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# **Chapter 7**

**Summary, conclusions, and perspectives**



Personalized medicine is the key to moving away from the conventional medical concepts of “one disease, one target” and “one-size-fits-all”.<sup>1</sup> Personalized medicine also includes monitoring the individual patient’s comprehensive profile of nutritional, psychological, lifestyle, and other factors, and it can facilitate the development of multiple therapeutic strategies aimed at providing the best possible course of treatment.<sup>1</sup> Phenotyping patients is believed to play an essential role in achieving personalized medicine.<sup>2</sup> Traditional Chinese medicine (TCM)–based diagnostics uses important information regarding personalized phenotypes (so-called “syndrome subtypes”) at a holistic level, and TCM can theoretically be explored using systems biology–based approach.<sup>2</sup> To investigate TCM-based diagnostics, a systematic, dynamic measurement is needed. Ultra-weak photon emission (UPE) provides a non-invasive, comprehensive measure of dynamics with respect to the physiological state of a living organism.<sup>3</sup> In addition, because UPE can be used to measure various physiological states, it can be used to identify putative diagnostic properties.<sup>3–6</sup> Measuring UPE may therefore approximate the organizational level of TCM-based diagnostics. Thus, UPE may serve as a potential tool for characterizing “syndrome subtypes”, providing objective data to support TCM-based diagnostics.

To test this hypothesis, we performed an explorative study in 44 pre-diabetic subjects. In this study, which is presented in **Chapter 3**, we combined UPE measurements with TCM-based diagnostics in order to identify personalized phenotypes (“syndrome subtypes”) in these subjects. Three physicians who were trained in TCM achieved 85% diagnostic consistency by standardizing 26 symptoms in pre-diabetic subjects, thereby identifying the following three “syndrome subtypes”: Qi-Yin deficiency, Qi-Yin deficiency with dampness, and Qi-Yin deficiency with stagnation.<sup>7</sup> Based on TCM-based diagnostic concepts, these three subtypes share a common fundamental cross-biological background— Qi-Yin deficiency—which can be used to reflect hypermetabolism-induced mild inflammatory status and

chronic fatigue syndrome.<sup>7</sup> The additional pathological factor is closely related to an unhealthy lifestyle and poor diet. Dampness can lead to complications such as metabolic syndrome, hypertension, and angionosis.<sup>7-9</sup> Another pathological factor—stagnation—may be associated with pressure and tension, thereby leading to emotional problems, impaired blood circulation, and diabetic peripheral neuropathy.<sup>7,8,10</sup> Thus, TCM-based diagnostics (i.e., the identification of specific “syndrome subtypes”) may provide important information with respect to developing a personalized profile for predicting pre-diabetic patients, thereby helping prevent the onset of diabetes-related complications.

A total of 16 UPE parameters were measured at four anatomical sites in our cohort of 44 pre-diabetic subjects; this analysis reliably identified the three TCM-based “syndrome subtypes”. In addition, a correlation network between these 16 UPE parameters and 26 symptoms (i.e., items) was also performed to indicate the associations and differences between these three phenotypes. These results indicate that UPE is a promising methodology for studying TCM-based diagnostics. This is the first evidence demonstrating the feasibility of combining UPE parameters with TCM-based diagnostics in order to investigate syndrome subtypes among pre-diabetic subjects. Future studies should include larger cohorts, more TCM-trained physicians and syndrome subtypes, and other disease cohorts in order to strengthen the value of this approach. Moreover, measuring UPE signals at additional anatomical sites in the human body may provide additional information in support of TCM-based diagnostics. Given the relationship between specific diseases and acupuncture points (as discussed in **Chapter 2**), combining UPE with TCM-based acupuncture theory may help with the selection of suitable anatomical sites for measuring UPE; this approach may also help characterize and standardize TCM-based acupuncture treatment both qualitatively and quantitatively. Moreover, similar analyses can be performed in combination with metabolomics based on various platforms in order to establish a comprehensive molecular and/or biochemical basis

of UPE and TCM-based diagnostics. If this molecular and individual phenotype information can be correlated with UPE parameters, then UPE might represent a highly sensitive, non-invasive technological platform for diagnosing disease and for studying the efficacy of various therapeutic agents, ultimately achieving the goal of personalized medicine.

In Chinese medicine, “personalized intervention” refers to the use of various Chinese herbal prescriptions for treating various disease “syndromes”.<sup>11</sup> The Chinese herbal prescription is prepared depending on the herb’s ethnopharmacological effects observed in clinical practice, thereby providing Chinese herbal medicine (CHM)–based concepts such as “indigenous medicinal materials” and herbal “taste” properties.<sup>12,13</sup> These CHM-based concepts are closely related to TCM-based diagnostics and reflect the individual’s holistic response to herbs from a multi-target, multi-dimensional systems pharmacology perspective. Although these CHM-based concepts are often interpreted using specific bioactive compounds present in the herbs, the herb’s ethnopharmacological effects may be due to more than just the bioactive compounds in the herb; indeed, other chemical components in the herbs may act synergistically with bioactive compounds to increase the herb’s therapeutic efficacy.<sup>14</sup> Therefore, a comprehensive, systematic measurement is needed in order to investigate CHM-based concepts. In this thesis, we used photon-induced delayed luminescence (DL)—a rapid, direct, systematic measurement—to study the holistic properties of a medicinal herb.

In **Chapter 4**, we discuss the development of a protocol for measuring DL in dried herbal materials. Our results indicate that the water content of herbal materials is an important factor for achieving stable, reproducible DL measurements. Therefore, the conditions used to store the herbal materials should be considered when analyzing DL data. To demonstrate the feasibility of our DL measurement protocol, we used DL to measure several herbal materials prepared under various conditions. The DL parameters reliably distinguished between herbs of different ages, herbs grown under

different environmental conditions, and herbs processed using different methods. Given that these conditions are closely related to the quality and therapeutic properties of Chinese herbal medicines,<sup>15–20</sup> we hypothesized that measuring DL may provide a novel technological platform for studying CHM-based concepts. To test this hypothesis, we conducted the experiments described in **Chapter 5** and **Chapter 6**. It worth noting that in Chapter 4 we measured DL for 5 min in order to investigate the long-term properties of herbal DL measurements. To identify differences in DL properties between herbs, it is not necessary to measure herbal samples for such a long time; indeed, measuring DL for as little as 1 min can usually provide sufficient information regarding DL parameters to allow for meaningful analyses.

In traditional Chinese medicine, the term “indigenous medicinal materials” is used to indicate medicinal plants that are produced under unique environmental conditions, therefore providing optimal quality and therapeutic properties.<sup>13</sup> This ethnopharmacological concept is based on the premise that environmental factors can directly influence the quality of the herb. In Chapter 5 both chemical analyses and DL measurements reflected that the quality and composition of medicinal rhubarb are influenced by altitude variations. The identified correlations between DL parameters and chemical constituents suggest that DL may also be correlated with the bioactive properties of rhubarb. To test this hypothesis, future studies should use a wider range of rhubarb samples and should include a comprehensive profile of secondary metabolites contained in rhubarb. Hence, identifying the correlation network between a comprehensive panel of secondary metabolites and DL parameters may reveal the true potential of using DL to predict the quality of rhubarb. The approach presented in Chapter 4 can also be used to investigate the effect of growing and/or processing conditions on the quality of other medicinal herbs. These studies may provide further evidence that DL is a powerful tool for assessing the quality of herbal medications.



In accordance with the theory of traditional Chinese medicine, all herbs are assigned a therapeutic description of “taste”, which is used to reflect the herb’s major ethnopharmacological category, thereby revealing the herb’s therapeutic properties.<sup>21</sup> This so-called “taste” property can help guide the preparation of various herbal formulas in order to realize personalized interventions.<sup>21</sup> As discussed in Chapter 6, DL parameters were able to distinguish between herbs in the “sweet” category and herbs in the other “taste” categories, and measuring dendritic cell-based immunomodulatory responses revealed that the immunostimulatory effect of “sweet” herbs differed significantly from “pungent” and “bitter” herbs, which generally support the results obtained using DL measurements. However, DL cannot be used to distinguish between “pungent” and “bitter” herbs. This indicates a possible limitation of using DL, and it may reflect the limited number of herbal materials that we studied, which justifies further investigation. First, another fitting method can potentially be used to extract different DL parameters in the herb’s DL profile.<sup>22</sup> These additional DL parameters may help differentiate between different “taste” herbs. In addition, DL spectral analysis may provide a potential method for studying the therapeutic properties of herbs based on their ethnopharmacological effects.<sup>23</sup>

Second, studying larger numbers of herbs, more categories of herbal “tastes”, and more components in herbal plants will help support the feasibility of this DL-based approach. Moreover, cell-based assays are not necessarily sufficient for providing a complete system-based approach for observing the pharmacological activity of herbal medicines. A complete system-based model (for example, zebrafish) may provide an additional platform for observing the comprehensive bioactivities of herbs that have been classified using DL. The preliminary experiments discussed in Chapters 5 and 6 were designed using DL measurements combined with CHM-based concepts. Our results indicate that DL may be widely applicable to the study of herbal medicines; in addition to reflecting the quality of specific herbs. Therefore,

DL is a promising technique that represents a robust technological platform for investigating Chinese herbal medicines both qualitatively and quantitatively.

In conclusion, both UPE and DL have high potential for studying the concepts of medicine at the systems levels. The results reported in this thesis can be used to develop future research strategies guided by traditional Chinese medicine-based concepts. As analytical and statistical methods improve, and as UPE and DL approaches are integrated further into medical research, UPE and DL will likely provide valuable new insights into personalized medicine.

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