# MATERIALS COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT

1. The Office of Research and Development, National Center for Computational Toxicology ("NCCT") of the U.S. Environmental Protection Agency ("EPA") agrees to transfer to

**Endogenics, Inc.** (Collaborator) the following Research Material:

**In vitro assay data derived from the ToxCast™ Program. This data is derived from a set of 320 chemicals which were analyzed using a variety of assay techniques.**

**Endogenics, Inc. agrees to provide to the EPA all Testing Results obtained by the Collaborator using the Research Material. EPA acknowledges that Collaborator owns all Testing Results and Recipient acknowledges that the EPA will make such Testing Results freely available to the public upon review and approval by the Recipient.**

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. This Research Material will be used solely in connection with the Research Plan, attached as Appendix A, by the Collaborator in his/her laboratory under suitable containment conditions.

2(a). Are the Research Materials of human origin?
___Yes
_X_ No

2(b). If Yes in 2(a), were the Research Materials collected according to 45 CFR Part 46, "Protection of Human Subjects?"
___Yes (Please provide Assurance Number:_____)
___No

3. 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 NCCT may publish or otherwise publicly disclose the results of the Research Plan, but if Collaborator has given CONFIDENTIAL information to the NCCT, such public disclosure may be made only after Collaborator 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.

4. The Collaborator 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 NCCT. The NCCT reserves the right to distribute the Research Material to others and to use it for its own purposes. When the Research Project is completed or the Materials CRADA is terminated, the Collaborator will cease access to and use of the Research Material, as directed by the NCCT.

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

6. The NCCT 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 NCCT 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. 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.

7. 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.

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

9. 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.

10. 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 mail or commercial courier addressed as follows:

If to the Collaborator:

Richard Newman
Endogenics, Inc.
280 S. Academy Ave., Suite 140
Eagle, ID 83616
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with at a copy to: Jeffrey W. Habig

If to the EPA:

Karen F. Dean
US EPA
National Center for Computational Toxicology (MD-B-205-01)
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Research Triangle Park, NC 27711
Phone 919-541-5037; fax 919-541-1194
Dean.karen@epa.gov

with a copy to: Thomas Knudsen (same address as above) knudsen.thomas@epa..gov

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

11. By entering into this Materials CRADA, The NCCT 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.

12. Either the NCCT 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.

13. This Materials CRADA constitutes the entire agreement between the Parties and supersedes any prior understanding or written or oral agreement.

# APPENDIX A

## RESEARCH PLAN

The Research Plan should be a short, concise explanation of the research project that will be conducted by the Laboratory and the Collaborator with the materials provided under the CRADA.

**Title: Cell-based modeling in the mouse embryonic stem cell (mESC) assay**

Purpose: This project will involve collaboration with Endogenics, Inc., (Endogenics) and EPA's Virtual Embryo project involving the National Center for Computational Toxicology (NCCT) and the ToxCast™ research program. The purpose of the project is to pilot a cell-level computer model that can be used to predict the pathway-level responses in biological signaling networks that drive tissue differentiation and homeostasis. The mouse embryonic stem cell (mESC) assay is being evaluated as a promising alternative to animal testing for assessing developmental toxicity. Cell types that differentiate from pluripotent stem cells in this assay system reflect the activity of specific cell-cell signaling pathways that are known to be important for early embryonic development (e.g., Wnt-signaling, Notch-delta, Receptor tyrosine kinases, TGF-beta, Sonic hedgehog and so forth). Studies at NHEERL are evaluating how chemicals may perturb these pathways by monitoring a multi-gene marker panel for specific differentiated cell types (e.g., cardiogenesis, neurogenesis, osteogenesis, and chondrogenesis and so forth) of relevance to developmental toxicity. Ultimately, EPA would use computational (*in silico*) models to predict which pathways are sensitive to certain chemicals, perform follow-up genomic experiments with specific chemicals to validate these predictions, and incorporate pathway-level detail into a 'virtual embryo' model for *in silico* reconstruction of developmental defects. This approach is consistent with EPA's Strategic Plan for Evaluating the Toxicity of Chemicals Toxicity (2009) and the NRC recommendations for Toxicity Testing in the Twenty-first Century: A Vision and a Strategy (2007).

Logistics: EPA will provide Endogenics with details on the experimental set-up of the mESC assay system, data from a multi-gene marker panel, and results from testing the response to 320 ToxCast™ chemicals. Endogenics will develop a pilot computational model, incorporating biological detail about cell signaling pathways and using gene expression data to simulate mESC output. Predictions from the computational model can inform the selection of TIGM.org library mutant mESC lines and other genetic approaches.