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Single-Walled Carbon Nanotube-Based Optical Nano/Biosensors for Biomedical Applications: Role in Bioimaging, Disease Diagnosis, and Biomarkers Detection

*Rumi Acharya, Tejal V. Patil, Sayan Deb Dutta, Jieun Lee, Keya Ganguly, Hojin Kim, Aayushi Randhawa, and Ki-Taek Lim**

The convergence of advanced nanotechnology with disease diagnosis has ushered in a transformative era in healthcare, empowering early and accurate detection of diseases and paving the way for timely interventions, improved treatment outcomes, and enhanced patient well-being. The development of novel materials is frequently the impetus behind significant advancements in sensor technology. Among them, single-walled carbon nanotubes (SWCNTSs) have emerged as promising nanomaterials for developing biosensors. Their unique optical, electrical, and biocompatibility properties make them promising candidates for enhancing the sensitivity and real-time monitoring capabilities of biosensors, as well as for enabling various bioimaging techniques. Recent studies have demonstrated the utility of SWCNTS-based biosensors in the real-time monitoring of biological analytes, such as nitric oxide and hydrogen peroxide (H_2O_2), with potential implications for disease understanding and therapeutic response assessment. Moreover, SWCNTSs have shown promise in bioimaging applications, including fluorescence, Raman spectroscopy, and photoluminescence imaging of biological samples. This article delves into the core principles, design strategies, and operational mechanisms that underpin SWCNTS-bioimaging techniques-based biosensors. It emphasizes on their unique properties and versatile functionalization of carbon nanotubes, laying the foundation for their integration into biosensor platforms and applications aimed at diagnosing a wide spectrum of diseases including infectious diseases, cancer, neurological disorders, and metabolic conditions.

1. Introduction

Biosensors have become revolutionary instruments in diagnostic technology, crucial in promptly and precisely identifying illnesses.[1–3] Integrating biology and sensor technology has given rise to sophisticated platforms that capitalize on the specific interactions between biological molecules and recognition elements, offering unprecedented sensitivity and selectivity.[1,4–6] The intersection of nanotechnology and biomedicine has given rise to innovative disease diagnosis and monitoring approaches.[1,4,7] The timeline of biosensors in disease diagnosis reflects a dynamic evolution over several decades (**Scheme 1**). The field of biosensors has witnessed remarkable evolution since its inception in the 1960s, with the pioneering work of Clark and Lyons, who developed the first enzyme-based electrode for glucose sensing. This marked the beginning of biosensor technology, which integrates biological components with a physicochemical detector to produce a signal proportional to the concentration of a specific analyte.[7,8] The 1980s witnessed a landmark achievement with

R. Acharya, T. V. Patil, S. D. Dutta, J. Lee, K. Ganguly, H. Kim, A. Randhawa, K.-T. Lim
Department of Biosystems Engineering
Kangwon National University
Chuncheon 24341, Republic of Korea
E-mail: ktlim@kangwon.ac.kr

R. Acharya, T. V. Patil, J. Lee, H. Kim, A. Randhawa, K.-T. Lim
Interdisciplinary Program in Smart Agriculture
Kangwon National University
Chuncheon 24341, Republic of Korea

S. D. Dutta, K.-T. Lim
Institute of Forest Science
Kangwon National University
Chuncheon 24341, Republic of Korea

The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/admt.202400279

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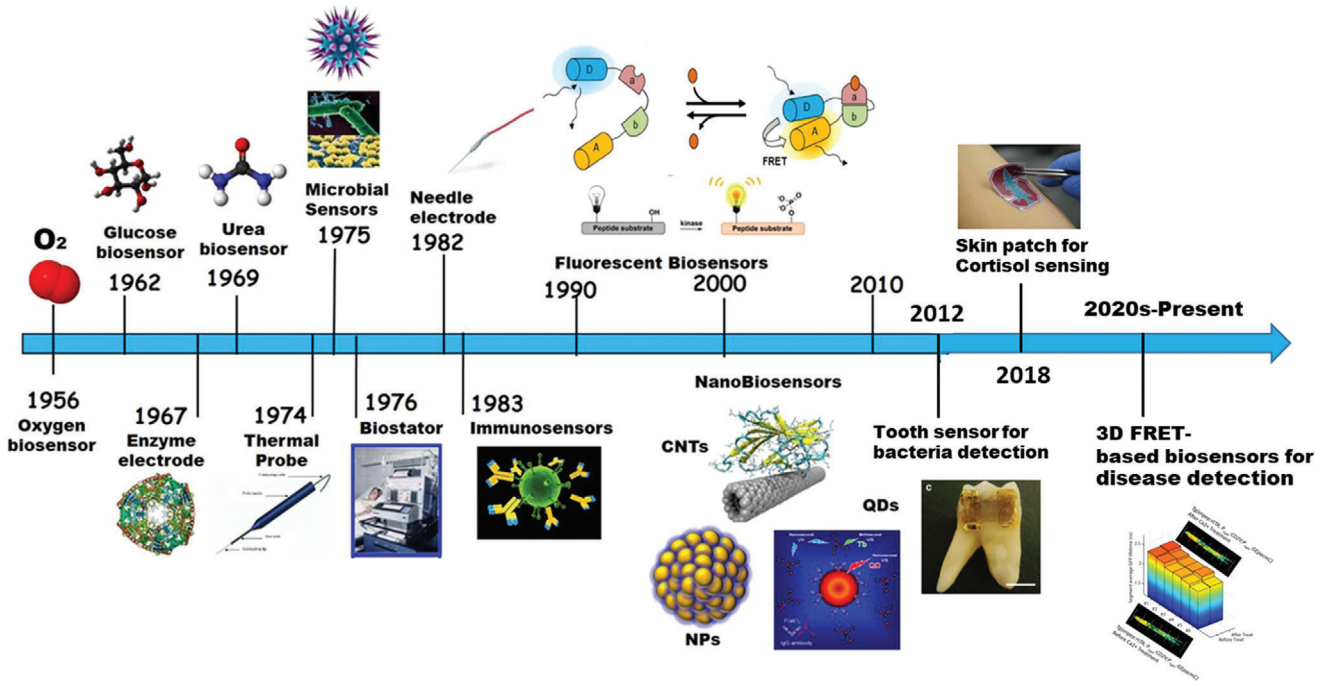


Scheme 1. Timeline of biosensor development. Reproduced with permission.[131] 2015, Front. Chem.

the commercialization of glucose biosensors, marking the inception of biosensors in clinical applications.[9] As technology advanced, the 1990s saw the diversification of biosensor applications, extending beyond glucose monitoring to include cholesterol, lactate, and urea detection. The integration of nanotechnology in the late 1990s and 2000s enhanced sensitivity and specificity, with nanomaterials like nanoparticles and nanotubes becoming integral components of biosensor designs. The advent of SWCNTSs, in particular, has opened new vistas in the realm of biosensing due to their unique electrical, mechanical, and optical properties.[10] SWCNTSs are essentially sheets of graphene rolled into tubes with diameters in the nanometer range, exhibiting remarkable strength, flexibility, and electrical conductivity. These properties make SWCNTSs ideal for biosensing applications, as they can be functionalized with biological molecules to detect a wide array of targets with high sensitivity and specificity.[7] The use of SWCNTSs in biosensors represents a significant advancement in the field, enabling the development of devices that are more sensitive, selective, and capable of detecting low concentrations of biomolecules.[11] This transition from traditional biosensor technologies to incorporating SWCNTSs underscores the continuous innovation and adaptation within the field, aiming to meet the increasing demands for rapid, accurate, and sensitive diagnostic tools. The relevance of SWCNTSs in biosensing is not merely due to their superior physical properties but also their compatibility with biological molecules. They can be easily functionalized with enzymes, antibodies, or nucleic acids, allowing for the specific detection of a wide range of analytes from glucose to cancer biomarkers and infectious agents like SARS-CoV-2.[8,9] This versatility has been pivotal in the development of point-of-care testing (POCT) devices, wearable biosensors, and integrated systems for real-time monitoring of health conditions. The integration of SWCNTSs into biosensor designs has thus been a critical step in the evolution of biosensors, offering new capabilities and expanding the potential applications of biosensors in healthcare, environmental monitoring, and beyond.[12] Overall, the historical development of biosensors from the first enzyme-based electrodes to the current state-of-the-art SWCNTS-based devices illustrates continuous innovation and improvement. The incorporation of SWCNTSs into biosensor technology represents a significant leap forward, enabling the creation of more sensitive, selective, and versatile biosensing platforms. As we continue to explore the potential of nanomaterials in biosensing, SWCNTSs stand out as a key material that bridges the gap between traditional biosensor technologies and the future of diagnostics and monitoring.

Developing sensitive and selective biosensors is crucial for early disease diagnosis, drug discovery, and environmental monitoring. Many existing biosensors, such as enzyme-linked immunosorbent assays (ELISAs) and electrochemical sensors, often face sensitivity, selectivity, and stability limitations. SWCNTSs exhibit a particularly advantageous property for biosensing applications with near-infrared (NIR) fluorescence. Unlike visible light, which is often absorbed by biological tissues, NIR light penetrates deeper, allowing for better detection clearer and more precise imaging within samples within the wavelength range of 650–1700 nm, offers a greater depth tissue penetration and minimal photon scattering, which is crucial for bioimaging and biosensing in complex biological environments Additionally, NIR fluorescence minimizes background noise caused by autofluorescence, a phenomenon where biological molecules naturally emit light in the visible region, potentially interfering with the signal of interest, thereby compromising sensitivity and specificity.[10,13–17] SWCNTSs are commonly described as

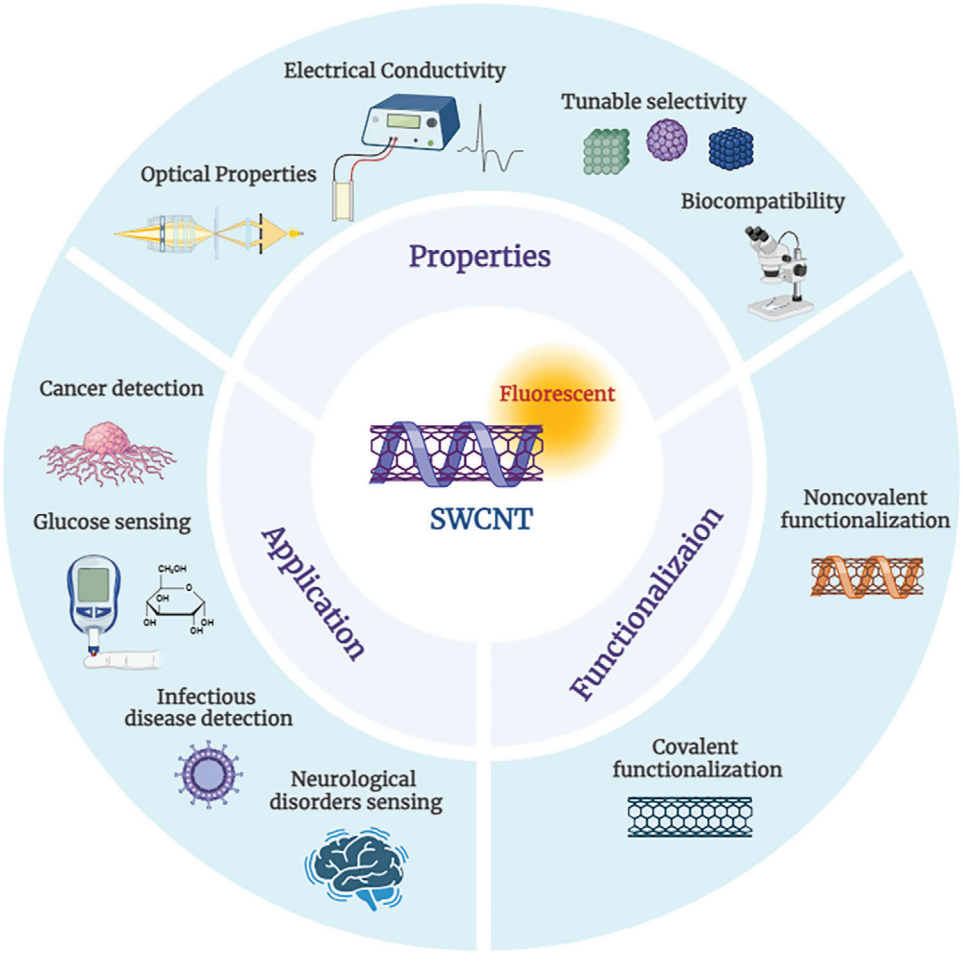
cylindrical structures made of rolled-up graphene.[18,19] They possess remarkable optical and electrical characteristics that vary based on their chirality and diameters.[20] The semiconducting variants of SWCNTSs include inherent energy bandgaps due to Van Hove singularities in the electronic density of states, which determine their optical characteristics.[21] 1) When exposed to light, these nanotubes exhibit very effective photoluminescence in the NIR range. This photoluminescence may be adjusted, remains stable under light exposure, and is influenced by the surrounding conditions. 2,3) It has recently been shown that SWCNTSs may be manipulated and isolated to achieve certain hues of light emission. Variations strongly influence the emission in the dielectric constant around the SWCNTSs.[10,22] The high sensitivity of SWCNTSs allows for the detection of perturbations at the surface of SWCNTSs at the level of individual molecules.[23,24] This indicates that SWCNTSs can be utilized as molecular sensors. In addition, the potential to create several species with varying emission capabilities allows for multiplexed imaging, which would be valuable for high-throughput screening (HTS) methods. NIR fluorescence emission is essential for in vivo applications of SWCNTSs. The highest tissue penetration of NIR wavelengths allows deeper biological system imaging and sensing. SWCNTSs are ideal for in vivo applications due to their NIR fluorescence emission. NIR light (650–1700 nm) is less absorbed and dispersed by biological tissues than visible light.[25,26] For deep tissue imaging and sensing, this increases penetration depth and signal-to-noise ratio. The NIR-II window (1000–1700 nm) is popular due to its better tissue penetration and lower background autofluorescence.[27,28] Deep tissue imaging with great spatial resolution and sensitivity is possible with NIR-II SWCNTSs. SWCNTSs' NIR emission allows non-invasive, real-time monitoring and imaging of biological processes in deep tissues, which is impossible with visible-range fluorophores.[22,29]

Surface functionalization of single-walled carbon nanotubes (SWCNTSs) has emerged as a pivotal strategy for achieving target-specific sensing in complex biological environments. This approach typically involves modifying the surface of SWCNTSs with complementary oligonucleotides, thereby enabling the selective detection of DNA sequences. Upon introducing target DNA, hybridization occurs between the target DNA and the complementary oligonucleotides on the SWCNTS surface.[10,21,22] This interaction leads to changes in the local dielectric constant around the SWCNTSs, which modulates their fluorescence properties. Such fluorescence changes serve as a detectable signal, indicating the presence of the target DNA. This mechanism underscores the potential of tailored SWCNTS-based materials to sensitively and selectively monitor specific substances of interest within complex biological fluids and even in vivo, facilitating advancements in diagnostics and biomedical research.[30] A thorough and methodical assessment of their mode of action and potential toxicity is necessary before considering any future clinical use. Indeed, proposals for producing SWCNTSs with safe-by-design methodologies, such as assuring biocompatibility and degradability, have been explored. Fadeel et al. (2023) highlight the importance of considering the entire life cycle of carbon nanotubes, from synthesis to disposal, in order to ensure their safety for human health and the environment. The authors emphasize the need for a safe-by-design approach that takes into account the potential risks associated with carbon nanotubes at each stage of their life cycle, including the design, production, use, and end-of-life phases.[31] Furthermore, a study by Alidori et al. investigated the long-term in vivo biocompatibility of SWCNTSs in mice. The results showed that SWCNTSs functionalized with polyethylene glycol (PEG) exhibited excellent biocompatibility and did not induce any significant toxicity or inflammation in various organs, even at high doses and after prolonged exposure. The authors suggest that the PEG functionalization plays a crucial role in enhancing the biocompatibility of SWCNTSs and reducing their potential risks.[32] These studies underscore the importance of incorporating safe-by-design (**Scheme 2**).[10,21,31,33]

Additionally, we will delve into this technology's challenges and prospects, shedding light on translating these biosensors from the laboratory to clinical settings. As we embark on this discussion through the amalgamation of carbon nanotubes and fluorescent in biosensor development, we invite readers to explore the intricate world of nanoscale diagnostics, where the convergence of interdisciplinary research has the potential to redefine the landscape of disease diagnosis and usher in a new era of precision medicine.[34]

2. Properties of SWCNTSs

SWCNTSs are formed by wrapping a single layer of graphene, just one atom thick, into a cylinder with a specific chirality and dimension. These characteristics, along with the roll-up vector, which defines the orientation of the nanotube's honeycomb lattice, significantly influence SWCNTSs' physical, chemical, electronic, and optical properties (**Figure 1**A,B).[35] Larger diameter nanotubes have greater persistence length and smaller level spacing in their electronic density of states, affecting their optical transitions. The persistence length of carbon nanotubes, which is a measure of their resistance to bending, has been shown to increase with increasing nanotube diameter. For example, a study demonstrated that the bending stiffness of SWCNTSs scales as the cube of their diameter, resulting in larger persistence lengths for nanotubes with larger diameters. Furthermore, the electronic density of states (DOS) of carbon nanotubes exhibits van Hove singularities, which are sharp peaks in the DOS that arise from the 1D nature of nanotubes.[36] The spacing between these singularities, known as the level spacing, decreases with increasing nanotube diameter. This smaller level spacing in larger diameter nanotubes affects their optical transitions, as the energy differences between the van Hove singularities correspond to the optical transition energies. The diameter-dependent optical properties of carbon nanotubes have been extensively studied both theoretically and experimentally. For instance, Weisman and Bachilo demonstrated that the optical transition energies of SWCNTSs are inversely proportional to their diameter. Similarly, Oyama et al. showed that the optical absorption peaks of SWCNTSs shift to lower energies with increasing nanotube diameter.[36,37] Additionally, the lattice structure determines the chemical interaction of SWCNTSs with adsorbed surfactants or polymers, enabling chirality-based separation and sorting techniques.[38] With diameters typically ≈1 nanometer and lengths ranging from 100 nanometers to several micrometers, SWCNTSs are 1D, high-aspect-ratio nanocarbon materials possessing large surface areas that can be easily functionalized. In their unmodified state, SWCNTSs are hydrophobic



Scheme 2. Schematic representation of SWCNTS-fluorescent biosensor showing its unique properties, functionalization, and applications in disease detection.

and prone to aggregation due to strong Van Der Waals attractive forces.[39,40] To achieve a colloidal suspension of individually dispersed SWCNTSs, they are typically non-covalently functionalized with amphiphilic molecules or polymers through a sonication process. Various biological applications, such as sensing, drug transport, nanoinjection, phototherapy, imaging, and artificial actuation, can be made possible for SWCNTSs with appropriate surface functionalization, rendering them biocompatible. SWCNTSs have an effective delivery use because of their high surface-to-volume ratio, which allows them to carry a significant cargo burden. siRNA and other oligonucleotides, for example, can be delivered universally by SWCNTSs as a drug delivery system (DDS) with circulation durations varying from minutes to hours. Drug administration of siRNA has been investigated in several cell lines concerning target protein knockdown, pharmacokinetics, toxicity, and anticancer efficacy.[41] Significant for gene-silencing applications, SWCNTSs may also enter cells and release siRNA into the cytoplasm.[42]

Moreover, recent research has shown that carbon nanotubes may transfer siRNA and plasmid DNA into a range of model and non-model plant species without assistance. Semiconducting SWCNTSs exhibit intense NIR fluorescence emission between 900 and 1600 nm and display distinct absorption peaks from the far UV to the NIR regions, unlike the broad absorption spectra of organic molecules. These absorption peaks, known as the E11, E22, and E33 transitions, arise from the van Hove singularities in the electronic DOS of SWCNTSs due to their 1D structure.[43,44] The E11 transition falls within the NIR range and is responsible for the characteristic NIR fluorescence emission of semiconducting SWCNTSs. The positions of these absorption peaks depend on the chirality and diameter of the SWCNTSs, with smaller diameter tubes exhibiting higher energy transitions. This unique absorption profile allows for selective excitation and detection, making SWCNTSs attractive for various optical sensing and imaging applications.[45] Moreover, they display remarkable photostability, devoid of photobleaching or blinking phenomena (Figure 1C).[46] These exceptional optical properties, coupled with robust functionalization capabilities, facilitate prolonged detection of SWCNTSs within biological samples, including tissues, blood, and cells, owing to the relative transparency of these biological media in the NIR spectral range (Figure 1D). For instance, human blood possesses a narrow optical transparency window between 900 and 1400 nm, permitting light penetration of ≈3–5 cm. While only a few conventional

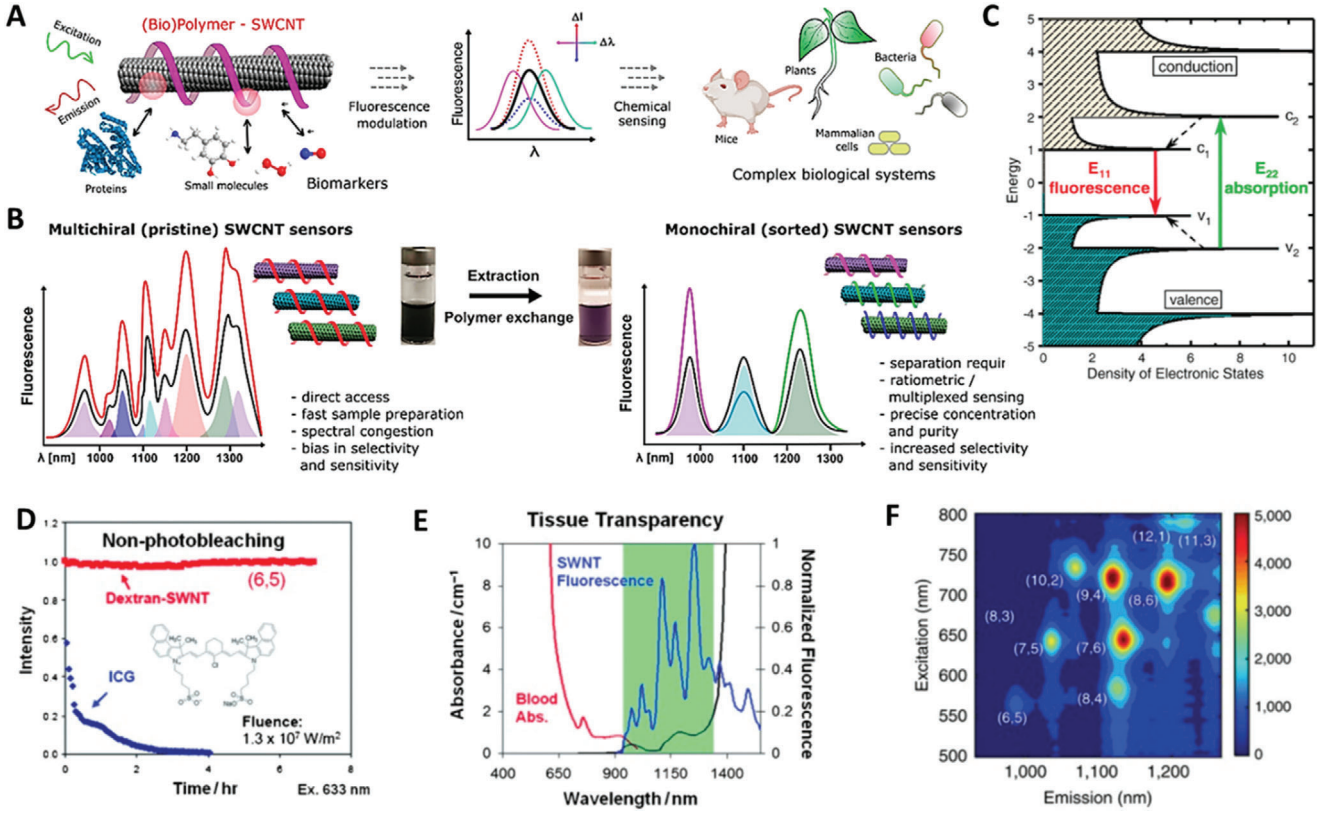


Figure 1. SWCNTS as biosensor: Properties, functionalization. A) The chemical environment in the area has an impact on SWCNTS fluorescence. Emission intensity or wavelength changes can be utilized to report on the interactions between significant biological molecules from various biological systems.DNA and other adsorbed biopolymers can modify this interaction. Reproduced with permission.[35] 2022, Anal. Chem; B) The spectra are congested as the virgin nanotube material comprises SWCNTSs with varied configurations (chiralities) that govern their emission spectrum. Reproduced with permission.[35] 2022, Anal. Chem; C) The electronic state density of a single-walled carbon nanotube structure that is semiconducting. The relevant excitation and emission transitions are shown by solid arrows, whereas nonradiative relaxation is shown by dashed arrows. Reproduced with permission.[46] 2016, NAT. Commun; D,E) Fluorophores, including indocyanine green (ICG), experience swift photobleaching with sustained illumination (depicted in blue). In contrast, SWCNTS emission (depicted in red) remains stable even under intense irradiation at a high fluence of 1.3 × 107 W m^{-2}. SWCNTSs predominantly fluoresce in the near-infrared range (900–1600 nm, shown in blue), where absorption by blood (depicted in red) and water (depicted in black) is minimal. Reproduced with permission.[46] 2016, NAT. Commun; F) Excitation–emission profile of polymer-functionalized SWCNTS suspension.Reproduced with permission.[46] 2016, NAT. Commun.

markers exhibit strong absorption or emission within this region, some suffer from limitations such as low photochemical stability or poor biocompatibility. Additionally, the physical dimensions of SWCNTSs, ranging from nanometers to a few microns, align with the typical size of biological molecules, enabling precise targeting and visualization. These remarkable characteristics make SWCNTSs highly attractive candidates for biomedical imaging, detection, and sensing applications,[47] and cells, owing to the relative transparency of these biological media in the NIR spectral range (Figure 1D). For instance, human blood possesses a narrow optical transparency window between 900 and 1400 nm, permitting light penetration of ≈3–5 cm. While only a few conventional markers exhibit strong absorption or emission within this region, some suffer from limitations such as low photochemical stability or poor biocompatibility. Additionally, the physical dimensions of SWCNTSs, ranging from nanometers to a few microns, align with the typical size of biological molecules, enabling precise targeting and visualization. These remarkable characteristics make SWCNTSs highly attractive candidates for biomedical imaging, detection, and sensing applications.[47]

2.1. Electrical Conductivity

CNTs (carbon nanotubes) are renowned for their exceptional electrical conductivity, allowing for the efficient transfer of charge carriers.[48,49] This property is leveraged in biosensors to enable rapid and ultrasensitive detection of biological analytes, such as proteins, nucleic acids, and small molecules. Due to their unique electrical properties, SWCNTSs are promising for biosensor applications. SWCNTSs are either metallic or semiconducting, depending on their chirality.[50] As Chirality is the angle and direction at which SWCNTSs roll the graphene sheet into a tube.[50,51] It is characterized by two indices (n and m) that specify the nanotube's diameter and graphene lattice angle with the tube axis. Chirality affects SWCNTSs' electronic characteristics, deciding whether they are metals, semiconductors, or semimetals.

Metallic versus Semiconducting Depending on chirality, SWCNTSs can be metallic or semiconducting. For instance, SWCNTSs are metallic when (n − m) is a multiple of 3, but semiconducting otherwise. Electronics and optoelectronics require precise conductivity control therefore, this difference is critical. SWCNTS carrier mobility and on-state current vary with chirality, for example, Type I SWCNTSs (mod (2n + m, 3) = 1) improve on-state current and carrier mobility with increasing chiral angle within the same family, while Type II SWCNTSs (mod = 2) do the reverse. They differ in electronic band structures, which affect contact barrier height between metal electrodes and SWCNTSs, junction, and intrinsic resistance.

The mechanisms of SWCNTS fluorescence modulation where NIR fluorescence is sensitive to the environment, making SWCNTSs ideal for biosensing. SWCNTS fluorescence may be regulated by electron transfer. For instance, the target analyte and functionalized SWCNTSs can extinguish SWCNTS fluorescence reversibly. A nonradiative Auger process quenches excitons by injecting an electron hole into the π-system at the protonation site. SWCNTS fluorescence is responsive to dielectric environment changes through solvatochromism. This sensitivity lets SWCNTSs' solvent or biological environment modulate fluorescence intensity and wavelength. SWCNTSs with greater diameters in nonpolar solvents have stronger surface-solvent interactions, resulting in stronger solvatochromic changes. Optical and electrical characteristics of SWCNTSs are affected by their chirality, including fluorescence. Chiralities affect emission wavelength and intensity, enabling selective detection and imaging.

Metallic SWCNTSs have a high electrical conductivity, while semiconducting SWCNTSs have a lower electrical conductivity that can modulate the adsorption of molecules.[52] This property makes SWCNTSs ideal for use in biosensors, as the change in electrical conductivity can detect the presence of specific molecules. For example, SWCNTS-based biosensors have been developed to detect various diseases, including cancer, diabetes, and infectious diseases. In a typical SWCNTS-based biosensor, the SWCNTSs are coated with a biorecognition element, such as an antibody or an enzyme. When the target molecule is present in the sample, it binds to the biorecognition element, causing a change in the electrical conductivity of the SWCNTS. This change in conductivity can be measured and used to quantify the amount of the target molecule in the sample.[53]

SWCNTS-based biosensors have several advantages over traditional biosensors, such as their high sensitivity, selectivity, and stability. Additionally, SWCNTS-based biosensors can be easily miniaturized and integrated into microfluidic devices. As a result, SWCNTS-based biosensors have the potential to revolutionize the field of disease diagnosis.[54]

2.2. Optical Properties

SWCNTS fluorescence is susceptible to environmental factors, exhibiting alterations in response to changes in pH, ionic strength, surface functionalization, and even single-molecule adsorption. The fluorescence signal of SWCNTSs is sensitive to the environment and can be modulated by the interaction of the SWCNTS with molecular analytes in its proximity.[11] The surface functionalization forms a corona phase surrounding the nanotube scaffold, which mediates this interaction and determines the fluorescence modulation upon surface binding. Several mechanisms can lead to the modulation of the emitted light upon target binding, including exciton quenching due to competitive non-radiative decay, a shift in the Fermi level leading to absorption bleaching, and reorientations of the solvent dipole moments in close proximity to the SWCNTS due to conformational changes of the corona resulting in a solvatochromic shift.[35] However, it is worth noting that the fluorescence of SWCNTSs may undergo modulation not only upon surface contact but also through mechanisms such as energy transfer, which may not necessarily require direct surface contact.[10,40] SWCNTS fluorescence originates from the radiative recombination of excitons characterized by high binding energy.[55] Target binding can modulate light emission in numerous ways. Competitiveness between non-radiative decay processes quenches excitons. An analyte binding to the SWCNTS surface can introduce novel non-radiative decay channels, such as charge transfer or energy transfer, that compete with exciton radiative decay, decreasing fluorescence intensity.[56] Studies have shown that nitroaromatic chemicals block SWCNTS fluorescence and detect neurotransmitters. The SWCNTS's Fermi level can change upon target binding, modulating fluorescence.[57] While adsorbing on the SWCNTS surface, analytes can contribute or absorb electrons, changing the nanotube's Fermi level. As the Fermi level shifts, electronic transitions become inhibited or less favorable, bleaching SWCNTS absorption bands.[58] Proteins and metal ions can be detected using this technique. Additionally, target molecule binding can modify SWCNTS corona phase conformation. Changing conformation can realign solvent dipole moments at the SWCNTS surface, causing a solvatochromic shift in fluorescence. In detecting biomolecules like DNA and proteins, binding-induced corona phase conformational changes shift the SWCNTS emission wavelength. When target binding modulates SWCNTS fluorescence, a combination of these mechanisms may be involved, depending on the analyte and experimental conditions.[59] Their exceptional optical properties make SWCNTSs ideal fluorescence signal transducers for sensing applications, offering advantages such as high photostability, negligible photobleaching, and physical dimensions comparable to typical target biomolecules (Figure 1E,F). The distinct chiralities of SWCNTSs, which arise from the different ways in which the graphene sheet can be rolled up to form a nanotube, result in a range of electronic and optical properties. This diversity in chiralities enables the development of multiplexed sensing platforms, where multiple analytes can be detected simultaneously by monitoring the emission of SWCNTSs across different wavelength channels. A study demonstrated the multiplexed detection of DNA sequences using a mixture of SWCNTSs with different chiralities, each functionalized with a specific DNA probe. By monitoring the emission of the SWCNTSs at different wavelengths, they were able to detect multiple DNA targets in a single sample. Similarly, a multiplexed sensor array based on SWCNTSs with different chiralities for the detection of volatile organic compounds (VOCs) has been developed,[11] The distinct emission wavelengths of the SWCNTSs allowed for the identification and quantification of multiple VOCs in a complex mixture.

Furthermore, the chirality-dependent emission of SWCNTSs has been exploited for high-throughput screening and hyperspectral imaging applications. Roxbury et al. used a library of SWCNTSs with different chiralities to screen for protein-SWCNTS interactions, enabling the rapid identification of protein targets that selectively bind to specific SWCNTS chiralities. Giraldo et al. demonstrated the use of SWCNTSs with different chiralities for hyperspectral imaging of cellular uptake and intracellular trafficking, allowing for the simultaneous tracking of multiple SWCNTS species within living cells.[60,61]

2.3. Tunable Properties

SWCNTSs, with their high-aspect ratio and high surface areas, can be readily functionalized. Without surface functionalization, they are hydrophobic and tend to bundle due to strong van der Waals attraction forces. However, they can be non-covalently functionalized with amphiphilic molecules or polymers by sonication to form a colloidal suspension of individually dispersed SWCNTSs. This functionalization can render them biocompatible, making them suitable for a wide range of biomedical applications, including sensing, drug delivery, nanoinjection, phototherapy, imaging, or artificial actuation.[62,63]

The high surface-to-volume ratio of SWCNTSs allows for a relatively large cargo load, making them efficient for delivery applications. For instance, SWCNTSs can serve as a universal drug delivery system for small interfering RNA (siRNA) and other oligonucleotides. They can penetrate cells and release siRNA into the cytoplasm, which is crucial for gene-silencing applications.[64] SWCNTSs have been used as optical sensors for biomarkers linked with human illnesses, such as various forms of cancer, glucose levels in diabetics, and H2O2 in reactive oxygen signaling pathways, by capitalizing on their unique optical features.[65] SWCNTSs functionalized with nucleic acids or peptides form stable complexes, even in intricate biological environments, demonstrating enhanced thermal stability up to 200 °C.[66] Notably, SWCNTSs functionalized with DNA sequences containing an endonuclease recognition site have been successfully utilized to investigate restriction enzyme activity by monitoring their fluorescent emissions. DNA-SWCNTS complexes have exhibited increased fluorescence intensity in response to neurotransmitters, enabling the successful detection of dopamine efflux in neuro progenitor cell cultures and acute brain slices.[67,68]

3. Fluorophore-SWCNTS Interactions in FRET-Based Biosensors

SWCNTS-fluorescent biosensors have revolutionized our ability to probe molecular interactions and cellular processes with exceptional precision and sensitivity.[69,70] This section delves into the foundational principles that underlie the design and functionality of FRET biosensors, with a particular focus on their applications in disease diagnosis. Bioimaging in disease detection encompasses diverse techniques, each employing distinct working principles to visualize and analyze biological structures at various scales.[70,71]

3.1. Small Organic Dyes and SWCNTSs

Small organic dyes, such as fluorescein, cyanine, and rhodamine derivatives, can be used as FRET donors or acceptors when coupled with SWCNTSs. Non-covalent interactions, such as π–π stacking and hydrophobic interactions, primarily govern the interaction between organic dyes and SWCNTSs. When the dye molecules are near the SWCNTS surface, the excited state energy of the dye can be transferred to the SWCNTS through FRET, resulting in quenching of the dye fluorescence and enhancement of the SWCNTS fluorescence.[72,73]

The efficiency of FRET between organic dyes and SWCNTSs depends on several factors, including the spectral overlap between the dye emission and SWCNTS absorption, the distance between the dye and SWCNTS, and the orientation of the dye relative to the SWCNTS surface. By carefully selecting the organic dye and optimizing the labeling strategy, researchers can design FRET-based biosensors that exploit the changes in FRET efficiency upon target binding to generate a detectable signal.[74,75]

3.2. Fluorescent Proteins and SWCNTSs

Fluorescent proteins, such as green fluorescent protein (GFP) and its variants, can also be used as FRET donors or acceptors in combination with SWCNTSs. The interaction between fluorescent proteins and SWCNTSs is typically achieved through genetic fusion or chemical conjugation. When the fluorescent protein is excited, the energy can be transferred to the SWCNTS through FRET, decreasing the fluorescent protein emission and increasing the SWCNTS fluorescence. The efficiency of FRET between fluorescent proteins and SWCNTSs is influenced by factors such as the spectral overlap, distance, and orientation of the fluorescent protein relative to the SWCNTS. By engineering fluorescent proteins with optimized spectral properties and designing appropriate fusion or conjugation strategies, researchers can develop FRET-based biosensors that respond to specific biological events or analyte binding.[76,77]

3.3. Quantum Dots and SWCNTSs

Quantum dots (QDs) are semiconductor nanocrystals with unique optical properties, such as size-tunable emission, broad absorption spectra, and high photostability. QDs can be used as FRET donors in combination with SWCNTSs as acceptors. The interaction between QDs and SWCNTSs can be achieved through various strategies, such as direct adsorption, covalent linking, or non-covalent assembly.[78]

When the QD is excited, the energy can be transferred to the SWCNTS through FRET, leading to a decrease in the QD emission and an increase in the SWCNTS fluorescence. The efficiency of FRET between QDs and SWCNTSs depends on factors such as the spectral overlap, distance, and relative orientation of the QD and SWCNTS. By exploiting the unique properties of QDs and designing appropriate QD-SWCNTS hybrid systems, researchers can develop highly sensitive and multiplexed FRET-based biosensors for various applications.[79] The interaction between these fluorophores and SWCNTSs is governed by various factors, such

Table 1. Different probes are used in optical biosensors in biomedical applications.

Probe	Description	Advantages	Limitations	Refs.
Fluorescent proteins (FPs)	Genetically encoded proteins that emit fluorescence upon excitation with light.	High specificity, non-toxic, can be expressed in living cells.	Relatively low brightness, limited range of emission wavelengths.	[167,168]
Organic dyes	Small synthetic molecules that emit fluorescence upon excitation with light.	Wide range of emission wavelengths, high brightness.	Non-specific interactions with biomolecules, photobleaching.	[167,168]
CRISPR/Cas12a probes	The sensor, termed CRISPR-SPR-Chip, enables amplification-free detection of target sequences within genomic DNA	Rapid and specific diagnosis.	Restricted multiplexing capability at the current stage of development	[169,170]
Mechanofluorescent DNA hydrogels	DNA hydrogels incorporating fluorescent dyes, engineered to exhibit strain-dependent fluorescence for sensing applications.	Show reversible fluorescence changes in response to mechanical deformation, targeted delivery.	Limited understanding of how to rationally tune the properties of DNA hydrogels	[97,171]
Epitaxial III–V/Si vertical heterostructures	Hybrid epitaxial III–V/Si vertical heterostructures were fabricated for applications in silicon photonics and optical biosensing	Epitaxial III–V/Si heterostructures for silicon photonics and biosensing	Lattice constants and thermal properties between III–V semiconductors and Si, which lead to issues like dislocations, cracks, and anti-phase domains.	[172,173]
Quantum dots (QDs)	Semiconductor nanoparticles with size-dependent emission properties.	High brightness, photostability, broad excitation, and emission spectra.	Potential cytotoxicity, and biocompatibility issues.	[71,167]
Graphene quantum dots (GQDs)	Nanoscale sheets of graphene with photoluminescent properties.	High biocompatibility, low toxicity, good photostability.	Quantum yield is lower than that of QDs.	[174,175]
Upconversion nanoparticles (UCNPs)	Nanoparticles that convert NIR light into higher-energy visible light.	Deep tissue penetration, low photobleaching.	Quantum yield is lower than that of QDs.	[176,177]
Genetically Encoded Sensors	Engineered sensors developed for a wide range of small molecules, ions, and metabolites or to report biophysical processes.	Enables real-time monitoring of cellular events and metabolite dynamics	Affinity limitations for detecting analyte levels in different concentration ranges	[178]

as spectral overlap, distance, and orientation, which influence the efficiency of the FRET process. By carefully selecting the fluorophore and optimizing the labeling or conjugation strategy, researchers can design FRET-based biosensors that exploit the changes in FRET efficiency upon target binding to generate a detectable signal. The unique properties of SWCNTSs, such as their near-infrared fluorescence and high photostability, make them attractive acceptors or donors in FRET-based biosensing applications.[80]

Therefore, small organic dyes, fluorescent proteins, and quantum dots can all be used as FRET donors or acceptors in combination with SWCNTSs to develop FRET-based biosensors. The interaction between these fluorophores and SWCNTSs is governed by various factors, such as spectral overlap, distance, and orientation, which influence the efficiency of the FRET process. By carefully selecting the fluorophore and optimizing the labeling or conjugation strategy, researchers can design FRET-based biosensors that exploit the changes in FRET efficiency upon target binding to generate a detectable signal. The unique properties of SWCNTSs, such as their near-infrared fluorescence and high photostability, make them attractive acceptors or donors in FRET-based biosensing applications. **Table 1** demonstrates different fluorescent probes in biosensors in disease detection and bioimaging.

4. Surface Modifications and Functionalization

SWCNTS-based biosensors typically consist of biosensors and sensors, with biomolecules or bio-receptors functionalized on them. SWCNTSs often function as sensors, where the concentration of the substance being analyzed is transformed into measurable physical signals (such as current, absorbance, mass, or acoustic variables) detected by the transducer. The various types of biosensors, those that rely on detecting changes in the electrical or optical properties of CNTs in response to target biomolecules, are particularly promising. SWCNTSs, which have all their atoms on the surface, are anticipated to possess greater potential than multi-walled carbon nanotubes (MWCNTs) for developing highly sensitive sensing devices.[81]

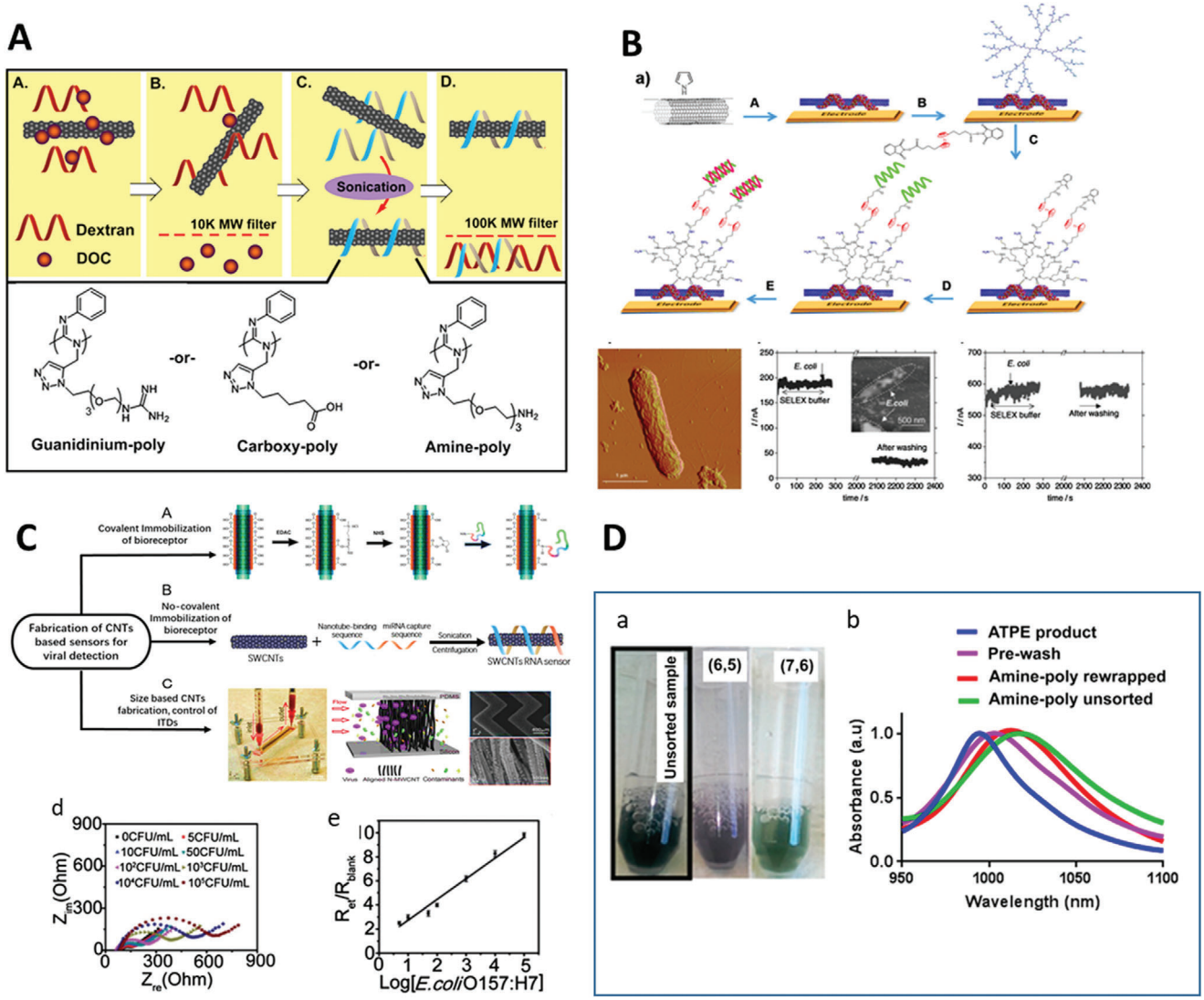


Figure 2. Fabrication and functionalization of SWCNTSs-FRET for sensing applications. A(a–d)) The schematic illustrates ATPE-enriched nanotubes in 0.1% DOC (orange circles), adding 2% w/w dextran (red). Centrifugal filtration (10 kDa MWCO) is employed to remove surfactant. After the second wash step, polycarbodiimide wrapping is introduced (blue). Probe tip sonication is performed. Dextran is eliminated using a 100 kDa MWCO centrifugal filter, and the residue is resuspended in DI H2O. Images depict the unsorted and rewrapped ATPE-sorted samples of (6,5) and (7,6) nanotube species.Reproduced with permission.[85] 2021, Nano. Lett.; B) Schematic represetation of the fabrication of a biosensor for detecting DNA. Reproduced with permission.[179] 2015. Anal. Chem.; C) Schematic representation of fabrication of viral detection. Reproduced with permission.[180] 2022, Elsevier; D) Absorbance spectra show the ATPE product in 0.1% DOC (blue), sorted nanotubes after one wash before poly carbodiimide addition (magenta), ATPE-sorted, amine-poly rewrapped nanotubes (red), and unsorted, amine-poly wrapped nanotubes (green).Reproduced with permission.[85] 2021, Nano. Lett.

The chiral-related electrical and optical properties of SWCNTSs make them particularly suitable for biosensors since they offer increased selectivity and feasibility by allowing the choice of certain semiconducting SWCNTSs.[64] They have notable optical properties influenced by their diameter, chirality, and surface characteristics.[82] These phenomena, such as photoluminescence (PL), arise from the distinctive interband transition between van Hove singularities. Most semiconducting SWCNTSs generate stable NIR fluorescence within the wavelength range of 800–1600 nm.[83] Binding target molecules on the surface allows for selective modulation of the fluorescence wavelength and quantum yield. The NIR window in biological tissue is found within the wavelength range of 700–1300 nm. Within this range, the scattering and absorption of blood and tissues can be effectively disregarded. Thus, SWCNTSs are regarded as a highly promising option for biological detection due to their unique properties as advanced optical biosensors.[84] **Figure 2** illustrates the fabrication and functionalization of SWCNTSs for FRET sensing applications. The schematic (A(a–d)) depicts the step-by-step procedure, starting with the enrichment of nanotubes using aqueous two-phase extraction (ATPE) in a 0.1% sodium deoxycholate (DOC) solution, represented by orange circles. A 2% w/w

dextran solution (red) is added to the enriched nanotubes. Centrifugal filtration with a 10 kDa molecular weight cut-off (MWCO) removes the surfactant. After the second wash step, polycarbodiimide wrapping (blue) is introduced, followed by probe tip sonication. Dextran is then eliminated using a 100 kDa MWCO centrifugal filter, and the residue is resuspended in deionized water. The images show the unsorted and rewrapped ATPE-sorted samples of (6,5) and (7,6) nanotube species. The absorbance spectra (D) compare the ATPE product in 0.1% DOC (blue), sorted nanotubes after one wash before polycarbodiimide addition (magenta), ATPE-sorted, amine-poly rewrapped nanotubes (red), and unsorted, amine-poly wrapped nanotubes (green), demonstrating the effectiveness of the functionalization process.[85]

4.1. Noncovalent Functionalization

The noncovalent functionalization of SWCNTSs is a flexible method that can improve their ability to interact with biological systems and make it easier to attach biomolecules for use in sensing applications. By employing π-π stacking interactions, SWCNTSs can be modified with aromatic biomolecules like DNA, proteins, or aptamers.[86–90] This modification allows for the specific and reversible binding of target analytes. Recent research has shown that noncovalent functionalization can be effectively used to create optical biosensors that are highly sensitive and specific in detecting a range of biomolecules, such as proteins, nucleic acids, and tiny compounds.[91–93] The noncovalent functionalization approach not only maintains the structural integrity of SWCNTSs but also guarantees effective signal transmission, rendering them very viable contenders for the advancement of optical biosensing.[94,95]

4.2. Covalent Functionalization

The process of covalently modifying SWCNTSs is a reliable method for customizing their surfaces to improve their compatibility with biological molecules. This is particularly useful in the creation of optical biosensors.[96] Covalent functionalization involves the formation of covalent bonds between the SWCNTSs surface and the functionalizing molecules. This approach provides a more stable and robust functionalization compared to noncovalent methods. Covalent functionalization can introduce specific functional groups onto the SWCNTSs surface, enabling the selective attachment of biomolecules for biosensing applications. However, covalent functionalization can disrupt the sp2 carbon network of SWCNTSs, potentially altering their electronic and optical properties. Therefore, careful control over the extent of covalent functionalization is necessary to maintain the desired properties of SWCNTSs.[56] For example, by covalently modifying with carboxylic acid or amino groups, it becomes possible to link targeted biomolecules like antibodies or enzymes to biosensing platforms. This ensures a high level of selectivity and sensitivity.[97] Recent studies have emphasized the effectiveness of covalent functionalization in producing stable and consistent SWCNTS-based optical biosensors. This has shown enhanced performance in transmitting signals and achieving lower detection limits.[98]

4.3. DNA sequence Functionalization

DNA sequences have been widely used for the functionalization of SWCNTSs in biosensing applications.[35] The noncovalent wrapping of SWCNTSs with single-stranded DNA (ssDNA) has been shown to enhance their dispersibility, biocompatibility, and stability in aqueous solutions. Moreover, DNA-functionalized SWCNTSs can be used for the selective detection of complementary DNA sequences through hybridization, enabling the development of DNA biosensors.[99] The use of aptamers, which are DNA or RNA sequences that can bind specifically to target molecules, has further expanded the applicability of DNA-functionalized SWCNTSs for the detection of various analytes, including proteins, small molecules, and metal ions. Jeng et al. conducted a study where they applied a DNA sequence to coat SWCNTS in order to identify single nucleotide polymorphism (SNP).[100] The manipulation of SWCNTS facilitated the identification of SNP by observing an enhancement in the emission energy at the highest fluorescence point in (6,5) nanotubes. Similarly, Clément's research group altered SWCNTS using single-strand DNA to detect neurotransmitters.[101] The measurement of optical signals was conducted using near-infrared fluorescence emitted by SWCNTSs. An investigation was conducted to detect significant biomolecules in a high-ionic strength solution (0.5XPBS). The rise in fluorescence intensities was shown to be inversely proportional to the electric current of the SWCNTSs, facilitating the identification of biomolecules such as dopamine, epinephrine, and ascorbic acid.[102,103]

4.4. Protein Functionalization

Proteins, such as enzymes and antibodies, have been used for the functionalization of SWCNTSs to develop highly selective and sensitive optical biosensors. The immobilization of proteins on the SWCNTS surface can be achieved through both noncovalent and covalent methods. Noncovalent protein functionalization often involves the adsorption of proteins onto the SWCNTS surface through hydrophobic interactions or electrostatic interactions. Covalent protein functionalization can be achieved through the formation of amide bonds between the amine groups of proteins and the carboxyl groups introduced onto the SWCNTS surface. Protein-functionalized SWCNTSs have been successfully employed for the detection of various analytes, including glucose, neurotransmitters, and disease biomarkers.[104,105] Recently, researchers Pinals and his team created a nanosensor capable of detecting the spike protein of the SARS-CoV-2 virus.[106] In order to achieve this objective, the authors modified SWCNTS by attaching the ACE2 protein. The study showed that ACE2-SWCNTS biosensors maintain their ability to sense in a surface-immobilized form, displaying a 73% increase in fluorescence within 5 s of exposure to 35 mg L^{-1} SARS-CoV-2 virus-like particles.

4.5. Other Corona Phases

In addition to DNA sequences and proteins, other corona phases, such as enzymes and surfactants, have been used for the

functionalization of SWCNTSs in biosensing applications. For example, GOx has been immobilized onto SWCNTSs using a pyrene-based crosslinker for the development of near-infrared continuous glucose monitoring sensors. Surfactants, such as sodium dodecyl sulfate (SDS) and sodium cholate (SC), have been used to noncovalently functionalize SWCNTSs, improving their dispersibility and biocompatibility. The choice of the specific corona phase depends on the target analyte, the desired biosensing mechanism, and the stability requirements of the sensor.[107]

Therefore, the functionalization of SWCNTSs through noncovalent and covalent methods, using various corona phases such as DNA sequences, proteins, enzymes, and surfactants, has greatly expanded their applicability in biosensing. The rational design of the SWCNTS functionalization strategy, considering the advantages and limitations of each approach, is crucial for the development of highly sensitive, selective, and stable biosensors.

4.6. Advantages of SWCNTSs for Optical Sensing

Optical sensing using SWCNTSs has several distinct benefits. In the emission range of SWCNTSs, the three critical figures of merit (FOM)—quantum yield, photostability, and tissue transparency—are all present, paving the way for creating fluorescence-based sensors applied to biology. Quantum yield is an important parameter that describes the efficiency of the fluorescence process in SWCNTSs. It is defined as the ratio of the number of photons emitted to the number of photons absorbed by the SWCNTS at a specific excitation wavelength. The quantum yield of SWCNTSs is typically lower than that of conventional fluorophores, such as organic dyes and quantum dots, due to the presence of non-radiative decay pathways, such as exciton quenching and energy transfer to metallic SWCNTSs.

It is important to note that the quantum yield of SWCNTSs is not dependent on the incoming excitation wavelength, as the absorption is calculated at the specific excitation wavelength used for the measurement. However, the quantum yield of SWCNTSs can be influenced by various factors, such as the chirality, length, and surface functionalization of the nanotubes, as well as the local environment and the presence of quenchers or enhancers. The quantum yield (ϕ), defined as the ratio of the number of photons emitted to the number of photons absorbed, is a crucial figure of merit for the effectiveness of fluorescence-based sensors. It is important to note that the quantum yield of SWCNTSs can exhibit dependence on the excitation wavelength, as the absorption efficiency of SWCNTSs varies across different wavelengths, affecting the number of photons absorbed and, consequently, the quantum yield. Therefore, when designing SWCNTS-based optical sensors, selecting an excitation wavelength that optimizes the quantum yield is essential for achieving high sensitivity and specificity in analyte detection.[108]

4.7. Exceptional Sensitivity

The exceptional sensitivity of SWCNTSs in the context of optical sensing is a key attribute that significantly enhances their utility in this field. This heightened sensitivity is evidenced by their remarkable effectiveness in chemoreceptive sensors, where SWCNTSs have demonstrated exceptional performance and simplicity. Furthermore, studies have established the high sensitivity of SWCNTSs to molecular charge transfer, highlighting their extraordinary responsiveness to subtle changes in their environment.[109]

Additionally, the unique ability of SWCNTSs to tune their functional properties through surface modifications further underscores their exceptional sensitivity, making them highly adept at detecting and responding to environmental changes. Moreover, SWCNTSs are known to exhibit highly enhanced sensitivity toward absorbates, further emphasizing their exceptional responsiveness in the context of gas sensing. This inherent sensitivity to environmental changes forms the basis for molecular recognition, making SWCNTSs pioneering candidates for optical sensors that rely on the detection of subtle variations for accurate analyte detection.[110,111]

4.8. Tunable Selectivity

The tailored selectivity for sensing optically is a significant advantage and contributes to their effectiveness in detecting and differentiating specific target molecules. This tailored selectivity is achieved through various methods, such as, Surfactant Modification: Altering the nature of surfactants has been shown to efficiently tailor both the selectivity and sensitivity of SWCNTSs vapor sensors. This method allows for the customization of SWCNTSs to selectively detect specific molecules, enhancing the overall selectivity of the optical sensing platform.[112,113]

Controlled Growth: The selective growth of SWCNTSs with a certain mean diameter can be achieved by adding appropriate amounts of specific gases. This controlled growth enables the customization of SWCNTSs for selective sensing applications, allowing for the precise detection of target analytes while minimizing interference from other molecules.[113,114]

Irradiation-Induced Functionalization: Selective irradiation of absorption features in SWCNTS samples has been shown to induce structure-specific functionalization, further enhancing their tailored selectivity for specific analytes. This method offers a means to customize SWCNTSs to detect specific molecules, contributing to the overall selectivity of the optical sensing platform.[114,115]

Surface Modifications and Interior Adjustments: The unique ability of SWCNTSs to modify their functional properties through surface modifications or interior space adjustments further underscores their potential for tailored selectivity in optical sensing applications. These modifications enable the customization of SWCNTSs to selectively detect specific target molecules, enhancing the overall selectivity and accuracy of the optical sensing platform.[115]

Practical Applications: The tailored selectivity of SWCNTSs in optical sensing is instrumental in enabling the precise and accurate detection of intended analytes, making them highly promising for developing highly selective optical sensors with diverse practical applications. This attribute positions SWCNTSs as

valuable candidates for developing robust and efficient sensing platforms with a wide array of real-world applications.[116]

4.9. Versatility in Practical Applications

SWCNTSs have been utilized as the sensing element in nanoscale optical biosensors, where their high sensitivity to environmental changes forms the basis for molecular recognition. This application highlights the practical versatility of SWCNTSs in developing highly sensitive and selective biosensors for a wide range of biological and environmental applications.[116,117] They have also been employed in developing chemo-resistive gas sensors, where their exceptional sensitivity to environmental changes has been leveraged to enhance the effectiveness and simplicity of the sensing platform.[115,118] This practical application underscores the versatility of SWCNTSs in developing robust and efficient gas-sensing technologies. The high sensitivity of SWCNTSs to environmental changes, the basis for molecular recognition, has been pivotal in pioneering their application in optical sensors. This foundational role in optical sensing further emphasizes the practical versatility of SWCNTSs in enabling highly sensitive and selective detection of target analytes.[10,115]

The versatile and practical applications of SWCNTSs in optical sensing are evident in their utilization as the sensing element in nanoscale optical biosensors, their role in enhancing the effectiveness of gas sensors, and their foundational contribution to molecular recognition in optical sensing technologies. These diverse applications underscore the potential of SWCNTSs to serve as highly sensitive and selective sensing platforms with a wide array of real-world applications.[119]

Another crucial factor that contributes to the success of SWCNTSs as optical sensors is their surface composition-dependent fluorescence. The fluorescence of SWCNTSs is highly sensitive to changes in their surface environment, which can be exploited for sensing applications.[10] The non-covalent functionalization of SWCNTSs with various molecules, such as DNA, proteins, or polymers, can modulate their fluorescence properties, enabling the detection of specific analytes.[120] For example, the adsorption of molecules onto the SWCNTSs surface can lead to changes in the local dielectric environment, resulting in a shift in the fluorescence emission wavelength or a change in the fluorescence intensity.[35] These changes in the fluorescence signal can be correlated with the concentration of the target analyte, allowing for quantitative sensing. Moreover, the surface composition-dependent fluorescence of SWCNTSs can be leveraged for the development of ratiometric sensors, where the ratio of the fluorescence intensities at two different wavelengths is used as the sensing signal. This ratiometric approach can help minimize the influence of external factors, such as fluctuations in the excitation source or variations in the sensor concentration, improving the reliability and reproducibility of the sensor.[35,121]

In addition to their surface composition-dependent fluorescence, SWCNTSs also exhibit excellent photostability, which is essential for long-term and continuous sensing applications. Unlike conventional fluorophores, which can undergo photobleaching upon prolonged exposure to light, SWCNTSs are highly resistant to photobleaching, maintaining their fluorescence signal over extended periods. Furthermore, the NIR fluorescence of SWCNTSs falls within the "tissue transparency window" (650–1350 nm), where the absorption and scattering of light by biological tissues are minimal. This allows for deeper tissue penetration and reduced background autofluorescence, enhancing the sensitivity and specificity of SWCNTS-based biosensors for in vivo applications.[122,123]

5. Applications in Disease Diagnosis

SWCNTSs have emerged as a promising nanomaterial for the development of biosensors, particularly in the field of medical diagnostics. The unique properties of SWCNTSs, such as their high surface area, excellent electrical conductivity, and optical properties, make them well-suited for the detection of various biomarkers and pathogens. SWCNTSs-based biosensors have shown great potential for applications in disease diagnosis, offering high sensitivity, selectivity, and rapid response times. In particular, the use of SWCNTSs as fluorescent probes has gained significant attention due to their NIR emission, which allows for deep tissue penetration and minimal background interference. This has opened up new possibilities for non-invasive and real-time monitoring of disease biomarkers and pathological processes. In this review, we will discuss the recent advances and applications of SWCNTSs-based biosensors in disease diagnosis, focusing on their use as fluorescent probes.

5.1. Cancer Detection

SWCNTSs are extensively researched for their application in fluorescence biosensors aimed at cancer detection.[60] They are employed to detect various cancer biomarkers and facilitate cancer screening. Below are some crucial details expanding on the utilization of SWCNTSs in biosensors that rely on fluorescence to detect cancer: creating adaptable and easily producible biosensors for cancer detection has utilized SWCNTSs as the sensing component. These biosensors utilize the distinctive characteristics of SWCNTSs to facilitate the identification of certain cancer biomarkers, hence aiding the progress of cancer screening technologies.[64] Cancer biomarkers have been identified using fluorescent biosensors based on SWCNTSs, specifically targeting the urokinase plasminogen activator (uPA) biomarker associated with metastatic prostate cancer. This application showcases the capability of SWCNTSs in facilitating the accurate and specific identification of crucial cancer markers. As a result, it aids in early cancer detection and monitoring. Researchers have created sensor systems using SWCNTS solutions to identify several indicators for gynecologic cancer in uterine lavage samples. This technique demonstrates the capability of biosensors based on SWCNTSs to detect many cancer indicators simultaneously, hence improving the effectiveness of cancer screening and diagnosis.[109] SWCNTSs have demonstrated the capability to detect cancer biomarkers with a high level of sensitivity using surface-enhanced Raman scattering (SERS).[15,64] The heightened sensitivity of this technology plays a crucial role in enabling the prompt and precise identification of cancer, therefore enhancing patient outcomes and treatment effectiveness.[124]

SWCNTSs have been employed for in vivo cancer imaging, showcasing their capability for multimodal imaging and targeted detection of cancer cells.[125] The distinctive characteristics of SWCNTSs, such as their ability to absorb NIR light and exhibit strong Raman signaling, have been utilized to facilitate precise identification and imaging of cancer cells. This highlights the promise of SWCNTSs in improved cancer detection methods. Creating adaptable and easily producible biosensors for cancer detection has utilized SWCNTSs as the sensing component. These biosensors utilize the distinctive characteristics of SWCNTSs to facilitate the identification of certain cancer biomarkers, hence aiding the progress of cancer screening technologies. SWCNTSs have demonstrated the capability to detect cancer biomarkers with a high level of sensitivity using SERS. The heightened sensitivity of this technology plays a crucial role in enabling the prompt and precise identification of cancer, therefore enhancing patient outcomes and treatment effectiveness.[126,127]

SWCNTSs have been employed for in vivo cancer imaging, showcasing their capability for multimodal imaging and targeted detection of cancer cells.[125] The distinctive characteristics of SWCNTS, such as their ability to absorb NIR light and exhibit strong Raman signaling, have been utilized to facilitate precise identification and imaging of cancer cells. This highlights the promise of SWCNTSs in improved cancer detection methods. To detect cancer markers, fluorescent biosensors have been used to detect cancer markers, such as proteins and nucleic acids, in biological samples. These biosensors can detect cancer markers at low concentrations, enabling early diagnosis and disease monitoring. fluorescent biosensors have been used to evaluate the efficacy of cancer drugs and kinase inhibitors.[128] These biosensors can detect drug-resistant cancer cells and evaluate the efficacy of specific drugs, providing valuable information for clinicians and physicians to design alternative therapeutic approaches. For visualization of molecular signaling events, fluorescent biosensors can be used to visualize subcellular molecular signaling events in real-time, allowing for the identification of novel targeting molecules and pathways and discoveries in clinical cancer research.[129] Point-of-care devices, such as fluorescent biosensors, can be integrated with microfluidic systems and developed into portable devices for point-of-care cancer diagnosis and treatment. These devices can provide rapid and accurate results, enabling early detection and personalized treatment of cancer. Due to their high sensitivity and specificity, fluorescent biosensors have shown great potential in cancer detection and monitoring. These biosensors can detect specific biomolecules and changes in the microenvironment associated with cancer cells, enabling early diagnosis and disease monitoring. They can also be used to evaluate and visualize molecular signaling events and develop point-of-care devices for cancer diagnosis and treatment efficacy of cancer drugs and kinase inhibitors.[130] Optical biosensors operate on the principle of detecting and measuring the interaction between target biomolecules and analytes through photon measurements (absorbance, reflectance, or fluorescence emissions) rather than electrons (**Figure 3**A,B). WCNT-based sensors provide the additional benefit of high photostability and low autofluorescence.[131] Kim et al. developed a SWCNTS-based optical sensor utilizing the fluorescence property of SWCNTSs for selective detection of adenosine 5'-triphosphate (ATP) in living cells (Figure 3C,D). Through the conjugation of luciferase enzyme to polymer-coated nanotubes, spatial and temporal information of NIR detection in ATP living cells was achieved, demonstrating a detection limit of 240 nM.[130] Figure 3E,F shows the fluorescence emission spectra of DNA-SWCNTS as a donor with relative intensity in both excited and stable states.

One notable example is the work by Williams et al., who developed a microarray-based biosensor using SWCNTSs functionalized with DNA aptamers for the multiplexed detection of cancer biomarkers. The biosensor was able to detect prostate-specific antigen (PSA), carcinoembryonic antigen (CEA), and mucin-1 (MUC1) with high sensitivity and specificity, demonstrating its potential for early cancer diagnosis.[132] Another significant contribution to the field was made by Chio et al., who developed a machine learning-based approach for the detection of ovarian cancer using an array of SWCNTSs functionalized with quantum defects. The "disease fingerprint" acquired from the near-infrared fluorescence emission spectra of the SWCNTS array was able to detect high-grade serous ovarian carcinoma in serum samples with 87% sensitivity and 98% specificity, outperforming the current best clinical screening test.[133]

In addition to the detection of cancer biomarkers, SWCNTSs have also been used for the detection of circulating tumor cells (CTCs), which are important indicators of cancer metastasis. Gao et al. developed a SWCNTS-based biosensor for the capture and detection of CTCs using aptamer-functionalized SWCNTSs. The biosensor exhibited high sensitivity and selectivity, enabling the detection of CTCs in blood samples from cancer patients. Furthermore, SWCNTSs have been employed for the detection of extracellular vesicles (EVs), which are secreted by cancer cells and play a crucial role in cancer progression and metastasis. Zhu et al. developed a SWCNTS-based biosensor for the detection of cancer-derived EVs using aptamer-functionalized SWCNTSs. The biosensor was able to detect EVs with high sensitivity and specificity, demonstrating its potential for cancer diagnosis and monitoring.[134]

5.2. Glucose Sensing

SWCNTS-based fluorescent biosensors have been developed to detect glucose, which has potential applications in medical diagnostics and therapeutics.[135] The research and development efforts in this area have demonstrated the potential of SWCNTS-based sensors for the optical detection of glucose, offering non-invasive and highly sensitive monitoring capabilities. These biosensors can be used to monitor glucose levels in blood, saliva, or urine, providing valuable information for diabetes management. Due to their high sensitivity and specificity, fluorescent biosensors have been used for glucose sensing. These biosensors enable continuous monitoring of glucose concentrations in real-time. One example of a fluorescent biosensor for glucose sensing is a FRET-based biosensor that quantifies glucose in culture supernatants of microbial cultivations. The biosensor consists of a glucose-binding protein sandwiched between two fluorescent proteins, constituting a FRET pair. Upon d-glucose binding, the sensor undergoes a conformational change, translated into a FRET-ratio change. The main advantage of fluorescent biosensors for glucose sensing is high sensitivity. These

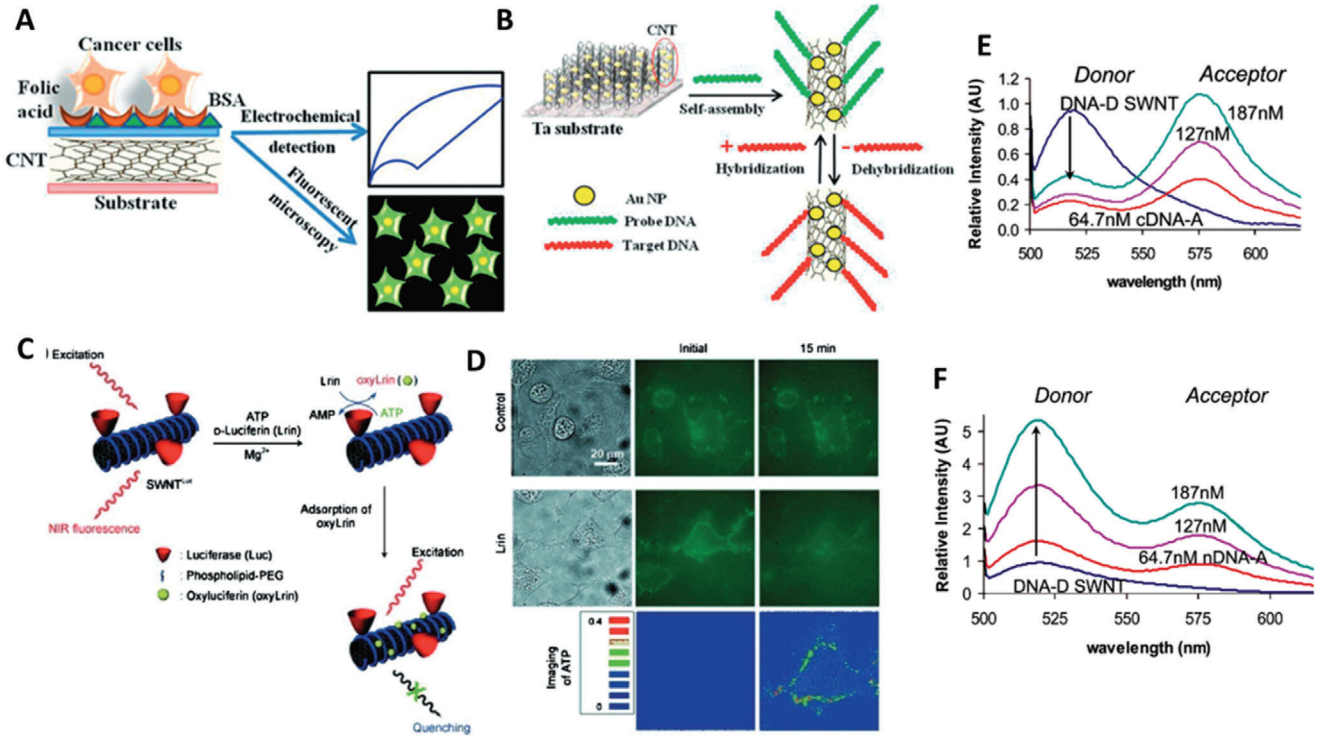


Figure 3. Novel approaches for cancer detection involve electrochemical and electronic CNT biosensors. A) A folic acid-targeted cytosensing strategy employs polydopamine-coated CNTs, enhancing electrochemical detection of cancer cells.Reproduced with permission.[131] 2018, ACS Sens. B) An electrochemical DNA biosensor for cancer detection utilizes gold nanoparticles/aligned CNTs, as depicted in the schematic representation.Reproduced with permission.[131] 2018, ACS Sens. C,D) The SWCNTS-based sensor exhibits selective recognition of ATP over interfering molecules such as AMP, CTP, and GTP, enabling spatiotemporal ATP detection in living cells. The fluorescence of SWCNTS is quenched by the oxidized production of d-luciferin, oxyluciferin. Fluorescence images of HeLa cells with the SWCNTS Luc sensor show quenching after the addition of Lrin (240 μM), correlating with ATP concentration.Reproduced with permission.[130] 2010, Angrew. Chem.; E,F) The intensity of DNA-D-NT at the donor emission spectra (maximum at 520 nm). Reproduced with permission.[181] 2015, Sensors.

biosensors can detect glucose levels at very low concentrations, making them suitable for early diagnosis and monitoring of glucose levels in patients with diabetes or other glucose-related disorders. Real-time monitoring: fluorescent biosensors enable continuous real-time monitoring of glucose concentrations in biological samples, particularly useful for optimizing insulin therapy in diabetic patients. FRET signals attenuate rapidly when fluorophore–fluorophore distances reach above 10 nm, making fluorescent-based glucose biosensors suitable for non-invasive, in vivo sensing. Integration with microfluidics and portable devices: fluorescent biosensors can be integrated with microfluidic systems and developed into portable devices for point-of-care glucose monitoring.

The composites of SWCNTSs-fluorescent enable the reversible manipulation of carbon nanotube aggregation, hence aiding in advancing glucose affinity sensors that might be used for non-invasive glucose monitoring. Prototype SWNT-Based Glucose Sensors: Extensive research has created the first models of glucose sensors that utilize SWNTs, such as enzyme-based and affinity sensors. These sensors encourage alternatives to conventional flux-based sensors by tackling fundamental issues and facilitating non-invasive and uninterrupted glucose monitoring. One of the seminal works in this field was reported by Barone et al., who developed a SWCNTS-based glucose sensor by immobilizing glucose oxidase (GOx) on the surface of SWCNTSs. The sensor exhibited a rapid response time, high sensitivity, and a wide linear range for glucose detection, demonstrating the potential of SWCNTSs for glucose monitoring.[136] Research has mostly concentrated on developing NIR optical glucose sensors using SWCNTSs. These sensors utilize the distinctive near-infrared characteristics of SWCNTSs, providing opportunities for improved glucose monitoring that is both non-invasive and very sensitive. Adaptable and Direct SWNT-Based Biosensors: A highly adaptable biosensor utilizing SWNTs has been detailed, demonstrating its ease of production and accurate measurement capabilities. This highlights its promising prospects for effective and efficient glucose sensing in real-world scenarios. More recently, Aeppli et al. developed a SWCNTS-based glucose sensor using a novel transduction mechanism based on the redox-mediated electron transfer between GOx and the SWCNTS. The sensor exhibited a wide linear range (0.1–25 mM glucose), high sensitivity, and excellent selectivity, with minimal interference from common electroactive species in blood.[137] Furthermore, Liang et al. developed a SWCNTS-based glucose sensor using a bioengineered GOx enzyme with enhanced stability and activity. The sensor exhibited a wide linear range (0.5–50 mM glucose), high sensitivity, and good stability, with a response time of less than 10 s.[138]

Using SWCNTSs in biosensors that rely on fluorescence for glucose detection has demonstrated considerable potential. This progress encompasses the creation of glucose detection platforms that incorporate composites and produce prototype glucose sensors. The progress made in this field demonstrates the capability of SWCNTSs to provide glucose monitoring that is both non-invasive, extremely sensitive, and continuous. This presents important alternatives to conventional glucose sensing methods.

Fluorescent biosensors have shown great potential in glucose sensing due to their high sensitivity, specificity, and real-time monitoring capabilities. These biosensors can be used for early diagnosis and monitoring glucose levels in patients with diabetes or other glucose-related disorders and for integration with microfluidics and portable devices for point-of-care applications.

5.3. Infectious Disease Detection

SWCNTSs have demonstrated substantial promise in the advancement of fluorescence biosensors for identifying contagious illnesses. Multiple research papers and articles have emphasized using SWCNTSs in biosensing and imaging. This application allows for quickly and accurately identifying infectious illness biomarkers, such as viruses and other pathogens. Below are some essential details explaining the utilization of SWCNTSs in biosensors that rely on fluorescence for detecting infectious diseases:

Swift identification of SARS-CoV-2 proteins: A study reported the rapid identification of SARS-CoV-2 spike (S) and nucleocapsid (N) proteins using a sensor based on SWCNTS. The sensor exhibited prompt reactions within five minutes and registered very sensitive detection thresholds for the S and N proteins, highlighting its capability for the swift and precise identification of viral biomarkers.

A multifunctional biosensor based on SWCNTSs has been reported. This biosensor is easy to fabricate and analyze. This biosensor can quickly and accurately identify biomarkers of infectious diseases, aiding in early illness diagnosis and treatment. Researchers have created an ultrasensitive sensor to detect the nucleocapsid protein (NP) of SARS-CoV-2 using SWCNTSs. The sensor exhibited a low detection threshold, making it a viable tool for precisely identifying viral biomarkers linked to infectious illnesses.

Swift detection of SARS-CoV-2 spike proteins was achieved using nanosensors based on SWCNTSs noncovalently functionalized with the human ACE2 receptor. The nanosensors exhibited prompt and accurate fluorescence activation upon contact with the virus, indicating their capability for quick and accurate identification of infectious diseases. Using SWCNTSs in biosensors that rely on fluorescence has demonstrated considerable potential in swiftly and accurately identifying biomarkers of infectious diseases, such as those linked to SARS-CoV-2 and other infections. The results emphasize the capability of biosensors based on SWCNTSs as useful instruments for detecting infections at an early stage, controlling their spread, and providing treatment for infectious diseases.

Using SWCNTS-based FRET in bioimaging proves to be a potent tool, as it enhances SWCNTS brightness, resulting in the advantage of higher signals and increased imaging depth within the tissue.[111] Another significant application of sensors in healthcare is the detection of pathogens. A collection of highly sensitive sensors designed for detecting bacterial biomarkers and infection-associated pathogens (**Figure 4A**) has been developed in this context. For one of these sensors, a specific conjugation of a small peptide to DNA-covered SWCNTSs facilitates surface modification. This modification allows the sensor to bind and detect lipopolysaccharides, crucial endotoxins, and subunits of the outer cell wall of Gram-negative bacteria.[35,139,140] Applying surfactant-aided ATPE and subsequent exchange to this DNA-peptide conjugate resulted in a monochiral (6,5) LPS(lipopolysaccharide) sensor, sensitive to lipopolysaccharides (LPS). The fluorescence of this sensor increased notably upon the addition of Escherichia coli LPS (Figure 4B). To achieve robust multispectral imaging, such sensors were incorporated into hydrogels, facilitating the remote detection of pathogenic bacteria. The set of nanomaterials was then interrogated at specific wavelengths (Figure 4C,D) through appropriate filter settings for the presence of bacteria-induced specific alterations in the fluorescence emission pattern of the nanosensors.[141] Differences in sensor responses were visualized using multivariate statistics such as principal component analysis (PCA), revealing distinct clusters, allowing differentiation of two prominent bacteria, *Staphylococcus aureus* and *Pseudomonas aeruginosa*, as well as their isolates after 72 h (Figure 4E).

5.4. Neurological Disorders

Fluorescent biosensors have shown potential in detecting and monitoring neurological disorders. These biosensors can detect specific biomolecules and changes in the microenvironment associated with neurological disorders, enabling early diagnosis and disease monitoring. In biological samples, fluorescent biosensors have been used to detect neurotransmitters such as dopamine, glutamate, and acetylcholine.[142] These biosensors can detect specific biomolecules associated with neurological disorders, enabling early diagnosis and disease monitoring. Fluorescent biosensors have been used to evaluate the efficacy of drugs for neurological disorders such as Alzheimer's and Parkinson's. These biosensors can detect drug-resistant neurological cells and evaluate the efficacy of specific drugs, providing valuable information for clinicians and physicians to design alternative therapeutic approaches.[137,143] Fluorescent biosensors enable continuous real-time monitoring of neurological disorders in biological samples, providing valuable information for disease diagnosis and treatment. Development of Point-of-Care Devices: fluorescent biosensors can be integrated with microfluidic systems and developed into portable devices to diagnose point-of-care neurological disorders. These devices can provide rapid and accurate results, enabling early detection and personalized treatment of neurological disorders. Due to their high sensitivity, specificity, and real-time monitoring capabilities, fluorescent biosensors have shown potential in neurological disorder detection. These biosensors can be used for early diagnosis and monitoring of neurological disorders and for integration with microfluidics and portable devices for point-of-care applications.[143,144]

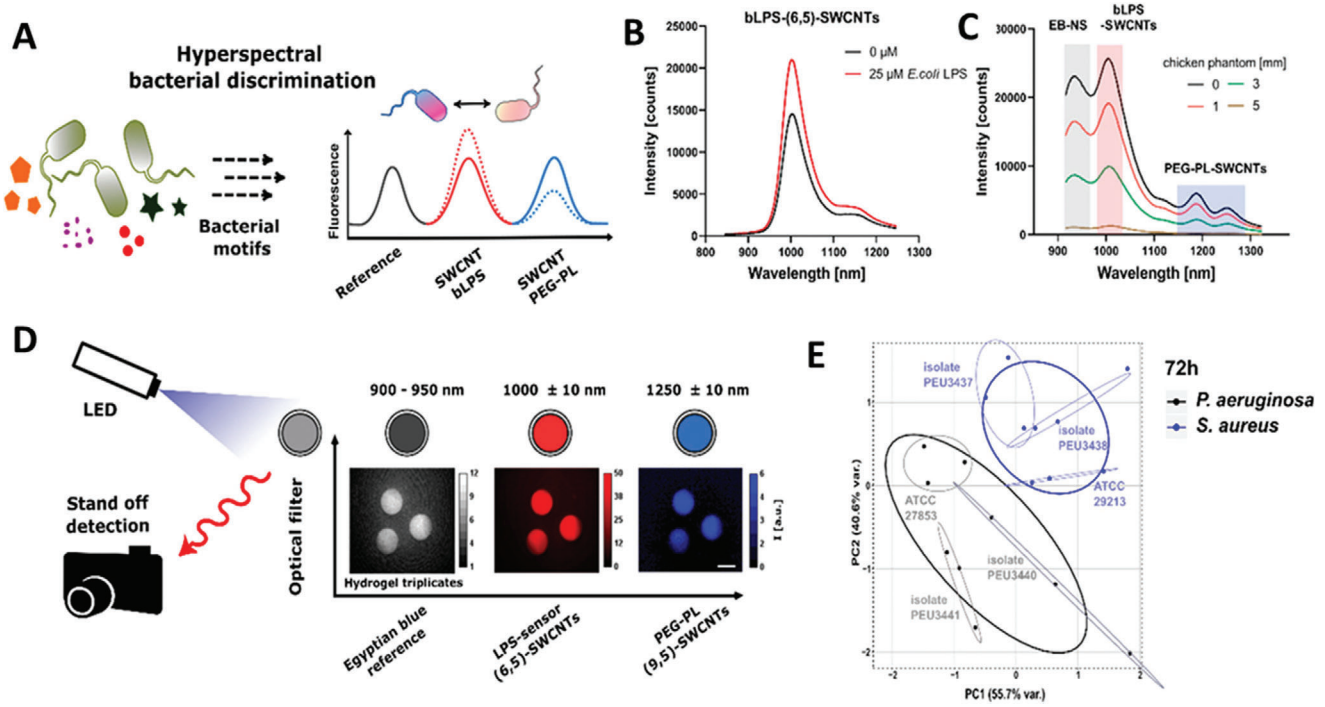


Figure 4. Detection of pathogen. A) Diagram showing process of bacterial metabolites alter many nanosensors' fluorescence emission. Reproduced with permission.[35] 2022, Anal. Chem.; B) In addition to *E. coli* LPS, monochiral bLPS-(6,5)SWCNTSs respond by increasing their emission. Reproduced with permission.[35] 2022, Anal. Chem.; C) The tissue phantom thickness affects the fluorescence intensities of the relevant nanosensors.Reproduced with permission.[35] 2022, Anal. Chem.; D) Incorporating all nanosensors into a functional hydrogel matrix and using NIR stand-off detection of the corresponding emission by optical filters to create three channels for emissions and colors. Reproduced with permission.[140] 2020, Nano. Commun.; E) Development, metabolism, and inoculation of bacteria, including various isolates of *P. aeruginosa* and *S. aureus*, cause different reactions in the nanosensors, which are then seen using in situ detection. A remote and hyperspectral bacteria detection approach is created by principal component analysis of the spectrally encoded sensor responses, which enables unambiguous discrimination after 72 h.Reproduced with permission.[35,140] 2020, Nano. Commun.

One approach for protein detection is to use the natural binding partner of the target protein as a recognition site on the SWCNTSs, achieved by using an antibody, an aptamer, or a DNA recognition sequence to exploit the original protein–protein or protein–DNA interactions for sensing applications. A label-free detection was demonstrated in Ahn et al. using nanotubes functionalized with chitosan polymer modified with nitrilotriacetic acid (NTA) chelator.[33,143,145] Chitosan was utilized owing to the accessibility of functional groups for additional modification. The NTA chelated $Ni2^{+}$ and served as a proximity quencher modulating the SWCNTS fluorescence intensity as a function of distance (**Figure** 5A,B). The NTA-Ni^{2+} group can bind to any hexahistidine-tagged (his-tag) capture protein, which is a natural binding site for the protein of interest. For example, a his-tagged protein A bound to the NTA-$Ni2^{+}$ group was used to capture human immunoglobulin G (IgG). Binding of the target protein leads to a modulation of the fluorescence intensity, enabling studying protein–protein interactions, protein glycoprofiles, and protein quantification.[143] In a study to investigate the impact of neurotransmitters on fluorescence spectra, solubilized HiPCO SWCNTSs in different polymers were used.[142] To determine fluorescent SWCNTSs adsorbed polymer phases, enabling selective detection of certain neurotransmitters, such as dopamine. Kruss et al. used a library of various polymers (n = 30) that included phospholipids, nucleic acids, and amphiphilic polymers to functionalize and suspend SWCNTSs in order to investigate how neurotransmitters affect the NIR fluorescence of the resultant band gap (Figure 5C–E). Several corona stages allow for the specific identification of neurotransmitters.[142]

5.5. Metabolic Disorders

SWCNTSs are being used to create fluorescent-based biosensors that may detect and monitor neurological diseases. SWCNTSs possess distinct physical and chemical characteristics that make them very suitable for imaging and sensing the brain's extracellular space (ECS) and detecting neurotransmitters and other essential biomolecules.[146] Below are notable applications and discoveries concerning the utilization of SWCNTSs in biosensors that rely on fluorescence for the diagnosis of neurological disorders. Due to their advantageous physical and chemical characteristics, SWCNTSs have been suggested as highly suitable options for imaging and sensing the brain's ECS.[147] SWCNTSs have features that make them suitable for viewing, characterizing, and chemically probing the brain's ECS. This area of study is mainly unexplored and holds significant potential for the advancement of innovative technology.[148]

Fluorescent nanosensors for neurotransmitter detection: SWCNTSs have been employed as fundamental components for

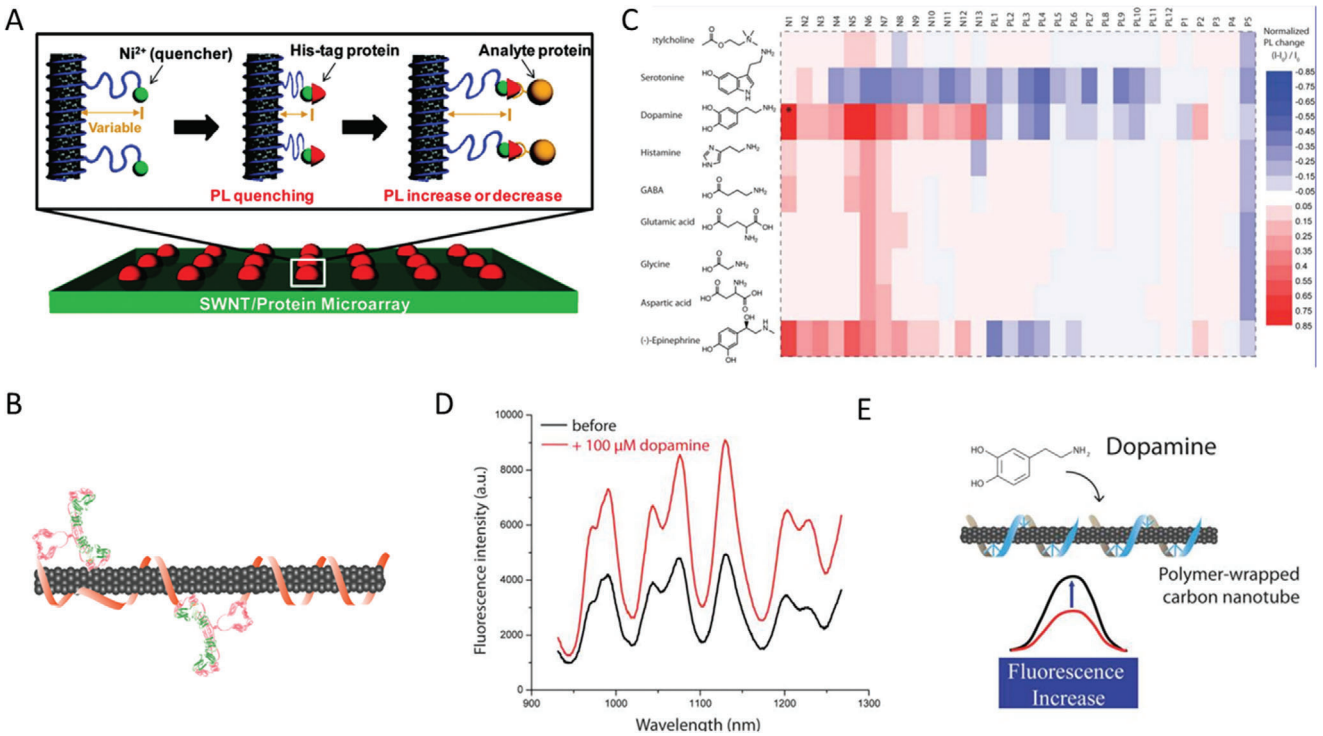


Figure 5. SWCNTS-based protein-protein interaction detection. A,B) Protein sensor array schematic with label-free and fluorescent SWCNTSs, the SWCNTS solution was functionalized with NTA-Ni2+ to bind his-tagged capture proteins and identify a captured protein interacting with a target protein. The NTA-Ni2+ groups first used their his-tag residues to immobilize the his-tagged capture proteins. Once a target protein was added to each area and bound to the appropriate capture proteins, the distance between the Ni2+ quencher and the surface of the SWCNTS shifted, causing a modulation in the fluorescence; Illustration of the anti-uPA–DNA–SWCNTS complexes. Reproduced with permission.[143] 2011, Nano. Lett.; C–E) Screening of SWCNTS-polymer conjugates for fluorescence modulation by neurotransmitters, the normalized fluorescence changes (I–I0)/I0 of different polymer-SWCNTS, the color-coded heat map shows the conjugates upon adding different neurotransmitters (100 μM).Reproduced with permission.[142] 2014, J. AM. Chem. Soc.

sensors and probes that identify neurotransmitters, such as catecholamines. The adjustable specificity of SWCNTS-based fluorescence sensors has demonstrated potential in detecting neurotransmitters, which might lead to breakthroughs in monitoring localized fluctuations in transitory chemical levels inside living tissues.[146] Non-Invasive Diagnostics utilizing NIR Fluorescent Sensors: Carbon nanotubes, such as SWCNTSs, are acknowledged as versatile optical biosensors that operate in the NIR range. These biosensors are crucial for fundamental research and non-invasive diagnostics. The distinctive optical characteristics of SWCNTSs render them highly desirable for the advancement of non-intrusive diagnostic instruments, particularly those designed to identify biomarkers linked to neurological illnesses.[149,150]

Overall, the utilization of SWCNTSs in fluorescent-based biosensors for detecting neurological disorders has demonstrated considerable potential in several domains, such as seeing and perceiving the brain's extracellular space, identifying neurotransmitters, and aiding in the creation of diagnostic instruments that do not need invasive procedures. The results emphasize the potential of biosensors based on SWCNTSs as helpful instruments for enhancing our comprehension of neurological illnesses and enhancing diagnostic capacities in this crucial area.[51,65,67,151]

Fluorescent biosensors have many medical applications, including cancer detection, glucose sensing, infectious disease detection, mechanobiology and ethnopharmacological screening, tissue-based biosensors, and pH and ion sensing.[152] As research advances in this field, fluorescent biosensors are expected to play an increasingly important role in various biological applications,[147a] including medical diagnostics, environmental monitoring, and fundamental research. Galassie et al. emphasized the potential of monochiral SWCNTS sensors in healthcare and illness diagnosis, such as cholesterol detection.[153] One of the earliest instances of chirality-pure sensors was achieved by DNA-specific SWCNTS wrapping in conjunction with other purification methods such as ion-exchange chromatography or ATPE.[154] Such constructed devices (**Figure 6**A) demonstrated a strong affinity for lipids such as cholesterol or sphingomyelin, likely by direct adsorption on the CTTC3TTC-(9,4)-SWCNTS surface.[153] When taken up by macrophages, hyperspectral imaging observed a particular blue shift in sensor emission (Figure 6B), demonstrating the strongest response for the (9,4)chirality.[155] To map oxidized low-density lipoproteins in vivo (Figure 6C) as a potential tool for studying and detecting excess disease-induced lipid buildup in the liver. The poly carbodiimide polymers chosen for functionalization have different zeta potentials

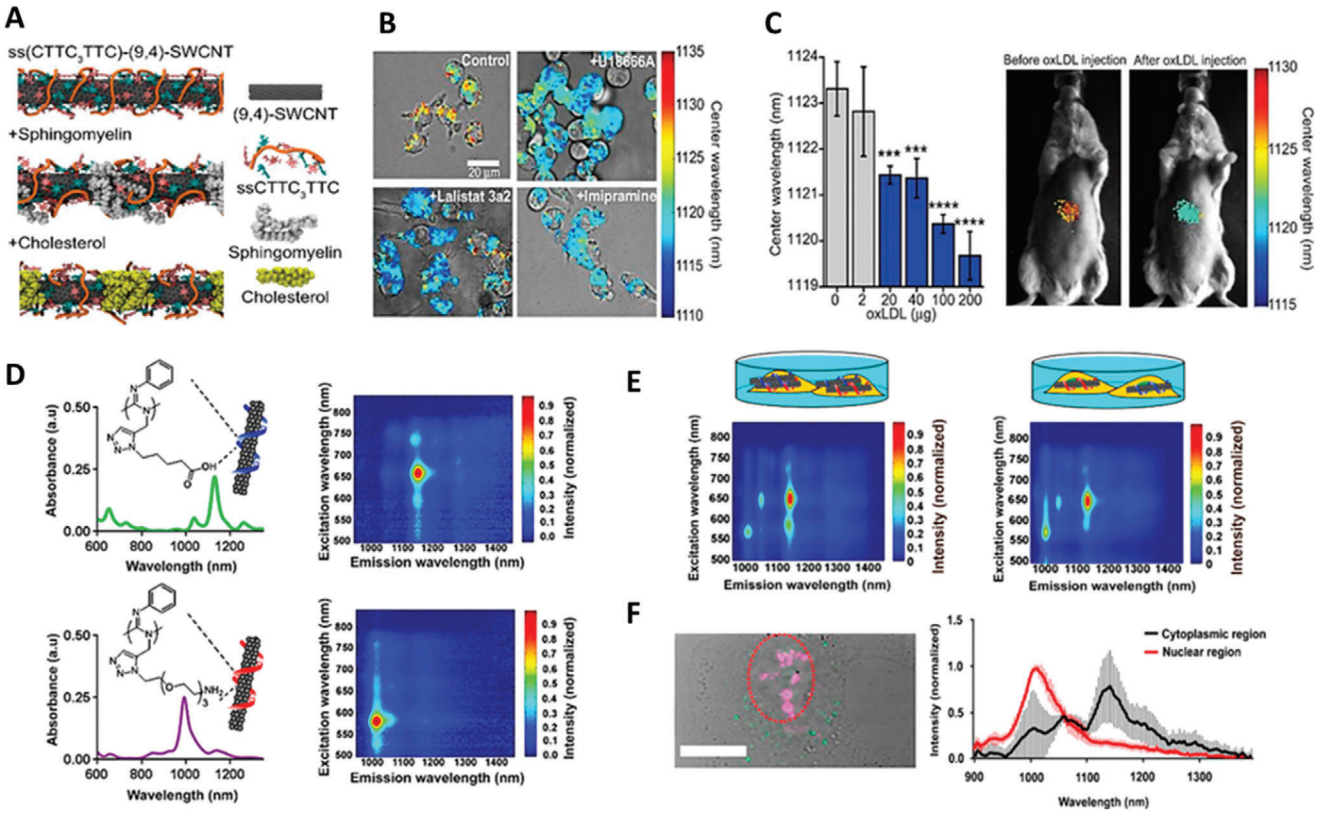


Figure 6. Sensing lipid accumulation and cellular localization: in vivo to identify metabolic conditions; A) Molecular dynamics simulations of isolated sDNA-CTTC3TTC-(9,4)-SWCNTSs imply that lipids (cholesterol or sphingomyelin) are adsorbed directly onto the surface of the nanotubes. Reproduced with permission.[35] 2022, Anal. Chem.; B) The overlays of transmitted light and fluorescence hyperspectral images demonstrate a specific blue-shift in the sensor emission wavelength of incubated target lipids.Reproduced with permission.[35] 2022, Anal. Chem.; C) Fluorescence hyperspectral imaging detects the endo-lysosomal lipid accumulation of oxidized low-density lipoproteins.Reproduced with permission.[153] 2018, Sci. Transl. Med.; D) Separated fractions of poly carbodiimide-modified SWCNTSs.Reproduced with permission.[35] 2022, Anal. Chem.; E) Co-incubation with nanosensors(left)leads to an energy transfer, targeting the same organelles, leading to a FRET-like mechanism of fluorescence enhancement of a certain chirality of SWCNTSs, enables live cell imaging.Reproduced with permission.[35] 2022, Anal. Chem.; F) Cellular structure detection with different nanosensor emission (975–1025 nm emission(magenta),1125–1175 nm emission(green)). Reproduced with permission. [85] 2021, Nano. Lett.

((6,5)amine-polySWCNTSsand (7,6)carboxy-polySWCNTSs), resulting in a Coulombic interaction between the primary amine group and carboxy acid group, leading to aggregation of SWCNTSs and thus inter nanotube (exciton) energy transfer.[35,85,153] Figure 6D shows the segmented regions of SWCNTSs modified with polycarbodiimide, containing carboxy-poly(7,6)- and amine-poly(6,5) SWCNTSs.[85,156]

Consequently, when cells were treated with both SWCNTS species, the (7,6)-SWCNTS chirality saw a relative fluorescence amplification, while the (6,5)-SWCNTSs were quenched (Figure 6E, left). The FRET effect was not detected when two cell cultures were treated individually with the two SWCNTS species and subsequently merged. (6,5)-SWCNTSs had a greater relative intensity (Figure 6E, right). Furthermore, the selective application of distinct surface chemistries may be exploited for multiplexed live cell imaging in various locations. As demonstrated in Figure 6F (6,5)guanidinium-poly-SWCNTSs are found in the nucleus of HeLa cells (magenta in brightfield), whereas (7,6)amine-poly-SWCNTSs are found in the cytosolic area (green in brightfield).[35,85,153]

6. Challenges and Limitations

Despite the tremendous promise of CNT-based fluorescence biosensors for disease diagnostics, several hurdles and constraints remain. A complete evaluation would most likely address these concerns to present a balanced picture of the current state of technology. Here are some important issues and limits related to SWCNTS-based fluorescence biosensors:

Biocompatibility Concerns: Potential cytotoxicity and long-term impacts on biological systems are the primary concern, especially because biocompatibility is crucial for the safe and successful diagnosis of CNTs in disease detection. For CNTs to be useful as fluorescence biosensors without endangering patients, it is crucial to functionalize and alter their surfaces to make them more biocompatible.[14] Uniform Functionalization: Achieving uniform and reproducible functionalization of carbon nanotubes with specific biomolecules can be challenging. Inhomogeneous functionalization may lead to variations in sensor performance, affecting sensitivity and reliability.[157] Nonspecific Binding SWCNTS-based biosensors may face challenges as

proteins and other biomolecules can adsorb onto the surfaces of carbon nanotubes through weaker interactions like physisorption, which is not selective and can lead to false signals in biosensors, especially in complex biological samples.[158,159] Strategies to minimize nonspecific interactions and improve the selectivity of the biosensors are essential.[160] The stability of SWCNTS-based biosensors over extended periods, especially under physiological conditions, is a critical factor for their practical applications. Numerous studies have demonstrated the appreciable stability of SWCNTSs in biological samples over a long time, which is a significant advantage of this nanomaterial. SWCNTSs exhibit excellent chemical and thermal stability, making them resistant to degradation in complex biological environments. Their unique structure and properties contribute to their ability to maintain sensor functionality over prolonged periods. For example, a study by Kim et al. demonstrated that a SWCNTS-based glucose biosensor maintained its sensitivity and selectivity for over 30 days when stored in a physiological buffer solution. Similarly, a SWCNTS-based DNA sensor showed stable performance for up to 6 months when stored at 4 °C. The functionalization of SWCNTSs with biocompatible coatings, such as polymers or proteins, can further enhance their stability and biocompatibility, preventing nonspecific adsorption and biofouling. These coatings act as protective layers, shielding the SWCNTSs from potential degradation factors in biological environments. However, it is important to note that while SWCNTSs themselves exhibit excellent stability, the long-term functionality of the biosensor as a whole may still be influenced by factors such as the stability of the biorecognition elements, the robustness of the immobilization methods, and the potential for sensor fouling over time. Interference and Background Signals: Background signals, interference from other biomolecules, or environmental factors can affect the accuracy and specificity of detection.[161] Developing strategies to minimize interference and enhance signal-to-noise ratios is essential. Device Miniaturization and Integration: While there is potential for point-of-care applications, miniaturizing SWCNTS-based fluorescent biosensors and integrating them into user-friendly devices pose engineering challenges. Practical implementation for widespread use requires addressing device size, portability, and ease of use.[162]

Regulatory hurdles in the translation of SWCNTS-based fluorescent biosensors from research to clinical applications may face regulatory challenges. Ensuring compliance with regulatory standards and demonstrating the safety and efficacy of these biosensors are critical for their acceptance in the medical field. Cost and Scalability: The cost of producing SWCNTS-based fluorescent biosensors, including the synthesis and functionalization of carbon nanotubes, may limit their widespread adoption. Scalability and cost-effectiveness are essential for practical applications, especially in resource-limited settings. Real-time Monitoring Challenges: SWCNTSs' NIR fluorescence and great photostability enable monitoring over time without signal loss.[163] Due to their seconds–minutes response periods, SWCNTS-based biosensors can also capture dynamic chemical interactions. SWCNTS-based biosensors have made tremendous progress in real-time monitoring, although there is still room for development. Improved temporal resolution and sensor design can capture faster and more subtle biological process changes.[30] Advanced sensor architectures, signal transduction processes, and SWCNTS-based biosensor integration with microfluidic systems for high-throughput and multiplexed real-time monitoring are being explored to overcome the remaining obstacles to fully harness the capabilities of this technology for continuous and real-time monitoring of intricate biological systems.[164] These findings will have substantial consequences for the identification of diseases, the development of new drugs, and the investigation of fundamental biological processes.[165,166] In addressing these challenges, researchers can pave the way for successfully applying SWCNTS-based fluorescent biosensors in disease diagnosis, offering highly sensitive and specific early detection and monitoring tools. Ongoing interdisciplinary collaborations and advancements in nanotechnology, materials science, and biology are essential for overcoming these limitations and realizing the full potential of this technology.[166]

7. Future Perspective and Conclusion

The potential of SWCNTS-based fluorescent biosensors to enhance bioimaging and biosensing applications is highly promising. As the study of this topic progresses, numerous crucial issues require focus and investigation in future endeavors that should prioritize the improvement of both the sensitivity and selectivity of fluorescence biosensors based on single-walled carbon nanotubes SWCNTSs. This may need the creation of innovative surface alterations, the use of composite materials, and the implementation of methodologies to enhance the amplification of signals. These advancements will enable the detection of analytes at even more diluted concentrations with greater accuracy. Incorporating SWCNTSs into multimodal imaging systems suggests a promising direction for future study. Researchers can enhance the capabilities of biological imaging and disease diagnostics by integrating fluorescence imaging with other modalities like Raman or photoacoustic imaging.

Further investigation into the in vivo uses of biosensors based on SWCNTSs is crucial. This entails examining the biocompatibility, biodistribution, and clearance profiles of these substances to enable their secure and efficient utilization for the real-time monitoring of biological processes and the advancement of diseases within live organisms. Translating SWCNTS-based biosensors from the laboratory to clinical settings is of utmost importance. This will need comprehensive validation studies, the capacity to scale up production processes, and careful attention to regulatory requirements to guarantee the safety and effectiveness of these products for diagnostic and therapeutic purposes. The utilization of SWCNTS fluorescence biosensors in point-of-care diagnostic gadgets has the capacity to completely transform the way healthcare is provided. Subsequent investigations should prioritize the development of portable and user-friendly technologies that can swiftly and precisely diagnose diseases at the patient's bedside or in situations with limited resources.

In conclusion, the distinct optical characteristics of SWCNTSs have established them as adaptable fundamental components for advancing fluorescent biosensors, which have extensive implications for applications in bioimaging and biosensing. The intrinsic properties of SWCNTSs, such as their near-infrared fluorescence, non-photobleaching characteristics, and wide surface area, provide significant benefits for the accurate and specific detection of various substances, including biomolecules,

pathogens, and disease biomarkers. As ongoing research progresses, there is significant potential for converting biosensors based on SWCNTSs into practical instruments for illness detection, real-time monitoring, and tailored medication. This advancement will eventually enhance healthcare outcomes and improve quality of life.

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Conflict of Interest

The authors declare no conflicts of interest.

Keywords

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[1] V. Chaudhary, V. Khanna, H. T. A. Awan, K. Singh, M. Khalid, Y. K. Mishra, S. Bhansali, C.-Z. Li, A. Kaushik, *Biosens. Bioelectron.* **2023**, *220*, 114847.
[2] D. Bhatia, S. Paul, T. Acharjee, S. S. Ramachairy, *Sens Int* **2024**, *5*, 100257.
[3] R. G. Kerry, K. E. Ukhurebor, S. Kumari, G. K. Maurya, S. Patra, B. Panigrahi, S. Majhi, J. R. Rout, M. del Pilar Rodriguez-Torres, G. Das, *Biomater. Sci.* **2021**, *9*, 3576.
[4] A. K. Singh, S. Mittal, M. Das, A. Saharia, M. Tiwari, *Alexandria Eng. J.* **2023**, *67*, 673.
[5] U. Chadha, P. Bhardwaj, R. Agarwal, P. Rawat, R. Agarwal, I. Gupta, M. Panjwani, S. Singh, C. Ahuja, S. K. Selvaraj, *J Ind Eng Chem* **2022**, *109*, 21.
[6] T. Thirugnanasambandan, S. Ramanathan, S. C. Gopinath, *Nano-Struct. Nano-Objects* **2024**, *38*, 101128.
[7] D. C. Ferrier, K. C. Honeychurch, *Biosensors* **2021**, *11*, 486.
[8] M. Ramesh, R. Janani, C. Deepa, L. Rajeshkumar, *Biosensors* **2022**, *13*, 40.
[9] M. Marzana, M. M. A. Khan, A. Ahmed, M. A. Jalil, M. M. Hossain, in *Nanomaterials for biocatalysis*, Elsevier, Amsterdam, Netherlands **2022**, pp. 689–714.
[10] J. Ackermann, J. T. Metternich, S. Herbertz, S. Kruss, *Angew. Chem., Int. Ed.* **2022**, *61*, 202112372.
[11] J. Janssen, M. Lambeta, P. White, A. Byagowi, *Biosensors* **2019**, *9*, 144.
[12] R. Varghese, S. Salvi, P. Sood, J. Karsiya, D. Kumar, *Colloid Interface Sci. Commun.* **2022**, *46*, 100544.
[13] M. Yoon, Y. Lee, S. Lee, Y. Cho, D. Koh, S. Shin, C. Tian, Y. Song, J. Kang, S.-Y. Cho, *Sensors & Diagnostics* **2024**, *3*, 203.
[14] W. Yang, K. R. Ratinac, S. P. Ringer, P. Thordarson, J. J. Gooding, F. Braet, *Angew. Chem., Int. Ed.* **2010**, *49*, 2114.
[15] A. A. Boghossian, J. Zhang, P. W. Barone, N. F. Reuel, J. H. Kim, D. A. Heller, J. H. Ahn, A. J. Hilmer, A. Rwei, J. R. Arkalgud, *ChemSusChem* **2011**, *4*, 848.
[16] F. Zhang, B. Z. Tang, *Chem. Sci.* **2021**, *12*, 3377.
[17] Y. Chen, S. Wang, F. Zhang, *Nature Reviews Bioengineering* **2023**, *1*, 60.
[18] N. Manikandan, S. K. VP, G. Rathis, T. Shabariganesh, *Mater Today Proc* **2021**, *47*, 4682.
[19] M. R. Predtechenskiy, A. A. Khasin, A. E. Bezrodny, O. F. Bobrenok, D. Y. Dubov, V. E. Muradyan, V. O. Saik, S. N. Smirnov, *Carbon Trends* **2022**, *8*, 100175.
[20] L. Xu, *Doctoral Thesis*, University of Basel, Basel, Switzerland **2020**.
[21] W. R. Algar, M. Massey, K. Rees, R. Higgins, K. D. Krause, G. H. Darwish, W. J. Peveler, Z. Xiao, H.-Y. Tsai, R. Gupta, *Chem. Rev.* **2021**, *121*, 9243.
[22] T. Watabe, K. Terai, K. Sumiyama, M. Matsuda, *ACS Sens.* **2020**, *5*, 719.
[23] T. Li, S. D. Soelberg, Z. Taylor, V. Sakthivelpathi, C. E. Furlong, J.-H. Kim, S.-g. Ahn, P. D. Han, L. M. Starita, J. Zhu, *Biosensors* **2022**, *12*, 149.
[24] J. Zhou, M. Bagheri, T. Jarvinen, C. Pravda Bartus, A. Kukovecz, H.-P. Komsa, K. Kordas, *ACS Appl. Mater. Interfaces* **2021**, *13*, 59067.
[25] Y. Yang, Y. Yang, Y. Cao, X. Wang, Y. Chen, H. Liu, Y. Gao, J. Wang, C. Liu, W. Wang, J.-K. Yu, D. Wu, *Chem. Eng. J.* **2021**, *403*, 126431.
[26] A. Refaat, M. L. Yap, G. Pietersz, A. P. G. Walsh, J. Zeller, B. Del Rosal, X. Wang, K. Peter, *J. Nanobiotechnol.* **2022**, *20*, 450.
[27] G. Hong, Y. Zou, A. L. Antaris, S. Diao, D. Wu, K. Cheng, X. Zhang, C. Chen, B. Liu, Y. He, *Nat. Commun.* **2014**, *5*, 4206.
[28] J. Cao, B. Zhu, K. Zheng, S. He, L. Meng, J. Song, H. Yang, *Frontiers in bioengineering and biotechnology* **2020**, *7*, 487.
[29] G. C. Mo, C. Posner, E. A. Rodriguez, T. Sun, J. Zhang, *Nat. Commun.* **2020**, *11*, 1848.
[30] S. Basu, A. Hendler-Neumark, G. Bisker, *Small* **2024**, 2309481.
[31] M. Kim, D. Goerzen, P. V. Jena, E. Zeng, M. Pasquali, R. A. Meidl, D. A. Heller, *Nat. Rev. Mater.* **2024**, *9*, 63.
[32] T. V. Galassi, M. Antman-Passig, Z. Yaari, J. Jessurun, R. E. Schwartz, D. A. Heller, *PLoS One* **2020**, *15*, e0226791.
[33] S. Kruss, A. J. Hilmer, J. Zhang, N. F. Reuel, B. Mu, M. S. Strano, *Adv. Drug Delivery Rev.* **2013**, *65*, 1933.
[34] S. Tyagi, F. R. Kramer, *Nat. Biotechnol.* **1996**, *14*, 303.
[35] R. Nißler, J. Ackermann, C. Ma, S. Kruss, *Anal. Chem.* **2022**, *94*, 9941.
[36] R. B. Weisman, J. Kono, in *Introduction to Optical Spectroscopy of Single-Wall Carbon Nanotubes*, World Scientific, Singapore **2019**, pp. 1–43.
[37] S. Van Bezouw, D. H. Arias, R. Ihly, S. Cambré, A. J. Ferguson, J. Campo, J. C. Johnson, J. Defillet, W. Wenseleers, J. L. Blackburn, *ACS Nano* **2018**, *12*, 6881.
[38] P. Ratre, N. Nazeer, R. Kumari, S. Thareja, B. Jain, R. Tiwari, A. Kamthan, R. K. Srivastava, P. K. Mishra, *Biosensors* **2023**, *13*, 226.
[39] C. Gao, M. Guo, Y. Liu, D. Zhang, F. Gao, L. Sun, J. Li, X. Chen, M. Terrones, Y. Wang, *Carbon* **2023**, *212*, 118133.
[40] T. Anilkumar, in *Carbon Nanotubes for Biomedical Applications and Healthcare*, Apple Academic Press, New Jersey **2024**, pp. 19–43.
[41] D. L. Kirkpatrick, M. Weiss, A. Naumov, G. Bartholomeusz, R. B. Weisman, O. Gliko, *Materials* **2012**, *5*, 278.
[42] P. P. Komane, Y. E. Choonara, L. C. du Toit, P. Kumar, P. P. Kondiah, G. Modi, V. Pillay, *J. Nanomater.* **2016**, *2016*, 9417874.
[43] M. R. Preciado-Rivas, V. A. Torres-Sánchez, D. J. Mowbray, *Phys. Rev. B* **2019**, *100*, 235429.

[44] M. V. Kharlamova, C. Kramberger, *Nanomaterials* **2021**, *12*, 42.
[45] F. Yang, M. Wang, D. Zhang, J. Yang, M. Zheng, Y. Li, *Chem. Rev.* **2020**, *120*, 2693.
[46] G. Bisker, J. Dong, H. D. Park, N. M. Iverson, J. Ahn, J. T. Nelson, M. P. Landry, S. Kruss, M. S. Strano, *Nat. Commun.* **2016**, *7*, 10241.
[47] M. F. Naseh, J. R. Ansari, M. S. Alam, M. N. Javed, in *Handbook of Green and Sustainable Nanotechnology: Fundamentals, Developments and Applications*, Springer, Berlin, Germany **2023**, pp 1985–2006.
[48] P. R. Bandaru, *J. Nanosci. Nanotechnol.* **2007**, *7*, 1239.
[49] A. Dillon, *Chem. Rev.* **2010**, *110*, 6856.
[50] S. Kumar, M. Nehra, D. Kedia, N. Dilbaghi, K. Tankeshwar, K.-H. Kim, *Prog. Energy Combust. Sci.* **2018**, *64*, 219.
[51] R. Nißler, F. A. Mann, H. Preiß, G. Selvaggio, N. Herrmann, S. Kruss, *Nanoscale* **2019**, *11*, 11159.
[52] H. Meskher, T. Ragdi, A. K. Thakur, S. Ha, I. Khelfaoui, R. Sathyamurthy, S. W. Sharshir, A. Pandey, R. Saidur, P. Singh, *Crit. Rev. Anal. Chem.* **2023**, 1, https://doi.org/10.1080/10408347.2023.2171277.
[53] D. K. Han, C. A. Li, S. H. Song, K. Cho, J.-S. Choi, S. E. Son, G. H. Seong, *J Anal Sci Technol* **2023**, *14*, 9.
[54] S. Kumar, H. Sidhu, A. K. Paul, N. Bhardwaj, N. S. Thakur, A. Deep, *Sensors & Diagnostics* **2023**, *2*, 1390.
[55] P. Galonska, J. M. Mohr, C. A. Schrage, L. Schnitzler, S. Kruss, *J. Phys. Chem. Lett.* **2023**, *14*, 3483.
[56] A. Spreinat, M. M. Dohmen, J. Lüttgens, N. Herrmann, L. F. Klepzig, R. Nißler, S. Weber, F. A. Mann, J. Lauth, S. Kruss, *J. Phys. Chem. C* **2021**, *125*, 18341.
[57] C. J. Shearer, A. Cherevan, D. Eder, *Adv. Mater.* **2014**, *26*, 2295.
[58] T. Shiraki, Y. Miyauchi, K. Matsuda, N. Nakashima, *Acc. Chem. Res.* **2020**, *53*, 1846.
[59] S. M. Monavari, F. Marsusi, N. Memarian, M. Qasemnazhand, *Sci. Rep.* **2023**, *13*, 3118.
[60] M. Safari, A. Moghaddam, A. S. Moghaddam, M. Absalan, B. Kruppke, H. Ruckdäschel, H. A. Khonakdar, *Talanta* **2023**, *258*, 124399.
[61] N. M. Iverson, P. W. Barone, M. Shandell, L. J. Trudel, S. Sen, F. Sen, V. Ivanov, E. Atolia, E. Farias, T. P. McNicholas, *Nat. Nanotechnol.* **2013**, *8*, 873.
[62] S. Malik, J. Singh, R. Goyat, Y. Saharan, V. Chaudhry, A. Umar, A. A. Ibrahim, S. Akbar, S. Ameen, S. Baskoutas, *Heliyon* **2023**, *9*, e19929.
[63] P. Liu, X. Mu, X.-D. Zhang, D. Ming, *Bioconjugate Chem.* **2019**, *31*, 260.
[64] P. Liu, Y. Jiao, X. Chai, Y. Ma, S. Liu, X. Fang, F. Fan, L. Xue, J. Han, Q. Liu, *J. Lumin.* **2022**, *250*, 119084.
[65] A. Hendler-Neumark, V. Wulf, G. Bisker, *ACS Sens.* **2023**, *8*, 3713.
[66] N.-N. Zhang, C.-Y. Lu, M.-J. Chen, X.-L. Xu, G.-F. Shu, Y.-Z. Du, J.-S. Ji, *J. Nanobiotechnol.* **2021**, *19*, 132.
[67] J. D. Harvey, H. A. Baker, M. V. Ortiz, A. Kentsis, D. A. Heller, *ACS Sens.* **2019**, *4*, 1236.
[68] Y. Miao, C. Gu, Y. Zhu, B. Yu, Y. Shen, H. Cong, *ChemBioChem* **2018**, *19*, 2522.
[69] W. C. Yang, S. Y. Li, S. Ni, G. Liu, *Aggregate* **2023**, *5*, e460.
[70] Y. Wu, T. Jiang, *Micromachines* **2022**, *13*, 1789.
[71] M. Imani, N. Mohajeri, M. Rastegar, N. Zarghami, *Anal. Biochem.* **2021**, *630*, 114323.
[72] M. Dong, J. Guo, Q. Liu, J. Zeng, X. Xiong, X. Gai, Y. Wang, Y. Wu, *J. Environ. Chem. Eng.* **2023**, *11*, 110131.
[73] A. Menon, Y. L. Slominskii, J. Joseph, O. P. Dimitriev, D. M. Guldi, *Small* **2020**, *16*, 1906745.
[74] M. Wu, X. Fu, J. Li, W. Zhao, X. Li, *Sep. Purif. Technol.* **2024**, *338*, 126328.
[75] Y. Su, B. Yu, S. Wang, H. Cong, Y. Shen, *Biomaterials* **2021**, *271*, 120717.
[76] R. E. Gwyther, N. P. Nekrasov, A. V. Emelianov, A. G. Nasibulin, K. Ramakrishnan, I. Bobrinetskiy, D. D. Jones, *Adv. Funct. Mater.* **2022**, *32*, 2112374.
[77] V. Zubkovs, S.-J. Wu, S. Y. Rahnamaee, N. Schuergers, A. A. Boghossian, *Chem. Mater.* **2020**, *32*, 8798.
[78] T. Basche, A. Bottin, C. Li, K. Muellen, J. H. Kim, B. H. Sohn, P. Prabhakaran, K. S. Lee, *Macromol. Rapid Commun.* **2015**, *36*, 1026.
[79] A. R. Gopal, F. Joy, V. Dutta, J. Devasia, R. Dateer, A. Nizam, *Part. Part. Syst. Charact.* **2024**, *41*, 2300072.
[80] M. J. Molaei, *Anal. Methods* **2020**, *12*, 1266.
[81] W. Zhou, X. Bai, E. Wang, S. Xie, *Adv. Mater.* **2009**, *21*, 4565.
[82] A. Zawadzka, P. Płóciennik, A. Korcala, P. Szroeder, *Optical Materials* **2019**, *96*, 109295.
[83] A. Abbas, S. Zehra, R. Aslam, M. Mobin, S. Islam bhat, in *Functionalized Carbon Nanotubes for Biomedical Applications*, (Eds: J. Aslam, C. M. Hussain, R. Aslam), Scrivener Publishing LLC, Beverly **2023**, pp. 197–223.
[84] S. Settele, C. A. Schrage, S. Jung, E. Michel, H. Li, B. S. Flavel, A. S. K. Hashmi, S. Kruss, J. Zaumseil, *Nat. Commun.* **2024**, *15*, 706.
[85] R. Langenbacher, J. Budhathoki-Uprety, P. V. Jena, D. Roxbury, J. Streit, M. Zheng, D. A. Heller, *Nano Lett.* **2021**, *21*, 6441.
[86] V. V. Sinitsyna, A. A. Vetcher, *Biomedicines* **2022**, *10*, 1079.
[87] K. de Almeida Barcelos, J. Garg, D. C. F. Soares, A. L. B. de Barros, Y. Zhao, L. Alisaraie, *J Drug Deliv Sci Technol* **2023**, *87*, 104834.
[88] A. Antonucci, J. Kupis-Rozmysłowicz, A. A. Boghossian, *ACS Appl. Mater. Interfaces* **2017**, *9*, 11321.
[89] A. J. Gillen, A. A. Boghossian, *Front Chem* **2019**, *7*, 612.
[90] N. T. Tung, P. T. Tue, T. Thi Ngoc Lien, Y. Ohno, K. Maehashi, K. Matsumoto, K. Nishigaki, M. Biyani, Y. Takamura, *Sci. Rep.* **2017**, *7*, 17881.
[91] Y. Zhou, Y. Fang, R. P. Ramasamy, *Sensors* **2019**, *19*, 392.
[92] M. Assali, N. Kittana, S. Alhaj-Qasem, M. Hajjyahya, H. Abu-Rass, W. Alshaer, R. Al-Buqain, *Sci. Rep.* **2022**, *12*, 12062.
[93] R. Dubey, D. Dutta, A. Sarkar, P. Chattopadhyay, *Nanoscale Adv* **2021**, *3*, 5722.
[94] H. Yoo, H. Jo, S. S. Oh, *Materials Advances* **2020**, *1*, 2663.
[95] D. R. Davies, A. D. Gelinas, C. Zhang, J. C. Rohloff, J. D. Carter, D. O'Connell, S. M. Waugh, S. K. Wolk, W. S. Mayfield, A. B. Burgin, *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 19971.
[96] E. Katz, I. Willner, *ChemPhysChem* **2004**, *5*, 1084.
[97] K. M. Abu-Salah, A. A. Ansari, S. A. Alrokayan, *Biomed Res. Int.* **2010**, *2010*, 715295.
[98] L. Chio, R. L. Pinals, A. Murali, N. S. Goh, M. P. Landry, *Adv. Funct. Mater.* **2020**, *30*, 1910556.
[99] S. Han, W. Liu, M. Zheng, R. Wang, *Anal. Chem.* **2020**, *92*, 4780.
[100] E. S. Jeng, J. D. Nelson, K. L. Prather, M. S. Strano, *Small* **2010**, *6*, 40.
[101] P. Clément, J. Ackermann, N. Sahin-Solmaz, S. Herbertz, G. Boero, S. Kruss, J. Brugger, *Biosens. Bioelectron.* **2022**, *216*, 114642.
[102] S. Daniel, T. P. Rao, K. S. Rao, S. U. Rani, G. Naidu, H.-Y. Lee, T. Kawai, *Sens. Actuators, B* **2007**, *122*, 672.
[103] J. Kupis-Rozmysłowicz, A. Antonucci, A. A. Boghossian, *ECS J. Solid State Sci. Technol.* **2016**, *5*, M3067.
[104] V. Zubkovs, H. Wang, N. Schuergers, A. Weninger, A. Glieder, S. Cattaneo, A. A. Boghossian, *Nanoscale Adv* **2022**, *4*, 2420.
[105] N. E. Kallmyer, J. Musielewicz, J. Sutter, N. F. Reuel, *Anal. Chem.* **2018**, *90*, 5209.
[106] R. L. Pinals, F. Ledesma, D. Yang, N. Navarro, S. Jeong, J. E. Pak, L. Kuo, Y.-C. Chuang, Y.-W. Cheng, H.-Y. Sun, *Nano Lett.* **2021**, *21*, 2272.
[107] V. Zubkovs, N. Schuergers, B. Lambert, E. Ahunbay, A. A. Boghossian, *Small* **2017**, *13*, 1701654.

[108] E. Hofferber, J. Meier, N. Herrera, J. Stapleton, C. Calkins, N. Iverson, *Nanomedicine* **2022**, *40*, 102489.
[109] J. Pan, F. Li, J. H. Choi, *J. Mater. Chem. B* **2017**, *5*, 6511.
[110] X. Wei, S. Li, W. Wang, X. Zhang, W. Zhou, S. Xie, H. Liu, *Adv. Sci.* **2022**, *9*, 2200054.
[111] C. Farrera, F. Torres Andón, N. Feliu, *ACS Nano* **2017**, *11*, 10637.
[112] S. Chatterjee, M. Castro, J. Feller, *Sens. Actuators, B* **2015**, *220*, 840.
[113] Y. Tian, M. Y. Timmermans, S. Kivistö, A. G. Nasibulin, Z. Zhu, H. Jiang, O. G. Okhotnikov, E. I. Kauppinen, *Nano Res.* **2011**, *4*, 807.
[114] Y. Zheng, S. M. Bachilo, R. B. Weisman, *J. Phys. Chem. Lett.* **2020**, *11*, 6492.
[115] O. V. Sedelnikova, V. I. Sysoev, O. A. Gurova, Y. P. Ivanov, V. O. Koroteev, R. Arenal, A. A. Makarova, L. G. Bulusheva, A. V. Okotrub, *Carbon* **2022**, *186*, 539.
[116] V. Shumeiko, E. Malach, Y. Helman, Y. Paltiel, G. Bisker, Z. Hayouka, O. Shoseyov, *Sens. Actuators, B* **2021**, *327*, 128832.
[117] V. Raphey, T. Henna, K. Nivitha, P. Mufeedha, C. Sabu, K. Pramod, *Mater. Sci. Eng., C* **2019**, *100*, 616.
[118] K. K. Zamansky, A. A. Osipova, F. S. Fedorov, D. S. Kopylova, V. Shunaev, A. Alekseeva, O. E. Glukhova, A. G. Nasibulin, *Appl. Surf. Sci.* **2023**, *640*, 158334.
[119] Y. Iizumi, M. Yudasaka, J. Kim, H. Sakakita, T. Takeuchi, T. Okazaki, *Sci. Rep.* **2018**, *8*, 6272.
[120] H. Wang, A. A. Boghossian, *Materials Advances* **2023**, *4*, 823.
[121] A. T. Krasley, E. Li, J. M. Galeana, C. Bulumulla, A. G. Beyene, G. S. Demirer, *Chem. Rev.* **2024**, *124*, 3085.
[122] R. Mohammadi, H. Naderi-Manesh, L. Farzin, Z. Vaezi, N. Ayarri, L. Samandari, M. Shamsipur, *J. Pharm. Biomed. Anal.* **2022**, *212*, 114628.
[123] J. Ackermann, J. Stegemann, T. Smola, E. Reger, S. Jung, A. Schmitz, S. Herbertz, L. Erpenbeck, K. Seidl, S. Kruss, *Small* **2023**, *19*, 2206856.
[124] C.-W. Lin, R. B. Weisman, *Nanomedicine* **2016**, *11*, 2885.
[125] R. Singh, S. Kumar, *Nanomaterials* **2022**, *12*, 2283.
[126] J. Zhao, D. Zhong, S. Zhou, *J. Mater. Chem. B* **2018**, *6*, 349.
[127] H. Huang, M. Zou, X. Xu, F. Liu, N. Li, X. Wang, *Trends Analyt Chem* **2011**, *30*, 1109.
[128] B. Kaur, S. Kumar, B. K. Kaushik, *Biosens. Bioelectron.* **2022**, *197*, 113805.
[129] A. M. Smith, M. C. Mancini, S. Nie, *Nat. Nanotechnol.* **2009**, *4*, 710.
[130] J. H. Kim, J. H. Ahn, P. W. Barone, H. Jin, J. Zhang, D. A. Heller, M. S. Strano, *Angew. Chem.* **2010**, *122*, 1498.
[131] C.-M. Tîlmaciu, M. C. Morris, *Front Chem* **2015**, *3*, 59.
[132] R. M. Williams, C. Lee, D. A. Heller, *ACS Sens.* **2018**, *3*, 1838.
[133] D. Amir, A. Hendler-Neumark, V. Wulf, R. Ehrlich, G. Bisker, *Adv. Mater. Interfaces* **2022**, *9*, 2101591.
[134] M. Kim, C. Chen, P. Wang, J. J. Mulvey, Y. Yang, C. Wun, M. Antman-Passig, H.-B. Luo, S. Cho, K. Long-Roche, *Nat. Biomed. Eng.* **2022**, *6*, 267.
[135] T. Rasheed, A. A. Hassan, F. Kausar, F. Sher, M. Bilal, H. M. Iqbal, *Trends Analyt Chem* **2020**, *132*, 116066.
[136] P. W. Barone, M. S. Strano, *J. Diabetes Sci. Technol.* **2009**, *3*, 242.
[137] K. Yum, T. P. McNicholas, B. Mu, M. S. Strano, *J. Diabetes Sci. Technol.* **2013**, *7*, 72.
[138] T. Yuwen, D. Shu, H. Zou, X. Yang, S. Wang, S. Zhang, Q. Liu, X. Wang, G. Wang, Y. Zhang, *J. Nanobiotechnol.* **2023**, *21*, 320.
[139] G. Selvaggio, M. Weitzel, N. Oleksiievets, T. A. Oswald, R. Nißler, I. Mey, V. Karius, J. Enderlein, R. Tsukanov, S. Kruss, *Nanoscale Adv* **2021**, *3*, 4541.
[140] R. Nißler, O. Bader, M. Dohmen, S. G. Walter, C. Noll, G. Selvaggio, U. Groß, S. Kruss, *Nat. Commun.* **2020**, *11*, 5995.
[141] G. Selvaggio, A. Chizhik, R. Nißler, I. Kuhlemann, D. Meyer, L. Vuong, H. Preiß, N. Herrmann, F. A. Mann, Z. Lv, *Nat. Commun.* **2020**, *11*, 1495.
[142] S. Kruss, M. P. Landry, E. Vander Ende, B. M. Lima, N. F. Reuel, J. Zhang, J. Nelson, B. Mu, A. Hilmer, M. Strano, *J. Am. Chem. Soc.* **2014**, *136*, 713.
[143] J.-H. Ahn, J.-H. Kim, N. F. Reuel, P. W. Barone, A. A. Boghossian, J. Zhang, H. Yoon, A. C. Chang, A. J. Hilmer, M. S. Strano, *Nano Lett.* **2011**, *11*, 2743.
[144] N. F. Reuel, J.-H. Ahn, J.-H. Kim, J. Zhang, A. A. Boghossian, L. K. Mahal, M. S. Strano, *J. Am. Chem. Soc.* **2011**, *133*, 17923.
[145] J. T. Nelson, S. Kim, N. F. Reuel, D. P. Salem, G. Bisker, M. P. Landry, S. Kruss, P. W. Barone, S. Kwak, M. S. Strano, *Anal. Chem.* **2015**, *87*, 8186.
[146] A. M. Münzer, Z. P. Michael, A. Star, *ACS Nano* **2013**, *7*, 7448.
[147] a) W. Yi, A. Khalid, N. Arshad, M. S. Asghar, M. S. Irshad, X. Wang, Y. Yi, J. Si, X. Hou, H. R. Li, *ACS Appl Bio Mater* **2023**, *6*, 2043; b) R. E. Langenbacher, in *In Situ Hybridization Nanoprobes to Investigate Mu Opioid Receptor Alternative Splicing*, Weill Medical College of Cornell University, New York **2021**.
[148] X. He, *Doctoral Dissertation*, Texas A&M University Libraries, Texas **2017**.
[149] J. Mondal, J. M. An, S. S. Surwase, K. Chakraborty, S. C. Sutradhar, J. Hwang, J. Lee, Y.-K. Lee, *Biosensors* **2022**, *12*, 731.
[150] a) P. V. Jena, C. Cupo, D. A. Heller, *Near Infrared-Emitting Nanoparticles for Biomedical Applications*, (Eds: A. Benayas, E. Hemmer, G. Hong, D. Jaque), Springer, Cham, New York City **2020**, pp. 103–132; b) H. Gong, R. Peng, Z. Liu, *Adv. Drug Delivery Rev.* **2013**, *65*, 1951.
[151] L. Liu, C. Yang, K. Zhao, J. Li, H.-C. Wu, *Nat. Commun.* **2013**, *4*, 2989.
[152] F. O. Gomes, L. B. Maia, J. A. Loureiro, M. C. Pereira, C. Delerue-Matos, I. Moura, J. J. Moura, S. Morais, *Bioelectrochemistry* **2019**, *127*, 76.
[153] T. V. Galassi, P. V. Jena, J. Shah, G. Ao, E. Molitor, Y. Bram, A. Frankel, J. Park, J. Jessurun, D. S. Ory, *Sci. Transl. Med.* **2018**, *10*, eaar2680.
[154] R. Nißler, L. Kurth, H. Li, A. Spreinat, I. Kuhlemann, B. S. Flavel, S. Kruss, *Anal. Chem.* **2021**, *93*, 6446.
[155] Y. Piao, B. Meany, L. R. Powell, N. Valley, H. Kwon, G. C. Schatz, Y. Wang, *Nat. Chem.* **2013**, *5*, 840.
[156] J. Budhathoki-Uprety, R. E. Langenbacher, P. V. Jena, D. Roxbury, D. A. Heller, *ACS Nano* **2017**, *11*, 3875.
[157] Y. Zheng, Y. Han, B. M. Weight, Z. Lin, B. J. Gifford, M. Zheng, D. Kilin, S. Kilina, S. K. Doorn, H. Htoon, *Nat. Commun.* **2022**, *13*, 4439.
[158] a) Y. Deng, L. Liu, J. Li, L. Gao, *Biosensors* **2022**, *12*, 776; b) R. J. Chen, S. Bangsaruntip, K. A. Drouvalakis, N. Wong Shi Kam, M. Shim, Y. Li, W. Kim, P. J. Utz, H. Dai, *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 4984.
[159] J. Y. Lichtenberg, Y. Ling, S. Kim, *Sensors* **2019**, *19*, 2488.
[160] a) V. Kumar, S. K. Raghuwanshi, S. Kumar, *IEEE Sens. J.* **2022**, *22*, 15661; b) H. Ehtesabi, *J. Sci.: Adv. Mater. Devices* **2020**, *5*, 436.
[161] L. Liu, X. Wei, Z. Yao, X. Li, W. Wang, Y. Wang, W. Zhou, F. Xiong, H. Kataura, S. Xie, *J. Phys. Chem. C* **2022**, *126*, 3787.
[162] P. Mishra, S. K. Tiwari, *Nanosensors for Futuristic Smart and Intelligent Healthcare Systems* **2022**, *1*, 19.
[163] H. Luo, S. Gao, *J. Controlled Release* **2023**, *362*, 425.
[164] J. H. Heo, M. Sung, T. Q. Trung, Y. Lee, D. H. Jung, H. Kim, S. Kaushal, N. E. Lee, J. W. Kim, J. H. Lee, *EcoMat* **2023**, *5*, e12332.
[165] Y. Xiang, C. Hu, G. Wu, S. Xu, Y. Li, *Trends Analyt Chem* **2023**, *158*, 116835.
[166] S. Gupta, C. Murthy, C. R. Prabha, *Int. J. Biol. Macromol.* **2018**, *108*, 687.
[167] A. K. Verma, A. Noumani, A. K. Yadav, P. R. Solanki, *Diagnostics* **2023**, *13*, 1375.
[168] C. Fang, Y. Huang, Y. Zhao, *Am. J. Transl. Res.* **2023**, *15*, 694.
[169] S. Nishitani, T. Tran, A. Puglise, S. Yang, M. P. Landry, *Angew. Chem., Int. Ed.* **2024**, *63*, 202311476.

[170] Z. Chen, J. Li, T. Li, T. Fan, C. Meng, C. Li, J. Kang, L. Chai, Y. Hao, Y. Tang, *Natl Sci Rev* **2022**, *9*, nwac104.
[171] R. Merindol, G. Delechiave, L. Heinen, L. H. Catalani, A. Walther, *Nat. Commun.* **2019**, *10*, 528.
[172] L. Chen, Y. Léger, G. Loget, M. Piriyev, I. Jadli, S. Tricot, T. Rohel, R. Bernard, A. Beck, J. Le Pouliquen, *Adv. Sci.* **2022**, *9*, 2101661.
[173] E. Tournié, L. Monge Bartolome, M. Rio Calvo, Z. Loghmari, D. A. Díaz-Thomas, R. Teissier, A. N. Baranov, L. Cerutti, J.-B. Rodriguez, *Light: Sci. Appl.* **2022**, *11*, 165.
[174] J. U. Sprenger, R. K. Perera, K. R. Götz, V. O. Nikolaev, *J. Vis. Exp.* **2012**, *66*, e4081.
[175] B. Hochreiter, A. Pardo Garcia, J. A. Schmid, *Sensors* **2015**, *15*, 26281.
[176] Y. Kamioka, K. Sumiyama, R. Mizuno, Y. Sakai, E. Hirata, E. Kiyokawa, M. Matsuda, *Cell Struct Funct* **2012**, *37*, 65.
[177] D. K. Tiwari, M. Tiwari, T. Jin, *Materials Advances* **2020**, *1*, 967.
[178] M. Sadoine, Y. Ishikawa, T. J. Kleist, M. M. Wudick, M. Nakamura, G. Grossmann, W. B. Frommer, C.-H. Ho, *Plant Physiol.* **2021**, *187*, 485.
[179] A. Miodek, N. Mejri, M. Gomgnimbou, C. Sola, H. Korri-Youssoufi, *Anal. Chem.* **2015**, *87*, 9257.
[180] M. Ovais, M. You, J. Ahmad, R. Djellabi, A. Ali, M. H. Akhtar, M. Abbas, C. Chen, *Elsevier* **2022**, *153*, 116659.
[181] S. Ding, A. A. Cargill, S. R. Das, I. L. Medintz, J. C. Claussen, *Sensors* **2015**, *15*, 14766.

Rumi Acharya is a doctoral student in biosystems engineering at Kangwon National University, South Korea. She received her master's degree from Guru Ghasidas University, India. Her research interests are nano biosensors and magnetogenetic therapy on cellular targets.

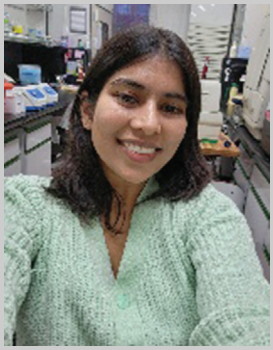
Tejal V. Patil is a doctoral student of biosystems engineering at Kangwon National University, SouthKorea. She received her master's degree from the Institute of Chemical Technology, Mumbai, India. Her research interest is developing biomaterials for application in bacteria eradication and tissue regeneration.

Sayan Deb Dutta is a postdoctoral research fellow at the School of Medicine, University of California Davis, United States. He was awarded the Shriners Hospital for Children Fellowship Training for surgical bioengineering. He received his doctoral degree from the Department of biosystems engineering at Kangwon National University, South Korea. He reviewed his master's degree from the University of Kalyani, India. His research interest is the synthesis of multifunctional nanomaterials for 3D printing and nanotheranostic applications for tissue engineering. Currently, he is working on exosome-based smart hydrogel patches for fetal tissue regeneration.

Jieun Lee is a master's student in biosystems engineering at Kangwon National University, South Korea. Her research is the development of various conductive 3D hydrogels for tissue regeneration and healing.

Keya Ganguly is a postdoctoral research associate at Kangwon National University. She received her doctoral degree from the Department of biosystems engineering at Kangwon National University, South Korea. She received her Master's degree from Presidency University, India. Her research interest is developing a multi-stimuli-assisted scaffolding platform for tissue engineering and biosensing.

Hojin Kim is a master's student in biosystems engineering at Kangwon National University, South Korea. His research interest is nanocellulose hydrogel for wound healing and sensing.



Aayushi Randhawa is a doctoral student in biosystems engineering at Kangwon National University, South Korea. She received her Master's degree from Bangalore University, India. Her research interests are in the synthesis of 3D-printed structures for the healing and regeneration of damaged bone tissues.

Ki-Taek Lim is a professor at the department of biosystems Engineering at Kangwon National University, South Korea. He received his doctoral degree from Seoul National University, South Korea, and joined as a postdoctoral research fellow at the University of Arkansas, USA. He has a strong knowledge of mechatronics and regenerative medicines. His research focuses on developing the bio-nanorobotics system with novel bioreactors and stem cell cultures for tissue-engineering applications.