Chapter 10
Microfluidic Platforms for Nanoparticle Delivery and Nanomanufacturing in Biology and Medicine

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Abstract Nanoparticles are rapidly emerging as promising vehicles for next-generation therapeutic delivery. These highly mobile nanomaterials exhibit large carrier capacity and excellent stability which, when combined with innate biocompatibility, have captured the focus of numerous research efforts. As such, the ability to deliver well-controlled subcellular doses of these functional nanoparticles, both for fundamental research at the single cell level and in related device manufacturing, remains a challenge. Patterning these nanomaterials on biologically compatible substrates enables both novel biological studies and nanomanufacturing avenues through precise spatial control of dosing. Delivering them directly to live cells enables further studies where transfection remains a challenge. This chapter describes a unique tool for functional nanoparticle delivery, called the Nanofountain Probe. The Nanofountain Probe is capable of both direct-write nanopatterning of these materials with sub-100-nm resolution and targeted in vitro injection to individual cells. To motivate the discussion, a brief overview of microfluidic tools developed to deliver nanoparticles is presented. We then focus on the function of the Nanofountain Probe and its application to functional nanodiamond-based biological studies and nanomanufacturing. Development and application of the Nanofountain Probe and other nanomaterial delivery systems will be critical in developing future nanoscale devices and arrays that harness these nanoparticles.

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10.1 Introduction

Nanoparticles have proven to be highly effective vehicles for delivery of biological and diagnostic agents. Their extreme surface-area-to-volume ratios and reactivity facilitate conjugation of large payloads [1]. Additionally, their subcellular size makes them highly intriguing for cell-uptake-mediated drug delivery. Combined with innate biocompatibility (e.g., diamond [2–6] and gold [7, 8]), these nanomaterials merit the tremendous attention they receive in the research community. Examples of applications under investigation include the use of nanoparticle–agent conjugates for gene regulation [9, 10] and delivery of a variety of therapeutics [5, 11–14]. Their potential impact on drug delivery is emergent in early experimental results showing moderated drug activity through controlled release from the nanoparticles [5, 12, 15].

Diamond nanoparticles, also known, previously, as nanodiamonds (NDs) or detonation diamonds after their method of production, have recently gained notoriety for their unique properties. These include proven biocompatibility [2–6], uniform particle distributions [16], large surface-area-to-volume ratio [17], near-spherical aspect ratio, and thoroughly explored carbon surface for various bio-agent attachments [18–20]. NDs have been functionalized with a range of assorted biological agents, such as therapeutics, proteins, antibodies, and DNA [5, 18, 21–25]. Like NDs, gold nanoparticles have proven biocompatible [7, 8] and are finding more and more applications in biodetection and chemical sensing, therapeutic delivery, labeling, and imaging [26]. In a recent example, gold nanoparticles were heterogeneously functionalized with antisense oligonucleotides and synthetic peptides [9]. The oligonucleotide functionalization allows the particles to pass freely into cells, without transfection agents. The peptides subsequently serve to improve cellular uptake and direct intracellular localization.

While a number of nanoparticle-based therapeutics have been approved for clinical use or are undergoing clinical trials, a far greater number are in the preclinical discovery and developmental stages [1, 27]. Beyond agent delivery, applications under investigation include biological labeling, biodetection, tissue engineering, targeted tumor destruction, and imaging contrast enhancement [27].

Owing to the numerous established and potential biological applications for nanoparticles, there is a need for tools which can precisely and consistently deposit controlled doses of these materials. Within the developmental phase, the ability to precisely deliver subcellular volumes of functionalized nanoparticles enables novel single cell studies in dosing, adhesion, and phenotype. For example, patterned arrays of gold nanoparticles were used to selectively control cell adhesion [28]. Also, virus-conjugated nanoparticle arrays were used to study cell infectivity on a single cell level [29]. Manufacturing of functional nanoparticle-based devices requires similar capabilities. As an added challenge, these devices often require massively parallel arrays of nanopatterned structures to be fully functional.

This chapter begins with a brief overview of tools developed for submicron patterning and direct in vitro delivery of functional nanoparticles. We then focus on a novel microfluidic device, called the Nanofountain Probe (NFP, [30–32]), capable of direct-write nanopatterning of liquid molecular and colloidal inks with sub-100-nm

resolution, as well as in vitro injection of functional nanoparticles. Past demonstrations of direct-write nanopatterning using the NFP include proteins [33] and DNA [34] in buffer solution, nanoparticle suspensions [35, 36], and thiols [30, 32]. As a case study with particular relevance to biology and medicine, we focus on the use of the NFP as a tool to deliver precise doses of functionalized diamond nanoparticles in two modes: (1) direct-write nanopatterning of drug-coated nanodiamonds on glass substrates for subsequent cell culture and dosing studies; and, (2) targeted single cell in vitro injection of fluorescently tagged nanodiamonds.

10.2 Tools for High Resolution Functional Nanoparticle Delivery

10.2.1 Nanopatterning on Solid Substrates

A number of direct transfer and directed self-assembly techniques have been designed to deliver nanoparticles to a substrate in a controlled manner [37]. A sample of these techniques is reviewed in the following.

10.2.1.1 Directed Self-assembly

In directed self-assembly, templates consisting of regions of greater and lesser affinity for the nanoparticles are created on a substrate. The nanoparticles then selectively adhere to regions of greater affinity to create the desired pattern. Techniques used to create the templates include electron beam and photolithography [38], dip-pen nanolithography [39–42], and microcontact printing [43, 44]. For example, electron beam irradiation was used to selectively reduce regions of self-assembled monolayers of NO_2-terminated silane on an SiO_2 substrate to NH_2-termination [38]. Citrate-passivated gold nanoparticles then selectively assembled onto the protonated NH_2-terminated regions. While sub-100-nm features are possible, the strong nanoparticle–substrate binding required for well-defined self-assembled features may not be desirable in cases where the drug or other agent must be released. Furthermore, while a variety of substrate–nanoparticle conjugations have been developed for directed assembly, the possibilities may be somewhat more limited for agent-coated nanoparticles.

Langmuir–Blodgett is a technique typically used to assemble continuous uniform thin films [45]. Amphiphilic molecules are first spread over a water surface, forming a monolayer at the liquid–air interface. The substrate is dipped in water, penetrating the surface layer of molecules, then withdrawn in a controlled manner. As the substrate is withdrawn, a monolayer from the surface of the water is extracted with it, leaving a uniform coating. However, by controlling the dewetting of dilute monolayers of gold and silver nanoparticles, well-ordered parallel line and spoke patterns could be formed with line widths down to the micrometer range [46].

10.2.1.2 Direct-write Nanopatterning

In direct-write techniques, the nanoparticles are transferred directly from the tool to the substrate, Some examples include dip-pen nanolithography [47–49], NFPs [35], microcontact printing [50–52], electrohydrodynamic [53] and ink [54] jet printing, nanopipettes [55, 56], microarrayers [28], surface patterning tools [57], and various forms of lithography [58, 59]. In microcontact printing, a polymer stamp containing the desired pattern in relief is coated with the desired ink. The stamp is then brought into contact with the substrate, allowing ink transfer. Depending on the feature sizes on the stamp, even single particle resolution has been achieved [52]. Ink jet printing techniques use similar technology as found in commercial printers. Here, the ink consists of a solution of nanoparticles. Using this technique nanodiamonds in solution, which are the focus of the case study below, were printed with minimum feature sizes on the order of 100 μm [60, 61]. Use of submicron nozzles and electrohydrodynamic jet printing allows for deposition with higher resolution [53].

10.2.2 In vitro Nanoparticle Injection

In addition to rigorous control over delivery factors (i.e., dosing), continuous in vitro nanoscale transfections without supplemental chemical procedures would be desirable in single cell studies. Previous methods of transfection include, but are not limited to: carrier-mediated transfer [62]; biological [63, 64], chemical [65, 66], or electrical plasma membrane permeabilization [67]; and direct injection [68–70]. Each method's advantages and disadvantages have been reviewed elsewhere [69, 71]. Within single cell studies, direct injection methods remain attractive due to their precise targeting and loading capability with virtually any biologically relevant agent. However, there are still several drawbacks associated with traditional cellular injection methods, such as the need for specialized equipment that require large pressure differences and cellular damage during injection due to the relatively large micropipette needle, typically on the micrometer scale [69, 71]. In order to address these issues, several methods employing nanoscale tools have been developed. These include nanoneedles [72–76], microcantilevers [77–80], optical nanoinjection [81], and electrochemical attosyringes [82]. In the unique cases of nanoneedles and microcantilevers, the intended injection material must first be immobilized on the exterior surface of the probe. Therefore, it must remain bound during the injection process, and then subsequently released within the cell. This generally requires specialized chemical modification of the probe surface [74, 76], a process which can be complicated for agent-coated nanoparticles. Another newly fabricated method, capable of injection in a parallel manner, utilized arrays of tightly packed upright nanosyringes [83]. The syringes are loaded with the cargo and act as a bed of needles upon which the cells are cultured. This method was used to deliver plasmids and quantum dots.

10.3 Case Study: Nanofountain Probes for Functional Nanoparticle Delivery

As an alternative to the aforementioned delivery methods, the Nanofountain Probe (NFP [30–32]) makes use of a unique design to achieve both sub-100-nm patterning and in vitro single cell injection of functionalized nanoparticles and biomolecules in liquid solution. The NFP is an atomic force microscope (AFM)-based delivery probe (Fig. 10.1). Liquid molecular "inks" stored in an on-chip reservoir are fed through integrated microchannels to apertured dispensing tips (Fig. 10.1a, inset) by capillary action. This allows continuous delivery either to a substrate for direct-write nanopatterning (Fig. 10.1b), or to a cell for in vitro injection (Fig. 10.1c). For direct-write nanopatterning, the sharp apertured tip geometry allows for a unique combination of resolution and generality in its ability to pattern a broad range of organic and inorganic molecules and nanoparticle solutions. Past demonstrations of direct-write nanopatterning include proteins [33] and DNA [34] in buffer solution, gold nanoparticles in aqueous suspension [35], thiols [30, 32], and drug-coated nanodiamonds [36]. Furthermore, under control of the AFM [75, 79], a ubiquitous research tool, accurate NFP tip placement and real-time force measurements are achievable with respective resolutions of nanometers and nanonewtons.

10.3.1 Direct-write Patterning of Functionalized Nanodiamonds

The NFP was used to precisely place repeatable doses of drug-coated NDs (drug–NDs) with sub-100-nm resolution [36]. NDs were coated with DOX, a commonly used chemotherapeutic which acts through intercalation with a cell's DNA, causing

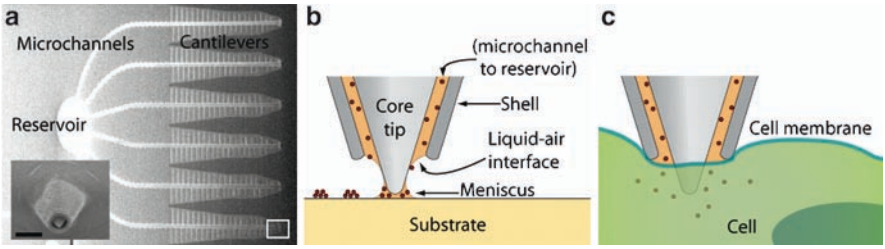

Fig. 10.1 Overview of nanoparticle "ink" delivery using the NFP. (**a**) SEM images showing a quarter section of the NFP chip (scale bar is 2.5 μm). Liquid ink is stored in an on-chip reservoir and fed through enclosed microchannels to apertured writing tips (*inset*) by capillarity. (**b**) For direct-write nanopatterning, the tip is brought into contact with the substrate where an ink meniscus forms. (**c**) For in vitro cellular injection, the tip is introduced to the cell membrane with a prescribed insertion force

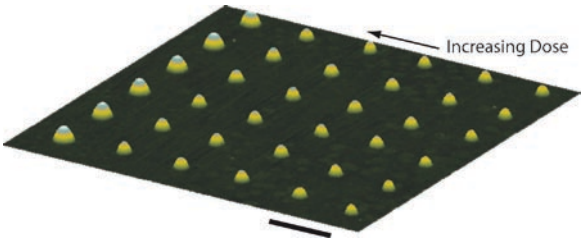

Fig. 10.2 Dot array of drug-coated nanodiamonds patterned on a glass substrate using the NFP [36]. The array is patterned with incrementally increasing feature size for spatial control of dosing. Scale bar is 4 μm

fragmentation and eventual apoptosis. Dot arrays of drug–NDs were patterned directly on glass substrates using the NFP (Fig. 10.2). To create each dot, the NFP was brought into contact with the substrate for a prescribed dwell time, then lifted and translated to the next point in the array. The feature size (both dot diameter and height) depend strongly on the square-root of the dwell time. Thus, the dose is readily controlled by the dwell time. Preservation of drug activity through the patterning process was confirmed through a TUNEL assay, with cells cultured on substrates patterned with dot arrays of drug–NDs showing significantly increased apoptosis [36]. While DOX was demonstrated as a case study, the broader utility of the technique is clear, as NDs have proven capability of carrying a variety of drugs and bioagents [5, 18, 21–25].

Nanopatterning drug–ND conjugates affords extremely precise quantitative and positional control of dosing. It was recently shown that DOX–NDs embedded in parylene are capable of controlled drug release over a period of months [15]. These embedded microfilms are currently being pursued as implants for targeted drug delivery. An attractive enhancement would be to replace the continuous drug–ND films currently used in these devices with patterned arrays using multiple drugs. This allows high fidelity spatial tuning of dosing in intelligent devices for comprehensive treatment. Furthermore, explicit patterning control of NDs would offer avenues for the construction of novel biological-nanoparticle assays [28] and in the immediate future nanomanufactured materials via seeding and nucleation of diamond thin film growth [84, 85].

10.3.2 Direct In vitro Injection

Beyond nanopatterning for biological studies and nanomanufacturing, the ability to directly inject doses of drug bound nanoparticles (e.g., NDs) into cells allows further study of the response of a single cell to a given dose. The ability of the NFP to facilitate these studies was demonstrated through injection of fluorescently tagged NDs.

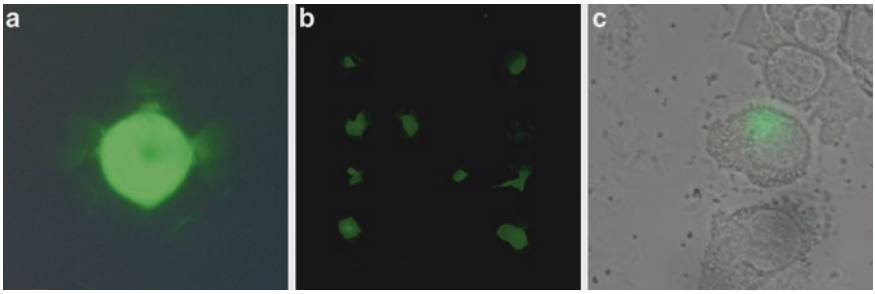

Fig. 10.3 Examples of in vitro single cell injection using the NFP. (**a**) Fluorescence image of an individual macrophage injected with fluorescein. (**b**) Fluorescence image of multiple individual macrophages injected with fluorescein in an "N"-shaped array. (**c**) Overlayed bright field and fluorescence images of an RKO colorectal carcinoma cell injected with fluorescently tagged nanodiamonds

Here, the positional accuracy and force sensitivity of the AFM, a pervasive tool in research, are leveraged to guide the NFP during targeted cell injection. As an initial feasibility study, live macrophages were injected with an aqueous fluorescein solution (Fig. 10.3a, b). Imaging of the cells after injection showed strong confinement of the fluorescent dose to individual cells, suggesting minimal damage to the cell membrane. Fluorescently tagged NDs were then prepared and similarly injected into a variety of cancerous and wild-type cell lines (Fig. 10.3c) [36]. Again, strong confinement of the injected dose was observed, and the ability to target specific regions of the cell demonstrated.

10.4 Discussion and Concluding Remarks

Despite their myriad applications in biology and medicine, nanoparticles are inherently difficult to deliver in precise subcellular doses. The apertured core-shell tip geometry of the NFP allows for a unique combination of patterning resolution and generality in its ability to pattern and deliver a range of liquid solutions. Combined with the positional and force sensitivity of the AFM, this geometry further enables minimally invasive delivery of functional nanoparticles directly to live cells. The combination of multiprobe arrays [30–32] and on-chip reservoirs for continuous ink delivery enables parallel nanomanufacturing for extended periods. The enabling capabilities of the NFP technology for future nanomanufacturing of drug delivery devices and single cell nanomaterial-mediated drug delivery studies are emergent in early examples of drug-coated nanodiamond delivery [36]. Lastly, future studies involving the patterned injection of DNA plasmids, siRNA, therapeutics and conjugated NDs also have exciting implications in determining and directing cellular response.

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