FINAL TECHNICAL REPORT

Project Title: A Combined Tissue Kinetics and Dosimetric Model of Respiratory Tissue Exposed to Radiation

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Project Team:

Project Objective: Existing dosimetric models of the radiation response of tissues are essentially static. Consideration of changes in the cell populations over time has not been addressed realistically. For a single acute dose this is not a concern, but for modeling chronic exposures or fractionated acute exposures, the natural turnover and progression of cells could have a significant impact on a variety of endpoints. This proposal addresses the shortcomings of current methods by combining current dose-based calculation techniques with information on the cell turnover for a model tissue. The proposed model will examine effects at the single-cell level for an exposure of a section of human bronchiole. The cell model will be combined with Monte Carlo calculations of doses to cells and cell nuclei due to varying dose-rates of different radiation qualities. Predictions from the model of effects on survival, apoptosis rates, and changes in the number of cycling and differentiating cells will be tested experimentally. The availability of dynamic dosimetric models of tissues

at the single-cell level will be useful for analysis of low-level radiation exposures and in the development of new radiotherapy protocols.

Background:

The health effect of primary concern with respect to establishing radiation protection limits is the radiogenic development of malignant disorders of various tissues, i.e. cancer. It appears that the specific changes in cells that lead to cancers of different tissues depend on the characteristics of the tissue. For example, in some tissues the inactivation of specific suppresser genes seems to be the critical event, while in other tissues it is the activation of a particular oncogene. However, cancers of most tissues share several characteristics that seem to be critical to the magnitude of the risk produced by low doses of ionizing radiation. In almost all cases, primary tumors seem to have developed from a single aberrant cell. Cancers are characterized by significant genomic instability, although it is unclear whether this characteristic developed early or late in the sequence of events leading to observed disease. Preneoplastic changes are generally much more common than cancer itself. These and other observations lead to a general picture of cancer as a sequence of ***changes in individual cells***. When an individual cell has accumulated a specific combination of genetic modifications, it will grow without limit, promote growth of its blood supply, and metastasize. Since radiation-induced mutation of a specific gene is a relatively rare event, the probability of modifying two or more genes in a specific cell (the product of the probability of each of the individual changes) is extremely small. Various mechanisms, including a proliferative advantage produced by the first modification and genomic instability induced early in the process, may contribute to an increased probability of producing the single cell with all of the properties of a malignant tumor. All of these processes may be detectable as small perturbations of the normal sequence of growth, division, differentiation, and apoptosis or exfoliation that characterizes

normal cells in a tissue. In healthy adult tissues there is equilibrium between cell production, differentiation, and loss that establishes a steady-state population distribution and allows the tissue to provide its normal functions in the organism. Spontaneous errors, such as overproduction of one cell type, are probably relatively frequent, but feedback systems generally correct the resulting imbalance by reducing production or inducing apoptosis, and a dynamic balance is maintained. Problems occur when aberrant cells, which do not respond to these feedback systems, are produced, or cells required for maintaining the balance are damaged. This results in one type of cell, which may be recognizable as a preneoplastic form, proliferating beyond its normal level in the tissue. As the number of these aberrant cells increases, the probability of one cell in that population acquiring an additional change in the progression towards cancer also increases. Radiation exposure, even at very low doses, may alter the frequency of changes that will allow abnormal cell population distributions to develop, as well as the probability of producing subsequent changes in individual cells of the expanded population. Bystander effects, induced genetic instability, and adaptive responses all increase the number of cells expressing an effect of irradiation, relative to the number of cells actually traversed by a directly ionizing particle. These effects may either increase or decrease the probability that a cell will accumulate the changes leading to malignancy; either way, they do change the effective target size for radiation-induced changes in the tissue. Previous attempts to model the radiation response of respiratory tissue have typically treated the tissue as an assembly of independent cells and have ascribed the response to the energy deposited in those cells. A number of different models of the human respiratory system have been used to calculate dose distributions for the estimation of carcinogenic risk to low-level exposures. Mercer and co-workers (1991) developed an airway model that divided the epithelial

lining into successive cylindrical shells in order to determine the absorbed dose due to radon daughter exposures. Individual cells were not a part of their model but they did use mean nuclear volumes of cell types that would be present in the shells. Similarly Brenner *et al.* (1995) have used a cylindrical shell model to calculate carcinogenic risk and quality factors for the human airway. They combined Relative Biological Effectiveness (RBE) determinations for transformation of mouse fibroblasts exposed to particles of varying Linear Energy Transfer (LET) with their tissue model to predict quality factors for radiation of similar LET in the human airway. Both of these models are essentially static with minimal recognition of the properties of the different cell types present in the conducting airways. Recently, a less static approach has been taken by Stewart and Traub (2000), where they use voxel constructs to model tumor response to radiotherapy. They used a Lethal-Potentially Lethal model to modify the response of volume elements over time. The model takes into account the cell density of different regions of a tumor and allows the assignment of different responses to the cell populations within those regions. All of the aforementioned models employ the same top-down approach of subdividing a tissue into putatively representative sections that can be easily modeled. ***We propose an alternative approach to the problem by building up the tissue construct from the bottom one cell at a time.***

Elkind (1994), Brenner *et al.* (1993) and others have pointed out that many low dose effects can be explained by the presence of cells in more radiosensitive stages of the cell cycle. Similarly, recent studies of the bystander-cell effects suggest that only a fraction of the cell population is susceptible to these changes at any particular time. Although most of the work examining cell-cycle sensitivity has been performed using rodent cells in culture, it is reasonable to expect that the response of normal human cells in tissue would have a similar dependency. In fact, treatment

of tumors by fractionation of the dose depends on differences in the proliferation rates of the normal and tumor cells. Sarkaria *et al.* (1995) have shown in a xenotransplantation model that alteration of the proliferation rate of tumor cells (which is equivalent to altering the cell cycle distribution) enhances cell killing. ***Therefore in order to examine the effects of low dose exposures it is essential that the proliferative capacity and cell cycle distribution of the cells in a tissue be included in dosimetric models.*** In this proposal we have chosen the human bronchiole as our tissue of interest for several different reasons. The lung is a target organ for radon exposure and for occupational exposures due to inhalation of contamination. The bronchiole is a major constituent of lung tissue and is believed to be the site where many cancers originate. It has a relatively simple epithelium with three basic cell types –basal, secretory, and ciliated cells. These are easily identified by morphology and there are cell-type specific markers for which monoclonal antibodies are readily available. Morphological measurements and data on proliferation rates have already been obtained by others (Boers *et al.*, 1998; Mercer *et al.*, 1994). Primary human bronchial cells can be obtained commercially. And finally, it will be possible in future to test the resulting model of a human bronchiole by using primary human bronchial cells in xenotransplantation experiments (Klein-Szanto, *et al.*, 1984).

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Status:

YEAR 1

The first phase of the project was completed on schedule. An extensive literature search was undertaken to identify data for bronchiolar cell and tissue parameters for the model. Limited data are available for the cell kinetics of bronchiolar cells and this area has been identified as one for which measurements will be undertaken in the near future. The published data were utilized to assign initial values to model parameters or inform the choices for the initial probability distributions (see Table 1).

A simplified four-dimensional (three spatial dimensions and a temporal dimension) model of human bronchiole has been implemented. The bronchiole is modeled as a regular hollow cylinder with the epithelial cells lining its interior. The cell types constituting the bronchiolar epithelium are basal, secretory, and ciliated ones. The average caliber of the bronchiolar wall, the average thicknesses of mucous and cilia layers, the average thickness of epithelium, and average depth of nuclei of cells at risk are taken into account. The approach currently implemented in the

model assumes that for the purposes of assessment of radiation damage to the cells only the nuclei of the cells should be modeled.

Table 1. Selected Model Parameters

Model Parameters	Value or Range	Distribution
Duration of G1 phase for basal cell	24 – 30 hrs	None (at present)
Duration of S phase for basal cell	6 – 8 hrs	None (at present)
Duration of G2 phase for basal cell	6 – 8 hrs	None (at present)
Duration of M phase for basal cell	2 hrs	None (at present)
Lifetime of the basal cell	6 – 8 days	Uniform
Lifetime of the ciliated and secretory cells	8 – 12 days	Uniform
Proliferative potential (basal cell)	0 - 7	Poisson (mean 4)
Basal cell diameter	20 microns	None
Secretory and ciliated cells diameter	25 – 30 microns	None (at present)
Basal cell nucleus diameter (spherical shape)	8 microns	None
Secretory and ciliated cell nuclei diameter (ellipsoid shape)	10 microns, 18 microns	None (at present)

The nuclei of the basal cells are randomly assigned positions on the wall of the regular cylinder taking into account the mean cell diameters and positions of the nuclei in the cells. To do this, the regular hexagonal grid is developed and superimposed on the cylinder wall. The size of the hexagonal cell is larger than the size of the basal cell nucleus, therefore each hexagon of the grid represents region that can contain one and only one basal cell. The nucleus of a basal cell is placed in the center of each hexagonal region, ensuring that basal cells are distributed on the

wall of the bronchiole. Then, the position of each nucleus is altered. As a result, an irregular (random) grid for the nuclei of the basal cells is built. Each basal cell has an individual lifetime clock position, cell-cycle clock position, a mean nuclear size, a proliferative capacity (randomly assigned number of possible daughter cells according to Poisson distribution with mean 4). A special subroutine defines which nodes of the “basal grid” contain pluripotent stem cells. The subroutine assures that no two stem cells are neighbors. Stem cells are distinguished by unlimited proliferative potential.

A second hexagonal grid is built to accommodate superficial secretory and ciliated cells. It is assumed that shape of secretory or ciliated cell can be considered hexagonal in a cross section, and the cell occupies the whole hexagon in the grid. The nuclei are essentially centered relative to the sidewalls of the cells. The nucleus of the cell is put in the center of the hexagon and then its position is slightly altered, using the algorithm developed for the basal cells. The positions of the nuclei of the daughter cells are calculated. The fact that the nuclei do not lie on the same depth is taken into account. Each secretory or ciliated cell has an individual lifetime clock position, record of the parent basal cell identifier and a mean nuclear size. Secretory and ciliated cells are considered to be terminally differentiated and therefore cannot proliferate.

When all possible positions for potential cells and cell types are defined for the basal layer, a subroutine starts to populate the remainder of the bronchiole. Once the bronchiolar construct is fully populated with cells, another subroutine continues modeling the cell loss (apoptosis), replacement and differentiation over extended time periods.

Figure 1. A) Basal grid and ciliated and secretory grid;
B) Composite bronchiole construct.

The model output provides data on the number of basal cells in different phases of a cell life-cycle and secretory to ciliated cells ratio after several generations of cell proliferation. There are discrepancies in the numbers of basal cells in different phases of a cell life-cycle compared to experimental data.

Table 2. Comparison of selected model outputs to experimental observations.

	Observed	Model
Percentage of cells in S or M phase	~ 3 %	5 - 10 %
Percentage of cells in G2 phase	~ 5 %	10 – 15 %
Secretory to ciliated cells ratio	50/50	50/50

The ratio of secretory to ciliated cells calculated by the model corresponds to the experimental data. The secretory and ciliated cells line out the bronchiole in random patches. This pattern reflects the real life situation.

Figure 2. Superficial layer of unfolded bronchiole: secretory (pink) and ciliated (violet) cell lining.

The results of this research were presented at the American Nuclear Society Conference in San Diego, CA, June 1 – 5, 2003. And an extended abstract has been published in the proceedings of the American Nuclear Society.

N. G. Ostrovskaya and J. R. Ford, Modeling the radiation response of respiratory tissue. *Transactions of the American Nuclear Society* **88**, 349, 2003.

YEAR 2

The second phase of the project was completed slightly behind the original proposed schedule. During the experimental testing and comparison to values reported in the literature we found that several of

the original parameter values needed to be adjusted and some of the subroutines needed to be reconfigured. New modifications the simulation are detailed in the following paragraphs.

The bronchiole is modeled as a regular hollow cylinder with the epithelial cells of three different types (basal, secretory, and ciliated) lining its interior. The caliber of the bronchiolar wall, the thicknesses of the mucosal and ciliated layers, and morphological cellular data are the input parameters for the model. For the purposes of assessment of radiation damage to the cells only the nuclei of the cells are modeled. Two separate hexagonal grids are superimposed on the cylinder wall to model the cell distribution in a tissue: one grid accommodates the nuclei of basal cells; while the other one contains the nuclei of ciliated and secretory cells. Use of two separate grids is justified by the pseudostratified structure of the bronchiolar epithelium. Mean cell diameters and the positions of the nuclei in the cells are taken into account. Some nodes of the “basal grid” contain pluripotent stem cells distinguished by unlimited proliferative potential. Stem cells comprise up to 3 percent of the total cell body in a bronchiole. The initial scheme of cell proliferation is presented below (Figure 3). Secretory and ciliated cells are considered terminally differentiated and therefore cannot proliferate.

Figure 3. Initial scheme of cell proliferation.

The lifetime of a non-stem basal cell is defined by the proliferative capacity of the cell: basal cell does not die until it depletes the number of possible divisions. Each bronchiolar cell has an individual life clock; basal cells have cell-cycle clock position. A basal cell goes through a cell cycle: G0/G1 (rest/growth), S (DNA synthesis), G2 (growth), M (mitosis).

Subroutines describing cellular kinetics - birth, growth, differentiation, proliferation (if applicable), and death – have been developed to simulate cell turnover in a normal epithelial tissue. Monte Carlo subroutines have been developed to simulate exposure to alpha particles. The computer model simulates tissue kinetics and radiation exposure in four dimensions: three spatial dimensions and a temporal dimension. Microdosimetric calculations are performed for cells traversed with radioactive particles. Each hit cell is provided with a record of energy deposition, and this record is passed to the progeny if the cell survives.

Results provided by the model for a pseudo bronchiole (input parameters are listed in Table 3) are presented below.

Table 3. Model input parameters

Airway diameter	596 μm
Airway section height	489 μm
Thickness of epithelium	30 μm
Thickness of mucous layer	5 μm
Basal cell region diameter (contains only one basal cell)	22 μm
Basal cell nucleus diameter (shape – sphere)	8 μm
Ciliated/Secretory cell diameter	14 μm
Ciliated/Secretory cell nucleus semiaxis (shape – ellipsoid)	6 μm, 4 μm, 4 μm
Basal cell cycle phase duration:	
G1	28, hour
S	10, hour
G2	4, hour
M	2, hour
Number of potential divisions for a basal cell	Poisson distributed, mean 4, maximum 9
Lifetime of ciliated/secretory cell	7 – 12 days
Irradiation scenario	Po-214 alpha particles Energy – 7.68682 MeV Activity – 1 Bq/cm ² Particles originate in the mucous layer of the bronchiole
Energy of cell inactivation	0.25 * Cell diameter * 100 keV/μm, keV
Time simulated	1 year
Simulation time step	1 hour

Simulation Results

The epithelium of the pseudo bronchiole contains up to 2,125 basal and up to 5,080 ciliated/secretory cells. This will correspond to a cell density of approximately 787,000 cells/cm² which is in the range of reported values. The basal cell to ciliated/secretory cell ratio is 0.29 / 0.71, To maintain the epithelial lining the number of stem basal cells is 208 (2.9% of total cell population) and the percentage of basal cells in each cell cycle phase has been calculated (Table 4).

Table 4. Average percentage of basal cells in each cell cycle phase.

Cell Cycle Phase	Percentage of Cells
G0/G1	79.4 ± 1.0
G0	44.4 ± 1.8
G1	35.0 ± 1.3
S	12.9 ± 0.7
G2	5.2 ± 0.4
M	2.6 ± 0.3

Labeling and mitotic indices calculated by the model are 3.85 and 0.7 percent, respectively. From this an average cell turnover time for the bronchiolar tissue is estimated to be 38.7 ± 4.2 days. This value is also in the range of values that have been estimated from actual cell labeling experiments carried out *in vivo* primarily in rodents.

The number of alpha particles emitted over one simulated year is 288,704 (recalculated activity is 0.999865 Bq/cm²). For a single simulation the numbers of cell traversals by alpha particles for basal and ciliated/secretory cells were 5,110 and 10,132 respectively. The

calculated hit probability per track is $5.27\text{E-}2$ (per track per hour is $6.03\text{E-}06$).

Microdosimetric calculations have been performed for the cells traversed with radioactive particles. The distribution of the chord lengths, $t(l)$, in a basal cell nucleus has been calculated (Figure 5). Probability density $f_1(z)$ of specific energy z deposited in a basal cell nucleus by Po-214 alpha particle emitted from the mucous layer has been calculated (see Figure 6). The frequency-mean specific energy per energy deposition event was found to be $z_F = 0.4$ Gy.

Figure 5. Distribution of chord lengths, $t(l)$, in a basal cell nucleus: d – nucleus diameter; $\circ$ – theoretical, $\blacktriangle$ – model.

Figure 6. Probability density $f_1(z)$ of specific energy z deposited in a basal cell nucleus by Po-214 alpha particle emitted from the mucous layer.

At the completion of the simulated year, 20.8% of the basal cells were descendants of the cells that undergone an energy deposition (up to 19 alpha traversals in one cell lineage). For the ciliated/secretory cells, the percentage of descendants of the cells hit by alpha particles was even higher - 21.1% (up to 20 alpha traversals in one cell lineage). However, these huge numbers are explained by the high activity (1 Bq/cm^2) assumed in the irradiation scenario. A high activity scenario was chosen to provide good statistics for microdosimetric calculations.

The results of this research were presented at the American Nuclear Society Conference in Pittsburg, PA, June 13 – 17, 2004. And an extended abstract has been published in the proceedings of the American Nuclear Society.

N. G. Ostrovskaya and J. R. Ford, A combined tissue kinetic and dosimetric model of an airway. *Transactions of the American Nuclear Society* 89: 57-58, 2004.

YEAR 3

The model has been revised and some improvements have been made. Data structures describing basal and secretory and ciliated cells have been changed that allowed to rework and optimize the algorithms describing cell turnover in the bronchiolar epithelium. As a result, a significant reduction of computational time has been achieved. Modules simulating exposure to low LET types of radiation were developed and used to investigate the evolution of cell populations under low dose rate (background) irradiation conditions. The model was used to predict changes in cell populations exposed to radiation.

Morphometric parameters of the basal and superficial cells have been adjusted to allow higher cell density in the simulated tissue (Table 5). This improvement brought cell density value in better agreement with the experimental data reported by others (Boers, 1998). The cell density

Table 5. Morphometric parameters for bronchiole and basal, secretory and ciliated cells.

Parameter	Value, μm
Airway diameter, generation 14	603 ^a
Airway height, generation 14	1700 ^a
Thickness of epithelium	30 ^a
Thickness of mucous layer	5 ^a
Basal cell region diameter ^b	14
Basal cell nucleus diameter, nucleus shape – sphere	8 ^c
Secretory/ciliated cell diameter ^b	9
Secretory/ciliated cell nucleus semiaxes, nucleus shape – ellipsoid	6, 4, 4

^a From Table 2 in *Publication 66* (ICRP, 1994).

^b The diameter of the circle inscribed in the hexagon of the grid.

^c Mercer *et al.* (1994).

about 1.9×10^6 cell/cm² has been achieved.

To better represent processes occurring in a real tissue, the circadian oscillations of the mitotic activity of proliferating cells have been implemented into the tissue kinetics sub-model. Human cells synthesize DNA (LI) more actively during the daytime and show higher mitotic activity (MI) in the night (Figure 7). Mitotic activity of the basal cells varies from 1% at noon to 2% at night, approximately. Basal cells synthesize DNA more actively during the daytime, 13.8% maximum; DNA synthesis slows to a minimum 9 % of the basal cells, at night. These levels of activity correspond to the experimental results summarized by Brown (1991). These values of MI and LI were obtained for the following input parameters for the duration of the cell cycle phases: G₁ (minimum) – 24 hrs, S – 8 hrs, G₂ – 4 hrs, M – 1 hr. We assumed that the lengths of S, G₂, and M phases do not change under normal conditions, while the duration of the G₁ phase is influenced by the circadian rhythm and ranges from 24 to 47 hours.

Figure 7. Circadian oscillations of the mitotic and labeling indices.

Internal radiation exposure has been simulated for both high-LET (α -particles) and low-LET (photons, electrons) radiations. The Monte Carlo subroutines have been developed to simulate the exposure to α -particles. A separate software module has been developed to model exposure of the bronchiolar epithelium to low-LET radiations. Since the independent development of a code for the Monte Carlo simulation of coupled photon-electron transport or electron transport alone is a time and personnel intensive task, we elected to use one of the industrial packages available for simulation of particle transport in materials. The module was developed using the Geant4 toolkit, a powerful software package designed for the Monte Carlo simulation of particle transport and interactions with matter. The Geant4 code uses condensed simulation algorithms for particle tracking, where the effects of the interactions (energy deposition events) are summarized at the end of a track segment. The length of the particle range for a single path step was set to one micron, which is the smallest resolvable distance in the basal and the secretory/ciliated hexagonal grids in the main simulation. Thus, the accuracy of the condensed history algorithm for particle tracking in matter is performed at the maximum resolution of the simulation.

Since photons and energetic electrons can travel distances that are much larger than the dimensions of the bronchiole, it is necessary to check if particles generated elsewhere in the lungs can reach and hit the epithelial cells of the bronchiole in question. To implement this, the approximate model of the human lungs and the rib cage was constructed (Figure 8). The geometry and dimensions of the lungs and the rib cage were partially adopted from the adult phantom developed in Oak Ridge National Lab.

The construction of the bronchiole in the Geant4 module is different from how it was done in the main program. The bronchiole is defined by two concentric cylinders representing the epithelial tissue. The

Figure 8. The approximate model of human lungs and rib cage. Left panel: Lungs and rib cage constructs. Right panel: Placement of the bronchiole in the lungs.

cell nuclei are not modeled. The lumen of the bronchiole is modeled as a separate cylinder to allow specifying the air as a material. The diameter and the height of the bronchiole, the thicknesses of the epithelium and the mucociliary layer, the elemental compositions and densities of the bronchiolar tissue and the air in the lumen are exactly the same as in the main program. The epithelial layer of the bronchiole excluding the mucociliary layer is specified as the detector volume. The bronchiole is randomly placed in the lungs (Figure 8).

The model assumes that the total activity in the lungs is proportional to the activity of the particles deposited in the bronchiole. The total activity in the lungs is calculated using the surface activity in the bronchiole and the surface areas of bronchi and non-respiratory bronchioles. The number of particles needed for the simulation of the long-term internal exposure is generated. Each particle is tracked till it comes to rest and the information on the events of energy deposition in the epithelial layer of the bronchiole is stored in a file in a string format. Each string contains the identifier of the primary particle, the coordinates

of the energy deposition point, and the amount of energy deposited in that point. Later, the main program parses this file to retrieve data for the energy deposition events and to identify the epithelial cells traversed by radioactive particles.

Cells traversed by ionizing particles may respond differently to a particular radiation insult. Cellular response depends on both the magnitude of the damage produced by radiation and the cell type. The model allows the simulation of different cellular responses to the damage depending on the amount of energy deposited in the cell nucleus: proliferating cells may undergo cell-cycle arrest, cellular repair, loss of reproductive capacity (the cell survives, but cannot longer divide), mitotic death, and finally radiation-induced apoptosis. For cycling basal cells, two forms of apoptosis are recognized: premitotic and postmitotic. For each traversed cell, the amount of energy deposited in the nucleus by ionization is calculated and the probability of survival is estimated as suggested by Griffiths *et al.* (1994). If the amount of energy deposited in the nucleus is lethal, the hit cell dies by apoptosis within one simulated hour. Otherwise, the cell induces the repair and tries to survive.

Following a radiation insult in either G₁-, S-, or G₂-phase of the cycle, a basal cell may induce cell cycle arrest to allow time for repair of DNA damage. The model calculates the time needed for repair based on the number of single-strand breaks (SSB) and double-strand breaks (DSB) produced in the cellular DNA. The yield of DNA breaks produced by radiation is reported to be about 40 DSBs and about 1000 SSBs per cell per Gy (Foray *et al.*, 1999; Ward, 1990). The number of the SSBs and DSBs produced in the cellular DNA is estimated from the specific energy deposited in the cell nucleus. The repair times for the SSBs and DSBs were estimated from the data reported by others.

To see whether the damaged epithelial cells accumulate in the bronchiolar tissue over time, the exposure to α -particles emitted by the

radon daughters Po-214 and Po-218, was simulated for 5-year period. The activity of Po-214 and Po-218 resulting from an exposure of 1 WL (working level) with atmospheric characteristics typical of mines was adopted from Harley (1998). One WLM is exposure of 1 WL in 170 h per month. We did not observe the accumulation of potentially damaged cells, i.e. cells hit by α -particles or descendant of such cells, over 5-year period (Figure 9).

Figure 9. Number of potentially damaged cells (hit cells or descendents of the hit cells) present in the epithelium at each hour over the simulated exposure period. Low-dose exposure to Po-214 and Po-218 α particles was simulated over 5-year period (1 WL exposure rate). A section of bronchiole used in this virtual experiment has 4590 basal cells and 10746 ciliated and secretory cells. Cell density is $1.9\text{E}+6/\text{cm}^2$.

To see whether the bronchiolar epithelial cells suffer damage from internally deposited β -particle emitters, the exposure to β -particles has been simulated for one year period. The daughter products of Rn-222 include Pb-214 and Bi-214 that are β - and γ -emitters. The average energies of β -particles emitted by these radio-nuclides vary from 0.02 to 1.27 MeV. Therefore, the exposure of the bronchiole was modeled for β -particles with energies 0.05, 0.1, 0.2, 0.5, 1.0, and 1.25 MeV. The average total number of potentially damaged epithelial cells produced by β -particles with different kinetic energies is about 380 cell/hour, which is much greater compared to the value calculated for α -particles (1 WL exposure rate). However, the average energy deposited by α -particles to the cell nucleus is about 200 times larger than the average energy deposited by β -particles. There is no cell killing by β -particles at low-dose exposures.

The average energies of γ -particles emitted by Pb-214 and Bi-214 radio-nuclides vary from 0.01 to 3.3 MeV. The representative energy values were picked based on the relative intensity of the γ -ray emission. It was found that a negligible amount of energy has been deposited in the nuclei of the cells of the bronchiolar epithelial layer. Hence, for the purposes of assessment of radiation damage to the cells of the bronchiolar epithelium, the exposure to internally deposited γ -emitters can be ignored.

Conclusions

The combined model of tissue kinetics and radiation response of human bronchiolar epithelium has been developed. The novelty of the approach used was to build the bronchiolar epithelial tissue construct from bottom up, cell by cell, taking into account geometric and morphometric parameters of human bronchioles and cells populating the bronchiolar epithelium. The model describes the bronchiolar epithelial

tissue kinetics and allows simulating the long term exposure to ionizing radiation. Validation of the model has been carried out by comparison the calculated values and the experimental data obtained by others. The model output results for the bronchiolar tissue kinetics are in good agreement with the reported experimental values. The model can be used to trace the accumulation of damage in the cells of the bronchiolar epithelium following exposure to different types of ionizing radiation. The model was used to simulate internal exposure to some of the daughter products of Rn-222. It was found that damaged cells **do not** accumulate in the bronchiolar epithelium following low-level exposure to α -particles (Po-214, Po-218) or β -particles (Pb-214, Bi-214).

The results of this research were presented as an invited talk in Risks and Modeling of Low Doses Mini-Symposium at the Radiation Research Society Annual Conference in Denver, Colorado, October 16 – 19, 2005. A doctoral dissertation has been accepted and published as a result of this research.

Natela Ostrovskaya, *Development of a combined model of tissue kinetics and radiation response of human bronchiolar epithelium with single cell resolution*, Texas A&M University, Department of Nuclear Engineering August 2005.

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Patents: **NONE**

Milestone Status Table: This should be a complete list of project milestones, anticipated completion dates and actual completion dates. The milestone identification number should correspond to the task numbers in your agreement to aid in tracking (example below).

ID Number	Task / Milestone Description	Planned Completion	Actual Completion	Comments
1	Phase 1			
1.1	Probability Distributions	3/1/03	3/1/03	
1.2	Initial 4D model	5/31/03	5/1/03	
1.3	Annual Report	8/31/03	8/28/03	
2	Phase 2			
2.1	Experimental Testing	3/1/04	9/04	
2.2	Radiation Exposure Modeling	5/31/04	10/04	
2.3	Annual Report	8/31/04	8/28/04	
3	Phase 3			
3.1	Revise Model	12/1/04	12/04	
3.2	Test Model	4/30/05	6/05	
3.3	Final Report	10/31/05	10/05	

Budget Data (as of date): The approved spending should not change from quarter to quarter. The actual spending should reflect the money actually spent on the project in the corresponding periods.

			Approved Spending Plan			Actual Spent to Date		
Phase / Budget Period			DOE Amount	Cost Share	Total	DOE Amount	Cost Share	Total
	From	To						
Year 1	6/02	5/03	\$97,492	\$0.00	\$97,492	\$71,001.80	\$0.00	\$71,001.80
Year 2	6/03	5/04	\$94,888	\$0.00	\$94,888	\$96,841	\$0.00	\$96,841.00
Year 3	6/04	8/05	\$96,881	\$0.00	\$96,881	\$118,667.12	\$0.00	\$118,667.12
Totals	6/02	8/05	\$289,261	\$0.00	\$289,261	\$286,509.92	\$0.00	\$286,509.92

Spending Plan for the Next Year:

Month	Estimated Spending
Not Applicable	