Biologic Agents and Reactivation Tuberculosis

Mahesh C Patel, MD

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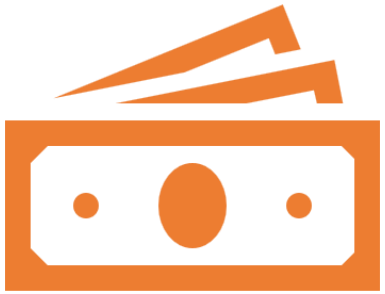


I have no financial disclosures

I have no conflicts of interest regarding the topic that I will be speaking about today

What are biologics?

Biological drugs = Biologics

Produced using a living system, such as a microorganism, plant cell or animal cell

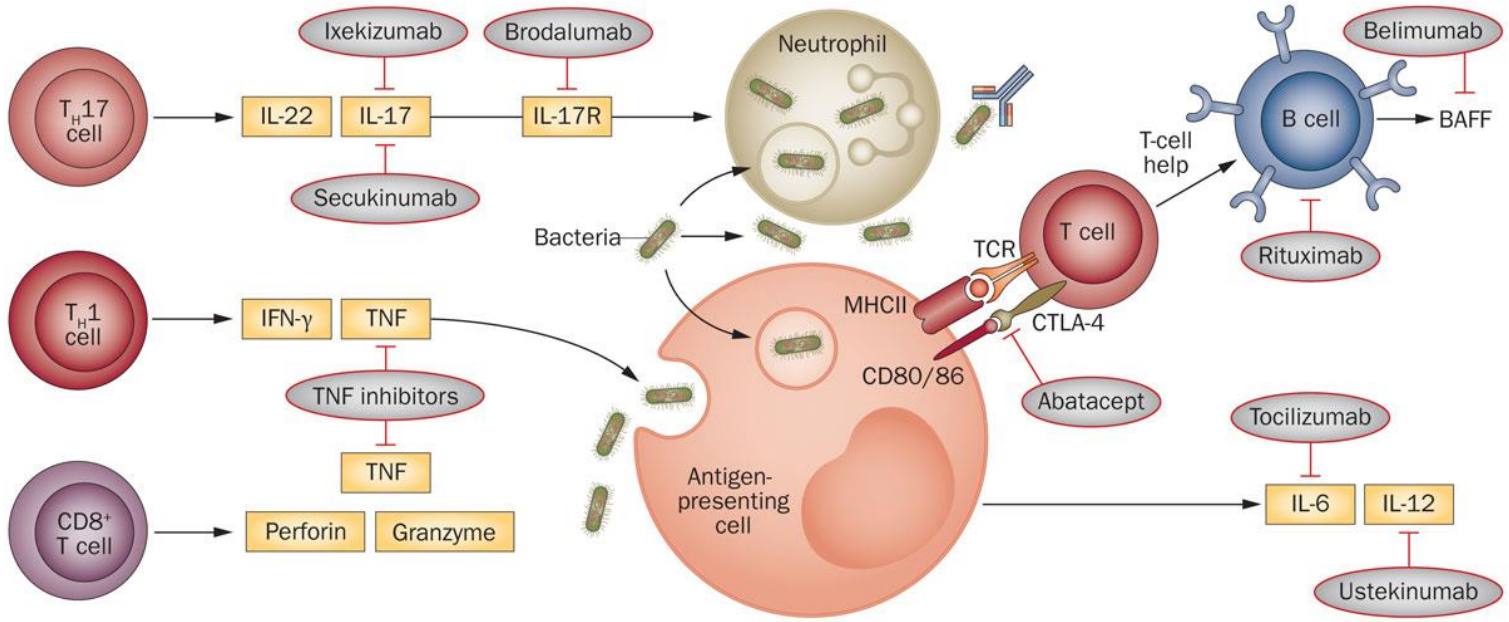
Larger, more complex molecules than typical drugs that are “small molecules”

Biological DMARDs					
Adalimumab, Certolizumab, Etanercept, Golimumab, Infliximab	Tumor necrosis factor (TNF)	Intravenous infusion/ subcutaneous injection	Stromal cell activation, angiogenesis, cytokine and chemokine expression, MMP production	Flares in patients with MS; high risk of *Herpes zoster*; reactivation of tuberculosis	(20)
Tocilizumab, Sarilumab	IL-6R	Intravenous infusion/ subcutaneous injection	T-cell migration and activation, FLS inflammatory response, osteoclast activation	Gastrointestinal perforations; severe liver failure	(21)
Abatacept	T-cell co-stimulation signal (CD80/ CD86)	Intravenous infusion/ subcutaneous injection	Effector T-cell and dendritic cell activation, B -cell infiltration, osteoclastogenesis	Moderate chances of serious infections	(20)
Rituximab	CD20 (cell marker expressed on B-cells)	Intravenous infusion	Circulating B-cells, a proportion of tissue B-cells and plasmablasts, autoantibody titers	Risk of *Herpes zoster*; rare risk of progressive multifocal leuko-encephalopathy	(22)
Targeted Synthetic DMARDs					
Tofacitinib	JAK1/3	Oral	Cytokine-dependent feedback loops and downstream effects	Risk of venous thromboembolism; *Herpes zoster* (baricitinib, tofacitinib); Hepatitis B reactivation (baricitinib)	(23)
Baricitinib	JAK1/2	Oral			
Upadacitinib, Filgotinib	JAK1	Oral			

MMP, matrix metalloproteinase enzymes; IL-6R, interleukin-6 receptor; FLS, fibroblast-like synoviocytes; JAK, Janus kinase; MS, multiple sclerosis.

Sandhu G and Thelma BK (2022) New Druggable Targets for Rheumatoid Arthritis Based on Insights From Synovial Biology. *Front. Immunol.* 13

Figure 2 Biologic agents can inhibit immunity to pathogens



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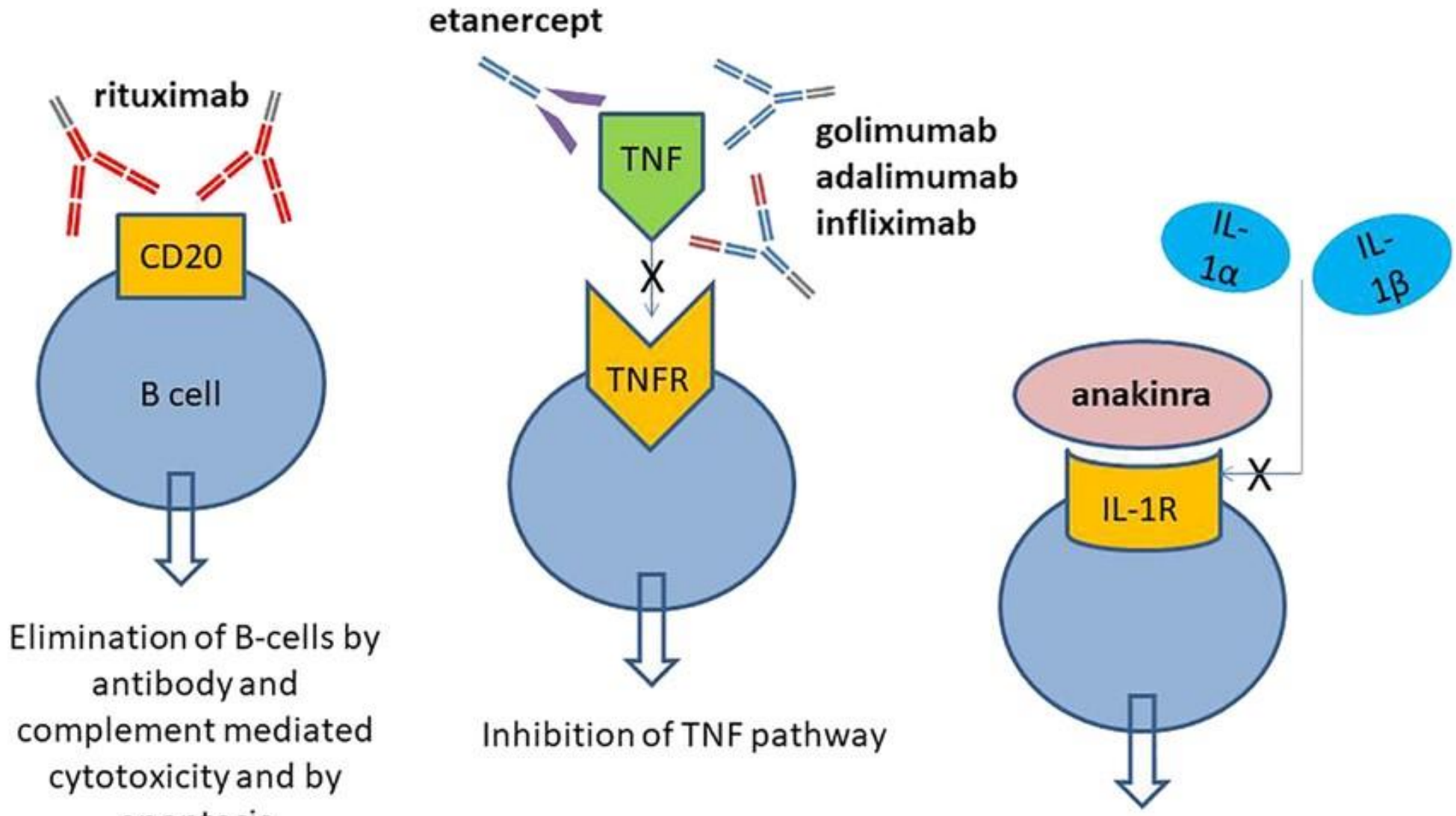

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TABLE 1. CURRENT AND EMERGING BIOLOGIC AGENTS FOR THE TREATMENT OF PSORIASIS.[1,5-7]

Drug	Target	Mechanism of Action	FDA Approval Status in PsO
Etanercept	TNF-α	TNF-α receptor IgG1 fusion protein that binds to soluble TNF-α	Approved 2004 Approved 2016 for patients 4 years of age and older
Infliximab	TNF-α	Chimeric monoclonal antibody that binds to both soluble and membrane-bound TNF-α	Approved 2006
Adalimumab	TNF-α	Human monoclonal antibody that binds to both soluble and membrane-bound TNF-α	Approved 2008
Ustekinumab	IL-12/IL- 23 p40	Human monoclonal antibody that binds to p40 subunit of IL-12 and IL-23	Approved 2009 Approved 2017 for patients 12 years of age and older
Secukinumab	IL-17A	Human monoclonal antibody that binds to IL-17A	Approved 2015
Ixekizumab	IL-17A	Humanized monoclonal antibody that binds to IL-17A	Approved 2016
Brodalumab	IL-17A receptor	Human monoclonal antibody prevents binding of IL-17A, IL-17F, and IL-25 to the shared IL-17RA receptor	Approved 2017
Guselkumab	IL-23 p19 subunit	Human monoclonal antibody binds selectively to the p19 subunit of IL-23 and inhibits its interaction with IL-23 receptor	Approved 2017
Tildrakizumab	IL-23 p19 subunit	Humanized monoclonal antibody binds selectively to the p19 subunit of IL-23 and inhibits its interaction with the IL-23 receptor	Approved 2018
Certolizumab pegol	TNF-α	Humanized monoclonal antibody that binds and neutralizes both soluble and transmembrane TNFα	Approved 2018
Risankizumab	IL-23 p19 subunit	Humanized monoclonal antibody binds selectively to the P19 subunit of IL-23 and inhibits its interaction with the IL-23 receptor	Approved 2019
Bimekizumab	IL-17A/F	Humanized monoclonal antibody neutralizes both IL-17A and IL-17F	Phase 3 trials ongoing
Mirikizumab	IL-23 p19 subunit	Humanized monoclonal antibody binds to p19 subunit of IL-23	Phase 3 trials ongoing
M1095	IL-17A/F	Anti-IL-17 A/F bispecific nanobody	Phase 1

PsO, psoriasis; TNF, tumor necrosis factor; IL, interleukin.

https://practicaldermatology.com/articles/2019-dec-supplement/mechanism-of-action-matters-a-review-of-new-and-emerging-biologics

Drug class	Agent	Target	Mode of delivery	Crohn's disease	Ulcerative colitis
JAK inhibitors	Tofacitinib	JAK1/JAK3	Oral	N/A	FDA approved
	Filgotinib	JAK1	Oral	Phase III recruiting	Phase IIb/III completed
	Upadacitinib	JAK1	Oral	Phase III recruiting	Phase III recruiting
	TD-1473	Pan-JAK (gut selective)	Oral	Phase II recruiting	Phase IIb/III recruiting
	Brepocitinib (PF-06700841)	TYK2/JAK1	Oral	Phase IIa recruiting	Phase IIb recruiting
	PF-06651600	JAK3	Oral		
	BMS-986165	TYK2	Oral	Phase II recruiting	Phase II recruiting
Anti-trafficking therapies	Vedolizumab SC	α4β7 integrin	SC	N/A	Phase III completed
	Etrolizumab	α4β7 and αEβ7 integrins	SC	Phase III recruiting	Phase III completed
	AJM300	α4 integrin	Oral	N/A	Phase III recruiting
	PF-00547659	MAdCAM	SC	Phase II completed	Phase II completed
IL-23 inhibitors	Risankizumab	IL23/p19 subunit	IV, SC	Phase III active, not recruiting	Phase III enrolling by invitation
	Brazikumab	IL23/p19 subunit	IV, SC	Phase IIb/III recruiting	Phase 2/OLE enrolling by invitation
	Mirikizumab	IL23/p19 subunit	IV, SC	Phase III recruiting	Phase III recruiting
	Guselkumab	IL23/p19 subunit	IV, SC	Phase II/III recruiting	Phase II/III recruiting
S1P receptor modulators	Ozanimod	S1PR1 and S1PR5	Oral	Phase III recruiting	Phase III completed
	Etrasimod	S1PR1, S1PR4 and S1PR5	Oral	Phase II/III recruiting	Phase III recruiting
	Amiselimod (MT-1303)	S1PR1	Oral	Phase II completed	N/A
PDE4 inhibitors	Apremilast	PDE4	Oral	N/A	Phase II completed
TLR9 agonist	Cobitolimod	TLR9	Topical (enema)	N/A	Phase IIb completed, Phase III planned

JAK, janus kinase; TYK 2, tyrosine kinase 2; S1P, sphingosine 1 phosphate; S1PR sphingosine 1 phosphate receptor; PDE4, phosphodiesterase 4; TLR9, toll-like receptor 9; α4β7, alpha4-beta7; αEβ7, alphaE-beta7; α4, alpha4; MAdCAM, mucosal addressin cell adhesion molecule-1; IL-23, interleukin 23; IV, intravenous; SC, subcutaneous; OLE, open label extension.

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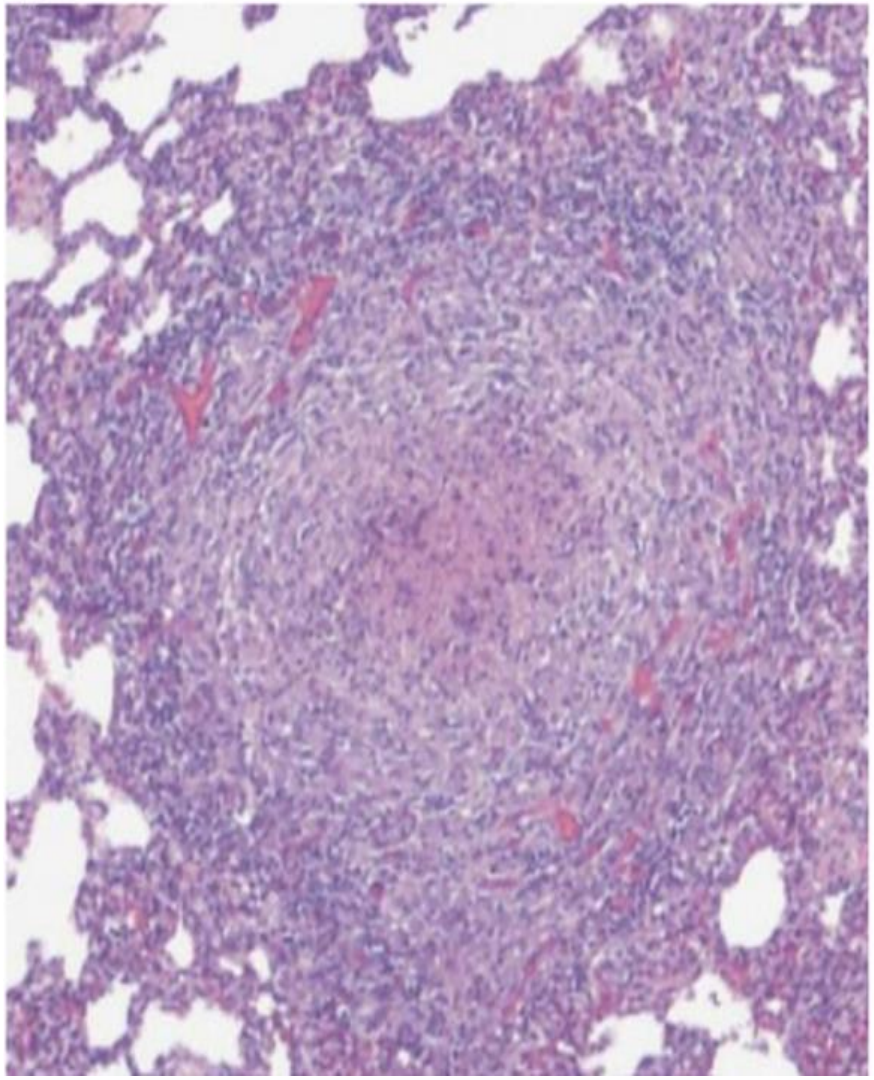
The Role of Cytokines in TB

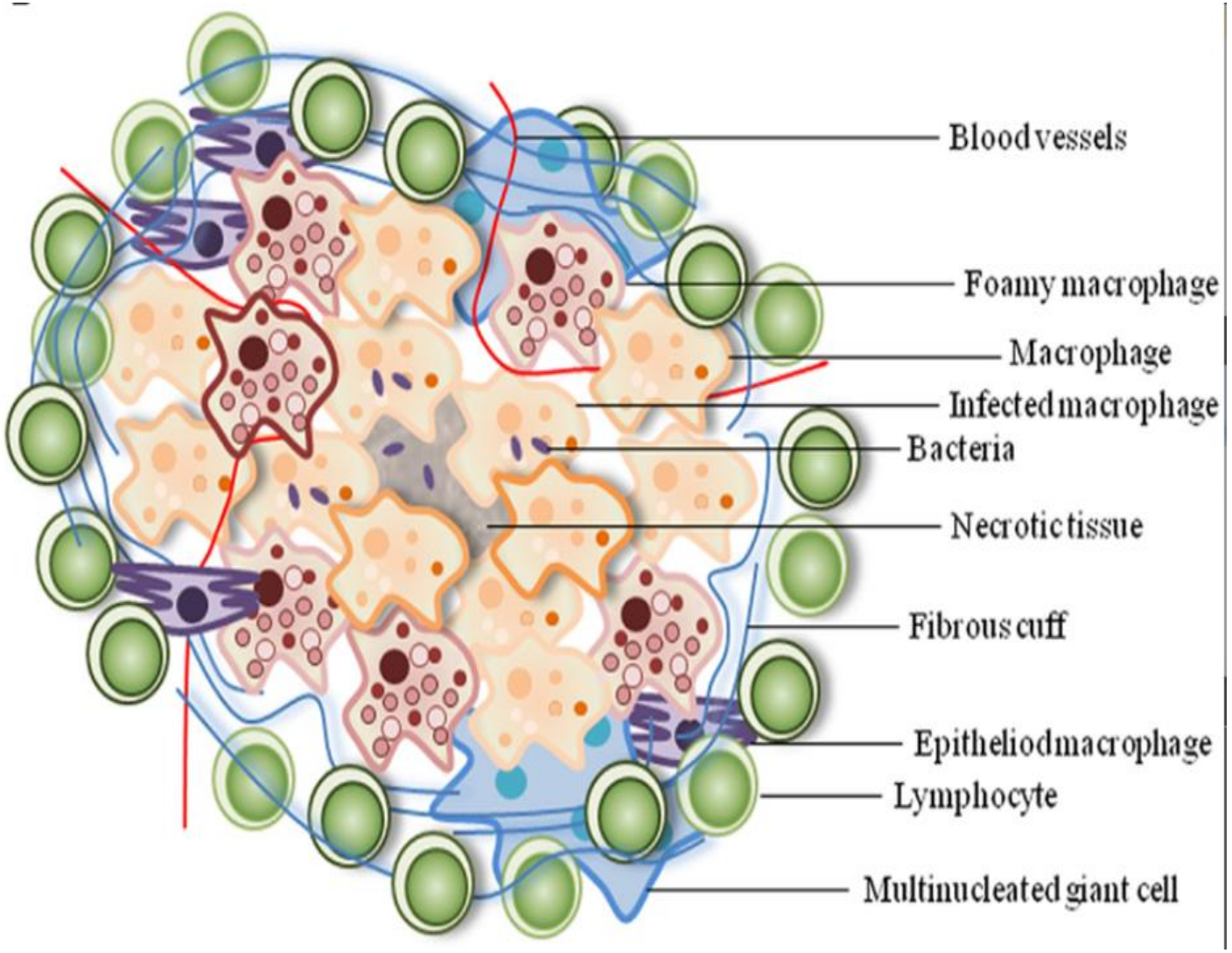
The positive and negative roles of cytokines in TB

TNFα	TNFR1, TNFR2 JNK, p38, NFκB	**Positive:** Essential for survival following Mtb infection. Initiation of innate cytokine and chemokine response and phagocyte activation **Negative:** Mediator of tissue damage
IFNγ	IFNGR1, IFNGR2 JAK/STAT	**Positive:** Essential for survival following Mtb infection. Coordinates and maintains mononuclear inflammation. Expressed by antigen specific T cells **Negative:** Potentially pathogenic
IFNα/IFNβ	IFNAR1, IFNAR2 JAK,TYK, ISG,ISRE	**Positive:** Required for initial recruitment of phagocytes to the lung **Negative:** Over expression of IFNα/IFNβ results in recruitment of permissive phagocytes and regulation of T cell accumulation and function
IL-6	IL-6R, gp130 JAK, STAT3, MAPK	**Positive:** Potentiates early immunity – non essential unless a high dose infection.
IL-1α/IL-1β	IL-1R1, IL1RAcP MyD88,IRAK4,NFκB	**Positive:** Essential for survival following Mtb infection. Induction of IL-17. Promotes PGE2 to limit Type I IFN
IL-18	IL-18Rα, IL-18Rβ MyD88,IRAK, NFκB	**Positive:** May augment IFNγ – non-essential. Regulator of neutrophil/monocyte accumulation. of neutrophil and monocyte accumulation, optimal induction of IFNγ by T-cells
IL-12 p40,p35	12Rβ1, IL-12Rβ2 JAK2, TYK2, STAT4	**Positive:** IL-12p40 and IL-12p35 essential for survival following Mtb infection. Mediate early T cell activation, polarization and survival. **Negative:** Over expression of IL-12p70 is toxic during Mtb infection.
IL-23 p40,p19	IL-23R, IL-12Rβ1 JAK2, TYK2, STAT3	**Positive:** Required for IL-17 and IL-22 expression during Mtb infection. Non-essential in low dose challenge required for long term control. **Negative:** Mediates increased pathology during chronic challenge
IL-27 EBI3,p28	IL-27Rα, gp130 JAK1/2,TYK2,STAT1/3	**Positive:** May control inflammation and reduce pathology **Negative:** Regulates protective immunity to Mtb infection by limiting the migration and survival of T cells at the inflamed site.
IL-35 p35,EBI3	IL-12Rβ2,gp130 STAT1/4	**Positive?** Regulate the availability of subunits of IL-12, IL-27 **Negative?** Potential immunoregulatory role.
IL-17A/F	IL-17RC, IL-17RA	**Positive:** Essential for survival following infection with some strains of Mtb. Induction and maintenance of chemokine gradients for T cell migration. **Negative:** Drives pathology via S100A8/A9 and neutrophils
IL-22	IL-22R1, IL-10R2 TYK2,JAK1,STAT3	**Positive:** Induces antimicrobial peptides and promotes epithelial repair, inhibits intracellular growth of Mtb in macrophages.

Let’s focus on the role of TNF-α in Tuberculosis

- TNFα is responsible for the proliferation and differentiation of immune cells as well as their migration
- Phagocytes in the lung and the invading Mtb, results in the production of multiple proinflammatory cytokines, including TNFα
- As infection progresses, TNFα plays a role in coordinating the chemokine response within the lung and in **facilitating the development of the granuloma**





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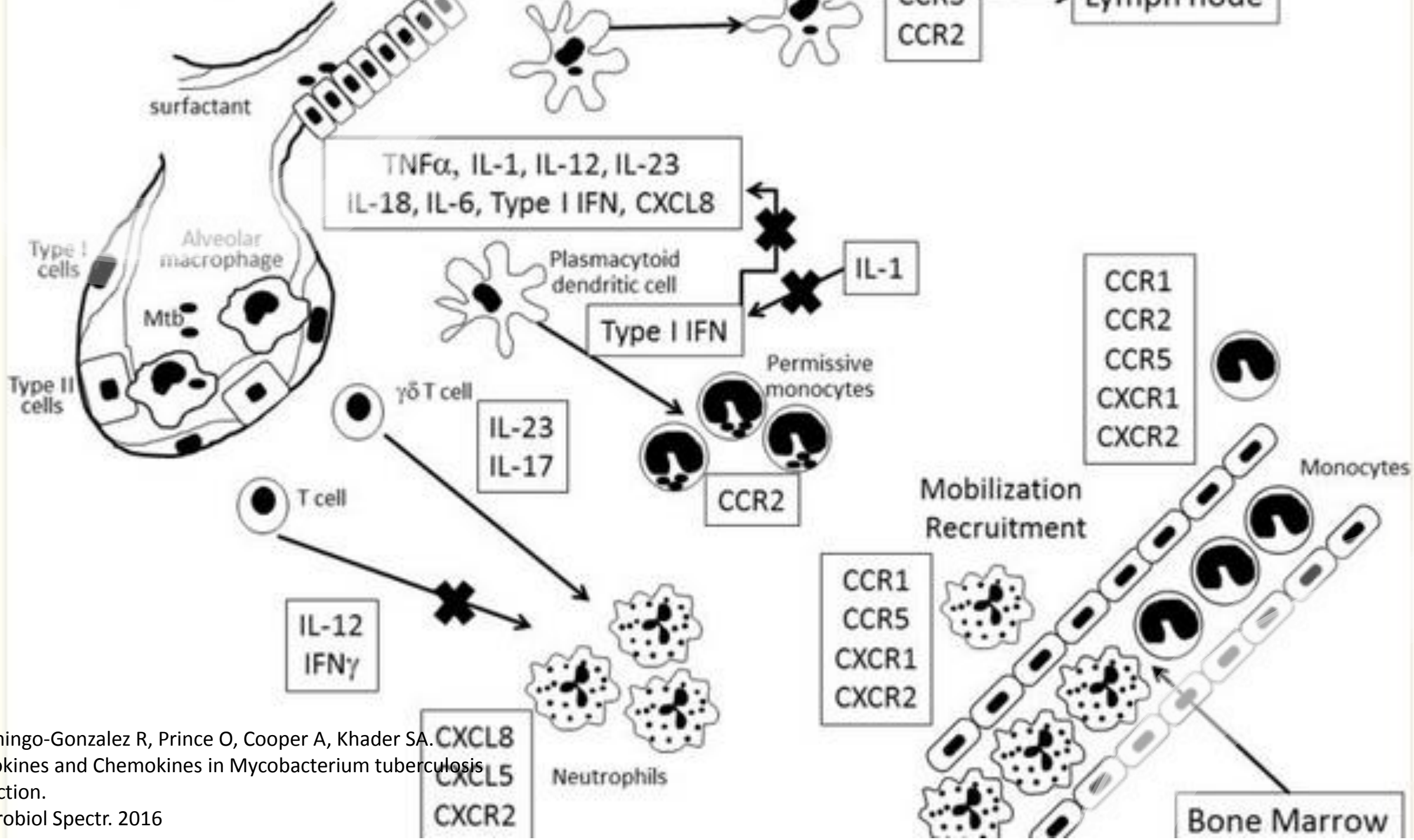

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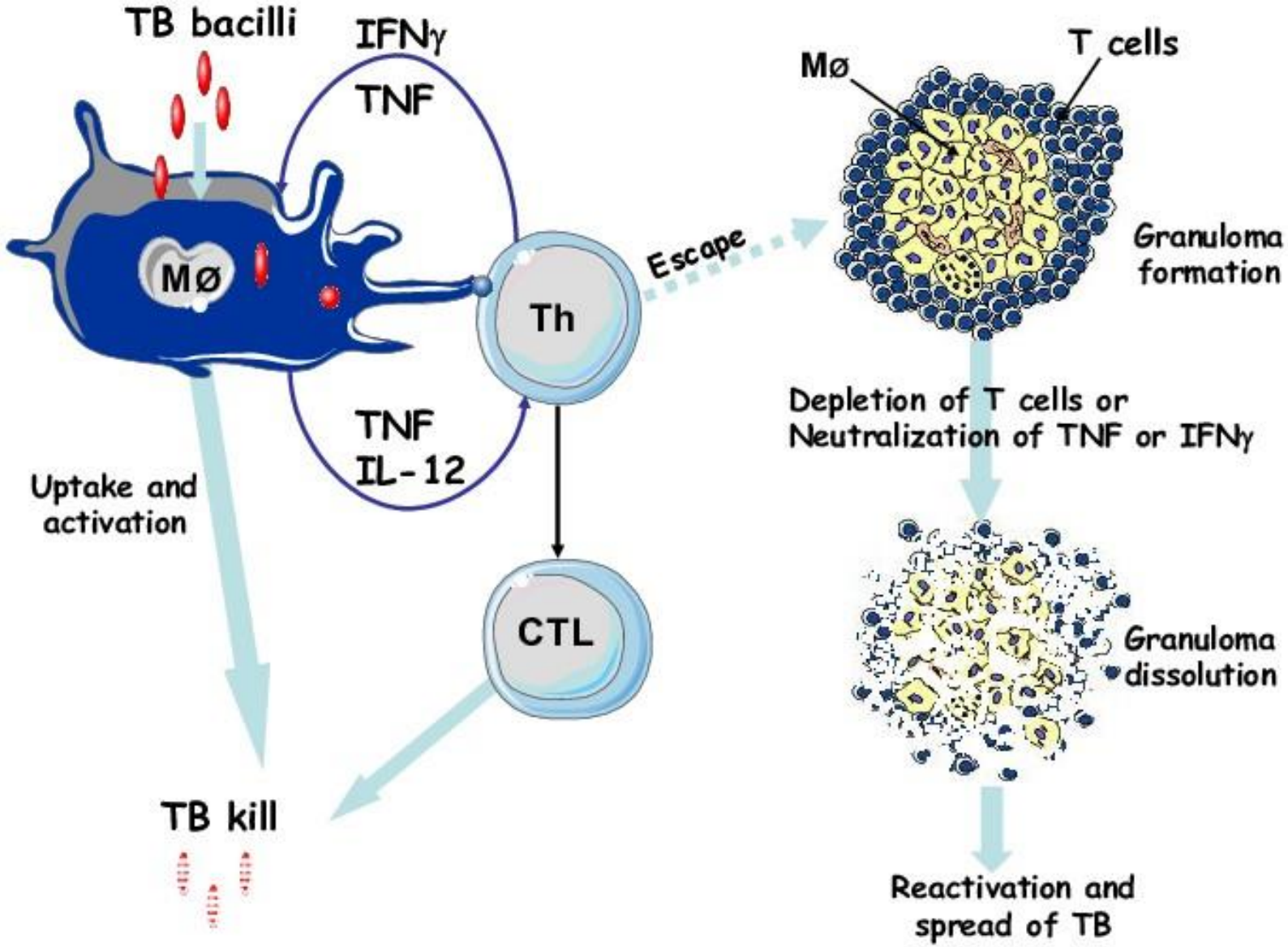

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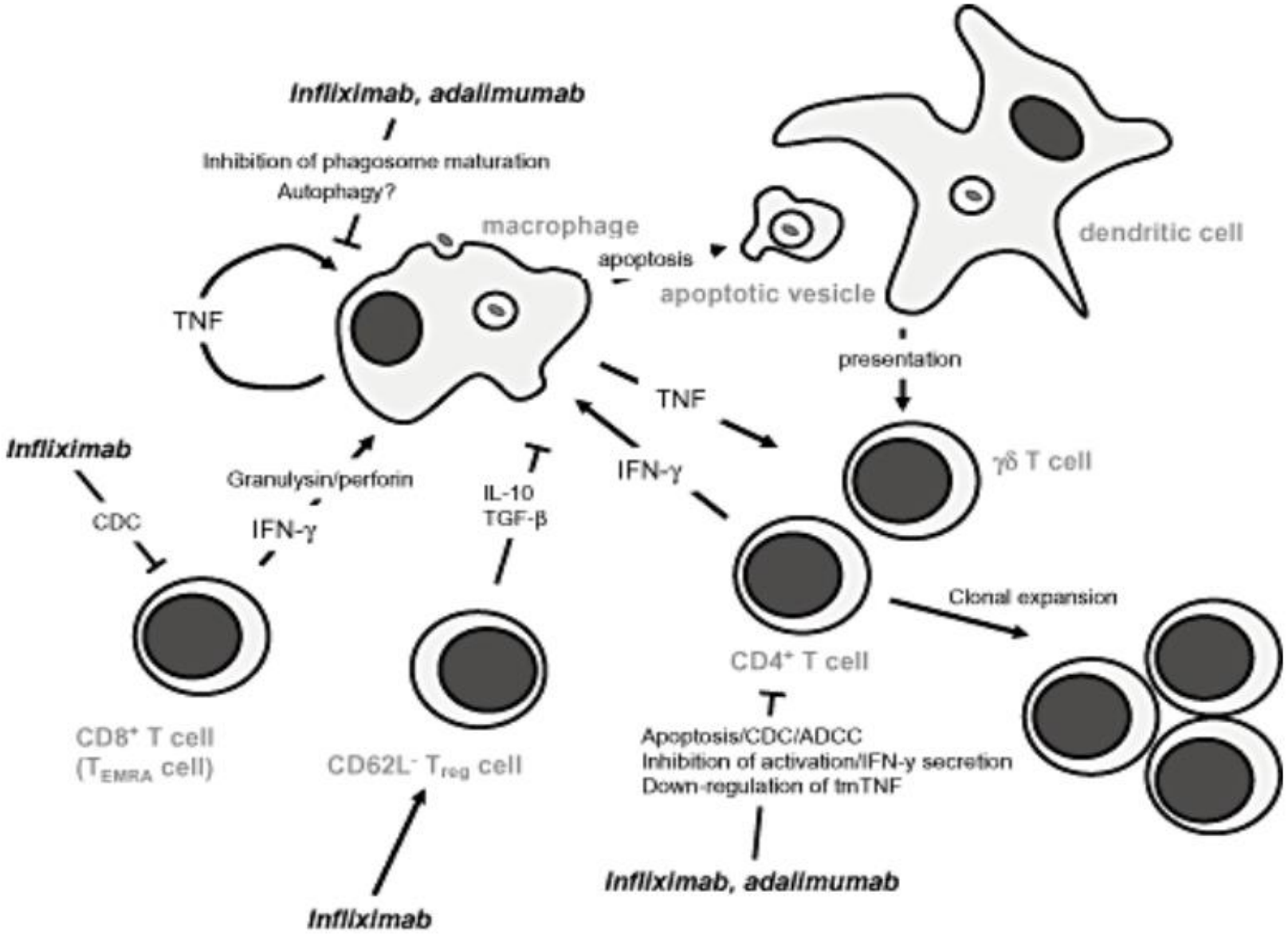

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TABLE 1 Drug-specific RR of TB

Biologic	FDA-approved indications (as of 1 November 2016)[a]	RR of TB compared to that in the general population
Adalimumab	AS, JIA, RA, Ps, PsA, Crohn's, UC	29.3 (95% CI, 20.3–42.4) (3) based on SIR (standardized for age and sex)
Infliximab	AS, RA, Ps, PsA, Crohn's, UC	18.6 (95% CI, 13.4–25.8) (3) based on SIR (standardized for age and sex)
Etanercept	AS, JIA, RA, Ps, PsA	1.8 (95% CI, 0.7–4.3) (3) based on SIR (standardized for age and sex) 3.5
Certolizumab pegol	AS, RA, PsA, Crohn's	No definite increase in RR in pooled data from RCTs (4)
Golimumab	AS, RA, PsA, UC	No definite increase in RR in pooled data from RCTs (5)
Rituximab	Chronic lymphocytic leukemia, non-Hodgkin lymphomas, granulomatosis with polyangiitis, microscopic polyangiitis, RA	No definite increase in RR in pooled data from RCTs (6)
Tocilizumab	JIA, RA	No definite increase in RR in pooled data from RCTs (7)
Vedolizumab	UC, Crohn's	No definite increase in RR from drug safety data (8)
Ustekinumab	Ps, PsA, Crohn's	No definite increase in RR from drug safety data (9) First choice in patients with PsA at high infection and TB risk (10)
Abatacept	JIA, RA	No definite increase in RR in pooled data from RCTs (6)

[a]AS, ankylosing spondylitis; Crohn's, Crohn's disease; JIA, juvenile idiopathic arthritis; Ps, plaque psoriasis; PsA, psoriatric arthritis; RA, rheumatoid arthritis; RCTs, randomized controlled trials; UC, ulcerative colitis.

Does treating for LTBI in these cases really help? YES

- **Carmona L, et al.** 2005.
  - Decrease in active TB disease rates by 78%

- **Liao TL, et al. 2016**
  - Incidence of TB in patients on anti-TNF-α treatment who HAD received LTBI treatment vs. incidence of TB in patients on anti-TNF-α treatment who HAD NOT received LTBI treatment
  - Etanercept (0/487) and rituximab (0/60) who received LTBI treatment developed TB, vs. Etanercept (121/26,880) and rituximab (2/6,119) who did not receive LTBI treatment.
  - One patient on adalimumab who had received LTBI treatment (1/459) developed TB vs. 66 patients with TB out of 10,713 patients on adalimumab who had not received treatment for LTBI.

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When is it OK to start on anti-TNF-α Therapy after LTBI treatment has been started?

- Different organizations/societies say different things
- Most say no need to wait or wait one month
- I agree with the American College of Rheumatology: unless these biologics are urgently needed (which is very rare), **wait one month after LTBI treatment has been started**

Do we need to obtain TB testing yearly?

- All patients should be monitored for signs/symptoms of TB for at least 6 months post cessation of anti-TNF-α therapy.
- No need to perform routine CXRs while on therapy (for those with an initial normal CXR)
- American College of Rheumatology (ACR) and CDC recommend yearly IGRA or TST only for those patients who have risk factors
  - Close contacts of persons known or suspected to have active tuberculosis
  - Foreign-born persons from areas that have a high incidence of active tuberculosis (e.g., Africa, Asia, Eastern Europe, Latin America, and Russia)
  - Persons who visit areas with a high prevalence of active tuberculosis, especially if visits are frequent or prolonged
  - Residents and employees of congregate settings whose clients are at increased risk for active tuberculosis (e.g., correctional facilities, long-term care facilities, and homeless shelters)
  - Health-care workers who serve clients who are at increased risk for active tuberculosis
  - Populations defined locally as having an increased incidence of latent *M. tuberculosis* infection or active tuberculosis, possibly including medically underserved, low-income populations, or persons who abuse drugs or alcohol
  - Infants, children, and adolescents exposed to adults who are at increased risk for latent *M. tuberculosis* infection or active tuberculosis.

For patients on TB disease therapy, how long should I wait until I start the biologic?

- No consensus here
- Many would say to wait to start the biologic until TB disease therapy has been completed

In summary…

- Risk of TB reactivation varies with biologic agent/drug
- Highest risk is with anti-TNF-α treatment (specifically, infliximab and adalimumab)
- Risks of other biologics (including Janus Kinase inhibitors) is unclear, so look at package insert and follow those recommendations
- Until we know more, any patient that is starting on a biologic and janus kinase inhibitor should be screened for TB disease and treated for latent TB infection (if applicable)

Questions??

- Contact Info
  - Mahesh C Patel, MD
  - Email: mp3@uic.edu