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Development of protein agent targeting integrins αvβ3 at a novel site by rational protein design

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Due to abnormal expression of integrins $\alpha_v\beta_3$ in various disease conditions, this integrin pair has been a focus as targets for drug development. Studies yield a few successful examples. Among them are various antibodies against the integrins, and most recently, Cilengitide, a RGD-based peptidomimetic.Nevertheless, most of current approaches focus on ligand-binding with goal of inhibition of integrin functions.A major draw-back of targeting ligand-binding of integrins is activation of integrin signaling by the developed agent, which largely limit the clinical success of the integrin ligand based antagonist/agonist. We report here development of a new class of therapeutically protein agent (Ref to as ProAgio) by rational protein design using a stable host protein. ProAgio is designed to target integrins $\alpha_v\beta_3$ at a novel site. ProAgio exhibits a strong *in vitro* activity in induction of apoptosis of integrin $\alpha_v\beta_3$ expressing cells. ProAgio induces apoptosis by recruiting and activating caspase 8 to the cytoplasmic domain of the targeted integrins. Tests with tumor xenografts show that ProAgio strongly inhibits tumor growth. Histology analyses indicate that tumor vessels are reduced, while the established vasculatures are not affected. The results confirm targeting of integrin $\alpha_v\beta_3$ as an anti-angiogenic agent. Toxicity analyses demonstrate that ProAgio is not toxic to mouse at very high doses. Our study develops an effective integrin targeting agent via a novel mechanism of action. Our approach provides a new platform for development of therapeutics by targeting integrins.

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