STATEMENT OF WORK (SOW)

<u>Instructions:</u> This document should be used for the acquisition of SERVICES. Instructions (and sample language) for completion are in red, and should be excluded from the completed document.

1.0 TITLE

Replication Competent Retrovirus (RCR) Testing

2.0 BACKGROUND

One of the main objectives of the Surgery Branch of the National Cancer Institute is to conduct basic and translational laboratory and clinical research aimed at improving the management of patients with cancer.

Our efforts in accomplishing this objective are varied and include an increasing number of gene therapy clinical trials. Most of our current clinical approaches in this area involve the generation of cell/gene transfer therapies following lymphodepleting chemotherapy. These immunotherapy studies were initially focused on the treatment of patients with metastatic melanoma; however, recent characterization of genes encoding T-cell receptors (TCRs) that are capable of recognizing common epithelial antigens have allowed us to expand these approaches for the treatment of patients with common epithelial malignancies. These TCRs targeting specific tumor antigens and/or cytokines are introduced into PG13, a murine NIH 3T3 cell line, in the context of a packageable retroviral genome, and the selected cell clone is used to generate a master cell bank (MCB) that constitutively produces retroviral vector particles. The MCB is then fully characterized and tested for biosafety before being used to generate a clinical-grade retroviral vector supernatant. It is this vector that then serves as the vehicle for gene delivery into patient's immune cells *ex vivo*.

2.1 OBJECTIVE

The objectives of this testing are the following:

- to assay for Gibbon Ape Leukemia (GALV) sequences using a quantitative PCR (qPCR) detection method;
- to assay for RD114 envelope sequences using the cell-based S+L- detection method; and,
- to assay for presence of adventitious virus with a cell-based method utilizing Vero, MRC-5, and NIH-3T3 cells.

3.0 SCOPE

Active monitoring for evidence of RCR and adventitious viral contaminant infection in patients enrolled in gene therapy clinical trials using retroviral vectors is currently required by the FDA. These recommendations were originally submitted in a letter to Sponsors of INDs Using Retroviral Vectors, dated September 20, 1993 and alternative timepoints for monitoring were subsequently provided in the January 2020 Guidance for Industry entitled, "Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up", which was based on data accumulated in ongoing gene therapy clinical trials using retroviral vectors. The RCR monitoring schedule recommended in the guidance for vector supernatant lots includes analysis of patient samples at the following time points: pre-treatment, 3-, 6-, and 12-months after treatment. If all post-treatment assays (i.e., 3-, 6-, and 12-month timepoints) are negative, then collection of the yearly follow-up samples will be discontinued for that individual, and yearly review of medical history will be sufficient for that individual. Additionally, the guidance recommends testing of end of production cells for RCR.

Finally, testing for the presence of adventitious virus that could be introduced during production of vector supernatant is described in ICH Topic Q5 A (R1): "Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Productions Derived from Cell Lines of Human or Animal Origin" (October 1997). This testing is recommended for cell lines utilized in the production of vector supernatant.

Two methods are currently in use and recommended by the FDA for detecting evidence of RCR infection in patient peripheral blood lymphocyte specimens: 1) detection of RCR-specific antibodies; and 2) analysis of patient peripheral blood mononuclear cells by polymerase chain reaction (PCR) for RCR-specific DNA sequences. The choice of assay may depend on the mode of vector administration and the clinical indication. For example, it has been shown that direct administration of vector producer cells or repeat direct injection of a vector can result in vector-specific antibodies which do not correlate with the presence of RCR (Refs. 3-4). Therefore, in cases where vector or vector-producing cells are directly administered, a PCR assay may be preferable over serologic monitoring. Additional instances where monitoring of patients by PCR may be preferred over serologic monitoring, are those cases where the patients are immunocompromised to an extent that antibody production may be minimal or not at all.

The method currently in use and recommended by the FDA for detecting evidence of RCR infection in patient cell infusion product is co-culture with a permissive cell line in order to amplify any potential RCR present.

The method currently in use and recommended for testing for presence of adventitious viral contaminants is a cell-based method involving at least two passages of cells to observe for cytopathic changes at varying temperatures.

4.0 CONTRACT REQUIREMENTS/ AND PERSONNEL QUALIFICATIONS

***In Vitro* Detection of Retrovirus by PCR for the GALV Envelope**

- The objective of this study is to assay for Gibbon Ape Leukemia (GALV) sequences using a quantitative PCR (qPCR) detection method.
- The testing procedure, volumes, and durations are according to established SOPs at the IU GTTL.
- The method for detecting GALV uses a real time qPCR technique that employs a probe and primer set designed to detect GALV sequences. Adequacy of the amount of test article material analyzed is assessed by a second probe and primer set designed to detect human apolipoprotein B (ApoB) gene sequences.
- DNA is purified from the test and control samples and amplified. The amplified product is analyzed for GALV envelope sequences by a radiolabeled gel blot probe. The film of the gel is visually examined for a band of expected size. Photographic records are retained.
- Test sample is 10^6 cells.
- Retention of representative samples is the responsibility of the Surgery Branch.
- Raw data pertaining to each report, a copy of the report, and records of the SOPs are maintained in the IU GTTL minimally 3 years after release to the Surgery Branch.
- The Surgery Branch will be provided a final study report that includes a summary of the assay and results.

***In Vitro* Detection of Retrovirus by S+L- for the RD114 Envelope**

- The objective of this study is to assay for RD114 envelope sequences using the cell-based S+L- detection method.
- The testing procedure, volumes, and durations are according to established SOPs at the IU GTTL.

- The method for detecting RD114 uses cell-based method in which the test sample is placed into culture with 293 cells and maintained in culture for three weeks to enhance the replication of any infectious retrovirus that may be present.
- Culture fluid is collected from the final passage, filtered and inoculated onto PG-4 cells. Each culture well of the PG-4 indicator cells are examined for foci at the time the indicator cells appear confluent. If present the foci are enumerated. All culture well observations are recorded.
- Test sample size is determined in consultation with IU GTTL.
- Retention of representative samples is the responsibility of the Surgery Branch.
- Raw data pertaining to each report, a copy of the report, and records of the SOPs are maintained in the IU GTTL minimally 3 years after release to the Surgery Branch.
- The Surgery Branch will be provided a final study report that includes a summary of the assay and results.

***In Vitro* Detection of Adventitious Viral Contaminants**

- The objective of this study is to assay for presence of adventitious virus with a cell-based method utilizing Vero, MRC-5, and NIH-3T3 cells.
- The testing procedure, volumes, and durations are according to established SOPs at the IU GTTL.
- The method for detecting the presence of adventitious virus involves using a cell culture technique in which Vero, MRC-5, and NIH-3T3 cells are inoculated with the test sample and appropriate controls and passaged for 14 days. All cultures are observed for cytopathic changes and evaluated for hemadsorption using guinea pig, chicken, and human type 'O' erythrocytes at temperatures of 2-8°C, 20-25°C, and 36-38°C.
- Tissue culture fluid from negative samples are inoculated onto fresh indicator cells and passaged 14 additional days. Cultures are observed for cytopathic changes and evaluated for hemadsorption using guinea pig, chicken, and human type 'O' erythrocytes at temperatures of 2-8°C, 20-25°C, and 36-38°C.
- Test sample size is determined in consultation with IU GTTL.
- Retention of representative samples is the responsibility of the Surgery Branch.
- Raw data pertaining to each report, a copy of the report, and records of the SOPs are maintained in the IU GTTL minimally 3 years after release to the Surgery Branch.
- The Surgery Branch will be provided a final study report that includes a summary of the assay and results.

5.0 TYPE OF ORDER

This is a Firm Fixed-Price Purchase Order.

6.0 PERIOD OF PERFORMANCE

As needed, to meet the FDA reporting requirements that the RCR and adventitious viral contaminant data for patients enrolled in each clinical protocol be reported annually with the IND annual report.

7.0 PLACE OF PERFORMANCE

Indiana University Gene Therapy Testing Laboratory
980 West Walnut St., R3-C668
Indianapolis, IN 46202
Phone: (317) 274-0340 / Fax: (317) 278-3327

STATEMENT OF WORK (SOW)

8.0 REPORT(S)/DELIVERABLES AND DELIVERY SCHEDULE

The deliverables shall consist of the RCR and adventitious viral contaminant testing results for peripheral blood lymphocytes and cell infusion specimens of patients treated on gene therapy protocols utilizing retroviral vectors and conducted by the Surgery Branch, which were obtained at specific time points as determined by the FDA ; and adventitious viral contaminant testing results for specimens of cells utilized in the production of retroviral vector supernatant manufactured by the Surgery Branch for patients enrolled in Surgery Branch gene therapy protocols.

The results will be delivered to Jennifer Pappas, MHS, Regulatory Affairs Manager, Clinical Monitoring Research Program (CMRP), Frederick National Laboratory for Cancer Research, Leidos Biomedical Research, Inc after completion of all required testing by IU GTTL.

9.0 PAYMENT

Payment shall be made _once_____. Payment authorization requires submission and approval of invoices to the COR and NIH OFM, in accordance with the attached payment provisions listed below:

The following clause is applicable to all Purchase Orders, Task or Delivery Orders, and Blanket Purchase Agreement (BPA) Calls: PROMPT PAYMENT (JUL 2013) FAR 52.232-25. Highlights of this clause and NIH implementation requirements follow:

I INVOICE REQUIREMENTS

A. An invoice is the Contractor's bill or written request for payment under the contract for supplies delivered or services performed. A proper invoice is an "Original" which must include the items listed in subdivisions 1 through 12, below, in addition to the requirements of FAR 32.9. If the invoice does not comply with these requirements, the Contractor will be notified of the defect within 7 days after the date the designated billing office received the invoice (3 days for meat, meat food products, or fish, and 5 days for perishable agricultural commodities, dairy products, edible fats or oils) with a statement of the reasons why it is not a proper invoice. (See exceptions under II., below.) Untimely notification will be taken into account in the computation of any interest penalty owed the Contractor.

1. Vendor/Contractor: Name, Address, Point of Contact for the invoice (Name, title, telephone number, e-mail and mailing address of point of contact).
2. Remit-to address (Name and complete mailing address to send payment).
3. Remittance name must match exactly with name on original order/contract. If the Remittance name differs from the Legal Business Name, then both names must appear on the invoice.
4. Invoice date.
5. Unique invoice #s for all invoices per vendor regardless of site.
6. NBS document number formats must be included for awards created in the NBS: Contract Number; Purchase Order Number; Task or Delivery Order Number and Source Award Number (e.g., Indefinite Delivery Contract number; General Services Administration number); or, BPA Call Number and BPA Parent Award Number.
7. Data Universal Numbering System (DUNS) or DUNS + 4 as registered in the Central Contractor Registration (CCR).

8. Federal Taxpayer Identification Number (TIN). In those exceptional cases where a contractor does not have a DUNS number or TIN, a Vendor Identification Number (VIN) must be referenced on the invoice. The VIN is the number that appears after the contractor's name on the face page of the award document.
9. Identify that payment is to be made using a three-way match.
10. Description of supplies/services that match the description on the award, by line billed.*
11. Freight or delivery charge must be billed as shown on the award. If it is included in the item price do not bill it separately. If identified in the award as a separate line item, it must be billed separately.
12. Quantity, Unit of Measure, Unit Price, Extended Price of supplies delivered or services performed, as applicable, and that match the line items specified in the award.*

* NOTE: If your invoice must differ from the line items on the award, please contact the Contracting Officer before submitting the invoice. A modification to the order or contract may be needed before the invoice can be submitted and paid.

B. Shipping costs will be reimbursed only if authorized by the Contract/Purchase Order. If authorized, shipping costs must be itemized. Where shipping costs exceed $100, the invoice must be supported by a bill of lading or a paid carrier's receipt.

C. Mail an original and 1 copy of the itemized invoice to:

National Institutes of Health
Office of Financial Management, Commercial Accounts
2115 East Jefferson Street, Room 4B-432, MSC 8500
Bethesda, MD 20892-8500

For inquiries regarding payment call: (301) 496-6088

In order to facilitate the prompt payment of invoices, it is recommended that the vendor submit a photocopy of the invoice to the "Consignee" designated for the acquisition in blocks 6A – 6E of the face page of the Order/Award document.

II. INVOICE PAYMENT

A. Except as indicated in paragraph B., below, the due date for making invoice payments by the designated payment office shall be the later of the following two events:

1. The 30th day after the designated billing office has received a proper invoice.
2. The 30th day after Government acceptance of supplies delivered or services performed.

B. The due date for making invoice payments for meat and meat food products, perishable agricultural commodities, dairy products, and edible fats or oils, shall be in accordance with the Prompt Payment Act, as amended.

III. INTEREST PENALTIES

A. An interest penalty shall be paid automatically, if payment is not made by the due date and the conditions listed below are met, if applicable.
   1. A proper invoice was received by the designated billing office.
   2. A receiving report or other Government documentation authorizing payment was processed and there was no disagreement over quantity, quality, or contractor compliance with a term or condition.
   3. In the case of a final invoice for any balance of funds due the contractor for supplies delivered or services performed, the amount was not subject to further settlement actions between the Government and the Contractor.

B. Determination of interest and penalties due will be made in accordance with the provisions of the Prompt Payment Act, as amended, the Contract Disputes Act, and regulations issued by the Office of Management and Budget.

IV. PROVIDING ACCELERATED PAYMENT TO SMALL BUSINESS SUBCONTRACTORS, FAR 52.232-40 (DEC 2013)

a) Upon receipt of accelerated payments from the Government, the Contractor shall make accelerated payments to its small business subcontractors under this contract, to the maximum extent practicable and prior to when such payment is otherwise required under the applicable contract or subcontract, after receipt of a proper invoice and all other required documentation from the small business subcontractor.
b) The acceleration of payments under this clause does not provide any new rights under the prompt Payment Act.

Include the substance of this clause, include this paragraph c, in all subcontracts with small business concerns, including subcontracts with small business concerns for the acquisition of commercial items.