Relevance and Follow-Up of Positive Results in *In Vitro* Genetic Toxicity (IVGT) Testing Project Committee

Presenter and Vice-Chair:

Bhaskar Gollapudi, Ph.D.

(The Dow Chemical Company)

Chair:

Veronique Thybaud

(sanofi-aventis)

Staff:

James Kim, Ph.D., DABT

January 2009 HESI Annual Meeting

IVGT Project Committee

Objectives

1. **To improve the scientific basis of the interpretation of results from *in vitro* genetic toxicology tests for purposes of accurate human risk assessment.**
2. **To develop follow-up strategies for determining the relevance of *in vitro* test results to human health.**
3. **To provide a framework for the integration of the *in vitro* testing results into a risk-based assessment of the effects of chemical exposures to human health.**

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Membership

- **Currently have 20 industry members**

- Amgen
- AstraZeneca
- BASF
- Bayer Healthcare Pharma
- Boehringer-Ingelheim
- Bristol-Meyers Squibb
- Coca-Cola
- The Dow Chemical Co.
- GlaxoSmithKline
- Johnson & Johnson
- L'Oreal
- Merck
- Mitsubishi
- Novartis
- Pfizer
- Procter & Gamble
- sanofi-aventis
- Schering Plough
- Servier
- Takeda

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Steering Committee

- Dr. Marilyn Aardema,
  Procter & Gamble, USA
- Dr. B. Bhaskar Gollapudi (Vice-Chair)
  Dow Chemical, USA
- Dr. Kerry Dearfield, USA
  USDA, USA
- Dr. George Douglas
  Health Canada, Canada
- Dr. Masa Honma
  Nat'l Institute of Health Sciences, Japan
- Dr. James Kim
  ILSI-HESI, USA
- Dr. David Jacobson-Kram
  US FDA, USA
- Dr. Peter Kasper
  BfArM, Germany
- Dr. James MacGregor (Scientific Advisor)
  Toxicology Consulting Services, USA
- Dr. Robert Rees
  GlaxoSmithKline, UK
- Dr. Jennifer Sasaki
  Johnson & Johnson, USA
- Dr. Veronique Thybaud (Chair)
  sanofi-aventis, France

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Context to IVGT Effort

- Relatively high rate of positive results in the *in vitro* tests
  - Primarily in the mammalian cell assays
- More importantly … low specificity
  - Many *in vitro* results, especially in the *in vitro* chromosome damage tests, not confirmed in the *in vivo* genetic toxicology tests and/or in carcinogenicity studies

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Consequences

- De-selection of potentially useful compounds of low risk to humans

- Trigger numerous additional studies, including *in vivo* and mechanistic studies, to further evaluate the level of concern and risk for humans

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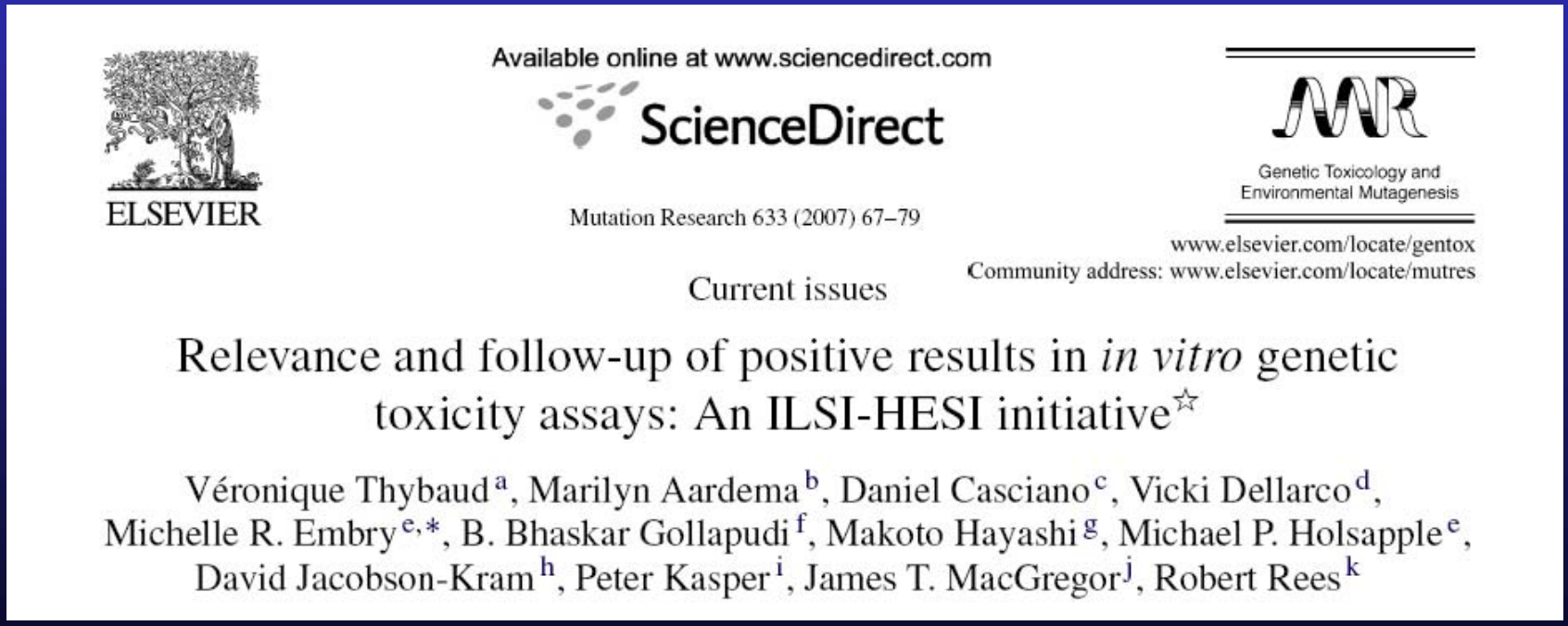
2006 IVGT Workshop Outcome

- Publication:



Available online at www.sciencedirect.com

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Mutation Research 633 (2007) 67–79

Genetic Toxicology and Environmental Mutagenesis

www.elsevier.com/locate/gentox

Community address: www.elsevier.com/locate/mutres

Current issues

Relevance and follow-up of positive results in *in vitro* genetic toxicity assays: An ILSI-HESI initiative☆

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- Recommendations for follow-up activities

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Follow-Up Activities

- Second workshop in June of 2007
- Three sub-groups/initiatives identified :

1. Examination of emerging technologies and new strategies
2. Development of a decision tree for follow-up strategies in case of positive findings
3. Development of quantitative information to support decision tree

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Subgroup 1

- New and Emerging Technologies Subgroup

  David Jacobson-Kram, Chair; Jennifer Sasaki, Co-chair

  - Workshop held in May 2008
    - Presentation and pros/cons analysis of new and emerging technologies potentially useful for:
      - screening tests
      - replacements for initial tests (long-term)
      - follow-up tests (piggy back on standard toxicity tests)
  - Manuscript of proceedings in progress
  - Potential next step: contribute to “ring-trial” using a few selected new technologies and a set of model chemicals

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Subgroup 2

- Review Subgroup

  Veronique Thybaud, Chair; Kerry Dearfield, Co-chair

  - Evaluation of existing assays (ranking)
  - Development of a decision tree for follow-up testing in case of in vitro positive results
  - Identification of needed improvements to the existing assays and the missing ones to aid in the decision process.
  - Manuscript in progress, next meeting in Feb 09

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Subgroup 3

- Quantitative Group

  Bhaskar Gollapudi and Jim MacGregor, co-chairs

  - Development of quantitative information to support the decision tree
  - First objective: *in vitro* to *in vivo* comparison and extrapolation
  - Threshold evaluation
  - Second objective: *in vivo* rodent to human comparison and extrapolation

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Subgroup 3

- Compile a short list of validation compounds
  - Select well-characterized agents that offer a rich data package of robust quantitative data
  - Run these compounds through various quantitative approaches to identify useful analysis methods
- Sponsor/enhance a database of quantitative data
  - Test quantitative method(s) on this expanded data set

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Summary

- New/Emerging Technologies Subgroup:
  - Manuscript in progress
  - Identification of assays to be further evaluated: contribution to collaborative work?
- Review/Decision Tree Subgroup:
  - Manuscript in progress
  - Might be presented at the IWGT meeting in August, 2009 for broader approval
- Quantitative Subgroup:
  - Identification of case studies (pilot study on small set of compounds)
  - Development of models to be validated with more compounds
  - Collaboration with Health Canada

- Workshop February 2-6, 2009 in Washington, DC

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….. moving genetic toxicology forward from purely a hazard identification science to better informing the human risk ….

Thank You!