出國報告(出國類別：其他)

第十八屆國際微粒體及藥物氧化研討會

會議報告

服務機構：國立中國醫藥研究所

姓名職稱：翁芸芳　研究員

派赴國家：中國、北京

報告日期：99 年 5 月 25 日

出國時間：99 年 5 月 16 日-99 年 5 月 20 日

摘 要 (200-300 字)

目的：了解藥物代謝作用之研究近況，與國際學者交換心得。內容包括: P450、nitric oxide synthase、UDP-glucuronosyl transferase、transporters 等之表現、調控、基因型。

經過：註冊及投稿均由網路作業，由台北搭機經香港，抵達北京機場後，搭巴士約 1 個小時至開會地點，參加學者包括來自歐、美、日本、韓國等地的學者，主辦地區大陸學者參加的很多，整個會議非常成功。

與會心得：藥物代謝為藥物研發之一項非常重要的臨床前及臨床使用主題，在細胞內微粒體上，由 P450 所組成之單氧酵素系統是動物負責毒、藥物代謝之主要氧化酵素系統之一，P450 之受質種類廣泛，外來物經 P450 代謝可產生解毒或活化毒性之代謝產物。因此，研究 P450 之功能與調控在藥理及毒理研究中深具重要性。其他包括結合酵素、運輸蛋白也扮演重要角色。此次會議主題包括:1 個 keynote、8 個 plenary lecture、18 個 symposium。18 個 symposium 包括：P450 structure and function， P450 redox parters in drug metabolism，Drug metabolism in brain，Regulation of drug-metabolizing enzymes and transporters in extrahepatic tissues，Novel aspects of the UGT enzyme family， Short talk on gene regulation，Receptor-mediated drug toxicity and efficacy，Drug-herb interaction，Prediction of adverse drug reactions， Metabolites in safety testing 等。藥物代謝明顯的為藥學學術及各藥廠在研發單位中一定有之重要測定，藥物代謝作用之調控也愈複雜。會場空間充足，空調良好，光線良好，使討論效果好。所發表的海報論文之發表收到許多讀者之發問，包括實驗結果之解釋。其他之海報論文也具有有趣之研究成果。

一、本 文

(一)、參加會議目的

了解藥物代謝作用之研究近況,與國際學者交換心得。內容包括: P450、nitric oxide synthase、UDP-glucuronosyl transferase、transporters 等之表現、調控、基因型。在細胞內微粒體上，由 P450 所組成之單氧酵素系統是動物負責毒、藥物代謝之主要氧化酵素系統之一，P450 之受質種類廣泛，外來物經 P450 代謝可產生解毒或活化毒性之代謝產物。因此，研究 P450 之功能與調控在藥理及毒理研究中深具重要性。另外在粒線體之 P450 在 steroid 之代謝及合成扮演重要角色。參加此會議目的除了了解 P450 之研究近況，並對藥物研發中，藥物代謝探討之進展有了解，且與國際學者交換心得。

(二)、參加會議經過

The conference of Microsomes and Drug Oxidations 開始於 1968 年，多在美國舉行，其他在歐洲及日本舉行。這次是第一次在大陸舉行。參加此會議之註冊及投稿均由網路作業，由台北搭機經香港，抵達北京機場後，搭巴士約 1 個小時至開會地點，參加學者包括來自歐、美、日本、韓國等地的學者，主辦地區大陸學者參加的很多，整個會議非常成功。大會準備了與會人士之午餐及晚餐的餐飲。會場空間充足，空調良好，音效良好，光線良好且座位排列空間適宜，桌子為長條桌適合作筆記。

(三)、與會心得與建議

此次會議此次會議主題包括 1 個keynote、8 個plenary lecture、18 個 symposium。18 個symposium包括：symposium 1、P450 structure and function。在了解基因型與P450 蛋白質之構造，研究其P450 與化學物質及P450 與其他單氧酵素組成分子間之交互作用極具重要性，symposium 2、P450 redox parters in drug metabolism， symposium 3、Drug metabolism in brain， symposium 4、

Regulation of drug-metabolizing enzymes and transporters in extrahepatic tissues，使用knock-in及knock-out mice進行調控作用探討。包括：phosphorylation、ubiquitination epigenetic regulation microRNA、epigenetic events，說明目前調控機轉之研究等。symposium 5、Novel aspects of the UGT enzyme family，symposium 6、Short talk on gene regulation，symposium 7、Receptor-mediated drug toxicity and efficacy。symposium 8、Drug-herb interaction，包括：影響transcription factors間的interaction，造成drug interaction，risk assessment for drug-drug interactions等symposium 9、Prediction of adverse drug reactions，進行LC-MS及GC-MS的分析等。 symposium 10、Metabolites in safety testing等，進行LC-MS及GC-MS的分析等。symposium 11、Drug-drug interactions、symposium 12、Posttranslational modification of drug-metabolizing enzymes、symposium 13、Metabolomics and bioinformatics、symposium 14、Tools for studying xenobiotic metabolism、symposium 15、Predicting drug-drug interaction、symposium 16、New trends in drug development、symposium 17、Metabolism of natural product drugs、symposium 18、Short talks on mechanism of xenobiotic toxicity。在細胞內微粒體上，由P450所組成之單氧酵素系統是動物負責毒、藥物代謝之主要氧化酵素系統之一，P450之受質種類廣泛，外來物經P450代謝可產生解毒或活化毒性之代謝產物。因此，研究P450之功能與調控在藥理及毒理研究中深具重要性。

其中，為考量細胞之primary culture在培養時，代謝活性一般明顯降低或喪失，blood flow是可能因素之一，而在流動培養液培養的細胞具部份較高的代謝活性。為大家所知黃麴毒素具毒性作用，加上其他的因素如肝炎病毒對產生肝癌具很大的相關性，在人體可取得之血液或尿液樣品，暴露指標為探討目的。對於調控機轉中，受體相關之細胞訊息傳遞及相互交談很複雜，包括: MicroRNAs、磷酸化、甲基化等作用參與其中。對於發炎反應，P450在不同組織中的角色及受調控影響可能不同，和病理及毒性或保護作用可能相關。

PROGRAM AT A GLANCE

SUNDAY May 16, 2010	MONDAY May 17, 2010	TUESDAY May 18, 2010	WEDNESDAY May 19, 2010	THURSDAY May 20, 2010
	8:00 – 8:40 Welcome, Keynote: Translating pharmacogenomics of DME into personalized Medicine (X. Wang, J. Hong – Chairs) **8:45 - 10:15 Plenary Session** **PL 1** – P450 structure and function - structure and drug design (J. Halpert, I.Pikuleva – Chairs)	**8:30 - 10:00 Plenary Session** **PL 3** – Nuclear receptor signalling and crosstalk (R Prough and M. Negishi – Chairs)	**8:30 - 10:00 Plenary Session** **PL 5** – Environmental xenobiotic metabolism and biomarkers in humans (CS Yang – Chair)	**8:30 - 10:00 Plenary Session** **PL 7** – Humanized mice - applications in drug development and risk assessment (F. Gonzalez – Chair)
	10:20 - 10:40 Coffee Break	**10:05 - 10:25 Coffee Break**	**10:05 - 10:25 Coffee Break**	**10:05 - 10:25 Coffee Break**
	10:45 - 12:15 Plenary Session **PL 2 –** The epigenetics of drug metabolism and transport) (M. Ingelman-Sundberg – Chair)	**10:30 - 12:00 Plenary Session** **PL 4 –** Identification of molecular and cellular targets of drug metabolites (F. Guengerich, W. Humphreys – Chairs)	**10:30 - 12:00 Plenary Session** **PL 6** – Pharmacogenomics of drug metabolism and transport (L. Kaminsky; T. Kamataki – Chairs)	**10:30 - 12:00 Plenary Session** **PL 8** – Transporter-P450 interplay, probe substrates and inhibitors – Y Sugiyama; L. Benet - Chairs)
	12:15 - Lunch	**12:15 - Lunch**	**12:15 - 1:00 Lunch**	**12:15 - 1:00 Lunch**
1:00 – 6:00 **Registration**	**12:45 - 1:45 Lunch presentation** *XBL-China*: The application of radio-isotope techniques in new drug R&D-DMPK *AB SCIEX*: Next generation LC/MS in pharma study/Use of QTRAP in discovery DMPK	**12:45 - 1:45 Lunch presentation** *Thermo Fisher*: Thermo Scientific LC-MS solutions for drug discover *Life Technologies*: Transporter –mediated uptake, efflux and metabolic function in cells		
	12:25 - 2:25 Poster Viewing	**12:25 - 2:25 Poster Viewing**	**1:00 Depart for Summer Palace**	**12:25 - 2:25 Poster Viewing**
6:00-8:00 **Welcome Reception**	**2:30 - 4:00 Symposia** **SY 1 –** P450 structure and function - structure and conformation (E. Scott – Chair) **SY 3 –** Drug metabolism in brain: its impact on pathogenesis and treatment of brain disorders (H. Strobel; V. Ravindranath- Chairs) **SY 5 –** Novel aspects of the UGT enzyme family (J. Miners; P. MacKenzie – Chairs)	**2:30 - 4:00 Symposia** **SY 7** – Receptor-mediated drug toxicity and efficacy (Q. Ma, Y. Yamazoe – Chairs) **SY 9 –** Prediction of adverse drug reactions: detection of reactive metabolites (J. Stevens – Chair) **SY 11** – Drug-drug interactions - modulation of drug-metabolizing enzyme activity (P. Hollenberg – Chair)		**2:30 - 4:00 Symposia** **SY 13 -** Metabolomics and bioinformatics in preclinical and clinical drug metabolism (R. Dai, A. Archakov – Chairs) **SY 15** - Predicting drug-drug nteractions (T. Tracy - Chair) **SY 17 –** Metabolism and action of natural product drugs (C. Liu Chair)
	4:00 - 4:20 Coffee Break	**4:00 - 4:20 Coffee Break**		**4:00 - 4:20 Coffee Break**
	4:20 - 5:50 Symposia **SY 2 –** P450 redox partners in drug metabolism (B.S. Masters; T. Omura – Chairs) **SY 4** – Regulation of drug metabolizing enzymes and transporters in extrahepatic tissues (M. Vore –Chair) **SY 6** – Short Talks on Gene Regulation (A. Liu; Y. Tian –Chairs)	**4:20 - 5:50 Symposia** **SY 8 –** Drug-herb interactions (W Xie, J. Huang – Chairs) **SY 10 –** Metabolites In Safety Testing - FDA new requirements and research strategies (A Nedderman, C.H. Yun –Chairs) **SY 12 –** Posttranslational modification of drug metabolizing enzymes (Y. Osawa; A. Correia – Chairs)	**6:30 Dinner at Beijing Golden Jaguar International Cuisine Collection**	**4:20 - 5:50 Symposia** **SY 14 -** Stem cells as tools for studying xenobiotic metabolism (P. Maurel – Chair) **SY 16** – Emerging topics and new trends in drug development (A. Lu - Chair) **SY 18** –Short Talks on Mechanisms of Xenobiotic Toxicity (B. Moorthy – Chair)
	6:00 Depart for Opera (7:30-9:30) at the National Grand Theatre (Meal on Bus)	**6:00 Depart for Banquet and Dedication Ceremony at the Palace Restaurant**		**6:00 – 6:20 Presentation of future meetings** (M. Ingelman-Sundberg – Chair) **Closing of Symposium**

建議：

參加此次第十八屆國際微粒體及藥物氧化研討會，參加此次第十八屆國際微粒體及藥物氧化研討會，會場的空間及位置安排的很好，環境也很好，交通尚為方便，雖然週邊飲食較不方便，但主辦單位已考慮此項，餐飲準備的相當的好，會議行程安排緊湊，主辦人非常盡心力，服務人員為學生，隨時都有好多位在，很值得學習。

(四)、攜回資料名稱及內容

攜回會議之摘要集，其會議內容包括：會程及摘要等。

二、附錄 1

發表論文摘要

Safrole Induced Cytochrome P450 1A Through The Aryl Hydrocarbon Receptor-Dioxin Responsive Element Signaling Pathway In Human Oral Epidermal Cells

Yune-Fang Ueng[1,2], Jin-Shun Yu[2], Eai-A Yen[2], Wen-Chi Pan[1], Pinpin Lin[3], Lih-Ann Li[3], and Chul-Ho Yun[4]

[1]National Research Institute of Chinese Medicine, Taipei 112, [2]Institute of Oral Biology, National Yang-Ming University, Taipei 112, [3]Division of Environmental Health and Occupational Medicine, National Health Research Institutes, Zhunan 350, Taiwan, R.O.C., and [4]Hormone Research Center and School of Biological Sciences and Technology, Chonnam National University, Gwangju, Korea

Background. Safrole is a natural plant constituent, found in sassafras oil and certain other essential oils. In betel quid-chewer, salvia safrole concentration could be as high as 420 μM. Cytochrome P450 (P450, CYP) 1 family plays a crucial role in the activation of oral toxins present in the main stream smoke and charcoal-broiled foods. **Results.** In an oral epidermal cell line, OECM-1, exposure to safrole resulted in a concentration- and time-dependent increase of the CYP1 marker, 7-ethoxyresorufin O-deethylation (EROD) activity. The 30-h exposure of cells to 420 μM safrole resulted in a maximal induction of EROD activity. Immunoblot analyses revealed that cellular CYP1A2 but not CYP1B1 protein level was increased by safrole. The levels of CYP1A1 and CYP1A2 mRNA were significantly increased. Safrole stimulated the translocation of arylhydrocarbon receptor (AhR) from cytoplasm to nuclei and enhanced the following dioxin-responsive element activation, whereas safrole did not alter the total expression level of AhR protein. **Conclusion.** These results demonstrate that exposure to safrole induces CYP1A through the AhR activation in oral cells.

Key words. safrole, cytochrome P450 1, oral cells

附錄 **2:**

Publication:

Y.-F. Ueng*, C.-S. Yu, I-A. Yen, W.-C. Pan, P. Lin, L.-A. Li, C.-H. Yun and K.-W. Chang, Induction of CYP1A1 and CYP1A2 by safrole in human oral epidermal cells: the involvement of aryl hydrocarbon receptor-dioxin responsive element signaling pathway, submitted.