EPA-Corteva MCRADA #1374-21

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

MATERIALS COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT (MCRADA)

This Materials Cooperative Research and Development Agreement ("MCRADA" or "Agreement") is entered into by and between

Corteva Agriscience, LLC.

which has its principal place of business at

9330 Zionsville Road, Indianapolis, IN 46268

("the Cooperator"), and the

Center for Computational Toxicology and Exposure (CCTE)

("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).

This Materials Cooperative Research and Development Agreement ("Materials CRADA") has been adopted for use by the Environmental Protection Agency ("EPA") for collaborations that will not exceed two years in term; will involve transfers of essential material ("Research Material"), but no other resources; and are unlikely to result in new intellectual property. Typical applications include short-term studies to: 1) test new reagents or research tools when such assessments require collaboration between provider and recipient institutions or 2) determine the feasibility, optimal study design, and/or resource requirements for a long-term study between the collaborating institutions. Collaborative research and development studies not meeting these criteria must be submitted for approval using the standard CRADA agreement.

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1. Determination of Provider and Recipient

IF EPA IS THE PROVIDER:

The _____ of the U.S. Environmental Protection Agency ("EPA"), PROVIDER, agrees to transfer to _____ RECIPIENT, the following Research Material:

IF COOPERATOR IS THE PROVIDER

The Corteva Agriscience, LLC., PROVIDER, agrees to transfer to the U.S. Environmental Protection Agency ("EPA"), RECIPIENT, the following Research Material:

Fixed cell culture plates (i.e. 384-well cell culture plates) with treated and stained HepaRG and U-2 OS cells for imaging and image analysis.

This Materials CRADA involves no other exchange of personnel or resources. This Agreement is made under authority of the Federal Technology Transfer Act, 15 U.S.C. ' 3710a.

2. 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?

   ☑ No

   ☐ Yes – I am seeking review and approval from the HSSRO.

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

☑ **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**

4. To the extent permitted by law, each Party agrees to treat as confidential any of the disclosing Party's written information about this Research Material that is stamped "CONFIDENTIAL" for a period of three (3) years from the date of the disclosure. The foregoing shall not apply to information that is or becomes publicly available or which is disclosed to a Party without a confidentiality obligation. Any oral disclosures by either party that the disclosing Party wishes to be treated as confidential shall be identified as being confidential at the time of disclosure and by written notice delivered to the receiving Party within (10) days of the oral disclosure. The Center may publish or otherwise publicly disclose the results of the Research Plan, but if Cooperator has given CONFIDENTIAL information to the Center, such public disclosure may be made only after Cooperator has had thirty (30) days to review the proposed disclosure to determine if it contains any CONFIDENTIAL information, to the extent such review period is permitted by law.

5. The RECIPIENT agrees to retain control over this Research Material, and further agrees not to transfer the Research Material to other people not under his or her direct supervision without advance written approval of the PROVIDER. The PROVIDER reserves the right to distribute the Research Material to others and to use it for its own purposes. When the Research Plan is completed or one (1) year has elapsed, whichever occurs first, or the Materials CRADA is terminated, the RECIPIENT will dispose of the Research Material as directed by the PROVIDER.

6. This 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 makes no representations that the use of the Research Material will not infringe any patent or proprietary rights of third parties. The

PROVIDER 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. The Center and the Cooperator 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 Cooperator 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. Subject Invention means any invention, conceived or first actually reduced to practice in the performance of this Agreement. Computer Software means computer software, computer programs, computer data bases, and documentation thereof developed, in whole or in part, under this Agreement.

8. 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.

9. 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. 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. 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:

IF TO THE COOPERATOR:

Jessica Larocca, Mammalian Toxicologist
Corteva Agriscience LLC, Predictive Safety Center
9330 Zionsville Road
Indianapolis, IN 46268
(317) 337-7948
jessica.larocca@corteva.com

With a copy to:

Vahid L. Aidun, Sr. Licensing Manager
Corteva Agriscience LLC
9330Zionsville Rd
Indianapolis, IN 46268
317.553.7932
vahid.aidun@corteva.com

IF TO THE CENTER:

Russell Thomas
U.S. EPA Center for Computational Toxicology and Exposure (CCTE)
109 T.W. Alexander (MD-D143-02)
Research Triangle Park, NC 27711
919-541-5776

With a copy to:

Samantha Plishka
Extramural Management Analyst
Center for Computational Toxicology & Exposure (CTTE)
Office of Research & Development (ORD)
Research Triangle Park, NC (RTP) 27711
Phone: 919-541-2657

AND

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

Any party may change such address by notice given to the other party in the manner set forth above.

12. 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 Cooperator 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. Either the Center or the Cooperator 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. This Materials CRADA constitutes the entire agreement between the Parties and supersedes any prior understanding or written or oral agreement.

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

16. 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. This Materials CRADA shall be effective upon execution by the Parties when the last signatory has signed the document. The term of this Materials CRADA is 24 months from execution.

18. The provisions of Articles 3, 5, 6, 9, and 15 shall survive the termination of this Materials CRADA.

THE CENTER

[redacted] Date: _____

THE COOPERATOR

[redacted]

APPENDIX A

RESEARCH PLAN

Cell Painting, a morphological profiling assay that multiplexes six fluorescent dyes, is a cutting-edge tool that is currently being leveraged for high-throughput toxicology screening. To date, cell painting has been applied to a number of different cell lines, such as U-2 OS, to examine the effects of chemicals on cellular morphology. A current gap in cell painting is that the cell lines that are being leveraged have minimal to no chemical metabolizing capacity, which therefore limits testing to individual parent compounds and neglects relevant metabolism processes. The HepaRG cell line is an immortalized human hepatic cell line that exhibits several key characteristics of primary hepatocytes, including expression of nuclear receptors and high P450 activity. Therefore, adapting the cell painting technique to HepaRGs will enable high-throughput and high-content toxicology screening capabilities to capture bioactivation of toxic metabolites and detoxification processes that are currently being missed.

The objective of this collaboration is to amend cell painting techniques to the HepaRG cell line and develop an image analysis pipeline. This will include characterization of the HepaRG cell culture conditions, staining protocols, and imaging techniques. The Provider shall conduct in vitro experiments to optimize cell painting staining techniques, and characterization of the HepaRG cell culture conditions (e.g. bile acid staining, urea, gene expression, metabolizing capacity.) Provider shall conduct in vitro toxicological experiments with the optimized cell painting protocol on known positive and negative control compounds from peer reviewed literature (e.g. Berberine). The provider shall also conduct in vitro cell painting experiments using the U-2 OS cell line as a comparator to the HepaRG model. The Recipient shall conduct imaging on the Opera Phenix and develop a data analysis pipelines in Harmony software. Provider shall ship fixed plates with treated and stained HepaRG and U-2 OS cells to Recipient for imaging. Recipient shall share data from the image analysis with Provider. HepaRG cell culture condition characterization shall be completed during the Term. HepaRG cell painting optimization experiments and imaging on the Recipient Opera Phenix shall be conducted during the Term. Expected outcomes include optimized cell painting protocol developed for the HepaRG cell line, data analysis pipeline on Harmony software, and a peer-reviewed publication describing the results of the Research Project. This is an in-kind collaboration and therefore no budget is necessary.