DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

[HHS Reference Nos. E–095–2000/0, 1, 2, 3 and 4]

Public Teleconference Regarding Licensing and Collaborative Research Opportunities for: A Promising Treatment for Inflammatory Arthritis Targeting the Pre-ligand Assembly Domain (PLAD) of Tumor Necrosis Factor Receptors; Michael J. Lenardo et al. (NIAID)

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

ACTION: Notice.

Technology Summary

The technology is an innovative treatment for inflammatory arthritis that involves modulating Tumor Necrosis Factor Receptor (TNFR) 1 signaling. NIH scientists have discovered that the Pre-ligand Assembly Domains (PLADs) of TNFR1 can be selectively blocked by soluble P60-PLAD protein compositions (P60 PLAD-Sol) which interfere with TNFR1 assembly thereby preventing the inflammatory effects of TNFα both *in vitro* and *in vivo*.

Technology Description

Current anti-TNFα arthritis treatments rely on the use of antibodies or fusion proteins directed against TNFα to reduce inflammation. The cytokine TNFα plays a key role in the pathogenesis of numerous autoimmune and inflammatory diseases including psoriatic, rheumatoid, and septic arthritis. It has been shown that blocking TNFα has a dramatic therapeutic effect; however, blocking TNFα also blocks TNFα's beneficial effects during immune responses that are mediated through TNFR2.

This invention involves a functional domain, which is essential for signaling involving receptors of the TNFR superfamily including TNFR–1 (p60), TNFR–2 (p80), FAS, TRAIL-R, LTR, CD40, CD30, CD27, HVEM, OX40 and DR4. PLADs can be isolated as functional polypeptides which can be useful in inhibiting the first step in TNFR mediated signaling, ligand-independent assembly of members of the TNFR superfamily. The ability to inhibit TNFR signaling suggests that these PLAD polypeptides may be useful in developing new therapeutic molecules or as therapeutic molecules themselves.

P60 PLAD-Sol has the benefit of selectively blocking only the signaling of TNFR1, not signaling mediated through TNFR2. Treatment of mice with the P60 PLAD-Sol ameliorated inflammatory joint disease with no side effects in 5 different animal models of arthritis including: collagen-induced arthritis, adjuvant and lipopolysaccharide induced arthritis, and joint disease due to TNF. Therefore, P60 PLAD-Sol may lead to novel inflammatory arthritis treatments that avoid the serious side effects associated with currently marketed therapeutics that directly block TNFα rather than TNFR1.

Competitive Advantage of Our Technology

More than 20% of the population in the USA currently seek arthritis treatment; of these over 2 million suffer rheumatic symptoms. Worldwide this figure is close to five million people. Existing commercially available anti-TNFα treatments are expensive: in the U.S. Enbrel®, Remicade®, and Humira® all cost more than $10,000 per year. In addition to this market there is the potential to treat other inflammatory based diseases such as Crohn's Disease and Multiple Sclerosis. Owing to the high price of these agents and their increased use in treatment, the market for TNFα inhibitors is expected to grow from $7.1 billion in 2005 to nearly $12 billion in 2014 in the United States, Western Europe, and Japan.

The existing TNF blockers, *e.g.*, Enbrel® (Etanercept—a dimeric fusion protein by Amgen/Wyeth), Remicade® (Infliximab—a mouse chimeric anti-TNF monoclonal antibody by J&J), and Humira® (Adalimumab—a humanized anti-TNF monoclonal antibody by Abbott) have been effective in the treatment of rheumatoid arthritis. They are beneficial in over 70% of patients including many who have not responded to Rheumatrex® (Methotrexate—an antimetabolite by STADA); however, serious and sometimes fatal side effects have been observed. In addition, the current costs of these drugs are prohibitive for many patients. This technology has the potential to be less expensive yet more effective than existing products.

For arthritis sufferers who are unresponsive to, or adversely affected by, current inflammatory arthritis treatments our technology is a new method of blocking inflammation that provides a more targeted action. Unlike the currently marketed anti-TNF medications, P60 PLAD-Sol has the potential to more effectively treat a broader range of inflammatory diseases with no known side-effects. The current anti-TNF drugs directly block the binding of TNFα to both TNFR1 and TNFR2. There is evidence that this inhibits the beneficial effects mediated by TNFR2, while arresting the disease-causing effects of TNFR1. This is because the P60 PLAD-Sol involves the use of small soluble proteins that preferentially target only the PLAD of TNFR1. In our models, a dose of a P60 PLAD-Sol (5 mg/kg) had similar effects to doses of Infliximab (10 mg/kg) and Etanercept (0.4 mg/kg) that have been used clinically in the amelioration of arthritis. As a selective TNFR1 blocking agent, this technology may avoid the serious side effects of these currently available compounds yet have enhanced efficacy.

Patent Estate

A PCT application, filed 9 February 2001 (WO 01/58953), has entered the national phase in the US, EP, AU and CA.

Next Step: Teleconference

There will be a teleconference where the principal investigator will discuss non-confidential information concerning this technology. Licensing and collaborative research opportunities will also be discussed. If you are interested in participating in this teleconference please call or email Mojdeh Bahar; (301) 435–2950; *baharm@mail.nih.gov*. OTT will then e-mail you the date, time and number for the teleconference.

Dated: October 2, 2006.

Steven M. Ferguson,

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

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Substance Abuse and Mental Health Services Administration

Current List of Laboratories Which Meet Minimum Standards To Engage in Urine Drug Testing for Federal Agencies

AGENCY: Substance Abuse and Mental Health Services Administration, HHS.

ACTION: Notice.

SUMMARY: The Department of Health and Human Services (HHS) notifies Federal agencies of the laboratories currently certified to meet the standards of Subpart C of the Mandatory Guidelines for Federal Workplace Drug Testing Programs (Mandatory Guidelines). The