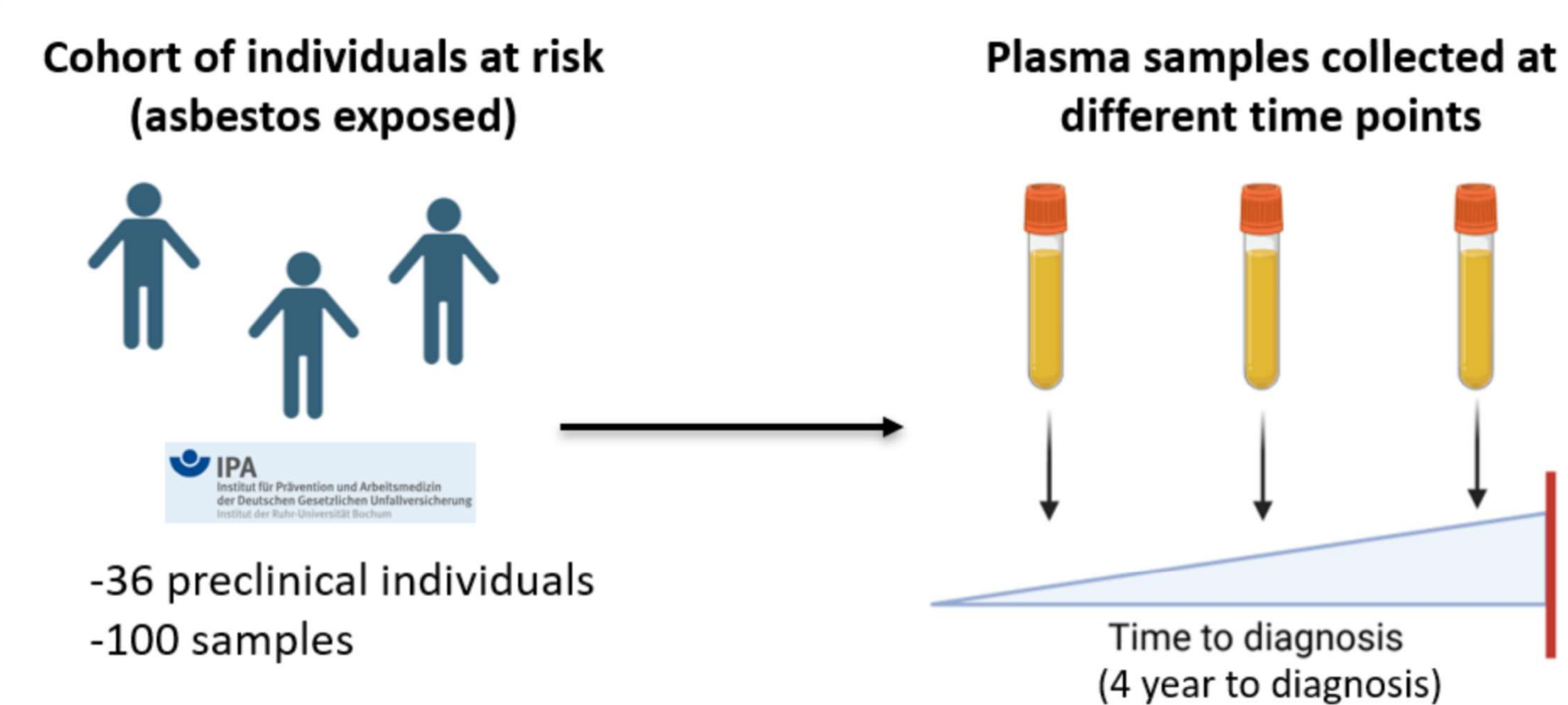


The evolution of pleural mesothelioma cancer assessed from the blood

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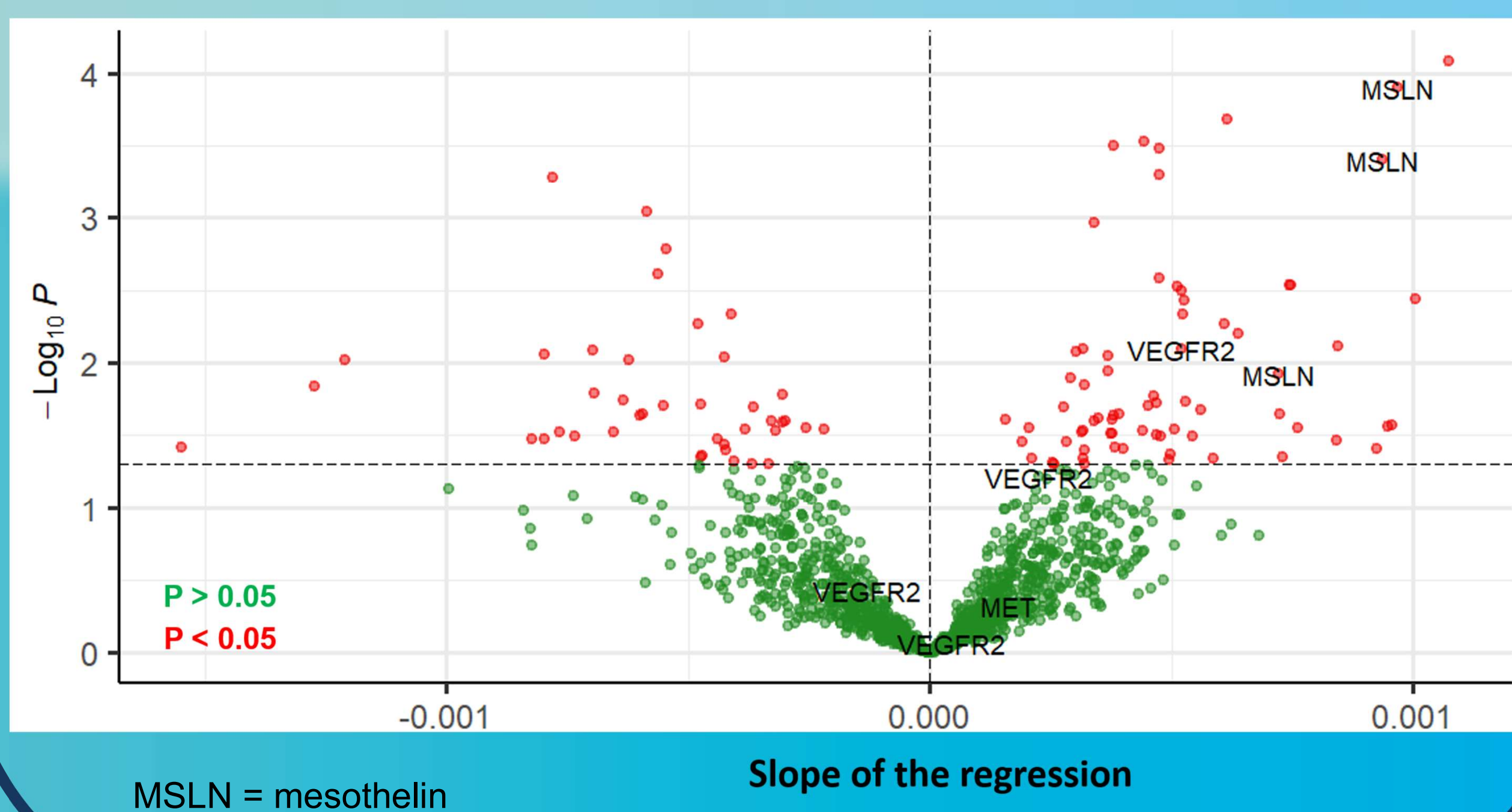
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Introduction The evolution of cancer might be reflected in the protein composition of the blood which collects information from the cancer and from the reactions of the host. Pleural mesothelioma (PM) has its cause mainly in the exposure to asbestos and it takes decades to develop and manifest. We study the concentration dynamics of the blood circulating N-glycoproteins during this latency period. The N-glycoproteins are heavily involved in tumorigenesis, inflammation and immune response. Their dynamics during the evolution of the cancer might reveal biological mechanisms relevant for early detection and early treatment interventions.

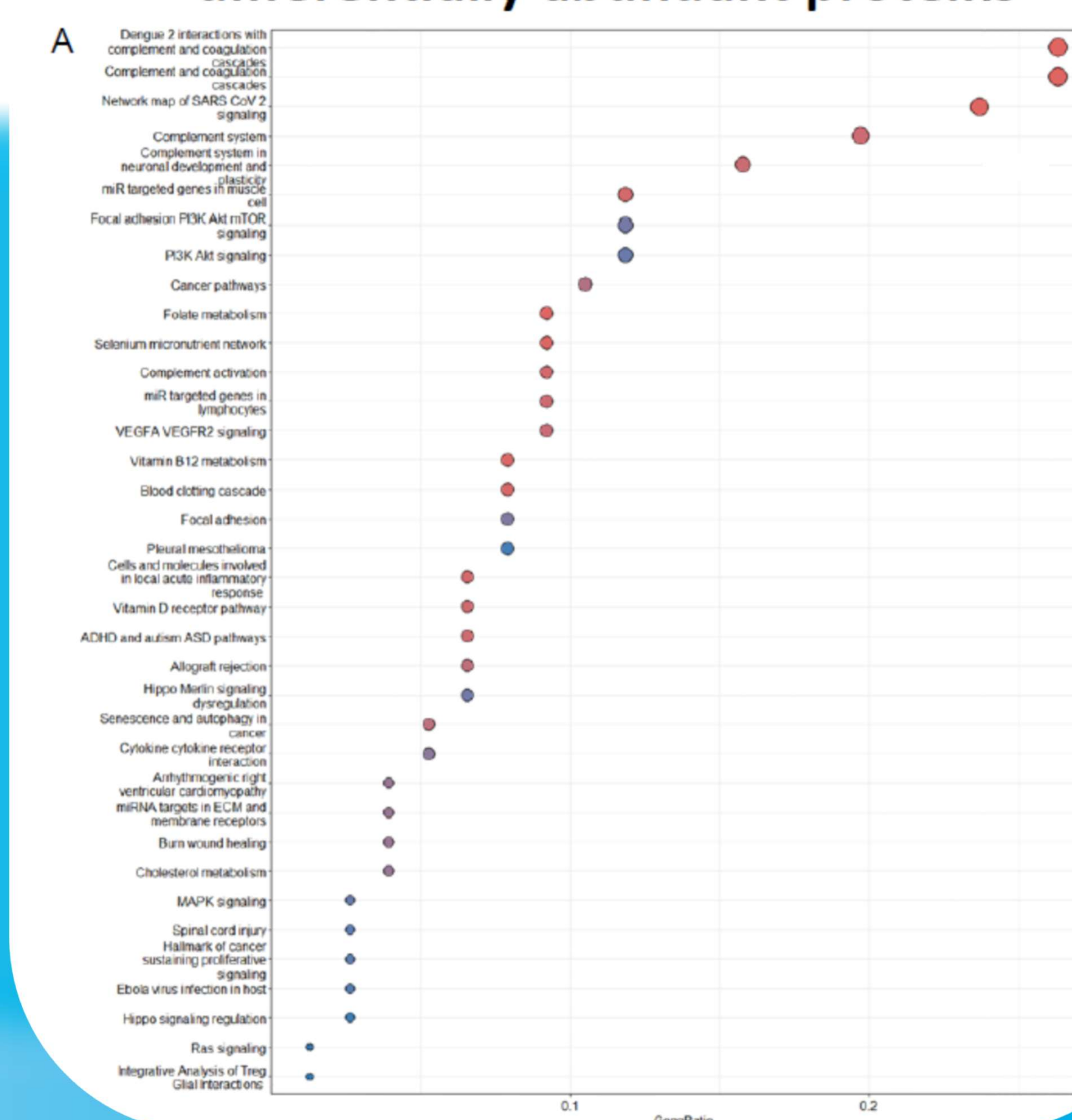


The DIA-MS proteomics workflow is applied to the study of the MoMar cohort, where pre-diagnostic plasma samples were collected longitudinally from individuals who developed pleural mesothelioma while on asbestos screening programs (IPA, Germany, figure above). For the DIA-MS study, the samples are processed using hydrazide chemistry-based protocols to enrich for the circulating N-glycoproteins. Linear models identify circulating N-glycopeptides (volcano plot below) with significant increase (right of the vertical dashed line) or decrease (left of the vertical dashed line) of concentration during the evolution of pleural mesothelioma.

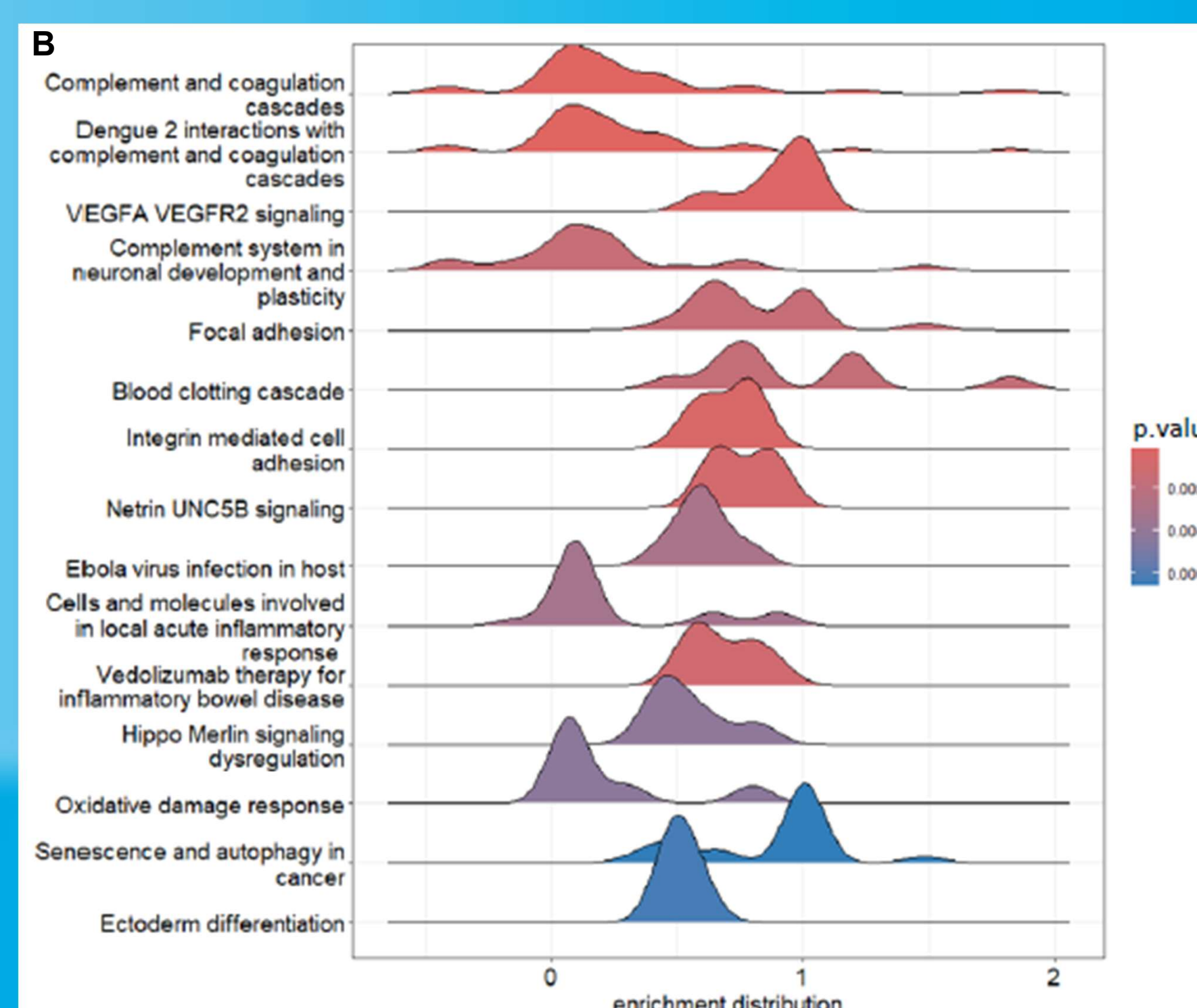
N-glycopeptides with significant concentration dynamic during mesothelioma evolution



Pathway enrichment analysis of the differentially abundant proteins

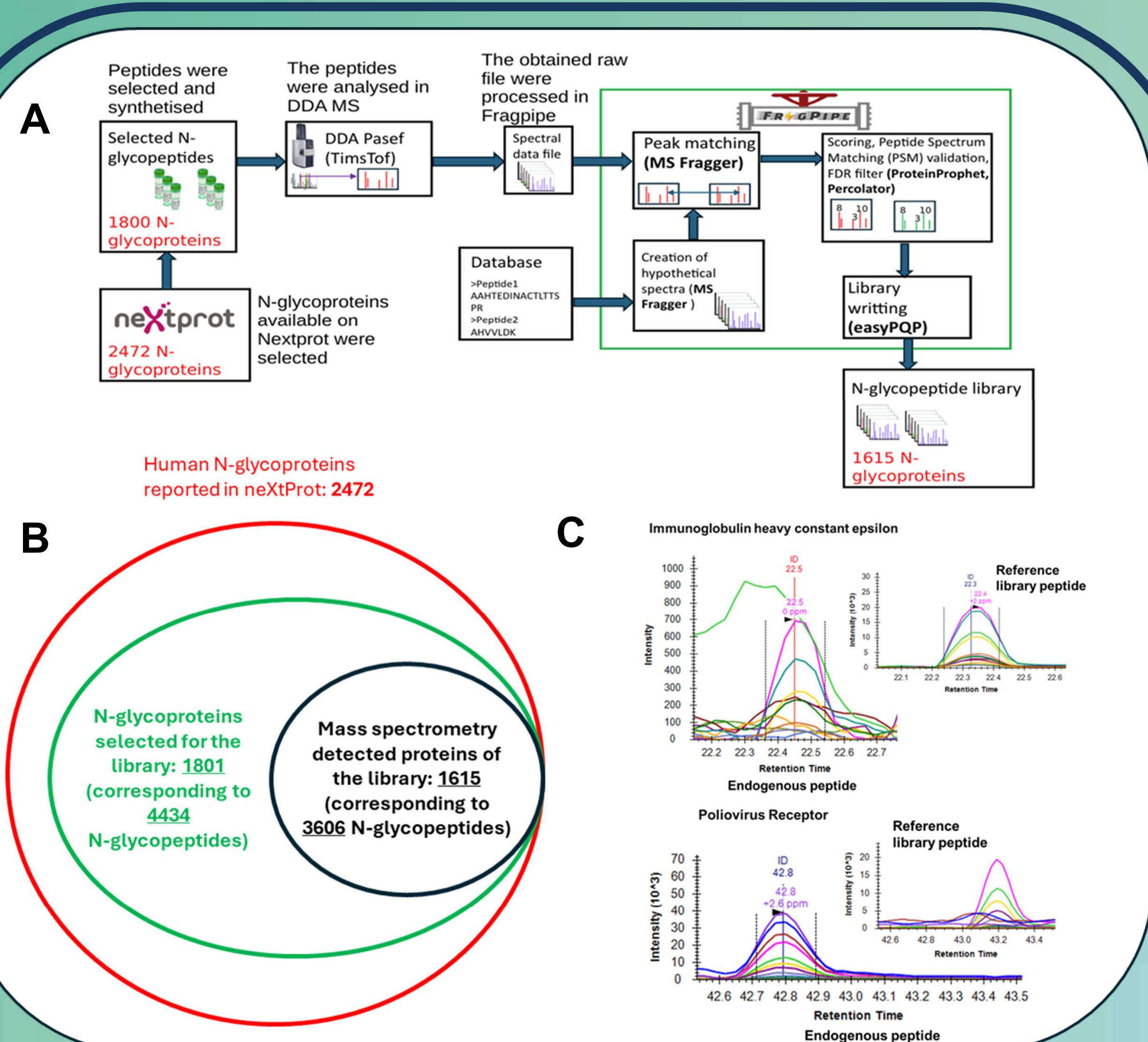


Pathway enrichment analysis is among the strategies applied to deconvolute the biological content of the N-glycoproteins circulating in blood. **A.** The example reports pathways from WikiPathways enriched among circulating N-glycoproteins detected in plasma samples from patients with pleural mesothelioma and compared to asbestos exposed healthy donors. **B.** Ridge plot obtained for the same cohort using Gene Set Enrichment Analysis showing the distribution of the log2 fold change of the N-glycoproteins associated with enriched pathways



Summary: Circulating N-glycoproteins can be detected in blood with concentration dynamics that follow the evolution of PM cancer and rich of biologically and potentially therapeutic relevant information.

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The DIA-MS (Data Independent Acquisition Mass Spectrometry) proteomics workflow established for the study of circulating N-glycoproteins during the evolution of pleural mesothelioma. Above the bioinformatics workflow (A) based on a comprehensive human N-glycopeptide spectral library of synthetic peptides produced for the project (B) with examples of N-glycopeptides identified in plasma (C). Below the integration (A) with library free methods to expand the detection of circulating N-glycoproteins (B and C).

Detection of circulating N-glycoproteins in plasma

Integration of two DIA-MS data analysis strategies

→ Combining library based and library free methods increase the number of N-glycoproteins detected.

Sensitivity of the detection

→ The library based strategy increases the number of low abundant N-glycoproteins detected.

