Appendix B: Example Materials Transfer Agreement

MATERIALS TRANSFER AGREEMENT

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

Recipient:
Point of Contact for Submission: Dr. Christopher Vulpe (Scientist), Sharon Lu (contract contact)
Organization: University of Florida Board of Trustees
Address: 223 Grinter Hall, Gainesville, FL 32611

1a. Provider agrees to transfer to Recipient's Investigator named below the following Research Material:

Chemicals and Materials

Five xenobiotic metabolism probe substrates (50uL of 500X stock solutions in DMSO). The substrates are:

- Terfenadine (CAS: # 50679-08-8),
- Phenacetin (CAS: # 62-44-2),
- Bupropion (CAS: # 34841-39-9),
- Chlorzoxazone (CAS: # 95-25-0), and
- 7-hydroxycoumarin (CAS: # 93-35-6).

Ten reference chemicals for cytotoxicity screening (50uL of 500X stock solutions in DMSO). The reference chemicals are:

- Benzo[a]pyrene (CAS #: 50-32-8),
- Aflatoxin B1 (CAS #: 1162-65-8),
- Cyclophosphamide monohydrate (CAS #: 6055-19-2),
- 2-naphthylamine (CAS #: 91-59-8),
- Acrylamide (CAS #: 79-06-1),
- 1,8-dinitropyrene (CAS #: 42397-65-9),
- doxorubicin hydrochloride (CAS #: 25316-40-9),
- 6-aminochrysene (CAS #: 2642-98-0),
- 8-methoxypsoralen (CAS #: 298-81-7), and
- 4-nitrophenol (CAS #: 100-02-7).

1b. The Recipient agrees to transfer to the EPA Investigator named below the following Research Material:

- All data or data summaries requested in the Transform Tox Testing Challenge Stage 2 Brief resulting from chemical screening performed on the probe substrates and reference chemicals.
- Samples for analytical testing by Federal Agency Sponsors of the Transform Tox Testing Challenges as described in the Stage 2 Challenge Brief.

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.

3. If the data or material that are being transferred constitute human subjects research, please visit the following intranet site to determine if your project needs review and approval by the HSRRO: http://intranet.ord.epa.gov/p2/hsr/human-subjects-review

Does the research involve specimens or data derived or collected from human subjects?

[X] No
[ ] Yes – I am seeking review and approval from the HSSRO. Assurance Number____

4. The Dual Use Research of Concern (DURC) Internal Review Entity (IRE) has determined that:

X This research does not meet the DURC definition and no additional review and oversight are required. The PI must report to the IRE any results or changes in the research such that one or more of the 7 categories of experimental effects may apply, or if the PI feels that the research may be DURC.

□ This research meets the DURC definition and requires additional oversight under the *USG Policy for Institutional Oversight of DURC*. Corresponding USG funding agency will be notified and a draft of the mitigation plan will be submitted within 90 days of this determination.

□ Mitigation Plan submitted to the funding agency on _____

□ Approved mitigation Plan on file

5. This Research Material will be used by Recipient's investigator solely in connection with the Transform Tox Testing Challenge described with specificity as follows. ***Please insert description here***:

We will use the CRISPR synergistic activation mediator (SAM) tool to induce the activation of 5 different metabolic enzymes in human embryonic kidney 293 (HEK293 cells). The activation of each gene requires expressing 3 components in the designated cells: a catalytically inactive Cas9 (dCas9) fused to a transcriptional activator (VP64), an activation helper protein MS2-P65-HSF1 and a guide RNA (gRNA) incorporating two MS2 RNA aptamers. Simultaneous activation of multiple metabolic enzymes requires expressing all the corresponding gRNAs in addition to the other activation components. Expression vectors incorporating the required activation components and gRNA sequences will be introduced into HEK293 simultaneously either by transient transfection or by lentiviral transduction to transiently or stably generate metabolically competent HEK293 cells respectively. To evaluate the metabolic capacity of our model cells, we will use the five corresponding xenobiotic metabolism probe substrates. Briefly, modified cells as well as controls will be incubated with each of the substrates at 2 time points (30 minutes and 18 hours). Following incubation, each reaction will be quenched with ice-cold acetonitrile and the contents will be immediately frozen at -80°C and shipped to the appropriate facility to measure parent chemical depletion rates. In addition to specific metabolic activity measurements, our model cells will be used in cytotoxicity screening of the designated ten reference chemicals. Metabolically competent and corresponding control cells will be treated with multiple doses of each chemical for 24 hours. Cell viability will be evaluated by measuring ATP levels using a luminescence-based assay (CellTiter Glo).

6. 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.

7. 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. When the Research Project is completed, the Research Material will be returned to the Provider or disposed, if directed by Provider.

8. 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.

9. 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.

10. 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 be responsible for all liabilities, demands, damages, expenses and losses arising out of Recipient's use for any purpose of the Research Material.

11. 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.

12. 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.

13. Will EPA develop any products or services from information or materials provided by the Recipient?

____ Yes – go to item A

__x__ No – skip to #13 (next clause)

Item A: The EPA has a long history of applying principles of quality assurance/quality control to all technical work conducted by or for the Agency (CIO 2106: USEPA Quality Policy). Given EPA is receiving metabolomics and screening data and will use the metabolomics and screening data for Agency purposes, the Recipient is required to provide EPA with documentation such as a quality manual, describing their organization's quality system. In lieu of such documentation, Standard Operating Protocols for compound handling and the assays performed are acceptable or documentation showing third party accreditation to a relevant standard and scope is also acceptable for documenting an organization's quality system. EPA requirements for quality management plans can be found at this URL: http://www.epa.gov/quality/qa_docs.html

14. 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 Contact Information:
Russell Thomas
National Center for Computational Toxicology (NCCT)
US EPA
109 TW Alexander (MD-D143-03)
Research Triangle Park, NC 27711
Tel: 919-541-5776
Thomas.russell@epa.gov

With a copy to:
Sandra Roberts
National Center for Computational Toxicology (NCCT)
US EPA
109 TW Alexander (MD-D143-03)
Research Triangle Park, NC 27711
919-541-3850
Roberts.sandra@epa.gov

For commercial courier address use:
4930 Old Page Rd.
Durham, NC 27703

AND

Sarah Bauer
EPA FTTA Program Coordinator
(Overnight courier address)
US EPA MC 8106R
Ronald Reagan building Room 71175
1300 Pennsylvania Ave NW
Washington, DC 20004
202-564-3267

Recipient's Contact Information:

David L. Day
Director, Office of Technology Licensing
University of Florida
747 SW 2nd Avenue
Gainesville FL, 32601
Phone: 352-392-8929
dlday@ufl.edu

15. Paragraphs 2, 7, 9 and 10 shall survive termination.

16. This Agreement shall be governed by and interpreted in accordance with Florida law, except where it conflicts with Federal law and regulations. Nothing contained in this Agreement shall be construed or interpreted as a waiver of sovereign immunity of the State of Florida beyond the waiver provided in Section 768.28, Florida Statutes..

17. The undersigned Provider and Recipient expressly certify and affirm that the contents of any statements made herein are truthful and accurate.

18. This Agreement shall enter into force as of the date of the last signature of the parties and shall remain in effect for three years from said date.

Any false or misleading statements made, presented, or submitted to the Government, including any material omissions, under this Agreement and during the course of negotiation of this Agreement are subject to all applicable civil and criminal statutes including 31 U.S.C. " 3801-3812 (civil liability), 18 U.S.C. ' 1001 (criminal liability), and 31 U.S.C. " 3729-33 (False Claims Act).

SIGNATURES

FOR THE RECIPIENT:

Principal Investigator

Christopher D. Vulpe
Professor
cvulpe@ufl.edu

11/02/16
Date

Authorized Representative of Institution

David L. Day
Director, Office of Technology Licensing

11/4/16
Date

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CERTIFICATION OF NO CONFLICT OF INTEREST (EPA ONLY)

I hereby certify that neither I nor any member of my immediate family will benefit in any material way from the execution or failure to execute the attached FTTA Cooperative Agreement or Licensing Agreement except to the extent of participation in royalty sharing as authorized by section 13 of the Stevenson-Wydler Technology Innovation Act, as amended by the Federal Technology Transfer Act of 1986 (15 U.S.C. 3710a et seq.).

I further certify that I have no knowledge of any such conflict by any other person who has participated in any material way in the initiation, design or development of the attached Agreement or who will participate in carrying it out.

FOR THE PROVIDER:

Principal Investigator

Steven O. Simmons
simmons.steve@epa.gov

10/26/2016
Date

Authorized Representative of Institution

Russell Thomas, Ph.D.
Director, EPA/ORD/NCCT

10/26/16
Date