Identifying multiple lines of evidence behind therapeutic target association with Parkinson's disease

EXPLORING NATURE FOR DRUG CANDIDATE IDENTIFICATION

Alchemab Therapeutics is redefining therapeutic discovery by studying individuals naturally resilient to disease. Their approach involves sequencing B cells from these rare individuals to identify **protective antibodies** and their **binding targets** - uncovering mechanisms that help the body resist disease progression. This strategy yields **high-confidence therapeutic candidates** with the potential to replicate those natural protective effects.

However, the nature of Alchemab's innovation brings a unique challenge: **validating novel targets that are virtually absent from the public scientific domain**. With no prior data to rely on, traditional validation routes fall short.

INNOVATIVE IDEAS POSE NOVEL CHALLENGES

Parkinson's disease (PD) remains one of the most complex neurodegenerative diseases - marked by **heterogeneous symptoms, diverse biological underpinnings**, and a **shortage of reliable biomarkers**. Its progression is slow, variable, and often silent in early stages. These factors severely hinder both therapeutic development and clinical trial design.

From their resilience-based platform, Alchemab identified a **promising novel target** expressed across human tissues, including the brain, and implicated in **lipid metabolism and inflammation regulation**. However, due to its novelty of this association, **existing data offered only limited and indirect clues** - falling short of establishing a clear link between the target and PD pathogenesis or progression.

To meet the complexity of this challenge, **AI-chemab partnered with Ardigen**, seeking both **AI-powered bioinformatics** and deep domain knowledge in **precision medicine**.

ARDIGEN'S SOLUTION: A COMPREHENSIVE MULTI-OMICS VALIDATION STRATEGY

We realised that investigating this target posed a unique analytical challenge: its biological function centers on **lipid substrates and products**, which are often **invisible in traditional blood-based assays** that focus on proteins. This meant that this target's dysfunctions could easily go undetected. **A superficial analysis would miss its role entirely**. Recognizing this, we applied a **multi-layered approach** designed to capture network-level consequences of disrupted lipid metabolism. Our validation strategy integrated **genomics, transcriptomics, proteomics, and longitudinal patient data**, aiming at delivering both **proof of association** and **mechanistic insights** into the target's role in PD. This effort was divided into two strategic work packages.

Work Package 1:
Establishing Foundational Knowledge (Due Diligence)

This phase focused on building a **knowledge base from scratch**. We conducted:

- A **deep literature synthesis** to compile all known data related to the target.
- A **bespoke genetic landscape report** using Ardigen's in-house tools, cataloging all known **SNPs, structural variants, and associated traits** related to the gene and its pathway.

This wasn't surface-level due diligence - it was a **custom intelligence dossier** designed to compensate for the lack of published evidence.

Work Package 2:
In-Depth Analysis of Disease Datasets (Omics Approaches)

Ardigen then launched a **full-scale omics investigation**, leveraging **The Michael J. Fox Foundation's PPMI dataset** - a globally renowned longitudinal cohort.

Data used included:

- **Bulk RNA-seq:** 4,600+ blood transcriptomic samples from 1,000+ individuals across 3 years.
- **Whole Genome Sequencing:** Genomic data from over 1,000 participants.
- **Proteomics:** SomaScan (CSF; ~4,900 proteins) and mass spectrometry (urine, ~4,300 proteins) each from ~ 1,000 participants.

This omics depth enabled us to investigate the target's connection not just with PD in general, but with **how PD progresses, varies, and expresses across subtypes and resilience phenotypes**.

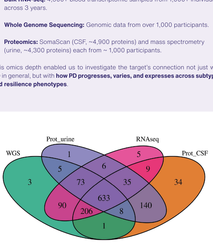

Fig 1. Omics Data Landscape: *Venn diagram illustrating the data overlap of participants across transcriptomic, genomic, and proteomic datasets, showcasing the integrated nature of Ardigen's multi-modal analysis.*

ILLUMINATING THE TARGET'S ASSOCIATION AND MECHANISTIC INSIGHTS

Patient Stratification:
Finding the Resilient

We started with performing exploratory data analysis (EDA) and consulted with clinical experts to define stratification criteria for PPMI participants. That enabled **clinically meaningful groupings** - such as separating individuals with slower from the ones with faster disease progression - for downstream contrasts and comparisons. We also divided participants based on their genetic status and - for some analyses - also levels of our primary target. This strategic groupings laid the **foundation for biologically and clinically relevant insights**, directly supporting precision drug development.

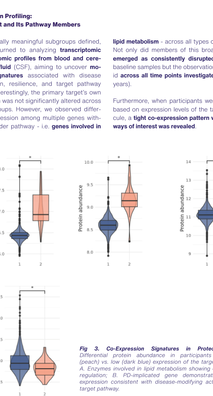

Fig 2. Identifying Resilient Patient Subgroups: *A. Kaplan-Meier plots from time-to-first-event analysis used to stratify PD patients by progression trajectories.; B. Hierarchical clustering of participants using longitudinal clinical data.*

Expression Profiling:
The Target and Its Pathway Members

With clinically meaningful subgroups defined, we next turned to analyzing **transcriptomic and proteomic profiles from blood and cerebrospinal fluid** (CSF), aiming to uncover **molecular signatures** associated with disease progression, resilience, and target pathway activity. Interestingly, the primary target's own expression was not significantly altered across clinical groups. However, we observed differential expression among multiple genes within its broader pathway - i.e. **genes involved in lipid metabolism** - across all types of analyses. Not only did members of this broad pathway **emerged as consistently disrupted** in PD in baseline samples but the observations kept valid **across all time points investigated** (up to 3 years).

Furthermore, when participants were grouped based on expression levels of the target molecule, a **tight co-expression pattern within pathways of interest was revealed**.

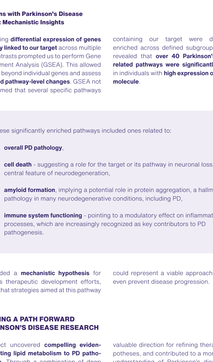

Fig. 3. Co-Expression Signatures in Proteomic Data: *Differential protein abundance in participants with high (peach) vs. low (dark blue) expression of the target molecule: A. Enzymes involved in lipid metabolism showing coordinated regulation; B. PD-implicated gene demonstrating altered expression consistent with disease-modifying activity of the target pathway.*

Genetic Landscape and Disease Association: Uncovering Genetic Predispositions

Given that our target is not believed to be secreted and **may act primarily within cells** the absence of differential expression in blood and CSF does not preclude functional differences at the site of disease. To further explore its potential involvement in PD, we next turned to genetic analysis to assess whether variants within the target gene itself were associated with disease risk or resilience. Our analysis, investigating 456 genetic variants within the target gene, found no direct link between these variants and Parkinson's Disease or any of the defined resilience phenotypes. However, again, specific genetic variants in **several other genes within the broader pathway did reveal significant associations.**

This implies that the genetic predisposition or protective mechanisms related to this critical biological system are **not confined to a single gene** but are **distributed across multiple functional components of the pathway**, offering multiple entry points for intervention.

Interactions with Parkinson's Disease Pathways: Mechanistic Insights

The recurring **differential expression of genes functionally linked to our target** across multiple clinical contrasts prompted us to perform Gene Set Enrichment Analysis (GSEA). This allowed us to move beyond individual genes and assess **coordinated pathway-level changes**. GSEA not only confirmed that several specific pathways containing our target were differentially enriched across defined subgroups, but also revealed that **over 40 Parkinson's Disease-related pathways were significantly enriched** in individuals with **high expression of the target molecule**.

These significantly enriched pathways included ones related to:

- **overall PD pathology**,
- **cell death** - suggesting a role for the target or its pathway in neuronal loss, a central feature of neurodegeneration,
- **amyloid formation**, implying a potential role in protein aggregation, a hallmark pathology in many neurodegenerative conditions, including PD,
- **immune system functioning** - pointing to a modulatory effect on inflammatory processes, which are increasingly recognized as key contributors to PD pathogenesis.

This provided a **mechanistic hypothesis** for Alchemab's therapeutic development efforts, indicating that strategies aimed at this pathway could represent a viable approach to slow or even prevent disease progression.

VALIDATING A PATH FORWARD IN PARKINSON'S DISEASE RESEARCH

This project uncovered **compelling evidence connecting lipid metabolism to PD pathophysiology**. Through a combination of deep profiling of various omics data, clinical stratification, and integrative genetic analysis, we identified a network of associated genes and processes that show **consistent and biologically meaningful patterns of disruption across patient subgroups**. These findings offered valuable direction for refining therapeutic hypotheses, and contributed to a more nuanced understanding of Parkinson's disease heterogeneity. Importantly, the work **supported Alchemab's strategic focus** by providing independent, data-driven validation for several pathway components and mechanisms already under consideration.

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