Nintedanib found effective for gastrointestinal stromal tumors

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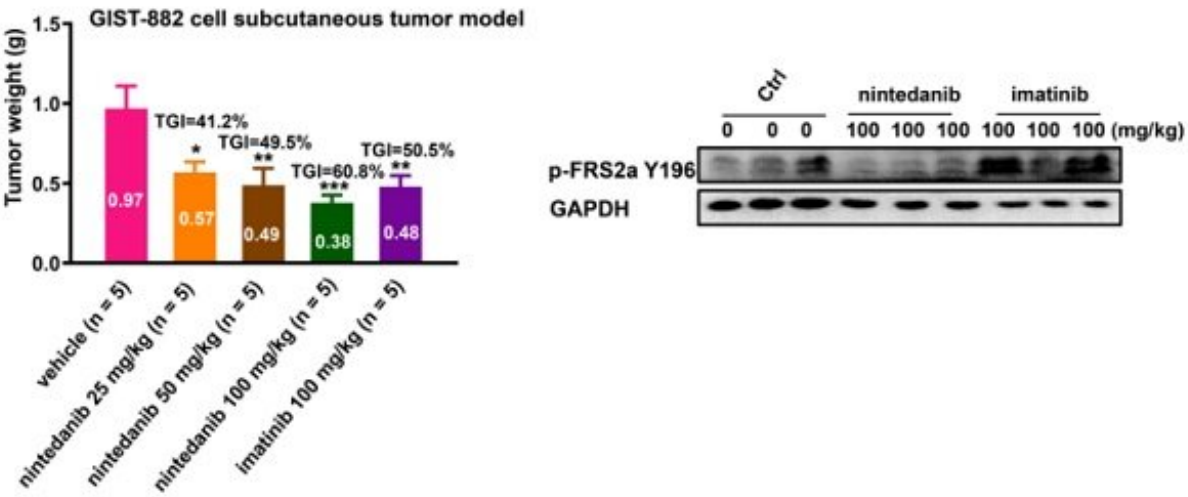

Nintedanib could be used in the treatment of drug-resistant gastrointestinal stromal tumors. Credit: Liu Juan

A research team led by Prof. Liu Qingsong and Liu Jing from the Hefei Institutes of Physical Science (HFIPS) of the Chinese Academy of Sciences (CAS) has recently found that nintedanib, a multikinase inhibitor of the receptor tyrosine kinase FGFR/VEGFR/PDGFR, could be used in the treatment of drug-resistant gastrointestinal stromal tumors (GISTs). Results were published in *Molecular Oncology*.

GISTs are mesenchymal tumors that usually occur in the gastrointestinal tract. Nearly 85% of GISTs bear oncogenic mutations in mast/stem cell growth factor receptor (KIT). As the first-line therapy, imatinib has significantly improves GIST patient survival. However, most patients eventually experience disease progression due to KIT secondary mutations. Besides, activation of alternative signaling pathways may also lead to drug resistance.

Although several second- and third-generation KIT kinase inhibitors could overcome some of the KIT mutations conferring resistance, the low clinical responses and narrow safety window have limited their broad application. Therefore, there is still an urgent need for effective drugs to overcome the problem.

In this study, through high-throughput screening, the research team found that nintedanib, which has been approved for the treatment of idiopathic pulmonary fibrosis and non-small-cell lung cancer, exhibited strong inhibitory effects against a panel of primary gain-of function mutations and secondary drug resistance mutations of KIT kinase, especially the T670I mutation.

In vitro experiments showed that nintedanib significantly inhibited the proliferation of GIST cell lines and human primary GIST cells through the KIT signaling pathway.

In addition, they found that nintedanib overcame resistance mediated by extracellular signal–regulated kinase reactivation caused by upregations of fibroblast growth factor activity. In vivo antitumor efficacy has also been observed in several xenograft GIST models.

This study provides evidence for the repurposing of nintedanib as a new therapy to improve the treatment of GIST patients with de novo or acquired resistance to imatinib.

More information: Juan Liu et al, Nintedanib overcomes drug resistance from upregulation of FGFR signalling and imatinib-induced KIT mutations in gastrointestinal stromal tumours, *Molecular Oncology* (2022). DOI: 10.1002/1878-0261.13199