Additional Information, Background and Examples

The following are background information and examples of research activities currently in progress at the FNLCR or anticipated to be conducted by the Contractor. The titles correspond to numbered sections in the Statement of Work.

NOTE: This document is for informational purposes only and is not part of the SOW.

1. INTRODUCTION

1.1 What is a Federally Funded Research and Development Center (FFRDC)?

Federally Funded Research and Development Centers (FFRDC) enable agencies to use private sector resources to accomplish tasks that are integral to the mission and operation of the sponsoring agency. As described in the Federal Acquisition Regulation (FAR), an FFRDC meets a "special long-term research and development need which cannot be met as effectively by existing in-house or contractor resources" (FAR 35.017 (a)(2)). An FFRDC is required to operate in the public interest, be free from organizational conflicts of interest, provide full disclosure of its affairs to the sponsoring agency and conduct its business in a manner that is consistent with its special relationship with the Government. Furthermore, FAR 35.017 (a)(3) states that "An FFRDC is operated, managed, and/or administered by either a university or consortium of universities, other not-for-profit or nonprofit organization, or an industrial firm as an autonomous organization or as an identifiable separate operating unit of a parent organization."

1.1.1 Legislative Authority

In 1972, the Frederick Cancer Research Center (FCRC) began operations under the authority of The National Cancer Act of 1971. The National Science Foundation (NSF) notified the NIH that the FCRC was officially designated as an FFRDC in 1975. In 2012 the FFRDC was designated as a National Laboratory now known as the FNLCR. It is a GOCO research facility sponsored by the NCI through the Department of Health and Human Services, in accordance with Federal Acquisition Regulation (FAR) 35.017. Under this authority, the FFRDC undergoes a periodic review for continuance every 5 years as an on-going program. NCI manages, administers, monitors and is responsible for the overall operation and use of the FFRDC.

1.2 FFRDC Vision, Performance Goals, and Strategic Program Objectives

1.2.1 Performance Goals

1.2.2 Strategic Program Objectives/Scope

1.2.2.1 National Mission Programs

Former NCI Director Dr. Harold Varmus established an advisory committee that recommended the FNLCR identify and undertake important and ambitious projects in cancer research that would be difficult to pursue without an orchestrated and multidisciplinary effort. These were subsequently deemed "National Mission Programs". The overall mandate and scope of these novel programs have varied according to the research objectives of each individual mission program and are purposely designed to have greater impact in biomedical cancer research. The following examples are illustrative actions and achievements of particular national missions:

- The RAS Initiative was the first National Mission Program to be launched in 2013 and was charged with exploring new approaches to identify therapeutic treatments for RAS driven cancers. RAS is the most common oncogene and is implicated in greater than 30% of all cancers, include 95% of pancreatic cancers and 45% of colorectal cancers. At the time that this flagship mission was launched, RAS was considered an "undruggable target". The initial goals of the program included fundamental research to provide greater understanding of oncogenic RAS in cancer biology and to build an open collaboration model across government, academic, and industrial researchers to re-energize efforts to discover RAS therapeutics. Tremendous progress has been made in structural biology, molecular dynamics, reagent generation and distribution, and support of the global RAS research community which has led to the discovery of novel and clinically promising RAS inhibitors.
- National Cryo-EM Facility, a state-of-the-art facility offering the extramural community data collection as well as new technology platforms and workflows to accelerate the development of next-generation tools for structural determination.
- COVID-19 pandemic response: The FNLCR components of SeroAct includes the Clinical Translational Serology and elements of the Serological Sciences Network, SeroNet. The objective of the Clinical Translational Serology is to catalyze translation of research tools and findings into public health changes that bring together and engage various government organizations, academics, and industry partners that can provide relevant information on public health for decision makers to manage the current and future status of the COVID-19 pandemic. The SeroNet's objective is to support a broad range of serological sciences research to advance our understanding of all aspects of the immune response to SARS-CoV-2. This will be accomplished by; 1) the expansion of the FNL's serology laboratory for commercial assay testing and establishment of the national reference standards and reagents and 2) creations of the coordination center that provides overarching technical project management of the following activities, capacity building serological testing centers, and the serological sciences centers of excellences extramural grantees of SeroNet.

1.2.2.2 Basic, Translational, and Clinical Research

1.2.2.3 Core Research Services

Examples of core research support activities include human cell therapy, Human Leukocyte Antigen and B-cell Lymphoma cell typing, nanomedicine pharmacokinetics, ultrasensitive detection of Simian and Human Immunodeficiency Virus, preclinical evaluation of antineoplastics for pancreatic cancer, gnotobiotics, and small animal imaging.

2. REQUIREMENTS

2.1 FFRDC Strategic Planning, Execution, and Innovation Scope

- Respond to the changing needs of the Government.
- Allow for and contribute to Government-approved facility tours.
- Standardize and streamline methods.
- Advise the Government about cost-effective service realignments when existing services have become commoditized and should be phased out, when community needs and usage patterns have changed, or when novel technologies or service improvements have become available.

2.1.1 Strategic Planning, Execution, and Innovation in Scientific Operation

- Enhance existing shared service capabilities
- Innovation of capabilities that could become new shared service, scientific publication and/or patentable inventions.
- Facilitate adaptation of new technologies into laboratory settings and stay at the cutting edge of the field.
- Training fellowships for technology innovation.

2.1.2 Strategic Planning, Execution, and Innovation in Business and Operations

n/a

2.2 FNLCR Technical Capabilities

n/a

2.3 Program Management

Program management entails developing integrated plans and schedules to achieve program objectives; actively seeking input from stakeholders; maintaining sufficient technical expertise to accomplish the work and manage activities/projects throughout the project/program lifecycle; maintaining equipment

and infrastructure; and utilizing appropriate technology and management systems to achieve cost efficiency, performance, and accommodate urgent and shifting priorities.

2.4 Scientific Operations

2.4.1 Advanced Scientific Computing and Bioinformatics

2.4.1.1 Data Science

n/a

2.4.1.2 Bioinformatics and Advanced Scientific Computing Methods

The contract operates under the broad definition that bioinformatics is the application of statistical and computational analytic methods to large datasets of e.g. biomolecules, commonly biopolymer sequence data such as genomic sequence data, and gene expression data at the RNA and protein level, but also including other kinds of macromolecule and small molecule data, such as metabolite profiles. Or imaging. It incorporates incorporate structural and functional information to provide statistical correlations for molecular variants (e.g. specific alleles, protein markers, and 16S rRNA species) in association with normal and disease states, drug responses, evolutionary distance between organisms, relative abundance of microorganisms within the microbiome and other relationships. Advanced computational methods are being utilized as needed, e.g. to analyze the composition of a number of different classes of molecules that can be measured by high throughput methods. Computational approaches will be used to e.g. characterize, model, and simulate higher order molecular structures and molecular interactions, to evaluate the bioavailability of candidate drugs, to elucidate molecular structures, and to perform quantitative image analysis. These computational methods form the foundation for many analytic workflows and expertise is needed in advanced scientific computing and bioinformatics, support for development and maintenance of analysis pipelines, and training in relevant computational and bioinformatics methods necessary to support the full spectrum of research.

2.4.1.3 Cloud Computing

The Government requires cloud architecture with dynamically scalable cloud computational capacity, cloud-native workflow services, and orchestration technologies. This requires expertise in cloud computing and a broad understanding that cloud computing offers many advantages for biomedical research, due primarily to the instantaneous scalability of cloud computational capacity (autoscaling), cloud architecture (e.g. virtual private clouds) and cloud-native workflow services and orchestration technologies (e.g. Kubernetes). In the cloud, researchers' ability to take the compute to the data is being supported, rather than transferring and redundantly storing ever-expanding caches of data around multiple separate computing resources. Moreover, the Government expects the amount of computational resources consumed to be dynamically scaled to demand, without additional infrastructure investment; thereby eliminating the need to choose between over-provisioning computational infrastructure to meet periodic spikes in demand or accepting the latency caused by bottlenecks in computational capacity. The cloud environments are also expected to be used to test and optimize new, experimental workflows that can be rapidly deployed without long-term hardware

commitments. Finally, the cloud environments are expected to provide access to extensible analytic platforms equipped with state-of-the-art capabilities and intuitive user interfaces where data and tooling can be easily shared, and large and disparate datasets can be rapidly integrated. This requires expertise in cloud computing that will fully utilize the power of cloud computing and successfully navigate its challenges by determining which efforts are best performed in the cloud, adapting and migrating existing workflows to the cloud, developing new cloud-native applications, transferring, storing and accessing data, and optimally leveraging cloud resources.

2.4.1.4 High-Performance Computing (HPC)

The Government expects support of computationally-intensive functions that do not require the flexibility or accessibility for non-technical users offered by the cloud and can be most efficiently provided with on premises computational resources. For example, steady loads of imaging or sequencing data processing can be reliably accomplished with less expense and minimal data transfer latency on computing resources proximal to the data-generating instrumentation. The FFRDC-operated Frederick Research Compute Environment (FRCE) HPC facilities operate in complementation to the NIH-operated Biowulf and/or other systems as required to offer extensive batch and parallel computational capacity based on modern HPC CPU and GPU nodes for such applications. The specialized FRCE environment is tailored to support FNLCR, NCI, and other stakeholders' data processing and analysis needs and includes high performance storage, SLURM batch job software, and high-speed network connectivity for Frederick-centric labs.

2.4.1.5 Engagement with Entities Within and Outside the NIH

The Government expects successful collaboration with other computationally focused entities within NCI, NIH, as well as other Federal and external partners engaged in advanced computational and data science efforts. To this end, state-of-the-art expertise in the development of the most advanced computational resources must be maintained. In order to leverage resources such as exascale computing for disease research, in consultation with NCI, leadership and coordinating engagement activities such as collaborations for developing or expanding computational approaches, participating in working groups for evaluating existing resources, future needs, and technology trends are required. The aim is to accelerate government research, coordinate with groups inside the NIH and raise visibility of government data science activities within the larger biomedical research community.

2.4.2 Animal Sciences

The FFRDC provides comprehensive animal-based research and research support services for the NCI/NIH/HHS, other Government scientists and the extramural community as directed by the Government. This support includes routine and specialized husbandry services on the NCI/NIH campuses (Bethesda and Frederick, or other government approved locations), animal facility management, and compliance with applicable regulations and guidelines. Animal science research and research support include veterinarian care, regulatory and protocol support, research technical support. Animal Sciences requires the implementation a modern software system to facilitate the tracking and maintenance of animal inventory, breeding, weekly accounting of occupied cages linked to user/protocol/cage type information, technical hours, and health status.

All procedures are conducted in a humane manner in a controlled environment, and all animal housing and procedures conform to the most recent regulations and guidelines that at present include American Association for Accreditation of Laboratory Animal Care (AAALAC) accreditation, the Guide for the Care and Use of Laboratory Animals, and all Public Health Services (PHS) and Animal Welfare Act regulations. Employed veterinarian(s) with VMD/DVM degree(s) provide clinical veterinary care, preventative medicine, training of personnel in the humane care and use of laboratory animals, and have primary responsibility for maintaining AAALAC accreditation and assuring compliance with The Guide, all PHS and Animal Welfare Act regulations, and other accreditations and compliances as designated by the Government.

The FFRDC currently operates an animal diagnostic laboratory to ensure disease prevention, detection and eradication for all designated areas that produce or house research animals or animal cells and tissues. The serological and molecular diagnostic systems that the lab employs includes assays designed specifically to identify the viruses, bacteria, and parasites that infect select rodents such as mice, rats, and guinea pigs, as well as other vertebrates. Diagnostic procedures provided include serological and molecular testing, genetic monitoring, and verification of defined flora in experimental animals; pathogen status, defined flora status and genetic integrity; high-throughput animal genotyping to identify animal (such as murine) strains; and state-of-the-art animal (such as murine) breeding strategies.

The Government also requires administrative support for the NCI-Frederick ACUC and the NCI-Bethesda ACUC (and other ACUCs as directed by the Government), assistance to principal investigators in preparing their Animal Study Proposals (ASPs), and scientific and technical expertise for *in vivo* experimentation (areas: animal modeling, preclinical drug efficacy, vaccine efficacy, pharmacokinetic, pharmacodynamic and toxicology studies).

Capabilities and capacities examples the Government requires include:

- Conventional, specific-pathogen free and gnotobiotic animal facilities
- Daily husbandry, breeding, experimental and surgical procedures, veterinary care, animal tagging, animal health surveillance; including selected amphibians, zebrafish, selected rodents, and non -human primates
- Cage washing services, and cleaning and disinfection of facility and animal holding equipment (e.g., racks, cages, filter tops, etc.) as necessary
- Ordering of research animals and supplies, including animal food, bedding, and caging
- Shipping of research animals
- Provide and maintain an animal inventory system
- Environmental monitoring
- Facility management and administration
- Receipt and quarantine of incoming animals and animal tissues
- Isolation of animals that may possess infectious hazards

- Provision of on-site facilities and technical capabilities for embryo, sperm, and/or caesarian rederivation of mouse strains, as well as for the quarantine of "rederived" rodents until their health status is confirmed
- Specimen collection, storage, and processing
- Isolating and identifying protists and parasites in specimens
- Coordinating diagnostic requests
- Diagnosing abnormal animal health conditions employing serological testing and other systems
- Interpreting diagnostic test results and reporting abnormal results
- Evaluating the health status of source colonies
- Implementing procedures for eradicating adventitious agents from cell cultures
- Developing and implementing novel diagnostic procedures
- Generating genetically engineered (transgenic and gene targeted) rodent tumor models
- Establishment of primary tumor cell culture
- Establishment of primary tumor cell lines from genetically engineered mouse (GEM), GEM-derived allograft (GDA), or patient derived xenograft (PDX) models
- Surgical techniques for generation of murine orthotopic transplant model cohorts
- Implanting tumor xenografts (including PDX) in mice
- Administering experimental drugs to animals, including targeted and immune-based drugs
- Administering experimental vaccine candidates and challenging animals using ABSL2 pathogens
- Developing protein- and nucleic acid-based assays to identify molecular pathways involved in tumor regulation and to evaluate *in vivo* responses to experimental drug treatments
- Assessing outcomes of drug treatments via histology, pathology, and small animal imaging, including magnetic resonance (MR), computed tomography (CT), single photon emission computed tomography (SPECT), ultrasound, and positron emission tomography (PET) imaging modalities
- Cryopreservation of animal models and specimens, including rodent embryos, sperm, or ovaries; and recovery of animal models from cryopreserved material
- (i) germ-free animal experimentation, (ii) developing and maintaining an axenic (germ-free) breeding colony, (iii) using ABSL2 pathogens in studies within the facility, (iv) testing different methods of rederiving multiple strains to germ-free status, and (v) supporting studies involving "wildling" mouse models with natural microbiota at specific body sites
- Genomics modification utilizing nuclease methodologies (including CRISPR) to generate somatic and germ-line mutations in cells and in whole organisms

2.4.3 Assay Development and Execution

Pharmacodynamics and Pharmacokinetics

Research support for the development of preclinical and clinical pharmacodynamic (PD) markers of target engagement; pharmacokinetic (PK) assays to assess drug absorption, metabolism and clearance; mechanism(s) of action; efficacy; and indicators of patient susceptibility for Food and Drug Administration (FDA)-approved, investigational, or novel preclinical agents using *in vitro* and/or *in vivo* models. Support may include the following types of activities:

- Implementing methodologies for measuring single, multiple or global gene, or protein expression or modification patterns, transfections to augment or suppress gene expression, microscopy (Scanning Electron Microscope (SEM), fluorescence), biochemical modulation, flow sorting and/or analysis of complex mixtures of cultured or patient-derived cells for the purposes of quantifying/isolating cells with different phenotypes, cell cycle analysis.
- Development and validation of sensitive methodologies to determine the impact of drug treatment on target(s) in tumors and selected normal tissues, downstream consequences, biomarkers and toxicity markers, which may include transcriptomic (microarray, QPCR), proteomic (quantitative, subcellular, chemical, and 2D PAGE), metabolomic, or methylomic technologies to derive mechanistic information or targeted molecular imaging (PET, MRI). Subsequent validation may be performed using technologies such as cell-based assays, ELISA, flow cytometry, western blotting, and immunohistochemistry.
- Evaluation of PD changes in various species, starting with the animal tumor model to correlate doses and/or plasma drug levels with impact on target in tumor and normal tissues; determine whether peak plasma levels, AUC or time above a threshold is required for target modulation.
- Development of appropriate surrogate tumor markers in relevant biospecimens, e.g., PBMCs, skin biopsy, saliva, urine, stool, buccal mucosa cells, circulating tumor cells (CTCs), circulating nucleic acids, exosomes.
- Oversight of the translation of PD assays to the clinical setting and assay of samples obtained in clinical trials, as necessary; development of procedures for biopsy of tumor and normal tissues using clinical instruments; formalization of Standard Operating Procedures (s) for biopsy ascertainment, specimen handling and analytical assays; and the transfer of SOPs to a clinical target validation laboratory or other laboratories as directed by the Government.

Clinical Target Validation Laboratory

To develop and validate RUO assays using tumor or surrogate tissues to evaluate molecularly-targeted therapies.

Metabolic Epidemiology

Metabolic epidemiology research seeks to understand the etiology of malignancies and the role of various lifestyle factors and unique exposures. Examples: development and performance of assays to

measure endogenous targeted metabolites, hormones, hormone metabolites and other small molecules in human biofluids.

2.4.3.1 CLIA Laboratories

The laboratory requires maintenance of CLIA certification to allow results to be used for clinical decisions and may also provide assays for preclinical animal models, as requested.

a) Molecular Diagnostics Laboratory

Examples: genomic analyses of patient samples in support of pharmacogenomics research at the NCI. Identification of DNA variants include those related to drug response, metabolism, excretion, and transport, including analysis of gene-drug interactions that inform dosing or administration of medicines to clinical trial patients.

Genomic assay technologies utilized for molecular diagnostic testing currently include: Nanostring LST, PCR and Sanger sequencing, Taqman or ddPCR, Ion Torrent, Illumina sequencing panels and Whole Exome Sequencing (WES), Oncoscan arrays, Pharmacoscan, CLIA Sanger verification of whole exome, CLIA Sanger verification of plasmids, TCR repertoire, Cell Free DNA (CfDNA) evaluated with targeted sequencing, NGS targeted sequencing, whole Exome/whole genome/RNA sequencing, single-cell sequencing, copy number analysis, methylation sequencing, microRNA sequencing, mass spectrometry, and proteogenomics. The laboratory also employs a Laboratory Inventory Management System (LIMS) for tracking patient-derived specimens and derivative samples for potential destruction upon patient request.

b) Clinical Diagnostics Laboratory

The Clinical Diagnostics Laboratory provides analysis of the immunological function of normal donors and patients, including assays for cytotoxic T lymphocytes, ELISPOT, T-cell proliferation, cytokine induction, and other immune cell function conducted on peripheral blood leukocytes, bone marrow cells and cells from other lymphoid organs.

Necessary assays to carry out these functions, optimize the methodology, and validate the assays for clinical use in a CLIA environment, are being continuously imported and/or developed. Examples of clinical diagnostics assays include:

- A circulating cfDNA/nucleic acid/proteomic/exosomic assay to use in pharmacodynamic trial monitoring.
- Multiplex cytokine and/or biomarker analysis in different matrices of serum, plasma, tissue culture medium, urine, saliva, and stool.
- Bioassays to evaluate and confirm cytokine activity.
- Establishment of routine and customized assays of lymphocyte functional activity including proliferation, ELISPOT, and various cytotoxicity assays such as ADCC and NK- and CTL-mediated target cell killing.
- Customized flow cytometry panels for clinical trial monitoring.

Biomarker Reference Standards Laboratory

The Government may request the establishment of a new CLIA-certified biomarker reference laboratory for standardizing laboratory assays and methodologies and for instituting quality control for reagents and technologies. This new laboratory may support collaborative, consortia-directed studies to validate assays including evaluating the accuracy, precision, reproducibility, stability, and performance characteristics (e.g., sensitivity, specificity, positive and negative predictive values) of tests in multi-center settings. The reference laboratory may be asked to conduct studies on a variety of assays to improve their performance characteristics.

2.4.4 Bioengineering

- Fabricating, calibrating, and validating simple microfluidic devices at the micro- and nano-scale for research use.
- 3D-printing of macroscale objects and devices.
- Tissue-printing and generating organs-on-chips.
- Performing 3D-tissue culture (e.g. simple and complex spheroids/organoids), cell culture on synthetic substrates and 3D-matrices, and tissue chips.
- Applying analytical methods for determining biophysical properties of cells and tissues, including rheology and microrheology, fluid dynamics and atomic force microscopy (AFM)-probing of cells and tissues.
- Designing and building electrical micro-systems such as wearable devices.
- Developing and applying synthetic biology technology for/to experimental and developmental therapeutics.

2.4.5 Biospecimen Processing

Best practices for collections and quality specimen management as defined by International Society for Biological and Environmental Repositories (ISBER) and the NCI best practices apply, but the Government reserves the right to determine which guidelines are to be employed. The personnel must be International Air Transportation Association (IATA) certified for shipping biological materials. Collection and transport kits, as well as logistical assistance for field studies, are to be provided provided as needed. The tasks require a comprehensive approach to project planning, providing input on project design, laboratory activities, logistical plans, budgeting, activity timelines, and SOP and SP generation, as requested. Contractor staff, including those at the NCI at Frederick Central Repository is available for investigator and collaborator visits to the physical storage and laboratory site(s) and for consults for specimen activities such as donor selection criteria, questionnaire design, and quality metrics for specimen use and selection. Examples of specimen processing and field support include:

- Biospecimen processing and aliquoting (blood fractionation, buccal cell processing, RNA/DNA extraction, PBMC cryopreservation).
- Normal donor program specimen processing (generating Quality Control (QC) material) of blood products, buccal cells, and urine; and specimen pre-analytical factor research.
- Freezing, flash-freezing of tissue in liquid nitrogen, and lyophilization.
- Normal donor program specimen processing (generating QC material) of blood products, buccal cells, and urine; specimen pre-analytical factor research.
- Separation and viable cryopreservation of cell lines, including routine assessment of viability.
- Cryopreservation of red blood cells to maintain enzymatic activity.
- Generation of primary cultures and established cell lines.
- Large-scale propagation of cell lines.
- Nucleic acid extraction (DNA and RNA).
- Distribution of specimens; shipping domestically and internationally.
- Support to field centers in collection procedures, equipment, materials kit development and sample transportation.

2.4.6 Cell Biology

- Cell motility and migration assays--Evaluation of cellular metastatic potential.
- Cell signaling assays--Interrogation of cellular pathways that underlie disease.
- Cell viability and proliferation assays--Assessing activities of candidate drug compounds.
- Exosome measurements--Monitoring pharmacodynamics of tumor drug response.
- Flow cytometry and cell sorting--Differentiation of hematopoietic stem cells and sorting of virus-infected cells.
- Mass cytometry/imaging mass cytometry--Simultaneous quantification of multiple cellular proteins.
- Single cell analysis--Assessment of cellular phenotypes in heterogeneous samples, either in dissociated samples or within the spatial context of the tissue and single cell immune profiling.

2.4.7 cGMP Production of Biopharmaceuticals and Vaccine Clinical Materials

Flexibility is essential as candidate formats include various vaccine platforms (e.g., DNA plasmids, viral vectors, self-assembling nanoparticles, virus-like particles) and recombinant antibodies (monoclonal, bispecific, and tri-specific). All steps to streamline workflow, evaluate GMP requirements for engineering runs and scale-up, and streamline documentation requirements in manufacturing must be documented.

2.4.7.1 General Requirements

- Support for all aspects of cGMP product development and manufacturing, including warehousing, procurement, shipping, Quality Assurance, Quality Control, maintenance, and preparation of regulatory documents for pre-Investigational New Drug (IND), IND and related submissions to support both domestic and international clinical trials.
- Establishment of Quality Systems to support manufacturing of vaccines, biopharmaceuticals and other biotechnology products including work performed by other federal contractors.
- Management of robust scaleup and bulk drug product manufacturing facilities and capabilities along with corollary infrastructure to generate filled vial Drug Product, and store/stockpile materials as requested by the Government.
- Facilitation for the transfer of technology into and out of the facilities (e.g. manufacturing processes and qualified / validated analytical methods) upon request.
- Responsibility for long term stability of clinical agents (manufactures onsite or received under cooperative agreements from other collaborators) under FDA and ICH guidelines.
- Operational support and maintenance of the facilities.
- Establishment of a Quality Agreement with the Government covering raw materials management and control, drug substance and drug product manufacturing, deviation reporting, release testing, stability testing, storage, shipping, and other associated items that would be covered under a sponsors Manufacturer's responsibilities.
- Participation by the Government in Contractor's Material Review Boards and Out of Specification (OOS) investigations, upon request.

2.4.7.2 Product Development and Manufacturing

- Project development and feasibility assessment.
- Process development for scale up manufacturing, including development of purification methods.
- Pilot scale and cGMP manufacturing of biotechnology-based products using a variety of established platforms (e.g. microbial fermentation, mammalian bioreactors) and establishment of new platforms as needed.
- Development, establishment, and cGMP manufacturing of products used for altering immune cells to create cell-based immunotherapy products (e.g. lentivirus vectors, gamma retrovirus vectors, CRISPR-based gene editing reagents).
- cGMP manufacturing of immune cell products using established and emerging platforms including Chimeric Antigen Receptor T cells, Tumor Infiltrating Lymphocytes, autologous and allogeneic cells modified by CRISPR-based gene editing.
- Shipping of clinical trial material, including receipt of patient-specific starting materials from clinical trial sites and shipment of patient-specific therapeutic products to clinical sites.

- Quality assurance (QA) services including validation, auditing, cGMP documentation.
- Regulatory Affairs support including preparation of manufacturing reports, Chemistry Manufacturing and Controls and other relevant sections for IND submissions as directed by the Government, and interaction with regulatory agencies).
- Quality Control and analytical assay development to support process analytics and ensure product quality throughout the project lifecycle; analytical assay development and methods to support characterization of allogenic and patient-specific and precision-medicine-based therapeutic products (e.g., autologous immune cell therapies and peptide vaccines).
- Stable cell line development (mammalian, fungal or other), including generation of master cell banks and/or working cell banks, pDNA generation, or other materials necessary for upstream production.
- Cell culture development (fed-batch and potential perfusion processes).
- Downstream development to include viral clearance studies.
- Formulation and Drug Product fill-finish.
- Analytical testing (in-process, characterization, and release testing).
- Regulatory support to enable successful Pre-IND, IND, and other regulatory filings.

2.4.8 Chemistry

- Synthesis of radiopharmaceutical compounds for imaging, treatment, monitoring efficacy and diagnosis of malignancies in animal model systems or humans.
- Synthesis of immunotoxins.
- Synthesis of reagents and probes to interrogate biological mechanisms from the molecular to organismal scales, e.g., chemical genomic studies to assess the activity of chemical compounds on gene expression.
- Purification of chemical compounds.
- Analysis of chemical compounds utilizing, for example, spectroscopic and chromatographic methods.
- Process chemistry and scale-up synthesis of candidate therapeutics for both preclinical and clinical research.
- cGMP manufacturing in support of IND-enabling toxicology studies and clinical trials.
- Formulation of compounds for administration to animals and humans.
- Scale-up production and purification of pure bioactive natural products.
- Production of crude natural product extracts from source organisms and pre-fractionated natural product samples from natural product extracts, expectation of ~750 macro-organism extracts and ~2,000 microorganism extracts per year.

- Maintenance and operation of a microbial production facility for the culture of natural microbial source organisms including fungi and bacteria, expectation of the production of 2,000-4000 L microbial cultures per year.
- Data management services:
    - A chemical registration system to register small molecules, peptides, and natural products and to support sample logistics (lot/inventory information).
    - Chemical structures and chemoinformatics to include calculated and measured physical properties, ADME/PK/toxicity data.
    - Bioanalytical analysis of molecule spectra and peak information to define purity, composition, and identity.
    - Compound and library enumeration to include synthetic routes, and tracking of methods, reagents, and materials.

2.4.9 Clinical Research Support

- Management framework that includes oversight and mentoring of good clinical practices.
- Broad range of technical support, administrative management services and program-dedicated research support programs, based domestically and internationally (typically government-to-government engagements), as requested.
- Mounting an initial effective rapid response to urgent and compelling public health concerns; then, post-event, establishing the capacity to sustain these programs and ensure readiness for future event response.
- Provide physicians, medical affairs scientists, expert nursing care, pharmacy and laboratory technicians, clinical project managers, regulatory and clinical trials staff, biostatisticians, and consultants/subject matter experts (including physicists, Artificial Intelligence specialists, medical technologists, and chemists to:
    - Serve as a liaison with clinical, regulatory and laboratory personnel on assigned protocols.
    - Serve as associate investigators.
    - Document patient care per protocol requirements.
    - Participate in clinical rounds.
    - Order diagnostic and related procedures, such as imaging per protocol.
    - Assist in skilled procedures performed by medical affairs/physicians (e.g., phlebotomy and IV catheter placements).
    - Coordinate patient schedules to meet the requirements of protocol interventions and data collections.
    - Collect clinical samples per protocol requirements.

- Provide overall study coordination.
- Provide protocol lifetime support (e.g., clinical research training and education).
- Manage clinical trial research portfolios.
- Select clinical trial sites.
- Provide data warehousing, management, and analysis, including biostatistics.
- Provide monitoring and quality assurance.
- Provide medical and technical writing for clinical trials (e.g., protocol development, regulatory communications, and publications).
- Coordinate courier services, air transport, and track sample shipments per approved protocol and other regulatory guidance. Courier sites include NCI Campus at Frederick, the Advanced Technology Research Facility (ATRF), the NIH Bethesda campus, and other locations within the Washington, D.C. metro area. Samples are transported in accordance with governing policies and regulations.
- Provide general programmatic support to the clinical research efforts (e.g., subcontracting, logistics, and procurement).
- Manage the NCI's ClinicalTrials.gov account, including registering all NCI-sponsored trials in NCI's ClinicalTrials.gov account and managing amendments and updates to NCI-sponsored trials.

2.4.10 Drug Discovery and Development

- Development and execution of cancer target validation assays and mechanism-of-action assays.
- Recommending and obtaining appropriate compounds and chemical libraries (including natural products) for screening and biochemical studies.
- Design and execution of cellular and biochemical screening assays, including high-throughput and fragment-based screening, to: identify active compounds; determine binding affinity of candidate compounds against cancer targets; and to screen candidate compounds and natural product samples against cancer cell lines and patient derived cells in 2D and 3D.
- Protein production and purification for high-throughput screening and biochemical studies.
- Structure-based drug design to identify lead compounds as candidate therapeutics against various agents. These services include using state-of-the-art methodologies in bioinformatics, chemoinformatics, virtual screening, molecular modeling, and structure determination (x-ray diffraction, NMR, and cryo-electron microscopy).
- *in vitro*, *in vivo*, and computational studies of compound absorption, distribution, metabolism, and excretion to assess the disposition of candidate drug compounds in patients.
- Chemical synthesis of candidate small molecule therapeutic compounds, including hit-to-lead medicinal chemistry based on data from *in vitro* and *in vivo* studies.

- *in vitro* compound profiling assays--enzyme or receptor panels, P450 inhibition, cellular panels, hERG.
- Pharmacokinetic analysis of biological samples obtained from animal models and patients in clinical trials for the purpose of monitoring the plasma concentrations of drugs and their metabolites over time.
- Toxicity testing of candidate drug compounds in various cell-based, tissue, organ, and animal systems. *In vitro* systems include fresh and/or cryopreserved human liver and lung slices and human hepatocytes.
- Re-supply of purified natural products.
- Formulation studies to support *in vivo* administration of candidate therapeutic compounds.
- IND-enabling toxicology studies in animals.
- *In vivo* studies of compound efficacy in gene engineered and patient-derived xenograft mouse model systems.
- Scale-up synthesis to support *in vivo* and clinical studies.
- Data management system to capture:
    - Single concentration and dose response results for HTS cell-based and biochemical screening assays.
    - *in vitro* and *in vivo* results from pharmacologic, ADME, PK, tolerability, and toxicological studies.
    - *in vitro* and *in vivo* laboratory protocols, SOPs, and other study related methods.
    - Description of quality methods used to define assay and/or study acceptance criteria.

2.4.11 Imaging

Includes visualizing biological structures from the subcellular to the organismal scalesto gain insights into the biology of cancer and viral infection, allowing investigators to interrogate disease mechanisms and monitor disease progression and response to treatment.

- Fluorescence microscopy
- Optical coherence tomography
- High-resolution, confocal imaging
- Photoactivation Localization Microscopy (PALM)
- Stochastic Optical Reconstruction Microscopy (STORM)
- Fluorescence Correlation Spectroscopy
- Fluorescence Lifetime Imaging Microscopy (FLIM)

- Two-photon microscopy
- Light sheet microscopy
- Dynamic light scattering
- Transmission and scanning electron microscopy (TEM/SEM)
- Cryo-Electron Microscopy (Cryo-EM)
- Focused ion beam SEM
- Atomic force microscopy
- Hyperpolarized magnetic resonance imaging
- Raman microscopy
- Animal imaging including small animals to characterize animal models, which are then used to perform efficacy studies.
- Characterization of new molecular imaging targets for early detection and effectiveness of therapy.
- Characterization of patient derived xenograft mouse models, and integration of imaging into drug development.
- Optical, including fluorescence, bioluminescence, and intravital imaging--for imaging tumors and time-dependent processes:
    - Ultrasound--for anatomical imaging, image-guided injections, cardiac function, and blood flow.
    - Mass spectrometry--for mapping the spatial distribution of proteins and cellular components
    - Magnetic resonance (MR), including hyperpolarized MR--for anatomical, functional, and metabolic imaging.
    - Photoacoustic--for anatomical imaging and measuring tumor progression.
    - Computed tomography--for anatomical imaging; and measuring tumor progression.
    - Single photon emission computed tomography (SPECT)--for measuring blood flow and tumor progression.
    - Positron emission tomography (PET)--for measuring tumor metabolism, receptor density and progression.
    - Hyperpolarized magnetic resonance imaging.
- Development of molecular imaging probes that can be used for early cancer detection and therapy in addition to monitoring real-time tumor growth and tumor responses to therapeutic interventions.

- Management of governmental imaging informatics as required including the NCI's imaging informatics for precision medicine (IIPM) effort, and the National Biomedical Imaging Archive (NBIA), which provides the core platform for The Cancer Imaging Archive (TCIA).
    - TCIA hosts a large archive of de-identified clinical cancer medical images, associated clinical data and related animal model data that are accessible for public download, and is providing those images to the CRDC Imaging Data Commons. Work includes development and updates to the NBIA platform in support of TCIA functionalities.
    - Support for TCIA Data Management includes management of imaging data in a variety of formats and venues, including robust de-identification of Personal Health Information from clinical images while retaining maximum supporting data, providing DOI references for all collections, integrating the TCIA with other data repositories, and allowing full public access repositories.

2.4.12 Information Technology

The work includes to research, evaluate, recommend, develop, implement, and manage information technology systems and services in support of Government research initiatives, projects, and programs and in support of the FFRDC business operations. The FFRDC utilizes Government provided IT products, processes, services, and support when applicable such as network, UC/AV, hosting, IT facilities, servers, storage, general engineering (platform, network), and service automation. The Contractor is expected to work in close coordination with Government IT management staff and to provide simple, effective solutions.

- ITSM/ITIL IT process management for cybersecurity, knowledge management, configuration management, continuous service improvement, IT asset management and other IT functions in a manner consistent with NCI and NIH policies.
- Consultation and solution development for scientific IT requirements and FFRDC business IT requirements.
- Web and software services including web hosting and maintenance, website design and content management; application and/or software configuration, integration, development, and maintenance; web/enterprise search and authentication and authorization integration.
- Cloud solutions and support, leveraging existing, authorized NCI cloud resources.
- Cybersecurity in the form of DevSecOps, Authority to Operate (ATO) assessment and documentation, vulnerability management, incident response, and Continuity Of Operations Planning (COOP) associated with FFRDC deployed systems.
- Explore and evaluate emerging IT technologies and their impact on scientific workflows and HPC environments.
- Assist with proof of concept/future HPC technology and applications.
- Support special and custom scientific workflows with fast storage and preprocessing capabilities.

- Support scientific IT such as:
    - Deploy, adapt, and maintain application software and configure computer interfaces in support of Scientific devices, advanced technology equipment, and associated workflows.
    - Assist with software application configuration and data workflows associated with complex, state of the art and legacy high-output, data generating equipment.
    - Review and advise on cloud and IT infrastructure optimization to support scientific equipment.
    - Support for specialized scientific database development and administration.
- Provisioning of on-site, custom, remote-access and/or classroom training to Contractor and Federal staff for specialty software, web programs, managed systems, in-house applications and advanced technologies and methods as needed.

2.4.13 Molecular Biology

2.4.13.1 Gene Sequencing and Genotyping

Sequencing activities are being performed on Next-Generation Sequencing platforms such as Illumina NovaSeq 6000, Ion Torrent S5™, Illumina MiSeq®, Illumina NextSeq® 2000 Pacific Biosciences Sequel, and Oxford Nanopore GridION.

- Whole Genome Sequencing--de novo assembly, haplotype resolution, structural variant detection and DNA epigenetic modification detection.
- Whole Exome Sequencing--large-scale structural variants detection across the entire exome.
- RNA Sequencing--full-length transcript sequencing for whole-transcriptome or gene-specific targets.
- Targeted Sequencing--long amplicon sequencing, full-length viral sequencing, full-length vector sequencing, targeted enrichment, and multiplexing strategies.
- Human Leukocyte Antigen (HLA) Typing--amplification of full gene for HLA class I; other HLA gene targets also available.
- Genotyping--utilizing sequencing or array technologies to identify Single Nucleotide Polymorphisms (SNPs) and other types of genetic variation (microsatellites, insertion/deletion mutations, methylation, etc.).
- Single-Cell Sequencing--single-cell DNA and RNA sequencing, single-cell immune profiling, single-cell assay for Transposase-Accessible Chromatin (ATAC)-seq and single-cell Copy Number Variation (CNV) analysis.
- Development of reagents and tools to utilize CRISPR and other nucleases to generate modifications in primary cells, cell lines and animal models.
- Analytical and preparative electrophoresis (TapeStation Systems 4150 and 4200, Pippin HT).

- Automated liquid handling (Agilent Bravo, Beckman BioMek FX, Mantis).
- Copy number variation analysis (Oncoscan arrays, Nanostring).
- Digital gene expression (NanoString nCounter System).
- Digital droplet PCR (BioRad QX200 ddPCR).
- Pharmacoscan
- DNA variant analysis and genomic optical mapping (Bionano Genomics).
- DNA-protein binding analysis, epigenomics - chromatin immunoprecipitation + sequencing (ChIP seq; Illumina).
- Gene expression and miRNA expression (10X Genomics, Affymetrix microarrays, Nanostring, HTG EdgeSeq platforms).
- qPCR (Applied Biosystems)
- Telomere length measurements using qPCR or Terminal Restriction Fragment analysis.
- Sanger sequencing (ABI 3500xL and 3730 xL DNA sequencers).
- SNP detection and DNA methylation analysis (Qiagen Pyromark; Illumina microarrays).
- Spatial Gene Expression Analysis, Spatial Transcriptomics--mapping spatial locations of RNA and proteins (using barcoded antibodies) in cells and tissues (10X Genomics Visium and Nanostring GeoMx platforms).
- *In situ* Sequencing such as ReadCoor RC2 and Cartana.

2.4.13.2 Protein Expression and Purification

Custom DNA cloning

- Subcloning
- Plasmid DNA preparation
- Site-directed mutagenesis
- Custom vector construction
- Gene optimization
- shRNA/miRNA expression and reporter constructs

Eukaryotic Expression:

- Expression of recombinant proteins using systems such as the baculovirus expression vector system (BEVS).
- Monoclonal antibody production.
- Recombinant protein expression in mammalian cells.

Expression in Lower Organisms:

- Transformations of bacteria and yeast strains.
- Colony screening for expression optimization in yeast.
- Expression screening in bacteria to maximize recombinant protein quantity and quality.
- Batch, batch-fed, or continuous fermentation in multiple yeasts and bacteria strains.
- TFF Concentration, buffer exchange and ultrafiltration.
- Cell lysate preparation and clarification.
- Analysis--SDS-PAGE, Western Blots, Dot Blots, etc.

Protein Purification:

- Micro-scale purification screening and optimization.
- Scale-up from micrograms to grams.
- Endotoxin testing and removal.
- Customized protein purification.

Mammalian Viruses

Production of custom recombinant lentivirus to study transgene or shRNA delivery for gene knockdowns *in vitro* and *in vivo*.

2.4.13.3 Other Molecular Biology Activities

An example of a program that utilizes multiple molecular biology capabilities involves identifying the heritable determinants of various forms of cancer. In this work, the contributions of germline and somatic genetic variations to cancer susceptibility and outcomes are investigated using high-throughput genome-wide association studies (GWAS) and targeted regional approaches. Support may include DNA extraction, whole genome sequencing, epigenetics, bioinformatics, and data exchange with genomic data repositories.

2.4.14 Nanotechnology

The Government primarily requires nanotechnology characterization to accelerate the translation of promising nanotechnology-based interventions developed by researchers from academia, Government, and industry into clinical trials.

- Physicochemical characterization such as measurement of nanoparticle size, topology, molecular weight, aggregation state, purity, chemical composition, surface chemistry, and other physical and chemical properties.

- *In vitro* protocols developed specifically for the evaluation of nanoparticle sterility, blood contact properties, toxicity, interaction with the immune system and other related *in vitro* biological properties.
- *In vivo* experiments tailored to evaluate the toxicity, immunotoxicity, pharmacokinetics, disposition and efficacy of nanoparticles intended as cancer therapeutics, imaging agents, or *in vivo* diagnostics.
- Examining common translation-limiting toxicities and Structure-Activity Relationship (SAR) studies.
- Nanotechnology-based drug formulation services to improve drug solubility and pharmacokinetic properties, reduce toxicity, and enhance their therapeutic window.
- Evaluation of nanotechnology-based diagnostics and therapeutics for use in non- cancer applications.
- Development/Support of nanotechnology informatics resources, such as the cancer Nanotechnology Laboratory portal (caNanoLab). This is a web-based portal designed to facilitate data sharing in the research community to expedite and validate the use of nanomaterials in biomedicine. The caNanoLab provides support for the annotation of nanomaterials with characterizations resulting from physico-chemical and *in vitro* nanomaterial assays, and the sharing of these characterizations and associated nanotechnology protocols in a secure fashion.
    - Continued development support for hosting, upgrades, and bug fixes.
    - Development of the API for improving the ease of access and data loading, and enabling data mining for computational modeling research.
    - Working with federal leads to prioritize feature requests.
    - Curating nanomaterial data and coordinating with federal leads in the selection of data sources.

2.4.15 Omics

Mass spectrometry instruments available at FNLCR include: Orbitrap Fusion Tribrid, Q Exactive, Q Exactive HF, LTQ-Velos Pro and TSQ-Triple Quadrupole mass spectrometers. Examples of a complex, matrixed omics projects include:

- NCI scientists investigate the contributions of germline and somatic genetic variations to cancer susceptibility and outcomes using genome-wide association studies (GWAS) and targeted regional approaches to identify the heritable determinants of various forms of cancer. The GWAS approach involves scanning the genomes from many different people/populations and looking for genetic markers that can be used to predict the presence of a disease. The goal is to understand how genes contribute to the disease and to use that understanding to help develop better prevention and treatment strategies.

- State-of-the-art assays of human and viral genetic variation utilizing the newest technologies and methods that include DNA extraction and sample handling; design, execution and analysis for genome wide association studies; validation and replication utilizing targeted genotyping techniques; epigenetic studies utilizing array-based methylation analysis; telomere length assessment; evaluation of copy number variation; whole exome sequencing and analysis for familial and population germline studies; and regional, targeted and whole genome sequencing (particularly long read technologies and applications).
- Analysis and bioinformatics data management services, including uploading of molecular characterization data and metadata to the NCI Genomics Data Commons.

- Proteomics research program at the FNLCR is the Clinical Proteomic Tumor Analysis Consortium (CPTAC). CPTAC generates, integrates, and analyzes multi-omics datasets on human cancer specimens to improve current understanding of tumor biology at the molecular level.
  - State-of-the-art omics technologies, harmonized workflows, analysis tools and pipelines to better understand the molecular processes of tumorigenesis and provide more accurate predictors of therapeutic responses.

2.4.15.1 Antibody and Protein Characterization

- Generating well characterized renewable fit-for-purpose affinity reagents.
- Exploring new methods for antibody production and characterization.
- Implementing phase display methodology when appropriate.
- Developing proteomic clinical assays for CPTAC within a CLIA-approved laboratory environment.
- Performing antibody characterization assays that include Western blot, immunoprecipitation mass spectrometry (IPMS), ELISA, surface plasmon resonance (SPR) affinity measurements, nucleic acid programmable protein array (NAPPA), immunofluorescence and immunohistochemistry.
- Operation of experimental technologies including Whole Exome Sequencing (Protein Simple) for quantitative western blot analysis, Octet (Forte Bio) for kinetic analysis, and Triple Quad (Shimadzu 8050 and AB Sciex 4500) for mass spectrometry studies and mass spectrometry characterization of proteins and modified proteins.
- Identification and characterization of protein and other macromolecular complexes using affinity purification, quantitative proteomics (e.g., SILAC, label free quantitation, dimethyl labeling at the peptide level, iTRAQ, and Tandem Mass Tagging (TMT)), followed by mass spectrometry analysis.
- Identification of post-translational modifications (PTMs) with special emphasis on phosphoproteomics analysis.

- Investigation of macromolecular interactions using a combination of pull-down methods to identify novel DNA-protein and RNA-protein interactions, isothermal titration calorimetry, and to study binding kinetics and affinities between two macromolecules.
- Protein characterization program (within the antibody operation) for comprehensive mass spectrometry-based proteomic characterization (global- and phospho-proteomes) and targeted, fit-for-purpose assays (direct MRM or iMRM).
    - To monitor genomic and proteomic readouts from clinical trials and to support preclinical research for both intramural and extramural scientists.
    - To improve protein identification and PTMs such as phosphorylation analysis in complex mixtures of proteins from biological and clinical specimens (tissues and fluids).

2.4.15.2 Proteomic Data Management

Support for management of proteomic data in a variety of formats and venues including:

- The Proteomic Data Commons -- the node of the NCI Cancer Research Data Commons (CRDC) that collects, harmonizes, and hosts open access proteomic data across a variety of sample types.
- Data Coordinating Center -- serves as a hub of NCI proteomics data and facilitates the transfer of data between investigators and disseminates to the wider research community.
- Assay Portal -- a centralized public repository of fit-for-purpose quantitative mass spectrometry-based proteomic targeted assays.
- Antibody Portal -- a community resource that provides access to a large number of standardized renewable affinity reagents (to cancer-associated targets) and accompanying characterization data.

2.4.16 Pathology

Pathology support requires experts in animal and human study design, diagnostics, phenotyping of genetically engineered mice, immunopathology, anatomic pathology, electron microscopy, toxicological pathology, and specimen classification/selection for tissue microarray construction or laser micro dissection or other areas of as needed. Pathology services include support for rodent necropsy, non-human hematology and clinical chemistry, gross examination and dissection of anatomic pathology specimens, fixed and frozen tissue embedding, microtomy, histological staining, pathology interpretation and reporting; and molecular pathology, including enzyme stain immunohistochemistry (IHC) and RNAscope® *in situ* hybridization from frozen/fixed animal and human tissues, paraffin and OCT tissue blocks, and slides; and DNA, RNA, CTCs and cf-DNA and protein yield and quality assessment.

- Collaborative activities for tissue-based technology development and validation across labs and with investigators to support the best scientific practice and innovations.

- IHC support includes: double and multiplex bright field IHC staining and evaluation; development and assessment of humanized, chimeric, or murine/other species monoclonal antibodies; and ensuring reproducibility of immunohistochemical techniques.
- Pharmacodynamic (PD) assessment of molecularly targeted anti-cancer agents, and genomic assessment for personalized medicine; includes comprehensive assessment of pathologic changes in preclinical and clinical studies for determining safety, efficacy and mechanism of action for novel therapeutic agents.
- Digital imaging studies including gross photography and either bright-field whole slide image scanning (WSI), or fluorescent digital whole-slide imaging. Digital photography, including digital microscopic immunofluorescence assay (IFA) Image segmentation and quantitative multiplex analysis.
- Telepathology, advanced digital image analysis, and quantification including deep learning-based algorithms (artificial intelligence) through multiple software platform options.
- Molecular and digital pathology that integrates human histological and molecular tissue profiling with analyses of environmental and genetic risk factors examine the impact of genetic variation on the biology of gene expression and protein function at the tissue level and to gain critical insights on cancer risk and progression.
- High capacity of processing tissue samples for histopathology, digital pathology, and molecular/genomic analyses for epidemiologic studies.
- Electron Microscopy (EM) support for pathology; including SEM and TEM for ultrastructural pathology as well as viral particle identification, etc.
- Expert guidance in protocol design regarding the most appropriate fixation, collection, preparation, and evaluation of biologic samples.
- Other activities associated with animal studies, such as obtaining biospecimens, endpoint assays, histopathology, data documentation, reports, etc.

2.4.17 Repositories

Items stored in the repositories include clinical and non-clinical biological specimens, and reagents including human and animal specimens, frozen tissue, whole blood, serum, plasma, peripheral blood cells, urine, stool, formalin-fixed paraffin-embedded (FFPE) blocks, slides, other bodily fluids, and environmental samples. The repositories provide ambient (room temp. and under gas/vacuum) and low/ultralow temperature (mechanical (4^{o}C, -20^{o}C, -80^{o}C), and liquid nitrogen (-80^{o}C, -150^{o}C, -196^{o}C)) storage capacity Storage units include mechanical units, liquid nitrogen units (LN2s) and a walk-in -80^{o}C unit with a -20^{o}C internal hallway (14 door freezer, Bahnson Environmental Specialties).

The repositories operate under Good Laboratory Practices (GLP) guidelines, Good Manufacturing Practices (cGMP) guidelines, Best Practices for repository management guidelines as defined by the ISBER and NCI, and IATA certification, where appropriate. The Government reserves the right to determine which guidelines are to be employed.

- Operation of repositories at the NCI Frederick campus and offsite.
- Curating specimens.
- Technical personnel for managing the repository, including receipt, inventory, storage, retrieval, distribution of specimens/samples, and monitoring of storage and transport units.
- Manual and automated processes for the receipt, inventory, storage, retrieval, and distribution of standard (1- and 2-D barcoded) and automation-formatted (barcoded on bottom of tube).
- Select packaging and training of IATA transport processes, domestically and internationally.
- Preparation of inventory, monthly storage cost reports and other reports, as requested.
- Maintenance of required storage units and facilities, as well as a documented and comprehensive Disaster Plan and Emergency Preparedness SOPs, to include pandemics.
- Maintenance of QC and QA programs, SOPs for routine and emergency operations, and QA reporting.
- Provision of adequate safeguards and emergency capabilities for physical repository and IT systems.
- Maintenance and updates of specimen input, tracking storage and retrieval IT systems (Biological Specimen Inventory system), which feed into the Contractor financial system(s) to support monthly vial and study level charging for activity and storage to Government sample custodians.
- Standard operating procedures for daily, weekly, monthly and yearly preventive maintenance (e.g., temperature monitoring, gasket cleaning, professional maintenance, calibration) of storage units per manufacturer's recommendations.
- Adequate records for all maintenance procedures (e.g., work done, tests performed, results, etc.).
- Procedures for repairing storage equipment and validating all new or repaired equipment, including appropriate record keeping.
- Oversight of repository operations by a repository quality board (or equivalent oversight committee) comprised of both Government stakeholders and Contractor personnel.

2.4.18 Structural Biology

- Rapid, no-cost access on a first-come first-served basis to qualified users with pre-screened grids ready for high-resolution cryo-EM data collection.
- All aspects of data collection, data analysis, communication with extramural users, scheduling, data transfer.
- Maintenance of Titan Krios, JEOL CryoARM200 microscopes, and Thermo Fisher Glacios microscopes.

- Efficient use of microscopes to keep wait times of facility users to a minimum.
- Broad accessibility to the facility to less experienced users by providing informative quality-controlled results, assistance with data analysis and support to potential users in sample preparation.
- Program to explore areas for cryo-EM technology development (this program currently utilizes Thermo Fisher Glacios and JEOL CryoARM200 microscopes):
    - Preparing specimen lamellae for TEM using Focused Ion Beams (FIB).
    - Streamlining purification protocols optimized for cryo-EM.
    - Exploring improved methods for specimen preparation.
    - Establishing cryo-EM workflows that can be used routinely for high-quality data collections.

2.4.19 Virology

- Investigating basic immunological, pathological, cellular, molecular, and biochemical aspects of AIDS-associated viral disease, and development of approaches for therapy and vaccine development, including the use of animal models.
- Producing and purifying viruses.
- Purifying and characterizing viral products.
- Producing and manipulating cultured cells, and isolating products from cultured cells.
- Performing assays for biological products.
- Developing and performing biochemical, biological, and immunological tests.
- Developing and improving assay technologies.
- Investigating the role of viruses in cancer.
- Analyzing phylogenetic and molecular aspects of cancer-related pathogens.
- Collection and management of clinical and biospecimen data corresponding to the samples, including clinical outcomes data.
- Support the management, curation and sharing of data from NCI/NIH-sponsored studies on emerging pathogens and provide program coordination support for NCI/NIH research programs in this domain.
- Fundamental studies on the nature of HIV drug resistance *in vivo*:
    - Characterizing the replicating population size and genetics of HIV in infected individuals before, during and after antiretroviral therapy.
    - Defining the genetic mechanisms, kinetics of emergence and decay, and clinical consequences of HIV drug resistance.

- Identifying the tissue and cellular sources of persistent viremia despite suppressive antiretroviral therapy.
- Testing novel therapeutics to reduce persistent viremia and deplete HIV reservoirs.

- Support to AIDS Clinical Trials:
  - Analysis of the immune function of patients infected with HIV prior to, during and following immunotherapy or other therapies.
  - Providing immune function testing support for experimental HIV vaccine trials. This includes assays to assess immune cellular function, performed on peripheral blood leukocytes, bone marrow cells or cells from other lymphoid organs; and comprehensive flow cytometry/hematology to define hematologic parameters in HIV patients.
- Laboratory to standardize, validate, and employ assays and reagents for new Human Papillomavirus (HPV) vaccine trials:
  - Basic and translational research and research support including technical support, laboratory management, administrative support and project management.
  - Research in the areas of serological standards, reagents and assay development.
  - Laboratory standards such as Good Clinical Laboratory Practices (GCLP).
  - Generation and testing of secondary standards, generation of virus-like particles (VLPs), and development of ELISA and other multiplex assays.
  - Test and provide data analysis of HPV vaccine trials samples.
  - Train other serology laboratories in monitoring antibody responses.
  - Testing samples collected from participants, in ongoing/planned clinical trials, using validated HPV antibody assays.
  - Assist with the identification and collection of serum samples from healthy donors, who have been inoculated with HPV vaccines, including the developmentof collection protocols.
  - HPV genotyping and gene sequencing to study the natural history of HPV infection and HPV vaccine efficacy.
- Support NIH research on serological testing of patients infected with SARS-CoV-2 and/or other emerging viral pathogens with activities that include the following:
  - Implementing and qualifying ELISA assays for IgM, IgG, and IgA
  - Rapidly identifying, procuring, and characterizing serum/plasma specimens from infected patients and necessary controls
  - Establishing panels and producing novel reagents for qualification/validation, of serological and other relevant immune assays, and distribution to the research community
  - Developing qualified assay standards for the serology community
- Operate a laboratory to:

- Generate and produce adenoviral and lentiviral vectors for expression of genes and shRNAs, in both animal and cell culture model systems.
- Design specialized viral vectors and constructions.
- Prepare and purify viral plasmids.
- Isolate nucleic acids in bulk.
- Develop and perform molecular and serological testing for the detection of cancer-related viruses.

2.4.20 Scientific Research and Development Program Management Support

- R&D program management for requested activities with a central coordination role in the support of NCI international and domestic studies, programs, and projects.
- Quantitative and qualitative data analysis and program evaluation of prime and subcontractor projects to include reviews of international and domestic studies, programs, projects, and data. Evaluation includes the measure of outputs, impacts and progress in specific programs and interventions, and tracking of research investments and their impact.
- Scientific technical writing, literature review, presentation and documentation support, and scientific publications, as appropriate.
- Assistance with scientific, technical, and administrative matters required to carry out the development of clinical research projects, training programs, and advanced technologies and methodologies regarding cancer education, detection, screening, cancer control and treatment in different regions of the world (high, middle, and low income regions), per Government direction.
- Logistical, administrative, and technical support to Government scientific meetings, conferences, investigator meetings, protocol meetings, training sessions and workshops, both domestic and international, including arrangement of domestic and international travel for non-Government experts.

2.5 FFRDC Work-In-Residence Program

n/a

2.6 Intellectual Property, Partnering, and Technology Transfer

n/a

2.7 Laboratory-Directed Exploratory Research

n/a

2.8 FFRDC Enterprise Planning

The goal of these initiatives is to increase efficiency and cost-effectiveness from a mission, science, and business perspective.

- Establish performance objectives with performance measures and targets for strategic efforts, to result in overall enterprise-wide performance improvement for the FFRDC.
- Evaluate, plan, develop and implement strategic enterprise-wide initiatives that optimize the scientific mission, Facilities Operations, Management, Maintenance and Engineering, Business Operation and Other Support across the FFRDC.
- Facilitation of scientific communication and the sharing of scientific ideas and technologies across the entire contract.
- Alignment with the NCI's scientific needs and leadership in the efforts to increase transparency and accountability across scientific practices.
- A collaborative relationship that can meet special long-term research or development needs that cannot be met as effectively by existing in-house or Contractor resources.
- Strong scientific expertise, and extensive experience in directing large scientific and industry operations.
- A management acumen that enables quick adaptation to new environments and better understanding of the complex scientific and administrative issues presented in FFRDC operations.
- Proactive implementation of a variety of strategic changes to help improve the overall FFRDC performance.
- Improved partnering collaborations with the research community and other Government agencies to integrate more effectively and efficiently.
- Improve cost estimation practices for all Contractor work.
- Streamline business operations and reduced operational costs enterprise-wide.
- Implementation of best practices enterprise-wide for efficient, safe, research operations.
- Improve risk-management practices, including risk awareness and mission supportive, cost-efficient, safety basis processes.
- Establishment and implementation of consistent work practices and operational processes.
- Improve pricing, products, and timeliness of delivery.
- Reduce administrative costs and lead times for both the Contractor and the Government.
- Increase awards to small business entities.

2.9 Facilities Operations and Management

The areas entail facility planning, and operations and management services to ensure all aspects of FFRDC research projects are conducted to support the FNLCR scientific mission. Research facilities present a unique challenge to operators due to the complexity of systems, health and safety requirements, long-term flexibility and adaptability needs, energy use, and environmental impacts.

- Maintenance all Government provided Furniture, Fixtures, and Equipment (FF&E); this includes scientific equipment, generators, chillers, and dedicated MEP systems such as air handling units (AHUs), dehumidification systems, heating, ventilation, and air conditioning (HVAC), etc.
- Continuity and reliability of operations, fulfillment of program requirements, and protection of life and property from potential hazards.
- QA/QC program
- Operations & Maintenance (O&M) service requests, along with providing twenty-four (24) hour emergency services seven (7) days a week:
    - Start up, maintenance, repair and operation of all buildings and associated utility systems.
    - Modification or rearrangement of scientific and/or administrative space(s) to meet the scientific needs.
    - Modification, repair, calibration, and installation of special research equipment
    - Custodial service to include Green Seal Standard for Commmercial and Institutional Cleaning Services GS-42, and emergency custodial services
    - Grounds keeping (landscaping & snow removal)
    - Day-to-day activities necessary for ensuring the building/built structure, and related systems and equipment.
    - Maintenance of roads and surfaces on NCI at Frederick property in coordination with United States Army Garrison (USAG)

<u>Design Architect of Record</u>

The Architect of Record (AOR) are in effect during the entire life cycle of a facility or item of equipment, including Federal and state laws, HHS/NIH requirements and specific design criteria defined by national codes and standards. The AOR and its supporting documents form a single reference source for project design, construction, commissioning, building activation, startup, operating and decommissioning requirements. As part of an Integrated Project Team (IPT), the work requires collaboration throughout all project stages including:

- Holding design charettes for design phases (35%/65%/95%) with key Government and Contractor project stakeholders to ensure meaningful design, equipment selection/validation and constructability reviews are accomplished.
- Coordination of all facility business lines and Directorates to ensure comprehensive analysis and design completion.

- Ensuring program requirements are met during planning, purchase and install of new technology. The critical functions of design management are identification of technical, quality, and commercial requirements and performance of item equivalency evaluations as needed.
- Monitor and re-evaluate material/equipment vendor selection, procurement, delivery, installation, commissioning and building activation.
- Collaborate with the Government and private entities on engineering, procurement, and refurbishment/construction to ensure effective sequencing.
- Collaborating and interfacing with other Government organizations when support and services are required to include design authority, operations, security, safety, facility maintenance, emergency management, design QA/Q, and change management.

2.9.1 Utilities Operations

Integrated facility management system that includes:

- Strategic planning for operational management and capital replacement of facility through life cycle analysis.
- Project management "inception to completion" to include resolving tasks in a timely manner, ensuring corrective actions are implemented (addressing full extent of conditions, root causes, and implement measures to prevent recurrence), prioritizing and tracking commitments and actions.
- Capturing, monitoring, and tracking historical building data to support strategic planning for facility life-cycle analysis by building type (e.g., office, lab, vivarium, repository), major equipment, energy, infrastructure capacity, location, operation costs and capital planning.
- Benchmarking and applying Key Performance Indicators (KPIs) for facility business lines (e.g., operations and maintenance (O&M), project management, engineering, custodial service) and project controls – cost & schedule.
- Documentation control to include change order management, 'trend' analysis, deficiencies, prioritization, reviews/approvals, and activity tracking.
- Comprehensive and timely project close-out process for all projects.
- Space management to ensure cost effective and efficient use of space. KPIs to include space utilization, Gross Area Per Occupant by each building, total cost of building per Square Foot (SF), cost per SF per Full Time Employee (FTE), utility costs, vacancy rate.
- Collaborative risk assessments with key NCI stakeholders.
- Accident Prevention Plan (APP) and activity hazard analysis to ensure safety management.
- Calculate the percent of completion, cost, and schedule to compare the approved budgeted and actual costs for projects in real time.
- Resource planning (Capacity vs Demand).

- Value Engineering (VE) in collaboration with NCI.
- Environmental Assessment (EA), National Environmental Policy Act (NEPA) as applicable
- Integrated project portfolio management application solution for planned work.
- Iintegrated asset management system for O&M that interfaces with project portfolio management application.
- Commissioning, building activation, and project close-out.
- Optimized energy performance for facilities to include Green Seal, United States Green Building Council (USGBC), Green Globe.

2.9.2 Workforce Planning and Management

n/a

2.9.3 Design and Procurement Strategy

- Perform a wide variety of Architecture, Engineering & Construction (AEC) services to ensure facility operations and management.
- Employ a variety of contracting mechanisms and award type vehicles.

2.10 Safety and Logistics

2.10.1 Environmental Protection/Safety Services

- Enforcement of appliable NIH and/or OSHA guidelines.
- Risk assessment and safety surveys of the facilities.
- Development of programs/policies at the request of the Government.
- Environmental regulatory compliance.
- Implementation of new or modified programs/policies with Governmental approval, after consultation with affected scientific programs and/or laboratories, and in accordance with NIH Guidelines when applicable. Safety programs and employee training examples include:
    - Industrial safety protocols
    - Occupational safety
    - Biologicals safety
    - Radiation safety

2.10.2 Occupational Health Services

- Medical care of staff:
  - Immediate medical response to urgent injuries/illness.
  - Triage and treatment of non-urgent injuries/illness.
- Health records management.
- Health monitoring:
  - Medical surveillance.
  - Employee wellness programs.
  - Employee health trainings.
- Management and operation of the Research Donor Program, which provides anonymously donated samples from healthy donors for use in local *in vitro* research.

2.10.3 Employee Safety

- Physical security.
- Access control.
- Emergency preparedness plans.
- Reporting and regulatory compliance systems.

2.10.4 Emergency Management/Preparedness

- Emergency Operations Preparedness Plan and Procedures, to include a communications system
  - Planning for events including natural disaster, technological and accidental, terrorist, and active shooter.
  - Maintaining and fielding a 24-hour emergency alert communications system for employee notification.
  - Conducting onboard training for new employees on the plan/procedures, and mandatory annual training for incumbent employees.
  - Maintaining the emergency contact directory.
  - Conducting an annual review of the emergency plan and updating as necessary.
- Continuity of Operations Plan (COOP) coordinated with NIH and the NCI at Bethesda campuses, the U.S. Army Garrison Fort Detrick, other entities recommended by the Government, and other Government/Contractor integrated teams.

- Incorporating fully integrated procedures and processes to protect the mission essential functions for daily operations prior to, during, or following a catastrophic event covering personnel safety.

2.10.5 Labware Services

- Pick up, transport, and deliver laboratory glassware and minimal plasticware within the NCI at Frederick Campus, ATRF, and any other identified NCI locations.
- Wash, sterilize and wrap all glass (or plastic) labware, per customers' preferred method.
- Operate labware cleaning, drying and other required equipment, such as the autoclave and washer.
- Maintain an adequate inventory of labware, and restock and maintain the inventory in the laboratory glassware cabinets throughout Government-identified locations.
- Maintain satellite dirty labware collection stations throughout Government-identified locations.
- Perform routine soap residue tests and monitor sterilization charts.
- Perform custodial, cleaning duties within the labware processing area.
- Determine and utilize the most cost-effective and timesaving pickup and delivery schedule, and communicate it to all service users.
- Return clean labware within two working days, or as specified by the Government.

2.10.6 Property Accountability

- Implement a property accountability program that encompasses a wide range of functions including a biennial accountability and reporting of inventories, property disposal, advertisement of goods surplus for reutilization, surplus monitoring, educational donations, property sales, as well as acquiring accountable equipment from other institutions and agencies.
- Protect, maintain, utilize, and account for all Government-owned property as delineated in the HHS Contracting Guide for Contract of Government Property and in accordance with Federal Acquisition Regulations (FAR) 52.245-1.
- Provide inventory oversight and policies regarding government-owned equipment purchased and used by subcontractors; this activity includes providing property decals for subcontractor-purchased property, conducting biennial inventories of subcontractor-purchased equipment, and performing closeout activities and property disposition.

2.10.7 Shuttle, Courier, and Internal Mail Services

n/a

2.10.8 Vehicle Fleet Management

n/a

2.10.9 Logistics

An online ordering system must be used for efficient and effective warehouse operation. Additional warehouse(s) may be required to be developed to meet future needs.

Central Supply Warehouse (Scientific Operations)

For maintaining inventory of expendable items routinely used throughout the FFRDC, including compressed gases, assorted scientific materials and animal care products.

- Order and maintain adequate inventory based on usage history, substantially cost effective and more expeditious compared to receiving supplies through an outside vendor.
- Communicate with customers to identify appropriate types and brands to be warehoused.
- Online ordering system must be used for an efficient and effective operation.

Maintenance Supply Warehouse

For maintaining inventory of expendable items routinely used by FOM, including compressed gases, for facility and equipment maintenance, repeated or routine renovations and general repair.

Property Compliance Department

Warehouse on the FNLCR campus to house surplus inventory until it can be reused, recycled, or disposed. All property categorized as “good” are being screened for reuse by other Government entities for a minimum of 14 days. Regular communication advertising “good” property to Government agencies is required. If equipment is not reused within the Government after being advertised thoroughly, equipment can be donated to education institutions or non-profit organizations.

2.11 Business Operations

- Provide suitable business practices and utilize agile resources in appropriate configurations to be flexible and to respond rapidly to changing requirements.
- Integrate common systems of internal controls across the FNLCR.
- Implement business processes that are risk-based, cross-functional, cost-effective, increase efficiency and enhance productivity.
- Identification and application of enterprise-wide processes, throughout the FNLCR Enterprise, to optimize and streamline business practices and administrative functions.

2.11.1 Acquisition Services/Purchasing Management

The FNLCR may when when authorized by the Government, enter into subcontracts for the performance of any part of the work under this Contract.

- Establish, execute, and administer various types of agreements including leases, consultant agreements, purchase orders, travel orders, maintenance agreements, Research/Research & Development (R/R&D) subcontracts, facility remodeling/refurbishment subcontracts, services subcontracts.
- Provide the opportunity for the Government staff to interact directly with subcontractor staff.
- Invite, as appropriate, Government Subject Matter Experts (G-SMEs) to contribute to the review of subcontractor proposals by providing feedback on meeting Government requirements, technical aspects, and cost reasonableness.

2.11.2 Audits and Assessments

n/a

2.11.3 Financial Management

This work requires an integrated financial management system, verifiably documenting financial stewardship and public accountability of taxpayer funds.

- Support Government planning, programming, budgeting, and evaluation processes.
- Collect, record and report all financial activities.
- Provide an effective internal control system for all expenditures.
- Provide the Government with full transparency into all financial cost reporting systems through reports, as requested by the Government to allow visibility into program and cost management.
- Identify and collect common productivity and labor cost data required to seek FNLCR-wide solutions, as requested by the Government.
- Maintain a state-of-the-art, dynamic, streamlined, flexible, integrated, and transparent financial management/cost reporting system, which is capable of tracking, evaluating, and projecting financial activities for projects.
    - Integrate data from scientific, FOM and other FNLCR support functions to provide detailed, accurate and timely reports for cost and scope, and accurate schedule estimates for contract mission and mission support functions.
    - Provide robust reports that contain enough detail and functionality for all direct and indirect costs to allow the Contractor and the Government to perform cost-benefit analyses to determine the appropriate level of support function and risk.
    - Develop additional custom ad hoc reports as needed.

2.11.4 Human Resources

2.11.4.1 Workforce Planning and Management

2.11.4.2 Recruitment

- Provide a full range of external and internal placement and recruitment services.
- Work collaboratively with management as needed to accurately determine and clearly write position technical requirements.
- Incorporate creative techniques to bring candidates to the FFRDC, such as Meet and Greet events to assess the technical capabilities of candidate(s).
- Ensure well qualified candidates are selected to fulfill positions.

2.11.4.3 Retention

Employee On-boarding

Develop and establish a program for management to bring new employees physically and virtually on-board to effectively begin employment including an employment orientation process designed to inform new employees about the agency, employment forms and procedures, employee benefits, and community outreach and resources available that support agency employment.

Employee Off-boarding

- Develop and establish secure and private off-boarding procedures for management to safely deactivate employees, both physically and virtually, from agency employment.
- Develop and implement an off-boarding survey to capture information and statistics related to employee satisfaction with their overall employment experience, to better recruit and retain future agency talent.

2.11.5 Legal Services

2.12 Other Support Functions

2.12.1 Cafeteria Services

- Operate and provide oversight for cafeteria services, furnish the facility and equipment.
- Offer meals and food services as designated by the Government including a full-service breakfast in the morning (AM) and full-service lunch in the afternoon (PM), Monday through Friday at the NCI at Frederick Campus and any appointed offsite NCI location.
- Provide Staff with appropriate kitchen attire as well as food and kitchen tools.
- Meal planning, advertisement, and food preparation.

- Inspect all locations on a periodic basis:
  - Using the NIH Food Safety and Sanitation Program as a model.
  - Conducted by food safety professionals, certified through the ServSafe Manager Certification Program, in accordance with the most recent edition of the U.S. Public Health Service, Food and Drug Administration, Food Code.
  - Provide a copy of the Food Establishment Inspection Report (by site) to the Government.

2.12.2 Conference Planning and Support

These services require prior approval by the Government, and include seminars and meetings on-site, virtual, and off-site as required.

- Comply with all Federal Government regulations and policies related to conducting conferences.
- Receipt and review of all paperwork for events to obtain Government approval.
- Secure vendors and ensure reimbursement of vendors for service provided.
- Ground transportation to/from events.
- Travel arrangements for sponsored non-employees attending events and reimbursement of related expenses.
- Hotel arrangements and associated payments.
- Event space rentals.
- On-site support, which may require providing food and beverage, arranging audio/visual (AV) assistance and reimbursement of related expenses.
- Prepare and distribute meeting materials as directed by the Government.
- Website creation, editing and monitoring services; display posters professionally; review and approve badging for events; create screen displays for upcoming events; create marketing material and advertise through multiple listservs, as well as other resources identified; and update the NCI and NIH Calendars of events.
- Operate and maintain the conference environment for the FNLCR on the Frederick Campus: scheduling, setup and configuration of the rooms, support for the conferences and support for the conference room equipment.

2.12.3 Publications, Visual Communications, Graphics, and Media

- Develop illustration and informational graphics using cutting-edge technologies.
- Write and edit using HHS and Associated Press style guides.
- Coordinate the design of scientific posters for print or digital use, which may include editing and production.

- Train researchers in scientific graphics, publications, and presentations.
- Produce or assist researchers with audio-visual materials.
- Maintain currency with emerging publication, communications, and graphics technologies as well as best practices at comparable institutions.
- Continually assess the respective needs of the local research community.

2.12.4 Scientific Library

n/a