SGR-2921, a potent CDC7 inhibitor, demonstrates significant anti-leukemic responses in patient-derived AML models representing difficult-to-treat disease

**Authors:** Hoeman Lad7, Hui Wang, Chris Atoriku, Zef Komo, Adam Levinson, Joseph Picotti, Steven Pine-Shepherd, Lin Tang, Daniel Weiss, Karen Alimanyana, D Hamish Wright, Kristian K Jensen
Schrodinger Inc., 1540 Broadway, New York, NY. *authors contributed equally to this work.

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**Introduction**
- CDC7 is a protein kinase that initiates and maintains DNA replication during the cell cycle S-phase by phosphorylating MCM proteins of the DNA helicase complex.
- CDC7 plays a critical role in the replication stress response by generating a platform for ATR checkpoint signaling and by activating components of the MCM2-7 complex and Cohesin complexes, which are critical for protection and restart of stalled DNA replication forks.
- Inhibition of CDC7 disrupts the ability of cancer cells to overcome replication stress and DNA damage.
- Acute myeloid leukemia (AML) is a rapidly proliferating cancer and is characterized by high replication stress and DNA damage.
- CDC7 inhibitors, and other agents that target replication stress and DNA damage response pathways, represent novel therapeutic opportunities in AML.

**Checkpont activation**
- SGR-2921 combination treatment with decitabine in patient derived AML samples results in synergistic anti-proliferative activity, in particular in p53 mutant models.

**Conclusion**
- SGR-2921 is a potent and selective CDC7 inhibitor.
- p53 mutated patient-derived AML models show higher sensitivity to SGR-2921 relative to p53 WT models and combination with decitabine results in synergistic anti-proliferative activity.
- SGR-2921 demonstrates dose dependent target engagement in multiple in vitro AML PDX SoC-resistant models representing difficult-to-treat disease.
- SGR-2921 shows dose-dependent AML blast reduction in a TP53 loss of function PDX model in vivo—differentiation from SoC (CTG-2227 model).
- In vivo treatment of AML PDX model (CTG-2240 model) with SGR-2921 results in dose dependent decrease in pMCM2 (target engagement) by IF IHC in spinal column.