AN INTEGRATED POC SOLUTION FOR DIAGNOSIS AND THERAPY MONITORING OF HEART FAILURE PATIENTS

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KardiaTool aim

KardiaTool will develop a novel personalized MNBS platform and bring a new laboratory proven concept from the laboratory to clinic, addressing priority needs in healthcare diagnosis and therapy monitoring for patients with symptoms for HF and patients with known HF.

The platform will incorporate key enabling technologies in the field of advanced materials:

- for the synthesis of magnetic nanoparticles (MNPs) and development of MNPs coatings, towards providing adequate physicochemistry and tailored surface properties,
- for the development of the Lab-on-Chip (LOC) and Point-of-Care (POC) device.

KardiaTool innovative features

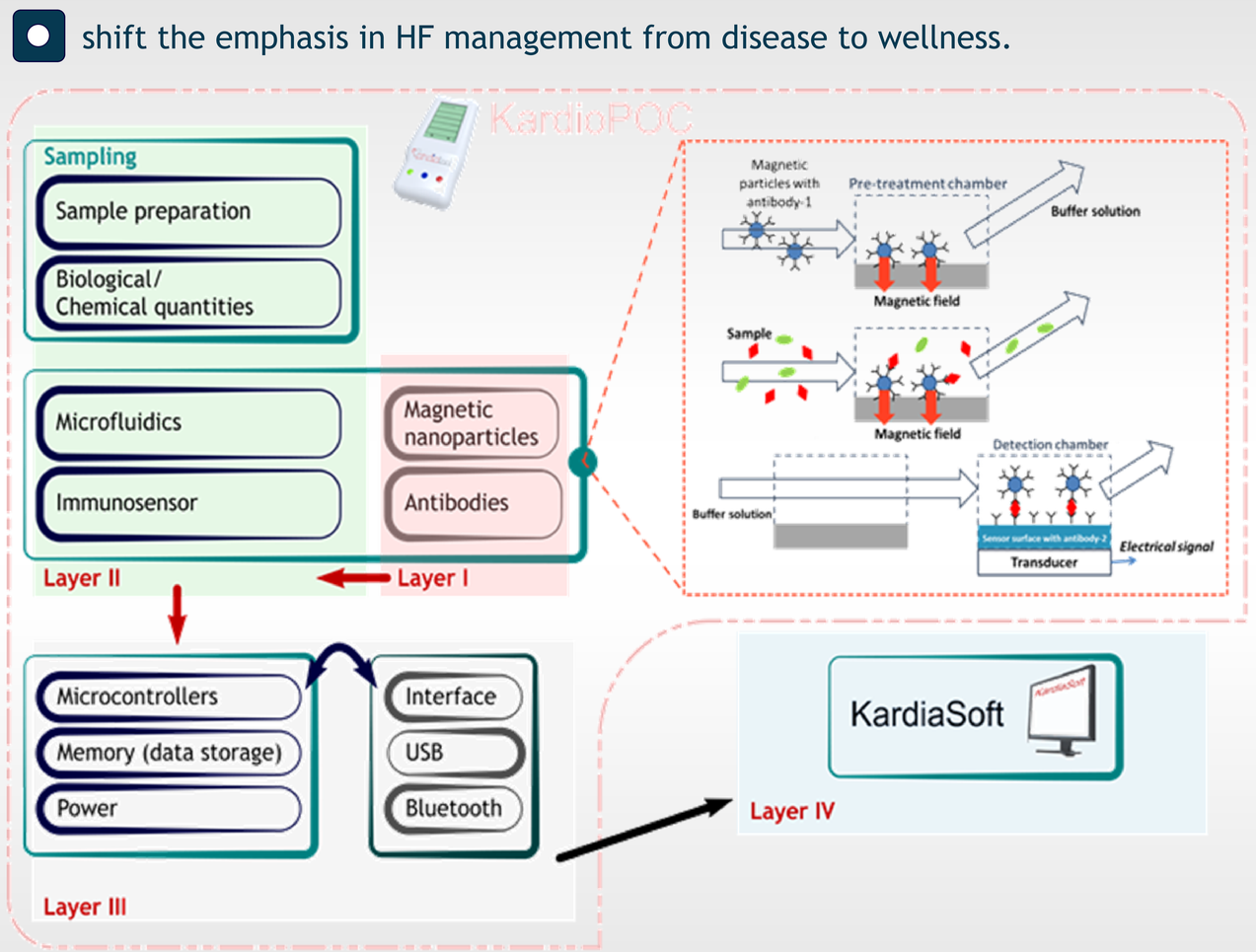
KardiaTool will include new features to:

- provide the capability of simultaneously measuring the following four saliva biomarkers: (i) N-terminal pro b-type natriuretic peptide (NT-proBNP), (ii) Tumor Necrosis Factor –a (TNF-a), (iii) Interleukin- 10 (IL-10), (iv) Cortisol,
- diagnose HF by detecting the disease at an early stage, when it is easier and less expensive to treat effectively,
- reduce the time, cost and failure of misdiagnosis,
- monitor therapy of HF patients and stratify them into groups of high and low risk for HF event (decompensation, mortality),
- shift the emphasis in HF management from disease to wellness.

KardiaTool platform

The KardiaTool platform consists of the following layers:

(i) *Layer I* includes the MNPs and the antibodies,
(ii) *Layer II* includes the saliva samples, the microfluidic system and the immunosensor component,
(iii) *Layer III* includes the microcontroller, the memory and the power supply, communication interface, instrumentation of LOC,
(iv) *Layer IV* includes the KardiaSoft.



KardiaSoft

It will be a multi-purpose and multifunctional computational tool that will be based on a variety of HF related data. The decision support processing is a critical component of KardiaSoft tool since it will provide valuable clinical information to the healthcare professionals and assist them in (i) diagnosis of HF, (ii) profiling and stratification of HF patients, (iii) prediction of HF adverse events, and (iv) therapy monitoring, in real time. The machine learning techniques, that will be tested, include decision trees and rule based approaches for HF diagnosis, clustering algorithms for profiling and patient stratification, dynamic techniques, which take time dependencies into consideration, for progress prediction and complex regression techniques for estimating the time and probability of HF adverse events. Through the detection of changes in the output of the above mentioned functionalities (i-iii) therapy monitoring will be achieved.

KardiaPOC

The KardiaPOC device combines:

i) Microfluidic system

A microfluidic cartridge consisting of a network of channels and chambers, as well as the microfluidic flow control elements, enabling precise fluid displacement for high reliability measurements will be developed. KardiaPOC microfluidic cartridge will be assembled to the LOC circuit board containing the magnetic and sensing chips.

ii) Nanocarriers

A new concept of nanocarriers consisting of MNPs functionalized with secondary antibodies for pre-concentration of the HF biomarkers will be followed. Functionalized MNPs made of iron oxide (Fe_3O_4-NPs), which have attracted much attention in the fabrication of bio-sensing systems, due to their unique properties (super-paramagnetism, biocompatibility, signal amplification, etc.) will be developed. One of the novelties associated to KardiaTool platform is the "*to and fro*" movement of the functionalized MNPs in the front chamber that hosts the electromagnet. This is achieved by the on/off switching of the electromagnet that will attract and liberate the nanocollector MNPs. This shall permit that the loading of the MNPs becomes possible not only by diffusion but also by convection.

iii) Immunosensors

Detection of saliva biomarkers requires high detectability. The ultimate state-of-the-art Field Effect Transistor designs will be used together with the MNPs to improve the electrochemical signal. Technologies for sample pre-treatment and pre-concentration chamber together with detection chamber will be integrated for the very first time in the same chip with maximized resolution and reliability in large volume scalable low cost devices.

iv) MEMS

Different types of coils with and without magnetic cores will be microfabricated with MEMS processing techniques on silicon wafers and will be tested for power limitations, performance and reliability within the microfluidic environment. More specifically, the following types of inductors will be evaluated: (i) square spiral inductor with air core, (ii) double spiral air core, (iii) single or double spiral with magnetic core, (iv) toroid with magnetic core. Finite Element Analysis of the coils will help to narrow down the designs that will be fabricated on silicon wafers for functionality tests.

v) Instrumentation

A new electronic circuit for the determination of the transconducatance of protein-modified HfO2 (Hafnium dioxide) Ion Sensitive Field Effect Transistor will be designed and fabricated. Major objectives and features of the instrumentation will be: (i) small form factor applying Surface Mount Devices, in smallest sizes, (ii) low power consumption using selected components, (iii) onboard power and memory management, (iv) standardized communication interfaces and data transfer, (v) processing unit for system control and measurement analysis, (vi) various functional blocks for the system control of the biochemical sensor: initialization, cartridge detection, drivers for micro-pumps and micro-coils and, (vii) various functional blocks for the Electrochemical impedance spectroscopy measurement.

KardiaTool proof of concept

The clinical testing consists of two stages:

- a small clinical testing for the design and development of the KardiaSoft tool (135 subjects),
- an early clinical testing for the validation of the KardiaTool platform (90 subjects),
- 45 subjects of Group I (patients with symptoms of HF and known HF),
- 90 subjects of Group II (patients with symptoms - hypertension, obesity - but without HF),
- 90 subjects of Group III (patients with acute HF).

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