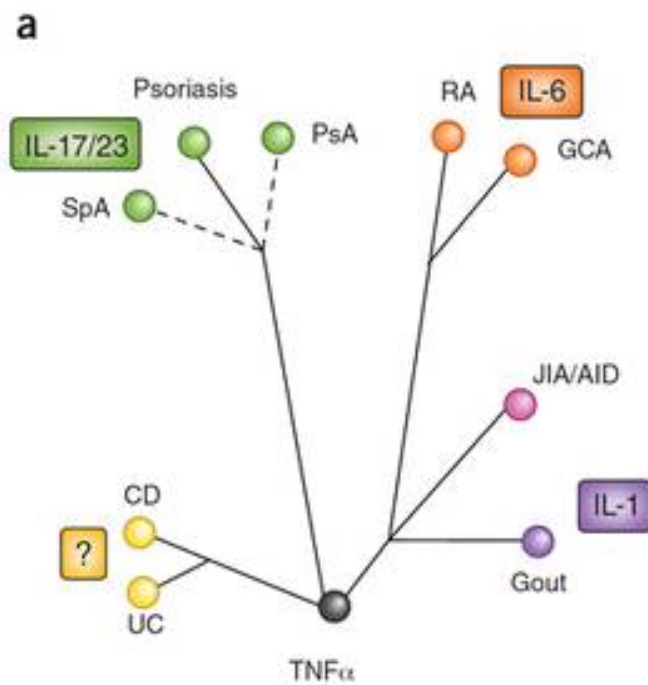


Molecular taxonomy tree of inflammatory cytokines in disease and efficacy of cytokine inhibition in chronic inflammatory diseases



b

CID	TNF	IL-6R	IL-1	IL-12/23	IL-17A
Rheumatoid arthritis	Green	Green	Grey	Grey	Grey
Giant cell arthritis	Green	Green	Grey	Grey	Grey
JIA/AID	Green	Green	Green	Grey	Grey
Gout	White	Grey	Green	Grey	Grey
Crohn's disease	Green	Grey	Grey	Light Green	Red
Ulcerative colitis	Green	Grey	Grey	Grey	Grey
Psoriasis	Green	Grey	Grey	Green	Green
Psoriatic arthritis	Green	Grey	Grey	Light Green	Light Green
Ankylosing spondylitis	Green	Grey	Grey	Light Green	Light Green
Multiple sclerosis	Red	Grey	Grey	Grey	Light Green
Drugs	Adalimumab Certolizumab Etanercept Golimumab Infliximab	Tocilizumab Sarilumab*	Anakinra Canakinumab Rilonacept	Ustekinumab Briakinumab*	Brodalumab* Ixekizumab* Secucinumab*

(a) Most of the chronic inflammatory diseases share clinical responsiveness to tumor TNF- α inhibition but substantially differ in their responsiveness to inhibition of other inflammatory cytokines, such as IL-6, IL-1 and IL-17 and IL-23 (IL-17/23), indicating a hierarchical structure of cytokine effects in various chronic inflammatory diseases. (b) The chart shows strong clinical efficacy of inhibition of each cytokine confirmed in randomized clinical trials of various chronic inflammatory diseases (CIDs) (or several independent observational studies in case of low prevalence diseases) (dark green), preliminary data on clinical efficacy (light green), no or mild clinical efficacy or no data on efficacy (gray) and disease-aggravating effect (red) upon cytokine inhibition of similar cytokine dependence (dashed blue squares). IL-12/23, combined inhibition of interleukin-12 and interleukin-23 by targeting p40; IL-6R, IL-6 receptor; RA, rheumatoid arthritis; JIA, juvenile idiopathic arthritis; AID, autoinflammatory disease including Still's disease; CD, Crohn's disease; UC, ulcerative colitis; PsA, psoriatic arthritis, SpA, spondyloarthritis, GCA, giant cell arteritis. Asterisks indicate drugs that are not approved to date.