Irradiation and hyperproliferative processes: Radiobiological aspects

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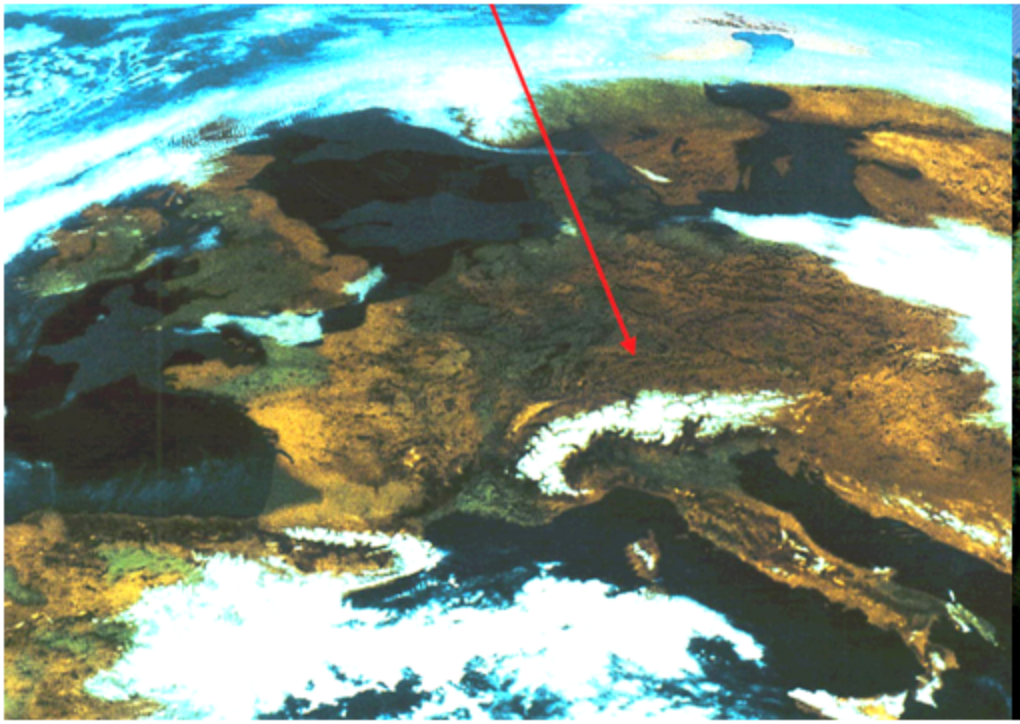
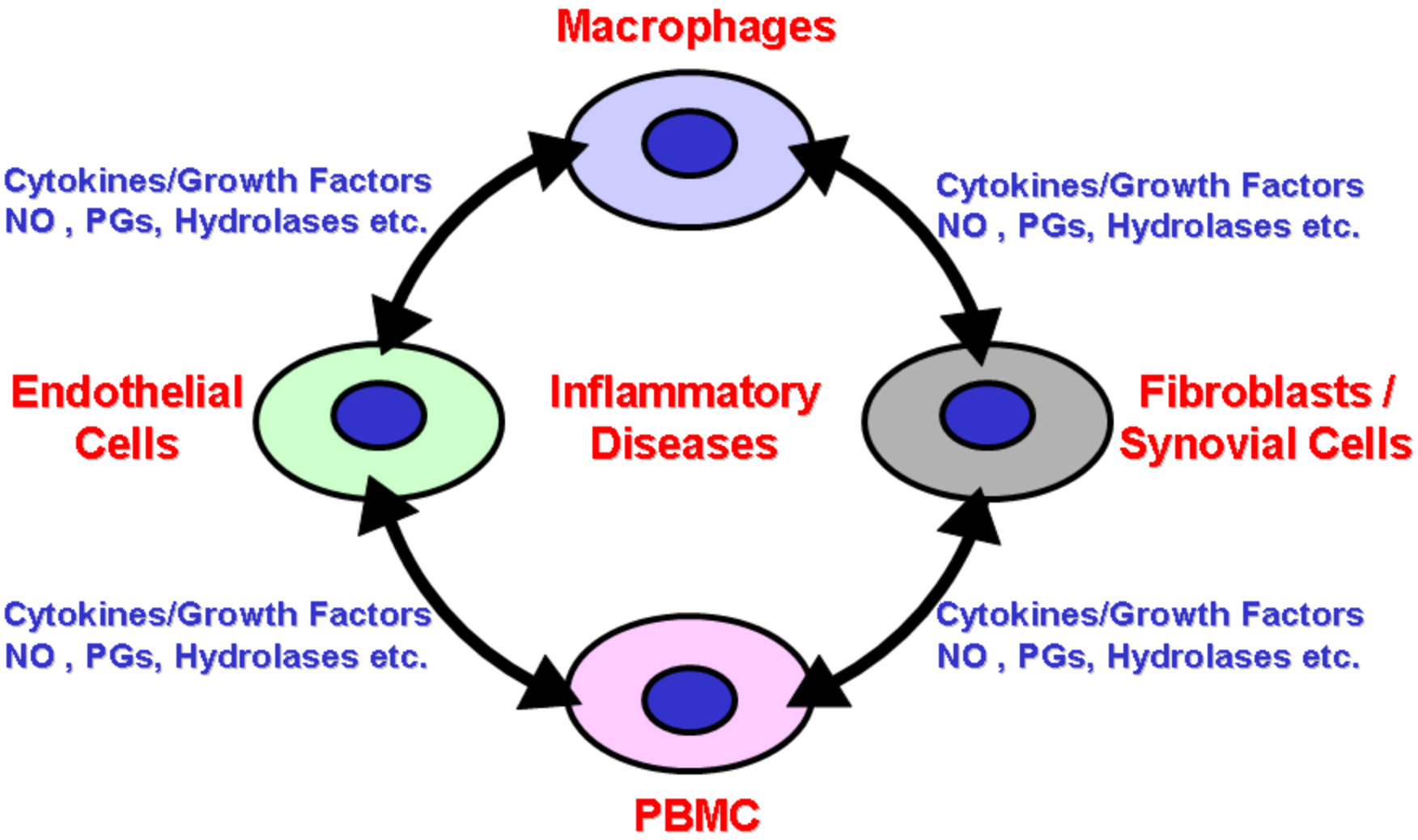
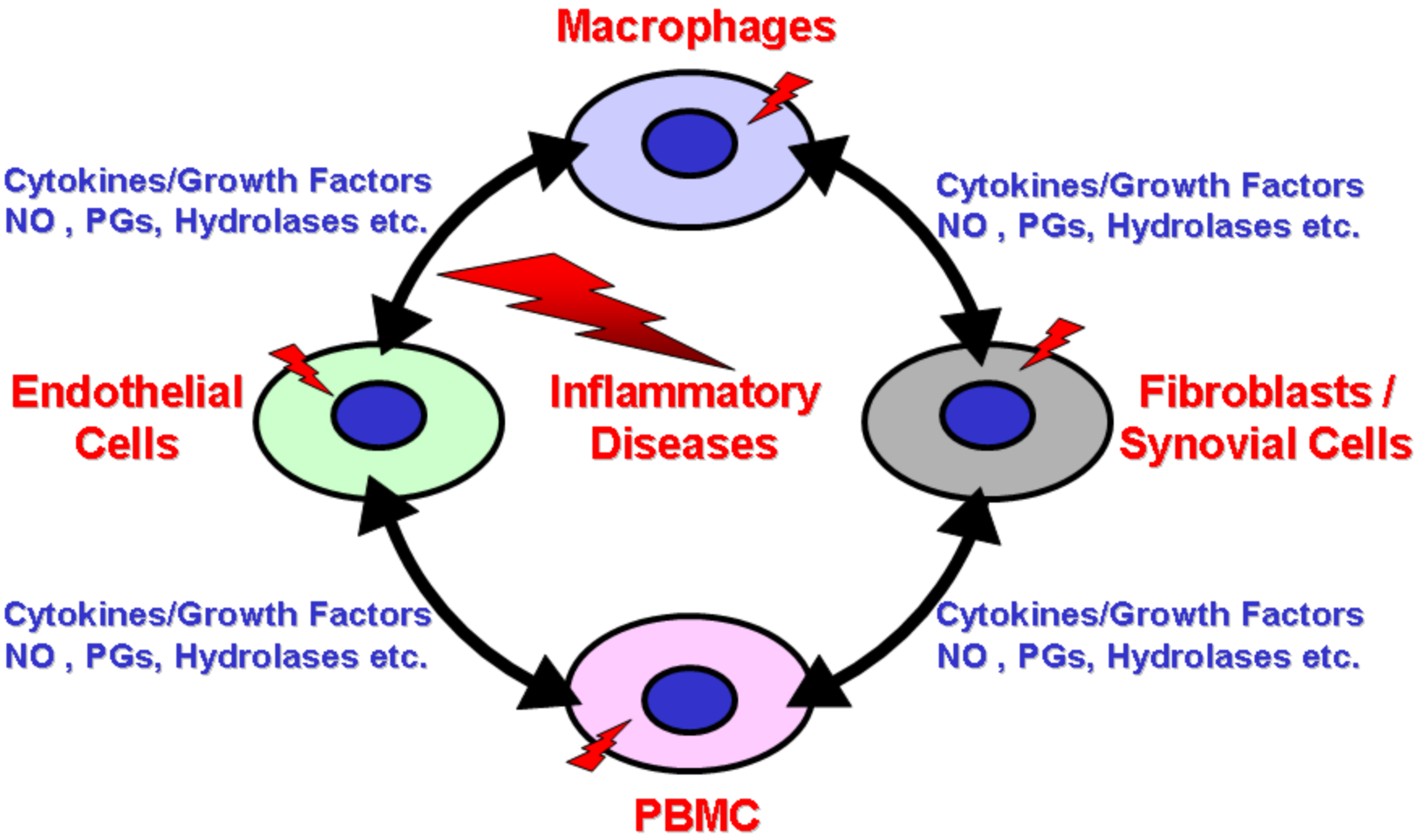


Inflammatory diseases are the consequence of complex multicellular interactions



Low dose radiation therapy (RT) modulates the complex multicellular interactions



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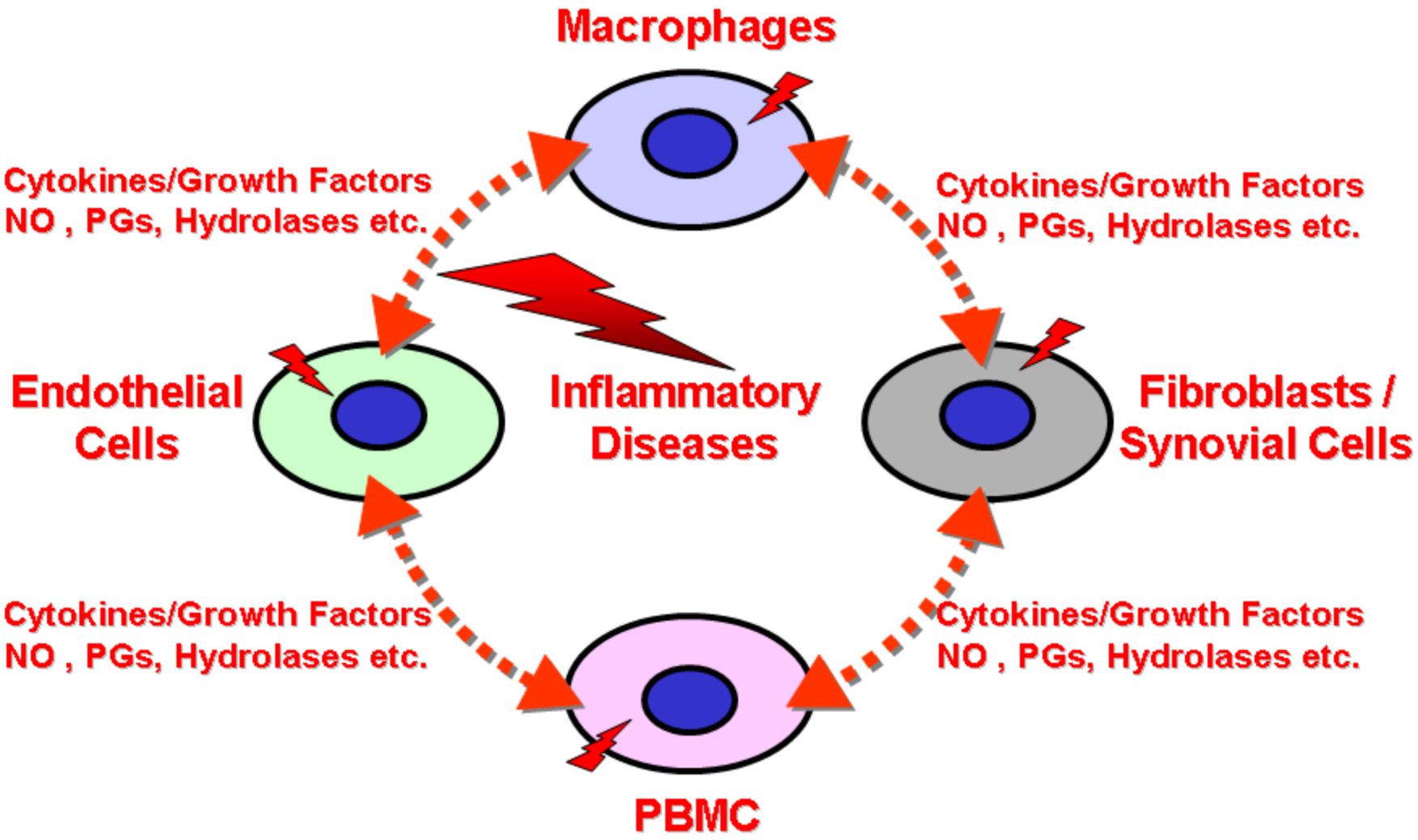


Two examples ....

- Arthritis

- Morbus Dupuytren

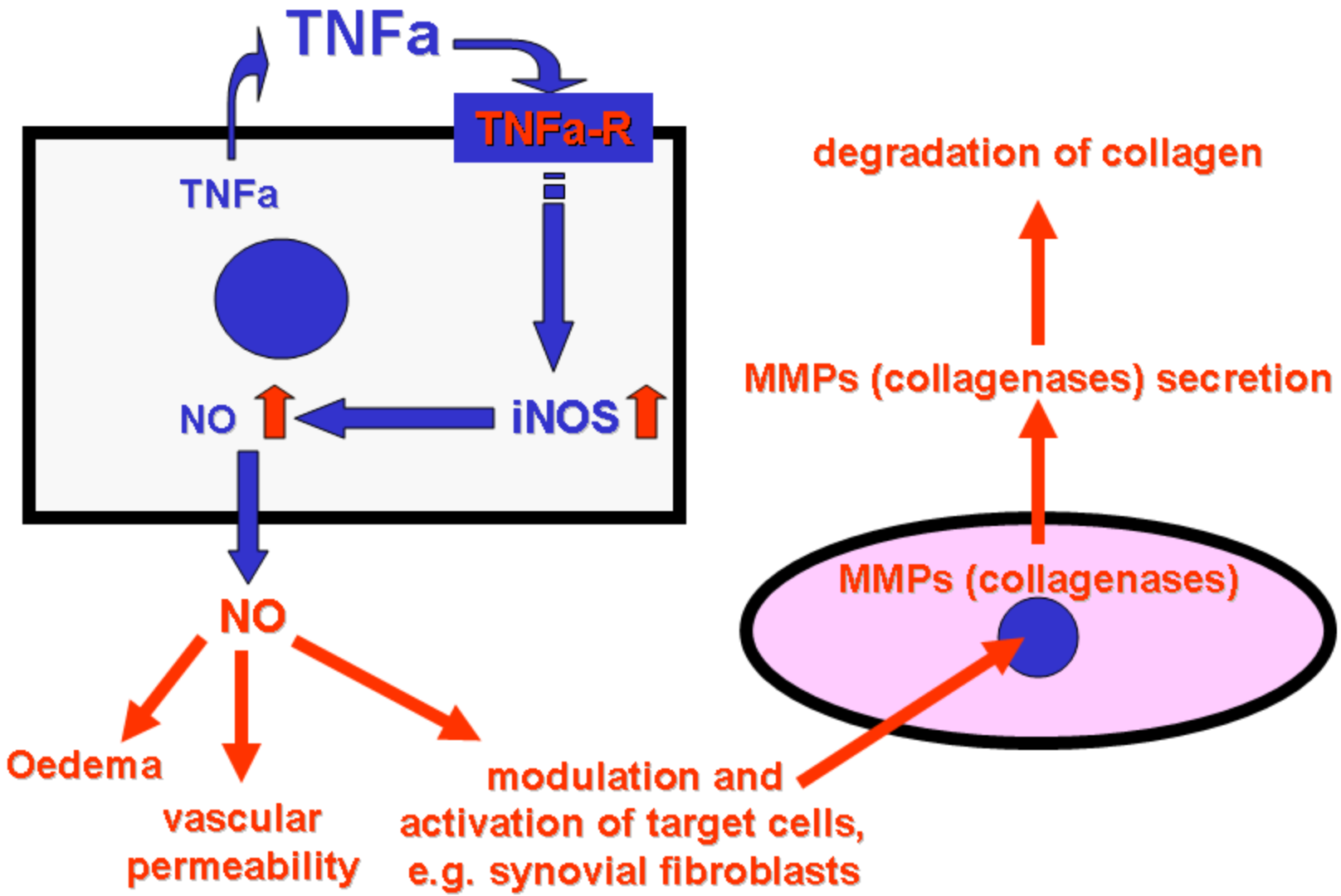
Radiation response of macrophages

Hildebrandt et al. Int. J. Radiat. Biol. 74, 1998

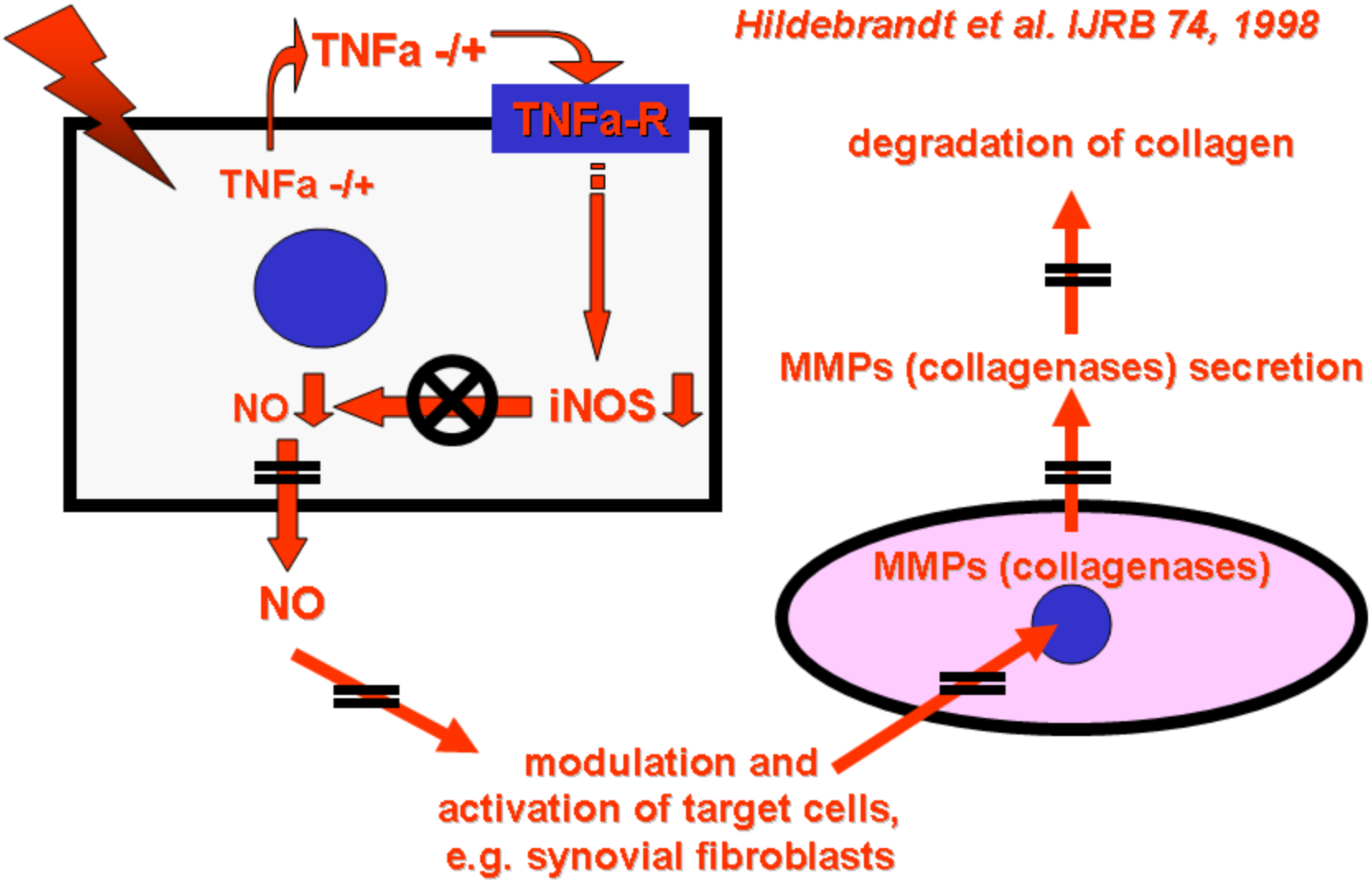
Irradiation of activated macrophages leads to dose dependent effects on *iNOS* and *NO*-production :

0.6 – 1.25 Gy :	significant down-regulation of iNOS and consequently reduced production of NO
5.0 – 10.0 Gy :	upregulation of iNOS but no significant effect on NO production
0.6 – 10 Gy :	undulating pattern of TNFa-production

Role of activated macrophages in the process of arthritis



Consequences of low dose RT on macrophage activity in arthritis



Morbus Dupuytren

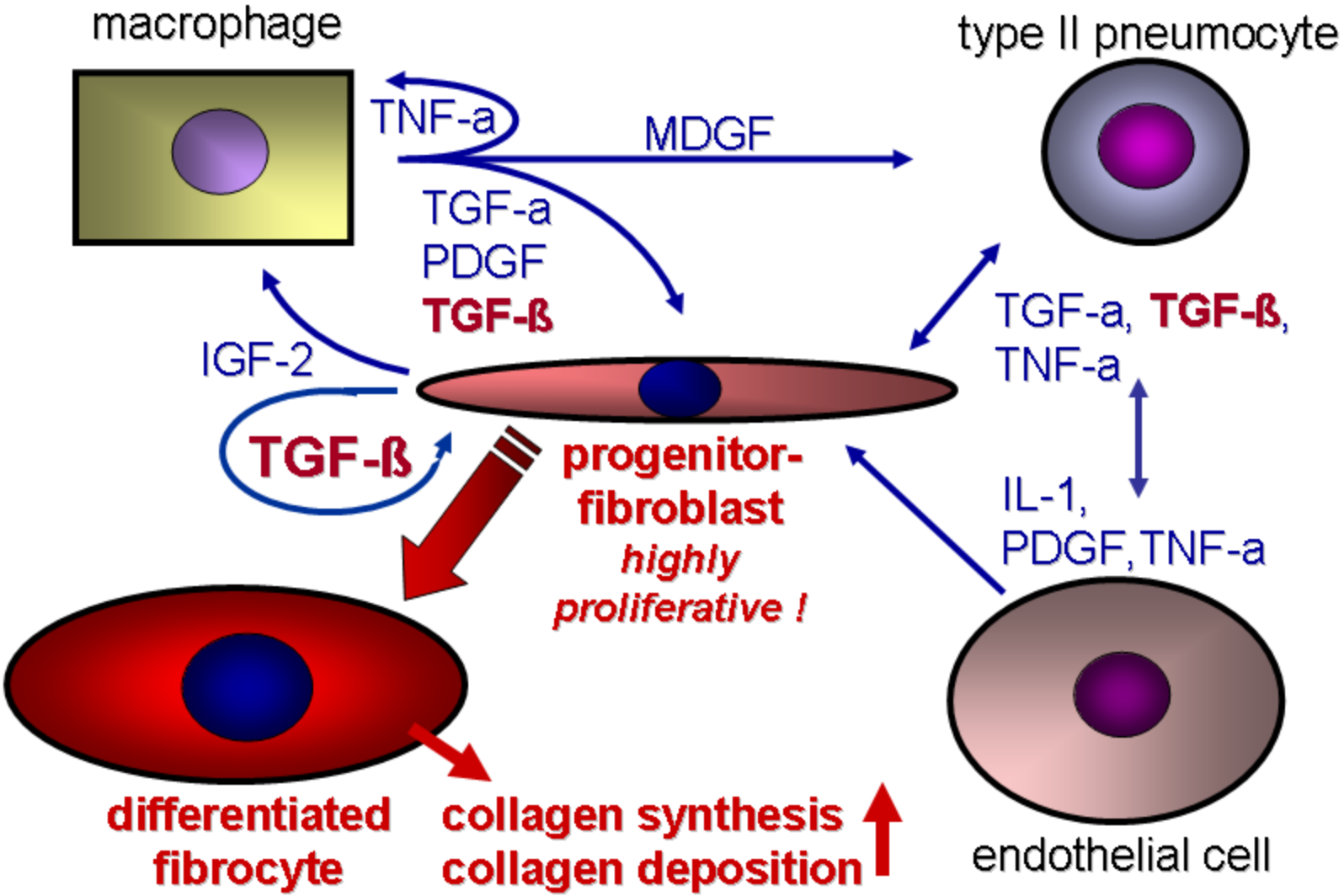
Morbus Dupuytren is a fibro-proliferative disease of the connective tissue manifested by disturbed contractility !

..... low dose RT reduces clinical symptoms of M. Dupuytren !!

Why ?

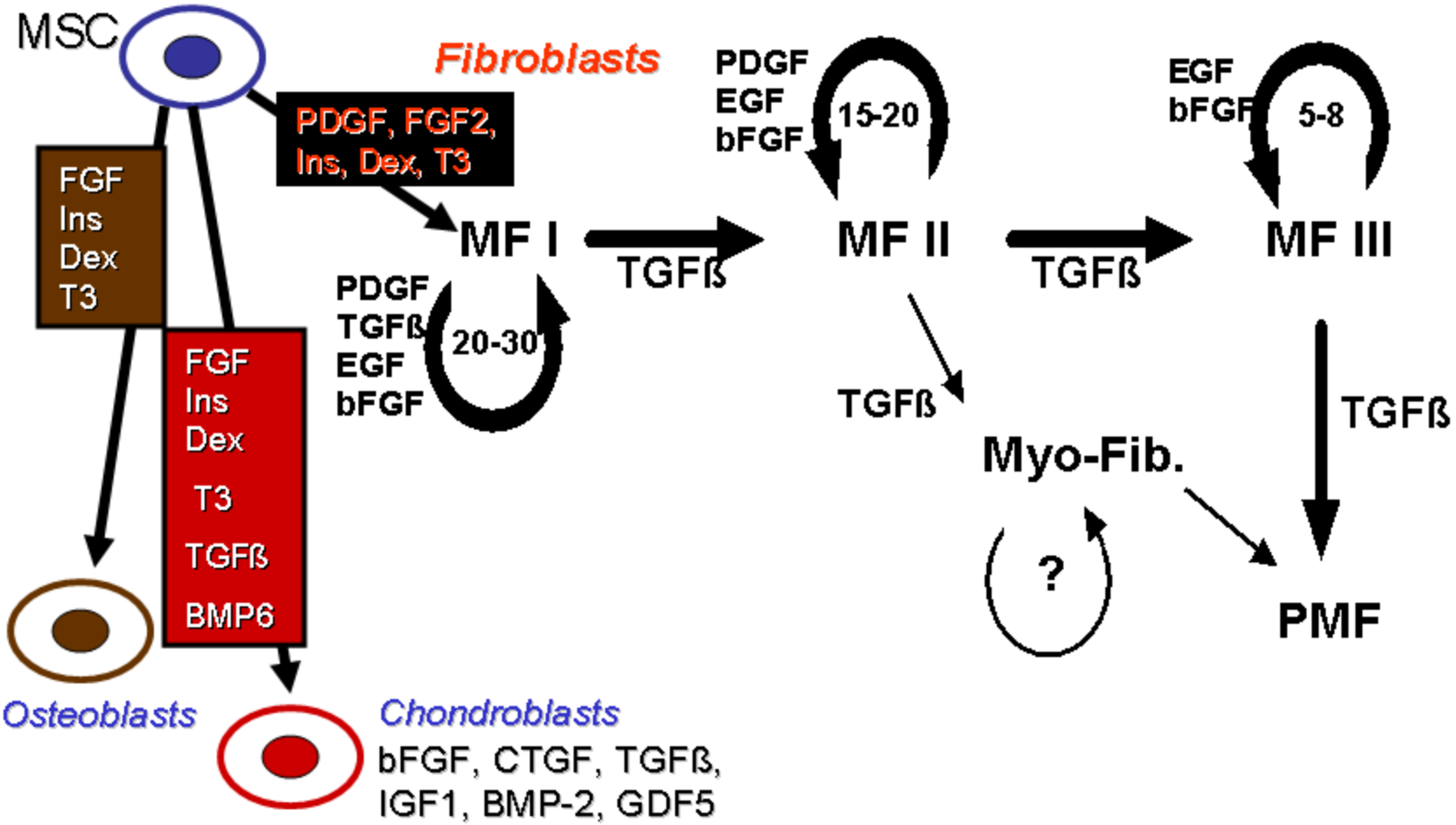
Fibroblasts as accessory cells interact with various cell systems

Rodemann et al. Radiother. Oncol. 1995



The fibroblast-fibrocyte cell system as part of the mesenchymal stem cell system

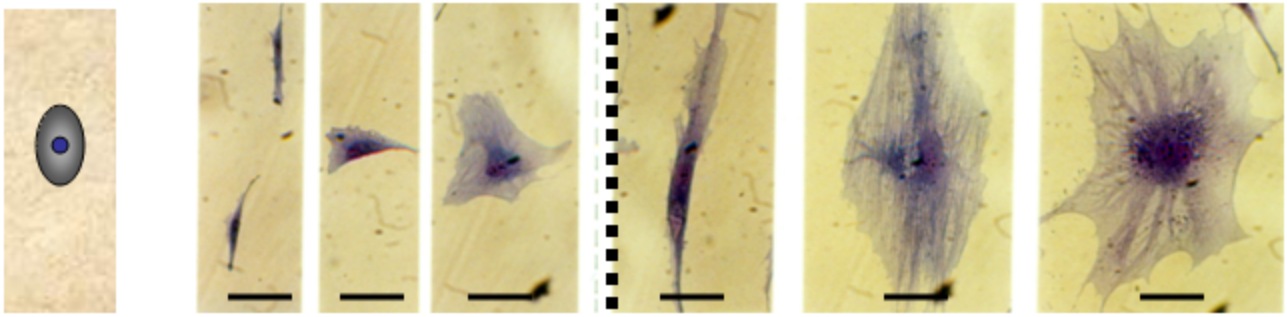
Proliferation and differentiation factors of the mesenchymal stem cell system



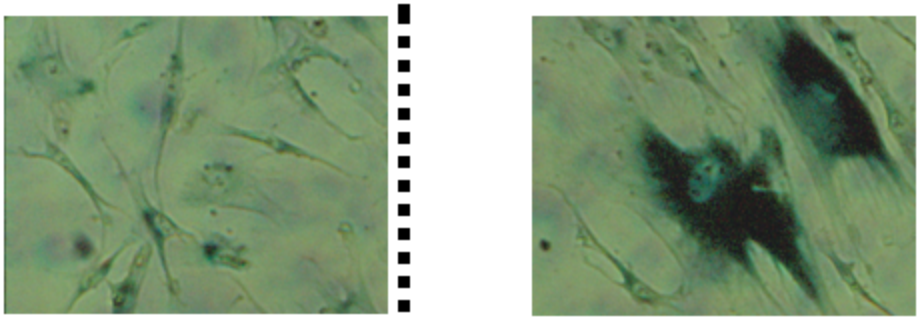
Differentiation sequence and markers of the fibroblast-fibrocyt cell system

Rodemann Differentiation 1989
Rodemann et al. Exp.Cell Res. 1989
Burger et al. Int.J.Radiat.Biol. 1998

MSC → MFI → MFII → MFIII → PMFIV → PMFV → PMFVI

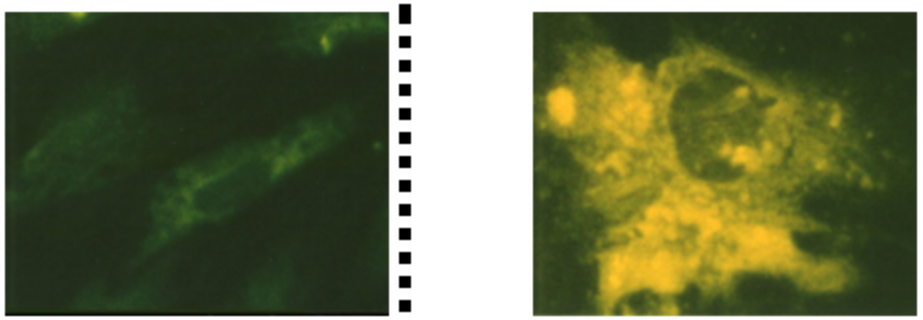


Differentiation lineage



Biochemical Markers

pH6 ß-Gal-activity



Type I collagen synthesis

Cell types of the fibroblast-fibrocyte cell system

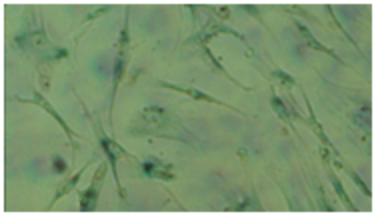
Bayreuther et al. J.Cell Sci. 1992
Rodemann et al. Kidney Int. 1996
Hakenjos et al. Int.J.Radiat.Biol.2000

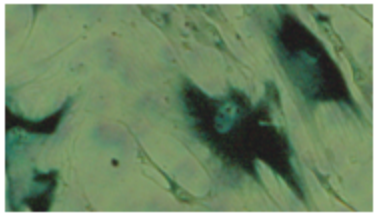
progenitor fibroblasts | functional fibrocytes

MF I → MF II → MF III → PMFIV → PMFV → PMFVI

cell division potential

20-30 | 15-20 | 5-8





in vivo-ratio

2 : 1

progenitor compartment | functional compartment

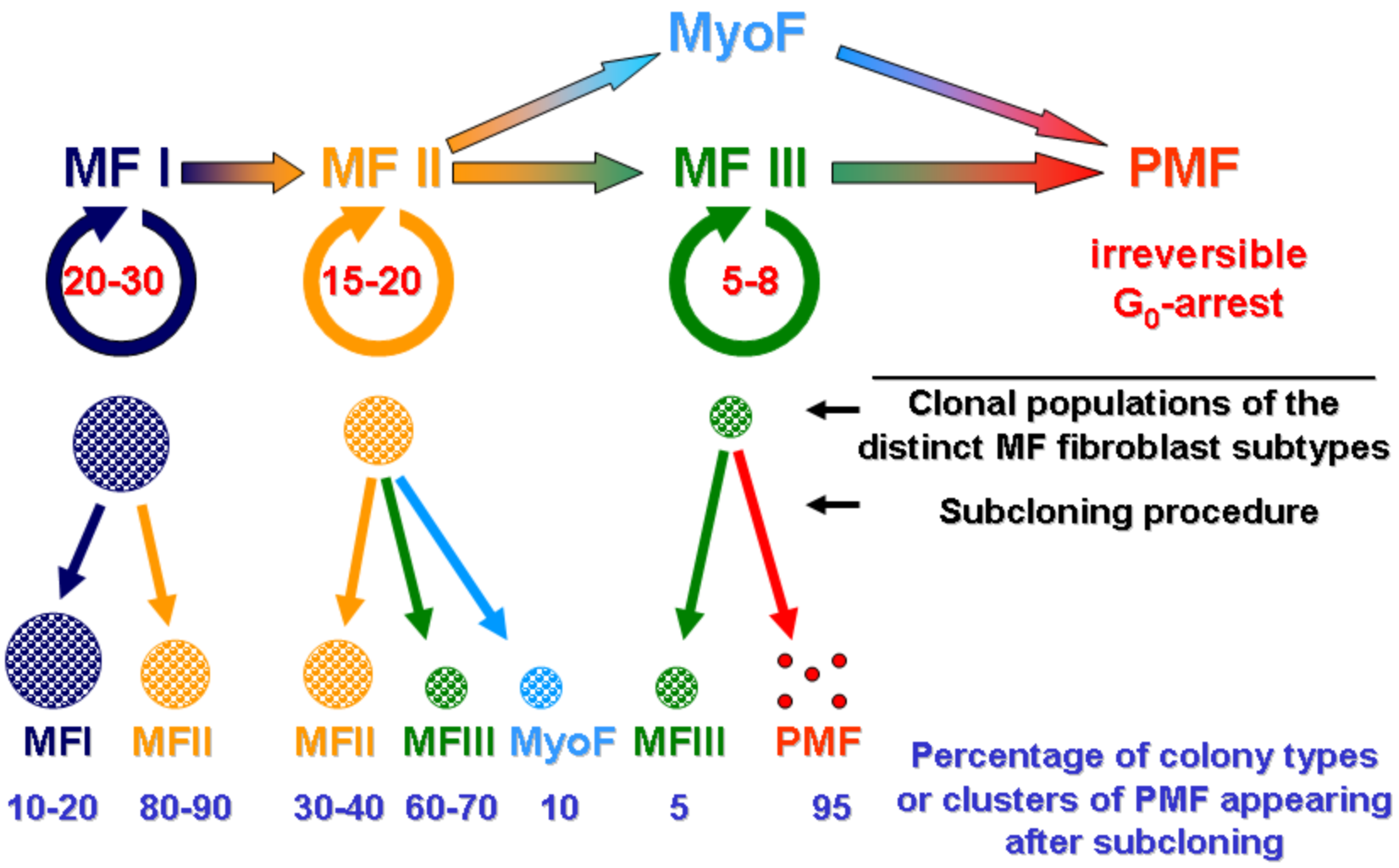
In-vivo-ratio of progenitor fibroblasts (MF) und postmitotic fibrocytes (PMF)

Bayreuther et al. J.Cell Sci. 1992
Rodemann et al. Kidney Int. 1996

Source:	skin biopsies of 25 female donors in the age range 20-80 years		
Method:	collagenase digest; single cells in primary culture		
Classification:	2000 cells of each donor specific primary culture were classiefied		
Results:	Mean	Percentage	Ratio
MF	1306 +/- 272	65 %	2
PMF	685 +/- 275	35 %	1

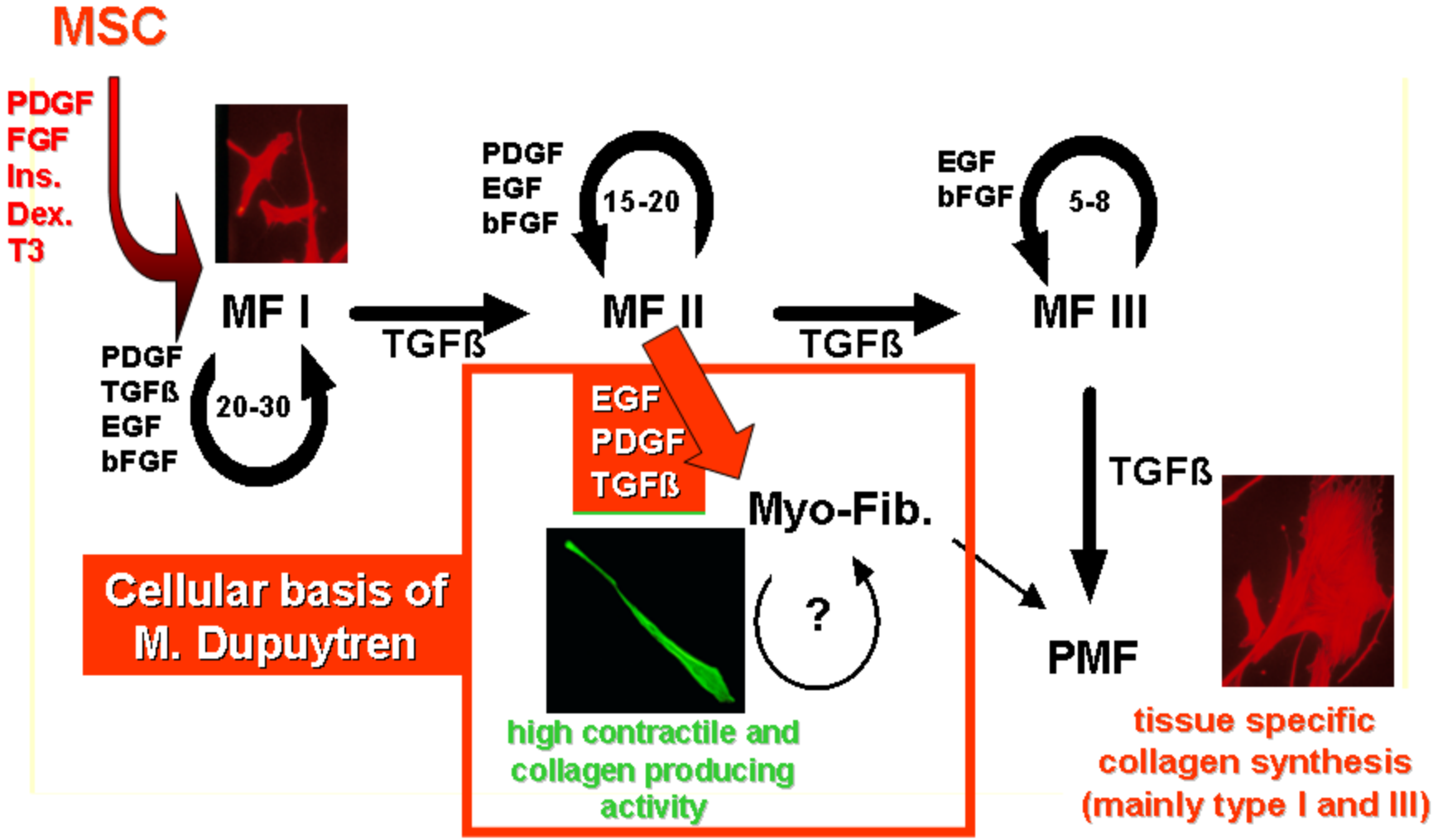
Proliferation- and differentiation pattern of fibroblast subtypes

Bayreuther et al. J.Cell Sci. 1992



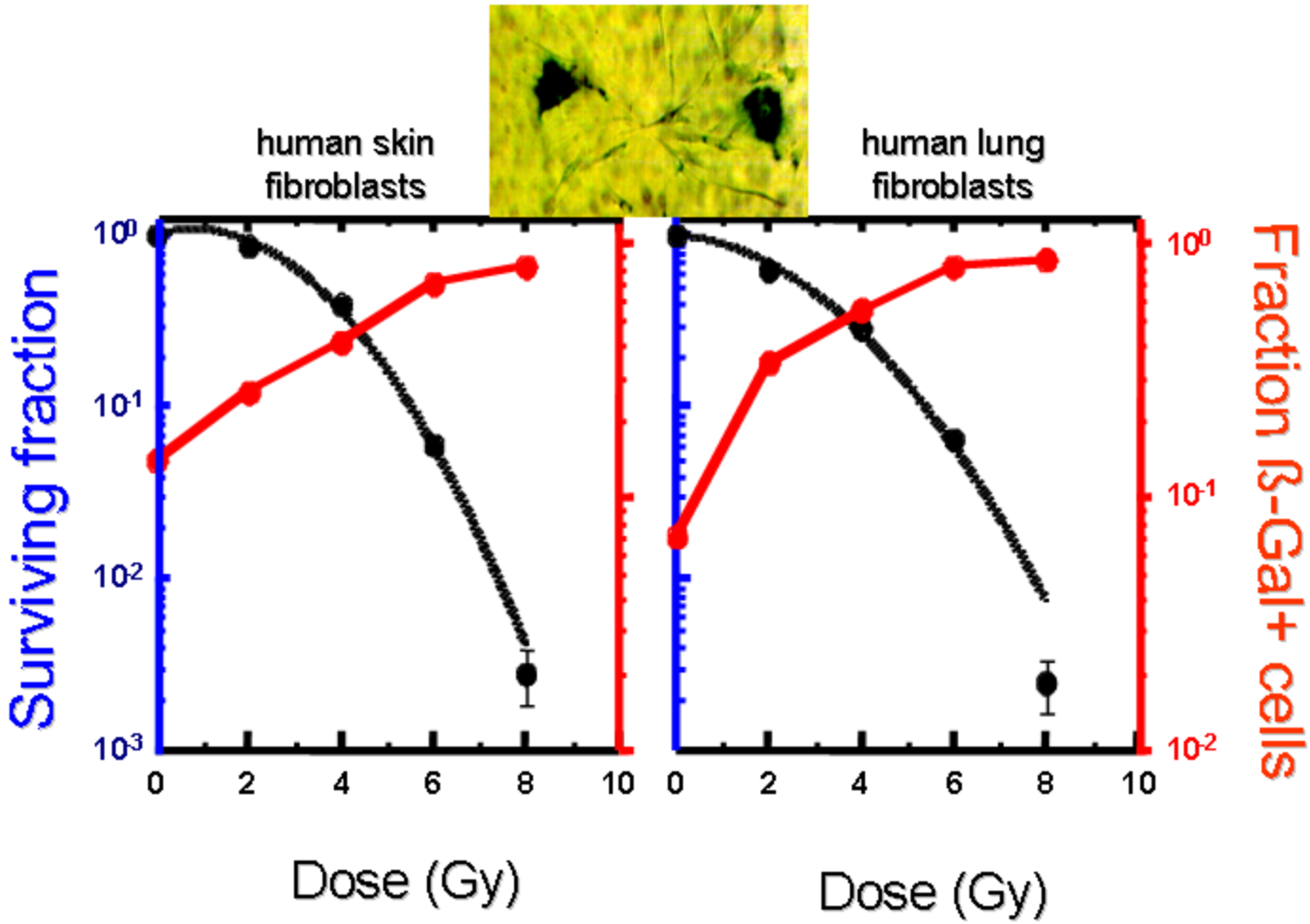
The fibroblast-fibrocyte cell system as part of the mesenchymal stem cell system

Importance in M. Dupuytren



Correlation of clonogenic survival and radiation-induced terminal differentiation

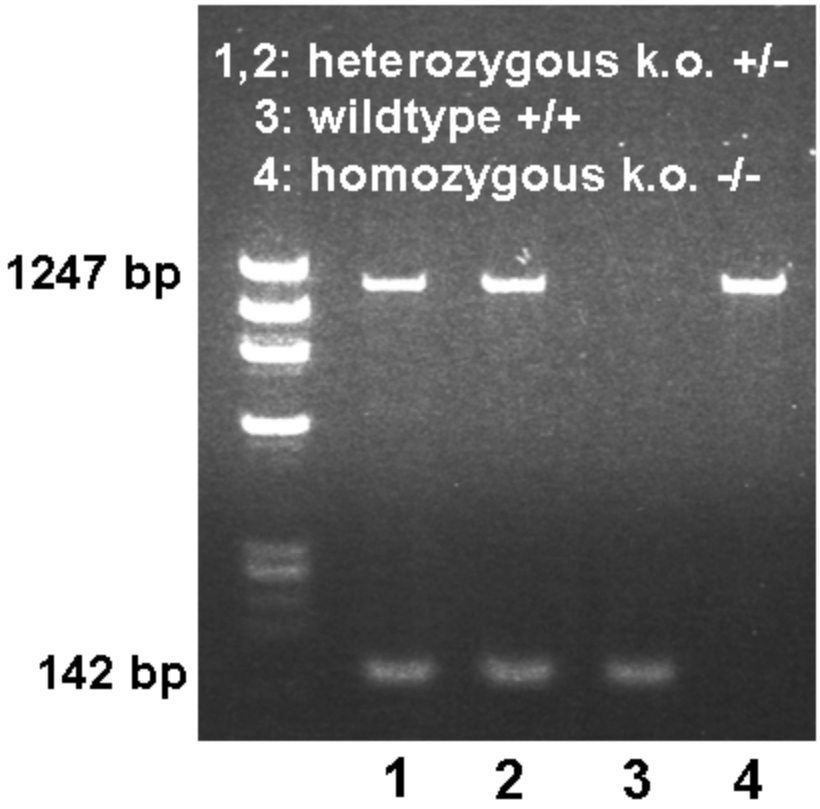
Rodemann et al. Scann. Microsc. 1991
Rodemann et al. Kidney Int. 1996
Hakenjos et al. 2000

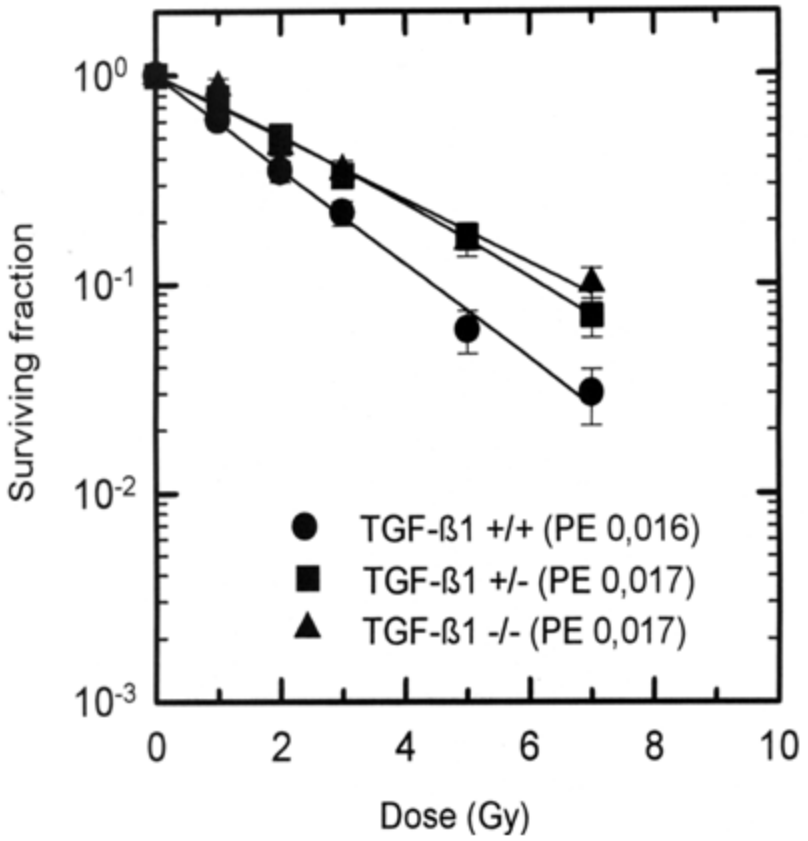


Role of TGFß1 in the radiation response of fibroblasts

TGF-ß1 Status determines radiation response of mouse lung fibroblasts

von Pfeil et al. Int.J.Radiat.Biol. 2002

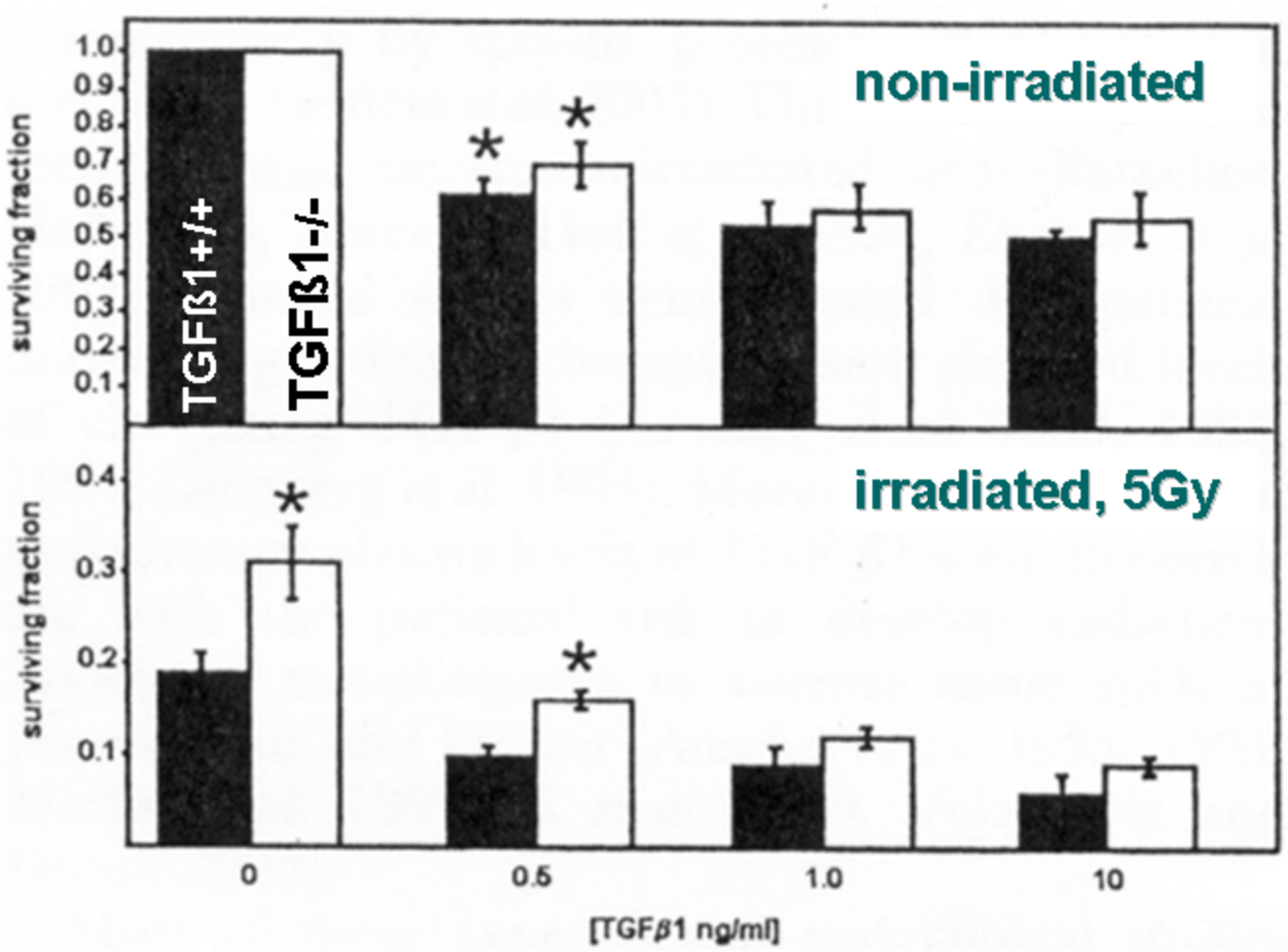




Role of TGFß1 for clonogenic activity of fibroblasts

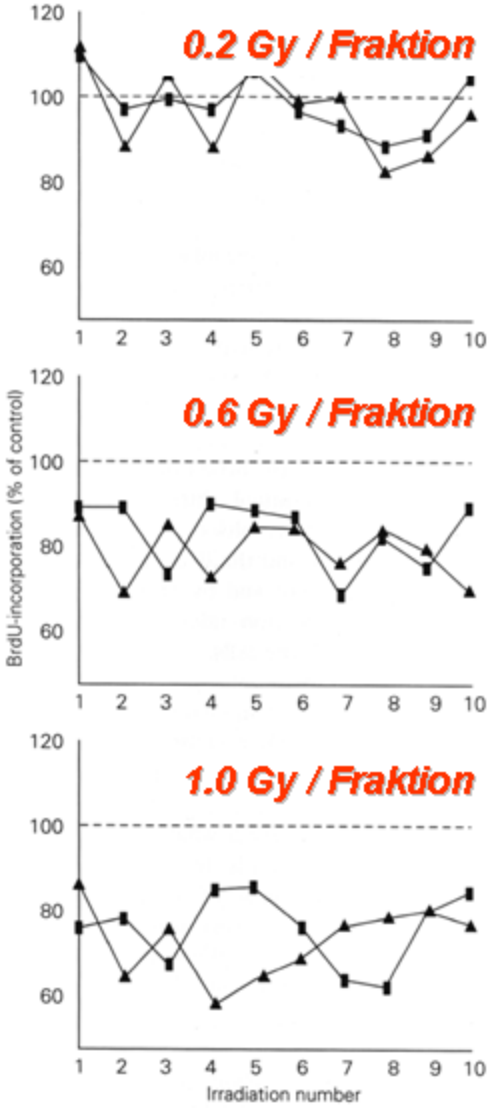
Effect of TGFß1 on clonogenic activity and radiation sensitivity of TGF-ß1 ko fibroblasts

von Pfeil et al. Int.J.Radiat.Biol. 2002



Fibroblast proliferation under low dose irradiation

(Bumann et al. Strahlenther. Onkol. 1995)

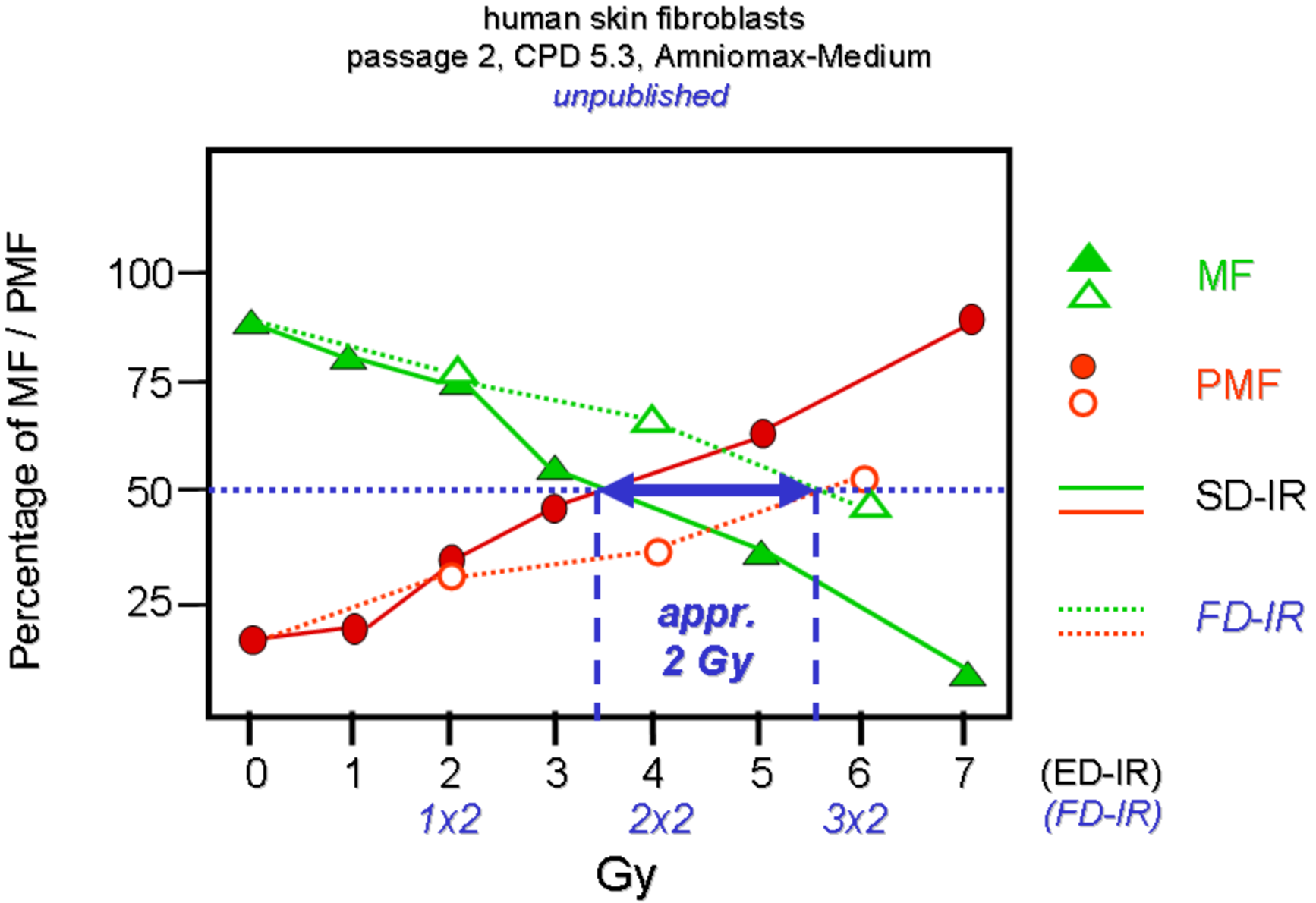


Human skin fibroblasts were irradiated between passage 4 und 14 with one fraction of the indicated dose per week over 10 weeks.

Incorporation of BrdU was applied to determine the proportion of proliferating cells.

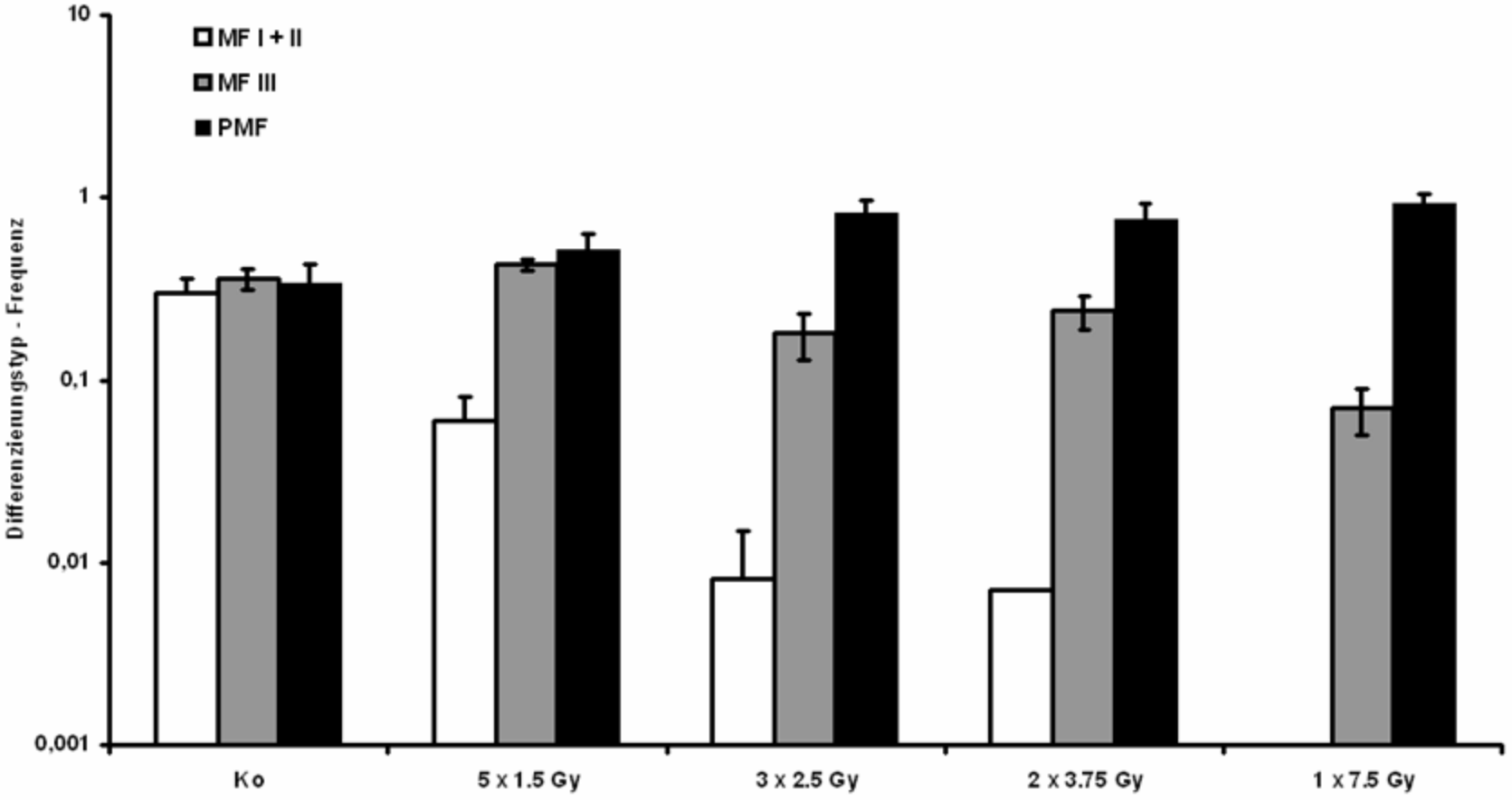
Unirradiated controls were set to 100 %.

Fibroblast differentiation as a consequence of single and fractionated dose irradiation



Fibroblast differentiation as a consequence of single and fractionated dose irradiation

human skin fibroblasts
passage 6, CPD 8.52, DMEM+20% FCS
unpublished



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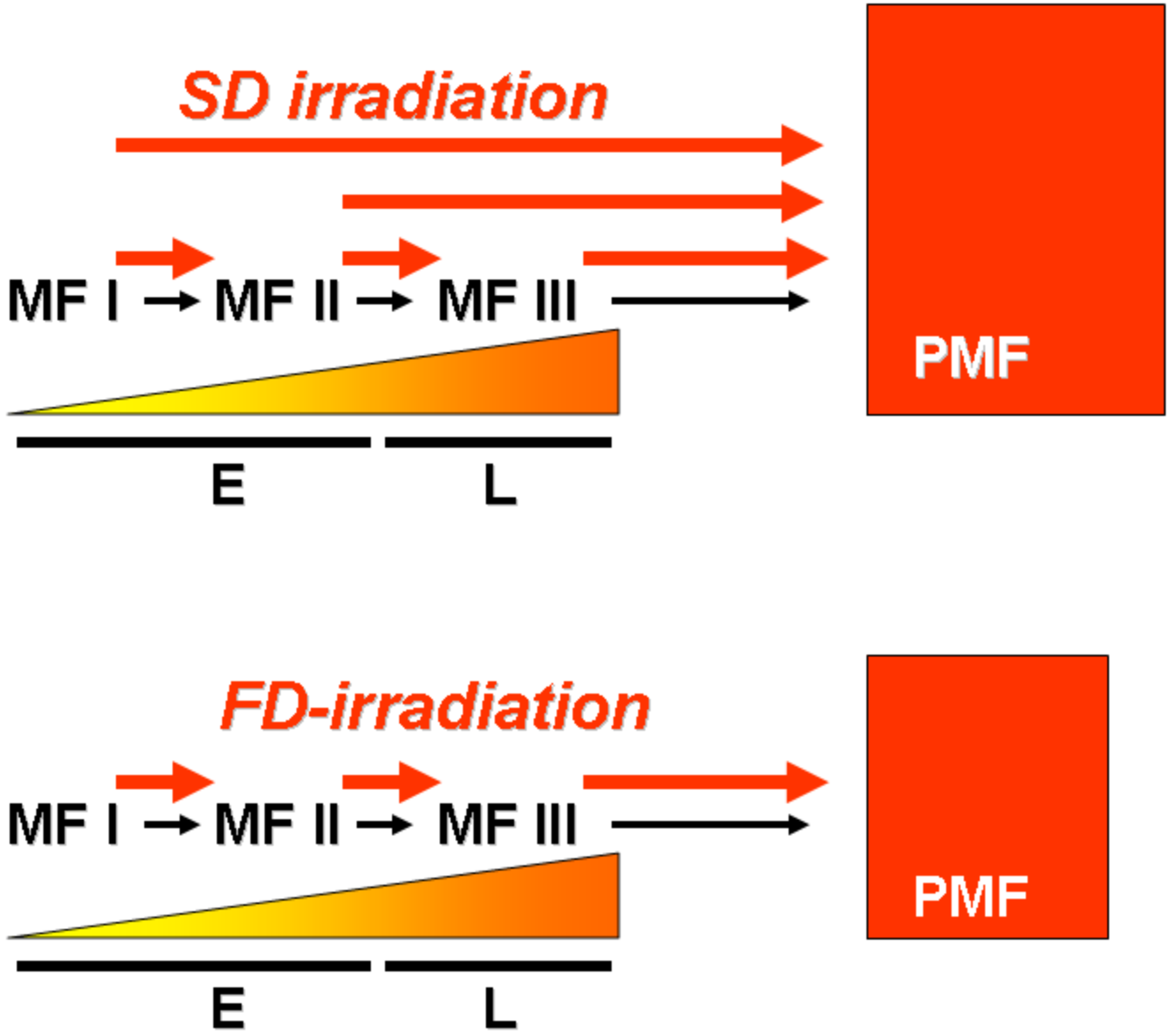

Effect of low dose RT on M. Dupuytren

- *low dose RT inhibits the differentiation/accumulation as well as proliferation of myofibroblasts !*
- *as a consequence contravctile activity is reduced !*