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Nanotools for Nanoanalysis and Nanomanipulation: A Review

Mazaher Ahmadi[a,*], Narges Bastan[a], Reyhaneh Amini[b], Fatemeh Goharpour[c], Maedeh Boroon[a], Rozhin Radmanesh[a], Sepideh Asadi[a] and Seyed Sepehr Uroomiye[d]

[a]*Department of Analytical Chemistry, Faculty of Chemistry and Petroleum Sciences, Bu-Ali Sina University, Hamedan, Iran*

[b]*Faculty of Chemistry and Petroleum Sciences, Shahid Beheshti University, Tehran, Iran*

[c]*Faculty of Basic Sciences, Bu-Ali Sina University, Hamedan, Iran*

[d]*Department of Pharmacology and Toxicology, Faculty of Pharmacy, Hamadan University of Medical Sciences, Hamadan, Iran*

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The recent decade has seen a huge impact of nanotechnology in different sciences. In analytical chemistry, nanomaterials have been utilized for various purposes from sample preparation to detection. The impact of nanotechnology in analytical science is not limited to the improvement of analytical methodologies. Nanomaterials have been utilized for nanomaterials analysis as nanotools. Nanotools are used to investigate and work with materials at the nanoscale. Nanotechnology has also enabled new applications such as nanoscale tips used for topological microscopy in atomic force microscopy, scanning tunneling microscopy, and magnetic force microscopy. These techniques utilize nanotechnology to improve their efficiency. Furthermore, nanotechnology has enabled the construction of tweezers and robots in the nanoscale. These nano-enabled tools (nanotools) have been successfully utilized for nanoanalysis and nanomanipulation. Atomic force microscopy, scanning tunneling microscope, and magnetic force microscopy are not only meant to image nanostructured surfaces but also they are utilized for the manipulation of materials at the atomic and nanoscale. Nanotweezers, nanorobots, and laser tweezers using nanoapertures are also able to manipulate nano and microscale materials. This paper reviews the principles and application of the mentioned nano-enabled techniques as nanotools in analytical chemistry with a focus on nanomaterials nanoanalysis and nanomanipulation as nanoanalytes.

Keywords: Atomic force microscopy, Scanning tunneling microscope, Magnetic force microscopy, Nanotweezers, Nanorobotics, Nanoapertures

INTRODUCTION

Specialized devices called nanotools are used to analyze and manipulate materials at the nanoscale. These devices are crucial for nanoanalysis and manipulation of nanomaterials at the atomic and molecular level with extreme precision and accuracy. Numerous disciplines, including biology, chemistry, physics, and nanotechnology, employ nanotools [1,2]. Nanotools allow scientists to investigate the characteristics and behavior of materials at the nanoscale, which may result in the creation of novel tools and uses. Generally speaking, nanotools are essential to advancing our knowledge of materials at the nanoscale and their uses in several disciplines [3]. Among these tools, atomic force microscope (AFM), scanning tunneling microscope (STM), magnetic force microscope (MFM), nanotweezers, nanorobotics, and nanoapertures have been reviewed in this paper.

*Corresponding author. E-mail: ahmadi.mazaher@yahoo.com

Atomic Force Microscope Probe Tips

As one of the scanning probe microscopy techniques, AFM was created to address the fundamental shortcoming of STM, which can only image conductive or semi-conducting surfaces. Atomic-level tracing of sample topology is possible using the AFM technique, formerly known as the scanning force microscope [4,5]. Measuring extremely tiny forces (less than one micronewton) between the probe tip and the sample surface was the purpose of the development of AFM in 1986. Forceps deviate or bend due to forces acting on the sample's surface; the forceps' deviation is measured by a detector as the needle goes over the sample's surface. The topographical image of the surface may be generated by the computer by measuring the deviation of the forceps. Optical techniques are used in the majority of available AFM devices to identify the forceps position [6]. Using a sharp tip that is two micrometers long and frequently has a diameter of less than 10 nm, the AFM examines the sample's surface. The needle, which is between 100 and 450 micrometers long, is found at the free end of a pair of tweezers [7]. The tip geometry and shape in AFM regulate lateral resolution. The radius of curvature at the apex of a pyramid formed by conventional microfabrication techniques is typically less than 10 nm [6]. A position-sensitive optical detector receives a reflected laser beam that strikes the rear of the tongs. The position of the laser beam on the detector is altered by bending the tongs, and a displacement as small as one nanometer may be measured by the position-sensitive optical detector. Several forces, often known as interatomic or van der Waals forces, contribute to the AFM forceps' deflection. An ideal AFM tip should have precisely specified geometry and chemistry, have the smallest feasible tip dimensions, and be able to image for an extended time without sacrificing resilience due to its consistent geometry. The goal of AFM analysis is to produce tips that are not only smaller but also work longer [6].

Silicon was employed as an AFM probe tip in the 1980s. However, as nanotechnology has advanced, silicon and silicon nitride have been replaced by new nanomaterials. Japanese scientists created the first nanomaterial-based probe tip in 1999. Since then, there has been an increase in the usage of nanomaterials as AFM probe tips to improve accuracy and efficiency. Nanomaterials can generate probe tips more precisely and efficiently because of their small size and special mechanical and electrical qualities. Furthermore, nanoparticles may be used to coat the tip surfaces, which increases the accuracy and dependability of the probe tips. Typically, nanomaterials like magnetic nanoparticles, carbon nanotubes (CNTs), or even functionalized proteins are used to make AFM probe tips. Clearness, strong durability resistance to wear, and good conductivity are all desirable properties in a probe. Probes with a metal coating are often appropriate for analyses with high conductivity or resolution. Adsorbed metal nanoclusters on two-dimensional materials produced on metal substrates present an appealing platform with additional controlled tip sharpening options. Different metals (*e.g.*, Ir, Au, Ni, Co, Pb, or Sn) may be readily included in these metal clusters to create nanotips with a variety of applications [8, 9].

Nanoparticles Used for Construction of AFM Tips

Metal nanoclusters. Because of their proximity to the electron's Fermi wavelength, metal nanoclusters, which are made up of several hundred atoms, typically have electrical and optical characteristics similar to molecules. They are found between nanoparticles and molecular compounds. Significant reductions in van der Waals interactions between tip and sample and improvements in spatial resolution may be achieved with AFM tips sharpened by removing metal nanoclusters [10].

Metal nanowire probe. High aspect ratio structures like nanowires are becoming a popular research subject. For nanowire scanning probes, toughness and endurance are just as critical as their basic shape. Tungsten nanowire probes have a diameter of 5 to 10 nm and are made up of a tungsten metal core encased in a 3 to 6 nm substance. This method successfully creates metal nanowire probes with high aspect ratios (lengths of 100 nm to 1.5 μm) and tiny curvature radii (1-2 nm), enabling the detection of particular single-walled nanotube topologies [11].

Carbon nanotube probes. Because of their small diameter, high surface area, mechanical strength, and well-defined structure, carbon nanotubes (CNTs) are thought to be the perfect material for AFM tips. In comparison to their typical silicon equivalents, CNT probes in AFM microscopy offer a longer lifespan, superior spatial resolution, and exceptional sensitivity. Typically, growth and assembly techniques are used to prepare CNT probes. These CNTs withstand wear well and have a high surface area. As a result, they more precisely represent the sample's correct form in sloping areas [6].

Assembled carbon nanotubes probe. This process entails growing, cleaning, and transferring CNTs into a cartridge before transferring them to the tip in the presence of an electric field. This process results in CNT tips with excellent mechanical stability and adhesion. This sort of approach is rather time-consuming to create CNTs on the tip of the probe since it requires monitoring with a scanning electron microscope during the transfer process [12].

Grown carbon nanotube probe. Increased bonding strength between CNT tips and AFM probes is possible with the direct development of CNTs using chemical vapor deposition (CVD). Hafner *et al.* employed a pore development approach [9]. The silicon tip is smoothed using contact-mode AFM imaging, and then hydrogen fluoride oxidation at the anode forms 50-100 nm diameter nanopores. Following electrodeposition, CVD is used to generate CNTs at 750 °C. The process yields tips with an average diameter of 10 ± 5 nm. The fact that this kind of tip is a multi-walled nanotube made of normal graphene walls was confirmed by transmission electron microscopy. The long-term mapping challenge of complex nanostructures can be resolved by scanning them with such CNT probes.

Composite probe

It is practically difficult to fabricate nanoprobes with the advanced mechanical properties, size, and shape required. By mixing many components to create composite materials, modern technology has made it feasible to develop macroscopic materials with unique functionality. When combining CNTs with other materials to create probes, the analytical performance of the resulting material is superior to that of the CNT probes alone [13]. Nakabayashi *et al.* suggested the fabrication of reinforced carbon-carbon composite nanotools by coating nanotubes with an amorphous carbon matrix. The synthesis of nanotools with high surface area can be aided by the combination of amorphous carbon and CNTs' mechanical characteristics. The surface area, strength, and size of CNTs may all be maintained while controlling unfavorable characteristics like flexibility and vibration. After 400 photos, the tip and image quality of these composite probes remain unchanged, producing extremely high image resolution and good wear resistance [13].

Conducting atomic force microscopy (CAFM) is a potent method for examining the mechanical and electrical characteristics of materials and electronics at the nanoscale. Nonetheless, the primary obstacle lies in the dependability of probe tips and how they interact with materials. The most popular probe tips for CAFM research are silicon coated with a thin layer (20 nm) of platinum or platinum-rich alloys, including Pt/Ir, because mechanical frictions are rapidly removed and the current density is large (> 102 A cm^{-2}). Doped diamond-coated silicon tips and solid doped diamond tips are more resilient, although they are expensive and frequently scratch the majority of samples' surfaces due to their high hardness. Solid platinum tips are becoming a more popular alternative to metal-coated silicone tips since they are cost-effective and work longer. Although it has been suggested that metal-coated silicon probes' tips might be shielded by graphene; these probes are not yet commercially available. While the topography and current maps produced with solid platinum probes and silicon probes coated with Pt/Ir exhibit extremely similar resolutions, solid platinum probes exhibit better durability [14].

Magnetic force microscopy probe tips. Studies about magnetic nanomaterials and nanostructures are particularly significant. Instruments like a magnetic force microscope (MFM) are used to study and take pictures of these materials. Sharp tips, or probes, are a crucial component of these devices. They are used to examine and quantify the magnetic characteristics of materials at the nanoscale, and they are crucial to obtaining high-accuracy MFM pictures. These tips are made of unique materials and patterns that enable them to interact with magnetic fields accurately and sensitively, gathering valuable information from the sample surface. Many studies in this sector are focusing on the design and optimization of these tips since they are crucial to the quality and accuracy of the pictures received from the MFM [15].

The performance and accuracy of the pictures acquired by the MFM are directly impacted by the features of these tips. These tips are made of nanoscale materials including cobalt, nickel, and magnetic alloys. Additionally, a thin coating is applied to them to boost the tips' sensitivity to magnetic fields. The nanotips' small size allows them to travel closer to the sample surface, allowing them to detect weaker changes in the magnetic field and generate pictures with better resolution [16]. These tips' performance is significantly influenced by their geometry and shape. Typically, the geometric shape is conical or triangular, with the right amount of sharpness and dimension. The tip's shape enhances the precision of magnetic pictures and makes it suitable for confined areas and surface structures [16]. The precise requirements of the study and the tool being utilized should be taken into consideration while determining the size and dimensions of these tips. The resolution and accuracy of the pictures produced will increase with decreasing tip size [16]. As a result of pressure and shocks during the MFM scanning process, these tips need to be extremely strong and resistant to bending. Nanotips are more resilient to corrosion, wear, deformation, memory effect, and corrosion because of their more stable magnetic characteristics. As a result, they last longer and require less maintenance or replacement [15, 16]. Owing to the potential for electric charges in the samples, the MFM probe tips need to have sufficient static electricity to aid with picture accuracy and avoid interference from charges being absorbed [16].

There is a wide range of uses for these tips as an effective instrument to explore and analyze the magnetic characteristics of materials at the nanoscale. These tips can image structures and magnetic surfaces at the nanoscale with high resolution. With these tips, one may obtain exceedingly clear and exact images of magnetic structures at the nanoscale. The MFM probe tips are ideal for assessing and examining magnetic materials as well as researching magnetic domains at the nanoscale, such as alterations in a material's magnetic field, direction, or structure [15,16].

Construction and characterization methods of probe. The first step in the construction of these tips is choosing a suitable material with magnetic characteristics at the nanoscale. Among these materials are ferroelectric-ferromagnetic nanoparticles, metal oxide magnetic nanoparticles, and magnetic metals including iron, nickel, and cobalt and their alloys. Then, a variety of processes, including mass growth, photolithography, sharpening, and nanoparticle manufacturing, are used to make the tips. Then, thin magnetic coatings can be applied to them to enhance their sensitivity to magnetic fields. Physical or chemical techniques can be used to apply these thin magnetic coatings to the tips [15,17]. The probe tips should be precisely described and tested when they are made. This step may involve assessing the probe tips' magnetic properties, evaluating their brightness (by varying the distance between the tip and the sample to observe variations in image brightness), characterization of the tip's shape and geometry, and assessing the resolution accuracy of the tips. To evaluate the functionality and properties of the tips, electrical and magnetic analysis can also be carried out [17]. These tips can now offer precise measurements and magnetic imaging of the materials. Additionally, increased productivity and advancements in the field of magnetic research will result from better tip design and manufacturing procedures [17].

Role of the probe tip in MFM. To utilize the MFM, first, an appropriate magnetic probe tip should be chosen and attached to the microscope needle head. Next, a specific tube should be put into the needle head and the tip should be positioned at an appropriate distance from the sample surface using a scanner. It is important to choose a distance between the tip and the sample that minimizes mechanical effects while allowing for quantifiable magnetic interactions. Next, the sample should be placed in an appropriate frequency external magnetic field, and a specific tube should be used to record any changes in the force of attraction between the sample and the tip. These variations show how the sample surface's magnetic field is distributed. Ultimately, by analyzing the sample's magnetic characteristics and employing the appropriate software, a high-resolution picture of the sample's surface is produced [18,19].

MFM probe tip research is still ongoing and contributes to the improved use of this potent instrument in magnetic nanomaterials research. Enhancing the technology of these tips can also lead to advancements in some fields of study, such as the physics of materials and nanomaterials, and enhance the quality and accuracy of the pictures that are produced. These suggestions are an effective means of examining and investigating magnetic characteristics at the nanoscale, and the more their functionality and design are refined and optimized, the more applications and novel studies in this area will be made feasible [15,17].

Scanning tunneling microscope probe tips. STM is the first developed scanning probe microscope which was invented in 1981. By limiting environmental disturbances and permitting the tip to move extremely closely to the sample surface, the STM was therefore recognized as the first instrument capable of producing three-dimensional pictures of solid surfaces with atomic resolution and precision [20]. STM is a technology for imaging and investigation of atomic-scale surface electrical characteristics. STM is limited to conductive material surface analysis. These microscopes have been employed as spectroscopic instruments or for imaging and producing pictures from the micro-scale to atomic dimensions with high resolution throughout a wide range of magnifications from 10^3 to 10^9 in the X, Y, and Z axes [21]. These instruments are applicable in many kinds of settings, including atmospheres, other gases, liquids, vacuums, and temperatures both below and above 100 Kelvin [22]. The STM device system comprises the sample holder, the tip and its associated assembly, the electronic controller, the computer housing the electronic controller, and the image processing software. STM operates on the quantum tunneling theory. An appropriate bias voltage is supplied in this procedure between the sample surface and the probe tip. Based on the phenomena of tunneling from the sample to the tip's atoms, a little electric current flows through when this tip is positioned between 0.3 and 1 nm from the sample's surface. Any slight variation in the distance between the probe tip and the sample surface generates a change in the electric current, which is then employed as a signal for STM imaging. In this instance, the tip on the surface carries out the scanning activity while the tunneling current varies from 0.2 to 10 nanoamperes [23]. The distance between the probe tip and the sample determines the tunneling current. With the use of piezoelectric activators, the tip travels in three directions to scan the surface. High-precision imaging is possible by the precise and controlled movement of the STM probe tip on the sample's surface, which is achieved by varying the alternating voltage delivered to the piezoelectrics [24].

Typically, STM probes come with a metal-tipped base or clamp to reduce wave fluctuations. Although a sharp tip is ideal, most tip preparation techniques result in a rough cross-section with several rough spots; the ones closest to the sample's surface cause tunneling. The tips are often created via abrasion, cutting, field diffusion or evaporation processes, ion wear, electrochemical polishing, or electrochemical etching, and are typically composed of metal components such as tungsten, gold, and platinum-iridium alloys. Tungsten wire and platinum-iridium alloy tips are the most popular materials for the STM tips. Whereas tungsten tips are produced by electrochemical etching tungsten wires, platinum-iridium tips are typically prepared physically [25]. Because of the weaker reactivity of platinum, platinum-iridium tips often offer higher atomic resolution than tungsten tips; on the other hand, tungsten tips have a more uniform shape and are more effective on samples with a steep slope. Through electrochemical etching, high aspect ratio platinum-iridium probes with precise shapes may be produced commercially for imaging deep and tiny pits and grooves. Deep grooves and nanoscale patterns and forms may be seen with probes with a radius of less than 50 nm [26].

It is possible to create objects atom by atom using this microscope. The STM tip may move or remove an atom from the sample surface and place it in the appropriate position by varying the height of the tip containing the desired atom and the tunnel current [27].

Silicon Nanotweezers

A class of micro-electromechanical (MEMS) devices known as silicon nanotweezers (SNT) are utilized for biomechanical and bioelectrical sensing at the nanoscale level, as well as for direct manipulation of extremely small objects including cells, biomolecules, and nanoparticles. MEMS systems are the outcome of integrating mechanical, electrical, and sensor components on a silicon layer with the aid of chip manufacturing technology, allowing for the integration of precise engineering tools at the molecular level [28]. The need for low-threshold biological molecule detection technologies that address environmental and health concerns is growing currently [29]. The intricacy of biophysical instruments like AFM, optical tweezers, magnetic tweezers, micropipettes, and microplates limits optical and magnetic manipulation despite their great accuracy [30]. SNTs are advised as a microsystem for molecular or cellular manipulation. SNT can manipulate and alter the characteristics of molecules in air and solutions by trapping them and monitoring their biomechanical and bioelectrical response when exposed to reactive substances in a short period of time. SNT has the potential to be a molecular and cellular probe for biological diagnostics as well as routine analysis. Among SNT's benefits are its samll size, low cost, quick reaction, and ability to analyze in small volumes. Drug screening and biological diagnostics are made possible by this method [29].

The exact and effective entrapment of a DNA packet between the device's two sharp points gave rise to the idea of SNT in 2003. Since then, SNT has worked to further increase the sensitivity, reproducibility, and mechanical and electrical measurements of a wide range of biological samples, DNA, filaments (filamentous molecules), and other environmental materials [30].

Molecular analysis is the goal of working with individual molecules. Because of this, the molecules need to be trapped before being transferred to different settings and solutions where the reaction may take place or the intended attribute can be assessed. A physical, mechanical, or electrical actuator is then utilized to perform the reaction, and changes in electrical conductivity that are proportionate to time are used to verify the response [29]. MEMS enables the development of unique electrodes to capture and control the electromechanical performance of samples, while on the one hand, nanotweezers are compact enough and compatible with microfluidic technology to handle samples in liquid. The design of SNT consists of three parts [29,31,32]:

(I) Nano silicon tweezers consist of two arms with sharp points that may move and alter form. These tips work by serving as an electrode to change molecules through the process of dielectrophoresis, after which their conductivity is measured. The actuator will move the other arm while the fixed arm remains stationary. The applied differential voltage between the two activation voltage ports will be used to modify the distance between the two electrodes. A capacitive sensor measures the movement of these two electrodes, which relates to the elongation of molecules. The objective is to submerge the electrodes in biological fluids; therefore, the SNT design should position the sensor at the opposite end of the arm to prevent contact with the liquid.

(II) A series of comb-drive actuators: Comb drives are a type of micromechanical actuator that operates by applying electrostatic forces between two electrically conducting combs. They are typically linear actuators.

(III) A differential capacitive sensor that determines pressure by observing variations in electrical characteristics like a capacitor.

Electrostatic forces are used in silicon-based nanotweezers. Their performance is voltage-dependent and controlled simply. Electrostatic forces between two electrodes must be investigated to construct a comb-drive actuator. The attraction forces generated by these actuators are limited to the two electrodes and can only be generated in a single direction. As a result, the design should be modified to incorporate two actuators for greater displacements as well as opening and shutting [30].

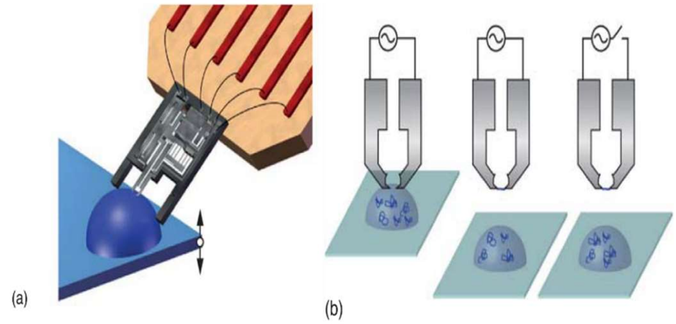

Fig. 1. The performance of SNT in detecting solution droplets and DNA in (a) represents the In-Droplet operation, SNT is installed on the printed circuit board and a drop of DNA is deposited on a cover plate and maintained by a micromanipulator and (b) represents the trapping of a DNA package by dielectrophoresis and recovery of its solution [30].

The nanotweezer chips are mounted on a printed circuit board for electrical connection with the measurement device after the clean chamber is built. Additionally, a robotic base holds it. The electrodes have a very basic function: when a voltage is provided to the actuator, a force is generated that causes the electrodes to move (Fig. 1) [30].

SNTs are fabricated using a silicon-on-insulator switch, one of the most used techniques for creating MEMS. With this technology, it is easy to construct thick comb-drive actuators that produce high force with sub-micron gaps. This approach involves layering silicon and insulation materials, followed by the placement of the required electrodes and connections on the layer. After silicon has been deposited, masks are used to apply the desired pattern to the silicon. The silicon layer is then deeply etched to create nanotweezers using the proper gases. The hard mold of the device is made in a thick silicon layer that is 550 µm in thickness. This layer will be machined, and after the excess layers are removed, SNT with a silicon switch will be formed on the insulator. The moving and active parts are modeled in the upper silicon layer, which has a thickness of 5 micrometers. This method maintains the moving parts' electrical insulation while enabling their mechanical connection. Following this procedure, a 50 nm-thick layer of aluminum evaporates on the other surface, serving as a support for DNA and other biomolecules as well as enhancing the device's electrical output and the conductivity of the SNT part sheet [29,33].

There are two methods of activation: electrostatic actuation and electromagnetic activation. In microscale and lower dimensions, electromagnetic forces are comparatively weak. Since current feeds the magnetic field, one of them is large power losses. Furthermore, a quite large external permanent magnet or coil is needed, which takes up space and is challenging to produce using conventional integrated circuit (IC) technology. Furthermore, lateral losses become more significant at high frequencies, decreasing the effectiveness of magnetic fields. Compatibility with the complementary metal oxide semiconductor (CMOS) system presents another difficulty for this technology, which can eventually restrict its use in particular applications [33]. Microelectrostatic actuators offer several benefits, including the ability to be readily miniaturized and controlled by electronics [34]. They also consume relatively little power, even if they occasionally require high-voltage circuits. However, they must be wrapped since they are susceptible to environmental impacts like moisture and dust. Movement is produced using electrostatic actuators. These activators can be used for self-testing optical beam valves, vibration sensors, scanners, etc. To reduce friction, the moving part is often supported by flexible electrodes. A comb-drive activation was used in place of the thermal activator in the device's second version [33].

To manipulate, excite, and precisely regulate molecules for use as sensors, bioelectronic chips, and quantum chips, as well as for disease detection, biochemical research, and nanoelectronic research, the following processes are involved in entrapping string molecules or filaments by SNT:

(I) Preparation of nanotweezers: Construction and fabrication of silicon grooves for the molecules to be inserted as well as nanotweezers.

(II) Beginning of the trapping process: The filaments to be trapped move near the silicon surface. Van der Waals forces will now form between the filaments and the silicon surface, preventing the filaments from peeling off the surface.

(III) Keeping the molecules: Van der Waals forces lock the molecules in place after they are affixed to the nanotweezers and maintain them there. This procedure makes it easier for molecules to be trapped and keeps them from escaping the silicon surface.

(IV) Stimulation and manipulation of molecules: Molecules can be stimulated and manipulated to a desired location by applying external pressures, such as electric or magnetic forces. Electrodes or magnetic and electric fields can apply these forces.

(V) Final registration and locking of molecules: Once the molecules are at the desired location, nanotweezers lock and hold them. By doing this, the nanotweezers' final registration is completed, and the molecules are positioned where they want to be [29].

Nanorobotics Manipulation

The goal of the multidisciplinary discipline of nanorobotics is to create, construct, program, and develop extremely small robots in nanoscales by fusing the concepts of material science, robotics, and nanotechnology. We are now seeing the use of nanorobots and microrobots in many disciplines, based on the spectacular achievements of nanotechnology and the development achieved in the field of nano/microsensors. The treatment of conditions like cancer, heart disease, neurological disorders, infections, diabetes, and other diseases has been revolutionized thanks to nanotechnology. This technology's ability in both molecular and atomic dimensions is a key component that gives nanorobots the capacity to modify material molecules and, using a predefined program, generate new structures. Nanorobots have a broad range of applications within the human body. Nanorobots can quickly recognize the biological environment and can do detailed examinations of the biochemical and biomechanical features of a given tissue. Additionally, smart chemotherapy makes use of nanorobots to target specific neoplasm cells and tissues while avoiding contamination of nearby healthy cells, allowing for faster cancer treatment (Fig. 2). Nanorobots are equipped with a variety of technologies, including nanoscale sensors, control systems, and actuators. They can recognize signals and unique circumstances, such as the existence of a certain kind of molecule or material, and relay this information to the control system. Artificial intelligence and software are used to train smart transistors and microchips that are embedded in nanorobots [35].

Nanorobots are any active structure that can carry out the following functions at the nanoscale: information processing, propulsion, sensation, manipulating or changing the

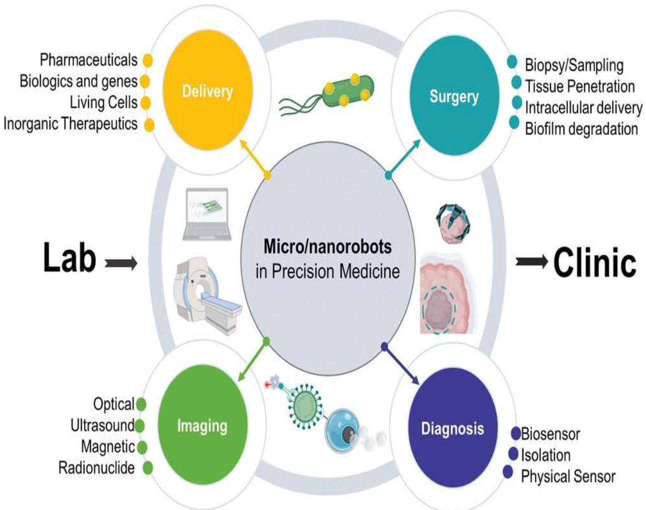

Fig. 2. Schematic of the current progress of nano and microrobotics in medicine [36].

environment, and stimulation [35]. Nanorobots have many advantages over humans and conventional tools, such as better durability and sustainability, significantly reduced operation times, faster relocation due to their small size, cost-effectiveness, higher accuracy, more effective disease treatment, fewer side effects, quicker recovery times, identification, repair, and remote surgery of inaccessible damaged organs.

These compact platforms work well for treating and preventing diseases. Nano and microrobot performance may be impacted by the minerals used in their construction, and it may also result in health issues. Natural materials are employed in the fabrication of biomimetic nanorobots to avoid this issue. The goal of biomimetic robots is to mimic natural components, processes, and patterns to address complicated human issues [35]. The integration of nanotechnology, physics, chemistry, biology, and material engineering science has resulted in the development of new tools such as nanorobots, nanomachines, nanites, and nanomites as a result of complications brought on by drug resistance, toxicity, and pharmacology-related issues in cancer treatment [35,37,38]. Different metals, diamonds, artificially produced proteins, and other minerals are used to fabricate mineral robots. The CNT sensor used in the construction of this robot lowers electrical resistance when it makes contact with a cancer cell. When the electrical resistance decreases, the quick electrical switch, or nanoelectromechanical relay, is activated, exposing the medications to the region determined by the mineral calculations made automatically by the nanorobot. But these robots are toxic, and the immune system has to eliminate them. Conversely, organic nanorobots are less toxic to human health. Biorobots or biomimetic nanorobots are other names for these robots. Robots can enter tumors through blood by the use of an external field [35].

Sensors and sensors driving power equipment are two key devices needed for biomimetic nanorobots to target a specific area in the body. At the nanoscale, sensors include biological, mechanical, magnetic, and thermal ones. Biomimetic nanorobots are equipped with biological sensors. These biosensors recognize targets by use of biological processes. Robot mobility also requires sensors to operate power equipment [35]. Three basic sorts of propulsion systems have been developed to enable nanorobots to carry out their tasks:

(I) Self-propulsion: centered on chemical processes, which were then transformed into kinetic energy, giving the gadget power and motion.

(II) Propulsion based on external stimuli: biocompatible due to their non-invasive nature.

(III) Propulsion based on bio-hybrid: primarily functions as a medication and is founded on the fusion of biological and engineering concepts [35].

Mammalian cell-based systems, pathogen-based systems, and biomolecule-based systems are some examples of biomimetic nanorobots with membranes derived from diverse natural sources that can monitor the cargo they transport in addition to carrying it to designated locations.

The primary concern is that these nanorobots, which are attached to the surface of tumors and move with the aid of flagella, are only effective on solid tumors like intestinal tumors that are large or striking in the chest. Bacterial nanorobots are derived from Salmonella bacteria and are used to target and treat tumors. DNA origami is a more recent robot that can recognize and cure cancers. This allows for the repetitive bending of a single continuous string to take on the appropriate form. These nanorobots' delivery methods are targetable, but they are immobile. Lee and his team have recently employed modified sperms and biomimicry nanorobots, derived from DNA origami technology, for the detection and treatment of cancer. Drugs are delivered to the tumor sites via the nanorobot, which attaches itself to the cancer cell. Tumors were found and their development halted in animal models; in a different research, sperm that had been genetically modified to carry anticancer medications were directed into tumor sites by magnetic force. This technique allows for the use of imaging, additional medications, and fewer side effects [39]. Because they enable early identification and the effective administration of medications with high efficiency and safety, biomimetic nanorobots have garnered a lot of attention as a novel approach to cancer therapy and diagnostics [36].

Nanorobotics Technology Using Magnetic Power

These robots, which can move and be controlled by magnetic forces, have a variety of uses, including sensors, medication administration, and minimally invasive surgery. The capacity of magnetic robots to move steadily and precisely over a crucial feature for medical applications as well as their adaptability to many conditions, including the liquid environments found inside the body, are among their benefits. The materials that make up these nanorobots are nanostructured and have magnetic characteristics. This kind of nanorobot is propelled by an external magnetic source. When a magnetic field is applied close to a robot, the robot is subject to forces of attraction or repulsion. The robot can move by varying these forces' magnitude and direction [40].

These small robots can lower side effects and administer the medication precisely where it is needed. These robots are capable of accurate internal body movements during minimally invasive surgery. These nanorobots can also be utilized as sensors to monitor and identify different bodily diseases. Nonetheless, the creation and use of magnetic nanorobots continue to face difficulties. Creating and manufacturing nanorobots with the right magnetic characteristics, precisely controlling robot motion, and creating the magnetic power systems needed to operate robots are a few of the difficulties [40]. We anticipate that as technology develops, these problems will be resolved and the applications for magnetic nanorobots will grow.

Electrochemical Clamps Nanorobots

One of the most crucial parts of building and operating nanorobots is electrochemical clamps that regulate surface forces and are a significant technological advancement in the field of nanorobotics and offer precise surface force control [41]. Typically, electrochemical clamps are made of electrochemical materials that can adapt to surface stresses by changing their volume and form. Surface forces like absorption and scattering may be precisely tuned and applied to the nanorobot using electrochemical forces, *e.g.*, by varying the voltage of the electrode. This method has the advantage of being able to precisely regulate surface forces, fine-tune in response to environmental changes, and be used in a variety of conditions, including the liquid environment found inside the body. The difficulties lie in creating and producing electrochemical clamps with the right characteristics, precisely regulating surface forces, and maximizing performance under various circumstances [41].

Using nanorobots for cell transformation entails carefully guiding and delivering these machines into the cells. With this technique, the intended procedure may be carried out precisely and directly within the cells. Controlling, deliberately altering, and enhancing the traits and attributes of cells or nanomaterials is the aim. Generally, the ability of nanorobots to manipulate and change cells opens up new possibilities in a variety of sectors, and we anticipate that this will lead to numerous advancements and discoveries in science and technology in the future [42].

Laser Tweezers Using Nanoapertures

The capacity to manipulate microscopic particles with light was first acknowledged in 1997 when Steven Chu, Claude Kuhn-Tanodjee, and William D. Phillips were given the Nobel Prize in Physics. Phillips is well-known for his work on laser cooling methods and atom trapping [43,44]. Arthur Ashkin won the Nobel Prize in Physics in 2018 in recognition of his groundbreaking research on optical tweezers and their use in biological systems (Fig. 3). Subsequently, the scientific community has witnessed notable advancements in sophisticated optical manipulation methods founded on optical tweezers [45].

The combination of nano-optical tweezers and holographic tweezers is another optical tweezers technique that has drawn interest. Nano-optical tweezers can separate individual nanoparticles from two nanotubes at the single molecule level and can dynamically control particles [47].

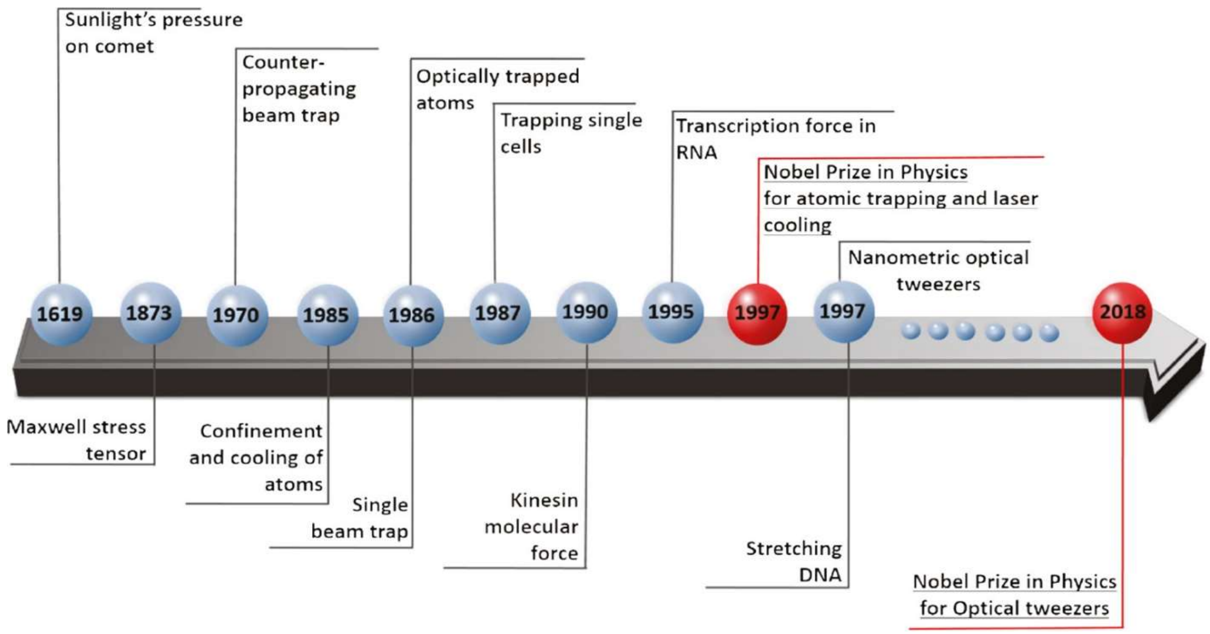

Fig. 3. The optical tweezers roadmap [46].

In the realms of biology and nanotechnology, such as respiratory syndrome virus-2 (SARS-CoV-2) and influenza virus, recent developments in nanoscale technologies have produced sophisticated instruments for the entrapment, tracking, and counteraction of single nanoscale particles. Researchers captured and monitored SARS-CoV-2 and influenza viruses during the coronavirus outbreak to study their epidemiological transmission (Fig. 4) [48].

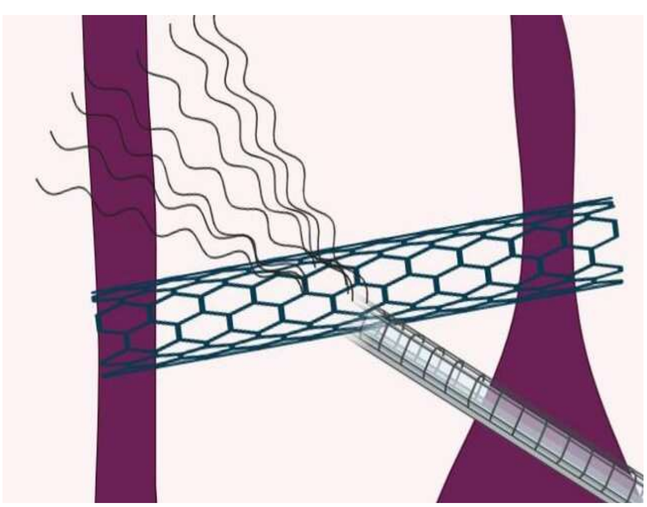

Fig. 4. Schematic representation of holding and manipulating nanoscale materials in a nano-optical tweezer [48].

Proteins are studied and DNA molecules are trapped and separated using nanoaperture-based optical tweezers, which are 1000 times more effective than traditional optical tweezers. Utilizing recent advancements in the realm of optical tweezers with nanoaperture, they may apply to single-molecule binding, protein-antibody interactions, protein-molecule interactions, and protein-DNA interactions [49]. Particles having momentum changes due to light absorption and scattering can be worked using optical tweezers [50].

Tweezers with lasers optical tweezers and confocal Raman spectroscopy are developed (LTRS). LTRS optically traps a single cell at the laser focus point using a highly concentrated laser beam. The combination of Raman spectroscopy with laser tweezers makes it possible to immobilize single cells or particles in suspension [51].

The study of motile cells in aqueous solution is yet another amazing feat of LTRS. Red blood cells, bacteria and yeast cells, liposomal membranes, and trapped microparticles may all be recognized and described using LTRS. The detection of bacterial spores in aqueous solution, when the spores are isolated from non-biological particles like polystyrene spheres, has been claimed to be possible using LTRS. Raman tweezers are a non-destructive means of detecting germs as compared to other established methods [52].

CONCLUSIONS

The use of nanotechnology for different applications has been growing during the past decade. Nanotechnology has been used to improve the efficiency of available applications [1]. However, nanotechnology has also enabled new applications such as nanoscale tips used for topological microscopy in AFM, STM, and MFM. These techniques utilize nanotechnology to improve their efficiency. Furthermore, nanotechnology has enabled the construction of tweezers and robots in the nanoscale. These nano-enabled tools (nanotools) have been successfully utilized for nanoanalysis and nanomanipulation. AFM, STM, and MFM are not only meant to image nanostructured surfaces but also they are utilized for the manipulation of materials at the atomic and nanoscale. Nanotweezers, nanorobots, and laser tweezers using nanoapertures are also able to manipulate nano and microscale materials.

The relationship between analytical science, nanotechnology, and nanoscience has historically taken two distinct forms: the use of nanomaterials produced by nanotechnology as analytical tools for the study of other materials, and the development of new analytical methods for the detection, quantification, and characterization of new nanomaterials as analytes. But, there is a new emerging application wherein nanotools are utilized for nanoanalysis and nanomanipulation. In nanoanalysis science and nanotechnology, the third wave comprises not only the fusion of two traditional methods into one single process but also the existence of two distinct types of nanoparticles that function as both nanoanalytes and nanotools at the same time, as well as the use of nanotools to determine or characterize nanoanalytes and extract information from the nanoworld. Finding new analytical chemistry and nanotechnology methods, as well as the synergy between nanotools and nanoanalytes because of their advantageous properties and specificity, are the main objectives of the third wave of nanoanalysis science and nanotechnology. This approach opens up new avenues for studying the nanoworld and raises the possibility of developing new, improved analytical processes.

REFERENCES

[1] A. Afkhami, T. Madrakian, M. Ahmadi, Analytical Nanochemistry, Elsevier, 2023.

[2] A. Afkhami, T. Madrakian, M. Ahmadi, Chapter 13 Nanotools for bioanalysis, in: A. Afkhami, T. Madrakian, M. Ahmadi (Eds.), Analytical Nanochemistry, Elsevier, 2023, pp. 297-333.

[3] A. Afkhami, T. Madrakian, M. Ahmadi, Chapter 12 -Nanotools for nanoanalysis, in: A. Afkhami, T. Madrakian, M. Ahmadi (Eds.), Analytical Nanochemistry, Elsevier, 2023, pp. 273-296.

[4] G. Haugstad, Atomic force microscopy: understanding basic modes and advanced applications, John Wiley & Sons, 2012.

[5] B. Voigtländer, Scanning probe microscopy: Atomic force microscopy and scanning tunneling microscopy, Springer, 2015.

[6] N.R. Wilson, J.V. Macpherson, Carbon nanotube tips for atomic force microscopy, Nat. Nanotechnol. 4 (2009) 483.

[7] P. Nguyen-Tri, P. Ghassemi, P. Carriere, S. Nanda, A.A. Assadi, D.D. Nguyen, Recent applications of advanced atomic force microscopy in polymer science: A review, Polymers 12 (2020) 1142.

[8] K. Xu, Y. Liu, Studies of probe tip materials by atomic force microscopy: a review, Beilstein J. Nanotechnol. 13 (2022) 1256.

[9] J.H. Hafner, C.L. Cheung, C.M. Lieber, Growth of nanotubes for probe microscopy tips, Nature 398 (1999) 761.

[10] A. Nain, Y.-T. Tseng, Y.-S. Lin, S.-C. Wei, R.P. Mandal, B. Unnikrishnan, C.-C. Huang, F.-G. Tseng, H.-T. Chang, Tuning the photoluminescence of metal nanoclusters for selective detection of multiple heavy metal ions, Sens. Actuators B 321 (2020) 128539.

[11] J. Bang, S. Coskun, K.R. Pyun, D. Doganay, S. Tunca, S. Koylan, D. Kim, H.E. Unalan, S.H. Ko, Advances in protective layer-coating on metal nanowires with enhanced stability and their applications, Appl. Mater. Today 22 (2021) 100909.

[12] A.D. Slattery, C.J. Shearer, J.G. Shapter, J.S. Quinton, C.T. Gibson, Solution based methods for the fabrication of carbon nanotube modified atomic force microscopy probes, Nanomaterials 7 (2017) 346.

[13] D. Nakabayashi, A. Moreau, V. Coluci, D. Galvão, M. Cotta, D. Ugarte, Carbon nanotubes as reinforcement

elements of composite nanotools, Nano Lett. 8 (2008) 842.

[14] J. Weber, Y. Yuan, F. Kühnel, C. Metzke, J. Schätz, W. Frammelsberger, G.N. Benstetter, M. Lanza, Solid Platinum Nanoprobes for Highly Reliable Conductive Atomic Force Microscopy, ACS Appl. Mater. Interfaces 15 (2023) 21602.

[15] H. Uršič, M. Šadl, U. Prah, V. Fišinger, Magnetic Force Microscopy of Multiferroic Bulk Ceramic Oxides, Crystals 13 (2023) 838.

[16] A.T. Escalante-Quiceno, O. Novotný, J. Neuman, C. Magén, J.M. De Teresa, Long-Term Performance of Magnetic Force Microscopy Tips Grown by Focused Electron Beam Induced Deposition, Sensors 23 (2023) 2879.

[17] S.A.H. Banuazizi, A. Houshang, A.A. Awad, J. Mohammadi, J. Åkerman, L.M. Belova, Magnetic force microscopy of an operational spin nano-oscillator, Microsyst. Nanoeng. 8 (2022) 65.

[18] P. Grütter, H. Mamin, D. Rugar, Magnetic force microscopy (MFM), Scanning Tunneling Microscopy II: Further applications and related scanning techniques, Springer 1992, pp. 151-207.

[19] O. Kazakova, R. Puttock, C. Barton, H. Corte-León, M. Jaafar, V. Neu, A. Asenjo, Frontiers of magnetic force microscopy, J. Appl. Phys. 125 (2019).

[20] G. Binnig, H. Rohrer, C. Gerber, E. Weibel, Surface studies by scanning tunneling microscopy, Phys. Rev. Lett. 49 (1982) 57.

[21] D. Drakova, Theoretical modelling of scanning tunnelling microscopy, scanning tunnelling spectroscopy and atomic force microscopy, Rep. Prog. Phys. 64 (2001) 205.

[22] A. Anirban, 40 years of scanning tunnelling microscopy, Nat. Rev. Phys. 4 (2022) 291.

[23] G. Doyen, E. Koetter, J. Vigneron, M. Scheffler, Theory of scanning tunneling microscopy, Appl. Phys. A 51 (1990) 281.

[24] J. Duan, J. Wang, L. Hou, P. Ji, W. Zhang, J. Liu, X. Zhu, Z. Sun, Y. Ma, L. Ma, Application of Scanning Tunneling Microscopy and Spectroscopy in the Studies of Colloidal Quantum Qots, Chem. Rec. (2023) e202300120.

[25] C.J. Chen, Introduction to Scanning Tunneling Microscopy Third Edition, Oxford University Press, USA2021.

[26] A.L. Gassó, Microscopy. https://miscircuitos.com/wp-content/uploads/2018/05/Scanning-Tunneling-Microscopy-Alberto-Lopez.pdf

[27] W. Ko, C. Ma, G.D. Nguyen, M. Kolmer, A.P. Li, Atomic-scale manipulation and in situ characterization with scanning tunneling microscopy, Adv. Funct. Mater. 29 (2019) 1903770.

[28] D. Collard, T. Lacornerie, M. Kumemura, N. Lafitte, H. Guillou, L. Jalabert, E. Lartigau, F. Cleri, T. Fujii, H. Fujita, Silicon Nanotweezers for real time biomechanical assay on DNA damage by therapeutic radiation beams, 16th Int Conf. on Miniaturized Systems for Chemistry and Life Sciences, Okinawa, Japan, 2012, pp. 1615-1617.

[29] D. Collard, Silicon nanotweezers for biomechanical and bioelectrical assays, Front. Biosci. (Elite Ed.) 5 (2013) 955.

[30] D. Collard, N. Lafitte, H. Guillou, M. Kumemura, L. Jalabert, H. Fujita, Silicon Nanotweezers for Molecules and Cells Manipulation and Characterization, Micro- and Nanomanipulation Tools (2015) 169.

[31] C. Yamahata, D. Collard, B. Legrand, T. Takekawa, M. Kumemura, G. Hashiguchi, H. Fujita, Silicon nanotweezers with subnanometer resolution for the micromanipulation of biomolecules, J. Microelectromechanical Syst. 17 (2008) 623.

[32] D. Collard, S. Takeuchi, H. Fujita, MEMS technology for nanobio research, Drug Discov. Today 13 (2008) 989.

[33] F. Ceyssens, S. Sadeghpour, H. Fujita, R. Puers, Actuators: accomplishments, opportunities and challenges, Sens. Actuators A 295 (2019) 604.

[34] S. Thomas, M. Ahmadi, T.A. Nguyen, A. Afkhami, T. Madrakian, Micro- and Nanotechnology Enabled Applications for Portable Miniaturized Analytical Systems, Paperback ISBN: 9780128237274, eBook ISBN: 9780128237281, 2021.

[35] S. Nehru, R. Misra, M. Bhaswant, Multifaceted Engineered Biomimetic Nanorobots Toward Cancer Management, ACS Biomater. Sci. Eng. (2022) 444.

[36] F. Soto, J. Wang, R. Ahmed, U. Demirci, Medical Micro/Nanorobots in Precision Medicine, Adv. Sci. 7

(2020) 2002203.

[37] A. Afkhami, T. Madrakian, M. Ahmadi, Chapter 14 -Toxic risks of nanomaterials used in analytical chemistry, in: A. Afkhami, T. Madrakian, M. Ahmadi (Eds.), Analytical Nanochemistry, Elsevier 2023, pp. 335-364.

[38] N.R. Jalal, F. Mollarasouli, M.R. Jalali Sarvestani, S. Khalili, S. Asadi, Z. Derakhshan, T. Madrakian, A. Afkhami, M. Ahmadi, Quantum Dots in Medical Detection/Diagnosis, 2023.

[39] T.-C. Lee, M. Alarcón-Correa, C. Miksch, K. Hahn, J.G. Gibbs, P. Fischer, Self-Propelling Nanomotors in the Presence of Strong Brownian Forces, Nano Lett. 14 (2014) 2407.

[40] H. Zhou, C.C. Mayorga-Martinez, S. Pané, L. Zhang, M. Pumera, Magnetically Driven Micro and Nanorobots, Chem. Rev. 121 (2021) 4999.

[41] A. Karg, V. Kuznetsov, N. Helfricht, M. Lippitz, G. Papastavrou, Electrochemical grippers based on the tuning of surface forces for applications in micro- and nanorobotics, Sci. Rep. 13 (2023) 7885.

[42] W. Chen, H. Zhou, B. Zhang, Q. Cao, B. Wang, X. Ma, Recent Progress of Micro/Nanorobots for Cell Delivery and Manipulation, Adv. Funct. Mater. 32 (2022) 2110625.

[43] K. König, Laser tweezers and multiphoton microscopes in life sciences, Histochem. Cell Biol. 114 (2000) 79.

[44]S. Chu, J. Bjorkholm, A. Ashkin, A. Cable, Experimental observation of optically trapped atoms, Phys. Rev. Lett. 57 (1986) 314.

[45] S. Chu, L. Hollberg, J.E. Bjorkholm, A. Cable, A. Ashkin, Three-dimensional viscous confinement and cooling of atoms by resonance radiation pressure, Phys. Rev. Lett. 55 (1985) 48.

[46] D.G. Kotsifaki, S.N. Chormaic, Plasmonic optical tweezers based on nanostructures: fundamentals, advances and prospects, Nanophotonics 8 (2019) 1227.

[47] J.D. Kolbow, N.C. Lindquist, C.T. Ertsgaard, D. Yoo, S.H. Oh, Nano-Optical Tweezers: Methods and Applications for Trapping Single Molecules and Nanoparticles, ChemPhysChem 22 (2021) 1409.

[48] R. Kumar, K. Gulia, M. Chaudhary, M. Shah, SARS-CoV-2, influenza virus and nanoscale particles trapping, tracking and tackling using nanoaperture optical tweezers: A recent advances review, J. Mater. Nano Sci. 7 (2020) 79.

[49] A.A. Al Balushi, A. Kotnala, S. Wheaton, R.M. Gelfand, Y. Rajashekara, R. Gordon, Label-free free-solution nanoaperture optical tweezers for single molecule protein studies, Analyst 140 (2015) 4760.

[50] R. Gordon, Biosensing with nanoaperture optical tweezers, Opt. Laser Technol. 109 (2019) 328.

[51] J.W. Chan, Recent advances in laser tweezers Raman spectroscopy (LTRS) for label-free analysis of single cells, J. Biophotonics 6 (2013) 36.

[52] C. Xie, J. Mace, M. Dinno, Y. Li, W. Tang, R. Newton, P. Gemperline, Identification of single bacterial cells in aqueous solution using confocal laser tweezers Raman spectroscopy, Anal. Chem. 77 (2005) 4390.