INTRODUCTION
Melanoma is a highly aggressive malignancy with an exceptional ability to develop resistance and no curative therapy is available for patients with metastatic disease who lack a BRAF mutation. Inhibition of apoptosis proteins (IAPs) play a key role in preventing cell death by antagonizing anti-apoptotic proteins (e.g. SMAC), but in melanoma expression levels of IAPs are generally high and depleting IAPs by siRNA tended to reduce cell viability, with XAP reduction being the most efficient (1). IAP antagonists have the ability to switch IAP-controlled pro-survival pathways towards apoptosis and cell death. Recent evidence suggests that a true dual antagonist of both cIAP1 and XIAP will promote strong apoptotic response via generation of ripoptosome complexes, with resultant caspase activation (2-3).

DISCOVERY OF AT-IAP, A DUAL cIAP1/XIAP ANTAGONIST
• Astex performed a fragment screen against XIAP-BRD domain via X-ray crystallography and 1D-NMR.
• Compound 1 is a non-alanine fragment hit which binds very weakly to both cIAP1-BRIs and XIAP-BRIs. Hit optimization using a structure based approach led to compound 2 with submicromolar activity.
• Further optimization yielded AT-IAP, which is a potent dual antagonist of cIAP1 and XIAP, chemically distinct from SMAC mimetics in the clinic.

The interactions between the piperazine warhead and the BRD domains of XIAP and cIAP are distinct and allow the development of antagonists with balanced profiles.

OBJECTIVES

• Previously, we have described the characterization of AT-IAP in melanoma cell lines and have demonstrated that AT-IAP is potent and selective in melanoma cell lines and patient derived melanoma models.

• The objective of this work is to identify a set of biomarkers which can predict in vivo activity of AT-IAP in cell lines and patient derived melanoma models.

• Establish the basis of clinical patient selection strategy.

A TUMOR BIOMARKER PREDICTS SENSITIVITY IN VITRO TO AT-IAP IN THE PRESENCE OF TNF-α

Not all cell lines/tumors respond to AT-IAP in presence of TNF-α. We have identified a genetic profile for tumors where TNF-α signaling can be switched from pro-survival to pro-apoptotic after treatment with AT-IAP.

CONCLUSIONS

• AT-IAP is a potent, balanced non-peptidic antagonist of both cIAP1 and cIAP2. This dual activity is a consequence of the novel non-alanine scaffolds which is derived from a hit found in a cross-linking from our fragment screen.

• In vitro cell line testing suggested significant activity against a panel of melanoma cell lines and PDXs, which was enhanced in the presence of TNF-α.

• A biomarker analysis demonstrated clear differences between sensitive and insensitive melanoma cell lines. However, in vivo anti-tumor effect was predicted much better by coupling the tumor biomarker with a microenvironment biomarker.

• Preliminary studies suggest that the two identified biomarkers could be used to predict single agent activity in other tumor types (see table below).

REFERENCES

[1] Trzesniak et al., Cancer Biology & Therapy, 2011, 12 (1), 47