Captor Therapeutics®

Intervention in Liver Cancer with Molecular Glue Degraders

March 2022

Michał Walczak, Chief Scientific Officer

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About Captor

A global, highly qualified team

Based in Wroclaw (Poland) and Basel (Switzerland)

Significantly oversubscribed IPO in April 2021

Five drug programs in large potential markets

~100 FTEs on board, almost half of them are PhD level specialists

1,100 m^2 of laboratory space equipped with state-of-the-art equipment

Pipeline

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

TPD-focused Competences in Place

PHARMACOLOGY

TARGET/E3 LIGASE ENGAGEMENT

POI DEGRADATION

REPORTER & ENDOGENOUS ASSAYS

BIOPHYSICS

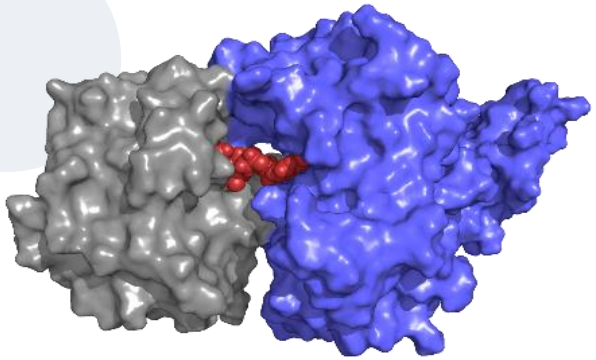
LIGAND BINDING
SPR, FP, NMR, BLI, DSF, FRET, BRET

TERNARY COMPLEX FORMATION

PROTEIN SCIENCES

LIBRARY OF E3 LIGASES

PROTEIN PRODUCTION & LABELING



MODELING

TERNARY COMPLEXES

DOCKING
LINKER DESIGN

MEDICINAL CHEMISTRY

DEGRADERS' BUIILDING BLOCKS

NEW E3 LIGANDS

HTS, FGLD, FOCUSED LIBRARIES

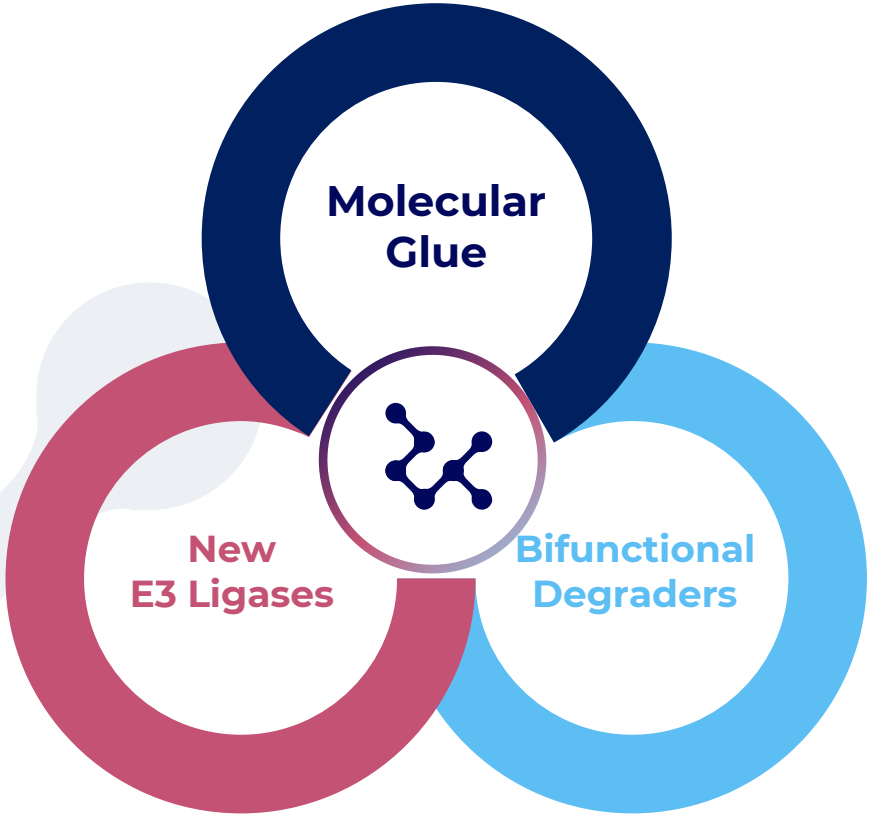
PROTEOMICS

SELECTIVITY PROFILING

NEW TARGET IDENTIFICATION

Approach

Molecular Glues
Small molecules with good drug properties that stabilize the interaction between the E3 Ligase and the target

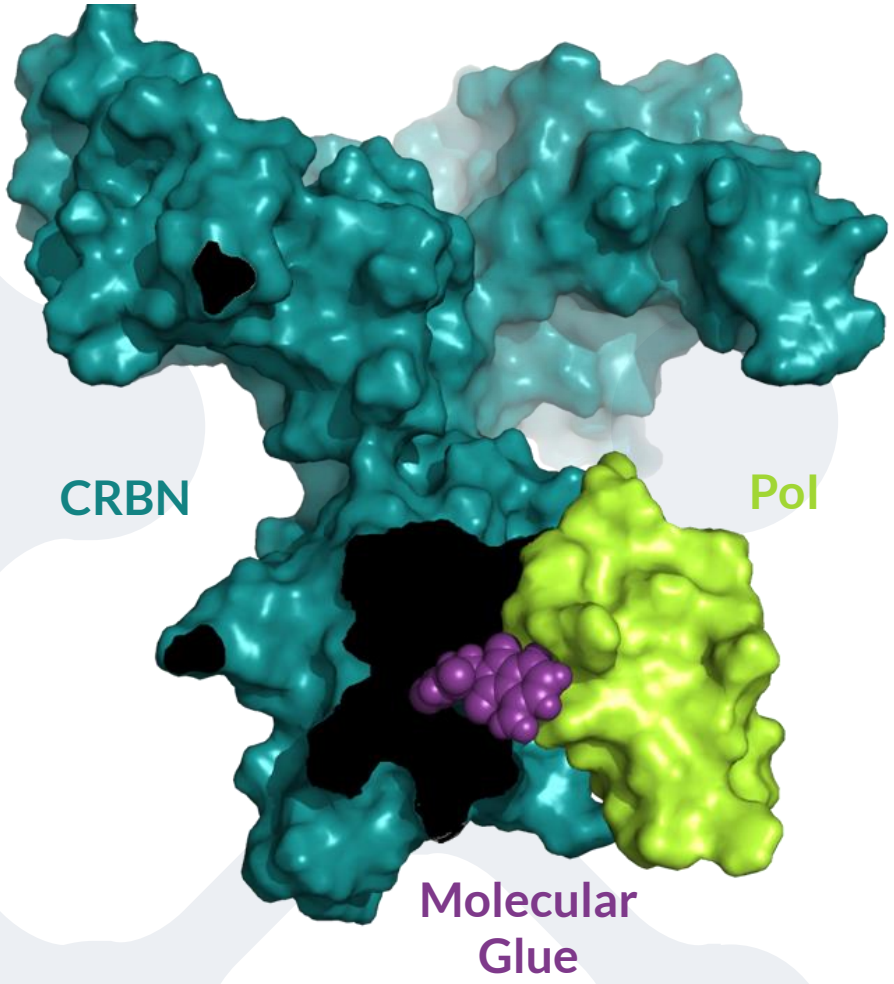


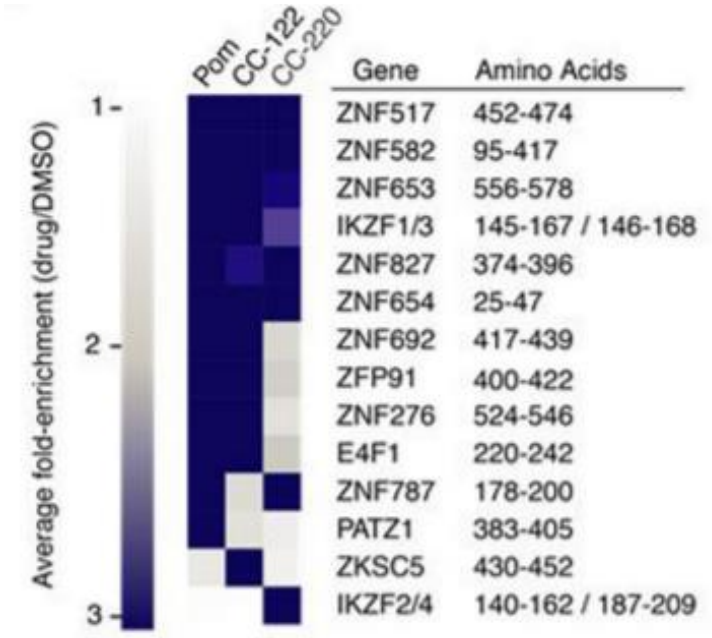
Core capabilities
- 100-person team with in-house biophysics, structural biology, HTS, chemistry, biology & proteomics
- Science leadership involved in degradation for > 10 years
- Application of DEL and Affinity Selection MS

Evolving LiLis™ Platform
To develop new generation degraders exploiting novel E3 ligases

Bifunctional Degraders
A modular approach to degrader discovery

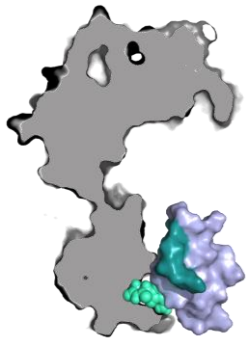
Molecular Glues and Cereblon Degrome





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

Molecular Glue Discovery Engine

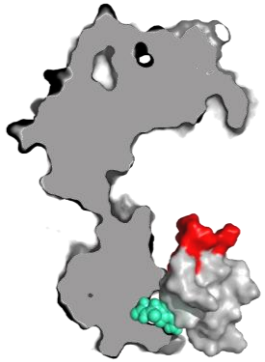


Extended positive degron

Degron sequence analysis

Protein-protein docking

Geometric AI

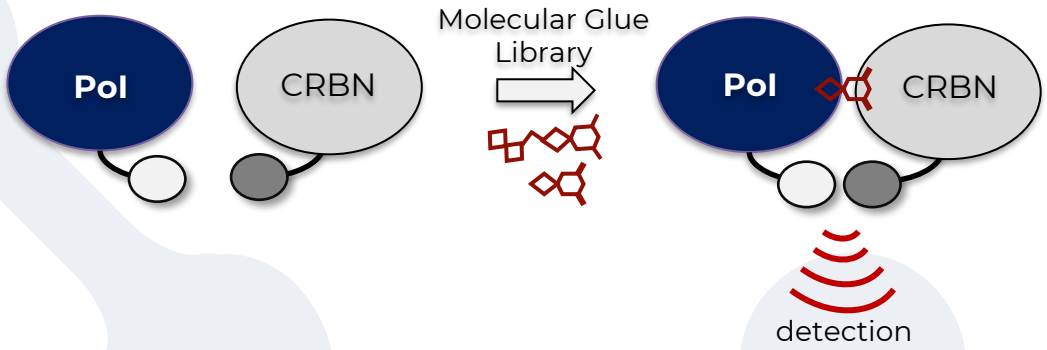


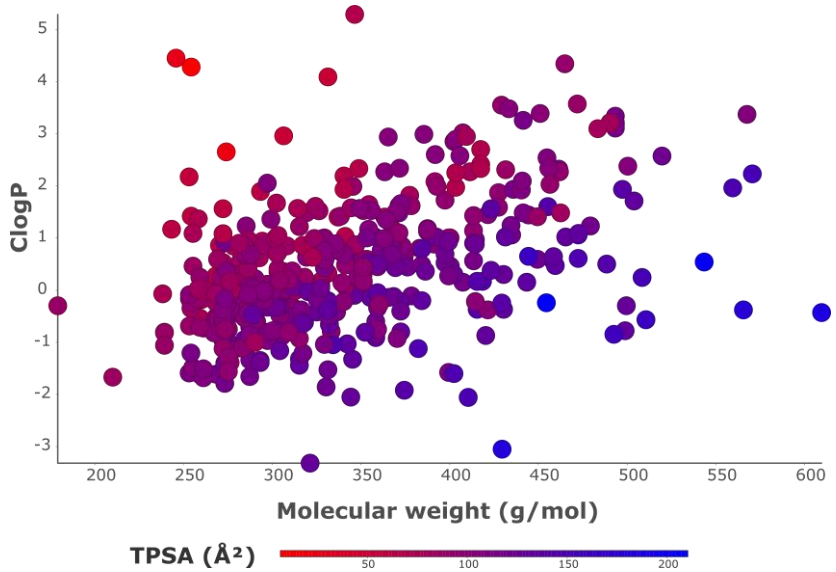
Extended negative degron

Protein production and testing

Data Augmentation

Molecular Glue Toolbox





High throughput CRBN recruitment assay developed

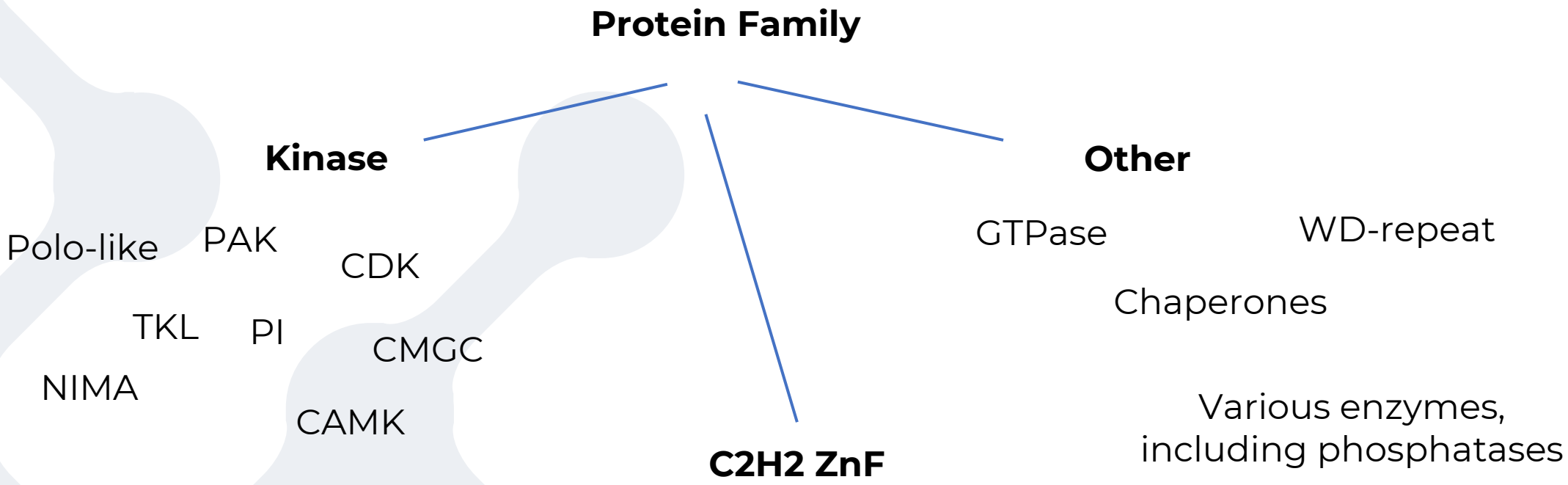
- Multiplexed by proteins
- Detection of weak recruiters (~10 µM) unlike cellular degradation assays
- High sensitivity (beyond proteomics)
- Control of the target levels

A growing library of molecular glues

- Excellent drug-like properties
- Focused library with high chance of identifying a chemical starting point to CRBN-degron containing proteins
- Patent applications filed for several chemotypes

Identification of CRBN-matching Degrons in Proteome

Continuous and iterative development of degron identification workflow
Identified over 80 (non-ZnF) proteins that contain putative CRBN degrons



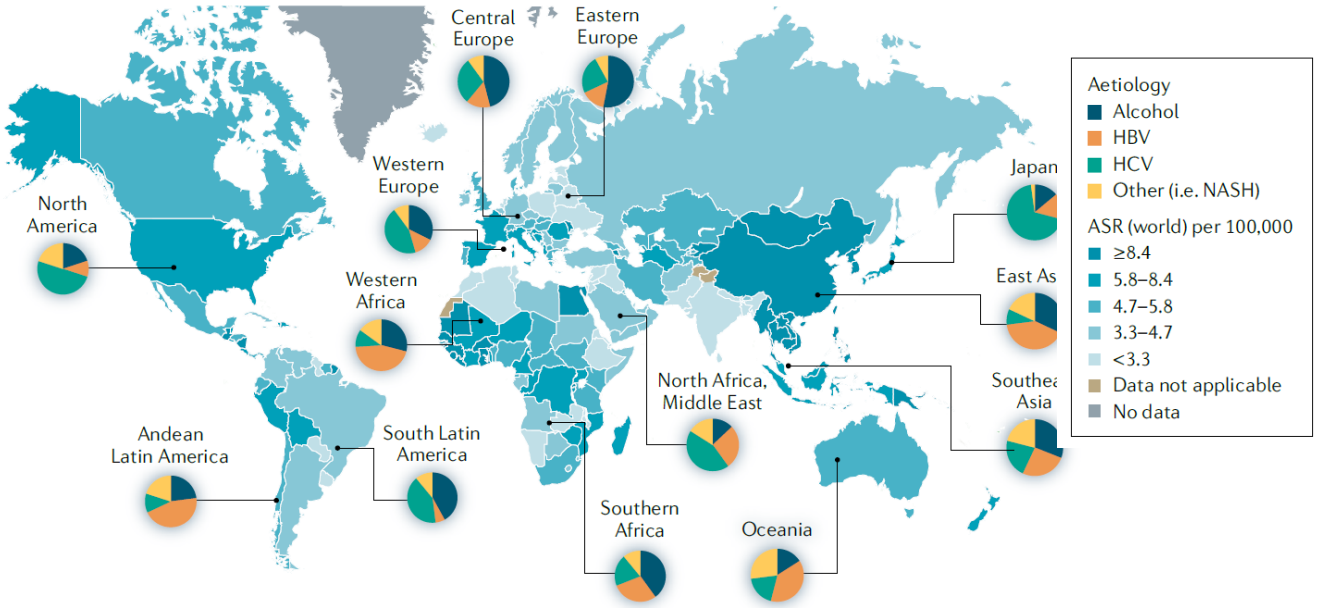
Hepatocellular Carcinoma – a Global Health Challange

- ~1 000 000 new cases each year, the 2nd most common cause of cancer mortality [1]
- Incidence growing worldwide [2]
- For HCC patients, the underlying liver disease impacts the quality of life, rendering treatment-related adverse events even more impactful [2]

References: [1] Global Cancer Statistics 2018, [2] Llovet et al. 2021, DOI: 10.1038/s41572-020-00240-3

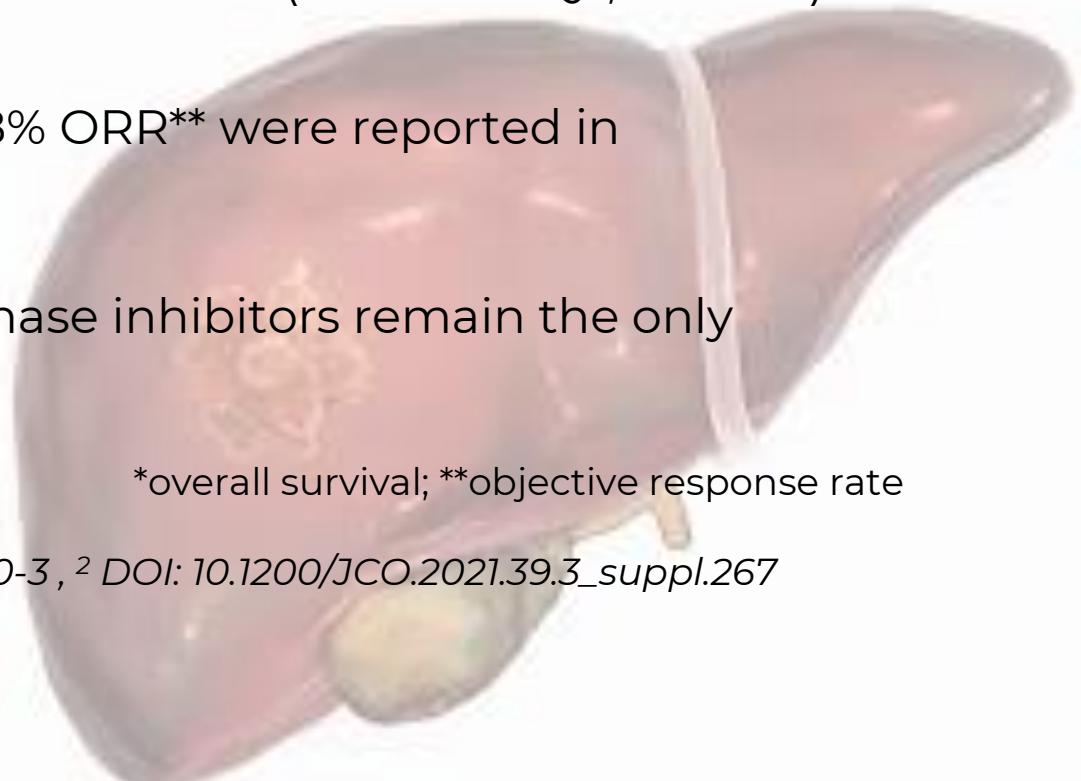
Figure: The major risk factors for HCC include cirrhosis of any etiology, chronic alcohol consumption, diabetes or obesity- related NASH, and infection by HBV or HCV [2]

DOI: 10.1038/s41572-020-00240-3



A Dramatic Need for New Treatments

- Curative treatments are restricted to early disease
- Recurrence rates after resection as high as 70% at 5 years[1]
- OS of Sorafenib < 3 months[1]
- In unresectable HCC the combination of **Atezolizumab** (TECENTRIQ®, a PD-L1) **plus Bevacizumab** (AVASTIN®)
    - 19.2 months median OS* and 29.8% ORR** were reported in IMbrave150 study[2]
- In 2nd line treatment of grade ≥3 the multikinase inhibitors remain the only option[1]

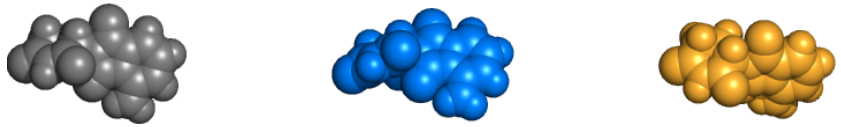


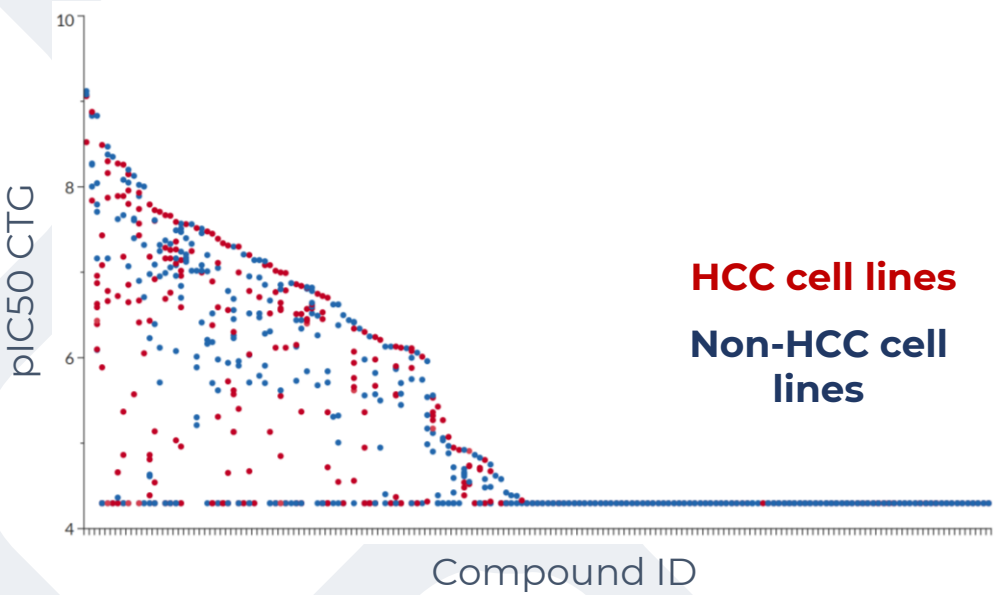
*overall survival; **objective response rate

References: [1]Llovet et al. 2021, DOI: 10.1038/s41572-020-00240-3 , [2] DOI: 10.1200/JCO.2021.39.3_suppl.267

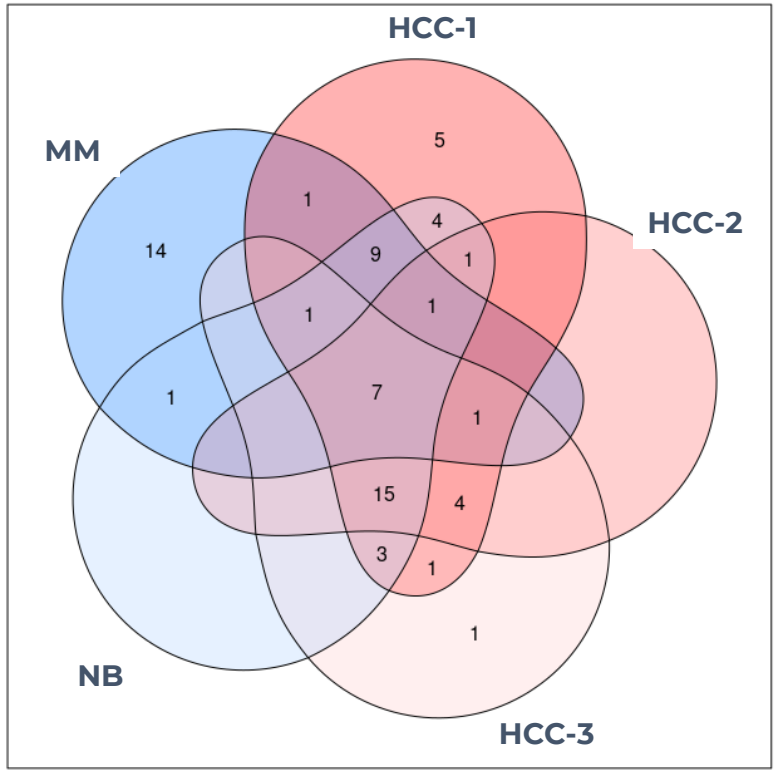
Phenotypic Cell Viability Screen

Classes of molecular glues





HCC cluster identification

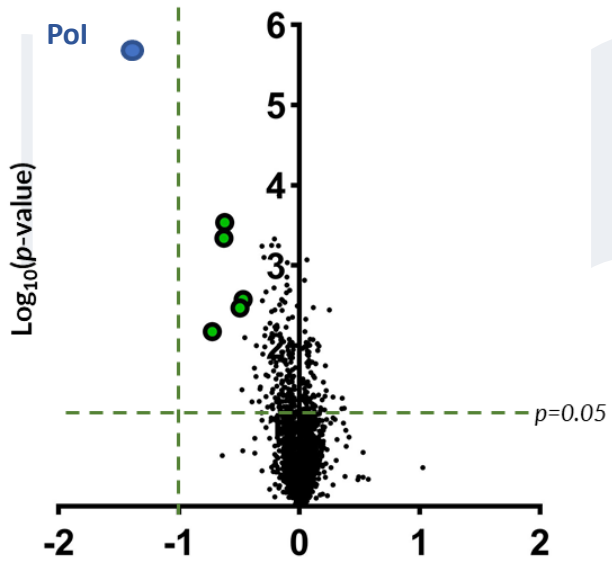


Positive selection - HCC clusters

Negative selection - haematological cluster

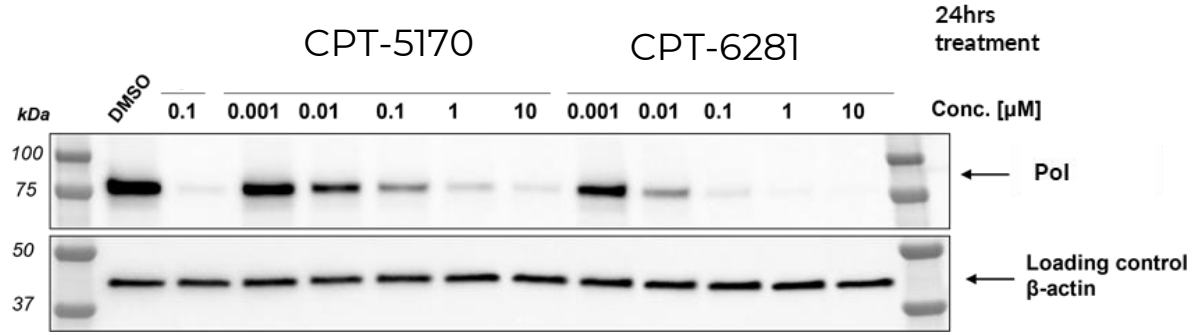
Targeting Liver Cancer with Molecular Glues

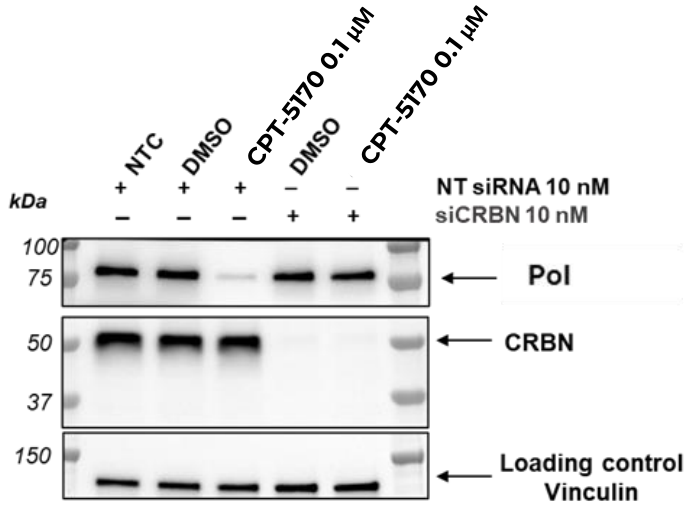
Downregulation of PoI in response to CT-01 compounds treatment in HCC-1 cells



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

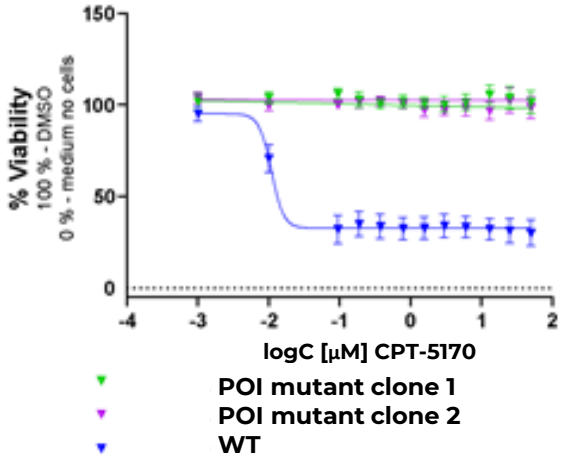
Potent and CRBN-dependent PoI degradation by CT-01 compounds in HCC-1 cells



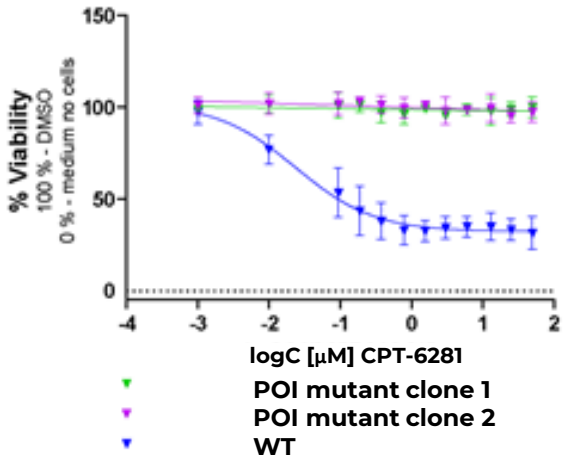


PoI-dependent Efficacy

CPT-5170



CPT-6281



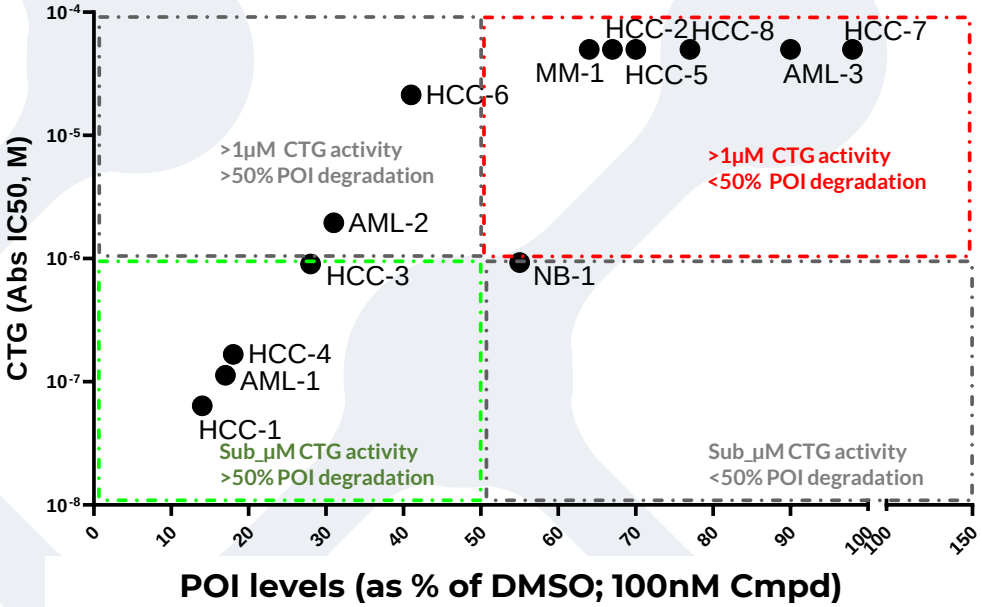
Cell viability after treatment (72 h)

POI mutation mitigated the cytotoxic effect of CPT-5170 and CPT-6281 in HCC cell lines

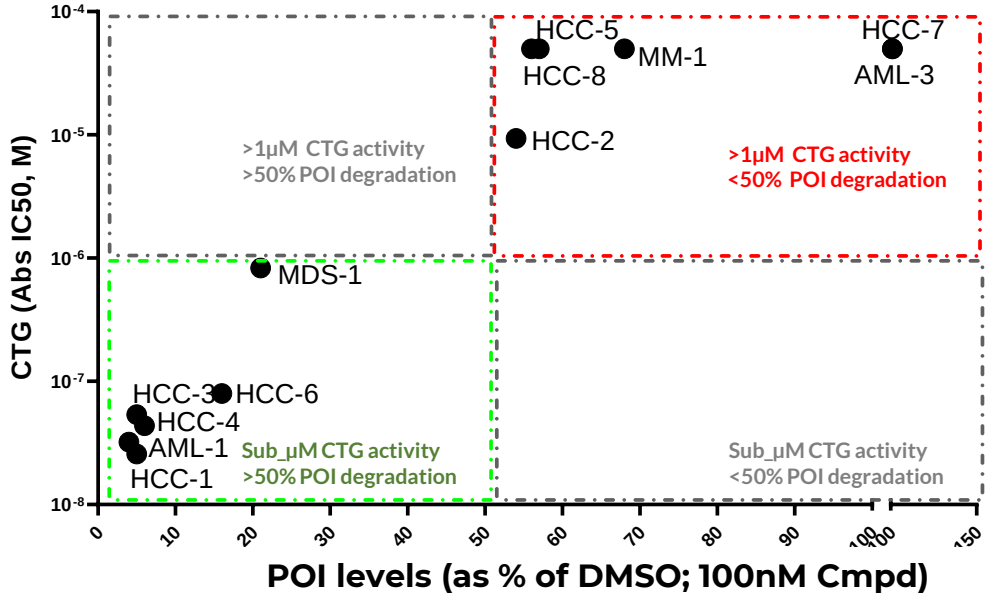
Increasing PoI Degradation Sensitizes HCC Cell Lines

Molecular Glue Evolution

CPT-5170



CPT-6281



Synergy in Combination with Marketed Drug

CPT-5170 [µM]

MARKETED DRUG [µM]	0	0.001	0.004	0.01	0.03	0.1	0.3	0.9	2.8	8.3	25
0	100 ±0	106 ±4	104 ±0	103 ±13	101 ±4	99 ±2	94 ±3	98 ±5	92 ±3	92 ±4	90 ±10
2.50E-05	106 ±6	104 ±6	96 ±2	96 ±0	92 ±5	93 ±3	85 ±5	82 ±12	75 ±7	74 ±7	75 ±3
2.50E-03	72 ±2	69 ±2	66 ±2	55 ±5	48 ±3	39 ±8	28 ±4	24 ±9	17 ±3	15 ±4	14 ±3
2.50E-01	66 ±3	67 ±3	63 ±1	50 ±5	39 ±6	30 ±8	20 ±4	14 ±3	12 ±2	10 ±1	10 ±1
2.50E+00	67 ±1	67 ±4	58 ±4	45 ±2	40 ±7	30 ±3	19 ±5	16 ±5	11 ±1	9 ±2	8 ±1
2.50E+01	48 ±11	45 ±5	35 ±16	26 ±9	21 ±4	11 ±5	9 ±5	7 ±4	6 ±2	6 ±1	3 ±0

% of control viability

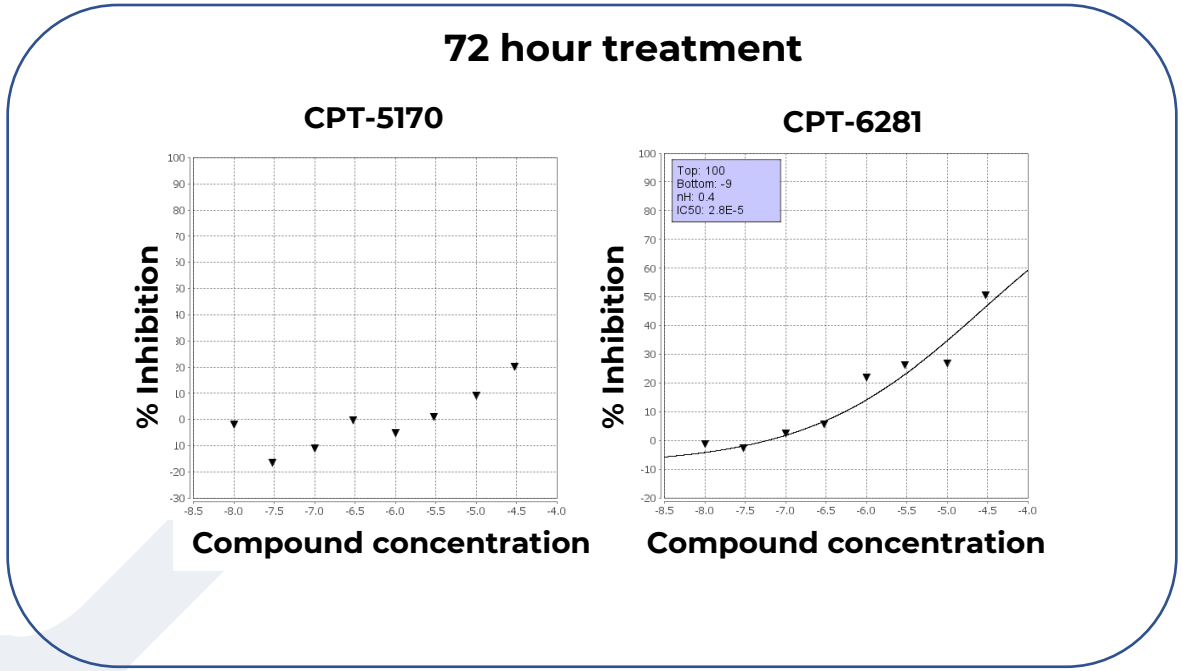
CPT-6281 [µM]

MARKETED DRUG [µM]	0	0.001	0.004	0.01	0.03	0.1	0.3	0.9	2.8	8.3	25
0	100 ±0	100 ±1	101 ±2	93 ±6	92 ±3	92 ±15	80 ±10	80 ±14	78 ±20	75 ±24	75 ±27
2.50E-05	112 ±15	108 ±10	106 ±18	102 ±17	92 ±21	91 ±27	76 ±24	68 ±24	67 ±25	65 ±26	62 ±26
2.50E-03	85 ±21	87 ±29	83 ±26	70 ±23	53 ±21	37 ±20	22 ±12	16 ±11	13 ±8	13 ±11	10 ±7
2.50E-01	78 ±21	80 ±23	77 ±23	62 ±22	45 ±25	27 ±18	13 ±6	11 ±8	8 ±5	9 ±7	6 ±3
2.50E+00	77 ±17	78 ±22	73 ±19	64 ±23	41 ±23	25 ±14	14 ±7	10 ±7	8 ±5	8 ±6	7 ±5
2.50E+01	70 ±27	63 ±25	51 ±25	36 ±21	23 ±14	14 ±12	8 ±7	5 ±3	4 ±3	3 ±2	2 ±2

% of control viability

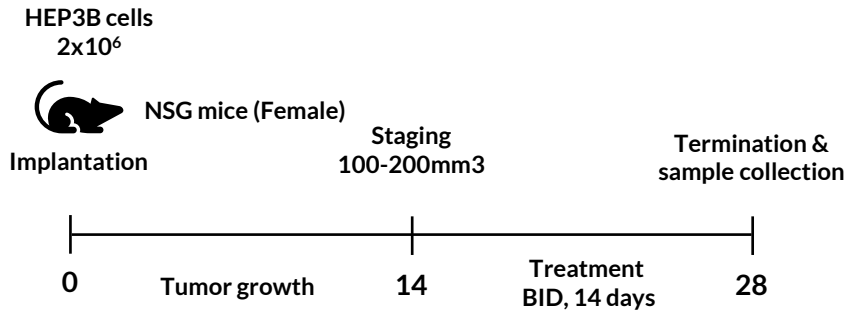
Strong synergy of potency and sensitivity of CT-01 degraders in combination with a marketed drug - CTG viability assay

Compounds Non-Toxic to Primary Hepatocytes

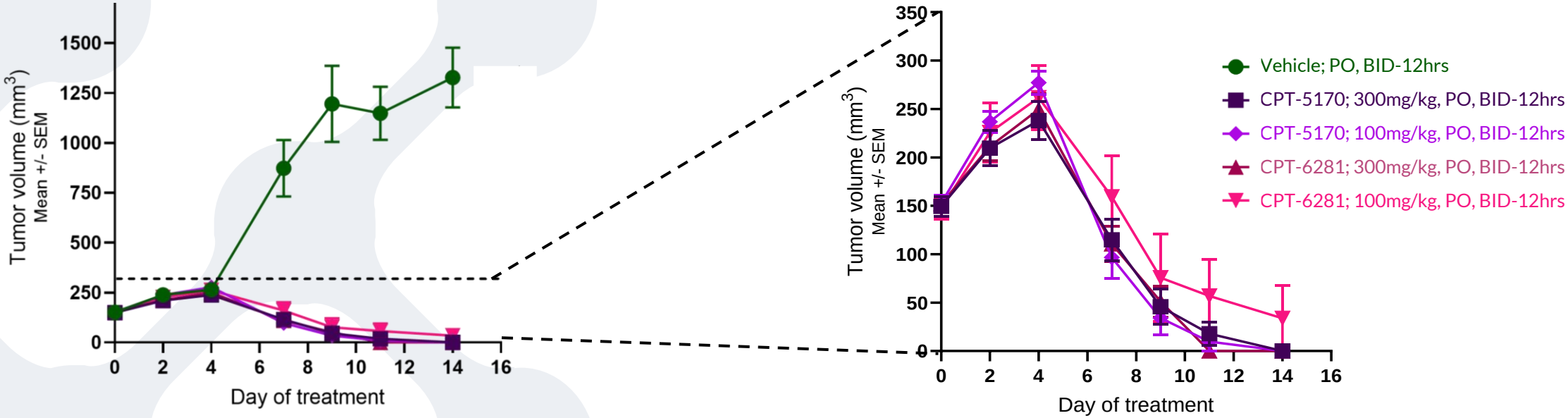


	Primary hepatocytes	HCC-1	HCC-2	HCC-3
CPT-5170	*not calculable*	33.8E-09	54.5E-09	105E-09
CPT-6281	2.8E-05	14.7E-09	29.3E-09	23.1E-09

Potent Anti-tumor Efficacy *in vivo*



9 x Group 1: Vehicle; PO, BID-12hrs
9 x Group 2: CPT-5170; 300mg/kg, PO, BID-12hrs
9 x Group 3: CPT-5170; 100mg/kg, PO, BID-12hrs
9 x Group 4: CPT-6281; 300mg/kg, PO, BID-12hrs
9 x Group 5: CPT-6281; 100mg/kg, PO, BID-12hrs



Summary & Outlook

1. Rationalization of Molecular Glue discovery yields potent degraders with selective activity across HCC cell lines
2. Developed Molecular Glues induce potent tumor regression
3. IND-enabling studies start in Q2 2022

Acknowledgements

Team Captor

Development of targeted oncogenic transcription factor degradation technology in the treatment of hepatocellular carcinoma (POIR.01.01.01-00-0740/19)

The goal of project is the development of a drug candidate in the treatment of hepatocellular carcinoma that allows the elimination of cancer cells through induced degradation of oncogenic transcription factor. The efficacy and bioavailability of the drug candidate will be tested in preclinical phase, followed by the Phase I clinical trials.

Project has a 8.1M EUR budget for years 2020-2023. The National Centre of Research and Development supports the project through 6.4M EUR grant-aid.