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**The p53 Tumor Suppressor Gene and the Tobacco Industry:  
Research, Debate, and Conflict of Interest**

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## Summary

**Background:** Mutations in the p53 tumor suppressor gene lead to uncontrolled cell division and are found in over 50% of all human tumors, including 60% of lung cancers. Research published in 1996 by Mikhail Denissenko et al. demonstrated patterned *in vitro* mutagenic effects on p53 of benzo[a]pyrene, a carcinogen present in tobacco smoke. We investigate the tobacco industry's strategies in responding to p53 research linking smoking to cancer.

**Methods:** We searched online tobacco document archives, including the Legacy Tobacco Documents Library and Tobacco Documents Online, and archives maintained by tobacco companies such as Philip Morris and RJ Reynolds. Documents were also obtained from the British American Tobacco Company depository near Guildford, England. Informal correspondence was carried out with scientists, lawyers, and tobacco control experts in the United States and Europe.

**Findings:** Individuals at the highest levels of the tobacco industry anticipated and carefully monitored p53 research. Tobacco scientists conducted research intended to cast doubt on the link between smoking and p53 mutations. Researchers and a journal editor with tobacco industry ties participated in the publication of this research in a peer-reviewed journal without clear disclosure of their tobacco industry links.

**Interpretation:** Tobacco industry responses to research linking smoking to carcinogenic p53 mutations mirror prior industry efforts to subvert the science linking smoking and lung cancer. The extent of tobacco industry involvement in p53 research and the undeclared conflict-of-interest discussed here demonstrate the need for consistent standards for the disclosure and evaluation of such conflicts in biomedical research.

**Key words:** tobacco, smoking, p53, lung cancer, tobacco industry.

## Introduction

Mutations in the p53 tumor suppressor gene are found in more than 50% of all human tumors,<sup>1</sup> including 60% of lung cancers.<sup>2</sup> In the normal cell, p53 defends against uncontrolled proliferation by causing G1 cell-cycle arrest and apoptosis (cell suicide) in response to DNA damage by radiation or mutagenic chemicals. p53 mutations contribute to tumor formation as they contribute to uncontrolled cell division regardless of DNA damage.

Because of tobacco use, lung cancer is the leading cause of cancer death in developed nations.<sup>3</sup> Benzo[a]pyrene, a potent carcinogen, was identified in cigarette smoke by Brown and Williamson Tobacco Company scientists as early as 1952.<sup>4</sup> In the 1990's, *in vitro* experiments<sup>5</sup> and human molecular epidemiology studies<sup>6</sup> demonstrated patterned damage to the p53 gene resulting from exposure to benzo[a]pyrene's mutagenically active metabolite (+/-)anti7 $\beta$ ,8 $\alpha$  dihydroxy-9  $\alpha$ ,10  $\alpha$ -epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene (BPDE). In 1996, Mikhail Denissenko and colleagues<sup>5</sup> at the Beckman Research Institute in Duarte, California published a landmark analysis of BPDE's interaction with p53 in the journal *Science*. Analyzing *in vitro* culture cells and bronchial epithelial cells exposed to BPDE, Denissenko et al. identified a pattern of adducts along the p53 gene that correlated strongly with database analyses of p53 mutations found in actual human lung tumors available at the time.<sup>7</sup> This finding provided strong molecular evidence of the direct carcinogenic effect of a tobacco smoke constituent, findings that were verified by subsequent epidemiological analyses of p53 mutation databases.<sup>6</sup>

This paper describes the tobacco industry's strategies to respond to Denissenko et al.'s findings and subsequent research linking tobacco smoke exposure to patterned p53 mutations. Previously secret tobacco industry documents demonstrate that prior to 1996 tobacco companies supported research projects investigating mechanisms of p53

mutagenesis. Following the publication of Denissenko et al., tobacco companies supported scientific studies designed to cast doubt on the link between p53 damage and BDPE in tobacco smoke. In one case, a journal editor with longstanding, undisclosed ties to the tobacco industry proposed such a research project to a tobacco company prior to the publication of similar studies in his journal. The publication of this research in the journal *Mutagenesis* occurred without clear disclosure of tobacco industry connections on the part of the authors, and without any disclosure of tobacco industry ties on the part of the editor.

## Methods

We examined tobacco industry documents made public as a result of litigation against the tobacco industry in the United States. Between September 2002 and November 2003 we searched tobacco industry document internet sites (University of California San Francisco Legacy Tobacco Documents Library <http://legacy.library.ucsf.edu/> and British American Tobacco (BAT) collection [www.library.ucsf.edu/tobacco/batco](http://www.library.ucsf.edu/tobacco/batco); archives maintained by RJ Reynolds and Philip Morris, [www.rjrtdocs.com](http://www.rjrtdocs.com) and [www.pmdocs.com](http://www.pmdocs.com); Tobacco Documents Online [www.tobaccodocuments.org](http://www.tobaccodocuments.org)). Searches began with general terms such as “p53” and “mutagenesis,” then were narrowed using Boolean operators such as “AND” and “OR” to include names, locations, dates, and reference (Bates) numbers. For example, using the Legacy Tobacco Documents Library, the search terms “p53,” “mutagenesis” and “tumor suppressor” each yielded 3,308 documents, 2,276 documents, and 875 documents. A search for “p53 AND mutation” yielded 410 documents.

An additional 15,000 pages were obtained in hard copy format from the British American Tobacco Document Depository in Guildford, England by arranging for a research assistant to search the depository for files indexed with terms including p53 and the names of people and journals identified through other internet searches.

Of the documents reviewed in hard copy and electronic format, 43 were selected for use in this report.

Additional information concerning the context of the events described in the tobacco documents and the identities of figures named in the documents were obtained using Lexis-Nexis Academic Universe (<http://www.lexis-nexis.com/>), Medline, and general internet searches (Google). Informal e-mail and print correspondence was carried out between May 2001 and March 2003 with individuals involved in events described in the documents to clarify the context and sequence of the events described. A number of print and e-mail communications concerning these events were made available to us by Pierre Hainaut.

#### *Role of Funding Source*

The funding sources had no involvement in the design or conduct of this study.

## **RESULTS**

### **Background: Industry Research Before 1996**

BAT established the Scientific Research Group (SRG), in 1986 “to coordinate and initiate BAT’s knowledge and research...on ‘the effects of smoking on the smoker’” through funding and monitoring of external research.<sup>8</sup> An anonymous 1993 BAT memo lists a number of external contracts, many of which were granted through the SRG.<sup>9</sup>, including one project regarding p53 and cancer mechanisms. This memo suggests that BAT did not require disclosure of the source of project funding when the results were published:

1. We are also making contributions to industry [sic] funded research in a number of countries...
2. The information on the research organizations supported by BAT should be regard as confidential.

3. In all cases where research is supported by BAT, research workers are free to publish their work without further reference to BAT.<sup>10</sup>

British American Tobacco (BAT) monitored work on p53 at the highest corporate levels from the late 1980's. In 1993, Richard Thornton, BAT Smoking Issues manager, wrote to then-BAT Chairman Barry Bramley, regarding BAT-funded research on p53:

*BAT and p53*

More papers are currently published on p53 than any other topic on cancer research...The SRG identified p53 as an important area some four years ago and the SRG currently supports two research projects relating to p53. Through one connection in particular we are often aware of work before it is published

*p53 and Litigation*

... Attempts to implicate tobacco by analysis of mutational spectra in p53 isolated from lung or other cancers may be foreseen.<sup>11</sup>

Our search of the documents does not indicate the identity of "the connection" by which the SRG received work before it was published.

The research projects on p53 mutations supported by the SRG included a grant to researchers at the Marie Curie Institute in Oxted, UK, a part of the UK cancer charity Marie Curie Cancer Care. According to a 1991 memo written by Thornton, "BAT have been supporting a basic research programme involving p53 at the Marie Curie Research Institute since 1987" that BAT noted as being "considered to have 'international standing.'"<sup>12</sup> The BAT-funded program was overseen by Graham Currie, former director of the Marie Curie Institute, and John Jenkins, PhD, then a researcher at the Institute. Currie and Jenkins were at the time co-editors of the peer-reviewed Journal *Oncogene*, of which Jenkins remains co-editor in November 2003.<sup>13</sup> During the 1980's and 1990's, they published widely on the molecular mechanisms underlying p53's regulation of the

cell cycle.<sup>14-16</sup> A 1993 SRG report states that “Dr. G. Currie” project was expected to receive £240,000 over eight years through 1993 for a project on “p53 and lung cancer” and “the importance of p53 to cell division.”<sup>9</sup>

SRG also hired external consultants to analyze trends in p53 carcinogenesis research, report new findings, and evaluate grant proposals. One of them, Francis Roe MD D.Sc, received £8000 from BAT in 1993.<sup>17</sup> In that year, Roe gave a presentation to the BAT Scientific Research Group, stating:

on-going research on oncogenes and gene-interventions might at any time lead either to solutions or to yet further problems for the Industry. For this reason it has been very wise for BAT to support the research of Dr. Jenkins and others at the Marie Curie Research Institute on p53 and other proto-oncogenes. Through this support the Company not only gets an early insight into the results of research on p53 but maintain access to expertise on oncogenes generally. The ready availability of this expertise might suddenly at any time be found to be of crucial importance.<sup>18</sup>

Beyond BAT’s p53 research program, other tobacco companies and industry groups monitored developments in p53 research and funded projects examining p53 in carcinogenesis. Anthony Tricker, a senior scientific advisor to Philip Morris (PM) who reported directly to Cathy Ellis, PM Worldwide Scientific Affairs and Director of Research at Philip Morris U.S.A. in 1994,<sup>19</sup> attended and provided PM with a report regarding a conference on p53 and molecular carcinogenesis in 1998.<sup>20</sup> RJ Reynolds (RJR) and the Council for Tobacco Research contracted with independent laboratories and university-based researchers to do basic research related to p53.<sup>12,21,22</sup>



## **Tobacco Industry Responses to *in vitro* Research Linking p53, Smoking and Cancer**

In October, 1996, Mikhail Denissenko et al.<sup>5</sup> at the Beckman Cancer Research Institute in Duarte, CA published the results of their *in vitro* analysis of the interaction of BPDE with p53 in the journal *Science*. Application of BPDE to HeLa cells, a standard *in vitro* culture cell, and bronchial epithelial cells resulted in strong and selective adduct formation along the p53 gene, occurring with greatest frequency at codons 157, 248, and 273. Additionally, the authors found that “the majority of lung cancer mutations at these three codon positions are G [guanine] to T [thymidine] transversions.” As shown by the analyses of p53 mutations found in actual human lung tumors available at the time,<sup>7</sup> these three codons were common sites of mutation in the p53 gene in lung cancer. They concluded that “our study thus provides a direct link between a defined cigarette smoke carcinogen and human cancer mutations.”<sup>5</sup>

The initial public responses of tobacco companies such as PM, BAT, and RJR downplayed the mechanistic significance of Denissenko et al.'s findings (Table 1) in their statements to investors, analysts, and journalists. These statements mirror tobacco industry arguments first made in 1954, that the precise mechanisms by which smoking might cause cancer remain unknown.<sup>4</sup>

Internally, tobacco companies reviewed the scientific and litigation implications of Denissenko's work and planned a number of new research projects in response. A technical review of the Denissenko paper dated October 18, 1996, was written for PM by Thomas Mueller, a scientist at the Institut fur Biologische Forschung (INBIFO) a German laboratory purchased by PM in 1970 “to do some of the things which we are reluctant to do in this country [USA].”<sup>23</sup> He states that Denissenko's work “presents solid evidence...[and] reveals, in fact for the first time, the coincidence of mutational hot spots described in epidemiological studies and adduct hot spots and suggests the BaP

metabolites may be involved in this process.”<sup>24,25</sup> A 1996 review of Denissenko et al. from the office of Cathy Ellis, Director of Research at PM USA proposes that PM “support additional research elsewhere” in an attempt to further define the mechanism of p53 damage by BPDE, investigate the feasibility of screening individuals for susceptibility to p53 damage, and research possibilities for product modification by PM.<sup>26</sup> A separate 1996 PM review notes a number of methodological shortcomings in the study, but states that

In spite of these limitations, were [sic] involved in the following efforts which address and evaluate the claims of this study from a number of different perspectives:

First, we have had and will continue to have discussions with key experts on the technical merit and significance of this work.

Second, carefully designed and controlled scientific studies will be performed to investigate the claims of the paper and continue to investigate the formation and reduction of B(a)P in cigarette smoke

Third, product development efforts will continue to pursue commercially viable methods of reducing B(a)P in cigarette smoke.<sup>27</sup>

A number of these proposed projects were “established at INBIFO,” including genetic sequence analysis of p53 mutational spectra in human and animal tumors “to assess the site and type of mutations.”<sup>28</sup>

Scientists with financial links to BAT also undertook critical reviews of the Denissenko paper. David N. Cooper of the University College of Wales in Cardiff appears in the records of BAT’s Scientific Research Group (SRG) beginning in 1991, when he made a presentation on new experimental techniques in molecular genetics.<sup>29</sup> A 1991 SRG memo written by RE Thornton emphasizes the applicability of Cooper’s work to p53 research:

Dr. Cooper's hypothesis was likely to apply to disease for which environmental agents had been invoked e.g. lung cancer. Given that mutations in p53 also appear to follow a pattern, at least in some cancers, it would be interesting to compare the patterns of mutation in some detail...Dr. Cooper indicated a willingness to have an on-going dialogue with BAT and I believe that this, and the above, are additional reasons for supporting him.<sup>30</sup>

Further, a 1993 SRG report notes the potential applicability of Cooper's work to the study of "spontaneously occurring genetic mutations to cancer,"<sup>31</sup> and the 1995 budget for SRG lists Cooper as expected to receive £25,000 for a report on "mutations and thrombotic disease."<sup>32</sup>

In July 1998, David N. Cooper, writing with Michael Krawczak, published a critique of Denissenko et al. in *Mutagenesis* arguing that Denissenko's review of p53 mutations in databases of actual lung tumors lacked sufficient non-smoking controls, rendering their data "unsubstantiated conjectures."<sup>33</sup> Based on an analysis of the p53 mutation databases used by Denissenko, Krawczak and Cooper conclude that Denissenko's results are "insufficient in general to prove that the p53 mutations associated with lung cancer are anything other than predominantly endogenous in origin."<sup>33</sup> No funding source or competing interests for the authors were disclosed.<sup>33</sup>

### **Tobacco Industry Response to Epidemiological Evidence Linking p53, Smoking, and Cancer**

In a study published in July 1998 in *Environmental Health Perspectives*, Tina Hernandez-Boussard and Pierre Hainaut<sup>6</sup> of the International Agency for Research on Cancer (IARC), a branch of the WHO in Lyon, France, analyzed 876 p53 mutations from human lung tumors using an online database maintained at IARC. They found a high frequency of mutations at codons 157, 248, and 273, confirming Denissenko et al.'s *in*

*vitro* findings. Hernandez-Boussard and Hainaut also found a higher frequency of guanine (G) to thymidine (T) transversions among smoking-associated lung tumors than lung tumors in non-smokers. They concluded that “p53 mutations in lung cancer from smokers carry highly significant fingerprints of exposure to tobacco smoke components, in particular BaP (Benzo-[a]-Pyrene). These fingerprints are not found in nonsmokers.”<sup>6</sup>

Tobacco companies’ research anticipated and sought to mitigate the impact of Hernandez-Boussard and Hainaut’s work. PM’s surveillance included securing an unpublished copy of the submitted abstract from their paper by May 8, 1998, prior to its publication that July.<sup>34</sup> Following the paper’s publication, Lorillard, another tobacco company based in the United States, funded studies to challenge Hernandez-Boussard and Hainaut’s findings. A 1999 Lorillard list of “potential areas for consideration” for new scientific projects includes “IARC p53 database analysis” and comparisons of the “smoker lung tumor p53 mutation profile” with the mutation profile associated with *in vitro* B[a]P exposure.<sup>35</sup> In 1999, two Lorillard scientists, Robert Leverette and Robert Lake submitted an abstract to the 2000 meeting of the American Association for Cancer Research arguing against the conclusions of Hernandez-Boussard and Hainaut. Through an analysis of published p53 mutation sequences in human lung tumors, Leverette and Lake found a “nonrandom pattern of mutations.” They concluded that this pattern was likely caused by “inherent organ/cell type factors rather than specific exposures.”<sup>36</sup> The abstract does not appear in the published proceedings of the meeting.

Another study was carried out by Thilo Paschke, an employee of the Verband der Cigarettenindustrie (VdC), the German association of cigarette manufacturers, from at least June 1999.<sup>37,38</sup> The VdC includes German companies as well as PM, BAT, RJR, Lorillard.<sup>39</sup> A June 13, 2000 email from Paschke to Chris Coggins, Lorillard Senior Vice President of Research and Development, reports: “I published my analysis of the [IARC

p53] database at a German conference on environmental mutagenesis...and submitted it to a journal on mutagenesis. I'll send you a preprint of the paper, if the referees accept it for publication."<sup>38</sup>

Paschke's paper was published in the November 2000 issue of *Mutagenesis*. Analyzing changes in the classification of smokers and non-smokers made in revisions of the IARC database released after Hernandez-Boussard and Hainaut's paper, Paschke argues against an increased rate of G to T transversions or increased frequency of mutations in p53 codons 157, 248, and 273 in smoker versus nonsmoker lung tumors. He argued that confounders "such as histological tumor type and gender, age, and ethnic origin" may have influenced Hernandez-Boussard and Hainaut's conclusions.<sup>40</sup>

Paschke's employment by the VdC is not acknowledged in his publication. He is listed as an employee of the Analytisch-Biologisches Forschungslabor. The association of this laboratory with the German tobacco industry as the research arm of the VdC is publicly known, but not specified in the article.<sup>40</sup>

On January 12, 2001, Pierre Hainaut, with Magali Olivier of IARC, and Gerd P. Pfeifer of the Beckman Research Institute in Duarte, CA, submitted a response to *Mutagenesis*.<sup>41</sup> They noted that Paschke used the IARC p53 database in a manner against the published recommendations for its use and concluded that: "since we do not know which references have been used by Paschke, indiscriminate inclusion of mutations in his dataset may partially explain what he sees as `discrepancies.'"<sup>42</sup>

In addition to addressing these technical issues, Hainaut et al. noted Paschke's undisclosed ties to the tobacco industry. Their response, as initially submitted to the journal stated that

the publication by Paschke originates from a private laboratory, the Analytisch-Biologisches Forschungslabor, which is sponsored by the German Association of Cigarette Manufacturers. The tobacco industry has a long and proven history of

undermining the publication and diffusion of information that might lead to increased restriction of tobacco use, or have a negative impact on their positions in litigation issues.<sup>41</sup>

James M. Parry, Editor of *Mutagenesis*, refused to allow Hainaut et al to include this material; he wrote them:

I am not willing to approve the publication of your...point about the scientific integrity of Dr. Paschke. I am not willing to allow the pages of *Mutagenesis* to be used for non-scientific purposes.... I now intend to forward your reply to Dr. Paschke together with a copy of this letter and indicate that he may provide a response to your comments. However, in any response from Dr. Paschke I will request that he provides an acknowledgement to any financial support to his work.<sup>43</sup>

Hainaut et al.'s letter and Paschke's reply were both published in the November 2001 *Mutagenesis*.<sup>42,44</sup> Paschke's reply again argues against a statistically significant difference between smoker and non-smoker p53 mutations, and cites a confounding effect of "systematic changes in smoking status data of identical entries" listed in serial versions of the IARC p53 database. Paschke included the following acknowledgement: "My study on the IARC p53 database was funded by the Forschungsgesellschaft Rauchen und Gesundheit. The Forschungsgesellschaft gets its financial funds [sic] from the Association of the German Cigarette industry."<sup>44</sup>

### **The Tobacco Industry's Relationship with the Editor of *Mutagenesis***

The editor of *Mutagenesis*, James Parry, had undisclosed ties to the tobacco industry during the time when Cooper and Krawczak's<sup>33</sup> and Paschke's<sup>40</sup> papers were published in the journal. Parry, founding editor and executive editor of *Mutagenesis* from 1983 to 2002, has held research and consultancy contracts with PM and BAT.<sup>45,46</sup> In

1986, he approached the Tobacco Advisory Council, a British consortium of tobacco companies, for funding of research on the *in vitro* genotoxicity effects of cigarette tar.<sup>47</sup> A 1993 memo from Richard Thornton, BAT Smoking Issues Manager, to Barry Bramley, then BAT Chairman, lists Parry as a consultant to BAT at a rate of £500 per day.<sup>46</sup> In 1993, he received £6,000 as a consultant to BAT's SRG.<sup>17</sup> His connections to the industry continued at least until 2001, when he was budgeted by PM to have received the final portion of a three-year grant worth £46,150 for a project studying genotoxicity in carcinogenesis.<sup>48</sup> We were unable to find any documents stating that his financial relationship with the industry ended.

BAT sought to use its connection to Parry to its advantage in dealing with committees regulating tobacco in the UK. In June 1988 Parry was scheduled to present his findings on the mutagenicity of tobacco smoke in relation to tobacco product variables, such as tobacco blend, to the United Kingdom Independent Scientific Committee on Smoking and Health (ISCSH).<sup>49</sup> The ISCSH provided research funding for Parry through the Tobacco Products Research Trust.<sup>49</sup> Reporting on a 1988 visit to Parry's research group, Eian Massey, Group Manager in Biology at BAT, expressed concern that Parry's presentation would be viewed by the ISCSH in "too simplistic a way" and that, in turn, "the ISCSH may choose to emphasize product developments" based on these results.<sup>49</sup> In May 1988, Richard Binns wrote a memo to other scientific advisors at BAT regarding Parry's upcoming presentation:

If some guidance can be achieved by *giving Parry some of your results* then you should do so. *Ask him to ensure that the results would be presented with his own, without specific reference to BAT.*<sup>50</sup> [emphasis added]

Eian Massey subsequently wrote to Parry in a letter dated June 3, 1988:

please find enclosed the chromosome aberration and Ames data on the comparison of smoke condensates...In presenting these along with your data to

the ISCSH, we would be grateful if you would not make any specific reference to BAT.<sup>51</sup>

The documents do not indicate whether Parry took the requested actions.

Parry also took the initiative in proposing projects to tobacco companies. In a memo to INBIFO scientist Wolf Reininghaus on December 19, 1996, Ruth Dempsey, PM Worldwide Scientific Affairs, reported:

I would like to pass on a suggestion from Jim Parry regarding research into p53 and response to the Dennisenko paper on BPDE. Jim suggested that it might be worthwhile [for someone] with the requisite knowledge, to access the Hollstein [IARC] p53 database and perform a full analysis of the information which was so fleetingly referred to in the "Science" article....Would there be anyone at INBIFO who would be interested in doing this?<sup>52</sup>

In April 2001, Parry's unacknowledged relationship with the tobacco industry was brought to the attention of Oxford University Press (OUP) by Curt Harris, M.D. editor of the OUP journal *Carcinogenesis* and co-founder of the IARC p53 database.<sup>53,54</sup> In April 4, 2001, Janet Boullin, Journals Editorial Director of Oxford University press, responded that:

OUP is treating the problem of undisclosed conflict of interest in *Mutagenesis* seriously and a letter went to Professor Parry yesterday... the letter asks that all future items sent to us for publication in *Mutagenesis* should be accompanied by a conflict of interest statement from the authors. I have also asked that the editors themselves each complete a form and return them to me.<sup>54</sup>

In March 2003, Boullin stated:

The conflict of interest statement was first introduced to the journal at the beginning of April 2001. All the editors at that time were asked to sign but not all did so. J. M. Parry stepped down officially as Editor at the end of 2001.



All the current editors have signed the conflict of interest statement and we posted a statement to this effect on the *Mutagenesis* Web site in the second week of March 2002.<sup>55</sup>

According to the *Mutagenesis* website as of November 2003 Parry remains a member of the *Mutagenesis* editorial board. The conflict of interest statement described above states only that the three current “Executive Editors declare that they have no involvements that might raise the question of bias in their roles as Editors of *Mutagenesis*,” but does not refer to conflicts of interest for members of the Editorial Board.<sup>56</sup> As of November, 2003, Parry’s financial ties to major tobacco companies had not been publicly acknowledged by *Mutagenesis* or its publisher, Oxford University Press.

## **DISCUSSION**

Tobacco industry strategies to respond to p53 research involved multiple levels of action. From 1986 forward, tobacco companies such as BAT and PM viewed p53 as a potential area of future regulatory or litigation concern, monitoring and funding p53 research both internally and at external institutions. Through its Scientific Research Group, BAT funded p53-related research at the Marie Curie Institute. This research program was carried out by prominent cancer scientists who were at the time co-editors of the journal *Oncogene*. Further, SRG practices at the time did not require disclosure of funding by grant recipients in publications.

Second, following the 1996 publication of Denissenko et al. in the journal *Science*, tobacco companies planned and carried out research programs to contradict laboratory and epidemiological findings linking tobacco smoke to lung cancer through specific mutations in p53. We have identified two instances where research arguing against the connection between tobacco smoke and patterned p53 mutations was undertaken and published by individuals with undisclosed financial links to tobacco

companies. The analyses of p53 databases published in *Mutagenesis* in 1998 by Krawczak and Cooper and by Paschke in 2000 lacked clear disclosure of competing financial interests for Cooper and Paschke. Both papers were published in *Mutagenesis*, whose editor-in-chief, James M. Parry, has an extensive, undisclosed history of working as a tobacco industry researcher and consultant. Lastly, in 1996, Parry proposed to a tobacco company that analysis of the p53 database be used as a response to the findings of Denissenko et al.

Barnes and Bero (1998) reported that review articles funded by the tobacco industry are 88 times more likely than non-industry studies to conclude that passive smoke is not hazardous to human health.<sup>57</sup> Scollo et al (2003) examined all published studies on the economic effects of smoke-free policies on the hospitality industry and found similar results: 94% of the tobacco industry supported studies concluded a negative economic impact compared to none of the non-industry supported studies.<sup>58</sup> While it is unclear to what extent tobacco companies influenced the publications of Krawczak and Cooper in 1998<sup>33</sup> and Paschke in 2000,<sup>40</sup> the publishers of *Mutagenesis* allowed articles with important legal and regulatory implications to be published with no discussion of conflicts of interest. This practice is not in accord with the voluntary standards concerning conflict-of-interest disclosure for biomedical journals as defined in by the International Committee of Medical Journal Editors, either as defined in 1997,<sup>59</sup> or as subsequently revised in 2001.<sup>60</sup> Since 2001, *Mutagenesis* has begun a practice of publishing statements of conflict of interest from its authors and executive editors. However, no acknowledgment has been made of conflicts of interest on the part of James M. Parry, who remained on the editorial board as of November, 2003.

The tobacco industry has an extensive history of working to undermine science linking smoking to adverse health events.<sup>4</sup> Recent examples include efforts to subvert second-hand smoke (SHS) research conducted in the United States,<sup>61</sup> in Europe at the

International Agency for Research on Cancer (IARC),<sup>62</sup> and in Japan by Takeshi Hirayama.<sup>63,64</sup> In each case, the public stances of tobacco companies sought to maintain controversy surrounding the negative health effects of smoking and SHS<sup>4,65</sup> through a number of actions,<sup>66</sup> including funding scientists to write publications critical of scientific methodology linking SHS to disease,<sup>61,67</sup> sponsorship of research aimed at obscuring the scientific evidence against SHS,<sup>68</sup> and creating an international scientific consultants program to influence public opinion on SHS.<sup>69,70</sup>

Since the 1950's, tobacco industry funding of scientists, consultants and editors often has occurred without acknowledgement of tobacco industry support.<sup>4,61,70,71</sup> In the early 1990's, tobacco companies paid \$156,000 to 13 scientists to write letters to the editor disputing the link between smoking and disease in journals including *JAMA*, *Lancet*, and the *Journal of the National Cancer Institute*.<sup>72</sup> Two tobacco industry consultants, John Todhunter and Gary Flamm, were paid \$25,000 for an article criticizing the Environmental Protection Agency's SHS regulatory review process in the *Journal of Regulatory Toxicology and Pharmacology (JRTP)*, where Flamm was a member of the editorial board.<sup>72</sup>

Gio Gori, associate editor of *JRTP*, has been a paid consultant of the tobacco industry since 1980, and has testified on their behalf regarding smoking and health.<sup>4</sup> He also received money from the industry to write letters disputing the link between SHS and health outcomes in *JAMA*, *Science*, and the *Wall Street Journal*.<sup>73-75</sup> Alvin R. Feinstein of Yale University was the editor of the *Journal of Clinical Epidemiology* and wrote extensively on the inadequacy of statistical methods used to link SHS to deleterious health outcomes.<sup>76</sup> He also criticized the efforts to discredit the tobacco industry by public health advocates. He did not disclose that at the same time he was a tobacco industry consultant and the recipient of "special project" funding overseen by tobacco industry lawyers.<sup>77</sup>

The direct etiological link between tobacco-induced p53 mutations and lung cancer is a potentially powerful tool that can connect a patient's disease to its specific cause. Such a tool could be useful in litigation and regulation concerning tobacco use, as it provides genetic proof of the health effects of tobacco both for the individual smoker and those exposed of second-hand smoke. This use of p53 is demonstrated by a 1997 deposition of Philip T. Cagle, a pathologist at the Baylor College of Medicine.<sup>78</sup> In his testimony for the trial of *Dunn, et al. vs. RJR Nabisco, et al.*, Cagle describes molecular changes in a lung tumor taken from Mildred Wiley, a victim of lung cancer that plaintiffs argued was induced by SHS. Cagle cites Denissenko et al. as evidence that the G to T transversion in codon 157 of p53 found in Wiley's tumor was related to tobacco smoke exposure.

The tobacco companies claim that they have changed their behavior and are now working with the public health community to "support a single, consistent public health message on the role played by cigarette smoking in the development of disease in smokers."<sup>79</sup> Their multifaceted response to p53 research and the unacknowledged potential conflict of interest on the part of individuals involved in publishing responses to contemporary p53 science as recently as 2001 suggests that the industry has not changed its practices. Further, our findings demonstrate a consequence of the lack of uniform adherence to standards for disclosing and assessing conflicts-of-interest in biomedical research and publishing. While the International Committee of Medical Journal Editors has outlined voluntary standards for conflict of interest disclosure,<sup>60</sup> at least one observer has noted that current editorial practices preclude a clear definition of when, as a result of competing interests, "the findings and interpretation of a particular study are rendered unsafe or, at the very least, too uncertain to be a substantive scientific contribution."<sup>80</sup> The extent of tobacco industry involvement in p53 research and the undisclosed conflicts of interest examined here provide an example of tobacco

industry strategy to confound the science linking smoking to adverse health effects.

These activities challenge authors, editors, and users of scientific literature to be vigilant in demanding and maintaining rigorous standards for disclosing and evaluating conflicts of interest.

**Table 1. Tobacco industry's rhetoric related to research on smoking and health.**

<b>1954</b>	<p><u>"A Frank Statement to Cigarette Smokers"</u></p> <ol style="list-style-type: none"> <li>1. That medical research of recent years indicates many possible causes of lung cancer.</li> <li>2. That there is no agreement among the authorities what the cause is.</li> <li>3. That there is no proof that cigarette smoking is one of the causes</li> <li>4. That statistics linking cigarette smoking with the disease could apply with equal force to any one of the many other aspects of modern life...<sup>4</sup></li> </ol>
<b>1996</b>	<p><u>Public Statement by Philip Morris October 18:</u></p> <p>The research is extremely interesting and merits careful review.... We look forward to pursuing this and other research in an attempt to learn more about what mechanisms may be at work and what can be done about it... The research reported today and the media attention being given to it are consistent with our long-held position that the mechanism by which a cell becomes cancerous is a complex process not yet explained.<sup>81</sup></p>
<b>1996</b>	<p><u>Martin Broughton, Chief Executive of BAT Industries, speaking to investors, analysts, and journalists October 30:</u></p> <p>There is still a lack of understanding of the mechanisms of diseases attributed to smoking.... The importance of this Science Magazine study may lie, not least, in the recognition that there are important missing links in the understanding of causation....It may lead to further research ...into the complex process by which a cell becomes cancerous. A process we and others have spent millions in trying to understand for many years now.<sup>82</sup></p>
<b>1996</b>	<p><u>Public Statement by R.J. Reynolds Tobacco Company October 17:</u></p> <p>That BaP will cause a mutation has been known for a long time...The authors themselves describe these findings as a coincidence. The press release's conclusion that these [the authors'] findings are the key to lung cancer is an overstatement.<sup>83</sup></p>

### **Conflict of Interest Statement**

The authors have no conflicts of interest to disclose.

### **Author Contributions**

All authors contributed to the formulation, drafting, and editing of this paper.

Bitton and Neuman located most of the tobacco industry documents.

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