

U.S. Environmental Protection Agency
Science Advisory Board
Looking to the Future
Renaissance Mayflower, 1127 Connecticut Avenue NW
Washington DC 20036
October 27, 2008

Abstracts and biosketches for speakers

Sustainable Paths to a Biofuel-Powered Transportation Sector: The Role of Innovation and Invention

Bruce Dale and Lee Lynd

Prior to the first industrial revolution, people were scarce and resources were plentiful. Now confronted with the opposite circumstance, humanity must mount a second industrial revolution featuring population stabilization, increased energy utilization efficiency, and adoption of new renewable and sustainable energy supply technologies. At present there are widely disparate evaluations of the potential of biofuels to play an important role in the transition to a sustainable world, and there is a pressing need to resolve this disparity. This presentation will address key issues associated with the feasibility and desirability of cellulosic biofuels used on a large scale - including energy balance, economic feasibility, land competition, carbon debts, and resource availability - with a focus on two questions: 1) Understanding the reasons underlying the different conclusions reached by different analysts, 2) identifying paths by which large-scale biofuels use would be feasible and desirable. Innovation and invention will play key roles in the development of a large scale biofuel industry, as they have in the development of the petroleum refining industry. The talk will close by commenting on the general applicability of lessons learned from the biofuel example.

Background Reading

- Bruce E. Dale. 2008. Biofuels: Thinking Clearly about the Issues. *Journal of Agricultural & Food Chemistry* 56:3885–3891.
- Joseph E. Carolan, Satish V. Joshi, and Bruce E. Dale. 2007. Technical and Financial Feasibility Analysis of Distributed Bioprocessing Using Regional Biomass Pre-Processing Centers. *Journal of Agricultural & Food Industrial Organization* 5 (SPECIAL ISSUE: Explorations in Biofuels Economics, Policy, and History):Article 10, pp 1-27.
- Seungdo Kim, Bruce E. Dale. 2005. Life cycle assessment of various cropping systems utilized for producing biofuels: Bioethanol and biodiesel. *Biomass and Bioenergy* 29:426–439.

Dale, Bruce

Michigan State University

Professor Dale is Professor of Chemical Engineering and former Chair of the Department of Chemical Engineering and Materials Science at Michigan State University. He received his bachelors degree (summa cum laude) in chemical engineering from the University of Arizona (Tucson) in 1976 and the masters degree from that same university in 1976. Dr. Dale then studied under Professor George T. Tsao at Purdue University, receiving his Ph. D. degree in 1979. Dr. Dale's first academic position was in the Department of Agricultural and Chemical Engineering at Colorado State University, where he rose to the rank of Professor in 1988. In that same year he joined Texas A&M University where he became Professor of Chemical Engineering and Professor of Agricultural Engineering. Dr. Dale also directed two large interdisciplinary research centers at Texas A&M: the Engineering Biosciences Research Center and the Food Protein Research and Development Center. In 1996 Dr. Dale became Professor and Chair of the Department of Chemical Engineering at Michigan State University, where he also holds an appointment in the Michigan Agricultural Experiment Station. Also in 1996 he won the Charles D. Scott Award for contributions to the use of biotechnology to produce fuels, chemical and other industrial products from renewable plant resources. In 2001 he stepped down as Chair to return to full time research and teaching.

Professor Dale's research and professional interests lie at the intersection of chemical engineering and the life sciences. Specifically, he is interested in the environmentally sustainable conversion of plant matter to industrial products- fuels, chemicals and materials- while meeting human and animal needs for food and feed. He led a National Research Council report entitled "Biobased Industrial Products: Research and Commercialization Priorities" which was published in May 2000.

Lynd, Lee

Dartmouth

Dr. Lee Rybeck Lynd is a Professor of Engineering and an Adjunct Professor of Biology at Dartmouth College, Professor Extraordinary of Microbiology at the University of Stellenbosch, South Africa, and cofounder, Director and Chief Scientific Officer of Mascoma Corporation, a biomass energy start-up. He has been a member of the Dartmouth Faculty since 1987. Dr. Lynd holds a B.S. degree in biology from Bates College, an M.S. degree in bacteriology from the University of Wisconsin, and masters and doctoral degrees in engineering from Dartmouth. Professor Lynd is an expert on utilization of plant biomass for production of energy. His contributions span the science, technology, and policy domains and include leading research on fundamental and biotechnological aspects of microbial cellulose utilization. He has led an active research group addressing these issues over the last two decades, authoring over 75 archival papers, book chapters, and reviews as well as 11 patents and patent applications. A frequently invited presenter on technical and strategic aspects of biomass energy, Professor Lynd has three times testified before the United States Senate and was a speaker at the 2007 Nobel Conference. In 2007 Dr. Lynd was the inaugural recipient of the Lemelson-MIT Sustainability prize for inventions and innovations that enhance economic opportunity and community well-being while protecting and restoring the natural environment. In 2005 he received the Charles D. Scott Award for distinguished contributions to the field of biotechnology for fuels and chemicals. Professional activities include: co-leader, the Role of Biomass in America's Energy Future project; Focus Area Leader for Biomass Deconstruction and Conversion, DOE Bioenergy Science Center; Biofuels industry representative, committee advisory to the Executive Office of President Clinton on Reducing Greenhouse Gas Emissions from Personal Vehicles; Editorial Board Member, Biotechnology and Bioengineering; and Manager, Link Energy Fellowship Program.

EPA-SAB October 27 Meeting Abstract

Kenneth G. Cassman¹, University of Nebraska

Rapid economic growth in the world's most populous countries, political instability in regions with greatest petroleum supplies, greater consumption than discovery of new petroleum reserves, and an abrupt rise in energy prices have driven global expansion of biofuel production from sugar, starch, and oil seed crops. As a result, a 50-year trend of declining real prices for the world's major crop commodities has been reversed, and we are in a demand-driven commodity market created by the convergence of energy and agriculture. Current rates of gain in crop yields are not adequate to meet this increased demand without a large expansion of crop area at the expense of rainforests, wetlands, and grassland savannah. Therefore, a large acceleration in the rate of crop yield gains on existing farm land is required, both here in the U.S. and globally, to ensure the environmental and economic sustainability of biofuel systems. But achieving yield gains while also reducing the negative environmental impacts of high-yield agriculture on soil and water quality and greenhouse gas (GHG) emissions has been an elusive goal. It requires a process of "ecological intensification" that involves interdisciplinary, systems-oriented research for which there has been little funding support from USDA, DOE, and NSF. Instead, most of our public-sector agricultural research portfolio has focused on measuring and understanding the environmental impact of agriculture without regard to crop productivity and on genetic crop improvement through biotechnology, while the private sector has emphasized productivity with little regard for environmental impact. To ensure the long-term viability of biofuel systems, these trends must change, and change quickly. A substantial increase in research investment is needed that is focused tightly on the *dual goals* of accelerating the rate of gain in crop yields and doing so in a manner that decreases the environmental footprint of agriculture. Although development of cellulosic (non-food crop) biofuels will reduce the competition between food and biofuels, large-scale commercialization of cellulosic biofuels (+4 billion L/yr annual production) is at least 7-10 years off. In the meantime, food-crop biofuels production capacity will continue to build out under present policies, and the environmental challenges embodied in this expansion must be addressed proactively.

Citations:

Cassman, K.G. 1999. Ecological intensification of cereal production systems: Yield potential, soil quality, and precision agriculture. *Proc. National Acad. Sci. (USA)* 96: 5952-5959.

Cassman K.G. and Liska A. J. 2007. Food and fuel for all: Realistic or foolish? *Biofuels Bioprod. Biorefin.* 1:18-23. <http://www3.interscience.wiley.com/cgi-bin/fulltext/114283521/PDFSTART>

Cassman KG, Dobermann A, Walters DT, and Yang H. 2003. Meeting cereal demand while protecting natural resources and improving environmental quality. *Ann Rev Environ Resour* 28: 315-358.

Council for Agricultural Science and Technology (CAST). 2006. Convergence of Agriculture and Energy: Implications for Research and Policy. CAST Commentary QTA 2006-3. CAST, Ames, Iowa.

Liska AJ, Yang HS, Bremer V, Walters WT, Kenney D, Tracy P, Erickson G, Koelsch R, Klopfenstein T, Cassman KG. 2007. Biofuel Energy Systems Simulator: LifeCycle Energy and Emissions Analysis Model for Corn-Ethanol Biofuel (ver. 1.0, 2007). University of Nebraska, www.bess.unl.edu.

Liska A. and Cassman KG. 2008. Towards standardization of life-cycle assessment metrics for biofuels: Greenhouse gas emissions mitigation and net energy yield. *J. Biobased Materials and Bioenergy* 2:187-203.

Naylor RL, Liska AJ, Burke MB, Falcon WP, Gaskell J, Rozelle SD, and Cassman KG. 2007. The Ripple Effect: Biofuels, Food Security, and the Environment. *Environment*. 49: 30-4.

¹ Heuermann Professor of Agronomy, and Director—Nebraska Center for Energy Sciences Research

Cassman, Kenneth G.

University of Nebraska

Dr. Kenneth G. Cassman currently serves as Director of the Nebraska Center for Energy Sciences, and is the B. Keith and Norma F. Heuermann Professor of Agronomy at the University of Nebraska. He received a BSc degree in biology from the University of California--San Diego (1975) and a PhD in Agronomy and Soil Science from the University of Hawaii (1979). His expertise is centered within the disciplines of soil science, agroecology, and plant ecophysiology. Research activities have focused on: (1) plant nutrition, root ecophysiology, soil fertility and nutrient cycling to improve fertilizer efficiency and to reduce negative effects on environmental quality; (2) crop yield potential, soil carbon sequestration, and greenhouse gas emissions in maize-based cropping systems of the USA Corn Belt; (3) the long-term sustainability of intensive crop production systems and global food security. Recently he has focused attention on the role of agriculture in contributing to renewable energy supplies through production of ethanol and biodiesel fuels from cereal, oilseed, and sugar crops and the environmental impact of expanded biofuel production from agricultural crops.

He served on the California Task Force on Sustainable Agriculture (1985-86), the Board of Directors for the Nebraska Crop Improvement Association (1996-2004), the Nebraska Crop Advisors Executive Board (1996-2002), the Council on Agriculture Science and Technology (CAST) Task Force on Animal Agriculture and Global Food Security (1996-99), Chair of the Nebraska Environmental Livestock Environmental Quality Task force (1998-2001), and on the Science and Policy Committee for the 3rd International Nitrogen Conference (2003-04). In addition, he has been active as an external program reviewer for a number of scientific institutions, including: CIMMYT (1997 and 2000), IITA (2001), ICRISAT (2008), the graduate program at the Wageningen Agricultural University in the Netherlands (1998), and the Department of Soil Science at the University of Wisconsin. Professor Cassman has been elected Fellow of the American Association for the Advancement of Science, the Agronomy Association of America, the Soil Science Society of America, and the Crop Science Society of America, and has received a number of national and international awards for research excellence. His research has been widely published in seminal journals.

Lifecycle Environmental and Health Costs and Benefits of Fossil and Renewable Fuels

by David Tilman, University of Minnesota*

Negative environmental and health consequences of fossil fuels and concerns about petroleum supplies have spurred the search for renewable transportation biofuels. To be a viable alternative, a biofuel should provide, in total across its full lifecycle, net energy gains and environmental benefits, be economically competitive, and be producible in large quantities without reducing food supplies. We use these criteria to evaluate, through life-cycle accounting, ethanol from corn grain, biodiesel from soybeans and cellulosic biofuels derived from alternative crops transformed into biofuels via either biochemical or thermochemical processes.

Corn ethanol yields 25% more energy than the energy invested in its production, whereas soybean biodiesel yields 93% more. Compared with ethanol, biodiesel releases just 1.0%, 8.3%, and 13% of the agricultural nitrogen, phosphorus, and pesticide pollutants, respectively, per net energy gain. Relative to the fossil fuels they displace, greenhouse gas emissions are reduced 12% by the production and combustion of ethanol and 41% by biodiesel. Biodiesel also releases less air pollutants per net energy gain than ethanol. These advantages of biodiesel over ethanol come from lower agricultural inputs and more efficient conversion of feedstocks to fuel. Neither corn ethanol nor soybean biodiesel can replace much petroleum without greatly impacting food supplies. Even dedicating the full 2005 U.S. corn and soybean crops to biofuels would meet only 12% of gasoline demand and 6% of diesel demand. Because of fossil energy needed to produce these crops and convert them to biofuels, the net energy gain from converting all US corn and soybeans to biofuels for each would only be 3% of current gasoline and diesel energy use.

Whether or not a given biofuel offers carbon savings and other environmental benefits relative to a fossil fuel depends on how the biomass crop is produced. Converting rainforests, peatlands, savannas, or grasslands to cropland to produce food-based biofuels in Brazil, Southeast Asia, and the United States creates a 'biofuel carbon debt' by releasing 17 to 420 times more CO₂ than the annual greenhouse gas (GHG) reductions these biofuels provide by displacing fossil fuels. In contrast, biofuels made from waste biomass or from biomass grown on abandoned agricultural lands planted with perennials incur little or no carbon debt and offer immediate and sustained GHG advantages. If grown with low inputs of agrichemicals, they also offer potentially great increases in the quality of surface and ground waters.

Fine particulate matter (PM_{2.5}) emissions from fossil fuels and biofuels, which can potentially impose large health costs on society, are another environmental concern that must be used in evaluating alternative energy sources. By using the EPA's RSM and BenMAP analytical tools on a county-by-county basis for the US, we quantified and then monetized the lifecycle climate and health effects of greenhouse gas (GHG) and fine particulate matter (PM_{2.5}) emissions from gasoline, corn ethanol, and cellulosic ethanol, we found that, for each billion ethanol-equivalent gallons of fuel produced and combusted in the US, climate and health costs are about \$500 million for gasoline, about \$600–1000 million for corn ethanol depending on biorefinery heat source (natural gas, coal, or corn stover), but only \$100–200 million for cellulosic ethanol depending on feedstock (corn stover, switchgrass, prairie biomass, or *Miscanthus*). Moreover, a spatially-explicit lifecycle analysis that tracked PM_{2.5} emissions and exposure relative to US population shows regional shifts in health costs dependent upon fuel production systems. Because climate and PM_{2.5} health costs are roughly equal, the total monetized benefit of shifting from gasoline to properly-produced cellulosic biofuels is twice as large as when only GHG benefits are considered.

*Based on collaborative projects with J. Hill, S. Polasky, E. Nelson, H. Huo, L. Ludwig, D. Bonta, D. Tiffany, J. Neumann, H. Zheng, J. Fargione, and P. Hawthorne

Tilman, G. David

University of Minnesota

Dr. G. David Tilman is Regents Professor of Ecology and holds the McKnight University Presidential Chair in Ecology at the University of Minnesota. He is an experimental and mathematical ecologist studying the impacts of the loss of biological diversity and of other types of human-driven global change on the functioning and stability of ecosystems and on the services that ecosystems provide society. David Tilman is deeply interested in the interface of science, society, ethics and environmental policy. He has given expert testimony to committees of the US Senate and House and to the White House's Office of Management and Budget, has had his scientific findings on biodiversity added to the Congressional Record by a member of congress, and given invited briefings to the Minnesota House and Senate. He has served on scientific advisory committees for the White House (the Biodiversity and Ecosystems Panel of the President's Committee of Advisors on Science and Technology), for Public Radio International's The World, and for the National Academy of Sciences (Board on Environmental Studies and Toxicology). In 1996 he founded a new publication, *Issues in Ecology*, to foster communication among ecologists, the public and governmental decision makers. He served as its Editor-in-Chief for eight years. He has also served on the editorial boards of scientific publications including *Science*, *Proceedings of the National Academy of Science*, and *Ecology*.

Honors include selection as a Guggenheim Fellow, and election as a Fellow of the American Association for the Advancement of Science, as a Fellow of the American Academy of Arts and Sciences and as a member of the National Academy of Science. Prizes and awards include Sweden's Per Brink Award, Pew Scholar in Conservation Biology, and the Ecological Society of America's Cooper Award and MacArthur Award. In 2001 he was designated the most highly cited environmental scientist for the decade by the Institute for Scientific Information, an honor he also received in 2003 and 2005 for the decades from 1992-2002 and 1995-2005.

After earning his Ph. D. at the University of Michigan in 1976, Dr. Tilman has spent his academic career at the University of Minnesota, but also has served as a Member of Princeton's Institute for Advanced Study, a Senior Visiting Fellow at Princeton University, and a Fellow of the National Center for Ecological Analysis and Synthesis.

Biofuels potential: The climate protective domain
Chris Field
Department of Global Ecology
Carnegie Institution for Science

cfield@ciw.edu
www.dge.ciw.edu

- Biofuels are the only currently viable option for powering the world's existing vehicle fleet, using fuels that potentially release less CO₂ than gasoline or diesel.
- Combined with geological storage, biofuels represent one of the few options for an energy source with negative CO₂ emissions, one that leads to a net decrease in atmospheric CO₂
- Many countries are investing in large biofuels programs, motivated by concerns over global change, energy security, and rural development.
- Liquid biofuels already provide some developing and developed countries with a local renewable energy resource and jobs for rural populations.
- There are many ways to do biofuels wrong, so that the costs in damage to the environmental or to human well-being exceed the benefits, but there are also some ways to do biofuels right.
- Current crops used to produce liquid biofuels are all food crops. With these crops, increasing the fraction allocated to biofuels can decrease the availability of food, and increasing the area can lead to loss of natural ecosystems rich in biodiversity or carbon stocks.
- Biofuels from waste, from crops grown with a focus on improving marginal or abandoned land, and from diverse natural ecosystems have the potential for net benefits in terms of climate, energy security, and rural development, with low or no costs in environmental degradation or human well-being
- Global production and use of liquid biofuels have tripled since 2000, with much more to come if current policy targets are implemented. With larger and larger levels of production, it becomes increasingly difficult to successfully manage environmental impacts.

Suggested reading

- Fargione, J., J. Hill, D. Tilman, S. Polasky, and P. Hawthorne. 2008. Land Clearing and the Biofuel Carbon Debt. *Science* **319**:1235.
- Field, C. B., J. E. Campbell, and D. B. Lobell. 2008. Biomass energy: the scale of the potential resource. *Trends in Ecology & Evolution*.
- Gallagher, E. 2008. The Gallagher Review of the indirect effects of biofuels production. The Renewable Fuels Agency, Hastings, East Sussex.
- Hill, J., E. Nelson, D. Tilman, S. Polasky, and D. Tiffany. 2006. Environmental, economic, and energetic costs and benefits of biodiesel and ethanol biofuels. *Proceedings of the National Academy of Sciences* **103**:11206.
- Searchinger, T., R. Heimlich, R. A. Houghton, F. Dong, A. Elobeid, J. Fabiosa, S. Tokgoz, D. Hayes, and T. H. Yu. 2008. Use of US Croplands for Biofuels Increases Greenhouse Gases Through Emissions from Land-Use Change. *Science* **319**:1238.

Field, Christopher

Carnegie Institution

Dr. Christopher Field is the director of the Carnegie Institution's Department of Global Ecology and professor by courtesy in the Department of Biological Sciences at Stanford University. Trained as an ecologist, Chris has conducted environmental research from tropical rainforests to deserts to alpine tundra in the Americas, Asia, Africa, and Australia. He is a specialist in global-change research. He has developed an evolutionary approach to understanding the spatial organization of plant canopies and the adaptive significance of leaf aging. These studies led to work on the role of nitrogen in regulating plant growth and photosynthesis. They also suggested ways that plant physiological responses could be summarized with a few parameters, providing a basis for predicting many aspects of ecosystem function at very large scales.

Recently, he has emphasized formalizing approaches for summarizing plant responses into models that simulate ecosystem exchanges of carbon, water, and energy at the global scale. These models, which synthesize surface data on climate and soils, satellite data on vegetation type and canopy development, and functional generalizations from physiology and ecology, help test hypotheses and understand the future status of terrestrial ecosystems, especially responses to and influences on global change factors like increased atmospheric carbon dioxide or altered climate. Field is active in developing the international community of global change researchers, with involvement in organizations like SCOPE, IGBP, and the Global Carbon Project. An author of more than 100 scientific papers, he is a member of the US National Academy of Sciences and a leader in several national and international efforts to provide the scientific foundation for a sustainable future.

Developmental origins of health and disease – role of epigenetic mechanisms

M.A. Hanson¹, P.D. Gluckman², G.C. Burdge¹, K.A. Lillycrop¹, K.M. Godfrey¹

¹ Division of Developmental Origins of Health & Disease, University of Southampton,

² Liggins Institute, University of Auckland

Epidemiological and animal studies show that small changes in the environment during development, e.g. in nutrient provision or balance, induce phenotypic changes which affect an individual's responses to their later environment. These may in turn alter the risk of chronic disease resulting from inadequate responses, e.g. to a rich environment leading to metabolic syndrome or cardiovascular disease. Recent research shows that animals exposed to such a mismatch between pre- and postnatal environment develop obesity, reduced activity, leptin and insulin resistance, elevated blood pressure and vascular endothelial dysfunction. We have found an important role for molecular epigenetic processes in producing such effects, processes which are targeted to promoter regions of specific genes in specific tissues but which also include changes in histone structure and post-transcriptional processes involving miRNAs. Such fine control of gene expression endorses the view that the mechanisms have been retained through evolution as a result of the adaptive advantage which they confer, rather than representing extreme effects of developmental disruption akin to teratogenesis. Moreover there may be adaptive advantage in a developmental cue inducing a phenotypic change in generations beyond the immediately affected pregnancy, and there is now a range of human and animal data which support this concept. Such effects – which might be termed non-genomic inheritance – may be mediated by a range of effects including alterations in maternal adaptations to pregnancy in successive generations or behavioural influences. Recent data however also show that epigenetic effects such as DNA methylation can be passed to successive generations. This suggests that they might persist through meiosis. Environmental toxins, including endocrine disruptors, can play a role in inducing greater risk of chronic disease even at low exposure levels, especially if they act via the normal epigenetic processes involved in developmental plasticity. Current research in this area is important for mechanistic understanding and for developing novel prognostic markers of later disease risk. It also emphasizes the long-term multi-generational effects which appropriate interventions may confer to reduce the risk of chronic disease in subsequent generations.

References

1. Gluckman PD, Hanson MA, Cooper C, Thornburg KL (2008). Effect of in utero and early-life conditions on adult health and disease. *New England Journal of Medicine* 359:61-73
1. Godfrey KM, Lillycrop KA, Burdge GC, Gluckman PD, Hanson MA (2007). Epigenetic mechanisms and the Mismatch concept of the Developmental Origins of Health and Disease. *Pediatric Research* 61 (Pt2):5R-10R
3. Burdge GC, Hanson MA, Slater-Jefferies JL, Lillycrop KA (2007). Epigenetic regulation of transcription: a mechanism for inducing variations in phenotype (fetal programming) by differences in nutrition during early life? *British Journal of Nutrition* 97:1036-1046

MAH and GCB are supported by the British Heart Foundation and PDG by the National Research Centre for Growth and Development

Hanson, Mark

University of Southampton

Dr. Mark Hanson is a British Heart Foundation Professor of Cardiovascular Science at the University of Southampton and President of the International Society for Developmental Origins of Health and Disease.

He has worked in the field of fetal and developmental physiology, and its implications for medicine, for nearly 30 years, establishing a research group at Reading University in 1979, moving to a joint appointment in Obstetrics & Gynaecology and Physiology at UCL in 1990, and founding the Centre for Developmental Origins of Health and Disease at Southampton University in 2000. Early achievements focused on defining neural, hormonal and local mechanisms involved in cardio-respiratory, behavioural and metabolic control in the fetus and neonate, initiating new thinking on fetal adaptations and responsiveness to the prenatal environment. The Centre was the first to make recordings demonstrating unequivocal arterial chemoreceptor function in late gestation, opening avenues for studying fetal reflex responses to hypoxia. This work was extended to the effects of acute and chronic hypoxia in altricial species (e.g. cat) to large precocial species (llama, sheep) to gain insights from differing maturational strategies. The Centre's seminal studies established the concept of postnatal resetting of chemoreceptor sensitivity, explored its mechanisms and relevance to respiratory failure, and developed a test of chemoreflex sensitivity which was applied to human babies, including those at high risk of sudden infant death. Its research simultaneously played a leading role in establishing brainstem processes involved in the characteristic reduction in breathing activity seen in the hypoxic fetus and newborn, and examined interactions between thermoregulation and breathing, e.g. bacterial endotoxin-induced pyrexia.

Throughout his career he has collaborated with clinical scientists in developing methods for studying the human fetus, including heart rate variability, Doppler ultrasonic measurement of vascular impedance, cardiac volume imaging and near infrared measurement of tissue oxidative state. This work has contributed to developments in human fetal monitoring. Extending the concept of fetal adaptive responses, his research group was the first to show perturbations in fetal cardiovascular and endocrine function induced by mild nutritional challenges without reductions in fetal growth. It was in the forefront in focusing on the importance of early gestation challenges, and in performing long-term follow up to adulthood of animals in which additional postnatal nutritional challenges were imposed. This demonstrated that prenatal nutrition can condition the animal's later cardiovascular, metabolic and hypothalamo-pituitary adrenal axis responses, relevant to later pathophysiology. This research has now shown that dietary, hormonal and pharmacological interventions can reverse aspects of the phenotype induced in early life, and this may have therapeutic implications. He has conducted detailed investigation of underlying epigenetic mechanisms, showing changes in DNA methylation, histone methylation and acetylation and small non-coding RNAs following a prenatal nutritional challenge and affecting expression of non-imprinted genes in a range of tissues.

Recent studies have examined the ways in which epigenetic processes can induce the equivalent of polyphenisms in mammals, and also the effects of endocrine disruptor chemicals. With Peter Gluckman he developed the influential concept of predictive adaptive responses, extending evolutionary and developmental biology concepts to human populations and we have extended this work to champion the field of evolutionary medicine. His recent studies utilise Southampton's human epidemiological cohorts, showing the importance of pre-pregnancy maternal body composition and diet to later fetal cardiovascular function. They will facilitate the translation of mechanistic insights to new early life markers of risk of later chronic disease and to methods of monitoring interventions. In collaboration with organisations such as The World Bank and WHO he is attempting to define the human cost of a poor start to life.

ABSTRACT

Epigenetics: The New Genetics of Disease Susceptibility

Randy L. Jirtle, Ph.D.

Department of Radiation Oncology

Duke University Medical Center, Durham, NC USA 27710

Human epidemiological and animal experimental data indicate that the risk of developing adult-onset diseases, such as asthma, diabetes, obesity, and cancer, is influenced by persistent adaptations to prenatal and early postnatal exposure to environmental conditions such as nutritional privation [1]. Moreover, the link between what we are exposed to *in utero* and disease formation in adulthood appears to involve epigenetic modifications like DNA methylation at metastable epiallele and imprinted gene loci.

Genomic imprinting is an epigenetic form of gene regulation that results in monoallelic, parent-of-origin dependent gene expression [2]. Since imprinted genes are functionally haploid, only a single genetic or epigenetic event is needed to dysregulate their function. This vulnerability means that imprinted genes are prime candidates for causative roles in human diseases that have a parental inheritance bias and an environmental component in their etiology. We recently developed computer-learning algorithms that predicted the presence of 600 imprinted genes in mice [3] and 156 imprinted genes in humans [4]. Not only are humans predicted to have fewer imprinted genes than mice, but there is also a mere 30% overlap between their imprinted gene repertoires. By mapping the human candidate imprinted genes onto the landscape of disease risk defined by linkage analysis, we are now poised to determine the importance of imprinting in the etiology of complex human diseases and neurological disorders.

Genes with metastable epialleles have highly variable expression because of stochastic allelic changes in the epigenome rather than mutations in the genome. The viable yellow agouti (A^{vy}) mouse harbors a metastable *Agouti* gene because of an upstream insertion of a transposable element. We have used the A^{vy} mouse to investigate the importance of nutrition in determining the susceptibility of offspring to adult diseases [5,6]. We have shown that maternal dietary supplementation during pregnancy, with either methyl donors (i.e. folic acid, vitamin B₁₂, choline and betaine) [5] or genistein [6], decreases adult disease incidence in the offspring by increasing DNA methylation at the A^{vy} locus. Moreover, these nutritional supplements can counteract the CpG hypomethylation caused by the endocrine disruptor, bisphenol A [7]. (Supported by NIH grants ES13053, ES08823, ES015165 and T32-ES07031, and DOE grant DE-FG02-05ER64101)

References

1. Jirtle, R.L., and Skinner, M.K. Environmental epigenomics and disease susceptibility. *Nat. Rev. Genet.* 8: 253-562, 2007
2. Jirtle, R.L., and Weidman, J.R. Imprinted and more equal. *Am. Sci.* 95: 143-149, 2007.
3. Luedi, P.P., Hartemink, A.J., and Jirtle, R.L. Genome-wide prediction of imprinted murine genes. *Genome Res.* 15: 875-884, 2005.
4. Luedi, P.P., Dietrich, F.S., Weidman, J.R., Bosko, J.M., Jirtle RL, and Hartemink, A.J. Computational and experimental identification of novel human imprinted genes. *Genome Res.* 17: 1723–1730, 2007..
5. Waterland, R.A., and Jirtle, R.L. Transposable elements: targets for early nutritional effects on epigenetic gene regulation. *Cell. Mol. Biol.* 23: 5293-5300, 2003.
6. Dolinoy, D.C., Weidman, J.R., Waterland, R.A., and Jirtle, R.L. Maternal genistein alters coat color and protects A^{vy} mouse offspring from obesity by modifying the fetal epigenome. *Environ. Health Perspect.* 14: 567-572, 2006.
7. Dolinoy, D.C., Huang, D., and Jirtle, R.L. Maternal nutrient supplementation counteracts bisphenol A-induced DNA hypomethylation in early development. *Proc. Natl. Acad. Sci. USA* 104: 13056-13061, 2007.

Jirtle, Randy

Duke University

Dr. Randy L. Jirtle is a professor of radiation oncology and an associate professor of pathology at Duke University, Durham, NC, where he has been a faculty member since 1977. He graduated with a B.S. degree in nuclear engineering in 1970 and a Ph.D. degree in radiation biology in 1976, both from the University of Wisconsin-Madison.

Jirtle's research interests are in epigenetics, genomic imprinting, and the fetal origins of disease susceptibility. He identified the imprinted IGF2R as a tumor-suppressor, and showed its inactivation increases tumor resistance to radiotherapy. Jirtle discovered a novel imprinted domain at human 14q32, and identified the Callipyge or beautiful buttocks locus in the homologous region of sheep. He subsequently traced the mammalian origin of genomic imprinting from monotremes to placental mammals. These studies provided the crucial data that allowed him to complete the first genome-wide mapping of human imprinted genes using a bioinformatic approach. The effort yielded candidate imprinted genes in chromosomal regions linked to complex human diseases and neurological disorders. Jirtle also demonstrated that maternal dietary supplementation of Avy mice during pregnancy, with either methyl donors or genistein, decreases adult disease incidence in the offspring by increasing DNA methylation at the Agouti locus. Moreover, these nutritional supplements were shown to block CpG hypomethylation caused by the endocrine disruptor, bisphenol A.

Jirtle holds two U.S. patents on imprinted genes and another one is pending approval. He has published more than 160 peer-reviewed articles, including ten publications featured on journal covers. His research has been featured in popular press accounts ranging from American Scientist and Discover to Allure. He was also a featured scientist this past year on the NOVA and ScienceNow television programs on epigenetics, and National Public Radio programs, The People's Pharmacy and The DNA Files. His enthusiasm for promoting the public understanding of epigenomics led him to create the website www.geneimprint.org, which has been designated by the scientific publisher Thomson ISI as an 'Exemplary Website in Genetics.' Jirtle has organized five international meetings and been an invited speaker at dozens of others. He has delivered five endowed lectures, and was invited to present his research at the 2004 Nobel Symposium on Epigenetics. He was honored in 2006 with the Distinguished Achievement Award from the College of Engineering at the University of Wisconsin-Madison. In 2007, Jirtle received an Esther B. O'Keefe Charitable Foundation Award and capped off the year with a nomination for Time Magazine's "Person of the Year." He was the inaugural recipient of the Epigenetic Medicine Award in 2008.

***Epigenetic Transgenerational Actions of Endocrine Disruptors on Reproduction and Disease:
The Ghosts in Your Genes***

Michael K. Skinner - Center for Reproductive Biology, School of Molecular Biosciences, Washington State University, Pullman, Washington.

Transgenerational effects of environmental toxicants (e.g. endocrine disruptors) significantly amplify the impact and health hazards of these compounds. One of the most sensitive periods to endocrine disruptor exposure is during embryonic gonadal sex determination when the germ line is undergoing epigenetic programming and DNA re-methylation. The model endocrine disruptors tested were vinclozolin, which acts as an anti-androgenic compound, and methoxychlor, that has metabolites that are estrogenic. Previous studies have shown that these endocrine disruptors can effect embryonic testis development to subsequently cause an increase in spermatogenic cell apoptosis in the adult. Interestingly, this spermatogenic defect is transgenerational (F1, F2, F3 and F4 generations) and hypothesized to be due to a permanent altered DNA methylation of the germ-line. This appear to involve the induction of new imprinted-like DNA methylation sites that regulate transcription distally. The expression of over 200 genes were found to be altered in the embryonic testis and surprisingly this altered transcriptome was similar for all generations (F1-F3). In addition to detection of the male testis disorder, as the animals age transgenerational effects on other disease states were observed including tumor development, prostate disease, kidney disease and immune abnormalities. Recent observations suggest transgenerational effects on behaviors such as sexual selection and anxiety. Therefore, the transgenerational epigenetic mechanism appears to involve the actions of an environmental compound at the time of sex determination to alter the epigenetic (i.e DNA methylation) programming of the germ line that then alters the transcriptomes of developing organs to induce disease development transgenerationally. The suggestion that environmental factors can reprogram the germ line to induce epigenetic transgenerational disease is a new paradigm in disease etiology not previously considered.

Anway M, Cupp AS, Uzumcu M and MK Skinner (2005) Epigenetic transgenerational actions of endocrine disruptors and male fertility. *Science* 308:1466-1469.

Anway MD, Leathers C and MK Skinner (2006) Endocrine Disruptor Vinclozolin Induced Epigenetic Transgenerational Adult Onset Disease. *Endocrinology* 147:5515-5523.

Crews D, Gore AC, Hsu TS, Dangleben NL, Spinetta M, Schallert T, Anway MD, Skinner MK (2007) Transgenerational epigenetic imprints on mate preference. *Proceedings of the National Academy of Sciences of the United States of America*. 3;104(14):5942-6.

Anway MD, Rekow SS, and MK Skinner (2008) Transgenerational epigenetic programming of the testis transcriptome by endocrine disruptor exposure at sex determination. *Genomics* 91:30-40.

Skinner, Michael

Washington State University

Dr. Michael K. Skinner is Professor and Director of Center for Reproductive Biology at Washington State University. He holds a Ph.D. from Washington State University and a B.A. from Reed College. His primary research addresses on molecular and cellular aspects of reproduction (testis/ovary biology) and transgenerational epigenetic mutagenesis. He has investigated how different cell types in a tissue interact and communicate to regulate cellular growth and differentiation, with emphasis in the area of reproductive biology. He has initiated an investigation of the effects of environmental toxicants on gonadal development has been initiated and found that the impact of endocrine disruptors on embryonic testis and ovary development demonstrated an epigenetic transgenerational phenotype on adult male fertility. Exposure of the embryonic testis at the time of sex determination caused an epigenetic reprogramming of the male germ-line that causes a variety of disease states in the adult and this phenotype is transferred through the male germ-line to all subsequent generations. His laboratory is investigating the underlying mechanism and phenotype of this epigenetic transgenerational phenomenon.