Overcoming platinum resistance in tumor cells by novel thioxodihydroquinazolinone (TDQ) small molecules

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Outline

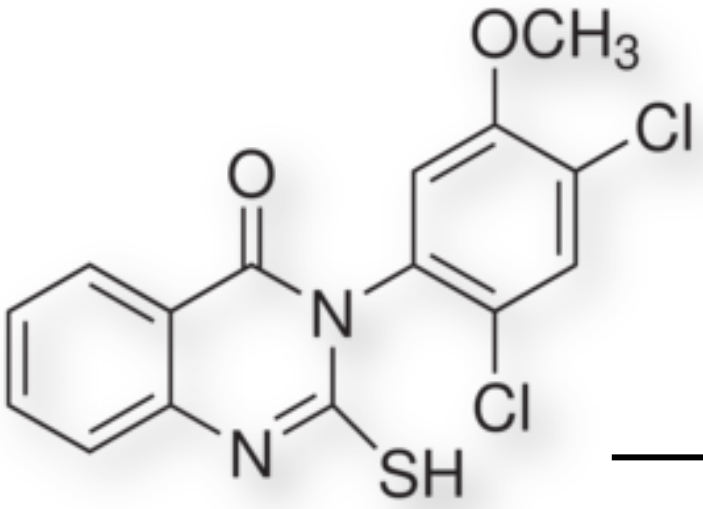
1. The synergistic effect of the combination of cisplatin with mdivi-1 (mitochondrial division inhibitor-1, the first TDQ class small molecule)

2. Chemical screening for more potent mdivi-1 analogs

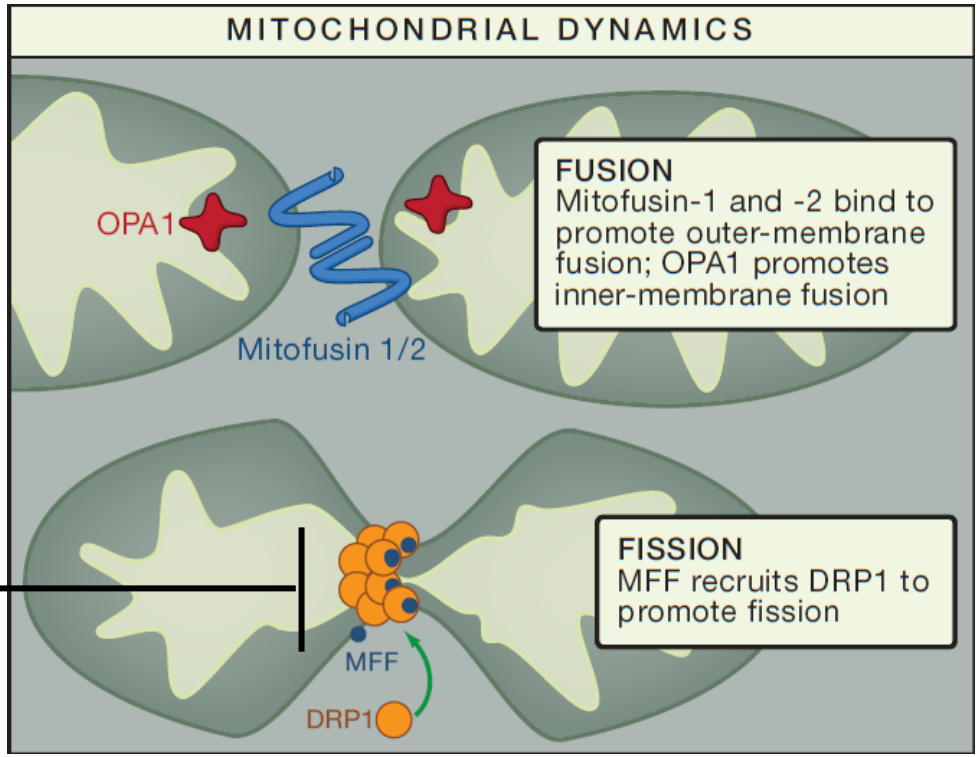
3. The mechanism of action of the combination

4. Future directions

Mdivi-1 (mitochondrial division inhibitor-1)



Mdivi-1



D. Green, and B. Van Houten. **(2011),** *Cell* 147(4):950-951.

Quinazolinone derivative, blocks polymerization of Drp1 and GTP hydrolysis

By inhibiting Drp1, mdivi-1 prevents mitochondrial fission-mediated apoptosis.

Cassidy-Stone, A., et al., *Dev Cell*. 2008, 14:193-204.

The therapeutic potential of mdivi-1

1. **Attenuating neurotoxicity and dopamine release deficits in Parkinson's disease model**. Rappold PM, et al., Nature communications. 2014, 5:5244.

2. **Attenuating doxorubicin-induced cardiotoxicity.** Gharanei M, et al., PLoS One. 2013, 8(10):e77713.

3. **Ameliorating pressure overload-induced heart failure.** Givvimani S, et al., PLoS One. 2012, 7(3):e32388.

4. **Protecting ischemic brain injury.** Cui M, et al., Molecular neurobiology. 2014.

5. **Reducing acute kidney injury.** Brooks C, et al., J Clin Invest. 2009, 119(5):1275-85.

The anti-cancer properties of mdivi-1

1. Tumor cell specific anti-mitotic effect by inducing acentrosomal mitotic spindles

Wang J, Li J, Santos L, Shuda M, Sobol R, Van Houten B* and Qian W*. Molecular Oncology. 2015;9(2):488-502.

2. Tumor cell specific synergistic effect with targeted agent TRAIL

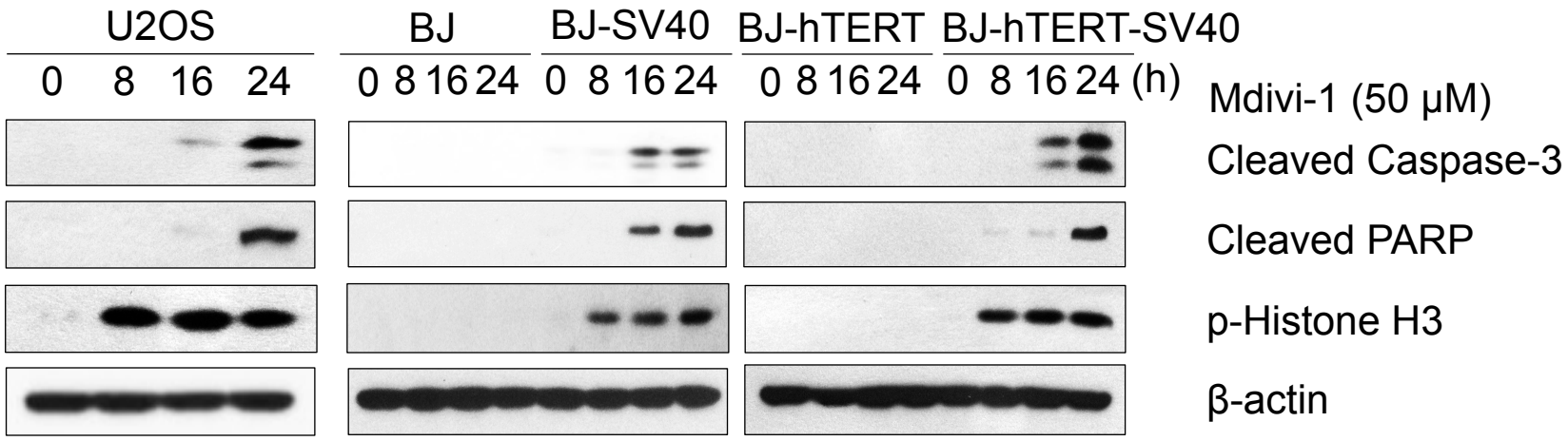
Wang J, Hansen K, Edwards R, Van Houten B*, Qian W*. Biochemical and Biophysical Research Communications. 2015;456(1):7-12.

3. Synergistic effect of mdivi-1 with cisplatin in platinum-resistant tumor cells

- Qian W*, Wang J, Roginskaya V, McDermott LA, Edwards RP, Stolz DB, Llambi L, Green D, and Van Houten B*. Oncotarget. 2014, 5(12):4180-94.

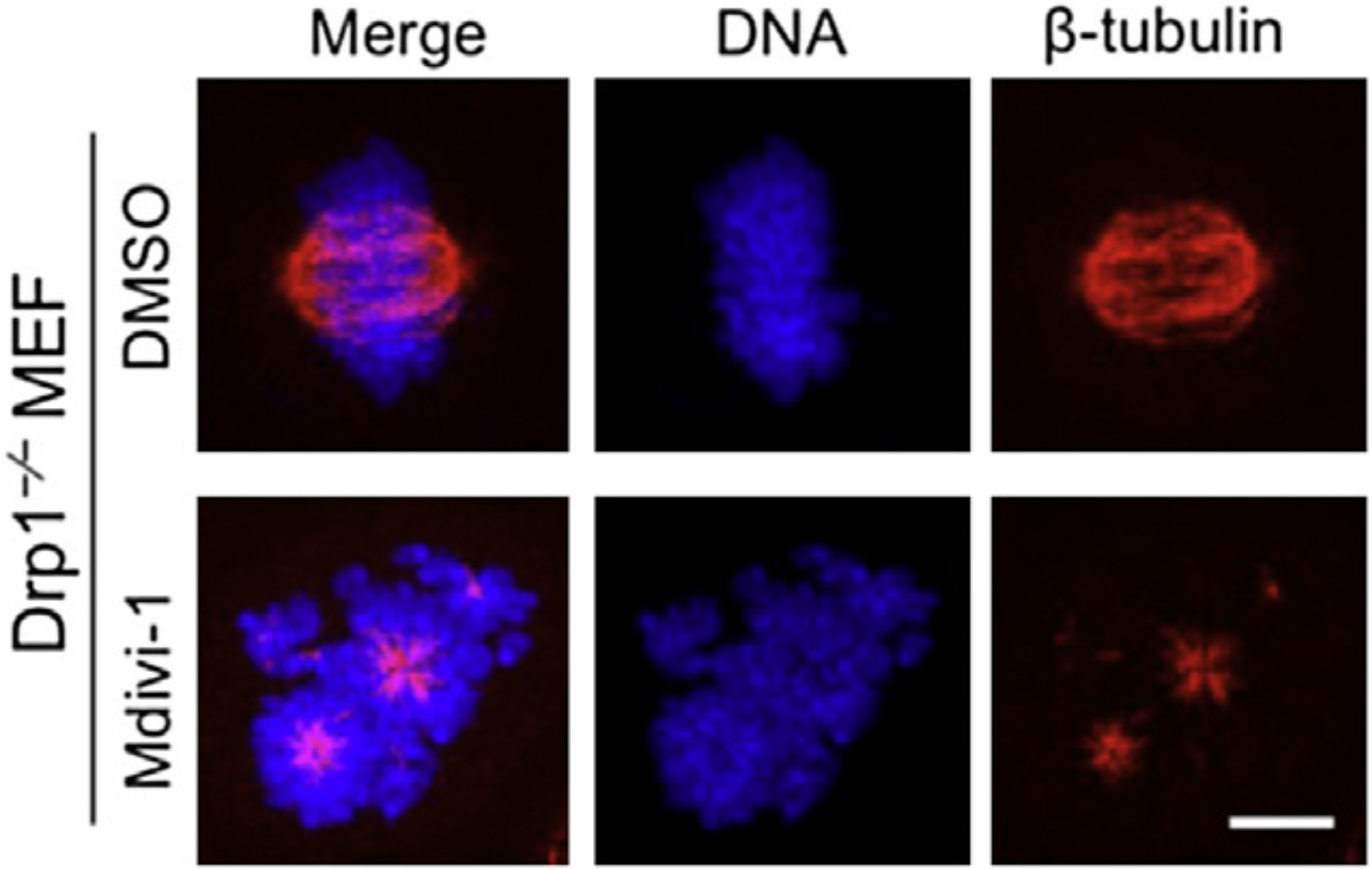
- Qian W*, Salamoun J, Wang J, Roginskaya V, Van Houten B, Wipf P*. Bioorg Med Chem Lett. 2015;25(4):856-63.

Mdivi-1 alone induces apoptosis only in tumor cells



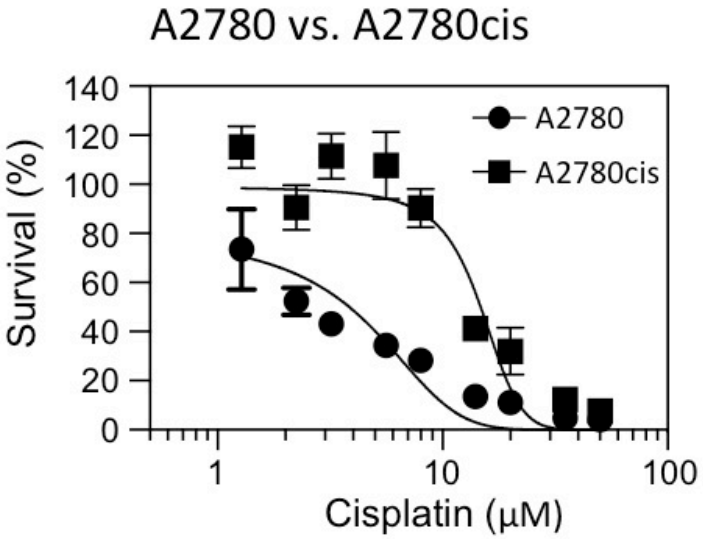
Wang J., et al, Molecular Oncology. 2015;9(2):488-502.

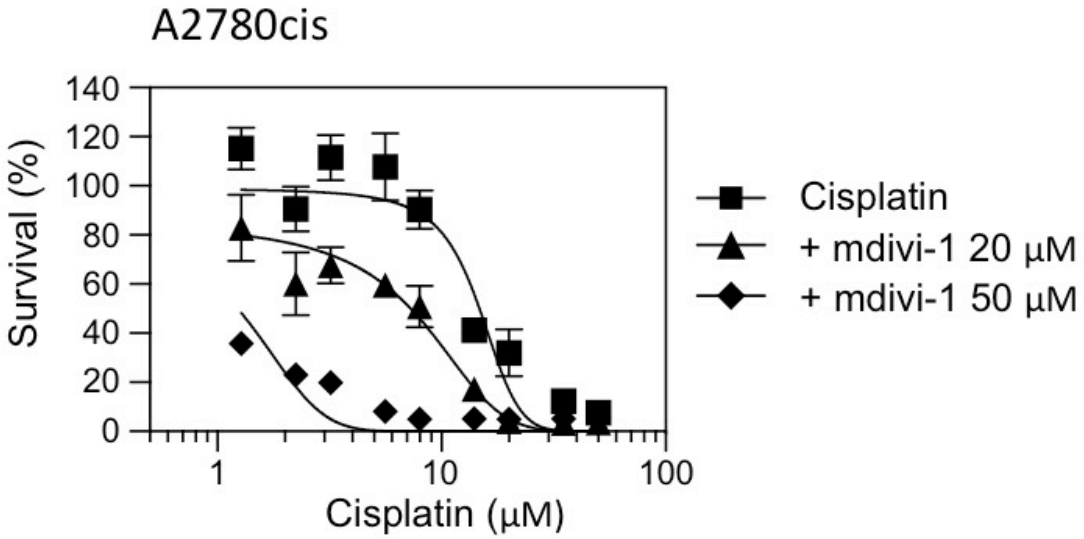
Mdivi-1 induces abnormal assembly of mitotic spindles only in transformed cells and is independent on Drp1



Wang J., et al, Molecular Oncology. 2015;9(2):488-502.

Mdivi-1 overcomes acquired cisplatin resistance in ovarian cancer cells





72 h exposure, MTS assay

Qian W*, et al, Oncotarget. 2014, 5(12):4180-94.

Cisplatin resistance: a significant clinical challenge

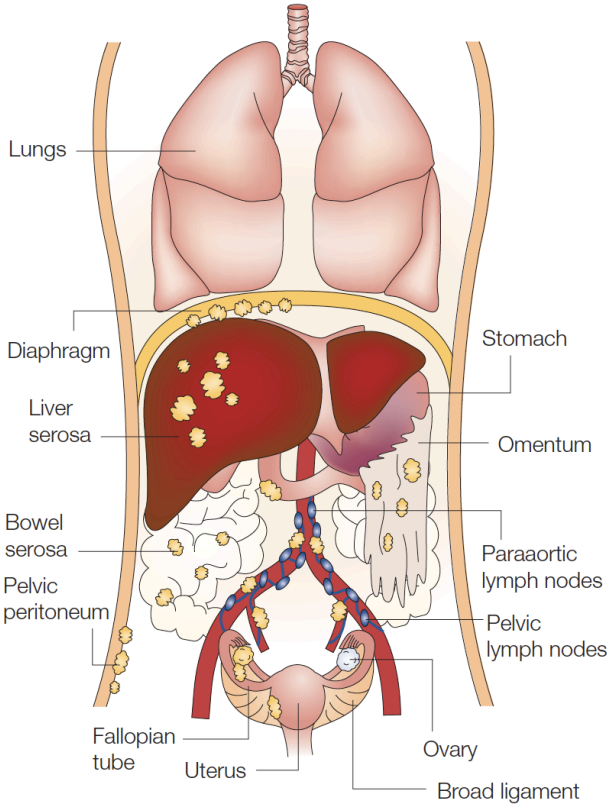
Table 1 | **Major mechanisms of resistance to cisplatin**

Molecular mechanisms	Examples of tumour type or cell line	References
Inactivation of cisplatin by glutathione, metallothionein or other sulphur-containing molecules	Ovarian cancer; bladder tumour; L1210 murine leukaemia; or small-cell lung cancer line	220–224
Increased repair of cisplatin adducts	Ovarian cancer; non-small-cell lung cancer line	225–227
Reduced cisplatin accumulation by changing the profile of uptake/efflux	Ovarian cancer; epidermoid carcinoma; oral squamous carcinoma	19,20,22
Increased cisplatin adducts tolerance and failure of apoptotic pathways	Ovarian cancer; L1210 murine leukaemia cell line	162,228,229

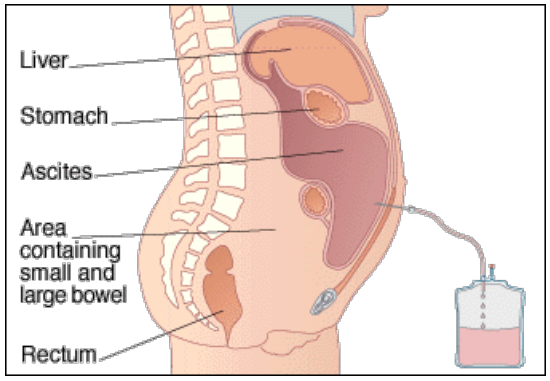
Platinum resistance is the single most important factor in determining prognosis in ovarian cancers, which is the most lethal disease among all cancers of the female reproductive system.

Wang, D., and S.J. Lippard. 2005. Nature reviews. Drug discovery. 4(4):307-20.

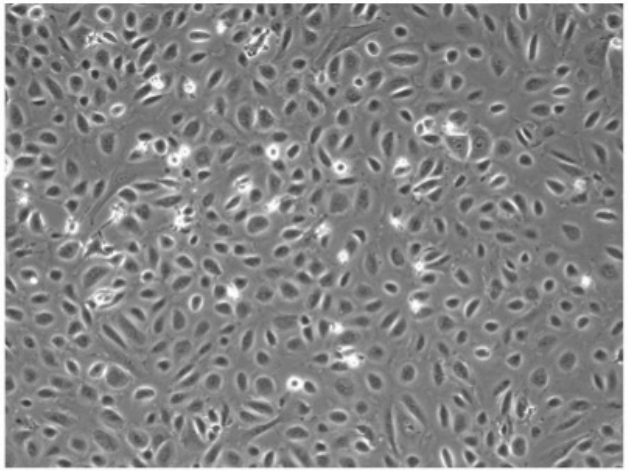
Isolation of human ovarian cancer cells from patient ascites



Naora, H., and D.J. Montell. 2005. *Nat Rev Cancer*. 5:355-366.



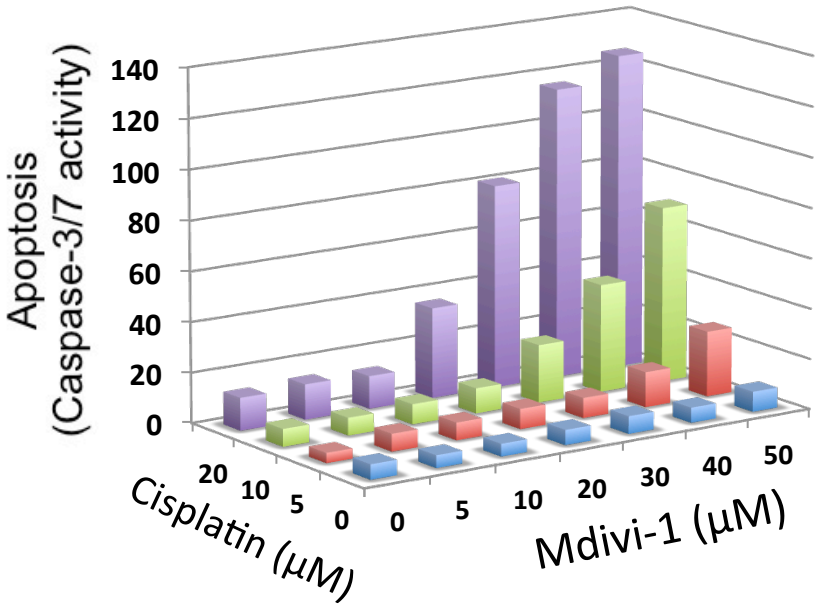
http://medipulse.blogspot.com/2010/08/ascites.html



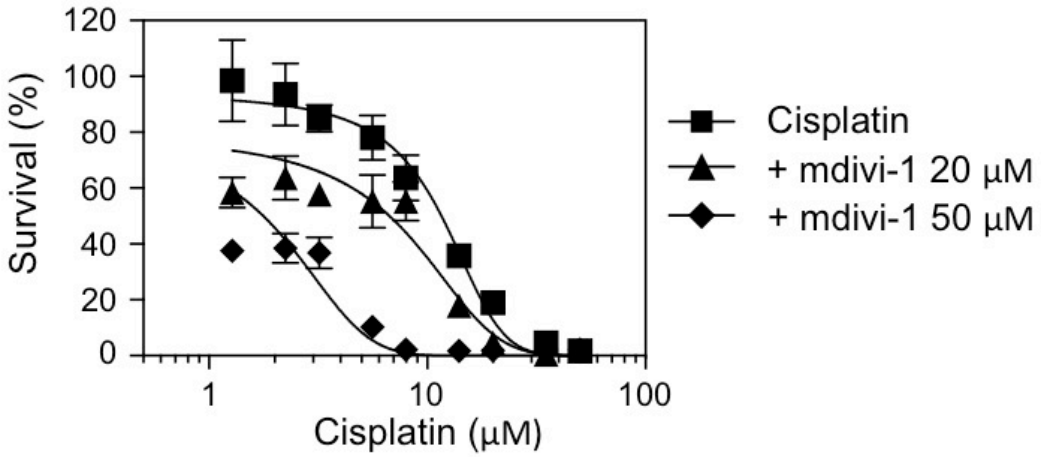
Confluent monolayer of ovarian cancer cells from ascites, depicting typical epithelial cobblestone morphology.

Mdivi-1 enhances cisplatin efficacy in primary ovarian cancer cells isolated from a cisplatin-refractory end-stage patient

20 h exposure

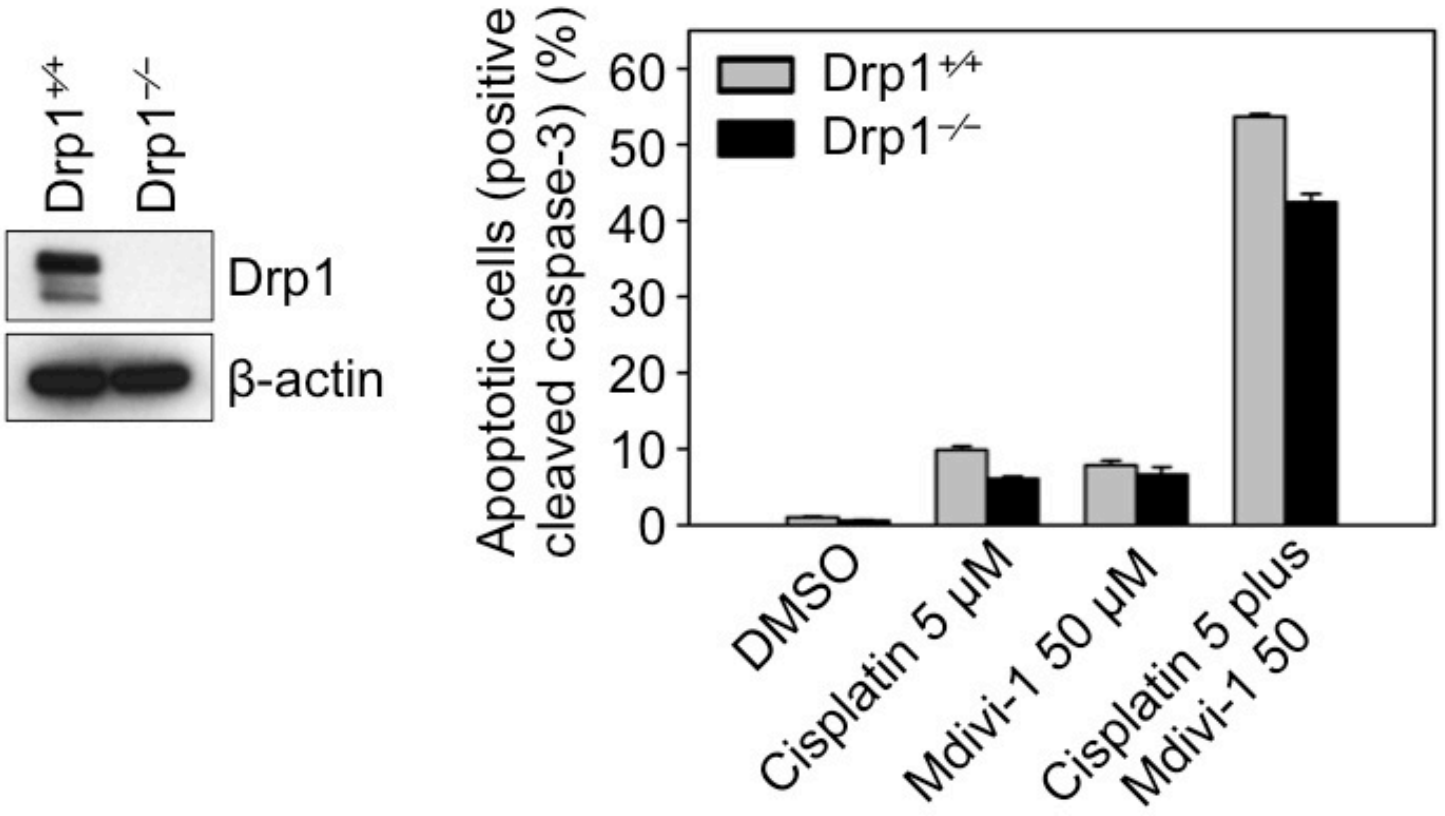


72 h exposure



Qian W*, et al, Oncotarget. 2014, 5(12):4180-94.

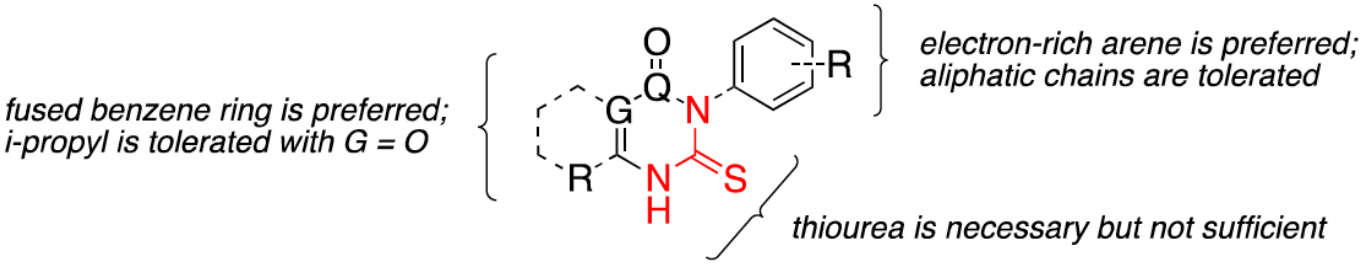
The synergistic effect of mdivi-1 and cisplatin is not dependent on Drp1 (the original proposed target of mdivi-1)



Qian W*, et al, Oncotarget. 2014, 5(12):4180-94.

Structure activity relationship (SAR) study of mdivi-1 derivatives (thioxodihydroquinazolinones) to improve potency and study the mechanism of action

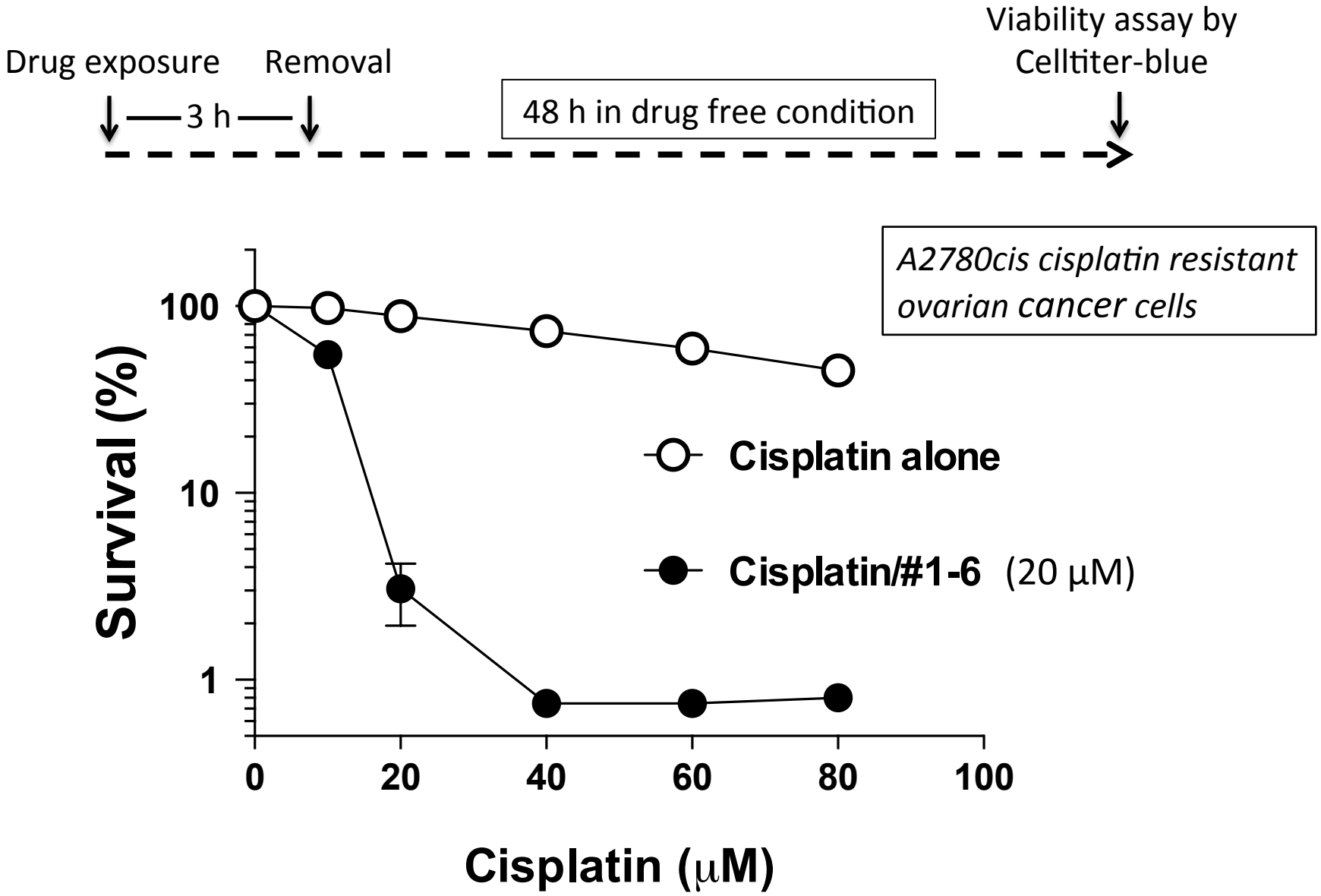
Dr. Peter Wipf



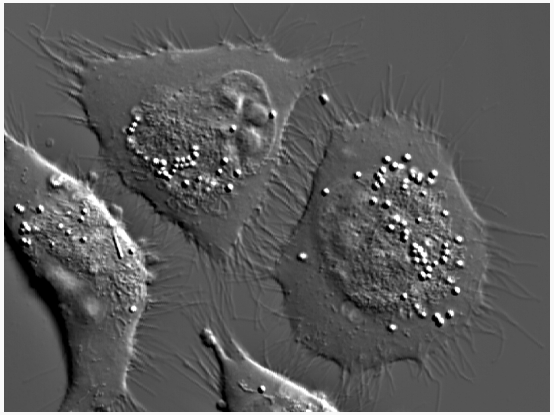
Qian W, et al, Bioorg Med Chem Lett. 2015;25(4):856-63.

55,000 chemicals → Computational selection → **69 candidates** → Activity screen → **11 hit compounds** → **4 more potent**

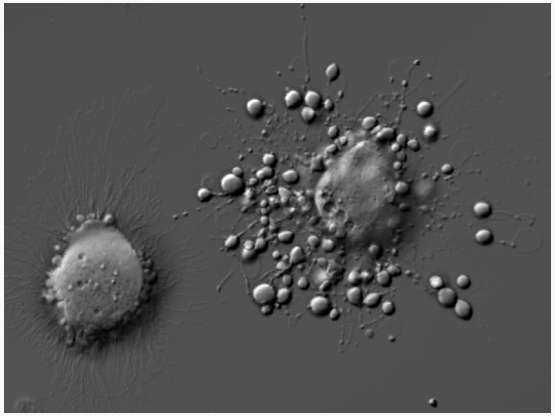
Short-term exposure with the combination is sufficient to reduces cell survival



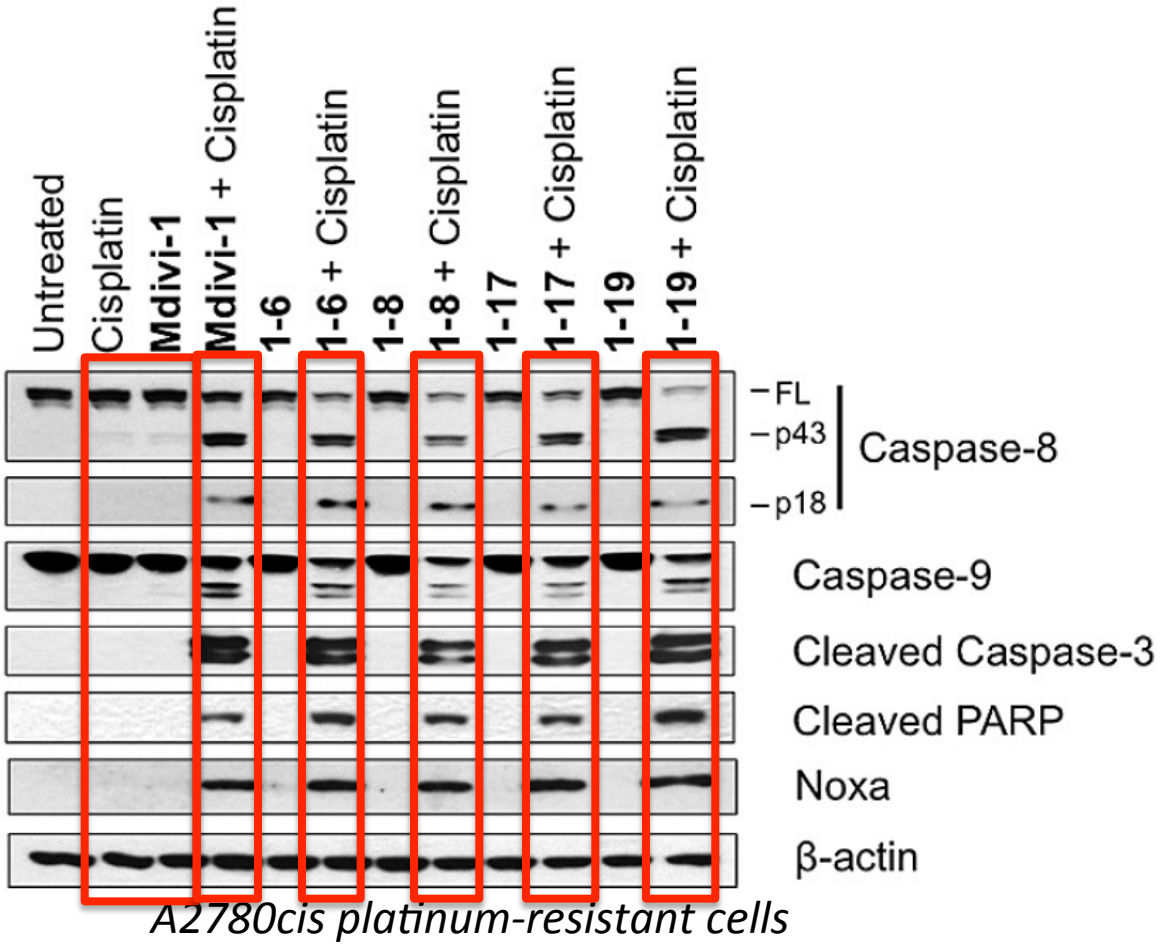
The combination of cisplatin and mdivi-1 induces apoptotic cell death



DMSO



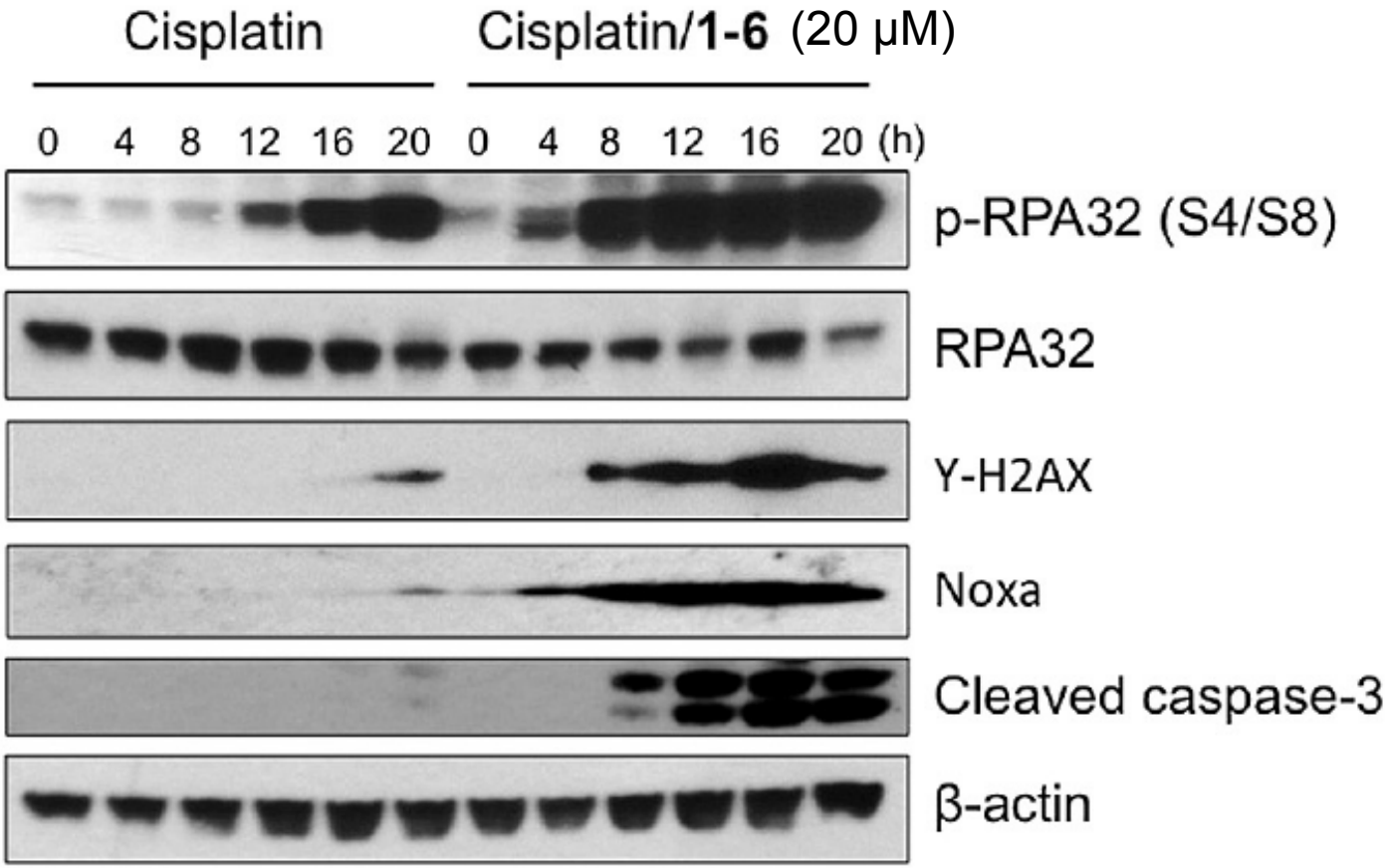
Cisplatin/mdivi-1



A2780cis platinum-resistant cells

Qian W, et al, Bioorg Med Chem Lett. 2015;25(4):856-63.

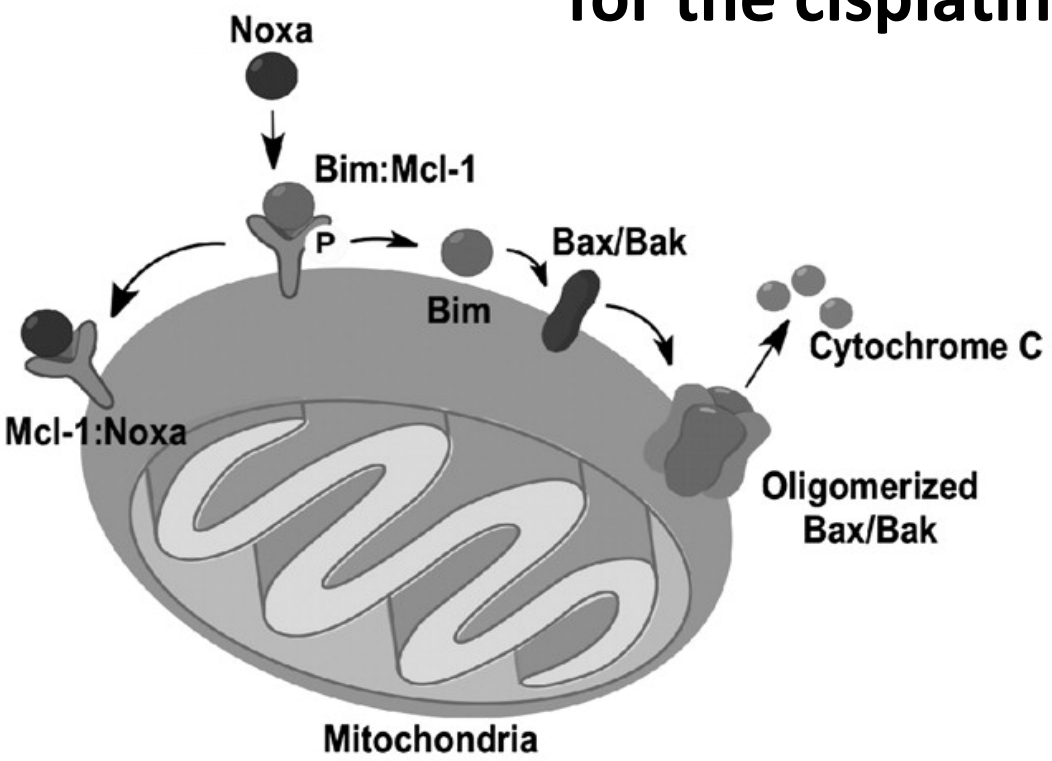
Combination of mdivi-1 and cisplatin enhances replication stress

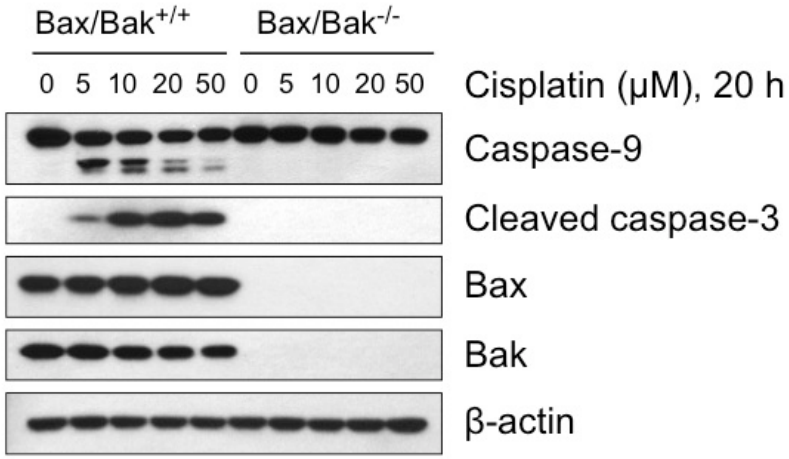


A2780cis platinum-resistant cells

Qian W, et al, Bioorg Med Chem Lett. 2015;25(4):856-63.

Proapoptotic Bcl-2 family proteins Bax and Bak are required for the cisplatin toxicity

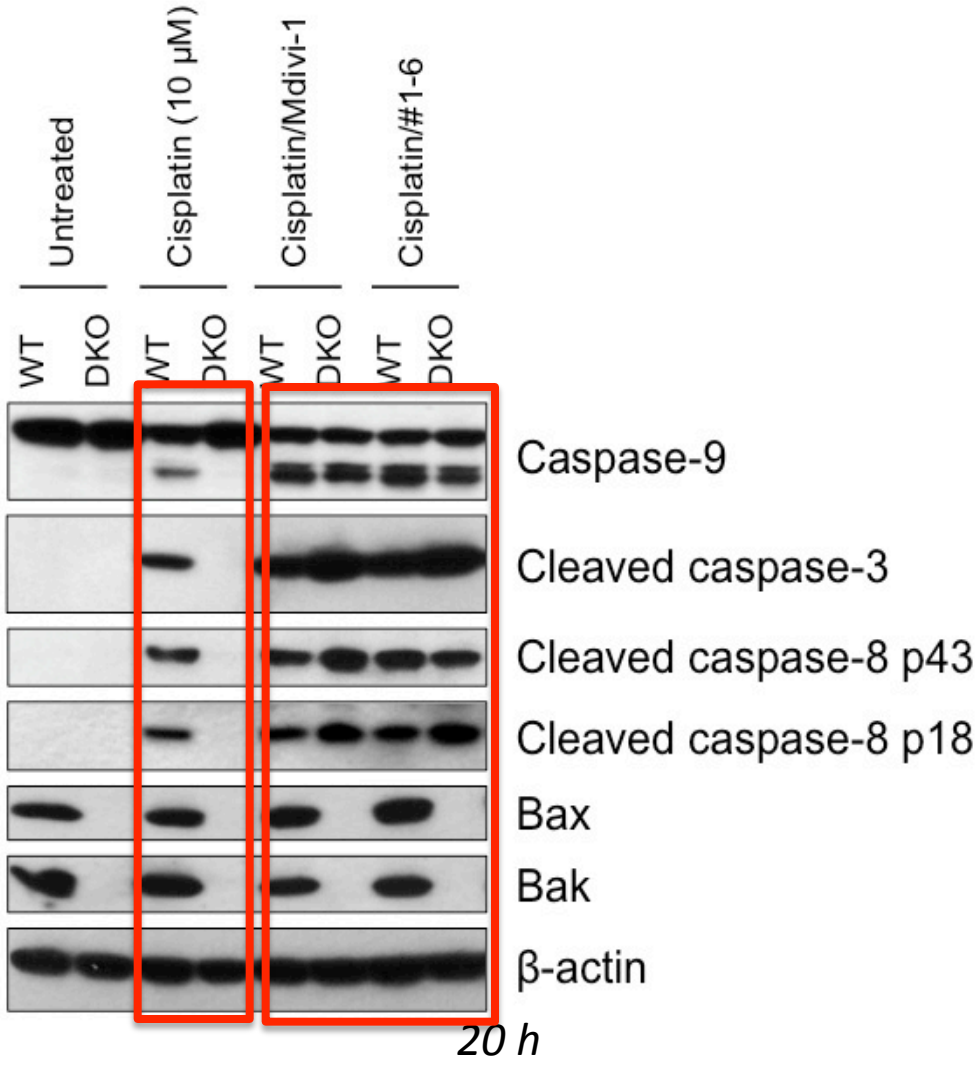




Modified from Mazumder S et al.
Cancer Res 2012;72:3069-3079

Bax expression correlates with the response to chemotherapy and overall survival in ovarian cancer

The combination of cisplatin and mdivi-1 bypasses Bax/Bak-mediated mitochondrial outer membrane permeabilization (MOMP)



Qian W, et al, Bioorg Med Chem Lett. 2015;25(4):856-63.

Inducing Bax- and Bak-independent apoptosis is an emerging therapeutic strategy

Development of agents to activate Bax/Bak-independent apoptosis

Seervi M, et al, A high-throughput image-based screen for the identification of Bax/Bak-independent caspase activators against drug-resistant cancer cells. Apoptosis. 2014;19(1):269-84.

Bax and Bak are required for the effects of many important anti-cancer agents

DNA damaging agents:
Etoposide (Wei, M. C., et al, Science 2001, 292, 727)
Bleomycin (Wang, G. Q., et al, J. Biol. Chem. 2001, 276, 34307)
5-FU (Wang, C., et al, Oncogene 2012, 31, 3177)

Anti-mitotic agents:
Taxol (Miller, A. V., et al, PLoS ONE 2013, 8, e60685)
Vinblastine (Upreti, M., et al, Mol. Cancer Ther. 2008, 7, 2224)

Targeted agents:
EGFR inhibitor **Gefitinibs** (Ariyama, H., et al, J. Cell. Biochem. 2006, 97, 724)
CDK inhibitors **Olomoucine**: (Garrofé-Ochoa, X., et al, Mol. Cancer Ther. 2008, 7, 3800)
CD20 monoclonal antibody **Rituximab** (Olejniczak, S. H., et al, Clin. Cancer Res. 2008, 14, 1550)

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Patents disclosure:

1. Title: Inhibition of dynamin related protein 1 to promote cell death. Patent No.: US 8,759,097. Inventors: Wei Qian and Bennett Van Houten.
2. Title: Combination therapy to enhance the anticancer efficacy of platinum drugs. U.S. Provisional Application No.: 62/013,943. Inventors: Wei Qian, Peter Wipf, and Bennett Van Houten.