HHS Public Access

Author manuscript

Exp Hematol. Author manuscript; available in PMC 2017 May 01.

Published in final edited form as:

Exp Hematol. 2016 May ; 44(5): 315–321. doi:10.1016/j.exphem.2016.02.007.

Regain control of p53: targeting leukemia stem cells by isoform-specific HDAC inhibition

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Abstract

Leukemia stem cells (LSCs) are self-renewable leukemia-initiating populations that are often resistant to traditional chemotherapy and tyrosine kinase inhibitors (TKI) currently used for treatment of acute or chronic myeloid leukemia (AML or CML). The persistence and continued acquisition of mutations in resistant LSCs represent a major cause for refractory disease and/or relapse following remission. Understanding the mechanisms regulating LSC growth and survival is critical for devising effective therapies that will improve treatment response and outcome. Several recent studies now indicate that the p53 tumor suppressor pathway is often inactivated in *de novo* myeloid leukemia through oncogenic specific mechanisms, which converge on aberrant p53 protein deacetylation. Here, we summarize our current understanding of various mechanisms underlying deregulation of histone deacetylases (HDACs), which could be exploited to restore p53 activity and enhance targeting of LSCs in molecularly defined patient subsets.

Introduction

Leukemia stem cells (LSCs), characterized by unlimited self-renewal capacity, are shown to be central to the initiation, growth and relapse of acute and chronic myelogenous leukemia (AML and CML). Studies in recent years have led to the view that the persistence of these clonal LSC subpopulations could be a major driving mechanism contributing to treatment refractory and/or relapse following remission [1-3]. It has also recently been brought to light that after chemotherapy treatment, clonal evolution from preleukemic hematopoietic stem cells (HSCs) could occur and promote development of chemoresistant relapse [4-6]. The heterogeneity and the dynamic nature of malignant disease progression appear increasingly complex. Meanwhile, it is now clear that new therapies more effective in targeting quiescent and chemoresistant LSCs are needed to improve treatment outcome and cure.

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The authors declared that no conflicts of interest exist.

The tumor suppressor protein p53 is arguably the most studied molecule due to its central role in coordinating regulatory circuits that sense and respond to a wide variety of stressors including DNA damage and oncogenic events and ultimately control fundamental cell fate decisions such as cell cycle progression, apoptosis, senescence, metabolism, and autophagy [7,8]. The important role of p53 in cancer is underscored by the fact that genetic mutations in *TP53* have been detected in approximately half of all human cancers and disruption of other p53 pathway components is prevalent in the remainder [9]. In myeloid leukemias, however, *TP53* mutations are relatively infrequent (less than 10%) and mostly associate with complex karyotype and therapy related neoplasms [10-13]. Nevertheless, *TP53* mutation is recognized as an adverse risk factor for chemotherapy response and prognosis [14,15]. As a master coordinator of important cellular processes, p53 function is regulated by a wide spectrum of post-translational modifications including phosphorylation, ubiquitination, acetylation, methylation and sumoylation [7,16-19]. It has been suggested that inactivation of non-mutated p53 frequently occurs through binding to its principal regulator MDM2, a E3 ubiquitin ligase that mediates degradation of p53 [20-22]. Compounds that directly interfere with the binding of p53 and MDM2, including Nutlins and MI-series inhibitors, have been developed and evaluated for anti-leukemia efficacy [23-32]. Multiple mechanisms have been observed to influence the efficacy of MDM2 inhibitors, underscoring the need to further dissect the heterogeneity and oncogene-specific mechanisms inhibiting p53 response in various types of leukemia. In particular, LSCs pertinent to refractory disease and relapse could rely heavily on alternative p53-inactivating mechanisms for survival and continued evolution during and following chemotherapy. Understanding these mechanisms presents new opportunities to specifically reactivate p53 and elicit LSC-selective vulnerability.

Histone deacetylases (HDACs) are enzymes that catalyze the removal of acetyl moieties from ε-amino groups of lysine residues in a variety of proteins, including histones and nonhistone proteins [33]. Based on homology to the yeast HDACs and their enzymatic activities, HDAC proteins are categorized into four classes, including class I (HDAC1, 2, 3 and 8), class II (HDAC4, 5, 6, 7, 9 and 10), class III (SIRT1, 2, 3, 4, 5, 6 and 7) and class IV (HDAC11). HDACs are widely recognized as important epigenetic regulators of gene expression via histone modification and chromatin remodeling. Many broad spectrum HDAC inhibitors have potent anticancer activities and are in various stages of clinical trials [33-38]. However, these inhibitors are highly toxic and lack selectivity, which have greatly hampered their clinical application and efficacy. More selective inhibition of mechanistically defined HDAC targets is needed to effectively eliminate cancer cells and minimize toxicity. Several members of the class I (HDAC1, 2 and 3) [39-41] and class III HDACs [42,43] are known to deacetylate the p53 protein. Given that acetylation modification of the p53 protein is essential for stabilization, nuclear localization, and transcriptional activation [44,45], p53 activity can be specifically altered by deregulation of HDACs. Here we focus on recent advances in our understanding of divergent p53-inactivating mechanisms and how deregulation of specific HDAC proteins could be exploited to restore p53 activity and enhance targeting of LSCs.

BCR-ABL activates SIRT1 expression in CML

CML has served as a paradigm for neoplasia evolution and targeted molecular therapy [46]. CML usually presents in a chronic phase and progresses through an accelerated phase followed by a terminal acute leukemia-like blast crisis [47]. It is uniformly associated with a chromosomal translocation t(9;22)(q34; q11) which results in the generation of *BCR-ABL* fusion gene. A unique feature of CML is that a single genetic lesion encoding the BCR-ABL fusion protein is sufficient to initiate malignant transformation of hematopoietic stem cells (HSCs). The use of tyrosine kinase inhibitor (TKI) to target BCR-ABL signaling has revolutionized the standard of care and greatly improved patient outcome. Treatment with TKI such as imatinib (IM), nilotinib, and dasatinib has been effective in inducing complete cytogenetic remissions and prolonging survival of chronic phase CML patients, but less effective against advanced phases of disease [48]. Even though TKI treatment effectively inhibited BCR-ABL kinase activity and reduced proliferation of primitive CML LSCs, it has been unable to eliminate residue LSC populations that may be potential sources of relapse [49-52]. In addition, mutations in BCR-ABL that confer resistance to TKI are common [53-55].

Sirtuin 1 (SIRT1) is a member of the sirtuin family of nicotinamide adenosine dinucleotide (NAD)-dependent deacetylases that regulate numerous biological processes, including aging, DNA repair, cell cycle, metabolism, and cell survival [56,57]. SIRT1 is shown to play important roles in the maintenance and differentiation of HSCs, especially under conditions of stress [58,59]. In CML, Wang et al. showed that SIRT1 deacetylase promotes acquisition of TKI resistant BCR-ABL mutations [60]. Given that acetylation is indispensible for transcriptional activation of p53 protein [44,45], SIRT1 functions as a negative regulator of p53 by deacetylating several lysine sites [42,43,61,62]. SIRT1 expression can be upregulated by multiple mechanisms including epigenetic silencing of a negative regulator HIC1 [63] or altered miRNA regulation [64]. In a study by Yuan et al., it was shown that BCR-ABL activates SIRT1 through STAT5 signaling and SIRT1 act as a survival pathway, which promotes oncogenic transformation and leukemogenesis [65]. Meanwhile, Li et al. showed that SIRT1 is overexpressed in primitive CML stem and progenitor cells compared to their normal counterparts [66]. Genetic knock-down of SIRT1 or pharmacological inhibition by the small molecule inhibitor tenovin-6 (TV-6) [67] impaired proliferation and induced apoptosis of CML stem and progenitor cells. In addition, combination of TV-6 with IM TKI treatment significantly reduced CML LSC growth and prolonged survival *in vivo*. Inhibition of SIRT1 led to enhanced p53 acetylation, and p53 activation is required for observed growth inhibitory effects of CML stem/progenitor cells. Another recent study by Wang et al. further demonstrated that genetic loss of SIRT1 depleted maintenance of CML LSCs [68]. Collectively, these studies establish that inhibiting the SIRT1-dependent survival pathway effectively activates p53 response and enhances targeting of CML LSCs. Combination of SIRT1 inhibitors with TKI could be efficacious for treating advanced CML disease and/or eradicating minimal residual disease.

FLT3-ITD induces SIRT1-c-MYC network in AML

AML is a form of highly heterogeneous hematopoietic malignancy with diverse cytogenetic, genetic and molecular abnormalities [69]. Identification of cytogenetic and genetic lesions

has revolutionized AML disease classification and prognosis stratification [70-73]. However, treatment outcome in the majority of patients remains poor, with frequent and fatal relapse. Seminal work by Lapidot et al. provided the first proof that the continued growth and propagation of AML depends on a rare population of leukemia-initiating LSCs [74]. With the advent of next generation sequencing technologies, the profound heterogeneity in genomic and epigenetic landscapes in AML is undoubtedly clear [75,76]. It has also allowed detection of stepwise acquisition of AML driving mutations and infer clonal architecture [4-6,77]. In addition, it has led to identification of preleukemic stem cells harboring one or few founding mutations and the ability to acquire additional mutations contributing to relapse. The dynamic clonal and subclonal evolution during or following treatment further contributes to the complexity and heterogeneity of therapy response and outcome in AML. In-depth understanding of molecular alterations and oncogenic mechanisms underlying diverse genetic lesions and LSC resistance is needed to devise effective targeted therapies.

Activating mutations in receptor tyrosine kinases and signaling components constitute one of the classical types of mutations associated with AML. FMS-like tyrosine kinase-3 (FLT3) internal tandem duplication (ITD) is observed in 25–30% of AML patients and predicts poor prognosis [78-84]. The ITD mutation disrupts the negative regulatory function of the juxtamembrane domain, rendering FLT3 receptor constitutively active [85-87]. FLT3-ITD mutation activates canonical receptor tyrosine kinase signaling, most prominently via STAT5, RAS/MAPK, and PI3K [86,88-91]. Expression of FLT3-ITD from the endogenous promoter results in loss of HSC quiescence and a myeloproliferation neoplasm, which is reversible by FLT3-TKI treatment [92]. There are several small molecule FLT3 TKIs including quizartinib (AC220) and sorafenib being evaluated in clinical trials; however, responses have been heterogeneous and transient [93-96]. These results suggest that the leukemia-initiating LSCs may be escaping FLT3 TKI-induced cytotoxicity [96-99].

In an effort to better understand drug resistance mechanisms, Li et al. showed that FLT3-ITD caused increased SIRT1 protein expression via enhanced expression of USP22 deubiquitinase induced by c-MYC [100,101], which is activated by PIM1 as well as SIRT1-c-MYC feed forward loop in FLT3-ITD AML cells [102,103]. Inhibition of SIRT1 by shRNA-mediated knock-down or pharmacological inhibitor TV-6 reciprocally increased c-Myc acetylation and reduced its stability. SIRT1 knock-down or inhibition by TV-6 resulted in enhanced p53 acetylation and p53 target gene expression. Combination of TV6 with AC220 reduced FLT3-ITD$^+$ AML CD34$^+$ cell growth and survival, and enhanced TKI-mediated targeting of AML LSCs *in vivo* [100]. Meanwhile, Sasca et al. demonstrated that tyrosine kinase signaling including STAT5 and RAS activation likely acts in concert to activate SIRT1 expression [104]. In addition, it is proposed that FLT3-ITD regulates p53 acetylation via the ATM-DBC1-SIRT1 axis, which could also be regulated by irradiation-induced genotoxic stress [104]. In murine AML models driven in combination with MLL-AF9 or RUNX1-ETO, the combination of TV-6 and TKI modestly enhanced inhibition of proliferation [104]. The impact of additional genetic and cytogenetic aberrations on the sensitivity to SIRT1 inhibition remains to be determined. It is noteworthy that this p53 activating effect elicited by SIRT1 inhibition was not seen in FLT3 non-mutated AML cells or normal cells, underscoring the importance of identifying oncogene-specific adaptive response in the face of chemotherapy and other targeted therapy. However, there appears to

be some discrepancy regarding whether SIRT1 activation was selective for FLT3-ITD$^+$ AML and not for AML with FLT3-TKD mutations. Further studies are needed to clarify the nature and spectrum of oncogenic stimuli rendering SIRT1 activation and sensitivity to SIRT1 inhibition.

HDAC8 mediates deacetylation of p53 in inv(16) AML

In AML, chromosomal abnormalities frequently result in transcription factor fusion proteins that contribute to the unique etiology and prognosis of distinct cytogenetic subsets [105]. As a master transcriptional regulator of hematopoiesis, the core-binding factor (CBF) complex is a common target of leukemia-associated mutations [106,107]. Among the most common cytogenetic aberrations found in AML patients is chromosome 16 inversion inv(16)(p13.1q22) or translocation t(16;16)(p13.1;q22) [108]. Inv(16) generates a fusion gene *Cbfb-MYH11*, leading to expression of a fusion protein CBFβ-SMMHC [109,110]. A series of studies revealed that CBFβ-SMMHC dominantly inhibits CBF function, impairs hematopoietic differentiation and predisposes for leukemia transformation [111-115]. Dominant inhibition of RUNX proteins, either through cytoplasmic sequestration [116,117] or constitutive repression [118,119], was considered the main leukemogenic mechanism of CBFβ-SMMHC chimeric protein. However, more recent studies indicate that functional RUNX proteins are in fact needed for CBFβ-SMMHC leukemogenesis and growth of CBF AML cells [120-124]. It was previously reported that p53 response was reduced by CBFβ-SMMHC [125], although the underlying mechanism was not clear. A recent study by Qi et al. revealed that CBFβ-SMMHC gains p53-inhibiting function via aberrant protein-protein interaction with HDAC8 and the p53 protein [126]. HDAC8 is a member of the zinc-dependent class I HDAC enzyme known to deacetylate lysine residues in a variety of proteins, including histones and transcription factors [127-129]. Qi et al. showed that like other members of class I HDAC, HDAC8 is capable of deacetylating the p53 protein. Thus, CBFβ-SMMHC promoted HDAC8-mediated deacetylation of p53 by recruiting HDAC8 and p53 into an aberrant protein complex. Consequently, p53 induction and target gene expression is largely inhibited in the presence of CBFβ-SMMHC. Although CBFβ-SMMHC binds p53 and HDAC8 independently via distinct protein domains, the p53-inhibiting activity is dependent on the presence of both p53 and HDAC8 proteins in the ternary complex. Depleting CBFβ-SMMHC or HDAC8 resulted in restoration of p53 acetylation and activation upon exposure to genotoxic stress such as irradiation. Genetic deletion of *Hdac8* in a conditional CBFβ-SMMHC knock-in mouse model dramatically diminished LSC transformation, as evidenced by greatly reduced AML incidence and delayed onset. Qi et al. also found that HDAC8 expression was significantly higher in the primitive CD34$^+$ population and that inv(16)$^+$ AML CD34$^+$ cells express 5-12 fold higher levels of HDAC8 compared to non-inv(16) AML or normal CD34$^+$ cells. In line with the differential HDAC8 expression, pharmacologic inhibition of HDAC8 enzyme using HDAC8 isoform-selective inhibitors (HDAC8i) [130,131] resulted in enhanced p53 acetylation, p53 target gene activation, and p53-dependent apoptosis selectively in inv(16)$^+$ AML CD34$^+$ cells while sparing the normal CD34$^+$ stem/progenitor population. This activity further translated into elimination of AML propagation and leukemia-initiating activity in both murine AML and human AML xenograft models *in vivo*. Importantly, HDAC8i treatment was capable of enhancing the chemosensitivity of inv(16)$^+$ CD34$^+$ cells. Despite having a relatively

favorable prognosis, only approximately half of the patients with inv(16) AML eventually achieve long-term survival with the standard chemotherapy regimens [132,133]. These results highlight the potential efficacy of HDAC8i in overcoming chemotherapy resistance and relapse of inv(16)$^+$ AML.

Conclusion

In recent years, several alternative p53 inactivation mechanisms specific to the underlying oncogenic lesions have been shown for CML, FLT3-ITD$^+$ AML, and inv(16)$^+$ AML. These divergent pathways converge on inhibiting p53 acetylation via deregulation of alternative protein deacetylases (Figure 1). These results partly explain the heterogenous response to other p53 activating agents such as MDM2 inhibitors. Given that *TP53* is rarely mutated in *de novo* myeloid neoplasm, these findings present new opportunities to regain control of p53 activity and enhance response to chemotherapy or other targeted therapies. Importantly, LSC populations relevant to refractory disease and relapse are selectively sensitive to perturbation of the specific protein deacetylase defined by the specific oncogenic mechanism. Thus, selective inhibition of context-specific HDAC isoforms is a promising approach to eradicate residual drug resistant LSCs, prevent further acquisition of mutations and reduce relapse. This highlights the importance to dissect the genetic and molecular heterogeneity, particularly in AML. These studies also demonstrate that by attacking cancer-specific vulnerability, the normal HSC counterpart can largely be spared. Further development of isoform specific HDAC inhibitors is critical to translate these insights into the clinic.

Acknowledgements

The authors would like to acknowledge the research support from the American Cancer Society (123278-RSG-12-140-01-CSM to Y.-H.K.), and the National Cancer Institute of the National Instituted of Health under award number R01CA178387 (to Y.-H.K.) and P30CA033572 (to COH). The content is solely the responsibility of the authors and does not represent the official views of the National Institutes of Health.

Reference

1. Dick JE. Acute myeloid leukemia stem cells. Ann N Y Acad Sci. Jun.2005 1044:1–5. [PubMed: 15958691]
2. Chan W-I, Huntly BJP. Leukemia stem cells in acute myeloid leukemia. Semin Oncol. Aug; 2008 35(4):326–35. [PubMed: 18692683]
3. Reinisch A, Chan SM, Thomas D, Majeti R. Biology and clinical relevance of acute myeloid leukemia stem cells. Semin Hematol. Jul; 2015 52(3):150–64. [PubMed: 26111462]
4. Corces-Zimmerman MR, Majeti R. Pre-leukemic evolution of hematopoietic stem cells: The importance of early mutations in leukemogenesis. Leukemia. Dec; 2014 28(12):2276–82. [PubMed: 25005245]
5. Shlush LI, Zandi S, Mitchell A, Chen WC, Brandwein JM, Gupta V, et al. Identification of pre-leukaemic haematopoietic stem cells in acute leukaemia. Nature. Feb 20; 2014 506(7488):328–33. [PubMed: 24522528]
6. Corces-Zimmerman MR, Hong W-J, Weissman IL, Medeiros BC, Majeti R. Preleukemic mutations in human acute myeloid leukemia affect epigenetic regulators and persist in remission. Proc Natl Acad Sci U S A. Feb 18; 2014 111(7):2548–53. [PubMed: 24550281]
7. Vousden KH, Lane DP. P53 in health and disease. Nat Rev Mol Cell Biol. Apr; 2007 8(4):275–83. [PubMed: 17380161]

8. Kruiswijk F, Labuschagne CF, Vousden KH. P53 in survival, death and metabolic health: A lifeguard with a licence to kill. Nat Rev Mol Cell Biol. Jul; 2015 16(7):393–405. [PubMed: 26122615]
9. Green DR, Kroemer G. Cytoplasmic functions of the tumour suppressor p53. Nature. Apr 30; 2009 458(7242):1127–30. [PubMed: 19407794]
10. Rücker FG, Schlenk RF, Bullinger L, Kayser S, Teleanu V, Kett H, et al. TP53 alterations in acute myeloid leukemia with complex karyotype correlate with specific copy number alterations, monosomal karyotype, and dismal outcome. Blood. Mar 1; 2012 119(9):2114–21. [PubMed: 22186996]
11. Wong TN, Ramsingh G, Young AL, Miller CA, Touma W, Welch JS, et al. Role of TP53 mutations in the origin and evolution of therapy-related acute myeloid leukaemia. Nature. Feb 26; 2015 518(7540):552–5. [PubMed: 25487151]
12. Haferlach C, Dicker F, Herholz H, Schnittger S, Kern W, Haferlach T. Mutations of the TP53 gene in acute myeloid leukemia are strongly associated with a complex aberrant karyotype. Leukemia. Aug; 2008 22(8):1539–41. [PubMed: 18528419]
13. Ok CY, Patel KP, Garcia-Manero G, Routbort MJ, Peng J, Tang G, et al. TP53 mutation characteristics in therapy-related myelodysplastic syndromes and acute myeloid leukemia is similar to de novo diseases. J Hematol Oncol. 2015; 8:45. [PubMed: 25952993]
14. Wattel E, Preudhomme C, Hecquet B, Vanrumbeke M, Quesnel B, Dervite I, et al. P53 mutations are associated with resistance to chemotherapy and short survival in hematologic malignancies. Blood. Nov 1; 1994 84(9):3148–57. [PubMed: 7949187]
15. Nakano Y, Naoe T, Kiyoi H, Kitamura K, Minami S, Miyawaki S, et al. Prognostic value of p53 gene mutations and the product expression in de novo acute myeloid leukemia. Eur J Haematol. Jul; 2000 65(1):23–31. [PubMed: 10914936]
16. Brooks CL, Gu W. P53 regulation by ubiquitin. FEBS Lett. Sep 16; 2011 585(18):2803–9. [PubMed: 21624367]
17. Marouco D, Garabadgiu AV, Melino G, Barlev NA. Lysine-specific modifications of p53: A matter of life and death? Oncotarget. Oct; 2013 4(10):1556–71. [PubMed: 24298606]
18. Brooks CL, Gu W. The impact of acetylation and deacetylation on the p53 pathway. Protein Cell. Jun; 2011 2(6):456–62. [PubMed: 21748595]
19. Dai C, Gu W. P53 post-translational modification: Deregulated in tumorigenesis. Trends Mol Med. Nov; 2010 16(11):528–36. [PubMed: 20932800]
20. Bueso-Ramos CE, Yang Y, deLeon E, McCown P, Stass SA, Albitar M. The human MDM- 2 oncogene is overexpressed in leukemias. Blood. Nov 1; 1993 82(9):2617–23. [PubMed: 8219216]
21. Bueso-Ramos CE, Manshouri T, Haidar MA, Huh YO, Keating MJ, Albitar M. Multiple patterns of MDM-2 deregulation in human leukemias: Implications in leukemogenesis and prognosis. Leuk Lymphoma. Mar; 1995 17(1-2):13–8. [PubMed: 7773150]
22. Seliger B, Papadileris S, Vogel D, Hess G, Brendel C, Störkel S, et al. Analysis of the p53 and MDM-2 gene in acute myeloid leukemia. Eur J Haematol. Sep; 1996 57(3):230–40. [PubMed: 8898928]
23. Vassilev LT, Vu BT, Graves B, Carvajal D, Podlaski F, Filipovic Z, et al. In vivo activation of the p53 pathway by small-molecule antagonists of MDM2. Science. Feb 6; 2004 303(5659):844–8. [PubMed: 14704432]
24. Ding K, Lu Y, Nikolovska-Coleska Z, Wang G, Qiu S, Shangary S, et al. Structure-based design of spiro-oxindoles as potent, specific small-molecule inhibitors of the mdm2-p53 interaction. J Med Chem. Jun 15; 2006 49(12):3432–5. [PubMed: 16759082]
25. Secchiero P, Zerbinati C, Melloni E, Milani D, Campioni D, Fadda R, et al. The MDM-2 antagonist nutlin-3 promotes the maturation of acute myeloid leukemic blasts. Neoplasia. Oct; 2007 9(10):853–61. [PubMed: 17971905]
26. Shangary S, Qin D, McEachern D, Liu M, Miller RS, Qiu S, et al. Temporal activation of p53 by a specific MDM2 inhibitor is selectively toxic to tumors and leads to complete tumor growth inhibition. Proc Natl Acad Sci U S A. Mar 11; 2008 105(10):3933–8. [PubMed: 18316739]

27. Kurosu T, Wu N, Oshikawa G, Kagechika H, Miura O. Enhancement of imatinib-induced apoptosis of BCR/abl-expressing cells by nutlin-3 through synergistic activation of the mitochondrial apoptotic pathway. Apoptosis. May; 2010 15(5):608–20. [PubMed: 20094798]
28. Ding Q, Zhang Z, Liu J-J, Jiang N, Zhang J, Ross TM, et al. Discovery of RG7388, a potent and selective p53–MDM2 inhibitor in clinical development. J Med Chem. Jul 25; 2013 56(14):5979–83. [PubMed: 23808545]
29. Zhang Z, Ding Q, Liu J-J, Zhang J, Jiang N, Chu X-J, et al. Discovery of potent and selective spiroindolinone MDM2 inhibitor, RO8994, for cancer therapy. Bioorg Med Chem. Aug 1; 2014 22(15):4001–9. [PubMed: 24997575]
30. Andreeff M, Kelly KR, Yee K, Assouline S, Strair R, Popplewell L, et al. Results of the phase I trial of RG7112, a small-molecule MDM2 antagonist in leukemia. Clin Cancer Res. Oct 12.2015
31. Carter BZ, Mak PY, Mak DH, Ruvolo VR, Schober W, McQueen T, et al. Synergistic effects of p53 activation via MDM2 inhibition in combination with inhibition of bcl-2 or bcr-abl in CD34+ proliferating and quiescent chronic myeloid leukemia blast crisis cells. Oncotarget. Oct 13; 2015 6(31):30487–99. [PubMed: 26431162]
32. Long J, Parkin B, Ouillette P, Bixby D, Shedden K, Erba H, et al. Multiple distinct molecular mechanisms influence sensitivity and resistance to MDM2 inhibitors in adult acute myelogenous leukemia. Blood. Jul 8; 2010 116(1):71–80. [PubMed: 20404136]
33. Bolden JE, Peart MJ, Johnstone RW. Anticancer activities of histone deacetylase inhibitors. Nat Rev Drug Discov. Sep; 2006 5(9):769–84. [PubMed: 16955068]
34. Carew JS, Giles FJ, Nawrocki ST. Histone deacetylase inhibitors: Mechanisms of cell death and promise in combination cancer therapy. Cancer Lett. May 5.2008
35. Frew AJ, Johnstone RW, Bolden JE. Enhancing the apoptotic and therapeutic effects of HDAC inhibitors. Cancer Lett. Aug 8; 2009 280(2):125–33. [PubMed: 19359091]
36. Ma X, Ezzeldin HH, Diasio RB. Histone deacetylase inhibitors: Current status and overview of recent clinical trials. Drugs. Oct 1; 2009 69(14):1911–34. [PubMed: 19747008]
37. Wanczyk M, Roszczenko K, Marcinkiewicz K, Bojarczuk K, Kowara M, Winiarska M. HDACi--going through the mechanisms. Front Biosci. 2011; 16:340–59.
38. Khan N, Jeffers M, Kumar S, Hackett C, Boldog F, Khramtsov N, et al. Determination of the class and isoform selectivity of small-molecule histone deacetylase inhibitors. Biochem J. Jan 15; 2008 409(2):581–9. [PubMed: 17868033]
39. Juan LJ, Shia WJ, Chen MH, Yang WM, Seto E, Lin YS, Wu CW. Histone deacetylases specifically down-regulate p53-dependent gene activation. J Biol Chem. Jul 7; 2000 275(27): 20436–43. [PubMed: 10777477]
40. Luo J, Su F, Chen D, Shiloh A, Gu W. Deacetylation of p53 modulates its effect on cell growth and apoptosis. Nature. Nov 16; 2000 408(6810):377–81. [PubMed: 11099047]
41. Ito A, Kawaguchi Y, Lai CH, Kovacs JJ, Higashimoto Y, Appella E, Yao TP. MDM2-HDAC1-mediated deacetylation of p53 is required for its degradation. EMBO J. Nov 15; 2002 21(22): 6236–45. [PubMed: 12426395]
42. Luo J, Nikolaev AY, Imai S, Chen D, Su F, Shiloh A, et al. Negative control of p53 by sir2alpha promotes cell survival under stress. Cell. Oct 19; 2001 107(2):137–48. [PubMed: 11672522]
43. Vaziri H, Dessain SK, Ng Eaton E, Imai SI, Frye RA, Pandita TK, et al. HSIR2(SIRT1) functions as an nad-dependent p53 deacetylase. Cell. Oct 19; 2001 107(2):149–59. [PubMed: 11672523]
44. Prives C, Manley JL. Why is p53 acetylated? Cell. Dec 28; 2001 107(7):815–8. [PubMed: 11779456]
45. Tang Y, Zhao W, Chen Y, Zhao Y, Gu W. Acetylation is indispensable for p53 activation. Cell. May 16; 2008 133(4):612–26. [PubMed: 18485870]
46. Melo JV, Barnes DJ. Chronic myeloid leukaemia as a model of disease evolution in human cancer. Nat Rev Cancer. Jun; 2007 7(6):441–53. [PubMed: 17522713]
47. Sawyers CL. Chronic myeloid leukemia. N Engl J Med. Apr 29; 1999 340(17):1330–40. [PubMed: 10219069]
48. Eiring AM, Khorashad JS, Morley K, Deininger MW. Advances in the treatment of chronic myeloid leukemia. BMC Med. 2011; 9:99. [PubMed: 21867560]

49. Holtz MS, Forman SJ, Bhatia R. Nonproliferating CML CD34+ progenitors are resistant to apoptosis induced by a wide range of proapoptotic stimuli. Leukemia. Jun; 2005 19(6):1034–41. [PubMed: 15815728]
50. Chu S, McDonald T, Lin A, Chakraborty S, Huang Q, Snyder DS, Bhatia R. Persistence of leukemia stem cells in chronic myelogenous leukemia patients in prolonged remission with imatinib treatment. Blood. Nov 17; 2011 118(20):5565–72. [PubMed: 21931114]
51. Barnes DJ, Melo JV. Primitive, quiescent and difficult to kill: The role of non-proliferating stem cells in chronic myeloid leukemia. Cell Cycle. Dec; 2006 5(24):2862–6. [PubMed: 17172863]
52. Corbin AS, Agarwal A, Loriaux M, Cortes J, Deininger MW, Druker BJ. Human chronic myeloid leukemia stem cells are insensitive to imatinib despite inhibition of BCR-ABL activity. J Clin Invest. Jan; 2011 121(1):396–409. [PubMed: 21157039]
53. Shah NP, Nicoll JM, Nagar B, Gorre ME, Paquette RL, Kuriyan J, Sawyers CL. Multiple BCR-ABL kinase domain mutations confer polyclonal resistance to the tyrosine kinase inhibitor imatinib (STI571) in chronic phase and blast crisis chronic myeloid leukemia. Cancer Cell. Aug; 2002 2(2):117–25. [PubMed: 12204532]
54. Branford S, Rudzki Z, Walsh S, Parkinson I, Grigg A, Szer J, et al. Detection of BCR-ABL mutations in patients with CML treated with imatinib is virtually always accompanied by clinical resistance, and mutations in the ATP phosphate-binding loop (p-loop) are associated with a poor prognosis. Blood. Jul 1; 2003 102(1):276–83. [PubMed: 12623848]
55. Hughes TP, Saglio G, Quintás-Cardama A, Mauro MJ, Kim D-W, Lipton JH, et al. BCR ABL1 mutation development during first-line treatment with dasatinib or imatinib for chronic myeloid leukemia in chronic phase. Leukemia. Sep; 2015 29(9):1832–8. [PubMed: 26118315]
56. Bordone L, Guarente L. Calorie restriction, SIRT1 and metabolism: Understanding longevity. Nat Rev Mol Cell Biol. Apr; 2005 6(4):298–305. [PubMed: 15768047]
57. Liu T, Liu PY, Marshall GM. The critical role of the class III histone deacetylase SIRT1 in cancer. Cancer Res. Mar 1; 2009 69(5):1702–5. [PubMed: 19244112]
58. Singh SK, Williams CA, Klarmann K, Burkett SS, Keller JR, Oberdoerffer P. Sirt1 ablation promotes stress-induced loss of epigenetic and genomic hematopoietic stem and progenitor cell maintenance. J Exp Med. May 6; 2013 210(5):987–1001. [PubMed: 23630229]
59. Ou X, Chae H-D, Wang R-H, Shelley WC, Cooper S, Taylor T, et al. SIRT1 deficiency compromises mouse embryonic stem cell hematopoietic differentiation, and embryonic and adult hematopoiesis in the mouse. Blood. Jan 13; 2011 117(2):440–50. [PubMed: 20966168]
60. Wang Z, Yuan H, Roth M, Stark JM, Bhatia R, Chen WY. SIRT1 deacetylase promotes acquisition of genetic mutations for drug resistance in CML cells. Oncogene. Jan 31; 2013 32(5):589–98. [PubMed: 22410779]
61. Yi J, Luo J. SIRT1 and p53, effect on cancer, senescence and beyond. Biochim Biophys Acta. Aug; 2010 1804(8):1684–9. [PubMed: 20471503]
62. Brooks CL, Gu W. How does SIRT1 affect metabolism, senescence and cancer? Nat Rev Cancer. Feb; 2009 9(2):123–8. [PubMed: 19132007]
63. Chen WY, Wang DH, Yen RC, Luo J, Gu W, Baylin SB. Tumor suppressor HIC1 directly regulates SIRT1 to modulate p53-dependent dna-damage responses. Cell. Nov 4; 2005 123(3):437–48. [PubMed: 16269335]
64. Strum JC, Johnson JH, Ward J, Xie H, Feild J, Hester A, et al. MicroRNA 132 regulates nutritional stress-induced chemokine production through repression of sirt1. Mol Endocrinol. Nov; 2009 23(11):1876–84. [PubMed: 19819989]
65. Yuan H, Wang Z, Li L, Zhang H, Modi H, Horne D, et al. Activation of stress response gene SIRT1 by BCR-ABL promotes leukemogenesis. Blood. Feb 23; 2012 119(8):1904–14. [PubMed: 22207735]
66. Li L, Wang L, Li L, Wang Z, Ho Y, McDonald T, et al. Activation of p53 by SIRT1 inhibition enhances elimination of CML leukemia stem cells in combination with imatinib. Cancer Cell. Feb 14; 2012 21(2):266–81. [PubMed: 22340598]
67. Lain S, Hollick JJ, Campbell J, Staples OD, Higgins M, Aoubala M, et al. Discovery, in vivo activity, and mechanism of action of a small-molecule p53 activator. Cancer Cell. May; 2008 13(5):454–63. [PubMed: 18455128]

68. Wang Z, Chen C-C, Chen W. CD150(−) side population defines leukemia stem cells in a BALB/c mouse model of CML and is depleted by genetic loss of SIRT1. Stem Cells. Oct 15.2015
69. Döhner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. N Engl J Med. Sep 16; 2015 373(12):1136–52. [PubMed: 26376137]
70. Marcucci G, Mrózek K, Bloomfield CD. Molecular heterogeneity and prognostic biomarkers in adults with acute myeloid leukemia and normal cytogenetics. Curr Opin Hematol. Jan; 2005 12(1): 68–75. [PubMed: 15604894]
71. Gaidzik V, Döhner K. Prognostic implications of gene mutations in acute myeloid leukemia with normal cytogenetics. Semin Oncol. Aug; 2008 35(4):346–55. [PubMed: 18692685]
72. Scholl S, Fricke H-J, Sayer HG, Höffken K. Clinical implications of molecular genetic aberrations in acute myeloid leukemia. J Cancer Res Clin Oncol. Apr; 2009 135(4):491–505. [PubMed: 19125300]
73. Marcucci G, Haferlach T, Döhner H. Molecular genetics of adult acute myeloid leukemia: Prognostic and therapeutic implications. J Clin Oncol. Feb 10; 2011 29(5):475–86. [PubMed: 21220609]
74. Lapidot T, Sirard C, Vormoor J, Murdoch B, Hoang T, Caceres-Cortes J, et al. A cell initiating human acute myeloid leukaemia after transplantation into SCID mice. Nature. Feb 17; 1994 367(6464):645–8. [PubMed: 7509044]
75. Sanders MA, Valk PJ. The evolving molecular genetic landscape in acute myeloid leukaemia. Curr Opin Hematol. Mar; 2013 20(2):79–85. [PubMed: 23380602]
76. Cancer Genome Atlas Research Network. Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. N Engl J Med. May 30; 2013 368(22):2059–74. [PubMed: 23634996]
77. Bodini M, Ronchini C, Giacò L, Russo A, Melloni GEM, Luzi L, et al. The hidden genomic landscape of acute myeloid leukemia: Subclonal structure revealed by undetected mutations. Blood. Jan 22; 2015 125(4):600–5. [PubMed: 25499761]
78. Nakao M, Yokota S, Iwai T, Kaneko H, Horiike S, Kashima K, et al. Internal tandem duplication of the flt3 gene found in acute myeloid leukemia. Leukemia. Dec; 1996 10(12):1911–8. [PubMed: 8946930]
79. Sallmyr A, Fan J, Datta K, Kim K-T, Grosu D, Shapiro P, et al. Internal tandem duplication of FLT3 (FLT3/ITD) induces increased ROS production, DNA damage, and misrepair: Implications for poor prognosis in AML. Blood. Mar 15; 2008 111(6):3173–82. [PubMed: 18192505]
80. Kindler T, Lipka DB, Fischer T. FLT3 as a therapeutic target in AML: Still challenging after all these years. Blood. Dec 9; 2010 116(24):5089–102. [PubMed: 20705759]
81. Thiede C, Steudel C, Mohr B, Schaich M, Schäkel U, Platzbecker U, et al. Analysis of flt3-activating mutations in 979 patients with acute myelogenous leukemia: Association with FAB subtypes and identification of subgroups with poor prognosis. Blood. Jun 15; 2002 99(12):4326–35. [PubMed: 12036858]
82. Fröhling S, Schlenk RF, Breitruck J, Benner A, Kreitmeier S, Tobis K, et al. Prognostic significance of activating FLT3 mutations in younger adults (16 to 60 years) with acute myeloid leukemia and normal cytogenetics: A study of the AML study group ulm. Blood. Dec 15; 2002 100(13):4372–80. [PubMed: 12393388]
83. Meshinchi S, Woods WG, Stirewalt DL, Sweetser DA, Buckley JD, Tjoa TK, et al. Prevalence and prognostic significance of flt3 internal tandem duplication in pediatric acute myeloid leukemia. Blood. Jan 1; 2001 97(1):89–94. [PubMed: 11133746]
84. Kottaridis PD, Gale RE, Frew ME, Harrison G, Langabeer SE, Belton AA, et al. The presence of a FLT3 internal tandem duplication in patients with acute myeloid leukemia (AML) adds important prognostic information to cytogenetic risk group and response to the first cycle of chemotherapy: Analysis of 854 patients from the united kingdom medical research council AML 10 and 12 trials. Blood. Sep 15; 2001 98(6):1752–9. [PubMed: 11535508]
85. Kiyoi H, Towatari M, Yokota S, Hamaguchi M, Ohno R, Saito H, Naoe T. Internal tandem duplication of the FLT3 gene is a novel modality of elongation mutation which causes constitutive activation of the product. Leukemia. Sep; 1998 12(9):1333–7. [PubMed: 9737679]

86. Mizuki M, Fenski R, Halfter H, Matsumura I, Schmidt R, Müller C, et al. Flt3 mutations from patients with acute myeloid leukemia induce transformation of 32D cells mediated by the ras and STAT5 pathways. Blood. Dec 1; 2000 96(12):3907–14. [PubMed: 11090077]

87. Fenski R, Flesch K, Serve S, Mizuki M, Oelmann E, Kratz-Albers K, et al. Constitutive activation of FLT3 in acute myeloid leukaemia and its consequences for growth of 32D cells. Br J Haematol. Feb; 2000 108(2):322–30. [PubMed: 10691863]

88. Kiyoi H, Ohno R, Ueda R, Saito H, Naoe T. Mechanism of constitutive activation of FLT3 with internal tandem duplication in the juxtamembrane domain. Oncogene. Apr 11; 2002 21(16):2555–63. [PubMed: 11971190]

89. Tse KF, Novelli E, Civin CI, Bohmer FD, Small D. Inhibition of flt3-mediated transformation by use of a tyrosine kinase inhibitor. Leukemia. Jul; 2001 15(7):1001–10. [PubMed: 11455967]

90. Hayakawa F, Towatari M, Kiyoi H, Tanimoto M, Kitamura T, Saito H, Naoe T. Tandem- duplicated flt3 constitutively activates STAT5 and MAP kinase and introduces autonomous cell growth in il-3-dependent cell lines. Oncogene. Feb 3; 2000 19(5):624–31. [PubMed: 10698507]

91. Yoshimoto G, Miyamoto T, Jabbarzadeh-Tabrizi S, Iino T, Rocnik JL, Kikushige Y, et al. FLT3-ITD up-regulates MCL-1 to promote survival of stem cells in acute myeloid leukemia via flt3-itd-specific STAT5 activation. Blood. Dec 3; 2009 114(24):5034–43. [PubMed: 19808698]

92. Chu SH, Heiser D, Li L, Kaplan I, Collector M, Huso D, et al. FLT3-ITD knockin impairs hematopoietic stem cell quiescence/homeostasis, leading to myeloproliferative neoplasm. Cell Stem Cell. Sep; 2012 11(3):346–58. [PubMed: 22958930]

93. Grundler R, Thiede C, Miething C, Steudel C, Peschel C, Duyster J. Sensitivity toward tyrosine kinase inhibitors varies between different activating mutations of the FLT3 receptor. Blood. Jul 15; 2003 102(2):646–51. [PubMed: 12663439]

94. Knapper S, Burnett AK, Littlewood T, Kell WJ, Agrawal S, Chopra R, et al. A phase 2 trial of the FLT3 inhibitor lestaurtinib (CEP701) as first-line treatment for older patients with acute myeloid leukemia not considered fit for intensive chemotherapy. Blood. Nov 15; 2006 108(10):3262–70. [PubMed: 16857985]

95. Weisberg E, Boulton C, Kelly LM, Manley P, Fabbro D, Meyer T, et al. Inhibition of mutant FLT3 receptors in leukemia cells by the small molecule tyrosine kinase inhibitor PKC412. Cancer Cell. Jun; 2002 1(5):433–43. [PubMed: 12124173]

96. Levis M, Ravandi F, Wang ES, Baer MR, Perl A, Coutre S, et al. Results from a randomized trial of salvage chemotherapy followed by lestaurtinib for patients with FLT3 mutant AML in first relapse. Blood. Mar 24; 2011 117(12):3294–301. [PubMed: 21270442]

97. Levis M. Quizartinib for the treatment of FLT3/ITD acute myeloid leukemia. Future Oncol. 2014; 10(9):1571–9. [PubMed: 25145428]

98. Swords R, Freeman C, Giles F. Targeting the fms-like tyrosine kinase 3 in acute myeloid leukemia. Leukemia. Oct; 2012 26(10):2176–85. [PubMed: 22614177]

99. Smith CC, Wang Q, Chin C-S, Salerno S, Damon LE, Levis MJ, et al. Validation of ITD mutations in FLT3 as a therapeutic target in human acute myeloid leukaemia. Nature. May 10; 2012 485(7397):260–3. [PubMed: 22504184]

100. Li L, Osdal T, Ho Y, Chun S, McDonald T, Agarwal P, et al. SIRT1 activation by a c-myc oncogenic network promotes the maintenance and drug resistance of human FLT3-ITD acute myeloid leukemia stem cells. Cell Stem Cell. Oct 2; 2014 15(4):431–46. [PubMed: 25280219]

101. Lin Z, Yang H, Kong Q, Li J, Lee S-M, Gao B, et al. USP22 antagonizes p53 transcriptional activation by deubiquitinating sirt1 to suppress cell apoptosis and is required for mouse embryonic development. Mol Cell. May 25; 2012 46(4):484–94. [PubMed: 22542455]

102. Choudhary C, Olsen JV, Brandts C, Cox J, Reddy PNG, Böhmer FD, et al. Mislocalized activation of oncogenic rtks switches downstream signaling outcomes. Mol Cell. Oct 23; 2009 36(2):326–39. [PubMed: 19854140]

103. Kim K-T, Baird K, Ahn J-Y, Meltzer P, Lilly M, Levis M, Small D. Pim-1 is up-regulated by constitutively activated FLT3 and plays a role in flt3-mediated cell survival. Blood. Feb 15; 2005 105(4):1759–67. [PubMed: 15498859]

104. Sasca D, Hähnel PS, Szybinski J, Khawaja K, Kriege O, Pante SV, et al. SIRT1 prevents genotoxic stress-induced p53 activation in acute myeloid leukemia. Blood. Jul 3; 2014 124(1): 121–33. [PubMed: 24855208]
105. Look AT. Oncogenic transcription factors in the human acute leukemias. Science. Nov 7; 1997 278(5340):1059–64. [PubMed: 9353180]
106. Speck NA, Stacy T, Wang Q, North T, Gu TL, Miller J, et al. Core-binding factor: A central player in hematopoiesis and leukemia. Cancer Res. Apr 1; 1999 59(7 Suppl):1789s–93s. [PubMed: 10197598]
107. Speck NA, Gilliland DG. Core-binding factors in haematopoiesis and leukaemia. Nat Rev Cancer. Jul; 2002 2(7):502–13. [PubMed: 12094236]
108. Liu PP, Wijmenga C, Hajra A, Blake TB, Kelley CA, Adelstein RS, et al. Identification of the chimeric protein product of the CBFB-MYH11 fusion gene in inv(16) leukemia cells. Genes Chromosomes Cancer. Jun; 1996 16(2):77–87. [PubMed: 8818654]
109. Liu P, Tarlé SA, Hajra A, Claxton DF, Marlton P, Freedman M, et al. Fusion between transcription factor CBF beta/PEBP2 beta and a myosin heavy chain in acute myeloid leukemia. Science. Aug 20; 1993 261(5124):1041–4. [PubMed: 8351518]
110. Liu PP, Hajra A, Wijmenga C, Collins FS. Molecular pathogenesis of the chromosome 16 inversion in the m4eo subtype of acute myeloid leukemia. Blood. May 1; 1995 85(9):2289–302. [PubMed: 7727763]
111. Castilla LH, Wijmenga C, Wang Q, Stacy T, Speck NA, Eckhaus M, et al. Failure of embryonic hematopoiesis and lethal hemorrhages in mouse embryos heterozygous for a knocked-in leukemia gene CBFB-MYH11. Cell. Nov 15; 1996 87(4):687–96. [PubMed: 8929537]
112. Castilla LH, Garrett L, Adya N, Orlic D, Dutra A, Anderson S, et al. The fusion gene cbfb myh11 blocks myeloid differentiation and predisposes mice to acute myelomonocytic leukaemia. Nat Genet. Oct; 1999 23(2):144–6. [PubMed: 10508507]
113. Kuo Y-H, Landrette SF, Heilman SA, Perrat PN, Garrett L, Liu PP, et al. Cbf beta-smmhc induces distinct abnormal myeloid progenitors able to develop acute myeloid leukemia. Cancer Cell. Jan; 2006 9(1):57–68. [PubMed: 16413472]
114. Kuo Y-H, Gerstein RM, Castilla LH. Cbfbeta-SMMHC impairs differentiation of common lymphoid progenitors and reveals an essential role for RUNX in early b-cell development. Blood. Feb 1; 2008 111(3):1543–51. [PubMed: 17940206]
115. Zhao L, Cannons JL, Anderson S, Kirby M, Xu L, Castilla LH, et al. CBFB-MYH11 hinders early t-cell development and induces massive cell death in the thymus. Blood. Apr 15; 2007 109(8):3432–40. [PubMed: 17185462]
116. Kanno Y, Kanno T, Sakakura C, Bae SC, Ito Y. Cytoplasmic sequestration of the polyomavirus enhancer binding protein 2 (PEBP2)/core binding factor alpha (cbfalpha) subunit by the leukemia-related PEBP2/cbfbeta-smmhc fusion protein inhibits PEBP2/cbf- mediated transactivation. Mol Cell Biol. Jul; 1998 18(7):4252–61. [PubMed: 9632809]
117. Adya N, Stacy T, Speck NA, Liu PP. The leukemic protein core binding factor beta (cbfbeta)-smooth-muscle myosin heavy chain sequesters cbfalpha2 into cytoskeletal filaments and aggregates. Mol Cell Biol. Dec; 1998 18(12):7432–43. [PubMed: 9819429]
118. Lutterbach B, Hou Y, Durst KL, Hiebert SW. The inv(16) encodes an acute myeloid leukemia 1 transcriptional corepressor. Proc Natl Acad Sci U S A. Oct 26; 1999 96(22):12822–7. [PubMed: 10536006]
119. Durst KL, Lutterbach B, Kummalue T, Friedman AD, Hiebert SW. The inv(16) fusion protein associates with corepressors via a smooth muscle myosin heavy-chain domain. Mol Cell Biol. Jan; 2003 23(2):607–19. [PubMed: 12509458]
120. Kuo Y-H, Zaidi SK, Gornostaeva S, Komori T, Stein GS, Castilla LH. Runx2 induces acute myeloid leukemia in cooperation with cbfbeta-smmhc in mice. Blood. Apr 2; 2009 113(14): 3323–32. [PubMed: 19179305]
121. Kamikubo Y, Zhao L, Wunderlich M, Corpora T, Hyde RK, Paul TA, et al. Accelerated leukemogenesis by truncated CBF beta-smmhc defective in high-affinity binding with RUNX1. Cancer Cell. May 18; 2010 17(5):455–68. [PubMed: 20478528]

122. Goyama S, Schibler J, Cunningham L, Zhang Y, Rao Y, Nishimoto N, et al. Transcription factor RUNX1 promotes survival of acute myeloid leukemia cells. J Clin Invest. Sep 3; 2013 123(9): 3876–88. [PubMed: 23979164]

123. Ben-Ami O, Friedman D, Leshkowitz D, Goldenberg D, Orlovsky K, Pencovich N, et al. Addiction of t(8;21) and inv(16) acute myeloid leukemia to native RUNX1. Cell Rep. Sep 26; 2013 4(6):1131–43. [PubMed: 24055056]

124. Hyde RK, Zhao L, Alemu L, Liu PP. Runx1 is required for hematopoietic defects and leukemogenesis in cbfb-myh11 knock-in mice. Leukemia. Mar 6.2015

125. Britos-Bray M, Ramirez M, Cao W, Wang X, Liu PP, Civin CI, Friedman AD. CBFbeta-SMMHC, expressed in m4eo acute myeloid leukemia, reduces p53 induction and slows apoptosis in hematopoietic cells exposed to dna-damaging agents. Blood. Dec 1; 1998 92(11):4344–52. [PubMed: 9834241]

126. Qi J, Singh S, Hua W-K, Cai Q, Chao S-W, Li L, et al. HDAC8 inhibition specifically targets inv(16) acute myeloid leukemic stem cells by restoring p53 acetylation. Cell Stem Cell. Nov; 2015 17(5):597–610. [PubMed: 26387755]

127. Buggy JJ, Sideris ML, Mak P, Lorimer DD, McIntosh B, Clark JM. Cloning and characterization of a novel human histone deacetylase, HDAC8. Biochem J. Aug 15; 2000 350(Pt 1):199–205. [PubMed: 10926844]

128. Van den Wyngaert I, de Vries W, Kremer A, Neefs J, Verhasselt P, Luyten WH, Kass SU. Cloning and characterization of human histone deacetylase 8. FEBS Lett. Jul 28; 2000 478(1-2):77–83. [PubMed: 10922473]

129. Hu E, Chen Z, Fredrickson T, Zhu Y, Kirkpatrick R, Zhang GF, et al. Cloning and characterization of a novel human class I histone deacetylase that functions as a transcription repressor. J Biol Chem. May 19; 2000 275(20):15254–64. [PubMed: 10748112]

130. Balasubramanian S, Ramos J, Luo W, Sirisawad M, Verner E, Buggy JJ. A novel histone deacetylase 8 (HDAC8)-specific inhibitor PCI-34051 induces apoptosis in t-cell lymphomas. Leukemia. May; 2008 22(5):1026–34. [PubMed: 18256683]

131. Huang W-J, Wang Y-C, Chao S-W, Yang C-Y, Chen L-C, Lin M-H, et al. Synthesis and biological evaluation of ortho-aryl n-hydroxycinnamides as potent histone deacetylase (HDAC) 8 isoform-selective inhibitors. ChemMedChem. Oct; 2012 7(10):1815–24. [PubMed: 22907916]

132. Prébet T, Boissel N, Reutenauer S, Thomas X, Delaunay J, Cahn J-Y, et al. Acute myeloid leukemia with translocation (8;21) or inversion (16) in elderly patients treated with conventional chemotherapy: A collaborative study of the french CBF-AML intergroup. J Clin Oncol. Oct 1; 2009 27(28):4747–53. [PubMed: 19720919]

133. Ustun C, Marcucci G. Emerging diagnostic and therapeutic approaches in core binding factor acute myeloid leukaemia. Curr Opin Hematol. Mar; 2015 22(2):85–91. [PubMed: 25635758]

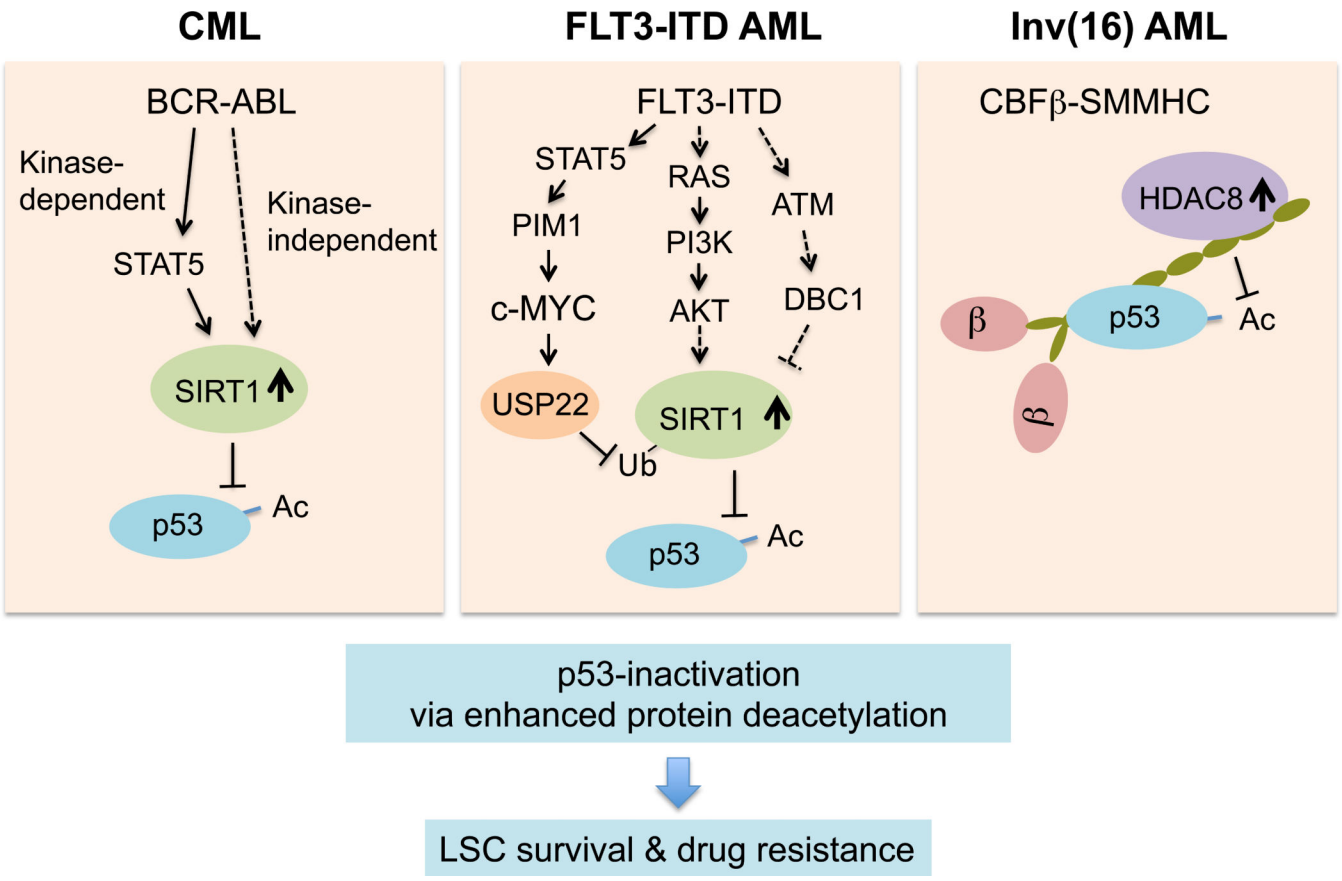

Figure 1. Multiple leukemogenic pathways converge on p53-inactivation through enhanced p53 protein deacetylation

SIRT1 deacetylase is stabilized and activated through multiple mechanisms downstream of BCR-ABL in CML (left) and FLT3-ITD (center) signaling in FLT3-ITD^{+} AML. In inv(16) AML (right), CBFβ-SMMHC fusion protein recruits HDAC8 and p53 in a protein complex, thereby promoting deacetylation of p53 by HDAC8. Inhibition of oncogenic context-specific deacetylase is a promising approach to specifically activate p53 pathway and enhance sensitivity of leukemia-initiating LSCs to TKI or chemotherapy.