the BBA to require the CPAC to submit a report on the following topics:

- Incorporation of original Medicare fee-for-service into the demonstration.
- Requirements of quality activities under the demonstration.
- Inclusion of a rural area in the demonstration.
- Requirements of a benefit structure under the demonstration.

The CPAC will also develop recommendations for how it should proceed in the future to carry out its responsibilities under the BBA.

Individuals or organizations that wish to make 5-minute oral presentations on the agenda issues should contact the Executive Director, by 12 noon, December 7, 2000, to be scheduled. The number of oral presentations may be limited by the time available. A written copy of the oral remarks should be submitted to the Executive Director, no later than 12 noon, December 11, 2000. Anyone who is not scheduled to speak, may submit written comments to the Executive Director, by 12 noon, December 11, 2000.

The meeting is open to the public, but attendance is limited to the space available. Individuals requiring sign language interpretation for the hearing impaired or other special accommodation should contact the Executive Director at least 10 days before the meeting.

(Section 4012 of the Balanced Budget Act of 1997, Public Law 105–33 (42 U.S.C.1395w–23 note) and section 10(a) of Public Law 92–463 (5 U.S.C. App.2, section 10(a))

(Catalog of Federal Domestic Assistance Program No. 93.773, Medicare—Hospital Insurance; and Program No. 93.774, Medicare—Supplementary Medical Insurance Program)

Dated: November 6, 2000.

Michael M. Hash,

Acting Administrator, Health Care Financing Administration.

[FR Doc. 00–29754 Filed 11–20–00; 8:45 am]

BILLING CODE 4120–01–U

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute: Opportunity for a Cooperative Research and Development Agreement (CRADA) Collaboration in the Identification, Characterization and Development of Inhibitors of the Smad3 Signaling Protein for Use in the Treatment of Wounds and Fibrotic Diseases Characterized by Chronic Inflammation

AGENCY: National Institutes of Health, PHS, DHHS.

ACTION: Notice.

The National Cancer Institute's Laboratory of Cell Regulation and Carcinogenesis (LCRC) has characterized the role of the Smad3 signaling molecule in wound healing and has developed several mouse models of fibrosis. NCI would like to use its expertise of Smad3 biology in a collaboration with an outside party to identify and characterize inhibitors of Smad3 activity.

SUMMARY: The National Cancer Institute (NCI) seeks a Cooperative Research and Development Agreement (CRADA) Collaborator to aid NCI in the identification and development of inhibitors of the function of the Smad3 signaling protein. Smad3 and a closely related gene, Smad2, act as nuclear transcriptional activators in response to intracellular signals from the transforming growth factor betas (TGF-betas) and activin molecules (1,2). The existence of these genes was first proposed after a screen for developmental mutations in the nematode led to the identification of three genes, sma-2, sma-3, and sma-4, that were homologs of *Drosophila* MAD, a protein with a role in the signaling of a TGF-beta superfamily ligand (3). The Smad2 and Smad3 signaling pathways play important roles in the cellular proliferation, differentiation and migration crucial to cutaneous wound healing and the induction of fibrosis in diseases characterized by chronic inflammation (4).

NCI has generated a line of mice that are homozygously deleted in the Smad3 gene ($Smad3^{ex8/ex8}$ mice). These mice have made it possible for NCI to examine the contribution of Smad3 in cutaneous wound healing. $Smad3^{ex8/ex8}$ mice survive into adulthood and show accelerated cutaneous wound healing characterized by an increased rate of re-epithelialization and a reduced local inflammatory infiltrate of monocytes and neutrophils. Thus, Smad3 appears to mediate in vivo signaling pathways that mediate key aspects of wound healing including influx of inflammatory cells and control of epithelial cell proliferation and migration. NCI's studies indicate that inhibitors of Smad3 function, such as specific, small molecule or antisense-related compounds, may accelerate cutaneous wound healing and may even be beneficial to other processes such as the treatment of extensive burns, the suppression of radiation-induced scarring, the growth of autologous skin grafts and the treatment of fibrotic diseases characterized by chronic inflammation.

NCI is looking for a CRADA Collaborator with a demonstrated record of success in the isolation and characterization of small molecule protein inhibitors. The proposed term of the CRADA can be up to five (5) years.

DATES: Interested parties should notify this office in writing of their interest in filing a formal proposal no later than January 22, 2001. Potential CRADA Collaborators will then have an additional thirty (30) days to submit a formal proposal. CRADA proposals submitted thereafter may be considered if a suitable CRADA Collaborator has not been selected.

ADDRESSES: Inquiries and proposals regarding this opportunity should be addressed to Holly Symonds Clark, Ph.D., Technology Development Specialist (Tel. #301–496–0477, FAX #301–402–2117), Technology Development and Commercialization Branch, National Cancer Institute, 6120 Executive Blvd., Suite 450, Rockville, MD 20852. Inquiries directed to obtaining patent license(s) for the technology NIH reference No. E–070–00/0, filed May 19, 2000 for ''Inhibition of Smad3 to Prevent Fibrosis and to Improve Wound Healing'' (Roberts and Ashcroft), should be addressed to Marlene Shinn M.S., J.D., Technology Licensing Specialist, Office of Technology Transfer, National Institutes of Health, 6011 Executive Blvd., Suite 325, Rockville, MD 20852, (Tel. 301–496–7056, ext. 285; FAX 301–402–0220).

SUPPLEMENTARY INFORMATION: A Cooperative Research and Development Agreement (CRADA) is the anticipated joint agreement to be entered into with NCI pursuant to the Federal Technology Transfer Act of 1986 and Executive Order 12591 of April 10, 1987 as amended by the National Technology Transfer Advancement Act of 1995. NCI is looking for a CRADA partner to aide NCI in the characterization and development of inhibitors of the function of the Smad3 signaling protein. The expected duration of the CRADA would be from one (1) to five (5) years.

The members of the transforming growth factor-beta (TGF-beta) superfamily are multi-functional growth factors that are responsible for a variety of biological processes in tissue homeostasis, differentiation, morphogenesis and development of multicellular animals (for reviews see 5, 6). They transduce their signals from the plasma membrane to nuclei of target cells through distinct combinations of a family of serine/threonine kinase receptors. Once activated by specific phosphorylation events, these receptors

transduce their signals through intercellular effectors known as the Smad proteins. In response to TGF-beta, specific Smad proteins become inducibly phosphorylated, form heteromers with a common partner, Smad4, and undergo nuclear accumulation where the complexes function as transcription factors (for reviews, see 7, 8, 9, 10). Two of the Smad proteins, Smad3 and its closely related homologue, Smad2, are downstream mediators of signals from TGF-betas 1, 2, 3 and activin, each of which has been implicated as an important factor in the cellular proliferation, differentiation and migration critical for cutaneous wound healing (11, 12).

Recently, animal models for a loss of Smad function have provided insight into the role of specific Smads in a variety of physiologic systems. NCI has created a line of mice null for Smad3 ($Smad3^{ex8/ex8}$). These mice survive into adulthood and show an accelerated rate of wound healing and an impaired local inflammatory response (13). Following full-thickness incisional wounds, the rate of wound healing was markedly accelerated in healthy $Smad3^{ex8/ex8}$ mice with complete re-epithelialization occurring by day 2 post-wounding in the $Smad3^{ex8/ex8}$ mice versus day 5 in wild-type mice, and with significantly reduced wound areas and wound widths. Total cell numbers of fibroblasts and inflammatory cells were markedly reduced in the wounds of the $Smad3^{ex8/ex8}$ mice, with intermediate numbers present in the heterozygous mice, compared with wild-type controls (13). The results from the characterization of the $Smad3^{ex8/ex8}$ mice implicate Smad3 in vivo both in the inhibition of re-epithelialization, with specific effects on keratinocyte proliferation, and in TGF-beta-mediated chemotaxis of monocytes and of neutrophils (14). NCI's results indicate that Smad3 may mediate in vivo signaling pathways that are inhibitory to wound healing, as its deletion leads to enhanced re-epithelialization and contracted wound areas. Thus, 'normal' wound healing may involve the suppression of endogenous Smad3 levels, but complete loss of this signaling intermediate, as in the $Smad3^{ex8/ex8}$ mice, further accelerates the wound-healing process. Through an extensive characterization of the $Smad3^{ex8/ex8}$ mice, NCI has shown that Smad3 is not necessary for production of fibronectin by fibroblasts, but likely does play a role in the elaboration of collagens (14). Furthermore, the improved wound healing observed in the null mice suggests that the inflammatory response is not critical for re-epithelization and wound closure but instead serves to clean wounds of infection as well as other auxiliary functions to the wound healing. Thus, through the creation and characterization of Smad3 null mice, NCI has shown that disruption of Smad3 in a clinical setting may be of therapeutic benefit in accelerating all aspects of impaired wound healing.

Preliminary studies with the Smad3 null mice indicate that they may be resistant to the induction of fibrosis in response to high dose radiation. According to these results, inhibitors of Smad3 could have clinical application in the prevention of fibrosis, including radiation-induced fibrosis, and scarring as in severe trauma and burn patients.

NCI plans to explore several types of Smad3 inhibitors including antisense oligonucleotides to the Smad3 sequence; mutated Smad3 polypeptides and peptide fragments; truncated or deleted forms of Smad3; and existing natural products or pharmaceutical chemical compounds—all of which could act to inhibit some aspect of Smad3 function. NCI is looking for a commercial partner to collaborate with the laboratory in the identification of novel Smad3 inhibitors and in the analysis of existing Smad3 inhibitors for clinical use in wound healing and in the prevention of fibrosis and scarring.

The described methods are the subject of a U.S. Provisional Patent Application, filed on May 19, 2000 by the Public Health Service on behalf of the Federal Government. Furthermore, the initial report and characterization of the invention is described in two published journal articles: Nature Cell Biology (1999) vol. 1:260–266 and Cytokine Growth Factor Rev. (2000) vol. 11(1–2):125–131.

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Under the present proposal, the overall goal of the CRADA will be to identify and characterize potential inhibitors of Smad3 function using in vitro assay systems and NCI's $Smad3^{ex8/ex8}$ null mice as a preclinical animal model. NCI speculates that the CRADA research will have two main phases including:

1. Identification and characterization of inhibitors of Smad3 function, and
2. Examination of the efficacy of the inhibitors for the treatment of various ailments and diseases.

NCI believes that this technology may have many applications including the treatment of cutaneous wounds and extensive burns and the prevention of fibrosis and scarring in diseases characterized by chronic inflammation.

Party Contributions

The role of the NCI in the CRADA may include, but not be limited to:

1. Providing intellectual, scientific, and technical expertise and experience to the research project.
2. Providing the CRADA Collaborator with information and data relating to the role of the Smad3 signaling protein in wound healing and in the development of radiation-induced fibrosis as determined through the NCI's analysis of the Smad3 null mice.
3. Providing the CRADA Collaborator with the necessary materials to collaborate in the identification and characterization of the Smad3 inhibitors.
4. Planning research studies and interpreting research results.
5. Carrying out research to analyze potential Smad3 inhibitors.
6. Publishing research results.
7. Developing additional potential applications of the identified Smad3 inhibitors.

The role of the CRADA Collaborator may include, but not be limited to:

1. Providing significant intellectual, scientific, and technical expertise or experience to the research project.
2. Planning research studies and interpreting research results.
3. Providing technical and/or financial support to facilitate scientific goals and for further design of applications of the technology outlined in the agreement.
4. Publishing research results.

Selection criteria for choosing the CRADA Collaborator may include, but not be limited to:

1. A demonstrated record of success in some or all of the following areas: molecular biology, the development of small molecule therapeutics, and high throughput screening of compounds.

2. A demonstrated background and expertise in growth factor and cytokine research.

3. The ability to collaborate with NCI on further research and development of this technology. This ability will be demonstrated through experience and expertise in this or related areas of technology indicating the ability to contribute intellectually to ongoing research and development.

4. The demonstration of adequate resources to perform the research and development of this technology (e.g. facilities, personnel and expertise) and to accomplish objectives according to an appropriate timetable to be outlined in the CRADA Collaborator's proposal.

5. The willingness to commit best effort and demonstrated resources to the research and development of this technology, as outlined in the CRADA Collaborator's proposal.

6. The demonstration of expertise in the commercial development and production of products related to this area of technology.

7. The level of financial support the CRADA Collaborator will provide for CRADA-related Government activities.

8. The willingness to cooperate with the National Cancer Institute in the timely publication of research results.

9. The agreement to be bound by the appropriate DHHS regulations relating to human subjects, and all PHS policies relating to the use and care of laboratory animals.

10. The willingness to accept the legal provisions and language of the CRADA with only minor modifications, if any. These provisions govern the distribution of future patent rights to CRADA inventions. Generally, the rights of ownership are retained by the organization that is the employer of the inventor, with (1) the grant of a license for research and other Government purposes to the Government when the CRADA Collaborator's employee is the sole inventor, or (2) the grant of an option to elect an exclusive or nonexclusive license to the CRADA Collaborator when the Government employee is the sole inventor.

Dated:November 12, 2000.

Kathleen Sybert,

Chief, Technology Development and Commercialization Branch, National Cancer Institute, National Institutes of Health.

[FR Doc. 00–29718 Filed 11–20–00; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Government-Owned Inventions; Availability for Licensing

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

ACTION: Notice.

SUMMARY: The inventions listed below are owned by agencies of the U.S. Government and are available for licensing in the U.S. in accordance with 35 U.S.C. 207 to achieve expeditious commercialization of results of federally-funded research and development. Foreign patent applications are filed on selected inventions to extend market coverage for companies and may also be available for licensing.

ADDRESSES: Licensing information and copies of the U.S. patent applications listed below may be obtained by writing to the indicated licensing contact at the Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, Maryland 20852–3804; telephone: 301/496–7057; fax: 301/402–0220. A signed Confidential Disclosure Agreement will be required to receive copies of the patent applications.

Enhanced Homologous Recombination Mediated by Lambda Recombination Proteins

Donald L. Court, Daiguan Yu, E-Chaing Lee, Hilary Ellis, Nancy A. Jenkins, Neal G. Copeland (NCI), DHHS Reference No. E–177–00/0 filed 14 Aug 2000, Licensing Contact: Dennis Penn; 301/496–7056 ext. 211; e-mail: *pennd@od.nih.gov*.

The present invention concerns methods to enhance homologous recombination in bacteria and eukaryotic cells using recombination proteins derived from bacteriophage lambda. It also concerns methods for promoting homologous recombination using other recombination proteins.

Concerted use of restriction endonucleases and DNA ligases allows in vitro recombination of DNA sequences. The recombinant DNA generated by restriction and ligation may be amplified in an appropriate microorganism such as E. coli, and used for diverse purposes including gene therapy. However, the restriction-ligation approach has two practical limitations: first, DNA molecules can be precisely combined only if convenient restriction sites are available; second, because useful restriction sites often repeat in a long stretch of DNA, the size of DNA fragments that can be manipulated are limited, usually to less than about 20 kilobases.

Homologous recombination, generally defined as an exchange of homologous segments anywhere along a length of two DNA molecules, provides an alternative method for engineering DNA. In generating recombinant DNA with homologous recombination, a microorganism such as E. coli, or a eukaryotic cell such as a yeast or vertebrate cell, is transformed with an exogenous strand of DNA. The center of the exogenous DNA contains the desired transgene, whereas each flank contains a segment of homology with the cell's DNA. The exogenous DNA is introduced into the cell with standard techniques such as electroporation or calcium phosphate-mediated transfection, and recombines into the cell's DNA, for example with the assistance of recombination-promoting proteins in the cell.

In generating recombinant DNA by homologous recombination, it is often advantageous to work with short linear segments of DNA. For example, a mutation may be introduced into a linear segment of DNA using polymerase chain reaction (PCR) techniques. Under proper circumstances, the mutation may then be introduced into cellular DNA by homologous recombination. Such short linear DNA segments can transform yeast, but subsequent manipulation of recombinant DNA in yeast is laborious. It is generally easier to work in bacteria, but linear DNA fragments do not readily transform bacteria (due in part to degradation by bacterial exonucleases). Accordingly, recombinants are rare, require special poorly-growing strains (such as RecBCD-strains) and generally require thousands of base pairs of homology. This invention teaches an improved method of promoting homologous recombination in bacteria.

In eukaryotic cells, targeted homologous recombination provides a basis for targeting and altering essentially any desired sequence in a duplex DNA molecule, such as targeting a DNA sequence in a chromosome for replacement by another sequence. This invention teaches methods useful for treating human genetic diseases, the creation of transgenic animals, or modifying the germline of other organisms.

Amelogenin Knockout Mice and Use as Models for Tooth Disease

Dr. Ashok Kulkarni et al. (NIDCR), DHHS Reference No. E–167–00/0, Licensing Contact: John Rambosek; 301/