# NXP800 versus cisplatin in ARID1a-mutated Ovarian Clear Cell Carcinoma xenograft models

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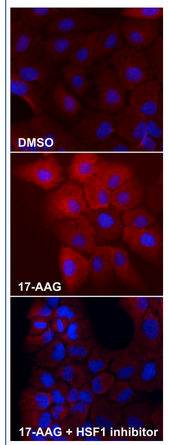
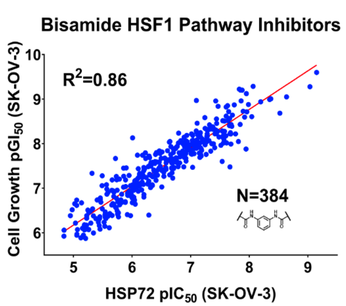
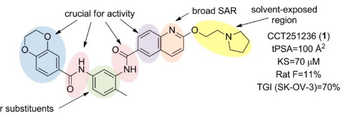
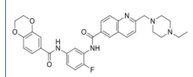
## Discovery and profile of NXP800




CCT251236 (**1**)
tPSA=100 Å²
KS=70 µM
Rat F=11%
TGI (SK-OV-3)=70%



**CCT361814**

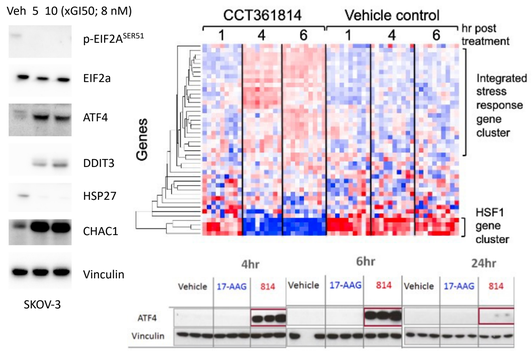
**Cell-Based Potency**
$GI_{50}$ (SKOV-3) = 6.9 nM
Unbound $GI_{50}$ (SKOV-3) = 3 nM
$IC_{50}$ (Cellisa, HSP72) = 86 nM

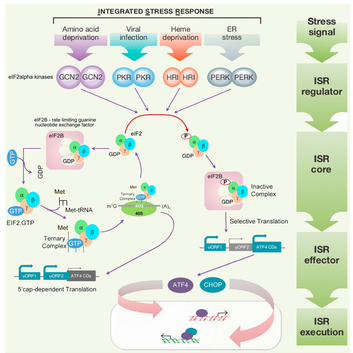
**Selectivity**
Dundee kinase panel (50 kinases) $IC_{50}$ > 10 µM
Cerep safety panel clean at 1 µM. Only confirmed activity is adenosine A2A receptor with $IC_{50}$ = 2 µM in antagonist mode
hERG $IC_{50}$ > 30 µM
No cyp inhibition

HSF1 pathway inhibitors identified by the ability to block the induction of HSP72 by HSP90 inhibitor 17-AAG

- Discovered N,N'-4-methyl-1,3-phenylenediamide core structure
- Screen run in U2OS human osteosarcoma cells, followed up in SK-OV-3 human ovarian cancer cells
- Highly potent, low nanomolar hit against the HSF1 pathway and cancer cell growth inhibition
- Optimized through lead compound/chemical tool to clinical candidate[1,2]
- NXP800 (CCT361814) has a clean profile across in vitro hERG, Cyp450, kinase and Cerep-Safety-87 assays

## Mechanism of action

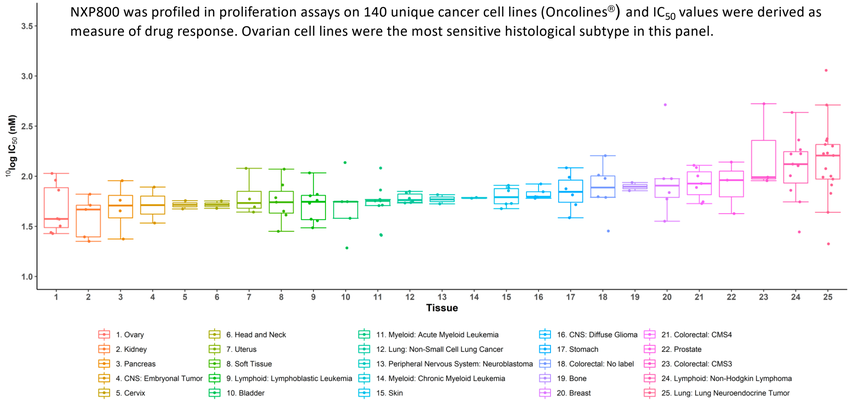



- Multiple cancer cell types treated with 5x GI50 NXP800 for 6 h and RNAseq profiled
  - significant enrichment of elevated integrated stress response (ISR) and ATF4-regulated genes
  - immunoblotting confirmed induction of ISR and ATF4
  - NanoString probeset confirmed elevated ISR/ATF4 and repressed HSF1 activity in vivo
- NXP800 treatment induces
  - prolonged activation of the ISR[3]
  - ISR activation blocks HSF1 activation
- Prolonged ISR/ATF4 activation and CHOP induction can result in cell death

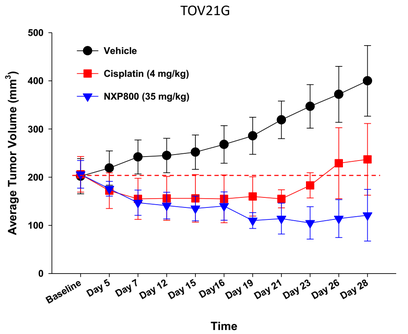
## Lineage-specific sensitivity

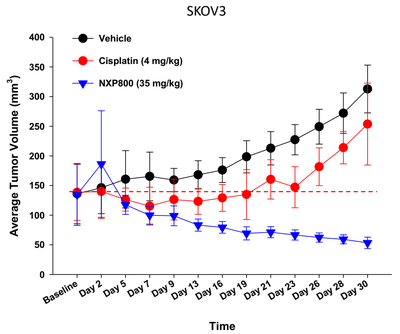
NXP800 was profiled in proliferation assays on 140 unique cancer cell lines (Oncolines®) and $IC_{50}$ values were derived as measure of drug response. Ovarian cell lines were the most sensitive histological subtype in this panel.

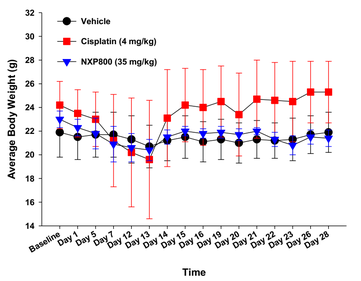


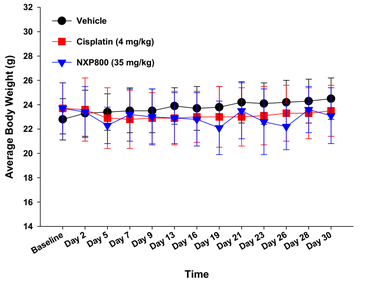

## NXP800 induces tumor regression in ARID1A mutated ovarian xenografts

Platinum sensitive[4] (TOV21G) and resistant[4] (SKOV3) xenografts were treated for 28 days with NXP800 (oral gavage, 35 mg/kg, 5 days on/2 days off) and cisplatin at the MTD[5] (i.p. 4 mg/kg X 3). NXP800 achieved superior efficacy compared with cisplatin at the mice MTD, demonstrating substantial tumor regressions at a well tolerated dose/regimen, both in platinum resistant and sensitive ovarian cancer xenografts.




## Summary

- NXP800 is a first-in-class, orally active inhibitor of HSF1 activation, biomarkers indicate a mechanism of action involving activation of the integrated stress response.
- Xenograft models of platinum sensitive and platinum resistant ovarian cancer with an ARID1A mutation show increased sensitivity to NXP800 compared to cisplatin demonstrating substantial tumor regression.
- Phase 1a trial comprising a dose-escalation commenced and first patient treated in January 2022 (www.clinicaltrials.gov/ct2/show/NCT05226507).
- A phase 1b trial will evaluate NXP800 in patients with ARID1A mutated ovarian clear cell and endometrioid carcinoma.

## Acknowledgements

*NXP800 is licensed to Nuvectis Pharma*

## Contact

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## References

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