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Meridian Medicine on Pharmacology

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Abstract

The meridian is a fundamental theory of Chinese Medicine. Based on this concept, Chinese Medicine physicians diagnose illnesses through analyzing the pulse of patients, and thereafter prescribe herbal formulae for remedy. During the past three decades, our research team found the meridian could be measured through pulse diagnosis. Meridians match to the harmonics of blood pressure pulse wave. With meridian theory, we discovered a series of compounds from *Cnidii Fructus* (Cnidium) which is a simplest herb formulae described in Shang Han Za Bing Lun. Including BMX, these compounds have being identified as HDAC8 inhibitor. Guided by the meridian effect on liver and gallbladder which dominate the blood perfusion of brain recorded in Chinese Medicine classic literature, BMX passes through BBB (blood brain barrier) in our study as expected. These results provide confidence to us for brain cancer therapy.

Keywords: Meridian; Resonance; HCV; Pathological matrix; Pharmacological matrix; Pulse diagnostic apparatus; HDAC; Immune-checkpoint inhibition; BMX

Abbreviations: HCV: Coefficient of Variations of Harmonics Magnitude; HDAC: Histone Deacetylases; BMX: Benadryl Maalox Xylocaine

Introduction

The meridian is a fundamental theory of Chinese Medicine for more than 3 thousand years. Chinese Medicine physicians diagnose illnesses through analyzing the pulse of patients, and thereafter prescribe herbal remedies based on the pathological excess or deficiency of the meridians. However, meridian is strange and abstract concept for conventional medicine. Compared to conventional western clinic which is based on anatomy and chemistry particles, traditional Chinese medicine physicians practice clinic following "Chi" and "Dao" (or "Principle"). What is "Chi"? After 25 years study of Pulse Diagnosis, we defined it as Wave or Periodic signal. Under this definition, we could recognize the reality between time and frequency domain phenomenon with Fourier Transform. Moreover, we could discovery the basis of Chinese Medicine based on mathematics and physics.

Discussion

Our research team tried to discover the secret of meridian since 30 years ago. We started from the pulse diagnosis which is a unique method in Chinese Medicine for measuring meridian. More than two thousand years, pulse diagnosis through pulse wave of blood pressure has always been the core diagnostic method recorded in the classics such as Huangdi Neijing (Yellow Emperor's Canon Internal Medicine), Nanjing (Classic on Medical Problems) and Shang Han Za Bing Lun (Treatise on Febrile and Miscellaneous Diseases). However, the theory of pulse diagnosis in Chinese medicine is unable to be well explained in modern hemodynamics.

In 1991, our research team found that the phenomenon of resonance in the arteries which has always been missing in current dynamics [1]. Subsequently in 1997, we derived a radial resonance equation to describe the property of the blood pressure wave propagation and transmission in the arteries [2]. From the resonance theory and the results obtained from both animal and clinical experiments, [3-5] we verified the one-coin two side's aspects of the pulse diagnostic method and derived a pulse apparatus according to this principle [6].

Through the pulse diagnostic apparatus, we could quantitatively analyze the pathological excess or deficiency of the meridians, and five zang-organs and six fu organs (pathological matrix) [7]. In addition, a series of pharmacology research analyses of acupuncture, [8,9] Chinese herbs, [10-12] herbs prescription formula [13-15] and western medicine on the reinforcing or reducing effect of meridians were being carried out. Meanwhile, with matrix operation, we were able to simulate the whole make up function of several herbs in a prescription formula (pharmacological matrix) [15].

In clinic, we found that the pathological indicator in pulse diagnostic apparatus-HCV (Coefficient of Variations of Harmonics Magnitude) could quantitatively show the severity of diseases and evaluate the outcome of patients after treatment [16,17]. Combining the pathological and pharmacological inverse pair matrixes, we could identify the indication of the prescription formulae recorded in Shang Han Za Bing Lun, such as the white tiger and green dragon formulae. The scientific study of the basic Chinese medicine is the basis of the integrative medicine [18-21].

With this Meridian Medicine concept, we discovered a series of compounds from *Cnidii Fructus* (Cnidium) which is a simplest herb formulae described in Shang Han Za Bing Lun. Including BMX, these compounds have being identified as HDAC8 inhibitor [22]. Histone Deacetylases (HDACs) are a group of enzymes that remove acetyl groups from histones and regulate expression of tumor suppressor genes. Numerous studies have demonstrated aberrant expression of Histone Deacetylases in human cancer. In several cancer types, overexpression of individual HDACs correlates with significant decreases in both disease-free and overall survival. As a result, HDAC inhibitors have gained much attention for cancer treatment lately. To date the FDA has approved three HDAC inhibitors for cutaneous/peripheral T-cell lymphoma, one for multiple myeloma. And many

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more HDAC inhibitors are in different stages of clinical development. However, the current HDACs have serious limitations, including poor efficacy in solid tumors and cardiac toxicity, due partly to their non-selectivity toward 11 HDAC isozymes. A number of individual HDAC-specific inhibitors have been developed, hoping to overcome these hindrances. Here we present BMX, a HDAC8-specific inhibitor developed by us for the treatment of brain cancer.

With the assistance of meridian principles, identify the herbs being used in traditional medicines for neurological indications. Then tested the extracts of the identified herbs *in vitro* for their effect. Later isolated the active ingredients (compounds) from the effective herbs. Then tested the individual ingredients *in vitro*. Selected the best compounds with high potency and low toxicity as candidates for further investigation. Optimizing the candidate compounds by chemical structure modification. Tested the potency and toxicity of all the derived compounds to find the desired compound, after BMX being selected and finally tested for BMX's HDAC enzymatic activity (Figures 1-2) (Table 1).

HDAC8-specific inhibitors are classified as class 1 anti-cancer substance which owns potential of regulating expression of tumor suppressor genes and immune-checkpoint inhibition. Meanwhile, we developed these compounds guided by the meridian effect on liver and gallbladder which dominate the blood perfusion of brain recorded in Chinese Medicine classic literature. As we expected, BMX passes through BBB (blood brain barrier) in our study. These results provide confidence to us for brain cancer therapy. After receiving the pre-clinic approval of FDA, we are designing the clinic study for brain cancer these days.

Conclusion

Meridian theory provides us a guide role to discover new drugs from herbs. There are thousands of herbs and foods classified with meridians in Chinese Medicine classic literature. This might be an ideal and economic direction for new drug development and new concept of pharmacology.

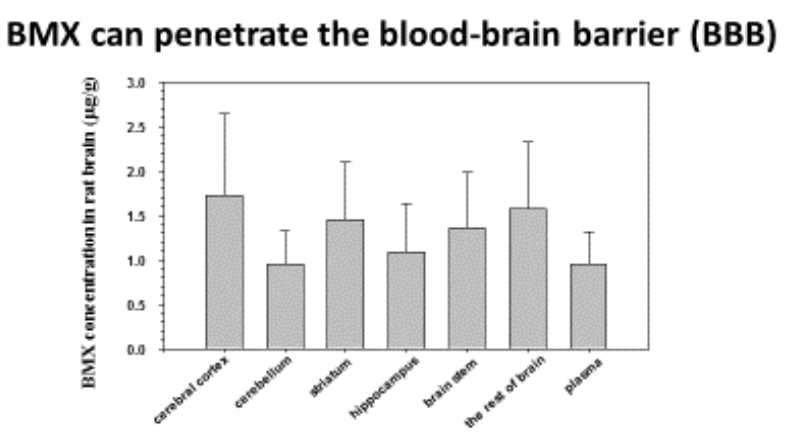

Figure 1: Penetration of BMX through BBB.

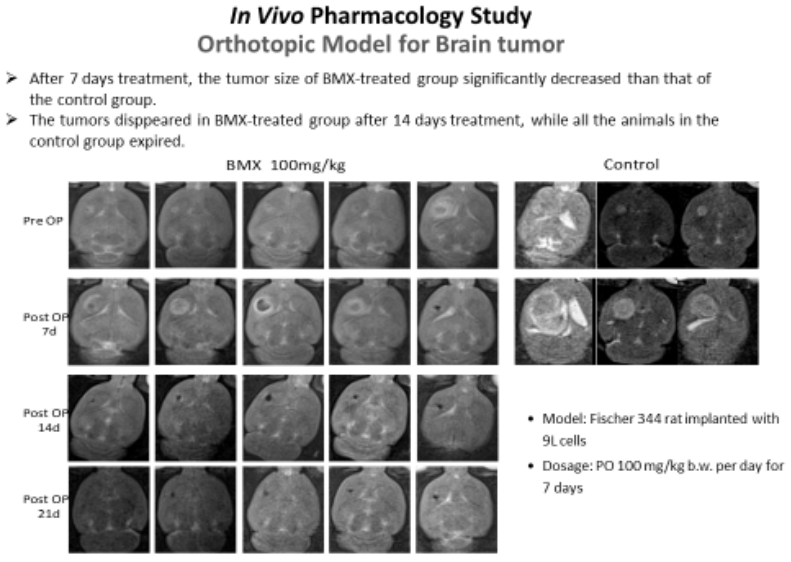

Figure 2: *In vivo* pharmacological study.

HDAC		BMX	Trichostatin A
HDAC-1	HILLSLOPE		-0.96
	IC50 (M)		3.37E-09
HDAC-2	HILLSLOPE		-0.85
	IC50 (M)		7.14E-09
HDAC-3	HILLSLOPE	-0.88	-0.93
	IC50 (M)	2.73E-05	5.55E-09
HDAC-4	HILLSLOPE		-0.3
	IC50 (M)		9.51E-08
HDAC-5	HILLSLOPE		-0.88
	IC50 (M)		6.99E-09
HDAC-6	HILLSLOPE		-1.22
	IC50 (M)		9.96E-10
HDAC-7	HILLSLOPE		-0.65
	IC50 (M)		2.46E-08
HDAC-8	HILLSLOPE	-1.09	-1.01
	IC50 (M)	8.31E-07	1.31E-07
HDAC-9	HILLSLOPE		-0.88
	IC50 (M)		1.39E-08
HDAC-10	HILLSLOPE		-0.88
	IC50 (M)		1.14E-08
HDAC-11	HILLSLOPE		-0.96
	IC50 (M)		6.15E-09
General Substrate: Fluorogenic peptide from p53 residues 379-382 (RHKKAc)			

HDAC		BMX	Trichostatin A
HDAC-1	HILLSLOPE		-0.76
	IC50 (M)		5.88E-09
HDAC-2	HILLSLOPE		-0.85
	IC50 (M)		9.93E-09
HDAC-3	HILLSLOPE	-0.88	-0.66
	IC50 (M)	2.73E-05	3.65E-09
HDAC-4	HILLSLOPE		-0.46
	IC50 (M)		3.52E-06
HDAC-5	HILLSLOPE		-0.76
	IC50 (M)		4.84E-09
HDAC-6	HILLSLOPE		-0.62
	IC50 (M)		1.01E-09
HDAC-7	HILLSLOPE		-0.27
	IC50 (M)		1.13E-07
HDAC-8	HILLSLOPE	-1.09	-0.53
	IC50 (M)	8.31E-07	1.47E-07
HDAC-9	HILLSLOPE		-0.66
	IC50 (M)		8.68E-06
HDAC-10	HILLSLOPE		-0.66
	IC50 (M)		4.89E-09
HDAC-11	HILLSLOPE		-1.1
	IC50 (M)		1.01E-08
Alternate Substrate 1: Ac-Leu-Gly-Lys(Ac) AMC (HDAC 1-3, 5-8, 10-11) Alternate Substrate 2: Ac-Leu-Gly-Lys(TFA)-AMC (HDAC 4, 9)			

Table 1: Enzymatic assay of Histone Deacetylases.

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