Captor Therapeutics®

Disturbing Cancer Resistance with Targeted Degradation of MCL-1

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28th October 2021

All images by Piotr Piatek

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About Captor

A global, highly qualified team:

- Based in Wroclaw (Poland) and Basel (Switzerland)
- Backed by private and non-dilutive public funds as well as funds raised in recent IPO
- Disruptive platform in drug discovery
- Five drug programs in large potential markets
- ~85 FTEs on board, almost half of them are PhD level specialists
- Joint experience from more than 11 leading international universities
- 1,100 m^2 of laboratory space equipped with state-of-the-art equipment

Company Pipeline

#	Indications	Modality	Discovery	Preclinical*	IND Filing	FIH**
CT-01	Hepatocellular carcinoma	MG				2023
CT-02	Autoimmunity Liquid tumors	MG				
CT-03	Liquid & solid tumors	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 I by 2023
BID – Bifunctional Degrader; MG – Molecular Glue

Captor Therapeutics®

MCL-1: A BREAKTHROUGH APPROACH TO A HIGH-POTENTIAL ONCOGENE

5

Resistance Mechanisms in Cancer

Intrinsic

Pre-existing, e.g.
- Subpopulation of cancer cells resistant to treatment or
- Mutant proteins irresponsive to drugs' activity

Extrinsic

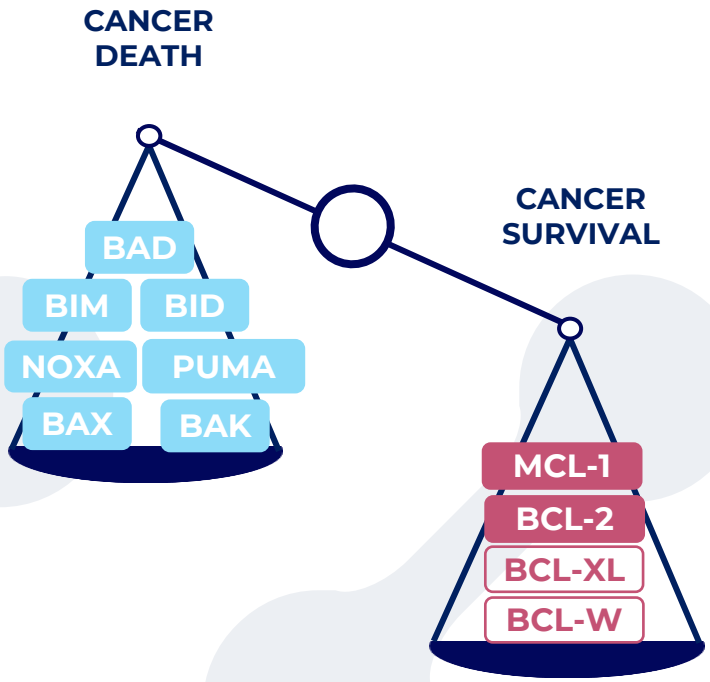
Acquired, e.g.
- Activation of alternative molecular pathway
- Secondary mutation in protein targets, e.g., BCR-ABL T315I

In a heterogenous cell population, only a minority of cells over-express MCL-1

Clonal selection from MCL-1 overexpressing cells in resistant tumor cells

M. Williams & R. Cook (2014) Oncotarget

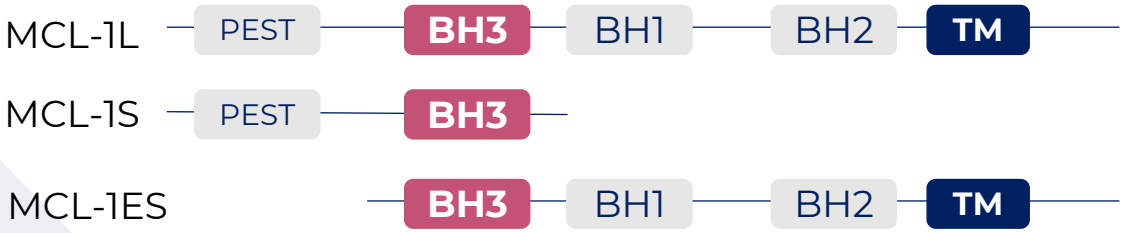
Antiapoptotic Proteins Are Important Drug Targets

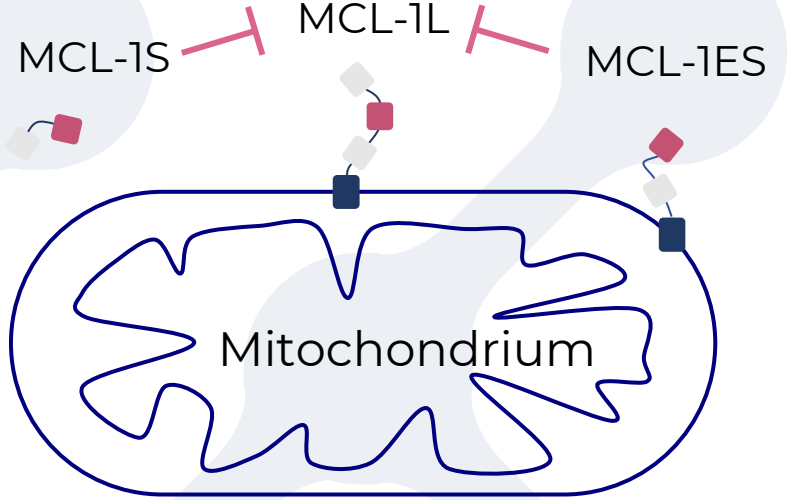


Imbalance in pro- and antiapoptotic proteins dictates the cancer cell survival

Venetoclax (Abbvie), a BCL-2 inhibitor is approved for the treatment of CLL and AML, with over $1.3B sales in 2020

MCL-1 – as a High Potential Oncology Target



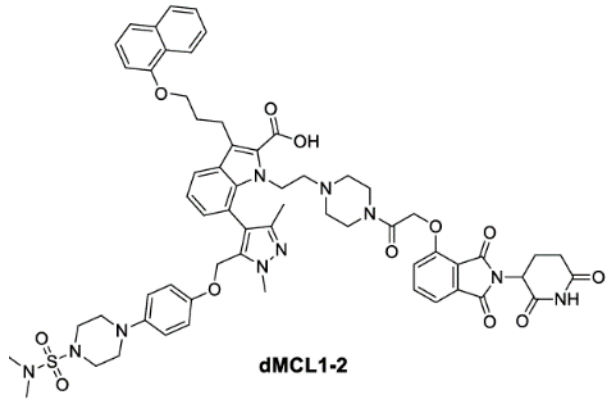


Splicing variants of the human MCL-1 gene

Wang H et al. (2021) J Hematol Oncol

MCL-1 inhibitor compounds in development

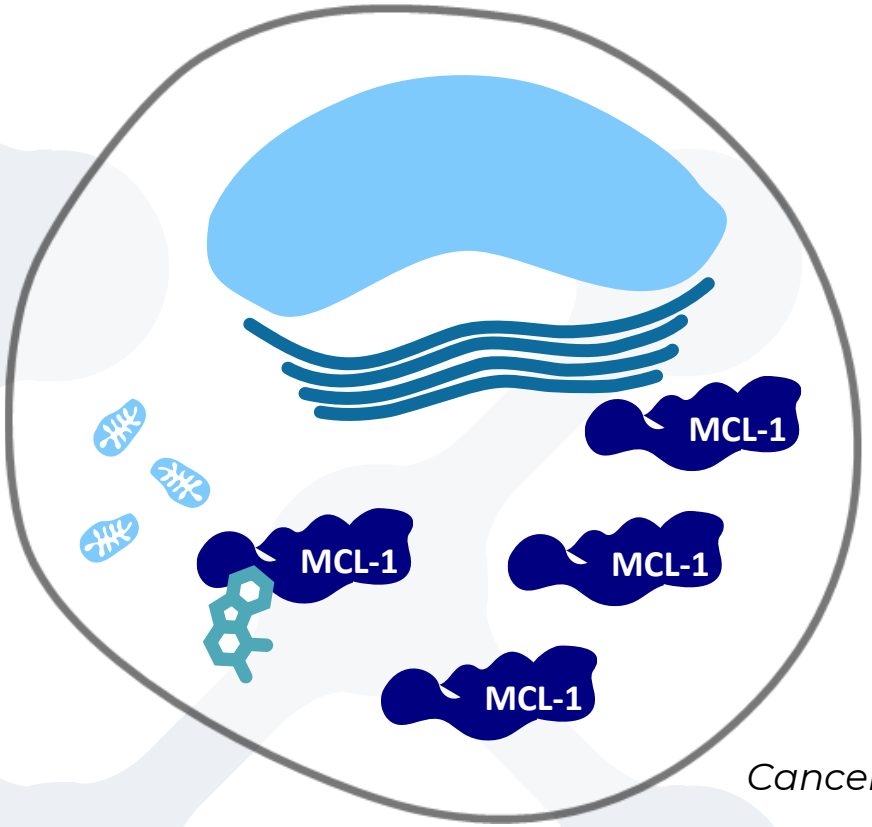
Compound	Company	Phase
MIK665	Servier/Novartis	I/II
AZD-5991	AstraZeneca	I
AMG176	Amgen	I
PRT1419	Prelude Therapeutics	I



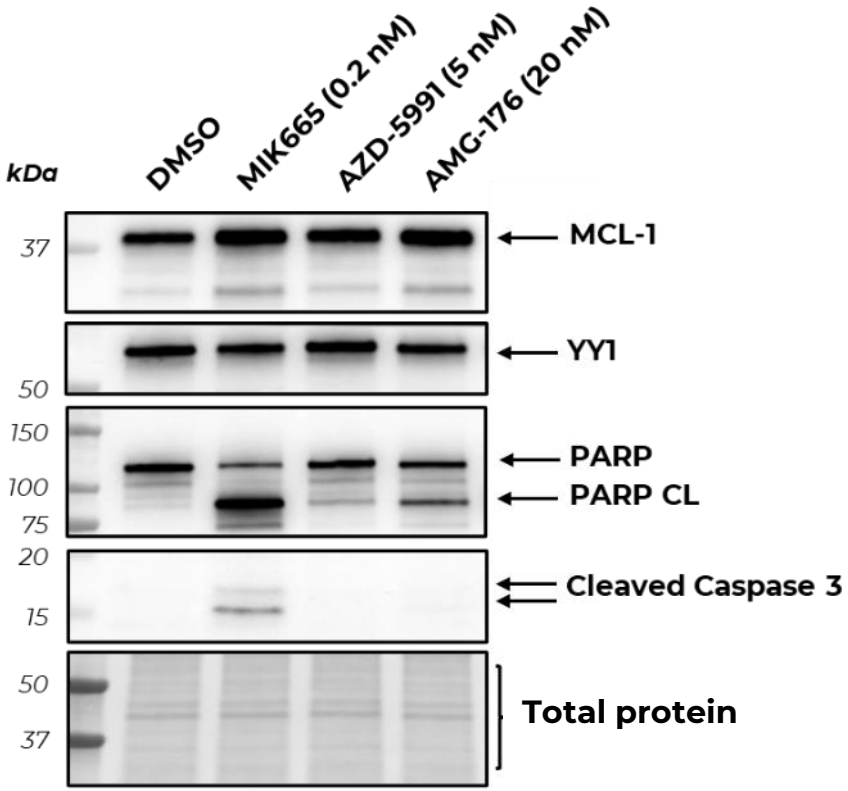
Papatzimas et al. (2019) J Med. Chem

Challenges in Targeting MCL-1 with Small Molecules

(1) MCL-1 inhibitors induce its accumulation in cells



Cancer cell



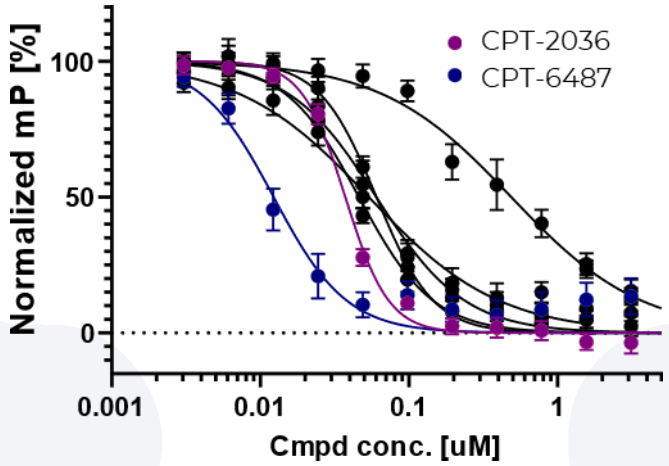
MV4-11, 6 hours

(2) Need for tight inhibition

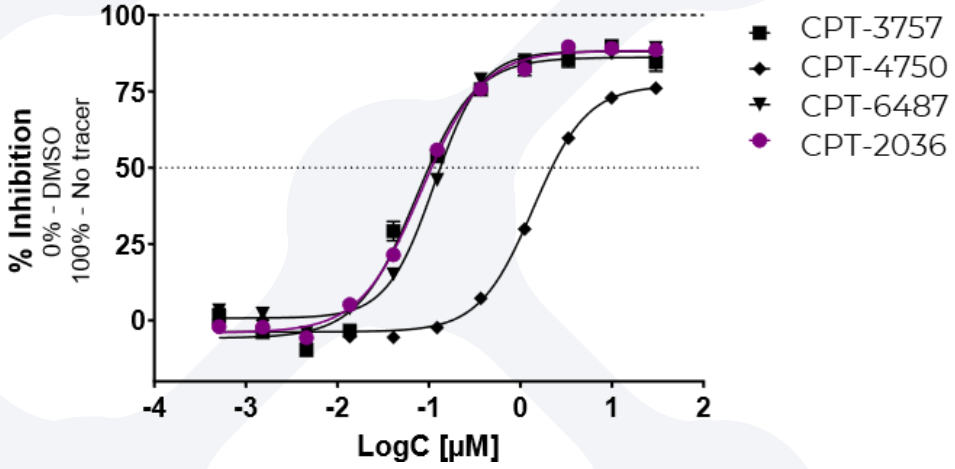
(3) Cardiotoxicity concerns

Biophysical Characterization of MCL-1 degraders

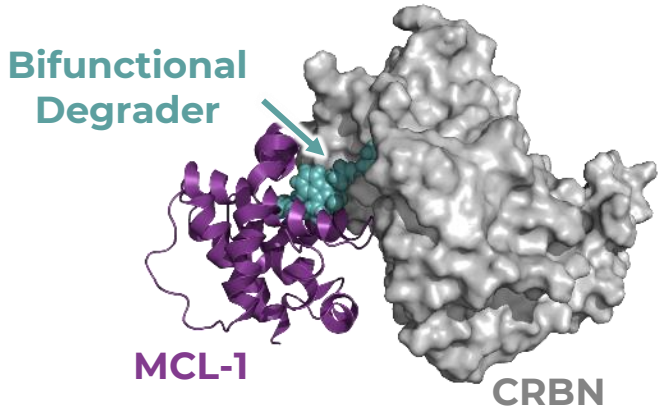
MCL-1 binding in FP assay

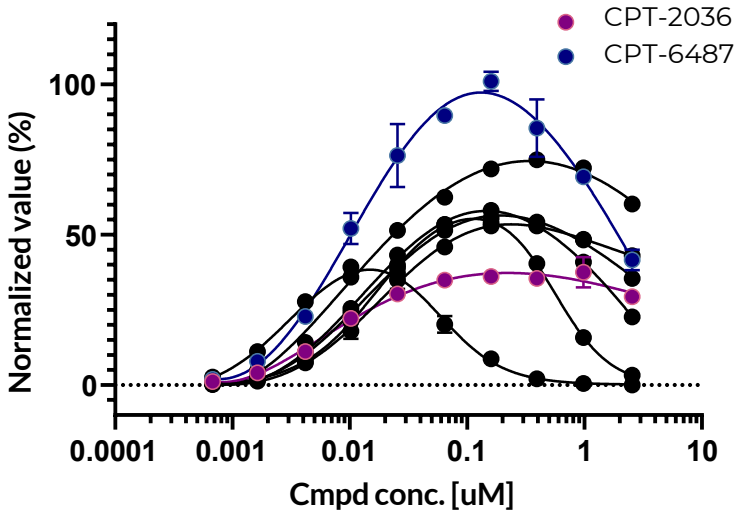


In cell CRBN-binding assay



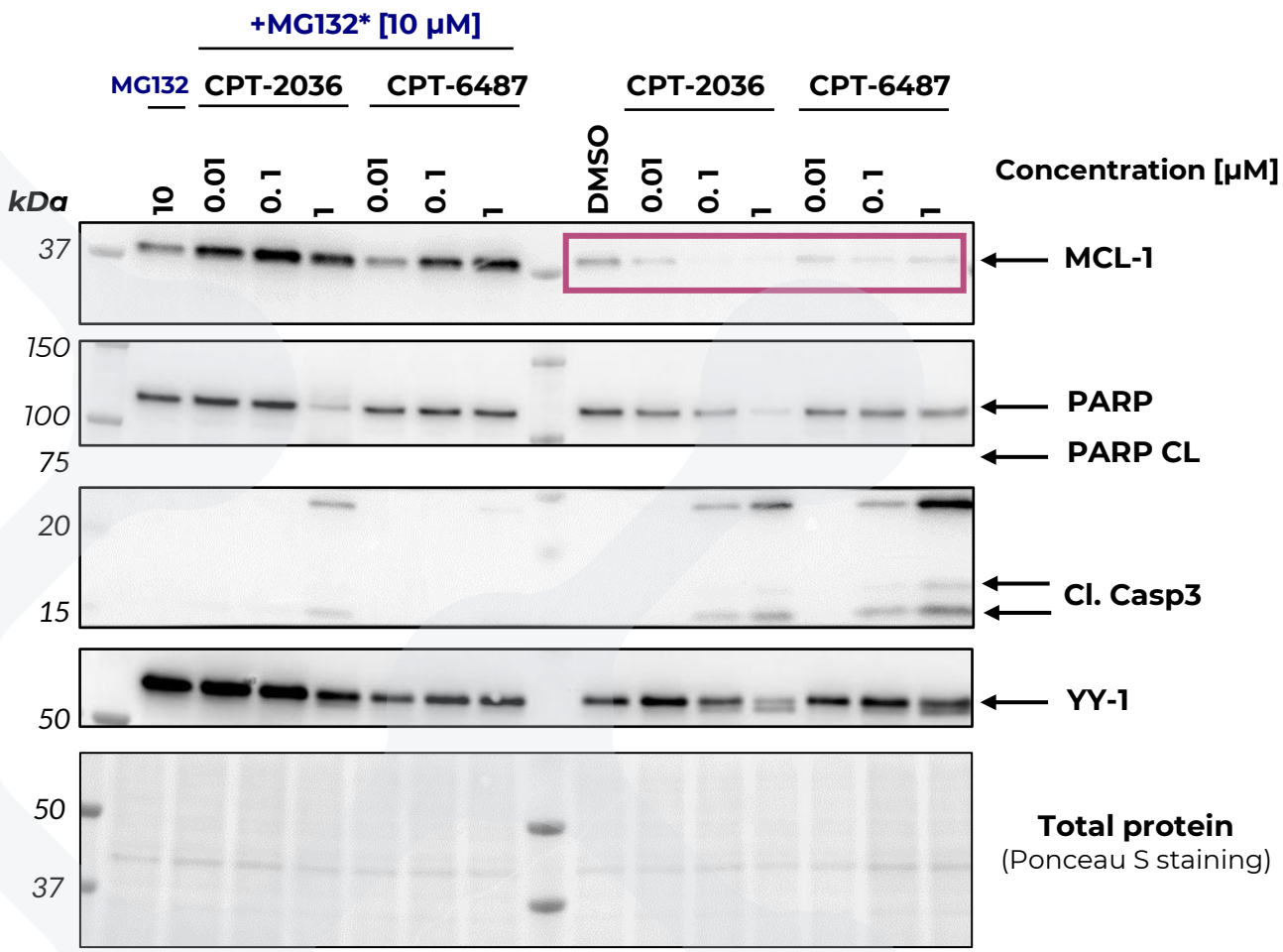
MCL-1 degreders cross plasma membrane in HEK293





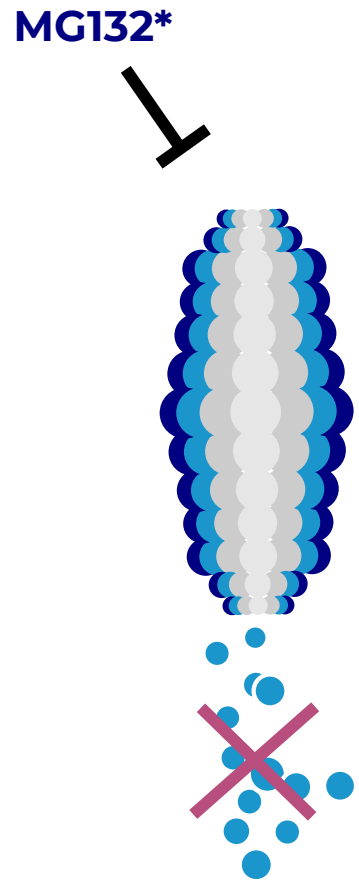
Ternary Complex Formation

Proteasome-dependent MCL-1 Degradation

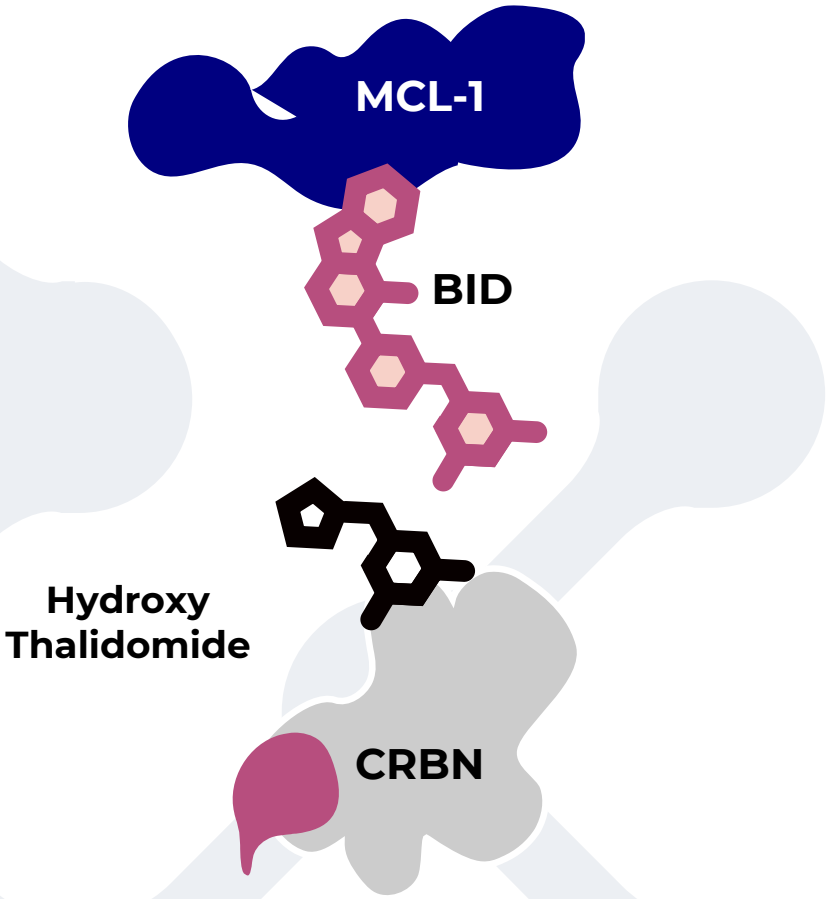


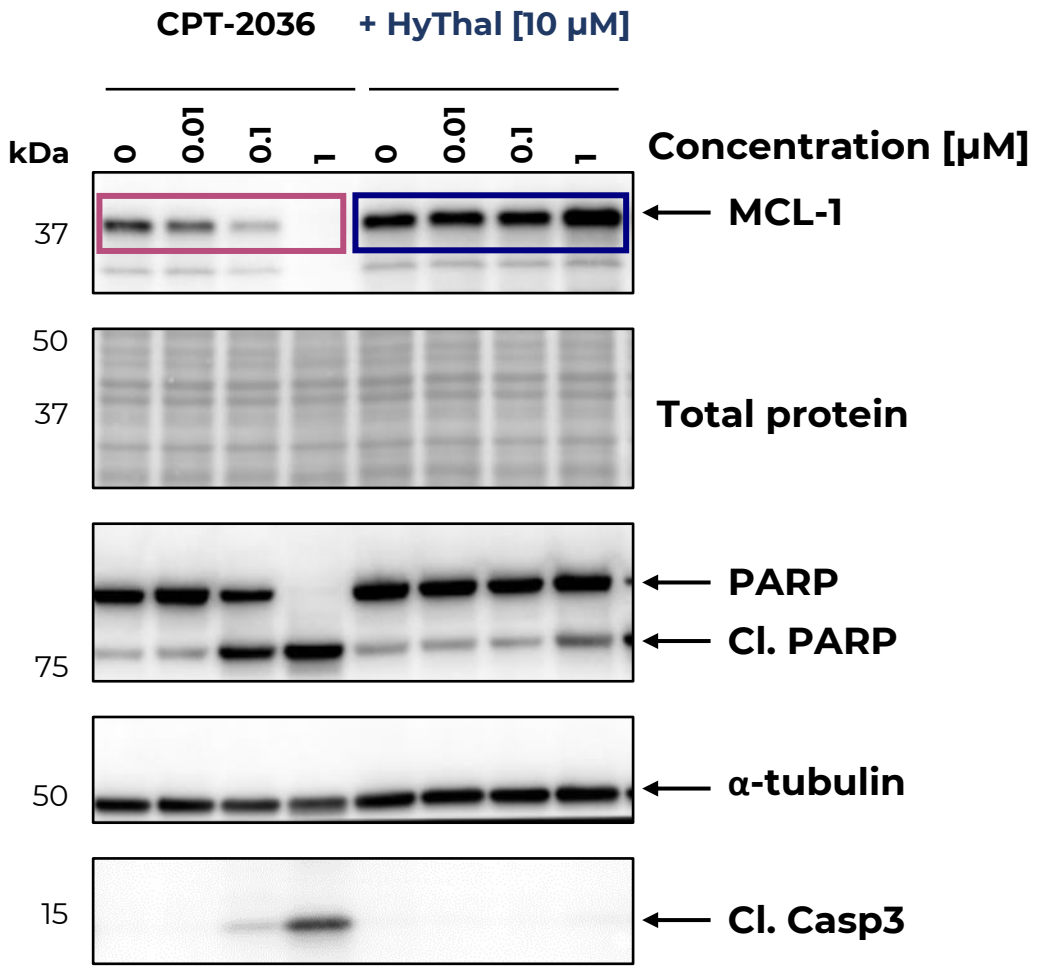
MV4-11, 24 hours

*MG132 – Proteasome inhibitor



CRBN-dependent MCL-1 Degradation

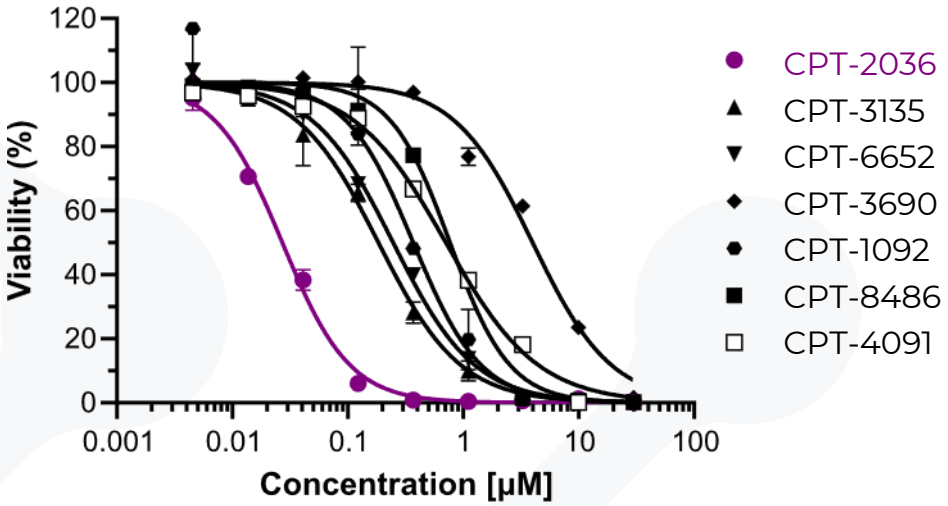




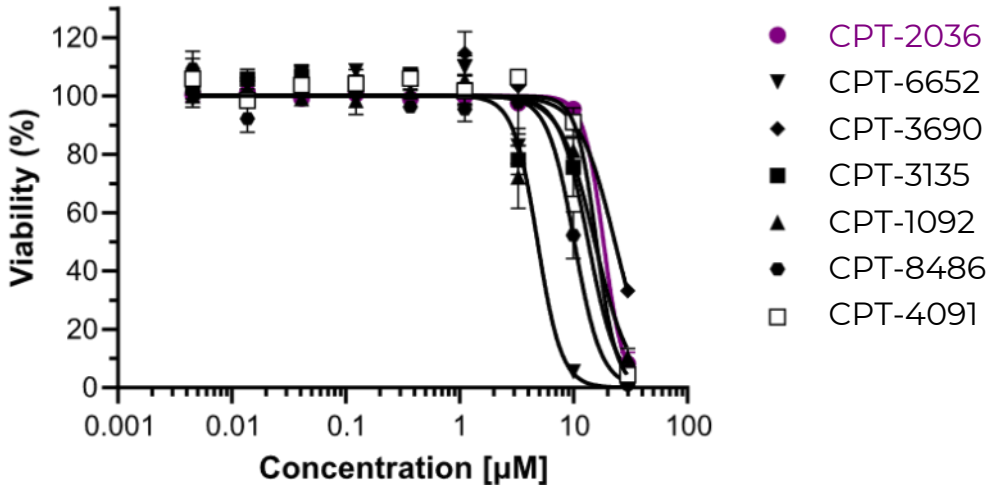
OPM-2, 6 hours

Cell Viability in MCL-1 Sensitive & Insensitive Cell Lines

MV4-11 (MCL-1-sensitive)

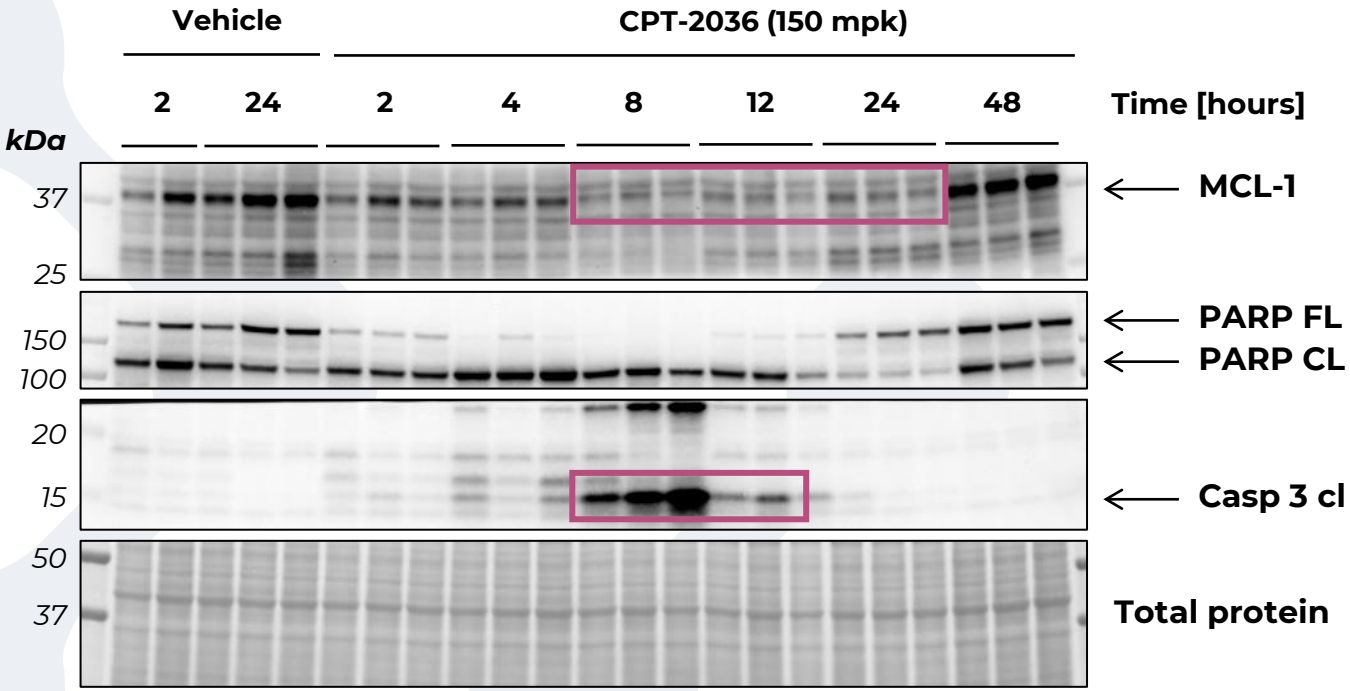


ARH77 (MCL-1-insensitive)

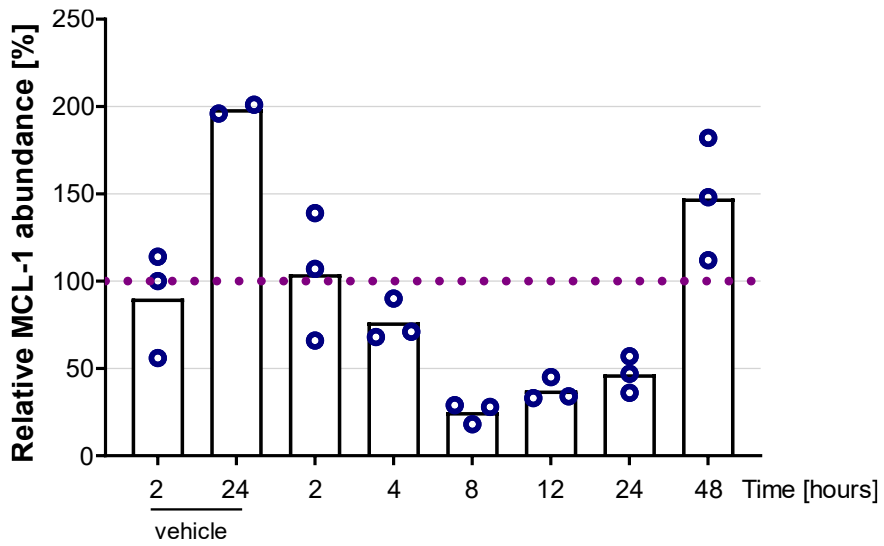


CPT-2036 is cytotoxic to MCL-1-dependent cell lines

In Vivo Degradation and Apoptosis Induction



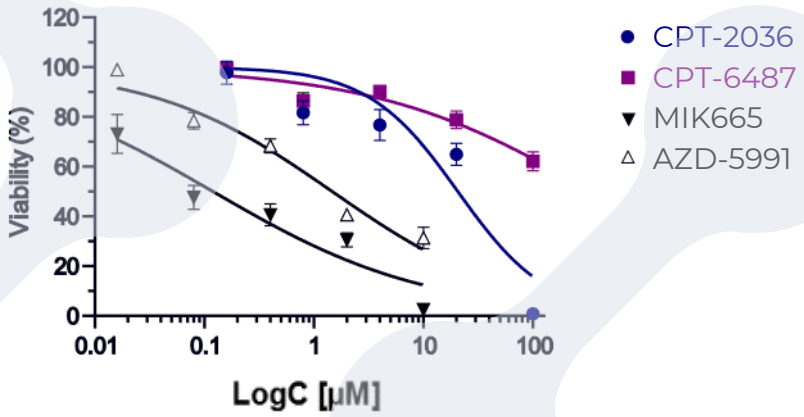
CB.17 SCID mice bearing subcutaneous MV4-11 xenografts; 150 mpk, i.p., single dose at t=0



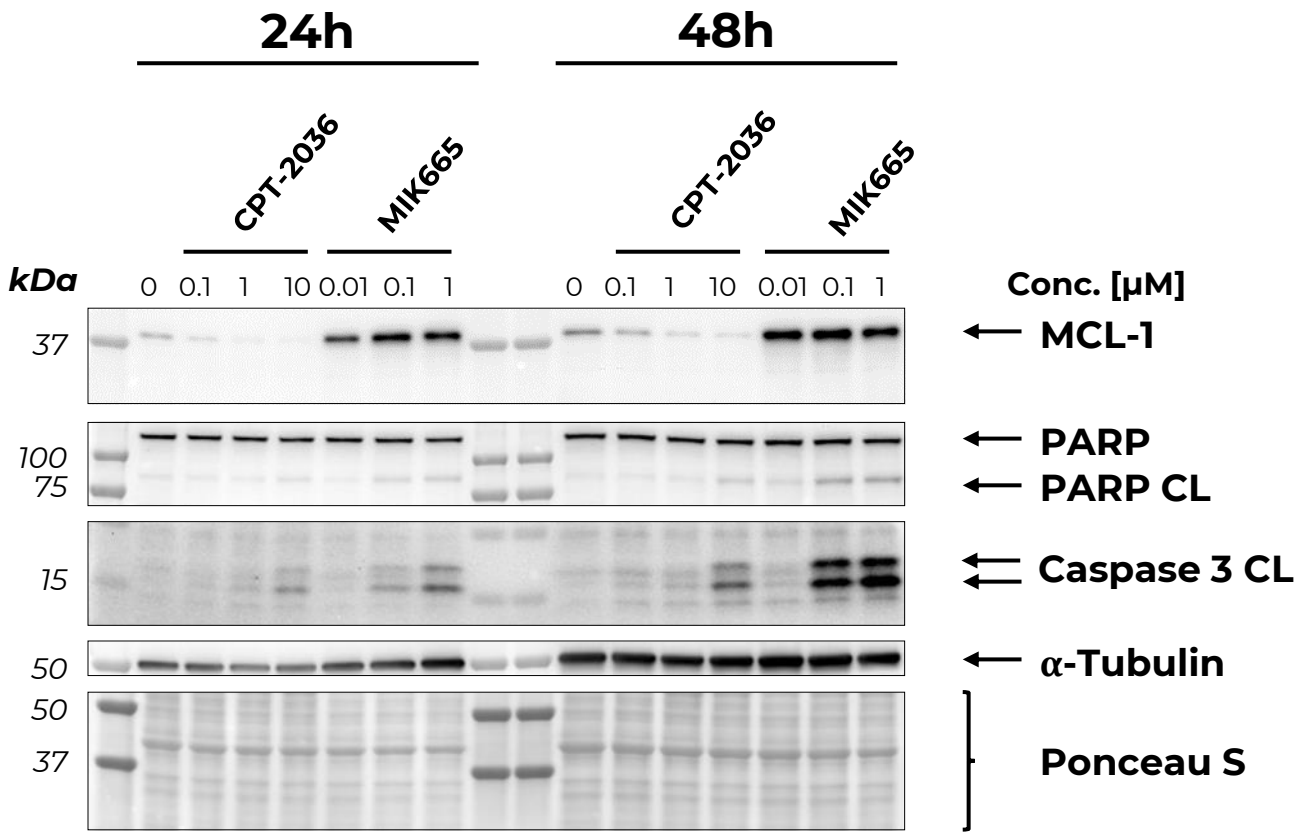
Potent MCL-1 degradation after single dose of CPT-2036

MCL-1 Degraders Show Reduced Cardiac Toxicity

Viability, 14 days treatement



iCell Cardiomyocytes



iCell Cardiomyocytes

Captor MCL-1 degraders don’t induce accumulation in cardiomyocytes

Summary

- Developed potent MCL-1 bi-functional degraders that induce apoptosis *in vivo* after single dose
- MCL-1 degraders show reduced cardiotoxicity compared to inhibitors
- IND-enabling studies planned for H1 2022

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