intracellular target of LF remained unknown until recently when NIH scientists discovered that LF proteolytically inactivates mitogen activated protein kinase kinase 1 and 2 (MAPKK1, 2). Using oocytes of the frog Xenopus laevis as well as tumor derived NIH3T3 (490) cells expressing an effector domain mutant form of the human V12Ha-Ras oncogene these scientists demonstrated that LF induced proteolysis of MAPKK 1 and 2, resulting in their irreversible inactivation. MAPKK 1 and 2 are components of the mitogen activated protein kinase (MAPK) signal transduction pathway, an evolutionarily conserved pathway that controls cell proliferation and differentiation in response to extracellular signals and also plays a crucial role in regulating oocyte meiotic maturation. Further, the MAPK pathway has been shown to be constitutively activated in many primary human as well as in tumor-derived cell lines. Consistent with this, treatment of V12Ha-Ras transformed NIH 3T3 cells with LeTx inhibits cell proliferation and causes their reversion to a non-transformed phenotype.

This invention specifically relates to in vitro and ex vivo methods of screening for modulators, homologues, and mimetics of LF mitogen activated protein kinase kinase (MAPKK) protease activity. Applications for this technology could be:

- A novel tool (LF) for the study of the cellular role of the MAPK pathway in normal or tumor cells.
- Investigation of LF for developing inhibitors for cancer therapy. By analyzing structural-functional relationships, additional compounds with improved specificity, increased potency, and reduced toxicity can be generated. Mimetics which block MAPKK activity or the determination of mechanisms of regulation of proteases that target MAPKK at or near the same site targeted by LF could be developed.
- A protease-based assay for LF by using a peptide to test for LF cleavage. There is no commercial test for anthrax. This assay could be used for testing soldiers for anthrax exposure.

Characterization of the interaction between LF and MAPKK at the amino acid level may lead to the generation of inhibitors which may prove useful in treating anthrax.

Inventors: Nicholas S. Duesbery (NCI), Craig Webb (NCI), Stephen H. Leppla (NIDCR), George F. Vande Woude (NCI).

Patent Status:

Vaccine for Shigella sonnei

Description of Technology: Shigellosis, an inflammatory enteric infection is on the World Health Organization’s priority list of disease to be prevented. It can be prevented by O-specific polysaccharide (O-SP)-protein conjugate vaccines in adults. But the highest incidence and severity of S. sonnei shigellosis is in young children and the O-SP-protein conjugate that was effective in adults cannot overcome the age-related immunogenicity of vaccines in this age group. Thus, a better immunogen is needed.

The immunogen claimed in this application uses O-SP formed by isolation of low molecular mass of O-SP-core fragments from the native product that allows a conjugate to be formed with a “sun” configuration as opposed to “lattice” type conjugates made previously, based on a synthetic saccharide conjugate of S. dysenteriae type 1 that induced significantly higher antibody levels than the “lattice” type conjugate. IgG antibody levels induced in young outbred mice with the “sun” configuration S. sonnei conjugate were higher than conjugates made with the full length O-SP.

This application claims the vaccine compositions described above, methods of making the vaccine compositions of the technology, and methods of preventing and/or treating Shigellosis.

Application: Development of Shigella sonnei vaccines and diagnostics.

Advantages: Known regulatory path for conjugate vaccines, potential reduction in number of doses of vaccine, pediatric vaccine.

Development Status: Vaccine candidates have been synthesized and preclinical studies have been performed.

Inventors: John B. Robbins (NICHD), Rachel Schneerson (NICHD), Joanna Kubler-Kiehl (NICHD), Christopher P. Mocca (NICHD), et al.

Publications:

Radiotracers for Imaging P-glycoprotein Transporter Function

Description of Technology: This invention offers technology to help treat certain brain diseases, such as Alzheimer’s disease and Parkinson’s, and may lead to more effective and personalized treatments. P-glycoprotein transporter (P-gp) acts as a pump at the blood-brain barrier to exclude a wide range of xenobiotics (e.g., toxins, drugs, etc.) from the brain and is also expressed in a tumor in response to exposure to established/prospective chemotherapeutics (a phenomenon known as multidrug resistance; MDR). The instant invention relates to compounds that are avid substrates for P-gp, and their preparation and use as radiotracers for imaging P-gp function in vitro and in vivo.

Applications: These radiotracers have potential application for investigating the function of P-gp at the blood-brain barrier for human subjects and patients in relation to neuropsychiatric disorders and in cancer. Their application may lead to a better general understanding of the role of P-gp in the unfolding of certain brain diseases (e.g., Alzheimer’s disease, Parkinson’s disease), and ultimately to more effective and personalized treatment. Likewise, these radiotracers may be applied in oncology to help understand MDR and its clinical manifestation, and to help seek out cancer therapies that avoid MDR.

Advantages: This class of radiotracer, typified by the described [11 C]dLop, is designed to restrict the formation of radiometabolites that would obstruct the measurement of P-gp function at the blood-brain barrier or at tumors. In this sense these radiotracers are vastly superior to progenitors (e.g., [11 C]verapamil, [11 C]loperamide), which can only give qualitative not quantitative information.

Development Status: Radiotracer studies in human subjects are in progress. Longer-lived versions of the radiotracers are in development.

Market: These radiotracers may be of interest to those wishing to market and/or apply such radiotracers in the medical imaging field.

Inventors: Victor W. Pike, Robert B. Innis, Sami S. Zoghbi, and Neva Lazarova (NIMH).

Publications:


Licensing Contact: RC Tang, JD, LLM: 301–435–5031; tangr@mail.nih.gov. Collaborative Research Opportunity: The National Institute of Mental Health Molecular Imaging Branch is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize radiotracers for imaging P-gp function. Please contact Victor Pike at pikev@mail.nih.gov for more information.

Dated: March 24, 2009.

Richard U. Rodriguez, 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

National Institutes of Health

Center for Scientific Review; Notice of Closed Meetings

Pursuant to section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), notice is hereby given of the following meetings.

The meetings will be closed to the public in accordance with the provisions set forth in sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C., as amended. The grant applications and the discussions could disclose confidential trade secrets or commercial property such as patentable material, and personal information concerning individuals associated with the grant applications, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

Name of Committee: Center for Scientific Review Special Emphasis Panel; Molecular Neuroscience.

Date: April 20–21, 2009.

Time: 9 a.m. to 3 p.m.

Agenda: To review and evaluate grant applications.

Place: National Institutes of Health, 6701 Rockledge Drive, Bethesda, MD 20892 (Virtual Meeting).

Contact Person: Deborah L. Lewis, PhD, Scientific Review Officer, Center for Scientific Review, National Institutes of Health, 6701 Rockledge Drive, Room 4118, MSC 7850, Bethesda, MD 20892, (301) 435–1224, lewisdeb@nigms.nih.gov.

Name of Committee: Center for Scientific Review Special Emphasis Panel; Topics in Developmental, Cellular and Molecular Biology.

Date: April 20, 2009.

Time: 2 p.m. to 4 p.m.

Agenda: To review and evaluate grant applications.

Place: National Institutes of Health, 6701 Rockledge Drive, Bethesda, MD 20892 (Telephone Conference Call).

Contact Person: Sherry L. Dupere, PhD, Scientific Review Officer, Center for Scientific Review, National Institutes of Health, 6701 Rockledge Drive, Room 5136, MSC 7843, Bethesda, MD 20892, (301) 435–1614, dupere@nih.gov.

Name of Committee: Center for Scientific Review Special Emphasis Panel; Member Conflict Review for UKDG Study Section.

Date: April 27, 2009.

Time: 1 p.m. to 3 p.m.

Agenda: To review and evaluate grant applications.

Place: National Institutes of Health, 6701 Rockledge Drive, Bethesda, MD 20892 (Telephone Conference Call).

Contact Person: Rass M. Shayiq, PhD, Scientific Review Officer, Center for Scientific Review, National Institutes of Health, 6701 Rockledge Drive, Room 2182, MSC 7818, Bethesda, MD 20892, (301) 435–2359, shayiqr@csr.nih.gov.

Name of Committee: Center for Scientific Review Special Emphasis Panel; Member Conflict: Memory and Neuroendocrinology.

Date: April 29, 2009.

Time: 3 p.m. to 5 p.m.

Agenda: To review and evaluate grant applications.

Place: National Institutes of Health, 6701 Rockledge Drive, Bethesda, MD 20892 (Virtual Meeting).

Contact Person: Edwin C. Clayton, PhD, Scientific Review Officer, Center for Scientific Review, National Institutes of Health, 6701 Rockledge Drive, Room 50950, MSC 7844, Bethesda, MD 20892, (301) 402–1304, claytone@csr.nih.gov.