Title: Inhibiting the EWS/FLI1/P300/CBP Axis as a Targeted Strategy for Ewing Sarcoma

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In addressing Ewing Sarcoma (ES), a pediatric bone cancer, this study investigates the efficacy of iP300w, a novel inhibitor targeting the P300/CBP axis, in suppressing tumor growth. Initial experiments demonstrated the indispensable role of P300/CBP in the proliferation and survival of ES cells through siRNA-mediated knockdown, establishing a rationale for exploring iP300w therapeutic potential. Subsequent in vitro and in vivo analyses revealed P300/CBP selectively decreases viability and proliferation in ES cell lines without affecting non-sarcoma cells, underscoring its specificity and highlighting the therapeutic relevance of targeting the P300/CBP axis.

Mechanistic insights revealed through transcriptional and protein-level analyses indicated the antitumor efficacy of P300/CBP inhibition is attributed to the downregulation of critical oncogenic drivers essential for ES progression. Findings uncovered EWS-FLI1 sustains ES cells in a non-senescent state, with P300/CBP inhibition unexpectedly inducing cellular senescence. This induction is characterized by halted cell proliferation and specific alterations in gene expression, akin to those observed with EWS-FLI1 knockdown. The combination of P300/CBP inhibition with senolytics emerges as a novel therapeutic strategy, leveraging the senescence-inducing effect of P300/CBP inhibition to promote the clearance of senescent cells, thereby potentiating antitumor efficacy. This approach proposes a significant advancement in the treatment of ES, particularly for cases refractory to conventional therapies.

Our findings highlight the critical role of the P300/CBP axis in ES pathogenesis and advocate for the clinical investigation of P300/CBP inhibition as a potential treatment modality. This study delineates the mechanisms underlying P300/CBP inhibition and its effects on tumor suppression and senescence induction. It contributes to the expanding therapeutic landscape for Ewing Sarcoma, suggesting a promising avenue for improving patient outcomes in this challenging malignancy.