A MagDot-Nanoconveyor Assay Detects and Isolates Molecular Biomarkers

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The ability to quickly analyze, separate, and manipulate multiple types of biomarkers from small sample volumes is a significant step toward personalized medicine.

Biomarkers are small molecules that can be objectively measured as an indicator of normal biological processes, disease conditions, or responses to drug treatment. Biomarkers may consist of proteins, small molecules, deoxyribonucleic acids (DNAs), or various ribonucleic acids (RNAs), such as messenger RNAs (mRNAs), micro RNAs (miRs), or small interfering RNAs (siRNAs), and the cells that manufacture them (Figure 1). Biomarkers can be used to identify the natural disease process (prognostic biomarkers), and may also indicate the potential clinical benefit of a specific treatment (predictive biomarkers).

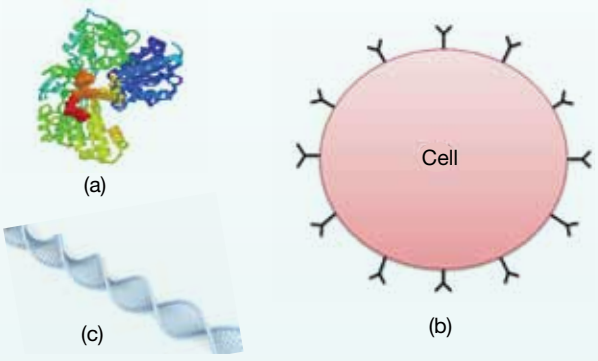
A simple biomarker is the concentration of the small molecule glucose, which is widely used to monitor diabetes and evaluate a patient's responsiveness to diabetic medications. Newer biomarkers, such as pharmacogenetic biomarkers, have the potential to identify which patients may benefit most from a therapy with the least amount of toxicity.

Appropriate biomarker selection is critical for new drug development, since only some patients may benefit from a targeted therapy. For example, the level of expression of the oncogene protein Her2/neu is predictive of the benefit of Her2 monoclonal antibody (Trastuzumab) therapy in breast cancer.

Improved technology for the detection and separation of biomarkers is needed to identify and validate predictive biomarkers. This will aid in the personalization of treatments and the development of novel therapeutics.

Biomarker assay challenges

Accurate detection of soluble biomarkers is crucial for eliminating false positives and false negatives in medical diagnostics. Many analytes are present at very low concentrations (possibly as few as one per cell), and it is not practical to extract large amounts of biological specimens (*e.g.,* blood, biopsy tissue) from patients undergoing treatment to increase their abundance. Thus, soluble-biomarker assays would ideally identify analytes at low levels approaching that of a single molecule. Unfortunately, many common bulk measurement techniques (*e.g.,* absorbance) cannot meet

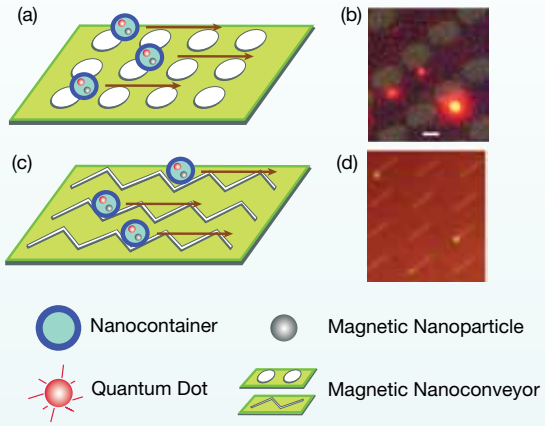


▲ **Figure 1.** There are several types of biomarkers whose number and type may change with disease: (a) free proteins that can be isolated from biological specimens such as blood and urine, (b) bound proteins that are located on the surface of cells, and (c) DNAs/RNAs obtained either by lysing cells or directly from the biological specimen. Source: Adapted with permission from *(15–16).* Copyright 2012 American Chemical Society.

this requirement. Assays that detect analytes through highly specific molecular interactions are desired, as small changes in molecular structure (*e.g.,* misfolded protein, mismatched DNA bases) may affect the overall biomolecular activity.

Cell-surface biomarkers present different challenges. Cell-surface biomarker assays must typically isolate the cell in order to detect its inherent biomarkers. For example, an aspect of predicting, diagnosing, and monitoring liquid tumors (*e.g.,* leukemia, lymphoma, and myeloma) and several immunodeficiency diseases (such as HIV/AIDS) involves analyzing the expression of proteins on the cell surface, typically via flow cytometry. The level of biomarker expression on the cell surface can serve as both a prognostic marker and a predictive marker, and can aid in identifying effective disease treatments.

Every cell population has a certain set of specific cell-surface markers, which can be used to identify cell type, lineage, and stage of differentiation. These markers can also be used to isolate specific populations of cells for tissue engineering, diagnostic, or research purposes. Such blood-based biomarkers are routinely used to identify blood cancers (*e.g.,* hematologic malignancies). However, identification of blood-based markers in solid tumor malignancies faces several technical challenges. For instance, in isolating extremely rare cells, such as circulating tumor cells (CTCs) or circulating fetal cells, it can be difficult to employ techniques such as flow cytometry to isolate the small number of cells that may be present in a highly heterogeneous population of cells.



▲ **Figure 2.** Nanoconveyor technology can be used to transport multiple individual nanocontainers, such as these that encapsulate fluorescent quantum dots for optical tracking and magnetic nanoparticles for controlled transport. Figures 2a and 2c are schematics of nanocontainer transport on microfabricated disks and wire array conveyors, respectively. Figures 2b and 2d are superimposed differential interference contrast (DIC)/fluorescence images of fluorescent-magnetic nanoparticles trapped on micropatterned disks (b) and zigzag wire conveyors (d). Source: Adapted with permission from *(17).* Copyright 2010 American Chemical Society.

Nanotechnology-based molecular detection

One possible way to address these issues is the use of nanotechnology-based molecular detection schemes. Nanotechnology has specific advantages in this application. Nanomaterials and the analytes they are designed to detect are similar in size. For example, DNA is 2 nm in diameter, whereas the average nanoparticle is 1–10 nm in diameter. In contrast, the large magnetic beads typically used for cell separations are on the order of several hundred nanometers to a few microns.

Nanomaterials also have many unique properties, such as the potential for superparamagnetic properties (*i.e.,* they become magnetic only in a magnetic field), fluorescence, and surface plasmon resonance, which can be directly converted into a detectable signal. Several ultrasensitive nanotechnology-based diagnostic assays capable of detecting attomolar (10^{-18} M, or ~100,000 molecules/L) or even single-molecule (10^{-23} M) concentrations of biomarkers have been developed. The presence of a target molecule can induce a conformational change in probe molecules, a change in an optical or electrical signal, or nanoparticle aggregation. These changes can be amplified and converted into detectable signals such as fluorescence or a voltage change. If these detectable signals are additive, the assay can have a quantitative capability, which is critical for monitoring disease progression and response to therapy.

Most of these assays are multistep processes, involving sample enrichment, target capture, amplification (*e.g.,* via polymerase chain reaction [PCR]), and signal detection. Although the molecules examined are all biological, they may differ dramatically in their structure and method of detection. Thus, most detection schemes focus on a single type of biomarker.

Whereas multiplexed detection of molecules of the same type is challenging (*e.g.,* by gene chips or proteomics arrays), detection of multiple types of molecules is extremely difficult. For example, flow cytometry can detect molecules on the cell surface (and interior molecules if the cell is permeable), but it typically cannot independently identify miRNA expression levels and must be coupled with another assay to do so. Thus, miRNA detection is typically performed using PCR amplification followed by biochemical analysis, which would not detect concomitant protein expression. Moreover, this PCR amplification/biochemical analysis technique is largely unable to separate detected molecular targets for further analysis, modification, or manipulation.

The ability to manipulate molecules is an important component of the nanoengineering of molecular structures and for small-scale synthesis (*e.g.,* supramolecular chemistry). A single, one-pot assay for detection, characterization, quantification, and separation of molecular and cellular biomarkers is therefore highly desired.

The following sections describe a nano-enabled technol-

ogy that may be able to perform parallel detection and separation of multiple targets (*e.g.,* cells, molecules). This assay is based on two previously developed platform technologies (Figure 2): patterned magnetic nanowires, *i.e.,* magnetic conveyors *(1)*, and fluorescent-magnetic nanoparticles, *i.e.,* MagDots *(2)*. The magnetic nanoconveyor technology was used to demonstrate the first simultaneous detection and manipulation of sub-100-nm nanoparticles *(2),* and has since been adapted for the detection and manipulation of cells and molecules, including both molecules bound to the cell surface and soluble molecules (Figure 3). The detection scheme varies depending on whether analyte molecules are bound or free. Bound molecules are detected using a fluorescent-magnetic composite nanoparticle targeted to the biomarker of interest, whereas the detection of free molecules is based on biomarker-induced aggregation of individual fluorescent and magnetic nanoparticles. Molecules and cells are then recovered and transported using an array of magnetic nanowires controlled by external electromagnets.

MagDot fluorescent-magnetic nanoparticles

Fluorescent quantum dots (QDs) and superparamagnetic iron oxide nanoparticles (SPIONs) have been used extensively in biology and medicine. Recently, there has been substantial interest in creating nanocomposites that are both fluorescent and magnetic.

QDs are semiconductor nanocrystals (~2–10 nm) with unique optical properties, including broad excitation spectra, narrow emission bandwidths, enhanced photostability compared to fluorescent dyes, and "blinking" (which allows tracking of a single particle). These properties are advantageous in molecular detection assays, because they permit multiplexing (up to eight colors) and quantitative detection. However, QDs are not very stable; particles are susceptible to decomposition under extreme pH conditions and ultraviolet illumination, or in the presence of some enzymes.

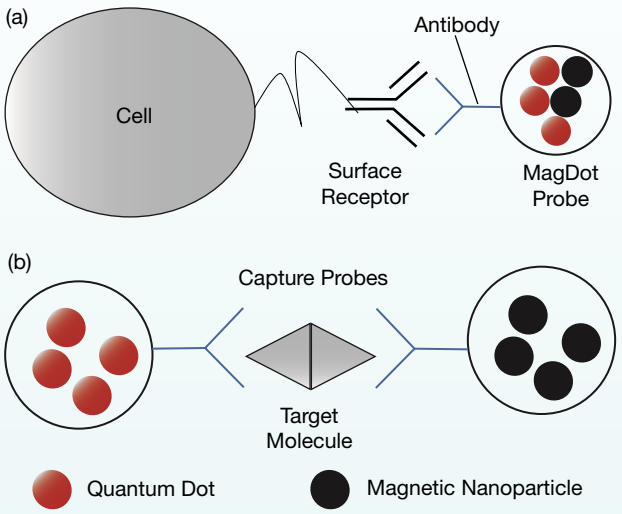
SPIONs are iron oxide (Fe_2O_3 or Fe_3O_4) nanoparticles with distinct magnetic properties that are useful in such applications as magnetic storage, biosensing, separations, targeted drug delivery, and magnetic resonance (MR) imaging. The size of these particles, typically less than about 10 nm, is smaller than that of a single magnetic domain, which gives rise to superparamagnetism: SPIONs are magnetic only in the presence of a magnetic field, and they do not aggregate in the absence of a magnetic field. SPIONs have been approved by the U.S. Food and Drug Administration (FDA) for *in vivo* applications and have been used as contrast agents in MR imaging.

Several research groups have explored synthesis approaches ranging from sequential crystallization *(3–5)* to crosslinking *(6)* to produce nanocomposites of these two particle types. Encapsulation methods have generally proven to be the most successful, because individual particle properties can be optimized and the encapsulating material provides a protective shield from the external environment *(2, 7, 8)*.

The approach employed for MagDot synthesis consists of encapsulating fluorescent QDs and SPIONs within a polymer micelle nanostructure *(9, 10),* and is based loosely on a micelle encapsulation approach pioneered by Dubertret *et al.* in 2003 *(11)*. Above the critical micelle concentration (CMC), amphiphiles that have hydrophobic and hydrophilic domains self-assemble into micellular structures, with their hydrophobic domains forming the nanostructure core and their hydrophilic domains forming the outer shell. Micelles can range from 10 nm to 70 nm in diameter *(8, 10, 11),* and changing the amphiphile can alter their size. Hydrophobic nanoparticles such as QDs and SPIONs can be encapsulated in the micelle core (Figure 4), protected from the aqueous environment by the hydrophilic shell. The resulting particles have both fluorescent and magnetic properties, which can be exploited for detection and separation, respectively.

Magnetic nanoconveyors

To accomplish molecular separation in addition to the detection achieved by measuring the fluorescence of MagDots, magnetic instrumentation is required, such as programmable, mobile magnetic traps (Figure 5) capable of transporting objects across an array surface. Traps can be fabricated in a variety of shapes (*e.g.,* wires, disks) using standard microfabrication techniques and electron beam

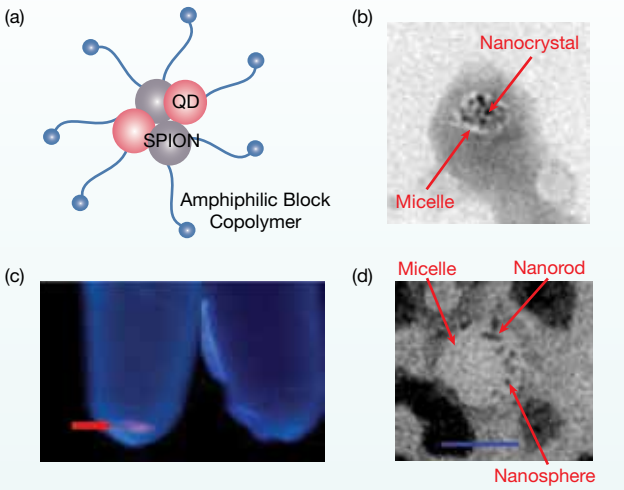


▲ **Figure 3.** Cells (a) and molecules (b) can be detected using multifunctional nanoparticles. In Figure 3a, cells are identified through the binding of nanocontainers encapsulating QDs and SPIONs bioconjugated with antibodies to cell surface proteins. In Figure 3b, nanocontainers encapsulating QDs and SPIONs are separately synthesized and conjugated with capture probes, which attach to the target molecule and form a fluorescent, magnetic sandwich-like structure.

lithography on a silicon substrate. Wires are magnetized by a strong, momentary magnetic field to create permanent traps at wire vertices. Disks contain traps at opposite points on their periphery in the presence of applied magnetic fields; magnetic fields in the plane (x-y fields) of the substrate are produced by cylindrical electromagnets, while a coil of current-carrying wire produces a magnetic field in the out-of-plane (z) direction (Figure 5b). Changing the applied fields via remotely controlled protocols maneuvers the trapped entities along directed pathways, either from wire vertex to wire vertex or from disk to disk. These traps generate piconewton forces that have previously been used to manipulate magnetic microbeads, unlabeled cells, and cells labeled with magnetic microbeads *(1, 12)*.

Two concerns hinder the extension of this work to the manipulation of small molecules *(1)*. The manipulation force generated must be sufficient to overcome Brownian motion, which can be considerable as the size of the target molecule declines, and objects smaller than the limit of resolution of standard optical microscopy (~ 200 nm) are difficult to track.

The combination of MagDots and magnetic nanoconveyors can overcome these challenges. Nanoconveyors generate the very high field gradients needed to manipulate small objects, and the fluorescent functionality of MagDots permits simultaneous tracking. We have shown that individual MagDots can be manipulated using magnetic nanoconveyors *(2)*, an important finding given the small MagDot size (~35 nm). This sets the stage for molecular detection and capture.



▲ **Figure 4.** Nanocontainers encapsulating QDs and SPIONs, shown here schematically (a) and in a negatively stained transmission electron microscope (TEM) image (scale bar = 50 nm) (b), display both fluorescent and magnetic properties in the presence of a magnet and UV excitation source (c). Figure 4d shows that the same technology can also be used to create nanocontainers encapsulating nanorods and nanospheres (scale bar = 50 nm), illustrating the versatility of nanomaterials that may be incorporated. Source: Adapted with permission from *(17)*. Copyright 2010 American Chemical Society.

Detection and separation of bound cell-surface biomarkers

The easiest extension of current practice is to evaluate markers bound on the cell surface. The cell itself is separated, and its expressed biomarkers are evaluated *in situ.*

In many cases, it is not sufficient to simply identify a cell as expressing (+) or not expressing (–) a biomarker. For example, the level of expression of many biomarkers in cancer can influence the choice of treatment. For instance, a quantitative measure of the expression levels of estrogen receptor in breast cancer can help characterize the aggressiveness of the disease and predict responsiveness to therapeutic interventions — cancers with high levels of estrogen expression benefit from endocrine therapy, whereas low expressers benefit most from traditional chemotherapy.

Often, purification, labeling, and characterization of biomarker expression in a desired cell population are carried out in stages, which can impact the yield and accuracy of biomarker detection. A one-step process for isolation and quantification of cell-surface biomarkers is thus highly desired.

The most common methods currently employed for this purpose are fluorescence-activated cell sorting (FACS), immunomagnetic separation, and affinity-based cell separations. Among these, FACS, which uses the presence or absence of specific fluorescence signal(s) emitting from a cell after laser excitation, can separate and quantify biomarker expression at the same time. In general, 10,000 to 100,000 detection events are required to validate a FACS result. This makes it difficult to analyze rare cells that are present at extremely low concentrations, such as circulating tumor cells. Large sample volumes, which are not practical for routine tests to monitor disease progression or response to therapy, may be required to obtain a useful result. Nanofabrication-based assays (such as the MagDot-nanoconveyor system described here) offer a clear advantage over FACS, because the working volume required can be dramatically reduced, sometimes to as little as a few microliters.

We have developed a highly sensitive assay for the separation and detection of bound cellular biomarkers using MagDots coupled with nanoconveyors. This assay provides one-step labeling and separation of specific cells from a heterogeneous population with *in situ* characterization of biomarker expression. MagDots encapsulating both QDs and SPIONs in the same micelle are conjugated with antibodies that target a specific cell population. MagDot-labeled cells are then trapped and manipulated using magnetic nanoconveyors.

An advantage of this platform is that, unlike the large magnetic beads typically employed, the MagDot size is similar to that of the biomarkers detected (2–10 nm), increasing the probability of 1:1 binding with surface biomarkers. Thus, the number of MagDots bound to the cell surface is propor-

tional to the number of biomarkers present. Exact quantification of the number of cell-surface biomarkers expressed may not be possible with this or any method because of potential dimerization; however, MagDots can provide a comparison of relative expression levels of different cells.

As a proof-of-concept demonstration, we targeted MagDots to CD45 receptors on the surface of leukocytes isolated from human blood. The magnetic functionality of MagDots was used to isolate and manipulate leukocytes on the nanoconveyor platform, and the fluorescent intensity was used to quantify the targeted protein. In the MagDot assay, both the fluorescence intensity (pixels/area) and the magnitude of force applied on the cell depend on the number of MagDots bound. Thus, it is possible to independently verify the number of bound MagDots using both particle fluorescence and magnetic mobility. The availability of two independent detection schemes increases the accuracy of the MagDot detection method.

We previously reported the quantification of biomarker expression based on magnetophoretic mobility in a high-throughput immunomagnetic separation assay *(13)*. In this current work, we determined the total number of MagDots bound to a cell by evaluating the average fluorescence intensity of a single MagDot, and comparing it with the total fluorescence intensity from the labeled cell. These numbers compare favorably with those obtained earlier via FACS analysis *(14)*. The addition of fluorescence as a detection method not only increases quantification, but also provides a visual representation of biomarker expression patterns, including their spatial distribution.

A significant advantage of the MagDot detection and separation technique over FACS is the small amount of sample required. A sample as small as 5 µL, the clinical equivalent of a pinprick, is often sufficient. Furthermore, the biomarker expression and distribution of an individual cell can be examined, whereas FACS provides population averages.

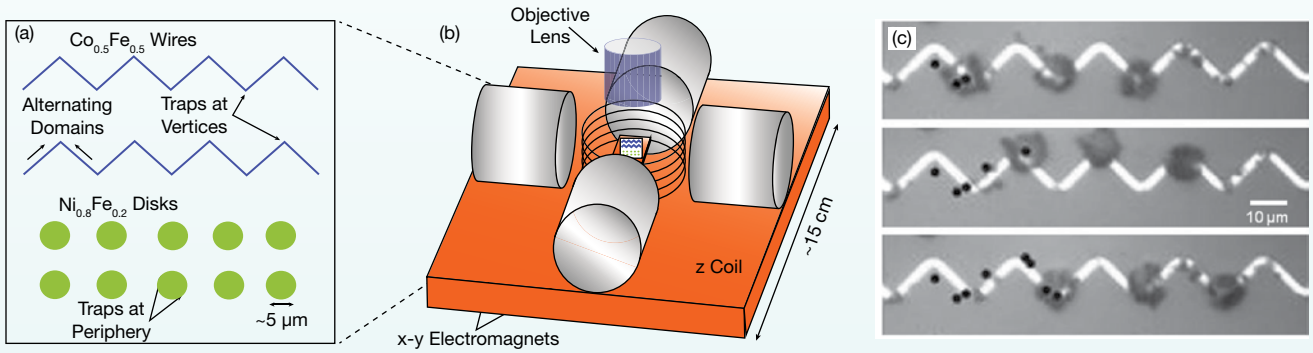
An important component of this detection scheme is the fluorescence intensity of MagDots, and we have shown that fluorescence intensity can be tuned by adjusting QD loading (results not shown). Additionally, the fluorescence displayed by MagDots is stable, unlike that of many fluorescent dyes.

Detection and separation of soluble molecular biomarkers

A challenge in adapting the cellular biomarker detection approach to the detection of small, soluble biomarkers is their dramatic difference in size. To detect biomarkers expressed on a cell surface, the entire ~10-µm-dia. cell is isolated, whereas separating molecular biomarkers requires the identification and manipulation of objects as small as a few nanometers.

To increase efficacy of the MagDot-nanoconveyor assay, we adopted a sandwich design, similar to that used in enzyme-linked immunosorbant assay (ELISA). Separate fluorescent and magnetic nanoparticle micelles bound with specific capture probes are introduced into the analyte sample. The capture probes are designed so that they bind to the target molecule and form a fluorescent-magnetic nanocomposite only in the presence of an analyte. This nanocomposite forms a sandwich-like structure with a fluorescent nanoparticle on one end, the analyte in the middle, and the magnetic nanoparticle on the other end. This nanocomposite can then be manipulated using nanoconveyors.

Similar to the assay for cell-surface biomarkers, the response of the captured target can be tracked using either fluorescent or magnetic properties, or both. In this case, because only nanocomposites formed by the analyte will contain both fluorescent and magnetic constituent micelles, the ability to visualize and manipulate a nanocomposite constitutes a detection signal. Since each molecule is



▲ **Figure 5.** The magnetic nanoconveyors shown in this schematic (a) are $Co_{0.5}Fe_{0.5}$ zigzag wires and $Ni_{0.8}Fe_{0.2}$ disks. Points on the periphery of a magnetized disk act as magnetic particle traps, whereas alternating magnetic domains in zigzag wires give rise to regions of high fields and field gradients at wire vertices. These regions act as traps for magnetic nanoparticles. The entire system (b), including the external electromagnets and coil required to apply magnetic fields, can be mounted on an optical fluorescence microscope. Application of fields can strengthen, weaken, or move traps, allowing for manipulation of trapped entities along directed pathways. In the third image (c), T-lymphocyte cells labeled with anti-CD3-conjugated 1-µm magnetic particles are propagated along wires. Source: Adapted from *(18)*. Copyright 2009 American Physical Society.

detected through the aggregation of fluorescent and magnetic nanoparticle micelles, the fluorescence intensity increases with increasing target molecule concentration. This provides a way to determine the concentration of analyte in solution. Similarly, the captured molecule can be transported by the nanoconveyors to a collection point using the programmable external magnetic field. Thus, molecular detection, quantification, and separation are all performed on the same platform.

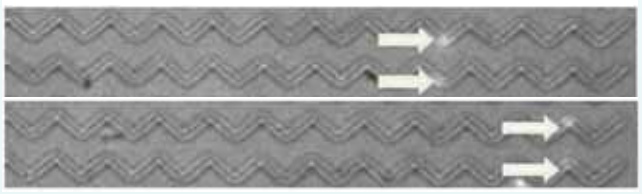
Minimal fluid handling has enabled sensitivities as high as 10^{-16} M with an ultrasmall sample volume of only 5 µL, and the detection and separation of as few as 1,000 molecules. Furthermore, because QDs are used as fluorescent probes, their size-tunable narrow emission spectra impart multiplexing capability. Detection and separation of protein and DNA targets on the same chip has been performed (Figure 6). The ability to multiplex detection and separation of multiple biomarker types is an important advance in biomarker detection.

Closing thoughts

Biomarker analysis is an increasingly important component of efforts to individualize and improve clinical care. The ability to rapidly analyze multiple types of biomarkers using small sample volumes is an important milestone toward personalized medicine. Nanotechnology offers many technological advantages in biomarker detection and separation because of the small size of nanocomponents and their unique, inherent properties. An advantage of the magnetic nanoconveyor approach described here is that cells and molecules are not only analyzed, but also isolated and manipulated, which could permit downstream sorting and analysis.

Assays capable of separation as well as detection may find applications outside of the clinic as well, for example in tissue engineering or supramolecular chemistry. In tissue engineering, a precise placement of cells can be achieved for constructing complex organ structures. In supramolecular chemistry, molecules can be arranged to build hierarchical structures.

Thus, the MagDot nanoconveyor platform offers an exciting new tool to isolate, quantify, and manipulate biomolecules and has promising potential in the identification and validation of additional biomarkers in various disease states. CEP



▲ **Figure 6.** The nanoconveyor technology can also be used to detect, isolate, and manipulate DNA via a MagDot sandwich.

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A MagDot-Nanoconveyor Assay Detects and Isolates Molecular Biomarkers

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Engineered Protein Templates Synthesize Inorganic Nanomaterials

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