Captor Therapeutics®

Research & Development Day

The Power of Targeted Protein Degradation (TPD)
and How It Could Redefine
the Hepatocellular Carcinoma (HCC)
Therapy Paradigm

May 18th 2022

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About Captor

A global, highly qualified team

- Based in Wroclaw (Poland) and Basel (Switzerland)
- Backed by private investment and non-dilutive public funds
- Significantly oversubscribed IPO in April 2021
- Disruptive platform in TPD drug discovery
- Five drug programs in large potential markets
- ~97 FTEs on board, almost half of them are PhD level specialists
- Joint experience from over 11 leading international universities
- 1,100 m^2 of laboratory space equipped with state-of-the-art equipment

Captor’s TPD Platform

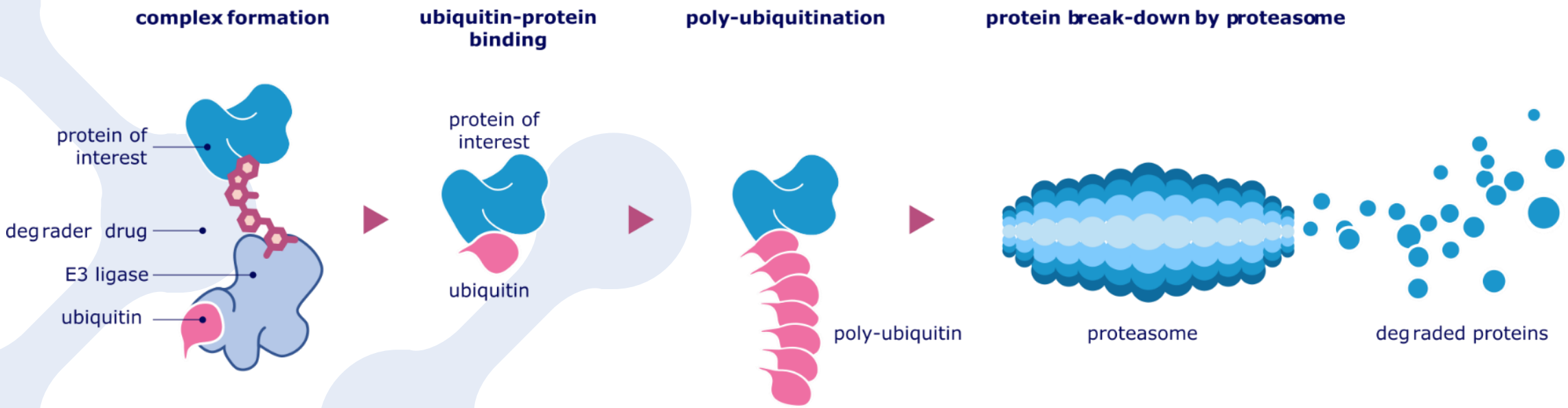
Michał Walczak, Ph.D.

Co-founder

Chief Scientific Officer

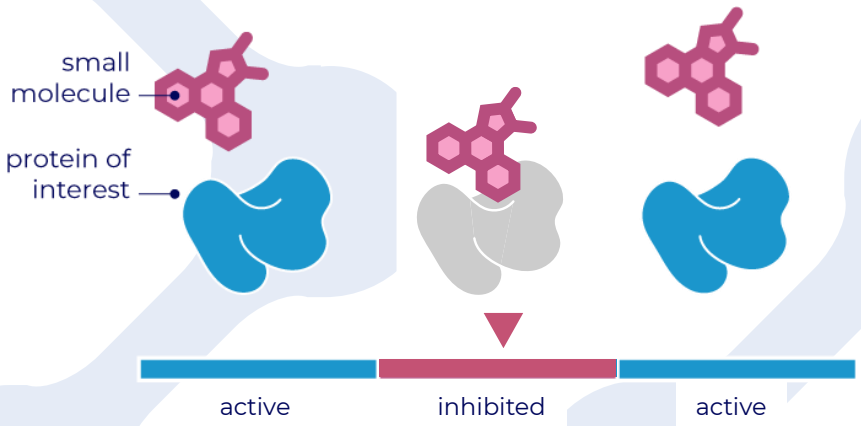
Captor Therapeutics®

Principle of targeted protein degradation



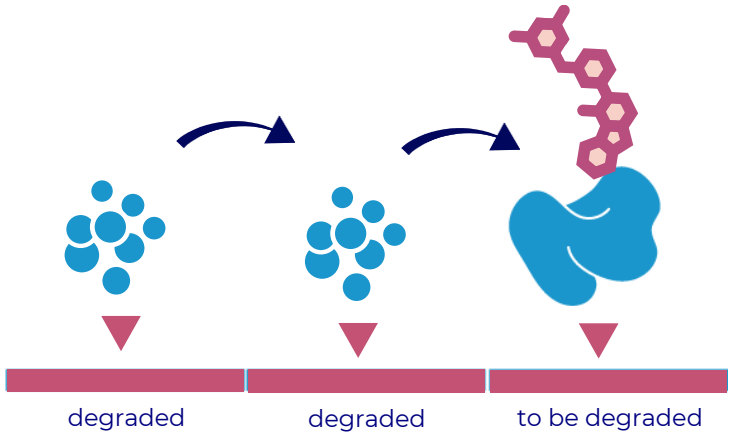
A totally different pharmacology

OCCUPANCY-DRIVEN EFFECT
classical small molecules



A small molecule inhibits one target protein molecule at a time and only when it is bound to it.

EVENT-DRIVEN EFFECT
degrader drug



A degrader drug can degrade multiple target proteins one after another.

A revolutionary approach

Targeted drugs (inhibitors, antibodies)

Benefits

+ Highly specific due to targeting
+ Fewer side effects
+ Efficacious in some previously untreatable diseases

Limitations

- Relatively small number of potential drug targets
- Often costly to develop and manufacture
- Resistance or tolerance over time
- Biologicals often injectable only

Targeted Protein Degradation

Benefits

+ 5x more druggable targets compared to traditional drugs
+ Potential in currently untreated diseases
+ Potential to overcome resistance to traditional drugs
+ Opportunity for oral delivery

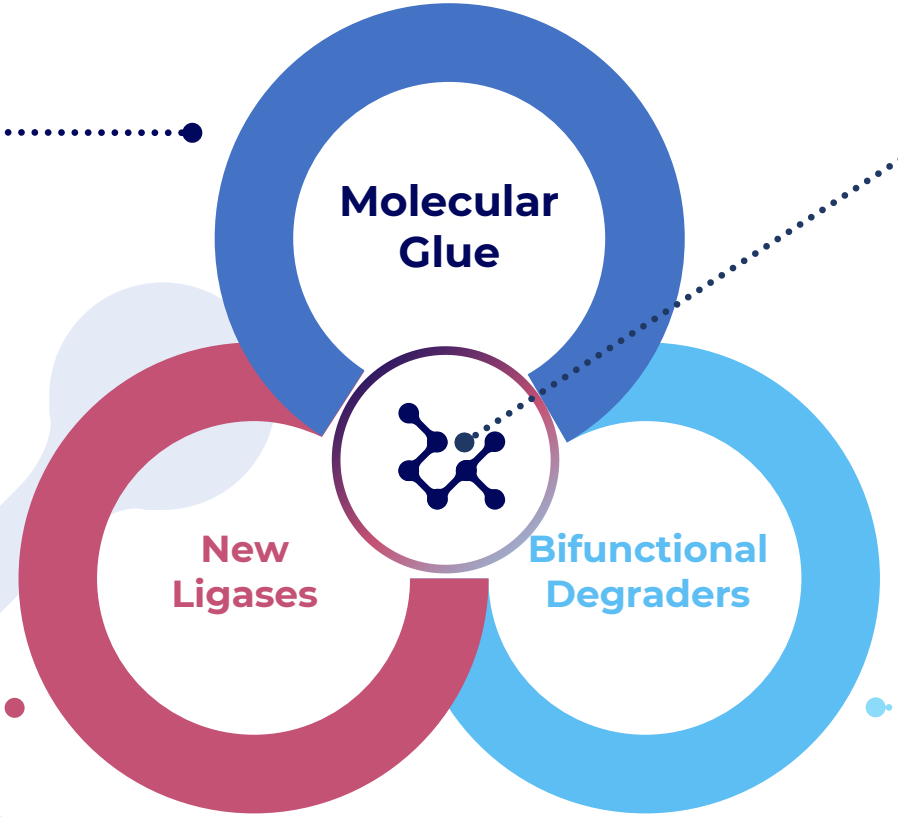
Limitations

- New and evolving field

Captor's Optigrade™ platform

Molecular Glues

- Screening paradigm rationalized to find new targets
- Library of proprietary CRBN-based molecular glues
- Selective degradation and novel efficacy profiles



Platform differentiation

- Lead compounds both in molecular glues and bifunctional degraders
- Structure-based hit finding and lead optimization
- Novel and proprietary chemistry

Evolving LiLis™ Platform

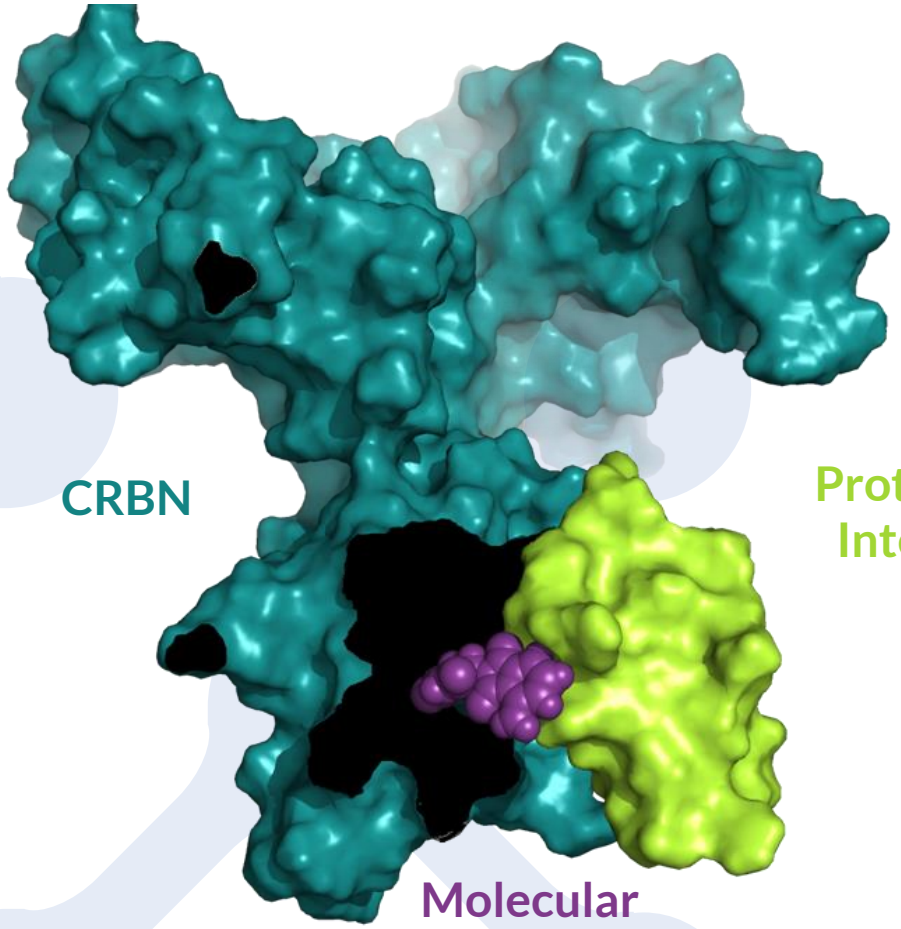
- Library of E3 Ligase proteins and ligands
- Potential improved safety
- Reduced opportunity for resistance
- Tissue specific expression

Bifunctional Degraders

- CRBN-based degraders co-degrade IKZF1/3 resulting in side effects
- Captor's ligands are highly selective
- Includes degraders against previously undrugged targets

Molecular Glue

Molecular glues and Cereblon degrome

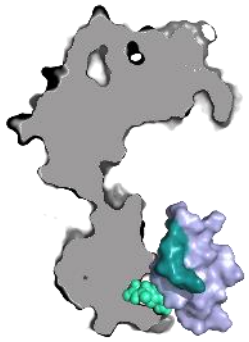


ZnF Target
ZNF517
ZNF582
ZNF653
IKZF1/3
ZFP91
IKZF2/4
PATZ1

Sievers Q., Petzold G. et al. *Science* (2018) 362(6414)

Molecular Glue

Molecular glue discovery engine

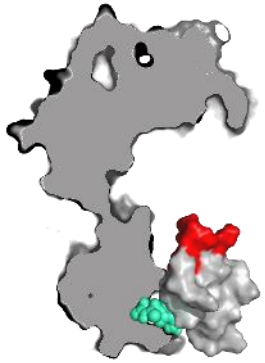


Extended positive degron

Degron sequence analysis

Protein-protein docking

Geometric AI

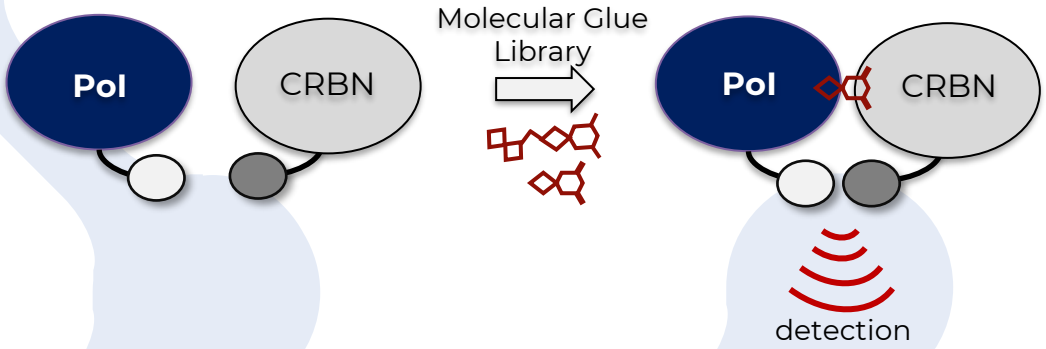


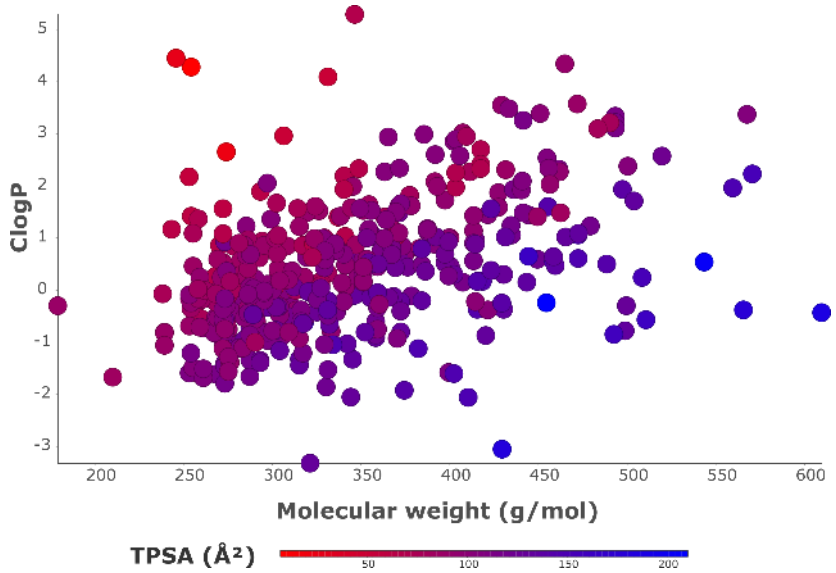
Extended negative degron

Protein production and testing

Data Augmentation

Molecular glue toolbox





High throughput CRBN recruitment assay developed

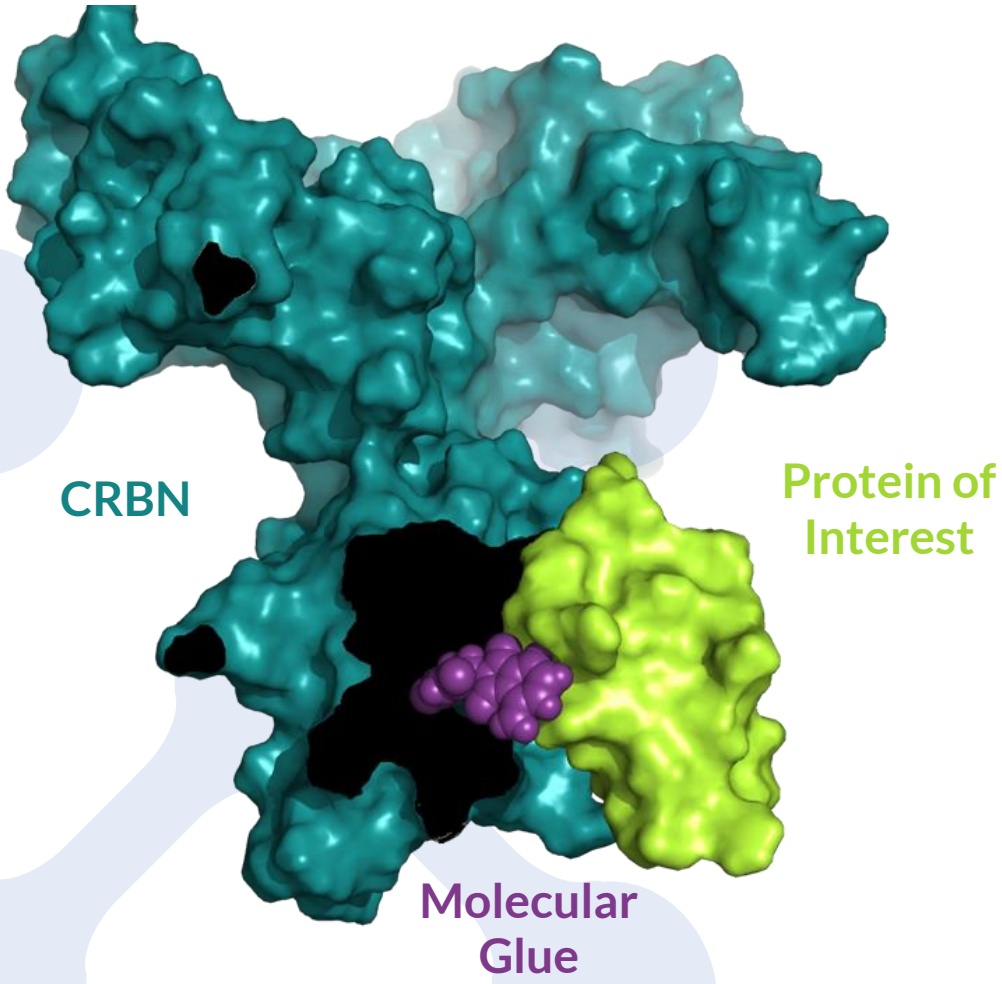
- Multiplexed by proteins
- Detection of weak recruiters (~10 µM) unlike cellular degradation assays
- High sensitivity (beyond proteomics)
- Control of the target levels

A unique library of molecular glues

- Excellent drug-like properties
- Rapidly growing focused library developed by structure-based design
- Many novel chemotypes recruiting new target classes
- Patent applications filed

Molecular Glue

Beyond the Cereblon ZnF degrome



ZnF Target	Non-ZnF Target
ZNF517	PLK kinases
ZNF582	NIMA kinases
ZNF653	PAK kinases
IKZF1/3	GTPases
ZFP91	WD repeat
IKZF2/4	Chaperones
PATZ1	Phosphatases

Sievers Q., Petzold G. et al. *Science* (2018) 362(6414)

Bifunctional degrader discovery

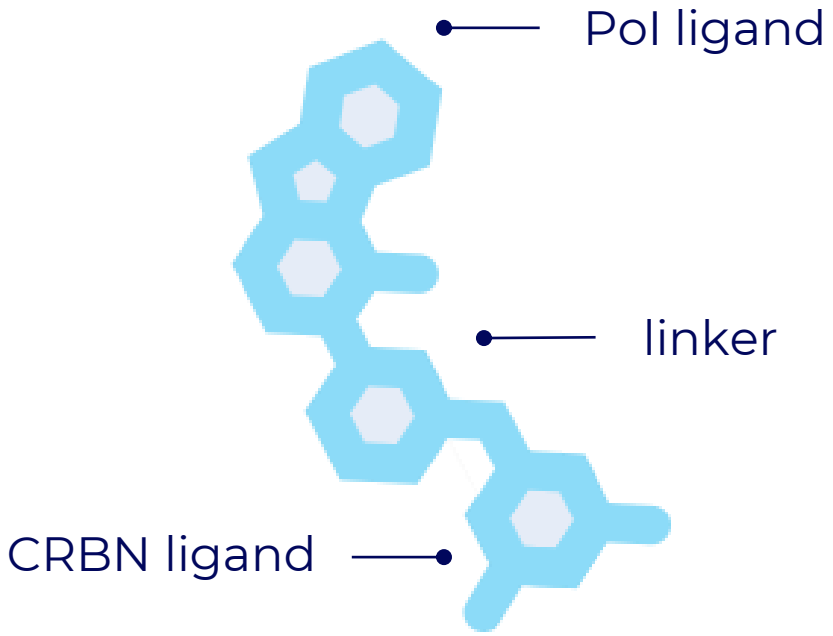
Bifunctional Degraders

Protein of Interest (PoI) ligand generation capabilities

- Modern ligand discovery methods (SBDD and FBLD)
  - Biophysical screening
  - X-ray crystallography
  - CryoEM and NMR via established collaborations
- Multiple libraries of compounds

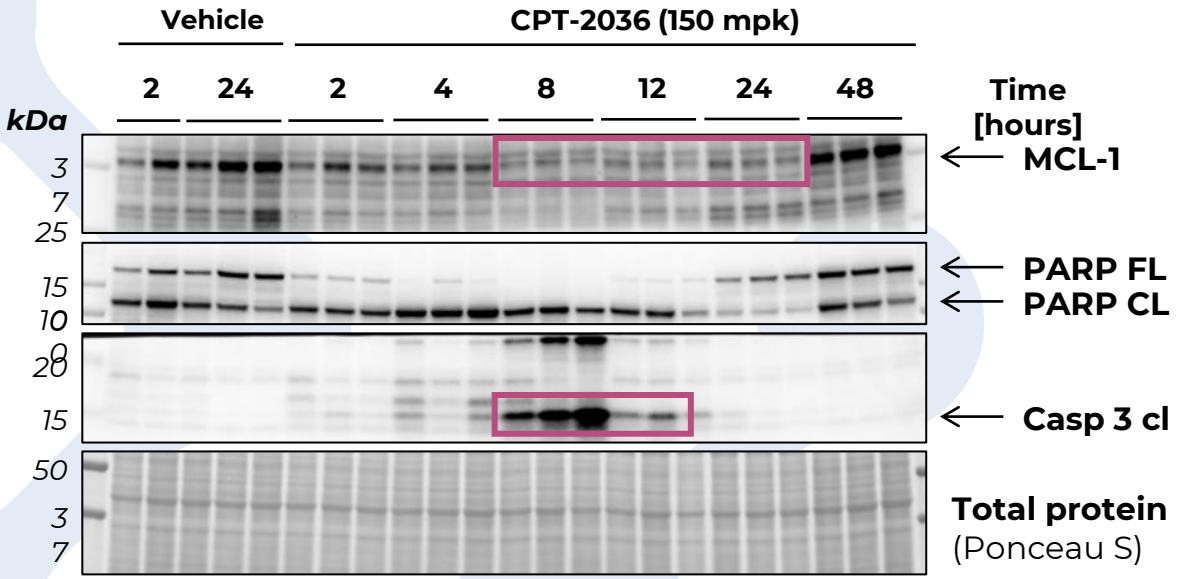
Proprietary CRBN ligands

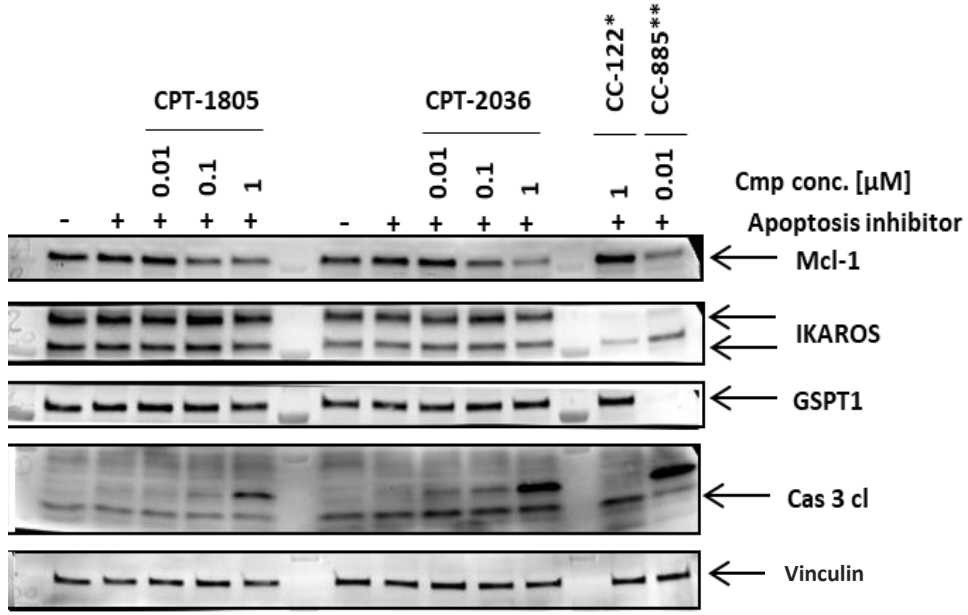
- Ligands with no intrinsic glue activity for higher selectivity
- Ligands with improved physicochemical properties



Selective bifunctional degraders of MCL-1 protein

Bifunctional Degraders





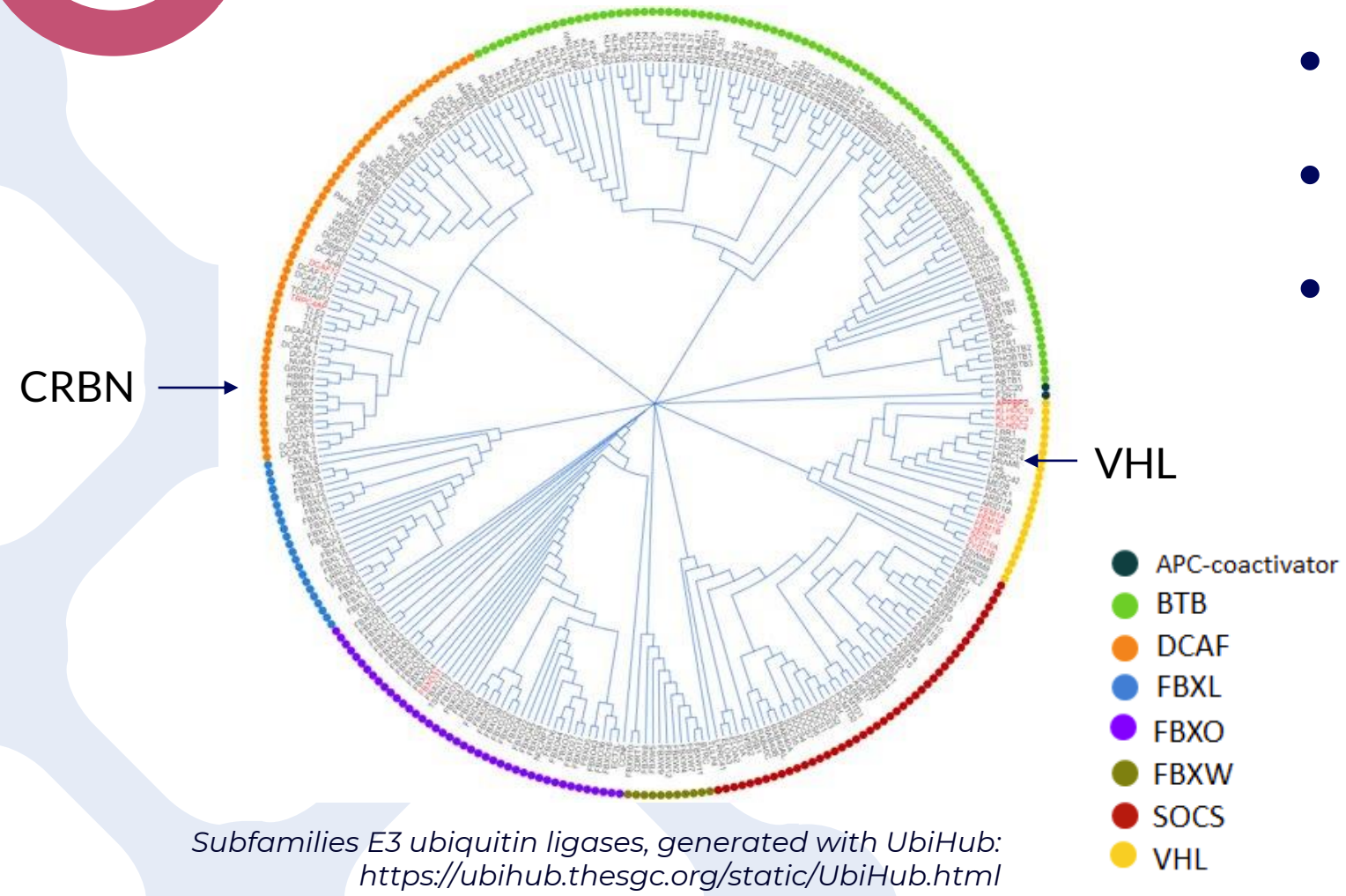
*CC-122 – IKAROS degrader (Celgene)
**CC-885 – GSPT1 degrader (Celgene)

Potent MCL-1 degradation and induction of apoptosis *in vivo*

MCL-1 degraders do not affect levels of neosubstrates IKAROS or GSPT1, unlike CC-122 and CC-885

Huge potential for degraders based on novel ligases

New Ligases



Subfamilies E3 ubiquitin ligases, generated with UbiHub: https://ubihub.thesgc.org/static/UbiHub.html

- There are ~600 different E3 ubiquitin ligases
- So far, ligands identified to only a small fraction of E3 ligases
- All clinical-stage degraders based on CRBN (and single one on VHL)

Selection of Novel Ligases for Next Generations of Degraders

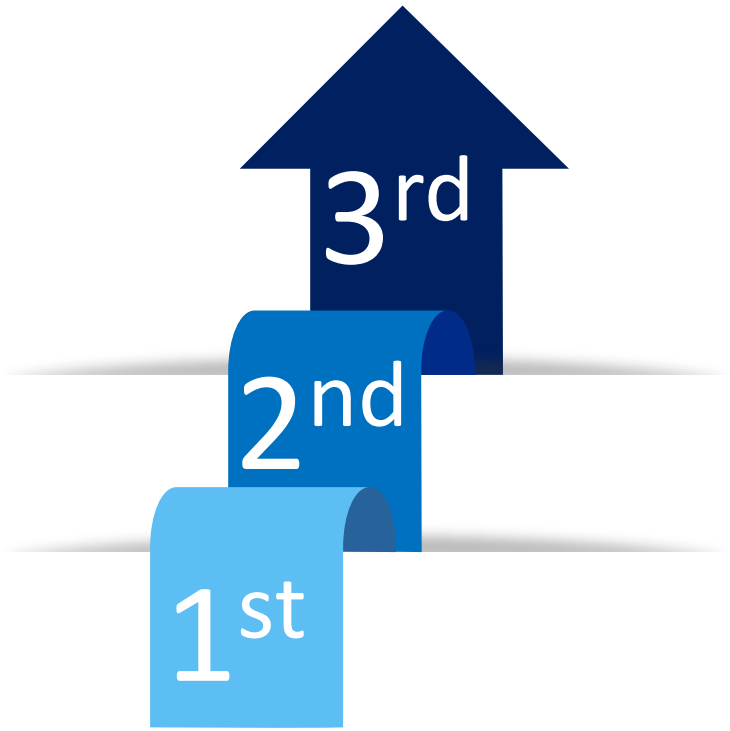
New Ligases

Captor's 3rd generation of degraders

Tissue specific expression
Role in diseases, e.g. cancer

Captor's 2nd generation of degraders

Essentiality
Safety
Production feasibility
"Ligand-able" and crystallizable
Assays available



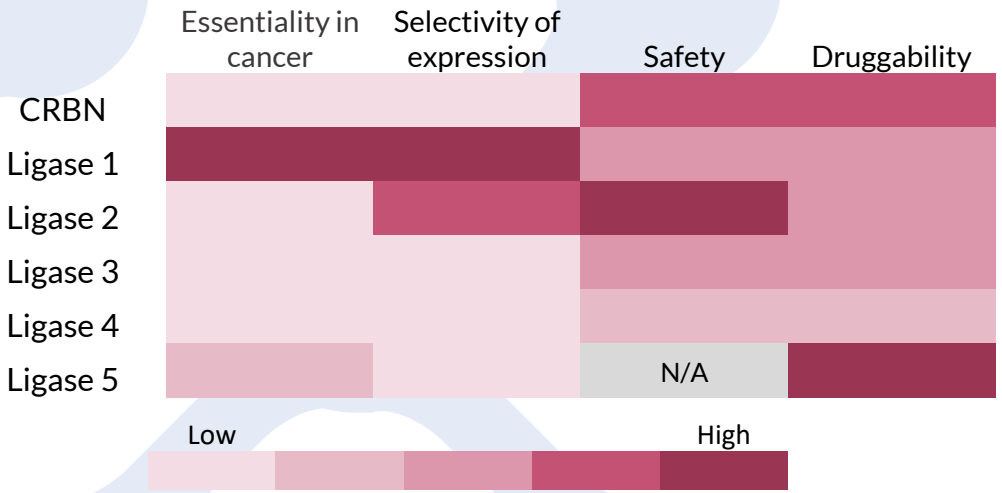
1st Generation

Discovered by luck/serendipity

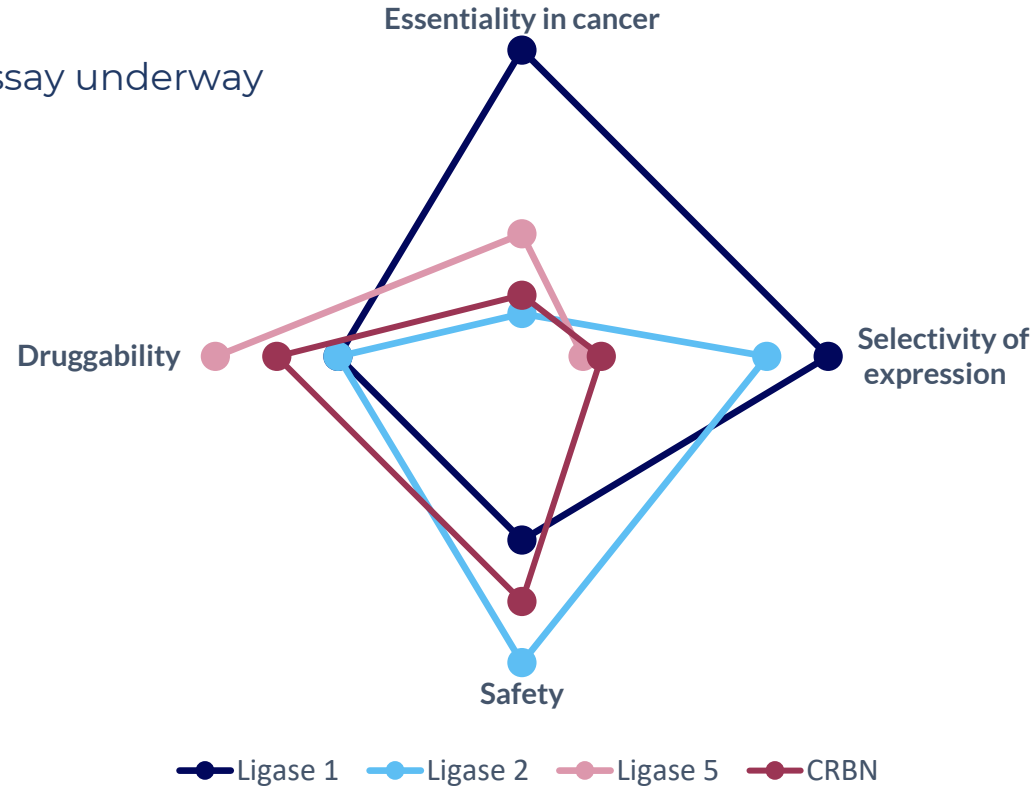
LiLis ™ - ligands to novel E3 ligases

New Ligases

- Expertise in E3 ligases: ~100 ligases expressed
- Ligase ligand generation for novel E3s with differentiated profiles
- Ligands identified and crystal structures solved
- Prototype degraders for 2 new ligases with a new assay underway



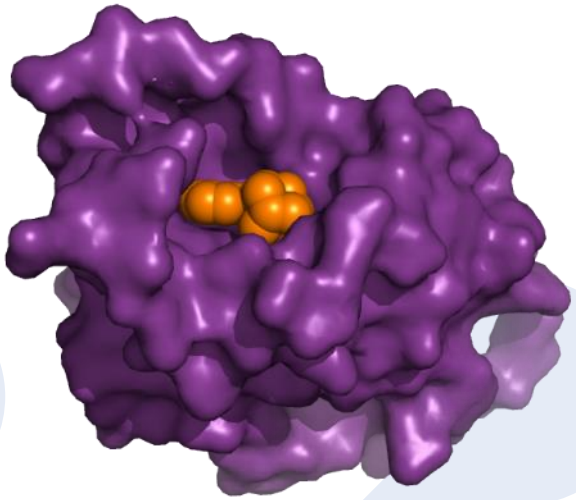
A snapshot of Captor's Ligase Knowledge Database



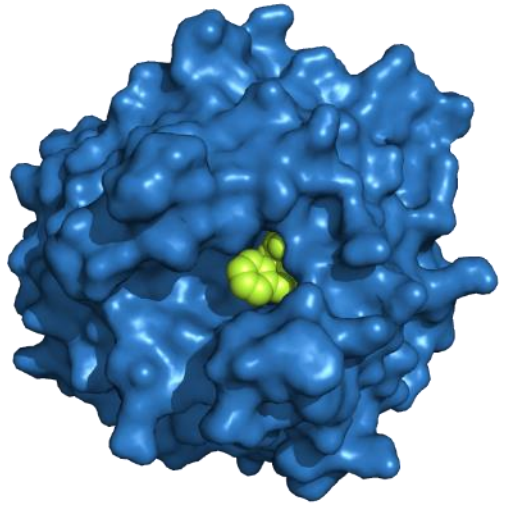
Multidimensional analysis of ligases' biological profile

New Ligases

Highly potent ligands identified for first two priority ligases



- FBS identified several hits (50µM to 1 mM)
- Current best ligand at ~20 nM
- > 60 structures, many with < 2A resolution



- Cullin-based substrate receptor
- Current best ligands at 400 nM
- > 10 X-ray structures with fragments solved

Critical capabilities in protein structural studies:
- X-ray crystallography in house
- NMR and Cryo-EM through local collaborations

The Captor pipeline

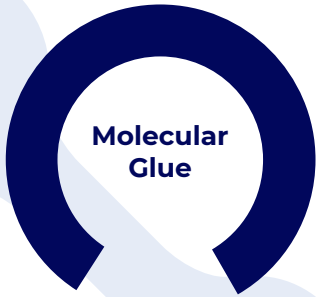
#	Indications	Modality	Discovery	Preclinical*	IND Filing	FIH**
CT-01	Hepatocellular carcinoma	**MG**				**2023**
CT-02	Autoimmunity Hematological cancer	**MG**				
CT-03	Liquid & solid tumors **MCL-1** target	**BID**				
CT-04	Colorectal cancer	**BID**				
CT-05	Autoimmunity Solid tumors & other	**BID**				

Partnered Program

	Gastrointestinal diseases, e.g. IBD			Partnership with Sosei Heptares		

**Preclinical stage include IND-enabling studies*
***First in Human; at least 2 projects expected to enter Phase 1 by 2023*
***BID** – Bi-functional Degrader; **MG** – Molecular Glue*

Drug candidates advancing towards the clinic



Project: CT-01
Positioning: Unique degradation profile
Main indication: hepatocellular carcinoma
Secondary indication: other solid tumors

- Anticancer activity in different HCC models *in vitro*
- Excellent *in vivo* efficacy with oral administration
- Full tumor regression observed at low doses

Project: CT-03
Positioning: First-in-class MCL-1 degrader
Main indications: blood cancers
Secondary indication: solid tumors

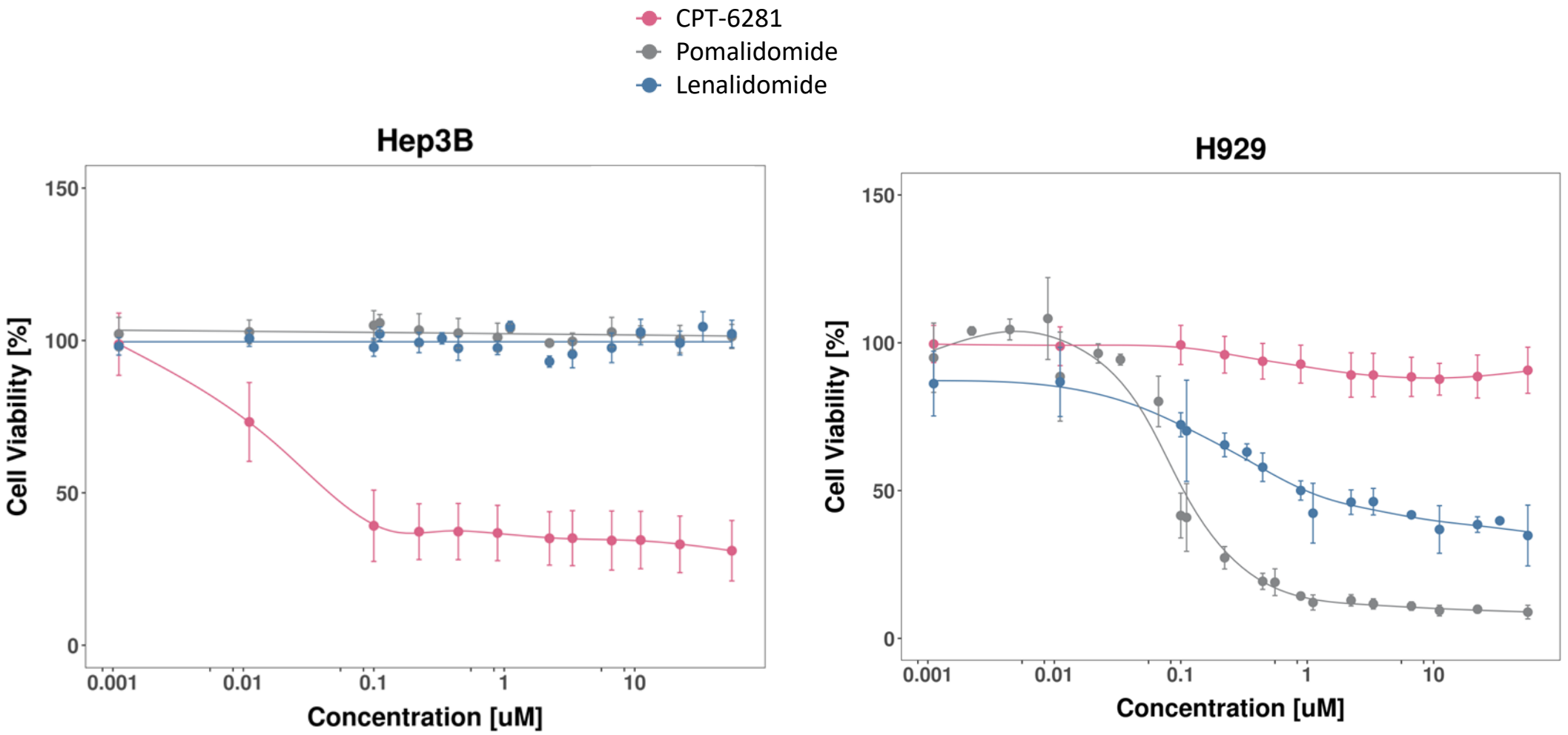
- Anticancer activity *in vitro* in both liquid and solid tumors
- Potent and sustained MCL-1 degradation *in vivo* after single injection
- Tumor shrinkage *in vivo* associated with MCL-1 degradation

To enter clinical stage in 2023

A Novel Approach to Hepatocellular Carcinoma (HCC) Therapy

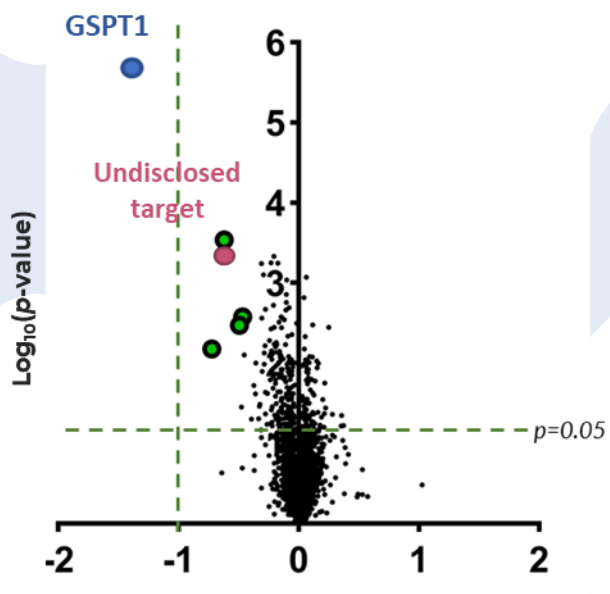
Paweł Dobrzański, Ph.D.
Biology Department Director
Captor Therapeutics®

Targeting HCC with Molecular Glues



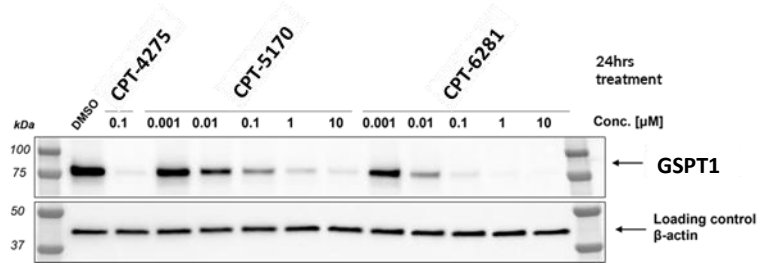
CPT-5170 and CPT-6281 have a unique degradation profile

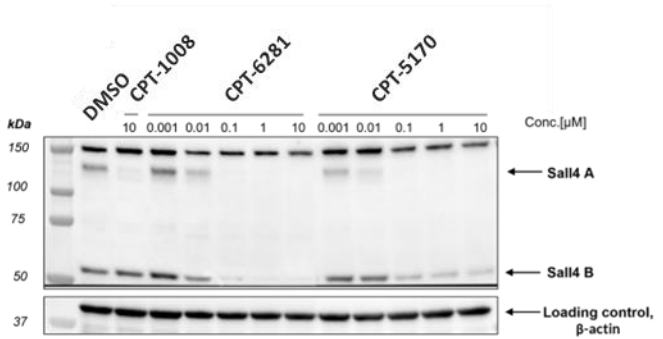
Proteins down-regulated in response to CT-01 compounds treatment in Hep3B cells

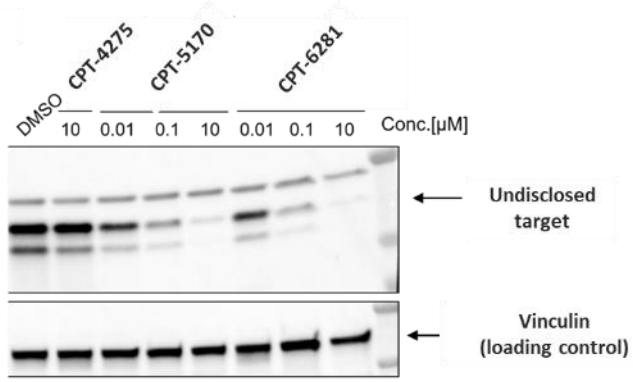


Log_2Fold-change
CPT-6281 (5µM) vs DMSO

Potent degradation of GSPT1, SALL4 and of an undisclosed target

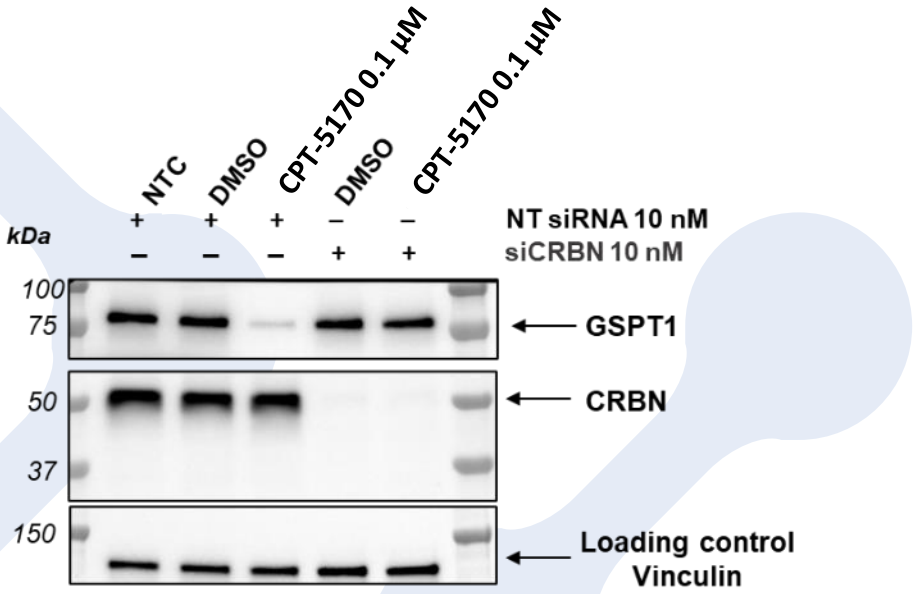


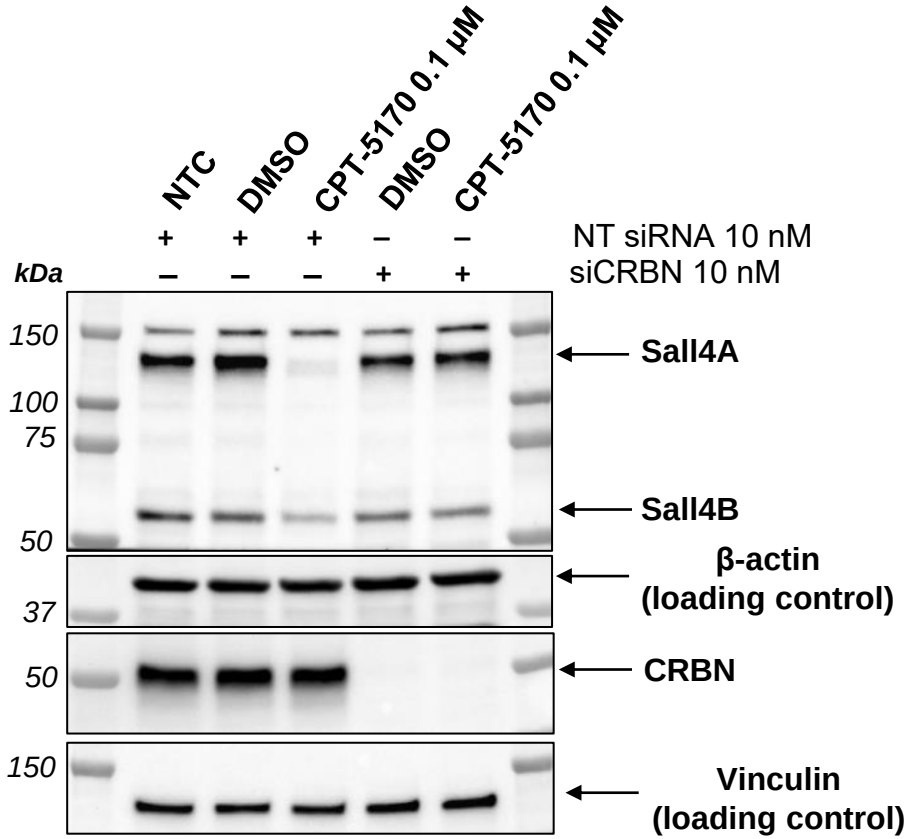




Hep3B cells, 24h treatment

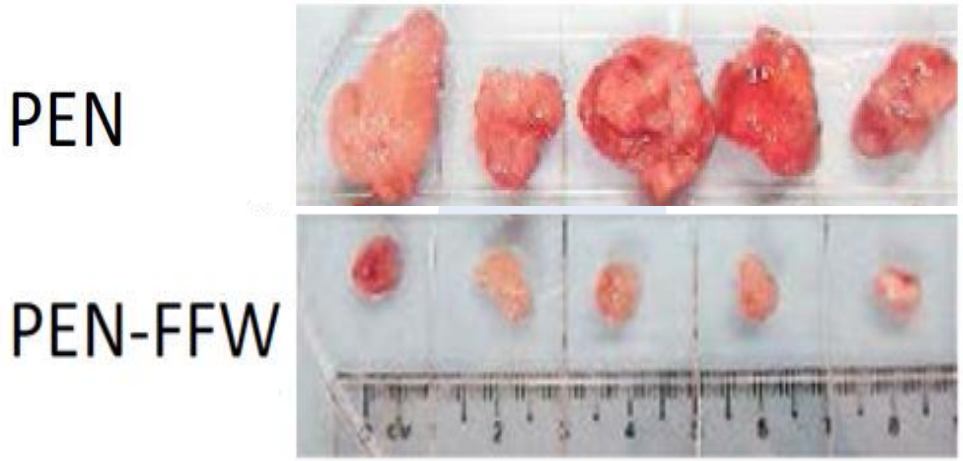
Degradation of CT-01 targets in Hep3B is Cereblon dependent





Rationale for targeting SALL4 in HCC

- SALL4 is a transcription factor which is silenced in the adult liver. It is re-expressed in a sub-group of hepatocellular carcinomas and in several other cancers
- SALL4 interacts with the NuRD complex to repress PTEN gene expression and to activate the AKT pathway
- SALL4+ HCC cells have more aggressive phenotype and are associated with poor prognosis



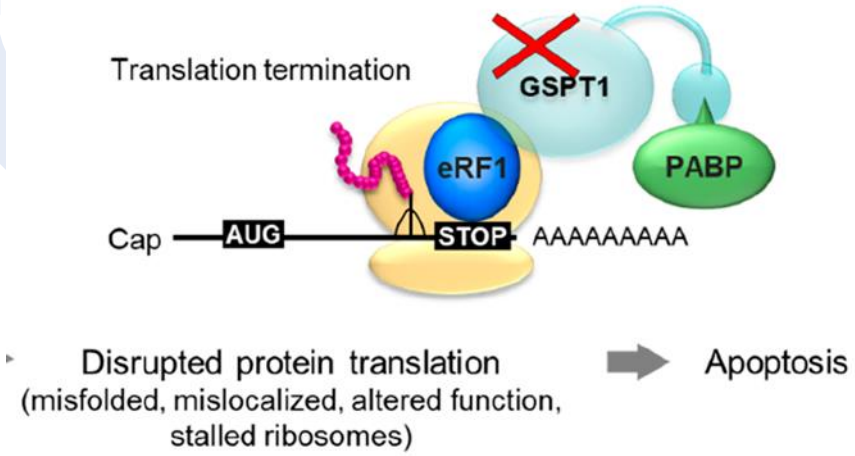
Yong KJ. N Engl J Med 2013; 368:2266-2276

Figure 1: PEN-FFW, a peptide disrupting SALL4-NuRD interaction, leads to dramatic inhibition of xenograft tumor growth (SNU398 - liver cancer).

Liu, Bee Hui et al. Proc Natl Acad Sci U S A. 2018 Jul 24;115(30):E7119-E7128

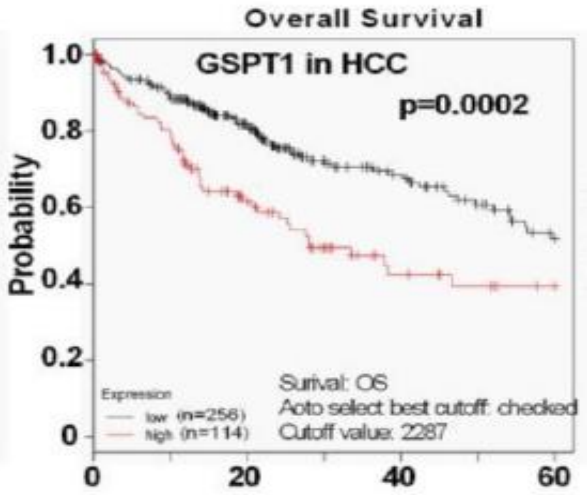
Rationale for targeting GSPT1 in HCC

GSPT1 (eRF3A) is a translation termination factor critical for the release of nascent polypeptides from ribosomes



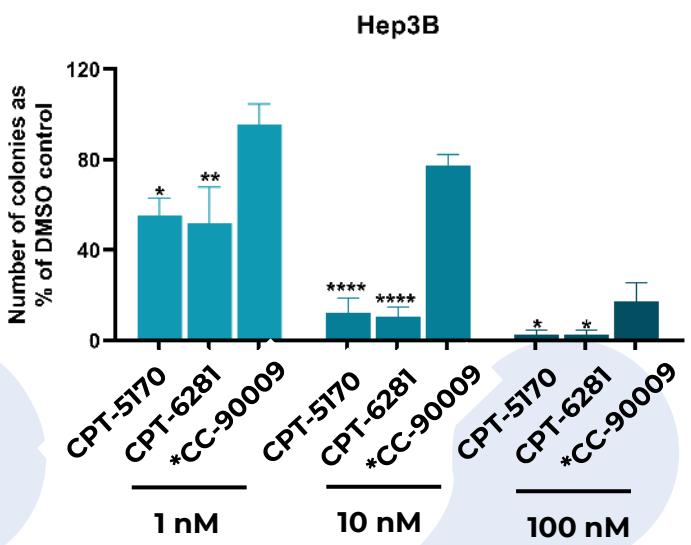
1. The rapid and continuous proliferation of highly malignant cancers requires efficient protein synthesis
2. Translational adaptations are crucial components of cancer development and progression
3. Multiple oncogenic signaling pathways drive tumorigenesis by converging on translation

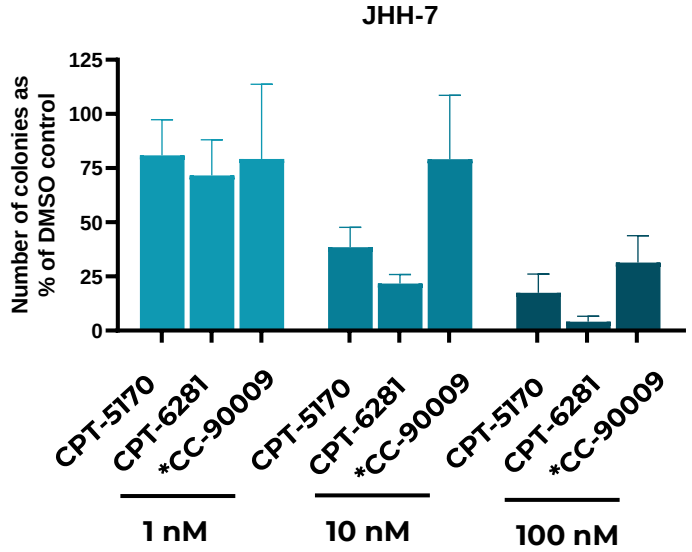
4. GSPT1 levels are increased in many cancers including HCC
5. High levels of GSPT1 expression in HCC are associated with a poor prognosis



Wu et al. J.Cancer 2020; 11(8)

CPT-5170 and CPT-6281 are more potent than CC-90009 in HCC cell lines





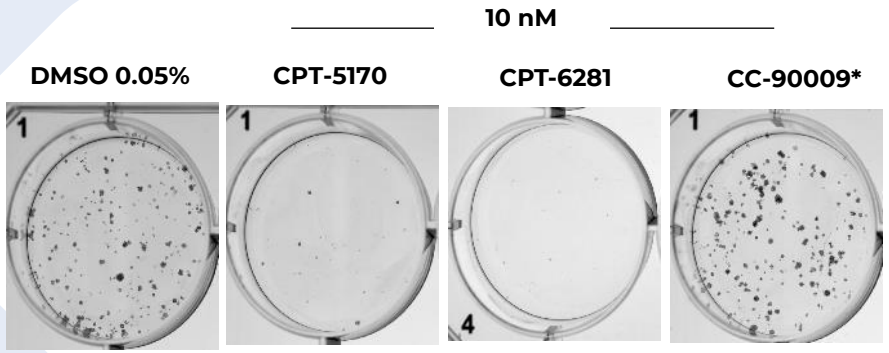
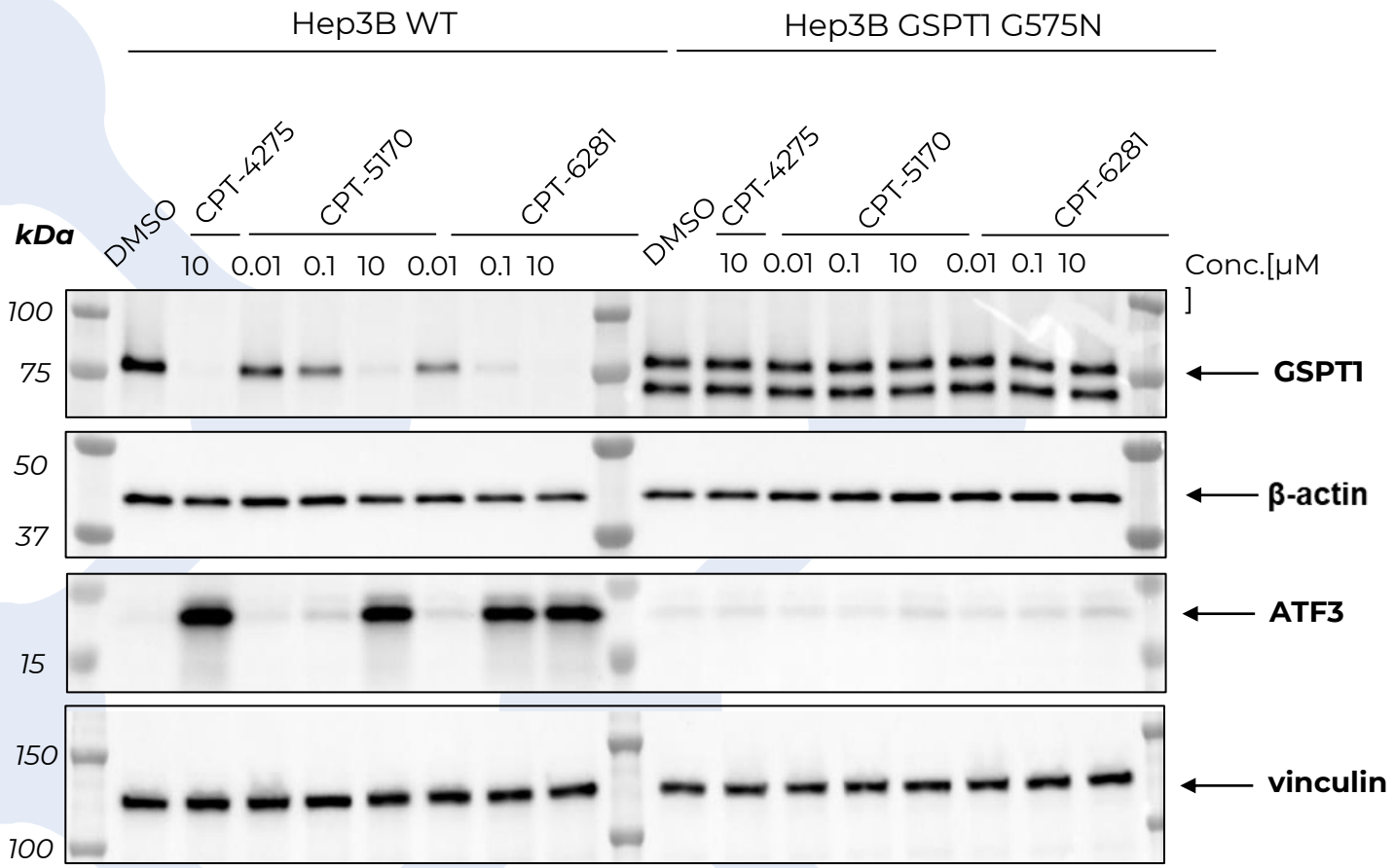
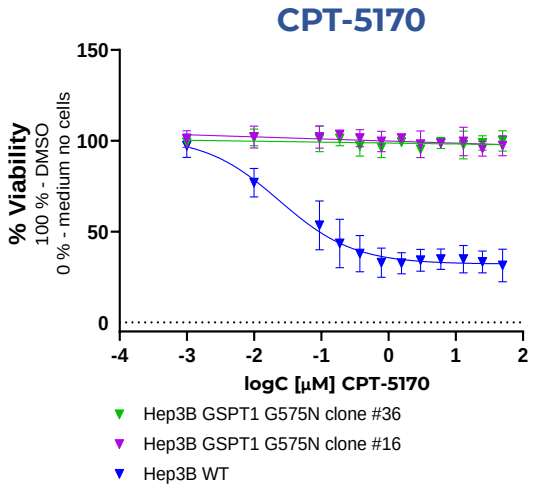


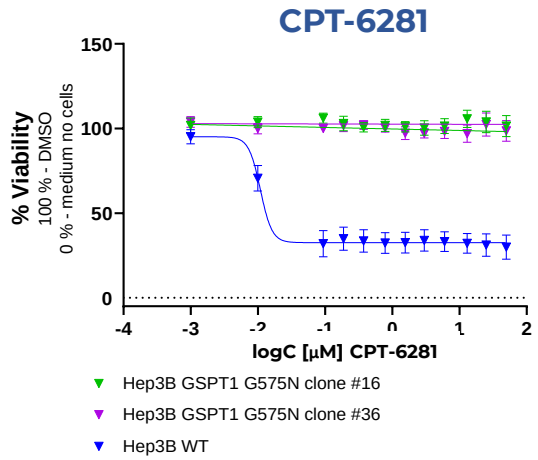
Fig. *Representative images of colony formation assay in Hep3B for DMSO control and 10 nM dose of tested compounds.*

***CC-90009 -** clinical-stage selective **GSPT1** degrader, (Celgene/BMS)

Degradation of GSPT1 by CPT-5170 or CPT-6281 mediates ISR[1] and apoptosis

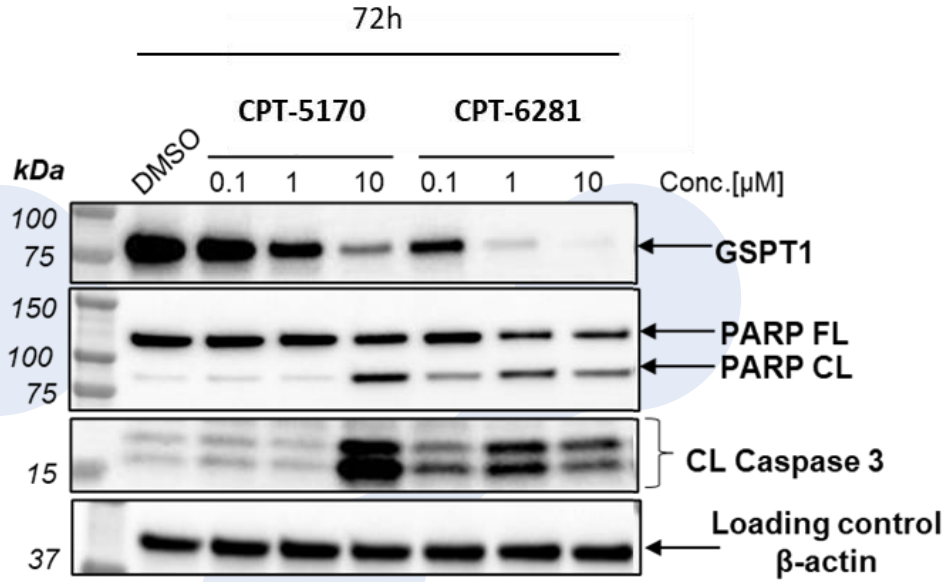


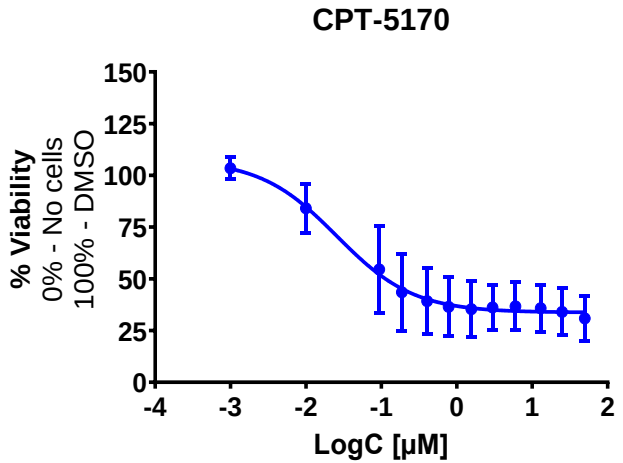


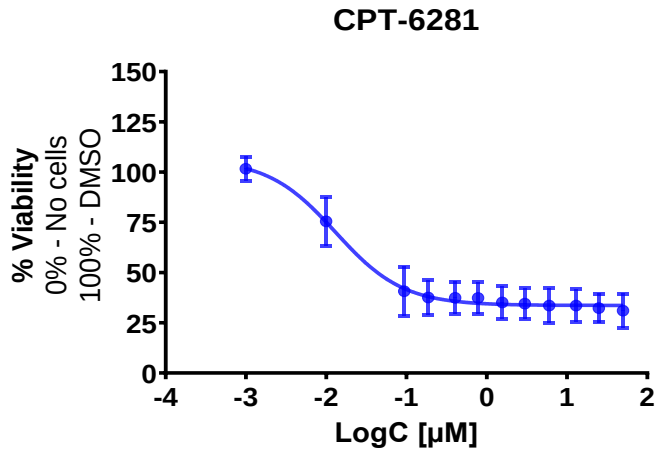


1 - Integrated Stress Response

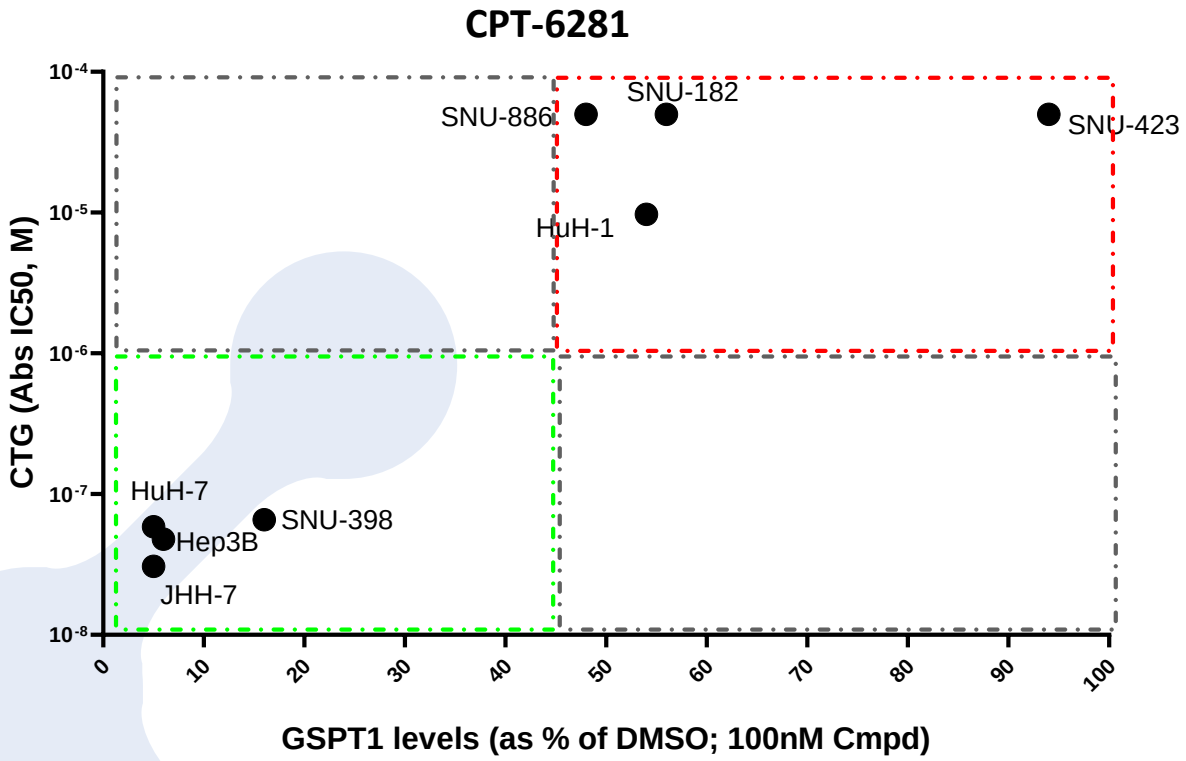
CPT-5170 and CPT-6281 induce apoptosis in Hep3B HCC cells



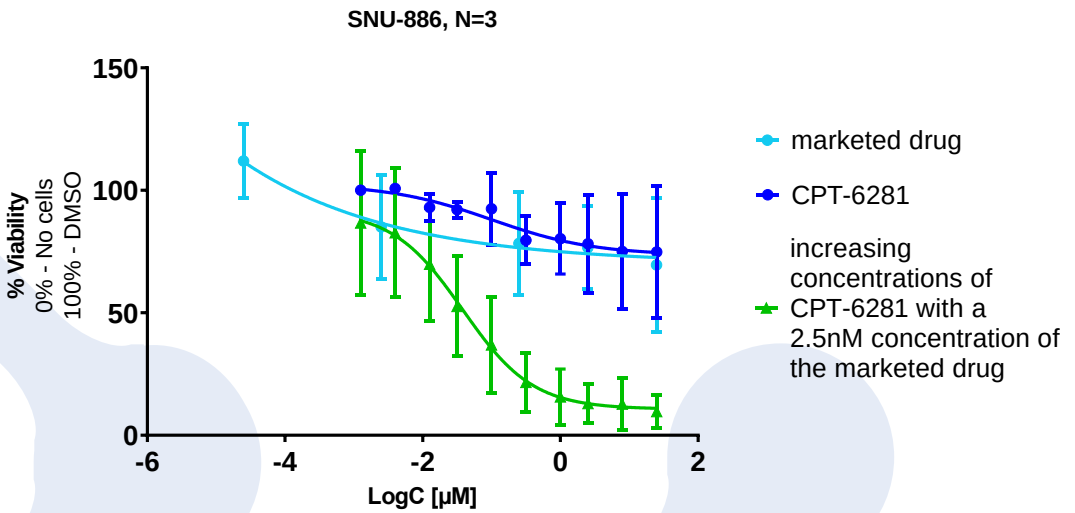


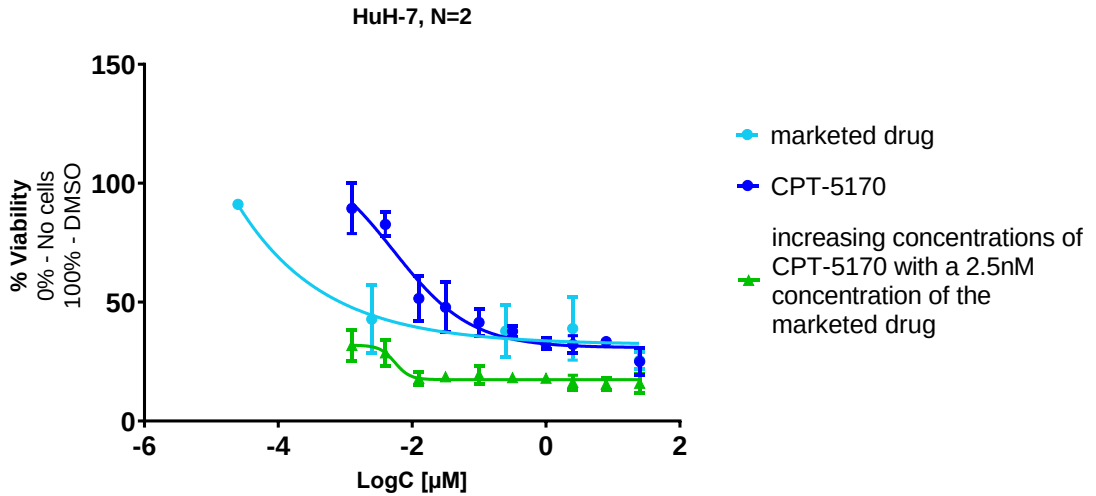


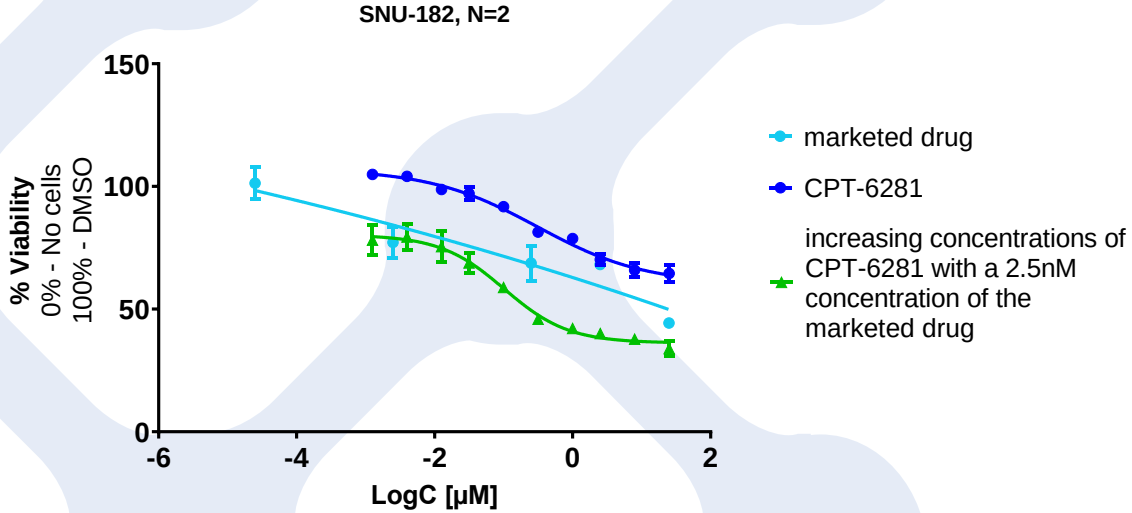
Efficacy of GSPT1 degradation correlates with cytotoxicity in HCC cell lines

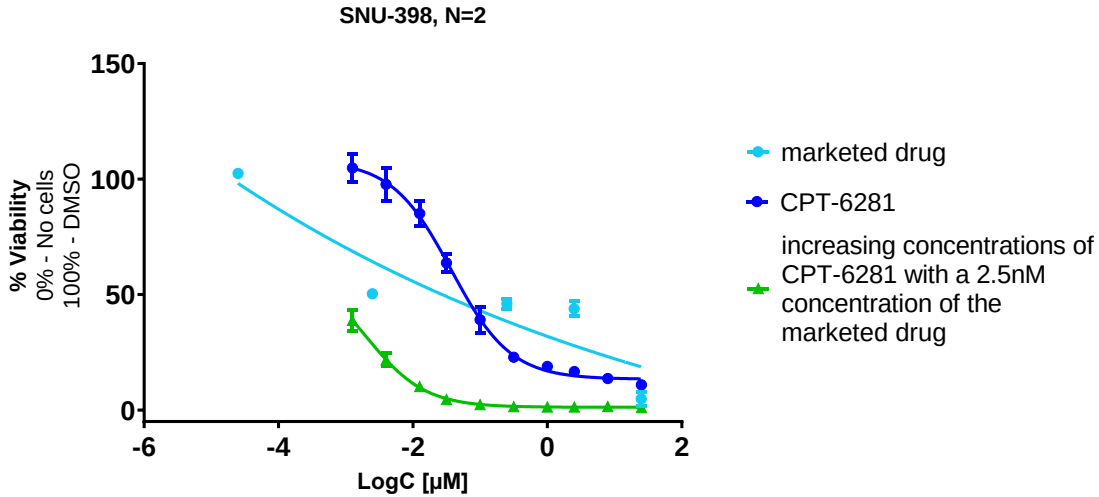


Combinatorial treatment results in a strong synergistic effect

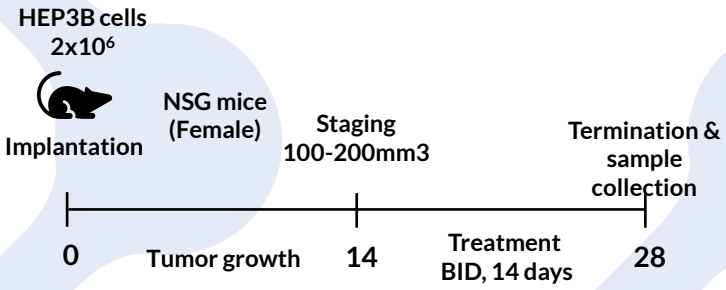


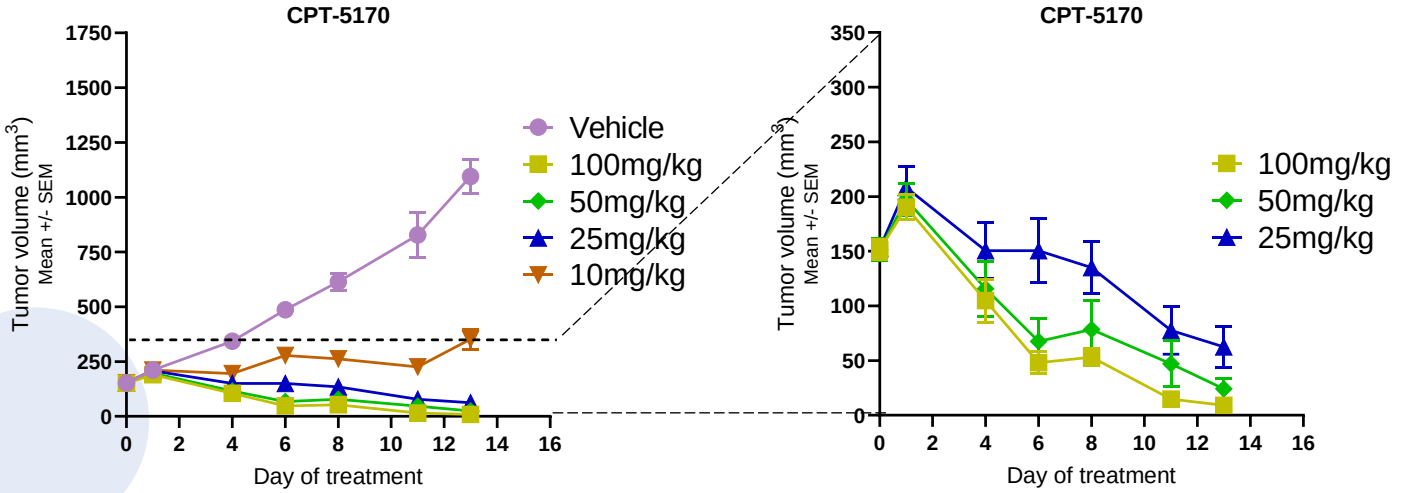


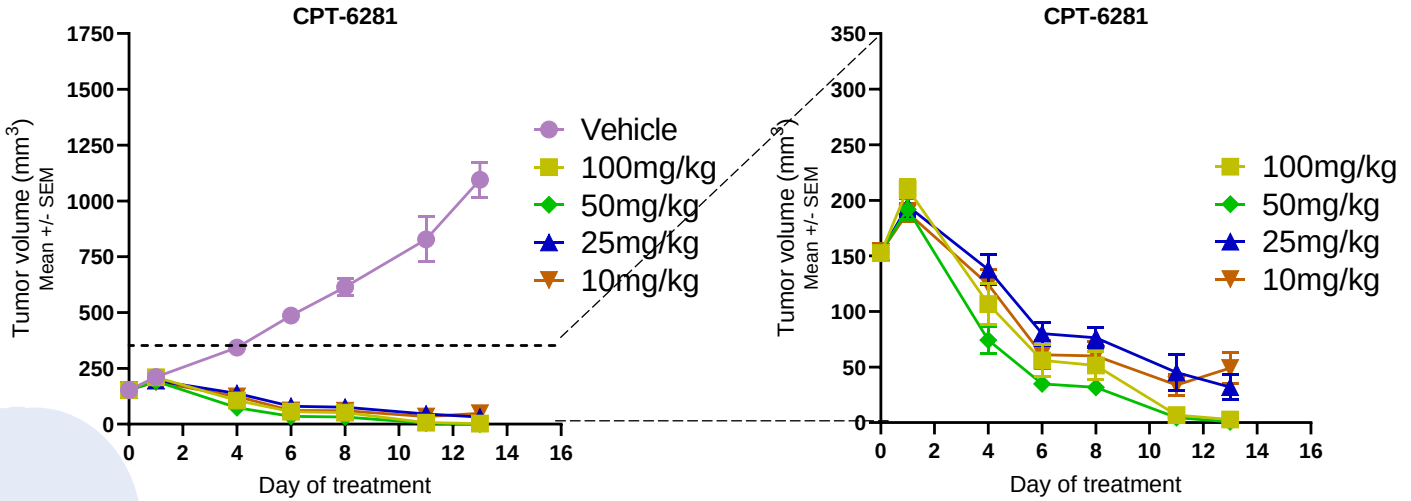




CPT-5170 and CPT-6281 Exhibited Very Strong Efficacy and Induced Tumor Regression at Low Doses



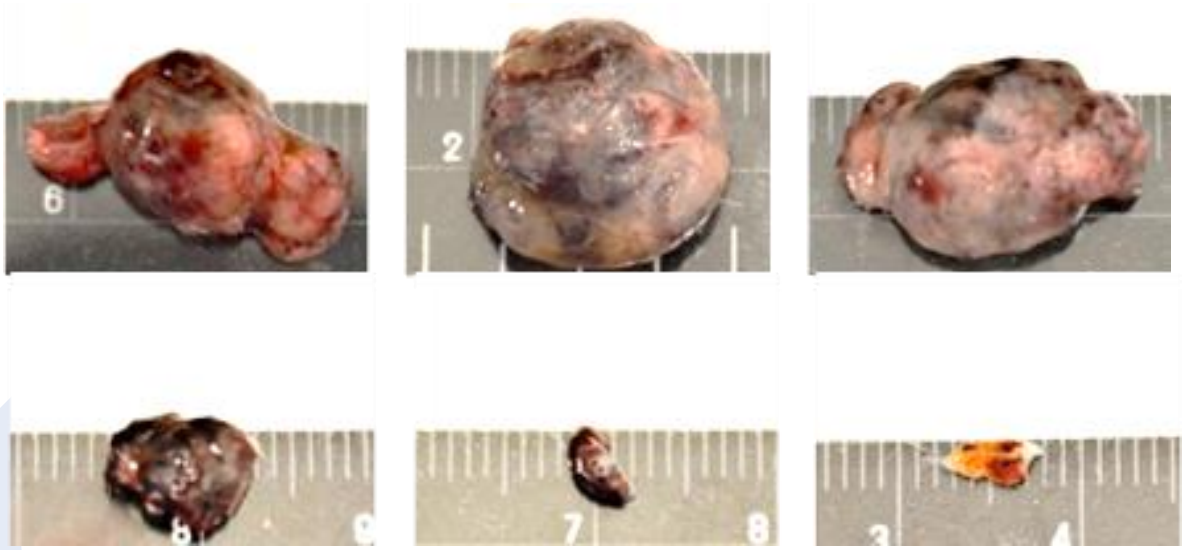




In vivo PoC: CPT-5170 and CPT-6281 suppressed growth and induced regression of Hep3B xenografts

Vehicle

CPT-6281 100 mg/kg



Summary

CPT-5170 and CPT-6281:

- are very potent molecular glues with high potential as a novel therapy for HCC
- induce degradation of GSPT1, SALL4 and of a novel undisclosed target
- induce Integrated Stress Response and apoptosis in Hep3B cells
- lead to robust tumor regression in an Hep3B xenograft model

The data provide a PoC and a strong rationale for development of CPT-5170 or CPT-6281 as novel therapy for HCC

Plans

1. Evaluation of CPT-5170 and CPT-6281 efficacy in PDX models of HCC
2. Evaluation of combinatorial therapy in HCC animal models
3. Characterization of the the benefits of degrading the undisclosed target
4. Identification of additional cancers sensitive to CPT-5170 and CPT-6281

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All images by Piotr Piatek

Projects are co-financed by the European Regional Development Fund:

Discovery and development of a new clinical drug candidate for the eradication of cancer stem cell in the treatment of hepatocellular carcinoma, through degradation of oncofetal transcription factor
(POIR.01.01.01-00-0740/19)

Discovery and development of non-toxic ligase ligands and their application in the treatment of autoimmunological diseases
(POIR.01.01.01-00-0741/19-00)

Inducing apoptosis with small molecules as therapeutic intervention in multiple severe malignancies
(POIR.01.01.01-00-0956/17-01)

Discovery and development of first-in-class of small molecule degrader as a drug candidate for the treatment of colorectal cancer
(POIR.01.02.00-00-0073/18-00)

Application of targeted protein degradation technology in the treatment of psoriasis and rheumatoid arthritis
(POIR.01.02.00-00-0079/18-00)

Development of an integrated technology platform in the field of targeted protein degradation and its implementation to the pharmaceutical market
(POIR.01.01.01-00-0931/19-00)

Elaboration of interaction assays suitable for screening of the chemical compounds used in a first-in-class drug development
(POIR.04.01.02-00-0147/16)