



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

GP-TCM

223154

D4.15

**Report on technical, economical, analytical aspects of the use
of functional genomics in *in vitro* research of CHM**



Document description	
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Abstract	The use of functional genomics in <i>in-vitro</i> research of CHM has been analyzed focusing on the use of omics techniques, according to their pros and cons. Several aspects have been considered, among which is their technical and analytical utility and feasibility, as well as their exploitation in the field. Despite a general agreement on their usefulness in CHM research, their use has not yet reached a widespread diffusion in the scientific community due to the difficulties in their introduction in the laboratory. Nevertheless, in the last few years, with the introduction of more user friendly techniques and a deeper understanding of systems biology approaches, there has been an increase in published work on omics techniques in CHM, suggesting new trends towards their dissemination.
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TECHNICAL, ECONOMIC AND ANALYTICAL ASPECTS OF THE USE OF FUNCTIONAL GENOMICS IN *IN-VITRO* RESEARCH OF CHM

1. Introduction

An analysis of the state of the art of the application of functional genomics in *in-vitro* TCM research was carried out in the last months of the project by WP4 members. The process was developed through several key stages both as part of the on-going process of scientific literature evaluation by WP4, initially reported in D4.6 and D4.7, as well as during face-to-face meetings. These included three 2011 meetings in London at King's College London of a group of WP4 members, the second GP-TCM annual meeting in Braga, and other email and telephone debates and exchanges of opinions, especially on the following occasions:

- a) the circulation of the WP4 questionnaire on the use of omics in TCM research (see D4-14 "*report of the discussion group on the use of functional genomics for in vitro CHM research*");
- b) the preparation of the two final reviews for *Journal of Ethnopharmacology* (Barlow D., et al 2012; and Buriani A. et al. 2012 *Journal of Ethnopharmacology*. in press);
- c) the circulation in 2011 among GP-TCM members and non-members of the "Grand Issues" survey, which polled opinions on grand priorities, challenges and opportunities in TCM research, one of which was dealing with the application of omics technologies in TCM research.

The WP4 coordination group thus collected and merged the most significant technical, financial and analytical aspects of functional genomics in *in vitro* research of CHM and synthesized them in the present deliverable.

Some of the reference documents of this deliverable were sent for publication, which took some time, thus causing the few months delay for the final draft of D4-15. Some of the contents of the present deliverable appear in the above-mentioned review papers.

2. Context

The validation of a biological effect requires the identification of molecular targets and mechanisms, and when using phytocomplexes as in Chinese Herbal Medicine research, this process is often hampered by the complexity of the molecular mixtures present in the



drug, with many different molecules participating to several simultaneous effects, with an impact either positive, sometimes synergistic, or negative, sometimes antagonistic. Using classical experimental *in-vitro* techniques has proven insufficient in the past for the characterization of complex molecular networks, until the advent of high throughput techniques and omics profiling. These allow the examination of simultaneous molecular effects occurring when using chemical mixtures and, with the help of bio-informatics, to look at such effects in their molecular details and dynamic correlations among components of the phytocomplex and the biological effects, keeping a global view on the biological system affected. At the same time, high-throughput assays can be used to 'fingerprint' herbs and botanical extracts, thus addressing another key issue in Chinese medicine research: quality control and sample variability, a pivotal aspect for reproducibility and standardization of biological effects, when using herbal preparations.

Thus the application of omics high-throughput technologies, with their potential to analyse *entire sets* of homogeneous macromolecules simultaneously (transcriptomics for gene transcripts, proteomics for proteins, and metabolomics for small metabolites), appears particularly fitting to address most of the problems encountered during TCM research which have hampered its wider application to the bio-medical mainstream. Some problems remain to be addressed, and are outlined in section 1.5,

3. Pub Med search on omics techniques and TCM research

Despite the apparent potential for application of omic analytical techniques and bioinformatics in herbal medicine studies, high costs and the multidisciplinary expertises required for their application, have constrained the speed of their dissemination to a slower pace than expected. To explore the actual extent of researchers' use of omics in TCM research we performed a specific PubMed bibliographical search in November 2011. The complete string for the Boolean search on PubMed, used to identify the omics papers dealing with TCM is shown in annex 1.

Briefly, the text string included all the omic techniques and systems biology approaches used in pharmaco-toxicological research. The string excluded all those papers without a direct interest in HCM. Papers on omics and Chinese herbs of general interest were excluded unless of some pharmacological or toxicological interest. The search on PubMed was performed on November 1st 2011.

TABLE 1

(PubMed search on pharmaco-toxicological papers published on CHM using omics)

year	no. original papers	no. reviews	Total papers using search string with no restriction on TCM	% with TCM reference in title or abstract versus no restriction in the search string on TCM
1998	0	0	68	0%
1999	1	0	91	1%
2000	1	0	78	1%
2001	3	0	111	3%
2002	1	0	130	1%
2003	2	1	163	2%
2004	6	0	209	3%
2005	8	3	213	5%
2006	3	1	220	2%
2007	10	2	257	5%
2008	18	1	352	5%
2009	11	1	306	4%
2010	29	4	298	11%
2011 (as of November 1 st)	24	4	304	9%
total	117	17	3307	4%

The results in TABLE 1 show that in just over ten years, around 3,300 research papers were published on omics. With a total of about 134 titles, omics applied to TCM research still represented a small fraction of omics in the field, even though in the last two years



the increase accelerated, especially in the field of metabonomics, while in the first few years omics use was restricted mostly to DNA microarrays.

4. Suggestions from the WP4 questionnaire on the use of omics in HCM research and the general survey on TCM grand issues.

Regarding the application of omics in TCM research, a questionnaire was circulated in spring 2011 among a group of GP-TCM researchers “D4.14 - *Discussion group on use of functional genomic techniques for in-vitro CHM research*”. The questionnaire addressed issues related to the use of omics techniques in TCM research and most researchers agreed on several pros and cons. GP-TCM members’ opinions were also collected during the “Grand Issues” survey. The most relevant conclusions were:

- omics techniques can, and increasingly do, contribute significantly to improve quality control of the test material at all stages of preparation and production and its standardisation;
- systems biology can contribute to increased participation of CHM in the scientific mainstream, thanks to its wider view of biological systems and closer view of simultaneous multiple effects exerted by phytocomplexes;
- omics technologies are excellent at providing information on whole classes of molecules. These can then either be studied further to establish the properties and functions of each, or to try to understand and validate the relationship between them and their functions;
- studies using omics and systems biology should be particularly good at generating new hypotheses on mechanisms for the effects of TCM and these hypotheses would need many additional approaches to substantiate them.
- one single omics methodology is not considered sufficient to investigate mechanisms of action of CHM. A well-consolidated pipeline should be used comprising *in-silico* evaluation, *in-vitro* and *in-vivo* validation through a combination of classical biochemical signalling work, conventional molecular biology, omics technology and bioinformatics.

5. Suggestions for good practice in the use of omics techniques in CHM research

Omics methodologies were developed in response to the need for information-rich, coherent molecular biological strategies and have been applied to different phases of CHM research starting from



- standardization and quality control of herbal formulae,
- characterization of target-mediated and downstream effects,
- identification of molecular mechanisms, and
- prediction of side effects and interactions with other drugs.

Thanks to their potential to unveil the complex pharmacological networks induced by complex herbal preparations, omics techniques can thus be considered a powerful tool to address many open questions in CHM research.

Nevertheless at least two main issues can be identified which need to be addressed when approaching the field of omics in CHM studies using experimental models of disease:

- a) There is an intrinsic problem of replicating the patterns of human disease in animal or cellular models. Both types of model are rarely a close representation of the clinical scenario and are not widely accepted as authentic (or standard) – indeed some animal or disease models are not even clearly characterized or validated. Therefore prior validation and standardization of animal models where omics could be applied to the study of TCM is an absolute requirement.
- b) Omics methods are extremely powerful but since they approach the basic components of the systems studied, they are also liable to significant inherent variability. A particular source of variability however that has not been generally considered in most publications on CHM in experimental models of disease is the generalized use of non-standardized research materials (in terms of the constituent herbs and herbal preparations), which itself promotes variation and can significantly reduce the scientific value of these studies. This implies that before using difficult and expensive omics technologies, it is necessary to have a robust control of plant mixture preparation (batch to batch variability), as well as the experimental model: cell cultures and animal system (organism variability as well as technical procedures). In addition, pharmacokinetic (absorption, distribution, metabolism and excretion) profiling of a given CHM will identify in-vitro and in-vivo bioavailable drug-related components and reveal determining factors for availability, dynamics and individual variations of 'real' active components at target sites of action.

(It should be noted that points a) and b) include several issues which were raised in D5.9, though in the context of animal studies)

Without addressing these two basic problems, omics research in TCM may fall foul of strict scientific precision. Given that omics technologies help to elucidate the mechanism of action of a given CHM treatment, we suggest that these studies have to be applied on those CHM treatments whose efficacy has previously been demonstrated. Since most

relevant pieces of evidence on efficacy come from clinical trials, it is advisable to start applying omics technologies to experimental models of diseases for which efficacy has been proven consistent in humans. This would render a number of TCMs relatively easy to deal with.

In this context the following workflow for applying omics in experimental *in-vitro* and *in-vivo* models can be proposed:

- 1) To use a TCM proven to be efficacious in an appropriate experimental model by gold-standard measurement methods.
- 2) To assess variability in TCM composition and select a uniform, representative, appropriately defined batch.
- 3) To use traceable cell lines under optimal conditions (avoiding overpassages, checking for mycoplasmas, tracing culture media components,...) and to assess variability in the organism population (e.g., cell cultures) by carrying out pre-testing omics studies including the generation of metabolic profiles.
- 4) To assess the known levels of analytical variation in relation to the changes observed (whether at the transcript, protein or metabolism levels).
- 5) To define precisely the experimental groups as well as their size in terms of number of cell types to make precise statistical analysis. It will also be desirable to choose a homogeneous experimental population as far as possible.
- 6) To check that the effects observed in cell cultures after TCM use, especially if chronic administration is necessary, are due to the treatment and not to some other variable (e.g., cell passage, proliferation, or other changes). As much data must be collected as possible in case any of the above differences need to be explained.

Also, one has always to keep in mind that the effects observed *in vivo* always need further research: there is the possibility that the original CHM components (which are the ones tested in the cell cultures) are not the active ones and that they undergo metabolic transformation in the intestine, the liver or somewhere else.

- 7) To perform the appropriate omic technique and analysis according to the currently available guidelines on omics standardisation in the literature, e.g., MIAME (Minimum Information About a Microarray Experiment) for transcriptomics, MIAPE (Minimum Information About a Proteomics Experiment) for proteomics or MSI (The Metabolic Standards Initiative) for metabolomics.

6. Conclusions

Despite a general agreement on the fact that omics might represent the best available approach for TCM research, as well as the widespread discussion in the scientific



community on the subject, too few laboratories have so far used omics in their research schemes, as shown by the recent PubMed search, in order to draw conclusions on the subject. With the evidence available we can only describe a state of the art of the subject and give some recommendations on advantages and disadvantages.

The advent of information-rich omic techniques has provided new powerful research tools in the field of Chinese herbal medicine (CHM). Using genomic, proteomic or metabolomic analysis it has become possible to examine simultaneous molecular effects occurring when using chemical mixtures like in CHM, opening new possibilities to study biological effects with a holistic approach, rather than a classical reductionist one, a new vision which goes beyond single molecule pharmacology and target specificity, embracing the entire equilibrium of a biological system undergoing simultaneous perturbations. Omics techniques are also very powerful and can be used either for purification, identification, and characterization of DNA, RNA, proteins and metabolites in all different biological contexts, in *in-vitro*, *in-vivo* and in clinical studies, thus facilitating interdisciplinary crosstalk and speeding up translation of scientific data from basic research to the clinic. These methods can also be used with a high degree of automation, allowing rapid analysis of very large numbers of samples. Moreover, a rather rapid improvement in the versatility of the methods is constantly developing, reducing the need of often cumbersome preparatory procedures. The help of bio-informatics, itself one of the fastest growing fields at all research levels, allows examination of biological effects with a global view on the biological system affected. Factorial analytical models can then decode the large quantity of raw information derived from the omics techniques, allowing correlation of the multiple components of phytocomplexes with their biological effects. Numerous software and databases have been built and their number is rapidly growing. It is noteworthy that high-throughput, information-rich assays can be used to fingerprint herbs and botanical extracts, thus addressing the other key issue of quality control and sample variability, pivotal for reproducibility and standardization of biological effects when studying herbal preparations. These applications make the use of omics techniques particularly appropriate for addressing many of the problems encountered in TCM research that have hampered its acceptance in the Western biomedical mainstream and its integration with Western medical practice.

Despite the many advantages of omic techniques, caution still surrounds their application to CHM and, in more general, to pharmacognosy, mainly because of the current limited laboratory experience. Nevertheless, there is a common and general recognition that a systems biology approach is the best answer to study phytocomplexes. The results obtained so far with omics applications have been promising but much more work needs to be undertaken to examine its full potential in CHM and wider TCM research. While all the omic techniques are slowly but firmly pushing their way further into CHM research,



the youngest of them, metabolomics, seems to be rapidly gaining ground with respect to the others. This is probably due to the relative simplicity of the experimental design which allows direct and detailed analysis of large numbers of easily prepared samples. What is really attractive about metabolomics though is the possibility of looking at complete metabolic pathways and their complex interactions, in just one snapshot, taking a whole picture of the downstream outcomes of any biological perturbation. This of course is equally true for *in-vitro* as well as *in-vivo* studies, and clinical studies, and would appear as the ultimate systems biology phenotyping and is particularly fit for studying TCM, which has its own holistic view of biological effects.

The question remains whether the application of omics technology is too expensive for routine use. A reduction in the initial economic investment needed to endow a lab with the instruments needed to run omics assays and analysis, as well as the improvement of the academic curricula in the field of omics and systems biology of TCM researchers, is hoped for to increase the pace of dissemination for these powerful techniques.



ANNEX 1

Complete string for the Boolean search on PubMed used to identify the omics papers dealing with TCM:

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and jurisprudence"[Mesh Terms] OR toxicology/l606[All Fields] OR toxicology/laboratory[All Fields] OR toxicology/lacdr[All Fields] OR toxicology/legislation[All Fields] OR "toxicology/manpower"[Mesh Terms] OR toxicology/medicine[All Fields] OR "toxicology/methods"[Mesh Terms] OR toxicology/microbiology[All Fields] OR toxicology/mouse[All Fields] OR toxicology/national[All Fields] OR toxicology/neurotoxicology[All Fields] OR toxicology/pathology[All Fields] OR toxicology/pharmacokinetics[All Fields] OR toxicology/pharmacology[All Fields] OR toxicology/potential[All Fields] OR toxicology/quality[All Fields] OR toxicology/ranking[All Fields] OR toxicology/regulatory[All Fields] OR toxicology/risk[All Fields] OR toxicology/safety[All Fields] OR toxicology/sensitisation[All Fields] OR toxicology/special[All Fields] OR "toxicology/standards"[Mesh Terms] OR toxicology/tdm[All Fields] OR toxicology/teratology[All Fields] OR "toxicology/trends"[Mesh Terms] OR toxicology'[All Fields] OR toxicology's[All Fields] OR toxicologyassoc[All Fields] OR toxicologycal[All Fields] OR toxicologyct[All Fields] OR toxicologyrutgers[All Fields] OR toxicoloical[All Fields] OR toxicology[All Fields] OR toxicolor[All Fields] OR toxicology[All Fields] OR toxicoloty[All Fields] OR toxicoloy[All Fields]) OR medicinal[All Fields] OR medical[All Fields] OR ("motor activity"[MeSH Terms] OR ("motor"[All Fields] AND "activity"[All Fields]) OR "motor activity"[All Fields] OR "activity"[All Fields])) AND ((microarray[Title/Abstract] OR microarray/biochip[Title/Abstract] OR microarray/proteomics[Title/Abstract] OR microarrays[Title/Abstract] OR microarrays/dna[Title/Abstract]) OR "gene expression profiling"[Title/Abstract] OR "gene array*"[Title/Abstract] OR (genomic[Title/Abstract] OR genomic/cytogenetic[Title/Abstract] OR genomic/epigenetic[Title/Abstract] OR genomic/epigenetic/transcriptional[Title/Abstract] OR genomic/epigenomic[Title/Abstract] OR genomic/epigenomics[Title/Abstract] OR genomic/postgenomic[Title/Abstract] OR genomic/proteomic[Title/Abstract] OR genomic/proteomics[Title/Abstract] OR genomic/transcriptomic[Title/Abstract] OR genomic/transcriptomic/peptidomic[Title/Abstract] OR genomics[Title/Abstract] OR genomics/bioinformatics[Title/Abstract] OR genomics/omics[Title/Abstract] OR genomics/proteomics[Title/Abstract] OR genomics/proteomics/bioinformatics[Title/Abstract] OR genomics/proteomics/metabolomics[Title/Abstract] OR genomics/proteonomic[Title/Abstract] OR genomics/toxicogenomics[Title/Abstract] OR genomics/transcriptomics[Title/Abstract]) OR (metabolomic[Title/Abstract] OR metabolomic/metabonomic[Title/Abstract] OR metabolomic/proteomic[Title/Abstract] OR metabolomics[Title/Abstract] OR metabolomics/metabonomics[Title/Abstract]) OR

**(proteomic[Title/Abstract] OR proteomic/genomic[Title/Abstract] OR
proteomic/glycomic[Title/Abstract] OR
proteomic/immunoproteomic[Title/Abstract] OR
proteomic/serologic[Title/Abstract] OR
proteomic/transcriptomic[Title/Abstract] OR proteomics[Title/Abstract]
OR proteomics/bioinformatics[Title/Abstract] OR
proteomics/genomic[Title/Abstract] OR
proteomics/genomics[Title/Abstract] OR
proteomics/glycoproteomics[Title/Abstract] OR
proteomics/metabolomics[Title/Abstract] OR
proteomics/peptidomics[Title/Abstract] OR
proteomics/phosphoproteomics[Title/Abstract] OR
proteomics/protein[Title/Abstract] OR
proteomics/transcriptomics[Title/Abstract]) OR "systems
biology"[Title/Abstract] OR (transcriptomic[Title/Abstract] OR
transcriptomic/genomic[Title/Abstract] OR
transcriptomic/peptidomic[Title/Abstract] OR
transcriptomic/proteomic[Title/Abstract] OR
transcriptomic/secretomic[Title/Abstract] OR
transcriptomics[Title/Abstract] OR
transcriptomics/bioinformatics[Title/Abstract] OR
transcriptomics/epigenetics[Title/Abstract] OR
transcriptomics/proteomics[Title/Abstract]) OR
(metabolomic[Title/Abstract] OR
metabolomic/metabonomic[Title/Abstract] OR
metabolomic/proteomic[Title/Abstract] OR metabolomics[Title/Abstract]
OR metabolomics/metabonomics[Title/Abstract]) OR
(metabonomic[Title/Abstract] OR
metabonomic/metabolomic[Title/Abstract] OR
metabonomics[Title/Abstract] OR
metabonomics/metabolomics[Title/Abstract]) OR "functional
genomics"[Title/Abstract]) AND ((herb[Title/Abstract] OR
herb/botanical[Title/Abstract] OR herb/drug[Title/Abstract] OR
herb/herb[Title/Abstract] OR herb/herbal[Title/Abstract] OR
herb/medicinal[Title/Abstract] OR herbal[Title/Abstract] OR
herbal/botanical[Title/Abstract] OR herbal/drug[Title/Abstract] OR
herbal/health[Title/Abstract] OR herbal/natural[Title/Abstract] OR
herbal/phytochemical[Title/Abstract] OR herbal/plant[Title/Abstract] OR
herbal/traditional[Title/Abstract] OR herbogenic[Title/Abstract] OR
herbogenomics[Title/Abstract] OR herbs[Title/Abstract] OR
herbs/drugs[Title/Abstract] OR herbs/medicine[Title/Abstract] OR
herbs/natural[Title/Abstract] OR herbs/phytotherapeutics[Title/Abstract]
OR herbs/phytotherapy[Title/Abstract] OR herbs/plants[Title/Abstract])
OR (plant[Title/Abstract] OR plant/chinese[Title/Abstract] OR
plant/experimental[Title/Abstract] OR plant/genome[Title/Abstract] OR
plant/herb[Title/Abstract] OR plants[Title/Abstract] OR
plants/experimental[Title/Abstract] OR plants/herbal[Title/Abstract] OR**



***plants/herbs[Title/Abstract])) AND (chinese[Title/Abstract] OR
TCM[Title/Abstract])***