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Using Toxicogenomic Research to Understand Disease Mechanisms: An Asthma Case Study

The February 8, 2007 meeting of the Committee on Emerging Issues and Data on Environmental Contaminants featured a workshop on the application of toxicogenomic research to understanding disease mechanisms, using asthma as a case study. The presenters focused on emerging techniques that allow investigators to track how environmental factors affect certain genes that play a role in asthma—a complex disease with a variety of genetic components and environmental stimuli—and other complex lung diseases.

Dr. David Schwarz, director of the National Institute of Environmental Health Sciences (NIEHS), described the rise in the prevalence, severity and cost of managing asthma and the burden this has placed on the U.S. public. It would be expensive to review all human genes for markers associated with asthma and other illnesses, but recent efforts to identify and focus on clusters of genes (haplotypes)—in what is called the HapMap program—are expected to reduce the cost of this effort 5000-fold. Combining this new knowledge of genetic clusters with a focus on exposures suggests new ways of understanding the causes and biological processes associated with asthma, according to Schwarz. Three subtypes of asthma appear to

be linked to different types of exposure. For example, some asthmatics respond only to ozone in air, house dust mites, or bacteria.

NIEHS researchers have determined that about 120 genes may have a strong impact on asthma and have identified one in particular, the transcription factor “RUNX3”, which appears to be central to asthma development. Meanwhile, other investigators have developed a breed of mouse that is missing this gene. These mice develop an asthma-like condition where their airways get inflamed, further confirming the key role played by this gene.

During his presentation, Schwarz also described research by Drs. Randall Jirtle and Michael Skinner (also presented at the Committee’s February 2006 workshop). This research examines how genetic changes resulting from different diets and other exposures can be inherited via gene modifications (e.g., methylation) that do not change the actual sequence of the gene. These types of changes are referred to as epigenetic changes. (See *Emerging Issues* Newsletter, Issue 10, http://dels.nas.edu/emergingissues/docs/EI_issue10.pdf).

The role of epigenetic changes can be dramati-

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About the Committee...

The Standing Committee on Emerging Issues and Data on Environmental Contaminants (the Standing Committee) was constituted by the National Academies at the request of the National Institute of Environmental Health Sciences to provide a public forum for communication among government, industry, environmental groups, and the academic community about emerging issues in the environmental health sciences. At present, the scope of the Standing Committee is focused on toxicogenomics and its applications in environmental and pharmaceutical safety assessment, risk communication, and public policy.

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Use of Toxicogenomics to Understand Toxic Effects and Improve Risk Assessment: A Workshop

The ability of toxicogenomics to inform risk assessment was explored during a workshop hosted by the National Research Council (NRC) Committee on Emerging Issues and Data on Environmental Contaminants. A previous NRC workshop (<http://books.nap.edu/catalog/11335.html>) addressed a similar topic. The planners of this workshop sought to move beyond general discussions of potential uses of toxicogenomics by focusing on toxicogenomic data and risk assessment questions for specific compounds—benzene and dibutyl phthalate (DBP). At the workshop, U.S. Environmental Protection Agency (EPA) officials described risk assessments for these chemicals, and researchers presented toxicologic and toxicogenomic data on them. Discussions among the participants were intended to address how toxicogenomics can inform risk assessments.

Dibutyl Phthalate (DBP) Case Study

EPA's DBP risk assessment (external peer-review draft) was presented by Robert Benson, EPA Region 8. The risk assessment reviewed studies that identified developmental, testicular, hepatic, and neurologic end points. This review focused on the most sensitive "critical effect"—a decrease in fetal testosterone—which was used to determine the reference dose (RfD).¹ To derive the RfD, the risk assessment included the use of two 10-fold uncertainty factors (to account for interspecies and intraspecies differences). Toxicogenomic data that indicated the reduction of mRNA and enzymes involved in testosterone synthesis provided the key to understanding the mode of action. Dr. Benson also mentioned that these data gave EPA additional confidence that the assessment identified the most biologically relevant end point.

Paul Foster, National Institute of Environmental Health Sciences, described male reproductive and development effects from phthalate exposures. He described testicular dysgenesis syndrome, a series of related adverse effects (reduced sperm production, testicular cancer, and undescended testis) in humans in comparison with the "phthalate syndrome" observed in rats exposed to certain phthalates, such as DBP. DBP reduces fetal testicular testosterone, but the compound does not directly interact with the nuclear androgen receptor that transduces testosterone action. DBP disrupts development of the male reproductive tract (a sequence of events including

hormone, gene expression, and morphologic changes) by perturbing androgen signaling in the fetal testes and by reducing testosterone production. The morphologic effects include a suite of male reproductive tract malformations and sexually dimorphic phenotypes, such as decreased anogenital distance and nipple retention. Other effects, for example, undescended testes and testicular germ cell alterations, also result from DBP exposures but are not related solely to reduced testosterone. Dr. Foster described a range of studies examining morphologic effects following DBP exposure and the doses at which they occur. His presentation emphasized the importance of the timing of exposure during development in inducing these specific effects.

Toxicogenomic data on DBP and related compounds was reviewed by Kevin Gaido, CIIT Centers for Health Research. His presentation, "Gene Expression Profiling Reveals New Targets in Phthalate-Induced Testicular Dysgenesis," evaluated differences in the microarray expression profiles of a series of phthalates with and without effects on male reproductive development to isolate key genes related to toxicity. About 30,000 genes were investigated, and the screening was able to differentiate between the toxic and the nontoxic phthalates differential expression of about 400 genes. Although less than half of the 400 genes had known ontologies (functions in biologic processes), those genes with described functions frequently had roles in lipid, cholesterol, or steroid regulation. Time-course studies in fetal rats were conducted to identify gene changes occurring immediately after DBP exposure. The studies indicated that testosterone production declined almost immediately, but genes involved directly in steroidogenesis were not affected until later time points. Microarray assays identified "immediate early genes" affected by phthalate exposure, and some of these genes were found to respond to DBP at lower phthalate levels than those required to reduce testosterone. However, it is unclear what role these early genes play in testosterone production or phthalate toxicity. Finally, Dr. Gaido described work contrasting the effects of phthalates on rats (fetal testosterone reduction) and the effects on mice (which are unresponsive to fetal testosterone). This research, including microarray assays, confirmed that most genes in mice involved in steroidogenesis and cholesterol synthesis are not affected by phthalates but that DBP exposure does cause a subset of the male reproductive tract malformations. Further research on these animal models will explore the basis of these differential effects.

EPA is conducting a case study of DBP to address

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¹An estimate (uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

Intellectual Property Issues for the Toxicogenomics Field

A workshop on “Intellectual Property Concerns for Toxicogenomics” was held June 29, 2005 in Washington, DC as part of the 13th meeting of the committee on Emerging Issues and Data on Environmental Contaminants. The objective of this workshop was to discuss current and evolving intellectual property (IP) laws and practices as they relate to toxicogenomics—specifically the intended or unintended effects of these laws and processes on the sharing of toxicogenomic data and application development. This workshop was chaired by Lawrence M. Sung, University of Maryland School of Law.

The workshop began with description of the IP protection framework and current issues in IP litigation. Next, technology transfer practices and considerations were described, as were mechanisms for building community datasets and preempting what some view as premature protection of public data.

Workshop participants also discussed what should be patented, how to improve patent quality, and the balance between encouraging development through IP rights and keeping data and technologies that are not near the product development stage, freely available.

Background

Christopher M. Holman, University of Missouri-Kansas City School of Law, opened the workshop with an overview of the current legal framework for the protection of IP. He described how IP can be protected using patents, trade secrets, contracts, and copyright, with patents being the most relevant for toxicogenomics. Patents exclude others from using one’s IP, as lawsuits may be a consequence of patent infringement.

What can be patented? Holman explained how the U.S. Supreme Court has stated that “anything under the sun” that is made by man, useful, inventive (novel and non-obvious), adequately described to the public, and adequately defined is patentable. To obtain a patent, non-obviousness of the invention must be demonstrated. Sung expanded on the importance of the non-obviousness standard and described how some concepts may be obvious based on information in the scientific literature (the “prior art”) even if they are not expressly stated in the scientific literature. Attempts to patent the discovery of a particular mechanism of action could fall into this category. Sung mentioned that patents are sometimes issued for claims that scientists within the field would consider to be obvious or lacking in utility.

Holman explained that although patents are presumed valid when they are issued by the patent office,

their validity can be challenged in the courts. Patents undergo more intensive scrutiny in litigation than during the patent office’s examination procedures, due to the greater resources at the disposal of patent litigants. It is common for issued patents to be found invalid in the courts. That said, patents still hold great power because of the presumption of validity. Reliance on litigation in the courts to invalidate a patent or constrain its application can be frustrating because patent validity is uncertain until years after the original patent is granted, and sometimes not until a case reaches the U.S. Supreme Court, according to Holman.

Patent reform

Sung explained that patent reforms were currently being debated in Congress and that post-grant opposition is the reform most relevant to toxicogenomics. Post-grant opposition provides a mechanism

for scientists to inform the patent office about relevant prior art and other challenges to the validity of a patent. It is intended to address concerns that patent validity is not really known until after the patent is issued.

Meeting the Non-Obvious Standard

Shifting from preventing inappropriate patents to considering what constitutes a non-obvious improvement to the prior art, workshop participants discussed whether and how scientists involved in data mining can add value to the existing data by identifying important patterns and characteristics. While the patentability of genetic sequences or expressed sequence tags (ESTs) has been debated, it is not only the generation of original data that is of intellectual value to the field. John Quackenbush, Harvard School of Public Health, asked when enough added value exists to qualify something as a new invention for the purposes of obtaining a patent. For example, if a scientist uses publicly available gene expression data to determine that a particular gene expression signature predicts a type of toxicity, is that patentable? George Elliott, U.S. Patent and Trademark Office, thought this question was difficult to answer without knowing the specific facts of a case, but Arti K. Rai, Duke University, told the audience that Duke University is filing for patents on expression patterns as diagnostics. Similarly, Mark Porter of Gene Logic Incorporated, noted that Gene Logic had filed for patents on gene expression signatures that appear to predict particular types of toxicity. Elliott

Don't take our word for it, listen for yourself!
Audio files and PowerPoint files of this workshop are available at http://dels.nas.edu/emergingissues/toxicogenomics_meet13.shtml.

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Risk Assessment

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how to use toxicogenomics information most effectively in risk assessment and how to develop a generalizable approach for using toxicogenomics data in risk assessment. Susan Euling, EPA, discussed this case study. Two questions were addressed: (1) Can the toxicogenomic data identify additional pathways affected by DBP which in turn may inform the understanding of modes and mechanisms of action,² and (2) can those data inform the understanding of interspecies differences in modes of action (particularly, whether there is cross-species conservation of steroidogenesis pathways). In the case study, EPA evaluated 29 developmental toxicity studies and 8 toxicogenomic studies (using RT-PCR and microarrays), all of which evaluated male rat tissues after in utero exposure to DBP. Male reproductive toxicity end points were examined to determine if they corroborated presumed or indicated new modes of action. Toxicogenomic data were evaluated to determine the pathways affected by DBP in male tissues and thus, possible modes and mechanisms of toxic action. For the microarray data, genes identified in all studies as being significantly altered were consistent in direction of effect. Dr. Euling also discussed a collaborative effort to reanalyze the raw toxicogenomic data using methods developed by researchers at EPA's STAR Bioinformatics Center at Rutgers University. This reanalysis confirmed the importance of the steroidogenesis pathway but also identified several other pathways affected by DBP exposure. Finally, Dr. Euling commented on research needs for toxicogenomics studies in risk assessment, including time-course studies over critical windows of effect and increased replicates and dose levels.

Benzene Case Study

Exposure to benzene results from smoking and contact with gasoline fumes. Exposures also occur in the occupational environment. Although benzene is a known human carcinogen, there is ongoing debate about the non-cancer risks of low-level exposures. Tracey Woodruff, EPA, discussed the agency's noncancer risk assessment for benzene and the mode of action and endpoints of the cancer risk assessment as they relate to the noncancer assessment. EPA focused its assessment on hematotoxic and immunotoxic effects—specifically, the reduc-

²Here, mode of action is the key event associated with the outcome (for example, decrease in testosterone). Mechanisms of action are the steps and molecular changes that occur following interaction of a chemical with the target site and resulting in the outcome (for example, those changes resulting in decreased testosterone).

tion in lymphocyte count in bone marrow—as these effects are observed at the lowest exposure level. The principal study used by the EPA in the assessment of occupational exposures to benzene focused on effects at the low-dose end of the dose-response curve. Dr. Woodruff described areas in which additional data, possibly generated from toxicogenomic studies, would be useful. Information about the mode of action might improve the understanding of the relative importance of metabolic transformation of benzene. If the same mode of action is identified in cancer and noncancer endpoints, the risk assessments could be harmonized. More information about the shape of the dose-response curve at low doses also would be valuable. Further information on interindividual variability due to genetics, age, or sex could help assess the appropriateness of the 10-fold uncertainty factor.

Qing Lan, National Cancer Institute (NCI), described studies on the effects of benzene. These studies evaluated hematologic changes in Chinese factory workers exposed to benzene at less than 1 part per million (ppm) (the Occupational Safety and Health Administration standard for an 8-hour exposure) compared with unexposed factory workers. Benzene decreased nearly all white-blood-cell (WBC) types. This change may be due to effects on progenitor cells in bone marrow, according to work by the collaborative research group, composed of investigators from the NCI, the University of California, Berkeley and the China Center for Disease Control and Prevention. To better understand the role of specific genes, the research group also explored the impact of factory workers' genetic variability on susceptibility to benzene toxicity. As hypothesized, workers with polymorphisms that may increase myeloperoxidase (MPO) activation of benzene to highly reactive chemicals or decrease NAD(P)H:quinone oxidoreductase (NQO1) detoxification of benzene metabolites were more sensitive to benzene's effects on the WBC count. Other important polymorphisms that affect WBC and progenitor cell counts are genes involved in the regulation of blood cell production.

Next, Nat Rothman, NCI, discussed the implications of the work described by Dr. Lan. It is unclear whether the subtle hematologic effects of benzene are early biomarkers of effect that might result in disease. That can be assessed by quantitatively studying the relationship between those biomarkers and disease. Specifically, the joint research group examined the relationship between decreased WBC count and hematologic malignancy in Chinese workers with low WBC counts who had been diagnosed with benzene poisoning. Dr. Rothman determined that the risk of hematologic malignancy among benzene-exposed workers was increased 42-fold, suggesting that WBC count alteration does predict disease. In addition to studying the impact of genetic polymorphisms on WBC, investigators at UC-Berke-

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Risk Assessment

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ley, in conjunction with the NCI research group, also examined benzene's toxicity pathways by studying gene expression in peripheral blood mononuclear cells (which are mostly lymphocytes). Studies showed that expression of genes involved in cytokine pathways, DNA replication initiation, apoptosis activation, and cell recognition was altered. Some of these genes were selected for further genetic analysis. In closing, Rothman summarized how toxicogenomic tools have been important in elucidating the relationship between benzene exposure and WBC biomarkers at the molecular level. The relationship between these biomarkers and risk should be examined further with prospective cohort studies in the general population to better assess the implications for risk assessment.

Leslie Recio, Integrated Laboratory Systems, Inc., discussed work that he conducted on benzene while at CIIT. The research used toxicogenomics (including gene-expression analyses and transgenic mice) to determine critical pathways of toxicity. Dr. Reico also showed how biomarkers can be developed to bridge human and rodent data. He described the use of human in vitro, rodent in vitro, and rodent in vivo data from progenitor cells to examine the role of the P53 tumor suppressor pathway in benzene toxicity. Transgenic mice possessing one P53 allele had increased prevalence of tumors and chromosomal aberrations following benzene exposure in comparison to normal mice (possessing both P53 alleles). Gene expression was also analyzed in the bone marrow of the normal and transgenic mice to determine other molecular pathways involved. Two genes (P21 and Wig 1) regulated by the P53 pathway were induced by benzene exposure, although to a lesser degree in the transgenic mice. The involvement of these genes, and especially their decreased involvement in the transgenic mice, adds to the evidence that the P53 pathway is important in benzene toxicity.

Using P21 and micronuclei (a type of chromosomal damage) as a biomarker of toxicity, Dr. Reico further explored benzene toxicity pathways by assessing the impact of mutations in various genes (CYP2E1, NQO1, mEH, DNA-PKC, and P53). This biomarker

is also measurable in human cells, creating a useful bridge between animal and human studies. The assays suggest that human and mouse progenitor cells are similarly sensitive to benzene's metabolite 1,4-benzoquinone.

Workshop Discussions

Breakout groups were formed to discuss and address a range of questions on the role of toxicogenomics in understanding the toxicity and improving the risk assessments of the case-study chemicals. The breakout-group questions centered on the use of toxicogenomics to elucidate a chemical's mechanism of toxicity, understand differences in susceptibility, determine critical windows of exposure in human development, and improve risk assessment. The resulting breakout-session summaries are on the standing committee's web site and provide a snapshot of the discussions at the workshop.

Linda Greer closed the workshop by reminding participants of the challenges risk assessors face in making decisions without all the data they would like to have. She commented that toxicogenomics will be useful, and probably faster than standard bioassays, in hypothesizing about and establishing the critical steps between exposure and toxicity. Although there will be challenges in assessing which genomic effects are adverse events, and the challenges will be magnified because so many effects can be observed in toxicogenomics, the challenges will not be new to researchers. Dr. Greer is optimistic that toxicogenomics will help improve understanding of the impact of timing of exposures. She asked whether gene-expression changes are now applicable to screening chemicals with little or no toxicity information. She pointed out that the limitations of the current approach of using structure-activity relationships for screening should be considered when assessing whether toxicogenomics would be an improvement or valuable complement for screening.

Finally Dr. Greer commented that uncertainty factors (UFs) used by risk assessors to accommodate gaps in data, including those for interspecies and interspecies variability, may soon be informed by toxicogenomic results.

Recent Workshop Summary

Validation of Toxicogenomic Technologies: A Workshop Summary

Based on a workshop held in July 2005, this report explores current validation strategies and associated issues, and then examined examples of validation approaches used in published studies where microarray technologies were used to evaluate a chemical's mode of action. This report is available free online at http://dels.nas.edu/emergingissues/workshop_reports.shtml.



Asthma Case Study

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cally illustrated by genetically identical mice who have different colored coats depending on whether certain genes have been methylated. Epigenetic modification of the mice genes correlates with the folic acid in their diets; these epigenetic changes are heritable and passed on to later generations. Epigenetic changes may also be responsible for identical human twins sharing many more similarities early in life than they do in their 50s and 60s as a result of differences in their environmental exposures, diets and diseases, Schwarz said. Understanding how environmentally-triggered genetic changes can lead to inheritance of an adverse health effect is of great interest to public health authorities.

NIEHS is rapidly building research capacity in toxicogenomics and epigenetics, by funding scientists inside and outside NIEHS to explore ways to inform our understanding of the connections be-

tween environmental factors, genetics, heritability and disease. In addition, NIEHS has launched a program that will allow basic researchers to explore questions in a new clinical research facility at NIEHS and begin the challenging task of expanding these techniques to large populations.

These programs will focus on four major areas that include: 1) developing personalized environmental sensors for tracking individual and area exposures; 2) seeking out and identifying biological evidence (“fingerprints”) of disease processes; 3) using these fingerprints to develop field-deployable devices for population research; and 4) merging environmental measures and biological response indicators with genetic studies to understand the development of disease.

Generating new knowledge using these emerging tools will increase our understanding of the complicated triggers of asthma and other environmentally-related diseases, allow insight into the basic biological processes underlying them, and suggest new ways to reduce disease burdens.

Intellectual Property Issues for the Toxicogenomics Field

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pointed out that the patent office welcomes more information from the scientific community about gene expression signatures because such information helps examiners stay current with the changing state of the art. Educating examiners about new science is recommended in the recent NRC report, *Reaping the Benefits of Genomic and Proteomic Research: Intellectual Property Rights, Innovation and Public Health*.

Technology Transfer

Brian R. Stanton of the National Institutes of Health (NIH), Office of Technology Transfer discussed the value of transferring technology, and the Bayh-Dole Act that allows federal grantees to essentially own and license their inventions. Technology transfer is the movement of information, materials, or know-how from one party to another, and may or may not involve patents. According to Stanton patents enable exclusive rights to be provided to entities that can invest the funds to develop patented technologies and information, promoting development of useful products from government-funded research. Stanton pointed out that a technology transfer policy can be structured to grant exclusivity to some while allowing others to use the information and technologies for free if they are not using it for product development. For genomic inventions, the NIH published *Best Practices for the Licensing of Genomic Inventions*.

Community Resource Projects and Placing Information in the Public Domain

Claire Driscoll, NIH, described community resource projects. As mentioned above, not all issued patents are considered appropriate by the scientists who understand the technologies and underlying data. At least one speaker noted that some entities try to obtain patents too early in the scientific discovery process and inappropriately restrict use of information by other scientists. Driscoll described placing data into the public domain as quickly as possible as a means of providing scientists a “level playing field” to prevent restrictions from being placed on uses of the data.

Arti Rai and Driscoll explained that rapidly releasing data into the public domain can have a big impact because it creates prior art. Rapid release is a defensive strategy for preventing others from patenting what is referred to as “precompetitive” data—data that is not close to the product development stage. Along these lines, Driscoll discussed NIH community resource projects that are intended to produce data that are needed by scientific communities and place data into the public domain where its use requires agreement not to impede the research of others. Funding is an incentive for grantees to participate in such community resource projects. Mark Rothstein, University of Louisville, noted that the government may need to play a primary role in generating and releasing data into the public domain, as the government is uniquely situated, controls funds,

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Intellectual Property Issues

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and can avoid conflicts of interest. Going beyond just putting data into the public domain, Stanton suggested that scientists also may want to consider describing obvious next steps and conclusions for their research when publishing results, to establish concepts as prior art.

In addition to licensing (exclusively or non-exclusively) information and preemptively placing information into the public domain, the group discussed other mechanisms for sharing toxicogenomics data. Specifically, William Mattes, the Critical Path Institute (C-PATH), and Edward M. Yoshida, Merck & Co, Inc., discussed the C-PATH collaboration in which pharmaceutical companies are sharing safety data with each other and the U.S. Food and Drug Administration. The goal of this project is to identify biomarkers that can be used to predict safety concerns in pharmaceuticals. Although the companies are limiting the data release to each other, rather than releasing the data into the public domain, Yoshida said it was significant that companies participating in this consortium have determined that there is more potential value in making the data available to the consortium than in keeping the data private for competitive advantage.

Audience members asked about balancing the placement of data in the public domain (where it cannot be patented) vs. encouraging patents so that

products of public-health value are developed, the original goal of the Bayh-Dole legislation. While Driscoll's efforts focus on the generation of public data, she and others emphasized that there is an appropriate time to patent data and technologies, when the information is closely linked with disease or could be developed into a commercial product.

Assessing Impact of Intellectual Property Efforts

The discussion also raised questions about how the public-health impact of federally-funded research can be measured to assess how universities and other entities are promoting the development of research findings into benefits for public health. Todd Sherer, Emory University, explained that this is typically measured by noting licensing revenue received by universities per research dollar. He does not think this is the best metric, and technology transfer offices like Emory University are exploring alternative metrics to assess impact.

In closing, this workshop explored IP mechanisms and database management policies that enable the sharing of toxicogenomics data and applications. Many detailed discussions could not be captured in this summary, but they are accessible via the audio and PowerPoint files on the committee's website <http://dels.nas.edu/emergingissues/>. In addition, the National Academies report *Reaping the Benefits of Genomic and Proteomic Research: Intellectual Property Rights, Innovation and Public Health* can be obtained at www.nap.edu.

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