Abstract: Genetic alterations at the RB transcriptional corepressor 1 (RB1) gene are frequent in several childhood and adult cancers. Studies in our laboratory identified UHRF1 (Ubiquitin-like, containing PHD and RING Finger domains 1) as a gene that is upregulated, and its protein overexpressed in retinoblastoma, osteosarcoma, small cell lung cancer and triple negative breast cancer. UHRF1 is a multifunctional protein involved in epigenetic regulation and has been shown to interact with pRB. Further, the RB/E2F pathway directly regulates UHRF1 expression. Our studies using genetically engineered mouse models of cancer indicate that the UHRF1 overexpression present in these cancers contributes to tumorigenesis and a more aggressive tumor presentation, affecting both tumor growth and metastasis. Targeting UHRF1 in these cancers results in a robust increase in overall survival. We are now developing strategies to target UHRF1 for therapeutic applications.