EPA – HESI – MCRADA # 1579-24

MATERIALS COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT (MCRADA)

This Materials Cooperative Research and Development Agreement ("MCRADA" or "Agreement") is entered into by and between Health and Environmental Sciences Institute (HESI), a Washington, DC based 501(c)(3) non-profit which has its principal place of business at 740 15th St. NW Suite 600 Washington, DC 20005 ("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:

   Cell and media samples from a human in vitro model Assay (qPCR) reagents: Primers and probes, RNA isolation kit, amplification/detection reagents.

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

   Assay (qPCR) data generated from the samples.

   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. Publication. The Center and the Collaborator agree to confer and consult prior to a publication based on the qPCR data generated by EPA under this Agreement to ensure that no Proprietary Business Information is released and that patent rights are not jeopardized. Prior to submitting a manuscript for outside review which contains the results of the research under this Agreement, or prior to publication if no such review is made, each party shall be offered at least 45 calendar days to review such proposed publication.

9. 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.

10. 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.

11. 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.

12. 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:

    Connie Mitchell
    740 15th St. NW Washington DC
    1-202-659-8404
    cmitchell@hesiglobal.org

    With a copy to:

    Syril Pettit
    740 15th St. Nw Washington DC
    1-202-659-8404
    spettit@hesiglobal.org

    (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
    Thomas.russell@epa.gov

    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
Plishka.samantha@epa.gov

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.

13. 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.

14. 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.

15. 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.

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

17. 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.

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

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

20. The provisions of Articles 3, 4, 5, 6, 7, 9, 10, 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: [redacted] Date _____

For the Collaborator:

By: [redacted]

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. Part of this effort is development of biological indicators of toxicity (e.g., biomarkers) that can be measured in short-term assays to assist in chemical hazard characterization. This research aims to investigate the utility of short non-coding short RNAs (e.g., microRNAs) as biomarkers for renal injury using an in vitro system, which is a target of environmental chemical exposure. To develop these biomarkers, CCTE will conduct a pilot study that will measure the effects of reference nephrotoxicants Cisplatin and Polymixin B on the release of microRNAs (miRNAs) from in vitro cultured human proximal tubule cell (PTC) monolayers as part of a collaborative effort with the miRNA Biomarkers Workgroup hosted by HESI's Emerging Systems Toxicology for the Assessment of Risk (eSTAR) Committee.

Specifically, HESI Workgroup researchers will culture cells and treat them at varying concentrations—1, 3, 10, and 30 µM—utilizing solvents DMF (0.2%) and DMSO (0.5%) as controls. The release of specific miRNAs, including miR-34a, miR-34c, miR-29c-3p, miR-486, miR-192, and miR-21, will be quantified, which had previously been identified a putative released biomarkers of proximal tubule cell toxicity (PMID: 33367795). Sampling will be conducted at 24, 48, and 72 hours after compound administration to capture the dynamics of miRNA release with toxic exposures over time.

For the analysis of miRNA, samples will be collected by HESI Workgroup researchers from both apical and basolateral media, as well as intracellularly, and will be analyzed using quantitative PCR (qPCR) by the US EPA. MiRNA expression measures from these samples (as measured by qPCR) will be sent to HESI and which will correlated with protein kidney injury markers such as ATP, LDH, TEER, KIM-1, NGAL, and Clusterin by HESI Workgroup collaborators. This pilot experiment will inform future studies and likely a publication based on these initial findings. This publication would support efforts to develop non-destructive in vitro measures of chemical toxicity, outlined in CSS 401.1.9, "Non-Destructive Cell-Based Assay Development to Enable Longitudinal Screening in Extant Assays".

As part of this agreement, HESI will supply cell culture samples (cell lysates and media) and "in kind" reagents to conduct the qPCR assays (RNA isolation kit, qPCR probes, and amplification/detection reagents). US EPA will conduct the measures and generate the qPCR

data, which will be shared with the HESI Workgroup to synthesize study findings.