Tofacitinib
(Xeljanz)

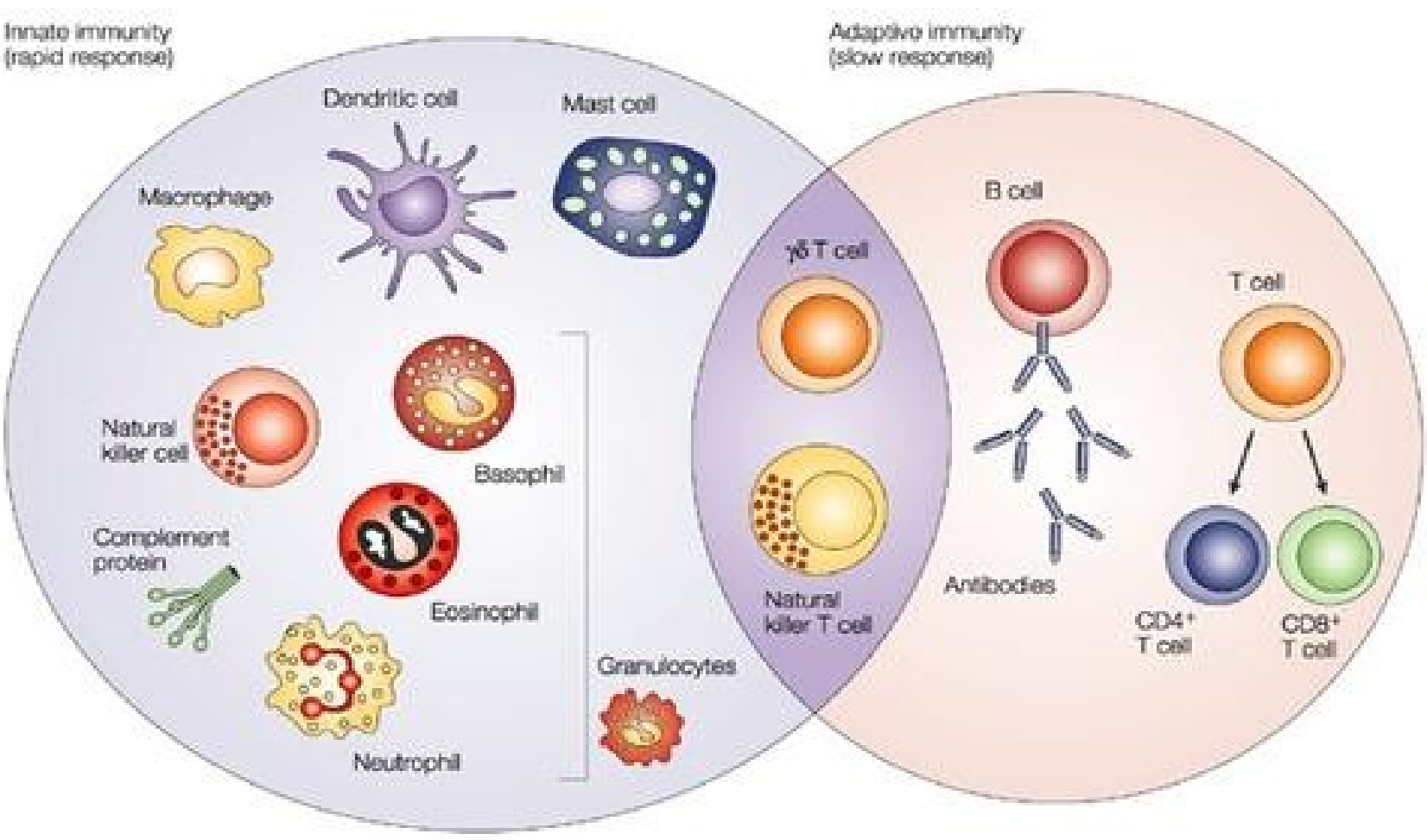
Marshall Porter & Lauren Ysais

Learning Objectives to Take with You

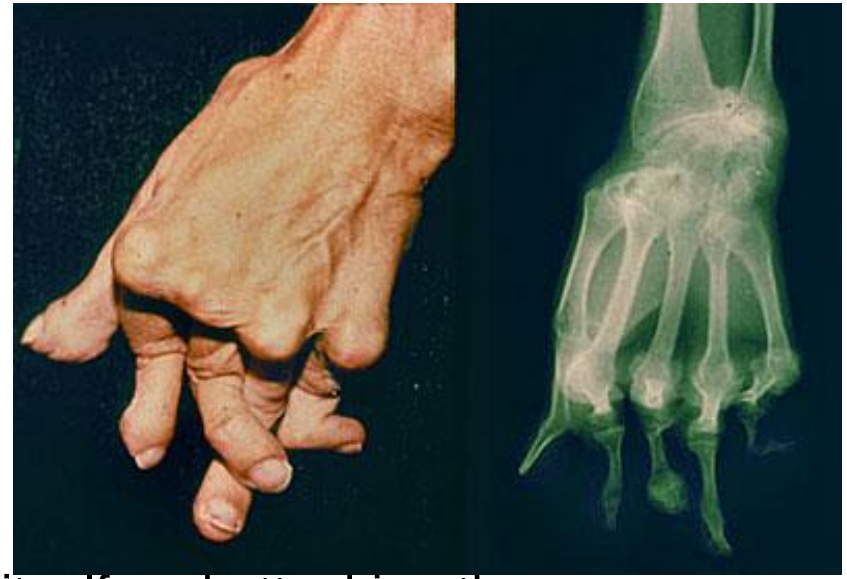
- A small molecule Janus Kinase (JAK) Inhibitor
- treatment for moderate to severe rheumatoid arthritis (RA)
- reduces cytokine production ameliorating inflammation in joints
- still undergoing post-market surveillance for long term side effects

Background:

- Tradename: Xeljanz
- a Janus Kinase (JAK) Inhibitor
- Jak family of intracellular tyrosine kinase proteins include: JAK 1, JAK 2, JAK 3, & TYK2
- JAKs are involved in intracellular signaling transduction of cytokines
- used to treat rheumatoid arthritis (RA)


Innate immunity
(rapid response)
Adaptive immunity
(slow response)
Dendritic cell
Mast cell
Macrophage
B cell
γδ T cell
T cell
Natural
killer cell
Basophil
Complement
protein
Eosinophil
Natural
killer T cell
Antibodies
CD4+
T cell
CD8+
T cell
Granulocytes
Neutrophil

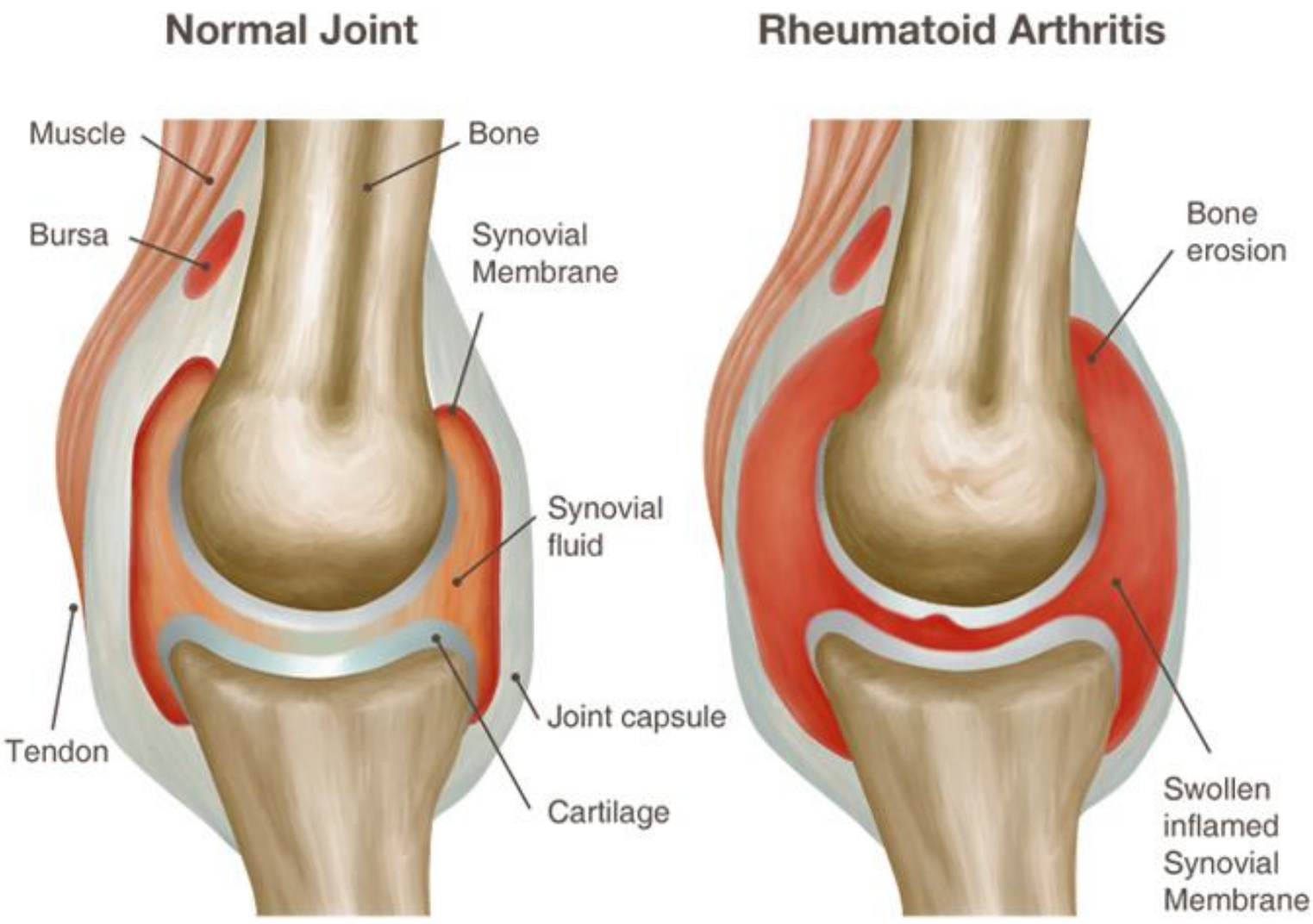
What is rheumatoid arthritis?



- 1.3 million in U.S. and
  27.3 million worldwide suffer from RA
- chronic inflammatory disease and autoimmune condition
- result of immune system turning on itself and attacking the membrane that lines the joints, the synovial membrane
- inflammation and damage to joints

Symptoms of RA:

- pain, swelling, tenderness, warmth in the joints
- stiffness and decreased mobility
- fatigue, energy loss, occasional fever
- pain & stiffness lasts for ~30 minutes or more in the morning, after long periods of rest, or during a flare-up
- muscles, ligaments, and tendons surrounding joint are weakened and as a result work improperly
- joint deformity

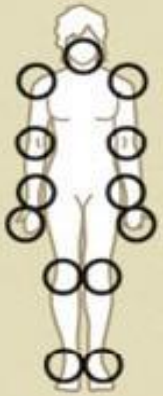

Normal Joint
Rheumatoid Arthritis
Muscle
Bone
Bursa
Synovial Membrane
Synovial fluid
Tendon
Joint capsule
Cartilage
Bone erosion
Swollen inflamed Synovial Membrane

Rheumatoid arthritis

One of the most common and debilitating forms of arthritis, three-quarters of the 2.1 million Americans affected are women.

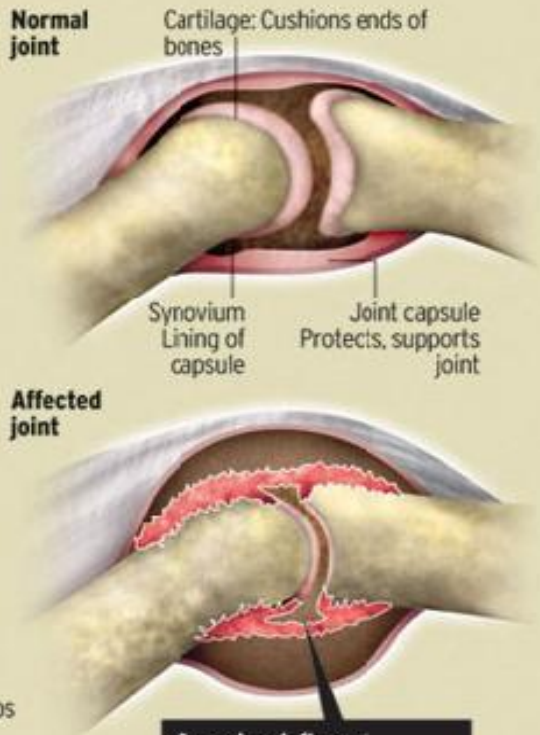
What is it

- Inflammatory condition; autoimmune disease; body's immune system attacks tissue lining joints; no known cure



Joints that may be affected

- Occurs symmetrically (both sides of body at once)
- Wrist, finger joints closest to hands are often affected



Symptoms, signs

Can vary widely

- 30 minutes or more of joint pain, stiffness after long rest
- Fatigue, low fever during flare-ups

Treatment

Lifestyle changes, pain and inflammation drugs, surgery, monitoring

Reason for early treatment: Bone damage begins in first year or two of disease

SOURCE: NATIONAL INSTITUTES OF HEALTH (U.S.), MAYO CLINIC, AMERICAN HEART ASSOCIATION, ARTHRITIS FOUNDATION (U.S.)

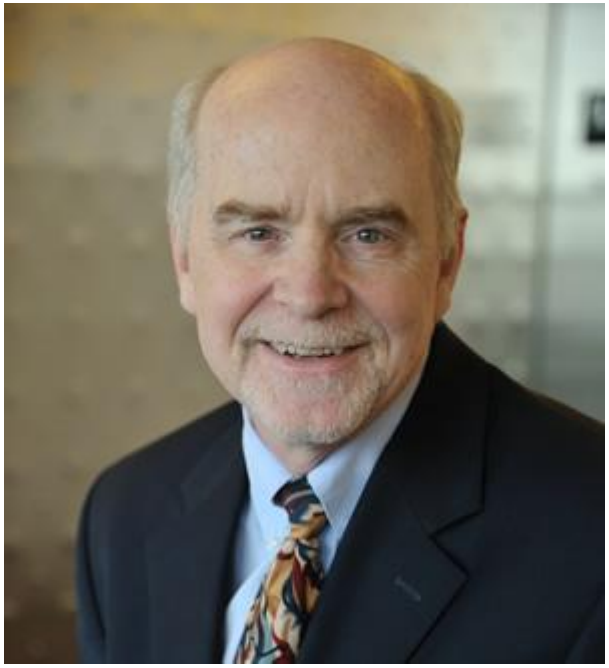
- joints in RA typically affected symmetrically
- common in wrists and fingers
- also affects the neck, shoulders, elbows, knees and ankles

- ➔ oral tablets
- ➔ dosage 5 mg twice daily
- ➔ prescription only
- ➔ Xeljanz used for patients unresponsive to methotrexate or other biologics treatments
  - ◆ ⅓ of patients nonresponsive so need another medication

Discovery & Development:

1993 John O’ Shea

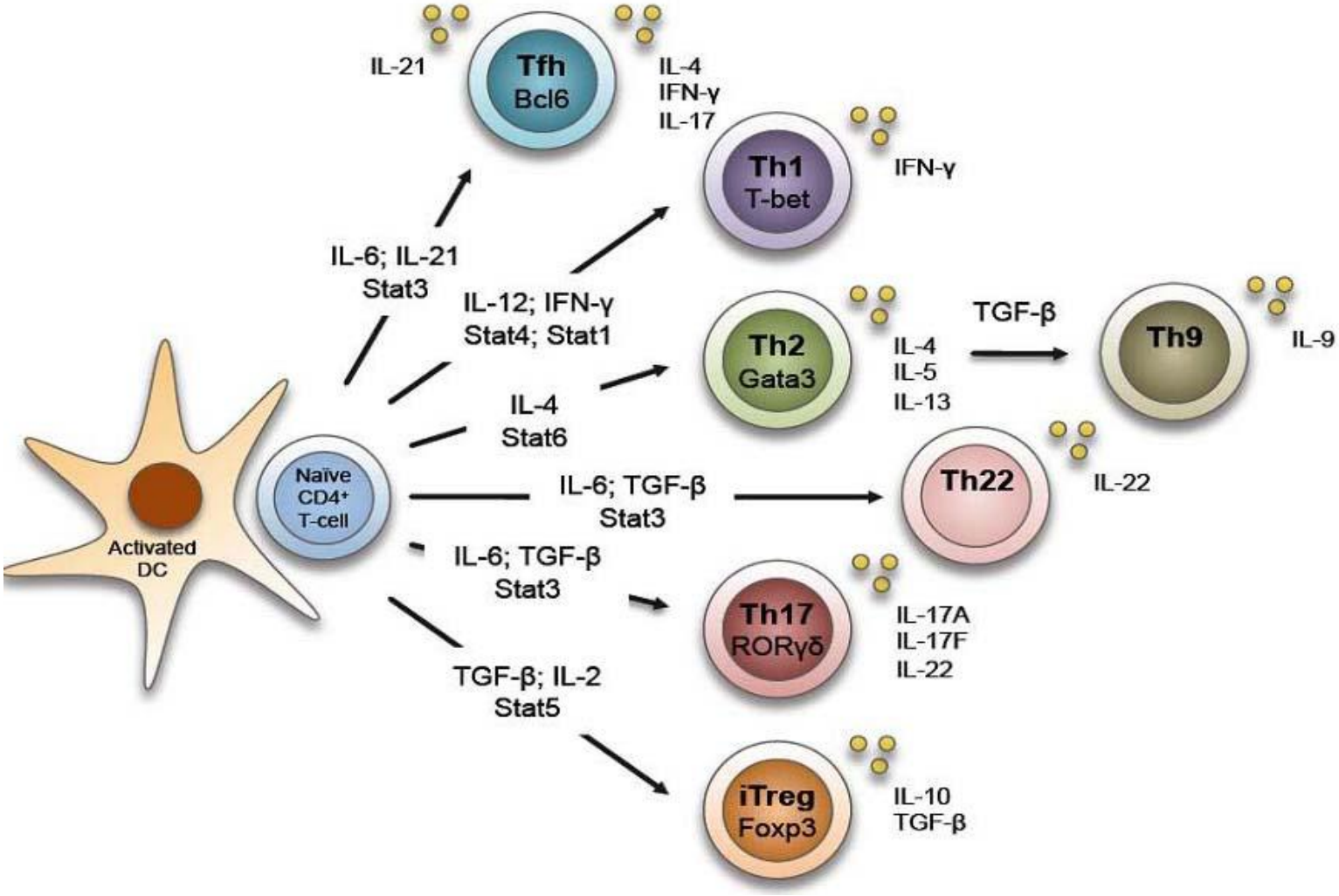
- immunologist at NIH
- cloned human JAK3 to define:
  - kinase structure
  - function
  - interaction with cytokines
  - role in inflammation



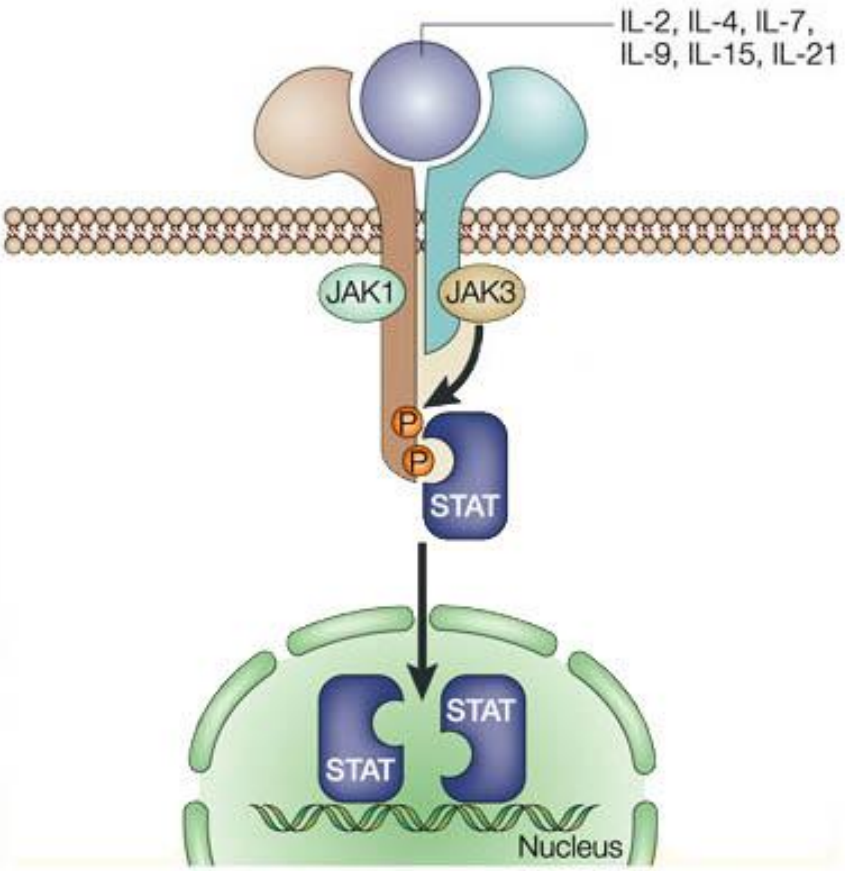
costs $2,055 per month

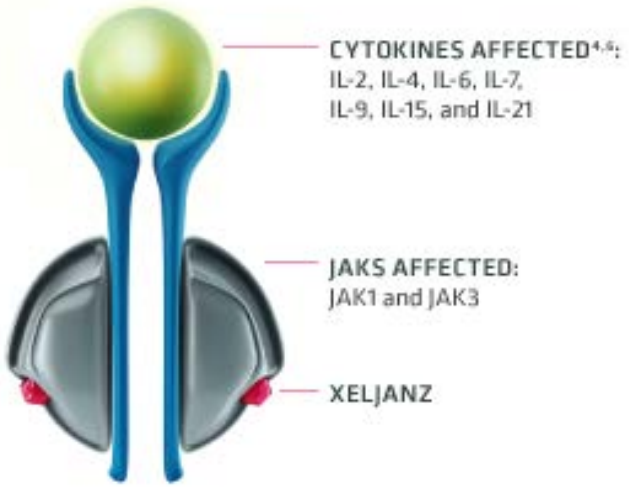
still ~7% cheaper than other current treatments

- 1994 NIH approaches Pfizer for partnership
  - Pfizer declines due to NIH policy
- 1996 NIH policy eliminated ⟹ Pfizer accepts
- Discovery & development took place at Pfizer exclusively
- November 6, 2012 FDA approves Tofacitinib


IL-21
Tfh
Bcl6
IL-4
IFN-γ
IL-17
Th1
T-bet
IFN-γ
IL-6; IL-21
Stat3
IL-12; IFN-γ
Stat4; Stat1
Th2
Gata3
IL-4
IL-5
IL-13
TGF-β
Th9
IL-9
IL-4
Stat6
Naive
CD4+
T-cell
Activated
DC
IL-6; TGF-β
Stat3
Th22
IL-22
IL-6; TGF-β
Stat3
Th17
RORγδ
IL-17A
IL-17F
IL-22
TGF-β; IL-2
Stat5
iTreg
Foxp3
IL-10
TGF-β

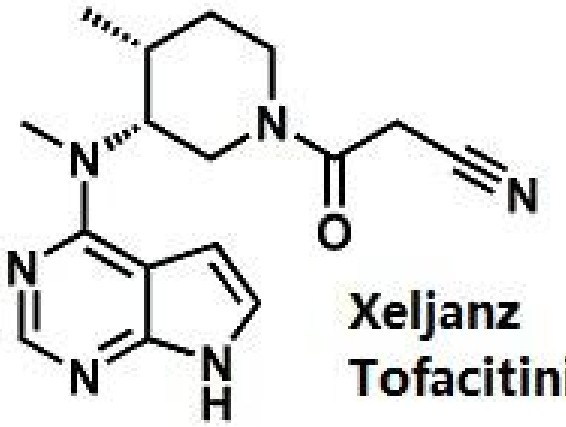
Molecular Targets & Mechanisms





- Tofacitinib binds to ATP binding cleft

Chemistry:



Xeljanz
Tofacitinib

Molecular Formula	$C_{16}H_{20}N_6O$
Molecular Weight	312. 17 g/mol
Hydrogen bond acceptors	7
Hydrogen bond donors	1
Rotatable bonds	4
Topological polar surface area	88.91
CLogP	0.31

http://www.guidetopharmacology.org/GRAC/LigandDisplayForward?tab=refs&ligandId=5677

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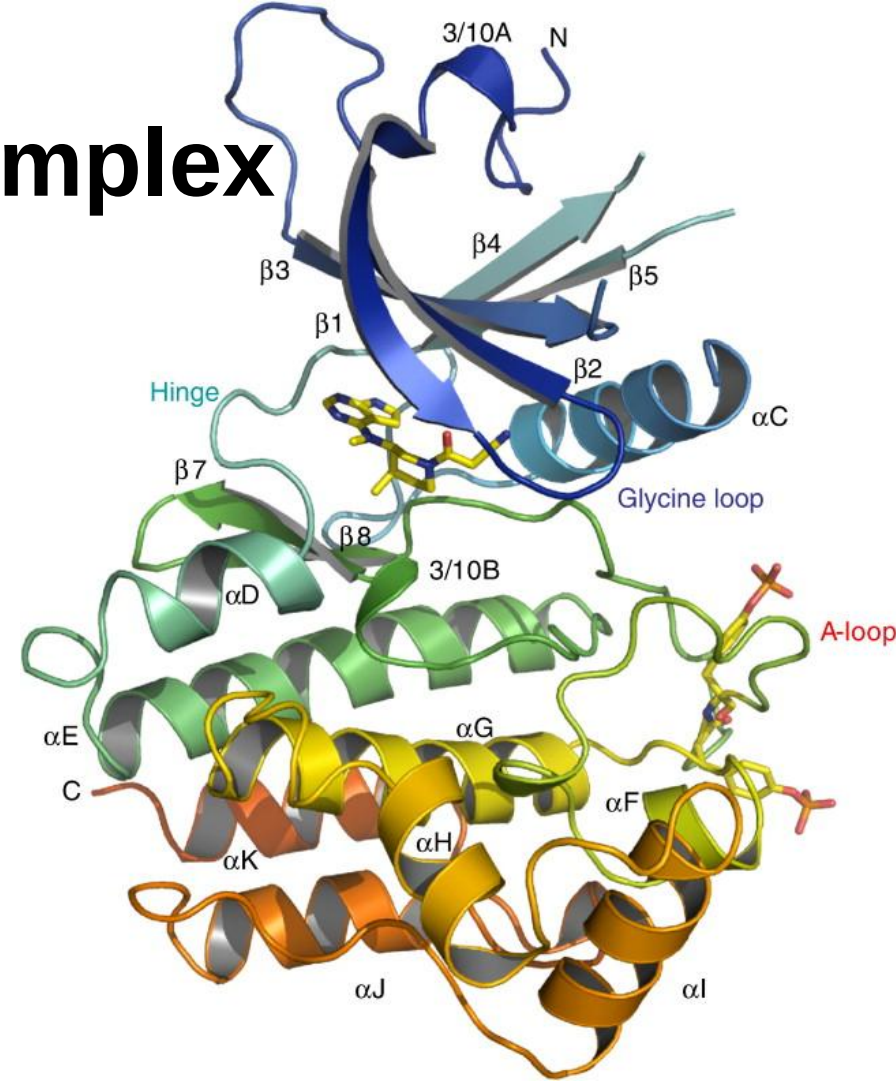
Carbon: Yellow
Nitrogen: Blue
Oxygen: Red

http://www.guidetopharmacology.org/GRAC/LigandDisplayForward?tab=refs&ligandId=5677

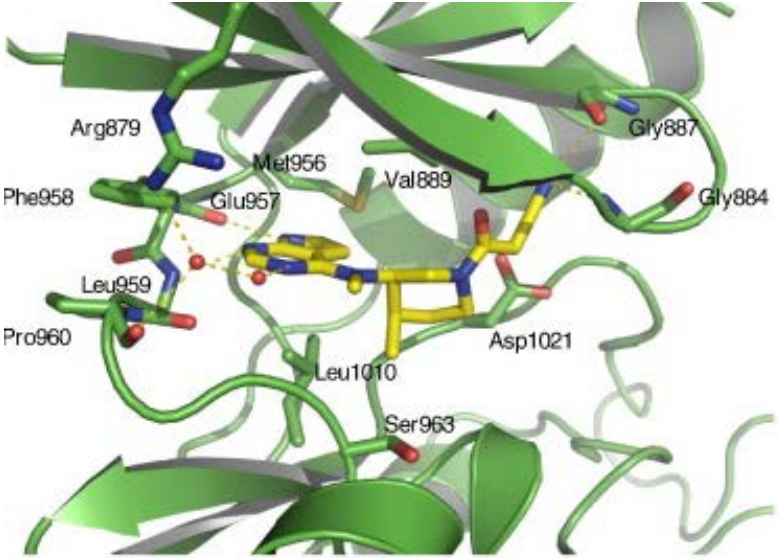
JAK PTK inhibitor Complex

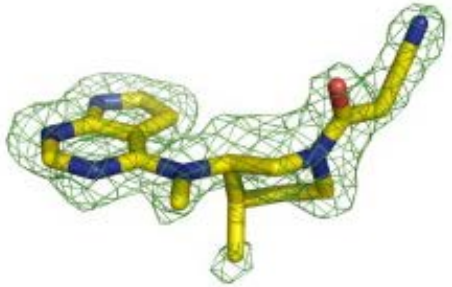
Protein Tyrosine Kinase Domain

Tofacitinib is ATP competitive inhibitor



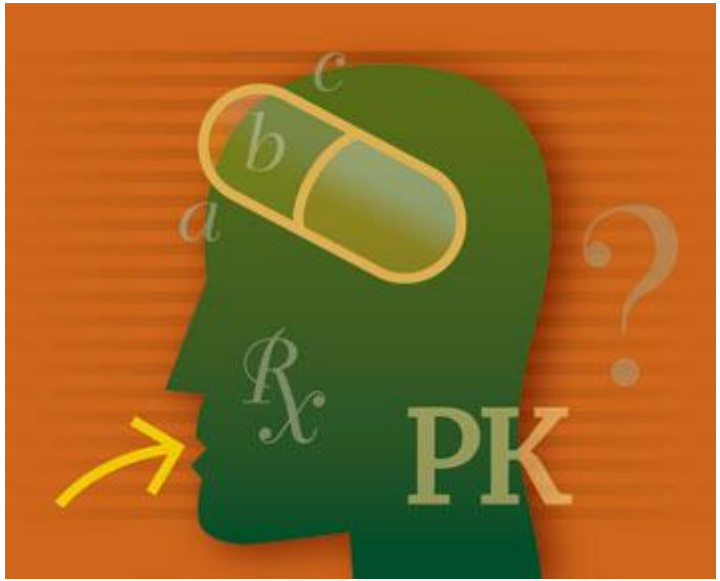
Binding Site: Hydrogen Bonds





Pharmacokinetics

- Bioavailability: 74%
- Rapid absorption and elimination
  - Peak plasma concentration at 60 min
  - Half life of 3.2 hrs
- Volume of Distribution of 87L
- Hepatic (70%) and Renal (30%) clearance
- 93.9% of dose recovered
- Metabolized primarily by CYP3A4/5



Metabolism

- Oxidation of Pyrrolopyrimidine and Piperidine
- Oxidation of piperidine side chain
- N-Demethylation
- Glucuronidation

Carbon: Yellow
Nitrogen: Blue
Oxygen: Red

Clinical Trials

Animal Models:

- Tested if Tofacitinib could modulate immune response
  - Used 2 rodent models of arthritis

mouse collagen-induced arthritis (CIA)

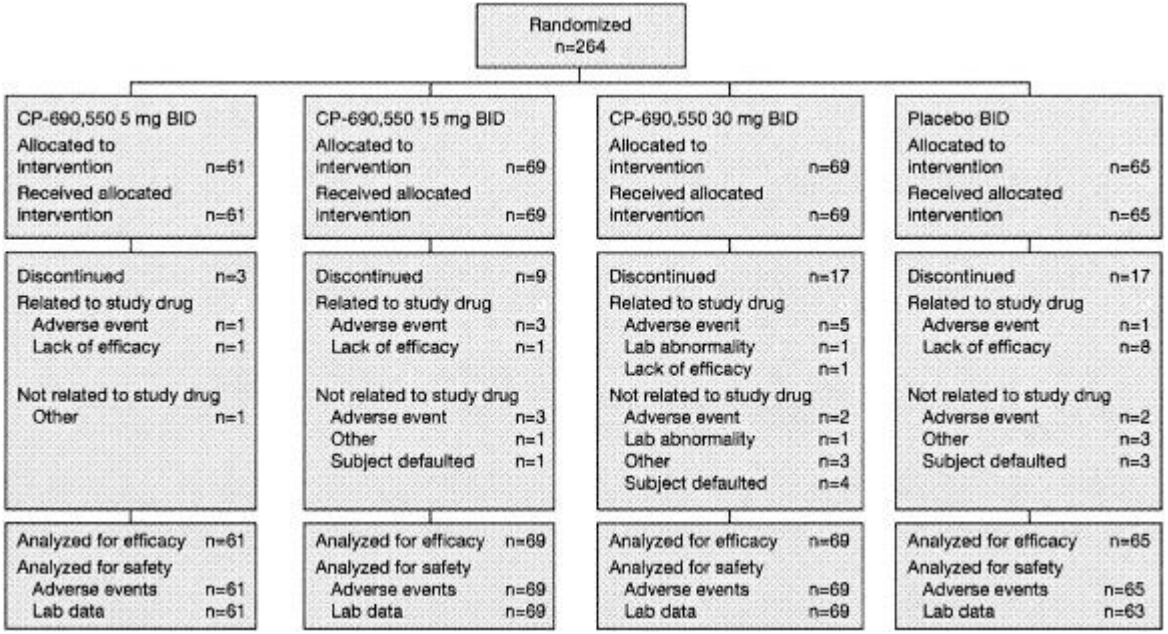
rat adjuvant-induced arthritis (AA)

- animals in both groups received Tofacitinib via osmotic mini-pump infusions at the following doses following disease induction (therapeutic):
  - 0 (control)
  - 1.5 mg/kg per day
  - 5 mg/kg per day
  - 15 mg/kg per day
- Arthritis assessed by clinical scores for the CIA model
- Paw swelling observed in AA model via a plethysmometer
- Animals were euthanized once study concluded and evaluated

Results:

- found dose-dependent reduction in signs of disease activity in both animals model Vs. untreated controls
  - ED_{50} of ~ 1.5 mg/kg per day corresponding to Tofacitinib serum levels of
    - 5.8 ng/mL in mice (day 28)
    - 24 ng/mL in rats (day 24)
- treatment with both 5 and 15 mg/kg per day doses of drug produced highly significant, near-total suppression, of clinical scores
- Tofacitinib treatment also resulted in dose dependent reduction of inflammation + damage to cartilage via histological evaluation
- CIA model looked at serum levels of IL-6
  - treatment with Tofacitinib dose at 15 mg/kg per day
  - significant reduction in levels of IL-6

Human Clinical Trials:



Objective:

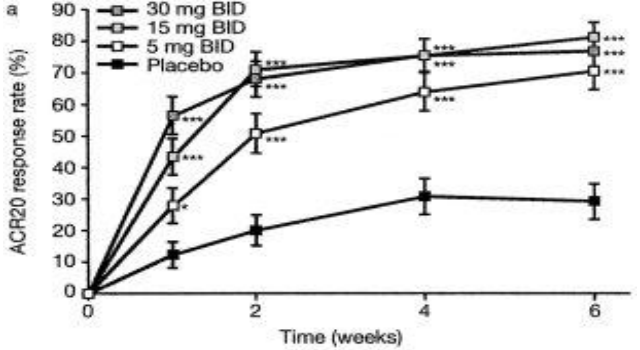
- determine the efficacy, safety, & tolerability of Tofacitinib at
- 3 different doses
- patients with RA who had inadequate or toxic response to other treatments

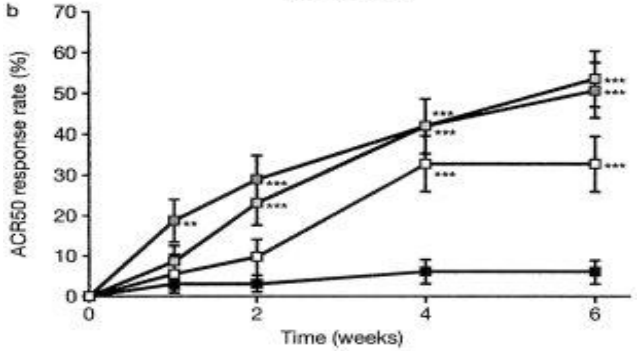
Methods:

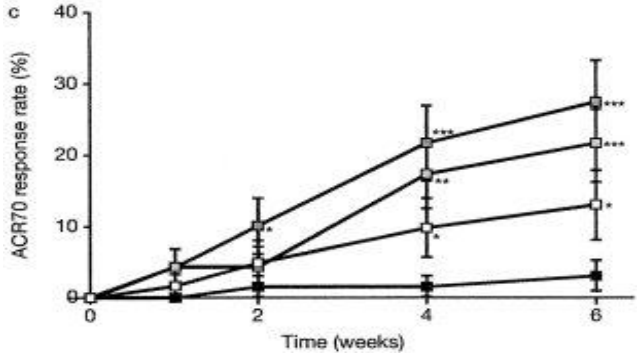
- n=264
- randomized equally to receive following doses of Tofacitinib
  - placebo
  - 5 mg
  - 15 mg
  - 30 mg
- dose take twice daily for 6 weeks
- followed for an additional 6 weeks after treatment period
- efficacy endpoint was the American College of Rheumatology 20% improvement criteria (ARC 20) response rate at 6 weeks

Results:

- by 6th week of treatment the following were the ARC20 response rates for the twice daily groups
  - 70.5% for 5mg
  - 81.2% for 15 mg
  - 76.8% for 30 mg
  - 29.2% for placebo (P <0.001)
- improvements seen in all disease activity with Tofacitinib-treated patients in all 3 treatment groups compared to placebo by week 1.
- ACR50 and ACR70 response rates observed also and significant improvement in all treatment groups by week 4.


a
30 mg BID
15 mg BID
5 mg BID
Placebo
ACR20 response rate (%)
Time (weeks)


b
ACR50 response rate (%)
Time (weeks)


c
ACR70 response rate (%)
Time (weeks)

Adverse Reactions:

- Most common adverse effect is headache, nausea, and infection
- This is due to immunosuppressive effects
- increase in mean low-density & high-density lipoprotein cholesterol
- increase mean serum creatinine levels (0.04-0.06 mg/dl)
- Other concerns involving heart health

Table 4. Commonly Reported Adverse Effects.[9]

Adverse Effect*	Placebo (%)	Tofacitinib 5 mg bid (%)
Discontinuation as a result of adverse effect	3	4
Infections	18	20
Diarrhea	2.3	4.0
Nasopharyngitis	2.8	3.8
Upper-respiratory-tract infection	3.3	4.5
Headache	2.1	4.3
Hypertension	1.1	1.6

Post-Marketing Surveillance

- 6 year study 2013-2019
- Verify adverse reaction
- Long term safety and efficacy
- Occurrence of malignant tumors