


MEDICAL AND SCIENTIFIC COMMITTEE ANNUAL LAY REPORT 2008

1	Lay Project Title:	Role of WIF1 in bone development and cancer
2	Grant Holder:	Dr David Thomas, A/Prof Paul Simmons
3	Unit/Institution:	Peter MacCallum Cancer Centre
4	Years Funded:	2007-2009
5	Funding 2008:	\$70,000
6	Lay Abstract (<i>please refer to the enclosed guide</i>) <p>Osteosarcoma is the most common cancer of bone and the third most common cancer in adolescents. Chemotherapy has improved prognosis but has reached a plateau in terms of increasing survival. Identifying genes involved is key to developing therapeutic targets to osteosarcoma. We identified that Wnt inhibitory factor-1 (WIF1), a secreted protein with a possible role in suppression of a cell growth, is not expressed in osteosarcoma. We have investigated the role of this protein both <i>in vitro</i> and <i>in vivo</i> in normal bone development and the effect of its loss in osteosarcoma. We have found WIF1 is highly expressed in the developing skeleton. In mice which do not express WIF1 (WIF^{-/-}), skeletal development was found to be relatively normal. However WIF^{-/-} mice, are predisposed to the development of osteosarcoma compared control mice using a carcinogen model of osteosarcoma. Further investigation of WIF1 found that re-expression of WIF1 in osteosarcoma cell lines stopped cell growth. The results from our studies represent a significant step forward in understanding the role of WIF1 in bone development and tumourigenesis. Secreted inhibitors have high therapeutic potential, and our hope is that these studies may eventually lead to the rational design of WIF1 mimetic agents to specifically inhibit tumour growth.</p>	
7	<p>Please list papers (NB: only papers arising from this research project), which have been published, or accepted for publication, in refereed journals by any of the principal investigators during 2008. Please include title, sequence of authors, first and last pages, name, volume and date of journal. If there are no publications, please provide details of your publication strategy for the next twelve months. <i>Briefly annotate major findings within these publications.</i></p> <p><i>Epigenetic silencing of Wnt Inhibitory Factor 1 accelerates osteosarcomagenesis in vivo.</i> Maya Kansara, Michael Tsang, Laurent Kodjabachian, Natalie A. Sims, Melanie K. Trivett, Mathias Ehrich, Alexander Dobrovic, John Slavin, Peter F.M. Choong, Paul J. Simmons, Igor B. Dawid, David M. Thomas. <i>Journal of Clinical Investigation</i>. In press. Manuscript accepted 21/1/09.</p> <p>Wnt signaling increases bone mass by stimulating osteoblast lineage commitment and expansion, and forms the basis for novel therapeutic strategies being developed for osteoporosis. These strategies include derepression of Wnt signaling by targeting secreted Wnt pathway antagonists, such as sclerostin. However, anabolic therapies for osteoporosis are associated with safety concerns regarding an increased risk of osteosarcoma. Wnt Inhibitory Factor 1 (Wif1), a secreted Wnt pathway antagonist, was identified in a high-throughput screen for epigenetically silenced tumor suppressor genes in osteosarcoma. <i>In vitro</i>, Wif1 suppresses β-catenin, induces differentiation in primary osteoblasts, and suppresses growth of osteosarcoma cell lines. Wif1 is highly expressed in the developing and mature murine skeleton and, although dispensable for normal development, targeted deletion of <i>Wif1</i> accelerates development of radiation-induced osteosarcomas <i>in vivo</i>. In</p>	

	<p>primary human osteosarcomas, silencing of <i>WIF1</i> by promoter hypermethylation is associated with loss of differentiation, increased β-catenin levels and increased proliferation. In conclusion, derepression of Wnt signaling by targeting secreted Wnt antagonists in osteoblasts may increase susceptibility to osteosarcoma.</p>
<p>8</p>	<p>Please list any symposia\plenary presentations relating to this research project, which were made at major national or international scientific meetings during 2008. Please indicate the level of your contribution, ie poster, speaker, invited speaker or session chair.</p> <p>Lorne Cancer Conference, February 2008, Lorne, Melbourne, Australia, poster presentation: WIF1 induces osteoblast differentiation, and is epigenetically silenced in osteosarcoma.</p> <p>Models and Mechanisms of Cancer, August 2008 Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, US, poster presentation: Wnt inhibitory factor is epigenetically silenced in human osteosarcoma, and acts as a tumor suppressor <i>in vivo</i>.</p> <p>Cancer Epigenetics, October 2008, Tidal River, Wilson's Promontory National Park, Melbourne, Australia, talk: Search for potential therapeutic targets in osteosarcoma using an epigenetic screen.</p>
<p>9</p>	<p>Certification by Grant Holder</p>
	<p>I confirm that the above de</p> <p>Signature: _____  _____ Date: 12 January 2009</p> <p>Name (please print): David Thomas</p> <p>_____</p>

THANK YOU FOR YOUR ASSISTANCE