The 1990s have seen major steps in the dissection of basic mechanisms of allorecognition, and renal graft survival has achieved unprecedented clinical results. Transplantation has turned into a widespread modality of therapy for patients with chronic renal failure that benefits thousands worldwide. Combinations of immunosuppressive agents have proved to be an effective strategy to inhibit diverse pathways of the multifaceted immune system, allowing the reduction of both dosage and adverse effects of each individual drug. As understanding of the molecular basis of the immune response has expanded rapidly, so have the possibilities for designing therapeutic interventions that are more effective, more specific, and safer than are current treatment options. As we reach the end of the century, several different and innovative approaches will add to this fascinating and complex therapy.
FIGURE 11-1
Mechanism of action for cyclosporine (CsA) and tacrolimus (Tac). The common cytoplasmic target for cyclosporine and tacrolimus is calcineurin. After binding to cyclophilin (Cyp), cyclosporine interacts with calcineurin, inhibiting its catalytic domain. Thus dephosphorylation of transcription factors is prevented, as exemplified by the nuclear factor of activated T lymphocyte (NF-AT). Despite having a different ligand called FK-binding protein (FK-BP), tacrolimus inhibits calcineurin in a similar way. Because phosphorylated transcription factors cannot cross the nuclear membrane, the production of key factors for lymphocyte activation and proliferation (i.e., interleukin-2, tumor necrosis factor-α, γ interferon, c-myc, and others) is inhibited [1]. NF-ATc—nuclear factor of activated T-lymphocyte-cytoplasmic form; P—phosphorus; Ca—calcium.

FIGURE 11-2
Proposed mechanism of action for rapamycin (rapa). Rapamycin binds to FK-binding protein (FK-BP). However, the immunosuppressive properties of rapamycin are not due to inhibition of calcineurin. Rapamycin blocks the activating signal delivered by growth factors (exemplified by the interleukin-2 [IL-2] receptor) by blocking the translation of the coding of messenger RNA (mRNA) for key proteins required for progression through the G1 phase of the cell cycle. In this model the mammalian target of rapamycin (m-TOR, also called FRAP or RAFT1), phosphorylates the translational repressor PHAS-1. Arrest of the cell cycle results, and the proliferation of lymphocytes is thereby inhibited. The full understanding of the mechanism(s) of action of rapamycin is the focus of intense research at this time [2]. eIF-4—translation initiation factor belonging to the Ets family; G(0,1, and 2)—quiescent; M—mitosis; S—synthesis.
**FIGURE 11-3**
Mechanism of immunosuppression of azathioprine and mycophenolate mofetil (MMF). Azathioprine and MMF prevent lymphocyte proliferation by way of inhibition of purine base synthesis, thus resulting in decreased production of the building blocks of nucleic acids (i.e., DNA and RNA). Azathioprine is metabolized to 6-mercaptopurine (6-MP), which is further converted to 6-mercaptopurine (6-MP) and guanosine monophosphate (GM P). MMF is metabolized to mycophenolic acid, which is a non-competitive inhibitor of the enzyme that converts inosine monophosphate (IMP) to GMP. The depletion of GMP may have effects other than inhibition of nucleic acid production. Some events of T-lymphocyte activation are independent of guanosine triphosphate (GTP), as is the assembling of certain adhesion molecules. ATP—adenosine triphosphate; HGPRT—hypoxanthine-guanine phosphoribosyl transferase; IMPD—inosine-monophosphate dehydrogenase; PRPP—phosphoribosyl pyrophosphate; 6-MP—6-mercaptopurine; TIMP—thioinosine monophosphate. (Adapted from de Mattos and coworkers [3,4].)

**FIGURE 11-4**
Summary of strategies for combining immunosuppressive agents. Currently, monotherapy (usually cyclosporine [Csa]) is not used in the United States. Dual therapy (involving cyclosporine or tacrolimus) is used commonly in Europe. Most centers in the United States use triple or quadruple therapy (induction or sequential). Some centers continue the induction with the antilymphocytic biologic agent for a predetermined period (usually 10–14 days), overlapping with the initiation of cyclosporine (or tacrolimus). Alternatively, the biologic agent is discontinued and cyclosporine (or tacrolimus) begun as soon as the graft function reaches a determined threshold, resulting in no overlap of these two agents. In living donor transplants, azathioprine (Aza) is commonly begun a few days before surgery. [5]. FK-506—tacrolimus; MMF—mycophenolate mofetil.