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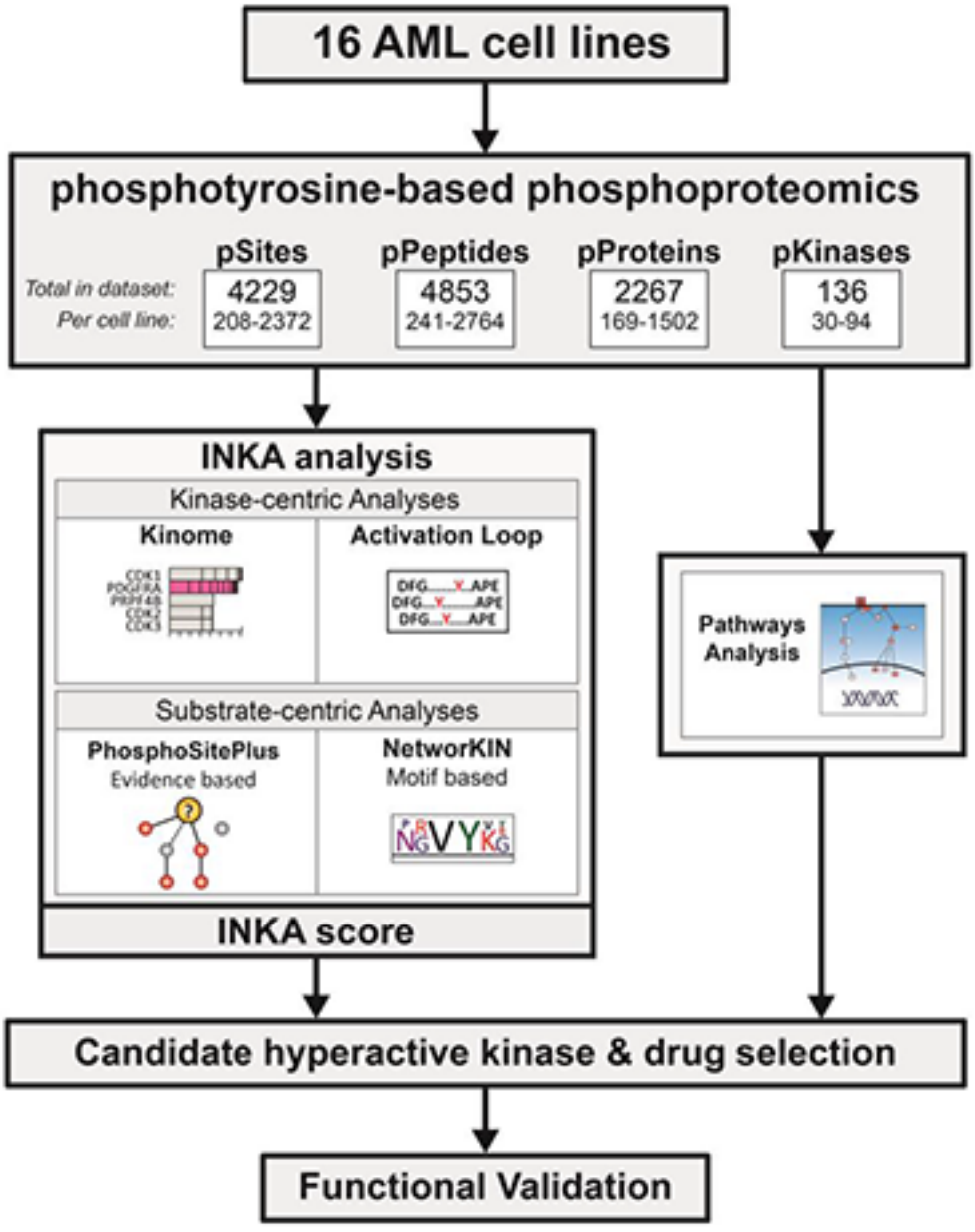
Algorithm identifies active kinases for AML treatment

Acute myeloid leukemia, or AML, is a cancer of the bone marrow and blood that progresses rapidly if left untreated. An estimated 19,000 new cases will be diagnosed this year with a five-year survival rate of 28.1%. Small-molecule kinase inhibitors are a potential treatment strategy for AML patients. However, due to molecular heterogeneity in AML, no single molecule has been clinically effective.



CAROLIEN VAN ALPHEN ET AL./MCP.

This schematic representation shows INKA analysis for a panel of acute myeloid leukemia cell lines.

In their recent study published in the journal **Molecular & Cellular Proteomics**, Carolien van Alphen and colleagues at the Amsterdam University Medical Center relied on an integrative inferred kinase activity, or INKA, algorithm to identify prospective small-molecule kinase inhibitors. For each given kinase, INKA performs a four-component analysis by determining the phosphorylation status of the kinase itself, its activation loop and all its possible substrates. INKA assigns a nonzero score to kinases with both kinase-centric and substrate-centric phosphorylation status.

A panel of 16 AML cell lines was chosen for pY-phosphoproteomics combined with INKA analysis to identify hyperphosphorylated active kinases. Due to the heterogeneous signaling in these cell lines, the analysis identified multiple phosphopeptides. INKA analysis of individual cell lines identified specific driver kinases, including PDGFRA, JAK2, KIT and FLT3. Using this approach, the researchers identified and functionally verified active tyrosine kinases in 10 cell lines. For the remaining six cell lines without a tyrosine kinase driver, they identified MAPK signaling as a potential drug target.

The authors concluded the study by applying their analytical strategy to clinical samples. Despite the lower amount of input sample, phosphoproteomic and INKA analysis identified similar driver kinases in patient samples to those in the cell lines. The in-depth analysis performed in this study provides a basis for future clinical applications for personalized treatment of AML patients.