#6525: Multi-drug algorithm to accurately predict best first-line treatments in newly-diagnosed acute myeloid leukemia (AML)

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Background

• New first-line treatments to complement chemotherapy have been recently introduced for AML, a blood malignancy with poor prognosis.

• Current **predictive biomarkers** to guide AML therapy selection either have low specificity (midostaurin plus intensive chemotherapy (MIC)), or are lacking for **intensive chemotherapy (IC)** or **venetoclax-azacitidine (VA)** treatments.

• We have previously identified phosphoproteomics as a **rich source of predictive biomarkers** in AML and other cancer types (**AML:** Dokal A., *ASCO Annual Meeting 2021*; Casado P., *Leukemia*, 2021; **Cholangiocarcinoma:** Khorsandi S.E., *Cancer Res.,* 2021; **NSCLC:** Dokal A, *Cancer Res*., 2021).

Here, using routine diagnostic samples we build phosphoproteomics-based models predicting response to three most commonly-used first line AML therapies: IC, MIC and VA.

Methods

Routine bone marrow and peripheral blood diagnosis samples (s, n=251) from 204 patients (p) subsequently treated with MIC (n=44/64 p/s), VA (n=66/74 p/s) or IC (n=94/113 p/s) were processed for phosphoproteomics (**Figure 1**). Patients (**Table 1**) were grouped into Good Responders (GR) and Poor Responders (PR) based on treatment outcome. For VA, patients that achieved complete remission (CR) were considered GR, while refractory (R) patients were considered PR. For MIC and IC, we considered CR patients without relapse within 6 months as GR, and those refractory or relapsed within 6 months as PR. Phosphopeptides that distinguish GR and PR groups in each cohort were incorporated in response prediction models that were them assessed via cross-validation.

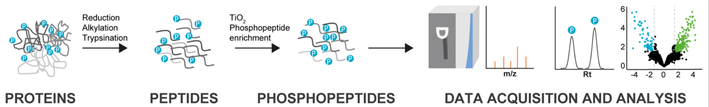

Figure 1. Experimental workflow.

Table 1. Cohort characteristics.

Model	Characteristics	Measurement	PR	GR
MIC (6 month cutoff)	Patient number	n (p)	10	34
	Sample number	n (s)	14	50
	Age in Years	Median (range)	67 (19-79)	59 (28-78)
IC (6 month cutoff)	Patient number	n (p)	46	48
	Sample number	n (s)	49	64
	Age in Years	Median (range)	45 (19-79)	39 (21-77)
VA (CR vs Refr.)	Patient number	n (p)	26	40
	Sample number	n (s)	31	43
	Age in Years	Median (range)	72 (64-87)	71 (31-89)

Phosphoproteomic analysis of **routine clinical samples** can identify **first-line treatments** that are **more likely to be effective** in newly-diagnosed **AML** patients

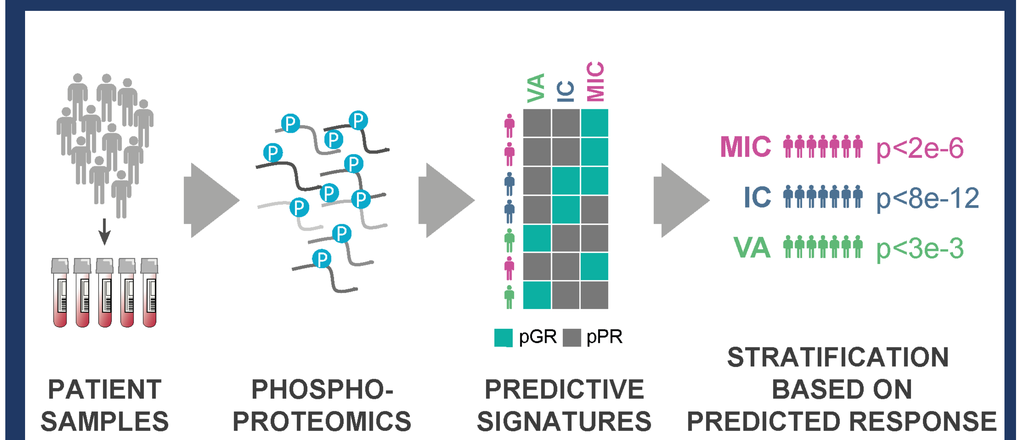

Figure 2. End goal: unified phosphoproteomic model combining our existing models predicting response to MIC, IC and VA. From a routine diagnostic sample, through phosphoproteomics analysis, to a single predictive model identifying which treatment gives the highest chance of response.

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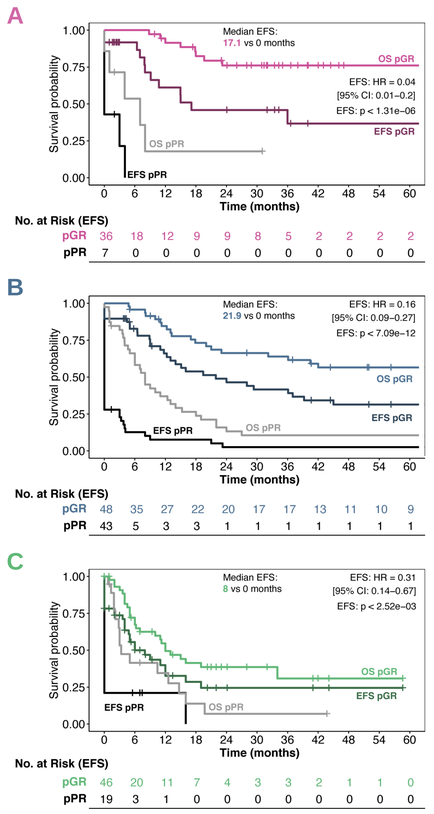
Results



• Between twenty and fifty phosphoproteomic biomarkers were identified as predictive of response for MIC, IC and VA treatments and were used to build predictive models.

• Training with cross-validation produced computational models that correctly predicted the outcomes of vast majority of cohort patients (**Figure 3**). All predictive models achieved high sensitivity (97%, 89% and 90%) and specificity (67%, 83% and 60%).

Figure 3. Event-free survival (EFS) and overall survival (OS) analysis using cross-validation. A respective prediction model was validated though cross-validation A. MIC, a response prediction model distinguishing between GR (defined as responding for longer than 6 months) and PR patients (defined as refractory and relapsed within 6 months) was assessed via cross-validation. B. IC, a response prediction model distinguishing between GR (defined as responding for longer than 6 months) and PR patients (defined as refractory and relapsed within 6 months) was assessed via cross-validation. C. VA , a response prediction model distinguishing between GR (defined as responding for longer than 6 months) and PR patients (defined as refractory and relapsed within 6 months) was assessed via cross-validation.
p – log-rank p. Axes were truncated at 5 years to visualize models' performance immediately after treatment.

Future directions

• Predictive models validation and refinement in retrospective cohorts from different geographies is ongoing and we welcome new collaborators.

• In parallel to this work, we are building a prognostic model to determine disease severity regardless of administered treatment.

• In the near future, a unified model to highlight best first-line treatment for individual patients (shown in **Figure 2**).

• Further data mining will broaden assay utility to suggest off-label treatments for patients predicted to be refractory to current drugs.