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A review of applications of principles of quantum physics in oncology: do quantum physics principles have any role in oncology research and applications?

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Literature Review

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Abstract

Background: Research in the applications of the principles of quantum physics in oncology has progressed significantly over the past decades; and several research groups with professionals from diverse scientific background, including electrical engineers, mathematicians, biologists, atomic physicists, computer programmers, and biochemists, are working collaboratively in an unprecedented and pioneering economic, organisational and human effort searching for a wider and more effective, potentially definitive, understanding of the cancers. It is hypothesised that the principles of quantum physics could open new and broader understanding of the cancers and the development of new effective, targeted, accurate, personalised and possibly definitive cancer treatment.

Materials and methods: This paper reports on a review of recent studies in the field of the applications of the principles of quantum physics in biology, chemistry, biochemistry and quantum physics in cancer research, including quantum physics principles and cancer, quantum modelling techniques, quantum dots and its applications in oncology, quantum cascade laser histopathology and quantum computing applications.

Conclusions: The applications of the principles of quantum physics in oncology, chemistry and biology are providing new perspectives and greater insights into a long-studied disease, which could result in a greater understanding of the cancers and the potential for personalised and definitive treatment methods.

Introduction

The applications of the principles of quantum physics continue to impact our everyday life. The basis of our computers, lasers, telecommunication and medical imaging industries, as well as our current understanding of the universe, is all built on the principles of quantum physics. In recent years, there have been several investigations in the field of chemistry, biology, biochemistry, computer science, mathematics and medical imaging using the principles of quantum physics for a better understanding of the cancers, their diagnosis and an effective or potentially definitive treatment methods.[1–75] In a recent study that was grounded on a novel mathematical model based on DNA sequencing and epidemiologic data from around the world, Tomasetti et al.[76] reported that nearly 66% of cancers occur by random mutations. Therefore, can this randomness be predicted by mathematical models that are based on the principles of quantum physics?

Research in the applications of quantum physics principles in oncology has progressed significantly, and several research groups consisting of professionals from different scientific branches, including electrical engineers, atomic physicists, biochemists, biologists, mathematicians, computer programmers, and professionals of several hospitals and universities worldwide, are collaboratively working in an unprecedented and pioneering economic, organisational and human effort searching for a broader and more effective, possibly definite, understanding of the cancers.[77] In this endeavour, quantum mechanics principles appear as the referential knowledge for illuminating cancer research at the atomic level, and to open new and broader perspectives for new effective, targeted, accurate and personalised treatments.[77] Uthamacumaran[1] has suggested that cancer has evolved through quantum-selective adaptations to the environment over the generations, and there is currently much debate and a good deal of excitement in the medical sciences that, one day, the cure for cancer may be found at a quantum level.[2] According to Davies,[78] there are many suggestions claiming that quantum mechanics not

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only provides the basis of shapes and sizes of organic molecules but also drives the operation of living organisms. The potential applications of the principles of quantum physics in oncology have been demonstrated in several areas.[3–18,29–31,33–64,71–75] Quantum physics principles have been used for significant advancements in oncology research through modelling of concepts such as quantum metabolism,[4–6,9,11,18,14,24,26–28] quantum biology,[7,8] quantum chemistry,[9,19–23] quantum biochemistry[10,11,24–27] and quantum entropy,[12,13] which have been used to provide new insights into the origin of cancer cells and its proliferation.[5] Quantum theory has proven to be relevant for developing models with the potential to explain biological and biochemical processes such as the effects of carcinogens on genes, the mechanism of interactions of chemotherapy drugs with DNA[9] and the understanding of DNA mutations and defective protein synthesis.[14]

The potential to be able to mathematically model the behaviour of cancer cells can likely assist researchers in understanding a patient's unique cancer and allow for the development of a more targeted and personalised treatment that can be adapted for patient's specific cancer treatment.[1] The principles of quantum physics have also been used to improve the sensitivity and efficiency in the detection of diseased tissue through the development of quantum cascade lasers.[15] According to Bassan,[15] the quantum cascade lasers is an improvement upon the current standard Fourier-transform infrared microscopy technology. The principles of quantum physics have been applied in the fabrications of nanomaterials such as quantum dots, which are small semiconductor spherical nanoparticles composed of heavy metals or organic materials.[16,17] Quantum dots have diameters of a few nanometres in size and demonstrate quantum principles such as quantum confinement, quantum tunnelling and semiconductor mechanics.[16] Quantum biological models are being developed to give a better understanding of biological processes such as imperfect protein synthesis, DNA mutations and imperfections in genetic processes such as transcription and translation.[14]

This narrative literature review covers applications of the principles of quantum physics as applied to research in oncology. Current applications of quantum physics principles and their future directions are examined to gain insights into the role of quantum mechanics in explaining why a cell becomes malignant, whether quantum physics principles really have a role in oncology research and its applications in cancer diagnosis and personalised treatment. Major topics discussed include quantum physics principles and cancer; quantum physics modelling techniques, including quantum metabolism, biochemistry and biological modelling; quantum dots and its applications in oncology; quantum cascade laser histopathology and quantum computing applications. Applications of quantum physics principles in oncology, chemistry and biology are providing new perspectives and greater insights into a long-studied disease, which could result in a greater understanding of the cancers and personalised and potentially definitive treatment methods.[5]

Quantum Physics Principles and Cancer

According to Jacobson,[12] quantum physics principles have the potential to explain the proliferation of cancer cells. He has reported that, although the role of shortening telomeres in cancer cells is unclear, there is a possibility that this shortening could create conditions that initiate cancer cell proliferation or prevention and can be explained with the principles of quantum physics.[12] Jafri et al.[13] have indicated that there is evidence suggesting that the reduction of telomere length elicits a DNA damage response, which triggers senescence and suppresses cell checkpoints that would normally induce apoptosis in cancer cells. It is hypothesised that there are quantum entropy conditions with transpositional states that can lead to cell cycle checkpoint alterations induced by increased energy demands in cells. This increased energy demand is theorised to occur as a result of energy asymmetry from exposure to carcinogens or ambient radiation, and the body attempts to restore the energy balance by increasing mitotic divisions that results in energy release.[12]

When cells experience oncogenic changes, they can develop the ability to bypass senescence or M1 phase, and the suppression of cell checkpoints caused by the quantum entropy imbalance supports this senescence bypass effect.[12] These cells can then divide until multiple sets of telomeres are shortened to the point where cells experience end-to-end chromosome fusion, which initiates a chromosome breakage–fusion–bridge cycle known as M2 crisis, where two sister chromatids lacking telomeres fuse together to form a bridge with a chromatin connection.[12,13] Telomerase is used as a defence mechanism by cancer cells to increase the length of telomeres, potentially preventing the loss of genes needed for survival and allowing for continuous replication.[12] Therefore its upregulation is seen in cancer cells with shortened telomeres, assisting in the longevity of the diseased cells. In the bypass of senescence M1 and progression to M2 crisis phase, the telomerase activity is not high enough to overpower the energy demands of quantum state entropy, and this causes telomerase to extend the telomeres in cancer cells, allowing them to proliferate.[12] The central idea of this hypothesis is that quantum entropy induces changes to cell checkpoints during crisis phase, which allows cancer cells to overtake normal cells through the manipulation of telomerase activities.[12]

Quantum Physics Principles Modelling Techniques

The principles of quantum physics have been used for modelling a number of studies in biological sciences, including genetics, investigations into the origin of cancer cells and cell function.[11,14,18] Quantum physics modelling techniques have been used to gain a greater understanding of the effects of chlorine ions on the structure of DNA, potentially leading to cancer induction via DNA damage.[18] Tavares et al.[11] have reported that the in silico approach that utilises the principles of quantum physics in modelling chemotherapy drugs is an efficient way to determine the electronic structures of chemotherapy drugs and provides insight into the development of new effective drugs. Djordjevic[14] has proposed that quantum modelling will replace classical modelling, elucidating that biological processes are influenced by quantum effects and that quantum modelling will provide a method of studying DNA errors and tumours, thus opening doorways for cancer research from a quantum principle perspective.

Quantum metabolism modelling

Quantum metabolism is a concept that uses the quantum theory of solids to describe the relationship between metabolic rate and cell size.[4] Demetrius et al.[5] used this approach to develop a model that compares the usage of the oxidative phosphorylation pathway versus glycolysis in cells and hypothesised that the origin of cancer cells is rooted in metabolic dysregulation, caused by environmental or genetic pressures. This then induces a switch in cellular metabolism methods in cancer cells from oxidative phosphorylation to glycolysis—a phenomenon that can be modelled using quantum

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metabolism approach. This hypothesis is based on the 'Warburg effect', which describes the upregulation of glycolysis over oxidative phosphorylation in cancer cells, where the ratios of oxidative phosphorylation and glycolysis were compared between cancer cells and normal cells. It was observed that aggressive tumour cells showed higher rates of glycolytic metabolism under aerobic conditions compared to normal cells or benign tumour cells.[6] The increase in lactic acid production that results from cancer cells using glycolysis lowers the pH of the tumour microenvironment and, according to the acid-mediated invasion hypothesis, creates an environment where H^+ ions can diffuse and alter tumour–stroma interfaces to further increase invasiveness.[6] Demetrius et al.[5] investigated the integration of quantum metabolism with the Warburg effect and demonstrated the potential of metabolic rate regulation as a method of impeding the transition of a tumour from benign to malignant and reported that the selective advantage of tumour cells is significantly impacted by methods of metabolism as well as the metabolic rate of competing healthy cells.

Quantum chemistry modelling

Quantum chemistry molecular modelling has emerged as a more accurate modelling method compared with techniques such as Brownian dynamics or atomistic molecular dynamic simulations, since it is capable of computing processes regarding the breaks and formation of bonds.[9] The model has successfully been used to investigate the effects of carcinogens on genes, histone deacetylation processes as well as assisted in the design of chemotherapy drugs.[9,19–21] Despite the successes of this quantum modelling technique, it is yet to gain a strong foothold in many research applications due to its current challenges.[9] According to Friedman et al.[9] the mathematical modelling of an entire protein using this approach can be very challenging due to the complexity of functions and interactions, and hence most quantum chemistry applications have focused on only certain key portions of enzymes such as the catalytic sites, rather than focusing on the entire or whole protein. Quantum chemistry modelling programs are also expensive and difficult to be understood by non-experts. Therefore, more investigations are required to develop models capable of calculating larger and more complex proteins. It has been reported[9,22,23] that this method could have more impact in the future, as more comprehensive models of more complex proteins are developed.

The advent of quantum computers might transform the field of quantum chemistry modelling as they can potentially reduce the complexity of quantum chemistry simulations. Quantum computing and quantum information processing is one of the most innovative research fields not only in computer and information sciences but also in chemistry, and the quantum simulation of electronic structure problems of atoms and molecules is one of the most intensively studied areas.[80] Considering that the practical applications of quantum computing to quantum chemistry is of significant importance, the implementation of quantum algorithms to empower quantum chemistry is the focus of quantum computing and quantum information processing.[80] Studies on quantum simulations of quantum chemical objects started when quantum computers were first proposed in the early 1980s, and it was suggested that a computer built with quantum mechanical elements, obeying quantum mechanical laws, will have the ability to efficiently simulate other quantum systems.[80] Computational time of a full-configuration interaction calculations on classical computers scales exponentially against the system size, and it might be an intractable problem to deal with for small molecules; however, time scaling becomes polynomial on quantum computers.[80]

Quantum biochemistry modelling

Quantum biochemistry modelling is another emerging field of quantum physics and oncology and which has achieved important advancements in the field of breast cancer treatment.[10] Mota et al.[10] utilised this method to study the oestrogen receptor and the binding mechanisms of tissue-selective synthetic agents (or selective oestrogen receptor modulators)—drugs commonly used to minimise the effects of oestrogen growth promotion on breast cancers. The new binding strength information achieved through quantum modelling of these anti-oestrogen treatment allows for a greater understanding of their receptor-based binding mechanisms, providing new insights into the current and future breast cancer treatment drugs.[10] The quantum biochemistry modelling technique has been combined with the conductor-like polarisable continuum model to determine the structure of the anticancer drug, pembrolizumab Fab conjugated to the PD-L1 receptor, blocking the PD-1 pathway.[11] The knowledge of these structures and interactions between chemotherapy drugs and their targets in determining their effectiveness and potential toxicity is extremely important.[11]

Quantum biology modelling

Quantum physics principles have attracted much attention for its potential to bring new perspectives to biological phenomena.[7] DNA strand breaks cleaved by endonucleases have been investigated using quantum biological modelling techniques, with superior performance over classical modelling techniques.[24] Quantum biology has been used to describe photosynthesis, olfactory and optical senses, magnetoreception and, more recently, provided insight into cancer biology.[7] It uses the principles of quantum mechanics such as superposition, quantum formalism, quantum coherence and quantum entanglement to explain biological events on macromolecular and cellular levels.[8] Quantum formalism defines a universal set of rules to define probabilities within a certain experimental setup or sample space, and covers cases when different experimental conditions are incompatible with one another.[8] This formalism principle has the potential to be extended to living systems since their complex dynamic nature introduces many possibilities for interactions of incompatible measurement conditions through an approach called quantum biology at a cellular level (QBCL). The QBCL approach suggests that the principles of formalism can be applied to the properties of biological systems with appropriate approximations to simplify and compensate for the inability to separate systems from environmental influence through the representation of linear operators, which do not necessarily commute, corresponding to different measurement scenarios.[8] According to Bordonaro and Ogryzko,[8] quantum biology approach at the cellular level can be used to effectively describe biological systems, with regard to the variability and selection conditions of cancer cells as opposed to using classical physics to describe these biological systems.

According to Plankar et al.,[25] quantum biological models must overcome the complication of isolating intracellular environments, thus making quantum phenomena within cells very challenging to calculate. However, quantum coherence that encompasses the vastness of this environment can be used to account for small molecules and the synchronisation of biological systems.[25] They suggested that quantum coherence can provide a simpler and more general approach to the complex modelling of biological

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phenomena and that biological coherence plays a major role in molecule and DNA regulation, and disruption to this coherence could be the cause of cancer.[25] They indicated that quantum coherence potentially impacts the development of cancer, by disrupting molecular and genetic regulation within the cell due to the destabilisation of energy flow and information processing within the cells.[25]

Quantum biology modelling and DNA repair

Cells in the body can normally repair and correct any damage that occurs in the DNA, often with the assistance of enzymes called endonucleases.[24] Type II restriction endonucleases are enzymes that recognise damaged sequences and create double-strand breaks in the phosphodiester bonds of DNA to splice out damaged sections, thereby preserving palindromic symmetry.[24] However, the mechanism by which the catalytic sites on the enzyme coordinate the cleavage of the DNA backbone has been unclear until recently.[24] The synchronisation of catalytic sites was recently studied using quantum biological modelling, and it has been proposed by Kurian et al.[24] that these enzymes demonstrate quantum entanglement (described as correlations that are stronger than can be observed in classical systems and can be independent of distance) and quantum coherence. They demonstrated that the substrate-assisted catalytic synchronisation process involves the quantum entanglement of electrons by orthodox type II restriction endonucleases to coordinate their catalytic centres in DNA phosphodiester bonds. They have been able to implement quantum entanglement in their model for the biological process of enzymatic cleavage, similar to other studies.[26,27]

Quantum mechanics modelling

The use of quantum mechanics and molecular modelling has gained interest with biologists, as it has helped improve the understanding of the mechanisms involved with covalent binding between chemotherapy drugs and DNA.[9] Quantum mechanical modelling has been employed to determine the binding processes of various minor groove binding anticancer drugs, such as those made of Ruthenium, which is a new-generation transition metal drug and a potential Cisplatin replacement.[28] Although classical molecular dynamics models may not accurately account for the electronic structure and energetics of transition metals due to predisposed force fields, quantum mechanics models are able to take these properties into consideration.[28] Spiegel and Magistrato[28] indicated that, although there are advantages in quantum mechanics modelling methods, such as accuracy and specificity, they are still often used in combination with other molecular modelling techniques to gain a more general perspective. The biochemical reactions studied often do not occur in an isolated environment, rather in a dense environment filled with a variety and abundance of atoms, making the combination of quantum mechanics and molecular modelling necessary for studying specific reactions in the diverse biological systems.[28] Despite the drawbacks in their lack of generality, quantum mechanics modelling methods are still extremely useful in such combination approaches. Indeed, quantum mechanical modelling should be the best we can have but might be too complex, and thus we might have to rely on simpler models that could have sufficient accuracy to be useful. However, as quantum mechanics modelling methods become more advanced and easier to use and understand, they may grow in popularity and in advance research that utilises computer-driven methods.[79]

Quantum Cascade Lasers

Infrared microscopy has been a key technique used for investigating the properties of tissues and has the ability to identify pre-diseased tissue forms with applications in the diagnosis of cancer.[71] Biopsy analysis methods that rely on staining procedures are very subjective, and molecular labelling can interfere with the structure or target molecule affinity in cell studies.[72] Fourier-transform infrared (FT-IR) microscopy is a labelling-free approach that uses vibrational spectroscopy to obtain a more accurate and in-depth analysis of diseased tissue without chemical labelling interference.[72] Although this approach is very effective for acquiring detailed chemical images of diseased and non-diseased tissues, it takes several hours to complete since it requires several million spectra.[15] Quantum cascade laser (QCL)-based infrared spectroscopy uses discrete frequency tunable lasers to produce bright mid-infrared light with high spectral power density.[72] The development of wide-field QCL infrared imaging systems offers an alternative method that is capable of fast microarray acquisition of large tissues.[73] The shorter measurement times of QCL as compared with FT-IR methods are associated with the high spectral brightness of quantum cascade lasers.[74]

Advances in this field of technology have allowed for more accurate identification and grading of cancerous tissue, as well as the determination of disease stage.[73–75] Pilling et al.[75] used quantum cascade lasers to accurately differentiate between malignant and non-malignant stroma in breast cancer patients. They imaged 207 breast tissue biopsies with high sensitivity and specificity within 13·6 hours. The malignant core samples were identified with 100% accuracy, while the non-malignant cores were classified with 86·7% accuracy (the reduced accuracy was caused by false-positives, where non-malignant stromas were classified as malignant). In the classification of all cores studied, no malignant cores were diagnosed as non-malignant, proving that QCL imaging provides a high level of accuracy in differentiating between malignant and non-malignant stroma. Similarly, Pilling et al.[73] demonstrated the potential of QCL imaging in detecting malignant prostate tumour tissue and found this method to be effective without significant compromise of accuracy. Kuepper et al.[74] investigated the feasibility of utilising quantum cascade laser-based infrared microscopy for quick, label-free, automated classification of colorectal cancer tissues, achieving precise results within minutes. They observed that the QCL method was 160 times faster than FT-IR methods. The faster image acquisition and measurement time make the quantum cascade laser a great candidate for tissue classification in oncology.[74]

The concern with the quantum cascade laser method of imaging is that it has been observed to have a higher signal-to-noise ratio compared with FT-IR spectroscopy.[71] Kuepper et al.[74] used a quantum cascade infrared microscope for a colorectal cancer histology classification method as a replacement of light source method for FT-IR-based microscopes. They observed that, when quantum cascade lasers were incorporated into the microscopes, these suffered from coherence effects, low laser stability and offset edges related to the fine movement accuracy of the microscope stage.[74] However, the level of accuracy and significant decrease in data collection time, compared to FT-IR methods, still make it a promising tool for application in clinical oncology.[73] As this technology gains popularity among researchers, quantum cascade lasers are becoming less expensive and more readily available, providing an alternative microscopy method for histopathology and vibrational microspectroscopy.[74] If improved processing algorithms are developed to

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overcome the current challenges of QCL, classification and differentiation of cancerous and healthy tissues using QCL histology methods could be performed with ease and would soon become a common tool in clinical applications.[74]

Quantum Dots Technology in Medicine

Quantum dots are nanocrystals made of semiconductor materials, such as silicon, that behave like individual atoms and contain quantised energy levels that can release different colours of light, which is dependent on the size of the nanocrystal. They are a novel form of nanotechnology that combines physics, chemistry, material science and biology and has potential prospects in bioimaging, drug delivery and disease diagnosis, such as sentinel lymph node mapping or tumour imaging.[29,30] They exhibit quantum properties such as quantum confinement, which represents changes in the electronic and optical properties of a particle once it reaches a very small size, such that its electrons are excited to a higher energy level and only a few transitions are present regarding oscillator strength and macroscopic quantum tunnelling effect.[16,31], There are promising clinical applications of quantum dots in cancer imaging and treatment with minimal side effects, compared with some common current cancer treatments such as chemotherapy or radiotherapy, thus giving quantum dots applications a potential advantage due to these benefits.[30] Several studies[3,33–35] have investigated its applications in gene therapy, photodynamic therapy, photothermal therapy, surgical oncology, as drug delivery vessels, for imaging and identifying tumours and metastases and in cancer treatment by slowing down cell growth or proliferation and inducing cell apoptosis.

The current lack of reliable and sensitive tumour diagnosis methods has placed quantum dots under the spotlight, as they have potential advantages over currently used fluorescent dyes.[16] The main advantages of quantum dots over traditional fluorescent dyes include their broad luminescence excitation spectra,[16] improved sensitivity, non-invasiveness, inexpensive and superior imaging and diagnosis abilities,[36] being highly luminescent and fluorescent,[37] and exhibiting optimal fluorescence for deep tissue imaging. These properties make these nanomaterials ideal for acquiring accurate images of deep-seated tumours.[34] Cho et al.[34] reported strong fluorescence both in vivo and ex vivo by quantum dots, allowing for optimal bioimaging in mice. They also reported that quantum dots can be used for multiple purposes at the same time —bioimaging for cancer diagnosis and as drug delivery vessels for chemotherapeutic treatment of cancer cells.[34]

Graphene quantum dots-based nanomaterials have gained great attention in multiple research applications, particularly in biomedical fields due to their unique physicochemical properties and outstanding biocompatibility compared with other nanomaterials. Thakur et al.[17] have found that graphene quantum dots are non-toxic compared with heavy metal semiconductor quantum dots and are able of producing an anticancer photothermal and photodynamic effect. Graphene quantum dots can be 'green-synthesised' from biological materials such as milk, rice-husk, fruits, and Indian fig leaves, which potentially reduces the toxicity seen in some types of quantum dots.[17] Thakur et al.[17] used these naturally sourced carbon precursors—Indian fig leaves—to produce graphene quantum dots and proposed the recycling of waste products to develop these nanomaterials in an economical and environmentally conscious way.[16,17] They proved that as the demand for quantum dots rises, their mass production from natural sources makes these nanomaterials environmentally friendly.[17]

Applications of Quantum Dots Technology in Medicine

Tissue imaging and labelling

Fluorescent dyes used for tumour imaging, which have been approved by the FDA, include 5-aminolevulinic acid, methylene blue and indocyanine green.[30] However, these traditional fluorescent dyes face challenges due to toxicity, tissue specificity, thermal and photostability under physiological conditions, poor imaging and rapid clearance from the body. They also exhibit poor wavelengths (such as 405/645 nm for 5-aminolevulinic acid, which can be easily absorbed by the tissue) and emission spectra that present limitations for deep tissue penetration.[30] Conversely, quantum dots exhibit unique optical and fluorescent properties that make them ideal for a variety of imaging applications and offer a number of advantages over these traditional fluorescent dyes, including symmetrical narrow emission spectra, near-infrared emission spectra, broad UV excitation, bright fluorescence, long fluorescence lifetime, longer retention (which allows for deep tissue imaging and tumour targeting), high photostability and a large Stokes shift.[16,30] The near-infrared spectrum from quantum dots allows for more accurate and deep tissue penetration for imaging, because near-infrared light shows lower absorption and scattering than the wavelengths used by the traditional fluorophore indocyanine green, which cannot penetrate deeper than 1 cm in tissue.[30] Quantum dots can be used for imaging in a variety of colours and achieve excitation from a single, relatively weak photon source, avoiding potential damage to the tissues or other biological materials.[38]

Quantum dots can be used for cell labelling by conjugating them to a specific antibody that binds with a cell surface target antigen, providing more precise imaging.[38] According to Bilan et al.,[38] quantum dots technology has a great potential for simultaneous labelling of multiple cells and tissue types and for both receptor-based extracellular tagging and intracellular deliveries via endocytosis. Some studies[38–40] have been able to achieve an intracellular delivery of quantum dots, and this is not an easy accomplishment as they must endure various stages of endocytosis, cytoplasmic transport and/or penetration of the nucleus, which is extremely dependant on the size and charge of quantum dots.[38] Delehanty et al.,[39] successfully labelled and imaged living cancer cells by both intracellular and extracellular deliveries with semiconductor fluorescent quantum dots, which allowed for complex cellular processes to be observed. Alibolandi et al.[41] also utilised the fluorescent capabilities of quantum dots to effectively perform in vivo imaging diagnostics on mouse models.

Gene targeting and therapy

Quantum dots can be conjugated with chemotherapy drugs and biological materials, such as ligands, which allows for effective targeting and treatment of cancerous cells.[42] These can be used to specifically target certain tissues, cells, organelles and other organic substances, often via conjugation with antibodies.[36] Gene therapy has been studied extensively as a potential treatment for cancers, as cancer genes can be specifically targeted and silenced by inserting new genes or RNA to either stop or reverse tumour growth.[43] Tan et al.[44] investigated the feasibility of using fluorescent quantum dots for gene silencing. They utilised chitosan-encapsulated quantum dots to successfully deliver and track HER2/neu siRNA to silence the targeted HER2 gene in the SKBR3 breast cancer cell line. They reported that RNA interference can be used as a gene silencing method via the insertion of double-stranded RNA that is partly complementary to the targeted gene and stopping its protein

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production by degrading its particular mRNA. Fluorescent quantum dots are being used as delivery agents of the interfering RNA to the interior of cells, as well as for delivery tracking of the siRNA.[44] Dong et al.[43] indicated that other tumour suppressor genes can be inserted into a targeted gene in cancer cells for growth inhibition. For example, microRNAs (miRNAs) are often found to be improperly regulated in cancerous tissue and can be targeted and silenced with gene therapy.[43] Dong et al.[43] investigated the use of graphene quantum dots for gene therapy, which are environmentally friendly and considered to have low toxic effects. They utilised photoluminescent graphene quantum dots to deliver miRNA probes in HeLa cancer cells, which inhibited their growth and induced apoptosis. One of the major challenges with the current gene delivery vehicles is the risk of toxicity of the delivery method (particularly viral methods, liposomes, polymeric particles and nanoparticles) on the targeted genes.[43] However, as studies[32–34,67–70] have shown, the quantum dots technology seemed to exhibit minimal toxicity. Quantum dots have the potential to provide an accurate delivery of interfering genes, tumour suppressor genes and fluorescent imaging methods to track the effectiveness of gene therapy, and all evidence points towards quantum dots as a useful, efficient gene delivery and imaging device for targeted gene therapy in cancer cells.[43]

Tumour imaging, diagnosis and treatment

The lack of effective methods for tracking tumours is currently a considerable challenge in the development of effective therapies for cancers.[58] Organic fluorophores are typically used for in vivo microscopy, but they have many limitations, including overlap of emission spectra and a need for multiple excitation lines for imaging multiple fluorophores. However, quantum dots have desirable properties such as narrow absorption spectra with multiphoton absorption between 700 and 1,000 nm and photobleaching resistance, which have the potential to overcome the above limitations.[58] Traditional fluorescent dyes such as fluorescein, tetramethyl rhodamine isothiocyanate and other near-infrared fluorophores have challenges with imaging in tissue deeper than 1 cm, whereas quantum dots have the ability to penetrate much thicker tissues.[30,59] Quantum dots containing crystalline cadmium and selenium cores have been found to be useful in creating inert tags that can track and image tumour progression without adverse effects on host's cell viability or disruption of tumour cells.[58]

Prostate cancer

Gao et al.[45] demonstrated the application of semiconductor quantum dots in cancer imaging and targeting using antibody-conjugated quantum dots to image and identify prostate tumours through the prostate-specific membrane antigen (PSMA). They showed that quantum dot probes could accumulate at tumour sites via enhanced permeability and retention in addition to antigen binding by cancer cell surface biomarkers.[45] Kerman et al.[46] used fluorescent imaging to illuminate quantum dot detection of the total prostate specific antigen (TPSA) on a synthetic carbon substrate and demonstrated that quantum dots in immunoassays offer the potential for a sensitive detection of TPSA cancer markers in undiluted serum samples. Lin et al.[47] used near-infrared CuInS2 quantum dots conjugated with the chemotherapy drug Daunorubicin (DNR) and MUC1 aptamer to simultaneously target, treat and image prostate cancer cells in vitro. They further reported that the conjugation of tumour-fighting drugs with near-infrared quantum dots could offer a higher drug payload, improved targeting, increased drug solubility and longer retention time.[47] The DNR-MUC1-conjugated quantum dots offer the potential for improved efficiency of chemotherapy by ensuring that the drugs are delivered to tumour cells that contain an overexpression of MUC1 proteins. This approach would minimise toxicity to normal cells, since the quantum dots would not target cells that do not excessively express this protein, thereby improving the effectiveness of each chemotherapy dose while reducing the negative side effects associated with the destruction of healthy cells.[47] Singh et al.[48] have indicated that the cell death mechanism of biosurfactant-stabilised CdS quantum dots could be useful in mediating apoptosis of prostate cancer LNCap cells by generating reactive oxygen species on the surface.

Breast cancer

Wu et al.[49] used immunofluorescent probes that were produced by conjugating quantum dots with streptavidin (a biotin-binding protein synthesised from *Streptomyces avidinii* and IgGs) to target human epidermal growth factor 2 (HER2) breast cancer cells. They found these quantum dot immunofluorescent probes to be more efficient at cell labelling compared with traditional fluorescent dyes.[49] Chen et al.[50] studied HER2 and hormone receptors, such as the oestrogen receptor and the progesterone receptor, in the nuclear receptor superfamily associated with breast cancer growth and proliferation. They used quantum dots-based spectral analysis to develop five molecular classifications of breast cancer. This new classification system has the potential to provide clinicians with a more comprehensive understanding of a patient's cancer, thereby assisting with patient-specific and personalised breast cancer identification and prognosis.[50] The identification of various hormone receptors as well as HER2 will allow for a unique personalised treatment with higher survival rates and quality of life.[50] Rizvi et al.[51] used near-infrared emitting quantum dots conjugated with anti-HER2 antibodies to provide HER2 localisation of cancer cells in vitro and chemically fixed the cells, supporting these findings. Alibolandi et al.[41] used quantum dots coated with polyethylene glycol (PEG) for targeted chemotherapy drug delivery to breast cancer cells. They reported that PEG coating is ideal for drug delivery since it demonstrates attractivity, colloidal stability and negates opsonisation on the quantum dot surface, which discourages bodily elimination by macrophages. Also PEG encapsulation of quantum dots allows for bioaccumulation at tumour sites due to the enhanced permeability and retention effect of cancer cells.[41] Ligands such as folate are being conjugated on quantum dots-based drug delivery systems to target the overexpressed folate receptors on breast and ovarian cancer cells for a more targeted chemotherapy vessel.[41]

Lung cancer

Lung cancer is particularly difficult to detect in its early stages with the traditional methods of chest X-rays, CT scans, bronchoscopy and sputum cytology, which lack sensitivity.[52] Quantum dot-labelled micro-well chip assays have been developed to detect lung cancer serum biomarkers (carcinoembryonic antigen, fragments of cytokeratin 19 and neuron-specific enolase) via a combination of suspension and planar microarrays.[52] This chip analysis method is high-throughput and beneficial as it utilizes inexpensive quantum dots as a cost-effective diagnosis method for lung cancer and is an alternate to traditional screening methods.[52] Quantum dots are useful for miRNA biomarker detection and is noninvasive, allows sensitive fluorescent imaging and has high specificity.[37] Chen et al.[53] and Fan et al.[37] used various miRNAs known to have

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altered expression in lung cancer cells as biomarkers to detect early-stage non–small cell lung cancer, utilising quantum dots in fluorescence microsphere suspension arrays. In these studies, the miRNAs used by Chen et al.[53] were miR-221, miR-222, miR-223 and miR-320, whereas Fan et al.[37] used miR-15b-5p/miR-20a-5p, miR-15b-5p/miR-16-5p. The method is non-invasive and can aid in detecting nodules <1 cm in diameter, which may be difficult to be detected via other methods.[37] Roshini et al.[29] used zinc oxide quantum dots (QDs) conjugated with Tangeritin (an organic polymethyoxyflavonoid known to have anticancer properties) on lung, breast, colon and leukemic cancer cells. They demonstrated that ZnO-Tan-QDs have cytotoxic effects when directly targeted at tumour cells in the lung, resulting in cell cycle arrest and preventing cell division and growth.[29]

Brain cancer

A significant challenge currently experienced in the treatment of brain cancer is the inability of imaging agents to penetrate through the blood–brain barrier. However, the microscopic size (usually <10 nm) of quantum dots can overcome this challenge, making it an ideal agent for imaging of brain tumours.[54–57] Bai et al.[55] demonstrated that quantum dots have promising potential for in vivo brain imaging due to the small size and narrow emission spectra. Quantum dots have also been combined with nanoparticles to enhance image-guided brain tumour excision procedures. A study by Sheng et al.[56] used superparamagnetic iron oxide nanoparticles, quantum dots and cilengitide (a peptide that targets glioma cells and eliminates signal transmission to prevent survival and proliferation) encapsulated within a theranostic liposome to target glial cells.[56] The fluorescent emissions of quantum dots were critical in improving visualisation and localisation of glioma cells in affected mice, which aided a complete surgical resection of the tumour.[56] A study by Fatehi et al.[57] used near-infrared quantum dots for in vivo targeting of the epidermal growth factor receptor variant III (EGFRvIII), which is a mutant version of the epidermal growth factor receptor and has been found to be expressed in a constitutively active state in a high proportion of brain cancer patients. The conjugation of near-infrared quantum dots with anti-EGFRvIII antibodies that are able to recognise EGFRvIII receptors provided increased accumulation at tumour sites, which could be confirmed with fluorescence microscopy of the brain. This method has the potential to provide an accurate and less invasive diagnosis of tumour location and aggressiveness in the brain.[57]

Photodynamic therapy

Photodynamic therapy has been in practice since the early 1900s. The technique uses a photosensitising agent delivered to diseased tissues, which is subsequently exposed to light in order to create reactive singlet oxygen species in the diseased tissue.[35] These singlet oxygen species cause cell damage and cytotoxic effects, inducing cell death in the affected tissue.[35] Photosensitisers such as phythalocynines do not perform optimally in deep tissue environment, can be phototoxic when the skin is exposed to sunlight and have limited specificity and tend to spread to other tissues, making these even more hazardous.[33] Current photosensitising agents that tend to become concentrated in aqueous solutions also present challenges, diminishing the amount of singlet oxygen and light exposure and thus reducing the effectiveness of tumour treatment.[60,61] Photodynamic therapy is highly selective to diseased tissues yet minimally invasive to healthy tissues, although it could cause greater light sensitivity and phototoxicity on spreading to surrounding healthy tissues.[33] Semiconductor quantum dots are being tested in place of traditional photosensitisers since they have the advantage of being activated with low-intensity near-infrared light and hence able to penetrate deeper tissues and thus ideal for deep seated tumours.[35] With their ability to minimise photosensitivity side effects and prevent aggregation in aqueous solutions, quantum dots provide a hydrophobic environment for the photosensitiser. Quantum dots have the ability to provide ideal dispersion of encapsulated photosensitisers and so could serve as fluorescent sensors for imaging and tracking purposes.[60] Thus, Zhang et al.[33] concluded that quantum dots are effective photosensitiser delivery agents for treating cancerous tumours with photodynamic therapy and that the technology could have dual effects on cancer cells—the production of the reactive oxygen species by quantum dots when exposed to near-infrared light and the release of heat from the light for photothermal therapy.[33] Photodynamic therapy and photothermal therapy (i.e., the use of heat to damage diseased tissue) can be used in combination for cancer therapy.[33] Although there are some concerns about the use of quantum dot-based photodynamic therapy because they may be poorly biocompatible,[33] the technology may become common place for cancer treatment, as toxicity and biocompatibility improves with more research.[60]

Surgical oncology

Despite recent advancements in non-surgical therapies, surgical resection of tumours remains the most frequently used method. High levels of local recurrence following a surgical resection has been attributed to the existence of microscopic sections of residual malignant tumour tissue that could not be identified with the current intraoperative imaging techniques.[7] The ability to clearly differentiate between cancerous and surrounding healthy tissues during surgery has a great clinical impact, since the removal of excessive healthy tissues could lead to a loss of organ function, and any cancer cells left behind during surgery could lead to recurrence.[62] However, recent advances in quantum dot technology indicate the potential to improve the success rates of complete removal of cancer cells during surgical treatments by enabling surgeons to better differentiate between malignant and healthy tissues and identify the regions of residual tumour cells.[7] These nanoparticles can be customised to target malignant tumour cells and microenvironments with high specificity and affinity through conjugation with targeted ligands such as monoclonal antibodies, peptides or small molecules.[45,63] Arndt et al.[7] used quantum dots coupled with epidermal growth factor receptor (EGFR, Her1) and fluorescence microscopy to differentiate between normal brain and tumour tissues in cell cultures, human biopsy samples, and mouse glioma models. Fluorescence emission from the quantum dots provided a clear distinction between glioblastoma cells and normal brain tissues on cellular and macroscopic levels. A study by Rizvi et al.[51] has demonstrated that near-infrared emitting quantum dots has potential applications in image-guided surgery.

Drug delivery

Quantum dots can be conjugated with biological materials, such as ligands and antibodies, to allow them to target certain areas in the body.[16] This bioconjugation trait can provide targeted drug delivery to tumours, assisting with drug uptake into cancer cells.[16] Cai et al.[42] loaded ZnO quantum dots with antitumor drug Doxorubicin and tethered to the targeting ligand hyaluronic acid with PEG for stabilisation in physiological conditions, which was

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taken up by A549 cancer cells for a targeted drug delivery therapy. ZnO quantum dots, which are biodegradable in the tumour microenvironment, allowed the release of Doxorubicin that targeted the cancer cells.[42] Quantum dots are excellent vessels for cell targeting and drug delivery because their spherical shape is ideal for conjugation and uniform adhesion with biomaterials such as ligands.[34] Cho et al.[34] developed a nanocarrier system by loading paclitaxel (a chemotherapeutic agent) onto the surfaces of composite multifunctional nanocarriers using a layer of biodegradable polylactic-co-glycolic acid (PLGA) for purposes of drug delivery. Conjugated quantum dots were used to investigate cell viability and targeting in an in vitro study using LNCaP and PC3mm2 prostate cancer cell lines. They further used an in vivo study on tumour-bearing mice model to confirm the targeting potential.[34] Cellular targeting of quantum dots was achieved via conjugation with an anti-prostate-specific membrane antigen (anti-PSMA) on their coating and receptors on the cell surface. Once targeted, fluorescent imaging capabilities were used to confirm drug delivery to the two cancer cell lines. They demonstrated the use of quantum dots as effective chemotherapeutic vessels while providing imaging capabilities via their fluorescent properties.[34]

Photothermal therapy

Photothermal therapy is the use of heat generated by near-infrared irradiation to kill cancer cells. Quantum dots can be used for this non-invasive and tumour-specific therapeutic option. Several studies[17,32,64] have demonstrated the potential of this technique in the treatment of cancer. In order for photothermal therapy to be effective, quantum dots must first enter the cancerous cell, possibly via conjugation with folate and its receptor.[64] Hu et al.[64] have observed that when irradiated with near-infrared light, quantum dots endocytosed within cancer cells, in that they were able to absorb light and produce heat, efficiently killing the cells they were applied to. Yao et al.[32] reported a synergistic use of quantum dots for simultaneous photothermal therapy and chemotherapy in vitro on 4T1 breast cancer cells. They loaded mesoporous silica nanoparticles with graphene quantum dots and doxorubicin hydrochloride (a chemotherapy drug) and delivered it to the cancer cells.[32] After being taken up by the cancer cells, the quantum dots were then irradiated with near-infrared light, which resulted in a photothermal effect in addition to the chemotherapy drug being released. Controlled drug release was caused by the pH sensitivity of graphene quantum dots, and an increase in temperature due to the carboxyl and hydroxyl surface groups effectively demonstrated cell death.[32] This combination of photothermal therapy and chemotherapy proved to be more cytotoxic to cancer cells than either treatment alone.[32] Thakur et al.[17] also reported a combination of photothermal and photodynamic effects by releasing singlet oxygen species via oxygen-rich functional groups on naturally doped graphene quantum dots. They used graphene quantum dots in an in vitro study on breast cancer cells and observed temperatures up to 49°C inducing apoptosis.[17] Zhang et al.[33] also investigated the combination of photothermal and photodynamic therapies in magnetoflourescent carbon quantum dots. They conjugated quantum dots with folic acid for targeting, and used riboflavin as a photosensitiser. Doxorubicin was also loaded as a chemotherapeutic drug, to be released upon exposure to near-infrared light. Once they targeted in vitro or in vivo cancer cells in mouse models, quantum dots were irradiated with near-infrared light, inducing apoptosis caused by the combination therapy.

Current Concerns with Quantum Dots Technology in Medicine

A major concern with the use of quantum dots in medicine is the potential cytotoxicity of some of the materials such as cadmium and zinc, which are commonly used as a base for the nanoparticles.[65] While there has been no evidence of short-term adverse effects from in vivo studies, their effects on metabolism and long-term biological implications require further investigation.[66] Mansur et al.[67] investigated the effects of cadmium- and zinc-based quantum dots using albino laboratory mice and observed no adverse effects. CdS and ZnS quantum dots at two different concentrations were intravenously delivered to the mice. Body weight, eating and drinking habits and energy levels of the mice were monitored over a period of 30 days, and the mice were euthanised to obtain the liver, spleen and kidney samples for fluorescent imaging and histology studies. Fluorescent imaging revealed that the majority of quantum dots were taken up by the liver but remained intact, and histological assessment revealed no significant tissue damage to the liver, spleen or kidney.[67] Hauck et al.[68] also used rats as a biological model to investigate the toxicity of quantum dots. They injected CdSe-ZnS core-shell quantum dots at various concentrations into the rats and measured the potential toxic effects over time as the particles were retained in the body. Although they did not observe any toxic effects, it was noted that toxicity effects could be specific to the shape, size and makeup of the quantum dots.[68]

Tang et al.[69] reported a systematic animal toxicity study of CdSe-ZnS core-shell quantum dots in healthy Sprague-Dawley rats. They characterised the biodistribution, animal survival, animal mass, haematology, clinical biochemistry and organ histology at different concentrations (2·5–15·0 nmol) over short-term (<7 days) and long-term (>80 days) periods. The results showed that the quantum dot formulations did not cause appreciable toxicity even after their breakdown in vivo over time. However, in order to generalise the toxicity of quantum dots in vivo, further investigations are still required, including the evaluation of quantum dot composition (e.g., PbS versus CdS), surface chemistry (e.g., functionalisation with amines versus carboxylic acids), size (e.g., 2 versus 6 nm), and shape (e.g., spheres versus rods).[69] Soo Choi et al.[70] reported that, on average, mammals have vascular pores that are ~5 nm, and any particle above this size will be transported relatively slowly through the bloodstream, and quantum dots above this size may not be excreted readily and can be retained in organs such as the liver, spleen and kidneys. Therefore, for a quantum dot to be approved for clinical use, it must be ≤5·5 nm.[34,70] Cho et al.[34] reported that the quantum dots used in their drug delivery study did not inhibit the mitochondrial dehydrogenase activity in human cells, and these nanocarriers, when not conjugated with the paxlitaxel chemotherapy load, were proven to be safe with no reduction in cell viability in concentrations up to 25 μg/mL. Zhang et al.[33] investigated the toxicity of quantum dots on tumour-bearing mouse models and found that the healthy liver, spleen, kidney, lung and heart of the mice were undamaged. Yao et al.[32] also confirmed the safety of quantum dots in physiological conditions, when 4T1 cancer cell viabilities indicated minimal changes across different concentrations of the nanocarriers alone.

Quantum Computing

Quantum computers are devices that harness and exploit the laws of quantum mechanics and used to solve problems in physics,

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chemistry, mathematics, cryptography, etc., that were once thought intractable, revolutionising the information technology and illuminating the foundations of physics. They will also have implications on our daily lives.[80–82] While traditional or classical computers represent information using strings of bits that encode information in strings of either a '0' or '1', quantum computers use quantum bits, or qubits, that can encode information in superposition states and thus can be in '0' AND '1' at the same time. The ability to make states with a large number of superpositions is that which gives quantum computers their main advantages.[82,83] For some problems, quantum computers would give an exponential gain compared with today's computers.[83]

Quantum chemistry is a field that will be much impacted by quantum computers.[80,84,85] We could imagine solving the dynamics of DNA mutations at atomic levels, thus understanding their behaviours and finding ways to stop the mutations. Simulations in quantum chemistry could also be useful for drug design and in the search for new chemical compounds.[82] Quantum computing and quantum information processing is one of the most innovative research fields not only in information sciences but also in interdisciplinary areas among physics, mathematics, chemistry, materials science, etc.[80] However, among the diverse subjects in quantum computing and quantum information processing, quantum simulation of the electronic structure of atoms and molecules is one of the most intensively studied areas. From the viewpoint of practical applications of quantum computing, quantum chemistry is of significant importance, and the implementation of quantum algorithms to empower quantum chemistry has been the focus of quantum computing and quantum information processing.[80] Studies on quantum simulations of chemical objects started when quantum computers were first proposed in the early 1980s. It was suggested that the computers built with quantum mechanical elements and obeying quantum mechanical laws have the ability to simulate other quantum systems efficiently.[80] Computational times of full-configuration interaction calculations scales exponentially against the system size in classical computers, and it might be an intractable problem to deal with for small molecules; however, time scaling becomes polynomial on quantum computers.[80]

Another area where quantum computers might be advantageous is in the quantum version of machine learning. With the ability to manipulate large amount of data more efficiently, machine learning can be significantly improved.[86,87] Machine learning that informs clinical practice in real time depends on growing databases by constantly updating medical records, and to deal with this complex challenge, one must require quantum computing to deliver results in real time. The availability of growing data to inform predictive models and quantum computing will enable clinicians to select personalised therapies for an individual based on running models continuously and predicting a treatment response while accounting for the various patient characteristics (race, age, gender, comorbidities, co-medications, genetic makeup, etc.).,[87,88] In radiotherapy, quantum computing could improve treatment planning and make online adaptive planning seamless. Computers are currently used to plan radiation treatment doses that conform tightly to the treating target without damaging surrounding healthy tissues. Quantum computers could allow faster and more precise treatment planning, including adaptive planning, and comparisons between all possible multi-criteria approaches. The end result would be an ideal radiation dose distribution tightly conforming to the treating target and thus leading to more effective treatment with reduced side effects.[88] Quantum processors would also play a major role in imaging genomics, radiation genomics and radiomics. These research areas have the potential to predict a patient's radiotherapy response and the risk of developing adverse effects based on their imaging characteristics.[89] These fields require the processing of very large imaging and genomics data and are currently hindered by the computational efficiency of present computers; however, quantum computers would revolutionise these fields.

One of the major roadblocks in the creation of a quantum computer is the fragility of quantum information. The interference that comes from the states in multiple superpositions can be easily destroyed in the presence of noise. This challenge for quantum computers can turn into an asset by way of designing states that are extremely sensitive to quantum sensors. Quantum sensors have found applications in geology, archaeology, oil logging, space missions and many other fields.[90] These will have the potential of imaging at the atomic level and make the devise highly sensitive to certain protein or chemicals that can play an important role in medical diagnostics.

Conclusion

Quantum physics principles have opened up new perspectives on cancer studies, are currently being used in several applications in oncology research and have potential future applications in the diagnosis and treatment of cancers. Quantum principles have been used to make advances in modelling in the field of biology, biochemistry and chemistry. Concepts such as quantum entropy and metabolism have been useful in creating models in oncology, to help understand and predict how cancer cells develop and proliferate. Quantum dots technology and quantum cascade laser methods utilise various quantum physics principles for helping with the identification, imaging and treating of cancers. Quantum physics principles will likely find its implementation in cancer diagnosis and treatment as we head towards personalised and potentially definitive treatment of cancers.[30]

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Statement of Search Strategy. The following databases were searched between September and December 2018 for relevant studies published for the period 2003–2018: Gale Cengage Academic OneFile, PubMed, Science Direct, American Chemical Society Journals, MEDLINE, SpringerLink, and Wiley Online Library. The literature search used the following terms: 'quantum applications in oncology', 'quantum cascade lasers', 'quantum biology', 'quantum biochemistry', 'quantum chemistry', 'quantum principles and cancer', 'quantum modelling and cancer', 'quantum dots in oncology', 'quantum dots and cancer', 'quantum dots imaging and tracking', 'toxicity of quantum dots', 'quantum dots for drug delivery', 'photodynamic therapy and quantum dots', 'photothermal therapy and quantum dots', 'quantum dots for gene therapy', 'quantum computers', 'quantum computing'. The searches were not limited by study design or language of publication. The full list of sources and the search strategy are available with the authors.

Conflict of Interest. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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