Acute radiation syndrome: hematopoietic characterization of a non-rodent model

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Introduction
There is a paucity of approved radiation medical countermeasures. Current regulations require evaluation of radiomitigators drug candidate efficacy and safety in a rodent and a non-rodent model prior to approval under the FDA Animal Rule. Characterization of the hematopoietic syndrome in Rhesus monkeys is used to support selection of the dosing regimen in this species.

Materials and methods
Cell blood counts were obtained from 120 Rhesus monkeys for 12 to 60 days after whole body radiation using a Cobalt-60 at radiation dose levels ranging from 400 to 1210 Gy. Irradiation was performed in two half-dose fractions (antero-posterior and postero-anterior) at dose rates between 43.6 and 57.9 cGy/min for 60-Cobalt (Theratron 780 or Theratron 1000) or at 94.8 cGy/min with a linear accelerator for the radiation dose of 1210 cGy (Varian Clinac 6EX, 6MV). Two (2) dosimeters (Thermoluminescent dosimeters or NanoDot, Landauer inc., Glenwood, IL) were placed at the apex of the sternum and at the corresponding level in the interscapular area on each animal. Evidences of pain or discomfort were treated with analgesia (buprenorphine, IM, 0.01-0.05mg/kg, at least every 8 hours) and nutritive supports (e.g. liquid diets) were provided if animals presented decreased appetite.

Results
A combination of thrombocytopenia and neutropenia was correlated to clinical outcome in irradiated Rhesus monkeys (Stickney et al., 2007). A dose dependent decrease in platelets and neutrophils was observed in the current model with nadirs that were proportional to the half-life of blood constituents and progenitor cell maturation kinetics. Similarly, a dose proportional decrease in lymphocyte counts was noted by Day 2 post-radiation. In addition, the total volume of blood samples is recognized to impact study outcome and requires careful planning in study design. Characterization of the hematopoietic changes can be used to select the relevant evaluation timepoints when conducting safety and efficacy studies in a Rhesus acute hematopoietic syndrome model.

Discussion
A combination of thrombocytopenia and neutropenia was correlated to clinical outcome in irradiated Rhesus monkeys (Stickney et al., 2007). A dose dependent decrease in platelets and neutrophils was observed in the current model with nadirs that were proportional to the half-life of blood constituents and progenitor cell maturation kinetics. Similarly, a dose proportional decrease in lymphocyte counts was noted by Day 2 post-radiation. In addition, the total volume of blood samples is recognized to impact study outcome and requires careful planning in study design. Characterization of the hematopoietic changes can be used to select the relevant evaluation timepoints when conducting safety and efficacy studies in a Rhesus acute hematopoietic syndrome model.

Conclusion
Radiation dose dependent changes were observed in the current model. The hematology profiles obtained in this non rodent acute radiation syndrome model were comparable to the response in radiation-exposed humans and confirm the value of this non-rodent model for drug development.

References