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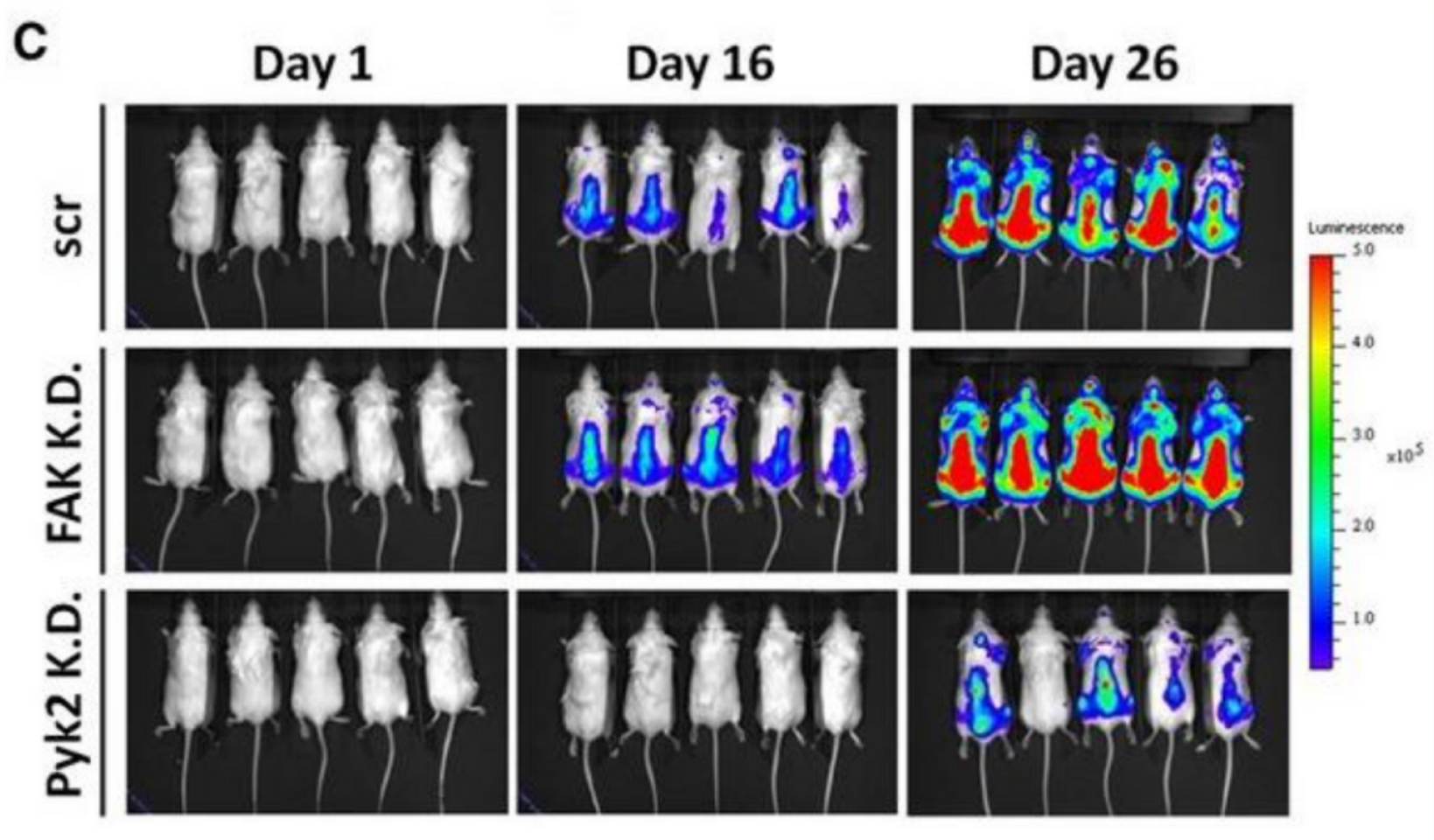
FINDING OF TUMOR PROGRESSION IN MULTIPLE MYELOMA STUDY



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Pyk2 promotes tumor progression in multiple myeloma

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Key Points

- Pyk2 plays a tumor-promoting role in MM progression via modulation of the Wnt/β-catenin signaling pathway.
- Pyk2 inhibitors represent a new therapeutic option against MM.

Proline-rich tyrosine kinase 2 (Pyk2) is a member of the focal adhesion kinase family that has been recently linked to tumor development. However, its role in modulating multiple myeloma (MM) biology and disease progression remains unexplored. We first demonstrated that patients with MM present with higher expression of Pyk2 compared with healthy individuals. By using loss-of-function approaches, we found that Pyk2 inhibition led to reduction of MM tumor growth in vivo as well as decreased cell proliferation, cell-cycle progression, and adhesion ability in vitro. In turn, overexpression of Pyk2 promoted the malignant phenotype, substantiated by enhanced tumor growth and reduced survival. Mechanistically, inhibition of Pyk2 reduced activation of Wnt/β-catenin signaling by destabilizing β-catenin, leading to downregulation of c-Myc and Cyclin D1. Furthermore, treatment of MM cells with the FAK/Pyk2 inhibitor VS-4718 effectively inhibited MM cell growth both in vitro and in vivo. Collectively, our findings describe the tumor-promoting role of Pyk2 in MM, thus providing molecular evidence for a novel tyrosine kinase inhibitor as a new therapeutic option in MM. (*Blood*. 2014;124(17):2675-2686)

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