NEW DNA-BINDING ANTIOXIDANTS AS TOPICAL RADIOPROTECTORS

Lobachevsky Pavel[1], Smith Andrea[1], Skene Colin[2], Anderson, Robert[3], White Jonathan[2], Martin Roger[1]

[1] *Peter MacCallum Cancer Centre, Melbourne, Australia*
[2] *Bio21 Institute and University of Melbourne School of Chemistry, Melbourne, Australia*
[3] *Department of Chemistry University of Auckland, Auckland, New Zealand*
roger.martin@petermac.org

To varying extents, damage to normal tissues impedes the success of cancer radiotherapy. Fortunately, in many settings the normal tissues at risk (for example oral, rectal mucosa) are accessible to topical application, motivating efforts to develop topical radioprotectors. Given the challenges of topical delivery, the potency the DNA-binding radioprotecting drugs that we have developed over more than a decade confers an important advantage in this endeavour.

The initial lead drug of the series, methylproamine, shares the bibenzimidazole structural feature with the commercially-available fluorescent DNA dyes Hoechst 33342 and 33258. In vitro exposure of cells before and during irradiation reduces the level of radiation-induced g-H2AX foci, as well as improving clonogenic survival, consistent with the mechanism of radioprotection involving attenuation of initial radiation-induced DNA damage. Pulse radiolysis studies indicate these DNA-binding antioxidants repair transient radiation-induced lesions in DNA, by charge transfer. This proposed mechanism mimics endogenous non-enzymic chemical repair that is discussed for example by Milligan and co-workers, who draw attention to the favourable oxidation potential of tyrosine, and its abundance in nucleosomal proteins, as the basis for repair of transient oxidising species. Thus a transient but potentially damaging radiation-induced “hole” in DNA is diverted to a less critical site, namely a DNA-binding antioxidant in the minor groove.

The clinical potential of methylproamine is limited by its cytotoxicity, but an extensive lead optimisation program (> 150 new analogues) has identified several new analogues with reduced cytoxicity, without compromise of radioprotective activity. The innate fluorescence of the minor-groove-binding drugs has facilitated the development of topical formulations to optimise delivery, through the barrier that protects the mucosa, to the nuclei of basal cells. The best of the new drug/formulation combinations have been shown to confer topical radioprotection of mouse oral mucosa. The radiobiological model used, developed by Professor Wolfgang Doerr in Dresden, involves irradiation of a small area (3mm x 3mm) of the ventral surface of mouse tongue with low energy (25keV) X-rays.

We are now in the closing stages of selecting a final lead for clinical studies.