



***In Vitro* and Animal Models of Partial-Body Dose Exposure: Use of Cytogenetic and Molecular Biomarkers for Assessment of Inhomogeneous Dose Exposures and Radiation Injury**

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The world-wide use of ionizing radiation that spans many disciplines for beneficial purposes has also led to hundreds of instances in which one or more persons were accidentally overexposed (Gonzalez 2007). International generic guidelines for early medical diagnosis and biodosimetric assessment of overexposed individuals are well established (Alexander et al. 2007; Blakely et al. 2005). These approaches, however, generally apply for assessment of whole-body exposures when, frequently, individuals involved in radiation accidents and cancer radiation-therapy patients exhibit non-homogeneous dose-exposure profiles. Research efforts have focused on development and validation of biodosimetric approaches applicable for radiation dose and injury assessment for partial-body or non-uniform distribution of dose.

Simulated partial-body exposures are typically modelled using *in vitro* blood or lymphocyte cultures. These studies often involve mixing increasing amounts of irradiated to non-irradiated cells immediately after *in vitro* radiation exposure. Various cytogenetic bioassays for radiation dose assessment, including dicentric, premature chromosome condensation, micronuclei, and fluorescent *in situ* hybridization or FISH assays (Lloyd et al. 1973, 1987; Blakely et al. 1995; Darroudi et al. 1998; Duran et al. 2002; Gotoh et al. 2005), have been applied in these simulated partial-body exposures or "mixing studies." Cytogenetic bioassays useful for partial-body dose assessment generally have dual features. First, radiation exposed cells can be discriminated from non-exposed cells and exhibit high percentage yields at low doses. Second, the degree of damage on a cellular basis can be quantified and exhibits meaningful dose dependency (Lloyd et al. 1973; Blakely et al. 1995; Gotoh et al. 2005).

These cytogenetic bioassays and other bioindicators (e.g., erythema, hair diameter) for radiation dose and injury assessment have also been used in animal partial-body radiation models. An external photon or high-LET radiation source is typically used with a radiation field that involves partial shielding to permit selective irradiation of discrete partial-body regions of animals (e.g., abdomen, lung, head, testes, isolated skin, etc.). In other cases, selective body regions (e.g., tibia, femur, abdomen, oral cavity, head, etc.) and organs (e.g., exteriorized intestine) are shielded and the remaining body parts are irradiated. For example, shielding one tibia of rats results in exposure of 95% of the marrow. These partial-body exposure models are often focused to address one or more of the acute radiation syndrome or sickness (ARS) sub-syndrome organ systems (e.g., haematopoietic, gastrointestinal, cutaneous) and other organ injuries (e.g., kidney and lung). Additional animal models used for this purpose include: mice, Syrian hamsters, dogs, miniature pigs, swine, and rhesus nonhuman primates. An x-ray dosimetry intercomparison was held among a number of laboratories involved in a partial-body irradiation study using mailed acrylic plastic



rat phantoms. They demonstrated the value of improvements in dosimetry and irradiation procedures for partial-body irradiations (Puite et al. 1980). Animal studies have also used radioisotopes that target specific organs (e.g., radioiodine therapy of thyroid) to permit partial-body exposures. Use of intensity-modulated radiation therapy (IMRT) offers promise for radiation dose painting to specific organs for enhancing research to identify and validate bioassays for partial-body exposures.

Blood biochemical markers of radiation exposure have been advocated for use in early triage and injury assessment of radiation casualties (Bertho et al. 2001; Blakely et al., 2003a, 2003b, 2007; Roy et al. 2005; Ossetrova et al. 2007). Biomarkers can fall into two classes: early expressed biomarkers of radiation injury or organ-specific injury biomarkers exhibited at varied intervals after radiation exposure in a dose- and time-dependent fashion and which are based on specific organ and tissue transit times. The blood plasma biomarker approach has several advantages. Early biomarkers of radiation exposure may contribute along with other early biodosimetric indices, clinical signs and symptoms, and evidence of physical dose to initiate use of non-toxic medical countermeasures that demonstrate greater efficacy when initiated 24 h after radiation exposure (Waselenko et al. 2004; MacVittie et al. 2005). Organ- and tissue-specific biomarkers, representing cell and tissue response to radiation injury, will leak tissue- and organ-specific bioindicators into blood. These measurements can provide useful diagnostic information about the temporal onset and severity of specific organ and tissue system injury. For example, blood biomarkers have been shown to be correlated with radiation-induced hematopoietic ARS severity (Mal'tsev et al. 2006), cell loss in bone marrow (Roy et al. 2005), and small-bowel epithelial mass (Ludgens et al. 2004).

Biomarkers along with clinical classification systems can assist in the prediction of clinical outcome, add new aspects for further research in understanding of ARS and, therefore, offer the ability to develop new strategies in medical care. Only a combined approach using clinical classification systems, biomarkers, other biodosimetric indices, and physical measurements will ensure the best strategy to formulate early medical-treatment decisions.

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