

# Correlation of the Microculture Kinetic (MiCK) Apoptosis Test Results with Drug Treatment Results in Cancer Patients

PRINCIPAL INVESTIGATOR:

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SPONSOR: DiaTech Oncology, LLC, Garry Latimer, CEO

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## **1.0 Background and Rationale:**

Identification of those patients with cancer who will or will not respond to a specific chemotherapy is important for making decisions regarding chemotherapy regimens as well as alternative management approaches. A laboratory test that could help to determine the sensitivity of an individual patient's tumor cells to specific chemotherapeutic agents would be valuable in choosing the optimal chemotherapy regimen for that patient with an expectation of increasing the response rate to the therapy. Several types of *in vitro* assays that measure tumor cell survival following exposure to cytotoxic agents have been evaluated for their ability to predict chemotherapy outcomes. As a group, these assays are referred to as drug resistance assays. In a resistance assay, the surviving tumor cells can be detected directly by their exclusion or metabolism of specific dyes. Alternatively, since some of tumor cells are proliferating, their survival can be detected by measurement of DNA synthesis by radiolabeled precursor incorporation or demonstration of clonogenic potential by growth into colonies in semi-solid culture medium. In several clinical studies, these assays were useful in detecting drug resistance and in predicting a poor prognosis for cancer patients. However, these resistance assays cannot detect sensitivity of an individual patient's tumor cells to a specific drug. Therefore, new methods determining

drug-sensitivity of the tumor cells of an individual patient and, thus, capable of both predicting a positive treatment outcome and guiding chemotherapy, would be of significant value.

Recently, an automated microculture kinetic (MiCK) assay for measuring drug induced apoptosis in tumor cells has been developed<sup>1-4</sup>. Apoptosis is a distinct mode of cell death which occurs under physiological conditions and yet can be induced in malignant cells by chemical and physical factors including antitumor drugs<sup>5-7</sup>. During the last decade, it has been recognized that chemotherapeutic agents exert their antitumor activity by triggering apoptosis in susceptible tumor cells<sup>8-17</sup>. This implies that the MiCK assay for apoptosis provides a mechanism-based approach to studying effects of cytotoxic agents on tumor cells. Unlike “resistance” assays that measure a fraction of cells surviving drug exposure, the MiCK assay measures a fraction of tumor cells killed by a chemotherapeutic agent via mechanism of apoptosis. Therefore the MiCK assay determines drug sensitivity, rather than resistance. Recently the MiCK assay has been shown to predict complete remission rate and survival in acute myeloid leukemia patients better than clinical criteria did<sup>18-20</sup>. In a limited study, the MiCK assay has been used to direct chemotherapy of the leukemia patients<sup>21</sup>.

The MiCK assay has also been used to study drug-induced apoptosis in solid tumors, including neuroblastoma and colon adenocarcinoma cell lines<sup>22-23</sup>. More recent data accumulated by DiaTech has demonstrated that the MiCK assay can detect drug induced apoptosis in primary cultures of tumor cells isolated from patients with ovarian carcinoma, gastric carcinoma, metastatic breast cancer and high grade soft tissue sarcoma. The purpose of this study is to correlate the results of the MiCK assay with short- and long-term results of treatments in cancer patients and evaluate the role of the MiCK assay in guiding chemotherapy of cancer patients.

## **2.0 Study Objectives:**

- 2.1 To correlate the MiCK assay results with objective response rates, symptom response rates, time to progression and survival of cancer patients treated with chemotherapy.
- 2.2 To evaluate the ability of the MiCK assay to guide chemotherapy of cancer patients, with emphasis on patients failing primary treatment, patients with unknown primary tumors, and patients with tumors difficult to treat such as carcinoma of lung.

## **3.0 Patient Population:**

### *3.1 Inclusion criteria:*

- 3.1.1 Patients with pathological diagnoses of cancer or leukemia
- 3.1.2 Patients must have tumor which is accessible for biopsy and agree to undergo tumor biopsy, or drainage of malignant effusion, and the specimen must be submitted for MiCK assay.
- 3.1.3 Patients for whom chemotherapy is planned.

### *3.2 Exclusion criteria:*

- 3.2.1 Patients with symptomatic/uncontrolled parenchymal brain or meningeal metastasis and tumors not accessible for biopsy.
- 3.2.2 Patients who are pregnant.

Pregnancy. During the course of the study, all patients of childbearing potential should be instructed to contact the treating physician if they suspect they might have conceived a child; for females, a missing or late menstrual period should be reported to

the treating physician. If pregnancy is confirmed by a pregnancy test, the patient must not receive chemotherapy in this study and must not be enrolled into the study or, if already enrolled, must be withdrawn from the study. If a male patient is suspected of having fathered a child while on the study, the pregnant female partner must be notified and counseled regarding the risk to the fetus. Pregnancy during the course of this study will be reported to the Principal Investigator as a serious adverse event. Women of child bearing potential are defined to include any female who has experienced menarche and has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not post-menopausal (defined as amenorrhea for more than 12 consecutive months); these includes also females using oral, implanted, or injectable contraceptive hormones, mechanical devices, or barrier methods to prevent pregnancy.

#### **4.0 Treatment Plan:**

4.1 The treating oncologist will decide what chemotherapy to use with each patient. The treating physician will be fully informed of the results of the MICK assay.

4.2 Tumor response, patient symptom response, time to progression on each chemotherapy regimen, and overall survival will be reported and correlated with MICK assay results.

#### **5.0 Definition of Clinical Response**

5.1 All patients will be evaluated for clinical response to chemotherapy as per standard protocol established for a specific malignancy.

5.1.1 Complete Remission CR is defined as total disappearance of clinically and radio logically detectable disease.

5.1.2 Partial Response PR is defined as at least 50% reduction of all measurable tumor lesions as measured by the sum of products of the perpendicular diameters of the greatest dimensions of measurable lesions, with no new lesions appearing; or by a greater than 30% reduction in the sum of diameters or unidimensionally measured tumors with no new lesions appearing, or by >50% reduction in tumor markers.

5.1.3 Stable Disease SD is defined as no CR, no PR and no PD

5.1.4 Progressive Disease PD is defined as appearance of any new tumor lesions or increase of 50% or more in the sum of products of the perpendicular diameters of the greatest dimensions of measurable existing lesions, or increase of 20% in the sum of diameters of unidimensional lesions, or 100% increase in tumor marker

**5.1.5 Time to progression TTP. The time from assay until progressive disease PD or death**

**5.1.6 Overall Survival OS. Time from assay until death**

**5.1.7 Symptom Response is evaluated by the physician based upon patient history and examination, and will be listed as improved, stable, or worse.**

## **6.0 Definition of the drug response in the MiCK assay.**

6.1 In the MiCK assay, the extent of drug-induced apoptosis is measured in Kinetic Units (KU) on a scale from 0 to 16 (Blood, 1998). Apoptotic responses in KU will be calculated for each dose of a tested drug or drug combination. The maximal numerical response induced by a drug will be considered the “best apoptotic response” to the drug.

6.2 The “best apoptotic response” to the drug will be compared to the clinical response to the drug to establish a numerical value of the *in vitro* response discriminating drug-sensitive and drug-insensitive tumors (establishing a numerical cut-off of sensitivity).

6.3 All response data will be given to the treating oncologist who will retain full choice of treatments.

6.4 Drug selection for testing with the MiCK assay against tumor cells will be based on the previous chemotherapy history of an individual patient with consideration of the future treatment plans. The drugs will be selected from a compendium of agents recommended for the treatment of the patient's malignancy and drugs suggested by the treating oncologist.

## **7.0 Statistics**

7.1 We will correlate tumor response, symptom response, TTP and OS with drug therapy with drug response in MICK assay for first chemo regimen after assay, and subsequent regimens.

7.2 We will compare tumor response, symptom response, TTP and OS for patients treated with drugs showing "best apoptotic response", drugs showing any apoptotic response ( $\geq 1.0$  KU) and drugs showing no apoptotic response ( $0 < 1.0$  KU).

## **8.0 Specimen collection, purification of tumor cells and sensitivity testing**

8.1 Specimen collection must be performed as per related DiaTech Standard Operating Procedures (SOP).

8.1.1 Collection of a Solid Tumor Biopsy Specimen is performed under sterile conditions, using excision biopsy technique, to obtain at least  $2 \text{ cm}^3$  of viable tumor tissue. The more viable tumor tissue is submitted for the study, the more chemotherapeutic agents can be tested against the tumor cells. Effusion specimen (peritoneal fluid, pleural fluid and effusions from other anatomical sites) should be collected in a commercial sterile container/bag with added Sodium Heparin (10 U/ml) to prevent clotting. The sample size should not be less than 500 ml. The specimen should not be fixed, or frozen.

- 8.1.2 Transportation: seal the transport tube/container/bag tightly. Label specimen with institution, patient name, date and time of collection, and anatomical site of collection. Place the transport tube/container/bag on ice pack (blue ice). Ice pack must be frozen before placing it to the container. Fill out the Study Requisition form and include with the transportation container.
  - 8.1.3 Place the 50 mL tubes or a container inside the zip-lock bag and seal. Place specimen and Cold Pak (blue ice) in a transport box. Place completed patient information forms and specimen transport box into FedEx plastic “Diagnostic Specimen Envelope” and seal. Complete and affix the FedEx Airbill to the outside of the Diagnostic Specimen Envelope. Be sure that the airbill is marked “FedEx Priority Overnight” delivery. Put \$5 value on the FedEx Airbill. Indicate “Human tissue for diagnostic studies” in the appropriate section of the FedEx Airbill. Call DiaTech Oncology at (514)-398-5174 (Mathieu Perree, lab manager) or (514)-398-5154 (general lab) with the Fed Ex Tracking Number. DiaTech must receive the specimen within 24 hours of collection. Specimens sent on Friday must be marked for Saturday delivery.
- 8.2 Tumor cell purification and their chemosensitivity testing will be performed as per related DiaTech SOPs.
- 8.2.1 Tissue biopsy and effusion specimens will be treated to obtain a suspension containing single tumor cells and/or small cell aggregates composed of 2-20 tumor cells. Using gradient centrifugation, red blood cell lysing, cell strainers, magnetic beads and other appropriate techniques, the tumor cell suspension will be enriched to at least 80% purity and no less than 90% viability. Immunocytochemical stains or,

when applicable, flow cytometry will be used to confirm the presence of specific tumor markers on purified cells. After purification, selected chemotherapeutic agents will be tested against purified tumor cells in the MiCK assay.

8.2.2 The purified tumor cells will be suspended in culture medium and plated in 96-well microtiter plates. Multiple concentrations of chemotherapeutic agents will be achieved by adding each respective agent to wells in 5  $\mu$ L aliquots. The ranges of final drug concentrations will be based on reports of pharmacokinetic studies of the drugs and their active metabolites in patients. Data processing and quantification of drug-induced apoptosis will be performed by a proprietary ProApoTest<sup>TM</sup> software. The extent of apoptosis will be determined and expressed as kinetic units (KU) of apoptosis.

## **9.0 Specimen's left over**

9.1 If a specimen contains more tumor cells than needed for testing their sensitivity to the drugs specified by the patient's oncologist, an excess of the tumor cells may be considered for use for other research studies conducted by DiaTech Oncology. Patients will be asked for their permission to use specimen's left over for research purposes by signing the following release included in the requisition form: *"You are participating in the Research Program which may result in improvements of the treatment outcome for cancer patients. There is no direct benefit for you at present time. Your physician is submitting to DiaTech a specimen containing your tumor cells. At DiaTech, we purify the tumor cells, count them, check their viability, and store them in the DiaTech Tissue Bank. All these procedures are performed at no cost to you or your family. Your cells may be used for the chemosensitivity testing for*

*research purposes or in other studies. Results of the research may be published, or used commercially in the area of new anti-cancer drug or treatment protocol development. To assure your privacy, should the results of the studies be published, you will be referred to only by number. Your signature below indicates that you agree to these terms”.*

If a patient refuses to sign the above release, the specimen's left over will be decontaminated using 10% formaldehyde for 24h and discarded as per related SOP. If a patient grants his/her permission for use on the specimen's left over in a future research, an excess of the tumor cells will be frozen and stored in liquid nitrogen indefinitely.

- 9.2 Specimen's left over may be used to study anti-tumor effects of chemotherapeutic drugs or drug combinations, to study mechanisms of drug resistance, to correlate phenotypic features of the tumor cells with their drug sensitivity profile.

#### **10.0** Plan of communication between *DiaTech oncology lab director*, Principal Investigator and co-Principal Investigator.

To insure proper communication the following communication means will be used: FedEx delivery of the printed materials, Phone & Fax, E-mail, Video-conferencing

- 10.1 At the time of submission of the patient's specimen for the study, relevant clinical information will be submitted to DiaTech in the form of a study requisition form prepared by the *referring oncologist* (or designated staff nurse) using FedEx courier service.
- 10.2 Upon receiving the specimen and requisition form and after purification of tumor cells from the specimen, *DiaTech personnel* will place a telephone call to the referring oncologist (co-PI) to discuss the case.

- 10.3 Upon completion of the patient's tumor drug sensitivity testing, results will be scored and introduced to the study data base. ***The DiaTech Oncology lab director*** will issue a study report and it will be faxed to the referring oncologist no later than 96h after receiving the specimen. After faxing the report, ***DiaTech pesrannel*** will call the referring oncologist to discuss the results.
- 10.4 After each 2 cycles of therapy, or at other intervals, the patient's treatment response will be evaluated by the referring oncologists (co-PI). A study Response Evaluation Form will be filled out and faxed to DiaTech to be included in the study data base.
- 10.5 DiaTech Study coordinator (Mr. Garry Latimer 615 377 9668) will contact each site co-PI or a designated nurse monthly to assure proper supply of transportation containers and to address administrative issues.

## **DIATECH ONCOLOGY**

### **PATIENT INFORMATION/INFORMED CONSENT**

**TITLE OF RESEARCH PROJECT:** Correlation of the  
Microculture Kinetic (MiCK) Apoptosis Test Results with Drug  
Treatment Results in Cancer Patients

**PRINCIPAL INVESTIGATOR:** Dr. Cary Present

**CO-PRINCIPAL INVESTIGATOR:**

**DISCLOSURE:** DiaTech Oncology is the sponsor of this study. Dr. Present is paid for consulting at DiaTech and participates in company stock options.

#### **GENERAL**

I have been asked to participate in a clinical research study. I have been told also that I have the option not to participate. This study is being carried out under the sponsorship of the DiaTech Oncology Corporation, an organization dedicated to patient chemosensitivity testing and clinical research in the field of cancer. DiaTech is a private company performing patient specific cancer chemosensitivity testing for patients and physicians. This research study will be listed with the National Cancer Institute (NCI). DiaTech Oncology is setting up a clinical study to demonstrate the ability of a new technology called the Microculture Kinetic (MiCK) assay to predict treatment outcome and to direct chemotherapy of cancer patients.

**The benefit to clinical sciences and to mankind that is thought by this study.**

The proposed study may allow for better selection of chemotherapeutic agents for the individual patients to improve therapy outcome.

**The possible benefit for me from this study.**

There is the potential to select the best chemotherapy drug for me.

**HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?**

Up to 2000 patients will participate in this study.

**WHAT IS INVOLVED IN THE STUDY?**

**Medical Tests:**

I understand that I will undergo a thorough evaluation prior to the initiation of treatment. This will consist of: physical examination which may include pelvic examination; blood counts, assessment of liver and kidney status through blood studies. Detectable tumor will be measured by examination, radiology tests and blood studies. A biopsy of my cancer or body fluids with cancer cells will be sent to DiaTech for the MiCK assay. Results will be sent to my doctor who will decide with me which drugs will be used to treat my cancer. Data from follow up evaluations after chemotherapy has been started will be submitted to the DiaTech for analysis as a part of the study to determine how well the MiCK assay has predicted by response to the chemotherapy.

**The parts of this study that are being done solely for this study.**

Treatments and Evaluations are standard care for my cancer. Therefore DiaTech Oncology is not offering any compensation for injury that may occur as a result of the treatments and evaluations. The only parts of this study that are being done solely for this study are comparisons of how well I respond to the chemotherapy compared to the results of the MiCK laboratory test.

**HOW LONG WILL I BE IN THE STUDY?**

At least 1 year.

**WHAT ARE THE RISKS OF THE STUDY?**

None related strictly to the study. However, chemotherapeutic drugs used for chemotherapy may not always be effective in eliminating the tumor and they may have severe adverse effects. Your physician will advise you of the risks and benefits of each drug your physician chooses for your therapy.

**PRIVACY AND CONFIDENTIALITY**

You have the right to privacy. You understand that all information will be held confidential and will not be released without your written permission to the extent permitted by law.

Efforts will be made to keep your name and personal information confidential. Absolute confidentiality cannot be guaranteed, however confidentiality will be maintained to the extent permitted by local, state, and federal law.

Your personal health information will be used and disclosed to DiaTech personnel for this research study. A decision to participate in this study means that you agree to the use and disclosure of your personal health information only for the purposes explained in this consent form.

During the course of this study the research team may use the following health information: all or part of your medical records, hospital records, doctor's office records, and results of tests, exams or procedures conducted for this study as described in this consent form. Only the researchers and hospital staff conducting this study will have access to your personal health information as necessary to conduct this research study.

Your personal health information may also be disclosed to representatives of the study sponsor, Diatech Oncology Company, the Food and Drug Administration (FDA) or other regulatory agencies, or Western Institutional Review Board to monitor the conduct of the study. There is the potential of further disclosure of your personal health information by these individuals or entities such that your information is no longer subject to protection under federal regulations governing the privacy of health information. This research may result in scientific presentations and publications, but precautions will be taken to make sure you cannot be identified in any way.

By signing this consent form, you authorize the use of your personal health information until the end of this study. You have the right to revoke your authorization to use your personal health information. The revocation must be in writing and sent to your medical oncologist. If you revoke your authorization it will not apply to prior uses or disclosures of your personal health information made in accordance with the purposes explained in this consent form.

If you refuse to provide authorization to use and disclose your personal health information for this study, the investigator may refuse to include you as a participant in this study.

Your right to access your health information used and disclosed for the study may be restricted as long as the research is in progress; however, your right to access will be reinstated, upon completion of the research study.

**Overview:**

**Detailed Information:**

## **Making Your Choices About Future Research**

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". **No matter what you decide to do, it will not affect your care.** If you have any questions, please talk to your doctor, nurse or other type of healthcare provider.

1. Do you give permission for your specimens, if still available after this research study is completed, to be used in future research to learn about, prevent, or treat cancer?

Yes      No

2. Do you give permission for your specimens, if still available after this research study is completed, to be used in future research to learn about, prevent or treat health problems other than cancer (for example: diabetes, Alzheimer's disease, or heart disease)?    **Yes**      **No**

**Please sign your name after you circle your answers.**

**Your signature: \_\_\_\_\_ Date: \_\_\_\_\_**

**Signature of Attending Doctor/Nurse: \_\_\_\_\_ Date: \_\_\_\_\_**

**REQUISITION FORM FOR THE DIATECH TUMOR STUDY  
FAX COMPLETED REQUISITION TO 514-398-4939**

Patient Name		Institution/Hospital	
Patient's Sex <input type="checkbox"/> M <input type="checkbox"/> F	Patient D.O.B. (mm/dd/yyyy)	Referring Physician	
Patient's Unique Identifier Number		Referring Physician Phone/Fax#	
Sender Specimen #	ICD9 code:	Send Report To:	
Specimen Type <input type="checkbox"/> Whole Blood <input type="checkbox"/> Bone Marrow <input type="checkbox"/> CSF <input type="checkbox"/> Lymph Node <input type="checkbox"/> Other (specify):		Date Time collected	<input type="checkbox"/> am <input type="checkbox"/> pm

**PATIENT'S DIAGNOSIS**

1. Original diagnosis (please specify subtype of the malignancy and staging):

Date the original diagnosis was made:

Is this the first presentation or relapse?

If prior systemic therapy was used, please describe **all drugs previously used**:

a. chemotherapeutic agents used (if known):

b. patient's response to the treatment (CR, PR, No response):

c. date of the most recent course of chemotherapy:

**Drugs to be considered for use and to be tested:**  
**Preferred:**  
**Others:**  
**Do not need to test:**

**COMPLETED BILLING INFORMATION**

Responsible Party		Responsible Party S.S. #		
Responsible Party Billing Address		City	State/Province	Zip Code
Responsible Party Telephone Number		Relationship to Patient <input type="checkbox"/> Self <input type="checkbox"/> Spouse <input type="checkbox"/> Other:		Patient Birth Day
Responsible Party Place of Employment		Employment Address		Business Telephone
Type of billing <input type="checkbox"/> Visa <input type="checkbox"/> Master Card				
Number <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> Exp. Date <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/>				

**INFORMED CONSENT FORM**

**To the patient.** Since you were diagnosed with a cancer, your physician has ordered the MiCK assay to determine the sensitivity of your tumor cells to chemotherapy drugs. Specimens submitted for the MiCK assay may contain more cells than required for the test. The tumor cells not used for the MiCK assay are stored under special conditions at low temperatures. They may be used in the future for research purposes. Results of the research may be published, or used commercially in the area of new anti-cancer drug development. To assure your privacy, should the results of the studies be published, you will be referred to only by number. Your signature below indicates that you agree to these terms.

\_\_\_\_\_

Patient Signature                      Date                      Signature of witness(es) (when applicable)                      Date

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