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Astex reveals structure of key drug metabolizing enzyme - cytochrome P450 3A4 - in Science

Cambridge, UK, 16th July 2004 - Astex Technology, the fragment-based drug discovery and development company, today announced that its scientists had published the 3-dimensional structure of human cytochrome P450 3A4, the most important drug metabolising enzyme. The crystal structure of the protein is reported in the leading science journal *Science*^[1]. This is the first time this structure has been published and follows another world first when Astex published in *Nature*^[2] the first 3-dimensional crystal structure of a human cytochrome P450 protein, CYP450 2C9. CYP450 3A4 is one of four key enzymes that are responsible for metabolizing more than 90% of drugs and cause significant attrition in the drug development process.

"We are delighted that we have published the crystal structure of human CYP450 3A4," said Dr Harren Jhoti, Astex's Co-Founder and Chief Scientific Officer. "These proteins are membrane-associated, complex structures and so represent a major challenge for structural biology. This is the second human cytochrome P450 structure we have solved, the first being human CYP450 2C9, reflecting our significant achievements in this important area of drug discovery. By exploring how these cytochrome P450s recognise drug molecules at the atomic level, we will be able to design rationally drugs with better metabolic and toxicity profiles and thus an improved chance of being commercialized."

CYP450 3A4 is generally regarded as the most important family member of these drug metabolising enzymes; it is estimated that as many as 50% of all known drugs interact with this form of cytochrome P450. However, CYP450 3A4 is also the most poorly understood member with respect to its drug metabolising action and represents a major problem in drug development. Astex's proprietary P450 structural information enables the company and its collaborators to generate lead compounds with optimal drug metabolism and pharmacokinetic properties and so reduce attrition rates in drug development.

Astex has research agreements with AstraZeneca, Aventis, Fujisawa and Mitsubishi Pharma focused on solving and utilising novel cytochrome P450 crystal structures.

Contacts:

Astex Technology:

Harren Jhoti PhD
Founder and Chief Scientific Officer
E-mail: h.jhoti@astex-technology.com

Katharine Harris
Head of Corporate Communications
E-mail: k.harris@astex-technology.com

Tel: +44 (0) 1223 226200
Web: www.astex-technology.com

Brunswick Group LLP:

Jon Coles / Wendel Carson / Chi Lo

Tel +44 (0) 207 404 5959

E-mail: astex@brunswickgroup.com

[1] Pamela A. Williams, Jose Cosme, Dijana Matak Vinkovic, Alison Ward, Hayley C. Angove, Philip J. Day, Clemens Vonrhein, Ian J. Tickle and Harren Jhoti. "Crystal structures of human cytochrome P450 3A4 bound to metyrapone and progesterone." 15 July 2004 published online at www.sciencexpresss.org; 10.1126/science.1099736

[2] Pamela A. Williams, Jose Cosme, Alison Ward, Hayley C. Angove, Dijana Matak Vinkovic and Harren Jhoti. 'Crystal structure of human cytochrome P450 2C9 with bound warfarin.' Nature July 2003, digital object identifier (DOI) number: 10.1038/nature01862

Notes to Editors

Cytochrome P450s are the most significant group of drug-metabolising enzymes in humans. The action of these proteins is the cause of adverse reactions to many marketed drugs and drug-combination therapies. In addition, many failures in drug development have been attributed to this class of proteins; drugs may be metabolized too rapidly before they have a chance to be effective, or they may be broken down into smaller molecules which may be toxic, or they can even interfere with the activity of CYP450s so that other drugs given at the same time cause side effects or become dangerous. The insight provided by the crystal structure of cytochrome P450s aims to improve the success rates and economics of drug development and result in safer and more effective new medicines.

The purpose of drug metabolism is to make the drugs more water-soluble so that they can be easily excreted from the body after their desired effect has been exerted. Four human cytochrome P450s (CYP 2C9, CYP 2C19, CYP 2D6 and CYP 3A4) account for the metabolism of nearly all clinically useful medications.

Astex has targeted 10 CYP450 proteins including seven human isoforms and three further mammalian isoforms in a major program of P450 structural biology research. Knowledge of the specific ways drugs bind to CYP450s can be exploited by Astex in novel strategies for drug design to modulate their potential for binding CYP450, while retaining compound potency and selectivity.

In addition to Astex's research agreements with pharmaceutical companies, Astex collaborates with world-leading experts in X-ray crystallography such as Global Phasing (Cambridge, UK), whose novel methodology has enabled significant breakthroughs in Astex's cytochrome P450 program.

Glossary

Pharmacokinetics looks at the action of drugs in the body, including the processes of absorption, transformation, distribution to tissues, duration of action and elimination.

About Astex

Astex is a biotechnology company producing novel small molecule therapeutics. Using its pioneering fragment-based drug discovery approach, Astex has rapidly established a broad pipeline of next generation, molecularly targeted oncology drugs, the first of which will enter clinical trials in 2005.

Astex's leading position in fragment-based drug discovery derives from its integrated discovery engine, Pyramid(TM). High-throughput X-ray crystallography is used to identify drug fragments bound to target proteins and to transform the fragments, using efficient medicinal chemistry, into potent, selective lead compounds. Pyramid (TM) has been successfully applied across a wide

variety of therapeutic targets, including those regarded as 'intractable' by the pharmaceutical industry, resulting in lead compounds for the potential treatment of cancer, inflammation and Alzheimer's disease.

Astex's unprecedented productivity in lead discovery has been endorsed by drug discovery alliances with major pharmaceutical companies including AstraZeneca, Aventis, Boehringer Ingelheim, Mitsubishi Pharma and Schering AG. Astex was established in 1999 and is well financed by leading, blue chip US and European investors (Abingworth, Advent International, Alta Partners, Apax, GIMV, HypoVereinsbank, Oxford Bioscience Partners, Schering AG and the University of Cambridge).

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