

# **RESURRECTION AND UPDATE OF CANCER THERAPY BY LOW-DOSE WHOLE BODY EXPOSURES TO IONIZING RADIATION**

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*REVIEW*

# **Cancer immunotherapy: how low-level ionizing radiation can play a key role**

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Edward J. Calabrese***

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# Comparison of doses in RT

- **External beam local RT of tumours:**  
**2 Gy daily** repeated until cumulative doses of ~ 80 Gy
- **Preparative total body irradiation (TBI)** (as part of autologous and allogeneic transplants):  
**12-15 Gy over 4 days**
- **"Low dose TBI"** (as part of non-myeloablative allogeneic transplantation):  
**a single dose of 2 Gy**
- **Low-dose total body irradiation (LD-TBI):**  
**0.10-0.15 Gy** two to three times/week for (typically) 5 weeks → **1.5 Gy cumulative final dose** (less than each of the listed beside)



# **Carcinogenic and immunosuppressive effects of ionizing radiation**

**Documented after exposures  
at high doses**

**What about low doses ?**





**Results of many epidemiological analyses and experimental studies indicate that short-term absorption of  $\leq 0.1$  Gy/Sv of low-LET radiation does not instigate and often inhibits the development of cancer**



# Epidemiological evidence

**At least 40 reports\* (1987-2016) evidencing no increase or *decreased* cancer mortality or incidence rates in residents of regions with elevated levels of natural radiation, nuclear workers from various countries, or patients exposed to radiation for medical diagnosis**

\* reviewed in Janiak et al., *Cancer Immunol Immunother*, 2017



# Recent experimental evidence\*

- > 25 reports indicating that low-dose total-body irradiations (LD-TBI) inhibit development of **primary and metastatic cancer in experimental animals** (no such effects after local irradiation of tumours)
- > 40 reports indicating that **LD-TBI stimulates various anti-neoplastic immune reactions** in mice and rats
- > 30 reports evidencing **concurrent LD-TBI- nduced inhibition of the development of cancer** in mice and rats **and stimulation of antineoplastic immunity**

\*\*reviewed in Yang et al. 2016; Cui et al. 2017; Janiak et al. 2017



# Antineoplastic effects of LD-TBI\*

> 25 reports (1996-2017):

LD-TBI inhibits development of primary and  
metastatic cancer in experimental animals

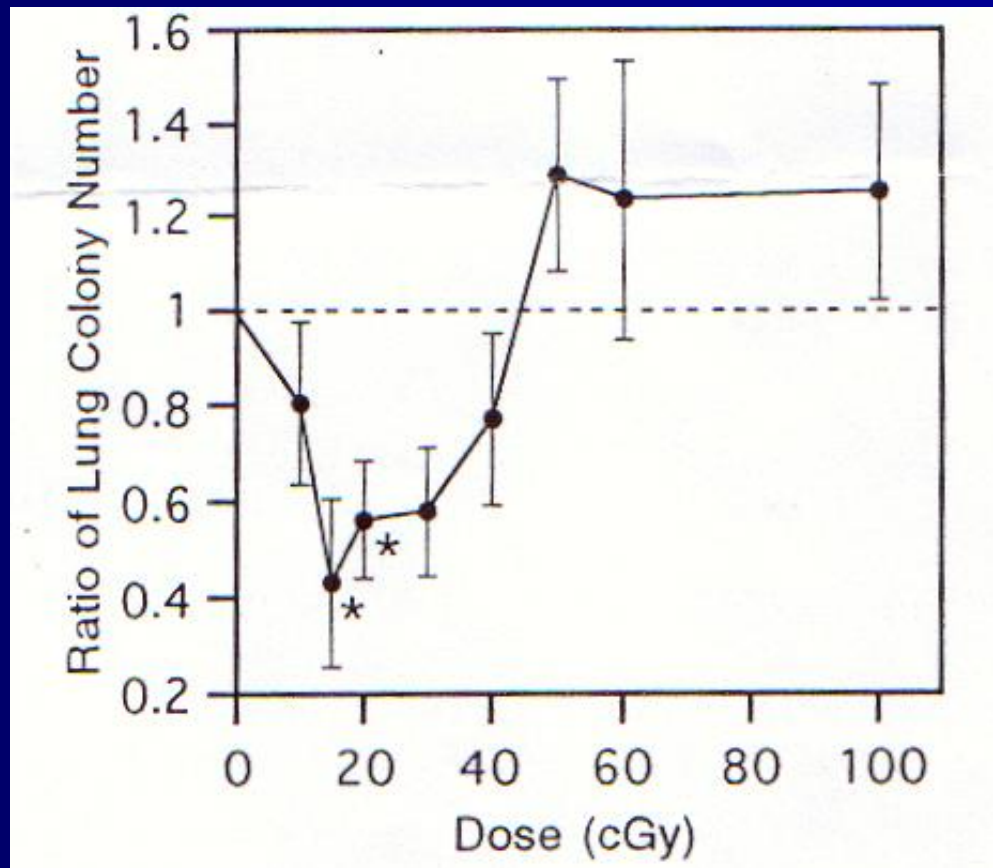
Upper threshold for the effect: 0.1- 0.2 Gy

\*reviewed in Janiak et al. *Cancer Immunol Immunother*, 2017



# Pulmonary tumour colonies in mice irradiated with X-rays prior to injection of tumour cells

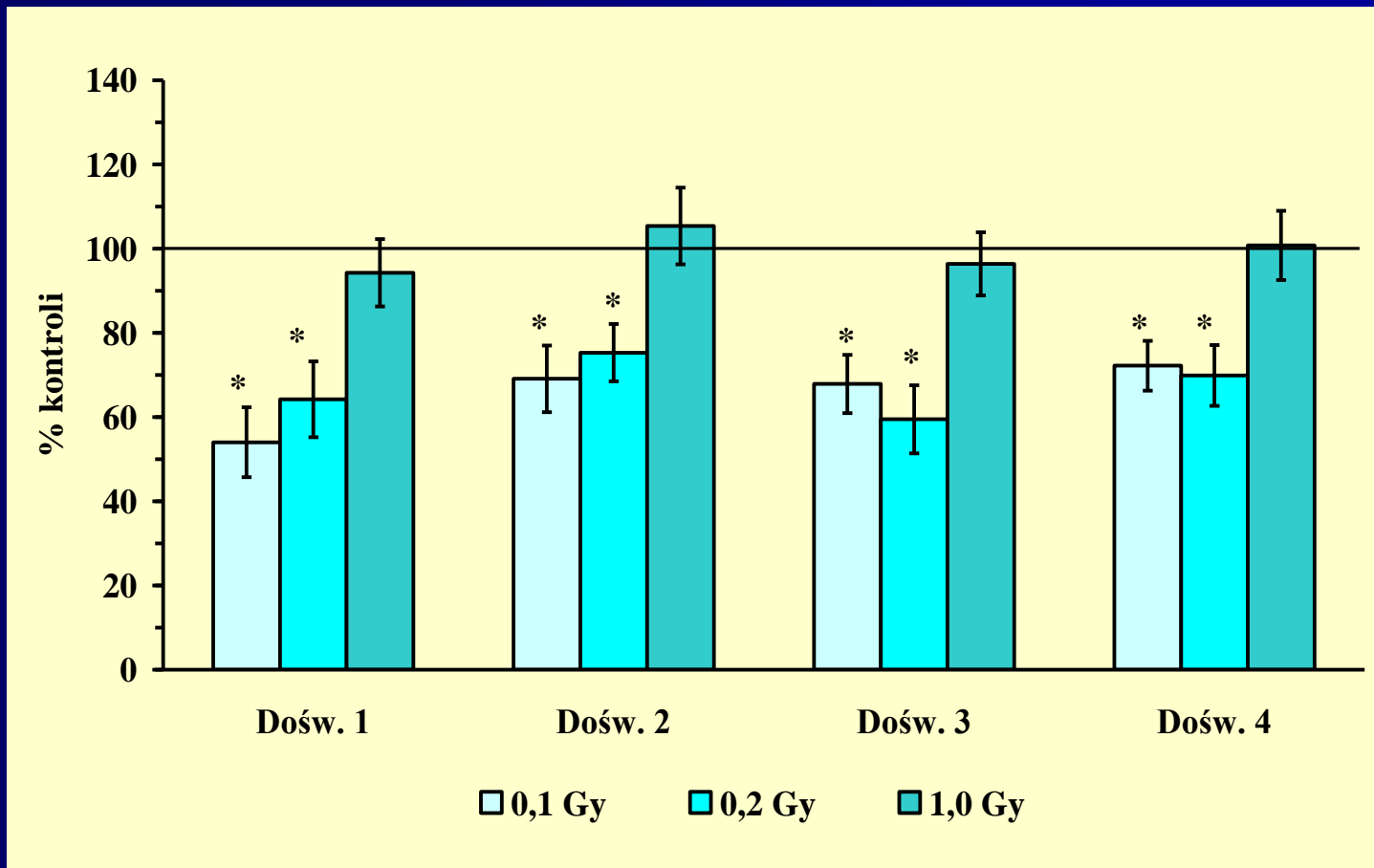
(Hosoi and Sakamoto *Radiother Oncol* 1993)





# Tumour colonies in the lungs of mice after single whole body exposure to X-rays

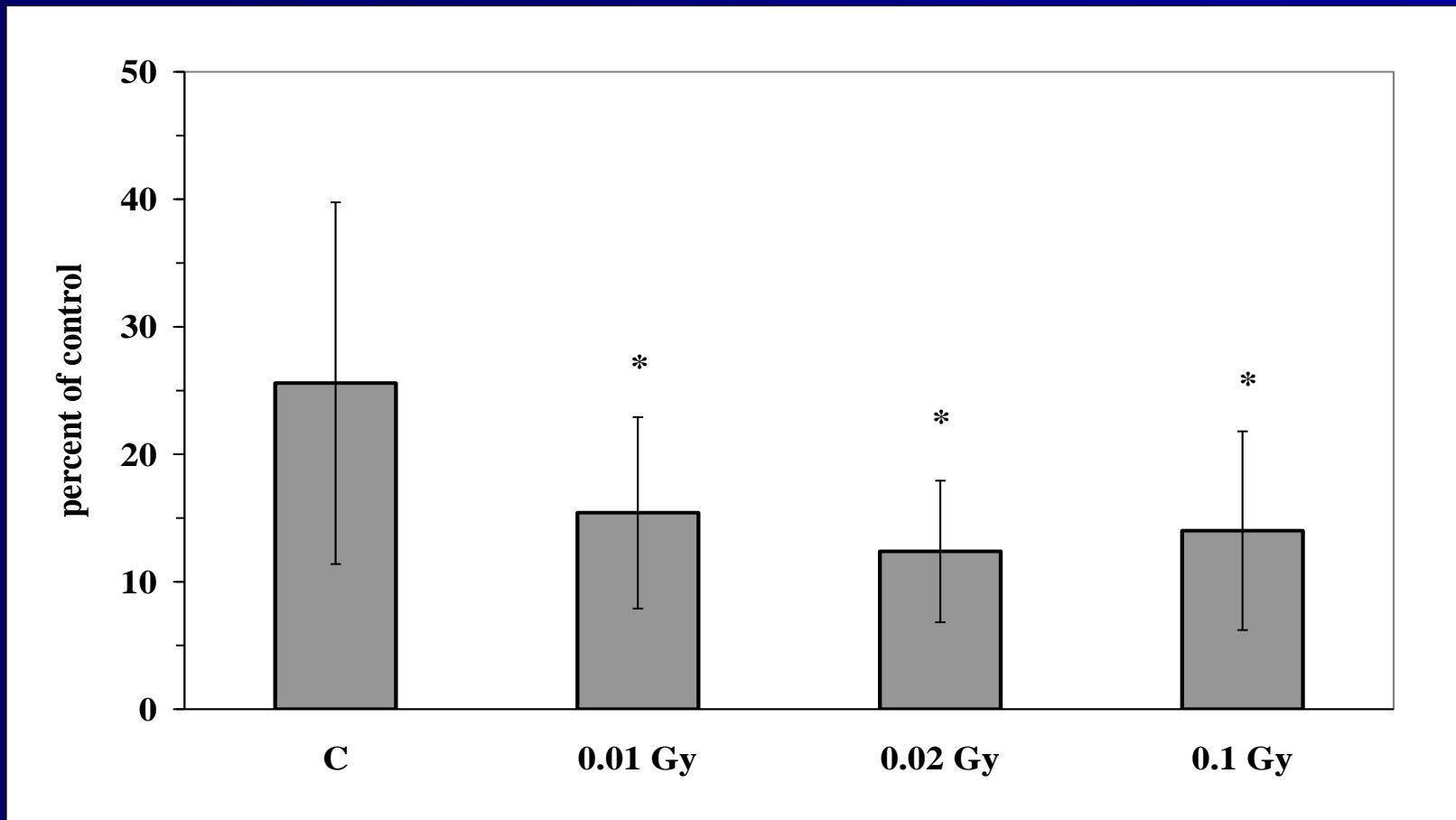
(Cheda et al. *Radiat Res* 2004)





# Tumour colonies in the lungs of mice after ten low-dose whole body exposures to X-rays

(Nowosielska et al. *Int J Radiat Biol* 2011)





# Immunomodulatory effects of LD-TBI\*

>40 reports indicating that whole body exposures of mice and rats to low doses of ionizing radiation stimulate various antineoplastic immune reactions

\*reviewed in Yang et al. 2016; Cui et al. 2017; Janiak et al. 2017





# Modulation of innate and adaptive immunity by low doses of ionizing radiation in rodents

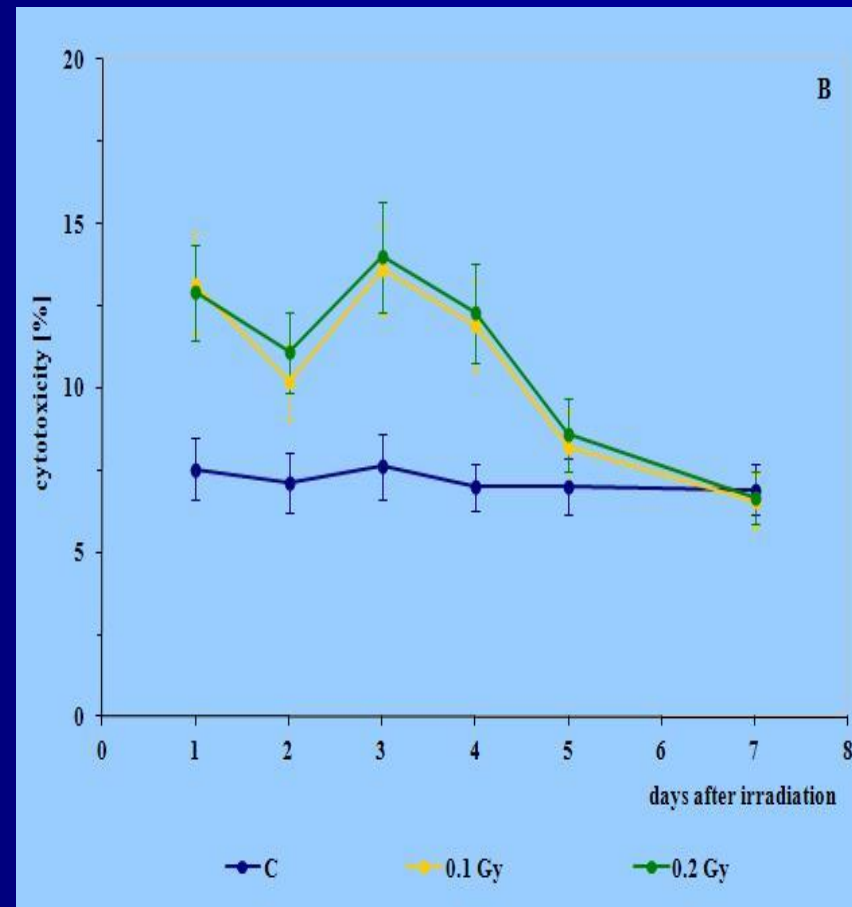
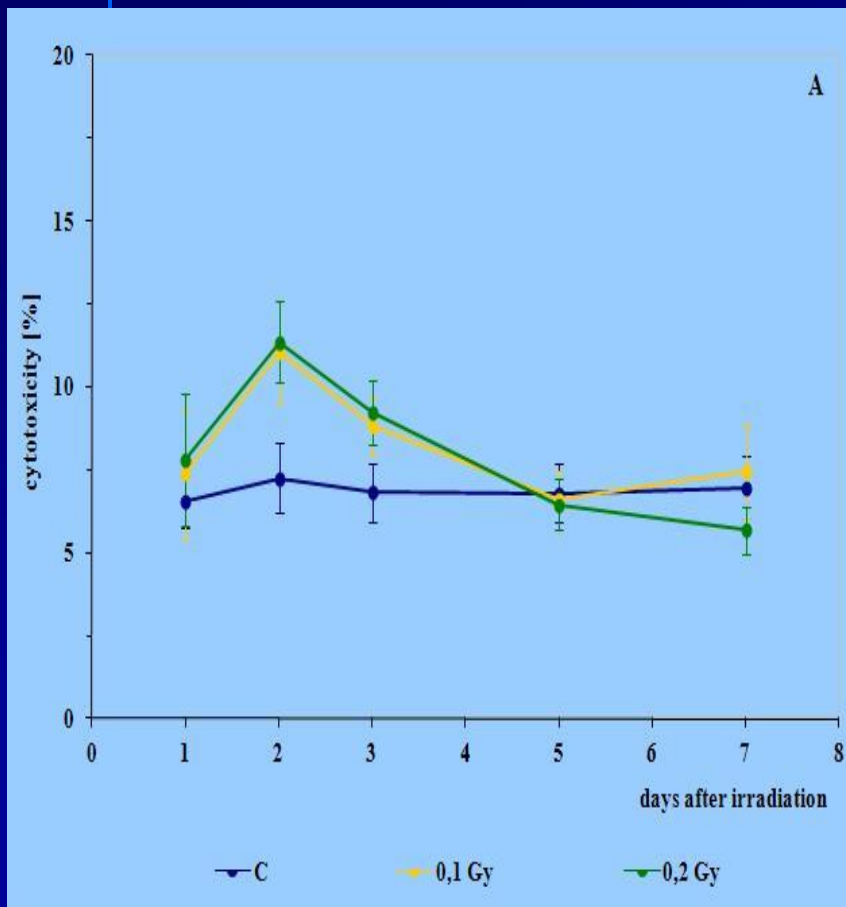
## *Reported stimulatory effects on:*

- **NK lymphocytes** [*Cheda et al 2004; Liu 2007; Shan et al 2007; Nowosielska et al 2006, 2011, 2012; Feng et al. 2017; Zhou et al. 2018*]
- **T lymphocytes** [*Gridley et al 2009; Song et al 2015; Zhou et al 2018*]
- **cytotoxic M $\phi$**  [*Pandey et al 2005; Shan et al 2007; Nowosielska et al 2006, 2011, 2012*]
- **monocytes** [*El-Saghire et al 2013*]
- **dendritic cells** [*Shigematsu et al 2007; Yu et al. 2018*]
- **Treg/Th17 balance** → conducive to tumour regression [*Duan et al 2014*]



# Cytotoxic activity of NK cells after single (A) or fractionated (B) TBI of BALB/c mice

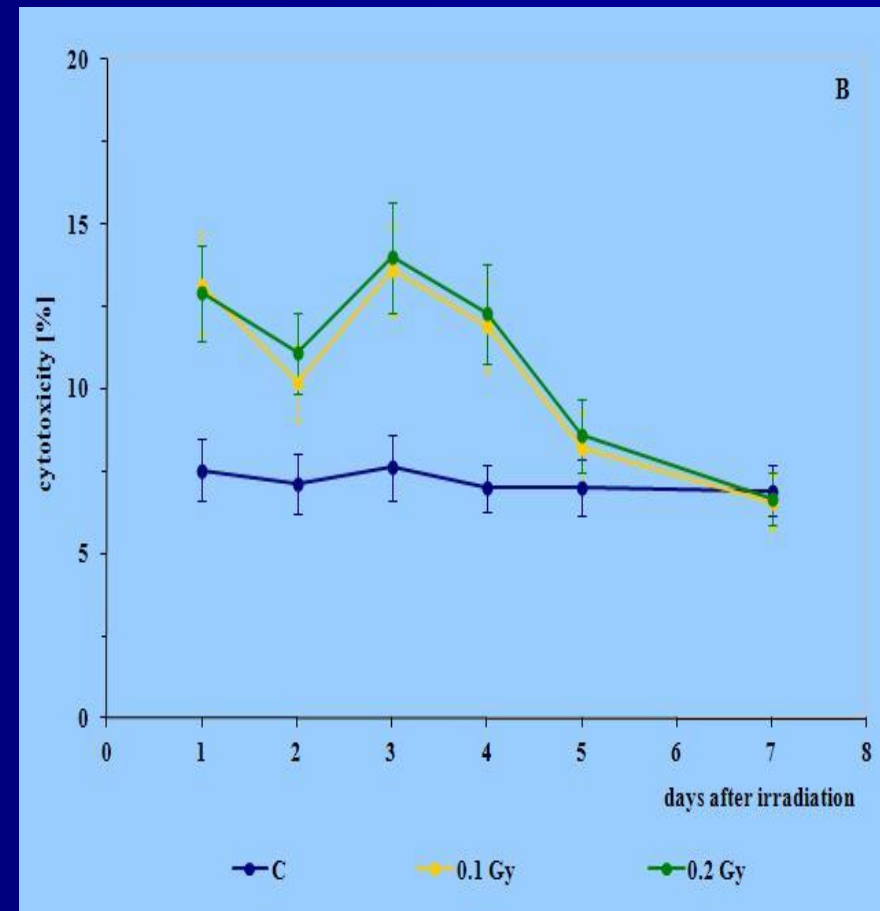
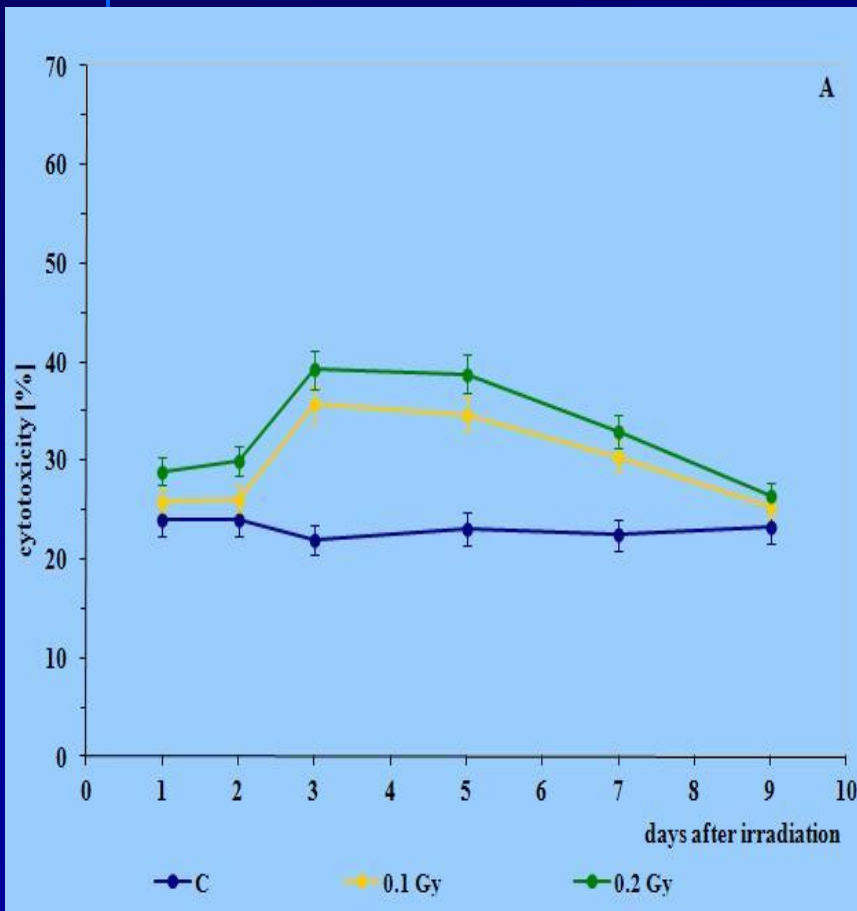
(Nowosielska et al. 2008, 2011)





# Cytotoxic activity of macrophages after single (A) or fractionated (B) TBI of BALB/c mice

(Nowosielska et al. 2008, 2011)





# Stimulation of splenic NK cells and peritoneal macrophages by exposure of mice to 0.1 Gy of X-rays

(Nowosielska et al. 2010)

Parameter	Single exposure	Fractionated exposure
	% of control	% of control
Cytotoxic activity of NK cells	154	170
Production of IFN- $\gamma$ by NK cells	163	202
Cytotoxic activity of M $\phi$	138	172
Production of NO by M $\phi$	345	287
Production of IL-1 $\beta$ by M $\phi$	172	144
Production of IL-12 by M $\phi$	470	587
Production of TNF- $\alpha$ by M $\phi$	126	491



# **Concurrent antineoplastic and immunomodulatory effects of LD-TBI\***

**> 30 reports** evidencing that LLR-induced inhibition of the development of cancer in mice and rats coincides with stimulation of antineoplastic immunity

\*reviewed in Janiak et al. *Cancer Immunol Immunother*, 2017



# Mechanisms of anti-neoplastic effects of low-level exposures to low-LET ionizing radiation

- Stimulation of ROS/NOS scavenging
- Stimulation of DNA repair (incl. repair of non-radiogenic DNA damage)
- Induction of death of transformed cells, endothelial cells in tumor vasculature, immunosuppressive cells (Treg lymphocytes, MDSCs, M2 M $\phi$ , N2 neutrophils, etc.)
- Inhibition of development and/or persistence of chronic inflammation
- **Stimulation of the immune system**



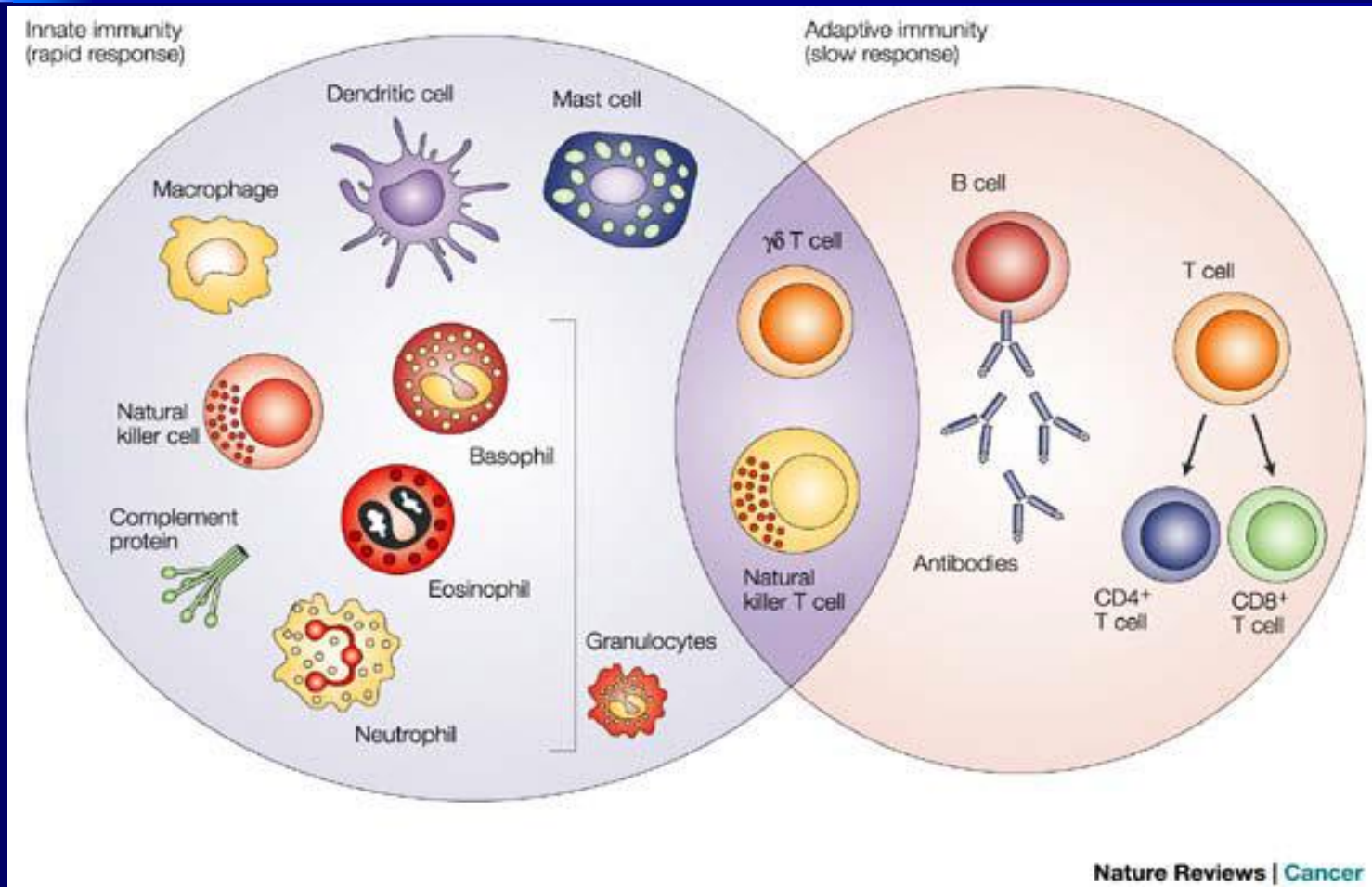
# **The immune system:**

## **the most potent guardian against neoplasia**





# Innate and adaptive immunity



Dranoff, *Nat Rev Cancer* 2004





# Does immune system effectively guard against cancer ?

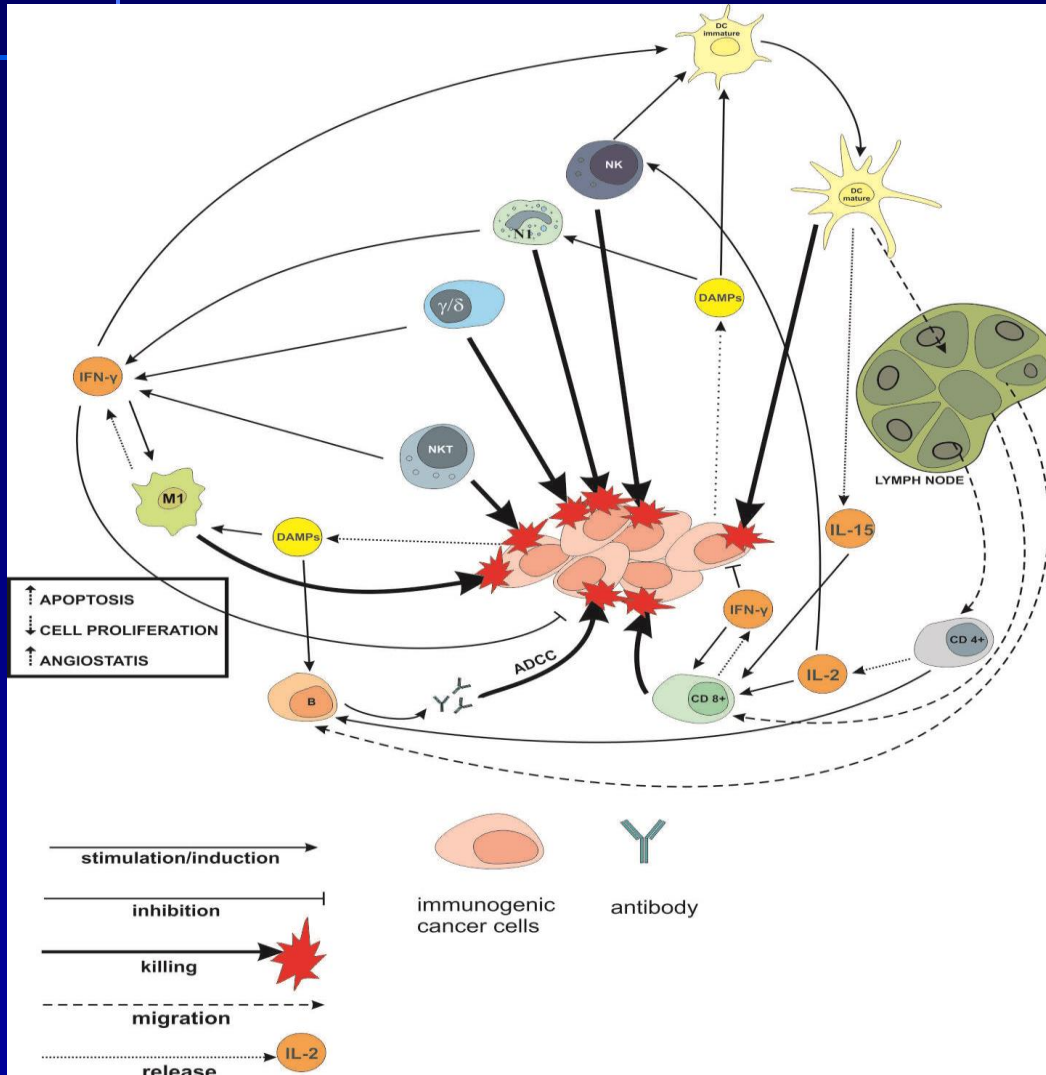
Earlier concept of ***cancer immunosurveillance***  
(activated adaptive response eliminates neoplastically transformed cells)

currently incorporated to:

***cancer immunoediting process – the three e's:***

- *elimination phase,*
- *equilibrium phase,*
- *escape phase.*

# Cancer immunoediting (1)



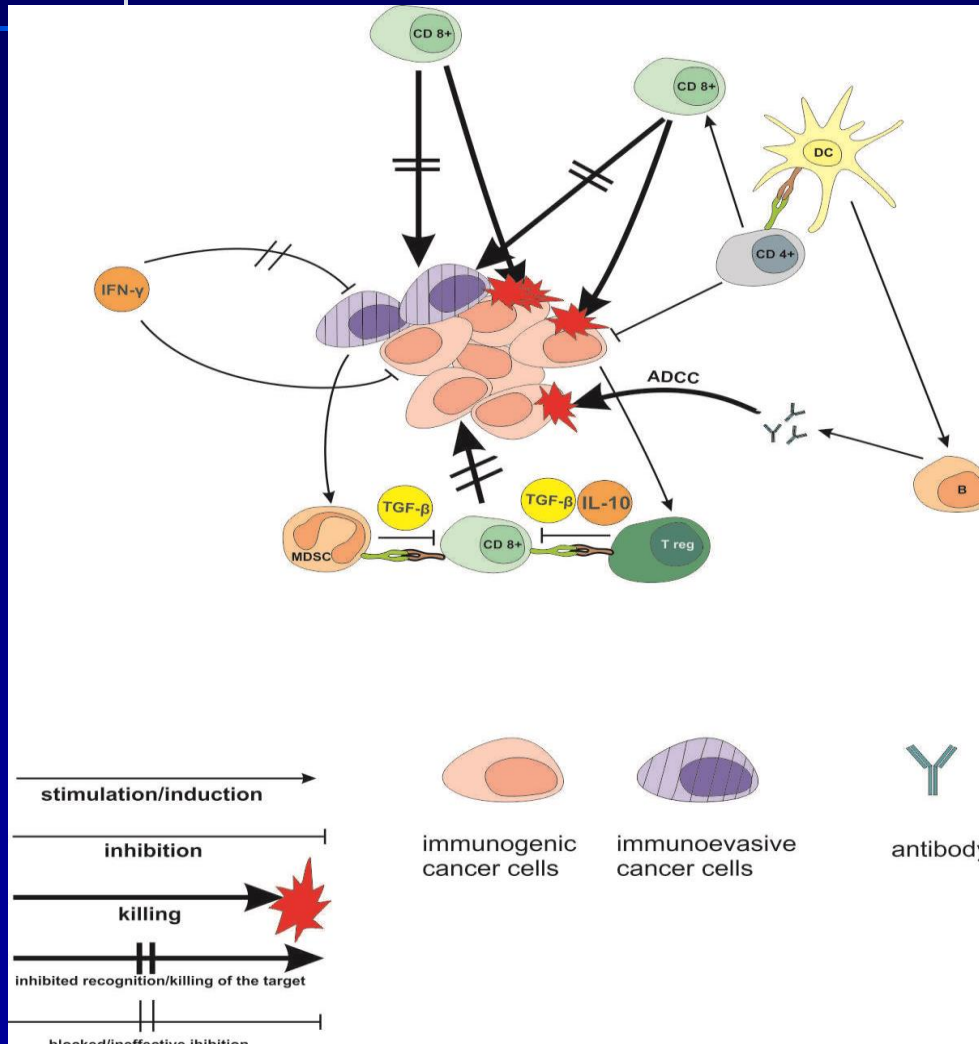
## Elimination phase

alarmed *innate* system (the first line of immunological defence) triggers *adaptive* response to specifically detect and destroy pre-neoplastic/neoplastic cells



**eradication of emerging cancer**

# Cancer immunoediting (2)

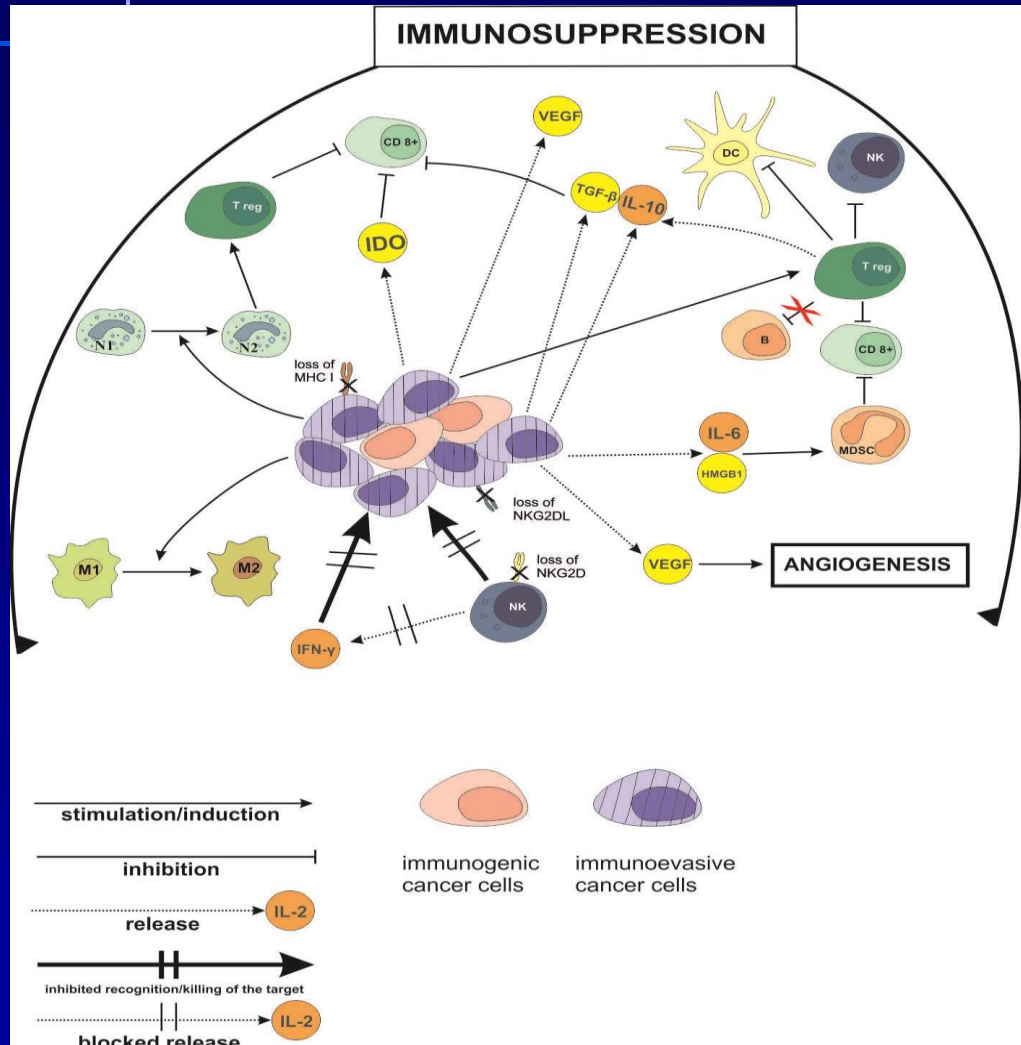


## Equilibrium phase

humoral and cellular, innate and adaptive immune mechanisms (IFN- $\gamma$ , IL-12, NK(T) cells, M $\phi$ , T and B cells) hold persisting cancer cells in check (= **cancer dormancy**), but also 'edit' the immune status of these cells and their environment



# Cancer immunoediting (3)



## Escape phase

proliferation of 'immuno-edited' (i.e., resistant to immune attack) neoplastic cells in immunosuppressive environment



**cancer progression**



# Cancer immunoediting process

(according to Schreiber et al. *Science* 2011)

**The immune system and other elements of tumour microenvironment protect against cancer progression, but also 'edit' the tumour cells and their microenvironment so that:**

- a) tumour cells become 'invisible' and/or resistant to immune attacks,**
- b) tumour-associated immune system becomes suppressed and/or supportive of tumour progression.**



# Immunotherapy – the *fifth pillar*\* of cancer therapy

## Aims:

1. Stimulation of anti-cancer immunity
2. Inhibition/reversal of the immune suppression

\* 1. *surgery* 2. *chemotherapy* 3. *radiotherapy* 4. *targeted therapy* 5. *immunotherapy*



# Radioimmunotherapy of cancer

- **Currently:** *in situ* and abscopal activation of various anti-neoplastic immune functions by local irradiation of tumours at 0.3-2.0 Gy per fraction.
- **Prospectively:** systemic stimulation/restoration of anti-cancer immunity by whole/half-body exposures to low LET radiation at about 0.1 Gy per fraction.





# Can low-level exposures block/ reverse immune suppression ?

## ■ Evidence from experimental studies:

- **Joo *et al.* 2012**: inhibition of immunosuppressive and pro-inflammatory activities of mast after their *in vitro* irradiation with  $\gamma$ -rays at 0.01 Gy;
- **Wang *et al.* 2014**: down-regulation of Treg cells in the blood and of CTLA-4 expression on the liver and spleen tumours in rats with liver cancer after irradiation of the spleen at 1 x and 3 x 150 mGy;
- **Prakash *et al.* 2013, 2016**: macrophage differentiation to an iNOS<sup>+</sup>/M1 phenotype that orchestrates effective T cells.

## ■ Indirect evidence from hitherto conducted clinical trials:





# Historical perspective

according to Block, Silva and Welsh, *J Radiat Oncol* 2017

From 1960s to 1990s: **low-dose total body irradiation (LD-TBI) was effectively used in treatment of lymphomas and leukaemias**

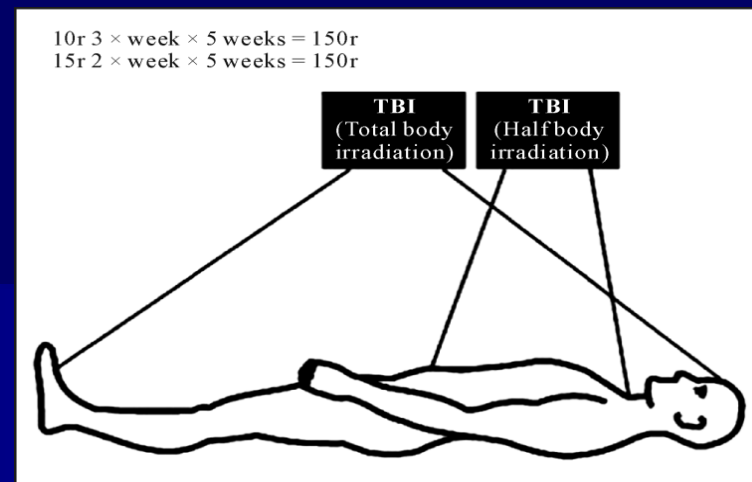
**LD-TBI have since fallen out of favour** due to advances in chemotherapy and immunotherapy,

*but*

**none of the other methods (esp. chemotherapy) has clearly proven superior to LD-TBI**



# Treatment of haematological malignancies with LD-TBI (1)

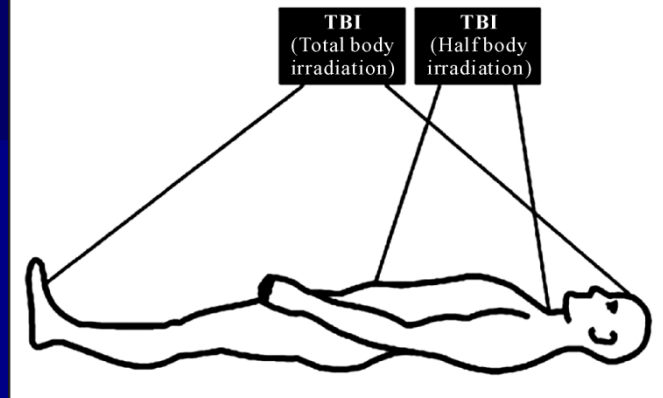


- Curative effects of total-body irradiations (TBI) of patients with multiple myeloma and lymphosarcoma [Holder 1965, Jacobs & Marasso 1965, Johnson 1975]
- Curative effects of total-body irradiations (TBI) of patients with stage III non-Hodgkin lymphoma (NHL) with  $\gamma$ -rays (0.15 Gy daily for five days and then 0.1-0.15 Gy every other day, or at longer intervals over 5-12 weeks to total doses 2.0-2.65 Gy) [Kazem 1975]
- Complete remission in 32 (80%) out of 40 patients with advanced lymphocytic lymphoma after TBI (as an initial and only therapy) at 0.15 Gy twice a week to a total dose 1.5 Gy [Chaffey et al. 1976]



# Treatment of haematological malignancies with LD-TBI (2)

$10r \times 3 \times \text{week} \times 5 \text{ weeks} = 150r$   
 $15r \times 2 \times \text{week} \times 5 \text{ weeks} = 150r$

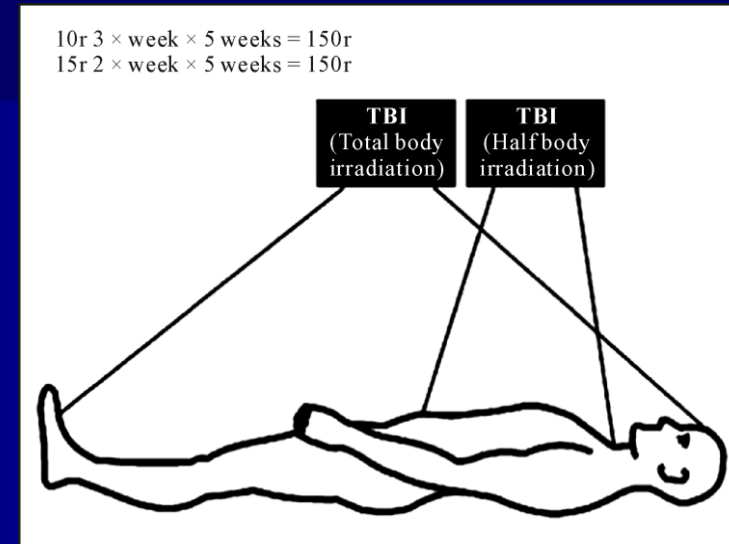


- Complete remission in 5 (80%) out of 9 patients with diffuse type of poorly differentiated lymphocytic (7 patients) and histiocytic (2 patients) lymphoma after chemotherapy followed by TBI at 0.15 Gy twice weekly to a total dose 1.2-1.8 Gy; clinical response correlated with improved mitogen responsiveness of circulating lymphocytes [Yonkosky et al. 1978]
- Complete remission in 8 (73%) out of 11 patients with stage III-IV NHL treated with chemotherapy (4 cycles from day 1) and WBI (3 cycles at 0.15 Gy each on days 21, 23 and 25; total dose 1.35 Gy) [Weick i wsp. 1983]



# Treatment of haematological malignancies with LD-TBI (3)

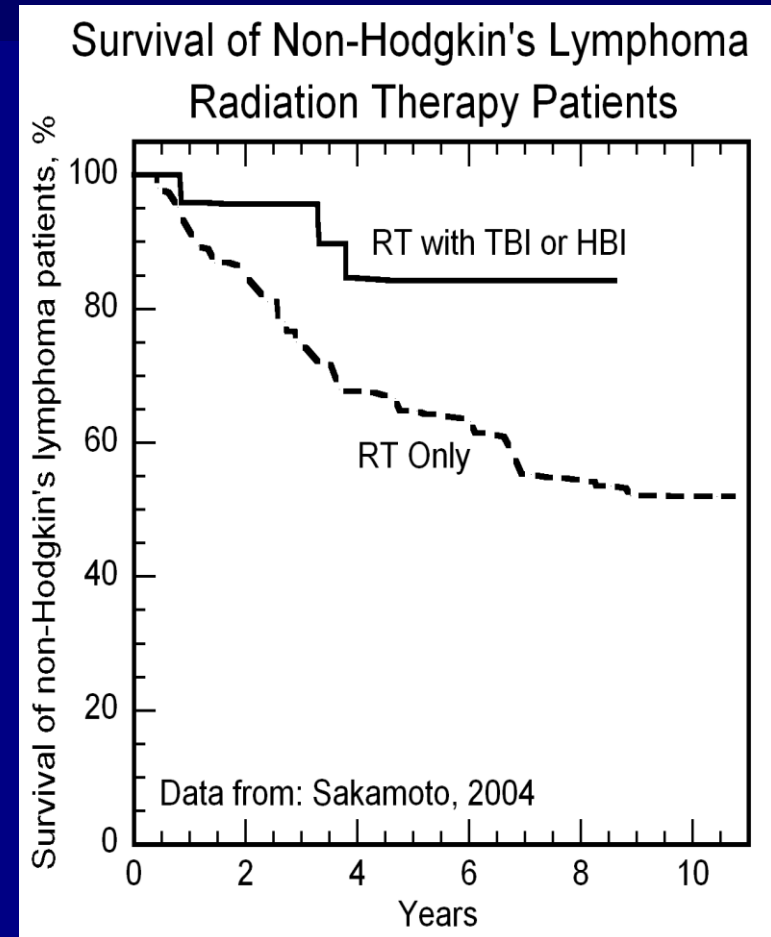
- Complete remission in 24 out of 26 patients with stage IV low-grade NHL after 2 courses of TBI (0.15 Gy daily/week, separated by a rest period of 2 weeks) [Richaud et al. 1998]
- Complete remission in 11 out of 35 patients and 2-y progression-free survival in 12 patients with relapsed or chemo-resistant NHL after TBI at 0.1-0.25 Gy several times a week (total dose 1.5-2.0 Gy) [Safwat et al. 2003]
- Complete 3-y remission in 61±9% patients with chemotherapy-remitted stage IIB, III and IV NHL after 2 courses of TBI (0.2 Gy daily x 4 + the same after 2 weeks; total dose 1.6 Gy); without TBI 3-y remissions in only 35±9% patients [Safwat et al. 2004]





# Treatment of haematological malignancies with LD-TBI (4)

Five-year survival of 84% of patients with stage I and II NHL total- or half-body irradiated with X-rays (at 0.1-0.15 Gy 2 x a week for 5 weeks) followed by local RT (2 Gy 5 x a week for 6 weeks) - compared to 65% surviving patients treated only with local RT [Sakamoto 2004]





# Treatment of haematological malignancies with LD-TBI (5)

## *Waldenström's macroglobulinemia* \*

a 78-y-old male who relapsed after therapy with chlorambucil : TBI with X-rays (0.15 Gy twice weekly for ten sessions (*Sep–Oct 1999*) → ↓ in circulating IgM, blood viscosity, and spleen volume; ↑ CD4:CD8 ratio; asymptomatic for almost 5 years [Welsh 2004]

\*a.k.a. *lymphoplasmacytic lymphoma*





# Treatment of prostate cancer with LD-TBI [Kojima et al. 2017]

- 60-y-old patient with removed prostate and PSA level >5: TBI with X-rays (0.15 Gy once a week for 30 weeks) → permanent cancer-free survival with ↓ of PSA level to 0.085;
- 54-y-old patient with inoperable cancer, bone metastases, and PSA level = 4.8: TBI with X-rays (0.15 Gy 3 x a week, 10 x) + 'radon sheet'\* (6 h per day for 10 months) → permanent ↓ of PSA level to 0.008, no signs of metastases

\*a flexible silicone sheet (44 x 93 cm) containing monazite and emanating ionizing radiation at 37  $\mu$ Gy/h



# Effects of moderate and high vs. low-level exposures to ionizing radiation

## INTERMEDIATE to HIGH DOSES

Induce death of normal cells and injure healthy tissues

Induce inflammation

Suppress immune functions

Induce secondary cancers

Can be used only locally

## LOW DOSES

Do not induce death of normal cells and do not damage healthy tissues

Attenuate (chronic) inflammation

Stimulate immune system

Do not induce secondary cancers

**As whole body exposures can be *the therapy of choice* for systemic or metastatic cancer**





# Emerging therapeutic options

Combination of LD-TBI irradiations with blockade of:

- inhibitory immune checkpoints (e.g., CTLA-4, PD-1);
- pro-neoplastic heat shock proteins (e.g., HSP-90);
- factors associated with immune-related adverse events (e.g., TNF $\alpha$ )
- other

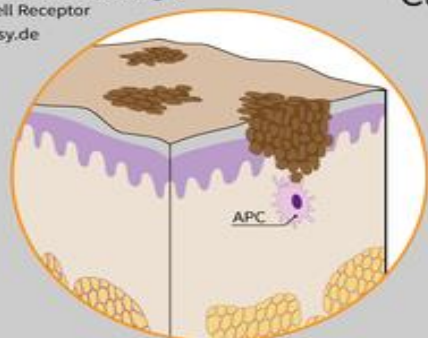


# Blocking of inhibitory immune checkpoints – a novel form of cancer therapy

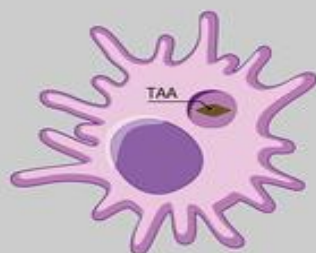
Nobel Prize for Medicine 2018

## Cancer Therapy by Inhibition of Negative Immune Regulation (CTLA4, PD1)

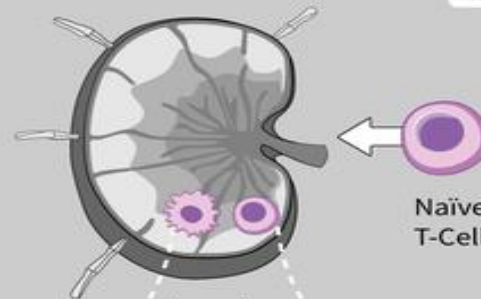
APC – Antigen-Presenting Cell  
TAA – Tumor-Associated Antigen  
TCR – T-Cell Receptor  
www.hegasy.de



Tumor  
(e.g. Melanoma)

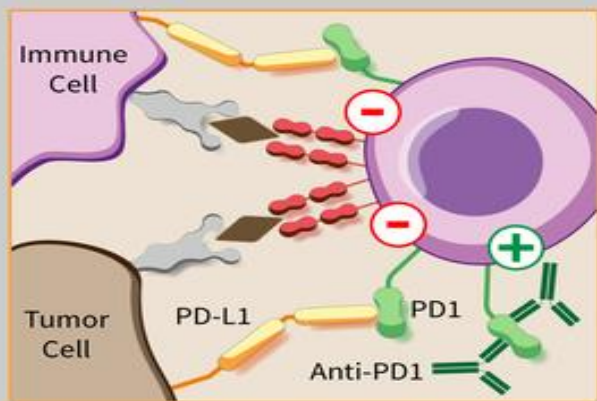


APC Containing TAA  
Migrates to Lymph Node



Lymph  
Node

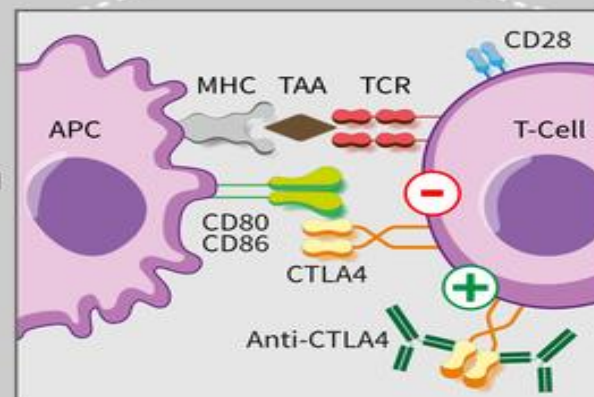
Naïve  
T-Cell



Tumor Microenvironment



T-Cell Migrates to  
Tumor Tissue



T-Cell Priming

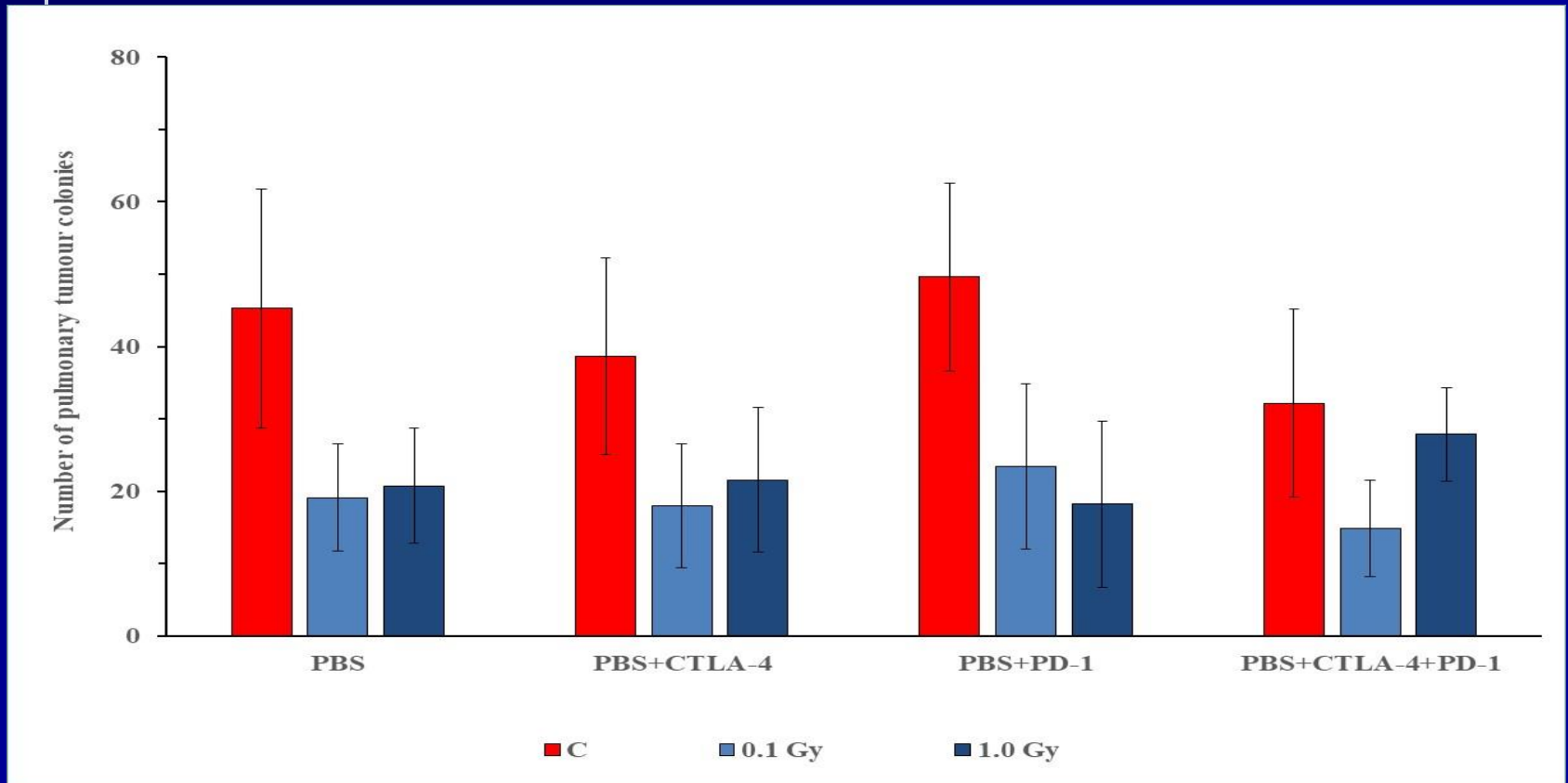


v2 - 10/2018



# Lung tumour colonies in mice after whole-body irradiations with X-rays\* and injection of anti-CTLA-4 and/or anti-PD-1 antibodies

(unpublished own results)



\*0.01 or 0.1 Gy/daily for 5 days up to total doses of 0.1 or 1.0 Gy



# Obstacles to clinical trials with whole-body exposures to LD=TBI

**Radiation safety regulations based on *unscientific* LNT model\*** resulting in rigorous control of actual and potential exposures to ionizing radiation

**\* any absorbed dose of radiation causes a finite increase in cancer risk  
→ 'no safe dose' myth**



**Unnecessary precautions taken by doctors and patients**



# Obstacles to clinical trials with whole-body exposures to LD-TBI (*contd.*)

## Fear of second malignancies (a corollary to LNT):

Travis et al. 1996: acute non-lymphocytic leukaemia in 4 out of 61 lymphoma patients treated with TBI combined with alkylating agents,

but:

- median bone marrow dose in the above patients = **5.2 Gy**;
- acute leukaemias are common in low-grade lymphomas, even without RT (due to defects in cellular immunity) [Ellis & Lishner 1993]
- possible role of alkylating agents;
- **negligible risk of second primary malignancies associated with irradiation at doses <0.1-0.2 Gy** [Tubiana 2009]



# Conclusions

- **Whole-body exposures of oncological patients to low-level radiation (LLR) is likely to inhibit progression of systemic cancer without eliciting untoward side effects.**
- **Anti-neoplastic effects of whole-body exposures to LLR depend on stimulation/restoration of efficient anticancer immunity.**
- **Targeting pro-cancer immunosuppression may rationalize the design of protocols using LLR as an adjuvant to other therapeutic modalities to enhance the curative gain and safeguard normal tissues against the toxicity of conventional chemo- and radiotherapy.**
- **It's time to advance clinical trials of whole/half-body exposures to LLR (alone or as an adjuvant to conventional therapeutics) in order to restore anticancer functions of the immune system, the most potent guardian against neoplasia.**



A photograph of a sunset over the ocean. The sun is low on the horizon, creating a bright orange and yellow glow that spreads across the sky and reflects on the water. The sky is filled with soft, wispy clouds. The ocean is dark blue with gentle waves.

**Thank you**

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# Selected clinical trials by Malik M. Qasim<sup>1</sup>

<sup>1</sup>Department of Engineering, University of Cambridge

Total body irradiation in non-Hodgkin lymphoma. *Strahlentherapie* 1975:

**16 out of 17 patients with non-Hodgkin lymphomas treated by total body irradiation went into remission.**

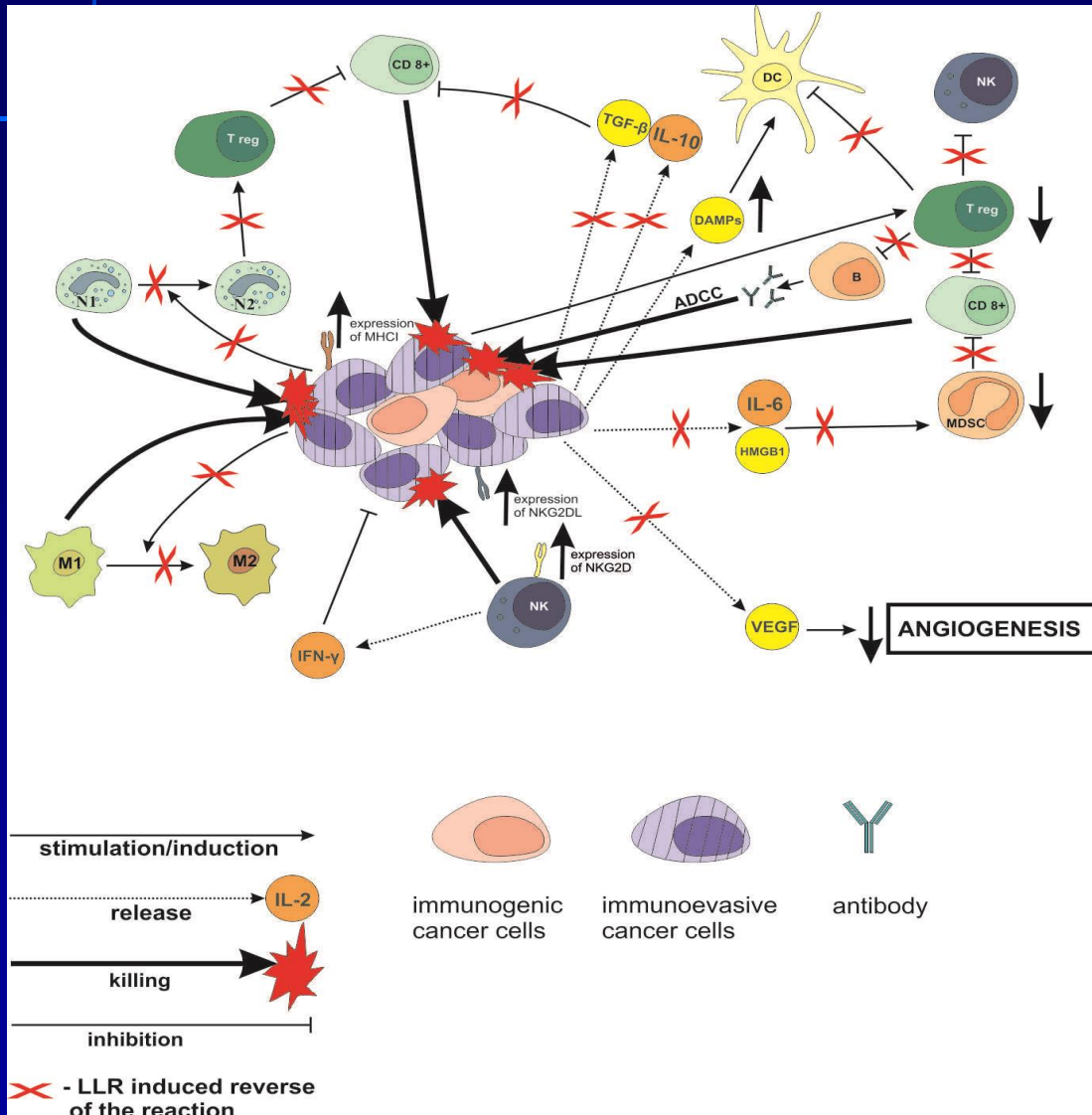
Half body irradiation (HBI) in metastatic carcinomas. *Clin Radiol* 1981:

**the relief of pain within 24-48 h in 76% of 129 cancer patients with bony metastases, 65% of the responders free from pain for the remainder of their life (3-10 months); reduction of large tumour masses for 5-20 weeks; the treatment well tolerated and haematologically safe.**

Systemic radiation and split-course radiotherapy for non-small-cell bronchial carcinoma. *Clin Radiol* 1986:

**26% of 138 patients with inoperable NSCLC, stage III, survived 4 years disease-free, as compared with 7% in the group where no systemic irradiation was applied.**





# Anticipated LLR-induced changes related to the *escape* phase



# **Anticipated LLR-induced changes during later stages of carcinogenesis**

- **Enhancement of the 'visibility' of cancer cells to immune effectors by:**
  - **stimulated expression by cancer cells of costimulatory molecules and ligands necessary for activation of cytotoxic immune effectors**
  - **recovery/upregulation of expression of 'danger signals' by the developing cancer**
  - **modulation of the structure and/or surface presentation of specific tumour antigens**
- **Reversal of immunosuppressive state of the tumour microenvironment**
- **Subversion of chronic inflammation relevant to tumour initiation and progression**
- **Stimulation of expression of ligands (eg. NKG2DL) on cancer cells activating cytolytic immune effectors**
- **Induction of the 'right' (immunogenic) type of cancer cell death**
- **Other?**



# Possible untoward effects of stimulation of the immune system

- May enhance rather than inhibit pro-neoplastic suppression of the function of the immune system [ref. ?? ];
- Can boost tumour outgrowth via T cell-mediated stimulation of the epithelial-mesenchymal transition (EMT) [Santisteban et al. 2009];



# Conclusions

- **Whole- or half-body exposures to LLR appear to be an effective anti-neoplastic treatment with no side effects and no/negligible risk of secondary cancer;**
- **The likely underlying mechanism is modulation of the (escape phase of the) cancer immunoediting process;**
- **Targeting cancer immunoediting may rationalize the design of protocols using LLR as adjuvant to other therapeutic modalities to enhance the curative gain.**



# Carcinogenesis

## Classical definition:

Multiphase process of **accumulation of mutations**, disregulations, rearrangements, deletions, and duplications **of cellular genes** resulting in the ability of cells to **uncontrolled invasive growth as tumours or neoplastic infiltrations.**

*[Great Medical Dictionary, PAS, 1996]*

## Updated definition:

Mutations and other changes in the genes are not enough, essential is also **disregulation** of defence/surveillance mechanisms **at cellular, microenvironmental, tissue, and organ levels.**

*[M. Tubiana, 2009]*



# Effects of currently used moderate- and high-level exposures to ionizing radiation

## INTERMEDIATE to HIGH DOSES

(May) induce death of normal cells and damage healthy tissues

(May) induce inflammation

(May) inhibit immune functions

(May) induce secondary cancers

Can be used locally

## LOW DOSES

?



# Anticancer effects of low-level radiation (LLR)

- Epidemiological studies: **decreased cancer mortality/incidence** among various groups of people exposed to low doses/dose rates of ionizing radiation
- Experimental studies: **inhibition of growth of primary and metastatic tumours** in experimental animals
- Clinical trials: **equally or more effective** in treatment of systemic cancers (NHL, CLL, other) **than conventional antineoplastic therapies**



# Macroscopic tumour colonies in the lungs of Balb/c mice after intravenous injection of syngeneic L1 sarcoma cells







# The immune system

## **Innate (inborn) - non-specific:**

- in all classes of plants and animals
- first-line defence
- triggers and shapes adaptive response
- effectors:

*humoral:* complement system, lysozyme, chemokines, cytokines

*cellular:* dendritic cells, NK lymphocytes, macrophages, granulocytes, mast cells

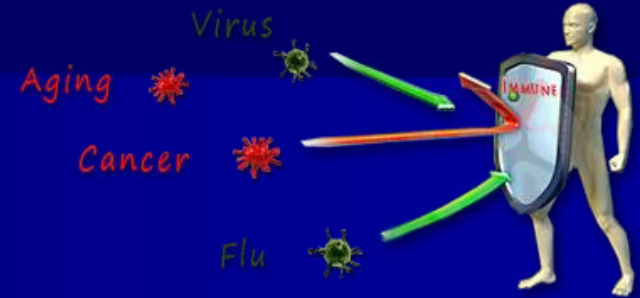
## **Adaptive (acquired) - specific:**

- only in vertebrates
- creates long-term immunological 'memory'
- effectors:

*humoral:* Abs produced by stimulated B lymphocytes

*cellular:* specifically stimulated T lymphocytes (Th, CTL, Treg)

**Both arms are involved in control of the development of cancer and  
CANCER IMMUNOEDITION**

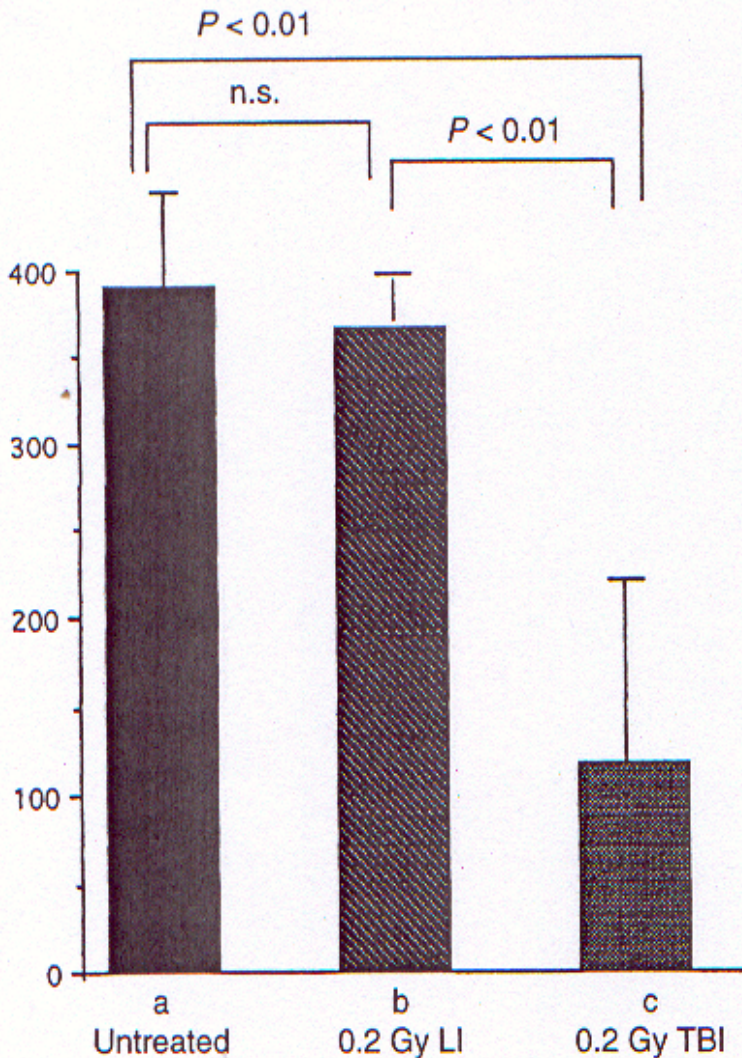


<http://ageless-society.com/immune-system-health/>



# Recently reported LLR-induced changes potentially related to cancer immunomodulation

- Stimulated secretion of IFN $\gamma$ , IL-1 $\beta$ , IL-2, IL-10, IL-12, IL-18, TNF $\alpha$  in favour of Th1 (anti-tumour) phenotype [*Liu 2007; Shan et al 2007; Nowosielska et al 2010*]
- Boosted NK lymphocyte- and macrophage-mediated as well as Ab-dependent cellular cytotoxicity (ADCC) after WBI ( $\leq 0.1$  Gy) of mice [*Liu 2007; Shan et al 2007; Cheda et al 2004; Nowosielska et al 2006, 2011, 2012; Sonn et al 2012; Yang et al 2014*]
- Stimulated proliferation of T lymphocytes related to up-regulation of surface CD2, CD3, and CD28 after WBI of mice at  $\leq 0.1$  Gy (*Liu 2007; Shan et al 2007*)
- Inhibited immunosuppressive and proinflammatory functions of mast cells after in vitro exposure to 0.01 Gy of  $\gamma$  rays (*Joo et al 2012*)



**Neoplastic colonies in lungs of WKHA rats implanted with KDH-8 tumour cells and locally (LI) or total body irradiated (TBI) with X-rays at 0.2 Gy**

**(Hashimoto et al., 1999)**



# High, intermediate, and low doses of ionizing radiation

(according to UNSCEAR)

**High absorbed doses** (acute exposure):  $\geq 1.0$  Gy

**Intermediate doses** (acute exposure): **0.1(0.2)-1.0 Gy**

***Low-level radiation (LLR):***

**Low absorbed doses** (acute exposures):  $\leq 0.1^*$  Gy

**Low-dose rate** (protracted/chronic exposures):  
 $\leq 0.1$  mGy/min.

*\* equivalent to 10-20 CT scans*