

Experimental and clinical information for the possible application of LDR- induced hormesis and adaptive response in medical practice

Lu Cai

*Departments of Medicine & Radiation
Oncology*

University of Louisville School of Medicine

Amherst, MA

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A stylized, dark brown mountain range graphic is positioned at the bottom of the slide, spanning the width of the image. The mountains are rendered in a simple, blocky style with varying shades of brown and tan to suggest depth and texture. The background of the slide is a gradient of blue and teal, transitioning from a darker blue at the top to a lighter teal at the bottom.

Background

- Distinct effects of LDR has been recognized more than 20 years ago, and extensively confirmed by subsequent studies in cultured cells *in vitro* and tissues *in vivo*, as shown by hormesis and adaptive response.
- However, due to the public fear of radiation and the current use of so-called linear no-threshold model for national and international radiobiological protection organizations, few studies on the potential application of these LDR-induced hormesis and adaptive response in clinical setting have been explored.

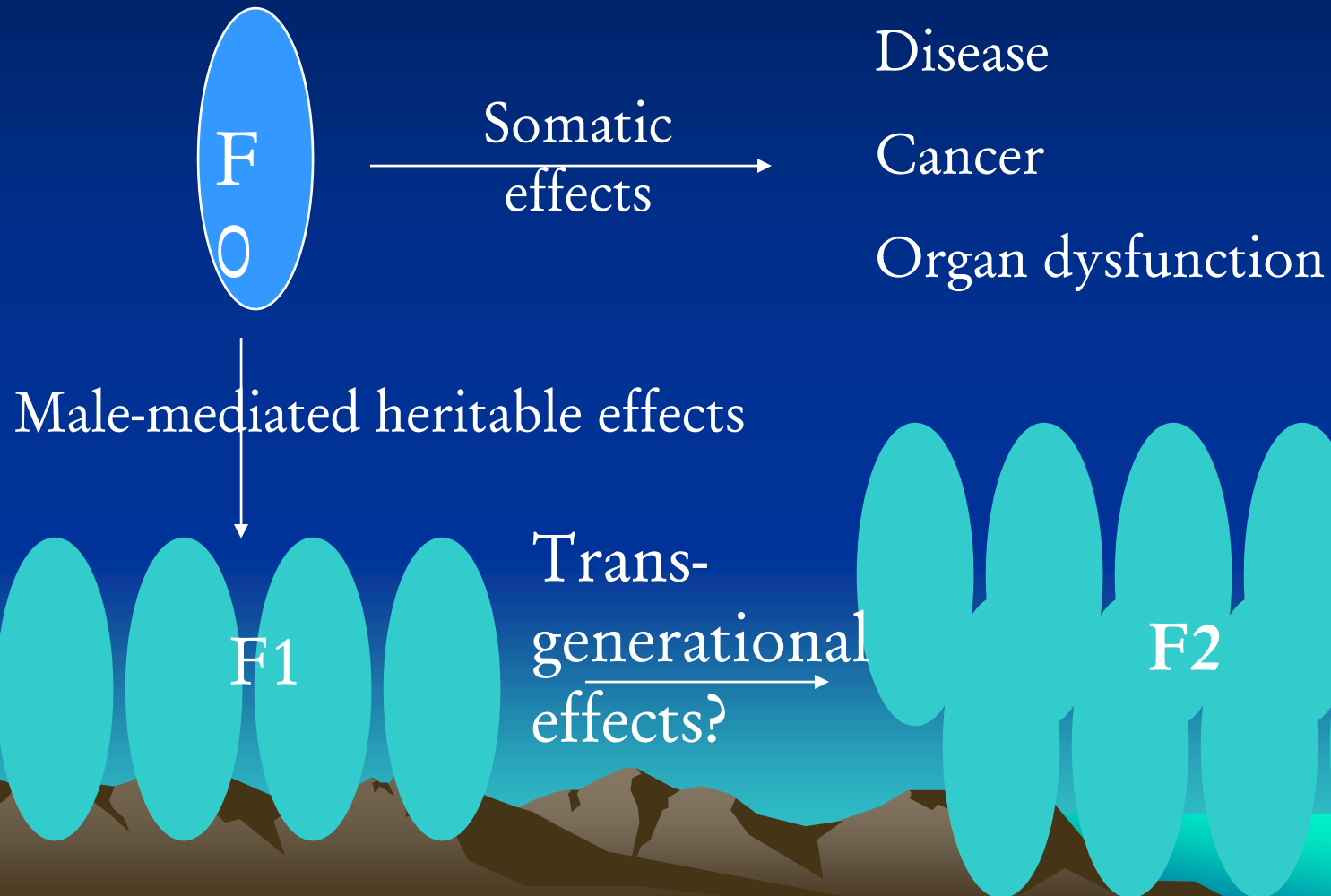


What are the biological or medical implications?

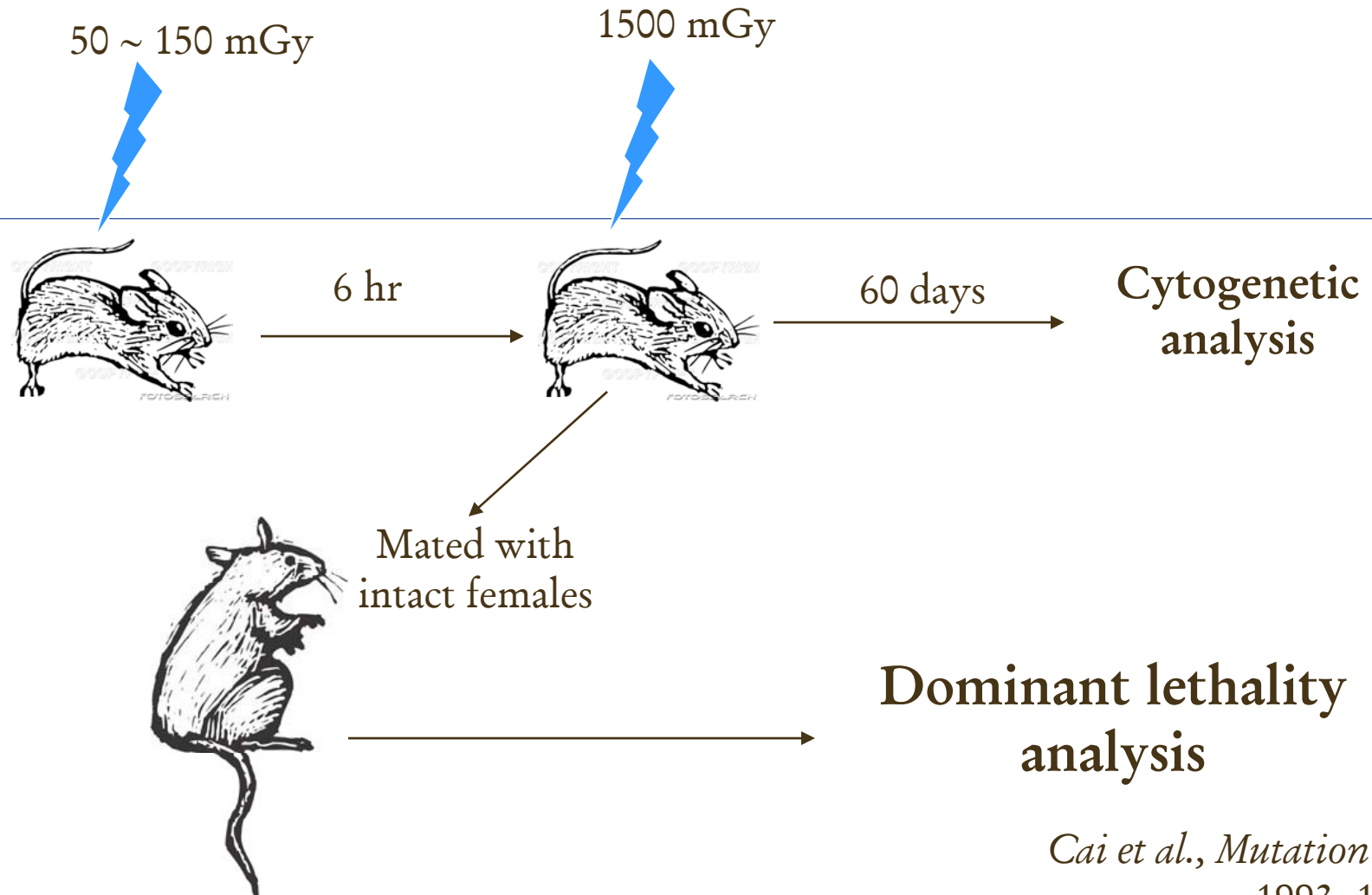
- Effects of LDR on male germ cells
- Anti-tumor studies & pre-protection
- Effects of LDR on normal and tumor cells
- Diabetes



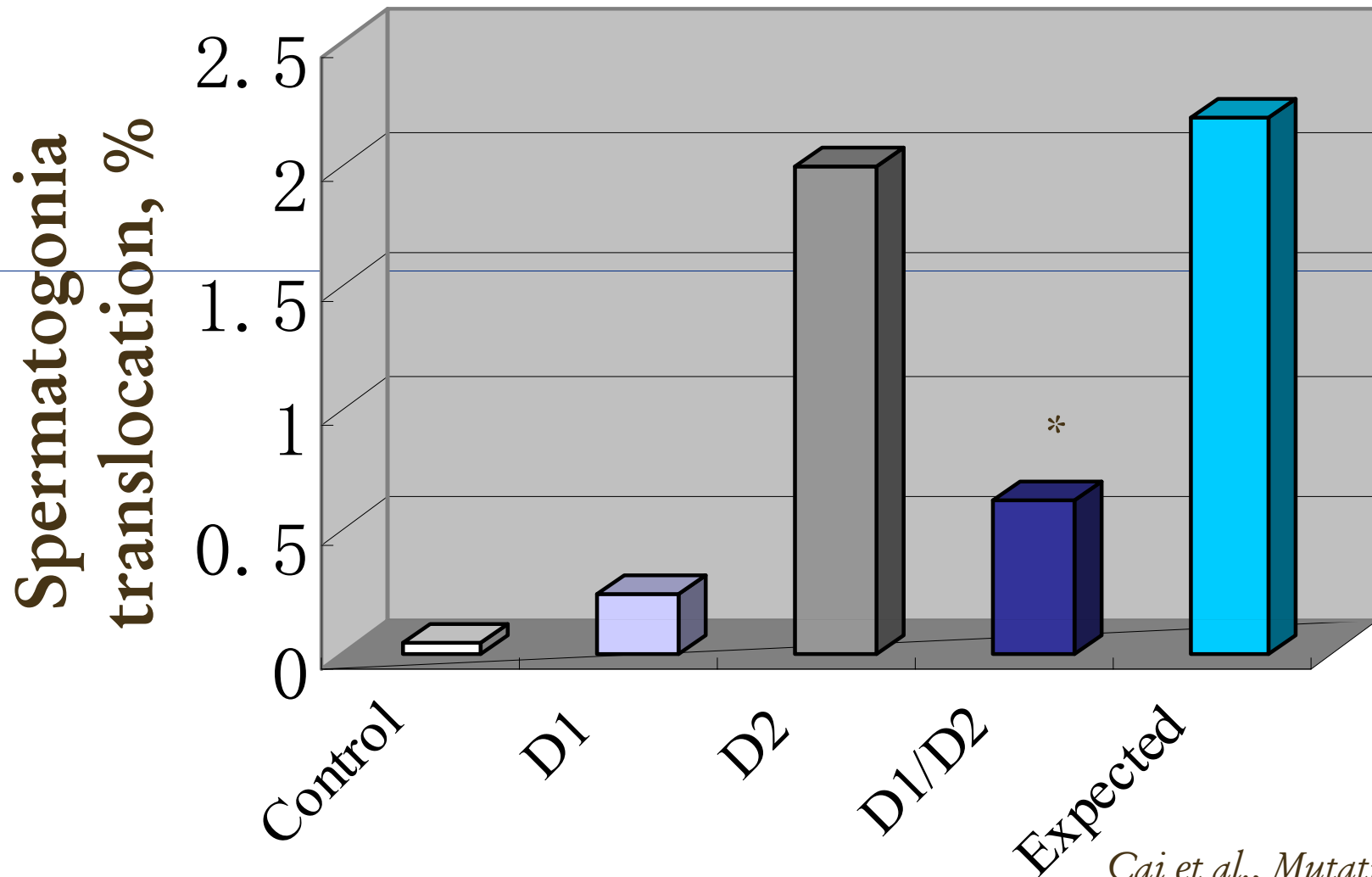
Why I am interested in LDR effect on male germ cells?



Cytogenetic effect of low-dose radiation on male germ cells

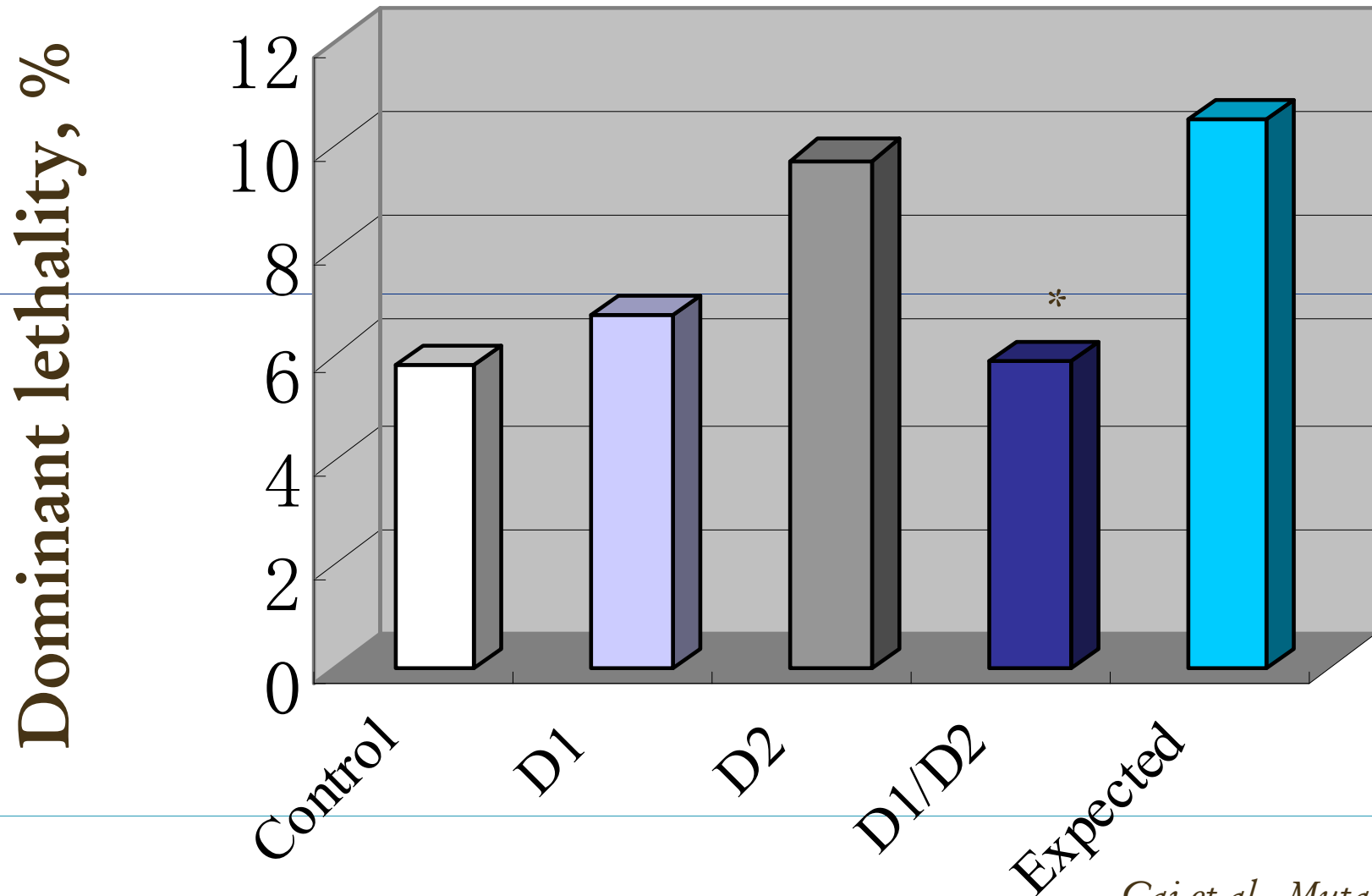


LDR-induced cytogenetic damage



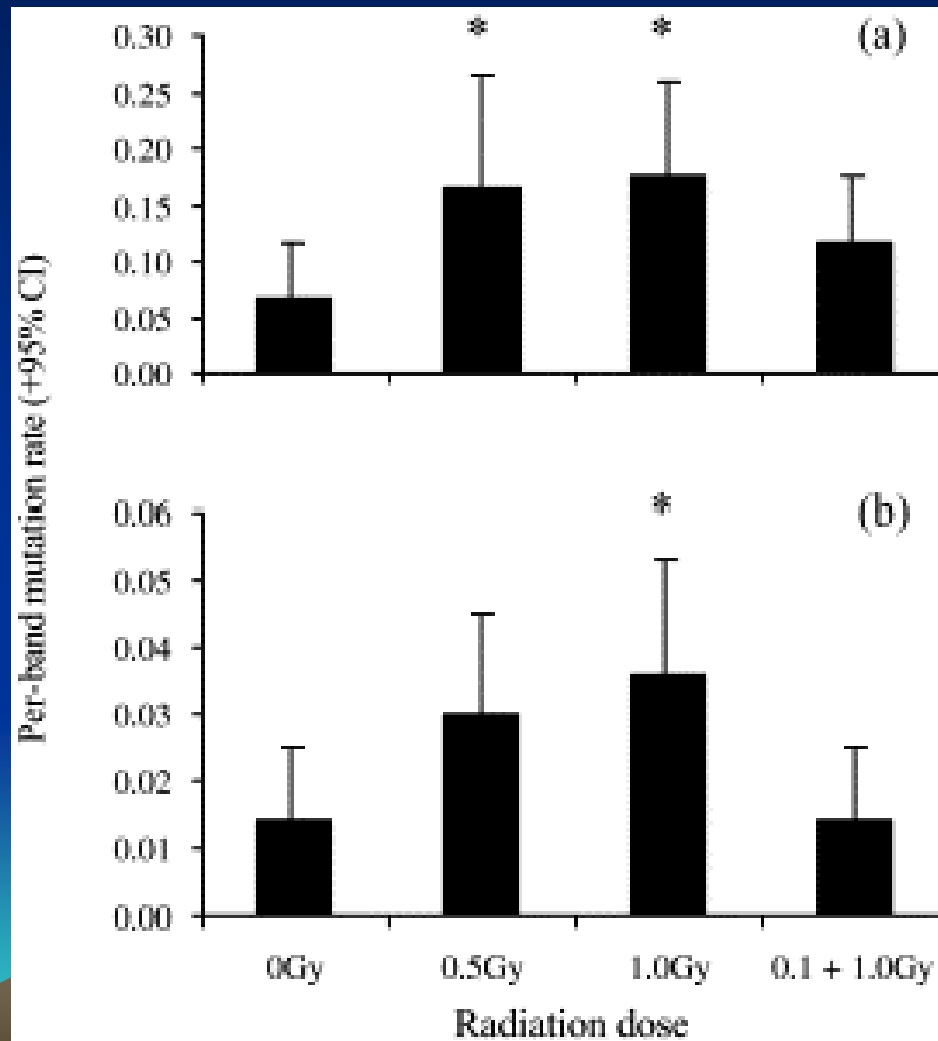
Cai et al., Mutation Res
1993, 1994

LDR-induced heritable effects

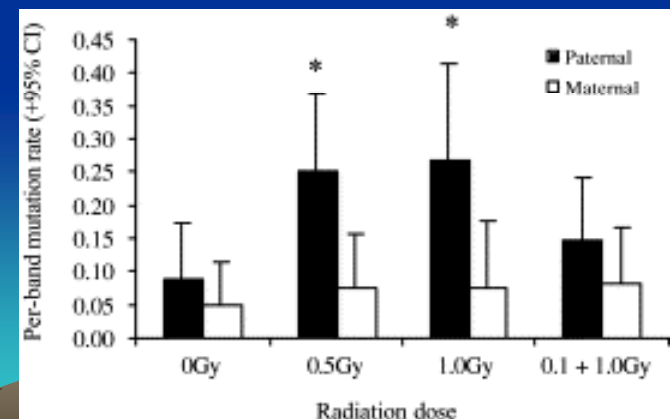


Cai et al., Mutation Res
1993, 1994

Somers CM, Sharma R, Quinn JS, Boreham DR. Gamma radiation-induced heritable mutations at repetitive DNA loci in out-bred mice. *Mutat Res.* 2004 Dec 2;568(1):69-78.



Overall germline mutation rates at ESTR loci in groups of mice where males were treated with four different doses of ionizing radiation from a cesium-137 source. Mutation rates were determined using (a) single locus markers *Ms6-hm* and *Hm-2* pooled, and (b) multilocus probe MMS10.



Several methods related to genomic effects

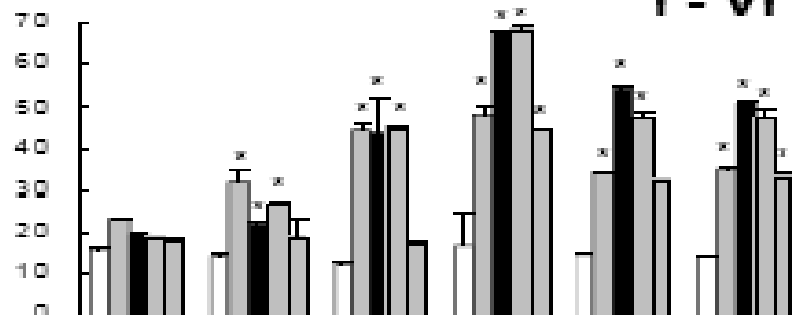
- Chromosomal aberrations
- DNA damage
- Embryo's Dominant lethality
- Inheritable syndromes
- Apoptotic cell death



Percentage of TUNEL positive cells, %

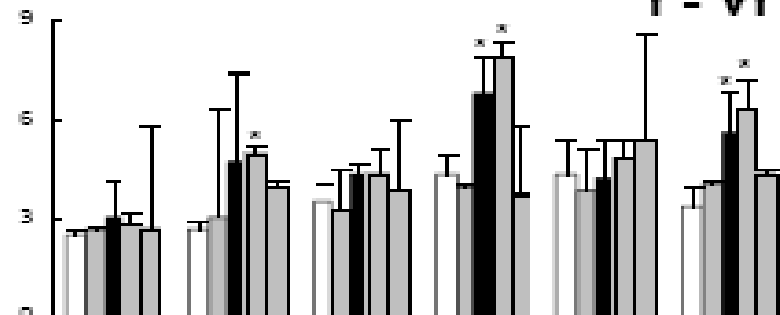
Spermatogonia

I - VI

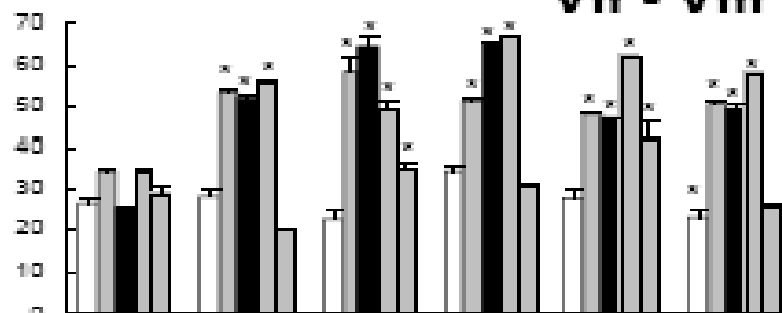


Spermatocytes

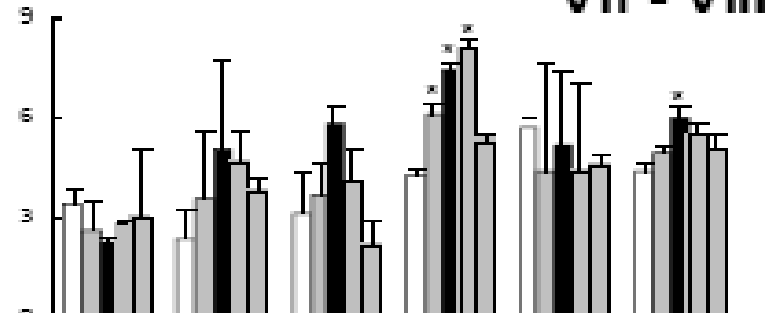
I - VI



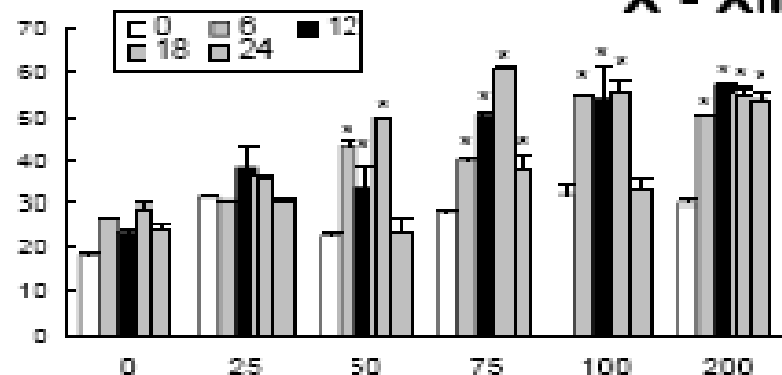
VII - VIII



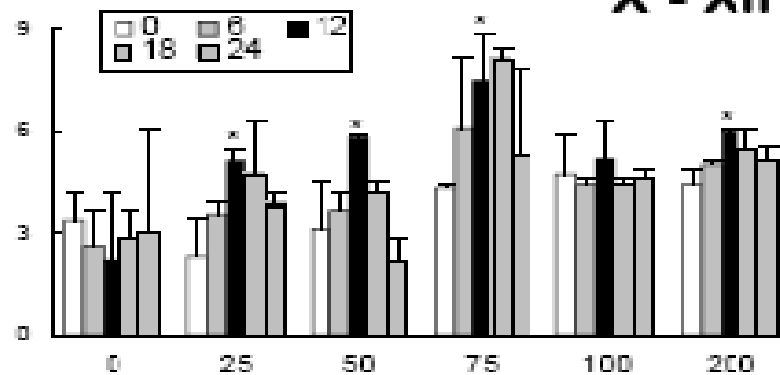
VII - VIII



X - XII



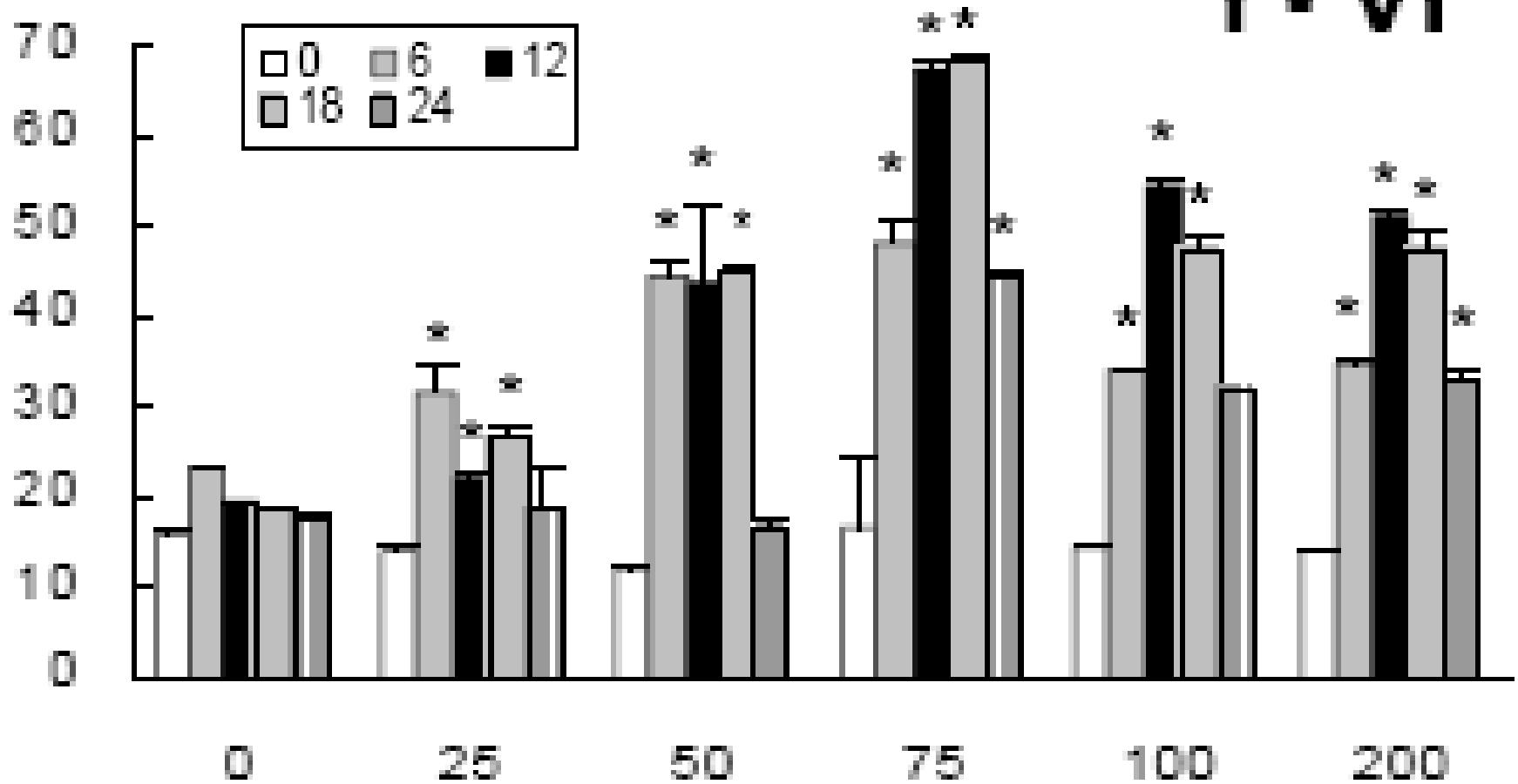
X - XII



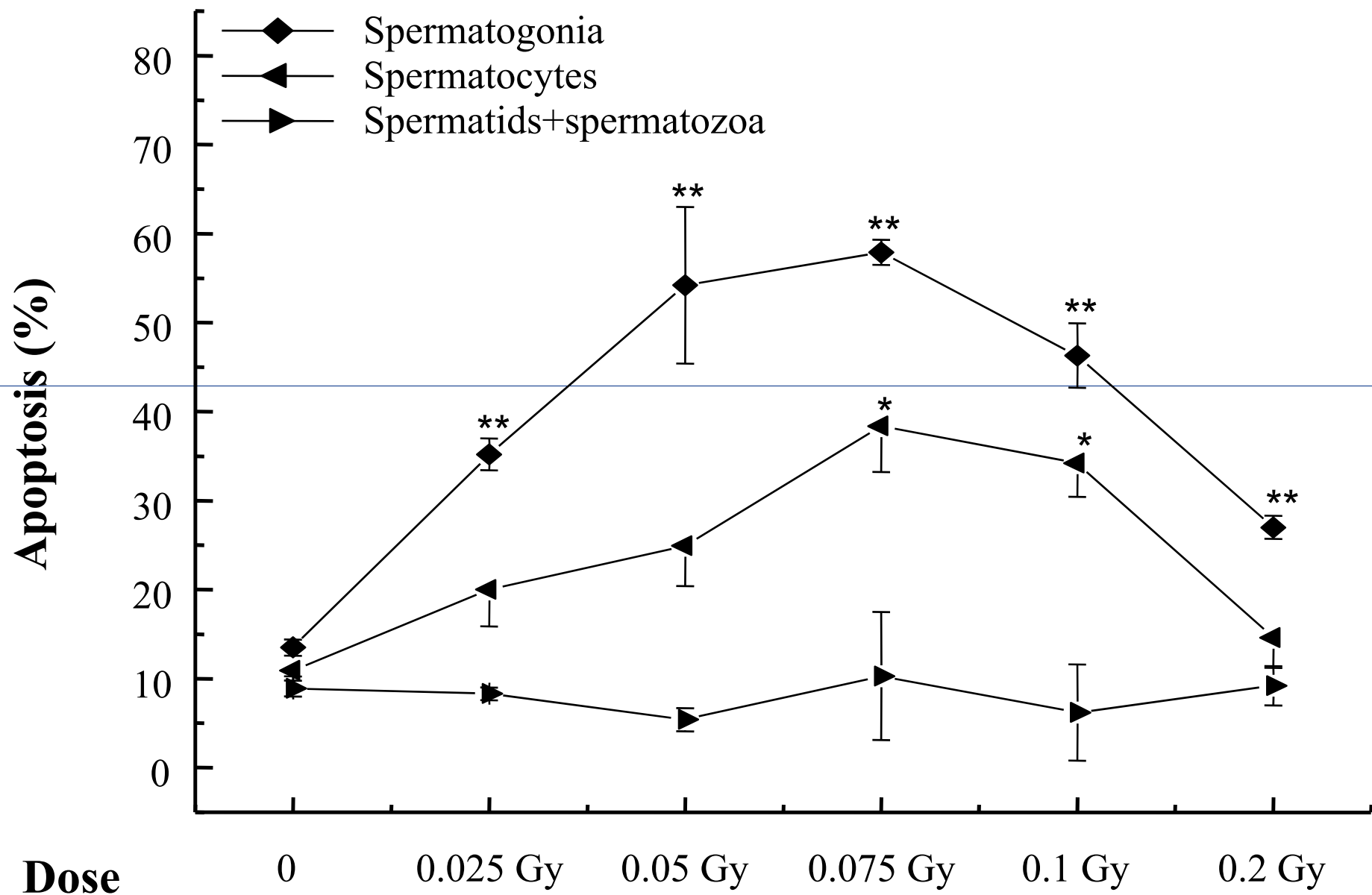
LDR doses (mGy)

Spermatogonia

I - VI



LDR doses (mGy) Liu et al., Radiation Res 2006





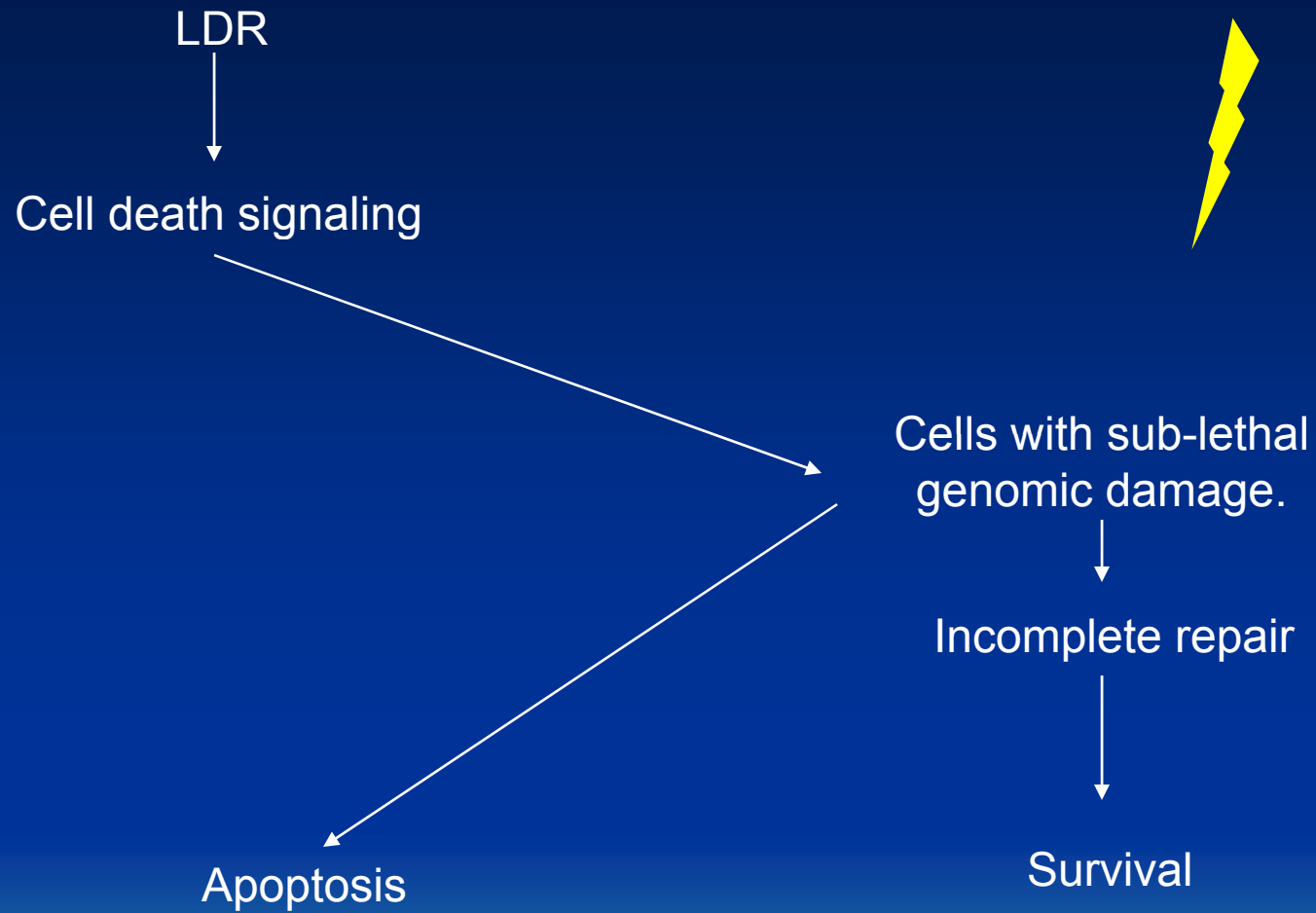
Cells with sub-lethal
genomic damage.



Incomplete repair



Survival



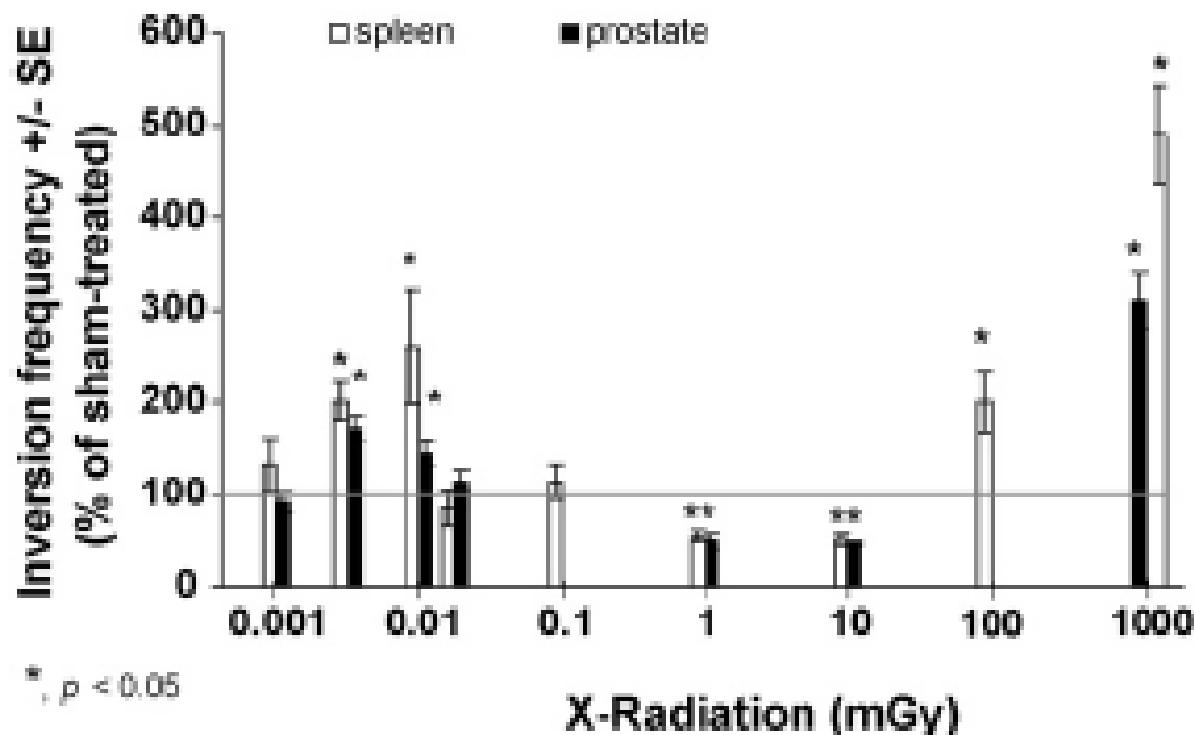


Fig. 3. Comparison of inversion frequency in pKZ1 spleen and prostate after single whole body exposure to X-radiation. The mean inversion frequency in prostate (data from this study) and spleen (data taken from Ref. [15]) is shown as a percentage of the sham-treated frequency. The bold line (100%) represents the sham-treated inversion frequency. *Statistically significantly different from sham-treated frequency.

Dr. Pamela J
Sykes's Group:

Zeng et al. 2006
Mutation Res.
602: 65-73

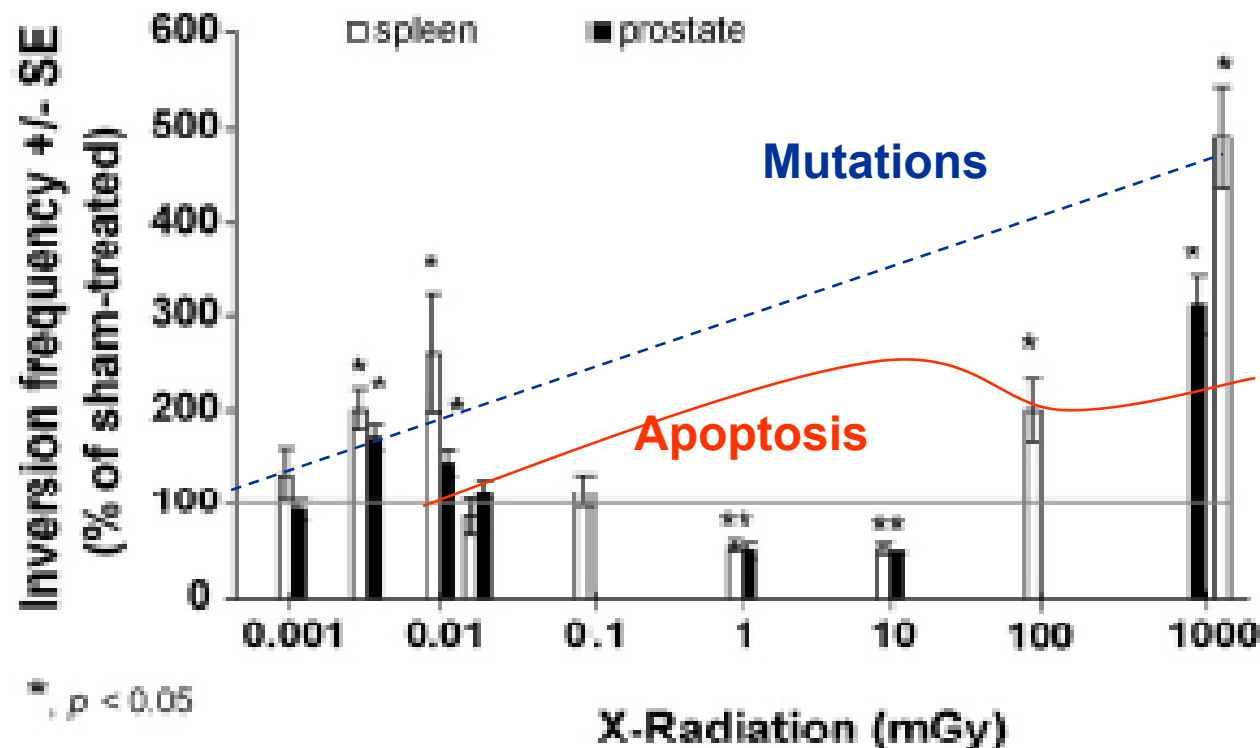
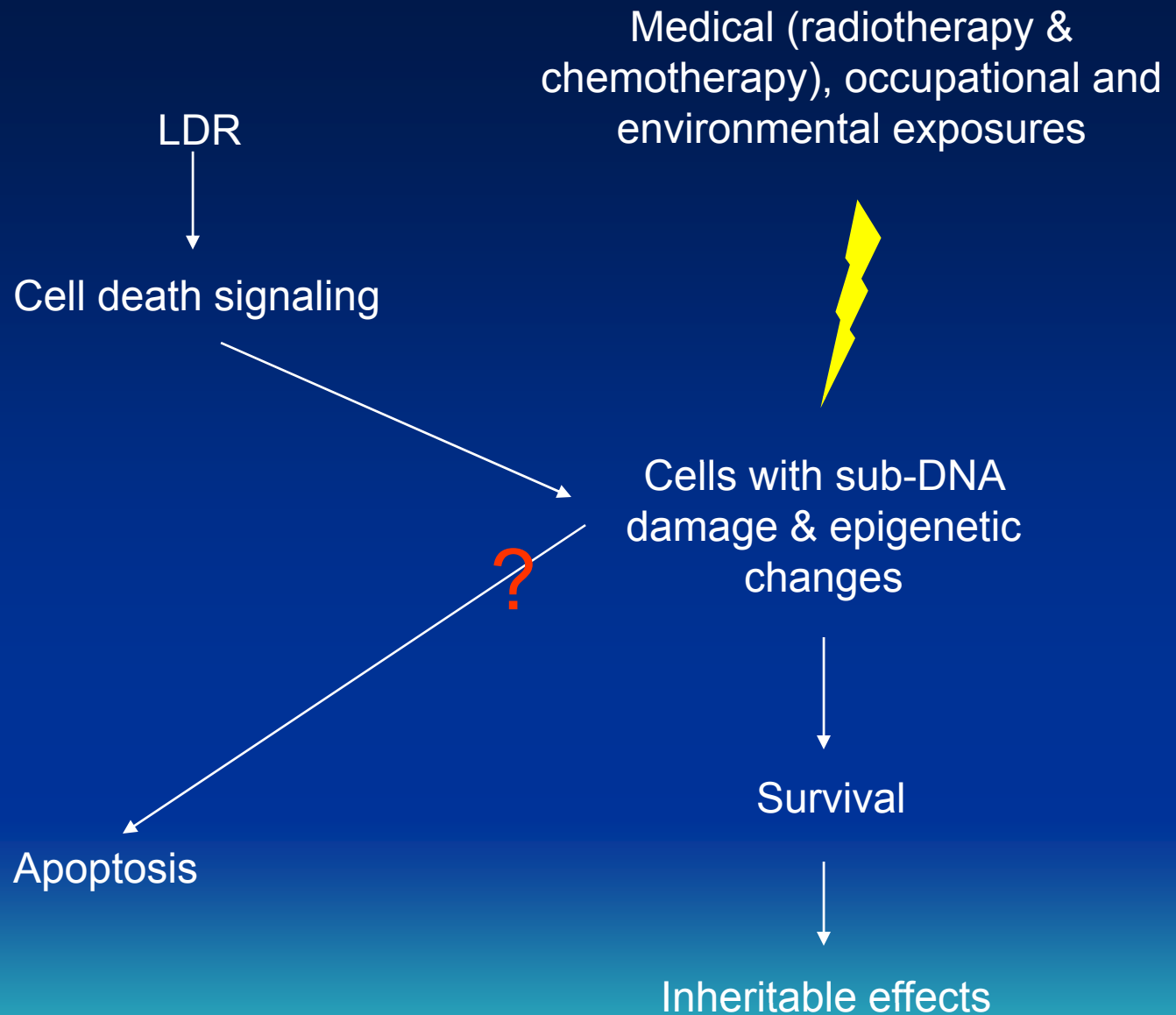


Fig. 3. Comparison of inversion frequency in pKZ1 spleen and prostate after single whole body exposure to X-radiation. The mean inversion frequency in prostate (data from this study) and spleen (data taken from Ref. [15]) is shown as a percentage of the sham-treated frequency. The bold line (100%) represents the sham-treated inversion frequency. *Statistically significantly different from sham-treated frequency.

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What is the next?



What are the biological or medical implications?

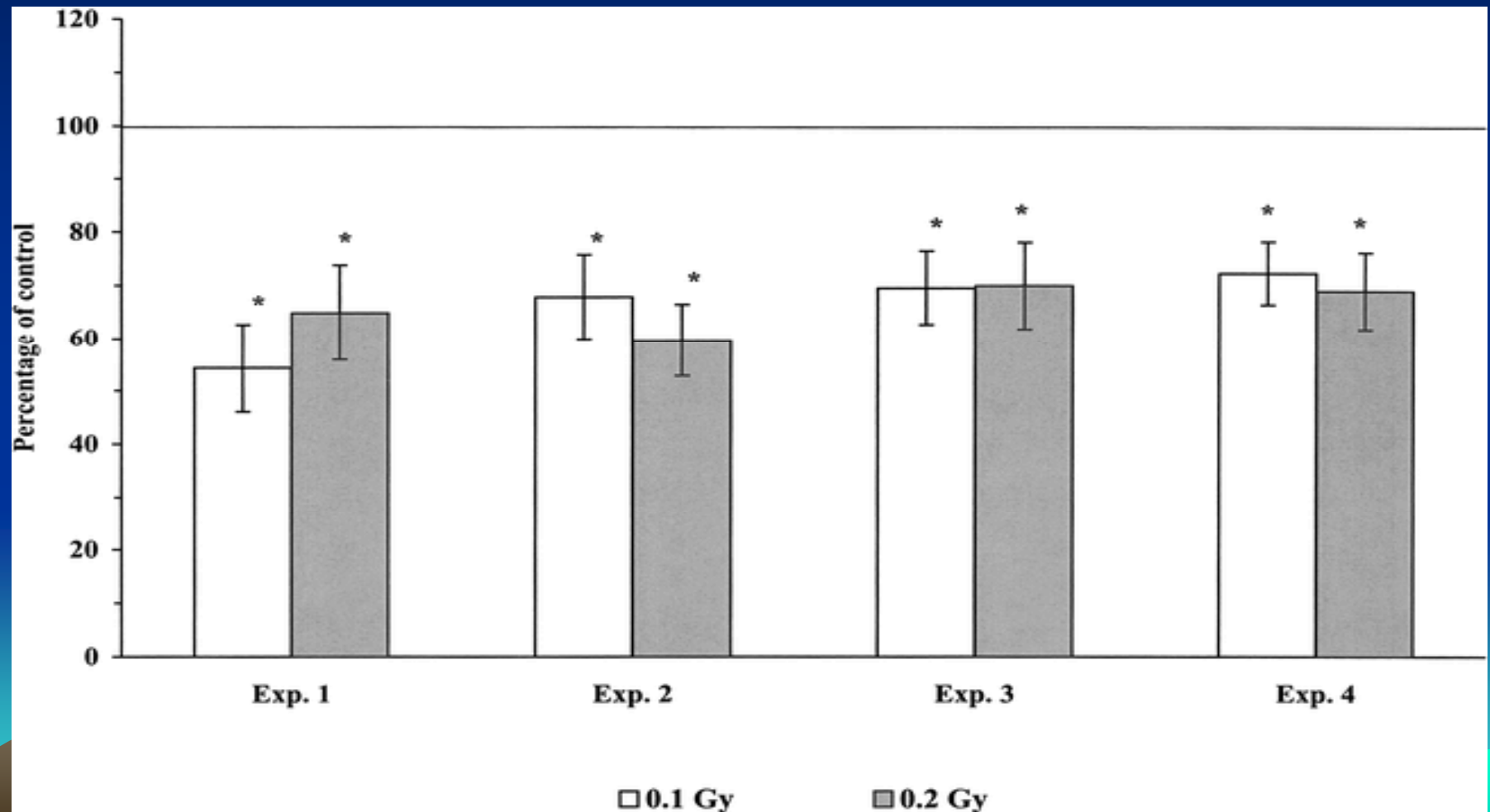
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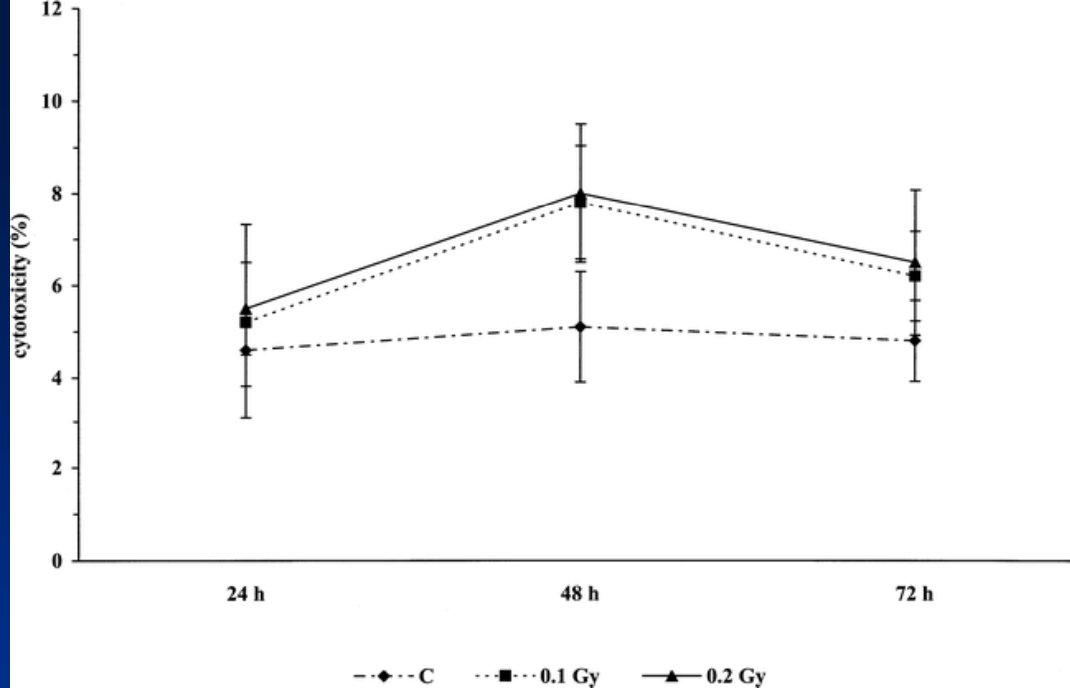


Cheda A, et al.

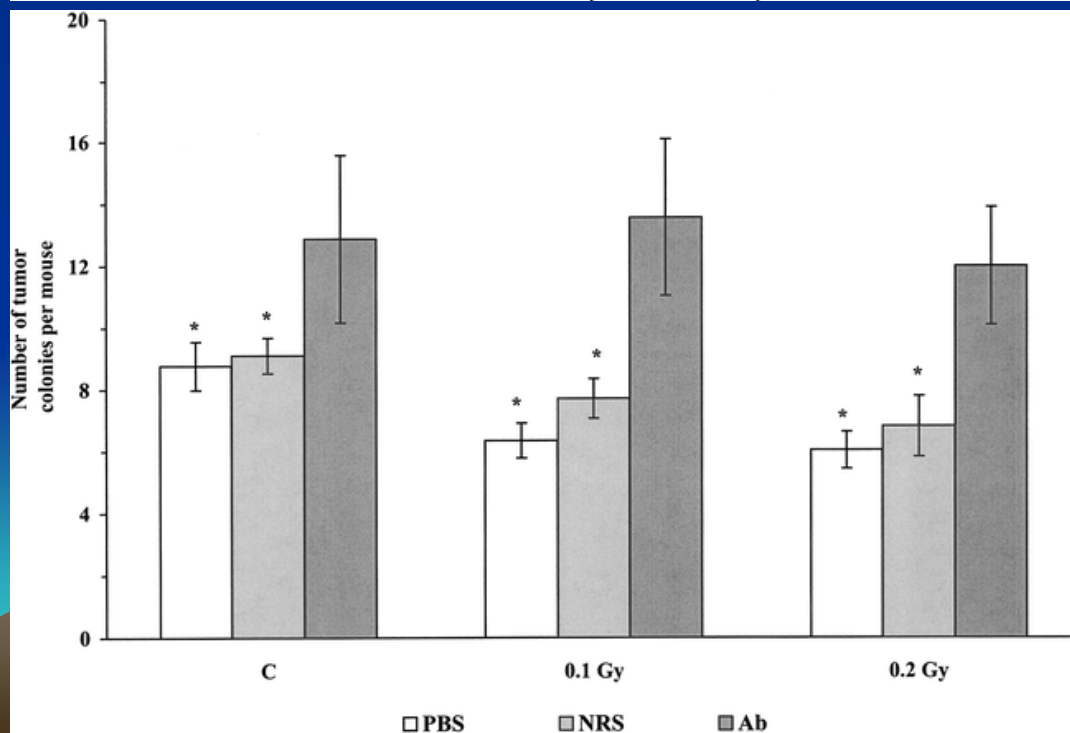
Single low doses of X rays inhibit the development of experimental tumor metastases and trigger the activities of NK cells in mice.

Radiat Res. 2004 Mar;161(3):335-40.





Cytotoxic activity of splenic NK cells (at 50:1 E:T ratio) on three consecutive days (24 h, 48 h, 72 h) after irradiation of mice with 0.1 or 0.2 Gy X rays. C, sham-exposed (control) mice; 0.1 Gy, mice exposed to a single TBI with 0.1 Gy X rays; 0.2 Gy, mice exposed to a single TBI with 0.2 Gy X rays. Data points are means \pm SD (bars) from three independent experiments; each experimental group consisted of at least three mice.



Numbers of tumor colonies in the lungs of mice pretreated with phosphate-buffered saline (PBS), normal rabbit serum (NRS), or anti-asialo GM₁ antibody (Ab) and injected with L1 sarcoma cells. Mean values obtained from two independent experiments \pm SD (bars) are presented; each experimental group consisted of 12 mice. C, sham-exposed (control) mice; 0.1 Gy, mice exposed to a single TBI with 0.1 Gy X rays; 0.2 Gy, mice exposed to a single TBI with 0.2 Gy X rays. *Indicates statistically significant ($P < 0.05$) difference from the Ab-treated mice



Low-dose total body irradiation augments the therapeutic effect of interleukin-2 in a mouse model for metastatic malignant melanoma.

[Safwat A](#), [Aggerholm N](#), [Roitt I](#), [Overgaard J](#), [Hokland M](#).

- To test the efficacy of combining LTBI and IL-2 in controlling lung metastases in a murine model for malignant melanoma compared to IL-2 alone.
- Ten-week-old female C57BL/6 mice were inoculated intravenously (on day 0) with 1 million B16F1 malignant melanoma cells. The mice received either no treatment (control group), LTBI alone (single fraction of 0.75 Gy), IL-2 treatment alone (30,000 CU x 2 daily for 5 consecutive days), or a combination of LTBI and IL-2.



- Tumor burden expressed as the percentage of lung area occupied with metastases, was the same in the control group ($8.1 \pm 4.9\%$), and in the group receiving LTBI alone ($8.3 \pm 4.5\%$). Tumor burden was reduced to $6.4 \pm 3.4\%$ in the IL-2 alone group, and further reduced to $3 \pm 1\%$ in the combined treatment group ($p < 0.001$).
- The combined treatment caused a significant increases in the number of NK cells, and macrophages infiltrating the metastatic sites.
- **CONCLUSION:** Combining LTBI and IL-2 treatment is synergistic and therapeutically more effective than IL-2 alone. This observation may have important clinical implications in the treatment of patients with metastatic malignant melanoma.

LDR



Early growth response gene-1 (egr-1)

**Egr-1 gene promoter + antitumor gene
into tumors**



LDR



Egr-1 gene promoter + antitumor gene
into tumors



Therapeutic effect of gene-therapy in combination with local X-irradiation in a mouse malignant melanoma model.

[Jin GH](#), [Jin SZ](#), [Liu Y](#), [Xu RM](#), [Yang JZ](#), [Pan XN](#), [Liu SZ](#).

- Plasmid containing mIL-18 and B7.1 genes downstream of Egr-1 promoter was constructed and used in gene-radiotherapy on malignant melanoma in C57BL/6J mice implanted with B16 cells.
- The treatment with plasmid pEgr-IL-18-B7.1 plus local X-irradiation showed more effective suppression of tumor growth than the treatment with radiation alone, pEgr-IL-18-B7.1 alone, or single gene pEgr-IL-18 (or pEgr-B7.1) combined with local X-irradiation.


- Anticancer immunity was found to be significantly upregulated in tumor-bearing mice treated with pEgr-IL-18-B7.1 plus local X-irradiation.
- IL-18 showed no direct killing effect on malignant melanoma cells in vitro.
- The mechanism of the combined therapy with pEgr-IL-18-B7.1 and local X-irradiation was apparently related with the stimulation of host anticancer immunity by increased secretion of IL-18 and up-regulated immunogenicity of the tumor cells by increased expression of B7.1 on their surface in addition to the direct effect of local X-irradiation on the tumor cells.



Mary Ann Liebert,

Therapeutic Effect of pEgr-IL18-B7.2 Gene Radiotherapy in B16 Melanoma-Bearing Mice.

[Yang J](#), [Jin G](#), [Liu X](#), [Liu S](#).

- To evaluate the antitumor role of genes B7.2 and IL18, the radiation-inducible dual-gene coexpression plasmid pEgr-IL18-B7.2 was constructed and its effects on tumor were detected both in vitro and in vivo.
 - After the introduction of pEgr-IL18-B7.2 into B16 melanoma cells, followed by X-ray irradiation, higher expression levels of B7.2 and IL18 compared with control were found both by flow cytometry and ELISA.
 - The tumors received 5 Gy of local X-ray irradiation every other day for a total of five treatments. B16 tumor growth slowed significantly when treated with pEgr-IL18-B7.2 plus X-radiation versus either treatment separately.
- 

- The tumors received 5 Gy of local X-ray irradiation every other day for a total of five treatments. B16 tumor growth slowed significantly when treated with pEgr-IL18-B7.2 plus X-radiation versus either treatment separately.
- Both 1 and 3 days after the last irradiation the group of mice with combined gene and radiation therapy showed significantly higher TNF-alpha secretion in peritoneal macrophages, up-regulated splenic cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells, and higher IFN-gamma secretion than those in either individual treatment group or the control group.
- The stimulation of host anticancer immunity by increased secretion of IL-18 and upregulated immunogenicity of the tumor cells by increased expression of B7.2 on their surface, in addition to the direct effect of local X-irradiation on the tumor cells, may contribute to the novel effect of the combined therapy.



Clinical observation for the use of LDR



Long-term results of low dose total body irradiation for advanced non-Hodgkin lymphoma.

[Lybeert ML](#), [Meerwaldt JH](#), [Deneve W](#).

- 68 patients received fractionated low dose total body irradiation (LTBI) as treatment for non-Hodgkin lymphoma (NHL).
- LTBI was given 3 times a week, midline dose 0.1 Gy, with total dose of 1.78 Gy.
- LTBI caused a significant increase in therapeutic response, at 5 and 10 years of patients who received LTBI as first treatment.
- No treatment related complications were noted.
- Subsequent chemotherapy in case of relapse was not hampered by previous LTBI.
- **The high response rate and extended response, without maintenance therapy, makes LTBI a preferable first line treatment for patients with advanced stage low grade NHL.**

Other clinical studies

- [Safwat A.](#)
The role of low-dose total body irradiation in treatment of non-Hodgkin's lymphoma: a new look at an old method.
Radiother Oncol. 2000 Jul;56(1):1-8.
- [Safwat A, et al.](#)
The potential palliative role and possible immune modulatory effects of low-dose total body irradiation in relapsed or chemo-resistant non-Hodgkin's lymphoma.
Radiother Oncol. 2003 Oct;69(1):33-6.
- [Safwat A, et al.](#)
A phase II trial of adjuvant low-dose total body irradiation in non-Hodgkin's lymphoma patients following standard CHOP.
Acta Oncol. 2004;43(5):480-5.
- [Safwat A, et al](#)
A phase II trial of low-dose total body irradiation and subcutaneous interleukin-2 in metastatic melanoma.
Radiother Oncol. 2005 Nov;77(2):143-7.

Radiation Therapy for Painful Heel Spurs : Results of a Prospective Randomized Study.

[Heyd R](#), [Tselis N](#), [Ackermann H](#), [Roddiger SJ](#), [Zamboglou N](#).

- 130 patients into two groups: the low-dose (LD) group (n = 65 heels) received a total dose of 3.0 Gy given in two weekly fractions of 0.5 Gy; in the high-dose (HD) group (n = 65 heels), two weekly fractions of 1.0 Gy were applied over 3 weeks (total dose 6.0 Gy).
- The results were assessed using a five-level function score which was documented before RT, at the end of each RT course, and at 6 weeks and 6 months thereafter.
- At 6-month follow-up, RT led to a significant reduction of symptoms in both groups. In the HD group, 31 sites were classified as excellent (score: 90-100), 13 as good (score: 70-85), twelve as moderate (score: 45-65), and nine as poor (score: 0-40). In the LD group, 35 sites were classified as excellent, eight as good, ten as moderate, and twelve as poor. **No statistical difference was revealed for two groups.**
- **CONCLUSION:** RT is an effective treatment option for the management of inflammatory heel spurs. The dose for an RT course should not exceed 3.0 Gy.

Demographic, clinical and treatment related predictors for event-free probability following low-dose radiotherapy for painful heel spurs – a retrospective multicenter study of 502 patients.

[Muecke R](#), [Micke O](#), [Reichl B](#), [Heyder R](#), [Prott FJ](#), [Seegenschmiedt MH](#), [Glatzel M](#), [Schneider O](#), [Schafer U](#), [Kundt G](#).

- A total of 502 patients treated between 1990 and 2002 with low-dose radiotherapy (RT) for painful heel spurs were analysed for prognostic factors for long-term treatment success.
- The median follow-up was 26 months, ranging from 1 to 103 months.
- **Overall** low-dose RT is a very effective treatment in painful heel spurs.



What are the biological or medical implications?

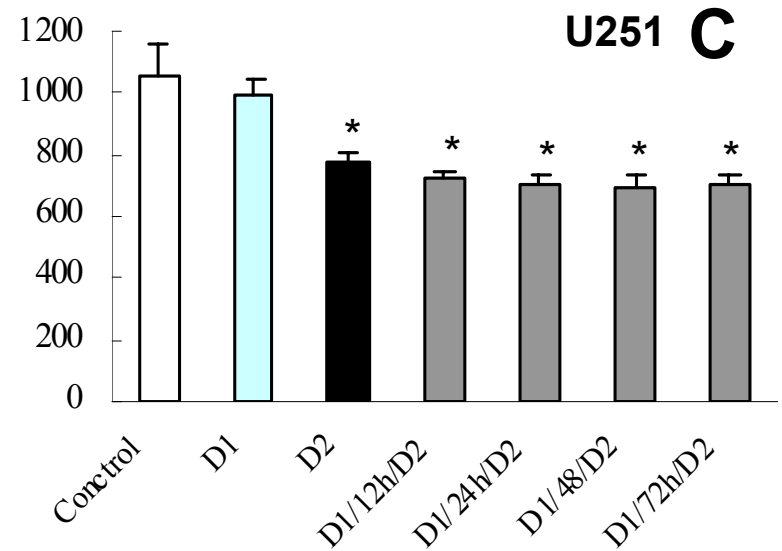
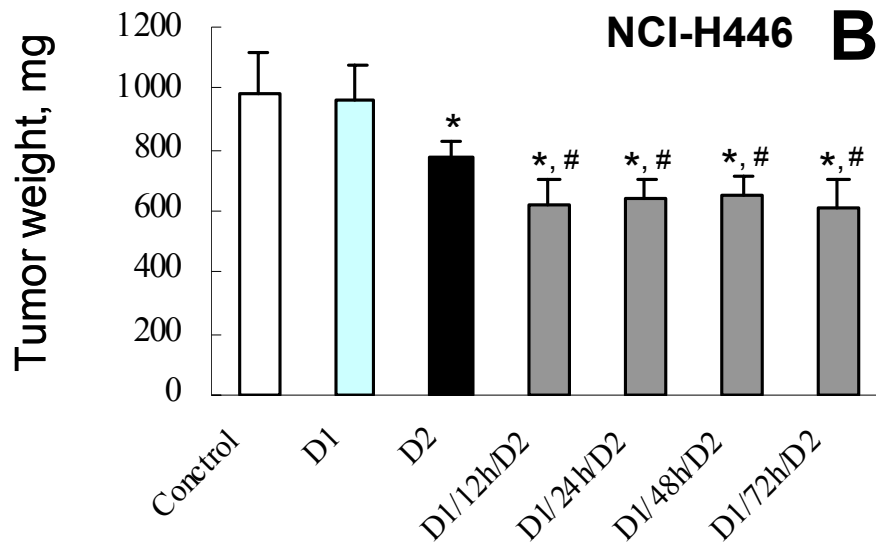
- Effects of LDR on male germ cells
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- Diabetes



Can we directly use LDR into clinics now?

- LDR may not only stimulate normal cell proliferation, but also stimulate the potent tumor cell proliferation or in situ tumor cell metastasis.
- LDR may not only enhance normal tissue resistance to subsequent radio- or chemo-therapy-induced side toxicity, but also make tumor cells become radio- or chemo-therapy resistance (drug resistance).





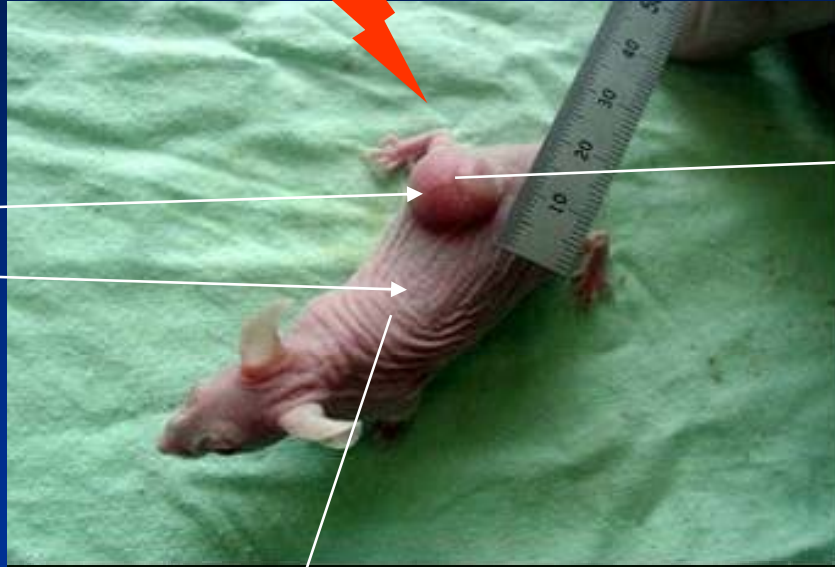
Summary

- Low-dose radiation induced a stimulating effect, and also a resistance to subsequently radiation-induced inhibition, in normal cell proliferation, but not in two leukemia and two solid tumor cells *in vitro*.
- The lack of these responses in tumor cells was further confirmed in tumor-bearing models.
- LDR may be used in clinics for cancer therapy or prevention of the relapse of surgically-removed early-diagnosed in situ tumor.

HDR or
chemotherapy



LDR



AR:

- Does not affect tumor sensitivity to radiotherapy or chemotherapy
- LDR-stimulated immunofunction to eliminate the residual cells after radio- or chemo-killed or after surgery

- Protect the normal tissue from radiotherapy or chemotherapy
- Increase therapeutic dose

What are the biological or medical implications?

- Effects of LDR on male germ cells
- Anti-tumor studies & pre-protection
- Effects of LDR on normal and tumor cells
- Diabetes



Physiol Chem Phys Med NMR. 1995;27(3):149-59.

Protection against alloxan diabetes by low-dose ^{60}Co gamma irradiation before alloxan administration.

Takehara Y, Yamaoka K, Hiraki Y, Yoshioka T, Utsumi K.

Center for Adult Diseases, Institute of Medical Science, Okayama, Japan.

We evaluated the protective effects of a single low-dose whole body ^{60}Co gamma irradiation against alloxan-induced hyperglycemia in rats. i) **In rats that did not receive alloxan, the superoxide dismutase (SOD) activity in the pancreas significantly increased after irradiation at a dose of 0.5 or 1.0 Gy.** ii) In rats that received alloxan, plasma lipid peroxide levels, pancreatic lipid peroxide levels and blood glucose were increased. However, **the increase in pancreatic lipid peroxide level was prevented by irradiation at a dose of 0.5 or 1.0 Gy; and the increase in blood glucose, by irradiation at 0.5 Gy.** iii) After alloxan administration, degranulation was observed in beta cells, but this was prevented by low-dose irradiation at 0.5 Gy.



Prevention of type I diabetes by low-dose gamma irradiation in NOD mice.

Takahashi M, Kojima S, Yamaoka K, Niki E.

Research Center for Advanced Science and Technology, University of Tokyo, Meguro, Japan.

Pretreatment with nonlethal, low-dose irradiation has been shown to have a protective effect against oxidative injury in animal tissues. Since oxidative injury of tissues is known to be a major cause of many human diseases, we examined the effect of low-dose irradiation on the progression of type I diabetes in mice. Nonobese diabetic (NOD) mice were treated with gamma irradiation and the progression of the disease was monitored. **An elevated level of glucose in urine was first detected at 15 weeks of age in the control NOD mice, whereas the detection was delayed as long as 7 weeks when the mice received a single dose of 0.5 Gy total-body irradiation between 12 and 14 weeks of age.**

The greatest effect was observed in the mice irradiated at 13 weeks of age. The increase in blood glucose and decrease in blood insulin were effectively suppressed by irradiation at 13 weeks of age. Both suppression of cell death by apoptosis and an increase in superoxide dismutase (SOD) activity were observed in the pancreas 1 week after irradiation. The results indicate that treatment with 0.5 Gy gamma rays suppresses progression of type I diabetes in NOD mice. This is the first report on the preventive effect of low-dose irradiation on disease progression.

Low Dose Radiation Overcomes Diabetes-induced Suppression of Hippocampal Neuronal Cell Proliferation in Rats

We investigated the effect of low dose radiation on diabetes induced suppression of neurogenesis in the hippocampal dentate gyrus of rat. After 0.01 Gy, 0.1 Gy, 1 Gy and 10 Gy radiation was delivered, the dentate gyrus of hippocampus of streptozotocin (STZ)-induced diabetic rats were evaluated using immunohistochemistry for 5-bromo-2-deoxyuridine (BrdU), caspase-3, and terminal deoxynucleotidyl transferase-mediated nick end-labeling (TUNEL) staining. The number of BrdU positive cells in the non-diabetic rats, diabetic rats without radiation, diabetic rats with 0.01 Gy radiation, diabetic rats with 0.1 Gy radiation, diabetic rats with 1 Gy radiation and diabetic rats with 10 Gy radiation were $55.4 \pm 8.5/\text{mm}^2$, $33.3 \pm 6.4/\text{mm}^2$, $67.7 \pm 10.5/\text{mm}^2$, $66.6 \pm 10.0/\text{mm}^2$, $23.5 \pm 6.3/\text{mm}^2$ and $14.3 \pm 7.2/\text{mm}^2$, respectively. The number of caspase-3 positive cells was $132.6 \pm 37.4/\text{mm}^2$, $378.6 \pm 99.1/\text{mm}^2$, $15.0 \pm 2.8/\text{mm}^2$, $57.1 \pm 16.9/\text{mm}^2$, $191.8 \pm 44.8/\text{mm}^2$ and $450.4 \pm 58.3/\text{mm}^2$, respectively. The number of TUNEL-positive cells was $24.5 \pm 2.0/\text{mm}^2$, $21.7 \pm 4.0/\text{mm}^2$, $20.4 \pm 2.0/\text{mm}^2$, $18.96 \pm 2.1/\text{mm}^2$, $58.3 \pm 7.9/\text{mm}^2$, and $106.0 \pm 9.8/\text{mm}^2$, respectively. These results suggest low doses of radiation paradoxically improved diabetes induced neuronal cell suppression in the hippocampal dentate gyrus of rat.

Key Words : Radiation; Hippocampus; Diabetes Mellitus

Jin Oh Kang, Sang-Ki Kim,
Seong-Eon Hong, Taek-Hyun Lee*,
Chang-Ju Kim*

Departments of Radiation Oncology and Physiology*,
School of Medicine, Kyung Hee University, Seoul,
Korea

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Address for correspondence

Jin-Oh Kang, M.D.
Department of Radiation Oncology, Kyung Hee
University Hospital, 1 Hoiki-dong, Dongdaemun-gu,
Seoul 130-702, Korea
Tel : +82-2-958-8664, Fax : +82-2-962-3002
E-mail : kangjoc@khmc.or.kr

LOW-DOSE RADIATION AND ITS CLINICAL IMPLICATIONS: DIABETES

Guo-Jun Wang ¹, Xiao-Kun Li ², Kazuo Sakai ³ and Lu Cai ^{1,4*}

¹ Department of Hematology and Oncology
The First University Hospital
Jilin University Medical College
Changchun 130021
P.R. China

² Department of Biopharmacy
College of Pharmacy
and Biopharmaceutical Research & Development Center
Jinan University
Guangzhou 510080
P.R. China

³ Low Dose Radiation Research Center
Central Research Institute of Electric Power Industry
2-1-1 Iwado-Kita, Komae
Tokyo, 201-8511

⁴ Departments of Medicine, Pharmacology and
Toxicology,
and Radiation Oncology
the University of Louisville School of Medicine
Louisville 40202
USA

ABSTRACT

Induction of hormesis and adaptive response by low-dose radiation (LDR) has been extensively indicated. Adaptive responses induced by LDR was not only resistant to damage caused by subsequently high-dose radiation, but also cross resistant to other non-radiation challenges such as chemicals. Mechanisms by which LDR induces the preventive effect on radiation- or chemical-induced tissue damage include induced or up-regulated expression of protective proteins such as heat shock proteins and antioxidants. Since oxidative damage to tissues is a major pathogenesis of many human diseases including diabetes, this review will summarize available data with an emphasis on the preventive effect of LDR on the development of diabetes and the therapeutic effect of LDR on diabetic cardiovascular complications. The available data indicated that pre-exposure of mice to LDR reduced the incidence of alloxan-induced diabetes, and also delayed the onset of hyperglycemia in diabetes-prone non-obese diabetic mice. Experiments with animals indicated the therapeutic effect of low-intensity or power laser (LIL or LPL) radiation on skin wound healing, which has stimulated clinical use of LIL to cure skin ulcer in diabetic patients. Mechanisms by which LDR prevents diabetes, though they are unclear now, may include the induction of pancreatic antioxidants to prevent β cells from oxidative damage and immunomodulation to preserve pancreatic function. For LIL therapeutic effects on diabetic wound healing, mechanisms may include its antioxidant action, immunomodulation, cell-proliferation stimulation as well as improvement of systemic and wound-regional microcirculation. Therefore, although there are only a few studies indicating LDR prevention of the development of diabetes, many studies have demonstrated LDR, specifically LIL, therapeutic effectiveness of diabetic wound healing. These preliminary results encourage further assessment of the clinical implications of LDR to diabetes-related areas.

Keywords: Low-dose radiation, hormesis, adaptive response, diabetes, diabetic complications

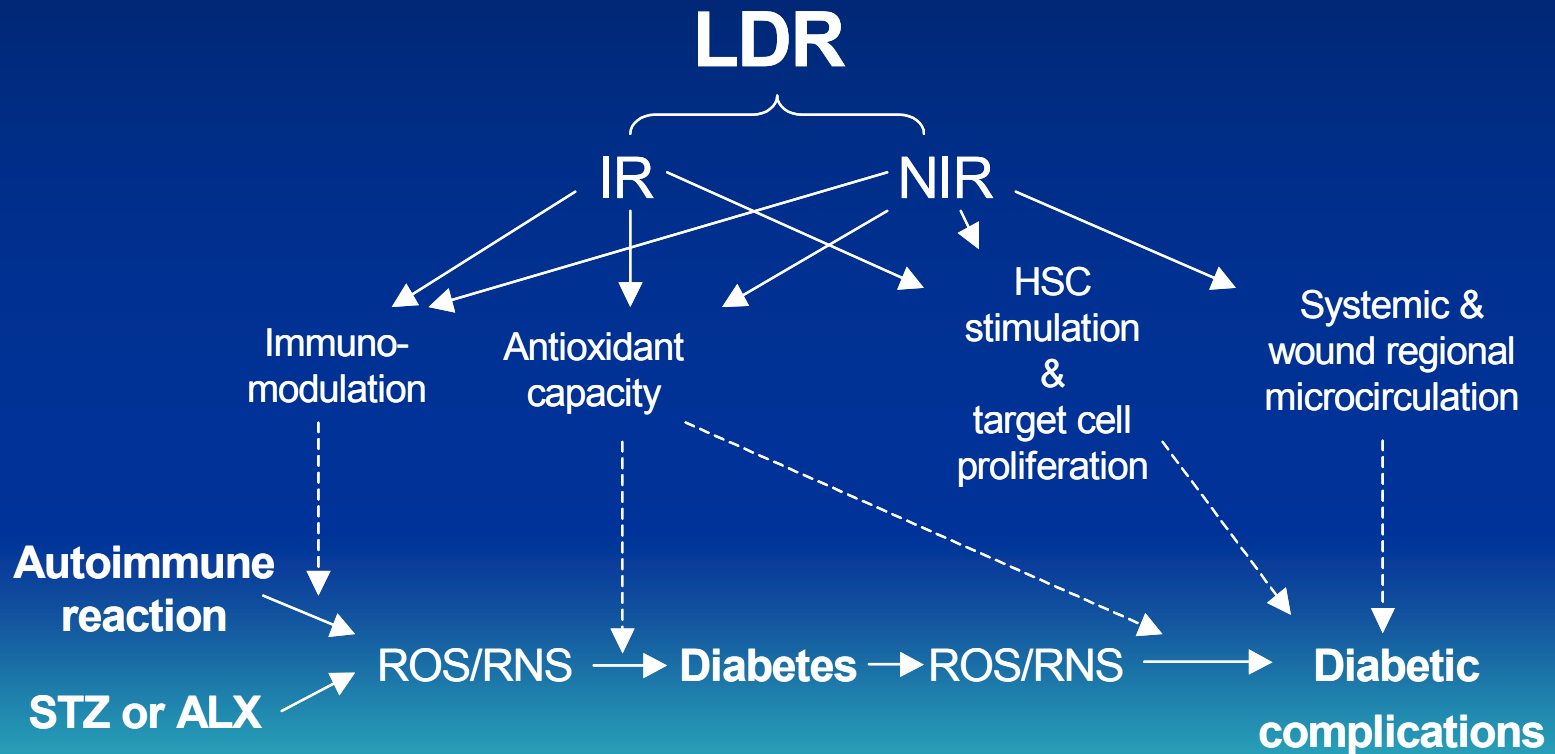
INTRODUCTION

NEWS Letters of
Biological
Effects of Low
Level Exposure
(BELLE) 2005

Effects of Low-dose radiation:

Hormesis, adaptive response & standby effects

Possible mechanisms by which LDR prevents diabetes and diabetic complications





Whole Body Exposure to Low-dose Gamma Radiation Promotes Kidney Antioxidant Status in Balb/c Mice.

[Pathak CM](#), [Avti PK](#), [Kumar S](#), [Khanduja KL](#), [Sharma SC](#).

Postgraduate Institute of Medical Education and Research.

We examined the effect of whole body low-dose gamma-irradiation on the status of the antioxidant defense system in the rodent kidneys at different time intervals. **Young male Balb/c mice** were exposed to whole body radiation from a (60)Co source at doses of **10, 25 and 50 cGy (48.78 cGy/min)**. Antioxidant status and lipid peroxidation were estimated in the kidneys at 4, 12 and 24 h after irradiation. Lipid peroxidation increased between 33% and 49% and reduced glutathione between 12% and 47% at 12 h at different radiation doses. Reduced glutathione level remained significantly ($p < 0.05$) elevated even at 24 h after irradiation to 25 cGy. Superoxide dismutase activity also increased by 37% at 12 h on exposure of animals to all the doses up to 50 cGy. **Catalase activity increased significantly at 12 h on exposure to 10 cGy and 50 cGy.** Interestingly, glutathione peroxidase activity increased by 31% at 4 h and subsequently returned to control levels at 24 h after exposure to 50 cGy. Glutathione reductase activity increased by 10-12% at 12 h after exposure to 25 cGy and 50 cGy. The results suggest that the **whole body exposure of animals to gamma radiation stimulates the antioxidant defense system in the kidneys within 4 to 24 h after irradiation, at doses of 25 cGy and 50 cGy.**



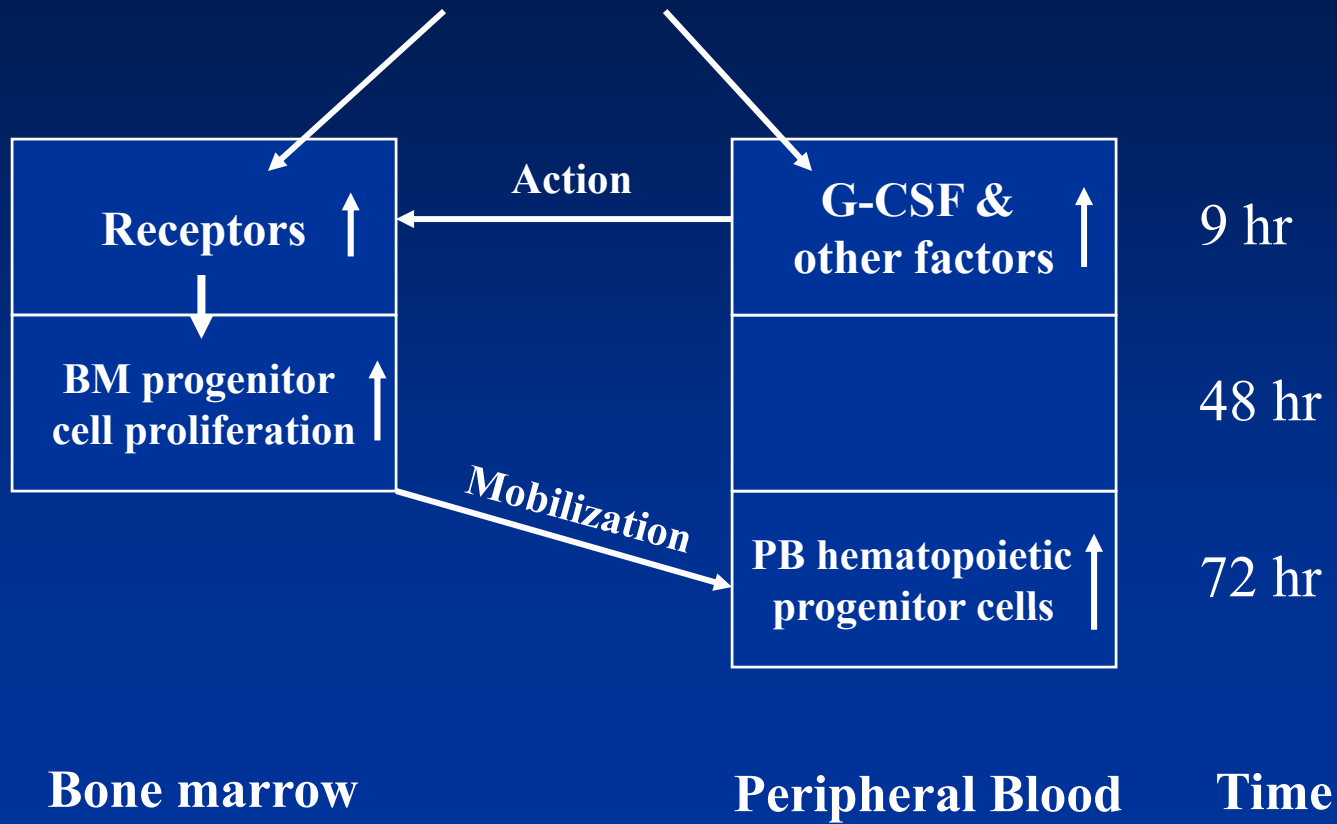
Low-dose radiation (LDR) induces hematopoietic hormesis: LDR-induced mobilization of hematopoietic progenitor cells into peripheral blood circulation.

Li W, Wang G, Cui J, Xue L, Cai L.

Department of Hematology and Oncology, First University Hospital, PR China.

OBJECTIVE: The aim of this study was to investigate the stimulating effect of low-dose radiation (LDR) on bone marrow hematopoietic progenitor cell (HPC) proliferation and peripheral blood mobilization. **METHODS:** Mice were exposed to 25- to 100-mGy x-rays. Bone marrow and peripheral blood HPCs (BFU-E, CFU-GM, and c-kit⁺ cells) were measured, and GM-CSF, G-CSF, and IL-3 protein and mRNA expression were detected using ELISA, slot blot hybridization, and Northern blot methods. To functionally evaluate LDR-stimulated and -mobilized HPCs, repopulation of peripheral blood cells in lethally irradiated recipients after transplantation of LDR-treated donor HPCs was examined by WBC counts, animal survival, and colony-forming units in the recipient spleens (CFUs-S). **RESULTS:** 75-mGy x-rays induced a maximal stimulation for bone marrow HPC proliferation (CFU-GM and BFU-E formation) 48 hours postirradiation, along with a significant increase in HPC mobilization into peripheral blood 48 to 72 hours postradiation, as shown by increases in CFU-GM formation and proportion of c-kit⁺ cells in the peripheral mononuclear cells. 75-mGy x-rays also maximally induced increases in G-CSF and GM-CSF mRNA expression in splenocytes and levels of serum GM-CSF. To define the critical role of these hematopoietic-stimulating factors in HPC peripheral mobilization, direct administration of G-CSF at a dose of 300 microg/kg/day or 150 microg/kg/day was applied and found to significantly stimulate GM-CFU formation and increase c-kit⁺ cells in the peripheral mononuclear cells. More importantly, 75-mGy x-rays plus 150 microg/kg/day G-CSF (LDR/150 G-CSF) produced a similar effect to that of 300 microg/kg/day G-CSF alone. Furthermore, the capability of LDR-mobilize donor HPCs to repopulate blood cells was confirmed in lethally irradiated recipient mice by counting peripheral WBC and CFUs-S. **CONCLUSION:** These results suggest that LDR induces hematopoietic hormesis, as demonstrated by HPC proliferation and peripheral mobilization, providing a potential approach to clinical application for HPC peripheral mobilization.

LDR



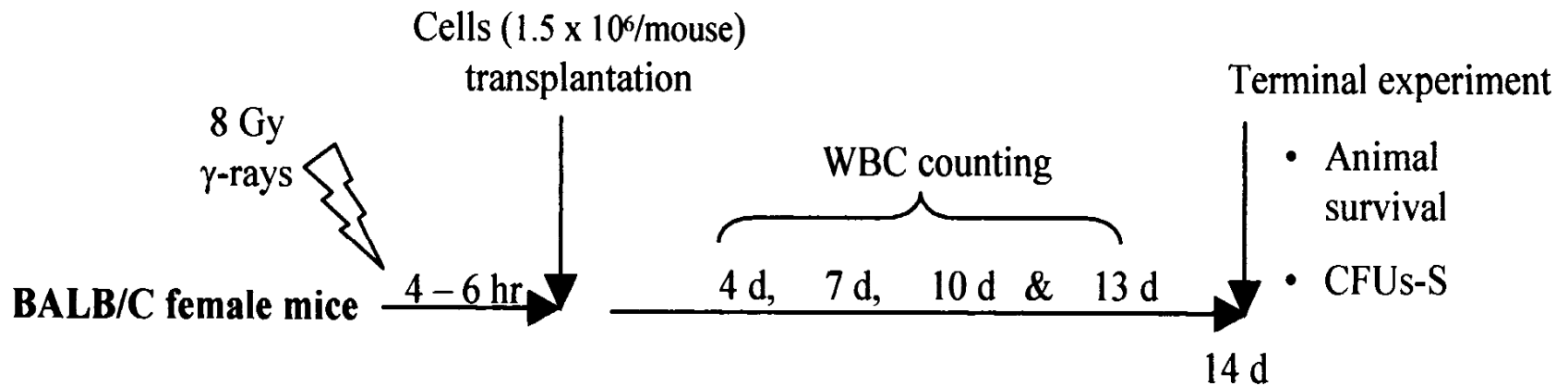
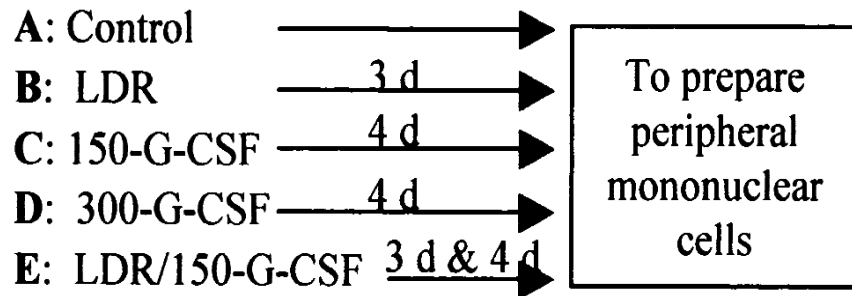
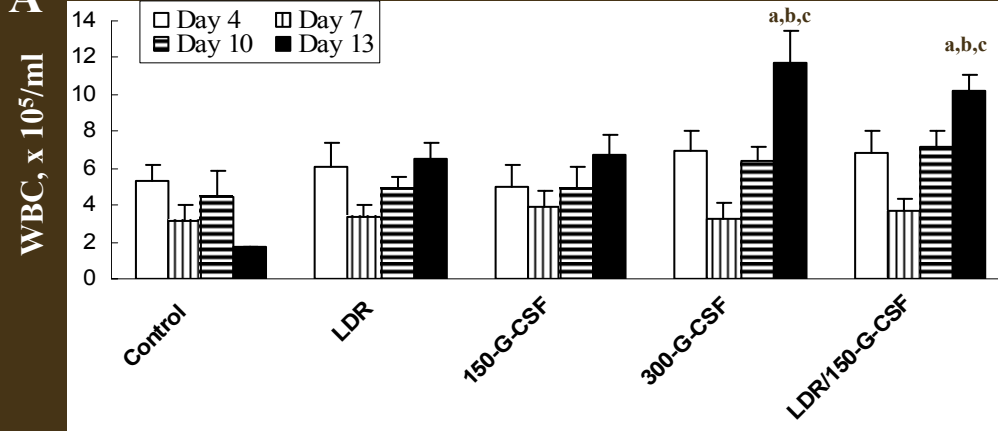
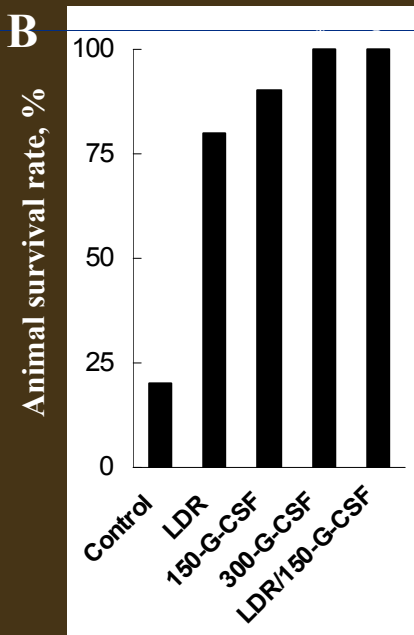
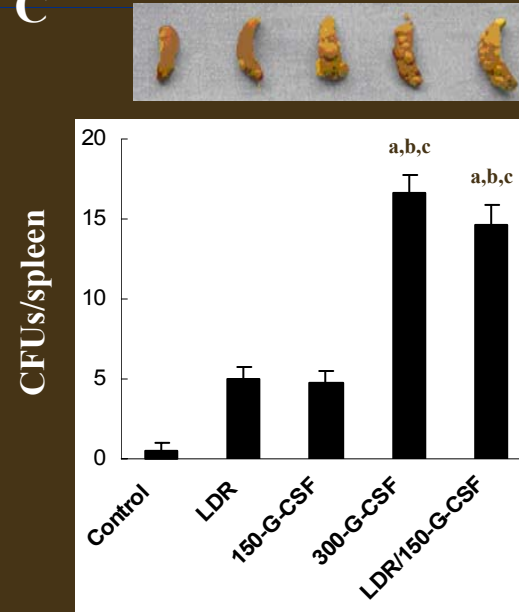
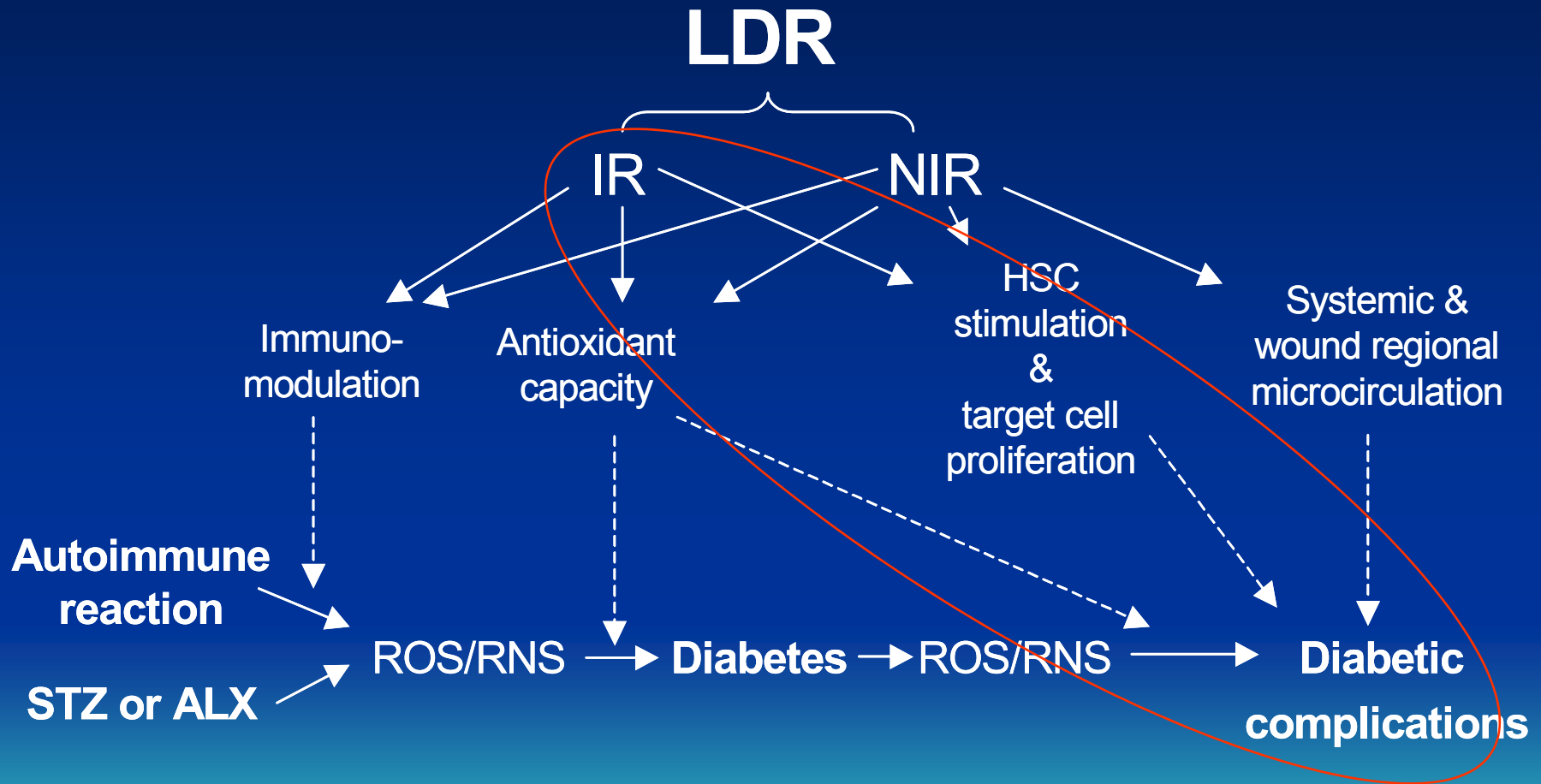
BALB/C male mice

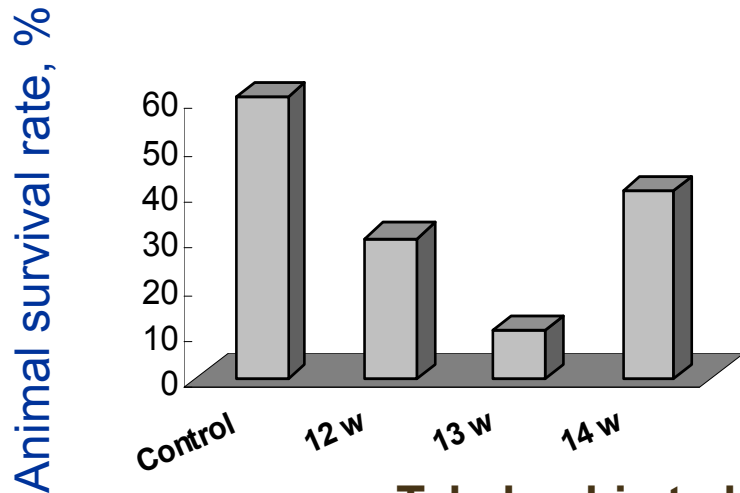
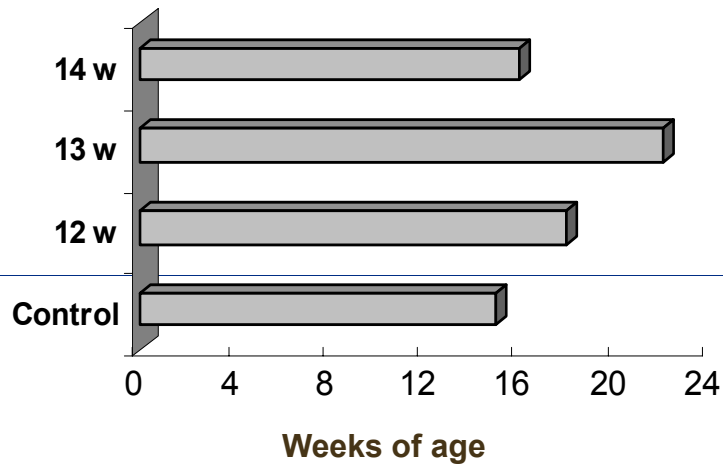
Figure 1. Scheme of experimental procedures for evaluation of LDR-mobilized HPCs. LDR: 75 mGy X-rays; 150-G-CSF or 300-G-CSF: 150 or 300 $\mu\text{g/kg/day}$ G-CSF administration; LDR/150-G-CSF: combining treatments of LDR and 150 $\mu\text{g/kg/day}$ G-CSF administration. WBC: white blood cells. “3 d” in **B** group indicates that mice were sacrificed 3 days after LDR; “4 d” in **C** and **D** groups indicates that mice were consecutively administrated with G-CSF for 4 days and then sacrificed; “3 d & 4 d” in **E** group indicates that mice were consecutively administrated with G-CSF for 4 days and irradiated with LDR at 3 days prior to the last administration of G-CSF, and sacrificed after the last G-CSF administration. For BALB/C female mice, “4 d, 7 d, 10 d, 13 d, and 14 d” indicate the time (days) after HPC transplantation.

A**B****C**

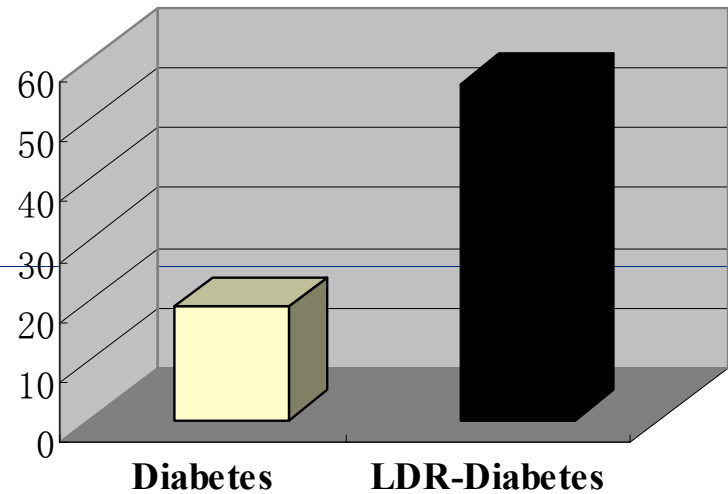
Possible mechanisms by which LDR prevents diabetes and diabetic complications



LDR reduce mortality of diabetic rats and testicular cell death



Animal survival rate, %



Diabetic rats were or not exposed to 75 mGy at 5 times/wk for 4 wks, until 12 wks.

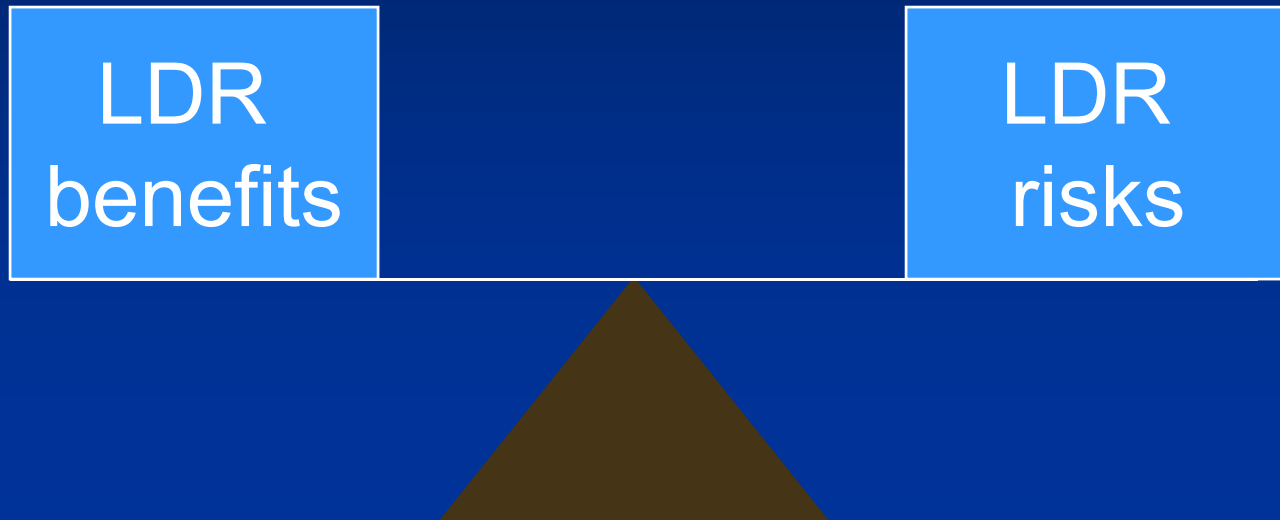
Takahashi et al. 2000

Summary

- Reduce genomic effects in offspring
- Enhancing radio-therapeutic efficiency
- Protective effects on normal tissues from radiotherapy
- Potentially manipulating the radiotherapy favor to kill tumor cells and protect normal cells
- Prevent diabetes and diabetic complications



How to balance?



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Thank you!

