



Editorial

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CD22 Δ E12 as a Molecular Target for RNAi Therapy in Mantle Cell Lymphoma



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Editorial

Non-Hodgkin lymphoma (NHL), is the most common lympho hematopoietic malignancy in the US with more than 70,000 new cases that contribute to more than 20,000 deaths per year (American Cancer Society: Cancer Facts and Figures 2017. Atlanta, GA: American Cancer Society, 2017). Mantle cell lymphoma (MCL) represents a subgroup of poor prognostic, high-risk NHL with an aggressive biology and short progression-free as well as overall survival that usually occurs in middle-aged or older adults (Median age: 68 years) [1-3]. MCL is a clinically and molecularly heterogeneous CD19+ B-lineage NHL comprising approximately 7 percent of adult NHL cases [1-28]. More than two thirds of the MCL patients present with advanced stage disease at diagnosis requiring treatment with a combination of chemotherapy and immunotherapy [11-15,17-18,25]. There is no evidence that any of the currently available treatment regimens can cure MCL and almost every MCL patient eventually develops therapy-resistant refractory disease. Therefore, identification and evaluation of non-cross resistant active new agents and new drug combinations against MCL, including exploratory single agent Phase II clinical studies in relapsed or refractory MCL, as well as more intense multimodality strategies with immuno-chemotherapy and hematopoietic stem cell transplantation for eligible patients, have been among focal points in translational lymphoma research [1-3,10,16-27]. The insights provided by translational and clinical research efforts have resulted in improvement of the overall survival in MCL and increased the number of available salvage treatment options for patients with recurrent disease [1,2]. New agents with promising single agent activity against relapsed MCL and hematopoietic stem cell transplantation protocols with less intensive conditioning regimens have been developed for treatment of relapsed MCL [20-23,26-28].

Our team was the first to identify CD22 exon 12 deletion (CD22 Δ E12) as the likely genetic cause for the chemo resistance-associated activation of SYK/MAPK, PI3-K/m-TOR and WNT pathways in aggressive B-lineage lymphoma and leukemia cells [29]. The CD22 Δ E12 genetic defect [29,30] involves CD22, an inhibitory co-receptor of human B-cells and B-cell precursors that acts as a negative regulator of multiple signal transduction pathways critical for proliferation and survival. Aggressive B-lineage lymphoma and leukemia cells express a dysfunctional CD22 due to deletion of exon 12 (CD22 Δ E12) arising from a splicing defect associated with homozygous intronic mutations [29,30]. Functional RNA interference (RNAi) experiments using CD22 Δ E12-specific siRNA and its nano scale formulations both in vitro and in vivo have confirmed the causal link between CD22 Δ E12 and the stemness features as well as aggressiveness and chemotherapy resistance of human B-lineage leukemia/lymphoma cells. Notably, forced expression of the mutant CD22 Δ E12 protein in transgenic (Tg) mice under control of the immunoglobulin enhancer E μ that is activated in early B-cell ontogeny prior to immunoglobulin gene rearrangements caused fatal B-lineage leukemia with lymphomatous features in C57/BL/6 mice [30,31]. This Tg mouse model recapitulated the gene expression profile of CD22 Δ E12+ human B-lineage lymphoma and leukemia cells, indicating that CD22 Δ E12 alone as a driver lesion is sufficient for malignant transformation and clonal expansion of B-lineage lymphoid cells [29,30]. Leukemia cells from CD22 Δ E12-Tg mice exhibit characteristic gene expression and protein expression profiles consistent with constitutive activation of multiple signaling networks, including the WNT, PI3-Kinase and MAPK/SYK pathways, mimicking the profiles of aggressive human B-lineage leukemia/lymphoma cells [31,32].

We recently reported that the CD22 Δ E12 defect has been detected in 97% of MCL cases [31-33]. As shown in Figure 1, the CD22 Δ E12 transcriptome was strongly represented in primary lymphoma cells from MCL patients. We have established a highly efficient small interfering RNA (siRNA) delivery platform based on a rationally designed cell-penetrating cationic helical polypeptide. We are now developing advanced multifunctional bioactive nanomaterials with optimized properties as siRNA delivery vehicles in an attempt to further improve the potency and broaden the therapeutic window of their nanocomplexes with therapeutic siRNA. We have reported membrane-penetrating endosomolytic hybrid nanocarriers for RNA interference therapy in poor prognosis B-lineage leukemias and lymphomas [32,33]. This nanoscale siRNA delivery platform has been

further optimized to enhance its translational impact potential [32-35]. We have complexed CD22 Δ E12-siRNA with a 200-mer polymer of the lead helical polypeptide to prepare a nanoscale formulation of CD22 Δ E12-siRNA. This unique nanoparticle formulation caused marked CD22 Δ E12 mRNA and protein depletion in neoplastic B-lineage leukemia and lymphoma cells and inhibited their clonogenic growth. These hybrid nano carriers are being functionalized with a MCL targeting moiety directed against the CD19 [36] surface receptor on MCL cells in order to achieve optimal delivery to and uptake by MCL cells to further reduce their potential toxicity and improve their efficacy. Polypeptide-based siRNA nano complexes with CD19-binding functionality could represent an important addition to the emerging new personalized treatment options for MCL.

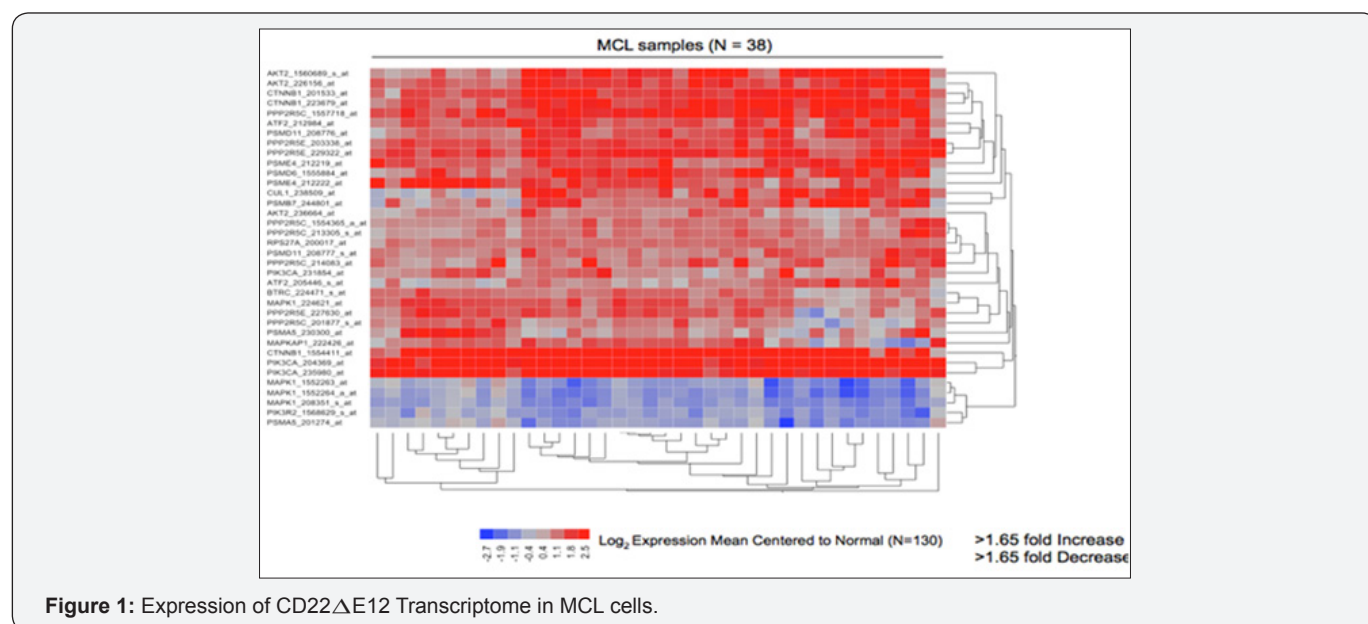


Figure 1: Expression of CD22 Δ E12 Transcriptome in MCL cells.

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