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Conducting research at the drug discovery stage using selected Captor projects

Piotr Kowalczyk – Principal Scientist Drug Discovery

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All images by Piotr Piatek

Piotr Kowalczyk – education

1992 – 1997: Warsaw University, Biology Faculty, Genetic Department

MSc with specialization in molecular biology

1997 – 2001: Medical Centre for Postgraduate Education, Warsaw
Oncology Center in Warsaw, Gastroenterology Department

PhD in Medical Biology

2015 – 2017: Koźmiński University, Warsaw

MBA Executive

2021: Medical University of Warsaw, Faculty of Health Sciences

D.Sc. (habilitation)

Piotr Kowalczyk – professional experience

2019 - 2021 : OncoArendi Therapeutics (Molecure), R & D Department

senior scientist / project leader

- development of small molecule inhibitors of chitin binding proteins (YKL-40) for the cancer and autoimmune disorders treatment

2010 - 2018: Selvita (RYVU), R & D Department:

senior scientist / principal investigator

- development of small molecule inhibitors of protein kinases, inflammasome and metabolic enzymes for the cancer and autoimmune disorders treatment

2005 - 20010: The University of Texas Health Science Center at San Antonio, Pharmacology Department

post doctoral fellowship / research scientist

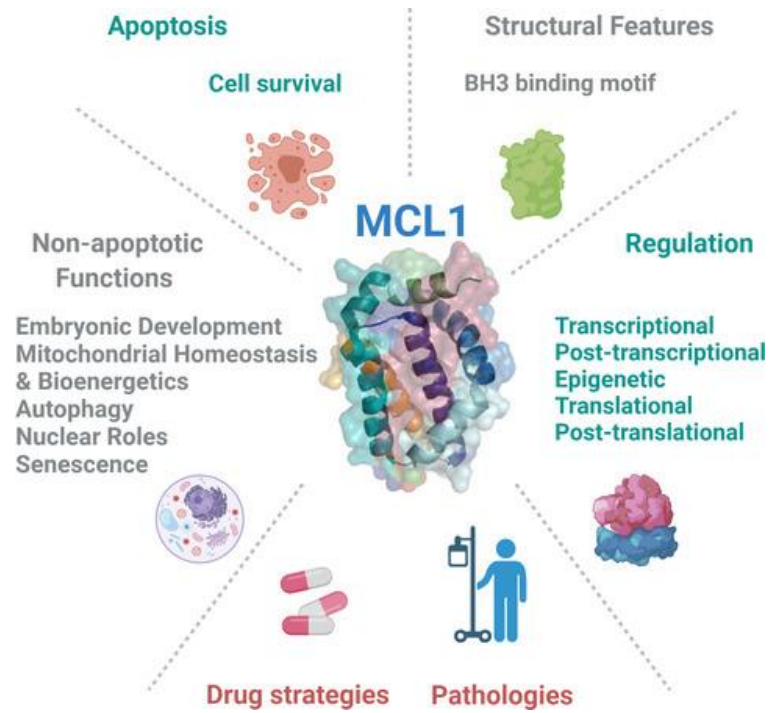
- dissociated glucocorticoid receptor activities and its involvement in the carcinogenesis in skin cancer
- natural compounds of plant origin in the prevention of carcinogenesis in a mouse model of skin cancer

2001 – 2005: Adamed Pharma, R & D Department

R&D specialist / project manager

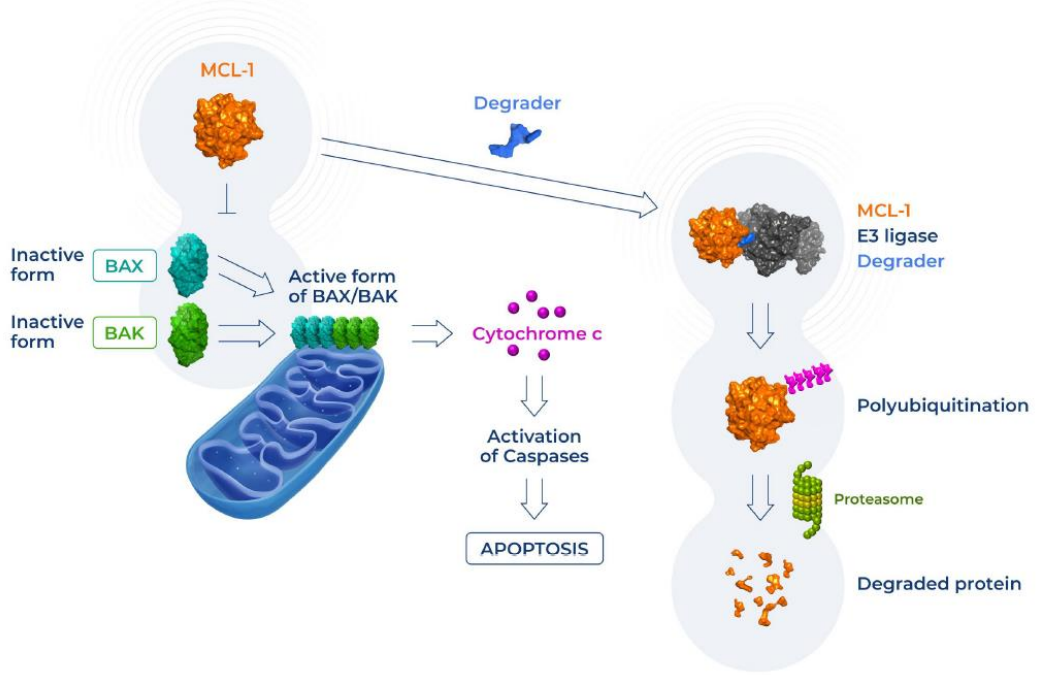
- development of small molecule PPAR modulators for the treatment of obesity and diabetes type 2

Targeting MCL-1 in cancer



MCL-1 role in cancer

- is involved in the regulation of apoptosis versus cell survival, and in the maintenance of viability but not of proliferation
- MCL-1 dysregulation occurs in many types of cancers and often correlates with poor prognosis and therapeutic resistance.
- knock-out studies revealed that among all different cancer types, the survival of haematological malignancies (AML, MM, NHL) and some of the solid tumours (e.g. SCLC, TNBC) depends on the MCL-1 expression



MCL-1 as a molecular target

- several MCL-1 inhibitors have been developed during the past decade and some of them have entered clinical trials, but no drugs have been approved for clinical use so far
- MCL-1 inhibitors can block only the anti-apoptotic function of the protein, while they leave intact other functions of the protein, that are important for cancer cell survival
- induced MCL-1 degradation affects all functions of the protein and thus could significantly suppress the growth of solid cancers and haematological malignancies

MCL-1 as a target in numerous anticancer therapies

MCL-1 is a key mechanism of drug resistance in cancer cells

Highly attractive target serving as a major survival signal in numerous cancers

Haematological malignancies

Multiple Myeloma (MM) | Acute Myeloid Leukaemia (AML) | Non-Hodgkin Lymphoma (NHL)

Selected solid tumours

Small cell lung cancer (SCLC) | Non-small cell lung cancer (NSCLC) | Triple-negative breast cancer (TNBC)

Despite years of effort no MCL-1 targeting drug has been approved

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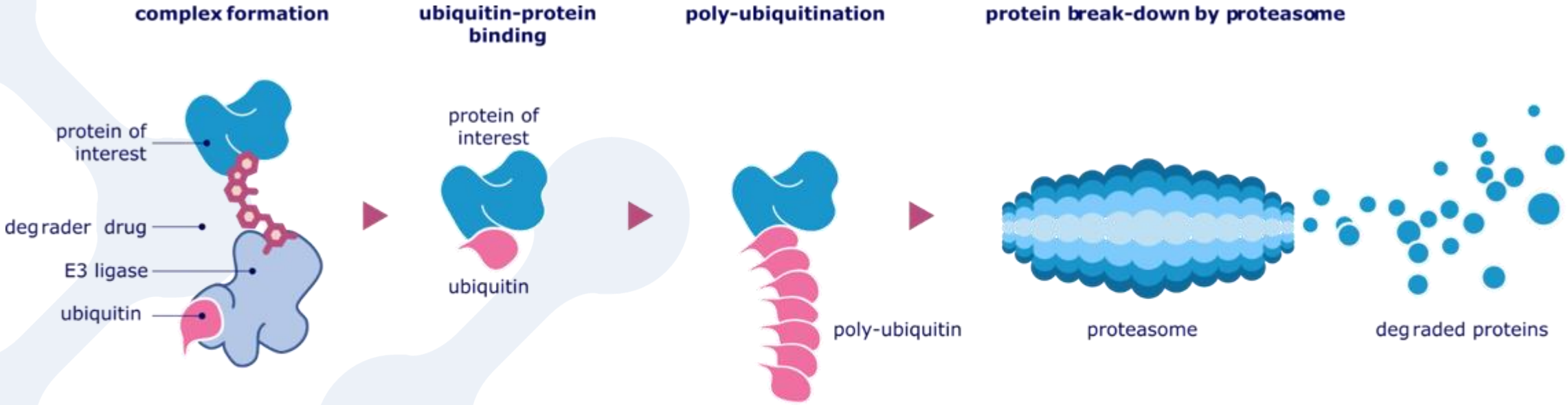
Principle of targeted protein degradation



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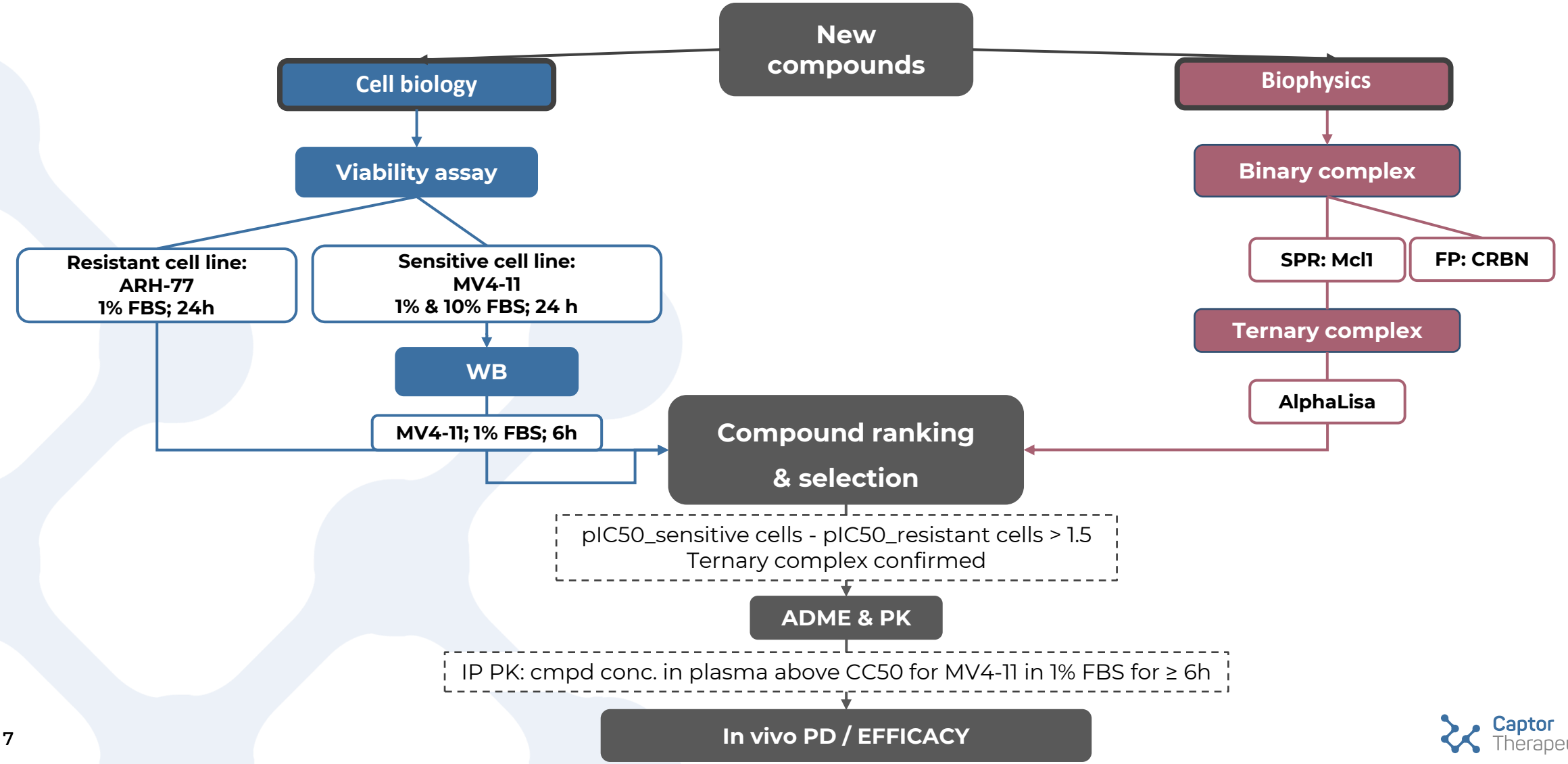
Project specific screening cascade



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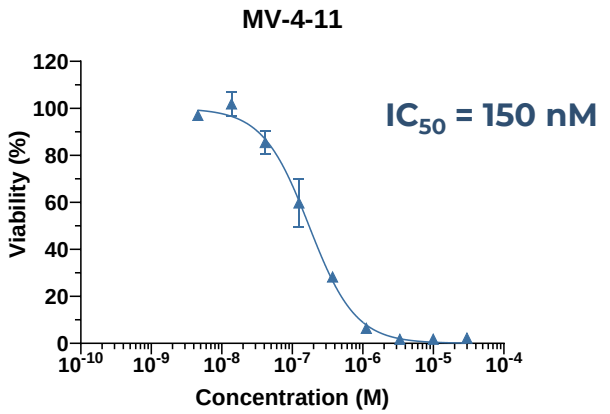
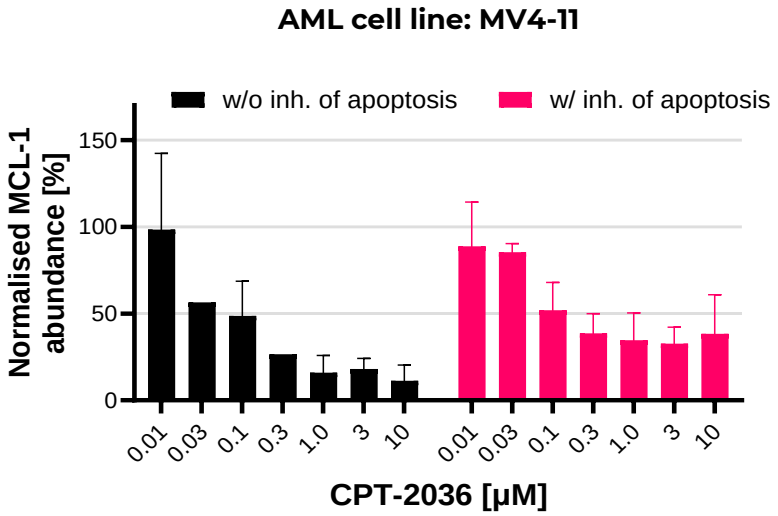
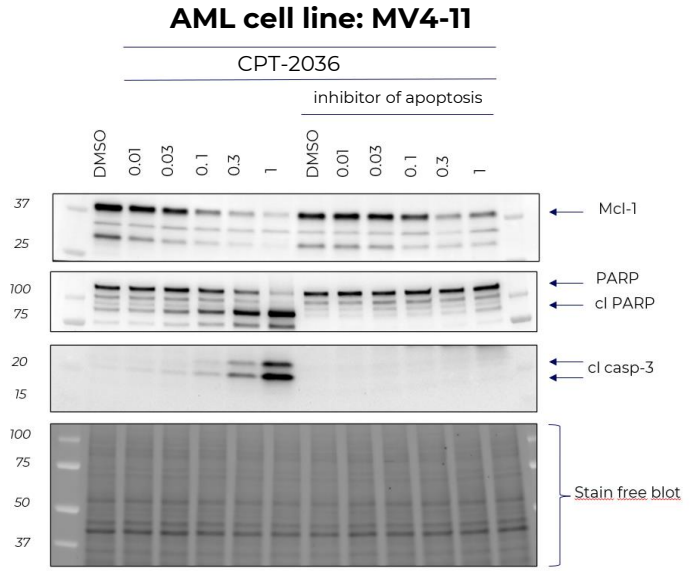
CPT-2036 *in vitro* potency

Viability assay – CTG (24 h treatment)



Degradation assay – WB (6 h treatment)





CPT-ABS-836 activity in the AML cell line:

- The compound has been tested in multiple haematological cancer cell lines. The most sensitive to the treatment was MV4-11 with IC_{50} = 150 nM.
- The compound induces MCL-1 degradation in a dose-dependent manner with DC_{50} = 100 nM.
- MCL-1 degradation induces caspase 3-dependent apoptosis.

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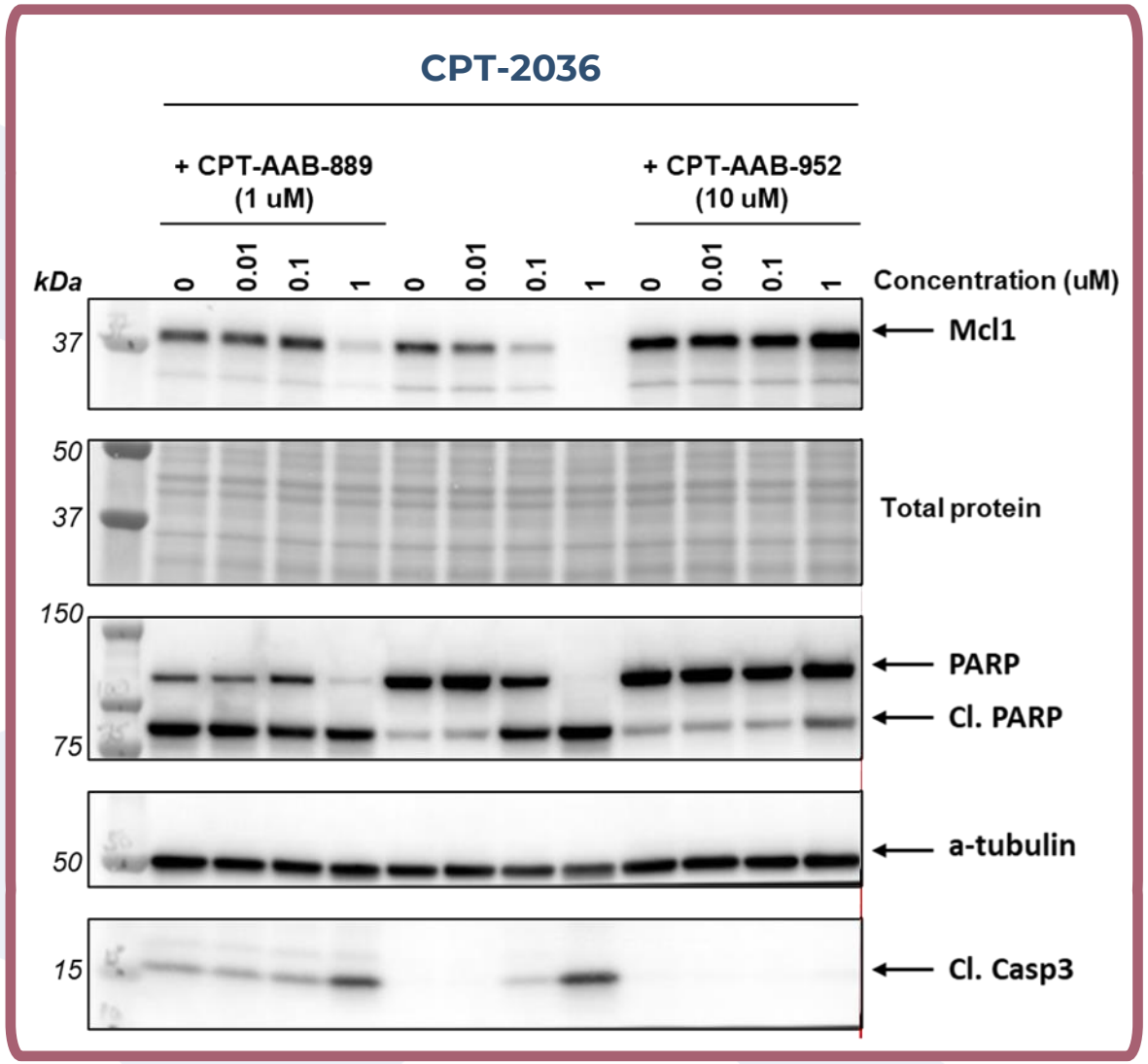
CRBN and proteasome dependency in OPM-2 cells



OPM-2 cells were pre-treated with the ligand or the inhibitor for 1 h and then treated with compounds in 1% FBS for 6 hours.

CPT AAB-889 – MG-132 (proteasome inhibitor),
CPT-AAB-952 – CRBN ligand (hydroxy-thalidomide)

CPT-2036 induces MCL-1 degradation in proteasome dependent manner

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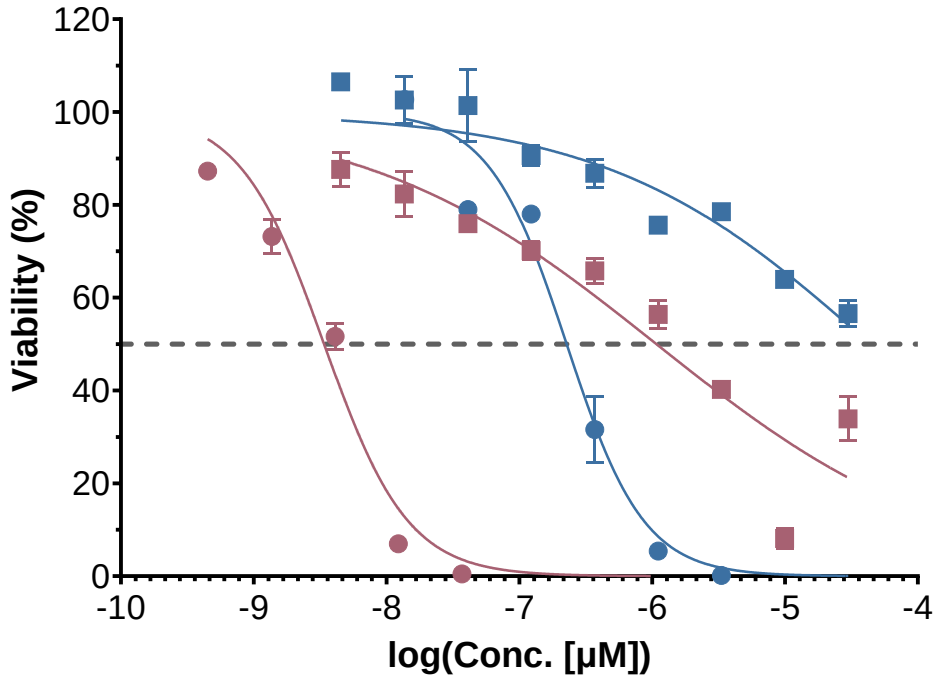
Cell line and PBMCs sensitivity to CPT-2036 & CPT-908



Cell line	pIC_{50} CPT-2036	pIC_{50} CPT-908
MV-4-11	6.5 ± 0.1	8.5 ± 0.2
MV-4-11 Ven-resistant	-	11.5 (N=1)
MV-4-11 Ven-resistant + Venetoclax	-	12.0 (N=1)
WSU-DLCL-2	5.4 ± 0.2	7.6 ± 0.1
DMS 114	6.2 ± 0.3	7.8 ± 0.1
OPM-2	6.6 ± 0.2	>8.3 ± 0.1
Hep3B	< 4.53	-
hsPBMC	4.9 ± 0.7	6.3 ± 0.5
hiPSC-CM	4.8 ± 0.8	5.8 (N=1)

Both compounds are active in multiple cancer cell lines

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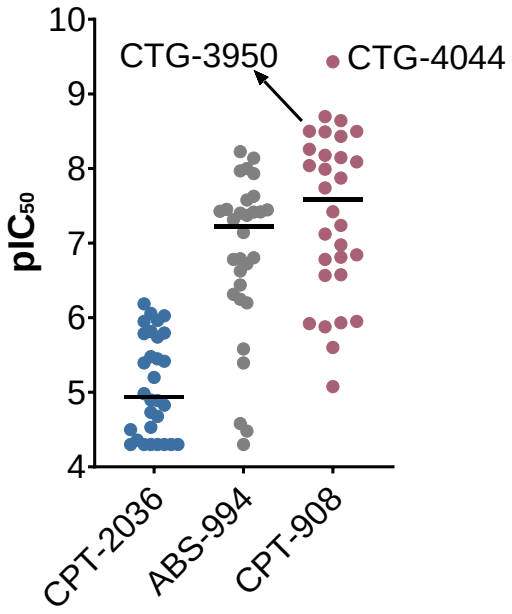
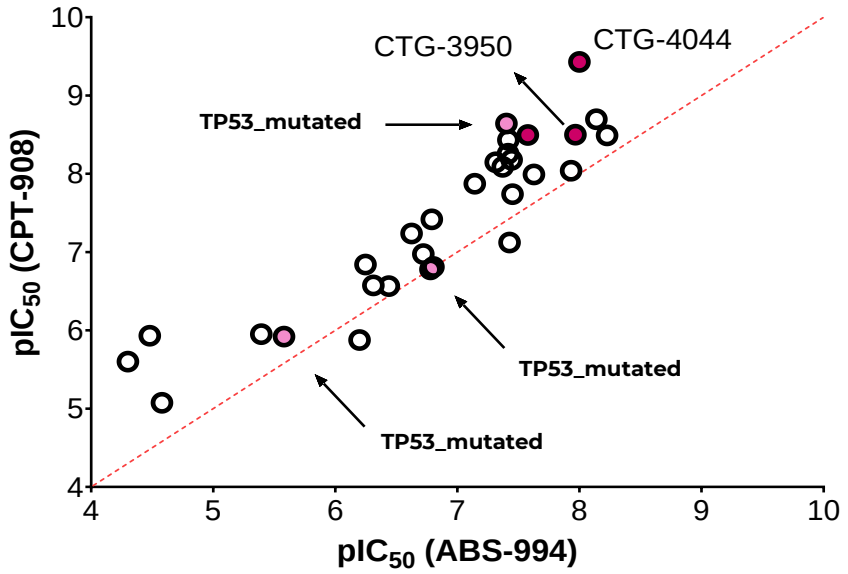
High potency of CPT-908 in AML *ex vivo* models

pIC_{50} values of tested compounds in each of the 30 AML *ex vivo* models



CPT-908 is more potent than ABS-994 in most of the tested models



ABS-994 - MIK665, MCL-1 inhibitor in Ph I/II (Servier/Novartis)
VitroScreen, Champions Oncology
CTG-4044 and CTG-3950 – patients resistant to Gilteritinib or Venetoclax, respectively

CPT-908 is more potent than MIK665 in a panel of 30 PDX cell lines and shows nM activity in cells refractory to gilteritinib and venetoclax

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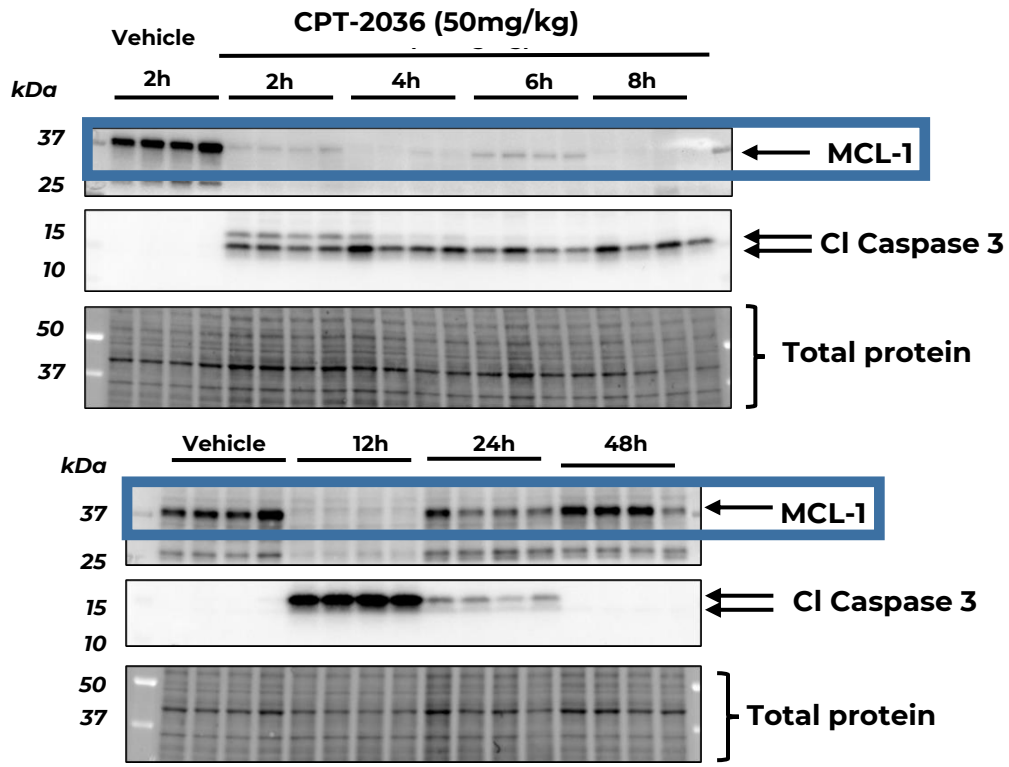
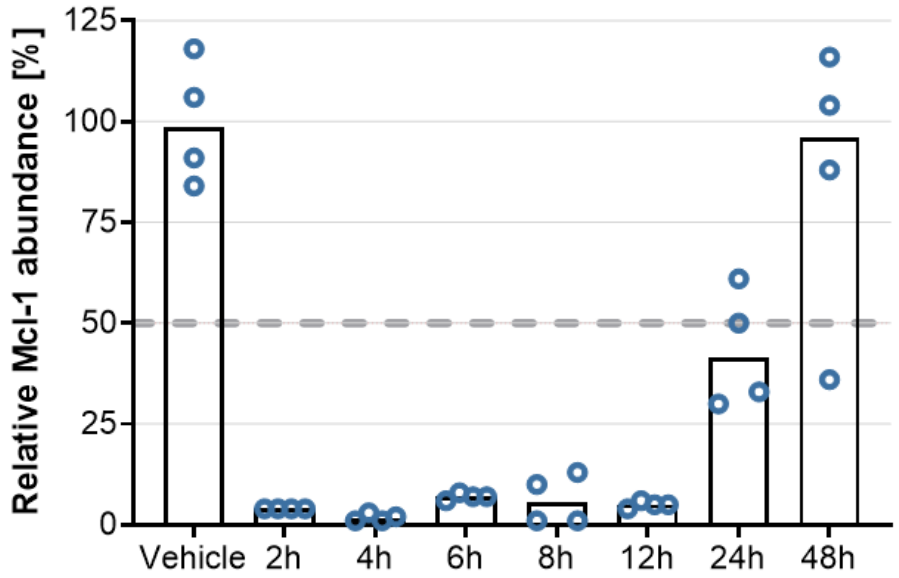
Strong PD effect upon single injection of CPT-2036 in mice





CB-17 SCID females, **MV4-11** xenografts (tumour volume >300 mm^3), IV injection

CPT-2036 formulated in: 40% DMA: solutol: PEG300 - 3:1:5, 60% Tris-HCl pH=8.0

CPT-2036 is a potent inducer of apoptosis in a single injection PK/PD study in MV4-11

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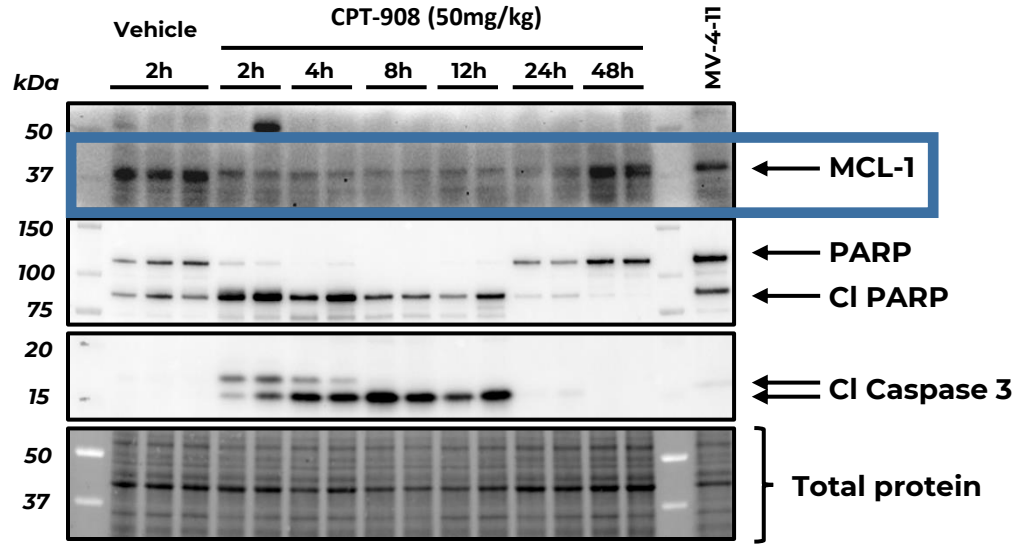
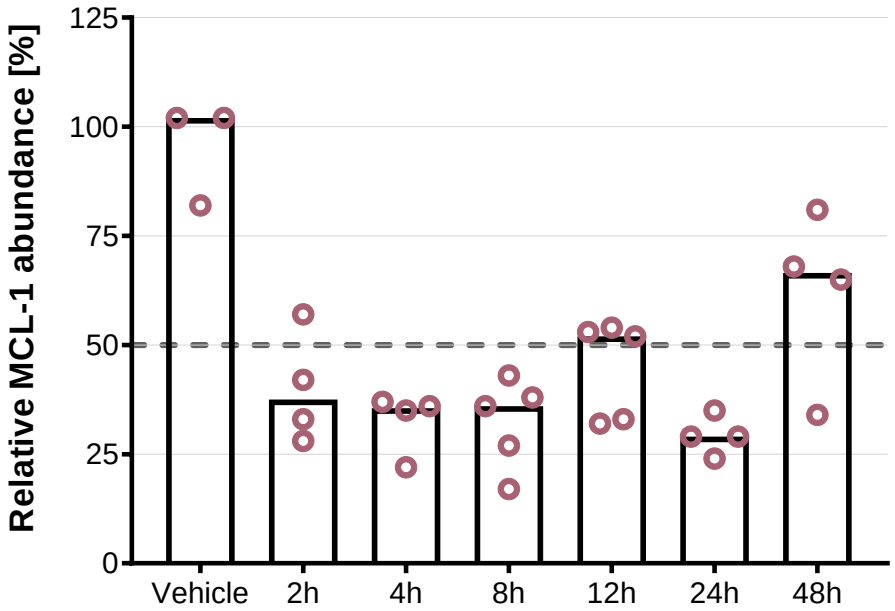
Strong PD effect upon single injection of CPT-908 in mice





CB-17 SCID females, **MV-4-11** xenografts (tumour volume >300 mm^3), IV injection

CPT-908 formulated in: 40% DMA: solutol: PEG300 - 3:1:5, 60% Tris-HCl pH=8.0

CPT-908 is a potent inducer of apoptosis in a single injection PK/PD study in MV4-11

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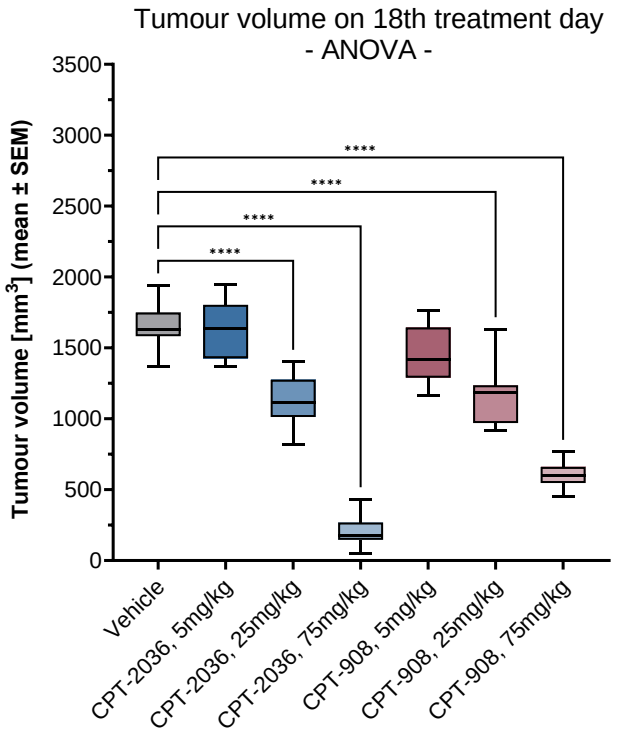
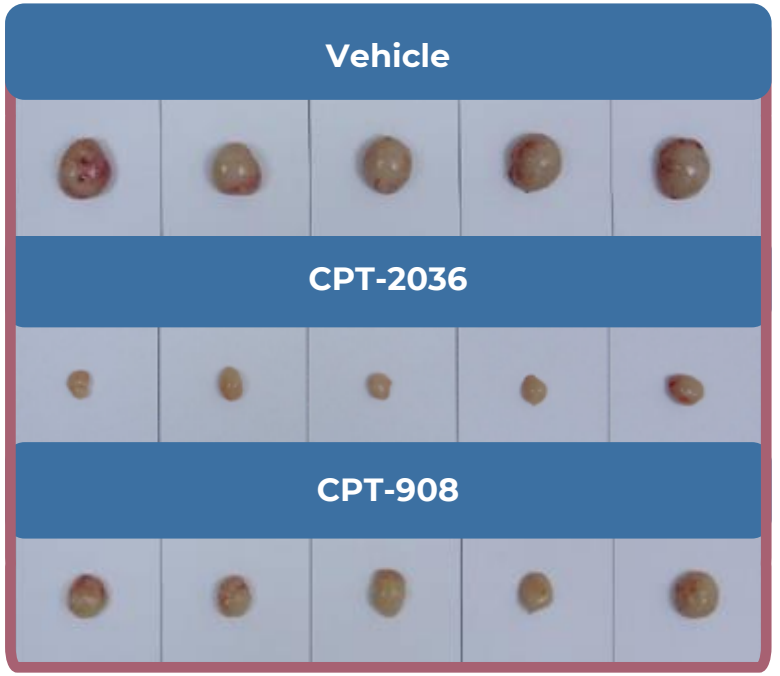
Efficacy of CPT-2036 & CPT-908 in MV4-11 leukaemia model





Compound	Dose [mg/kg]	Δ inhibition (day 18) [%]
CPT-2036	75	107
	25	44
	5	10
CPT-908	75	80
	25	37
	5	16

NOD.SCID female mice; **MV4-11** xenografts (tumour volume >150 mm^3); 18 days of dosing

CPT-908 & CPT-2036 potently inhibit tumour growth in MV4-11 model
No effect of the treatment on body weight was observed

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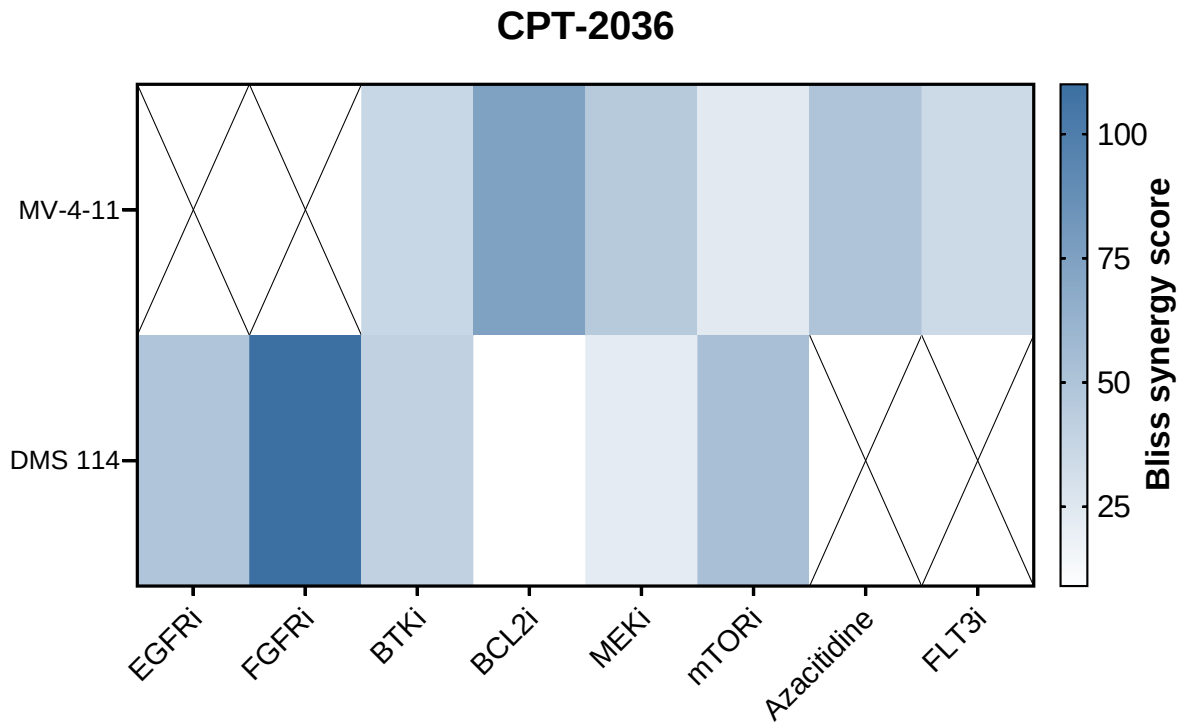
CPT-2036 in combination with chemotherapeutic agents

Co-treatment with **CPT-2036** and different chemotherapeutic agents in **MV4-11** and **DMS 114** for 72 h. Viability assessed by CTG assay.



CPT-2036 shows synergy with different approved drugs including venetoclax and FGFR2 inhibitors

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ADME properties of CPT-2036 & CPT-908

ASSAY	Parameter	CPT-2036			CPT-908		
		mouse	monkey	human	mouse	monkey	human
Plasma stability	Remaining @120 min [%]	**59.2**	-	85.0	**0.2**	102.9	83.5
	T-half [min]	**> 120**	-	> 120	**< 15**	**> 240**	**> 240**
PPB	FU	0.06	0.02**	< 0.01	NC*	-	N/A***
	Recovery [%]	36.0	65.4**	99.3	NC*	-	100.7
Microsomal stability	Remaining @60 min [%]	32.1	-	36.0	57.9	-	60.3
	T-half [min]	37.1	-	41.5	75.2	-	85.0
	Clint [µl/min/mg]	18.7	-	16.8	18.4	-	16.3

*NC – not calculated, compound was unstable in plasma
** performed with increased compound conc. (100 µM)
***N/A - not applicable, compound was not detected in the buffer chamber

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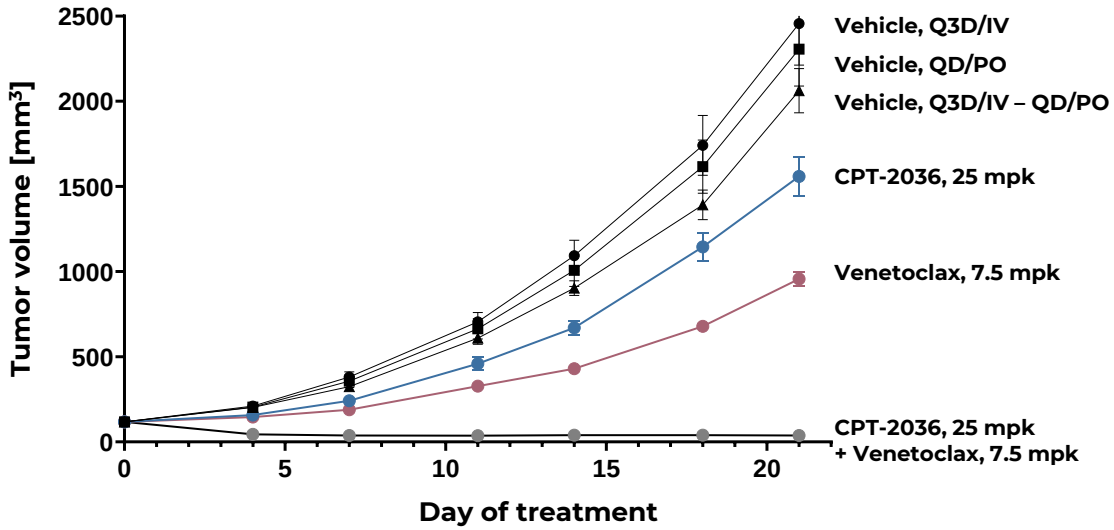
Highly potent CPT-2036 regresses tumors in mice at low dose when used in combination with venetoclax



Regression of large tumors was observed for both CPT-2036 and venetoclax, with the most favorable outcome for their combination

ABS-836 was administered 8 times, every 3 days (Q3D) intravenously and venetoclax was administered daily (QD) orally

CPT-206 in combination with venetoclax strongly inhibits cancer growth in MV-4-11 Human Leukemia Xenograft Model in Female NOD/SCID Mice

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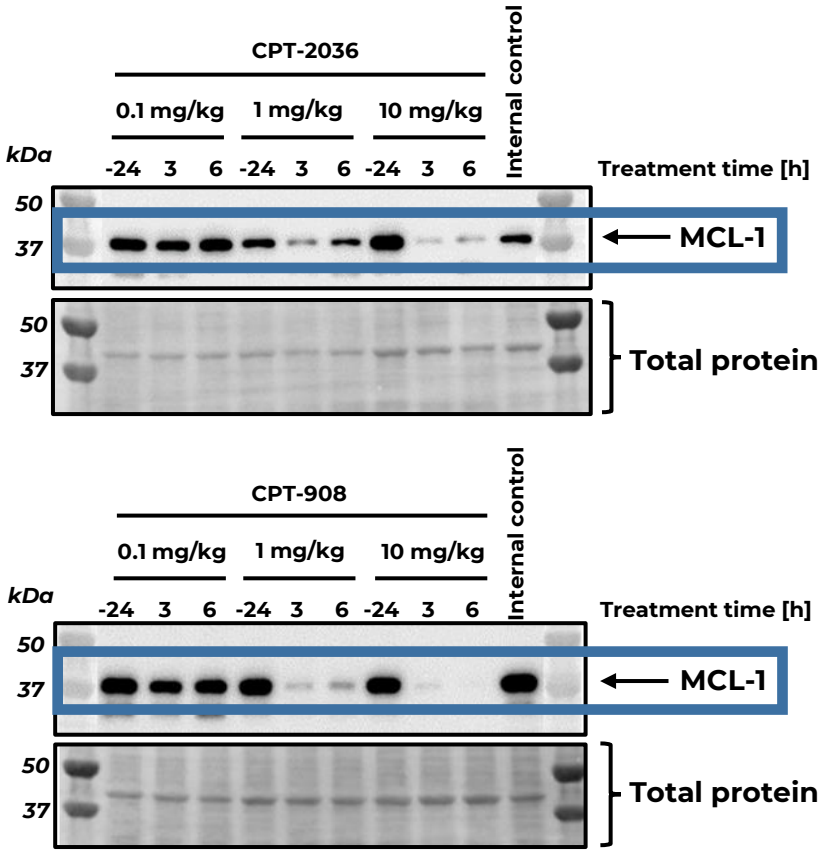
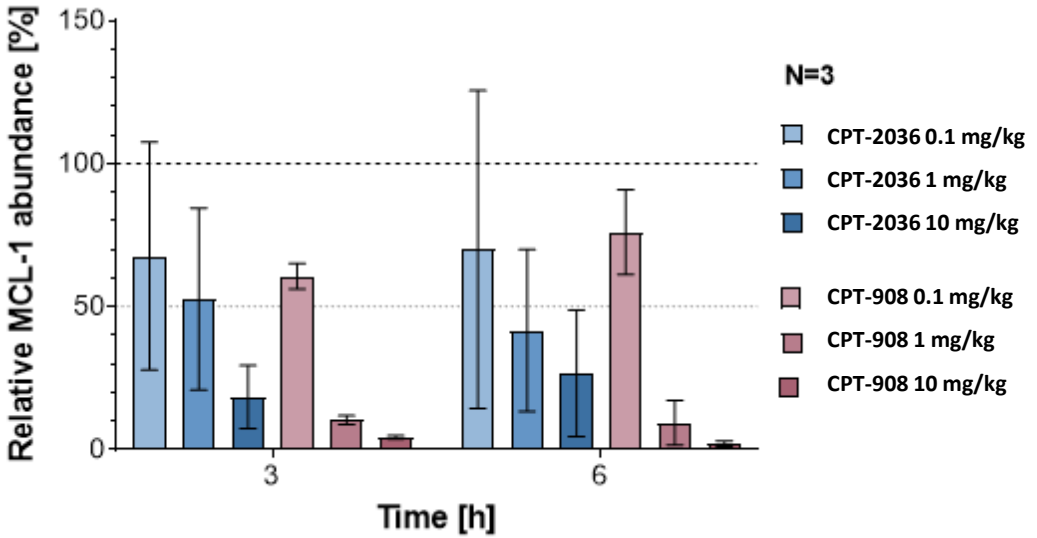
Strong PD effect of both CPT-908 & CPT-2036 in NHP PBMCs





Male Cynomolgus Monkey, IV injection

Compounds formulated in: 10% DMSO/ 15% solutol/ 75% Tris-HCl pH=7.6

CPT-908 is >10x more potent in NHP than CPT-2036

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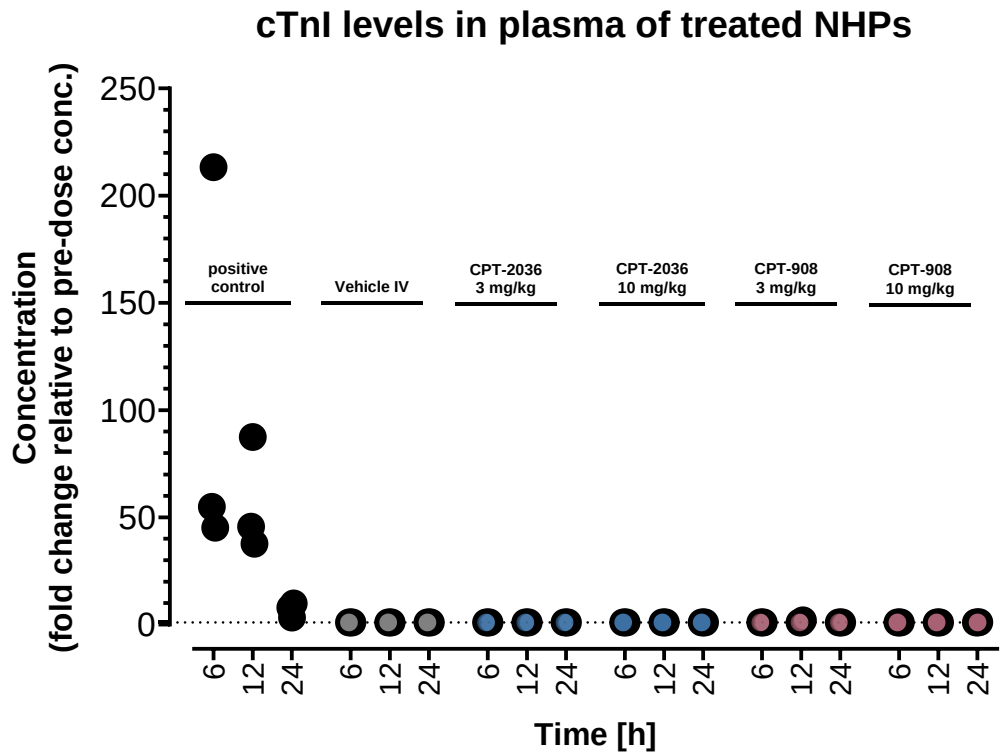
Troponin I levels in plasma of NHPs after the treatment with MCL-1 degraders



No observed changes in cardiac troponin levels were significantly different from the vehicle control

*Cardiotoxic positive control - Isoproterenol 3mg/kg, Vasopressin 0.3mg/kg

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MCL-1 degraders offer pharmacology distinct from inhibitors

- MCL-1 degraders lead to a drop of MCL-1 levels, unlike inhibitors that accumulate MCL-1
- Reduction of MCL-1 by 50-70% results in apoptosis induction (monoallelic KO of MCL-1 is viable and without phenotype)
- Optimized degraders, CPT-2036 and CPT-908, are synergistic with different drugs
- CPT-908 is more potent than the clinical inhibitor, MIK665 (Servier/Novartis), in patient-derived AML cells
- MCL-1 degraders given in excess of the effective dose do not affect Troponin-I levels in NHPs

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