**INTRODUCTION**

The inhibitor of apoptosis (IAP) proteins are attractive targets for cancer therapy as they are deregulated in many tumours and contribute to resistance to anticancer therapies. These proteins are characterized by baculoviral IAP repeat (BIR) domains, to which the cell’s own IAP antagonist SMAC (second mitochondria-derived activator of caspases) binds. Peptidomimetic compounds based on the N-terminal AVP sequence of SMAC have been developed, but these are largely selective for cIAP over XIAP.

More recently it has been suggested that an ideal antagonist will have equal activity against both cIAP and XIAP and that dual antagonism of cIAP1 and XIAP in inflammatory tumours can lead to a switch in TNF-α signalling away from being pro-survival towards being pro-apoptotic. We used our fragment-based drug discovery approach to generate non-alanine, non-peptidomimetic IAP antagonists, which have dual potency for XIAP and cIAP1. Here we describe the characterization of these compounds in a range of models, including models of melanoma and leukemia where we have seen enhanced sensitivity in cell line testing.

**OPTIMISATION OF FRAGMENTS: BINDING ASSAY DATA**

Pyramid™ fragment screening identifies a non-alanine 6I

HP optimization via structure based drug design

Potent dual XIAP- and cIAP antagonist

**CELLULAR ACTIVITY OF AT-IAP**

**Asay**

**Description**

**EC_{50} (nM)**

XIAP Cell Assays

HEK293-XIAP-Caspase-9 (3.3 nM) * 5.7

HEK293-XIAP-SMAC (3.3 nM) * 22.0

ML-IAP Cell Assay

HEK293-ML-IAP-SMAC (3.3 nM) * 11.0

cIAP1 Cell Assay

MDA-MB-231 (cIAP1 degradation) * 0.37

EVSA-T 0.89

Cell Proliferation Assays

MDA-MB-231 4.2

HCT-116 (insensitive control) >10,000

* IAP immunoprecipitation (I.P.) and cIAP1 degradation assays set up using the Mesoscale Discovery (MSD) platform

**REFERENCES**


**SUMMARY AND CONCLUSIONS**

- In vivo and in vitro results demonstrated significant activity against a panel of melanoma and leukemia cell lines, which was enhanced on addition of exogenous TNF-α (1ng/ml)
- Biomarker analysis demonstrated clear differences between sensitive and insensitive cell lines
- In vivo single agent efficacy demonstrated in the A375 melanoma cell line xenograft model, and is being tested in other cell line xenograft models (melanoma and leukemia)
- AT-IAP sensitivity is currently being assessed against a cell panel from 20 different melanoma patient-derived xenografts (PDX) in colony formation assays set up in the presence or absence of added TNF-α (1ng/ml)
- Current work is focussed on the validation of a biomarker strategy to predict single agent activity of AT-IAP in patients
- AT-IAP is being tested in melanoma PDX efficacy studies predicted to be sensitive based on prior biomarker analysis

**MELANOMA & LEUKEMIA XENOGRAFT PD DATA**

- Degradation of cIAP1 and induction of apoptosis markers observed in both tumour types

**MELANOMA XENOGRAFT EFFICACY MODEL**

- AT-IAP was well tolerated 50 mg/kg, p.o. q.d. – no significant body weight loss

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