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# Discovery of structure-based small molecular inhibitor of αB-crystallin against basal-like/triple negative breast cancer development *in vitro* and *in vivo*

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αB-crystallin (CRYAB) is present at a high frequency in poor prognosis basal-like breast tumours, which are largely absent of oestrogen, progesterone receptors and HER2 known as triple-negative breast cancer (TNBC). CRYAB functions as a molecular chaperone to bind to and correct intracellular misfolded/unfolded proteins such as vascular endothelial growth factor (VEGF), preventing nonspecific protein aggregations under the influence of the tumour microenvironment stress and/or anti-cancer treatments including bevacizumab therapy. Directly targeting CRYAB can sensitize tumour cells to chemotherapeutic agents and decrease tumour aggressiveness. However, growing evidence shows that CRYAB is a critical adaptive response element after ischemic heart disease and stroke, implying that directly targeting CRYAB might cause serious unwanted side-effects. Here, we used structure-based molecular docking of CRYAB and identified a potent small molecular inhibitor, NCI-41356, which can strongly block the interaction between CRYAB and VEGF165. The disruption of the interaction between CRYAB and VEGF165 elicits in vitro anti-tumour cell proliferation and invasive effects through the down-regulation of VEGF signalling in the breast cancer cells. The observed in vitro anti-tumour angiogenesis of endothelial cells might be attributed to the down-regulation of paracrine VEGF signalling in the breast cancer cells after treatment with NCI-41356. One hundred micromolar intraperitoneal injection of NCI-41356 greatly inhibits the tumour growth and vasculature development in *in vivo* human breast cancer xenograft models. Our findings provide "proof-of-concept" for the development of highly specific structure-based alternative targeted therapy for the prevention and/or treatment of TNBC.

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