Casual Friday Series

RA and the Debilitated Patient

A Biogenetix Clinical Presentation

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- *Information in this presentation is not intended, in itself, to diagnose, treat, reverse, cure, or prevent any disease. While this presentation is based on medical literature, findings, and text, The following statements have not been evaluated by the FDA.*
- *The information provided in this presentation is for your consideration only as a practicing health care provider. Ultimately you are responsible for exercising professional judgment in the care of your own patients.*

Lifestyle + Genetics = Chronic Health Condition

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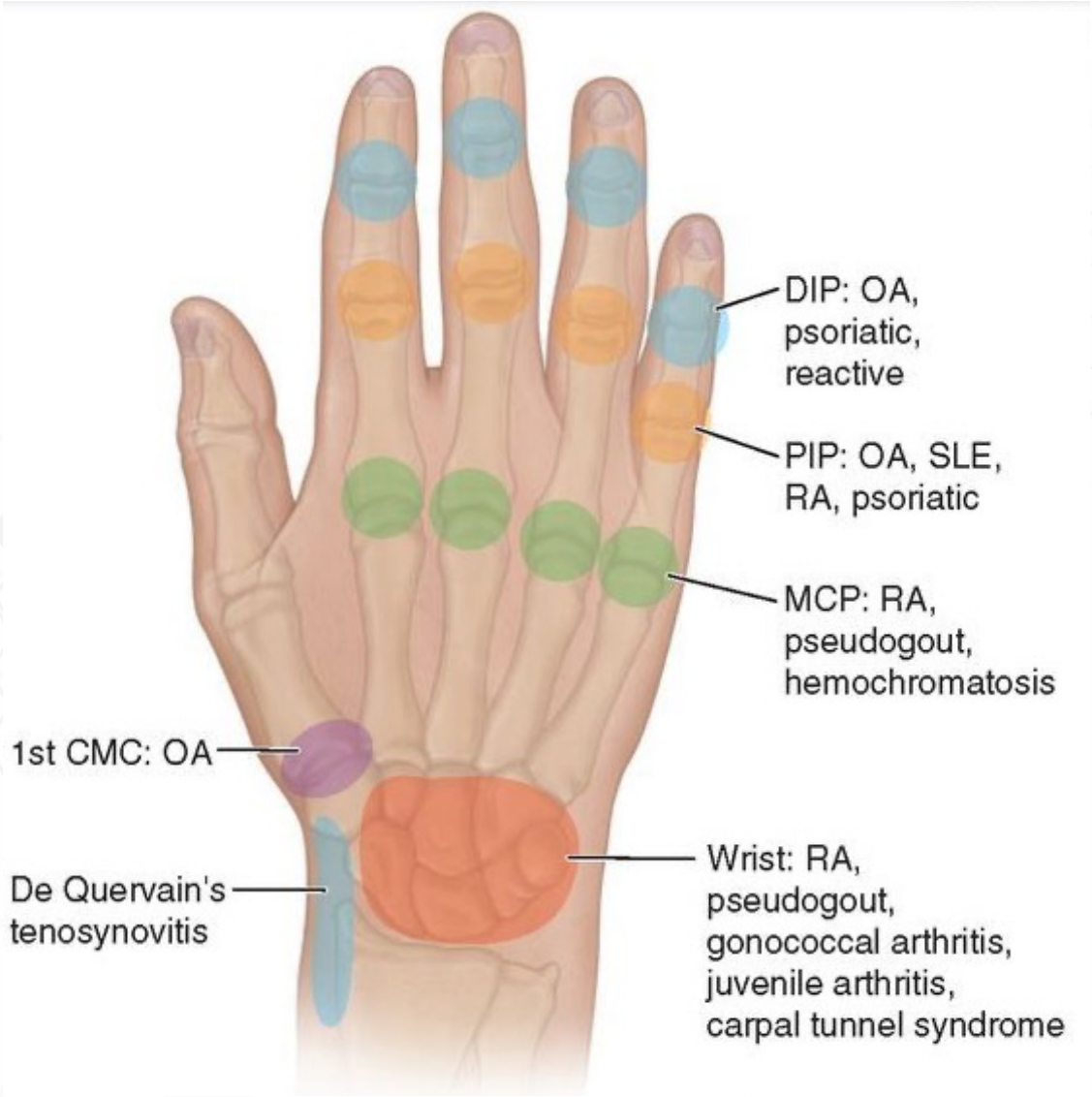
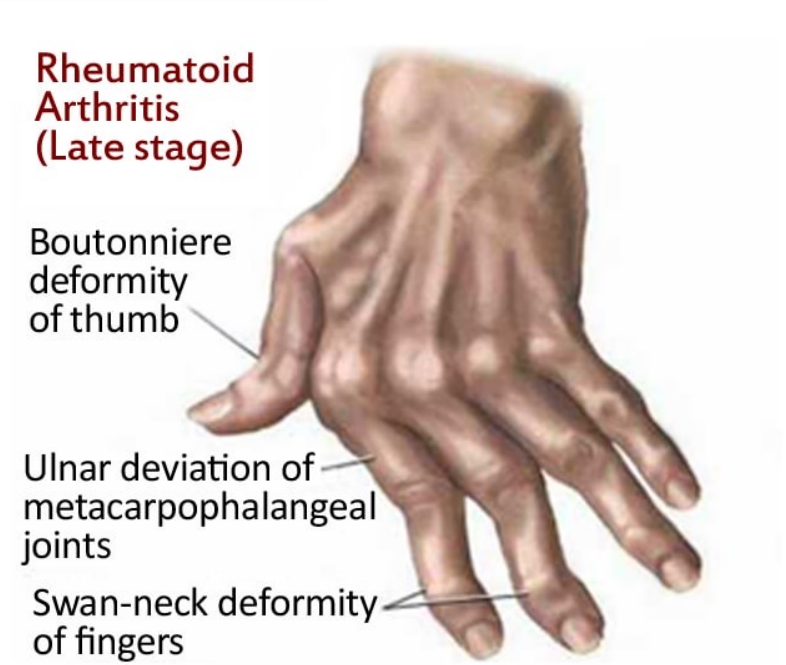
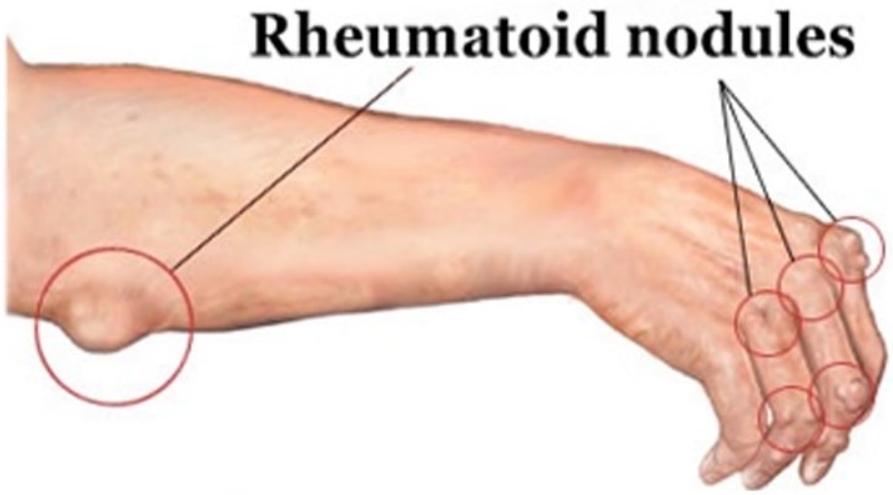
Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies

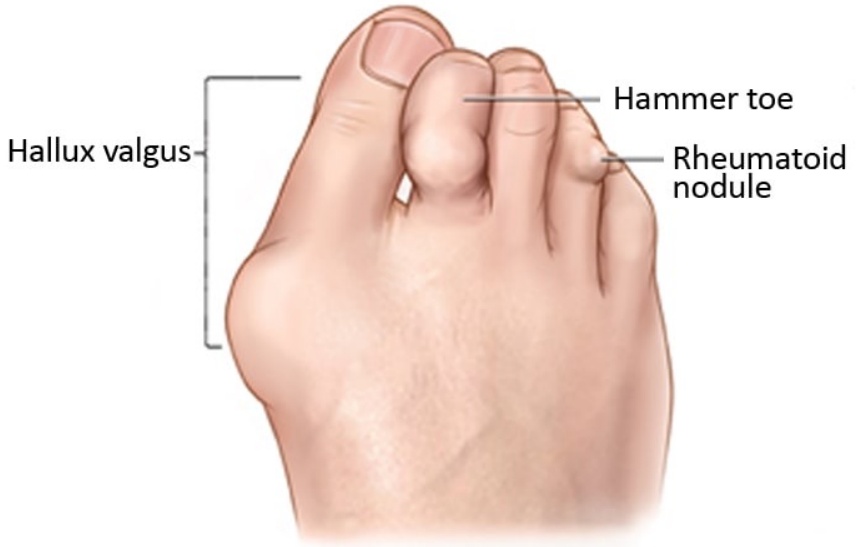
Qiang Guo,[1,2] Yuxiang Wang,[1] Dan Xu,[2,3] Johannes Nossent,[3,4] Nathan J. Pavlos,[2] and Jiake Xu[✉2]

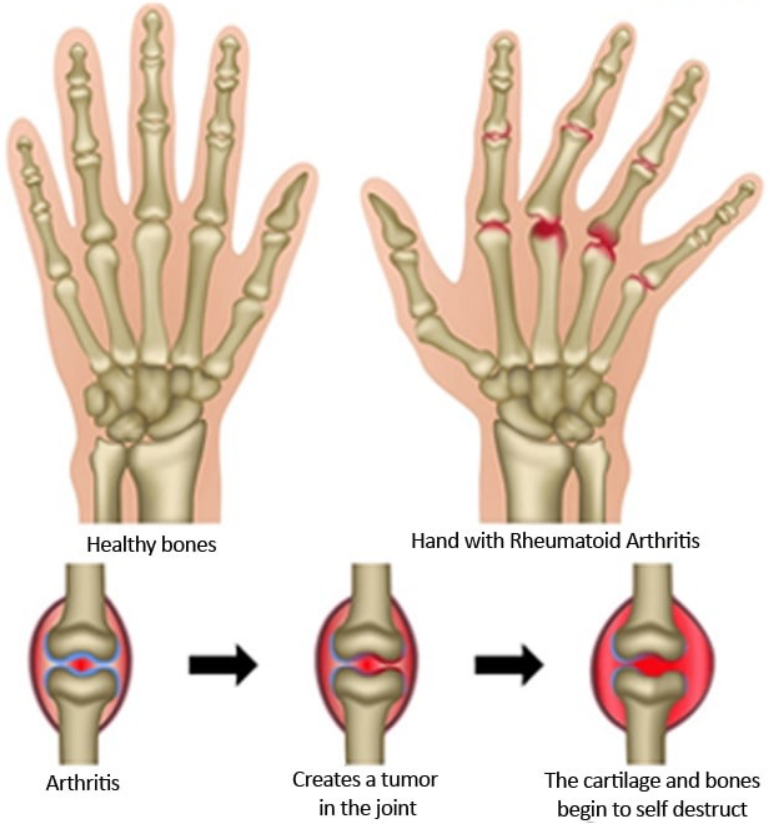
Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that primarily affects the lining of the synovial joints and is associated with progressive disability, premature death, and socioeconomic burdens. A better understanding of how the pathological mechanisms drive the deterioration of RA progress in individuals is urgently required in order to develop therapies that will effectively treat patients at each stage of the disease progress. Here we dissect the etiology and pathology at specific stages: (i) triggering, (ii) maturation, (iii) targeting, and (iv) fulminant stage, concomitant with hyperplastic synovium, cartilage damage, bone erosion, and systemic consequences. Modern pharmacologic therapies (including conventional, biological, and novel potential small molecule disease-modifying anti-rheumatic drugs) remain the mainstay of RA treatment and there has been significant progress toward achieving disease remission without joint deformity. Despite this, a significant proportion of RA patients do not effectively respond to the current therapies and thus new drugs are urgently required. This review discusses recent advances of our understanding of RA pathogenesis, disease modifying drugs, and provides perspectives on next generation therapeutics for RA.


DIP: OA, psoriatic, reactive
PIP: OA, SLE, RA, psoriatic
MCP: RA, pseudogout, hemochromatosis
1st CMC: OA
De Quervain's tenosynovitis
Wrist: RA, pseudogout, gonococcal arthritis, juvenile arthritis, carpal tunnel syndrome









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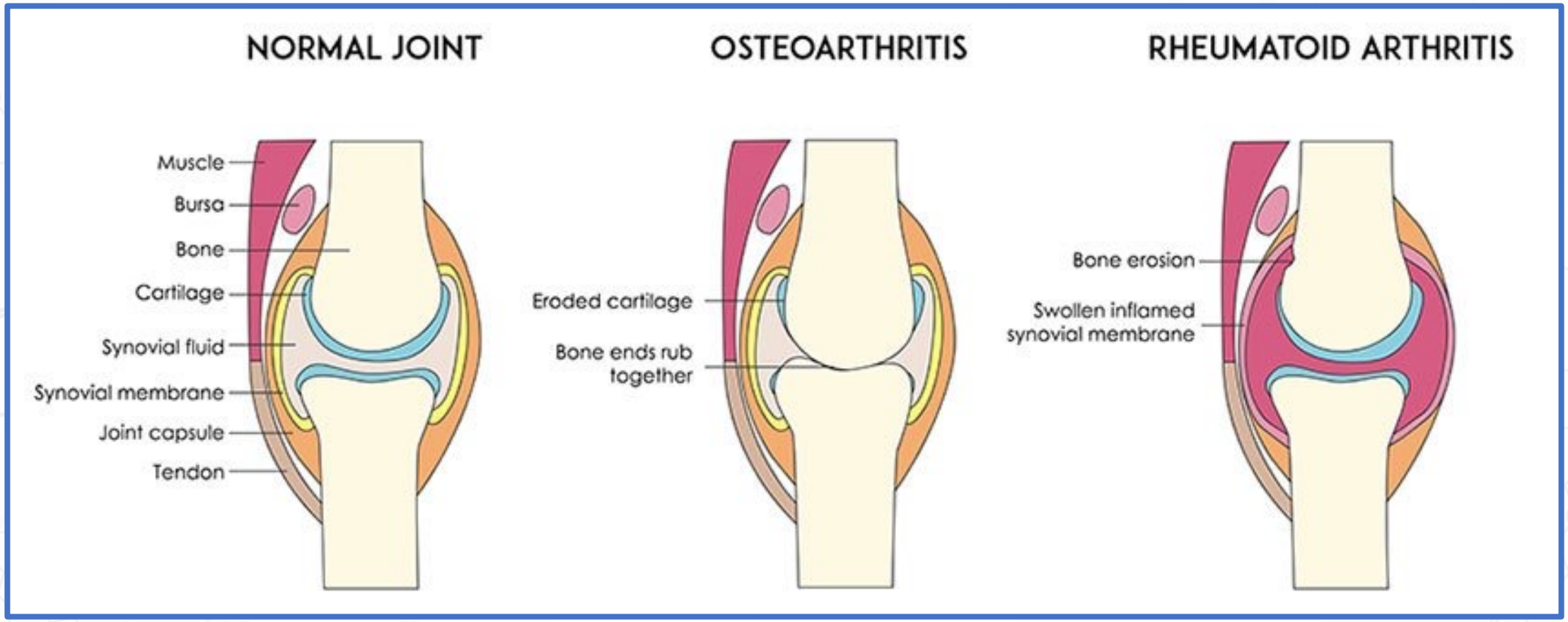

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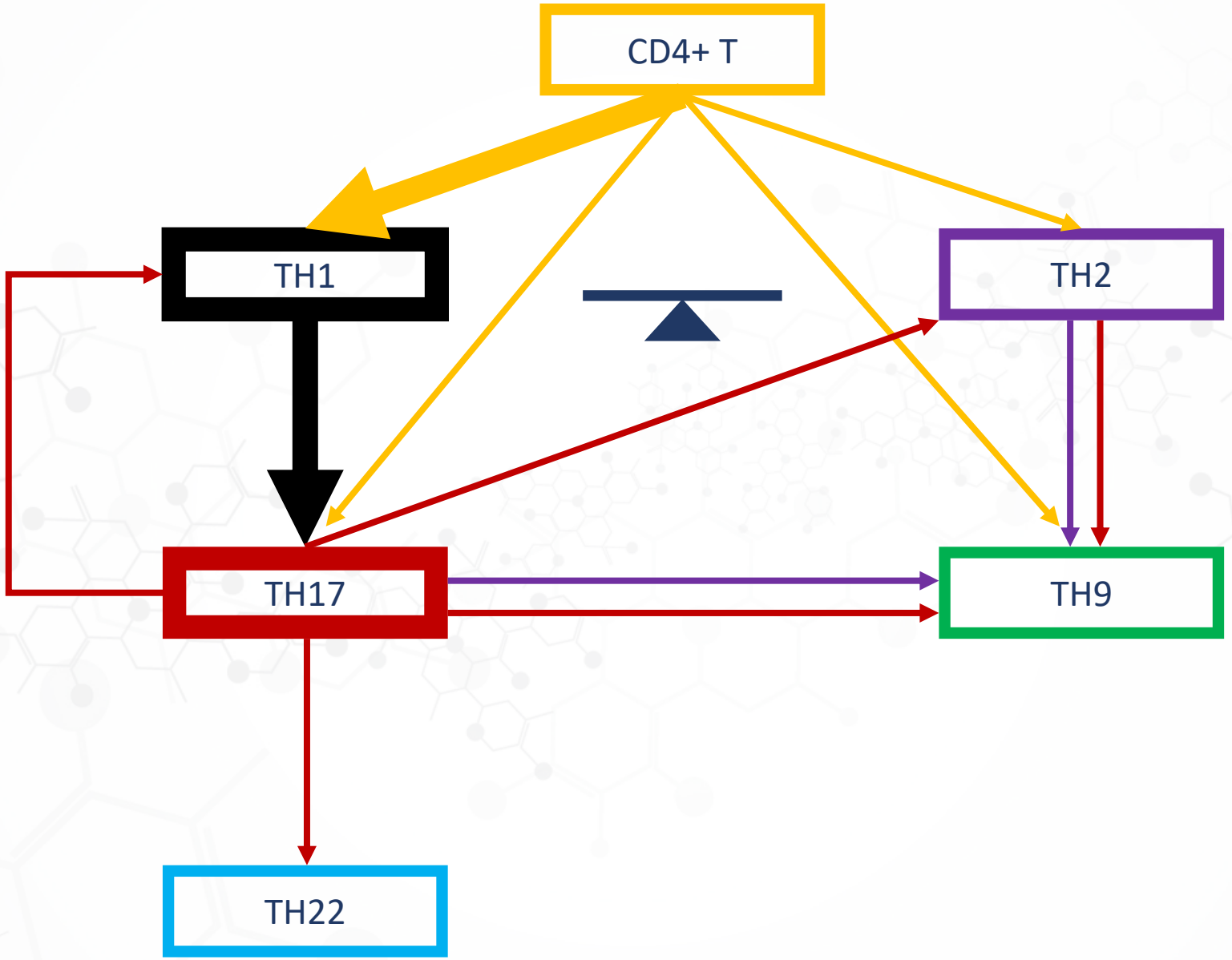
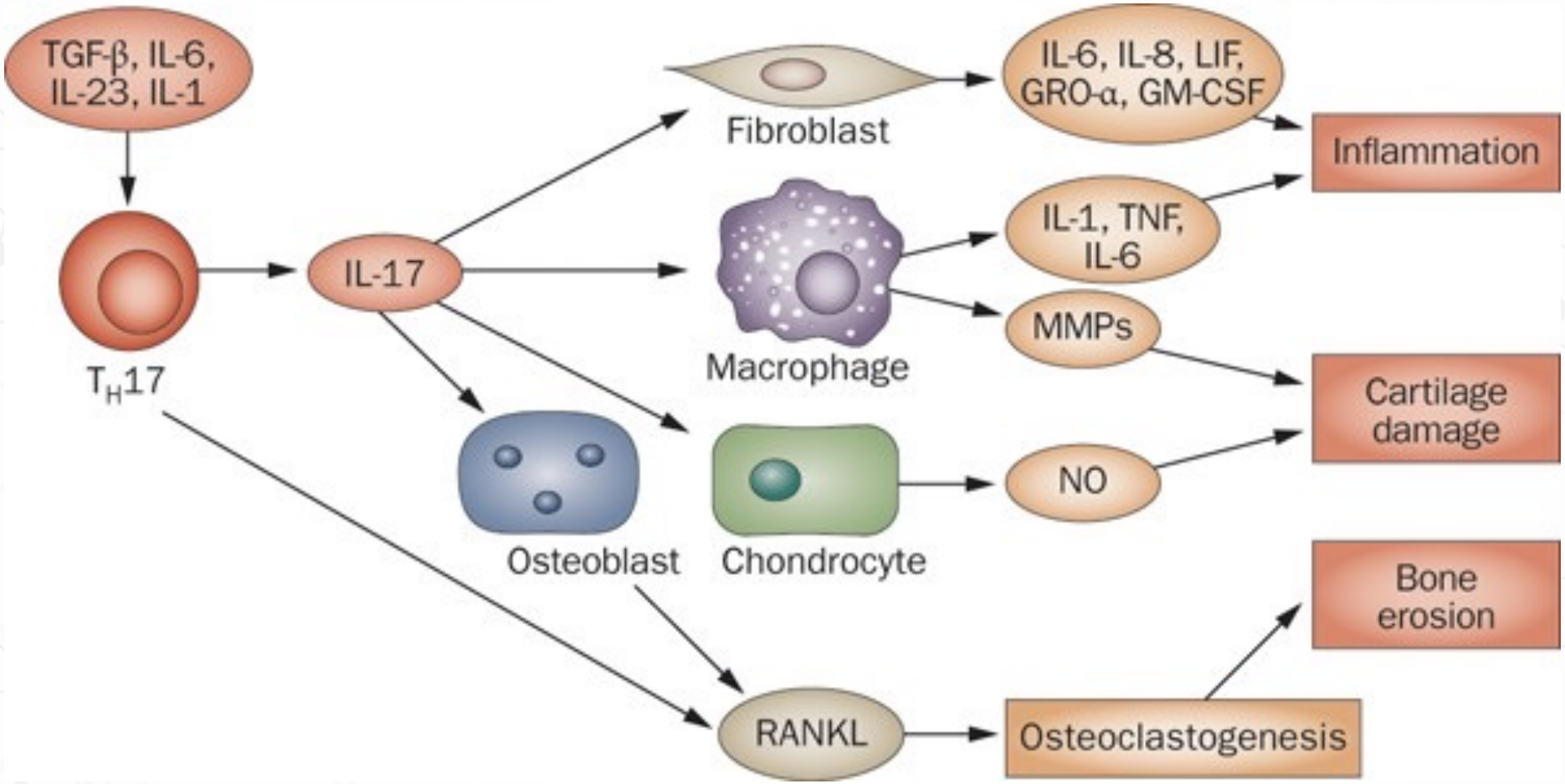

CD4+ T
TH1
TH2
TH17
TH9
TH22
(Dermatologic)



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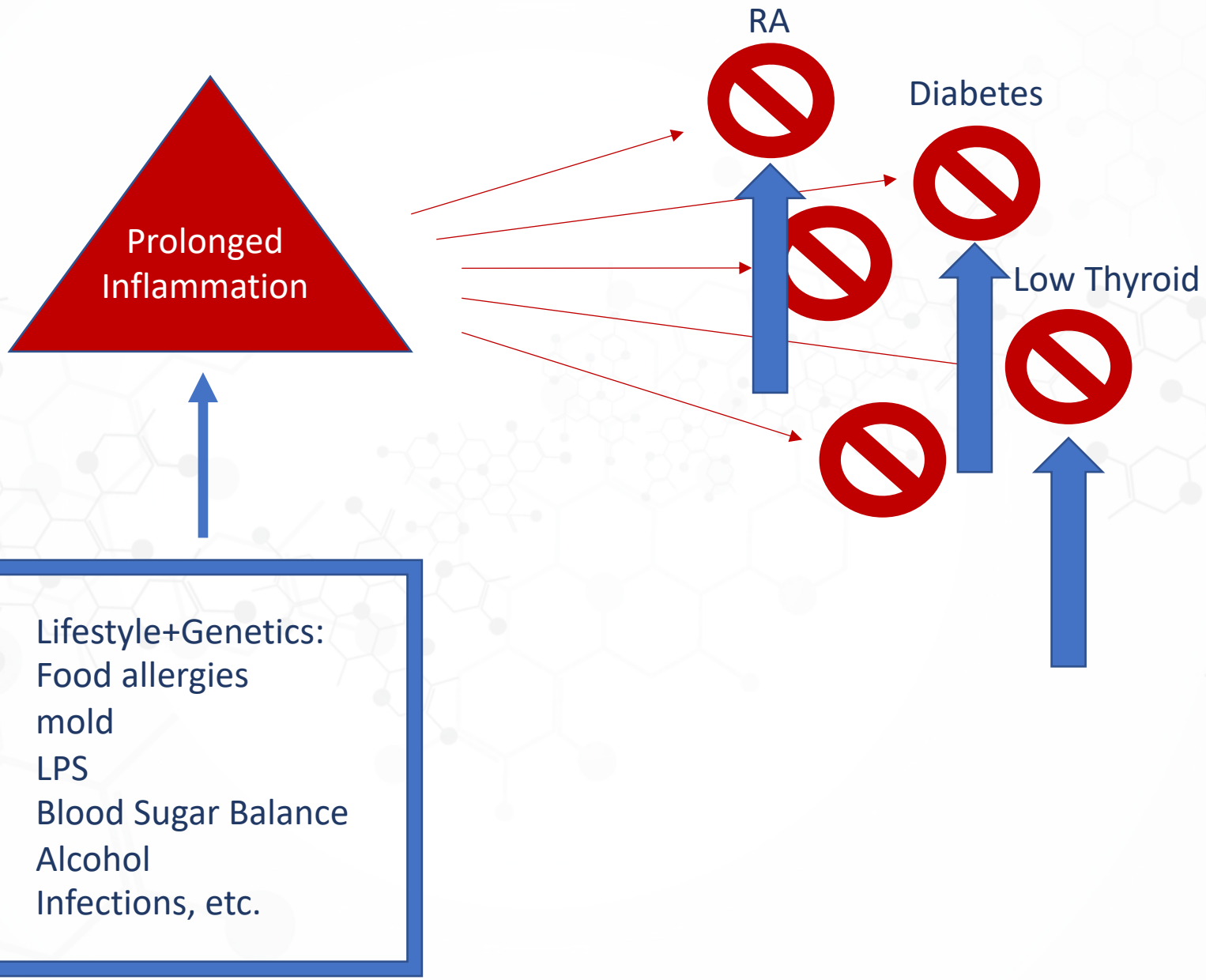
RA
Diabetes
Low Thyroid
Prolonged Inflammation
Lifestyle+Genetics:
Food allergies
mold
LPS
Blood Sugar Balance
Alcohol
Infections, etc.

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While there is currently no cure for RA, the treatment strategy aims to expedite diagnosis and rapidly achieve a low disease activity state (LDAS). There are many composite scales measuring the disease activity such as the Disease Activity Score using 28 joints (DAS-28), Simplified Disease Activity Assessment Index (SDAI), and Clinical Disease Assessment Index (CDAI).[6] To achieve full suppression of the activity of the disease (clinical remission), rheumatologists need to monitor disease activity continuously and accurately and to adjust the treatment regimen accordingly. Universally applied pharmacologic therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids have proven effective in relieving stiffness and pain, but do not moderate disease progression. Over the last 20 years, the effectiveness of DMARDs has gained much attention as these can efficiently attenuate disease activity and substantially decrease and/or delay joint deformity.[7] The therapy classification includes the traditional synthetic drugs, biological DMARDs, and novel potential small molecules. Historical DMARDs such as auranofin, minocycline, azathioprine, and cyclosporine are rarely implemented as modern therapies. Several biological DMARDs have recently emerged including TNF-inhibitor (Amjevita, Renflexis, Erelzi, Cyltezo, Imradl), anti-CD20 antibody (Truxima, Rixathon), IL-6 receptor antibody (Kevzara), RANKL antibody (Pralia), and JAK inhibitor (Olumiant). Despite the increasing number of new drugs and treatment regimes, complete long-term disease remission is not achieved for many patients and thus new therapeutic options are required. This review provides a contemporary appraisal of recent literature on the pathogenesis of RA and the potential of new pharmacological interventions for optimizing RA treatment regimes.

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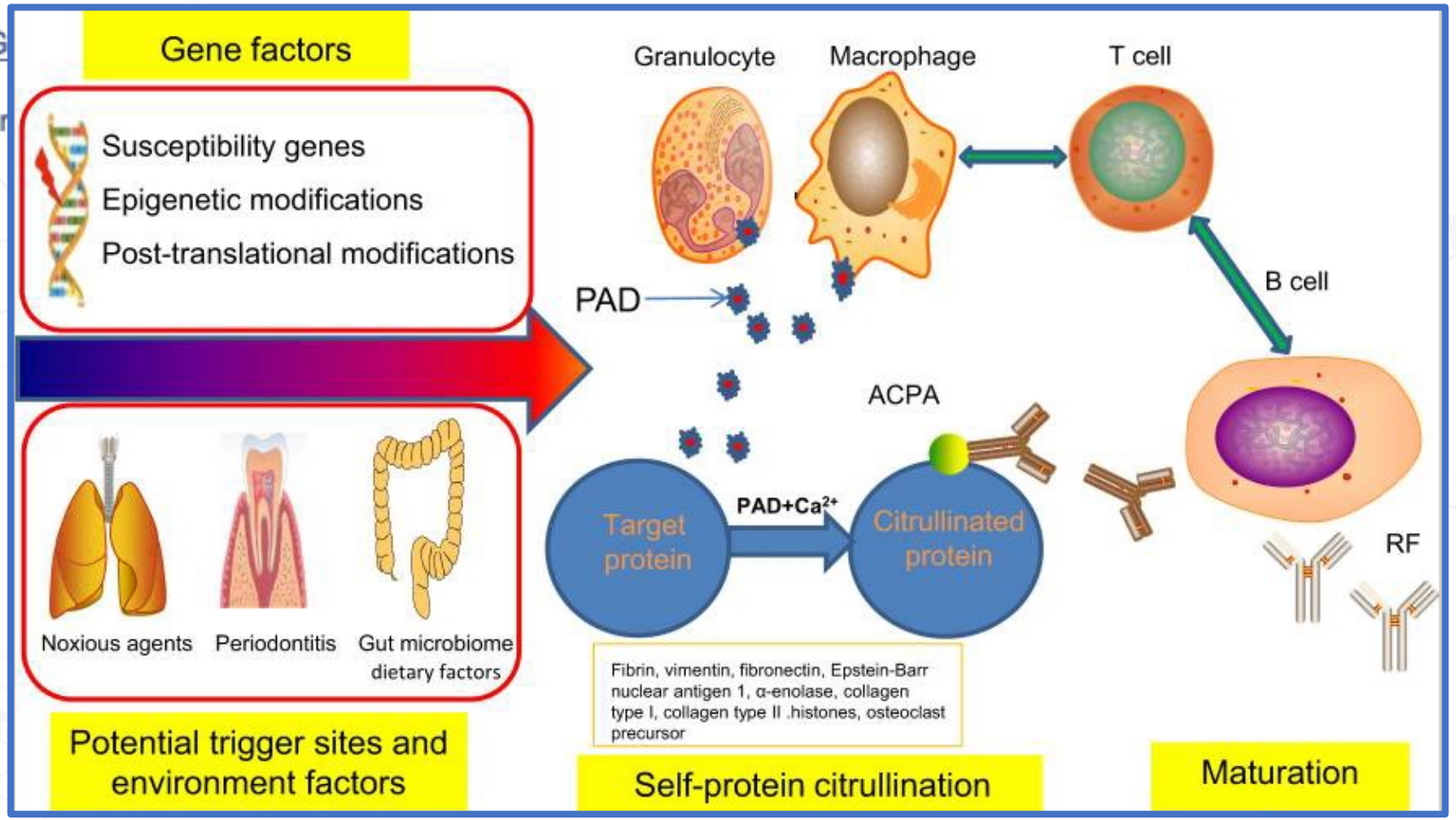

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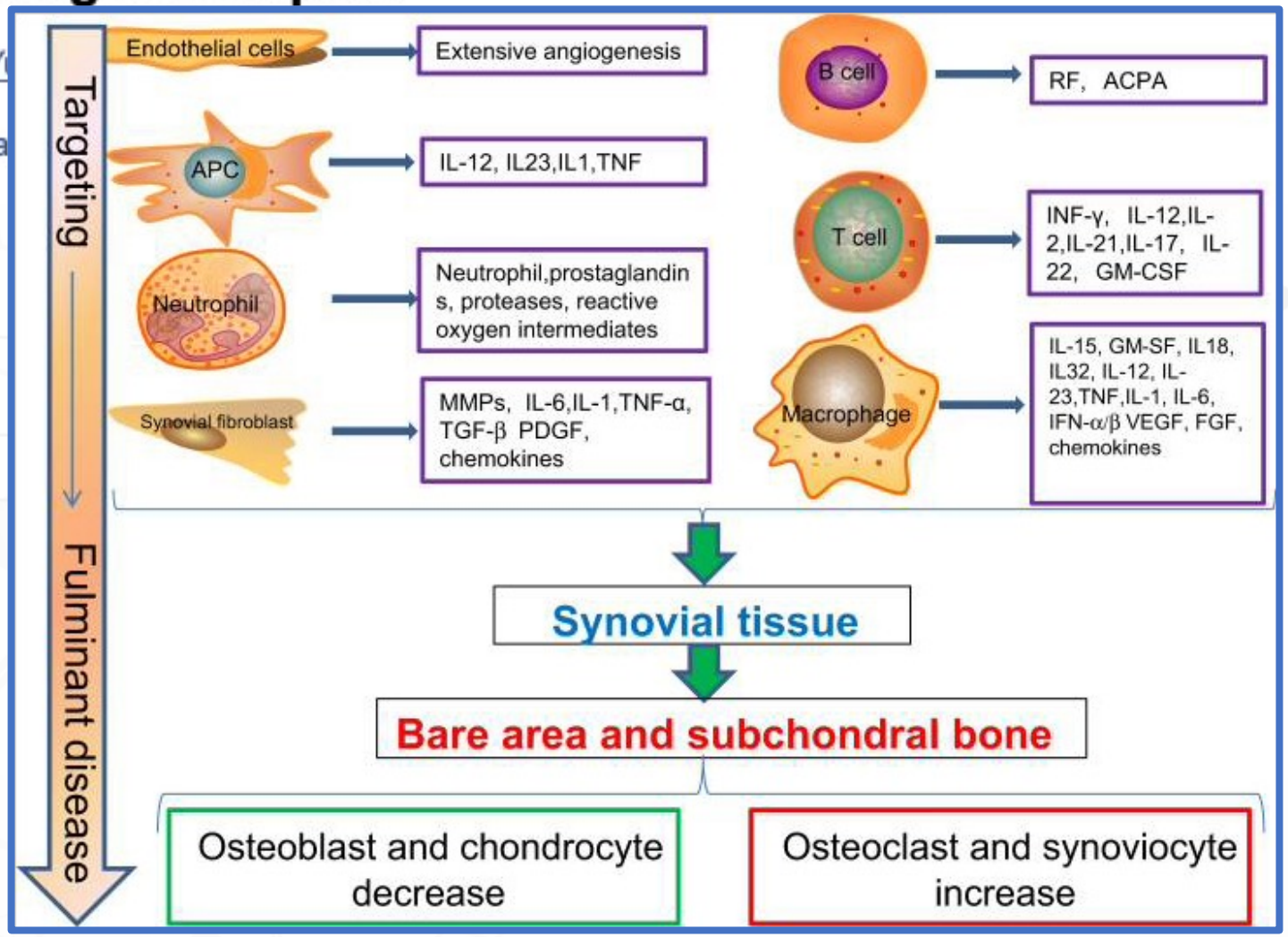
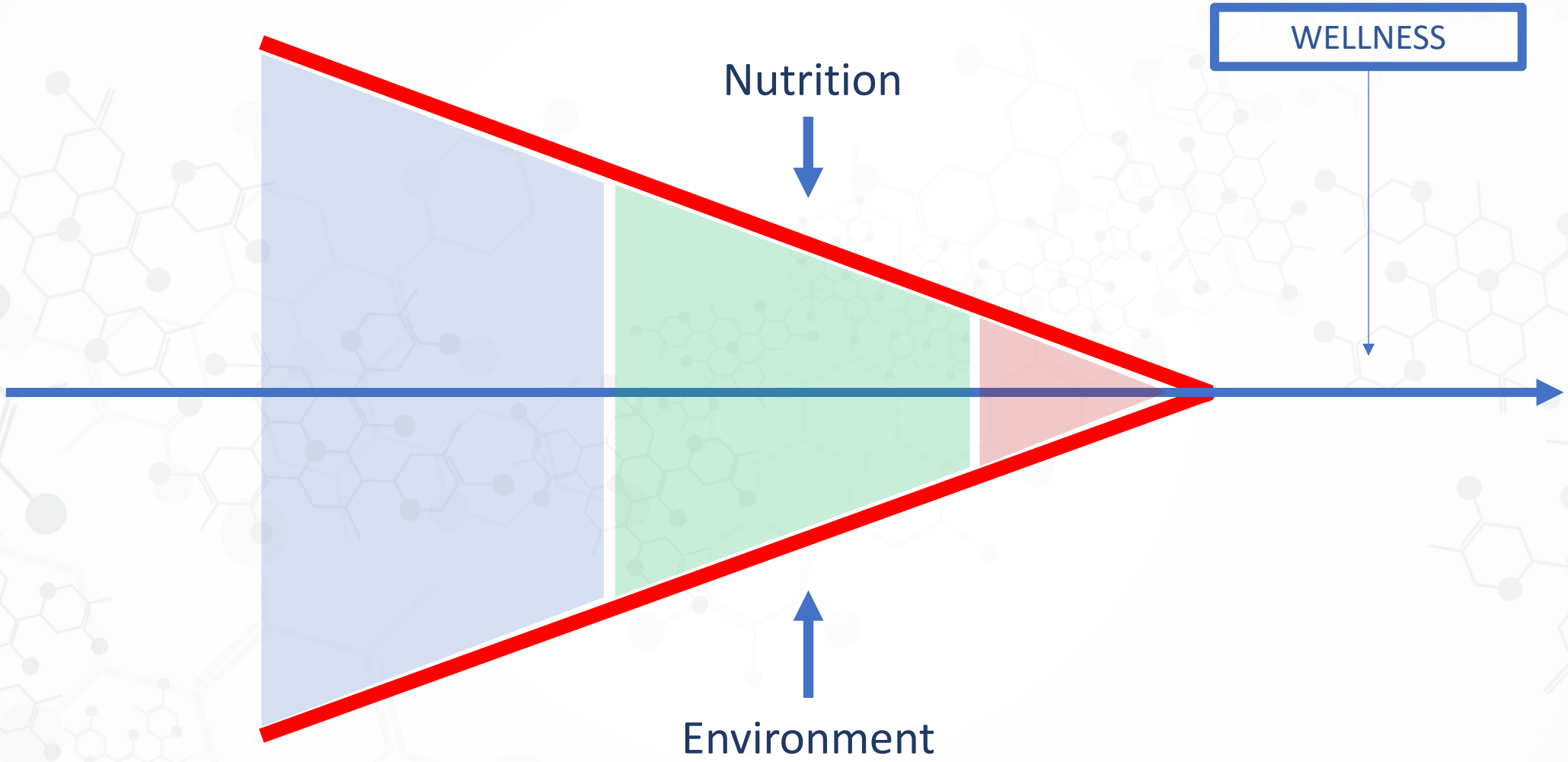


Table 1

Modern pharmacologic therapies for rheumatoid arthritis

Classification	Name	Mechanism of action	Potential mechanisms	Side Effect
Conventional synthetic DMARDs	Methotrexate	Analog of folic acid	Folate-dependent processes; Adenosine signaling; Methyl-donor production; Reactive oxygen species; Adhesion-molecule expression; Cytokine profiles Eicosanoids and MMPs.	Increased liver enzymes, pulmonary damage.
	Leflunomide/ Teriflunomide	Pyrimidine synthesis inhibitor	DHODH-dependent pathway; Leukocyte adhesion; Rapidly dividing cells; NF-kB; Kinases; Interleukins; TGF-β.	Hypertension, diarrhea and nausea, hepatotoxicity.
	Sulfasalazine	Anti-inflammatory and immunosuppression	Cyclooxygenase and PGE2; Leukotriene production and chemotaxis; Inflammatory cytokines (IL-1, IL-6, TNF-α); Adenosine signaling; NF-kB activation.	Gastrointestinal, central nervous system, and hematologic adverse effect.
	Chloroquine /Hydroxychloroquine	Immunomodulatory effects	Toll-like receptors; Lysosomotropic action; Monocyte-derived pro-inflammatory cytokines; Anti-inflammatory effects; Cellular immune reactions; T cell responses; Neutrophils; Cartilage metabolism and degradation.	Gastrointestinal tract, skin, central nervous system adverse effect and retinal toxicity.
Biological DMARDs Antibody-based therapies				
TNF-α targeted therapy	Infliximab	TNF-α inhibitor	Phagocytosis and pro-inflammatory cytokines; Chemoattractant; Adhesion molecules and chemokines; Treg cell function; Function of osteoclasts, leukocytes, endothelial and synovial fibroblasts.	Infection (pneumonia and atypical tuberculosis) injection-site reaction.
	Adalimumab			Hypertension.
	Etanercept			Severe /anaphylactoid transfusion reaction.
	Golimumab			
	Certolizumab pegol			
B-cell targeted therapy	Rituximab	B cell depleting	Fc receptor gamma-mediated antibody-dependent cytotoxicity and phagocytosis; Complement-mediated cell lysis; antigen presentation; B cell apoptosis; Depletion of CD4+ T cells.	Infection, hypertension, hypogammaglobulinemia, viral reactivation, vaccination responses.
	Ofatumumab			Late-onset neutropenia.
	Belimumab	Inhibitors of B cell function		Severe/anaphylactoid transfusion reaction.
	Atacicept			
	Tabalumab			
T-cell targeted therapy	Abatacept	CD28/CTLA4 system	Autoantigen recognition; Immune cell infiltrate; T cells activation.	Infection, malignancy.
	Belatacept	CD80/CD86		
Interleukin targeted therapy	Tocilizumab	IL-6 inhibition	Innate and the adaptive immune system perturbation; Acute-phase proteins.	Infections (most notably skin and soft tissue), increases in serum cholesterol, transient decreases in neutrophil count and abnormal liver function.
	Anakinra	IL-1 inhibition	Inflammatory responses; Matrixenzyme.	Injection site reactions, infections, neutropenia, malignancy.
	Canakinumab			
Future drug and target	Toll like receptors;[165] Bruton's tyrosine kinase;[151] Phosphoinositide-3-kinase pathway;[166] Transforming growth factor-beta;[167] Neuropathways;[168] Dendritic cell[169]			

Protocols



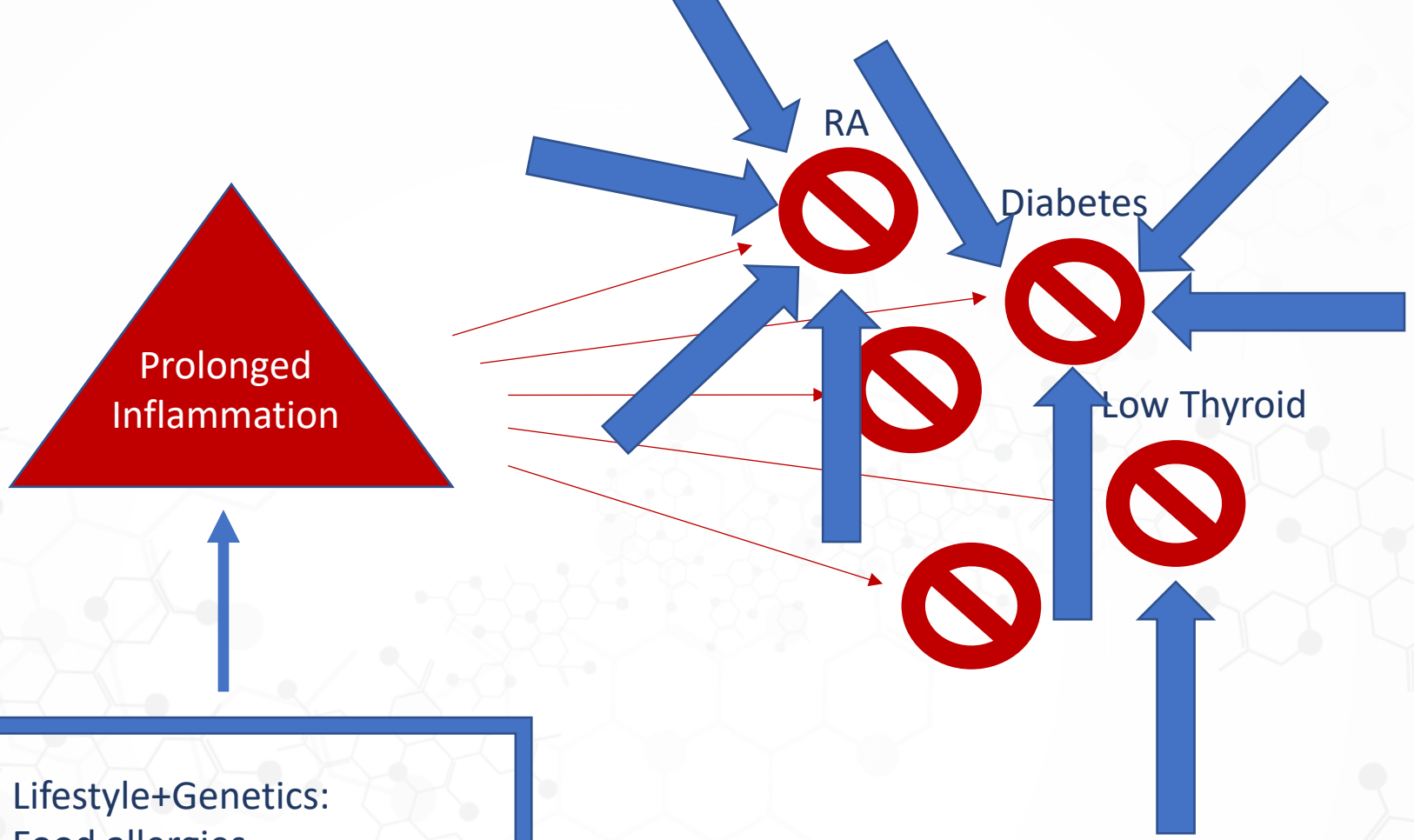
Supplement Facts

Serving size: 1 Capsule
Servings per container: 120

	Amount Per Serving	% Daily Value*
BCM-95® Turmeric Extract (*Curcuma longa*)(rhizome)(95% total curcuminoids complex, including curcumin, curcuminoids, and volatile oils)(86% curcuminoids) (65% curcumin)	500 mg	†

* Percent Daily Values are based on a 2,000 calorie diet.
† Daily Value not established.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5003001/



Lifestyle+Genetics:
Food allergies
mold
LPS
Blood Sugar Balance
Alcohol
Infections, etc.

Biogenetix: 833-525-0001

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