Available online on 15.08.2022 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

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Review Article

Advancement of Near Infrared techniques in diagnosis and treatment of cancer

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Article Info:

Article History:

Received 18 June 2022
Reviewed 26 July 2022
Accepted 02 August 2022
Published 15 August 2022

Cite this article as:

Sharma N, Ankalgi AD, Thakur U, Ashawat MS, Sharma N, Advancement of Near Infrared techniques in diagnosis and treatment of cancer, Journal of Drug Delivery and Therapeutics. 2022; 12(4-S):192-198

DOI: http://dx.doi.org/10.22270/jddt.v12i4-s.5599

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Abstract

Near-Infrared photoimmunotheraphy (NIR-PIT) is newly developed therapy for cancer treatment, by using a specific monoclonal antibody (mAb) conjugated to a photoactive agent i.e. IRDye 700DX. In this technique, the conjugate of specific monoclonal antibody - photoactive agent is administered intravenously to cancer patient. When NIR light is applied, the monoclonal antibody - photoactive agent conjugate (APC) is excited and selectively kill the cancer cell without harming neighbouring normal cell. NIR light alters the chemical structure of APC and damages the cancer cell membrane. For the diagnosis of tumor, it is possible to observe the movements of erythrocyte in tissues by using diffuse correlation spectroscopy (DCS). DCS flow measurements are carried out by observing photon speckle variations induced by moving tissue scattering. Another diagnostic tool is Near-infrared spectroscopy (NIRS), which is based on endogenous chromophores difference between healthy tissue and cancer by using diagnostic indicator i.e. oxy-haemoglobin or deoxyhaemoglobin, lipid or water bands. NIRS is being used in a variety of biological and pharmaceutical research fields, including brain imaging, cardiovascular radiology, formulation and quality/process control, and even clinical trial. In this review article, we describe the Near-Infrared photoimmunotheraphy (NIR-PIT) with its mechanism, role of DCS & NIRS in cancer diagnosis and various application of NIR-PIT.

Keyword: Near-infrared immunotherapy (NIR-PIT); diffuse correlation spectroscopy (DCS); Near-infrared spectroscopy (NIRS); Cancer treatment; Cancer diagnosis.

Introduction:

Cancer is major public health problem globally and is 2nd leading cause of death in United State[1]. It's a disease of genes that regulates proliferation, differentiation and cell death[2]. According to the study in United State, there will be approximate 1,918,030 cases of cancer identified in 2022[3]. In case of male, there will be high occurrence of prostate cancer, lung and bronchus cancer, urinary bladder cancer, colon and rectum cancer, but in case of female, there will be more chances of breast cancer, lung and bronchus cancer, colon and rectum cancer, uterine corpus and thyroid cancer, respectively[4]. The main and challenging task in cancer research is to develop a method which is accurate, fast, inexpensive and suitable for improving the health of cancer patient[5]. Nowadays, cancer is diagnosed by different techniques such as include nonionizing or ionizing radiological techniques such as X-ray mammography, ultrasound imaging, computed tomography (CT), positron emission tomography (PET) and functional magnetic resonance imaging (fMRI)[6]. The computed tomography and ultrasound technique only provides the morphological information about tumors, and other techniques like PET and fMRI gives the functional information.

In recent years, Near-Infrared spectroscopy (NIRS) is commonly used for the diagnosis and monitoring of cancer because this is a fast, simple, inexpensive and convenient technique[2]. Due to its important feature, it is a better technique than other expensive diagnostic techniques (like fMRI, PET, CT etc.) for measurement the optical properties of tissue[7-10]. Near-Infrared Diffuse correlation spectroscopy (DCS) is another important technique for the diagnosis of cancer. DCS directly detect the RBCs motion and speckle fluctuation of NIR light in biological tissue[11,12].

Now days, some available method used for the cancer treatment in clinics are chemotherapy, radiotherapy and surgery. But various newly developed therapies like immunotherapy, targeted therapy, gene therapy, magnetic hyperthermia therapy and phototherapy i.e. photothermal therapy (PTT) and photodynamic therapy (PDT) commonly adopted or used in clinical trials. PTT and PDT both are responsible for killing tumor cells by heat in PTT or through reactive oxygen species under irradiation on light in PDT. The external stimuli helpful in destruction of tumor but the side effects from this is quite strong. NIR light has greater penetration ability in deep tissue therefore, it is good source of light for treating cancer. When the NIR light is applied, the photoactive agents changes the conformation and destroy cancer cell without harming surrounding healthy tissue[13].

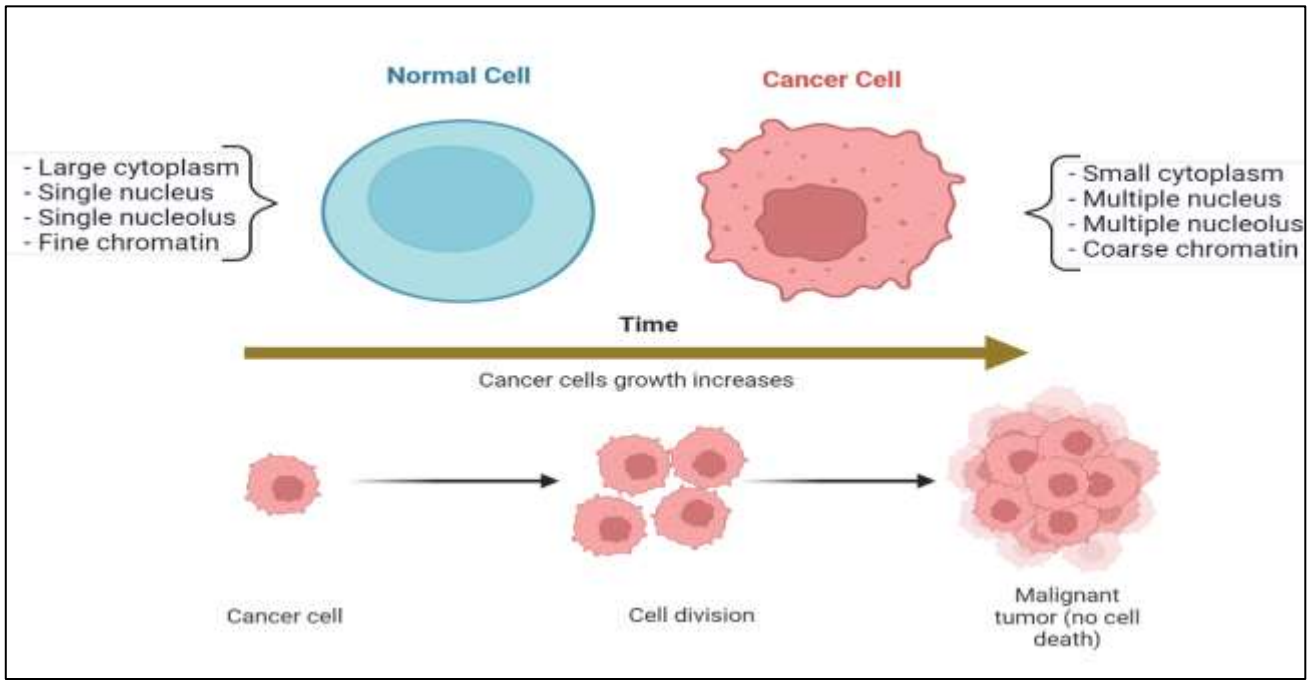

Figure 1: Difference between Normal and Cancer Cell

Near-Infrared Photo-immunotherapy:

Near-Infrared photoimmunotheraphy (NIR-PIT) is newly developed therapy for cancer treatment, by using a specific monoclonal antibody (mAb) conjugated to a photoactive agent i.e. IRDye 700DX. (Fig.2)[14]. The monoclonal antibody (mAb) used in this NIR-PIT has specific property to bind to cancer cell antigen, and this characteristic make it more specific than other techniques. In this technique, the conjugate of specific monoclonal antibody - photoactive agent is administered intravenously to cancer patient. This conjugate after administration reaches to the cancer site and bind to the antigen, which is present on the surface of cancer cell (Fig.3).

In NIR-PIT, Near-infrared (NIR) is used as source of light at the range 690nm. This NIR light penetrates the body tissue around few centimetres, and cause no harm to normal cell. When NIR light is applied, the monoclonal antibody - photoactive agent conjugate (APC) is excited and selectively kill the cancer cell without harming neighbouring normal cell. The photoactive agent (IRDye700DX) is water soluble dye and has no biotoxic or phototoxic property. The unbound IRDye700DX, which detaches from APC is not toxic and is freely eliminated from body in urine. Therefore, this NIR-PIT technique of using specific monoclonal antibody - photoactive conjugate and NIR light at range 690nm helpful in killing cancer cell without damaging normal cells[15,16].

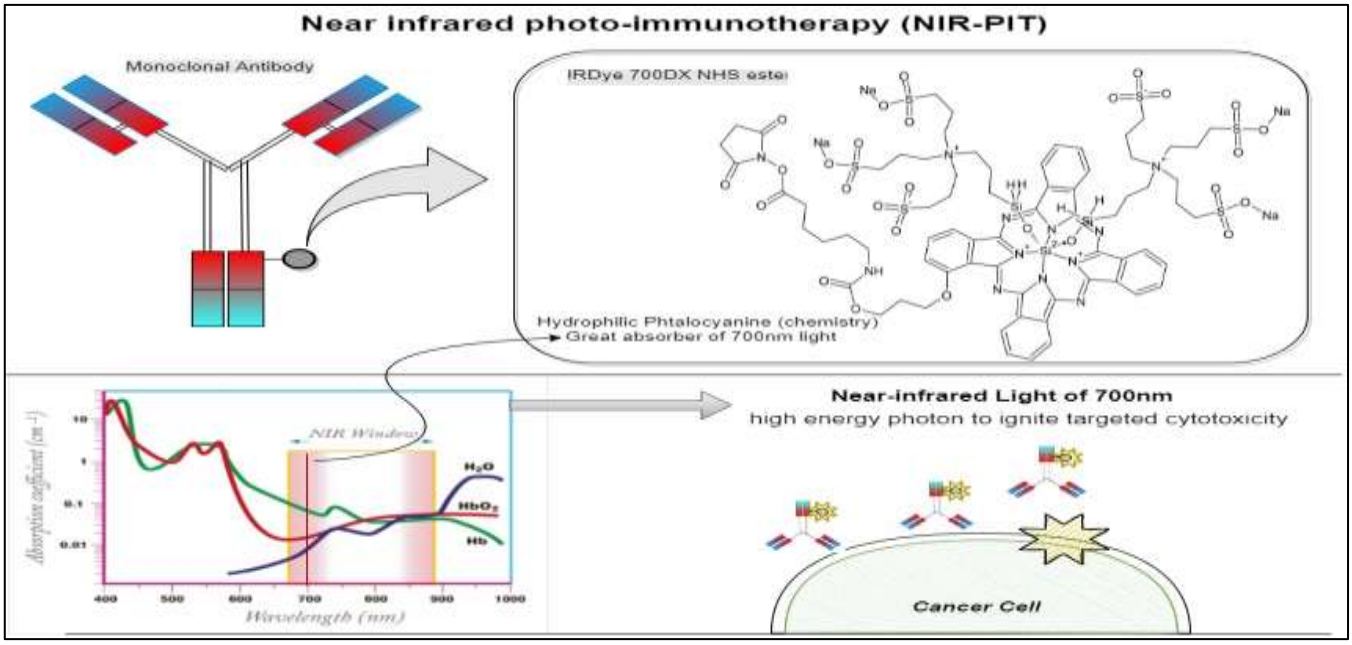

Figure 2: Near-Infrared Immunotherapy

(**Fig.2** a framework for describing NIRPIT-based targeted cancer treatment. Monoclonal antibody are used as targeted molecules because to their high binding selectivity. A hydrophilic phthalocyanine dye (IRDye 700) is used as a "Nano-dynamite" reagent because it absorbs near-infrared light at a wavelength of 700 nm and only produces high cytotoxicity when linked to cell membranes. Because IR700 dye absorbs near-infrared light at 700 nm, it is used as a cytotoxicity initiator)

In NIR-PIT, light can penetrates the body tissue only few centimetre (approx. 2cm). So, it's a better technique for treating superficial tumor[17]. In case of lungs and pleural cavity tumor, NIR light is passed much further through air in lungs[18-21]. But in solid tissue, NIR light source must be placed near to the tumor because NIR light is rapidly diminished in more solid tissue[22].

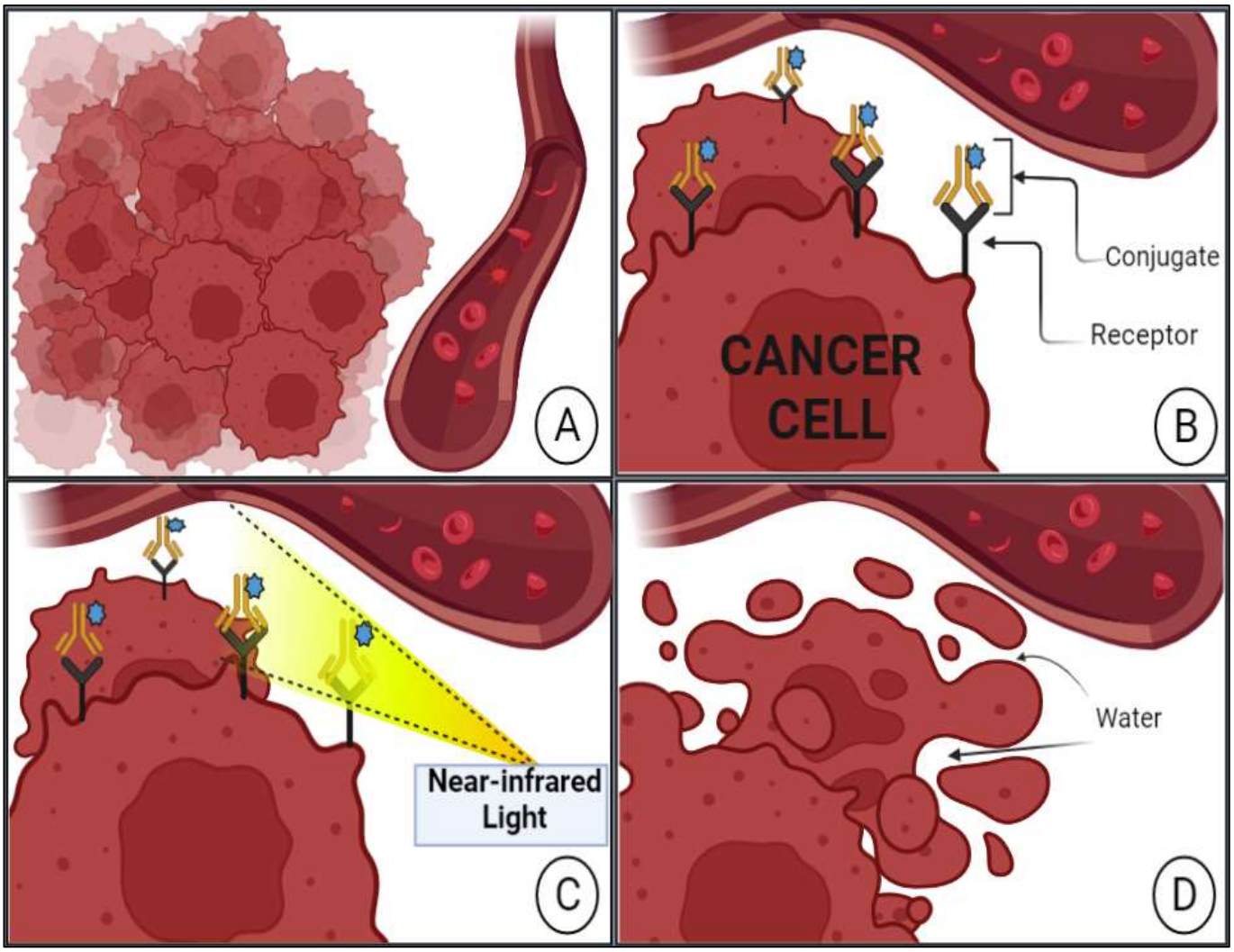

Figure 3: Successive microscopic pictures for cellular cytotoxicity caused by NIR-PIT

Preparation of Antibody-photoactive conjugate:

For preparing antibody-photoactive conjugate, Incubate the monoclonal antibody with IRDye 700DX and 0.1 mol./L Na_2HPO_4 (maintain pH-8.5) at room temperature (20-25℃) for one hour. After that, mixture is passed through gel filtration column, and then antibody – photoactive conjugate (APC) is injected into body by intravenous route. This leads to binding of antibody-photoactive conjugate to the cancer cells. When NIR light is exposed, photochemical ligand reaction occurs by which hydrophilic side chain of IRDye 700DX releases and this makes a remaining molecule hydrophobic. The unbound IRDye700DX from antibody – photoactive conjugate, easily eliminated from body by urine[23,24].

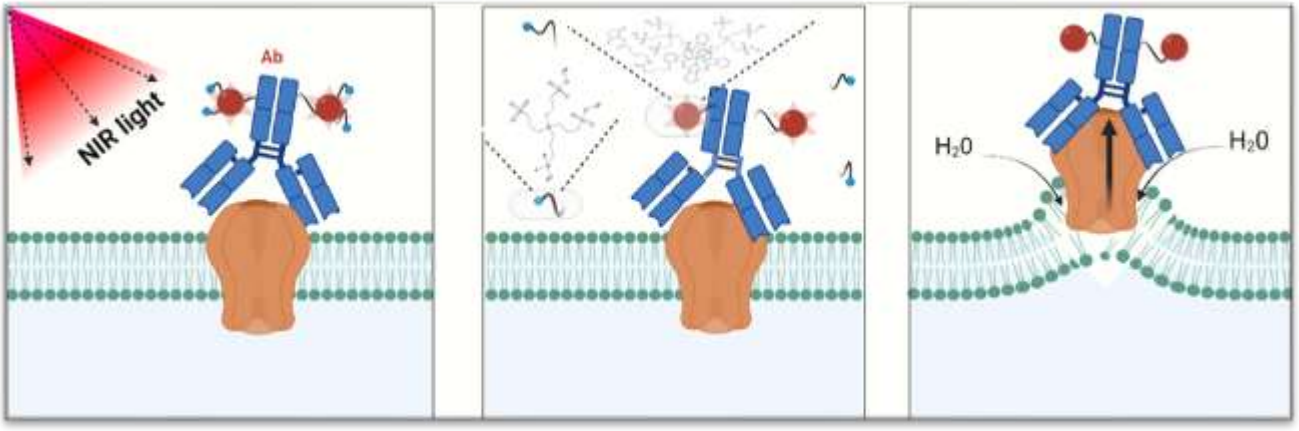

Figure 4: Diagram showing the physicochemical changes occur in APC during NIR light exposure

Role of Diffuse Correlation Spectroscopy for Cancer Diagnosis:

It is possible to observer the movements of erythrocyte in tissues using diffuse correlation spectroscopy (DCS) while yet retaining the benefits of near-infrared spectroscopy[25,26]. Diffuse correlation spectroscopy is carried out by determining photon fleck oscillations brought on by scatters movement in body tissues. The primary cause of these oscillations in non-muscular tissues is movement of erythrocytes within blood arteries; however, complications, particularly in muscular tissues, might include shifting artefacts and fibre shearing[27,28]. Other benchmarks, such as power laser Doppler[29], Doppler ultrasound[30,31], Fluorescent microsphere flow measurements, Xenon-CT[32], Xenon-CT[33],are also used for measurements of blood flow variations in tissues. In order to detect the optical characteristics of deep tissues using NIRS, a pair of source and detector fibres are positioned close together along the tissue surface (Fig.). Through the source fibre, a laser transmits NIR light into the tissues, which is then detected by a photo-detector through the detector fibre. It is well known that photon migration in tissue has the characteristics of a diffusive process, during which photons undergo absorption and scattering processes. Blood oxygen saturation, total haemoglobin concentration, oxygenated haemoglobin concentrations and deoxygenated haemoglobin concentrations may all be measured using the differences in NIR absorption spectra between the main tissue chromophores[25,28].

Different probe designs are needed for the various circumstances that DCS might be employed in. Three sample probes are shown in Figures 5 (B) through (D). In investigations of tumour that are near to the body surface, the first probe [Fig. (B)] with straight or 90-degree bent fibres is employed (e.g. breast cancer, head and neck cancer). The second probe [Fig. (C)] is a non - contact probe positioned on the image plane of a mechanical camera that is set at a specific distance from the tumour surface. By allowing unhindered illumination from the treatment light through to the tumour during photodynamic therapy, this innovative noncontact configuration enables ongoing monitoring of tumour hemodynamic changes. The 3rd probe [see Fig. (D)] has several side-firing fibres placed in a tiny catheter that may be introduced into tissues or tumor with the least amount of tissue damage. Different boundary conditions [for example, semi-infinite geometry in Figures (B) and (C) or infinite geometry in Figure (D)] should be utilised for various probe-tissue interactions. Practically every advancement in NIRS probe design is transferable to DCS usage, and it is simple to construct hybrid NIRS and DCS probes by adding additional detector and source fibres[34-38].

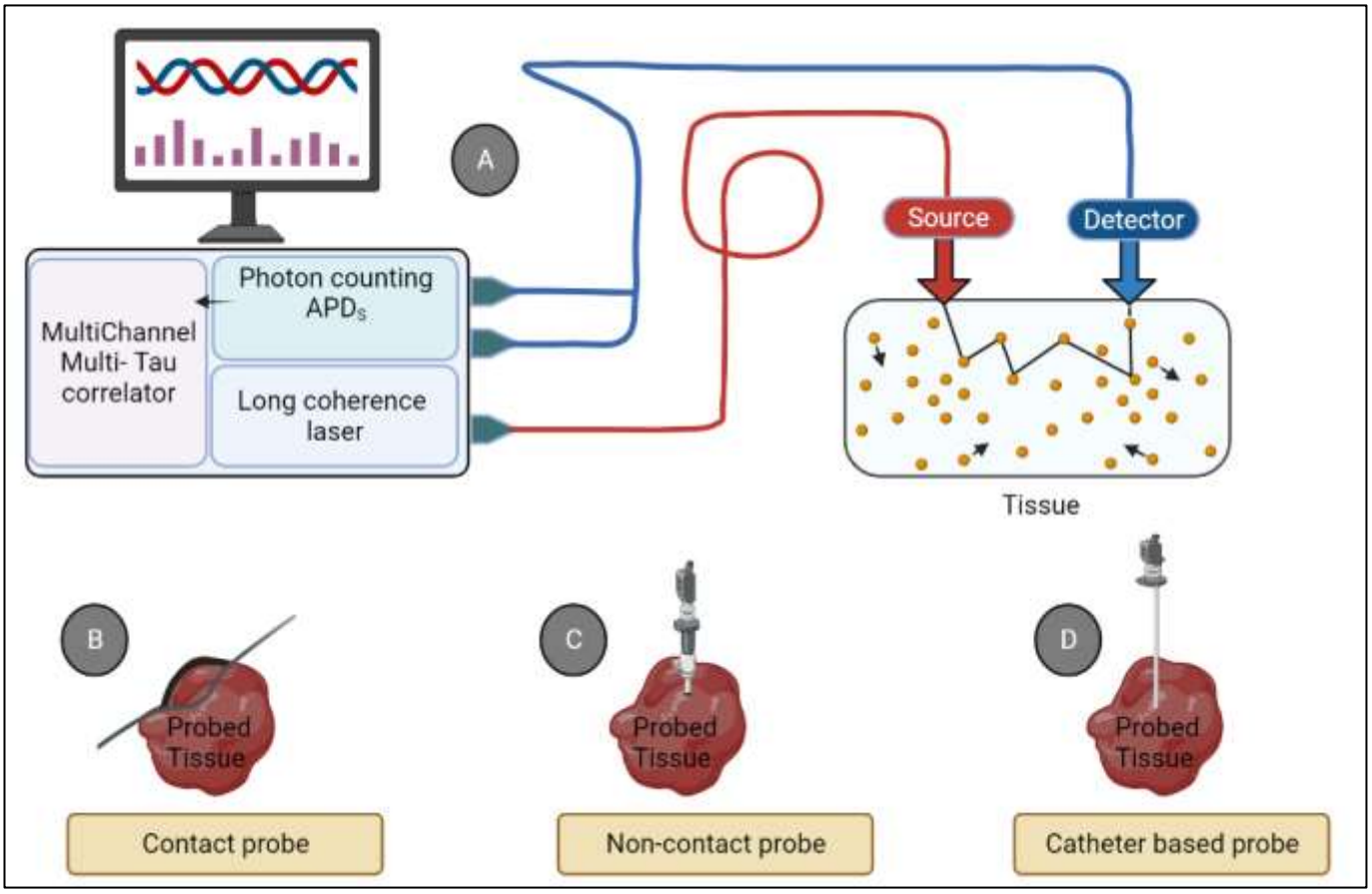

Figure 5: Diffusion Correlation Spectroscopy Instrumentation and probes type.

Role of Near-infrared Spectroscopy in Cancer Diagnosis

The development of diagnostic techniques to improve the ability to distinguish between cancerous and healthy tissues has received a lot of attention in recent years. Oncologists have used a variety of molecular techniques as effective tools for examining chemical changes at the molecular spectroscope level[39-41]. For instance, infrared spectroscopy (IR) methods are frequently used to examine biological tissues; the resultant spectra are made up of distinct bands arising from all vibration modes of bimolecular components present in the tissue, such as nucleic acids, proteins, and lipids. Each biomolecule generates a unique infrared spectrum that carries

information about several functional groups inside the molecule. The spectral bands' strength and frequency depend on the relative concentration, vibration frequencies, and polar characteristics. A whole tissue spectrum can communicate distinctive details about the molecular structure and composition that precede the transition from a normal to a malignant state. Near-infrared (NIR) spectroscopy has received interest recently for the biological investigation of numerous disorders, including malignancies[42-45].

A potential use of NIR technology to non-invasive and minimally invasive methods of diagnosis is made possible, in particular, by the development of fibre optic probes. NIR spectroscopy may be divided into long-wave and short-wave NIR intervals[46]. Due to the dominance of hem proteins and cytochromes in the short-wave NIR range, this region primarily offers data on tissue blood flow, oxygen saturation, and consumption. The combination and overtone vibrations of O-H, C-H, and N-H groups in the long-wave NIR range provide information on the chemical makeup of tissues. The structure and concentration of different components are truly reflected in a tissue's NIR spectrum. The biochemistry, composition and physiology of cancerous tissues are different from normal tissues. Any change in the tissues' chemical makeup can be found and used for diagnostic reasons. NIR spectroscopy has been used by certain researchers in investigations on breast, gastric, pancreatic, prostate and colorectal tissues. A tissue sample frequently results in a complex NIR spectrum, which is made up of several wide, weak, non-specific, and overlapping bands, in contrast to the IR spectrum, which corresponds to the overtone combinations of different chemicals[47]. An InGaAs detector and FT-NIR spectrometer (Thermo Fisher, USA) were used to conduct the NIR spectroscopy research[48].

In the range of 5500-7000 cm^{-1}, the variations between cancer and normal samples may be more readily seen; these variations include peak shape and intensity. The initial overtones of N-H, O-H bonds, and C-H combinations, as well as the first overtone of C-H stretching (5500–6000 cm1), are responsible for these peaks in this area. Such findings make sense because DNA, protein, lipids, and water make up the majority of the differences in the composition of cancer and healthy tissues. The majority of the bands in the NIR range really came from the vibration modes of various functional groups in the molecules of biological components in tissues and cells. A NIR spectrum is basically a combination of the fingerprints of several substances, including proteins, carbohydrates, lipids and water[45,46].

Applications of NIR-PIT

NIRS is being used in a variety of biological and pharmaceutical research fields, including brain imaging, cardiovascular radiology, formulation and quality/process control, and even clinical trial. A computer, an NIR spectrometer, a fiber-optic accessory with NIR illumination, and sensing fibres make up the conventional NIR measuring system. Radiation-emitting fibres are used to deliver the radiation to the tissue from an LED, broad-band thermal, or laser source. The photons that are transmitted or reflected back from the tissue are gathered by the detecting fibres and will be sent to the spectrometer for examination. The chromophores (DNA, proteins, haemoglobin, water, cytochromes, and lipids) absorb light at various wavelengths[2].

The NIR-PIT treatment has been carried out effectively using APCs that target a variety of antigens, including EGFR in the cases of lung[20], skin[49], and breast cancer; human epidermal growth factor receptor-2 in the cases of gastric cancer[50]; mesothelin in the cases of mesothelioma, pancreatic, and ovarian cancer;[(51)] prostate specific membrane antigen in the cases of prostate cancer[52], in hepatocellular carcinoma, glipican 3 (GPC3) is used, and in malignant lymphoma, CD20 is used[53]. Deeply sitting tumours are treated with NIR light exposure using fibro-optical diffusers that introduced through endoscopes[54], or catheter needles techniques that could be readily adaptable to medical practice.

Conclusion

NIR-PIT is a novel cancer treatment with several use. This technique is highly specific for cancer treatment by using monoclonal antibody i.e. IRDye 700DX. The antibody-photoactive conjugate attaches to cancer cell. When NIR light is applied, the monoclonal antibody - photoactive agent conjugate (APC) is excited and selectively kill the cancer cell without harming neighbouring normal cell. A wide variety of cancers might be treated with little to no adverse effects by employing different light delivery techniques. DCS and NIRS are two important technique for the diagnosis of cancer. In DCS, flow measurements are carried out by observing photon speckle variations induced by moving tissue scattering. NIRS is based on endogenous chromophores difference between healthy tissue and cancer by using diagnostic indicator i.e. oxy-haemoglobin or deoxyhaemoglobin, lipid or water bands. In several animal models, the NIR-PIT not only cures the local tumors but also reduces or prevents systemic metastasis and recurrence. In the future, NIR-PIT has a strong potential to become a widely used cancer therapy.

Acknowledgement

The authors are thankful to the laureate Institute of pharmacy, Kathog, Jawalamukhi, Himachal Pradesh 176031, India. We are also grateful to the principal and management for providing the necessary facilities for completing this review article successfully.

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