

THE UNIVERSITY OF TEXAS

MD Anderson  
Cancer Center

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# Acute Myeloid Leukemia (Promyelocytic) with Novel *IRF2BP2-RARA* Fusion SH2017-0180

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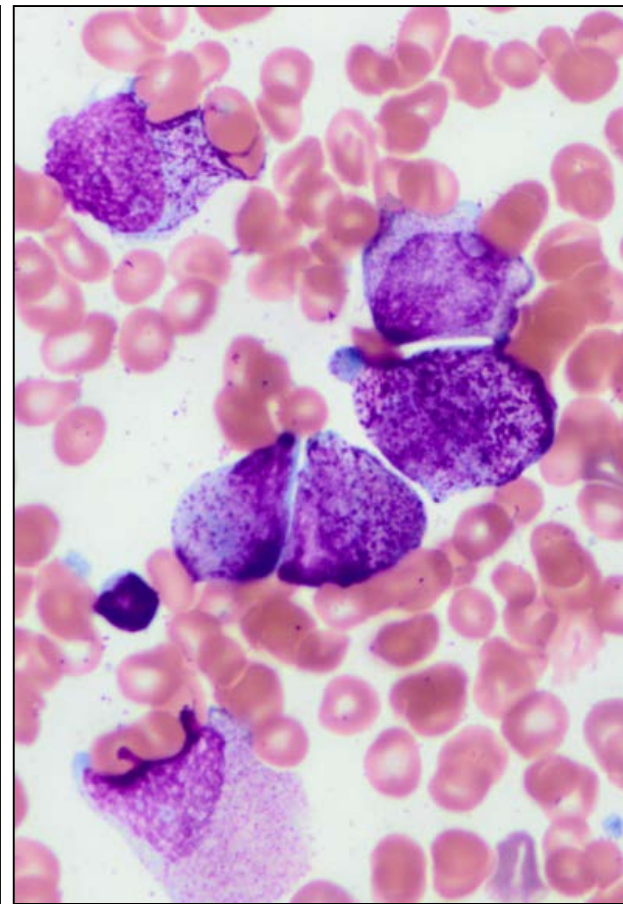
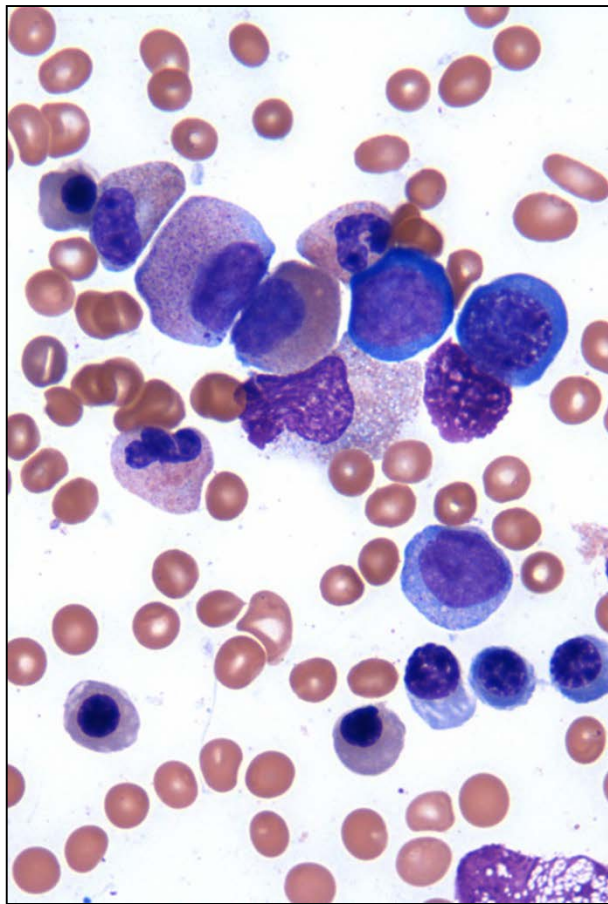
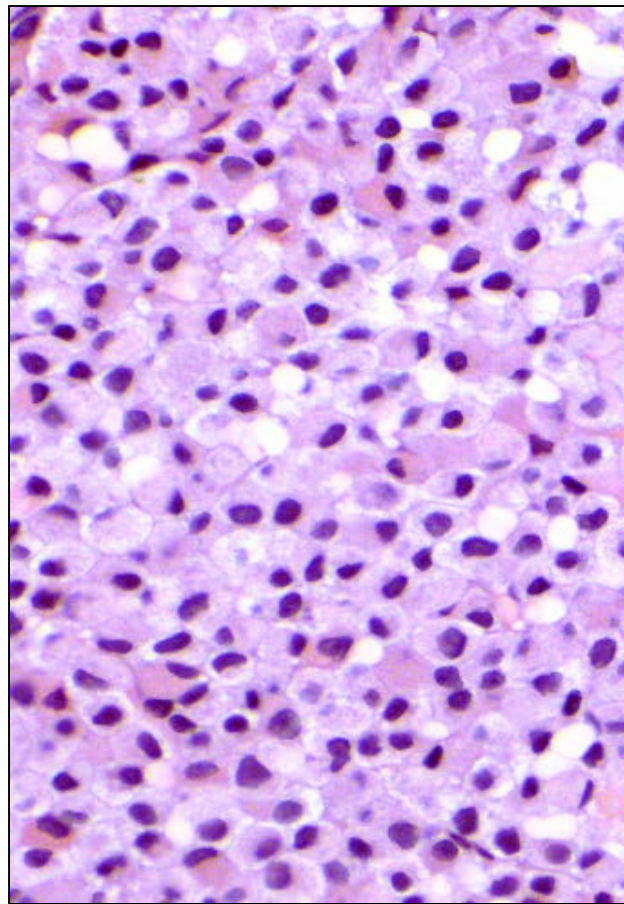
Department of Hematopathology  
University of Texas MD Anderson Cancer Center

No relevant financial relationships to disclose

# Clinical History

- 19-year-old female
- Presented with ecchymoses and epistaxis
- Outside workup suggested leukemia vs storage disorder
- CBC: WBC 4.5 K/uL, Hgb 9.1 g/dL, platelet 29 K/uL
- Coagulation
  - PT: 19.6 sec (ref 12.7-15.0 sec)
  - aPTT: 46.3 sec (ref 24.7-35.9 sec)
  - D-Dimer: >20 mcg/mL (ref 0.00-0.40 mcg/mL)
  - Fibrinogen: 60 mg/dL (ref 202-450 mg/dL)

# Morphologic Findings

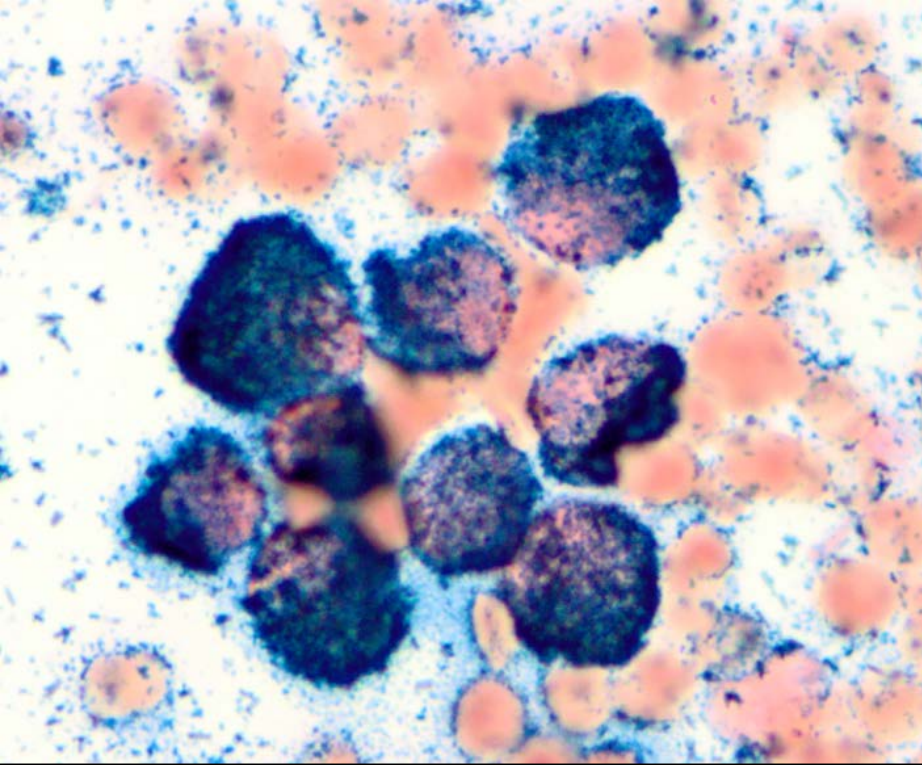


Abnormal Cells: 60%

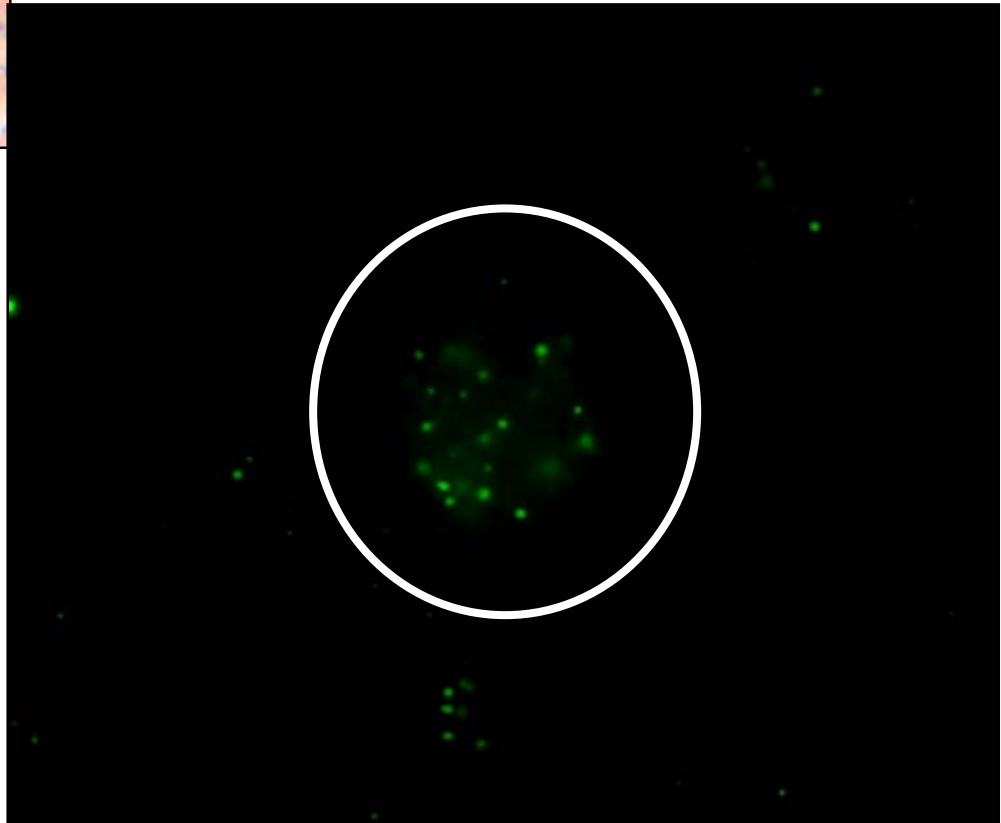
No obvious Auer rods

# Special Stains

PML Oncogenic Domain (POD)  
Immunofluorescence



Myeloperoxidase (MPO)



# Flow Cytometry

## Aberrant promyelocytic immunophenotype

- **Positive:** CD13, CD15, **CD11a** (dim partial), **CD18** (dim partial), CD33, CD38, CD45 (dim), CD117 (partial), CD123, and MPO (uniform strong)
- **Negative:** CD10, CD14, **CD34**, CD36, CD41, CD56, CD64, **HLA-DR**, TdT, B-cell and T-cell markers

# Cytogenetic Findings

- 46,XX[20]
- *PML-RARA* FISH:
  - *PML-RARA* Fusion Probe: No fusions
  - *RARA* Breakaport probe: No *RARA* rearrangement

# Molecular Diagnostics

## Leukemia Translocation Panel: Negative for

- t(8;21)(q22;q22); *RUNX1-RUNX1T*,
- inv(16)(p13.1q22) *CBFB-MYH11* variants A, D, E
- t(15;17)(q22;q12); *PML-RARA* long form, short form, alternate form
- t(9;22)(q34;q11.2); *BCR-ABL1* e1a2, e13a2, e14a2
- t(12;21)(p13;q22); *ETV6-RUNX1*
- t(1;19)(q23;p13.3); *E2A-PBX1*
- t(4;11)(q21;q23); *MLL-AF4*
- t(6;9)(p23;q34); *DEK-NUP214*.

## Oligonucleotide microarray: Negative for

- t(15;17)(q22;q21)/*PML-RARA*
- t(5;17)(q35;q21)/*NPM1-RARA*
- t(11;17)(q13;q21)/*NUMA1-RARA*
- t(11;17)(q23;q21)/*ZBTB16-RARA*

### Mutation Profile:

NM\_002524(*NRAS*): c.35G>A  
p.G13D, (<5%)

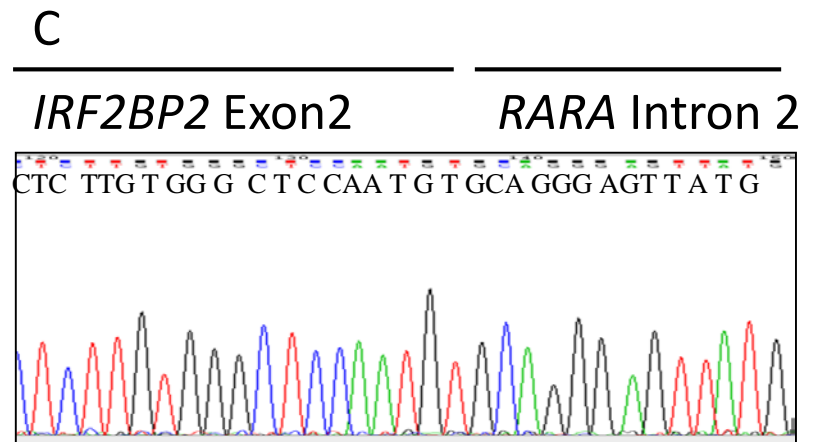
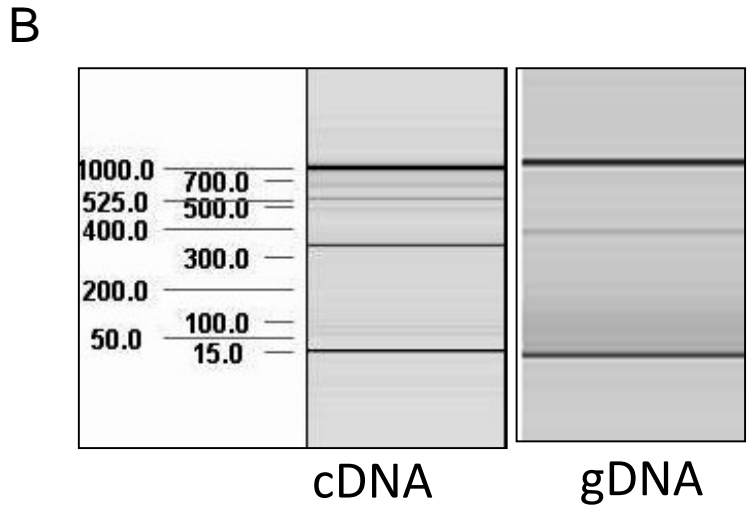
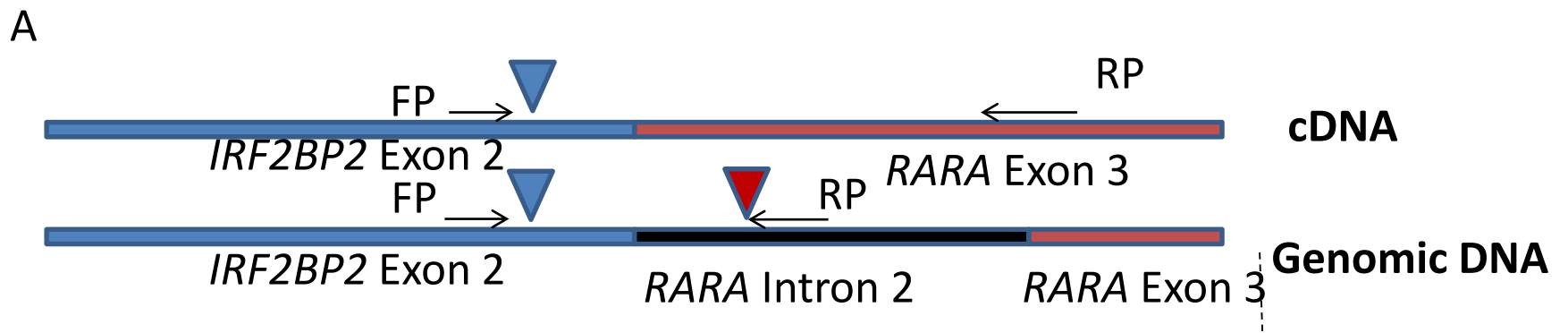
# Diagnosis and Treatment

- BM morphologic findings and the presence of DIC suggested acute promyelocytic leukemia
- Induction:
  - ATRA, arsenic trioxide (day 2) and Gemtuzumab (day 6)
- Remission: 5 weeks after diagnosis
- Consolidation (8 months): ATRA, arsenic trioxide
- Relapsed: 2 months after end of consolidation (10 months after first induction)
- Salvage Therapy:
  - ATRA, arsenic trioxide and idarubicin
  - Haploidentical SCT



# Additional Molecular Studies (Research)

- RNAseq :
  - Fusion reads involving,
    - Interferon regulatory factor 2 binding protein 2 (*IRF2BP2*) exon 2
    - *RARA* exon 3
- Confirmed by PCR (M13-tagged primers):
  - cDNA (RT-PCR)
  - gDNA (PCR):
    - *IRF2BP2* breakpoint (exon 2); chr1:234742961
    - *RARA* breakpoint (intron 2); chr17:38502042
- Sanger Sequencing



# Our Diagnosis

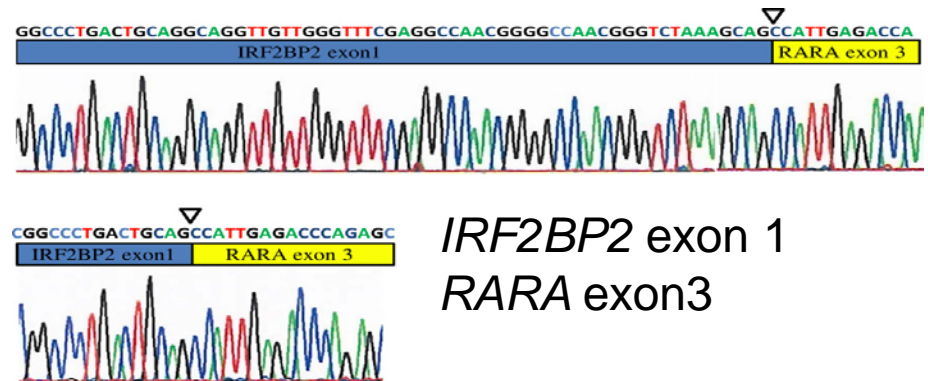
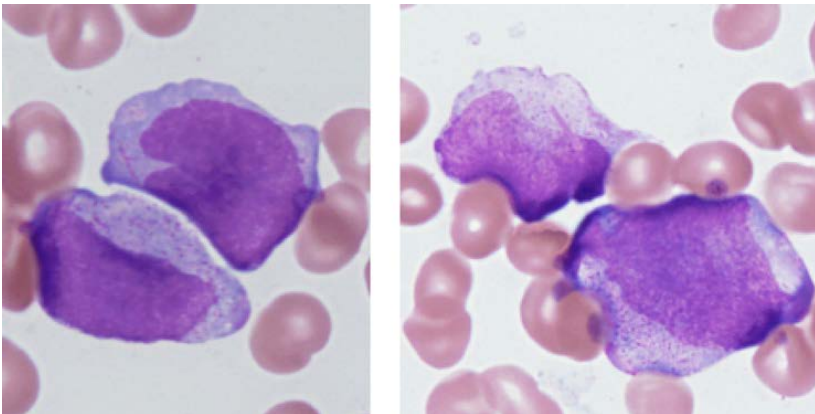
Acute Myeloid Leukemia (Promyelocytic), with Novel  
*IRF2BP2-RARA* Fusion

# Final Consensus Diagnosis

Acute Promyelocytic Leukemia with Variant *RARA*  
Rearrangement, *IRF2BP2-RARA*

# 2<sup>nd</sup> Case of APL with *IRF2BP2-RARA* Fusion

- 68 year old female
- Pancytopenia, but, no DIC
- No response to ATRA monotherapy
- Remission with Idarubicin+cytarabine+GO
- Multiple relapses
- Died 27 months after diagnosis

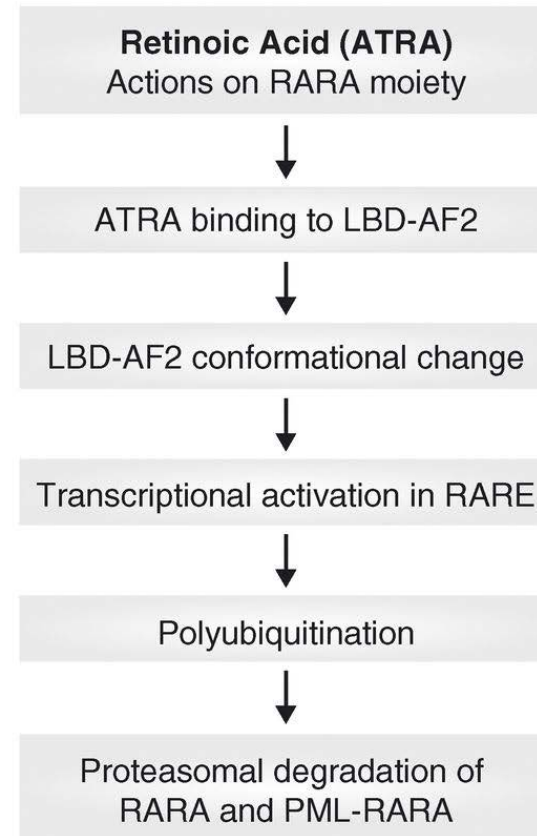
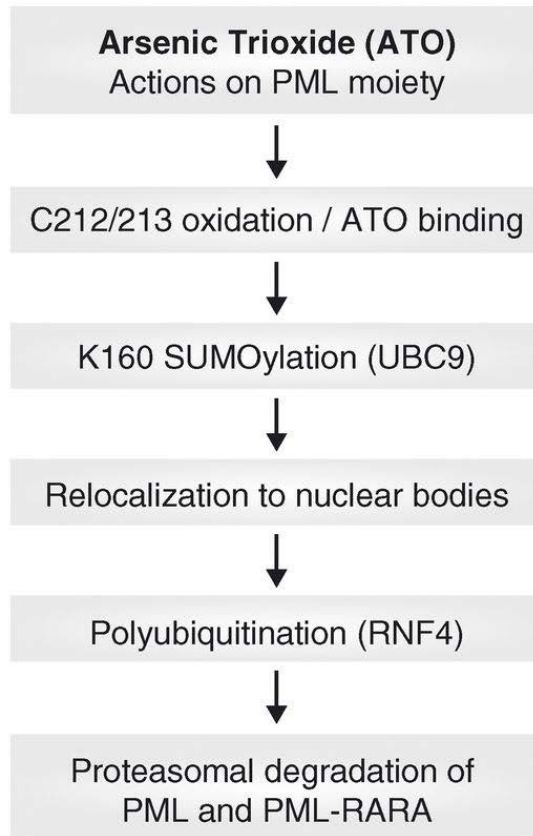
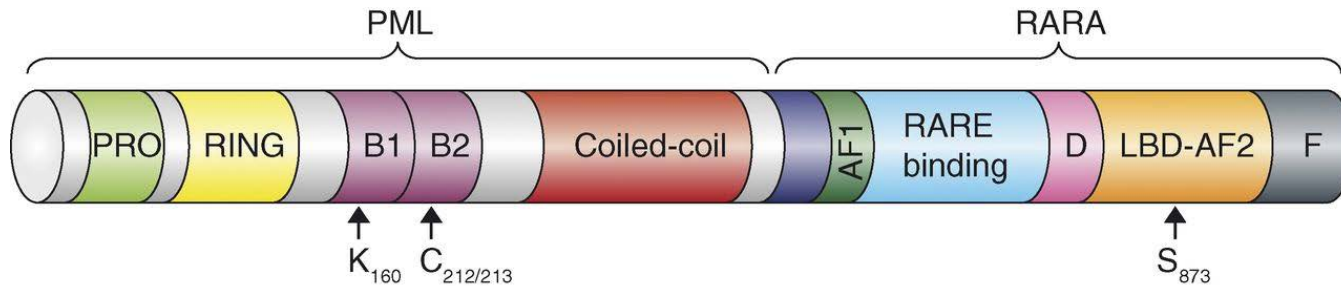


# RARA Translocations in APL

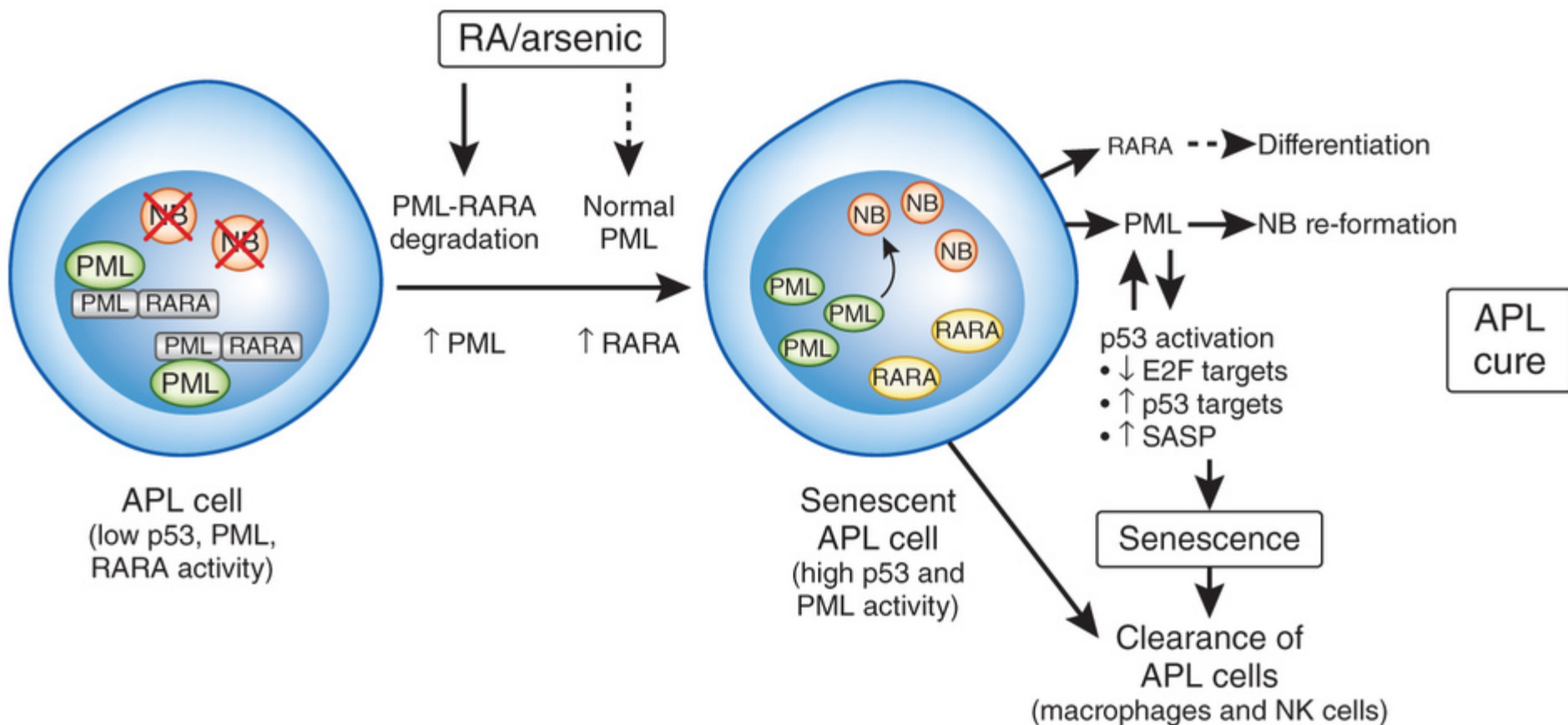
- Commonly involved t(15;17)(q24.1;q21.2)/PML-RARA
- Associated with response to ATRA and good outcomes
- Variant RARA fusions are uncommon, but, create significant diagnostic and therapeutic challenges

Translocation	Partner	ATRA Response
t(5;17)(q23;q21)	Nucleophosmin ( <i>NPM1</i> )	Sensitive
t(11;17)(q13;q21)	nuclear mitotic apparatus ( <i>NUMA1</i> )	Sensitive
t(17;17)(q21;q24)	cAMP-dependent protein kinase type I alpha regulatory subunit ( <i>PRKAR1A</i> )	Sensitive
t(4;17)(q12;q21)	FIP1-like 1 ( <i>FIP1L1</i> )	Sensitive
t(X;17)(p11;q12)	BCL6 corepressor ( <i>BCOR</i> )	Sensitive with relapses
der(17)(q21.3;q23)	signal transducer and activator of transcription 5b ( <i>STAT5B</i> )	Resistant
t(11;17)(q23;q21)	zinc finger and BTB domain containing 16 ( <i>ZBTB16</i> ), previously promyelocytic leukemia zinc finger ( <i>PLZF</i> )	Resistant

# Synergistic Effect of Arsenic Trioxide and ATRA

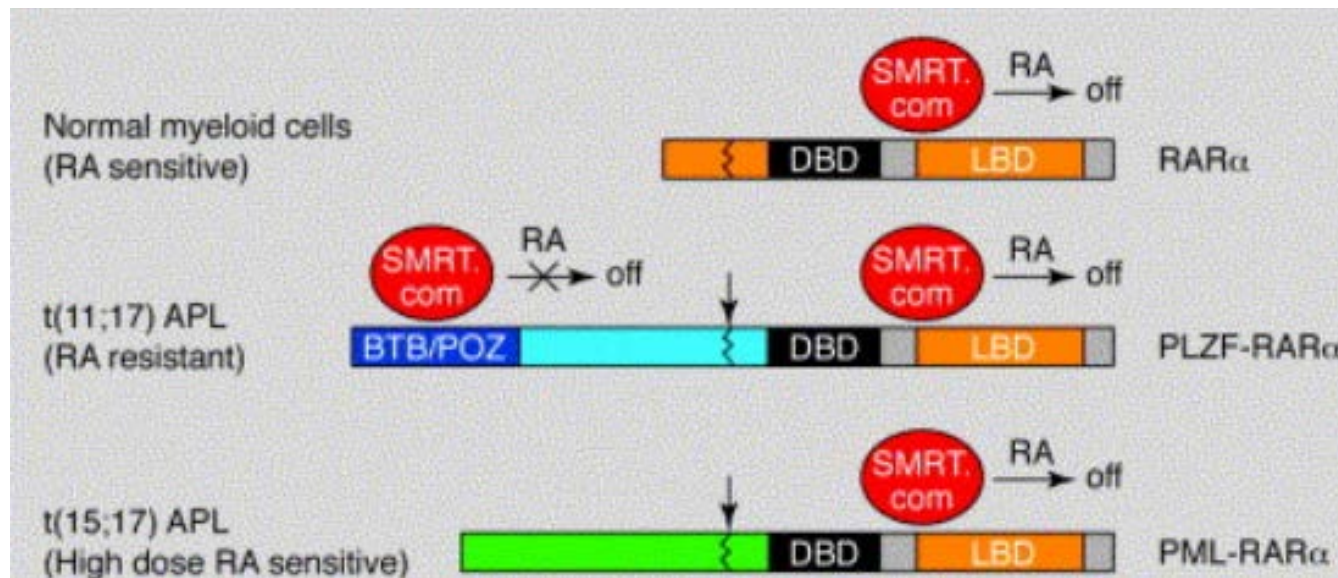


# PML-p53 Axis Drives Cure in APL



# ATRA Resistance in Variant Translocations

- N-CoR/SMRT complex interaction with ZBTB16, STAT5b implicated in resistance
- IRF2BP2 is known to bind to N-CoR co-repressors



N-CoR: Nuclear Receptor Co-Repressor

SMRT: Silencing Mediator for Retinoid and Thyroid receptors)



# Interferon Regulatory Factor 2 Binding Protein 2 (IRF2BP2)

- Located at 1q42.3, contains 2 exons
- Encodes a nuclear protein that binds IRF2.
- IRF2BP2 overexpression inhibits apoptosis by impeding p53 function.
- Represses transactivation of nuclear factor of activated T cells (NFAT), which in turn regulates cell cycle, differentiation, apoptosis, angiogenesis.
- Rare reports of fusions with *CDX1* (mesenchymal chondrosarcoma), *NTRK1*, *CALM1*, *NEROD2*

# Interesting Features of This Case

- First reported case of novel *IRF2BP2-RARA* fusion, which expands the list of *RARA* partners.
- The patient initially responded well to ATRA, arsenic trioxide and Gemtuzumab.
- Early relapse suggests a more aggressive clinical course and/or require more intensive therapy.
- Highlights the importance of morphologic examination to establish the diagnosis of APL, especially in cases with variant *RARA* fusions

# Follow-Up

- In remission, 39 months after haploidentical SCT
- Recently gave birth to a healthy baby boy, 51 months after initial diagnosis

# Thank You

Molecular Insights  
in Patient Care

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## Identification of a Novel Fusion Gene, *IRF2BP2-RARA*, in Acute Promyelocytic Leukemia

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