0352: ADDITIVE EFFECT OF GNS561, A NEW LYSOSOMOTROPIC SMALL MOLECULE, IN COMBINATION WITH CISPLATIN OR GEMCITABINE FOR THE TREATMENT OF INTRAHEPATIC CHOLANGIOCARCINOMA

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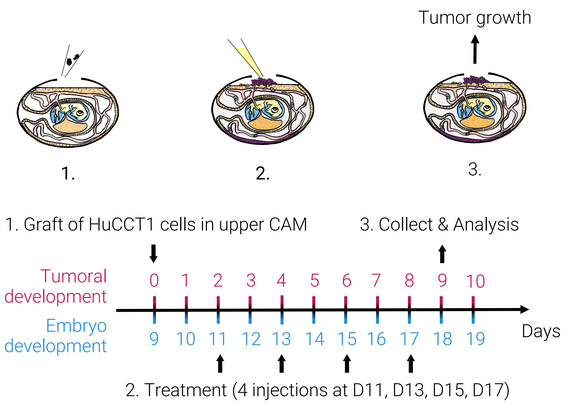
Introduction

- Intrahepatic cholangiocarcinoma (iCCA) is a rare malignant tumor of the biliary tract with growing incidence and dismal prognosis.
- To date, the recommended first-line therapy remains gemcitabine-platinum combinations, with modest efficacy.
- Here, we investigated the antitumor activity of GNS561, a small molecule with high liver affinity and orally available, in multiple in vitro iCCA models (cell lines and patient-derived cells) and in a chicken chorioallantoic membrane (CAM) xenograft model and assessed its activity in combination with gemcitabine (gem) and cisplatin (cis).

Methods

- Measure of cell viability and caspase 3/7 activation using CellTiter Glo® and Caspases-Glo® 3/7 assays (Promega)
- Drug combinations analysis with MacSynergy
- Autophagic flux was studied by LC3-II quantification
- Lysosomes detection using LysoTracker Red
- Assessment of In vivo GNS561 activity using HuCCT1 cells in a CAM xenograft model (treatment every 2 days during 8 days)
- Toxicity evaluation by scoring the number of dead embryos and looking for morphological or functional abnormalities in the surviving embryos



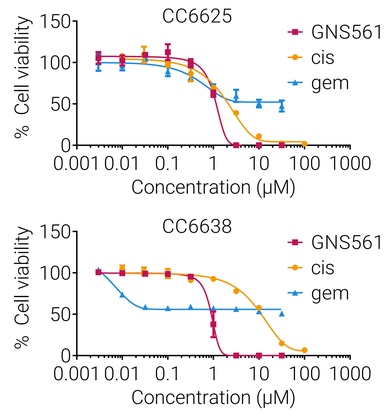
Results

A GNS561 is potent in iCCA cell lines (72h) and in iCCA patient-derived cell lines (7 days)

	Mean IC_{50} ± SD (µM)		
Cell line	GNS561	cis	gem
HuCCT1	1.5 ± 0.2	16.5 ± 0.5	75% max. inh. at 15 µM
RBE	1.7 ± 0.1	8.2 ± 1.2	60% max. inh. at 6 µM

	GNS561		cis		gem	
Model	IC_{50} (µM)	Max. inh.	IC_{50} (µM)	Max. inh.	IC_{50} (µM)	Max. inh.
CC6205	1.56	99.9%	0.03	86.4%	1.62	99.5%
CC6638	0.86	100.0%	> 10	49.2%	10.54	93.5%
CC6279	1.48	100.0%	0.01	83.7%	6.17	98.8%
CC6625	1.14	100.0%	13.61	52.6%	1.89	98.2%
CC6658	1.23	100.0%	0.53	90.0%	0.85	99.8%

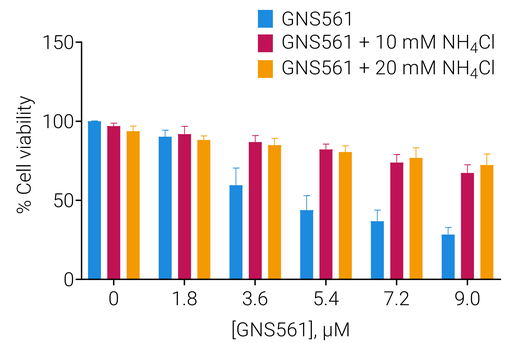
B In patient-derived cell lines, GNS561 was efficient in models with low sensitivity to gemcitabine (7 days)



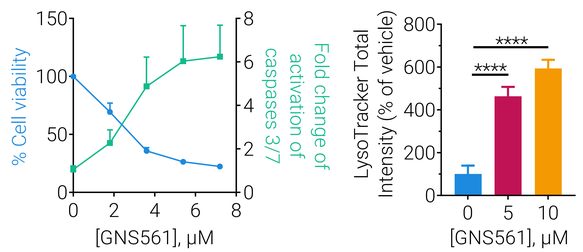
C Additive combinations of GNS561 with cis and gem (RBE, 72h)

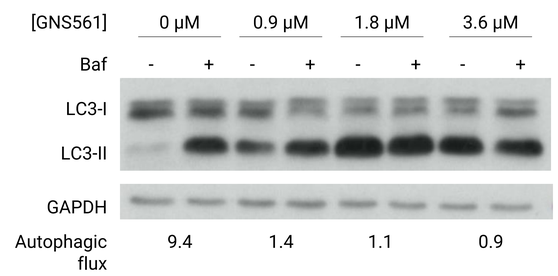
	95% confidence interval (µM²%)			
	GNS561 / cis		GNS561 / gem	
	SYNERGY	ANTAGONISM	SYNERGY	ANTAGONISM
Mean	47	-22	14	-22
SD	39	10	5	12

D GNS561-mediated cell death was related to its lysosomotropism (RBE, 24h)

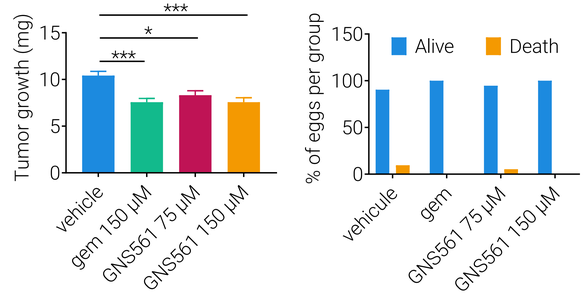


E GNS561 induced apoptosis via caspase activation and lysosomal dysregulation (dose-dependent build-up of enlarged lysosomes and autophagy flux inhibition) (RBE, 24h)





F GNS561 effect was confirmed in a CAM xenograft model, with a good tolerance at doses high enough to induce an antitumor effect



Conclusion

- **Based on this study, we provide a rationale for targeting lysosomes as a promising therapeutic strategy in iCCA in human clinical trials and use of GNS561 alone or in combination with gemcitabine and cisplatin.**
- **GNS561 is currently tested in a phase 1b/2a international clinical trial (NCT03316222).**

References & Contacts

Brun S, Bassissi F, et al. « GNS561, a new lysosomotropic small molecule, for the treatment of intrahepatic cholangiocarcinoma ». Invest New Drugs. 2019

SB, CA, FB, CS, MN, JT, MR, JC, ER and PH are employees of Genoscience Pharma. SB, CA, FB, CS, ER and PH are shareholders of Genoscience Pharma. SB, FB, JC and PH are co-inventors of a pending patent of GNS561 in cancer.

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