

# [Mll gene encodes for a set domain](https://assignbuster.com/mll-gene-encodes-for-a-set-domain/)

MLL associatedtranslocations are found in 70% of infant leukaemia’s less than 2 years of age1. Normally, the MLL gene encodesfor a SET domain histone methyltransferase that catalyzes histone H3 lysine 4methylation at particular regions and in mixed lineage leukemia, the catalyticSET domain responsible for H3K4 methyltransferase property is lost and theremaining MLL protein is fused  to avariety of partners such as AF4, AF9, ENL and AF10 by chromosomaltranslocations in a balanced manner which causes the overexpression of leukemiapromoting genes2. Various cellular proteins likePI3K, GSK3?, mTOR, cyclin dependent kinases, histone deacetylases and histonemethyltransferases are targeted for the treatment of mixed lineage leukemia. Keywords-Mixedlineage leukemia, translocation, histone methyltransferase, apoptosis, differentiationI.

IntroductionMixed Lineage Leukemia pathology associated withhaemopoetic cells is under a hot bebate from the last two decades. MLLassociated translocations are found in 70% of infant leukaemia’s under the ageof 2 years with a very poor prognosis1. Mixed lineageleukemia display co-expression of lymphoid as well as myeloid antigens henceinfants with MLL translocation show both myeloid and lymphoid blast cellpopulation3. Normally, theMLL gene encodes for a SET domain histone methyltransferase that catalyzes themethylation of lysine 4 of histone H3 (H3K4) at particular regions 4.

In MLL, the catalyticSET domain responsible for H3K4 methyltransferase activity is lost and theremaining MLL protein is fused  to avariety of partners such as AF4, AF9, AF10 and ENL by balanced chromosomal translocationsand rearrangements2. Amino terminalportion of MLL protein is fused to fifty distinct binding partners 5. The fusionproducts retain the abilty to locate gene specific recognition regions  even after translocation and interact directlyor  indirectly with other histonemethyltransferaes like DOTIL6.

DOT1Linteracts with six unique MLL fusion proteins created by chromosomal translocationsi. e. MLL-AF4, MLL-AF9, MLL-ENL, MLL-AF10, SET-NUP214, CALM-AF107. The fusionproducts gain the ability to recruit Dot1L to the aberrant gene regions andincrease the expression of genes responsible for promotion of  leukaemia 8.

There is stilllack of good quality therapeutics for mixed lineage leukemia due to lack ofsmall molecule inhibitors that will directly target MLL9. The focus ofthe review will be on the recent published work as well as therapeutic targetsfrom the last 2 decades. II. PI3K as a therapeutic target of MLL Recentreports have shown that Simaltaneous inhibition of  PI3K/mTOR  has shows anticancer activity in MLLrearranged leukaemias10.

In vivoPI3K/mTOR inhibition has shown to  reducetumour progression and also shown to increase survival in MLL-AF9 xenograftmouse model10. BEZ, rapamycinand MK-2206 have shown good in vitro activity as well as have shown goodactivity in mice tumour models by inhibiting PI3K, mTOR and AKT pathways10.  III. CDK4/CDK6 as a therapeutic target of MLLInMLL there is a cell differentiation block which can be broken by using smallmolecules like CDK6 inhibitors11. CDK6 as atherapeutic target for mixed lineage leukemia was identified by Plakle et al., 201412. PD-0332991 is a dualinhibitor of CDK4/CDK6 which is clinical trials for  treatment of breast cancers as well asPD-0332991 have shown strong growth inhibition in MLL rearranged  leukemic cells 12.

Currenttreatment of MLL is chemotherapy and allogenic stem cell transplantation inselected cases13. IV. Small molecule inhibitors of histone deacetylases as treatment of MLLIthas  been shown recently that  HDAC inhibitors induce   apoptosisin MLL rearranged cell by autophagy 14. Inhibition ofhistone deacetylase by VPA (valproic acid) in cells  harbouring MLL induced cell cycle arrest(G1-phase) and apoptotic cell  death  in MLL-AF9 expressing cell lines15.

V. Retinoic acid and Vitamin D as important drugs for MLLMLL-AF9 expressing leukemic cell line MOLM-14undergoes differentiation when exposed to ATRA or 1, 25-dihydroxyvitamin D316.  Simultaneoustreatment of MLL cells with Retinoic acid and epidrug 5-azacytidine has shownto inhibit growth of  MLL positiveleukemic cells17 VI. Glycogen Synthase kinase 3 is an important target to control MLLGlycogenSynthase kinase3 has shown to  supportMLL leukemia proliferation18.

GSK3 inhibitionhas shown to induce G1 growth  arrest andcell death  in MLL transformed cells18. GSK3-? inhibition has shown to increase survival in mouse model of MLL associated leukaemic18. Specific GSK-3 inhibitorSB-415286 has been repored to inhibit growth  by induction of  apoptosis in leukemic cells19.

VII. Combinationof Sirt1 activators and DOT1L inhibitor for the treatment of mixed lineageleukemia Activationof SIRT1 and at same time inhibition of DOTIL has been shown  be an effective therapy for mixed lineage leukemia20. SIRT1activation  mediated silencing of theMLL-AF9 leukemia has been shown to be  enhanced by simultaneous DOT1L inhibition20.

SIRT1 activatorSRT1720 in combination with DOTIL inhibitor augment has been reported  to cause apoptosis induction in mixed lineageleukemia cells20. VIII. ?-catenin as a therapeutic target of MLLIt has been reported  that Leukemic stem cells have a more  self renewal and drug résistance property 21. ?-catenin establishes the growth of mixedlineage  leukemia  Leukemic stem cells22. Reversal of LSC to PLSC has shown to significantlyreduces the growth of  mixed lineageleukemia  cells by  ?-catenin downregulation or  suppression  23.

IX. TET1 is a direct target of MLL-fusion proteins andis an important therapeutic targetTET1 has shown to be  highly  expressed  in MLL-rearranged leukemia cells withleads  to drastic  increase of 5-hydroxymethylcytosine levels24. TET1 has shown to be an associated parter ofMLL which is leads to increased  growth 24. Overexpressed of TET1  in MLL rearranged leukemia has shown to beresponsible for overexpression of leukemia promoting genes Hoxa9 Pbx3 and Meis125.

TET1 overexpression has shown  increases proliferation and inhibit cell deathof MLL cells26. Recent report suggested that TET1 knockdownor therapeutic intervention of TET  prevent MLL rearranged leukemia27. X. BET family members and MLLIt has been shown that BET family members i. eBromodomainT, Bromodomain2, Bromodomain3 and Bromodomain 4  recruit MLL fusiononcogene proteins to diverged genic regions and increase the expression of  leukemia inducing  genes BCL2, CDK6 and C-MYC28. It has beenshown that inhibition of bromodomain proteins could provide a new novel approachfor the treatment of mixed lineage leukemia28 . XI. DOTIL inhibitors for the treatment of MLL It has been shown that inhibition of DOTIL by smallmolecules  kill mixed lineage leukemiacells by inhibiting H3K79 hypermethylation at the promoters of leukemiapromoting genes29.

Inhibition ofDOT1L has shown to  increase apoptosis incells carrying MLL rearrangement cells  as well as in mouse model of MLL30. EPZ5676 andEPZ004777 are the currently available DOT1L inhibitors which are in researchand development for the treatment of mixed lineage leukemia31. XII. Lysine specific demethylaseinhibitors for the treatment of MLLLSD1 is shown to be  essential for proliferation and growth  ofleukemic stem cells containing MLL-Fused oncogenes32 LSD1 (Lysinespecific demethylase1) is shown to be  highly up regulated in mixed lineage leukemia 32. It has beenshown that Lysine specific demethylase inhibitors  promote differentiation and apoptotic celldeath of MLL cells33. XIII.

Menin and MLL interactionblockersBorkin et al. recently developed  potent  inhibitors  blocking interaction of leukemia associatedprotein MLL and menin  34. These compounds showed to  inhibit the growth of leukemia cells in vitroas well as prolonged the survival of MLL leukemic mice34. Inhibiting the interaction between  Menin   and MLL   has shown to cause downregulation of Hox Agenes and differentiation of MLL-Rearranged Leukemic cells34. Borkin et al. Showed that  MI-463 and MI-503 blocked  the MLL Menin interaction, resulted in  increased  cell death and differentiation 34. XIV. Conclusion Varioussmall molecule inhibitors are in research and development for the treatment ofmixed lineage leukemia.

All Currently available treatments for mixed lineage leukemiahave low efficacy as well as high toxicity. So there is a need to develop newdrugs as well as to identify new therapeutic targets for mixed lineage leukemia