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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