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Label-Free Cancer Cells Detection Using Optical Sensors

MAHMOUD AL AHMAD[1], (Senior Member, IEEE), ADEL NAJAR[2], AMINE EL MOUTAOUAKIL[1], NIDA NASIR[1], MINAS HUSSEIN[1], SHAIMA RAJI[1], AND ALI HILAL-ALNAQBI[3]

[1]Electrical Engineering Department, College of Engineering, United Arab Emirates University, Al Ain 15551, United Arab Emirates
[2]Physics Department, College of Science, United Arab Emirates University, Al Ain 15551, United Arab Emirates
[3]Electromechanical Technology, Abu Dhabi Polytechnic, Abu Dhabi 111499, United Arab Emirates

Corresponding author: Mahmoud Al Ahmad (m.alahmad@uaeu.ac.ae)

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ABSTRACT Rapid and accurate label-free-based discrimination techniques between normal and cancer cells play an important role in non-invasive screening systems. Significant differences in cell composition for normal and cancer cells have been reported. Their interaction with light will cause a change in the optical absorption and transmission response. Hence, the advances in optical absorption methods along with signal processing could provide fingerprints that enable such discriminations and classifications. Here, we discriminate and identify several types of cells, such as BEAS-2B, HCC-827, THLE2, Hep G2, MCF 10A, and MDA MB231, in addition to HeLa and HEK-293T; each suspended in a homogeneous solution without labeling and using optical absorption-based method. Empirically, the cancer cells exhibit higher transmittance intensity when compared to normal ones from the same tissue type. Furthermore, the cells (both cancer and normal types) exhibit higher transmittance as per the following order: liver, lung, and breast. However, the normal cell suspensions exhibit higher optical absorption than cancer cells. The modifications of the optical response from normal to cancer state were explained mainly by morphological changes, modification of its physiological and biochemical properties that affect the refractive index and allowing them to be differentiated from each other.

INDEX TERMS Label free, detection, cells, sensors, optical, cancer.

I. INTRODUCTION

The rapid and uncontrolled growth of cancer cells causes deficiency by stopping body's control mechanism from functioning. The screening and distinction between healthy and cancer cells require new, rapid and efficient methods and techniques. Non-invasive screening systems are very critical and have not been developed yet. The efficiency of optical techniques resides in their ability to provide real-time measurements at a lower cost compared to other detection techniques.

Sensor array methods are useful for many bio-analyses. An array of nanoparticles and conjugated polymers releases the fluorescent polymer from the gold-nanoparticle quencher when it comes in contact with bacteria. Hence variant fluorescence responses generated by the bacterial surfaces gives an efficient detection and identification [1]. Contrast agents like folate-substituted poly (p-phenyleneethynylene) (PPE) can be used to image KB cancer cells with high selectivity and with minimal cytotoxicity to normal cells [2]. Nose-based polymer sensor arrays show a noble approach for advanced diagnostic and biophysical processes involving cell surfaces. It is used to distinguish among normal, cancerous and metastatic cells having similar genetic background, in an easy way, without any need of knowledge related to the exact receptors or ligands in order to distinguish between cell states, types and status [3]. Helen et al. give another example of ultra-sensitive magnetic field sensors where antibody conjugated magnetic nanoparticle reagents are used in breast tumor cell detection. These cells were sensed using Superconducting Quantum Interference Device (SQUID) that is based on the promising, viable and fast magnetic relaxometry technique [4]. To achieve this, they identified a set of breast cancer cell lines using various levels of plasma membrane such as human epidermal growth factor-like receptor 2 (Her2) using the flow cytometry. Carbodiimide method was used to conjugate Anti-Her2 antibody to super-paramagnetic iron (II, III) oxide nanoparticles. Those labeled particles were incubated with cancerous cell lines and envisioned by

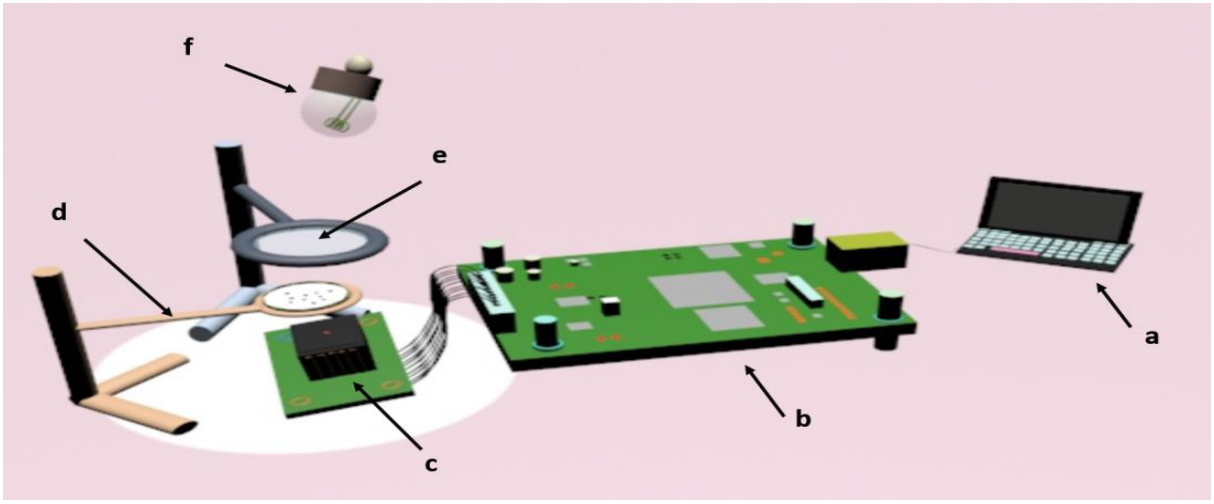

FIGURE 1. Schematic for the experimental Setup: (a) laptop equipped with HMS Evaluation software used for measurements acquisition, (b) Evaluation board (C113451-01) for interface purpose, (c) Optical sensor (C11708 MA from Hamamatsu/Japan) + sensor board (C113451-02), (d) Sample holder, (e) Convex lens holder and (f) Xenon Light Source.

magnetic relaxometry, Prussian blue histochemistry and confocal microscopy. Moreover, Fourier Transform Infrared (FTIR) spectroscopy advances is used in the development of sensitive biomarkers to determine cell-mutation injury and cancer prospect in animal and human populations [5]. Along with this, FTIR also helps in determining the protein secondary structure [6]. Experimental results showed that the resultant infrared (IR) spectra of the cancer cells indicated a significant increase in infrared absorption as compared with normal cells in the band, around 1080 cm^{-1}, 1120 cm^{-1} and 1240 cm^{-1} for NCI-N87, SNU-1, and AGS respectively. These spectral variations are related to changes of the phosphate backbone in normal and cancer gastric cells, hence counted as a potential diagnosis tool for gastric cancer [7].

In addition, other researches determine and compare the optical properties of various normal and cancerous skin cells. In the wavelength range 350-1200 nm, melanin is the eminent radiation absorber in the epidermis while in the UV region of less than 300 nm, aromatic amino acids, nucleic acids, urocanic acid, and melanin are the main epidermal absorbers [8]. Human dermis of thickness 20-650 μm, shows angular dependence of HeNe laser light scattering having a total attenuation constant of 190 cm^{-1}, with both the absorption and the scattering coefficient at 2.7 cm^{-1} and 187 cm^{-1} respectively [9]. A similar study has shown that there are significant differences in the scattering of healthy and cancer tissues within the spectral range of 1050-1400 nm. Furthermore, notable variations had not been seen for the cell absorption, within the same range [10]. The objective of all these studies was to select the spectral range where there are the maximal differences of both absorbing and scattering coefficients along with phase functions [11].

To realize relevant non-invasive measurements, label-free-based methods with fluorophores are not used because they may affect the biochemical properties of the cells. In addition, the measured optical spectrum contains much information that can be used in the characterization of the optical properties of cells. A detailed theoretical modeling for the dependency of the single cell absorbance on that of the cell suspension has been investigated [12]. In this work, optical-based mini-spectrometer sensor is used to discriminate between normal and cancer cells.

II. EXPERIMENTAL DESIGN

The experimental setup used to measure the light absorption intensity is illustrated in Fig. 1. It consists of a light source and a hardware/software combination. The xenon light source with a high intensity (450W) is from Newport [13], while the hardware part consists of a mini-spectrometer (C11708 MA from Hamamatsu/Japan) sensor connected to an evaluation board (C113451-01) through a sensor board (C11351-02 from Hamamatsu/Japan) that can transfer data to a PC. An analyzer software (HMS Evaluation software) is particularly dedicated to the Hamamatsu Mini-spectrometer [14], and is used to process the acquired data.

As per the setup, the arc lamp focuses light on the sample through convex lens, and the mini-spectrometer illustrated in Fig. 2(a) is fixed under sample so that it can measure light transmitting through the sample. The mini-spectrometer optical sensor converts the light to an electrical signal that evaluates the absorption level of the sample. The output signal of the sensor represents the analog-digital (A/D) count that will be converted to a light level using the HMS Evaluation software (from Hamamatsu/Japan). The wavelength of the xenon must match the wavelength of the used optical sensor since it is a significant feature that affects the measurements of the sample where the range of used wavelength is 640-1010 nm. Fig. 2(b) represents the model to link the cell suspension to transmittance.

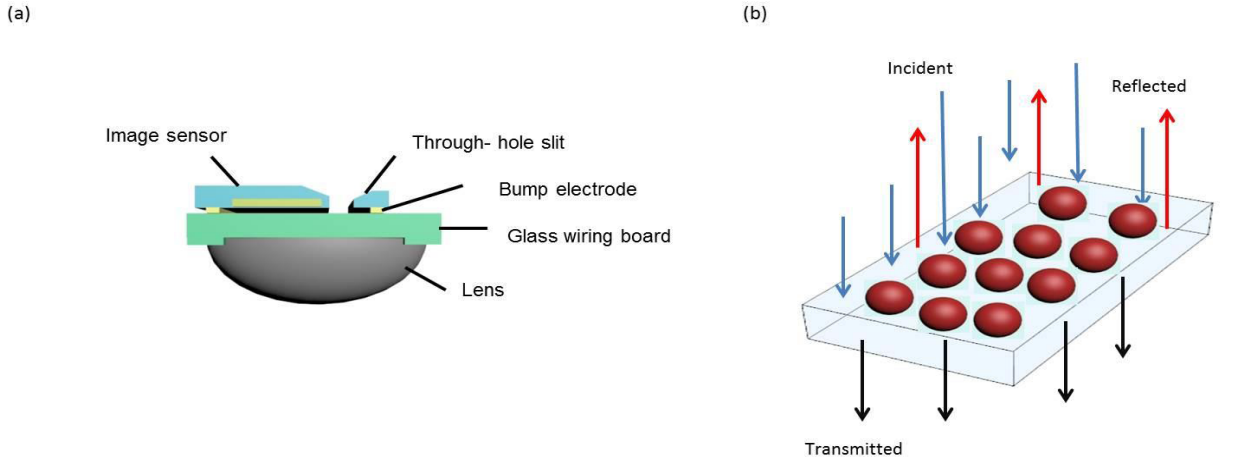

FIGURE 2. Illustrations of the measurement principle: (a) Optical sensor (C11708 MA) details along with the b) transmission definition.

III. RESULTS AND DISCUSSION

The optical transmission was measured in normal and cancerous cells. Three types of normal cells: BEAS-2B, THLE2, and MCF 10A and their corresponding cancerous cells: HCC-827, HepG2, and MDA MB 231, respectively; were obtained from the American Type Culture Collection (ATCC) [15]. The cells were cultured on a large scale under the appropriate conditions for the experiment, trypsinized according to the ATCC guidelines, and counted. The cells in each suspension are homogeneous; i.e. each suspension contains one type of cell, since each suspension was made from a single cell line. All kind of cultured cells (normal and cancer) was double-checked using the confocal fluorescence microscope to make sure that all suspensions are homogenous. The microscope has been also used to count the number of cells in each suspension. The total number of each suspension has been adjusted to 10^7 cells per mL with an average error of 5% using the hemocytometer. After the preparation of the cell suspensions, their response was measured and collected using the experimental setup. Fig. 3 shows the measured optical transmission versus the wavelength.

The level of transmittance is measured over the wavelength of 640-1010 nm (i.e. the range of the mini-spectrometer sensor). All suspension intensities have been subtracted individually from the holder intensity to eliminate the holder effect. From Fig. 3, the cancerous cells have a higher optical transmittance level compared to their corresponding normal cells. Furthermore, it is notable that for both cancer and normal cells, the order of the transmittance levels from high to low was as follows: Liver, lung and breast. Since the refraction index of the cancer and normal cells of the same type is different [16], optical-based techniques can be used for the differentiation among these cells [17]. These shifts in the wavelength and the intensity levels, due to the nature of the cell compositions, have been also reported by other groups [18].

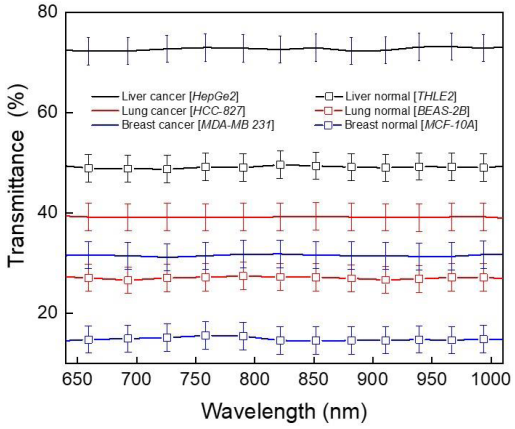

FIGURE 3. Optical transmission versus wavelength for normal and cancerous cells. Each line represents the average of 15 measurements and the bar lines represents the maximum and minimum range of the corresponding response. The multiple measurements were conducted on different aliquots taken from the same sample suspension; on the same region spot. These measurements were performed using the optical sensor C11708 MA from Hamamatsu/Japan. The y axis has been adjusted to the percentage as the unit.

When the cell changes from a normal state to a cancerous one, it undergoes physiological, biochemical and morphological changes [19]. This is due to the alteration and the modification of its metabolic, genomic and proteomic properties [20]. Such changes affect the refractive index, causing the alteration of the optical characteristics of the cells, and allowing them to be differentiated from each other.

Based on Kirchhoff's law of radiation [21], which correlates the optical absorbance (A), transmittance (T), and reflection (R) along with the incident wave (I), as per the following equation:

$$I = A + T + R \tag{1}$$

The optical absorption density of the light in normal cells has been measured to be higher in the cancerous cells from

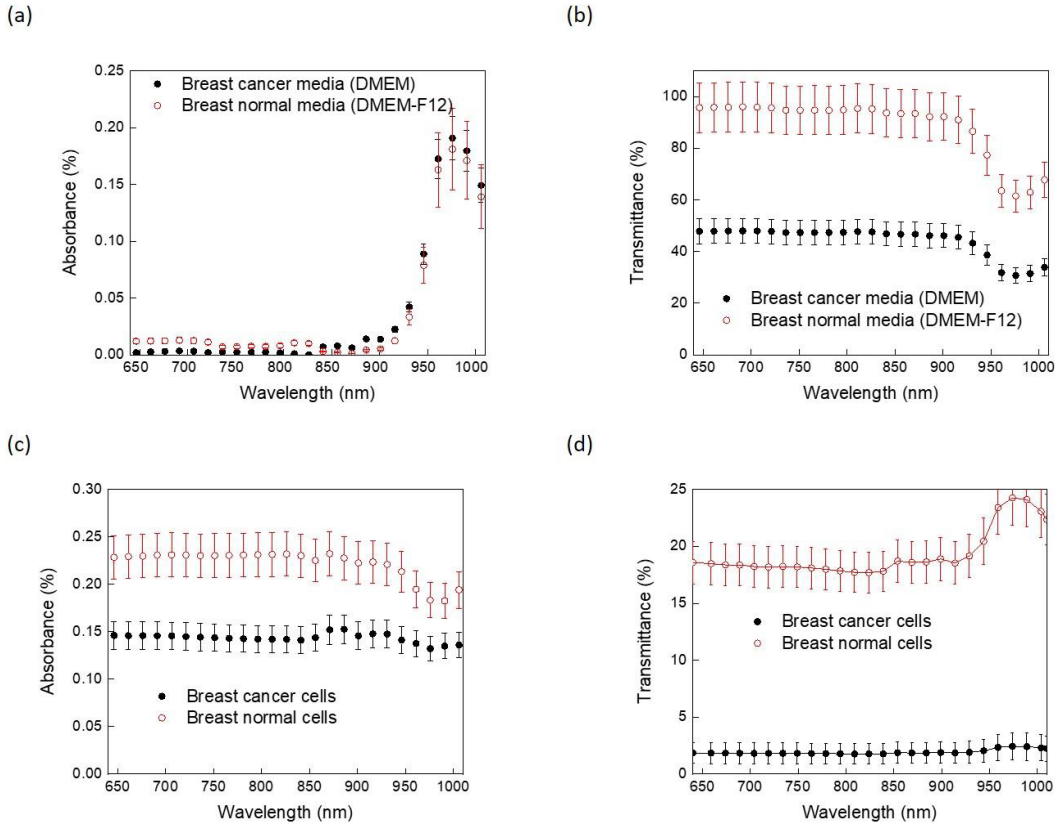

FIGURE 4. Absorption and transmission response of both normal and cancer breast cells' suspensions and its respective media i.e. DMEM and DMEM-F12, respectively: (a) absorption curves for respective media, (b) transmission for curves for respective media, (c) absorption for breast normal and cancer cells suspensions and (d) transmission levels of for breast normal and cancer cells suspensions. Each line represents the average of 5 measurements and the bar lines represents the maximum and minimum range of the corresponding response. The multiple measurements were conducted on different aliquots taken from the same sample suspension; on the same region spot. These measurements were performed using the optical sensor JASCO (V-670) from JASCO/Germany. The y axis has been adjusted to the percentage as the unit.

the same tissue. This is due to the surface area of the normal cell being larger when compared to its corresponding surface area of the cancer cell. Moreover, the cancer cells shrink in size, leading to a loss of surface subjected to light, i.e. low absorption in the cancer cell. Cancer cells exhibit a stronger cell-surface-negativity charge than the normal ones because of the sialic acid residues [22]. Thus, this creates a barrier shield around the cell surface that reflects significantly the amount of light causing less absorption. Meanwhile, the normal cells exhibit a lower conductive behavior that allows less light reflection and more absorption [23]. The metabolic differences between cancerous and normal cells leads to several variations in cellular parameters, such as their size.

Bashkatov et al. investigated the optical properties on a wide spectral region from 400-2000 nm, which revealed that the μ-scattering is predominant in the infrared (IR) region [24]. μ-scattering is the reduced-scattering-coefficient spectrum, which is a combination of the Mie and Rayleigh scattering spectra [24]. Einstein et al. have reported that the reflectance [25] for cancer cells is higher than the one for normal cells from the same tissue. In another work reported by Salman et al., the absorption has been measured for cancer and normal cells [26]. The absorption spectra in UV range showed a higher absorption of normal cells than that of cancer cells. Furthermore, Zhu et al. reported the identification of concourses cells based on common features extracted from hyperspectral microscopic images [27]. Although his data shows a fluctuation in the measured transmission versus the wavelength, the transmission for cancerous cells at a higher wavelength is higher than that for the normal ones.

To confirm our previous observation, UV-Visible spectrophotometer [28] has been used to measure the absorption and transmission responses for both normal and cancer breast suspensions and their corresponding mediums. The measured absorption and transmission for both control and suspensions responses are presented in Fig. 4. DMEM and DMEM-F12 mediums were used to grow the breast cancer (MDA-MB231) and the normal breast cell (MCF-10A), respectively. Both used medium exhibits the same responses as shown in Fig. 4(a). Meanwhile, the transmission curves, shown in Fig 4(b), demonstrate a higher light transmission in DMEM-F12 compared to that in DMEM. Each media was used as a calibration baseline for its corresponding sample suspension. The de-embedding of the media and the

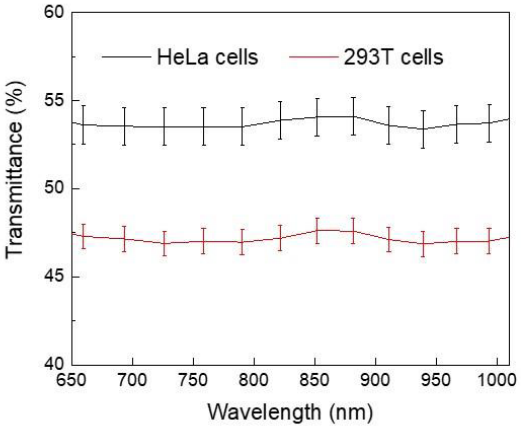

FIGURE 5. Optical transmission versus wavelength for 293T normal and HeLa cancerous cells. Each line represents the average of 15 measurements and the bar lines represents the maximum and minimum range of the corresponding response. The multiple measurements were conducted on different aliquots taken from the same sample suspension; on the same region spot. These measurements were performed using the optical sensor C11708 MA from Hamamatsu/Japan.

holder contributions is performed automatically during the measurements.

The measured absorption and transmission responses for the sample suspensions are depicted in Fig. 4(c) and (d), respectively. Fig. 4(c) shows that the breast normal cell suspensions exhibit a higher absorbance than the breast cancer cells suspensions do. On the other hand, Fig. 4(d) reveals that the breast cancer cells exhibit a higher transmittance than the breast normal cells do. All the responses presented in Fig. 4(c) and (d) exhibit a smooth behavior and the differences between the two kinds of normal and cancer breast cells are constant throughout the measured wavelength range. These measurements also show an identical smooth absorption, in a perfect agreement with those measured using the experimental setup explained in Fig. 1.

To explore the outlined method for other cells types further, two cell lines has been added: one normal (293T) and one cancerous (Hela) cell to provide more insight into our results and approach. The corresponding responses are displayed in Fig. 5 along with measurements presented in Fig. 3. This measurement revealed the efficient use of light properties to signal the difference between normal and cancerous cells.

The outlined method detects the transmittance of light after passing through the cell suspension, the intensity of which depends on the amount of light that has been either absorbed or reflected(or scattered), so the measurements can be considered more holistic since rather than separately assessing the level of light reflection (due to cells surface properties or cell granularity) or light absorption (relies on cell components and composition), we have measured the remaining effect that results after deducting all these factors.''

Light scattering plays a crucial role in diagnostic and optical imaging applications. Measuring the intensity of light scattered at different angles can reveal information about the different cellular parameters. Forward scattered light (FSC), which conveys information about the size of a cell, is detected at small angles between 0.5-2° [29], while the side scattered light (SSC), which reflects the complexity of cell exterior or interior structures, is detected at larger angles between 15-135° [29]–[30]. For example, Mourant et al. demonstrates that when light passes through a cell, most of the incoming light scatters because of the nucleus and that, scattering at angles greater than 100° is associated with the DNA content of the cells [31]. Mitochondria is another intracellular structure which affects scattering, it is suggested to cause light scattering at angles up to 90°. In another study it has also been mentioned that mitochondria and other similar sized constituents of the cell, contributes to scattering at large angles [32], whereas nuclei leads to scattering at small angles [33]. The nuclei size, cell shape and the refractive index variation of cells contributes to light scattering in the cell [34]. Alterations has been observed in the shape of the mitochondria due to excess of calcium by the help of optical scatter imaging [35]. It is well known that tissues made up of normal or cancer cells exhibit different properties, densities and composition. In practical medical situation where obtaining such biopsies is challenging, such characterization can be done by converting both types tissues (surrounding normal tissue and cancerous tissue) into cell suspensions by using conventional techniques or methods, normalize the number of cells and then use our setup for the optical characterization. However, we should emphasize here that the change in absorption can result from the presence of various kinds of cells and can differ due to the different nature of the extracellular matrix. Such difference can be exploited more and interpreted as a general optical property of cancerous tissue when in suspension.

IV. CONCLUSION

In summary, a fast label-free-based optical measurement method able to distinguish between normal and cancerous cells is demonstrated. Such method is expected to have an impact in developing non-invasive screening systems for cancer detection. Several types of cells: BEAS-2B, HCC-827, THLE2, HepG2, MCF 10A and MDA MB231 in addition to HeLa and HEK-293T have been investigated. Each solution is homogeneous, and its cell count number has been adjusted to 107 cells per mL, with a maximum average error of 5% using the hemocytometer. The variations in the optical responses in all measurements between the cancer and normal cells from the same tissue do exceed the error percentage in cell count; hence, the deviation in cell counts does not affect the optical results. Empirically, the investigated cancer cells in this study exhibit a higher transmittance intensity levels when compared to the normal investigated ones. Our findings show that the transmittance level of investigated normal cells is lower than that of the investigated cancerous ones throughout the wavelength range of 640-1010 nm. The change in optical response is due to the morphological, physiological and biochemical properties when the cell turns from normal to cancer. As a

whole, the optical-based methods will open up a new route to detect and identify in a label-free manner.

V. METHODS AND MATERIALS

A. CELL LINES USED AND THEIR CULTURE

All the cell lines were obtained according to the American Tissue Culture Collection (ATCC) standards and cultured in the media specific to each type of cells. Different types of cell lines have different characteristics and nutritional requirements for the survival and growth *in vitro* [36]. The media used for the culture of the cells provides optimal growth and nutritional conditions specific for the cells [37]. The constituents used for the normal cells might not be required for the cancer cells and vice-versa. The culture conditions and methods used are described in detail below:

1) BEAS 2B CELLS

The cells were cultured on pre-coated culture plates according to ATCC guidelines. Culture plates were pre-coated with a pre-coating mixture of 0.01mg/ml fibronectin, 0.03 mg/ml bovine collagen type I and 0.01 mg/mL bovine serum albumin dissolved in BEBM (all reagents were purchased from Sigma-Aldrich) in bronchial epithelial basal medium (BEBM). The BEGM Bullet Kit (Lonza / Clonetics Corporation) was used to prepare growth medium for BEAS 2B cells. Gentamycin/Amphotericin (GA) was discarded from the kit but all other additives in the kit were included in the basal medium. The media was supplemented with 1% penicillin-streptomycin (100 units/mL of penicillin and 100 mg/mL of streptomycin) (Gibco). The cells were trypsinized using 5% Trypsin - 0.53mM EDTA solution containing 0.5% polyvinylpyrrolidone (PVP).

2) CC-827 CELLS

ATCC recommends the use of RPMI-1640 (Roswell Park Memorial Institute Medium, HyClone), which has been supplemented 10% heat-inactivated FBS (HyClone, US) as the base medium. The cells were trypsinized using 0.25% Trypsin - 0.53mM EDTA solution.

3) THLE2 CELLS

The cells were cultured on pre-coated plates. A pre-coating mixture of collagen I (2.9 mg/mL) - fibronectin (1 mg/mL) - bovine serum albumin (1 mg/mL) (reagents from Sigma-Aldrich) in bronchial epithelial basal medium (BEBM) was used. BEGM Bullet Kit (Lonza/Clonetics Corporation) was used to prepare growth medium for THLE-2 cells. Gentamycin/Amphotericin (GA) and Epinephrine were discarded from the kit but an extra 5 ng/mL of epidermal growth factor (EGF), 70 ng/mL of phosphoethanolamine, and all other additives in the kit were included in basal medium. The media was supplemented with 10% heat-inactivated fetal bovine serum (FBS) (HyClone, US) and 1% penicillin-streptomycin (100 units/mL of penicillin and 100 mg/mL of streptomycin) (Gibco). The cells were trypsinized using 0.5% Trypsin - 0.53mM EDTA solution according to ATCC guidelines.

4) HEPG2

Hep G2 cells were grown in culture plates in DMEM medium supplemented with 10% FBS (HyClone, US) and 1% Penstrep (Gibco). The cells were trypsinized using 0.5% Trypsin - 0.53mM EDTA solution according to ATCC guidelines.

5) MCF 10A CELLS

MCF 10A cells were cultured in DMEM/Ham's F-12 (GIBCO-Invitrogen, Carlsbad, CA) supplemented with 100 ng/ml cholera toxin, 20 ng/ml epidermal growth factor (EGF), 0.01 mg/ml insulin, 500 ng/ml hydrocortisone, 5% heat inactivated horse serum and 1% Penstrep (Gibco). All of the growth factors were purchased from Sigma, USA. 3.0 mL 0.05% trypsin, 0.53 mM EDTA was used for cell detachment [38].

6) MDA MB 231 CELLS

MDA MB 231 cells were cultured in DMEM (Dulbecco's modified Eagle's Minimal Essential Medium, HyClone) supplemented with 10% fetal bovine serum (FBS; HyClone Laboratories, Logan, UT, USA) and 1% penicillin-streptomycin solution (Gibco).

7) 293T CELLS

The cells were cultured according to ATCC guidelines. The base medium for the 293T cell line is DMEM (Dulbecco's Modified Eagle's Medium, HyClone) supplemented with 10% FBS (Fetal Bovine Serum) and antibiotics like PenStrep (Penicillin Streptomycin, Gibco) and Gentamicin. The cells were maintained under humidified air with 5% CO_2 at 37°C.

8) HELA CELLS

The base medium used for the HeLa cell line is DMEM (Dulbecco's Modified Eagle's Medium, HyClone) supplemented with 7% FCS (Fetal Calf Serum) and antibiotics like PenStrep and Gentamicin. The cells were maintained under humidified air with 5% CO_2 at 37°C according to ATCC guidelines.

All the cells were maintained under humidified air with 5% CO_2 at 37°C.

B. OPTICAL SENSOR

The optical sensor, or the ultra-compact mini-spectrometer integrating MEMS is a sensor that converts the variable attenuation of light waves as they pass from end to end or reflect off substances into signals [14]. The used optical sensor is Mini-Spectrometers C11708MA. Spectrophotometers are used widely in chemical analysis, color measurements, color monitoring for printing machines, color control devices, fruit sugar content measurements, environmental measurements, component analysis, etc. The features of the used sensor in this research were: Thumb size $= 27.6 * 16.8 * 13$ mm, Weight $= 9$ g. The spectral response ranges from 640 to 1010 nm and the spectral resolution is 20 nm.

Furthermore, it was used to measure and study the chemical analysis of various types of Bio-Cells by observing the absorbance level of the tested Bio-Cells in order to determine whether it is a normal or a cancerous cell.

The output signal of the optical sensor shows the light incident on each pixel or average A/D count at specific wavelength range. For instance, the detection of low-light-level increases the light signal output to a level where the signal can be processed. The output graph of the sensor shows as average A/D Count vs Wavelength.

C. LIGHT SOURCE

Optical sensor can detect two types of light sources, one is the optical fiber light source and the other one is monochromatic light source (xenon light source). In this experiment, we used the xenon light source since the optical fiber source is more complicated and works at specific conditions that don't match our experimental requirements. 450-1000 W Research Arc Lamp Sources [13], is the type that we used in our experiment. These types of light sources have long lifetime and provide high-intensity UV to near-infrared light (NIR) output with minimum light ripple. The following data indicate the setting of the used light source: Current (18.0-20A), power (450-501W) and lamp output voltage is 4.2V.

D. UV-VIS SPECTROMETER

JASCO (V-670) from Germany was used to measure the optical transmission and absorption of normal and cancer cells [28]. A beam of light source is separated into its component wavelengths by a diffraction grating. Each monochromatic beam is split it into two equal intensity beams. One beam is focused on the sample through a small transparent container with cells in its solution. The reference beam passes through an identical cuvette with only the media. An electronic detector was used to measure the light intensities with I_0 is the intensity of the reference and I from the sample. The transmission is presented as $T=(I/I_0)$ and the absorption as $A=\log (I_0/I)$.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

MA and AH conceived the concept and supervised the project. MA, NN, MH, AM and AN performed the optical experimental work and analyzed the measurements. SR prepared the cells samples and their medium. All authors discussed the results and commented on the manuscript.

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MAHMOUD AL AHMAD (SM'11) received the B.Sc. degree in electrical engineering from Birzeit University, Ramallah/West Bank, in 1999, and the M.Sc. and Dr. Ing. degrees in microwave engineering from Technische Universitaet Muenchen, Munich, Germany, in 2002 and 2006, respectively. He is currently a faculty member with the Electrical Department, University of United Arab Emirates. His research interest involves in the design and fabrication of self-powered low powered nano-based electronic devices and systems along with applied electromagnetic for biomedical applications. He has ten years of electronic materials and device fabrication research, with universities, national laboratory, and industrial experiences. He has managed several research projects and teams with annual budgets of up to US$1 million. He is also the Principle (Lead) Author of around 55 published articles in journals and international conferences and has over 40 presentations at international conferences, among which several were invited. He has conducted a research in energy harvesting technologies and frequency agile circuits at the Siemens AG/CNRS and King Abdullah University. He has published over one hundred publications in various journals and international conference proceedings and more under review. He holds several international patents granted in the US, GCC, and EU.

ADEL NAJAR received the Ph.D. degree in physics from the University of Renne in 2007. He currently an Assistant Professor with the Physics Department, United Arab Emirates University. His research interest focused on optical and photonics areas.

AMINE EL MOUTAOUAKIL received the Ph.D. degree in electrical and communication engineering from Tohoku University in 2011. He is currently an Assistant Professor with the Electrical Engineering Department, United Arab Emirates University. His research interest is focused on developing smart microsystem.

NIDA NASIR received the B.Tech. degree in electronics and communications engineering and the M.Tech. degree in microwave engineering from the APJ Abdul Kalam Technical University, Lucknow, India, in 2013 and 2015, respectively. She is currently pursuing the Ph.D. degree with the United Arab Emirates University, Al Ain, UAE. She is also a Research Associate with United Arab Emirates University. Her research interests are electrical characterization, biomedical, and communications.

MINAS HUSSEIN received the B.Sc. degree in electrical engineering from UAE University.

SHAIMA RAJI received the M.Sc. degree in cell biology. She is currently a Research Assistant with the Department of Electrical Engineering, UAE University.

ALI HILAL-ALNAQBI received the M.Sc. and Ph.D. degrees in bioengineering (biotechnology) from the University of Strathclyde in 2000 and 2005, respectively, and the MBA in leadership studies from the Sawyer Business School (Suffolk University) and the PGD (Post-Doctoral Fellow) in biotechnology from Harvard University, both in 2008. He is currently an Associate Professor with the Mechanical Department, University of United Arab Emirates. His area of interest includes bioreactors, tissue mechanics, membranes, and polymers, 3D culturing including micro carriers and collagen matrix, nano particles, and modeling. He holds two patents in U.K. and USA for Serviceable Bioreactors and three provisional patents in the US patent office.