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Clonal myeloid disorders are characterized by genetic alterations that activate cytokine signaling pathways and stimulate cell proliferation. These activated signaling pathways have been extensively studied as potential therapeutic targets, and tyrosine kinase inhibitors have indeed had extraordinary success in treating BCR/ABL-positive chronic myeloid leukemia. However, although inhibitors of other activated kinases have been developed that perform well in preclinical studies, the therapeutic efficacy of these drugs in patients has been unimpressive. This article discusses potential reasons for these discordant results and outlines recent scientific advances that are informing future efforts to target activated kinases in clonal myeloid disorders.

**Tyrosine Kinase Inhibitor Treatment for Newly Diagnosed Chronic Myeloid Leukemia** 577

Jerald P. Radich and Michael J. Mauro

Chronic myeloid leukemia (CML) is a myeloproliferative disorder that accounts for approximately 10% of new cases of leukemia. The introduction of tyrosine kinase inhibitors has led to a reduction in mortalities. Thus, the estimated prevalence of CML is increasing. The National Comprehensive Cancer Network and the European Leukemia Net guidelines incorporate frequent molecular monitoring of the fusion BCR-ABL transcript to ensure that patients reach and keep treatment milestones. Most patients with CML are diagnosed in the chronic phase, and approximately 10% to 30% of these patients will at some time in their course meet definition criteria of resistance to imatinib.

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Ami B. Patel, Thomas O'Hare, and Michael W. Deininger

Chronic myeloid leukemia is increasingly viewed as a chronic illness; most patients have a life expectancy close to that of the general population. Despite progress made using BCR-ABL1 tyrosine kinase inhibitors (TKIs), drug resistance via BCR-ABL1–dependent and BCR-ABL1–independent mechanisms continues to be an issue. BCR-ABL1–dependent resistance is primarily mediated through oncoprotein kinase domain mutations and usually results in overt resistance to TKIs. However, BCR-ABL1–independent resistance in the setting of effective BCR-ABL1 inhibition is recognized as a major contributor to minimal residual disease. Efforts to eradicate persistent leukemic stem cells have focused on combination therapy.

**The Development and Use of Janus Kinase 2 Inhibitors for the Treatment of Myeloproliferative Neoplasms**

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Gabriela S. Hobbs, Sarah Rozelle, and Ann Mullally

Following the discovery of the JAK2V617F mutation, Janus kinase (JAK) 2 inhibitors were developed as rationally designed therapy in myeloproliferative neoplasms (MPNs). Although JAK2 inhibitors have clinical efficacy in MPN, they are not clonally selective for the JAK2V617F-mutant cells. Because activated JAK-signal transducer and activator of transcription (STAT) signaling is a common feature of MPN, JAK2 inhibitors are efficacious regardless of the specific MPN phenotypic driver mutation. The Food and Drug Administration approved the JAK1/JAK2 inhibitor, ruxolitinib, for the treatment of myelofibrosis and polycythemia vera. Additional JAK2 inhibitors are currently in advanced phased clinical trials.

**Mechanisms of Resistance to JAK2 Inhibitors in Myeloproliferative Neoplasms**

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Sara C. Meyer

Myeloproliferative neoplasms are driven by activated JAK2 signaling due to somatic mutations in JAK2, the thrombopoietin receptor MPL or the chaperone calreticulin in hematopoietic stem/progenitor cells. JAK2 inhibitors have been developed, but despite clinical benefits, they do not significantly reduce the mutant clone. Loss of response to JAK2 inhibitors occurs and several mechanisms of resistance, genetic and functional, have been identified. Resistance mutations have not been reported in MPN patients suggesting incomplete target inhibition. Alternative targeting of JAK2 by HSP90 inhibitors or type II JAK2 inhibition overcomes resistance to current JAK2 inhibitors. Additional combined therapy approaches are currently being evaluated.

**Tyrosine Kinase Inhibitors in the Treatment of Eosinophilic Neoplasms and Systemic Mastocytosis**

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Jason Gotlib

The World Health Organization's semimolecular classification of eosinophilias emphasizes neoplasms driven by fusion tyrosine kinases. More than 80% of patients with systemic mastocytosis carry the KIT D816V mutation, the primary driver of disease pathogenesis. Genetic annotation of these diseases is critical and affords opportunities for targeted therapy. This article discusses our understanding of the mutated tyrosine kinome of eosinophilic neoplasms and systemic mast cell disease, and the successes and limitations of available therapies. Use of tyrosine kinase inhibitors as a bridge to hematopoietic stem cell transplantation, and development of more selective and potent tyrosine kinase inhibitors is also highlighted.

**The Development of FLT3 Inhibitors in Acute Myeloid Leukemia**

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Jacqueline S. Garcia and Richard M. Stone

FLT3 mutations, generally associated with a poor prognosis, are found in approximately one-third of patients with acute myeloid leukemia (AML) and represent an attractive therapeutic target. FLT3 inhibitors undergoing clinical evaluation include first-generation relatively non-specific small molecules and second-generation compounds with higher potency and

selectivity against mutant FLT3. Recently presented results from a prospective randomized clinical trial will likely lead to a change in the standard of care for younger patients with FLT3-mutated AML: addition of the multi-targeted FLT3 inhibitor midostaurin to standard induction and consolidation chemotherapy. Thus, personalized therapies for this subset of AML will soon be possible.

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Gabriel Ghiaur and Mark Levis

The presence of FLT3 mutations in acute myeloid leukemia (AML) carries a particularly poor prognosis, making the development of FLT3 inhibitors an imperative goal. The last decade has seen an abundance of clinical trials using these drugs alone or in combination with chemotherapy. This culminated with the recent approval by the US Food and Drug Administration of Midostaurin for the treatment of FLT3-mutated AML. Initial success has been followed by the emergence of clinical resistance. Although novel FLT3 inhibitors are being developed, studies into mechanisms of resistance raise hope of new strategies to prevent emergence of resistance and eliminate minimal residual disease.

**Kinase Inhibitor Screening in Myeloid Malignancies** **693**

Jeffrey W. Tyner

Kinase pathways are primary effectors of many targeted therapy approaches for cancer. Kinase pathways can be dysregulated by mechanisms far more diverse than chromosomal rearrangements or point mutations, which drove the initial application of kinase inhibitors to cancer. Functional screening with kinase inhibitors is one tool by which we can understand the diversity of target kinases and candidate drugs for patients before fully understanding the mechanistic rationale for kinase pathway dysregulation. By combining functional screening with genomic data, it is also possible to accelerate understanding of these mechanistic underpinnings.

**Identification and Targeting of Kinase Alterations in Histiocytic Neoplasms** **705**

Neval Ozkaya, Ahmet Dogan, and Omar Abdel-Wahab

Histiocytic disorders represent clonal disorders of cells believed to be derived from the monocyte, macrophage, and/or dendritic cell lineage presenting with a range of manifestations. Although their nature as clonal versus inflammatory nonclonal conditions have long been debated, recent studies identified numerous somatic mutations that activate mitogen-activated protein kinase signaling in clinically and histologically diverse forms of histiocytosis. Clinical trials and case series have revealed that targeting aberrant kinase signaling using BRAF and/or MEK inhibitors may be effective. These findings suggest that a personalized approach in which patient-specific alterations are identified and targeted may be a critically important therapeutic approach.