Immunological alteration by silica and silicate:

case-oriented and experimental analyses

Takemi Otsuki[1)], Haruko Sakaguchi[1)],
Tamayo Hatayama[1)], Satomi Hatada[1)],
Yoshie Miura[1)], Akiko Takata[1)],
Hironobu Katsuyama[2)], Fuminori Hyodoh[1)]

[1)]Department of Hygiene, [2)]Public Health, Kawasaki Medical School, Japan

Autoimmune disorders complicated with silicosis

IMMUNOLOGY

The fairly rapid development of multiple well-circumscribed peripheral nodules (0.5 to 5.0 cm in diameter) which resemble metastatic tumors was first described in coal miners with rheumatoid arthritis. In miners with serum positive for rheumatoid factor, the pulmonary lesions may precede joint involvement. Smaller, apparently simple silicotic nodules may rapidly enlarge with activity of rheumatoid arthritis and then partially clear in response to adrenal corticosteroids. Histologic examination shows that lesions contain thin layers of dust in addition to the necrotic collagen and active inflammatory zone of rheumatoid nodules. Cavities may be formed by expectoration of necrotic material. The nodules may stabilize or calcify. Later experience has shown that serologic tests for autoimmunity (antinuclear antibody) are frequently positive (over 40 percent) in the accelerated silicosis of sandblasters. In this group of patients, about 10 percent have clinical autoimmune connective tissue diseases, including rheumatoid arthritis, localized and general scleroderma, and systemic lupus erythematosus. Studies of cellular immunity are under way using alveolar macrophages and lymphocytes obtained from bronchial washings through the flexible bronchoscope.

from
Pulmonary Diseases and Disorders Second Edit, Vol 1
Fisherman,A.P. McGraw-Hill/New York

(7) *Rheumatoid syndrome*

The progression of silicosis and the appearance of the lesions in the presence of rheumatoid arthritis or rheumatoid factor without rheumatoid arthritis has already been alluded to and are important in that they are likely to be mistaken for active tuberculous disease. Eleven cases (2 per cent) of 'rheumatoid modified' silicotic nodules were found in 576 autopsies on European gold-miners studied at the Johannesburg Pneumoconiosis Research Unit (Chatgidakis and Theron, 1961), and cases have been recorded during life in women in the German pottery industry (Otto, 1969).

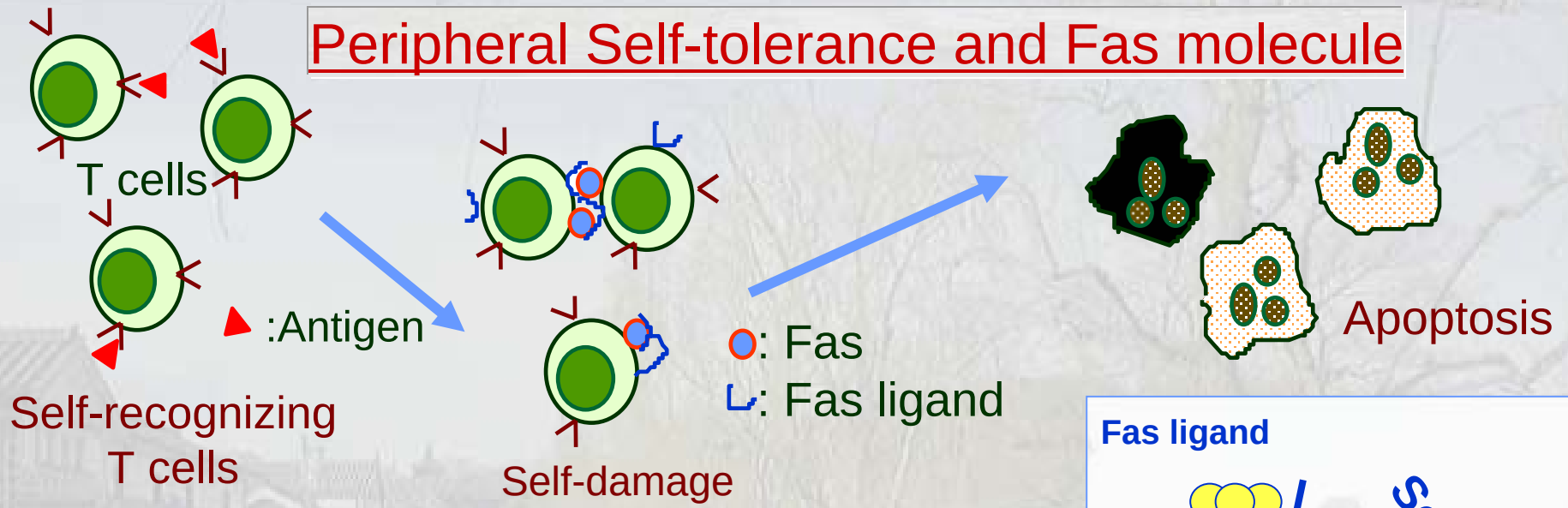
(8) *Scleroderma (progressive systemic sclerosis)*

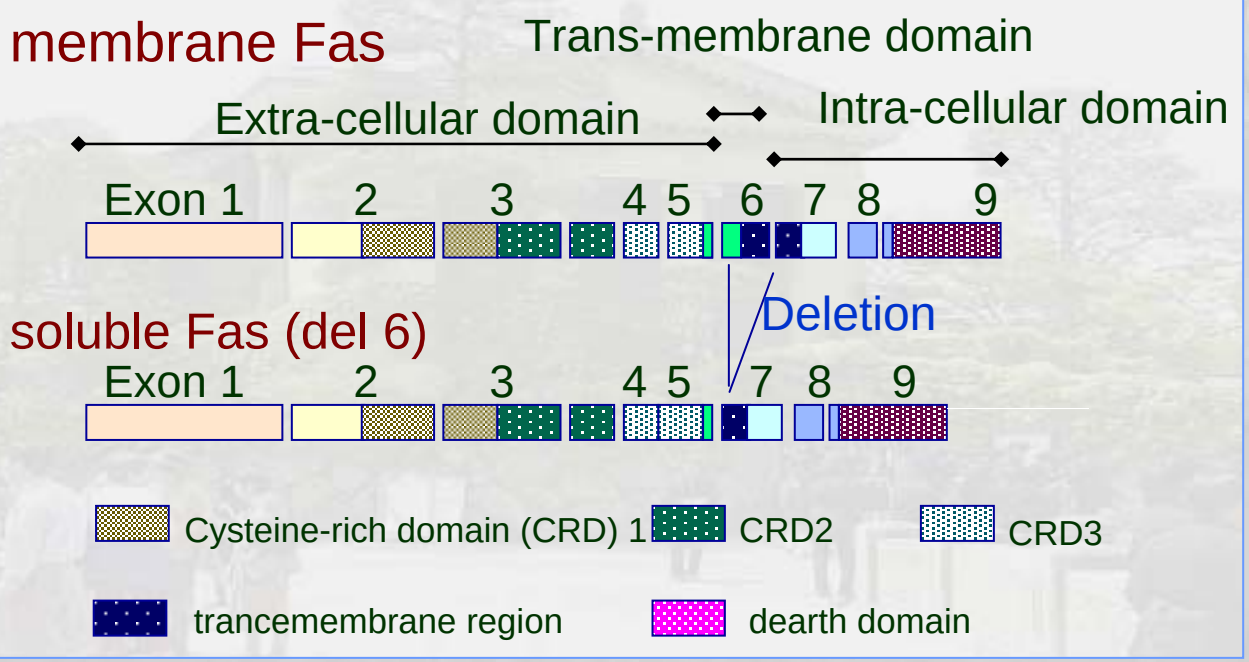
An unusually high incidence of scleroderma has been reported among gold-miners (Erasmus, 1960), coal-miners, stone-masons and pottery and foundry workers with pneumoconiosis (Rodnan *et al.*, 1966), although not a single case seems to have been observed in British coal-miners (Rogan, 1960). Byrom Bramwell, in 1914, first drew attention to the association of silicosis and scleroderma (which he attributed to the holding of cold chisels) in stone-masons.

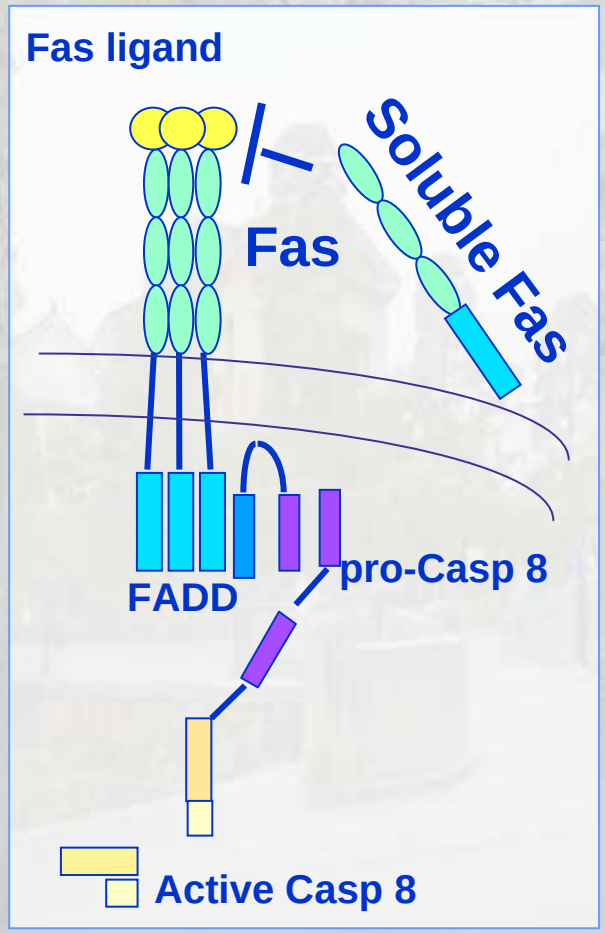
This would seem to be a chance association but Rodnan *et al.* (1966) have advanced evidence suggesting that the prevalence of scleroderma is higher in workers with silicosis (or coal pneumoconiosis) than in the general population. Further investigation in which the standards of diagnosis are clearly defined is necessary. Immunological factors which influence the lungs and other organs may play a part in pathogenesis, but there is no suggestion that silicosis (or any other pneumoconiosis) causes scleroderma via immunological or other agencies. Diffuse interstitial fibrosis (fibrosing 'alveolitis'), by contrast, is a well recognized manifestation of progressive systemic sclerosis (Hayman and Hunt, 1952).

from
OCCUPATIONAL LUNG DISORDERS
Parkes, W.R. Butterworths, press/London

Peripheral Self-tolerance and Fas molecule







Clin Exp Immunol 1997; 110:303–309

Elevated soluble Fas/APO-1 (CD95) levels in silicosis patients without clinical symptoms of autoimmune diseases or malignant tumours

A. TOMOKUNI, T. AIKOH, T. MATSUKI, Y. ISOZAKI, T. OTSUKI, S. KITA*, H. UEKI†, M. KUSAKA‡, T. KISHIMOTO§, & A. UEKI *Departments of Hygiene, *Primary Health Care & Preventive Medicine and †Dermatology, Kawasaki Medical School, Kurashiki, ‡Department of Internal Medicine, Kusaka Hospital, Bizen, and §Department of Internal Medicine, Okayama Rosai-Hospital, Okayama, Japan*

The serum from silicosis patients (and SLE, SSc) showed elevation of soluble Fas compared with those of healthy volunteers.

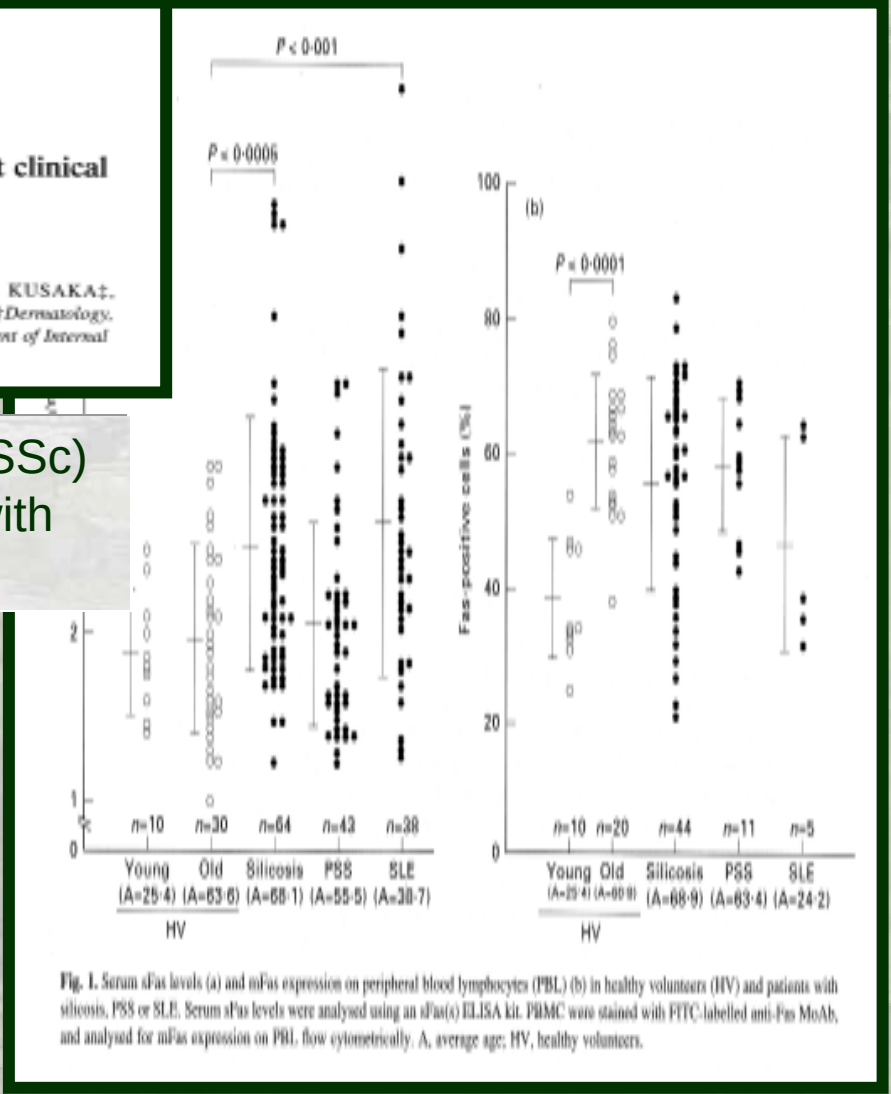
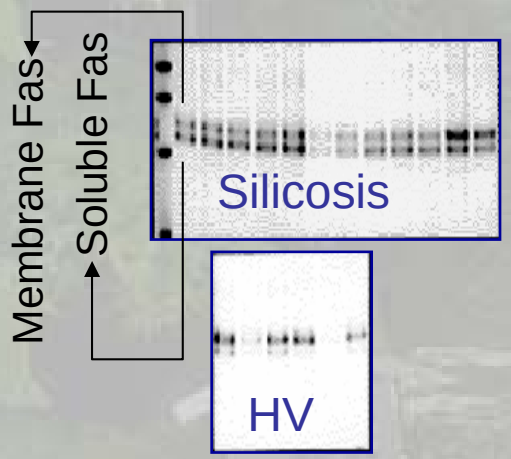


Fig. 1. Serum sFas levels (a) and mFas expression on peripheral blood lymphocytes (PBL) (b) in healthy volunteers (HV) and patients with silicosis, PSS or SLE. Serum sFas levels were analysed using an sFas(s) ELISA kit. PBMC were stained with FITC-labelled anti-Fas MoAb, and analysed for mFas expression on PBL flow cytometrically. A, average age; HV, healthy volunteers.

Gene expression of soluble and membrane Fas in PBMC



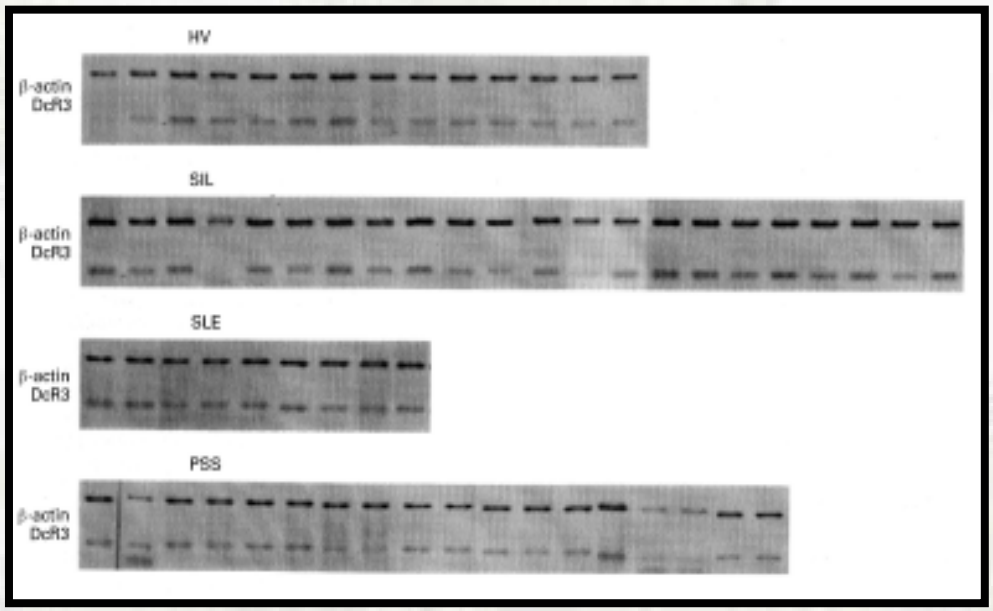
m/s Fas expression ratio

0.78±0.43

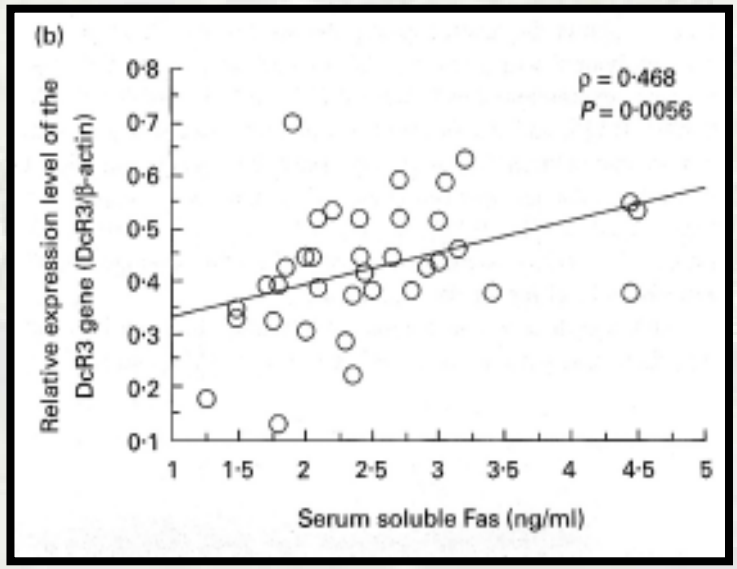
p <0.001

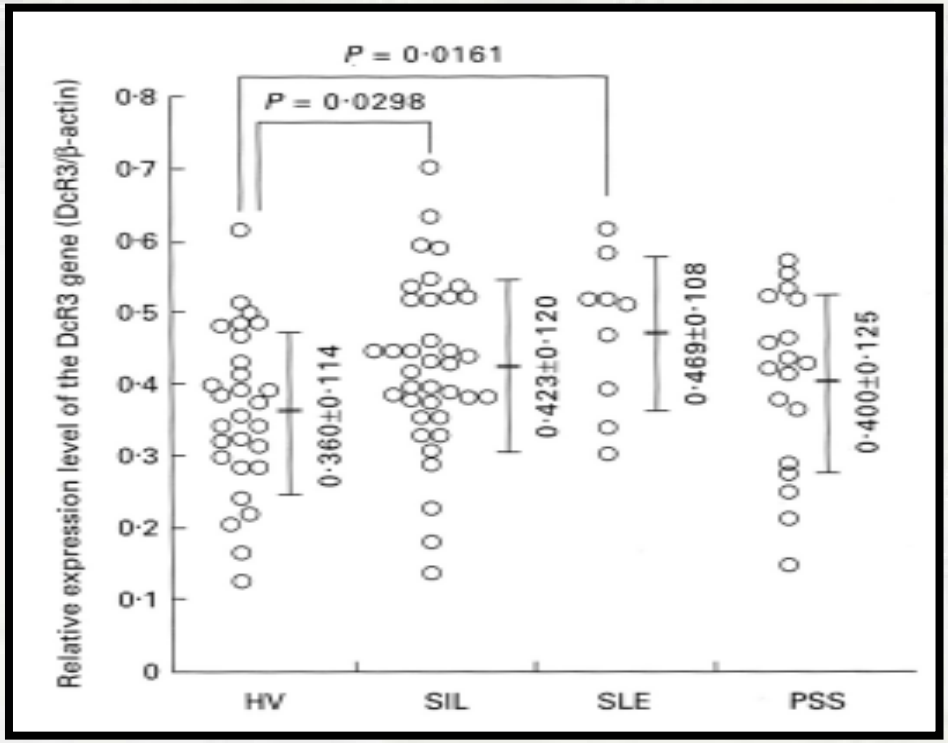
2.37±0.89

Soluble Fas is elevated in message and protein levels in silicosis



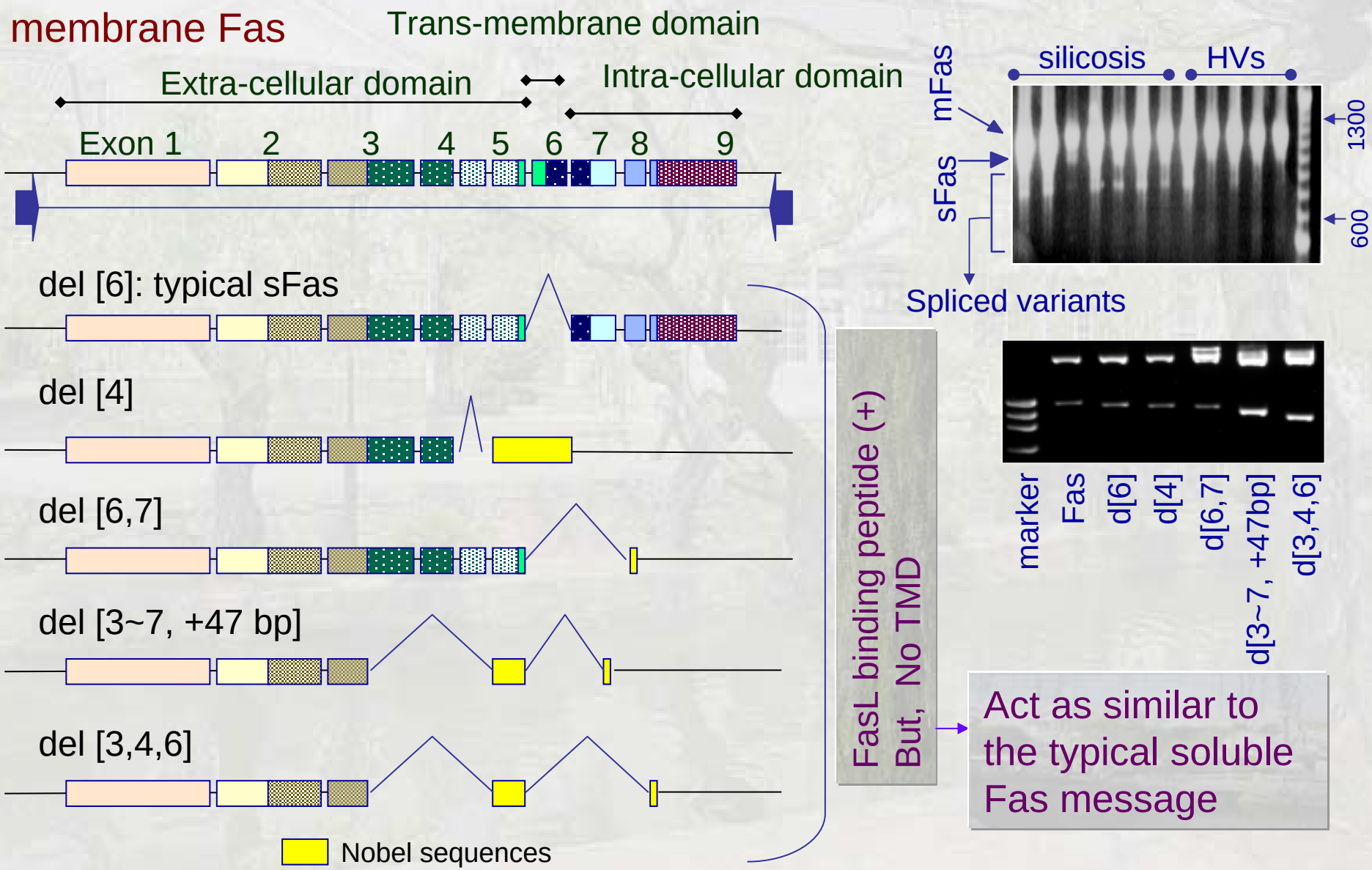
The expression of DcR gene, which function as similar to the soluble Fas, in PBMC from silicosis patients was significantly higher than that of HVs.





The relative expression levels of DcR3 gene in silicosis patients showed positive correlation with serum soluble Fas levels.

Detection of other Fas gene spliced variant-messages, which seemed to function similar to typical soluble Fas message

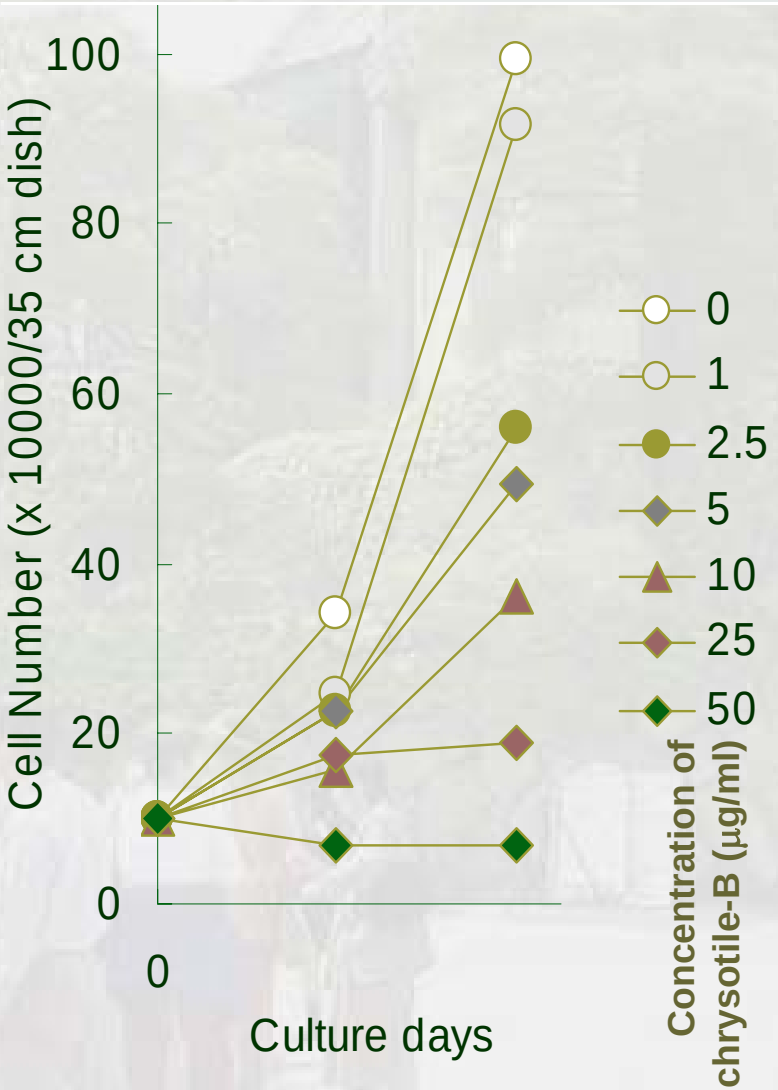


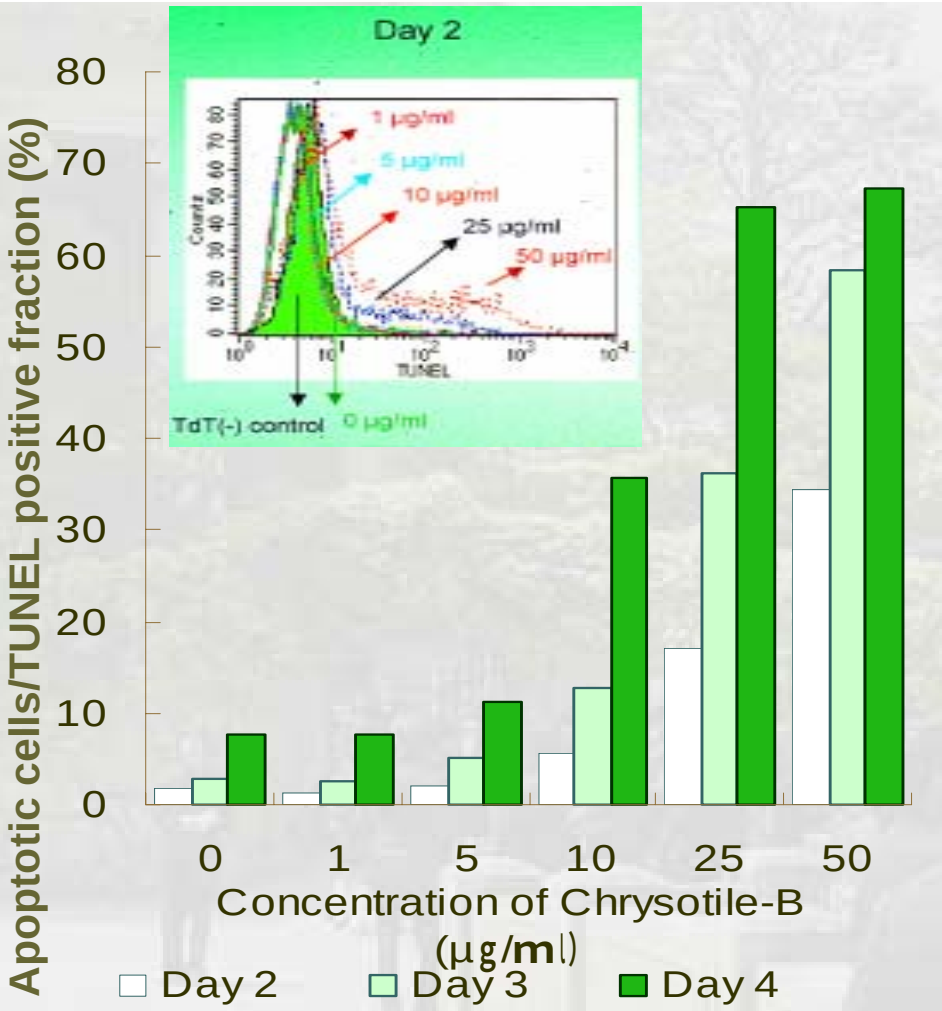
Factor Analysis from Clinical and Experimental Parameters

Parameters 58 silicosis patients, M [51], F [7]		1	2	3	4	5	6	7
Excess sFas gene expression	ratio			.641			.399	
mFas	%					.923		
Serum sFas	ng/ml		.654					
Ig G	mg/ml		.801					
X-ray classification	No [0] – 4C [7]			-.828				
Symptomatic Dyspnea	slight [1]- severe [3]					.406	-.458	
Duration Exposure	Years	-.441			-.534			-.407
PO2	torr	-.765						
A-aDO2	torr	.909						
PCO2	torr				.787			
ANA (Titer)	<40 [1] ->160 [3]		.616		.488			
Serum sFasL	Ng/ml							
FEV 1.0	%							.772
%VC	%							
V25/H								.618
	Contribution rate (%)	**22.6**	**14.5**	**10.7**	8.4	7.5	6.8	6.3

Factor 1 : Respiratory Factor, F 2: Immunological Factor (independent)
F 3: Splicing alteration of Fas gene might occur in patients with slight radiological changes. ***<< Individual factor >>***

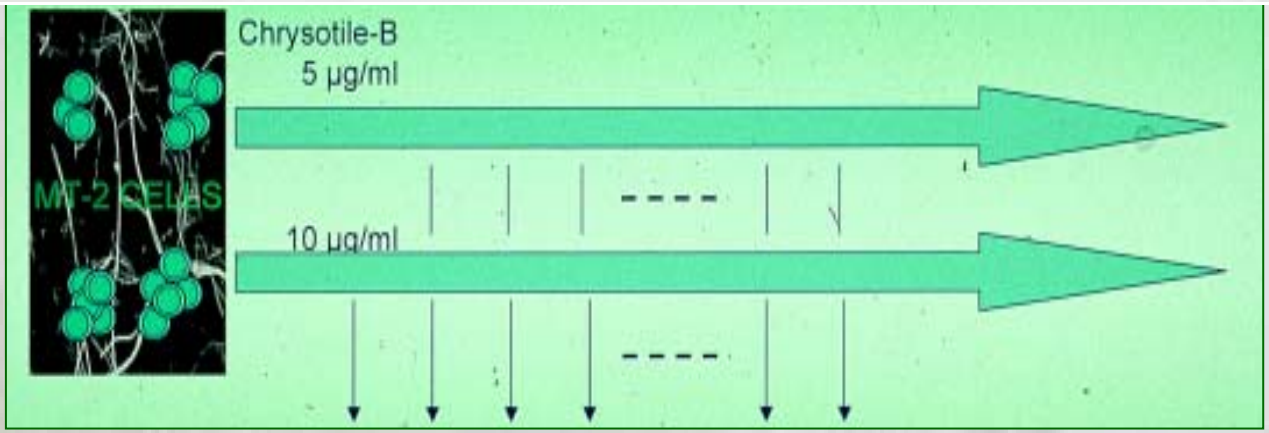
Growth inhibitory, and apoptosis-inducing effects of an asbestos, chrysotile-B, on HTLV-immortalized human polyclonal CD4+ T cell line, MT-2



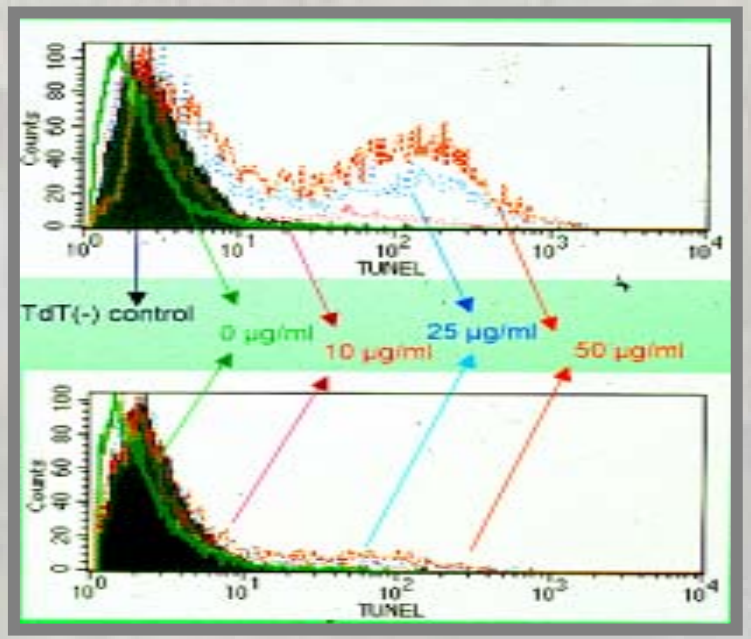


Analyzed by TUNEL method

Trial to establish sub-line resistant to chrysotile-B-induced apoptosis

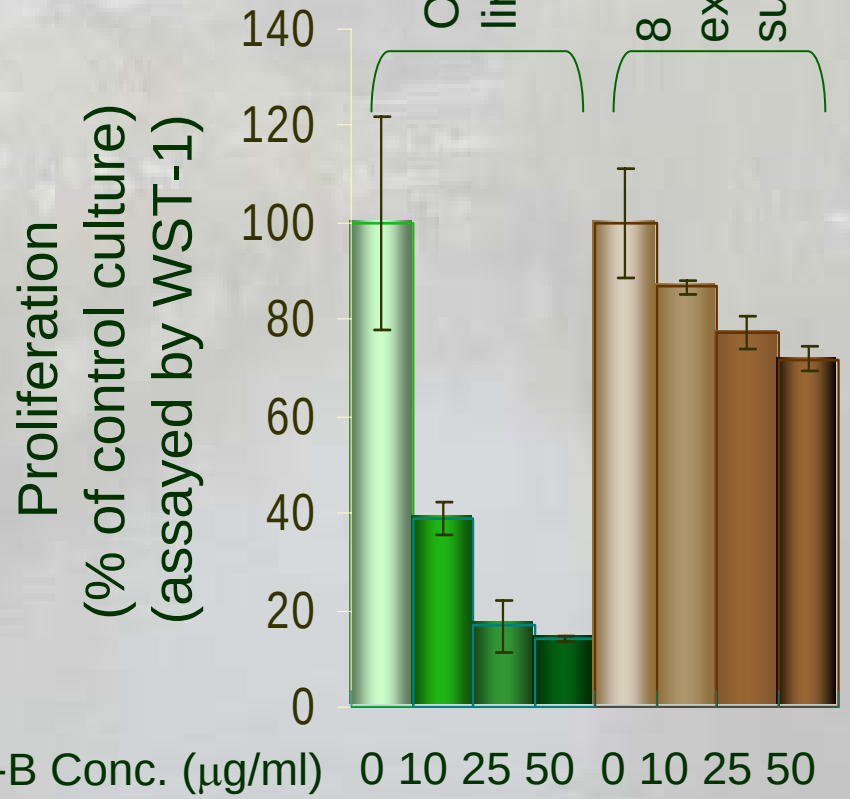


Original line

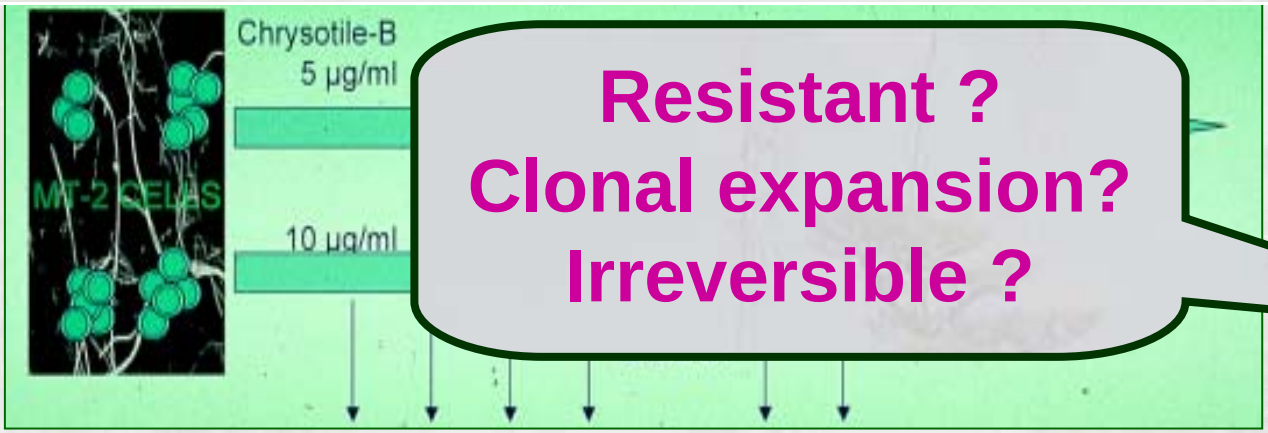


8 months exposed subline

TUNEL analysis



Trial to establish sub-line resistant to chrysotile-B-induced apoptosis



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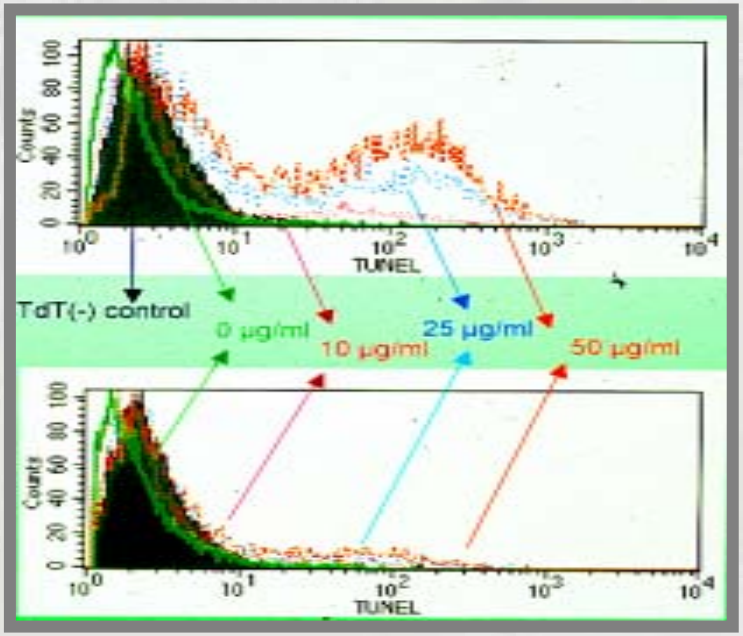

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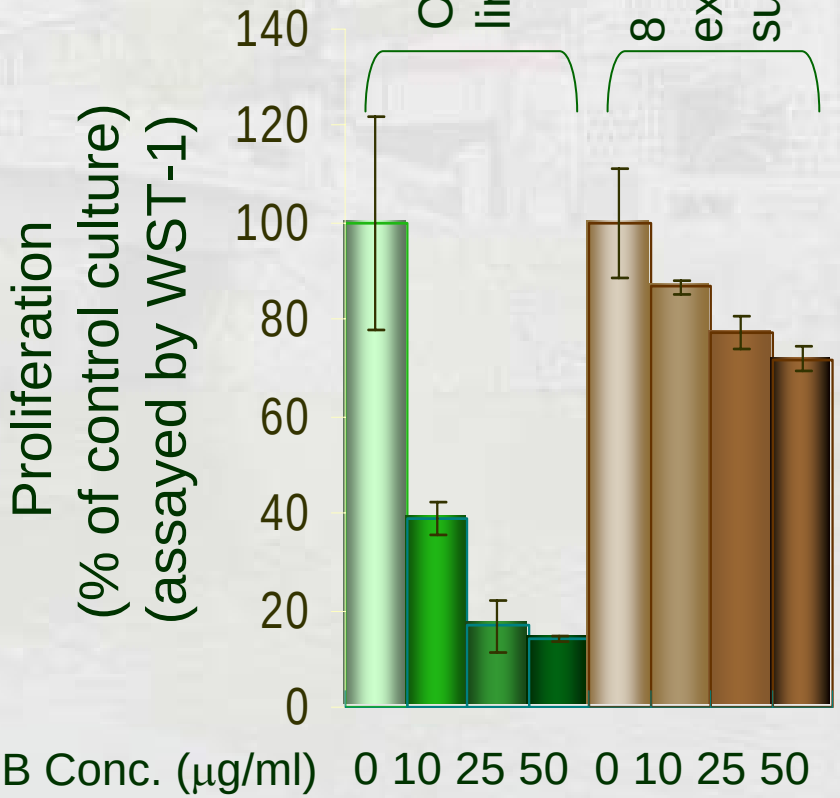
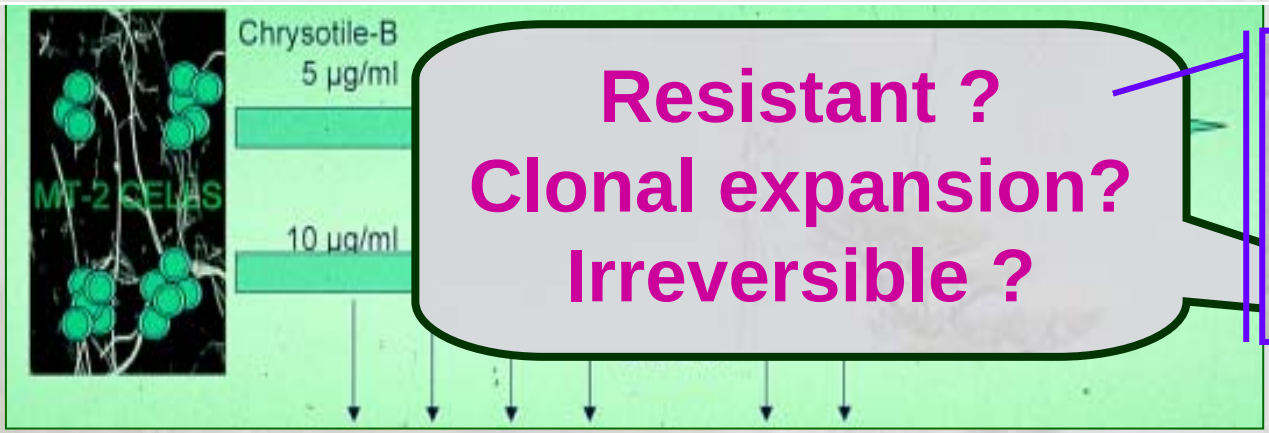


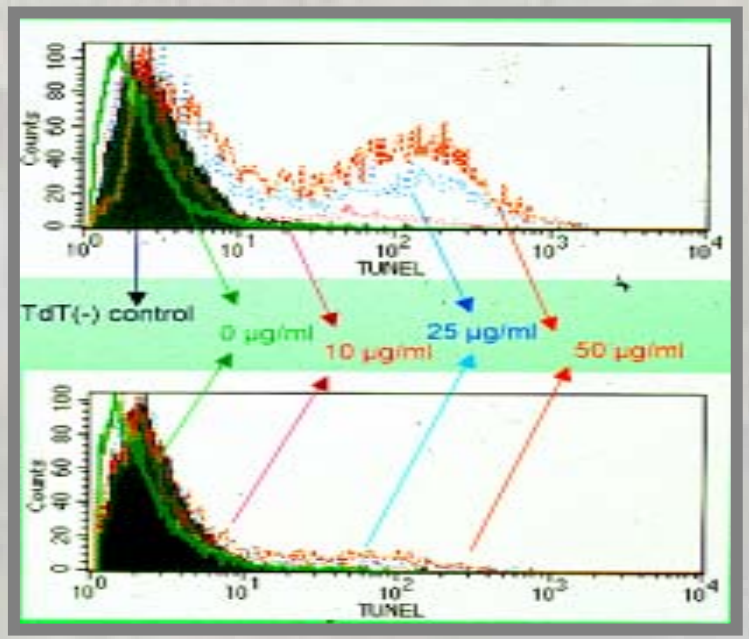
Trial to establish sub-line resistant to chrysotile-B-induced apoptosis



Resistant ?
Clonal expansion?
Irreversible ?

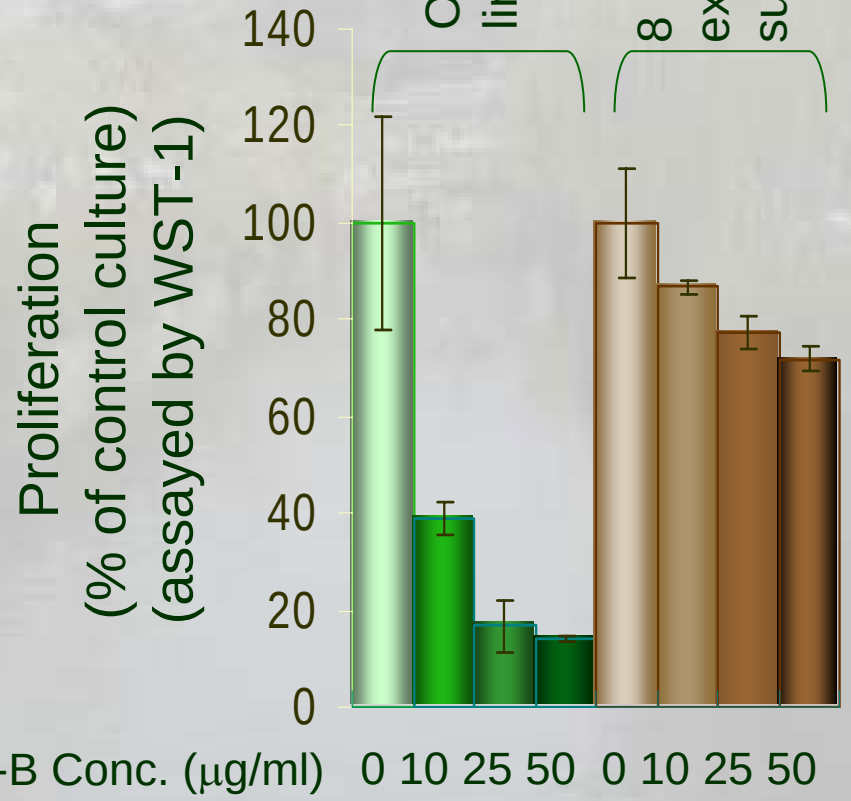
Should be studied in the future

Original line



8 months exposed subline

TUNEL analysis



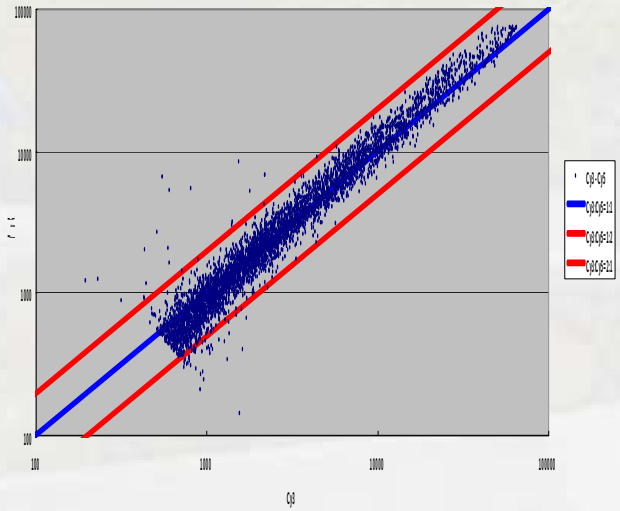
cDNA microarray analysis between original and resistant lines

Overlayed image

Up-regulated genes (selected):

- papalog: encodes a member of the poly(A) polymerase family
- clcn5：a voltage-gated chloride channel.
- tll2：encodes an astacin-like zinc-dependent metalloprotease
- cxadr: receptor for virus
- scya8: chemokine, small inducible cytokine A8 precursor (CCL8) (Monocyte chemotactic protein 2) (MCP-2)

Cy5:Resistant sub-line



Cy3: original line

Down regulated genes (selected)；

- Scyb13：CXCL13 (B lymphocyte chemoattractant) (CXC chemokine BLC) (B cell-attracting chemokine 1) (BCA-1)
- ptprn：protein tyrosine phosphatase, receptor type (Autoantiboy in Type I DM）
- Eif4a1：eukaryotic translation initiation factor 4a, isoform 1
- Ndufb6：B17 subunit of mitochondrial respiratory chain complex I
- Ube2n：Ubiquitin-conjugating enzyme. Proteins destined for proteasome-mediated degradation may be ubiquitinated. Ubiquitination follows conjugation of ubiquitin to a conserved cysteine residue of UBC homologues.

Discussion

- Silicosis patients showed several abnormalities in Fas-mediated apoptotic pathway of lymphocytes.
- These experimentally extracted parameters were differed from respiratory factors such as the results of blood gas analysis, X-ray classification, and duration of exposure.
- Chrysotile-B, an asbestos, induced apoptosis of human polyclonal T cell line, MT-2.
- Continuous exposure of low-concentration of chrysotile-B to MT-2 cells caused resistant phenotype against chrysotile-B-induced apoptosis.
- Several genes were altered in chrysotile-B-resistant sub-line of MT-2 analyzed by cDNA microarray.
- Future analyses are required to clarify the immunological effects of silica and silicate to find mechanisms involved in silica-induced disruption of autoimmunity and modification of tumor-immunity laid on the progression of malignant transformation caused by these substances.