Synthetic Macrolides Inhibit Breast Cancer Migration

Description of Technology:

This technology relates to the synthesis of several novel macrocylic compounds (macrolides) built upon a quinic acid-containing scaffold, which are potent inhibitors of tumor cell migration. Specifically, the new molecules have been shown to inhibit breast cancer cell migration *in vitro.*

Tumor metastasis or cell migration is a multi-step process in which primary tumor cells spread or migrate by invading adjacent tissues and/or metastasizing to distance sites. Thus, one approach to cancer treatment may be the inhibition of tumor migration. The initial observation that migrastatin, a macrolide natural product first isolated from a Streptomycete, inhibits tumor cell migration gave rise to the synthesis of the analogs with increased potency and tumor cell selectivity reported here.

Applications:

These compounds may be the basis for new antimetastatic and antiangiogenic drugs. Some of the novel macrolides that have been designed and synthesized inhibit tumor cell migration with low nanomolar to sub-micromolar IC_{50} values via a mechanism that appears to be similar to that of migrastatin and its analogs. The synthetic protocol used is straight forward and relatively high yielding, and has the potential to be further simplified.

The new compounds may be used to treat a pathologic condition that may be ameliorated by inhibiting or decreasing cell migration or metastasis, to decrease anchorage-dependent growth of tumor cells, or to treat any pathologic condition characterized by neovascularization.

Advantages:

The new molecules have been shown to inhibit breast cancer cell migration *in vitro*. Breast cancer is the most common female cancer in the United States, the second most common cause of death in women and the main cause of death in women ages 45 to 55. Despite early diagnosis and treatment, recurrence of the cancer including distant tumor growth or metastases is common. Accordingly, there is a need for compounds, such as those described in this invention, that inhibit cell migration and angiogenesis.

Development Status:

- Synthesis of several analogs has been carried out.
- Migration of breast cancer cells has been demonstrated to be inhibited *in vitro* at sub-micromolar IC_{50} values.
- The lead compound has been demonstrated not to be cytotoxic at levels up to 100 micromolar.
- Scaled up synthesis of the most potent macrolide is presently being scaled up to enable for future testing in a mouse model of breast cancer.

Inventors:

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Publication:

Metaferia, BB, Chen, L, Baker, H, Huang, X-Y, Bewley, CA Synthetic Macrolides that Inhibit Breast Cancer Cell Migration *in vitro.* J Am Chem Soc. 2007 Mar 7;129(9):2434-5. Epub 2007 Feb 13. (No abstract available.)

Patent Status:

DHHS Reference No. E-098-2007, a provisional application has been filed.

Licensing Status:

Available for exclusive or non-exclusive licensing

Licensing Contact:

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Collaborative Research Opportunity:

The National Institute of Diabetes and Digestive and Kidney Diseases, Laboratory of Bioorganic Chemistry is seeking parties interested in collaborative research to develop larger scale syntheses of the most potent macrolides and/or analogs thereof, and to conduct toxicology and other efficacy studies related to these macrolides. Please contact Dr. Carole Bewley at caroleb@mail.nih.gov or Rochelle S. Blaustein at Rochelle.Blaustein@nih.gov for more information.

Research Focus and Selected Publications for Principal Investigator

Carol A. Bewley, Ph.D. Laboratory of Bioorganic Chemistry

The primary research interests of Dr. Bewley's laboratory are (1) multi-faceted studies of biologically active natural products, also known as secondary metabolites, (2) the design of peptide and protein inhibitors and probes of HIV-1 entry, and (3) the discovery and characterization of novel carbohydrate binding proteins from under-studied sources.

Natural products chemistry. The members of Dr. Bewley's laboratory have observed that natural products are an ideal starting point for identifying new inhibitors of macromolecular receptors and biological processes. Ongoing projects include isolation and complete structure elucidation of natural product inhibitors of mycobacterial enzymes and HIV-1 membrane fusion using multidimensional NMR and modern spectroscopic techniques; determination of mechanism of action using bioassays and biophysical techniques; determination of the structural basis of activity by NMR methods; and, for some cases, structure-guided design and synthesis of natural product mimics or analogs.

Peptide and protein inhibitors of HIV-1 entry. A simplistic but generally accepted model for the initial step of HIV infection, or HIV-1 envelope-mediated membrane fusion, involves stepwise binding of the surface envelope glycoproteins gp120/gp41 to cellular receptors CD4 and CCR5 or CXCR4. Peptides and proteins derived from these receptors can block HIV-1 fusion, can provide valuable mechanistic probes for studying fusion events, and can elicit antibodies directed toward these molecules. Current projects include engineering stable trimeric gp41 N-helices as inhibitors and immunogens, chemical synthesis of post-translationally modified coreceptor-derived peptides and analogs, and high resolution structural studies of each.

Novel carbohydrate-binding proteins. Protein-carbohydrate interactions play a critical role in countless biological processes and recognition events ranging from sperm-egg interactions leading to fertilization, leukocyte homing during the course of inflammation, and trafficking of tumor cells during metastasis. Alternatively, the vast majority (if not all) of microorganisms and pathogens display specific glycan structures and/or carbohydrate binding proteins on their cell or membrane surfaces. This project involves discovery of novel carbohydrate binding proteins isolated from under-studied sources such as cyanobacteria and eubacteria, and comprehensive studies of carbohydrate specificity and recognition for these proteins by glycan profiling and biophysical techniques, evaluation of antimicrobial or antiviral activities and high-resolution structure determination by NMR or X-ray crystallography.

Publications:

1. Louis JM, Bewley CA, Gustchina E, Aniana A, Marius Clore G Characterization and HIV-1 Fusion Inhibitory Properties of Monoclonal Fabs Obtained From a Human Non-immune Phage Library Selected Against Diverse Epitopes of the Ectodomain of HIV-1 gp41. J Mol Biol (353): 945-51, 2005. [Full Text/Abstract]

2. Gustchina E, Louis JM, Bewley CA, Clore GM. Synergistic inhibition of HIV-1 envelope-mediated membrane fusion by inhibitors targeting the N and C-terminal heptad repeats of gp41. J Mol Biol. 2006 Dec 1;364(3):283-9. [Full Text/Abstract]

3. Williams DC Jr, Lee JY, Cai M, Bewley CA, Clore GM Crystal structures of the HIV-1 inhibitory cyanobacterial protein MVL free and bound to Man3GlcNAc2: structural basis for specificity and high-affinity binding to the core pentasaccharide from n-linked oligomannoside. J Biol Chem (280): 29269-76, 2005. [Full Text/Abstract]

4. Bewley CA, Ray S, Cohen F, Collins SK, Overman LE Inhibition of HIV-1 envelope-mediated fusion by synthetic batzelladine analogues. J Nat Prod (67): 1319-24, 2004. [Full Text/Abstract]

5. Bewley CA, Cai M, Ray S, Ghirlando R, Yamaguchi M, Muramoto K New carbohydrate specificity and HIV-1 fusion blocking activity of the cyanobacterial protein MVL: NMR, ITC and sedimentation equilibrium studies. J Mol Biol (339): 901-14, 2004. [Full Text/Abstract]