

## STATEMENT OF WORK

### SCOPE

This contract will support the development of potential cancer preventive agents using mechanism-based screening assays *in vitro* and *in vivo*. The screening assays will evaluate the ability of test agents to inhibit, reverse, or delay early carcinogenesis through a variety of endpoints, including histopathology, pharmacokinetics, pharmacodynamics, molecular targets and pathways, transformation, proliferation, and apoptosis, using state-of-the-art experimental methodologies.

### I. Task Areas

As part of this Statement of Work (SOW), procurement of chemopreventive agents shall be done through a collaboration with the Contracting Officer's Representative (COR) and with final approval of COR. The Government shall provide agents that are deemed relevant by NCI, but are not available to the Contractor from commercial sources.

The Contractor shall perform work in these Task Areas as outlined in each Task Order.

#### 1. Task Area 1 -- Evaluation of Chemopreventive Agents by Screening Assays *In Vitro*

The Contractor shall validate biologic reagents, assay systems, and experimental procedures in anticipation of further agents development for clinical application.

The Contractor shall:

- A. Experimental Material – general: Establish cell free systems, grow, and maintain rodent, human or other primary cell cultures, cell lines and tissues used in mechanism-based cell transformation studies as follows:
  - i. Use of *in silico* approaches, including virtual chemical libraries and high through-put methodologies.
  - ii. Use of advanced cell culture facilities.
  - iii. Use of advanced molecular endpoints to identify potential chemopreventive agents.
  - iv. Use of advanced pharmacokinetics and pharmacodynamics methodologies.
- B. Experimental Material – specific: Utilize well-defined biological reagents including:
  - i. Cell lines that can be transformed by complete carcinogens or transformed by sub-carcinogenic doses of complete or incomplete carcinogens,
  - ii. Primary cell or organ cultures that can be transformed,
  - iii. Cell-free systems measuring enzyme inhibition/activation or other endpoints,
  - iv. Cell lines expressing receptors or other factors, such as:
    - a. Epidermal growth factor receptor (EGFR)
    - b. Tumor growth receptors that can be used as targets for chemopreventive agents.
- C. Experimental Approaches: Provide mechanism-based *in vitro* systems in order to assist the COR in prioritizing agents for future studies
  - i. Employ *in vitro* systems that will permit an evaluation of potential efficacy of chemopreventive agents in the presence of initiating and/or promoting substances such as physical, chemical or viral carcinogens.
  - ii. Facilitate assessment of agents' efficacy;
  - iii. Determine the effects on specific target sites in one or more *in vitro* systems;

- iv. Enable streamlining of toxicology testing costs to assist the COR in the pre-selection of the test compounds;
- v. Accelerate rate at which chemicals are evaluated.

D. Experimental Endpoints: Establish assay endpoints *in vitro*, which shall include:

- i. High throughput and virtual screens, including use of chemical libraries
- ii. Spontaneous immortalization;
- iii. Direct transformation evaluated by:
  - a. Anchorage independent growth
  - b. Foci of morphologically altered cells
  - c. Clonogenicity
  - d. Tumor formation in nude mice;
- iv. Molecular approaches for further evaluation of D.i. and D.ii. above.

**2. Task Area 2 --Evaluation of Chemopreventive Agents Using Screening Assays *In Vivo***

The contractor shall evaluate chemopreventive agents using criteria for agents shown to be efficacious *in vitro*; these may include agents where data already exists regarding their effectiveness in animal models. The contractor shall validate biologic reagents, assay systems, and experimental procedures prior to their application in the procurement, development, and selection of test agents *in vivo*.

A. Animal Models: The Contractor shall conduct screening assays *in vivo* using animal models of chemoprevention, including:

- i. Performing chemoprevention studies in at least one tumor model,
- ii. Using laboratory animals such as mice, rats, other rodents and relevant avian models; and more specifically models where tumors arise spontaneously, models which involve carcinogen-induced cancers and genetically engineered (GEN) models
- iii. Using animal model systems of relevance to high-incidence human cancers, such as:
  - a. Colon
  - b. Prostate
  - c. Breast (mammary gland)
  - d. Lung
  - e. Skin
  - f. Bladder
  - g. Cervix
  - h. Esophagus
  - i. Oral mucosa
  - j. Ovary
  - k. Pancreas.

B. Experimental approaches using animal models:

- i. Determine efficacy of agents in animal models for:
  - a. Inhibiting carcinogenesis,
  - b. Modulating processes associated with carcinogenesis.
- ii. Identify agents with a strong mechanistic rationale for which no previous test results exist.
- iii. Confirm published preclinical results of agents prior to clinical investigation.

- iv. Analyze chemopreventive agents for purity, homogeneity, and stability in administering vehicles.
  - v. Use multiple administration routes, including gavage, topical, inhalation, injection, or pellet implantation.
  - vi. Administer carcinogens, promoters, hormones, and/or chemopreventive agents to laboratory animals as indicated.
- C. Endpoints using Animal Models:
- i. Monitoring tumorigenesis, body weight, and clinical appearance.
  - ii. Performing gross necropsies in test animals.
  - iii. Performing histopathological examination of selected tissues in different strains and species of animals used.
  - iv. Preserving tissues, serum, and urine from laboratory animals for molecular and analytical studies.
  - v. Performing statistical analysis of tumor inhibition results including tumor incidence, tumor multiplicity, and tumor latency.
  - vi. Analyzing of normal tissue and tumor samples using immunohistochemical or other techniques, *e.g.*, proliferation or apoptosis.
  - vii. Considering agents exhibiting chemopreventive activity *in vivo* for further studies such as:
    - a. Dose dependency;
    - b. Optimal time of treatment
- D. Animal Facility: The Laboratories shall be accredited by or registered as follows:
- i. The Contractor shall have an approved Animal Welfare Assurance for the Office of Extramural Research (OER), Office of Laboratory Animal Welfare (OLAW) (<http://grants.nih.gov/grants/olaw/olaw.htm>), Office of the Director, NIH, as required by Section I-43-30 of the Public Health Service Policy on Humane Care and Use of Laboratory Animals. The Contractor shall maintain such assurance for the duration of this contract, and any subcontractors performing work under this contract involving the use of animals shall also obtain and maintain an approved Animal Welfare Assurance.
  - ii. The Contractor shall be fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) International or equivalent and maintain that accreditation for the life of the contract. Information about AAALAC accreditation is available at [www.aaalac.org](http://www.aaalac.org).
  - iii. The Contractor shall comply with the Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals (<http://grants.nih.gov/grants/olaw/references/phspol.htm>) and conduct work in compliance with recommendations established in the Guide for the Care and Use of Laboratory Animals ([http://www.nap.edu/openbook.php?record\\_id=5140](http://www.nap.edu/openbook.php?record_id=5140)).
  - iv. United States Department of Agriculture (USDA).
  - v. Institutional Animal Care and Use Committee (IACUC) shall approve all animal procedures under this contract.