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This press release is an English translation of a Japanese-language press release. The official language of this press release is Japanese, and the Japanese version takes precedence over the English version in terms of content and interpretation.

<Press Release>
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# Publication of Research on the Discovery of CLK Inhibitor Rogocekib

Kanagawa Japan

22th September 2025 –Chordia Therapeutics Inc. (Head Office: Fujisawa City, Kanagawa Prefecture; CEO: Hiroshi Miyake, "Chordia") and researchers of Takeda Pharmaceutical Company have published their findings on the discovery of the CLK inhibitor rogocekib (CTX-712), currently under development by Chordia. The research has been published online in *ACS Medicinal Chemistry Letters*.

## Summary

Rogocekib is a novel small-molecule compound that inhibits the phosphorylation of serine/arginine-rich (SR) proteins by CLK kinases, thereby inducing abnormal RNA splicing and imposing excessive stress on cancer cells, ultimately leading to cell death. This publication outlines the medicinal chemistry efforts that led to the discovery of rogocekib. Human cells possess four CLK kinases (CLK1, CLK2, CLK3, and CLK4), and this study focused on CLK2. Starting from the lead compound T-025, the research team conducted X-ray crystal structure analysis with T-025 bound to the CLK2 protein, which revealed the binding mode of T-025. Based on these insights, the compound's scaffold was boldly redesigned to improve pharmacokinetic properties. Through further structure optimization, rogocekib was developed with both potent CLK kinase inhibitory activity and favorable pharmacokinetic profiles. In addition to its strong anti-proliferative effects on cancer cells *in vitro*, rogocekib demonstrated robust antitumor efficacy in animal models.

## Key Highlights

- X-ray crystal structure analysis revealed the binding mode between lead compound T-025 and the CLK2 protein. To improve the pharmacokinetic properties of T-025, we created a compound with a different scaffold, which served as the starting point for the discovery of rogocekib.
- Based on this new scaffold, we proceeded with structure optimization and discovered rogocekib, which exhibits strong CLK kinase inhibitory activity.

Rogocekib showed $IC_{50}$ values of 0.69, 0.46, 3.4, and 8.1 nM against CLK1, CLK2, CLK3, and CLK4, respectively.

- Kinome profiling against 468 kinases confirmed that rogocekib exhibits high selectivity for CLK kinases with minimal effects on other kinases.
- Rogocekib demonstrated improved solubility, a key factor in pharmacokinetics, and demonstrated oral bioavailability in mice, suggesting the potential for development as an oral drug.
- Rogocekib exhibited strong anti-proliferative effects on human cancer cells *in vitro*. *In vivo* efficacy studies showed robust antitumor activity at doses of 25, 37.5, and 50 mg/kg (administered twice daily, twice weekly), with complete suppression of tumor growth observed at the highest dose.

## Publication Details

Discovery of Rogocekib (CTX-712): A Potent and Selective CLK Inhibitor for Cancer Treatment
*ACS Medicinal Chemistry Letters*, Sep. 20, 2025
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## About the Journal

*ACS Medicinal Chemistry Letters* is an international journal published by the American Chemical Society (ACS), dedicated to the rapid dissemination of innovative research in medicinal chemistry and drug discovery. The journal covers a wide range of topics including small-molecule design, target identification, mechanism of action studies, structure optimization, and pharmacokinetics.

## Glossary of Terms

| Term | Explanation |
|---|---|
| Kinase | A general term for proteins that add phosphate groups to substrate proteins. |
| Absorption | A property that indicates how much of a drug's active ingredient is taken into the bloodstream after oral administration. |
| X-ray Crystal Structure Analysis | The process of examining the shape of molecules or proteins and their interactions. |
| Structure Optimization | The process of gradually modifying the chemical structure, which serves as the blueprint of a drug, to enhance efficacy, reduce side effects, and improve pharmacokinetics. |
| Splicing | The process of maturing mRNA. |
| Serine/Arginine-rich (SR) Proteins | A group of proteins that regulate RNA splicing and are characterized by regions rich in the amino acids serine and arginine. |
| Phosphorylation | The addition of phosphate groups to substrate proteins, which regulates the on/off function of those proteins. |
| Pharmacokinetics | The changes in drug concentration in the body after administration; also referred to as PK. |

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| Solubility | A numerical value indicating how easily a drug's components dissolve in water or other liquids. |
| CLK | Abbreviation for CDC2-Like Kinase, an enzyme that catalyzes the transfer of phosphate groups to target proteins and plays an important role in splicing. |
| $IC_{50}$ | The concentration of a drug or compound required to inhibit a specific biological function by 50%; the smaller the value, the stronger the effect at lower doses. |
| RNA | Abbreviation for ribonucleic acid, a substance necessary for protein synthesis from genetic information in DNA. Includes messenger RNA (mRNA) transcribed from genomic DNA and transfer RNA (tRNA) used during protein synthesis. |

**About Chordia Therapeutics**

Chordia's lead asset, rogocekib (CLK inhibitor CTX-712), is under Phase 1/2 clinical study in the US. Rogocekib potentially targets the vulnerability of cancer and is expected to deliver benefits to patients of various types of cancer. In addition to rogocekib, Chordia is engaged in the research and development of several assets, including CTX-177, a MALT1 inhibitor, CTX-439, a CDK12 inhibitor, and GCN2 inhibitors. For more information, please contact our website https://www.chordiatherapeutics.com/en/.