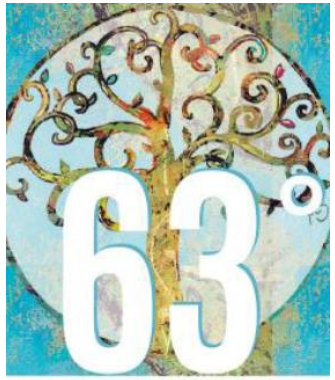


Patologia Autoimmunitaria nell'Anziano

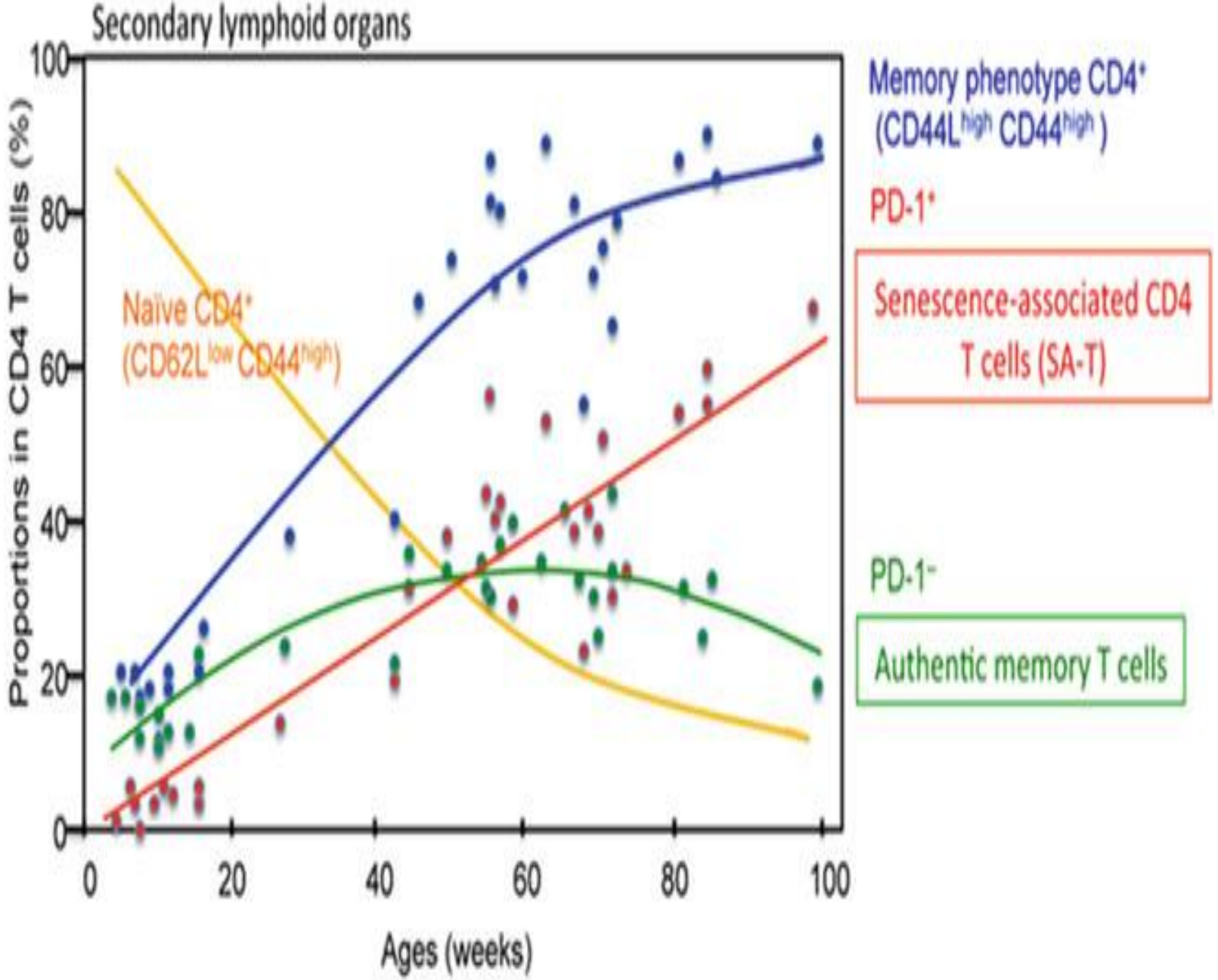
Marco Matucci Cerinic

Università di Firenze

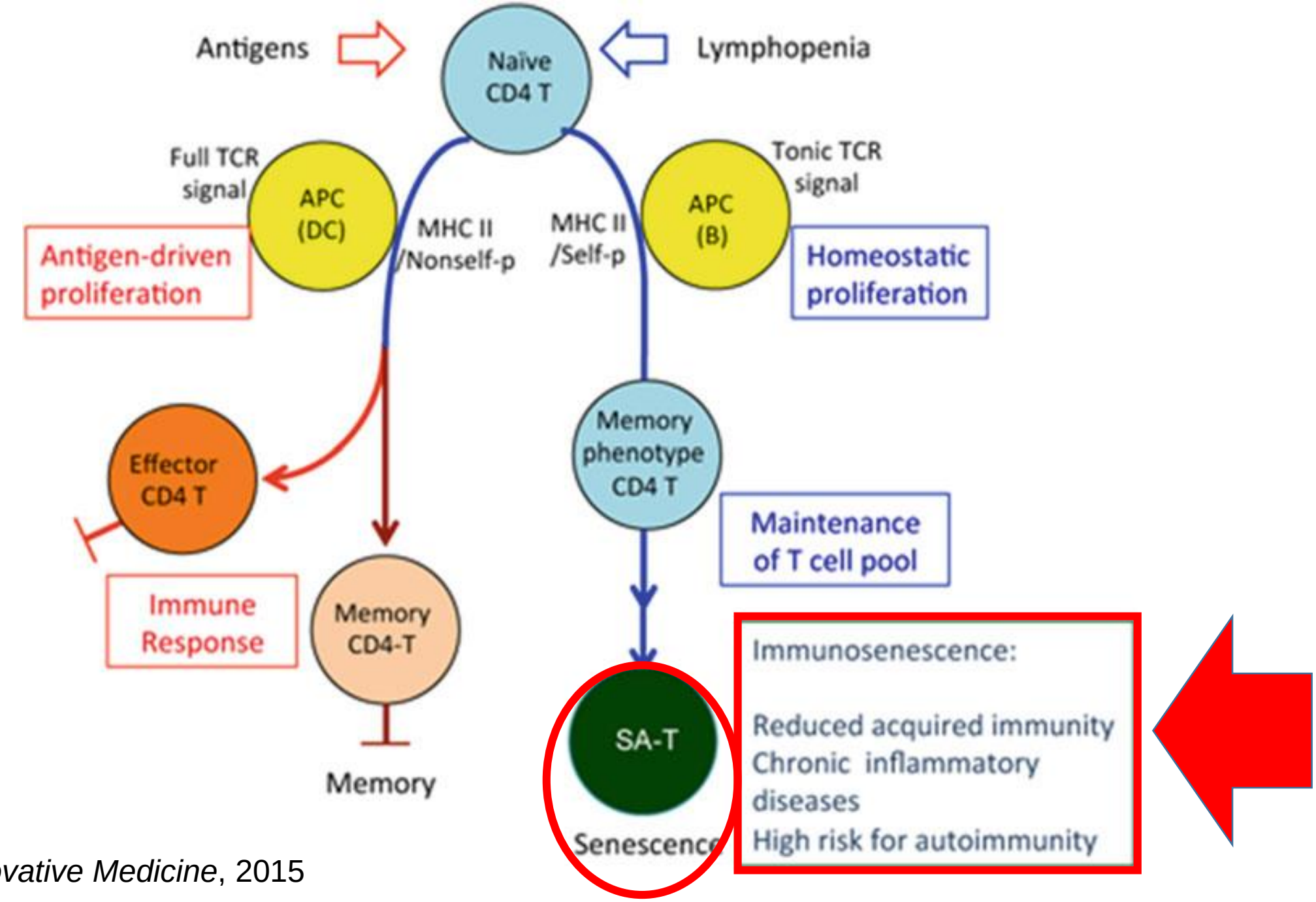
During ageing, the immune system undergoes a complex series of remodeling/restructuring events involving almost all compartments – both the innate and the adaptive system

(a) a reduction in immune response (immunosenescence),
(b) an increase in the inflammatory and oxidation background (inflammaging),
(c) a production and release of autoantibodies

Franceschi C, et al : Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. Mech Ageing Dev 2007; 128: 92;
De la Fuente M, et al J: An update of the oxidation-inflammation theory of aging: the involvement of the immune system in oxi-inflamm-aging. Curr Pharm Des 2009; 15: 3003–
Ramos-Casals M, et al Autoimmunity and geriatrics: clinical significance of autoimmune manifestations in the elderly. Lupus 2003; 12: 341



Stahl, E.C., Brown, B.N., 2015. Cell therapy strategies to combat immunosenescence Organ 11 (4), 159–172.



Minato T *Innovative Medicine*, 2015

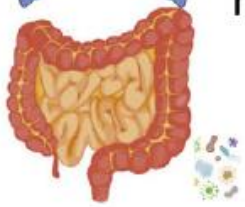
late-stage differentiated CD8 T cells, some of which may really be replicatively senescent (i.e. arrested due to DNA damage and/or short telomeres) triggering a cell senescence program similar to that of fibroblasts and characterised by a *cytokine/chemokine secretion pattern*
known as the
"**senescence-associated secretory profile**" (SASP)
may also contribute to tissue damage in a manner resembling granzymopathies

Voskoboinik, I., Whisstock, J.C., Trapani, J.A., 2015. Perforin and granzymes: function, dysfunction and human pathology. Nat. Rev. Immunol. 15 (6), 388–400.

Tchkonia, T., Zhu, Y., van Deursen, J., Campisi, J., Kirkland, J.L., 2013. Cellular senescence and the senescent secretory phenotype: therapeutic opportunities. J. Clin. Invest. 123 (3), 966–972.

Facteurs intrinsèques (hôte)

Génétique



Altérations des muqueuses et du microbiote

Atrophie de la peau

et de la masse musculaire (sarcopénie)

Vieillissement

Immunosénescence

Facteurs extrinsèques (environnement)

Comorbidités

Régime alimentaire

Activité physique

Traitements

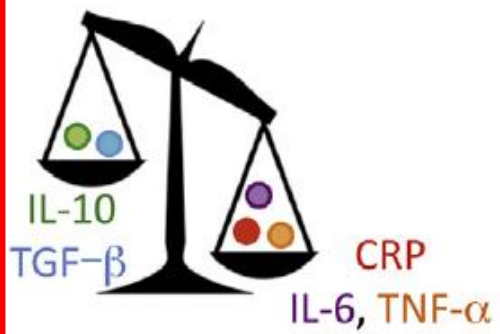
Stress, anxiété, dépression

Inflammation chronique

Changements des sous-populations lymphocytaires

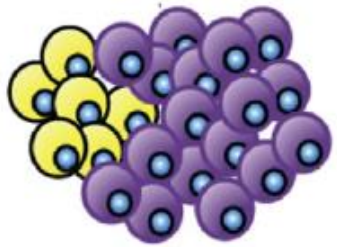
Accumulation de cellules sénescentes

Raccourcissement des télomères



Involution thymique

Moins de cellules naives



Plus de cellules mémoire oligoclonales

Conséquences cliniques

↗ Pathologies auto-immunes, maladies cardio-vasculaires, cancers

↗ Sévérité des infections

↘ Efficacité des réponses vaccinales

Levels of inflammatory mediators in the serum, most commonly IL6, are usually found to be higher in elderly people, and have been associated with frailty and mortality.

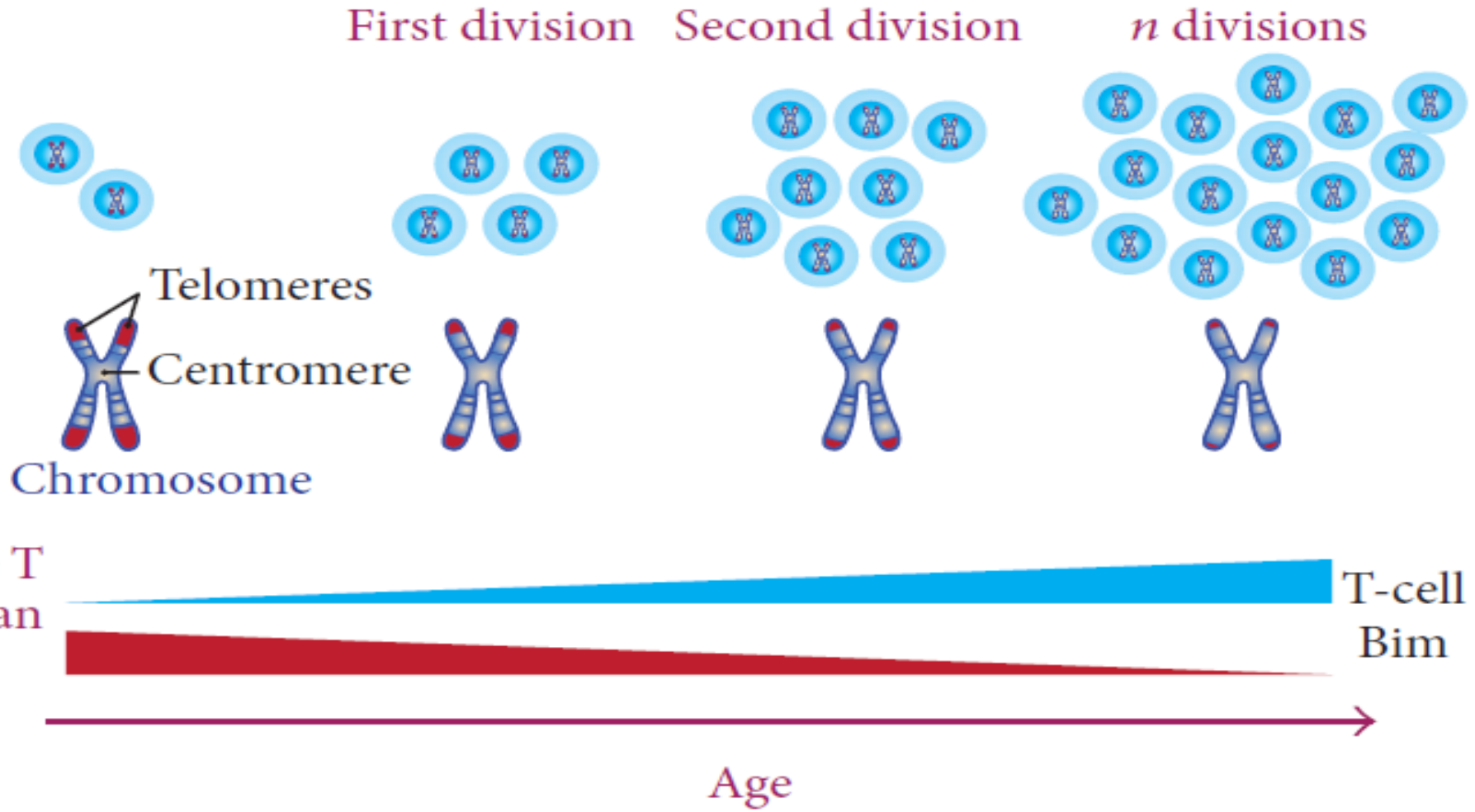
This phenomenon of **“inflammaging”** is often considered to be a part of “immunosenescence

Michaud, M., Balardy, L., Moulis, G., Gaudin, C., Peyrot, C., Vellas, B., et al., 2013. Proinflammatory cytokines, aging, and age-related diseases. J. Am. Med. Dir. Assoc. 14 (12), 877–882.

Franceschi, C., Bonafe, M., Valensin, S., Olivieri, F., De Luca, M., Ottaviani, E., et al., 2000. Inflamm-aging. An evolutionary perspective on immunosenescence. Ann. N. Y. Acad. Sci. 908, 244–254

Inflammaging may also result from the dysregulated activities of immune cells other than CD8+ T cells, of course, especially innate immune cells which tend to be pro-inflammatory as an essential part of their function

One of the important causes of dysfunctional immune responses is telomere abnormalities which may lead to autoimmunity.



Numerous studies have shown an association between mean telomere length in peripheral blood mononuclear cells (PBMCs) and different diseases

R. B. Effros, "Telomere/telomerase dynamics within the human immune system: effect of chronic infection and stress," *Experimental Gerontology* 2011; 46: 135–140.

reports of **telomere length alteration** in patients with

- *Rheumatoid Arthritis* (*PNAS 2003;* 100: 13471–6),
- scleroderma (*Br J Rheumatol 1996* 35: 732–7),
- systemic lupus erythematosus (*Clin Immunol 2001;*99:211–21)
- polyangiitis with granulomatosis (*Kidney Int* 2003; 63: 2144–51)
- Psoriasis & atopic dermatitis (*J Immunol 2000; 1*65: 4742–7),

suggests an *excessive cell replication* with their corresponding telomere erosion.

These findings have been interpreted as evidence of T-cell accelerated proliferation in the autoimmune process.

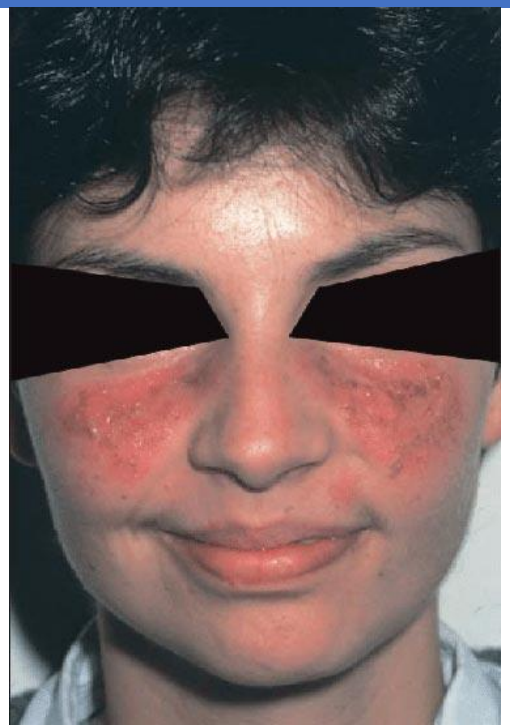
Table 2. Distribution of autoantibodies among Danish centenarians ($n = 140$)

Subjects having	*n*	(%)
Autoantibodies	111	(79.3)
Both non-organ and organ specific autoantibodies	34	(24.3)
Only non-organ specific autoantibodies	66	(47.1)
Only organ specific autoantibodies	11	(7.9)
No autoantibodies at all	29	(20.7)

In the elderly…

age-related transformations redesign the immune architecture and the balance between proinflammatory and anti-inflammatory protective factors, as well as between proapoptotic and antiapoptotic signals.

Systemic Lupus Erythematosus
is a disease of the reproductive stage of women,



the severity of the disease appears to decrease with age and after menopause
SLE usually has a milder course

SLE in elderly patients

1. SLE which transits in elder age
2. Elderly onset SLE

Drug Induced SLE

should always be considered in the elderly.

The drugs that most commonly induce SLE are:

- β-blockers,
- procainamide, hydralazine,
- isoniazid,
- methyldopa, carbamazepine,
- interferon-a
- tumour necrosis factor
- α blockers

Autoimmun Rev 2010 10: 46-50

Late onset SLE

SLE occurs between 3 and 18% in individuals older than 50 years

Maddock RK JAMA 1965; 191: 137–8

female/male sex ratio declines with age.

2.5 to 9 in elderly vs 9.1 to 14.4 in young people

R. Cervera, et al., *Medicine* 1993;72: 113–24.

Lupus in older adults

- Associated with Sjögren's syndrome
- ↑ RF and antinucelar antibodies
  Milder disease course
- Frequency of 3–18% compared to all SLE cases
- Ocurrence of serositis and pulmonary involvement
- F/M sex ratio from 2.5 to 9

Elderly SLE

- clinical manifestations such as malar rash and photosensitivity , compromising renal disease (lupus nephritis and nephrotic syndrome), lymphadenopathy, and thrombocytopenia, arthritis are less frequent
- **Raynaud's phenomenon, serositis, cytopenias, and pulmonary involvement are more frequent clinical manifestations**

- Serological profiles exhibit alterations. Elderly SLE has

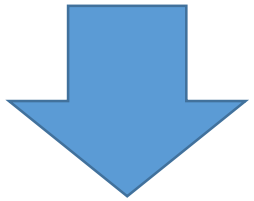
❖ **high frequency of rheumatoid factor (33% versus 20%) antinuclear antibodies**

❖ **low frequency of antiribonucleoprotein (anti-RNP, 10% versus 21%) and anti-Sm (9% versus 17%).**

ARD 1991; 50: 702–5, 1991; Medicine 2004; 83: 348–59.

Elderly SLE frequently overlaps with other diseases.

- **Late-onset rheumatoid arthritis,**
- **endocarditis,**
- **tuberculosis,**
- **neoplasia,**
- **polymyalgia rheumatica,**
- **temporal arteritis,**
- **Sjogren's Syndrome**



response to treatment, prognosis, and course of the disease are different

The treatment of elderly SLE

- Elderly SLE patients are often ***polymedicated*** patients, in whom side effects of treatments are more frequent.
- possible ***drug interactions*** should always be considered in the elderly.

- The management of the disease in these older patients depends on the ***type and severity of disease manifestations.***
- The use of **antimalarial agents** such as hydroxychloroquine is an important aspect of SLE treatment, unless contraindicated.
- Other treatments mostly include NSAIDs, corticosteroids and immunosuppressive agents, depending on which organs are involved.

Hydroxichloroquine

- **reduce the risk of flares and overall damage in SLE,**
- **is very effective for treating both articular and cutaneous manifestations**

Costedoat-Chalumeau N, et al Joint Bone Spine 2009; 77 : 4-5

Toxicity from antimalarial agents is of serious ophthalmological concern because there may be little if any visual recovery, even after cessation of the drug.[54]
The contraindications:

- hypersensitivity to any 4-aminoquinoline compound
- any type of retinopathy, including ager elated macular degeneration

ophthalmological examination should be more frequent than in young age and includes:

- **full ocular examination,**
- **automated visual field**

And at least one of this investigations once a year of:

- multifocal electroretinogram (mfERG),
- spectral domain optical coherence tomography (SD-OCT)
- Fundus autofluorescence
-

. Ophthalmology 2011; 118 : 415-

Immunesuppressants

- Patients with ISN/RPS 2003 **class III or IV lupus nephritis** should receive high doses of ***corticosteroids and cyclophosphamide or mycophenolate mofetil***, similarly to younger patients.
- **manifestations of SLE, neuropsychiatric complications** are treated with ***high doses of corticosteroids and immunosuppressive drugs***.
- ***aspirin*** is indicated in the presence of antiphospholipid antibodies for the prevention of venous and arterial thromboses.

J Am Soc Nephrol 2009 ;20 :1103-12; Lupus 2011 20 : 206-18

Biotherapies

The main targets of these new treatments are the B lymphocytes, the co-stimulatory molecules and the cytokine network.

The first trials, such as the LUNAR (LUpus Nephritis Assessment with Rituximab) and EXPLORER (Exploratory Phase II/III SLE Evaluation of Rituximab) studies (for rituximab, a CD20-blocking agent), did not reach their primary endpoints, partly because SLE is a heterogeneous disease and because these studies used inappropriate end points.

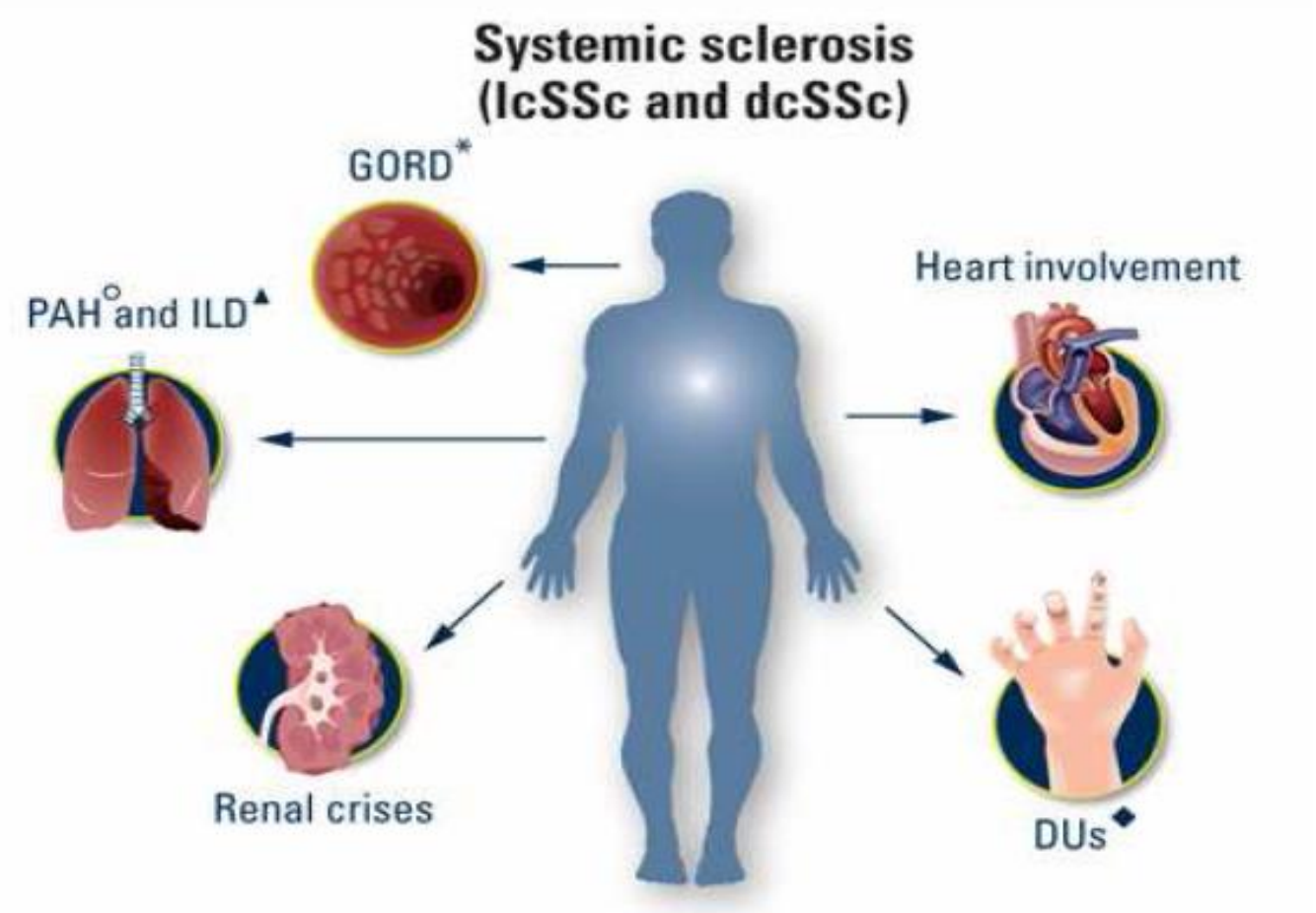
Belimumab , a B-lymphocyte stimulator (BLyS)-blocking agent, because they used more well defined patient populations as well as composite endpoints that are more appropriate for SLE.However,

the oldest of patients were excluded from most of these studies and no clear efficacy data are yet available in late-onset SLE

the infectious and neoplastic side effects of immunosuppressive agents and biotherapies are important issues in these older patients, who are often predisposed to the development of more severe infections and in whom drug-induced immunosuppression may facilitate the development of neoplasia.

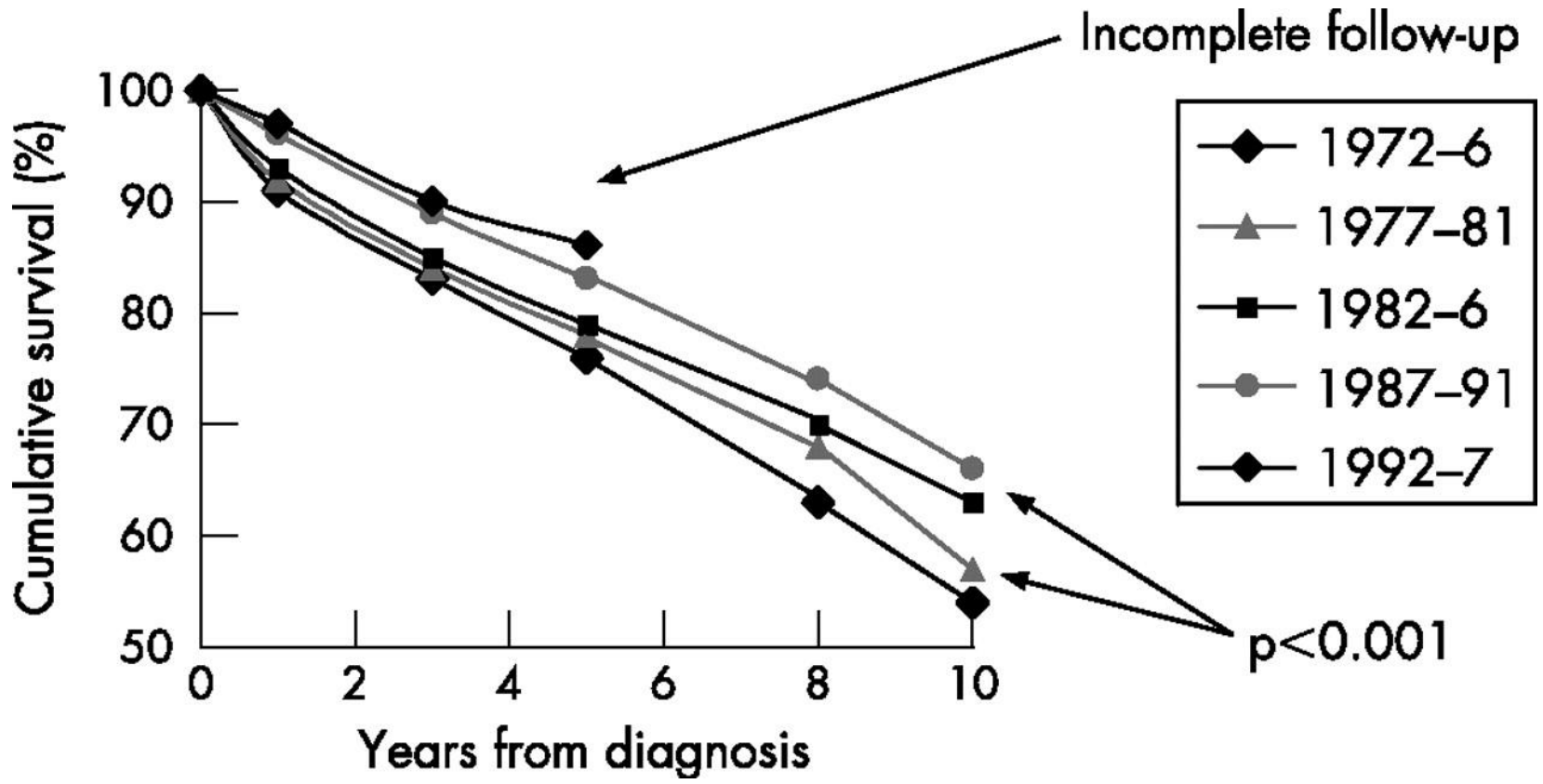
Arthritis Rheum 2010; 62 : 222-33; Ann Rheum Dis 2010; 69 Suppl.3: 549; Lancet 2011; 26; 377 : 721-31

Systemic Sclerosis: **a multisystem disorder**



Systemic Sclerosis: **Mortality**

Survival of patients with systemic sclerosis between 1972 and 2002.



Steen V D , Medsger T A Ann Rheum Dis 2007;66:940-944

ARD

Systemic Sclerosis: Epidemiology

1. **Age-peak occurence : 35-65 ys**
2. **Female-male ratio : 7 : 1**
3. **Racial variation : in black population higher incidence and more severe disease**

French multiethnic study: higher prevalence of SSc among non Europeans , with dcSSc and ILD more common

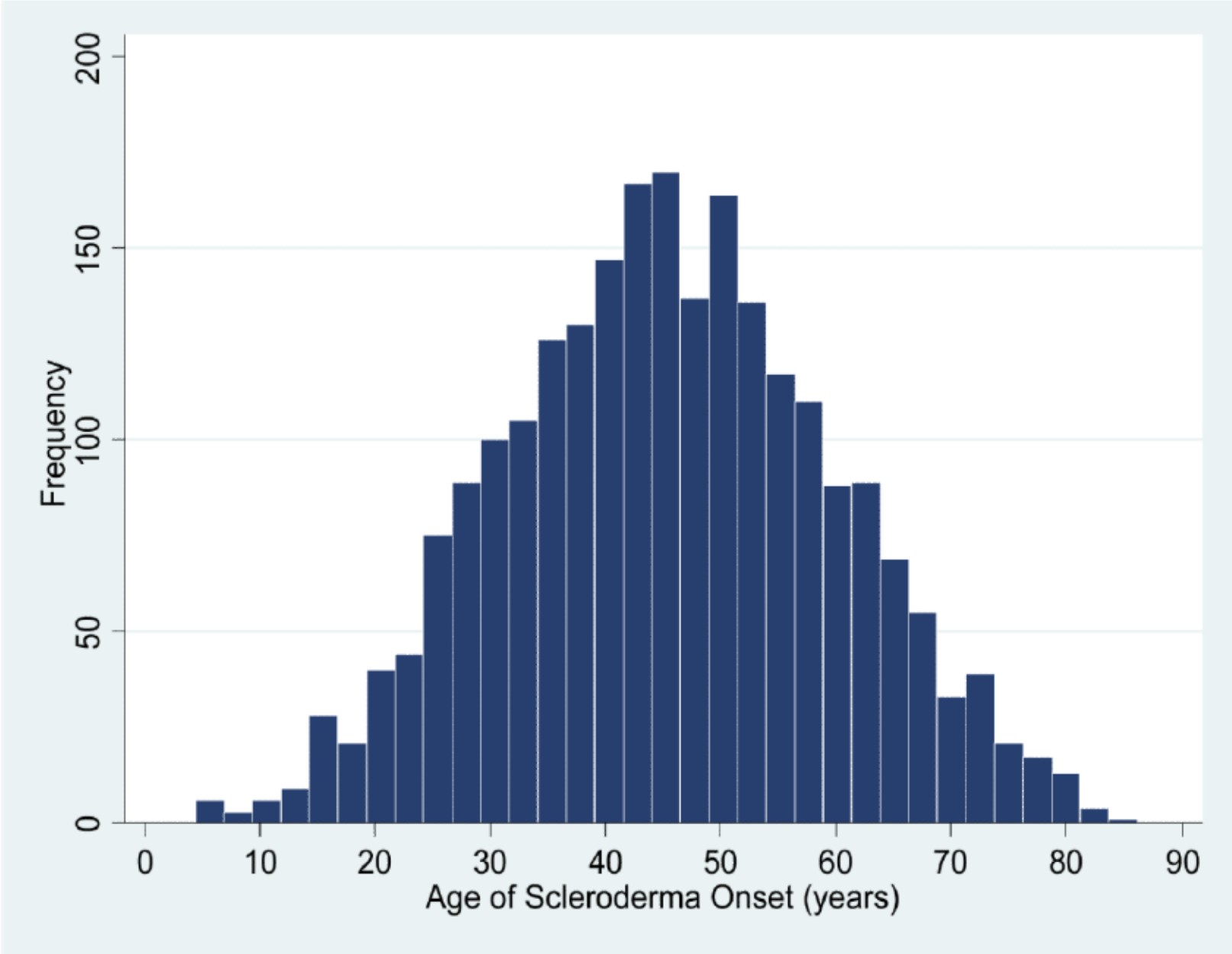
Genetic backgroud incidence

Familial clustering

Monozygot twins have only a 5% concordance for SSc but 90% concordance for presence of autoantibodies (ANA...)

HLA haplotypes and polymorphisms in immune regulatory genes

Environmental factors



J Rheumatol. 2011 ; 38: 1317–25

Demographics, disease duration, and serologic profile among 2300 SSc patients evaluated from 1990–2009.

	Age of onset < 65 years (n = 2084)	Age of onset > 65 years (n = 216)	p-value
Female	1725 (83%)	184 (85%)	0.369
African-American	379 (18%)	24 (11%)	0.040
Limited subtype	1302 (62%)	147 (68%)	0.108
Smoking status current or former[§]	992 (48%)	105 (50%)	0.601
Median number of visits to Scleroderma Center, range	3 (1,28)	2 (1,19)	<0.001
Mean number of years of follow up from first visit to Scleroderma Center among patients with >1 visit[§§] (± SD[*])	5 ± 4	4 ± 3	<0.001
Age of first non-RP symptom in years	45 ± 12	71 ± 5	<0.001
Age of RP onset in years[†]	40 ± 13	65 ± 13	<0.001
Years from RP onset to first non-RP SSc symptom[†]	3 ± 8	6 ± 13	<0.001
Years from first non-RP SSc symptom to diagnosis of SSc by physician[††]	2 ± 5	0.5 ± 2.4	<0.001
Serology			
ANA	1259/1306 (96%)	120/124 (97%)	0.831
Anti-topoisomerase I	277/1175 (23%)	18/107 (17%)	0.112
Anti-centromere	348/1288 (27%)	50/119 (42%)	0.001
Anti-U1RNP	102/1084 (9%)	3/99 (3%)	0.033

whether the limited versus the diffuse cutaneous subset of disease predominates in the elderly is a matter of ongoing debate.

J Rheumatol. 2011 ; 38: 1317–25

Late onset SSc

Whether the SSc disease phenotype varies with older age of SSc onset is unclear. This lack of clarity stems in part from inconsistent previous descriptions of SSc features in the elderly.

- case descriptions suggested that late-age onset SSc represented a ***milder form of disease with limited morbidity and minimal skin and internal organ involvement***

(Br Med J. 1979 2:1313–4.; Postgrad Med J. 1979; 55:192–3)

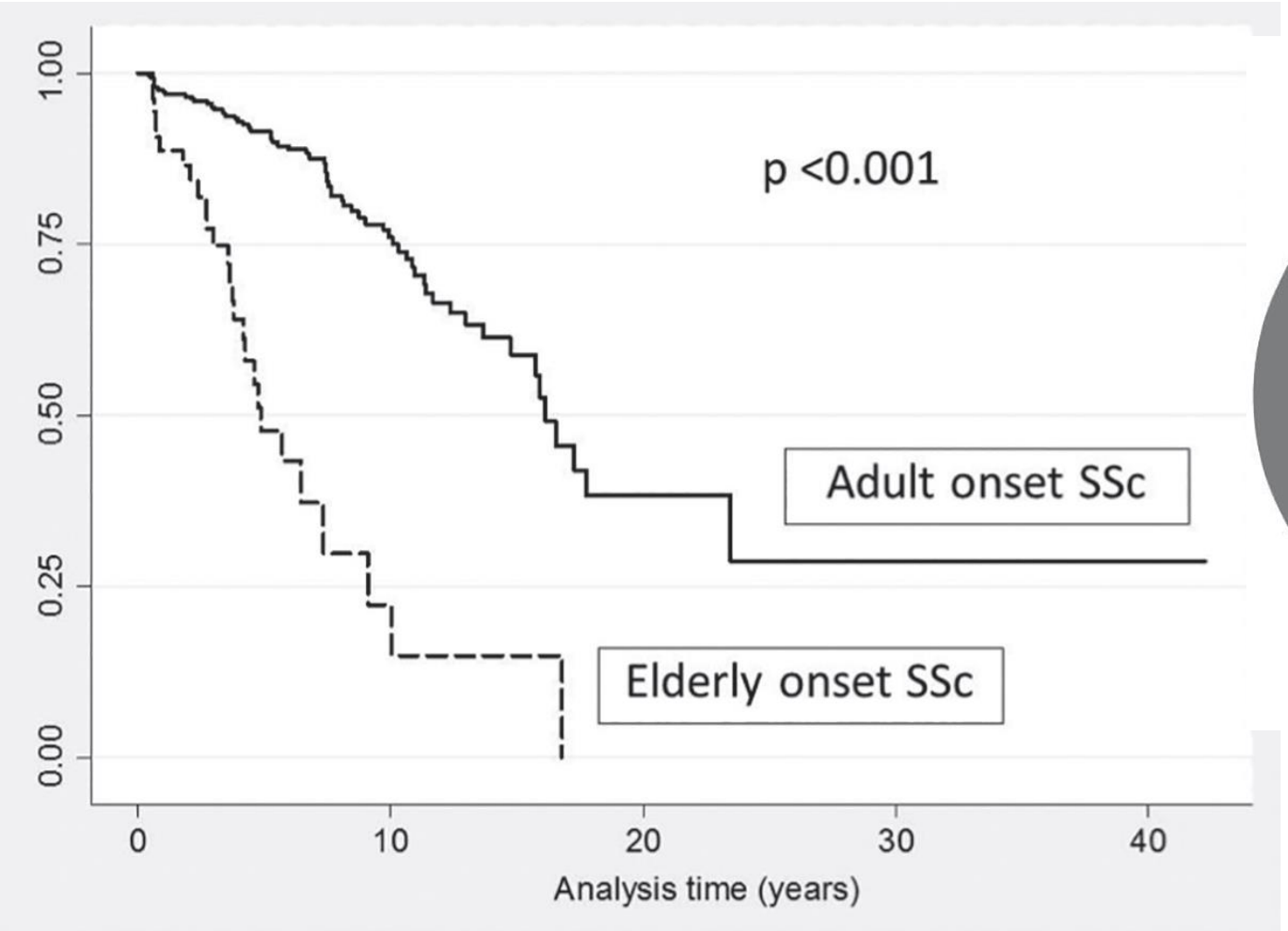
but….

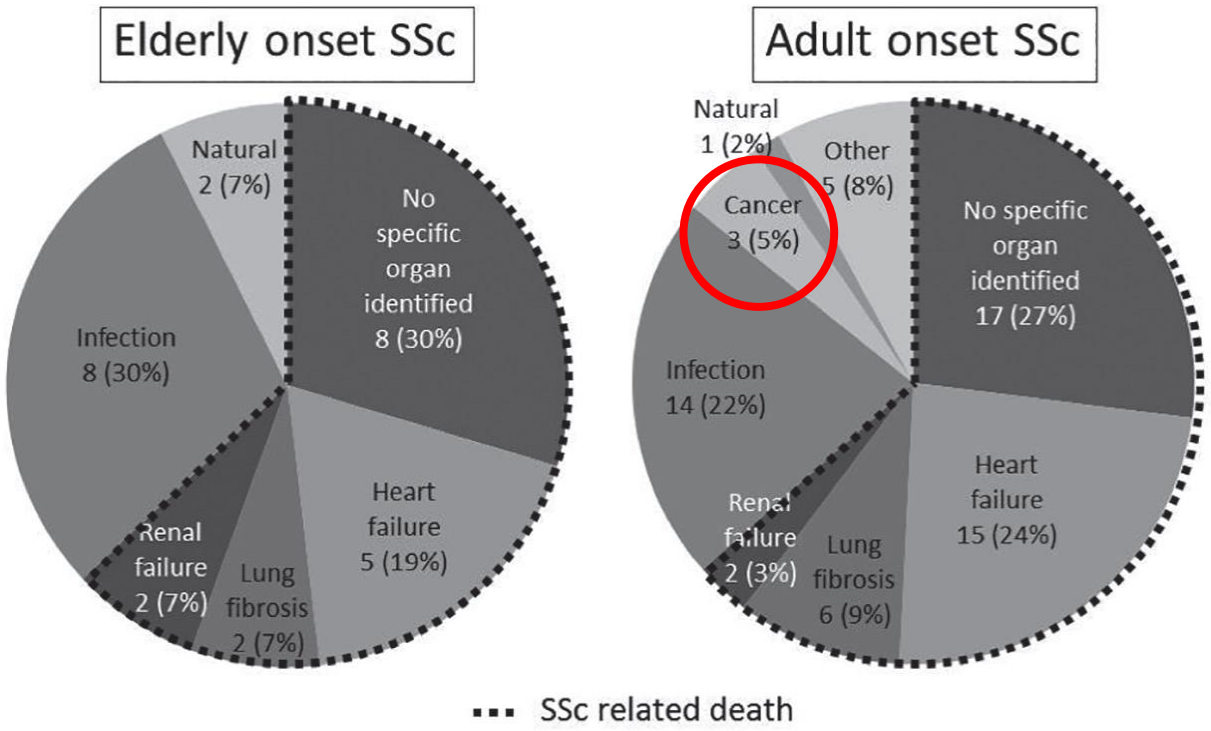
subsequent larger case series, demonstrated the ***severity and breadth of organ involvement in late-age onset SSc***

(Br Med J (Clin Res Ed).1981;282(:948.12; Clin Rheumatol. 2006 25:831–4.; Clin Rheumatol. 1992 11:483–5).

Clinical characteristics and mortality rate of Thai elderly-onset systemic sclerosis.

Apipattarakul R et al Clin Exp Rheumatol.2018 ;36 Suppl 113(4):76-81..





Late-onset systemic sclerosis—a systematic survey of the EULAR scleroderma trials and research group database

Thomas Hügle[1], Philipp Schuetz[2], Thomas Daikeler[3], Alan Tyndall[3], Marco Matucci-Cerinic[4], Ulrich A. Walker[3], Jacob M. van Laar[1] and EUSTAR members*

A total of **123** patients with SSc ***onset at or beyond 75 years*** of age were identified. Compared with patients <75 years they had more frequently

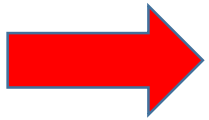
- **Limited** than diffuse SSc and a **higher prevalence of anti-centromere autoantibodies.**
- Fewer old patients had digital ulcers. The modified Rodnan's skin score, the prevalence of lung fibrosis and renal crisis did not differ significantly between groups.

.

Pulmonary hypertension (PH) measured by echocardiography was more prevalent in the late-onset group, as well as arterial hypertension and diastolic dysfunction

Rheumatology 2011;50:161–165

Parameter	Age <75 years	Age ⩾75 years	*P*-value
MRSS, median (IQR)	7 (3–14)	7 (3–12)	0.57
Synovitis, %	15.8	15.5	0.94
Joint contracture, %	30.1	26.4	0.38
Digital ulcer, %	31.3	22.1	0.03*
Tendon friction rubs, %	10.5	10	0.84
Muscle weakness, %	25.7	21.4	0.28
Muscle atrophy, %	12.8	10.6	0.46
Proteinuria, %	5.8	6.7	0.68
RP, %	95.2	92.6	0.19
Conduction block, %	9.7	21.8	<0.001**
Diastolic function abnormal, %	16.1	29.6	<0.001**
Diastolic failure, %	5.8	6.7	0.68
PH (echocardiographic), %	20	35	<0.001**
Lung restrictive defect, %	30.7	29.8	0.83
Lung fibrosis, %	36.4	30.1	0.16
Oesophageal symptoms, %	67.0	59.8	0.09
Intestinal symptoms, %	23.2	26.2	0.77
Renal crisis, %	2.2	0.82	0.29
Dyspnoea, %	34.3	40.9	0.127
Palpitation, %	23.8	21.3	0.50
CK elevation, %	8.2	3.3	0.05*
Arterial hypertension, %	20.2	40.6	<0.001**
Elevated acute phase reaction, %	29.9	44.5	0.001**
DL_{CO} (% of normal), median (IQR)	53 (−76)	45 (−73)	0.30
Reduced left ventricular function, %	5.2	6.3	0.6



Rheumatology 2011;50:161–165

Conclusion

- L’autoimmunità è significativamente aumentata ne’età anziana
- Ogni malattia autoimmunitaria ha un profilo clinico peculiare, spesso insidoso ed atipico e pertanto può rappresentare un problema per il medico
- Sono abitualmente ritenute malattie con decorso più moderato che possono essere controllate con un adeguato trattamento
- Spesso le comorbidità complicano il quadro clinic e rendono difficile la terapia

Conclusioni- Lupus nell’anziano

- I paz hanno manifestazioni cliniche e sierologiche diverse dallaforma del giovane ede hanno talvolta prognosi peggiore in seguito ad interessamento d’organo più grave e presenza di comorbidità

- Una adeguata terapia è necessaria per contenere l’evoluzione di malattia cercando di evitare un ulteriore danno da farmaco

Conclusioni- Sclerosi Sistemica nell'anziano

- Rispetto alla forma del giovane la SSc nell'anziano è caratterizzata da una forma limitata gravata da una significativa incidenza di ipertensione polmonare
- Fra le comorbidità le neoplasia hanno un ruolo fondamentale
- Una diagnosi precoce ed un pronto approccio terapeutico sono necessari per evitare l'evoluzione della malattia
- la sfida per il medico è riuscire a trattare il paziente evitando il danno da farmaci a carico degli organi (cuore, rene, GI)

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