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

GP-TCM

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D.1.10

A final report that incorporates discussions, recommendations, issues and challenges raised at the Final Conference

Document description	
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Abstract	This report provides the discussions, recommendations as well as issues and challenges addressed by WP1 Coordination Team at the Final Conference.
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WP1 Session, 15:30-16:45, 12th April 2012

Chair: Professor Peter Hylands

Minutes: Dr Svetlana Ignatova

Presentation session (Delivered by: Professor Monique Simmonds, Royal Botanic Gardens, Kew)

1) Objectives of WP1

- Design a standard system for the quality control of Chinese herbal medicines (CHM) in the EU;
- Design a system that will provide greater transparency about the complexity of CHM nomenclature, thus clarifying plant identities and improving data gathering on CHM species;
- Propose guidelines as a basis for the rational development of research methods to authenticate and monitor the quality of CHM plants entering the trade. Guidelines will aim to avoid duplication of research efforts and maximise the use of modern molecular and chemical techniques, especially a functional genomic approach.

2) WP1 membership and leadership

Lead organisation: Royal Botanic Gardens, Kew (Kew): The work undertaken by WP1 has benefited from the input of many beneficiaries and general members. Over the three year about 50 people have contributed to the work of the WP1.

3) Year 3 WP1 activities

- Face-to-face meetings have occurred at other consortium- wide activities such as the annual conference in Braga, Portugal July 2011.
- WP1 activities have been addressed in numerous teleconferences calls and at scientific and business meetings.
- Members have worked closely with those in other Work packages to discuss aspects of quality control as the information required for quality control can vary depending on whether the plants are required for laboratory research or product-production and clinical trials.
- Four deliverables have been submitted (D 1.5 –D1.8)
- Results have been presented at a range of meetings including: 8th World Congress of Chinese Medicine (WCCM) held in September 2011 (London, UK), Shanghai TCM & Natural Products International Meeting in October 2011 (Shanghai, China) and the Association of Traditional Chinese Medicine and Acupuncture UK Annual Conference in November 2011 (London, UK) and the Global Business of Biodiversity in December 2011, London, 12th international congress of Ethnopharmacology in February 2012, Kalkata, India as well as other meetings in China and Europe.
- Members have participated in discussions leading to creation of the new GP-TCM research association and in the creating of a new database being developed at the royal botanic gardens, Kew for collating information about medicinal plant names (medicinal plant name index and information services).

- Members have participated in grants including a Maria Curie Initial Training Network application.

4) Year 3 WP1 deliverables

- D 1.6* - Procedures and recommendations for quality control of plants used in CHM.

  The report provides a detailed overview of the information that authors should try and provide about the plants used in CHM in academic publications. If followed this would enable the comparative analysis of biological data presented in papers to be more robust as authors would have a better idea about the quality of the starting material use in these studies.

- D1.7* - Report on the knowledge gaps about the quality control of plants used in CHM.

  Report provides an overview of the literature about the 5 plants and fungus used in the CHM formula Liu Wei Di Huang Wan. The findings showed that although the number of references about each species varies greatly depending on the search engine used and the terms used to search the literature, few contained robust data about the plants. What is clear is that there is very little scientific information in these papers about what the quality of the six plants/fungi used in Liu Wei Di Huang Wan should be. For some plants there is a wealth of scientific information about the chemistry of the plants and their proposed and actual medicinal properties. However, very few of these publications link directly back to the traditional use of the plant as used in Liu Wei Di Huang Wan. The formula was selected because it is widely used in China and thus it was assumed that the uses would be supported by publications.
  Data about the nomenclatural issues and the chemistry of some of the target plants assessed from reviewing 400 publications has been presented by WP 2 in D2.10. Some of the gaps could most likely be filled by a more intensive review of the Chinese literature, especially in books or standard operating procedures used by the manufactures of the Liu Wei Di Huang Wan product. However, this review of the literature has shown that there is very little relevant information available about the criteria for quality control in the academic literature outside China.

- D1.8* - Identify availability of vouchered collections of different species used in CHM, along with DNA data, chemical finger prints and information about extraction methods etc.

  This report provides a summary of were taxonomically verified samples are of some of the species used in Liu Wei Di Huang Wan as well as the availability of DNA sequence information available from taxonomically verified samples, processing information and whether there are procedures in place for the Good Agriculture Practises for the production of the plants. Overall, the Flora of China now provides information about the names of most of the species used in not only Liu Wei Di Huang Wan but for most of the plants used in CHM. These Latin binomial names can be linked to the pharmaceutical names and PinYin names in the Chinese Pharmacopeia, although this does require some botanical knowledge as well as an understanding of the pharmacopeia systems. Within China and Europe there are taxonomically verified samples that can be used to assist scientists verify their samples before starting experiments. The fact that the majority of species used in Liu Wei Di Huang Wan are cultivated and being grown under Good Agricultural Practises would indicate that it would be possible to get material from these sources for experimental work. However, a high proportion of plants used in CHM are still wild harvested, although more entering cultivation. To support the cultivation of quality plants there should be

greater exchange between those evaluating the biological activity and the associated chemical fingerprint of the material used with those breeding the plants.

- D1.9* - An overview report for the Final Conference

  This report provides an overview of the key output headings of WP1 and has been submitted to the Steering Committee.

- D1.10 - A final Report

  This report provides an overview of the key findings of WP1. Comments raised at the Final Conference, along with the minutes will be incorporated into this report. The full report will be presented after the conference in April 2012.

- D1.11 - Scientific Papers

  The key scientific outputs from the WP1 are listed below. The report will be updated after the Final Conference to include other outputs from members not yet collated.

  - Chan, K, Shaw, D., Simmonds, M.S.J., Leon, C.J**.,** Xu, Q., Lu, A., Sutherland, I. Ignatova, S., Zhu, Y-P.,Verpoorte, R.,Williamson, E.M., Duez, P. (2012) Good practice in reviewing and publishing studies on herbal medicine, with special emphasis on Traditional Chinese Medicine and Chinese *Materia Medica J Ethnopharm.* 40: 469-475

  Associated outputs on quality control produced by members of WP1 include:

  - Chen, S. Yao, H. Han, J. Liu,C. Song, J. Shi, L. Zhu, Y. Ma, X. Gao, T. Pang, X. Luo, K. Li, Y, Li, X, Jia, X. Lin, Y, Leon, C. (2010). Validation of the ITS2 Region as a Novel DNA Barcode for Identifying Medicinal Plant Species. PloS ONE 5(1): e8613.doi:10.1371/journal.pone.0008613
  - Chen, S. Lin, Y. Qian, Z. Leon, C.J. (2010). A colored identification atlas of Chinese materia medica and plants as specified in the pharmacopoeia of the People's Republic of China. Chinese Pharmacopoeia Commission and Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences, People's Medical Publishing. 2 vols. 1,200 pp.

* NB. There was a delay in the first year in the identification of the key species to be evaluated for quality control by WP1. This has resulted in delays in some of the later deliverables but WP1 is now on target to have completed all reports by the end of the project.

5) Experiences gained over the three year project

Problem	**Resolution**
Meetings	Initially it had been planned to have more face-to-face meetings, these are essential to initiate tasks and to evaluate the findings. However, because of the distance among the members and the time constraints greater use was made of telephone conferences, especially when presentations were discussed. Face- to-face meetings are also essential to share and develop ideas as has been illustrated with the development of grants, papers and the new GP-TCM Association.

	It is also very important to have an effective Project Manager for the overall project.
Getting information about the selected species	Devised a table to assist link the different names that can be given to a plant. However, this is not an easy task and more research with plant users is needed to fully evaluate the best way of presenting information about plant names and constructing a database to support this activity. There is a fast amount of information about the biological activity of plants used in CHM. However, it is very difficult to evaluate the quality of the information. The members of WP1, WP2 and WP4 produced a set of criteria that can be used to evaluate the basic information that authors should provide about the plants they use (or plant-derived materials). Collaborations with members in China assisted WP1 identify more relevant information about key species published in papers available within China.
Quality control requires information about the purpose of the use of the plants and there has been little exchange of information among WPs	There is a challenge in relating how plants are used in CHM compared with the treatment of specific diseases in western medicine, especially as most papers research the use of plants in the development of new drugs not their traditional uses. Members in the consortium often found it surprising at the lack of quality control in the plants they worked on. It was clear that there were some assumptions that this was not an issue, and if it was then it could be left to the botanists. However, botanists need information from chemists and other researchers to assist them identify "quality" plants. There is a sequence of activities that is required in developing quality control methods. Once the identification of the plant has been confirmed then it is important to know about the chemical profile of the plant, especially the chemistry of the material associated with beneficial activity. To assist gather this type of information emphasis should be placed on specific diseases and the task allocated to groups with multiple skills to undertake the searchers so that the scientists with different skills can work together. The activities associated with this task were divided between members of WP1 and WP2 with input from WP4. There was input from other WP but it would require a longer timeframe to bring all the information together.
Obtaining accurate information about specific information	Restrict the scope of references used and only cite from manuscripts that have confirmed the identification of the plants. Criteria has significantly reduced the number of papers that need to be reviewed
Lack of time available for work to be undertaken	Restrict the volume of work to a manageable level with each task having a deputy. More people willing to assist when the tasks they are asked to help with are small. Greater integration of scientists from China with those from Europe.

6) Overview of all deliverables for WP1

- D1.1 - Kick-off WP meeting (took place with WP2)
- D1.2 - Webpage setup and maintained

- D1.3 - Priority list of plants (Report)
- D1.4 - Mechanism and database for linking different plant names (static tables developed for key species)
- D1.5 - Several workshops held (Workshops held but increased use of telephone conferences)
- D1.6 - Procedures and recommendation for Quality Control (Report)
- D1.7 - Knowledge gaps (Report)
- D1.8 - Availability of plants and information to assist Quality control (Report)
- D1.9 - Overview report for final conference (Report)
- D1.10 - Report for final conference (Report)
- D 1.11 - Overview of scientific papers.

7) WP1 plans for future activities towards the extended lifespan of the FP7 GP-TCM project

- Results of the gap analysis of the plants will be written up for publications. It is estimated there will be two further publications from the work undertaken in this WP.
- Results of the findings of the WP are also very relevant for all areas of medicinal plant research and will be presented at conferences. For example, the CGCM meeting in Macao in August 2012, a project and the first annual conference of the newly formed GP-TCM Research Association in Shanghai in October 2012.
- Marie Curie Initial Training Network.
- Further related grant applications.
- The Medicinal Plant Name Index and Information Services, Royal Botanic Gardens, Kew (Wellcome Trust funded project)

8) WP1 suggestions to the GP-TCM Research Association regarding the future of quality control:

- It is important that more scientists involved in medicinal-plant based research or in researching plant-derived substances have a better understanding of the need to check the quality of their starting material and how this can be done. Increased awareness of the importance of vouchers (species or samples of the batches of drugs tested)
- Special Interest Groups working on specific diseases link their findings about the activity and chemistry of plants so that a better understanding of what quality relates to in terms of the profile of compounds in an active extract. This will assist with plant breeding and the supply of good quality material.
- Activities should be undertaken when possible in groups that are international and multidisciplinary to increase understanding and awareness of the spectrum of issues related to quality control; academic and regulatory.

9) WP Finances (details of your current WP budget):

The budgetary accounts have been co-ordinated through the finance department at the Royal Botanic gardens, Kew. At the end of the final conference, there will be small reserve that will

be used, if the consortium is extended, to allow selected WP members to attend a conference in China later in 2012 and attend meeting of the new GP-TCM Association.

10) Final Conclusions of WP1

- Members of WP1 have worked closely with members in WP2 and WP4 to identify the information available in the literature about the chemistry and activity of a range of species used in Liu Wei Di Huang Wan. It is clear that there is a greater need to improve the botanical content of papers on TCM and that journals can ask authors to provide more information about the plants being studied. This would assist improve literature searches and increase the robustness of comparative studies on plants.

- Quality control of plants is very complex and clearly requires input from multiple disciplinary teams using traditional and modern techniques to enable quality material to be supplied from sustainable sources.

- The majority of the objectives of the WP have been fulfilled; however, more information about substitutes and adulterant of the key plants entering the trade in China is required.

11) Discussion session (led by Professor Rob Verpoorte)

- How best to develop the lessons learn from WP1 in the GP-TCM Research Association and to the wider group of scientists?

  Results of Discussion: It was agreed that more attention should be placed on ensuring that the plant material used in studies on TCM is authenticated and that at the very least vouchers should be kept of the material so that the identification can be confirmed. It was realised that the chemistry of the plants can vary and this can be difficult to control. The workshop discussed the challenges of checking the authentication of TCM formula that can contain multiple species.

  More information also needs to be obtained about the influence of processing on the chemistry and thus the quality of the plants used in TCM.

- Going forward how we link the components of quality control together: botany; chemistry, activity should this be through systems biology?

  Results of Discussion: This was not discussed in detail at the meeting. However, previous discussions have highlighted the importance of this approach in addition to the more classical methods. It is clear that we need to be able to provide more evidence about the influence of TCM and the current cell based systems are recognised as having limitations.

- How do we enable authors and reviewers to improve their knowledge about the need to check their starting material as few have enough knowledge to evaluate whether they have “quality plants”?

  Results of Discussion: It was agreed that scientists editing or reviewing manuscripts could highlight issues associated with the lack of information about the authentication and quality of the plant material used in experiments. It was suggested that some of the key journals could have some key basic requirements that authors would need to address: name of plant (Latin scientific binomial as well as pharmaceutical name) voucher sample, any if possible information about the chemistry of the sample being tested). The meeting also discussed the needs for greater clarity on the needs for improved quality control for material being used by the TCM industry and the development of monographs. It was agreed that the

traders and scientists want to improve the quality control of the material being used in TCM, although both groups may take different approaches as to how this might be achieved. Therefore there is a need for both groups to share their experiences and for the scientists to help develop methods that can be used by the traders.

- What are the challenges in linking traditional uses with modern uses and how do we relate this to quality?

  Results of the Discussion: The meeting discussed some of the challenges associated with the development of formula based on granules. Currently there is very little scientific knowledge about how the chemistry of granules relates to the profile of compounds in a traditionally made formula. This could have an impact on the dose required and on overall efficacy. The meeting felt that this was an area needing more research as more material was entering the west in granular forms and the use of granules was increasing in China.