EPA – University of Florida Board of T – MCRADA # [1577-24]

MATERIALS COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT (MCRADA)

This Materials Cooperative Research and Development Agreement ("MCRADA" or "Agreement") is entered into by and between University of Florida Board of Trustees, a public body corporate of the State of Florida which has its principal place of business at UF Innovate | Tech Licensing, 747 SW 2nd. Ave., Suite 108, 2015 SW 16th Ave ("the Collaborator"), and the Center for Computational Toxicology and Exposure ("CCTE" or "the Center"), of the U.S. Environmental Protection Agency ("EPA") under the authority of Title 15, United States Code §§ 3710a-3710d (commonly known as the Federal Technology Transfer Act of 1986).

1. Research Material.
   (a) The Collaborator agrees to transfer to the Center the following Research Material:

   • U2-OS (osteosarcoma), HepaRG (liver hepatocyte), and HepG2 (liver hepatocyte) cell lines transduced with:

   • Three custom CRISPR libraries (GenVarLOF libraries 1, 2 and dual) cloned into the LentiCRISPRv2 vector which targets ~1500 genes which have common loss of function mutations in the human population.

   (b) The Center agrees to transfer to the Collaborator the following Research Material:

   • Data generated from image acquisition of cell morphology of acquired cultures exposed to reference compounds.

   • Data generated from gene expression measures from acquired cultures exposed to reference compounds.

   This Materials CRADA involves no other exchange of personnel or resources.

2. Human Subjects Research Ethics and Oversight. The Research Material does not involve specimens or data derived or collected from human subjects and therefore does not need review and approval by the Human Subjects Research Review Official (HSSRO).

3. Dual Use Research of Concern (DURC). The DURC Internal Review Entity (IRE) has determined that this research does not meet the DURC definition and that no additional review and oversight under the *USG Policy for Institutional Oversight of DURC* are required. The Principal Investigator (PI) must report to the IRE any results or changes in the research such that one or more of the 7 experimental effects of concern may apply, or if the PI feels that the research may be DURC.

4. No Transfer. The recipient of the Research Material agrees to retain control over the Research Material transferred to them and further agrees not to transfer the Research Material to other people not under their direct supervision without advance written approval of the provider of said Research Material. The recipient of the Research Material shall not use the Research Material received under this Agreement for any other purpose other than the research as described in Appendix A ("RESEARCH"). The provider of the Research Material reserves the right to distribute their own Research Material to others and to use it for their own purposes.

5. Privileged Information.

   (a) Proprietary Business Information. The Collaborator may assert a confidentiality claim for information submitted to EPA under this Agreement that it believes is a trade secret or confidential commercial or financial information subject to the provisions of 40 C.F.R. Part 2, Subpart B (collectively, "Proprietary Business Information"). To assert a confidentiality claim, the Collaborator should place a notice employing language such as "trade secret," "proprietary," or "company confidential" on all information that it delivers to EPA under this Agreement that it asserts is Proprietary Business Information. EPA agrees that any information claimed as, or believed to be, Proprietary Business Information which is furnished by the Collaborator to EPA under this Agreement will be used by EPA only for the purpose of carrying out this Agreement and will not be disclosed, copied, reproduced, or otherwise made available in any form whatsoever to any other person, firm, corporation, partnership, association, or other entity without consent of the Collaborator, except as such information may be subject to disclosure under the Freedom of Information Act (5 U.S.C. § 552), EPA's regulations at 40 C.F.R. Part 2 Subpart B, other Federal statutes, or by a court of competent jurisdiction. If no claim of confidentiality accompanies the information at the time it is submitted to EPA, and EPA does not expect that the Collaborator would assert a proprietary business information claim if it knew EPA proposed to disclose the information, then the information may be made public with no further notice to the Collaborator.

   (b) Other Privileged Information. Other information submitted under this Agreement, such as certain types of personally identifiable information (PII), may also be considered privileged. Privileged information will not be disclosed, copied, reproduced, or otherwise made available in any form whatsoever to an external, non-Agency person, firm, corporation, partnership, association, or other entity, except as required by the Freedom of Information Act (5 U.S.C. § 552), EPA regulations, other Federal statutes, or by a court of competent jurisdiction.

6. No Warranty. The Research Material is provided as a service to the research community. IT IS BEING SUPPLIED TO THE RECIPIENT WITH NO WARRANTIES, EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. The provider of the Research Material makes no representations that the use of the Research Material will not infringe any patent or proprietary rights of third parties. The provider of the Research Material shall not be liable for any claims or damages arising from the recipient's use of the Research Material; however, no indemnification is provided or intended.

7. Intellectual Property. The Center and the Collaborator believe that no Subject Inventions or Computer Software will be created during the work specified in this Agreement. Should it appear that any activity of this Agreement might involve the creation of Subject Inventions or Computer Software, the Center and the Collaborator will negotiate a standard CRADA in good faith. The standard CRADA will assign responsibilities for obtaining patents or other intellectual property rights pertaining to the Subject Inventions or Computer Software and will provide for appropriate allocation of any patent or intellectual property rights resulting from those Subject Inventions or Computer Software. For the purposes of this section, "Subject Invention" means any invention, conceived or first actually reduced to practice in the performance of this Agreement, and "Computer Software" means computer software, computer programs, computer data bases, and documentation thereof developed in whole or in part under this Agreement.

8. Disputes. Any dispute arising under this Agreement which cannot be readily resolved shall be submitted jointly to the signatories of this Agreement. A joint decision of the signatories or their designees shall be the disposition of such dispute. If the signatories are unable to jointly resolve a dispute within a reasonable period of time after submission of the dispute for resolution, the matter shall be submitted by EPA to the Administrator of EPA or the Administrator's designee for resolution. Nothing in this Agreement will prevent the Collaborator from pursuing such additional administrative remedies as may be available and, after exhaustion of such administrative remedies, pursuing available judicial remedies.

9. Severability. The illegality or invalidity of any provisions of this Materials CRADA shall not impair, affect, or invalidate the other provisions of this Materials CRADA.

10. Assignment. Neither this Materials CRADA nor any rights or obligations of any Party hereunder shall be assigned or otherwise transferred by either Party without the prior written consent of the other Party.

11. Notices. 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:

(a) If to the Collaborator:

University of Florida Board of Trustees
JIm O'Connell, Director, Tech Licensing
747 SW 2nd Ave. Suite 108, Gainesville, FL 32601
jimoconnell@ufl.edu
352-392-8929

If applicable: With a copy to:

Chris Vulpe
2187 Mowry Drive, Building 470 Rm 113
PO Box 110885
Gainesville, FL 32611
(352) 294-5821
cvulpe@ufl.edu

(b) If to the Center:

Russell Thomas
Center Director
U.S. EPA Center for Computational
Toxicology and Exposure (CCTE)
109 T.W. Alexander (MD-D-143-02)
Research Triangle Park, NC 27711
919.541.5776

If applicable: With a copy to:

Samantha Plishka
Extramural Management Analyst
U.S. EPA Center for Computational
Toxicology and Exposure (CCTE)
109 T.W. Alexander (MD-B-205-01)
Research Triangle Park, NC 27711
919.541.2657

AND

Kathleen Graham
EPA FTTA Program Coordinator
graham.kathleen@epa.gov
ftta@epa.gov
(303) 312-6137

Either party may change the contact information set out above by notice given to the other party in the manner set forth above.

12. No Endorsement. By entering into this Materials CRADA, the Center does not directly or indirectly endorse any product or service provided, or to be provided, whether directly or indirectly related to either this Materials CRADA or to any patent or other intellectual property license or agreement which is related to this Materials CRADA. The

Collaborator shall not in any way state or imply that this Materials CRADA is an endorsement by the U.S. Government or any of its organizational units or employees of any such product or service.

13. Termination. Either the Center or the Collaborator may unilaterally terminate this entire Agreement at any time by giving written notice to the other party at least thirty (30) days prior to the desired termination date.

14. Entire Agreement. This Materials CRADA constitutes the entire agreement between the Parties with respect to this subject matter and supersedes any prior understanding or written or oral agreement with respect to this subject matter.

15. Governing Law. This Materials CRADA shall be construed in accordance with Federal law as applied by the Federal courts in the District of Columbia.

16. Power and Authority. The undersigned expressly certify and affirm that the contents of any respective statements made or reflected in this Materials CRADA are truthful and accurate and that the signatories hereto have the authority to bind their respective organizations to this agreement.

17. Effective Date. This Materials CRADA shall be effective upon execution by the Parties when the last signatory has signed the document.

18. Term. The term of this Materials CRADA is 24 Months from execution.

19. The provisions of Articles 3, 4, 5, 6, 7, 8, 9, and 15 shall survive the termination of this Materials CRADA.

IN WITNESS WHEREOF, the Parties have caused this Agreement to be executed by their duly authorized representatives as follows:

For the Center:

By: _____ Date _____

For the Collaborator:

By: _____ Date: _____

EPA – University of Florida Board of T – MCRADA # [1577-24]

APPENDIX A

RESEARCH PLAN

The Center for Computational Toxicology and Exposure within the Office of Research and Development is heavily invested in developing New Approach Methodologies (NAMs) to better define the potential hazards of thousands of environmental chemicals with unknown impacts on human health. These techniques can be used to generate molecular profiles (such as transcriptome or phenotypic profiles) that can aid in NAMs data interpretation for mechanism and potential hazards. Novel genetic editing techniques, such as CRISPR-based methods, can introduce genetic-based susceptibility factors into NAMs that allow for evaluating chemical exposure hazards on higher risk subpopulations. Incorporating functional genomic approaches will augment efforts to build a tiered strategy for developing and using NAMs for environmental chemical screening.

As a proof-of-concept study, we will target ~1500 genes that are known to have loss-of-function due to genetic polymorphisms prevalent in the population. To mimic these genetic-mediated impacts, we will utilize a CRISPR/Cas9 strategy using pooled single guide RNAs which will target these genes of interest. These pool of modified cells will then be assessed using NAMs, characterizing both cell morphologic and transcriptional changes with and with out perturbation by chemical exposure. Under this M-CRADA, modified cells will be sent to CCTE for NAMs assessment. Resultant analysis will then be shared to the University of Florida and may result in collaborative publications.

Specific Aims:

1) Liver and osteosarcoma cell lines will be transduced with three custom CRISPR libraries cloned into the LentiCRISPRv2 vector which will mediate the loss of expression of ~1500 gene targets (performed by the University of Florida).

2) Baseline morphological and gene expression alterations in these transformed cell populations will be assessed by cell painting and single cell RNA sequencing methods (performed by the Center for Computational Toxicology and Exposure).

3) Shifts in morphological and gene expression alterations in this transformed cell population due to reference chemical exposure will be assessed by cell painting and single cell RNA sequencing methods (performed by the Center for Computational Toxicology and Exposure).