

## “A systems view on the future of medicine: inspiration from Chinese Medicine?”

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In the past decade major changes were seen in the field of industrial drug research: big Pharma companies focused on consolidating their market positions by fusions or takeovers and governments became more and more restrictive in allowing new drugs to the market, using both economic and medical arguments. This came together with a marked decline in the number of novel drugs approved. At the same time globalization and new upcoming economies change the scene and the market for pharmaceuticals.

At present, drugs are available for most major diseases. However, developing drugs that are better than the existing ones becomes more and more expensive and less successful, with a meager number of about 20+ novel chemical entities coming to the market every year. One reason for this stagnation might be that many chronic diseases are clearly multi-factorial and that the main strategy in drug discovery is too much based on the paradigm of “single target – single compound”.

At the same time the globalization and rapid economical growth of large countries like Indian and China have facilitated opening up their traditional medicinal systems to the rest of the world. These systems are based on thousands of years of experience. In the countries themselves, traditional forms of medicine are still playing important roles. Sometimes two systems are used in competition, sometimes in a mixed constellation. In a number of countries, both Western and traditional medicine are taught at university level.

Considering the core of the western medicines arsenal, the majority is based on Eurasian-Mediterranean traditions (e.g., morphine, atropine, salicylate, digoxin) and some from outside cultures (e.g. tubocurarine, cocaine, quinine, reserpine, ephedrine, artemesinin). In the past century novel molecules have been developed based on these natural products and even in the past 25 years about half of the new chemical entities that came to the market were natural products, natural products derivatives or synthetic analogues of natural products (Newman and Cragg, 2007).

The pharmaceutical industry, while having moved away from natural products as primary source for drug discovery is now realizing that traditional medicinal systems might provide new insights or new leads. The recent successful development of artemisinin from Chinese medicine, is a good example of the potential of this approach.

Another reason for the renewed interest in traditional forms of medicine is that many pharmacologists are increasingly realizing that the “one disease – one target – one drug” concept is not always leading to successful cures, in particular not with chronic and degenerative diseases. By contrast, traditional forms of medicine often take a more “holistic” approach. Because of the complexity of diseases, i.e. most have multifactorial causes, a multifactorial medication seems an obvious solution.

The successes in treating AIDS patients were achieved by application of mixtures of drugs, rather than a treatment with a single compound. However, considering the difficulties to develop a single compound into a medicine, the development of a combination of compounds will be exponentially more complex. On the other hand in traditional medicine the use of mixtures is common practice. From the explanation of the role of the different ingredients in a mixture as given in Chinese medicine, one may hypothesize that one or more plants could be responsible for the activity, whereas others are "helpers" that could for example improve absorption, whereas other ingredients will reduce side effects. In any case the "holistic" and personalized approach as usually is said to be practiced in e.g. Chinese and Ayurvedic medicine might be interesting for developing novel concepts for many aspects of pharmaceutical development: biopharmacy (uptake), pharmaceutical technology (formulation), pharmacology (effects, novel targets), pharmacogenetics (personalized treatment), medicinal chemistry (novel leads, synergy, prodrugs), pharmacognosy (production, quality control).

The key issue is how to study the complexity of such medicines. No doubt that the reductionist approach of screening all medicinal plants in an HTS mode would result in hits and leads, but this does not lead to novel insights in e.g. role of synergy or prodrugs. Instead a systems biology approach, which one might consider as reversed drug discovery approach, would probably be better: back to an observation based science without any hypothesis (bias) to start with. The way our ancestors found curare, all known caffeine containing plants, opium, belladonnae, *Artemisia annua*, plants containing cocaine, or quinine etc. They were good observers using all their senses to discover useful plants and concepts in their environment. Nowadays we still have these same senses plus many "-scopic" methods allowing us to see much more than our ancestors did. Systems biology typically is working along this line, observing (measuring) as many different parameter as possible, e.g. the "-omics", physiological parameters, developmental parameters, and environmental parameters, and using various chemometric methods to extract information such as correlations and similarities from large data sets. Such an approach enables identifying compounds in *in-vivo* test systems (animal experiments, clinical trials) that are connected with activity, but not necessarily are the sole active compound(s). Instead they may work in synergy with others, or are prodrugs.

These considerations were reasons for the Netherlands' Top Institute Pharma to organize a one-day workshop in collaboration with the TTI Green Genetics on "A systems view on the future of medicine: inspiration from Chinese Medicine?"

This workshop brought together some 70 experts and interested persons from different backgrounds, such as industry, academia and research institutes, government and regulatory bodies to discuss this theme based on several theses, after first having heard lectures of 5 experts on various aspects of Chinese medicine. The key for understanding Chinese medicine is respect and understanding the culture in which it is embedded.

The day's first speaker, Jan Schroën, gave an overview of the foundations of Chinese medicine in Taoist philosophy. Subsequently he tried to translate this to our Western way of thinking by describing a three dimensional space in which the 6 characteristics of human wellbeing as considered by the Chinese can be placed. The position in this space determines the treatment, the intervention by a Chinese medicine trained medical doctor. Western scientists have to learn new ways of thinking and should be open minded to come to a better understanding of Chinese medicine. One may translate this to a systems biology type of approach to understanding and translating Chinese knowledge to western science.

The second speaker, Jan van der Greef, discussed the systems biology approach as he and his group are applying to successfully study Chinese medicines. Several examples were given, among other a preparation of *Dioscorea nipponica* in which several saponins are present that showed a synergistic effect in stimulating the cardiac function. He particularly emphasized the importance of diagnosis, and the understanding of the Chinese way of diagnosing diseases.

Meindert Danhof discussed the problems of studying combination therapies from a pharmacokinetic-pharmacodynamic point of view. Already in a mixture of two compounds this becomes extremely complex as, for example, the two compounds will at any moment after administration be present in different ratios, requiring at least three dimensional models to predict the effect of a combination of drugs. Conclusion: a systems approach, though difficult, needs to be applied for the analysis of the interactions between the components in a mixture. This should lead to the design of rational combinations of compounds using the complex mixtures as present in Chinese medicine as a source of inspiration. To be able to apply any of the modeling methods compound-related activity and concentration activity relationships should be known.

The next speaker Peter Hylands focused on the importance of quality management and quality control. As in most cases the active compounds are not known, the quality control must be based on a systems approach, linking metabolic profiles with activity. By measuring the metabolic profiles of a large number of accessions of a plant by means of NMR, GC-MS, LC-MS or MS(-MS) and relate this by means of multivariate analysis to relevant biological activity measurements (in-vivo or in-vitro), marker signals for activity can be identified, and critical upper and lower limits of these signals can be defined for the quality control of the plant material. Eventually the compounds responsible for these signals can be identified and used as standards for future quality control. Activity can concern both pharmacological and toxicological aspects of the material.

The final speaker Dr. Xiaorui Zhang, educated as a traditional medical doctor and nowadays team coordinator of the WHO Traditional Medicine Programme in Geneva, described the importance of traditional medicine worldwide and the essential differences between Western and traditional medicine. Essentially the western approach is a reductionist one: find the cause of a disease in the human body. The Chinese is a holistic one in which the total environment of the human being is considered. She said "*A common feature of most systems of Traditional Medicine is that they take a 'holistic' approach towards the sick individual and treat disturbances on the physical, emotional, mental and living environment levels simultaneously.*"

The WHO has adopted at the 62nd WHO Assembly May 2008 a resolution (61.21) for a global strategy on public health, innovation and intellectual property. This is based on the WHO Traditional Medicine Strategy which has as key objective: ensuring safety, efficacy and quality of traditional medicines. The resolution particularly emphasizes the need for setting priorities concerning diseases and building up the human capacities worldwide for coming to evidence based traditional medicines. An important need is a common language that facilitates communication and understanding between traditional medicine practitioners and researchers of conventional medicines. To come to evidence-based traditional medicines clear rules are needed for what evidence is required, and high quality studies should be performed. For example, many of the clinical studies performed so far did not fulfill all scientific requirements to be really conclusive. This is in part due to problems specific to medicinal plants, e.g. what controls to use, and how to deal in a clinical trial with the aspect of individualization of therapeutic interventions.

Loaded with all the information of the presentations the participants discussed six theses concerning the potential market of Chinese medicine in Europe and the US, the potential of systems biology to study multifactorial medicines, the problems of variable quality in studying activity of Chinese medicine, registration based on clinical trials and safety data, reversed drug discovery by starting with clinical trials to come to leads and the need of western and Chinese specialists to develop innovative ways to develop novel medicines or treatments from Chinese medicines.

Obviously such theses lead to a variety of views which are difficult to summarize in general statements. A major issue in all discussions was quality, which raised the question why there is not more work done on the horticultural aspects. For example, production of medicinal plants in green houses under good agricultural practice would be a major step forward to the reproducible quality eventually needed for registration as medicines, but also for clinical trials this will be crucial. Concerning the reversed drug discovery, clinical evidence in combination with a systems biology/pharmacology approach would be of great interest to unravel the possible modes of action of Chinese medicine, including the presence of prodrugs and synergy. Synergy, it was mentioned, is something that cannot easily be engineered for pure compounds, therefore the reversed pharmacology offers an interesting option to discover this sort of interaction between compounds (Wang et al. 2008).

As overall conclusion it became clear that we may expect an explosion of research projects in the field of Chinese medicine, which will at least lead to validation of a number of Chinese medicines and eventually to evidence-based Chinese medicines entering the global market. It may also lead to novel drugs following the present concept of single target – single compound, assuming that the potential problems of IP-rights on traditional knowledge can be solved.

If synergy can be proven to be an important factor for the activity of Chinese medicine, this will give novel impulses to apply this principle more widely in pharmacotherapy. The recently approved application in the EU FP7 program on health for a large European network on "Good Practices in Traditional Chinese Medicine Research in the Post-genomic Era" can be seen as an example of the actions needed to come to better understanding of Chinese medicine and which will encourage high level scientific collaborations between scientists of the two worlds. This network is coordinated by Qihe Xu, MD & PhD, Department of Renal Medicine, King's College London and includes and encompasses 30 groups, among which 5 from China, covering all aspects of research on Chinese medicine.

We all have a great learning experience ahead!

#### **references**

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