Astex to disclose the structure of its HSP90 inhibitor, AT13387, at the AACR-NCI-EORTC Annual Meeting 2009

Cambridge, UK, 9th November 2009

Astex Therapeutics, the UK based biotechnology company developing targeted therapies for oncology, announced today that it is to make a first public disclosure of the chemical structure of its potential best-in-class HSP90 inhibitor, AT13387, and will present new preclinical data on the compound at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, 15-19th November 2009 in Boston, USA . Earlier this month Astex announced that it had signed a Cooperative Research and Development Agreement (CRADA) with the National Cancer Institute (NCI) to collaborate on the study of AT13387 for the treatment of cancer.

Astex's first presentation will focus on the discovery of AT13387, its highly potent, non-ansamycin HSP90 inhibitor that is currently in Phase I clinical trials for the treatment of cancer, and will include the first disclosure of the chemical structure of the compound. AT13387 is the third drug candidate that Astex has discovered in house and serves to illustrate how efficiently Astex's fragment-based drug discovery approach can be used to identify compounds suitable for clinical testing. A second presentation on AT13387 will focus on new preclinical data demonstrating the extended pharmacodynamic action of the drug in multiple tumour xenograft models. These new data illustrate that AT13387 has a significantly longer duration of action compared to natural product based or other synthetic small molecule HSP90 inhibitors in the field, a property that could allow for less frequent dosing of AT13387. A potential benefit of highly potent and long acting HSP90 inhibitors, such as AT13387, is their ability to maintain their anti-tumour effect while minimising the potential for undesirable side effects associated with systemic exposure, thereby enhancing the therapeutic opportunities available to patients.

A third Astex presentation at the AACR-NCI-EORTC conference will summarise Astex's drug discovery research on the novel cancer target Methionine aminopeptidase 2 (MetAP2). MetAP2 is a metalloenzyme essential for post-translational modification of newly formed proteins and is a target for the natural product-derived anti-angiogenic agent, TNP470, that has been investigated in early clinical trials. Using its fragment based drug discovery platform Pyramid™, Astex has identified non natur product-derived inhibitors that interact in a novel way with MetAP2. These early leads provide opportunities for further optimization of these compounds' drug like properties aimed at removing the toxicities associated with TNP470 and related natural product based inhibitors of MetAP2.

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Editors Notes

Astex Poster Presentations

(1) Presentation Title: Fragment-based Drug Discovery of the synthetic small molecule HSP90 inhibitor AT13387

Abstract Number: A211
Session ID: Poster Session A
Session Title: Heat Shock Proteins 1
Session Date and Time: Monday Nov 16, 2009 12:30 PM - 2:30 PM
Location: Halls C-D, 2nd Floor, Hynes Convention Center

Authors: Christopher W. Murray, Maria G. Carr, Gianni Chessari, Miles Congreve, Joseph E. Coyle, Philip J. Day, Lynsey Fazal, Martyn Frederickson, Brent Graham, Jonathan Lewis, Rachel McMenamin, M. Alistair O'Brien, Sahil Patel, Glyn Williams, Andrew J. Woodhead and Alison J.-A. Woolford

Abstract:

Heat Shock Protein 90 (HSP90) is a member of a family of molecular chaperone proteins which directs the folding of polypeptides into functional configurations affecting stabilisation and activation. Many of these proteins are oncogenes regulating tumour cell growth, survival and apoptosis. This poster will focus on the screening and medicinal chemistry work that

led to the identification of AT13387, a high affinity HSP90 inhibitor that is currently in clinical trials for the treatment of cancer.

A fragment screening campaign was conducted against the N-terminal domain of HSP90 to detect very low molecular weight compounds (Molecular Weight <250 Da) that bound to the ATPase active site. The screening produced a small fragment which was co-crystallised with HSP90 and had an affinity of 790ìM. Three iterations of structure-guided medicinal chemistry led to the identification of a lead compound with 0.5nM affinity for the enzyme, good cell activity and confirmed mechanism of action in cells. The fragment to lead optimisation increased affinity by over a million fold but resulted in a molecule that was only 6 heavy atoms larger than the fragment starting point. Such an efficient optimisation campaign is unprecedented in the field of fragment-based drug discovery.

Subsequent lead optimisation focussed on the improvement of in vivo distribution properties via the addition of basic moieties to the lead molecule. These compounds showed encouraging in vivo pharmacology and biological profiles and further medicinal chemistry work led to the discovery of AT13387, an inhibitor with sub-nanomolar affinity, prolonged duration of action and excellent in vivo anti-tumour efficacy.

This poster represents first disclosure of the structure of AT13387 and illustrates how a fragment-based drug discovery approach can be efficiently used to discover compounds suitable for clinical testing in oncology.

(2) Presentation Title: Comparison of long term pharmacodynamic actions of the synthetic small molecule HSP90 inhibitor AT13387 in multiple xenograft models

Abstract Number: A217
Session ID: Poster Session A
Session Title: Heat Shock Proteins 1
Session Date and Time: Monday Nov 16, 2009 12:30 PM - 2:30 PM
Location: Halls C-D, 2nd Floor, Hynes Convention Center

Authors

John Lyons, Jayne Curry, Tomoko Smyth, Isobel Harada, Lynsey Fazal, Matthias Reule, Brent Graham and Neil Thompson

Abstract

AT13387 is a novel small molecule inhibitor of HSP90. a member of a family of molecular chaperones. Previously we highlighted an association between the high affinity binding of AT13387 to the N-terminal ATPase domain of HSP90 and the duration of target inhibition in tumour cell lines in vitro. Further, AT13387 was shown to inhibit HSP90 and deplete client proteins in tumour xenografts longer than other, lower affinity inhibitors in the class. Here we have expanded the investigation to a wider number of tumour cell lines and to in vivo xenograft models and demonstrate that AT13387 has an extended pharmacodynamic action in tumours compared to other HSP90 inhibitors. We reason that the cumulative effects of these properties allow for less frequent dosing thus maximising efficacy whilst minimising systemic exposure and the potential for side effects.

This study reports extended inhibition of HSP90 by AT13387 in a wider range of tumour cell lines in vitro. A 24hr exposure of A375 (melanoma) cells to AT13387 suppressed the expression of client proteins for 72 hrs or more. However in other cell lines such as NCI-H1975 (lung) and BT474 (breast), the suppression of client proteins by AT13387 was found to last in excess of 7 days.

The pharmacodynamic action of AT13387 in vivo has been compared with that of 17-AAG and SNX-5422 in A375 and NCI-H1975 xenografts in nude mice. Following a single dose of each agent, we have investigated and compared the time course of the suppression of levels of several client proteins (e.g. AKT, CDK4) and the phosphorylation of key growth/survival signalling components (e.g. pERK, pS6, pAKT). These effects were rapidly induced in tumours following treatment with AT13387 and levels remained suppressed for up to 96 hrs. The durability of the AT13387 effects was significantly greater than for the other competitor compounds. Investigation of tumour growth in these models demonstrated that the longer pharmacodynamic action of AT13387 ensured that efficacy could be maintained on a once weekly schedule, whereas such a schedule for the other agents resulted in a significant loss of their anti-tumour effects.

These data provide further support for the potential benefit of long acting HSP90 inhibitors as a way of maintaining anti-tumour effects whilst minimising potential for undesirable effects associated with systemic exposure.

(3) Presentation Title: The physiological form of MetAP2 can be inhibited through binding to either of the two active-site metals

Abstract Number: A1
Session ID: Poster Session A
Session Title: Angiogenesis and Antiangiogenesis Agents 1
Session Date and Time: Monday Nov 16, 2009 12:30 PM - 2:30 PM
Location: Halls C-D, 2nd Floor, Hynes Convention Center

Authors

Nicola G. Wallis, Valerio Berdini, Gilbert Besong, Gianni Chessari, Joe Coyle, Brent Graham, Andrew Madin, Alistair O'Brien, Caroline J. Richardson, Kirsten Smith, Neil T. Thompson, Mladen Vinkovic, Pamela A. Williams

Abstract

Methionine aminopeptidases (MetAP) are metalloenzymes that remove the N-terminal initiator methionine from newly synthesized polypeptides allowing essential post-translational modifications such as acetylation and myristoylation to take place. MetAP2, one of the two eukaryotic forms of the enzyme, was identified as the target of fumagillin, a natural product with anti-angiogenic properties that inhibits the proliferation of endothelial cells. Clinical activity has been seen for a semi-synthetic analogue of fumagillin, TNP470, suggesting MetAP2 is a good target for inhibiting angiogenesis.

In vitro, MetAP2 appears to have sites for two divalent metal ions within its active site but there has been much discussion around the identity and number of metal ions actually present in the physiological states of the various MetAPs. An understanding of the physiologically relevant metalloform of the enzyme is essential for designing inhibitors that are active in cells. We have used tool compounds that bind the active site metals in diverse ways to investigate the relevance of the two potential metal binding sites in MetAP2.

Using our fragment-based screening approach, Pyramid™, we screened the manganese form of the MetAP2 enzyme. We identified multiple low-molecular weight fragment hits and confirmed their modes of binding to the two metals in the active site of MetAP2 by X-ray crystallography. Three hit series, which bound metal 1 only, metal 2 only or both metals 1 and 2, were chosen for further optimisation using structure-based drug design. Optimised lead compounds had potent inhibitory activity against the in vitro MetAP2 enzyme (~100 nM) and in HUVEC proliferation assays, whilst also showing greater than 1000-fold selectivity for MetAP2 over MetAP1. Examples from each series, representing different active site metal binding modes, were used as tool compounds to investigate the mechanism of action in cells. The levels of the MetAP2 substrate, 14-3-3, were monitored by western blot in HUVECs treated with these compounds. Levels of methionylated 14-3-3 increased upon treatment with compounds from each of our series indicating the substrate was not being processed and that in each case the compound was inhibiting MetAP2 in these cells.

These data indicate that the physiological form of MetAP2 can be inhibited by compounds which bind solely to either of the two active-site metals, suggesting that both metals must be present in the intra-cellular form of MetAP2 and allowing multiple approaches to inhibiting this key angiogenic target. The lead series identified here provide chemically diverse scaffolds for further optimization of drug like properties.

About Astex Therapeutics

Astex is a UK-based biotechnology company that discovers and develops novel small molecule therapeutics. Using its pioneering fragment-based drug discovery platform Pyramid™, Astex has built a pipeline of five molecularly targeted oncology drugs, of which three are currently being tested in clinical trials and two are in pre-clinical development.

In addition to its proprietary research programmes, Astex's productivity in lead discovery has been endorsed through numerous partnerships with major pharmaceutical companies, including AstraZeneca, Bayer-Schering, Boehringer Ingelheim, Novartis and Johnson & Johnson.

For further information on Astex please visit the Company's website at www.astex-therapeutics.com