The \( t(5;12) \) translocation is associated exclusively with chronic myelomonocytic leukemia (CMML) in humans, and results in the expression of the TEL/PDGF\( \beta \)R fusion protein. A murine bone marrow transplant assay was used to test the transforming properties of TEL/PDGF\( \beta \)R in vivo. Expression of the native fusion protein in whole bone marrow was associated with the development of a rapidly fatal myeloproliferative disease in mice closely recapitulating the human disease, CMML. Remarkably, besides granulocytic cells, no other cell lineages were affected. To assay the residues required for the transformation of primary hematopoietic cells, a series of signaling mutants of the TEL/PDGF\( \beta \)R fusion protein was constructed. A total of ten tyrosine phosphorylation sites critical for the binding of various SH2 domain containing signaling intermediates were replaced with phenylalanine. All of the phenylalanine (F-) mutants tested were able to confer factor independence to a murine prolymphocytic cell line, Ba/F3. To confirm the validity of these results and their relevance to human disease, each F-mutant was tested in the bone marrow transplantation assay. In contrast to the cell culture data, murine transplantation with the F-series mutants revealed that different F-mutants had distinct transforming properties in vivo. In transplanted animals, tyrosines 579/581 were critical for the development of myeloproliferative phenotype. F-mutants with these residues mutated had no evidence of myeloproliferation but instead developed T-cell lymphomas. In cell culture, these residues are critical for the activation of STAT5, suggesting that STAT5 plays a key role in the development of CMML in this model system. In summary, we have developed a murine model for CMML and have identified the molecular determinants for the development of this phenotype.