RESEARCH ARTICLE

Multifunctional nanometer Photonics Technology for Precision Biomedicine

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Abstract: New methods based on nanomaterials, such as biomolecular detection, photothermal therapy, photodynamic therapy and targeted drug delivery, are gradually becoming important diagnostic and therapeutic means in the field of biomedicine. The combination of nanotechnology and photonics can precisely control the interaction between light and substance in nanometer range, thus making the biomedical diagnosis and treatment technology more precise and stable. The development of multi-work energy nano-photonics for precision biomedicine at home and abroad. These four aspects are to improve the stability of nano-biomedicine by relying on optical technology. The precise monitoring of tumor nanotherapeutic process is realized by optical technology, the mechanism of nano-biomedicine is deeply understood by optical technology, and the new means of fine biomedical research on front edge is obtained by new optical technology.

Keywords: Biooptics; functional monitoring and imaging; nanomaterials; optical diagnostic medicine

1. Introduction

Nano-biomedicine is a new field of nano-biotechnology which is produced by the organic combination of biomedical technology and nano-technology. The development of Nano-biomedicine has a great impact on medicine. In the past few decades, many nanomaterials with the function of drug diagnosis and drug delivery have been applied to biomedicine, and some drugs based on nanotechnology have also appeared. The application of nanotechnology theory and methods to modern medicine and biology opens up a world beyond the micron scale, and the physiological and pathological processes at the cellular level occur at the nanometer scale. Therefore, nanotechnology can solve many important scientific and technological problems in medicine and biology.

At present, the main research contents of Nano-biomedicine include nano-biosensor, nano-probe imaging, nano-disease treatment and so on. Nano-biosensor is a kind of technology that uses nano-technology to detect the content of specific biological molecules. It has the characteristics of real-time measurement in cells, no damage or micro-damage to cells. DNA hybridization[3], salt concentration of metal cations and anions, biomolecular recognition of biotin-streptomycin, biomolecular recognition of antibodies and antigens[4,5] can be detected by nano-biosensors. In addition, nano-biosensors can also be used to analyze the toxicity of hazardous substances in the evaluation of physiological reactions induced by dangerous substances such as gene expression, membrane damage, apoptosis and oncosis. Rapid and early diagnosis of diseases can be achieved by utilizing the high sensitivity and specificity of nano-biosensors. Nanoprobe imaging combines optical detection methods with optical nanoprobe molecules to image cells or tissues or even organisms, and then obtains the biological information[7]. At present, nanoprobe imaging includes optical imaging, magnetic resonance imaging, positron emission tomography, single photon diffraction imaging and photoacoustic imaging. Tumor cells were labeled with nanoprobes to monitor the growth, metastasis and drug re-

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sponse of labeled tumor cells in vivo, revealing the cellular and molecular mechanisms of tumor initiation and development. Nanoprobe imaging has the advantages of high signal intensity, good targeting effect and controllable metabolic kinetics[9]. It has been widely used in clinical and basic research, and has introduced a new concept for clinical diagnosis. Nano-disease therapy is a kind of treatment method with nano-drug as carrier. It improves the absorption and stability of drugs, improves the properties and targeting of drugs, prolongs the action time of drugs, and then increases the therapeutic effect, and has less side effects. The commonly used nanotechnology includes three types: nano drug loading, photothermal therapy and photodynamic therapy. Drug-loaded nanoparticles, by modifying the surface of specific nanoparticles, can connect or embed molecular drugs to the outer layer of nanoparticles, which is conducive to drug storage, and can improve the absorption of drugs by organisms and the stability of drugs[10,11]. Nano-drug-loading not only establishes new drug delivery routes, but also enables the development of high-yield, automated, large-scale, low-cost, easy to carry and store, easy to take, low-dose and low side effects. Photothermal therapy (PTT) uses targeted recognition technology to concentrate drugs near tumor tissues, and converts light energy into heat energy under the irradiation of external light source (usually near infrared light), induces protein degeneration and destroys cell membrane, thus killing cancer cells. However, the laser intensity required to destroy cancer cells far exceeds the damage threshold of surrounding tissues, killing cells and causing damage to other tissues, such as skin. The introduction of nanotechnology solves this problem very well. Gold nanorods can accurately control local temperature, and then realize the treatment of metastatic lymph nodes under near infrared laser irradiation[13]. Multispectral photoacoustic tomography/X-ray computed tomography guided photothermal therapy[14] can be achieved by modifying gold nanorods, such as BiS-based gold nanorods. Based on the non-destructive characteristics of nano-materials photothermal therapy, it can also be used in cancer cell imaging[15,16] while treating diseases, thus achieving multi-modality and accurate cancer treatment. Photodynamic therapy (PDT) is a method of treating tumor diseases with photosensitive drugs and laser activation. Photosensitizers absorb the energy of photons and then transfer it to oxygen to produce reactive oxygen species (ROS) molecules, which then attack cell structures by oxidation[17,18]. But the photosensitizers in traditional PDT absorb visible light and penetrate shallowly, so they can only be used in the treatment of superficial diseases such as skin diseases. Using upconversion nanoparticles as carriers, not only therapeutic drugs can be precisely transported to the vicinity of lesions, but also long wavelength excitation can increase the penetration depth of PDT, making it possible for deep tumor therapy[19–22].

2. Nano-Photonics Technology for Precision Biomedicine

The application of nano-science and technology in biomedicine can develop more sensitive and rapid diagnostic techniques and more effective methods of treatment. At the same time, it can understand the process and mechanism of life activities at a more micro level. However, in order to improve the diagnosis and treatment of disease, the surface modification of the imported nanomaterials is usually carried out to improve the drug targeting and drug loading, but this will cause some damage to healthy tissues. Therefore, the precise monitoring of the interaction between nanopharmaceuticals and organisms will improve the stability of nanomedicine and further understand the mechanism of nanomedicine diagnosis and treatment. It is of great significance to reduce the toxic and side effects of nanomaterials.

Combining advanced optical technology with bio-nano-medicine, non-ionizing radiation provides imaging, sensing and photosensitive treatment of non-invasive living cells or tissues, which can provide new and accurate tools for life science and medical fields. Compared with non-optical diagnostic and therapeutic methods, optical technology has high spatial and temporal resolution. By means of non-destructive real-time dynamic monitoring of the activity and response of labeled cells in living small animals, it can be used in tumor detection, gene expression, protein molecular detection, drug screening and evaluation of drug efficacy. It plays a huge role. After more than ten years of development, the concept of nanomedicine has expanded to the fields of clinical diagnosis and medical treatment. Fig. 1 illustrates the multi-modality diagnosis and treatment, including multi-modality imaging, in vivo sensing and targeted therapy, achieved by combining optical technology with nano-biomedicine. Multifunctional nanoparticles (such as quantum dots, metal nanoparticles, embedded dyes, etc.) can be used as imaging probes for in vivo cell imaging or stimulating drug delivery[23,24], which not only binds to targeted agents, small molecule active peptides and biocompatible polymer coat-

ings on nanoparticles, but also can be used as an imaging probe. Several or more therapeutic drugs are added or encapsulated in nanoparticles for experimental control and selective drug delivery, targeting only malignant tumors or selective subcellular localization without damaging normal cells and tissues.

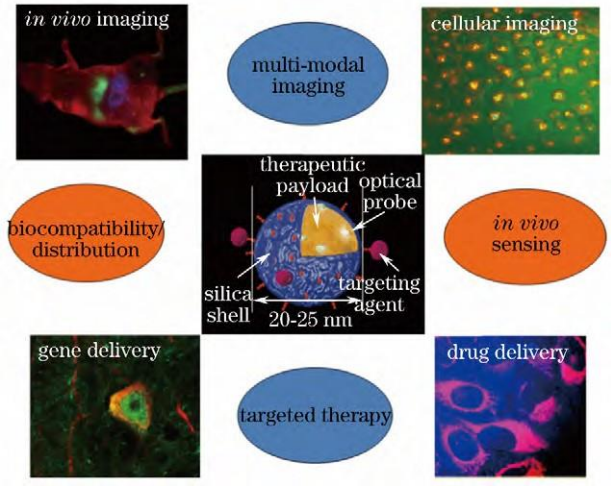

Figure 1; Multifunctional nanoparticles combined with cancer diagnosis and treatment strategy[23].

In recent years, the integration of nanotechnology and photonics has become a frontier interdisciplinary field, bringing new knowledge and technological innovations to biomedicine, making it possible to refine biomedicine. The mechanism of action and new methods of biomedical fine research are reviewed. The applications of precise nano-biomedical based on advanced optical technology are summarized. Their applications in biology are introduced with specific examples.

2.1 Improved stability of nanomedicine by optical technology

Nanomedical research can provide information about intracellular or intercellular structures, regulation, signaling, and movement. Nanotechnology can be used to obtain life information at the nanoscale, to carry out disease prevention, diagnosis and rehabilitation. Although Nanobiomedical research has many advantages, nanoparticles are prone to occur in vivo or in cells. Photonics, as a carrier of information and energy, has good properties. For its spatial compatibility and parallelism, photonics was introduced into traditional nanomaterials, using the optical imaging of biological tissues, fluorescence enhancement and detection, biological spectra and diagnostics, The diagnosis and photodynamic diagnosis in laser medicine can improve the stability of the original technology.

Taking surface enhanced Raman spectroscopy (SERS) as an example, although the intensity of Raman signal is greatly enhanced by local plasma resonance (LPR) of metal nanoparticles, the Brownian motion of metal nanoparticles results in instability of signal at low concentration. Optical tweezers technology can effectively solve this problem, and provide a technical possibility for ultra-fine SERS detection of single molecule concentration. The conventional optical tweezers assisted SERS sensing platform is shown in Fig. 2[25]. In 2010, Rao *et al*.[26] adsorbed silver nanoparticles onto DNA molecules, used optical tweezers Raman microscopy to detect a single DNA molecule, and then used two-optical tweezers and Raman spectroscopy to study the binding of metal nanoparticles to a single DNA molecule. Reaction. In 2016, Fazio *et al*.[27] studied the detection methods of biological molecules (phenylalanine, serum albumin, lysozyme) at the concentration limit by optical tweezers Raman microscopic platform. The lowest concentration reached microgram order. In the same year, Wright *et al*.[28] captured decahedral nanoparticles by optical tweezers and successfully measured a small number of lipid molecules by Raman scattering. Optical tweezers Raman scattering technology combines optical trapping technology with Raman scattering, and can be applied to the study of cells and biological molecules. The technique imprisons cells and nanoparticles with optical tweezers, which improves the signal stability and provides more space and convenience for practical operation.

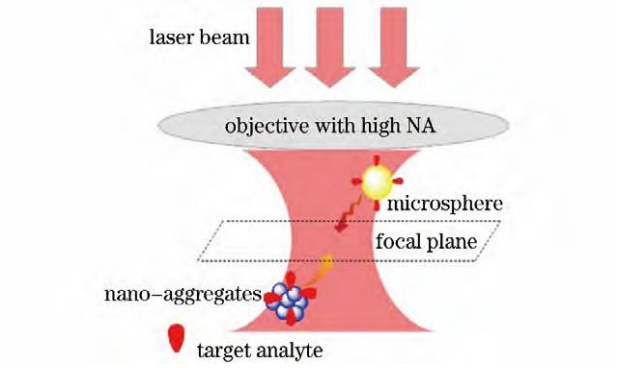

Figure 2; Schematic diagram of conventional optical tweezers assisted SERS sensing platform[25].

PDT is a minimally invasive, highly selective anticancer therapy, but it depends on the accumulation of Guang Min in the tumor. Guang Min, however, is affected by the sound of surrounding environment (such as pH), which may be metabolized during transport in vivo, so that the tumor area cannot absorb sufficient Guang Min agents. Or cause the accumulation of drugs to exist heterogeneity[29]. Thus, the controlled release of drugs can be realized by the introduction of nano-optics technology, and the stability of PDT can be improved by polar earth. Tong *et al*.[30] PDT, was constructed by synthesizing DOX-UCNPs@ mSiO2/TiO2-TC multi-energy nanoparticles. Photonics and chemotherapeutic conjunctions of one-body nano-diagnostic and therapeutic platform. TiO2, as a Guang Min agent, has high viability and excellent chemical stability. TC as a crosslinking agent can encapsulate DOX in SiO2 space to prevent drug release in vivo. Excitation of multifunctional nanoparticles under near infrared light radiation Reactive oxygen species (Ros) produced by TiO2 can also induce photodegradation and drug release of TC crosslinkers. By controlling the release of drug by light, the drug can be controlled and the stability of PDT can be greatly improved by keeping the drug unaffected by other factors in vivo.

2.2 Rely on optical technology to achieve precise monitoring of tumor nanoscale treatment process.

Nanotherapy is a new kind of science and technology, which utilizes molecular manipulation technology and human molecular interaction at the molecular level to carry out disease prevention, diagnosis, treatment and rehabilitation, and improve health status. Nano-drug-loading technology can improve the absorption and stability of drugs, prolong the action time of drugs, increase the efficacy; PTT has the characteristics of short time, obvious efficacy, can alleviate pain in patients; PDT has the advantages of minimally invasive, highly selective, effective, no drug resistance and so on. However, these technologies need to use nanoparticles as drug carriers, and nanoparticles are toxic and poorly controllable. They can not monitor and control drug delivery and release in real-time during the treatment process, and can not confirm whether nanoparticles reach the tumor region, which brings a lot of trouble for accurate treatment of tumor. Photonics technology has many advantages, such as no direct contact with tissue, no direct damage to biological drugs, high sensitivity, and fast time response. Combining with multi-functional nanoparticles, it has formed a safe, fast and efficient nano-tumor treatment method, which makes it possible to accurately monitor the treatment process.

PDT is an important non-invasive method for the treatment of cancer and other diseases, and has been used in clinical diagnosis and treatment of cancer. However, traditional PDT is usually excited by visible light, which limits the penetration depth of biological tissue. Near infrared light with wavelength of 650-950 nm has the characteristics of deep penetration and small absorption, which can produce a clearer optical image. Up-conversion nanoparticles excited by near-infrared light can effectively convert near-infrared light into visible light or ultraviolet light, and then activate the traditional photosensitizer molecules to produce reactive oxygen species, so as to carry out photodynamic therapy for deep tissue tumors. Because 980 nm laser has strong absorption in biological tissues, Zhan *et al*.[31] attempted to change the excitation wavelength of upconversion nanoparticles in 2011, using a low-cost 915 nm near-infrared laser instead of 980 nm laser, successfully suppressed. The absorption of water and the thermal effect of tissue. In 2013, Wen and[32] put forward another change of NaGdF4... Yb, Nd, Yb core-shell structure up-conversion excitation wavelength method, but this structure is not suitable for fluorescence resonance energy transfer biological applications. In 2014, Shen *et al*.[33]

reported Nd3+, Yb excited by a 800 nm laser 3 + and activator Co doped NaYF4 system, but for the Co doped system, Nd The strong quenching effect between 3 + and activator leads to very weak upconversion luminescence. In the same year, Wang, etc.[34] a new type of NaYF4 was constructed by using upconversion nanomaterials. Yb / h. Nd NaYF4 core shell structure, as shown in **Figure 3.** Based on the up-conversion core-shell structure excited by 808 nm laser, low-thermal photodynamic therapy and up-conversion cell imaging monitoring can be achieved simultaneously, but the penetration depth of this wavelength light is not deep.

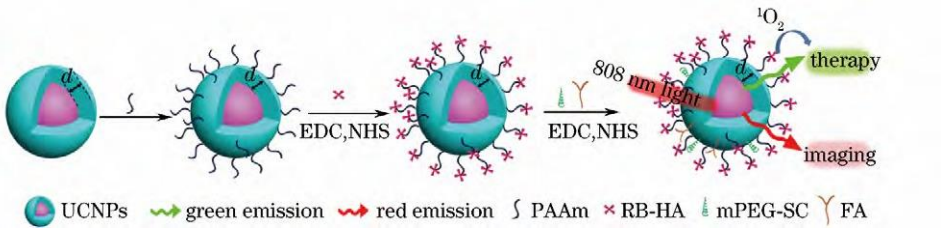

Figure 3; Structure and operation of up-conversion nanoplatforms for PDT and imaging 808nm laser excitation[34].

The second near-infrared window with wavelengths of 1100-1350nm and the third near-infrared window with wavelengths of 1600-1870nm have longer attenuation lengths than the first near-infrared optical window due to the reduction of scattering and absorption. Imaging of deep tissue[35]. Near infrared second window fluorescence imaging can clearly observe the anatomical characteristics of tissue depth, but most water-soluble organic molecular weight yields are low, limiting the time resolution and penetration depth. In 2017, Antaris *et al*.[36] used CH-4T to tailor supramolecular assembled proteins, resulting in a 110-fold increase in fluorescence quantum yields. Bright molecular complexes can be rapidly imaged in the second window of near-infrared light at a speed of 50 fra. Me / s, using this complex and near infrared second window synergistic effect can observe the heart circulation of mice. Diversity fluorescence imaging of biological systems is a focus of nano-biomedicine. Current fluorescence channels are limited to visible light and the first near-infrared spectral region. In order to reduce background fluorescence and achieve deep-level imaging, Zhu *et al*.[37] developed a molecular imaging agent NIR-II. Depending on buoyancy density differences, high purity NIR-II fluorescent antibody conjugates were prepared. It can be used as a specific molecular probe for NIR-II. The needle is used for 3D staining of brain tissue in polychromatic molecular imaging at the window of the IR IR. In 2015, Diao *et al*.[38] used large-diameter semiconductor single-walled carbon nanotubes (SWCNTs) for in vivo fluorescence imaging in the long wavelength near infrared region (1500-1700 nm, NIR-II), the imaging agent can be observed depth of 3 mm, width of 3-4. The micron capillaries and the ability to map the blood flow velocities of multiple vessels at the same time make NIR-II a high performance optical in vivo imaging technique.

Introducing optical technology into tumor nanomedicine can carry out medical operations and disease prevention and treatment that traditional medicine can't do at nanometer scale, so as to manipulate drug molecules more accurately at cellular and molecular levels, and then effectively monitor the distribution and treatment of nanoparticles, so as to achieve accurate monitoring of tumor treatment. Control[39].

2.3 Rely on optical technology to understand the mechanism of nanomedicine

With the development of nanomedicine, more and more nanomaterials are used in biomedicine. Nanomaterials can be used as effective carriers of chemotherapeutic drugs, targeting drug delivery to local tumors, to reduce the toxic side effects of chemotherapeutic drugs. However, some nanomedicine can only verify the effectiveness of nanomedicine by observing whether tumors can be controlled and whether tumor cells can spread or not, without grasping the treatment mechanism of nanomedicine, and can not fundamentally control the process of drug treatment. The combination of optical imaging, multi-spectral fluorescence imaging and multi-modality imaging technology with Nano-biomedicine can continuously track the process of drug delivery in vivo and accurately understand the dynamics of drug delivery and treatment, which can make a great contribution to the mechanism of nano-medicine.

Near-infrared laser irradiation can induce the release of drug molecules on nanocarriers absorbed by near-infrared radiation, but the rapid increase of local temperature leads to increased thermal vibration which can weaken the interaction between drug and carrier[40]. In 2017, Dong *et al*.[41] used bioluminescence imaging and multispectral fluorescence

imaging techniques to visualize the entire process of drug delivery to tumor treatment. Furthermore, based on real-time imaging localization and tracking, the relationship between drug release and distribution, carrier location and degradation, and tumor growth or inhibition was further illustrated. The visualization of drug delivery system provides a new way for the research of nano biomedical mechanism. In the same year, Li *et al.*[42] developed a new type of nanoparticles under the guidance of bimodal imaging based on the cooperative assembly of small molecule chemotherapeutic drugs and photothermal agents. After the near-infrared laser triggers the tumor site, nanoparticles release therapeutic drugs, which are then ingested by tumor cells through slow absorption and endocytosis. Co-localization of acidic lysosomes triggers the sudden release of these pH-sensitive nanoparticles, resulting in efficient accumulation of drugs in cells, thereby reducing the toxic effects on normal cells in the blood circulation system. At the same time, the imaging ability of nanoparticles can be used to monitor the endocytosis, intracellular release and chemotherapeutic drug transport, and realize the non-invasive continuous tracking of drug delivery process in vivo. It accurately reflects the dynamic process of drug delivery and treatment, which is the potential trend of nanodrug carrier mechanism research.

Understanding the interactions between nanoparticles and cells provides a clear understanding of how cells communicate with the outside world and the mechanisms by which viruses or nanoparticles invade cells. In 2017, Liu *et al.*[43] for the first time linked the aggregation state of nanoparticles with the real-time movement of cells by real-time monitoring the process of DNA-modified gold nanoparticles entering cells and their transport trajectories in cells, proving that nanoparticles existed as single particles in the early stage of endocytosis. In the process of transportation, it is gradually aggregated and fused with vesicles, as shown in **Figure 4.** Nanoparticles exist in a single-particle state around the cell membrane, and distribute in the cytoplasm as small aggregates when they are engulfed into the cells. The nanoparticles aggregate rapidly to the nucleus and lysosome along the microtubules, and exist in a large aggregation state near the nucleus and lysosome. The assimilation mechanism of gold nanoparticles was observed by controlling the temperature. When the temperature decreased, the phagocytosis decreased, indicating that the assimilation depended on energy. Fluorescence and plasma imaging demonstrated that the transport of gold nanoparticles depended on the size of clusters rather than on the types of organelles (such as nucleosomes and lysosomes). This study proposes an effective nano-diagnosis and treatment method, and provides a guarantee for the effective health management of nano-biomedical.

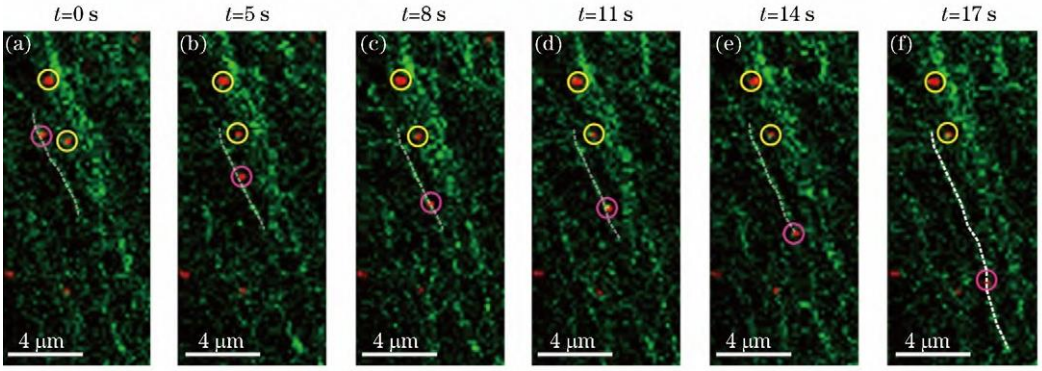

Figure 4; Two-dimensional motion of fPlas-gold on a microtubule captured by a fluorescence microscope[43]**.** (Rose-purple circles represent high-speed particles, and two yellow circles represent low-speed particles)

2.4 Rely on new optical technology to obtain new frontiers in biomedical research.

Despite the steady and efficient development of biomedical technology in recent years, the mechanisms of many major problems, including cancer metastasis, embryonic development, and brain function, remain unclear. In order to study these important biomedical problems more deeply, we must resort to some powerful new tools. For example, the use of photogenetic techniques to precisely locate and stimulate neurons without invading them has radically changed the state of neuroscience research and provided a revolutionary approach to neuroscience; gene editing is a technology that can precisely modify the genome, enabling gene targeting Mutations, knock-ins, simultaneous mutagenesis at multiple sites and deletion of small fragments, and so on, enable precise gene editing at the genomic level; cell tracing technology can be used to determine whether drug cells can maintain biological activity after entering the organism,

whether they can reach the target position, whether they can achieve the desired effect, and then. It is possible to comprehensively evaluate the efficacy and side effects of the new therapy before clinical practice.

Almost all the key technologies for the research of Frontier biomedical problems depend more or less on the introduction of new photonics technology. The following is a case study of cell tracing technology. Cell tracing technology can acquire real-time information related to these cells in two dimensions of space and time by modifying certain markers in a specific cell. It can dynamically monitor the survival, distribution, differentiation, migration, and prognosis of these cells in vivo, and then reveal them at the cellular level. Many important mechanisms related to the origin of life. As an important technical tool, cell tracer technology has been widely used in basic research and clinical application of modern biomedicine. Early cell tracing techniques usually only modified the same marker for a certain class of cells to monitor their overall differentiation and reproduction. With the development of biomedical technology, it is gradually realized that the tracer study of population cell average effect may cover up a lot of important individual information closely related to the life process or the origin of disease. Therefore, biomedical research pays more and more attention to the acquisition of individual cell specific information, which is also detailed. The development of cell tracer technology has raised new requirements. In order to achieve more precise biomedical research, researchers use nanoparticles or quantum dots linked to small molecules such as proteins or viruses to monitor in real time the interactions between proteins or viruses and other substances in cells, and then study their effects on the process of life changes in host cells[45,46]. It provides a more precise detection method for the biomedical field.

Currently, the hottest research in biomedicine, such as cancer metastasis, embryonic development, cell therapy, etc., urgently needs the following technology. 1) In the field of cancer mechanism research, how to prevent metastatic cells from invading other parts of the body has been the core problem to be solved urgently. Recently, researchers have discovered that seemingly identical cancerous cells may contain specific individual cancer cells, which are the seeds of cancer, resistant to chemotherapy and cause cancer recurrence years later. This is the famous cancer stem cell theory[47]. Cancer stem cells are a group of special cells in tumors that can initiate and maintain cancer development through self-renewal and differentiation. The difference between cancer stem cells and conventional cancer cells is very small, so in order to clarify their working mechanism, it is necessary to label each cell differently in the cell community composed of a considerable number of cancer cells, so as to specifically trace the differentiation and metastasis behavior of each cell, compare and find out the special behavior. Cancer stem cells systematically study their behavior patterns. 2) The ultimate problem in the study of biological development is to unlock the evolutionary mystery of how a few embryonic progenitor cells can produce most of the cells that make up the adult organs in constant differentiation. To carry out these studies, biologists need to independently label each generation of cells, clearly monitor the generation of daughter cells, and use the inheritance of daughter cells from the markers to reconstruct the cell lineage. This technique of continuous tracing of cells of different differentiation generations is called cytogenetics in developmental terms. Tracking technology[48]. 3) In the application of Next Generation Cell Therapy, researchers are devoting themselves to developing new drug cells to improve the efficacy of drug cells and reduce side effects; moreover, by properly controlling the antigen activity caused by drug cells, the targeting of drug cell attacks can be more precise[49]. Before these new drug cells enter clinical trials, the efficacy and side effects of drug cells must be assessed by cell tracing techniques, which also requires labeling in the same tissue of cells of different kinds of drugs, or even of different cell cycle stages or different differentiation generations of the same drug cells. To observe the difference of their curative effects. In addition, an important trend in next-generation cell therapy is the combination of drugs, with emphasis on monitoring the resulting efficacy additions and side effects. This process must also be labeled and traced specifically for different genetically modified drug cells.Therefore, there is an urgent need to develop a new cell tracer technology which can distinguish a large number of individual specific targets of single cell and monitor them dynamically in real time.

To do this, it is necessary to find a multi-dimensional information technology to simultaneously label specific information carriers for individual differences in the cell community to be studied, and to be able to use these differences in information carriers to clearly identify each individual cell in the dynamic observation. Gene editing technology is currently the most successful tracer technology for multicellular targets. In 2016, Yu *et al*.[50] used gene editing techniques to modify the corresponding "barcode" DNA fragments for each cell's differentiation without affecting cell func-

tion, as if they were putting barcodes on the back of every item in the supermarket, so they could pass the experiment. Cell gene screening revealed that 10 target tracer cells were found in a community of nearly 4000 cells. In the same year, McKenna *et al*.[51] successfully applied the similar gene barcode technique to the tracing of zebrafish phylogeny. It was found that only five of the 1138 gene variants of 4-month-old zebrafish produced more than 98% of the blood cells.

Although gene editing technology can successfully achieve a large number of single cell specific markers, it is difficult to use this technology in vivo or in vivo cell movement, migration and transformation process for real-time, dynamic tracking observation. Compared with gene editing technology, optical technology is more conducive to real-time, dynamic labeling and tracing of cells, and is most conducive to the reuse of information, that is, like gene editing, to trace a large number of single-cell specific targets in the form of barcode. In order to achieve a large number of single cell specific target tracing, we must have enough information carriers, and optical wavelength is one of the most conducive physical dimensions of information reuse. In optical communication, dense wavelength division multiplexing (DWDM) technology has been able to make each wavelength functionally similar to an IP address, thus enabling parallel transmission of a large number of wavelength-multiplexed information. Similar ideas are equally effective for cell tracing, which emits specific wavelengths of markers to label cells, differentiates each cell by specific wavelengths detected by cell imaging, and differentiates them.

Recently, two different research teams have put forward similar solutions almost at the same time. They used fluorescent dyes as gain materials to coat the shell with spherical polymer or oil droplets of micron size. The resonance of Echo Wall mode was formed by total reflection of light in the shell. The spontaneous emission of fluorescent dyes was successfully converted into stimulated radiation, and the optical labeling based on intracellular laser emission was realized. As shown in Fig. 5 (a), Humar *et al*.[53] used plastic microspheres to coat dyes to construct a micrometer laser (green) based on Echo Wall resonance, thereby realizing dynamic tracing of cancer cells. In the experiment, Humar and others use blue LED as the pump light source, and the laser threshold is only 2.4 nJ, as shown in Fig. 5 (b). When the excitation power reaches 38nJ, the source can emit a very narrow bandwidth single wavelength laser, and the wavelength can be adjusted in the gain spectrum by changing the diameter of the microsphere. This technology will provide a new generation of multi-cell specific target tracing technology with better water-solubility, simpler operation, better real-time dynamic performance, differentiable marker information and comparable to gene editing technology for the study of biological development, cancer mechanism and cell therapy technology. It will be useful for the next generation of biomedicine. Basic research and clinical application research is of great significance.

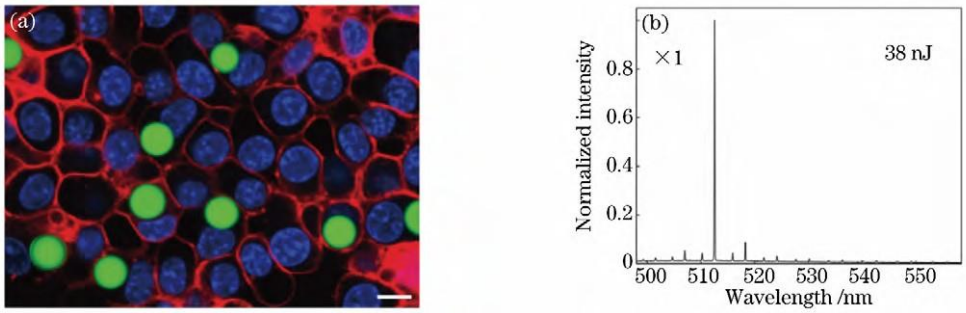

Figure 5; Cell tracing application using living cell plastic microsphere laser as marker [53].Confocal Imaging of (a) Primary Mouse macrophages Spectra of; (b) single fluorescent beads pumped by 38nJ Laser**.**

Although labeling different kinds of single cells with lasers of different emission wavelengths can be used to trace a large number of single-cell specific targets in real-time, these techniques have to solve the following three technical problems to be applied to specific biomedical problems: 1) Oversized lasers Big. In the study of Schubert and Humar, the resonator of the laser is composed of echo wall resonance mode, so the size of the microspheres should not be too small, the average size of the microspheres is 4-20 microns. This seems to be a cell marker.

Too large, a single laser almost fills up the entire cell, directly affecting the fine. Cell viability is difficult to study for long time. 2) the emission wavelength is hard to adjust accurately. Although Schubert and Humar's studies have confirmed that the emission wavelength can be adjusted by adjusting the size of the shell-coated materials, the controllability is poor and the adjustment accuracy is not high, which makes it difficult to meet the practical requirements for a

large number of single-cell specific target tracing applications. 3) new generation cells can not inherit markers. Because each cell only labeled a single laser, the new cells can not inherit the corresponding labeled laser, making the above technology can not meet the basic needs of cell tracing for cell differentiation monitoring.

In summary, although the use of intracellular micron lasers is expected to achieve a large number of single-cell specific target dynamic tracing, and real-time dynamic observation performance is superior to gene editing technology, but in order to obtain wider practical application, we must solve the above mentioned laser size is too large, the emission wavelength is difficult to adjust accurately. There are three key problems that the cells of the Cenozoic and the new generation cannot inherit markers. In view of the three key problems mentioned above, our group is using plasma nano-lasers to replace the micron lasers in Fig. 5 in order to realize the research of multicellular specific tracing. Based on the principle of surface plasmon exciton stimulated radiation amplification, we have obtained nano-lasers with an average diameter of less than 100 nm, which can be used to replace the micron lasers based on Echo Wall resonance. In this case, the size of the laser is comparable to that of the nanoprobe commonly used in bio-optical imaging, and cell tracer markers do not significantly affect cell activity; and a large number of nano-lasers with the same emission wavelength can be labeled in a single cell, just like the usual nanoprobe markers, in cell differentiation. Cenozoic cells will also have a certain number of homologous nano-lasers with the mother cell, so that the technology can be successfully used in cell differentiation tracer research, the realization of nano-scale biomedical diagnosis and treatment, related work will be published after finishing.

3. Concluding remarks

This paper mainly introduces the advantages of optical technology in nano-biomedicine, such as stability, accuracy, treatment mechanism and new methods of diagnosis and treatment. Optical means can improve the stability of Raman signal, enhance the intensity of detection signal and enhance the controllability of drugs. With the deep penetration of the second window of near infrared spectroscopy, it is possible to monitor the distribution of nanoparticles and target therapy in vivo. Multimodal optical imaging can monitor the interaction mechanism between nanoparticles and cells and their trajectories in vivo. Multifunctional nanophotonics technology (such as photogenetic technology, gene editing technology, cell tracing, etc.) as a new generation of biomedical fine research means, has important significance for biomedical basic and clinical application research.

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