Title:- Identification of small molecule stabilizers of the IkBα NF-kB p50:p65/RelA complex for lung cancer.

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The inflammatory response coordinates various signalling pathways and is mediated by the transcription factor nuclear factor kappa-light-chain enhancer (NF-κB) of resident tissue cells and immune cells. Inflammatory responses play a crucial role in the immune system, autoimmune diseases, and cancer. NF-κB is directly regulated through protein−protein interactions, including those with p50:p65/RelA dimer and IκBa to form a trimeric complex in the cytoplasm. IkBa serves to sequesters the p50:p65/RelA dimer in an inactive state. IkBa becomes phosphorylated and subsequently degraded. This liberates the p50:p65/RelA dimer, which is its active form that moves to the nucleus to act as a transcription factor. These pathways are often deregulated in a number of cancers. In this study, we used artificial intelligence molecular screening to obtain a set of small molecule compounds predicted to target a binding site within the p50:p65/RelA: IκBa trimer complex. These compounds were screened on lung cancer cell lines using a luciferase assay, and the function of positive hits was further evaluated and validated using an assay to assess for small molecules acting as 'Molecular glues'. Our study identified a novel strategy to potentially stabilise the p50:p65/RelA: IκBa trimer complex with the potential to reduce the inflammatory pathway which is deregulated in cancer.