REVIEW

The p53 tumor suppressor protein: meeting review

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The p53 protein is finally swimming into focus. This became clear at the Sixth International p53 meeting, which was held in Israel in Tiberias on the shores of the Sea of Galilee in early November 1992. In recent years, the p53 protein has captured the imagination of a broad spectrum of biomedical researchers. Because of its potentially central role in human cancer, there is considerable impetus to understand how it functions normally and how this function is changed in tumor cells. Progress along many lines was reported at the recent meeting, and some of the work presented raised new issues and posed new questions. Unfortunately, although virtually all of the presentations at the meeting were interesting, space does not permit the discussion of each of them in this short meeting review. In summing up the various topics, we divide this commentary into two parts dealing, respectively, with wild-type and mutant forms of p53.

Wild-type p53

DNA binding and transcriptional regulation

Over the past 2 years, it has been established that p53 is a sequence-specific DNA-binding protein that can regulate transcription. Binding sites have been identified, and target genes are beginning to emerge. Examination of the different domains of the polypeptide reveals further clues as to its function and regulation. Among the new binding sites identified are regions within the mouse *Thy1* and *mdm-2* genes [G. Zambetti (A. Levine laboratory, Princeton, NJ)] and the *GADD45* gene [M. Kastan, Johns Hopkins University], all of which are located within introns rather than regions 5' to promoters. All binding sites catalogued to date conform to varying extents to the previously identified p53 consensus sequence [El Dierry et al. 1992; Funk et al. 1992].

Many sites that are bound by p53, when linked to a reporter construct, allow activation of transcription, although the extents of activation vary. However, in one survey, a poor correlation between strength of binding and extent of activation was observed, suggesting that additional features of transcription or DNA binding are involved [S. Kern (B. Vogelstein laboratory, Johns Hopkins University)]. M. Tarunina (J. Jenkins laboratory, Marie Curie Research Institute) described experiments

with site-directed oligomerization-defective mutant p53 proteins indicating that the ability of p53 to activate promoters bearing strong versus weak p53 binding sites may be related to the ability of the protein to form oligomers. Evidence that a p53 dimer is a functional DNA-binding unit was also presented by Tarunina.

One example of a p53-responsive element that does not detectably bind purified p53 protein was described by G. Lozano (University of Texas), who provided evidence that a DNA sequence within an intron of the p53 gene itself, containing an NF- κ B family consensus sequence, is activated by p53. Generally, however, it appears that in cell transfection studies, p53 represses expression from templates that lack p53 binding sites. Moreover, p53 inhibits transcription from simple basal (T. Shenk, Princeton), as well as activated (C. Prives, Columbia University), promoters in vitro. T. Shenk reported the observation that p53 forms a complex with the TATA binding protein (TBP) in vitro. Shenk also provided evidence that p53 can be found in immunoprecipitates of TBP from cells. The fact that p53 activates expression of the *mdm-2* gene, as reported by both the Levine and Oren (Weizmann Institute) groups, suggests the intriguing possibility that there is a regulatory feedback loop between the two genes because of the observation that the *mdm-2* gene product, shown to bind to p53, strongly inhibits the ability of p53 to activate transcription [Mormand et al. 1992].

Structural features

Domain analysis of p53 has progressed rapidly [see Fig. 1]. The p53 protein can be divided into three regions: (1) the amino terminus, containing the transcriptional activation region; (2) the central portion of the molecule, containing highly conserved sequence blocks throughout which the majority of oncogenic mutations are located; and (3) the carboxyl terminus, containing both oligomerization and nuclear localization sequences. P. Tegtmeier's group (State University of New York, Stony Brook) showed that the ability of p53 to repress growth requires the full-length protein, although it is interesting that the amino terminus of p53 could be replaced by the activation domain of VP16 and still retain growth repression function. Results of collaborative experiments with

Figure 1. Structural domains on the human p53 protein. The shaded boxes containing roman numerals represent the five regions of p53 that are conserved from *Xenopus* to primates. The three nuclear localization signals (NLS) are also shown. Indicated above are the known phosphorylation sites on p53 (P): the amino-proximal four sites (putative kinases include the double-stranded DNA protein kinase and casein kinase I), and the two carboxy-terminal sites that have been shown to be phosphorylated by cdc2 and cdk2 kinases (CDK site) or casein kinase II (CKII site). The asterisks in the center show residues that have been found to be mutated in human tumors, with the hot spots identified by amino acid number. Shown below what is current information about the various domains of p53. Ad E1b p55 is the adenovirus E1b p55 protein, TBP is the TATA-box binding protein, and Hsc 70 refers to the heat shock cognate protein.

N. Pavletich and C. Pabo (MIT) were reported (C. Prives), showing that by using partial proteolysis of p53, sequences within the central portion are necessary for its sequence-specific DNA-binding properties. These results may well be related to the observation by J. Milner (University of York) who, from comparison with other protein sequences, has identified putative metal-binding sites within the central region and who has shown that maintenance of the wild-type conformation of p53 is dependent on metal binding.

On the basis of several talks at this meeting, however, perhaps the most complex region of p53 is the carboxyl portion. The extreme carboxyl end (~30 residues) contains a region that negatively regulates the ability of p53 expressed in bacteria to bind specifically to DNA (D. Lane, University of Dundee). When absent or bound to the carboxy-terminal-specific antibody PAb 421, or phosphorylated by purified casein kinase II, p53 binds well to its cognate site, whereas without any of these treatments bacterial p53 binds extremely poorly. This finding may be relevant to experiments described by D. Meek (University of Dundee), showing that mutation of the casein kinase II phosphorylation site at murine p53 residue 386 disrupts p53 growth suppression function.

The p53 carboxy-terminal region is also necessary for the ability of the protein synthesized in reticulocyte lysates to bind to heat shock proteins and to be degraded by the human papillomavirus (HPV) E6 protein in vitro (J. Milner). J. Jenkins reported that the carboxy-terminal portion of the molecule contains a potent DNA strand-reannealing activity, although, because such an activity was not apparent with the full-length protein, the signif-

icance of this observation remains to be determined. Somewhat unexpectedly, the region of p53 that interacts most avidly with TBP is the carboxy-terminal portion, rather than the more predictable amino-terminal region containing the activation domain (T. Shenk). The carboxy-terminal portion of the molecule contains an oligomerization domain (roughly amino acids 330–365; Sturzbecher et al. 1992), which was examined for its role in transformation by both M. Oren's and P. Tegtmeier's groups. Constructs expressing only amino acids 302–360 (Oren) or 315–390 (Tegtmeier) are sufficient to transform cells. That this process functions by a dominant-negative mechanism was supported by M. Oren's interesting results showing that this carboxyl region of the protein forms a complex with full-length p53 and the resulting hetero-oligomer is severely defective in DNA binding. Clearly, the carboxyl domain is a very busy region of p53. It is therefore surprising how few tumor-derived mutations map to this region.

Biological pathways

What is the normal biological function of p53? Several speakers addressed this important question. Two possible roles for wild-type p53 were identified, one as an inducer of differentiation and another as a checkpoint gene product that serves to cause cell cycle arrest in response to DNA damage. V. Rotter (Weizmann Institute) described two types of experiments supporting a role for p53 in the process of differentiation. First, results were presented showing that wild-type p53 induces B cells to

proceed to a more advanced stage in the pathway of B-cell differentiation. Second, Rotter reported that when transgenic mice were produced bearing the p53 promoter adjacent to a chloramphenicol acetyltransferase (CAT) reporter, analysis of CAT expression in different tissues of the transgenic animals led to the observation that the testes expressed the constructs most strongly. Consistent with this was the observation that high levels of p53 were detected in the testicular seminiferous tubuli, in particular in those cells that are arrested in the pachytene stage of meiosis when transcription is arrested.

M. Bar-Ely (University of Texas M.D. Anderson Cancer Center, Houston) described experiments in which mutant or wild-type p53 constructs were transfected into human osteosarcoma Saos-2 cells that were then injected into nude mice. Metastases produced by the wild-type form of p53, but not by the mutant form, consisted entirely of differentiated bone tissue. Friend virus-transformed erythroleukemia lines expressing a temperature-sensitive *val135* mutant murine p53 express hemoglobin, a marker of differentiation, at 32°C when the p53 is in a wild-type conformation but not at 37°C when in the mutant conformation (S. Benchimol, Ontario Cancer Institute, Toronto).

The existence of the p53 null mouse indicates that functional p53 is not necessary during early development (Donehower et al. 1992). However, this important and widely cited "knock-out" experiment does not definitively rule out a function for p53 in murine development. First, there may be redundancy for such a function in fetal life. Second, it remains possible that the genetic background of the mouse (and other animals) may be crucial for determining the impact of p53 because p53-interacting alleles may behave differently in different settings. This possibility is strengthened by the fact that L. Donehower (Baylor University) reported dramatic differences in the tendencies of p53 null mice derived from different strains to develop tumors. Finally, it is noteworthy that M. Mechali (Institut Jaques Monod), has shown that *Xenopus laevis* oocytes and early embryos contain substantial quantities of p53 protein as well as RNA. These data suggest that a role for p53 in early development (possibly nonessential) may still be identified.

It is clear, however, that the existence of p53 null cells means that the presence of p53 is not an absolute requirement for cell division. This is consistent with the suggested checkpoint role for p53 that is derived from several previous and current observations from the laboratories of M. Kastan and D. Lane. Both groups reported that levels of p53 increase when cells are exposed to DNA-damaging agents. In a somewhat grisly example of this a member of the Lane laboratory allowed a small section of his arm to be UV irradiated; several punch biopsies were then taken of the irradiated area as well as an adjacent nonirradiated area. Immunostaining of biopsy tissue revealed that high levels of p53 had accumulated in the deep dermis of the irradiated zone. Among other agents mentioned that induce p53 were ionizing radiation (IR), mitomycin C, etoposide, introduction of a

DNA restriction enzyme into the nuclei of the cells, and even (as a cautionary note) the process of DNA transfection itself. One of the more important implications of these experiments is that they identify, for the first time, a physiologically relevant situation in which p53 is over-expressed. This, in turn, makes it possible to fit disparate observations into a model for a regulated p53 functional pathway (Fig. 2).

Kastan reported an elegant series of experiments that outline a pathway in which p53 functions. His group had reported previously that cells bearing no p53 or mutant p53 do not display G₁ arrest after DNA damage but that p53 null cells, after introduction of wild-type but not mutant p53 constructs, display DNA damage-induced G₁ arrest (Kuerbitz et al. 1992). He has now shown that cells from patients with the inherited disorder ataxia-telangiectasia (AT), which is manifested by hypersensitivity to DNA-damaging agents and predisposition to cancer, fail to increase their levels of p53 in response to IR. Importantly, Kastan and colleagues have identified a potential target of p53 in normal cells, the product of the *GADD45* gene, which is among a series of genes whose expression is stimulated when cells are exposed to DNA damage (Fornace et al. 1989). Not only was a strong correlation between *GADD45* RNA synthesis and p53 accumulation noted by Kastan, but cells of AT patients fail to accumulate both p53 and *GADD45* after exposure to IR. The link between *GADD45* and p53 was made even tighter by Kastan who, in collaboration with the Vogelstein laboratory, showed that the *GADD45* gene contains a strong p53-responsive element, conserved between humans and hamsters, that conforms closely to the p53 consensus binding sequence. These experiments suggest that cells with mutant p53 or no p53 should sustain a larger number of mutations than ones that contain functional wild-type p53. Relevant to this, T. Tlsty (University of North Carolina) described the advantages of a sensitive assay that measures gene amplification as a function of genetic instability to examine a possible role for p53. Her finding that p53 null cells are markedly more prone to amplification of the *CAD* gene (using PALA selection assays) than are cells bearing wild-type p53 is consistent with the hypothesis that p53 is a determinant of genetic stability in cells and may function as a checkpoint gene. Although these data fit nicely into a framework in which cells with wild-type p53 sustain fewer mutations because of the checkpoint function of

Figure 2. Regulatory pathway involving p53 in response to DNA damage.

the tumor suppressor, a talk by J. Lee (Mount Sinai, Toronto) indicates that the situation may be somewhat more complex: In transgenic mice, the presence of mutant p53 in hematopoietic cells increases their resistance to γ radiation.

Viral gene products interfere with p53 function

The fact that at least three different classes of DNA viruses encode gene products that bind to p53 provides strong testimony as to the central role(s) of p53 in cell function. Presumably, the potential ability of wild-type p53 to arrest cells in G₁ is an activity that viruses must abrogate to produce a proper milieu for efficient replication. How such viruses affect p53 is therefore of considerable interest. By directly binding to p53, SV40 large T antigen blocks its ability to bind to DNA and activate transcription [C. Prives; J. Huibregste (Howley laboratory, NIH)]. However, T antigen may exert an equally important indirect effect on p53 function. Reports from C. Finlay (Princeton), J. Manfredi (C. Prives laboratory), and W. Deppert (Heinrich-Pette Institut) provided evidence that p53 is functionally altered by T antigen in a manner that is independent of direct physical interactions between the two proteins but requires the regions of T antigen that are involved in binding to the retinoblastoma susceptibility gene product (pRb), p107, and/or p300. J. Pipas (University of Pittsburgh) reported results of collaborative experiments with T. van Dyke (also at University of Pittsburgh) that different T-antigen mutants varying in their abilities to bind to p53 or RB/p107 or p300 displayed different cell-type transformation or tumor profiles in cell culture studies and transgenic mice, respectively. These experiments provide excellent *in vivo* models for the roles of p53 and pRb in different cell types.

Perhaps the most significant link between viruses and human cancer emerges from studies of HPV. The ability of the E6 gene product of oncogenic forms of HPV to induce the degradation of p53 is potentially of great importance. J. Huibregste (P. Howley laboratory, NIH) described the cloning and characterization of the gene that encodes the E6-associated protein (E6AP), which mediates the interaction between E6 and p53 and induces p53 degradation. The gene encodes a ~100-kD protein with little homology to other proteins in the Protein Sequence Database other than a recent entry that itself encodes a rather mysterious protein. Clearly, however, as more data about E6AP are obtained, new and important information is likely to emerge, which may eventually provide insight into the normal mode of regulation of p53 levels in cells, now known to be controlled post-transcriptionally. As was the case demonstrated for T antigen, T. Unger (P. Howley laboratory, NIH) showed that E6 inhibits the ability of p53 to activate transcription in cell transfection assays. T. Tlsty also reported that wild-type p53-bearing cells induced to express oncogenic forms of HPV E6 also displayed increased gene amplification.

Mutant p53

Mutations are specific for tumor type

The p53 gene is the most commonly altered locus in a variety of human cancers. Typically, one allele of p53 is rearranged or deleted such that there is no expression of protein and the remaining allele sustains a missense mutation. This results in expression of a mutant p53 protein in the absence of any wild-type p53. It is now clear that there are different mutational hot spots, depending on the particular type of cancer. Mutations at codons 175, 248, 273, and 282 are found most commonly in colon cancer, whereas a mutation at codon 273 predominates in brain tumors, a mutation at codon 249 occurs frequently in liver cancer in patients from regions with high exposure to aflatoxin (C. Harris, NIH; M. Ozturk, Centre Leon Berard), and mutations at codons 242 and 273 are more prevalent in lung cancer (C. Harris). Codons 172, 213, and 248 are hot spots for mutation of p53 in Burkitt's lymphoma (K. Wiman, Karolinska Institute). The exact nature of the nucleotide alteration can indicate the action of specific types of carcinogens. For example, G $\rightarrow$ T transversions are more common in China than they are in Europe (Ozturk). CpG dinucleotides appear to be most commonly altered, particularly at codons 175, 248, and 273. Finding this type of mutagenesis in colon, liver, and lung cancer was expected because these tumor types have long been suspected to be caused, at least in part, by exogenous carcinogens. Sequencing analysis of p53 mutations in breast tumors suggests, for the first time, a role for environmental carcinogenesis in the formation of these tumor types, a potentially intriguing prospect (J. Prosser, MRC, Edinburgh). T. Soussi (Institut de Genetique Moleculaire) noted that there is a strong bias at codon 175 for a G $\rightarrow$ A transition. His group then constructed a codon 175 library generating nearly all possible amino acid substitutions at that position. When the properties of these mutant p53 proteins were examined *in vitro*, including the ability to bind to mutant and wild-type-specific antibodies, to bind to DNA, and to *trans*-activate a promoter containing a p53 binding site, several but not all of the mutants were altered in these activities. Some mutants, although identified in cancer patients, did not produce a protein that was altered by the above criteria, suggesting that not all tumor-derived p53 mutants are functionally changed or defective.

Li-Fraumeni syndrome

A great deal of excitement was generated several years ago when it was shown that p53 mutations can be carried in the germ line and appear to contribute to the propensity for certain families to develop cancer at a high rate. The original studies with this Li-Fraumeni syndrome showed that the identified missense mutations appeared to be clustered in the central part of the protein, particularly around codons 240–260. Preliminary experiments *in vitro* showed that these mutant p53 proteins were much more wild type in their activity than

the typical tumor-derived mutant p53 proteins. However, contrary to these early studies, more extensive analysis reveals that the germ-line mutations found in Li-Fraumeni families are not clustered but can be found throughout the p53 gene (T. Frebourg, Massachusetts General Hospital; J. Prosser). Furthermore, in vitro analysis of such mutations, particularly in cotranslation assays that tested whether these mutant p53 proteins could drive wild-type p53 into a mutant conformation, show that some of the Li-Fraumeni mutant p53 proteins are not distinguished as being less active than the tumor-derived mutants (S. Srivastava, Uniformed Services University of the Health Sciences, Bethesda). Thus, there appears to be no intrinsic difference in the mutant p53 proteins themselves whether the mutations were originally identified as germ line or tumor derived. Because fibroblasts derived from Li-Fraumeni patients do not appear to be transformed, these results suggest that either the level of expression of mutant p53 or the presence of an intact wild-type allele may be the crucial factors in whether such mutant p53 proteins will contribute to altered growth properties and oncogenesis.

Early vs. late event?

The finding of germ-line mutations in the p53 gene of Li-Fraumeni patients suggests that p53 alteration is an early event in the generation of tumors in this syndrome. Consistent with this notion, some strains of mice that are homozygous for a deletion of p53 form tumors efficiently by 6 months of age, suggesting that p53 alterations may be an early event in tumorigenesis (L. Donehower). Also consistent with this is Tlsty's observation that seemingly normal cells from p53 null mice are orders of magnitude more genetically unstable, as determined by their propensity for gene amplification. Furthermore, direct modification of the p53 gene has been suggested as initiating the route of carcinogenesis by aflatoxin in liver cancer (C. Harris), as well as other chemicals in some animal models (P. May, CNRS). However, at the same time, other animal model systems suggest that p53 mutation is a late event. Benzo[*a*]pyrene carcinogenesis results in p53 mutation, but the nature of the mutation shows that it did not arise by direct mutagenesis by this agent (P. May). Activation of the *Fli-1* gene by proviral integration is the first event during multistage progression of Friend virus-induced erythroleukemia, with p53 rearrangement or deletion occurring much later in the process (Y. Ben-David, Sunnybrook Health Science Center, Toronto). In a skin tumor mouse model, p53 mutation is associated with late stages of carcinoma rather than the early stage of papilloma formation (C. Kemp, Beatson Institute).

Animal models may, however, have limited usefulness in understanding certain types of human cancer. For example, despite the clear importance of p53 mutation in human liver cancer, mutation of p53 is rarely seen in hepatocellular carcinoma in rodents (P. May). It was pointed out that in contrast to the situation in human cancer where p53 mutation is the most common alter-

ation, in most rodent cancers activation of the *ras* proto-oncogene is most commonly found (C. Harris). In HPV-induced cervical carcinoma, mutation of p53 appears to be associated with the late metastatic stage of the disease (K. Vousden, Ludwig Institute, St. Mary's). Perhaps the timing of the alteration of p53 may be specific for a particular tumor type. Alternatively, as has been suggested previously, what is important for oncogenic progression may be the accumulation of a number of genetic lesions, among them alteration of p53, and the precise sequence of those alterations may not be critical. Although p53 may be a determinant of the G₁ checkpoint in mammalian cells, there are additional checkpoints in S and G₂ that probably do not involve p53. Lesions in genes involved in these alternate checkpoints may also be important in initiating carcinogenesis; and, as discussed below, mutation of p53 may play a role in maintenance as well as initiation of the oncogenic state.

Molecular characterization of tumor-derived mutants

Because the codons that are mutated in p53 are scattered throughout the coding region, it was believed that all of these mutations exert a common global conformational effect on the protein. Early biochemical studies suggested that all of the tumor-derived mutants were similar; but it is becoming increasingly clear that different mutations produce p53 proteins with varying activities. Oncogenic strains of HPV express an E6 protein that has been shown to target the degradation of wild-type p53 both in cells and in reticulocyte lysates in vitro. Different tumor-derived mutants are also degraded like wild type (mutants with substitutions at codons 181 and 273), whereas others are resistant (mutants with substitutions at codons 173, 232, 245, and 249), even though this latter group does bind to E6 (K. Vousden). Systematic mutagenesis of conserved region 2 in mouse p53 has produced a range of mutants with varying abilities to interact with wild-type and mutant-specific monoclonal antibodies or SV40 large T antigen and to repress or activate different promoters in cotransfection assays (D. Simmons, University of Delaware). One simple conclusion is that each mutant must be analyzed independently because location within the gene does not allow prediction of its effect. More importantly, results such as these imply that different tumor-derived p53 mutant proteins have differing properties and that the notion that all of these mutations exert a single effect is too simplistic.

Recent studies show that different tumor-derived mutants are distinguishing themselves from others by appearing to be temperature sensitive in various in vitro assays. *his-273* is temperature sensitive for specific DNA binding (C. Prives), mutation at codon 247 is temperature sensitive in a *trans*-activation assay (T. Unger), and *pro-175* is temperature sensitive for targeted degradation by HPV E6 (K. Vousden). In some cases, *his-273* appears to function as a wild-type protein in cells (P. Chumakov, Engelhardt Institute of Molecular Biology, Russian Academy of Sciences). These observations underscore the po-

tential importance of protein conformation in the activities of mutant p53 proteins.

Tumor-derived mutant p53 proteins display gain of function

The fact that there is selective pressure in human cancer for the expression of mutant p53 proteins rather than no expression at all (as is seen, e.g., with pRb) adds credence to the idea that mutant p53 proteins may contribute to the gain of some growth-altering function rather than represent a mere inactivation of wild-type p53 activity. K. Vousden reported that a large number of cervical carcinomas are associated with HPV and the p53 in these tumors is wild type. HPV-negative cervical carcinomas, on the other hand, have mutant p53 proteins. When HPV-positive carcinomas progress to metastasis, the resulting tumors contain mutant p53, suggesting that even if wild-type p53 is effectively inactivated by HPV E6, additional mutagenesis is necessary for metastasis. Definitive evidence that p53 mutants are not neutral came from an experiment from A. Levine's laboratory in which various tumor-derived mutant p53 proteins were expressed in a nontumorigenic mouse cell line lacking any endogenous p53 expression. When such cells were subsequently injected into nude mice, efficient tumor formation ensued only with mutant p53-expressing cells. Furthermore, G. Zambetti described cotransfection reporter assays showing that tumor-derived mutants, but not wild-type p53, activate the multidrug resistance promoter in Saos-2 cells that lack endogenous p53 expression. All of these results reinforce the provocative notion that the selective pressure in favor of expression of mutant p53 proteins in human cancer is the result of some positive activity of these proteins. The prevalence of mutant p53 proteins in human cancer and any future attempts at using p53 as a focal point for diagnosis or therapy will require a full understanding of the nature of these gain-of-function activities of mutant p53 proteins.

The future of p53 research

Some of the intriguing findings presented at the 1992 Israeli meeting raise new questions. By the time of the next meeting (tentatively set for 1994 in Toronto, Canada), it is anticipated that at least some answers will be forthcoming. Additional target genes that p53 binds and activates are likely to be revealed, and further insight into how and when p53 activates or represses transcription will likely develop. Likewise, it is highly likely that either by biochemical means or the use of yeast screens, such as were presented at the meeting by members of S. Field's (State University of New York, Stony Brook) and B. Vogelstein's laboratories, new proteins that bind to p53 will be identified. The challenge will then be to determine which of these interactions are physiologically relevant. Some of the more intriguing questions to be illuminated include what controls the levels of p53 in normal cells and why are mutant p53 proteins frequently much more stable in cells than is the wild-type form?

How do p53 mutants contribute to tumor progression? A p53-mediated suicide response has been documented by Oren and colleagues (Yonish-Rouach et al. 1991). How are the data reconciled that show, on the one hand, that p53 induces apoptosis, and on the other, that it causes growth arrest? Furthermore, are either of these inhibitory functions related to the possibility that p53 may induce differentiation of some cell types? Finally, on a more practical level, can compounds be developed or identified that either destroy mutant p53 present in tumor cells or cause mutant p53 to regain wild-type function? Questions such as these are likely to keep members of the field very busy at least until the next p53 meeting.

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