

*Minutes from the June 23, 2005
Meeting of the NTP Board of Scientific Counselors
High Throughput Working Group (HTSWG)*

<u>CONTENTS</u>	<u>Page</u>
I. ATTENDEES.....	2
II. INTRODUCTIONS.....	2
III. MOLECULAR LIBRARIES (ML) PROGRAM AT NIH.....	2
IV. CHARGE TO THE WORKING GROUP.....	3
V. GENERAL DISCUSSION OF HTS ASSAYS.....	3
VI. OUTLINE FOR A POTENTIAL WORKSHOP.....	4
VII. ACTIONS FROM THE MEETING.....	6

Attachment 1: HTSWG Charge

Attachment 2: Agenda

Attachment 3: Roster of HTSWG Members

I. ATTENDEES

The National Toxicology Program (NTP) Board of Scientific Counselors High Throughput Screening Working Group (HTSWG) met on June 23, 2005, in Auditorium C of the Rodbell Auditorium, Rall Building, National Institute of Environmental Health Sciences, 111 T. W. Alexander Drive Research Triangle Park, North Carolina.

The following individuals attended the meeting:

High Throughput Working Group members

Pauline Gee, MDS Pharma Services
Shuk Mei Ho (Chair), University of Massachusetts Medical School
Patricia (Kate) Johnston, Consultant
Jeffrey Lawrence, Merck & Co. Inc.,
Kenneth Lewis, OpAns, LLC
Christopher Lipinski, Pfizer Global Research and Development
Charlene McQueen, University of Arizona

NIEHS staff

John Bucher
William Caspary
Jonathan Freedman
Grace Kissling
Christopher Portier
Barbara Shane
Cynthia Smith
Kristine Witt
Mary Wolfe

II. INTRODUCTIONS

The meeting was convened at 1PM. The meeting was closed to the public. Dr. Ho welcomed the participants who introduced themselves. The focus of the meeting was to initiate plans for a workshop on HTS.

III. MOLECULAR LIBRARIES (ML) PROGRAM AT NIH

Dr. Portier provided background information on the Molecular Libraries (ML) program at NIH. He said the NIEHS High Throughput Screening (HTS) program would be somewhat linked to the ML program, but NIEHS would also have its own separate program of testing, either on-site or conducted through contract agreements. Dr. Portier outlined the issues he thought would be important relating to the development of an HTS program at NIEHS. He said the types of assays, chemical design, number of replicates, and number of plates is an important aspect in designing the NIEHS assays to complement those of the ML program. Another issue related to the HTS initiative would

be to inform the federal agencies with whom the NIEHS collaborates on the usefulness of the HTS program and how it could be used for risk assessment. He said the molecular targets emphasized in the ML program might be different from the end points that the NIEHS pursues. He mentioned the level of grants that NIH has funded: a contractual grant with Discovery Partners International (DPI), the funding of 9 test centers around the country, the funding of P20 grants to 7 centers that will be developing better fluors and probes to measure HTS and 30 R03 grants to investigators who will be developing specific assays amenable to HTS. It is hoped that the assays funded by the R03 grants would eventually be acceptable to the ML group for testing in an HTS format either at NIH or at one of the funded test centers.

IV. CHARGE TO THE WORKING GROUP

Dr. Portier said that the charge to the working group for this planning meeting is to develop an outline for a workshop that will be held in the near future. The duration of the workshop will depend on its format. He said the first objective is the education of NIEHS and NTP scientists as to the usefulness and potential of HTS. He said the NTP is hoping that HTS assays will allow the NTP to set testing priorities based on results from a battery of HTS assays. Also, he is hopeful that the suite of HTS assays chosen will aid in the identification of classes of toxic chemicals by studying only 2-3 chemicals in that class. This would also allow the development of predictions as to how chemicals with similar structures might respond in biological systems. The workshop's focus on the dissemination and interpretation of data from HTS assays should not only target the toxicology community, but should address the dissemination and interpretation of HTS assay data by the broader scientific and regulatory community. There is concern among industry, academia, and the public about what sort of data will be generated and how it will be applied to risk assessment. It is important that the data be subjected to careful review to avoid any errors in the application of these data for predicting toxicity. How the NTP communicates the results of its testing to the public and to its regulatory partners and the scientific community will be critical. Dr. Ho agreed that communication is very important.

V. GENERAL DISCUSSION OF HTS ASSAYS

Dr. Christopher Lipinski said HTS is a process, not a goal. He said members of the Society for Bimolecular Screening (SBS) have extensive experience and are experts regarding HTS and hence the NTP should become involved with the society. He further stated that HTS expertise resides almost exclusively within industry. Dr. Kate Johnston noted that because HTS is a process, there are numerous steps where errors may occur as well as interference by a number of confounding factors. She added that new targets must be validated and validation must occur at each step of the process. It is extremely important that these details be carefully worked out prior to initiating a HTS program. Dr. Johnston expressed concern that data from the NIH testing program will be made public through PubChem. Dr. Kenneth Lewis and she opined that primary data may be of poor quality and low reliability and should not be used for analysis. Secondary targeted assays are required to produce usable data.

Since the targets for the NTP chemicals are unknown, the tier used for initial testing will be important. The first tier should test whether the chemical alters a step in a pathway known to be involved in the carcinogenic process such as DNA damage. A second tier using a medium throughput assay could follow.

Dr. John Bucher said it would be important to hear the views of the pharmaceutical industry and to include *in vitro* assays in the workshop. For workshop attendees, it was suggested that the *in vitro* toxicology community be targeted also, rather than limiting attendance to the HTS community, because it was felt that the former would have a good grasp of the types of targets and processes and a clear understanding of *in vitro* cell based assays and protocols, as compared to the pharmaceutical HTS community. Dr. Lewis suggested that a policy expert or legalist be involved in the workshop, because these issues will impact substantially on the function of the HTS program.

Discussion of HTS related meetings

Several HTS-related meetings were identified and it was thought that attendance by NTP staff might be informative.

- SBS Geneva meeting on September 16-21. Christine Giordano from Danbury, CT is the Executive Director of SBS and can be contacted for more details.
- IBC meeting in mid-August
- IBC meeting in San Francisco in December where assay development will be discussed.

VI. OUTLINE FOR A POTENTIAL WORKSHOP

The HTSWG discussed the types of attendees for the workshop. *They should include HTS experts from industry, persons with experience in *in vitro* toxicology who can provide critical input about the design and utility of HTS methods, and early users of the data such as lawyers and policymakers. The HTSWG drafted a preliminary outline for the workshop to include (1) an industry overview and perspective describing how assays are conducted and their utility for prediction, (2) a presentation on education of the toxicology community to alleviate their concern of the use of HTS for prediction and to get their support; and (3) policy and legal issues.

Different alternative formats for the workshop were discussed, but it was decided that a two-day meeting in November or December 2005 would be best. The group next discussed the structure of such a 2-day informational workshop.

Day 1

The morning session for the workshop would address six topics.

- Dr. Portier would discuss the purpose of the HTS workshop in an introductory presentation.
- Dr. Janzen could give the next talk on the history of HTS and the importance of analysis in HTS because of his expertise and knowledge.
- Dr. Lipinski would discuss chemical libraries.

- Dr. Oprea, University of New Mexico, or Dr. Stanley Young at NISS could discuss conceptual aspects of HTS. This talk would cover second level triage and present a couple of case studies.
- Dr. Daniel from the UK could present a discussion of the difficulties associated with *in vitro* prediction based on HTS assays.
- Dr. Bucher would make the final presentation describing how public health decisions are made from toxicology studies.

The afternoon could be devoted to regulatory aspects and decision-making; Dr. Sam Cohen was proposed as a moderator,

- Two talks being given by representatives from EPA or FDA.
- One speaker from academia.
- One speaker to present regulatory aspects and how they are conveyed to the public; Dr. Hillary Carpenter, Minnesota Department of Health was suggested for this presentation.
- Two presentations by representatives from the ACC and PETA.

Day 2

The next morning would be devoted to breakout groups. Discussion as to who should chair the breakout groups and the members of each breakout group then ensued. The HTSWG proposed the breakout groups have 5-7 participants. The end of July was set as a target for finalizing the list of attendees. During the first two hours of the breakout group sessions, representatives could make 20-30 minute presentations on relevant subtopics and then discussion could follow. Proposed topics and participants (in parenthesis) for the breakout groups include:

- Targets for cell based assays specifically relating to carcinogenicity and reproduction (co-chairs Kate Johnston and Dr. Kim Boekelheide, Brown University as a member)
- New targets and predictive toxicogenomics (chair Dr. Tim Zacharewski, Michigan State University with Drs. Raymond Tenant, NIEHS and Christopher Bradfield, University of Wisconsin as members)
- Chemicals for study including compound handling and stability (co-chairs Drs. Lipinski and John Schwab of NIH with Drs. Oprea and John Lazo as members)
- Study design including logistics of dose response, replication on plates etc. (co-chairs Drs. Lewis and Janzen with Dr. Richard Storer, Merck, as a member)
- Validation and database construction and management (co-chairs Drs. Pauline Gee and Stanley Young with Drs. Walter Piegorsch, University of South Carolina and Nigel Green, Pfizer as members)
- Policy (chair Dr. Jonathan Freedman, NIEHS, with Drs. Kevin Crofton, EPA, Bob Kavlock, EPA, Brian Spear, Abbott, and Hillary Carpenter as members)

Plenary Session

The afternoon of the second day would entail 30-minute presentations by the chair of each breakout group describing the group's conclusions. The workshop would conclude with an overall summary of the conclusions.

Dr. Portier said the NTP would be contacting the HTSWG with suggestions of a date for the workshop and would like to have additional names for participants on the different working groups.

The meeting adjourned at 3:52PM.

VII. ACTIONS FROM THE MEETING

- Decide on a date for a 2-day workshop to be held in Washington DC in November or December, 2005
- Finalize the format for the workshop
- Decide on the types and number of break out groups
- Ask the HTSWG for names of attendees and invited speakers

NTP BOARD OF SCIENTIFIC COUNSELORS HIGH THROUGHPUT SCREENING WORKING GROUP

Purpose

The NTP envisions that over the next decade our rapidly expanding knowledge of the physiological, biochemical, and molecular bases of disease will lead to the development of, and a gradual transition to, higher throughput methods for predicting the toxicological impacts of environmental agents. Thus, the NTP plans to build a testing program using less expensive, higher throughput, alternative assays for screening a large number of substances and establishing priorities for additional, more extensive agent-specific mechanistic studies.

The concept of high throughput screening (HTS) is based on the use of automated processes to evaluate hundreds to thousands of agents rapidly for activity within *in vitro* biological systems under a variety of conditions. HTS may also be used to test complex mixtures or combinations of experimental conditions not testable in classical *in vivo* assays. The assays will target the key pathways, molecular events, or processes linked to carcinogenicity and/or reproduction/development endpoints. The NTP anticipates that these assays will use a wide range of exposure concentrations and both human and animal materials (cells, tissues, genes, receptors, etc.) to aid in extrapolating from animals to humans and from high to low exposures. Mechanistic endpoints initially targeted by the HTS program may include genotoxicity, cytotoxicity, cell proliferation, apoptosis, and critical receptor-mediated activities for which, ideally, commercially available assays may already exist; new assays may be developed and automated at NTP contract laboratories.

In order to gain scientific input on HTS and its application for the NTP testing and research program, the NTP will establish the High Throughput Screening Working Group of the NTP Board of Scientific Counselors (“the HTSWG”). The HTSWG will be a technical advisory body to provide a structured and formal mechanism for bringing knowledgeable experts together to address the development and use of HTS by the NTP in its testing and research program. Specifically the HTSWG will provide advice to the NTP Board of Scientific Counselors on HTS.

Function

The HTSWG shall provide guidance and advice to the NTP Board of Scientific Counselors on the development and selection of assays and procedures to be used for HTS, as well as the development of interpretative models for using HTS data to predict human or animal responses with acceptable accuracy. Once the program has been implemented, the HTSWG shall conduct periodic reviews advising on the overall merit and quality of the activities and whether the data generated can be used for predicting the toxicological impacts of environmental agents. Members may also assist in the identification of an initial set of chemicals to test by HTS.

Structure

The HTSWG shall consist of a Chairperson (a current member of the NTP Board of Scientific Counselors) appointed by the Director of the NTP and up to 10 scientists drawn from industry, academia, or government with expertise in, but not limited to, mechanisms of carcinogenicity, reproduction/development, development of *in vitro* assays, high throughput testing systems, chemistry, informatics and data management, computational toxicology, gene expression, cell cycle control and apoptosis, oxidative stress, and receptor biology.

The NTP Liaison and Scientific Review Office within the Office of the Director of the

Environmental Toxicology Program will provide management and support services to the HTSWG.

Meetings

The working group is expected to meet annually or at the call of the Chair as need dictates. A government official shall be present at all meetings. The NTP will make the HTSWG meetings as accessible as possible to the public and follow appropriate National Institutes of Health (NIH) guidelines for the management, oversight, and conduct of working groups. The Chair will report on the activities of the HTSWG to the NTP Board of Scientific Counselors on a regular basis.

Compensation

HTSWG members shall be paid at a daily rate equivalent to that of members of the NTP Board of Scientific Counselors, plus per diem and travel expenses. Members who are officers or employees of the U.S. government shall not receive compensation for service.

Termination

The HTSWG shall continue its activities until deemed by the NTP Board of Scientific Counselors as no longer necessary with approval by the Government official.

NTP Board of Scientific Counselors

Agenda
NTP Board of Scientific Counselors Meeting
High-Throughput Working Group
Planning Meeting

Rodbell Auditorium C, Rall Building
National Institute of Environmental Health Sciences
Research Triangle Park, NC
June 23, 2005

1:00 PM	Introductions	Chair, Dr. Shuk-Mei Ho, University of Massachusetts
1:10	Welcome	Dr. Christopher Portier, NIEHS
1:15	Charge to the HTSWG	Dr. Portier
1:30	Planning activities for the Workshop <ul style="list-style-type: none">• Potential date• Introductory talks<ul style="list-style-type: none">◦ Topics and speakers• Breakout groups<ul style="list-style-type: none">◦ Current and future assays◦ Chemicals for study◦ Study design◦ Database and analyses• Break-out group leaders and additional members	Dr. Ho
4:45	Additional agenda items	Dr. Ho
5:00	ADJOURN	Dr. Ho

**NTP Board of Scientific Counselors High Throughput Screening
Working Group (HTSWG)**

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