In-Depth Characterization of the P2 Enrichment Workflow

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Introduction

Plasma biomarkers are critical for early disease detection, monitoring treatment response, and tracking disease progression. However, plasma proteomics remains challenging due to its extreme dynamic range: the 22 most abundant proteins account for more than 99% of total protein content, obscuring lower-abundance, disease-relevant proteins in mass spectrometry–based analyses. Conversely, affinity-based platforms operate using predefined panels, limiting discovery to known markers and proteins for which suitable reagents are available. Particle-based protein corona workflows address these limitations by selectively enriching subsets of plasma proteins through adsorption to particle surfaces, thereby reducing dynamic range and improving detection of less abundant proteins. In addition, defining a consistently measurable plasma core proteome could facilitate biomarker discovery by enabling robust quantification of specific circulating proteins across samples while preserving unbiased access to disease-relevant biology.

Materials and Methods

Figure 1: Schematic workflow for *P2-iST*. The workflow is compatible with and optimized for a wide range of plasma and serum collection types.

Results

The P2 Core Proteome

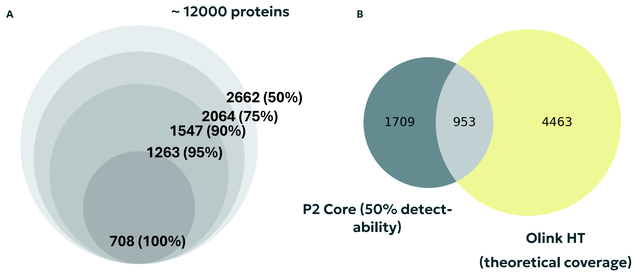


Figure 2: (**A**) Analysis of over 1,700 EDTA plasma samples from 25+ sites worldwide, spanning healthy donors and multiple disease indications (oncology, neurodegeneration, aging, and metabolic disorders). Without data imputation, 708 proteins were consistently quantified across all samples; (**B**) Venn diagram displaying complementarity between P2 Core (50% detectability) with the *Olink HT* panel.

P2 Core Proteome Is Consistently Enriched Across Multiple Collection Methods

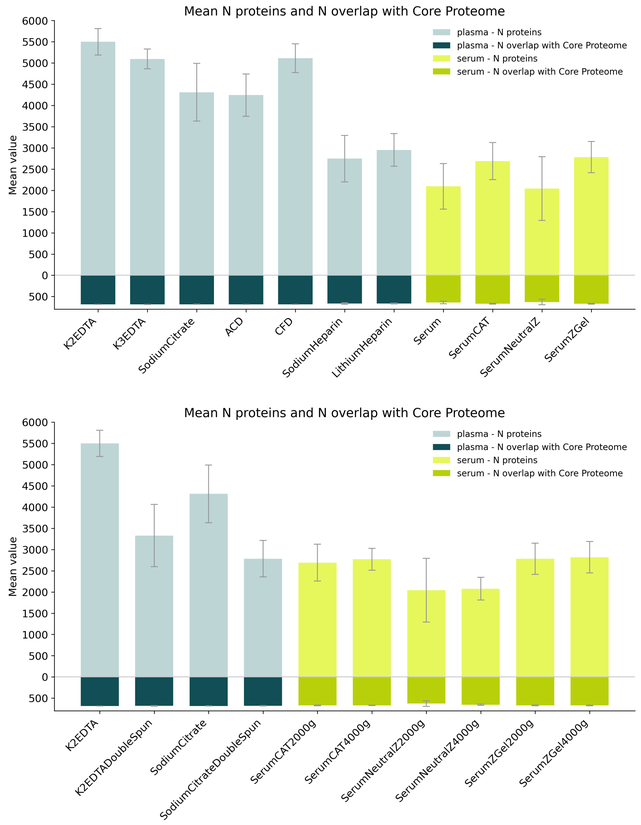
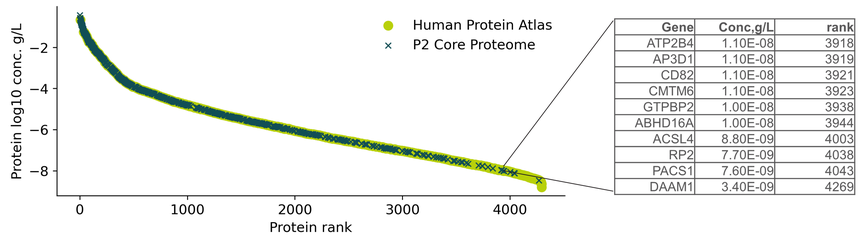


Figure 3: Consistent detection of the core proteome (>90%) across multiple plasma and serum collection methods (**upper panel**), independent of centrifugation speed and time (**lower panel**). ACD: acid citrate dextrose; CFD: citrate fluoride dextrose; SerumCAT: serum clot activator tube; SerumNeutralZ: serum without CAT; SerumZGel: CAT and gel separator.



Gene	Conc,g/L	rank
ATP2B4	1.10E-08	3918
AP3D1	1.10E-08	3919
CD82	1.10E-08	3921
CMTM6	1.10E-08	3923
GTPBP2	1.00E-08	3938
ABHD16A	1.00E-08	3944
ACSL4	8.80E-09	4003
RP2	7.70E-09	4038
PACS1	7.60E-09	4043
DAAM1	3.40E-09	4269

Figure 4: The P2 core proteome mapped to protein concentrations from the Human Blood Atlas[1], spanning the full dynamic range. The ten lowest-abundance proteins are highlighted in the table.

Extracellular Vesicle Proteins Are Enriched by P2

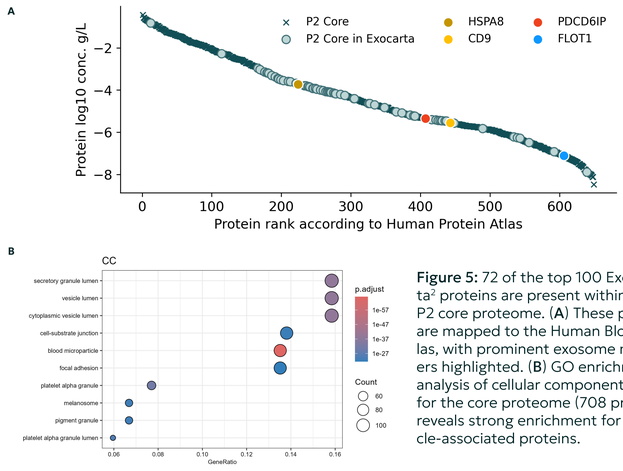


Figure 5: 72 of the top 100 ExoCarta[2] proteins are present within the P2 core proteome. (**A**) These proteins are mapped to the Human Blood Atlas, with prominent exosome markers highlighted. (**B**) GO enrichment analysis of cellular components (CC) for the core proteome (708 proteins) reveals strong enrichment for vesicle-associated proteins.

Conclusion

- *P2-iST* is compatible with a wide range of plasma and serum collection types.
- Investigation of the enrichment mechanism revealed a subset of proteins (P2 core proteome) that are consistently and reproducibly detected across 1000s of EDTA plasma samples.
- The P2 core proteome is stable across various collection methods and sample processing procedures.
- Vesicle-associated proteins and extracellular vesicles are enriched by P2, consistent with recent findings by Völlmy et al.

References

1 Schwenk et al. J. Proteome Res. 2017, 16, 12, 4299–4310

2 Mathivanan et al. Journal of Molecular Biology, 2016, Volume 428, Issue 4

3 Völlmy et al. J. Proteome Res. 2026

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Conflict of Interest Disclosure: Arthur Viodé, Sandra Schär, Liliana Malinovska, Polina Shichkova, Martin Mehnert, Wouter van Bergen, Christopher Below, Yuehan Feng, and Roland Bruderer are employees of Biognosys AG; Jan Muntel and Alan Shomo are employees of Biognosys Inc. Xaver Wurzenberger, Patrick Schreiner, Katharina Limm, and Nils Kulak are employees of PreOmics GmbH.