UE Life Sciences Inc.

Annual Progress Report: 2011 Nonformula Grant

Reporting Period

July 1, 2013 – June 30, 2014

Nonformula Grant Overview

UE Life Sciences Inc. received $878,244 in nonformula funds for the grant award period June 1, 2012 through November 27, 2014. Accomplishments for the reporting period are described below.

Research Project: Project Title and Purpose

Commercial Prototype Development and Clinical Validation of Low-Cost Hand-Held Breast Scanner – The purpose of this project is to further develop and clinically validate a low-cost, easy-to-use mobile medical technology that can noninvasively (from the surface of the breasts) detect and classify breast tumor by measuring its mechanical properties in-vivo. For women with dense breasts, women at higher than normal risk due to genetic and family history and women younger than 40 years of age, conventional tools and methods (Mammogram, Clinical Breast Exam) are less effective. For these women, patented Piezoelectric Finger Sensor (PEFS) technology may offer a suitable adjunctive screening solution. Pilot clinical study results for breast cancer/abnormality detection and classification are promising; 71 cases ex-vivo with 94% sensitivity, and 40 cases in-vivo with 86% positive predictive value. PEFS detected 9 out of 11 clinician non-palpable tumors and 1 invasive cancer missed on mammogram.

Anticipated Duration of Project

6/1/2012 – 11/27/2014

Project Overview

Clinical Research Objective: To further develop and clinically validate Piezoelectric Finger Sensor (PEFS) based mobile breast scanner.

Aim 1: To develop a low-cost, accurate and easy-to-use hand-held breast scanner for commercial application:
Sub-Aim 1a: To develop software and signal processing algorithms.
Sub-Aim 1b: To reduce the overall procedure duration.
Sub-Aim 1c: To integrate low-power electronics within the PEFS sensor.
Sub-Aim 1d: To develop connectivity with various mobile operating system environments.

Specific Aim 2: To clinically validate the effectiveness of PEFS breast scanner:

Sub-Aim 2a: To correlate PEFS findings with conventional exams for tumor *identification*, in-vivo.

Sub-Aim 2b: To correlate PEFS findings with conventional exams for tumor *classification*, in-vivo.

Sub-Aim 2c: To compare the efficacy of PEFS against hand-palpation using gelatin breast phantoms.

Methods for achieving the above objectives and aims:

Sub Aim 1a: Apply image processing and frequency analysis techniques to earlier raw PEF data to extract physical features, use MatLab and Simulink to implement filters and digital signal processing algorithms. The tuning of the analysis will be based on a 'metaheuristic' optimization approach.

Sub Aim 1b: Build multiple array (4x4) PEFS sensor, positioning by optical sensor or gyroscope integration.

Sub Aim 1c: Redesign the controller board circuitry for miniaturization to 3"x3".

Sub Aim 1d: Application Programming Interface (API) enables building native mobile application.

Sub Aim 2a, 2b: Under an IRB-approved clinical study, consenting women meeting the study criteria will be enrolled in the study. Asymptomatic women presenting to the clinic for routine breast exam and symptomatic women scheduled to undergo pathological exam will be examined by a trained technician using PEFS but blinded to mammogram/pathology results. Results will be documented and analyzed for efficacy metrics.

Sub Aim 2c: General population women will be requested to palpate a mechanical gelatin breast phantom to detect embedded 'tumor-like' lumps first by using the PEFS device and then by using bare hands. The same test will be repeated by clinicians/technicians skilled in performing Clinical Breast Exam (CBE). Results will be compared.

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Other Participating Researchers

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Ari Brooks, MD; Brian Englander, MD – employed by Pennsylvania Hospital
Ian White, MS – employed by DesignDesign Inc.
Evan Malone, PhD – employed by NextFab Studios

Expected Research Outcomes and Benefits

The expected research outcome is a commercially built, accurate, easy-to-use, low-cost and portable medical device that can be used by physicians at the clinic and potentially even by the general population at home, to routinely monitor breasts for small abnormal structures. The research project will validate the device's efficacy in comparison with conventional modalities in being able to identify and classify various breast abnormalities.

The resulting outcome will be a mobile medical device ready for FDA 510(k) and other regulatory submissions.

As per Census.gov, 25% (1.6m) of women in Pennsylvania and 40m women in the USA are currently expected to be between the ages of 20 and 40 years. For these women, PEFS will make it easier to accurately detect nonpalpable lumps, which are otherwise difficult to locate at an early stage by the current standard of care, i.e., Clinical Breast Exam (CBE) or Breast Self Exam (BSE); hence addressing a sizeable health disparity.

PEFS will allow accurate documentation of each test, making it possible to compare past exams with new and track changes in breast anatomy over time. This type of trending feature is not possible with manual palpation. Although challenging from the regulatory perspective, PEFS may also help reduce the number of unnecessary biopsies every year that do not identify any malignancy.

PEFS will offer similar benefits to women in various high-risk or vulnerable segments including women with dense breasts, women at high risk due to genetics or family history, women with inadequate or no insurance and women deterred from breast screening due to pain during the exam.

In summary, the research project will facilitate the overall commercialization of the PEFS technology leading to regulatory submissions and in building clinical confidence within the medical fraternity.

Summary of Research Completed

During the second phase of the project, we concluded the design and engineering aims to develop a low-cost, accurate and easy-to-use hand-held breast scanner. The iBreastExam device (also referred to as iBE in this report) is now ready for clinical evaluations, US FDA filing and further commercialization. The sub-aims below summarize the progress achieved during this phase of the project.

<u>Sub-Aim 1a:</u> New signal processing algorithms were developed to reduce quantization noise introduced by the limited spatial resolution of the 16 sensors. Creating a smooth contiguous spatial data matrix required unique interpolation schemes to develop an aesthetically pleasing image that accentuates the clinical findings (Fig.3). The output frames are now capable of characterizing the lesion for size, location, stiffness and shape information.

Noise reduction algorithms were revised and applied to the spatial data to avoid misrepresentation of artifacts as clinical findings. Certain clinical conditions such as anatomy (example: ribs of a thin individual) often appear as artifacts on the iBE. Separation of these artifacts from true lesions was addressed using artificial intelligence and feature extraction algorithms. Artifacts were further addressed by declassifying lesions that appeared distributed as opposed to centralized. Bilinear and bi-cubic interpolation further refined the data to create smooth image visualization, removing the "blocky" nature of the piezoelectric sensor geometry. Additionally, anti-aliasing blurring was implemented, resulting in smooth topological mapping of the discrete data (Fig.1).

Sub-Aim 1b: iBE system is dependent on transient voltage responses and hence the scanning time has a practical lower limit. Testing and evaluation verified that this limit was not optimized. We further modified the circuitry to increase the decay rates, thereby reducing the single scan time to 250ms per 16 PEF scan. This resulted in a 15-fold improvement over the previous iBE system. iBE system now provides a continuous data stream as opposed to single snapshot, per scan.

Software assisted positioning is developed and tested. The user is now guided through a breast examination to perform routine screening in a pre-determined sequence (Fig.5). The breast tissue is divided into adjoining segments spanning the entire breast area. The software then informs the user where specifically to place the iBE sensor. The software assisted positioning conserves battery power since there are no active sensors employed for positioning. Based on the feedback from the clinicians, software assisted positioning is user-friendly and requires minimal training. It also eliminates the need for expensive sophisticated positioning hardware that is not likely to have the spatial resolution necessary to be effective.

Sub-Aim 1c: The new electronics are now capable of measuring 16 analog inputs (16 PEF fingers) through 8 ADCs though a high speed/low noise multiplexor. Protection Zener diodes were added to protect these ADC inputs and new circuitry was implemented to monitor the health of the PEF fingers and driving circuitry. This information is made available on the electronics through LED indicators and is available through the API interface in the software. Battery monitoring hardware was implement to provide battery statistics through the software interface. Industrial design of the iBE enclosure is completed with the support of DesignDesign Inc. (Fig.2) and commercial-grade components are made using vacuum casting process. The new industrial design houses all the components including the electronics and is also designed to be ergonomic, easy-to-use and ready for compliance testing (required to obtain US FDA clearance) procedures.

Form factor of the electronics board was modified to accommodate inside the new, iBE commercial grade prototype enclosure design (Fig.1). We had 20 of the newly designed boards fabricated and populated at NextFab Studio, using industry standard electronics fabrication techniques, maximizing quality assurance and minimizing probability of faulty manufacturing. All boards were tested prior to integration into the iBE enclosure.

Sub-Aim 1d: A software package called "iBEConnect" was initiated and the current version is

3.0. It is developed for the Windows 8 platform and is designed for tablet (touch enhanced) operation. iBEConnect now implements user management, patient management, reporting and settings related capabilities. It also performs maintenance, calibration, and iBE-sensor health assessment. Battery statistics are provided as well. A new database structure is implemented using MySQL, which handles data management and statistical data analysis. Fig.4 provides system screen-shots.

The entire software is hosted in the cloud environment (DropBox), offering the ability to remotely update new versions and collect scan data from multiple locations, simultaneously and in near-real time. The software is able to record the entire iBE scan procedure, event-by-event along with the voice of the operator/physician, allowing the development team to experience the procedure in playback mode. Currently the software is compatible with tablet form factor and the graphical user interface (GUI) is completed for the mobile-phone environment.

Testing and Validation: iBE units have been bench tested for inter-operator, intra-operator and inter-device repeatability for size, location, stiffness and shape evaluation. In addition, we tested the units using accelerated wear and tear procedures to determine mean time between failures (MTBF) and to learn and improve battery consumption and accuracy. Model tissue and inclusions described in Phase 1 report were used for this testing as well. Result summaries are provided in Table 1.

Sub-Aim 2a: Dr. Ari Brooks (Clinical PI) moved his practice from Hahnemann Hospital to Pennsylvania Hospital in September 2013. Due to this reason, we were unable to start the clinical study as planned at Hahnemann Hospital. We applied and got approval for an extension for this project such that we can complete the clinical evaluation as stipulated in Sub-Aim 2a and 2c.

Sub-Aim 2b milestone: The progress made on the PEFS compression array system regarding the sensor design, electronics and software algorithm has been transferred to PEFS shear array system for tumor classification. Prototype design of the PEFS shear array system is shown in Fig. 6. Single PEFS shear array has been used to collect data from model breast tumors with inclusions embedded inside. Elastic and shear moduli data have been derived from the induced voltage data collected on the breast models and it has been shown that shear to elastic moduli ratio is equal to ~0.3 ($G/E \cong 0.3$), which is the expected value to be obtained from model tissue with no inclusion and also containing inclusions with smooth surfaces. Upon further verification of the shear array system, it will be applied for use in *in-vivo* tumor classification.

Sub-Aim 2c milestone: Palpation of each lesion was documented with a binary yes/no result depending on if the subject could feel the lesion or not. The subjects were instructed to place the iBE unit on the lesion to perform a scan. If there was an iBE finding at that location, as determined by the subject after adequate training, the data was tagged as a true positive, otherwise, the data was tagged as a false negative. A summary of the results is shown in Table 2. Different operators and inclusions were placed at random locations in between the two silicone layers to obtain statistically significant data. The results showed that 2x4 iBE array was able to successfully detect the inclusions underneath the 10 mm thick silicone layer varying from 5 mm to 25 mm in size. It should also be noted that in both model tissue studies, the experimental

results were similar when tested by different operators. This proves that iBE system results on the aforementioned model tissue experiments were operator-independent.

1. Complete iBE commercial system prototype.

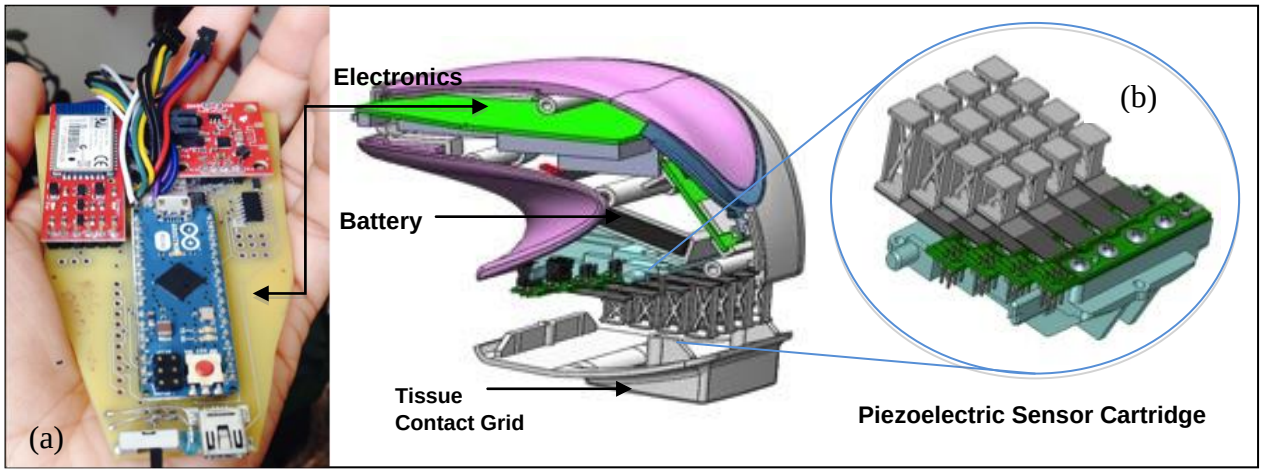

Figure 2. iBE System components; (a) Electronics; (b) Piezoelectric Sensor Cartridge.

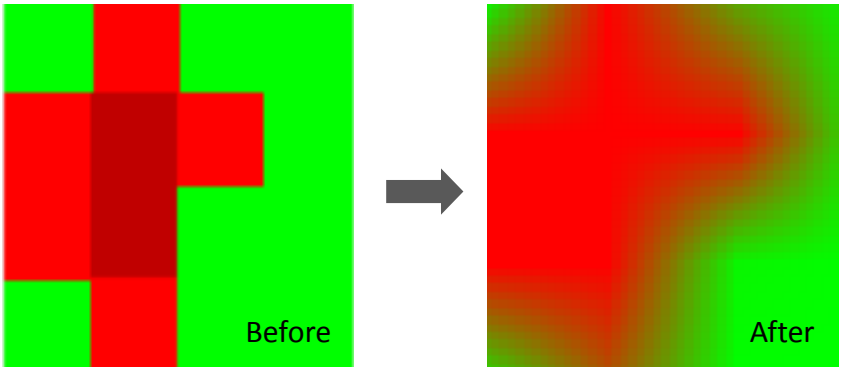

Figure 3. Bilinear, bicubic interpolation and anti-aliasing blurring techniques create smooth, contiguous frames

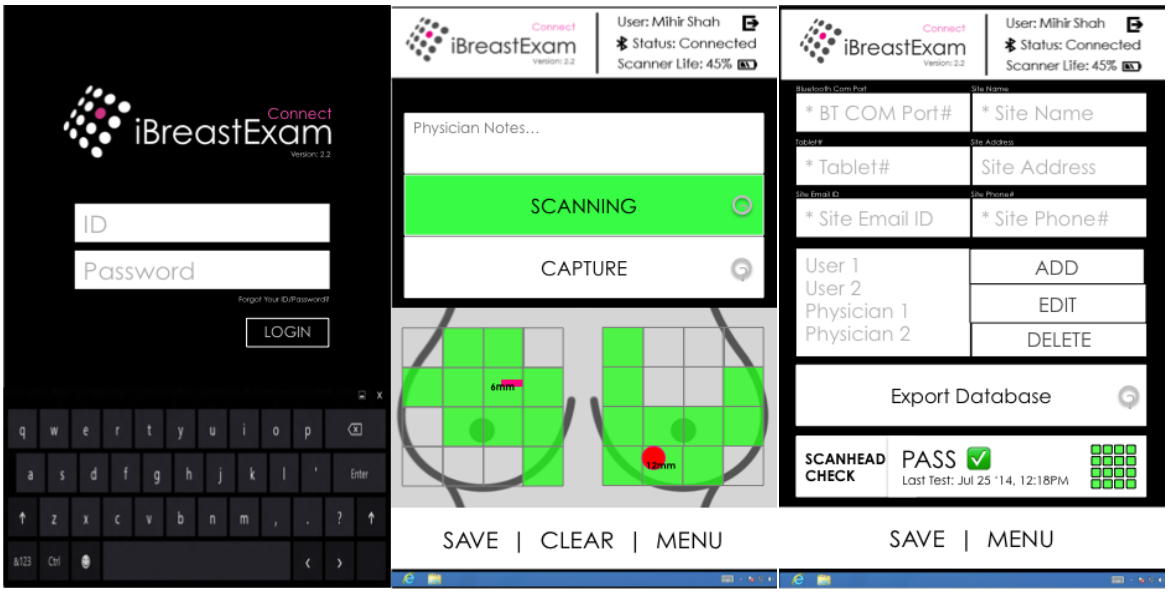

Figure 4. System Screen Shots.

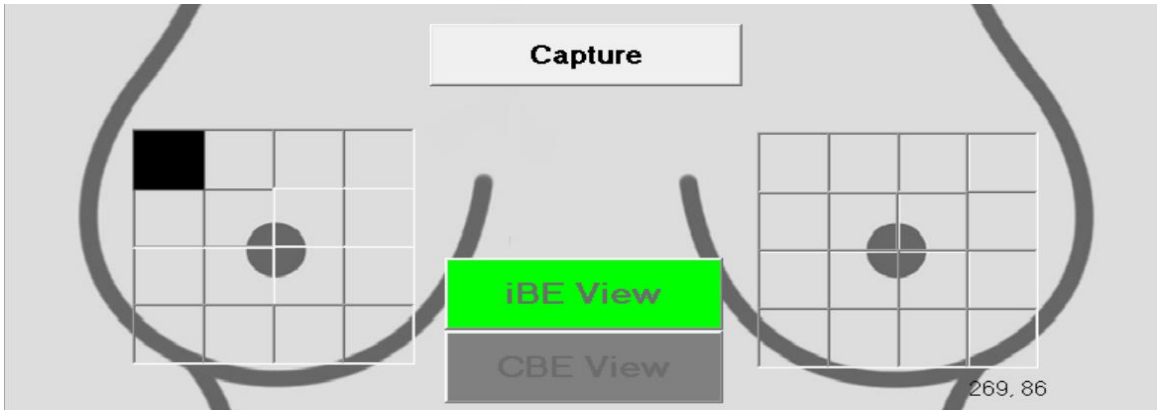

Fig. 5: Software assisted positioning

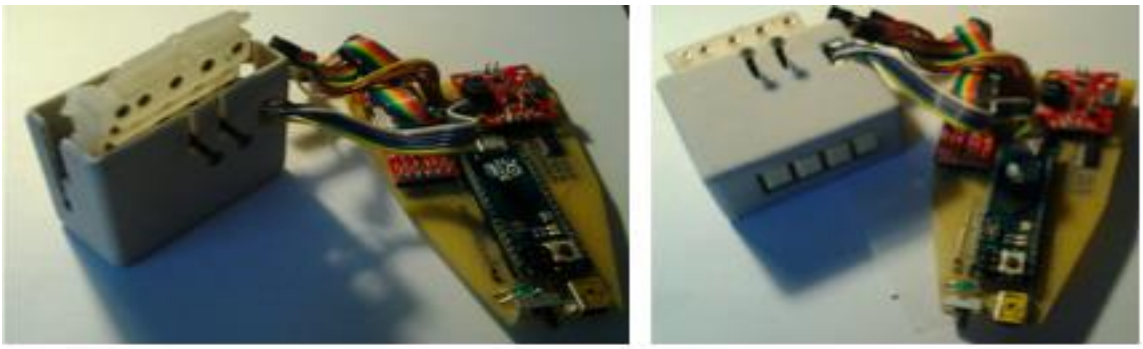

Fig 6: Pictures of the PEFS shear array system consisting of single PEFS Figure 1. Complete iBE

Table 1

	Accuracy	Description
Intra-operator Repeatability	98%	Single user to scan lesions repeatedly with same results
Inter-operator Repeatability	96%	Multiple users to scan lesions repeatedly with same results
Inter-device Repeatability	100%	Single user to scan lesions with 2 different devices with same results
Size Evaluation (8mm, 1.3cm)	98%	Ability to detect the size of a lesion with ± 5mm accuracy
Stiffness (relative)	97%	Ability to classify stiffness using three discrete stiffness levels
Shape	100%	Ability to classify Circular vs. Tubular

Table 2

Lesion	Lesion Coordinate	Correlation Accuracy
A (8mm spherical, 1cm deep)	3cm, 4cm	96%
B (1.3cm spherical, 1cm deep	5cm, 2cm	100%
C (1.3cmm spherical, 2cm deep)	4cm, 4cm	94%