Paul Klee: 1879-1940
Rond 1925
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 peripheral and visceral vasculature
  - Variable involvement of extracellular 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

Diffuse variant
Introduction

Limited
Epidemiology

- Incidence: 15 – 20 / 1,000,000 pj
- Prevalence: 150 – 250 / 1,000,000
Epidemiology

AGE AT ONSET OF SCLERODERMA

New cases/million population per year

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Clinical picture

- Raynaud + progressive skin changes
Clinical picture

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

![Survival Rates in Scleroderma](image-url)

**SURVIVAL RATES IN SCLERODERMA**

- Diffuse SSc (n = 697)
- Limited SSc (n = 217)
- Anti-Scl-70 AB (n = 241)
- Anti-centromere AB (n = 130)

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Pathophysiology

fibroblasts

T- and B-cells

Endothelial cells
Pathophysiologie

Activation and infiltration of mononuclear cells

Endothelial cell
Vessel obliteration

Fibroblast
Cutaneous and tissue fibrosis

Production auto-antibodies
Selective Up-Regulation of PDGFR by Fibroblasts in Scleroderma.

What activates mononuclear cells?
- CMV
- Retrovirus
- Microchimerism
- Silica
- Organic solutions
Pathophysiologie

- **Endothelial cells**
- **Probably under the influence of TGF-β**
  - Thrombocyt aggregation
  - PDGF $\uparrow$
  - CTGF $\uparrow$
  - NO $\downarrow$
  - Endothelin $\uparrow$

$\Rightarrow$ Vessel obliteration + Tissue hypoxia
Treatment

- Organ specific:
  - Kidney: ACE inhibitors
  - Lungs
    - Pulmonary hypertension:
      - Bosentan
      - Sildenafil
      - Prostacycline
    - Pulmonary fibrosis: immunosuppression
      - Steroids
      - Cyclofosfamide
      - Anti-TNF
  - Gastrointestinal: metoclopramide, domperidon
  - Skin: ?
Effect of current treatment
Future treatments?
The fibroblast
Fibroblast

- Most important cell of the connective tissue
- Supports extracellular matrix
- Produces precursors of all components of the extracellular matrix
  - Collagen
  - Glycosaminoglycans (e.g. hyaluronic acid)
  - Reticular and elastic fibers
  - Glycoproteins
The fibroblast as cell of the immune system

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

<table>
<thead>
<tr>
<th>Chemokines</th>
<th>N</th>
<th>Hematopoietic tissue</th>
<th>Lung</th>
<th>Breast</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>I-Normal</td>
<td>II-Pathologic</td>
<td>III-Normal</td>
</tr>
<tr>
<td>IL-8</td>
<td>39</td>
<td></td>
<td>*</td>
<td>0.000 (I)</td>
</tr>
<tr>
<td>MCP-1</td>
<td>41</td>
<td></td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>RANTES</td>
<td>35</td>
<td></td>
<td>*</td>
<td>0.017 (I)</td>
</tr>
<tr>
<td>MIP1-α</td>
<td>35</td>
<td>*</td>
<td>0.033 (I)</td>
<td>0.022 (I)</td>
</tr>
<tr>
<td>Eotaxin</td>
<td>30</td>
<td>*</td>
<td>0.010 (I)</td>
<td>*</td>
</tr>
</tbody>
</table>

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.
Core business of the fibroblast
Granulation tissue
Apoptosis
The dysregulated fibroblast

- Together fibrosing diseases are the main cause of morbidity and mortality in North America, Europe and Japan
Liver disease
General fibrotic disease
Fibroblast

Tissue injury

Inflammation and/or mechanical stress

Migration
Proto-myofibroblast
stress fibers (cytoplasmic actin)
Proliferation

Myofibroblast
stress fibers (α-SM actin)

Contractility
ECM deposition

Acute mild damage

Granulation tissue resolution
ECM remodeling

Severe chronic damage and/or inappropriate inflammatory response

Pathological repair
Wounds with uncontrolled proliferation (e.g., hypertrophic scar, fibrosis)

“Normal” scar

Repair
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

<table>
<thead>
<tr>
<th>Fibrotic process</th>
<th>Alterations</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In vivo animal models</strong></td>
<td></td>
<td></td>
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<tr>
<td>Renal fibrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thy-1 antibody induced (rats)</td>
<td>↓ Smad7 expression</td>
<td>62</td>
</tr>
<tr>
<td>TGFβ transgenic (mice)</td>
<td>↓ Smad7 expression</td>
<td>63</td>
</tr>
<tr>
<td>db/db (mice)</td>
<td>↓ Smad3 expression</td>
<td>67</td>
</tr>
<tr>
<td>Ovalbumin-induced airway fibrosis</td>
<td>↑↑ Smad2 phosphorylation, ↑↑ Smad3 expression</td>
<td>68</td>
</tr>
<tr>
<td>Postinfarction myocardial fibrosis</td>
<td>↑ Smad3 expression</td>
<td>87</td>
</tr>
<tr>
<td>Pulmonary fibrosis in Smad3-null mice</td>
<td>↓ collagen production</td>
<td>74</td>
</tr>
<tr>
<td><strong>In vitro cell culture</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myofibroblast transdifferentiation</td>
<td>↑↑ Smad2 phosphorylation, ↓ Smad7 expression</td>
<td>60</td>
</tr>
<tr>
<td>Hepatic cells from fibrotic liver</td>
<td>↑↑ Smad3 phosphorylation, ligand-independent</td>
<td>64</td>
</tr>
<tr>
<td>Smad3/4 nuclear accumulation</td>
<td>Smad3/4 nuclear accumulation</td>
<td></td>
</tr>
<tr>
<td>Hepatic cells from fibrotic liver</td>
<td>↑↑ Smad3 expression, ↓ Smad7 expression</td>
<td>88</td>
</tr>
<tr>
<td>Smad3-null hepatic cells from CCL4-induced liver injury</td>
<td>↓ collagen induction</td>
<td>41</td>
</tr>
<tr>
<td>Dermal fibroblasts from keloid lesions</td>
<td>↑ Smad3 phosphorylation</td>
<td>65</td>
</tr>
<tr>
<td>Dermal fibroblasts from scleroderma</td>
<td>↑↑ Smad3 expression</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>↑↑ Smad2/3 phosphorylation</td>
<td>61, 66</td>
</tr>
<tr>
<td></td>
<td>↑↓ Smad7 expression</td>
<td>61</td>
</tr>
</tbody>
</table>
Targeting bad guys
Fig. 2. Effect of anti-TGF-β alone or in combination with ACE inhibitor on blood pressure, proteinuria and renal histology in diabetic rats. °p < 0.05, **p < 0.01 vs. control; *p < 0.05 diabetic rats.
Targeting good guys

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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

TGF-β  PDGF-R

Proliferation
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)

Own work
Culture of Fibroblasts (GO-27)

5 days after culture

5 days after culture

5 days after culture

10 weeks after culture
Imatinib blocks PDGF-BB induced proliferation sufficiently above 1.25μg/ml
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.
Imatinib mesylate (IM; 2.5 ug/ml) blocks TGF-β₁ (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

![Graph showing KCO RCL percentages over dates from 2-7-2006 to 14-11-2007.](image)
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 Crow¹

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 29.3±9.4 compared to 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-ScI70 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
- ........
- ............
- ................