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Identification of phenanthridinone based inhibitors of BRD2-BD2 bromodomain by structure-based drug discovery approach

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Epigenetics, through the modulation of genetic information, involve a fundamental life process, such as cell-proliferation, cell development and decision between cell survival and cell death. Alteration of epigenetic function, which causes abnormal cellular functions, can lead to the development of cancer, neurodegeneration, autoimmune/inflammatory diseases, metabolic diseases and viral infections. Hence, the epigenetic targets are of great importance to discover new drug molecules for various major diseases. One of the epigenetic 'reader' proteins, bromodomain containing proteins recognized acetylated-lysine histones (H3 and H4) and non-histones, such as the tumor suppressor, p53. The BET family nuclear proteins possess two tandem bromodomains (BD1 and BD2) and a conserved extra-terminal domain. The BRD2 protein, a BET family member, recognizes mono-acetylated and di-acetylated histones through N- and C-terminal bromodomains. The BRD2 protein are reported to possess potential role in the pathogenesis of cancer, defects in embryonic stem cell differentiation, seizures and neurodegenerative disorders. Drug discovery of small molecule inhibitors targeting BRD2/BRD4 are in the pipeline, and some of them are already in clinical trials for the treatment of cancer. We have recently discovered compounds, by structure-based drug design method, which significantly inhibit the second bromodomain, BD2 of BRD2. The crystal structures of the BRD2-BD2 inhibitor complexes were determined at atomic resolution by using the X-ray diffraction data collected on the beamline, BM14 at ESRF, France. The drug discovery process such as in-silico screening, co-crystal structure determination, binding study and cell-based assay of the BRD2-BD2 complex will be discussed.

Biography

Padmanabhan Balasundaram is working as a Professor and Head of the Department of Biophysics, NIMHANS, Bangalore, India. He is a Structural Biologist and has more than 22 years of work experience blended with industry and academic careers. He has worked in various international organizations including Mitsubishi Chemical Corporation, ERATO-JST, RIKEN in Japan, the University of Washington, Seattle, USA, Laurus Lab Pvt. Ltd., Hyderabad, India. His group is now focusing on structure-based drug discovery on the protein targets associated with neurological disorders including Parkinson's disease (PD), ALS and glioma. He earned his PhD in Biophysics and Protein Crystallography from All India Institute of Medical Sciences (AIIMS), New Delhi, India.

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