Biological-Based Cancer Hormetic Relative Risk Model and Implications for Low Dose Radiation Risk Assessment, Cancer Prevention, and Cancer Therapy

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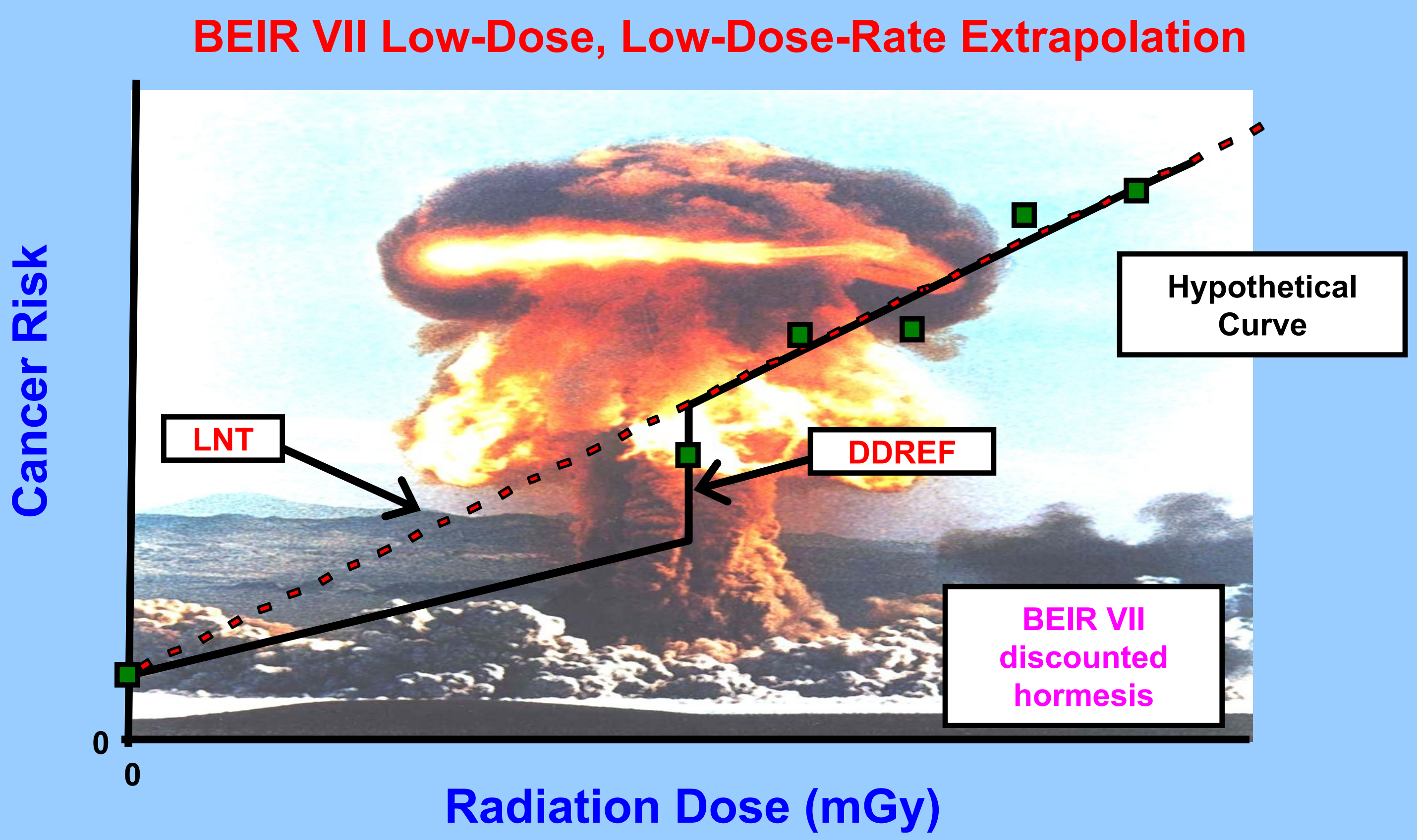
Background

Life on earth evolved in a low-level ionizing radiation environment comprised of terrestrial radiation and cosmic rays. Today we all reside in an ionizing radiation environment comprised of both natural background radiation and radiation from human activities (e.g., Chernobyl accident). An evolutionary benefit of the interaction of low-level, low linear-energy-transfer (LET) ionizing radiation with mammalian life forms on earth is adapted protection. Adapted protection involves low-dose/dose-rate, low-LET radiation-induced high-fidelity DNA repair in cooperation with normal apoptosis (presumed p53 related), activation of an auxiliary apoptosis mechanism (presumed independent of p53), and induced immunity (Scott 2006a). These induced protective processes constitute a system of protection against genomic instability-associated diseases including cancer. Stochastic threshold radiation doses (which differ for each individual) are required for activating the indicated protective system components (Scott 2005a, 2006a; Scott *et al*. 2006).

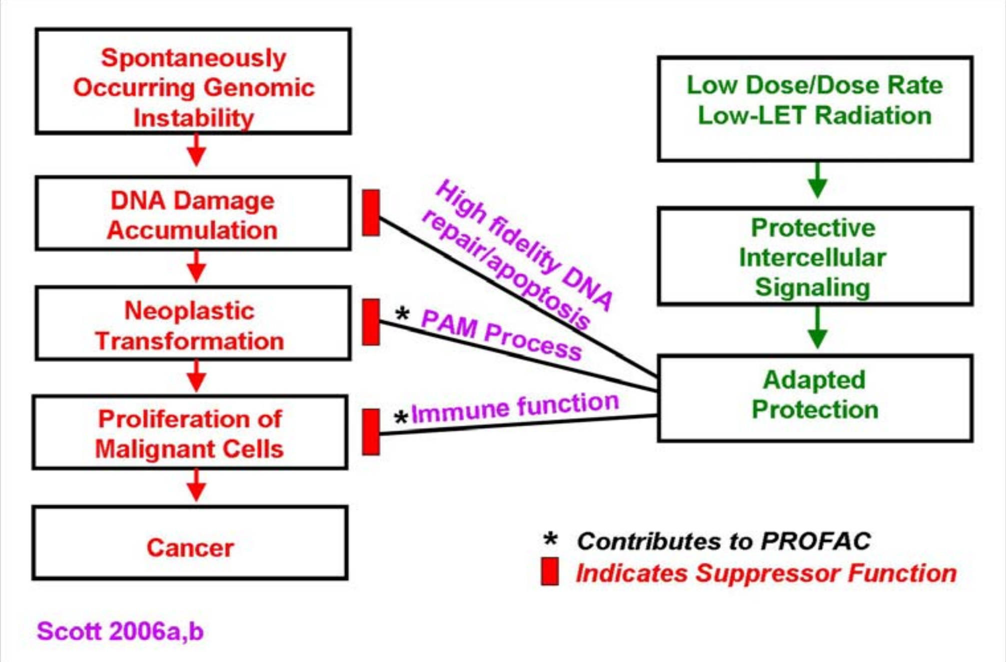
When activated, the high fidelity DNA repair prevents the occurrence of cells with persistent genomic instability. However, severely damaged cells may undergo normal apoptosis rather than DNA repair, thereby also preventing the occurrence of genomically unstable cells. Mildly and modestly damaged cells may attempt repair of DNA damage and, depending on the repair fidelity, commit errors (misrepair) leading to genomically unstable cells that could contribute to disease development. A transient, auxiliary, protective-apoptosis-mediated (PAM) process (presumed p53 independent) when activated by an above-threshold, low-LET radiation dose can remove genomically unstable cells whether they arise spontaneously or as a result of environmental and other insults. High fidelity DNA repair also appears to require a stochastic threshold radiation dose. Fortunately, such thresholds can be exceeded by natural background radiation exposure over a relatively short time (Scott 2006b).

Background (Continued): Current Regulatory Risk Assessment Paradigm



- Low-dose cancer risk assessment is based on the linear no-threshold (LNT) assumption and high dose-rate data.
- With the LNT assumption, a straight line is drawn from observed risks at high doses and dose rates (e.g., A-bomb victim data) to a projected risk at low doses. This line intersects the vertical axis at the spontaneous frequency.
- To account for low doses and dose rates (e.g., from natural background radiation), a low dose and dose rate effectiveness factor (DDREF) is used. The straight line used intersects the spontaneous frequency. Excess risk can never be less than the spontaneous frequency (i.e., hormetic effects excluded).

Background (Continued): Radiation-Induced Adaptive Response



Spontaneously Occurring Genomic Instability

DNA Damage Accumulation

Neoplastic Transformation

Proliferation of Malignant Cells

Cancer

Low Dose/Dose Rate Low-LET Radiation

Protective Intercellular Signaling

Adapted Protection

High fidelity DNA repair/apoptosis

* *PAM Process*

**Immune function*

* *Contributes to PROFAC*

🟥 *Indicates Suppressor Function*

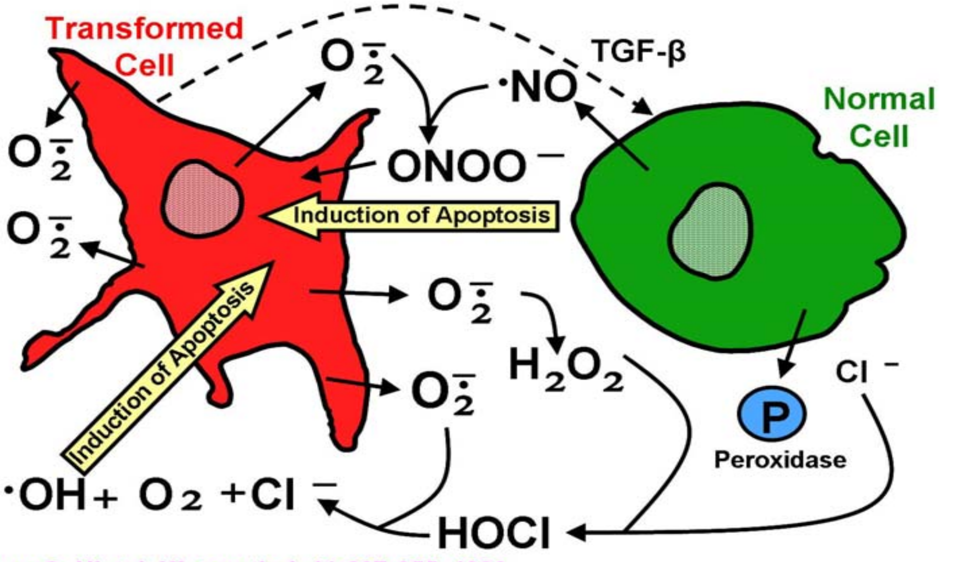
Scott 2006a,b

Low-dose/dose-rate radiation induced system of protection includes activated high-fidelity DNA repair/apoptosis (presumably p53 dependent), the PAM process (presumably p53 independent), and immunity.

Scott 2006a,b

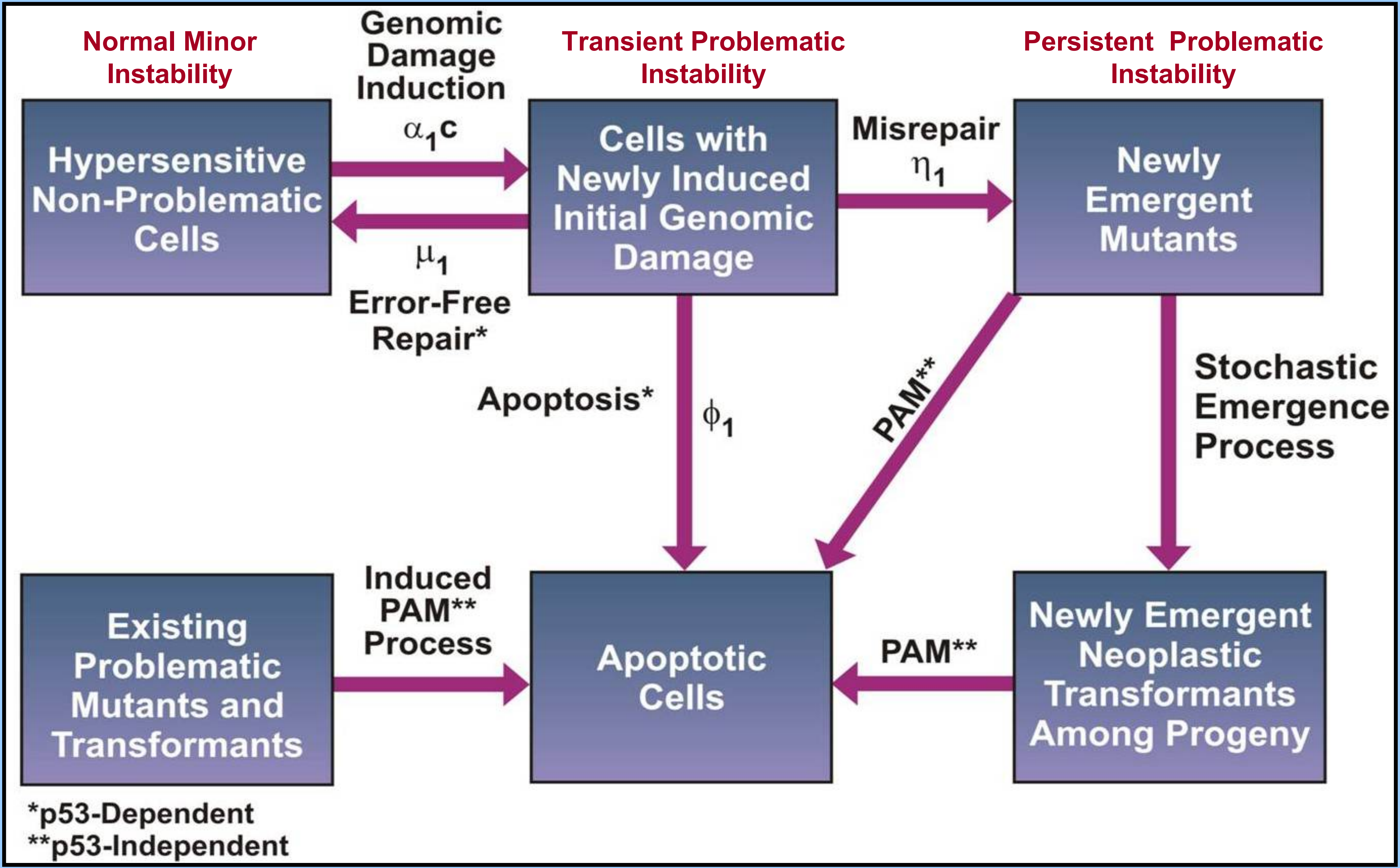
$O_2\cdot^-$	**Superoxide anions**
$\cdot NO$	**Nitric oxide**
Cl^-	**Chloride ion**
H_2O_2	**Hydrogen peroxide**
$\cdot OH$	**Hydroxyl radical**
O_2	**Oxygen**
HOCl	**Hypochlorous acid**
TGF-β	**Transforming growth factor beta**

PAM Process In Fibroblast: Protective Intercellular Signaling



Bauer G. Histol. Histopathol. 11:237-255, 1996

Background (Continued): NEOTRANS$_3$ Model



Low Doses and Dose-Rates of Low-LET Radiation Protect Us From Harm: Adapted Protection

- Protect against cell killing by alpha particles (Satin Sawant's work)
- Protect against chromosomal damage (Ed Azzam's group)
- Protect against mutation induction (Pam Sykes' group), even when the low dose follows a large dose (Tanya Day's work).
- Protect against neoplastic transformation (Les Redpath's group).
- Protect against cancer occurrence (epidemiological and animal data).
- Suppress metastasis of existing cancer (Kiyohiko Sakamoto's group).
- Extend tumor latent period (Ron Mitchel's group).
- Protect against diseases other than cancer (Kazuo Sakai's group).

The indicated results implicate hormetic dose-response curves that relate to induced adapted protection (i.e., adaptive response).

Research Approach

Our research has focused on quantitatively characterizing (i.e., modeling) the suppression of deleterious stochastic effects (mutations, neoplastic transformations, and cancer) via low-dose, ionizing-radiation-induced adapted protection. Our dose-response characterizations are based either directly or indirectly on our biological-based NEOTRANS$_3$ model (Scott 2004, 2005a,b, 2006a,b,c; Scott *et al*., 2006). The model accounts for two components of adapted protection [DNA repair/apoptosis (normal) and the PAM process]. Cancer relative risk (*RR*) is assumed to be proportional to the neoplastic transformation *RR.* For cancer induction by low-LET radiation, the relative risk (*RR*) at low doses has a hormetic character in that *RR* decreases over what is called Transition Zone A as the dose increases above the background "*b*" radiation dose up to a dose *D (maximum threshold for activating protective processes) that is dose-rate dependent. Above *D**, *RR* remains suppressed below the spontaneous level at *RR = 1-PROFAC* for a range of doses that also depend on dose rate. This is the Zone of Maximal Protection.**

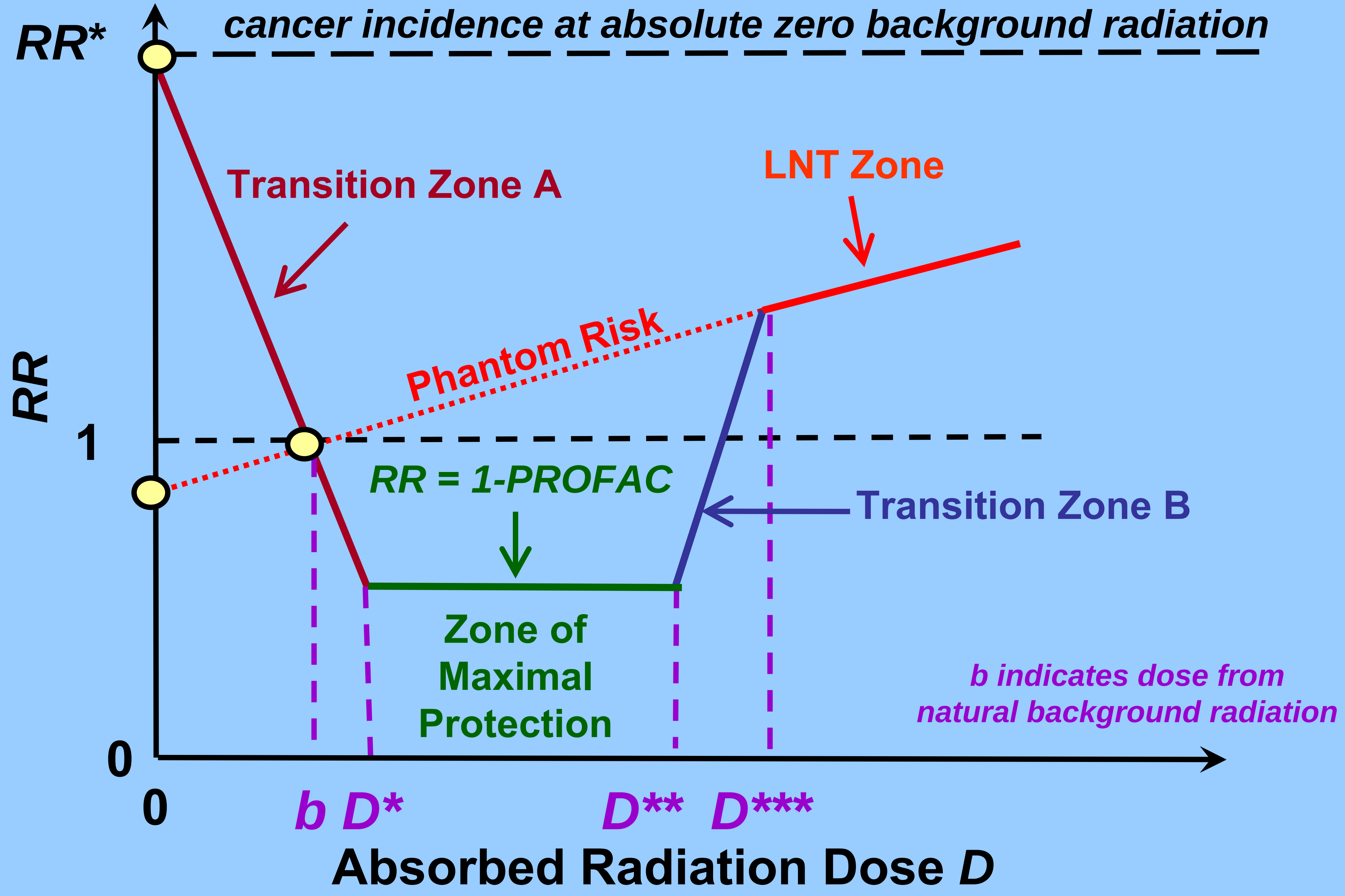
The *PROFAC* gives the expected proportion (0 to 1) of cancer cases that are avoided due to radiation-induced adapted protection (also called hormesis) and accounts for protection associated with both the PAM process and induced immunity. Decreasing dose rate extends the dose range of suppression of *RR* (Redpath 2006). With further increase in dose, some of the protection is lost (PAM process is inhibited and immunity is not induced) due to exceeding stochastic thresholds (Transition Zone B) for inhibition of these protective processes. At doses above where the inhibitory thresholds occur, *RR* is expected to be linear for a range of doses.

Approach (Continued)

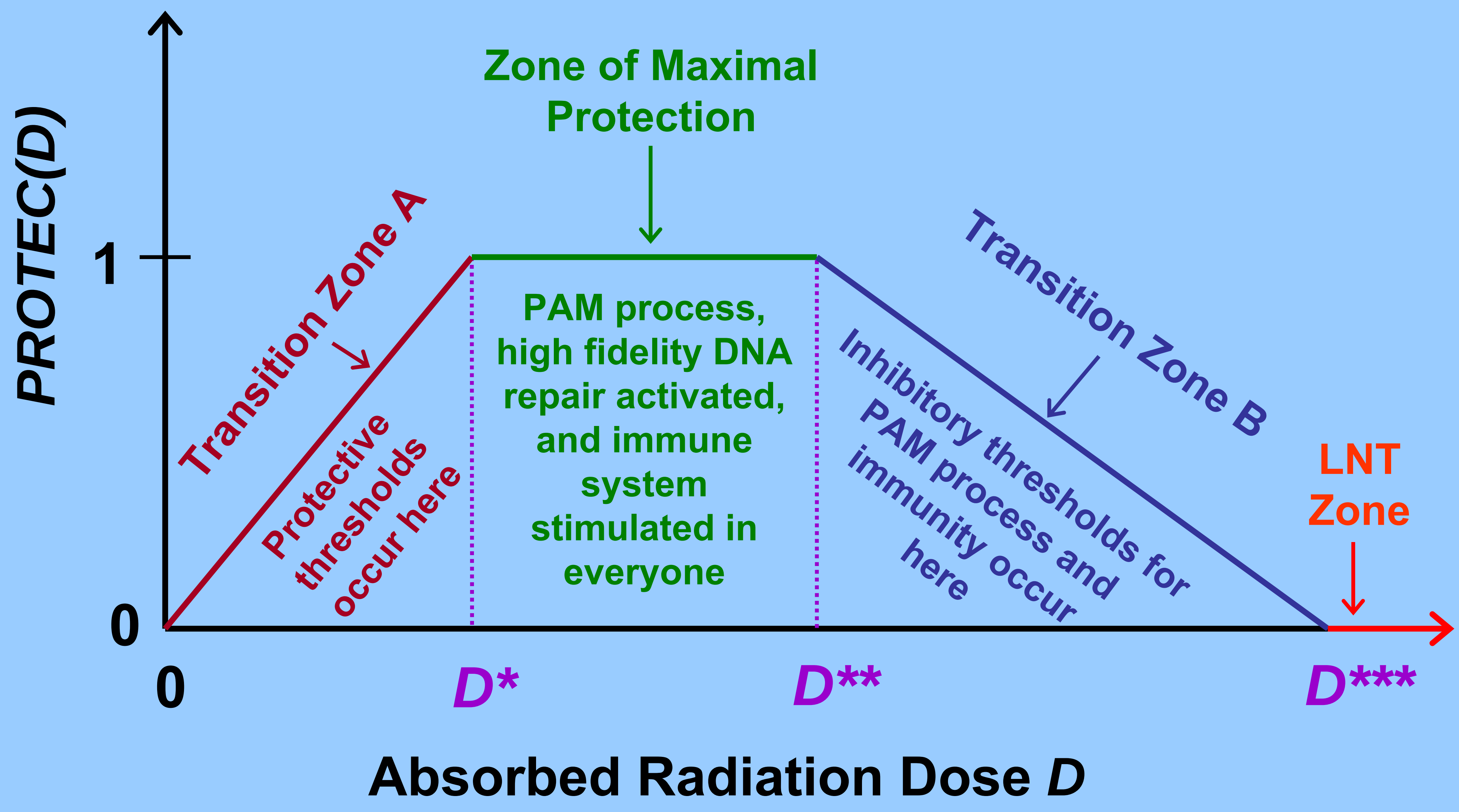
This dose zone of linearity is where most of the epidemiological studies supposedly confirming the linear no-threshold (LNT) hypothesis have been conducted. The indicated LNT portion of the dose-response curve extrapolates to *RR = 1* at the background radiation dose *b*. We have published our view about the fallacy of this extrapolation (Scott 2005b) and point out in the indicated publication that *RR* is orders of magnitude more likely to decrease at low doses of low-LET radiation rather than to increase by a small amount as would be expected based on the LNT hypothesis when dose is increased above the background radiation dose *b*.

Our approach to risk modeling also allows evaluation of the impact of reducing background radiation doses to near absolute zero radiation. Because of the loss of adapted protection when the low-LET dose progressively drops below individual-specific thresholds (Transition Zone A) for activating the indicated protective processes, cancer RR increases to a maximum *RR as the radiation dose decreases to absolute zero radiation. For doses below the natural background radiation level, our modeling results indicate that only the low-LET component to the dose is needed for characterizing cancer *RR* (Scott 2006b). The shape of the dose-response curve for this dose zone depends on the form of the distribution of the stochastic threshold for activating the protective processes. For a uniform distribution from 0 (i.e., absolute zero radiation dose) to a dose *D** (which is thought to exceed the natural background low-LET radiation dose), *RR* is expected to decrease linearly from its maximum, *RR**, at *0* dose to a minimum of *1-PROFAC* at *D**. The *PROFAC* as used here is a population average.**

Hormetic Relative Risk (HRR) Model



Protection Probability Function *PROTEC(D)*



Hormetic Relative Risk Function RR_{HRR} for $D \geq b$

$$RR_{HRR} = PROTEC(D)RR_{HR} + [1 - PROTEC(D)]RR_{LNT}$$

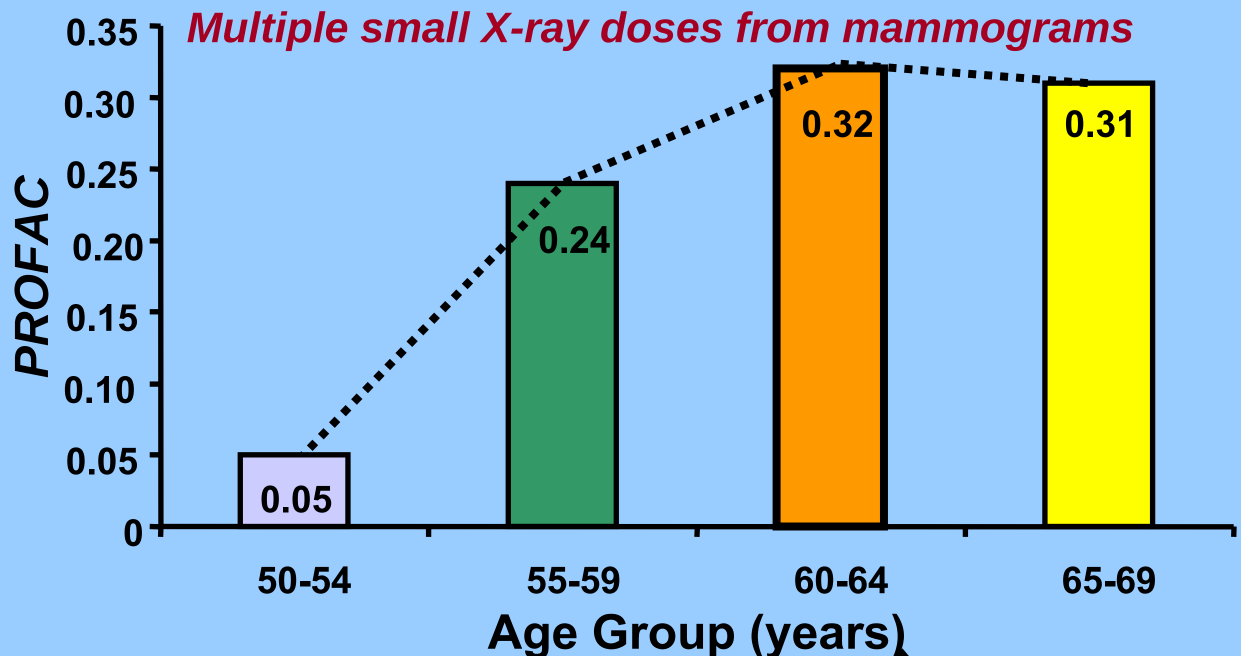
$$RR_{HR} = (1 - PROFAC)RR_{LNT}$$

$$RR_{LNT} = 1 + [(1 - B)/B]K(D - b)$$

$RR_{HRR} = RR^* - (RR^* - 1)S$ for $S < 1$

PROTEC(D) is the protection probability function
$S = D/b$ is normalized dose relative to *b*.

Radiation-Induced Adapted Protection in Adults and In Populations of All Ages

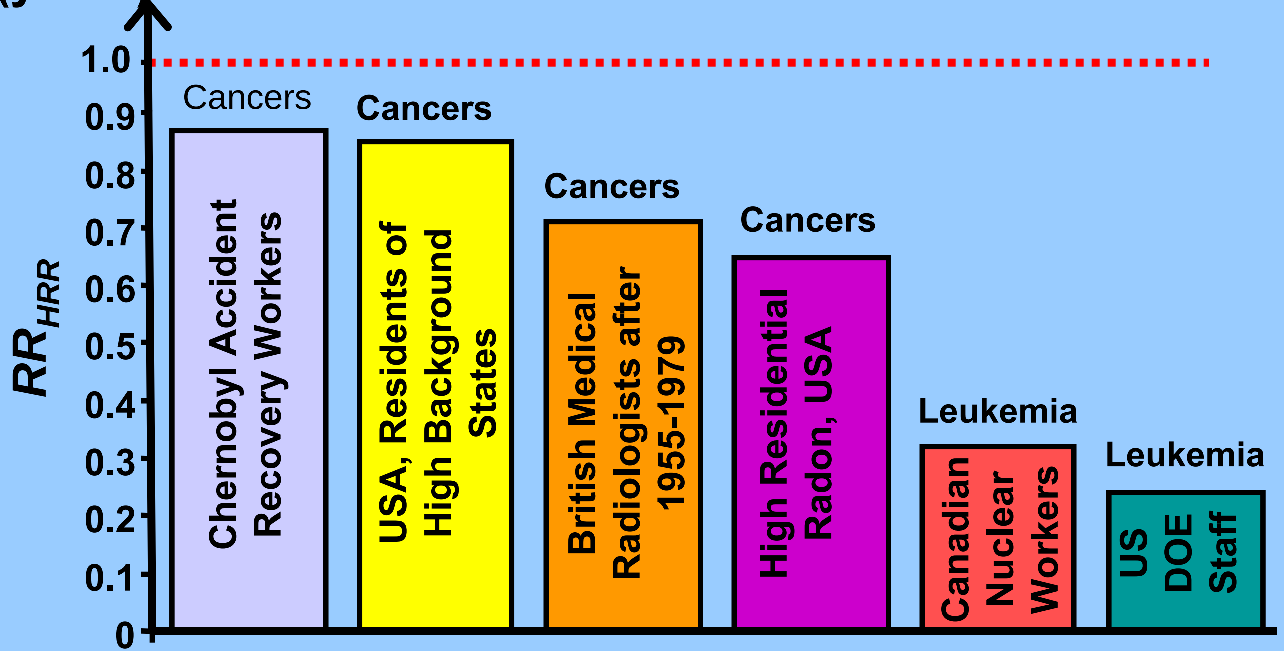


Multiple small X-ray doses from mammograms

Based on data from Nyström *et al*. The Lancet 2002; 359(9310):909-919.

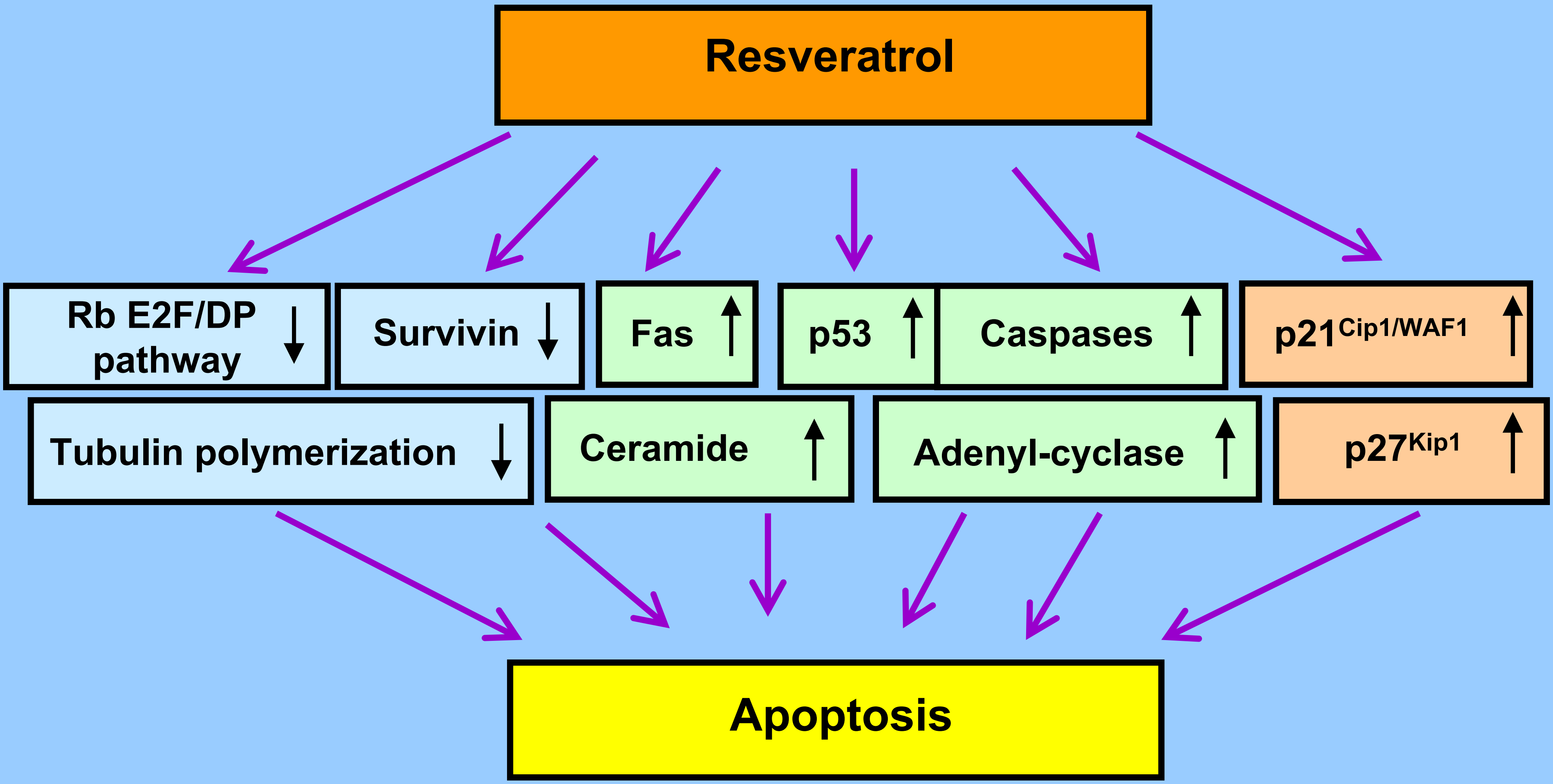
***RR*$_{HRR}$ < 0.85 cannot be due to healthy worker effect**

Sponsler R and Cameron JR. Int. J. Low Radiat. 1(4):463-478, 2005



Novel Low-Dose Cancer Therapy

- **Use small (e.g., 1 mGy) multiple doses (or chronic low rates).**
- **Also use small multiple doses of an apoptosis-sensitizing agent (e.g., resveratrol) along with an antiangiogenic drug.**



Resveratrol

Rb E2F/DP pathway ↓

Survivin ↓

Fas ↑

p53 ↑

Caspases ↑

$p21^{Cip1/WAF1}$ ↑

Tubulin polymerization ↓

Ceramide ↑

Adenyl-cyclase ↑

$p27^{Kip1}$ ↑

Apoptosis

Multiple pathways to apoptosis
(Aggarwal *et al.* Anticancer Research 24:3-60, 2004)

How Adapted Protection is Inappropriately Discounted by Ecological/Epidemiological Studies

- All radiation assumed harmful, including doses from diagnostic low-LET radiation (e.g., routine chest X-rays, CT scans, nuclear medicine diagnostic procedures).
- Persons receiving low doses included with controls when evaluating the shape of the dose-response curve.
- Low-dose data are excluded, ignored, or assigned low statistical weight.
- Evidence for nonlinearity is ignored.
- Ecological data showing hormesis are discounted based on poor dosimetry.
- DNA repair, protective apoptosis, and induced immunity are ignored.
- Lifespan prolongation is not considered.
- Hormetic effects missed due to assuming a healthy worker effect.
- Years of radiation dose accumulation are simply thrown away (called dose lagging) changing threshold-like dose responses into what appears to not have a threshold.

Conclusions

- The LNT hypothesis is not supported by cancer frequency data for low-dose, low dose-rate low-LET irradiation. The data are more consistent with the HRR model.
- Low doses and dose-rates of low-LET radiation (including natural background radiation) protect from mutations, neoplastic transformations, cancer, and suppress cancer metastasis. High doses facilitate metastasis.
- Repeated exposures (or chronic low rate exposure) over a prolonged period to small doses of low-LET radiation in combination with antiangiogenic therapy and tumor sensitization therapy (e.g., application of resveratrol) might greatly increase the frequency of cancer cures while limiting harm to patients from their treatment.

Additional References

- Redpath JL. Radiation-induced neoplastic transformation in vitro, hormesis and risk assessment. *Presentation given at 5th International Conference on Hormesis*. University of Massachusetts, Amherst, MA. June 6-8, 2006.
- Scott BR. A biological-based model that links genomic instability, bystander effects, and adaptive *response*. *Mutation Research*. 568:129- 143, 2004.
- Scott BR. Stochastic thresholds: A novel explanation of nonlinear dose-response relationships. *Dose-Response.* 3:547-567, 2005a.
- Scott BR. Low-dose radiation risk extrapolation fallacy associated with the linear-no-threshold model. *BELLE Newsletter*. 13(2), Part 2:22-27, December 2005b.
- Scott BR. Low-dose radiation-induced protective process and implications for risk assessment, cancer *prevention*, and cancer therapy. *Dose-Response.* In press, 2006a.
- Scott BR. Hormesis and the control of genomic instability. *In* New Research on Genomic Instability, Nova Science Publishers, Inc., Hauppage, NY 11788, accepted, 2006b.
- Scott BR, Haque M, and Di Palma J. Biological basis for radiation hormesis in mammalian cellular *communities*. *International Journal of Low Radiation*. In press, 2006.