Proteolytic degradation is an essential cellular process which is primarily carried out by the 20S proteasome core particle (CP), a protease of 720 kDa and 28 individual subunits. Vertebrates harbor three distinct CP-types, the constitutive proteasome, the immunoproteasome and the thymoproteasome, which vary in their subunit compositions and thus in their substrate specificities. During the last two decades molecular insights into the biogenesis, regulation and catalysis identified the proteasome as an attractive drug target. Due to the central biological functions of the individual CPs, approved inhibitors have, depending on the targeted subunits, therapeutic effects on blood cancer and autoimmune diseases.