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

GP-TCM

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D7.6

Publication on utility of functional genomics in CHM research and development

Joint Month 24/30 Report

Document description	
Name of document	Publication on utility of functional genomics in CHM research and development (Month 24/30 Report)
Abstract	This joint Month 24/30 Report summarises the results of 3 years of WP7 efforts on this new topic. This part of the project gathered much momentum from May 2011 when Prof. Olavi Pelkonen of University of Oulu, Finland, led the discussions and writing of a perspective on utility of functional genomics in CHM research and development. A new task force was established to examine how emerging functional genomics technology can be applied to the R&D of TCM. A manuscript "Omics and its potential impact on R&D and regulation of complex herbal products" was submitted to *Journal of Ethnopharmacology* on 9th November 2011 and accepted for publication on 23rd January 2012.
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1 INTRODUCTION

There is accumulating evidence that using modern genomics, transcriptomics, proteomics and metabolomics (**"omics"**) methodologies to revisit traditional medicines will lead to new insights, and will offer opportunities for evidence based drug development of TCM and other complex herbal products (CHPs). Currently there is no regulatory requirement of omics-based data in any submitted dossier to any regulatory agency, including for conventional drugs and CHP. However, it has been acknowledged that such studies are being increasingly performed, and almost certainly will eventually be included into regulatory submission dossiers, possibly initially as supplementary materials.

This joint Month 24/30 Report summarises the results of 3 years of WP7 efforts on this new topic. This part of the project gathered much momentum from May 2011 when Prof. Olavi Pelkonen of University of Oulu, Finland led the discussions (Section 2 below) on utility of functional genomics in CHM research and development. A co-opted member of the Committee on Herbal Medicinal Products (HMPC) in European Medicines Agency (EMA) and a well-known expert in *in-vitro* testing & *in-vivo* approaches for elucidating and predicting metabolism and interactions of drugs, Professor Pelkonen agreed to lead the writing of a perspective on utility of functional genomics in CHM research and development.

A new task force was established to examine how emerging functional genomics technology can be applied to the R&D of TCM.

The team consists of:

- Olavi Pelkonen (University of Oulu, Finland)
- Markku Pasanen (University of Eastern Finland, Finland)
- John C. Lindon (Imperial College London, UK)
- Kelvin Chan (The University of Sydney and University of Western Sydney)
- Liping Zhao (Shanghai Jiao Tong University, China)
- Greer Deal (Global Regulatory Services, UK)
- Qihe Xu (King's College London, UK)
- Tai-Ping Fan (University of Cambridge, UK)

The two central questions of Deliverable D.7.6 and their current status are:

Deliverables	Central questions	Current status

D7.6 - Functional genomics	• What are the latest methodology & technology available for the quality control/assurance of CHM products? • What functional genomics/other 'omics methodology and techniques have actually been used for R&D of CHM products?	Literature search in conjunction with WP1 (Quality Control) & WP2 (Extraction and Component Analysis) will be needed. Review of literature on CHM products development for which 'omic' techniques have been applied can be summarised, correlated and coordinated with WP3 (toxicity), WP4 (in vitro), WP5 (in vivo) and WP6 (clinical studies).

2 MONTH 24/30 UPDATE

2.1 Initial draft for discussion

To address these issues, Prof Olavi Pelkonen drafted the following framework on 25th May 2012, for discussion on the 2nd paper by WP7 on utility of functional genomics in CHM research and development.

ADME-T scheme employing 'omics' for herbal medicinal products

Study specifics	Purpose	Methods	Outcome
Herbal substance preparation	identification and quantitation of major and minor components	LC-(TOF)MS	"xenometabolome" of the preparation (composition of the preparation; principal 'active' components)
Subcellular organelles (microsomes), primary and permanent cells in culture	metabolism, identification and quantitation of metabolites	LC-(TOF)MS	in vitro "xenometabolome" after metabolism rate of metabolism (clearance), metabolic profile
major and minor constituents	Identification of metabolizing enzymes	recombinant enzymes, enzyme-selective inhibitors, antibodies	enzymes catalyzing different pathways (especially of 'active' components)
Intestinal cells (Caco-2 etc), hepatocytes in culture	permeation, transporters, metabolism	LC-MS, inhibitors of transporters	rate of permeation, contribution of transporters
Cryopreserved primary hepatocytes, HepaRG cells	hepatotoxicity	cytotoxicity (MTT, LDH etc) All omics techniques for identifying: Nrf-2 biomarkers Other biomarkers	quantitative in vitro potential of hepatotoxicity
Other cells (renal, neural, immune etc)	other toxicities	All omics techniques for identifying biomarkers	assessment of potential toxicity

Volunteers, patients Administration of preparation or components	in vivo kinetics of herbal and/or components	LC-MS biomarkers	in vivo "xenometabolome". Bioavailability in vivo biomarkers for detecting product-associated changes

LC-MS, liquid chromatography-mass spectrometry; LC-(TOF)MS/MS, liquid chromatography-(time-of-flight)tandem mass spectrometry; MTT, tetrazolium salt (cytotoxicity assay); LDH, lactate dehydrogenase (cytotoxicity assay);

2.2 Main focuses of the proposed review: This article should search literature beyond herbal products and summarise what has been reported on the application of "omics" in regulation of any drugs and then discuss its implications on regulation of CHP and CHM.

Authors:
WP7 members: Prof. Olavi Pelkonen, Prof. John Lindon, Prof. Liping Zhao, Prof. Kelvin Chan, Mrs. Greer Deal, Dr. Qihe Xu and Dr. Tai-Ping Fan
External authors: Prof. Markku Pasanen (University of Eastern Finland and EMA/SWP)

2.3 Mission of the paper

To what extent is it possible/desirable to apply omics-enabled in vitro and in vivo toxico/pharmacokinetic, -dynamic and efficacy/toxicity/clinical testing methods to the investigation of conventional drugs and complex herbal products, for the purposes of regulatory scrutiny and potential acceptance?

Omics as stated by FDA "Omics technologies are high throughput technologies used to analyze various kinds of macromolecules, simultaneously; for example, transcriptomics measures many transcripts, proteomics measures many proteins and metabolomics measures many metabolites. High throughput technologies are large scale methods to purify, identify, and characterize DNA, RNA, proteins and other molecules. These methods are usually automated, allowing rapid analysis of very large numbers of samples." (FDA-TRACK Research Glossary Page; Last Updated: 05/04/2011).

2.4 Some central questions of this perspective

- To what extent are 'omics' techniques used for the regulation of conventional pharmaceuticals – current status in various regulatory agencies?
- How should 'omics' techniques be applied to obtain reliable results for complex mixtures regarding pharmacological and toxicological effects, to inform regulatory decisions?
- Should common transparent "omics" data bases be established; hepatotox, kidneytox, vascular/cardio tox etc. How to specify "reference material" and the validity of variables used?

2.5 Outline of the paper

1. Summary

2. Background

Currently, there are no requirements to perform and to include omics-based studies in the dossier to the regulatory agency. However, it has been acknowledged that such studies are being increasingly performed and those studies could be included into the dossier as supplementary material.

3. Regulatory considerations: current initiatives and situation

All major drug regulatory agencies are in the process of assessing the usefulness of omics-based studies in the assessment of new pharmaceuticals. Industry has launched initiatives, e.g. safety testing consortium, to assess the usefulness of omics techniques in toxicity testing and to discover novel biomarkers to be used in translational and human clinical studies.

EMA
- Pharmacogenetics/genomics - voluntary basis only, if significant foundings have been made. Already applied to several pharmaceuticals in cancer therapy for instance tamoxifen case, abacavir etc. No initiatives to apply other omics unless they are part of biomarker activity – at the moment not clear. SWP and EFPIA toxicologists had an initiative to make a discussion forum for omics in toxicology/safety testing – not existing any more.

FDA
- voluntary basis only like in EU, ICH processes are coming slowly behind some initial activities.

Japan, Korea and others?

4. Regulatory considerations: possibilities of 'omics' for TCM

Preclinical phase
- pharmacodynamics and safety pharmacology
  biomarker identification and development
- pharmacokinetics (ADME)
- toxicology

Clinical phase
- pharmacokinetics
- use of biomarkers

5. Discussion and conclusions

6. References

3. Impact of the 2nd Annual GP-TCM Meeting in Braga, Portugal (21-23 July 2011)

At the meeting, Professor Pelkonen produced an updated framework of this deliverable for discussion. All the participants agreed that his proposal to be most timely and valuable for the whole GP-TCM project. (See D7.5 Month 24/30 Report)

4 OUTCOME: 2ND WP7 MANUSCRIPT PUBLISHED IN *JOURNAL OF ETHNOPHARMACOLOGY*

As part of D.7.5 and D7.7, we submitted this manuscript on 9 November 2011. Following revisions, it was accepted for publication on 23 January 2012; and appeared online on 22 March 2012. The paper version will be disseminated at the GP-TCM Final Conference and GP-TCM Congress. It can be cited as follows: Omics and its potential impact on R&D and regulation of complex herbal products. Pelkonen O, Pasanen M, Lindon JC, Chan K, Zhao L, Deal G, Xu Q, Fan TP. **J Ethnopharmacol.** 2012 140(3):587-93. This article is open-access: http://www.sciencedirect.com/science/article/pii/S0378874112000487.

The Abstract of this manuscript is shown below.

Abstract

In traditional Chinese medicine (TCM), multicomponent and principally plant-derived drugs are used for disease prevention, symptom amelioration and treatment in a personalized manner. Because of their complex composition and consequent multiple targets and treatment objectives, the application of omics techniques and other integrative approaches seems inherently appropriate and even necessary for the demonstration of their potential preclinical and clinical safety and efficacy. This perspectives article provides proposals for the application of omics methods to the investigation of complex herbal products (CHP), including Chinese herbal medicines (CHM), both in vitro and in vivo, for preclinical and clinical toxicity, pharmacokinetics, pharmacodynamics and efficacy tests. Ultimately, such approaches could aid regulatory scrutiny and potential acceptance, although currently there is no regulatory requirement of omics-based data in any submitted dossier to any regulatory agency, including for conventional drugs and CHP. However, it has been acknowledged that such studies are being increasingly performed, and almost surely will eventually be included into regulatory submission dossiers, possibly initially as supplementary materials. Specifically for CHM and CHP, omics can play a role both in determining product composition and its variability and in monitoring biological effects in carefully selected platforms. Predicting the future is difficult, but it seems possible that regulatory acceptance of omics techniques and a systems biology approach for the study of TCM, CHM and CHP will not be long delayed. It is expected that current studies and plans employing omics techniques and other integrative approaches will prove to be positive and informative.

Graphical abstract