UPDATE
National Toxicology Program
U.S. Department of Health and Human Services

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Headquartered at the
National Institute of Environmental
Health Sciences • NIH-HHS

What's Inside:

Birnbaum discusses 12th ROC at congressional joint hearing

By Ian Thomas reprinted from *eFACTOR*, May 2012

Birnbaum was accompanied to the hearing by members of the NIEHS staff located in Bethesda, MD. (Photo courtesy of Steve McCaw)

NIEHS/NTP Director Linda Birnbaum, Ph.D., addressed questions regarding NTP's 12th Report on Carcinogens (RoC) April 24 during a U.S. House of Representatives joint subcommittee hearing. Testifying in front of the Committee on Science, Space, and Technology, Subcommittee on Investigations and Oversight, as well as the Committee on Small Business, Subcommittee on Healthcare and Technology, Birnbaum addressed a wide range of questions regarding the RoC's contents, and the rigorous peer review process by which scientific research and public feedback are used during its compilation.

"The RoC is a science-based, public health document that provides information about the relationship between the environment and cancer," explained Birnbaum. "The Report lists a wide range of substances, including metals, pesticides, drugs, natural and synthetic chemicals, and biological agents that are considered cancer hazards for people in the U.S."

Launched in 1978 as part of the Public Health Services Act, the RoC takes into account a number of different factors when determining a substance's potential hazard for cancer. These include such things as the amount and duration of exposure, as well as an individual's susceptibility to a substance. Still, Birnbaum was quick to point out that the RoC is not a tool for risk assessment.

"This is not a regulatory document," she noted. "However, the RoC does provide decision makers and the public with information they can use to make decisions about exposures to cancer-causing substances."

A pair of categories

The RoC lists substances in one of two categories, "known to be carcinogens" and "reasonably anticipated to be carcinogens."

For a substance to be listed in the known category, there must be sufficient evidence from human studies that indicates a causal relationship between exposure to the substance and human cancer. For a substance to be classified in the reasonably anticipated category, it must fit one of three scenarios: limited evidence it causes cancer from studies in humans; sufficient evidence it causes cancer from studies in animals; or evidence that the substance is a member of a class of substances already listed in the Report or that it causes biological effects known to lead to the development of cancer in humans. "The decision to list a substance in the RoC is based on scientific judgment, with consideration of all relevant research data and input from both advisory groups and the public," said Birnbaum.

Involving the public

While the preparation of each edition of the RoC involves a multi-step process, including expert advisory reviews, independent external peer reviews, and outside input from agencies, such as the

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U.S. Food and Drug Administration, U.S. Environmental Protection Agency, and Consumer Product Safety Commission, among others, Birnbaum added that anyone can nominate a substance for listing or removal from the Report, be it a field-leading scientist or a private citizen.

"In the case of the 12th RoC, we actually increased the number of opportunities for public review and input," said Birnbaum, adding that public comments were solicited on six different occasions.

Looking ahead

As NTP moves forward on the 13th RoC, Birnbaum and her staff have revised the process for preparation of the report with regard to the transparency and efficiency, while continuing to maintain the rigorous investigative standards for which the document has long been known.

"We believe the RoC is, and will remain, an important public health document, because it empowers the public and decision makers with the information they need to make informed choices about potentially cancer-causing substances and hazards," said Birnbaum. "However, a process like this can never be too thorough, which is why it's vital for us, as researchers, to always be mindful of new ways to improve it."

(Ian Thomas is a public affairs specialist for the NIEHS Office of Communications and Public Liaison and a regular contributor to the Environmental Factor.)

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NTP board supports systematic review new carcinogen concepts

By Robin Mackar reprinted from *eFACTOR*, July 2012

The literature-based analysis capabilities of the National Toxicology Program (NTP) took center stage during its Board of Scientific Counselors meeting June 21-22 at NIEHS.

Ruth Lunn, Dr.P.H., director of the Office of the Report on Carcinogens (RoC), and her staff, were well prepared to present the board with concepts outlining the planned reviews for five substances proposed for potential inclusion in the RoC, while Kris Thayer, Ph.D., and her Office of Health Assessment and Translation (OHAT) team wowed the board with their plans to bring systematic review methodology and new information management tools into their literature-based evaluations.

Systematic review will enhance transparency

"The board is very enthusiastic and supportive of the NTP taking a leadership role in systematic review," said BSC chair David Eastmond, Ph.D., of the University of California, Berkeley, as he summarized the sentiments of the board, after hearing an engaging presentation by Thayer.

"Systematic review is a scientific investigation that focuses on a specific question, and uses explicit, prespecified methods to identify, select, summarize, and assess the findings of similar but separate studies," Thayer explained. "It's traditionally been used for evaluating health care

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Upcoming Events

September 5-6, 2012

Scientific Advisory Committee on Alternative Toxicological Methods

NIEHS
111 TW Alexander Drive
Research Triangle Park, NC

September 19-21, 2012

International Workshop on Alternative Methods for *Leptospira* Vaccine Potency Testing: State of the Science and the Way Forward

U.S. Department of Agriculture
Center for Veterinary Biologics
National Centers for Animal Health
Ames, Iowa, USA

October 1-2, 2012

Peer Review of Draft NTP Monograph on Developmental Effects and Pregnancy Outcomes Associated with Cancer Chemotherapy Use during Pregnancy

NIEHS
111 TW Alexander Drive
Research Triangle Park, NC

November 28-29, 2012

NICEATM-ICCVAM
Alternatives to the Pertussis Test

Natcher Conference Center, NIH
Bethesda, MD

December 11-12, 2012

NTP Board of Scientific Counselors

NIEHS
111 TW Alexander Drive
Research Triangle Park, NC

http://ntp.niehs.nih.gov/go/calendar

interventions but, from what we've seen over the past year, it's going to be a really powerful tool for conducting our literature-based evaluations and helping NTP develop evidence-based conclusions."

Thayer stressed that a systematic review does not eliminate the need for expert judgment, nor does it guarantee reproducibility in the overall evidence-based conclusions, but she emphasized how it will enhance transparency and allow for more consistent data collection and evaluation.

A critical initial step of conducting a systematic review, she said, is to develop a protocol, or predefined approach, that outlines how the evaluation will be conducted. Thayer added that the NTP will engage technical experts, interagency partners, and members of the public, to refine the scope of an evaluation and create the systematic review protocol. Thayer finished by walking the board through a series of demonstrations of how a protocol might work from start to finish.

Board member David Dorman, D.V.M., Ph.D., of North Carolina State University, and others, applauded NTP for taking a lead role in bringing this approach to fruition and encouraged the NTP to share these tools with others. "The need for this cannot be overstated," said new Board member Robert Chapin, Ph.D., of Pfizer. "It will be the shining jewel for the NTP."

Further enhancing the environment of animals in NTP studies

King-Herbert outlined plans to further enrich the environment of rodents being used in NTP studies. (Photo courtesy of Steve McCaw)

Angela King-Herbert, D.V.M., who leads the NTP Laboratory Animal Management Group, updated the board on plans to enhance environmental enrichment in rodent studies. King-Herbert explained how environmental enrichment seeks to enhance an animal's well-being. She said there is not a standardized approach for how this should occur. "It can include, for example, things like ensuring that the animals are socially housed and creating an environment that promotes the animal's natural behaviors."

King-Herbert said the approaches for environmental enrichment proposed by NTP are in accordance with the 2011 Guide for the Care and Use of Laboratory Animals. She discussed how the NTP will phase in two different enrichment items, including crinkled natural kraft paper and plastic rectangular shelters, and how the NTP will closely monitor the impact of the enrichment. An NTP animal welfare committee has been established to oversee these activities. The Board discussed the complexities of understanding the potential impacts of environmental enrichment on toxicity studies, but also expressed its strong support for moving forward.

Strategic plan update, green light on genetic toxicity testing

Other meeting items included an update from NIEHS/NTP Director Linda Birnbaum, Ph.D., on the nearly finalized NIEHS strategic plan. "This plan will be a blueprint for the entire field of environmental health sciences," Birnbaum said.

NTP genetic toxicologist Kristine Witt received the green light from the board, which unanimously voted to approve a concept that would expand the NTP's genetic toxicity testing capabilities to include human cells. And, OHAT's Andrew Rooney, Ph.D., received praise for completion of the NTP Monograph on Health Effects of Low-level Lead. ●

(Robin Mackar is the news director in the NIEHS Office of Communications and Public Liaison.)

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Witt was well prepared to respond to questions from the board about how the NTP is planning to broaden the scope of its genetic toxicity testing contract. (Photo courtesy of Steve McCaw)

Rooney is all smiles, now that the NTP low-level lead evaluation is completed. (Photo courtesy of Steve McCaw)

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Report on Carcinogens process in action

As part of the new process for preparing the RoC, Lunn and her staff presented the board with five draft concepts on substances being considered for review for possible listing in future editions of the RoC. The five substances — 1-bromopropane, cumene, ortho-toluidine, pentachlorophenol and trichloroethylene — came from a longer list of 15 nominated substances that received input from the public in January. Each draft concept outlined the rationale for the nomination and the NTP's approach for conducting the cancer evaluation. A web page will be developed and continuously updated for each substance reviewed.

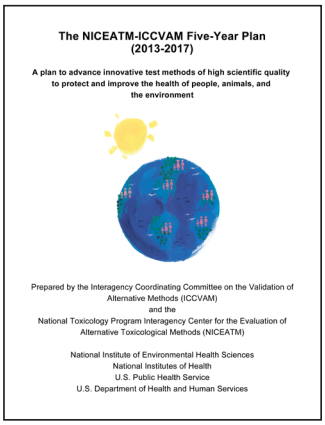
The board reviewed and commented on each draft that outlined the NTP's proposed evaluation strategy that may vary depending on the complexity of the scientific information on the substance.

Birnbaum and NTP Associate Director John Bucher, Ph.D., thanked the board members for their valuable input. Birnbaum will make the final decision this summer on the substances that will be developed into monographs and proceed through the RoC evaluation process.

Bucher emphasized to the board how the NTP has improved the RoC process. "The NTP monograph developed for each substance that undergoes study will clearly show how we reached our conclusions. It will be a more transparent process."

NICEATM seeks comment on draft plan for 2013–2017

By Debbie McCarley and Cathy Sprankle reprinted from *eFACTOR*, July 2012


The NICEATM-ICCVAM Five-Year Plan
(2013-2017)

A plan to advance innovative test methods of high scientific quality to protect and improve the health of people, animals, and the environment

Prepared by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)
and the
National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

National Institute of Environmental Health Sciences
National Institutes of Health
U.S. Public Health Service
U.S. Department of Health and Human Services

The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) is taking public comments until Aug. 13 on a draft five-year plan developed in collaboration with the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). ICCVAM is an interagency committee of the federal government that NICEATM administers. The plan is available on the NICEATM–ICCVAM website. (http://iccvam.niehs.nih.gov/docs/5yearplan.htm)

The document will provide strategic direction for NICEATM and ICCVAM during 2013–2017. It outlines how, consistent with ICCVAM's statutory duties and purposes, NICEATM and ICCVAM will contribute to the transformation of safety testing, by fostering and promoting the incorporation of scientific advances and innovative technologies into new improved test methods, and integrated testing and decision strategies.

ICCVAM was established to promote development, validation, and regulatory acceptance of new toxicology and safety testing methods. New test methods that take advantage of advances in technology can better characterize the safety and potential hazards of chemicals and chemical products, which in turn can provide better protection of people, animals, and the environment. New test methods also provide the opportunity to use fewer or no animals for chemical safety testing, or to enhance animal well-being, and lessen or avoid pain and distress in those cases where animal testing is still necessary.

In 2008, NICEATM and ICCVAM published a five-year plan for 2008-2012. The plan described ICCVAM's vision to play a leading role in fostering and promoting the development, validation, and regulatory acceptance of scientifically sound alternative test methods, both within the federal government and internationally.

Responding to the fact that the time period covered by the current five-year plan was coming to a close, last November, NICEATM published a request for comment on development of a five-year plan for 2013-2017. Comments received were considered, as NICEATM worked with an ICCVAM subcommittee in early 2012 to develop the draft plan that was released last month.

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"Recent advances in emerging science and technology innovations are driving transformative changes in toxicology and how safety testing is performed," noted ICCVAM vice chair Joanna Matheson, Ph.D., of the Consumer Product Safety Commission, who is chairing the ICCVAM subcommittee. "For example, data from *in vitro* testing batteries and integrated decision strategies, that consider chemical and toxicological database information, are becoming more important to regulatory decision-making. The next five years will be an essential transition period for NICEATM and ICCVAM in this changing regulatory toxicology environment."

"In developing this plan, we recognize the need to be able to take advantage of advances in science and technology that will take place over the next five years," commented Rear Adm. William Stokes, D.V.M., who is director of NICEATM. "We want to best position NICEATM and ICCVAM to promote and help translate the incorporation of new science into improved and innovative test methods that better characterize the safety or hazard of new chemicals and products. These improved methods will better protect people's health, and are also expected to reduce and replace animal use in testing."

The draft 2013–2017 Five-Year Plan is available on the NICEATM–ICCVAM website. The five-year plan will be discussed at the September meeting of the Scientific Advisory Committee on Alternative Toxicological Methods. Those wishing to submit a comment on the plan may do so via a form on the NICEATM–ICCVAM website, or via email to niceatm@niehs.nih.gov, by Aug. 13, so that the advisory committee can consider public comments in their review of the draft plan.

(Debbie McCarley is a special assistant to Stokes. Cathy Sprankle is a communications specialist with ILS, Inc., support contractor for NICEATM.)

Call for comments

A notice announcing the availability of the draft plan was published on June 13 in the Federal Register. The draft plan describes four broad strategic opportunities for NICEATM and ICCVAM to foster and promote development, validation, and regulatory acceptance of scientifically sound alternative test methods by the federal government and other organizations.

- Promote the application and translation of innovative science and technology, to develop predictive alternative test methods and efficient and predictive integrated testing and decision strategies.
- Advance alternative test methods and testing strategies, through new evaluation activities for focus areas initially identified in the 2008-2012 five-year plan and new focus areas for 2013-2017.
- Facilitate regulatory acceptance and use of alternative methods, through high-quality test method evaluations and effective outreach and communication.
- Develop and strengthen partnerships with the broad range of ICCVAM stakeholders.

NIEHS and NICEATM invite comments on the draft plan from all ICCVAM stakeholders. In addition, comments are sought on how NICEATM and ICCVAM can most effectively contribute to the evolving transformation of safety testing. Stakeholder comments will be considered in finalizing the draft plan, prior to planned publication in December 2012.

Questions about NICEATM and ICCVAM activities can be addressed to William Stokes, D.V.M., director of NICEATM (see contact information below). Copies of documents mentioned in this update can also be obtained by contacting NICEATM.

Contact Information: niceatm@niehs.nih.gov; phone 919-541-2384; fax 919-541-0947.

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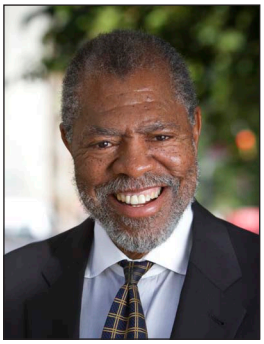
Olden named to head EPA programs

By Eddy Ball reprinted from *eFACTOR*, July 2012



When Olden came to NIEHS in 1991, he said his goal was to raise the Institute's image among key officials in the executive and legislative branches, to make the NIEHS a prime-time player in environmental health nationally and worldwide. (Photo courtesy of CUNY)

In a May 31 email to agency staff, U.S. Environmental Protection Agency (EPA) official Lek Kadeli announced the appointment of NIEHS Director Emeritus Ken Olden, Ph.D., to head two high-profile programs.

Kadeli, who is acting assistant administrator of the EPA Office of Research and Development, wrote that Olden will direct both the National Center for Environmental Assessment (NCEA) and the Human Health Risk Assessment Program (HHRA) effective July 2. Kadeli wrote that he expects Olden to make important contributions to the programs. "Ken comes to EPA with a strong legacy of promoting scientific excellence in environmental health."

Olden served as director of NIEHS and NTP from 1991 to 2005, when he left his leadership role and became a lead researcher in the Laboratory of Molecular Carcinogenesis Metastasis Group. In 2008, he accepted an offer from the City University of New York (CUNY) to be founding dean of the new School of Public Health at Hunter College, a unique program with an urban public health focus.

Olden led the development of the curriculum and recruitment of 26 tenure-track faculty. In early 2011, Olden moved with the school from its temporary home to a new eight-story, 147,000-square-foot green building in East Harlem. Last summer, the Council on Education for Public Health (CEPH) announced its accreditation of the CUNY School of Public Health (SPH) at Hunter College for a five-year term extending to July 1, 2016.

From the outset, Olden saw his role at CUNY as a three-year commitment to get the new school underway. "Once the transition to our new location is complete, my task [here in New York] will be over," Olden said when accreditation was announced.

According to a story about his appointments in the June 8 issue of Inside EPA, Olden will oversee efforts to revamp the agency's Integrated Risk Information System (IRIS), which produces many of EPA's most influential and sometimes controversial risk assessments. Industry has complained that the assessments are overly conservative, public health advocates have complained about delays, and last year the National Academy of Sciences issued a critical report outlining recommendations for improving IRIS.

Olden succeeds NCEA Acting Director Rebecca Clark, who served for two years following the departure of the program's long-time former director, Peter Preuss. Olden's primary assignment will be at NCEA headquarters in Washington, D.C., although Research Triangle Park, N.C.-based regional director John Vandenberg said he anticipates Olden will also have office space at the facility in N.C. ●

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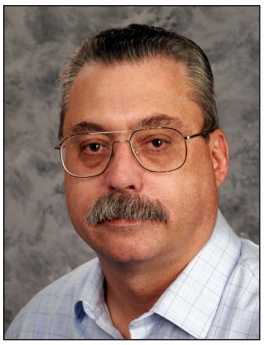

Lead researcher Michael Waalkes (Photo courtesy of Steve McCaw)

Arsenic turns stem cells cancerous, spurring tumor growth

By Robin Mackar reprinted from *eFACTOR*, May 2012

NIEHS researchers have discovered how exposure to arsenic can turn normal stem cells into cancer stem cells and spur tumor growth. The findings were published April 4 online in the journal Environmental Health Perspectives.

Inorganic arsenic, which affects the drinking water of millions of people worldwide, has been previously shown to be a human carcinogen. A growing body of evidence suggests that cancer is a stem cell-based disease. Normal stem cells are essential to normal tissue regeneration and to the stability of organisms and processes. But cancer stem cells are thought to be the driving force for the formation, growth, and spread of tumors.

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Michael Waalkes, Ph.D., and his team at the National Toxicology Program Laboratory had previously shown that normal cells become cancerous when they are treated with inorganic arsenic. This new study shows that when these cancer cells are placed near, but not in contact with normal stem cells, the normal stem cells very rapidly acquire the characteristics of cancer stem cells. It demonstrates that malignant cells are able to send molecular signals through a semipermeable membrane, where cells can't normally pass, and turn the normal stem cells into cancer stem cells.

The key to cancer proliferation

"This paper shows a different and unique way that cancers can expand by recruiting nearby normal stem cells and creating an overabundance of cancer stem cells," said Waalkes. "The recruitment of normal stem cells into cancer stem cells could have broad implications for the carcinogenic process in general, including tumor growth and metastases."

This reveals a potentially important aspect of arsenic carcinogenesis and may help explain observances by researchers working with arsenic that arsenic often causes multiple tumors, of many types, to form on the skin or inside the body.

Waalkes' lab started working with stem cells about five years ago. The researchers used a prostate stem cell line, not embryonic stem cells.

"Using stem cells to answer questions about disease is an important new growing area of research. Stem cells help to explain a lot about carcinogenesis, and it is highly likely that stem cells are contributing factors to other chronic diseases," Waalkes said.

Stem cells are unique in the body. They stay around for a long time and are capable of dividing and renewing themselves. "Most cancers take 30 or 40 years to develop," said Linda Birnbaum, Ph.D., director of NIEHS and NTP. "It makes sense that stem cells may play a role in the developmental basis of adult disease. We know that exposures to toxicants during development and growth can lead to diseases later in life."

Next, the laboratory team will look to see if this finding is unique to arsenic or if it is applicable to other organic and inorganic carcinogens.

Citation: Xu Y, Tokar EJ, Sun Y, Waalkes MP. 2012. Arsenic-transformed malignant prostate epithelia can convert noncontiguous normal stem cells into an oncogenic phenotype. Environ Health Perspect; doi:10.1289/ehp.1204987 [Online 4 April 2012].

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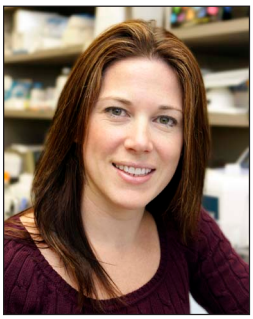
Hormones and Cancer highlights NIEHS/NTP paper

By Eddy Ball reprinted from *eFACTOR*, April 2012



The Hormones and Cancer paper is Whirledge's second publication as a member of the NIEHS Molecular Endocrinology Group and as first author. (Photo courtesy of Steve McCaw)

Dixon's group studies rodent reproductive tissue and tissue samples taken from cycle-staged, premenopausal women that are part of the NIEHS/George Washington University Uterine Fibroid Study. (Photo courtesy of Steve McCaw)

The journal Hormones and Cancer is highlighting a new paper by NIEHS and NTP scientists as one of nine available free at the journal's website. The bimonthly journal is beginning its third year, as a publication of the Endocrine Society, with an updated cover design and new leadership for its mission of advancing basic and clinical research on hormonally influenced cancers of endocrine glands.

In a message of congratulations to the paper's first author, NIEHS postdoctoral fellow Shannon Whirledge, Ph.D., incoming Editor-in-Chief Carol Lange, Ph.D., wrote, "Hormones and Cancer has selected your recent paper for its high significance to our field and made it available as a free download." As such, the paper forms part of the important first impression the journal makes on potential subscribers and prospective members of the Endocrine Society, who receive open access as part of their membership.

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Whirledge, who is a member of the NIEHS Molecular Endocrinology Group headed by lead researcher John Cidlowski, Ph.D., co-authored the paper with Cidlowski, the senior author, and lead researcher Darlene Dixon, D.V.M., Ph.D., head of the NTP Molecular Pathogenesis Group, the second author.

Linking glucocorticoids to cellular proliferation in uterine fibroids

According to the study, it is reported that women over age 45 have more than a 60 percent lifetime risk of developing uterine fibroids, or leiomyomas, benign tumors of the uterus that are the leading cause for hysterectomies in the U.S. Fibroids pose a significant public health concern, due both to their prevalence and associated symptoms, including heavy bleeding, pain, infertility, and complications during pregnancy and labor.

Although estrogen has been clearly linked to fibroid development and growth, Whirledge and her colleagues suspected that other factors, including the steroid hormone glucocorticoid receptor (GR) binding, are involved. "We hypothesized that glucocorticoids might also block estrogen-regulated gene expression or biological functions important for leiomyoma growth," they wrote, "[with] the potential to improve current strategies in the development of treatment for uterine leiomyomas."

In vitro results suggest potential efficacy of *in vivo* intervention

Using immortalized human uterine leiomyoma cells and uterine smooth muscle cells supplied by Dixon, the team performed a series of detailed experiments to determine expression of GR and estrogen receptor, gene expression, and cell proliferation. The researchers were able to identify gene expression changes differentially regulated with treatment by both the synthetic glucocorticoid dexamethasone (Dex) and estrogen (E2) that may play a role in an antagonistic relationship. Dex and E2 had significant effects on the expression of genes involved in inflammatory and cell proliferation pathways. By interfering with cell phase progression, Dex treatment decreased cell proliferation, a key to stemming the aberrant growth characteristic of fibroids, and cotreatment with E2 did not reverse the effect.

"This study provides the first evidence that glucocorticoid and estrogen antagonism acts not only in a global manner, but also in a cell-specific manner in the uterus, specifically a uterine tumor in which many questions remain regarding the regulation of its endocrinology," the researchers explained. "The clinical implications of the current findings are significant and have the potential to improve current strategies in the development of treatment for uterine leiomyomas."

Looking ahead to clinical applications of their findings, the research team said that translating their discoveries into a therapeutic intervention will require further study to better understand the molecular processes involved in glucocorticoid antagonism and whether the findings can be replicated in an intact uterine environment. ●

Citations:
Lange CA. 2012. Hormones and Cancer: A Bright Future. Horm Cancer. Apr;3(1-2):1-2.
Whirledge S, Dixon D, Cidlowski JA. 2012. Glucocorticoids Regulate Gene Expression and Repress Cellular Proliferation in Human Uterine Leiomyoma Cells. Horm Cancer; doi: 10.1007/s12672-012-0103-0 [Online 7 February 2012].

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Upcoming workshop on Leptospira vaccine potency testing

By Debbie McCarley and Cathy Sprankle reprinted from *eFACTOR*, June 2012

An upcoming workshop will focus on improved methods and approaches for *Leptospira* vaccine potency testing that may also help reduce, refine, and replace animal use. The "International Workshop on Alternative Methods for *Leptospira* Vaccine Potency Testing: State of the Science and the Way Forward" will take place Sept. 19-21 at the U.S. Department of Agriculture (USDA) Center for Veterinary Biologics at the National Centers for Animal Health in Ames, Iowa.

The National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) at NIEHS is organizing the workshop in collaboration with the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and partner organizations in the International Cooperation on Alternative Test Methods. The organizing committee for the workshop includes scientists from the National Institute of Allergy and Infectious Diseases (NIAID) and the Centers for Disease Control and Prevention, as well as from the USDA and other U.S. and international government agencies.

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Leptospirosis is a neglected tropical and zoonotic disease

Leptospirosis is a bacterial zoonotic disease caused by spirochetes of the genus *Leptospira*. More than 500,000 human cases of leptospirosis occur worldwide each year, with a fatality rate of up to 25 percent in some regions. Designated as a neglected tropical disease by the NIH and a neglected zoonotic disease by the World Health Organization, leptospirosis is a global research and public health priority. According to Suman Mukhopadhyay, Ph.D., bacterial zoonoses program officer, NIAID is currently funding several major leptospirosis research grants, which include investigations of mechanisms involved in the infectious cycle, enhanced tools for clinical diagnosis, and target identification for therapeutic intervention and development of potential vaccines for humans.

In the U.S., *Leptospira* vaccines are used in cattle, swine, and dogs to protect them from disease and to reduce the risk of animal-to-human transmission. Human vaccines are also available in some countries outside the U.S. Manufacturers test the potency of vaccine lots prior to their release to ensure their effectiveness. However, methods currently used to test the potency of *Leptospira* vaccines involve large numbers of laboratory animals. Many of these animals experience significant unrelieved pain and distress, with *Leptospira* vaccine testing accounting for over one-third of the animals reported to the USDA in this category.

NICEATM and ICCVAM promote the translation of innovative science and technology into improved alternative methods that are more efficient and that can also reduce, refine (enhance animal well-being and lessen or avoid pain and distress), and replace animal use. One of their highest priorities is promoting development and use of improved alternative test methods for vaccine potency and safety testing. NICEATM, ICCVAM, and their international partners recently identified *Leptospira* vaccines as a top priority.

About the workshop

This workshop will bring together international scientific experts from government, industry, and academia to review recent advances in science and technology, in addition to available methods and approaches for *Leptospira* vaccine potency testing. The main focus of the workshop will be on improved methods and approaches and that may provide improved accuracy, efficiency, and worker safety, and that are more humane and use fewer or no animals. Participants will develop a strategy to achieve global acceptance and implementation of scientifically valid alternative methods. A poster session will feature presentations on current research, development, and validation of alternative methods for *Leptospira* vaccine potency testing.

For more information

Registration information and a workshop program will soon be available on the NICEATM-ICCVAM website. NICEATM and ICCVAM also invite the submission of abstracts for scientific posters to be displayed during this workshop. Abstracts should be submitted by August 13.

(Debbie McCarley is a special assistant to Rear Adm. William Stokes, D.V.M., director of NICEATM. Cathy Sprankle is a communications specialist with ILS, Inc., support contractor for NICEATM.)

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NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

ICCVAM 2010–2011 Biennial Report Now Available

The *Biennial Progress Report 2010-2011: Interagency Coordinating Committee on the Validation of Alternative Methods* is now available on the NICEATM–ICCVAM website. The *Biennial Progress Report* describes activities and progress by NICEATM and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) during 2010 and 2011.

During the past two years, NICEATM, ICCVAM, and ICCVAM member agencies contributed to the national and/or international endorsement and adoption of 14 new and updated alternative safety testing methods. Since ICCVAM was established, NICEATM, ICCVAM, and the ICCVAM member agencies have contributed to the acceptance of over 50 alternative methods to protect the health of people, animals, and the environment while reducing, refining, and replacing animal use.

Selected highlights from the *Biennial Progress Report* include:

- On behalf of NICEATM and ICCVAM, NIEHS signed an agreement to add the Republic of Korea to the International Cooperation on Alternative Test Methods (ICATM). ICATM was established in 2009 by the United States, the European Union, Japan, and Canada to expedite the worldwide validation and regulatory acceptance of improved alternative test methods.
- The Organisation for Economic Co-operation and Development (OECD) adopted an international guidance document prepared by NICEATM and ICCVAM for two *in vitro* test methods that can be used to reduce animal use for identifying potentially poisonous substances. NICEATM led the international validation studies for the two cytotoxicity test methods, which can reduce animal use by up to 50% for each test.
- U.S. Federal agencies and the OECD adopted several new versions and applications of the murine local lymph node assay (LLNA); an alternative method recommended by ICCVAM to assess whether substances may cause allergic contact dermatitis. The recommendations reduce animal use for each test by 20-40% and support expanded use of the LLNA for nearly all testing situations. Two new "green" versions of the LLNA were adopted that do not require radioactive reagents and that will allow laboratories worldwide to take advantage of animal welfare benefits provided by the LLNA.
- U.S. Federal agencies adopted ICCVAM-recommended alternative test methods and procedures that will further reduce, refine, and replace animal use for eye safety testing. These include the routine use of medications to avoid most if not all pain and distress when it is necessary to use animals for required safety testing, and the first *in vitro* test method that can be used in a "bottom-up" approach to identify substances that are not considered eye hazards.
- NICEATM, ICCVAM, and their ICATM partners convened the first international workshop on alternative methods for human and veterinary vaccine potency and safety testing. The workshop recommended priority research needed to develop improved and more efficient test methods that can also reduce, refine, and replace animal use. A focused workshop on human and veterinary rabies vaccine test methods was held in 2011, and additional focused workshops are planned for 2012 (see announcements below) and 2013.
- ICCVAM completed international evaluation of an *in vitro* test method proposed as a screening test to identify substances with potential endocrine activity. The test method uses engineered human cells to identify substances that induce or inhibit activation of the human estrogen receptor. Use of this test method may reduce the number of animals necessary for endocrine disruptor screening.
- NICEATM and ICCVAM convened two workshops on *Best Practices for Regulatory Safety Testing* to promote the use of improved and more efficient test methods that can also reduce, refine, and replace animal use. Participants learned how to select and use approved alternative methods to assess the safety or potential hazards of chemicals and products.

The *Biennial Progress Report* is available on the NICEATM–ICCVAM website at: http://iccvam.niehs.nih.gov/about/ICCVAMrpts.htm.

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Hold the Date: International Workshop on Alternatives to the Murine Histamine Sensitization Test (HIST) for Acellular Pertussis Vaccines to be Held November 28-29, 2012

NICEATM will convene an "International Workshop on Alternatives to the Murine Histamine Sensitization Test (HIST) for Acellular Pertussis Vaccines: State of the Science and the Path Forward" on November 28-29, 2012. The workshop will be held at the William H. Natcher Conference Center at NIH headquarters in Bethesda, Maryland. NICEATM is organizing the workshop in collaboration with ICCVAM and ICATM partner organizations.

Pertussis, also known as whooping cough, is a highly contagious bacterial disease that was a major cause of childhood mortality until vaccines became available. Regulatory authorities require safety, potency, and purity testing prior to release of pertussis or pertussis-containing vaccines. The murine histamine sensitization test (HIST) is a key safety test performed to ensure that pertussis toxin in these vaccines has been effectively inactivated. However, such testing may involve large numbers of mice, some of which can experience significant unrelieved pain and distress. An international workshop organized in 2010 by NICEATM, ICCVAM, and their international partners identified the HIST as a high priority for future research, development, and validation of alternative test methods that could further reduce, refine, or replace animal use for acellular pertussis vaccine safety testing.

The upcoming workshop will provide a forum to discuss and review protocols and available data from an ongoing study of *in vitro* alternatives to the HIST test. The workshop will review new innovative methods and approaches for acellular pertussis vaccine safety testing that may provide greater accuracy, precision, and efficiency, while using fewer or no animals. Finally, the workshop will address the path toward validation, global acceptance, and implementation of scientifically valid alternative methods for acellular pertussis vaccines.

Registration information and a workshop program will soon be available on the NICEATM–ICCVAM website. The workshop is open to the public with no charge for attendance, but all attendees are encouraged to preregister by November 16, 2012. If you have questions about the workshop or would like more information, please contact NICEATM at niceatm@niehs.nih.gov.

NICEATM Requests Nominations of High Throughput Assays for the Tox21 Program

The "Tox21" partnership, which includes NTP, the NIH Center for Translational Therapeutics, the Environmental Protection Agency's National Center for Computational Toxicology, and the Food and Drug Administration, aims to improve hazard assessment of substances potentially harmful to humans and the environment. This will be done using integrated high throughput screens that provide information on substances' effects on biological pathways related to toxicity.

NICEATM is accepting nominations of high throughput screening (HTS) assays on behalf of the Tox21 Consortium and its Assays and Pathways Working Group. Nominated assays determined to be compatible with the HTS program will support Tox21 by providing data on endpoints that serve as biomarkers for initiating or downstream events in toxicity pathways. Of particular current interest are assays that evaluate effects to the following pathways:

- Biological pathways: Wnt, SHH (aka SONIC hedgehog), Delta-notch, TGF-beta, receptor tyrosine kinase (aka RTK) and retinoid
- Endocrine pathways: estrogen, thyroid, adrenal, and androgen

Data collected in the Tox21 initiative will be used in the near term to prioritize uncharacterized substances for regulatory testing using both traditional and novel test methods. The eventual goal of Tox21 is to use HTS methods to generate data that will allow risk assessors to more accurately predict the effects of regulated substances on human health and the environment.

Information about nominating assays and NICEATM support of Tox21 can be found on the NICEATM–ICCVAM website.

Contact Information: Dr. William S. Stokes, D.V.M., Director, NICEATM, NIH/NIEHS, P.O. Box 12233, MD K2-16, Research Triangle Park, NC 27709; T: (919) 541-2384; FAX: (919) 541-0947; niceatm@niehs.nih.gov.

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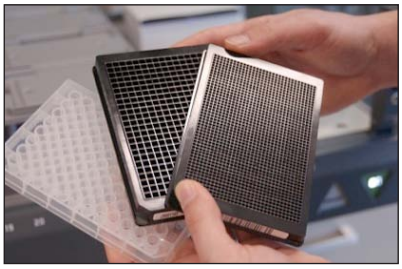

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The NTP website offers electronic files of the Report on Carcinogens and the library of NTP Technical Reports and NTP Toxicity Reports. The PDF files of these reports are available free-of-charge through the NTP website at http://ntp.niehs.nih.gov (see Resources).

Contact Information: NTP Office of Liaison, Policy and Review, NIEHS, P.O. Box 12233, MD K2-03, Research Triangle Park, NC 27709; T: (919) 541-0530; FAX: (919) 541-0295; CDM@niehs.nih.gov

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