MATERIALS TRANSFER AGREEMENT

Provider:

U.S. Environmental Protection Agency (EPA)
Office of Research and Development (ORD)
National Center for Computational Toxicology (NCCT)

Recipient: University of North Carolina at Chapel Hil
308 Bynum Hall, CB#4105
Chapel Hill, NC 27599-4105

on behalf of:
Drs. Alexander Tropsha and Ivan Rusyn

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1. Provider agrees to transfer to Recipient's Investigator named below the following Research Material, prior to full and open public release:

A. In vitro assay data derived from Phase I of the ToxCast Program. This data is derived from a set of 308 unique chemicals which were analyzed using a variety of assay techniques. Below, this is referred to as the "ToxCast Data".
B. In vivo whole animal toxicology summary data derived from Office of Pesticide programs (OPP) Data Evaluation Records (DERs) and compiled in the EPA Toxicology Reference Database (ToxRefDB). This data is derived from a subset of the 308 ToxCast Phase I chemicals. Below, this is referred to as the "ToxRefDB Data".
C. Summary descriptions of the individual data sets.
D. Individual subsets of this data will be delivered to the recipient after they have been prepared for use at the EPA and cleared for release to the Recipient.

2. This Research Material may not be used in human subjects. The Research Material will be used only for research purposes by Recipient's investigator in his/her laboratory, for the research project described below, under suitable containment conditions. This Research Material will not be used for screening, production or sale, for which a commercialization license may be required. Recipient agrees to comply with all Federal rules and regulations applicable to the Research Project and the handling of the Research Material.

2(a). Were Research Materials collected according to 45 C.F.R. Part 46, "Protection of Human Subjects?"
____ Yes (Please provide Assurance Number:_____)
____ No
_X_ Not Applicable (Materials not collected from humans)

3. This Research Material will be used by Recipient's investigator solely in connection with the following research project ("Research Project") described with specificity as follows *(use an attachment page if necessary)*:

A. **Add brief detail on specific applications. Be specific--tailor for each recipient.**
   a. **Example: Analysis of the data using methods developed by the recipient or with which the recipient has expertise.**
   b. **Example: Extraction of chemical or biological signatures that can be used to link the in vitro assay data with in vivo toxicology.**

(See attached)

4. In all oral presentations or written publications concerning the Research Project, Recipient will acknowledge Provider's contribution of this Research Material unless requested otherwise. To the extent permitted by law, Recipient agrees to treat as confidential, any of Provider's written information about this Research Material that is stamped "CONFIDENTIAL" for a period of three (3) years from the date of its disclosure to recipient. The foregoing shall not apply to information that is or becomes publicly available or which is disclosed to Recipient without a confidentiality obligation. Any oral disclosures from Provider to Recipient which Provider wishes to be treated as confidential shall be identified as being Confidential at the time of the disclosure and by written notice delivered to Recipient within thirty (30) days after the date of the oral disclosure. Recipient may publish or otherwise publicly disclose the results of the Research Project, but if Provider has given Confidential information to Recipient, such public disclosure may be made only after Provider has had thirty (30) days to review the proposed disclosure to determine if it includes any Confidential information, to the extent such review period is permitted by law.

5. The Recipient will provide to the Provider all testing results obtained by the Recipient using the Research Material. Recipient acknowledges that the Provider will make such testing results freely available to the public.

6. This Research Material represents a significant investment on the part of Provider and is considered proprietary to Provider. Recipient's investigator therefore agrees to retain control over this Research Material and further agrees not to transfer the Research Material to other people not under his/her direct supervision without advance

written approval of Provider. Provider reserves the right to distribute the Research Material to others and to use it for its own purposes.

7. This Research Material is provided as a service to the research community. It is being supplied to Recipient with no warranties, express or implied, including any warranty of merchantability or fitness for a particular purpose. Provider makes no representations that the use of the Research Material will not infringe any patent or proprietary rights of third parties.

8. Recipient shall retain title to any patent or other intellectual property rights in inventions made by its employees in the course of the Research Project. However, if said inventions contain any portion of the Research Material, are derived from the Research Material, or could not have been produced but for the use of the Research Material, Recipient agrees to contact the Provider to determine what ownership interests, if any, the Provider may have, and, where applicable, to negotiate in good faith the terms of a commercial license. Inventorship for a patent application or a commercialized product based on said inventions shall be determined according to United States patent law.

9. When Provider is the EPA: Recipient agrees not to claim, infer, or imply endorsement by the Government of the United States of America (hereinafter referred to as "Government") of the Research Project, the institution or personnel conducting the Research Project or any resulting product(s). Recipient agrees to hold the Government harmless and to indemnify the Government for all liabilities, demands, damages, expenses and losses arising out of Recipient's use for any purpose of the Research Material.

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To the extent permitted by the N.C. Tort Claims Act, G.S. 143-291, et seq.,

10. When Recipient is the EPA: Provider will not be liable to EPA for any claims or damages arising from EPA=s use of the Research Material.

11. The Provider shall have the right to terminate this Agreement at any time if Recipient breaches any of the terms of this Agreement. Upon termination, Recipient shall return to the Provider all unused portions of the Research Materials.

12. All notices pertaining to or required by this Agreement shall be in writing and shall be signed by an authorized representative and shall be delivered by hand (including private courier mail service) or sent by certified mail, return receipt requested, with postage prepaid, addressed as follows:

Provider's Official and Mailing Address:

STATEMENT OF WORK

Addendum to the Materials Transfer Agreement

Between

The United States Environmental Protection Agency

National Center for Computational Toxicology (NCCT)

And

University of North Carolina at Chapel Hill

Carolina Center for Computational Toxicology

Principal Investigators: Alexander Tropsha, PhD, and Ivan Rusyn, MD, PhD.

Title of Project: Cheminformatics Analysis of ToxCast Data

Goal: Develop Predictive Chemical Toxicity Models of Biological Endpoints Studied by the ToxCast™ program

ToxCast™ program is "profiling over 300 well-characterized chemicals (primarily pesticides) in over 400 HTS endpoints" (http://epa.gov/ncct/toxcast/). The ToxCast dataset provides rich experimental information on *in vitro* and *in vivo* toxicity of chemical, which enables the development of advanced Quantitative Structure Toxicity Relationship (QSTR) methodologies for the estimation of chemical toxicity. This project is poised to address directly the three critical strategic objectives of the EPA's Framework of the Computational Toxicology Program (www.epa.gov/comptox/comptox_framework.html): (1) improve linkages across the source-to-outcome continuum, (2) develop approaches for prioritizing chemicals for subsequent screening and testing, and (3) deliver better methods and predictive models for quantitative risk assessment.

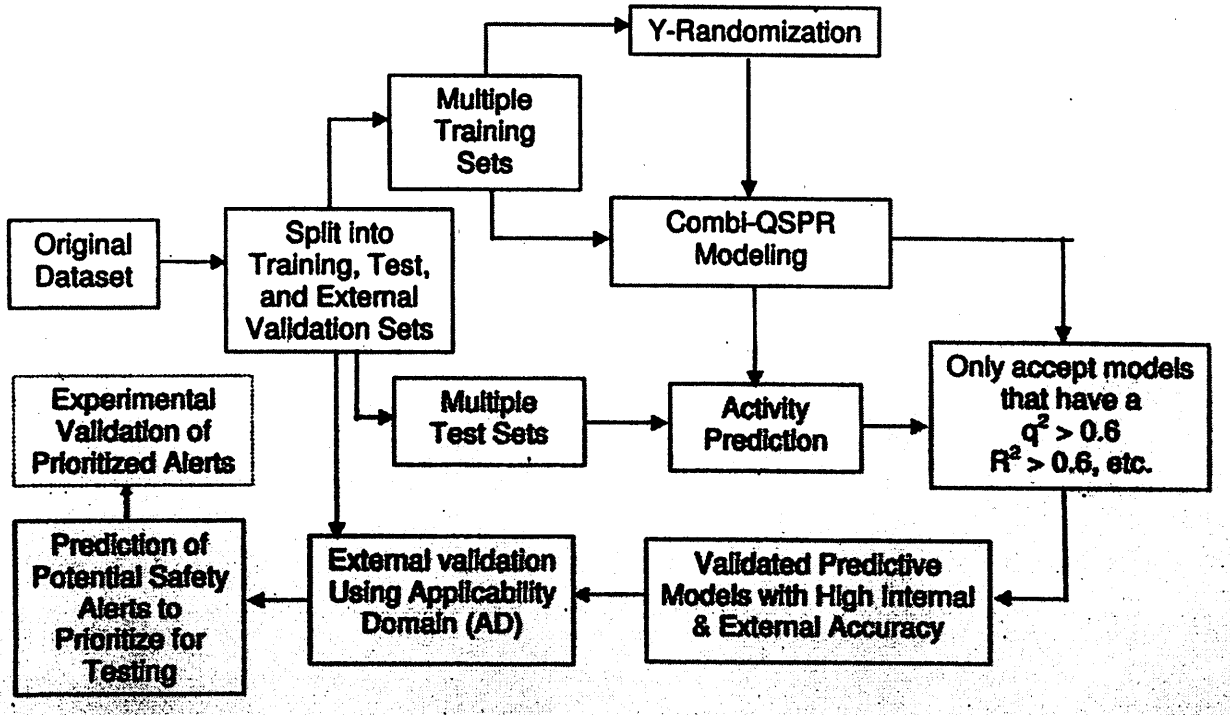
The modeling framework that will be used in this project has been refined over many years of our research in the areas of general Quantitative Structure Activity Relationships (QSAR) methodology development and applications including novel data analytical approaches, molecular descriptors, model validation schemes, overall QSAR workflow design and proposed inclusion of multidimensional experimental end-points including toxicological and toxicogenomic data. In this project we endeavor to extend our studies and deliver tools and models that go far beyond the scope of traditional QSAR modeling by directly engaging the entire "source-to-outcome" continuum of modern experimental toxicological research. Our research will entail rigorous analysis of interrelationships between chemical structure, high-throughput toxicity screening (HTS), multiple "-omics" data, and data from chronic toxicity studies. To address all strategic objectives of the EPA's

Framework while keeping focus on the accurate prediction of environmental and health risk assessment of chemical agents, we will develop QSTR methodologies that employs not only conventional chemical descriptors of molecular structures but also combine those descriptors with experimentally-derived biological endpoints. The ultimate goal of this project is to deliver robust modeling tools and accurate computational predictors of specific toxicity endpoints to prioritize both chemical agents and animal strains for *in vitro* and *in vivo* testing.

This project will pursue the following major specific objectives:

1. Develop rigorous end point toxicity predictors based on the QSAR modeling workflow and conventional chemical descriptors
2. Develop novel computational toxicogenomic models based on combined chemical and biological descriptors through QSAR modeling workflow

These objectives synchronize with two types of computational models that in our practice contribute to the enterprise of toxico-cheminformatics . The first is more traditional and deals with the development of QSTR models using chemical descriptors for single toxicological end point data. In this case, we develop models that correlate chemical structure (represented by its chemical descriptors) and the experimental (phenotypical, e.g., carcinogenicity) end point data as the target property. These types of models will be explored under Specific Objective 1. The second deals with building models on the basis of genome-wide transcriptional profiles or multiple high-throughput biological assays (e.g., those collected in ToxCast™ program) that can be regarded as biological descriptors of chemical structures. These descriptors can be used in QSTR modeling either by themselves or in combination with conventional chemical descriptors. This line of investigation will be pursued under Objective 2. The modeling workflow is summarized below:



The ultimate goal of this project is to develop and deliver to EPA both modeling tools and computational predictors of in vivo toxicity that could help prioritize environmental agents for in-depth experimental investigation. The rigor of the modeling and especially, model validation approaches practiced by our group will afford most reliable predictors that should help EPA save time and resources in achieving the goals of the ToxCast™ project.