CASA INTERNAZIONALE DELLE DONNE

ReDO Teniamoci per mano

I farmaci di ieri e di oggi in Reumatologia

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Fondazione Policlinico Universitario "A. Gemelli"

Gemelli

Fondazione Policlinico Universitario A. Gemelli
Università Cattolica del Sacro Cuore

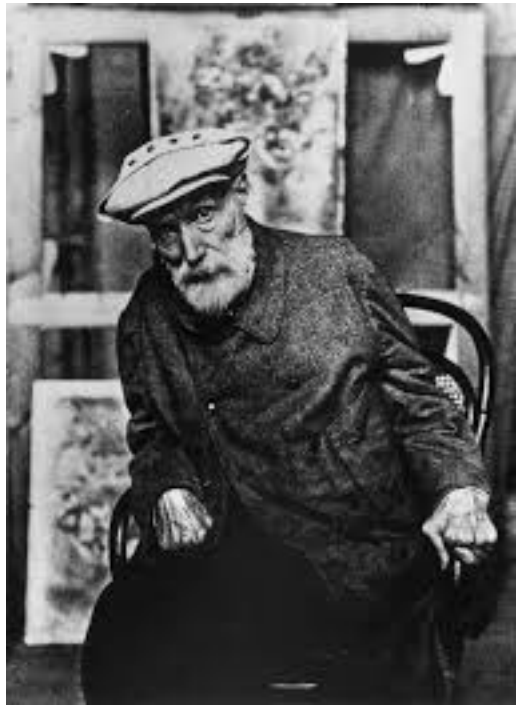
Famous people

Edith Piaf

Christian Barnard

Paul klee

Renoir



Lady Gaga

Anna Marchesini

History of rheumatology

- *Rheuma* is derived from the Greek term indicating “a substance which flows,” a humor that originates in the brain and causes various illnesses.
- In 1642 Guillaume Baillou claimed that “what arthritis is in a joint is what rheumatism is in the whole body,” raising the idea that arthritis is but one manifestation of systemic processes.
- In 1858 A Garrod suggested the term “rheumatoid arthritis” and differentiate it from gout in 1892.
- In 1940, Bernard Comroe coined the term *rheumatologist*,
- In 1949, Hollander used the term *rheumatology* in his textbook *Arthritis and Allied Conditions*.

Colchicine

- Colchicine is one of the oldest remedies still in use today.
- It is derived from the bulb-like corms of the Colchicum autumnale plant, also known as autumn crocus.
- Its history as an herbal remedy for joint pain goes back at least to the 1500 BCE Egyptian manuscript, the Ebers Papyrus
- The active ingredient, colchicine, was isolated in the early **1800's** and remains in use today as a purified natural product.
- In view of the long history of colchicine's use in medicine, it is perhaps surprising that it was not until **2009** that colchicine was approved by the U.S. Federal Drug Administration.

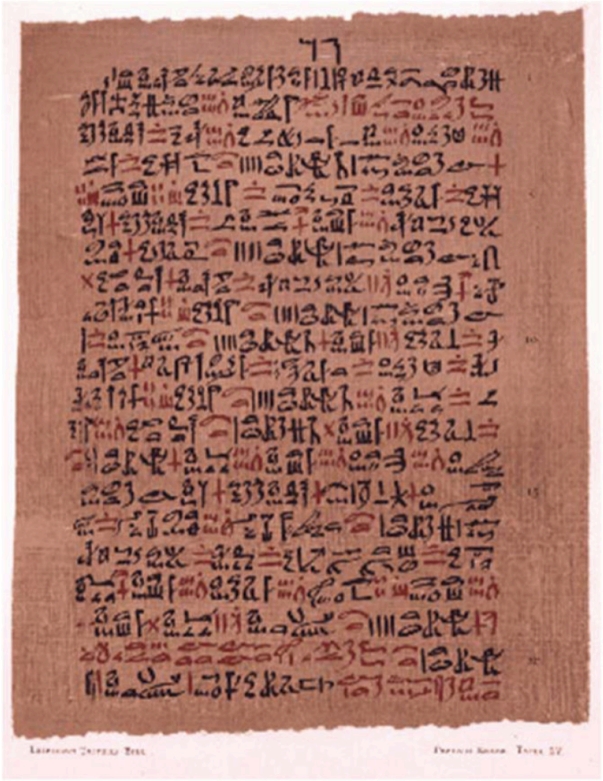


Figure 1.
The Ebers Papyrus is one of the most important medical documents from ancient Egypt. It was produced ca 1550 BCE, and is currently housed in the library of the University of Leipzid, Germany. Image is public domain from the National Library of Medicine NIH Archives. https://www.nlm.nih.gov/archive/20120918/hmd/breath/breath_exhibit/MindBodySpirit/IIBa18.html

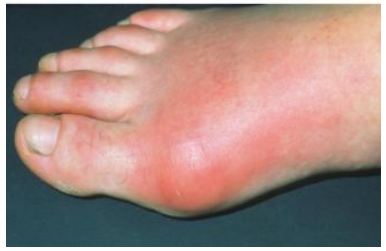
Br J Dermatol. 2018 February ; 178(2): 350–356. doi:10.1111/bjd.15896.

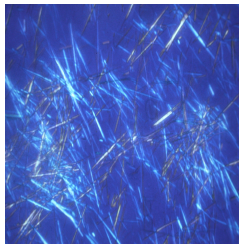
Colchicine: an ancient drug with novel applications

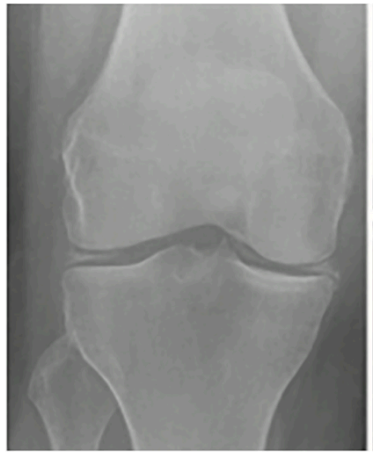
B. Dasgeb[2,3], D. Kornreich[2], K. McGuinn[2], L. Okon[2], I. Brownell[4], and D. L. Sackett[1]

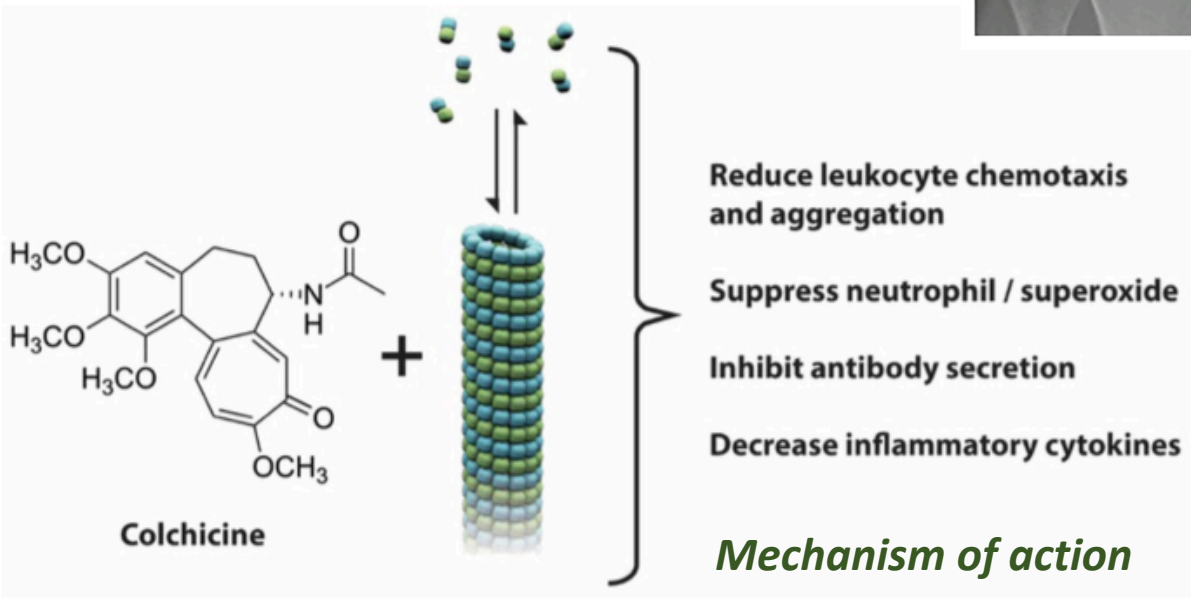
Disease	Level of evidence	Reference
Actinic keratosis	1^	30–32
Behcet's disease	1	22
Chronic urticaria	2	27
Epidermolysis bullosa acquisita	2/3	23,24,41
Granuloma annulare	3	42
Henoch-Schonlein purpura	3	43
Hidradenitis suppurative	3*	44
Idiopathic plantar eccrine hidradentis	3	45
Linear IgA	3	46,47
Leukocytoclastic vasculitis	1*	25
Neutrophilic urticaria	3	48
Nodular vasculitis	3	49
Purpura annularis telangiectoides	3	50
Pyoderma gangrenosum	3	51,52
Recurrent apthous stomatitis	1/2	28,29
Relapsing polychondritis	3	53,54
Scleredema	3	55
Sclerederma diabeticorum	3	56
Sweet's syndrome	2	26
Urticarial vasculitis	3	57

Gout and pseudo gout

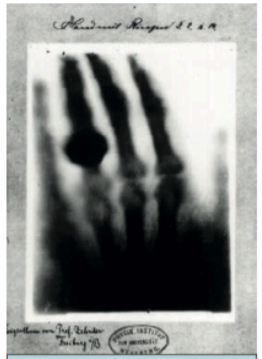






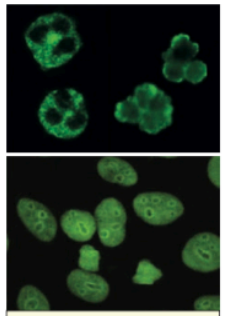


Mechanism of action



(1890s) First radiographs

LE cell discovered



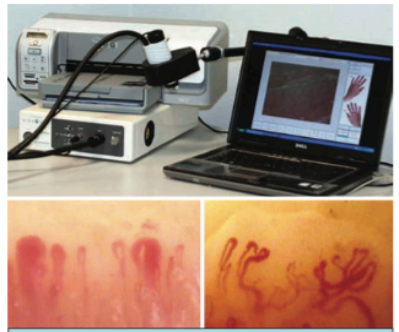
(1950s) ANAs demonstrated

(1960s) CT developed

Association between HLA-B27 and ankylosing spondylitis first reported

Nailfold capillaroscopy first used to detect early SSc microvascular damage

(1980s) ANCAs first described



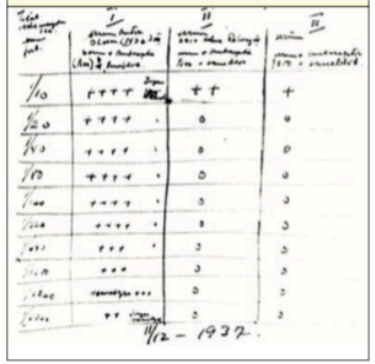
(1990s) Video capillaroscopy

RAMRIS presented

RFs and ACPAs included as RA classification criteria

1890 1937 1948 1950 1960 1970 1973 1980 1987 1990 2000 2001 2005 2010 2013

RF first discovered

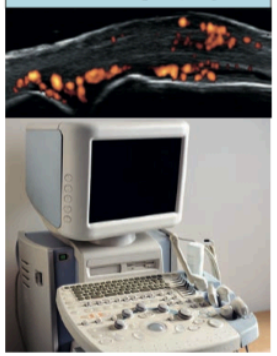


(1970s) Advent of joint ultrasonography and MRI

ACR classification criteria for RA include detection of radiographic erosions

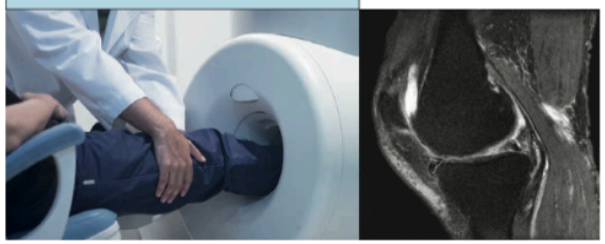
EULAR guidelines for musculoskeletal ultrasonography in rheumatology developed

(1970s to 2000s) Power Doppler ultrasonography



Nailfold capillaroscopy first used to grade SSc severity

(1970s to 2000s) MRI

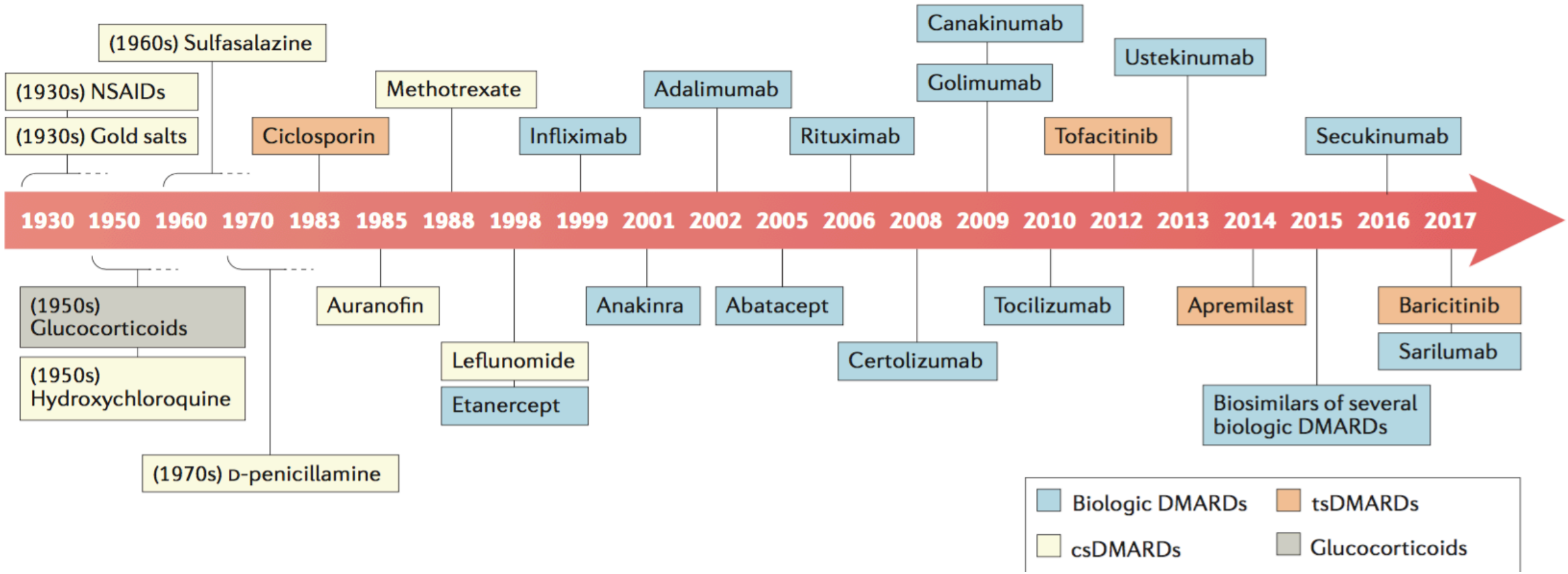


Capillaroscopic analysis included in EULAR–ACR classification guidelines for SSc

Advances in laboratory analyses

Advances in imaging

Managing rheumatic and musculoskeletal diseases — past, present and future



HISTORY OF RA DRUGS

1860: **sodium salicylate**

1899: **aspirin**

1949: **phenylbutazone** (NSAIDs)

1965: **indomethacin**

1935: **gold salts**

Forestier J. J Lab Clin Med 1935

1939: **sulfasalazine**

McConkey B. Agents Actions 1978

1950: **glucocorticoids**

Hence PS. Ann Intern Med 1952

1958: **cloroquine**

Cohen A. Arthritis Rheum 1958

1962: **hydroxycloroquine**

Scull E. Arthritis Rheum 1962

HISTORY OF RA DRUGS

1965: **D-Penicillamine**

Dixon A. Arthritis Rheum 1965

1972: **cytotoxic drugs** (azathioprine and cyclophosphamide)

Levy J. Arthritis Rheum 1972

1951: aminopterin: anti-metabolic analogue of the folic acid

Gubner R. Am J Med Sci 1951

1980s: **methotrexate**

Weinblatt ME. N Eng J Med 1985

1979: **cyclosporine A**

Herrmann B. Akt Rheumatol 1979

1998: **leflunomide**

NSAIDs history

Salicylates have probably been used for centuries.
In the 4th century BC, Hippocrates, Celsus, Galen, and others recorded the use of willow bark and other plants known to contain salicylates to treat fever and pain.

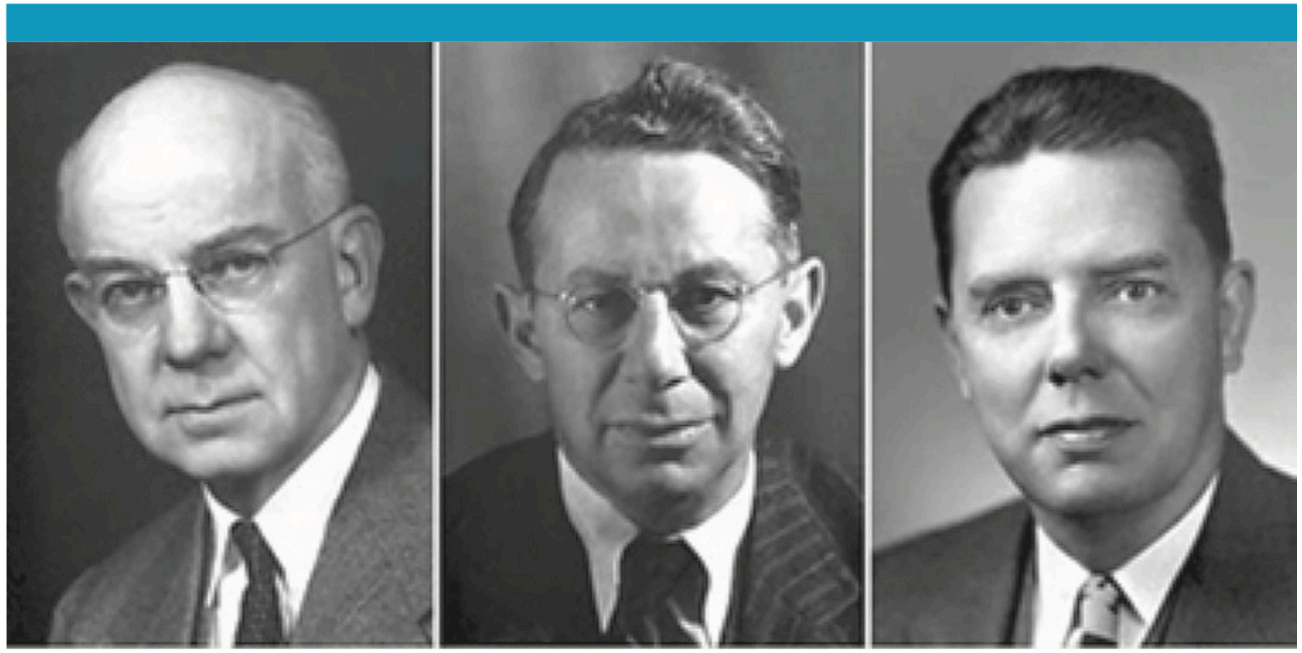
1760s—Dr. Edward Stone publishes his experience with willow bark as an antipyretic when dried.
1829—Salicylic acid isolated from willow bark.
1853—Gerhardt buffers salicylic acid with sodium and acetyl chloride, creating acetylsalicylic acid (ASA; aspirin).
1860—ASA chemically synthesized (Kolbe and Hoffman).
1899—Aspirin introduced in the United States as a powder (Bayer Company).
1949—Phenylbutazone, the first alternative to salicylates, introduced.
1960s—Indomethacin introduced.
1970s—J.R. Vane (1971) demonstrates that ASA, indomethacin and salicylate all exert their effect by COX inhibition (Nobel Prize in Medicine, 1982).
—Ibuprofen, fenoprofen calcium, naproxen, and tolmentin introduced.
1990s—Introduction of the specific COX-2 inhibitors.

It has been reported that Felix Hoffman of Bayer Company chemically synthesized aspirin in response to complaints from his arthritic father about the bitter taste of salicylates. He gave this new medicine to his father and it helped his arthritis. This constituted the first Phase I, II, and III testing of a drug, which for new drugs today takes many millions of dollars and an average of 10 years!

Non-steroidal anti-inflammatory drugs for treatment of rheumatic diseases

Medication	Dose	Possible side effects
Diclofenac potassium	100-200 mg/24 h, divided into 2-4 reception	For all NSAIDS: abdominal pain, or stomach, cramps, discomfort, edema (oedema), diarrhea, nausea, vomiting, heartburn, dizziness, headache, allergic reactions
Diclofenac sodium	100-200 mg/24 h, divided into 2-4, or 100 mg in the form of retard	
Etodolak	800-1200 mg/24 h, divided into 2-4 reception. In the form of retard 1 dose 400-1000mg/24 h	
Ibuprofen	1200-3200 mg/24 h, divided into 3-4 reception	
Indomethacin	50-200 mg/24 h, divided into 2-4, either in the form of retard 75 mg 1 times a day, 75 mg 2 times daily	
Ketoprofen	200-225 mg/24 h divided into 3-4 reception or retard-150-200 mg/24 h 1 times	
Meloxicam	7.5 -15 mg/24 h 1 times per day	
Naproxen	500-1500 mg/24 h divided 2 reception	
Nimesulide	100-200 mg/24 to 1-2 reception	
Piroxicam	20 mg/24 h in 1-2 reception	

Nobel prize in 1950



•Kendall, Reichstein ed Hench ricevono il premio Nobel per la medicina.

Hench aveva osservato che la gravidanza era in grado di affievolire i sintomi dell'artrite reumatoide

Ll cortisone fu isolato nel 1936 da Tadeusz Reichstein in Svizzera e da Edward Calvin Kendall e Oskar Paul Wintersteiner negli Stati Uniti.

.

Nel 1948 il dottor Lewis Serat della casa farmaceutica Merck riuscì finalmente a produrre l'ignota sostanza: era iniziata l'era dei corticosteroidi, dei veri e propri farmaci miracolosi che riuscirono a combattere uno straordinario numero di malattie.

Glucocorticoids:

GCs have beneficial antiinflammatory effects through numerous mechanisms.

Genomic

- GCs diffuse passively across cell membranes, bind to intracellular GC receptors (cGCRs), and this complex is chaperoned to the nucleus where it binds to GC response elements on DNA.
- GCs bind and block promoter sites of proinflammatory cytokine genes: interleukin-1 (IL-1).
- GCs recruit transcription factors to promoter sites encoding regulatory proteins and antiinflammatory molecules (IκB, lipocortin-1, IL-10, IL-1R, others)
- GCs inhibit production of proinflammatory transcription factors (NF-κB, AP-1, others) resulting in inhibition of production of proinflammatory cytokines, adhesion molecules, and COX-2.

Non Genomic

- GCs bind to cGCRs causing release of inhibitory proteins such as Src.
- GCs bind to membrane GCRs on lymphocytes and monocytes leading to antiinflammatory effects.
- GCs at very high doses (>100 mg/day prednisone) intercalate into cell membranes reducing calcium and sodium cycling across the membrane, which has antiinflammatory effects. This may explain differential effects of high-dose “pulse” steroids.

Glucocorticoids

Innate immune system

- ✓ GCs upregulate enzymes that degrade bradykinin resulting in vasoconstriction. This causes less swelling and pain.
- ✓ GCs suppress production of prostaglandins by inducing synthesis of lipocortin-1 which inhibits phospholipase A-2 mediated liberation of arachidonic acid from cell membranes.
- ✓ GCs inhibit NF-κB which suppresses COX-2 synthesis. Does not affect COX-1 so platelet function is preserved.
- ✓ GCs interfere with phagocytosis and cytokine production by macrophages and neutrophils.
- ✓ Neutrophilia occurs as a result of increased release from bone marrow and decreased migration out of vasculature resulting from inhibition of adhesion molecule production and decreased cellular adherence to vessel walls.
- ✓ GCs decrease release of eosinophils from bone marrow and increase apoptosis (eosinopenia).

Adaptive (acquired) immune response

- ✓ Dendritic cells undergo increased apoptosis.
- ✓ T cells are redistributed to tissues (lymphopenia).
- ✓ Inhibits T helper, type 1 (Th1) > Th2 and Th17 cytokine production. Leads to anergy.
- ✓ B cells less affected by GCs than T cells.
- ✓ Immunoglobulin production preserved unless prolonged high-dose GCs.
- ✓ Monocytes redistributed to tissues (monocytopenia).

TABLE 82-3 Glucocorticoids Grouped in Terms of Biologic Activity

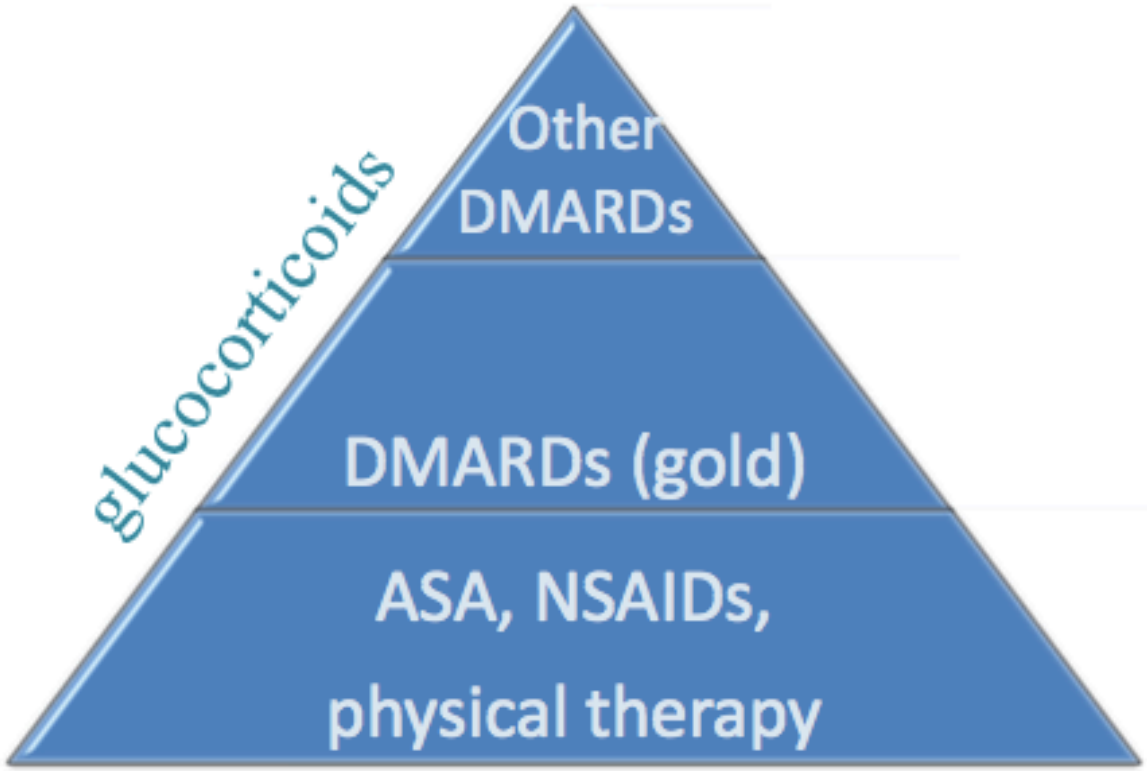
SHORT-ACTING (Half-Life 12 hours)	INTERMEDIATE-ACTING (Half-Life 12 to 36 hours)	LONG-ACTING (Half-Life 48 hours)
Hydrocortisone	Prednisone	Paramethasone
Cortisone	Prednisolone	Betamethasone
	Methylprednisolone	Dexamethasone
	Triamcinolone	

TABLE 82-1 Examples of Steroid Responsive Rheumatic Diseases

A. Selective complications of connective tissue diseases:
Rheumatoid arthritis
Systemic lupus erythematosus
Polymyositis/dermatomyositis
Sjögren's extra-salivary gland manifestations
B. Vasculitis disorders (initial treatment)
C. Crystalline disease flares
D. Polymyalgia rheumatica

Minimize duration of GC therapy and dose

Historical pyramid: 'Go low, go slow'



1940 and 1950: the standard approach involved "physical medicine and rehabilitation"
Splints (i.e. for prevention of ulnar deviatio), bed rest, correct posture in bed, bed exercise programs. Moisty, dry heat, waxes, cold, massage heliotherapy

Acetylsalicylic acid was often used and since **1960s** NSAIDs became the second tier
1950s: glucocorticoids

1965: Coperman's textbook (UK): gold should never be the treatment of first choice in early cases, many of whom do remarkably weel on simple conservative meeasures

2nd line DMARDs: SSZ, antimalarials, MTX (MTX emerged as major advance during the **1990s** with long term effectiveness)

Pathogenic (Basic) therapy of inflammatory rheumatic diseases

- Disease modifying antirheumatic drugs (DMARDs) - the basic drugs from diverse group of funds that reduce the symptoms of rheumatoid arthritis (RA) and other inflammatory autoimmune diseases.
- In addition, there is increasing evidence that treatment with DMARD, especially if appointed early in the course of the disease, can delay the progression of cartilage and bone.
- When the RA is not responding to treatment DMARD, can be applied biological therapy. Biologicals alter the action of cytokines

International Journal of
Rheumatic Diseases

International Journal of Rheumatic Diseases 2016; **19**: 844–851

Landmark papers on the discovery of methotrexate for the treatment of rheumatoid arthritis and other systemic inflammatory rheumatic diseases: a fascinating story

Anand N. MALAVIYA

Subbarow synthesised 4-aminopteroylglutamic acid (aminopterin) **1940-48**

In the **1940s–50s** several laboratories in the United States had demonstrated that cortisone and the folic acid antagonist 4-aminopteroylglutamic acid (aminopterin) exerted powerful inhibitory effects on the proliferation of mesenchymal cells. In their landmark 1951 paper Gubner and colleagues in New York established that cortisone and aminopterin were effective in the same spectrum of disorders.

'Why should these toxic cancer drugs be used in a benign condition like rheumatoid?' was the argument.

Hoffmeister published his work on LD-MTX in RA for the first time only in the year **1972.** This paper demonstrated the safety and efficacy of LD-MTX.

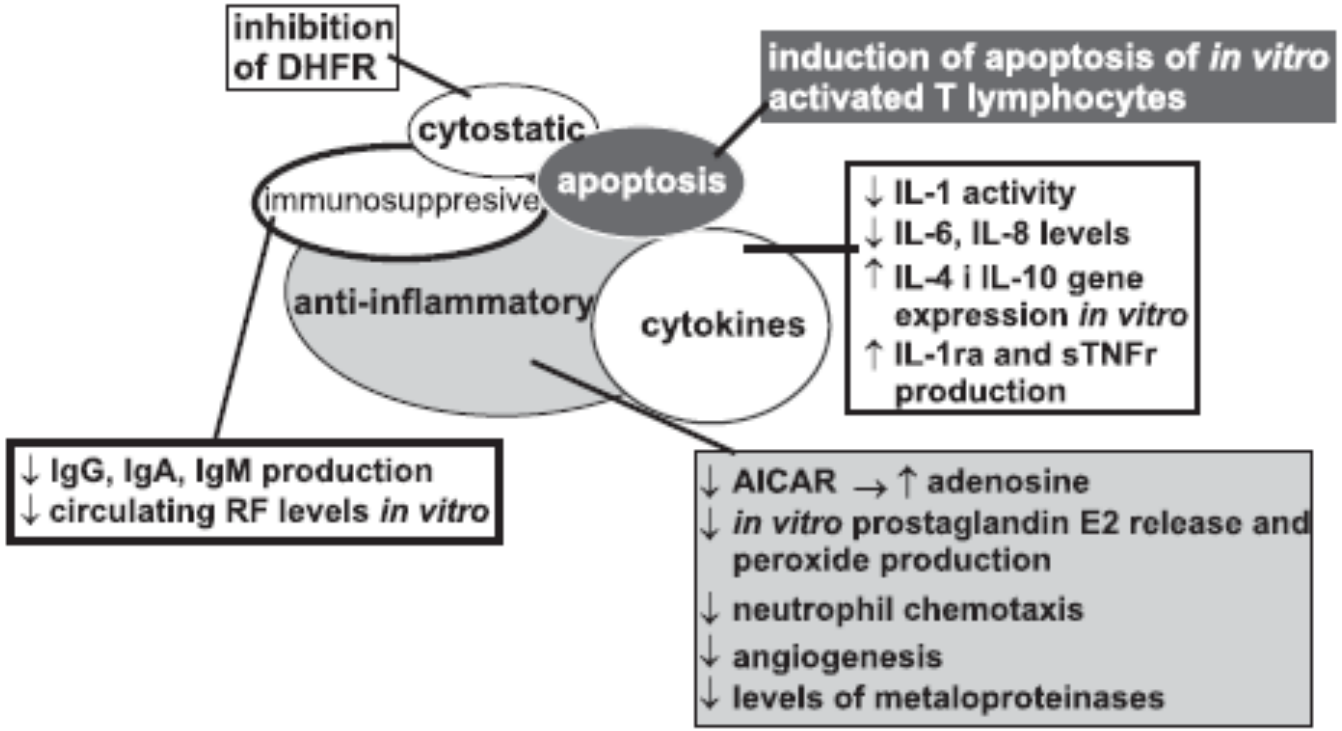
In **1984–85,** four different groups of workers published their seminal work on the results of randomized controlled trials of LD-MTX and its long-term follow-up in the treatment of RA.

D-MTX was approved for use in the treatment of RA by the US Food and Drug Adminis- tration in **1988**

Review

Methotrexate in rheumatoid arthritis

Jerzy Świerkot, Jacek Szechiński

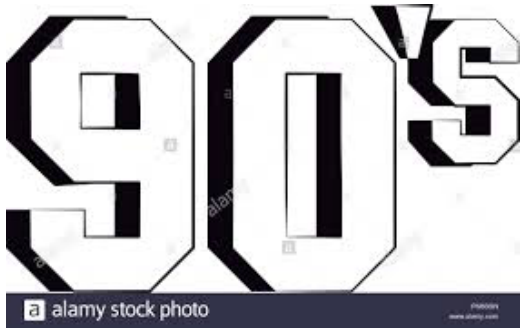


Swierkot Jet al, *Pharmacol Rep* 2006

Medication	Dosage	Possible side effects
Leflunomid	10-20 mg/day in 1. Treatment begins with a dose of 100 mg support screens from 3 consecutive days	Diarrhea, dizziness, hair loss, hypertension, increased transaminase, leukopenia, rash on the skin
Methotrexate	7.5-20 mg/week	Discomfort in the stomach, skin rash, headache, photosensitivity, increased transaminase, leukopenia, ulcers in the mouth, weakness, fatigue
Mycophenolate Mikofenolat	1.5-day	Diarrhea, moderate leukopenia
Sulfasalazine	500-3000 mg daily in 2-4 reception	Abdominal pain, diarrhea, increased sensitivity, reduced appetite, nausea, vomiting, rash on the skin

Pathogenetic (Basic) drugs

Medication	Dosage	Possible side effects
Azathioprine	50-150 mg/day in 1-3 reception	Leukopenia, increased transaminase
Cyclophosphamide	50-150 mg per day in single dose	Hematuria, hair loss, leukopenia, amenorrhea, nausea, vomiting
Cyclosporine	100-400 mg daily in 2 reception	Hypertension, increased hair growth, reduced kidney function, hypertrophy of gum, tremor
Hydroxychloroquine	200-600 mg daily in 2-1 reception	Violation of, diarrhea, rash



The nineties:

the fate of the pyramind,
the "strategic trials"
the measures to assess rheumatoid arthritis

RA Treatment Options

Disease modifying anti-rheumatic drugs (DMARDs)

In the past: DMARD treatment was initiated when "NSAIDs/GC no longer worked"

Now: every RA patient is candidated to receive DMARDs therapy as soon as possible

"A suspected diagnosis of RA may be sufficient to initiate DMARD"

EULAR recommendations for the management of rheumatoid arthritis. ARD 2010

Biological therapy

- The particular interest is the use of monoclonal antibodies.
- These drugs have very high specificity, which provides a selective effect on certain links in the immunopathogenesis of disease, minimally affecting normal functioning mechanisms of the immune system.
- This can significantly reduce the risk of "generalized" imunosupresed, which is typical of many drugs, especially glucocorticoids and cytotoxic drugs.

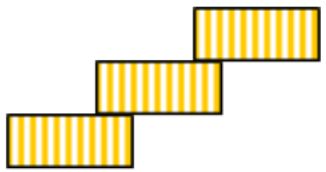
Basic therapy

- **When to start** an understanding that changes in the joints can occur within the first 12 months of the debut of RA, led to the earlier introduction of DMARD and more aggressive combination DMARD.

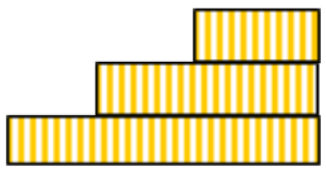
- **Monotherapy** - Methotrexate is considered standard therapy for DMARD.

- **Combination therapy** Join one or two DMARD therapy with methotrexate for the background is often used in an attempt to improve clinical response in those patients who did not give an answer to monotherapy with methotrexate. The most commonly used combinations of DMARD - "triple therapy" (methotrexate + hydroxychloroquine sulfosalazin +) or methotrexate plus a biological agent.

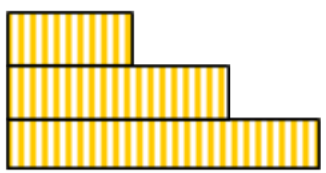
Treatment strategies with drugs



1. Sequential monotherapy



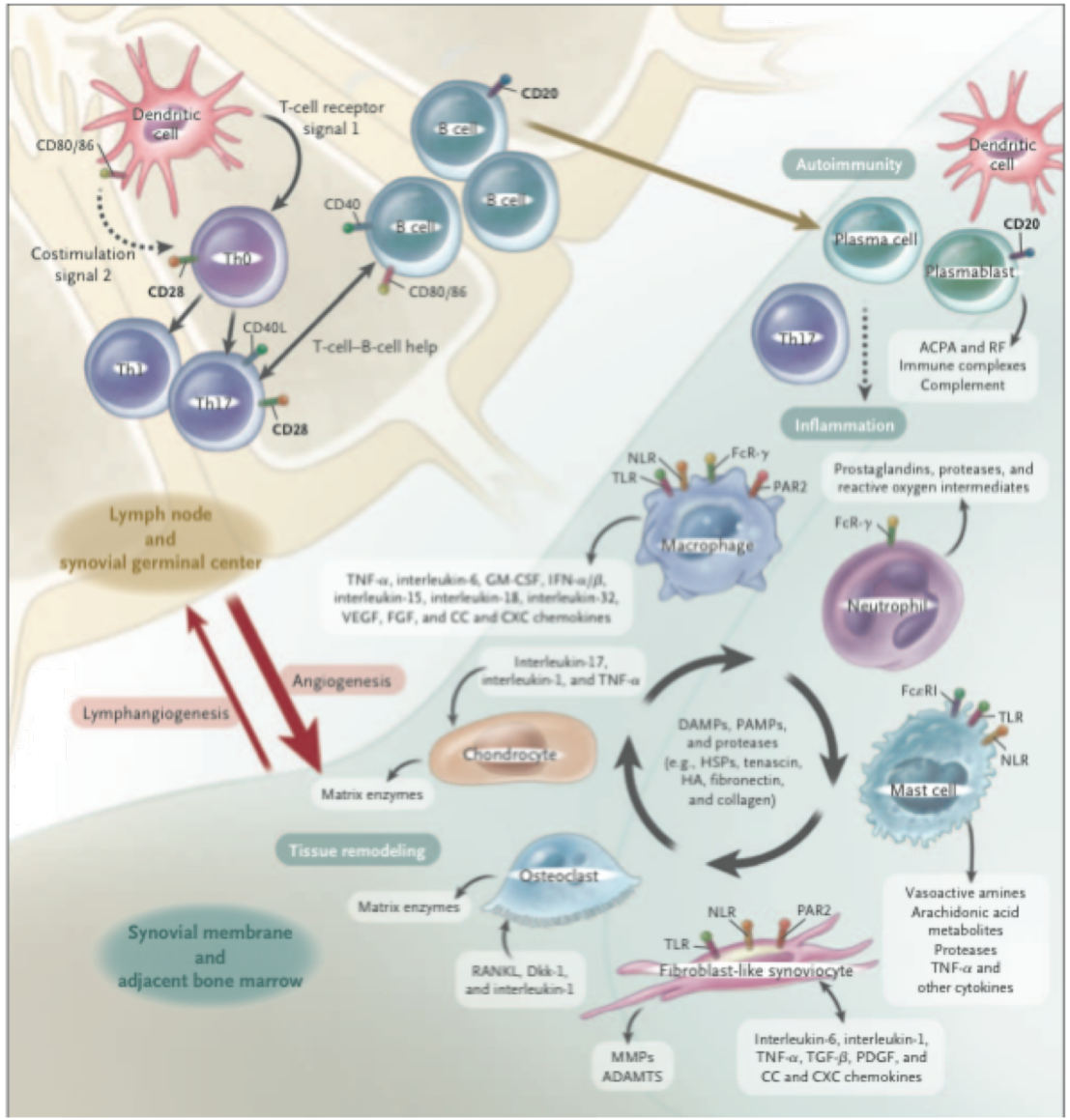
2. Step-up (ascending) combination therapy



3. Step-down (descending) combination therapy

4. Combination with a biological agent

La patogenesi dell'artrite: i farmaci biologici

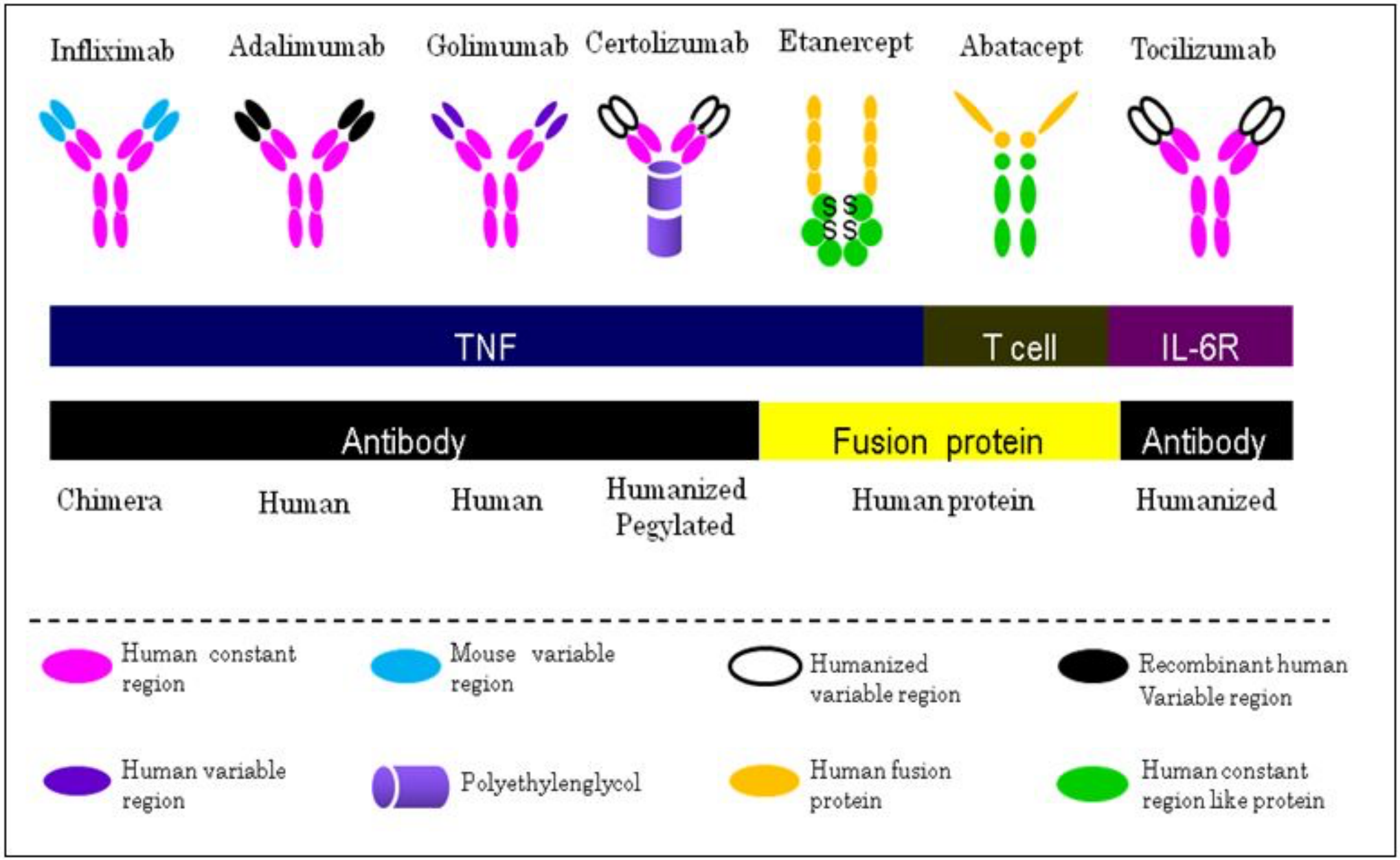


McInnes IB and Schett G. N Engl J Med 2011

Farmaci attualmente disponibili per il trattamento delle artriti infiammatorie

DMARDs
MTX
Arava
Salazopyrina
Ciclosporina
Clorochina

bDMARS	target	EV/SC	frequenza
Infliximab	Anti-TNF	ev	8 settimane
Adalimumab	Anti-TNF	sc	2 settimane
Etanercept	Anti-TNF	sc	1 settimana
Golimumab	Anti-TNF	sc	4 settimane
Certolizumab	Anti-TNF	sc	2 settimane
Roactemra	Anti-IL6R	ev/sc	4 settimane/ 2 settimane
Anakinra	Anti-IL1R	sc	Ogni giorno
Rituximab	Anti-CD20	ev	Ogni 6-9 mesi
Abatacept	Costimulatory signal T cells	ev/sc	Ogni mese
Ustekinumab	Anti-IL12/IL23	sc	Ogni 3 mesi


Infliximab
Adalimumab
Golimumab
Certolizumab
Etanercept
Abatacept
Tocilizumab
S S
S S
TNF
T cell
IL-6R
Antibody
Fusion protein
Antibody
Chimera
Human
Human
Humanized
Pegylated
Human protein
Humanized
Human constant region
Mouse variable region
Humanized variable region
Recombinant human Variable region
Human variable region
Polyethylenglycol
Human fusion protein
Human constant region like protein

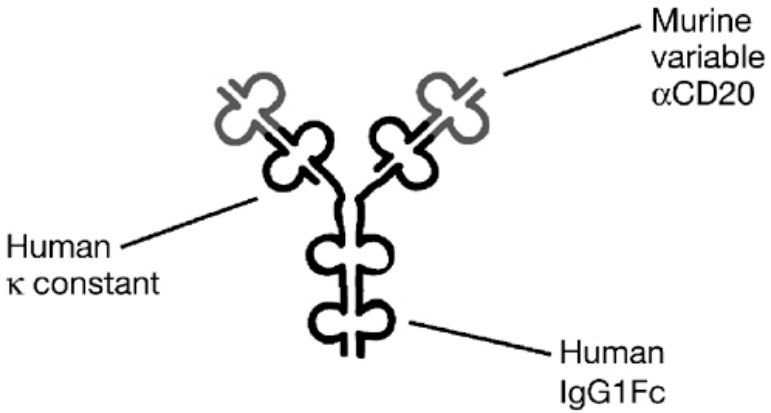
MABTHERA®
RITUXIMAB
B CELL THERAPY. SEROPOSITIVE RESULTS.

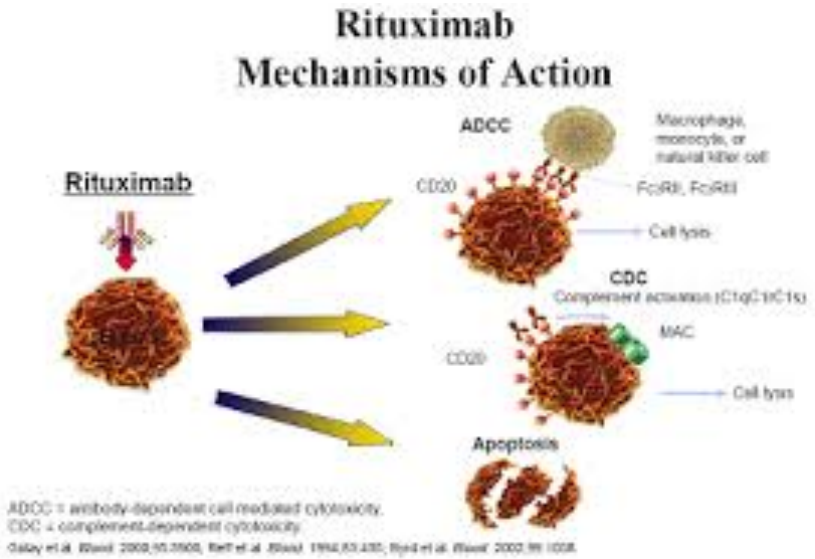
2 linea

Anticorpo monoclonale chimerico murino/umano antiCD20

Rheumatoid Arthritis
Vasculiti ANCA

Rituximab





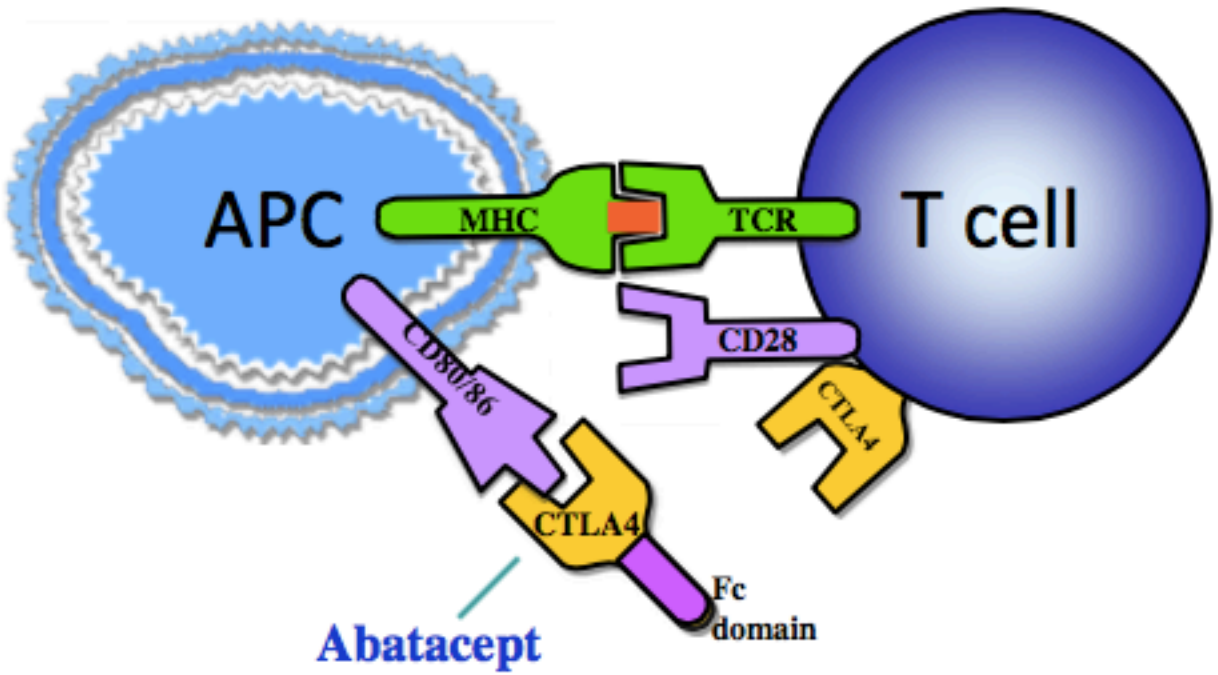
In monoterapia e in associazione con MTX

2 infusioni da 1 grammo a distanza di 2 settimane da ripetere ogni 6-9 mesi

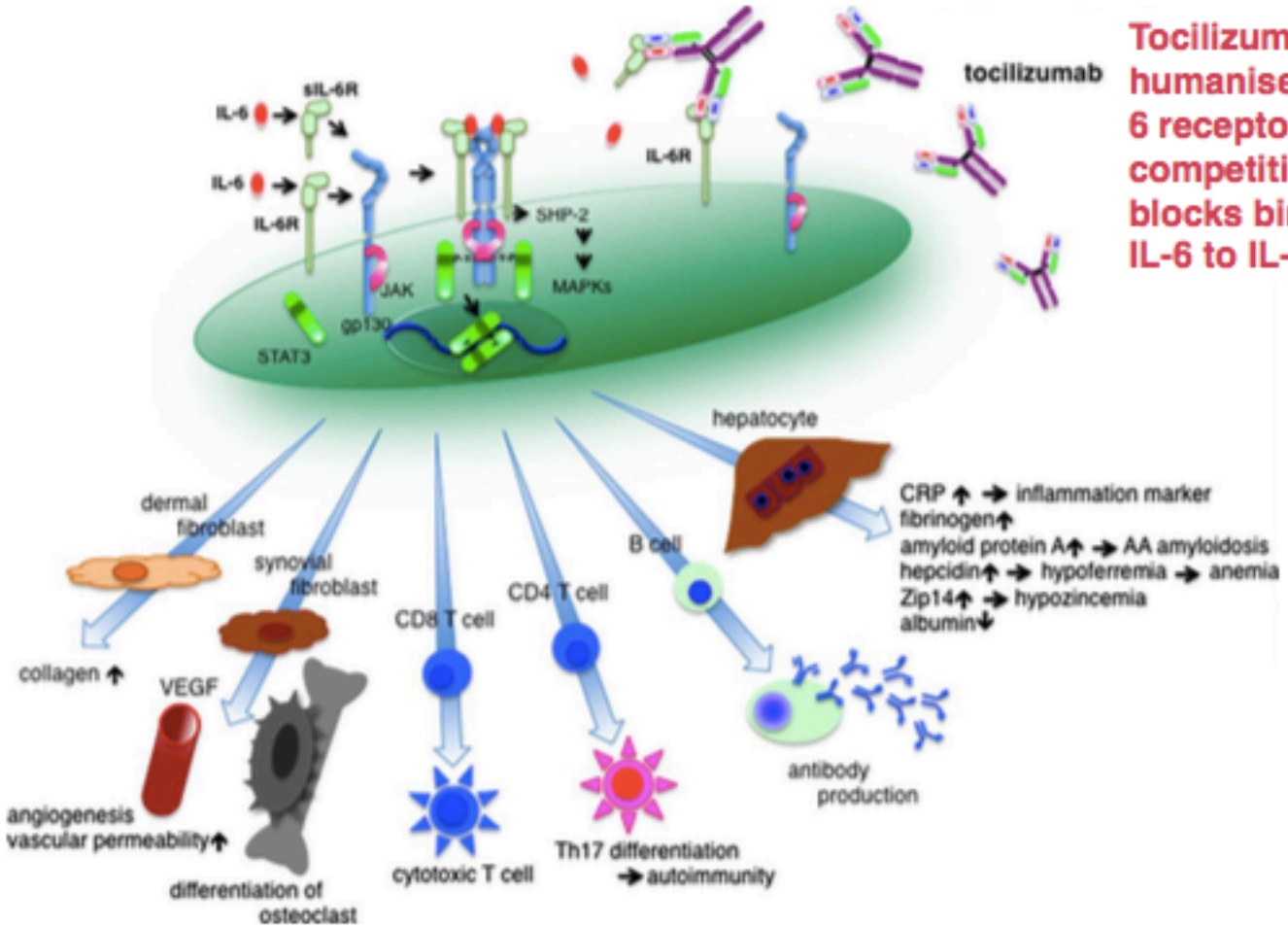
Infusione lenta

CTLA4 Ig - Abatacept

Abatacept is a recombinant fusion protein consisting of the **extracellular domain of human CTLA4** and a fragment of the **Fc domain** of human IgG1. This molecule binds to CD80 and CD86 and thereby inhibits T cell co-stimulation.



Tocilizumab binds to soluble and membranous IL-6R



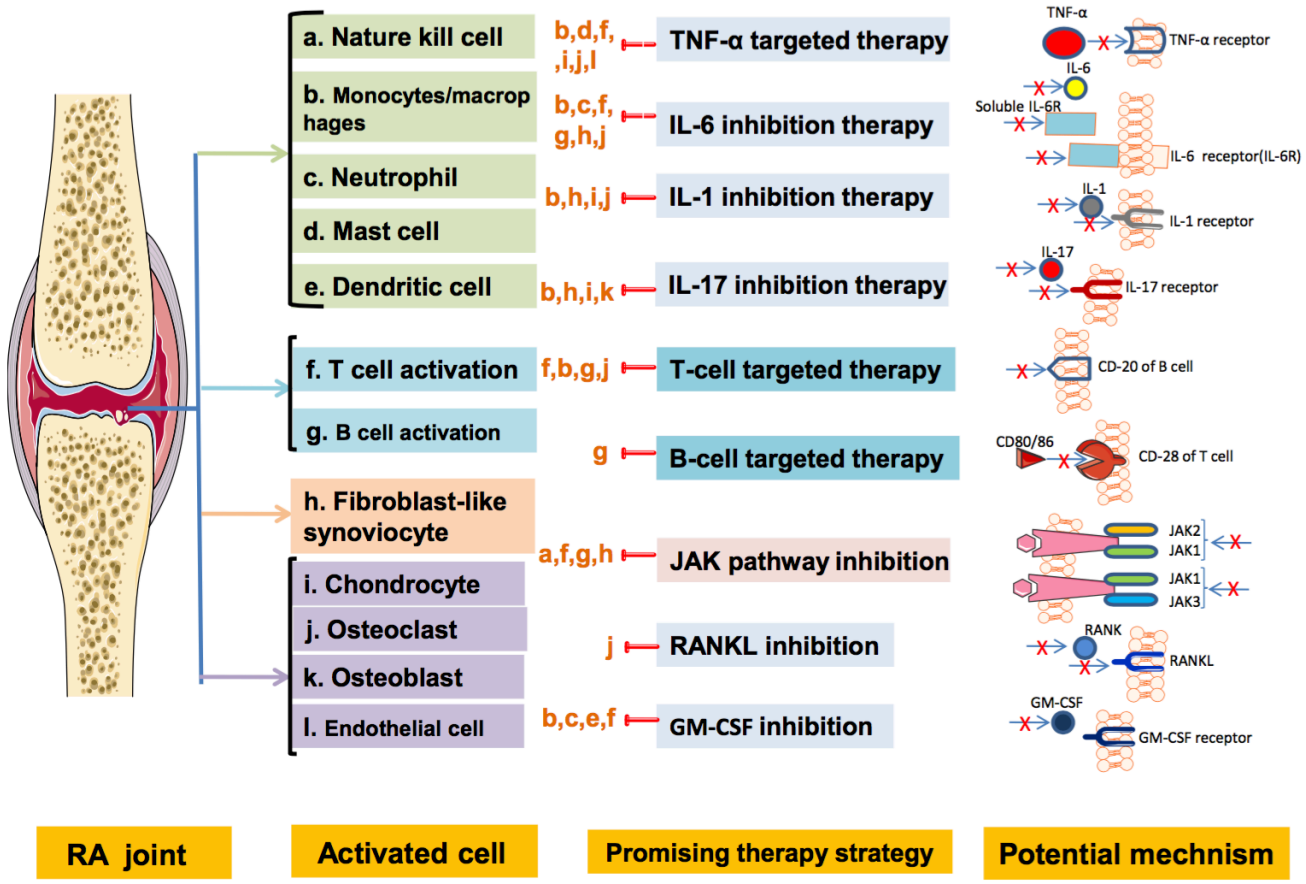
Tocilizumab, a humanised anti-IL-6 receptor mAb, competitively blocks binding of IL-6 to IL-6R

Tanaka et al. FEBS Letters 2011

REVIEW ARTICLE OPEN

Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies

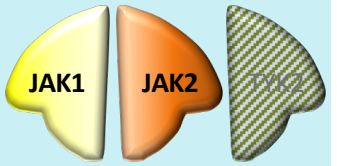
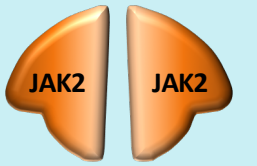
Qiang Guo[1,2], Yuxiang Wang[1], Dan Xu[2,3], Johannes Nossent[3,4], Nathan J. Pavlos[2] and Jiake Xu[2]



Cytokines Signal Through Different JAK Combinations

- **Four JAK family members: JAK1, JAK2, JAK3, and TYK21**
- JAKs mainly **work in pairs** within the cell and signal via JAK/STAT combinations
- **JAKs work in different combinations**
- **JAK1 and JAK3 are required for γ-chain cytokine receptor signaling**

Example of Cytokines That Signal Through JAK/STAT Combinations

γ-chain cytokines*	IFN-γ	IL-10, IL-20 IL-22 Type I IFNs (IFNα/IFNβ)	IL-12 IL-23	IL-6†, IL-11, IL-27, CTF-1, CNTF, G-CSF, LIF, OSM	EPO, TPO GM-CSF, GH, IL-3, IL-5
					
STAT 1, 3, 5, 6	STAT 1, 3, 5	STAT 1, 3, 5	STAT 3, 4	STAT 1, 3, 5	STAT 5

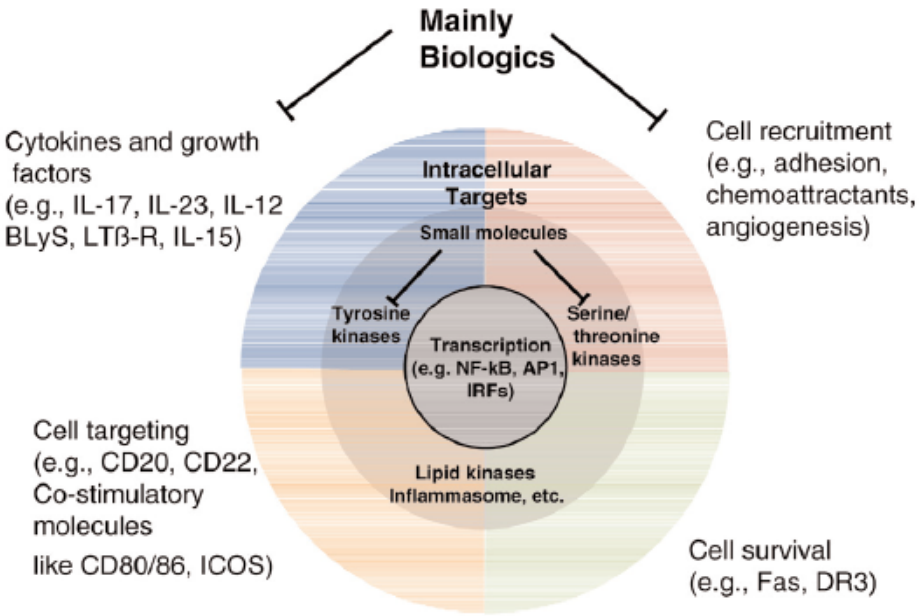
- γ-chain cytokines=IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. †Type II cytokine receptors such as those for the gp130 subunit sharing receptors IL-6 and IL-11 as well as IL-10, IL-19, IL-20, and IL-22 mainly signal through JAK1, but are also associated with JAK2 and TYK2[2]

O'Sullivan LA. *Mol Immunol.* 2007;44:2497-506. 2. Ghoreschi K, et al. *Immunol Rev.* 2009;228:273-287.

DEBATE Open Access

What is the future of targeted therapy in rheumatology: biologics or small molecules?

Attila Mócsai[1,2*†], László Kovács[3†] and Péter Gergely[4†]



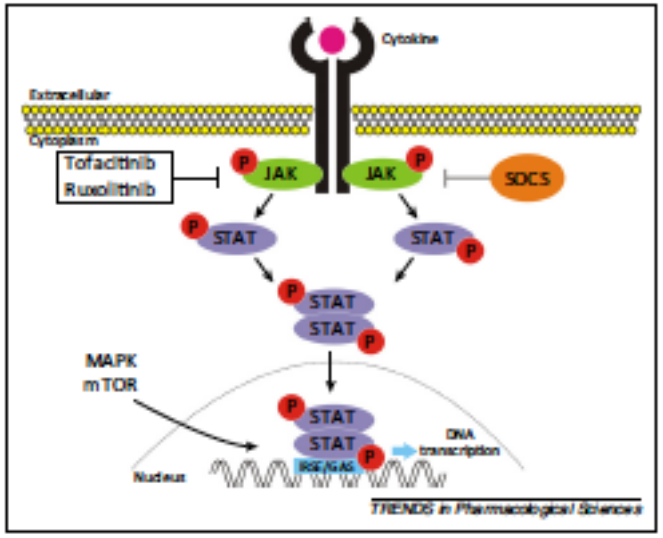


Table 2 The use of Jak-family kinases by cytokines and other intercellular mediators

Ligand	Jak-kinase
IL-6, IL-11, CNTF, CT-1, LIF, OSM, IL-27 (EBI3 + p28), IL-31, IL-35 (p35 + EBI3)	Jak1, Jak2, Tyk2
G-CSF, IL-12 (p40 + p35), **angiotensin**	Jak2, Tyk2
Leptin, GM-CSF, IL-5, IL-3, IL-23 (p40 + p19), **serotonin, α-thrombin**	Jak2
Chemokines	Jak2, Jak3
IL-2	Jak1, Jak2, Jak3
IL-4, IL-9, IL-7, IL-15, IL-21	Jak1, Jak3
IL-13	Jak1, Jak2, Tyk2
IL-19, IL-20	Jak1, ?
IL-22, IL-26, IL-28A, IL-28B, IL-29, interferon (IFNα/β), IL-10	Jak1, Tyk2
IL-24	Jak1, ?
GH, Epo	Jak2
Thrombopoetin	Jak2, Tyk2
IFN-γ, **PDGF**	Jak1, Jak2
TLSP	Jak1, possibly Jak2
EGF	Jak1

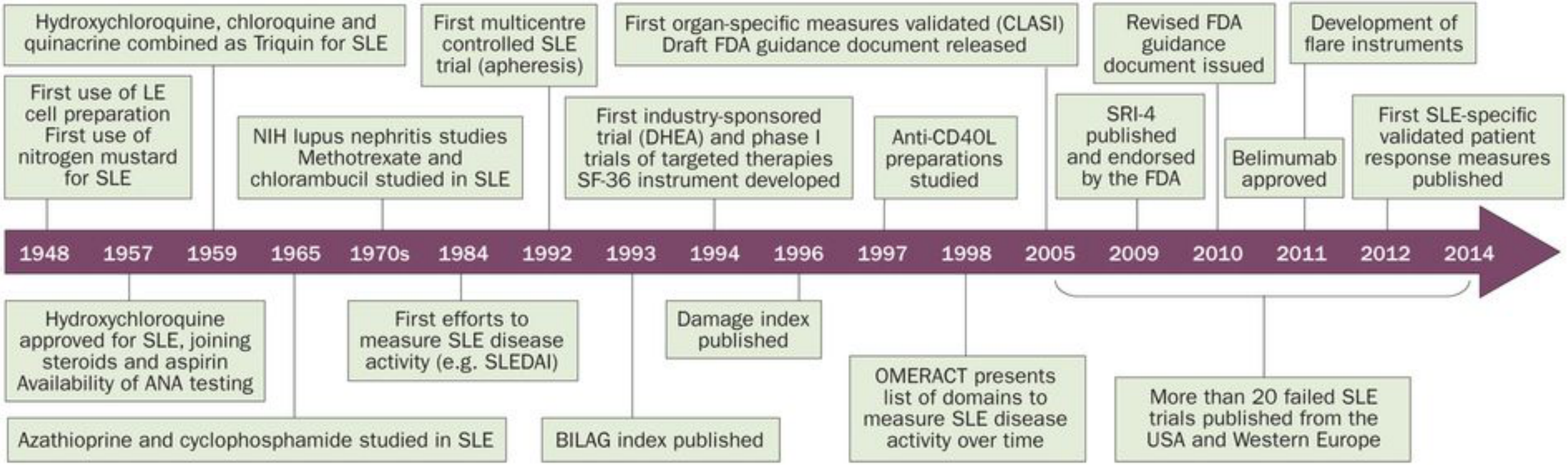
Perché le “small molecules”:
1. Sono per somministrazione orale
2. Non selettive e più ampio effetto off-target
3. Sono rivolte verso meccanismi intracellulari

Types of Treatments for RA: Nomenclature

Disease Modifying Antirheumatic Drugs (DMARDs)			
Synthetic DMARDs (sDMARDs)		**Biological DMARDs (bDMARDs)**	
Conventional synthetic (csDMARDs	**Targeted synthetic (tsDMARDs)**	**Biological originator (boDMARDs)**	**Biosimilar (bsDMARDs)**
MTX, SSZ, LEF	*Tofacitinib* *Baricitinib*		

Smolen JS, et al. Ann Rheum Dis 2014 Jan;73(1):3-5.

Another History: Systemic lupus erythematosus



Nature Reviews | Rheumatology

THERAPY MILESTONES

1950s: STEROIDS

1970s: CYCLOPHOSPHAMIDE

2010s: RITUXIMAB

With the advent of the immunosuppressive therapies,
the 1-year mortality of AAVs could be reduced over the time from almost **80%**
without any treatment to **3-18%** with current immunosuppressive regimens

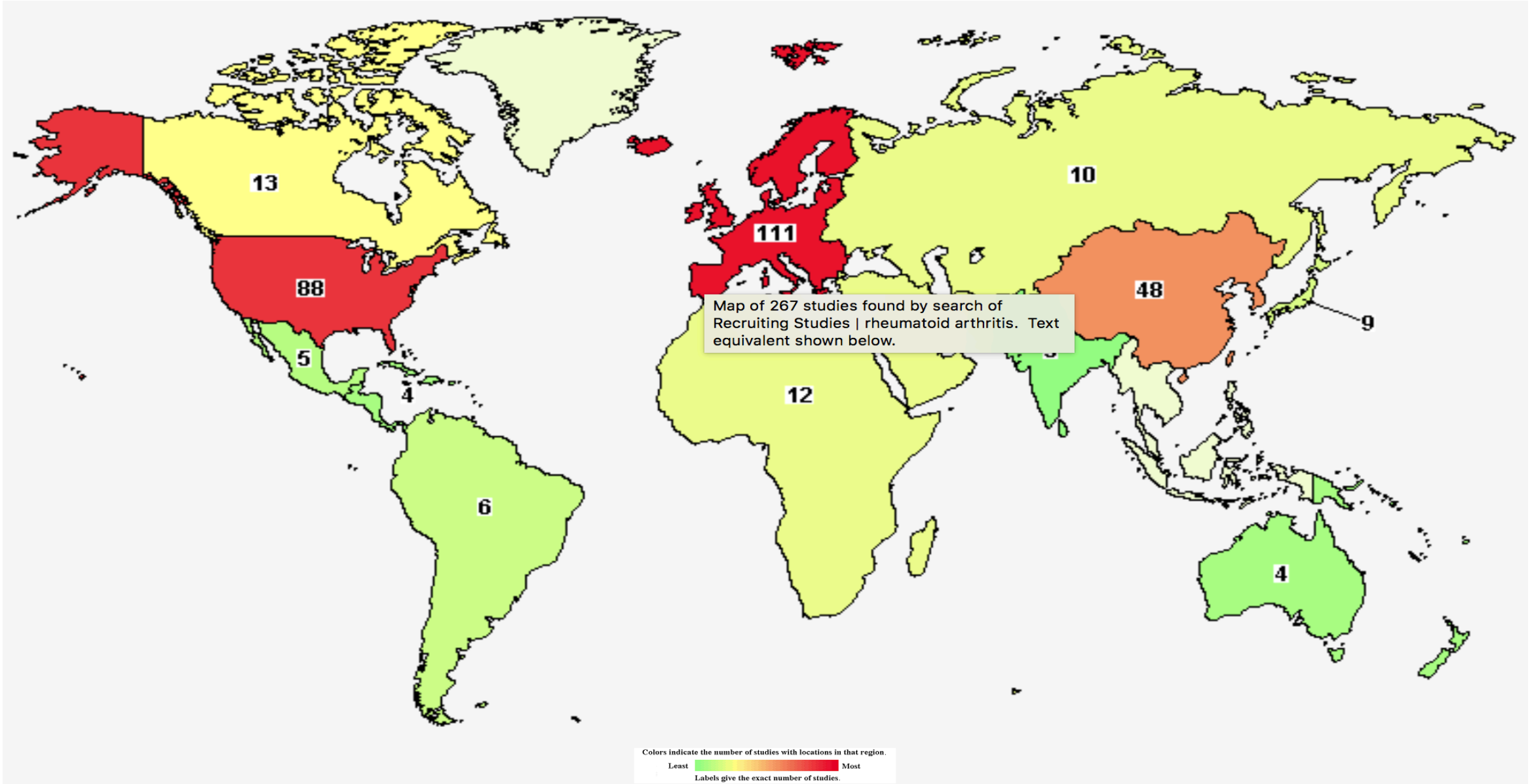
Right drug, right patient, right time: aspiration or future promise for biologics in rheumatoid arthritis?

1 yy → RCT

20 yy — 40 yy — 80 yy

- **Treat to target**
- ***Remission***
- ***Low disease activity***
- **Avoid disability**
- **Avoid radiologic progression**

Romão *et al. Arthritis Research & Therapy* (2017) 19:239



Source:https://ClinicalTrials.gov

….rheumatology in arts

Horton’s arteritis

Rheumatoid arthritis

Grazie