MATERIAL TRANSFER AGREEMENT

This Material Transfer Agreement ("MTA") has been adopted for use by Cellceutix Corporation, 100 Cummings Center, Suite 151-B, Beverly, MA 01915 ("Cellceutix") in all transfers of research material ("Research Material") whether Cellceutix is identified below as its Provider or Recipient.

Provider: Cellceutix Corporation
Provider's address: 100 Cummings Center, Suite 151-B, Beverly, MA 01915

Recipient: Beth Israel Deaconess
Recipient's address: 330 Brookline Avenue, Boston, MA 02215

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

2. **THIS RESEARCH MATERIAL MAY NOT BE USED IN HUMAN SUBJECTS.** This Research Material will only be used 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 commercial purposes such as serving, 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.

2(a). Are Research Materials of human origin? _____yes____X____no

2(b). If yes in 2(a), were Research Materials collected according to 45 CFR 46 "Protection of Human Subject?" _____yes_____no

Please provide Assurance Number: _____

3. This Research Material will be used by Recipient's investigator solely in connection with the following research project ("Research Project") described with specificity as follows (use an attachment page if necessary):

See ATTACHED Research Project entitled **"Assessment of the Therapeutic Potential of Kevetrin in Melanoma and Renal Cell Carcinoma"** at end of document below

4. Recipient shall obtain written approval on Research Project protocol and procedures from Cellceutix before starting the Research Project. Recipient shall not publish or disclose results of the Research Project without written consent from Cellceutix. Recipient also agrees to include a member of the Cellceutix team as a research collaborator and author in all Research Project publications or publications involving the Research Material named above.

5. 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 her or his 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, or three (3) years have elapsed, whichever occurs first, the Research Material will be destroyed by Recipient or otherwise disposed of as mutually agreed by Provider and Recipient. Furthermore, Information regarding the Research Project, apart from publications as mentioned above, will be considered confidential and will be treated as such by Recipient.

6. This Research Material 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.

7. Cellceutix shall retain title to any patent or other intellectual property rights in inventions made by Recipient's employees in the course of the Research Project. Unless prohibited by law from doing so, Recipient agrees to hold Provider harmless and to indemnify Provider for all liabilities, demands, damages, expenses and losses arising out of Recipient's use for any purpose of the Research Material.

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

9. The validity, interpretation, performance and enforcement of this Agreement shall be governed by the laws of the Commonwealth of Massachusetts, without regard to its choice of law provisions. The parties hereto hereby irrevocably and unconditionally consent to the exclusive jurisdiction of the courts of the Commonwealth of Massachusetts and the United States District Court for the District of Massachusetts for any action, suit or proceeding (other than appeals therefrom) arising out of or relating to this Agreement, and agree not to commence any action, suit or proceeding (other than appeals therefrom) related thereto except in such courts.

IN WITNESS WHEREOF, we, the undersigned as duly authorized representatives, agree to all terms and conditions stated above, and by our signatures, place this Agreement into full effect as of the last date written below.

LEGAL ADDRESSES AND BANKING DETAILS OF THE PARTIES

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Assessment of the Therapeutic Potential of Kevetrin in Melanoma and Renal Cell Carcinoma

Rationale: In most melanomas and renal cell carcinomas (RCC), the gene encoding the tumor suppressor p53 is neither mutated, deleted, nor epigenetically silenced. Because the p53 gene is fundamentally intact in these tumors, it may be possible to exploit the nuclear and/or mitochondrial pro-apoptotic functions of p53 in the treatment of these malignancies.

p53 signaling is virtually always incapacitated in tumor cells. In RCC and melanoma – tumors with an intact p53 gene - the signaling pathways downstream of p53 are presumably disabled by the overexpression of various antagonists that destabilize p53 (e.g. HDM2) or interfere with its transcriptional activity (e.g. iASPP, HDMX). This reliance on p53 antagonists – in particular, HDM2 – as a means of limiting p53 function suggests that these tumors might be susceptible to drugs that block HDM2. Prior work from our lab with an investigational HDM2 antagonist (1), however, has demonstrated that this approach has negligible pro-apoptotic activity *in vitro* and only modest activity against melanoma and RCC xenografts when the HDM2 antagonist is used as a single agent. Despite the lack of single agent activity, however, the drug was highly lethal against some melanoma cell lines when used in combination with the multikinase inhibitor sorafenib. The pro-apoptotic activity of this drug combination was shown to be dependent on the mitochondrial translocation of p53 and independent of its transcriptional activity. These data suggest that an agent that activates p53 function in the mitochondria (e.g. Kevetrin) might be particularly effective in the treatment of RCC and melanoma.

Proposed Study Design: We propose to assess the effects of Kevetrin alone and in combination with two FDA-approved multikinase (primarily VEGFR2) inhibitors. Prior data from our laboratory indicate that agents of this

class can augment the pro-apoptotic and antitumor effects of HDM2 antagonists and will presumably have a similar effect with Kevetrin.

RCC: Kevetrin will be first evaluated as a single agent for its ability to induce apoptosis in the human RCC cell lines 786-0 and A498 *in vitro*. These assays will involve exposure of the cells to the drug followed by flow cytometry to assess staining with propidium iodide (PI) and Annexin-FITC. In the event that the drug induces apoptosis as determined by flow cytometry, we will investigate the apoptotic mechanism by examining cell lysates for caspase activation and PARP cleavage. Subcellular fractions of treated cells will be examined for mitochondrial translocation of p53 and nuclear translocation of AIF. We will also determine the extent to which the apoptotic activity of the drug is inhibited by caspase inhibitors (e.g. ZVAD) and agents known to selectively block p53 function in the nucleus (pifithrin-a) and in the mitochondria (e.g. pifithrin-μ).

To assess the effects of Kevetrin *in vivo*, the drug will be studied as a single agent and in conjunction with the FDA-approved VEGFR antagonist sunitinib. In these xenograft studies, 1.0 x 10^7 786-0 or A498 human RCC cells will be implanted subcutaneously into the flanks of 40 nude/beige mice. Once tumors have reached the diameter of 7 mm, the tumor-bearing mice will be divided into 4 treatment groups and treated with Kevetrin alone (200 mg/kg IP MWF), sunitinib alone (50 mg/kg by gavage), saline (control), or both sunitinib + Kevetrin. Mice will be treated for 21 days. Tumor size will be measured thrice weekly. On day #10, three mice from each treatment group will be sacrificed and their tumors excised and divided into two halves. One half will be frozen for subsequent biochemical analysis and the other half fixed in formalin for paraffin embedding. At the end of the study (Day #21 or when the control tumors reach a diameter of 20mm, whichever comes first), the remaining mice will be sacrificed and their tumors excised and processed as described above for the Day #10 tumors. Study endpoints include:

1.	Serial tumor measurements to show the antitumor activity of single agent Kevetrin and that of a Kevetrin/sunitinib combination in RCC xenografts

2.	Analysis of tumor vascularity as determined by IHC (microvessel density with anti-CD31 antibody). It is expected that p53 activation and VEGFR inhibition would act in synergy to suppress tumor angiogenesis.

3.	IHC and western blot analysis to determine the effects of each agent individually and in combination on a). p53 levels and subcellular localization; b). expression of p53-dependent genes such as p21; c). induction of tumor cell apoptosis as determined by caspase 3 activation and TUNEL assay. If increased apoptosis is detected in the tumors from treated mice, we will also assess the ability of the drug(s) to induce AIF nuclear translocation.

Melanoma: Kevetrin will be evaluated as a single agent for its ability to induce apoptosis in melanoma cell lines A375, SKMel5 (both of which have the $BRAF^{V600E}$ mutation), SKMel2 (which has an NRAS mutation), and SKMEL31, (which has wild type BRAF and NRAS genes). The methods by which apoptosis will be assessed are identical to those proposed above for the RCC studies.

To determine the activity of Kevetrin against melanoma xenografts, the drug will be studied alone and in combination with the VEGFR antagonist Axitinib. The rationale for this plan is based on our previous work with an HDM2 antagonist which demonstrated limited antitumor activity when used as a single agent but sustained tumor non-progression when used in combination with the multikinase inhibitor sorafenib. The decision to substitute Axitinib for sorafenib is based on its more potent VEGFR inhibitory activity.

For these xenograft studies, 1 x 10^7 A375, SKMel2, and SKMEL31 melanoma cells will be implanted subcutaneously into the flanks of 40 nude/beige mice. Once tumors have reached the diameter of 7 mm, the tumor-bearing mice will be divided into 4 treatment groups and treated with Kevetrin alone, axitinib alone (30 mg/kg daily), saline (control), or both Kevetrin + axitinib. Mice are treated daily by gavage for 21 days. Tumor size is measured thrice weekly. On day #10, three mice from each treatment group will be sacrificed and their tumors excised and divided into two halves. One half will be frozen for subsequent biochemical analysis and the other half fixed in formalin for paraffin embedding. At the end of the study (Day #21 or when the control tumors reach a diameter of 20mm, whichever comes first), the remaining mice will be sacrificed and their tumors excised and

processed as described above for the Day #10 tumors. Study endpoints will be the same as those proposed above in the RCC analyses.

Drugs: The sunitinib used in these studies will be unused clinical grade material provided to us by patients who are no longer receiving the drug. The investigational VEGFR2 antagonist axitinib will be purchased from LC Laboratories**.**

References:

1. Liu Q, Mier JW, Panka DJ. Differential modulatory effects of GSK-3b and HDM2 on sorafenib-induced AIF nuclear translocation (programmed necrosis) in melanoma. Mol Cancer 2011; 10:115.

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