**INTRODUCTION**

- HSP90 is a molecular chaperone that directs the folding and maturation of its client proteins, many of which are oncoproteins regulating tumour cell growth, survival and activation.
- Here we describe the identification of the clinical candidate, AT13387, discovered by applying fragment-based drug design to the N-terminal domain of HSP90.
- Fragment-based drug discovery is a rapidly growing alternative to high throughput screening in which very small molecules are screened by specialist techniques such as NMR and X-ray.
- Only relatively small libraries of fragments are required and observed fragment hits possess high potency when normalised to their size (high ligand efficiency).

**FRAGMENT-BASED DISCOVERY OF AT13387**

- Fragment screening of 1500 fragments identified many hits including fragment 1, a known respiratory drug.
- Despite its poor initial ligand efficiency and potency, the X-ray structure indicated two good design ideas.
- Superposition on the natural product radicicol (top middle) suggested conversion to a resonon.
- Replacement of the methoxy group with non-planar phenoxides should provide better fit to the proximal lipophilic pocket (top right).
- Small isotopic replacements of the methoxy group of fragment 1 were synthesised.
- Isopropyl(7) and isobutyl(9) were the best examples showing approximate 10-fold improvement.
- Both analogues gave superior hydrophobic contact in the proximal lipophilic pocket as illustrated for compound 2 (above left).

- Amide replacements were synthesised based on examination of the experimental binding mode.
- Tertiary amides were prioritised to preserve the conformational load observed in fragment 1.
- Isocyanide 3 was one of the most potent offering a 30-fold improvement over compound 2.

- The resorcinol is over 100-fold more potent than the corresponding phenol, and shows good cell activity with a confirmed mechanism of action.

**CONCLUSIONS**

- The phenol fragment 1 was identified using fragment screening.
- Structure-guided medicinal chemistry was used to identify the highly ligand efficient lead molecule 4.
- Only 60 compounds were synthesised in going from fragment 1 to lead 4.
- AT13387 was identified after a lead optimisation campaign centred on increasing the volume of distribution and reducing off-target activities.
- Pharmacokinetic profiling of AT13387 in plasma, blood, brain muscle and tumour after a single 80mg/kg IP dose shows compound retention in only tumour suggesting an opportunity for a greater therapeutic window.

AT13387 was dosed weekly or twice weekly by the ip route up to day 21. A treatment group consisted of 8 animals. AT13387 shows good efficacy in this and other models.

Pharmacodynamic studies show that a single ip dose of 90mg/kg of AT13387 resulted in loss of client proteins Raf1 and CDK4 for 72 hours or more. There was also a concomitant increase in HSP70 and cleaved PARP levels, the latter being indicative of apoptosis.

**REFERENCES**

- AT13387 was chosen as a clinical candidate after further profiling during a candidate selection phase.
- The accompanying poster (A217 by Lyons et al) gives more details on the favourable biological profile of AT13387.
- AT13387 is currently in Phase I clinical trials for the treatment of cancer.

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