

# **Teaser Memorandum**

Korea Institute of Science and Technology

A PHARMACEUTICAL COMPOSITION CONTAINING DAURINOL FOR THE PREVENTION AND TREATMENT OF CANCERS



### **Executive Summary**

- Founded in 1966, KIST is a premier multi-disciplinary research institute in Korea. Our goal is to research, develop, and transition creative, original technologies that are necessary to advance our nation's science and technology base.
- We are going to apply the National R&D program to further develop daurinol as a anti-cancer agent which has lower hematological toxicity. Since we are seeking a partner company who recognizes the potential of daurinol.

#### Industry Sector :

Human Health/ Therapeutics/ Intervention

Therapeutic Target :

Cancer

#### State of Development :

*In vivo* test completed, Cancer target identified, Mode of action studied, Preclinical studies being planned

#### Key Technology Highlights

Potent anti-tumor effects with low side effects such as hematological toxicity

Daurinol is a plant arylnaphthalene lignan, that has potent anticancer effects with very low side effects such as myelosuppression. It doest not induce damage on normal tissues including liver, kidney, and colon. Myelosuppression, a decrease of blood cell production due to bone marrow cell abnormalities, is one of the most common and serious side effects of cancer chemotherapy.

Daurinol is a natural plant lignan from ethnopharmacological plant

Daurinol is a natural product isolated from *Haplophyllum dauricum* growing in Mongolia. According to the ethnopharmacological study, *H. dauricum* has historically been used to treat tumors in Russia.

A novel alternative to the clinical anti-cancer agent etoposide

Despite its potent anti-tumor activity, clinical use of etoposide is limited due to its side effects, including myelosuppression and the development of secondary leukemia.

#### Proposal Abstract

- □ Daurinol, a novel plant arylnaphthalene lignan, is a promising potential candidate for the anti-cancer agent with side effects that are less severe than those of etoposide, a synthetic aryltetraline lignan. Daurinol is isolated from the Russian or Mongolian medicinal plant, *Haplophyllum dauricum*, which historically has been used to treat tumors.
- □ We also speculated that daurinol has less side effects compared to etoposide which is known to attenuate cancer cell proliferation via the inhibition of DNA synthesis. Finally, we confirmed the *in vivo* anti-tumor effects and side effects of daurinol and etoposide in nude mice xenograft models. Daurinol displayed potent anti-tumor effects without any significant loss of body weight and changes in hematological parameters, whereas etoposide treatment led to decreased body weight and white blood cell, red blood cell, and hemoglobin concentration.

#### **IP Owner Summary**

#### Korea Institute of Science and Technology

Business Field :

Natural Medicine

Discovery of pharmaceutical materials from natural products to treat cancer, dementia, obesity, diabetes.

Functional Food

Developing functional food materials from the prevention of cancer and senile diseases using domestic and foreign plants including edible wild vegetable.

#### Personal Description of Researcher

□ Name : Chu Won Nho

- Present Position :
  - Head of Functional Food Center
- Major : Nutritional toxicology
- □ Research interest :
- Cancer chemoprevention, Natural products Office address:
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#### Market Feasibility

- Domestic and global market size:
  - Domestic market size : \$2 billion
  - Global market size : \$80 billion

 Domestic and foreign market opportunity (competitors and competing product) : opportunity available on worldwide or domestic marketing

#### Trend & Partnership

- Future outlook and trends related to technology : Natural anti-cancer drug are getting the spotlight in the international market.
- Technology Transfer and commercialization conditions : Exclusive or non-exclusive on worldwide or domestic basis
- Type of business relationship sought (including licensing availability) : Opportunity available for licensing or technology transfer



#### **Technology Overview**

#### Technology Platform

Daurinol is a natural product isolated from the ethnopharmacological and a novel topoisomerase  $II\alpha$  inhibitor, having potent antitumor effects with low hematological toxicity. Daurinol could be a novel alternative to the clinical anti-cancer agent such as etoposide.

#### Background and unmet needs

Myelosuppression is one of the most common and serious side effects of cancer chemotherapy. Clinically, myelosuppression is characterized by hematological changes, such as a decrease in the number of red blood cells (anemia), white blood cells (leucopenia or neutropenia), and platelets (thrombocytopenia). Etoposide (VP-16), a clinical anti-tumor drug, is famous for topoisomerase II posion and used to treat various human cancers including small cell lung cancer and testicular cancer. In spite of its potent anti-tumor activity, clinical use of etoposide is limited due to its side effects such as myelosuppression and the development of secondary cancers, particularly etoposide-induced leukemia. Therefore, discovery of a novel alternative, which has low side effects or ameliorate hematological damages induced by chemotherpy, is one of the most important topics in cancer research.

#### Discovery and Achievements

Both daurinol and etoposide inhibited proliferation of various cancer cells *in vitro* via interruption of DNA synthesis by inhibition of human topoisomerase IIa. Etoposide is a topoisomerase II poison, on the other hand, daurinol is a catalytic inhibitor of topoisomerase IIa.

Etoposide induces G2/M arrest, severe DNA damage, and the formation of giant nuclei in HCT116 cells *in vitro*. The induction of DNA damage and nuclear enlargement due to abnormal chromosomal conditions should give rise to genomic instability, resulting in the toxic side effects of etoposide. In contrast, daurinol induces S arrest but does not induce DNA damage and formation of giant nucleus (Fig. 2). Therefore, we speculated that daurinol has less side effects compared to etoposide due to these differences.

Finally, we confirmed the *in vivo* anti-tumor effects and side effects of daurinol and etoposide in nude mice xenograft models. Daurnol (1, 5, 10, 20 mg/kg) and etoposide (20 mg/kg) were administered by intraperitoneal injection twice to three times a week to the total 120 mg/kg dosage (maximum). Daurinol displayed potent anti-tumor effects without any significant loss of body weight and changes in hematological parameters, whereas etoposide treatment led to decreased body weight and white blood cell, red blood cell, and hemoglobin concentration (Fig. 4, Table 1).





#### Fig. 1. Chemical structures of daurinol and etoposide F

Fig. 2. In contrast to etoposide, daurinol does not induce the nuclear enlargement *in vitro*.



Fig. 3. In vivo anti-tumor effects of daurinol and etoposide. Fig. 4. Comparison of daurinol and etoposide.

Table. 1 Effects of daurinol and etoposide on the hematological parameters in nude mice xenograft model.

	Control, 0 mg/kg	Daurinol			Etoposide, 20 mg/kg
		5 mg/kg	10 mg/kg	20 mg/kg	
WBCs (×10 <sup>3</sup> cells/µl)	4.07 ± 2.42	2.60 ± 1.12	1.86 ± 0.74	$1.63 \pm 0.91$	$0.92 \pm 0.43^*$
RBCs (×10 <sup>3</sup> cells/µl)	9.66 ± 0.41	9.55 ± 0.37	8.82 ± 1.20	9.24 ± 1.03	7.74 ± 0.49*
Hemoglobin (g/dl)	15.59 ± 0.61	15.33 ± 0.68	$14.27 \pm 1.98$	14.78 ± 1.60	12.31 ± 0.76*
Hematocrit (%)	48.61 ± 2.48	47.29 ± 2.09	$43.48 \pm 6.38^{\dagger}$	45.44 ± 5.34	37.36 ± 2.92*
Platelets (×10 <sup>3</sup> cells/µl)	1418 ± 145	$916 \pm 457^{\dagger}$	1220 ± 462	1091 ± 470	1733 ± 263

#### Toxicological data

- Further toxicological studies should be needed.
- Daurinol did not induce toxic phenotypes such as weight loss and hair loss.
- Daurinol did not induce any significant damage on normal tissues including liver, kidney, and colon in nude mice xenograft model.



#### Patents and Publications Country Appln. No. Status Description A pharmaceutical composition containing daurinol for the USA Pending 12/529,828 prevention and treatment of cancers A pharmaceutical composition containing daurinol for the Korea Granted 10-0861320 prevention and treatment of cancers A pharmaceutical composition containing daurinol for the PCT Pending PCT/KR2007/004945 prevention and treatment of cancers

## Contact Point

KHIDI (Korea Health Industry Development Institute) is currently receiving inquiries from interested parties in this transaction. If you are interested, please contact any of the KHIDI professionals below :

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