Chulabhorn Research Institute and Chulabhorn Graduate Institute

Special Lecture

Sialyltransferase Inhibitors Suppress Cancer Metastasis in Vitro and in Vivo

by

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Laboratory of Medicinal and Bioorganic Chemistry
Institute of Chemistry
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TAIWAN

10:00 – 11:30

on

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at

Room 606, 6th Floor, Service Building
Title: Sialyltransferase Inhibitors Suppress Cancer Metastasis in Vitro and in Vivo

Abstract:

Alteration of sialylation in cell surface is known to play an important role in tumor cell progression, invasion and metastasis. Modifications of sialylation in vivo are mediated by several glycoprotein- and glycolipid-specific sialyltransferases (STs). Overexpression of STs has been implicated in physiological and pathological conditions associated with tumor metastasis. For example, hypersialylation of $\beta_1$ integrins through ST6Gal-I promotes cancer progression by up-regulating cell motility in vitro, then the absence of hypersialylation favors carcinoma differentiation in vivo. It is now clear that ST3Gal-I is also acting as a tumor promoter in breast cancer and exerts its effect in tumor development in transgenic mice model. Recently, pioneering studies have shown that $\alpha$-2,6-ST (ST6GalNAcV) can mediate breast cancer metastasis to the brain. Thus, the discovery of pharmacological ST inhibitors could be of great interest.

In an effort to explore cell-permeable and low cytotoxic ST inhibitors for alteration of sialic acids on cancer cell surfaces, the development of nanomolar inhibitors, peptidyl lithocholic acid derivatives, of STs was achieved and some of these inhibitors were found to have significant effects in not only inhibition of breast cancer cell migration in vivo but also decrease of sialoglycoproteins formation via a mechanism that modulates ST function in vitro and might subsequently regulates the biological half-life time of glycoproteins. We have shown that ST inhibitors suppress cancer cell metastasis in vitro and in vivo partly through inhibition of ST activity to attenuate integrin sialylation, thus inhibiting FAK/paxillin signaling activity.
Basic information

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1. Education

• Ph.D. (Chemistry, Advisor: Lawrence M. Sayre), Case Western Reserve University, OH, USA, 1992/8 – 1997/6.
• M.S. (Chemistry, Advisor: Lilian Liu Kao), National Taiwan Normal University, Taipei, Taiwan, 1986/9–1989/6.
• B.S. (Chemistry), National Taiwan Normal University, Taipei, Taiwan, 1981/9–1986/6.

2. Current position and professional experience

• Adjunct Associate Professor, Doctoral Degree Program in Marine Biotechnology, National Sun Yat-Sen University, Kaohsiung 804, TAIWAN (2011/2– ).
• Associate Research Fellow, Institute of Chemistry, Academia Sinica (2007/4– ).
• Assistant Research Fellow, Institute of Chemistry, Academia Sinica (2001/7–2007/4 ).
• Postdoctoral Research Fellow (with Prof. Frank M. Rauschel), Texas A&M University, TX, USA (1999/7-2001/6).
• Postdoctoral Research Fellow (with Prof. Harry Morrison), Purdue University, IN, USA (1997/7-1999/6).
• Teaching Assistant, National Taiwan Normal University, Taipei, Taiwan (1991/7-1992/6).
• Graduate Research Assistant, National Taiwan Normal University, Taipei, Taiwan (1986/7-1989/6).
• Teaching Assistant and Undergraduate Research Assistant, National Taiwan Normal University, Taipei, Taiwan (1984/9-1986/6).

3. Research experience (before 2001/7-)

• Organic Synthesis:
Synthesis of chiral steroid derivatives, pentodilysine (pen K<sub>2</sub>, a Maillard crosslink from aging lens), E, Z-ethylidene-2-(methoxy)-bicyclo[2,2,1]hept-2-ene, E-epoxyurocanic acid derivatives, fluorescein isothiocyanate-histamine, 9-cyanothiopyronine hydrochloride, <sup>13</sup>C-“high-potential” flavins, vinca alkaloids and indole derivatives.

- **Photochemistry and Material Science:**
  Developing “antenna chromophores” to harvest photons and mapping the steroid photonic network; Studies of photonic wire in zeolite.

- **Agents for Photodynamic Therapy:**
  Design and synthesis of silicon containing new chemical entities for photodynamic therapy (PDT).

- **Mechanisms of Enzymes and Rational Design of Medicinal Agents:**
  Research had involved the studies of mechanism of monoamine oxidase by using chemical models and the exploration of horseradish peroxidase's molecular mechanism of action. Design and synthesis of mechanism-based inactivators and inhibitors.

- **Protein Mutagenesis and Enzymatic Synthesis:**
  Research focuses on rationally engineered mutants of phosphotriesterase for synthesis of chiral organophosphates, organophosphonates and organophosphonothionates. Exploration of reversal mutants of phosphotriesterase by enantioselective fluorogenic assay. Conversion of prochiral compounds into individual enantiomers and application of enzymatic synthesis in organic synthesis.

### 4. Laboratory: Research interests (after 2001/7-)

- **Drug Discovery in Antimetastatic and Antiproliferative Agents:**
  Expanding access to lead identification through natural product screening and organic synthesis allows the discovery of invaluable new chemical entities against cancers.

- **Enzyme Kinetics and Mechanism:**
  Elucidation of catalytic mechanism for proton relay system and its biological role *in vitro* and *in vivo*.

- **Enzymatic Bioremediation:**
  Discovery of new functions of proteins to detoxify the environmental contaminants (insecticides) and exploration of detoxification pathways.

- **Cellular (Animal) Studies:**
Identification of cellular target protein, pathway and drug metabolites in vitro (bionanotechnology strategy) and in vivo.

- Artificial enzyme:
  Establishment of the catalytic power of hydrogenases or hydrolases using an artificial catalyst, mimic of the active site complex of metalloenzyme.

5. Major awards and honors

- 2011: Received an Asian Core Program (ACP) Lectureship Award (to Thailand) at The 6th International Conference on Cutting-Edge Organic Chemistry in Asia (ICCEOCA-6) and The 2nd New Phase International Conference on Cutting-Edge Organic Chemistry in Asia (NICCEOCA-2), 11-15 December 2011, Hong Kong.
- 2009 24th biomedical Joint Annual Conference Poster Award, 2009年第24届生物醫學聯合學術年會優秀看板論文壁報獎競賽"優良看板論文壁報獎" (江吉祥, 李文山*, 洪文俊*; Inhibition of sialylation of beta1 integrin and CXCR4 by a lithocholic acid-based sialyltransferase inhibitor suppresses cancer metastasis).
- Academic Research Award (Teaching Assistant level), National Science Council, Taiwan, 1987.
- Academic Research Award (Teaching Assistant level), National Science Council, Taiwan, 1986.

6. Publications


13. “Application to the Understanding of Parasite’s Defense System and Route to the Discovery of Potent Glutathione S-Transferase Inhibitors”, Wei-Jen Lo, Yu-Ching Chiou, Yu-Ting Hsu, Wing See Lam, Ming-Yun Chang, Shu-Chuan Jao, and Wen-Shan Li, Bioconjugate Chem. 2007, 18, 109-120.


7. **Patents**


8. **Technical Report:**


2. 探討酵素的新功能, 李文山, 2007生物技術產業年鑑, 產業論壇, 1-16.

**Appendix:**