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

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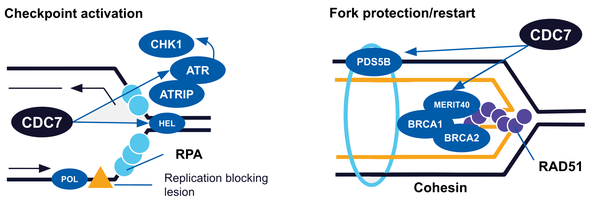
Abstract #2801

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 [1,2] and by activating components of the BRCA1-A (MERIT40) and Cohesin complexes (PDS5B), which are critical for protection and restart of stalled DNA replication forks.[1,3,4] Inhibition of CDC7 disrupts the ability of cancer cells to overcome replication stress and DNA damage.[1,5]
- Acute myeloid leukemia (AML) is a rapidly proliferating cancer and is characterized by high replication stress and DNA damage.[6,7]
- CDC7 inhibitors, and other agents that target replication stress and DNA damage response pathways, represent novel therapeutic opportunities in AML.



Schematics adapted from Nucleic Acids Res. 2021 May 7;49 (8):4239-4257

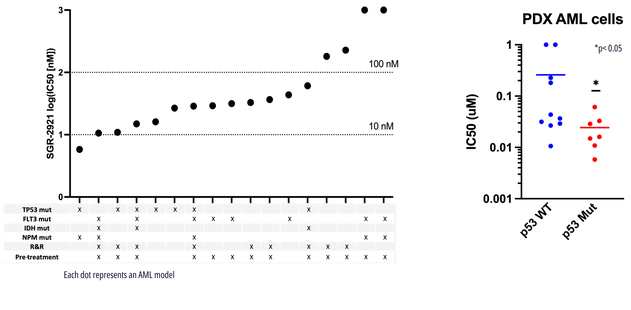
SGR-2921 is a selective and potent inhibitor of CDC7

- SGR-2921 is a potent and selective CDC7 inhibitor, demonstrates better activity across biochemical and in cell-based target engagement and cell viability assays compared to other clinical-stage CDC7 inhibitors.
- SGR-2921 is a low MW inhibitor with good aqueous solubility, as well as desirable cell permeability and kinome selectivity.

Compound	ADP-Glo IC_{50} (nM)	MSD pMCM2 (S53) IC_{50} (nM)		CTG IC_{50} (nM)	
		MOLM-16	MV-4-11	MOLM-16	MV-4-11
SGR-2921	**0.0115**	**1.23**	**1.03**	**8.45**	**57**
TAK-931	0.0343	4.69	5	77	998
LY3143921	0.4022	137	132	4557	12136
AS-0141	1.0	57	34	109	405
XL-413	0.5765	353	255	680	8565

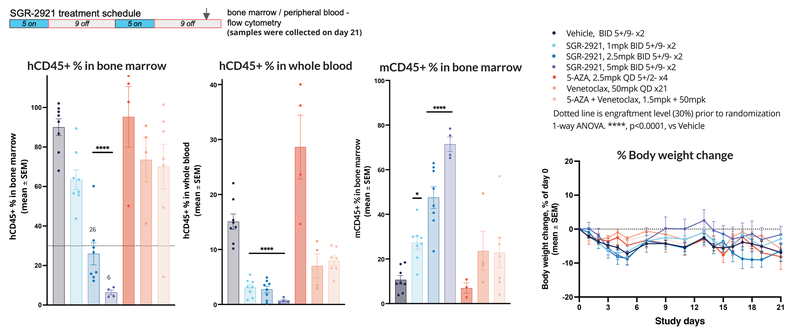
(IC_{50}s are the mean of N=3 experiments)

SGR-2921 shows potent anti-proliferative activity in AML patient-derived samples independently of driver mutations

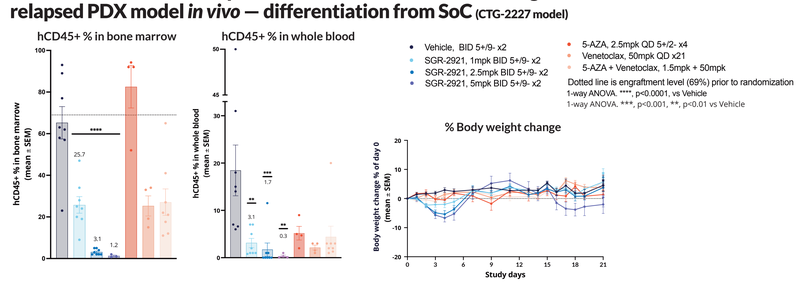


Each dot represents an AML model

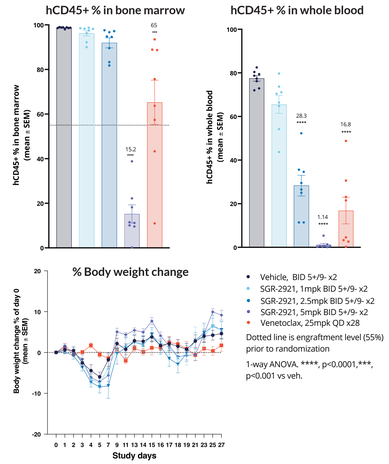
SGR-2921 shows dose-dependent AML blast reduction in a TP53 loss of function PDX model *in vivo* — differentiation from SoC (CTG-2457 model)



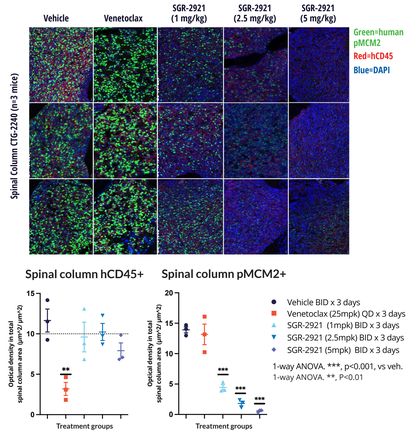
SGR-2921 shows dose-dependent AML blast reduction in a high-risk mutation and relapsed PDX model *in vivo* — differentiation from SoC (CTG-2227 model)



SGR-2921 shows significant AML blast reduction in bone marrow of a KMT2A-rearranged PDX model (CTG-2240 model)



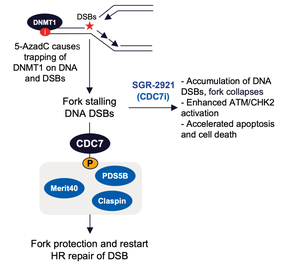
In vivo treatment of AML PDX model (CTG-2240) with SGR-2921 results in dose dependent decrease in pMCM2 (target engagement) by IF IHC in spinal column



SGR-2921 combination treatment with decitabine in patient derived AML samples results in synergistic activity *ex vivo*, particularly in p53 mutant models

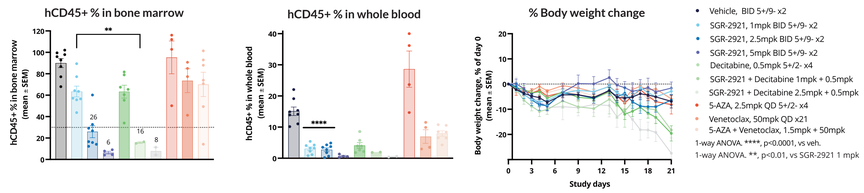
Model	CTG-2457	CTG-3661	CTG-2240	CTG-2453	CTG-3674	CTG-2702	CTG-2233	CTG-3438
TP53	Mut (Insertion)	Mut (Ser241Phe, Arg175His)	Mut (P72R)	Mut (P72R)	WT	WT	Mut (P72R)	WT
SGR-2921 IC50 (nM)	100	61	41	43	35	351	16	28
Decitabine IC50 (nM)	4780	470	1070	193	146	10000	106	632
SGR-2921 Decitabine (ZIP Synergy score)	28	23	17.5	13.3	12	NA	-15	-24

Synergy Score: 30, 20, 10, 0, -10, -20, -30

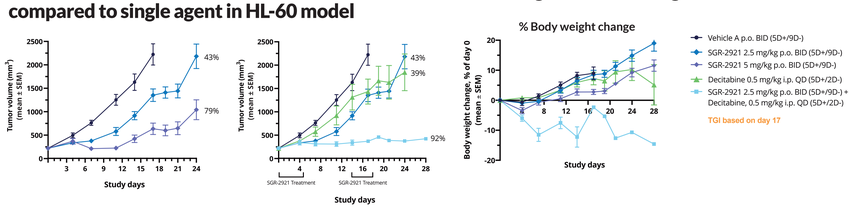


Decitabine (Aza-dC) and azacitidine (Aza-C) are cystine analogs that are metabolized to 5-Aza-2-deoxy-cytidine, incorporated into DNA and covalently trapped on DNA methyltransferases, causing replication stress and DNA damage (Orta et al. *Nucleic Acids Research*, 2013, Vol. 41, No. 11). Decitabine is more efficiently incorporated into DNA relative to azacitidine, and we have previously shown that SGR-2921 combination treatment in AML cell lines shows synergistic anti-proliferative activity at lower doses of decitabine relative to azacitidine, likely due to the increased incorporation of decitabine into DNA.

SGR-2921 combination treatment with decitabine results in synergistic tumor growth inhibition compared to single agent in AML PDX model (CTG-2457)



SGR-2921 combination treatment with decitabine results in significant tumor growth inhibition compared to single agent in HL-60 model



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 *ex vivo*, and combination with decitabine results in synergistic anti-proliferative activity.
- SGR-2921 demonstrates dose dependent target engagement and single agent activity in multiple *in vivo* AML PDX SoC-resistant models representing difficult-to-treat disease.
- SGR-2921 shows synergistic activity in combination with decitabine in p53 mutated CDX and PDX AML models *in vivo*.
- A Phase 1 dose-escalation study of SGR-2921 in patients with AML or myelodysplastic syndrome was recently initiated. NCT#05961839

(1) Mol Cell. 2021 Feb 4;81(3):426-441 (2) Oncogene. 2008 May 29;27(24):3475-82 (3) Genes Dev. 2015 Sep 15;29(18):1955: 2506; (4) J Biol Chem. 2020 Jan 3;295(1):146-157 (5) Sci Adv. 2021 May 21;7(21):eabf0197 (6) Cancer Res. 2009 Nov 15;69(22):8652; (7) Cancer Research Communications (2022) 2 (6): 503–517 Schematics adapted from Nucleic Acids Res. 2021 May 7;49(8):4239-4257

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