

# *Late Effects of Particle Radiations*

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*PTCOG 48*  
*Heidelberg, Germany*  
*2 October 2009*



# *Overview of Presentation*

- Brief Review of Particle Late Effects
- Brief Review of Berkeley CPRT Design
- Scope of Clinical Follow-Up
- Challenges & Limitations
- Summary

## *Individuals at risk for late effects of heavy-ion exposure*

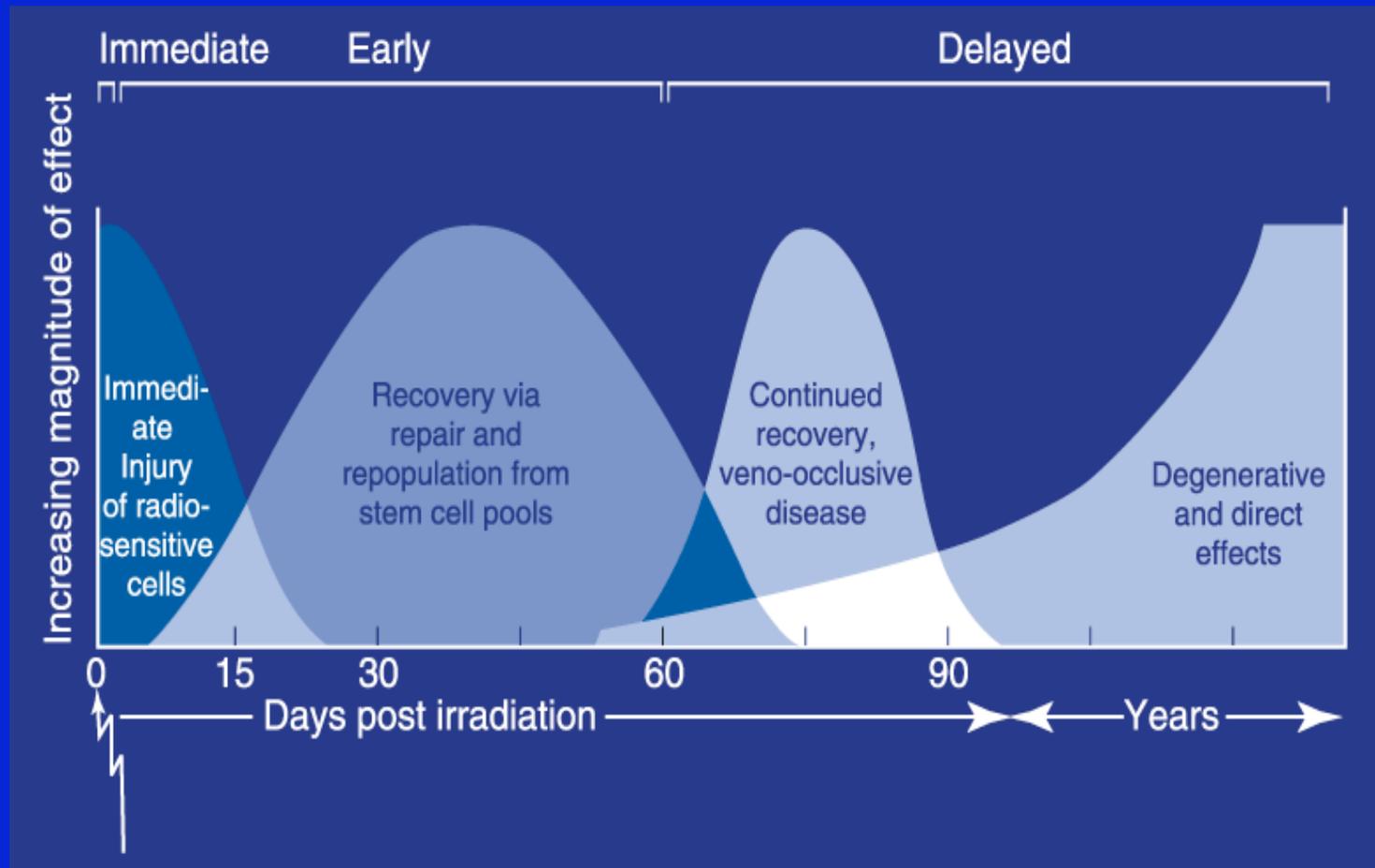
- **Space travelers**

- Whole body exposures to mixed radiation types and ionization qualities totaling  $\ll 1$  Gy protracted over several years

- **Particle radiotherapy patients**

- Partial body high doses  $> 60$  GyE exposures targeted to tumor sites but with lower doses to adjacent normal tissues usually in a 5-day per week regime over the course of several weeks

## *Temporal Relationships Among Somatic Effects*



L. P. Fajardo, M. Berthrong, R. E. Anderson, Radiation Pathology,  
Oxford University Press, 2001.

## *Overview of Radiation Injury in Organs and Tissues*

- **Ionizing radiation injures normal cells through various molecular pathways**
- **In general, the radiation sensitivity of a given tissue, and in turn of a given organ, depends on the radiation sensitivity of the key cells in the system.**
- **Also important in radiation sensitivity are several physical and biological variables: dose size, dose mode (internal or external), dose-rate, fractionation, size of the irradiated field, time of observation after exposure, condition of the stroma and vascular supply, time of observation.**

# *Radiation Lesions*

**IMMEDIATE:** DNA damage in highly sensitive, rapidly proliferating cells

**EARLY:** Progressive necrosis and loss of epithelial cells with denudation of villi, hemopoietic, spermatogonia, and spermatocyte depletion

**LATE:** Epithelial compartment: Atrophy, necrosis, metaplasia, atypia, dysplasia, neoplasia

Stromal compartment: Fibrosis, fibrinous exudate, atypical fibroblasts, lack of cellular inflammatory response

Vascular compartment: Alterations in capillaries and arterioles

**Radiation**

**ROS**

**Redox Proteins**

**DNA**

**Membranes**



**Signal Transduction**

**Cytokine Expression**

**Growth Factor Activation**

**ECM Remodeling**

**Protease Cascades**

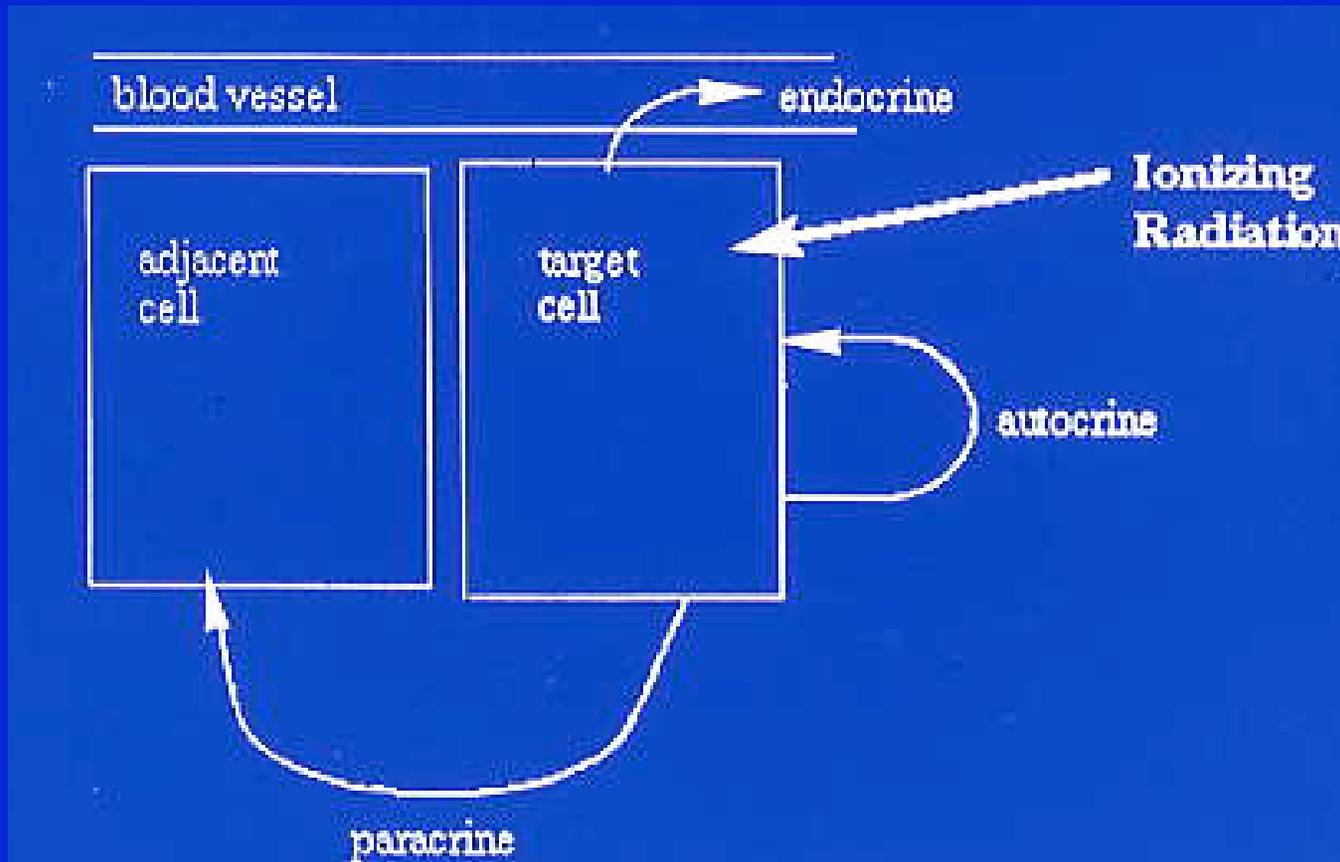
**Apoptosis**

**Transformation**

**Dysplasia**

**Carcinogenesis**

*Radiation can trigger autocrine, paracrine, and endocrine changes*



A photograph of the Space Shuttle Atlantis in space. The shuttle is a small, dark silhouette against a bright yellow background, which is the Earth's surface. The shuttle is positioned in the center-right of the frame. The image is framed by a thick blue border.

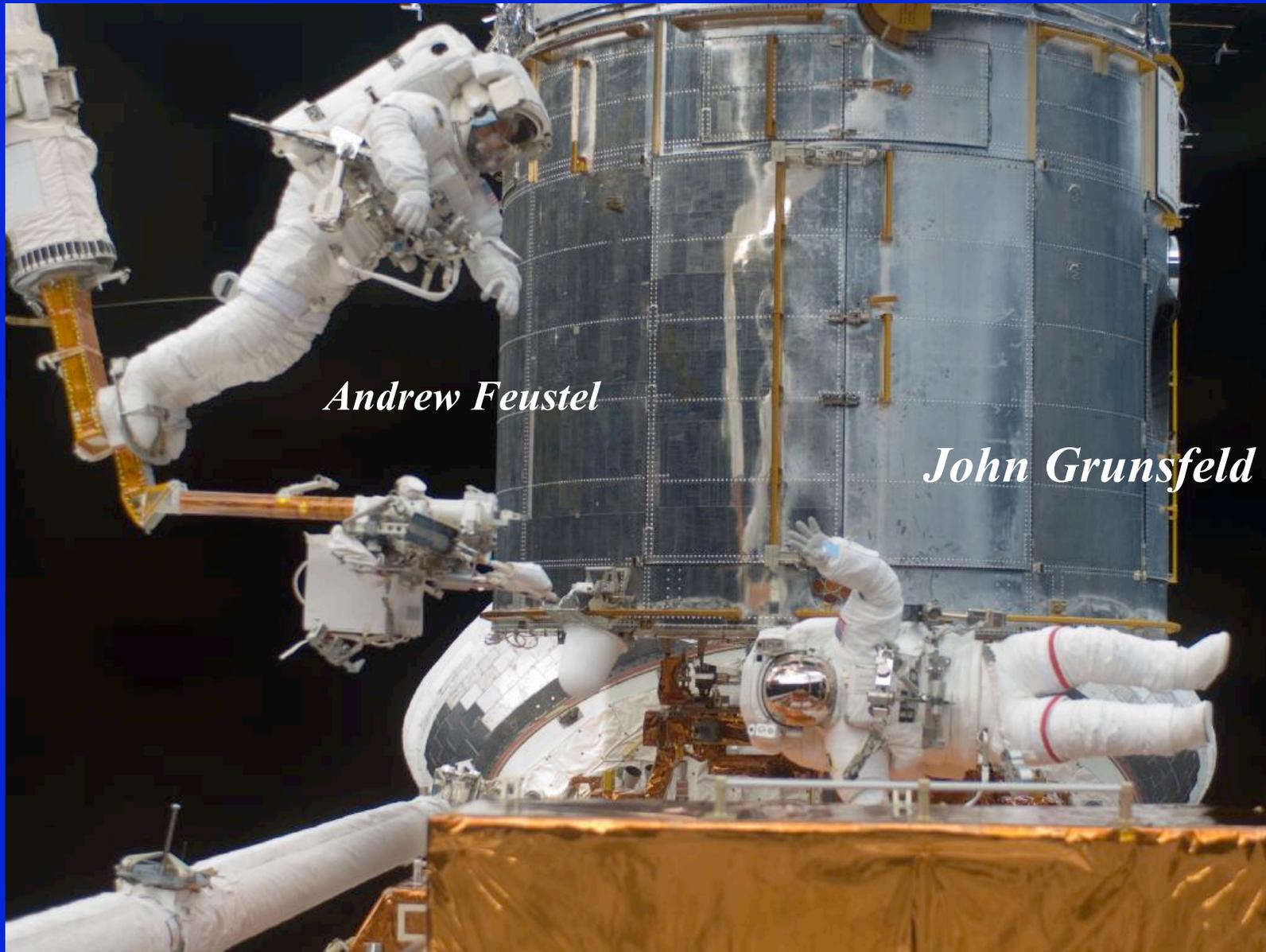
*Space Shuttle  
Atlantis  
May 12, 2009*



*Michael Good*



*John Grunsfeld*



*Andrew Feustel*

*John Grunsfeld*



# *Bioastronautics 2005 Critical Path Roadmap*

## *Radiation Risk Rank*

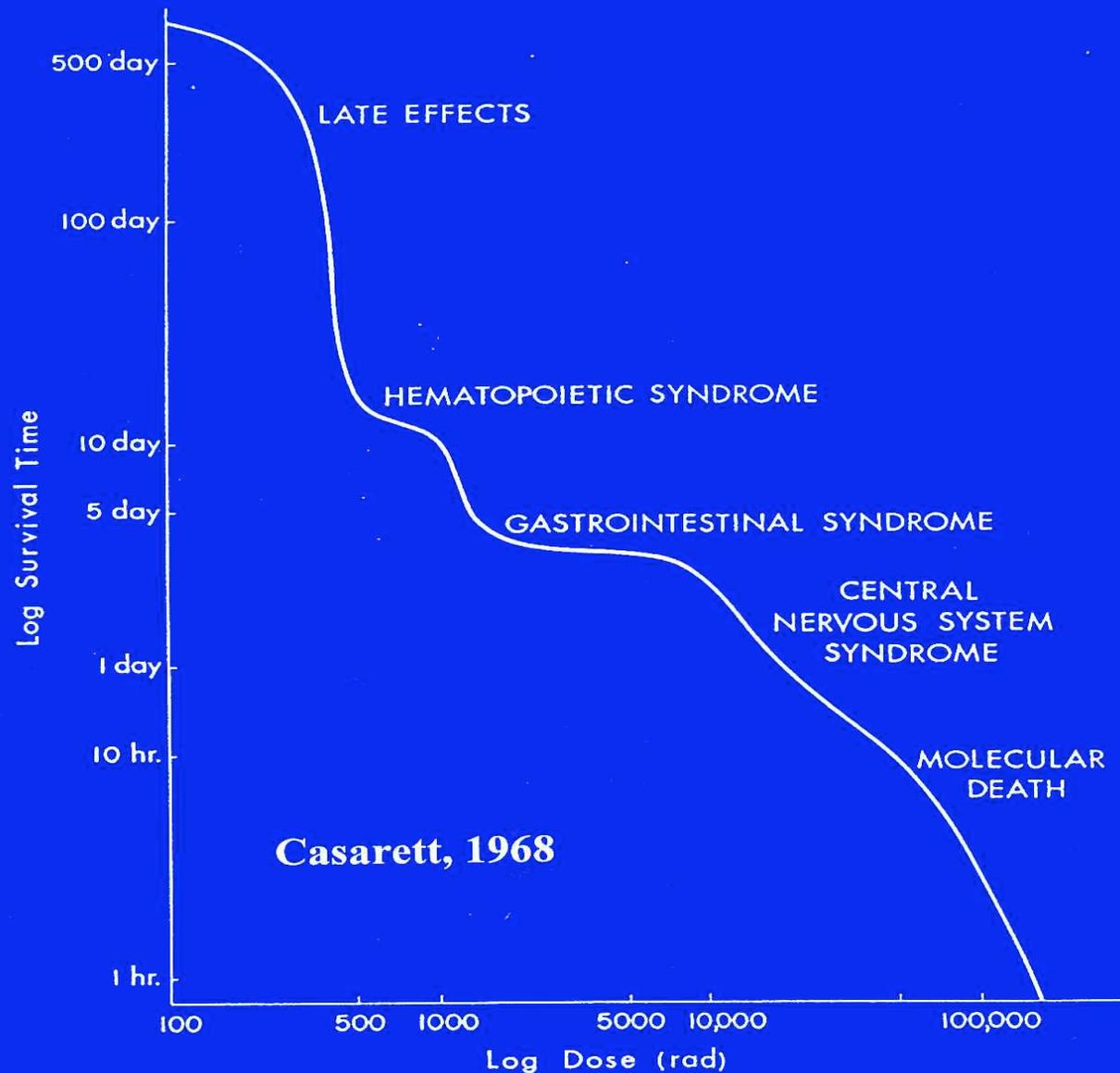
## *Risk*

- |   |                                      |
|---|--------------------------------------|
| 1 | Radiation-induced carcinogenesis     |
| 2 | Central Nervous System (CNS) damage  |
| 3 | Chronic and degenerative tissue risk |
| 4 | Acute radiation risk                 |

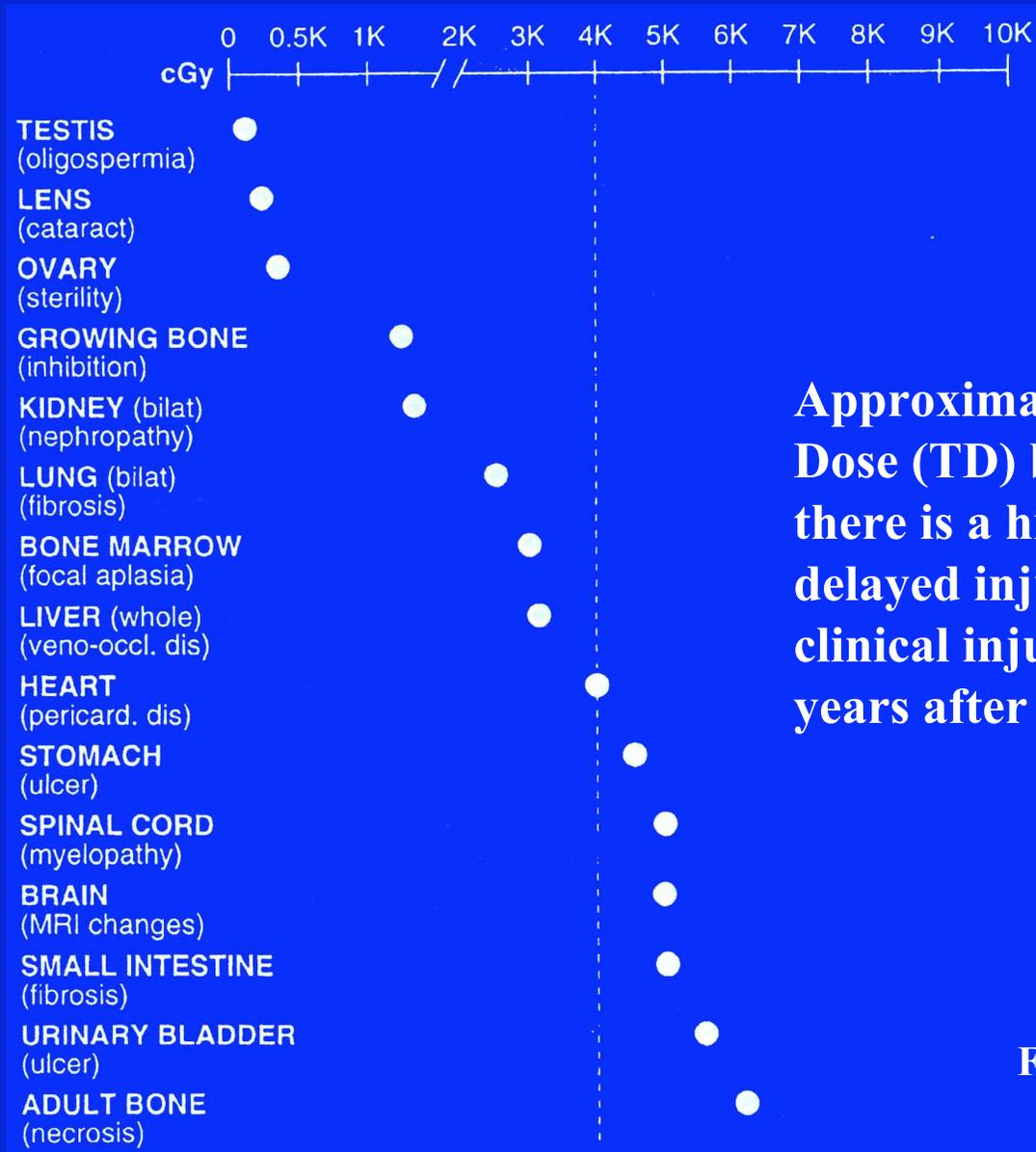
## *Noncancer Chronic and Degenerative Tissue Risks from Radiation*

- Cataract
- Cardiac and vascular damage
- Gastrointestinal effects
- Neurodegeneration
- Fibrosis
- Immunological Effects
- Endocrine Effects
- Hereditary Effects

# Dose vs. Survival Time for Single Total-Body Irradiation of Adult Rats



# Variation in Radiation Sensitivity Among Adult Human Organs



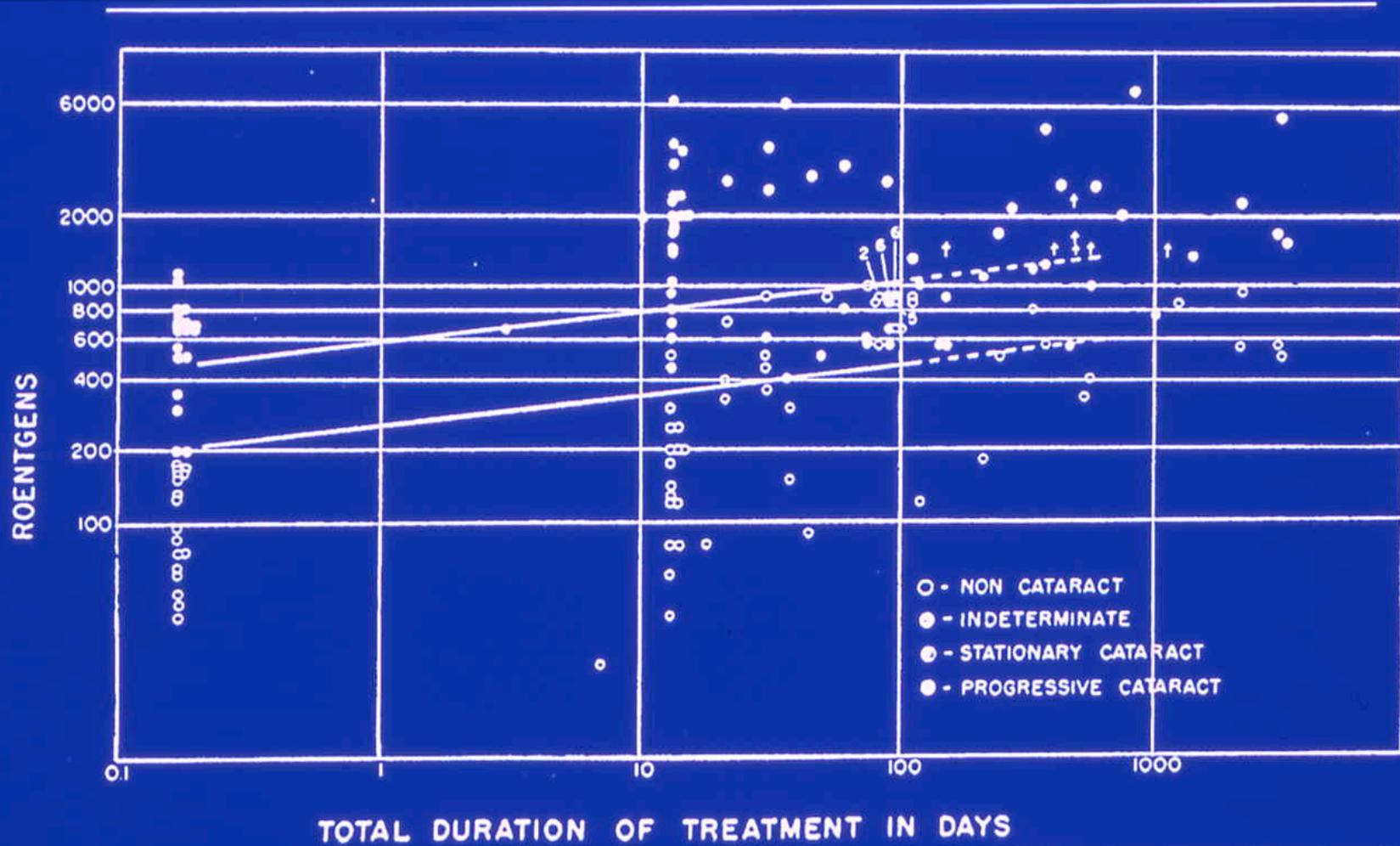
**Approximate Tolerance Dose (TD) beyond which there is a high probability of delayed injury, e.g. 5% clinical injury within 5 years after exposure.**

Fajardo et al., 2001

## *Radiation Cataract in Humans Treated with RT for Cancer*

- Opacification of transparent lens has been attributed to damage of the germinative epithelium resulting in a defective differentiation of lens fiber cells.
  - Clinical cataract incidence has been correlated with percent lens in the radiation field
- Review of RT case histories with lens exposure by Merriam & Focht in 60's indicated no opacities were observed with single acute doses of less than about 2 Gy, with the lens tolerating a higher dose with increased fractionation and overall treatment time.
- There is a dose-dependent latency in the appearance of the opacity after lens exposure, with higher doses showing cataract sooner.

# *Dose for Cataract/Non-Cataract Cases Plotted vs. Overall Treatment Time*



Merriam and Focht, 1962

***Radiation Cataractogenesis:  
A review of recent studies***

Ainsbury EA, Bouffler, SD, Dorr W, Graw, J,  
Muirhead CR, Edwards, AA, and Cooper J

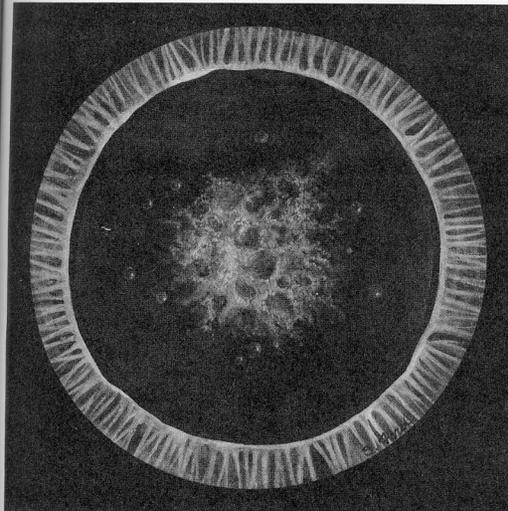
***Radiation Research 172:1-9 (2009)***

## *Conclusions*

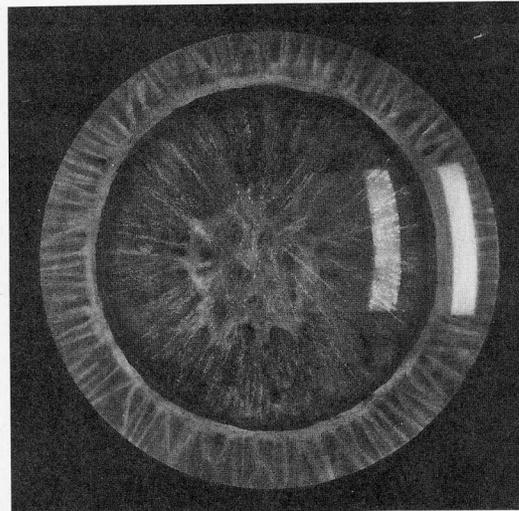
- Etiology of cataracts is not fully known, but is likely multifactorial.
- Much of the published evidence for radiation cataract at low dose is contradictory but pointing to little or no dose threshold.
- Not clear whether a mutational mechanism or one based on lens cell function, differentiation, cell killing and/or death is operating.

Ainsbury et al., 2009

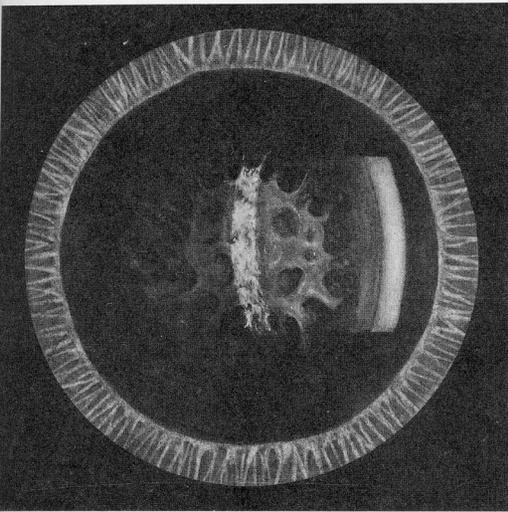
# Radiation-induced Cataract



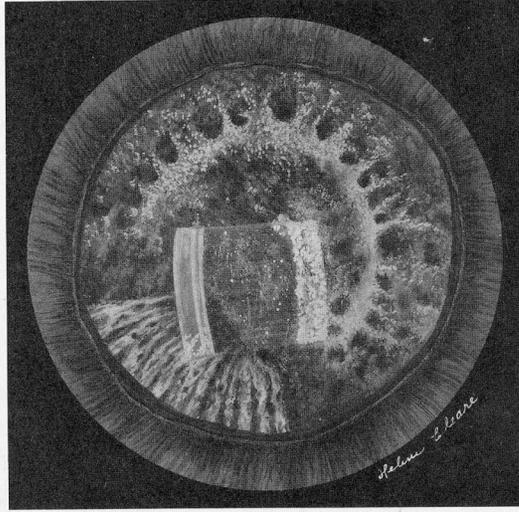
a



c



b

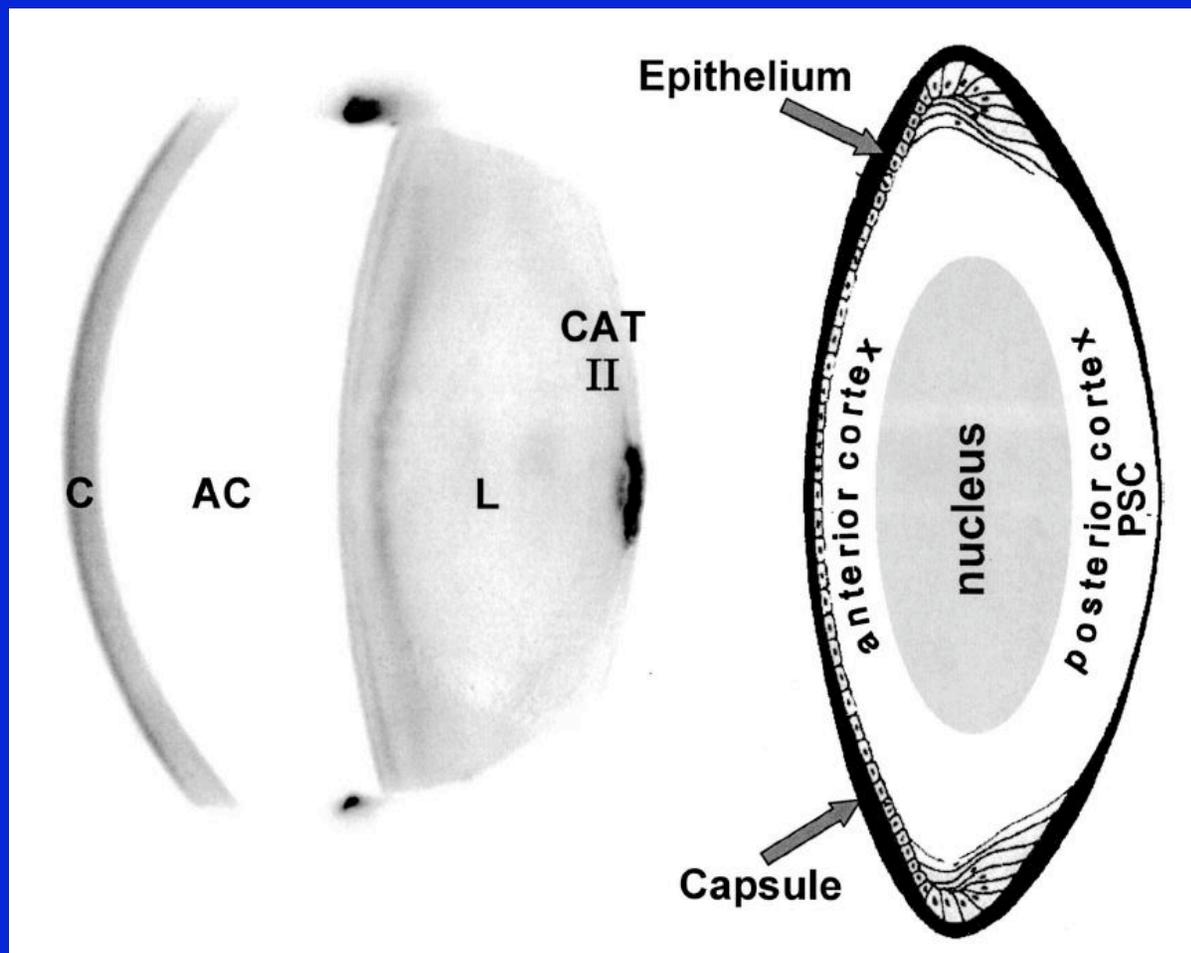


d

- a. early central changes
- b. more dense center
- c. extension to periphery
- d. advanced anterior changes

Gordon et al, 1995

# *Cataract from a Chernobyl Clean-up Worker*



*Worgul et al., Radiat. Res. 167, 233, 2007*

## *Conclusions from Cataract Studies of Exposed Individuals from Chernobyl Accident*

- Linear-quadratic dose-response models yielded mostly linear associations with weak evidence for upward curvature
- The data do not support the ICRP 60 risk guideline assumptions of a 5-Gy threshold for “detectable opacities” from protracted, primarily low-LET, radiation exposures, but rather point to a dose-effect threshold of under 1 Gy.
- Thus, given that cataract is the dose-limiting ocular pathology in current eye risk guidelines, revision of the allowable exposure of the human visual system to ionizing radiation should be considered.

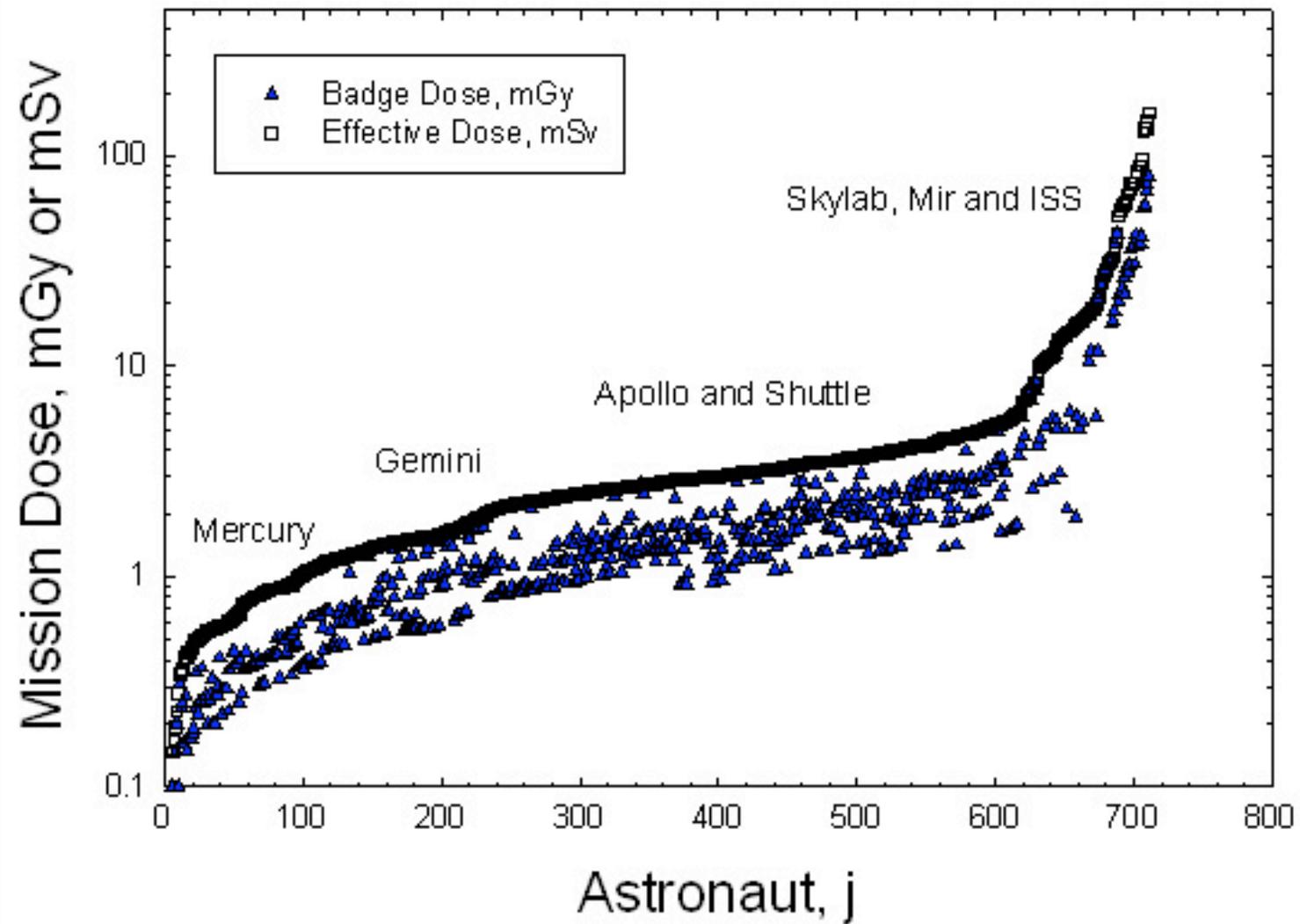
***Worgul et al., Radiat. Res. 167, 233, 2007***

*RADIATION RESEARCH 156, 460-466 (2001)*

## Space Radiation and Cataracts in Astronauts

F.A. Cucinotta,<sup>a</sup> F.K. Manuel,<sup>b</sup> J. Jones,<sup>a</sup> G. Iszard,<sup>b</sup> J. Murrey,<sup>c</sup> B. Djojonegro<sup>c</sup>  
and M. Wear<sup>c</sup>

<sup>a</sup>NASA Johnson Space Center, <sup>b</sup>Kelsey-Seybold Clinic, and <sup>c</sup>Wyle Laboratories,  
Houston, TX 77058



*Cucinotta et al., 2002*

## AVERAGE PERSONNEL-BADGE DOSES AND LENS EQUIVALENT DOSES IN NASA PROGRAMS

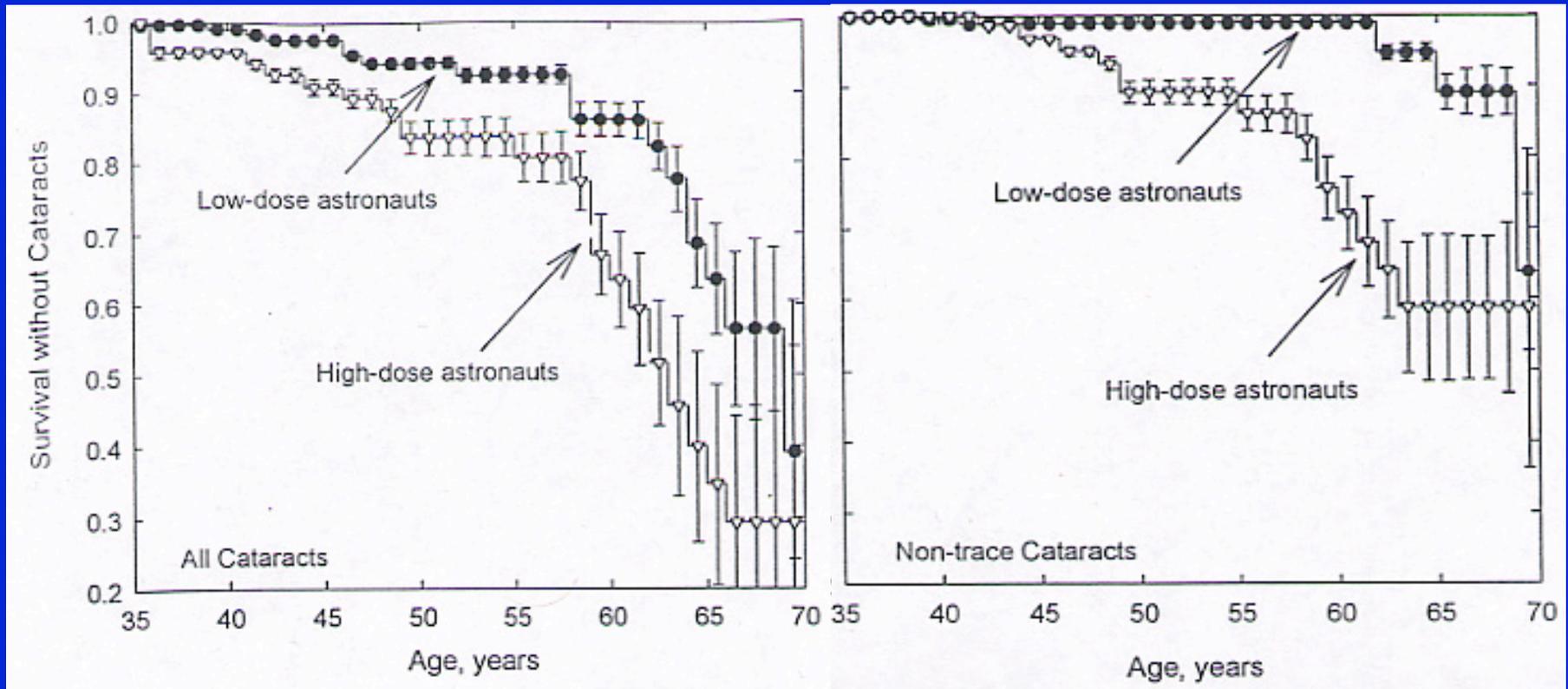
NASA Program	No. of Astronauts	Average Days	Average Badge Dose (mGy)	Average Lens Dose (mSv)
Mercury (33°)	6	0.37	0.1	0.2
Gemini (29°)	20	4.04	1.2	2.0
Apollo	33	9.48	4.1	14.0
Skylab (50° x 435 km)	9	57.2	43.2	87.0
Apollo-Soyuz (50° x 230 km)	3	9.0	1.1	3.1
Shuttle (28.5° < 400 km)	210	8.8	0.9	1.7
Shuttle (28.5° > 400 km)	84	7.8	9.7	12.0
Shuttle (39°)	50	12.7	1.3	2.8
Shuttle (>50°)	233	8.7	1.7	3.6
NASA-Mir (51.6° x 350 km)	7	120.1	43.1	91.0

Cucinotta et al., 2001

# Probability of Survival Without Cataracts as a Function of Age

Low-dose group:  
Avg 3.6 mSv

High-dose groups:  
Avg. 45 mSv



Cucinotta et al., 2001

***Relative Hazard Ratios at Age 60 Comparing the High-Dose Group to the Low-Dose Group***

Cataract type	Lens dose from all radiation sources	Lens dose from space radiation only
All	1.51 (0.64, 3.59)	<b>2.35 (1.01, 5.51)</b>
Non-trace	2.47 (0.76, 8.01)	<b>8.04 (2.51, 25.7)</b>
Cortical or dot	1.64 (0.51, 5.27)	1.44 (0.46, 4.65)
Nuclear	0.83 (0.18, 3.81)	3.47 (0.79, 15.3)
PSC	1.1 (0.67, 18.1)	5.76 (0.97, 34.2)
PSC, Nuc or Mixed	1.33 (0.37, 4.83)	<b>3.73 (1.05, 13.3)</b>

## *Rationale*

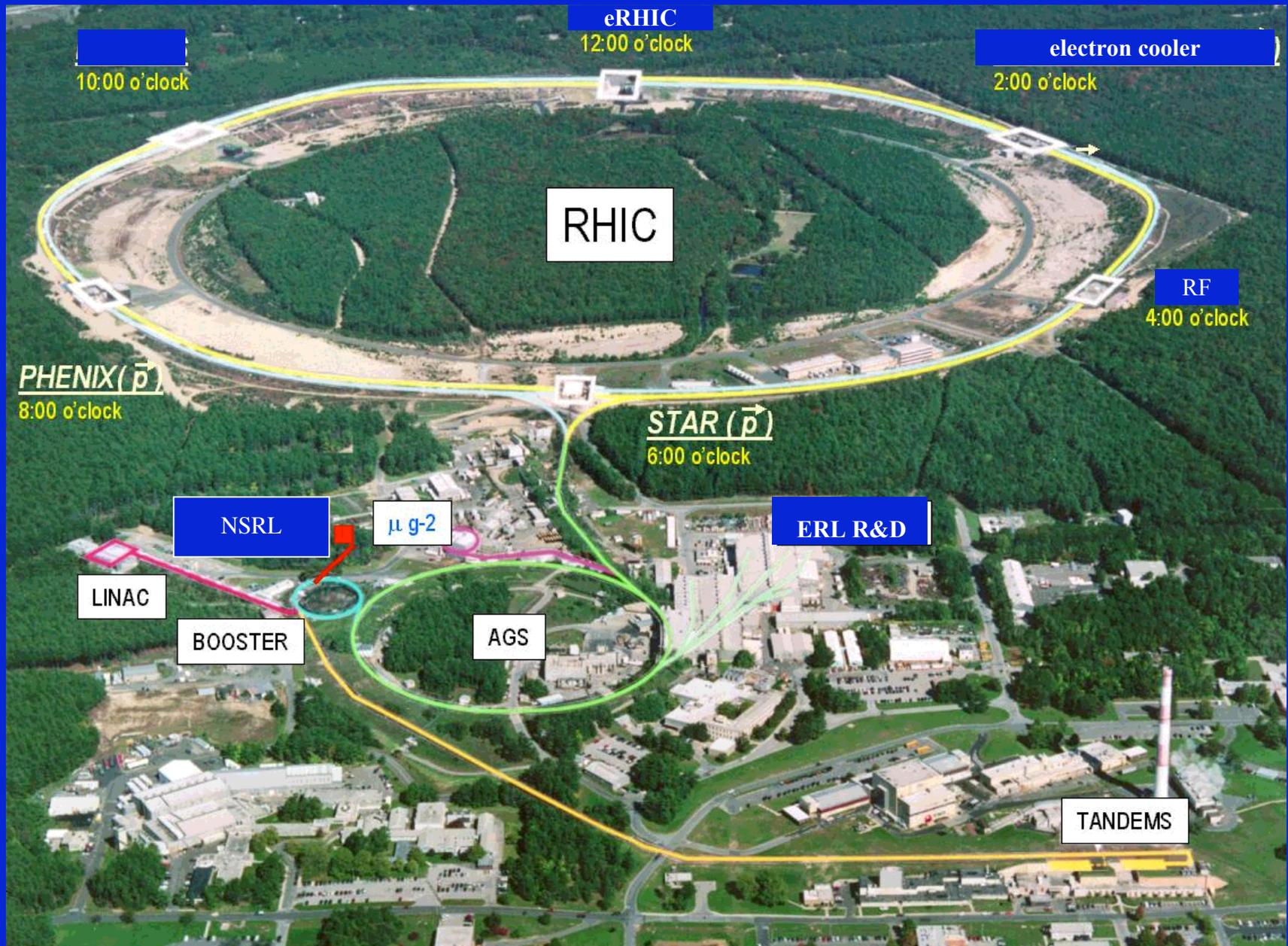
*-Radiation can cause cataract.*

*-There is a dose-dependent latency after radiation exposure before cataract appears.*

*-At low doses the latency is longer.*

*-It has been assumed that not much happens during this latency period.*

*-We are studying molecular antecedents to frank cataract during the latency period to identify molecular markers early enough to allow biological countermeasures to be devised*



*Brookhaven National Laboratory, Upton, NY and  
NSRL--NASA Space Radiation Laboratory*

# Risk Of Late Effects

- Is there a rat strain difference in radiation-induced susceptibility to mammary carcinomas & benign tumors?
- Compared four rat strains:  
(ACI, F344, Sprague-Dawley, Wistar)  
irradiated with 0.05-2 Gy  $\gamma$ -rays or  
peak 290 MeV/amu carbon ions

Imaoka et al., *Int. J. Radiat. Oncol. Biol Phys*, 2007

# Risk Of Late Effects

- Carbon ions significantly induced mammary carcinomas in *Sprague-Dawley* rats, but less so than in other strains
- Dose-effect relationship for carcinoma was concave downward with an RBE of 2.0 at therapeutic dose fraction, but an RBE of 10 at low doses

Imaoka et al., *Int. J. Radiat. Oncol. Biol Phys*, 2007

# Risk Of Late Effects

- Immunohistochemically, 14 of 18 carcinomas were positive for estrogen receptor  $\alpha$ . All carbon-induced carcinomas were free of common *H-ras* and *Tp-53* mutations
- Lung metastasis of 7 % was characteristic of carbon-ion irradiated rats

Imaoka et al., *Int. J. Radiat. Oncol. Biol Phys*, 2007

# Risk Of Late Effects

- Data show clear genetic variability in the susceptibility to carbon-ion-induced mammary carcinomas.
- This makes a clear point for the importance of precise dose localization in carbon radiotherapy
- Lack of common point mutations in **H-ras** and **Tp53** in carbon ion tumors is notable

Imaoka et al., *Int. J. Radiat. Oncol. Biol Phys*, 2007

# Risk Of Late Effects

- Investigated genetic risk of late urinary morbidity after carbon ion therapy in prostate cancer patients looking at single nucleotide polymorphisms (SNPs) in 118 candidate genes and the association with urinary morbidity
- Genetic variations in five genes (**ATM**, **TGF- $\beta$ 1**, **LIG4**, **ERCC2**, and **CYP2D6\*4**) are linked to adverse tissue responses to photons

Suga et al., *Int. J. Radiat. Oncol. Biol Phys*, 2008

# Risk Of Late Effects

- SNPs in five genes were defined as “risk genotypes for carbon genitourinary morbidity” including **SART1, ID3, EPDR1, PAH and XRCC6.**
- Approximately 90% of the patients in the case group with Grade 1 or greater effects had three or more risk genotypes

Suga et al., *Int. J. Radiat. Oncol. Biol Phys*, 2008

# Risk Of Late Effects

- **SART1, ID3, and XRCC6** encode nuclear proteins.
- **SART1** functions as a splicing catalyst of tri-snRNP and in tumor-specific immunity
- **ID3** (inhibitor of DNA binding 3) negatively regulates cell differentiation by inhibiting DNA binding of certain helix-loop-helix transcription factors
- **XRCC6** (X-ray repair complementing defective repair in Chinese hamster cells 6) is also known as KU70 and acts as a DNA helicase II subunit involved in DNA repair, apoptosis, and drug resistance
- **EPDR1** is a putative type II transmembrane calcium-dependent cell adhesion molecule
- **PAH** (phenylalanine hydroxylase) encodes a cytosolic protein that converts phenylalanine to tyrosine

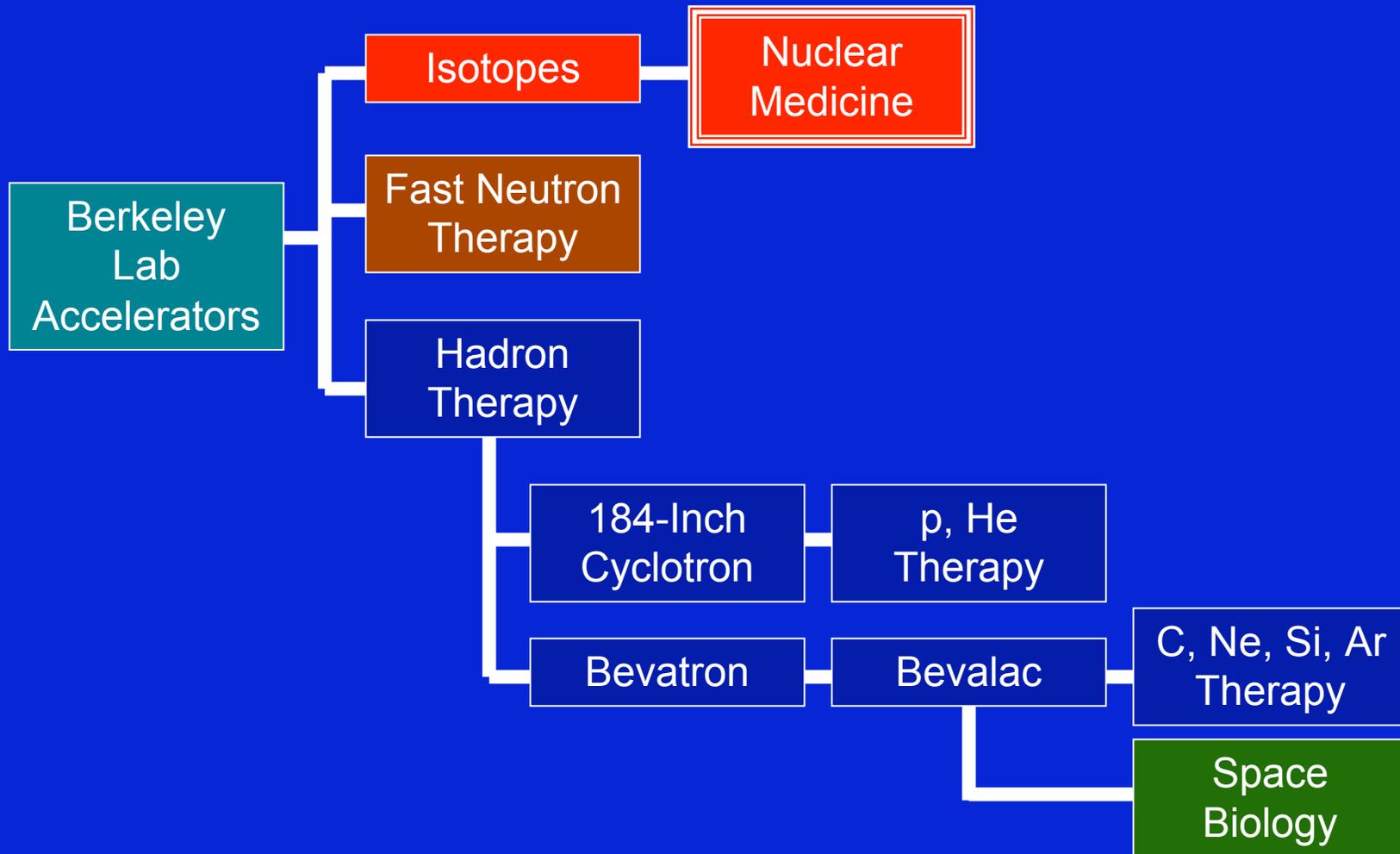
Suga et al., *Int. J. Radiat. Oncol. Biol Phys*, 2008

# Risk Of Late Effects

- The results indicate that patients with late urinary morbidity after carbon ion radiotherapy can be stratified according to the total number of risk genotypes they harbor.
- This study involved 197 prostate patients and 227 healthy donors.
- Multiple loci appear to contribute to the risk of urinary morbidity.

Suga et al., *Int. J. Radiat. Oncol. Biol Phys*, 2008

# *Biomedical Research at Berkeley Lab*



# *Milestones in Hadron Therapy at LBNL*

1955	1975	1976	1977	1982	1987	1992
Pituitary Treatment	1st He pt		1st C, Ne pt Eye treatment			
		Phase-1 He	Phase I-II Ne	Phase I-II Ne & He		
		1st Comp Tx Plan			3D planning	
			LBNL CT	LBNL MRI		
					Image Correlation	

*Late Effects Follow-Up of Charged  
Particle Radiotherapy Patients*

HSC IRB approval 10 March 2009

## *Motivation & Goal of Late Effects Follow-Up*

- The Berkeley Charged Particle Radiotherapy Trials of 1975-1992 represent the earliest particle-treated cohort.
- Follow-up of these patients ended shortly after 1993 with the forced closure of the BEVALAC, despite an outstanding review of the NIH medical/biology part.
- UCSF's Dept of Radiation Oncology in the Helen Diller Comprehensive Cancer Center recently supported effort at LBNL to initiate a retrospective evaluation of these patients 20-30 years after treatment.

# *Clinical Trials at LBNL-UCSF*

*1975–1992*

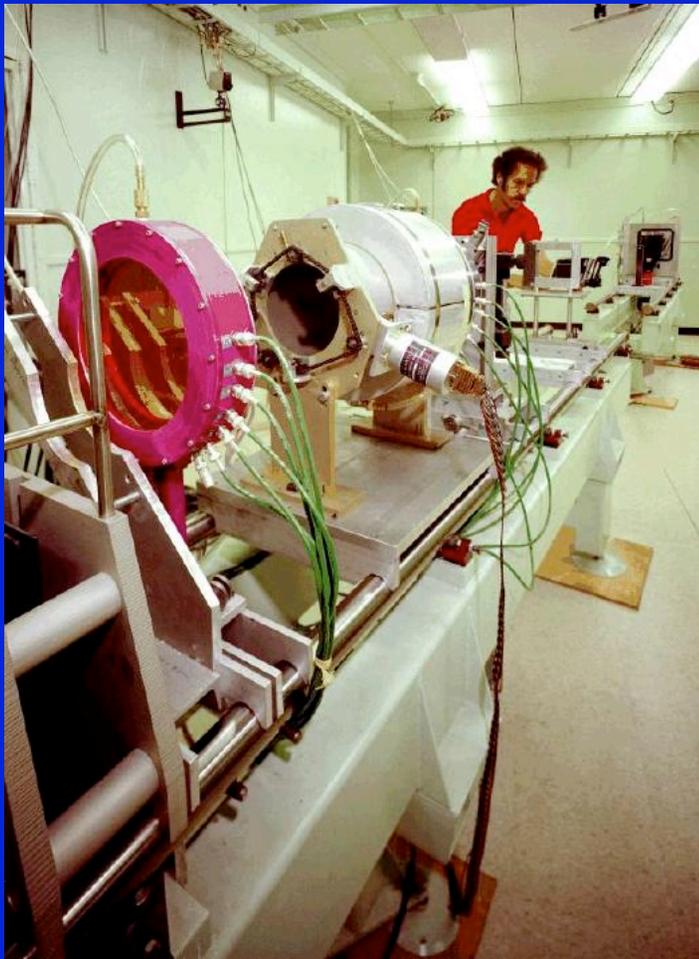


*Joseph Castro, MD  
Radiation Oncologist,  
who conducted the  
LBNL clinical trials.*

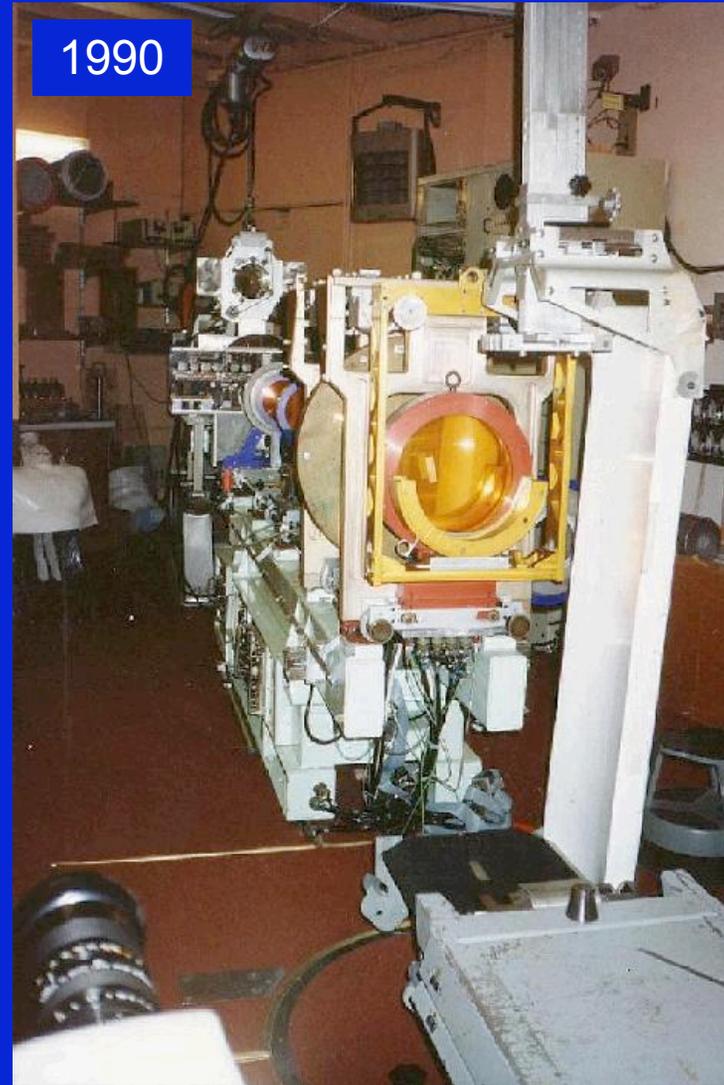
<i>1st He patient</i>	<i>6/75</i>
<i>1st C patient</i>	<i>5/77</i>
<i>1st Ne patient</i>	<i>11/77</i>
<i>1st Ar patient</i>	<i>3/79</i>
<i>1st Si patient</i>	<i>11/82</i>
<i>Total patient treated 1977–1992</i>	<i>1314</i>
<i>He patients</i>	<i>858</i>
<i>Heavier ions</i>	<i>456</i>

# *Charged Particle Treatment at Bevalac*

The patient-treatment beam line.  
1975



1990



## *PEBAs Developed at Berkeley*



*The PEBA camera has served as a preliminary model for larger, more sensitive cameras at GSI that are used quite extensively in their light-ion treatment trials.*

# *Development of Therapy Delivery Methods*

- *Tumor Localization*

- *Tumor localization by CT, MRI, PET and radioactive beam produced at the Bevatrac*
- *Patient immobilization and verification of beam delivery through accurately transferring information among these data sets.*

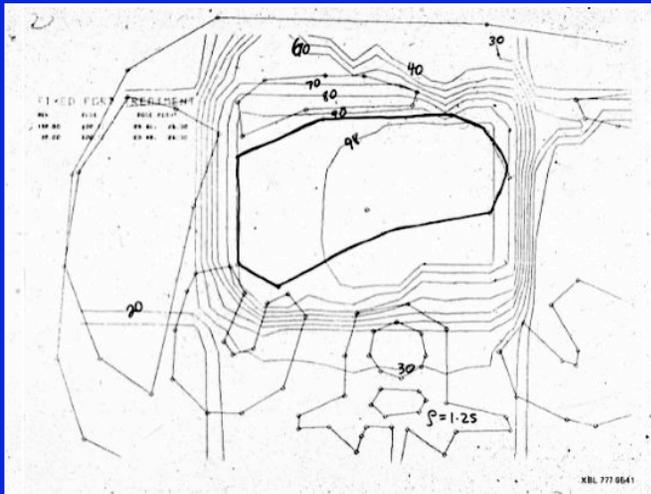
- *Beam Delivery Methods*

- *Wobbler*
- *Raster scanner*
- *3D conformal therapy delivery*

- *Beam-Delivery Control Code and Therapy Planning Code*

- *The computer code used to control the beam in the human therapy facility was an innovative system of the highest quality*
- *Unblemished safety record in human cancer therapy*

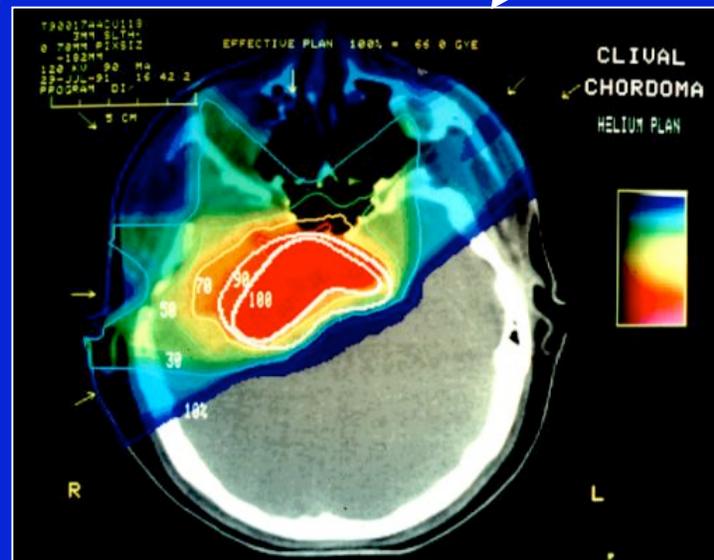
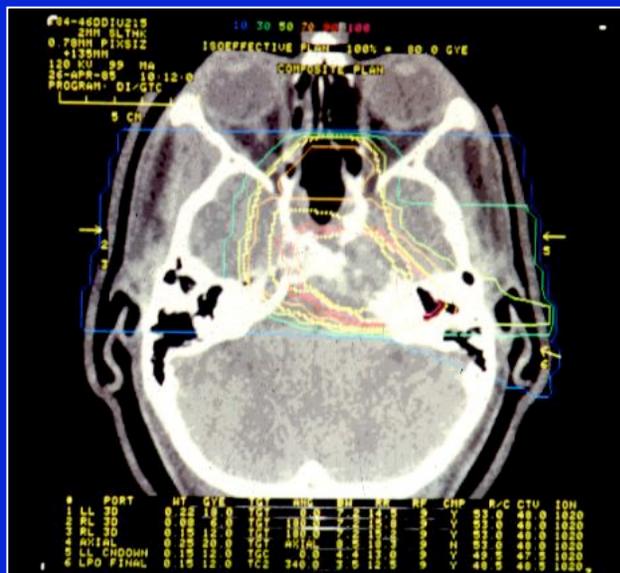
# Evolution of Therapy Planning



1977

1985

1992



# Clinical Trial Results at LBNL-UCSF, 1975-1992

## *HELIUM IONS*

- *We have clearly demonstrated that the use of helium ions at LBNL (and protons elsewhere) is of value in the treatment of unresectable or partially resectable neoplasms in critical locations such as the orbit, eye, skull base, head and neck, juxtaspinal area, retroperitoneum, biliary tract and pelvis.*
- *The measured and safe clinical implementation of proper techniques led to outstanding success in treating skull base and juxtaspinal tumors with an unparalleled (in the past) control and higher rates survival.*
- *The hallmark of charged particle therapy with protons and helium ions is precise dose localization with tight margins to spare normal tissues.*
- *The LBNL/MGH/PSI results formed a model for future applications with charged particles.*

## *Clinical Trial Results at LBNL-UCSF, 1975-1992*

### *HIGH-LET CHARGED PARTICLES*

- *At LBNL, several high-LET ions were available. Neon ions were chosen for the most extensive use although carbon, silicon and argon were tried in a few patients.*
  - *While neon ions were capable of controlling some tumors, particularly slow growing salivary and soft tissue tumors, there were significant late effects on normal tissues.*
  - *Their inability in several studies to do any better than helium ions suggested that dose distribution was more important than high-LET.*
  - *The biophysical and clinical judgment was that carbon ions had the best biologically-corrected dose-localization and should be used in the future charged particle trials. This was communicated to our overseas colleagues as our machine (BEVALAC) was shut down due to financial considerations.*

## Treatment Outcome Comparing Neon, Neutrons and Conventional Xray Therapy for Selected Types of Tumors

<u>Tumor and Endpoint</u>	<u>Neon</u>	<u>Neutrons</u>	<u>Xray</u>
<b>Macroscopic Salivary Gland Ca</b> (Long term local control) N=18	61%	60-70%	25-36%
<b>Macroscopic Paranasal Sinus Ca</b> (Long term survival)	69%	30+%	32-40%
(Long term local control) N=10	69%	50-86%	N/A
<b>Macroscopic Soft Tissue Sarc</b> (Long term local control) N=12	56%	50-54%	30-50%
<b>Macroscopic Sarcoma of Bone</b> (Long term local control) N=18	59%	49-55%	21-33%
<b>Locally Advanced Prostate Ca</b> (5 yr actuarial local control) N=12	75%	77%	30-50%

Reprinted from: Linstadt, Castro and Phillips: Neon Ion Radiotherapy: Results of the Phase I-II Clinical Trial. Submitted to Int. J. Rad. Onc. Bio. Phys.

## *Timeline of Late Effects Study Design funded since Sept 2009*

- **Phase 1 (<3 mo)**--Chart review only to ascertain number of surviving patients from public records
- **Phase 2 (<9 mo)**--If surviving subject number is statistically adequate, seek HSC approval for subject contact to ascertain willingness to participate in clinical follow-up and normal tissue late effects evaluation

## *Patient Numbers*

- 1465 patients in study design of CPRT program treated with He, C, Ne, Ar or Si (includes He with HCP boost).
- In 1992 at the close of the program, there were 516 patients surviving patients (240 females and 276 males).

## *CPRT Late Follow-Up Team*

- Eleanor Blakely, Ph.D.
- Mack Roach III, MD, FACR
- Kavita Mischra, MD
- Igor Barani, MD
- Inder Daftari, Ph.D.
- Vivian Weinberg, Statistician
- Jackie Iler
- Anand Badri

## *Limitations & Challenges*

- **Time** since completion of study
- **Diversity** in Rx protocol and imaging due to evolving optimization of Charged Particle Research effort and to improving imaging options over course of study
- **Task** of sorting through 281 archived boxes of human subjects records and extracting pertinent vital information on patient disease and treatment



Volume 15 Number 4  
July/August 2009

*Special Issue  
on Charged  
Particle  
Therapy*

## *Future Needs\**

- A prospective **particle- and treatment-related data registry** to expand the number of in silico analyses in addition to collecting solid clinical data.
- A model-based approach using validated predictive **normal tissue complication probability-models** that can be imbedded into dose planning comparative studies.

*\*Brada et al., Current Clinical Evidence for Proton Therapy, Cancer Journal 15:319-324 (2009)*

# *Proton Beam Therapy & the Convoluting Pathway to Incorporating Emerging Technology into Routine Medical Care in the US\**

- Emanuel et al\*\* point out that “an intervention’s value resides in its ability to reduce mortality, morbidity, or save money, not in its unique mechanism of action”.

*\*Steinberg & Konski, Cancer Journal, 2009*

*\*\* Emanuel et al., JAMA, 298:1323-1325, 2007*

# *Systematic Review: Charged-Particle Radiation Therapy for Cancer\**

- To review evidence about the benefits & harms of charged-particle radiation therapy for patients with cancer.
- 8 randomized and 9 non-randomized clinical trials compared Rx with or without charged particles.
- **No comparative study** reported statistically significant or important differences in overall or **cancer-specific survival** or in **total serious adverse events**

*\*Terasawa et al., Ann Internal Med, 2009*

# *New Era for Charged Particle Radiobiology*

- Human genome mapped & being mined for tumor and normal tissue data on radioresponse
- Powerful new genomic & proteomic tools available
- Networks of gene & protein pathways identified
- Focus on individualized medicine
- Tailored 3-D image-guided & intensity modulated physics
- Theoretical biophysical modeling is guiding treatment optimization

# *Charged Particle Radiobiology Needs Continue*

- What are the risks of secondary cancers & late effects?
- Can we identify the radiosensitive patient who should be treated with a more conservative treatment plan?
- How can we reduce unnecessary dose outside of treatment volume?
- Are there pediatric tumors we should not consider treating?
- Can specific chemotherapies enhance charged particle therapy?
- Can we further optimize with hypofractionation?
- What is the best biological model for validating dose effectiveness?

## *Conclusions*

- Late effects are associated with irradiated normal tissue volumes which can be reduced with charged particle therapy, and dictate which particle beam is optimal for a specific clinical site
- A clinical follow-up of patients treated at LBNL is underway
- Low-dose tissue effects at tumor margins need further study
- Need for more acute molecular studies underlying late effects

# ***Acknowledgements***

***Supported by  
NASA Grant #NNJ07HC791  
and  
UCSF Subcontract to LBNL***