DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Public Teleconference Regarding Licensing and Collaborative Research Opportunities for: TRICOM—A Synergistic Triad of Costimulatory Molecules Used in Cancer Vaccines for the Prevention and Treatment of Cancer

AGENCY: National Institutes of Health, Public Health Service, HHS.

ACTION: Notice.

SUPPLEMENTARY INFORMATION: Note that this teleconference, licensing and CRADA opportunity will address the treatment of all cancers excluding colorectal, melanoma and prostate cancer.

Technology Summary

TRICOM is a triad of costimulatory molecules used in vector-based cancer vaccines that employ a combination of T-cell costimulatory signals together with tumor associated antigens (TAAs) to greatly enhance the immune response against a variety of cancers. Already several TRICOM-based cancer vaccines incorporating TAAs have shown promising results during clinical stage development. Pre-clinical development of other TRICOM-based vaccines continues, which makes use of newly discovered TAAs and T-cell activating peptides derived from TAAs that would allow targeting cancers expressing poorly immunogenic TAA. Certainly, this cancer vaccine technology has a high potential for leading to a new approach in the prevention and/or treatment of cancer.

Competitive Advantage of Our Technology

- The technology is beyond proof-of concept, supported by laboratory and clinical trial results and numerous publications.
- Recent Phase II clinical data are also available (to qualified licensees) employing TRICOM based vaccines.
- Further clinical studies are ongoing.
- Given the relatively more advanced stage of development of this technology, fewer validation studies are required compared to other immunotherapy related technologies.

Technology Description

Cancer immunotherapy is an approach where tumor associated antigens (TAAs), which are primarily expressed in human tumor cells, and not expressed or minimally expressed in normal tissues, are employed to generate a tumor-specific immune response. Specifically, these antigens serve as targets for the host immune system and elicit responses that results in tumor destruction. The initiation of an effective T-cell immune response to relatively weak antigens requires two signals. The first one is antigen-specific via the peptide/major histocompatibility complex and the second or ''costimulatory'' signal is required for cytokine production, proliferation, and other aspects of T-cell activation.

The TRICOM technology employs avirulent poxviruses to present a combination of costimulatory signaling molecules with tumor-associated antigens (TAAs) to activate T-cells and break the immune systems tolerance towards cancer cells. This is achieved using recombinant poxvirus DNA vectors that encode both T-cell costimulatory molecules and TAAs. The combination of the three costimulatory molecules B7.1, ICAM–1 and LFA–3, hence the name TRICOM, has been shown to have more than the additive effect of each costimulatory molecule when used individually to optimally activate both CD4+ and CD8+ T cells. The result is that when a TRICOM based vaccine expressing TAAs is administered it greatly enhances the immune response against the malignant cells expressing those TAAs. By changing the TAAs used for immunization with TRICOM vaccines immune responses can be generated to diverse types of cancers. The versatility of the vector-based TRICOM based vaccine is that it allows including several TAAs to help maximize the effectiveness. Transgenes reflecting alterations of TAAs can also be inserted into TRICOM based vaccines to further enhance immunogenicity.

The addition of the two well-known TAAs, carcinoembryonic antigen (CEA) and MUC–1, to the TRICOM vector results in the PANVAC vaccine, which is used in a prime and boost vaccine strategy. It is well established that the overexpression of these two TAAs is associated with the presence of a variety of carcinomas; therefore PANVAC is potentially effective against a range of tumor types.

New TAAs are being continually identified. One such example is Brachyury. Although Brachyury has been well known for its role in developmental cell biology, it has now been implicated in tumor cell invasion and metastasis. Pre-clinical data indicates that Brachyury is aberrantly expressed on tumors of lung, intestine, stomach, kidney, bladder, uterus, ovary, and testis, and in chronic lymphocytic leukemia. Additionally, in combination with costimulatory molecules, it can effectively activate T-cells to kill cells that originated from these tumors. Therefore, as one example, Brachyury combined with TRICOM also has potential as a cancer immunotherapy for the treatment of several tumors.

Availability

The technology is available for exclusive and non-exclusive license. Some potential licensing opportunities involving recombinant poxviral vectors containing transgenes are as follows:

- TRICOM (alone or with a transgene or transgenes for a tumor antigen(s) and/or an immunostimulatory molecule).
- PANVAC (CEA–Muc1–TRICOM), with CEA and Muc1 transgenes also containing enhancer agonist epitopes.
- Recombinant fowlpox–GM–CSF.
- Brachyury and/or other TAAs with TRICOM.

Applications and Modality

Vector-based TRICOM (alone or with a transgene(s) for a tumor antigen and/or an immunostimulatory molecule(s)), PANVAC and combinations thereof can be a potential novel approach for the prevention or treatment of cancer (with the exclusion of prostate cancer, prostatic diseases, melanoma, and colorectal cancer) and infectious diseases.

Market

With the identification of molecular targets associated with cancer, the focus of drug development has shifted from broadly acting cytotoxic drugs to targeted therapeutics in the hope of finding drugs that selectively kill cancer cells and do not harm normal cells. Historically, because the expertise of pharmaceutical companies has been in the domain of small molecule therapeutics, several compounds have been developed that inhibit the abnormal biochemical activity of cancer cells. This approach has been successful to an extent as illustrated by the kinase inhibitors and EGFR inhibitors. However, as for chemotherapeutics, cancer cells frequently acquire drug resistance to targeted small-molecule therapeutics rendering them ineffective in the long run. In addition, these small-molecules produce adverse side effects which can prevent the administration of the maximum effective dose. An alternative approach to overcome these problems relies on the use of biologics such as antibodies and vaccines.

The biotechnology industry has principally focused on an immunotherapy approach using monoclonal antibodies (mAb) to enlist the help of the patient's own immune

system. This approach has successfully led to several FDA approved and marketed mAbs. Typically, cancer cells are less susceptible to acquiring resistance to antibodies; however, as seen for trastuzumab, resistance can occur. Another limitation of mAbs is that they activate only part of the immune system and do not produce future immunity against the cancer. Currently, monoclonal antibodies are the only immunotherapy available for treating cancer. More recently, cancer vaccines are being developed as an improvement on the immunotherapy approach. It is expected that activating the cells of the immune system should be greatly more effective in killing cancer cells with the added benefit that it would lead to a sustained surveillance by the patient's own body that prevents the tumor from reemerging in the future.

Vaccines have been very successful in the prevention of infectious diseases, and are now being evaluated for the treatment of cancer. The development of a cancer vaccine could result in a paradigm shift in the treatment and clinical management of cancer. Currently, there are no cancer vaccines approved for the U.S. market but this could change with the development of the TRICOM-based technology of costimulatory vaccines that is designed to magnify the immune response against cancer cells and lead to prolonged cancer immunity.

PANVAC, using TRICOM, has much potential for becoming a therapeutically effective cancer vaccine. It has been successful in Phase I and II clinical studies demonstrating a high safety profile and that it is a good candidate for initiating pivotal efficacy studies. Recently, very encouraging results were announced for prostate cancer therapy using PROSTVAC™ which is a vaccine based on the same technology platform as PANVAC, which further validates this technology platform. PANVAC is a decidedly mature technology that holds promise to transform the treatment of cancer.

Patent Estate

The portfolio includes the following issued patents and pending patent applications:

1. U.S. Patent No. 6,969,609 issued 29 Nov. 2005 as well as issued and pending foreign counterparts [HHS Ref. No. E–256–1998/0];

2. U.S. Patent Application No. 11/321,868 filed 30 Dec. 2005 [HHS Ref. No. E–256–1998/1]; and

3. U.S. Patent No. 6,756,038 issued 29 Jun. 2004 as well as issued and pending foreign counterparts [HHS Ref. No. E–099–1996/0];

4. U.S. Patent No. 6,001,349 issued 14 Dec. 1999 as well as issued and pending foreign counterparts [HHS Ref. No. E–200–1990/3–US–01];

5. U.S. Patent No. 6,165,460 issued 26 Dec. 2000 as well as issued and pending foreign counterparts [HHS Ref. No. E–200–1990/4–US–01];

6. U.S. Patent No. 7,118,738 issued 10 Oct. 2006 as well as issued and pending foreign counterparts [HHS Ref. No. E–154–1998/0–US–07];

7. PCT Application No. PCT/US97/12203 filed 15 Jul. 1997 [HHS Ref. No. E–259–1994/3–PCT–02];

8. U.S. Patent Nos. 7,410,644 issued 12 Aug. 2008 and U.S. Patent Application No. 08/686,280 filed 25 Jul. 1996 [HHS Ref. No. E–259–1994/3–US–08 and/4–US–01];

9. U.S. Patent No. 6,946,133 issued 20 Sep. 2005 as well as issued and pending foreign counterparts [HHS Ref. No. E–062–1996/0–US–01];

10. U.S. Patent Application No. 11/606,929 filed 1 Dec. 2006 [HHS Ref. No. E–062–1996/0–US–11];

11. U.S. Patent Nos. 6,893,869, 6,548,068 and 6,045,802 issued 17 May 2005, 15 Apr. 2003 and 4 Apr. 2000 respectively, as well as issued and pending foreign counterparts [HHS Ref. Nos. E–260–1994/1–US–03, US–02, US–01]; and

12. U.S. Patent No. 7,368,116 issued 6 May 2008 [HHS Ref. No. E–260–1994/1–US–04];

13. U.S. Patent Application No. 12/280,534 filed 21 Feb. 2007, which published as US–2009–0035266 on 5 Feb. 2009, as well as pending foreign counterparts [HHS Ref. No. E–104–2006/0–US–06];

14. PCT Application No. PCT/US2008/055185 filed 27 Feb. 2008, which published as WO 2008/106551 on 4 Sep. 2008 [HHS Ref. No. E–074–2007/0–PCT–02].

Note that some of the patent estate above is available for non-exclusive licensing only.

Cooperative Research and Development Agreement (CRADA) Opportunities

A CRADA partner for the further codevelopment of this technology in all cancers with the exception of prostate, melanoma and colorectal cancer is currently being sought by the Laboratory of Tumor Immunology and Biology, Center for Cancer Research, NCI. The CRADA partner will (a) generate recombinant poxviruses expressing specific tumor-associated antigens, cytokines, and/or T-cell costimulatory factors, (b) cooperate to analyze the recombinant poxviruses containing these genes with respect to appropriate expression of the encoded gene product(s), (c) supply adequate amounts of recombinant virus stocks for preclinical testing, (d) manufacture selected recombinant vaccines for use in human clinical trials (with the exception of trials for prostatic diseases, melanoma, and colorectal cancer), (e) submit Drug Master Files detailing the development, manufacture, and testing of live recombinant vaccines to support the NCI-sponsored IND and/or company-sponsored IND, (f) supply adequate amounts of clinical grade recombinant poxvirus vaccines for clinical trials conducted at the NCI Center for Cancer Research (CCR), and (g) provide adequate amounts of vaccines for extramural clinical trials, if agreed upon by the parties, and conduct clinical trials under company-sponsored or NCI-sponsored INDs. NCI will (a) provide genes of tumor-associated antigens, cytokines and other immunostimulatory molecules for incorporation into poxvirus vectors, (b) evaluate recombinant vectors in preclinical models alone and in combination therapies, and (c) conduct clinical trials (with the exception of trials for prostatic diseases, melanoma, and colorectal cancer) of recombinant vaccines alone and in combination therapies.

Next Step: Teleconference

There will be a teleconference where the principal investigator, Dr. Jeffrey Schlom, will discuss this technology. Licensing and collaborative research opportunities will also be discussed. If you are interested in participating in this teleconference, please call or e-mail Sabarni Chatterjee; 301–435–5587; *chatterjeesa@mail.nih.gov*. OTT will then e-mail you the date, time, and number for the teleconference.

Dated: April 29, 2009.

Richard U. Rodriguez,

Director, Division of Technology Development and Transfer, Office of Technology Transfer, National Institutes of Health.

[FR Doc. E9–10479 Filed 5–5–09; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

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National Institute on Alcohol Abuse and Alcoholism; Notice of Closed Meeting

Pursuant to section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. App.), notice is hereby given of the following meeting.