# Systemic sclerosis: from pathophysiology to treatment


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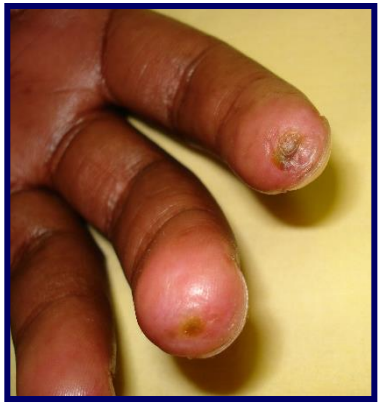
# Conflicts of interest

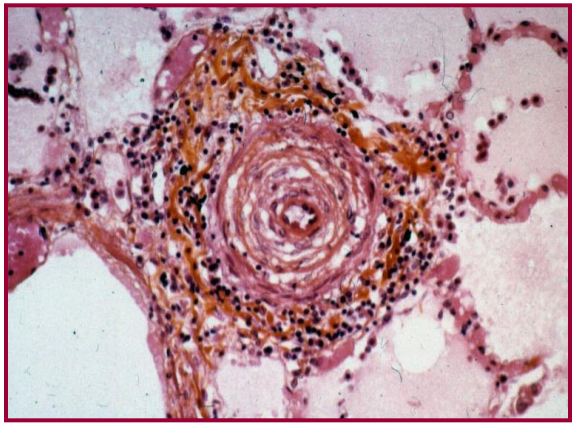
- **Consultant**: Actelion, CSL Behring, LFB Biotechnologies, Lilly, Pfizer, Octapharma
  - Financial support to ARMIIC
- **Investigator**: Actelion, CSL Behring, Pfizer
- **Financial support (grants to ARMIIC)**: Actelion, CSL Behring, GSK, LFB Biotechnologies, Pfizer
- **Invited conference**: SOBI, Roche, Actelion, CSL Behring, Octapharma, GSK, LFB Biotechnologies, Pfizer, Lilly, UCB pharma

# SYSTEMIC SCLEROSIS

## ➢Vascular hyperreactivity

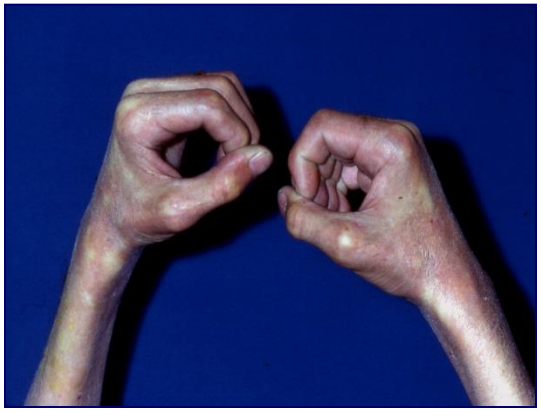
Raynaud's phenomenon
Renal crisis
Pulmonary arterial hypertension

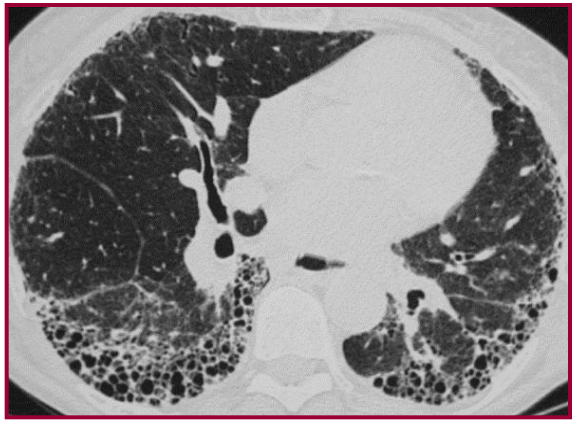




## ➢Fibrosis

Skin
Lung
Bowell
Heart

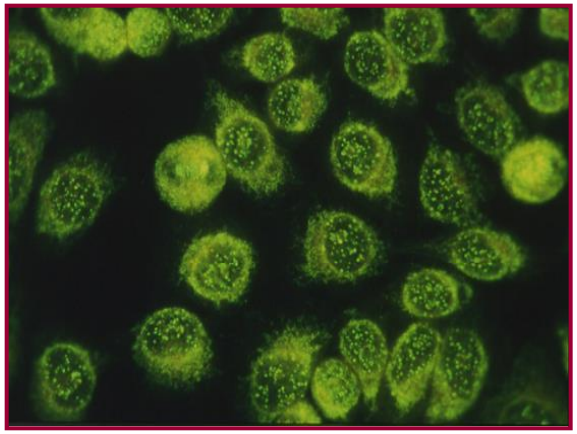


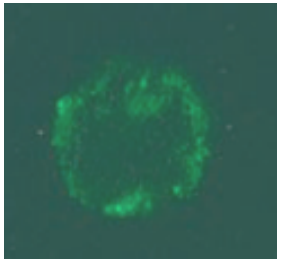


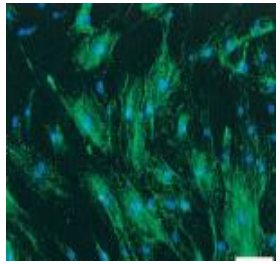
## ➢Autoimmunity

Autoantibodies
- Anti-Scl70
- Anti-centromere
- Anti-ARNPolIII

Ac anti-fibroblasts







# Understanding the pathophysiology of systemic sclerosis

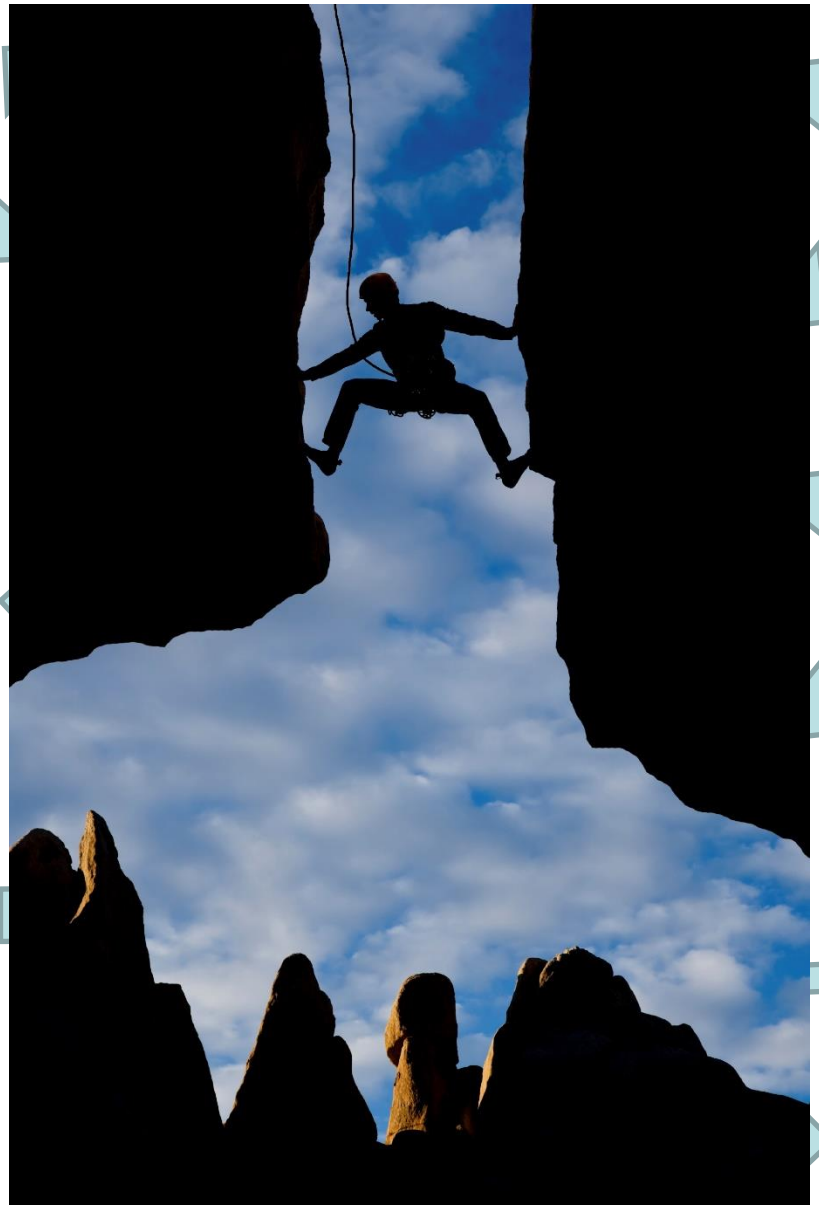
Fibrosis

Inflammation

Fibroblasts

Monocytes

Dendritic cells



Vascular involvement

Autoimmunity

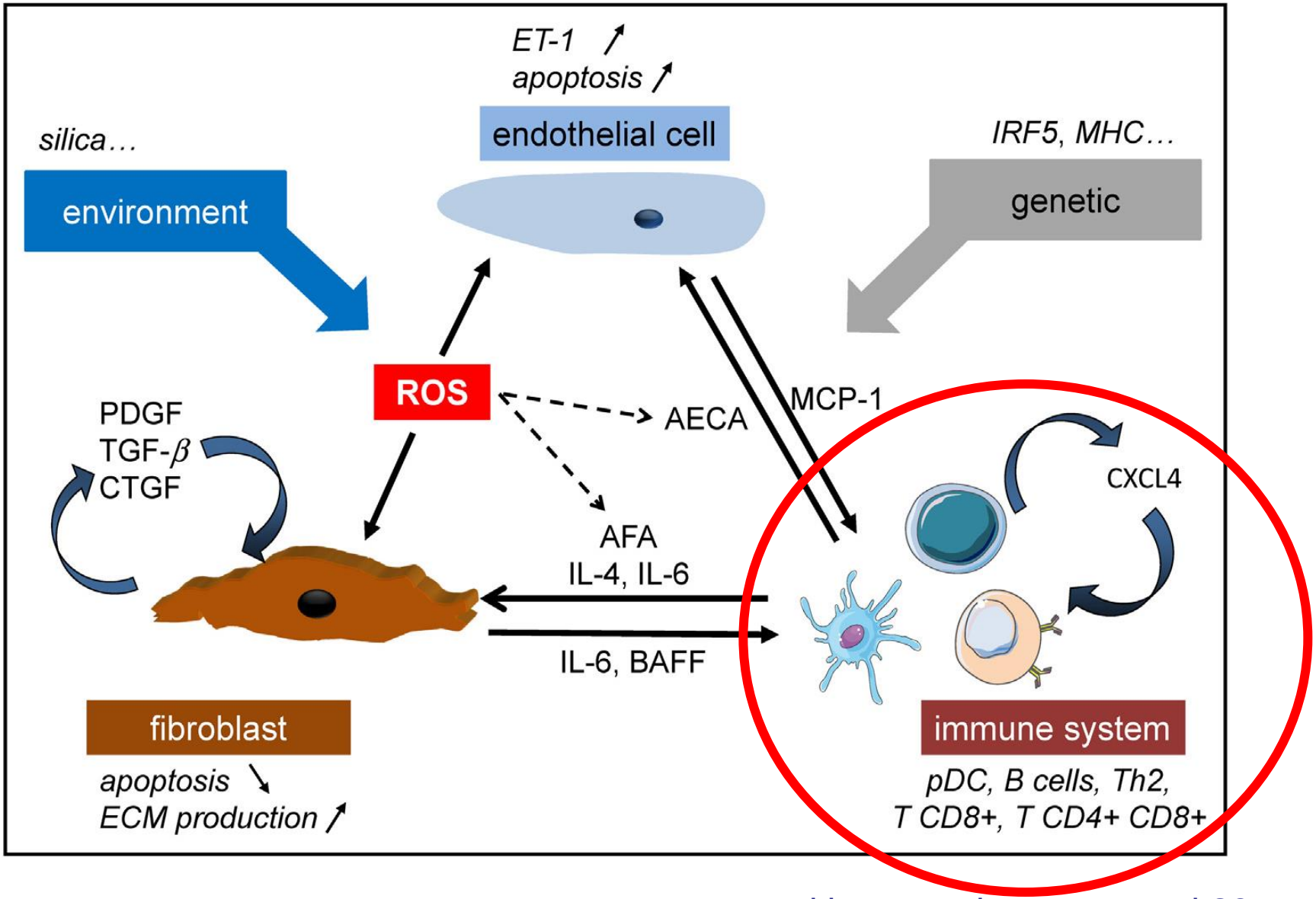
Endothelial cells

Vascular smooth muscle cells

Lymphocytes

Autoantibodies

# Systemic sclerosis: pathophysiology




Dumoitier N et al. Presse Med 2014

# Systemic sclerosis: susceptibility genes

## Fibrosis

***Fibrillin-1 (FBN1)***

***Fibronectin (FN))***

***Secreted Protein Acid and Rich Cystein (SPARC) or osteonectin***

***Connective tissue growth factor (CTGF)***

***TGF-β***

***Serotonin 5-HT2A receptor***

***Interleukine-1α et 1β***

***Matrix metalloproteinase (MMP)***

## Vascular involvement

***VEGF***

***Endothelin and its receptors***

***Hypoxia-inducible factor 1A***

***Endothelial nitric oxide synthase (eNOS/NOS3) and inducible NOS (iNOS/NOS2)***

***Fibrinogen***

***Stromal cell-derived factor 1 (SDF-1/CXCL12):)***

## Autoimmunity

**CMH-HLA: HLA II and autoantibodies** (*HLA-DRB1*01-DBQ1*0501 associated to ACA )*

**Lymphocytic activation : STAT4,TBX21 regulators of TH1-TH2 balance;**

***Protein tyrosine phosphatase nonreceptor type 22 (PTPN22),***

*B cell scaffold protein with ankyrin repeats 1 (BANK1)*

*B lymphocyte kinase (BLK);*

*Tumour necrosis factor alpha-induced protein 3 (TNFAIP3);*

*Interleukin-23 receptor*

**Innate immunity: IRF5, control of IFN production**

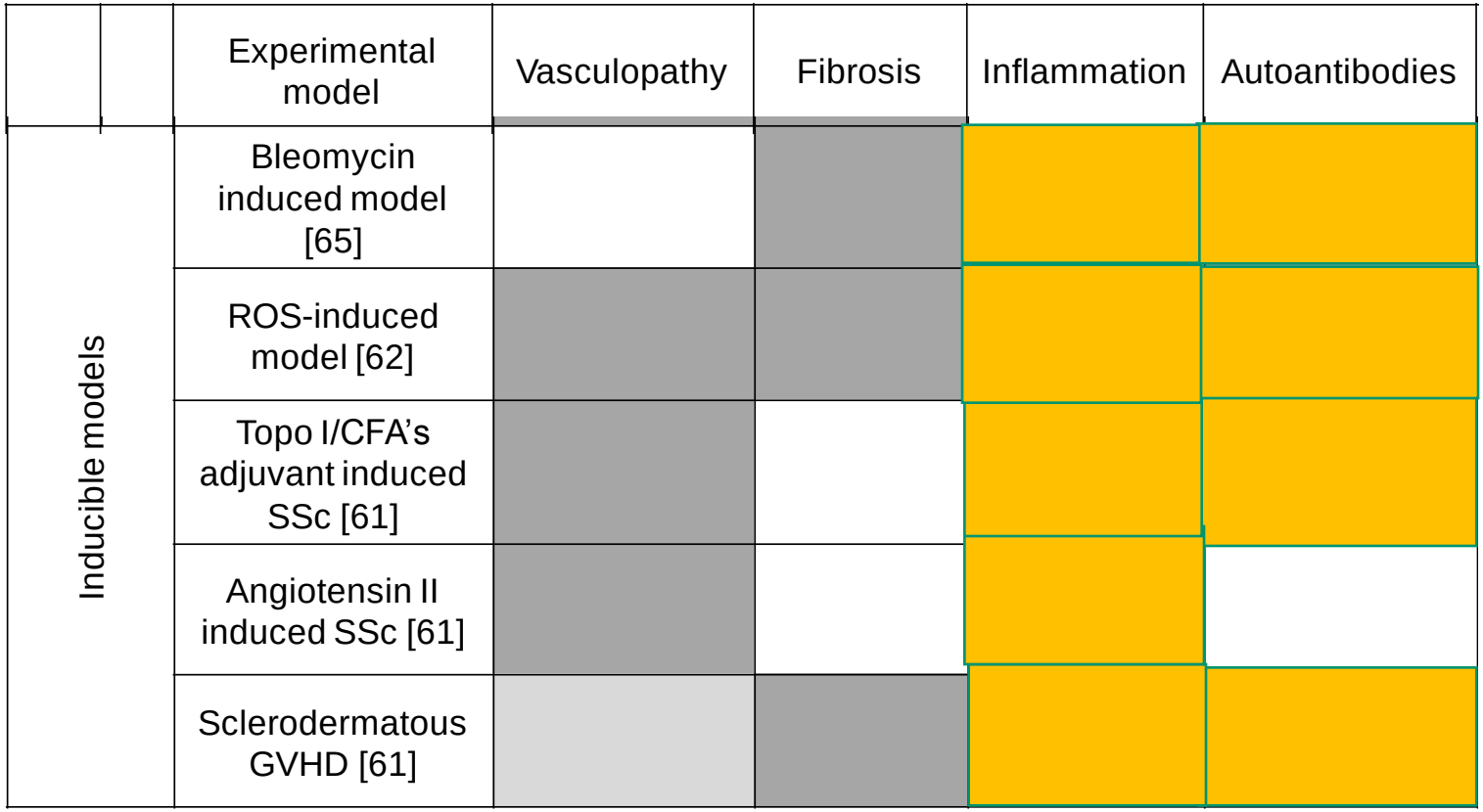
*Romano E, Clin Exp Rheumatol, 2011*

# Animal models of SSc (I)

| | | Experimental model | Vasculopathy | Fibrosis | Inflammation | Autoantibodies |
|---|---|---|---|---|---|---|
| Genetic models | Spontaneous | Tsk-1 [46] | | | | |
| | | Tsk-2 [52] | | | | |
| | | UCD-200 UCD-206 [54] | | | | |
| | | TβRIIΔk and $TBRI^{CA}$ [56, 57] | | | | |
| | Genetic modification | Caveolin $1^{-/-}$ [61] | | | | |
| | | Fra-$2^{-/-}$ [61] | | | | |
| | | $Fli1^{\Delta CAT/\Delta CTA}$ [58] | | | | |
| | | Fli1 endothelial cell KO [58] | | | | |

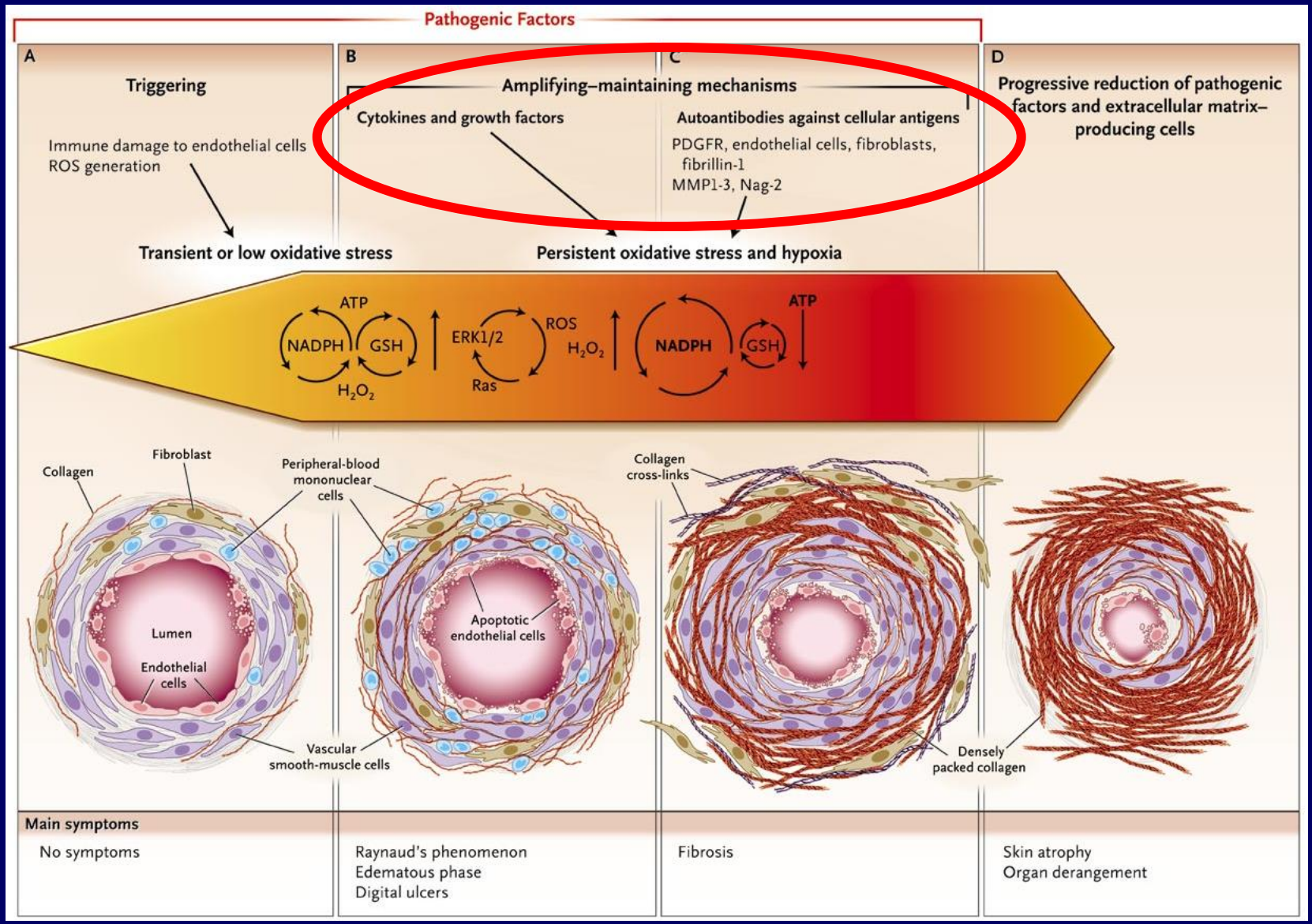
Dumoitier N et al. Presse Med 2014

# Animal models of SSc (II)




Dumoitier N et al. Presse Med 2014

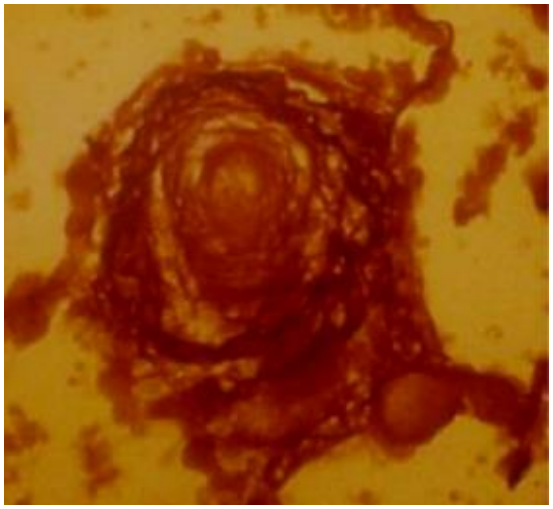
# Systemic sclerosis: lesions at different stages



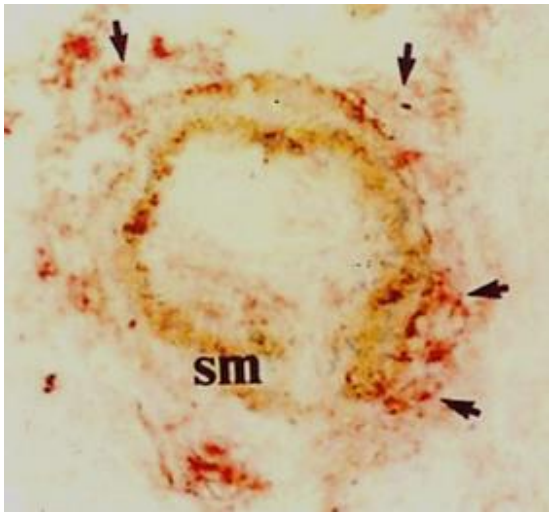

Gabrielli A. *NEJM* 2009

# Endothelin-1 expression in pulmonary and renal vasculature

## PAH

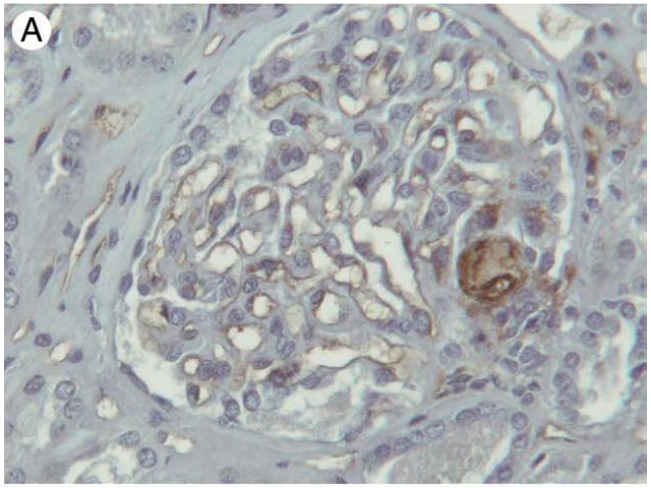


Sirius red stain - collagen

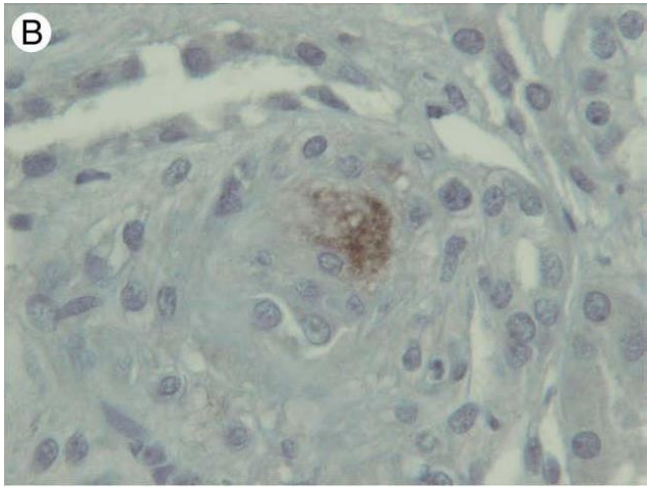



Immunolocalisation of ET-1 ligand

## Scleroderma renal Crisis



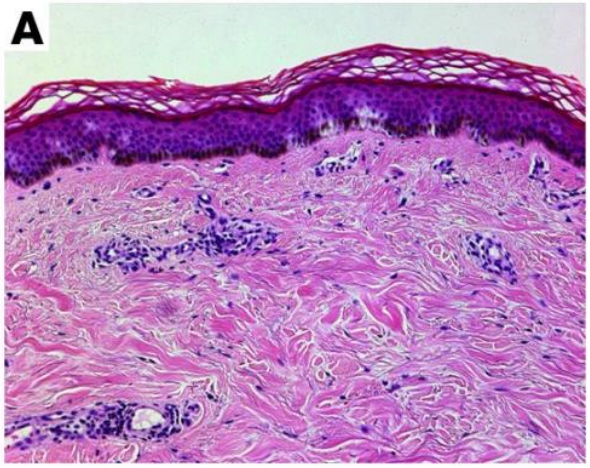

ET-1 in glomerular thrombosis and along glomerular basement membranes




ET-1 in arteriolar thrombosis

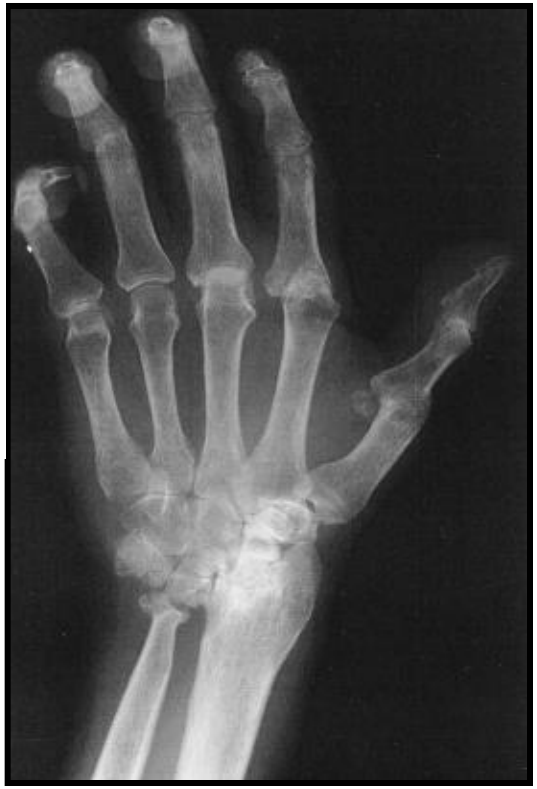
**Mouthon et al. Human Pathol 2010**

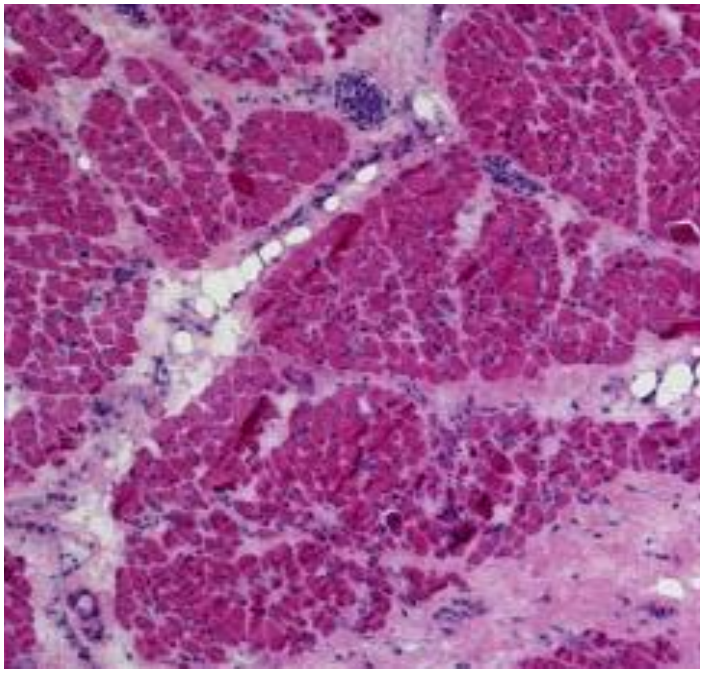
# Inflammatory disease




(**A**) Early diffuse cutaneous SSc

- Moderate fibrosis
- Inflammatory infiltrates in the dermis and near the dermal-epidermal junction, predominantly around small blood vessels





**HE staining**
**Necrosis, atrophy, fibrosis**
**Perimysial inflammation**

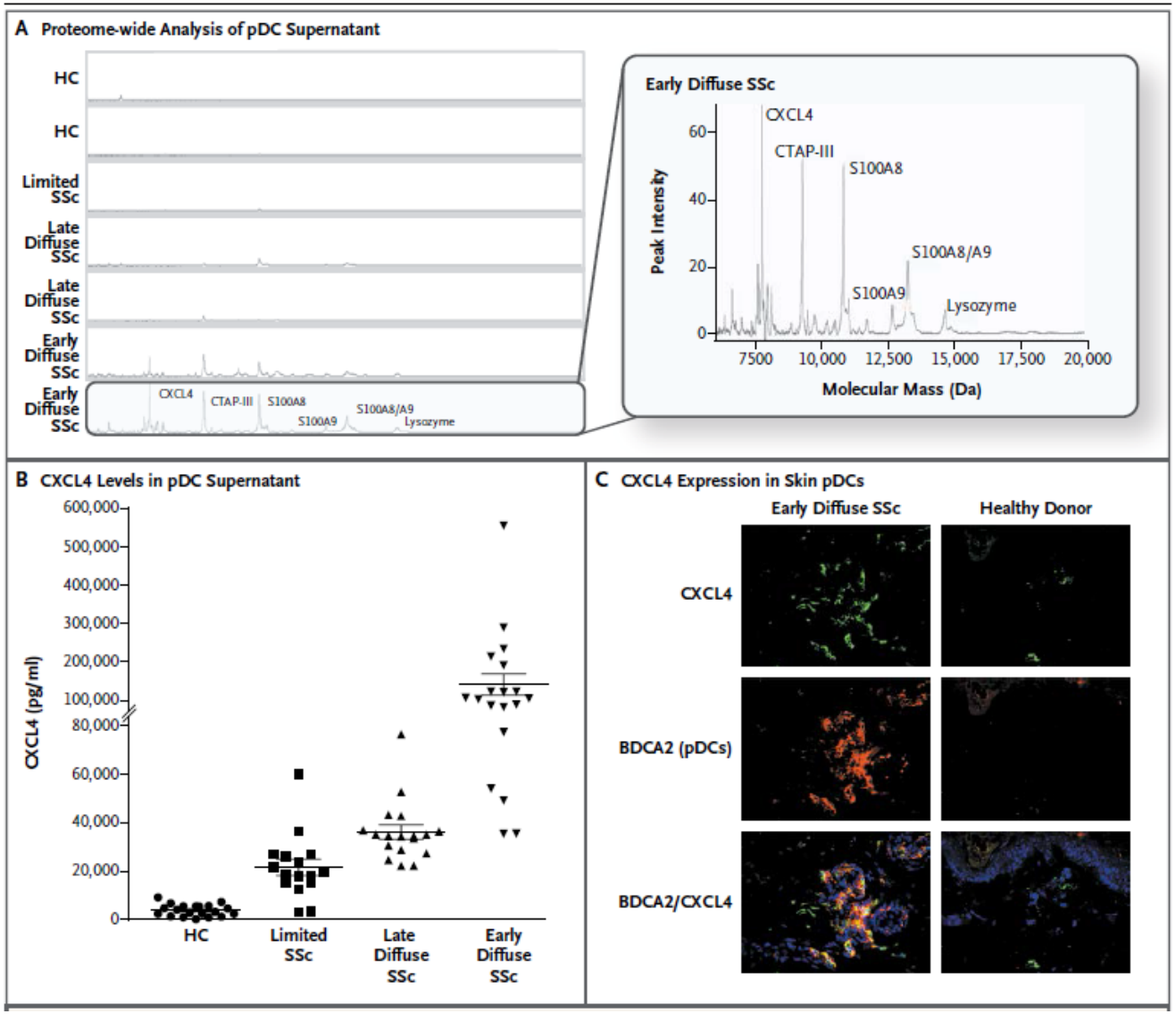
# Elevated levels of cytokines in SSc

- **Growth factors**
  - **TGF-β, CTGF, VEGF, FGF, etc**
- **Interleukins**
  - **IL-2, IL-4, IL-6, IL-10, IL-13, etc**
- **Chemokines**
  - **MCP-1, IL-8 (CXCL8), TARC, fractalkine, etc**
- **Other cytokines**
  - **TNF-α, etc**

**CTGF = connective tissue growth factor; FGF = fibroblast growth factor; IL = interleukin; MCP = monocyte chemoattractant protein; TARC = thymus and activation-regulated chemokine; TGF = tumour growth factor; TNF = tumour necrosis factor; VEGF = vascular endothelial growth factor**

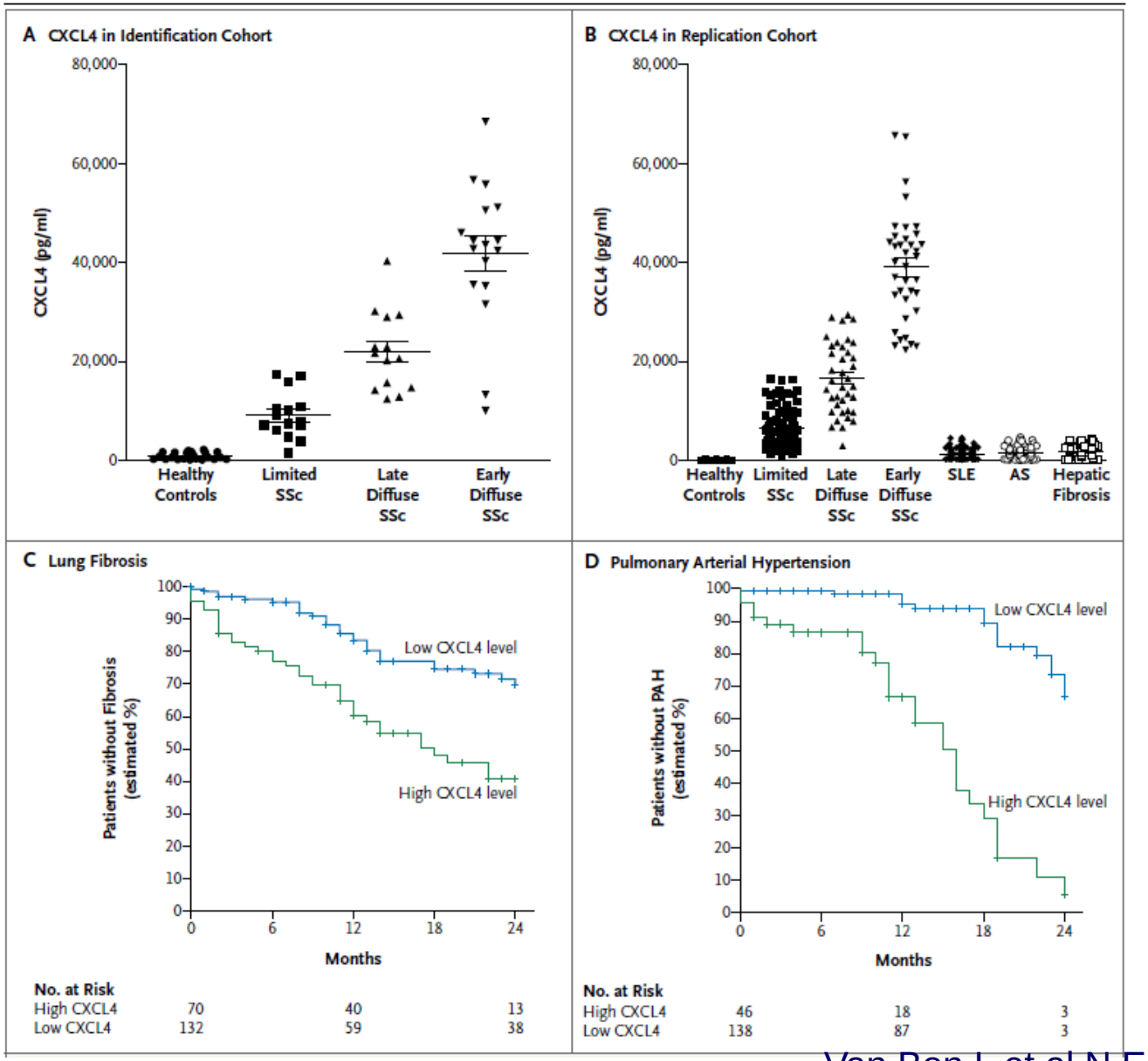
**Slide courtesy of Kazuhiko Takehara.**

# Identification of CXCL4 as the Major Protein Product of Plasmacytoid Dendritic Cells in Systemic Sclerosis.




Van Bon L et al N Engl J Med 2014

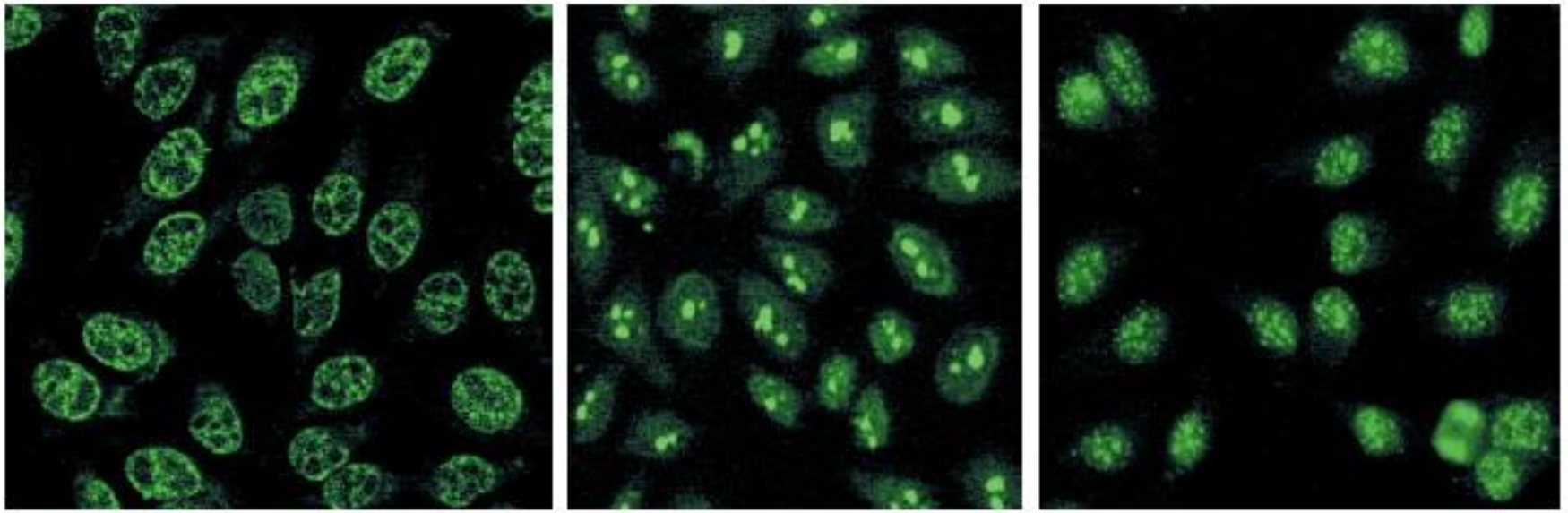
# Increased Levels of Circulating CXCL4 in Systemic Sclerosis and the Association with Lung Fibrosis and PAH




Van Bon L et al N Engl J Med 2014

# Autoantibodies in scleroderma

A

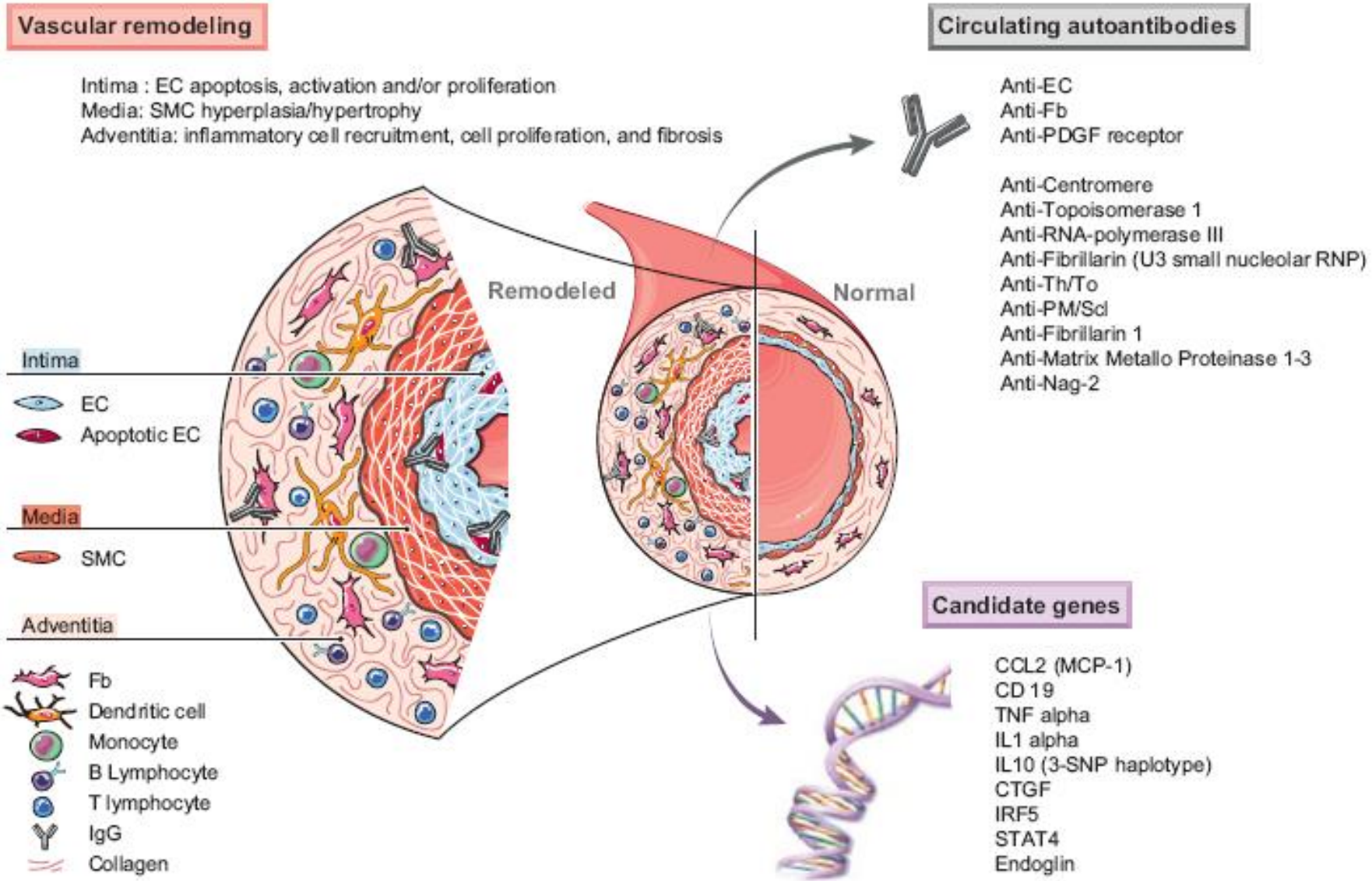


B

| Classic Autoantibodies | Clinical Features | New Autoantibodies | Role |
|---|---|---|---|
| Anti–topoisomerase I | Diffuse cutaneous scleroderma | Anti–endothelial cell | Induce apoptosis of endothelial cells |
| Anticentromere proteins | Limited cutaneous scleroderma, pulmonary hypertension | Anti–FBN 1 | Activate normal human fibroblasts |
| Anti–RNA polymerase I/II | Diffuse cutaneous scleroderma, renal involvement | Anti–MMP 1 and 3 | Prevent degradation of ECM proteins |
| Antipolymyositis, sclerosis | Polymyositis, calcinosis | Anti-PDGFR | Stimulate normal human fibroblasts through Ha-Ras-ERK1/2-ROS |
| Antifibrillarin (U3RNP) | Diffuse cutaneous scleroderma, internal-organ involvement | Anti–Nag-2 | Induce endothelial-cell apoptosis |
| Anti-Th/To | Limited cutaneous scleroderma, pulmonary fibrosis | | |

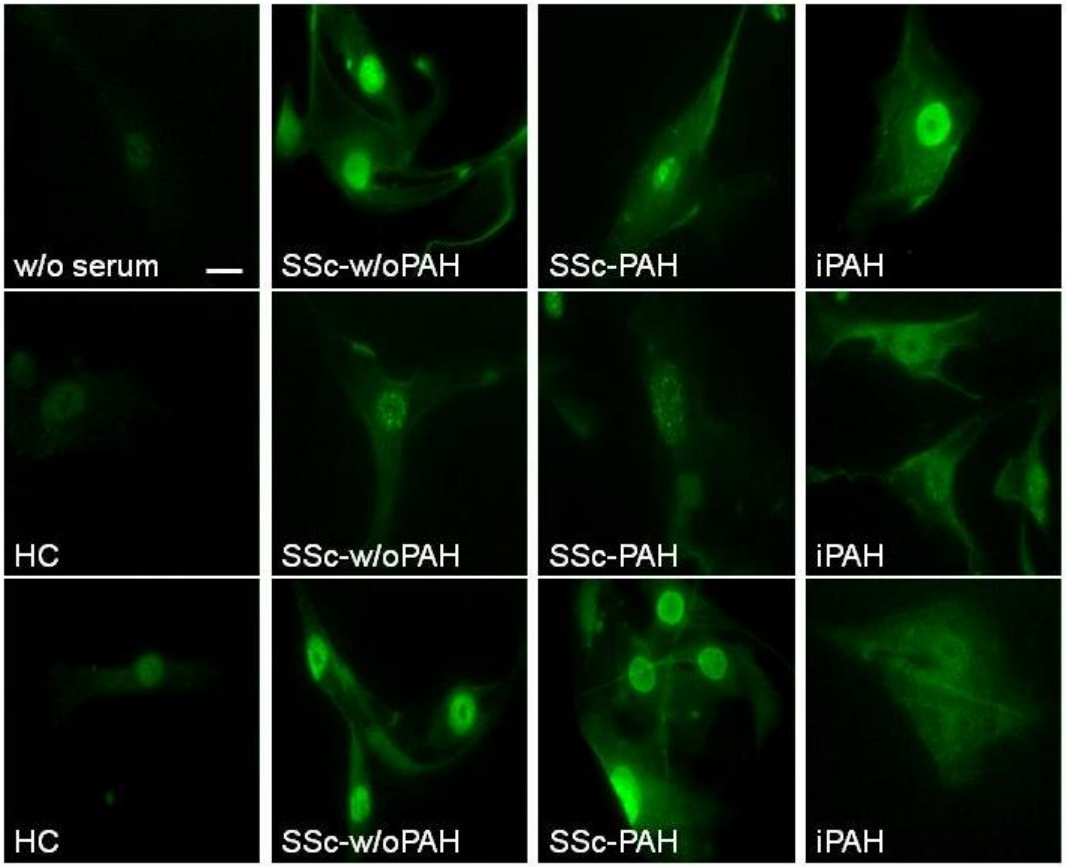
Gabrielli A, *et al. N Engl J Med* 2009

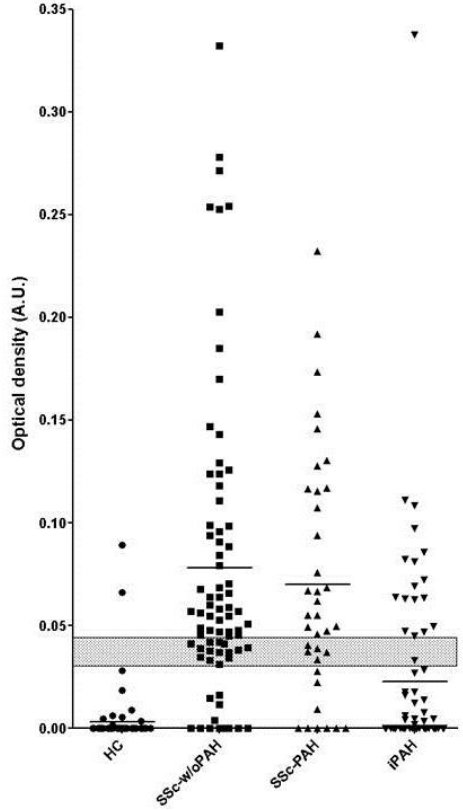
# Pulmonary vascular remodeling in SSc-PAH

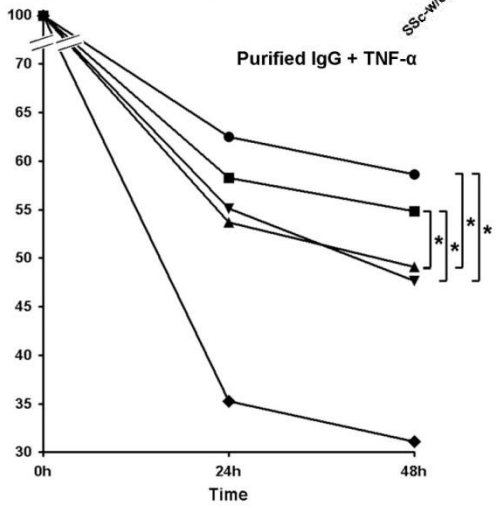



Le Pavec J et al 2010 AJRCCM

# Anti-vascular smooth muscle cell antibodies in systemic sclerosis and PAH: Detection of anti-stress-induced-phosphoprotein 1 (STIP1) IgG antibodies




**Inhibition of contraction**

Bussone et al.Ann Rheum Dis 2011

# Pulmonary Lymphoid Neogenesis in Idiopathic Pulmonary Arterial Hypertension

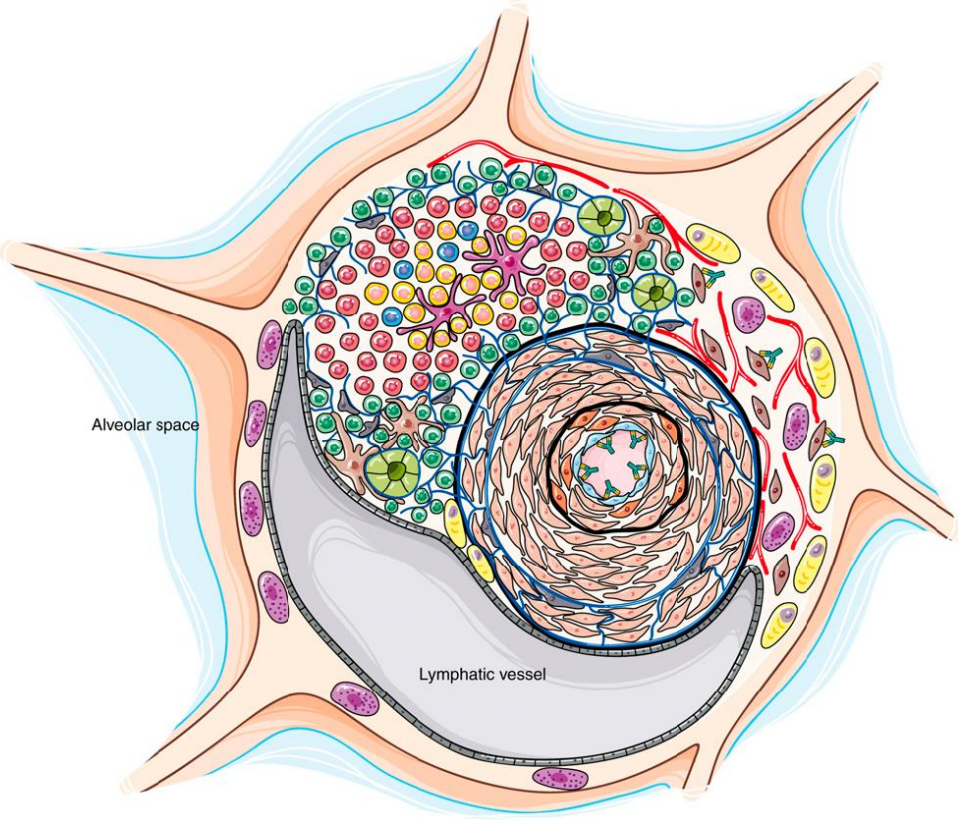
## AT A GLANCE COMMENTARY

### Scientific Knowledge on the Subject

Work on chronic inflammatory disorders and autoimmune diseases suggests that pathogenic antibodies and T cells may be generated locally, in the targeted organ, in highly organized ectopic lymphoid follicles commonly called *tertiary lymphoid tissues*. Despite the importance of inflammatory influx in idiopathic pulmonary arterial hypertension (IPAH) lesions, lymphoid neogenesis has not been studied.

### What This Study Adds to the Field

The presence of highly organized perivascular follicles in IPAH lungs argues for specific immune-adaptive mechanisms in the pathophysiology of the disease. It is highly important to understand how modulating factors that drive and maintain lymphoid neogenesis in IPAH lungs can contribute to disease progression.




Perros F et al. AJRCCM 2012

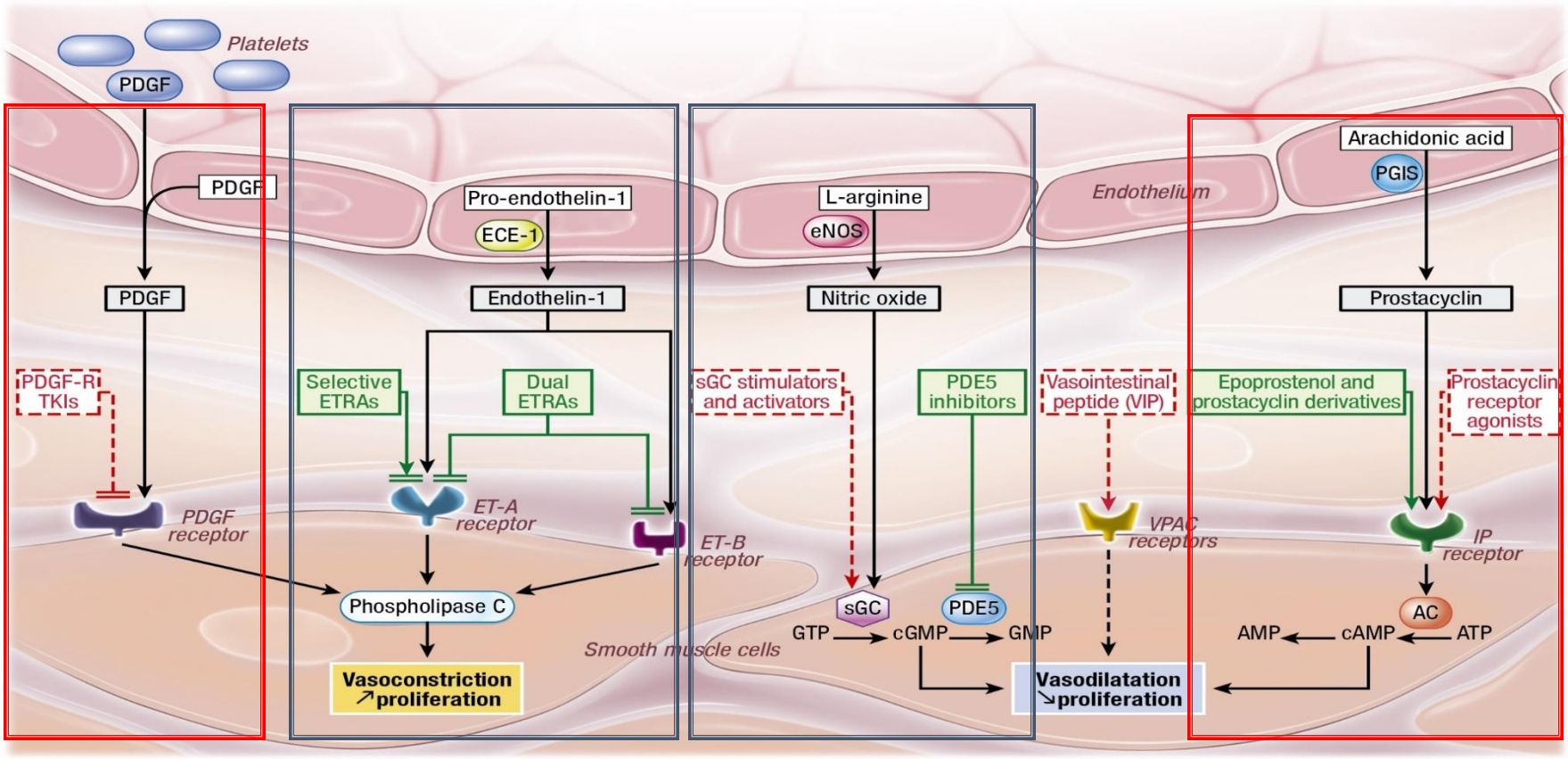
# SSc: involvement of B lymphocytes

- Abnormal B cell signalling in TSK/+ mice[1]
- Presence of B cells in skin[2] and in lungs from SSc patients[3]
- Expanded naive B cells and diminished but activated memory B cells[4]
- Presence of serum autoantibodies and elevated serum levels of cytokines such as IL-6 which correlate with skin fibrosis
- Elevated serum BAFF levels correlate with disease severity[5]
- Preliminary results from pilot studies in SSc patients with rituximab[2,6]


1. Saito E, *et al. J Clin Invest* 2002; 109:1453–62.
2. Bosello, *et al. Arthritis Res Ther* 2010; 12:R54.
3. Lafyatis R, *et al. Arthritis Rheum* 2007; 56:3167–8.
4. Sato S, *et al. Arthritis Rheum* 2004; 50:1918–27.
5. Matsushita T, *et al. Arthritis Rheum* 2006; 54:192–201.
6. Lafyatis R, *et al. Arthritis Rheum* 2009, 60:578-83.

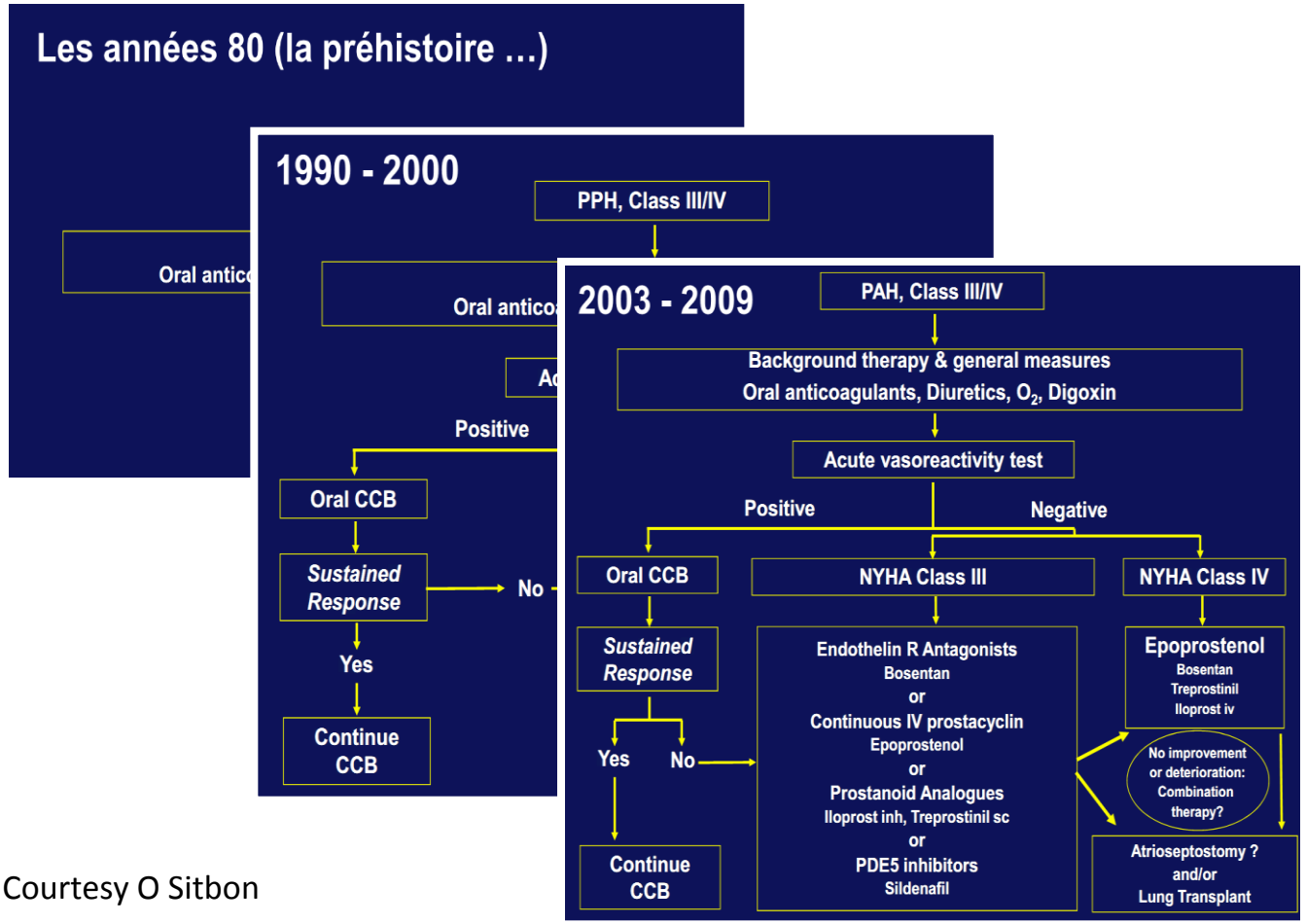
# Traitement

# Current and Emerging Targets and Therapies in PAH




O'Callaghan DS, Savale L, Montani D, Jaïs X, Sitbon O, Simonneau G & Humbert M. Nat Clin Practice Cardiol 2011; 19:526-538

# Les algorithmes thérapeutiques dans l'HTAP




Courtesy O Sitbon

# Nouveaux traitements évalués depuis 2009

| | SERAPHIN[1] | PATENT[2] | IMPRES[3] |
|---|---|---|---|
| Molécule | Macitentan | Riociguat | Imatinib |
| Classe thérapeutique | ERA à forte affinité tissulaire | Stimulateur GC soluble | Inhibiteur de tyrosine kinase |
| Critère principal de jugement | Morbi-mortalité | TM6 | TM6 |
| Durée | ~ 96 semaines | 12 semaines | 24 semaines |
| Patients, n | 742 | 443 | 202 |
| Traitement antérieur | Naïf ou monothérapie (PDE5i) | Naïf ou monothérapie (ERA) | Association (≥ bithérapie) |
| Résultat principal | Réduction de 45 % des évènements de morbi-mortalité (10 mg) | TM6 +36 m | TM6 +32 m, mais > 30 % sorties d'essai groupe imatinib |
| Tolérance | Elévation enzymes hépatiques : pas de différence avec placebo. Diminution Hb | Vasodilatation systémique, hypotension (Hémoptysies) | Effets secondaires ++, Hématomes sous-duraux, Rapport bénéfice/risque discutable |

1. Rubin LJ, *et al.* Presented at CHEST 2012. 2. Ghofrani HA, *et al.* Presented at CHEST 2012. 3. Hoeper MM, *et al.* Presented at CHEST 2011.

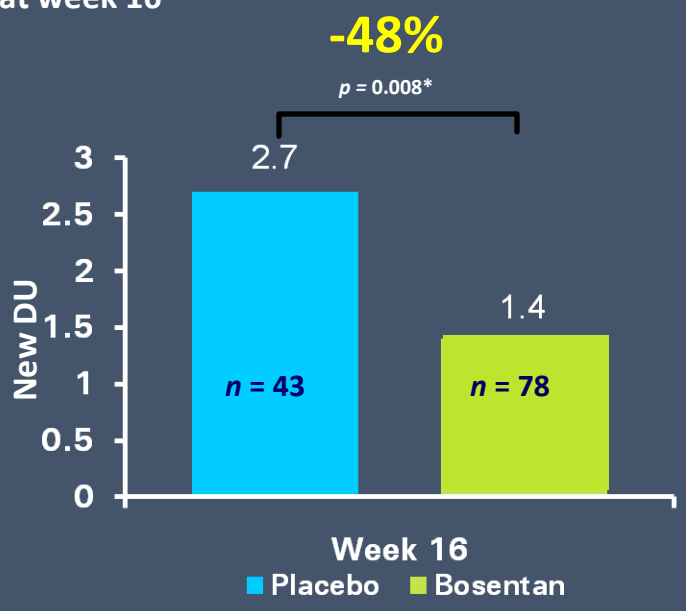
# Prevention in the occurrence of new DU

- Calcium channel blockers (CCBs)
  - The preventive role of CCBss has never been evaluated
- Prostacyclin
  - No evidence from literature that iloprost can prevent DU
  - Heterogeneity among clinicians regarding duration and frequency of infusions
  - Recommended dose: 0.5 to 2 ng/kg/mn for 6 to 8 h/d during 5 days; minimum six weeks between 2 infusions
- Bosentan[1,2]
  - Two prospective randomised studies demonstrated the efficacy of bosentan in preventing the occurrence of DU in SSc
- Atorvastatin[3]
  - 84 pts double-blind RCT – 40 mg atorvastatin vs placebo

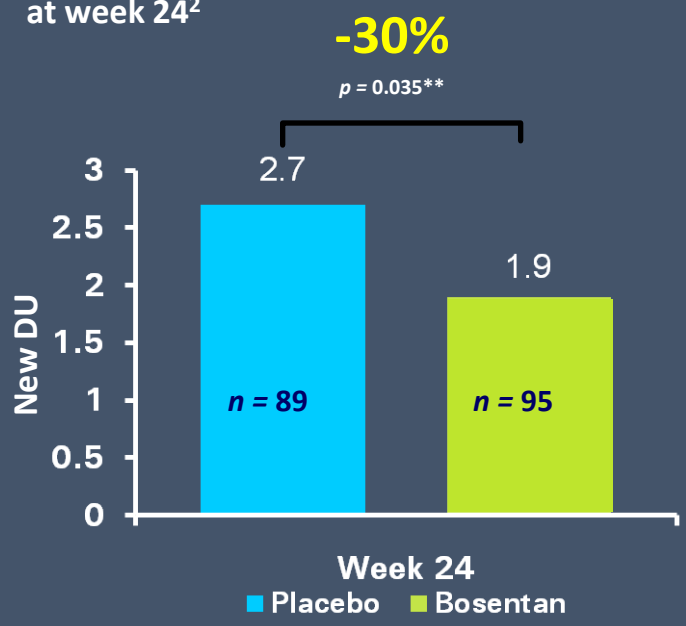
**Abou-Raya A, *et al*. *J Rheumatol* 2008; 35:1801-8.**

# Effect of bosentan in reducing the number of new DU

**RAPIDS-1: Occurrence of new DU at week 16[1]**




**RAPIDS-2: Occurrence of new DU at week 24[2]**





1. Korn JH, *et al*. *Arthritis Rheum* 2004; 50:3985-93.
2. Matucci Cerinic M, *et al. Ann Rheum Dis* 2011; 70:32-38.

# Treatment of SRC

**Early diffuse SSc**
**Hypertension (diastolic blood pressure > 100 mmHg)**

↓

**Initiate captopril at 6.25-12.5 mg every 8 hours, then increase dose to 50 mg tid**

↓

**Insufficient results at 72 h: Continue ACEi and add calcium channel blockers**

↓

**Insufficient results: Continue ACE inhibitors and calcium channel blockers and add intravenous α-/β-blockers and/or minoxidil**

↓

**Oliguric renal insufficiency: Early dialysis**

↓

**Continue ACE inhibitors, maintain normal blood pressure (120-140/70-90 mmHg)**

↓

**If improvement of renal function, stop dialysis**
**If dialysis is still necessary after two years, then put the patient on a waiting list for renal transplantation**

Teixeira et al 2007 Ann N Y Acad Sci;
Mouthon et al. Clin Rev Allerg Immunol 2009
Penn et al. QJM 2012

# PNDS

- Aucun traitement de fond antifibrosant ou immunosuppresseur n’a permis d’obtenir une amélioration de la survie dans une étude prospective randomisée.

# Methotrexate in early diffuse SSc

- Two RCT have shown that methotrexate improves skin score in early diffuse SSc.
  - RCT involving 29 SSc patients with diffuse SSc or limited SSc (mean duration of skin involvement 3.2 years), methotrexate (intramuscularly at a dose of 15 mg/week for 24 weeks) showed a trend towards improvement of the total skin score (p=0.06 vs placebo).
  - RCT involving 73 patients with early diffuse SSc, methotrexate (orally at 10 mg/week for 12 months, decreased the the modified Rodnan skin score (ES 0.5; 95% CI 0.0 to 0.9) compared with placebo in an intention-to-treat analysis.

van den Hoogen FH et al. Br J Rheumatol 1996;35:364–72
Pope JE et al. Arthritis Rheum 2001;44:1351–8.
Kowal-Bielecka O et al. Ann Rheum Dis 2009. ;68:620–628

# Mycophenolate mofetil in diffuse cutaneous SSc a retrospective analysis

- 109 patients treated with MMF and 63 control subjects receiving other immunosuppressive drugs
- 12% of patients experienced adverse reactions (gastrointestinal (GI) tract disturbances, infections).
- MMF was discontinued due to disease stabilization in 9%, side effects in 8% and no effect on the disease activity in 14% of the patients.
- Significantly lower frequency of clinically significant pulmonary fibrosis in the MMF-treated cohort (P=0.037) and significantly better 5-yr survival from disease onset and from commencement of treatment (P=0.027 and P=0.012, respectively).
- No significant difference between the two groups (modified Rodnan skin score and FVC).

**Nihtyanova SI et al. Rheumatology 2006**

# EULAR ODP
# ESOS
# Observational study of treatment outcome in early diffuse cutaneous systemic sclerosis

**PI: Ariane Herrick**

**Manchester, UK**

The ESOS steering Committee

Dr Ariane Herrick
Mrs Edith Brown
Dr Laszlo Czirjak
Professor Chris Denton
Dr Jorg Distler
Dr Oliver Distler
Ms Kim Fligelstone
Mr Will Gregory
Dr Roger Hesselstrand
Dr Mark Lunt
Professor Luc Mouthon
Ms Rachel Ochiel
Professor Alan Silman
Dr Madelon Vonk

# Treatment

**The following protocols were decided on:**

**1. MMF. Recommended dose 500mg bd for 2 weeks increasing to 1gm bd.**

**2. Cyclophosphamide. Possible regimes:**

- **IV. Minimum monthly dose 500 mg/m2, recommended duration 6-12 months.**
- **Oral. 1-2mg/day for one year.**
- **Cyclphosphamide regimes may be followed by oral immunosuppressant of clinician's choice (most likely azathioprine or MMF) or no further immunosuppression.**

**3. Methotrexate. Either oral or subcutaneous. Target dose 20-25mg weekly.**

**4. No immunsuppressant treatment**

# Treatment of early diffuse SSc

Low dose prednisone: only if arthritis/myositis

Methotrexate: if polyarthritis/myositis

Cyclophosphamide: if worsening ILD

Mycophenolate mofetyl: no major visceral involvement

Plus classical support

Expert rec: early rehabilitation

# Stem cell transplantation in SSc

**Table 1. Treatment regimens used in the three controlled trials of SCT in SSc to date**

| | Transplant | Control |
|---|---|---|
| ASTIS | Mobilization: cyclophosphamide $2 \times 2\,g/m^2$, G-CSF 10 μg/kg | 12-monthly i.v. pulse cyclophosphamide $750\,mg/m^2$ |
| | Leukapheresis/CD34+ selection: CD34+ $\geq 2 \times 10^6$/kg | |
| | Conditioning: cyclophosphamide 200 mg/kg, rabbit ATG $3 \times 2.5$ mg/kg | |
| | Re-infusion of CD34+ cells | |
| ASSIST | Mobilization: cyclophosphamide $2 \times 2\,g/m^2$, G-CSF 10 μg/kg | 6-monthly i.v. pulse cyclophosphamide $1\,g/m^2$ |
| | Apheresis and cryopreservation without manipulation | |
| | Conditioning: cyclophosphamide 200 mg/kg | |
| | Rabbit ATG 0.5 mg/kg (day 5), and $4 \times 1.5$ mg/kg (day 4 to 1) | |
| | Re-infusion unmanipulated stem cells | |
| SCOT | Mobilization: G-CSF 16 μg/kg | $1 \times$ cyclophosphamide $500\,mg/m^2$ initially and then |
| | Leukapheresis/CD34+ selection | 11-monthly i.v. cyclophosphamide $750\,mg/m^2$ |
| | Conditioning: TBI (800 cGy) cyclophosphamide $2 \times 60$ mg/kg, equine ATG $6 \times 15$ mg/kg | |
| | Re-infusion of CD34+ cells | |

ASTIS trial, Autologous Stem cell Transplantation International Scleroderma trial; ATG, antithymocyte globuline; G-CSF, granulocyte colony-stimulating factor; i.v., Intravenous; SCOT trial, Scleroderma: Cyclophosphamide Or Transplantation trial; TBI, total body irradiation. Table reproduced from [14] (with kind permission from Springer Science + Business Media B.V).

**Van Laar et al. Current Op Rheumatol 2013**

## Autologous hematopoietic stem cell transplantation vs IV pulse cyclophosphamide in diffuse cutaneous SSc: a randomized clinical trial.

- **OBJECTIVE:** To compare efficacy and safety of HSCT vs 12 successive monthly intravenous pulses of cyclophosphamide.
- **DESIGN, SETTING, AND PARTICIPANTS:** phase 3, multicenter, randomized (1:1), open-label, parallel-group, clinical trial conducted in 10 countries at 29 centers.
- **INTERVENTIONS:** HSCT vs intravenous pulse cyclophosphamide.
- **MAIN OUTCOMES AND MEASURES:** The primary end point was event-free survival, defined as time from randomization until the occurrence of death or persistent major organ failure.
- **RESULTS:** 156 patients were randomly assigned to receive HSCT (n = 79) or cyclophosphamide (n = 77).
- During a median follow-up of 5.8 years, 53 events occurred: 22 in the HSCT group (19 deaths and 3 irreversible organ failures) and 31 in the control group (23 deaths and 8 irreversible organ failures).
- During the first year, there were more events in the HSCT group (13 events [16.5%], including 8 treatment-related deaths) than in the control group (8 events [10.4%], with no treatment-related deaths).
- At 2 years, 14 events (17.7%) had occurred cumulatively in the HSCT group vs 14 events (18.2%) in the control group; at 4 years, 15 events (19%) had occurred cumulatively in the HSCT group vs 20 events (26%) in the control group.
- Time-varying hazard ratios (modeled with treatment × time interaction) for event-free survival were 0.35 (95% CI, 0.16-0.74) at 2 years and 0.34 (95% CI, 0.16-0.74) at 4 years.
- **CONCLUSIONS AND RELEVANCE:** Among patients with early diffuse cutaneous systemic sclerosis, HSCT was associated with increased treatment-related mortality in the first year after treatment. However, HCST conferred a significant long-term event-free survival benefit.

Van Laar J et al. Jama 2014 Jun 25;311(24):2490-8

# Treatment of SSc-ILD

- **PPI**
- **Cyclophosphamide**
- **Low dose corticosteroids (10 mg/j)**
- **Oxygen**
- **Lung transplantation**

- **Rehabilitation**

**Available online** http://arthritis-research.com/content/10/5/R124

Research article

Open Access

# Effects of cyclophosphamide on pulmonary function in patients with scleroderma and interstitial lung disease: a systematic review and meta-analysis of randomized controlled trials and observational prospective cohort studies

Carlotta Nannini[1], Colin P West[2,3], Patricia J Erwin[4] and Eric L Matteson[1]

**Table 2**

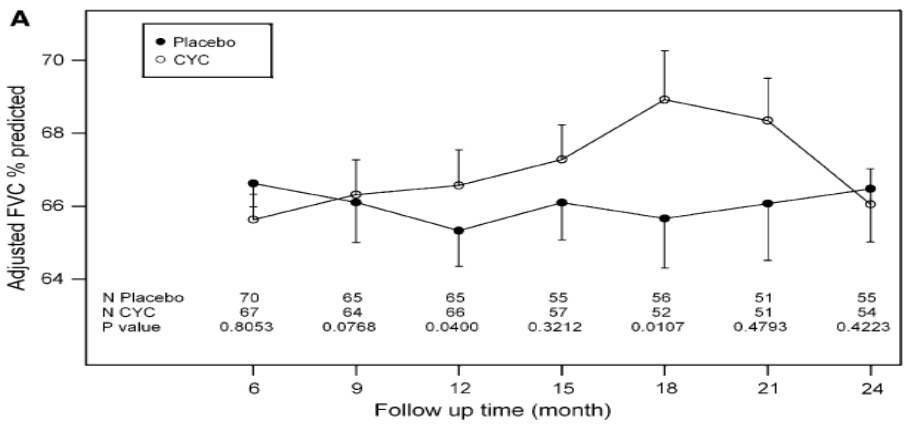
**Randomized clinical trial study characteristics**

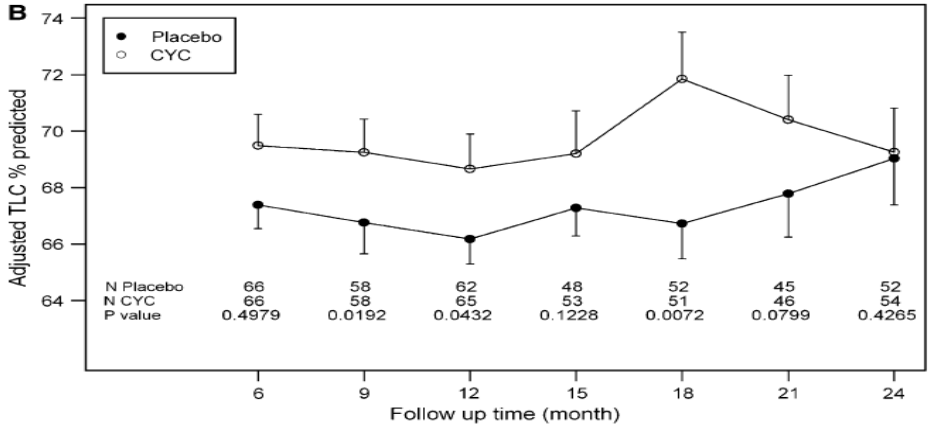
| Study | Number of patients | Mean age (years) | Outcome measure[a] | CYC treatment | Placebo/ alternative treatment | Corticosteroid | Length of follow-up (months) |
|---|---|---|---|---|---|---|---|
| Hoyles and colleagues [10] | 45 | 55 | FVC, 80.1 ± 10.3 | Intravenous, 600 mg/m$^2$ monthly | Placebo | Prednisone 20 mg alternate days | 12 |
| | | | DLCO, 52.9 ± 1.6 | | | | |
| Nadashkevich and colleagues [11] | 60 | 38 to 36 | FVC, 90.3 ± 1.9 | Oral, 2 mg/kg/ day monthly | AZA 2.5 mg/kg | Prednisolone 15 mg/day | 12 |
| | | | DLCO, 83.5 ± 1.6 | | | | |
| Tashkin and colleagues [1] | 158 | 47.9 ± 1.0 | FVC, 67.6 ± 1.3 | Oral, 1 mg/kg/ day | Placebo | None | 12 |
| | | | DLCO, 47.2 ± 1.6 | | | | |

Data presented as mean ± standard deviation. AZA, azathioprine; CYC, cyclophosphamide; DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity. [a]Percentage predicted value at baseline.

# Effects of 1-Year Treatment with Cyclophosphamide on Outcomes at 2 Years in Scleroderma Lung Disease

Donald P. Tashkin[1], Robert Elashoff[2], Philip J. Clements[1], Michael D. Roth[1], Daniel E. Furst[1], Richard M. Silver[3], Jonathan Goldin[4], Edgar Arriola[5], Charlie Strange[3], Marcy B. Bolster[2], James R. Seibold[6], David J. Riley[6], Vivien M. Hsu[6], John Varga[7], Dean Schraufnagel[7], Arthur Theodore[8], Robert Simms[8], Robert Wise[9], Fred Wigley[9], Barbara White[9], Virginia Steen[10], Charles Read[10], Maureen Mayes[11], Ed Parsley[11], Kamal Mubarak[12], M. Kari Connolly[13], Jeffrey Golden[13], Mitchell Olman[14], Barri Fessler[14], Naomi Rothfield[15], Mark Metersky[15], Dinesh Khanna[1], Ning Li[2], and Gang Li[2], for the Scleroderma Lung Study Research Group*



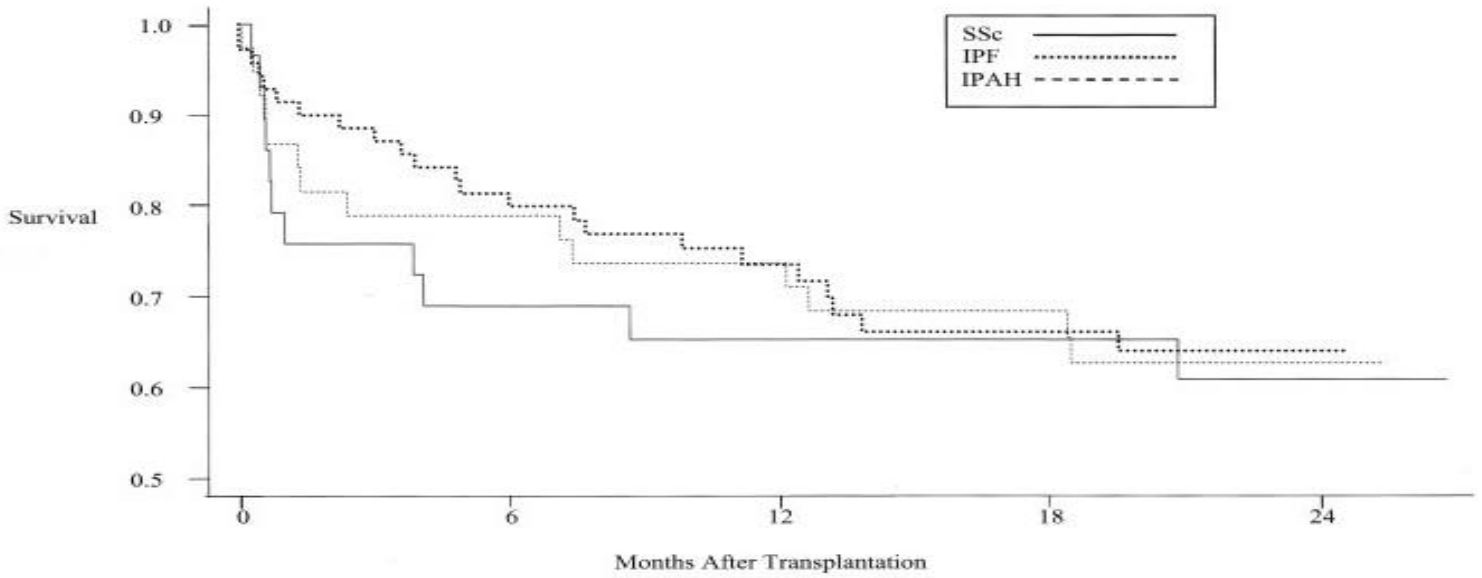




**A retrospective analysis of the Scleroderma Lung Study data identified the severity of reticular infiltrates on baseline HRCT and the baseline MRSS as patient features that might be predictive of responsiveness to CYC therapy**

Roth et al Arthritis Rheum 2011

# Lung transplantation

- **29 SSc patients,70 patients with IPF and 38 with IPAH**
- **During 2 years of followup, 11 patients with scleroderma (38%), 23 with IPF (33%), and 14 with IPAH (37%) died.**
- **Cumulative survival at 2 years was comparable (64%).**




Schachna L. et al. Arthritis Rheum 2006

# One-Year Survival of Adults with Systemic Sclerosis Following Lung Transplantation: A Nationwide Cohort Study.

- A total of 3763 adults were transplanted during the study period and met inclusion criteria: 229 with SSc, 201 with PAH, and 3333 with ILD
- The 1-year unadjusted mortality rate following LTx per 100 person-years was 21.4 among adults with SSc, 19.0 among adults with PAH, and 17.8 among adults with ILD.
- Adults with SSc had a 48% increased risk of death at 1 year following LTx compared to adults with ILD, but no increase in risk of death at 1 year compared to adults with PAH.

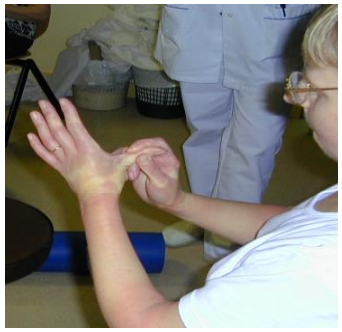
Abstract 1797. ACR Boston 2014

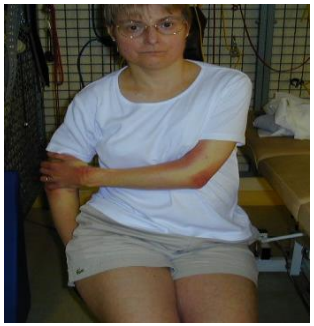
# Joint involvement in systemic sclerosis: Treatment

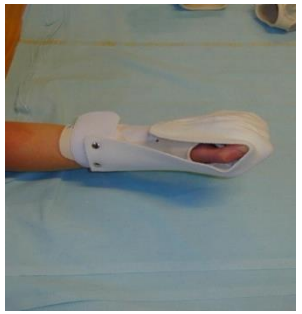
- ✓ Colchicine
- ✓ Low dose prednisone
- ✓ Methotrexate
- ✓ Biologics
  - ✓ Rituximab
  - ✓ Tocilizumab
  - ✓ Abatacept
- ✓ Surgical procedures
- ✓ Physiotherapy
- ✓ Occupational therapy

# Rehabilitation and systemic sclerosis

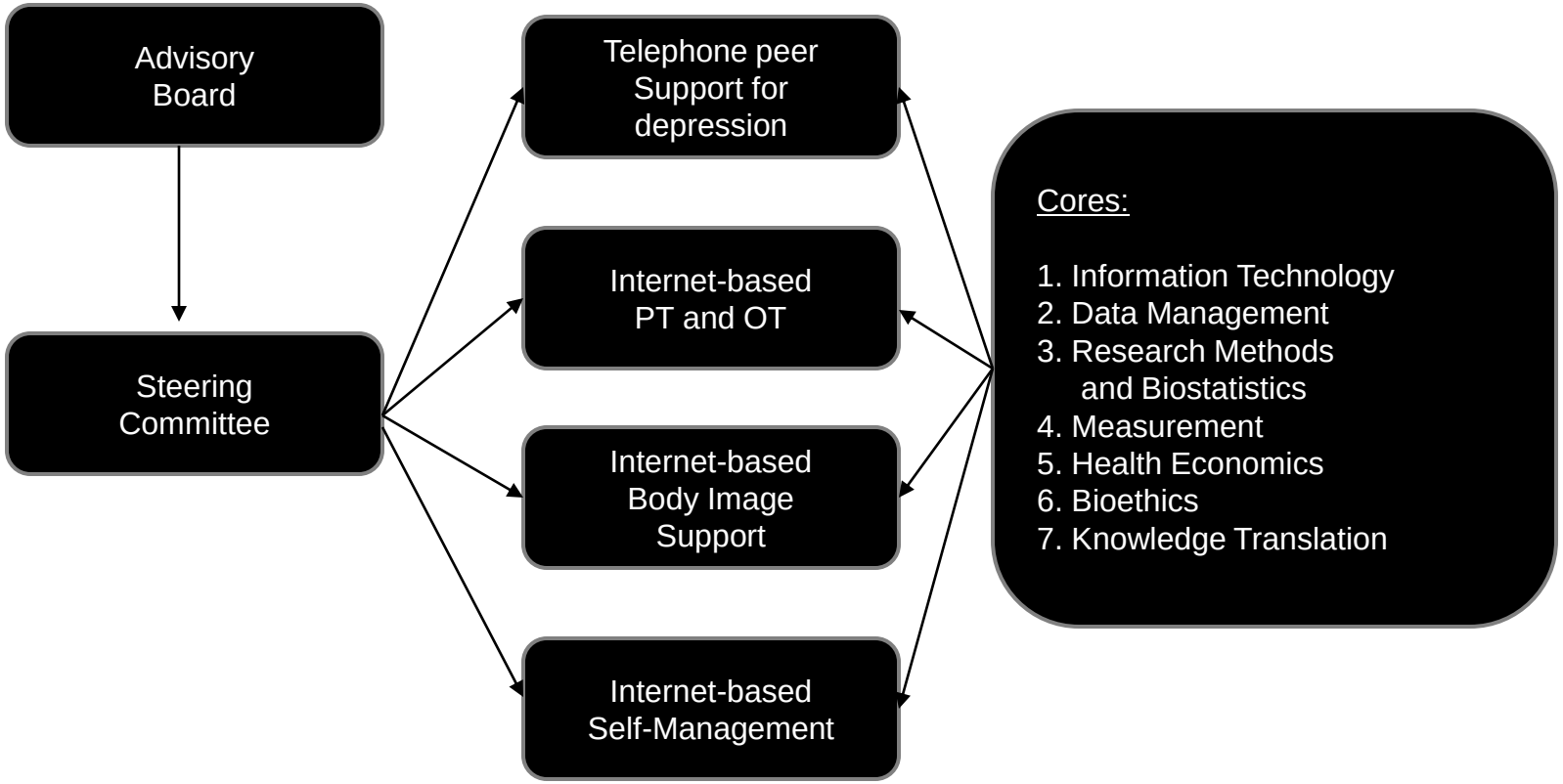
- Multicenter randomized controlled study
  - Randomization: Zelen method
  - 220 patients
  - Primary criteria : HAQ
  - 12 supervised rehabilitation sessions
  - Daily non supervised rehabilitation sessions
  - Analysis of qualitative and quantitative observance







# Scleroderma Patient-centered Intervention Network (SPIN)




**Courtesy Brett Thombs**

Thombs et al. Clin Exp Rheumatol. 2012

# Traitements de la sclérodermie systémique en fonction de l'organe atteint

| Manifestations | Traitement |
|---|---|
| **Pneumopathie infiltrante diffuse** | Cyclophosphamide<br>Corticothérapie à faible dose (10 mg/j) (discutée)<br>Oxygénothérapie<br>Transplantation monopulmonaire ou bipulmonaire |
| **Hypertension artérielle pulmonaire** | Oxygénothérapie<br>Anticoagulants<br>Diurétiques<br>Époprosténol<br>Antagonistes des récepteurs de l'endothéline : bosentan, sytaxentan<br>Inhibiteurs de la 5-phosphodiestérase (sildénafil)<br>Atrioseptostomie<br>Transplantation cardiopulmonaire |
| **Cœur** | Inhibiteurs calciques<br>Inhibiteurs de l'enzyme de conversion de l'angiotensine<br>Antiarythmiques<br>Diurétiques |

Mouthon L et al, Presse Med 2006

# Traitements de la sclérodermie systémique en fonction de l'organe atteint

| | |
|---|---|
| **Crise rénale** | Inhibiteurs de l'enzyme de conversion de l'angiotensine<br>Inhibiteurs calciques par voie intraveineuse<br>Épuration extrarénale<br>Transplantation rénale |
| **Atteinte vasculaire périphérique** | Inhibiteurs calciques<br>Analogues de le prostacycline<br>Antiagrégants<br>Antagonistes des récepteurs A et B de l'endothéline : bosentan (prévention de la survenue de nouvelles ulcérations digitales) |
| **Atteinte digestive** | **Œsophage :** inhibiteurs de la pompe à protons, prokinétiques (métoclopramide, dompéridone)<br>**Estomac :** érythromycine (1 mg/kg 3 à 4 fois par jour)<br>**Grêle :** octréotide (50 à 100 µg/j), antibiotiques (norfloxacine, amoxicilline) |
| **Atteinte articulaire** | Anti-inflammatoires non stéroïdiens<br>Corticoïdes à faible dose (10 mg/j)<br>Méthotrexate |
| **Myopathie** | Corticoïdes à forte dose (jusqu'à 1 mg/kg)<br>Méthotrexate |

Mouthon L et al, Presse Med 2006

# Conclusions

- Progrès importants effectués dans la prise en charge des manifestations vasculaires, beaucoup plus de difficultés dans le traitement de la fibrose
- Inhibiteurs de tyrosine kinase décevants
- Regain d'intérêt pour la composante inflammatoire/autoimmune et une approche immunomodulatrice/immunosuppressive.

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