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Advanced Biophotonics Techniques: The Role of Optical Tweezers for Cells and Molecules Manipulation Associated With Cancer

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Rapid advances in Biophotonics are revolutionizing the illumination of several diseases and, among them, the monitoring of cancer pathogenesis and therapy. Today, several efforts aim to miniaturize the Biophotonics tools, leading to the namely Nanobiophotonics. This scientific field refer to the development of novel technologies, biosensors, and drug delivery systems for prevention, diagnosis, and treatment of diseases at the nanoscale, in sub-cellular and molecular level. Modern non-invasive laser-based techniques are applied in different domains, from practical, clinical applications to molecular and cellular biology fundamental research. Among the plethora of photon-based techniques, optical trapping is a very promising tool for improving the understanding of cancer at cellular level. Recently, optical tweezers are revived as a potential technique for cell characterization, tracking cells behavior and probing interactions forces between cells, cells-biomolecules, and cells-nanoparticles. In this review, we aim to exhibit the state-of the art advances of Biophotonics in the diagnostic and therapeutic field of cancer focusing on the role of optical tweezers.

Keywords: biophotonic techniques, optical tweezers, cancer diagnosis, cancer therapy, cells characterization

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INTRODUCTION

Biophotonics is an emerging multidisciplinary research area, embracing all light-based technologies applied to the life sciences and medicine. The expression itself is the combination of the Greek syllables' "bios" standing for life and "phos" standing for light [1]. In Biophotonics, the "conventional" light is monochromatic laser or laser-like non-ionizing radiation and the basic biomedical applications to all levels of biological structures are divided into two major fields. The first is devoted to diagnostic and imaging applications (*in vivo* and *in vitro*, in cellular or molecular level) and the second to therapy or surgery using photon radiation (e.g., biostimulation, tissue removal-surgery, photodynamic therapy, cell micromanipulation) [2]. Modern non-invasive laser-based optical research techniques prove to be more and more useful in the biomedical field, covering very different domains, from practical, clinical applications to molecular and cellular biology fundamental research [3, 4].

Today, several efforts aim to the miniaturization of Biophotonics tools, leading to Nanobiophotonics [5, 6]. This advanced scientific field refers to the research and development of novel technologies, biosensors, and drug delivery systems for prevention, diagnosis, and treatment of diseases at the nanoscale, in sub-cellular and molecular level and for the dream of personalized therapy [7]. Moreover, laser-based techniques and instrumentation have driven to a new era in cell

biology, the intracellular nanosurgery [8]. This technology has allowed the ability to perform precise nano-incisions in cells and manipulation of intracellular structures or even at the level of individual genes within the nucleus [9]. Laser nano-surgery combined with monitoring devices can lead from intracellular ablations to *in vivo* subcellular dissections [10, 11].

Among the plethora of photon-based techniques, optical tweezers, with the ability of applied Biophotonics interventions in living cells, is a very promising tool in cancer field [12, 13]. Optical tweezers technique is a non-invasive biomedical tool with advanced applications in biology [14], medicine [15], and nanotechnology [16]. The ability to "touch" the microcosmos non-invasively, while performing nanometer-precision and submicrometric analysis, using a single optical tool, is a revolutionary technique. Optical tweezers can manipulate cells, viruses, bacteria and macromolecules. Using the optical trapping technique, a cell can be selectively, non-invasively and non-destructively manipulated to a phagocyte, attached to its surface cell receptor and trigger the initiation of the phagocytosis process [17]. Optical tweezers are capable to grab, tracking and manipulate small virus such as influenza [18]. This review highlights the novel photon-based theranostics modalities for cancer confrontation focusing on the role of optical tweezers. The advanced applications of optical tweezers in biology and Nanomedicine are presented. New potential prospects of the optical tweezers in the cancer field are also provided.

BIOPHOTONICS AND THERANOSTICS IN CANCER

Biophotonics in Diagnosis of Cancer

Biophotonics is a relatively novel interdisciplinary discipline that integrates lasers, optoelectronics, photonics and biomedical sciences, dealing with the interaction between non-ionizing light quanta and biological materials, including tissues, cells and even sub-cellular structures and molecules in living organisms [19]. In the literature, there are a variety of research and clinical studies based on cellular and sub-cellular diagnosis *via* flow cytometry [20], light-microscopy techniques and laser-induced fluorescence spectroscopy such as: Epifluorescence microscopy [21], immunofluorescence microscopy [22], optical coherence tomography [23], confocal microscopy [24], Total Internal Reflection Fluorescence - TIRF microscopy [25], Two-Photon Laser Scanning Microscopy–TPLSM [26], Fluorescent Resonance Energy Transfer–FRET [27], PhotoActivated Localization Microscopy - PALM [28], nanolaser confocal spectroscopy [29]. These techniques enable real-time and/or *in situ* imaging of living tissue at high resolution and high contrast, without physically dissecting the tissue. These imaging techniques can find great applications in Nanomedicine.

Multiple imaging modes can offer complementary information and overcome the limitations of each single modality. The combination of optical imaging with computed tomography (CT), magnetic resonance imaging (MRI), Positron Emission Tomography (PET) and Single-photon emission computed tomography (SPECT) can enhance size resolution and penetration depth [30]. Near-Infrared Fluorescence (NIRF) imaging is highly attractive for early non-invasive detection of cancer due to its high penetration depth and low autofluorescence [31]. Different types of multicomponent nanoparticles like PEGylated Au/SiO2 nanocomposites conjugated with Fluorescein isothiocyanate (FITC) [32], Iron Oxide NPs encapsulating in Human Serum Albumin (HAS) [33] etc. have been designed to act as dual contrast agents offering multimodal imaging (**Figure 1**). The combination of CT, MR, PET and SPECT modalities with fluorescence imaging modalities can allow extension of imaging across the dynamic range of size resolution and penetration depth from deep-body with size resolution of ~ 1 mm to thin penetration depths of few hundred microns or millimeters with size resolutions to single-cell or even subcellular resolution [34–36].

In recent years, the biophotonics techniques have been integrated with machine learning methodologies based on artificial neural networks (ANNs) [37–39]. This will give a boost in the Biophotonic fields to obtain real-time decision-making systems for doctors, biologists, pathologist etc. by analyzing a large datasets of image data and spectral data [37]. For example, ANNs were used to diagnose tongue squamous cell carcinoma based on the difference in Raman Spectral signature between healthy and malignant cells for the accurate intraoperative discrimination between healthy and cancerous margins [40]. **Figure 2** shows a schematic image of the workflow of the combination of Raman spectroscopy with machine learning models for tissue discrimination. ANNs have been applied to Scanning Enhanced Raman Spectroscopy opto-physiology data to probe metabolite gradients in a variety of cell lines such as HeLa and HUVEC [41]. Machine learning models have been created to identify DNA damage in a nasopharyngeal carcinoma cell line (CNE2) after x-ray radiation [42] from spectral data obtain by silver nanoparticle-based surface-enhanced Raman scattering (SERS) [43]. Deep learning models have been applied in γ-H2AX immunofluorescence images to quantify the number of γ-H2AX foci for the detection of DNA double-strand breaks. The γ-H2AX foci is a sensitive biomarker for the quantification of the DNA damage [44]. These foci are formed specifically at sites of DNA double-strand breaks after ionizing radiation exposure as a cellular response of the lymphocytes in peripheral blood [45, 46].

Biophotonics in Therapeutics of Cancer

Recent theranostics techniques are combined with nano-imaging and nanomaterial-based drug delivery techniques for an effective and targeted disease management [47–49]. Metallic nanoparticles, semiconductor quantum dots and carbon nanotubes have been used as photosensitizer agents for photo-triggered diagnosis and photo-triggered therapy [50, 51]. Antibodies, peptides and small molecules can be labeled with fluorescence dyes and conjugated to nanoparticles producing targeted optical imaging probes for cancer detection [52, 53]. Nanocarriers can be served as multi-modal theranostics systems [54] or as "Trojan Horses" [55] carrying multiple therapeutic and

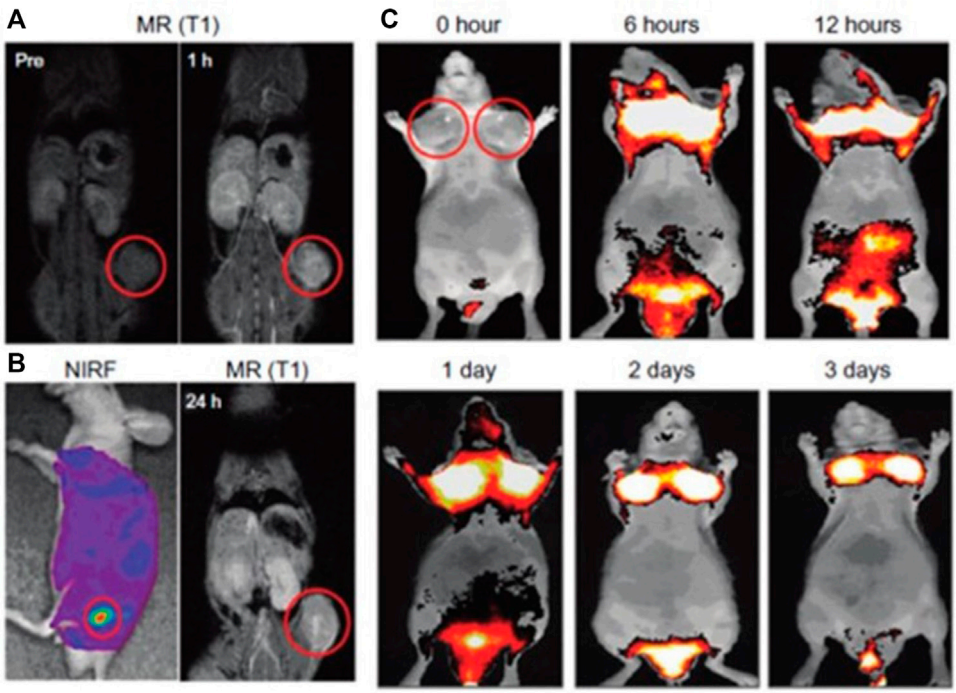

FIGURE 1 | (A–C) *In vivo* magnetic resonance (MR)–near-infrared fluorescent (NIRF) dual-modality imaging of SCC7-bearing mice. Cy5.5-chitosan nanoparticle-Gd(III) nanoparticles were injected into the SCC7-bearing mice, and the mice were visualized by using MR and NIRF imaging. Red circles indicate tumor sites. **(A)** *In vivo* MR imaging showed T1-positive contrast effects 1 h after injection at the tumor sites. **(B)** Both NIRF and T1-weighted MR images were simultaneously observed after 1 day post injection of Cy5.5-CNP-Gd(III). *In vivo* NIRF imaging showed brighter NIRF intensity at the tumor site. *In vivo* MR imaging 24 h after injection showed bright contrast effects at the tumor site. **(C)** *In vivo* NIRF imaging showed the accumulated Cy5.5-CNP-Gd(III) nanoparticles over time at the tumor sites. Reprinted (adapted) with permission from [44], Nam et al., 2010). Copyright (2021) American Chemical Society.

imaging agents directed to tumors. They can provide simultaneously diagnostic information and targeted drug delivery by photon-based stimulus through fluorescence [56], photodynamic [57, 58] and photothermal treatment [57].

In modern anti-cancer modalities, the majority approaches the delivering of new drugs which are behaving as a "Trojan horse", by introducing the active, cytotoxic compound in a nanoparticle and "decorating" its surface with a ligand that trigger the cancer cell into taking it up. Imaging can be used to trace the delivery of the drug inside the body and simultaneously to activate the release of the drug by an external stimulus such as laser light [59, 60]. Functionalized nanoparticles can act both as contrast agents and photosensitizers for photothermal (PT) [61] or photodynamic treatment (PDT) [62]. Among the large variety of NPs, metal NPs (AuNPs) are in the cutting edge of the nanomedicine due to their unique physical, optical and electronic properties [63, 64]. When metal NPs excited by visible or infrared monochromatic light with laser wavelength corresponding to their Surface Plasmon Resonance (SPR), the conduction electrons of the metal can be subjected to coherently oscillation and convert the electromagnetic energy into heat providing targeted tumour disruption *via* hyperthermic damage [65]. Photodynamic therapy has come again to the forefront due to the new class of photosensitizers (PS) which enhance PTD efficiency. The encapsulation of PS such as verteporfin or methylene blue into nanocarriers seems to overcome some of the barriers of the PS i.e., poor selectivity to the target tissues, the low extinction coefficients, their lipophilicity, the photobleaching of the PS etc. The synergia of nanomedicine with biophotonic techniques could lead to a localized "surgery" causing tumor disruption or removal without invasiveness [62].

Nano-image guided surgery plays an emerging role in the field of personalized tumour surgery [65, 66]. Fluorescence-imaging guided surgery can be used for sentinel lymph node mapping or to distinguish the margins of a tumor in microscopic scale and in real time. Using fluorescence imaging in the near-infrared (NIR) window (700–1,300 nm) is superior to visible light due to high penetration depth, negligible tissue autofluorescence, low scattering offering higher sensitivity and better signal-to-noise ration. Nanoparticles like quantum dots, liposomes or supermagnetic NPs can be conjugated with NIR fluorescence dyes acting as targeted optical imaging probes to offer high selectivity and specificity [67]. Recently, Upconverting Nanoparticles (UCNPs) have been introduced in Biophotonics and nanophotonics as very promising theranostic intratissue probes in biological tissues [68, 69]. Their unique property to convert near-infrared (NIR) light into visible or ultraviolet light *via* photon upconversion mechanism will permit interventions to deeper tissues pathologies with minimum healthy cells destruction.

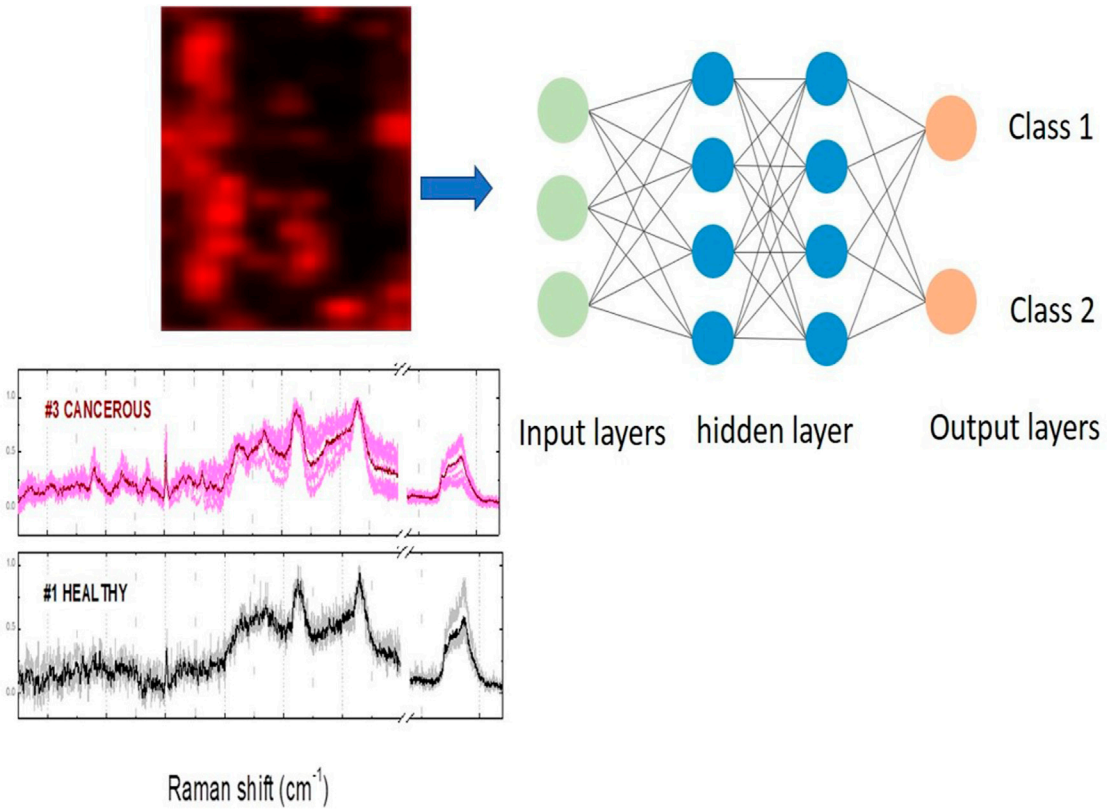

FIGURE 2 | A schematic illustration of machine learning methodology applied in Raman spectroscopy. Image features or spectral images are used as inputs to the artificial intelligence algorithm and the class output can be normal or tumour for discrimination between healthy and cancerous tissues.

THE ROLE OF OPTICAL TWEEZERS IN BIOPHOTONICS

Over 30 years of exploration after the first report of damage-free optical trapping of virus and bacteria by Ashkin [70], optical tweezers have found innumerable applications in cell biology and living systems studies [71]. The optical trapping technique uses one or more laser beams to selectively manipulate position, motion, and dynamics of micro- and nanostructures. This phenomenon is based on the optical forces of the order of few piconewtons exerted as the electromagnetic radiation (photons) changes its momentum when it interacts with matter. For the theoretical and experimental study of the optical forces, two models have been developed, considering the particle diameter *(d)* compared to the wavelength (λ) of the incident light: the geometric model that refers to the case where the dimensions of the particle are much larger than the wavelength (Mie particle, $d>>\lambda$) [72, 73] and the electromagnetic model for particles of dimensions much smaller than the wavelength (Rayleigh particle, $d<<\lambda$) [74, 75]. In case of $d \sim \lambda$, generalized electromagnetic theories have been applied such as the generalized Lorentz-Mie theory, which describes the scattering of a flat electromagnetic wave by a sphere of any size, in the case of Gaussian bonds [76]. The optical force exerted on a cell depends on the particle's shape, size, its surface and the cytoplasmic refractive index. Therefore, the biochemical changes that happens in the cell cytoplasm or membrane are reflected to its behavior under the optical trap [77].

Optical tweezers are used extensively for studying living cells, e.g., for hemorheology studies, blood microcirculation and biomechanical properties [77, 78]Click or tap here to enter text. They can be used as passive "force clamps" to induce and study elastic deformations in individual cells [79]Click or tap here to enter text. They are a tool for calculating the stiffness and torsion rate by measuring sub-micrometric cell deformations, which are caused by optical forces. Researchers used optical tweezers to elongate human erythrocytes through the dual optical trapping of silicone spheres attached to the cell membrane or by line optical tweezers (**Figure 3**) and to determine their degree of torsion. The shear modulus was calculated by measuring the cell membrane deformation in function with the optical forces exerted to the membrane *via* small optically trapped silica beads [80]Click or tap here to enter text. The bending modulus of the membrane was estimated by measuring erythrocyte's folding time in function with laser power under the effect of line optical tweezers [81]Click or tap here to enter text. Optical tweezers have been used to induce rotation and folding of erythrocytes to study their elastic properties and diagnose malaria in them [78, 82]. Click or tap here to enter text. Zhao *et al* [83]Click or tap here to enter text. proposed and implemented an optical shield scheme, based in far-field Bessel

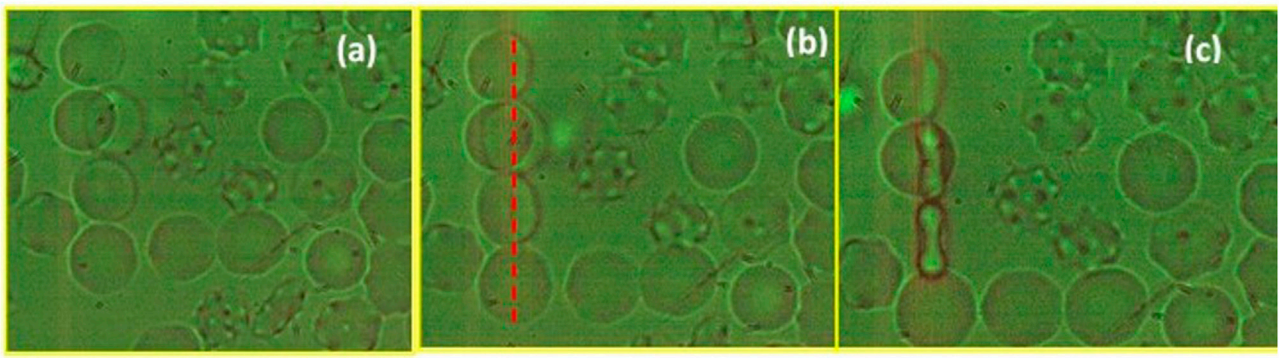

FIGURE 3 | (A) Three red blood cells under a line optical tweezers. The RBCs are trapped simultaneously, **(B)** are folded gradually and **(C)** orient its long axis in the direction of the electric field of incident beam. Dotted red line is the direction of the line optical trap. Optical tweezers act as a tool for the evaluation of erythrocyte's deformability which is an important biomarker for circulation efficiency.

beam, for manipulating individual cells in a crowded environment (e.g., single blood cell, individual lymphocytes from an inguinal lymph node). Holographic optical tweezers have been developed by using spatial light modulators to trap and move many cells simultaneously [84, 85]. This offers the opportunity to create arrays of living cells into gel matrix or microfluidic networks and potentially to create artificial tissues [86]. Line optical tweezers created with holographic optical trapping technique have been used for measuring the effective interaction potential for pairs of colloidal particles [87].

In addition to other biomedical areas, there have been great advances in optical trapping and its combination with other Biophotonics tools in neuroscience research, for studying the physical properties and intrinsic forces of neurons, their communication modalities, as well as some of the fundamental neuronal growth and dynamics function [88]. Optical tweezers can be combined with Raman spectroscopy to characterize and monitor the physical and chemical properties of cells. For example, Laser tweezers Raman spectroscopy was used to monitor the changes in the oxygenation state of human red blood cells while they were stretched by the optical forces [89, 90]Click or tap here to enter text.

So far, no clinical application in human has been implemented by using optical tweezers. Infrared optical tweezers have been used to trap and manipulate erythrocytes in the blood capillaries in the ear of a mouse. Optical tweezers were capable to interfere to the blood stream by trapping erythrocytes or removing a blockage [91]Click or tap here to enter text. A very challenging also demand is the miniaturization of the biophotonic set-ups opening new, fascinating possibilities for *in vitro* single cell experiments like flow cytometry, laser induced fluorescence and for *in vivo* detection of diseases. Optical tweezers can be coupled with nanophotonic biosensor devices based on integrated fiber optics and microfluidics devices for the implementation of lab-on-a-chip platforms. They can probe complex biophysical and biomechanical processes governing cell-cell interactions, cell–surface interactions, cell sorting and drug delivery/testing [92–94]Click or tap here to enter text. **Figure 4** illustrates a simple implementation of an advanced optical tweezes system integrating with microfluidics devices to perform single cell manipulation and sorting between target with NPs cancer cells and healthy cells. Moreover, the selective observation of cells-nanoparticles interactions will lead to a better understanding of the interaction mechanisms and to more targeted treatments.

THE APPLICATION OF OPTICAL TWEEZERS IN CANCER FIELD AND FUTURE PERSPECTIVES

The ability to selectively manipulate single cells can have many advantages *in vivo* for the diagnosis and treatment of metastatic cancer cells which can travel through the bloodstream and the lymph system [79, 95]Click or tap here to enter text. The understanding the biophysics of individual cell deformation offers the means for new perspectives in cancer prognosis, diagnosis, and treatment. Changes in the ability to deform cell shape [96] combined with changes in cell adhesion affect cell reproduction, cell signal transmission, and cell metastasis potential [97]. Qian Zhao et al. demonstrated the optical manipulation of two lymphocytes under living conditions. The lymphocytes were optically trapped directly as they isolated from a lymph node using a Bessel beam created by an axicon and a lens [83]. Trapping and manipulation of single cells in living environments is expected to help the study of how natural killer cells react to cancer cells or to selectively bring killer cells into contact with other target cells [83].

Researchers have reported the use of optical trapping as a tool to measure the minimum cell-cell adhesion time as a line cell is trapped and brought into proximity to another [95]. They observed that the average minimum adhesion time increases significancy in neural tumor cells compared to healthy cells. Moreover, they induced chemically differentiation in various cell line and tumors and proved that optical tweezers are able to assess the differentiation status of cancerous cells by measuring the minimum cell-cell adhesion time. Discrimination of individual cancer cells have been also reported by using Laser Tweezers Raman Spectroscopy coupling with a microfluidic flow

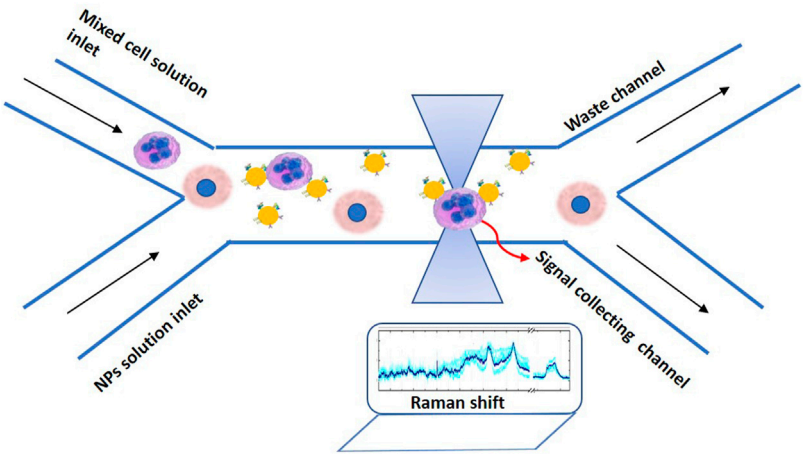

FIGURE 4 | Schematic representation of dual-beam optical tweezers coupled with microfluidics device to manipulate and recognize targeted with functionalized NPs tumour cells from healthy cells. The system can be integrated with other spectroscopic set-ups such as a Raman microscope to collect signals for cell discrimination and characterization.

chamber [98]. Single cells are optically trapped, analyzed and discriminate according to the differences in their spectral fingerprint [98, 99].

Holographic optical tweezers can be used to discriminate normal, cancerous and drug-treated cancerous leucocytes by measuring the trapping forces using escape force method [100]. This method could become equivalent with the conventional methods such as flow cytometry without using fluorescent-based markers. Moreover, holographic optical tweezers can be combined with upconversion luminescence encoding for screening cancer biomarkers [101]. A bead array of carboxyl functionalized polystyrene beads was formed and stay stable with holographic optical tweezers. The beads were labelled with upconverting nanoparticles probes (UCNPs) of two different emission colors for the detection of two liver cancer biomarkers, carcinoembryonic antigen and alpha fetal protein. UCNPs are able to excited from near-infrared (NIR) light region and emitted in the visible region with extremely low background luminescence. This imaging-based stable suspension array offers the detection of dual cancer biomarkers with quite sensitivity and specificity providing a new alternative method for cancer diagnosis [101].

The mechanical properties of cancer cells membranes such as bending modulus [102] and fluidity [103] have been also measured by using optical tweezers and the standard stretching methods with the microbeads attached to the cell membrane [80]. The biomechanical properties of living cells are closely related to the health status and function of human cells [96, 102, 104]. Guo et al. measure with accuracy the bending modulus and the surface membrane tension of breast cancer cells [105]. Moreover, decreased elongation times are recorded when cells were treated with cytochalasin D or the membrane protein caveolin was over-expressed. Xuanling Li et al. showed that the fluidity and the invasiveness in the membrane of small cell lung cancer cell line SHP77 increased significancy after the transfection with small RNA miR-92b-3p. This could help to understand better cancer cell metastasis/invasion [106].

High-precision optical tweezers have been developed for protein folding experiments. Optical tweezers were used to apply mechanical forces and to monitor proteins unfolding [107]. Recent studies correlate the folding and misfolding of human membrane proteins with cancer [108]. The way that proteins fold from linear chains to three-dimensional structures or *vice versa* is under great interest in biology [109, 110]. Single proteins or protein complex can be tethered between two microbeads by using DNA linkers or antibody linkers. The beads are trapped by using a dual optical tweezers and can be pulled away by alter the distance between the laser traps. Thus, protein unfolding is induced by the mechanical forces and the kinetics of the protein can be monitoring [107, 111] The mechanical forces at which folding transitions take place depend on the pulling speed [111].

During the last few years, optical tweezers were proposed as a tool to probe the Casimir interactions between microspheres inside a liquid medium, erythrocytes and membrane proteins [112–114]. The Casimir effect is a quantum phenomenon arising from quantum fluctuations which can give rise to long-range attractive forces between two uncharged particles [112]. Recent studies demonstrate that the Casimir forces between two particles can be measured by the optical trapping of the particles in suspensions [115]. Physicists manifest that the proteins of cellular membranes can communicate with each other by using Casimir forces. Examples include the force exerted by a single DNA molecule and forces in kinesin or other moto proteins [116]. This finding gives to optical tweezers technique the potential for novel quantitative applications in molecular biology of cancer.

Nowadays, advanced optical tweezers platforms have been built-up to operate at single-molecule level without the need of fluorescence dyes or tethers. Plasmonic tweezers are capable to manipulate with high sensitivity molecules such as proteins, DNA etc. [117, 118] attached on metallic nanostructures exploiting the Localized Surface Plasmon Resonance (LSPR) phenomenon

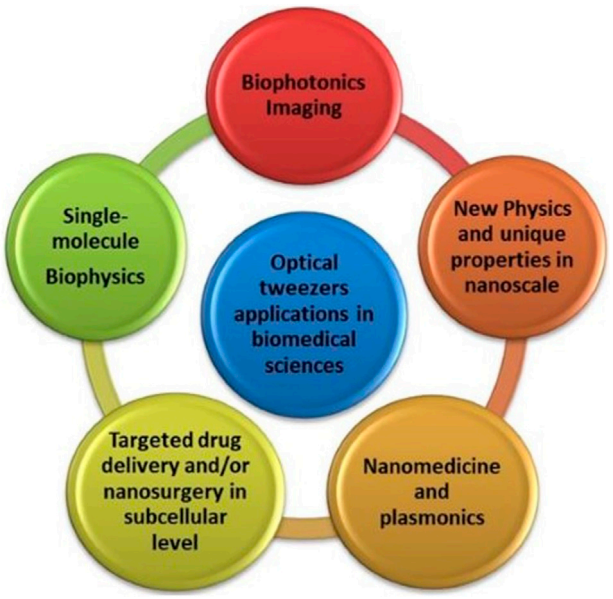

FIGURE 5 | Schematic illustration of some interconnected components of advanced Biophotonics techniques for cellular and molecular manipulation through optical tweezers.

which can exist on a dielectric-metal interface [119]. LSPR is a coherent, collective spatial oscillation of the conduction electrons in a metal nanostructure, which can be directly excited by visible and near infrared light. The SPR occurs when the real part $\varepsilon_r(\omega)$ of the complex dielectric constant of the metal and the dielectric constant of the surrounding medium satisfied the relationship: $\varepsilon_r(\omega) = -2\varepsilon_m$ [120]. This phenomenon enables the incident light to confine into a region smaller than the light wavelength enhancing the oscillating electric field of the light which strengthens the optical forces.

Gordon and his collaborators have developed novel plasmonic configurations which provide stable and flexible traps for biomolecules [121, 122]. Very recently, the smallest virus particle, PhiX174, was optically trapped by using double nanohole apertures in gold nanofilms. The virus was analyzed by using Plasmon Tweezers integrating with Raman Spectroscopy [123]. Plasmonic tweezers have also thermal effects through the resonated oscillations of the conductive electrons of the metallic nanostructures which convert the electromagnetic energy into heat. This might give new perspectives in photothermal cancer therapy for a more targeted treatment. Already, plasmonic photothermal therapy was studied extensively based on various types of metallic nanoparticles as photosensitizers [124, 125]. Moreover, in 2021, Shen et al. reported that UCNPs from highly doping lanthanide ions in NaYF4 nanocrystals can be optically manipulated and demonstrate much higher optical trap stiffness compared to gold nanoparticles [126]. The photoluminescence of UPCNPs could provide new fascinating theranostic interventions by single-cell manipulation and sensing. **Figure 5** illustrates all the interconnected multidisciplinary fields of the advanced Biophotonics techniques for cellular and molecular manipulation through optical tweezers.

CONCLUSION

Biophotonic techniques have proved to be a powerful tool in the field of cancer theranostics. Among them, optical tweezers can spur new approaches to cancer treatment and to the understanding of cancer mechanisms at cellular and sub-cellular level. Nowadays, integrated systems based to optical tweezers are capable to manipulate to each other cells, biomolecules and nanocarriers with high sensitivity and selectivity providing information about their biomechanical properties (e.g., membrane fluidity, elasticity etc), their biochemical and biophysical properties (e.g., spectral fingerprints) and tracking their interactions (e.g., adhesion time, adhesion forces etc). Overall, the unique capabilities of optical tweezers in combination with the development of advanced miniaturized devices and artificial intelligence methodologies will be a boon for the cancer confrontation.

AUTHOR CONTRIBUTIONS

Conceptualization, writing—original draft preparation ES.

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