The Impact of Bystander Effects and Adaptive Responses in the Health Risks of Low Dose Ionizing Radiation

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Two phenomena have been recently implicated in the effects of low level ionizing radiation

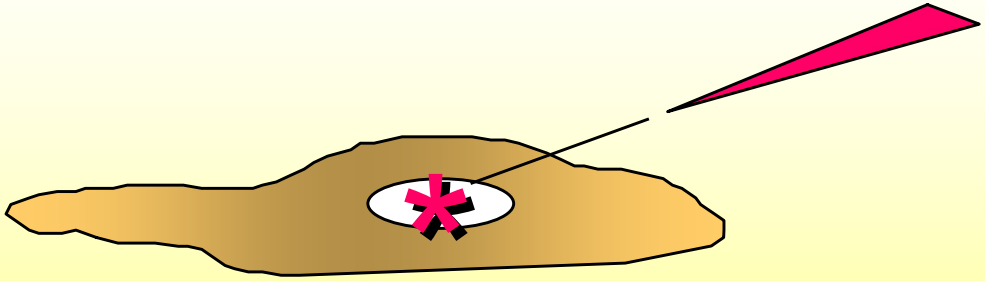
- Bystander effects
- Adaptive responses

Discuss:

- Conformity of the results with traditional thinking and accepted practices
- Their mechanisms & the potential implication to radiation protection

Traditional Thinking:

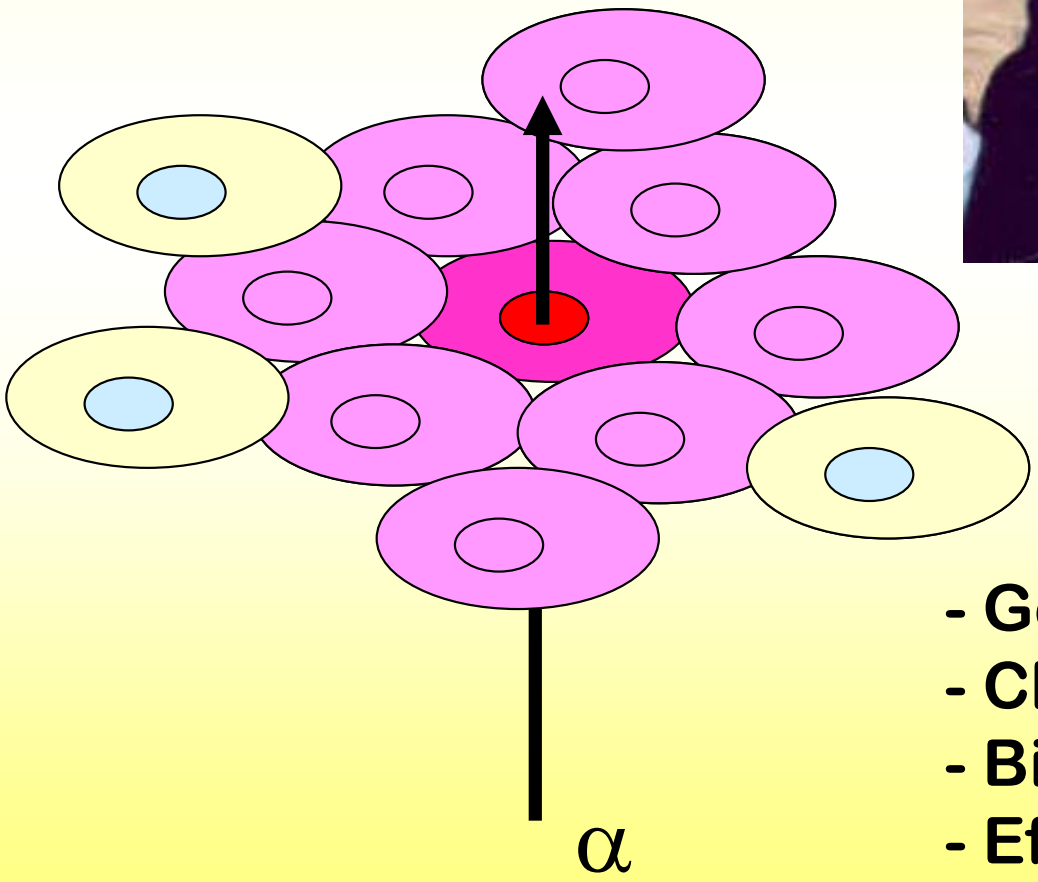
Radiation traversal through the nucleus of cell is a prerequisite to produce genetic damage or an important biological response



Evidence for non-DNA Targeted Effects of Ionizing Radiation

- Genomic instability experiments
- Nuclear gene mutations/chromosomal damage occur following irradiation of the cytoplasm
- **Bystander effects**

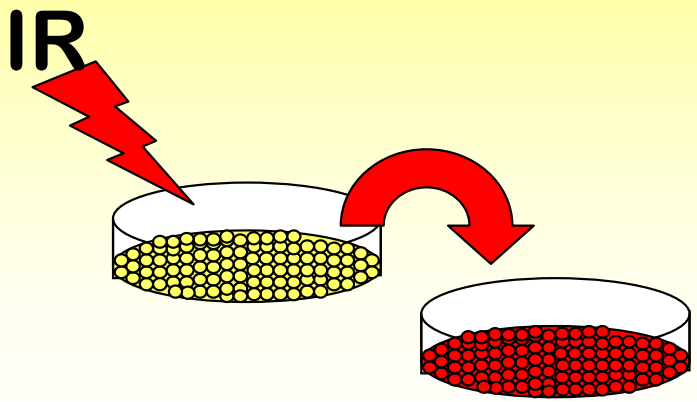
Bystander effects in cell cultures exposed to low fluences of α-particles



- Genetic changes
- Changes in gene expression
- Biochemical changes
- Effects on survival

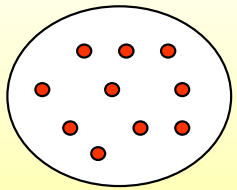
Other protocols

Medium Transfer

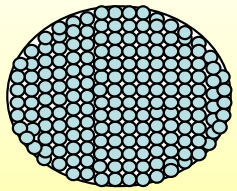


Co-Culture

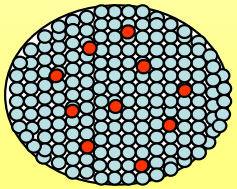
^{3}H-Thymidine Labeled cells

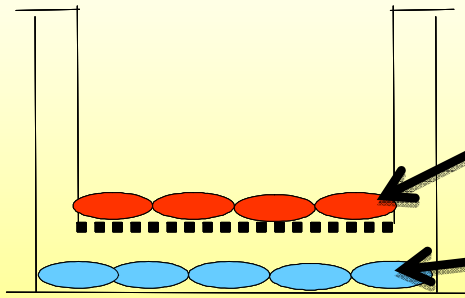


Bystander cells



Co-culture





Bystander Effects **show that biological signals may be transmitted from irradiated to non-irradiated cells**

In general, they have been considered to amplify the (*damaging*) effects of radiation!

The bystander effect has been mainly considered to be a low dose/low fluence phenomenon (relevance to risk at low doses!)

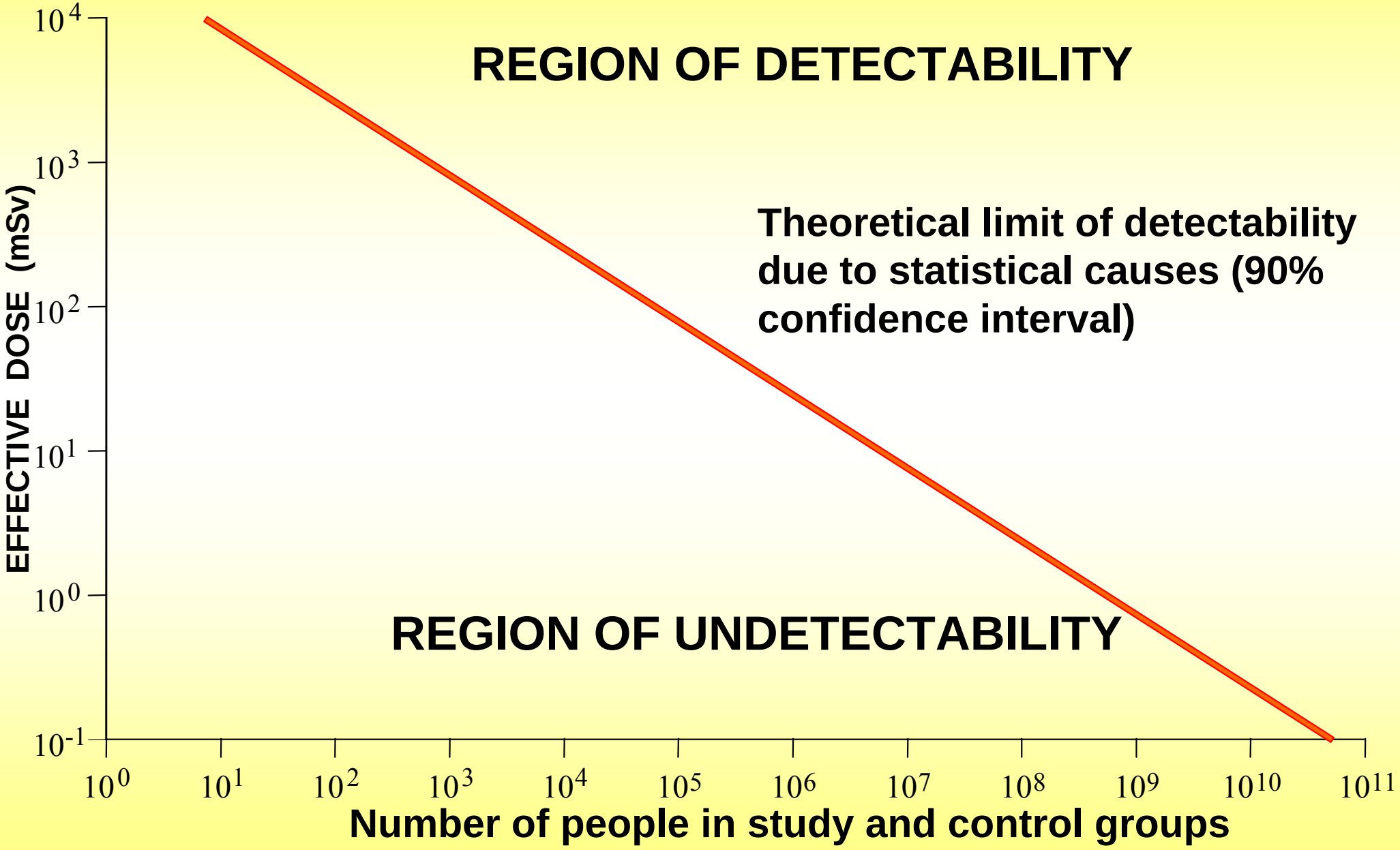
- During their lifetime, humans are mainly exposed to **low dose radiation**

- Thus, **evaluation of risks** for human health, at low doses (low dose-rate), constitutes an important issue in **radiation protection**

The frequency of human exposure to low dose ionizing radiation has been on the increase

(Diagnostic radiology: > 2 billion procedures/year worldwide, many involving children)

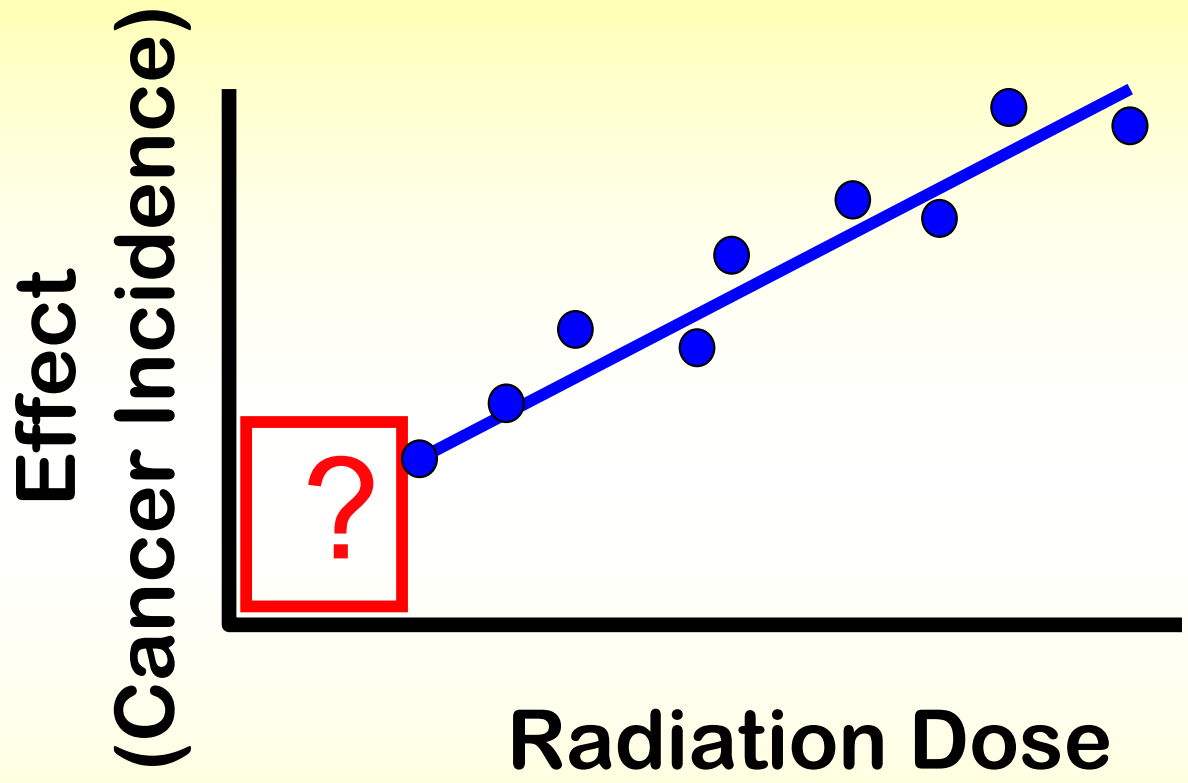
Limits of Epidemiology



Courtesy of Dr. Zenat Carr

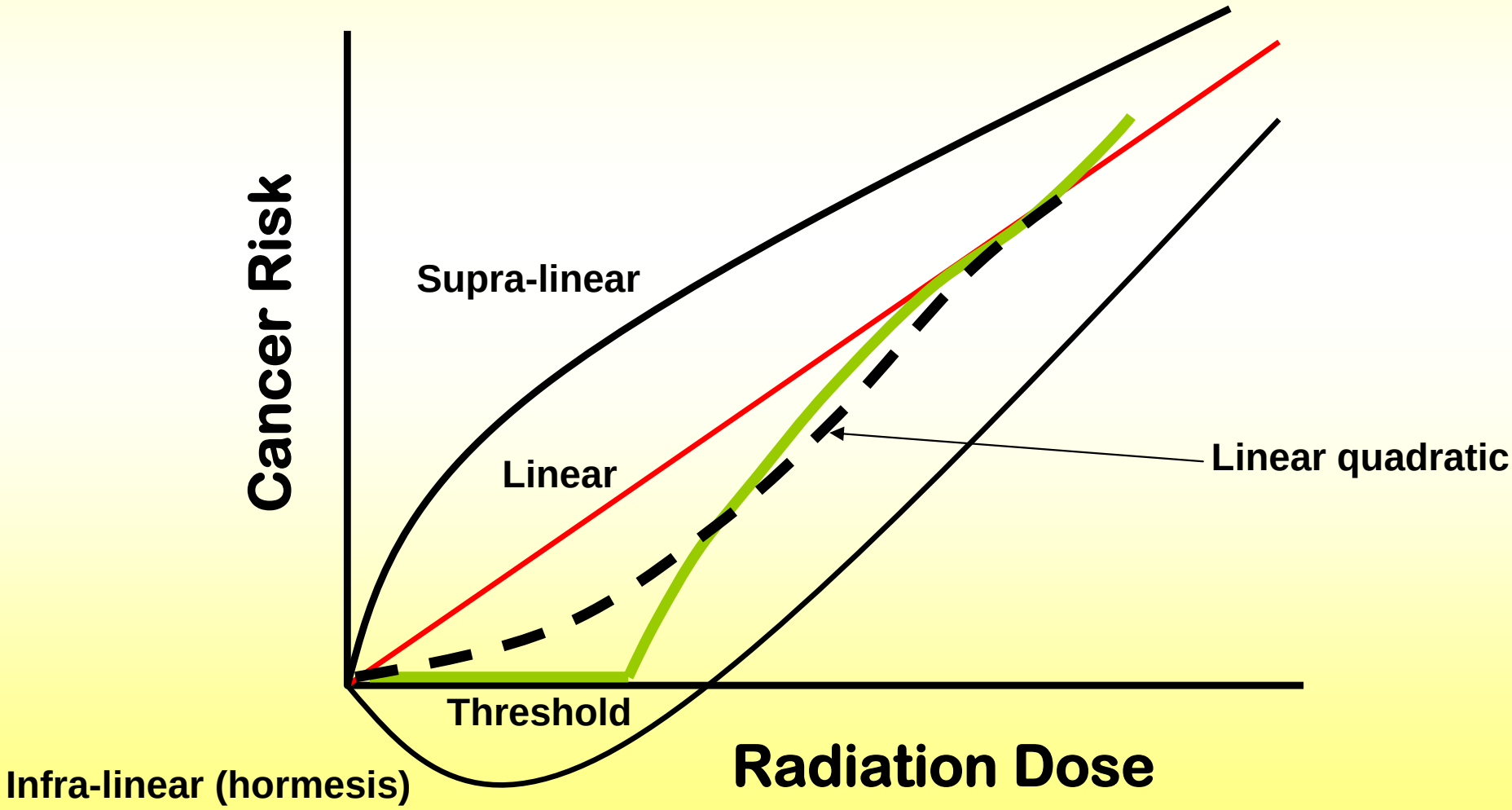
Due to limitations in the statistical power of current human **epidemiological studies** in determining risks from low dose radiation exposures, **mechanistic studies** are being considered essential to understand biological effects, and to help evaluate risks at low doses

Health Risk and Dose



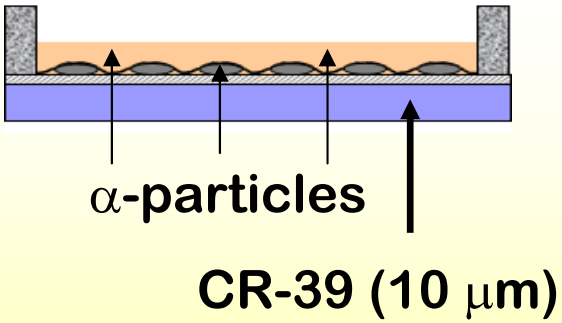
Whereas high doses effects are well-characterized, those caused by low doses are extrapolated from effects quantified at high doses

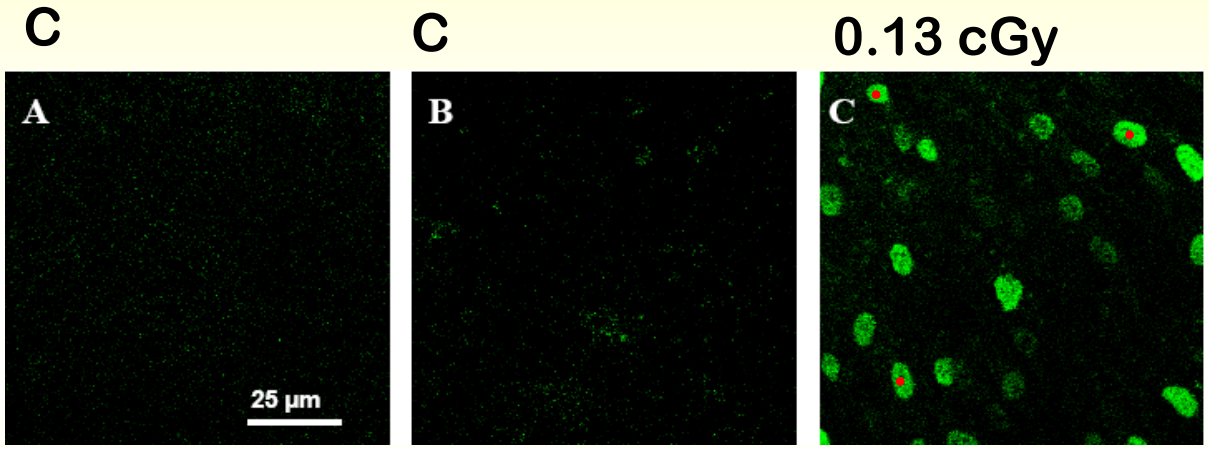
Possible extrapolations of radiation-induced cancer risk to doses where epidemiology cannot yet go

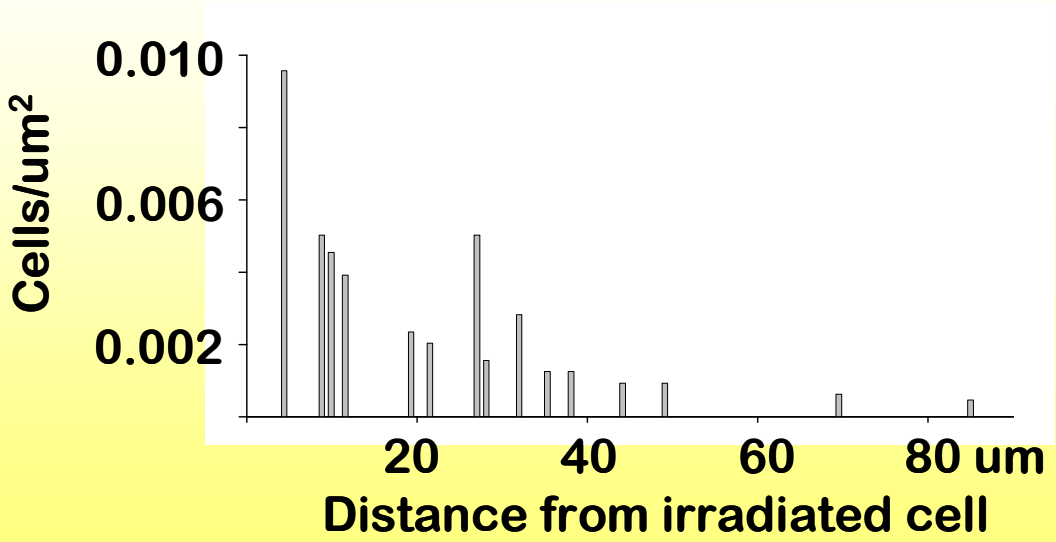


How extensive are bystander effects?

Expression of $p21^{waf1}$, a stress responsive protein, in *confluent* cell cultures exposed to low fluence α-particles: Extent of propagation of the bystander effect







Biological effects in unirradiated human tissue induced by radiation damage up to 1 mm away

Oleg V. Belyakov*†, Stephen A. Mitchell*, Deep Parikh‡, Gerhard Randers-Pehrson*, Stephen A. Marino*, Sally A. Amundson*, Charles R. Geard*, and David J. Brenner*§

Studies used α-particle micro-beam irradiation & the biological end-points of apoptosis and DNA damage

***PNAS*, 2005**

With relevance to risk assessment, there is evidence that stressful bystander effects, in cell populations exposed to low fluences of α-particles (a high LET radiation), persist and are *transmitted* to daughter cells

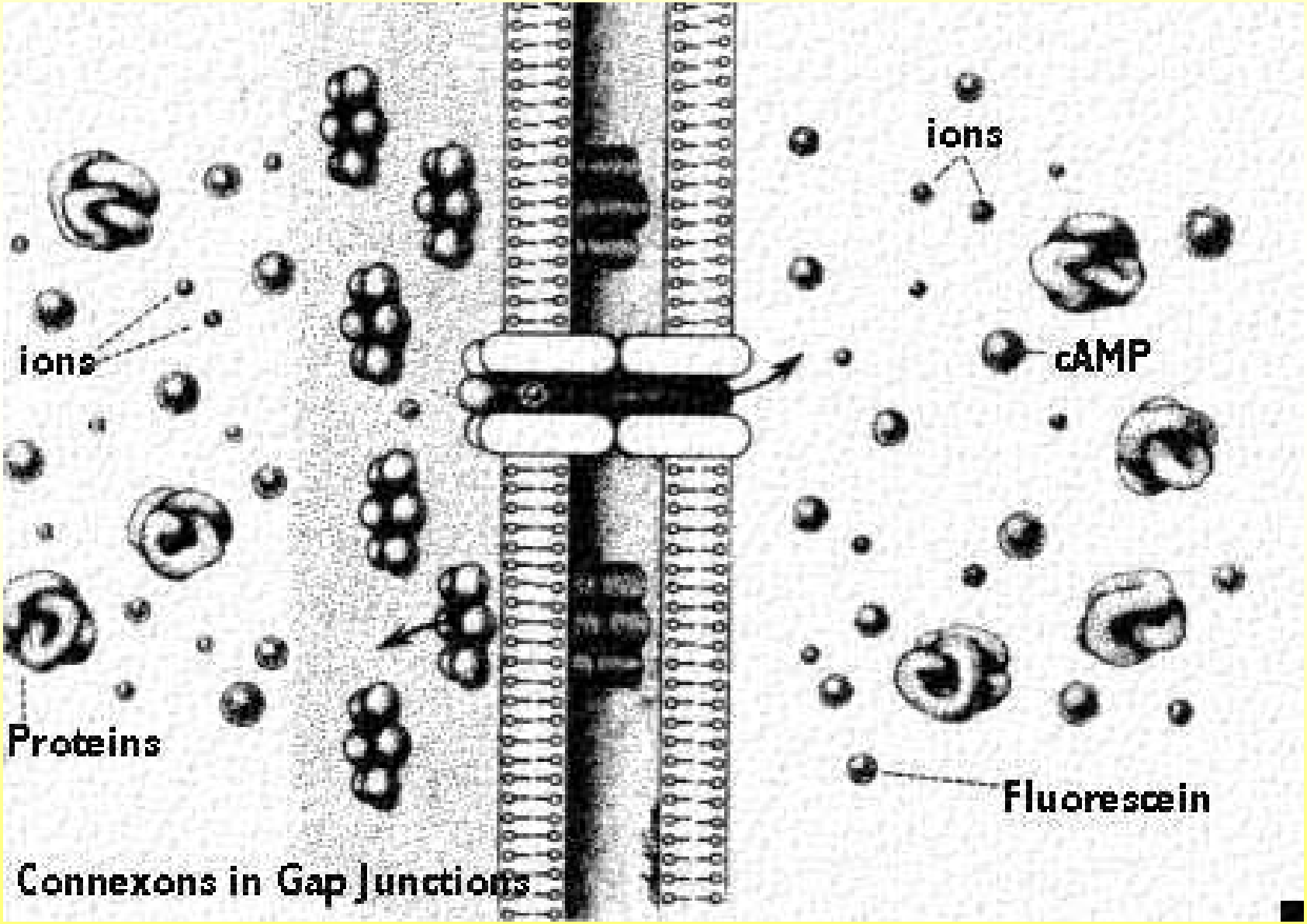
Kadhim *et al.*, *Nature* (1992)
Lorimore *et al.*, *PNAS* (1998)
Azzam et. al., *Radiat. Res.* (2006)

Possible Mechanisms

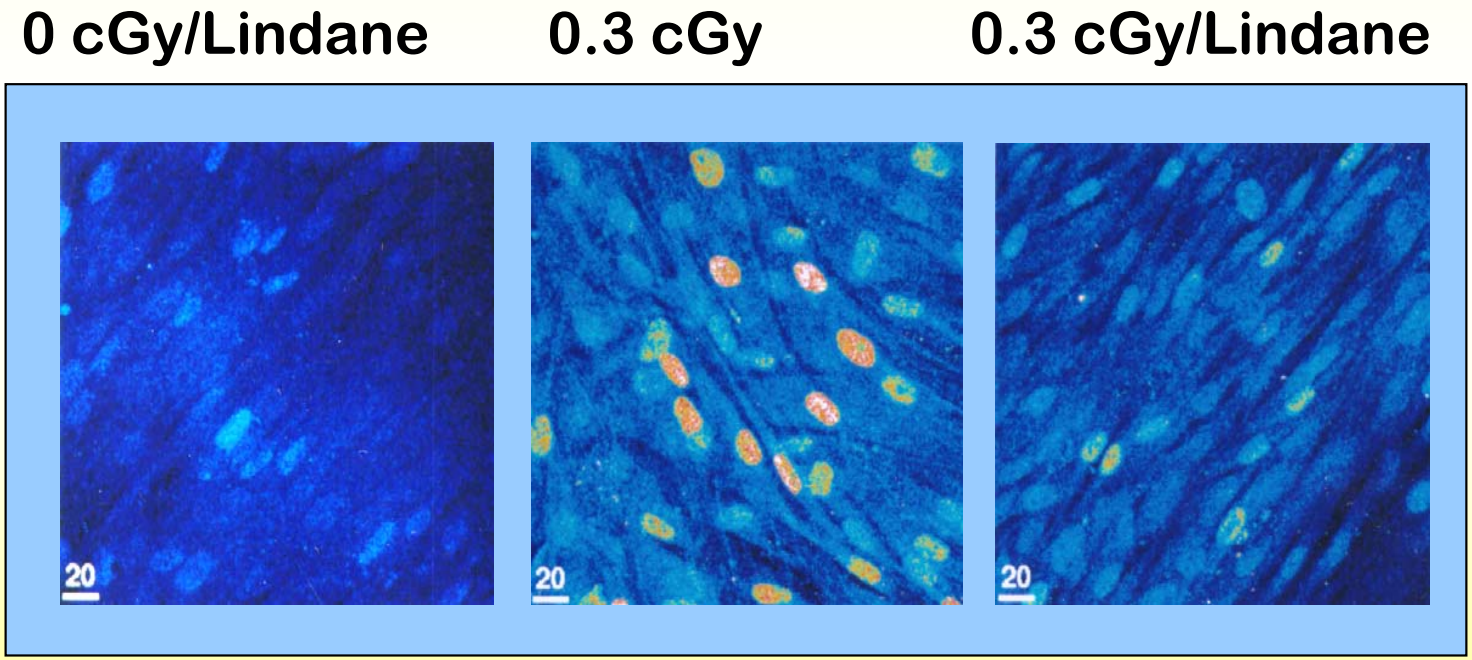
- **Cell to cell communication:**
  - Gap-junctions
  - Secreted factors
- **Oxidative metabolism**
- Involvement of signaling pathways induced by cytoplasmic or membrane originating targets
- Others (e.g. mechanical forces, proximity effects, …)

Direct Cell to Cell Communication

The role of gap-junctions



Expression of $p21^{waf1}$ in confluent normal human cell cultures exposed to low fluence α-particles in presence or absence of an Inhibitor of gap-junction communication



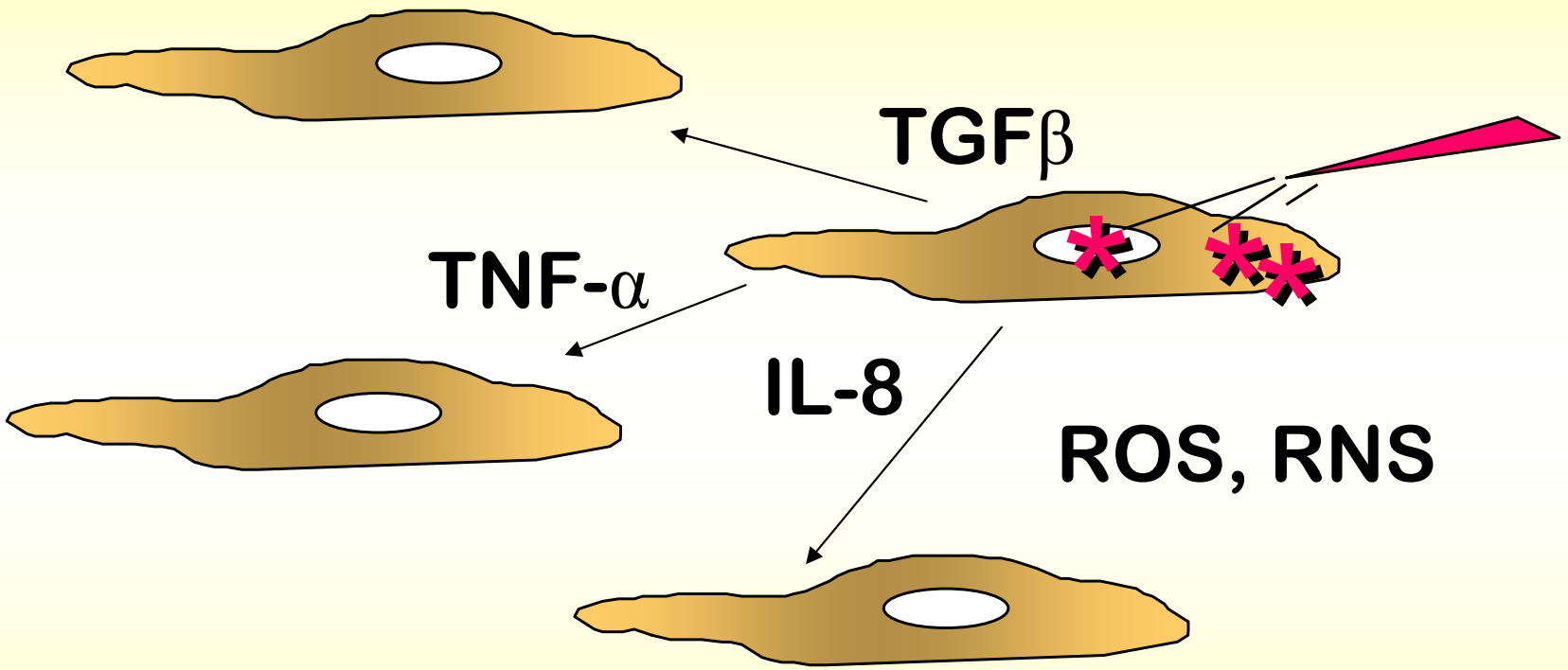
Azzam et al., 1998, 2001

Which molecules are communicated between irradiated and non-irradiated cells?

Identifying such molecules may help our understanding of mechanisms & formulation of countermeasures to attenuate potential harmful effects

The bystander effect involves *two-way* communication between irradiated and bystander cells

Role of Diffusible factors



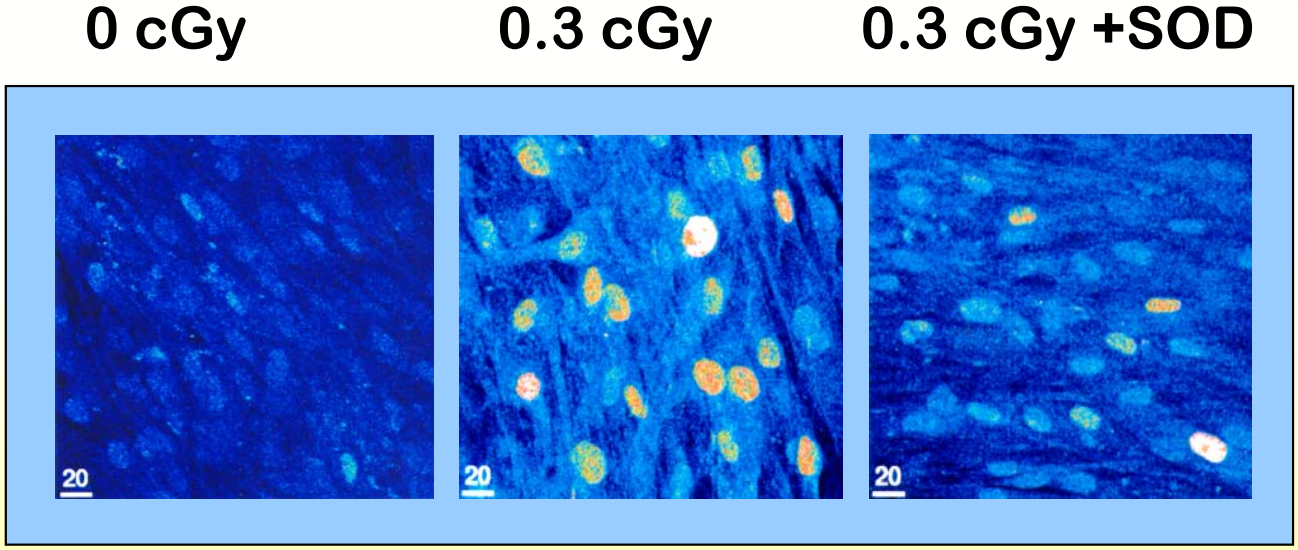
Laboratories of C. Mothersill, A. Gűerci, E. Wright, K. Prise, M. Kadhim, B. Lehnert , H. Matsumoto, K. Held, P. O'Neil, …

Bystander effects suggest:

Irradiated cells may produce a communicable signaling factor or a physical change

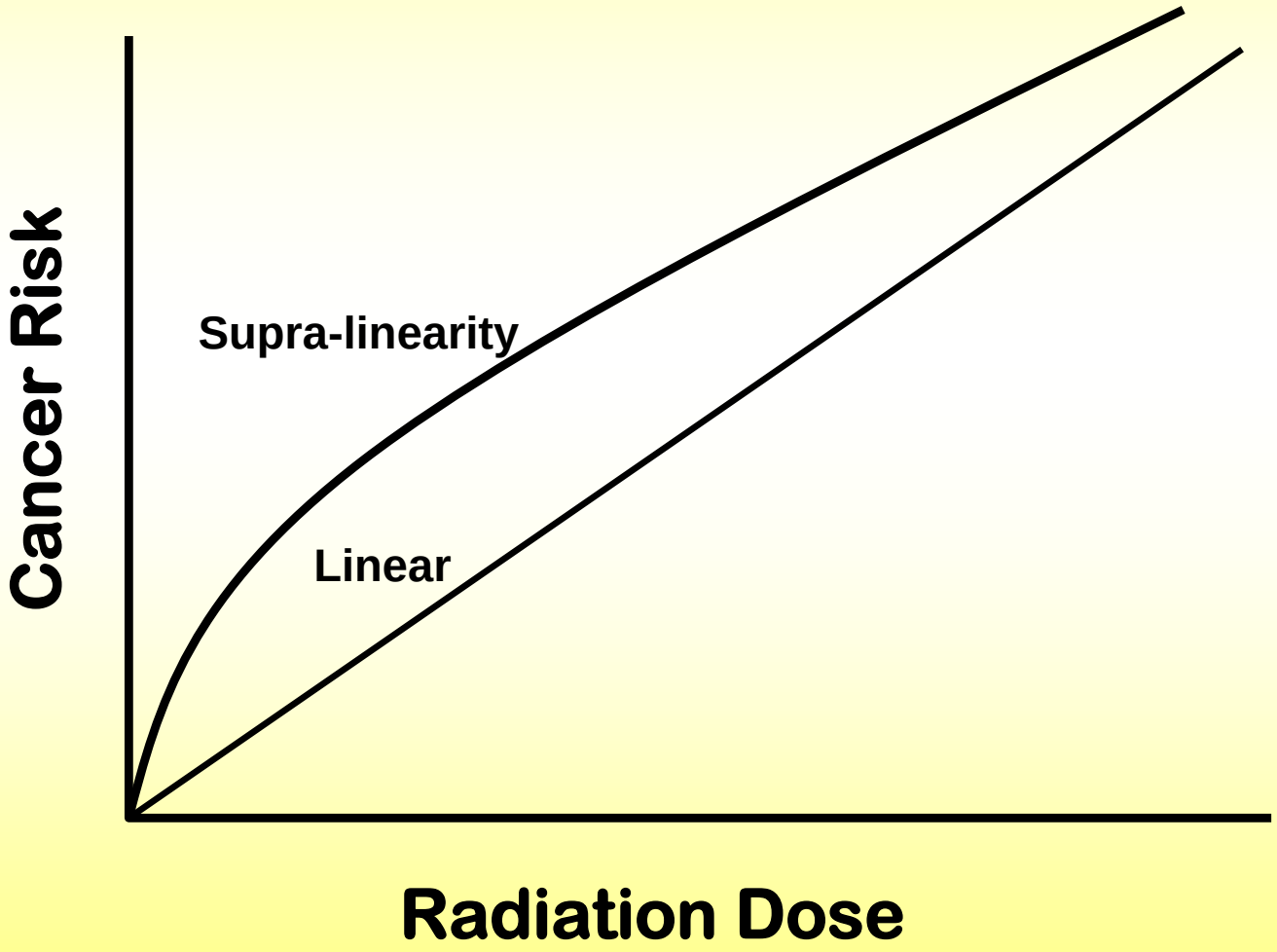
Depending on their mode of intercellular communication and their state (e.g. redox environment), bystander cells may or may not be receptive to stressful signal(s)

$p21^{WAF1}$ expression in α-particle irradiated AG1522 normal human diploid fibroblasts



Azzam *et al.*, 2002

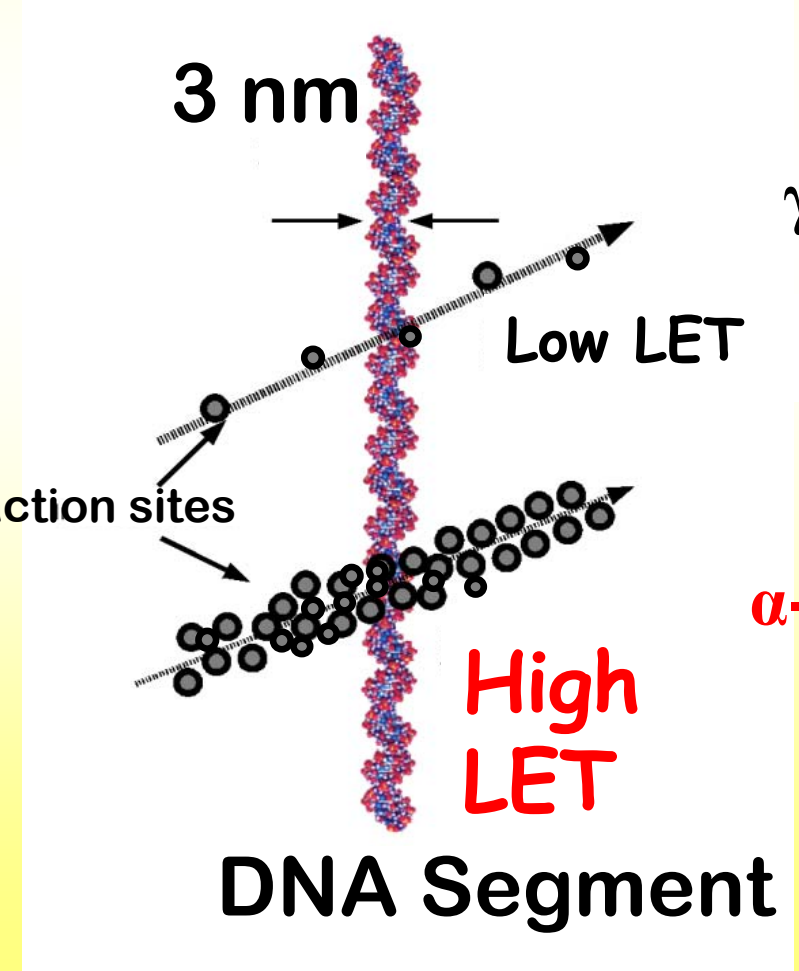
Bystander Effects induced by high LET IR and the Linear-no-Threshold Hypothesis



Radiation Biophysics

Radiation deposits energy in tracks

The lowest dose a cell can receive is one track

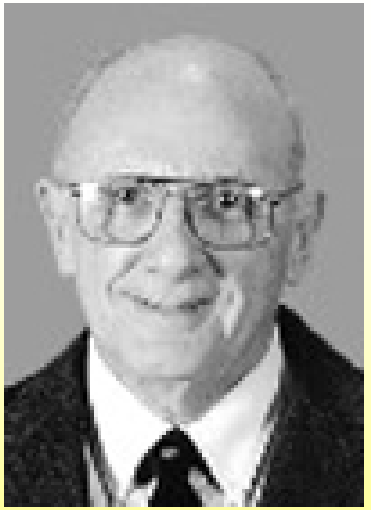


γ- ray: ~ 0.1 cGy

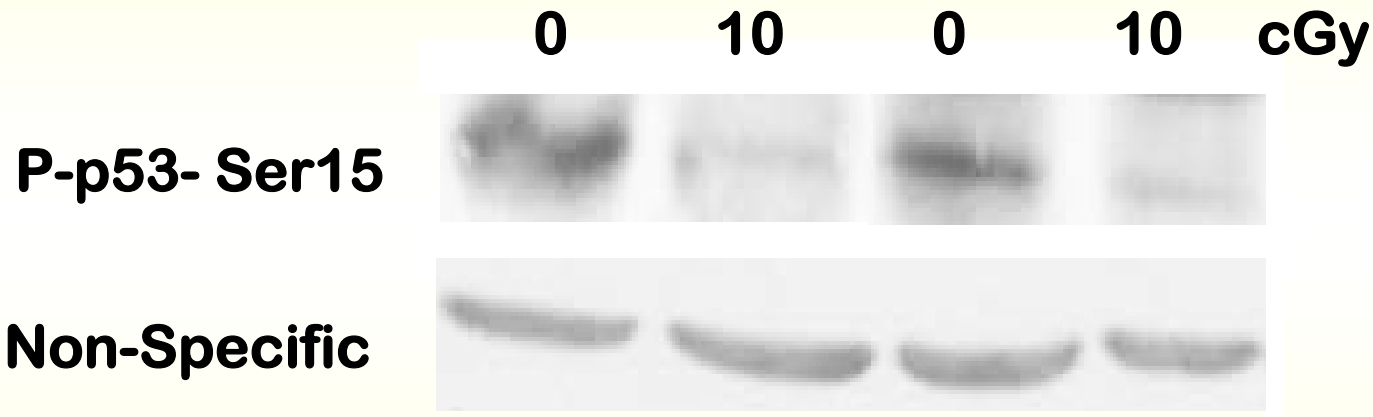
α-particle: ~ 10-70 cGy

Expression of protective effects in cell populations exposed to low dose/low LET radiation

1929-2008



Effect of low dose γ-Rays delivered at variable dose-rate on expression of a marker of DNA damage

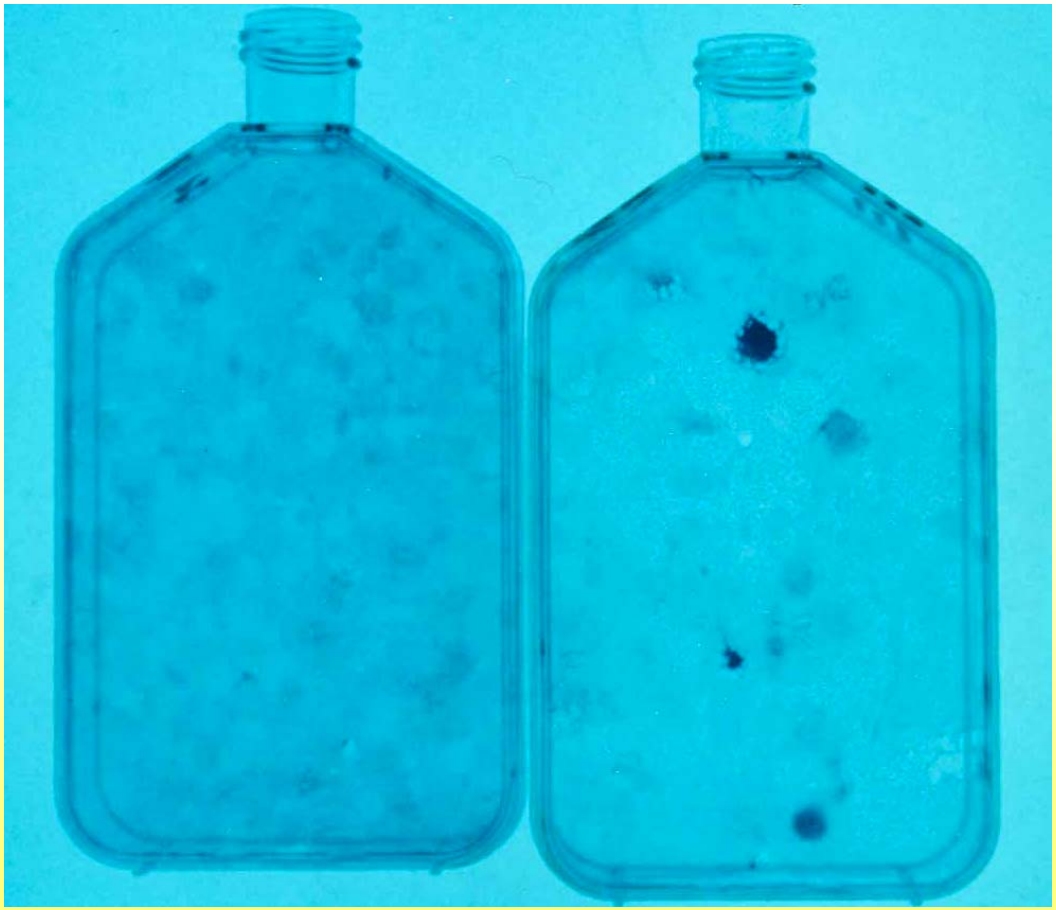


Exposure to 10 cGy delivered over 48 h, at variable dose-rate, reduces phospho-serine 15-p53 to a level below control

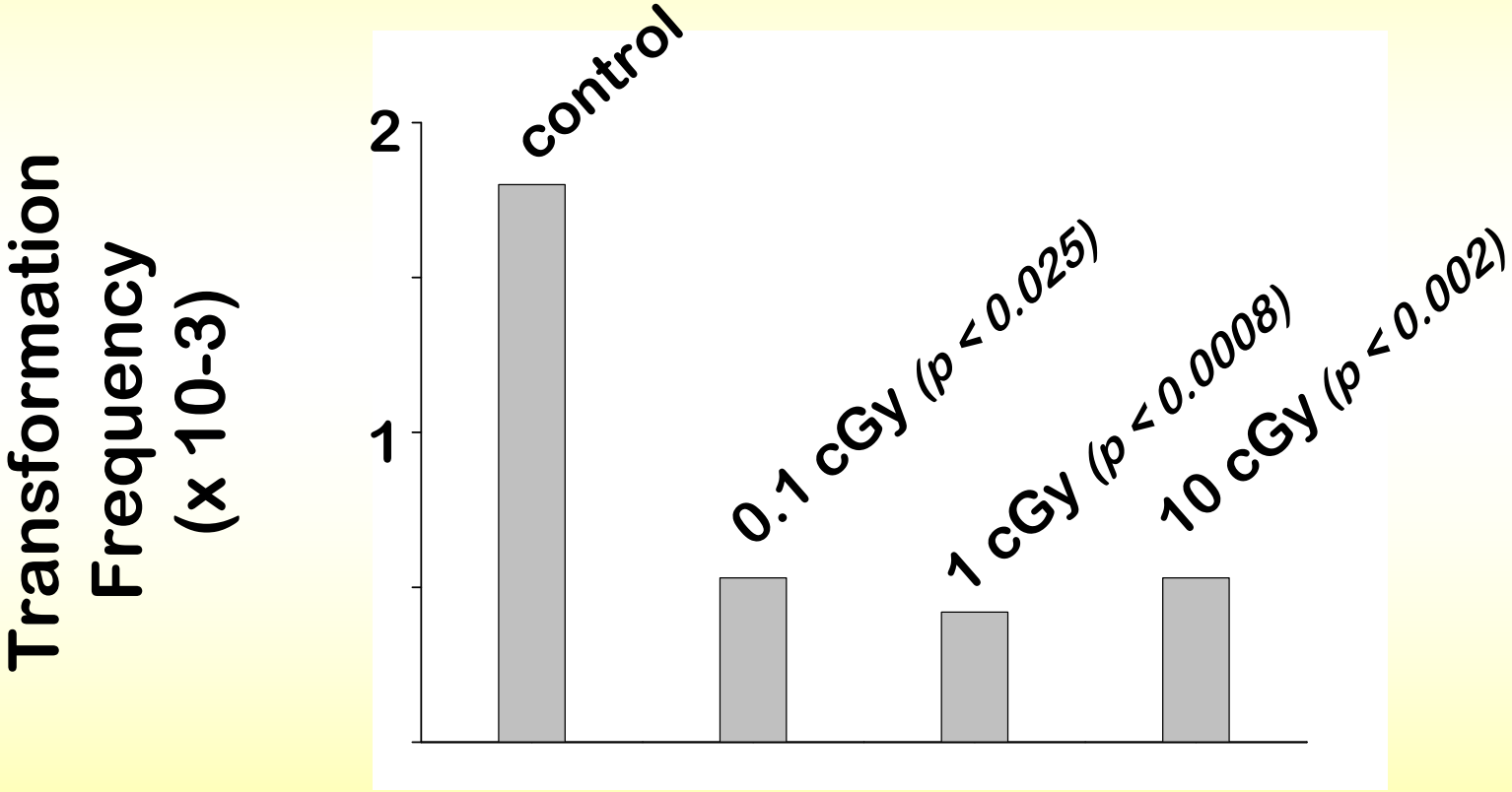
Adaptive response and Risk of Neoplastic Transformation

Neoplastic transformation assay using mouse embryo cells

Control Irradiated

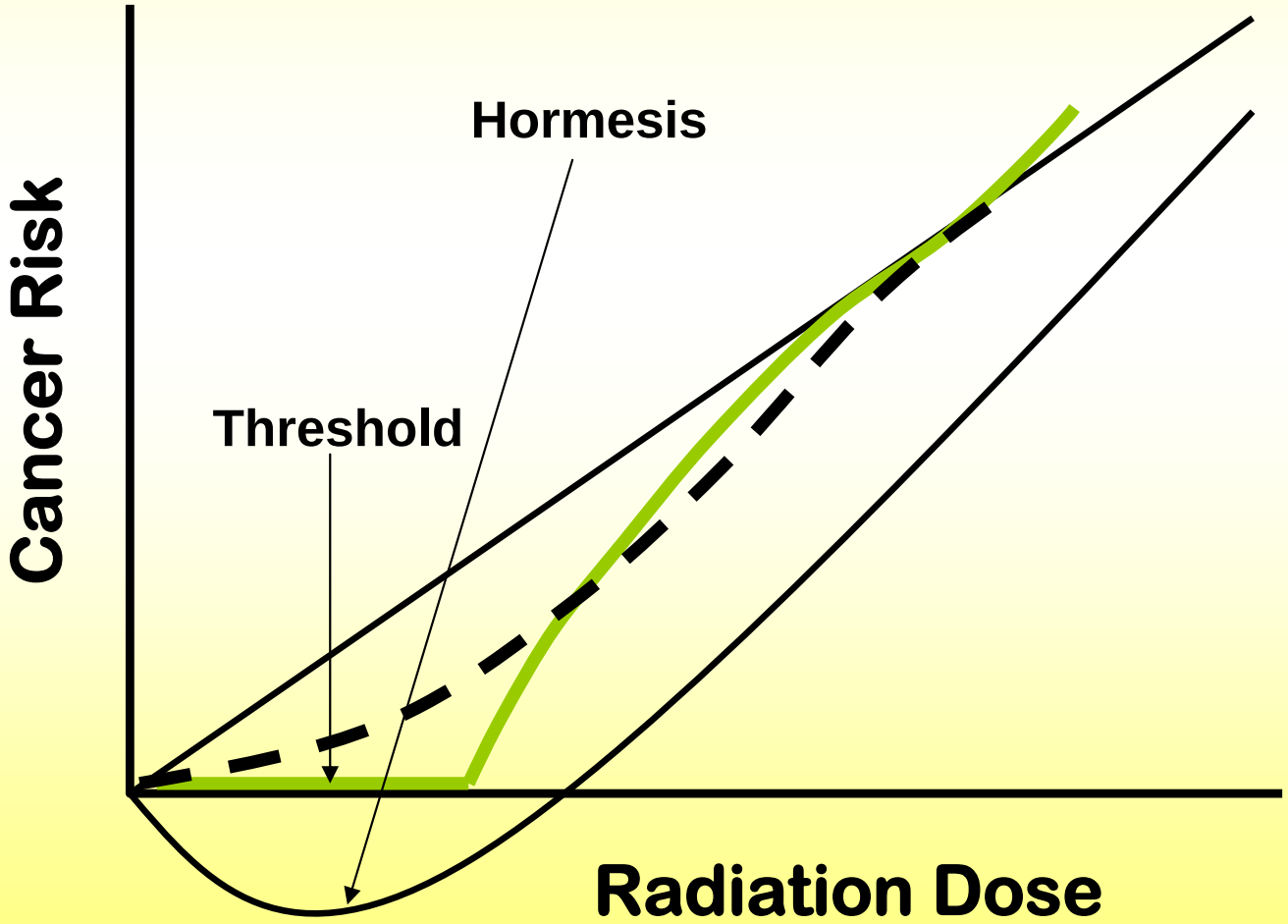


Low Dose γ-Rays Reduces the Spontaneous Transformation Frequency in Mouse Embryo Cells

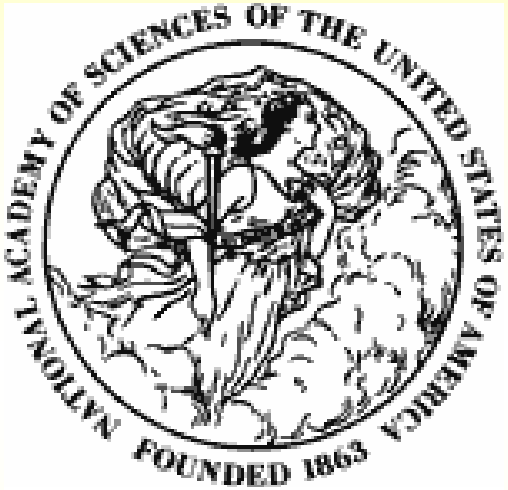


Azzam et al., 1996

Possible extrapolations of radiation-induced cancer risk to doses where epidemiology cannot go



Cancer Risks at Very Low Doses



BEIR VII

&

RADIOBIOLOGY

can guide

empirical epidemiological analyses

especially in areas where there is uncertainty

BEIR VII: Research Needs

1. Determination of the level of various molecular markers of DNA damage as a function of low dose ionizing radiation

2. Determination of DNA repair fidelity at low doses, and whether repair capacity is independent of dose

3. Evaluation of the relevance of adaptation, low dose hypersensitivity, bystander effect, and genomic instability for radiation carcinogenesis

4. Identification of molecular mechanisms for postulated hormetic effects at low doses

5. Tumorigenic mechanisms
6. Genetic factors in radiation cancer risk

Conclusion:

The system of radiation protection needs to be simple and applicable to all (men, women, children, radiosensitive persons ..)

Acknowledgement

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