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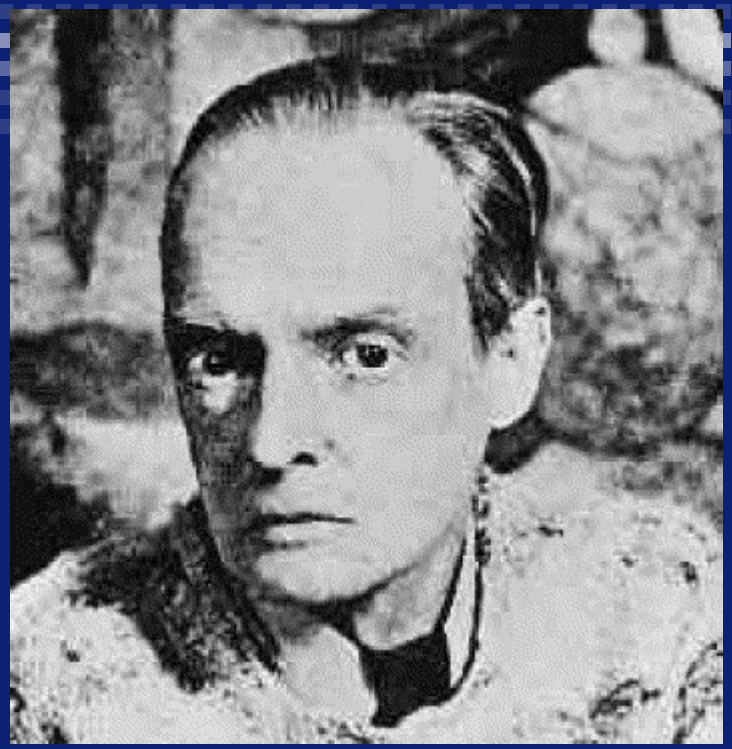

Paul Klee: 1879-1940

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Rond 1925

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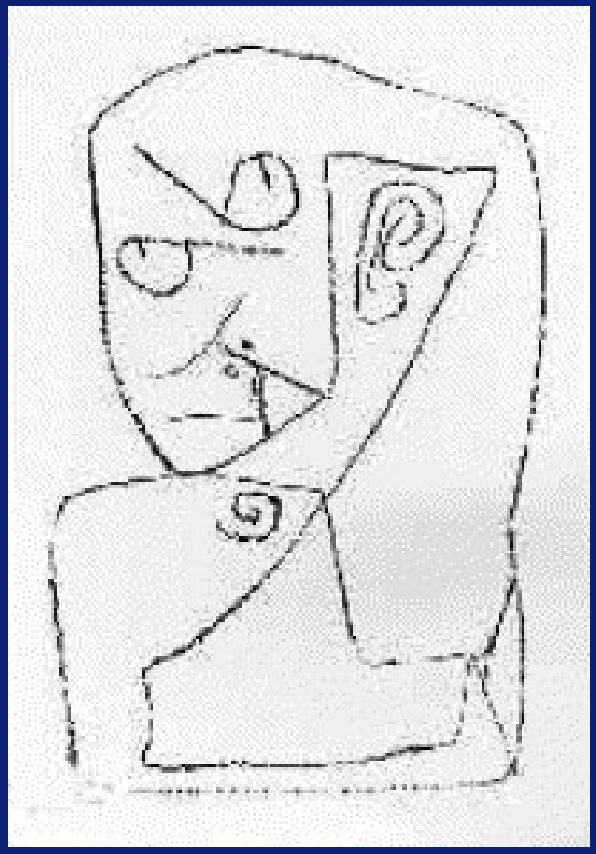
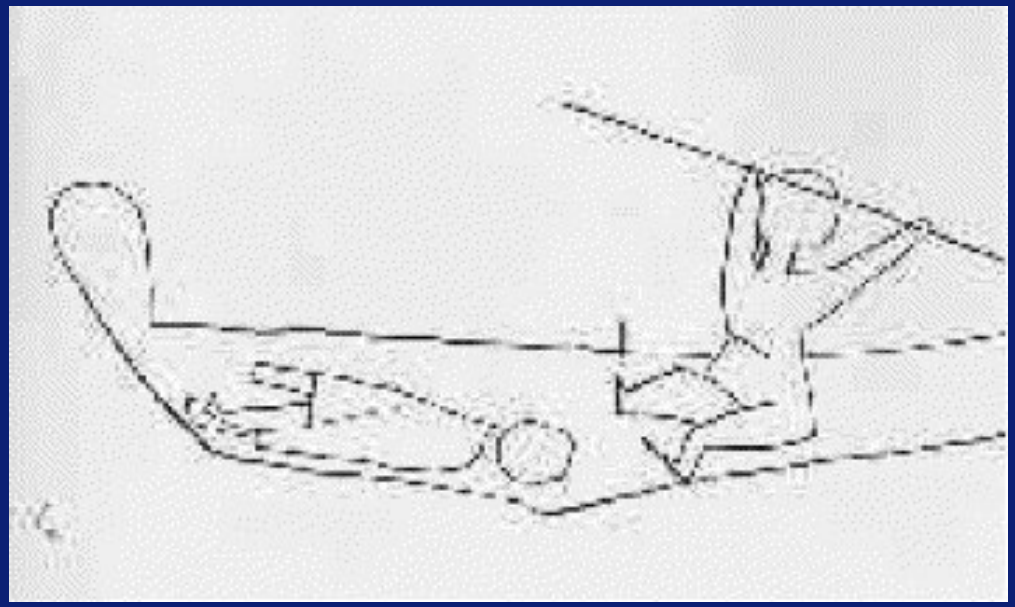
1940



1940



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A new approach in the treatment of systemic sclerosis

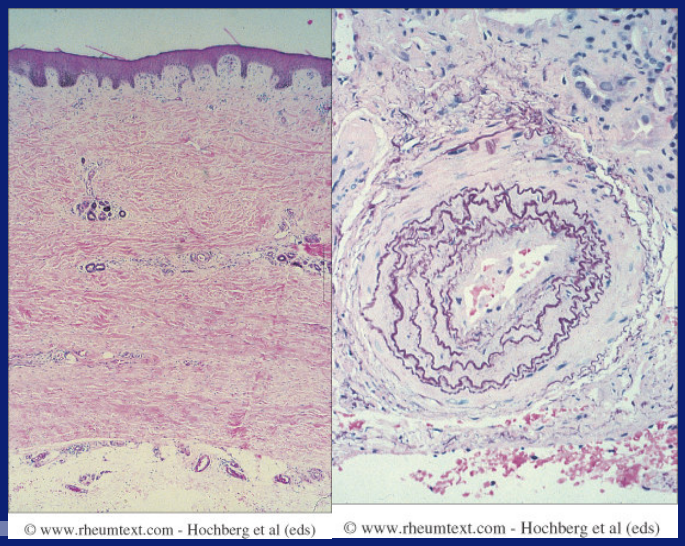
Paul van Daele

- Clinic
- Science
- Science in the clinic

Clinic

Introduction

- Definition:
  - Systemic auto-immune diseases
  - Fibrotic arteriosclerosis of periferal and visceral vasculature
  - Variable involvement of extracellulair matrix accumulation (esp. collagen) in skin and viscera
  - Specific auto-antibodies
  - Various subsets with specific clinical phenotype



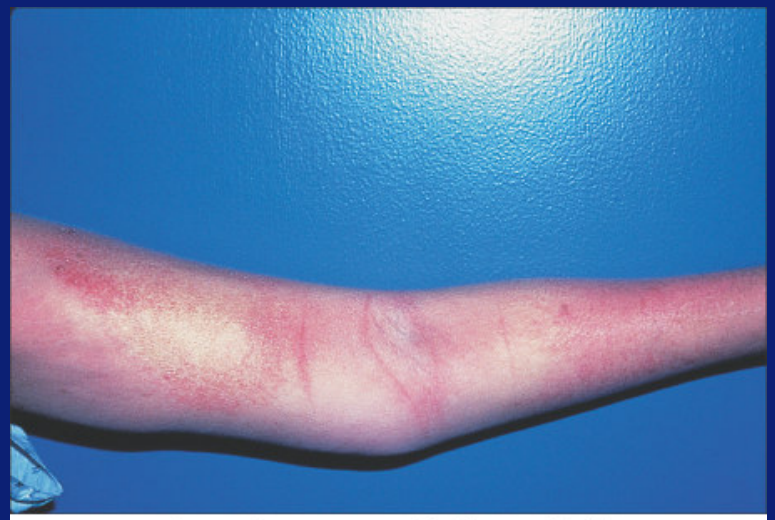
Auto-antibodies in systemic sclerosis

- Scl-70
- CENP A
- CENP B
- RP11 (RNAP-III)
- RP155 (RNAP-III)
- Fibrillarin
- NOR-90
- Th/To
- PM-Scl100
- PM-Scl75
- Ku, PDGFR
- Ro-52

Introduction

- Subtypes:
  - Diffuse scleroderma
  - Limited scleroderma (CREST)
  - Sine scleroderma
  - Overlap syndromes
  - Undifferentiated connective tissue disease

Introduction



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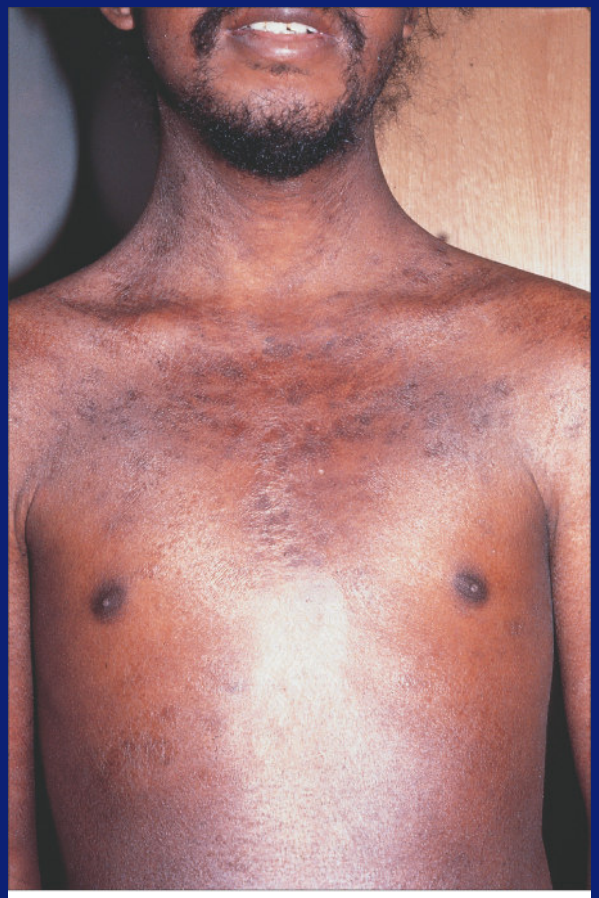

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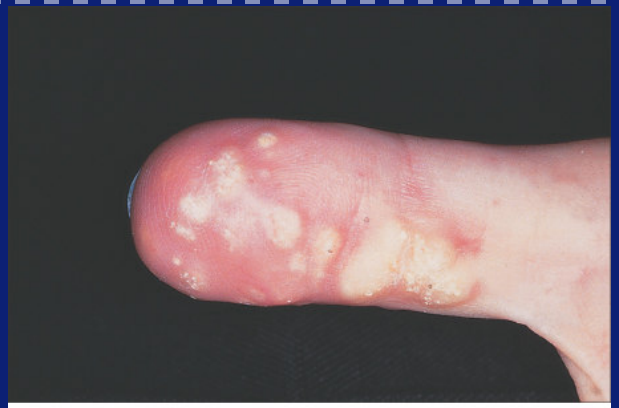
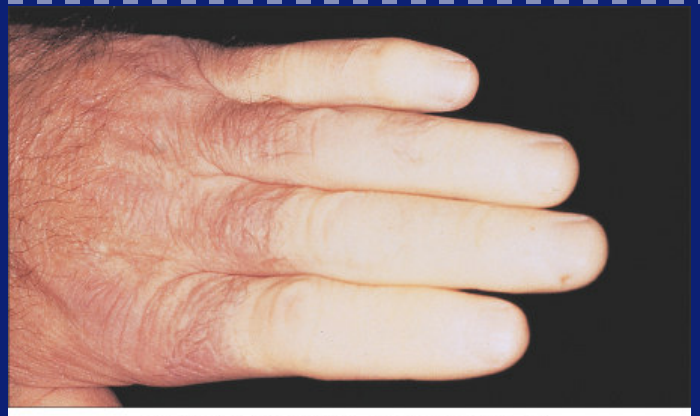
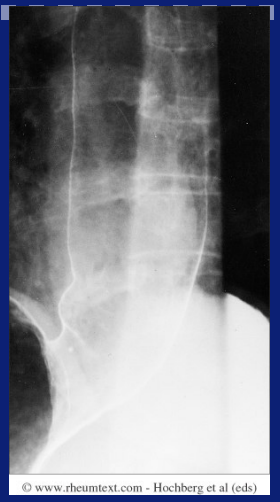
Diffuse variant

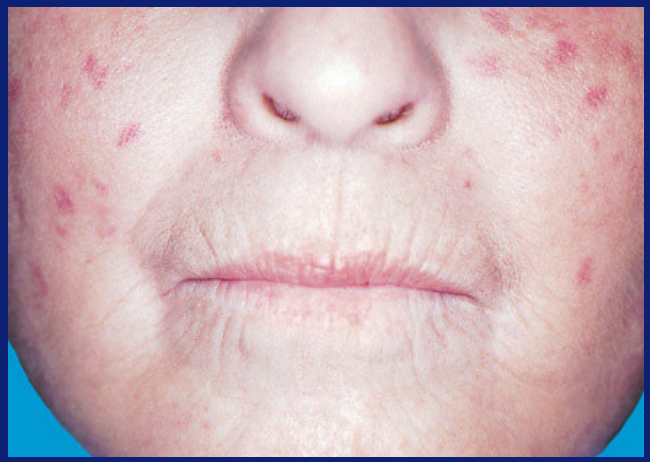
Introduction







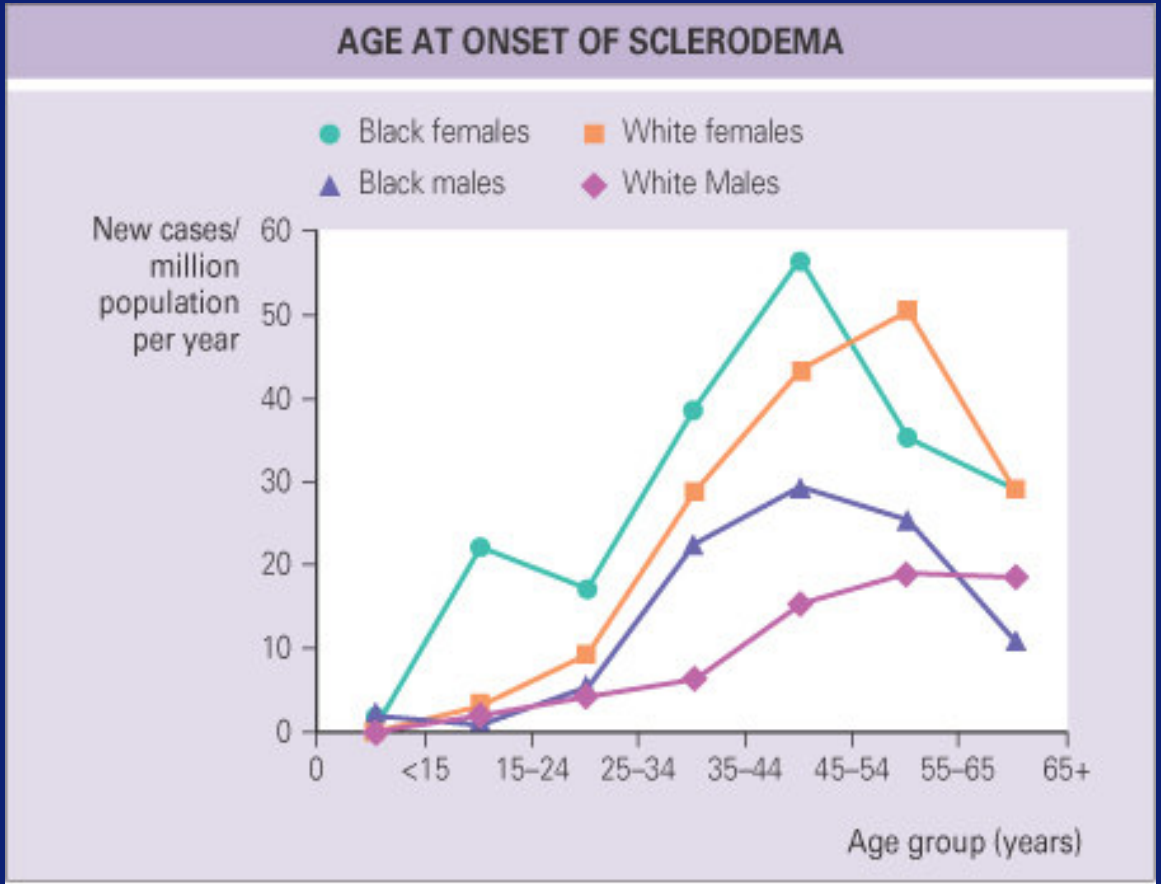
Limited



Epidemiology

- Incidence: 15 – 20 / 1.000.000 pj
- Prevalence: 150 – 250 / 1.000.000

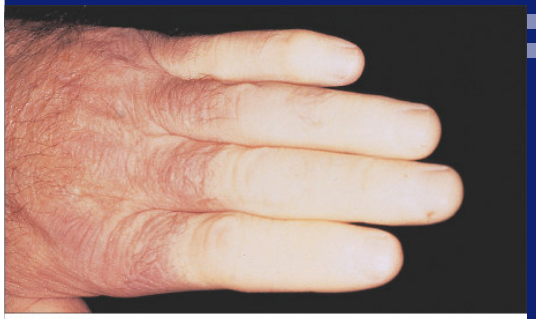
Epidemiology



Clinical picture

- Raynaud + progressive skin changes

Clinical picture



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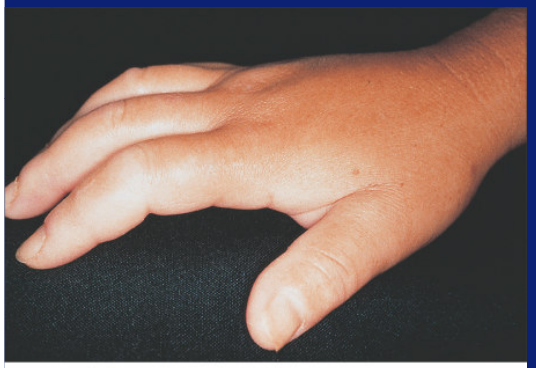

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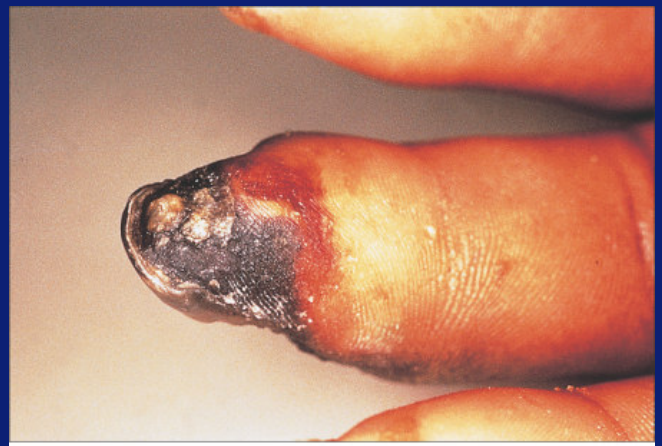

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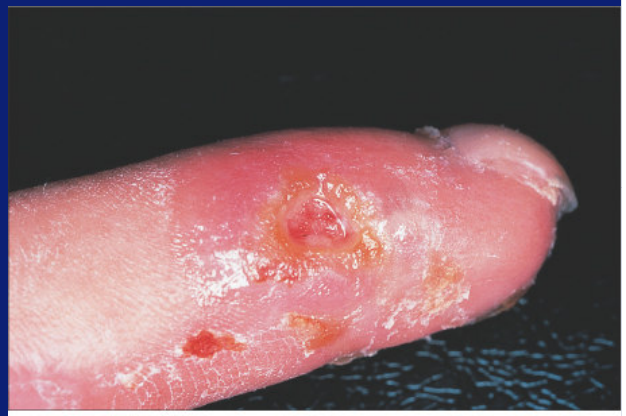

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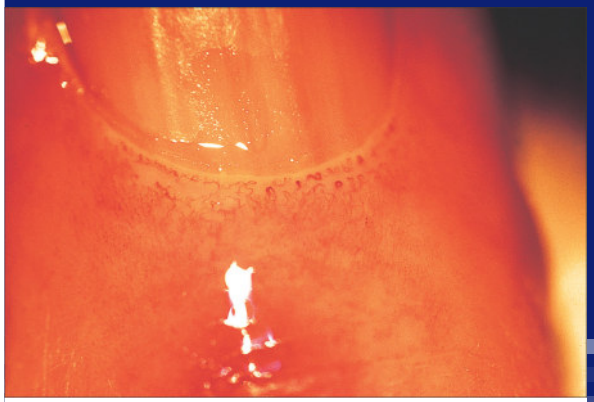

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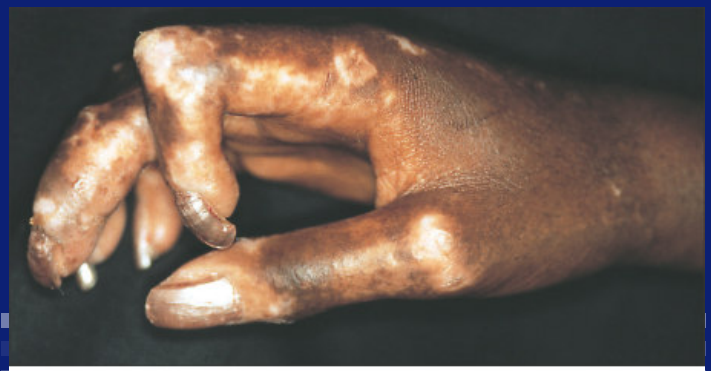

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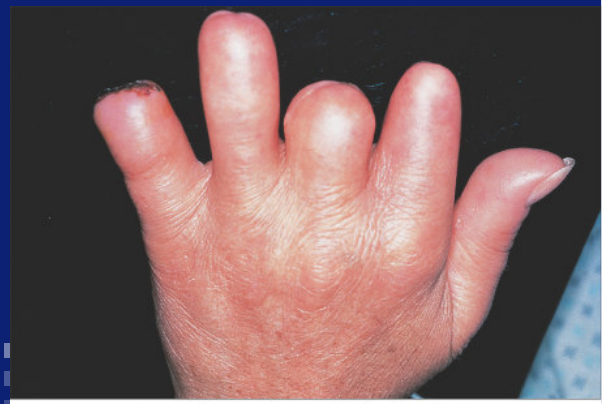

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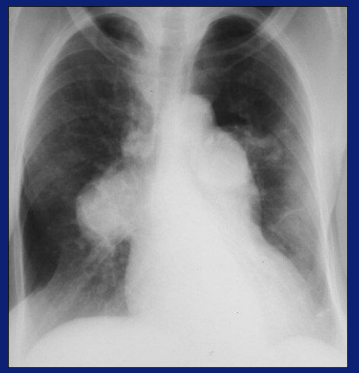
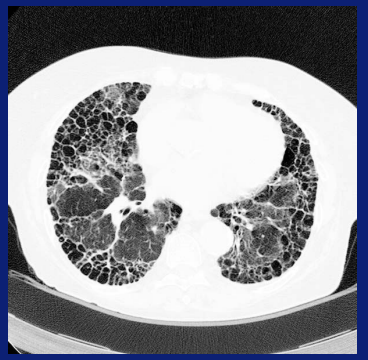
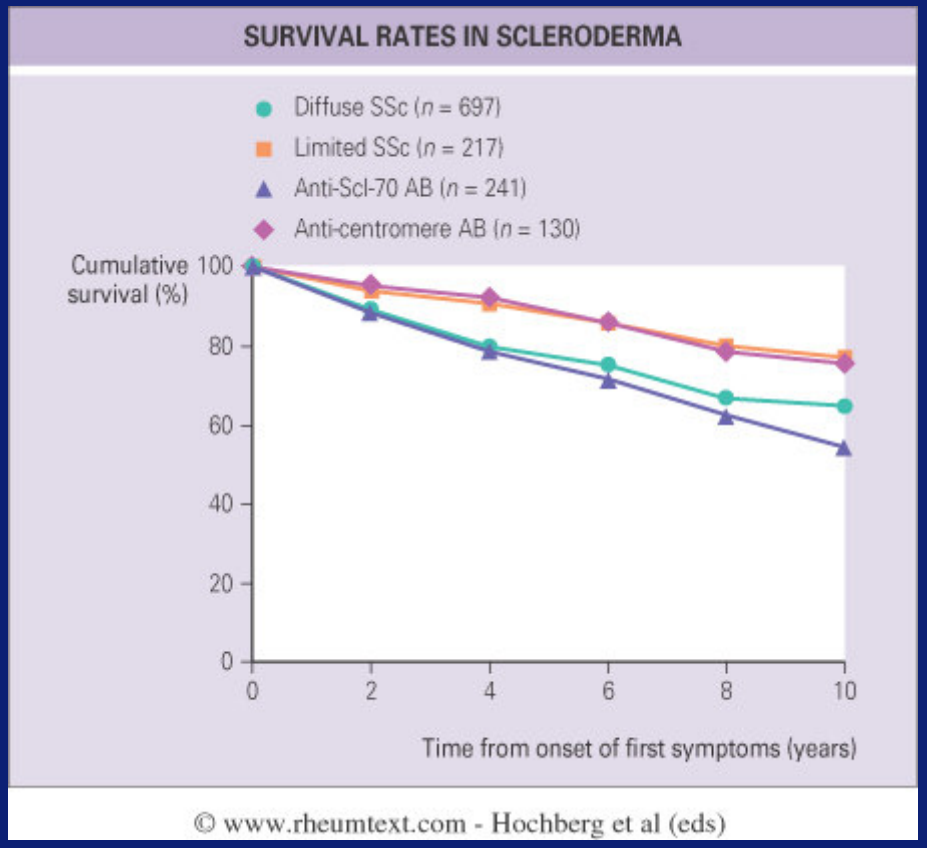
Clinical picture

- Raynaud + progressive skin changes
- Involvement internal organs
    - Gastrointestinal tract
    - Lungs
    - Kidney
    - Heart

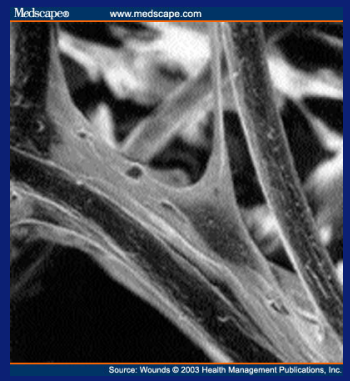




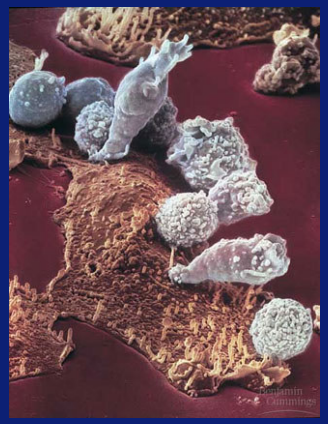
Clinical picture

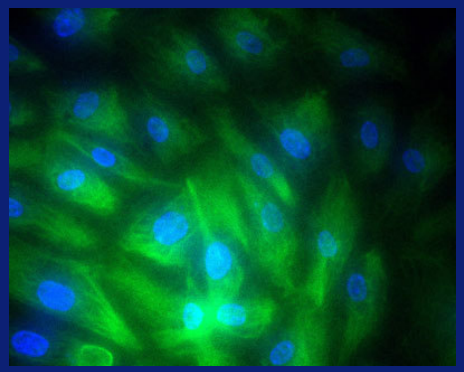


Pathofysiology



fibroblasts

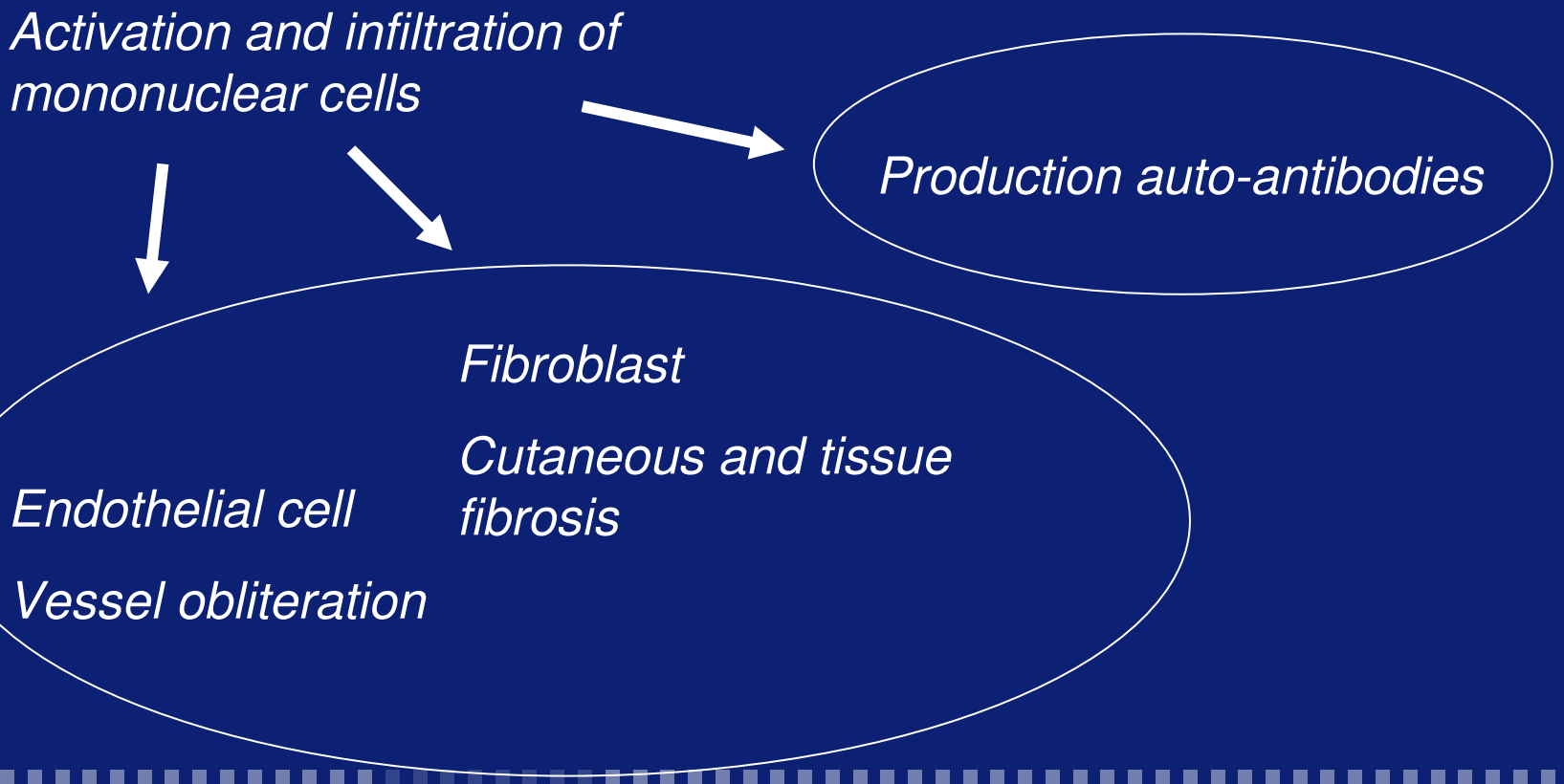




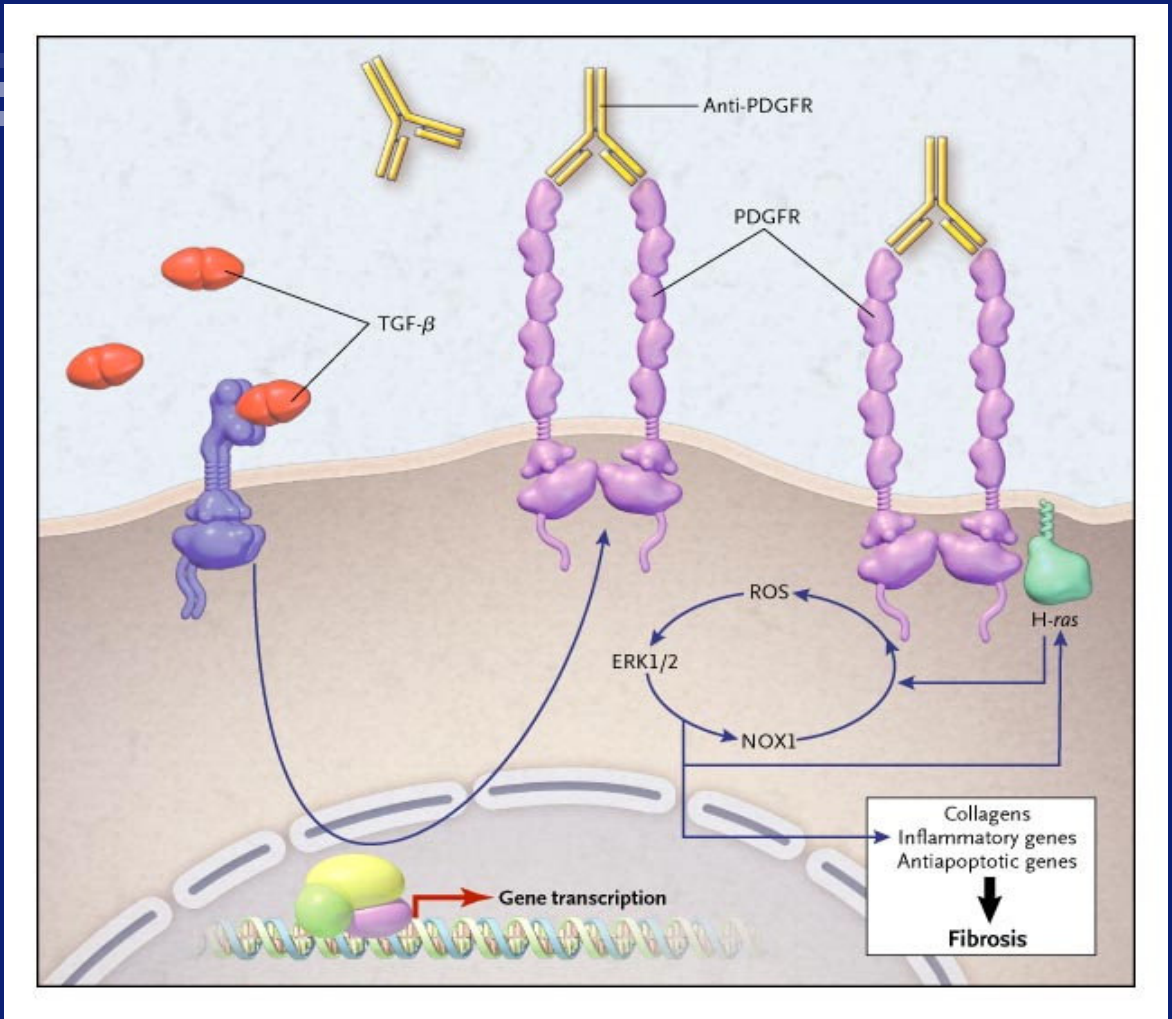
T- and B-cells

Endothelial cells

Pathofysiologie



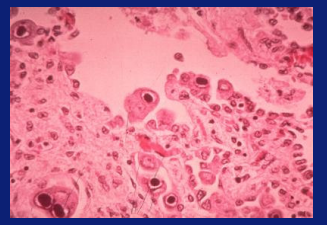
Selective Up-Regulation of PDGFR by Fibroblasts in Scleroderma.



Tan FK. N Engl J Med 2006;354:2709-2711.

Pathofysiology

- What activates mononuclear cells?
  - CMV
  - retrovirus
  - Microchimerism
  - Silica
  - Organic solutions



Pathofysiologie

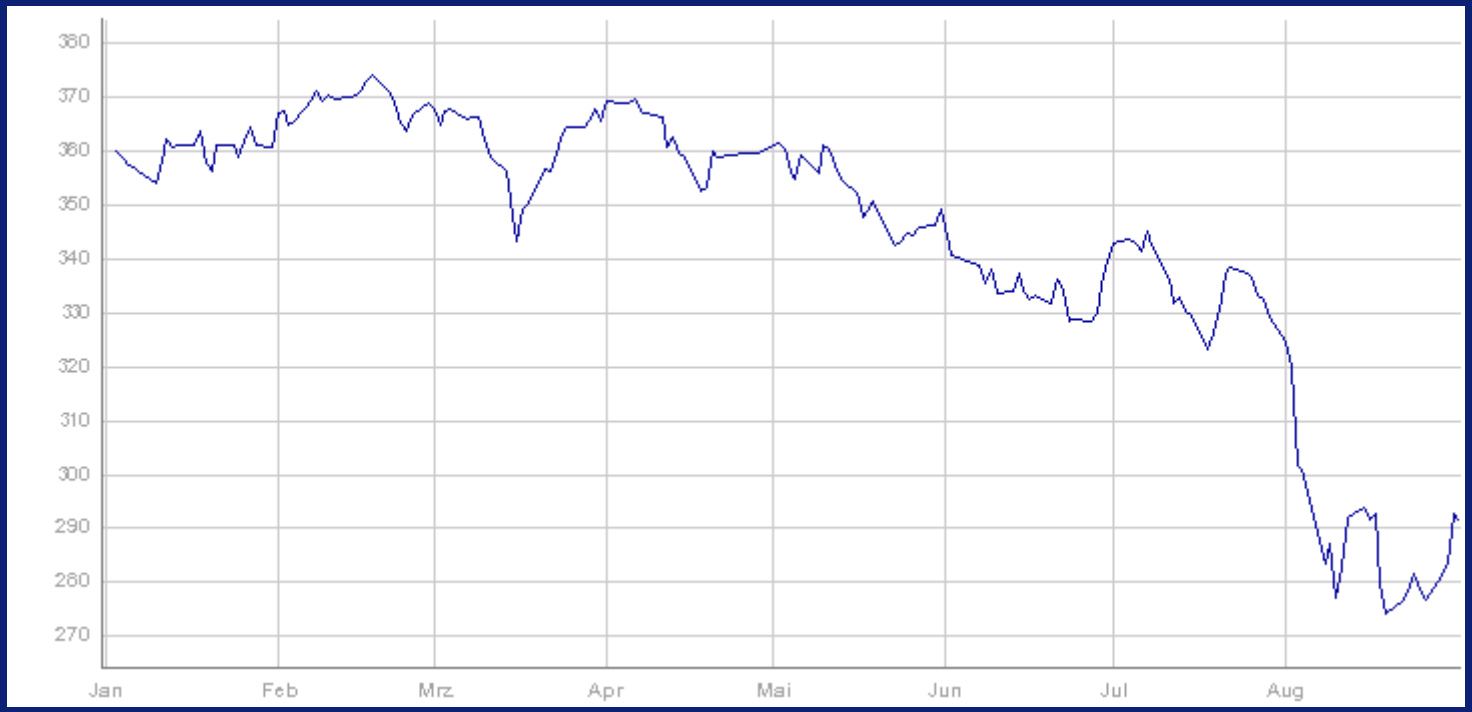
- *Endothelial cells*
- *Probably under the influence of* TGF-β
  - Thrombocyt aggregation
  - PDGF ⬆
  - CTGF ⬆
  - NO ⬇
  - Endotheline ⬆

Vessel obliteration +
Tissue hypoxia

Treatment

- Organ specific:
  - Kidney: ACE inhibitors
  - Lungs
    - Pulmonary hypertension:
      - Bosentan
      - Sildenafil
      - Prostacycline
    - Pulmonary fibrosis: immunosuppresion
      - Steroids
      - Cyclofosfamide
      - Anti-TNF
  - Gastrointestinal: metoclopramide, domperidon
  - Skin: ?

Effect of current treatment



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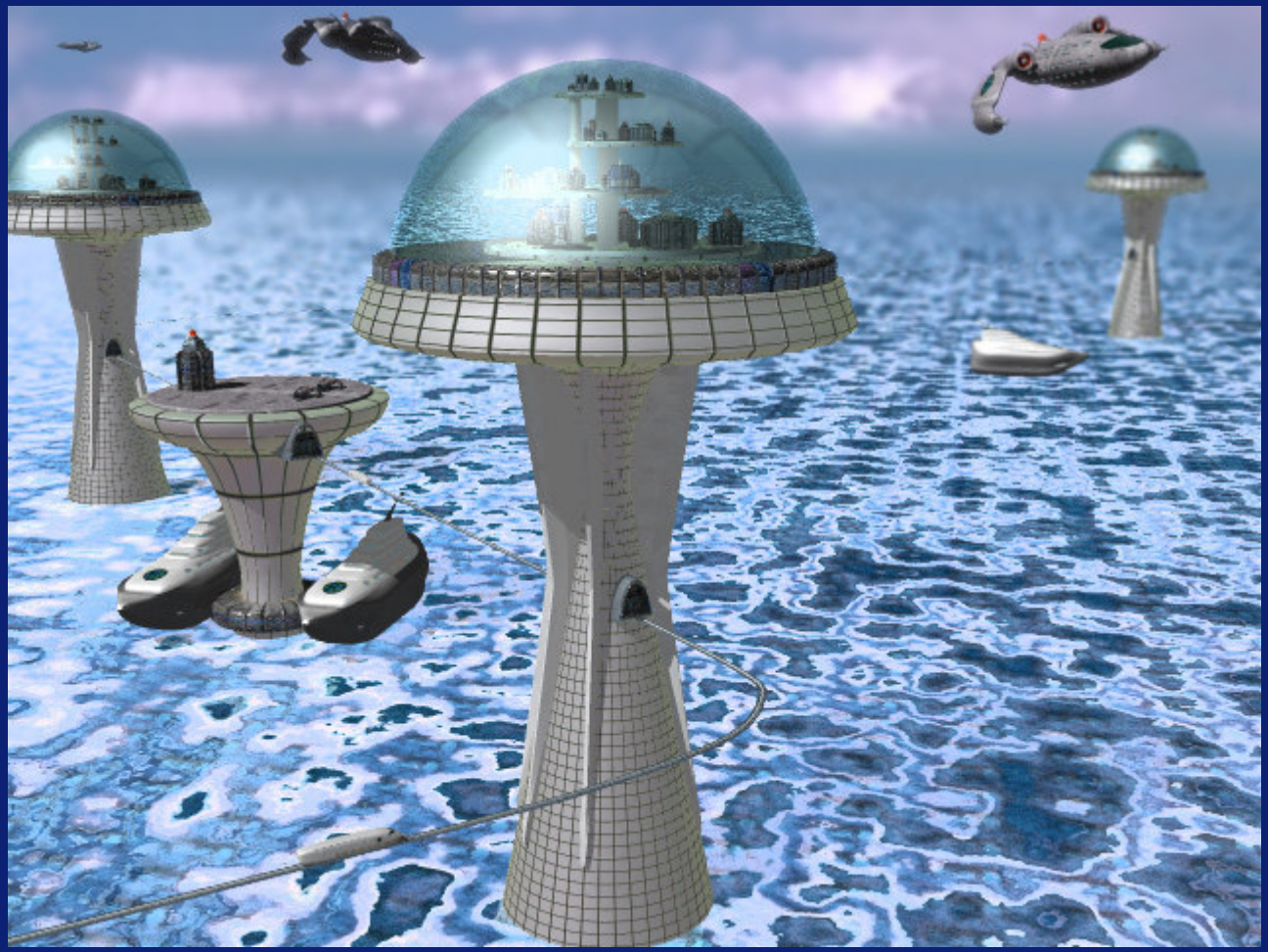
Future treatments?



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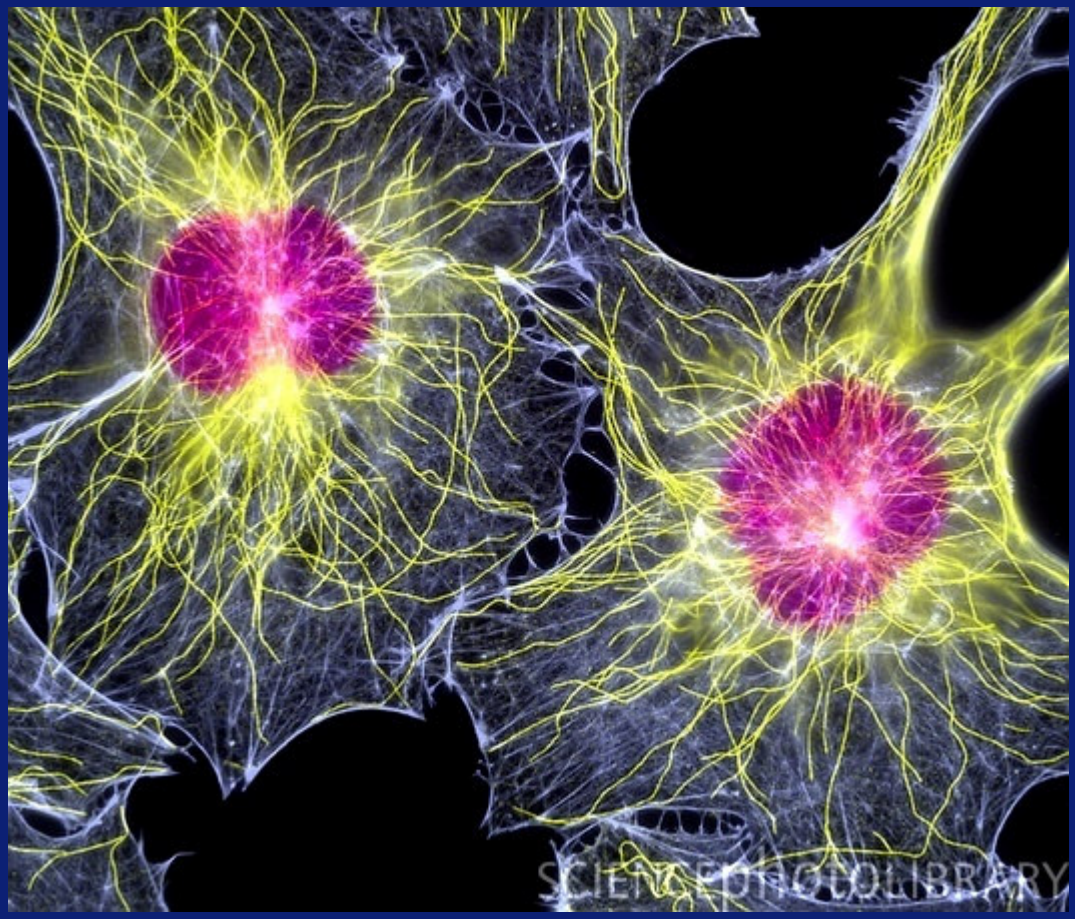
Science

The fibroblast



Fibroblast

- Most important cell of the connective tissue
- Supports extracellulair matrix
- Produces precursors of all components of the extracellulair matrix
  - Collagen
  - Glycosaminoglycans (e.g. hyaluronicacid)
  - Reticulair and elastic fibers
  - Glycoproteins

The fibroblast as cell of the immunesystem

Table 1. Variation in chemokine production between human fibroblasts from different anatomic sites and pathologic settings

		Fibroblast tissue origin[a]					
		Hematopoietic tissue		Lung		Breast	
Chemokines	N[b]	I-Normal	II-Pathologic	III-Normal	IV-Pathologic	V-Normal	VI-Pathologic
IL-8	39	*	*	0.000 (I)	0.025 (I)	*	*
MCP-1	41	*	*	*	*	*	*
RANTES	35	*	*	0.017 (I)	*	*	0.025 (I)
MIP1-α	35	*	0.033 (I)	0.022 (I)	*	*	*
Eotaxin	30	*	0.010 (I)	*	*	*	0.029 (I)

a) Grouping of fibroblasts is as described in Sect. 4.1. Numbers are the exact *p* values as estimated by the Mann-Whitney U test. Only significant values ($p < 0.05$) are shown. Parentheses indicate the group used for comparison.

b) N = total number of tested samples.

Eur. J. Immunol. 2000. *30:* 914–919

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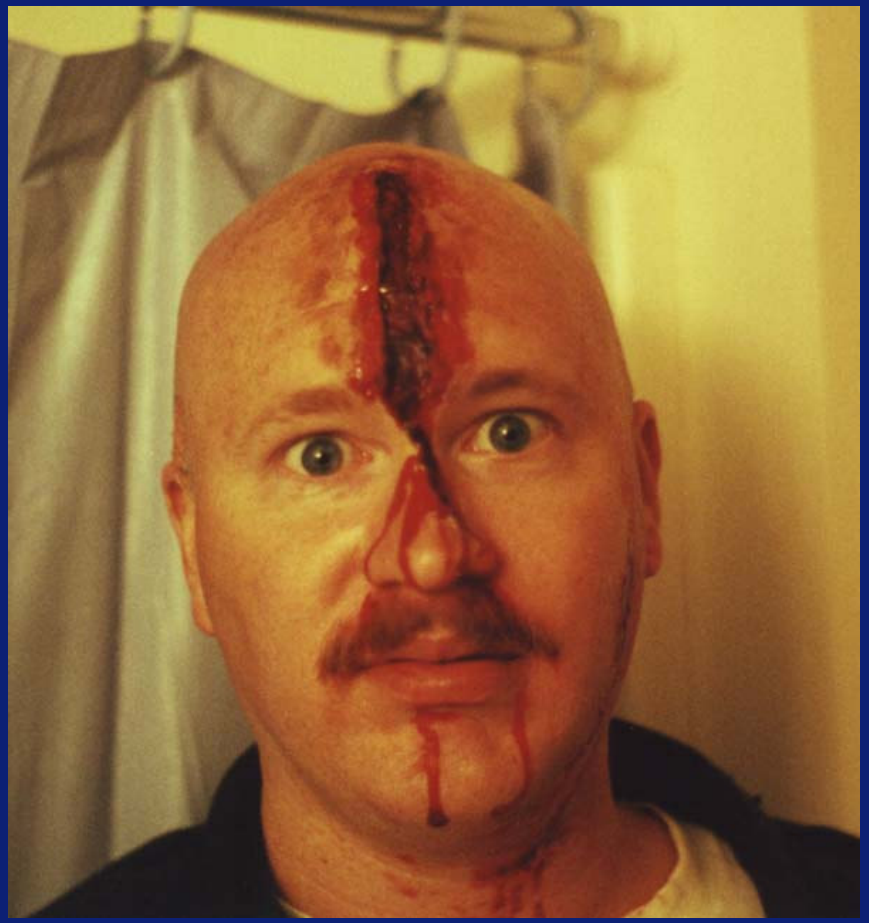
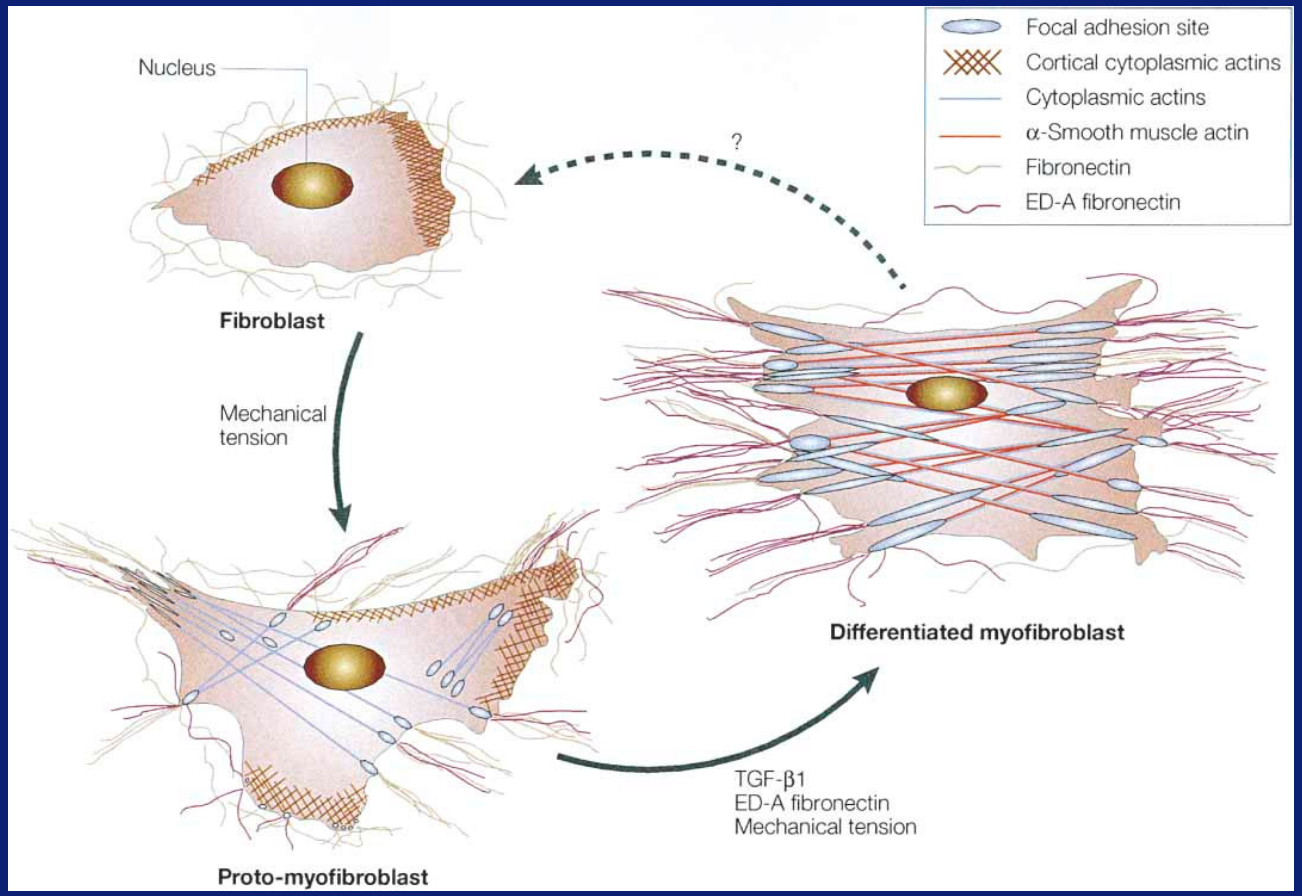
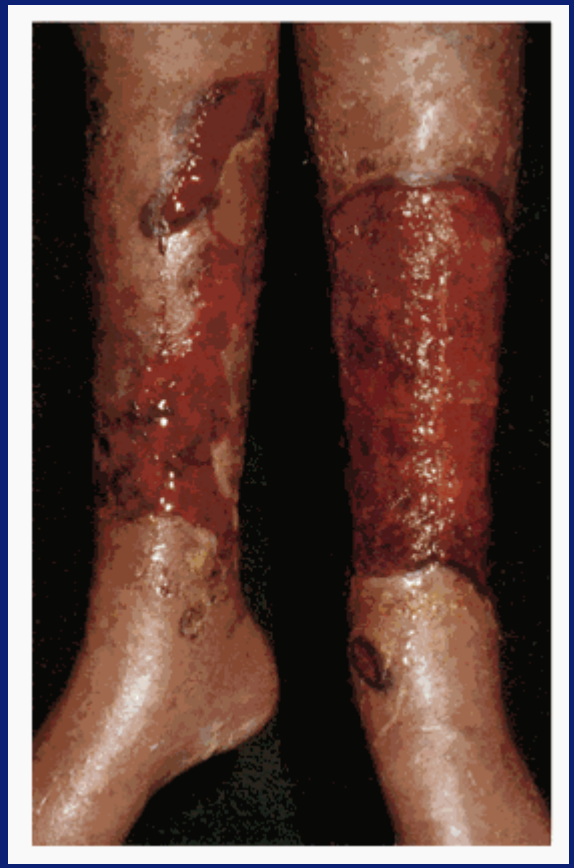
Core business of the fibroblast

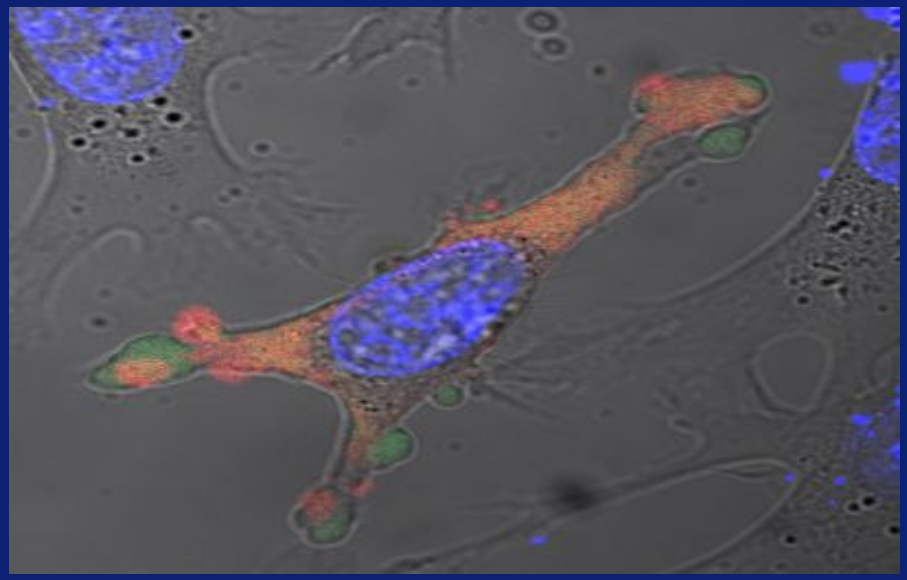


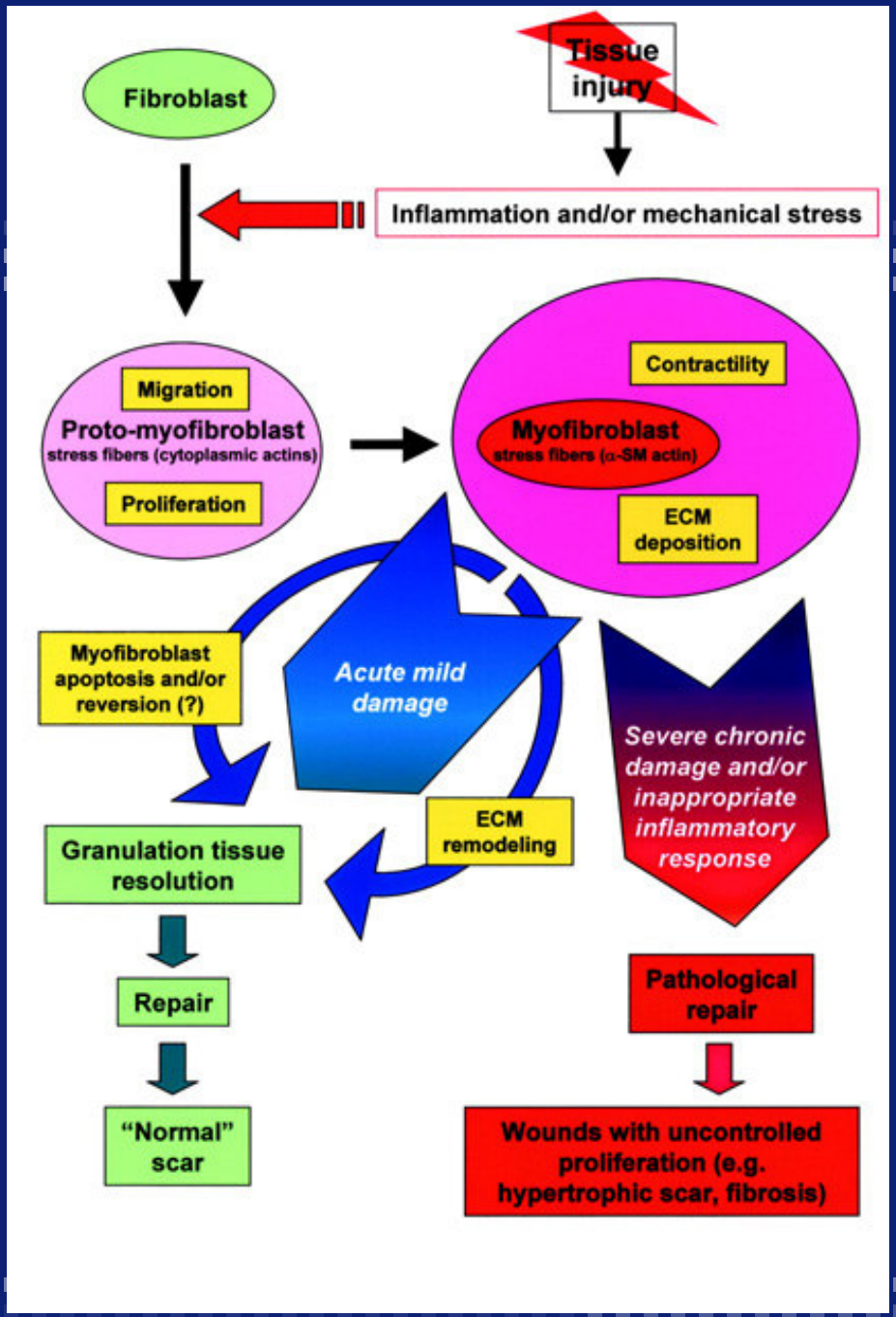

Focal adhesion site
Cortical cytoplasmic actins
Cytoplasmic actins
α-Smooth muscle actin
Fibronectin
ED-A fibronectin
Nucleus
?
Fibroblast
Mechanical tension
Differentiated myofibroblast
TGF-β1
ED-A fibronectin
Mechanical tension
Proto-myofibroblast

Granulation tissue



Apoptosis

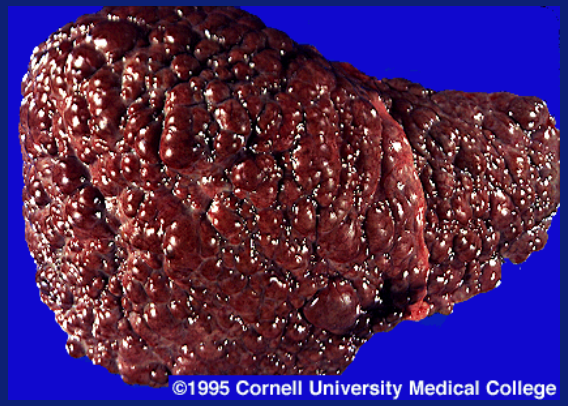



Fibroblast
Tissue injury
Inflammation and/or mechanical stress
Migration
Proto-myofibroblast
stress fibers (cytoplasmic actins)
Proliferation
Contractility
Myofibroblast
stress fibers (α-SM actin)
ECM deposition
Myofibroblast apoptosis and/or reversion (?)
Acute mild damage
Severe chronic damage and/or inappropriate inflammatory response
ECM remodeling
Granulation tissue resolution
Repair
"Normal" scar
Pathological repair
Wounds with uncontrolled proliferation (e.g. hypertrophic scar, fibrosis)

The dysregulated fibroblast

- Together fibrosing diseases are the main cause of morbidity and mortality in North America, Europe and Japan
- (WHO 2002; The World Health Report 2002, Geneva)

Liver disease



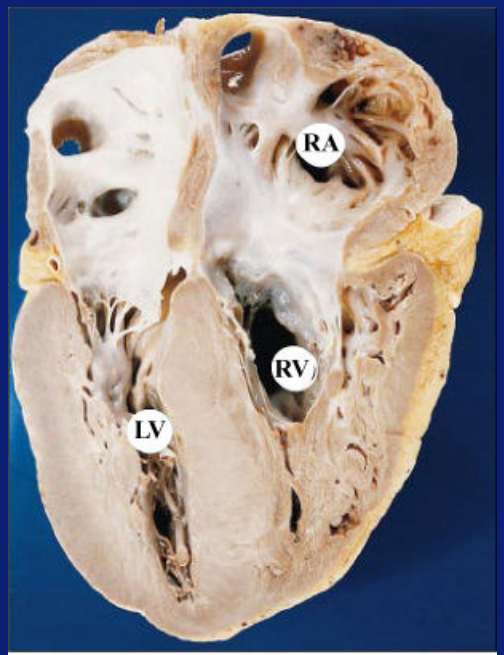
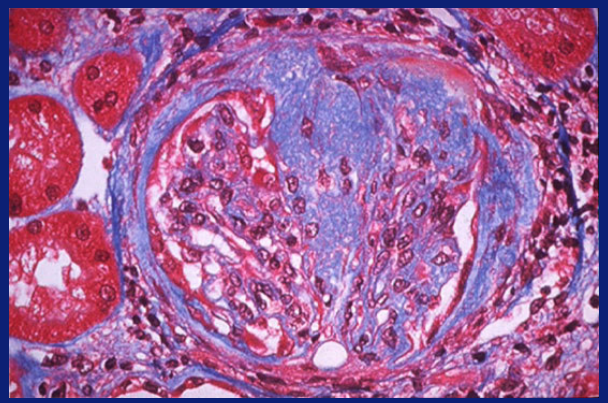
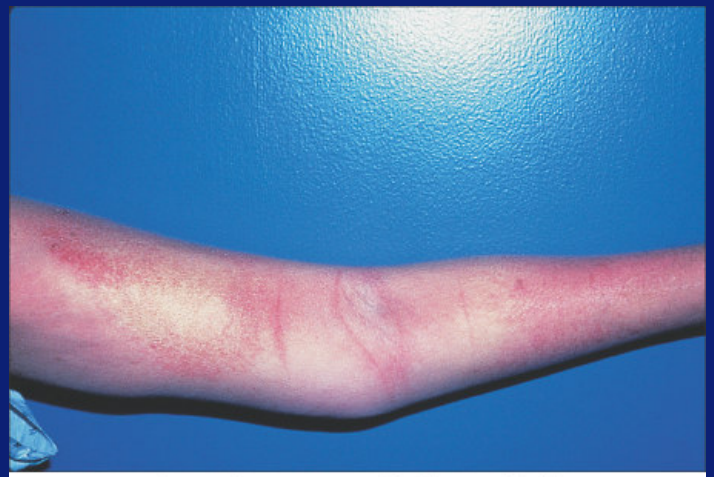


Fig. 2 - Longitudinal section of the heart, showing the 4 chambers. Marked concentric and symmetric hypertrophy of the left ventricle (LV) can be seen. Right atrium (RA) and ventricle (RV) show hypertrophy and mild dilation.



General fibrotic disease



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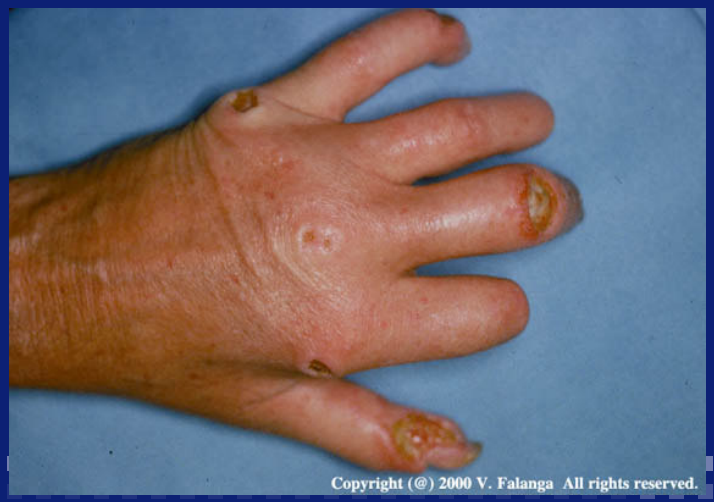

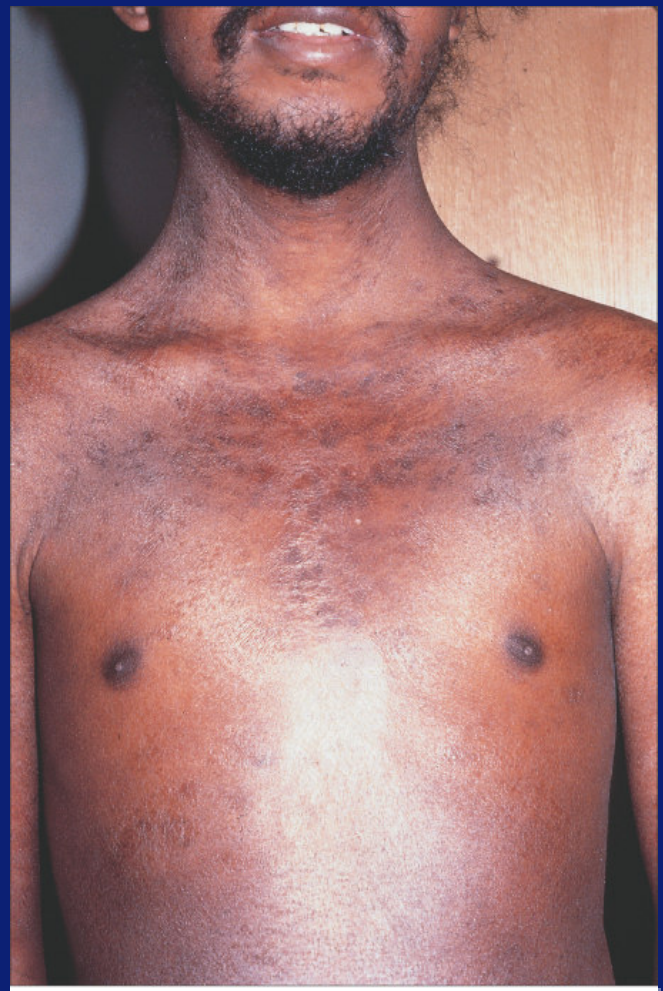

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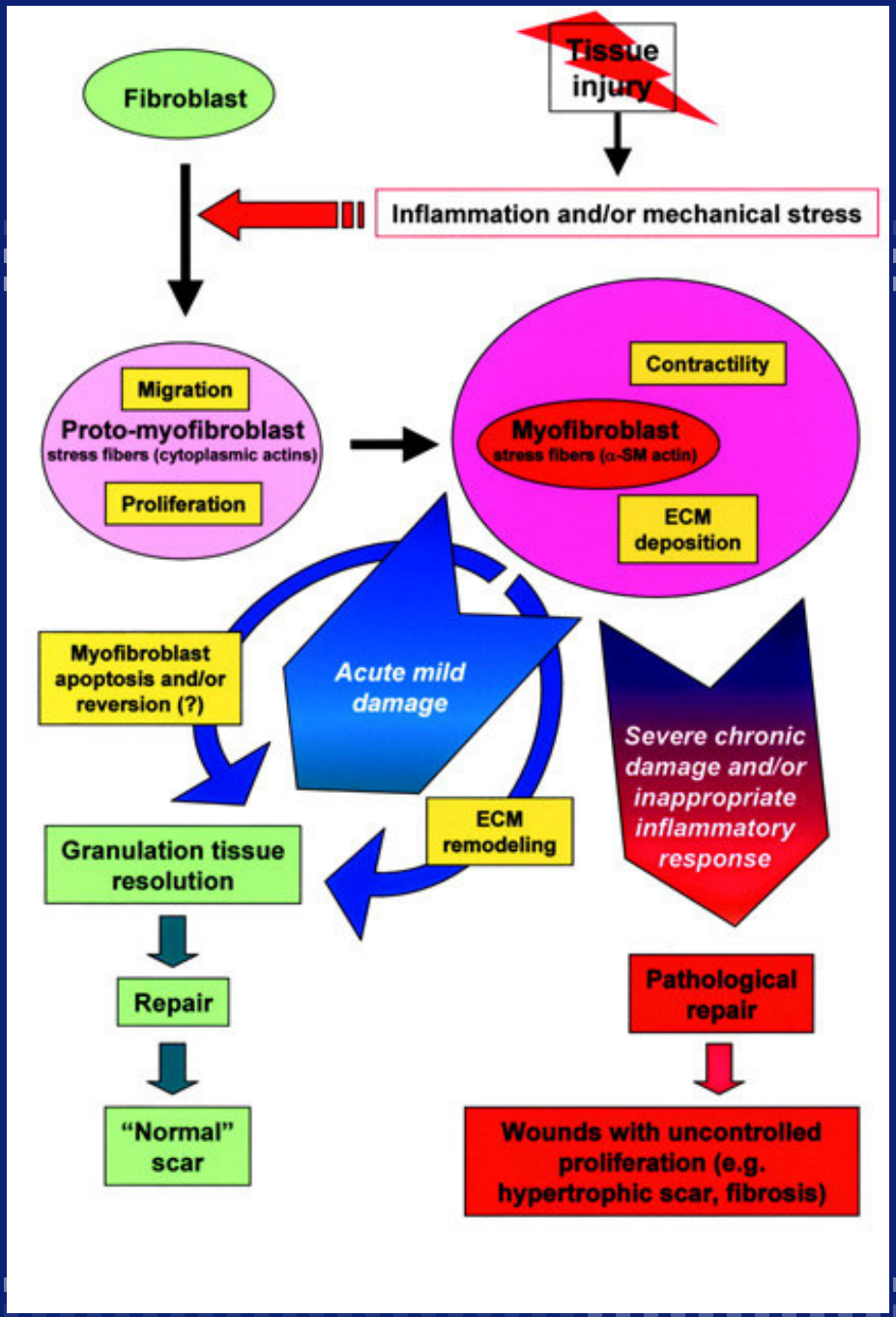
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Tissue injury
Inflammation and/or mechanical stress
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Proliferation
Contractility
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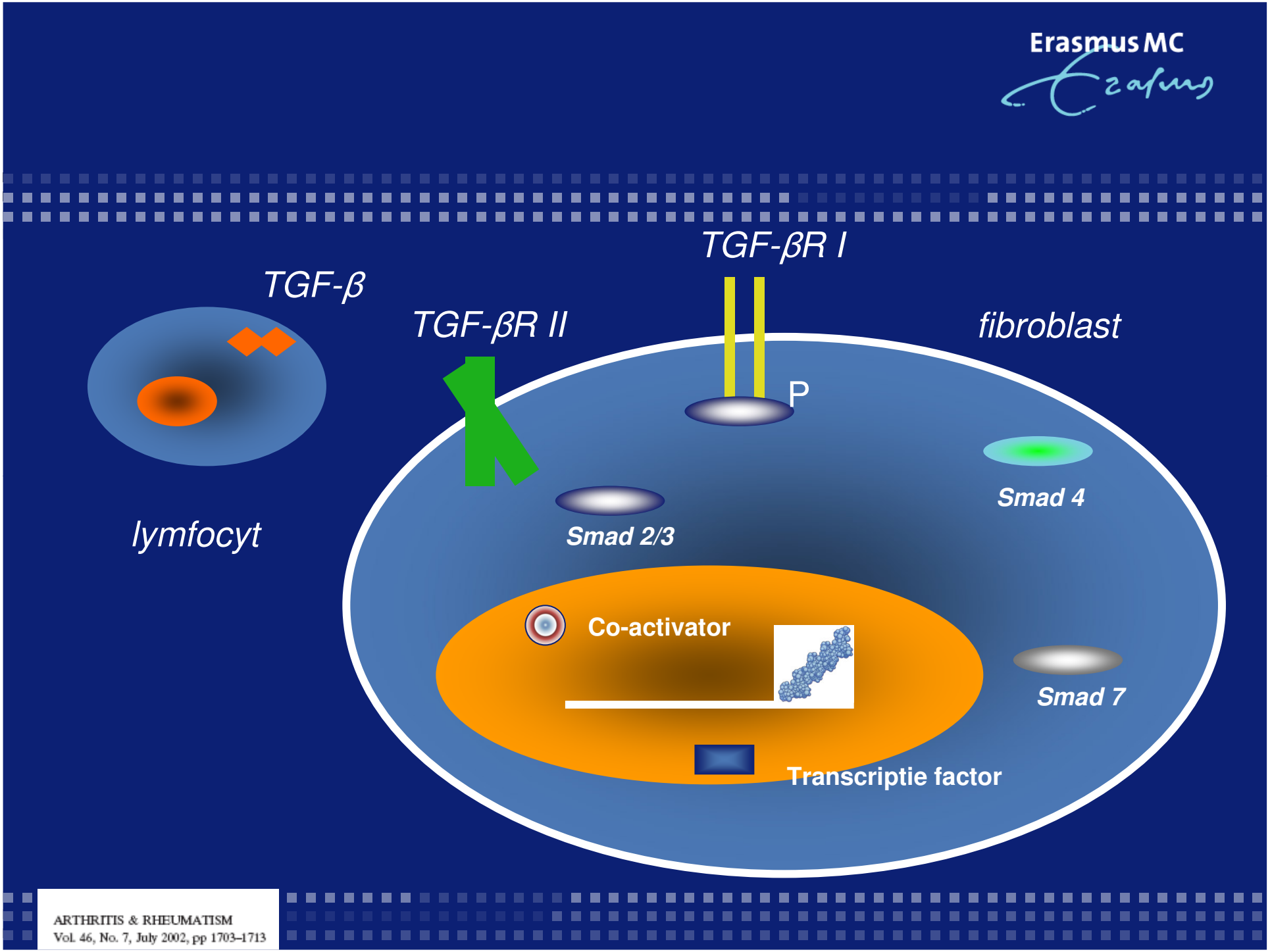

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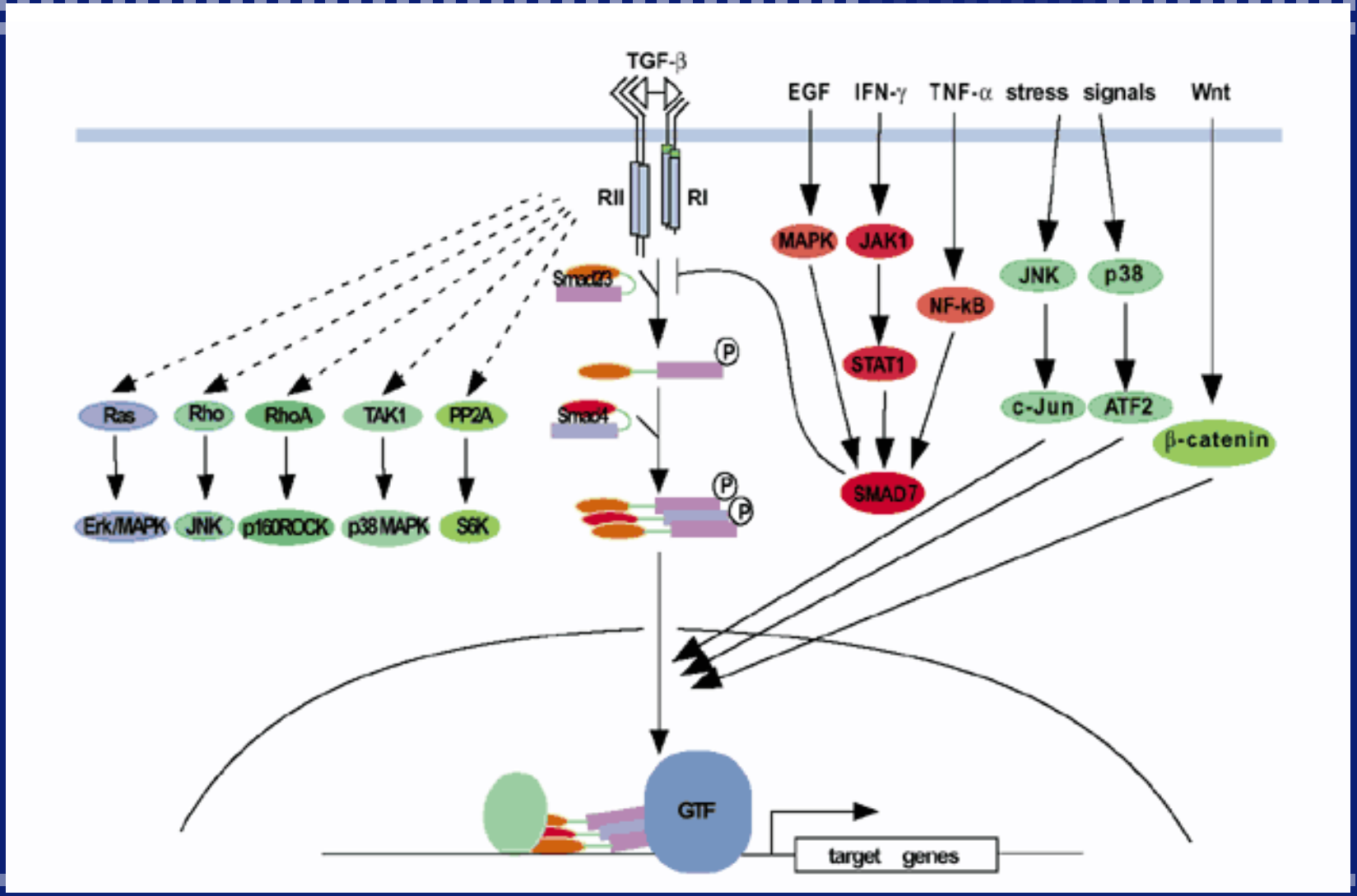
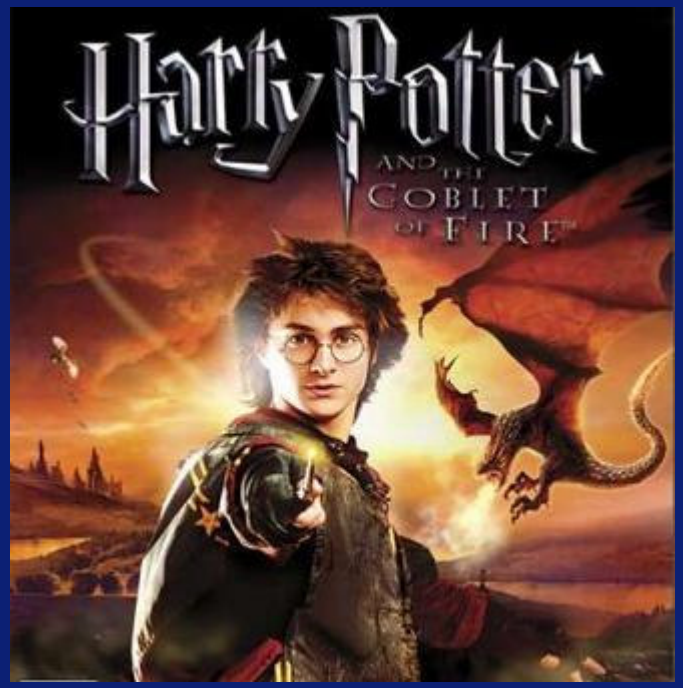
Vol. 46, No. 7, July 2002, pp 1703–1713


TGF-β
EGF
IFN-γ
TNF-α
stress signals
Wnt
RII
RI
MAPK
JAK1
JNK
p38
NF-kB
STAT1
c-Jun
ATF2
β-catenin
SMAD7
Ras
Rho
RhoA
TAK1
PP2A
Erk/MAPK
JNK
p160ROCK
p38 MAPK
S6K
Smad4
P
GTF
target genes

Mechanisms: Good guys – bad guys



- Smad 7

- Smad 2/3
- Smad 4
- TGF-Beta

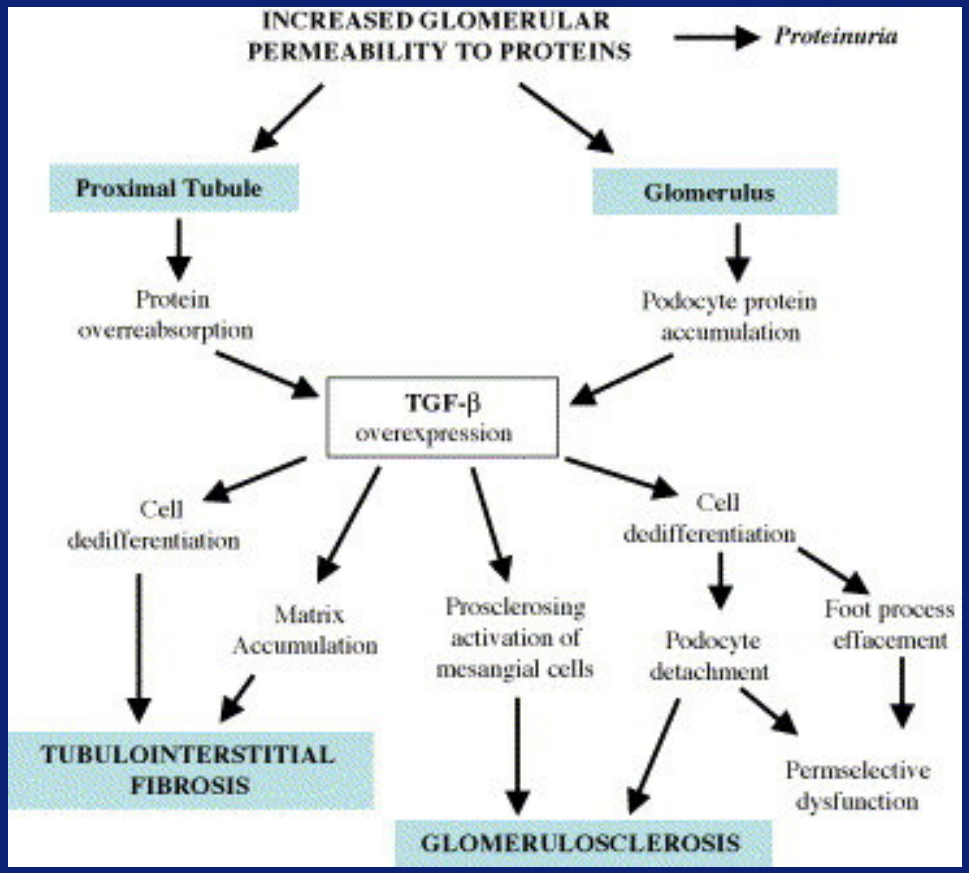
Targeting bad guys

Table 2. Alterations in transforming growth factor β (TGFβ)/Smad signaling in fibrosis

Fibrotic process	Alterations	Ref.
In vivo animal models		
Renal fibrosis		
Thy-1 antibody induced (rats)	⇓ Smad7 expression	62
TGFβ transgenic (mice)	⇓ Smad7 expression	63
db/db (mice)	⇓ Smad3 expression	67
Ovalbumin-induced airway fibrosis	⇑ Smad2 phosphorylation, ⇑ Smad3 expression	68
Postinfarction myocardial fibrosis	⇑ Smad3 expression	87
Pulmonary fibrosis in Smad3-null mice	⇓ collagen production	74
In vitro cell culture		
Myofibroblast transdifferentiation	⇑ Smad2 phosphorylation, ⇓ Smad7 expression	60
Hepatic cells from fibrotic liver	⇑ Smad3 phosphorylation, ligand-independent Smad3/4 nuclear accumulation	64
Hepatic cells from fibrotic liver	⇑ Smad3 expression, ⇓ Smad7 expression	88
Smad3-null hepatic cells from CCl_4-induced liver injury	⇓ collagen induction	41
Dermal fibroblasts from keloid lesions	⇑ Smad3 phosphorylation	65
Dermal fibroblasts from scleroderma	⇑ Smad3 expression	66
	⇑ Smad2/3 phosphorylation	61, 66
	⇓ Smad7 expression	61

Arthritis & Rheumatism Vol.46, 7 Pages: 1703-1713

Targeting bad guys



Cytokine & Growth Factor Reviews
Volume 17, Issues 1-2 , February-April 2006, Pages 89-96

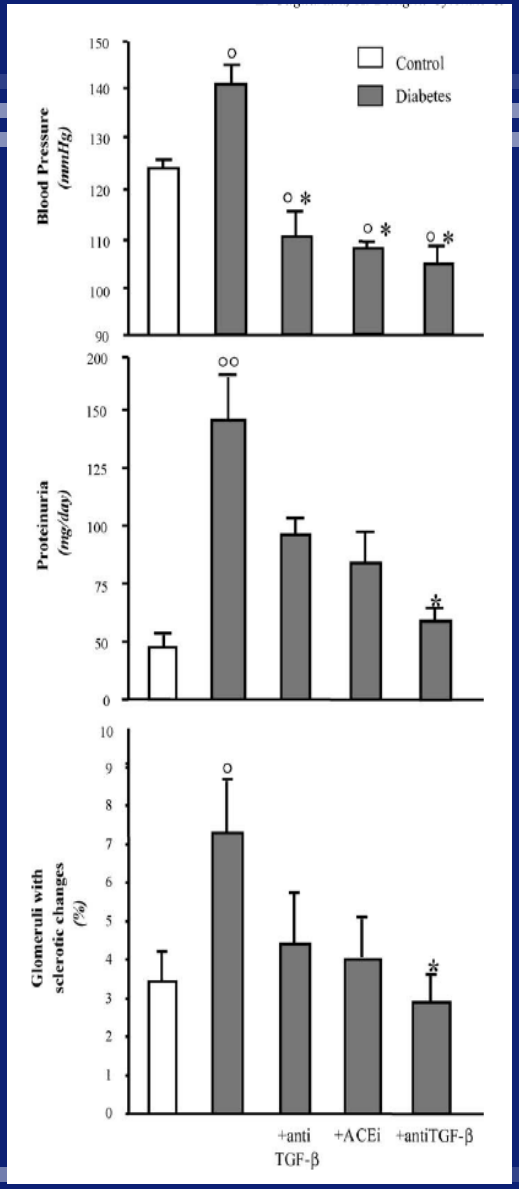
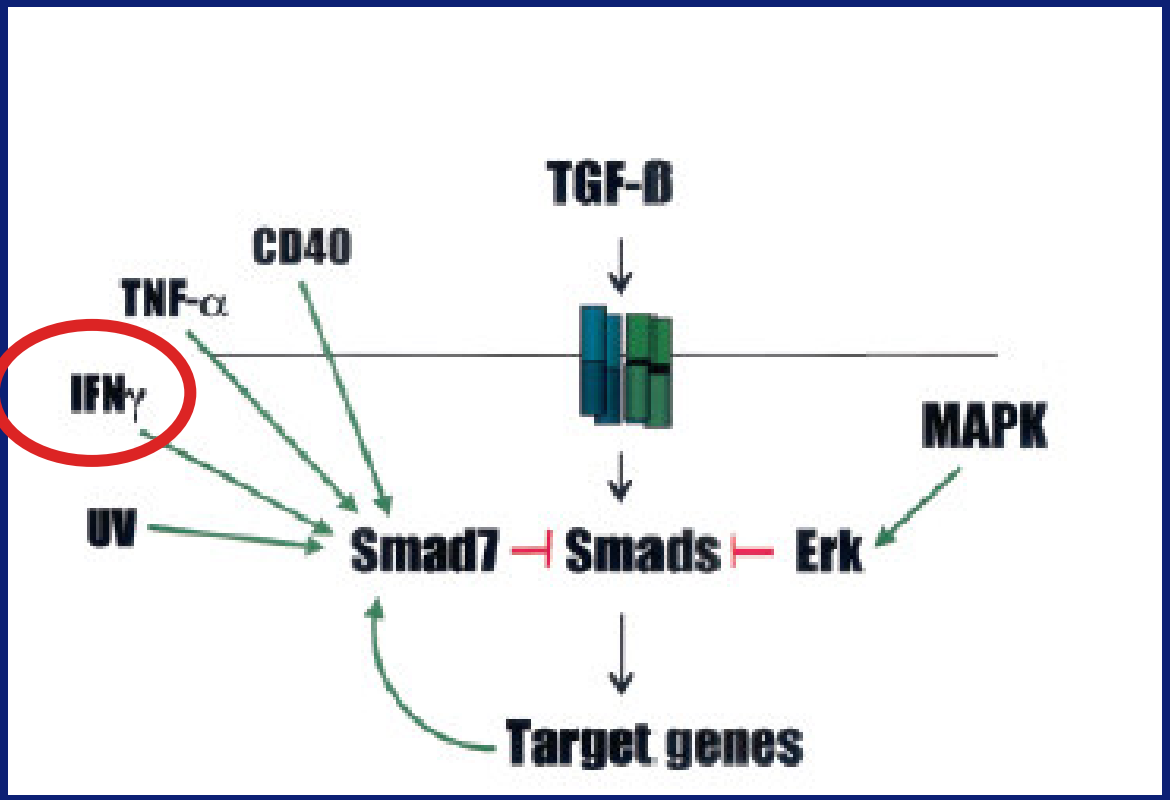


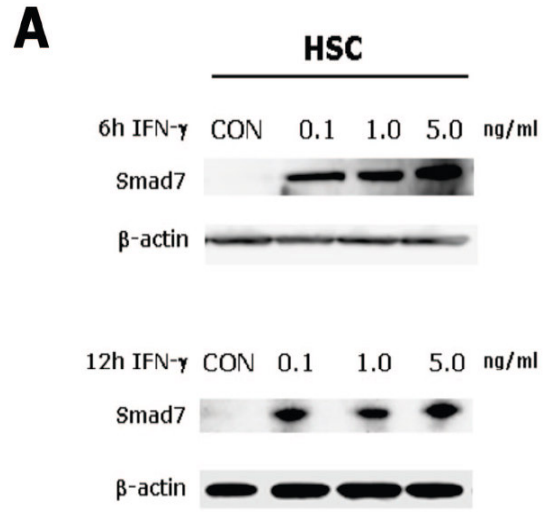
Fig. 2. Effect of anti-TGF-β alone or in combination with ACE inhibitor on blood pressure, proteinuria and renal histology in diabetic rats. $^{o}p < 0.05$, $^{oo}p < 0.01$ vs. control; $^{*}p < 0.05$ diabetic rats.

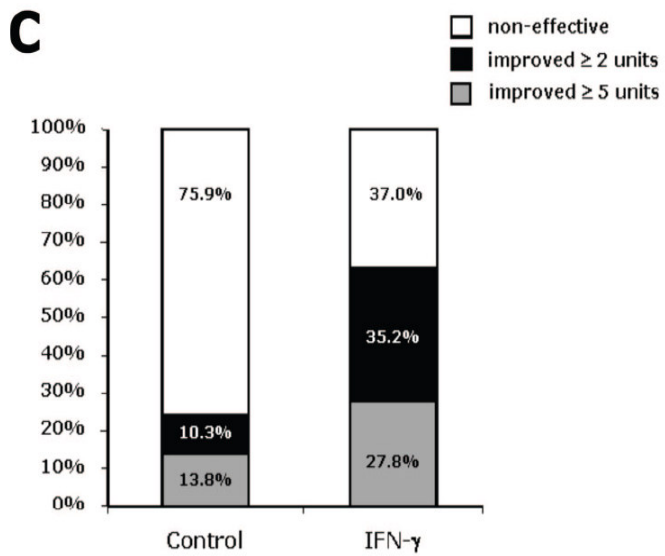
E. Gagliardini, A. Benigni / Cytokine & Growth Factor Reviews 17 (2006) 89–96

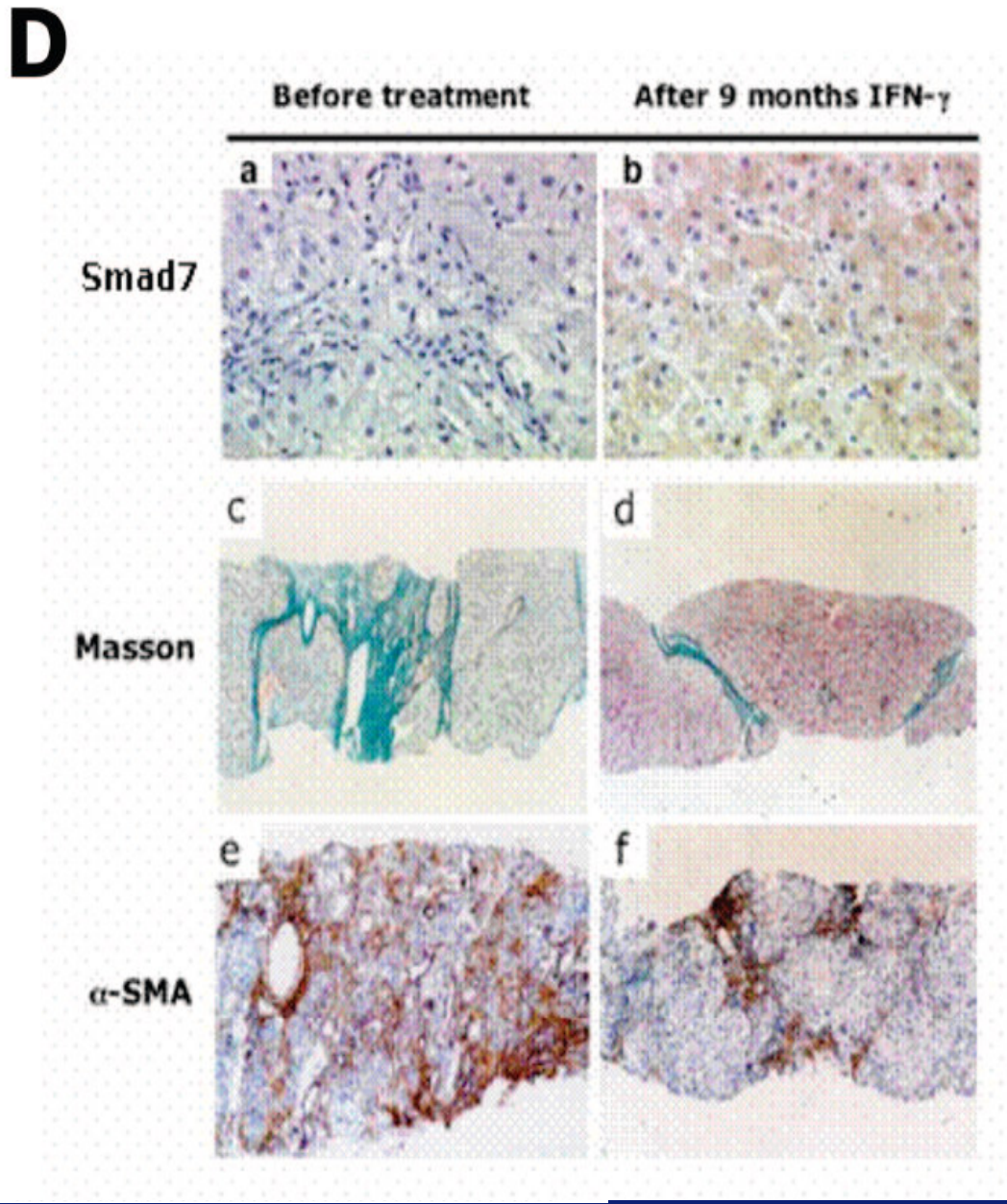
Targeting good guys



Arthritis & Rheumatism Vol.46, 7 Pages: 1703-1713







Alcohol Clin Exp Res, Vol 29, No 11, 2005: pp 121S–131S

Direct targeting of the fibroblast

Interferon gamma

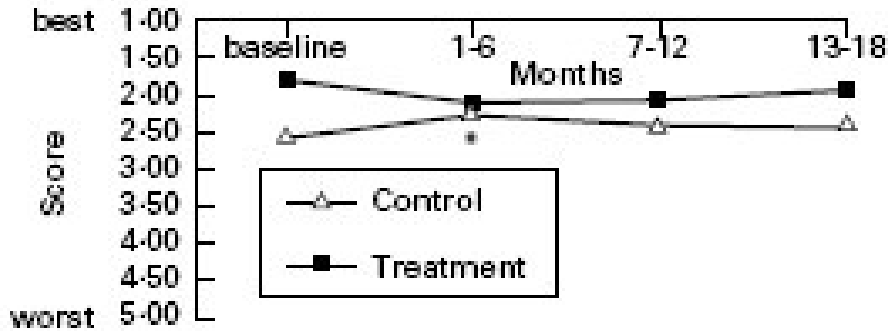
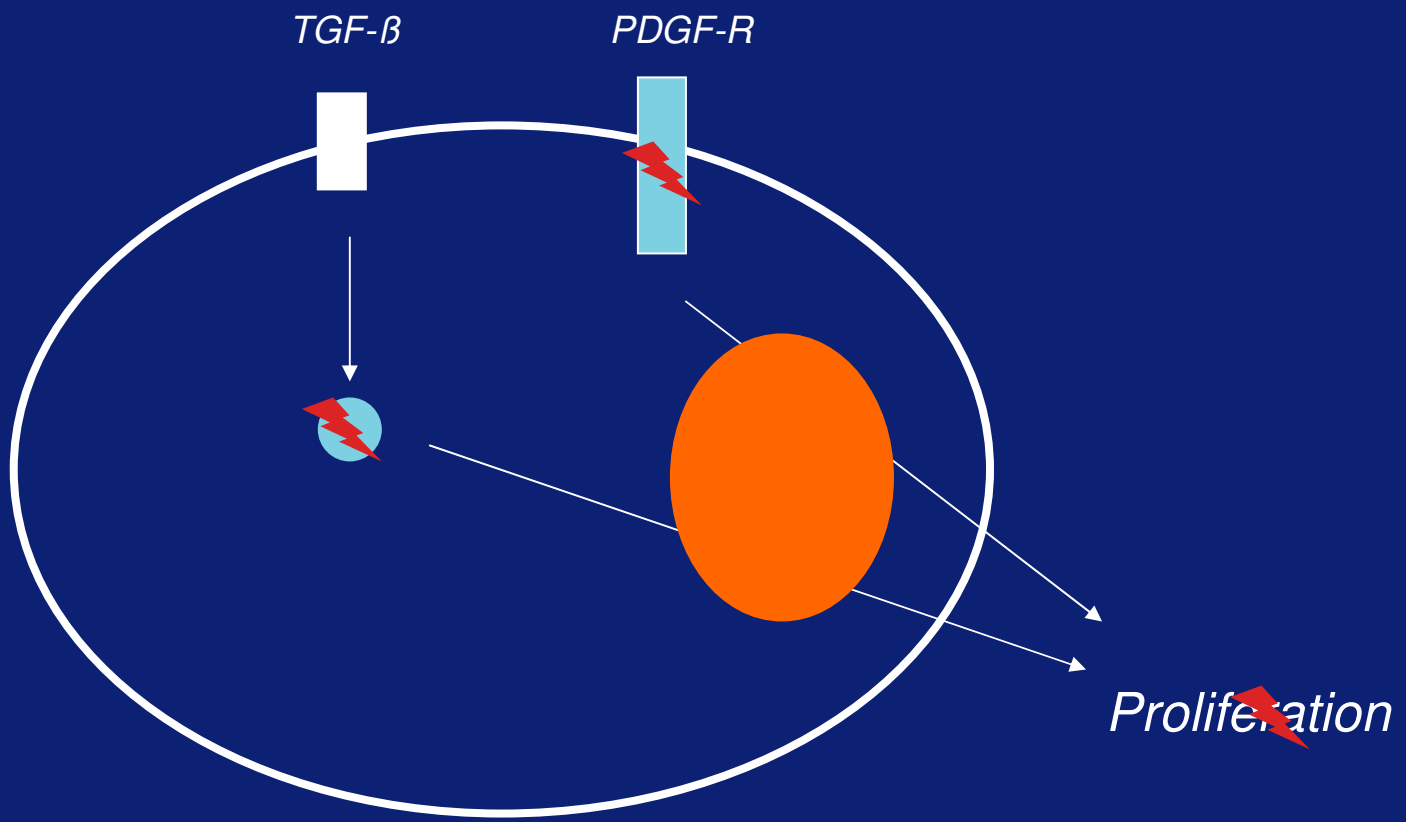
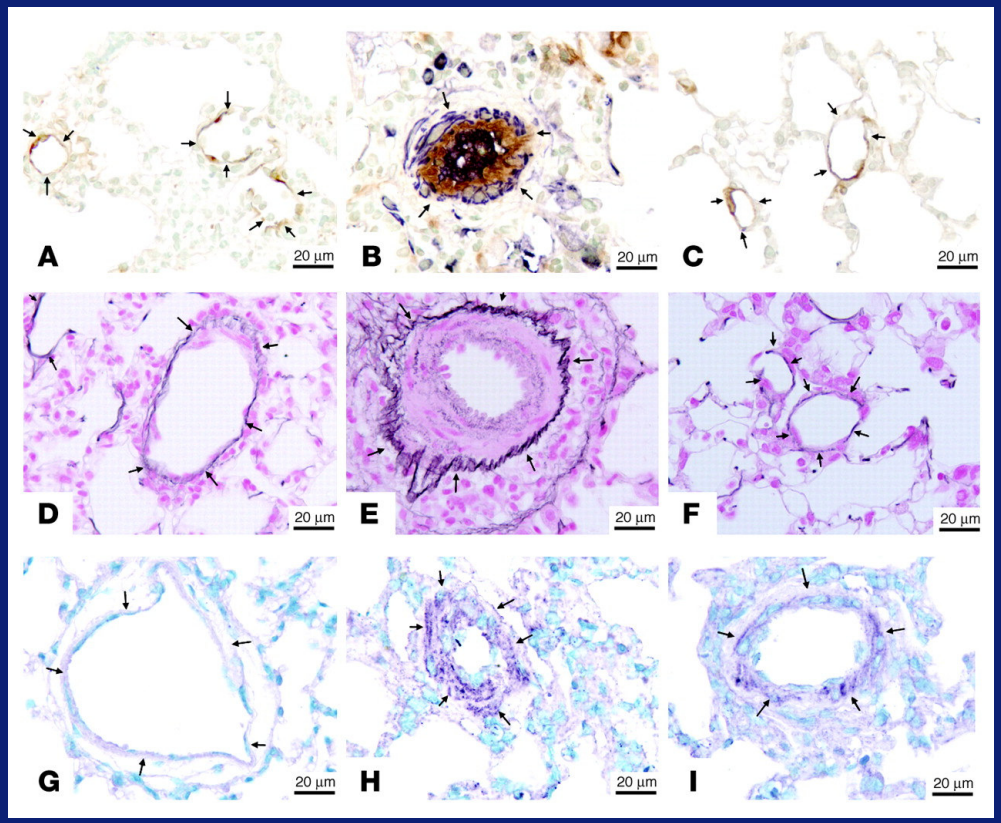


Fig. 5. Quality of life improved significantly in the control patients (*$P < 0.05$ compared with baseline).

Tyrosine kinase remmers



Effects of STI571 on the degree of muscularization (A-C), medial wall thickness of small pulmonary arteries (D-F), and PDGF-B expression (G-I)

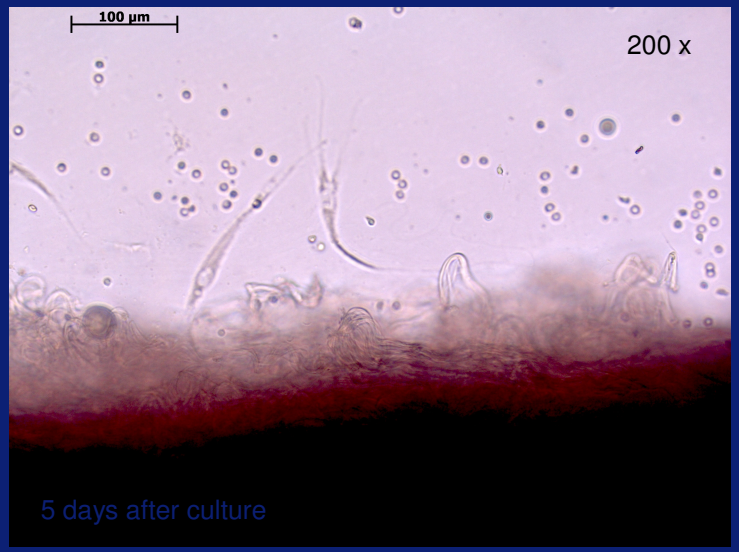


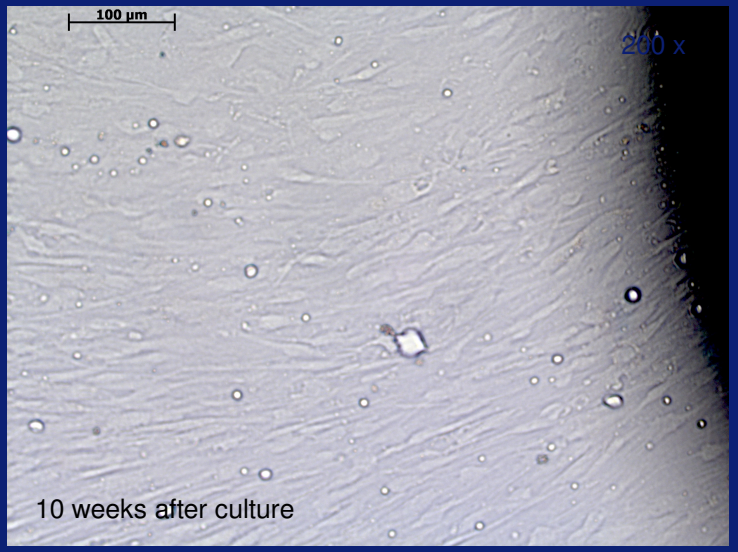
Schermuly, R. T. et al. J. Clin. Invest. 2005;115:2811-2821

Erasmus MC

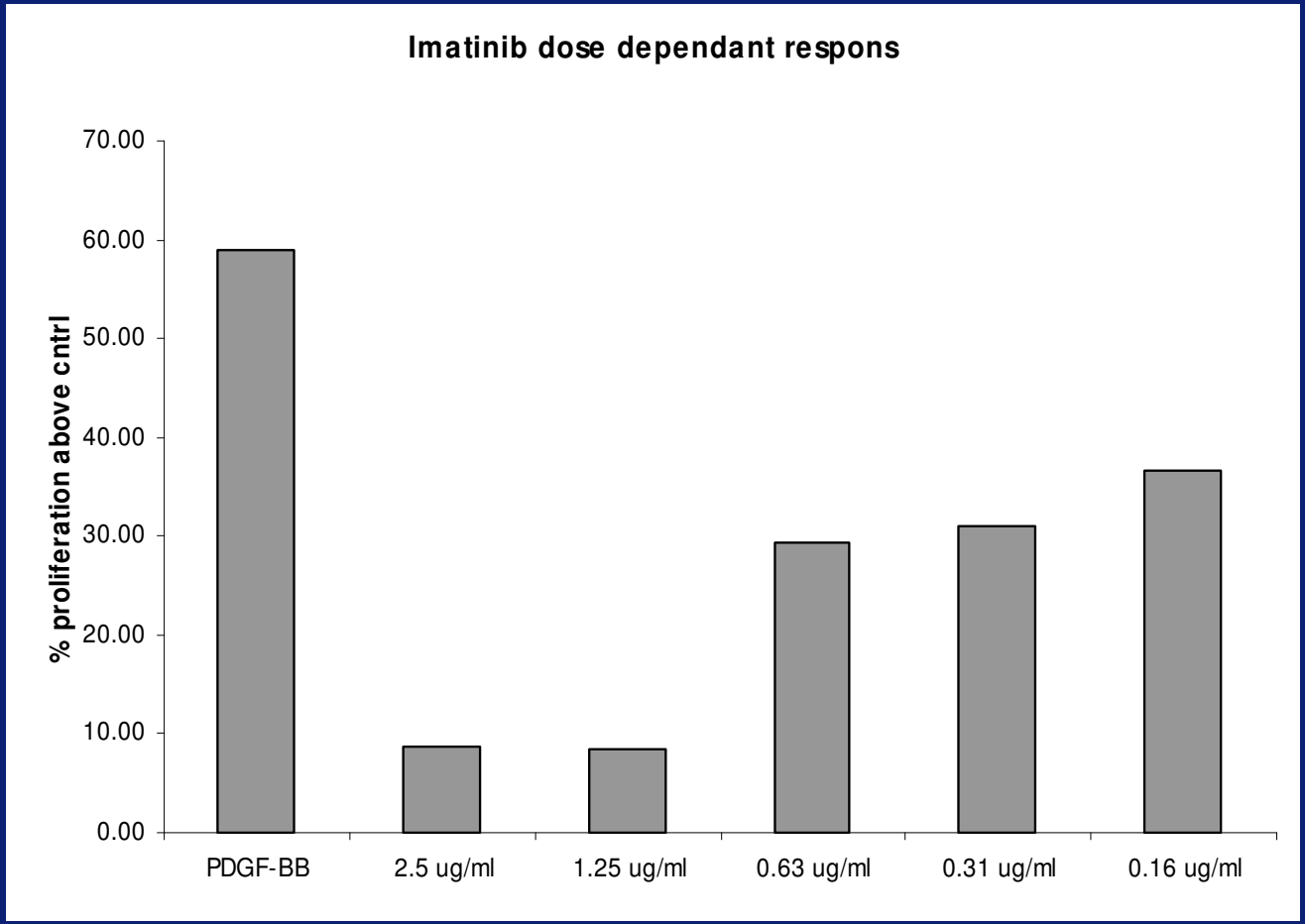
Own work

Culture of Fibroblasts (GO-27)



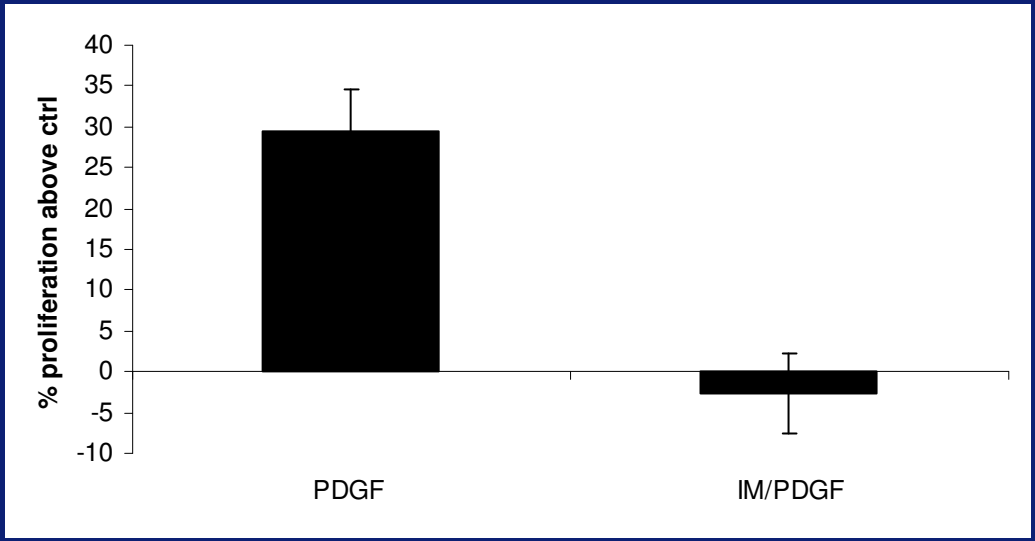


Imatinib blocks PDGF-BB induced proliferation sufficiently above 1.25μg/ml



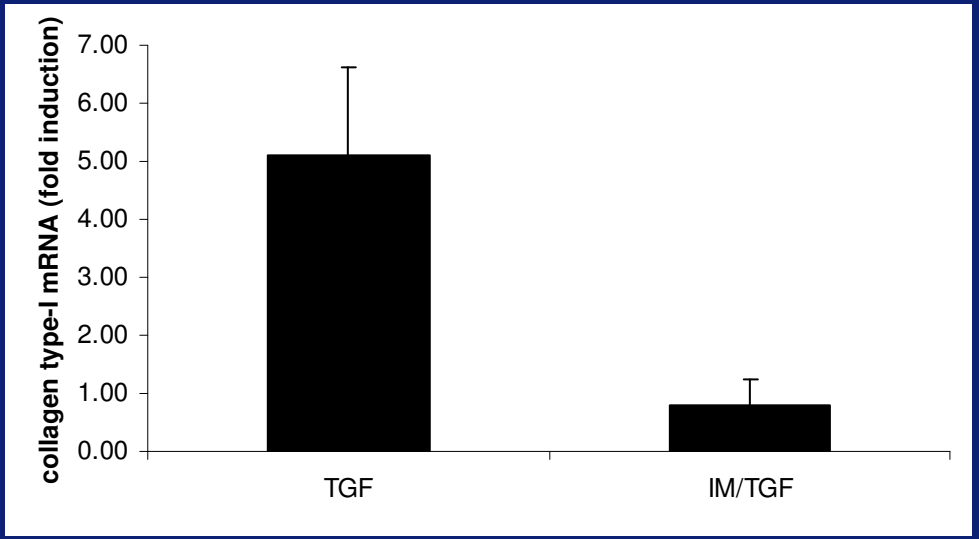
Van Steensel, Dik

Patient 1



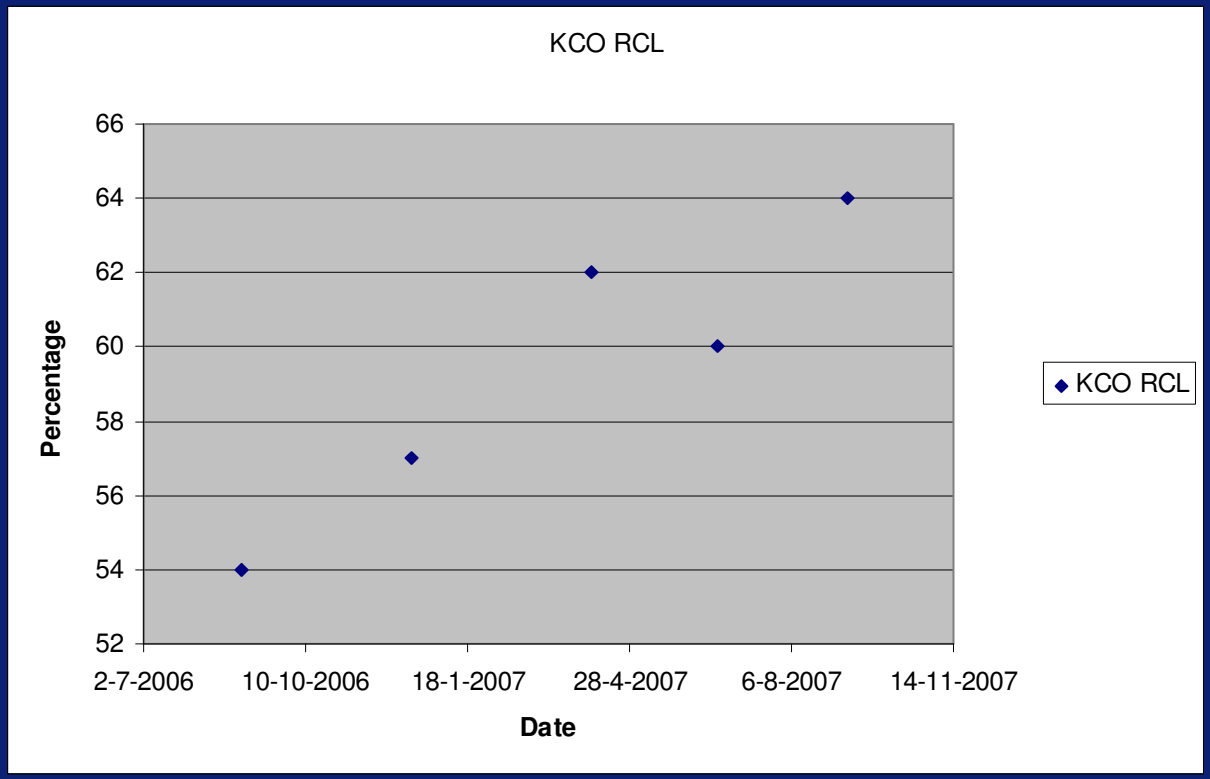
Imatinib mesylate (IM; 2.5 ug/ml) blocks PDGF (50 ng/ml)-induced proliferation of bronchial fibroblasts obtained from a patient with SSc. Data are presented as the mean ± sd of three independent proliferation experiments. * $p < 0.05$.

Patient 1



Imatinib mesylate (IM; 2.5 ug/ml) blocks TGF-β_1 (10 ng/ml)-induced expression of collagen type-I mRNA (6 hours stimulation) in pulmonary fibroblasts obtained from a patient with SSc. Data are presented as mean ± sd of three independent measurements on one experiment. * $p < 0.05$.

Pulmonary function test patient 1

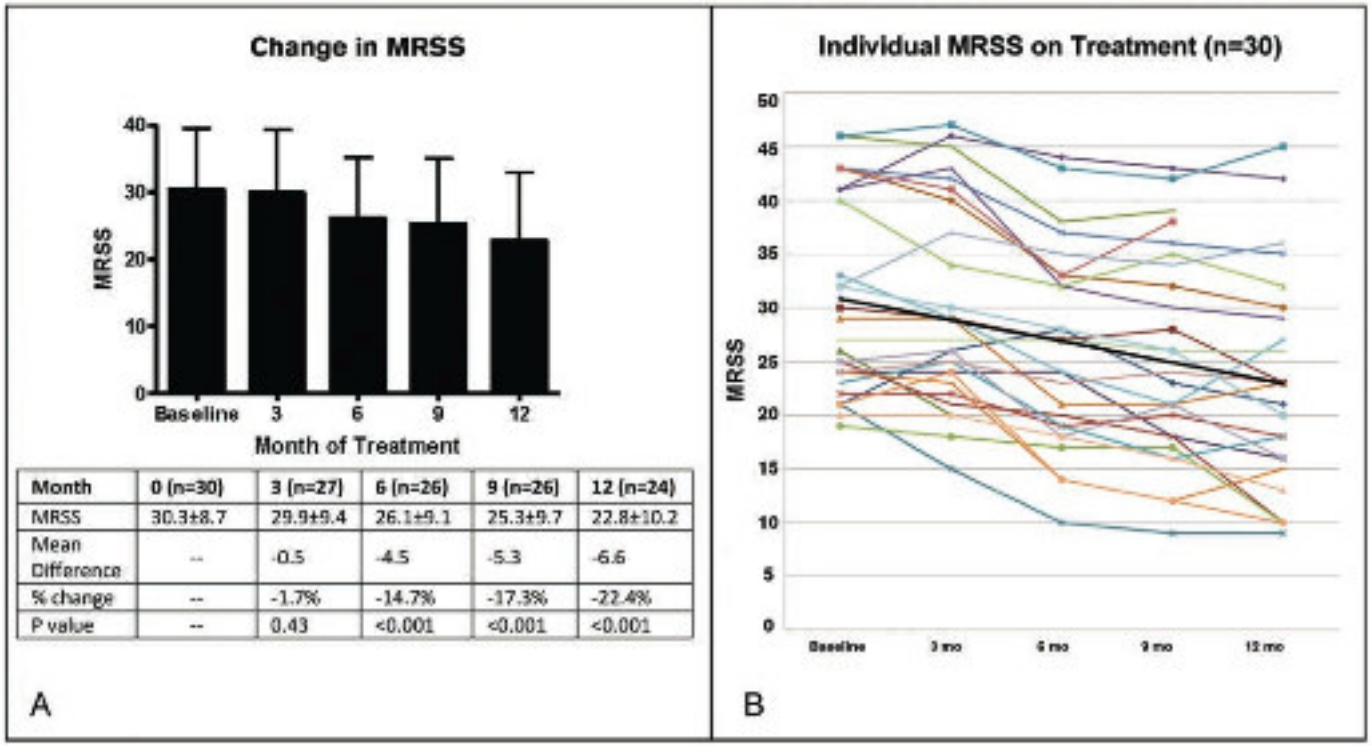


Erasmus MC

Imatinib mesylate (Gleevec) in the treatment of diffuse cutaneous systemic sclerosis: results of a 1-year, phase IIa, single-arm, open-label clinical trial

Robert F Spiera,[1] Jessica K Gordon,[1] Jamie N Mersten,[1] Cynthia M Magro,[2] Mansi Mehta,[1] Horatio F Wildman,[2] Stacey Kloiber,[1] Kyriakos A Kirou,[1] Stephen Lyman,[1] Mary K Crow[1]

Ann Rheum Dis 2011;**70**:1003–1009. doi:10.1136/ard.2010.143974



Month	0 (n=30)	3 (n=27)	6 (n=26)	9 (n=26)	12 (n=24)
MRSS	30.3±8.7	29.9±9.4	26.1±9.1	25.3±9.7	22.8±10.2
Mean Difference	--	-0.5	-4.5	-5.3	-6.6
% change	--	-1.7%	-14.7%	-17.3%	-22.4%
P value	--	0.43	<0.001	<0.001	<0.001

Figure 1 Modified Rodnan skin score (MRSS) over the duration of the trial in all patients on treatment. At baseline the MRSS was 30.3±8.7 (n=30). After 3 months of imatinib therapy the MRSS was 29.9±9.4 compared with a baseline mean of 30.4±9.1 in this group (n=27); p=0.428. After 6 months the MRSS was 26.1±9.1; p<0.001 compared with baseline mean of 30.6±9.2 in this group (n=26). After 9 months the MRSS was 25.3±9.7; p<0.001 (n=26). After 12 months of treatment the mean MRSS was 22.8±10.2 compared with a baseline MRSS of 29.4±8.6 in this group (n=24); p<0.001. (A) As bar chart and (B) as individual patient plots. Black line is mean trendline.

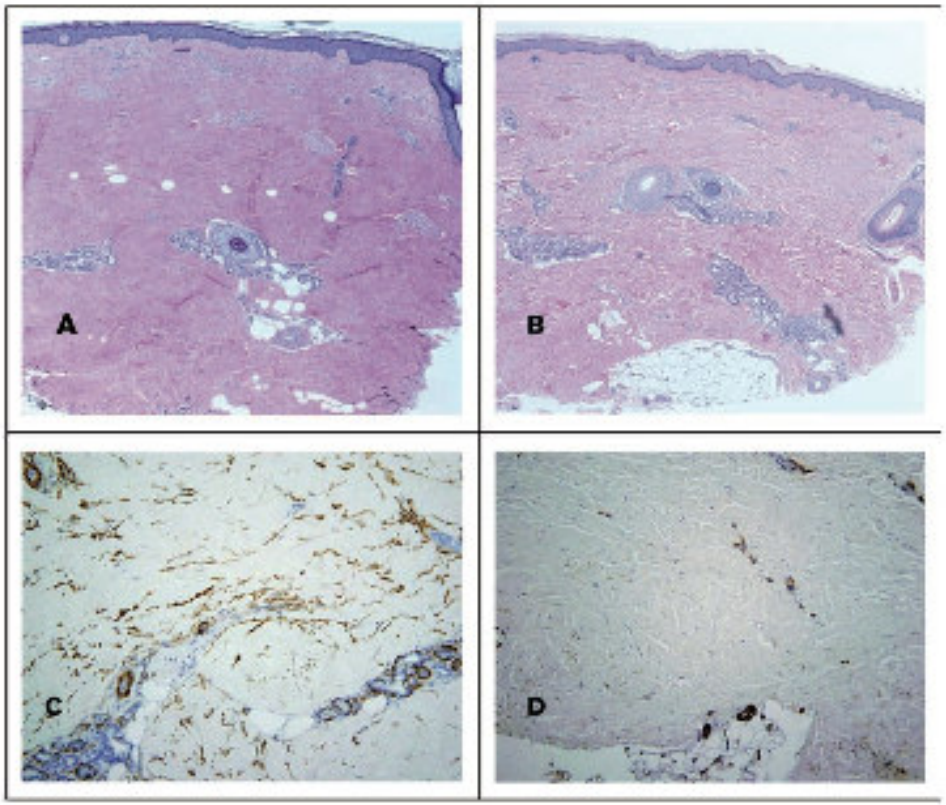


Figure 2 (A–D) Depicted are skin biopsy specimens before and after 12 months of imatinib therapy in a single patient at 4× magnification. (A and B). H&E: After treatment there was a decrease in skin thickness. In the post-treatment specimen the collagen bundles are less thick and there is an increase in the interstitial spaces between the bundles. There are also increased numbers of adnexal structures in the post-treatment specimen. This individual patient is anti-Scl70 positive, with a disease duration of 4 months at baseline who had an improvement in MRSS of 9 points over the course of 12 months. In C and D are depicted anti-α-smooth muscle actin staining before treatment in panel C and post-treatment in D, showing a decline in the intensity of staining.

Plans for the future

- Systemic sclerosis
- Pulmonary fibrosis
- Fibrosing orbitaprocesses / Graves
- ……..
- ……
- ……