Development of personalized health monitoring using ultra-weak photon emission based on systems medicine concepts

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Chapter 1

Introduction

Background

In the past century, medical science has improved considerably and has provided tools for managing nearly all major diseases, including autoimmune diseases, cardio- and cerebrovascular disease, and cancer. At the same time, adverse drug reactions and side effects have become increasingly important issues. For example, in the United States, adverse drug reactions range from the sixth to the fourth leading course of death among hospitalized patients.[1] In addition, adverse drug reactions are closely related to drug safety and efficacy in the human body. Strikingly, most drugs work as intended in fewer than half of patients, meaning that a particular drug can be effective in some individuals (the so-called responders), but fail to be effective in others (i.e., non-responders), thereby leading to the possibility of adverse drug reactions. This situation has prompted us to rethink the conventional drug development model of "one drug fits all", a model that is based on double-blind clinical trials designed to predict a drug's average therapeutic outcome in the broadest, most homogenous groups of patients. However, a growing body of evidence supports the notion that a patient's response to a given drug can depend on a variety of integrated factors, including the patient's age, nutritional state, lifestyle, emotional state, and the surrounding environment.[2] Given that each individual has a unique profile with respect to these complex factors, we must revise our thinking to achieve the concept of "the right therapy, with the right drug, in the right patient".[2] Therefore, individualized predictive medicine—i.e., personalized medicine—is becoming the focus of shifting away from the "one drug fits all" approach.[3]

Personalized medicine

The goal of personalized medicine is to develop a therapy using the right drug, at the right dose, at the right time, in the right patient.[1] Personalized medicine is based on the notion that each patient's disease can be unique, and therefore each patient requires individual treatment.[4] This notion suggests that disease profiles vary among individuals with respect to the cause, progression, and response to therapy.[4]

Therefore, the key to achieving truly personalized medicine lies in the diagnosis of disease. Developing a novel, effective strategy for diagnosing disease in individual patients can lead to a more effective personalized approach to disease management and prevention.[5] To understand the importance of effective diagnostics, we must first understand the notions of dynamic health and disease. Fig. 1 schematically illustrates a dynamic system that can respond automatically and effectively in the resilient state (allostasis), thereby maintaining healthy status (homeostasis).[5,6] When this dynamic system experiences a reversible pathological event, the appropriate intervention returns the system to homeostasis.[5] However, of this dynamic system loses its ability to regulate itself, irreversible pathology and disease develop.[5,6]

The presence of a dynamic system that regulates health and disease indicates that many chronic diseases involve processes that are long-term, nonlinear, multifactorial and highly complex.[5,7] For example, type 2 diabetes is multifactorial in origin and is associated with genetic factors, metabolic disorders, and lifestyle-related risk factors.[8,9] Type 2 diabetes can be present in an early, undetected form for more than ten years, during which dysglycemia increases the risk of severe complications.[10]

Therefore, conventional diagnostics and treatment may not be completely effective in this dynamic state, and personalized diagnostics may enable the clinician to monitor the dynamic state in both health and disease; moreover, it may also help identify biomarkers in the early stages of chronic disease, as well as helping develop a suitable intervention for individual patients.[5,11]

Importantly, personalized diagnostics can be used to capture phenotype information for specific patients, thereby leading to the development of personalized healthcare strategies (Fig. 2).[5,11] Recently, a metabolomics-based approach has provided researchers with the opportunity to understand the changes that occur in the comprehensive metabolite profile in body fluids during various conditions, including changes in nutrition, environment, psychological state, and disease stage.[11] Thus, it is now possible to stratify patient populations into distinct phenotypes based on

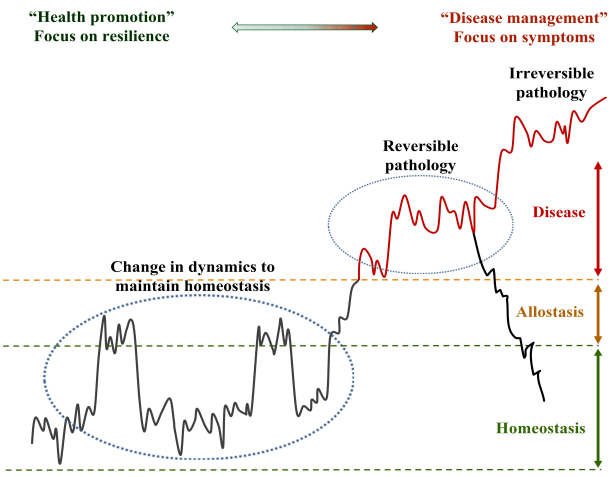

Fig. 1 Schematic diagram illustrating a dynamic system of regulation in both health and disease.

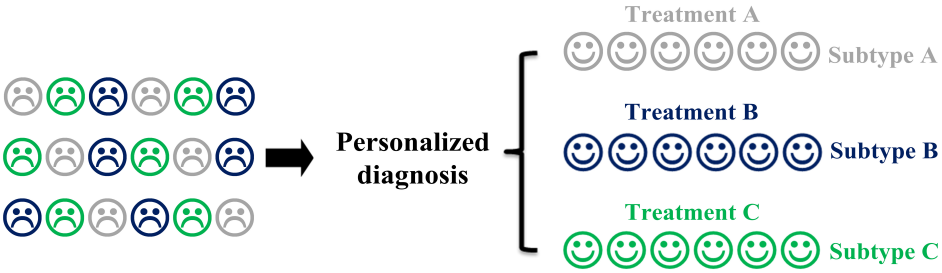

Fig. 2 Schematic diagram illustrating the use of personalized diagnostics to stratify patient populations. The treatment used corresponds to each patient's subtype, ultimately leading to personalized medicine for individual patients in each subtype.

molecular biomarker profiles, an approach that has been proposed for solving the aforementioned responder/non-responder issue, thereby achieving personalized medicine.[11] Interestingly, many studies regarding patient phenotypes are guided by the concepts of traditional Chinese medicine (TCM)–based diagnostics.[12–18] This indicates that TCM-based diagnostics can contribute extremely valuable information regarding personalized medicine.

Traditional Chinese medicine–based concepts

Traditional Chinese medicine (TCM)-based concepts are based on a holistic view of health and disease and therefore represent systems-based medicine.[5] Because TCM

and Western medicine differ with respect to their views regarding diagnostic goals, they also use different diagnostic methodologies.[19] In Western medicine, pathological factors are believed to cause disease; therefore, research and the development of therapeutic strategies focus primarily on these pathological mechanisms.[19] In contrast, TCM-based diagnostics focuses on the body's *response* to these pathological factors; therefore, TCM-based diagnostic strategies aim to examine the patient's overall functional state.[19] According to the TCM theory, one's overall functional state defines whether one is experiencing health or disease.[20] This state depends on the dynamic balance among complex interactions between one's physiological state and other factors such as age, gender, emotional state, seasonal fluctuations, and pathological factors.[20] The patient's dynamic response to these interactions provides a functional profile of the patient's disease-related symptoms and/or signs.[21] In addition, these symptoms and/or signs can be diagnosed by physicians trained in TCM using several approaches, including palpation, listening and smelling, inspection, and inquiry, thereby identifying specific "syndrome subtypes" within a specific disease.[22] For example, rheumatoid arthritis can be differentiated generally into "Heat syndrome" and "Cold syndrome" in order to describe different patterns within patient populations based on TCM-based diagnostics.[5]

Importantly, the identification of "syndrome subtypes" is the most important concept guiding personalized interventions using Chinese herbal medicine (CHM),[21] an approach that has been used in China for thousands of years to maintain health and treat disease.[23] In this long history, the Chinese have observed a wide variety of responses to herbs in many clinical settings and have established many important concepts with respect to the pharmacological actions and therapeutic effects of CHM.[23] For example, so-called "indigenous medicinal materials"—which refers to herbal medicines produced in a specific geographic region—may actually represent the optimal responses and therapeutic effects in the human body.[24] Another crucial

concept is based on the therapeutic categories of herbs, which are closely related to "syndrome subtypes".

CHMs are usually marked by specific descriptors to classify their therapeutic properties according to their effects in patients.[23] Herbs with specific descriptors are targeted to specific syndromes. For example, herbs with a "Heat-cleansing effect" can be used to treat "Heat syndrome", and these herbs are often marked by a "cold" descriptor.[25] In addition, herbs with a "sweet" descriptor are generally used to treat "Deficiency syndrome", as these herbs can nourish the body, thereby promoting health.[26] Herbs with different therapeutic descriptors can be combined to prepare a Chinese herbal formula, which can be used to treat complex syndromes such as "Deficiency of both Qi and Yin syndrome", providing personalized interventions for treating unique "syndrome subtypes" within a specific disease.[21,27] In summary, the basic concept in TCM is to combine individual diagnostics with individual interventions. Therefore, exploring TCM-based concepts may provide fresh insight into personalized healthcare and management strategies. However, TCM-based diagnostics and CHM-based treatments are descriptive, phenomenological concepts; therefore, objective, evidence-based data is needed in order to support these concepts. Applying a systems biology–based approach has been proposed to achieve this goal.[5]

Systems biology–based approaches

The aim of systems biology is to understand living organisms at the systems level,[28,29] thereby promoting personalized medicine.[3,5] The field of systems biology is extremely broad, and multi-technology approaches should be used for specific research purposes.[28] To develop a systems biology–based approach, we must first understand the hierarchical structure of a living organism, ranging from the biochemical and molecular levels to the cellular and organ levels, all the way to the integrated systems level, as well as the system's dynamics over time.[7,29] To date, so-called "omics"-based technologies (e.g., genomics, proteomics, metabolomics, etc.) have been used to study different hierarchical structures in a biological system.[5,29,30]

In addition, statistical tools such as clustering and network tools have been used successfully to analyze large amounts of data obtained using omics-based technologies.[31] Thus, a research approach for measuring and analyzing biological systems has been established.

Because TCM-based diagnostics (i.e., "syndrome subtypes") reflects the body's physiological and pathological status at a large-scale organizational level, systems biology–based approaches may provide a suitable method for studying this status. Recently, metabolomics-based approaches were used to investigate "syndrome subtypes" of specific diseases guided by TCM-based diagnostics.[12–18] Metabolomics provides a comprehensive overview of the molecular metabolites in a biological system and can be used to establish the physiological and/or pathological status of a living organism.[32] In principle, this approach is suitable for studying TCM-based diagnostics. However, because metabolomics can only be performed using currently available analytical platforms, it may not necessarily cover the entire metabolome. In addition, metabolomics provides a picture of the system's physiological and/or pathological status at a single point in time, but does not provide information regarding the system's dynamics. Therefore, metabolomics may not completely reflect TCM-based diagnostics, and complementary tools are still needed in order to further characterize TCM-based diagnostics at an integrated, dynamic systems level. In this thesis, we propose that measuring ultra-weak photon emission may provide a suitable technique for studying TCM-based diagnostics.

Ultra-weak photon emission

Measuring ultra-weak photon emission (UPE) is a non-invasive method for recording the physiological state in living organisms.[33–37] Recent studies suggest that UPE may reflect the biological rhythms of the human body with time-dependent dynamics.[38] In addition, UPE may provide insight into nonlinear regulatory processes (e.g., coherence) at a high systems level.[7] Moreover, UPE can be used to measure a variety of physiological states, thereby providing potential diagnostic

applications.[36] Therefore, measuring UPE may approximate the organizational level of TCM-based diagnostics, providing objective data that can be used to characterize "syndrome subtypes". On the other hand, TCM-based diagnostics—which focuses on obtaining a holistic pattern of systems—may improve our understanding of UPE patterns measured in the human body, thereby contributing to the development of novel strategies for achieving personalized medicine.[7] To study CHM-based characteristics at the same systems level as TCM-based diagnostics, a comprehensive measuring tool is also needed. Photon-induced delayed luminescence (DL), which is the long-term emission of photons from various materials following excitation with light, has been proposed for use in studying the therapeutic properties of Chinese medicinal herbs.[39] Therefore, combining a systems biology–based approach with photon emission and robust statistical tools may provide fresh insight into TCM-based concepts, leading to personalized diagnostics and interventions and ultimately achieving personalized medicine.

Scope and outline of this thesis

The studies described in this thesis were performed in order to develop personalized approaches to health monitoring using UPE and DL methods in combination with TCM-based concepts. Fig. 3 provides a schematic overview of the following two research aspects in this thesis: *i*) studying TCM-based diagnostics using UPE measurements (Fig. 3, *left*) and *ii*) studying CHM-based characteristics using DL analyses (Fig. 3, *right*). To investigate systems-based diagnostics by combining UPE with TCM-based concepts, we first studied the Chinese literature published from 1979 through 1998, as a vast amount of research in this period was based on UPE and/or TCM-based diagnostics; these results are presented in **Chapter 2**. Our analysis revealed that UPE has clear potential in terms of improving our understanding of the systems-level view regarding health and disease, guided by TCM-based diagnostics. Next, we investigated whether UPE can be used as a tool to identify the three distinct "syndrome subtypes" in subjects with early-stage type 2

diabetes; the subtypes were diagnosed by physicians who were trained in TCM-based diagnostics. In this preliminary study, which is presented in **Chapter 3**, statistical analyses such as logistic regression and correlation networks provide the first evidence that UPE parameters can be used to differentiate between "syndrome subtypes" identified using TCM-based diagnostics.

In **Chapter 4**, we discuss systems interventions regarding CHM-based concepts (e.g., herbal therapeutic properties) using DL based on a stable, reproducible experimental protocol to optimize DL excitation time, herbal powder size, and the remaining water content in the dried herbal materials. DL is a promising method for examining both the quality and therapeutic properties of dried Chinese herbal materials. In **Chapter 5**, we used an established protocol to study the feasibility of using DL to measure differences in the quality of herbal medicines. In this chapter, both DL measurements and chemical analysis were used to reflect differences in the therapeutic quality of rhubarb due to differences in environment factors. We then linked DL parameters to specific bioactive compounds in rhubarb. In **Chapter 6**, we used DL to characterize the therapeutic categories of herbal materials. To provide biological relevance to the DL results, we also performed an in vitro dendritic cell−based immunomodulatory assay. Finally, in **Chapter 7** we present and discuss conclusions and future perspectives regarding the studies presented in this thesis.

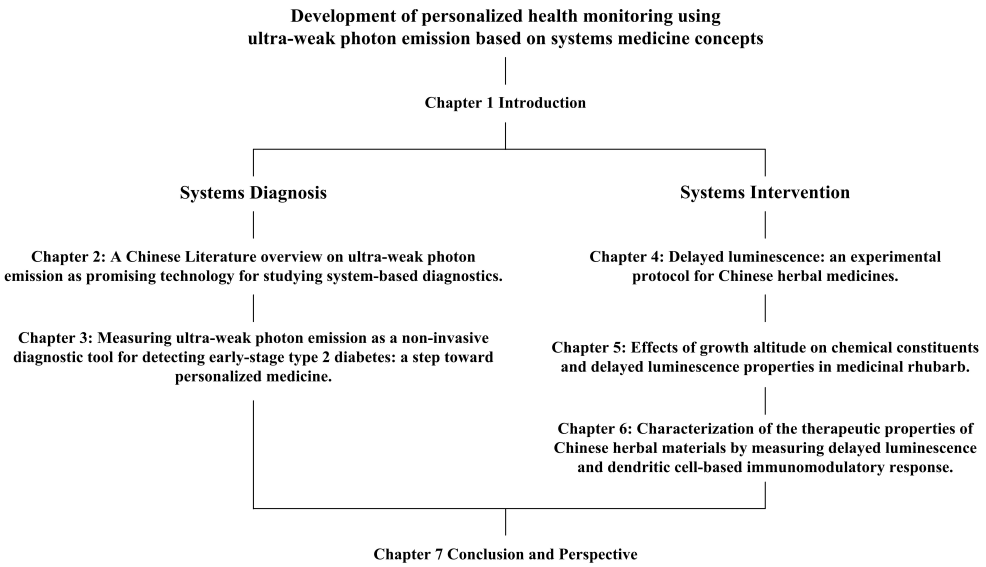

Fig. 3 Schematic overview of the framework in this thesis.

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