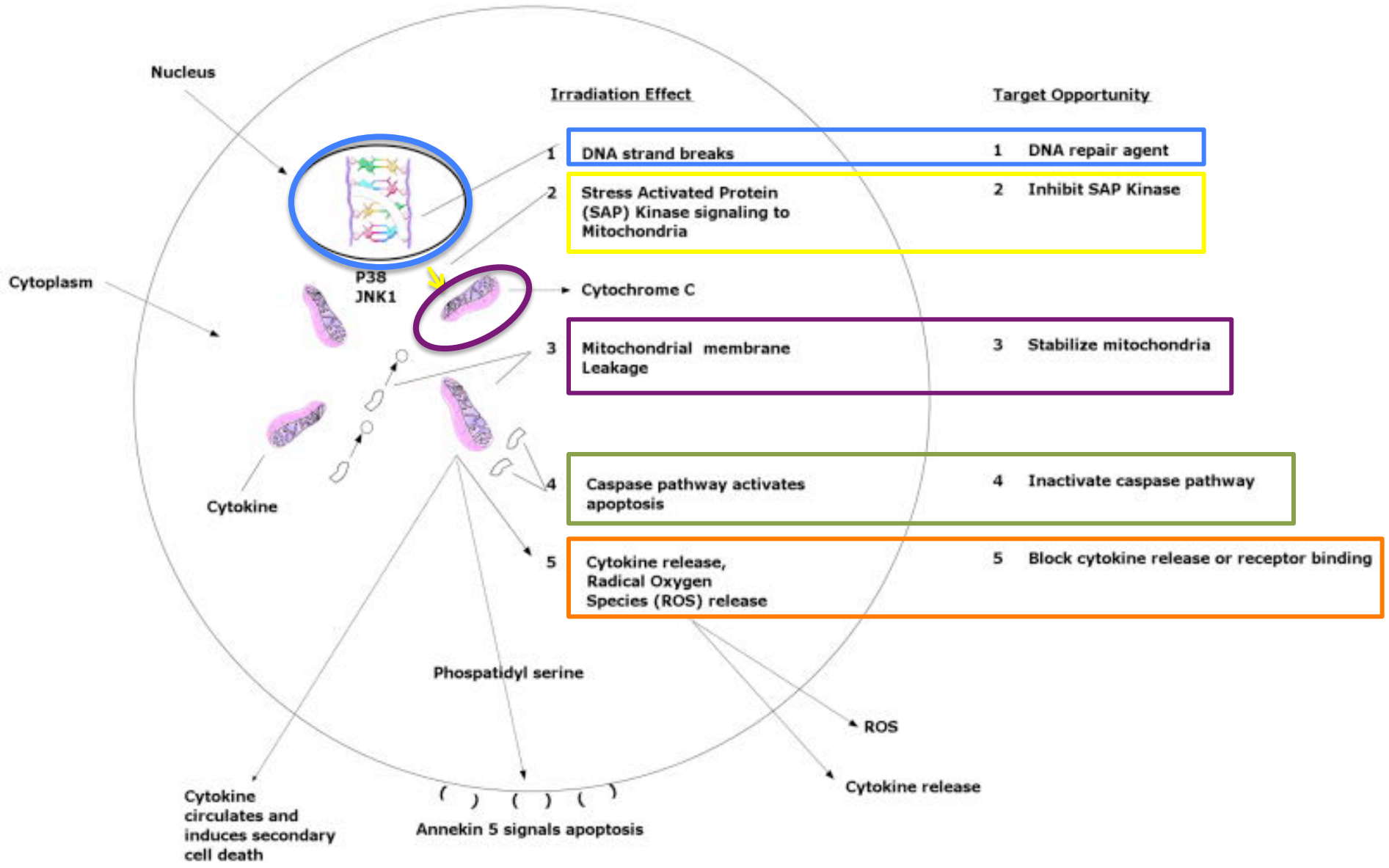
Modulazione farmacologica della risposta dei tessuti sani alle radiazioni ionizzanti

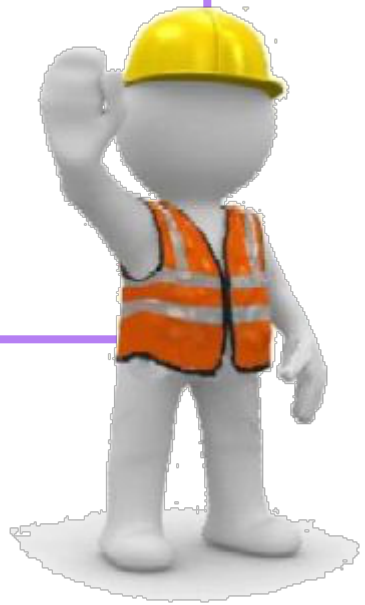
Daniela Greto
Università degli Studi di Firenze

Targets for development of radioprotector agents based on molecular pathways of the irradiation response

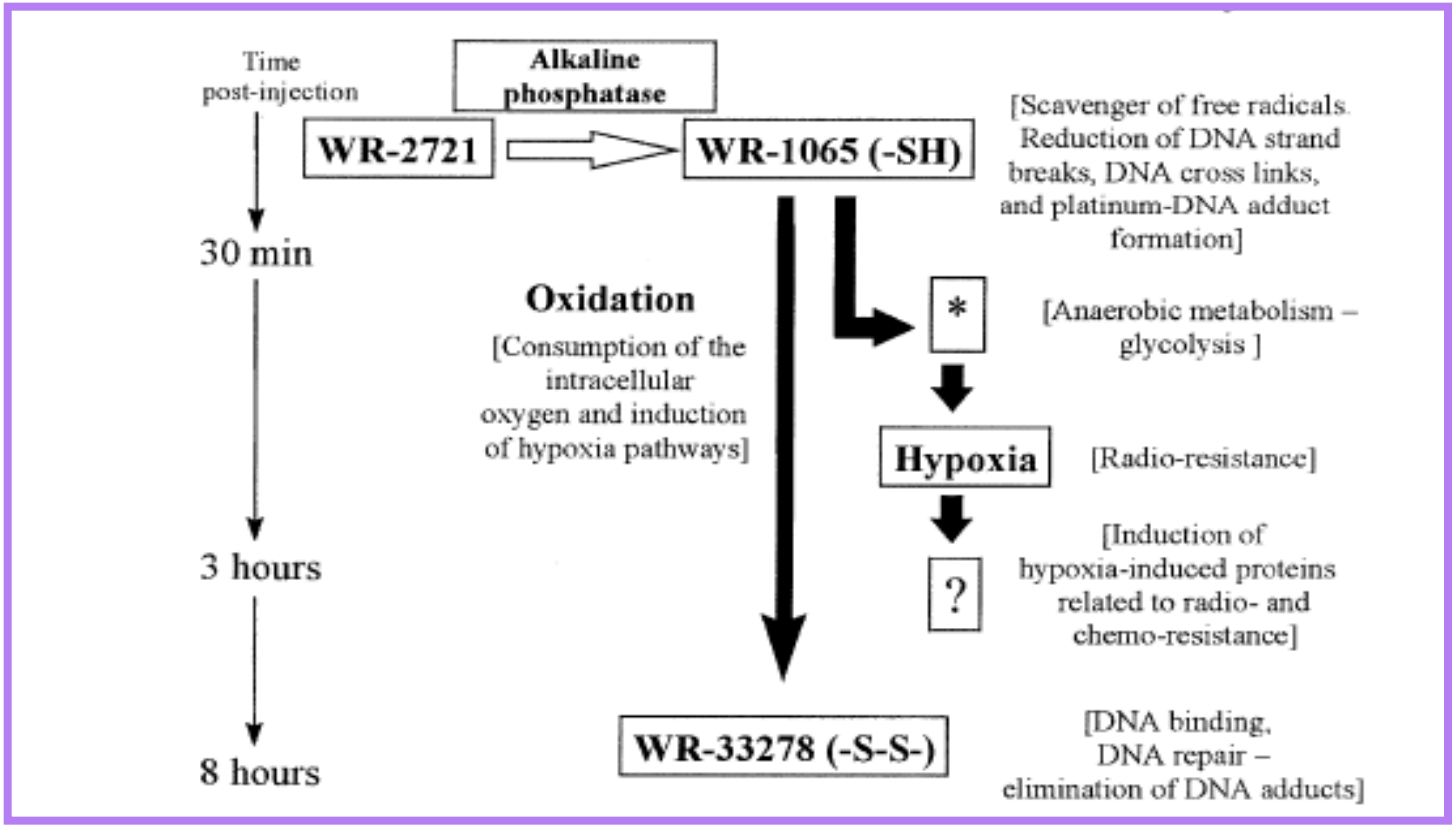


Greenberger JS, In Vivo 2009; 23: 323-36

Approaches
must be
strictly selective
for healthy tissues
and
must be safe



Amifostine



FDA approval: to reduce the cumulative renal toxicity associated w/ administration of CCDP in ovarian cancer and to reduce xerostomia in postoperative RT for H&N cancer

Koukourakis MI. Anticancer Drugs 2002; 13: 181-209

Phase III Randomized Trial of Amifostine as a Radioprotector in Head and Neck Cancer

By David M. Brizel, Todd H. Wasserman, Michael Henke, Vratislav Strnad, Volkar Rudat, Alain Monnier, Francois Eschwege, Jay Zhang, Lesley Russell, Wolfgang Oster, and Rolf Sauer

Purpose: Radiotherapy for head and neck cancer causes acute and chronic xerostomia and acute mucositis. Amifositine and its active metabolite, WR-1065, accumulate with high concentrations in the salivary glands. This randomized trial evaluated whether amifostine could ameliorate these side effects without compromising the effectiveness of radiotherapy in these patients.

Patients and Methods: Patients with previously untreated head and neck squamous cell carcinoma were eligible. Primary end points included the incidence of grade ≥ 2 acute xerostomia, grade ≥ 3 acute mucositis, and grade ≥ 2 late xerostomia and were based on the worst toxicity reported. Amifostine was administered (200 mg/m² intravenous) daily 15 to 30 minutes before irradiation. Radiotherapy was given once daily (1.8 to 2.0 Gy) to doses of 50 to 70 Gy. Whole saliva production was quantitated preradiotherapy and regularly during follow-up. Patients evaluated their symptoms through a questionnaire during and after treatment. Local-regional control was the primary antitumor efficacy end point.

Results: Nausea, vomiting, hypotension, and allergic reactions were the most common side effects. Fifty-three percent of the patients receiving amifostine had at least one episode of nausea and/or vomiting, but it only occurred with 233 (5%) of 4,314 doses. Amifostine reduced grade ≥ 2 acute xerostomia from 78% to 51% ($P < .0001$) and chronic xerostomia grade ≥ 2 from 57% to 34% ($P = .002$). Median saliva production was greater with amifostine (0.26 g v 0.10 g, $P = .04$). Amifostine did not reduce mucositis. With and without amifostine, 2-year local-regional control, disease-free survival, and overall survival were 58% versus 63%, 53% versus 57%, and 71% versus 66%, respectively.

Conclusion: Amifostine reduced acute and chronic xerostomia. Antitumor treatment efficacy was preserved.

J Clin Oncol 18:3339-3345. *© 2000 by American Society of Clinical Oncology.*

Palifermin
(Recombinant Human Keratinocyte Growth Factor)

is an N-terminal, truncated version of endogenous keratinocyte growth factor with biologic activity similar to that of the native protein, but with increased stability.

FDA approval: prophylaxis of mucositis in patients receiving etoposide, cyclophosphamide and total body irradiation of 12 Gy prior to hematopoietic stem cell transplantation for hematological malignancies.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Palifermin for Oral Mucositis after Intensive Therapy for Hematologic Cancers

Ricardo Spielberger, M.D., Patrick Stiff, M.D., William Bensinger, M.D., Teresa Gentile, M.D., Ph.D., Daniel Weisdorf, M.D., Tarun Kewalramani, M.D., Thomas Shea, M.D., Saul Yanovich, M.D., Keith Hansen, M.D., Stephen Noga, M.D., Ph.D., John McCarty, M.D., C. Frederick LeMaistre, M.D., Eric C. Sung, D.D.S., Bruce R. Blazar, M.D., Dieter Elhardt, Ph.D., Mon-Gy Chen, M.S., and Christos Emmanouilides, M.D.

N Engl J Med 2004;351:2590-8

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Palifermin for Oral Mucositis after Intensive Therapy for Hematologic Cancers

Materials and Methods: 212 patients with hematologic cancers (fractionated total-body irradiation plus high-dose chemotherapy) and autologous hematopoietic stem-cell transplantation
106 patients received palifermin (60 µg per kilogram of body weight per day) and 106 received a placebo intravenously for three consecutive days immediately before the initiation of conditioning therapy.

Results: Palifermin administration resulted in:

1. Lower incidence of oral mucositis : 63% vs. 98% (P<0.001).
2. Reduction in the incidence of grade 4 oral mucositis : 20 % vs. 62 %(P<0.001)
3. Reduction in the use of opioid analgesics: 212 mg of morphine equivalents vs. 535 mg of morphine equivalents (P<0.001)
4. Lower incidence of use of total parenteral nutrition : 31 % vs. 55 % (P<0.001).

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Palifermin Decreases Severe Oral Mucositis of Patients Undergoing Postoperative Radiochemotherapy for Head and Neck Cancer: A Randomized, Placebo-Controlled Trial

Michael Henke, Marc Alfonsi, Paolo Foa, Jordi Giralt, Etienne Bardet, Laura Cerezo, Michaela Salzwimmer, Richard Lizambri, Lara Emmerson, Mon-Gy Chen, and Dietmar Berger

Materials and Methods:
186 patients with stages II to IVB carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx. Patients received 60/66 Gy after complete (R0) or incomplete resection (R1), respectively, at 2 Gy/fraction and five fractions per week. Cisplatin 100 mg/m2 was administered on days 1 and 22 (and on day 43 with R1). Patients were randomly assigned to receive weekly palifermin 120 µg/kg or placebo from 3 days before and continuing throughout radiochemotherapy

Results: Severe OM was seen in 51% patients administered palifermin and 67% administered placebo (P . 027). Palifermin decreased the duration (median, 4.5 v 22.0 days) and prolonged the time to develop (median, 45 v 32 days) severe mucositis.
After median follow-up of 32.8 months, 23 deaths (25%) had occurred in both treatment arms, and disease had recurred in 25 (27%) and 22 (24%) of palifermin- and placebo-treated patients, respectively.
The most common study drug– related adverse events were rash, flushing, and dysgeusia.

RGTA: ReGeneraTing Agent

Heparan Sulphate mimetic biopolymers

Mimic protecting properties
of heparan sulfates
toward HBGF
(Heparan Binding Growth Factors)

Modify inflammation kinetics

Inhibit activities of plasmin, cathepsin G, neutrophil elastase

(Escartin, EMBO J 2003)

Protect and enhance bioavailability of FGF-2 and TGF-β1

Stimulation of tissue rapair
correction of collagen abnormalities

(Tardieu, J Cell Physiol 1992)
(Desgranges, FASEB J 1999)

RGTA: ReGeneraTing Agent

Heparan Sulphate mimetic biopolymers

- Benefits in tissue repair in several preclinical models
  - **Bone** (Blanquaert, 1995)
  - **Skin** (Meddahi, 1996)
  - **Muscle** (Desgranges, 1999)
  - **Digestive tissues** (Escartin, 2003)
  - **5 FU induced mucositis** (Morvan, 2004)

Int. J. Radiation Oncology Biol. Phys., Vol. 74, No. 4, pp. 1242–1250, 2009
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0360-3016/09/$–see front matter

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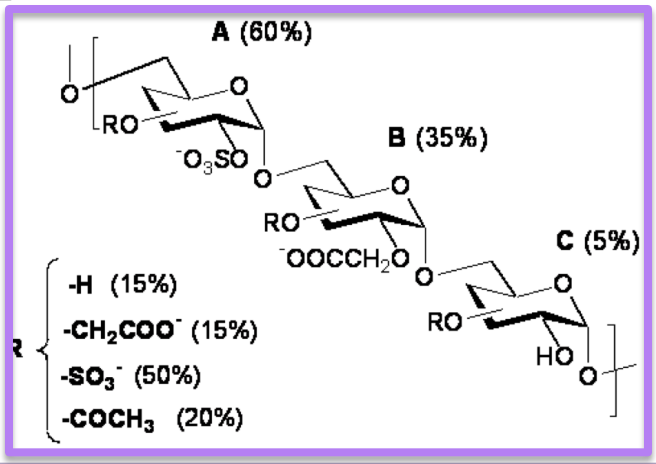
doi:10.1016/j.ijrobp.2009.03.006

BIOLOGY CONTRIBUTION

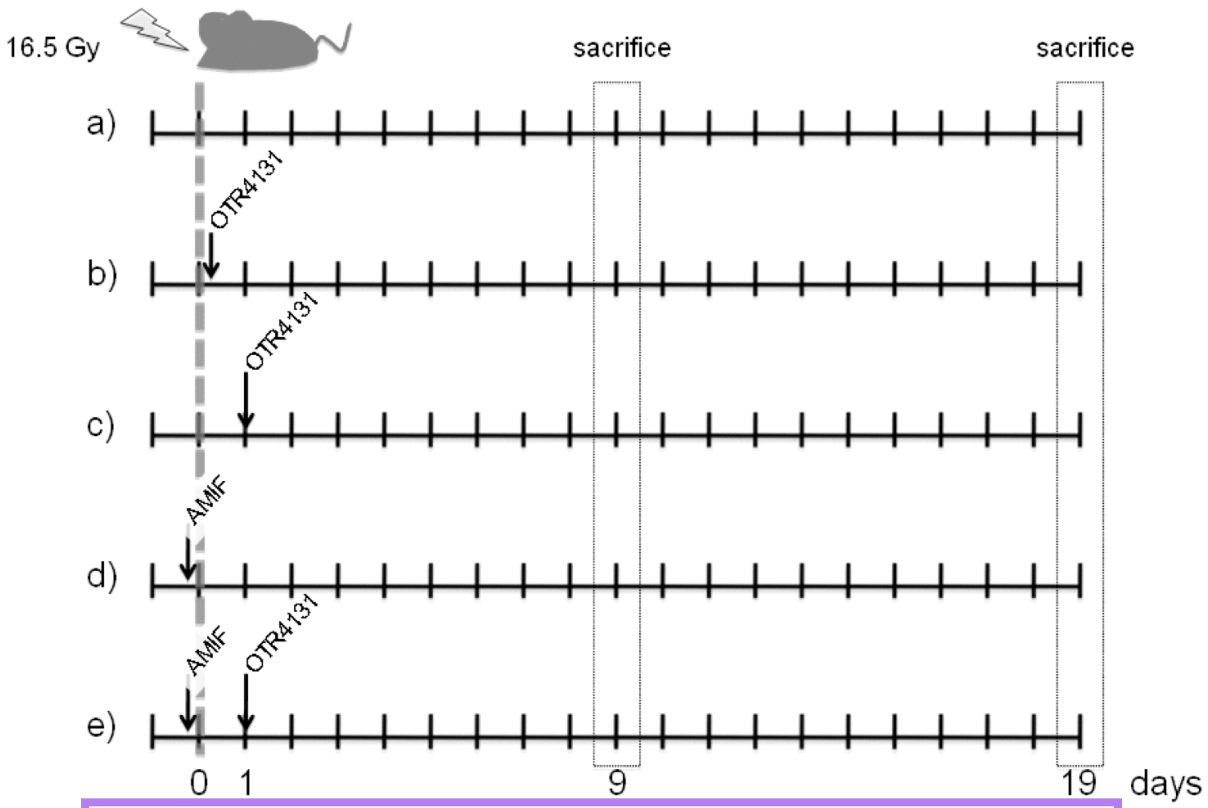
DIFFERENTIAL EFFECT TRIGGERED BY A HEPARAN MIMETIC OF THE RGTA FAMILY PREVENTING ORAL MUCOSITIS WITHOUT TUMOR PROTECTION

Monica Mangoni, M.D.,*† Xiaoli Yue, Ph.D.,‡ Christophe Morin, Ph.D.,‡ Dominique Violot, M.Sc.,* Valerie Frascogna, M.Sc.,* Yungan Tao, M.D.,* Paule Opolon, M.D., Ph.D.,§§ Marine Castaing, Ph.D.,‡‡ Anne Auperin, M.D., Ph.D.,‡‡ Giampaolo Biti, M.D.,† Denis Barritault, Ph.D.,§ Marie-Catherine Vozenin-Brotons, Ph.D.,* Eric Deutsch, M.D., Ph.D.,* and Jean Bourhis, M.D., Ph.D.*



RGTA: ReGeneRating Agents

Radiation-induced mucositis



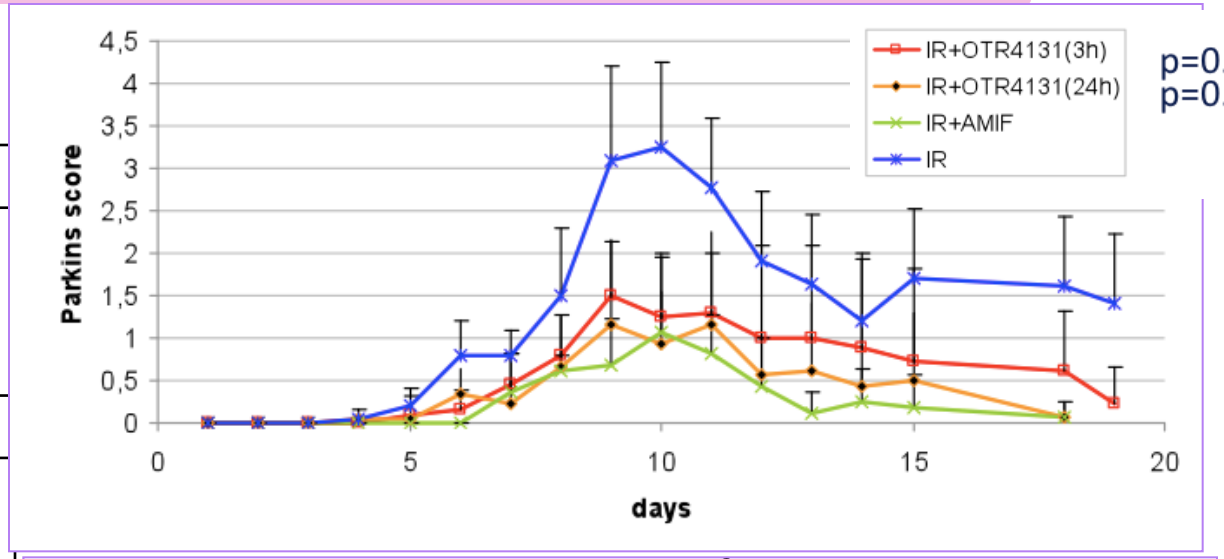
- RGTA (OTR 4131) 1mg/kg 3h or 24h after IR
- Amifostine 200mg/kg 10 min before IR

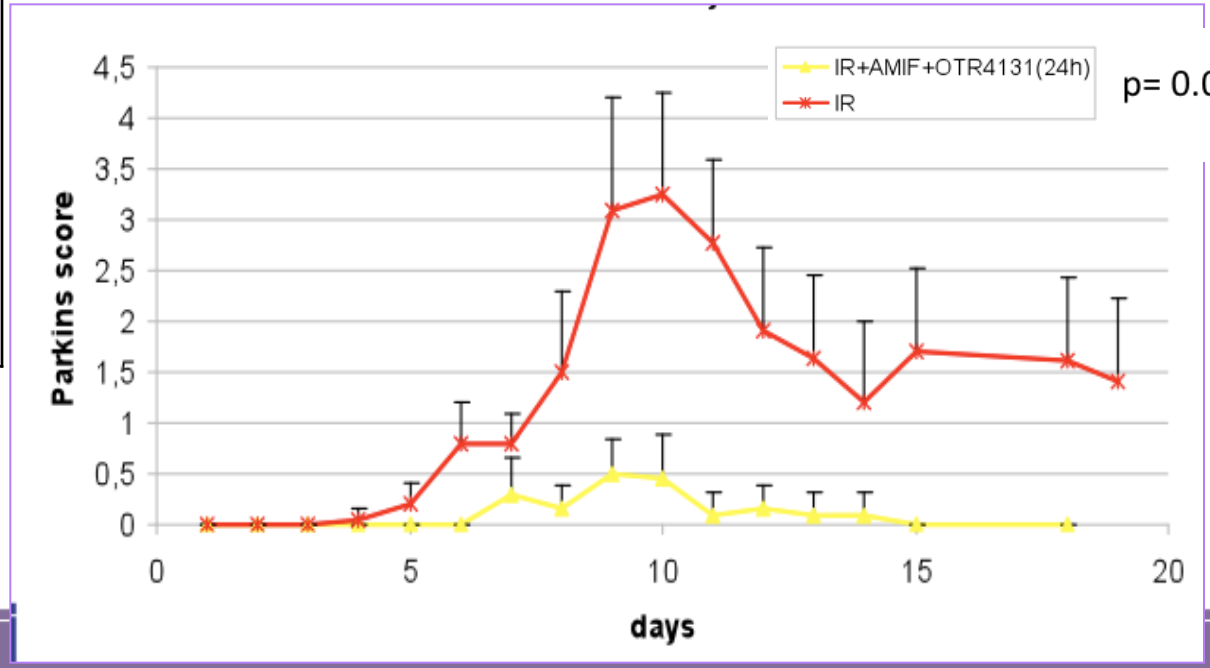
RGTA-OTR4131 prevents acute radiation-induced mucositis

Parkins score

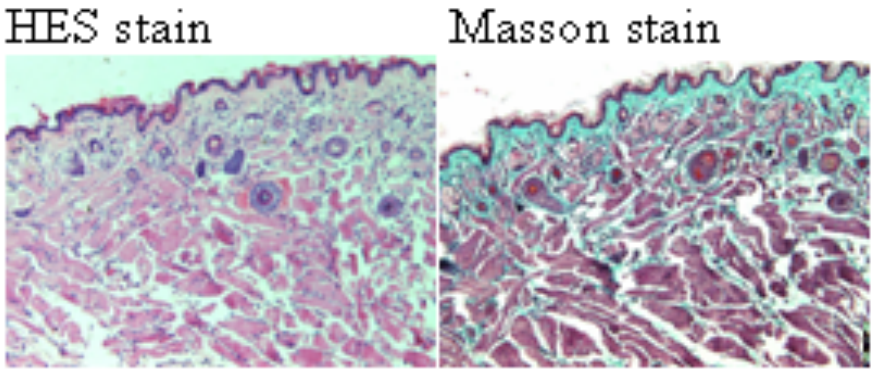
Oedema score	
0,5	**50-50 doubtful if any swelling**
1	**Slight but definite swelling**
2	**Severe swelling**
Erythema scores	
0,5	**50-50 doubtful if abnormally pink**
1	**Slight but definite reddening**
2	**Severe reddening**
3	**Focal desquamation**
4	**Exudate or crusting involving about ½ lip area**
5	**Exudate or crusting involving more than ½ lip area**

(Parkins, Radiother Oncol 1983)

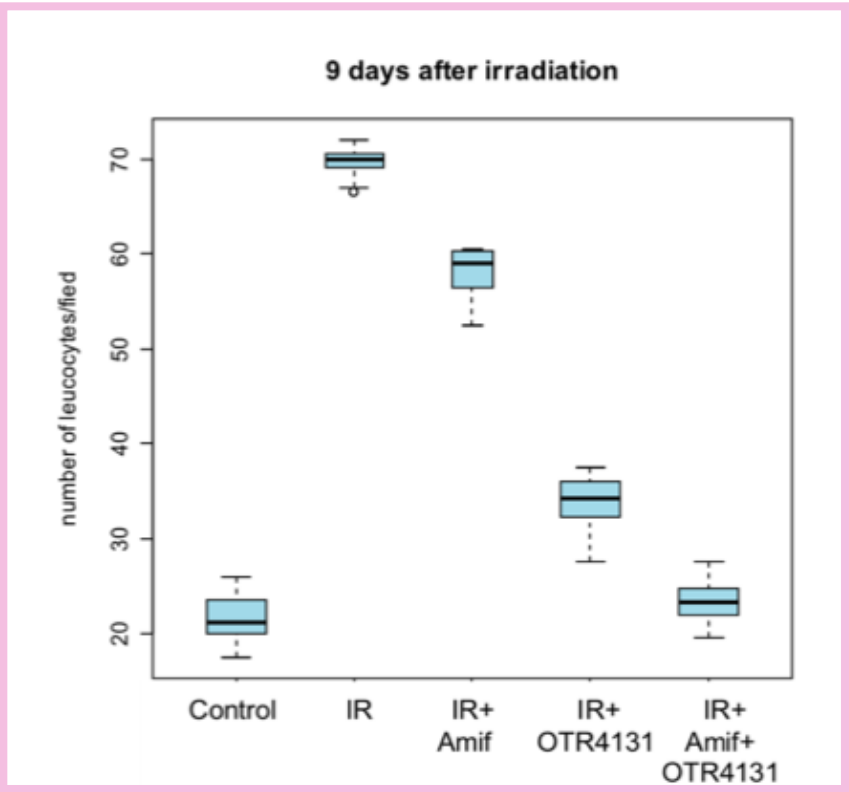


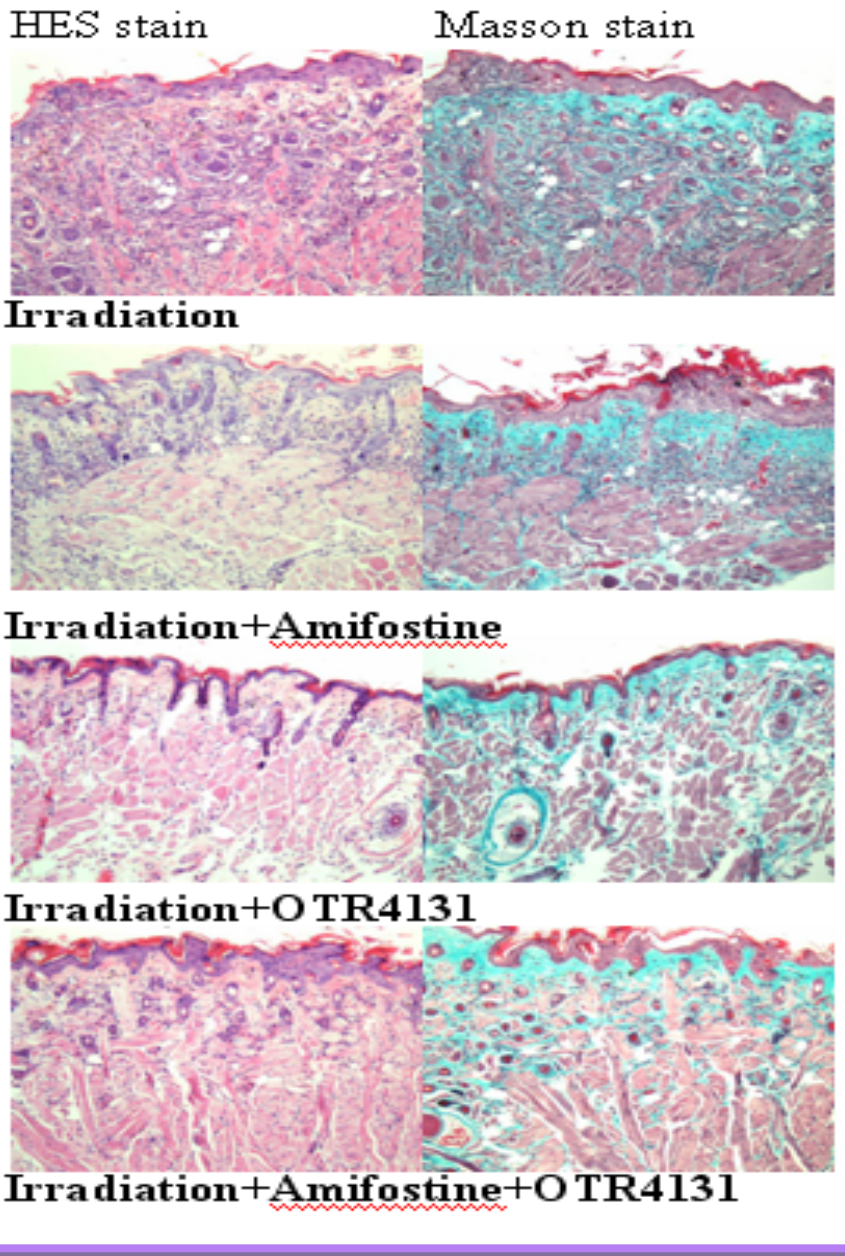


9 days after irradiation

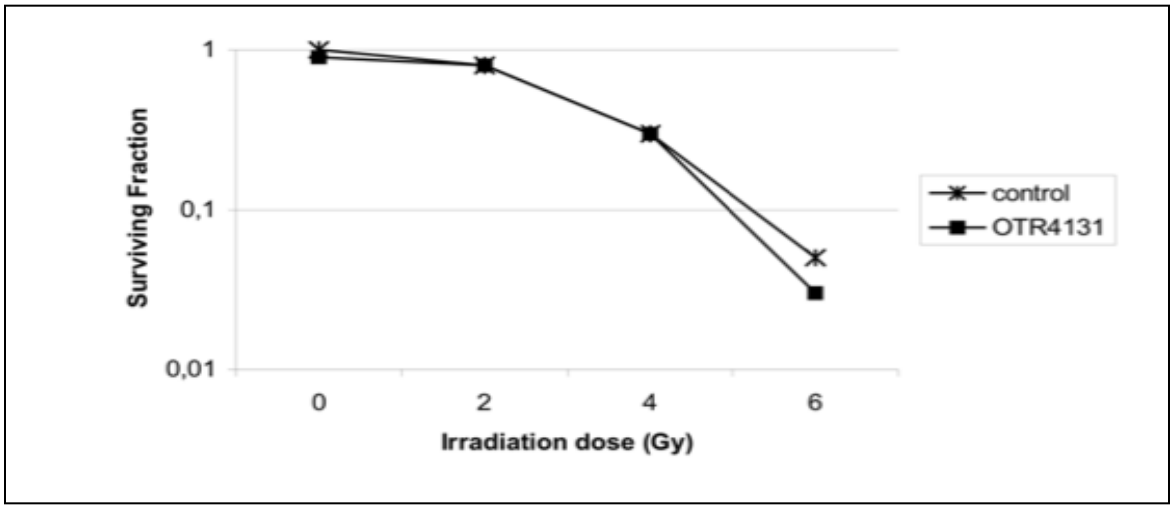


Control

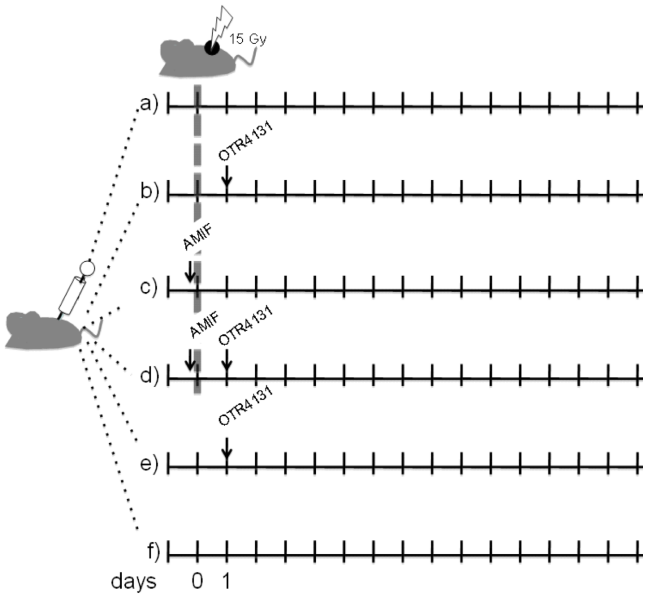


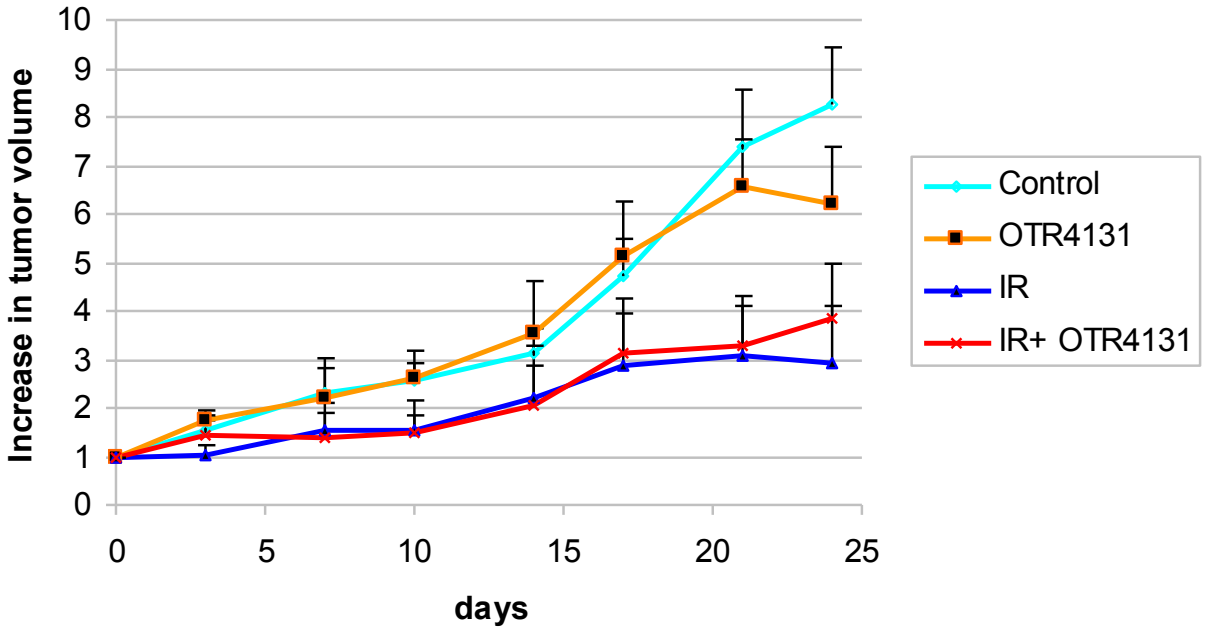


Effect of RGTA-OTR4131 on HEP-2 tumor



RGTA 10µg/ml
HEP-2 cells





Effect of RGTA in radiation induced mucositis in mice

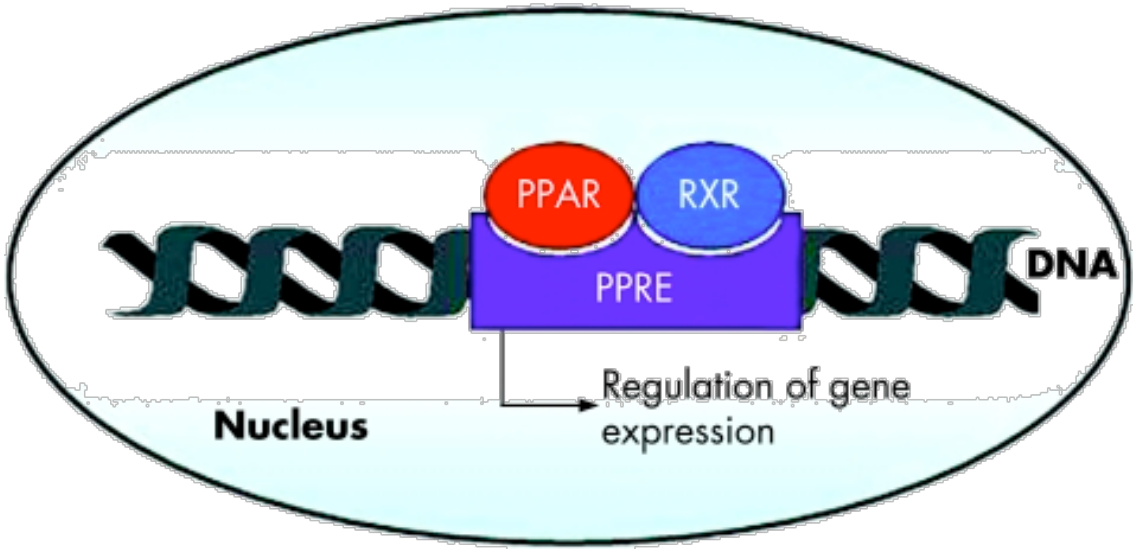
- ✓ RGTA-OTR4131 exibits marked protective activity against radiation induced mucositis in mice
- ✓ Combination RGTA-OTR4131+ amifostine completely abrogated radiation induced mucositis
- ✓ No suggestions of tumor protection

PPARγ

peroxisome proliferator-activated receptor γ

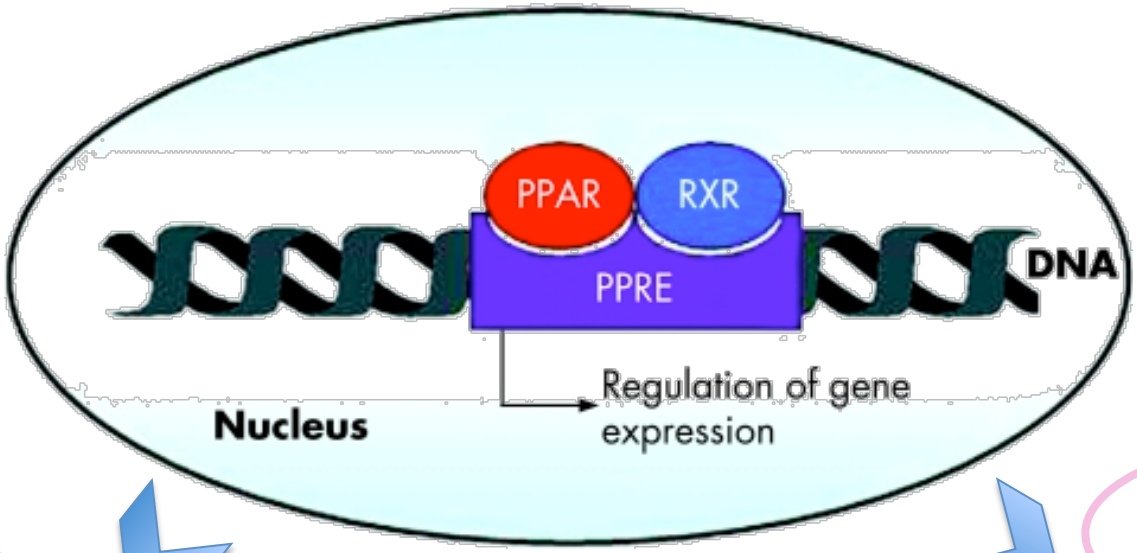
ligands

Il recettore gamma per gli attivatori dei perossisomi (PPAR-γ) è un membro della superfamiglia dei recettori nucleari steroidei in grado di regolare la trascrizione di numerosi geni mediante la formazione di eterodimeri con il recettore per l'acido 9-cis retinoico (RXR).



Natural ligands of PPARγ:
- prostaglandins
- leukotrienes

Synthetic ligands of PPARγ:
-Thiazolidinediones (rosiglitazone, pioglitazone)
-5 aminosalicylic acid (5ASA)



Adipogenesis

Lipid synthesis

Carbohydrate metabolism

Fibrogenesi

Infiammazione

Crescita/apoptosi e differenziamento

ELSEVIER

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0360-3016/07/$–see front matter

doi:10.1016/j.ijrobp.2006.09.036

RAPID COMMUNICATION

ADMINISTRATION OF THE PEROXISOMAL PROLIFERATOR-ACTIVATED RECEPTOR γ AGONIST PIOGLITAZONE DURING FRACTIONATED BRAIN IRRADIATION PREVENTS RADIATION-INDUCED COGNITIVE IMPAIRMENT

WEILING ZHAO, PH.D.,* VALERIE PAYNE, B.S.,* ELLEN TOMMASI, B.S.,† DEBRA I. DIZ, PH.D.,† FANG-CHI HSU, PH.D.,‡ AND MIKE E. ROBBINS, PH.D.*

*Department of Radiation Oncology, Brain Tumor Center of Excellence; †Hypertension and Vascular Disease Center; and ‡Department of Biostatistical Sciences, Wake Forest University School of Medicine, Winston-Salem, NC

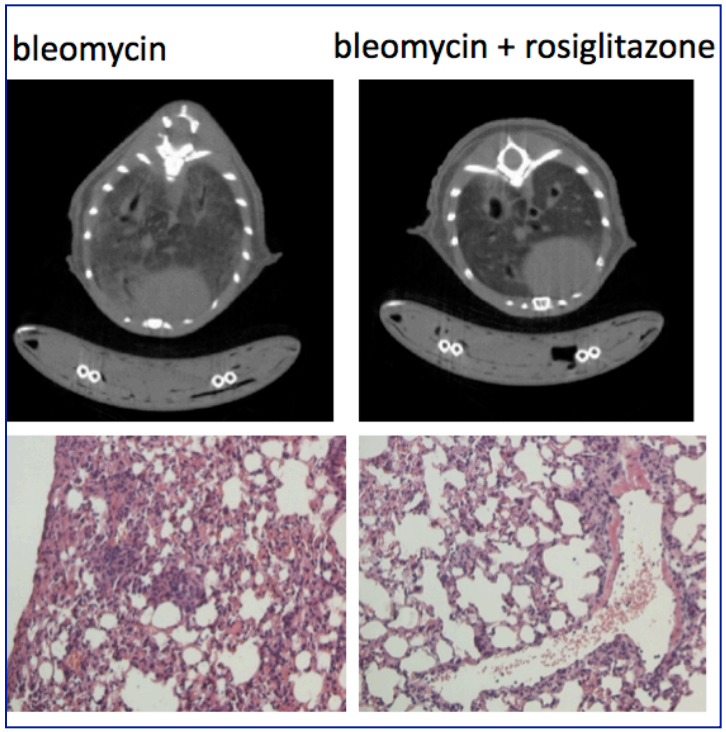
Materials and Methods: Young adult male F344 rats received one of the following:

1. fractionated whole brain irradiation (WBI)
2. sham-irradiation and normal diet;
3. WBI plus Pio (120 ppm) before, during, and for 4 or 54 weeks postirradiation
4. sham-irradiation plus Pio
5. WBI plus Pio starting 24h after completion of WBI.

RESULTS:

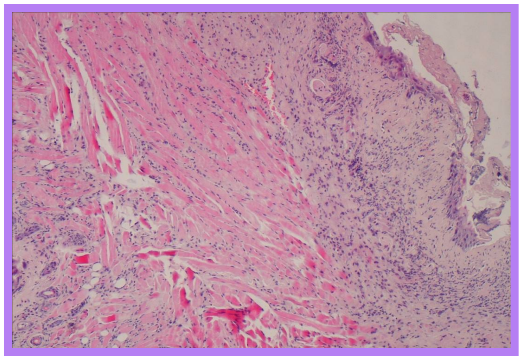
Administration of Pio before, during, and for 4 or 54 weeks after WBI prevented the radiation-induced cognitive impairment.

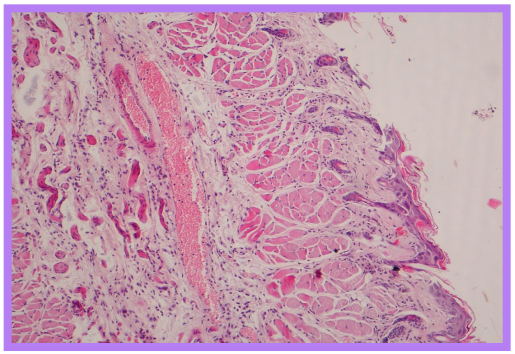
Rosiglitazone(RGZ)



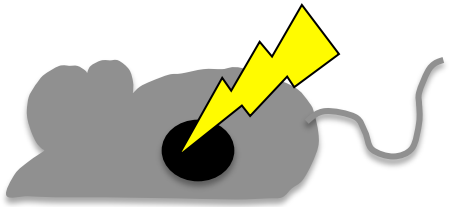
pulmonary fibrosis

- ✓Mangoni M, et al. EJC, 2011; S1: 217-8
- ✓Mangoni M et al, ESTRO 31
- ✓Sottili M et al, AIRB





acute radiation-induced mucositis

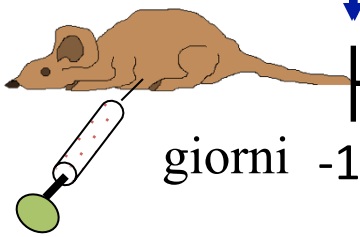


Hep-2 tumour xenograft

Fibrosi polmonare

C57black/6J
femmine
7 settimane

Rosiglitazone 5mg/Kg ogni giorno (gavage)

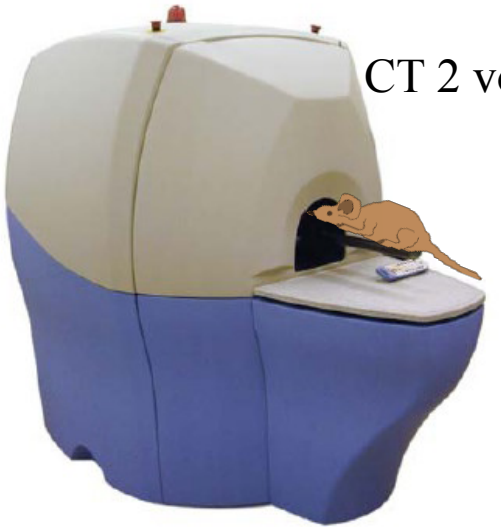


giorni -1 0 2 4 6 8 10 15 20 25 31

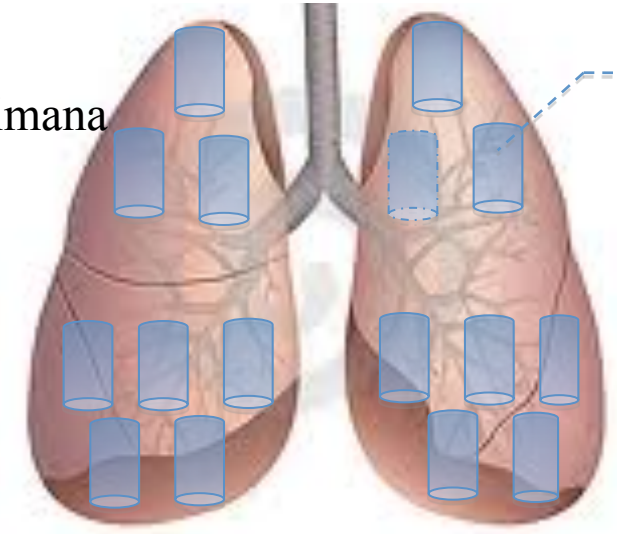
sacrificio

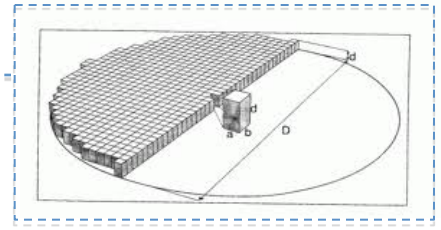
Bleomicina 40mg/Kg ip
ogni
2 giorni
(5 somministrazioni totali)

Gruppo 1 = controllo
Gruppo 2 = Bleomicina
Gruppo 3 = Bleomicina+RGZ



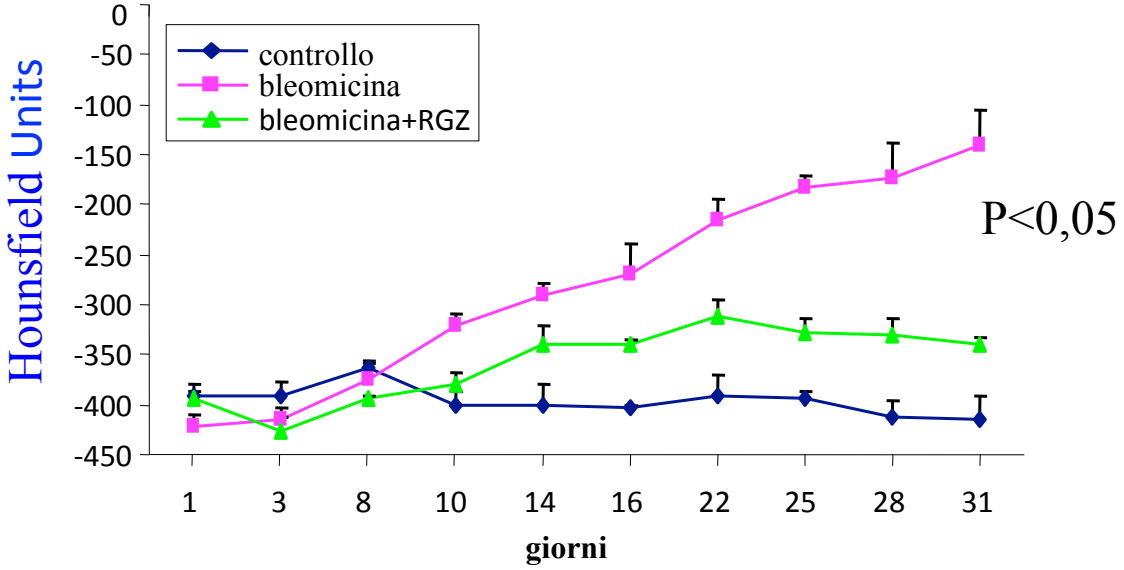
CT 2 volte a settimana



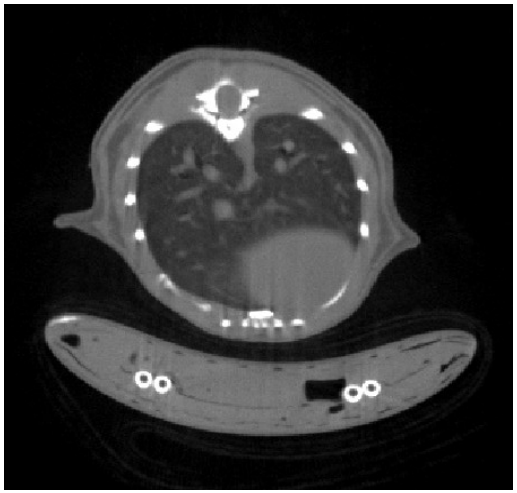
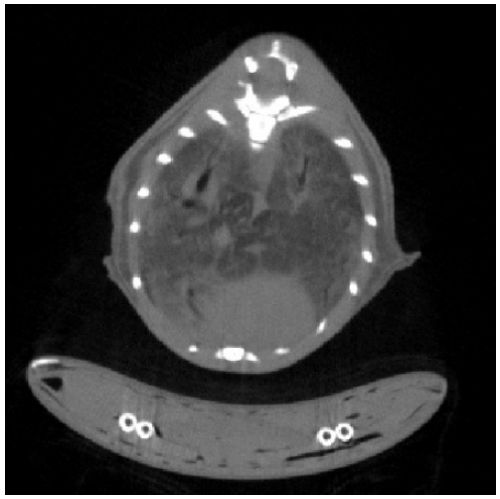
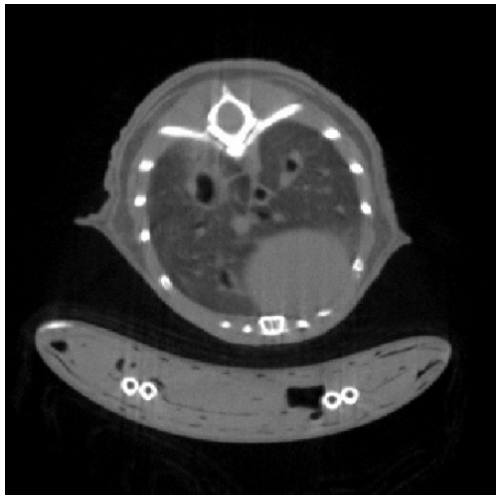
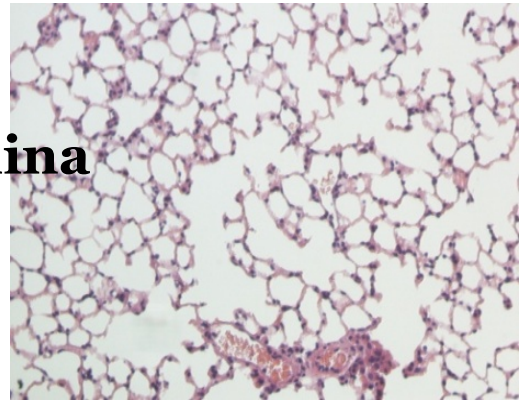
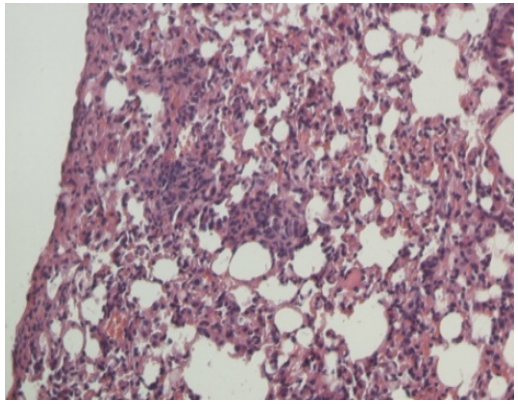
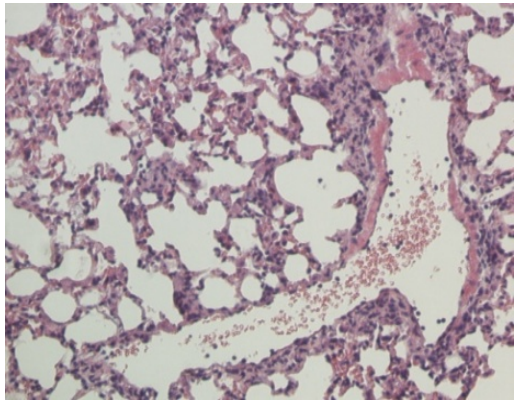


determinazione di corrispondenti volumi all' apice e alla base dei polmoni in Hounsfield Units

Substances	HU
Bone	+ 400
Water	0
Fat	- 120
Air	- 1000



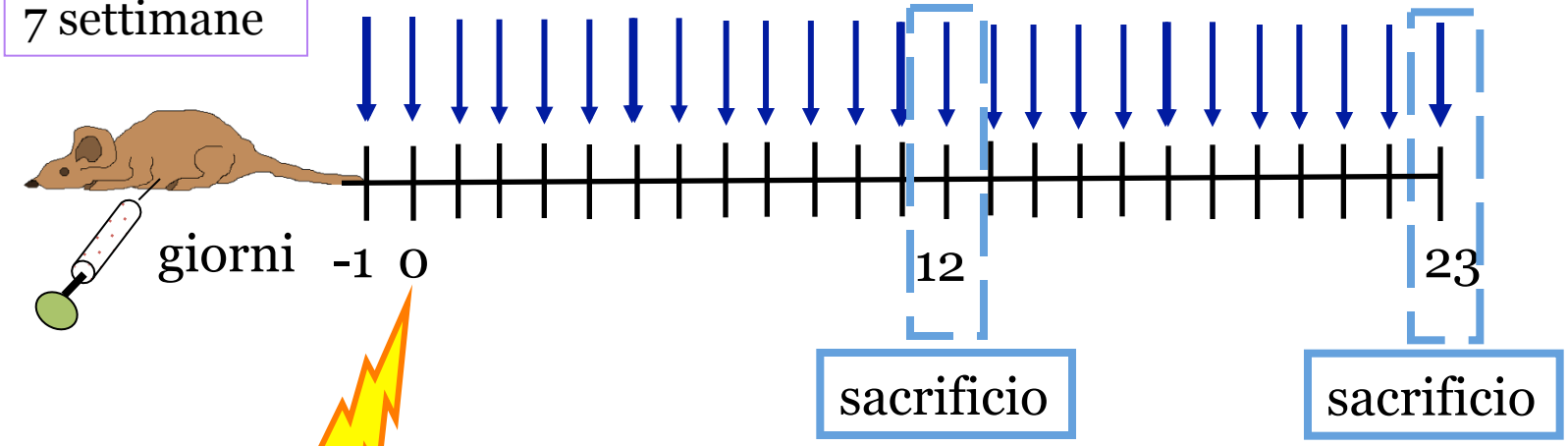
giorno 31

	controllo	bleomicina	bleomicina + rosiglitazone
CT			
ematossilina eosina			

Mucosite orale

C57black/6J
femmine
7 settimane

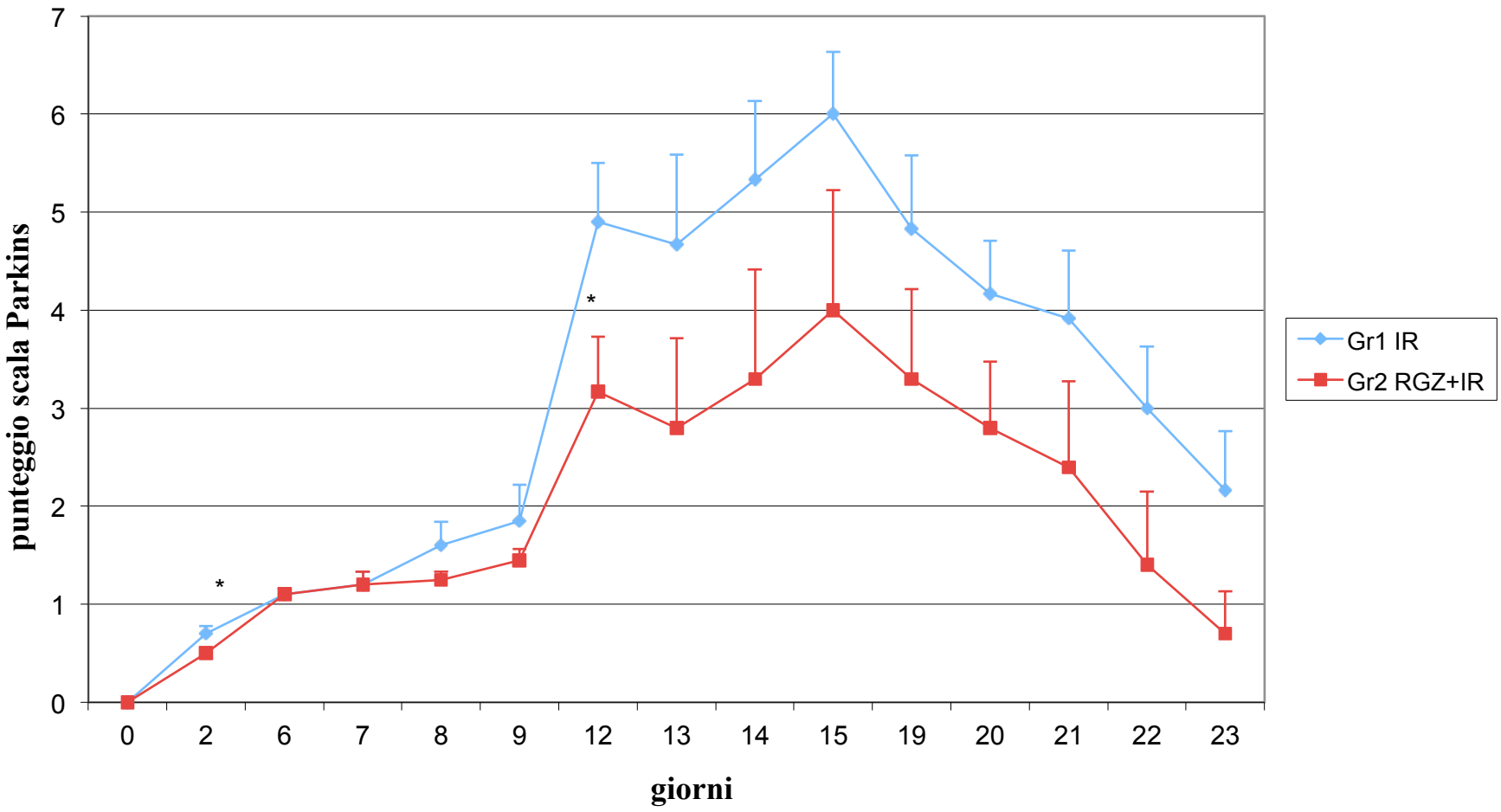
Rosiglitazone 5mg/Kg ip ogni giorno



Valutazione giornaliera dei sintomi
con scala Parkins

Gruppo 1 = controllo
Gruppo 2 = IR
Gruppo 3 = IR+RGZ

*p<0.05 vs. IR


Mucosite
punteggio scala Parkins
0
1
2
3
4
5
6
7
0
2
6
7
8
9
12
13
14
15
19
20
21
22
23
giorni
*
*
Gr1 IR
Gr2 RGZ+IR

Research in the last 10 years

Mentha Piperita

Dimethyl Sulfoxide

Recombinant KGF

caffeine

5-aminosalicylic acid

R-spondin1

Fullerene Nanoparticle DF-1

protein kinase Cε

FGF

Sesamol

Histamine

Curcumin

Aloe

TLR 2/6 Agonist

Interleukin-1α

Gamma-tocotrienol

inhibitor of cyclooxygenase 2

ginseng

Anti TGFβ antibody 1D11

WR1065

Flaxseed

Methylproamine

Melatonin

Sphingosine-1-Phosphate

Disulfiram

Lidocaine

α-phospho-tyrosine

PRAVASTATIN

CpG-oligodeoxynucleotides

l-Arginine

GLUCAGON-LIKE PEPTIDE-2

Lipopeptide Agonists of TLR2

Ascorbic Acid

Dietary Antioxidants
L-selenomethionine, vitamin C, vitamin E, succinate, α-lipoic acid and N-acetyl cysteine

Mn SOD gene therapy

vanillin

Inhibition of the tumor necrosis factor-alpha

Pyrroloquinoline Quinone

pentoxifylline

inhibitors of CDK4/6

Antioxidant activity

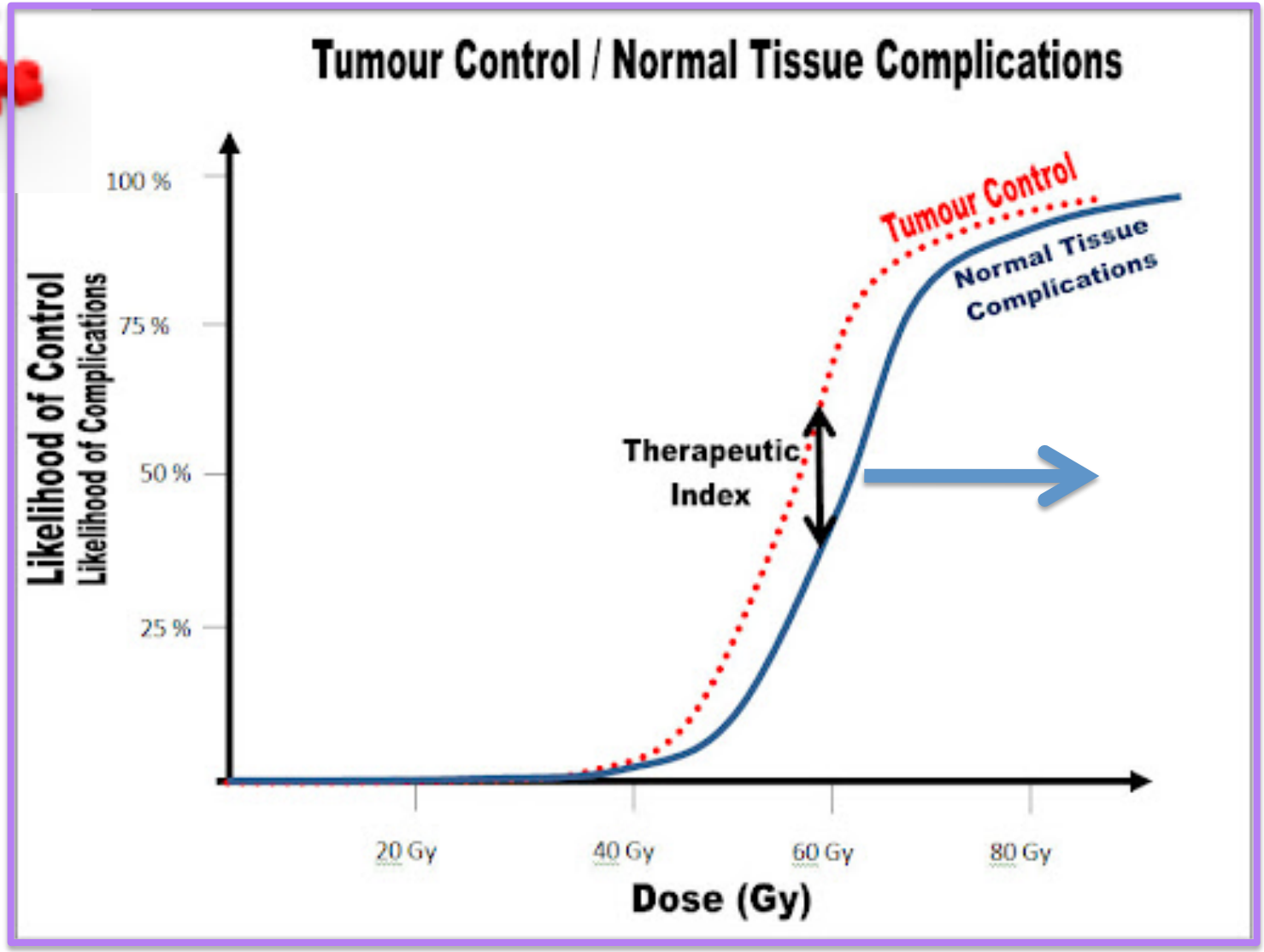
Inhibition of apoptosis

Cytokine release

Resistance at DNA damage

DNA DSB repair

membrane stabilization



Greenberger JS *In Vivo. 2009 ; 23: 323–336.*