Volume 6, Issue 2

July 2007

Institute Update

BITS & PIECES

- WE'VE MOVED: our new address is 30 W. Watkins Mill Road, Gaithersburg , MD. All other contact information has remained the same
- Sign up now for the 2007 Practical Methods Workshop Oct. 9-11. Visit our webpage for more details
- Rodger Curren and Hans Raabe will attend the 6th World Congress on Alternatives to Animal Testing Aug. 21-25, Tokyo, Japan
- The Phenion® Full Thickness Skin Model and Its Applications: Sept. 19-20, 2007. www.phenion.com
- 2007 In Vitro Alternatives Forum: Strategies for Use and Acceptance, Sept. 25, 2007 www.iivs.org

See Page 3 for more details

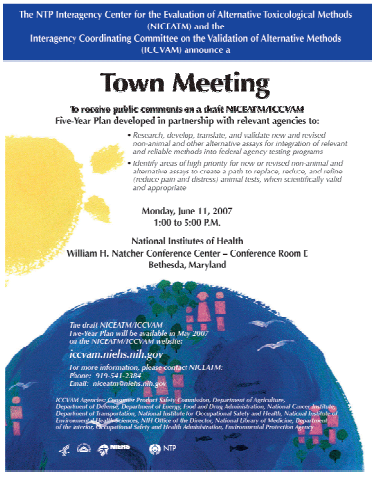
- 14th Congress on Alternatives to Animal Testing; Linz 2007 Sept. 28-30, 2007 www.zet.or.at
- Evidence Based Toxicology Forum: Oct. 15-18, 2007 www.ebtox.org

Inside this issue:

NICEATM/ICCVAM Five Year Plan

In response to requests from the Appropriations Committee of the U.S. House of Representatives and the U.S. Senate, NICEATM/ICCVAM is preparing a Five-Year Plan covering the period of 2008-2012. The Draft Plan outlines how NICEATM-ICCVAM will facilitate the research, development, translation, validation and regulatory acceptance of alternative test methods that reduce, refine and replace the use of animals in testing, while maintaining scientific quality and the protection of human health, animal health, and the environment. The plan identifies four Key Challenges:

1. to identify priority areas and facilitate the activities associated with these areas;
2. to incorporate innovative research initiatives which will lead to new alternative test methods;
3. to encourage acceptance and approval of alternative test methods to reduce, replace or refine the use of animals; and
4. to develop and strengthen both national and international partnerships to facilitate the progress of the activities.



The Draft Plan was made available for public comment on the NTP web-site (http://iccvam.niehs.nih.gov/docs/5yearplan.htm) and was also presented at a Town Meeting in Bethesda, MD on June 11, 2007. Oral comments were given by one independent consultant and four organizations including IIVS. Several of the general comments urged ICCVAM to take more of a leadership role and to focus on replacement (rather than reduction or refinement) alternatives. Others felt that the plan fell short of supplying strategic objectives including deliverables and timelines. Rodger Curren of IIVS suggested that a web-based scorecard could be used as a mechanism to track ongoing progress. This type of interface would also allow stakeholders to identify areas in which they can assist in the process.

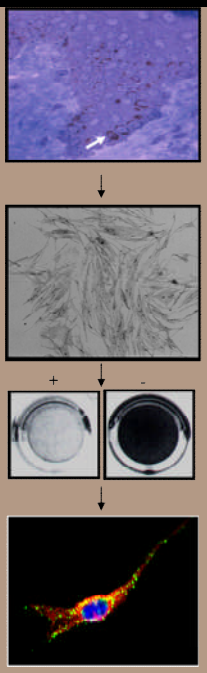
Subsequent to the Town Meeting, a working group from ICCVAM's Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) presented their own Review of the Draft Plan. Please see the Supplement of this issue for a synopsis.

Moscow Seminar Spreads Awareness of Alternatives

Rodger Curren was recently invited to participate in a conference organized by the Procter & Gamble Company to spread awareness of alternative testing methods in Russia and Kazakhstan. The goals of the meeting were to raise interest in EU approaches to validation and acceptance of alternative methods, to explore applicability of the 3Rs in accordance with the European Cosmetics Directive, and to provide new perspectives of the usability of alternatives in the EU and Russia. The seminar was widely attended, with guests including representatives of the Russian Ministry of Industry and Energy, the Ministry of Health, and members of local industry associations. Other experts from the ECVAM, OECD, Vrije Universiteit Brussels, and HSUS also presented their experience on safety assessment based on alternative test methods.

Technical Notes - Skin Pigmentation As An In Vitro Target

The skin is an extremely important organ, representing the body's physical barrier against mechanical, chemical, and microbial factors that may significantly affect our physiological status. In addition to those functions, the skin, through its pigments, provides a unique defense system against the harmful effects of UV radiation. In that respect, melanin is the most important of these pigments and its biosynthesis is a complex pathway regulated by several enzymes, tyrosinase being the rate-limiting one. Melanin production takes place in highly specialized cells, called melanocytes, within membrane-bound organelles referred to as melanosomes. Melanosomes are transferred via dendrites to surrounding keratinocytes, where they play a critical role in photo-protection forming the melanin caps that reduce UV-induced DNA damage in the epidermis.



In vitro studies focused on pigmentation generally involve two types of mammalian melanocytes which are either commercially available or which can be provided by laboratories in the pigmentation research field:

- normal mammalian melanocytes (primary cells and cell strains) which are usually available from donors in limited quantities and have a finite lifespan
- transformed mammalian cells which are capable of unlimited replication and can be maintained indefinitely in culture (immortalized).

In vitro studies on mammalian melanocytes are extremely helpful for both pharmaceutical and cosmetic industry-oriented investigations but are not limited to those specific areas. Alterations in melanin biosynthesis are usually monitored by assaying for the activity of enzymes in the normal synthetic pathway. Tyrosinase is the most important of these enzymes and is frequently used as the end-point when actives are tested for their action on mammalian pigmentation; however, *in vitro* assays for other enzymes and factors involved in melanin biosynthesis pathway are now available and could be potentially used in screening for the efficiency of actives impacting the melanin production. Changes to the pigment biosynthesis rate are readily visible following the treatment of melanocytes in culture with actives of interest and are easily detectable using standard laboratory equipment. A selection of assays targeting melanin biosynthesis, tyrosinase enzymatic activity, etc. are available. Protocols can be developed specifically for finding actives targeting the increase of melanin production (such as pharmaceutical compounds with potential use in vitiligo treatment or new exciting self-tanners) or for finding better actives for skin lightening. These latter assays are of great interest especially for the cosmetic industry and equally so for the treatment of different hyperpigmentary disorders or conditions (melasma, freckles, solar lentigines etc.).

For more specific information on skin pigmentation please contact Dr. Emilia Costin at 301.947.6524 or ecostin@iivs.org

IIVS' Continued Commitment to Quality Results in New Ventures

In a continuation of IIVS' commitment to quality, Amanda Ulrey and Rodger Curren presented a 90 minute session titled "Emerging Technology - Introduction to and Guide to Auditing In Vitro Toxicology Studies" at the annual U.S. Society of Quality Assurance Meeting. The session was attended by over 100 quality assurance professionals. Since the use of *in vitro* alternatives is expanding throughout the cosmetics, personal care, household product and pharmaceutical industries as screening tools or replacements for animal studies, quality assurance auditors are increasingly asked to provide in-life data, and facility inspections of these assays and the laboratories that conduct them. The session provided QA auditors with background information on the emergence of *in vitro* assays and their path to regulatory acceptance, some practical examples of what a QA auditor should look for during an inspection of an *in vitro* laboratory, and a summary of some of the ways in which industry is currently using *in vitro* test methods.

IIVS also recently partnered with ECVAM to design and implement a new program aimed at providing a quality assurance audit of prepared background review documents (BRDs). BRDs contain a large amount of data compiled from a number of sources. These data are analyzed in a variety of ways to determine the potential utility of the assay described. Since determinations on the potential validity of many assays are based on the information contained within these BRDs, it is critical that the data be correct and reliable. An independent QA audit is a way to gather evidence to give the project management team confidence in the information presented within the BRD. An audit protocol was created and followed by the auditors from IIVS and ECVAM while conducting the work. The audits provided valuable insight into the contents of the BRD and revisions are underway to correct and clarify the information presented.

Gates of the JRC in Ispra, Italy

Workshop for European Coalition to End Animal Experiments

The European Coalition is comprised of key animal protection societies from all over Europe as well as international partner organizations such as the Coalition for Consumer Information on Cosmetics (US) and Eurogroup for Animal Welfare (EU). Established in the 1990's to lobby the European Parliament over the issue of cosmetics testing, the campaigning alliance now meets regularly to discuss initiatives regarding the use of laboratory animals including the revision of EU Directive on the Welfare of Laboratory Animals (Directive 86/609), the 7th Amendment to the Cosmetics Directive and REACH legislation. During one such meeting, a satellite workshop titled *Non-Animal testing Methods: Theory & Practice* was held for members. Co-organizers of the workshop included IIVS, the National German Center for Alternatives to Animal Experiments (ZEBET) and the German Animal Welfare Academy (Deutscher Tierschutzbund). Held in Neubiberg, Germany at the headquarters of the Deutscher Tierschutzbund, participants heard lectures and discussed the use of *in vitro* methods for areas such as eye irritation, skin corrosion, phototoxicity and genotoxicity. Attendees were provided with a tour of the laboratory facility of the Academy and saw demonstrations of selected methods first hand. For more information on the Coalition please visit www.eceae.org.

Dr. Manfred Liebsch of ZEBET demonstrates direct reduction of MTT to course participants.

In Vitro Alternatives Forum

To commemorate its 10th Anniversary, IIVS will organize a meeting to discuss critical aspects of the *in vitro* toxicology field – from science to policy. The program will cover topics from novel new methods to analysis of how mature assays are used on a daily basis by industry. Sponsored by a contribution from Beauty Avenues, *The 2007 In Vitro Alternatives Forum: Strategies for Use and Acceptance* will be held on September 25, 2007 in Gaithersburg, MD. The meeting will update stakeholders on the status of alternative methods and hurdles faced in their use and acceptance. In addition, programs designed to implement alternatives in regulatory testing requirements in the US and other countries will be discussed. Speakers include representatives from the scientific, regulatory and policy communities such as ECVAM, ICCVAM, The Humane Society Legislative Fund, The Procter & Gamble Company and IIVS. New applications and technologies will be presented by Capsant Neurotechnologies. To learn more about the meeting please visit www.iivs.org.

SAP Member Highlight – Prof. Dr. Thomas Hartung

Dr. Hartung has been a member of the Institute's Science Advisory Panel since his appointment as the Head of ECVAM in 2002. After receiving his Ph.D. (Biochemical Pharmacology) and M.D. (Toxicology), Dr. Hartung worked as an assistant professor in Konstanz, Germany. From 1996-2002 he served as CEO of the Steinbeis Technology Transfer Center for In Vitro Pharmacology and Toxicology. In 2003 he became an honorary full professor of the University of Konstanz. As Head of ECVAM Dr. Hartung is responsible for organizing efforts to promote the scientific and regulatory acceptance of non-animal tests and to co-ordinate the independent evaluation of such tests. Dr. Hartung has published over 200 scientific papers and has served on the editorial boards of ATLA and ALTEX in addition to being the Vice President of the Middle-European Society for Alternatives to Animal Experiments. This year Dr. Hartung received the Society of Toxicology's Enhancement of Animal Welfare Award in recognition of his efforts in accelerating the alternative methods validation process. We are pleased that Dr. Hartung is able to fit the IIVS SAP meetings into his busy schedule, keeping the panelists informed of recent progress in the validation status of alternatives internationally.

CELEBRATING 10 YEARS!

Institute for In Vitro Sciences, Inc.

Advancing Science & Animal Welfare Together

We've Moved!!
30 W. Watkins Mill Road, Suite 100
Gaithersburg, MD 20878

Phone: 301-947-6523
Fax: 301-947-6538
Email: info@iivs.org

IIVS Welcomes Two New Contributors!

Beauty Avenues

As a division of Limited Brands, Beauty Avenues is committed to furthering their understanding of the development, validation and practical testing approaches that provide sound scientific basis for supporting the safety assessment of their products. In addition to continuing its notable testing program with IIVS to support products for Bath and Body Works and Victoria Secret Beauty Brands, Beauty Avenues has made a contribution to support the Institute's Educational and Outreach programs to further the advancement of alternative methods.

Mary Kay Corporation

To reflect its compassion for animals, Mary Kay Inc. does not conduct, or request on its behalf, any testing of products or ingredients on animals. This has been the Mary Kay Inc. policy for nearly 20 years and they are committed to continuing this effort in the future. In addition, they support globally recognized organizations, such as IIVS, in the search for alternative testing methods and have an active *in vitro* testing program to assess products and ingredients for safety and efficacy.

"What's New at Our House"

IIVS proudly welcomes our newest Study Director, Dr. Emilia Costin. Dr. Costin received her B.S. degree in Biology from the University of Bucharest (Romania) in 1997 and her M.Sc. degree in Molecular Biology in 1998. While still in the M.Sc. program, Emilia was employed by The Institute of Biochemistry of The Romanian Academy in Bucharest where she soon enrolled in the PhD training program. She received her PhD (Cum laude) in 2001 from the Institute of Biochemistry and followed this with a postdoctoral position at The National Institutes of Health, National Cancer Institute, Laboratory of Cell Biology, Pigment Cell Biology Section (2001-2005). Emilia was involved in several projects while at NIH, most of them focused on the intracellular trafficking and maturation of melanosomal proteins. After completing her postdoctoral fellowship at NIH, Emilia worked at Avon Products, Inc. as a senior research scientist for the Bioscience Group.

Teri Wallace, Quality Assurance and Client Services Associate, recently completed her work at Johns Hopkins University and received her Master's of Science in Biotechnology. We congratulate Teri on her achievement and look forward to her application of this new knowledge in her position at IIVS.

Rodger Curren is the recipient of the 2007 Björn Ekwall Memorial Award. This Award recognizes Rodger's outstanding contribution in the field of *in vitro* toxicology, particularly promoting the development, optimization, validation and acceptance of alternative test methods. The award will be presented at the 25th Workshop of the Scandinavian Society for Cell Toxicology, taking place in Salzau, Germany September 19-22, 2007. We join with all of Rodger's colleagues and friends in congratulating him on this honor.

Rodger and Björn Ekwall at Uppsala University in the early '90s.

In recognition of his exceptional dedication to the programs, employees and clients of IIVS, **Hans Raabe** has been appointed Vice President and an Officer of the corporation. All of us at IIVS are appreciative of Hans' efforts and congratulate him on his expanding role.

New Address: IIVS has completed the move to its new facility. Still located in Gaithersburg, MD, our new space is comprised of a 2,500 sq. ft. laboratory and 4,200 sq. ft. office space. To plan a site visit and tour our new facility, please contact Amanda Ulrey, Head of Quality Assurance at aulrey@iivs.org.

Volume 6, Issue 2 supplement

July 2007

Institute Update Supplement

NICEATM/ICCVAM Five Year Plan

A meeting of ICCVAM's Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) was held on June 12, 2007 in Bethesda, Maryland to present a document entitled "Review of the Draft Five-Year Plan by the SACATM Working Group." Formed in May 2007, the purpose of this Working Group (WG) was to review how well the Plan addressed the following objectives:

1. Research, development, translation and validation of new and revised non-animal and other alternative assays for integration into federal agency testing programs and
2. Identification of areas of high priority for new and revised non-animal and alternative assays for replacement, reduction and refinement of animal tests.

For each objective the Draft 5-Yr Plan was critically analyzed for current and planned activities and how well they matched the above objectives.

In considering if the Draft Plan was Comprehensive, the WG stated that the Plan contains an "impressive compilation of activities" either being conducted or managed by the 15 ICCVAM federal agencies as well as method-development activities in Europe and Japan. The review suggested that, given the large volume of activities and the complexities of challenges faced, it is critical to have a comprehensive and clearly articulated Five-Year Plan. Improvements in the Draft Plan would include an explanation of the criteria used for setting priority areas. The Working Group also suggested identification of endpoints for which partial or full replacement of animal use is achievable in the near-term and pointed to previously submitted comments by ILSI/HESI and the HSLF.

When considering if the Draft Plan was Strategic the Working Group stated that - although it is difficult to assimilate information from 15 federal agencies - the Draft Plan fell short "in articulating a clear vision and strategic perspective" and "read more like a catalogue of activities rather than a plan." They suggested that the Plan focus on perhaps "2-3 highest priority areas that cut across the ICCVAM agencies and develop a detailed plan to carry them out with near-term and far-term goals." The WG went further to encourage the Plan to incorporate procedural as well as scientific challenges. "The (Working Group) understands that some perceive the current ICCVAM validation process as too expensive, time-consuming, and a very high hurdle for alternative methods. As part of the Five-Year Plan, would it be beneficial for ICCVAM/NICEATM to consider opening up a dialogue with the scientific, stakeholder, and regulatory communities to see if there may be ways to utilize more streamlined processes that do not sacrifice scientific rigor."

Asking if the Plan was Detailed with Clearly Defined Priorities and Milestones, the WG suggested it might be beneficial to use a SWOT type of analysis (Strengths, Weaknesses, Opportunities and Threats). It was suggested that this type of analysis would help provide a clear "road-map for NIECEATM/ICCVAM to identify the highest priority objectives,

to plan to achieve these objectives and to make real and lasting impacts" regarding alternative assays. "As it stands right now, the activities of NICEATM/ICCVAM appear to be governed by a 'first come/first served' process rather than by a process designed to achieve results with the greatest impact or to assign limited resources based on the highest priority issues."

The Working Group also considered if the Plan Described Clearly Defined Roles and did it Clearly Identify Gaps. The Group felt that since it was difficult to discern the specific responsibilities of ICCVAM from other agencies, the Plan should emphasize more clearly what NICEATM/ICCVAM itself can accomplish and should include more details for the highest priority areas. Although the plan articulates research and development activities of the federal agencies that comprise ICCVAM, it does not focus on the gaps that exist on the pathway to integration of a method into regulatory testing frameworks. Most importantly the Working Group "believes it is incumbent upon the ICCVAM agencies themselves – as critical stakeholders- to fully embrace the 3Rs and exert the leadership needed to assure that the validated methods delivered by the efforts of NICEATM and ICCVAM are actualized into regulatory testing frameworks as soon as practicable." The review suggested that the Plan include a table of methods that have been previously reviewed and approved by ICCVAM and the agencies' actions on those tests.

Finally, when assessing if the Plan Addresses Communicating with and Engaging Stakeholders, the Working Group points out that such communication is vital to success and that the Plan could be strengthened to incorporate more opportunities for education, training and communication activities.

Excerpts are taken from the "Review of the Draft NICEATM-ICCVAM Five-Year Plan by the SACATM Working Group." To read the Review in its entirety, please visit www.iivs.org What's New.