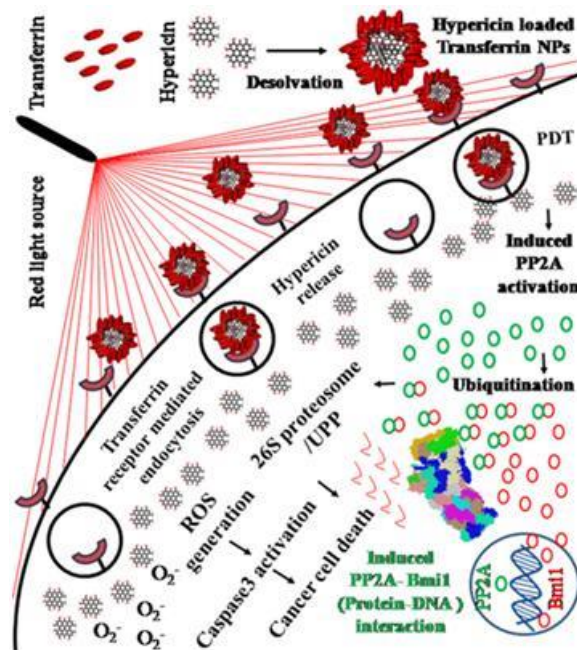


## Hypericin-loaded transferrin nanoparticles induce PP2A-regulated BMI1 degradation in colorectal cancer-specific chemo-photodynamic therapy

The present study carried out at Regional Centre for Biotechnology (RCB), Faridabad enlightens the targeted photodynamic therapy (PDT) with potential photosensitizer hypericin nanocomposite in the development of epigenetic-based CRC therapy. For this study, hypericin-loaded transferrin nanoformulations (HTfNPs) were synthesized, thus, overcoming the compromised hydrophobicity and poor bioavailability of the placebo drug. Targeted PDT with hypericin nanocomposite-induced BMI1 degradation assisted colorectal cancer (CRC) retardation.



In the present study, transferrin nanoparticles were reported to control the premature release of hypericin and improve its availability with better targeting at the disease site. Targeted intracellular internalization to colon cancer cells having a differential expression of transferrin receptors, *in vivo* biodistribution, stability and pharmacokinetics provide promising applications in the nanodelivery system. The *in vitro* anticancer efficiency, cell cycle arrest at the G0/G1 phase, and elevated reactive oxygen species (ROS) generation confirm the anticancer effect of nanoformulation.

In the exploration of mechanism, nanotherapeutic intervention by activation of PP2A, Caspase3 and inhibition of BMI1, EZH2, 3P<sub>k</sub>, NF $\kappa$ B was evident. An exciting outcome of this study uncovered the camouflaged role of PP2A in the regulation of BMI1. PP2A

mediates the ubiquitination/degradation of BMI1, which is revealed by changes in the physical interaction of PP2A and BMI1. This study confirms the anticancer effect of HTfNP-assisted PDT by inducing PP2A-mediated BMI1 ubiquitination/degradation demonstrating an epigenetic-driven nanotherapeutic approach in CRC treatment.

Epigenetically regulated therapeutic intervention of cancer is an emerging era of research in the development of a promising therapy. Epigenetic changes are intrinsically reversible and providing the driving force to drug resistance in CRC. The regulation of polycomb group (PcG) proteins, BMI1 and EZH2, and the associated CRC progression hold promises for a novel treatment regime. Dr. Prasenjit Guchhait (Professor, RCB), co-authored a research article with other collaborators.

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