



PLX51107, a promising novel bromodomain and extra-terminal inhibitor in chronic lymphoid leukemia treatment

Claes Wahlestedt, Ines Lohse

University of Miami Miller School of Medicine, Miami, FL, USA

Correspondence to: Claes Wahlestedt, MD, PhD. University of Miami Miller School of Medicine, Miami, FL, USA.

Email: cwahlestedt@med.miami.edu.

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Historically hematopoietic malignancies were classified as genetic diseases depending on a small number of driver mutations. Nevertheless, the exact molecular mechanisms driving disease development of malignancies such as chronic lymphoid leukemia (CLL) still remain elusive in most part. The relatively small number of recurrent mutations cannot account for the clinical heterogeneity of the disease and the development of an aggressive phenotype in the absence of high-risk mutations (1,2), suggest that disease progression in CLL can be largely attributed to epigenetic changes. Whole genome sequencing efforts in patients with CLL have uncovered aberrations in a number of epigenetic modifiers (writers, readers and erasers) providing evidence for a strong epigenetic component in disease development and progression (3-5). Indeed, the genetic analysis of a small subset of CLL patients demonstrated the existence of recurrent changes in DNA methylation that are associated with disease progression (6). While the impact epigenetic writer and readers modifying DNA, methylation has been evaluated on disease states and as a potential therapeutic option, only a few studies have aimed to evaluate epigenetic readers such as bromodomain proteins. Bromodomain and extra-terminal (BET) family proteins are key regulators of gene expression that recognize acetylated lysine residues on histone tails. Interaction between BET proteins and acetyl-lysine orchestrate complex molecular interactions that facilitate changes in lysine acetylation resulting changes in gene expression. Although BET inhibitors have captured the attention of the cancer community in general, and not least the leukemia community (7-11), little is known about the involvement of BET proteins in leukemia development,

progression and outcome.

Dr. Ozer and colleagues (12) have recently provided insight into the function of BRD4 in CLL and strong evidence for the therapeutic targeting of BET proteins and specifically BRD4 in these patients. In a cancer that is typically characterized by minimal genetic changes despite increasing aggressiveness, the authors uncovered a core transcriptional program of CLL that is regulated through BRD4.

Using primary patient-derived CLL B cells, the authors show a ubiquitous expression of a number of bromodomain-containing proteins and a significant overexpression of BRD4 suggesting a role for BRD4 in the regulation of transcription. Indeed, analysis of genome-wide BRD4 occupation revealed an enrichment of chromatin-bound BRD4 in transcriptionally active regions, indicating BRD4 recruitment to regions of open chromatin and active enhancers while untranscribed areas of the genome displayed no BRD4 binding. Specifically super-enhancers adjacent genes that are aberrantly expressed in CLL show higher BRD4 load. The authors identified a small set of BRD4 target genes. In addition to a set of genes that have been shown to play critical roles in CLL biology, Dr. Ozer and colleagues discovered a set of BRD4 target genes revealing an involvement of BRD4 in the BCR signaling pathway. BRD4 regulation of BCR components such as PLCG2, ZAP70, and PI3K may be responsible for changes in CLL maintenance and expansion and account for increased aggressiveness in the absence of novel mutations. This data makes a BRD4-targeting approach especially exciting in CLL.

Dr. Ozer and colleagues designed the BET inhibitor PLX51107 with the intention of targeting CLL driver genes. In an approach using structure-guided chemistry to optimize target binding and pharmacokinetic properties, the authors designed a BET inhibitor that engages the BRD4 Trp81-Pro82-Phe83 (WPF) shelf and the ZA channel (a specificity loop defined by αZ and αA helices) and this molecule may therefore be different from other available BET inhibitors. At low nanomolar concentrations PLX51107 targets all BET protein family members and the bromodomains of CBP and EP300, all of which have been previously involved in a multitude of malignancies, resulting in broad activity in hematological malignancies *in vivo* and *in vitro*. In mice with *de novo* leukemia PLX51107 treatment significantly reduced disease burden and increase survival. These mice displayed significant changes in transcription profiles resulting in a marked reduction in spleen size and reduced lymph node invasion. In contrast to some of the currently available molecules, PLX51107 appears to display a low toxicity profile even in a daily dosing regimen and at physiologically relevant plasma concentrations.

Although BRD4 has been shown to regulate cancer-specific genes, such as c-MYC, its activity is not limited to those genes. The therapeutic window for treatment with BET inhibitors arises, at least in part, from the overexpression of BRD4 in hematopoietic diseases. However, since BET proteins regulate a wide range of target genes it remains unlikely that treatment effects can be attributed to the inhibition of a single pathway. On the other hand, this lack of pathway specificity may represent a benefit with respect to the development of treatment resistance. The simultaneous targeting of multiple pathways with the same molecule hold the potential for stronger and extended treatment responses without the added toxicity that comes from multiple compound combinations. This will be specifically interesting for the treatment of patients with an aggressive CLL phenotype and relapsed/refractory disease. The preclinical data provided by Dr. Ozer and colleagues suggests that PLX51107 may be a valuable treatment approach for other hematological malignancies and supports a rapid transition of the molecule into clinical trial.

In summary, this study by Ozer *et al.* demonstrated the importance of BRD4 for the progression of CLL and provided a critical link between epigenetic changes and increased CLL aggressiveness. Expression of BET proteins shape the transcriptional landscape and provide a compelling rationale for the use of BET inhibitors as single

therapy or in combination with BCR inhibitors. The BET inhibitor PLX51107 presents a novel molecule for further exploration for the use in CLL and other hematological malignancies.

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