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

GP-TCM

223154

D5.9

Recommendations on the application of functional genomic studies and chemical synthesis to the study of CHM in animal models of disease

Document description	
Name of document	Recommendations on the application of functional genomic studies and chemical synthesis to the study of CHM in animal models of disease
Abstract	The main problems of functional genomics studies applied to the CHM in animal models of disease are outlined and several recommendations are proposed
Document identifier	D5.9
Document class	Deliverable
Version	1
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Date of creation	20 April 2011
Date of last modification	30th June 2011
Status	Final
Destination	European Commission
WP number	WP5

RECOMMENDATIONS ON THE APPLICATION OF FUNCTIONAL GENOMICS

Background: CHM are used as combinations and act multi-systemically. Researchers on the whole try to research into efficacy and mechanism of action of either a single or small combination of a few active ingredients from CHM in the research, which cannot fully recapitulate the effect of the complex mixture. This is why we have focused our studies in WP5 in 'true' CHM preparations (i.e. Herbal Mixture of 3 or more Herbs prepared following the principles of Traditional Chinese Medicine).

There have been many recent attempts to explain the theoretical meaning of evidence-based Traditional Chinese Medicine (TCM). The recent introduction of the ''omic''-technologies (genomics, transcriptomics, proteomics and metabolomics) may allow us for the first time to analyse complex modes of action and may thereby increase the speed of our understanding of combination therapies and synergistic effects. ''Omic''-technologies are today high-throughput techniques. Jointly applied in combination with bioinformatics, they could be named as ''molecular system biology approach'' [1]. These research techniques have provided insight into the mechanisms of TCM in a way not previously possible. However, most of them are still based on the "reductionism" philosophy, whereas TCM is based on "holism" philosophy. There are different molecular biology approaches considered "OMICs" in the area of animal studies of CHM: i) Herbogenomics, which is defined as the analysis of the biological effect on the target organs of a particular herbal medicine preparation through a profiling of the affected genomic and proteomic alterations. Indeed, herbogenomics is just the application of genomic and proteomic analysis to the herbal mixture action. By doing so, herbogenomics provides a mechanistic understanding of the efficacy and toxicity of a particular herbal medicine preparation. The technology of herbogenomics has been under exponential development and increasingly applied in the basic research and clinical studies of traditional Chinese medicine [2] ii) Metabonomics (or metabolomics), which dovetails beautifully with the philosophy of systems biology, because it provides a 'top-down', integrated view of biochemistry in complex organisms, as opposed to the traditional 'bottom-up' approach that investigates the network of inter actions between genes, proteins and metabolites in individual cell types [3]. Metabonomics broadly aims to measure the global, dynamic metabolic response of living systems to biological stimuli or genetic manipulation. The focus is on understanding systemic change through time in complex multi cellular systems [3]. Metabonomics reflects the function of organisms from terminal symptoms of metabolic network and understand metabolic changes of a complete system caused by interventions in holistic context [3,4].

Practical problems for implementation: In summary, the studies on complex systems involving 'true' CHM have made full use of the "omics" technology to provide precise description and molecular mechanism that is instantly realizable to the scientific community. While these efforts seem to be sufficiently "scientific", there are three main problems which need to be addressed by the research workers in the field of CHM in animal models of disease:

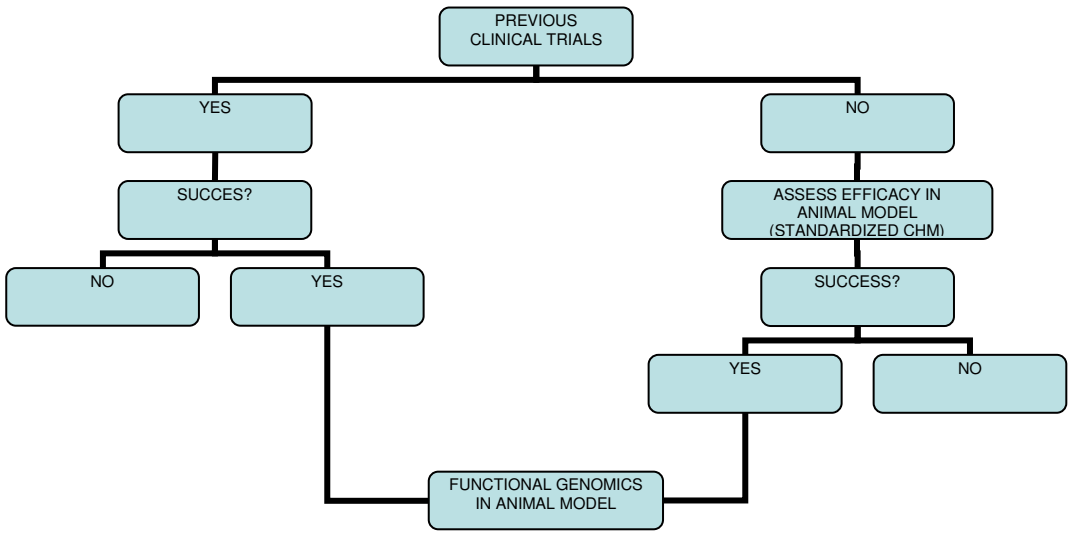
1) The intrinsic problem of replicating the disease patterns remains unsolved. Animal models of all possible human disease patterns are never a close representation of the clinical scenario. The models used in these studies are not widely accepted as authentic, or standard. After all, there seems to be no criteria on the "golden standard" of patterns. Nowadays, some animal or disease models are not even clearly characterized or validated. Therefore previous validation and standardization of animal models where OMICs and CHM could be applied is an absolute requirement as occurs in western medicine research. In fact, toxicity of western drugs before human use is always tested in animal models. Trying to connect western medicine and traditional oriental medicine using metabolomics or herbogenomics approaches is probably premature at this stage since there is no definitive clinical characterization of traditional oriental medicine [5] and metabolomics are still confounding and controversial concepts. We suggest that the diseases on which CHM has been demonstrated efficacy and advantages over western medicine should be summarized and the ones which more resemble human disease patterns might be recommended to start with "omics" study of CHM.

2) The high reproducibility of “omics” as a multiple technique requires low variability in the analyzed systems to lead reproducible results: since they are extremely powerful approaches to the basic components of the study systems, they are also very sensitive to the variability of them (trascriptomics more than metabolomics since NMR is highly reproducible). However, the rule in most publications on CHM in animal models of disease is the generalized use of non-standardized research materials (in terms of herbs and herbal preparations) [6], which are likely to not support reproducibility and comparability of research on the same herbs and thus significantly reduce the scientific value and impact of these studies (D5.7 and D5.10). This implies that before using the difficult and expensive “omics” technologies, it is necessary a robust control of plant mixture preparation (batch to batch variability) as well as the animal system (animal to animal variability as well as technical procedures). In addition, pharmacokinetic (absorption, distribution, metabolism and excretion) profiling of a given CHM will identify *in vivo* available drug-related components and reveal determining factors for availability, dynamics and individual variations of ‘real’ active components to target sites of action, thus, the data should be obtained and correlated to results of “omics” study.

3) Another weakness is the selection of CHM for study: since there are so many of them available for study, there is the need of determining priorities. Yet this is no easy task. It is very difficult, if not at all impossible to coordinate studies on such an immense scale. Even getting everyone to agree on the standard research protocol would be quite hard to achieve. Who got the authority to set the criteria? Who got the resources to implement those criteria? A wide agreement between WPs resulting in a list of CHM mixtures or herbs to be considered, needs to occur before OMICS can be performed. Efforts on delivering this list are currently taking place.

Recommendations: Without addressing the basic problems faced by individual researchers and sporadic institutes, the “state of art” TCM research in the post genomic era may fall foul of discipline, and descend to the “state of anarchy”. 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 animal models of diseases for which efficacy has been proven in clinical trials. This would render a number of CHMs reasonably easy to deal with.

We propose the following scheme for applying “omics”:



Additionally, we propose the **following workflow for applying "omics"**:

1) To use a CHM proven to be efficacious in an appropriated animal model by gold-standard measurement methods

2) To assess variability in CHM composition and select a uniform batch

3) To assess variability in the animal population by carrying out pre-dose omics studies including metabolic profiles

4) To assess the known levels 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 animals to made accurate statistical analysis. It will be desirable to choose homogeneous animal population as much as possible.

6) To check that the effects observed in animals after TCM use, especially if chronic administration is necessary, are due to the treatment and not to some other artefact, (e.g. aging or body weight changes, simply not eating because animals feel unwell, changes in gut microflora, etc). Collect as much meta-data as possible in case any of the above differences need to be explained.

7) To perform the appropriated OMIC technique and analysis accordingly to the available guidelines on -omics standardisation in the literature, [e.g. MIAME for transcriptomics, MIAPE for proteomics, SMRS for metabolomics]

Networking: Successful contribution of WP5 and WP4 members to this deliverable has been occurring. Experts in animal models, in vitro models as well as OMICs have revised bibliography regarding OMICs in TCM and OMICs in animal models and delivered reflexions in documents that have been considered as valuable material to build this deliverable. Several issues addressed in this draft have been shared with the ongoing abstract for the review "OMICs in TCM" that will be submitted to J Ethnopharmacology.

1.1 References

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