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A drug from poison: how the therapeutic effect of arsenic trioxide on acute promyelocytic leukemia was discovered

RAO Yi[1*], LI RunHong[2] & ZHANG DaQing[2]

[1]*Peking-Tsinghua Center for Life Sciences at Peking University School of Life Sciences, Beijing 100871, China;*
[2]*Peking University Health Sciences Center, Beijing 100871, China*

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It is surprising that, while arsenic trioxide (ATO) is now considered as "the single most active agent in patients with acute promyelocytic leukemia (APL)", the most important discoverer remains obscure and his original papers have not been cited by a single English paper. The discovery was made during the Cultural Revolution when most Chinese scientists and doctors struggled to survive. Beginning with recipes from a countryside practitioner that were vague in applicable diseases, Zhang TingDong and colleagues proposed in the 1970s that a single chemical in the recipe is most effective and that its target is APL. More than 20 years of work by Zhang and colleagues eliminated the confusions about whether and how ATO can be used effectively. Other researchers, first in China and then in the West, followed his lead. Retrospective analysis of data from his own group proved that APL was indeed the most sensitive target. Removal of a trace amount of mercury chloride from the recipe by another group in his hospital proved that only ATO was required. Publication of Western replication in 1998 made the therapy widely accepted, though neither Western, nor Chinese authors of English papers on ATO cited Zhang's papers in the 1970s. This article focuses on the early papers of Zhang, but also suggests it worth further work to validate Chinese reports of ATO treatment of other cancers, and infers that some findings published in Chinese journals are of considerable value to patients and that doctors from other countries can benefit from the clinical experience of Chinese doctors with the largest population of patients.

leukemia, arsenic trioxide, acute promyelocytic leukemia

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Acute promyelocytic leukemia (APL) had been one of the most aggressive and fatal forms of acute leukemia, but is now one of the most treatable form of leukemia. While there are still room for improvement in treating APL, significant progress has been made in the last few decades by the applications of cytarabine (arabinosyl cytosine, Ara-C) [1], anthracyclines [2–4], arsenic trioxide (As_2O_3, ATO) [5–8] and all-trans retinoic acid (ATRA) [9,10].

The discoveries of cytarabine, anthracyclines and ATRA are well known, whereas the history of the discovery of ATO therapy remains unknown. Most APL researchers cited papers published in the 1990s, which were 20 years later than the original papers. Some authors also seem to be confused about the original discoverer of ATO. These mistakes are regrettable when ATO is now considered to be "the most biologically active single drug in APL" by a panel of International Leukemia Experts for the European LeukemiaNet [11] or "the single most active agent in patients with APL" [12] and that the combination of ATO and ATRA holds the promise to "replace conventional approaches for most, if not all, patients in the very near future" [12]. The past decade has witnessed the general acceptance of ATO

*Corresponding author (email: yrao@pku.edu.cn)

[13] and accumulating proof of more ATO applications from relapsed APL to newly diagnosed APL [14,15].

Ignorance of, and confusions about, the early work result in part from the fact that the original papers were published in the Chinese language and in journals that are obscure even to most Chinese readers, although there are other factors of a more complex nature. This article summarizes the early papers from the discovery of ATO treatment of leukemia to the general acceptance of the use of ATO in treating APL. We also provide a list of the early papers in English for Western authors to use in citations.

We note that the authors of the present article have not worked on leukemia and write this article in our roles as researchers in the history of science. We hope that those working on leukemia can go into more details of the original work.

1 Cultural milieu and historical peculiarities of the discovery

In the 1960s and early 1970s, China was in a political turmoil known as the Great Proletarian Cultural Revolution. Although its origins lie in the political intentions of Mao ZeDong, the supreme leader of China at the time, the Cultural Revolution has affected more than one generation of Chinese people directly and indirectly. Some would view what is happening in China now in part as a consequence of, or a reaction to, the Cultural Revolution, with most viewing the Cultural Revolution as negative, if not disastrous.

Of the many leftist policies during the Cultural Revolution, most were harmful, but some had mixed or even positive effects intended or unintended by the policy maker(s). One policy directly related to Mao was to improve the medical conditions of rural China by sending doctors from urban hospitals to the countryside in "Circulating Medical Teams". Doctors in such teams will go to multiple villages and members of the team will rotate. Another policy was to emphasize the importance of traditional Chinese medicine and drugs. The interception of these two led to many claims of findings of great effects of some Chinese medicine or treatment, most of which were abandoned within a few years. However, a few have withstood the test of time. The discovery of ATO was one such example.

Arsenic has been used for a long time, both in China and in the West. Several traditional Chinese medical recipes contain arsenic, but they were combinations of multiple chemicals with unclear targets. Western uses of arsenic were also ill-defined [16]. For example, Thomas Fowler of Britain invented a solution containing potassium arsenite ($KAsO_2$) in 1786, and used it for agues, remittent fevers and periodic headaches [16]. After leukemia was discovered in 1845, Fowler's solution was used in treating leukemia in 1865, and again in 1931 [17]. Arsenic and irradiation were the main forms of treatment for chronic myelocytic leukemia (CML) until 1953, when they were replaced by chemotherapy with busulfan [16,17]. Arsenic treatment of leukemia was no longer a standard drug for leukemia from then on. In China, Guan JiRen, a doctor in Harbin Medical University, tried to use Fowler's solution to treat leukemia in 1958 and came to the conclusion that it was ineffective [18]. In the 1950s and 1960s, Zhou AiXiang in Beijing and Gu DeQing in Shanghai used combinations that included arsenic sulfate to treat leukemia [19]. It is also doubted that arsenic sulfate can be turned into ATO because the preparation of the Chinese medicine did not involve the high temperature required for the conversion of arsenic sulfate into ATO. In 1972, a report appeared in *Anti-Cancer Battle News of Liaoning Province*, a publication explicitly labeled as "internally circulated materials" under the authorship of Chaoyang People's Hospital Department of Pediatrics [20]. It reported the treatment of 16 cases of acute granulocytic leukemia children by a combination of arsenic and chemotherapy. Because this treatment did not separate arsenic from the chemotherapy available then, it was unclear whether arsenic was helpful as an addition to chemotherapy, nor was it known how effective the combination was: success rate among the 16 patient was not reported and blood analysis was shown for only one patient [20]. A 1974 review by the Chinese Academy of Traditional Medicine summarized different approaches and medicines for leukemia treatment by traditional Chinese medicine listed As_2S_3 and toad venom (and others, including pure chemicals of Western invention) [21]. It cited [19] and [20] as supporting the use of As_2S_3. It should be noted that neither Gu nor Zhou has reduced their recipes to a single component, even today [22]. Because the preparation and processing of the Chinese medicine containing As_2S_3 did not involve the high temperature required for the conversion of arsenic sulfate into ATO, the relation of arsenic sulfate with ATO in such recipes is unclear. The 1974 review did not provide a conclusive recommendation on the type of Chinese medicine for the treatment of leukemia. Toad venom and quite a number of other medicines discussed in that review have not become a standard therapy for any type of leukemia. In summary, by 1974, it was unclear which of the traditional Chinese drugs can be used to treat leukemia and the effectiveness of those tested by then were uncertain.

In the early 1970s, Han TaiYun, a pharmacist of the First Affiliated Hospital of Harbin Medical University, was a member of a circulating medical team. He learned that a countryside practitioner of traditional Chinese medicine used a combination of arsenic, mercury and toad venom to treat lymphatic tuberculosis and cancers. In March 1971, Han made a solution that contained these three components, which he called "713" (after the year and month of his preparation) or "Ailin (literally meaning cancer effective)". Intramuscular injection showed effects in some cancer patients. The "713" solution was hotly sought after locally for a while but faded soon from the public because of its tox-

icity. The target diseases of 713 were undefined, nor were the active chemical in 713.

Zhang TingDong was a doctor in the same hospital as Han. Zhang was born in 1932 and graduated in the 1950s from Harbin Medical University, after studying the regular (Western) medicine. He took classes of traditional Chinese medicine in the 1960s. He worked in the Department of Traditional Chinese Medicine of the First Affiliated Hospital of Harbin Medical University. He was initially asked by the Health Bureau of the Heilongjiang province to examine the validity of the claims of the countryside practitioner and later collaborated with Han.

2 Original discovery of the effective treatment of APL by ATO: 1973–1979

After 1972, Zhang and colleagues focused their research on leukemia. They also analyzed the components of "713" and suggested that arsenic was solely responsible for the therapeutic effect, whereas mercury caused kidney toxicity and toad venom caused hypertension. Neither of the latter two was therapeutically useful for leukemia. From then on, their recipe of Ailin I was mainly arsenic trioxide and a trace amount of mercury (at a ratio of 100∶1 by weight), without toad venom.

The first paper by Zhang and Han was published in 1973 in a local Chinese journal. Zhang TingDong, Zhang PengFei, Wang ShouRen and Han TaiYun reported that they had used "Ailin solution" (also known as "Ailin I") to treat six cases of chronic granulocytic leukemia [5]. They explicitly stated that the components of the solution were ATO and a trace amount of mercury chloride. All six patients improved after the treatment. They also mentioned that acute leukemia patients were being treated, but with no results in that paper.

In 1974, under the collective institutional authorship of the Department of Traditional Chinese Medicine and the Department of Laboratory Medicine of Harbin Medical University, they published a report in the university journal [6], summarizing the treatment of 17 cases of leukemia patients from January 1973 to April 1974. After going through different types of leukemia, they reported that Ailin I was effective in treating multiple types of leukemia, leading to complete remission (CR) in acute leukemia patients. In 1976, they used an institutional authorship to publish a report on five cases of acute leukemia in which they had achieved CR.

In 1979, Rong FuXiang and Zhang published two cases of acute granulocytic leukemia, one with CR for four and a half years and the other for three years [7].

A second paper by Zhang and Rong in 1979 summarized their treatment results from 55 cases of acute leukemia [8]. Twenty-three leukemia patients were treated with Ailin I alone (from 1973 to 1974), 20 were treated with Ailin I in combination with Western chemotherapy and other Chinese medicines from 1975 to 1976, and 12 treated with Ailin I plus other Chinese medicines and chemotherapy from 1977 to 1978. For each patient, they presented leukemia subtypes and clinical observations. All 55 cases improved to some extent, with a remission rate of 70% and with CR in 12 cases. Side effects were small with the doses they used. They then applied 10 times the equivalent of what they used for adult human patients to 12 rabbits. No toxicity was observed in the heart, the liver, the spleen or the kidney of the rabbits.

While the 1973 paper reported their pioneering findings, the second 1979 paper represented their understanding of the therapeutic effect [8]. There are three important questions about early work of Zhang and colleagues: (i) Had they shown that the therapeutic effect came from Ailin I, but not from other Western chemicals or Chinese medicines? (ii) Had they realized that the effect of Ailin I came from ATO but not from mercury in the solution? (iii) Had they known the effect of ATO on APL?

Answers for all three questions can be found in [8] which explicitly stated that (i) significant improvement was observed in three patients (one adult and two children) using only Ailin I, but no other Western or Chinese drugs. At the time of publication, the children had survived for more than four years and the adult more than nine months. When using other Chinese medicines, Zhang and Rong pointed out that those were not used for treatment of leukemia, but for supporting the general health of the patients so that they could tolerate more treatments; (ii) the effective component of Ailin I was ATO (on page 11 of their paper); (iii) acute granulocytic leukemia (M3 type of the French-American British FAB classification, also known as APL) was the most sensitive to the treatment, which was a conclusion reiterated on pages 10 and 11 of their paper.

We can see that, by 1979, Zhang and his collaborators had clearly reached our current understanding that ATO could treat leukemia, especially that of the M3 subtype or APL.

3 Further studies by the Zhang group from the 1980s to the 1990s

In 1981, a paper under an institutional authorship with a footnote indicating Zhang as the supervisor (with eight other authors) reported 73 cases of acute granulocytic leukemia patients, with a CR of 24% and remission rate of 86% after Ailin I treatment [23]. In 1982, Zhang and Li presented a report to a national meeting on 22 cases of CR by Ailin I and on 98 cases of non-lymphatic leukemia. In 1982 and 1983, Zhang published reviews of his work [24,25].

In 1984, Zhang and Li [26] published a summary of 81 cases which they had treated since 1971. Among the 22 cases of CR, they pointed out that seven were of the M2

type and 15 were of the M3 type. They again stated that the effect on M3 type was particularly obvious. Zhang [27] published another paper on the effect of Ailin I on non-lymphatic acute leukemia.

In 1991, Sun et al. [28] continued the work of Zhang and Li [26]. They reported that Ailin I had been used to treat 32 APL cases from 1974 to 1985, with CR in 19 cases and that 16 cases had survived for more than five years. This confirms the high success rate for ATO treatment of APL.

In 1992, Sun et al. [29] published a short "Sharing Experience" paper, reviewing materials identical to the 1991 paper. Oddly, most English papers cite this 1992 paper for the discovery of ATO treatment of APL, although both papers were in Chinese.

Because Zhang TingDong's papers from the 1970s to the early 1990s included a trace amount of mercury chloride, in addition to ATO (at a ratio of 1∶100 by weight), strictly speaking, they had not proven that mercury chloride did not have a positive effect, despite the fact that their 1973 paper had mentioned that only ATO was the effective ingredient in Ailin I.

In 1995 and 1996, Zhang Peng and colleagues from the same hospital as Zhang TingDong published two papers which showed the effectiveness of ATO alone without mercury [30,31]. The 1995 paper was an abstract, which did not explicitly state that mercury chloride was not included in the 713 solution, although Zhang later said that they used only ATO. The 1996 paper did show that ATO, but not mercury chloride, was used. They treated 130 APL patients from 1992 to 1995, among which 72 went through one or more courses of treatment. A CR of 73% was observed in patients undergoing initial treatments and 52% in recurrent patients [31].

In the process of uncovering the history of ATO research, we found no evidence that leukemia classification by traditional Chinese medical theories was useful for discovering the target of ATO. Here we separate traditional Chinese medicine into drugs and theories. Had the traditional Chinese medical theories (CMTs) been helpful for developing ATO as a treatment for leukemia? Zhang and colleagues discussed five types of leukemia based on CMT classification, there was no difference of ATO on different CMT types [6–8]. In this regard, the Western classification of leukemia was helpful. When they completely gave up the CMT classification, the effect was more obvious. Interestingly, their first paper in 1973 did not mention CMTs, but their later papers in the 1970s and 1980s did. Lack of evidence for the utility of CMTs does not disprove the CMTs, but it is so far unclear whether the CMTs are important or essential for scientific studies of traditional Chinese drugs.

4 Chinese contributions to APL treatment

Anthracyclines (including daunorubin) and cytarabine became frontline treatment for APL because of research in the West [1–3]. Chinese contributions in the discoveries of ATO and ATRA came after those, but have significantly improved APL treatment. Here we place the Chinese discoveries in the historical context.

In 1973, Zhang and colleagues of China reported the therapeutic effect of ATO on leukemia [5], and Zhang and Rong [8] in 1979 suggested that APL was particularly sensitive to ATO.

In 1977, Collins et al. [32] at the NCI successfully established a cell line (HL-60) from an APL patient. Collins et al. used it to screen for chemicals which could induce the differentiation of HL-60 cells to mature into normal cells. In 1980, Breitman et al. [33] discovered that all-trans retinoic acid (ATRA) and 13-cis retinoic acid induced HL-60 differentiation into mature cells. Related chemicals such as Vitamin A was 1000 fold less effective. They suggested that "this compound could provide a new therapeutic tool in the treatment of acute myeloid leukemia".

In 1981, Breitman et al. [34] tested drug sensitivity of leukocytes from the peripheral blood of leukemia patients and found that cells induced to differentiate by ATRA all came from two patients with APL. Olsson and Brietman [35] in 1982 showed that retinoic acid could also induce U-937 lymphoma cells to differentiate. In 1983, Honma et al. [36] from Japan reported the effects of multiple chemicals on inducing differentiation of cells from different leukemia patients, and found that ATRA was among those capable of inducing the differentiation of leukocytes from APL patients. Koeffler [37] in 1983 summarized *in vitro* studies including cellular differentiation by retinoic acid and other chemicals, viewing ATRA and 13-cis retinoic acid as equivalent in differentiating APL leukocytes.

Single cases of APL treatment by 13-cis retinoic acid were reported by four groups: Flynn et al. [38] in 1983 from Minnesota, USA; Nilsson [39] in 1984 from Lund, Sweden; Daenen et al. [40] in 1986 from the Netherland; and Fontana et al. [41] in 1986 from west Virginia, USA.

In 1985, Wang Zhen-Yi of Shanghai Second Medical College could obtain ATRA (but not 13-cis retinoic acid) from a local source. He used it to successfully treat a five-year-old girl. In 1987, his group published a paper in the English edition of the *Chinese Medical Journal*, reporting the use of ATRA (alone or in combination) for the treatment of six APL patients [9]. In 1988, Wang's group published their use of ATRA in the treatment of 24 APL patients in *Blood* [10]. It cited Breitman et al. [33,34] and Koeffler [37], which reported the effects of ATRA and 13-cis retinoic acid on inducing the differentiation of leukemia leukocytes, as well as Flynn et al. [38], Nilsson [39], Daenen et al. [40], and Fontana et al. [41] which reported treatment of APL patients by 13-cis retinoic acid.

Huang et al. [10], but not Huang et al. [9] (both in English, but the 1988 paper published in the US and the 1987 paper in China), drew international attention. Direct com-

munication with French doctors also helped. The finding of Wang group with ATRA were soon replicated. In 1989, Chomienne et al. [42] from France compared the effects of ATRA and 13-cis retinoic acid with two APL patients for each chemical and felt that ATRA were more effective. In 1990, the same French group, after working with leukocytes from 22 APL patients *in vitro*, concluded that ATRA was 10 times more effective than 13-cis retinoic acid [43]. The effect of ATRA was also confirmed by Chinese doctors (e.g., Chen et al.) [44]. In 1991, Warrell et al. [45] in the US replicated the findings of the Wang group in China and the Degos group in France with nine out of 11 APL patients successfully treated by ATRA. Since then, ATRA was well recognized for APL treatment. In 1997, Tallman et al. [46] reported their studies of 346 APL patients, in which they compared the therapeutic effects of ATRA and the previously standard chemotherapy with daunorubin and cytarabine, and found it to be more effective if ATRA was used for both induction and maintenance.

In 1992, Duan et al. [47] published *in vitro* studies of the effect of ATO on leukemic cells. In 1995, Huang and coworkers from Dalian, China reported that a tablet with multiple components derived from traditional Chinese medicine (herbs and minerals) led to 98% CR in 60 APL patients [48]. One of the components contained arsenic disulfide.

In 1995 and February 1996, Zhang Peng and colleagues from Harbin reported their success in using ATO in achieving 73% of CR in 130 APL cases from 1992 to 1995. No cross-resistance was observed between ATO and ATRA [30,31].

In August 1996, Chen GuoQiang and 18 other authors (including Zhang TingDong in the middle and Chen Sai-Juan, Wang Zhen-Yi and Chen Zhu as the last authors) reported work from Shanghai Hematology Institute that used *in vitro* culture leukemic cells for mechanistic studies of the therapeutic effect of ATO on leukemia at the molecular level [49].

In 1997, Xu JingShu, Duan JingMian, Xu Ying, Xin XiaoMin, Song XiaoHong and Zhang TingDong reported a case of who had recurrent APL three times [50]. The patient was treated with Ailin I every time and had survived for 20 years.

In 1997, Chen et al. [51] from Shanghai published dose-dependent effect of ATO on leukemic cells *in vitro*. Shen et al. [52] from Shanghai reported that they used pure ATO to treat 15 APL patients, among which 10 cases with only ATO. CR was achieved in 90%.

In 1998, Soignet et al. [53] from the Memorial Sloan-Kettering Cancer Hospital and Cornell Medical College reported in the *New England Journal of Medicine* that they had treated 12 recurrent APL cases with ATO and observed CR in 11 cases. The mechanisms were thought to be partial cellular differentiation and apoptosis.

The Soignet et al. paper helped general international acceptance of ATO as a treatment of APL, which could not be achieved by many papers published in China by Chinese doctors over the previous two decades.

5 Lack of recognition

ATO has now been well accepted (and generally used) nationally and internationally, saving lives in China and other countries. However, the discoverer remains largely unknown in academic and medical communities, although there was a 2001 story about him in the *New York Times* [54]. It is more striking that, while the discovery of the effect of ATRA on APL has led to both national and international awards to Wang Zhen-Yi, not a single national or international award has been given to Zhang TingDong or any of his Harbin colleagues for the discovery of the therapeutic effect of ATO on APL, although ATO was discovered more than a decade before ATRA and is recognized as "the most biologically active single drug in APL" by International Leukemia Experts for the European LeukemiaNet [11].

The reason for lack of recognition is not due to controversies. There was a patent contention by Hongde Sun, a member of Zhang's group. It was quite late and the judge ruled in Zhang's favor. Peng Zhang insisted that he was the first to show the effect of ATO alone, without mercury. Zhang and Rong [8] had suggested that ATO alone was effective, but they had not shown data with ATO alone. Both Sun and Zhang Peng have made important contributions, but it is clear that Zhang TingDong has played an undisputed key role in his persistent work from the 1970s to the early 1990s which turned the often fuzzy arsenic treatment with variable results into practically useful treatment with beneficial effects.

In 1998, Chen et al. [55] published in a Chinese journal that "from the early 1970s, Harbin Medical University discovered through clinical practices that arsenic trioxide could effectively treat APL. In the past two years, we have collaborated with HMU and used arsenic trioxide solution to treat APL patients resistant to ATRA and conventional chemotherapy", affirming the work and priority of Harbin, though Zhang's name and papers in the 1970s did not appear in the review [55].

Almost no English paper realized that Zhang had published his findings from 1973 to 1979. English papers, including those by Chinese scholars, only cited Sun et al. [29] and sometimes Zhang Peng et al. [31] as the first paper(s) for ATO treatment of leukemia. For example, Soignet et al. [53], which replicated the findings of Zhang in the 1970s and played a major role in the international acceptance of ATO treatment for APL, mentioned "recent Chinese reports" of CR in APL by ATO, and cited only Sun et al. [29], Zhang Peng et al. [31], and Shen et al. [52]. It is impossible to know from the Soignet et al. paper that the original findings were made in the 1970s by Zhang TingDong because both the tone and the citations made it seem that Chinese

discoveries were made in the 1990s.

A 1996 news report in *Science* did mention Zhang [56], but stated that Zhang published his paper in 1992.

Zhang has published few English papers. In 2001, he and Chen GuoQiang were co-first authors (with Wang Zhen-Yi, Chen SaiJuan in the middle and Chen Zhu as the corresponding author) of a review about ATO in an international journal *Oncogene* [57]. In the introduction, they stated "recent" studies of ATO treatment of APL, citing the 1996 paper of Chen et al. [49]. On the second page, they stated that the research on ATO began in 1971, without citing any publications, and that they had treated more than a thousand patients of different types of cancers including "chronic granulocytic leukemia, lymphoma, esophageal cancer, and particularly APL", but again without citing any literature. Thus, Zhang, presumably as the first author of an English paper, neglected to cite his own early papers, effectively burying the pioneering findings in the 1970s.

In 2002, Zhu et al. [58] published a review in *Nature Reviews Cancer*. In the figure illustrating milestones in APL treatments, Zhang TingDong in the 1970s were placed, but the citation in the text was Sun et al. [29] and the explanation in the reference list credited Sun et al. [29] as "first report of As_2O_3 therapy in APL".

Both Sun et al. [29] and Zhang et al. [31] were published in Chinese, and neither of them cited papers from the 1970s. Thus, even if any international scholars attempted to obtain English translations of the 1992 and 1996 papers, they would not know the original 1970 papers.

In 2008, Wang Zhen-Yi and Chen Zhu [59] reviewed progress in APL treatment in *Blood*, with its first citation of ATO as the Zhu et al. [58] review, and further citations for ATO treatment of APL being Sun et al. (1992) [29], Zhang et al. (1996) [31], Chen et al. (1996) [49], Shen et al. (1997) [52] and Niu et al. (1999) [60].

In 2011, Chen et al. [61] published a review of the therapeutic effect of ATO on leukemia, which stated "in the early 1970s, a group from Harbin Medical University in northeastern China tested Ailing-1 containing 1% ATO and a trace amount of mercury chloride in a variety of cancers by intravenous administration", without mentioning the researchers or citing papers of the 1970s. The review then cited Sun et al. (1992) [29] for showing that "Ailing-1 induced CR in 21 of 32 patients with APL with an impressive 10-year survival rate of 30%" before stating that "the efficacy of pure ATO in treating relapsed APL was then reported by Shanghai Institute of Hematology (SIH) in 1996–1999", citing Shen et al. (1997) [52] and Niu et al. (1999) [60], ignoring the papers of Zhang Peng et al. from Harbin Medical University who had published a paper in 1995 and one in 1996 [30,31], which stated that they had used ATO alone (without a trace amount of mercury chloride).According to a 2013 blog by Zhang Peng, his results were known to Chen and others who attended a national meeting in 1995 [62].

A 2011 paper on a 10-year follow-up study of ATO treatment of APL published by Au et al. [63] from Hong Kong cited a paper published by US authors in 2001.

Thus, no authors who can read Chinese have cited any of the 1970s papers in their English publications. In the current climate that English authors do not go to original papers in even French or German, it is no wonder that they do not know the titles and authors of the original papers published in Chinese. The contributions of Zhang TingDong and the precise timing of his discovery are therefore virtually unknown in the international academic and medical communities.

6 Implications of paying attention to work published in Chinese

In the past, there is a general negligence of clinical studies carried out in China. Language is only part of the reason. With the large number of patients in China, many doctors in China have more clinical experience than most doctors in Western countries. Some, even though a small fraction of, Chinese doctors may have insights into treatments that they have only published in Chinese journals.

In the case of ATO, for example, Chinese doctors including Zhang and others have reported ATO treatment of multiple cancers, from liver, stomach and colon cancers to lymphomas [64–66]. These are worth further test and validation.

An indirect inference is that rigorous studies of components of Chinese medicine may lead to more discoveries. For example, drugs used tentatively by Chinese hospitals or marketed aggressively by Chinese companies (without prior stringent tests), may prove to be more powerful and specific after rigorous studies, and become more internationally acceptable and will eventually help more patients and save more lives.

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1 Ellison R R, Holland J F, Weil M, et al. Arabinosyl cytosine: a useful agent in the treatment of acute leukemia in adults. Blood, 1968, 32: 507–523
2 Boiron M, Weil M, Jacquillat C, et al. Daunorubicin in the treatment of acute myelocytic leukaemia. Lancet, 1969, 293: 330–333
3 Bernard J, Weil M, Boiron M, et al. Acute promyelocytic leukemia: results of treatment by daunorubicin. Blood, 1973, 41: 489–496
4 Bernard J, Weil M, Jacquillat C I. Treatment of acute granulocytic leukemias. Ann Rev Med, 1974, 25: 39–50
5 Zhang T D, Zhang P F, Wang S R, et al. Preliminary clinical observations of six cases of leukemia treated by "Ailin solution" (in Chinese)[1]. Med Pharm Heilongjiang, 1973, (3): 66–67

1) Files of the major Chinese papers cited in this article can be accessed at the blog of the author: http://blog.sciencenet.cn/blog-2237-658474.html

6 Departments of Traditional Chinese Medicine and Laboratory Medicine of the First Affiliated Hospital of Harbin Medical University. Therapeutic observations of 17 cases leukemia treated with Ailin No.1 and dialectic theory (in Chinese). J Harbin Med Univ, 1974, (2): 25–30
7 Rong F X, Zhang T D. A report on long term survival of two cases of acute granulocytic leukemia (in Chinese). J New Med Pharm, 1979, (6): 31–34
8 Zhang T D, Rong F X. Treatment of acute granulocytic leukemia by Ailin No.1 and dialectic theory (in Chinese). Med Pharm Heilongjiang, 1979, (4): 7–11
9 Huang M E, Ye Y C, Chen S R, et al. All-trans retinoic acid with or without low dose cytosine arabinoside in acute promyelocytic leukemia: report of six cases (in Chinese). Chin Med J, 1987, 100: 949–953
10 Huang M E, Ye Y C, Chen S R, et al. Use of all-trans retinoic acid in the treatment of acute promyelocytic leukemia. Blood, 1988, 72: 567–572
11 Sanz M A, Grimwade D, Tallman M S, et al. Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. Blood, 2009, 113: 1875–1891
12 Tallman M S, Altman J K. How I treat acute promyelocytic leukemia. Blood, 2009, 114: 51260–51235
13 Sanz M A, Lo-Coco F. Modern approaches to treating acute promyelocytic leukemia. J Clin Oncol, 2011, 29: 495–503
14 Powell B L, Moser B, Stock W, et al. Arsenic trioxide improves event-free and overall survival for adults with acute promyelocytic leukemia: North American Leukemia Intergroup Study C9710. Blood, 2010, 116: 3751–3757
15 Estey E H. Newly diagnosed acute promyelocytic leukemia: arsenic moves front and center. J Clin Oncol, 2011, 29: 2743–2746
16 Sears D A. History of the treatment of chronic myelocytic leukemia. Am J Med Sci, 1988, 296: 85–86
17 Jolliffe D M. A history of the use of arsenicals in man. J Royal Soc Med, 1993, 86: 287–289
18 Guan J R. Leukemia: clinical analysis of 49 cases (in Chinese). Heilongjiang Med, 1958, (2): 22–34
19 Gu D X. Preliminary observations of the therapeutic effect of the traditional Chinese medicine “55” on leukemia (in Chinese). Harbin J Trad Chin Med, 1964, 5: 24
20 Chaoyang People’s Hospital Department of Pediatrics. Experience of using a combination of arsenic and chemotherapy to treat leukemia (in Chinese). Anti-Cancer Battle News of Liaoning (internally circulated materials, be careful in safekeeping, by the Office of Cancer Prevention and Treatment Research of Liaoning Province), 1972, (7): 23–24
21 Hematology Group of the Department of Internal Medicine at Xiyuan Hospital of the Chinese Academy of Traditional Medicine. Treatment of leukemia by traditional Chinese medicine (in Chinese). Guangdong Med, 1974, (5): 31–37
22 Zhou A X. Research on Qinghuang San treatment of leukemia (in Chinese). Chin J Integrat Trad West Med, 1998, 18: 582–583
23 Department of Traditional Chinese Medicine of the First Affiliated Hospital of Harbin Medical University (Supervisor: Zhang T D. Writers: Li Y S, Hu X C. Participants: Li M X, Zhang P F, Rong F X, et al.). A clinical summary of 73 cases treated by Ailin No.1 combined with the dialectic theory (in Chinese). Chin Med Pharm Heilongjiang, 1981, (4): 28–30
24 Zhang T D. Comments on questions about designing clinical research with combined Chinese and Western medicine (in Chinese). J Integrat Trad Chin West Med, 1982, 2: 180–181
25 Zhang T D. Understanding and treatment of leukemia by Chinese medicine (in Chinese). J Trad Chin Med, 1983, (3): 71–74
26 Zhang T D, Li Y S. Clinical findings and experimental research of Ailin No. 1 in treating acute granuloleukemia (in Chinese). J Integrat Trad Chin West Med, 1984, 4: 19–20
27 Zhang T D. Diagnosis and treatment of acute non-lymphatic leukemia (in Chinese). J Integrat Trad Chin West Med, 1985, 5: 713
28 Sun H D, Ma L, Hu X C, et al. A report on 16 acute promyelocytic leukemia cases of long term survival treated by Ailin No.1 in combination with traditional Chinese dialectic theories (in Chinese). Inf Trad Chin Med Pharm, 1991, (6): 39–41
29 Sun H D, Ma L, Hu X C, et al. Ailin I treated 32 cases of acute promyelocytic leukemia (in Chinese). Chin J Integrat Chin West Med, 1992, 12: 170–172
30 Zhang P, Wang S Y, Hu L H, et al. “713” (As_2O_3) treatment of 117 cases of acute promyelocytic leukemia: clinical observations and mechanistic investigations (in Chinese). J Harbin Med Univ, 1995, 29: 243
31 Zhang P, Wang S Y, Hu L H, et al. Treatment of 72 cases of acute promyelocytic leukemia with intravenous arsenic trioxide (in Chinese). Chin J Hematol, 1996, 17: 58–62
32 Collins S J, Gallo R C, Gallagher R E. Continuous growth and differentiation of human myeloid leukemic cells in suspension culture. Nature, 1977, 270: 347–349
33 Breitman T R, Selonick S E, Collins S J. Induction of differentiation of the human promyelocytic leukemia cell line (HL-60) by retinoic acid. Proc Natl Acad Sci USA,1980, 70: 2936–2940
34 Breitman T R, Collins S J, Keene B R. Terminal differentiation of human promyelocytic leukemic cells in primary culture in response to retinoic acid. Blood, 1981, 57: 1000–1004
35 Olsson I L, Breitman T R. Induction of differentiation of the human histiocytic lymphoma cell line U-937 by retinoic acid and cyclic adenosine 3′: 5′-monophosphate-inducing agents. Cancer Res, 1982, 42: 3924–3927
36 Honma Y, Fujita Y, Kasukabe T, et al. Induction of differentiation of human acute non-lymphocytic leukemia cells in primary culture by inducers of differentiation of human myeloid leukemia cell line HL-60. Eur J Cancer Clin Oncol, 1983, 19: 251–261
37 Koeffler H P. Induction of differentiation of human acute myelogenous leukemia cells: therapeutic implications. Blood, 1983, 62: 709–721
38 Flynn P, Miller W, Weisdorf D, et al. Retinoic acid treatment of acute promyelocytic leukemia: *in vitro* and *in vivo* observations. Blood, 1983, 62: 1211–1217
39 Nilsson B. Probable *in vivo* induction of differentiation by retinoic acid acid of promyelocytes in acute promyelocytic leukemia. British J Haematol, 1984, 57: 365–371
40 Daenen S, Vellenga E, van Dobbenbugh O A, et al. Retinoic acid as antileukemic therapy in a patient with acute promyelocytic leukemia and *Aspergillus pneumonia*. Blood, 1986, 67: 559–561
41 Fontana J A, Roger I S, Durham J P. The role of 13-cis retinoic acid in the remission induction of a patient with acute promyelocytic leukemia. Cancer, 1986, 57: 209–217
42 Chomienne C, Ballerini P, Balitrand N, et al. Retinoic acid therapy for promyelocytic leukemia. Lancet, 1989, 334: 746–747
43 Castaigne S, Chomienne C, Daniel M T, et al. All-trans retinoic acid as a differentiation therapy for acute promyelocytic leukemia. I. Clinical results. Blood, 1990, 76: 1704–1709
44 Chen Z X, Xue Y Q, Zhang R, et al. A clinical and experimental study on all-trans retinoic acid treated acute promyelocytic leukemia patients. Blood, 1991, 78: 1413–1419
45 Warrell Jr R P, Frankel S T, Miller Jr W H, et al. Differentiation therapy of acute promyelocytic leukemia with tretinoin (all-trans-retinoic acid). N Engl J Med, 1991, 324: 1385–1393
46 Tallman M S, Andersen J W, Schiffer C A, et al. All-trans-retinoic acid in acute promyelocytic leukemia. N Engl J Med, 1997, 337: 1021–1028
47 Duan J X, Xin X M, Wang F Q, et al. Anti-cancer effect of Ailin No. 1 on leukemic cells of acute promyelocytic leukemia patients (in Chinese). Pract J Oncol, 1992, (2): 29–30
48 Huang S L, Guo A X, Xiang Y, et al. Clinical study on the treatment of APL mainly with composite Indigo Naturalis tablets (in Chinese). Chin J Hematol, 1995, 16: 26
49 Chen G Q, Zhu J, Shi X G, et al. *In vitro* studies on cellular and molecular mechanisms of arsenic trioxide (As_2O_3) in the treatment of acute promyelocytic leukemia. As_2O_3 induces NB4 cell apoptosis with downregulation of Bcl-2 expression and modulation of PML-

RAR α/PML proteins. Blood, 1996, 88: 1052–1061
50 Xu J S, Duan J M, Xu Y, et al. A case of APL survival of 20 years with treatment by Ailin I (in Chinese). Chin J Hematol, 1997, 18: 476
51 Chen G Q, Shi X G, Tang W, et al. Use of arsenic trioxide (As_2O_3) in the treatment of acute promyelocytic leukemia (APL), I: As_2O_3 exerts dose-dependent dual effects on APL cells. Blood, 1997, 89: 3345–3353
52 Shen Z X, Chen G Q, Ni J H, et al. Use of arsenic trioxide (As_2O_3) in the treatment of acute promyelocytic leukemia (APL), II: clinical efficacy and pharmacokinetics in relapsed patients. Blood, 1997, 89: 3354–3360
53 Soignet S L, Maslak P, Wang Z G, et al. Complete remission after treatment of acute promyelocytic leukemia with arsenic trioxide. N Engl J Med, 1998, 339: 1341–1348
54 Rosenthal E. Chairman Mao's cure for cancer. New York Times, May 6th, 2001
55 Chen G Q, Chen S J, Wang Z Y, et al. (1998). Mechanisms and prospects of arsenic treatment of acute promyelocytic leukemia (in Chinese). Chin J Integrat Trad Chin West Med, 1998, 18: 581–582
56 Mervis J. Cancer research: ancient remedy performs new tricks. Science, 1996, 273: 578
57 Zhang T D, Chen G Q, Wang Z G, et al. Arsenic trioxide, a therapeutic agent for APL. Oncogene, 2001, 20: 7146–7153
58 Zhu J, Chen Z, Lallemand-Breitenbach V, et al. How acute promyelocytic leukaemia revived arsenic. Nat Rev Cancer, 2001, 2: 705–714
59 Wang Z Y, Chen Z. Acute promyelocytic leukemia: from highly fatal to highly curable. Blood, 2008, 111: 2505–2515
60 Niu C, Yan H, Yu T, et al. Studies on treatment of acute promyelocytic leukemia with arsenic trioxide: remission induction, follow-up, and molecular monitoring in 11 newly diagnosed and 47 relapsed acute promyelocytic leukemia patients. Blood, 1999, 94: 3315–3324
61 Chen S J, Zhou G B, Zhang X W, et al. From an old remedy to a magic bullet: molecular mechanisms underlying the therapeutic effects of arsenic in fighting leukemia. Blood, 2011, 117: 6425–6437
62 Zhang P. The history of discovering arsenic trioxide (in Chinese). http://blog.sciencenet.cn/blog-870683-663068.html, 2013
63 Au W Y, Kumana C R, Lee H K K, et al. Oral arsenic trioxide-based maintenance regimens for first complete remission of acute promyelocytic leukemia: a 10-year follow-up study. Blood, 2011, 118: 6535–6543
64 Li Y S, Zhang T D, Wang X R, et al. Investigation of the dynamics of Ailin No. 1 on human liver cancer cells (in Chinese). Res Cancer Prevent Treat, 1988, 15: 1–3
65 Liu L X, Zhu A L, Chen W, et al. Effect of arsenic trioxide on hepatocellular carcinoma and its mechanistic studies. Chin J Surg, 2005, 43: 33–36
66 Guo H X, Chen W, Liu L X, et al. Recent status of the effect of arsenic trioxide on colon cancer. Chin J Integr Trad West Med Dig, 2006, 14: 207–209