UNIVERSITÀ DEGLI STUDI DI BRESCIA

UNIVERSITE PARIS SUD

Ruolo e azione fibrolitica degli inibitori farmacologici della via Rho/ROCK in diversi modelli di fibrosi animale radioindotta:

studi *in vivo* e *in vitro*

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PRINCIPLES OF RADIATION EFFECTS ON NORMAL TISSUES

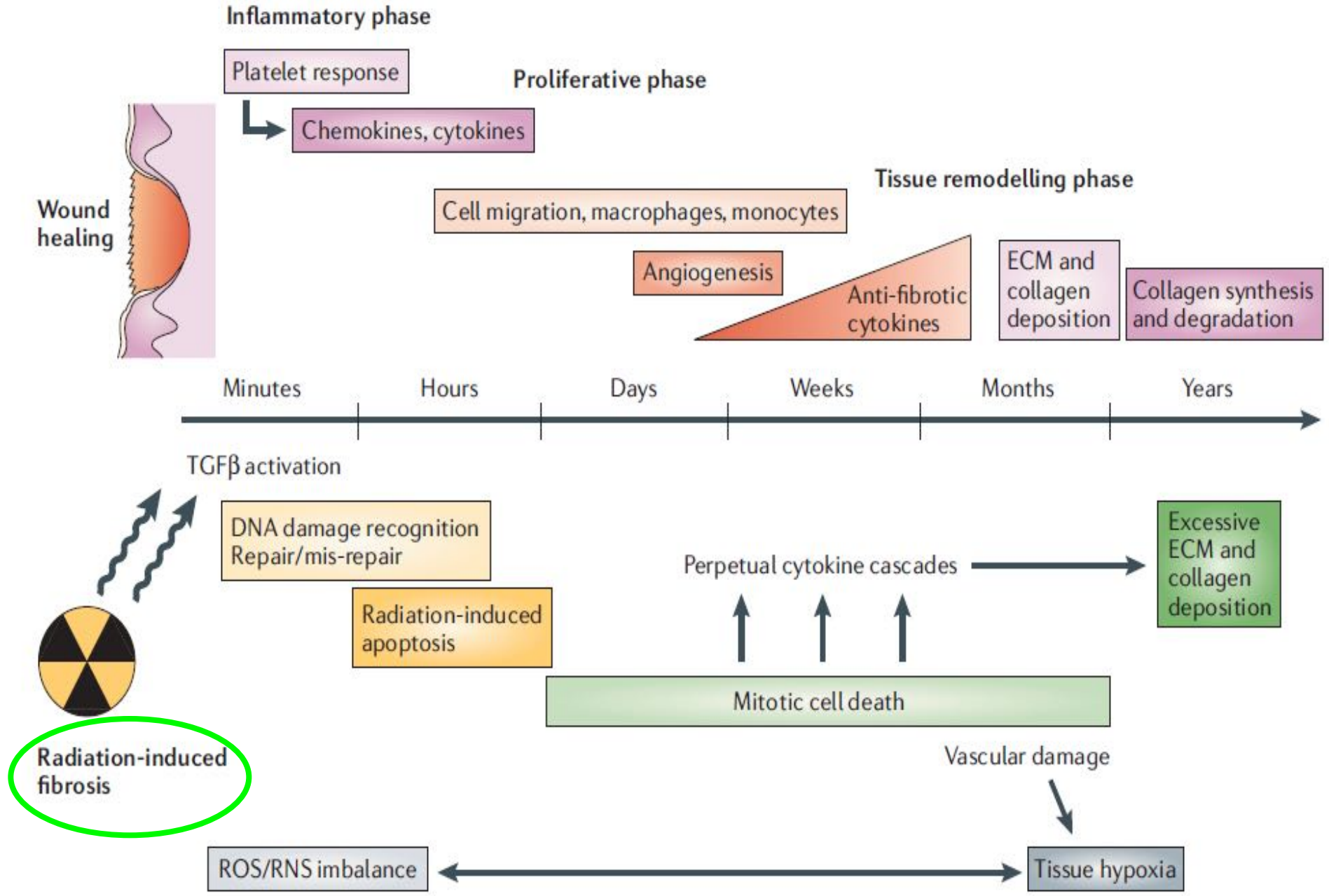
Radiation therapy remains a cornerstone of modern cancer management.

In Italy, > 150000 new patients every year need a treatment.

All effective cancer therapies that have been developed so far are associated with a risk of various side effects and, as an increasing number of people are cancer survivors, **preventing or reducing late side effects has increasingly become a priority.**

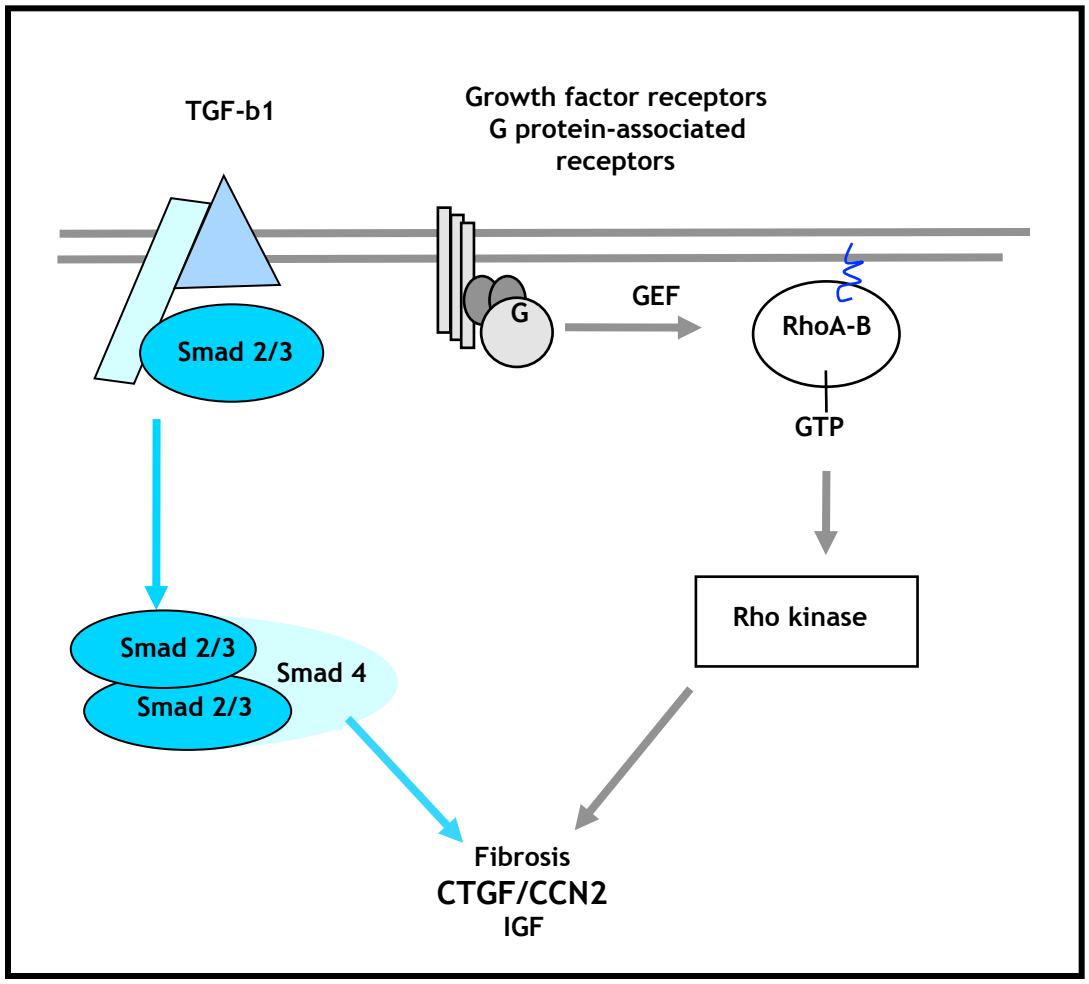
An important challenge to modern radiation therapy is to increase the tolerance of normal tissues, in order to improve the quality of life of the patients and to enhance local tumor control.

The recent progress made by technological advances has reduced radiation-induced complications especially in dose-limiting organs like the **intestine** and **lungs** that indeed still remains two major dose limiting organs.



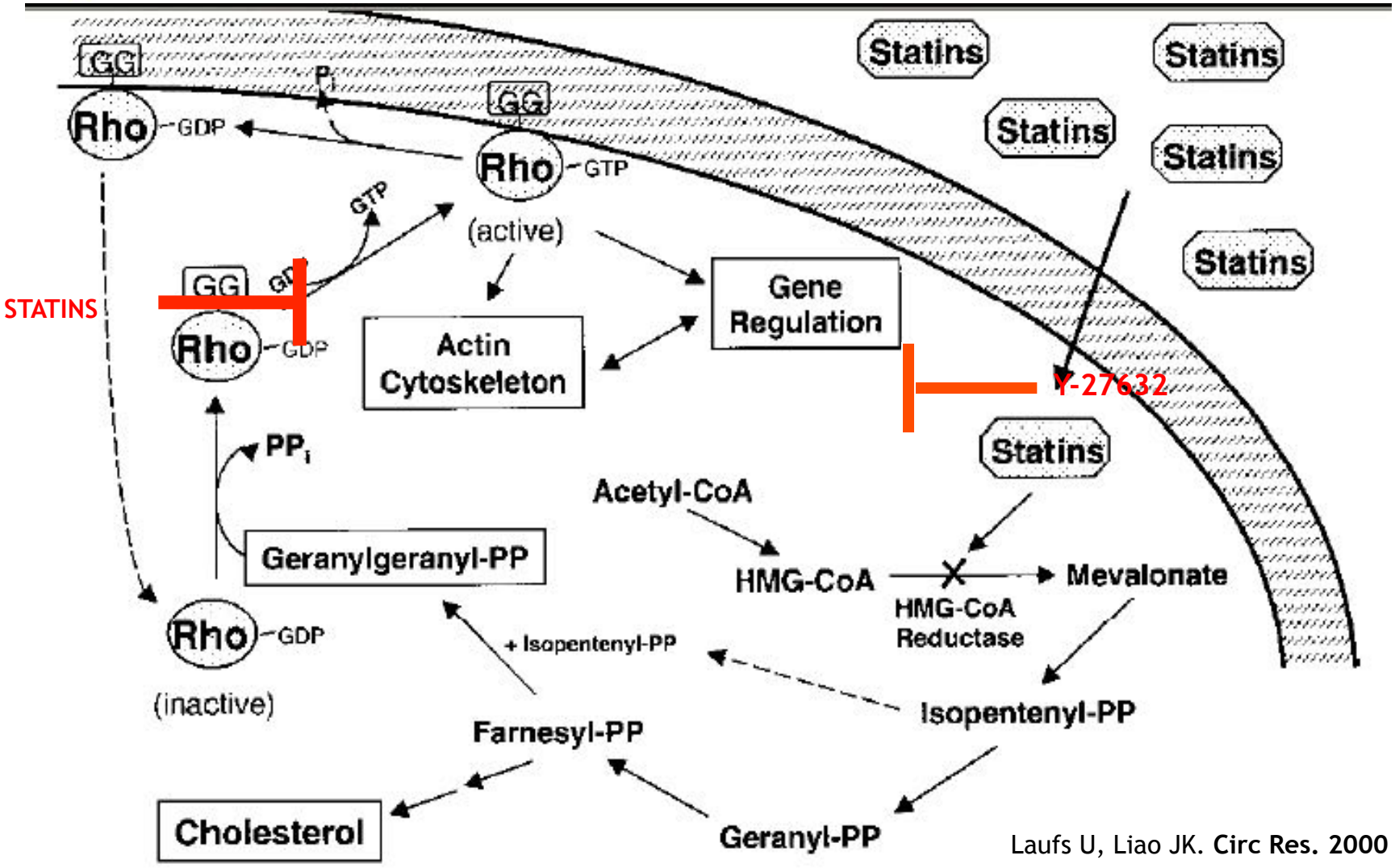
Bentzen SM, **Nat Rev Cancer. 2006**

CTGF and Rho/ROCK PATHWAY



Haydont V et al., **World J Gastroenterol 2007**
Haydont V et al., **Brit J Radiol 2007**
Haydont V et al., **Int J Radiat Oncol Biol Phys 2007**
Haydont V et al., **Radiotherapy and Oncology 2005**
Bourgier C et al., **Gut 2005**

Targeting the Rho/ROCK pathway



Laufs U, Liao JK. **Circ Res. 2000**

QUESTION:

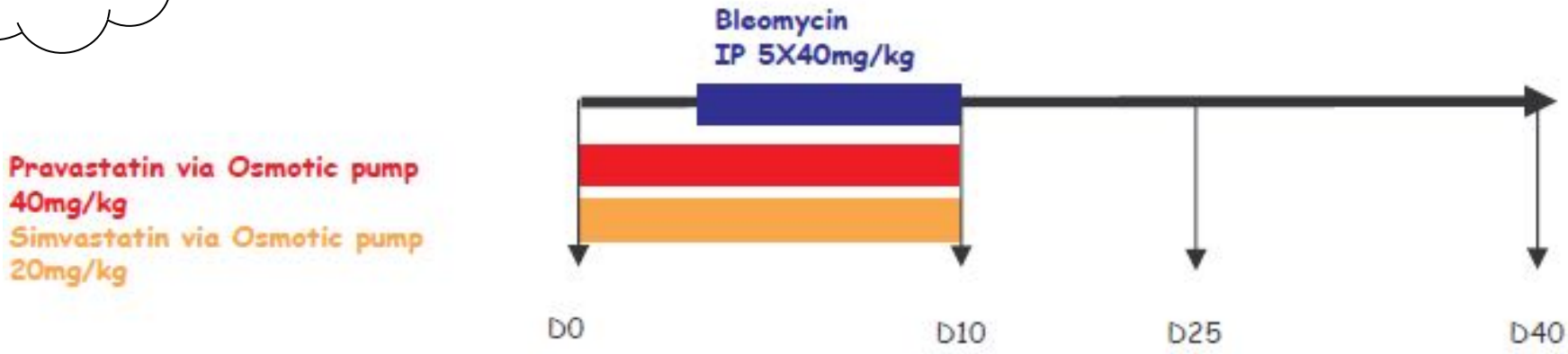
Is the anti-fibrotic action displayed by Rho/ROCK inhibitors (Pravastatin, Simvastatin and Y-27632) restricted to the gut or could be applied to other organs?

The anti-fibrotic effect of Rho/ROCK inhibitors in LUNG fibrosis

EXPERIMENTAL MODEL OF LUNG FIBROSIS AND DRUG ADMINISTRATION

By BLM

TREATMENT SCHEDULE IN PRAVASTATIN PREVENTING-TREATMENT GROUP



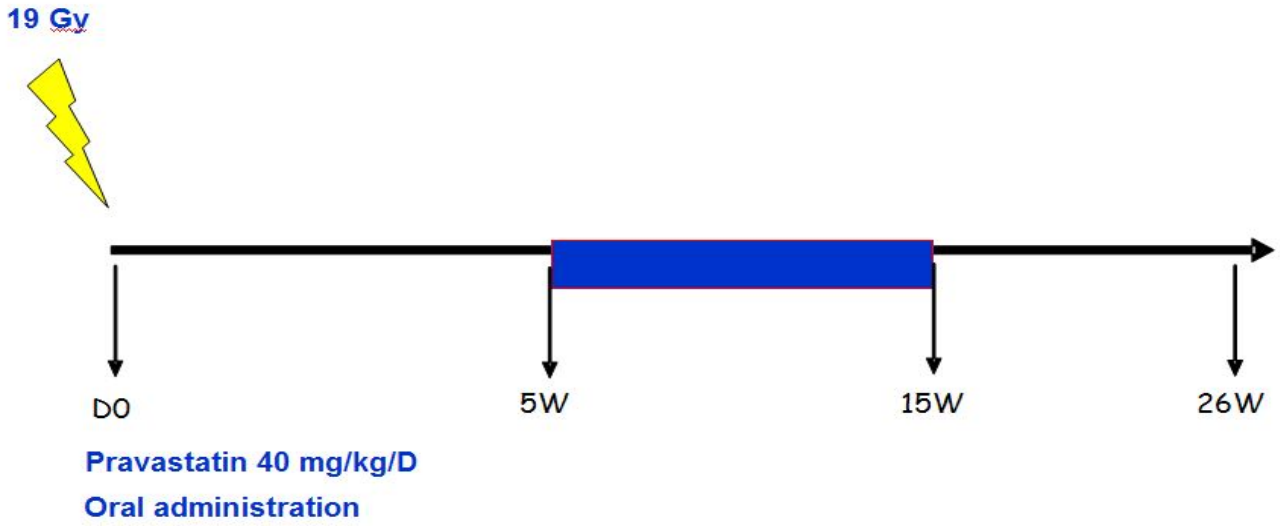
TREATMENT SCHEDULE IN PRAVASTATIN CURATIVE-TREATMENT GROUP

Shimizu Y. et al., **Am J Respir Crit Care Med. 2001**

EXPERIMENTAL MODEL OF LUNG FIBROSIS AND DRUG ADMINISTRATION

By IR

TREATMENT SCHEDULE IN PRAVASTATIN CURATIVE-TREATMENT GROUP



HISTOLOGICAL EXAMINATION AND IMMUNOHISTOCHEMISTRY

Lungs are collected for histology and immunohistochemistry.
Lung sections were stained with Hematoxilin-Eosin-Saffranin (HES) and examined using conventional light microscopy.
Expression of TGF-βRII, RhoB and CCN2 were studied in lungs irradiated mice.

	LUNG	
	Ab primary	Ab secondary
TGF-BRII	1:100	HRP-conjugated secondary antibody 1:5000
RhoB	1:100	
CCN2	1:50	

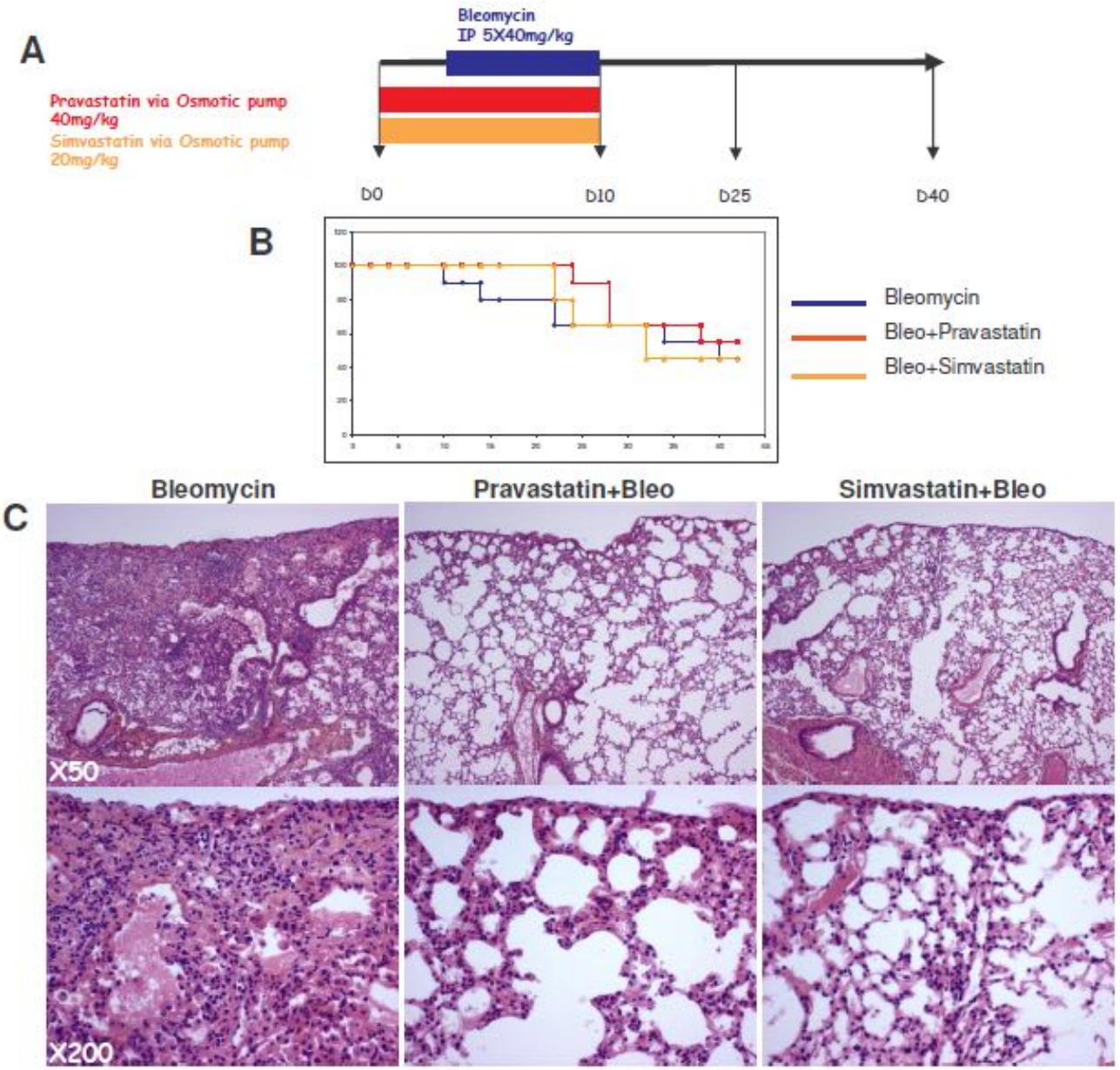
RESULTS

Current Drug Targets, 2010, *11*, 1395-1404

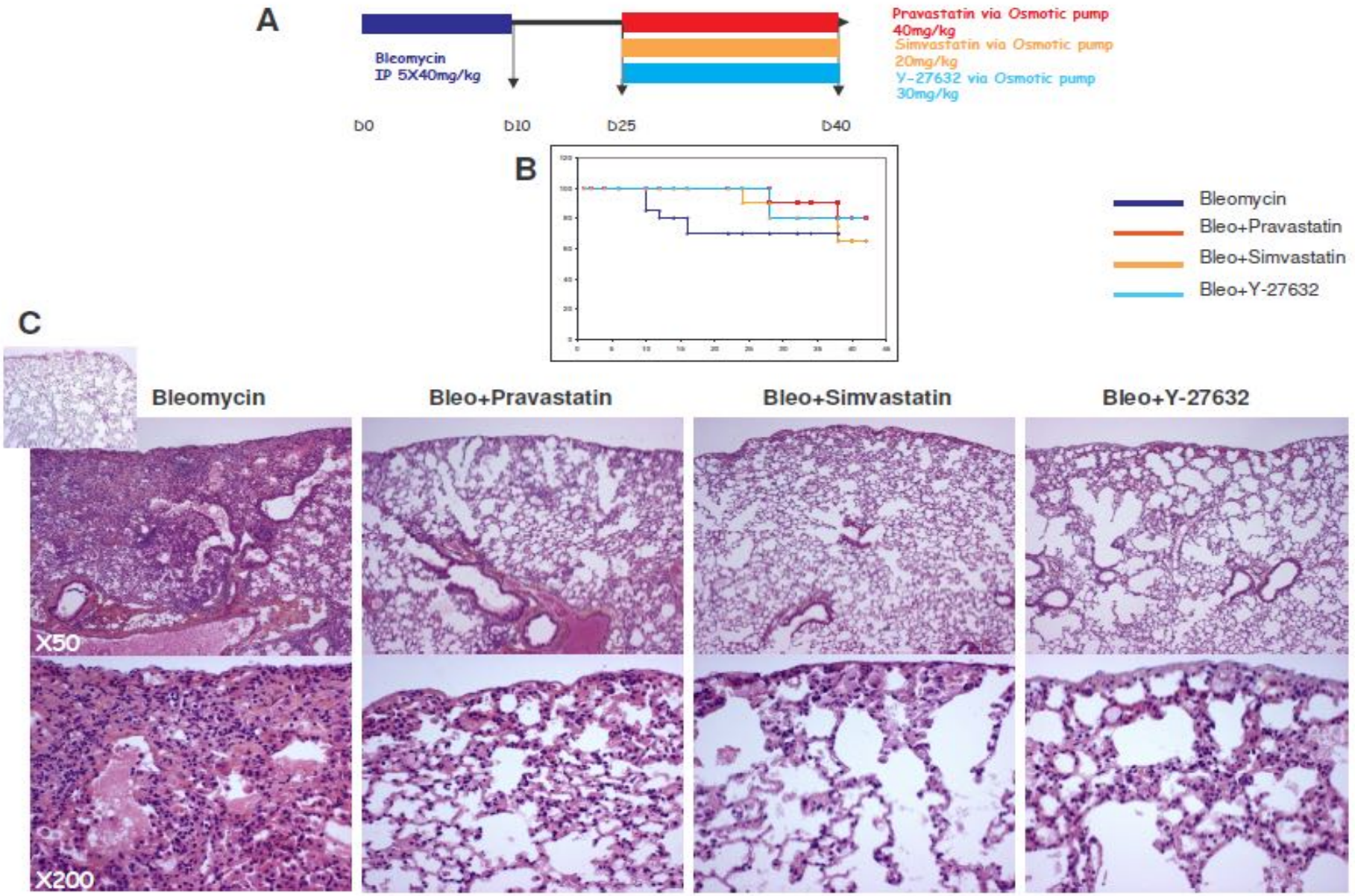
Modulation of the Rho/ROCK Pathway in Heart and Lung after Thorax Irradiation Reveals Targets to Improve Normal Tissue Toxicity

Virginie Monceau[1,2], Nadia Pasinetti[1,6], Charlotte Schupp[1], Fred Pouzoulet[1,5], Paule Opolon[3] and Marie-Catherine Vozenin[*,1,2,4]

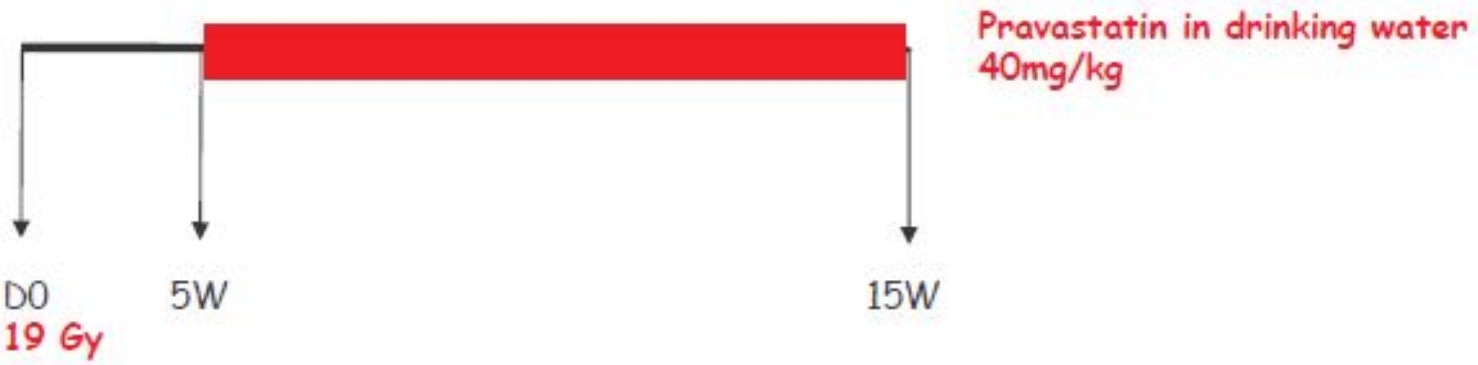
Pharmacological inhibitors of the Rho/ROCK pathway prevent BLM-induced lung fibrosis

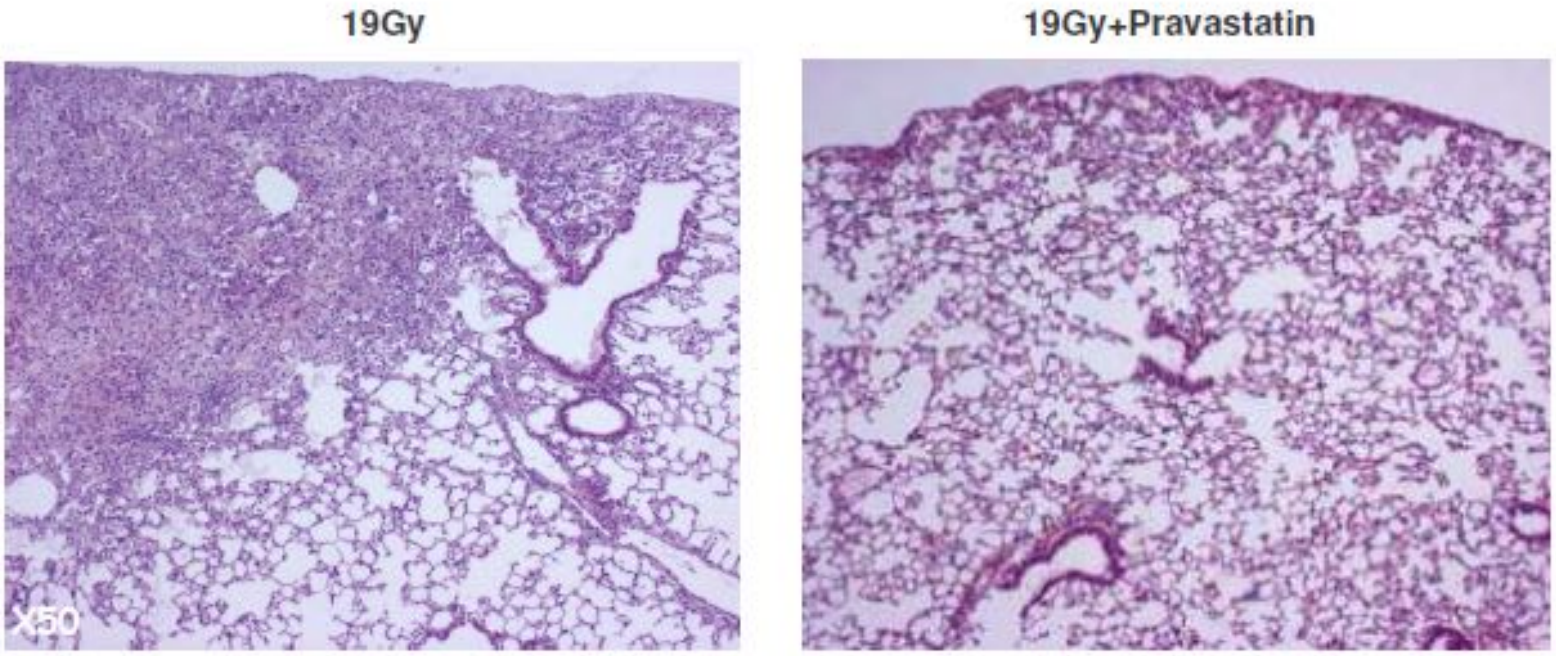


Pharmacological inhibitors of the Rho/ROCK pathway reverse BLM-induced lung fibrosis

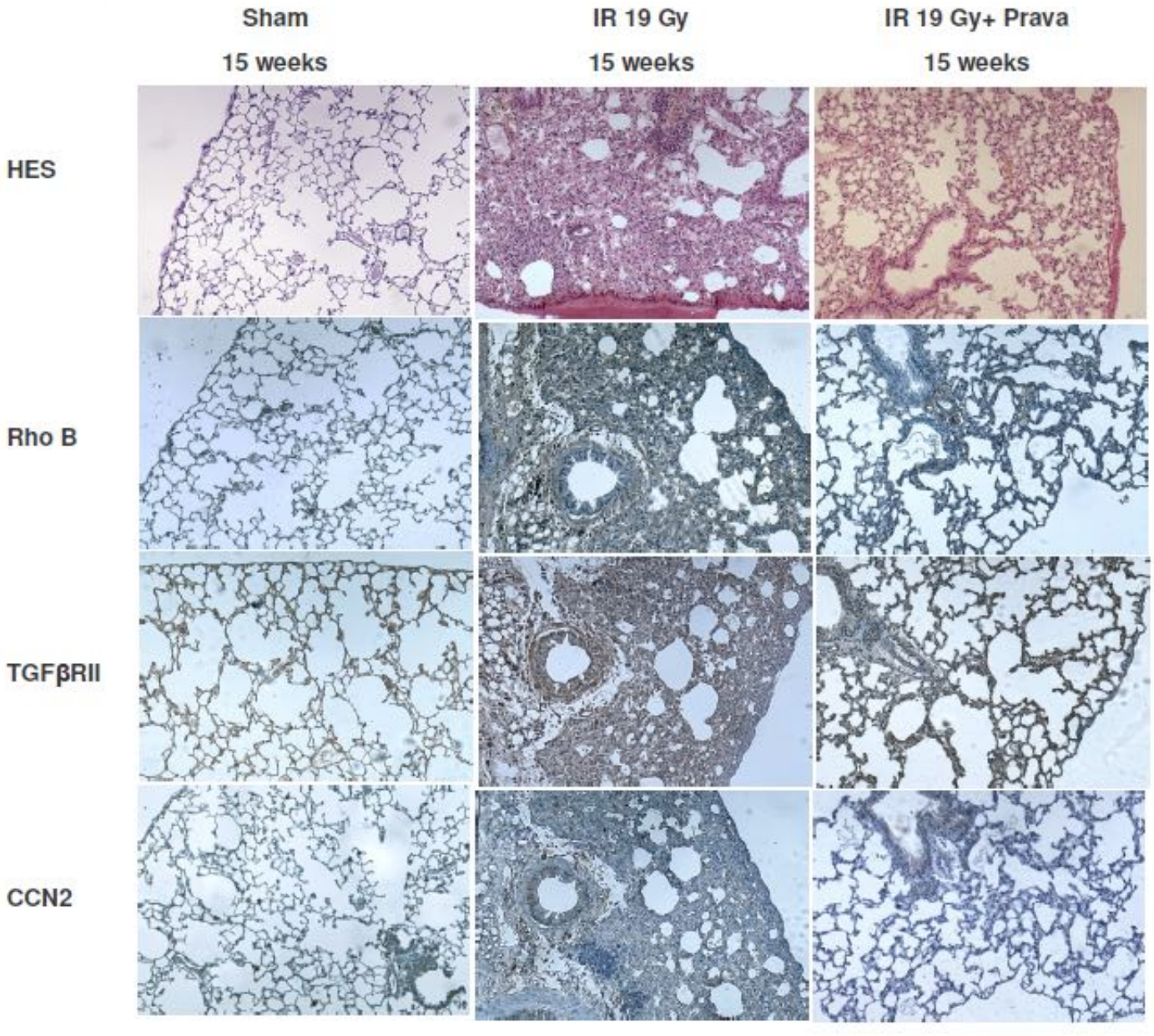


Pravastatin reverse radiation-induced lung fibrosis





Pravastatin modulates the fibrogenic cascade involving TGF-βRII and Rho in the lungs

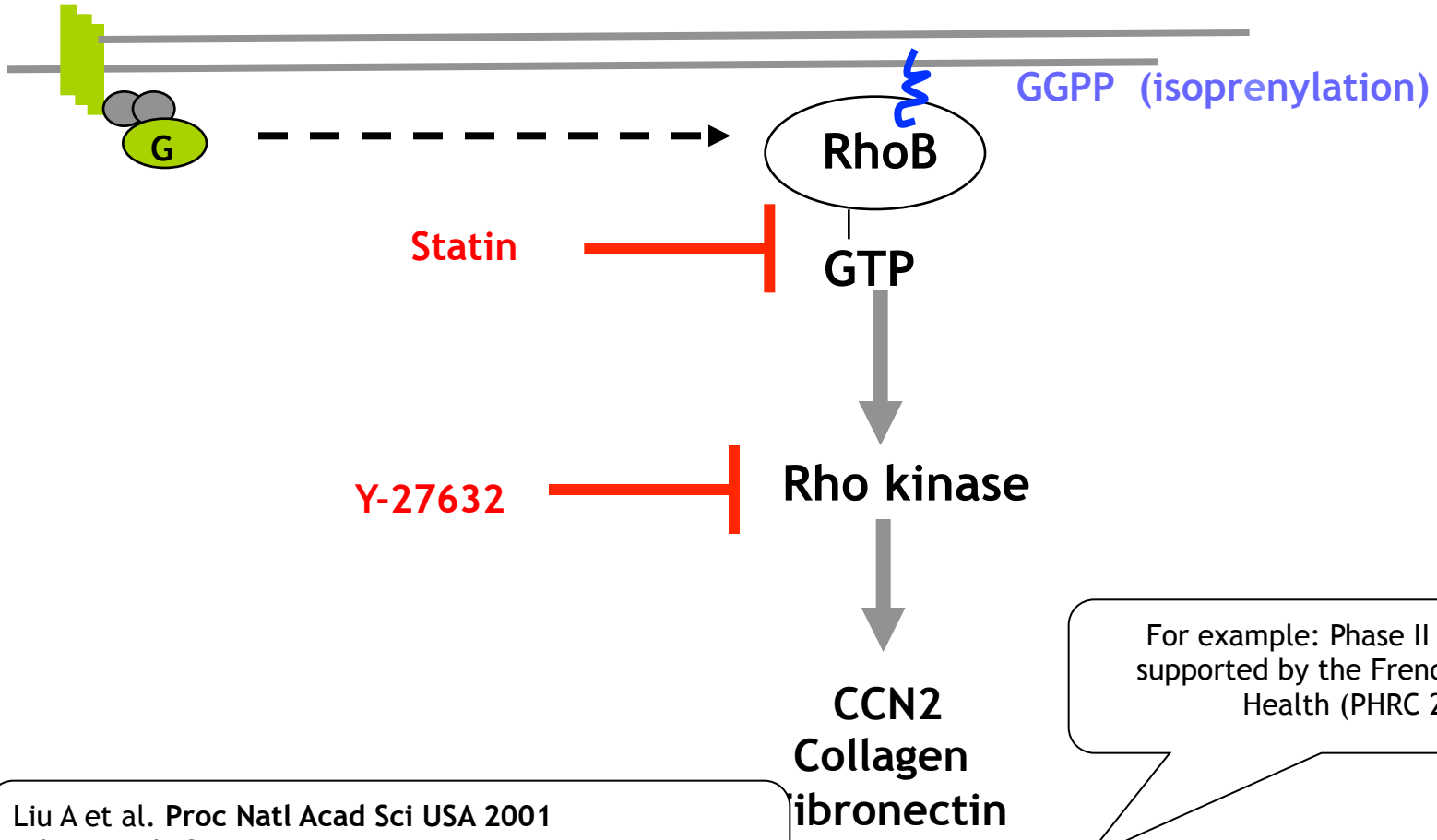


CONCLUSION

For both irradiation and BLM-treated mice, the use of pharmacological inhibitors of the Rho/ROCK cascade improved histological structure and normalized the expression of fibrogenic markers IN LUNG.

These data suggest that Rho/ROCK activation by fibrogenic agents may be **neither organ-specific nor agent-specific**, but more likely **A COMMON RESPONSE TO THE CHRONIC WOUND HEALING (ACTIVE FIBROTIC) PROCESS.**

Targeting the Rho/ROCK pathway to prevent and reverse Bleomycin induced lung fibrosis and reverse radiation induced lung fibrosis



For example: Phase II clinical trial supported by the French Ministry of Health (PHRC 2010)

Liu A et al. **Proc Natl Acad Sci USA 2001**
Ader I et al. **Oncogene 2002**
Milia J et al. **Cell death and differentiation 2005**

into the clinic
Combined treatments
RhoB contribution in control tumour radiosensitivity