CONTRACT CONCEPT REVIEW

NTP Board of Scientific Counselors Meeting
June 16, 2015

Title: **Studies to Evaluate the Toxicologic Potential of Selected Test Agents for the National Toxicology Program (NTP)**

Presenter: **Molly Vallant, Program Operations Branch**

Purpose:

The objective of this contract is to facilitate NTP's efforts to characterize the potential adverse effects of chemical, physical, or biological agents by conducting in vitro and in vivo studies with special emphasis on mechanistic endpoints. The scope of the required activities is too great, and the space and personnel needed to conduct these studies exceed those available at the NIEHS; therefore, studies are to be carried out through contract mechanisms.

Background and Significance:

NTP has a long history of conducting general toxicity and carcinogenicity studies in laboratory animals as part of its mandate to characterize the toxicity of agents of public health concern. Through this contract, NTP will explore new approaches to toxicology testing by incorporating in vitro testing and mechanistic endpoints into short and long term NTP testing protocols. Examples of new approaches will include biochemical, molecular, physiological assays.

In general, toxicology studies are conducted according to the Specifications for the Conduct of Studies to Evaluate the Toxic and Carcinogenic Potential of Chemical, Biological and Physical Agents in Laboratory Animals for the National Toxicology Program -January 2011 and subsequent revisions; http://ntp.niehs.nih.gov/ntp/Test_Info/FinalNTP_ToxCarSpecsJan2011.pdf. Specific study designs (or portions there of) may require the use of the Specifications for the Conduct of Studies to Evaluate the Reproductive and Developmental Toxicity of Chemical, Biological and Physical Agents in Laboratory Animals for the National Toxicology Program -May 2011 and subsequent revisions; https://ntp.niehs.nih.gov/ntp/test_info/finalntp_reprospecsmay2011_508.pdf Contractors will be directed regarding studies or portions of studies that require these specifications.

Studies are conducted to evaluate the toxicity of test agents by various routes of exposure. The design of in vivo studies will vary depending on the test agents, route(s) of exposure, and endpoints to be evaluated. Studies will typically utilize Harlan Sprague Dawley rats and B6C3F1/N mice; however, other stocks/strains or other species (e.g. hamsters, dogs, rabbits, and guinea pigs) may be utilized. Study duration may be from

one to a few days up to lifetime; exposure may begin *in utero* or in young animals; the route of administration may be oral (dosed feed, dosed water, gavage), dermal, inhalation, or parenteral (intraperitoneal, subcutaneous, intravenous, intratracheal). Occasionally, dosing may also be administered by cannulation. Details for typical study designs and for individual routes of administration are found in the NTP Specifications cited above.

The NTP anticipates that the following study design elements will be frequently encountered.

- In vitro studies using tissues, cells or cell components will be conducted on a group of chemicals (e.g. 20-25 chemicals). The results of these studies will be used to select a smaller group (e.g. five) for five-day toxicology and toxicogenomic studies. The results of the five-day studies will then be used to select a smaller number of chemicals (e.g. one or two) for 28- or 90-day studies.

- Study designs will frequently include biochemical/molecular assays, ("Omics") including toxicogenomics, gene expression studies such as miRNA microarrays to capture small RNA species for microarray or qPCR applications http://www.qiagen.com/products/catalog/sample-technologies/rna-sample-technologies/mirna/mirneasy-mini-kit), qRT-PCR http://www.lifetechnologies.com/search/global/searchAction.action?query=taqman&resultPage=1&resultsPerPage=15&autocomplete=), Nanostring™ technologies which would allow Nexgen Sequencing Gene expression profiling by RNAseq (e.g. mRNA or miRNA) or genomic sequencing (e.g. whole genome, exome sequencing) by DNAseq multiplexing of many transcripts and several samples at once http://www.nanostring.com/.

- Neurotoxicity endpoints will include detailed clinical observations, functional observation battery, motor activity, Morris water maze, prepulse startle inhibition, etc. Newer technologies for gait analysis such as used by DigiGait, Motorater, or Catwalk may also be utilized.

- Other functional toxicologic assessments (e.g., cardiac function using radio telemetry to assess QT prolongation, pulmonary function using Flexivent or plethysmography, fertility assessment, etc.) may be conducted.

Proposed Changes to the Current Statement of Work:

The proposed Statement of Work (SOW) will include all current capabilities for carrying out in vivo toxicology studies and will be revised to include more capabilities for carrying out in vitro studies and evaluating mechanistic endpoints. There will also be more emphasis on performing perinatal exposure studies with neurobehavioral endpoints.