# The Late Summer (August) 2013 Newsletter of The GP-TCM Research Association

**1. Karl-Franzens-Universitaet Graz successfully hosted the 12th CGCM Meeting (27-29 August 2013) and the 2nd Annual GP-TCM RA Meeting (30 August 2013), with high-quality scientific exchange on TCM and great social gatherings. More reports and photos will be featured in the next Issue.**

The Bauer Family with Tai-Ping & Dorothy Fan

Singing "龙的传人(Descendants of the Dragon)"

Celebrating the successful 2nd GP-TCM RA Meeting at Aiola Upstairs with Keynote Speakers *Prof. van der Greef*, *Academician Yung-Chi Tommy Cheng*, *Prof. Geoffrey Burnstock FRS* and *Academician Xinsheng Yao*.




**2. The GP-TCM RA is now a registered charity!!**
Following the amendments of our Bylaws, the GP-TCM RA has registered with The Charity Commission for England and Wales on 12 August 2013 (Registered Charity Number 1153356). This is an important milestone of our Association.

## 3. Six New Corporate Members of the GP-TCM RA:

Our warmest welcome to

- East Linden Beijing http://www.eastlinden.net
- Guangxi Botanical Garden of Medicinal Plants, Nanning, China http://www.gxyyzwy.com
- Northwest University http://english.nwu.edu.cn
- Shanghai Hutchison Pharmaceuticals Ltd http://www.chi-med.com/eng/business/shpoverview.htm
- Waters Corporation http://www.waters.com/waters/home.htm?locale=en_US
- Yangtze River Pharmaceuticals Ltd http://www.yangzijiang.com/en/

**4. The GP-TCM RA to become an Interested Party of the HMPC of the EMA in September 2013.** During the HMPC May 2013 meeting the HMPC adopted revised list of interested parties as informed in the HMPC meeting report. The next meeting will be on 16-17 September, in which the GP-TCM RA is expected to become an interested party.
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/document_listing/document_listing_000193.jsp&mid=WC0b01ac0580028e96
http://www.ema.europa.eu/docs/en_GB/document_library/Committee_meeting_report/2013/06/WC500143962.pdf

**5. Peter Hylands appointed to MHRA Committee**

Professor Peter Hylands, Head of the Institute of Pharmaceutical Science, King's College London, and Treasurer of the GP-TCM Research Association, has been appointed to the Herbal Medicines Advisory Committee of the Medicines and Healthcare Products Regulatory Agency (MHRA), the executive agency of the United Kingdom Department of Health that regulates all medicines and medical devices in the UK. The role of the committee is to advise on the safety, quality and efficacy of medicines and medicinal products in relation to human use. He is already a member of the Expert Advisory Group: Herbal and Complementary Medicines, of the British Pharmacopoeia Commission.

**6. Update on *Science TCM Special Feature* 2014.** Over the past six months, Dr Tai-Ping Fan has been in delicate negotiations with *Science* staff about the best way to move forward with the *Science TCM Special Feature* originally scheduled for 2013. On 21 June, he sent an 8-page letter to the new Editor-in-Chief of *Science* Dr Marcia McNutt, updating her on the progress. This led to a productive Skype teleconference on 29 August between Tai-Ping Fan's team [Prof van der Greef (The Netherlands), Prof Peter Hylands (UK), Prof Liang Liu (Macau; deputized by Prof Zhi Hong Jiang), Prof Aiping Lu, Hong Kong] and Dr McNutt's team (Beth Rosner, Bill Moran, Ruolei Wu). After wide-ranging discussions, it was agreed to increase the original 48-page Special Feature to 60 pages, covering the past, present and future of TCM in the form of invited reviews, perspectives and hypotheses. Three separate issues containing 20 pages each will be published in July, September and November 2014, respectively, and collated into a single volume in December 2014. Notably, World Health Organization, China State Administration of Traditional Chinese Medicine, US FDA, US NIH-National Center for Complementary and Alternative Medicine (NCCAM) have all agreed to contribute to this landmark endevaour. In addition to the Special Feature, TCM-related webinars will also be organized in the future.

**7. MHRA warning over dangerous Traditional Chinese Medicines. 20 August 2013**

http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON307398

The Medicines and Healthcare products Regulatory Agency (MHRA) is warning people not to use a number of unlicensed Traditional Chinese Medicines (TCMs) after they were found to contain dangerously high levels of lead, mercury and arsenic. One product, Bak Foong Pills, which is used for the treatment of menstrual pain, has been recalled in Hong Kong after it was found to contain up to twice the level of lead permitted by the Hong Kong Government. Another TCM, Hairegenerator, used for the treatment of hair loss, has also been recalled in Hong Kong after a sample was found to contain 11 times the permitted level of mercury.

The Swedish National Food Agency (SFNA) has also found extremely high levels of arsenic in products going by a variety of names. These include Niu-Huang Chieh-tu-pein, Divya Kaishore Guggul and Chandraprabha Vati. These are used for the treatment of mumps, sore throat, tonsillitis, toothache, skin infections, anorexia and fever in young children. All of these products are unlicensed and are not authorised for sale in the UK. They have, however, been found to be available on the internet and people are warned to exercise extreme caution when buying unlicensed medicines as they have not been assessed for safety and quality and standards can vary widely.

Richard Woodfield, MHRA's Head of Herbal Policy said: "The adulteration of traditional Chinese medicines with heavy metals is a significant international problem and can pose a serious risk to public health. "Natural does not mean safe. To help you choose an herbal medicine that is suitable for you, look for a product that has a Traditional Herbal Registration (THR) or product licence number on the packaging. These products have met the acceptable quality and safety standards. "If you think you have taken any of these products please speak to your doctor for advice. If you think you have suffered a side effect from these, or any medicines, please tell us about it through our Yellow Card Scheme."

**8. Brazil Anvisa - traditional herbal classification**

http://www.raps.org/focus-online/news/news-article-view/article/3880.aspx

The Board of Brazil's National Agency for Sanitary Surveillance (Anvisa) approved on 30 July 2013 the launch of a consultation on the creation of a new category of traditional herbal products whose effectiveness and safety could be established through reports of traditional use and literature references. Once finalized,

the proposal would create two separate categories of products, herbal medicines and traditional herbal products. The traditional herbal products would not need to be prescribed. A second consultation will also be launched proposing Guidance for the Registration of Herbal Medicines and Notification of Traditional Herbal Products, which would assist companies in determining the appropriate classification for their products.

### 9. Chinese Herbs & Pesticides

https://www.mayway.com/pdfs/maywaymailers/Skye-Sturgeon-QM-Chinese-Herbs-&-Pesticides-08-2013.pdf?goback=.gde_77622_member_265903640#

## Journal Club

### 1. Chinese Herbal Drug Improves Spine Injuries

http://www.dddmag.com/news/2013/08/chinese-herbal-drug-improves-spine-injuries?et_cid=3435181&et_rid=45532557&type=headline

A new study published in *Restorative Neurology and Neuroscience* demonstrates that Chinese herbal medicine Ji-Sui-Kang (JSK), given systemically for three weeks after injury in rats, improved locomotor function, reduced tissue damage, and preserved the structure of neural cells compared to control rats. The report also includes data showing that JSK may first act to reduce inflammation and cell apoptosis and death, and boost local oxygen supply while, later on, it appears to restore function and promote tissue regeneration.

Although Chinese herbal medicines have traditionally been used for a variety of ailments, the rationale for their use relies more on anecdotal evidence than the results of modern-day controlled experiments.

“A number of anecdotal reports from Chinese medicine practitioners indicate that treatment with a novel herbal formulation, JSK, for periods of one week or three months improved functional recovery,” said co-lead investigator Shucui Jiang, head of the Hamilton NeuroRestorative Group at McMaster University in Hamilton, Ontario, Canada. “Our present study provides an important and necessary foundation for further studies of JSK.”

In this study rats began JSK treatment immediately after undergoing spinal cord injury. Within seven days, hindlimb locomotor function was significantly better in JSK-treated rats compared to those receiving only saline. JSK-treated rats continued to have better motor function than controls throughout the 21-day test period and treated animals appeared to support their weight better and have more coordinated movements.

When the investigators looked at histological samples of the spinal cord, they found that the architecture of the spinal cord was better preserved in JSK-treated animals and the size of the injured area was significantly smaller seven days after injury. JSK-treated animals also showed more intact axons and myelin in the injured areas compared to controls. Other encouraging signs were less deposition of fibrinogen in the injured areas of JSK-treated animals, a decrease in pro-inflammatory COX-2 expression, and fewer cell deaths at the lesion site (as measured by caspase-3 staining).

JSK also increased the expression of growth-associated protein 43 (GAP43), a marker of neuronal development and axonal regeneration, and neuroglobulin, a protein found in cerebral neurons that is thought to help neurons survive and recover after trauma. “Our data suggest that JSK may enhance tissue recovery by reducing cell growth inhibitors and by promoting the proliferation of cells within the injured spinal cord,” says co-lead investigator Michel Rathbone, Division of Neurology, Department of Medicine, McMaster University, Hamilton, Ontario, Canada.

Other findings suggest JSK might help protect against injury caused by damage to spinal cord blood vessels. For instance, JSK increased vascular endothelial growth factor (VEGF), a protein involved in the formation and growth of blood vessels, down-regulated clotting-associated genes, and promoted factors that contribute to vasodilation.

The authors say that JSK targets multiple biochemical and cellular pathways that may help protect against the primary traumatic injury as well as subsequent secondary injuries that evolve over time.

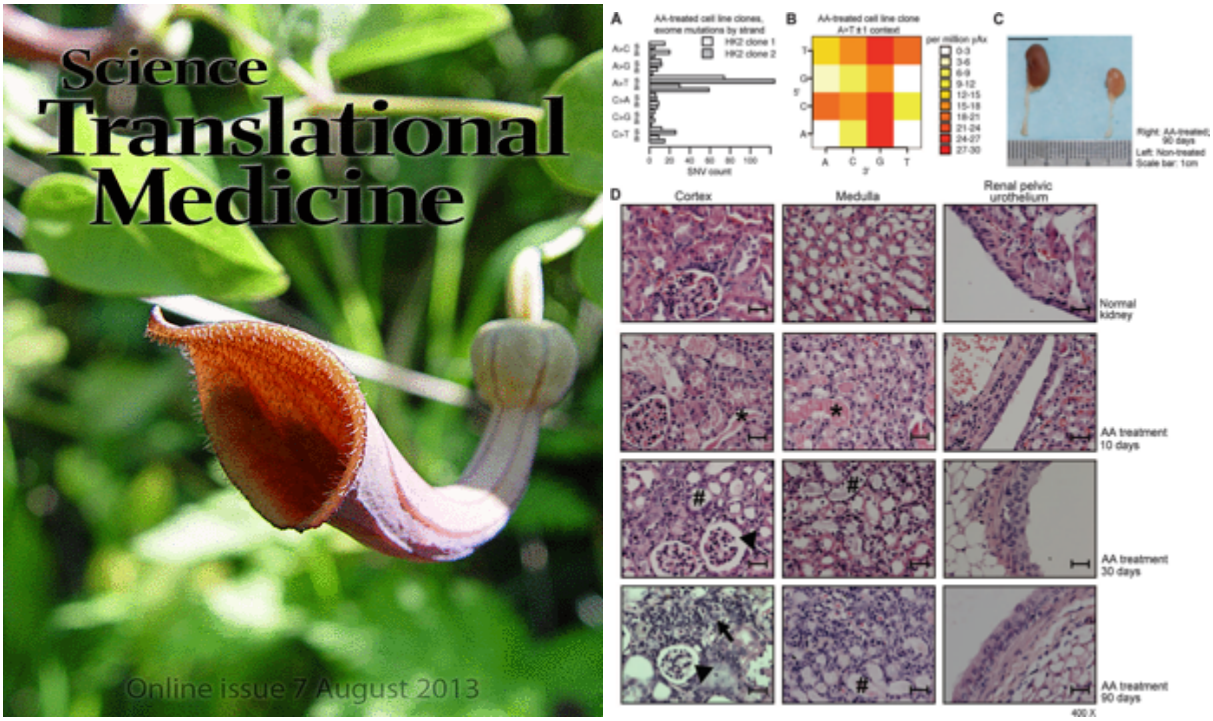
The authors do not disclose the complete herbal composition of JSK for proprietary reasons. Some of its ingredients include ginseng, rhizoma (chuan xiong), glycyrrhizae radix (gan cao), paeoniae alba radix (bai shao) and cinnamomi cortex (rou gui).

**2. Effects of a novel herbal formulation JSK on acute spinal cord injury in rats.** *Restor Neurol Neurosci.* 2013 Jun 12. [Epub ahead of print] **Purpose:** Acute spinal cord injury (SCI) triggers multiple

cellular and molecular pathways; therapy aimed at only one pathway is unlikely to succeed. Anecdotal reports indicate that a novel herbal formulation (JSK-Ji-Sui-Kang) may enhance recovery in humans with SCI. We investigated whether JSK's therapeutic effects could be verified in a well-established SCI model in rats. **Methods:** Therapeutic effects of JSK were tested using standard behavioral assessment, histological, immunochemical and microarray analysis. Phytochemical fingerprinting of JSK was performed using high performance liquid chromatography coupled with photodiode array detection and electrospray ionization-mass spectrometry. JSK or vehicle was gavaged to rats 24 hours after SCI and daily thereafter for 3 weeks. **Results:** Locomotor function significantly improved ($n = 12$; $p < 0.05$), tissue damage was reduced ($p < 0.01$; $n = 6$) and more axons and myelin were observed in JSK-treated compared with vehicle control animals. JSK significantly enhanced expression of neuroglobin, vascular endothelial growth factor and growth-associated protein 43, and reduced the expression of caspase 3, cyclooxygenase-2, RhoA ($p < 0.05$; $n = 6$) and fibrinogen ($p < 0.01$; $n = 6$). RNA microarray indicated that JSK altered transcription of genes involved in ischemic and inflammatory/immune responses and apoptosis ($p < 0.05$; $n = 3$). **Conclusions:** JSK appears to target multiple biochemical and cellular pathways to enhance functional recovery and improve outcomes of SCI. The results provide a basis for further investigation of JSK's effects following SCI.

## 3. Toxin found in herbal remedies and certain foods linked with upper urinary tract cancer

Using whole-exome sequencing of Taiwanese upper urinary tract cancer patients exposed to aristolochic acid and patients with no suspected exposure, researchers found an average of 753 mutations in each tumor from the toxin-exposed group compared with 91 in tumors from the non-exposed group. This level of mutation is more than that found in melanomas caused by ultraviolet radiation and lung cancer caused by smoking. The predominant mutation type in the exposed tumors was an A substituted with a T, according to Poon *et al* and Hoang *et al*. The *Science Translational Medicine* findings illustrate how sequencing can pinpoint carcinogens involved in cancer clusters.




A Not-So-Harmless Plant. Shown is a flower of *Aristolochia baetica*, one of the many species that make up the genus *Aristolochia*. Members of this genus are found in most parts of the world and have been used as herbal remedies in Asia for centuries. In recent years, aristolochic acid, a chemical compound found in these plants, was shown to cause kidney damage and urinary tract cancers. It has since been banned in several countries, but many people are still exposed to it through herbal mixtures or as an accidental contaminant. Now, Poon et al. and Hoang et al. have discovered that exposure to aristolochic acid leaves a tell-tale pattern of mutations in patients' DNA and may be responsible for more cancers than previously suspected.

**3a. Genome-Wide Mutational Signatures of Aristolochic Acid and Its Application as a Screening Tool. Song Ling Poon et al. (2013).** *Sci Transl Med* 7 August 2013: Vol. 5, Issue 197, p. 197ra101. DOI: 10.1126/scitranslmed.3006086

Aristolochic acid (AA), a natural product of *Aristolochia* plants found in herbal remedies and health supplements, is a group 1 carcinogen that can cause nephrotoxicity and upper urinary tract urothelial cell carcinoma (UTUC). Whole-genome and exome analysis of nine AA-associated UTUCs revealed a strikingly high somatic mutation rate (150 mutations/Mb), exceeding smoking-associated lung cancer (8 mutations/Mb) and ultraviolet radiation–associated melanoma (111 mutations/Mb). The AA-UTUC mutational signature was characterized by A:T to T:A transversions at the sequence motif A[C|T]AGG, located primarily on nontranscribed strands. AA-induced mutations were also significantly enriched at splice sites, suggesting a role for splice-site mutations in UTUC pathogenesis. RNA sequencing of AA-UTUC confirmed a general up-regulation of nonsense-mediated decay machinery components and aberrant splicing events associated with splice-site mutations. We observed a high frequency of somatic mutations in chromatin modifiers, particularly KDM6A, in AA-UTUC, demonstrated the sufficiency of AA to induce renal dysplasia in mice, and reproduced the AA mutational signature in experimentally treated human renal tubular cells. Finally, exploring other malignancies that were not known to be associated with AA, we screened 93 hepatocellular carcinoma genomes/exomes and identified AA-like mutational signatures in 11. Our study highlights an unusual genome-wide AA mutational signature and the potential use of mutation signatures as "molecular fingerprints" for interrogating high-throughput cancer genome data to infer previous carcinogen exposure.

**3b. Mutational Signature of Aristolochic Acid Exposure as Revealed by Whole-Exome Sequencing. Margaret L Hoang et al. (2013).** *Sci Transl Med* 7 August 2013: Vol. 5, Issue 197, p. 197ra102. DOI: 10.1126/scitranslmed.3006200.

In humans, exposure to aristolochic acid (AA) is associated with urothelial carcinoma of the upper urinary tract (UTUC). Exome sequencing of UTUCs from 19 individuals with documented exposure to AA revealed a remarkably large number of somatic mutations and an unusual mutational signature attributable to AA. Most of the mutations (72%) in these tumors were A:T-to-T:A transversions, located predominantly on the nontranscribed strand, with a strong preference for deoxyadenosine in a consensus sequence (T/CAG). This trinucleotide motif overlaps the canonical splice acceptor site, possibly accounting for the excess of splice site mutations observed in these tumors. The AA mutational fingerprint was found frequently in oncogenes and tumor suppressor genes in AA-associated UTUC. The AA mutational signature was observed in one patient's tumor from a UTUC cohort without previous indication of AA exposure. Together, these results directly link an established environmental mutagen to cancer through genome-wide sequencing and highlight its power to reveal individual exposure to carcinogens.

## Funding opportunities and Awards

**EU Prize for Women Innovators – apply by 15 October 2013, 5:00 pm (Brussels time)**

After a successful first edition in 2011, the European Commission has launched the second edition of the **EU Prize for Women Innovators to reward three women** who have developed outstanding innovations and brought them to market. The contest is open to **all women who have founded or co-founded their own company** and who have at some point in their career benefited from the EU's research framework programmes or the Competitiveness and Innovation framework programme. The first prize is **EUR 100,000**, second prize **EUR 50,000** and the third prize **EUR 25,000**. With this Prize, the European Commission aims to raise awareness about the contribution, potential and importance of Women researchers to entrepreneurship and to encourage women to exploit the commercial and business opportunities offered by their research projects and become entrepreneurs. Compete and tell your story now to inspire other women to follow in your footsteps! Applications can be submitted via the competition website on: www.ec.europa.eu/women-innovators

## Acknowledgements

Contributions from Prof. **Rudolf Bauer** (Austria), Mrs. **Greer Deal** (UK), Prof. **Pierre Duez** (Belgium), Dr. **Tai-Ping Fan** (UK) and Dr. **Qihe Xu** (UK) are gratefully acknowledged.