SY-1425 (tamibarotene) Induces Profound Transcriptional Changes in AML Tumors with High Retinoic Acid Receptor Alpha

Chris Fiore¹, Michael McKeown¹, Emily Lee¹, Matthew L Eaton¹, Christian C Fritz¹
¹Syros Pharmaceuticals, 620 Memorial Drive, Cambridge, MA 02139

Abstract 1523

Retinoic acid receptor alpha (RARα) regulates myeloid differentiation and proliferation through the regulation of specific gene expression. When unfused by a t(15;17) (t(RARα/ATRA)), APL cells exhibit differentiation and proliferation. Retinoic acid receptor alpha (RARα) is a transcription factor that binds to specific DNA sequences called RAREs. RAREs are present throughout the genome and consist of 12 bp DNA binding motifs. Two related RARα isoforms exist, RARα-α and RARα-β. RARα-α integrates with other transcription factors to bind to RAREs and regulate the expression of target genes. RARα-β binds to RAREs to regulate transcription. The presence of RARα in APL cells suggests a potential therapeutic target for this disease. Retinoic acid and related compounds, such as ATRA, are potent activators of RARα. Treatment of APL cells with ATRA leads to an increase in expression of RARα target genes and differentiation of APL cells into mature myeloid cells. Sensitivity to ATRA varies among APL patients, with some patients showing a super-response to ATRA, while others show resistance.

Sensitivity to SY-1425 is associated with RARE SE

Expression changes upon treatment

- SY-1425 is a first-in-class, potent and selective RARα agonist with favorable PK properties and is approved in Japan for the treatment of R/R APL, which is characterized by fusions between RARA and other transcription factor genes.
- Sensitivity of non-APL AML cells to SY-1425 is correlated with RARA enhancer strength, as RARA-high AML cells are sensitive and RARA-low are not.
- SY-1425 induces the expression in genes in RARA-high non-APL AML cell lines that are also induced by retinoids in APL cells.
- These mechanistic similarities, including transcriptional and epigenomic responses to SY-1425, support the clinical potential of SY-1425 in RARA-high AML.
- Based on SY-1425’s well-established safety and efficacy profile in R/R APL and our strong preclinical data, we have initiated a biomarker-directed Phase 2 clinical trial in genomically defined subsets of AML and MDS patients with high levels of RARA gene expression (clinicaltrials.gov, NCT02807558).

Conclusions

SY-1425 induces enhancer formation at RARα-bound loci

Volcanic plots of response to SY-1425 vs. vehicle for H9C2 cells (top) and OCI-AML3 and APL cell lines. SY-1425 reduces peaks in OCI-AML3 and OCI-AML3 and the APL cell line.

A subset of non-APL AML patients have a super-enhancer (SE) at RARA

H9C2 cells and APL cell lines are shown.

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SY-1425 transcriptional response depends on RARα level

Gene expression changes induced by SY-1425 in RARα-high AML are similar to those of APL cells treated with retinoids

APL genes sets are in the top 5 gene sets (of out 2775) identified by enhancers induced in SY-1425 in RARα-high AML.

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Gene expression response to SY-1425

Percentage of genes in each set that are upregulated by SY-1425 (FDR<0.05 and log2 fold change >1) in each cell line. RARα-bound genes contain a RARα ChIP-seq peak near the transcription start site in the RARα-bound datasets. SY-1425 induces enhancer formation at RARα-bound loci

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