

Basic Research Results That Do Not Support the BEIR VII Report Conclusions Regarding the Linear-no-threshold Risk Hypothesis

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Summary

- **BEIR VII is wrong** about the LNT model being valid for low-LET radiation.
- **Cancer risk could decrease** after low-dose or low-dose-rate exposure.
- **Background low-LET radiation may be protecting us** from cancer and other diseases.

Low Dose Cancer Risks Usually Based on LNT Hypothesis

Linear-no-threshold hypothesis: even the smallest amounts of radiation are harmful:

- **Cancer risk doubles when dose doubles.**
- **It triples when dose triples.**

BEIR VII Report (NAS 2005)

- **BEIR VII Committee concluded that the LNT hypothesis was correct and represented the best possible risk characterization!**
- **Even background low-LET radiation was stated to be harmful!!!!**

French Academy of Sciences, National Academy of Medicine Joint Report (2005)

“...this report raises doubts on the
validity of using the LNT for evaluating
the carcinogenic risk of low doses...”

*Exact opposite conclusion from BEIR VII
(Phase 2) Report!!!!*

Possible Interpretations of BEIR VII Implications

- Don't stand close to anyone at an EMS poster (**we all are radioactive**).
- Don't fly home on airplanes (**cosmic rays**).
- Don't watch TV (**x rays**).
- Don't live at high altitudes (**cosmic rays**).
- Don't breath too much (**radon is in the air**).
- Don't eat vegetables and fruits (**they contain radioisotopes**).

Protective Biological Processes Can Be Induced By Radiation

- **Repair of DNA damage** (HRR, NHEJ, BER, NER, MMR, lesion bypass, template switching).
- **Apoptosis** (p53-dependent and p53-independent).

Activation thresholds for such processes change the slope of the dose-response curves for mutations and neoplastic transformation, and therefore likely also for cancer induction.

Protective Bystander Effect

- Form of **natural defense** involving protective signaling.
- Induced by low-dose low-LET radiation and other stressors.
- ROS, RNS and specific cytokines (e.g., **TGF- β 1**) participate in signaling.
- **Enhanced DNA repair** capacity in bystander cells.
- **Selective removal of bad bystander cells.**

Bauer G. Anticancer Res. 20:415, 2000.

Damage Threshold Implicate Dose Thresholds

“Recent works suggest that there is a **threshold of damage** under which low doses and dose rates do not activate intracellular signaling and repair systems...”

French Academies Report 2005.

Stochastic Thresholds

- **Molecular damage thresholds** implicate stochastic dose thresholds.
- **StoThresh** is special name given.
- **Likely common** in biological systems.
- **Vary between different individuals, tissues/organs.**
- **Vary between *in vitro* replicates.**

Scott B.R. et al. NonLinearity 1(1):93, 2003.

Model for Low-Dose Radiation-Induced Stochastic Effects

- Updated NEOTRANS₃ model recently published.
- Accommodates protective signaling effects.
- Applies to low doses.
- Implemented via Bayesian statistical methods.

Scott B.R. Mut. Res. 568:129, 2004.

Scott B.R. and Haque M. Mut. Res. Submitted.

Protective Processes Associated with Current NEOTRANS₃ Model

- Presumptive-p53-dependent, **high-fidelity DNA repair/apoptosis**.
- Presumptive-p53-independent, **protective apoptosis mediated (PAM) process**.

Note: p53-independent pathways to apoptosis known to be associated with HRR (e.g. paths involving p73, JNK/FAS).

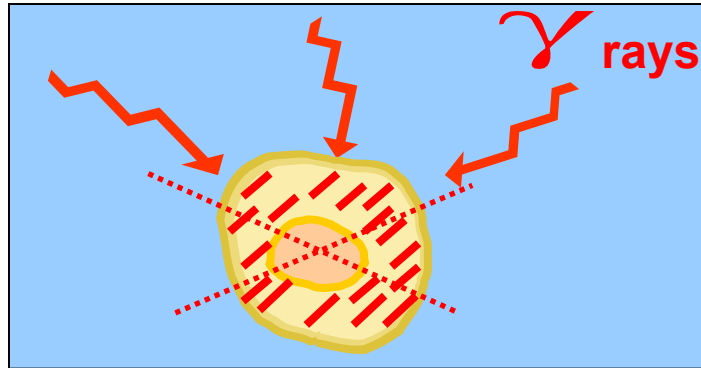
Protein Initiators of DNA Double-Strand Break Repair or Apoptosis

- **HRR: ATM, ATR, BRCA1.**
- **NHEJ: DNA-PK.**

Components of the BRCA1- associated genome surveillance complex.

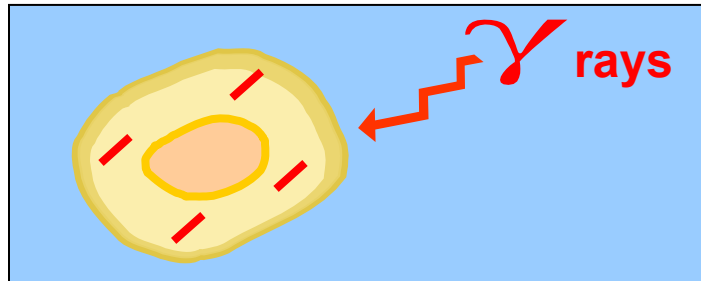
NEOTRANS₃ Model Modes of Protecting Against Stochastic Effects

Moderately damaged cell



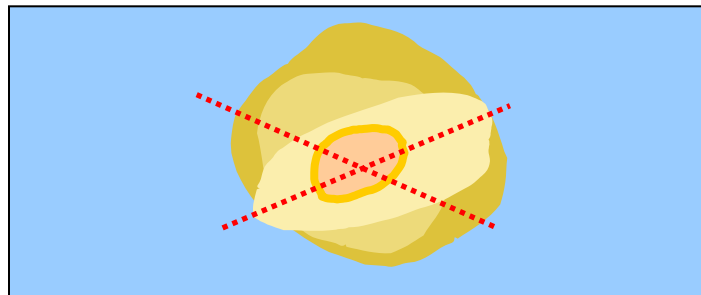
p53-related death sentence

Mildly damaged cell



p53-related DNA repair

Bystander bad cell



p53-independent death sentence: PAM process

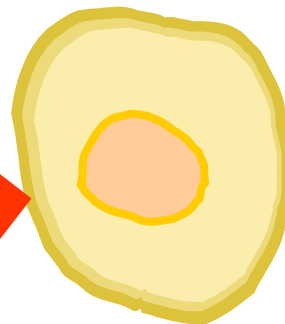
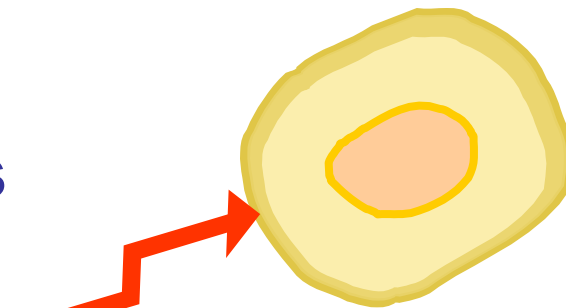
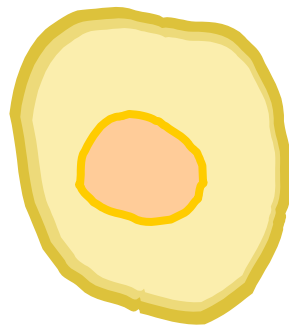
PAM Process: The Good, The Bad and Ugly(?) Cells

Target Cell Population

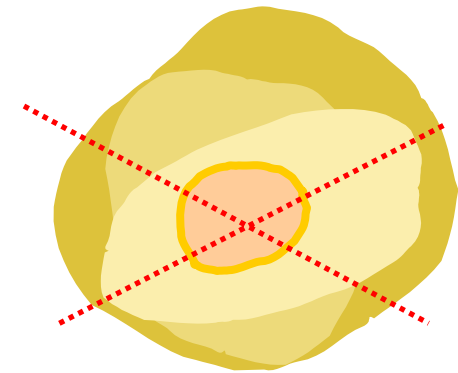
Good cells

mildly damaged

Good Cells



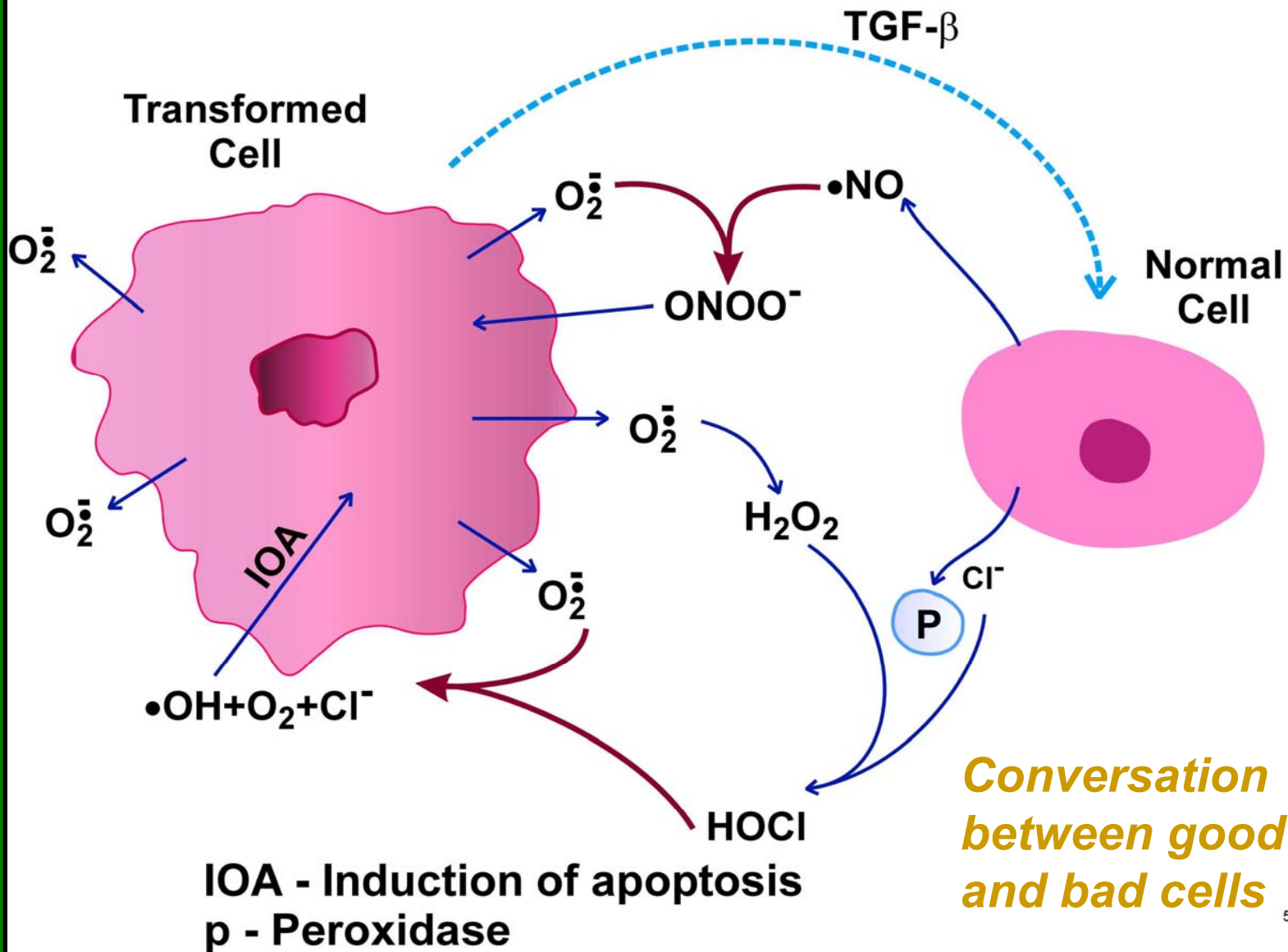
Bad Cell



γ -radiation hit

Apoptotic death sentence

PAM PROCESS



Stochastic Thresholds Associated with NEOTRANS₃ Model

- D_{PAM} , activates PAM as well as high-fidelity DNA repair/apoptosis.
- D_{off} , inactivates PAM but not high-fidelity DNA repair/apoptosis.

$$D_{\text{off}} \gg D_{\text{PAM}}$$

After very high doses and after high-LET irradiation lesion bypass may be the preferred repair method.

Temporal Aspects of PAM

- Takes about **4-6 hours to become fully active.**
- Lasts for at least a day after activation.
- **Duration can be extended** by reducing dose rate and extending exposure time.

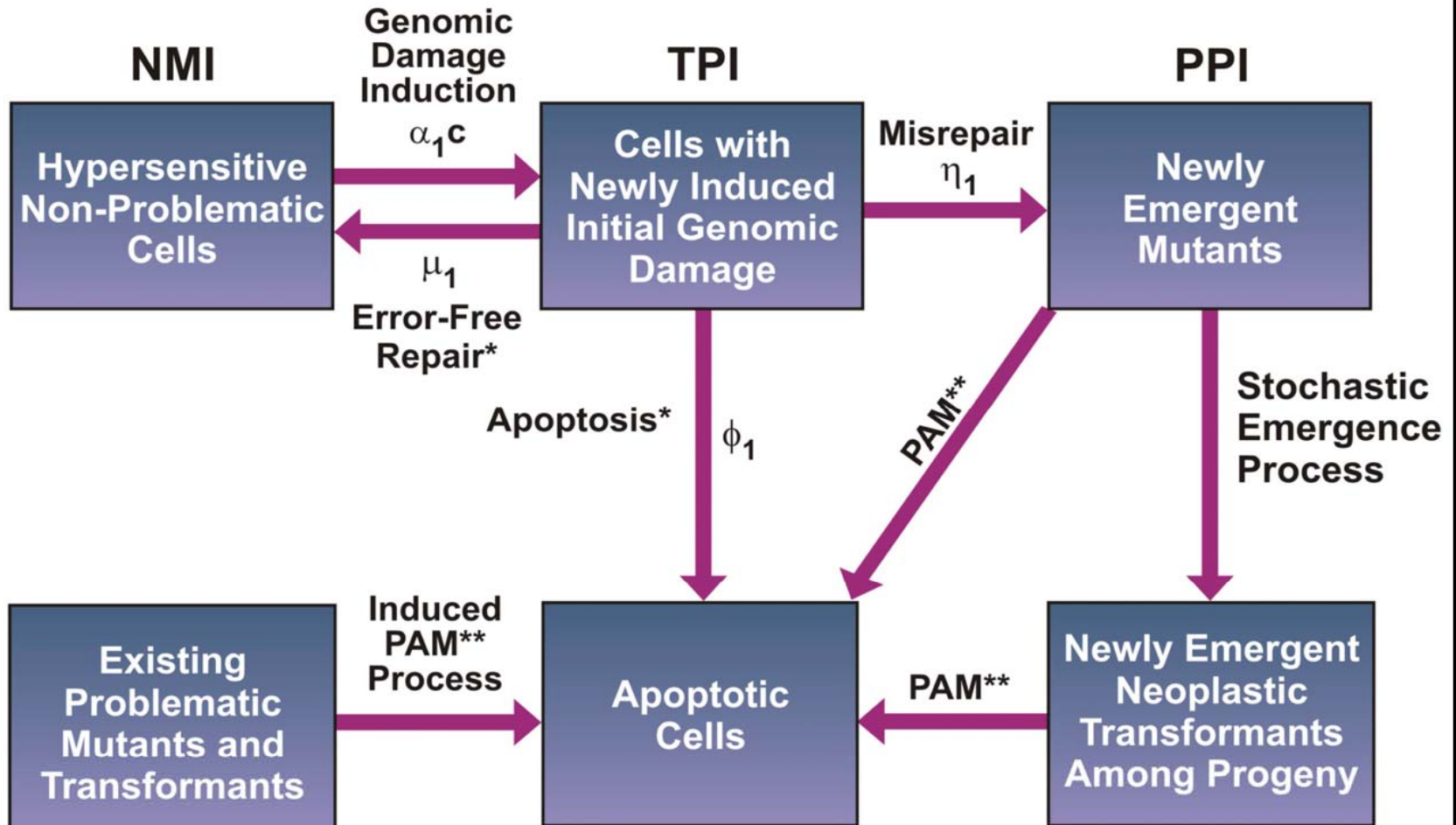
Scott B.R. Mutat. Res. 568:129, 2004.

Scott B.R. NonLinearity (in press).

Genomic Instability States Associated with NEOTRANS₃ Model

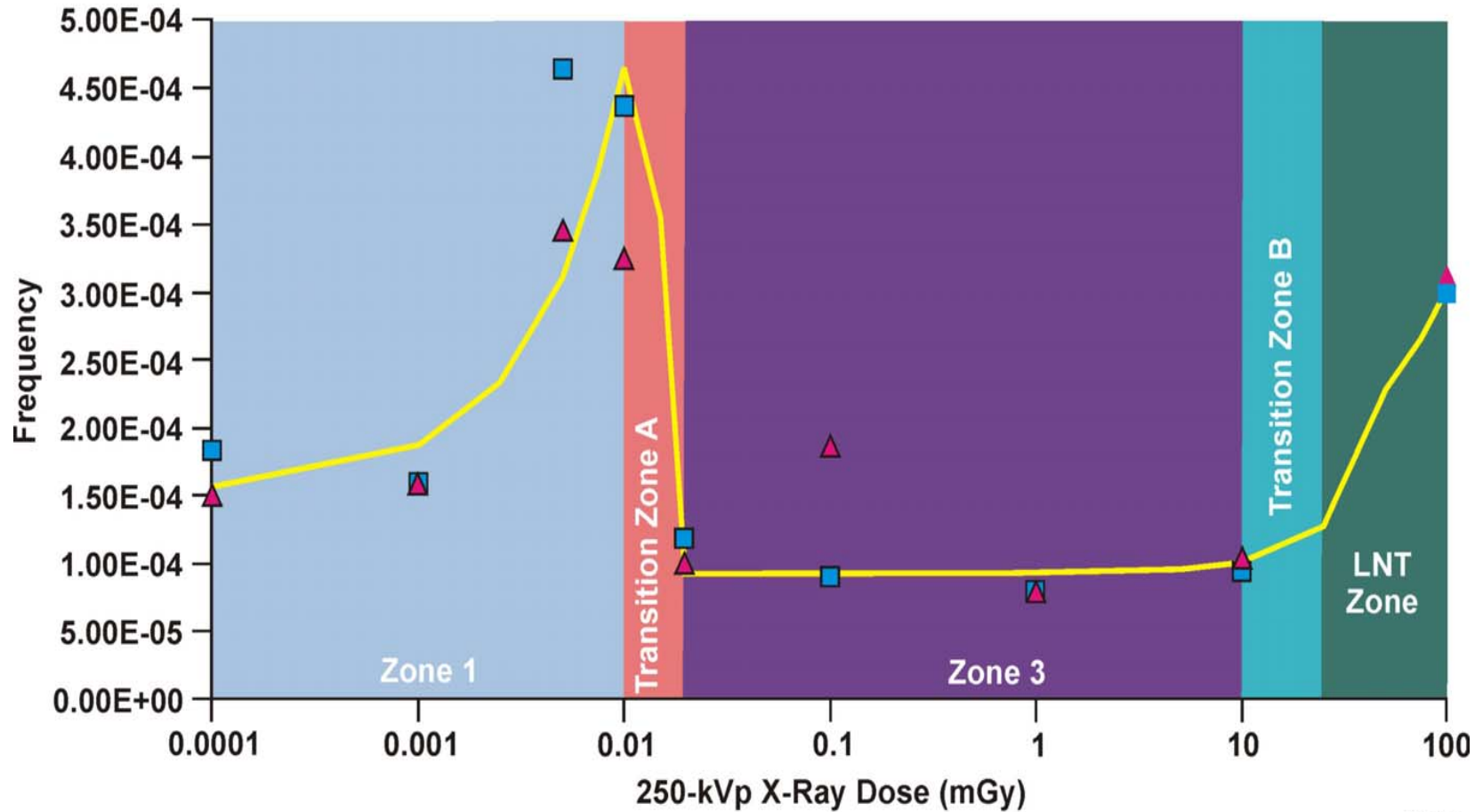
- Normal minor instability (**NMI**).
- Transient problematic instability (**TPI**).
- Persistent Problematic instability (**PPI**).

NEOTRANS₃ MODEL



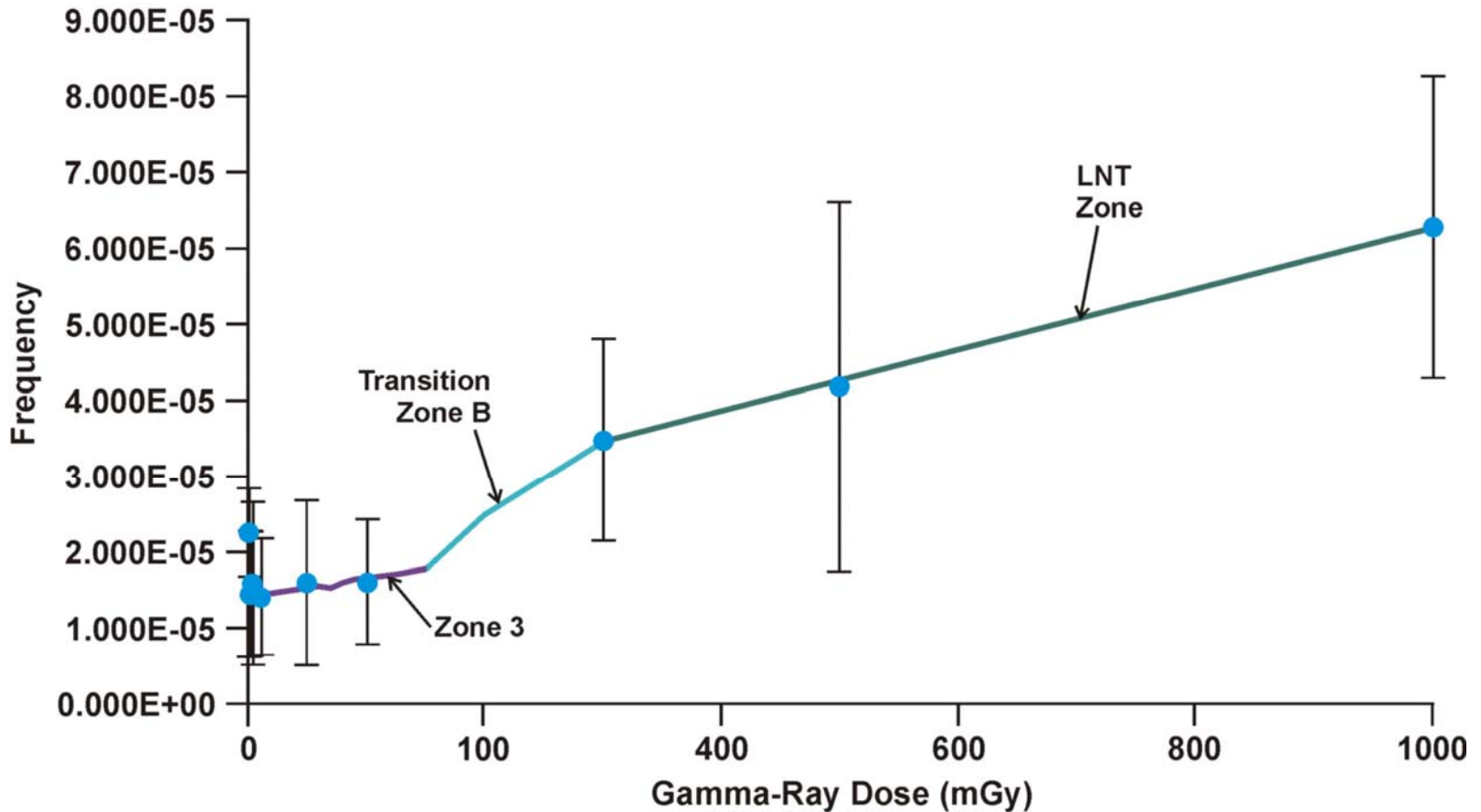
*p53-Dependent
 **p53-Independent

Inversion Mutation Frequency in pKZ1 Mice: Spleen data from Hooker *et al.* (2004)

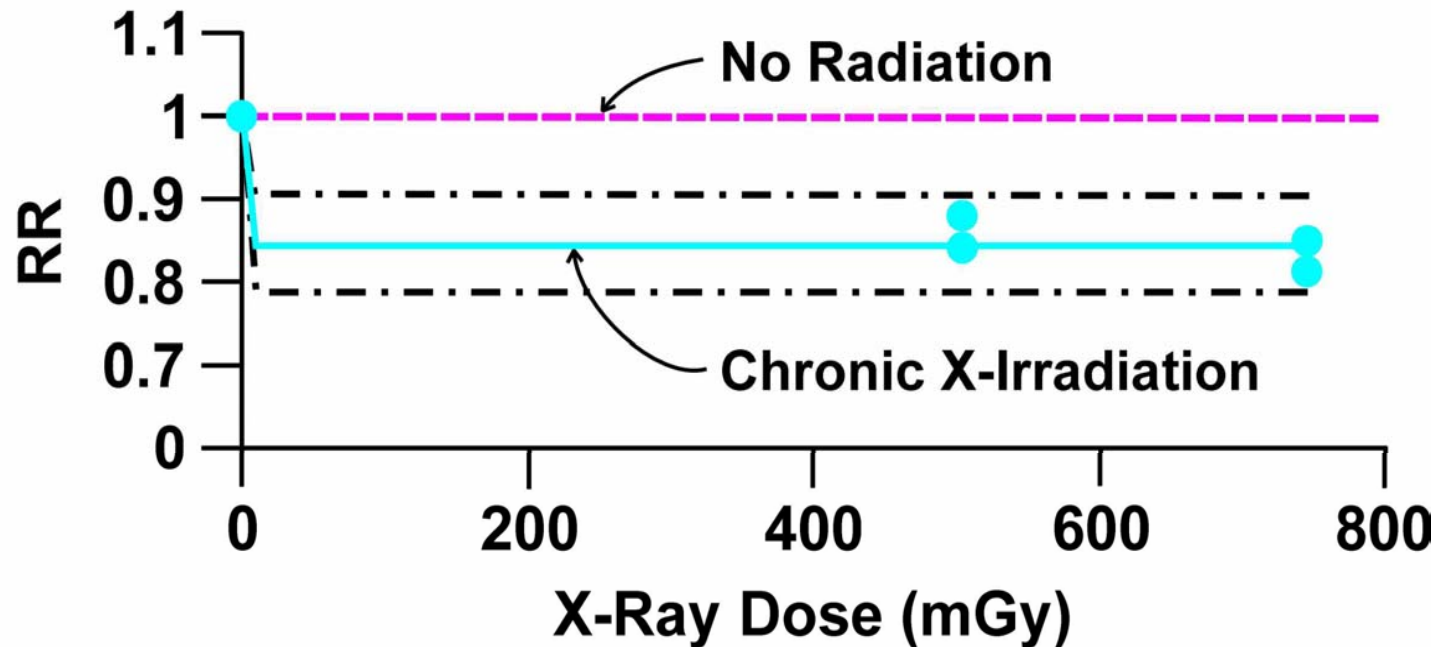


Average weekly background low-LET radiation ≈ 0.02 mGy.

Transformation Frequency: HeLa x Skin Fibroblast Hybrid Cells (Redpath *et al.* 2001)



LUNG CANCER MORTALITY RELATIVE RISK: CANADIAN TB PATIENTS

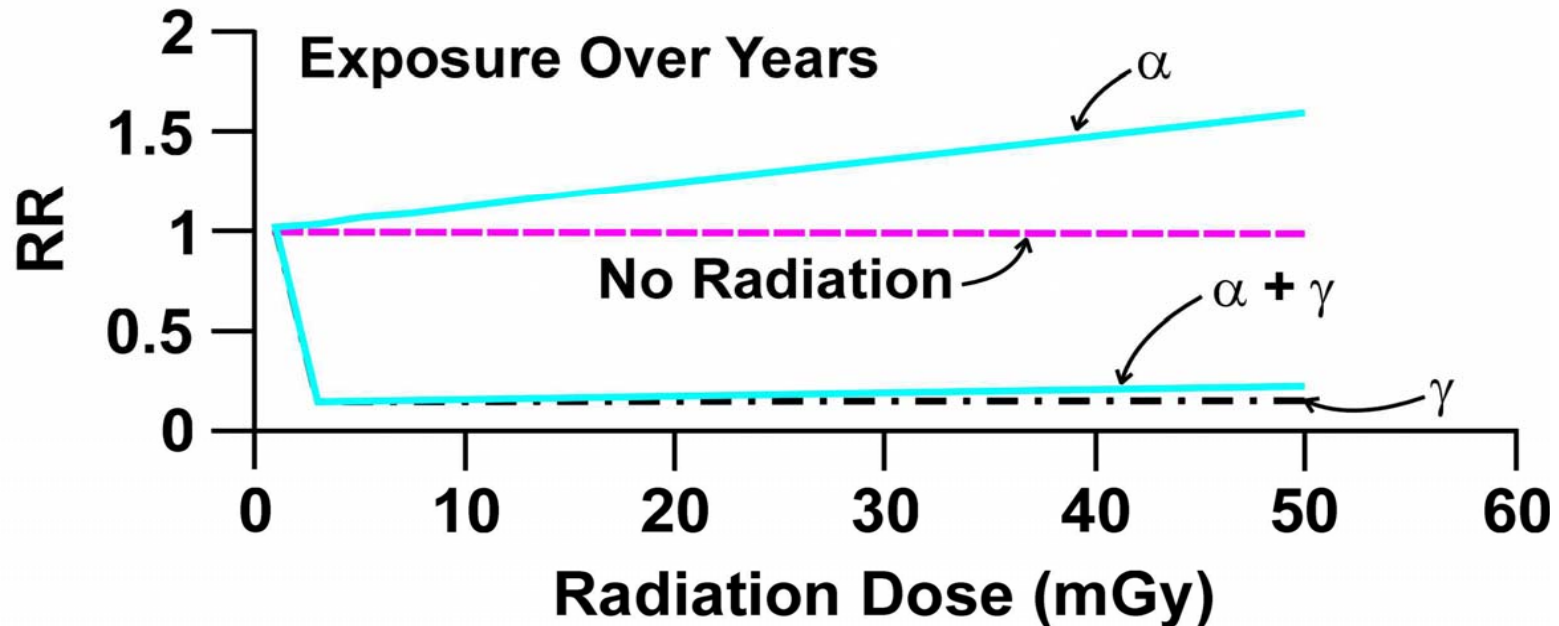


5354-7

Data from Howe 1995.

Blue curve based on NEOTRANS₃ model.

LUNG CANCER RELATIVE RISK: MAYAK WORKERS



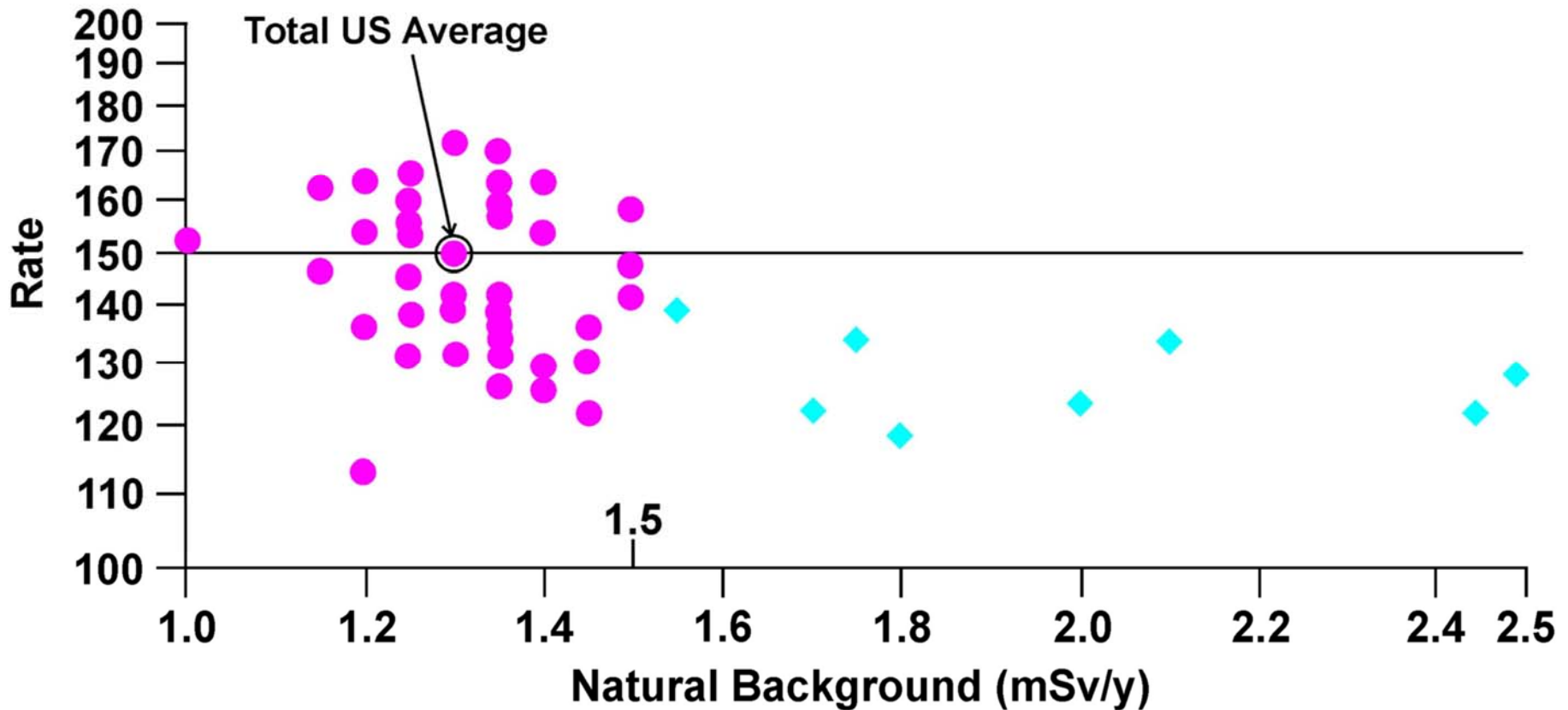
5354-8

PROFAC = 0.86 (86% cancers prevented)

PAM protected against cigarette smoke and alpha radiation induced cancers

ANNUAL CANCER MORTALITY/100,000 FOR US STATES (1950-1967)

Frigerio and Stowe, (1976)



Ratio of Observed to Expected Leukemia & Lymphoma Cases by Elevation Above Sea Level^a

Elevation (feet)	Ratio for Males	Ratio for Females
0-500	1.02	1.0
501-1000	0.99	1.01
1001-2000	0.97	0.98
2001-5310	0.81	0.94

^a163 metropolitan areas (Craig et al. 1961)

Low-Dose-Rate Gamma Irradiation Suppresses Cancer

- **10,000 Taiwanese residents** lived in Cobalt-60 contaminated apartments 9 to 20 years.
- Average gamma-ray dose about 400 mGy.
- **Cancer deaths reported to decrease by more than 95%!!!!**
- **Comment: 95% value being questioned by some US critics.**

Chen W.L. et al., Journal of American Physicians and Surgeons 9(1):6, 2004.

Conclusions

- **BEIR VII is wrong** about the LNT model being valid for low-LET radiation.
- **Cancer risk could decrease** after low-dose or low-dose-rate exposure.
- **Case-control study unlikely to reveal risk decrease at doses < 100 mGy due to low power.**
- **Cohort studies with internal controls likely to miss risk decrease at doses < 100 mGy.**

Further Implications of our Research

- **Background radiation appears to be protecting us from cancer and other diseases!**
- **Low-LET irradiation can reduce cancer risk below the spontaneous level!**
- **Low-LET irradiation appears to protect against cancer induction by other carcinogens!**
- **A dose-rate-dependent, effective threshold likely exists for inducing excess cancer by low-LET irradiation!**

Collaborators and Other Support

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From: Dan Benz, FDA