Holy BCR-ABL Fusion Protein! Is It Really Chronic Myelogenous Leukemia?

Student Group Names Kept Anonymous
Department of Biology, Lake Forest College, Lake Forest, IL 60045, USA

Chronic myelogenous leukemia (CML) is a multilineage hematologic malignancy that progresses in three distinct stages: a chronic phase, a poorly defined accelerated phase, and a blast phase often resulting in death. CML is a pluripotent hematopoietic stem cell disorder characterized by the Philadelphia chromosome translocation and resultant production of the constitutively activated BCR-ABL tyrosine kinase. The Philadelphia chromosome is created by the translocation between a gene of unknown function on chromosome 22, denoted BCR, with the coding sequence for the c-ABL gene on chromosome 9 and appears in myeloid, erythroid, megakaryocytic, and lymphoid cell types of CML patients. The exact structure and function of the BCR and ABL genes are still unclear. Additionally, it is unclear as to how these genes play a role in CML eventually leading to its characteristic increased cell proliferation and decreased differentiation and apoptosis. Numerous experimental models have established that BCR-ABL is an oncogene sufficient to produce CML-like disease in mice. Further research has shown the crystallized structure of the oligomerization domain of the BCR gene, which is needed to activate the ABL tyrosine kinase. The use of molecularly targeted drugs has offered new hope for treatment of CML and other cancers while proving that cancer may eventually become a manageable chronic disease analogous to diabetes and arthritis.

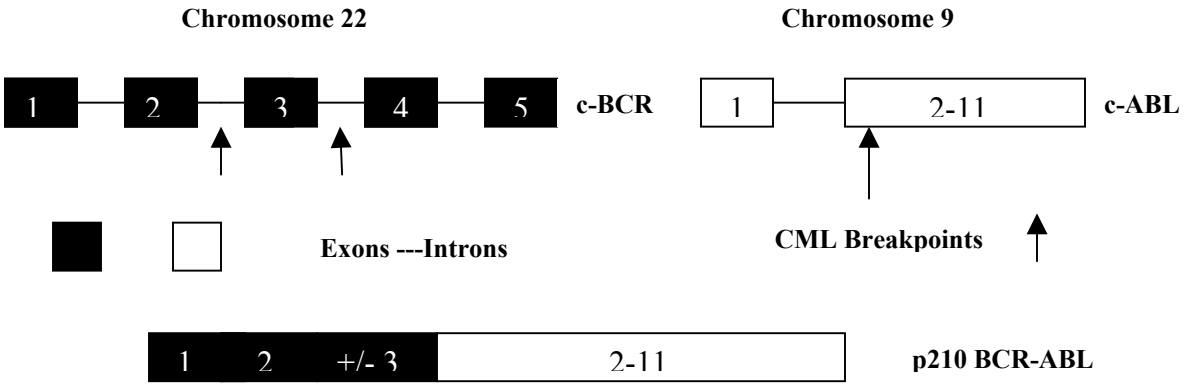

Figure 1 **The Philadelphia Chromosome.** The majority of CML cases involve a chromosome abnormality found only in leukemic white blood cells. In CML, a break occurs between the first and second axon of c-ABL. When this break occurs, nearly all of the c-ABL is translocated to chromosome 22, into the BCR gene. The breakpoint in BCR at the second or third axon results in the p210 BCR-ABL fusion protein that exhibits constitutive tyrosine kinase activity.