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**TARGETING THE NOTCH PATHWAY: A POTENTIAL THERAPEUTIC APPROACH FOR
DESMOID TUMORS**

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BACKGROUND: Desmoid tumors (DTs) are rare mesenchymal lesions that can recur repeatedly. When feasible, DTs are surgically resected; however, this often results in high recurrence rates. Recently, treatment with PF-03084014, a potent γ -secretase inhibitor (GSIs), has been shown to have antitumor activity in several tumor types by affecting the WNT/ β -catenin pathway. Consequently, Notch pathway inhibition by PF-03084014 might be a promising approach for DT treatment.

METHODS: The expression of Notch pathway components was analyzed in DT tissues and cell strains using immunohistochemistry and western blotting, respectively. A panel of DT cell strains was exposed to PF-03084014 and evaluated for cell proliferation. Antitumor effects were assessed via cell cycle, apoptosis, and migration and invasion analysis. Cells treated with PF-03084014 were characterized by gene array analysis combined with IPA.

RESULTS: Our results showed that Notch pathway components are expressed at different levels in DTs. We showed that Hes1 is overexpressed in DT tumors compared to dermal scar tissue, and that PF-03084014 caused significant decreases in NICD and Hes1 expression in DT cell strains. PF-03084014 decreased DT cell migration and invasion and also caused cell growth inhibition in DT cell strains, most likely through cell cycle arrest. Gene array analysis combined with IPA showed that WISP2 possibly regulates Notch and WNT pathways after treatment with PF-03084014 through integrin.

CONCLUSION: Our findings suggest that the Notch pathway is an important DT therapeutic target. Furthermore, PF-03084014 has significant antitumor activity against DTs, and may comprise an alternative strategy for DT treatment.