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1. REPORT DATE (DD-MM-YYYY) 18-06-2007		2. REPORT TYPE Final		3. DATES COVERED (From - To) 01-May 2001 --30-Sep 2006	
4. TITLE AND SUBTITLE Synthesis and Manipulation of Biofunctional Magnetic Particles				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER N00014-01-1-0782	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Whitesides, George M. Ingber, Donald E. Prentiss, Mara Xia, Younan				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) President and Fellows of Harvard College Office for Sponsored programs 1350 Massachusetts Avenue, Suite 600 Cambridge, MA 02138				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) Office of Naval Research 875 North Randolph St. Arlington, VA 22203-1995				10. SPONSOR/MONITOR'S ACRONYM(S) ONR	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION/AVAILABILITY STATEMENT Distribution Unlimited				DISTRIBUTION STATEMENT A Approved for Public Release Distribution Unlimited	
13. SUPPLEMENTARY NOTES					
14. ABSTRACT The most important conclusions of this program for biology are that mechanical forces (here, generated magnetically) applied to the surface of cells provides a method of stimulating cells, and of reading out their response (via changes in the cytoskeleton) to changes in their environment. Magnetic interactions have many characteristics required for broad utility in biomedicine: in particles, i) magnetic forces can be much stronger than optical forces; ii) they are not screened or attenuated (as are optical and electrostatic forces) by the medium; iii) the availability of nanoscale magnetic particles, and to modify the properties of these particles through surface chemistry, provides a method of applying large forces locally and to specific receptors or targets; iv) cells respond readily to mechanical stimulation by magnetic forces; v) magnetic interactions provide the basis for a range of methods for separations of cells and molecules.					
15. SUBJECT TERMS superparamagnetic beads, magnetic tweezers, micro-total analytical systems, magnetic interactions					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT UL	18. NUMBER OF PAGES 10	19a. NAME OF RESPONSIBLE PERSON George M. Whitesides
a. REPORT Unclass	b. ABSTRACT Unclass	c. THIS PAGE Unclass			19b. TELEPHONE NUMBER (Include area code) 617-495-9430

FINAL REPORT

GRANT #: N00014-01-1-0782

PRINCIPAL INVESTIGATOR: George M. Whitesides, Ph.D.

INSTITUTION: Harvard University
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GRANT TITLE: Synthesis and Manipulation of Biofunctional Magnetic Particles

AWARD PERIOD: 1 May 2001 - 30 September 2006

OBJECTIVE: The overall objectives of this program were to develop methods to fabricate and manipulate magnetically responsive, superparamagnetic beads with sizes in the range from a few to a few thousand nanometers, and to use these structures for various functions in cell and molecular biology. The specific tasks included:

- Providing methods of controlling the surface chemistry of these particles, and of attaching ligands to them that are useful in biological applications.
- Using them for preconcentration of samples for biological analysis.
- Using them to manipulate mammalian cells.
- Using them as the basis of "magnetic tweezers", to apply forces to individual, interacting biomolecular systems, and to measure force-distance curves.
- Using them as the basis for magnetic readout of cell-based sensors.
- Developing programmable systems that would allow magnetic beads to be moved to predetermined positions in a planar array.
- Demonstrating integration of these magnetic systems with microfluidics, and with complementary methods of detection to enable new types of micro-total analytical systems.

APPROACH: The team involved four investigators, each with complementary responsibilities. Xia synthesized a variety of superparamagnetic particles, either as homogeneous materials or as core-in-shell structures; Whitesides synthesized and attached ligands to these particles, and otherwise engineered their surface properties; Ingber used the particles in experiments with mammalian cells, both to examine their ability to stimulate cells mechanically and to read out the response of the cell to chemical and mechanical stimulation; Prentiss used them in biophysical experiments to examine interactions between proteins and ligands. Together this group covered the range of research activities: synthesis and fabrication; materials science; biosurface science; mammalian cell biology; biophysics.

ACCOMPLISHMENTS: We summarize the accomplishments of the research under three headings:

1. Synthesis and Fabrication of Magnetic Nanoparticles.

- Coating superparamagnetic iron oxide nanoparticles with silica shells. We have demonstrated a method based on sol-gel chemistry for coating individual iron oxide nanoparticles with conformal, uniform shells. The thickness of silica coating could be controlled in the range of 2-100 nm by adjusting the concentration of tetraethylorthosilicate (TEOS), a sol-gel precursor to silica. The multifunctional core-shell particles are useful in

a number of areas because they can be simultaneously manipulated with an externally applied magnetic field and tracked in situ using conventional fluorescence microscopy.

- **Synthesizing Core-Shell Superparamagnetic Particles.** To increase the magnetization susceptibility of the core-shell particles, we modified the coating procedure to incorporate more than 100 iron oxide nanoparticles into each silica shell. In a typical synthesis, organophilic iron oxide nanoparticles were extracted from a ferrofluid and re-dispersed in toluene. The suspension was then added to an alcoholic medium to produce emulsion drops consisting of aggregates of iron oxide nanoparticles and toluene. When TEOS was introduced into the system, it hydrolyzed and formed silica coating around each emulsion drop.
- **Exploration of new materials for encapsulating magnetic nanoparticles.** We incorporated iron oxide nanoparticles into monodispersed amorphous selenium (a-Se) colloids by regulating the reaction temperature during the synthesis of a-Se. The surfaces of these a-Se colloids could then be coated with conformal and smooth shells made of Pt and/or SiO₂. Finally, the Se cores could be selectively removed by etching with hydrazine. The spherical morphology and superparamagnetism were maintained in all these synthetic steps.
- **Development of new methodologies for nanocrystal synthesis.** To prepare magnetic nanoparticles coated with noble metals (e.g., gold, palladium, and platinum) that can present a well-established surface for forming biochemically relevant self-assembled monolayers (SAMs) with alkanethiols, we have systematically investigated the formation of noble metal nanocrystals in a solution phase. We can now control the size, shape, crystallinity, and structure (solid vs. hollow) of the nanocrystals.
- **Nanorods.** We extended existing methods of synthesizing metallic structures in ferromagnetic materials—especially nickel—with nanometer dimensions. The most successful of these fabrications is that for nickel nanorods, based on the electrochemical deposition of nickel metal through pores in a nanoporous membrane.

2. Uses of Magnetic Interactions in Biochemistry and Biophysics.

- **High-Field Concentrators.** One of the key components to magnetic manipulations in biochemistry will be the availability of ultrahigh-field magnetic field gradients. We fabricated such systems, based on sharp edges and thin sheets of ferromagnetic materials.
- **Combined Magnetic-Microfluidic Cell Separations.** We developed an efficient method for separating molecules or living cells from flowing fluids within a microfluidic system using magnetic micro- and nano-particles.
- **Understanding the forces between molecules centrally important in molecular biology.** Our methods complement optical tweezers and atomic force microscopy; however, they also add precise temperature control and have the advantage of measuring ~1000 such interactions in parallel.
- **Magnetic Measurement of Force-Distance Curves for Molecular Interactions.** This work has focused on solving the technical problems necessary to make magnetic tweezers into a tool broadly useful in biophysics, especially control of the surface chemistry of these systems, and applications in DNA-DNA and protein-ligand interactions.
- **Application of magnetic colloidal particles to proteomics.** Solid-phase extraction of glycopeptides (SPEG) coupled with quantitative proteomic analysis using mass spectrometry has shown great potential for investigating glycoproteins from cells, tissues, and body fluids in an effort to discover new diagnostic biomarkers or therapeutic targets.

3. Applications of Magnetic Particles in Cell Biology.

- **Magnetic Actuation of Mechanical Force Application to Cells.** We developed a broad range of methods for attaching small ferromagnetic or superparamagnetic beads to transmembrane receptors on the exterior surface of the cell, applying mechanical stresses (tension or shear) to the cell by manipulating these beads using external magnetic field gradients, and monitoring subcellular structural rearrangements on the nanometer to micrometer scale. The influence of these forces on the mechanical and biochemical behavior of the cell provides information about the way in which the cell senses and responds to mechanical stimulation. These methods also offer the potential to use mammalian cells as sensors for biological interactions. A toxin, for example, might be detected by its influence on cellular response.
- **Magnetic Analysis of Intracellular Structure and Mechanics in Living Cells.** To better understand how cells respond to changes in mechanical forces, static and dynamic tensional forces were applied to magnetic microbeads bound to cell surface integrins while simultaneously measuring dynamic changes in bead displacement induced by the applied force. These studies revealed that cells exhibit various adaptation responses to different frequencies of force application, and that these are mediated by assembly of specialized cytoskeletal anchoring complexes, known as "focal adhesions", at the site of force application. Magnetic methods also map out intracellular strain fields within living cells in response to mechanical (magnetic) stress application. These studies have revealed that mechanical forces are transferred across discrete cytoskeletal elements over long distances through the cytoplasm to structures in the nucleus and on the surface membrane at the opposite pole of the cell.
- **Electromagnetic needles with submicron pole tip radii for nanomanipulation of biomolecules and living cells.** A novel temperature-controlled electromagnetic microneedle was fabricated to generate custom magnetic field gradients for biomedical and biophysical applications. An electropolishing technique was developed to sharpen the magnetic pole tip to any desired radius between 200 nanometers and 20 micrometers. The electromagnetic needle can be used to apply strong static or dynamic forces (>50 nN) to micrometer- or nanometer-sized magnetic beads.
- **Magnetic Control of Signal Transduction.** The magnetic micromanipulation methods have been used to activate intracellular signaling cascades that lead to gene transcription by applying force specifically to transmembrane integrin receptors. Signaling molecules specifically activated by magnetic force applied to integrins include stress-sensitive ion channels and cAMP signaling components. This work relies on the ability of use magnetic interactions to work at a distance without direct contact with the cell, and to apply force on a scale greater than the traction forces cells exert on the bound beads.
- **Magnetic-Guided Molecular Self-Assembly.** We developed a magnetic method to self-assemble extracellular matrices with defined structural anisotropy on the nanometer scale that may be useful for cell culture and tissue engineering applications.
- **Magnetic Media for Cells.** Paramagnetic buffers provide a new method of manipulating diamagnetic in a magnetic field, by allowing the manipulation of the "apparent density" of the cell by changing the magnitude of the external field.

CONCLUSIONS: The most important conclusions of this program for biology are that mechanical forces (here, generated magnetically) applied to the surface of cells provides a method of stimulating cells, and of reading out their response (via changes in the cytoskeleton) to changes in their environment.

Magnetic interactions have many characteristics required for broad utility in biomedicine: in particles, i) magnetic forces can be much stronger than optical forces; ii) they are not screened or attenuated (as are optical and electrostatic forces) by the medium; iii) the availability of nanoscale magnetic particles, and to modify the properties of these particles through surface chemistry, provides a method of applying large forces locally and to specific receptors or targets; iv) cells respond readily to mechanical stimulation by magnetic forces; v) magnetic interactions provide the basis for a range of methods for separations of cells and molecules.

SIGNIFICANCE: This work has provided a range of new, magnetically based techniques for biomedicine, biochemistry, and biophysics. It has demonstrated a range of new uses of magnetic materials--superparamagnetic nanoparticles, core-in-shell particles, paramagnetic buffers--and techniques--for synthesis, separations, biophysics, and manipulations of cells--in biochemistry, biophysics, and cell biology. These materials and techniques contribute to biomedicine by:

- Providing routes to magnetic nanoparticles, for applications that include (or have the potential to include) cell sorting, molecular separations, fundamental cell biology, MRI contrast enhancement
- Demonstrating uses of these materials and techniques in fundamental cell biology, especially in studies of the cytoskeleton, and of mechanisms by which cells interact mechanically with their environment
- Offering new, magnetically based tools to biomedical researchers in a range of fields.\
- Clarifying the interaction of DNA with itself.
- Providing new tools to synthetic chemists (for example, one of these systems -- silica colloids loaded with iron oxide nanoparticles -- has been successfully applied to the automated, high-throughput, and reproducible analysis of glycoproteins).

PATENT INFORMATION:

Whitesides:

Four potential inventions were identified, in whole or in part, from work at Harvard on this award. However, at this time all Harvard cases related to this award have been inactivated. Two had only a provisional application filed and abandoned, and no applications were filed on the other two. The details are as follows:

Case 2355 abandoned - title: "Magnetic Trap for Living Cells Suspended in a Paramagnetic Buffer", provisional application filed 7/9/04--abandoned.

Case 2282 abandoned - title: "Targeting Magnetic Particles to Specific Cells in a Monolayer Using Patterned Permanent Magnets"--no filings.

Case 2280 abandoned - title: "A Ferromagnetic Photoresist for the Fabrication of MicroElectroMechanical Systems". Provisional filed 9/21/04--abandoned.

Case 1950 abandoned - title: "Fabrication of Magnetic Microfiltration Systems Using Soft Lithography"--no filings.

Ingber:

"Differential Treatment of Selected Parts of a Single Cell with Different Fluid Components Takayama S, Ostuni E, LeDuc P, Naruse K, Ingber DE, Whitesides GM, inventors." US Patent 6,653,089; 2003, Nov 25

Microfluidic devices for magnetic separation in continuous flow. Inventors: Xia N, Hunt TP, Mayers BT, Alsberg E, Whitesides GM, Westervelt RM, and Ingber DE, inventors. (pending)

"Nanomanipulation of Biomolecules and Living Cells." Ingber DE, Matthews BD, Lavan DA, Overby DR, inventors. (pending)

"Magnetically Guided Self-assembly of Fibrin Matrices with Ordered Nano-Scale Structure for Tissue Engineering." Ingber DE, Alsberg E, inventors. (pending)

Xia:

US Patent application pending for: "Methods of Nanostructure Formation and Shape Selection" (Xia, Y. and Sun, Y., 2005)

AWARD INFORMATION:

Whitesides:

2001 Doctorate Honoris Causa, University of Twente, The Netherlands
2003 Kyoto Prize in Advanced Technology (Inamuri Foundation, Japan)
2004 Paracelsus Prize (Swiss Chemical Society)
2004 Jacob Heskel Gabbay Award in Biotechnology and Medicine
2005 2004 Dickson Prize in Science (Carnegie Mellon University)
2005 Dan David Prize (Dan David Foundation, Israel)
2005 Welch Award (Welch Foundation)
2005 National Academy of Engineering
2005 Linus Pauling Medal (Oregon, Portland, Puget Sound sections, ACS)
2005 Honorary Fellow of the Royal Society of Chemistry (UK)
2006 U.A.A. Dhirubhai Ambani Lifetime Achievement Award (India National Science Academy)
2007 Priestley Medal, American Chemical Society
2007 American Institute of Chemistry, Gold Medal

Ingber:

2001 Distinguished Lecturer in Medical Science, Mayo Clinic, Rochester, MN
2001 Finalist, M.I.T. 50K Entrepreneurship Competition
2002 Co-Chairman, Keystone Symposium on "Biological Response to Extracellular Matrix"
2002 MIT Bioengineering Society Distinguished Lecture
2002 Broadhurst Lecture, Schepens Eye Research Institute
2002 Selected as one of Esquire Magazine's "The Best and Brightest"
2004 Pomerat Memorial Lecturer, University of Texas at Galveston
2004 Appointed the first Judah Folkman Professor of Vascular Biology at Harvard Medical School and Children's Hospital
2005 Talbot Lecture and Medal in Theoretical and Applied Mechanics, University of Illinois, Urbana-Champaign
2005 Lou Siminovitch Lecture, Canadian Institute for Health Research, University of Toronto
2006 Medal of the Atheneum, University of Padova, Padova, Italy

Prentiss:

None.

Xia:

2002 Camille Dreyfus Teacher Scholar, Camille and Henry Dreyfus Foundation
2005 Leo Hendrik Baekeland Award, North Jersey Section, American Chemical Society
2006 NIH Director's Pioneer Award

PUBLICATIONS AND ABSTRACTS (for total period of grant):

Whitesides:

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9. "Unconventional Nanofabrication", Gates, B. D., Xu, Q., Love, J. C., Wolfe, D. B. and Whitesides, G. M., *Annual Review of Materials Research*, 2004, 34, 339-372.
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Prentiss:

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