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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

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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

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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

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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,