



## Dosimetry for *in vivo* studies of the effects of low doses of ionizing radiation in humans

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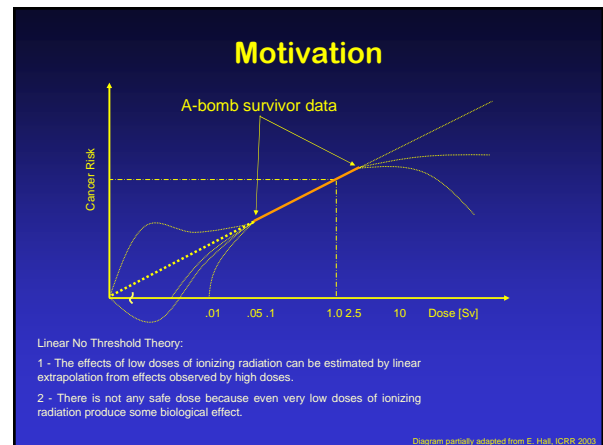
Summary

## Acknowledgements

UC Davis	Zelanna Goldberg Robin Stern Allison Santana Susanne Berglund Chad W. Schwietert
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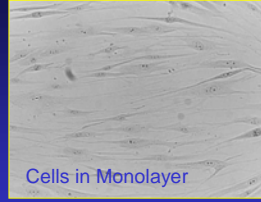
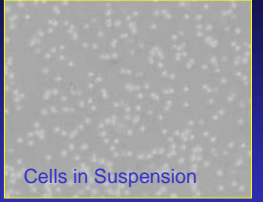
## Motivation

Knowledge of low dose effects impacts risk assessment

- shielding requirements for facilities from submarines to hospitals
- use of radiation in diagnosis and therapy
- regulations regarding handling of radioactive materials
- response to naturally occurring radioactive materials (Radon)
- ...

→ need low dose research !

## Limitations of in vitro studies

Cells in Monolayer
Cells in Suspension

- Artificial substrates / physiological fluid surrogates
- Usually single cell type, often immortalized or transformed
- Lacks vascular perfusion/innervation

Images courtesy of Chad W. Schwietert

### Cells in tissues

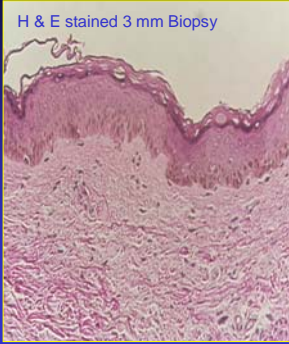


Image courtesy of Chad W. Schwieter

**H & E stained 3 mm Biopsy**

**Epidermis:**

- keratinocytes, melanocytes, dendritic cells, nerve cells, hair cells, secretory columnar epithelial cells

**Dermis:**

- fibroblasts, myofibroblasts, endothelial cells, smooth muscle cells, dendritic cells, nerve fibers, inflammatory /immune cells (macrophages, PMN, eosinophils, mast cells, B & T lymphocytes), collagen fibers, and elastin fibers

### Motivation


To allow the incorporation of in vitro data into risk assessment models translational data in humans must be obtained.

Humans are irradiated daily for the treatment of their cancers and provide a population where prospective data can be obtained.


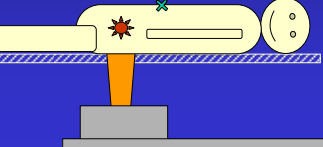
Radiotherapy patient volunteers offers a wide range of dose points if one can find out where to take the sample (pre-specified dose, good accessibility).

→ need human data ! .. and have an idea how to get it !

### Sampling approach



To assess the biological effects of low dose radiation on humans, skin tissues may be sampled outside the primary radiation fields of radiotherapy patients in areas that still receive quantifiable doses.







### Dosimetry Challenge

Identification of tissue areas that will receive a pre-specified low dose of ionizing radiation is essential for the establishment of meaningful dose-response curves.

Doses in the range of 1-10 cGy are of particular interest for biological investigation.

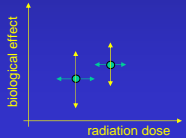
Locations are outside the treatment field.

### Motivation

Given that the irradiation of biological material is quantified with a physical dose and that observed biological effects are related to this dose, the accuracy of the physical dosimetry is very important .

Results in radiation biology are only as good as the radiation dosimetry they are based on.



Good radiation dosimetry ensures small dose bins / error bars and therefore reliable conclusions.


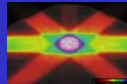
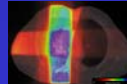
→ physics is crucial !

### Plan A Dosimetry Approach

Clinical treatment planning systems are not designed to accurately describe the locations of low dose areas (such as 0.5% of max dose).

Monte Carlo simulations with the PEREGRINE system were used to identify areas of the skin that receive low dose IR delivered in radiation therapy.

PEREGRINE was developed at LLNL and has been FDA approved for clinical use. It has been licensed to Nomos Corp. The PEREGRINE research center is now located at UCDMC.

### Peripheral Dose (PD)

**Dose components**

- head leakage
- scatter from collimators
- phantom scatter

### PEREGRINE Monte Carlo

The code samples photons and electrons from a source and tracks them through the patient using random numbers and microscopic particle-interaction probabilities.

### PEREGRINE Monte Carlo

As each particle interacts, it sets in motion other particles that are also tracked; and the code sums each particle's contribution to the absorbed radiation dose.

### Dosimetry Approach

Out of field dosimetry (peripheral dose) was a new application for the PEREGRINE system.

For verification purposes Monte Carlo simulations were compared to phantom measurements in a clinical setting.

### Measurements

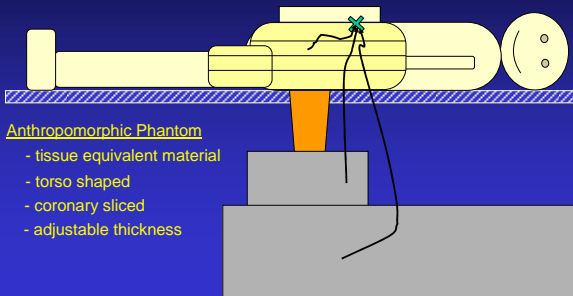
- (1) Monte Carlo calculations were compared to measurements taken using a Farmer ionization chamber in a Solid Water® slab phantom outside a single beam.
- (2) Verification of the entire dosimetry procedure was tested on a newly designed and created anthropomorphic phantom that was set to variable thicknesses to more accurately mimic patient set-up and variation in patient size.

### Measurements

- (2) Verification of the entire dosimetry procedure was tested on a newly designed and created anthropomorphic phantom that was set to variable thicknesses to more accurately mimic patient set-up and variation in patient size.

Calibrated Thermoluminescence (TLD) detectors were used as reference.

### Verification measurements

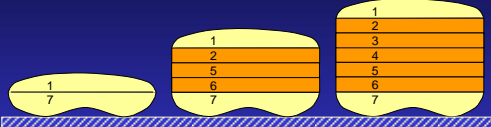


Anthropomorphic Phantom

- tissue equivalent material
- torso shaped
- coronary sliced
- adjustable thickness

### Verification measurements

Radiological PHantom with Adjustable Thickness (RPHAT)



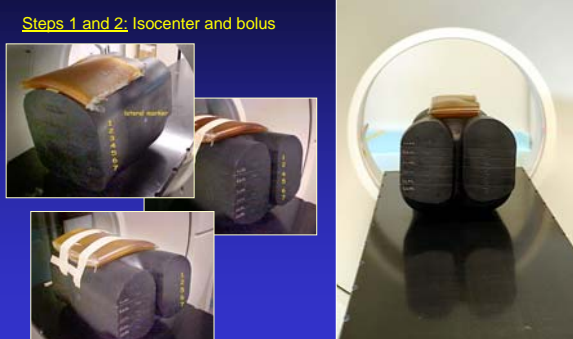
- unique slices 1 and 7 always used
- slices 2, 3, 4, 5, 6 optional
- side edge smooth for all combinations

US patent 7,151,252

J Lehmann, R Stem, J Levy, T Daly, Ch Hartmann Siantar, Z Goldberg, "Radiation phantom with humanoid shape and adjustable thickness (RPHAT)," Phys. Med. Biol. 49(9), N125 - N129 (2004).

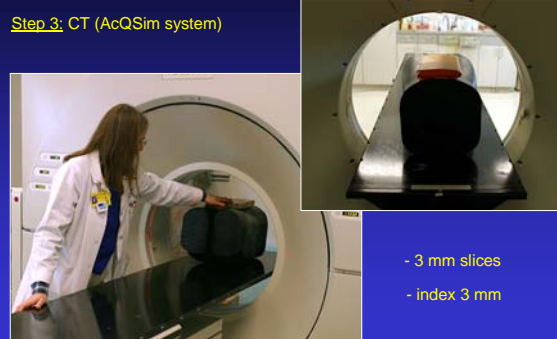
### Verification measurements

Steps 1 and 2: Isocenter and bolus



### Verification measurements

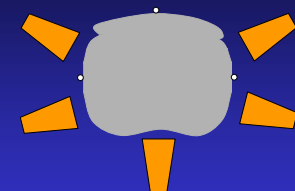
Step 3: CT (AcQSim system)



- 3 mm slices
- index 3 mm

### Verification measurements

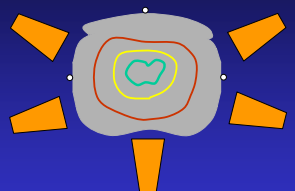
Step 4: Create treatment plan



- transfer CT data to planning computer (AcQSim/AcQPlan)
- find isocenter and mark it in system
- create "regular" prostate treatment plan (5 beams)

### Verification measurements

Step 5: Perform PEREGRINE calculation



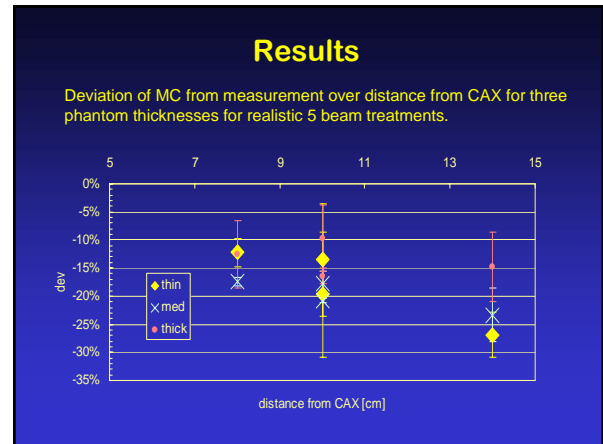
- transfer data to PEREGRINE system
- calculate dose distribution and find appropriate points

## Verification measurements

Step 6: Expose dosimeters with treatment plan



- Measurements with calibrated TLDs for different phantom thicknesses at different distances from CAX at midline
- Five beam setups with and without MLC shaping investigated

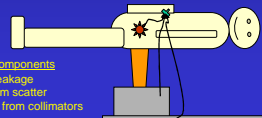


## Discussion

The under-prediction for the 5-beam treatment can best be explained by the fact that the accelerator head outside of the primary beam is not modeled in detail. Thus under-estimation of the contribution of head scatter is expected.

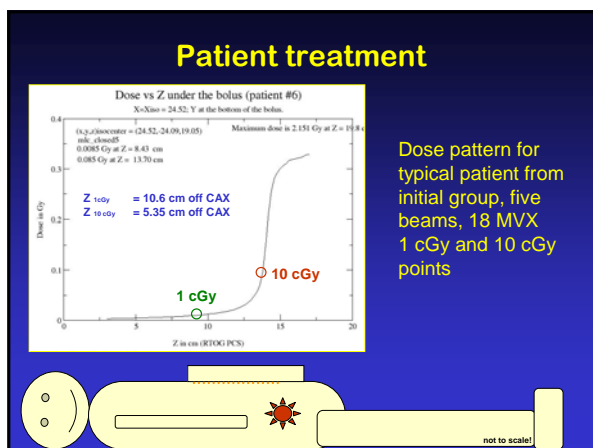
Comparison between PEREGRINE and BEAM/DOSXYZ Monte Carlo code systems showed similar results, suggesting that discrepancies with measurements are not code-specific.

Since the deviation is systematic, it is possible to correct for it with a single factor and allow the biological experiments to proceed.



Dose components

- head leakage
- phantom scatter
- scatter from collimators



### Patient treatment

Second group of patients: Three 1 cGy points



A close-up photograph of a patient's skin. Three yellow adhesive tapes are placed horizontally across the skin. The leftmost tape is labeled '4', the middle one 'b', and the rightmost one '2'. There are small blue markings on the skin between the tapes.

### Patient treatment

Patient with bolus at treatment table



A photograph showing a patient lying on a treatment table. A medical professional is standing by the patient's side, adjusting a white bolus on their back. The patient is wearing a patterned hospital gown.


### Sampling Procedure



cleaning of biopsy site

Two photographs showing the preparation of a biopsy site. The top image shows a hand cleaning the skin with a swab. The bottom image shows a small white square marker placed on the skin.

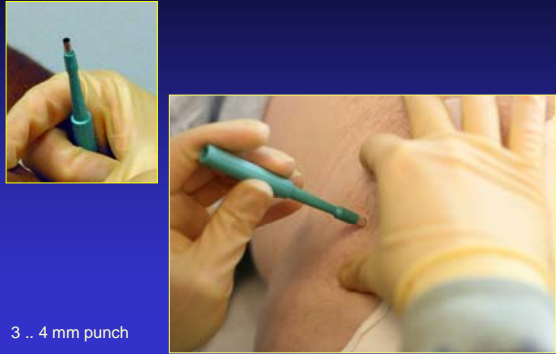
### Sampling Procedure



local anesthesia

A close-up photograph of a hand injecting a small amount of liquid from a syringe into a patient's skin.


### Sampling Procedure



3 .. 4 mm punch

Two photographs showing the use of a punch biopsy tool. The top image shows the tool being held by a gloved hand. The bottom image shows the tool being used to take a sample from the patient's skin.

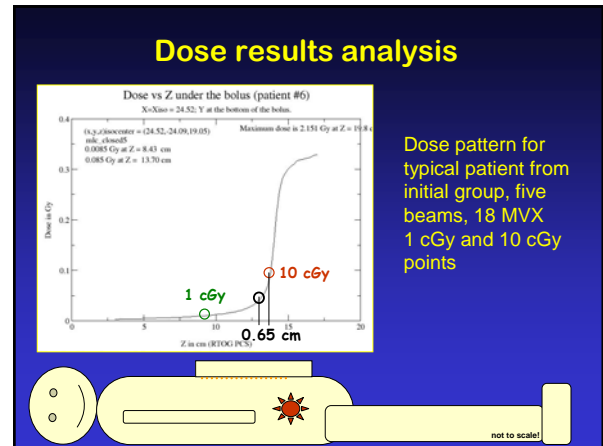
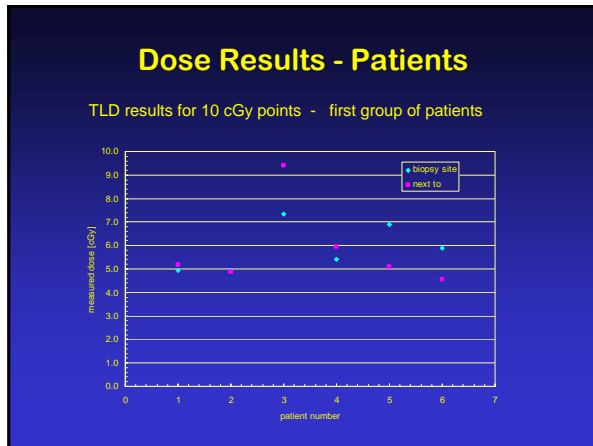
### Sampling Procedure



3 .. 4 mm punch

Two photographs showing the use of a punch biopsy tool. The top image shows the tool being held by a gloved hand. The bottom image shows the tool being used to take a sample from the patient's skin, with tweezers visible in the inset.

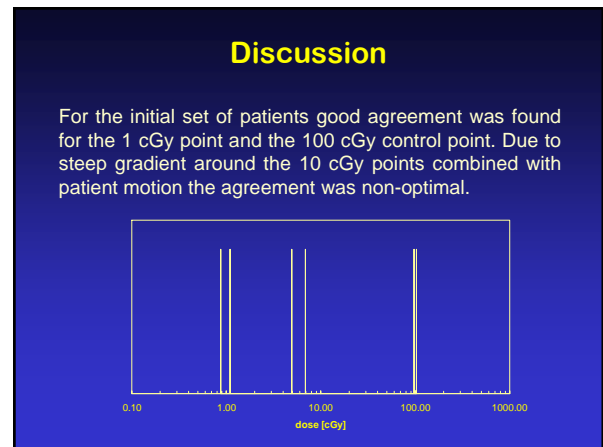




### Discussion

For the initial set of patients good agreement was found for the 1 cGy point and the 100 cGy control point. Due to steep gradient around the 10 cGy points combined with patient motion the agreement was non-optimal.

Desired dose [cGy]	Measured average [cGy]	Standard deviation relative
1	0.98	11 %
10	5.9	17 %
100	100.3	3 %




### Plan B

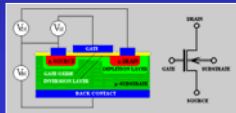
## MOSFET in vivo measurements

metal-oxide-semiconductor (MOS) field effect transistor (FET)

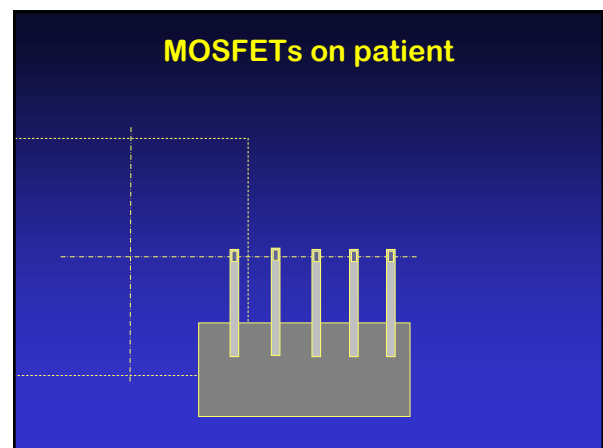
- very small detectors – minimal field distortion
- can be read out immediately after exposure while still on the patient's skin

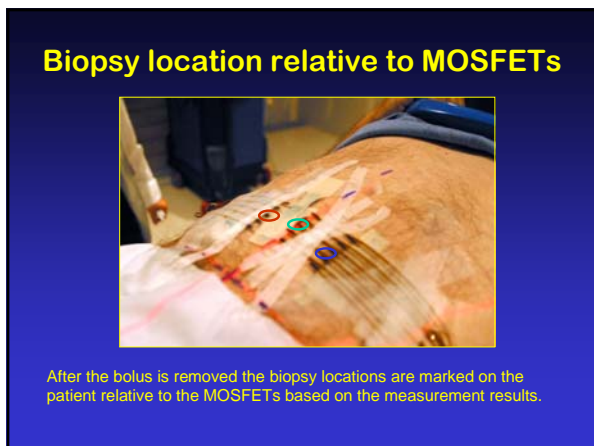
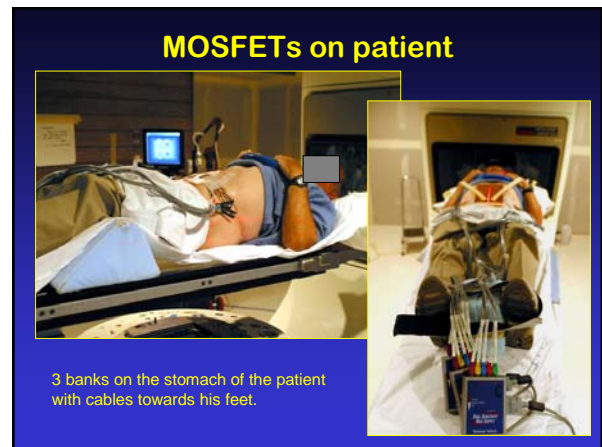
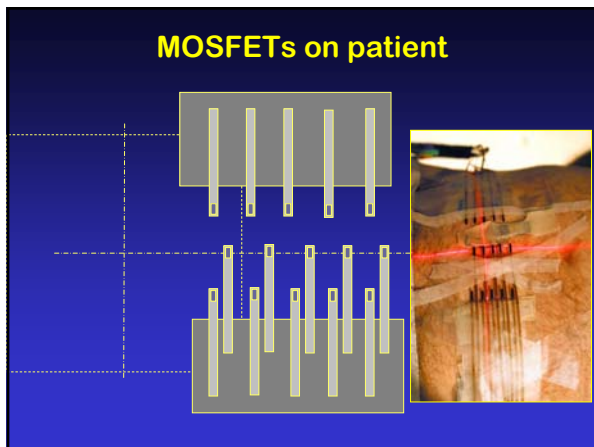
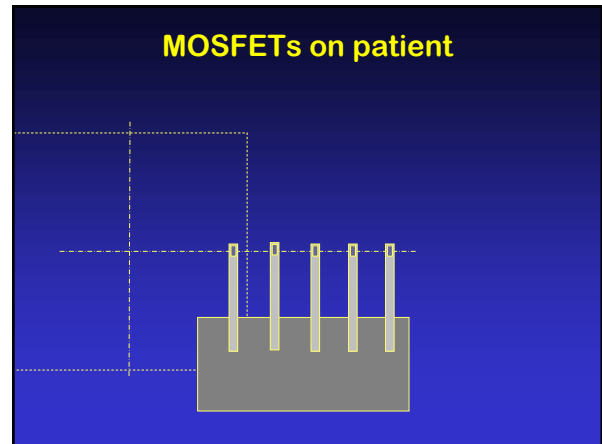
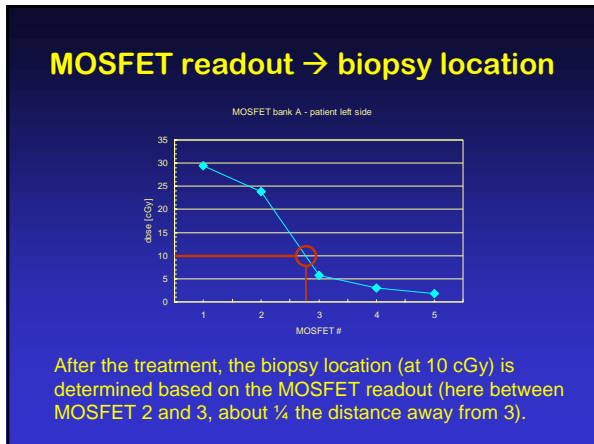


- dose is known precisely, including any patient motion, like breathing
- using an array of MOSFETs the biopsy location can be interpolated **after** irradiation



<http://ece-www.colorado.edu/~bart/book/mosmetro.htm>






### Interim Summary

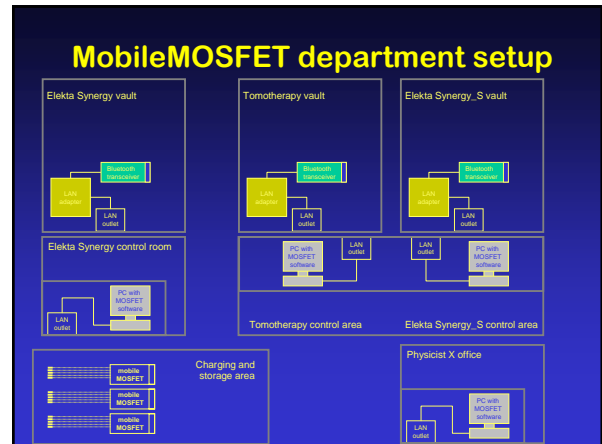
Using PEREGRINE Monte Carlo simulation we can prospectively identify biopsy locations receiving a radiation dose of 1 cGy during radiation treatment (prescription: 2 Gy) with an uncertainty of less than 15% (SD).

Arrays of MOSFET detectors can be used in *in vivo* measurements to find the location of 10 cGy points in the gradient of the field edge.

## MOSFET and MobileMOSFET



AutoSense – stable at 5 cGy and above  
mobileMOSFET – stable down to 1 cGy (0.6 cGy) .




## Summary

Low dose research with radiation therapy patient volunteers enables the collection of translational data in humans.

Solid physical dosimetry is essential for meaningful biological results.

In radiotherapy patients it is possible to identify locations that receive 1 and 10 cGy (0.5 and 5% of prescribed dose) with an uncertainty of better than 15%.



# Thank you!

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### Contact Information

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## Publications

R Stern, J Kurylo, Ch Hartmann Siantar, J Lehmann, and Z Goldberg, "Film dosimetry in the peripheral region using multiple sensitometric curves," *Med. Phys.* 31(2), 327-332 (2004).

J Lehmann, R Stern, J Levy, T Daly, Ch Hartmann Siantar, Z Goldberg, "Radiation phantom with humanoid shape and adjustable thickness (RPHAT)," *Phys. Med. Biol.* 49(9), N125 - N129 (2004).

J Lehmann, R Stern, T Daly, D Rocke, C Schwietert, G Jones, M Arnold, Ch Hartmann Siantar, and Zelanna Goldberg, "Dosimetry for quantitative analysis of low dose ionizing radiation effects on humans in radiation therapy patients," *Rad Res* 165 (2) 240-247 (2006)

Z Goldberg, D Rocke, C Schwietert, S Berglund, A Santana, J Lehmann, R Stern, and Ch Hartmann Siantar, "Human In Vivo Dose Response to Low Dose Low LET Ionizing Radiation Exposure," *Clin Cancer Res.* 12(12) 3723-3729 (2006)

S Berglund, C Schwietert, A Jones, R Stern, J Lehmann and Z Goldberg, "Optimized Methodology for Sequential Extraction of RNA and Protein from Small Human Skin Biopsies" *Journal of Investigative Dermatology*, in press