Pulse Radiolysis studies on the Release of Cytotoxins from Electron Affinic Anticancer Prodrugs following their One-Electron Reduction.

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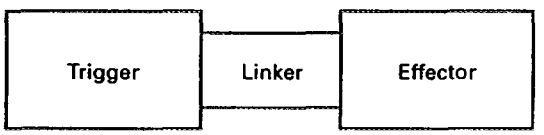
New approaches to killing chemoresistant and radioresistant hypoxic cells of solid tumours include the selective release of potent cytotoxins from relatively non-toxic prodrugs through reductive metabolism and/or radiolytic reduction[1]. Central to these studies, is an understanding of the mechanism of cytotoxin release and the basis of hypoxia-selectivity, since such information can be used to design compounds of high potency against solid tumours. Pulse radiolysis studies can offer unique insights into these underlying mechanisms in aqueous solution through the determination of (i) thermodynamic one-electron reduction potentials (E(1)) of the prodrugs, (ii) rate constants for the formation and spectral charaterization of one-electron reduced prodrugs, (iii) the kinetics release of the cytotoxins from one-electron reduced prodrugs and (iv) the influence of molecular oxygen on the obligate radical intermediates. Two main classes of prodrugs are being investigated.:-



(a) Nitroaromatic benzylquaternary compounds. These compounds consist of an electron-affinic nitroaromatic moeity (the 'trigger') linked through a benzylquaternary centre with a sidechain (the 'linker' unit) to a potent cytotoxic moeity (the 'effector').
(b) Transition metal complexes incorporating a bound ligand which is cytotoxic when released.

A series of different triggers, which are found to vary greatly in the rate constant for release of the effectors upon one-electron reduction of the prodrugs, will be discussed. Release of effector from a prodrug does not solely depend upon the type of trigger but can also be dependent on the type of linker and released effector. For example, whereas fast quantitative release of the mustard effector mechlorethamine is seen from the quaternary nitroimidazole upon one electron reduction, release of *N*-[2-(dimethylamino)ethyl] acridine-4-carboxamide (DACA), requires a higher level of reduction of the same trigger. Release of cytotoxic ligands from metal complexes requires that the metal centre is reduced. When the E(1) of the metal centre is lower than DACA bound as a ligand, reduction is seen to occur solely on the ligand without release from the metal centre.

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[1]W.A.Denny, W.R.Wilson and M.P.Hay, *Brit J. Cancer* (1996) 74, (Suppl. XXVII) S32-S38.