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Nerviano 2007

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"E io ti guarirò":

in bilico tra guaritori, ciarlatani, miracoli e miracolati

Dalla Grande Madre a Maria Vergine: evoluzione

antropologica della figura femminile

Il genoma umano:

credevamo di sapere tutto, e invece ...

Artrosi: alla fine ci caschiamo tutti. Come ritardare e curare

Ma che fine ha fatto la "Sindrome Metabolica?" Chiariamoci le idee

Artrite Reumatoide:

come ti ho cambiato la storia naturale

Ho la pressione alta: ci sono novità in vista?

Artrite Reumatoide (AR)

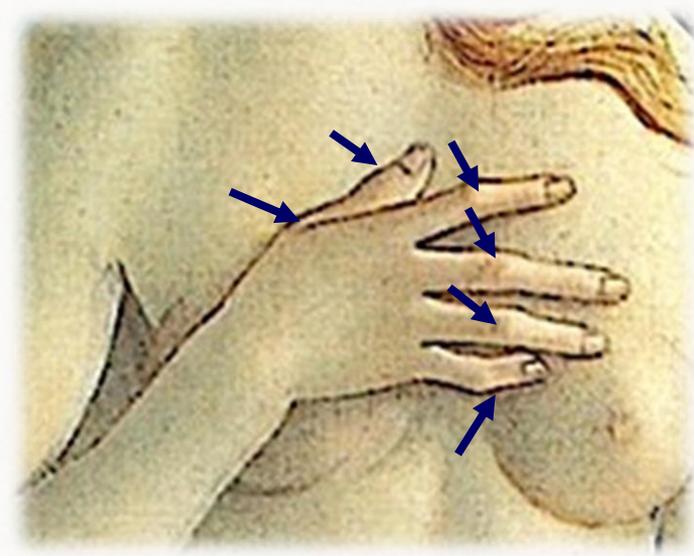
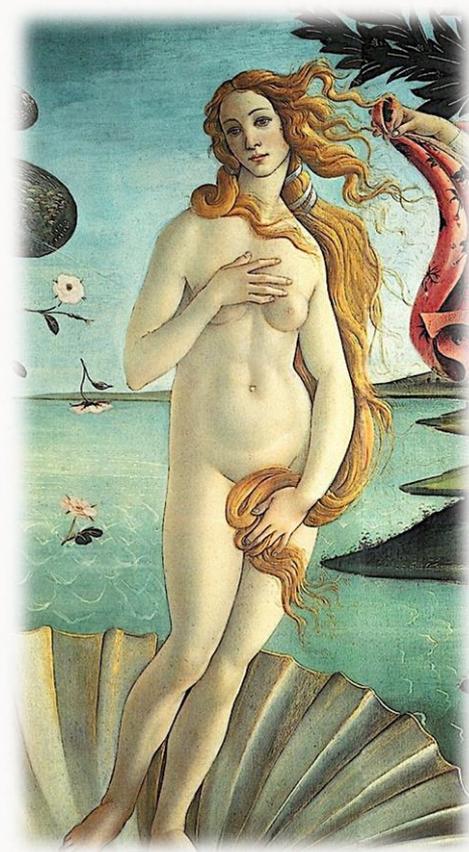
Poliartrite infiammatoria cronica, anchilosante, progressiva, idiopatica(?), autoimmune. (Harrison's Principle of Internal Medicine, 18° ed 2012)

Malattia comune, autoimmune, idiopatica (?), progressiva, **multi-sistemica**, associata a progressiva **inabilità**, complicazioni sistemiche, **mortalità precoce**, costi **socio-economici**. (I. B. McInnes & G. Schett, NEJM, dic 2011)



AR: storia

- 100.000 anni fa: osteoartrite
- 3.000 a.C.: indiani nord America: segni di AR
- Mummie egizie con AR
- 300 d.C.: Costantino con AR
- 1483: Venere di Botticelli AR
- 1785: diagnosi di AR
- 1899: aspirina
- 1936: cortisone
- Anni ' 50: FANS
- Anni ' 60: DMARDs (Sali d' oro ...)
- Anni ' 70: + immunosoppressori
- Anni' 90: + farmaci biologici
- ? Vaccino: **abbandonato**



AR: epidemiologia

(3-5 : 1 donne)

Mondo

0,3 – 1,5%

prevalenza

3 – 9/10.000

incidenza

Italia

0,7% (410.000)

6/10.000

Esordio: 80% 40-60 aa. AR Giovanile (5%) . Familiarità: si (10%)

Novità: incidenza > con età; donne:uomini tende a 1 in anziani

Inabilità: 90% → a 20 anni da esordio ?

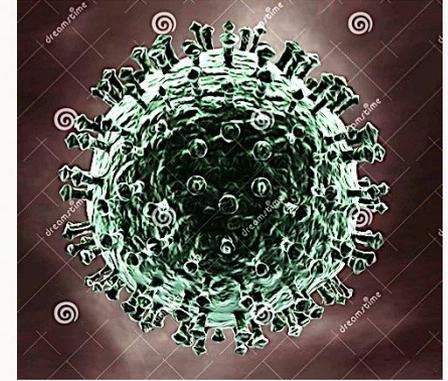
Spettanza di vita: -4 anni (uomini); -10 anni (donne) ?

Italia Costi: € 14-23.000/ paziente/ anno

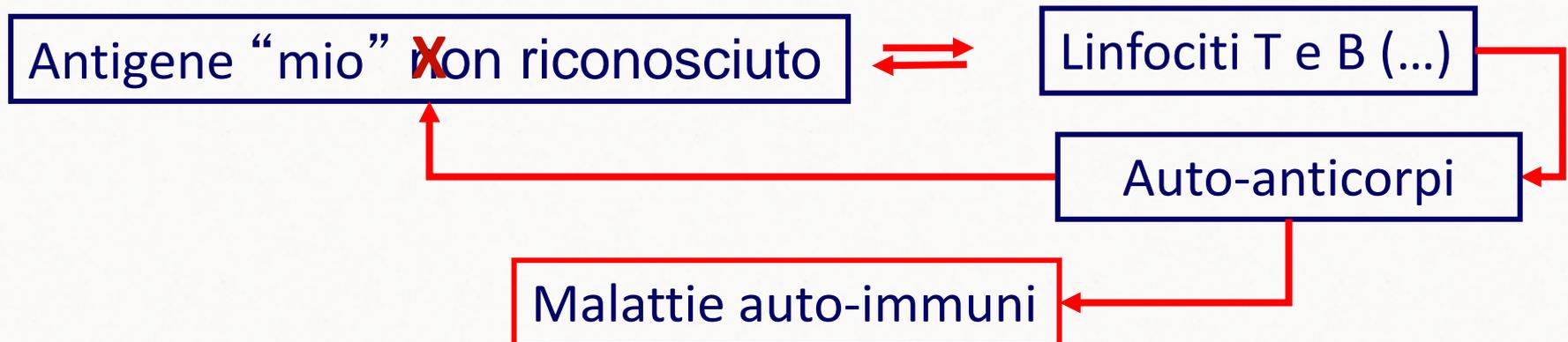
Totali: € 1 mld diretti; € 5 mld indiretti)

AR malattia autoimmune: che significa

Il sistema immunitario distingue il “sé stesso” dal “non sé stesso” (miei antigeni da antigeni estranei)



Es.: 1) il corpo rigetta il trapianto
2) il trapianto rigetta il corpo (GvHD)



AR: etio-patogenesi

'90. Geni "espressi" HLA*
DR 4 (70%); HLA DR 10
(Spagna e Italia); HLA DR3
(Arabi).

*Antigeni Leucocitari Umani

Oggi. Geni "polimorfi con
singolo nucleotide" legati a
AR: 21!

HLA, IL, TNF,

Table 1. Candidate Genes with Single-Nucleotide Polymorphisms (SNPs) Linked to Rheumatoid Arthritis and Their Potential Function in Pathogenesis.*

Candidate Gene and Pathway	SNP Locus	Function Relevant to Pathogenesis
T-cell activation		
<i>HLA-DRB1</i> †	6p21	HLA DRB1 allele (also known as the shared epitope) involved in MHC molecule-based antigen presentation and responsible for self-peptide selection and T-cell repertoire; first discovered and still by far the strongest genetic link to rheumatoid arthritis
<i>PTPN22</i>	1p13.2	Lymphocyte-specific nonreceptor tyrosine phosphatase involved in regulation of activation threshold of lymphocytes; second genetic link described in rheumatoid arthritis
<i>AFF3</i>	2q11.2	Transcription factor for lymphoid development
<i>CD28</i>	2q33.2	Costimulatory molecule for T-cell activation
<i>CD40</i>	20q13.12	Costimulatory molecule that enhances interactions between T and B cells and increases auto-antibody production
<i>CTLA4</i>	2q33.2	Costimulation suppressor that regulates interactions between T cells and antigen-presenting cells
<i>IL2RA</i>	10p15.1	High-affinity receptor for interleukin-2 on lymphocyte subsets
<i>IL2</i>	4q27	Cytokine that regulates activation of T cells, particularly regulatory T cells
<i>IL-21</i>	4q27	Cytokine that regulates differentiation of T cells, particularly Th17, and activation of B cells
<i>PRKCQ</i>	10p15.1	Member of the protein kinase C family that regulates T-cell and macrophage activation
<i>STAT4</i>	2q32.3	Transducer of cytokine signals that regulate proliferation, survival, and differentiation of lymphocytes
<i>TAGAP</i>	6q25.3	Rho-GTPase enzyme involved in T-cell activation
NF-κB pathway		
<i>REL</i>	2p16.1	Proto-oncogene member of the NF-κB family that regulates leukocyte activation and survival
<i>TNFAIP3</i>	6q23.3	Signaling protein and negative regulator of TNF-α-induced NF-κB activation
<i>TRAF1</i>	9q33.1	Regulator of TNF-α-receptor superfamily signaling (e.g., to NF-κB and JNK)
Other pathways		
<i>BLK</i>	8p23.1	B-lymphoid tyrosine kinase involved in B-cell receptor signaling and B-cell development
<i>CCL21</i>	9q13.3	Chemokine implicated in germinal-center formation
<i>FCGR2A</i>	1q23.2	Low-affinity IgG Fc receptor that regulates macrophage and neutrophil activation and immune-complex clearance
<i>PADI4</i>	1p36.2	Enzyme that converts arginine to citrulline, creating autoantigens in rheumatoid arthritis
<i>PRDM1</i>	6q21	Protein that acts as a repressor of β-interferon gene expression
<i>TNFRSF14</i>	1p36.32	TNF-α-receptor superfamily member with proinflammatory activity

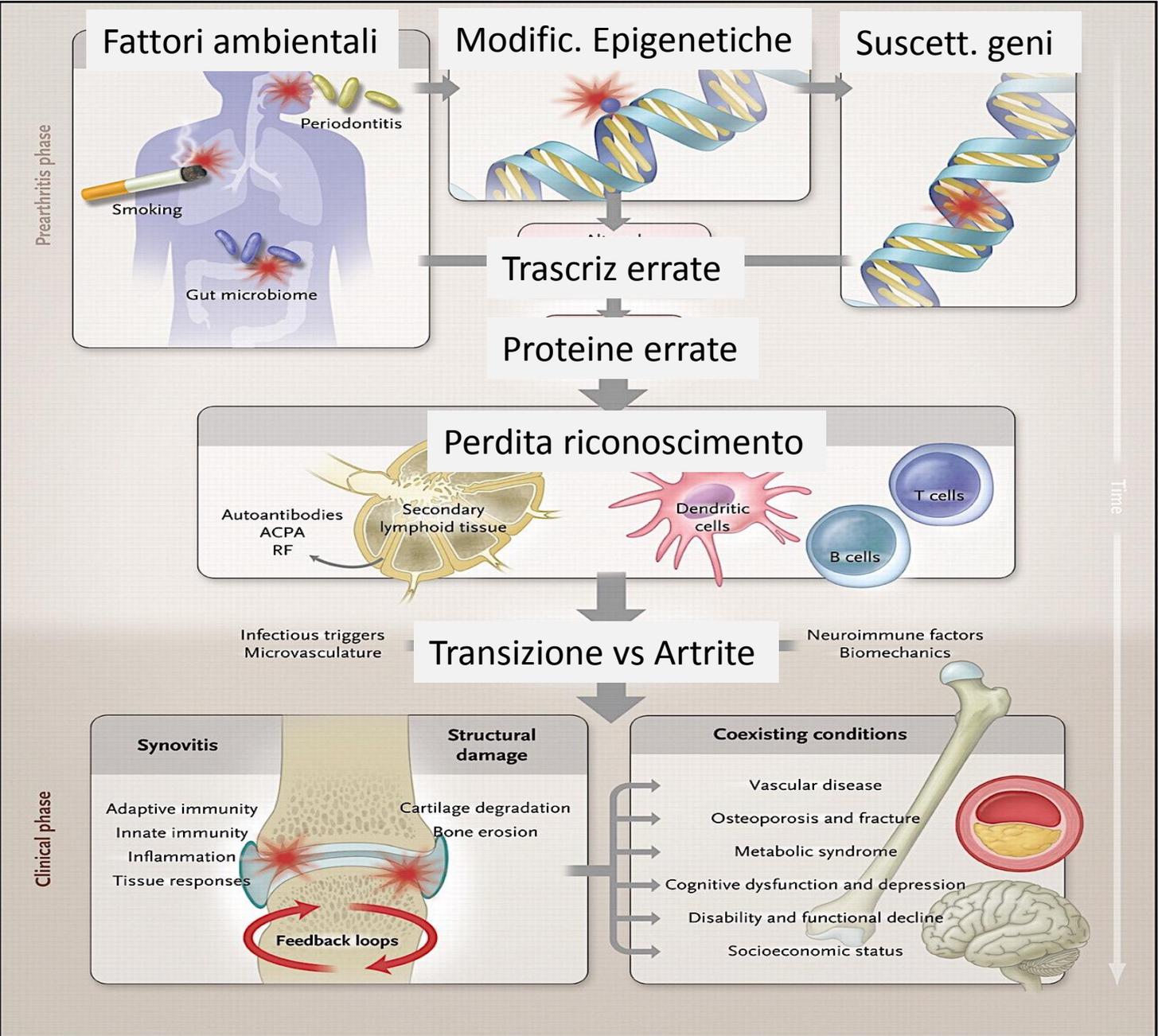
* GTPase denotes guanosine triphosphatase, JNK Jun N-terminal kinase, MHC major histocompatibility complex, NF-κB nuclear factor κB, Th17 type 17 helper T cells, and TNF-α tumor necrosis factor α.

† Different *HLA-DRB1* alleles, not only the shared epitope, are associated with rheumatoid arthritis and with distinct immune responses to citrullinated antigens. In addition, *HLA-DP* and *HLA-DQ* loci (outside the *HLA-DRB1* region) have been associated with rheumatoid arthritis.



The NEW ENGLAND
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AR: eziologia e patogenesi



AR: etio-patogenesi

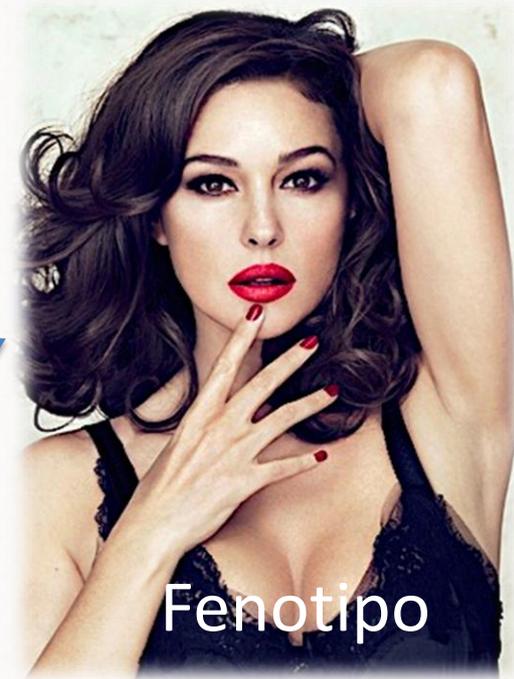


Genotipo



Ambiente

Caso



Fenotipo



Fenotipo

AR: etio-patogenesi. Esempi

Gemelli omozigoti



→ 15-30%

Gemelli eterozigoti



→ 5%

AR: etio-patogenesi. Esempio

Stress negativi

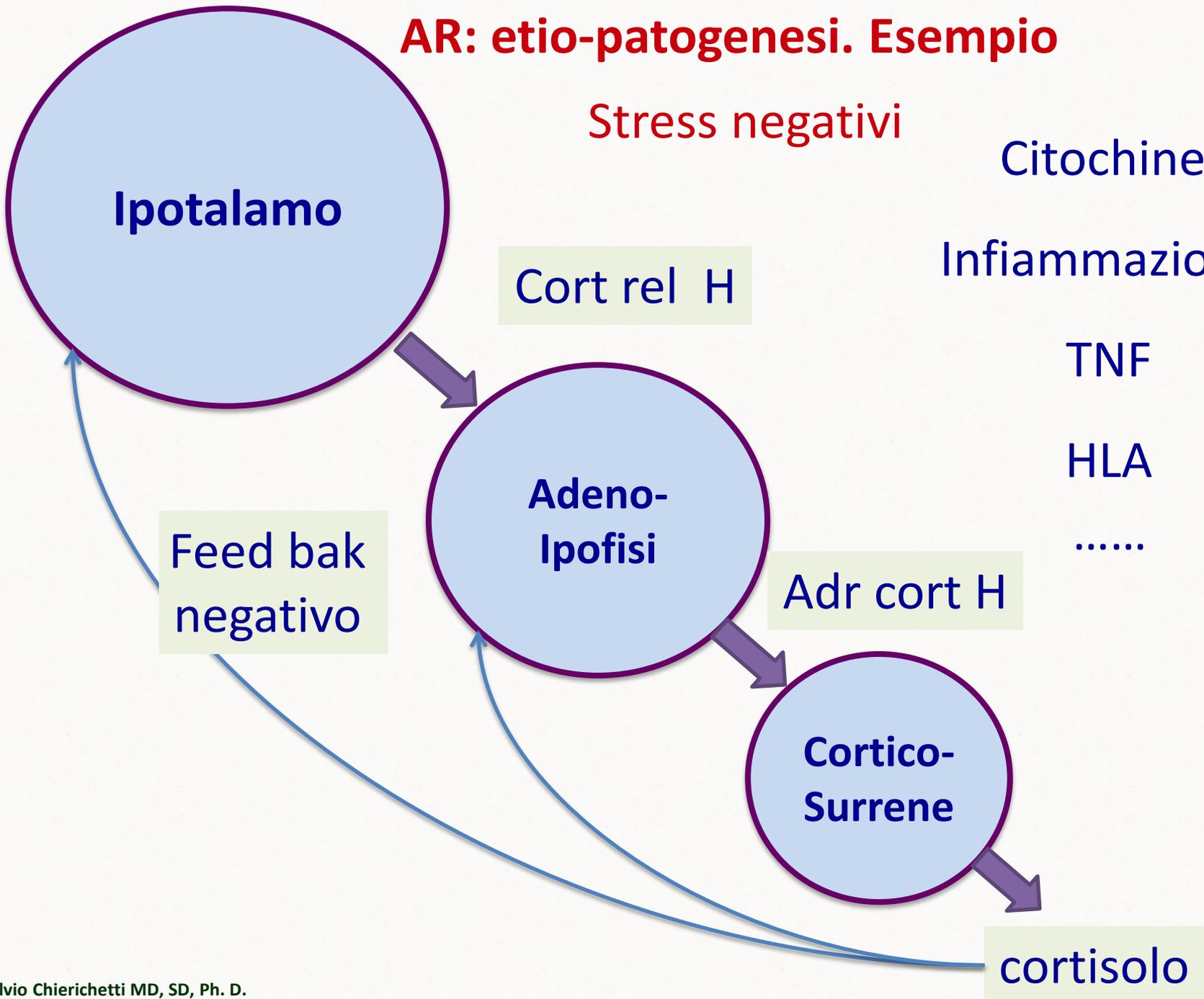
Citochine

Infiammazione

TNF

HLA

.....



AR: patogenesi clinica

Ginocchio normale

Cartilagine

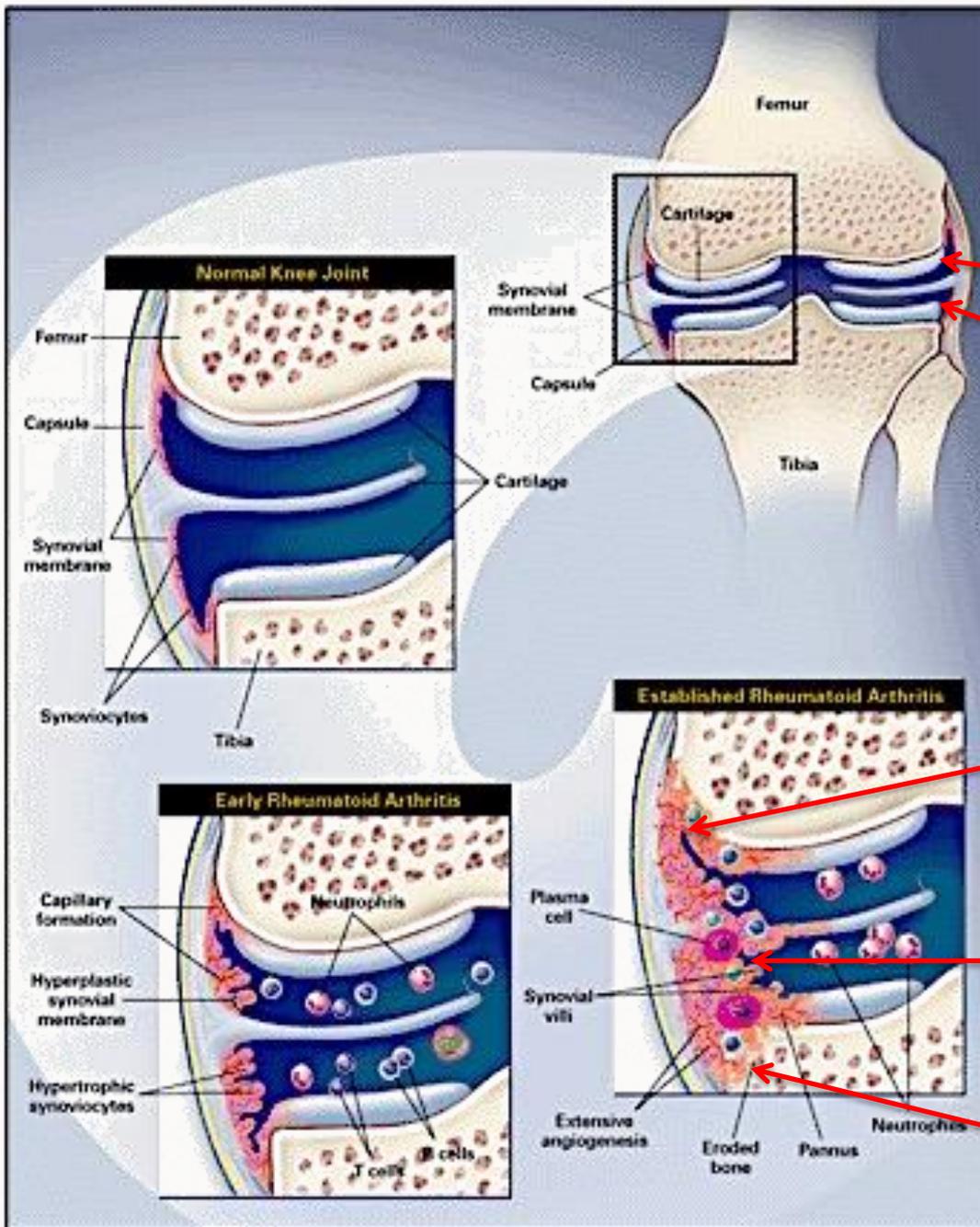
Sinovia

Ginocchio con AR

Iperplasia e
vascolarizzazione sinovia

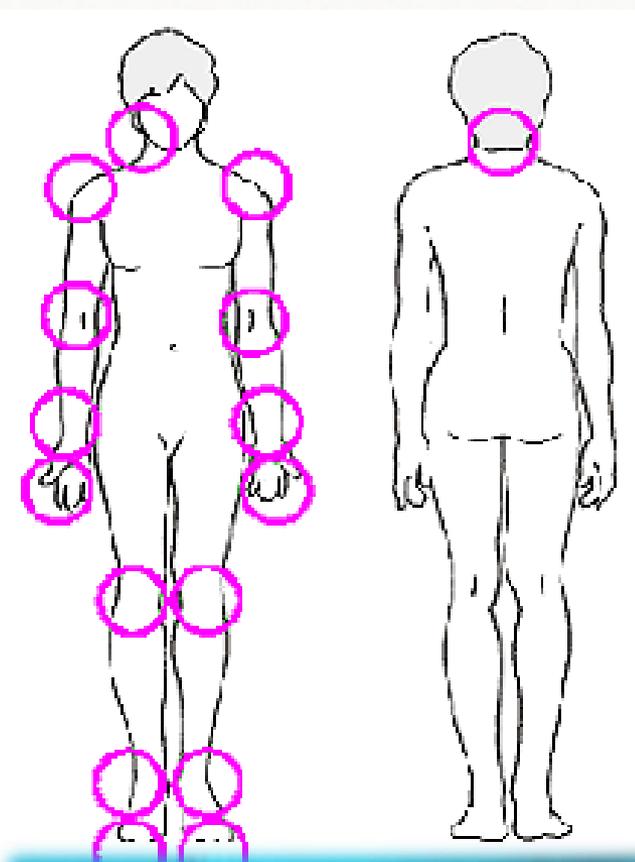
Flogosi: leuco T, B,
Citochine ...

Erosione osso e
capi articolari.



AR: risultati su articolazioni.
Erosioni, deformità, Op, ...





AR: clinica

Esordio: 90% insidioso



Malessere, inappetenza,
debolezza, febbre

Sinovite manifesta



Esordio: 10% acuto



Poliartrite, febbre,
linfonodi, milza ...



Articolazioni:



Piccole, simmetriche



➤ Deformazione art.

➤ Limitazione funzionale

➤ Vita quotidiana



➤ Dolore (anche mov passivo)

➤ Gonfiore "soffice"

➤ Rigidità mattutina (>1 ora)

AR: clinica

Interessamento extra articolare: 50-60% (15% severo)

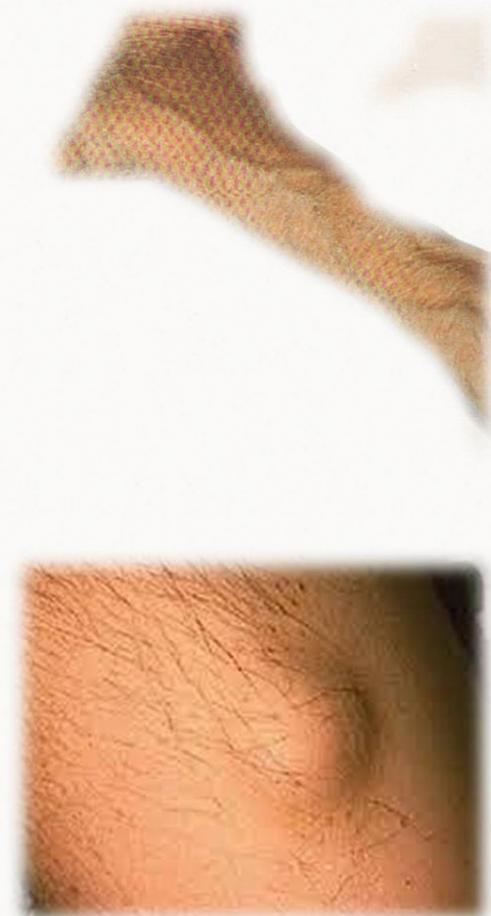
Noduli reumatici periarticolari
(20-30%) olecrano, ulna,
tendine Achille ... pleura, meningi ...

Asintomatici

Complicanze precoci/ tardive

- Pericarditi
- Vasculiti
- Neuriti
- Polineuropatie
- Rene, fegato, cervello
-

Indice di aggressività



AR: diagnosi

Facile se tipica

Difficile se subdola

Imperativo: diagnosi precoce

Terapia tempestiva!

Ritardare danno articolare (invalidità)

Ritardare/ evitare danni d'organo! (Spett. di Vita)

AR: terapia, anni '70 – '80

Fans: ASA, indometacina, cloroquina
Butazolidine ...

Cortisone

DMADRs: Sali d'oro, d.penicillamina ...

AR: terapia, anni '81 – 2000

Metotrxato '86

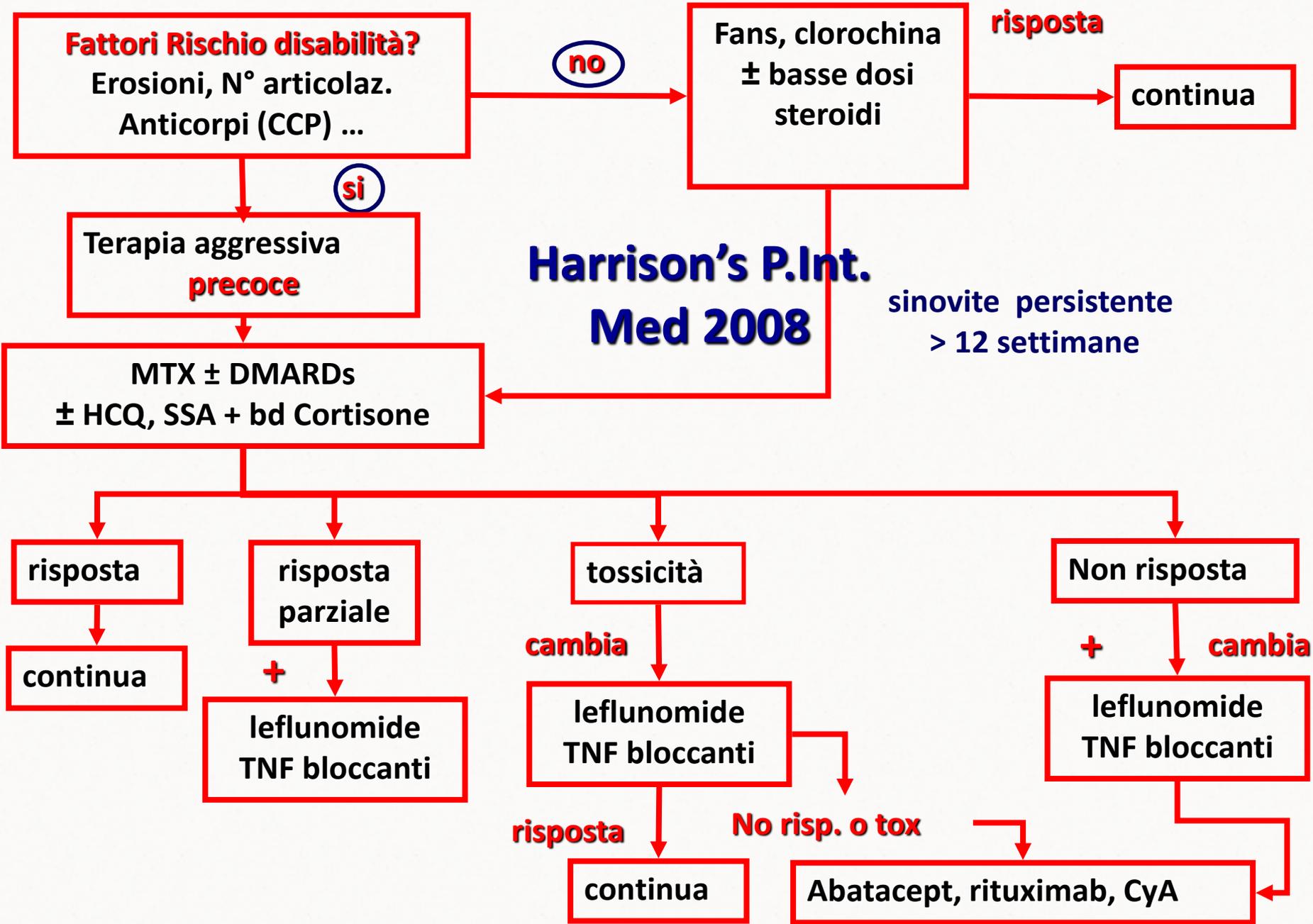
Ciclosporina '92

Leflunomide '98

AR: terapia, dal 2000

Farmaci biologici (ingegneria genetica): anticorpi monoclonali, inibitori vari IL, CTK, TNFs ...

AR: terapia.



AR: i farmaci biologici. Il perché della loro importanza

Modificano il decorso della malattia

Ritardano disabilità

Allungano periodi di remissione

Riducono danni articolari

“Le manifestazioni gravi della malattia, vasculiti, scleriti, amiloidosi, danni d’organo ... sono diventate rare” McInnes, NEJM 2011

A condizione che le terapie inizino alla diagnosi

Quale è il problema?

AR: farmaci biologici e costi

Farmaco	€ /paziente/anno
Adalimumab (Lumira)	12.400
Certolizumab (Cimzia)	10.250
Etanercept (Enbrel)	10.000
Golimumab (Simponi)	11.700
Infiximab (Remicade)	8-19.600
Tocilizumab (RoActembra)	12.400
Rituximab (Mabthera)	5.2-10.500
Abatacept (Orencia)	12.500

AR: costo totale teorico / anno

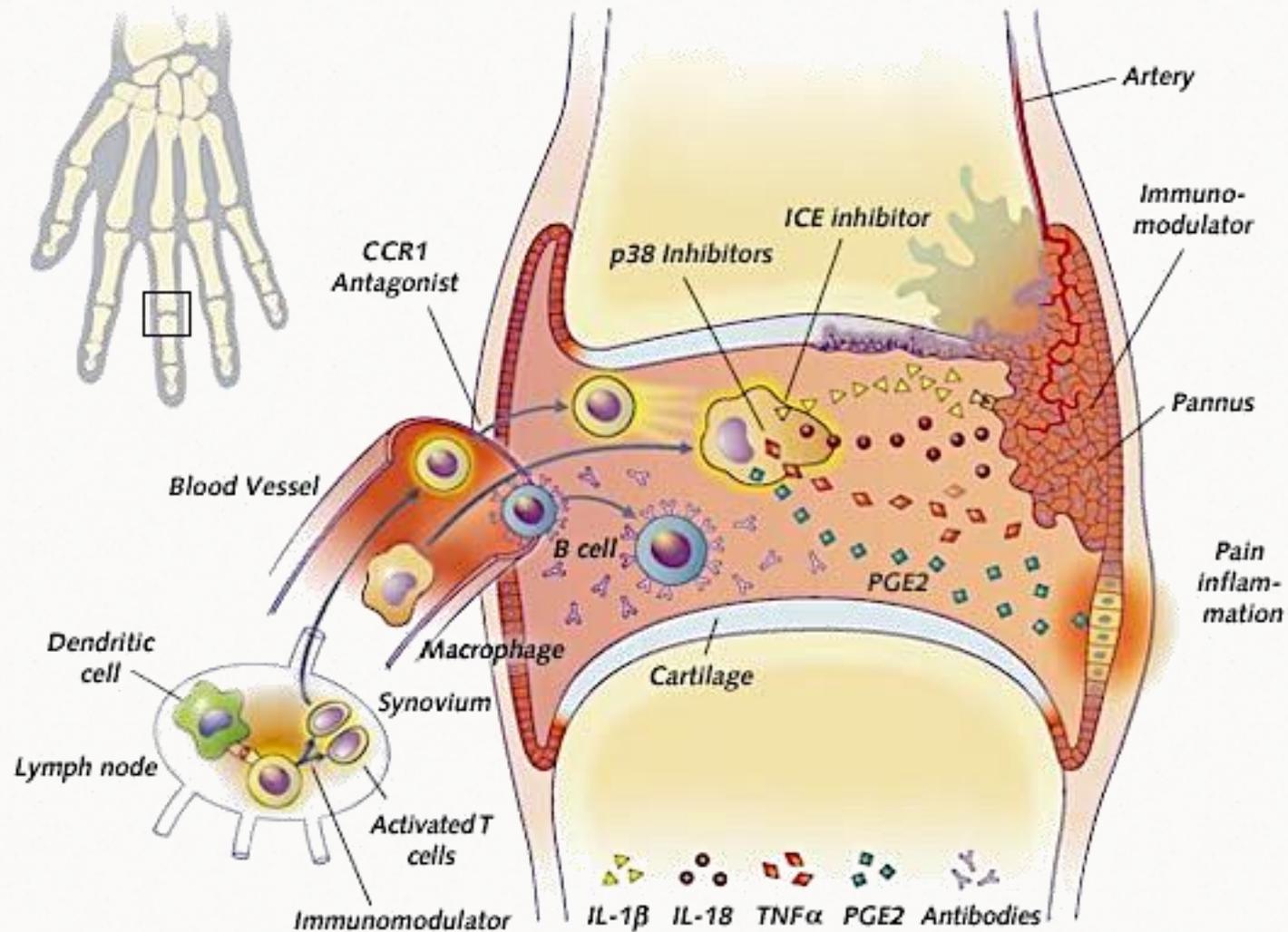
n. pazienti: 410.000	Costo medio /anno /paz Farmaci biologici	€ 10.000
	Costo medio terapie associate	€ 1.000
		€ 11.000

€ 4.510.000.000 diretti

€ 25.000.000.000 totali

AR: la domanda senza risposta

Rheumatoid arthritis



Perché tutto parte dalla sinovia?

A detailed marble sculpture of a tiger's head, shown in profile with its mouth open, revealing its teeth. The sculpture is light-colored with some darker veining. The background is a dark, textured surface, possibly a wall or a piece of fabric. The text "Grato per la vostra Attenzione" is overlaid in the center of the image in a blue, sans-serif font with a white outline.

Grato per la vostra
Attenzione

A photograph of a classical marble sculpture in a museum. The central focus is a chariot pulled by two horses, with a driver seated in the middle. The horses are depicted in a dynamic, rearing posture. To the left, a muscular male figure stands on a pedestal. The background features a large window with a grid pattern and a classical column. The text 'Arrivederci al 9 aprile: Iperensione' is overlaid in red.

**Arrivederci al 9 aprile:
Iperensione**