recombination induction in mammalian cells in vitro (possibly even in animals *in vivo*), thus enabling a more mechanism-based risk assessment as a follow-up in place of conducting the conventional secondary genotoxicity tests that may have questionable relevance to evaluating carcinogenic risks. Recent data from our laboratories and literature provide the evidence for differentiating mechanisms of genotoxic and carcinogenic mechanisms via toxicogenomics [8, 10-12] and this approach is also pursued by EPA, NTP and by Carcinogenomic initiative in Europe. The major advantage of toxicogenomics is in providing mechanistic information applicable to risk assessment and assessing carcinogenic agents that are not genotoxic. The genomic approach would make an important step in developing the application of systems biology for use in risk estimation including development of relevant biomarkers.

PROJECT PROPOSAL

Topic: Genomic Analysis of Cancer Signaling (Hedgehog, Notch, Wnt) Important in Stem Cell Maintenance and Renewal as a Predictor of Cancer Risk Following *In Vivo* and *In Vitro* Exposure to Environmental Carcinogens

Submitted by: Donald Delker, Ph.D. (NHEERL), David Dix, Ph.D. (NCCT), Richard Judson, Ph.D. (NCCT), and William Ward, Ph.D. (NHEERL), U.S. Environmental Protection Agency, Durham, NC; Brian Howard, Ph.D. and Steffen Heber, Ph.D., North Carolina State University, Raleigh, NC

The identification of common key events in the development of cancer following environmental chemical exposure is of utmost importance to the regulatory community. Use of common key events in the risk assessment process provides a stronger framework for making accurate comparisons among chemical classes as well as facilitates the estimation of cumulative risk. Measurement of permanent alterations to cellular DNA have for many years been the standard for estimating cancer risk to environmental chemicals. However, not all chemical carcinogens damage DNA and the prediction of carcinogenicity of non-genotoxic chemicals has been problematic. Because cancer is considered a disease of clonally expanded de-differentiated cells with stem cell like properties, the genomic analysis of signaling pathways involved in stem cell maintenance and renewal *in vivo* might provide a useful alternative for estimating cancer risk following short term environmental chemical exposure. Several well studied signaling pathways important in stem cell maintenance and renewal are commonly deregulated during carcinogenesis including Hedgehog, Notch, and Wnt pathways. These pathways are transiently activated to promote stem cell self-renewal in normal tissues whereas continuous activation is associated with the development of many types of human cancer. Therefore, the genomic characterization of alterations in these pathways in response to environmental chemicals could provide a means for which researchers might predict the potential carcinogenicity of chemical agents after short term *in vivo* exposures (<30 days). Previous work from our laboratory and others have identified alterations in the Wnt signaling pathway in target tissues as early as two weeks following chemical carcinogen exposure while little or no change was observed in this pathway following non-carcinogen exposure (Glatt et al. 2005 and Ward et al. 2006). The observed alterations in Wnt signaling gene transcripts were also dose-dependent and correlated well with the relative potency of the chemical carcinogen. In this proposal we describe research objectives that will facilitate the genomic characterization of alterations in these signaling pathways as predictors of the carcinogenic potential of environmental chemicals.

We propose research initiatives in three main areas:

1. Mine existing databases of gene expression profiles generated *in vivo* by known chemical carcinogens or non-carcinogens for evaluation of Hedgehog, Notch, and Wnt pathway activation.
2. Mine *in vitro* datasets generated from the EPA ToxCast^{TM} screening and prioritization program for identifying chemicals that activate these cancer pathways.
3. Categorize genes acting in concert in each signaling pathway with respect to concurrent up-regulation or down-regulation for estimation of gene clusters that are predictive of disease outcome.

Potential Impacts of This Project are as follows:

1. Provide an alternative means whereby environmental chemicals might be classified as carcinogenic or non-carcinogenic based on their sustained activation of Hedgehog, Notch, and/or Wnt pathway activation critical to the expansion of deregulated stem cells.
2. Provide important information regarding gene clusters that are transcriptionally co-regulated by carcinogen exposure that can be used as weight of evidence in the cancer risk assessment process.

To our knowledge, this issue is not being addressed by any other organization or forum.

References:

1. W.O. Ward, D.A. Delker, J.W. Allen, D.C. Wolf, S. Hester, S-F. Thai, and S. Nesnow (2006) Toxicol Pathol, 34:863-878.
2. C.M. Glatt, M. Ouyang, W. Welsh, J.W. Green, J. O'Connor, S.R. Frame, N.E. Everds, and D.A. Delker (2005) Environ Health Perspect, 113:1354-1361.

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HESI Application of Genomics to Mechanism-Based Risk Assessment
New Topic Selection Form

Name: _____ **Affiliation:** _____

Phone: _____ **Email:** _____

Background: In mid-2007, the HESI Committee on the Application of Genomics to Mechanism-based Risk Assessment issued an open call for proposals for new research topics for 2008. These proposals were to consider important areas in need of a focused multisector, collaborative effort to be undertaken by the HESI Genomics Committee.

The new activity that is adopted may build directly upon work already conducted or may take the Committee in a new direction. The Committee is eager to adopt an exciting and impactful new program and as such is open to proposals that may differ in focus or execution from those activities previously undertaken. The strong multi-sector infrastructure and proven track record of the Committee make it a valuable resource for addressing new areas in genomics. The Committee is open to considering a broad range of projects/activities including (but not limited to) developing white papers, organizing workshops/continuing education courses, synergizing pre-competitive data and concepts, and designing and executing novel experimental programs.

This form will be used to solicit feedback on these proposals. You may rank the activities even if you are not currently a member of the HESI Genomics Committee!

Explanation of Scoring:

Scoring reflects you/your organization's current interest level. It does not necessarily represent a commitment to participate should the topic go forward.

Level of interest:	**LOW**		**MEDIUM**		**HIGH**
Priority Score:	**0**	**1**	**2**	**3**	**4**

HIGH = I / my organization would be willing to commit resources (i.e., "sweat equity" and/or financial support) for this project.

MEDIUM = My organization and/or I may be willing to commit resources to support this project.

LOW = My organization is not likely to commit resources for this project.

New Topics: The following topics were presented for consideration at the November 7-8, 2007, meeting of the HESI Committee on Genomics (NOTE: Presentations will be available on the HESI website). Please indicate your level of enthusiasm for each topic by assigning a priority score (0, 1, 2, 3, 4).

Score	Topics for consideration in 2008 (continued on next page)
_____	Moving from Rodent to Non-rodent Expression Profiling in Preclinical Safety Assessment. Presented by Dr. J. Stevens, Lilly
_____	Practical Experiences in Applying Toxicogenomics to Risk Assessment: A Workshop/Case-Study Approach. Presented by Dr. C. Afshari, Amgen
_____	Predictive Cardiovascular Risk Assessment by Genomic Methods. Presented by Dr. B. Berridge, GSK
_____	Embryonic Model Systems as a Surrogate Assay for Proliferative Potential of Test Compounds. Presented by Dr. K. Brannen, BMS
_____	Validation of a New *In Vitro* Testing Paradigm for Detecting Chemical Carcinogenicity and Development of Biomarkers for Chemical Carcinogenesis Applicable to Risk Assessment. Presented by Dr. J. Aubrecht, Pfizer
_____	Genomic Analysis of Cancer Signaling (Hedgehog, Notch, Wnt) Important in Stem Cell Maintenance and Renewal as a Predictor of Cancer Risk Following *In vivo* and *In Vitro* Exposure to Environmental Carcinogens. Presented by Dr. D. Delker, U.S. EPA

Past experience with the HESI Application of Genomics to Mechanism-Based Risk Assessment Committee indicates that a topic with the best chance of developing into a successful program / project possesses some or all of the following characteristics:

- The topic identifies an issue with the potential to be resolved.
- The topic presents an issue that is best resolved through partnerships among scientists from government, academia and industry.
- The topic provides a foundation for developing sound science for emerging regulatory and public health issues.
- The topic provides an opportunity to make significant contributions on an international level.

If you have questions or comments about the specific topics being considered in 2007 and/or the HESI Application of Genomics to Mechanism-Based Risk Assessment Committee in general, please contact:

Syril Pettit, HESI Senior Scientific Program Manager
PH: 202-659-3306 (ext 189)
Email: spettit@hesiglobal.org

Please complete the front page of this form and return to Ms. Regina Graham (fax: 202-659-3617) by Friday, November 16, 2007.

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HESI Technical Committee on Genomics in Mechanism-Based Risk Assessment

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Taiho Pharmaceutical Company, Ltd.
Tanabe Seiyaku Company, Ltd.

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HESI Technical Committee on Genomics in Mechanism-Based Risk Assessment
Plenary Meeting
November 7-8, 2007

Anticipated Attendees

Afshari, Cindy
Director
Amgen Inc.

Aubrecht, Jiri
Senior Research Scientist
Pfizer Global Research & Development

Augustine, Karen *(via webcast)*
Research Fellow Reproductive Toxicology
Bristol Myers Squibb

Bauer, Yasmina
Lab Head
Actelion Molecular Biology

Becker, Richard
Sr. Toxicologist
American Chemistry Council

Berridge, Brian
Director, Regulatory & Discovery Pathology
GlaxoSmithKline

Birchfield, Norman
U.S. Environmental Protection Agency

Bjeldanes, Erik *(via webcast)*
Product Manager
Agilent Technologies

Boedigheimer, Michael
Amgen Inc.

Boland, Joseph
Director - Product Development
Gene Logic Inc.

Brannen, Kimberly
Research Investigator
Bristol-Myers Squibb

Charlap, Jeff *(via webcast)*
Bristol-Myers Squibb

Chen, Tao
U.S. Food & Drug Administration

Ciaccio, Paul
Principle Scientist II
AstraZeneca Pharmaceuticals

Claude, Jean-Roger
Professor
AFSSAPS

Claude, Nancy
Director of Toxicology
SERVIER Group

Corton, Chris
U.S. Environmental Protection Agency

Currie, Richard *(via webcast)*
Syngenta

Dearfield, Kerry
Scientific Advisor for Risk Assessment
U.S. Department of Agriculture

Delker, Don
Acting Branch Chief
U.S. Environmental Protection Agency

Dominique, Masset *(via webcast)*
Head of Toxicology Unit
French Safety Health Product Agency
(AFSSAPS)

Dunn II, Robert
Scientific Director
Amgen Inc

Elayan, Ikram
Pharm/Tox Reviewer
U.S. Food & Drug Administration

Elespuru, Rosalie
U.S. Food & Drug Administration

Ellinger-Ziegelbauer, Heidrun
Bayer HealthCare AG

Engelward, Bevin
Association Professor
Massachusetts Institute of Technology

Eshete, Feleke
Pharmacologist
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Falls, Greg
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Fitzpatrick, Julie
Staff Scientist
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Fostel, Jennifer
National Institute of Environmental Health
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Frueh, Felix
U.S. Food and Drug Administration

Fuscoe, James
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Toxicology
U.S. Food & Drug Administration

Gazin, Vincent
AFSSAPS (French Regulatory Agency)

Gollapudi, B. Bhaskar
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The Dow Chemical Company

Hamadeh, Hisham
Amgen Inc

Hanig, Joseph
Associate Director for Research Policy
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Harlow, Patricia
Pharmacologist
U.S. Food & Drug Administration

Harrouk, Wafa *(via webcast)*
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Herman, Eugene
U.S. Food & Drug Administration

Hester, Susan
U.S. Environmental Protection Agency

Hoflack, Jean-Christophe
F Hoffmann - La Roche AG

Hyduke, Daniel
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Idahosa, Ehi *(via webcast)*
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Kanno, Jun
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Kanwal, Charu *(via webcast)*
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Lawton, Michael
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Li, Henghong
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Lyon, Jonathan
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Pettit, Syril
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Snyder, Ronald *(via webcast)*
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Thurmond, Scott
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Vickers, Alison
Allergan Inc.

Vidal, Jean-Marc
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Ward, William
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Weis, Brenda
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National Institute of Environmental Health Sciences

Wolfinger, Russell
Director
SAS Institute, Inc.

HESI Technical Committee on Genomics in Mechanism-Based Risk Assessment

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International Life Sciences Institute Code of Ethics and Organizational Standards of Conduct

Statement of Purpose

The goal of the International Life Sciences Institute's (ILSI) Code of Ethics and Organizational Standards of Conduct is to assure that ILSI members, scientific advisors, consultants, other key stakeholders in ILSI scientific activities, and users of ILSI's scientific work products are aware of the ethical principles guiding the organization's structure and the tenets behind the organization's adherence to rigorous, peer-reviewed scientific investigation and scientifically balanced, evidence-based work products.

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