DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

REQUEST FOR PROJECT TEAM MEMBER APPLICATIONS FOR CONDUCTING CLINICAL TRIALS USING HU5F9-G4 (NSC# 809249)

The National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) is accepting Project Team Member Applications for a project using Hu5F9-G4, an anti-human cluster of differentiation (CD) 47 monoclonal antibody being developed by CTEP as an anticancer agent in collaboration with Forty Seven Inc. Hu5F9-G4 is a first-in-class anticancer therapeutic agent targeting the CD47 signal regulatory protein alpha (SIRPα) axis (Liu *et al*., 2015a; Huang *et al*., 2017). CD47 is a key molecule mediating cancer cell evasion of phagocytosis by the innate immune system (Huang *et al*., 2017). Hu5F9-G4 binds to human CD47 on target malignant cells, blocks the anti-phagocytic signal to macrophages, enhances tumor cell phagocytosis, and elicits an anti-tumor T-cell response (Huang *et al*., 2017; Liu *et al*., 2017). Hu5F9-G4 has demonstrated antitumor activity in breast, ovarian, brain, and bladder cancers, acute myeloid leukemia (AML), non-Hodgkin's lymphoma (NHL) and other malignancies in preclinical studies (Liu *et al*., 2015a).

Hu5F9-G4 has demonstrated strong single agent activity in solid tumors as well as strong preclinical efficacy in cutaneous T-cell lymphoma (CTCL) and central nervous system (CNS) tumors. At the present time, CTEP's preliminary drug development plans are to sponsor phase 1 monotherapy and combination trials of Hu5F9-G4 in combinations with antitumor antibodies such as mogamulizumab for the treatment of cutaneous T-cell lymphoma (CTCL), and dinutuximab for pediatric tumors such as neuroblastoma, as well as to conduct studies in other tumors. The role of the project team is to evaluate all available evidence to modify and refine this initial plan.

It is anticipated that CTEP will activate 1-2 different single agent and combination trials with Hu5F9-G4, with additional studies to be conducted after these initial trials. The project team will include:

1. **Clinician Scientists** with expertise in phase 1 studies and with an interest in CTCL, pediatric, and other tumors (fill out **Part A** of the attached Application; Clinician Scientists must belong to a qualifying NCI grant funded institution as defined at the end of this letter);
2. **Translational scientists** with an interest in biomarker development in CD47-targeting therapeutics (fill out **Part B** of the attached Application and see the submission instructions at the end of this letter); and
3. **Basic scientists** with expertise in macrophage biology and the innate immune system's anti-tumor response (fill out **Part C** of the attached Application and see the submission instructions at the end of this letter).

Prospective team members may apply for multiple roles using a single application form by completing all the appropriate parts. The project team will be recruited nationally and will prioritize the research questions regarding Hu5F9-G4 in single agent and combination trials, including prioritization of biomarker studies. It is anticipated that the clinicians on the drug project team will be tasked with writing the Letters of Intent describing the study design, based upon the team's recommendations, for CTEP approval, and that these clinicians will ultimately lead the clinical studies. It is also anticipated that other extramural members of the drug project team will stay involved in the subsequent design and execution of the proposed trials. It is anticipated that the project team will complete its work in three months or less.

Background/Rationale

CD47 is widely expressed and has been identified as a key molecule mediating cancer cell evasion of phagocytosis by the innate immune system (Liu *et al*., 2015a). It provides an anti-phagocytic signal by binding to the N-terminus of SIRPα on immune cells and suppresses phagocytosis (Huang *et al*., 2017). Hematopoietic stem cells transiently upregulate CD47 expression to escape phagocytosis by macrophages before and during mobilization (Jaiswal *et al*., 2009). The pathological role of CD47 is commonly responsible for the escape of malignant cancer cells from immune-surveillance. CD47 expression is increased on the surface of cancer cells from many diverse human tumor types including head and neck cancer, melanoma, breast, lung, ovarian, colon, bladder, prostate, leiomyosarcoma, glioblastoma, medulloblastoma, oligodendroglioma, glioma, lymphoma, leukemia, and multiple myeloma (Chan *et al*., 2009; Jaiswal *et.al*., 2009; Majeti *et al*., 2009; Chao *et al*., 2010a; Chao *et al*., 2010b; Chao *et al*., 2012; Krampitz *et al*., 2016; Edris *et al*., 2012; Gholamin *et al*., 2017). CD47 overexpression has been associated with poor prognosis in leukemia, NHL, bladder cancer, breast cancer, and other cancers (Huang *et al*., 2017; Majeti *et al*., 2009; Chao *et al*., 2010a; Chan *et al*., 2009; Willingham *et al*. 2012). Furthermore, elevated CD47 messenger RNA (mRNA) expression correlates with a worse overall survival for multiple types of cancer (Willingham *et al*., 2012). In murine xenograft studies, CD47-blocking antibodies can inhibit human cancer growth and metastasis by enabling the phagocytosis of cancer stem cells (CSCs) from various hematological malignancies and solid tumors. CD47-blocking antibodies have been shown to exhibit potent synergy with tumor-specific monoclonal antibodies, such as rituximab, cetuximab, and trastuzumab (Chao *et al*., 2010a; Weiskopf *et al*., 2013). Thus, CD47 has a strong potential as a therapeutic target for the treatment of a variety of malignancies.

Hu5F9-G4 is a recombinant humanized anti-CD47 monoclonal antibody of the IgG4 kappa isotype containing a Ser-Pro (S-P) substitution in the hinge region (position 228) of the heavy chain to reduce fragment antigen-binding (Fab) arm exchange (Liu *et al*., 2015a). Hu5F9-G4 blocks the interaction of CD47 with its ligands and enables phagocytosis of human cancer cells. The activity of Hu5F9-G4 is primarily dependent on blocking CD47 binding to SIRPα and not on the recruitment of fragment crystallizable (Fc)-dependent effector functions. Most normal cells lack expression of pro-phagocytic signals and are unaffected by Hu5F9-G4 binding to CD47 (Feng *et al*., 2015). However, blockade of CD47 in tumors can enhance macrophage phagocytosis of cancer cells, and in preclinical studies, this results in a profound antitumor effect against solid tumors and hematological malignancies (Liu *et al*., 2015a; Chan *et al*., 2009). Combinations with antitumor antibodies such as rituximab can provide potent pro-phagocytic signals to macrophages and result in synergistic antitumor effects when combined with CD47 blockade (Chao *et al*., 2010a). This mechanism of synergistic interaction with monoclonal antibodies with active Fc domains is broadly applicable to a wide range of antitumor antibodies in current clinical use.

Mechanism of Action

Hu5F9-G4 is an anti-CD47 monoclonal antibody that disrupts the CD47/SIRPα interaction to induce macrophage-mediated phagocytosis (Liu *et al*., 2015a). Hu5F9-G4 selectively binds to CD47 on tumor cells and prevents it from binding to SIRPα. This inhibits CD47/SIRP signaling causing the activation of macrophages through induction of pro-phagocytic signaling mediated by calreticulin which initiates specific tumor cell phagocytosis (Chao *et al*., 2010b). Inhibiting CD47 signaling initiates an anti-tumor T-lymphocyte immune response and T-cell mediated killing (Liu *et al*., 2015b).

Nonclinical Studies of Hu5F9-G4

Hu5F9-G4 has demonstrated promising activity in AML, NHL, pediatric brain tumors, and colorectal cancer (CRC) xenografts (Chan *et al*., 2009; Willingham *et al*., 2012; Liu *et al*., 2015a; Gholamin *et al*., 2017). Preclinical studies demonstrated that Hu5F9-G4 has anti-tumor activity in various tumor cell lines and primary cancer cells when administered either as a monotherapy or in combination with other anti-cancer therapies (Liu et al., 2015a; Gholamin *et al*., 2017; Chan *et al*., 2009; Willingham *et al*., 2012).

In vivo pharmacology studies were conducted using xenograft models, in which human cancer cells or cell lines were transplanted into immunodeficient non-obese diabetic (NOD)/severe combined immune deficiency (SCID) mice (Takenaka *et al.*, 2007). These mice were derived on the NOD background which possesses a mouse SIRPα allele able to bind human CD47. These mice possess no B or T lymphocytes or natural killer cells due to the SCID alleles. Thus, activity of Hu5F9-G4 in these models is dependent on other effector mechanisms.

The pharmacokinetics (PK) and toxicokinetics (TK) of Hu5F9-G4 have been studied in the cynomolgus monkey (Liu *et al*., 2015a). Hu5F9-G4 was administered as a single intravenous (IV) infusion at 0, 0.1, 0.3, 1, 3, 10, and 30 mg/kg in separate animals. Single-dose administration of Hu5F9-G4 PK data demonstrated that only the 10 and 30 mg/kg dose levels were able to transiently achieve serum levels in the range associated with efficacy in xenograft studies. Hu5F9-G4 was generally well tolerated, and no treatment-related effects were noted on a comprehensive list of clinical observations, food consumption, body weights, or clinical chemistry parameters indicative of renal, hepatic, or cardiac effects. Hu5F9-G4 caused a dose-dependent anemia associated with reticulocytosis and spherocytosis in all animals which occurred approximately 5-7 days after the infusion. In all animals, the anemia spontaneously resolved and returned to baseline levels after 2 weeks. Consistent with its known function in regulating red blood cell (RBC) phagocytosis, Hu5F9-G4 caused a transient anemia likely due to erythrophagocytosis but was otherwise well tolerated.

Clinical Studies of Hu5F9-G4

Hu5F9-G4 has been under investigation as monotherapy as well as in combination with other agents in a number of clinical studies for the treatment of advanced oncologic malignancies; a brief outline is provided below (Table 1)

Table 1: Hu5F9-G4 clinical trial listing on Clinicaltrials.gov

NCT	Phase	Agent(s)	Disease/Indication	Study Start-End	Status/Sponsor	Planned Accrual	Abstract
NCT02216409	**1**	**Hu5F9-G4**	**Advanced Solid Tumors**	**08/2014-12/2018**	**Forty Seven, Inc.**	**96**	**Agoram *et al*., 2018, Sikic *et al*., 2018**
NCT02678338	**1**	**Hu5F9-G4**	**AML/Myelodysplastic syndrome (MDS)**	**11/2015-1/2019**	**Forty Seven, Inc.**	**40**	**None**
NCT02953509	**1b/2**	**Hu5F9-G4/ Rituximab**	**NHL/Diffuse large B-cell lymphoma (DLBCL)**	**11/2016-1/2023**	**Forty Seven, Inc.**	**72**	**Advani *et al*., 2018a, Advani *et al*., 2018b**
NCT02953782	**1b/2**	**Hu5F9-G4/ Cetuximab**	**Colorectal neoplasms/Solid Tumors**	**11/2016-3/2023**	**Forty Seven, Inc.**	**112**	**None**
NCT03248479	**1b**	**Hu5F9-G4/ Azacitidine**	**Relapsed/refractory (R/R) AML/MDS**	**9/2017-8/2022**	**Forty Seven, Inc.**	**96**	**None**
NCT03558139	**1b**	**Hu5F9-G4/ Avelumab**	**Solid Tumors/Ovarian Cancer**	**5/2018-5/2023**	**Forty Seven, Inc.**	**32**	**None**

Data from the ongoing first in human phase 1 monotherapy trial of Hu5F9-G4 in advanced solid tumor patients (NCT02216409) and the phase 1b/2 rituximab combination trial in relapsed/ refractory (R/R) B-cell NHL (NCT02953509) suggest that Hu5F9-G4 was well tolerated and demonstrated antitumor activity (Sikic *et al*., 2018; Advani *et al*., 2018a). In the phase 1 monotherapy trial, patients were administered up to 45 mg/kg of Hu5F9-G4 IV weekly (QW) without defining a maximum tolerated dose (Sikic *et al*., 2018). The recommended phase 2 dose (RP2D) is 1 mg/kg priming dose Week 1 followed by 30 mg/kg QW and then shifting to 30 mg/kg every two weeks (Q2W). The most common adverse events (AEs) were fatigue, chills, pyrexia, anemia, headache, lymphopenia, hemagglutination, transient hyperbilirubinemia, and myalgias. The

most common tumor types in the dose escalation study included CRC, ovarian, adenoid cystic, breast, pancreatic, and squamous cell head and neck cancer. Two patients (ovarian and fallopian) had confirmed partial responses (PR) and were treated for 23 and 41+ weeks. In 13 CRC patients treated with ≥20 mg/kg, 6 had stable disease (SD) with a median treatment duration of 18 weeks.

In the phase 1b/2 trial of Hu5F9-G4 in combination with rituximab, patients were given 1 mg/kg Hu5F9-G4 priming dose with higher weekly maintenance doses to mitigate on-target toxicities, specifically anemia (Advani *et al*., 2018a; Advani *et al*., 2018b). Maintenance doses were escalated from 10 to 30 mg/kg with standard dose rituximab. Twenty-two heavily pre-treated patients with R/R diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) were enrolled in the Phase 1b study. Patients had a median of four prior therapies (range two to nine), and 90% of patients were rituximab-refractory. No clinically significant safety events were observed; the most common AEs were anemia and infusion-related reactions. AEs were predominantly Grade 1 or 2 except anemia which was Grade 3. The RP2D of 30 mg/kg Q2W after Cycle 1 was selected. Across all doses, the objective response rate was 50%, and 36% achieved complete response (CR). The rates of objective response and CR were 40% and 33%, respectively among DLBCL patients and 71% and 43%, respectively, among FL patients. At a median follow-up of 6.2 months among DLBCL patients and 8.1 months among FL patients, 91% of the responses were ongoing.

CTEP's Plans for Hu5F9-G4 Development

1. Characterize and understand interactions between innate and adaptive immune systems.
2. Facilitate pharmacodynamic (PD) biomarker development using DCTD Immune Biomarker Program.
3. Potential trials could involve areas of high unmet needs:
    a. Combinations with antibodies in other tumors
        i. Combinations with chemokine receptor 4 (CCR4)-targeting antibody, mogamulizumab in cutaneous T cell lymphoma
        ii. Pediatric cancers where antibody opsonization could be optimized, such as with dinutuximab, the anti-GD2 antibody with proven clinical activity in neuroblastoma
    b. Combination with interleukin (IL)-15 for enhanced immunotherapy (Antibody-Dependent Cellular Cytotoxicity [ADCC] with ADCP)

It is expected that additional clinical trial concepts will be developed by the project team.

<u>Correlative Studies of Interest to CTEP</u>

Correlative studies may include but are not limited to exploring PD biomarkers, including characterizing CD47 expression interactions between the innate and adaptive immune systems using DCTD Immune Biomarker Program.

Hu5F9-G4 Project Team Selection, Composition, and Tasks

The HuF59-G4 drug project team will meet regularly by WebEx to review available evidence and determine promising strategies, identify biomarkers to evaluate these strategies, and formulate clinical trial designs to test these strategies. The project team will be composed of intramural and extramural members. The extramural members will include clinician scientists with experience in phase 1 studies in pediatric cancers and CTCL; translational scientists with expertise in biomarker development; and basic scientists with expertise in macrophage biology and the innate immune system's antitumor response. Since the clinician scientists selected for the project team will be expected to lead the clinical trials that come out of this process, the evaluation criteria for the clinician scientists will include not only clinical trial expertise but also their documented record of accrual to early phase studies in pediatric tumors, CTCL, and other cancers.

Questions regarding this request for applications may be addressed to Elad Sharon, M.D., M.P.H., Medical Officer, Investigational Drug Branch, CTEP, DCTD, NCI (phone: 240-276-6565; e-mail: sharone@mail.nih.gov).

CTEP recognizes the importance of encouraging and supporting young investigators as they embark upon a clinical cancer research career. CTEP highly encourages Career Development Applications (CrDAs) from these investigators and their mentors to participate as Project Team members and to develop Career Development Letters of Intent (CrDLs) after conclusion of Project Team activities.

Project Team Member Applications (PTMAs) should contain a clear indication of the applicant's desired role on the Hu5F9-G4 Project Team (clinician scientist, translational scientist or basic scientist). The PTMA should also be accompanied by an NIH Biosketch containing a personal statement customized to this project. The PTMAs should be sent to the Protocol and Information Office (PIO) at the address below by **5:00 PM Eastern Time (ET), January 11, 2019**. The most recent version of the PTMA form, which has been distributed with this communication, must be used. PTMAs should be submitted electronically to:

PIO, CTEP/DCTD/NCI
E-mail: CTEPPTMASubmissions@mail.nih.gov

Please note that Clinician Scientists may only participate through association with the ETCTN, an NCTN Group, or a consortium (see below), and will need to submit the PTMA through their ETCTN LAO's Coordinating Center or the Group/Consortium Operations office, as applicable. That organization will then need to submit the Clinician's application to PIO on your behalf to confirm that they are in support of the proposal. Please allow sufficient time for your organization's review. Qualifying clinical institutions include:

- ETCTN Participating Institution (under UM1 grant)
- NCTN Group member institution (under U10 grant; Alliance, COG, ECOG-ACRIN, NRG Oncology, or SWOG)
- Institutional affiliation with the Pediatric Brain Tumor Consortium (PBTC), Adult Brain Tumor Consortium (ABTC), or Cancer Immunotherapy Trials Network (CITN)

Basic and **Translational Scientists** who belong to a participating ETCTN institution (Lead Academic Organization [LAO] or Affiliated Organization [AO]) **must** submit applications through your LAO's Coordinating Center. Please allow sufficient time for your organization's review. Basic and Translational Scientists from non-ETCTN-affiliated institutions may submit their applications directly to PIO.

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