Official Title: Pilot study evaluating the utility of OncoCEETM (Cell Enrichment and Extraction) technology, a novel immunocytochemical microfluidic device, in the diagnosis of leptomeningeal metastasis (LM) from solid tumors through identification of circulating tumor cells (CTCs) in cerebrospinal fluid (CSF)

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COLUMBIA UNIVERSITY MEDICAL CENTER
CONSENT FORM AND HIPAA AUTHORIZATION FORM

Protocol Title: Pilot study evaluating the utility of OncoCEE^{TM} (Cell Enrichment and Extraction) technology, a novel immunocytochemical microfluidic device, in the diagnosis of leptomeningeal metastasis from solid tumors through identification of circulating tumor cells in cerebrospinal fluid

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Biocept, Inc

You are being asked to participate in a research study. This document will explain what the study is about, what you will be asked to do, and the risks and benefits of participating in the study so that you can make a decision whether or not you want to participate. Your participation is voluntary which means you can decide whether or not you want to participate. If you decide not to participate, your care at Columbia University Medical Center will not be affected and your doctor will discuss your treatment options. You will be given a copy of this form to take home and discuss with your family, friends, or your doctor. If you have any questions, you should ask the study team. If you decide to participate, you will be asked to sign a copy of this form.

Why is this study being done?

You are being asked to participate in this study because you have been diagnosed with cancer and will be undergoing lumbar puncture to evaluate for the presence of leptomeningeal metastasis, a complication in which the cancer spreads to the membranes (meninges) surrounding the brain and spinal cord. This condition is typically diagnosed by examining the cerebrospinal fluid obtained from the lumbar puncture using standard cytopathologic analysis. However, this analysis is insensitive and leptomeningeal metastasis is currently being underdiagnosed. Magnetic resonance imaging (MRI) of the central nervous system can help improve diagnostic capability but even with the addition of MRI, diagnostic sensitivity is still lacking.

The purpose of this research study is to determine if a new technology, the OncoCEE^{TM} Cell Enrichment and Extraction technology, will help accurately diagnose leptomeningeal metastasis of cancer. This technology does this by identifying circulating tumor cells in the cerebrospinal

fluid. This study will compare the OncoCEE™ Cell experimental technology to standard cytopathologic analysis. Approximately 46 research subjects will be recruited into this study over an expected duration of 24 months.

What are the study groups?

At the time of your lumbar puncture, cerebrospinal fluid will be withdrawn in accordance with normal operating procedures and sent for standard testing (including cytopathologic analysis) as directed by your medical and/or neuro-oncologist. In addition, one more 10 mL vial (i.e. 2 more teaspoons) of cerebrospinal fluid will be withdrawn and sent to a specialized laboratory in San Diego, owned by Biocept, Inc. There, the sample will be tested for circulating tumor cells, which may ordinarily be missed by standard analysis, using a technology called OncoCEE™. If tumor cells are identified, they will be tested for hormone receptor and HER2 status. We will then correlate the findings with the hormone receptor and HER2 status of your existing primary and/or metastatic tumor biopsies. In an exploratory analysis, Biocept will then analyze that same cerebrospinal fluid sample for the presence of cell free DNA, which may independently suggest that cancer has spread to the meninges; further analysis of the cell free DNA may provide data regarding the mutational status of the cerebrospinal fluid cancer cells. Lastly, at the time of the lumbar puncture, we will collect two 10 mL vials (i.e. 4 teaspoons) of blood from a peripheral vein. We will send this blood sample to Biocept's lab to be evaluated for circulating tumor cells using OncoCEE™ technology. If identified, these circulating tumor cells will be checked for the presence of hormone receptors and HER2 status. The sample will also be checked for the presence of cell free circulating tumor DNA. The peripheral blood findings will be correlated with the cerebrospinal fluid findings to complete this exploratory analysis.

If the results of the initial lumbar puncture do not demonstrate circulating tumor cells upon analysis at Biocept, we will collect an additional vial of cerebrospinal fluid at the next lumbar puncture needed for your standard medical care to assess for the development of leptomeningeal metastasis over time. Two additional peripheral blood samples will also be collected at this time. These samples will also be analyzed at Biocept's laboratory.

The results of the circulating tumor cells in the cerebrospinal fluid will not be returned to your doctor, and thus will not influence your treatment. The ultimate goal is for the OncoCEE™ test to serve as an improved diagnostic tool for leptomeningeal metastasis. With a more sensitive diagnostic tool we can avoid unnecessary treatment delays, as well as complications and discomfort from repeat diagnostic testing.

You will follow-up in clinic two months and six months after the first lumbar puncture. These are standard of care clinical visits.

How long will I be in this study?

You will be enrolled in the trial after a decision has been made by your medical and/or neuro-oncologist to perform a lumbar puncture to assess for leptomeningeal metastasis. After the cerebrospinal fluid sample is obtained for the study on the day of the lumbar puncture, as well as a sample of peripheral blood, no additional follow up will be needed for the purposes of the study. You will continue to see your medical and/or neuro-oncologist as part of standard follow

up for cancer treatment. You will follow-up in clinic two months and six months after the first lumbar puncture. These are standard of care clinical visits.

It is possible that information regarding your clinical outcome could be used to correlate to findings from the cerebrospinal fluid and blood testing performed as part of the study.

If you then undergo an additional lumbar puncture needed for your standard medical care, we will again collect one 10 mL vial (two teaspoons) of cerebrospinal fluid in addition to the volume collected for standard analysis, as well as two 10 mL vials (four teaspoons) of peripheral blood.

For your reference, a study calendar is included at the end of this consent form.

What am I being asked to do? What extra tests and procedures will I have if I take part in this study?

In order to be a participant in this study, one additional 10 mL vial (two teaspoons) of cerebrospinal fluid will be collected on the day of your lumbar puncture. We will also collect two 10 mL vials (four teaspoons) of peripheral blood. Beyond this, no additional exams or procedures are required. The procedure date will be agreed upon by you and your treating medical and/or neuro-oncologist.

Because the possible significance of any results of the genetic testing that will be performed on your tumor specimen is not known, the results of these studies will not be given to you. You should be aware that insurance companies sometimes use information from genetic testing to deny coverage to applicants. This study involves research in genetics that could be used to develop such genetic testing in the future. At present, any information obtained from this research cannot be considered to provide meaningful information about the health of a study participant. Therefore, if you decide to participate in this research study and agree to genetic research, and if you are asked, you should state that you have not had a genetic test.

Even without your name and other identifiers, your genetic information is unique to you. There is a potential risk that someone will identify you from your genetic information or learn something about you by looking at your genetic information; this risk may increase in the future as technologies advance and more researchers study your genetic information. The Genetic Information Non-discrimination Act (GINA) is a federal law that prevents insurance companies from using your genetic information to deny health insurance coverage. The law also prevents employers from getting or using genetic information for employment-related decisions. However, the law does not prevent companies that provide life insurance, disability insurance or long-term care insurance from using genetic information.

There will be an additional component to this study, in which we collect an additional 10 mL vial of cerebrospinal fluid and additional two 10 mL vials of peripheral blood at the time of the next lumbar puncture needed for your standard medical care. For example, if your initial lumbar puncture does not demonstrate circulating tumor cells, it is possible that your physician may request that you repeat a lumbar puncture for follow up. This component would allow us additional opportunities to evaluate the sensitivity of the OncoCEE^{TM} test, while at the same time

providing a unique window into the development and progression of leptomeningeal metastasis over time.

Making Your Choice

Please read the sentences below and think about your choice. After reading, initial "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB's phone number. In signing consent for this study, you are agreeing to the following: one additional 10 mL vial (two teaspoons) of cerebrospinal fluid and an additional two 10 mL vials (four teaspoons) of peripheral blood collected at subsequent lumbar punctures to learn about the diagnosis and progression to leptomeningeal metastasis in cancer if your physician determines that a repeat lumbar puncture is clinically indicated.

The following are optional aspects to enrolling into the study:

1. I agree to have the cerebrospinal fluid and additional peripheral blood used in future research to learn about, prevent, or treat cancer.
   Yes_____ No_____

2. I agree to have my tumors specimens that have already been collected used in research to learn about, prevent, or treat cancer.
   Yes_____ No_____

What possible risks or discomforts can I expect from taking part in this study?

Risk will primarily be attributed to the additional cerebrospinal fluid required for the study; withdrawing excess amounts of cerebrospinal fluid can induce modest nausea, positional headache and/or light headedness. Evaluating this cerebrospinal fluid for circulating tumor cells presents no risks to you. Drawing a sample of peripheral blood may cause mild pain and discomfort. Evaluating this blood for circulating tumor cells posing no risk to you.

<u>Loss of confidentiality</u>

A risk of taking part in this study is the possibility of a loss of confidentiality. Loss of confidentiality includes having your personal information shared with someone who is not on the study team and was not supposed to see or know about your information. The study team plans to protect your confidentiality. Their plans for keeping your information private are described in the ' Who will see my medical information?' section of this consent form.

There may be other risks of taking part in this research study that we don't know about. If we learn about other risks, we will let you know what they are so that you can decide whether or not you want to continue to be in the study.

What possible benefits can I expect from taking part in this study?

This study is unlikely to provide any immediate benefits to you, but it will help better our ability to diagnose leptomeningeal metastasis in the future. This study may help us learn things that may help people in the future, including research subjects who develop leptomeningeal metastasis and are looking to undergo treatments targeted to their specific leptomeningeal tumors.

What are my other choices if I do not take part in this study?

You do not have to take part in this study to get treatment for your condition. If you decide not to take part in this study, you have other choices. For example:

- Getting diagnostic procedures for your cancer without being in a study
- Taking part in another study
- Getting no diagnostic procedures

Talk to your doctor about your choices before you decide if you will take part in this study.

When is the study over? Can I leave the study before it ends? Can I stop taking part in this study?

This study is expected to end after all subjects have completed all of the research procedures and all of the information has been collected. The study may be stopped at any time by the study doctor, if (s)he feels it is necessary for your health or safety. In addition, your participation will end if the investigator or collaborator stops the study earlier than expected.

If you decide to participate, you are free to change your mind at any time. This decision will not interfere with your future care. For your safety, you should tell us if you want to stop being in the study. You may be asked to come back for a final visit. The study doctor may also ask to continue to collect information about your health if you decide to end your participation.

What if new information becomes available about the study?

During the study, you will be told in a timely manner about new information or changes in the study that may affect your willingness to continue in the study. When informed of this new information, if you agree to continue in the study, you or your legally authorized representative will be asked to sign an updated consent form.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. The information collected during this study will be kept in a research file located on a secure floor of the hospital where only the study doctor and the research staff will have access to the information. The results of research procedures will be placed in your medical record and may be accessible to employees of the hospital that are not part of the research team. This information may also be

viewed by your insurance company during routine audits. Information that does not become part of your medical record will be stored in your study file in a secure location. Some of your health information from this study will also be kept in a central database for research. We will do everything we can to keep your data secure, however, complete confidentiality cannot be promised.

Your samples will be de-identified. Your specimens will be assigned a code number, and separated from your name or any other information that could identify you. The research file that links your name to the code number will be kept in a locked file cabinet or an encrypted data file and only the investigator and authorized study staff will have access to the file.

Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. The following individuals and/or agencies will be able to look at and copy your research records:

- The principal investigator, study staff, Columbia University staff, New York Presbyterian Hospital staff, and other medical professionals who may be evaluating the study
- Authorities from Columbia University and New York Presbyterian Hospital, including the Institutional Review Board ('IRB') a group of people who review the research with the goal of protecting the people who take part in the study
- The United States Food and Drug Administration ('FDA') and/or the Office of Human Research Protections ('OHRP')
- The funding agencies of this study, National Institutes of Health (NIH) and Biocept Inc., including persons or organizations working with or owned by the funding agencies

If the results of this research project are published or presented at a scientific or medical meeting, you will not be identified. Otherwise, all results will be kept confidential and will not be divulged (except as required by law) without permission.

If you sign this document, you give permission to individuals and agencies listed above to use or disclose (release) your health information that identifies you for the research study.

The health information that we may use or disclose (release) for this research includes:

- all information collected during the research described in this Informed Consent Form for research; and
- health information in your medical records that is relevant to the Research.

The health information listed above and in your medical records may be used by and/or disclosed (released) to the researchers and their staff, representatives of government agencies, review boards, and other persons who watch over the safety, effectiveness, and conduct of research.

Columbia University Medical Center is required by law to protect your health information. By signing this document, you authorize Columbia University Medical Center to use and/or disclose

(release) your health information for this research. Those persons who receive your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it and may share your information with others without your permission, if permitted by laws governing them.

Please note that you do not have to sign this Authorization, but if you do not, you may not receive research-related treatment.

Please note that you may change your mind and revoke (take back) this Authorization at any time, except to the extent that Columbia University Medical Center has already acted based on this Authorization. To revoke this Authorization, you must write to: Privacy Officer, Columbia University, 630 West 168th Street, mail box 159, New York, N.Y. 10032. However, if you revoke this Authorization, you will not be allowed to continue taking part in the Research. Also, even if you revoke this Authorization, the Researchers and the Collaborator may continue to use and disclose the information they have already collected as permitted by the Informed Consent Form.

While the Research is in progress, you may not be allowed to see your health information that is created or collected by Columbia University in the course of the Research. After the Research is finished, however, you may be allowed to see this information.

This Authorization does not have an expiration date.

Are there other ways my health information, cerebrospinal fluid samples and blood sample may be used in the future?

Your de-identified health information, cerebrospinal fluid samples and blood samples may be used for a number of purposes to further the understanding of leptomeningeal metastasis in cancer and to develop new cancer drugs. These purposes include: 1) Biocept Inc. internal research and development; 2) CUMC/NYPH internal research and development; 3) Research services provided by Biocept Inc to third parties such as academic (university) or government researchers, or pharmaceutical or biotechnology companies.

Because our research study is funded by the National Institutes of Health (NIH), we are required to submit your clinical data in coded form to one or more databases managed by the NIH. We may submit your clinical data in coded form to one or more other government or private databases developed to make data accessible to researchers. Some of these databases permit public unrestricted access to the data. The data may be the combined data of many people of individual level data. Any data that is submitted will not be labeled with your name or other information that could be used to easily identify you.

What happens if I am injured or hurt because I took part in this study?

Taking part in this research study may result in injury or harm to you. In the event of an injury resulting from your participation in this study, you should seek appropriate medical care and inform the study doctor. In the event of an emergency you should go to an emergency room.

If you are injured or harmed as a result of participating in the study and receive medical care through the NewYork-Presbyterian Hospital (NYPH), a Columbia doctor, or any other health provider, you will be sent a bill for whatever medical care you receive. All or part of your bill may be paid by your health insurance.

Columbia University and New York Presbyterian Hospital (NYPH) are not offering to pay you for pain, worry, lost income, the cost of your medical care or non-medical care costs that might occur as a result of your taking part in this study. However, you do not waive any of your legal rights in signing this form.

Will I be paid for being in this study?

You will not receive any payment or other compensation for taking part in this study.

What are the costs of taking part in this study?

The additional testing on the cerebrospinal fluid and blood will be collected at no cost to you. You and/or your insurance plan will need to pay for the costs of the standard medical care you receive while you are taking part in this study. You will be responsible for any deductibles, premiums, co-pays/co-insurance that you usually have when seeking medical treatment.

Ask your doctor or nurse for help finding the right person to talk to if you are unsure which costs will be billed to you or your insurance provider.

Who can answer my questions about this study?

You can talk to your study doctor if you have any questions or concerns about this study or if you think you have been injured as a result of taking part in the study. In addition, you should contact the principal investigator: Dr. Kevin Kalinsky. 212-305-0170.

If you have any questions about your rights as a research subject, you should contact the Columbia University Institutional Review Board by phone at (212) 305-5883 or by email at irboffice@columbia.edu.

More information about taking part in a research study can be found on the Columbia University IRB website at: http://www.cumc.columbia.edu/dept/irb.

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).
A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Statement of Consent and HIPAA Authorization

I voluntarily consent to participate in the study. I have read this consent form, which includes information about the nature and the purpose of the study, as well as a description of study procedures.

I have discussed the study with the investigator or study staff, have had the opportunity to ask questions and have received satisfactory answers. The explanation I have been given has discussed both the possible risks and benefits to participating in the study and the alternatives to participation.

I understand that I am free to not participate in the study or to withdraw at any time. My decision to not participate, or to withdraw from the study will not affect my future care or status with this investigator.

I confirm that I have informed the investigator or study staff to the best of my knowledge of: any medication/drug that I have taken in the month before the start of the study; and any medication/drug that I am taking or plan to take, whether prescribed or not. I agree to cooperate with the study investigator/staff and will report any unexpected or unusual symptoms.

I understand that I will receive and may keep a copy of this signed and dated consent form. By signing and dating this consent form, I have not waived any of the legal rights that I would have if I were not a participant in the study.

Study Subject
Print Name _____

Signature _____ Date _____

Person Obtaining Consent
Print Name _____

Signature _____ Date _____

Signature of Legally Authorized Representative, if applicable
Print Name _____

Signature _____ Date _____

Witness, if applicable
Print Name _____

Signature _____ Date _____

Study Calendar

	Pre-Enrollment	Lumbar Puncture (LP) #1	LP #2 (if clinically indicated, i.e. previously negative tap)	LP #3 (if clinically indicated, i.e. previously negative tap)	Clinical Follow-up (2 and 6 month after LP #1)
Informed Consent	X				
Inclusion/Exclusion	X				
Standard Cytologic Assessment (spinal fluid)		X	X	X	
OncoCEE (spinal fluid)		X	X	X	
OncoCEE (peripheral blood)		X	X	X	