A WHOLE-BODY PHARMACOKINETIC MODEL FOR THE EARLY ASSESSMENT OF TARGETED RADIONUCLIDE THERAPY AGENTS

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Early assessment of targeted radionuclide therapy (TRT) agent effectiveness based on its pharmacokinetic (PK) properties could provide a means to expedite agent development or rejection. A whole-body PK model was developed that not only simplifies the complex radiation dosimetry and physiology of TRT but also provides criteria for normal tissue and tumor PK parameters that achieve effective TRT while limiting toxicity. Because biologically effective dose (BED) may be more of a relevant quantity than absorbed dose for establishing tumor response relationships, the model was expanded to include BED.

The model consisted of two coupled normal body compartments and one decoupled tumor compartment. Differential equations were used to develop an equation that predicted TRT efficacy. PK scenarios were created by pairing normal body influx and efflux parameters with a range of tumor influx and efflux parameters. Each PK scenario yielded a maximum delivered tumor absorbed dose that limited the whole body dose to 2 Gy. The dose rate and repair rate were used for BED. The relationships between the tumor influx-to-efflux ratio (k_{34}:k_{43}), central compartment efflux-to-influx ratio (k_{12}:k_{21}), central elimination (k_{el}), and tumor repair rate (μ), and tumor BED were investigated.

The model was used to find the PK parameters for NM404 and FLT within a xenograft model. The TCC of both Compartment 1 and tumor were fit to the equations of the model using Levenberg-Marquardt. The parameter errors were propagated into dosimetry uncertainties.

Sensitivity functions were derived for each PK parameter that described the change in TCC as a result of a change in the PK parameter value at each time. Cramer-Rao Lower Bounds (CRLB) theory was used to derive optimal sampling schedules based on the sensitivity of the derived PK parameters. The experimental and optimal sampling schedules were compared by running simulations that measured the precision and accuracy of the measured PK parameters.

The TRT PK model that was developed has the capability of predicting effectiveness when PK parameters are known. This work also represents a step in the direction of establishing relative PK criteria of when the BED formalism is more applicable than absorbed dose for TRT.