MEDICAL AND SCIENTIFIC COMMITTEE

ANNUAL LAY REPORT 2014

Lay Project Title:	Exploring the potential of the combination of old and new radioprotecting drugs to reduce normal tissue damage in cancer radiotherapy patients
Chief Investigator(s):	Dr Pavel Lobachevsky, Prof Roger Martin, Dr Olga Martin
Unit/Institution:	Trescowthick Research Laboratories, Peter MacCallum Cancer Centre
Years Funded:	2012-2014

1	*Radiotherapy plays a major role in cancer treatment, but even with the most sophisticated equipment to target the radiation to tumours, some nearby normal tissue is inevitably irradiated, and the consequent side-effects limit overall outcomes. This prompted the development of radioprotectors, to enable protection of normal tissues such as, for example, oral and rectal mucosa, by topical application. Methylproamine is the first lead of a new class of DNA-binding radioprotectors that emerged from research in our lab, and more than 100 new methylproamine analogues have been synthesised and evaluated in a commercially-funded development program at PeterMac. Two of these analogues have shown activity as topical radioprotectors of mouse oral mucosa.* *This project emerged following our earlier discovery that the combination of methylproamine with a classical radioprotector from the aminothiol family, developed more than 50 years ago provides much more protection than either drug alone, in cell culture (in vitro). A similar in vitro result was obtained with M2PB, a new methylproamine analogue. Then we established that the combination of M2PB with the old aminothiol radioprotector was also more efficient than either drug alone, in vivo, using a mouse model, that evaluates radiation-induced damage to mouse intestine.* *We continued studies with another preclinical model, which evaluates radiation induced damage to oral mucosa (namely ulceration of mouse tongue). We demonstrated that the combination of topical application of M2PB with systemic administration of the aminothiol reduces radiation induced mucositis in mouse tongue more efficiently than either drug alone.* *We also conducted experiments using molecular DNA damage model which supported the hypothesis that the enhanced effect of the combination of two radioprotectors results from different mechanisms of action and different subpopulations of DNA damage involved in radioporotection by each of the compounds.* *We also demonstrated that DNA-binding radioprotectors are able to reduce the level of radiation induced mutations, and the extent of this reduction was greater following application of the combination of M2PB and the classic aminothiol radioprotector. Such mutations in normal tissues following cancer radiotherapy may result in induction of secondary cancers. These findings therefore indicate the significant potential of the new DNA-binding radioprotectors to improve cancer radiotherapy.*
2	**Please list <u>all papers arising from this research project</u>, which have been published, or accepted for publication, in refereed journals since the commencement of this grant. Please list in chronological order, include title, sequence of authors, first, and last pages, name, volume and date of journal.** *Three manuscripts are in preparation. A substantial part of this research constitutes the PhD*

	project of Jai Smith, a PhD student in our lab, with expected thesis submission in 2015.
3	**Please list any presentations relating to this research project that were made at scientific meetings during 2014.** 1. *26th Lorne Cancer Conference, Mantra Lorne, Lorne, Victoria, Australia, February 13 - 15, 2014.* *Presentation title: Radioprotection by combination of DNA binding antioxidants and aminothiol radical scavengers. Poster presentation.* 2. *26th Lorne Cancer Conference, Mantra Lorne, Lorne, Victoria, Australia, February 13 - 15, 2014.* *Presentation title: New DNA-binding radioprotectors which repair transient radiation induced DNA lesions. Poster presentation.* 3. *Heavy Ion Accelerator Symposium, Australian National University, Canberra, Australia, June 30 – July 2, 2014.* *Presentation title: Additive Radioprotection by the Combination of DNA Binding Antioxidants and Aminothiol Radical Scavengers. Poster presentation* 4. *60th Annual Meeting of the Radiation Research Society, Las Vegas, NV, USA, September 21 - 24, 2014.* *Presentation title: Radioprotection of the mouse oral mucosa by the combination of DNA binding antioxidants and aminothiol radical scavengers. Poster presentation*
4	**Certification by Chief Investigator**
	I confirm that the above details are correct. Signature:  Date: 27/02/2015 Dr Pavel Lobachevsky