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Cancer drug profiling platform fuels discovery of patient stratification markers

The precision medicine services company Oncolines B.V. is accelerating cancer drug development by identifying drug response biomarkers in over 200 genetically characterized cancer cell lines.

Despite advances in the treatment of cancer and increased investment in cancer research, many drug candidates fail in the clinic. Using the right preclinical models, identifying biomarkers to select the patient population most likely to respond, and demonstrating target engagement are key elements to accelerate cancer drug development and improve patient outcomes.

Oncolines B.V., founded in 2021 as a spin-off company of the Netherlands Translational Research Center B.V. (NTRC), and acquired by Symeres in January 2023, offers cell-line assays and bioinformatics services to clinical and preclinical cancer drug discovery companies around the globe (Fig. 1).

Based in Oss (the Netherlands), Oncolines' technology platform supports both early and late drug discovery projects as well as proof-of-concept clinical studies. "We help our clients to characterize their small molecules and biologicals through determination of activities, selectivity and mechanism of action," said Guido Zaman, managing director and founder of Oncolines.

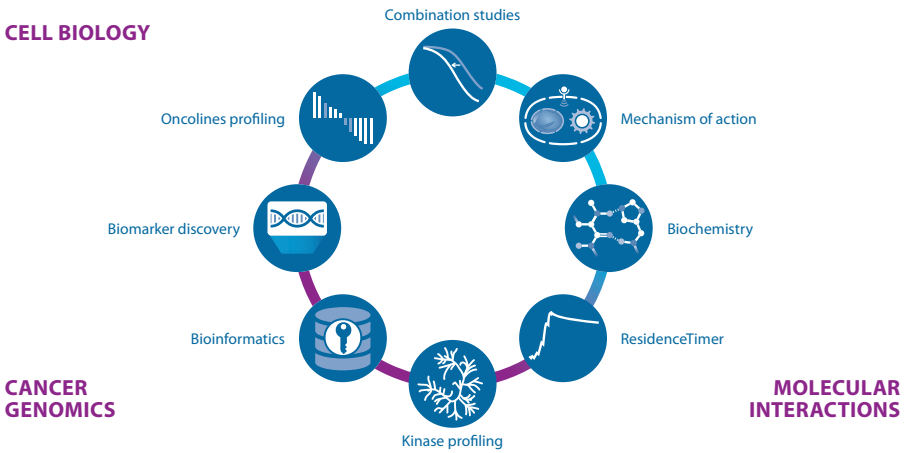

Fig. 1 | Oncolines' services.

Oncolines profiling

Oncolines can profile the effects of drug candidates in over 200 fully characterized human cell lines representing a broad range of solid tumors and blood cancers. "We have characterized the cancer gene mutation status and gene expression of all Oncolines' cell lines; we know exactly which oncogenes are switched on, and which tumor suppressors are switched off," Zaman explained.

The sensitivity of cells to a drug candidate is determined in viability assays and correlated to the cancer gene mutation status of the cell lines. This type of study reveals novel markers of drug sensitivity that can be used to decide which animal model to use for next proof-of-concept experiments. Ultimately, these biomarkers can be used as selection markers for patient stratification.

For example, Oncolines profiling of 10 preclinical and clinical inhibitors of threonine tyrosine kinase (TTK) showed that cell lines with activating mutations in the *CTNNB1* gene, which encodes the Wnt pathway signaling regulator β-catenin, were up to five times more sensitive to the TTK inhibitors than those with the wild-type *CTNNB1* gene[1]. This finding was confirmed in a xenograft model of a *CTNNB1*-mutant cell line in which TTK inhibition resulted in a significant reduction in tumor growth[1].

Since mutations in *CTNNB1* occur at relatively high frequency in endometrial cancer and hepatocellular carcinoma, patients with these types of cancer may be more likely to respond to TTK inhibitor therapy. Indeed, preliminary data from a phase 1/2 study of the TTK inhibitor NMS-01940153E indicated promising activity in two patients with unresectable hepatocellular carcinoma[2].

Comparative analyses to find points of difference

"Many companies are working on the same targets and concepts, so it is very important for them to be able to differentiate their compound from others," Zaman said. In addition to identifying drug response biomarkers for patient stratification, Oncolines can perform in-depth bioinformatics analyses based on the activity fingerprints of over 200 reference anticancer agents. "By comparing the profiles and behavior of drug candidates in Oncolines' cell panels to the data of reference anticancer agents, we can gain insights into the candidate's mechanism of action and determine how similar or different it is to drugs already on the market or in development," Zaman added.

A recent study, in which 21 kinase inhibitors newly approved by the US Food and Drug Administration (FDA) and 13 previously approved comparators were profiled by Oncolines, uncovered important differences between inhibitors that act on the same primary target, including activities on new targets[3]. These results could lead to their use in new patient populations and aid treatment decisions.

Oncolines also offers drug combination screens that can identify cross reactivities and synergistic effects. Such data are useful for guiding the development of new drugs, and for repositioning or finding new indications for drugs that are already on the market.

Added value: results at the touch of a button

Oncolines' visualization tools are used to produce powerful interactive reports and slide shows. "Rather than providing data in spreadsheets, our clients receive reports that filter out the most relevant findings from large scale, data-rich studies, such as Oncolines profiling and SynergyFinder, preventing data overwhelm," Zaman said.

Oncolines' flexible and tailored approach has already attracted over 100 internationally leading pharmaceutical clients. The client base keeps expanding as the company takes steps towards its ambition to translate artificial intelligence (AI)-driven drug discoveries into small molecules.

"There are a growing number of companies applying AI techniques to small-molecule drug discovery seeking to validate their concepts in the lab," said Zaman. "We are ideally placed to help them make a 'Go/NoGo' decision based on our independent and unbiased analyses".

1. Zaman, G. J. R. et al. *Mol. Cancer Ther.* **16**, 2609–2617 (2017).
2. Reig, M. *NMS-01940153E, an MPS1 inhibitor with anti-tumor activity in relapsed or refractory unresectable Hepatocellular carcinoma.* Oral presentation at 34th EORTC-NCI-AACR (October 2022).
3. Kooijman, J. J. et al. *Front. Oncol.* **12**, 953013 (2022).

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