Radiation-Adaptive-Response-Based Cancer Risk Modeling

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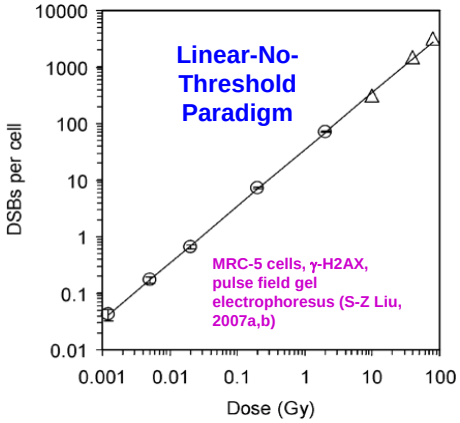


LNT Dogma: DNA double-strand breaks (DSB) are an LNT function of radiation dose; thus, cancer induction is also an LNT function of dose.

Systems Radiation Biology Perspective for Cancer Risk Assessment

- Although the risk of DSB rises linearly with dose, a second risk relates to the probability that initial DSB will lead to cancer.
- The second risk is a nonlinear function of dose.*

**Low dose radiation can activate protective responses at different organizational levels (Bauer 2007;Boreham 2008;Cuttler 2007; Feinendegen 2007; Jin et al. 2007; Liu 2007a,b; Scott and Di Palma 2006; Scott et al. 2006; Scott 2008).*

- Bauer G. 2007. Int J Radiat Biol 83:873-888.
- Boheham D. 2008. DOE Low Dose Workshop.
- Cuttler J. 2007. Dose-Response 5:292-298.
- Feinendegen L. *et al.* 2007. Atoms for Peace: An International Journal 1(4):336-353.
- Jin SZ et al. 2007. Dose-Response 5:349-358.
- Liu S-Z. 2007a. Dose Response 5:59-47, 2007.
- Liu S-Z. 2007b. May 2007 Seminar.
- Scott BR and Di Palma J. 2006. Dose-Response 5:230-255.
- Scott BR et al. 2006. Int. J. Low Radiation 4(1):1-16.
- Scott BR. 2008. Dose-Response, submitted.

Low-Dose, Low-LET Radiation Protects Us

- Protects against chromosomal damage (Ed Azzam's group)!
- Protects against mutation induction (Pam Sykes' group), even when the low dose follows a large dose (Tanya Day's work)!
- Protects against neoplastic transformation (Les Redpath's group)!
- Protects against high dose chemical- and radiation-induced cancer (Kazou Sakai's group)!
- Enhances immune system defense (Shu-Zheng Liu's group)!

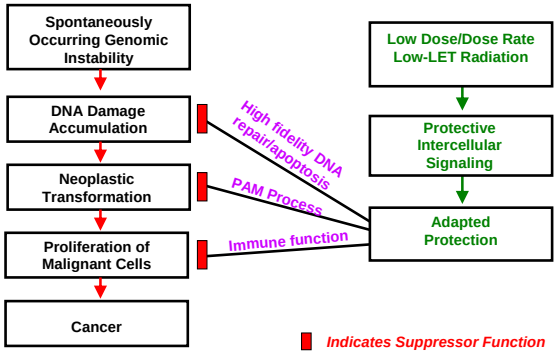
Low-LET Radiation Protects Us (continued)

- Suppresses cancer induction by alpha radiation (Chuck Sanders group)!
- Suppresses metastasis of existing cancer (Kiyohiko Sakamoto's group)!
- Extends tumor latent period (Ron Mitchel's group)!
- Protects against diseases other than cancer (Kazuo Sakai's group)!

Contributors to Low-Dose, Low-LET Radiation Induced Protection

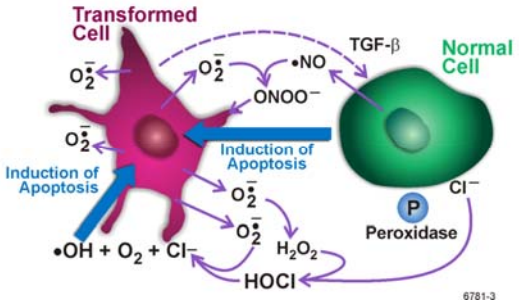
- Induced DNA DSB repair, for doses above a threshold (*K. Rothkamm's group*), which may be dose-rate dependent (*W. Olipitz and colleagues*).
- Stimulate immunity against cancer (*S-Z Liu's group)*.
- **P**rotective **a**poptosis **m**ediated (**PAM**) process postulated years ago to selectively remove genomically unstable cells (mutant, micronucleated, neoplastically transformed and other aberrant cells).
- Found later to have already been demonstrated by *G. Bauer's group* (for elimination of transformed fibroblast) and extensively studied and referred to as intercellular induction of apoptosis.
- Now also demonstrated by M. Barcellos-Hoff's group for elimination of genomically unstable cells.

Systems-Radiation-Biology Related, Activated Natural Protection (ANP) against Cancer



Scott 2006a,b

Protective Apoptosis Mediated (PAM) Process in Fibroblast

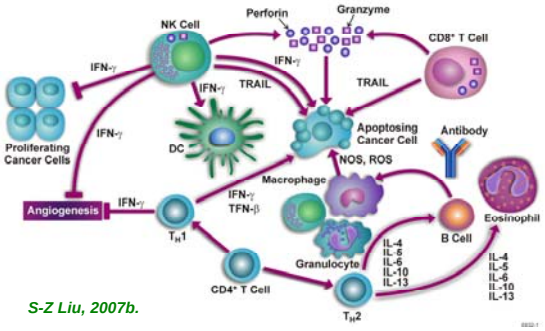


G. Bauer 2000: Autocrine self-destruction

PAM Process Signaling Efficiency Likely Increases with Age

- Most tissues harbor "dormant" tumorigenic (precancerous) cells (J. Folkman's group).
- The body burden of the precancerous cells is thought to increase with age.
- The PAM process signaling efficiency is thought to increase as the number of precancerous cells increases (G. Bauer's group) and therefore is thought to increase with age.

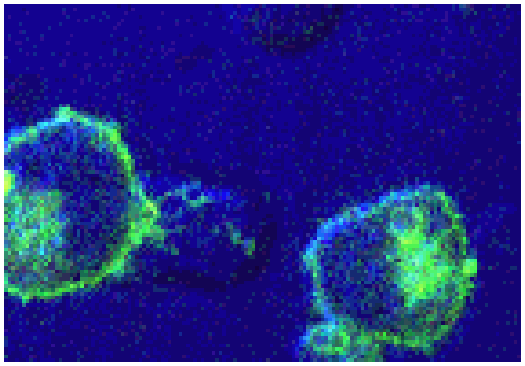
Systems-Biology-Related Tumor Control Stimulated by Low-Dose Radiation



S-Z Liu, 2007b.

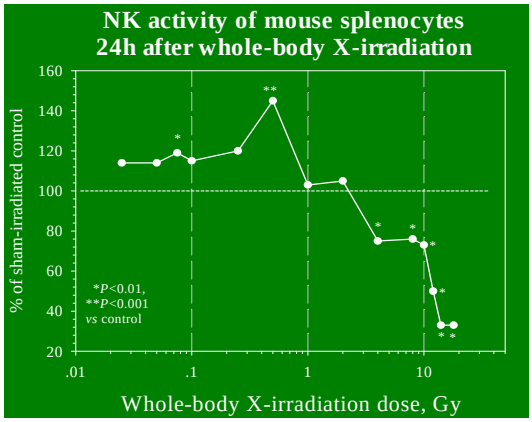
G. Dranoff. Nat Rev Cancer 4: 11-22, 2004.

Cytotoxic T Lymphocyte Destroying Cancer Cell (*S-Z Liu, 2007*)



Low-Dose X-Ray Stimulated Cellular Immunity in Mice (*S-Z Liu, 2007b*)

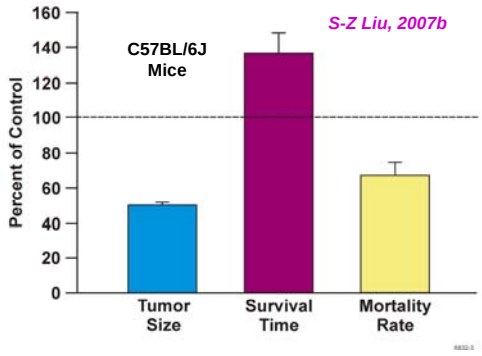
Parameter	Dose (mGy)	Change (%)	*P* value
NK activity	75	+19	< 0.05
Mac. activity	75	+52	< 0.05
Cytotoxic T Lymphocytes	75	+40	< 0.01
Antibody depen. cell mediated cytotoxicity	75	+30	< 0.05
T cell proliferat.	77	+101	< 0.01



Fan XH and Liu S-Z. JNBUMS 1989, 15:551

Low-Dose X-Ray ANP Against Lung Cancer

75 mGy 24h before Lewis lung cancer cell implantation



Thymic Lymphoma Study of S-Z Liu

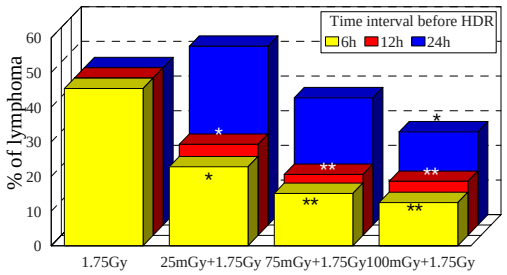
- Low dose X rays (25, 75, or 100 mGy) given before large X ray dose (1.75 Gy) to mice.
- Time interval between low and high dose was 6, 12, or 24 hours.
- Four cycles of dosing were given apparently to reduce acute toxicity.

S-Z Liu, 2007b.

Low Dose ANP Against High Dose X-Ray Induced Thymic lymphoma in C57BL/6J Mice: Evidence for Stochastic Thresholds

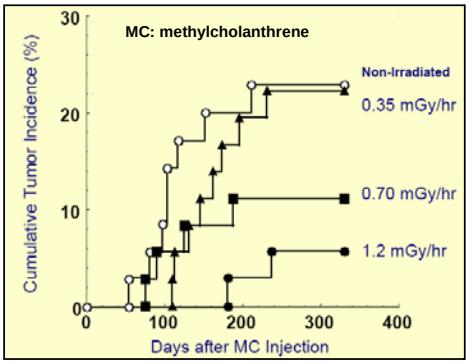
HDR=1.75 Gy x 4

S-Z Liu, 2007b



*P<0.05, **P<0.01 *vs* 1.75Gy x 4

Low-Dose-Rate Gamma Ray ANP against MC-Induced Skin Tumors

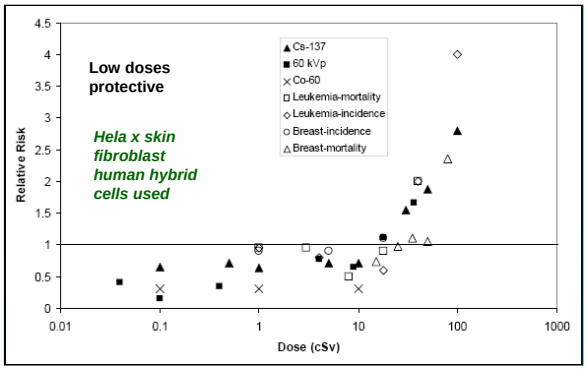


K. Sakai, 2005 International Dose-Response Conference presentation

Hormetic Relative Risk (HRR) Model for Low-Dose-Radiation-Induced Cancer

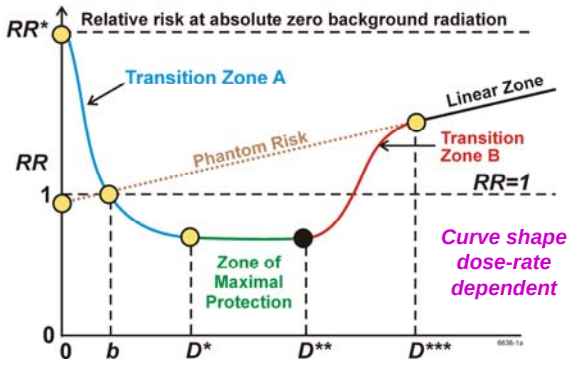
- Key Assumption: Cancer arises from cells with persistent genomic instability through a series of stochastic changes, independent of how the instability originates, but dependent on the number of cells with this instability in an organ.
- The PAM process induction and immune system stimulation are statistically independent.
- Low-dose stochastic thresholds activate protection.
- High-dose stochastic thresholds inhibit protection.
- Under the indicated assumptions, cancer *RR* would be expected to be proportional to neoplastic transformation *RR* as has been demonstrated by L. Redpath and colleagues.

Similar Relative Risks for Cancer and Neoplastic Transformation (*In Vitro*)

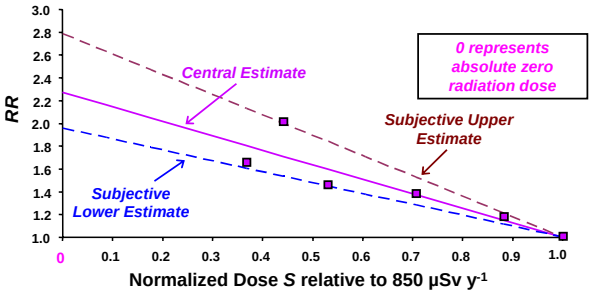


L. Redpath, International Dose-Response Conference (IDRC) 2006

Adaptive-Response-Based HRR Model: Population Average *RR*



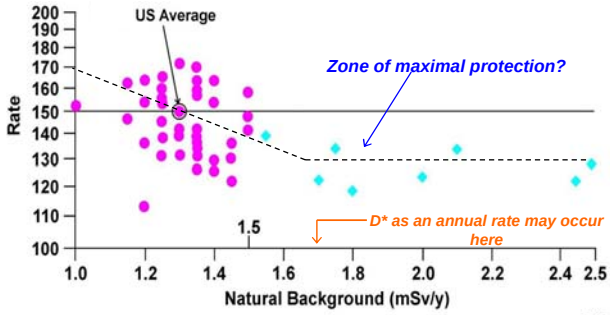
Transition Zone A Data for Average *RR* for All Cancers: Cities and States of India



Only gamma- ray exposures were evaluated. *RR = 1* at *b* = 850 μSv y^{-1}.

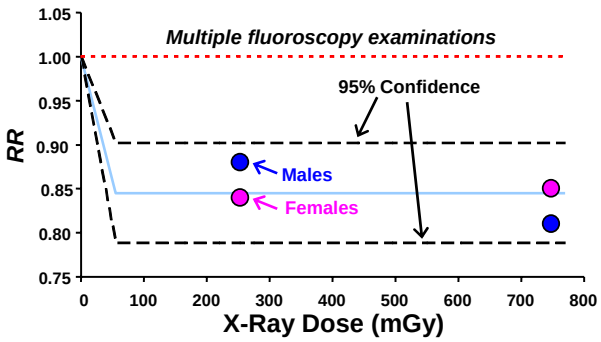
Data of Nambi KSV and Soman SD. Health Physics 53,1987

Evidence for Zone of Maximal Protection: Annual Cancer Mortality/100,000 in US States 1950 to 1967



Data of Frigerio and Stowe, IAEA Publication 1976.

Evidence for Zone of Maximal Protection against Lung Cancer for Canadian TB Patients



Data from Howe GR. Radiat. Res. 142:295-304,1995. Similar findings have been reported for breast cancer (Miller. N. Engl. J. Med. 321:1285-1289, 1989)

Absolute and Relative Risk for Cancer Induction

Risk = $R = (1 - PROFAC)[R_0 + (1-R_0)\mathbf{K'D}]$

D is column matrix of radiation-specific doses.

K' is row matrix of corresponding slope parameters (pseudo parameters) K_i.

R_0 is the risk for spontaneous cancer.

PROFAC is a protection factor, which is presumed to account for protection via both the PAM process and immune system stimulation.

Relative risk = $RR = R/R_0$.

Risk is averaged over the irradiated population for a given ***D***.

Protection Factor (*PROFAC*)

- *PROFAC* is also a pseudo-parameter and population average.
- *PROFAC* = 0 when no ANP,

  $0 < PROFAC \leq 1$ otherwise.
- The *PROFAC* for a given cancer type gives the expected proportion of cancer cases prevented when ANP occurs.

Combined α + γ Irradiation

$\mathbf{K'D} = K_\alpha D_\alpha + K_\gamma D_\gamma$

For low doses and low dose rates,

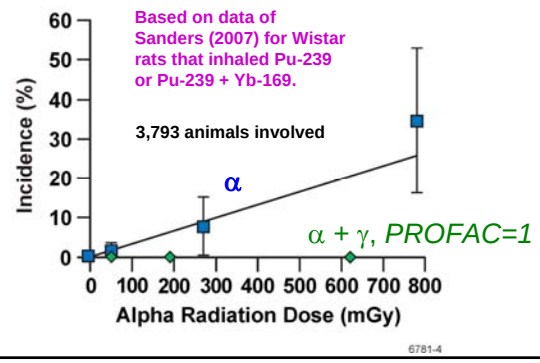
$K_\alpha D_\alpha + K_\gamma D_\gamma \approx K_\alpha D_\alpha$.

K_α appears evolutionarily conserved for mammals.

Expected Influence of Genetic and Epigenetic Risk Factors

- Risk factors related to DNA repair abnormalities could impact K_α and K_γ.
- Risk factors related to p53-dependent apoptosis could impact K_α and K_γ.
- Risk factors related to abnormal PAM process could impact *PROFAC*.
- Risk factors related to deficient immune functions could impact *PROFAC*.

Gamma-Ray ANP Against Alpha Radiation Induced Lung Cancer



PROFACs for Radon-Spa Areas in Japan (Misasa)

Cancer Site or Type	100**PROFAC* (%) Females	Males
Leukemia	47 ± 1.6	56 ± 1.6
Stomach	55 ± 1.6	60 ± 1.6
Breast	74 ± 1.4	(results not reported)
Lung	81 ± 1.2	53 ± 1.6
Colon/rectum	86 ± 1.1	70 ± 1.5

Radon exposure involves a gamma radiation component, which is considered responsible for activating the PAM process and inducing immunity. ***Data from Mifune et al. 1992***

Lung Cancer *RR* for Mayak Workers Exposed to $\alpha + \beta$ Radiations (Scott 2008)

α Dose Range (mGy)	Mean Baseline Incidence per 100,000	Observed Average *RR*	Model Simulated Average
0 - 12	41 ± 25	0.39	0.36
12.1 - 50	57 ± 41	0.53	0.56
51 - 200	76 ± 55	1.58	1.59
201 - 800	86 ± 93	4.65	4.66
801 - 3200	99 ± 106	28.1	28.1

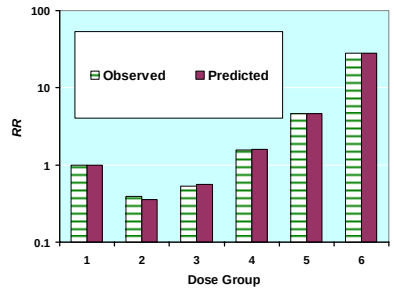
Estimated Population Averages for K_α and *PROFAC* for Mayak Worker Population

$K_\alpha = 1.2\text{x}10^{-4} \pm 9.0\text{x}10^{-5}$

PROFAC = 0.86 ± 0.07

Both distributions were asymmetric.

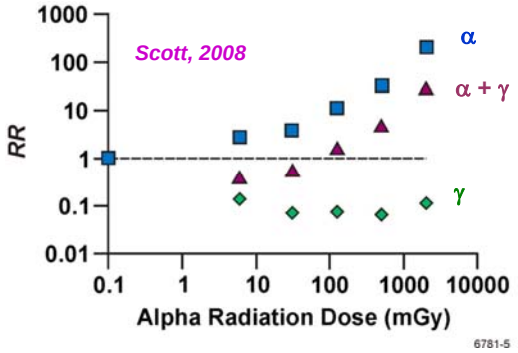
Mayak Worker Group Average Lung Cancer Relative Risk: α + β Radiation



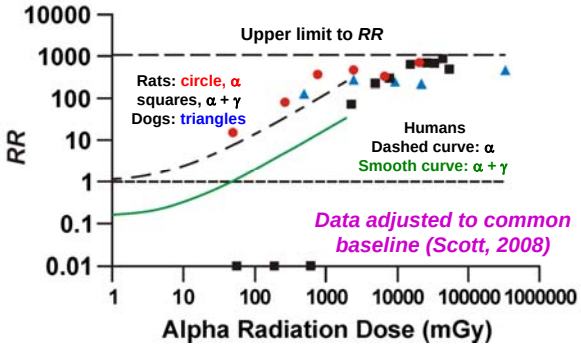
Alpha Radiation Dose Range (mGy) by Group

1: 0 - 0
2: >0 – 12
3: 12.1 – 50
4: 51 – 200
5: 201 – 800
6: 801 – 3200

Predicted Mayak Worker Group Average Lung Cancer *RR*



Lung Cancer *RR* for Different Species: α or α + γ Irradiation



Evidence of K_α Being Evolutionarily Conserved for Mammals

- **K_α (Wistar rats, 2 studies) = $2.4 \times 10^{-4} \pm 1.3 \times 10^{-4}$ mGy^{-1}**
- **K_α (F344/Crl rats) = $1.0 \times 10^{-4} \pm 5.0 \times 10^{-5}$ mGy^{-1}**
- **K_α (Beagle dogs) = $1.7 \times 10^{-4} \pm 1.0 \times 10^{-5}$ mGy^{-1}**
- **K_α (humans) = $1.2 \times 10^{-4} \pm 9.0 \times 10^{-5}$ mGy^{-1}**

Parameter evolutionary conservation: parameter distributions have large overlap.

Scott (2008).

Implications for Low-Dose-Radiation Cancer Therapy

- Unlike high total-body doses that suppress the immune system and promote cancer metastasis, low doses stimulate immunity against cancer (i.e., ANP) and prevent metastasis.
- Low-dose, low-LET-radiation ANP is transient, suggesting that multiple small doses or low-rate chronic exposure (e.g., via radio-immunoglobins) would be more efficient in curing cancer than a single, brief exposure to a low radiation dose.
- The optimal cancer-therapy schedule of multiple doses or of dose-rate pattern should depend on the onsets and durations of the protective signals (PAM process, immune system stimulation), which are not presently known.

Implications for Low-Dose-Radiation Therapy (continued)

- Cancer cells are resistant to undergoing apoptosis.
- New research is demonstrating ways of sensitizing cancer cells to undergo apoptosis (e.g., gene and cytokine therapy, drugs such as resveratrol).
- Applying low-dose radiation therapy in combination with multiple small doses of apoptosis-sensitizing agents could increase the effectiveness of the cancer therapy.
- Adding multiple small doses of an antiangiogenic agent to destroy tumor blood vessels could further increase the effectiveness of the therapy.

Conclusions

- The low-dose and low-dose-rate results presented do not support the LNT risk model when low-LET radiation is involved.
- The HRR model which accounts for low-LET-radiation ANP is more appropriate for low-dose/low-dose-rate cancer risk assessment.
- Low doses and dose rates of low-LET radiation stimulate the bodies natural defenses (ANP), while high doses and dose rates are suppressive.
- Multiple small doses or extended continuous low-rate exposure appear to greatly increase the duration and dose range of ANP.

Conclusions (continued)

- Low-dose-radiation therapy could be used in combination with other low-dose therapies (e.g., gene, cytokine, drug [e.g., resveratrol, antiagiogenic]) to cure existing cancer without severely injuring the patient (combined low-dose therapy).
- New research is needed in order to better understand the onsets and durations or radiation-ANP-related signaling.
- Such information is essential for developing optimal protocols for low-dose cancer therapy.

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- Zoya Tokarskaya, Russia
- Galina Zhuntova, Russia

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