Cancer research within the last decades elucidated signaling pathways and identified genes and proteins that lead or contribute to malignant transformation of a cell. Discovery of the Bcr-Abl oncoprotein as the molecular abnormality causing chronic myeloid leukemia (CML) paved the way for the development of a targeted anticancer therapy. The substantial activity of imatinib mesylate (STI571, Glivec) in CML and Philadelphia (Ph)-chromosome positive acute lymphoblastic leukemia (Ph+ ALL) changed the therapeutic approach to Ph+ leukemia and rang the bell for a new era of anticancer treatment. However, when the phenomenon of relapse occurred despite continued imatinib treatment, we had to learn the lesson that imatinib can select for a resistant disease clone. If such a clone still depends on Bcr-Abl, it either carries a BCR-ABL point mutation that prevents binding of the drug or expresses the fusion protein at high levels. Alternatively, leukemia cells that harbor secondary genetic alterations resulting in Bcr-Abl-independent proliferation are selected for their growth advantage in the presence of imatinib. Point mutations in the BCR-ABL kinase domain prevent binding of imatinib but still allow binding of ATP, thus retaining Bcr-Abl kinase activity. Mutated BCR-ABL is frequently detected in cases of imatinib-resistant Ph+ leukemia and therefore represents the main
challenge for the investigation of alternative strategies to either overcome resistance or to prevent the emergence of a resistant leukemic clone.