Are all APLs created equal?
Background

• RARα translocations in acute promyelocytic leukemia (APL)
• Mouse models recapitulate the human phenotype
• Current treatments utilize retinoic acid (RA) to induce differentiation and arsenic trioxide to induce apoptosis
• Human patients have variable response to therapy
Retinoic acid (RA) and As$_2$O$_3$ treatment in transgenic models of acute promyelocytic leukemia (APL) unravel the distinct nature of the leukemogenic process induced by the PML-RAR$\alpha$ and PLZF-RAR$\alpha$ oncoproteins

Eduaro M. Rego, Li-Zhen He, Raymond P. Warrell, Jr., Zhu-Gang Wang, and Pier Paolo Pandolfi

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Fig. 1. Effects of treatment with As2O3, RA, or As2O3 + RA on the survival of leukemic TM PML-RAR[alpha] and PLZF-RAR[alpha]
Fig. 3. Effects of treatment with As2O3, RA, or As2O3 + RA on the induction of apoptosis in leukemic cells sorted from the liver of transplanted NM

Fig. 4. Effects of treatment with As2O3, RA, or As2O3 + RA on the induction of differentiation in leukemic cells sorted from the liver of transplanted NM

Fig. 5. In vivo and in vitro effects of RA or RA + As2O3 treatments on the PML-RAR[alpha] and PLZF-RAR[alpha] oncoproteins

Questions remaining:

• What are the inherent differences/similarities between PML-RARα and PLZF-RARα at the molecular level?
• How/why does PLZF-RARα respond differently to RA?
• Is expression of PLZF-RARα required for tumor maintenance?
What are the inherent differences between PML-RARα and PLZF-RARα at the molecular level?

• Gene expression analysis on random APLs from humans followed by identification of the fusion gene
• Correlate gene expression in PML-RARα vs. PLZF-RARα vs. normal myeloid cells

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Possible results: Common genetic pathways upregulated
How/why does PLZF-RARα respond differently to RA?

• Additional analysis of gene expression profiles generated in previous section.
• New gene expression analysis comparing cultured PML-RARα ± RA and PLZF-RARα ± RA.
Possible results: Inhibition of Hox signaling

* : HoxB3 inhibits differentiation → normal & PML do not express B3
* : HoxD4 promotes differentiation → PLZF does not express D4 or B4
Is expression of PLZF-RARα required for tumor maintenance?

- Tetracycline-regulated transgenic expression
Possible results

Expression of PZLF-RARα required

Expression of PZLF-RARα not required