Methotrexate works via:

A) Inhibition of leucovorin
B) Inhibition of dihydrofolate reductase
C) Activation of inosine monophosphate dehydrogenase
D) Inhibition of phospholipase A2

**Methotrexate**

- **MECHANISM:**
  - Irreversibly blocks dihydrofolate reductase needed for de-novo purine synthesis
  - Inhibits adenosine deaminase
- **ADVERSE:**
  - Radiation recall
  - Teratogenic for both egg and sperm
  - Uncommon: pneumonitis, pulmonary fibrosis
  - Marrow suppression
  - Hepatotoxicity (renally cleared)*

**Drug-Drug Interactions with MTX**

<table>
<thead>
<tr>
<th>Hepatotoxicity</th>
<th>Synergistic toxicity</th>
<th>Decreased renal elimination</th>
<th>Displacement of MTX from ptn binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>EtOH Retinoids</td>
<td>EtOH TMP-SMX</td>
<td>Sulfonamides Salicylates NSAIDs Nephrotoxins -AG's, CSA PCN's Colchicine Probenecid</td>
<td>Sulfonamides Salicylates Barbiturates Phenytoin Phenobarbital</td>
</tr>
</tbody>
</table>

**A 34 year-old patient with psoriasis accidentally takes his methotrexate daily. A white blood cell count reveals that he is neutropenic. Treatment requires:**

- A) niacinamide
- B) folinic acid (leucovorin)
- C) thiamine
- D) ethylendiamine
- E) cobalamine
Patients taking methotrexate should avoid

- A) erythromycin
- B) cotrimoxazole (Bactrim®)
- C) cephalaxin
- D) propranolol
- E) folic acid

Azathioprine (Imuran)

- MECHANISM: pro-drug of 6-mercaptopurine, then converted by HGPRT to 6-thioguanine, which acts as a purine analog
- ADVERSE:
  - Systemic: marrow suppression, lymphoma, infxns, hepatitis, pancreatitis
  - Cutaneous side effects: Raynaud’s and pellagra-like symptoms

Azathioprine

6-Mercaptopurine (6-MP)

Azathioprine

Hypoxanthine guanine phosphoribosyl transferase (HGPRT)

6-thioguanine (Active metabolites)

Inactive metabolites

Bone marrow suppression

6-thioguanine methyltransferase (TPMT) (which prior to dosing azathioprine)

Bone marrow suppression

The most serious adverse effect of 6-thioguanine in the treatment of bullous pemphigoid is

- A) hepatotoxicity
- B) renal toxicity
- C) pulmonary fibrosis
- D) myelosuppression
- E) peripheral neuropathy

Question

Azathioprine (Imuran) is the immediate precursor of which active metabolite?

A) 6-mercaptopurine
B) Hydroxyurea
C) Cyclophosphamide
D) 6-hydroxyoxycytosine
E) 6-thioguanine (secondary active metabolite via HGPRT)

Question

Allopurinol has a significant interaction with azathioprine via what enzyme pathway?

A) TPMT
B) Xanthine Oxidase
C) HGPRT
D) Thymidylate Synthetase
The enzyme that best predicts azathioprine myelosuppression and therapeutic response is:

- A) dihydrofolate reductase
- B) glucose-6-phosphate dehydrogenase
- C) hypoxanthine-guanine phophoribosyl transferase
- D) thiopurine methyltransferase (TPMT)
- E) xanthine oxidase

**Mycophenolate Mofetil (Cellcept)**

- **MECHANISM:** non-competitive inhibition of inosine monophosphate dehydrogenase (IMP dehydrogenase) – involved in de-novo purine biosynthesis
  
  - “Problems with Purines”
    - Azathioprine
    - Mycophenolate mofetil

**Questions**

Mycophenolate mofetil (MMF) is a non-competitive inhibitor of:

- A) Inosine monophosphate dehydrogenase (IMP dehydrogenase)
- B) HGPRT
- C) Azathioprine
- D) Xanthine-5 phosphate dehydrogenase

- ADVERSE:
  - GI side effects (N/V, diarrhea)
  - Rare bone marrow toxicity

The mechanism of action of mycophenolate mofetil is inhibition of:

- A) IL-2 response to T-cell activation
- B) dihydrofolate reductase
- C) DNA polymerase
- D) purine biosynthesis
- E) actin polymerization
The most common adverse reaction from mycophenolate mofetil therapy for refractory atopic dermatitis is:
- A) genitourinary urgency
- B) gastrointestinal disturbances
- C) anemia
- D) herpes zoster infection
- E) tinnitus

Hydroxyurea
- MECHANISM: Inhibits ribonucleotide reductase
- ADVERSE, Systemic:
  - Hepatitis, renal toxicity
  - Anemia is the most common finding (25%)
  - Megaloblastic changes (100%)
  - Leukopenia (7%), thrombocytopenia (3%)

Hydroxyurea
- ADVERSE, Cutaneous:
  - Poikiloderma of dorsal hands, band-like over fingers/toes; diffuse hyperpigmentation; vasculitis
  - Leg ulcers, radiation recall, acral erythema, dermatomyositis-like cutaneous eruptions

Question
What is the primary mechanism of action of hydroxyurea?
A) Inhibition of dihydrofolate reductase
B) Inhibition of IL-12
C) Stimulation of RANTES
D) Inhibition of ribonucleotide reductase

Question
Which occurs in all patients receiving hydroxyurea?
A) Anemia
B) Leukopenia
C) Megaloblastic changes
D) Thrombocytopenia

Cyclophosphamide
- MECHANISM: DNA cross-linker
  - Nitrogen mustard derivative (alkylating agent)
- ADVERSE:
  - BM suppression, lymphoma, leukemia, bladder cancer, SCC
  - Hemorrhagic cystitis -> transitional cell carcinoma (reduce with mesna)
  - Azoospermia (rare); premature ovarian failure
5-Fluorouracil

MECHANISM:
- pyrimidine analog; covalently binds to thymidylate synthetase, inactivating the enzyme complex and preventing the conversion of dUMP to dTMP

ADVERSE:
- IV: Serpentine supravenous hyperpigmentation
- Topical = Efudex®, Carac®

Question

5-FU acts mainly through inhibition of:
A) Ribonucleotide reductase
B) Thymidylate synthetase
C) DNA phosphorlyase
D) Dihydrofolate reductase

Question

Bleomycin has been reported to cause which of the following:
A) Sclerodermoid changes
B) Flagellate hyperpigmentation
C) Raynaud’s phenomenon
D) Radiation recall
E) All of the above

Bleomycin

MECHANISM:
- DNA damaging agent – M/G2 specific

ADVERSE:
- Skin: flagellate hyperpigmentation, sclerodermoid changes/acral sclerosis, Raynaud’s phenomenon, nail hyperpigmentation, neutrophilic eccrine hidradenitis, radiation recall/enhancement
- Pulmonary fibrosis

Question

Cyclosporine affects T-lymphocytes mainly via inhibition of:
A) IL-8
B) Calcineurin
C) AP-3
D) CYP 3A4
E) IFN-alpha

The Calcineurin Inhibitors

Systemic: Cyclosporine,
Tacrolimus/FK506
Topical: Tacrolimus (Protopic®),
Pimecrolimus (Elidel®)

Cytokine Production

IL-2
**Tacrolimus (FK506)**
- A) upregulates IL-8
- B) interferes with IL-2 production
- C) causes pustular psoriasis flares
- D) unlike CSA is free of renal toxicity
- E) is an allylamine

**Cyclosporine Adverse Effects**
- Gingival hyperplasia
- Hypertrichosis
- Renal dysfunction
- Hypertension
- Hyperuricemia
- Hyperkalemia
- Hypomagnesemia

**Question**
An adjustment in cyclosporine dosage should be made when a patient’s baseline creatinine increases by:

- A) 10%
- B) 15%
- C) 20%
- D) 25%

**A patient with severe psoriasis is to begin treatment with cyclosporine. Which of the following medications should be discontinued?**
- A) triamterene – K-sparing
- B) HCTZ
- C) furosemide
- D) bumetanide
- E) ethacrynic acid

**A side effect common to both cyclosporine and PUVA therapy is**
- A) hypertension
- B) hypertrichosis
- C) hypertriglyceridemia
- D) photosensitivity
- E) paraesthesias

Photo courtesy of Dr. Linda Wang
The proposed mechanism of action of dapsone in inflammatory skin disorders involves:

A) Inhibition of neutrophil myeloperoxidase
B) Inhibition of complement
C) Inhibition of IL-8
D) Inhibition of folic acid pathway

Dapsone: Special Considerations
- Hemolysis
- Methemoglobinemia
- Neuropathy – primarily motor, but can include sensory
- Hepatitis and hypalbuminemia
- Agranulocytosis – time course 3-12 weeks; potentially fatal: may present with fever, pharyngitis, and signs of sepsis
- Dapsone-hypersensitivity syndrome – mononucleosis-like rxn with fever, generalized cutaneous eruption, and hepatitis, eosinophilia

Dapsone: Methemoglobinemia
- Cimetidine (400 mg tid) and vitamin E have been demonstrated to decrease methemoglobin formation
- In an emergency, oral methylene blue (100 to 300 mg/d) can be used to decrease methemoglobin levels

Question
Protection against hemolytic anemia and methemoglobinemia when using dapsone may be afforded by:
- A) Vitamin E 800 IU/day
- B) Vitamin A 1,000,000 IU/day
- C) Iron supplementation
- D) Ginger ingestion 1 hr prior to Dapsone
**Question**

Which of the following is true regarding dapsone neuropathy?

A) It is primarily a sensory neuropathy  
B) It is reversible  
C) Wasting of hand muscles is commonly seen – motor > sensory!  
D) These patients frequently have other signs of dapsone toxicity

---

**Foot drop is most likely to be an adverse reaction to:**

- A) gold  
- B) dapsone  
- C) plaquenil  
- D) prednisone  
- E) azathioprine

---

**Question**

A pt with Sweet’s syndrome on dapsone acutely develops fever, rigors, and signs of sepsis. The most likely diagnosis is:

A) Dapsone hypersensitivity syndrome  
B) Agranulocytosis  
C) Deep fungal infection  
D) Hepatitis

---

**Antimalarials**

- **MECHANISM:**
  - unclear  
  - immunomodulatory and anti-inflammatory activity; also photoprotective  

- **ADVERSE:**
  - GI upset  
  - Pigmentation changes  
  - Ocular toxicity

---

**Chloroquine, Hydroxychloroquine, Quinacrine**

- Chloroquine, Hydroxychloroquine
  - Blue-black pigmentation of pretibial > face, extremities, ear cartilage, oral mucosa, gingiva, hard palate, nails

- Quinacrine (yellow)
  - fades in 4 mos of stopping drug

---

**Question**

Which of the following is an advantage of quinacrine over other antimalarials?

A) Safety in pregnancy  
B) Less hematologic toxicity  
C) No ocular toxicity – can use in combination  
D) No neurotoxicity
Ocular Adverse Effects of Antimalarials

**Reversible**
- Corneal deposition (Fabry’s like): halos, blurred vision, photophobia
- Loss of accommodation
- Premacularopathy: no visual change, retinal pigment deposition, para & pericentral scotoma

**Irreversible**
- True retinopathy:
  - "Bull’s eye" pigment deposition
  - Central scotoma

**Visual acuity changes**

**Question**

What is the mechanism of action of thalidomide?

A) Inhibition of dihydrofolate reductase  
B) Inhibition of TNF-α  
C) Inhibition of IL-8  
D) Stimulation of IFN-α

Thalidomide

**MECHANISMS:**
- Potent suppressor of TNF-alpha and IL-12  
- Decreases neutrophil chemotaxis and phagocytosis

**SPECTRUM:**
- Drug of choice for erythema nodosum leprosum (ENL)  
- Used in HIV mucosal ulcerations and aphthous stomatitis, prurigo nodularis, cutaneous lupus

**Thalidomide Adverse Effects**

- Teratogenic: *days 21-36 – phocomelia
- Neuropathy
  - Most common: symmetric painful paresthesias of the hands and feet and mild proximal muscle weakness  
  - Motor neuropathy is reversible; sensory neuropathy may be irreversible
- Hypercoagulability

**Question**

What is the most common presentation of thalidomide-induced neuropathy?

A) Only motor neuropathy  
B) Mixed motor and sensory neuropathy  
C) Only sensory neuropathy  
D) Spastic diplegia

Thalidomide is the drug of choice for which of the following diseases?

- A) tuberculoid leprosy
- B) sarcoidosis
- C) lobomycosis
- D) erythema nodosum leprosum
- E) yaws
Consider for all biologics:
- screen for latent TB; monitor for infections
- increased malignancy/lymphoma risk
- pregnancy class B except efalizumab (C)
- increased ANA positivity

Which of the following wart treatments induces IFN-alpha?

- A) Podofilox
- B) 5-FU
- C) Imiquimod
- D) Cantharidin
- E) Liquid nitrogen

Which of the following chemotherapeutic agents has been linked to acneiform eruptions?

- A. Bleomycin
- B. Cytarabine
- C. Doxorubicin
- D. Cetuximab – anti-EGFR therapy
- E. Cisplatin

Imiquimod

- MECHANISM: synthetic ligand for Toll-like Receptors TLR-7 and TLR-8
- Induces cytokines: IFN-α, TNF-α, IFN-γ, IL-12

Which of the following agents binds to a shared subunit of IL-12 and -23?

- A. Golimumab
- B. Leflunomide
- C. Ustekinumab
- D. Infliximab
- E. Adalimumab
Ustekinumab (Stelara®)

- MECHANISM: a human IL-12/23 monoclonal antibody
  - binds with high affinity to the shared P40 subunit of human interleukins 12 and 23
- Blocking Th1 and Th17 pathways

Which should be considered in a patient with fevers, arthralgias, an urticarial rash, and an IgM monoclonal gammopathy?

A. Infliximab  
B. Ustekinumab  
C. Golimumab  
D. Anakinra (Kineret®)  
E. Leflunomide

Anakinra (Kineret®)

- MECHANISM: IL-1 receptor antagonist
- APPLICATIONS:
  - Schnitzler's Syndrome  
  - Rheumatoid arthritis  
  - Muckle-Wells Syndrome  
  - Familial Mediterranean Fever  
  - Cold urticaria; familial cold autoinflammatory syndrome  
  - Chronic infantile neurologic cutaneous and articular (CINCA) syndrome  
  - Angioedema

Which should be considered in a patient with retiform purpura, eschars, and renal failure?

A. Intravenous immunoglobulin  
B. Sodium thiosulfate  
C. Coumadin  
D. Systemic corticosteroids  
E. Cyclosporine

Sodium thiosulfate

- MECHANISM: chelation of calcium salts, antioxidation, vasodilation
- APPLICATIONS:
  - Calciphylaxis  
  - Nephrogenic systemic fibrosis  
  - Calcification cutis  
  - Cyanide toxicity
- ADVERSE: N/V, HA, rhinorrhea, anion gap metabolic acidosis

In this patient who has failed a calcium channel blocker and is developing ulcerations, what therapy would you choose?

A. Revatio® (sildenafil)  
   - phosphodiesterase-5 (PDE-5) inhibitor  
   - pulmonary arterial htn; Raynaud's
Which of the following molecules is inhibited by apremilast?

A. BRAF  
B. PDE3  
C. **PDE4**  
D. MEK  
E. Tyrosine kinase (RTK inhibitor)

**Apremilast**

- **MECHANISM:** small molecule inhibitor of PDE4 (thalidomide analog)
- **APPLICATIONS:**
  - Psoriasis/PsA
  - Behcet's
  - RA, ankylosing spondylitis
  - DLE, LP, cutaneous sarcoid
- **ADVERSE:** GI/diarrhea, HA, nasopharyngitis, fatigue

Which of the following functions as an IgE monoclonal antibody?

A. Golimumab  
B. Tocilizumab  
C. Certolizumab  
D. **Omalizumab**  
E. Leflunomide

**Omalizumab (Xolair®)**

- **MECHANISM:** IgE monoclonal Ab
- **APPLICATIONS:**
  - Urticaria
  - Asthma
- **ADVERSE:** anaphylaxis (1 to 2 patients /1000)

Which of the following is the mechanism of ipilimumab?

A. MEK inhibition  
B. MEK activation  
C. **CTLA-4 inhibition**  
D. CTLA-4 activation  
E. ERBB4 activation

**Ipilimumab**

- **MECHANISM:** CTLA-4 inhibition
- **APPLICATIONS:**
  - Metastatic melanoma
  - Unresectable melanoma
- **ADVERSE:** colitis (#1), dermatitis, autoimmune phenomena
Which side effect caused the most patients to discontinue vismodegib?

A. dysgeusia  
B. nausea  
C. weight loss  
D. muscle spasms  
E. hair loss

Vismodegib

- **MECHANISM:** antagonist of the smoothened receptor (SMO), part of the hedgehog signaling pathway
- **APPLICATIONS:**
  - Metastatic, recurrent, inoperable BCC
  - Basal cell nevus syndrome
- **ADVERSE:** muscle spasms, dysgeusia, N/V, diarrhea, fatigue, hair loss, weight loss

Tofacitinib (Xeljanz®)

- **MECHANISM:** inhibits JAK3 and JAK1
  - Interferes with JAK-STAT signaling pathway
- **APPLICATIONS:**
  - RA, PsA, psoriasis
  - Some data for AA, vitiligo, atopic dermatitis
- **ADVERSE:** infections, lipid profile changes

Secukinumab (Cosentyx®)

- **MECHANISM:** human monoclonal antibody against IL-17A
- **APPLICATIONS:**
  - Ps, PsA, ankylosing spondylitis
- **ADVERSE:** candidiasis, IBD exacerbation
- **UNIQUE:** no boxed malignancy warning

Which enzyme is inhibited by tofacitinib?

A. JAK4  
B. MEK  
C. JAK3  
D. BRAF  
E. MEK3

Which is the mechanism of action of secukinumab?

A. IL-23A monoclonal Ab  
B. IL-23C monoclonal Ab  
C. **IL-17A monoclonal Ab**  
D. IL-23C monoclonal Ab  
E. IL-12C monoclonal Ab
Ixekizumab (Taltz®)

- **MECHANISM:** human monoclonal antibody against IL-17A
- **APPLICATIONS:**
  - Ps (not currently approved for PsA)
- **ADVERSE:** candidiasis, IBD exacerbation
- **UNIQUE:** - no boxed malignancy warning
  - vs. secukinumab: no latex in syringe; perhaps more patients able to maintain efficacy

### Which drug history would be most important to pick up?

A. Doxycycline  
B. Hydralazine  
C. Omeprazole  
D. Cisplatin  
E. Bleomycin

### Drug-induced lupus vs. Drug-induced SCLE

<table>
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<th>Common culprits</th>
<th>Drug-induced lupus</th>
<th>Drug-induced SCLE</th>
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<tr>
<td>Hydralazine</td>
<td>Isoniazide</td>
<td>Hydrochlorothiazide</td>
</tr>
<tr>
<td>Procainamide</td>
<td>Penicillamine</td>
<td>Terbinafine</td>
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<tr>
<td>Penicillamine</td>
<td>Diltiazem</td>
<td>Griseofulvin</td>
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<tr>
<td>Diltiazem</td>
<td>Minocycline</td>
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<td>Minocycline</td>
<td>Anti-TNF therapy</td>
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<td>Anti-TNF therapy</td>
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<thead>
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<th>Drug-induced SCLE</th>
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<tr>
<td>Anti-Histone</td>
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<td>Anti-Ro</td>
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<table>
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<tr>
<th>Clinical presentation</th>
<th>Drug-induced lupus</th>
<th>Drug-induced SCLE</th>
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<tbody>
<tr>
<td>Arthralgias (&gt;90%), fatigue, fever (cutaneous findings in &lt;20%)</td>
<td></td>
<td>Photosensitive rash</td>
</tr>
</tbody>
</table>