

## WIF1 AS A THERAPEUTIC AGENT IN OSTEOSARCOMA

Kansara, Maya<sup>1</sup>, Laurent Kodjabachian<sup>2</sup>, Michael Tsang<sup>2</sup>, Dass Crispin<sup>3</sup>  
Natalie, Sims<sup>3</sup>, Melanie, Trivett<sup>1</sup>, John, Slavin<sup>1</sup>, Mathias Ehrich<sup>4</sup>, Alex Dobrovic<sup>1</sup>, Peter F.M.  
Choong<sup>3</sup>, Igor Dawid<sup>2</sup>, David M Thomas<sup>1</sup>.

<sup>1</sup>Ian Potter Foundation Centre for Cancer Genetics and Preventative Medicine, and Sir Donald and Lady Trescowthick Laboratories, Peter MacCallum Cancer Centre, Victoria, Melbourne, Australia. <sup>2</sup>Laboratory of Molecular Genetics, NICHD, NIH, Bethesda, Maryland 20892, USA. <sup>3</sup>St Vincent's Hospital, Fitzroy, Victoria, Melbourne, Australia. <sup>4</sup>SEQUENOM Inc, 3595 John Hopkins Court, San Diego, CA 92121.

Osteosarcoma is the most common primary malignancy of the bone and the third most common cancer in adolescents. Treatment often entails aggressive surgery with intensive adjuvant chemotherapy, and causes life-long morbidity in a young population. The 5-year survival of patients with metastatic or recurrent disease is less than 25%, unchanged over the past 15 year. There are no curative systemic therapies available for unresectable osteosarcoma, and there have been no new effective systemic therapies developed over the past 20 years. We identified Wnt inhibitory factor 1 (WIF1), a secreted inhibitor of the canonical Wnt pathway to be epigenetically silenced in human osteosarcoma. Loss of WIF1 was associated with impaired differentiation and increased proliferation. *In vitro*, treatment with recombinant WIF1 protein not only suppressed colony formation but also induced differentiation of osteosarcoma cell lines. Importantly, *Wif1*<sup>-/-</sup> mice were predisposed to the development of both spontaneous and radiation induced osteosarcoma. These data make WIF1 a clinically appealing drug candidate for osteosarcoma. Secreted inhibitors have high therapeutic potential, and our hope is that these studies will eventually lead to the rational design of WIF1 mimetic agents to specifically inhibit tumour growth.