MOLECULAR TARGETING OF BRAF MUTATIONS

*BRAF* is the most commonly mutated gene associated with melanoma, found in more than 50 percent of patients. The gene encodes a cytoplasmic kinase that is a member of the MAPK signal-transduction pathway, which is activated when growth factors bind to receptors on the cell surface. In the inactive state a segment of the BRAF protein known as the P-loop closes over the protein’s active site A. Binding to RAS triggers phosphorylation of BRAF, converting it to an active state, which continues to send a cell proliferation signal to the nucleus via MEK/MAPK B. More than 90 percent of melanoma patients have a BRAF mutation that locks the P-loop in an open position, keeping BRAF in an active state and bypassing the need for activation by RAS. The experimental drugs PLX4032 and GSK2118436 were specifically designed to occupy the area of the open P-loop where they block the activation of MEK C.