Seventh International Workshop on Ataxia-Telangiectasia

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Abstract
Ataxia-telangiectasia (A-T) is a rare hereditary syndrome involving cerebellar degeneration, immunodeficiency, cancer risk, and radiosensitivity. Since the cloning of the A-T gene, ATM, in 1995, research on this pleiotropic disease and its molecular basis has expanded tremendously. ATM is a large protein kinase that appears to be one of the primary sensors of DNA strand-break damage. The vast majority of mutations in ATM result in truncation and destabilization of the protein, but certain missense and splicing errors have been shown to result in a less severe phenotype. A-T heterozygotes have been shown to have a slightly increased risk of cancer, but their increased in vitro radiosensitivity does not seem to result in any in vivo sensitivity. ATM does seem to act as a classic tumor suppressor gene in T-prolymphocytic leukemia, and LOH at the ATM locus is a common event in some tumor types, suggesting a general role for ATM in cancer. Recent work has shown the interaction of ATM with proteins involved in cell cycle control, and the direct phosphorylation of some of these interactors by ATM. ATM knockout mice have been created by several groups, and recapitulate the immunodeficiency, radiosensitivity, cancer risk, and fertility defects of A-T, although the effect on the cerebellum is slight. These diverse topics, and their integration into a global understanding of A-T, were the basis of the 7th International A-T Workshop.

Introduction
A-T is a recessive hereditary chromosomal instability syndrome with a 100–250-fold excess of lymphoid malignancies as well as a more modest excess of epithelial tumors in patients. There is some evidence that epithelial tumors are more frequent in A-T carriers, and LOH including the A-T locus at 11q23.1 is a frequent event in ovarian, breast, and cervical cancer, suggesting that the A-T gene plays an important role in malignancy. The focus of A-T research today is to define the molecular mechanisms by which the A-T gene product, ATM, acts to recognize chromosomal damage and prevent this damage from becoming lethal or transforming, as well as to better understand the role that mutations in ATM have in causing cancer, and whether constitutional heterozygosity has any implications for chemotherapy and radiotherapy.

In addition, A-T involves progressive cerebellar degeneration, immunodeficiency, gonadal dysgenesis, ocular and cutaneous telangiectasia, and high serum AFP. A-T patients are sensitive to ionizing radiation, and cultured A-T cells fail to execute cell cycle checkpoints immediately after DNA strand-break damage and exhibit excessive apoptotic cell death. This pleiotropic disease has intrigued and puzzled researchers for many years, a situation that is gradually being resolved now that the ATM gene is accessible for molecular characterization, and several strains of Atm knockout mice have been created.

The Seventh International Workshop on A-T was held in Clermont-Ferrand, France on November 22–24, 1997, hosted by the Jean Perrin Cancer Center and the Association pour la Recherche sur l'Ataxie Télangiectasie, a French organization of A-T families. This workshop has been held in various cities every 2–3 years since 1980 and has followed the early characterization of the complex clinical and cellular phenotype, the efforts to clone the A-T gene(s) by both positional and functional complementation strategies, and now the characterization of the ATM gene and its role in cellular physiology. As more has become known about the abnormal responses of A-T cells to DNA strand breaks, and also as it has become clear that relatives of A-T patients had an increased incidence of cancer, researchers from other fields have become interested in A-T not just as a rare disease, but as one involving a gene fundamental to genomic stability. Thus, the workshops have grown in attendance from a handful of scientists at the first meeting to over 150 researchers and clinicians from 19 countries at the Seventh International Workshop on A-T, accompanied by several A-T patients and their families. Since the cloning of the ATM gene in 1995, additional comprehensive workshops have been sponsored by the A-T Children's Fund.

Gatti (1) presented a review of the disease from the first description by Syllaba and Henner in 1926 to the present. The long road from the description of the clinical syndrome (2) to the complementation studies that implied the existence of at least four disease genes (3), the unsuccessful attempts to clone the A-T gene(s) by functional complementation, the genetic localization of the gene(s) to 11q22–23 (4), the cloning of the single gene responsible (5), and the current state of ATM molecular biology reminded the participants of how much work by so many researchers had already been accomplished. Shiloh, whose laboratory first announced the identification of the A-T gene, ATM (5), discussed how the characterization of ATM reconciled the pleiotropic clinical phenotype with a defect in a single protein, bringing the study of A-T full circle. ATM is a protein kinase that responds to DNA strand-break damage by arresting all phases of the cell cycle while simultaneously preventing cell death. The lack of these checkpoints, combined with excessive sensitivity to the lethal effects of DNA strand-break damage, together account for the cancer risk, immune deficiency, gonadal dysgenesis, and characteristic chromosomal instability seen in A-T, although the exact mechanism of cerebellar degeneration is still unclear. The complementation of A-T cells in culture by the introduction of recombinant ATM protein and the phenotype of Atm−/− mice confirm that the correct gene has been cloned (6–9). Lavin discussed the molecular role of ATM in cell cycle checkpoints after DNA strand-break damage and the defects found in A-T cells in the induction of p53 and other checkpoint effects (10, 11). In keeping with its role as a primary DNA strand-break sensor, ATM seems to associate dynamically with numerous nuclear factors and complexes immediately after DNA strand-break damage.
proteins in large nuclear and microsomal complexes with the ability to signal to a variety of other effector molecules. These three introductory talks concerning the disease itself, the gene responsible and its protein product, and the dysfunction of A-T cells in response to DNA strand breaks set the stage for the meeting, where the latest advances in the molecular genetics, cell physiology, and epidemiology of ATM were discussed.

**Mutations in the ATM Gene**

The Sixth International Workshop on A-T took place on the verge of the cloning of the A-T gene, so it was most appropriate to begin with a session discussing ATM mutations found in A-T patients. Here, the discussion of the variable and constant clinical features was revisited by Taylor in his review of the phenotypes of A-T patients in the United Kingdom with a milder clinical course, milder immune defects, and/or less severe radiation sensitivity in their cultured cells. The less severe disease of a group of patients who shared a common A-T mutation on at least one chromosome was explained by a "leaky" splice-site mutation in the ATM gene and the presence of a small amount of normal ATM (12). Similar findings were reported by Shiloh on a group of Italian A-T variants (13). The phenotype of other variant patients in whom ATM mutations have not been found may be due to defects in different genes. Taylor also suggested that the expression of abnormal ATM protein with either missense mutations or in-frame deletions may be correlated with the risk of leukemia, lymphoma, and breast cancer, and that the cancer risk associated with the A-T syndrome may not be spread evenly among the patients.

The German ATM Consortium, Van’t Veer, Prudente, and Gatti each presented data showing that mutations in ATM can be found in every part of the gene, and that the great majority truncate the protein and reduce its expression to undetectable levels. Missense mutations were described, but they do not seem to be common in A-T. The majority of ATM mutations were also unique to a family, although founder effects were described. For example, the Costa Rican population harbors five founder mutations responsible for ~95% of A-T alleles as well as private mutations (14). The study of this population demonstrated the usefulness of creating rapid assays for a handful of population-specific mutations, allowing the detection of most of the mutations in a new sample of the same population to be done quickly and cheaply. This approach will not be useful for more outbred populations, because the large size of the ATM gene and the lack of mutational hot spots make screening for mutations time-consuming and difficult. A database of ATM mutations is accessible at http://www.vmnc.org/vmrc/atm.htm.

The degree of immunodeficiency is a variable feature of the A-T phenotype (for a review, see Ref. 15). Some patients are troubled continuously with severe infections, whereas others suffer only mild or undetectable immunodeficiency. One theory to account for this wide variation among patients was that different mutations may have different effects on immune gene rearrangement or immune cell survival, particularly for missense and in-frame deletion mutations, where an altered protein may be expressed and have partial function. For example, a recently described patient with classical ataxia and radiosensitivity but no immune defect was found to be a compound heterozygote for a missense mutation in the kinase domain and a truncation of nine amino acids at the carboxyl terminus of ATM, and Toyoshima et al. (16) hypothesize that this combination of mutations may allow some function of ATM in immune cells. The idea that the immunophenotype can be predicted from the molecular genotype, however, is not supported by any general correlation between genotype and phenotype, because patients with similar mutations may have different immunophenotypes, and patients with dissimilar mutations may have similar immune function. Thus, it seems that much of the variation in this part of the A-T phenotype may be due to other genetic or environmental factors.

### ATM and Cancer

The fact that A-T homozygotes have a greatly increased risk of cancer is clear, but the risk to heterozygotes is, as yet, unclear. Stoppa-Lyonnet reviewed the literature concerning this field and pointed out that the risk of breast cancer in known A-T heterozygotes was real but was less than previously estimated (e.g., Refs. 17–20). Lenoir considered which kind of breast cancer families, if any, might be due to ATM mutations and suggested that the low penetrance of ATM mutations and their association with later-onset breast cancer in A-T families, combined with the commonness of breast cancer, may explain the recent unsuccessful attempts to identify ATM mutations in breast cancer families. The situation is confounded by the difficulty of detecting all ATM mutations in a population, because the most efficient techniques currently available for the detection of A-T alleles require the mutant allele to be expressed as a truncated protein. Laake and Borreson-Dale screened for the Norwegian founder mutation present in 55% of Norwegian A-T patients and found 1 A-T carrier in 447 consecutive breast cancer cases in Norway, as well as a carrier of the Norwegian founder mutation along with 2 additional A-T carriers among 88 Swedish breast cancer cases (21). They are currently looking for LOH in these tumors, because the loss of the wild-type allele should be common if lack of ATM function is truly contributing to the development of cancer in these patients. Taking the complementary approach of assessing the status of relatives of A-T patients where heterozygosity for a ATM mutation was confirmed, they found a relative risk for all cancers of 1.66 and a relative risk of 2.68 for breast cancer in the Norwegian and Danish populations (22). In other studies of A-T relatives, Chessa found no evidence of increased cancer risk, whereas Stoppa-Lyonnet supported an increased relative risk of cancer in A-T carriers. Bendix presented preliminary data that also did not support a high frequency of A-T heterozygosity in unselected breast cancer cases. These studies confirm that although there is an increased risk of cancer in A-T carriers, this risk is small.

Wolman made the observation that ATM mutation seems to be correlated with unusual morphology of breast tumors. Tumors in A-T heterozygotes tended to be lobular and have colloid changes more frequently than those of noncarriers, suggesting that it may be more fruitful to seek ATM mutations in specific types of breast tumors. Sturie looked at the level of ATM mRNA in breast cancer, benign breast lesions, and normal breast tissue and found that normal tissue expressed the highest levels of ATM, benign lesions expressed less, and breast carcinomas expressed the least ATM mRNA. Preliminary mutation analyses did not reveal any mutations in the ATM kinase domain, but the results suggest that the ATM gene may be involved in neoplastic breast disease by an epigenetic mechanism.

Whereas ATM heterozygosity may not be a major genetic determinant in cancer, ATM seems to play a classic tumor suppressor role in T-prolymphocytic leukemia, which is highly associated with loss or mutation of the ATM locus (23). This rare malignancy, although seen in young adult A-T patients (24), usually affects older patients and is associated with somatic loss of both ATM alleles in the tumor, rather than germ-line mutation of one allele and somatic mutation of the second allele. Similar results were presented by Schaffner, Stern, Yuille, and Vorechovsky, showing allele loss or mutation of ATM in this rare cancer. Missense mutations were relatively more common in these somatic events, rather than the predominance of truncating mutations seen in A-T patients, although most of the mutations were still predicted to be inactivating due to the change of conserved
residues in the active site of the ATM kinase (23). Vorechovsky suggested that the incidence of ATM mutation in T-lymphocytic leukemia may be underestimated due to the inefficiency of mutation detection for this large gene, and that ATM may be a key gene in the malignant transformation of T cell.

The idea that ATM might act as a tumor suppressor gene in other sporadic tumors is supported by the high frequency of LOH including the ATM locus at 11q23.1 (25–27). Five groups presented data on LOH at the ATM locus on 11q23.1 in tumors; these concerned breast, ovarian, and colon cancer. LOH at ATM affected 30–40% of breast tumors. Rio showed data suggesting that ATM loss was associated with larger tumor size, whereas, in the same survey, LOH at BRCA1 was associated more strongly with higher grade and negative hormone receptors, suggesting that these genes act in different pathways in tumorigenesis. In ovarian carcinoma, Launonen detected LOH at ATM in 61% of cases, with the majority simultaneously deleted at 11q23.2–q25, where a second tumor suppressor locus is thought to be located. LOH at ATM was not correlated with prognosis, whereas the more distal deletion was correlated with a more aggressive tumor. Grancho suggested that ATM loss is not common in colon tumors. The existence of a second tumor suppressor locus about 500 kb distal to ATM has been suggested recently, based on LOH studies with closely spaced markers (28). Given the large regions commonly deleted in cases of LOH, it is therefore difficult to determine the relative importance of these two genes in any given tumor. It is essential to continue these studies by investigating the remaining allele in cases of LOH at ATM.

**ATM and Radiation Sensitivity**

It was first reported more than 30 years ago that A-T patients are exquisitely sensitive to ionizing radiation. Tatsumi now reports that A-T cells exhibit a predominance of deletion mutations at a test locus after irradiation. The abnormal response to irradiation seen in A-T homozygotes is often seen to a lesser degree in A-T heterozygotes, and it seems reasonable that heterozygotes expressing this defect may also be more prone to malignancy. It has long been one of the goals of A-T research to discover a way to detect A-T heterozygotes in an effort to remove these sensitive individuals from the standard radiotherapy protocols and therefore deliver increased and more effective doses to normal individuals without increased morbidity. In keeping with this reasoning, radiation overreactors might prove to be a cancer patient population that is rich in A-T heterozygotes. Despite this, even though many A-T heterozygotes are moderately radiosensitive in vitro, heterozygosity at ATM does not account for a significant portion of radiotherapy overreactors. While this report was in preparation, van Beizen presented a family with three male siblings affected with a mild resting tremor, rearrangements of chromosomes 7 and 14 typical of A-T, and elevated AFP. While the cloning of the ATM gene, the question of whether the NBS represented a true variant of A-T, possibly due to an unusual ATM mutation, could be addressed. It is now clear that NBS is caused by defects in a gene distinct from ATM, and the genetic and functional mapping of the NBS gene to 8q21 was reported by Chrzanowska, Saar, Concannon, and Komatsu (30, 31). While this report was in preparation, an NBS gene, NBS1, was cloned (32, 33), and the biochemical relationship between the two gene products can now be studied.

Clinical and biochemical studies of NBS have continued. Follow-up of Polish NBS patients by Chrzanowska (34) revealed that ovarian failure in NBS females is quite profound, but only a slight delay in puberty was observed in males, and intelligence in preschool NBS children progressed from mild to moderate retardation by the age of 14 years. Jongmans and Komatsu both investigated whether NBS cells exhibited defects similar to those of A-T cells after irradiation (35, 36). p53 induction was attenuated after irradiation of NBS cells, although not as severely as in A-T cells, as was transcriptional activation of WAF1/CIP1 and execution of the G1-S cell cycle checkpoint. NBS cells also exhibited a prolonged accumulation of cells in G2 after irradiation. A-T and NBS lymphoblastoid cell lines exhibited similar levels of chromosomal damage in response to DNA strand-breaking agents, but Stumm demonstrated that NBS cells differed in their response to alkylating agents. These data, as well as the clinical findings, suggest that the NBS gene product performs similar functions to ATM, possibly acting in the same pathway.

In addition to NBS, several patients with some but not all of the hallmarks of A-T have been described and studied over the years, typically presenting with a mild clinical course and/or intermediate radiosensitivity. van Belzen presented a family with three male siblings affected with a mild resting tremor, rearrangements of chromosomes 7 and 14 typical of A-T, and elevated AFP, but near normal radiosensitivity and immunological tests. Linkage analysis of this family was consistent with the ATM locus at 11q23.1 being the disease-causing gene in this family, although no mutations in the coding or promoter regions of ATM have been found as yet.

**ATM Functions**

The phenotype of A-T cells in culture had been studied in detail for many years before the cloning of the ATM gene. The speculation that the A-T gene product would be involved in the signaling pathway that led to cell cycle checkpoints in the presence of DNA strand breaks and that the pleiotropic phenotype would be due to defects in many different points in a complex web of signaling interactions is now being confirmed (37, 38). The cloning of the gene immediately led to a broader understanding of A-T functions, because ATM belongs to an extended family of similar genes, and the phenotypes of defects in these genes replicate subsets of the A-T phenotype in several model
systems, including fruit flies and yeast (5). An example of the functional overlap between these large protein kinases was given by Meyn, who showed that the yeast TeI1 protein could suppress spontaneous hyperrecombination and could partially suppress excessive apoptosis of A-T cells after irradiation.

Lavin and Kedar discussed their investigation of the cell cycle checkpoint defects in A-T cells and the molecular pathways involved (39). Their results and those of others suggest that in addition to p53, c-Abl is involved in executing the G1-S-phase checkpoint after irradiation, and that ATM binds constitutively to c-Abl and activates the kinase activity of c-Abl both in whole cells and in 

in vitro assays with a recombinant ATM phosphatidylinositol 3'-kinase domain fragment (40, 41). Other interacting proteins are being identified through yeast two-hybrid screens or coimmunoprecipitation and suggest that the molecules required for cell cycle progression are associated with several regulatory and inhibitor molecules in a large complex, and that cell cycle progression may be regulated by cross-phosphorylation and autophosphorylation of this complex.

Uhrhammer and Chen showed that ATM fragments expressed in the antisense orientation in normal cells could impose a radiosensitive phenotype (42). ATM antisense expression reduced ATM protein levels in the normal cells, increased the number of chromosome aberrations per metaphase, reduced cellular survival, and abrogated cell cycle checkpoints after irradiation. This recreation of the A-T phenotype will be useful for a wide variety of experiments in which it is essential to have isogenic cell lines with and without ATM function. Uhrhammer showed that ATM antisense introduced into two B-cell lymphoma cell lines could increase the radiosensitivity of the cells regardless of their initial radiation survival and p53 status, suggesting that ATM antisense might be a useful gene therapy strategy for cancer patients.

Humar et al. (43) extended the study of programmed cell death after irradiation of A-T cells. A subset of A-T lymphoblastoid cells underwent apoptosis during the first 3 h after irradiation, although they did not show any defect in double-strand break rejoining capacity. This response was not dependent on activated p53, because activated p53 could not be detected in the cells. This early apoptotic response is in addition to the late apoptotic response of A-T lymphoblastoid cells, which occurs 2–5 days after irradiation, when the cells are arrested in G2 (44). Although Humar et al. reported normal capacity for rejoining DNA strand breaks, Tachibana reported reduced fidelity of repair, confirming the work of Thacker et al. (45).

Dantzler investigated the activity of PARP, an enzyme involved in the detection of DNA strand breaks, the deficiency of which causes acute radiation sensitivity in mice (46). Given the similarities in the functions of ATM and PARP, it is possible that the two proteins act in concert or in the same pathway. A-T cells showed no deficiency in PARP activity; however, immunoprecipitation showed an association between ATM and PARP. Double knockout mice (PARP−/−; ATM−/−) are currently being made, and it will be interesting to see if there is a synergistic effect of the two deficiencies.

A key advance in the study of A-T, and one of great importance to developing new therapeutic strategies for the patients, is the development of a mouse model by disruption of the murine Atm gene. As Wynshaw-Boris reviewed, the phenotype of ATM−/− mice is very similar to that of human homozygotes: the mice are radiosensitive; they develop cancer at high frequency; they have immunodeficiency; and they are infertile (7, 8). There are also some differences in the phenotype of the ATM−/− mice; for example, although there is histologically detectable degeneration in the brain, they do not seem to have ataxia or progressive cerebellar degeneration, only a subtle defect in coordination (47). Other differences include a more severe meiotic defect and the homogeneity of malignancy in the mice, with 100% of ATM−/− mice developing T-cell lymphoma at an early age.

Ashley and Plug demonstrated the association of Atm and another member of the phosphatidylinositol 3'-kinase family, Atr, with the synaptonemal complexes of chromosomes in meiosis I of the mouse (48). During early meiosis I, as the chromosomes begin to condense, Atr and Rad51 appear together with additional proteins in foci along the unsynapsed axial elements in both normal and ATM−/− mice. These foci are known as early RNs and are thought to be involved in the check for homology in preparation for reciprocal recombination. In normal mice, as soon as the chromosomes synapse, Atr leaves the RN and Atm appears in its place, along with the addition of RPA. Atm and RPA remain associated with the RN as it is processed into a late RN, where DNA strand breaks and recombination are thought to occur. Thus, it seems that Atm is present at the sites of DNA strand breaks, presumably to monitor the correct processing of the break and ensure an orderly progression through meiosis I. In ATM−/− mice, pairing is initiated normally; however, without functional Atm at the RN, the synaptonemal complex begins to fragment, becoming progressively more abnormal, until the cell is morphologically apoptotic. Plug found that fragmentation often occurred at foci of RPA, indicating that it was the synapsed axes that were breaking, and implying that the DNA strand breaks that occur as an obligatory step of recombination were not held together by the maturing RN in the absence of Atm.

McElligot showed that the signaling molecule Chk1/Rad27sp also associated with meiotic chromosomes, although at a time later than Atm and Atr, and that this did not occur in ATM−/− spermatocytes (49). He also showed that the kinase activity of Atr was dependent on Atm. BRCA1 was found to colocalize with Atr on meiotic chromosomes, but its function was not dependent on Atm. Both McElligot and Meyn showed that apoptosis in ATM−/− spermatocytes was not dependent on p53, in contrast to fibroblasts. Expression of p53 in spermatocytes of ATM−/− mice created in the Xu and Leder labs was undetectable, whereas in normal spermatocytes, p53 was highly expressed. This result is in contrast to ATM−/− mice created by Wynshaw-Boris, which may have a slightly more severe phenotype and apparently express high levels of p53 in spermatocytes (50). These different results need to be confirmed and can perhaps be explained by genetic background differences between the mouse strains or differences in the experimental protocols.

Diagnosis and Medical Aspects

A detailed immunohistochemical analysis of cerebellar changes in A-T patients was performed by Becker-Catania. She reported ectopic Purkinje cells in the granular cell and molecular layers of A-T patient cerebella as well as dysmorphic and degenerating axons similar to those seen in elderly people and disorganization of parallel fibers in the molecular layer. These findings suggested a developmental abnormality, with the loss of Purkinje cells being a later event. Thus, it seems that the primary lesion in the central nervous system of A-T patients may not be in the cerebellum.

Phenotypic heterogeneity in A-T was revisited by Sanal, who documented differences in immunoglobulin deficiencies in a survey of 56 patients and found minimal correlation between immunoglobulin patterns and susceptibility to infections. The immune defect in A-T was studied further by Zielen, who, like Sanal, reported an impaired ability to generate IgG against polysaccharide vaccines in almost all patients, whereas antibody responses to protein antigens were normal. A-T lymphocytes showed increased levels of activated

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CD4 cells and higher expression of the preapoptotic marker CD95 (Fas/Apo1), as shown by Schubert. This finding is consistent with the model of ongoing cell loss in A-T. Regueiro and Porras also reported elevated natural killer cell levels in a group of Spanish and Costa Rican patients. Throughout the meeting, the lack of obvious correlation between the A-T molecular genotype and clinical phenotype (in particular, the variation in immune defects, but also the variation in the course of the cerebellar degeneration) led the participants to discuss repeatedly how to define A-T. Aside from cases with a very clear A-T phenotype, it seems difficult to decide whether using highly restrictive criteria is more appropriate than using a broader clinical definition. It has been shown that some variant patients have ATM mutations, but other rare patients may have defects in other genes. This issue remains to be resolved.

In the end, the focus of the workshop shifted back to viewing the patients as individuals needing medical care. The mission of the workshop was not only to present the latest molecular findings and hypotheses, but to broaden awareness of the disease among clinicians and discuss therapeutic strategies. Being a rare disorder, and one that seems difficult to decide whether using highly restrictive criteria is more appropriate than using a broader clinical definition. It has been shown that some variant patients have ATM mutations, but other rare patients may have defects in other genes. This issue remains to be resolved.

Future Directions

The field of A-T research has diverged explosively since the Sixth International Workshop on A-T and the cloning of the ATM gene. In 1994, it was predicted that the Seventh International Workshop on A-T would focus squarely on gene therapy for A-T (51). Unfortunately, ATM gene therapy is impractical at this time, but the unraveling of the role of ATM in DNA damage signaling opens other doors for research and therapy. In the future, it is expected that a better understanding of the variability of the A-T phenotype will be reached, possibly using a refined definition of the disease. We also expect to better define the epidemiological and molecular roles of ATM in sporadic and familial cancer and perhaps to use ATM antisense as a therapeutic tool to combat various cancers. It is hoped that the Eighth International Workshop on A-T will provide some of these answers.

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References


