

Epigallocatechin gallate prodrugs as anticancer agents

Information Summary

| | |
|----------------------|--|
| Reference code: | ROI 05062/05063 |
| Technology overview: | The invention provides prodrugs of (-)-Epigallo catechin gallate derivatives that overcome the low absorption of the natural product. The mechanism is mediated in part by inhibition of the proteasome. |
| Application: | The preferred compound is indicated for breast cancer and androgen independent prostate cancer with possibility of other tumor indications. |
| Validation: | preclinical efficacy against human tumors in mouse xenograft models. Safety assessment and pilot scale synthesis |
| Inventor: | Chan Tak-Hang ; Dou Q. Ping et. al |
| Opportunity: | Exclusive license to extensive patent portfolio. |
| Contacts: | John DiMaio Ph.D. (514) 398-8949 john.dimaio@mcgill.ca |

Technology Description

The invention provides prodrugs of (-)-Epigallo catechin gallate derivatives that overcome the documented low absorption of the natural product. The compounds of the invention exhibit enhanced cellular uptake, induce apoptosis and exhibit potent activity in tumor xenograft models at concentrations where the natural product (-)-EGCG is inactive. The preferred compound has been demonstrated in animal models to have superior tumor reduction activity than (-)-EGCG in CWR22R xenograft (an androgen

independent prostate cancer) and in MDA-MB-231 human cancer breast cells in mice.

The invention also provides a simple process of manufacture of the preferred compounds.

Medical and market need:

Catechins are natural product extracts. The Catechins (-)-epigallocatechin-3-gallate (EGCG), (-)-epigallocatechin (EGC), epicatechin-3-gallate (ECG) and (-)epicatechin (EC) are the principal polyphenolic constituents of green tea. (-)-EGCG is the most abundant catechin, which has been reported to be chemopreventive at high doses and exhibit antibacterial, antiviral, and hypocholesterolemic effects. However, (-)-EGCG has low bioavailability. In one study (-)-EGCG showed 0.012% bioavailability following oral administration in rodent. This property renders these natural products attractive nutraceuticals but ineffective as potential therapeutics, except at very high doses.

Opportunity:

Catechins are natural product extracts. The Catechins (-)-epigallocatechin-3-gallate (EGCG), (-)-epigallocatechin (EGC), epicatechin-3-gallate (ECG) and (-)epicatechin (EC) are the principal polyphenolic constituents of green tea. (-)-EGCG is the most abundant catechin, which has been reported to be chemopreventive at high doses and exhibit antibacterial, antiviral, and hypocholesterolemic effects. However, (-)-EGCG has low bioavailability. In one study (-)-EGCG showed 0.012% bioavailability following oral administration in rodent. This property renders these natural products attractive nutraceuticals but ineffective as potential therapeutics, except at suprathreshold doses.



Dr. Tak-Hang (Bill) Chan

Professor Emeritus, McGill University

B. Sc. (University of Toronto, 1962) M. A.

(Princeton University, 1963) Ph. D.

(Princeton University, 1965)

Merck Sharpe & Dohme Award,

1982 Senior Killam Fellow,

1983-85 R. U. Lemieux Award,

1993 Fellow, Royal Society of Canada

Honorary Professor: Academia Sinica, Peking University, Lanzhou University

Professeur émérite, Université McGill

B.Sc., University of Toronto (1962)

M.A., Princeton University (1963)

Ph.D., Princeton University (1965)

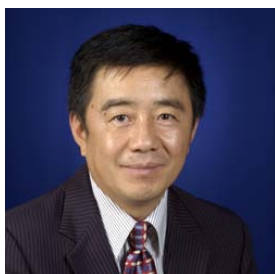
Prix Merck Sharpe & Dohme,

1982, Boursier principal Killam,

1983-1985, Titulaire du prix R. U. Lemieux Award,

1993 Boursier, Société royale du Canada

Professeur honoraire, Academia Sinica, Peking University, Lanzhou University



Dr. Q. Ping Dou

Professor, Wayne State University

PhD in Chemistry from Rutgers University in 1988,

Postdoctoral training in molecular biology and pharmacology at Dana-Farber Cancer Institute and Harvard Medical School

Faculty member of the University of Pittsburgh, University of Pittsburgh Cancer Institute, H. Lee Moffitt Cancer Center & Research Institute, and the University of South Florida. Currently Barbara Ann Karmanos Research

Institute; Wayne State University. Research areas of cell cycle, apoptosis, proteasome and green tea, anticancer/chemopreventative drug discovery. Current research focuses on molecular targeting and the cancer-preventative mechanisms of green tea polyphenols, soy isoflavones, tannic acid and other natural products.

Professeur, Wayne State University

Ph.D. Chimie, Rutgers University (1988)

Stage postdoctoral en biologie moléculaire et en pharmacologie au Dana-Farber Cancer Institute et à la Harvard Medical School

Membre de la faculté de l'University of Pittsburgh, de l'University of Pittsburgh Cancer Institute, du H. Lee Moffitt Cancer Center & Research Institute et de l'University of South Florida. Actuellement en service au Barbara Ann Karmanos Research Institute; domaines de recherche de la Wayne State University : cycle cellulaire, apoptose, protéasome et thé vert et découverte d'un médicament anticancéreux/chimio-préventif. Les recherches actuelles se concentrent sur le ciblage moléculaire et les propriétés anticancéreuses des polyphénols que contient le thé vert, des isoflavones de soya, de l'acide tannique et autres produits naturels.