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An Inverse Docking Approach for Identifying New Potential Anticancer Targets

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Abstract : Inverse docking is a relatively new technique that has been used to identify potential receptor targets of small molecules. Our docking software package MDock is well suited for such an application as it is both computationally efficient, yet simultaneously shows adequate results in binding affinity predictions and enrichment tests. As a validation study, we present the first stage results of an inverse-docking study which seeks to identify potential direct targets of PRIMA-1. PRIMA-1 is well known for its ability to restore mutant p53's tumor suppressor function, leading to apoptosis in several types of cancer cells. For this reason, we believe that potential direct targets of PRIMA-1 identified in silico should be experimentally screened for their ability to inhibitcancer cell growth. The highest-ranked human protein of our PRIMA-1 docking results is oxidosqualene cyclase (OSC), which is part of the cholesterol synthetic pathway. The results of two followup experiments which treat OSC as a possible anti-cancer target are promising. We show that both PRIMA-1 and Ro 48-8071, a known potent OSC inhibitor, significantly reduce theviability of BT-474 breast cancer cells relative to normal mammary cells. In addition, like PRIMA-1, we find that Ro 48-8071 results in increased binding of mutant p53 to DNA in BT- 474cells (which highly express p53). For the first time, Ro 48-8071 is shown as a potent agent in killing human breast cancer cells. The potential of OSC as a new target for developing anticancer therapies is worth further investigation.

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