Good Practice in Traditional Chinese Medicine Research in the Post-genomic Era

GP-TCM

223154

D3.8

A report published in the Final Conference

Document description	
Name of document	A report published in the Final Conference
Abstract	The present report comments the slides presented in Report D3.7. This document will be exploited for presenting a summary of WP3's work over the full course of the project including science and technology developments and contributions as well as summary of all work performed. This report will be published in the proceedings of the Final conference.
Document identifier	D3.8
Document class	Deliverable
Version	1
Author(s)	Prof. Pierre Duez, Prof. Liu Xinmin, Prof. Hani El-Nezami with other WP3 members
Date of creation	10th April 2012
Date of last modification	28th April 2012
Status	Final
Destination	European Commission
WP number	WP3

TABLE OF CONTENTS

1 OBJECTIVES OF REPORT D3.8 4

2 PRESENTATION SESSION (PROF. DUEZ PIERRE): 4

3 DISCUSSION SESSION (TO BE LED BY: PROF. KELVIN CHAN) 11

4 MINUTES OF THE PRESENTATION AND DISCUSSION (COMPILED BY PROF. EL-NEZAMI) 12

1 OBJECTIVES OF REPORT D3.8

The present report comments the slides presented in Report D3.7. This document will be exploited for presenting a summary of WP3's work over the full course of the project including science and technology developments and contributions as well as summary of all work performed **(Chair:** Prof. Pierre Duez; **Discussion moderator**: Prof. Kelvin Chan; **Minutes:** Prof. Hani El-Nezami).

This report has been published in the proceedings of the Final Conference.

2 PRESENTATION SESSION (PROF. DUEZ PIERRE):

The WP presentation session will focus on the following subjects:

- *"Aristolochia intoxications"*, a brief overview of a major toxicity encountered in Europe in patients treated by a Chinese herb. Presentation by Prof. Joëlle Nortier.
- A brief introduction to the WP objectives.

  The research protocols, standards and methods for the evaluation of the safety and efficacy of TCM, including CHMs, are more complex than those for conventional medicines. Indeed, TCM present a unique set of pharmaceutical theories that include particular methods for processing, combining and decocting CHMs, which probably contribute to reduce their eventual toxicities and enhance their efficacies. The evaluation of CHMs safety is complicated by multiple factors, such as the geographical origin of plant material, different processing techniques, dosage, route of administration and compatibility with other medicines. WP3 aims to review the application to TCM/CHMs of *(i)* safety evaluation methods that combine newly evolved and rapidly developing techniques, such as genomics, informatics, metabolomics-centred systems biology, with essential animal, cell culture and molecular biology experiments; and *(ii)* current pharmacovigilance practices in EU and China.
- A brief history of WP membership and leadership development: ~500 words.

  The current membership of WP3 is as follows:

  - Co-coordinators: Prof. Duez Pierre (Belgium), Prof. Xinmin Liu (China)
  - Beneficiary members : Dr. Hani El-Nezami (Assistant Hong Kong), Prof. Alberto Dias (Portugal), Prof. Yanjiang Qiao (China), Prof. Peter Hylands (UK), [helped by Dr Zhou Jue (China) and Dr Fan Qu (China)], Prof Kelvin Chan (UK), Dr Joëlle Nortier (Belgium), Prof. Caroline Stévigny (Belgium), Dr. Ling Dong (China)
  - Non-beneficiary members : Prof Elizabeth Williamson (University of Reading UK), Prof Zuguang Ye (China Academy of Chinese Medical Science China), Dr Debbie Shaw (Guy's & St Thomas' NHS Foundation Trust), Prof Y. James Kang (University of Louisville School of Medicine USA)., Dr. Ning Wang (Public Research Centre of Health, Luxembourg), Prof. Jean-Marie Colet (Belgium), Prof. Ge Lin (The Chinese University of Hong Kong, China), Prof. Olavi Pelkonen (University of Oulu, Finland), Dr. Graeme Ladds (Pharsafer Associates Limited, UK), Prof. Odd Georg Nilsen (Norwegian University of Science and Technology, Norway), Prof. Thomas Efferth (University of Mainz, Germany), Prof. Moustapha Ouedraogo (University of

Ouagadougou, Burkina Faso), Prof. Joseph Kahumba (University of Lubumbashi, DR Congo), Prof. Jean-Baptiste Simbi Lumbu (University of Lubumbashi, DR Congo).

Along the 3 years of the project, the membership has evolved as follows : Dr. Ling Dong (China) was appointed beneficiary member; Dr. Zhou Jue and Dr Fan Qu were suggested as further reinforcement by Dr P. Hylands; Prof. Shuming Li definitely resigned; leading experts in toxicology joined WP3 as non-beneficiary members: Prof. Ge Lin, Prof. Olavi Pelkonen, Dr. Graeme Ladds, Prof. Odd Georg Nilsen, Prof. Thomas Efferth; experts from Africa who meet similar preoccupations with the use of local medicinal herbs also joined as non-beneficiary members: Prof. Moustapha Ouedraogo, Joseph Kahumba and Jean-Baptiste Simbi Lumbu.

Professor Xinmin Liu introduced major contributors who allowed a thorough investigation of pharmacovigilance practices in China, Professors Zhang Li, Yan Jingbo, Yang Xiaohui and Ronald H. B. Meyboom.

- Year 3 WP activities:
  - During this year a series of e-mails and discussions notably allowed:
    - To discuss the finalisation of 2nd year deliverables
    - To prepare the Braga conference (2nd AGM)
    - To prepare the final WP3 report
    - To obtain feedback on the draft for the SOP literature panel and complete the SOP review : *"Good practice in reviewing and publishing studies on herbal medicine, with special emphasis on traditional Chinese medicine and Chinese materia medica"*
    - To finalize the planned reviews :
      - *"Review of current and "omics" methods for assessing the toxicity (genotoxicity, teratogenicity and nephrotoxicity) of herbal medicines and mushrooms"*
      - *"Pharmacovigilance of herbal medicine"*
      - *"Pharmacovigilance practice and risk control of Traditional Chinese Medicine drugs in China: Current status and future perspective"*
  - A joint workshop was organized with WP1, WP3, and WP7 members and experts of the EDQM European Pharmacopoeia TCM workgroup (Strasbourg, France, 29 September 2011). P. Duez presented a short talk: *"GP-TCM – Introduction & brief progress of WP3"*.
  - Two workshops were organized (09/2011) by X. Liu and Z. Ye in IMPLAD, Beijing and in Louzhou Medical College, Sichuan Province, China, for discussing review manuscripts on pharmacovigilance in China and neuro-toxicity of CHMs.
  - P. Duez visited X. Liu's laboratory for discussing WP3 questions and future joint collaborations on TCM. They visited Prof. Deng Xuliang's labs in Peking University for exploring possibility to submit new joint programme on TCM research to MOST, China.

- X. Liu introduced GP-TCM to Mr Yu Wenmin, Deputy Director of the State Administration of Traditional Chinese Medicine (SATCM), China, and Ms. Wang Xiaoping, Director of Department of international cooperation of SATCM, China in Beijing (http://www.satcm.gov.cn/web2010/zhengwugongkai/guojihezuo/guojijiaoliuyuhezuo/2011-11-02/14902.html).
- X. Liu and Z. Ye presented GP-TCM activities at the *"International Symposium of Drug Discovery from Chinese Materia Medica and its Sustainable Use"*, Beijing, 12/2011 (organized by Specialty Committee of Chinese Materia Medica, World Federation of Chinese Medicine Societies, jointly with IMPLAD and the Chinese Academy of Medical Sciences.
- P. Duez organized a 3-months writing session for WP3 reviews, jointly with M. Ouédraogo, C. Stévigny, J. Nortier and T. Baudoux.
- J. Nortier was invited in Taipei, Taiwan by the Taiwan Urological Association (01/2012) for a Symposium *"Aristolochia-related nephropathy and urothelial carcinoma"* to present a lecture about her clinical and experimental experience in aristolochic acid nephropathy.
- P. Duez was invited for conferences that allowed to introduce WP3 activities at *(i)* the University of Lubumbashi, RD Congo (01/2011), *(ii)* the Seminar on THMP registration in the EU, Beijing, China (10/2011), *(iii)* the Workshop on herbal exports to US & EU markets, Chengdu, China (10/2011), *(iv)* the Agronomic University of Hanoi, Vietnam (03/2012).

- Year 3 deliverables
  - Month 30, D3.4.3: *"Several web-based workshops will be promoted among partners and external collaborators to compare and discuss results, and to elaborate a final monograph" (Part 3)*

    The third year of WP3 was marked by a series of e-mail discussions among members aiming to coordinate and finalize the reviewing work. The problems encountered and a summary of possible solutions are discussed in the present report that is meant as an update of D3.4 versions 1 and 2

    This deliverable was delayed as coordinators preferred to concentrate on finalizing planned reviews. The final version is being prepared (03/2012)
  - Month 36, D3.7: *" Prepare a programme for the Final Conference"*
  - Month 36, D3.8: *" A report published in the Final Conference"*
  - Month 36, D3.9: *" Review papers published in scientific journals"*

- Year 3 experiences gained and lessons:
  - 3 years is quite long… life happens and some strong commitments gradually faded; some reinforced and others appeared.
  - Major issue: Lack of manpower; dedicated group, but overloaded in practice.
  - A major problem already encountered and discussed at the 1st and 2nd AGM is a serious lack of response from WP3 members. The WP3 Co-coordinator has felt a distinct lack of support for producing deliverables and is clearly overloaded. E-mails and (limited) participation to teleconferences were unsuccessful in attracting feedback and getting data for inclusion.

- Deadlines for finalizing reviews were not clear enough; at the Braga meeting, WP3 members had decided to prepare a first draft for 01/2012 whereas the deadline for finalized reviews was in fact 15/12/2011….
- In the absence of commitment, part of the remaining budget was used to organize a 3-months writing session with vital contribution from a skilled and experienced non-beneficiary member. This was the only way we could actually finalize planned reviews.

- WP summary to Year 1-3:
  - Following a somewhat laborious setting-up of the group, the WP3 kick-off meeting, "Functional genomics and toxicological studies applied to Traditional Chinese Medicines", was held on 24th and 25th October 2011 in Brussels La Hulpe, bringing together 8 WP3 groups from both China and Europe (out of a total of 13 groups), the coordinator of WP5 and 3 guests from Belgium and DR Congo (see deliverable D-3-1).
  - WP3 reached a consensus in defining significant toxicity issues with regard to herbal medicines: *"Possible harmful reaction to the body which is not related to therapeutic effect. Toxicity can then be classified into (i) side effects (covered by pharmacodynamics and often predictable), (ii) reactions occuring as a result of overdose, overduration, tolerance, dependence-addiction (covered either by pharmacodynamics and pharmacovigilance), (iii) hypersensitivity, allergic and idiosyncratic reaction (covered by pharmacovigilance), (iv) mid-term and long-term toxic effects (liver, renal, genotoxicity, teratogenecity, neurotoxicity, cardiotoxicity,…)"*. It has been agreed that point *(iv)* is certainly the most important field for "omics" predictive toxicology.
  - The review work deeply investigated toxicity issues and concluded it was quite difficult to precisely identify gaps in knowledge. A general consensus among WP3 members is that:
    - only very few papers published to date have applied functional genomics techniques and/or data to the evaluation of herbal medicines toxicity;
    - the current state of knowledge on CHMs composition, pharmacology and toxicity makes it almost impossible to correctly inventory toxic CHMs, nor every CHMs possibly containing well-known risk pharmacophores, except in some exceptional circumstances.
    - reports of toxicity in literature often deal with combinations ➔ the review should "flag" that this a combination and we don't know which herb is harmful
  - A web-based survey was organized to gain knowledge on the perception of herbals safety by "consumers"; the notion of "consumer" has been defined and a survey aimed at the different stakeholders identified was devised and distributed either in paper or electronically (the survey is available online in French, English and Chinese). WP7 and key persons from various organisations implicated in TCM regulation were contacted with limited success. As of May 2011, a total of 151 completed questionnaires were received, either through the Survey Monkey system (55 in English; 15 in French; 30 in Chinese) or by e-mail (in English and in Chinese). Results from the survey indicate that it is quite difficult to integrate the public concerns on the safety of TCM practice, especially with the different views and opinions among medical, medicinal and paramedical professionals, distributors, regulatory officials, and patients. Non-well-controlled advertisements and the lack of good labelling system for herbal medicines certainly contribute to blur the activity and safety issues for many patients.
  - T

hree reviews were organized and published in the Journal of Ethnopharmacology :

- *"Review of current and "omics" methods for assessing the toxicity (genotoxicity, teratogenicity and nephrotoxicity) of herbal medicines and mushrooms"*

  The increasing use of traditional herbal medicines around the world requires more scientific evidence for their putative harmlessness. To this end, a plethora of methods exist, more or less satisfying. In this post-genome era, recent reviews are however scarce, not only on the use of new “omics” methods (transcriptomics, proteomics, metabonomics) for genotoxicity, teratogenicity, and nephrotoxicity assessment, but also on conventional ones. The present work aims *(i)* to review conventional methods used to assess genotoxicity, teratogenicity and nephrotoxicity of medicinal plants and mushrooms; *(ii)* to report recent progress in the use of “omics” technologies in this field; *(iii)* to underline advantages and limitations of promising methods; and lastly *(iv)* to suggest ways whereby the genotoxicity, teratogenicity, and nephrotoxicity assessment of traditional herbal medicines could be more predictive.

  Literature and safety reports show that structural alerts, in silico and classical in vitro and in vivo predictive methods are often used. The current trend to develop “omics” technologies to assess genotoxicity, teratogenicity and nephrotoxicity is promising but most often relies on methods that are still not standardized and validated. Hence, it is critical that toxicologists in industry, regulatory agencies and academic institutions develop a consensus, based on rigorous methods, about the reliability and interpretation of endpoints. It will also be important to regulate the integration of conventional methods for toxicity assessments with new “omics” technologies.

- *"Pharmacovigilance of herbal medicine"*

  Pharmacovigilance is essential for developing reliable information on the safety of herbal medicines as used in Europe and the US. The existing systems were developed for synthetic medicines and require some modification to address the specific differences of medicinal herbs. Traditional medicine from many different cultures is used in Europe and the US which adds to the complexities and difficulties of even basic questions such as herb naming systems and chemical variability. Allied to this also is the perception that a ‘natural’ or herbal product must be safe simply because it is not synthetic which means that the safety element of monitoring for such medicines can be overlooked because of the tag associated with such products. Cooperation between orthodox physicians and traditional practitioners is needed to bring together the full case details. Independent scientific assistance on toxicological investigation, botanical verification can be invaluable for full evaluation of any case report. Systematic pharmacovigilance is essential to build up reliable information on the safety of

  herbal medicines for the development of appropriate guidelines for safe effective use.

- *"Pharmacovigilance practice and risk control of Traditional Chinese Medicine drugs in China: Current status and future perspective"*

  Traditional Chinese Medicine (TCM), including Traditional Chinese Medicine drugs (TCM drugs), has been playing a very important role in health protection and disease control for thousands of years in China. Relying on natur

al products, mainly of herbal origin, used either as raw materials for decoction, as prepared herbal medicines or as formulated traditional medicines, TCM is still widely accepted by Chinese people, especially for chronic diseases treatment. This extensive use warrants safety measures and so TCM drug safety monitoring and risk management are becoming increasingly important tasks for the Chinese State Food and Drug Administration (SFDA).

The Adverse Drug Reaction (ADR) monitoring system in China was established both for western and TCM drugs in 1989 as a voluntary reporting system with a National Center collecting and compiling reports. About 10% - 15% of the ADR reports received by the National Center are related to TCM drugs and mainly pertaining to the formulated products.

Serious or multi-case reports on individual TCM drug or formulated products are detailed in the Chinese ADR Information Bulletin to inform the public and Drug Administrative authorities for risk management. In certain cases, the suspension of a particular TCM preparation is decided by SFDA China.

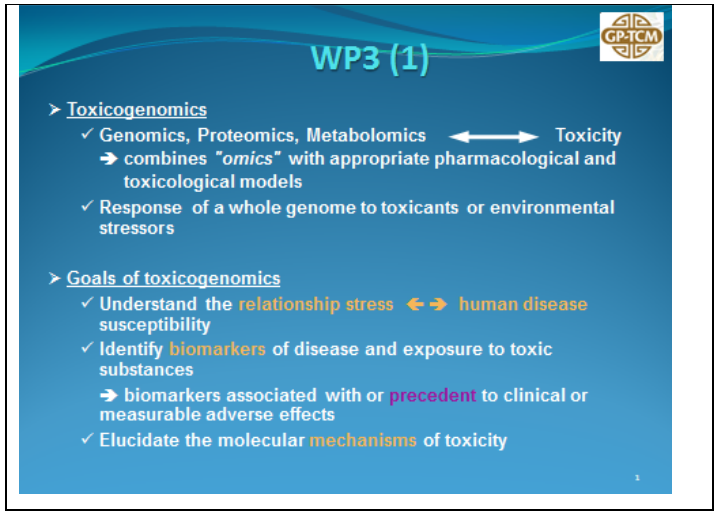
The model of safety monitoring and risk management of TCM drugs is still under exploration. Indeed, the characteristics and risk factors associated with these drugs require both proper understanding and control of the risk by strengthening standardization of clinical applications, basic science research, quality control in manufacturing, exploration of the actives monitoring methodology and enhancement of international communication and cooperation.

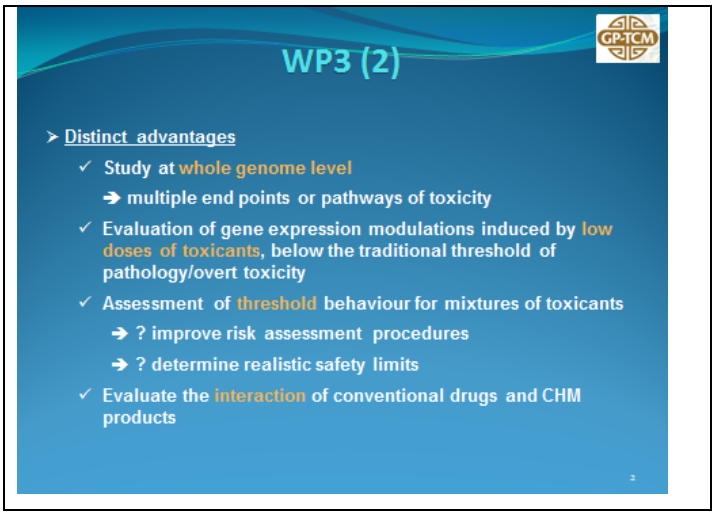
- WP3 plans for future activities towards the extended lifespan of the FP7 GP-TCM project (likely the end of October 2012 as we have applied for).
    - Further data on genotoxicity have been included in a review in preparation :
        - *"Potential genotoxicity of traditional Chinese medicinal plants and phytochemicals: an overview"*.
    - Contacts will be taken with WP3 members to verify if it is possible to go further on the missing pieces of the reviews and possibly organize a second writing session.
- WP3 suggestions to the GP-TCM Research Association regarding the future of the area covered by your WP (most BoD members will be among the audience).
    - Safety issues remain a very important part of TCM modernization
    - Development of early predictive tests and biomarkers is clearly needed

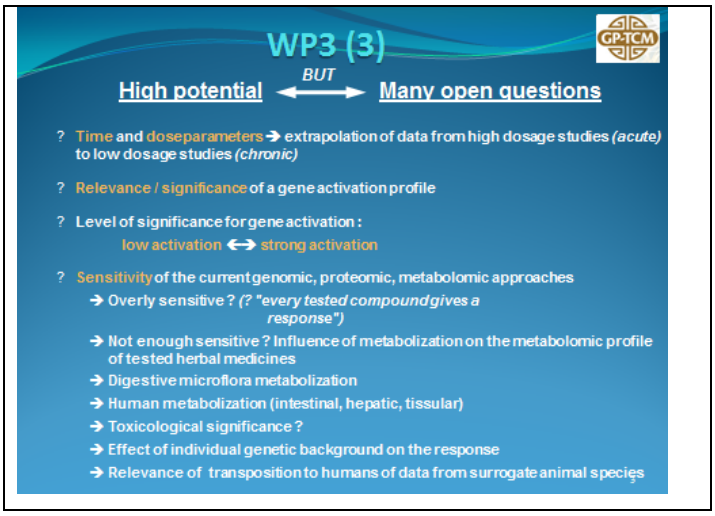
- WP3 Finances (details of your current WP budget):

Year 1 : Organisation WP3 kick-off Meeting 23rd - 25th October 2009	
Hotel+ conference rooms + breakfasts + dinners,…	€ 6298.30
Reimbursement transport	€ 3574.96
Total Year 1	€ 9873.26
Year 2 – Year 3	
Office supplies	€ 618.93
Documentation	€ 1,026.11
WP3 3-months Writing session (transport, hotel, per diem)	€ 7,937.75
Total Year 2 – Year 3	€ 9582.79
Grand total	€ 19,456.05

- Final Conclusions of WP3:







3 DISCUSSION SESSION (TO BE LED BY: PROF. KELVIN CHAN)

- How to share our knowledge, experience about CHMs toxicity between EU and China?
- Can we propose guidelines about safety evaluation and adverse reactions reporting of CHMs?
- Can we propose recommendations and directions for future research in assessing the toxicity of CHMs?

- Can we sort out CHMs according to safety and known/probable toxicities: proven toxic herbs (e.g. pyrrolizidine alkaloids, aristolochic acids,… containing plants); highly suspected herbs; (supposedly) detoxified toxic herbs (e.g. Aconitum); probably safe herbs; proven safe herbs ?
- Which areas can be identified as toxicity evaluation bottlenecks?
- Which research areas would be interesting to be funded by EU for resolving the gaps in knowledge?

4 MINUTES OF THE PRESENTATION AND DISCUSSION (COMPILED BY PROF. EL-NEZAMI)

- Prof Pierre Duez gave an overview of the WP3 activities over the last 3 years.
- Prof Joelle Nortier introduced a case study about the toxicity of aristolochic acids (AAs) among Belgian women.
- The discussion was led by Prof Kelvin Chan, the main point raised whether this work can be carried out by the association in the future.
- 3 points were raised, one regarding teratogenicity of Chinese medicine, and whether there is a correlation between animal data and human data. Also regarding the pharmacovigilance, whether there is a need to implement surveillance program specifically targeting herbal medicines.
- In relation to teratogenicity, there are clear indications in the Chinese Pharmacopeia about which herbal medicine should be avoided by pregnant women. Also the availability of animal model that would predict the toxicity of herbal medicine is quite challenging. Also the point of developing validated biomarkers is quite important however, it is also necessary that such biomarkers should represent precocious rather than late stage toxic effect.
- A report on the use of AAs-containing drugs in Taiwan was brought to the attention of the audience; this study indicates that half Taiwanese population are consuming herbal medicine and around half million consume products that may contain AA. Such data are quite alarming.
- An interesting point brought on whether there is an increased incidence of cancer in countries where Chinese herbal medicines are consumed.
- Also an article in N.Eng.J.Med highlighting that AAs can be found in a series of herbal products which are available in the market (contamination?). Also several herbal products sold in India and South America may contain AA.
- It was also brought to the audience attention that the Taiwanese government has banned the sale of 5 Chinese herbal products that may contain AAs. The situation in China might be different where only one herbal product containing AA is currently banned.