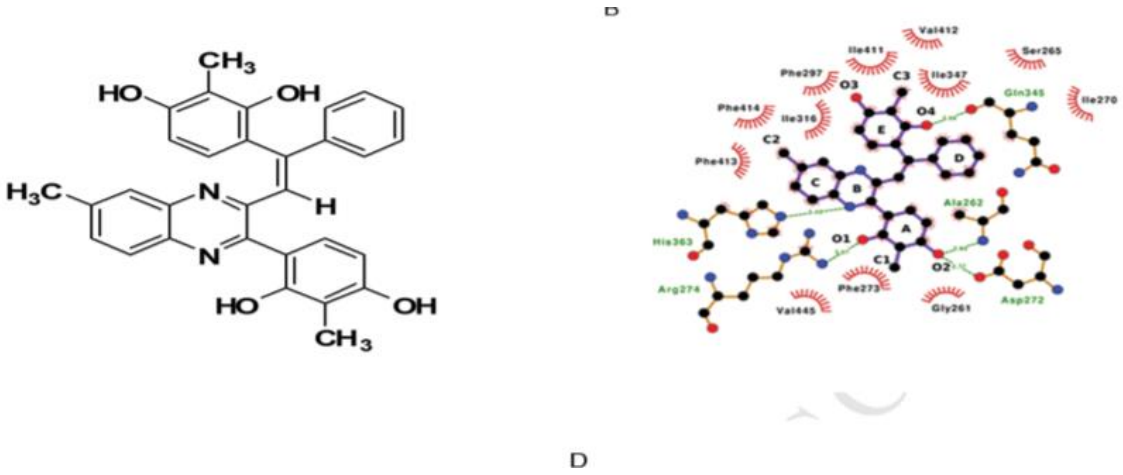
Discovery of a novel inhibitor of HDAC SIRT1 which kills colon cancer cells

A team of scientists and their chemist collaborators at DBT's Center for DNA Fingerprinting and Diagnosis (CDFD), Hyderabad, have discovered of a novel anti-cancer molecule (4bb) which specifically kills colon cancer cells. It is a small molecule inhibitor of human histone deacetylase, and SIRT1. Team investigated the effect of 4bb on viability of colon cancer cells and its molecular mechanism of action for better understanding of how it works within the cell to stop growth of colon cancer cells.



In human cells, to fit our long genetic material, DNA into tiny nucleus, it is wrapped around beads made of histone proteins, this complex of DNA and protein is called Chromatin. Chromatin structure can be altered by chemically modifying the DNA and the histone proteins by acetylation, methylation etc. These modifications do not change the composition of the DNA. However, they can change gene expression *i.e.*, the program by which proteins are formed within a cell. Such changes are called Epigenetic changes.

Cancer is a major health problem world over. Currently existing drugs are not satisfying as they cause traumatic side effects. Therefore, the need for development of more specific and relatively non toxic drugs is quite urgent. Epigenetic therapeutics of cancer such as inhibitors of DNA methyltransferases and histone deacetylases (class I and classII) are already being used in combination with the standard cytotoxics with encouraging results. The Sirtuins (class III NAD-dependent deacetylases) are being considered as important targets for cancer therapeutics as their level increase in many cancers. As these are enzymes, inhibition of sirtuin's deacetylase activity allows re-expression of silenced tumor suppressor genes, leading to reduced growth of cancer cells.

However, no sirtuin inhibitors have entered into the clinic yet as an anticancer agent. The NAD+-dependent protein deacetylase SIRT1 is an important target for epigenetic therapeutics of colon cancer as increase in its level is associated with cancer progression. SIRT1 represses tumor suppressor, p53 function via deacetylation, promoting tumor growth. Therefore, inhibition of SIRT1 activity is of great therapeutic interest for the treatment of colon cancer. In vitro, 4bb is a significantly more potent SIRT1 inhibitor than β-naphthols such as sirtinol, cambinol. The viability of colon cancer cells reduces with increasing concentration of 4bb, but, does not affect the viability of normal dermal fibroblasts depicting cancer cell specificity. Further, 4bb treatment increased p53 acetylation, Bax expression and induced caspase 3 cleavage suggesting that the death of HCT116 colon cancer cells occur through intrinsic pathway of programmed cell death (apoptosis).

Overall, we presents 4bb as a new class of human SIRT1 inhibitor and suggest that inhibition of SIRT1 by 4bb induces programed cell death of colon cancer cells at least in part via activating p53 by preventing p53 deacetylation, increasing Bax expression and inducing caspases. Therefore, this molecule provides an opportunity for lead optimization and may help in development of novel, nontoxic epigenetic therapeutics for colon cancer. This would aid in the development of novel Sirtuin inhibitor as a potential anti-cancer drug either by itself or in combination with cytotoxics and other epigenetic drugs such as methytransferase inhibitor or HDAC inhibitor. In addition, determination of the molecular basis of anti-tumor effect will help in understanding of functions of Sirtuins in cancer formation.

The research work titled “A novel SIRT1 inhibitor, 4bb induces apoptosis in HCT116 human colon carcinoma cells partially by activating p53” by Ananga Ghosh, Amrita Sengupta, Guru Pavan Kumar Seerapu, Ali Nakhi, E. V. Venkat Shivaji Ramarao, Navneet Bungc, Gopala Krishnan Bulusuc, Manojit Pal and Devyani Haldar” was published in journal “Biochemical and Biophysical Research communications”.

Link: https://www.semanticscholar.org/paper/A-novel-SIRT1-inhibitor%2C-4bb-induces-apoptosis-in-Ghosh-Sengupta/ef46965bea972dcfea8bdf1a9bde9e20596edcde

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