

development within the LTIB for many years. During that time, there has been continual advances in the field of antibody development within LTIB via extensive intramural research, corporate sponsored CRADA projects, and independent corporate development under licensing arrangements.

When the excellent tumor targeting characteristics of anti-TAG-72 monoclonal antibody B72.3 in the clinic were observed, the LTIB developed a series of second generation, higher affinity monoclonal antibodies for TAG-72. This "CC" series, of which monoclonal antibody CC49 is the prototype, has been extensively characterized both preclinically and clinically. Radiolabeled CC49 shows much better tumor targeting in the clinic than B72.3. CC49 reacts with the majority of the following carcinomas: Colorectal, gastric, pancreatic, non-small cell lung, ovarian, endometrial, breast and prostate.

The LTIB has also developed a series of anti-carcinoembryonic antigen monoclonal antibodies (COL series). The prototype (COL-1) reacts to the vast majority of gastrointestinal and pancreatic cancers, and also to 50% of breast cancers and 70% of non-small cell lung cancers. A Phase 1 trial has just been completed with radiolabeled COL-1.

The LTIB has shown successful tumor targeting in cancer patients with radiolabeled forms of both monoclonal antibodies which are the primary focus of these collaborations: CC49 and COL-1. Phase I therapy trials for both monoclonal antibodies have been completed. Additionally, radiolabeled forms of CC49 are currently in Phase II clinical trials for colorectal, breast, ovarian, and prostatic cancer as a murine monoclonal antibody.

As a corollary, the progression of the technology can be illustrated in two specific examples of ongoing research collaborations which will not be a part of the present CRADA:

(A) The LTIB, NCI initially developed a monoclonal antibody designated B72.3, which reacts to the pancacinoma antigen termed TAG-72. This breakthrough technology provided the basis for the first and still only monoclonal antibody approved by the FDA for any *in vivo* use in cancer. Under a separate licensing agreement, Cytogen Corporation conjugated B72.3 with ¹¹¹In and developed Onco Scint CR/OV[®] for oncologic imaging to be used in conjunction with CT scan. OncoScint CR/OV[®] has been approved for use in both colorectal cancer and ovarian cancer.

(B) Under a separate CRADA agreement, a Phase III multicenter trial is also in progress employing ¹²⁵I-labeled murine CC49 with an intraoperative hand held probe as a method of radioimmunoguided surgery.

Additional Background Information

- The LTIB has shown via immunohistochemistry that anti-TAG-72 and anti-carcinoembryonic antigen monoclonal antibodies complement each other extremely well in overcoming antigen heterogeneity. Serum assays for carcinoembryonic antigen and TAG-72 (CA72-4) are also complementary in that non-coordinate expression is observed.

- Previous collaborative studies on the use of the CC49 and COL-1 monoclonal antibodies as drug conjugates demonstrated anti-tumor effects in animal models.

- The LTIB has recently developed CDR grafted (humanized) forms of monoclonal antibody CC49, and other novel genetically engineered immunoglobulin forms for CC49 could be the subject of any CRADA. Similar constructs of anti-carcinoembryonic antigen monoclonal antibodies could also be the subject of any CRADA.

- Recent clinical trials have supported the preclinical observations that recombinant interferon will selectively upregulate both TAG-72 and carcinoembryonic antigen expression on the surface of tumor cells. This finding should enhance both diagnostic and therapeutic uses of these classes of monoclonal antibodies, and these studies could be included as CRADA activities.

- The NIH has exclusively licensed the rights for monoclonal antibody CC49 for use with the radioimmunoguided surgery intraoperative probe as part of a separate collaboration.

- A comprehensive list of publications relating to this technology, intellectual property and background licensing information, and general CRADA information will be provided upon initial contact with NCI.

Party Contributions

The role of the National Cancer Institute includes the following:

- (1) Develop novel recombinant forms of monoclonal antibodies.

- (2) Initial characterization of hybridoma cell lines producing monoclonal antibodies.

- (3) Conduct preclinical testing (tumor targeting and therapy) of these monoclonal antibodies both *in vivo* and *in vitro* as unlabeled immunoglobulin forms and/or as antibody conjugates.

- (4) Conduct preclinical studies on the use of biologic response modifiers to upregulate tumor targeting and therapy.

- (5) Analyze pharmacokinetics and anti-immunoglobulin responses in some clinical trials.

The role of the successful corporate sponsor(s) will include:

- (1) Develop high producer clones of the monoclonal antibodies and recombinant immunoglobulin producing cells lines and cultures supplied by the NCI and optimize production and purification procedures for experimental tumor targeting and therapy studies.

- (2) Produce and purify clinical grade (GMP) monoclonal antibodies for clinical trials and submit Drug Master Files in support of the monoclonal antibody production.

- (3) Conduct toxicity studies as required by the FDA.

- (4) Develop methodologies for the conjugation of monoclonal antibodies with (A) Radionuclides, (B) Drugs and/or toxins, (C) Pro-drugs, (D) Bifunctional antibodies.

- (5) Submit IND application in support of clinical trials.

- (6) Conduct clinical trials using monoclonal antibody and immunoglobulin forms.

The role of both the National Cancer Institute and the successful corporate sponsor(s) will include:

- (1) Optimize purification schemes for immunoglobulin forms, prior to and post conjugation.

- (2) Collaborate on clinical trial design including protocols using biologic response modifiers (e.g., recombinant interferon).

- (3) Collaborate on data analysis in support of clinical trials.

Selection Criteria

Proposals submitted for consideration should fully address each of the following qualifications:

- (1) Experience in the GMP production, purification, quality control of monoclonal antibodies and regulatory requirements of monoclonal antibody clinical trials.

- (2) Experience in the conjugation of monoclonal antibodies with one or more of the following: (A) Radionuclides, (B) Drugs and/or toxins, (C) Pro-drugs, (D) Bifunctional Antibodies *and* the analyses of these reagents.

- (3) Ability to provide necessary reagents on a timely basis.

- (4) Experience in conducting clinical trials.

- (5) Willingness to cooperate with the National Cancer Institute in the collection and evaluation of data.