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

GP-TCM

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Recommendations on the application of functional genomic studies to the study of CHMs in patients

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D6.8 - Report on recommendations on the application of functional genomic studies to the study of Chinese Herbal Medicines (CHMs)in patients:

Due to a relative lack of good quality studies in this area, it was not possible to identify appropriate material around the chosen disease areas prioritised for GP-TCM special focus. Instead the studies reviewed highlight the general approach and scope that such new approaches offer.

1. THE ROLE OF "OMICS" OR "HIGH THROUGH PUT" TECHNOLOGIES IN CHM RESEARCH:

The development and application of the high-throughput screening technologies (HTS) is in the process of significantly changing research perspectives towards traditional medicines including CHM. With HTS or the "omic"-technologies, a multitude of molecules on the gene (genomics, transcriptomics) or the protein level (proteomics, metabolomics) can be estimated simultaneously, providing an innovative technological platform for an analysis of the composition of complex mixtures and their multi-targeted mode of actions.

These developments mean that the search for single "active principles" in plants, based on the assumption that a plant has one or a few ingredients that determine its therapeutic effects, can now evolve into an approach that is more appropriate to traditional medical practices such as CHM like CHM. In these systems it is generally assumed that a synergy of all ingredients of the plant(s) will bring about the maximum therapeutic efficacy. (For the definition of synergy from a pharmacological perspective please see Wagner & Ulrich-Merzenich et al. 2009a,b). The HTS provide a promising tool to cope with the analytic challenges arising from this approach in several different domains:

- authenticity and quality of plant material
- analysis of the mode of action of single plants and multicomponent mixtures
- assessment of the toxicity of CHM
- drug metabolisation (individual drug responses)

1.1) The authenticity and quality of the plant material:

Establishing authenticity and herb quality has historically relied on morphological and chemical methods. Metabolomic fingerprinting by GC-MS, HPLC-MS or NMR-spectroscopy are now increasingly being used with the aim of developing metabolomic profiles. DNA-based assays have also been introduced to complement the morphological and chemical methods in order to generate molecular "bar codes" for the correct identification of medicinal plants (Sucher & Carles 2008). A recent review (Heuble 2010) of the most commonly used DNA-based technologies (RAPD, RFLP,ARMS, CAPS, AFLP, DAF, ISSR, SDR, sequencing, hybridization and microarrays), included comments on their strengths and their limitations using examples from Chinese medical plants . There is increasing demand to establish open access data banks in a multidisciplinary effort for medicinal plant research and to include e.g. the data (profile) from the European Pharmacopea, in order to develop a common standard for the characterisation of plants (Ulrich-Merzenich et al. 2009). This would be desirable as a long-term objective for CHM. In the meantime basic plant material used in clinical trials should be quality assured using conventional methods of standardisation (chromatographic fingerprint and if available fixed content of biological active substances).

1.2) Analysis of the mode of action of single plants and multicomponent mixtures:

At present, most of the data and thus evidence evaluating the mode of action of CHM relies on the analyses of watery or alcoholic extracts prepared from single plants, rather than from traditional multi-herb decoctions. However relating a specific mode of action to single or even several plant components is highly problematic. Plant(s) have a multitude of components, which differ in their composition with the method of preparation. Interaction among each other and with the target metabolism will also differ according to the composition as well as the preparation. The therapy is multi-targeted and is not adequately explained by an over simplistic focus on single targets.

The use of the HTS-methodology will support the evaluation of the multi-target mode of actions of plants that result from both the way they are prepared and combined within a herbal formula. Their use, however, cannot solve compositional changes of plant(s) or their preparations, but they will eventually support a fast identification of “surrogate” plant components which represent the activity of the plant extract which then could be used to provide markers for standardization of herbal products.

The primary focus of research at present is the reproducibility of profiles of plant components or their combinations using different HTS-technologies. Issues like the permitted magnitude of variation for each technology still need to be addressed. The inclusion of available pre-clinical (and clinical) data using HTS-methods in the documentation of clinical trials would also be desirable.

1.3) Assessment of the toxicity of CHM

Even though CHM is commonly regarded as safe, incidents of nephrotoxicity from the use of Aristolochia species, reports of hepatotoxicity, and adulteration of herbal products with conventional drugs have created understandable public health concerns about CHM. As a consequence increasing attention has been placed on toxicity studies. Melchart et al. (2001) for example demonstrated that about 3.5 % of the analysed CHM imported from China was contaminated with heavy metals.

Recent developments in the field of toxicogenomics may, in the long term, offer tools to enable faster predictions of the toxicological potential of single and also importantly multi-component preparations. Toxicogenomics combines insights from toxicology, genetics, bioinformatics and other HTS-technologies with the aim of predicting toxicity and potential adverse events on the basis of molecular expression profiles (Ulrich-Merzenich et al. 2009). Gene expression data are expected to be more sensitive than traditional toxicological endpoints (Searfoss et al.2004). There is an ongoing collaborative effort to establish a public infrastructure on an international scale for a toxicogenomic database. An overview of the efforts in the public sector to create a toxicogenomic database has been given by Mattes et al. (2004). These databases are constantly updated and can already be used for the screening of potentially toxic ingredients of CHM, e.g. triptolides from Trypterygium-species. Theoretical information about the potentially toxic endpoints can now be obtained before starting a trial. However, these databases are still under development and many of the plant ingredients may not yet be found. In addition, these databases do not (yet) give information on concentration limits for toxic effects. For current research into CHM using these tools would be desirable. However, in the long term, the toxicogenomic assessments along with other HTS-methods (e.g. proteomics, metabolomics), in conjunction with traditional toxicology testing, should become part of the standard assessment for the quality and safety of CHM.

1.4) Drug metabolism (individual responses)

In addition to the potential toxicity of plant components or of their metabolites, the potentially different metabolisation capacity of each patient should also be considered. The metabolisation of drugs depends to a certain degree on the genotypes of key liver enzymes. For example there are 74 allelic variants for cytochrom P450 (CYP) and a series of subvariants for CYP2D6. Based on these genotypes patients have been classified into ultrarapid, extensive, intermediate or poor metabolisers – primary related to lipophile basic substances (Zhou, 2009a; Zhou, 2009b). Thus, knowledge of different gene profiles of patients will enable predictions of possible toxic effects - not only from synthetic drugs, but also from CHM. These data may be instrumental in solving questions regarding major differences in the response to CHM. (The FDA of the USA has already named tests (e.g. the AmpliChip CYP450) as suitable for the use in clinical studies). These recommendations should support the safe use of presently available CHM, but also facilitate the development of novel, safe methods for the administration of CHM formulations.

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