from the device is monochromatized with liquid-N_2 cooled double crystal monochromator, and will be focused by using K-B mirrors fabricated with Elastic Emission Machinery. Ray trace calculation with the designed configurations shows achievable beam size at sample position corresponds to 1 x 2 μm^2 with 10^{10} phtons/sec. Beam size is designed to be changeable from about 1~25 μm^2 according to designed experiments. The new beamline will largely benefits users by cutting off their wasting time to optimize crystallization conditions especially for smaller and lower quality crystals. The beamline will provide high quality diffraction datasets from micro crystals. Besides, users will be able to probe single-crystal volumes from a heterogeneous protein crystal using the micro-beam. Designed optics and instrumentations to be equipped such as an automated sample changer, advanced software to avoid serious radiation damages and so on will be also presented.

Keywords: protein crystallography, synchrotron X-ray diffraction, synchrotrons

MS.15.5

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Microcrystallography at Diamond: Facilities for crystal optimization and structure determination

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The I24 microfocus macromolecular crystallography beamline at the Diamond Light Source comes into operation in 2008. The beamline is tuneable from 6.5 - 25 keV and offers versatility in beam size and shape at both sample position and detector position by utlizing a two-stage demagnification incorporating a movable final Kirkpatrick-Baez mirror pair. The beamline incorporates a CATS sample mounting robot that will also enable diffraction screening of crystallization conditions in 96 well plates. This facility will provide invaluable feedback for the crystallization efforts in the Wellcome Trust funded Membrane Protein Laboratory at Diamond. Significant design and build effort has been put into versatility, stability and the generation of a low background sample environment for the measurement of diffraction data. The design concepts of I24 will be described and preliminary results from beamline commissioning will be presented.

Keywords: synchrotron X-ray instrumentation, microcrystals, biological macromolecular crystallography

MS.16.1

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Fragment-based drug discovery: From crystal to clinic

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Fragment-based screening is a powerful method for the identification of attractive chemistry start points against specific drug targets. These initial low molecular weight fragment hits typically have uM to mM potency but are shown to be highly ligand efficient. Astex Therapeutics uses its proprietary platform, PyramidTM, utilising high-throughput X-ray crystallography and other biophysical techniques, to identify high quality fragment hits against a broad range of therapeutic targets. The availability of structural information from the screening phase provides a detailed map of the active and secondary fragment binding sites allowing the chemist to design molecules that maximise interaction with the protein target. Rapid progress can be achieving reducing the time taken to identify a clinical candidate by many years. To highlight the success of our approach, AT7519 (a CDK inhibitor) and AT9283 (Aurora inhibitor), which are both currently in Phase I clinical trials will be discussed together with another non-kinase oncology target, HSP90.

Keywords: structure-based drug design, anticancer drugs, X-ray crystallography

MS.16.2

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Role of structures in designing anti-AIDS drugs targeting reverse transcriptase

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HIV-1 reverse transcriptase (RT) is the target for almost half of the approved anti-AIDS drugs. The non-nucleoside (NNRTI) drugs bind RT at an allosteric pocket whereas the nucleoside (NRTI) drugs compete with nucleotides and act as DNA chain terminators. Both NRTIs and NNRTIs are challenged by emergence of drug resistance mutations in RT. Understanding the roles of mutations is important in designing effective drugs. A systematic structure based design of diarylpyrimidine (DAPY) NNRTIs, including the recently approved drug TMC125 (Intelence/etravirine), has revealed that adding strategic flexibility to a drug molecule can help overcome the effects of resistance mutations by reorienting (wiggling) and repositioning (jiggling) in the binding pockets. Our recent high resolution (1.8 Å) crystal structures of wild-type and mutant RT/TMC278 (riplivirine) complexes demonstrate how the DAPY NNRTI TMC278 wiggles and jiggles to fit into the pockets of wild-type, and L100I+K103N and K103N+Y181C mutant RTs. Mechanisms of NRTI resistance are highly complex and structurally distributed over broad areas of RT. The NRTI resistance mutations that discriminate a nucleoside analog from its corresponding nucleotide can occur at steps involving binding to RT, catalytic reaction of polymerization, translocation of nucleic acid after incorporation, and/or through excision. Our current structures of NRTI resistant mutant RT/DNA/dNTP (and analog) complexes help in understanding complementary clinical and biochemical data, and the combined insights will help in developing more effective drug combinations in the clinic and also in designing new and improved NRTIs.

Keywords: HIV, drug resistance, structural flexibility

MS.16.3

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Monoamine oxidases and LSD1: Similar chemistry for neurotransmitter and chromatin modification

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Monoamine oxidases (MAOs) and the histone demthylase LSD1 are evolutionarily related enzymes that catalyze the oxidative deamination of their substrates. They represent a spectacular example of how similarities in the chemistry of the catalyzed reaction can constrain evolution, despite different biological functions and cellular localizations. MAOs bind the outer mitochondrial membrane and play a central role in the metabolism of neurotransmitters such as dopamine and serotonin. MAO's rise to prominence in the biomedical community originated in the early fifties from Zeller's finding that MAO was the target for hydrazine inhibition which could function in treating depression. Since then, a huge number of MAO inhibitors have been developed and several of them have been used for the treatment of Parkinson's disease and depression. Our structural studies have shown that most of the known MAO inhibitors function through a mechanism-based mode that generates a covalent adduct with the FAD cofactor. LSD1 is a more recently discovered enzyme. It is responsible for the demethylation of Lys4 of histone H3. LSD1 is implicated in tumorigenesis and there are increasing efforts to identify LSD1 inhibitors. The crystal structure of LSD1 reveals a different substrate-binding site but similar catalytic machinery compared to those exhibited by MAO structures. This similarity is proving to be particularly insightful, prompting researchers to exploit the knowledge gained from MAO inhibition studies to develop effective LSD1 inhibitors. We shall present a comparative analysis of LSD1 and MAOs with a focus on the relevance of the structural investigations for understanding the mechanisms drug action and for the design of new inhibitor molecules targeting these amine oxidase enzymes.

Keywords: enzyme inhibitor design, enzymatic catalysis, chromatin

MS.16.4

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CPADD(Closest Packing Approach for denovo Drug Design) to inhibit VEGF/R and Notch/RBP/MAM systems

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CPADD generates almost all possible ligand structures that fit with a binding pocket of target protein(s), by extracting chemical structures among closest packing putative atom network. It has succeeded in finding active compounds for all projects so far both on enzymes and on PPI (Protein-Protein Interaction) systems. In this presentation, results on VEGF/VEGFR and Notch/RPB/MAM systems are shown. As the first screening, inhibition of HUVEC-proliferation by VEGF inhibitors and inhibition of Notch reporter gene expression by Notch inhibitors were evaluated. As the second screening, the abilities of selected compounds to suppress the LS174T-tumor growth were estimated using the xenograft model. Several promising compounds significantly suppressed the tumor growth in their single use without the loss of body weight. Combined use with Avastin or chemotherapeutic agents showed stronger tumor growth inhibitory effects than Avastin or chemotherapeutic agents alone.

Keywords: inhibitor, VEGF, notch

MS.16.5

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A family wide approach to structure-based inhibitor design for protein tyrosine phosphatases

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The protein tyrosine phosphatase (PTP) family is a large and diverse group of enzymes that together with protein tyrosine kinases control signaling pathways in the cell. Deregulation of PTPs has been linked to a range of human diseases, including cancer, diabetes, obesity and arthritis, and certain members of the family are recognised drug targets. PTPs exhibit high similarity in their overall fold but changes in the region surrounding the active site pocket can be exploited to achieve inhibitors through structure based rational design. We have screened a focused compound library and identified several small molecule inhibitors of PTPs many of which are selective against certain members of the family. In a biochemical assay these compounds inhibit phosphatase activity with IC50 values in the low micro molar range. At the Structural Genomics Consortium (SGC) PTPs have been studied for several years and 22 structures have been deposited in the protein data bank. With successful protocols for producing well diffracting crystals in place we are now developing a family based method for soaking crystals with the established inhibitors. The aim is to produce chemical probes specific for particular PTPs but to find means of taking advantage of the similarities between members of the family to reach this goal. Results with PTPs have so far identified crystal forms where the active site is in the open conformation due to crystal contacts between neighbouring molecules. This conformation is not optimal for binding compounds that inhibit activity, thus new crystal forms are being sought. By August, the latest results will be presented together with the evolved methodology for high-throughput generation of complex structures.

Keywords: ligand binding of proteins, structural genomics, cellular signaling

MS.17.1

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Time-resolved diffraction at atomic resolution: What's here now and what's next?*

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Monochromatic time-resolved diffraction experiments of excited-state geometry are flux limited even at third generation sources. For sub-microsecond experiments polychromatic techniques are needed. To avoid the known complexities of the Laue method we use a 'raw intensity' technique in which the intensity response to laser irradiation is directly extracted from dark-light pairs of frames,