

Radiation-induced mucositis: protective activity of a dextrane derivative.

M Mangoni

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Oral mucositis

The most common and clinically significant toxicity of HNC treatment → **2/3 of patients**

ERYTHEMA AND ULCERATIONS



- ✓ impaired nutrition, risk of infection, rapid deterioration of the quality of life
- ✓ delayed treatment and dose reduction

No approved treatment for OM

CURRENT THERAPIES

- Bland rinses: saline or sodium bicarbonate
- Topical anesthetics: lidocaine, benzocaine
- Mucosal coating agents
- Analgesics
- Steroids

No approved treatment for OM

AGENTS IN CLINICAL TRIALS

AGENT	CHARACTERISTICS
Amifostine	<ul style="list-style-type: none">• Free-radical scavenger• Prevents the upregulation of inflammatory pathways
Glucagon-like peptide-2 (GLP-2)	<ul style="list-style-type: none">• Epithelium-specific growth factor• May reduce intestinal mucositis
Glutamine supplementation (AES-14)*	<ul style="list-style-type: none">• Amino acid• Mitigates treatment-induced glutamine deficiency• Replenishes glutamine• Exerts mucoprotective effects
Palifermin†	<ul style="list-style-type: none">• Keratinocyte growth factor• Increases cellular proliferation• Mediates epithelial cell repair
Tocopherol	<ul style="list-style-type: none">• Antioxidant• Potent form of vitamin E
Velafermin	<ul style="list-style-type: none">• Growth factor• Reduces mucosal barrier injury by increasing mucosal thickness• Stimulates epithelial cell division• Decreases inflammation by reducing the production of pro-inflammatory cytokines

Posner and Haddad, Novel Agents for the Treatment of Mucositis
J Supp Oncol 2007; 5 (9 Suppl 4): 33-9

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Approved by the FDA in 2004 to decrease incidence and duration of severe OM in pt undergoing high-dose CT w/wo RT followed by bone marrow transplant for hematologic cancers

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An Engineered Biopolymer Prevents Mucositis Induced by 5-Fluorouracil in Hamsters

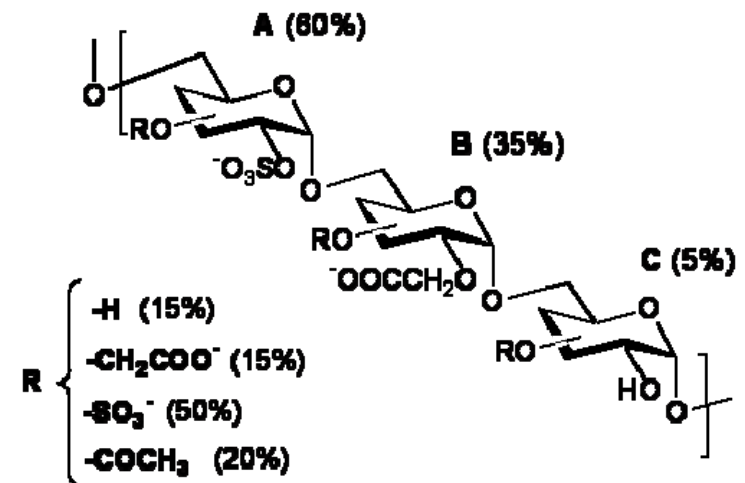
Frédéric O. Morvan,^{*} Brigitte Baroukh,^{*}
Dominique Ledoux,[†] Jean-Pierre Caruelle,[†]
Denis Barritault,[†] Gaston Godeau,^{*} and
Jean-Louis Saffar^{*}

RGTA improved 5FU induced mucositis in hamsters

RGTA® (ReGeneraTingAgents)

Family of dextran derivative biopolymers

- ✓ provided with heparan-mimetic properties
- ✓ devoid of heparin associated anticoagulant properties



RGTA® (ReGeneraTingAgents)

- ✓ protectors of the endogenous HBGF
- ✓ effective in stimulating tissue repair in several *in vivo* models:

bone: *Blanquaert F et al. Ann Endocrinol 1994*

Skin: *Meddahi A et al. Diabetes Metab 1996*

Muscle: *Desgranges P et al. FASEB J 1999*

GI tract: *Benoit J et al. Int J Colorectal Dis 1998*

Escartin Q et al. EMBO J 2003

5-FU induced mucositis: *Morvan OF et al. Am J Pathol 2004*

Purposes

- ✓ to evaluate RGTA-OTR4131 on radiation-induced mucositis in mice

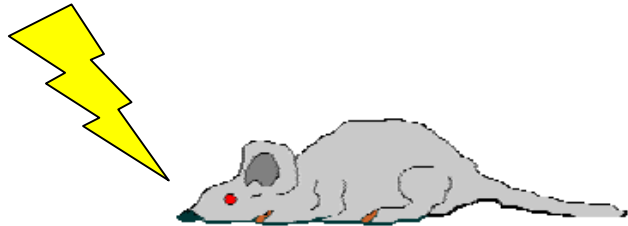
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 - 1.amifostine and
 - 2.amifostine+RGTA

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- ✓ to evaluate RGTA-OTR4131 on radiation-induced mucositis in mice
- ✓ to compare the effects of RGTA to
1.amifostine and 2.amifostine+RGTA
- ✓ to test potential interference of RGTA on tumor response to IR

Mucosal lip reaction to ionizing radiation



C57 black mice

Single dose of **16.5 Gy** selectively on oral region

Diet: liquid food (Renutryl®500)

Reagents: RGTA®-OTR4131

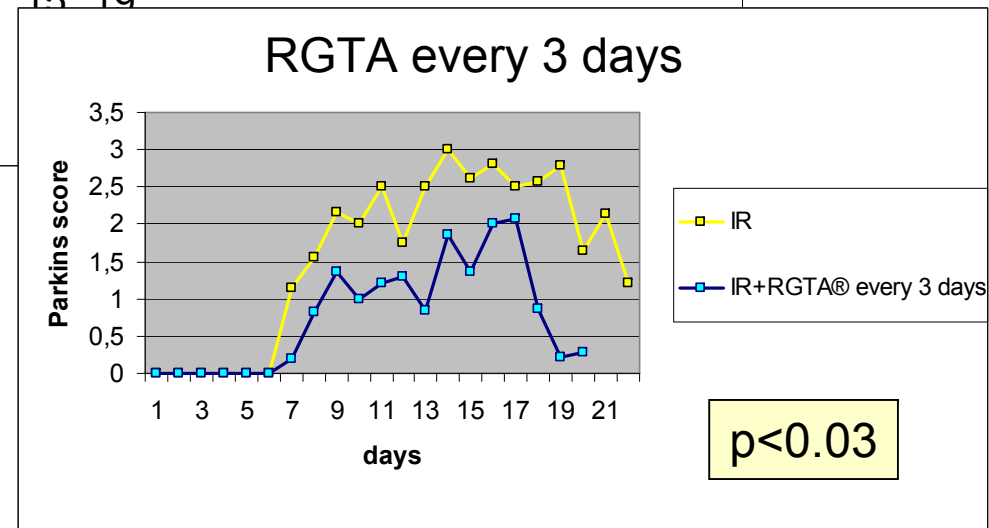
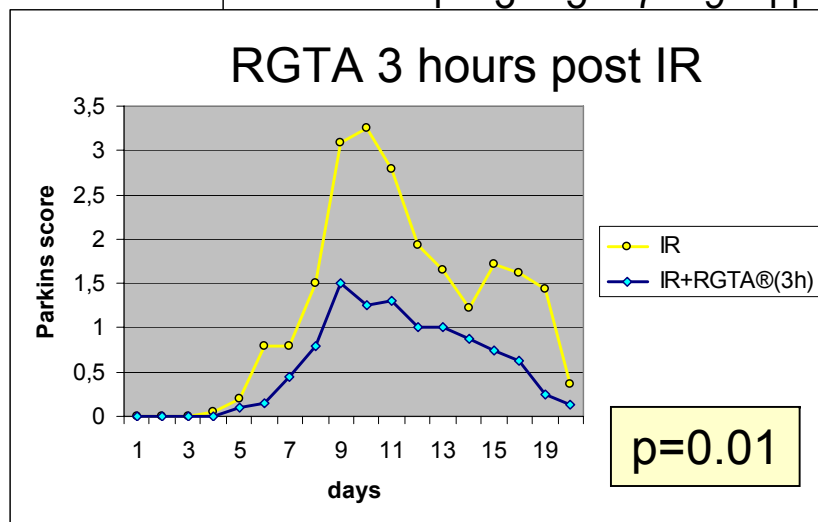
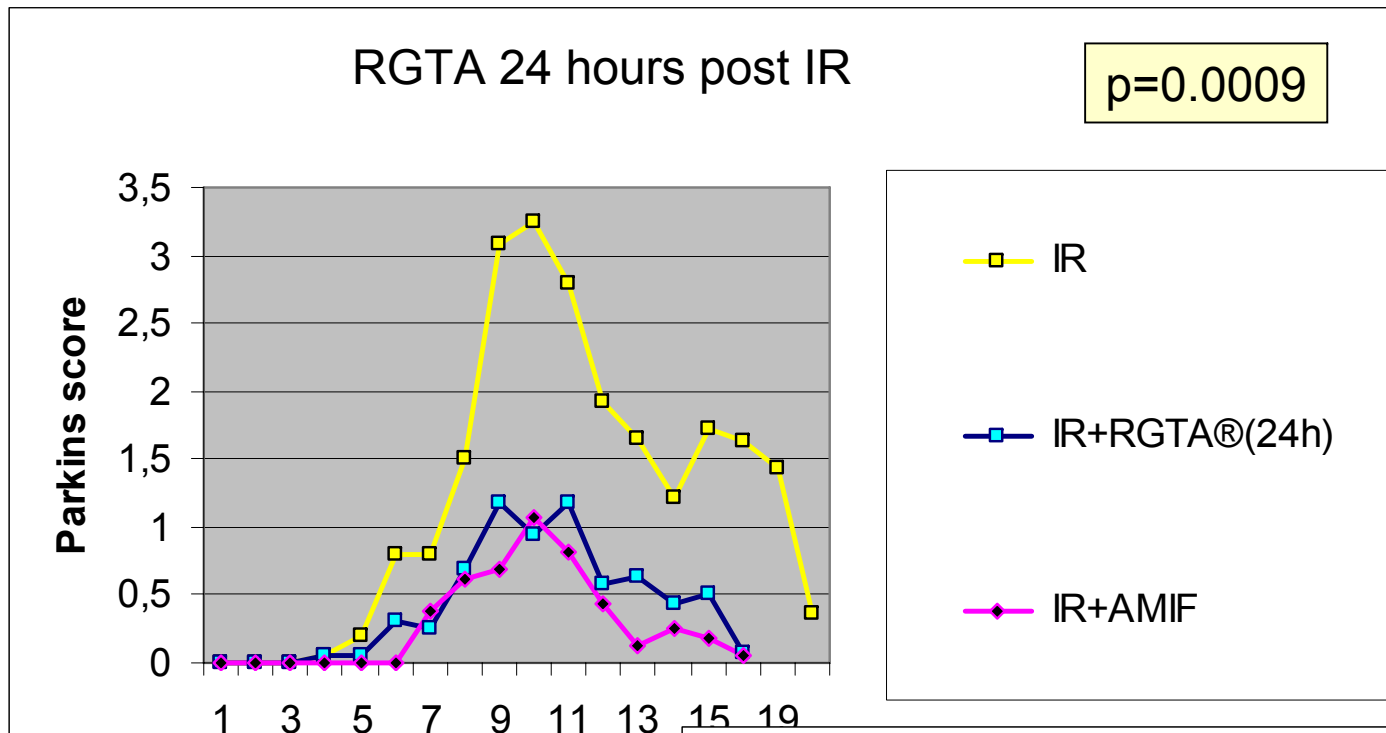
Amifostine (Ethyol®)

Parkins' scoring system *Parkins CS et al. Radiother Oncol 1983*

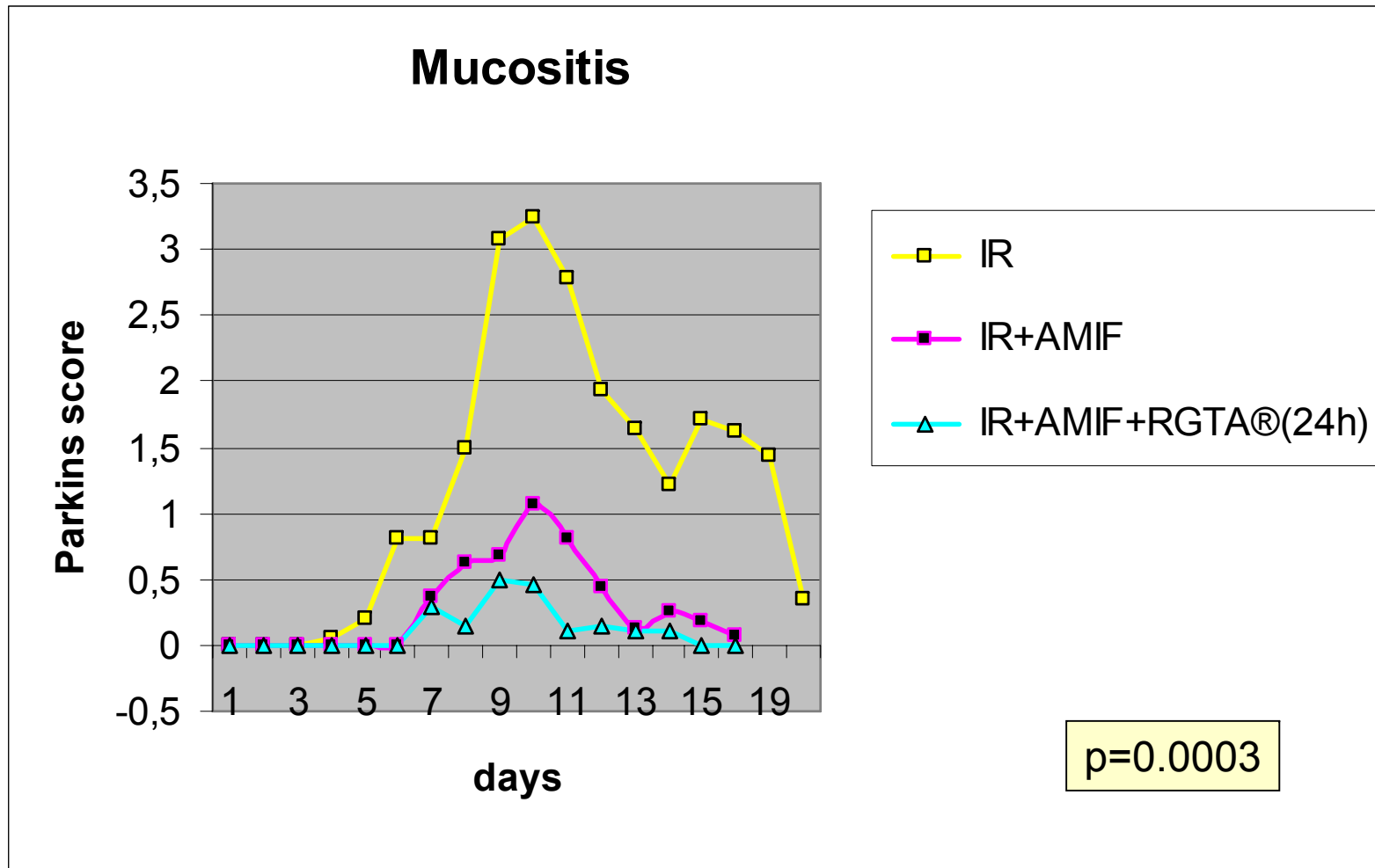
Oedema score	
0,5	50-50 doubtful if any swelling
1	Slight but definite swelling
2	Severe swelling

Erythema score	
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

Mucosal lip reaction to ionizing radiation

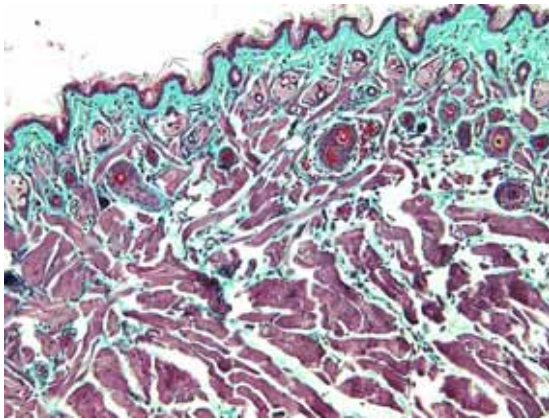


Amifostine-RGTA combination



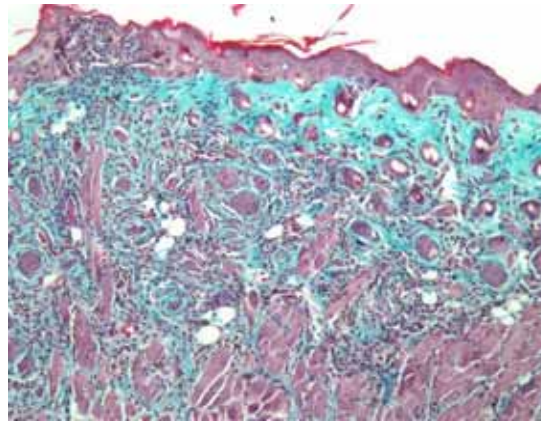
Histopathological analysis

9 days after IR

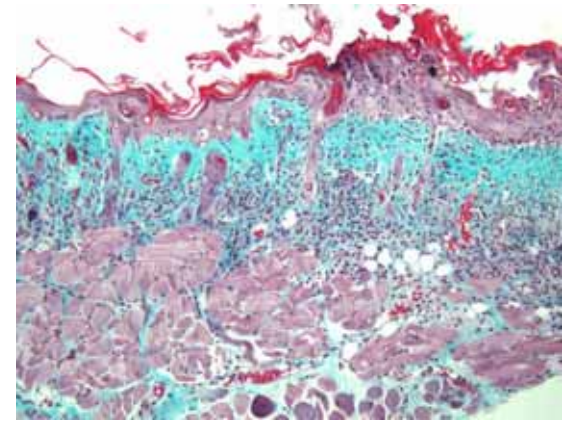


Normal tissue

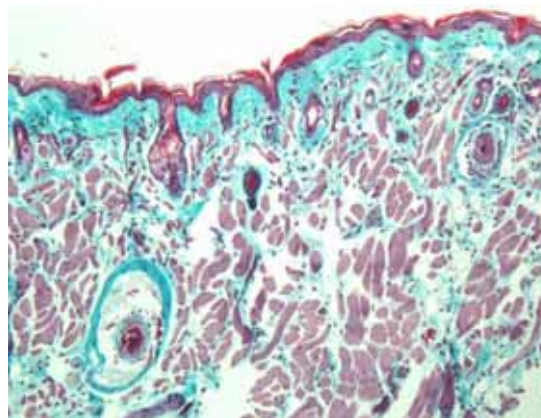
Masson staining



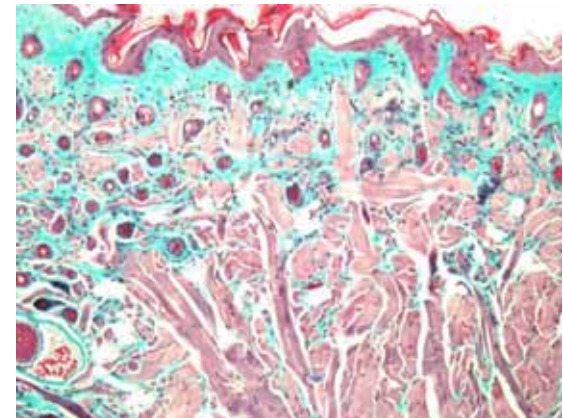
16.5Gy Irradiation



Irradiation+Amifostine



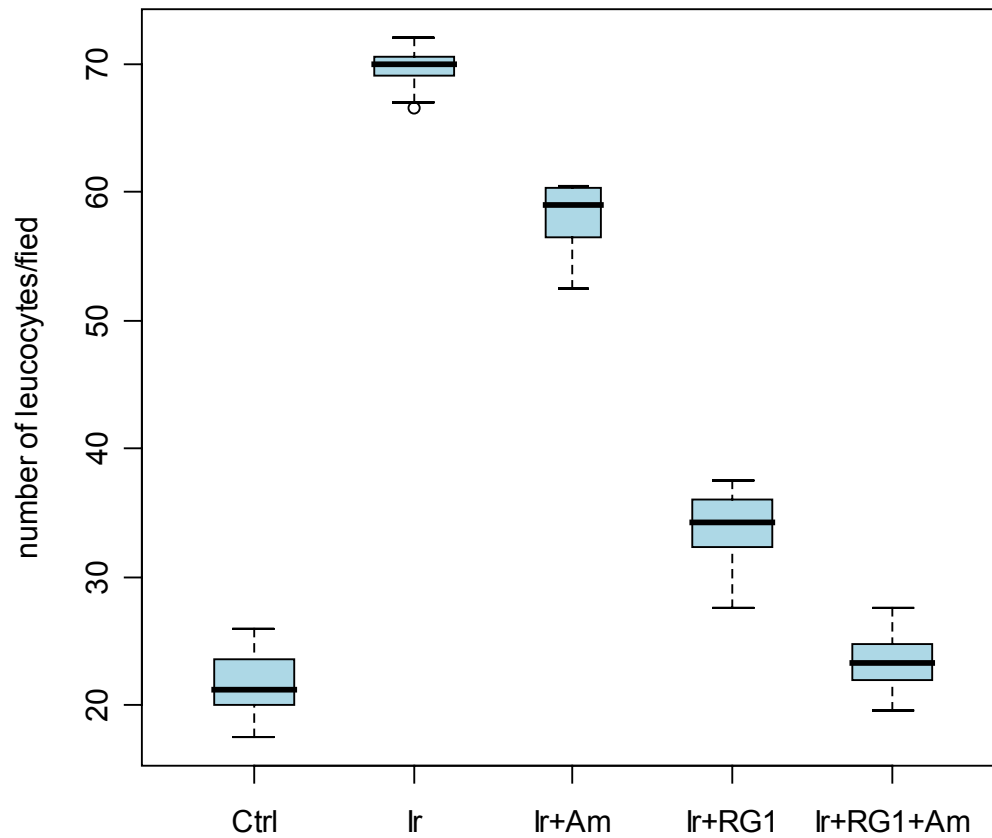
Irradiation+RGTA



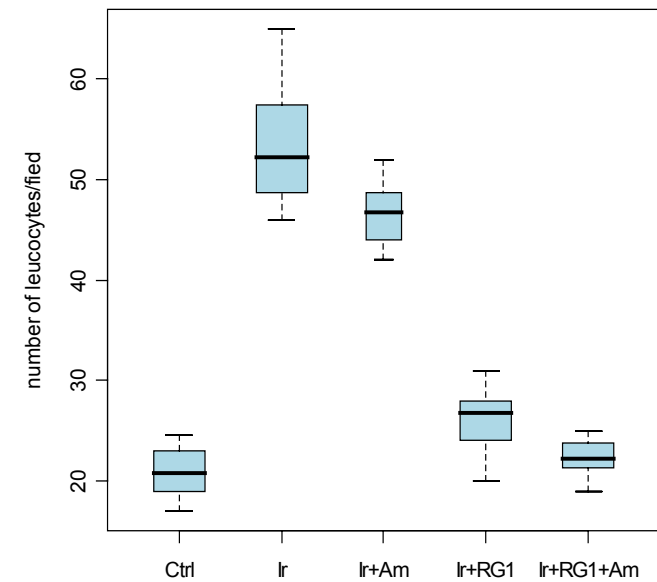
Irradiation+Amifostine+RGTA

Leukocyte infiltration

9 days after irradiation

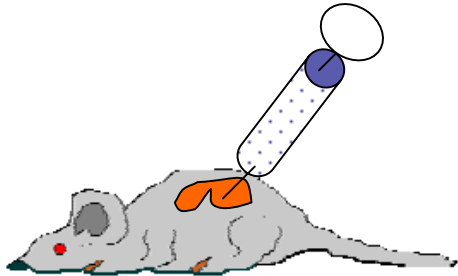


19 days after irradiation



**Does RGTA-OTR4131
protect tumor?**

Effect of RGTA on tumor growth *in vivo*

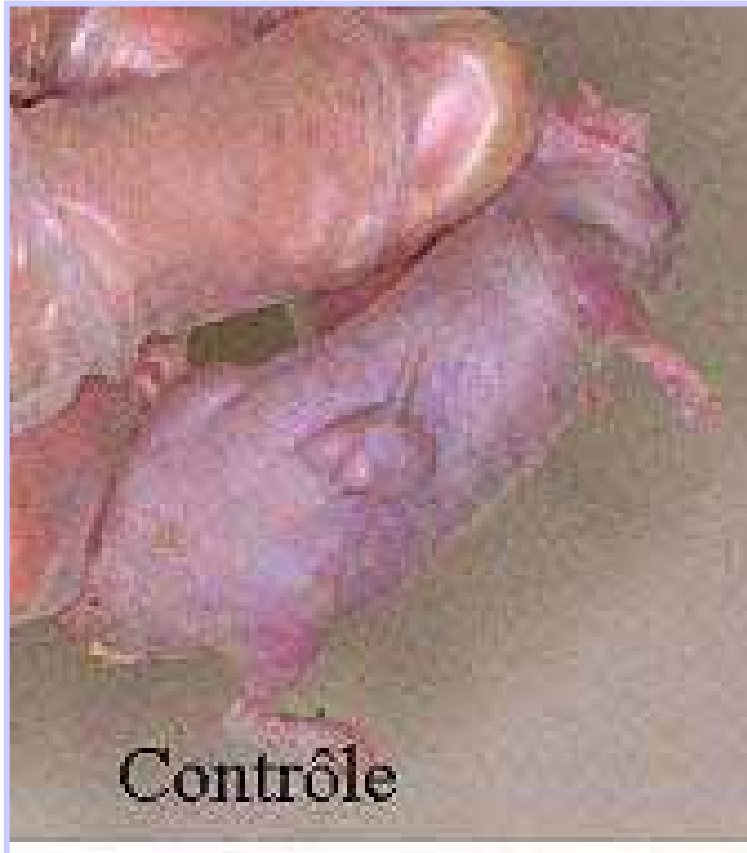


Balb/c nude mice

Tumor cell lines: HEP2; HT29

Single dose of **15 Gy** selectively on tumor

Reagents: RGTA®-OTR4131

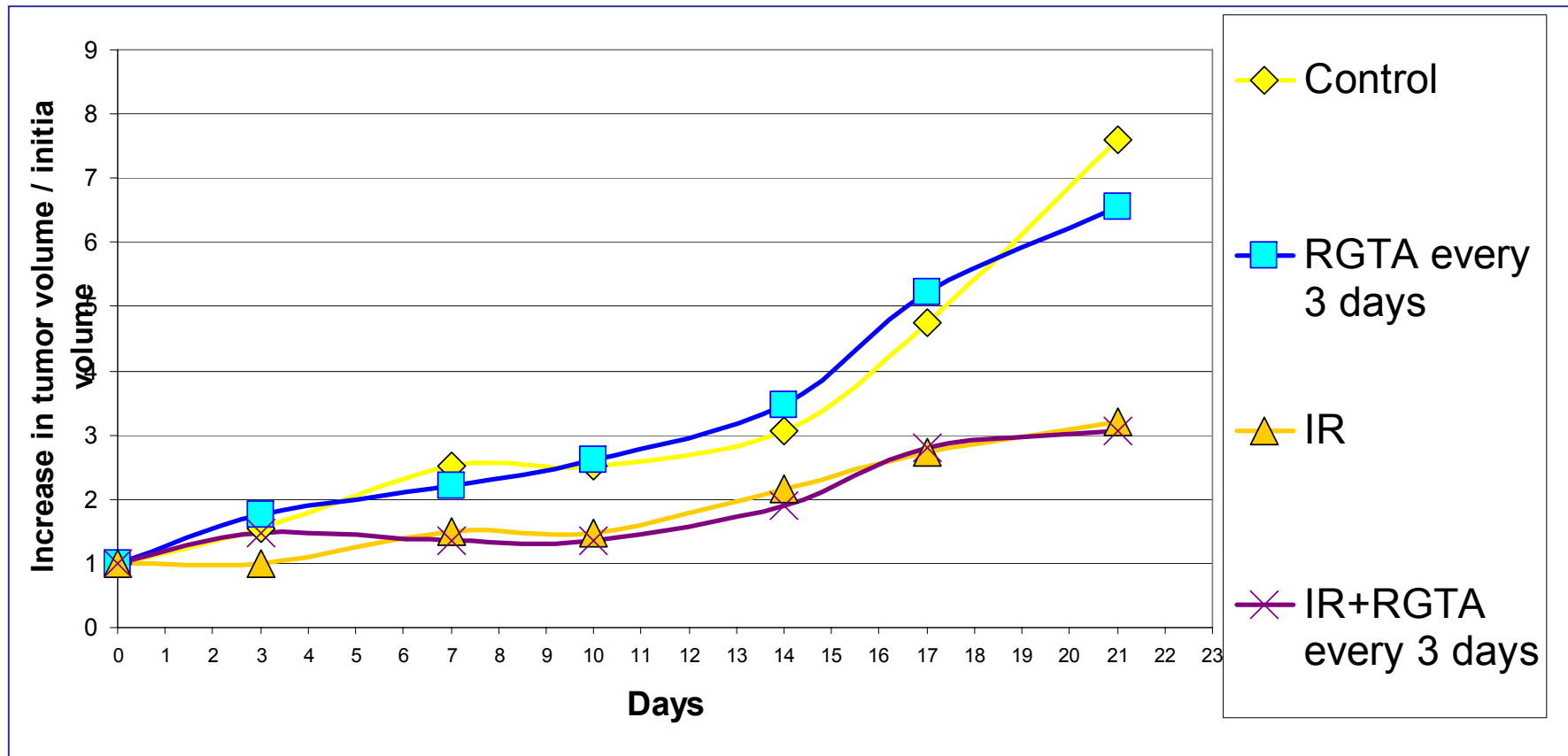


Tumor response:

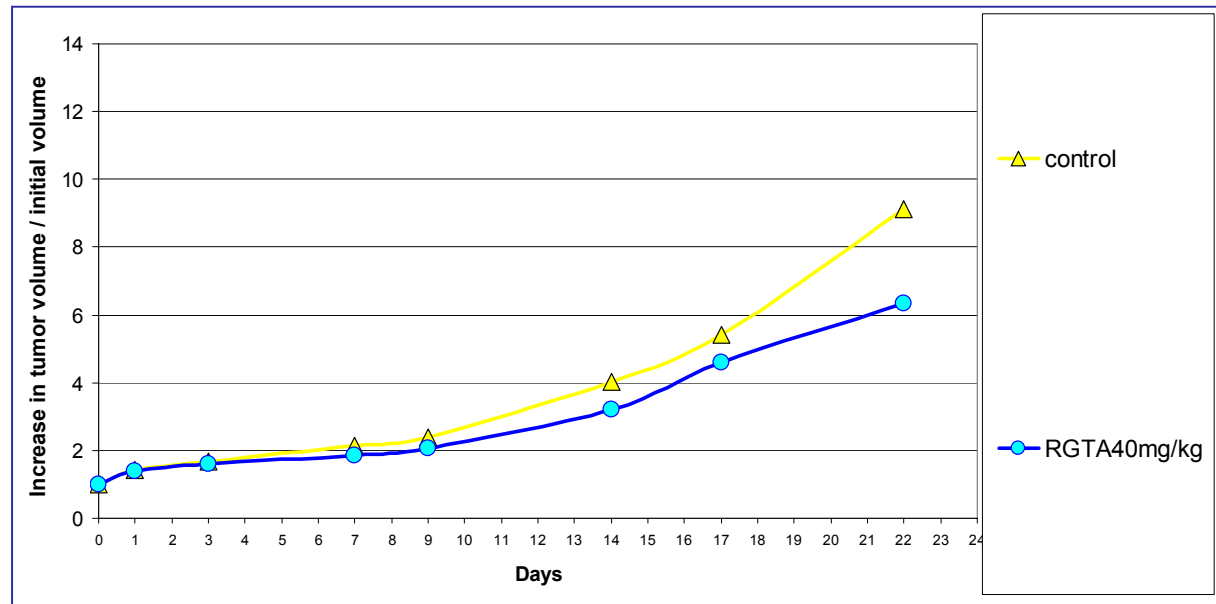
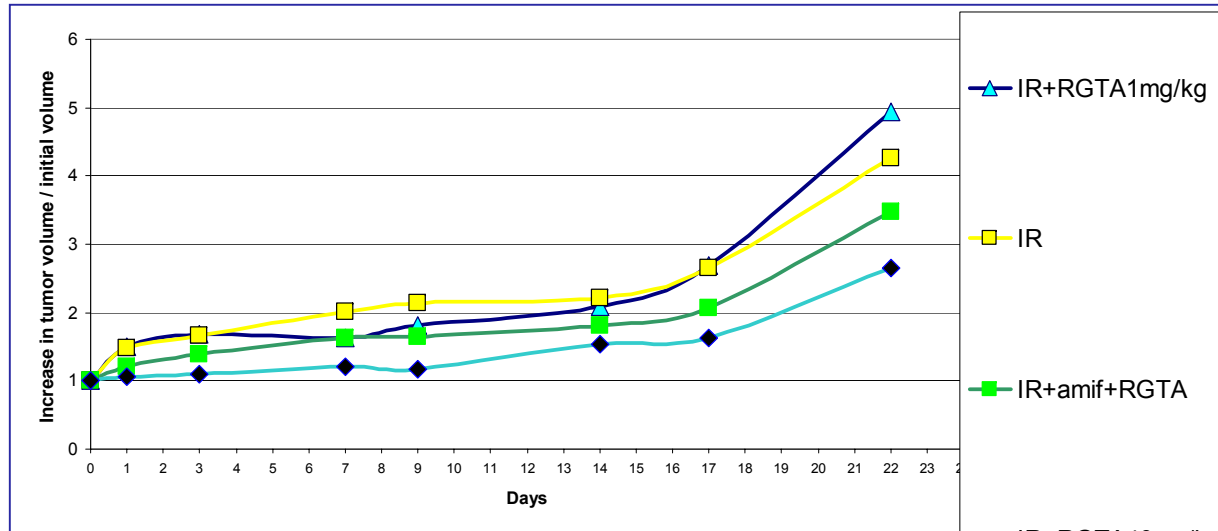
$$\text{Tumor volume} = \frac{\text{length (mm)} \times \text{width}^2 \text{ (mm)}^2}{2}$$

Effect of RGTA on tumor growth *in vivo*

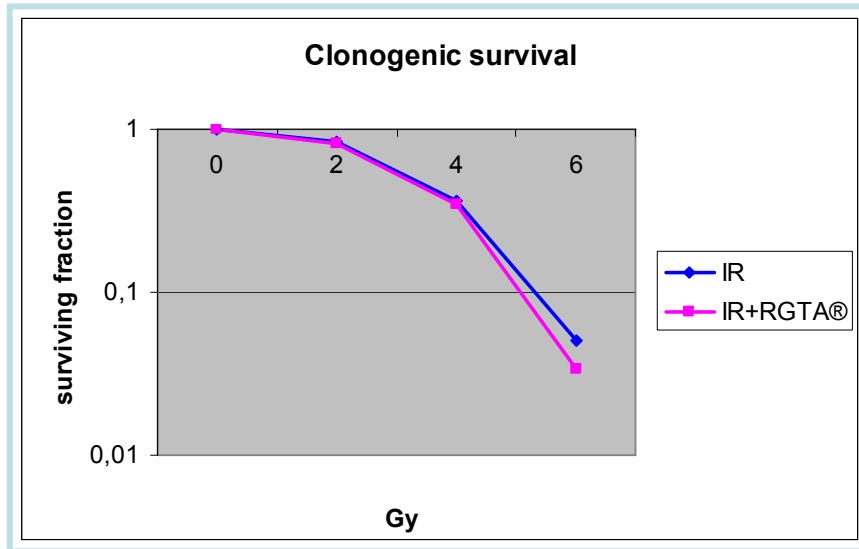
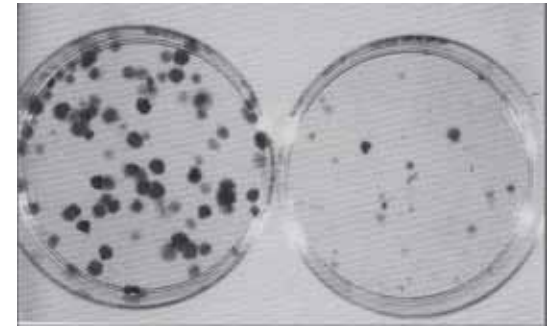
HEP-2 xenograft



Effect of RGTA on tumor growth *in vivo*

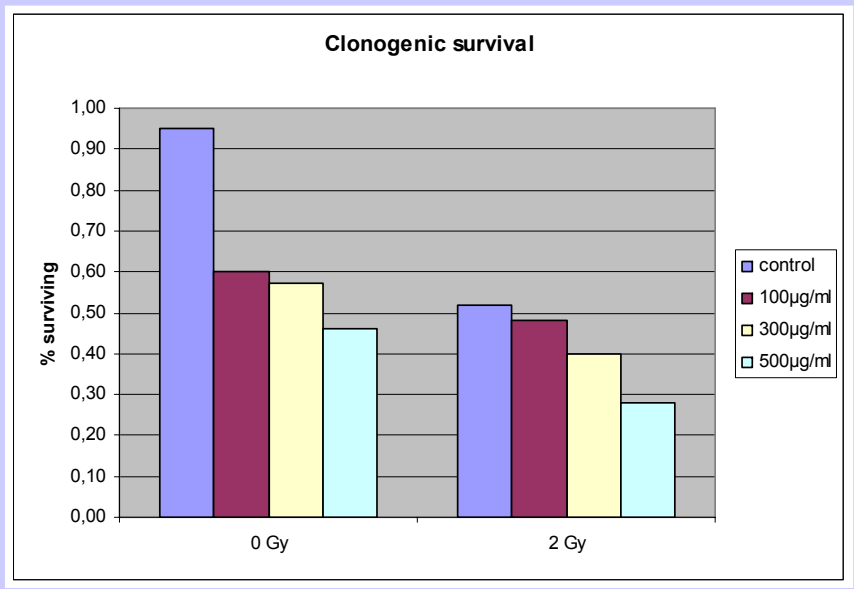


In vitro radio-sensitivity assay



HEP-2 cell line
 γ -IR: 0-2-4-6 Gy
Reagents:RGTA 10 μ g/ml

HT-29 cell line
 γ -IR: 0-2 Gy
Reagents:RGTA 100-300-500 μ g/ml



Conclusions

- ✓ In mice, RGTA protects normal tissue from radiation-induced damages.

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- ✓ In mice, RGTA protects normal tissue from radiation-induced damages.
- ✓ The association of RGTA with amifostine improves the mucosal protection.
- ✓ Absence of tumor protection.

Ongoing

- Radioprotective effects on GI & lung tissue
- Optimal sequencing and dosing with fractionated IR

Acknowledgments

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