVQPGGSLRLSCAAS...
QVQLLESGGSLVQPGGSLRLSCAAS...
QVQLLESGGSLVQPGGSIRLSCARS...

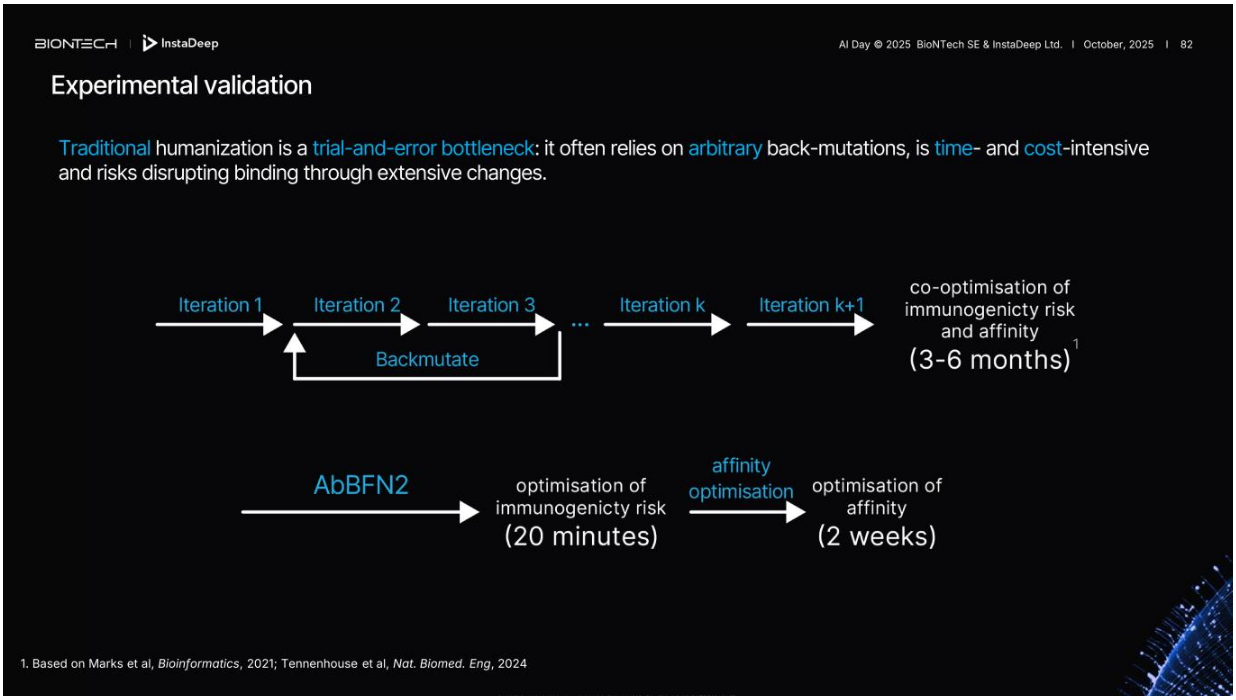
>80%: Success rate (overall)

>90%: Success rate (tractable candidates)

46.6: Number of mutations (1 objective)

56.9: Number of mutations (5 objectives)

[1] 91 high-risk unseen sequences with multiple sequence liabilities were optimised. For each sequence, 4 candidates were generated with up to 15 recycling iterations. Results are reported for the best variant for each candidate.



Experimental validation

Traditional humanization is a trial-and-error bottleneck: it often relies on arbitrary back-mutations, is time- and cost-intensive and risks disrupting binding through extensive changes.

Iteration 1 → Iteration 2 → Iteration 3 → … Iteration k → Iteration k+1 → co-optimisation of immunogenicty risk and affinity (3-6 months)[1]

Backmutate

AbBFN2 → optimisation of immunogenicty risk (20 minutes) → affinity optimisation → optimisation of affinity (2 weeks)

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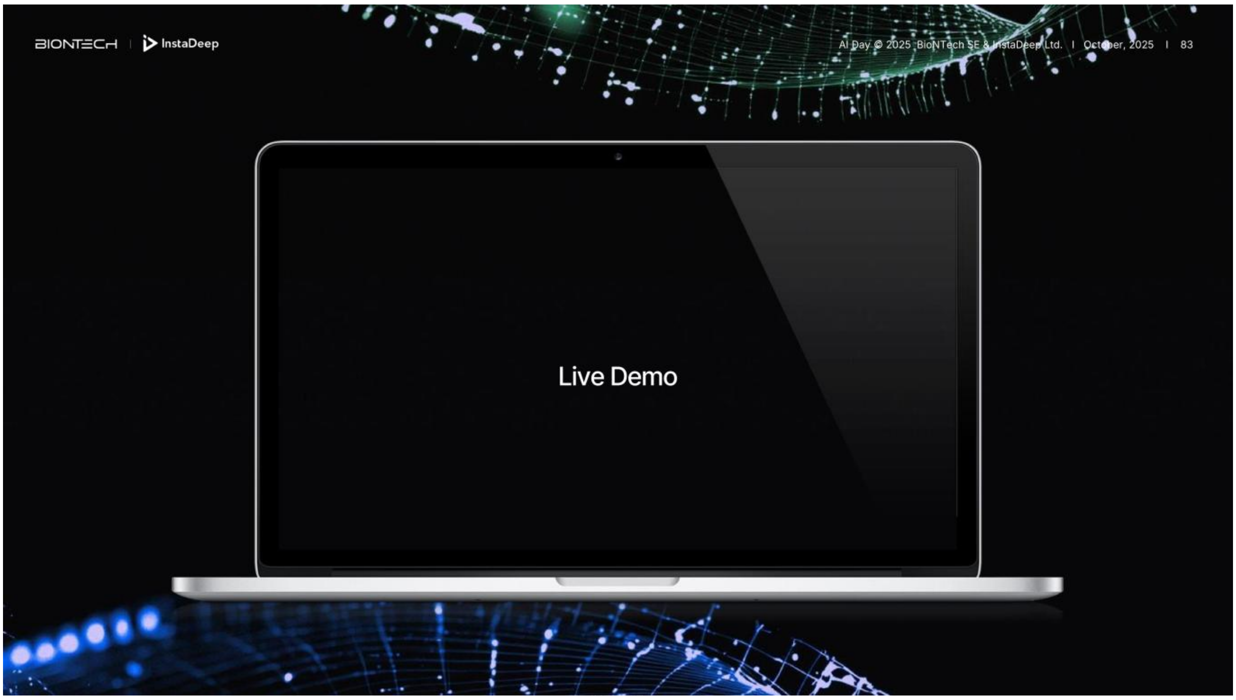
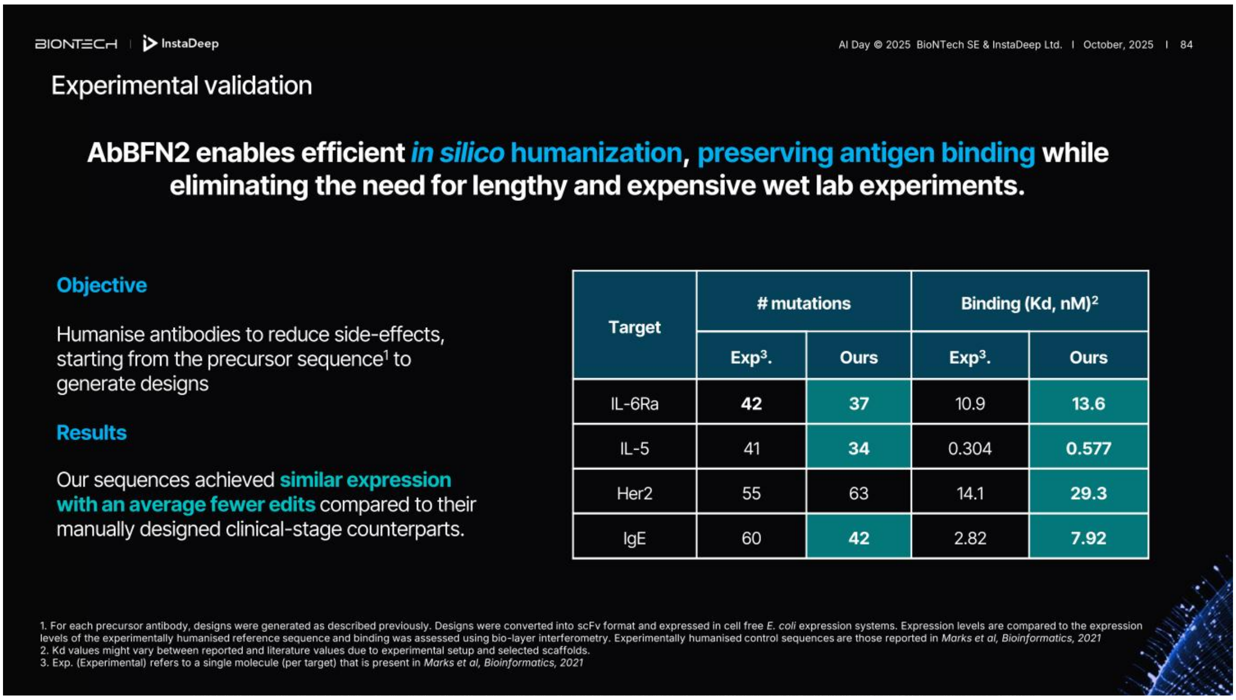
1. Based on Marks et al, *Bioinformatics*, 2021; Tennenhouse et al, *Nat. Biomed. Eng*, 2024



Live Demo



Experimental validation

AbBFN2 enables efficient *in silico* humanization, preserving antigen binding while eliminating the need for lengthy and expensive wet lab experiments.

Objective

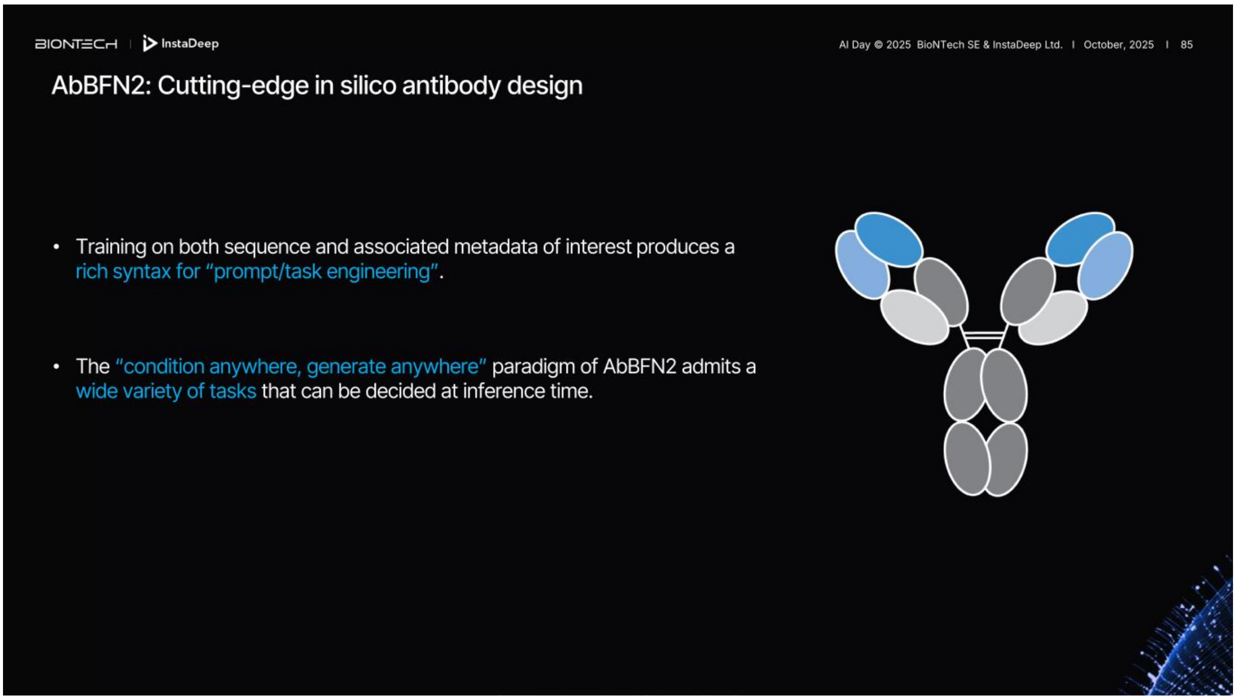
Humanise antibodies to reduce side-effects, starting from the precursor sequence[1] to generate designs

Results

Our sequences achieved **similar expression with an average fewer edits** compared to their manually designed clinical-stage counterparts.

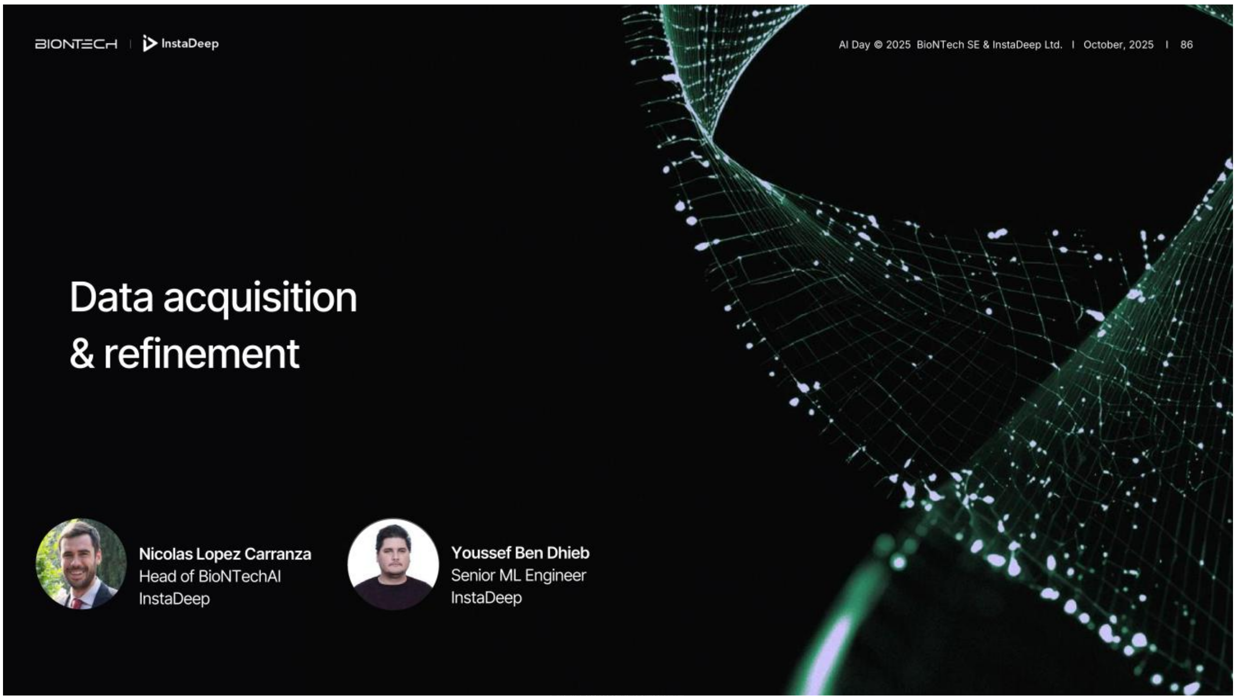
Target	# mutations		Binding (Kd, nM)[2]	
	Exp[3].	Ours	Exp[3].	Ours
IL-6Ra	**42**	**37**	10.9	**13.6**
IL-5	41	**34**	0.304	**0.577**
Her2	55	63	14.1	**29.3**
IgE	60	**42**	2.82	**7.92**

1. For each precursor antibody, designs were generated as described previously. Designs were converted into scFv format and expressed in cell free *E. coli* expression systems. Expression levels are compared to the expression levels of the experimentally humanised reference sequence and binding was assessed using bio-layer interferometry. Experimentally humanised control sequences are those reported in *Marks et al, Bioinformatics, 2021*
2. Kd values might vary between reported and literature values due to experimental setup and selected scaffolds.
3. Exp. (Experimental) refers to a single molecule (per target) that is present in *Marks et al, Bioinformatics, 2021*



AbBFN2: Cutting-edge in silico antibody design

- Training on both sequence and associated metadata of interest produces a rich syntax for "prompt/task engineering".
- The "condition anywhere, generate anywhere" paradigm of AbBFN2 admits a wide variety of tasks that can be decided at inference time.



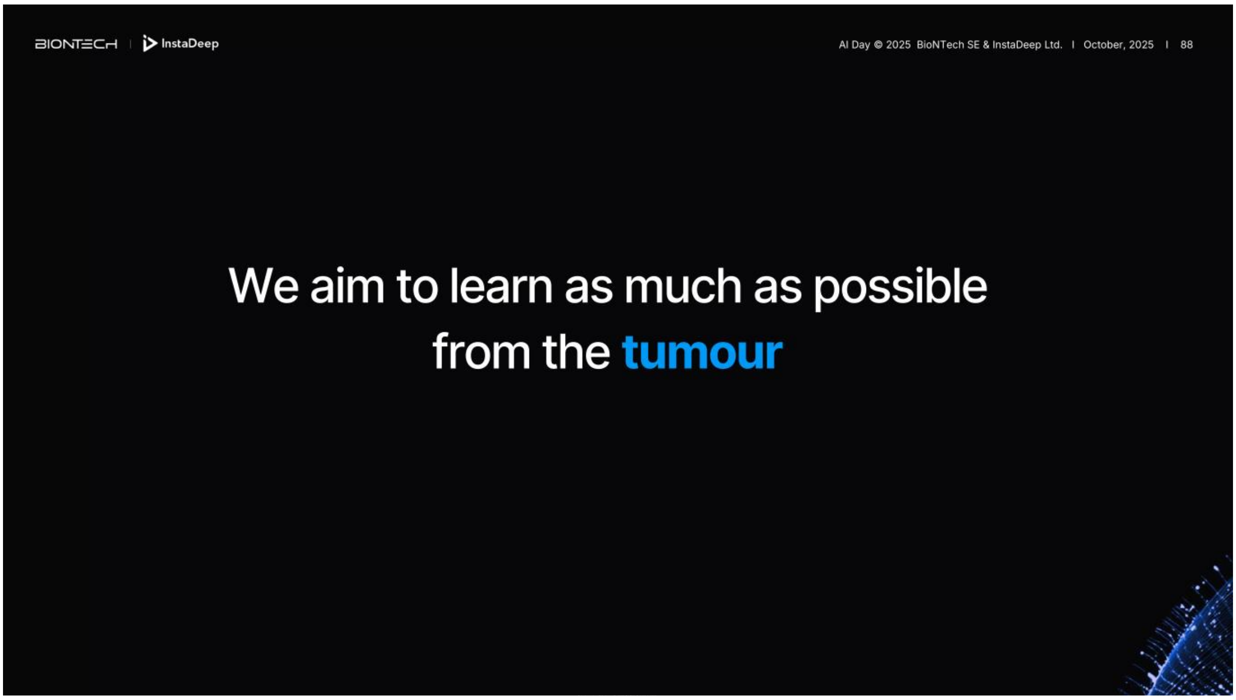
Data acquisition & refinement

Nicolas Lopez Carranza
Head of BioNTechAI
InstaDeep

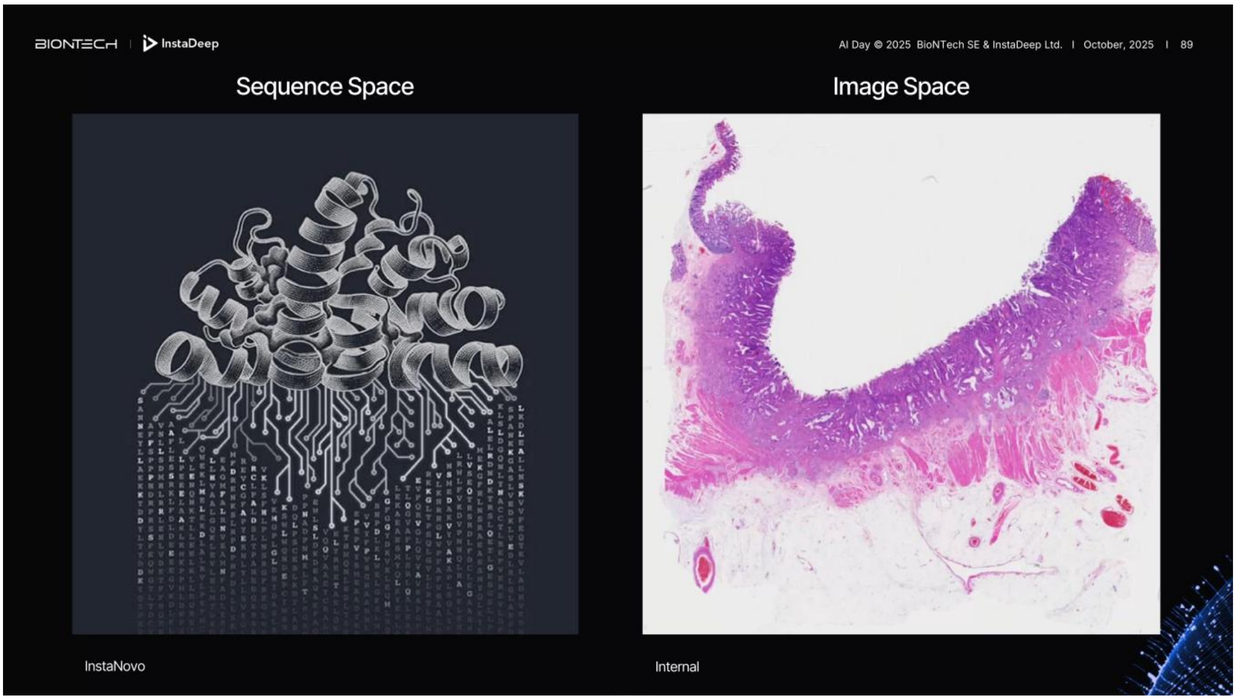
Youssef Ben Dhieb
Senior ML Engineer
InstaDeep

BioNTech AI strategy is **driven by data**

Potential for continued improvement as more data are generated and analysed



We aim to learn as much as possible from the **tumour**

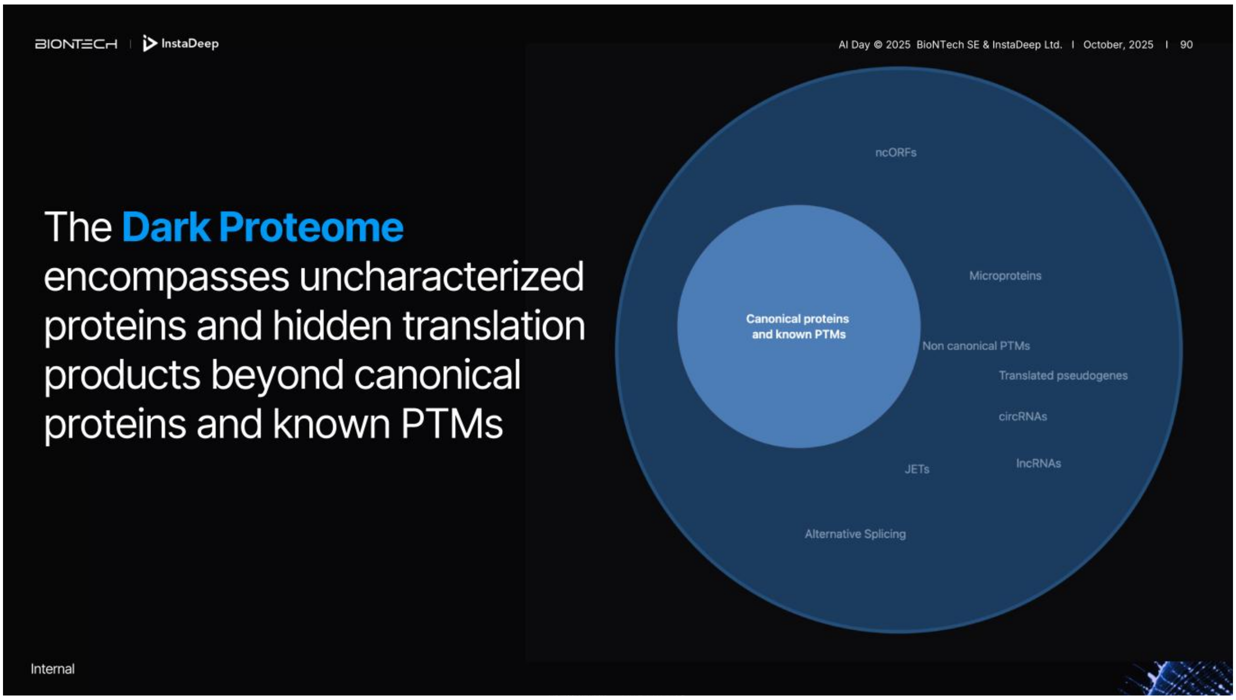


Sequence Space

Image Space

InstaNovo

Internal



The **Dark Proteome** encompasses uncharacterized proteins and hidden translation products beyond canonical proteins and known PTMs

Canonical proteins and known PTMs

ncORFs

Microproteins

Non canonical PTMs

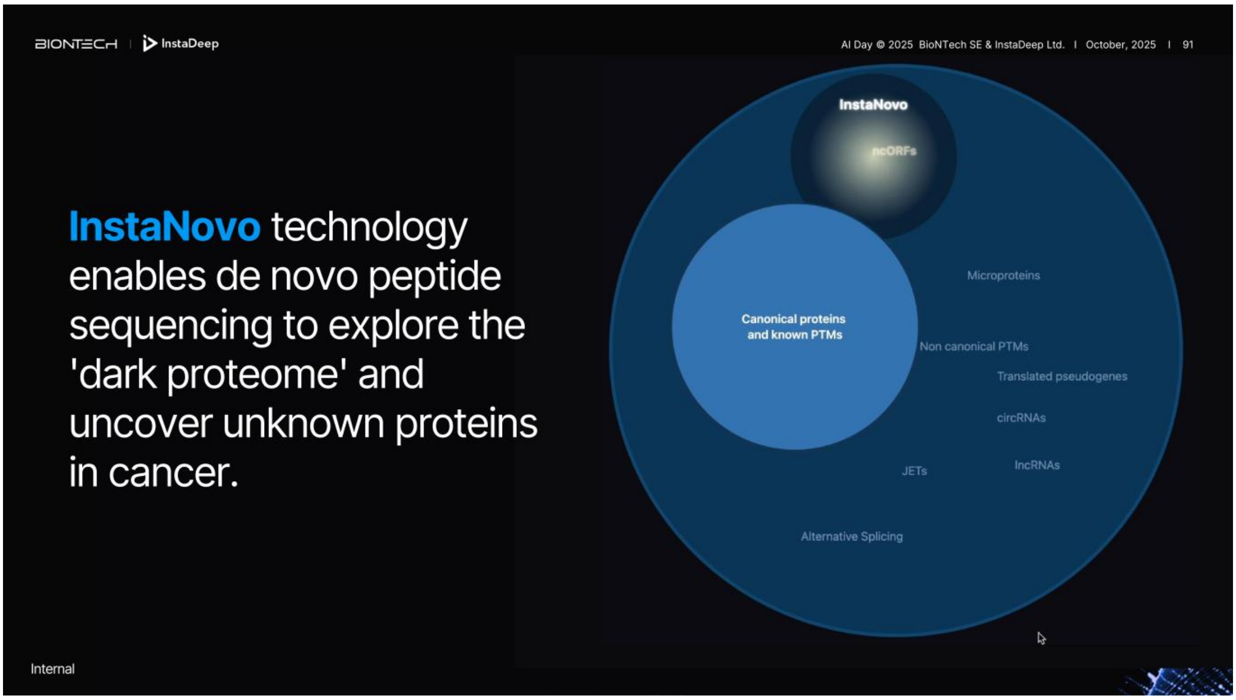
Translated pseudogenes

circRNAs

lncRNAs

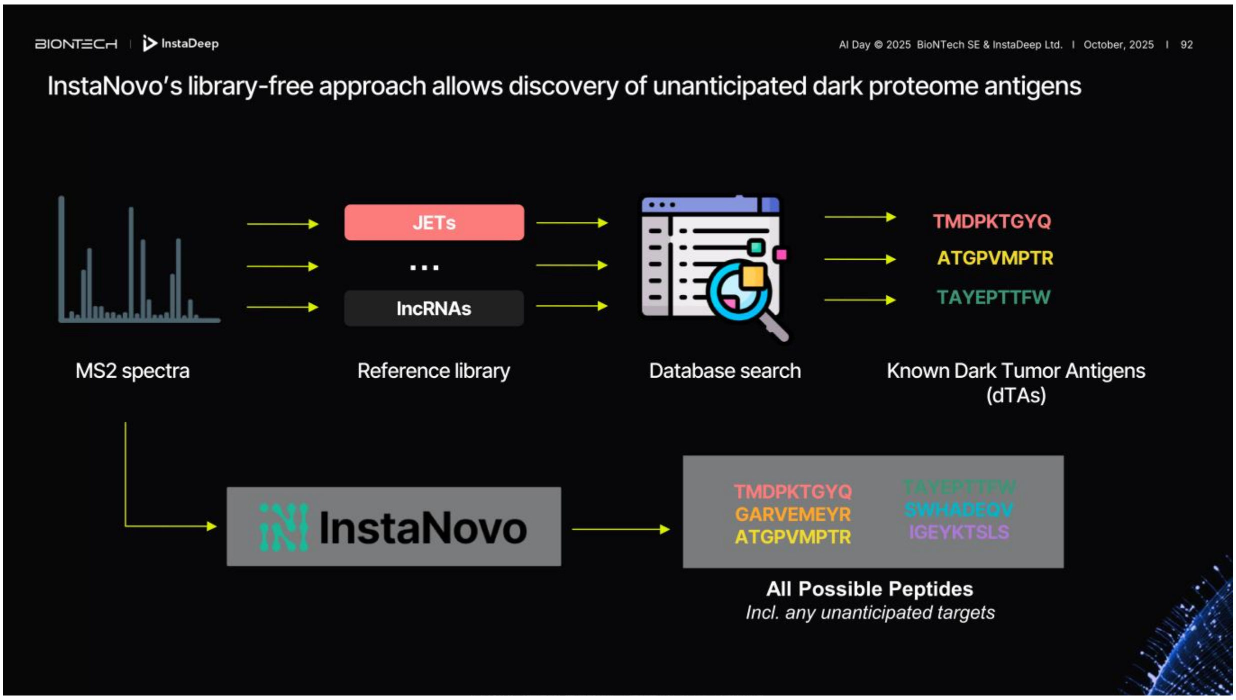
JETs

Alternative Splicing



InstaNovo technology enables de novo peptide sequencing to explore the 'dark proteome' and uncover unknown proteins in cancer.

Internal



InstaNovo's library-free approach allows discovery of unanticipated dark proteome antigens

MS2 spectra

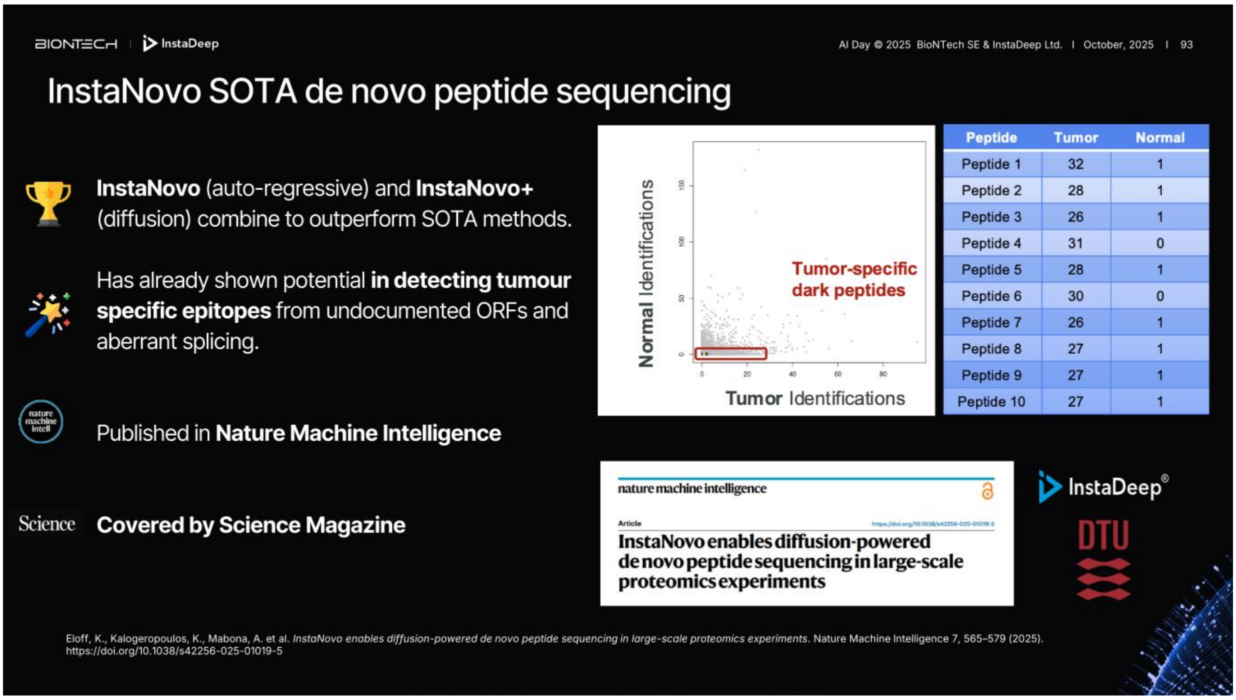
Reference library

Database search

Known Dark Tumor Antigens (dTAs)

All Possible Peptides

Incl. any unanticipated targets



InstaNovo SOTA de novo peptide sequencing

- 🏆 **InstaNovo** (auto-regressive) and **InstaNovo+** (diffusion) combine to outperform SOTA methods.
- Has already shown potential **in detecting tumour specific epitopes** from undocumented ORFs and aberrant splicing.
- Published in **Nature Machine Intelligence**
- **Covered by Science Magazine**

Peptide	Tumor	Normal
Peptide 1	32	1
Peptide 2	28	1
Peptide 3	26	1
Peptide 4	31	0
Peptide 5	28	1
Peptide 6	30	0
Peptide 7	26	1
Peptide 8	27	1
Peptide 9	27	1
Peptide 10	27	1

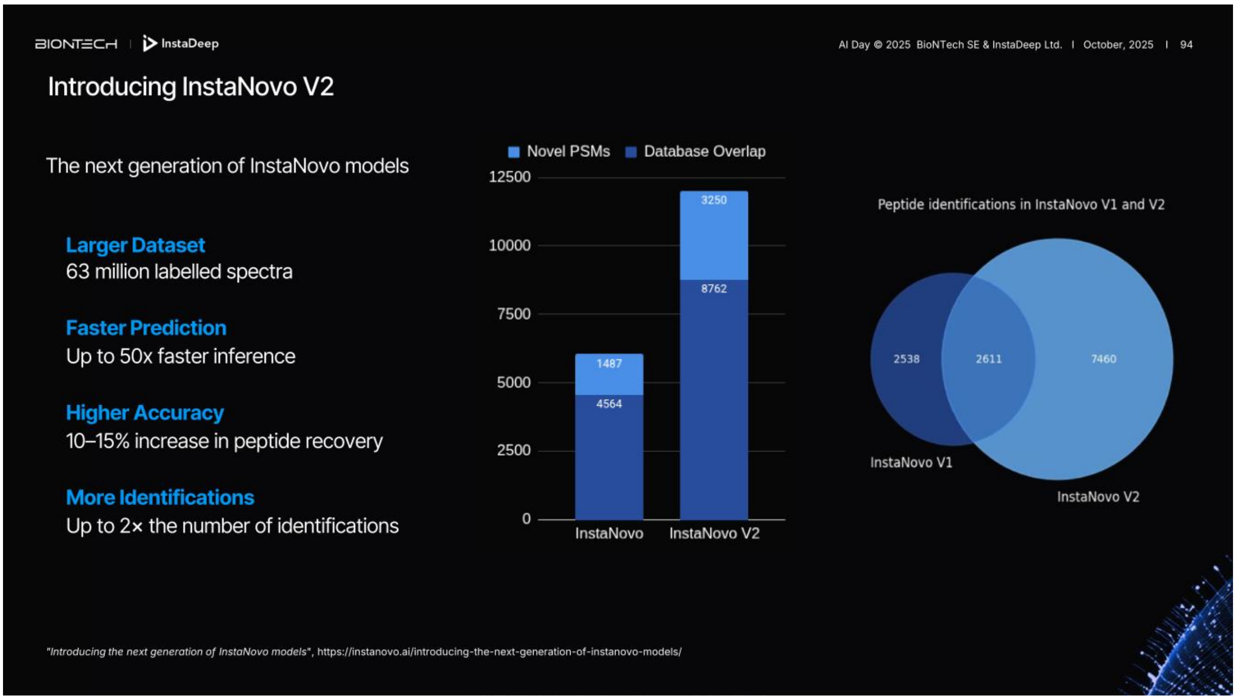
nature machine intelligence

Article

https://doi.org/10.1038/s42256-025-01019-5

InstaNovo enables diffusion-powered de novo peptide sequencing in large-scale proteomics experiments

Eloff, K., Kalogeropoulos, K., Mabona, A. et al. *InstaNovo enables diffusion-powered de novo peptide sequencing in large-scale proteomics experiments*. Nature Machine Intelligence 7, 565–579 (2025). https://doi.org/10.1038/s42256-025-01019-5



Introducing InstaNovo V2

The next generation of InstaNovo models

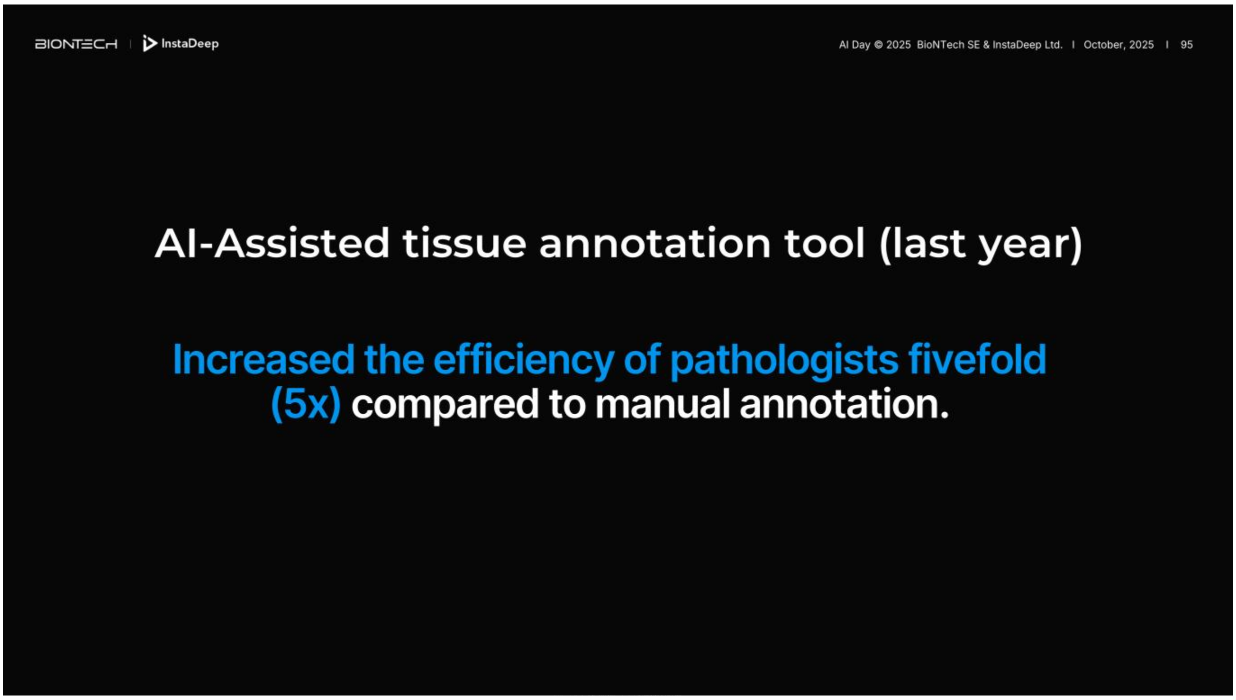
Larger Dataset
63 million labelled spectra

Faster Prediction
Up to 50x faster inference

Higher Accuracy
10–15% increase in peptide recovery

More Identifications
Up to 2× the number of identifications

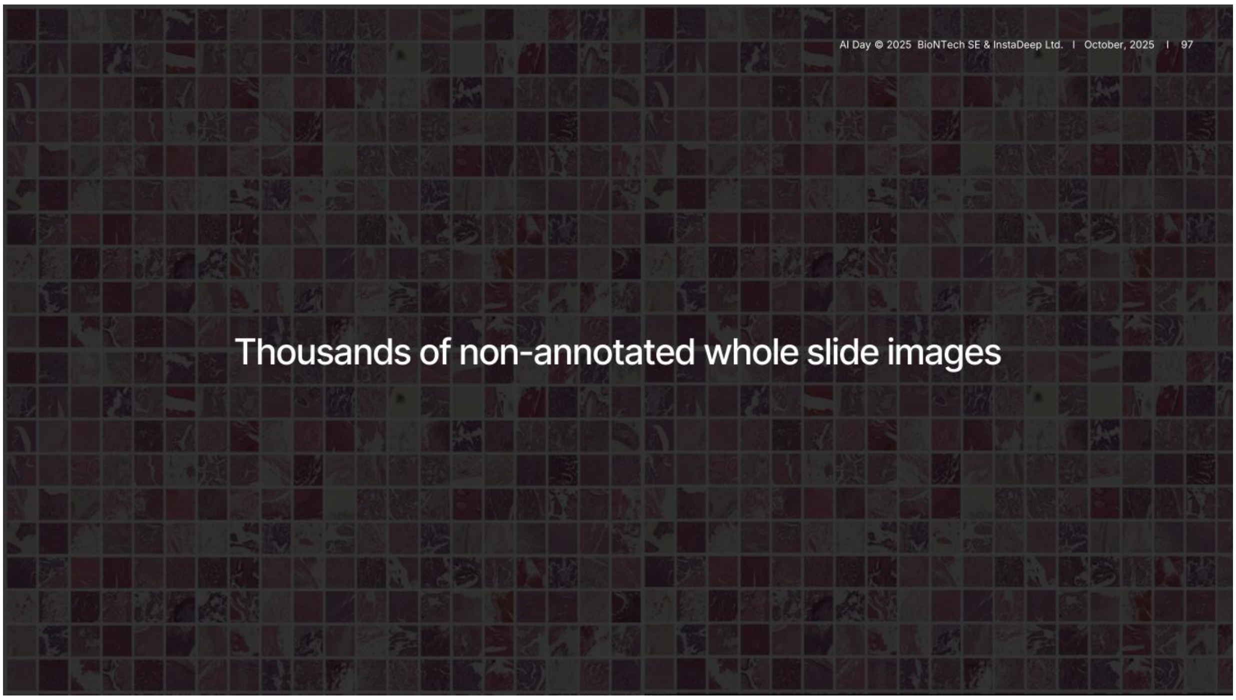
"*Introducing the next generation of InstaNovo models*", https://instanovo.ai/introducing-the-next-generation-of-instanovo-models/



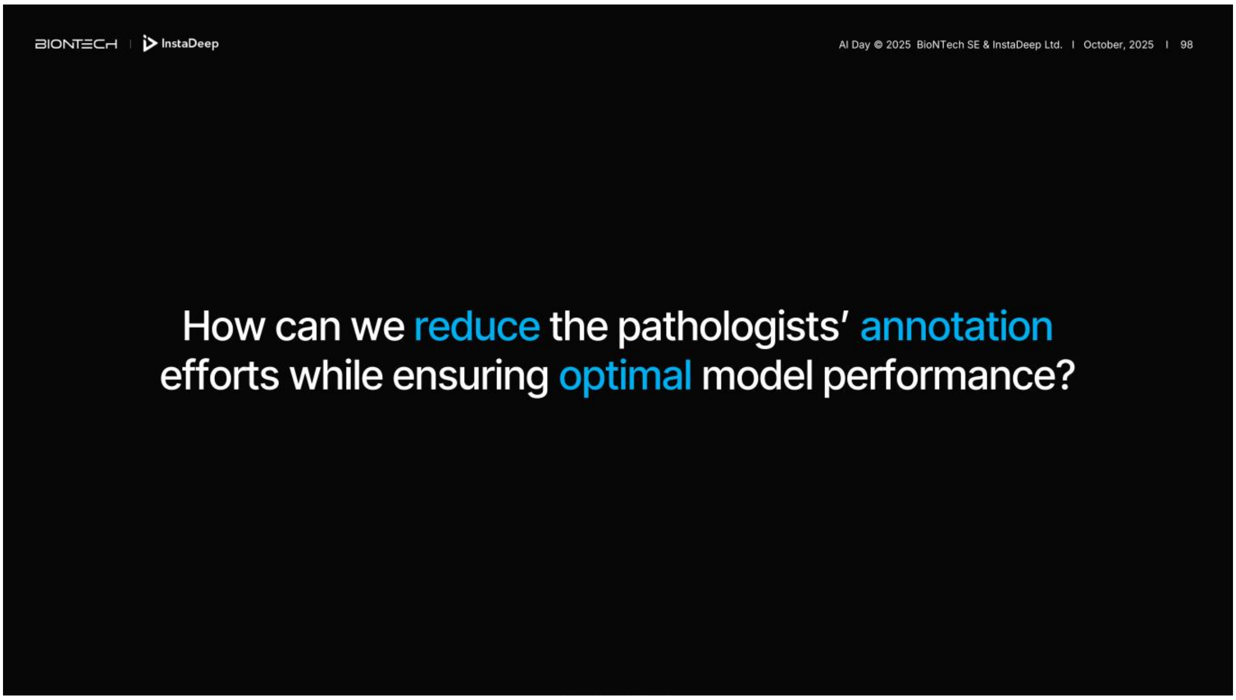
AI-Assisted tissue annotation tool (last year)

Increased the efficiency of pathologists fivefold (5x) compared to manual annotation.

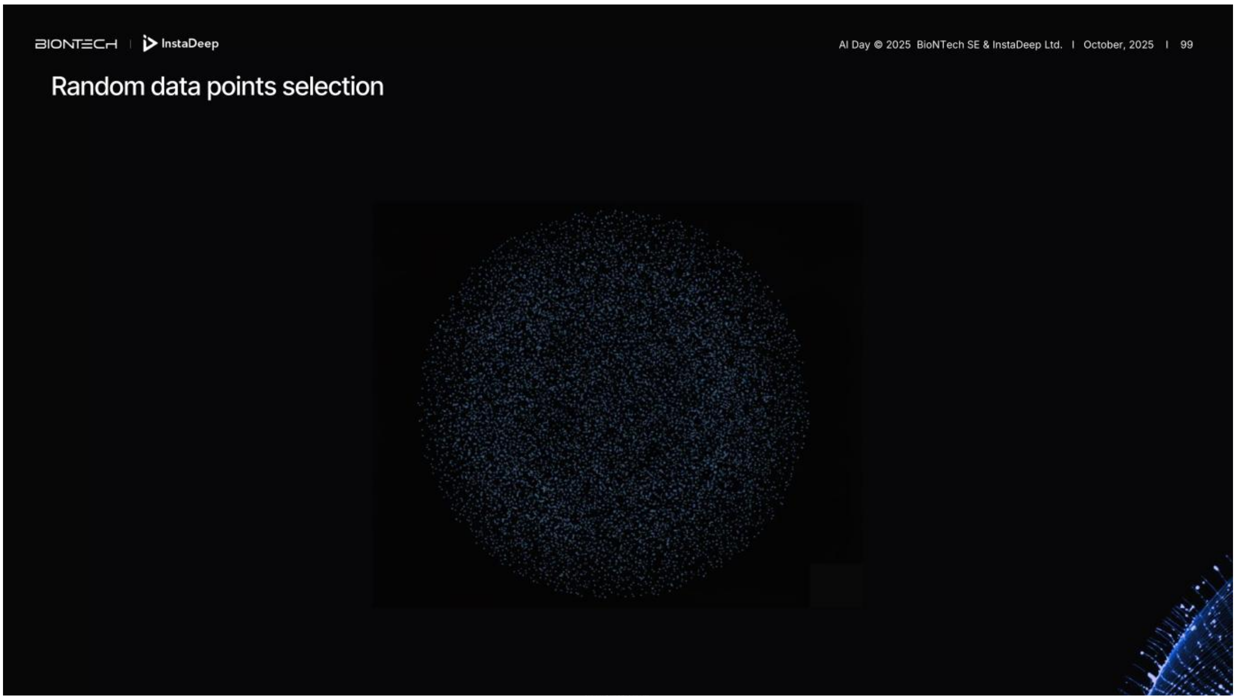
5× faster pathologists — but still not enough



Thousands of non-annotated whole slide images

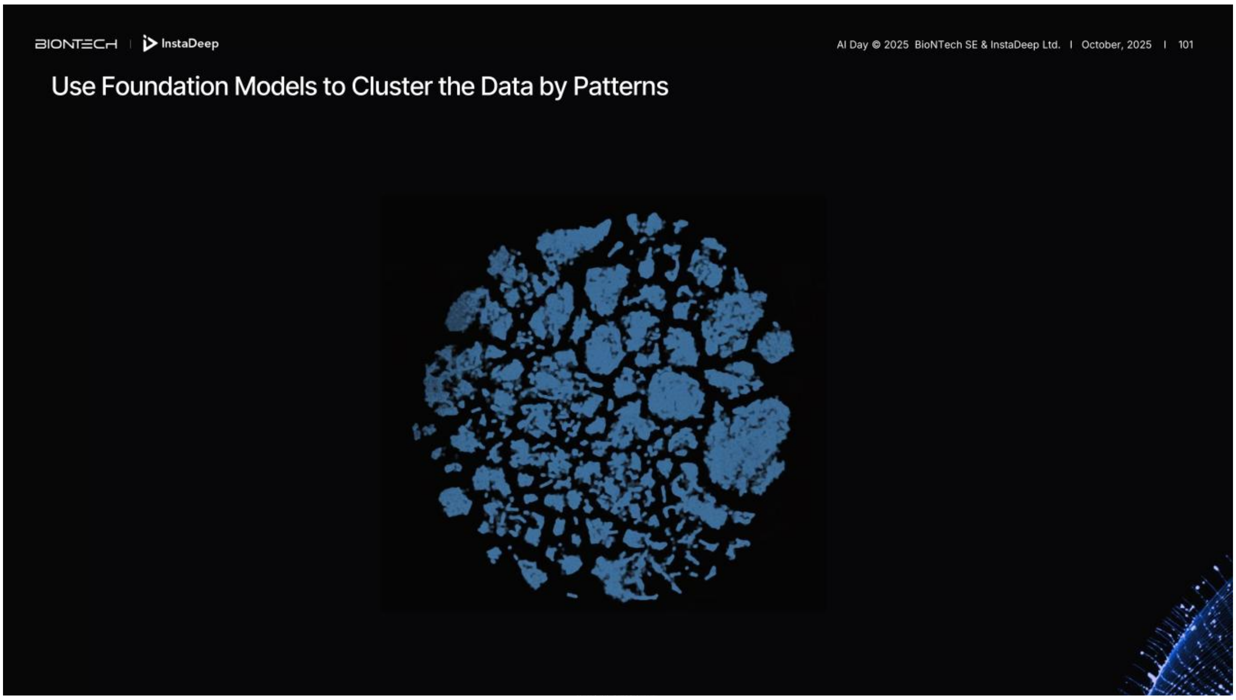


How can we reduce the pathologists’ annotation efforts while ensuring optimal model performance?

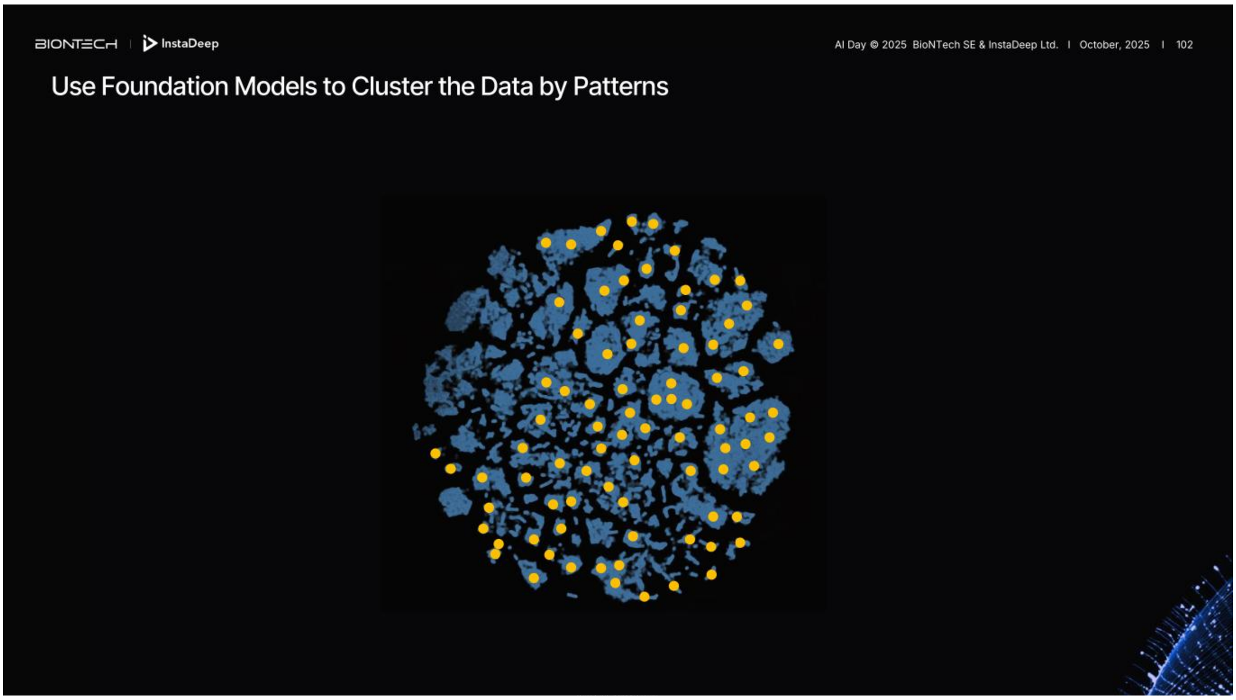


Random data points selection

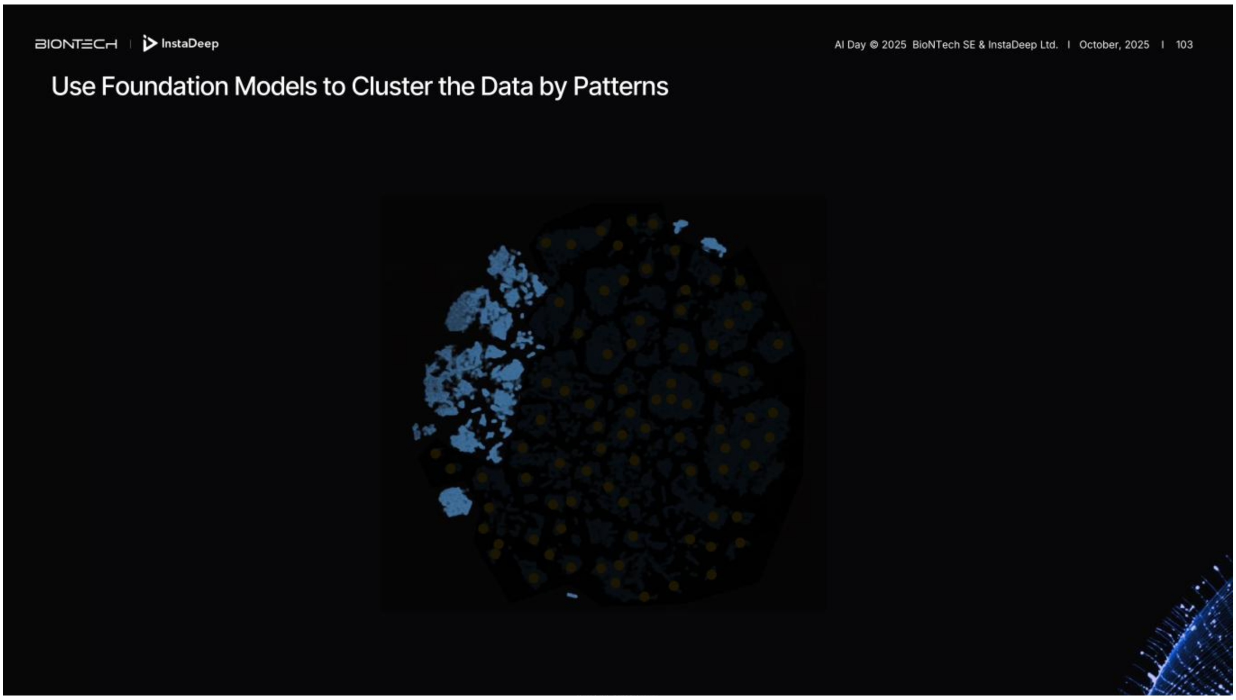
Random Data Points Selection



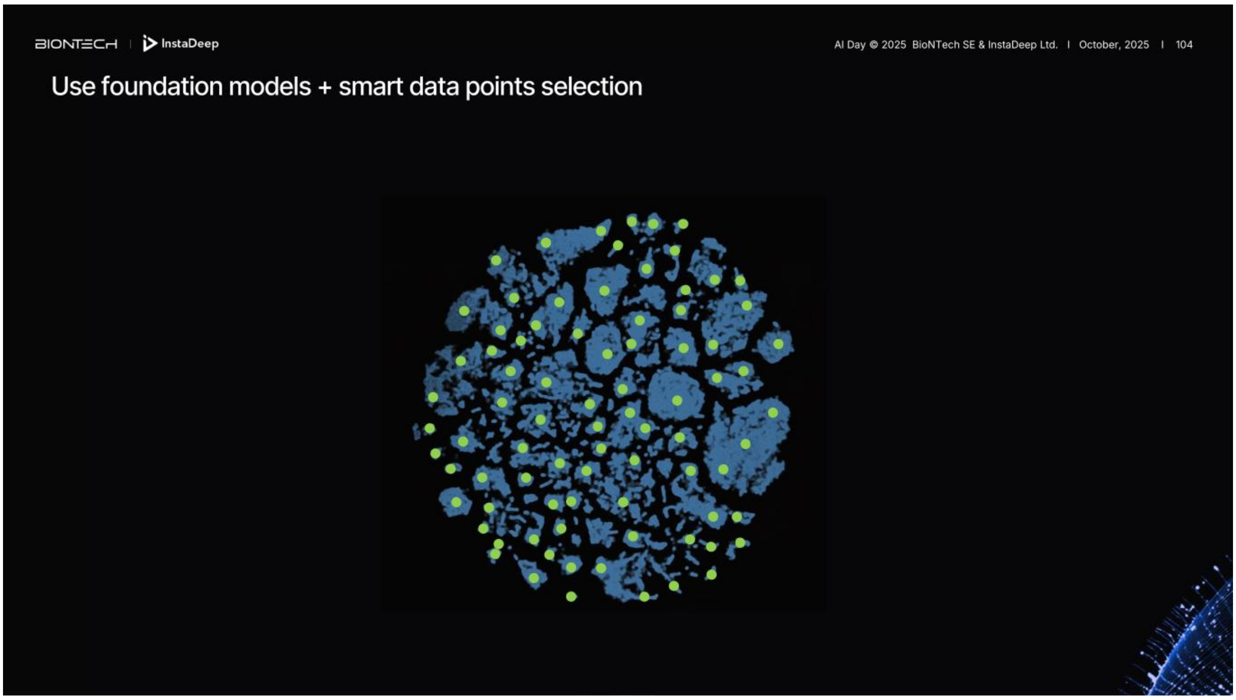
Use Foundation Models to Cluster the Data by Patterns



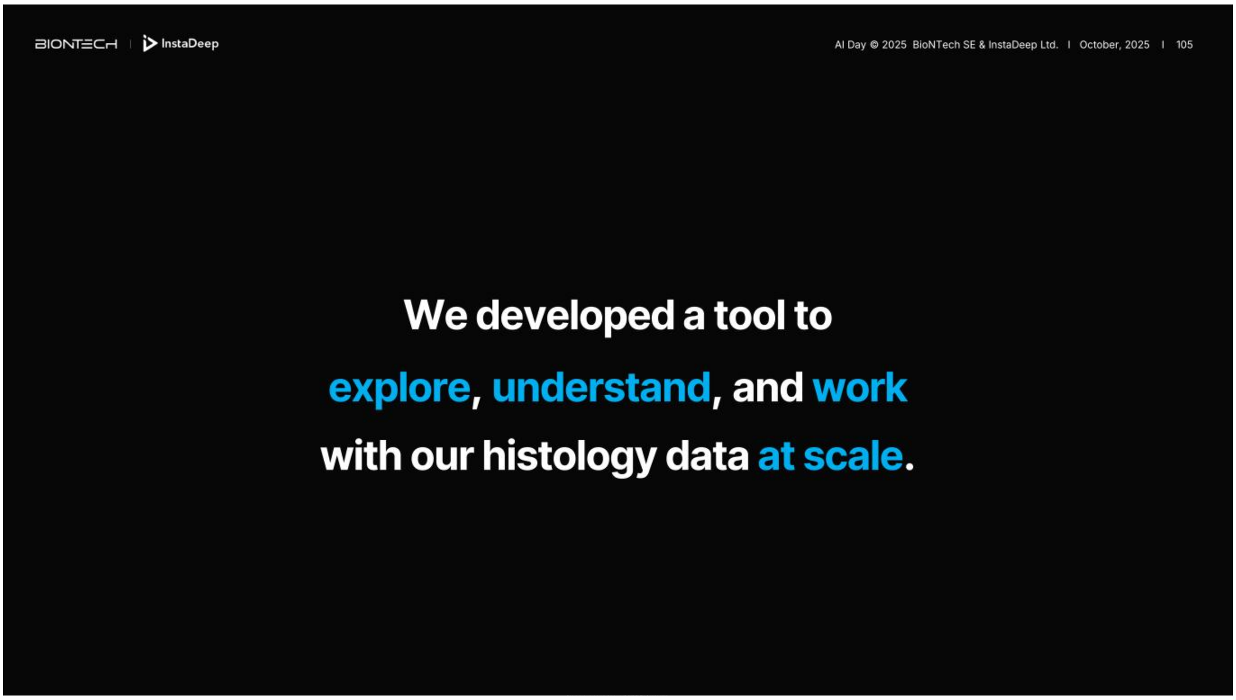
Use Foundation Models to Cluster the Data by Patterns



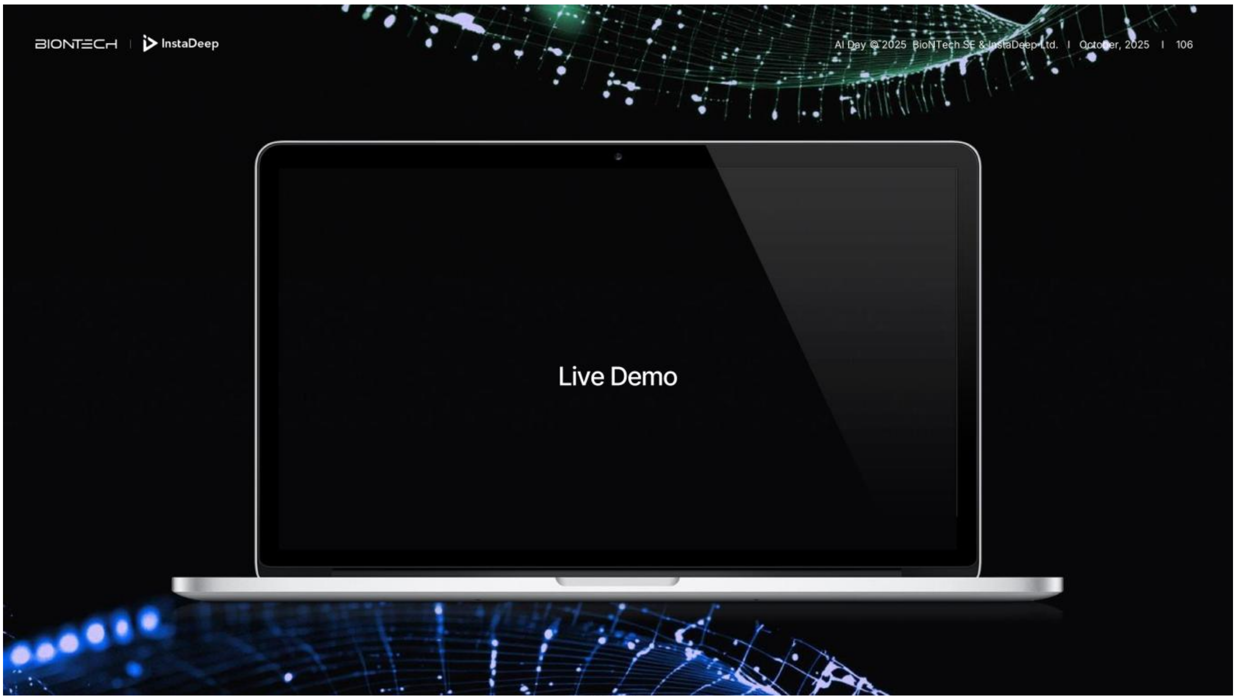
Use Foundation Models to Cluster the Data by Patterns



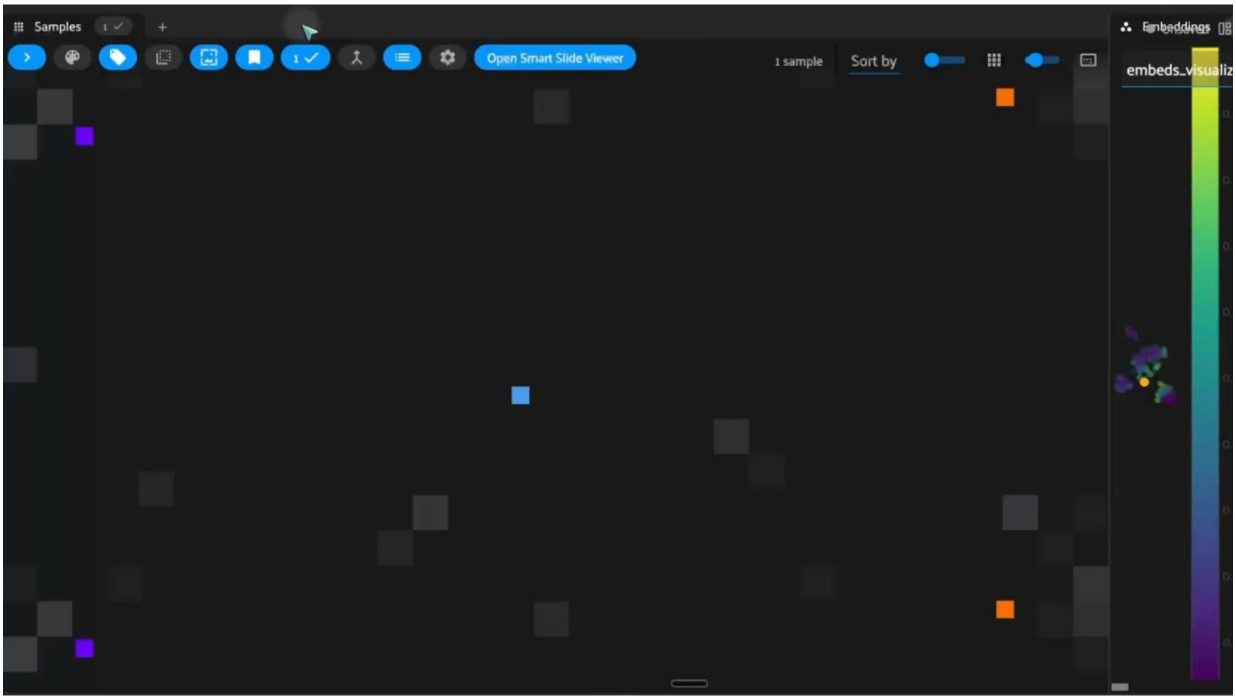
Use foundation models + smart data points selection

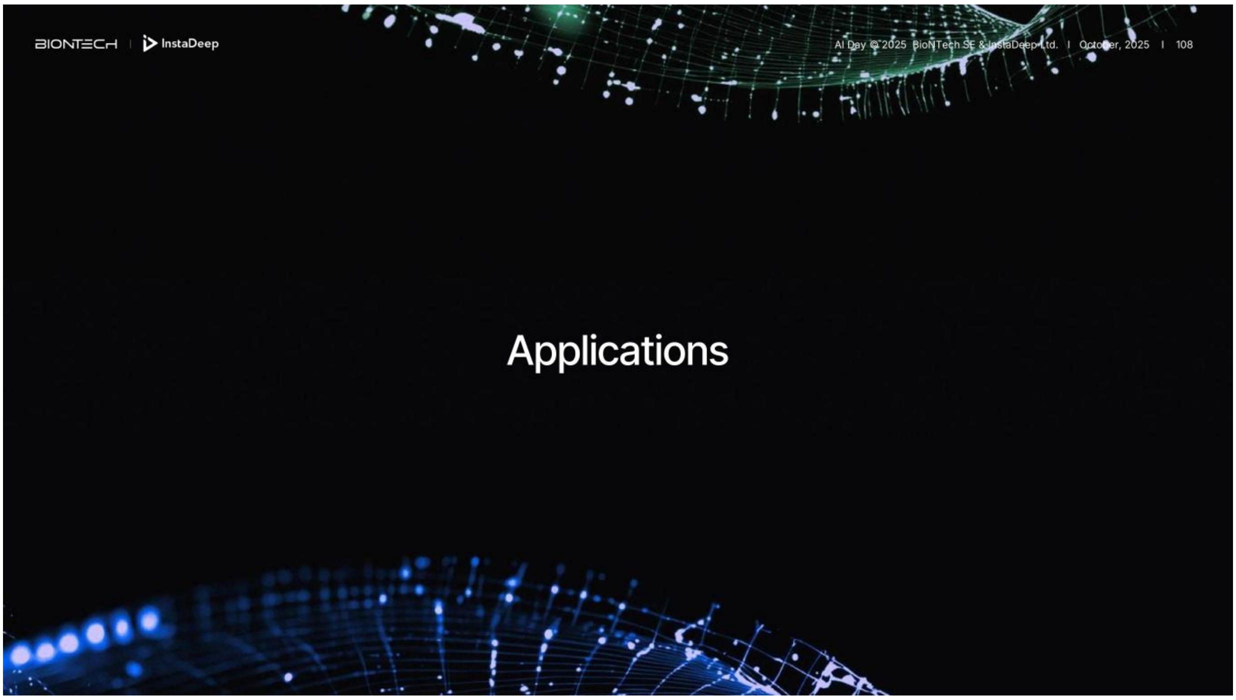


We developed a tool to
explore, understand, and work
with our histology data at scale.

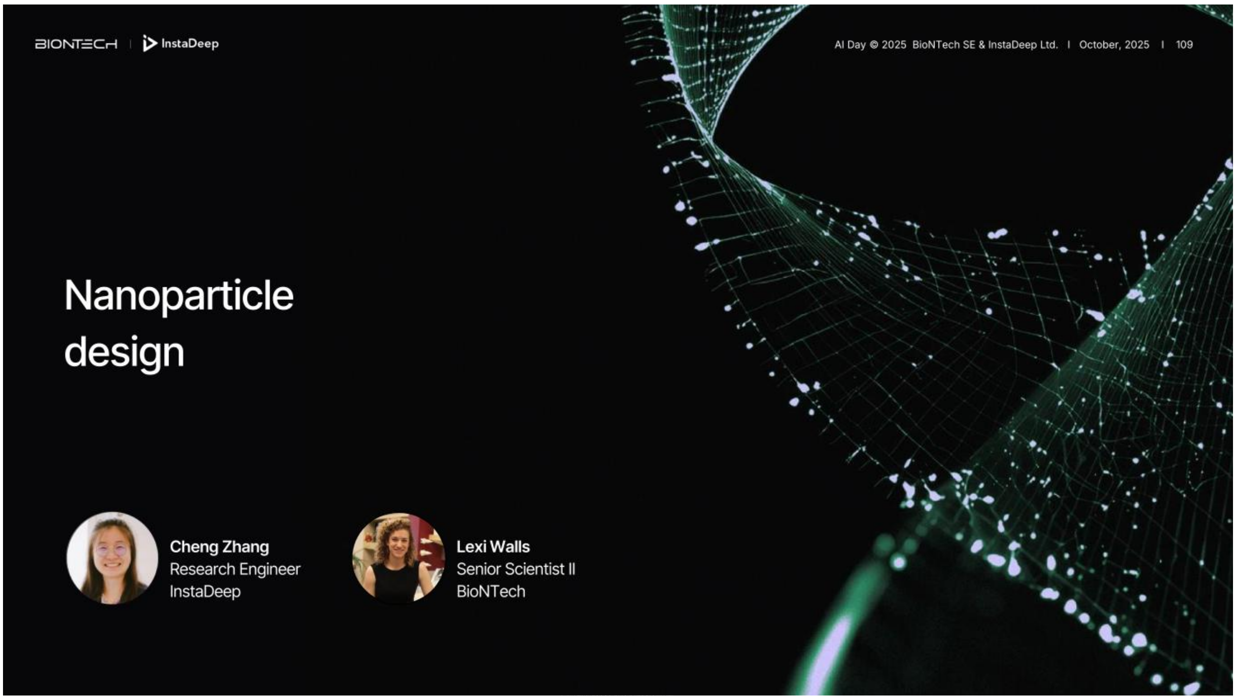


Live Demo


Samples
1 ✓
+
1 ✓
Open Smart Slide Viewer
1 sample
Sort by
Embeddings
embeds_visualiz



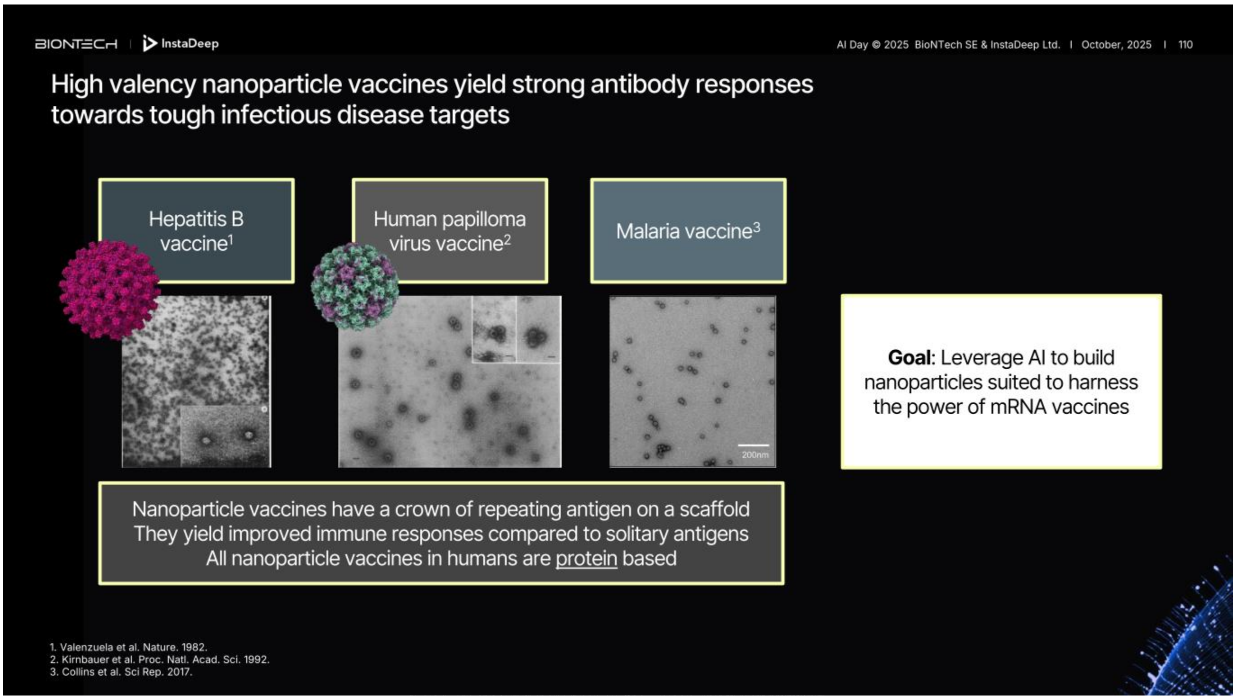
Applications



Nanoparticle design

Cheng Zhang
Research Engineer
InstaDeep

Lexi Walls
Senior Scientist II
BioNTech



High valency nanoparticle vaccines yield strong antibody responses towards tough infectious disease targets

Hepatitis B vaccine[1]

Human papilloma virus vaccine[2]

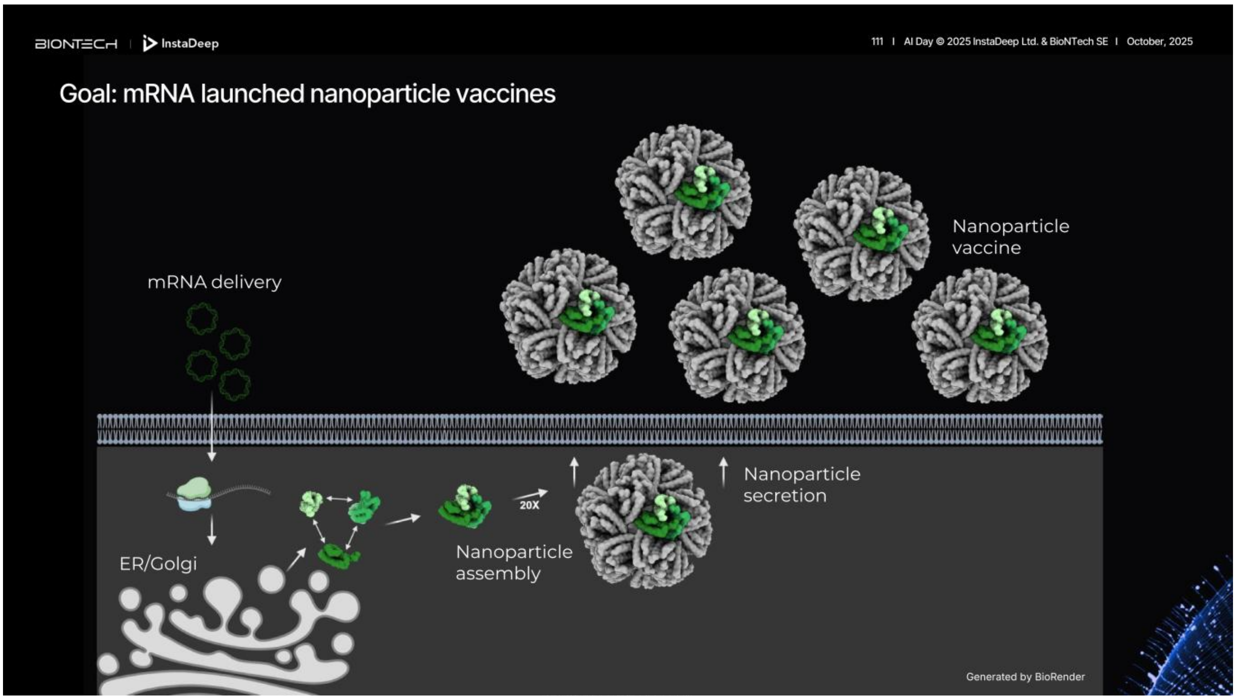
Malaria vaccine[3]

Nanoparticle vaccines have a crown of repeating antigen on a scaffold
They yield improved immune responses compared to solitary antigens
All nanoparticle vaccines in humans are protein based

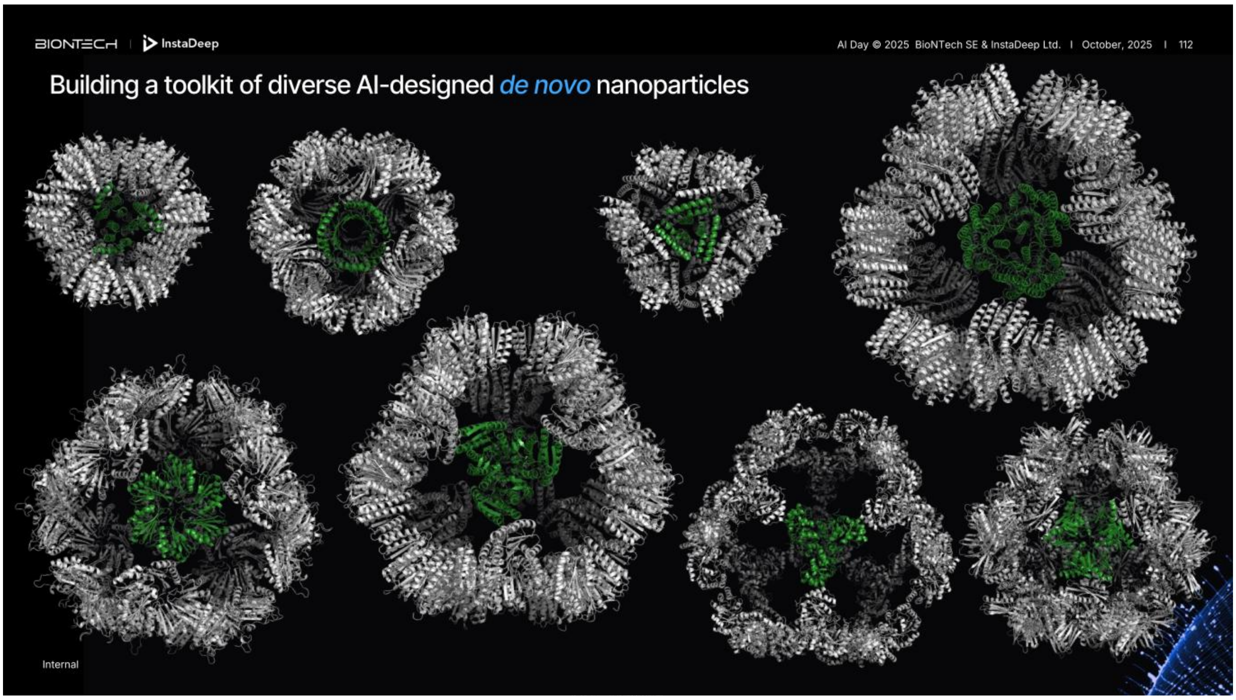
Goal: Leverage AI to build nanoparticles suited to harness the power of mRNA vaccines

1. Valenzuela et al. Nature. 1982.
2. Kirnbauer et al. Proc. Natl. Acad. Sci. 1992.
3. Collins et al. Sci Rep. 2017.

Goal: mRNA launched nanoparticle vaccines

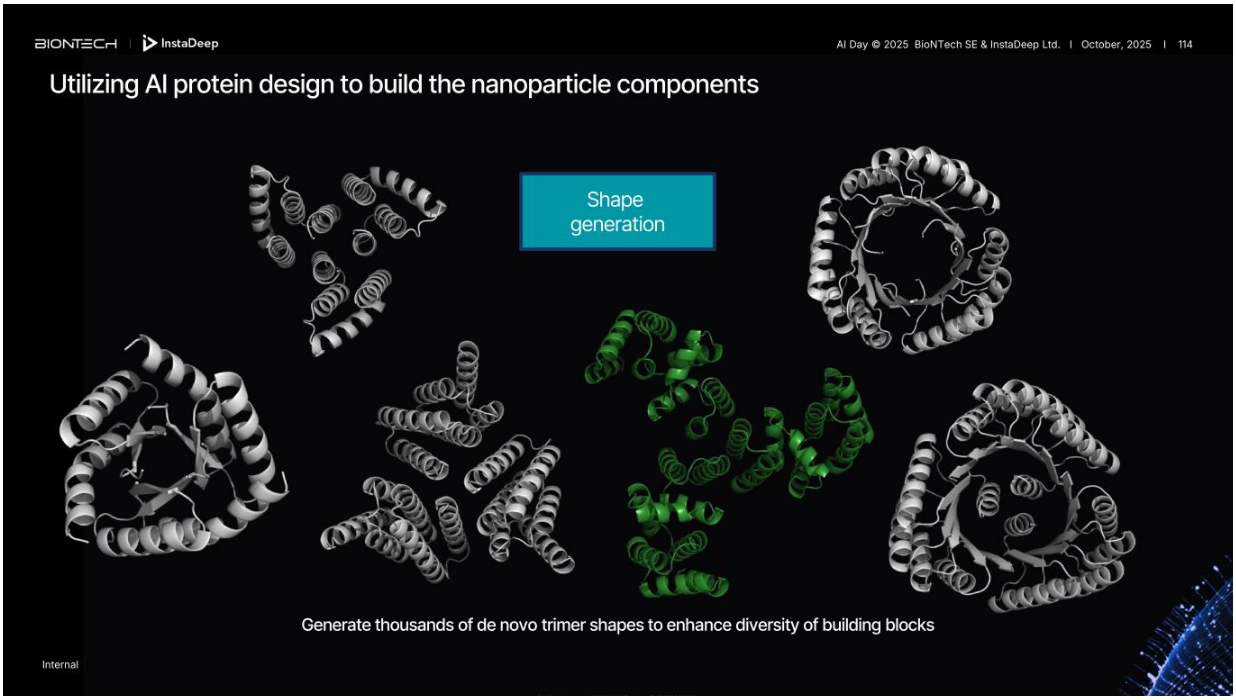


Generated by BioRender



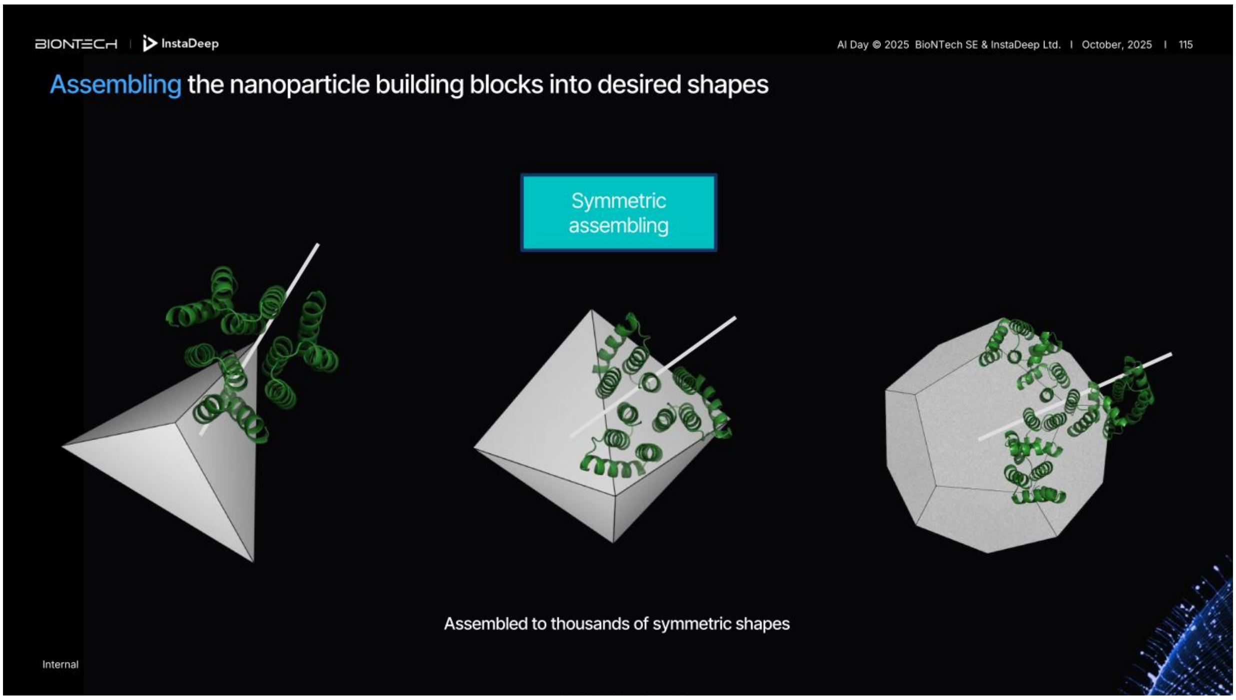
Building a toolkit of diverse AI-designed *de novo* nanoparticles

Building a nanoparticle piece by piece



Utilizing AI protein design to build the nanoparticle components

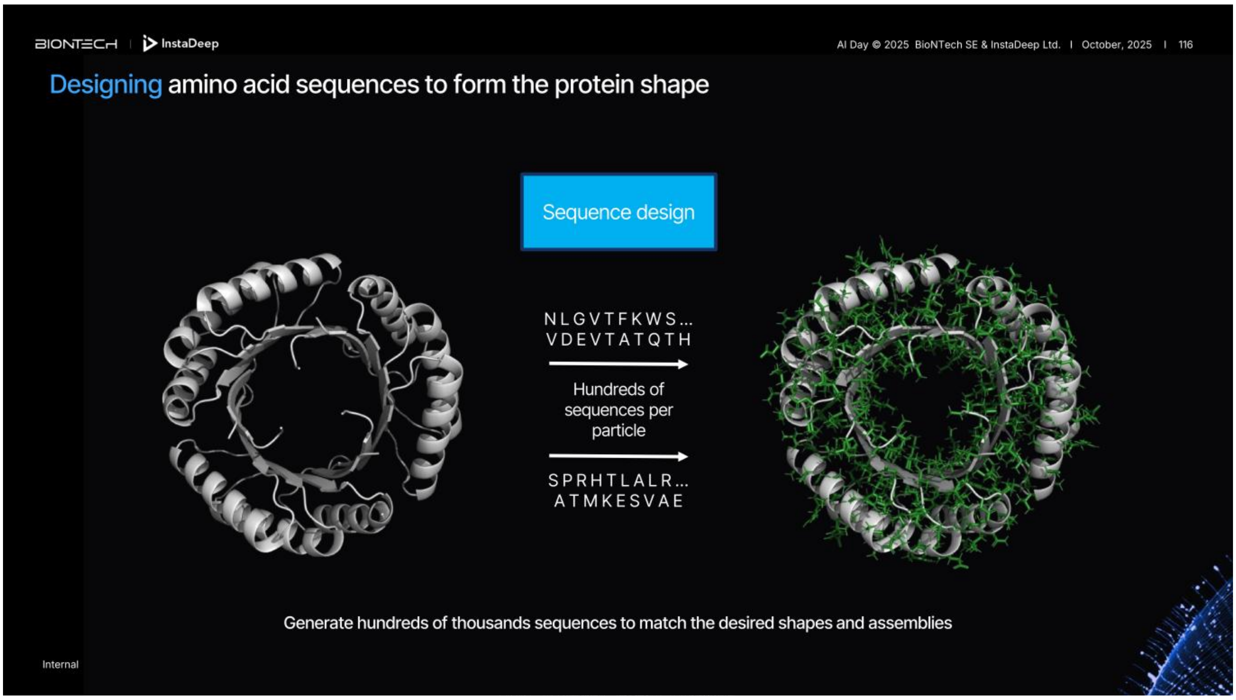
Generate thousands of de novo trimer shapes to enhance diversity of building blocks



Assembling the nanoparticle building blocks into desired shapes

Symmetric assembling

Assembled to thousands of symmetric shapes



Designing amino acid sequences to form the protein shape

Sequence design

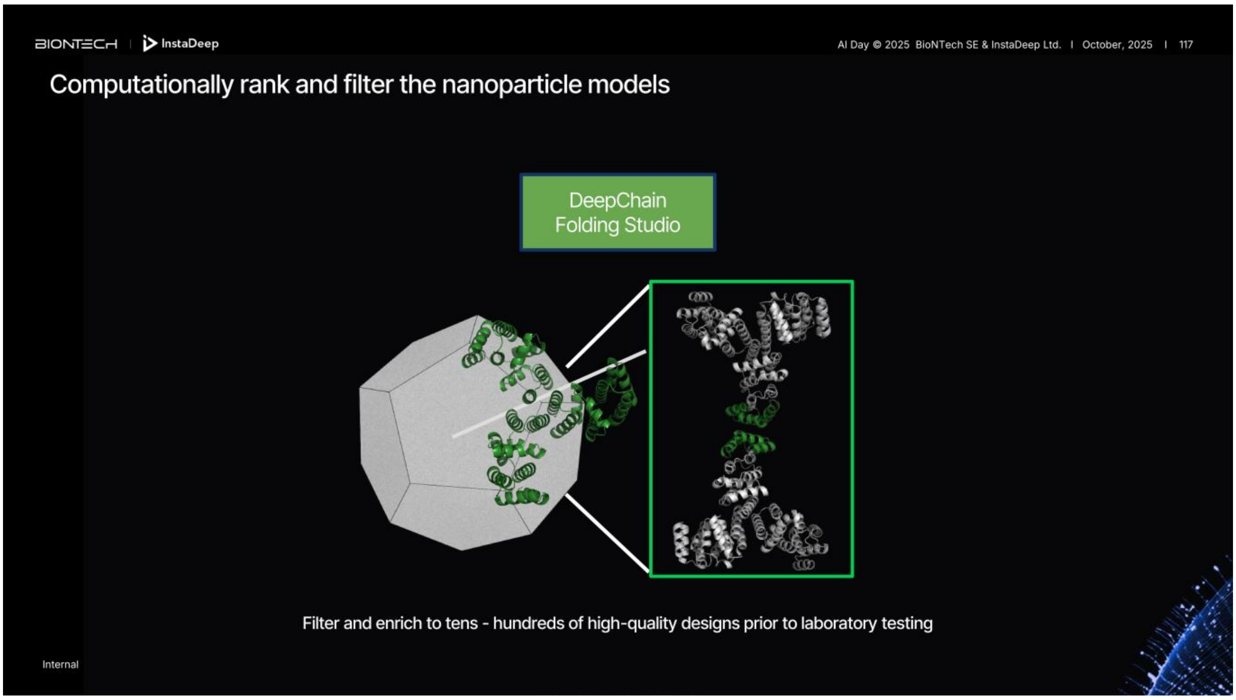
NLGVTFKWS…
VDEVTATQTH

Hundreds of sequences per particle

SPRHTLALR…
ATMKESVAE

Generate hundreds of thousands sequences to match the desired shapes and assemblies

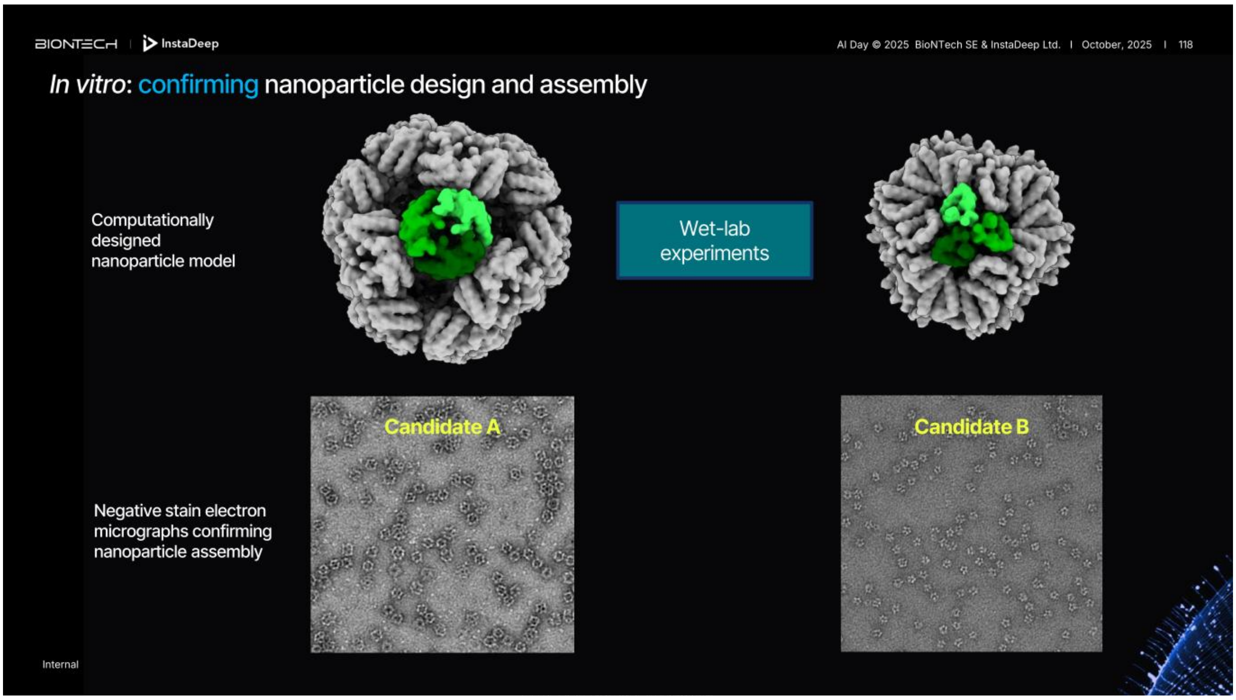
Internal



Computationally rank and filter the nanoparticle models

DeepChain
Folding Studio

Filter and enrich to tens - hundreds of high-quality designs prior to laboratory testing



In vitro: confirming nanoparticle design and assembly

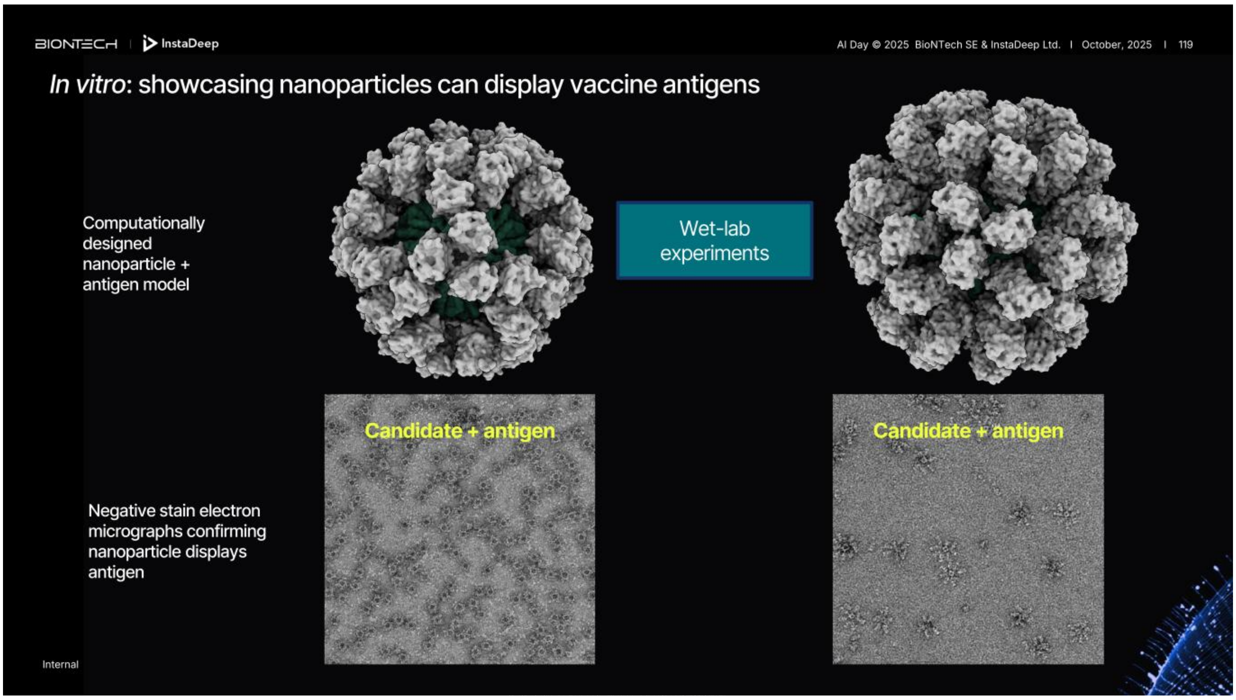
Computationally designed nanoparticle model

Wet-lab experiments

Negative stain electron micrographs confirming nanoparticle assembly

Candidate A

Candidate B

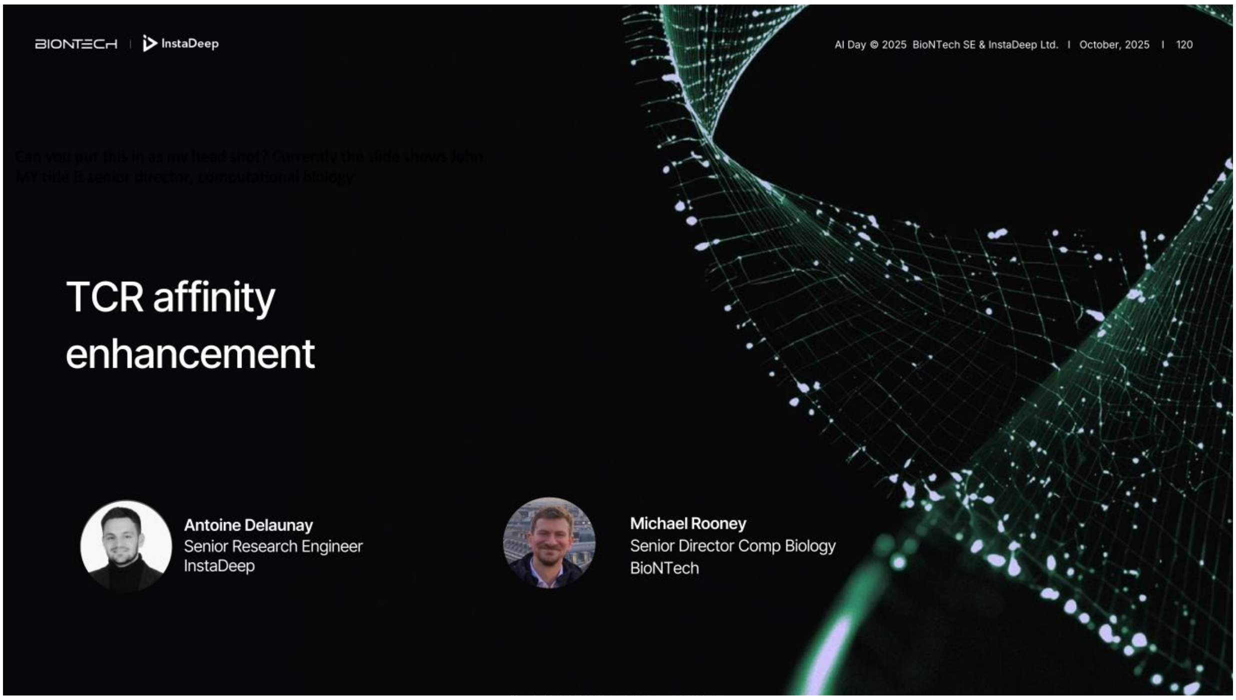


In vitro: showcasing nanoparticles can display vaccine antigens

Computationally designed nanoparticle + antigen model

Wet-lab experiments

Negative stain electron micrographs confirming nanoparticle displays antigen

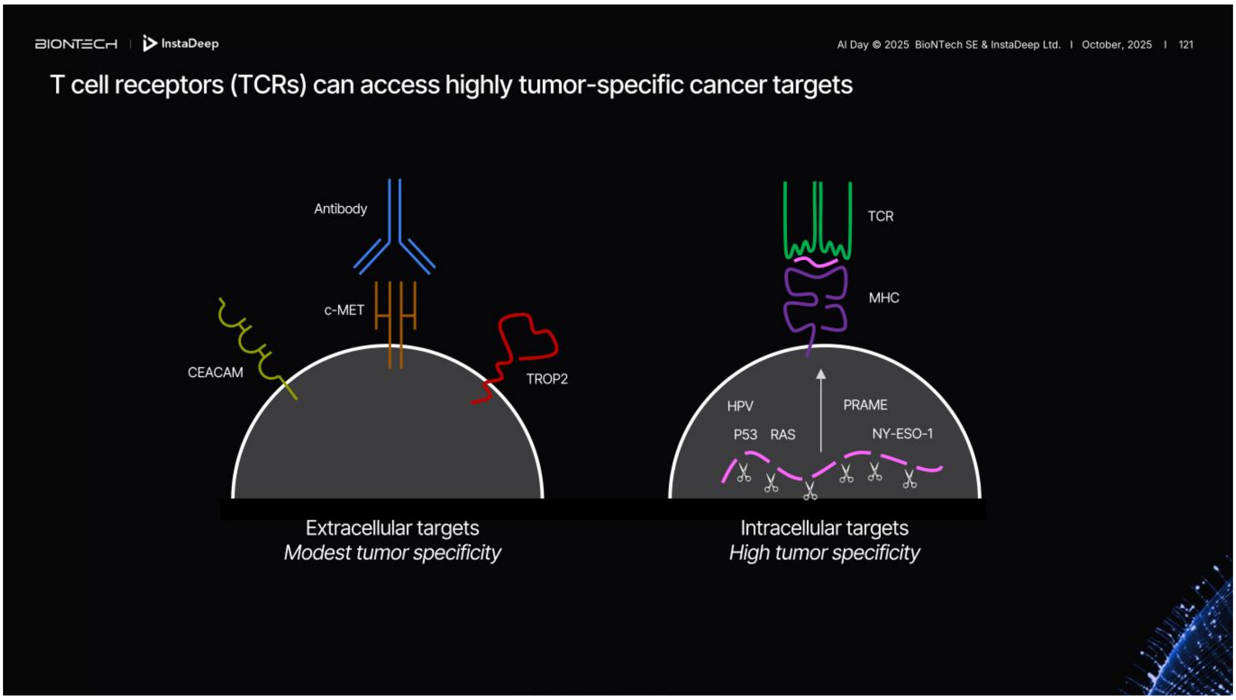


Can you put this in as my head shot? Currently the slide shows John.
MY title is senior director, computational biology

TCR affinity enhancement

Antoine Delaunay
Senior Research Engineer
InstaDeep

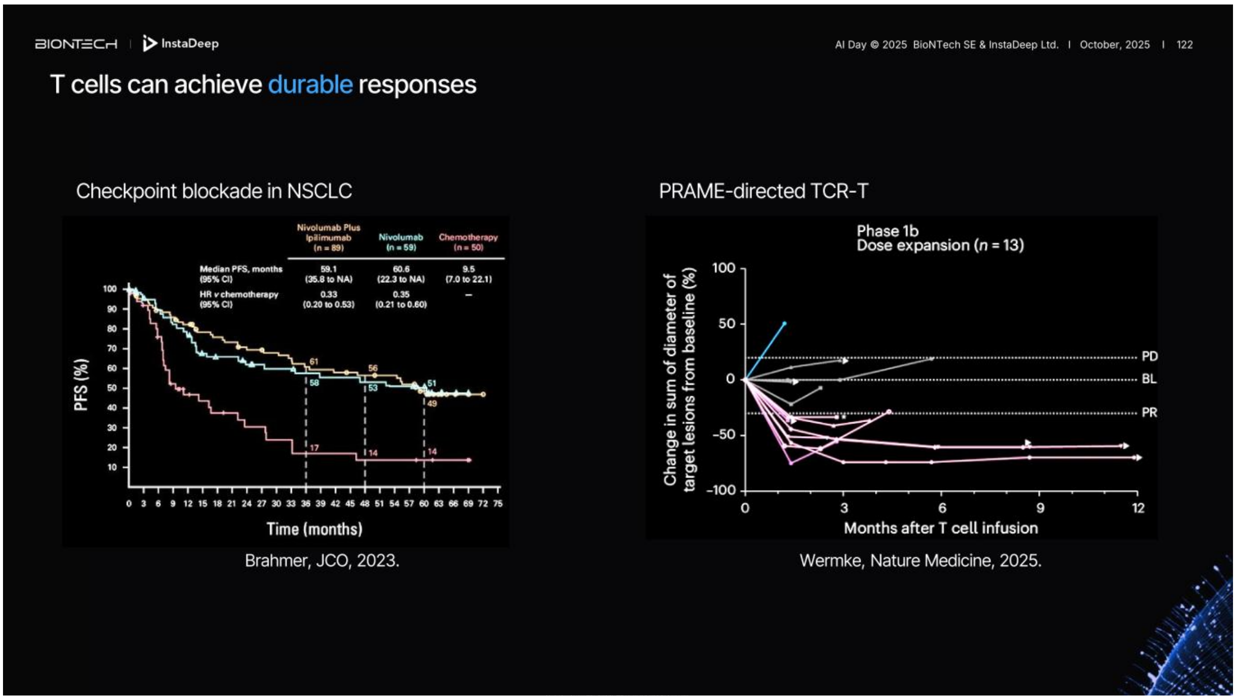
Michael Rooney
Senior Director Comp Biology
BioNTech



T cell receptors (TCRs) can access highly tumor-specific cancer targets

Extracellular targets
Modest tumor specificity

Intracellular targets
High tumor specificity



T cells can achieve durable responses

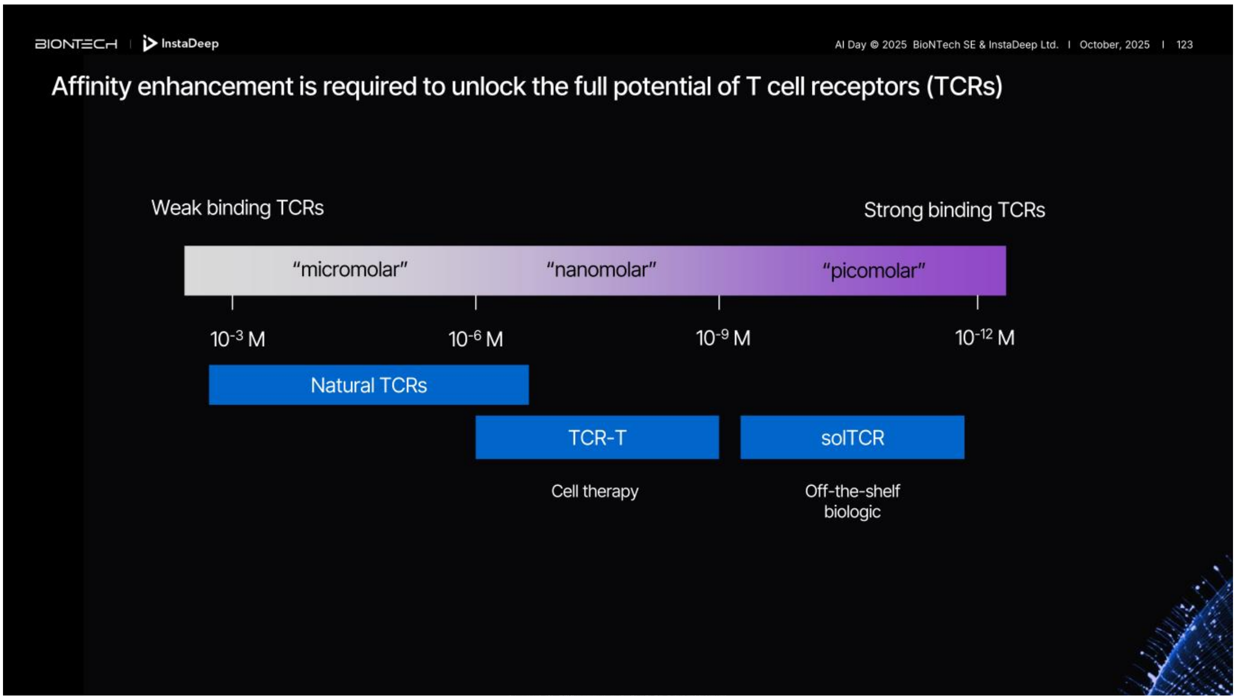
Checkpoint blockade in NSCLC

	Nivolumab Plus Ipilimumab (n = 89)	Nivolumab (n = 59)	Chemotherapy (n = 50)
Median PFS, months (95% CI)	59.1 (35.8 to NA)	60.6 (22.3 to NA)	9.5 (7.0 to 22.1)
HR v chemotherapy (95% CI)	0.33 (0.20 to 0.53)	0.35 (0.21 to 0.60)	–

Brahmer, JCO, 2023.

PRAME-directed TCR-T

Wermke, Nature Medicine, 2025.



Affinity enhancement is required to unlock the full potential of T cell receptors (TCRs)

Weak binding TCRs

Strong binding TCRs

"micromolar" "nanomolar" "picomolar"

10^{-3} M 10^{-6} M 10^{-9} M 10^{-12} M

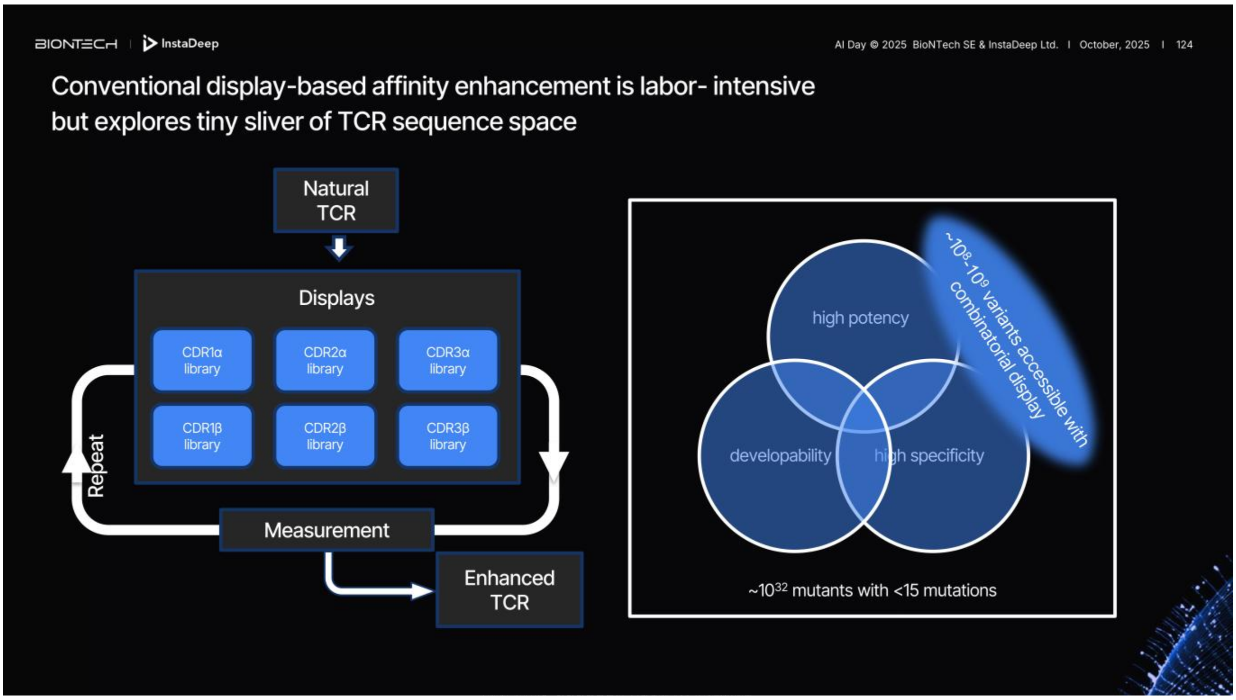
Natural TCRs

TCR-T

Cell therapy

solTCR

Off-the-shelf
biologic



Conventional display-based affinity enhancement is labor- intensive but explores tiny sliver of TCR sequence space

Natural TCR

Displays

CDR1α library

CDR2α library

CDR3α library

CDR1β library

CDR2β library

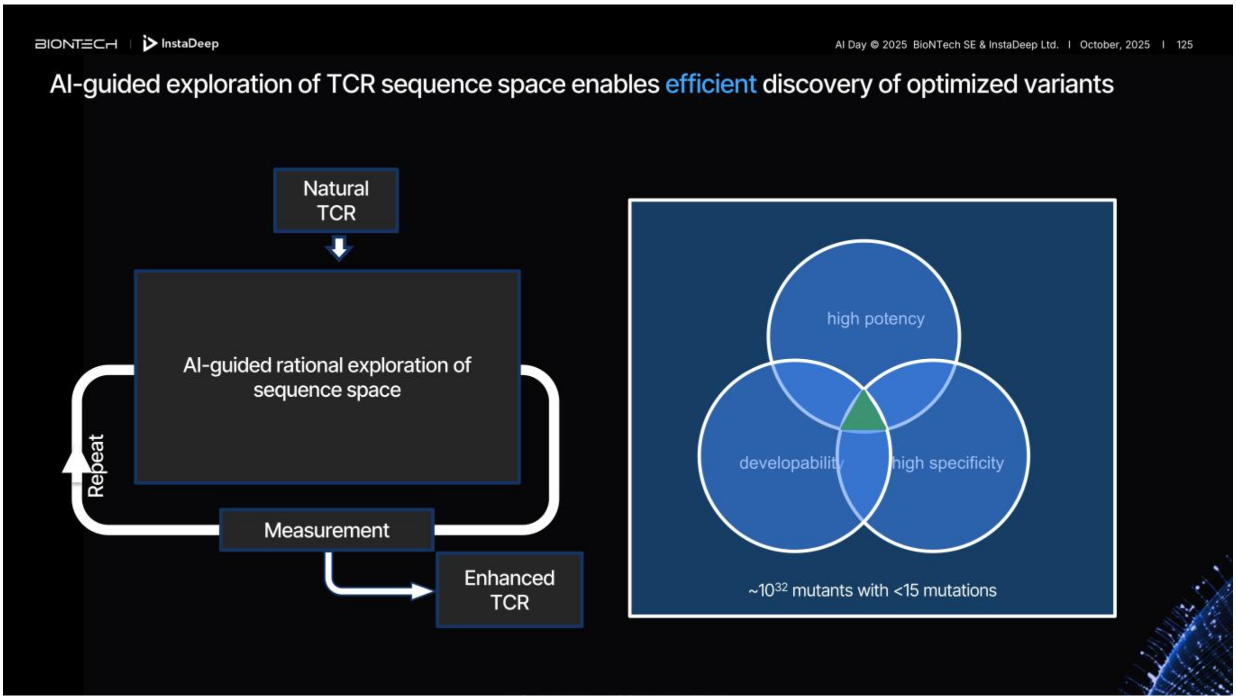
CDR3β library

Repeat

Measurement

Enhanced TCR

~10^{32} mutants with <15 mutations



AI-guided exploration of TCR sequence space enables efficient discovery of optimized variants

Natural TCR

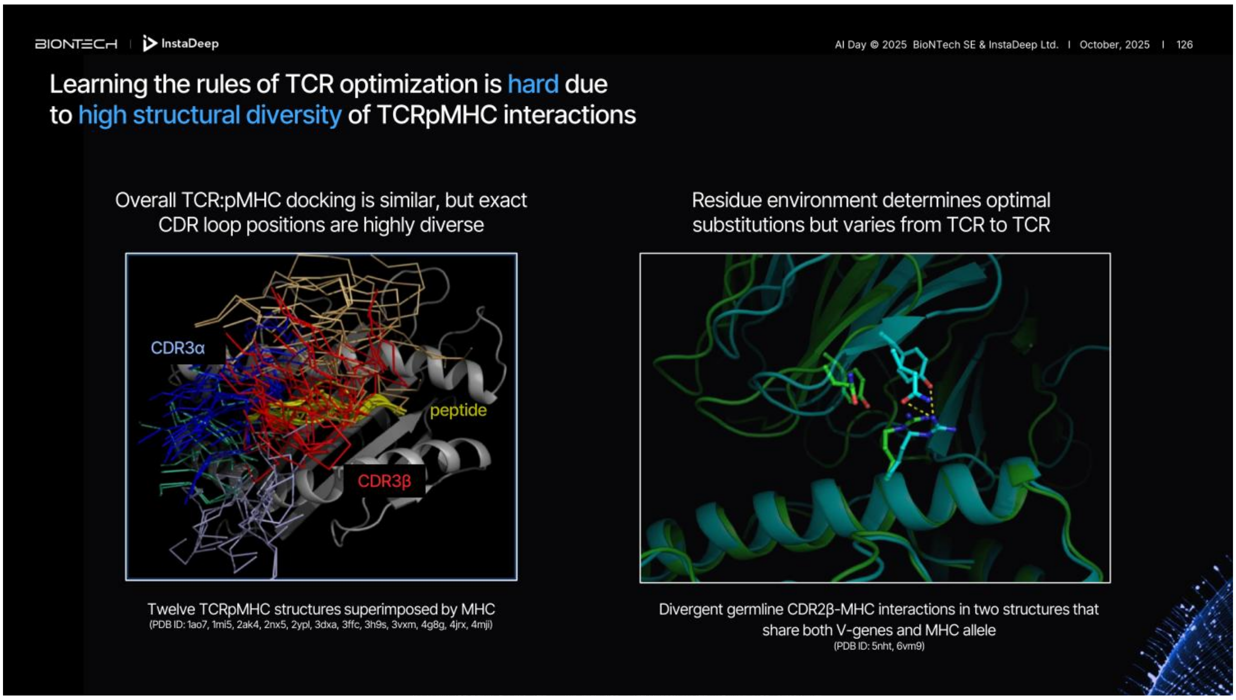
AI-guided rational exploration of sequence space

Repeat

Measurement

Enhanced TCR

~10^{32} mutants with <15 mutations



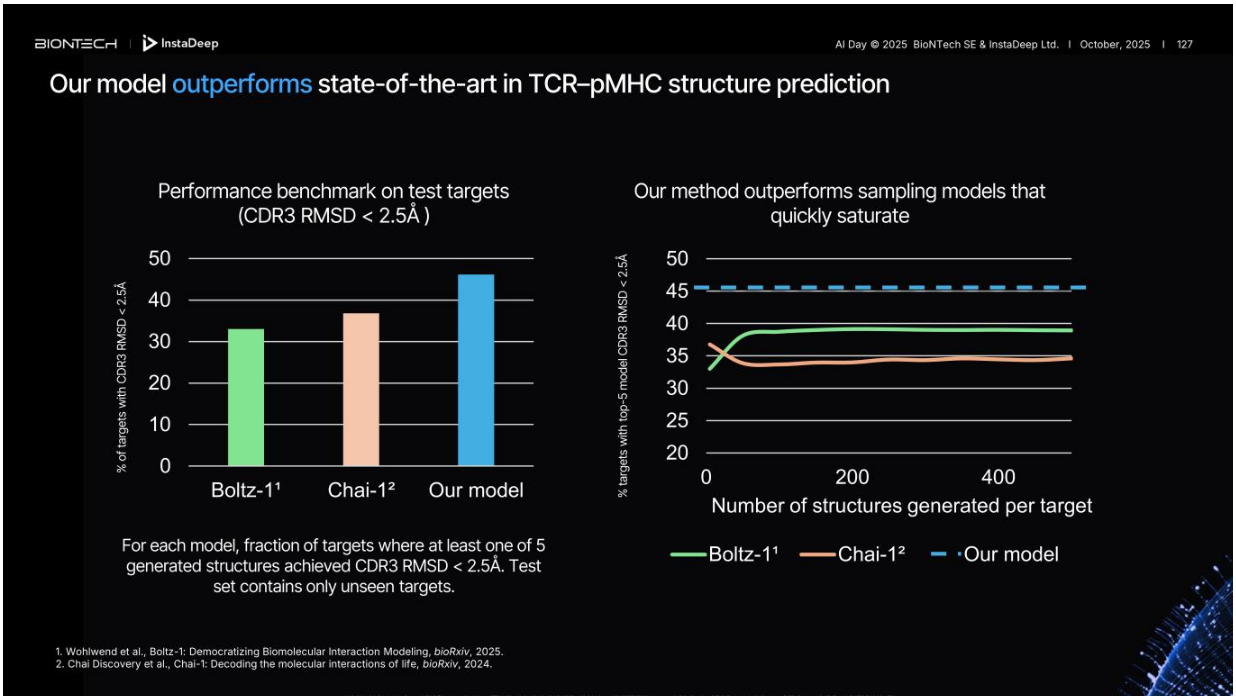
Learning the rules of TCR optimization is hard due to high structural diversity of TCRpMHC interactions

Overall TCR:pMHC docking is similar, but exact CDR loop positions are highly diverse

Twelve TCRpMHC structures superimposed by MHC
(PDB ID: 1ao7, 1mi5, 2ak4, 2nx5, 2ypl, 3dxa, 3ffc, 3h9s, 3vxm, 4g8g, 4jrx, 4mji)

Residue environment determines optimal substitutions but varies from TCR to TCR

Divergent germline CDR2β-MHC interactions in two structures that share both V-genes and MHC allele
(PDB ID: 5nht, 6vm9)



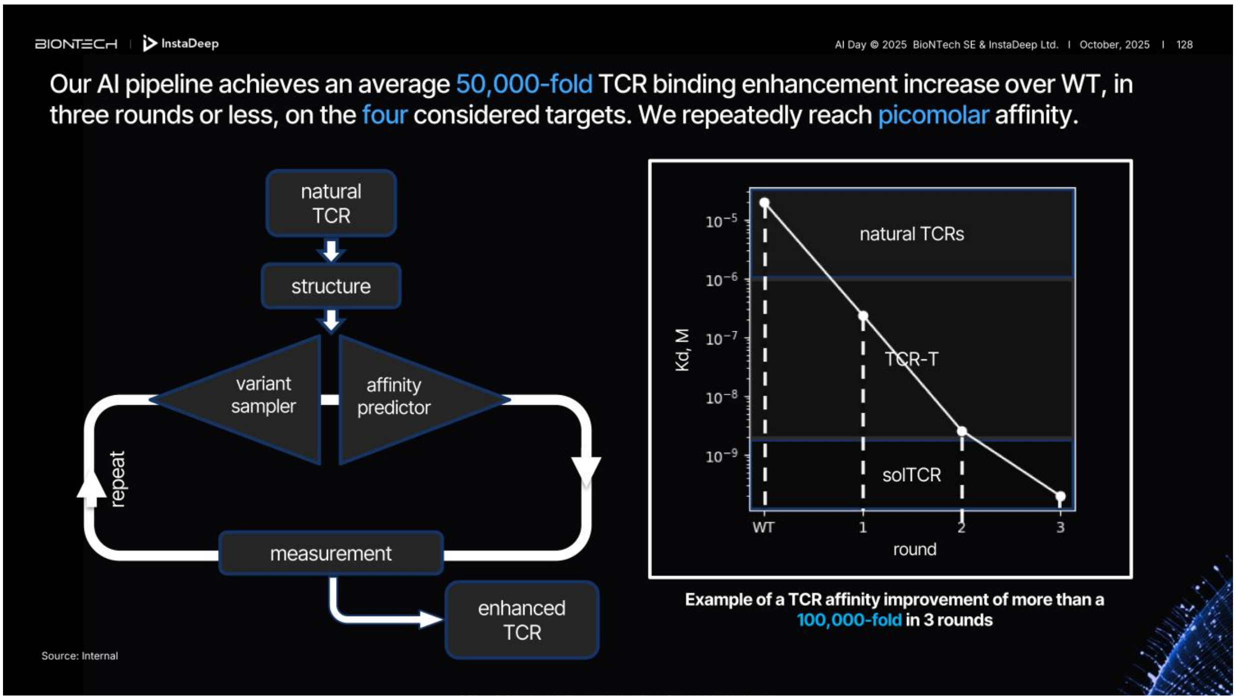
Our model outperforms state-of-the-art in TCR–pMHC structure prediction

Performance benchmark on test targets (CDR3 RMSD < 2.5Å)

For each model, fraction of targets where at least one of 5 generated structures achieved CDR3 RMSD < 2.5Å. Test set contains only unseen targets.

Our method outperforms sampling models that quickly saturate

1. Wohlwend et al., Boltz-1: Democratizing Biomolecular Interaction Modeling, *bioRxiv*, 2025.
2. Chai Discovery et al., Chai-1: Decoding the molecular interactions of life, *bioRxiv*, 2024.

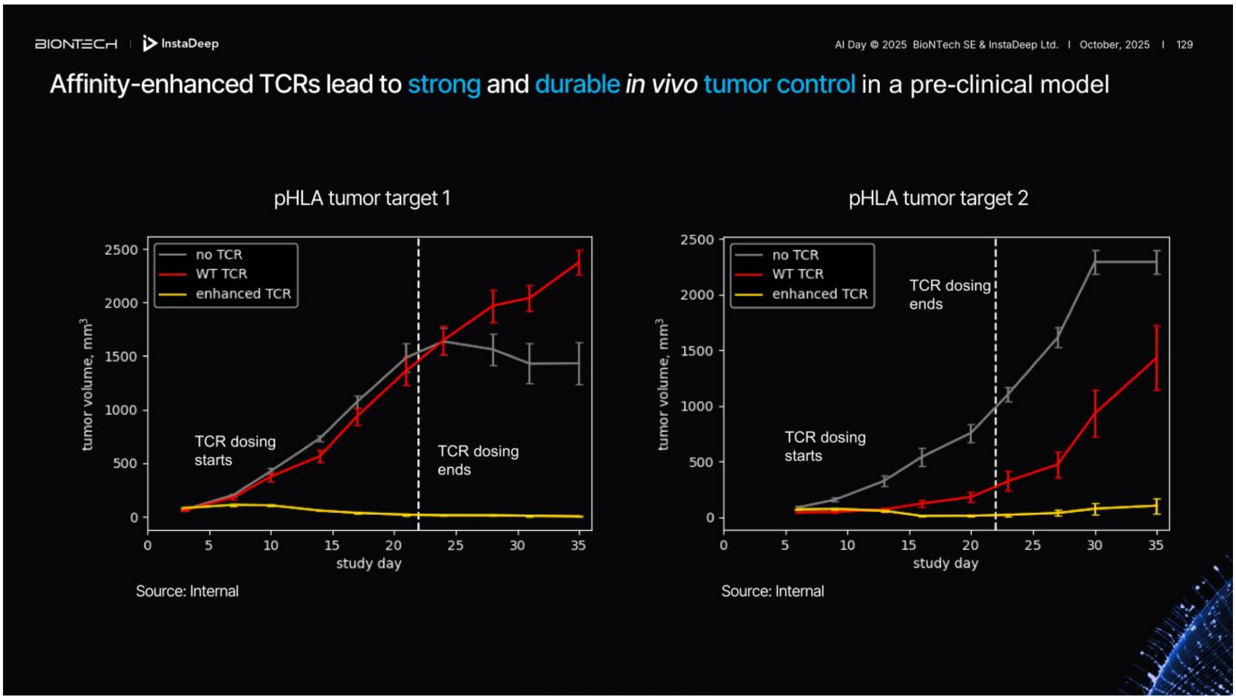


Our AI pipeline achieves an average 50,000-fold TCR binding enhancement increase over WT, in three rounds or less, on the four considered targets. We repeatedly reach picomolar affinity.

natural TCR
structure
variant sampler
affinity predictor
measurement
repeat
enhanced TCR

Example of a TCR affinity improvement of more than a 100,000-fold in 3 rounds

Source: Internal



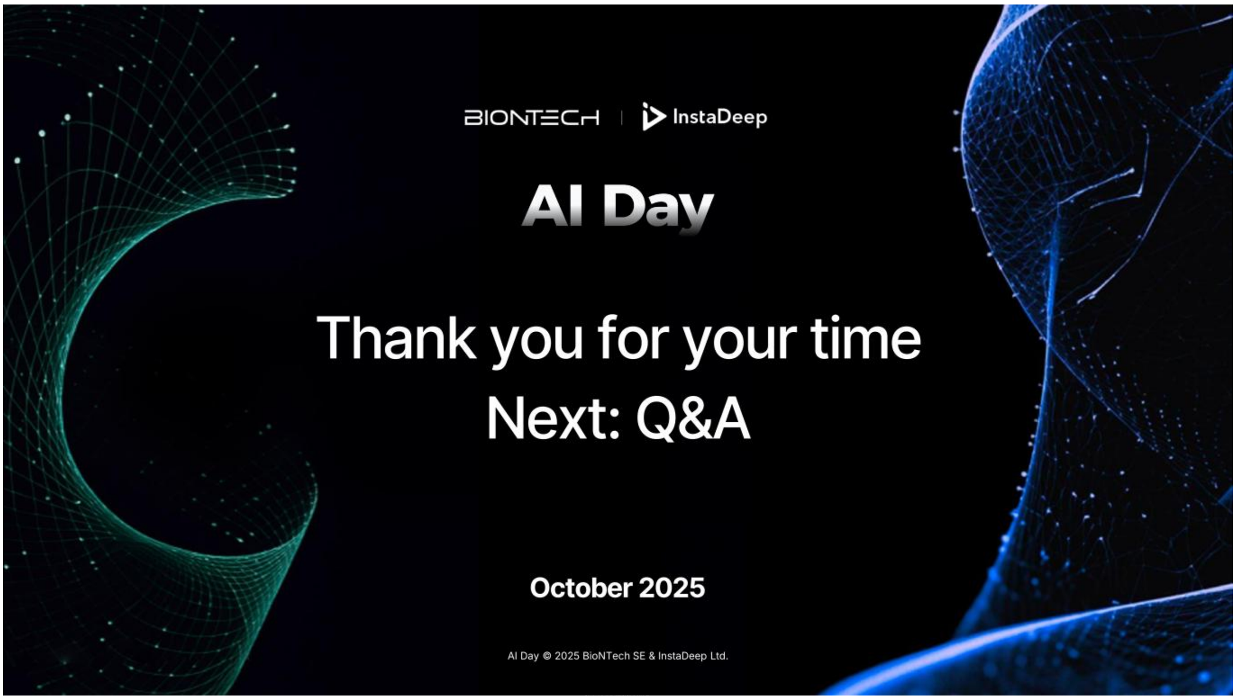
Affinity-enhanced TCRs lead to strong and durable *in vivo* tumor control in a pre-clinical model

pHLA tumor target 1

Source: Internal

pHLA tumor target 2

Source: Internal



BIONTECH | InstaDeep

AI Day

Thank you for your time

Next: Q&A

October 2025