

of detecting nucleic acid and amino acid sequences as well as modulators of such PTC taste receptors. The ability to taste PTC has been shown to be correlated with the ability to taste other bitter substances, many of which are toxic. Thus variation in PTC perception and knowledge of the genetic basis of these variants can be used to aid the development of a variety of taste improvements in foods and orally administered medications.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Government-Owned Inventions; Availability for Licensing

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

ACTION: Notice.

SUMMARY: The inventions listed below are owned by an agency 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.

Thalidomide Analogs

Nigel Greig (NIA),
U.S. Provisional Patent Application
filed 17 Sep 2003 (DHHS Reference
No. E-189-2003/0-US-01),
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Inflammatory processes associated with the over-production of cytokines, particularly of tumor necrosis factor-alpha (TNF- α), accompany numerous

neurodegenerative diseases, such as Alzheimer's disease and ALS, in addition to numerous common systemic conditions, such as rheumatoid arthritis, septic shock, graft-versus-host disease, Crohn's disease and erythema nodosum leprosum (ENL). TNF- α has been validated as a drug target with the development of the inhibitors Enbrel (Amgen, Thousand Oaks, CA/Wyeth, Princeton, NJ) and Remicade (Centocor, Malvern, PA/Schering-Plough, Orange, NJ) as prescription medications for rheumatoid arthritis. Both, however, are large macromolecules and hence are expensive to produce, require direct intravenous or subcutaneous injection, and have negligible brain access. The classical orally active drug, thalidomide (N- α -phthalimidoglutarimide), a glutamic acid derivative, is being increasingly used in the clinical management of a wide spectrum of immunologically-mediated and infectious diseases, and cancers. Its clinical value in treating ENL derives from its TNF- α inhibitory activity. Specifically, it inhibits TNF- α protein expression at the post-transcriptional level by facilitating turnover of the mRNA (Sampaio *et al.*, 1991 & 1993; Moreira *et al.*, 1993). More recent research has shown similar inhibitory action of COX2 protein expression (Fujita *et al.*, 2001). These actions are mediated post-transcriptionally via AU-rich elements found in the 3' untranslated regions (3'-UTRs) of each mRNA (Kruys *et al.*, 1994; Chen *et al.*, 1995). Thalidomide's anti-angiogenesis activity derives from its inhibitory actions on basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) (D'Amato *et al.*, 1994; Figg *et al.*, 2002). The agent, additionally, acts as an inhibitor of the transcription factor, NF κ B and a co-stimulator of both CD8+ and CD4+ T cells (Haslett *et al.*, 1998). However, the action of thalidomide to lower TNF- α levels and inhibit angiogenesis is not particularly potent and it therefore represents an interesting lead compound for medicinal chemistry.

Novel structural modification of thalidomide was achieved towards the discovery of original and potent isosteric analogues. The present invention relates to thalidomide analogues and, in particular, thiothalidomides (sulfur-containing thalidomide analogues), methods of synthesizing the analogues, and methods for using the analogues to modulate TNF- α and angiogenesis activities in a subject. Disclosed analogues potently inhibited TNF- α secretion, compared to thalidomide, via

post-transcriptional mechanisms that decreased TNF- α mRNA stability via its 3'-UTR (Zhu *et al.*, 2003). Actions to inhibit angiogenesis were determined in widely accepted ex vivo assays.

Methods and Compositions for Treating Diseases and Disorders Associated With Natural Killer T-Cells

John R. Ortaldo, Robert H. Wiltout
(NCI)

U.S. Provisional Application No. 60/
488,339 filed 17 Jul 2003 (DHHS
Reference No. E-282-2002/0-US-01)
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435-5031; joycec@mail.nih.gov.

The invention relates to the discovery that C12 beta-D-galactosyl ceramide may be used to deplete or inactivate NKT cell populations. These findings suggest methods for using C12 beta-D-galactosyl ceramide to treat conditions that would benefit from depletion of NKT cells, such as certain auto-immune diseases (*e.g.* lupus, MS) and AIDs.

The presence of NKT cells can be associated with either beneficial effects or pathology. Deficiencies in NKT cells are associated with at least some types of autoimmune disease, including type 1 diabetes and autoimmune gastritis in mice. In contrast, NKT cells augment autoantibody secretion and lupus development in lupus-prone mouse models and therefore lupus patients may benefit from the depletion of NKT cells. The remission state of multiple sclerosis (MS) is also associated with decreased levels of NKT cells, suggesting NKT cell depletion as a method of treatment for MS.

The above-mentioned invention is available for licensing on an exclusive or a non-exclusive basis.

Leu574 of HIF-1 α as a Molecular Basis for Therapeutic Application

L. E. Huang (NCI)
U.S. Provisional Application No. 60/
465,565 filed 25 Apr 2003 (DHHS
Reference No. E-281-2002/0-US-01)
Licensing Contact: Catherine Joyce; 301/
435-5031; joycec@mail.nih.gov.

The hypoxia-inducible factor 1 (HIF-1) is a transcription factor that plays a pivotal role in cellular adaptation to oxygen availability. HIF-1 α protein is a subunit of HIF-1. Although the gene for HIF-1 α is constitutively expressed, it is an extremely short-lived protein under normoxic conditions and is targeted for destruction via the proteasome pathway by an E3 ubiquitin ligase (the VHL protein).

The invention relates to the discovery that mutations or deletions of Leu574 result in a more stable form of HIF-1 α . Therefore, the invention relates