inflammatory nodule count with no increase in the draining fistula count[54]. Additional approved indications include psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, uveitis, and Crohn disease in adults as well as JIA and Crohn disease in children ≥2 years and ≥6 years of age, respectively. There have also been reports of successful adalimumab therapy for pustular psoriasis[55], sarcoidosis, pyoderma gangrenosum, Behçet disease, other neutrophilic dermatoses, and dermatomyositis.

#### Dosages
Adalimumab is supplied in 10–80 mg prefilled syringes and a 40 mg autoinjector; it is administered subcutaneously. For the treatment of psoriasis, an initial loading dose of 80 mg is typically given, followed by 40 mg on day 8 and then 40 mg every other week. The approved regimen for hidradenitis suppurativa is a loading dose of 160 mg, 80 mg on day 15, and then 40 mg weekly starting on day 29. The pediatric dosing approved for JIA is every-other-week administration of 10 mg, 20 mg, or 40 mg for children who weigh 10–14 kg, 15–29 kg, or ≥30 kg, respectively. Loss of efficacy of adalimumab over time related to the production of anti-adalimumab antibodies can occur and may be prevented by the concurrent administration of low-dose weekly methotrexate; loss of efficacy has also been associated with the development of antinuclear antibodies[31]. The concomitant use of adalimumab and methotrexate is approved for the treatment of psoriatic arthritis, rheumatoid arthritis, and JIA.

#### Side effects
Side effects shared with other TNF inhibitors, including risk of infection with mycobacteria (see Fig. 128.5) and fungi, are discussed above and summarized in Tables 128.6 and 128.9[56].

#### Interactions
The concomitant administration of other targeted immune modulators with adalimumab may increase the risk of infection and should be avoided[57].

#### Use in pregnancy
Adalimumab is classified as pregnancy category B. Its safety during lactation is unknown.

### *Golimumab*
Golimumab (Simponi®) is a human recombinant IgG1 monoclonal antibody with specificity for human TNF[53]. It is approved for the treatment of psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, and ulcerative colitis; it can be administered along with methotrexate. Golimumab may also be useful in the treatment of other conditions that respond to TNF inhibitors. It is supplied in a 50 mg prefilled syringe or autoinjector that is administered subcutaneously monthly for psoriatic arthritis[58].

### *Certolizumab*
Certolizumab pegol (Cimzia®) is a pegylated Fab fragment of a humanized monoclonal antibody with specificity for human TNF. It is approved for the treatment of psoriatic arthritis, rheumatoid arthritis, and Crohn disease. Certolizumab may also be useful in the treatment of other conditions that respond to TNF inhibitors. It is supplied in a 200 mg prefilled syringe and administered subcutaneously. For psoriatic arthritis, 400 mg is given at weeks 0, 2 and 4, followed by 200 mg every 2 weeks or 400 mg monthly for maintenance[59].

## Interleukin-12/23 and Interleukin-23 Inhibitors
### *Introduction*
Ustekinumab (Stelara®) is a monoclonal antibody that targets IL-12 and IL-23, whereas guselkumab (Tremfya™), risankizumab, and tildrakizumab are monoclonal antibodies that target IL-23.

### *Mechanism of action*
Ustekinumab is a human IgG1 monoclonal antibody that binds with high affinity and specificity to the p40 subunit that is shared by the heterodimeric IL-12 and IL-23 cytokines (Fig. 128.9D). IL-12 has a critical role in the development of Th1 cells and NK cell activation, whereas IL-23 is necessary for the generation of Th17 cells (see Fig. 4.10). Guselkumab, risankizumab, and tildrakizumab target the p19 subunit of IL-23.

### *Indications*
Ustekinumab and guselkumab are approved for the treatment of adults with moderate to severe plaque-type psoriasis, with ~65–80% and ~80–90% of patients achieving a 75% improvement in their PASI score[60,61,61a,61b]. Ustekinumab is also approved for adults with psoriatic arthritis and Crohn disease. In addition, there are anecdotal reports of its benefit in the treatment of other dermatologic conditions, such as hidradenitis suppurativa and pyoderma gangrenosum. Risankizumab and tildrakizumab are being investigated in phase III trials for the treatment of moderate to severe plaque-type psoriasis in adults[61c,61d].

### *Dosages*
For the treatment of psoriasis, ustekinumab is administered as a subcutaneous injection of 45 mg or, for patients whose weight is >100 kg, 90 mg; it is given at weeks 0 and 4, and then every 12 weeks. It is available as a 45 or 90 mg prefilled syringe, a 45 mg single-dose vial, and a solution for intravenous infusion in patients with Crohn disease. Guselkumab is administered as a subcutaneous injection of 100 mg at weeks 0 and 4, and then every 8 weeks.

### *Contraindications*
Ustekinumab and IL-23 inhibitors are contraindicated in patients with known sensitivity to the agents, and they should be avoided in patients with serious active infections or malignancies.

### *Major side effects*
Ustekinumab is associated with an increased incidence of mucocutaneous candidiasis (~5% of patients) and a potential risk of severe and disseminated infections with mycobacteria and *Salmonella*. These particular infections mirror those seen in patients with genetic deficiencies in the IL-12/IL-23 signaling pathway (see Fig. 60.2). Assessment for tuberculosis is required at baseline and typically repeated annually during therapy with all IL-12/23 or 23 inhibitors (see Table 128.7). Patients with untreated latent tuberculosis should receive antituberculous therapy prior to beginning treatment.

A possible excess of major adverse cardiovascular events (MACEs) such as myocardial infarction or stroke was noted in patients who received anti-IL-12/23 therapy in individual clinical trials, but meta-analyses and a 5-year follow-up study did not find a significant increase in the risk of MACEs associated with the use of these agents[62–64]. Although the effects of IL-12/23 inhibitors on vascular inflammation and thrombosis, especially early in the course of therapy, remain to be determined, cardiovascular risk factors should be assessed prior to initiating treatment. Other potential severe side effects of ustekinumab are listed in Table 128.6. Injection site reactions can occur but are less frequent than with the TNF inhibitors. Retiform purpura progressing to cutaneous necrosis on the leg was reported in a patient treated with ustekinumab[65].

### *Interactions*
Live vaccines should be avoided (see Table 128.10). The response to vaccines may be muted. Other targeted immune modulators should not be administered together with ustekinumab or IL-23 inhibitors. The concomitant administration of other immunosuppressive agents might increase the risk of infection.

### *Use in pregnancy*
Ustekinumab is pregnancy category B; guselkumab was approved after June of 2015 and therefore was not labeled with a pregnancy category. The safety of these drugs during lactation is unknown.

## Interleukin-17 Inhibitors
Currently, three IL-17 inhibitors have been approved for the treatment of psoriasis: ixekizumab and secukinumab, which target IL-17A, and brodalumab, which blocks the IL-17 receptor A (Fig. 128.9E). A review of their shared contraindications, major side effects, interactions, and use in pregnancy is followed by a discussion of issues that relate specifically to individual drugs.

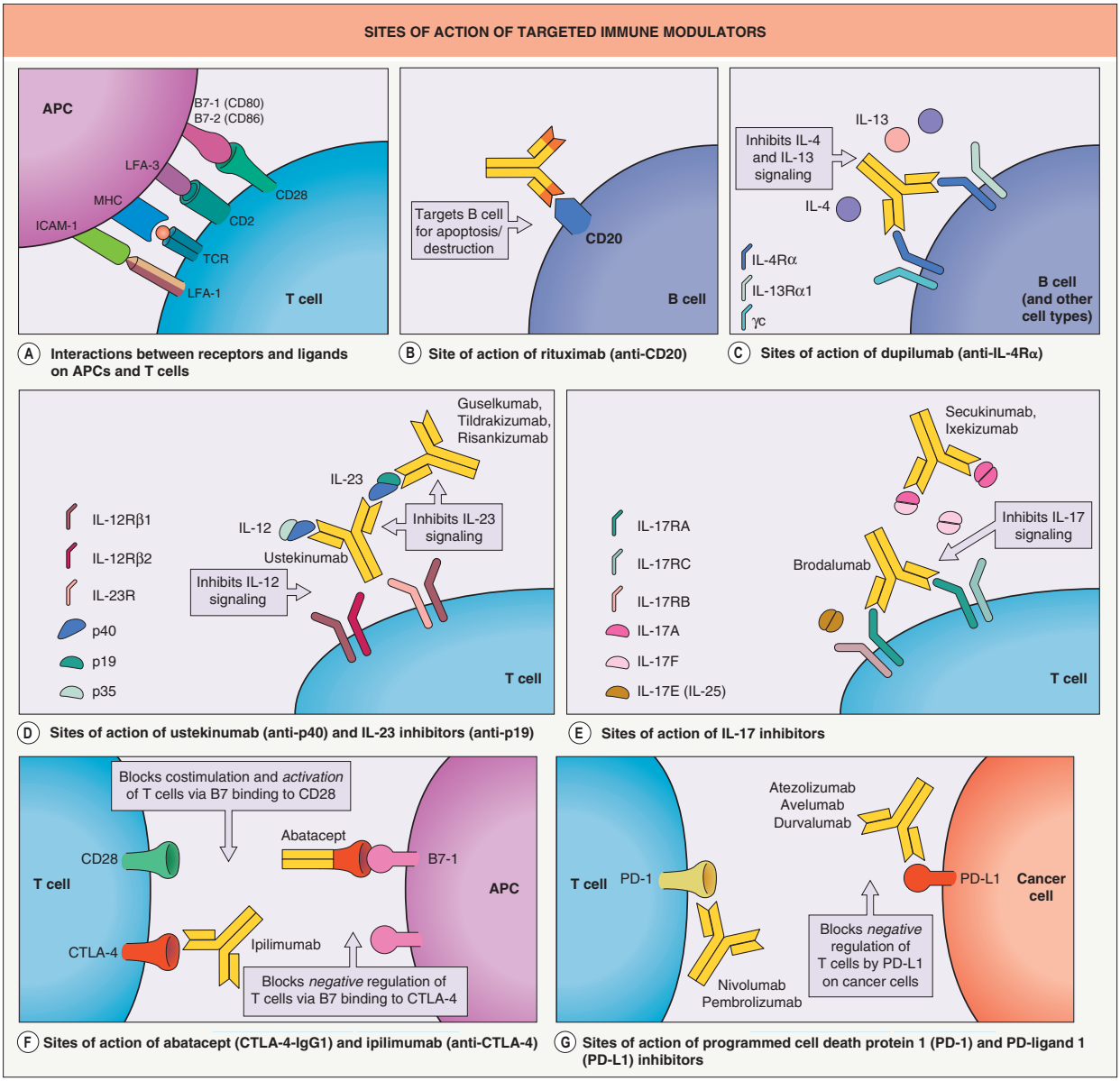


**Fig. 128.9 Sites of action of targeted immune modulators. A** Activation of T cells requires two signals. The first occurs when the major histocompatibility complex antigen interacts with the T-cell receptor (TCR). A second costimulatory signal is required for T-cell activation to occur. **B** Site of action of rituximab. **C** Sites of action of dupilumab. **D** Sites of action of ustekinumab. **E** Sites of action of IL-17 inhibitors. **F** Sites of action of abatacept and ipilimumab. **G** Sites of action of programmed cell death protein 1 (PD-1) and PD-ligand 1 (PD-L1) inhibitors. APC, antigen-presenting cell; CTLA-4, cytotoxic T-lymphocyte antigen 4; ICAM, intercellular adhesion molecule; IL, interleukin; LFA, lymphocyte function antigen; MHC, major histocompatibility complex; R, receptor.

### *Contraindications*

Each IL-17 inhibitor is contraindicated in patients with a known hypersensitivity to that particular agent or components of its formulation. These medications should be used with caution in patients with chronic/recurrent infections or inflammatory bowel disease, with Crohn disease representing a contraindication for brodalumab (see below). Administration of an IL-17 inhibitor should be avoided or discontinued in patients with a serious active infection.

### *Major side effects*

The most common adverse events in clinical trials of IL-17 inhibitors were nasopharyngitis, upper respiratory tract infections, and injection-site reactions[66–68]. Hypersensitivity reactions have also been reported, including anaphylaxis, angioedema, and urticaria. Mucocutaneous candidiasis, most often oral or vulvovaginal, develops in ~5% of patients[67,69]; this reflects the important role of IL-17 in defense against *Candida* (see Fig. 60.2)[70]. These infections are typically mild or moderate and resolve with standard treatment[67]. Neutropenia (<1500 cells/mm$^3$) occurs in ~1–2% of patients, which is similar to the frequency in patients receiving etanercept[66,68]. Assessment for tuberculosis is required at baseline and typically repeated annually during therapy (see Table 128.7). Patients with untreated latent tuberculosis should receive antituberculous therapy prior to beginning treatment.

New onset and exacerbation of Crohn disease and ulcerative colitis have occurred in patients receiving IL-17 inhibitors. An increased

risk of adverse cardiovascular events was not observed in clinical trials.

### *Interactions*

Live vaccines should be avoided (see Table 128.10). To avert a potential increased risk of infection, other targeted immune modulators should not be coadministered with IL-17 inhibitors.

### *Use in pregnancy*

Secukinumab is pregnancy category B; the other IL-17 inhibitors were approved after June of 2015 and therefore were not labeled with a pregnancy category. There are no available data on IL-17 inhibitor use in pregnant women, although human IgG is known to cross the placenta. No evidence of harm to the fetus was observed in pregnant monkeys receiving up to 19–30 times the maximum recommended human doses of ixekizumab, secukinumab, and brodalumab; however, there were a few neonatal deaths in the ixekizumab group. Safety during lactation is unknown.

### *Ixekizumab*

#### Mechanism of action

Ixekizumab (Taltz®) is a humanized IgG4 monoclonal antibody that binds and inhibits IL-17A, resulting in neutralization of IL-17A homodimers and IL-17A/F heterodimers (see Fig. 128.9E). In its hinge region, there is substitution of proline for serine which prevents the formation of half-antibodies (half-mers) that can undergo Fab-arm exchange with endogenous human IgG4.

#### Indications

Ixekizumab is approved for the treatment of moderate to severe plaque-type psoriasis in adults, and ~85–90% of patients achieve a 75% improvement in their PASI score within 12 weeks of beginning treatment[66].

#### Dosages

Ixekizumab is administered as a subcutaneous injection, with a loading dose of 160 mg followed by 80 mg every 2 weeks for 12 weeks and then every 4 weeks. It is supplied in 80 mg prefilled syringes and autoinjectors.

### *Secukinumab*

#### Mechanism of action

Secukinumab (Cosentyx®) is a human IgG1κ monoclonal antibody that binds with high affinity and selectivity to IL-17A (see Fig. 128.9E).

#### Indications

Secukinumab is approved for moderate to severe plaque psoriasis in adults. Approximately 75–85% and 65–75% of patients treated with the 300 mg and 150 mg doses, respectively, achieve a 75% improvement in their PASI score[71]. It is also approved for psoriatic arthritis and ankylosing spondylitis.

#### Dosages

Secukinumab is administered as a subcutaneous injection of 300 mg at weeks 0, 1, 2, 3, and 4; thereafter, it is given every 4 weeks. A dose of 150 mg may be considered for patients weighing <90 kg. It is available in 150 mg prefilled syringes and autoinjectors.

### *Brodalumab*

#### Mechanism of action

Brodalumab (Siliq™) is a human IgG2κ monoclonal antibody that selectively binds the IL-17 receptor A, inhibiting its interactions with IL-17A/F and IL-17E (also known as IL-25) (see Fig. 128.9E).

#### Indications

Brodalumab is approved for the treatment of moderate to severe psoriasis in adults who have failed or become unresponsive to other systemic therapies. Approximately 80–85% and 60–70% of patients treated with the 210 mg and 140 mg doses, respectively, achieve a 75% reduction in their PASI score[69].

#### Dosages

Brodalumab is available in prefilled syringes and administered as a 210 mg subcutaneous injection every 2 weeks.

#### Additional contraindications and major side effects

Contraindications and major side effects shared with other IL-17 inhibitors are described above. Brodalumab is contraindicated in patients with Crohn disease. Suicidal ideation and completed suicides occurred during clinical trials of brodalumab[72]. As a result, this medication is only available through a restricted Risk Evaluation and Mitigation Strategy (REMS) program, which requires provider and pharmacy certification as well as a patient–prescriber agreement form.

## Dupilumab

### *Introduction*

Dupilumab (Dupixent®) is a monoclonal antibody that targets the IL-4 receptor α subunit (IL-4Rα).

### *Mechanism of action*

Dupilumab is a human IgG4 monoclonal antibody that specifically binds to the IL-4Rα subunit of heterodimeric IL-4 and IL-13 receptors (Fig. 128.9C). This blocks signaling by these cytokines and the resultant Th2-mediated inflammation.

### *Indications*

Dupilumab is approved for the treatment of adults with moderate to severe atopic dermatitis, and ~50% of patients achieve a 75% improvement in their Eczema Area and Severity Index (EASI) score[73]. Clinical trials for pediatric atopic dermatitis are underway.

### *Dosages*

Administration is via subcutaneous injection of 600 mg in week 0 and then 300 mg every other week.

### *Contraindications*

Dupilumab is contraindicated in patients with known sensitivity to the drug or components of its formulation.

### *Major side effects*

The most common side effects are injection site reactions and conjunctivitis (see Table 128.6), with each occurring in ~10% of patients.

### *Interactions*

Live vaccines should be avoided (see Table 128.10).

### *Use in pregnancy*

There are no available data on use in pregnant women, although human IgG is known to cross the placenta. No evidence of harm to the fetus was observed in pregnant monkeys receiving up to 10 times the maximum recommended human dose. Safety during lactation is unknown.

## Interleukin-1 Inhibitors

### *Introduction*

Currently, there are three approved IL-1 antagonists: anakinra, canakinumab, and rilonacept. Dermatologic uses of these medications include treatment of cryopyrin-associated periodic syndrome (CAPS) and the pustular eruptions and bone lesions (e.g. osteomyelitis) of the autosomal recessive *d*eficiency of the *I*L-1 *r*eceptor *a*ntagonist (DIRA) (see Tables 45.2 & 45.6). CAPS represents a spectrum of autosomal dominant disorders featuring urticarial lesions and variable extracutaneous manifestations associated with gain-of-function mutations in the gene that encodes cryopyrin, a protein that functions in an "inflammasome" complex that produces IL-1β (see Fig. 4.2). A review of these agents' shared contraindications, major side effects, and interactions is followed by a discussion of issues that relate specifically to individual drugs.

### *Contraindications*

Each IL-1 antagonist is contraindicated in patients with a known hypersensitivity to that particular agent or components of its formulation. Administration should not be initiated in patients with active infections, and discontinuation should be considered if a serious infection develops.