Kinomica Ltd
kinomica.com

KScan: personalizing medicine with phosphoproteomics

Kinomica uses its cutting-edge phosphoproteomics platform KScan to identify molecular signatures predictive of drug response in clinical samples.

In many diseases, getting the right medicines to the right patients depends on understanding the specific details of their particular pathologies. Kinases—and the complex signaling networks that they regulate—enable cells to interpret, adapt, and interact with their environment; consequently, deregulation of cell signaling drives cancer pathogenesis. While genomics, transcriptomics, and standard proteomics can provide clues about pathway activity changes, these methods rarely capture what really counts: the actual, real-time activity of kinases.

Kinomica has developed a powerful solution to address this challenge: the KScan phosphoproteomics platform, which combines single-shot, label-free liquid chromatography–tandem mass spectrometry-based phosphoproteomics with Kinomica's proprietary databases and bioinformatics tools (Fig. 1). KScan quantifies tens of thousands of protein–phosphorylation events and interprets these data to generate activity readouts for hundreds of kinases. While genomic, transcriptomic, and traditional proteomic approaches report proxies, such as the presence of genomic mutations, or transcript/protein expression, KScan captures a personalized snapshot of the kinase activities, signaling pathway states, and the network circuitry driving individual cancers.

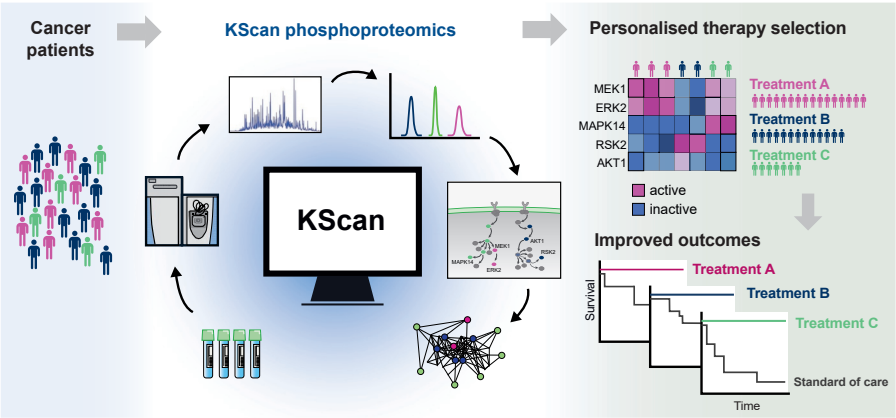

Fig. 1 | The KScan phosphoproteomics platform.

Validation of KScan

Kinomica's vision of using KScan to identify patients most likely to benefit from a given therapy has been demonstrated in an ongoing project focused on treatment of acute myeloid leukemia (AML) with the small-molecule protein kinase inhibitor midostaurin (Rydapt, Novartis) in combination with chemotherapy. Midostaurin, which targets the FLT3 receptor (WT and/or mutant), was approved by the US Food and Drug Administration in 2017 on the basis of efficacy in clinical trials with AML patients carrying tumor mutations in the *FLT3* gene of their leukemic blasts, and is stratified to these patients through a companion diagnostic test for *FLT3* mutational status.

Less than one-third of AML patients present with a *FLT3* mutation, and are therefore eligible for midostaurin in combination with standard chemotherapy. Of these *FLT3* mutation-positive (FLT3+) AML patients, ~60% appear to benefit from midostaurin. Amongst *FLT3* mutation-negative (FLT3-) AML patients, which comprise more than two-thirds of all AML patients, ~40% were shown to benefit from midostaurin in a phase 2b trial[1], but are currently ineligible for midostaurin treatment. This means that there is a subset of ineligible patients who could benefit from midostaurin, and many eligible patients who do not.

Kinomica is working to address this problem using its proprietary KScan platform. Preclinical studies with cancer cells derived from AML patients treated with midostaurin ex vivo demonstrated that phosphoproteomic signatures in the pre-treatment samples were significantly more predictive of sensitivity to midostaurin than *FLT3* mutational status[2]. The clinical relevance of these signatures was confirmed by a retrospective analysis of pre-treatment samples from 55 FLT3+ AML patients who went on to receive midostaurin plus chemotherapy. Using machine learning, optimization of the signatures further improved the predictive accuracy of response to therapy and of survival.

Crucially, patients whose samples were positive for a specific predictive phosphoproteomic signature survived four to five times longer than signature negative patients receiving the same treatment, but with a different underlying signal pathway dysfunction[3]. Development of a laboratory-developed test to reliably assess this signature in clinical samples is currently underway. Furthermore, in patients who were refractory to midostaurin combined with chemotherapy, KScan identified highly active molecular pathways in pre- and post-treatment samples that were not present in responsive patients. These pathways represent potential therapeutic vulnerabilities of midostaurin plus chemotherapy-resistant cancer cells, and are potential alternative drug targets, either to combat this resistance[4] or for new upfront therapies.

The observation that phosphorylation signatures identified by KScan outperform *FLT3* mutational status at predicting midostaurin response indicates that they could hugely benefit both AML patients and healthcare providers alike. First, by ensuring that all patients who may benefit from midostaurin receive it, including FLT3- patients; second, by sparing patients for whom midostaurin will likely be ineffective from unnecessary side effects; and third, by saving healthcare providers millions in wasted treatment costs, and enabling clinicians to direct patients to other treatments more effective for their individual condition.

Expanding the scope of KScan

With this first ever successful demonstration that phosphoprotein signatures are predictive of drug response in the clinical setting, Kinomica is poised to extend KScan to other drugs and cancer indications, including solid tumors. Beyond these development-stage applications, Kinomica is working to create KScan-based precision medicine products—namely, tests performed by Kinomica and partner labs—that will help guide clinicians during treatment decision making. Kinomica welcomes discussions with future partners who wish to collaborate and utilize KScan to get the right treatment to the right patient.

1. Fischer, T. et al. *J. Clin. Oncol.* **28**, 4339–4345 (2010).
2. Casado, P. et al. *Leukemia* **32**, 1818–1822 (2018).
3. Dokal, A. et al. *J. Clin. Oncol.* **39** (Suppl.), 7019-7019 (2021).
4. Nobre, L. et al. *Blood* **138** (Suppl. 1), 3462 (2021).

CONTACT
David Britton
Co-founder & Chief Scientific Officer
Kinomica Ltd
Alderley Edge, UK
Email: d.britton@kinomica.com