Preclinical study of Chronic radiation cystitis and cell therapy treatment

IRSN
INSTITUT DE RADIOPROTECTION ET DE SÛRETÉ NUCLÉAIRE

Faire avancer la sûreté nucléaire

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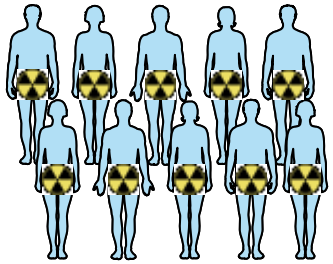
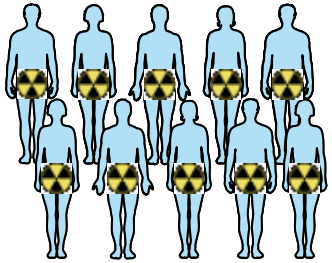
Acute and chronic radiation cystitis

Population concerned





Pelvic Radiotherapy

Days- months

Acute complications
40% of patients
Acute radiation cystitis

6 months – 20 years

Chronic complications
5 - 10 % of patients
Chronic radiation cystitis

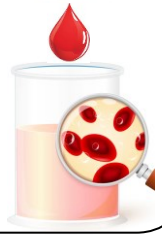
Mithal et al., 1993
Rigaud et al., 2004

Symptoms and treatment of chronic radiation cystitis

Incontinence

Pain

Hematuria



Decrease the quality of life

No curative treatment
Only symptomatic treatments (hyperbaric oxygen therapy, oral and intra-vesical agents)

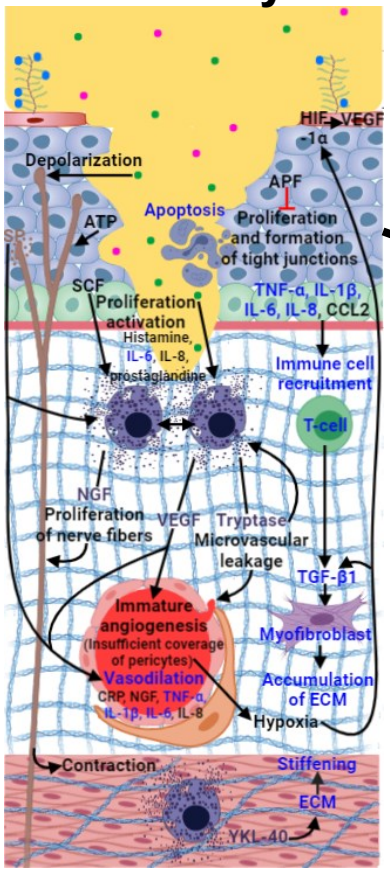
Transient effects that may induce serious complications

Few studies on chronic radiation cystitis
Little known molecular mechanisms

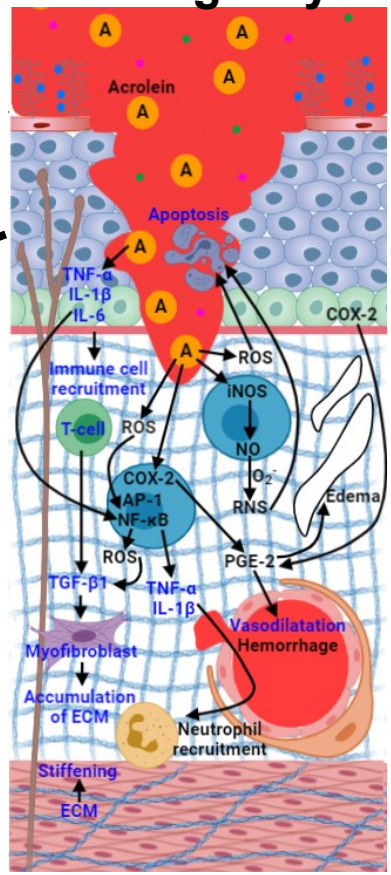
Preclinical research to develop innovative treatments

Similar pathology

Interstitial cystitis



Hemorrhagic cystitis



Urothelium dysfunction

Inflammation

Fibrosis

Ad-Mesenchymal Stem Cells (MSCs)

Kim et al., 2016
Song et al., 2015
Sant et al., 2007
He and Walls, 1997
Jiang et al., 2013;
Homma et al., 2016
Tyagi et al., 2018
Choi et al., 2018
Fry et al., 2018

Lee et al., 2003
Baygan et al., 2007
Dantas et al., 2010
Hu et al., 2003
Korkmaz et al., 2007
de Vries and Freiha, 1990

↑ Tissue regeneration

↓ Inflammation

↓ Fibrosis

Hypothesis: MSCs reduced inflammation, fibrosis and increase tissue regeneration in CRC?

Local bladder irradiation in rats with SARRP*

Experimental conditions: 5 rats for each condition and for each euthanasia time.

Irradiated Rats

20-30 Gy
40 Gy
50-80 Gy

Unirradiated Rats

Acute radiation cystitis | Chronic radiation cystitis

1 2 3 4 5 6 7 8 9 10 11 12 Months

* Small Animal Radiation Research Platform

Euthanasia of rats and analysis of the effects of MSCs on CRC (vascular damage, urothelium dysfunction, chronic inflammation, fibrosis)

Acute radiation cystitis | Chronic radiation cystitis

1 2 3 4 5 6 7 8 9 10 11 12 Months

Local bladder irradiation in rats with SARRP*

3 Injections of 5 million MSCs intravenously

HES
Red Sirius
immunolabelling

Tissue

Physiological:
Metabolic cage once a month for 24 hours

Transcriptomics

RT-qPCR
(TLDA : Taqman low density array)

Experimental conditions: 10 rats for each condition and for each euthanasia time.

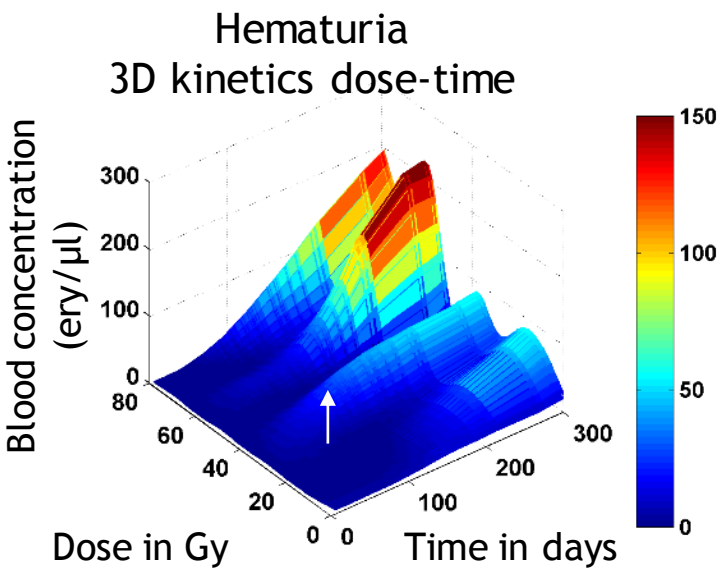
Experimental conditions for each time of euthanasia

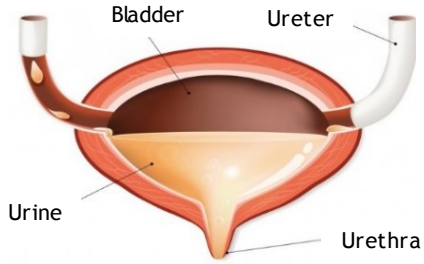
Irradiated Rats

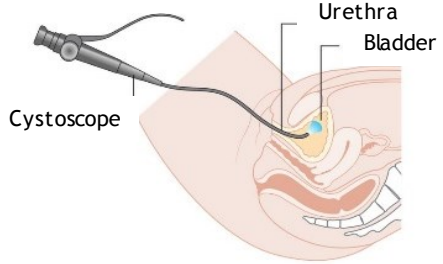
10 Vehicle 10 Unirradiated Rats

10 MSC 10

Hematuria and visualization of the bladder wall by cystoscopy

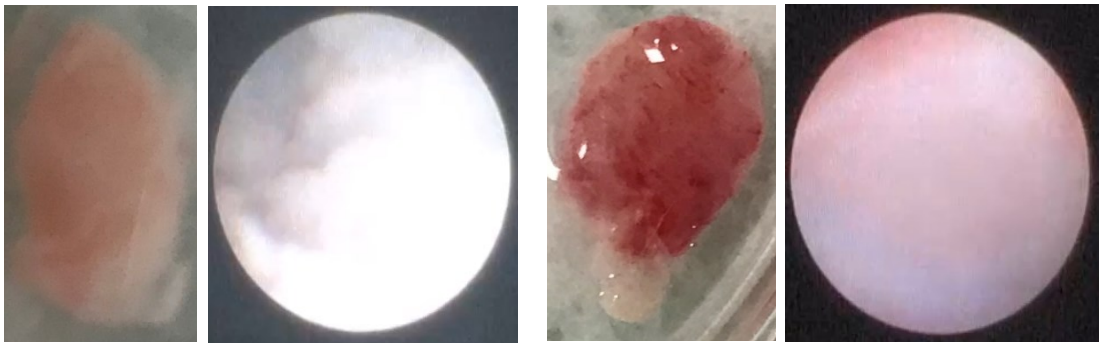






Cystoscopy at 6 months post-irradiation

Non-irradiated | Irradiated at 40 Gy



40 Gy :

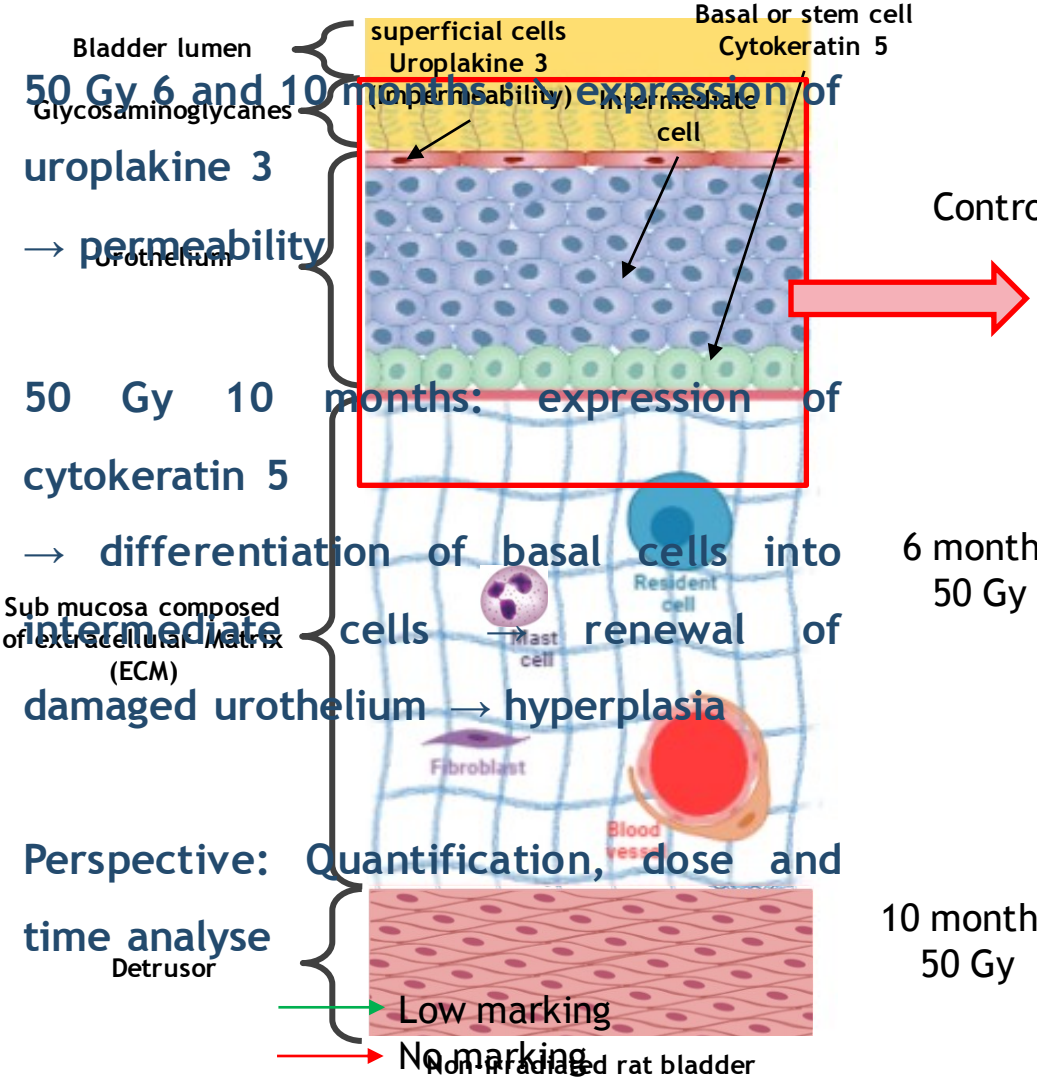
- ↗ hematuria, occurring early
- Vascular lesions at 6 months post-irradiation

Urothelium dysfunction

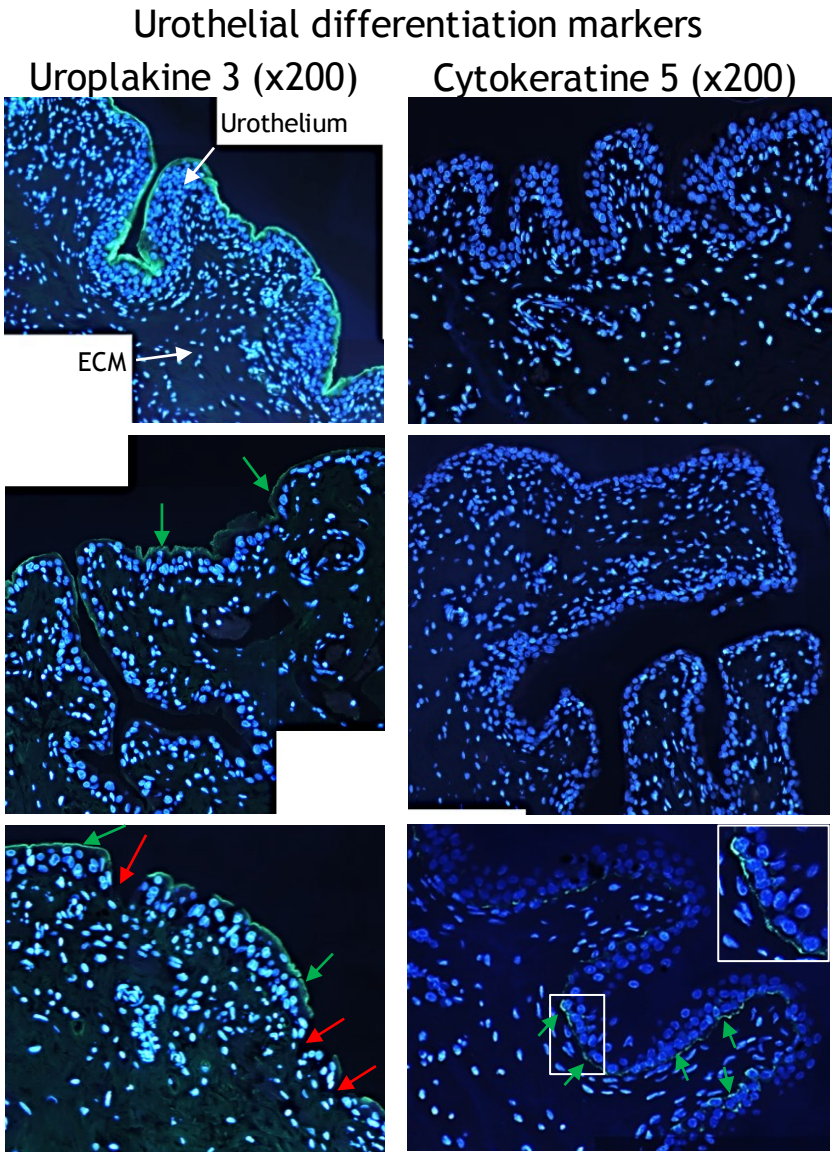
50 Gy 6 and 10 months : expression of uroplakine 3 → permeability

50 Gy 10 months: expression of cytokeratin 5 → differentiation of basal cells into intermediate cells → renewal of damaged urothelium → hyperplasia

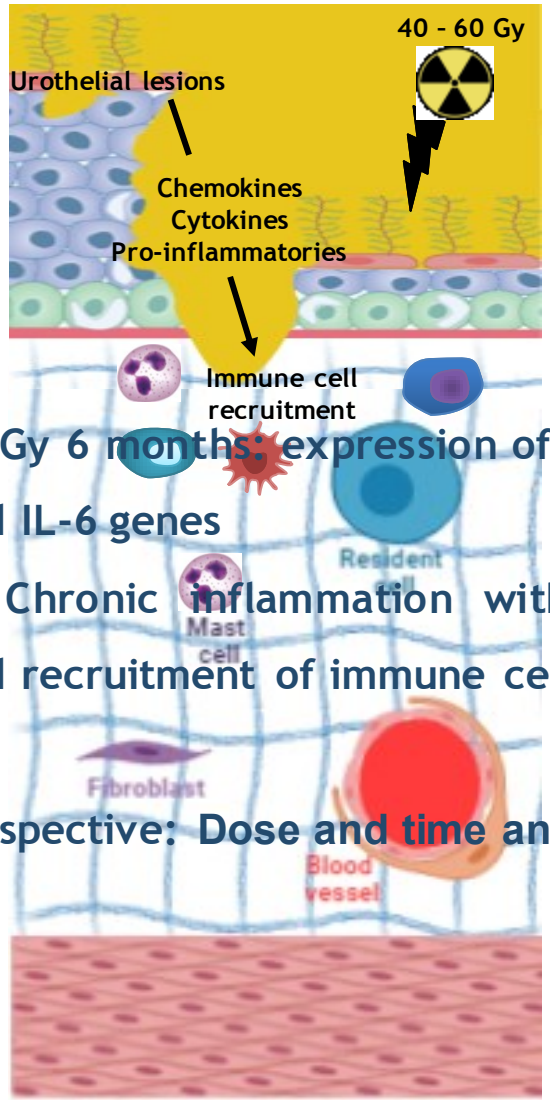
Perspective: Quantification, dose and time analyse

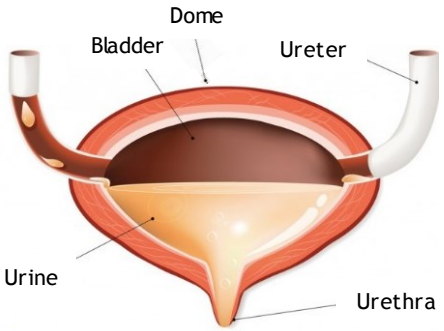


Urothelial differentiation markers



Inflammation at 6 months post-irradiation





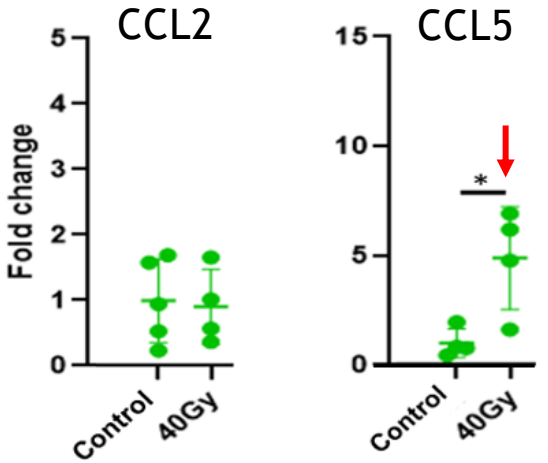
40 Gy 6 months: expression of CCL5, IL-1β and IL-6 genes

→ Chronic inflammation with activation and recruitment of immune cells

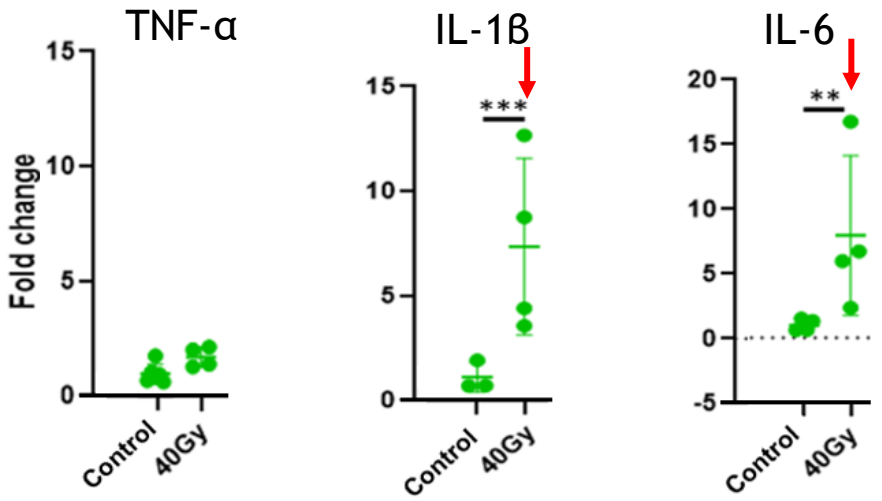
Perspective: Dose and time analyse

qPCR

Chimiokines

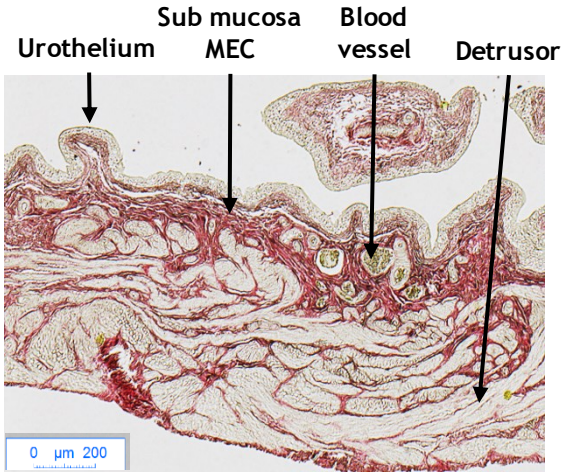


Pro-inflammatory cytokines

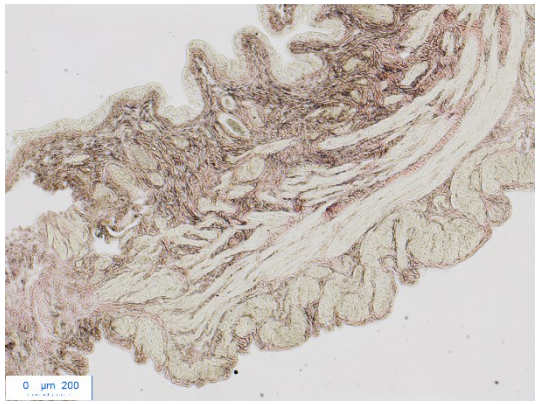


Fibrosis at 6 months post-irradiation

Red sirius (X50)

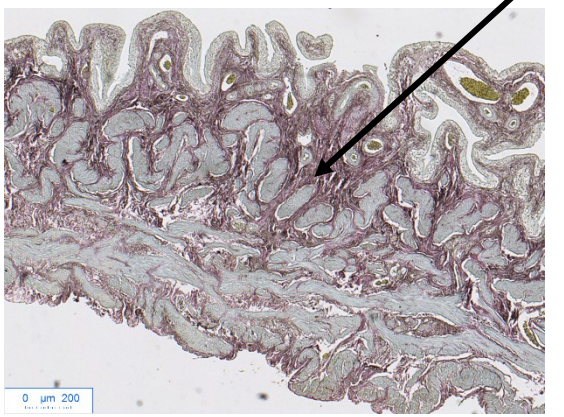


Control

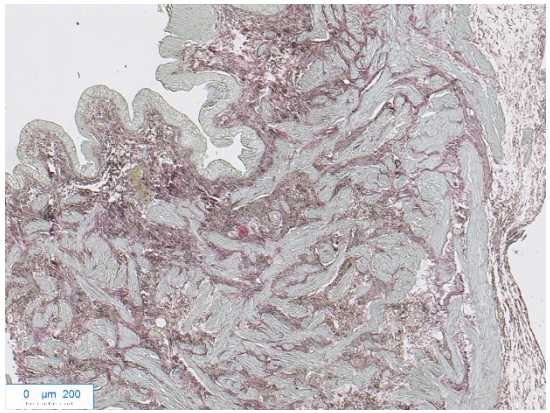


40 Gy

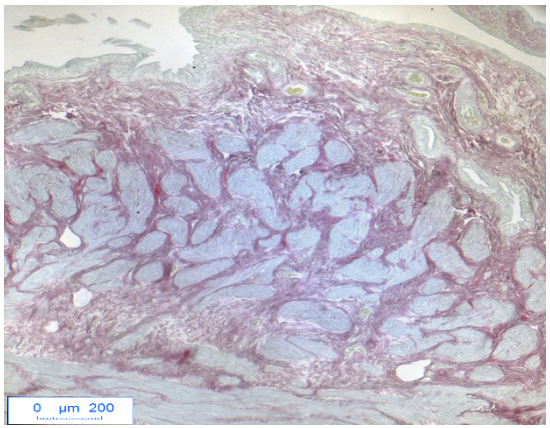
50 Gy



60 Gy



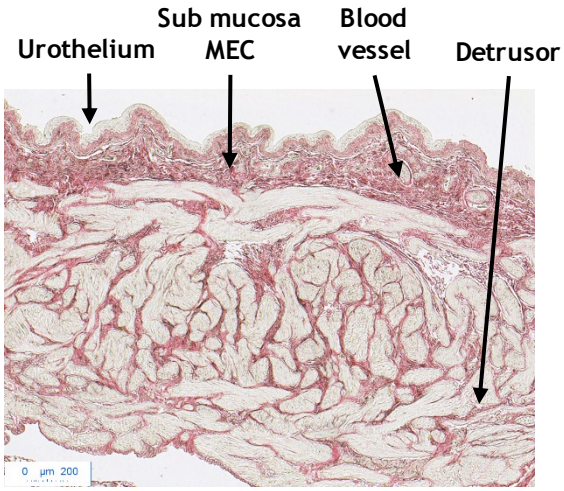
70 Gy



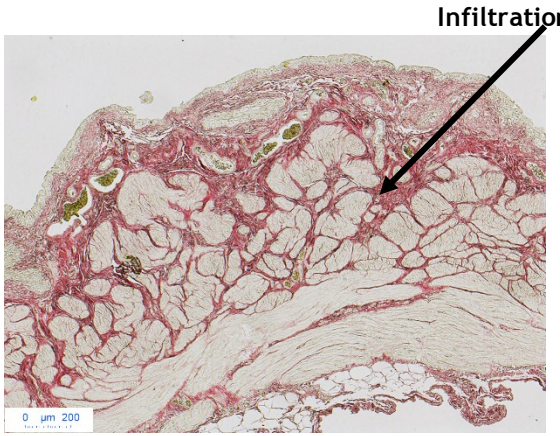
80 Gy

Fibrosis at 10 months post-irradiation

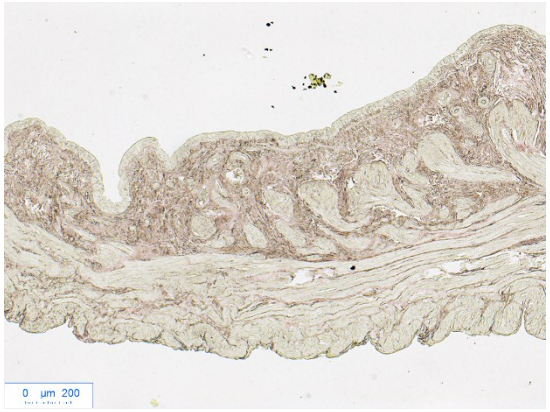
Red sirius (X50)



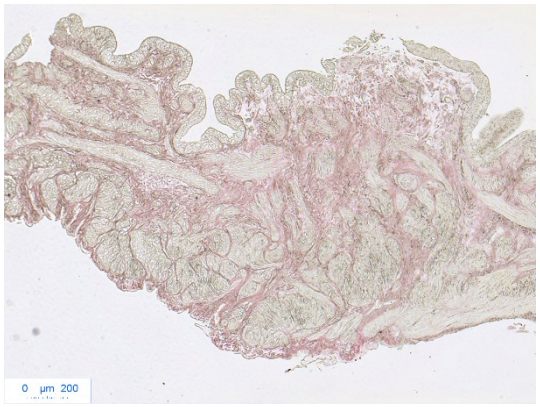
Control



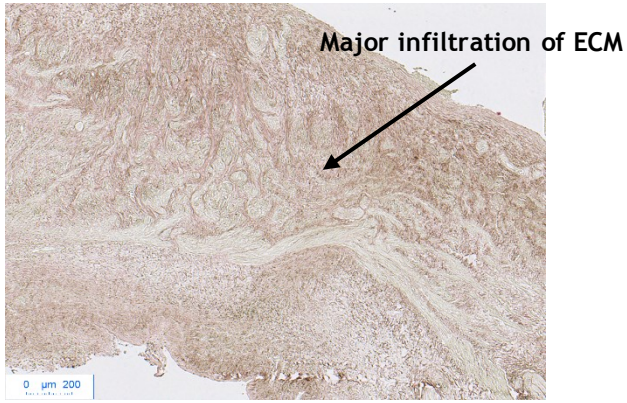
40 Gy



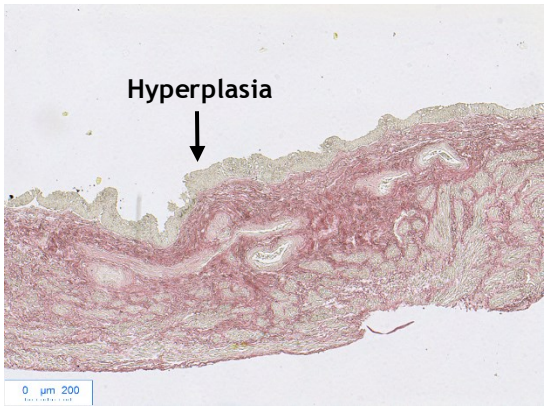
50 Gy



60 Gy



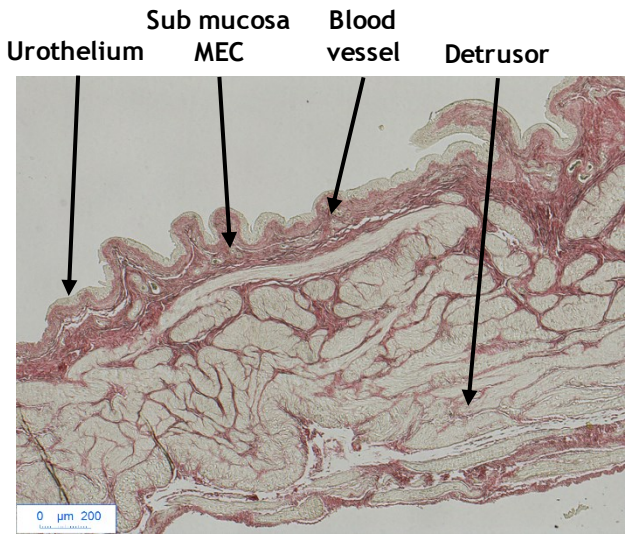
70 Gy



80 Gy

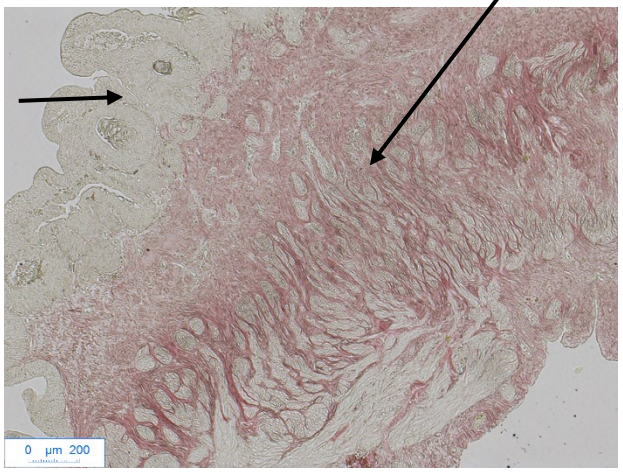
Fibrosis at 12 and 15 months post-irradiation for 40 Gy

Red sirius (X50)

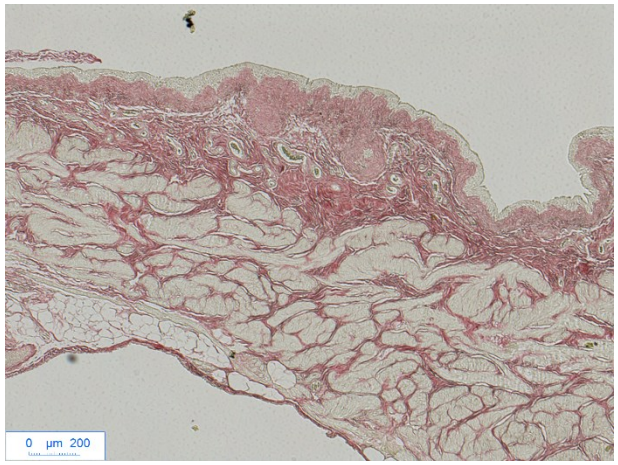


Control

12 months

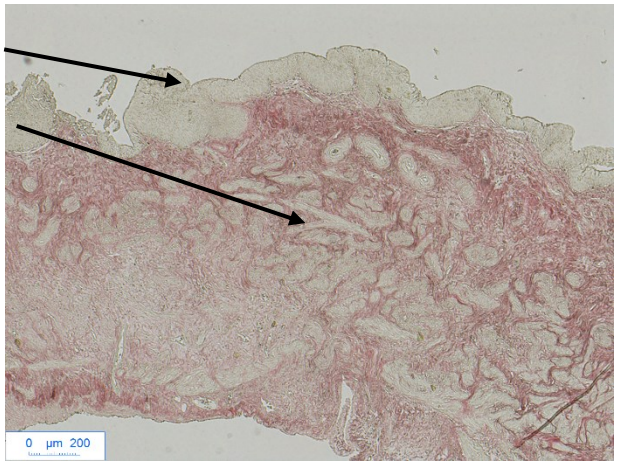


40 Gy



Control

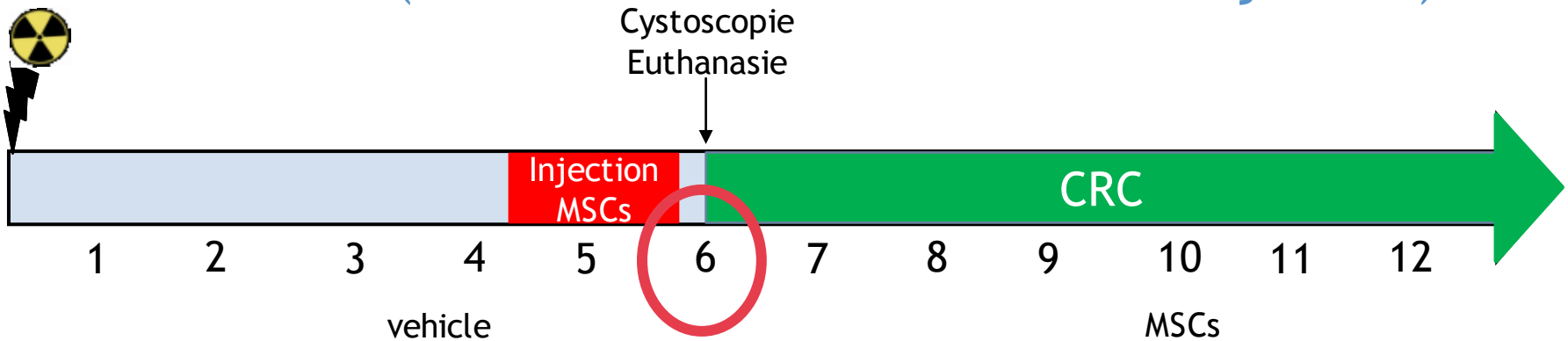
15 months



40 Gy

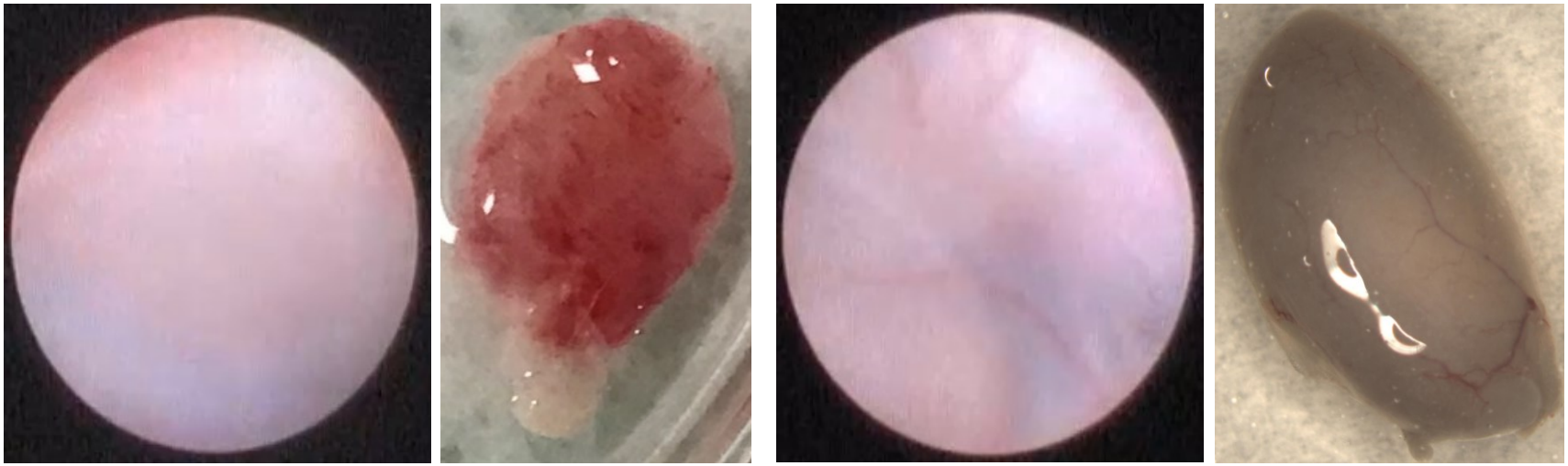
Increase fibrosis with dose and time

Visualization of the bladder wall by cystoscopy at 6 months post-irradiation (1.5 months after the first MSC injection)



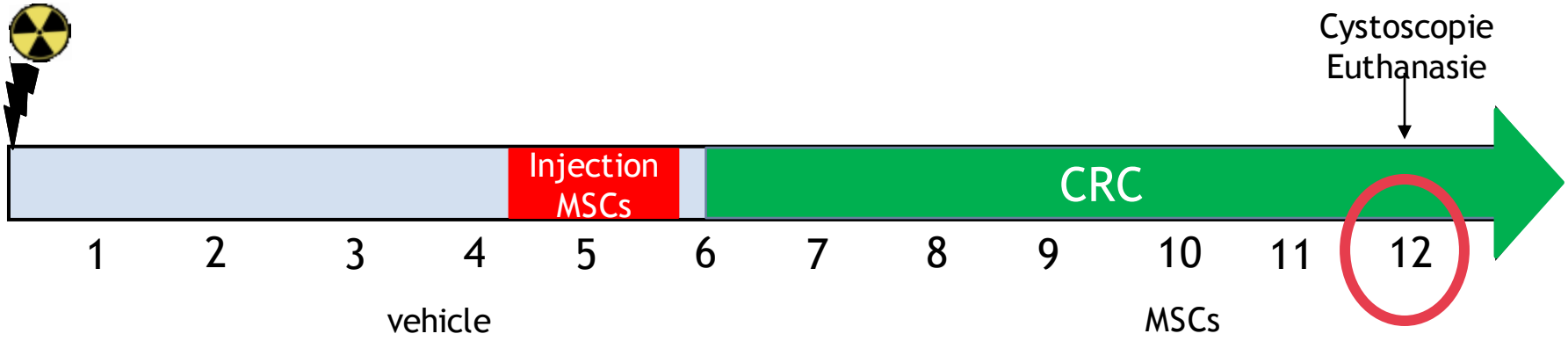
vehicle | MSCs

Irradiated at 40 Gy

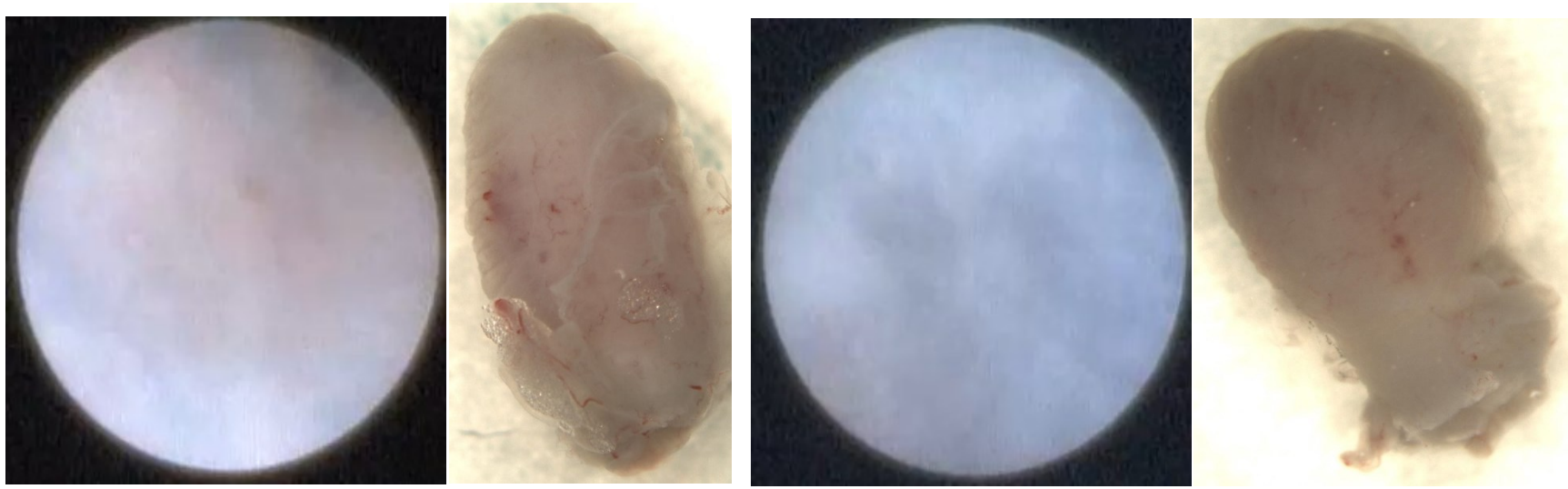


MSCs: ↘ vascular damage caused by irradiation

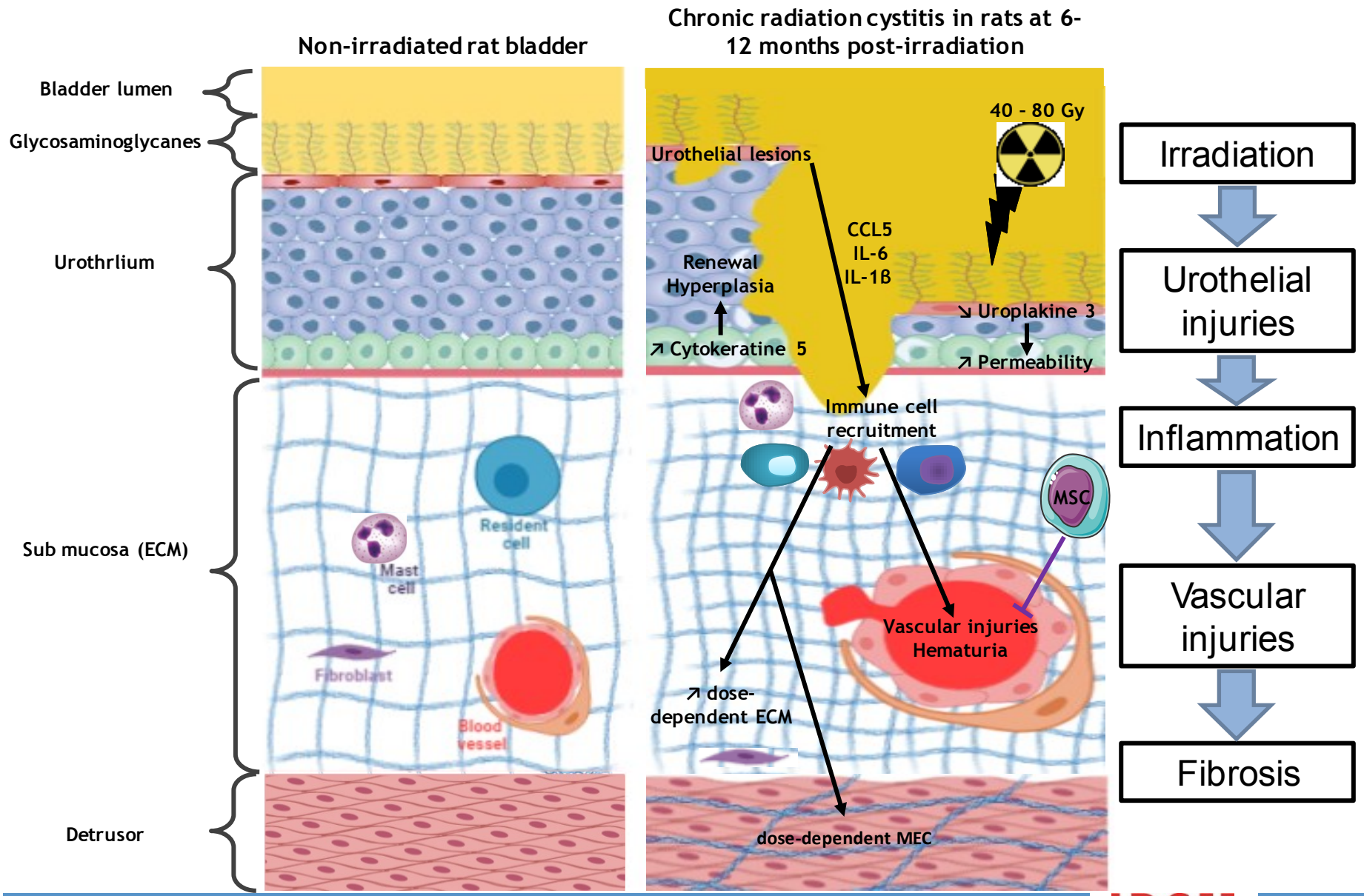
Visualization of the bladder wall by cystoscopy at 12 months post-irradiation (7.5 months after the first MSC injection)

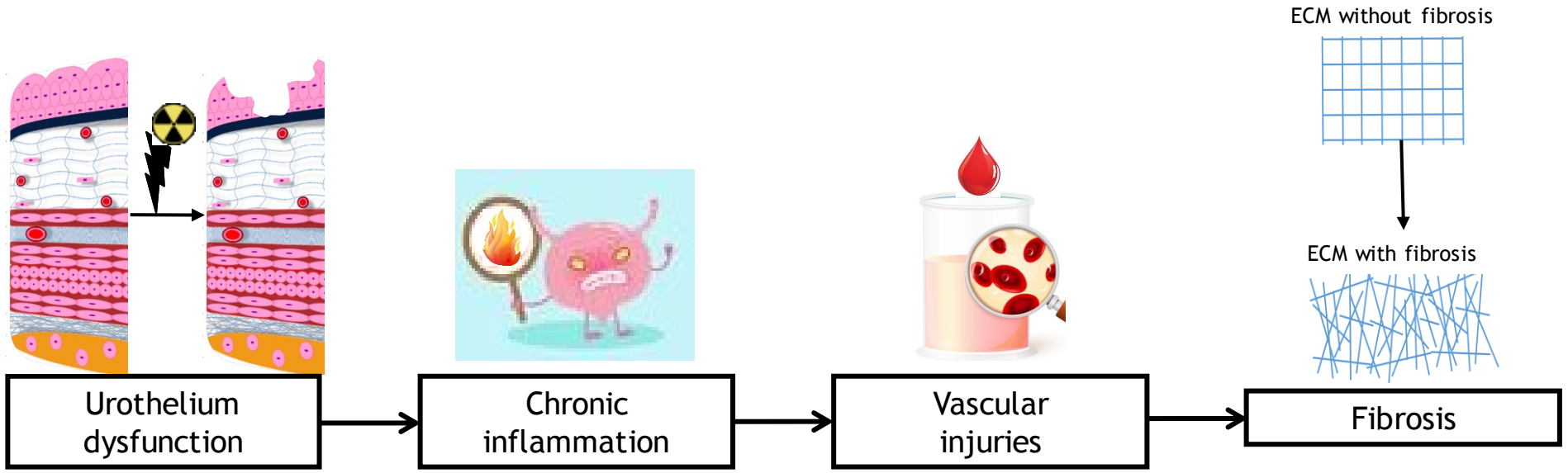


Irradiated at 40 Gy



MSCs: ↘ over time in vascular damage caused by irradiation


Non-irradiated rat bladder
Chronic radiation cystitis in rats at 6-12 months post-irradiation
Bladder lumen
Glycosaminoglycanes
Urothrlium
Sub mucosa (ECM)
Detrusor
Mast cell
Resident cell
Fibroblast
Blood vessel
40 - 80 Gy
Urothelial lesions
CCL5
IL-6
IL-1ß
Renewal
Hyperplasia
↗ Cytokeratine 5
↘ Uroplakine 3
↗ Permeability
Immune cell recruitment
MSC
Vascular injuries
Hematuria
↗ dose-dependent ECM
dose-dependent MEC
Irradiation
Urothelial injuries
Inflammation
Vascular injuries
Fibrosis



Model Characterization :

- Quantification
- Analyze different doses
- Analyze longer time

Effect of MSC treatment:

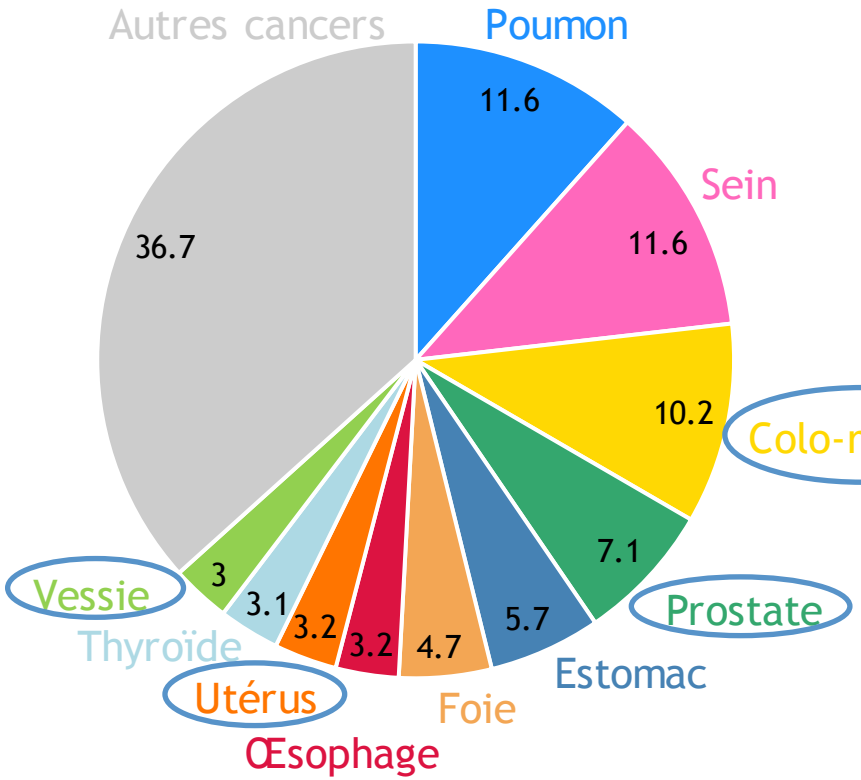
- Transcriptomics studies: Inflammation
- Tissue studies: Urothelium dysfunction, fibrosis
- Physiological studies: Vascular injuries

Thank you for your attention

Member of the GSEA: Animal monitoring and assistance in experimentation
A. Benadjaoud: Biostatistics
Mr. Dos Santos: Radiation to rats

Cancers et radiothérapie

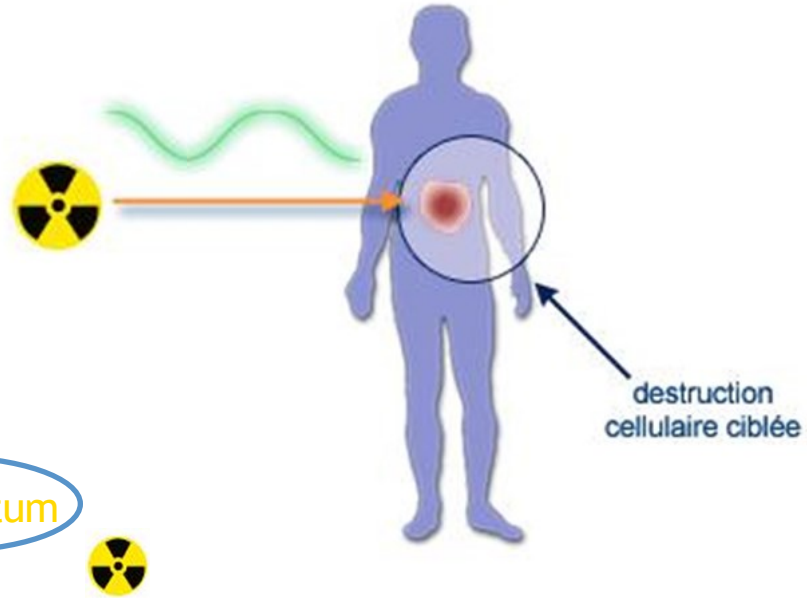
Fréquence des nouveaux cas de cancer estimé en 2018



Total : 18 078 957 personnes

WHO Global Cancer Observatory

Principe de la radiothérapie

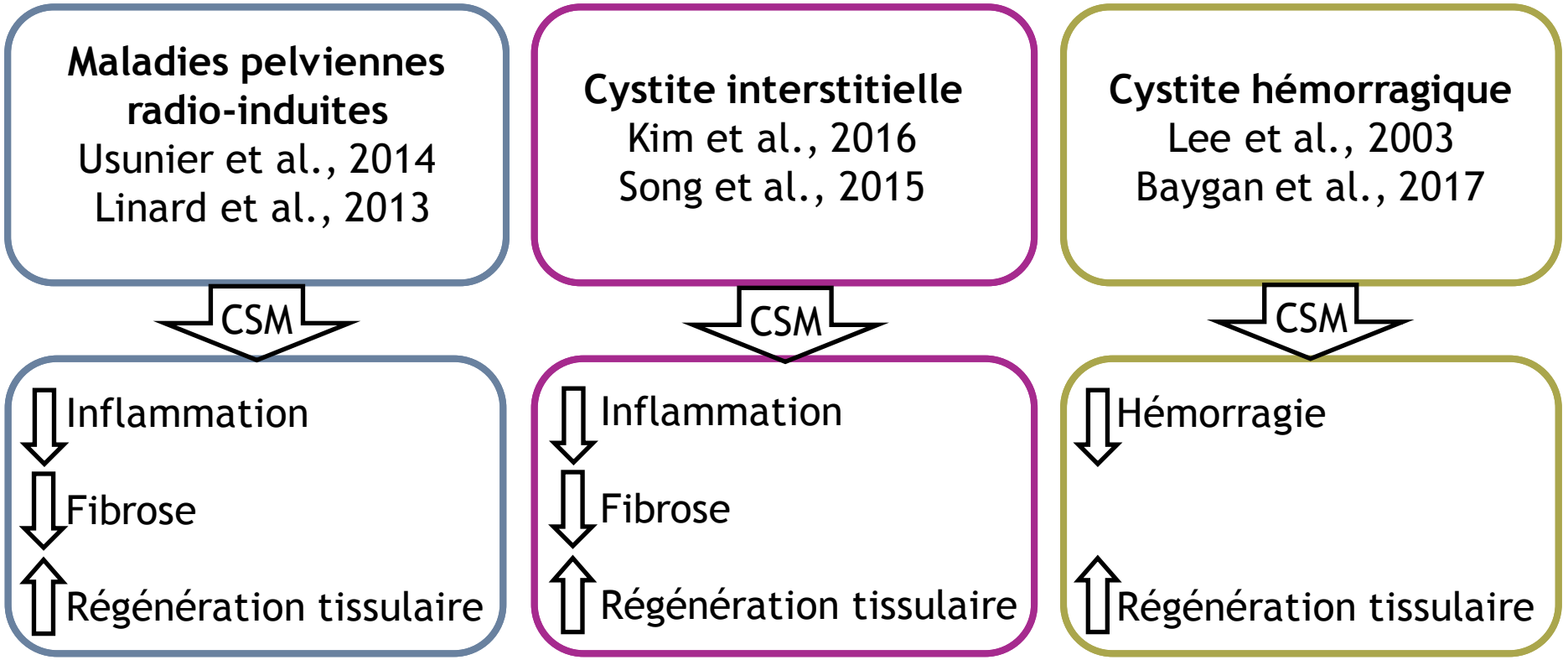


Radiothérapie :

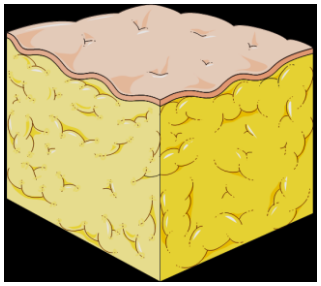
- Canal anal
- Col de l'utérus
- Endomètre
- Vulve
- Prostate

→ Organe à risque : Vessie

Thérapie cellulaire par les cellules souches mésenchymateuses (CSM) des cystites et maladies pelviennes radio-induites



Injection des cellules souches mésenchymateuses



Tissu adipeux

Isolement
Purification
Culture

Injection par intraveineuse

3 injections espacées de 2 semaines
5 millions de CSMs par injection

Grade de la cystite radique

Tableau II. Cystite radique : critères tardifs de toxicité génito-urinaire RTOG/EORTC.

Grade 0 asymptomatique

Grade 1

Dysurie : légère

Hématurie : microscopique

Fréquence : / 2 h

Grade 2

Dysurie : modérée

Hématurie : intermittente

Fréquence : / 1 h

Grade 3

Dysurie : sévère

Hématurie : fréquente

chirurgie mineure e.g. coagulation

Fréquence : / 0,5 h

Capacité vésicale : réduction, 150 cc

Grade 4

Hématurie : cystite hémorragique sévère

Capacité vésicale : vessie rétractée (< 100 cc)

Grade of hemorrhagic cystitis

Table 1 | RTOG/EORTC grading of hematuria events

Hematuria morbidity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Acute hemorrhagic radiation cystitis (RTOG scale)	NA	NA	Gross hematuria with or without clot passage	Hematuria requiring transfusion	Death from uncontrolled hematuria
Late hemorrhagic radiation cystitis (RTOG/EORTC scale)	Minor telangiectasia (microscopic hematuria)	Generalized telangiectasia (macroscopic hematuria)	Severe generalized telangiectasia (macroscopic hematuria)	Severe hemorrhagic cystitis	Death from uncontrolled hematuria

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; RTOG, Radiation Therapy Oncology Group.

Traitement:

Intravesical instillation :
- Aluminium
- Formalin
- Alun
- Pentosan polysulfate

Traitement hyper bar

Smit SG, Heyns CF. Management of radiation cystitis. Nat Rev Urol. 2010 Apr;7(4):206-14. doi: 10.1038/nrurol.2010.23. Epub 2010 Mar 9. Review. PubMed PMID: 20212517.

Introduction: Side effects and treatment

Treatments :

Oral or parental agents

- Sodium pentosan polysulfate
- Tetrachlorodecaoxide
- Pentoxifylline

Hematuria

Low and very short-term effects

Cystoscopy

- Fulguration
- Botulinum toxin

Hematuria

Low and very short-term effects

Intravesical installation

- Aluminum salts
- Silver nitrate
- Formalin

Hematuria

Pain

No effect after stopping treatment

Rigaud et al., 2010

Introduction: Side effects and treatment

Treatment :

Hyperbaric oxygen therapy (HBOT)

Objective ↑ Oxygen levels →

- ↑ Regeneration
- ↓ Hypoxia
- Hematuria

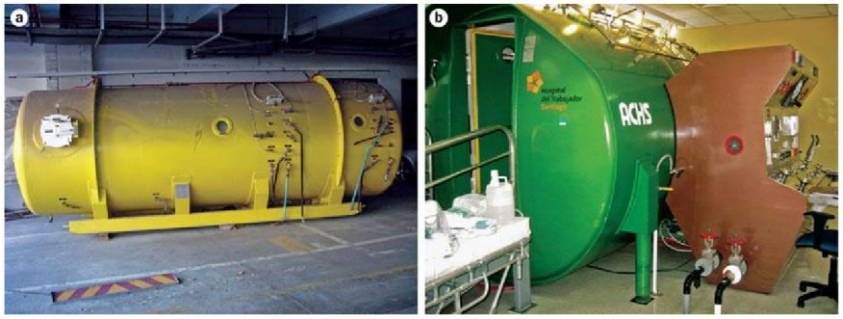


Figure 1 Hyperbaric oxygen chambers
a | Newly delivered hyperbaric chamber prior to installation. **b** | Hyperbaric oxygen chamber with control panel.
Smit and Heyns, 2010

↓

30–40 sessions, 100% oxygen, for 80–90 min, 2 months

↓

75% improvement within 6 months

Disadvantage

- → Long, adequate and rare equipment, patient monitoring
- → Not very effective, effects over a few months, year

Need for a relevant model and curative treatments

Rigaud et al., 2010
Orcasson et al., 2019

Method of irradiation: Local bladder irradiation

Objective:

- Creation of a model of chronic radiation cystitis in rats

- New method of irradiation using SARRP

➔ Irradiator for small animals (similar characteristic to clinical models)

SARRP

- Small Animal Radiation Research Platform (SARRP, Xstrahl)

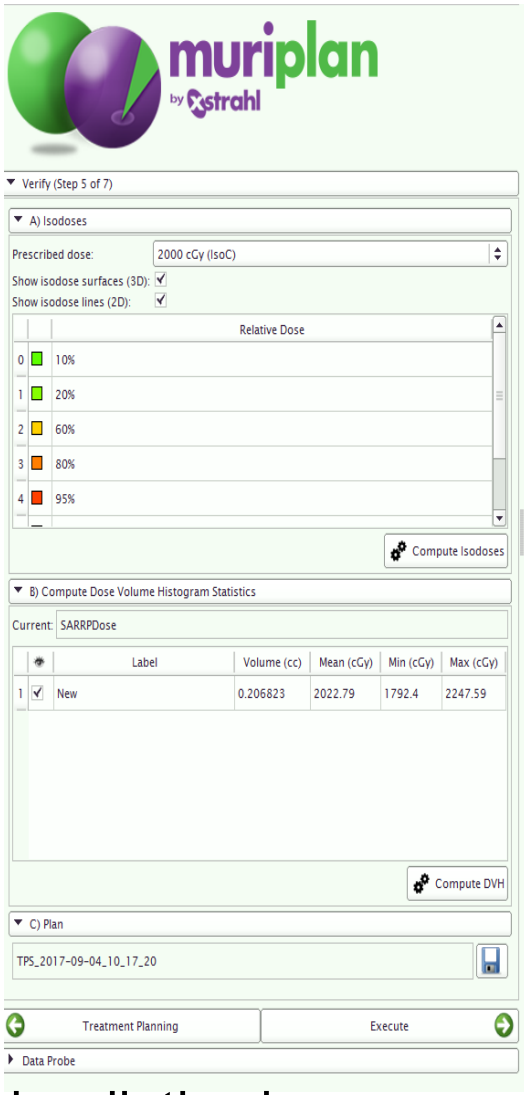
- Single or multi beam(s)

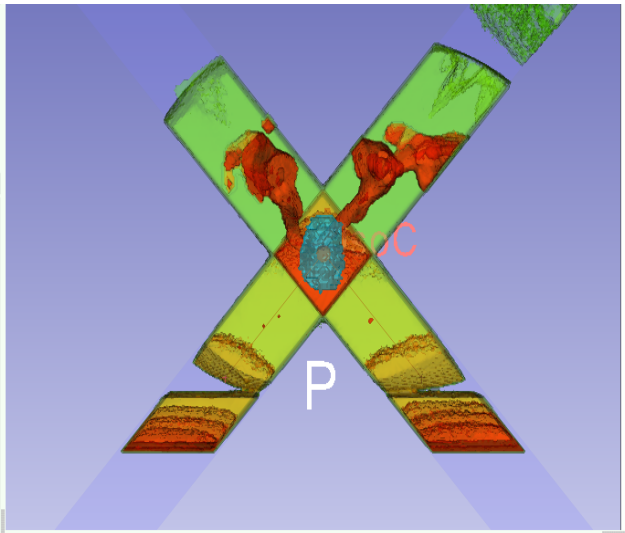
- Combined with scanner imaging and treatment plan software (MuriPlan) => stereotaxy

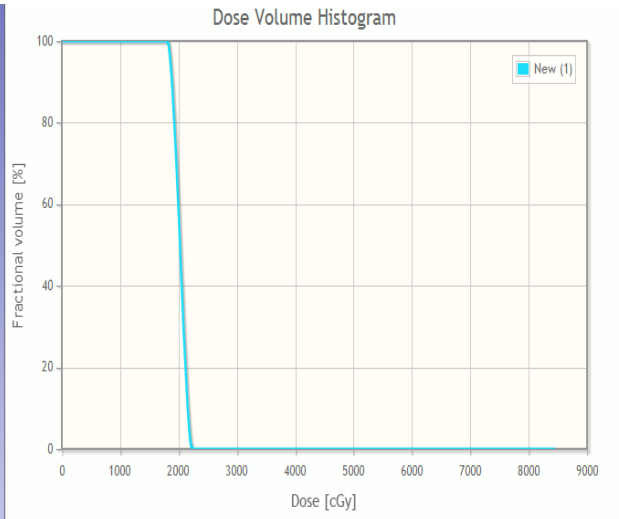
- 4 available field sizes: 10x10 mm², 7x7 mm², 3x3 mm² and Ø 1 mm

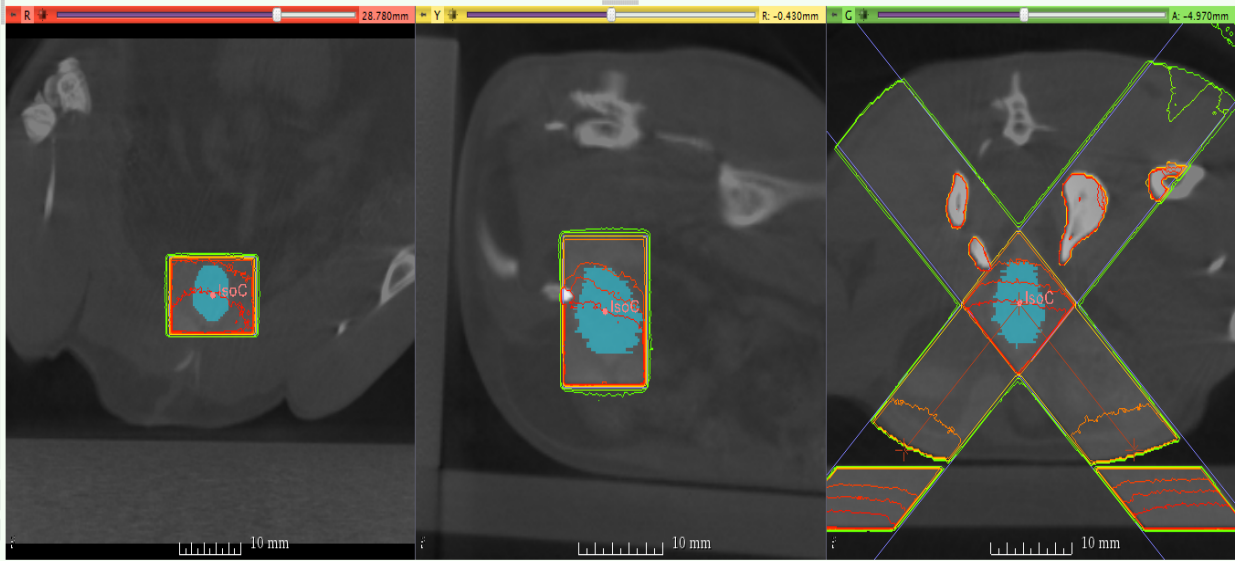
Picture of SARRP
Dr M. Dos Santos, LRAcc

Method of irradiation: Local bladder irradiation





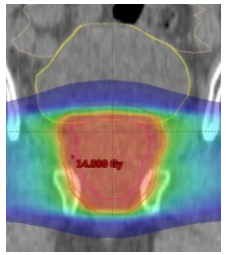


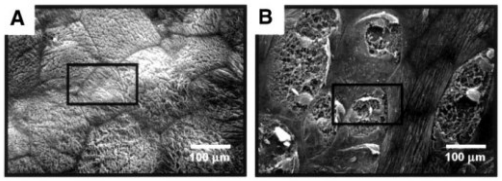


- 2 irradiation beams
- Maximized the dose on the bladder and minimized the dose on surrounding tissues

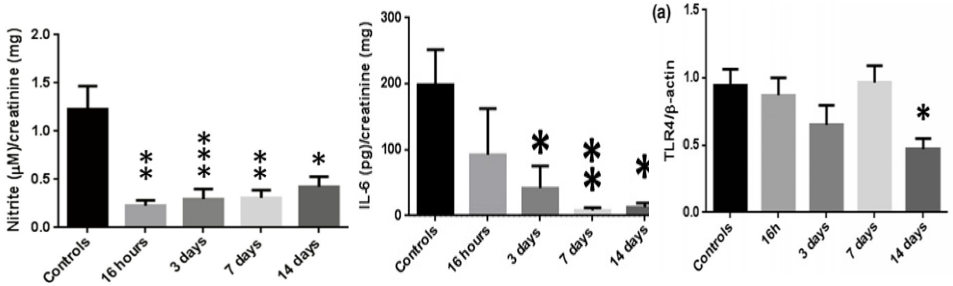
Pre-clinical model of CRC

In Rats receiving (irradiation totale vessie)





Jurado-Bruggeman et al.; 2017



✓ 35 Gy, Urothelium dammage 48h (Kanai et Eperly 2002)

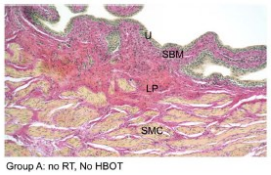
✓ 20 Gy killed 16 h to 14 days later (Giglio et al. 2012)

- Bladder irradiation increased the expression of IL-1 and collagen in the bladder, while TLR4 and IL-6 expressions were decreased in the urothelium concomitantly with a decrease in mast cells in the submucosa and urine levels of IL-6 and nitrite.

✓ 20 Gy all 29 days (Oscarsson 2017)

- Bladder irradiation increased the expression of 8-OHdG, SOD2, HO-1, NRFα, IL-10, TNF and tended to increase TGF-β

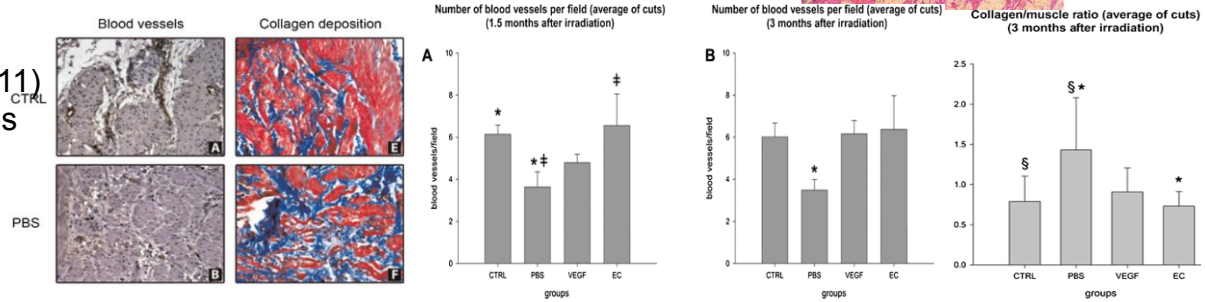
29 days Urothelium, SBM=Submucosa, LP=Lamina Propria, SMC=Smooth Muscle Cell layer



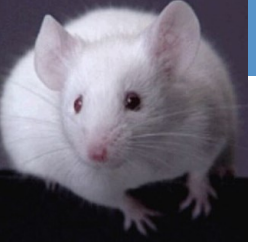
No significant macro or microscopically changes in the urinary bladder could be observed by bladder irradiation

✓ 20Gy killed 1,5 and 3 months (Soler 2011)

- 1,5 month vascular abnormalities
- 3 months collagen deposition



✓ 20 Gy all exhibited small and contracted bladders 6 months after treatment (Vale JA 1993)



Pre-clinical model of CRC

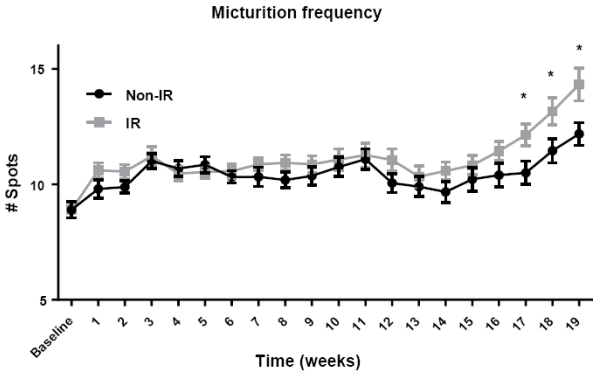
In mice receiving

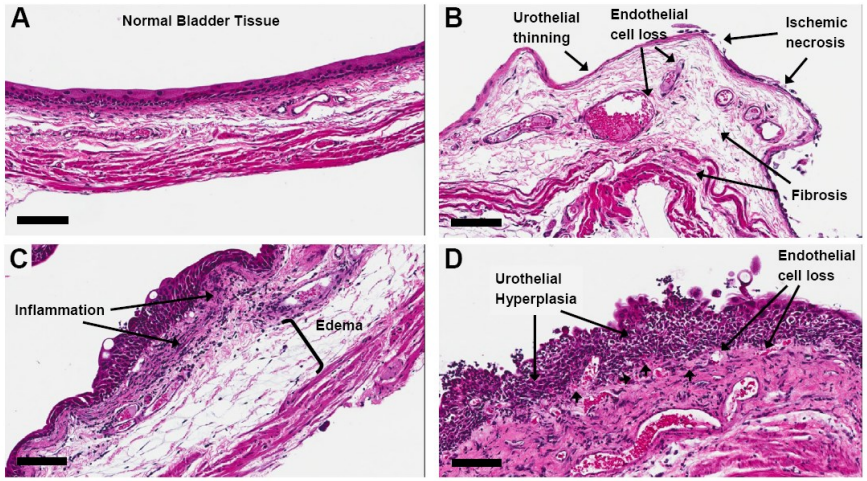
✓ 15 Gy , 20% developed fibrotic bladders,

✓ 15–20 Gy exhibited increased frequency and decreased bladder volume (Stewart 1991).

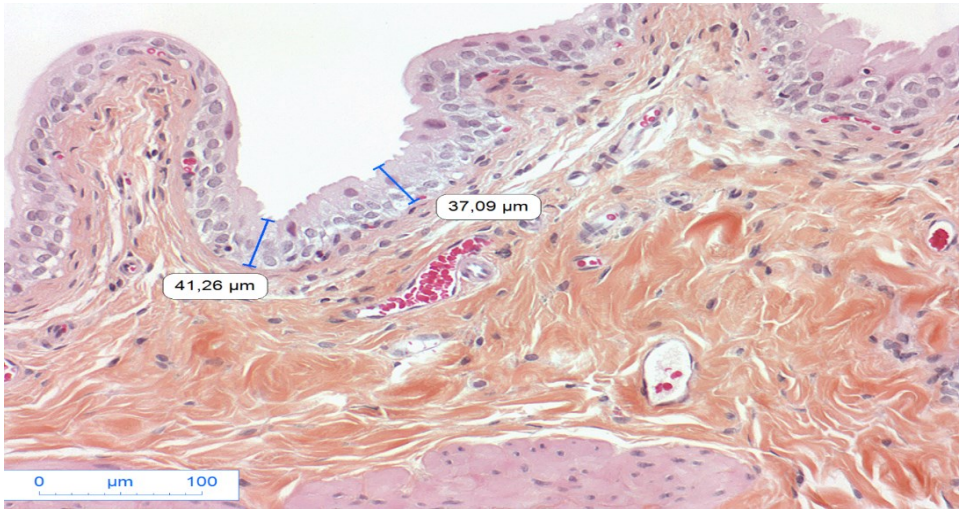
✓ 20 Gy SARP 2 faisceaux ((Zwaans et al. 2016)

- Starting at 17 weeks after treatment, micturition frequency was significantly higher
- Pathological changes include fibrosis, inflammation, urothelial thinning, and necrosis.
- At a site of severe insult, we observed telangiectasia, absence of uroplakin-3 and E-cadherin relocalization



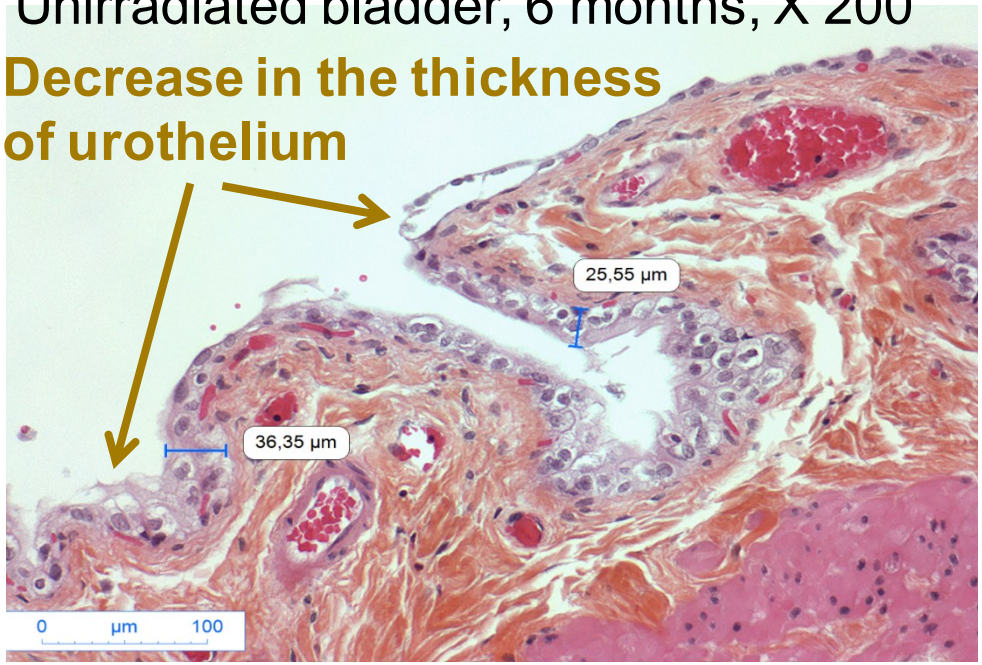


Tissue study: urothelium damages (HES)

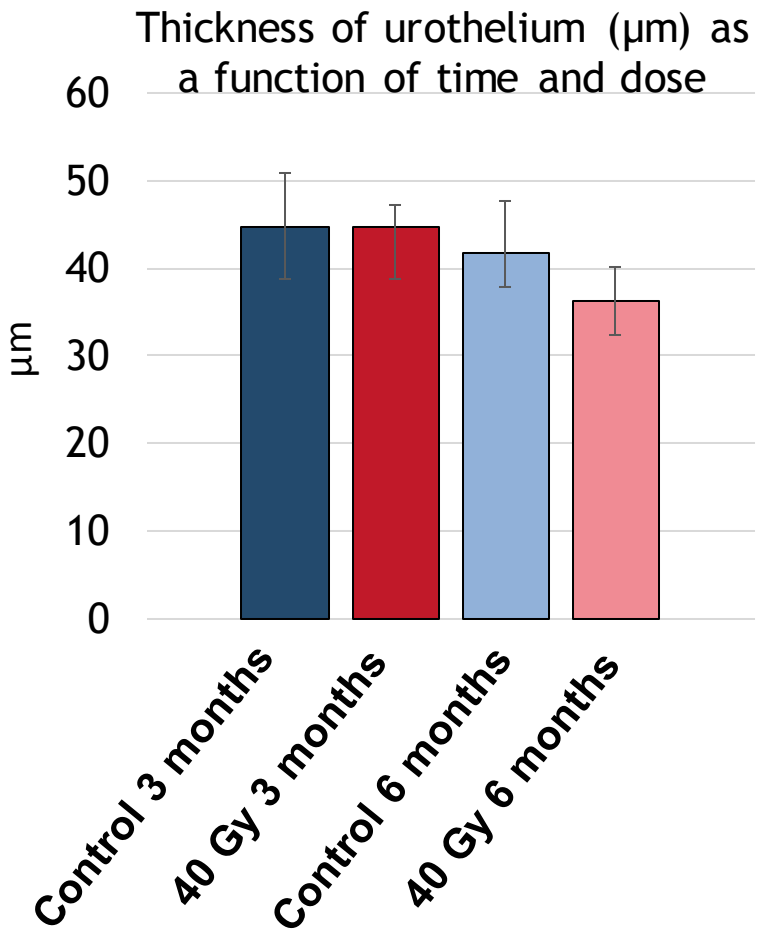


Unirradiated bladder, 6 months, X 200

Decrease in the thickness of urothelium



Bladder irradiated at 40 Gy, 6 months, X 200

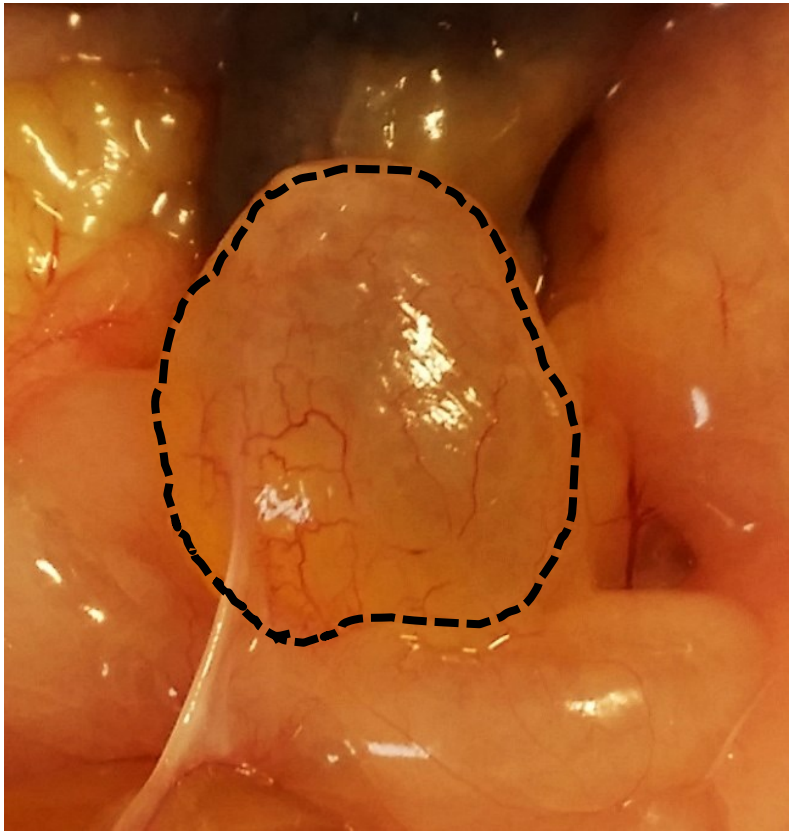


Degradation of the urothelium structure

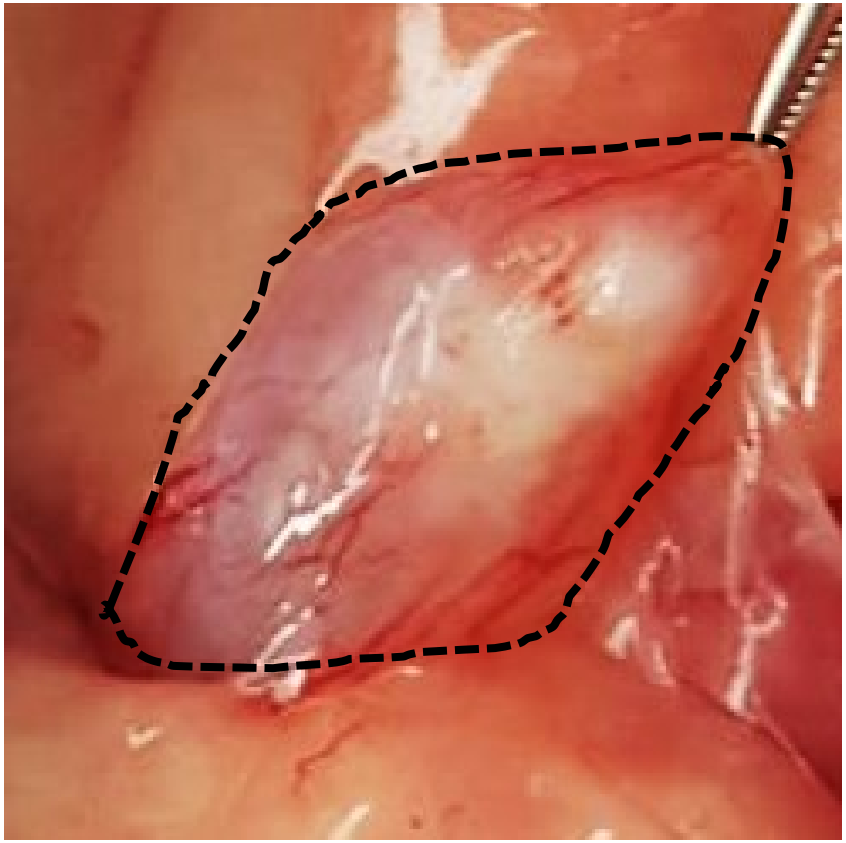
HES: Hematoxyline, Eosin, Safran

clement.brossard@irsn.fr
IRSN

Conclusions:



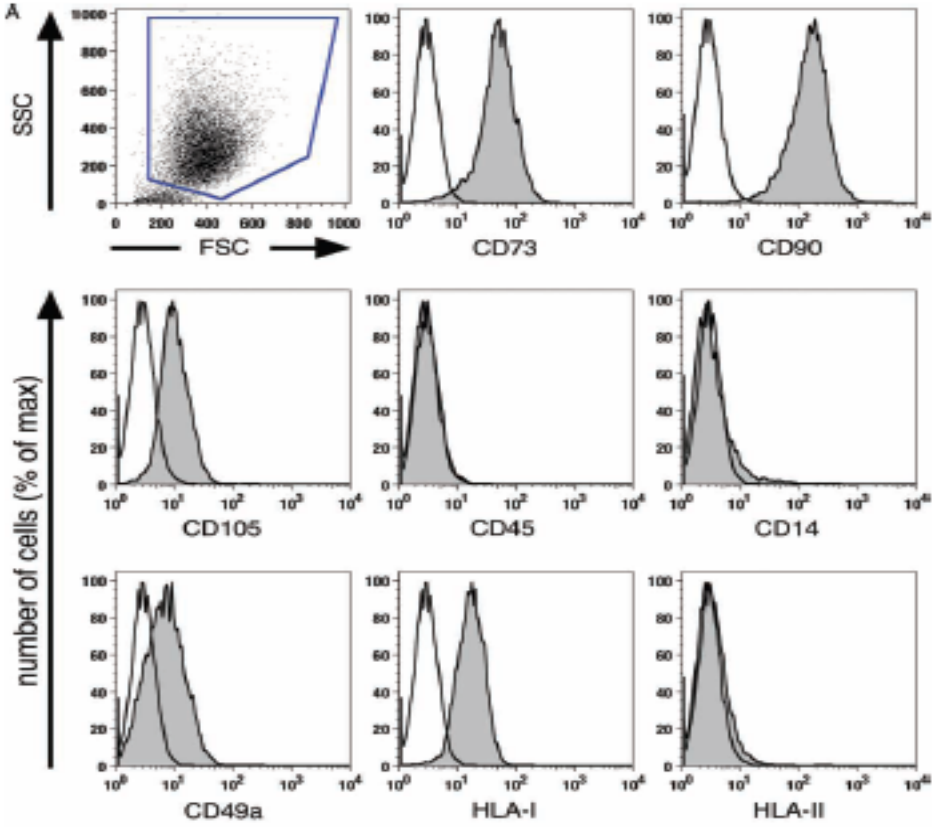
Unirradiated bladder, 10 months



Irradiated bladder, 40Gy 10 months

At 10 months, onset of apparent fibrosis in a few rats 40 Gy

Protocol injection: Characterization of MSCs



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Cytotherapy (2009) Vol. 11, No. 2, 114–128
informa healthcare

Characterization of bone marrow-derived mesenchymal stromal cells (MSC) based on gene expression profiling of functionally defined MSC subsets

Ariane Tormin[1], Jan C. Brune[1], Eleonor Olsson[1,2], Jeanette Valcich[1,2], Ulf Neuman[3], Tor Olofsson[4], Sten-Eirik Jacobsen[1,5] and Stefan Scheding[1,6]

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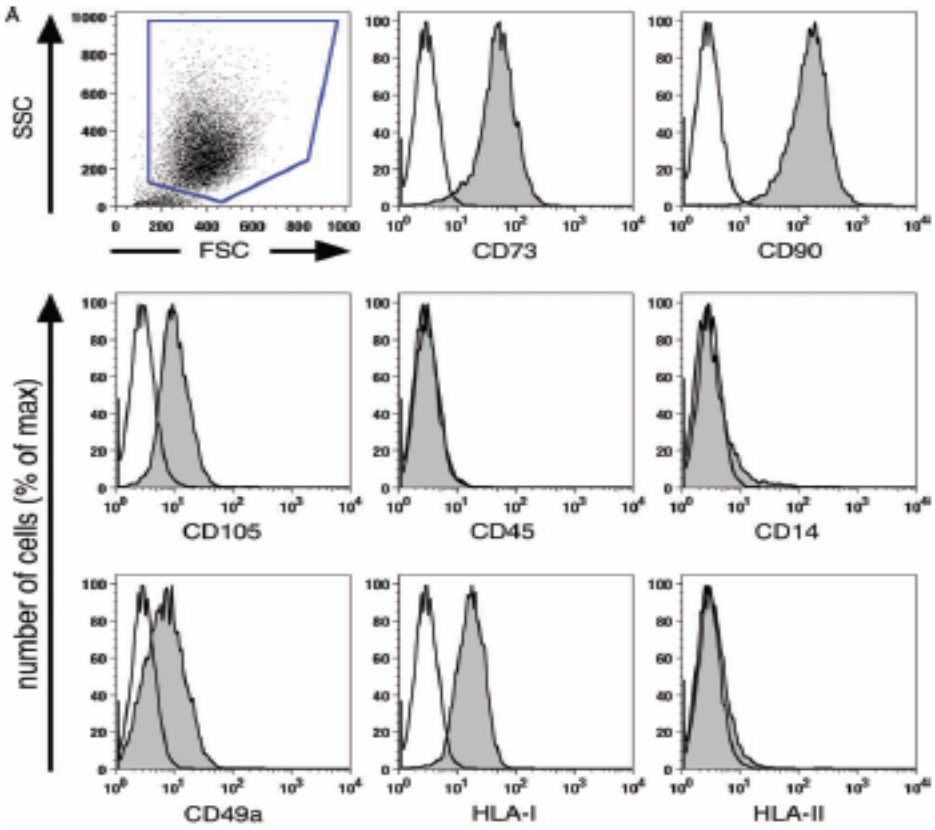

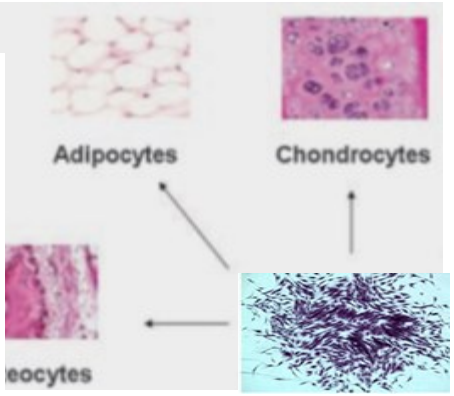

MSCs

Liu 2009

International Society for Cellular Therapy ISCT

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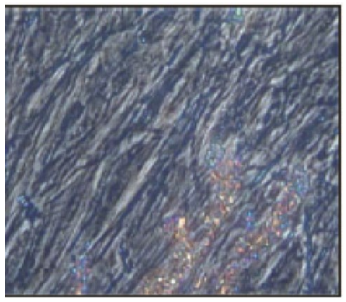
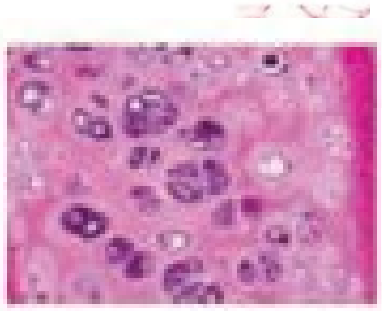
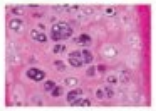
Protocol of injection: Characterization of MSCs

Chondrogenic differentiation
(Bleu Alcian)

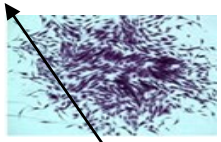




Chondrocytes



Chondrocytes

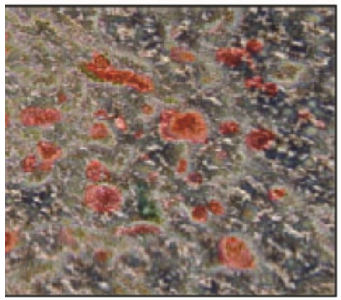


Osteocytes

MSCs

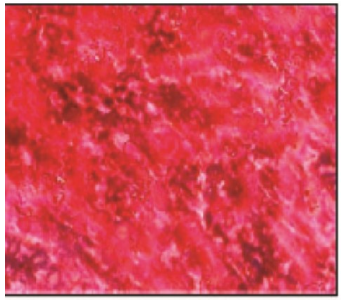
Liu 2009

Adipogenic differentiation
(Noir Soudan IV)



Adipocytes

Osteogenic differentiation
(Von Kossa et Alizarin)



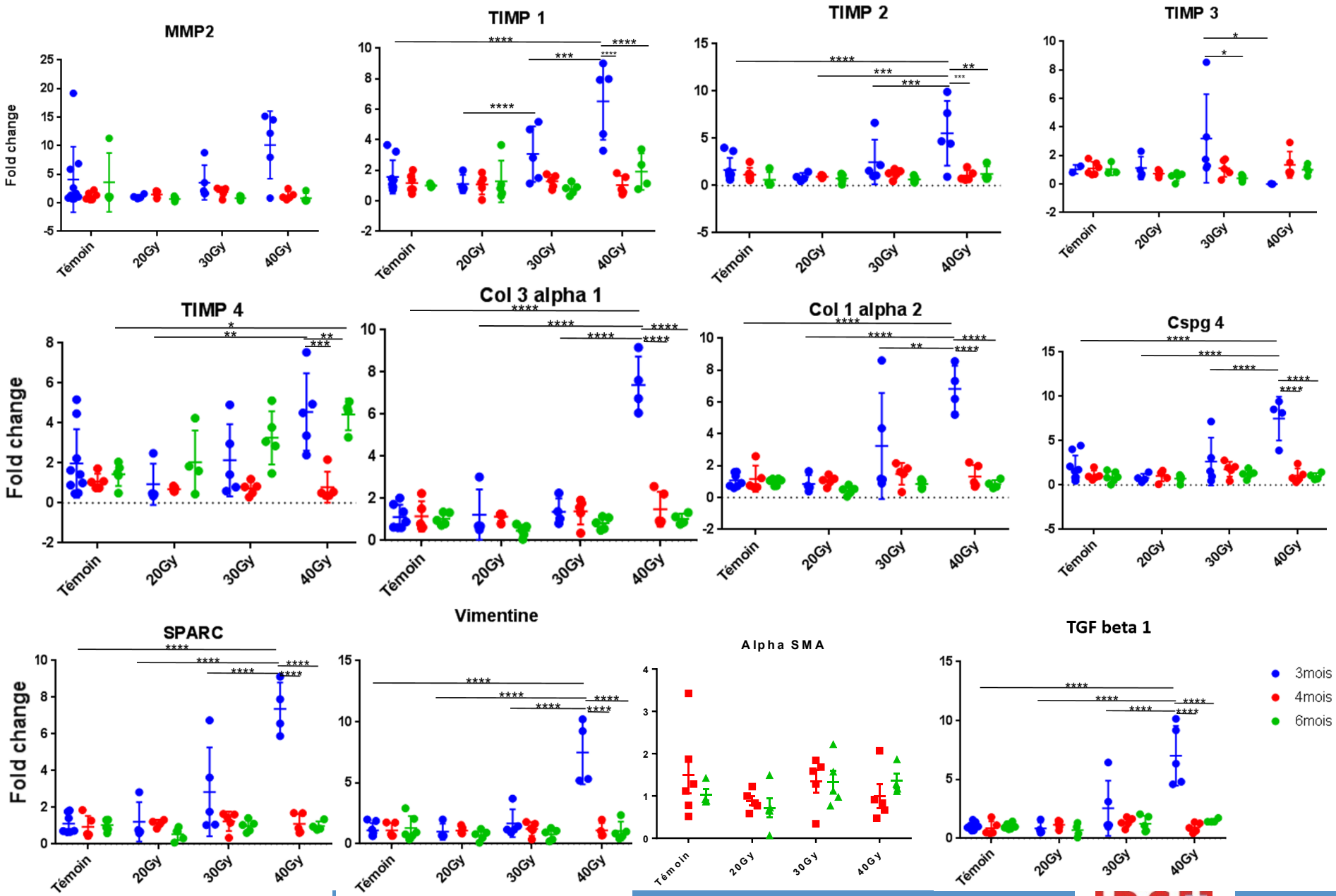
Osteocytes

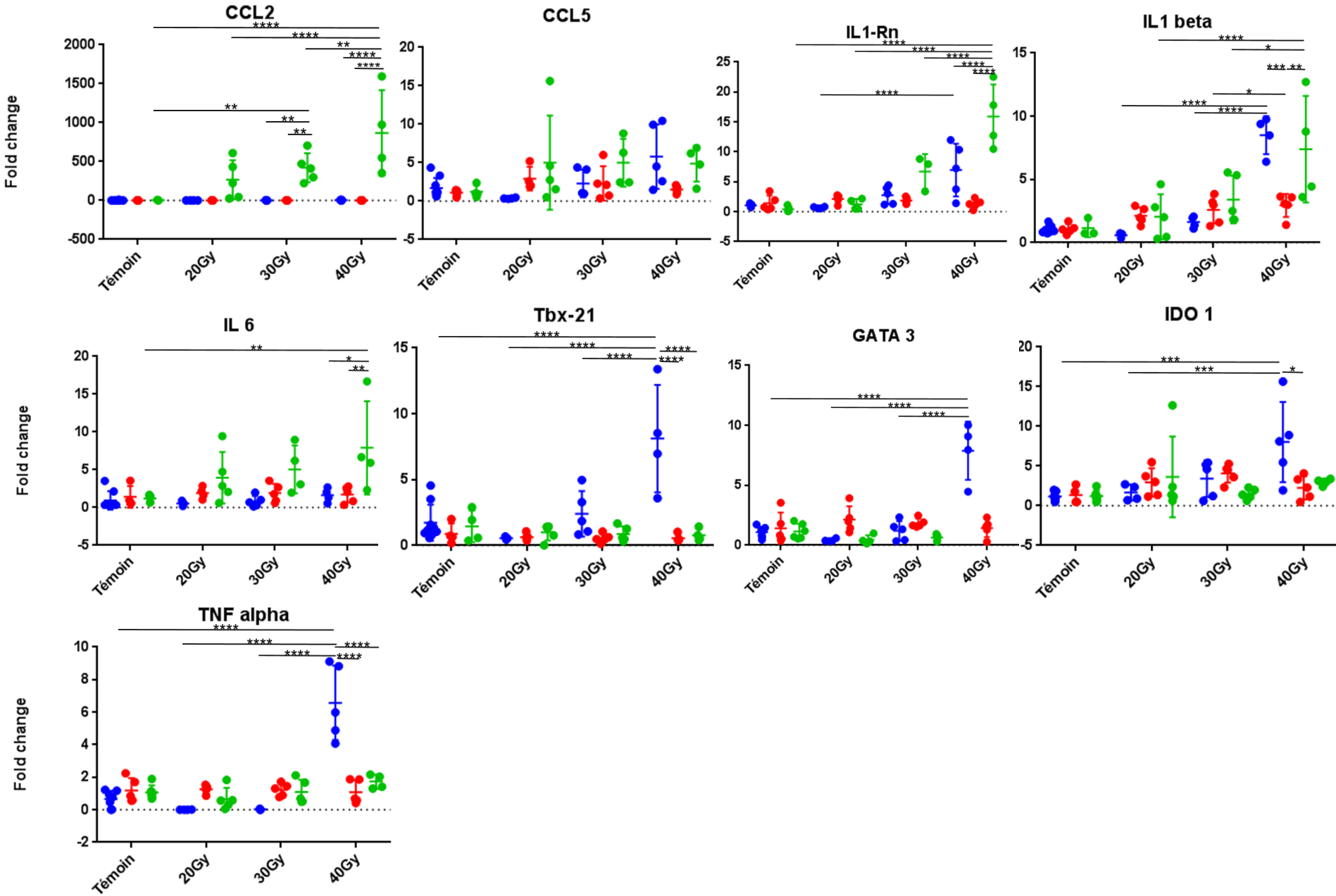
Mouiseddine et al., 2006

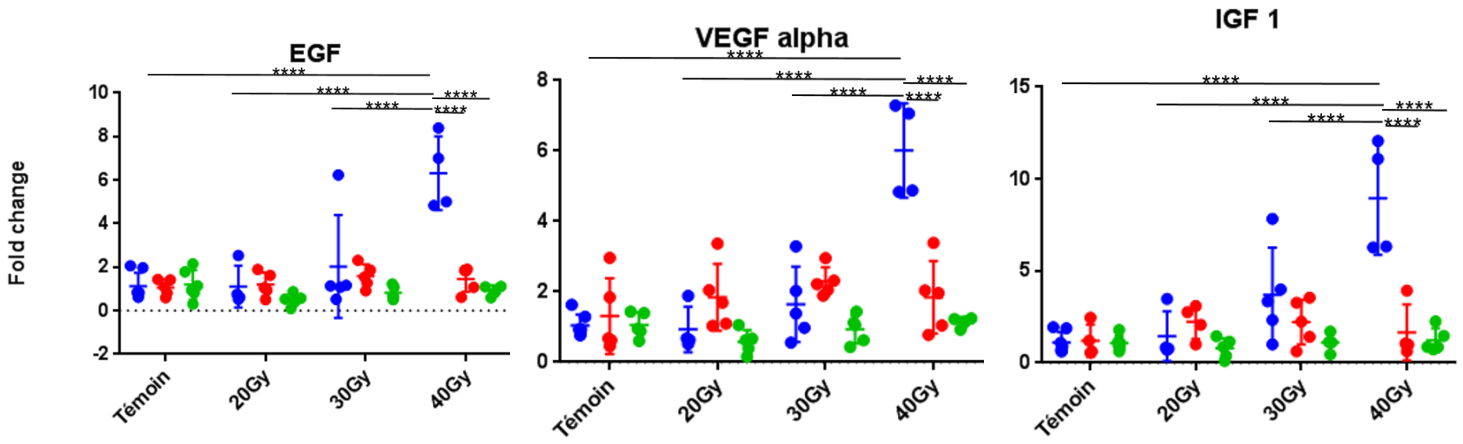
MSCs pathways of action on preclinical fibrosis models

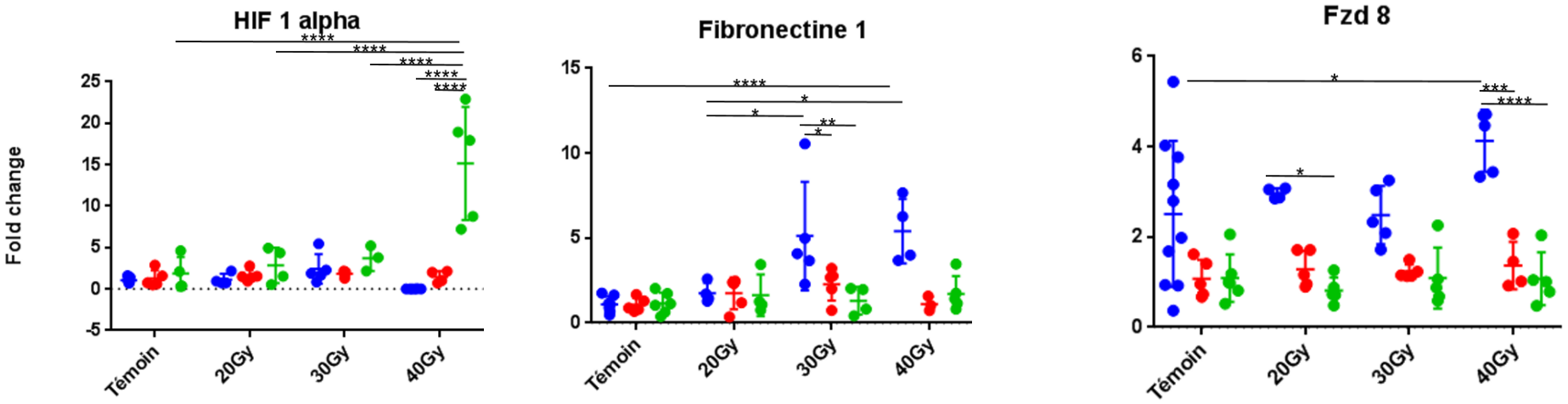
Mode of action	Mechanism	References
Immunomodulation	Decrease in inflammatory infiltration Polarity change of macrophages: M1 -> M2 Decrease in the expression and secretion of pro-inflammatory cytokines (TNF-α, IL-1, IL-6...) Decrease in apoptosis	Linard et coll., 2013 Zhou et coll., 2013 Semedo et coll., 2009 Horton et coll., 2013
Inhibition of the TGF pathway-β1	Decreased expression and secretion of TGF-β1 Decrease in the activation of the Smad channel Decrease in the number of myofibroblasts	Ueno et coll., 2013 Wu et coll., 2014 Jang et coll., 2014 Li et coll., 2013
Pro-angiogenic/anti-oxidant	Increase in the expression and secretion of antioxidant enzymes (NQO1, HO-1, SOD...) Pro-angiogenic effect: increase in VEGF and FGF-2 Augmentation de la prolifération des cellules endothéliales	Chen et coll., 2011 Kinnaird et coll., 2004 Niu et coll., 2008 Kinnaird et coll., 2004
Remodelage matriciel	Decrease in the expression and production of MEC components Rebalancing the MMP/TIMP balance	Moodley et coll., 2009 Mias et coll., 2009 Ebrahimi et coll., 2013

Usunier et al., 2013


MMP2
TIMP 1
TIMP 2
TIMP 3
TIMP 4
Col 3 alpha 1
Col 1 alpha 2
Cspg 4
SPARC
Vimentine
Alpha SMA
TGF beta 1
Fold change
Témoin
20Gy
30Gy
40Gy
3mois
4mois
6mois


CCL2
CCL5
IL1-Rn
IL1 beta
IL 6
Tbx-21
GATA 3
IDO 1
TNF alpha
Fold change
Témoin
20Gy
30Gy
40Gy


EGF
VEGF alpha
IGF 1
Fold change
Témoin
20Gy
30Gy
40Gy


HIF 1 alpha
Fibronectine 1
Fzd 8
Fold change
Témoin
20Gy
30Gy
40Gy

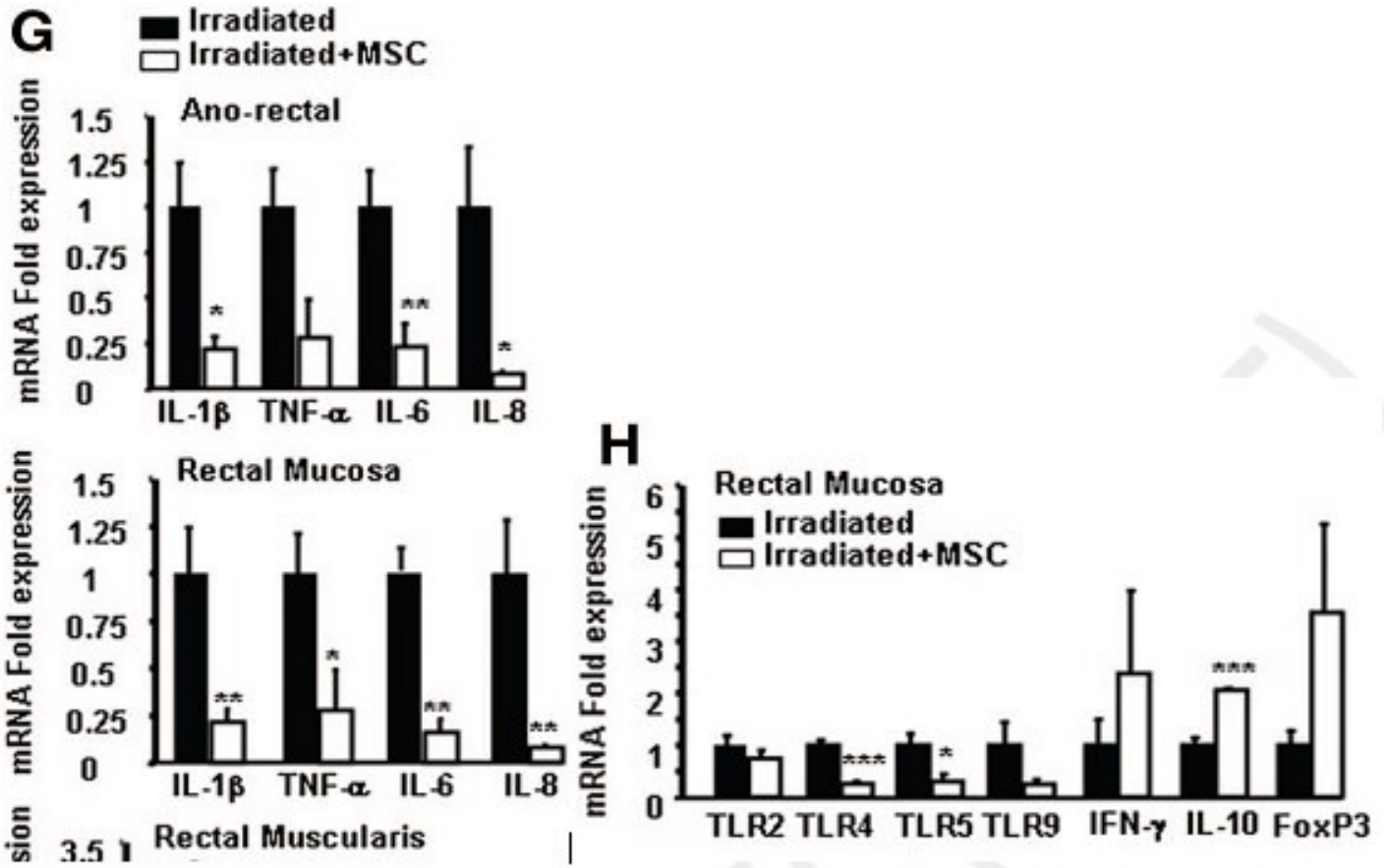
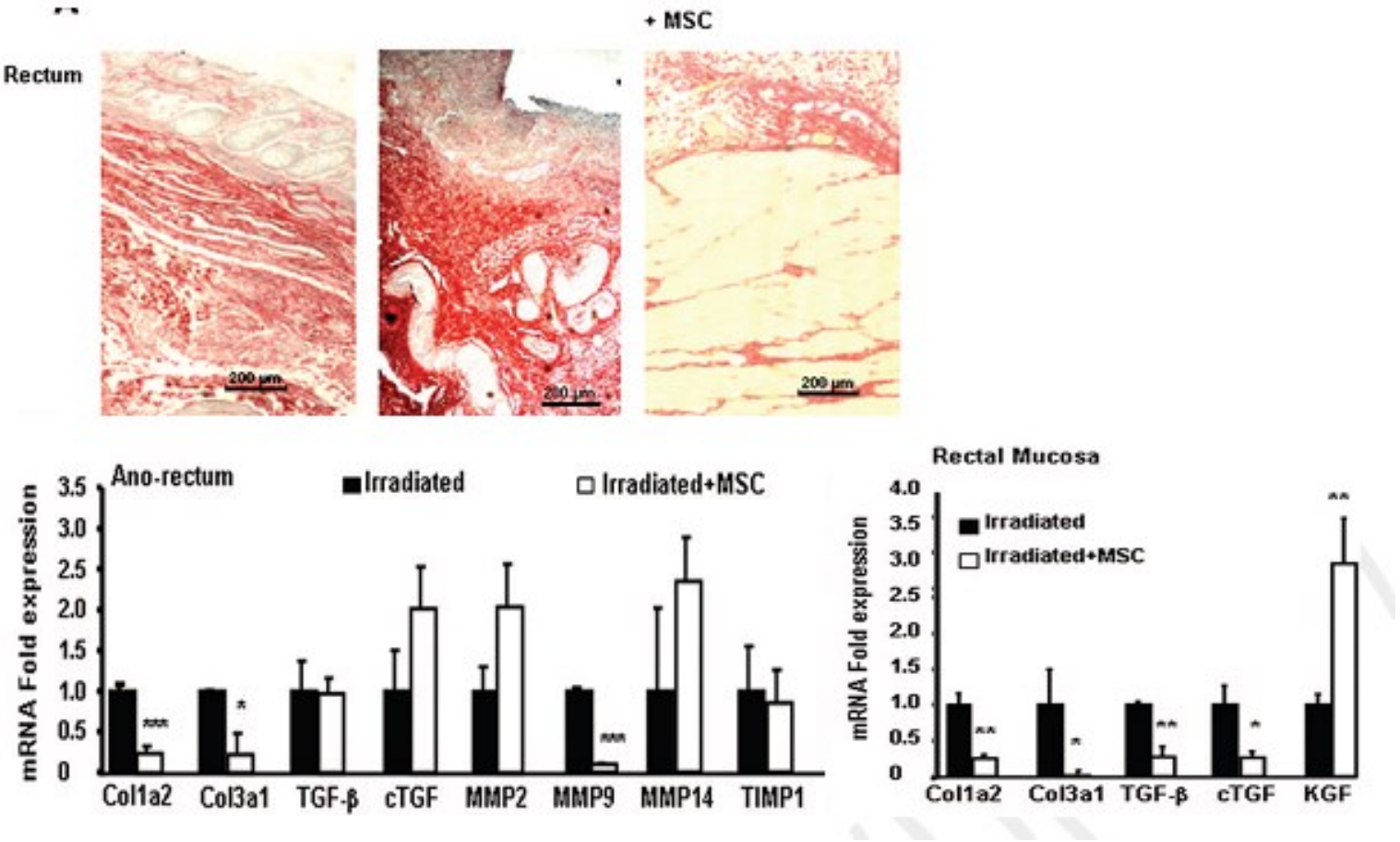


Figure 24. Experimental efficacy and anti-inflammatory effect of MSC injections.

Linard et al., 2013



Linard et al., 2013

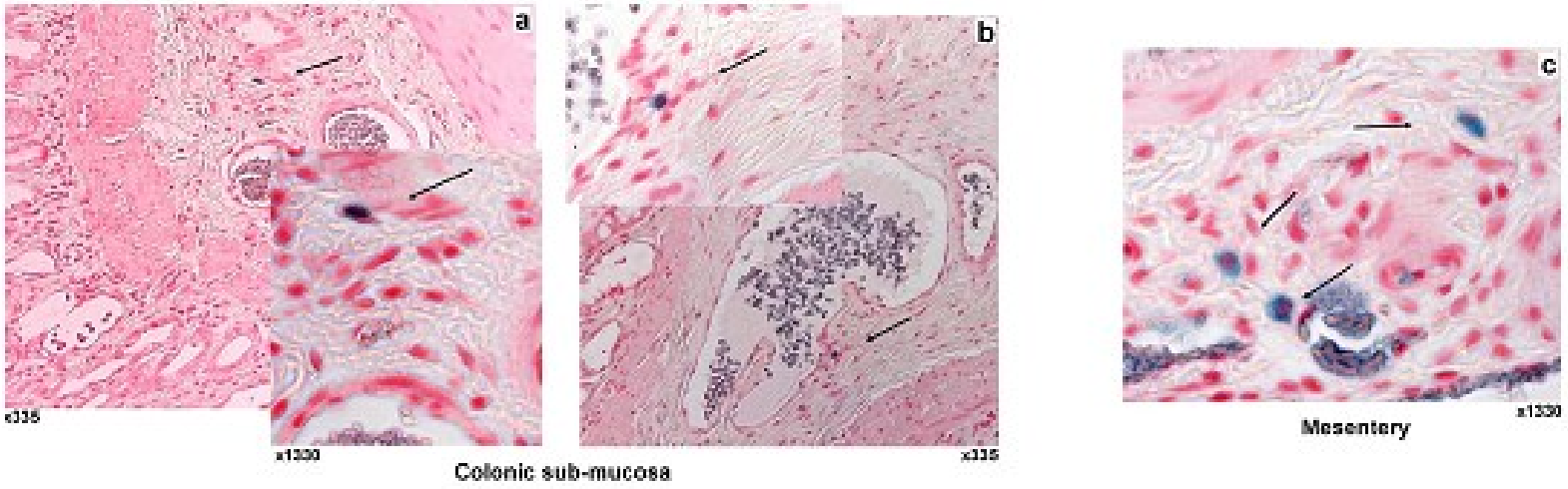


Figure 33: MSC engraft in colonic mucosa one week after injection and disappeared at 2 weeks

Intravenous injected MSC-GFP engraft in the colon. Detection of GFP-MSC (black arrow) in irradiated (a, b) colonic sub-mucosa or (c) mesentery, 1 week after injection using GFP-specific antibodies. Magnification, x335 and x1330.

Sémont et al., 2010

Matériel :

- Milieu MSCs : MEMα, SVF 20%, PS, Glut
- Milieu PBS, SVF 10%
- Collagénase type I (Sigma C0130-1g)
- 6 tubes 50ml avec collagénase à 0.1% dans du milieu de digestion : MEMα, PS, Glut
- Boite de pétri en verre

• Prélèvement de la graisse

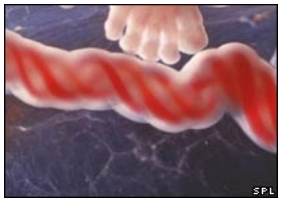
La graisse est prélevée au-dessus de la patte entre la peau et le péritoine, mise dans 5mL de PBS 1X.

• Digestion (x3)

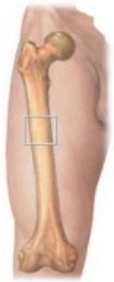
On coupe la graisse en petits morceaux, que l'on met dans du MEMα + collagénase à 0,1% (x2 tubes/digestion). Incubation **pdt 30 min à 37°C** avec agitation.
On récupère les cellules avec une filtration 100µm, la graisse non digérée est remise en MEMα + collagénase à 0,1%.
Sur les cellules filtrées, on ajoute du milieu contenant du SVF pour diluer la collagénase.
On effectue une centrifugation pour rassembler toutes les cellules, filtration sur 40µm et ensuite numération.
(4ml au 5è en bleu acétique)

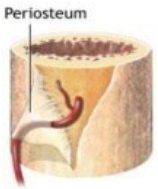
• Culture

P0 1000¢/cm² soit $0{,}150.10^6$¢/150cm² en milieu MSCs
CFU-F 1000¢/F25cm² en triplicat

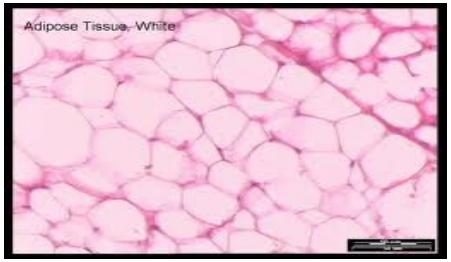


Umbilical cord
Wharton's jelly

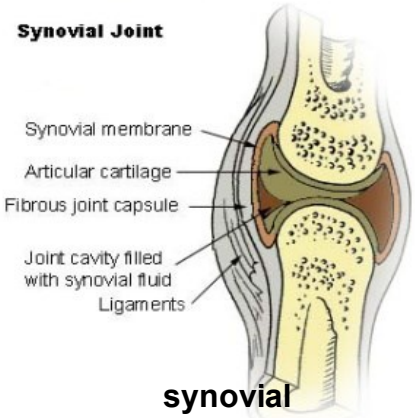




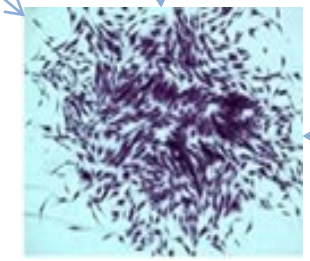
Bone marrow
periosteum



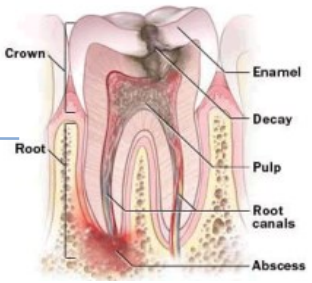
Adipose tissue



synovial
membranes



Sources of
MSCs



Dental pulp

MSC homing after intramuscular or intraveinous injection (0.5x10⁶ CSM) *(Vilata 2008)*

STEM CELLS AND DEVELOPMENT 17:993–1004 (2008)
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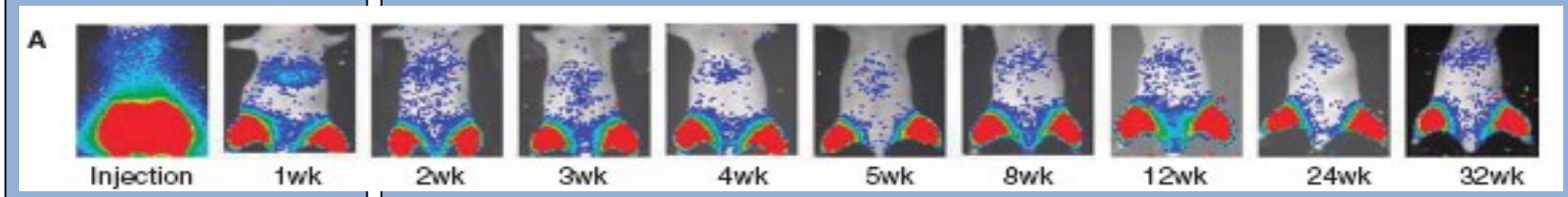
DOI: 10.1089/scd.2007.0201

Biodistribution, Long-term Survival, and Safety of Human Adipose Tissue-derived Mesenchymal Stem Cells Transplanted in Nude Mice by High Sensitivity Non-invasive Bioluminescence Imaging

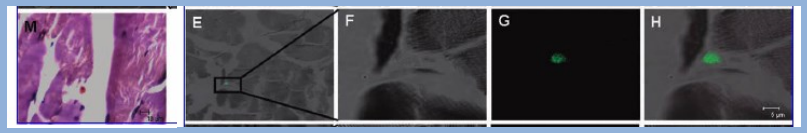
Marta Vilalta,[1] Irene R. Dégano,[1] Juli Bagó,[1] David Gould,[2] Mònica Santos,[2] Mariano García-Arranz,[4] Ramon Ayats,[5] Carme Fuster,[5] Yuti Chernajovsky,[2] Damián García-Olmo,[4] Nuria Rubio,[1] and Jerónimo Blanco[1]

Intramuscularly (IM) inoculated MSC.



75 % of MSC lost the first week

Number surviving cells remains stable over 32 weeks



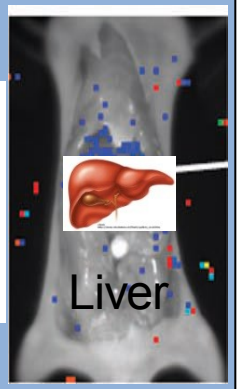
Histological localization of MSC

Tail vein (IV) inoculated MSC

MSC are first trapp in lung (*Schrepfer 2007*)

MSC first retained in lung Cleared after one week

1.5% of cells detected in abdomen (persisted 32 weeks)



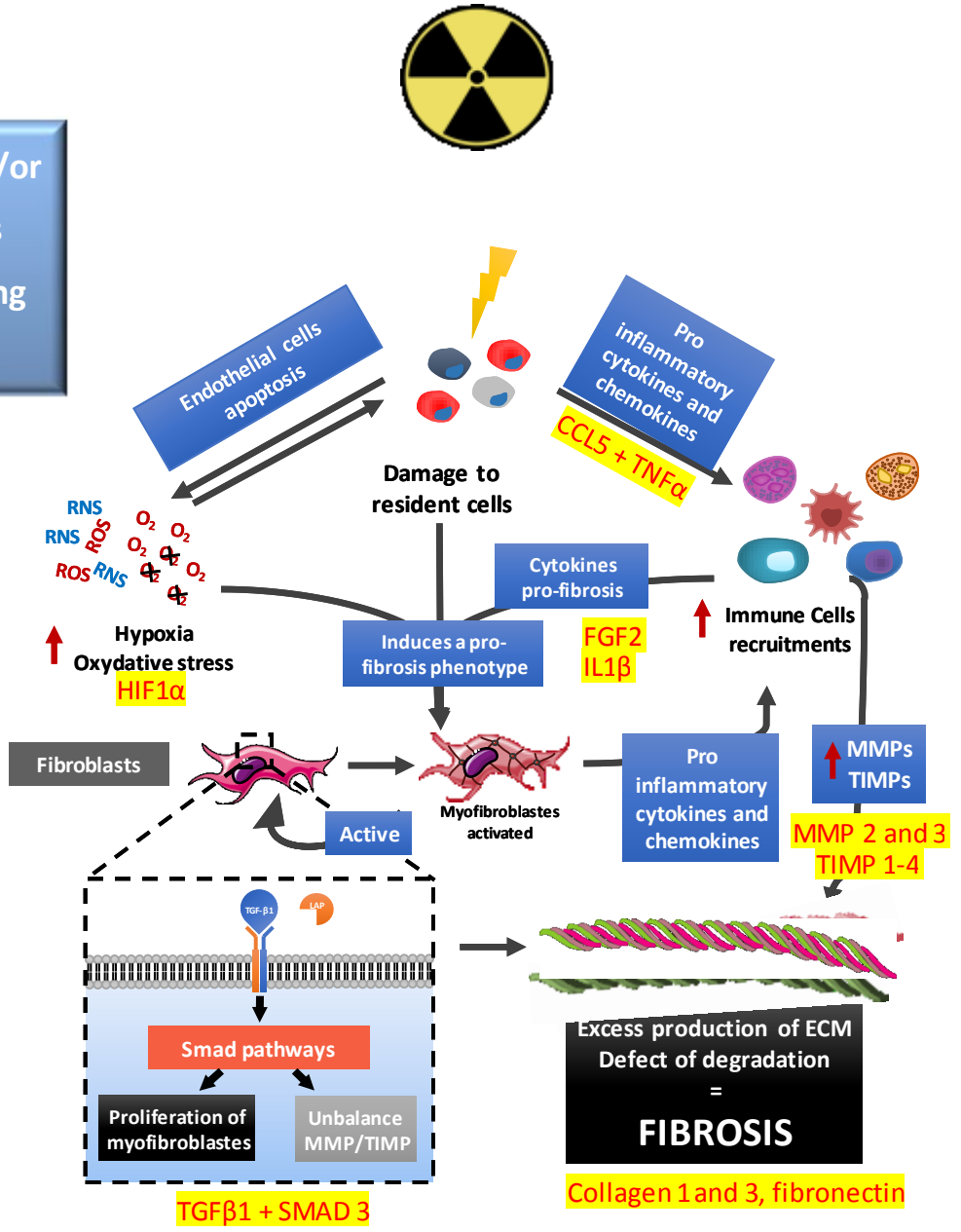
IV and IM Liver preferred target organ for colonization

" Fibrosis is defined by the overgrowth, hardening, and/or scarring of various tissues and is attributed to excess deposition of extracellular matrix components including collagen " *(Wynn TA, 2008)*

Cytokine pro fibrosis secreted following irradiation

Activation of extracellular matrix secreting cells

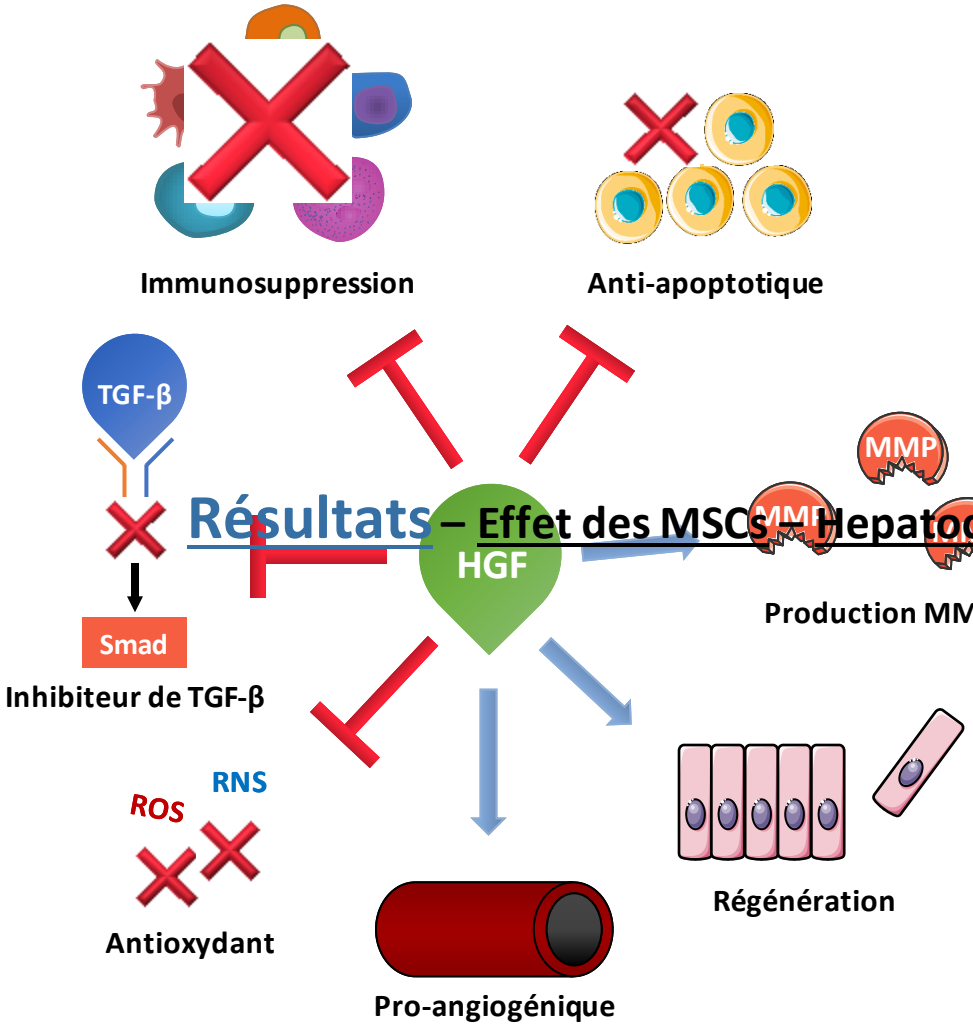
Imbalance of the accumulation/degradation of the ECM



HIF1α = results of M2

ECM: ExtraCellular Matrix

Résultats – Effet des MSCs : Hepatocyte Growth Factor - Propriétés



Hepatocyte Growth Factor (HGF)

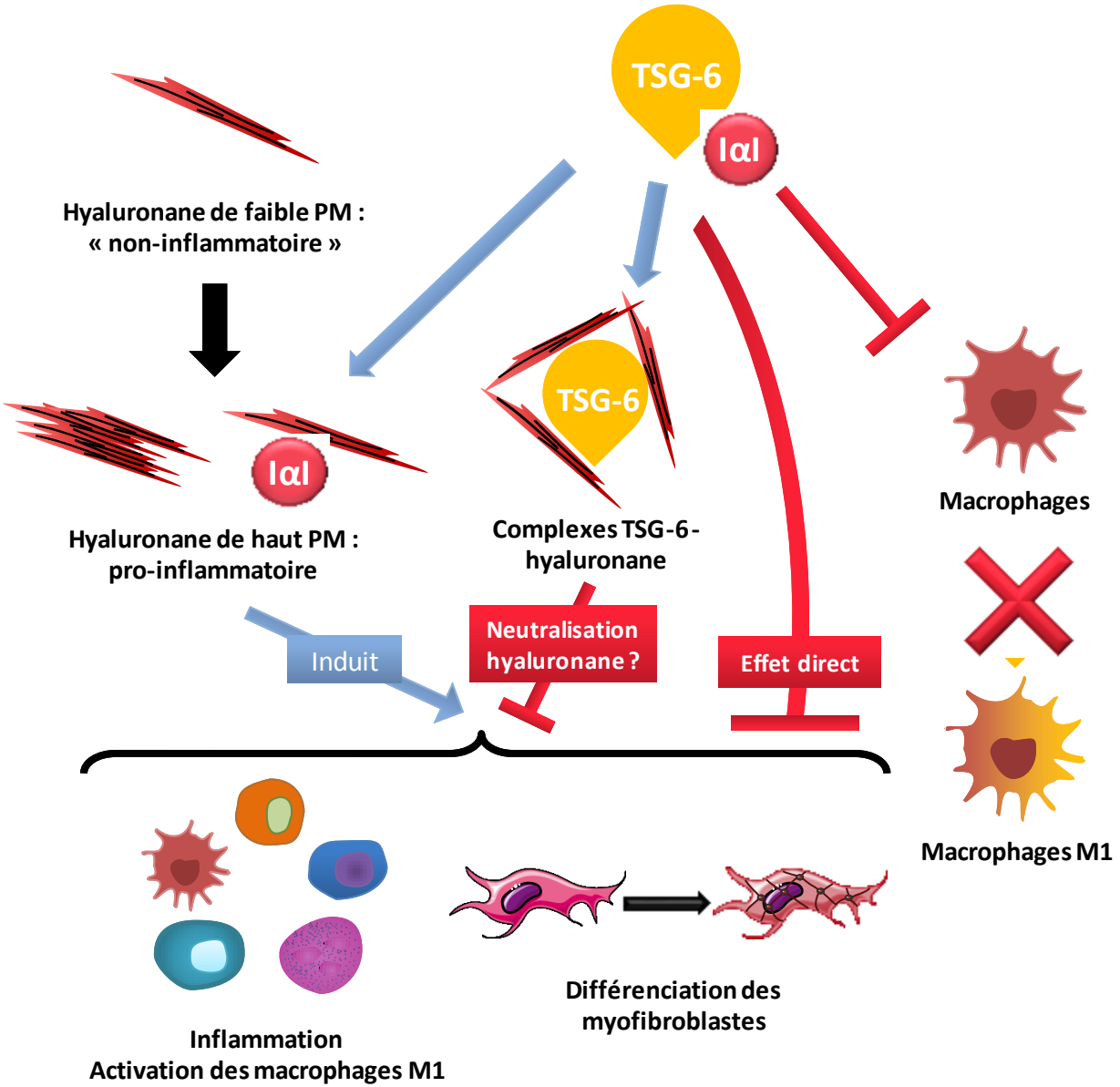
Facteur de croissance pléiotropique

Exprimé dans de nombreux tissus en cas de lésion

Pouvoir anti-fibrosant démontré

Sécrété par les MSCs dans plusieurs modèles de fibrose (rein, foie, poumon)

Implication du HGF sécrété par les MSCs lors de la fibrose colorectale radio-induite ?



TNF-stimulated Gene-6 (TSG-6)

Protéine immunomodulatrice

Exprimé lors de l'inflammation (induit par TNF-α)

Stimule/réduit l'inflammation

Sécrété par les MSCs dans plusieurs modèles de fibrose (rein, peau) : effet anti-fibrosant

Implication du TSG-6 sécrété par les MSCs lors de la fibrose colorectale radio-induite ?

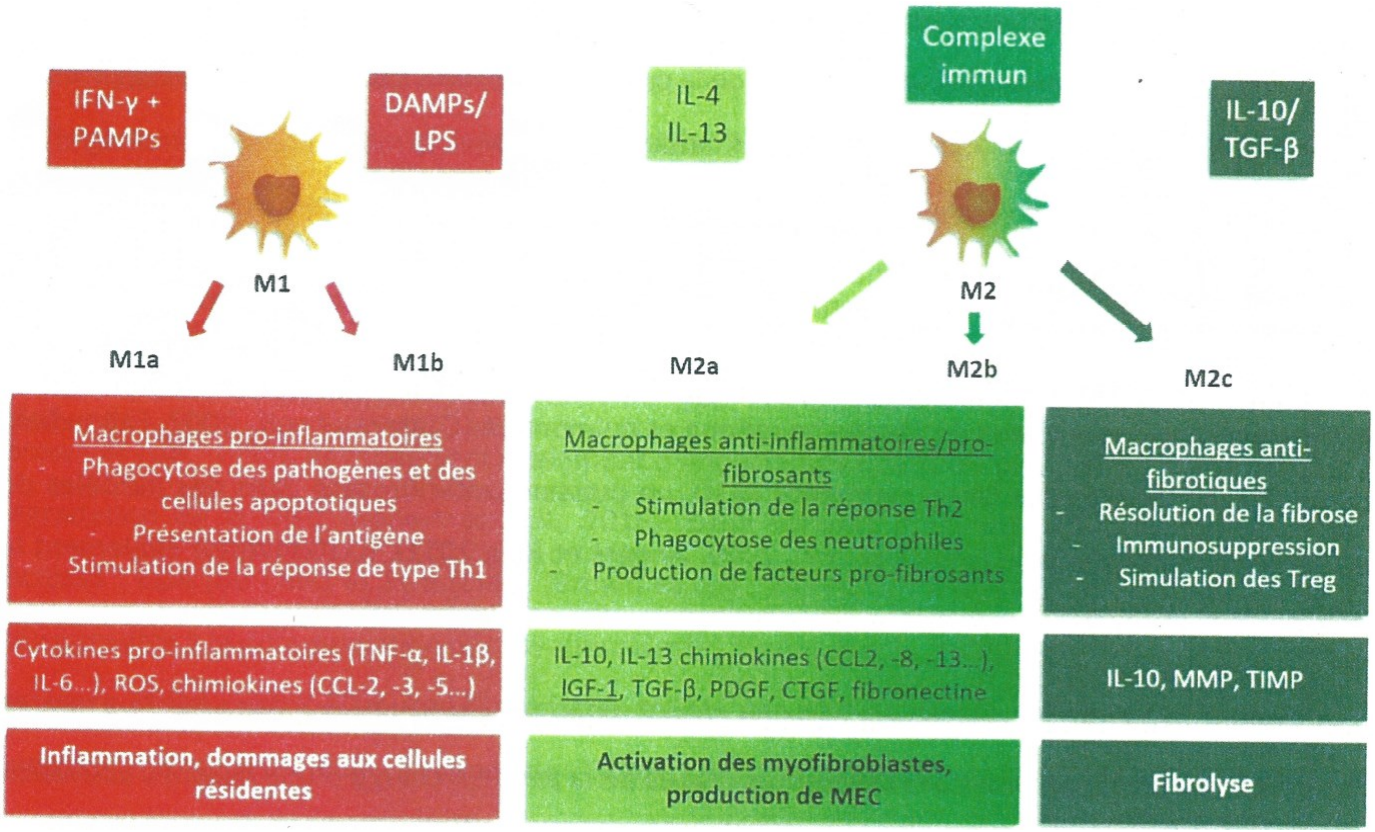


Figure 8 : Caractéristique des différents états de polarisation des macrophages.

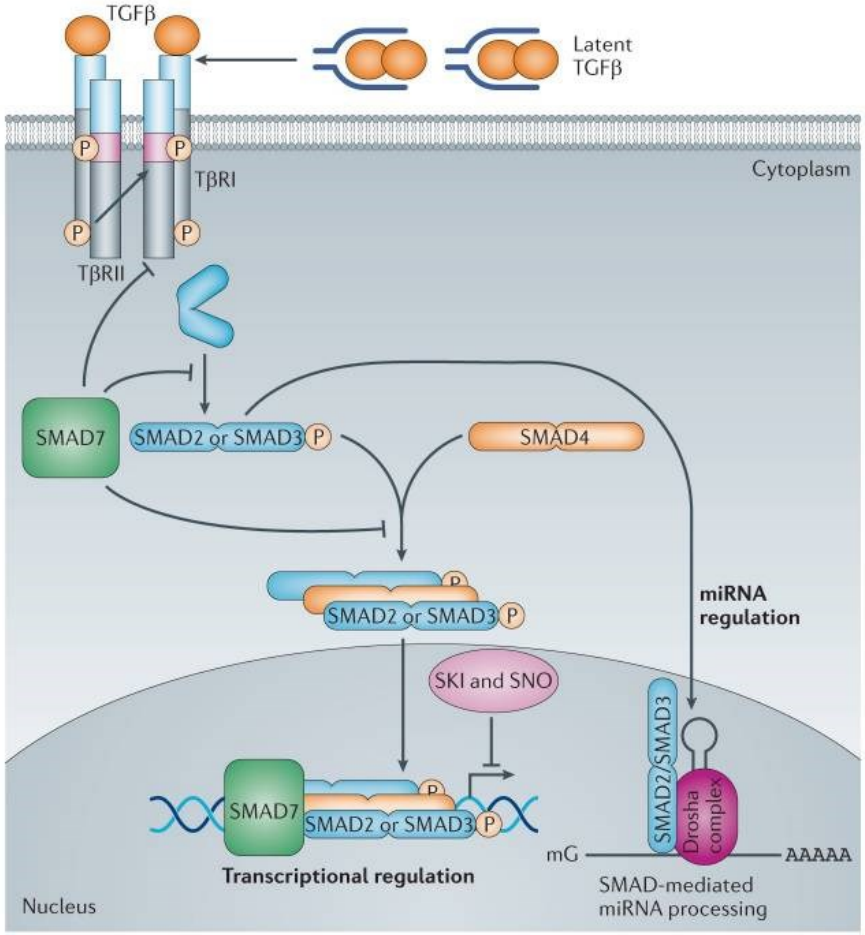
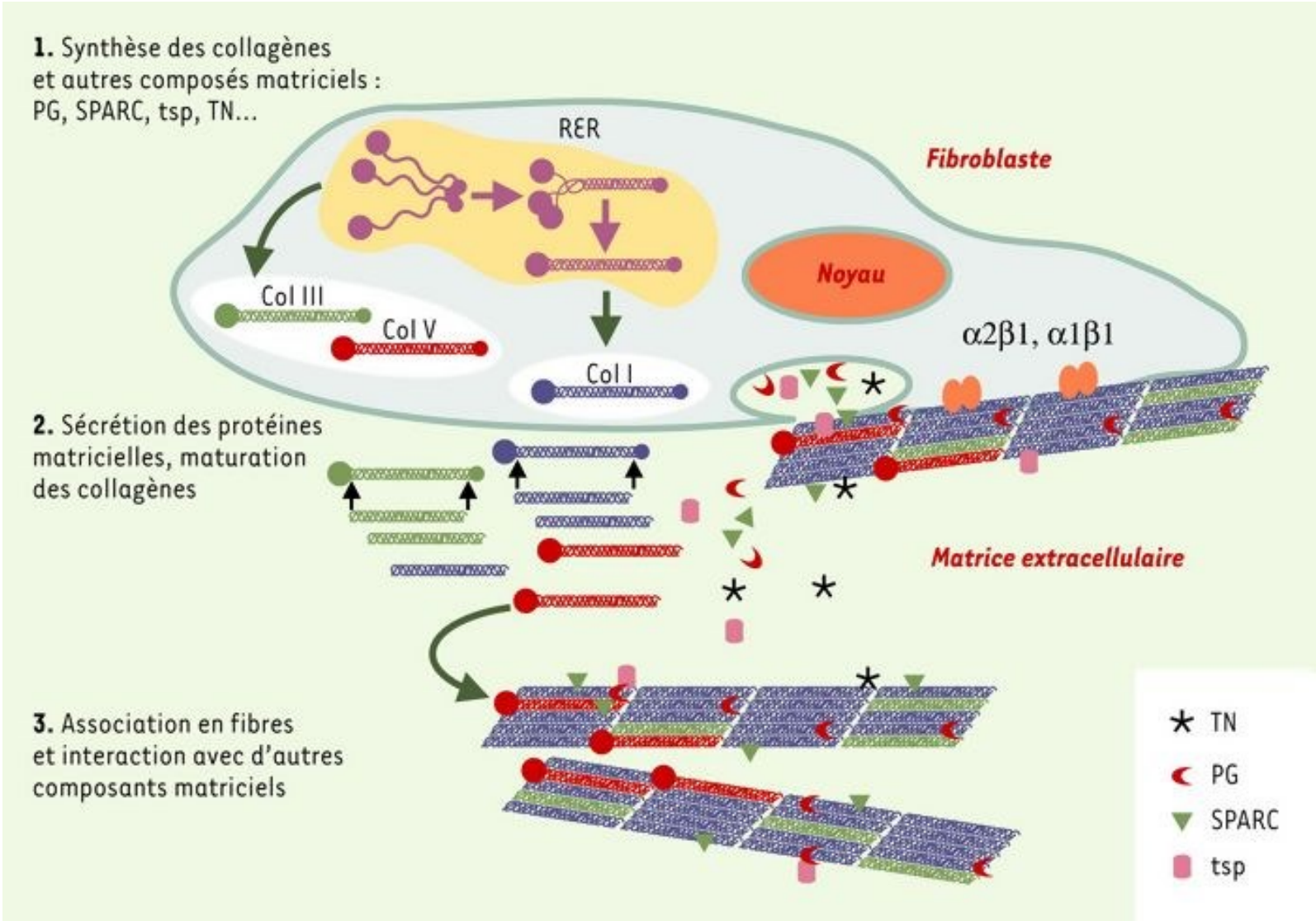
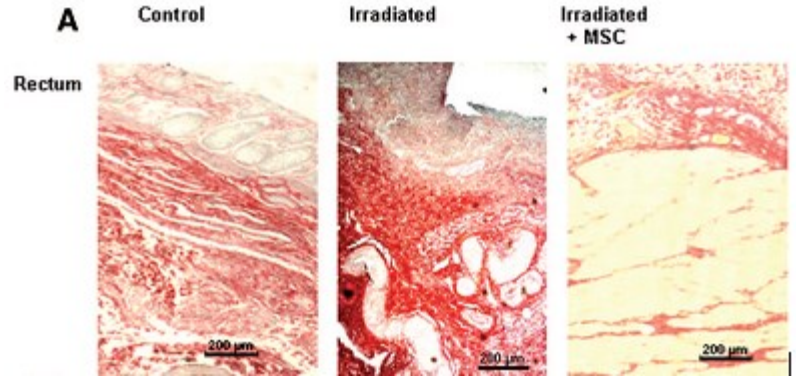


Figure: mécanismes d'activation et d'inhibition de la voie Smad (D'après Akhurst, 2012) (Akhurst and Hata, 2012)


1. Synthèse des collagènes et autres composés matriciels : PG, SPARC, tsp, TN...
RER
Fibroblaste
Noyau
Col III
Col V
Col I
α2β1, α1β1
2. Sécrétion des protéines matricielles, maturation des collagènes
Matrice extracellulaire
3. Association en fibres et interaction avec d'autres composants matriciels
TN
PG
SPARC
tsp

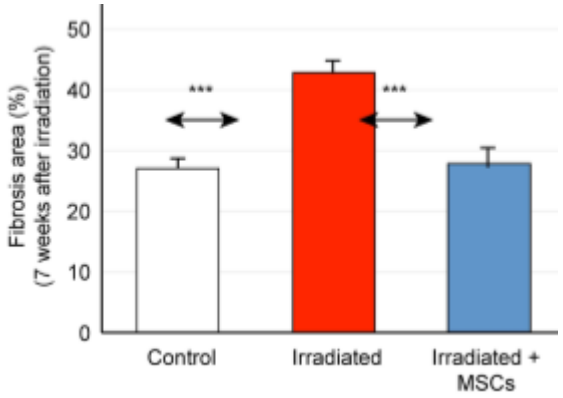
Protocol of intravenous injection:

- 5 millions of MSCs significantly improve the epithelial injury score
- Iterative injections in established radiation-induced lesions restore mucosal damages.



Linard et al., 2013; Bessout et al., 2014

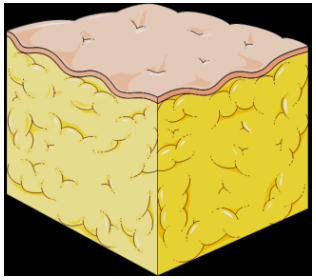
- Injection frequency ≥ 1 week
- MSCs injections are more effective during the initiation phase of fibrosis



Usunier et al. 2014
Colorectal fibrosis

Protocol injection: Chronic Radiation Cystitis

Adipose tissue



Isolation
Purification
Expansion

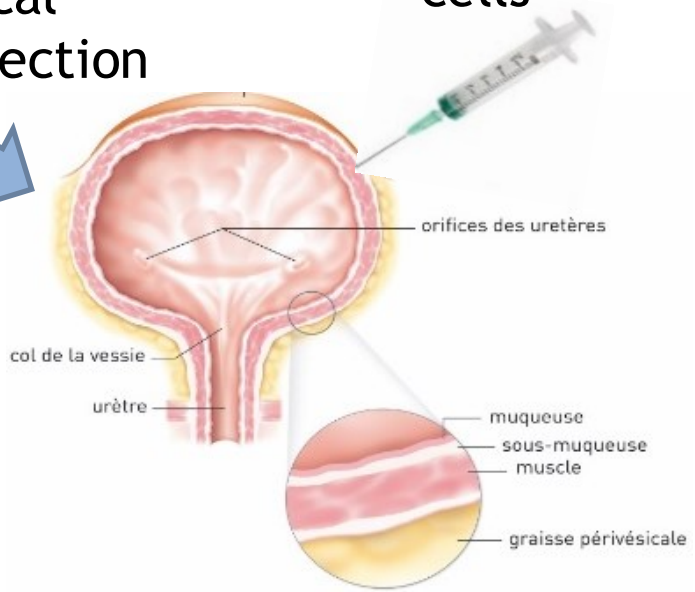
MSCs

Intravenous injection

5 millions cells[1]

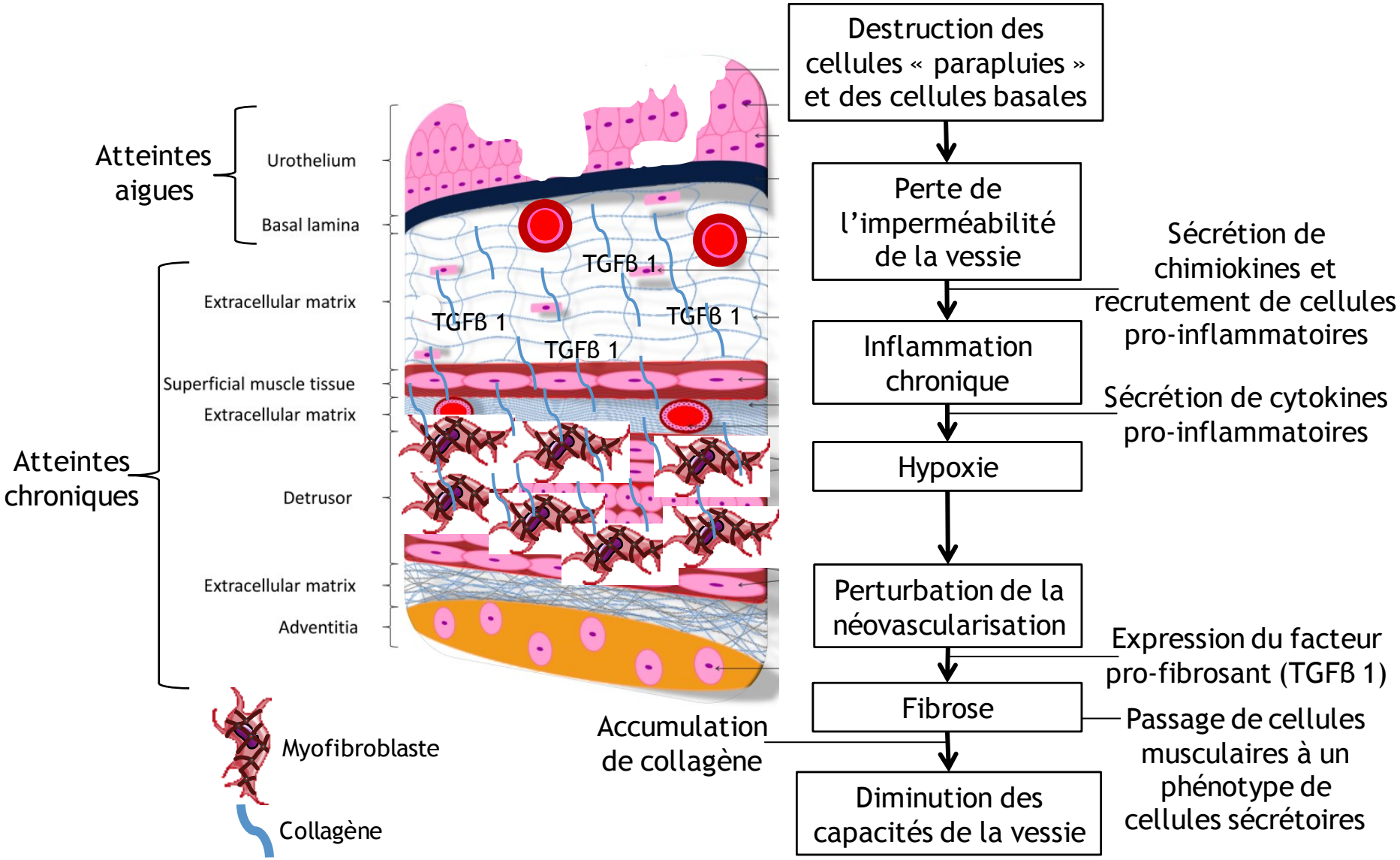
Local injection

1 millions cells[2,3,4]

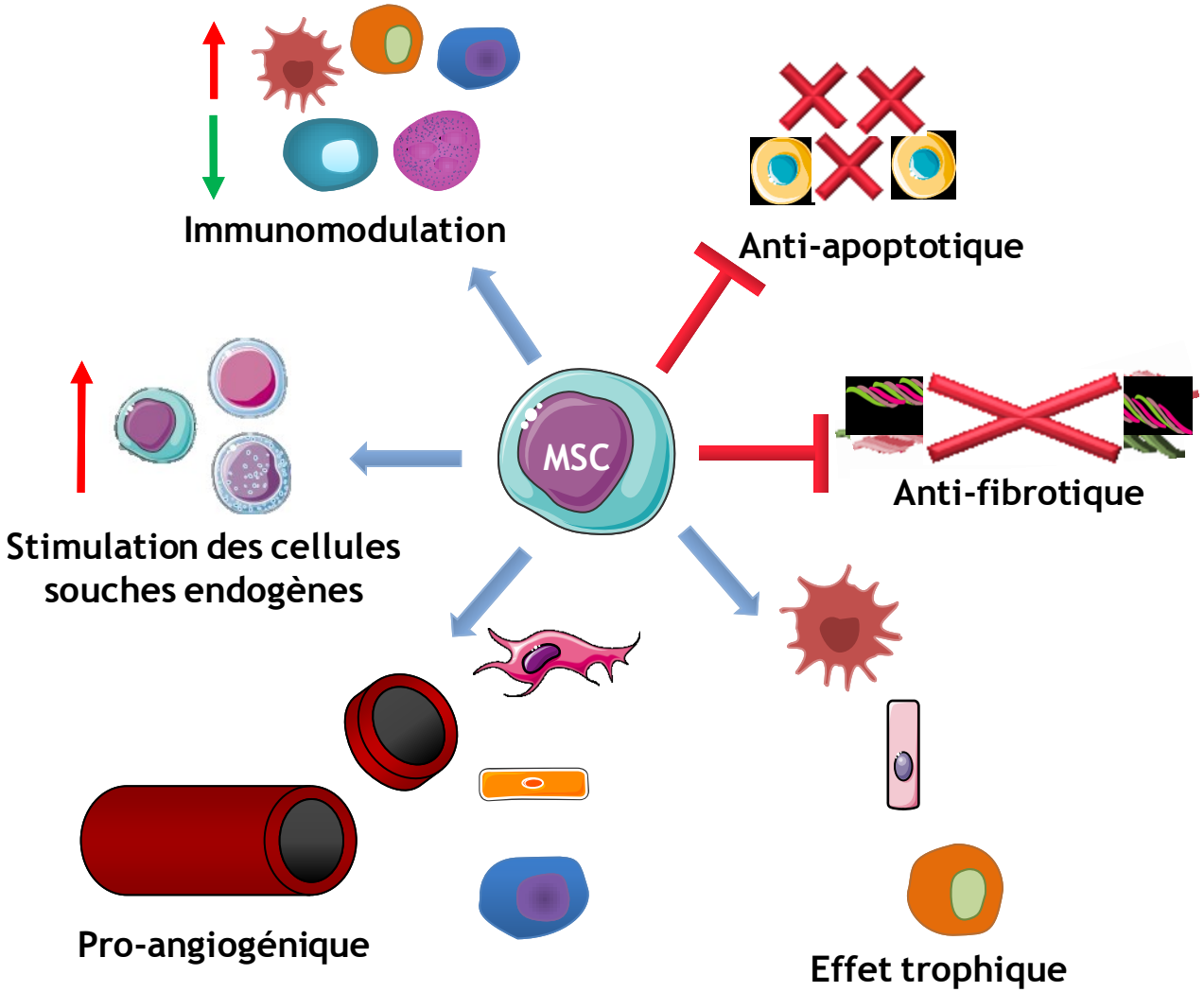


1:Kanno et al.; 2014
2: Kim et al.; 2016
3: Lee S.W et al.; 2018
4: Salehi-pourmehr H. et al.; 2019

Mécanisme de la cystite radique chronique



Fonctions des cellules souches mésenchymateuses



Principaux récepteurs de chimiokines exprimés sur les différents types de cellules immunitaires

Cellules	Récepteurs
Lymphocyte B	CXCR4, CXCR5
Basophile, éosinophile	CCR3
Neutrophile	CXCR1, CXCR2
Lymphocyte TCD8	CCR5, CX3CR1, CXCR1, CXCR3, CXCR6
Cellule dendritique immature	CCR1, CCR6
Cellule dendritique mature	CCR7
Macrophage	CCR1,CCR2, CCR5
Cellule Th1	CCR1, CCR5, CXCR3, CXCR6
Mastocyte	CXCR1, CXCR2
Monocyte	CCR5, CX3CR1, CCR1, CCR2
Cellule Th2	CCR3, CCR4, CCR8, CXCR4
Cellule NK	CX3CR1, CXCR1, CXCR3, CXCR4, XCR1