Arsenic, a targeted curative therapy of APL[a]

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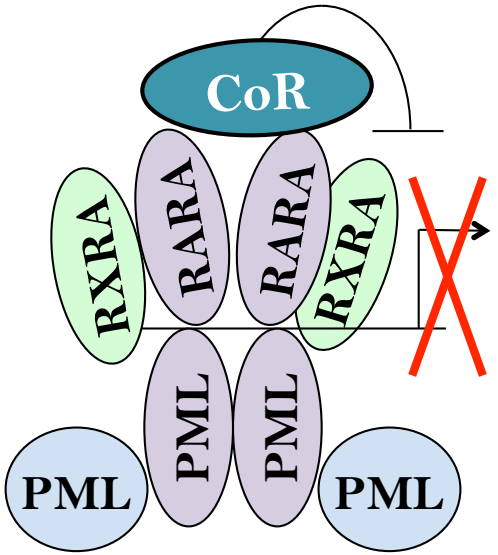
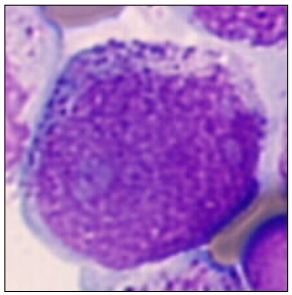
[a] Trisenox® (ATO) is indicated for induction of remission, and consolidation in adult patients with: newly diagnosed low-to-intermediate risk acute promyelocytic leukaemia (APL) (white blood cell count, ≤ 10 x 10^3/µl) in combination with all-trans-retinoic acid (ATRA). ATO is not indicated for the treatment of children with APL. Teva does not support off-label use of ATO.

HQ/TNX/17/0042

Transcription therapy?

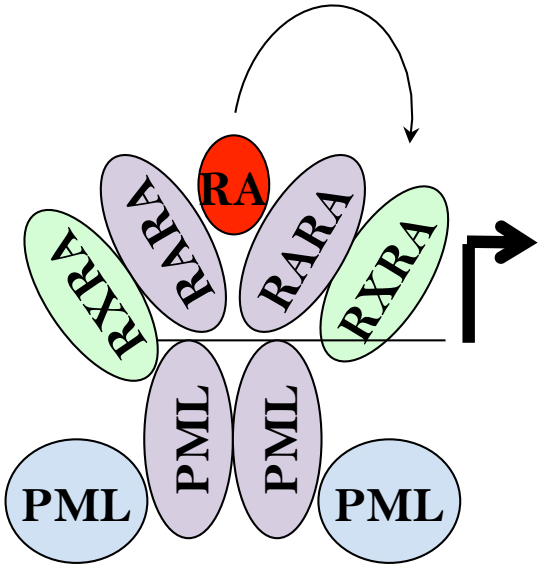


Transcriptional repression

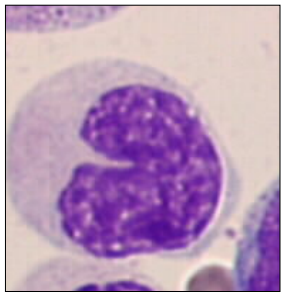


Activation by retinoic acid

Dimerization
Relaxed specificity
Enhanced repressor binding…



Activation Differentiation



CoR, corepressor protein; PML, promyelocytic leukemia; RA, retinoic acid; RARA, retinoic acid receptor alpha; RXRA, retinoid X receptor alpha.

PML/RARA disrupts PML bodies

PML Forms the shell

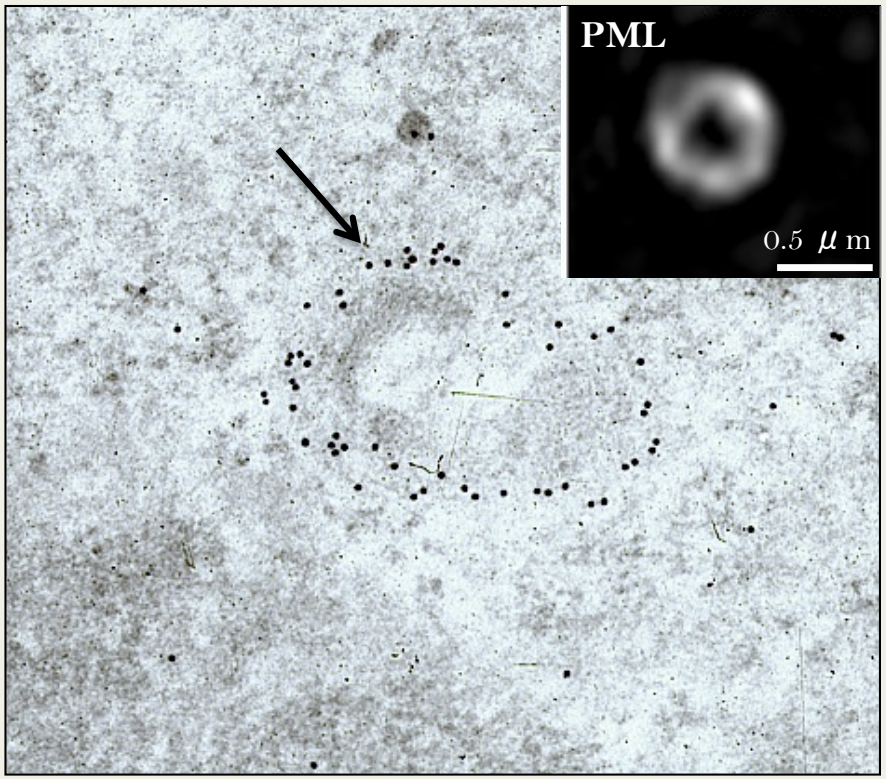
Recruits partner proteins

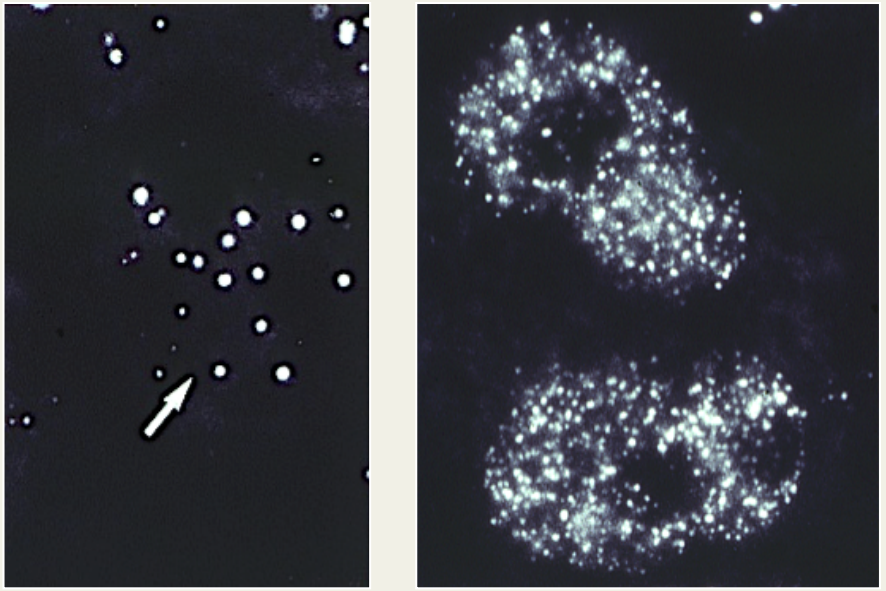
Controls p53/senescence

PML/RARA Disrupts PML NBs

Blunts p53 signaling

Apoptosis resistance



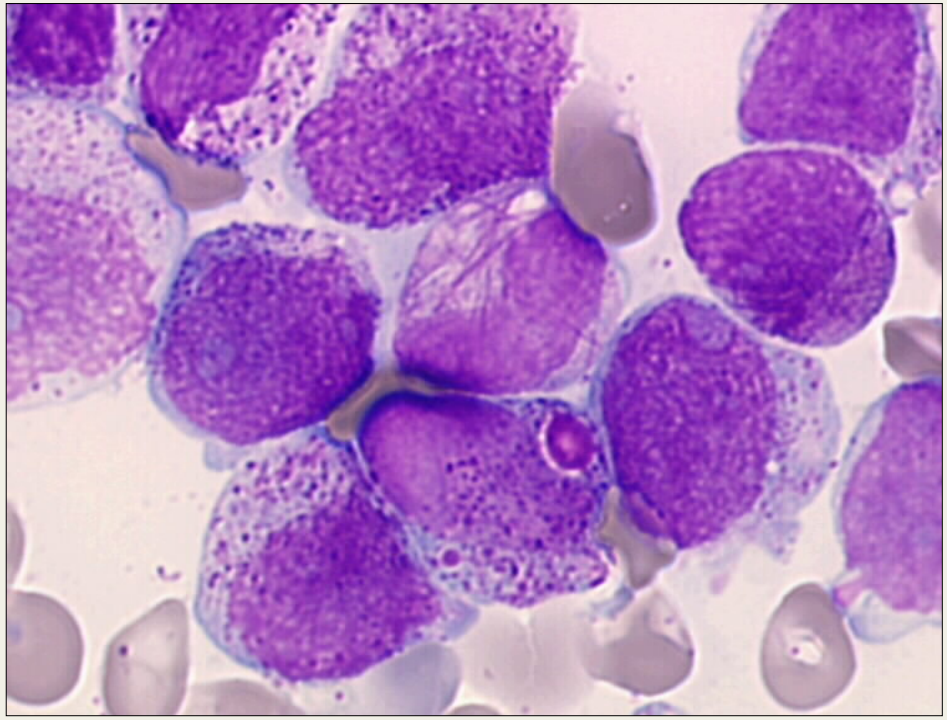


PML **PML + PML/RARA**

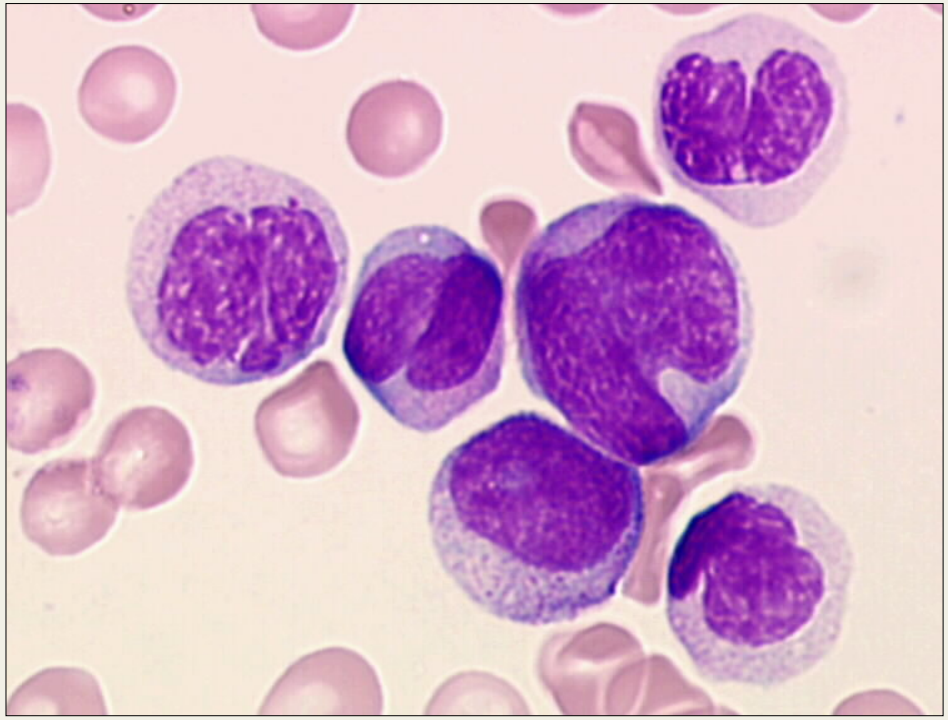
NB, nuclear body.

Daniel MT, et al. Blood. 1993;82:1858-67. Dyck JA, et al. Cell. 1994;76:333-43.
Grignani F, et al. Cell. 1993;74:423-31. Koken MH, et al. EMBO J. 1994;13:1073-83.

Arsenic in APL



Control



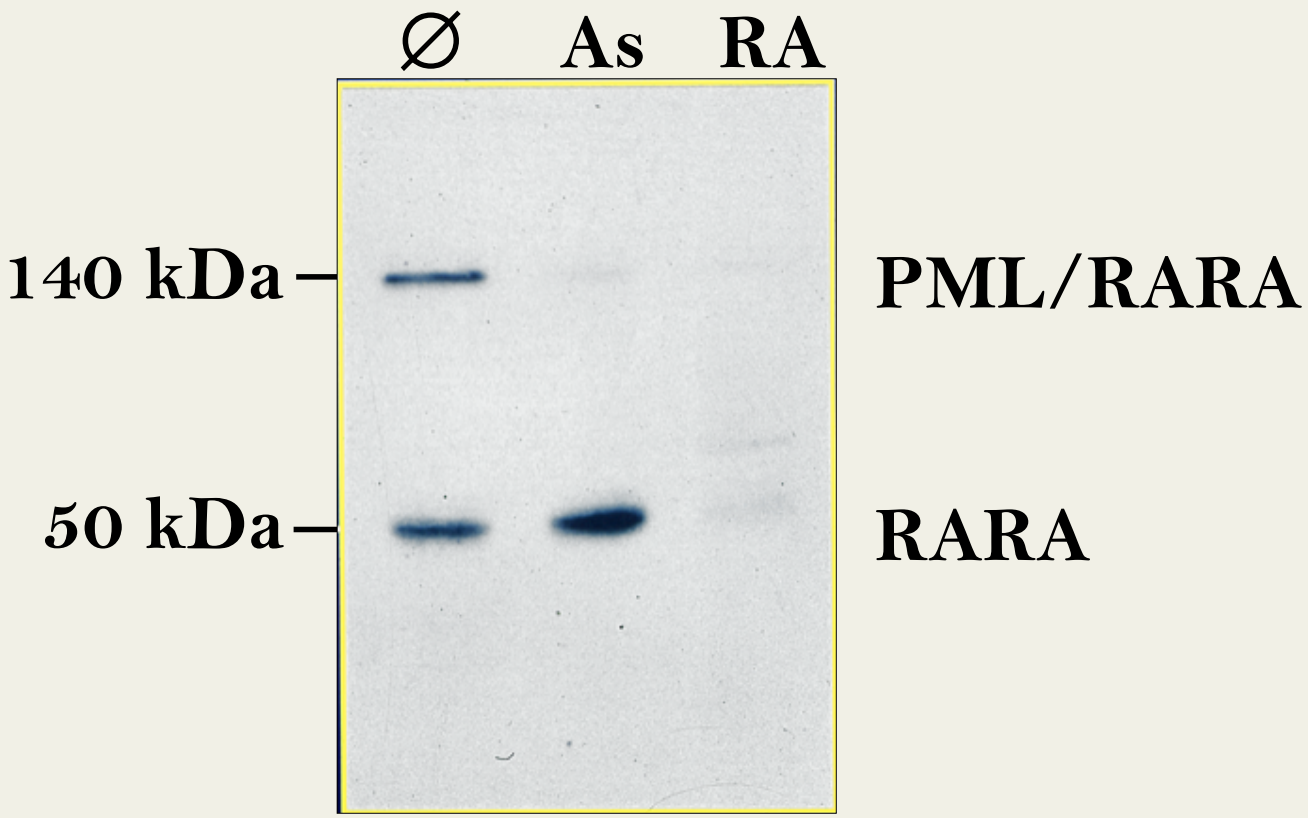
Arsenic

Clinical responses 95% complete remission
70% cure, **single agent**!

Incompatible with the transcriptional model!

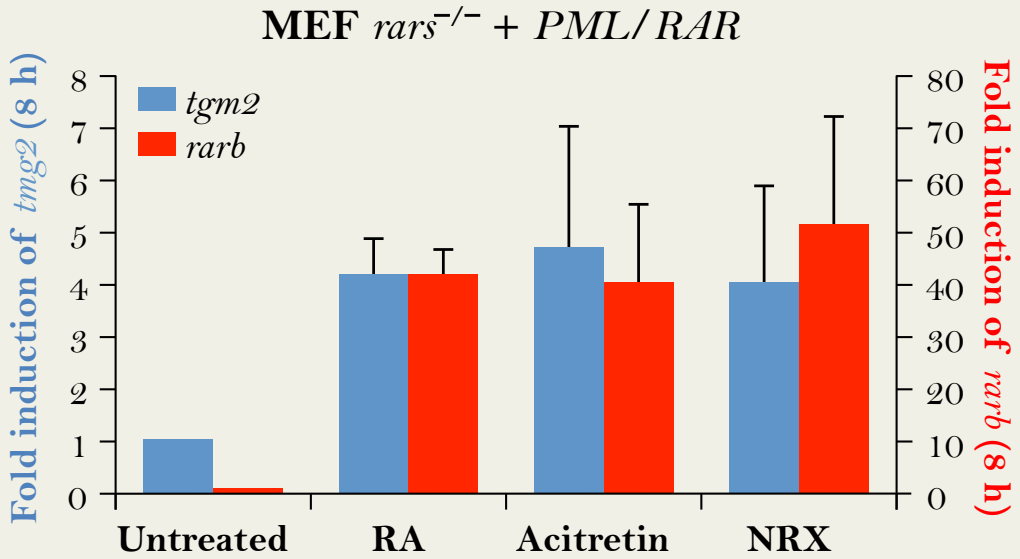
Chen GQ, et al. Blood. 1996;88:1052-61 and 1997;89:3345-53.

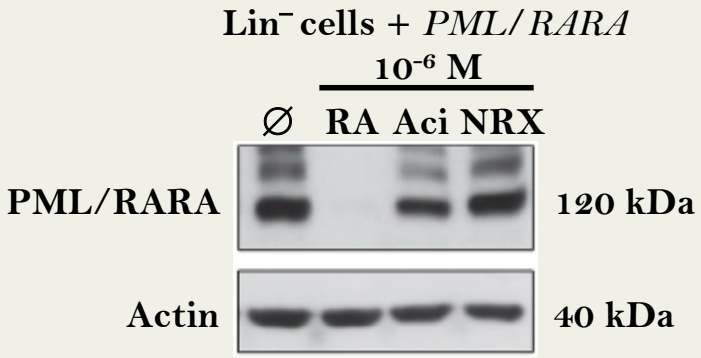
RA and arsenic degrade PML/RARA

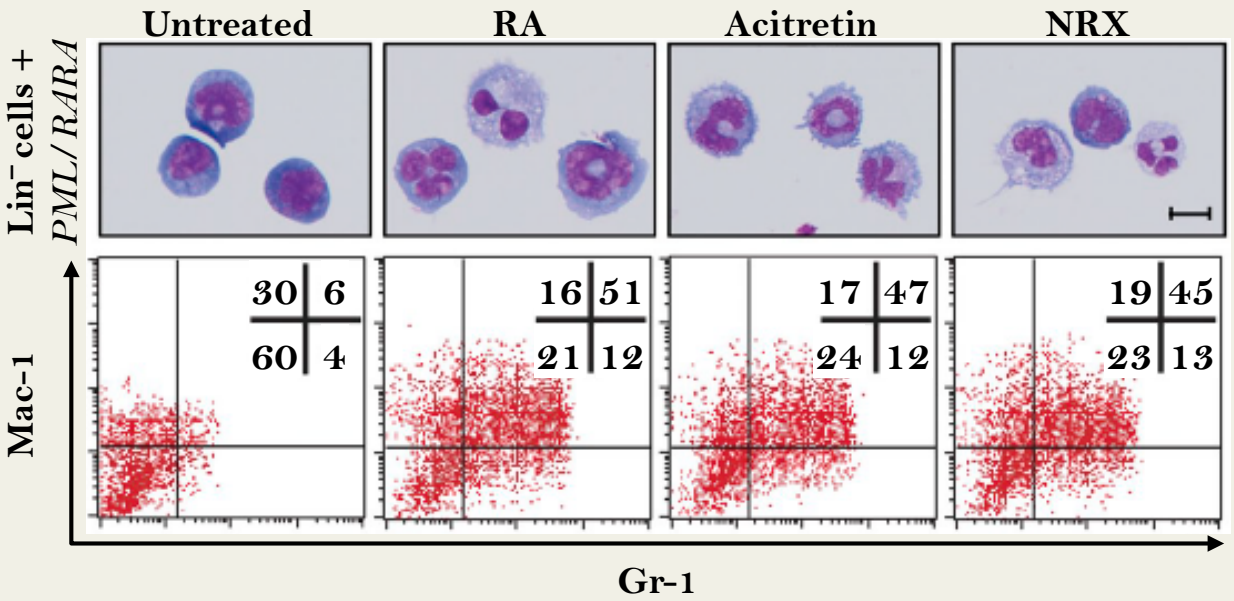


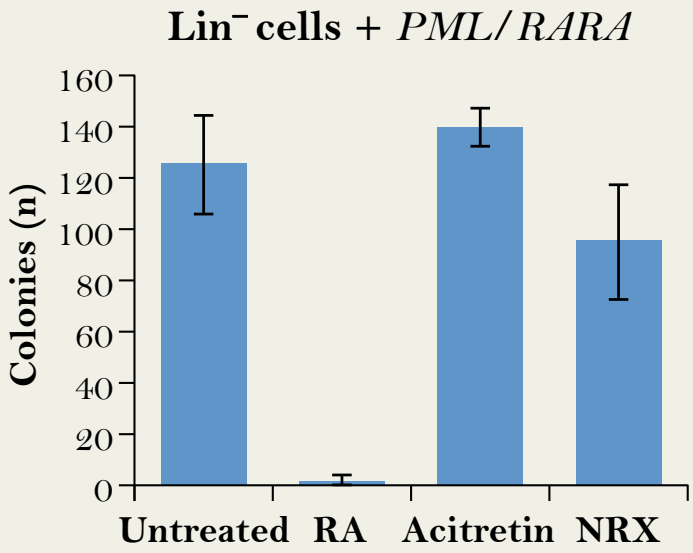
Chen GQ, et al. Blood. 1997;89:3345-53.
Lallemand-Breitenbach V, et al. J Exp Med. 1999;89:1043-52 and 2001;193:1361-71.
Zhu J, et al. Proc Natl Acad Sci USA. 1997;94:3978-83 and 1999;96:14807-12.

Pharmacologically uncoupling differentiation and response







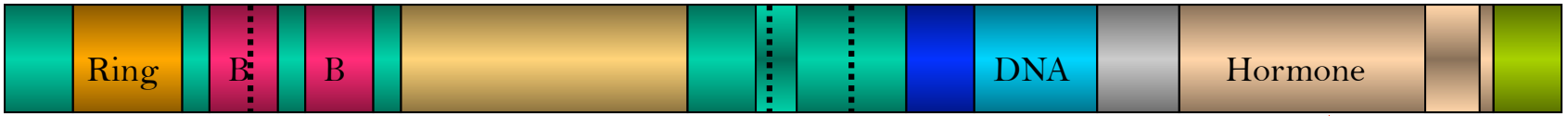


Lin−, lineage negative; MEF, mouse embryonic fibroblasts; NRX, NRX195183 (a RARA-specific agonist).

Ablain J, et al. J Exp Med. 2013;210:647-53.

PML/RARA degradation

PML / **RARA**



ATO

Oxidation + direct binding
Nuclear body aggregation
SUMO conjugation
Poly-ubiquitination by RNF4
Proteasome

Degradation

AR

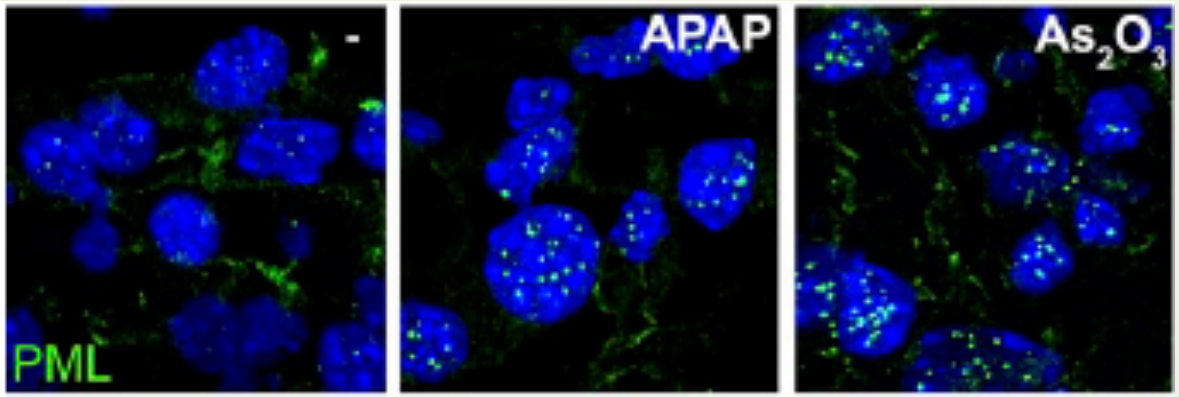
Proteasome

Degradation

ATO, arsenic trioxide;
SUMO, small ubiquitin-like modifier.

Jeanne M, et al. Cancer Cell. 2010;18:88-98. Lallemand-Breitenbach V, et al. J Exp Med. 2001;193:1361-71. Lallemand-Breitenbach V, et al. Nat Cell Biol. 2008;10:547-55. Zhang XW, et al. Science. 2010;328:240-3. Zhu J, et al. Proc Natl Acad Sci USA. 1997;94:3978-83 and 1999;96:14807-12.

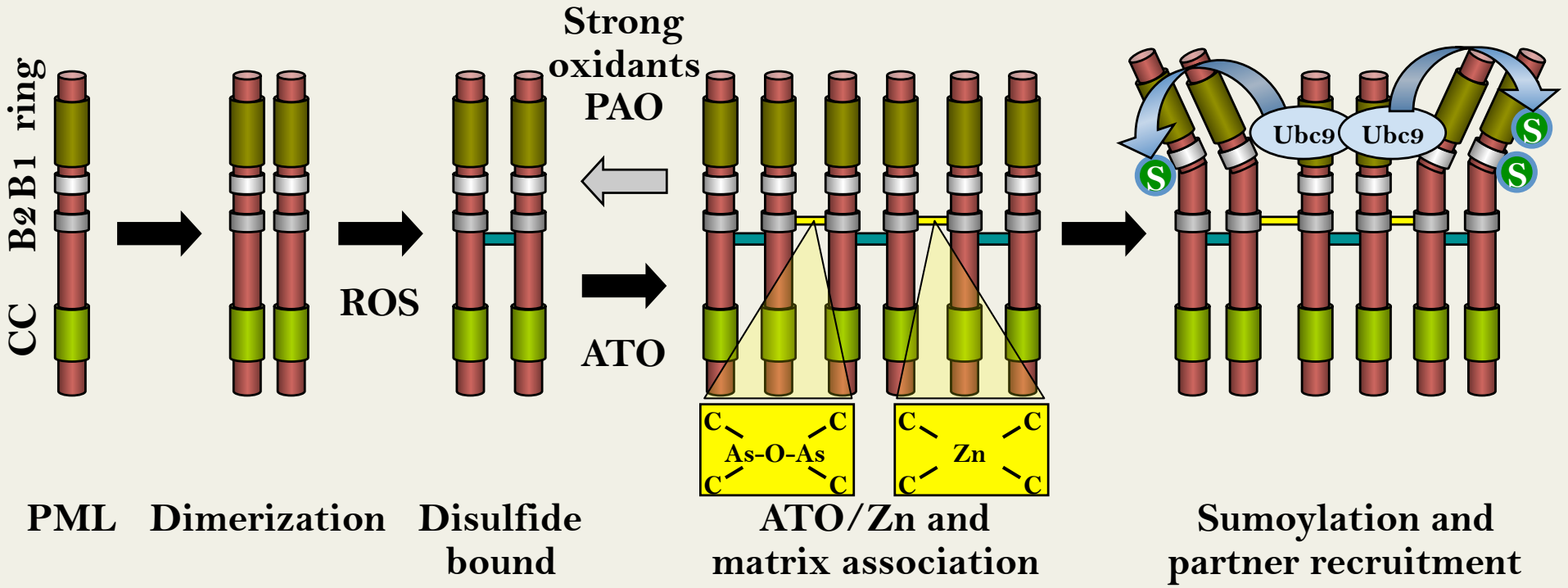
PML as a ROS sensor



PML box 2

KPL**CC**SCALLDSS

As

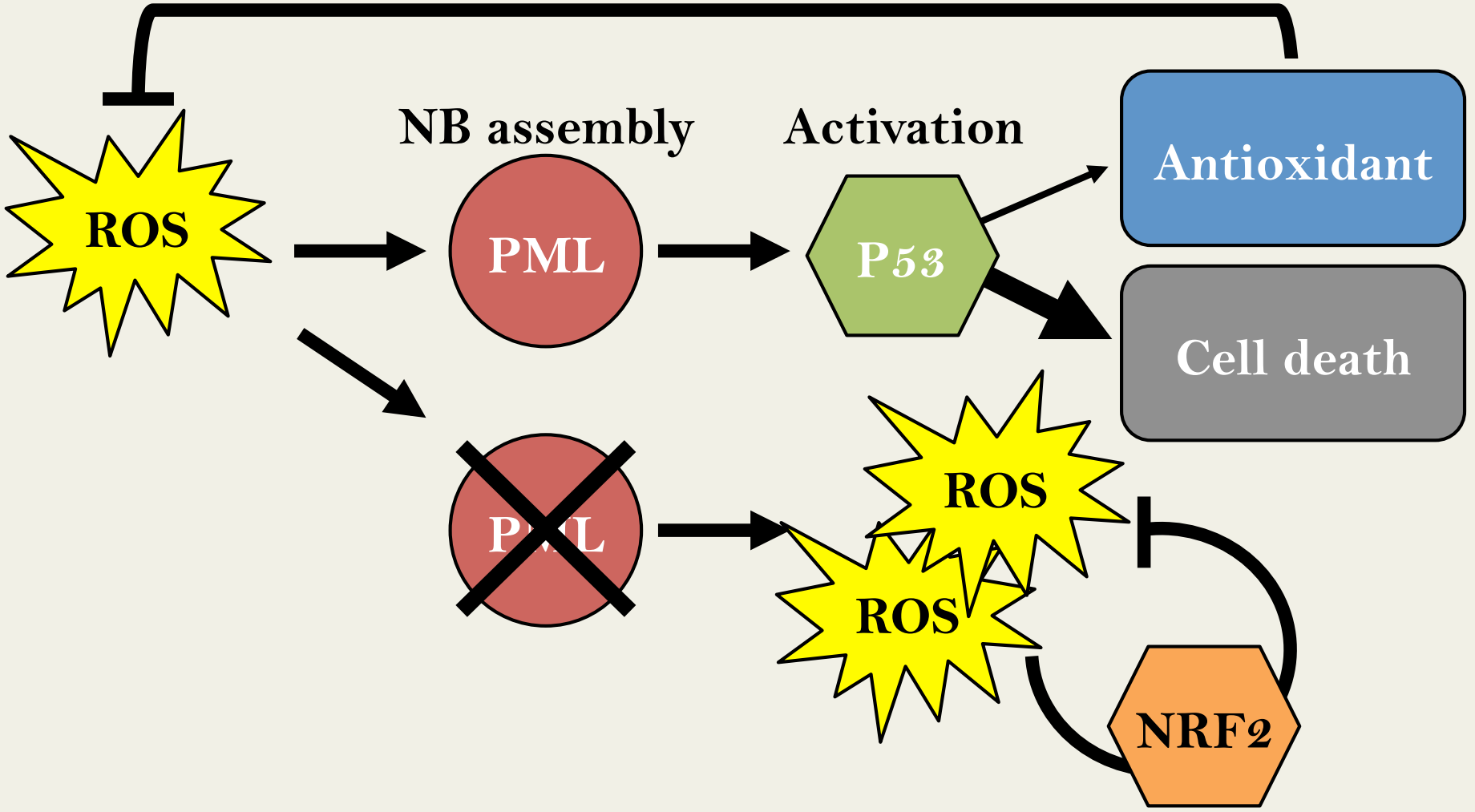


PML **Dimerization** **Disulfide bound** **ATO/Zn and matrix association** **Sumoylation and partner recruitment**

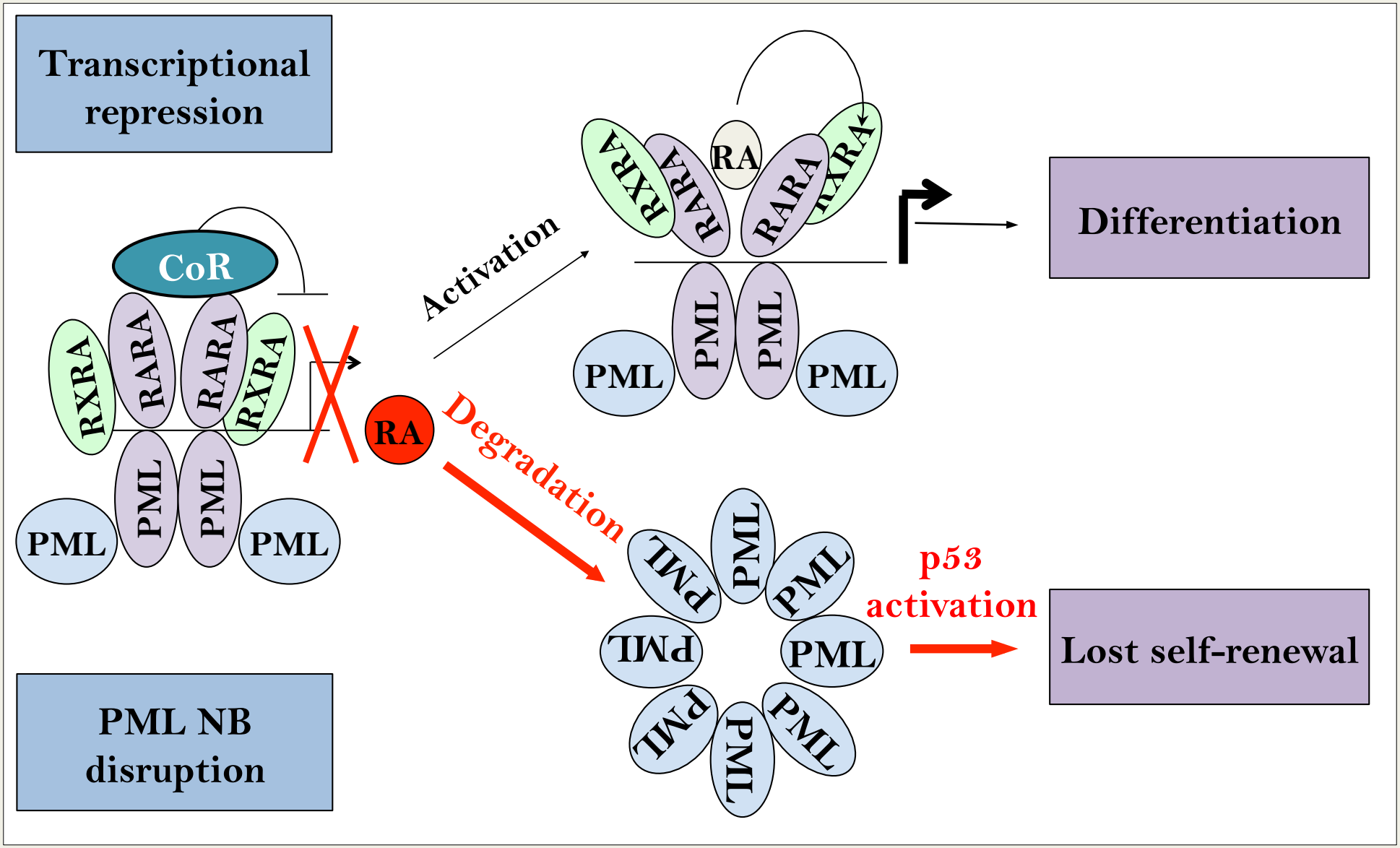
PAO, phenylarsine oxide;
ROS, reactive oxygen species.

Jeanne M, et al. Cancer Cell. 2010;18:88-98. Lallemand-Breitenbach V, et al. J Exp Med. 2001;193:1361-71 and Nat Cell Biol. 2008;10:547-55. Sahin U, et al. J Cell Biol. 2014;204:931-45. Zhang XW, et al. Science. 2010;328:240-3. Zhu J, et al. Proc Natl Acad Sci USA. 1997;94:3978-83.

PML as a physiologic ROS sensor



Degradation therapy



Ablain J, et al. Nat Med. 2014;20:167-74. Nasr R, et al. Nat Med. 2008;14:1333-42.

RA and arsenic antagonize for differentiation *ex vivo*

Cytofluorometric analysis of cell surface antigen marker expression: percentages of positive cells among leukemia blast cells derived from 4 patients with APL[a]

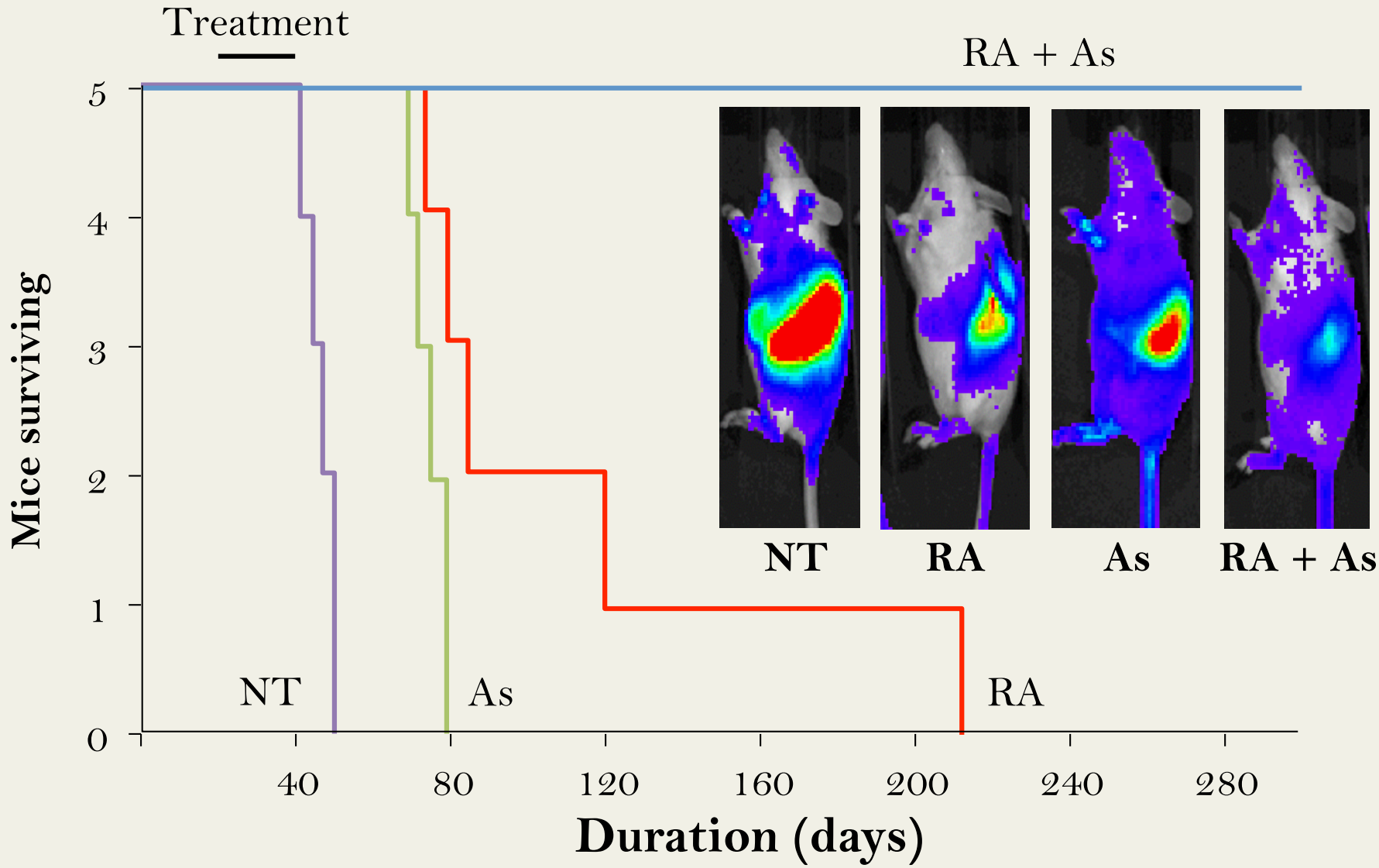
Marker	C0	C7	ATRA	ATO	ATRA + ATO	C0	C7	ATRA	ATO	ATRA + ATO
			Patient 1					**Patient 2**		
CD11b	30	19	86	13	42	68	12	89	17	NE
CD11c	2	1	74	8	13	4	3	69	11	NE
CD15	22	34	99	97	97	10	37	95	92	NE
CD18	10	4	59	3	NE	4	8	57	23	NE
			Patient 3					**Patient 4**		
CD11b	10	2	51	3	5	10	4	79	3	31
CD11c	0	0	51	2	32	0	0	54	1	17
CD15	2	29	100	98	99	3	6	99	69	99
CD18	54	48	94	58	50	37	33	95	33	79

[a] All patients had the t(15;17) translocation. The blast cells were cultured for 7 days in medium alone (control) or in the presence of 1 μM ATRA, 1 μM ATO, or a combination of these agents.

C0, control at day 0 of culture; C7, control at day 7 of culture; NE, not evaluated.

Shao W, et al. J Natl Cancer Inst. 1998;90:124-33.

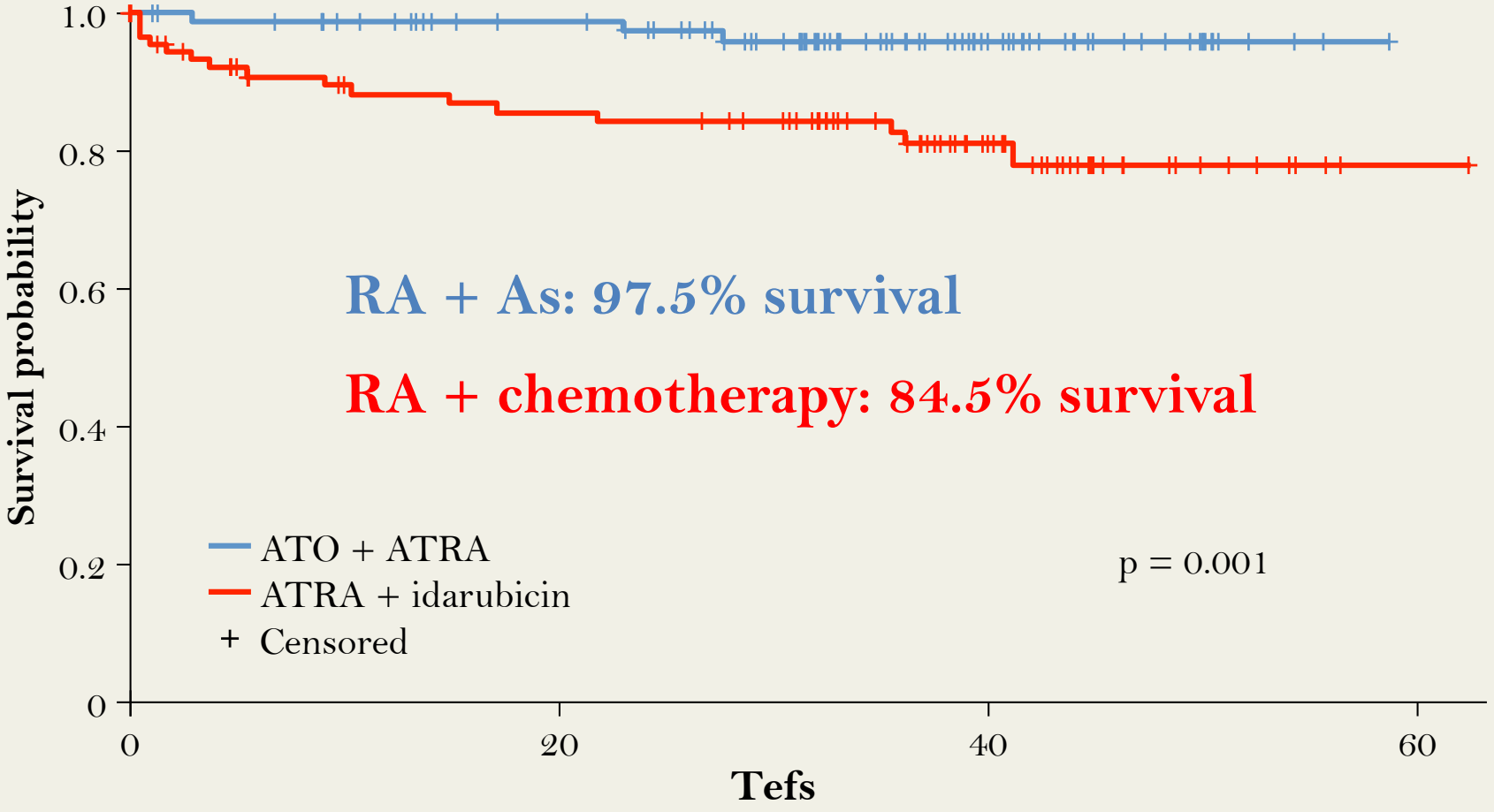
…but synergize for cure!



Lallemand-Breitenbach V, et al. J Exp Med. 1999;89:1043-52.
Nasr R, et al. Nat Med. 2008;14:1333-42.

NT, no treatment.

RA and arsenic synergize in APL



Patients go off treatment
Oral therapy with arsenic sulfur

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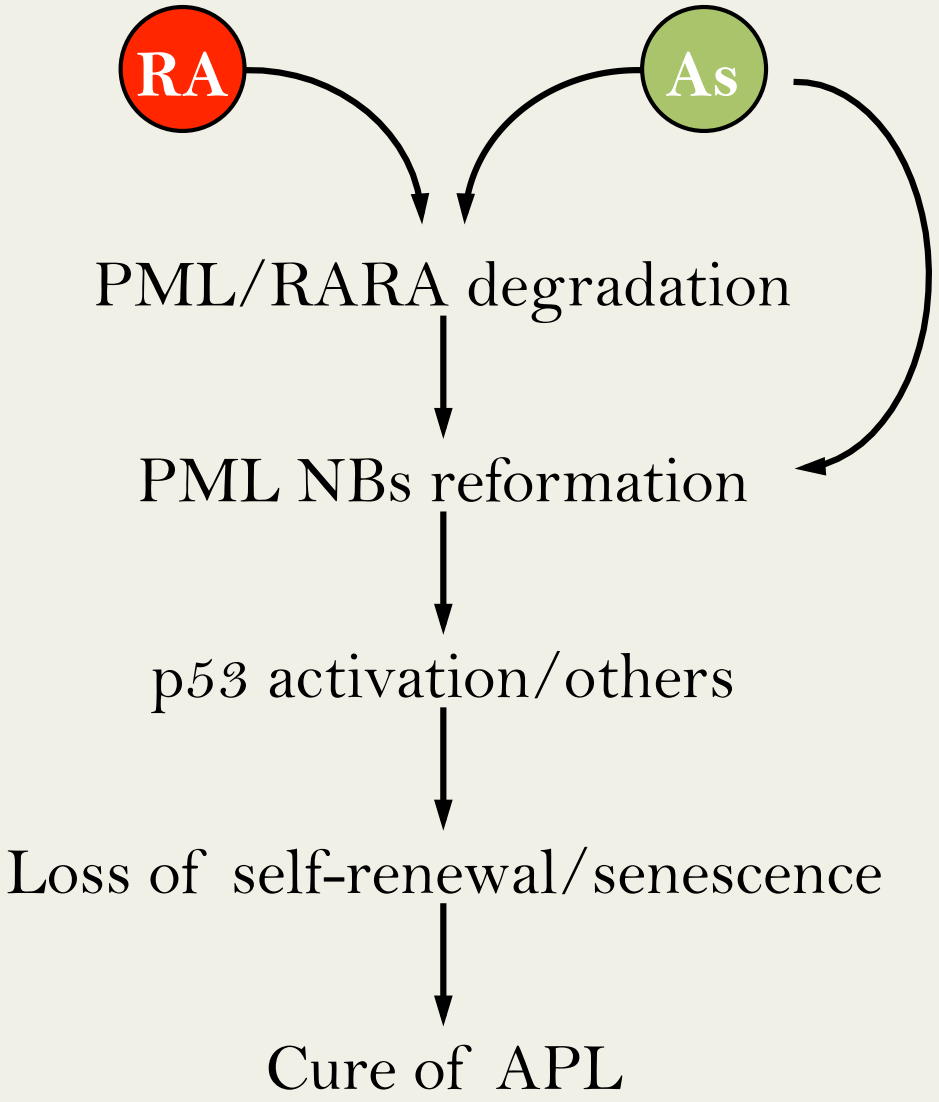
Hu J, et al. Proc Natl Acad Sci USA. 2009;106:3342-7.
Lo-Coco F, et al. N Engl J Med. 2013;369:111-21.
Shen ZX, et al. Proc Natl Acad Sci USA. 2004;101:5328-35.
Zhu HH, et al. J Clin Oncol. 2013;31:4215-21 and N Engl J Med. 2014;371:2239-41.

Explaining synergy



Therapy-resistant patients establish the model

- **RA-resistance:** mutation in the ligand-binding domain of the RARA moiety of PML/RARA

- **Arsenic resistance:** highly clustered mutations in the arsenic-binding site of the PML moiety of PML/RARA

PML B box 2

KPLCCSCALLDSS

- **Therapy resistance:** through mutation of the arsenic-binding site of PML!
  - Establish the **role of normal PML** in patients' cure

Goto E, et al. Blood. 2011;118:1600-9.
Lehmann-Che J, et al. N Engl J Med. 2014;371:1170-2.
Zhu HH, et al. N Engl J Med. 2014;371:2239-41.