Multidrug-resistant neuroblastoma cells are responsive to arsenic trioxide at both normoxia and hypoxia

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Abstract
Despite intensive treatment, the outcome of high-risk neuroblastoma patients is poor with acquired multidrug resistance as an important cause. Previously, our group has shown that arsenic trioxide (As$_2$O$_3$) kills multidrug-resistant neuroblastoma cells grown in vitro and in vivo at clinically tolerable doses. Regions of tissue hypoxia often arise in aggressive solid tumors, and hypoxic tumors exhibit augmented invasiveness and metastatic ability in several malignancies. Furthermore, hypoxia may impair the treatment efficiency; therefore, we have studied the cytotoxic effect of As$_2$O$_3$ on neuroblastoma cells grown under normoxic as well as hypoxic (1% oxygen) conditions. At both normoxia and hypoxia, 2 and 4 μmol/L As$_2$O$_3$ induced evident cell death in the drug-sensitive SH-SY5Y and IMR-32 cells as well as in the multidrug-resistant SK-N-BE(2)c (with a mutated p53) and SK-N-FL cells after 72 hours of exposure. In contrast, the conventional chemotherapeutic drug etoposide showed lowered efficiency in hypoxic IMR-32 cells. In accordance with our previously published results, although not to the same extent as in their normoxic counterparts, Bax is proteolytically cleaved also in neuroblastoma cells exposed to As$_2$O$_3$ at hypoxia. This suggests that similar molecular mechanisms are involved in As$_2$O$_3$-induced neuroblastoma cell death during hypoxia compared with normoxia. Together, our results support As$_2$O$_3$ as a potential candidate drug as a complement to conventional treatments for high-risk neuroblastoma patients and perhaps also for patients with other multidrug-resistant solid tumors. [Mol Cancer Ther 2005;4(7):1128–35]

Introduction
Neuroblastoma is a childhood malignancy derived from the sympathetic nervous system and accounts for 8% to 10% of all cancers in children. Intensive chemoradiotherapy supported with bone marrow transplantation and followed by 13-cis-retinoic acid treatment has improved the survival for high-risk neuroblastoma patients (1). Still, the majority of neuroblastoma patients eventually develop progressive disease, which is refractory to further therapy. A major contributing factor to chemotherapeutic treatment failure of neuroblastoma is the development of resistance to multiple and functionally unrelated cytotoxic drugs, and as a consequence, the long-term survival rate of this group of neuroblastoma patients is only about 30% (1–3).

As$_2$O$_3$ has been used for therapeutic purposes for centuries, and recently, it has been successfully employed in the treatment of acute promyelocytic leukemia (APL) where several reports have shown that low doses of As$_2$O$_3$ can with minimal toxicity induce complete remission in patients with relapsed APL (4–6). Moreover, the potency of As$_2$O$_3$ to induce cell death in vitro has been shown in a variety of cancer cells including non-APL leukemia and lymphoma cells (7, 8) as well as solid tumors like neuroblastoma (9–11) and tumors originating from prostate, kidney, cervix, and bladder (12). The underlying mechanisms of As$_2$O$_3$-induced cytotoxicity are complex and include induction of apoptosis, cellular differentiation, degradation of the t(15;17)-specific fusion protein PML/retinoic acid receptor-α seen in APL, growth inhibition, induction of autophagy, and inhibition of angiogenesis (13–16). In different cell lines, As$_2$O$_3$ has been shown to induce apoptosis by down-regulation of Bcl-2 (13), activation of caspases (17), modulation of p53 (17), generation of reactive oxygen species (ROS; ref. 18), and uncoupling of the mitochondrial potential (19).

We and others have shown that clinically relevant concentrations of As$_2$O$_3$ promote cell death in vitro and in vivo not only in drug-sensitive neuroblastoma cell lines but also in the multidrug-resistant p53-mutated/deleted neuroblastoma cell lines, SK-N-BE(2) and LA-N-1 (9–11). These promising results support the possible use of As$_2$O$_3$ in combination therapy in high-risk neuroblastoma patients, and a phase II clinical trial with As$_2$O$_3$ is presently done at the Memorial Sloan-Kettering Cancer Center. We have shown that the As$_2$O$_3$-induced neuroblastoma cell death seems not to involve induced neuronal differentiation but includes increased expression and proteolytic activation of Bax, down-regulation of Bcl-2, and to a slight extent, activation of caspase-3 (9, 10). The activation of Bax seems to be a key event because inhibition of the Bax cleavage prevented As$_2$O$_3$-induced cell death (10). The activation of Bax was also shown to be independent of functional p53 (10), a feature of great interest because deletions or mutations in...
p53 often are seen in high-risk neuroblastoma patients with relapsed, refractory disease (20, 21). In contrast, drugs commonly used in induction treatment of children with advanced neuroblastoma were only able to induce cell death and hence cleavage of Bax in drug-sensitive neuroblastoma cells (10), indicating that a different cytotoxic pathway is induced upon \(\text{As}_2\text{O}_3\) treatment.

Hypoxic microenvironments are frequently found in solid tumors as a result of inefficient vascular supply and high oxygen consumption of rapidly proliferating malignant cells. Tumor hypoxia is associated with malignant progression, lower sensitivity to chemotherapy and radiotherapy, increased metastatic potential, and poor prognosis (22, 23).

Many of the features in hypoxic tumors are mediated by the hypoxia-inducible factor-1 (HIF-1α) and HIF-2α, transcription factors which modulate the expression of several genes involved in both short-term adaptive mechanisms (e.g., glucose transport and switch to anaerobic metabolism) and long-term adaptive mechanisms (e.g., angiogenesis; ref. 24).

In addition to these features, we recently showed that hypoxia alters the gene expression in neuroblastoma cells toward an immature phenotype (25, 26). Because there is a correlation in neuroblastoma between low stage of differentiation and poor clinical outcome, hypoxic adaptation could contribute to increased malignancy of the tumor. Hypoxia-induced dedifferentiation is not restricted to neuroblastoma cells but is also seen in other types of tumors like breast cancer (27) and prostate cancer (28). It has been shown that an \(\text{As}_2\text{O}_3\)-resistant APL cell line became sensitive and underwent apoptosis when the treatment included both \(\text{As}_2\text{O}_3\) and all-trans retinoic acid, a combination which greatly accelerated differentiation in these cells (29).

To evaluate the proliferative capacity of neuroblastoma cells after \(\text{As}_2\text{O}_3\) treatment, SK-N-BE(2) cells were seeded at day 0 and varying concentrations of \(\text{As}_2\text{O}_3\) were added at day 1. After 72 hours of treatment, the cells were reseeded under hypoxic conditions, 1% O\(_2\), were created in a Hypoxia workstation 400 (Ruskinn Technology, Leeds, United Kingdom) connected to a Ruskinn gas mixer module.

\(\text{As}_2\text{O}_3\) was dissolved in 1.0 mol/L NaOH; vincristine, carboplatin, and doxorubicin were dissolved in distilled \(\text{H}_2\text{O}\) and etoposide in DMSO. All cytotoxic drugs were purchased from Sigma (St. Louis, MO).

**Cell Viability and Proliferation Assays**

The cells were seeded at day 0 under normoxic conditions and the cytotoxic drugs were added at day 1. Thereafter, the cells were grown under normoxia or hypoxia for 72 hours. When indicated, the cells were grown under normoxia or hypoxia for 72 hours before the cytotoxic drugs were added. In these experiments, the cells were reseeded under hypoxic conditions 1 day before initiation of the drug treatments. To assess cell viability, the cells were collected and stained with trypan blue (Sigma). Approximately 200 cells per culture were counted using a light microscope. All treatments were done in triplicates and the experiments were repeated three or four times. The amount of viable cells was compared with untreated normoxic or hypoxic controls, respectively, which were both set to 100%.

The effect of cytotoxic drugs under normoxic conditions was determined in 96-well plates by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay (CellTiter 96, Promega, Madison, WI), according to the manufacturer’s recommendation. All experiments were done in triplicates and repeated thrice.

To evaluate the proliferative capacity of neuroblastoma cells after \(\text{As}_2\text{O}_3\) treatment, SK-N-BE(2) cells were seeded at day 0 and varying concentrations of \(\text{As}_2\text{O}_3\) were added at day 1. After 72 hours of treatment, the cells were replated in 96-well plates and grown for 24 to 72 hours where 0.5 \(\mu\text{Ci} \ [\text{H}]\text{thymidine (Amersham Bioscience, Bucks, United Kingdom) was added at the last 24 hours of culture. The cells were harvested and proliferation was measured by incorporation of [\text{H}]\text{thymidine in a beta scintillation counter.**}

**Immunoblot Analysis**

Cells were lysed in 10 mmol/L Tris-HCl (pH 7.2), 160 mmol/L NaCl, 1% Triton X-100, 1% sodium deoxycarbole, 0.1% SDS, 1 mmol/L EGTA, and 1 mmol/L EDTA in the presence of Complete Protease Inhibitor (Roche Molecular Biochemicals, Mannheim, Germany). For the HIF-1α Western blot, the cells were harvested under hypoxic conditions. Equal amount of protein was separated on an SDS-PAGE and blotted onto a Hybond C membrane (Amersham Bioscience) for the HIF-1α Western blot or an Immobilon-P membrane (Millipore Corp., Bedford, MA) for the Bax Western blot. The following primary antibodies and antiserum were used: anti-actin-antibody (ICN Bio-medical, Aurora, OH) diluted 1:2,000, Bax antiserum (BD Pharmingen, San Diego, CA) diluted 1:2,000, anti-caspase-3 antibody (Alexis Biochemicals, San Diego, CA) diluted 1:500, anti-glyceraldehyde-3-phosphate dehydrogenase...
antibody (Chemicon International, Inc., Temecula, CA) diluted 1:2,000, anti-HIF-1α antibody (Novus Biologicals, Littleton, CO) diluted 1:1,000, and anti-PKCα (c-20) antibody (Santa Cruz Biotechnology, Santa Cruz, CA) diluted 1:200. The proteins were visualized using horseradish peroxidase–conjugated anti-mouse antibody from Amersham Pharmacia Biotech (Arlington Heights, IL) and Jackson Immunoresearch Laboratories, Inc. (West Grove, PA) and anti-rabbit antibody from DAKO (Glostrup, Sweden) and a Super Signal detection system (Pierce Chemical Co., Rockford, IL).

Immunocytochemistry
Cell pellets were fixed with 4% buffered paraformaldehyde, paraffin embedded, and cut into 4-μm-thin sections. The sections were microwave treated with a target retrieval solution (DAKO) at pH 9.9 and the cells were stained with an anti-Ki-67 antibody (DAKO) diluted 1:500. Cell staining was done in a DAKO ChemMate 500 using the Envision protocol according to the manufacturer’s instructions.

Results
Arsenic Trioxide Induces Cell Death in Hypoxic Multidrug-Resistant Neuroblastoma Cells
We examined three neuroblastoma cell lines, grown under normoxic and hypoxic (1% oxygen) conditions, with regard to their responsiveness to As2O3. In normoxic cultures, the results confirmed our recently published data showing that the p53-mutated and multidrug-resistant neuroblastoma cell line SK-N-BE(2)c is as sensitive to As2O3 as the drug-sensitive SH-SY5Y and IMR-32 cell lines; all cell lines displaying IC50 values in the low micromolar range after 72 hours of treatment (10; Fig. 1A). In addition, As2O3 is toxic to the neuroblastoma cells under hypoxic conditions (Fig. 1A). When treated with 4 μmol/L As2O3 at normoxia and hypoxia, the cultures displayed 45% to 65% of dead cells. At both 1% and 21% oxygen, exposure of the cells to As2O3 gave rise to a concentration-dependent increase of cells with rounded morphology as well as detached floating cells (Fig. 1B). To assure that As2O3 treatment did not prevent induction of a hypoxic response, we investigated the accumulation of the hypoxia-induced transcription factor HIF-1α in normoxic and hypoxic cells treated with 4 μmol/L As2O3 for 4 hours (Fig. 1C). As expected, at normoxia, no HIF-1α protein could be detected in either untreated or As2O3-treated cells (Fig. 1C, lanes 1 and 2), whereas a marked accumulation was observed in untreated hypoxic cells (Fig. 1C, lane 3). Upon treatment with As2O3 at hypoxia, a robust HIF-1α protein stabilization was detected suggesting that an adaptation to the hypoxic environment was induced in these cells (Fig. 1C, lane 4).

To further show the efficiency of As2O3 on hypoxic neuroblastoma cells, we wanted to include an additional multidrug-resistant neuroblastoma cell line. We have previously compared several neuroblastoma cell lines with regard to their sensitivity to vincristine, etoposide, doxorubicin, and carboplatin (9, 10), all of which are chemotherapy drugs commonly used in the induction treatment of high-risk neuroblastoma. In comparison with all previously tested cells, we have now identified the MYCN-amplified SK-N-FI cells to be one of the most drug-insensitive cell line (Fig. 2A), displaying resistance to all of the abovementioned drugs at clinically relevant concentrations (30–33). However, despite their multidrug-resistant phenotype and in accordance with the results obtained with the SK-N-BE(2)c cells, the amount of viable SK-N-FI cells was markedly reduced after treatment with...
As$_2$O$_3$ for 72 hours, displaying an IC$_{50}$ value in the low micromolar range (Fig. 2A). As$_2$O$_3$ induced a pronounced cell death in SK-N-FI cells also under hypoxic growth conditions (Fig. 2B). At hypoxia after 72 hours of treatment with 4 µmol/L As$_2$O$_3$, the proportion of proliferating cells were decreased in all cell lines, indicating that the reduction of viable neuroblastoma cells to some extent is due to decreased proliferation.

In the SK-N-BE(2)c cells, showing the highest percentage of Ki-67-positive cells in the normoxic untreated control, the reduction of Ki-67 positivity was much more marked upon As$_2$O$_3$ treatment at normoxia (Fig. 3A). However, in all cell lines, the combination of As$_2$O$_3$ treatment and hypoxic growth conditions did not increase the growth inhibition seen with either of the treatments alone (Fig. 3A). To address the possibility that As$_2$O$_3$ induces a selection of cells with low proliferative capacity, cells treated with As$_2$O$_3$ for 72 hours were replated and grown in the absence

Arsenic Trioxide Responsiveness in Hypoxic Neuroblastoma Cells Is Due to Induction of Cell Death and to Some Extent Inhibition of Proliferation

It has been shown in different types of cancer cell lines that treatment with As$_2$O$_3$ induces cell death as well as growth inhibition (34). To investigate the possible involve-
of As$_2$O$_3$. As shown in Fig. 3B, there was a reduction in number of surviving replated SK-N-BE(2)c cells from cultures previously treated with As$_2$O$_3$; however, the proliferation rates of As$_2$O$_3$-treated cells were comparable with that of untreated cells. These results together with the results presented in Figs. 1 and 2 suggest that the As$_2$O$_3$ responsiveness in normoxic and hypoxic neuroblastoma cells is due to induction of cell death and only to some extent inhibition of proliferation and in addition, no selection of slow proliferating cells seems to occur during treatment.

**Proteolytic Cleavage of Bax and a Slight Activation of Caspase-3 in Hypoxic Neuroblastoma Cells upon Treatment with As$_2$O$_3$**

Previously, we have shown that at normoxia As$_2$O$_3$ provoked Bax expression in neuroblastoma cells and that p21 Bax was proteolytically cleaved into a p18 Bax form (10), which is more proapoptotic (35, 36). In addition, As$_2$O$_3$ treatment only induced a slight activation of caspase-3 and inhibition of caspase-3 did not prevent cell death, whereas inhibition of Bax cleavage was associated with a decreased As$_2$O$_3$-induced cytotoxicity (10). This suggests that activation of Bax is a key event in As$_2$O$_3$-induced cell death in normoxic neuroblastoma cells and that As$_2$O$_3$ activates a cytotoxic pathway different from that induced by the conventionally used drugs. To clarify whether As$_2$O$_3$ induces a similar cell death pathway in hypoxic neuroblastoma cells, we did Western blot analyses on cell lysates from normoxic and hypoxic cells treated with 2 or 4 µmol/L As$_2$O$_3$ for 72 hours. In accordance with the normoxic samples, the proteolytic activation of Bax was induced in hypoxic SK-N-BE(2)c cells with increasing concentrations of As$_2$O$_3$ (Fig. 4). However, the proportion of cleaved Bax was not as large in the As$_2$O$_3$-treated hypoxic cells as in the normoxic cells (Fig. 4). Caspase-3 was activated to a slight extent in a dose-dependent manner upon As$_2$O$_3$ treatment and the levels of activation were comparable in the normoxic and hypoxic SK-N-BE(2)c cells (Fig. 4).

**Neuroblastoma Cells Preexposed to Hypoxia Are Sensitive to As$_2$O$_3$**

In the experiments described in Figs. 1 and 2, As$_2$O$_3$ treatment was initiated at the same time as the hypoxic growth condition was induced. However, in tumor environments, there are most likely areas exposed to hypoxia for varying periods of time. Experimental systems where the cells already have been adapted to a hypoxic environment mimics tumor areas exposed to hypoxia for longer periods and allow hypoxia-mediated dedifferentiation (25, 26) and stabilization of proapoptotic as well as antiapoptotic proteins (37) to occur before drug exposure. To further evaluate the potency of As$_2$O$_3$ in hypoxic cells, the multidrug resistant SK-N-BE(2)c cells and the drug-sensitive IMR-32 cells were thus preexposed to normoxic or hypoxic conditions for 72 hours before induction of As$_2$O$_3$ treatment under normoxia or hypoxia for 72 hours. In accordance with the results presented in Fig. 1, both the SK-N-BE(2)c cells and the IMR-32 cells showed a sustained sensitivity to As$_2$O$_3$ under hypoxic growth conditions, although the cells already had adapted to hypoxia when the As$_2$O$_3$ treatment was initiated (Fig. 5). In both cell lines, the percentage of dead cells reached about 45 % after treatment with 4 µmol/L As$_2$O$_3$ at normoxia as well as hypoxia and the cell death was consistent with the cell viability data.

**Influence of Hypoxia on Cell Death Induced by Etoposide in Drug-Sensitive Neuroblastoma Cells**

Several reports indicate that some cytotoxic drugs are less efficient in a hypoxic environment (38, 39), but the results described above suggest that As$_2$O$_3$ does not belong to that group of substances, at least not for treatment of...
neuroblastoma cells. To compare the efficiency of \( \text{As}_2\text{O}_3 \) with other drugs, we examined IMR-32 cells, grown under both normoxic and hypoxic (1% \( \text{O}_2 \)) conditions, with regard to its responsiveness to the conventional chemotherapeutic drug etoposide, a drug previously shown to have decreased efficiency under hypoxic conditions (22, 39). The effects of etoposide were tested both without (Fig. 6A) and with (Fig. 6B) preexposure to hypoxia. In agreement with our previous results (10), 72 hours of treatment with 0.5 \( \mu \text{mol/L} \) etoposide induced an evident cell death in IMR-32 cells grown under normoxia (Fig. 6). However, a significant difference in cell death as well as amount of viable cells was shown in the hypoxic IMR-32 cells compared with their normoxic counterparts upon etoposide treatment (Fig. 6). At 0.2 \( \mu \text{mol/L} \) etoposide, the cytotoxic effect was markedly reduced at hypoxia, which was seen both when the etoposide treatment was initiated at the same time as the hypoxic growth condition was induced (Fig. 6A) and even more pronounced when the cells were preexposed to hypoxia 3 days before the addition of etoposide (Fig. 6B). These results show that in contrast to \( \text{As}_2\text{O}_3 \), etoposide exhibits a clearly reduced efficacy under hypoxic conditions in IMR-32 cells.

**Discussion**

In this study, we show a potent cytotoxicity of \( \text{As}_2\text{O}_3 \) in two drug-sensitive as well as two multidrug-resistant neuroblastoma cell lines both under normoxic and hypoxic growth conditions. We also show that the \( \text{As}_2\text{O}_3 \) responsiveness seen in hypoxic neuroblastoma cells is only to some extent due to hypoxia- or \( \text{As}_2\text{O}_3 \)-induced growth inhibition but mainly depends on induction of cell death. These results together show that the cytotoxic efficiency of \( \text{As}_2\text{O}_3 \) is sustained under low oxygen pressures, which is important from a clinical point of view; that is, \( \text{As}_2\text{O}_3 \) is a potential candidate drug in treatment of solid tumors with hypoxic areas like neuroblastoma. The fact that \( \text{As}_2\text{O}_3 \) seems to activate a cytotoxic pathway different from that induced by the conventionally used drugs during induction treatment of neuroblastoma and as a result is able to kill multidrug-resistant neuroblastoma cells (10) lends support to the ongoing efforts to introduce the use of \( \text{As}_2\text{O}_3 \) in combination with existing treatment protocols for patients with multidrug-resistant neuroblastomas.

The precise molecular mechanisms by which \( \text{As}_2\text{O}_3 \) induces neuroblastoma cell death are yet to be determined. Our previously published results suggest that proteolytically activation of the proapoptotic protein Bax is an important mechanism in normoxic neuroblastoma cells (10). Here we show that cleavage of Bax also occurred in \( \text{As}_2\text{O}_3 \)-treated hypoxic cells but was not as pronounced as in the normoxic cells. This may indicate that induction of \( \text{As}_2\text{O}_3 \)-induced cell death under hypoxic conditions and that complementary cell death mechanisms may be activated. Further analyses are required to be able to establish to what extent the mechanisms involved in \( \text{As}_2\text{O}_3 \)-induced cell death differ in neuroblastoma cells grown under normoxic or hypoxic conditions. In addition to oxygen pressure, other differences like genotypically changes may influence the mechanisms of \( \text{As}_2\text{O}_3 \)-induced cytotoxicity. For instance, published data indicate that \( \text{As}_2\text{O}_3 \) induces cell death of myeloma cells by two different mechanisms depending on the p53 status of the cell (40, 41). It is not known whether this is true also for neuroblastoma cells. However, we do show here and in our previous study (10) that \( \text{As}_2\text{O}_3 \) is a potent cytotoxic drug in wild-type p53 expressing as well as in p53-mutated/deleted multidrug-resistant neuroblastoma cells and that Bax is proteolytically activated by \( \text{As}_2\text{O}_3 \) treatment in all these different cells.

Pronounced \( \text{As}_2\text{O}_3 \)-induced cell death is still seen when the neuroblastoma cells were preexposed to hypoxia for 3 days before induction of treatment, which shows that the potency of \( \text{As}_2\text{O}_3 \) is still intact in cells with a well-developed hypoxic phenotype (25, 26). It is possible that the hypoxic environment contributes to cellular conditions supporting the cytotoxic effect of \( \text{As}_2\text{O}_3 \). For instance, oxidative stress with generation of ROS is believed to be one of the major pathways for arsenic-mediated cytotoxicity (18, 42, 43), although the mechanism(s) and pathway(s) whereby these ROS are generated remain largely unknown. There is also growing evidence that mitochondrial ROS are produced during hypoxia (44). Thus, the combination of hypoxia and \( \text{As}_2\text{O}_3 \)-derived ROS may contribute to the induced cell death seen in hypoxic conditions.
Arsenic Trioxide Kills Hypoxic Neuroblastoma Cells

neuroblastoma cells. Based on the literature, there is a formal possibility that hypoxic growth conditions may lead to cellular adaptations, which impair the efficiency of cytotoxic drugs (22, 38, 39). For instance, growth at hypoxia dedifferentiates neuroblastoma cells (25, 26) and a low differentiation stage is correlated to more aggressive neuroblastoma tumors and a poor response to treatment.

In contrast, it has been shown that a resistant APL cell line underwent apoptosis upon combined treatment of As2O3 and all-trans retinoic acid, which greatly accelerated differentiation in the cells (29). However, our group has previously shown that As2O3, alone or in combination with retinoic acid, does not induce neuronal differentiation in neuroblastoma cells (9), and although we have not investigated the differentiation stage of the hypoxic As2O3-treated cells, we show that the cytotoxic potency of As2O3 is sustained at hypoxia, despite that hypoxia promotes a stem cell–like phenotype in neuroblastoma cells (25, 26).

When the efficiency of As2O3 and the conventionally used drug etoposide was compared at hypoxia, it became clear that their different mechanisms of action influenced their ability to kill hypoxic neuroblastoma cells. In contrast to As2O3, etoposide showed a reduced cytotoxicity in hypoxic neuroblastoma cells, results that are in keeping with those reported by Unruh et al., which show their ability to kill hypoxic neuroblastoma cells. In vitro studies on cellular and molecular mechanisms of arsenic trioxide (As2O3) in the treatment of acute promyelocytic leukemia: As2O3 induces NB4 cell apoptosis with downregulation of Bcl-2 expression and modulation of PML-RAR a/PML proteins. Blood 1986;88:1052 – 61.


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