Introducing the 2013 JALA Ten

Dean Ho

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Introducing the 2013 JALA Ten

JALA Editor-in-Chief Dean Ho[1]

We are pleased to present this year's JALA Ten honorees, which highlight significant breakthroughs across the intersection of automation, diagnostics, therapeutics, imaging, manufacturing, and beyond. Examples include new paradigms in design, nucleic acid–based therapeutics, the development of novel nanolithography approaches, and cellular interrogation and control, among others.

Nominations hailed from all corners of the research universe including universities; companies, both early stage and established; and government research laboratories. Honorees have developed new approaches that range from the fundamental to those that have been successfully transitioned into commercial products.

Innovation is a team effort, and this year's selections demonstrate the remarkable progress that can be realized when top scientists and engineers combine their talents with those of translationally minded clinicians and entrepreneurs toward realizing important advancements that will ultimately improve the quality of health care. It is this same scope that is evident across the membership of the JALA Editorial Board and the principles that guide our publishing philosophy.

The JALA Editorial Board would like to thank all of the enthusiastic nominators for their thoughtful and comprehensive assessments of their respective submissions and salutes the honorees for their continued efforts toward demonstrating the importance of continued support for research and development, enabling innovation to benefit nearly every facet of biology and medicine.

Optimizing Design Outcomes

By Francesco Ciucci[1], Tomonori Honda[2], and Maria C. Yang[2]
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[2]Massachusetts Institute of Technology, Cambridge, MA, USA

One common way to represent a complex engineering system (for example, an aircraft or a desalination plant) is as an overall system that encompasses many subsystems, such as a power subsystem and a structural subsystem. A continuing challenge in the early stages of designing complex engineering systems is making design tradeoffs between subsystems so that the overall system can achieve the best possible performance. One accepted strategy is to apply game theory to a design, treating subsystems as "players" that pass information to each other until the

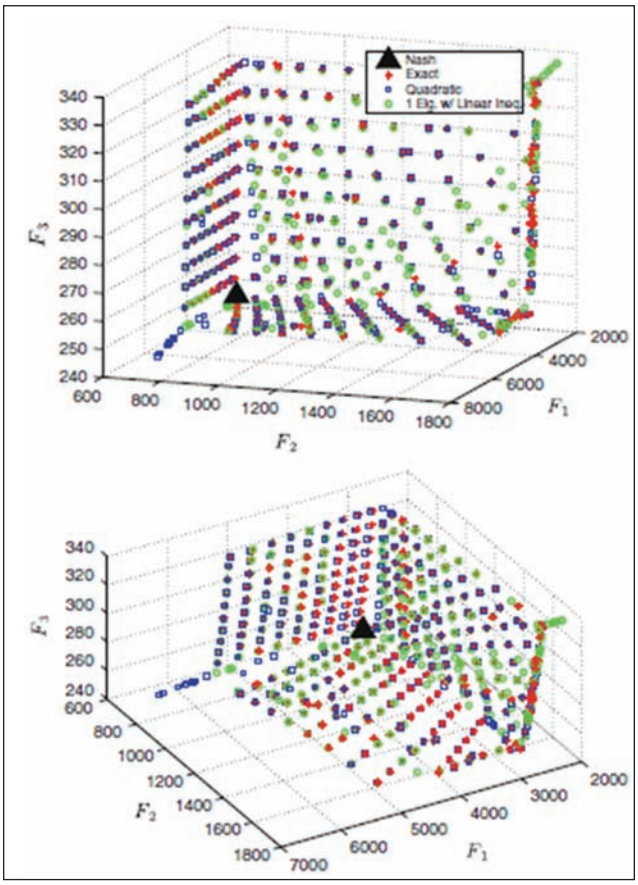

Figure 1. Reprinted with permission from Ciucci F, Honda T, Yang MC. An Information Passing Strategy for Achieving Pareto Optimality in the Design of Complex Systems. *Res. Eng. Des.* **2013**, *23*(1), 71–83.

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overall system reaches optimality. Current game theoretic approaches pass simple point information and can achieve a Nash equilibrium. This article explores the value of passing additional information by putting it in the form of a quadratic and also a Hessian (compressed into an Eigenvalue), thus making the system more cooperative and therefore lead to highly desirable Pareto optimal solutions. The approach is illustrated through three case examples: (1) a mathematical design problem with two players, (2) an aircraft design problem with two players, and (3) the design of a speed reducer with three players. This article demonstrates that a Pareto solution can be reached in all three of these cases. Using this strategy, designers of complex systems have the potential to achieve more effective design outcomes.

High-Throughput Three-Dimensional Tracking of Human Sperms Using Computational On-Chip Imaging

By Ting-Wei Su[1], Liang Xue[1], and Aydogan Ozcan[1]
[1]University of California, Los Angeles, Los Angeles, CA, USA

This work demonstrates a novel lens-free on-chip imaging technique that can track the three-dimensional (3D) trajectories of >1500 individual human sperms within an observation volume of ~8 to 17 mm^3 with submicron accuracy and ~10 to 12 ms temporal resolution. This high-throughput imaging platform achieves more than an order of magnitude larger imaging volume compared with other microscopy tools permitting us to report, for the first time, the helical trajectories of human sperms, an observation that could not be reported before our work, mostly because of tight 3D radii of such helices as well as the rapid rotation speed of human sperms.

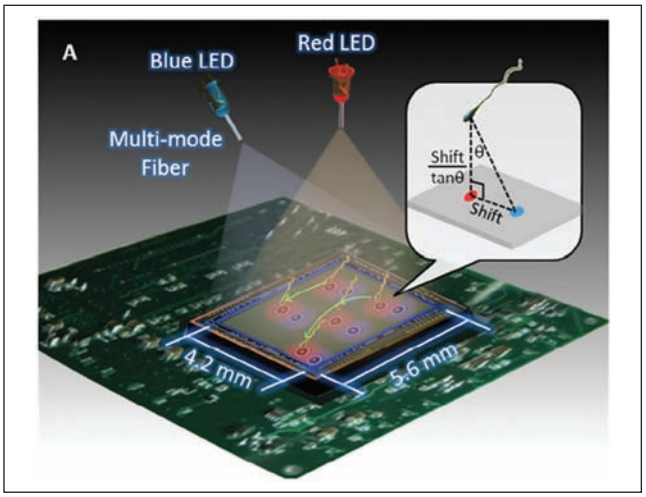

Figure 2. Reprinted with permission from Su T-W, Xue L, Ozcan A. High-Throughput Lensfree 3D Tracking of Human Sperms Reveals Rare Statistics of Helical Trajectories. *Proc. Natl. Acad. Sci. U. S. A.* **2012**. DOI: 10.1073/pnas.1212506109

Cantilever-Free Scanning Probe Molecular Printing

By Louis Giam[1] and Chad A. Mirkin[1]
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Cantilever-free scanning probe molecular printing techniques (polymer pen lithography and hard-tip, soft-spring lithography) merge the advantages of dip-pen nanolithography and

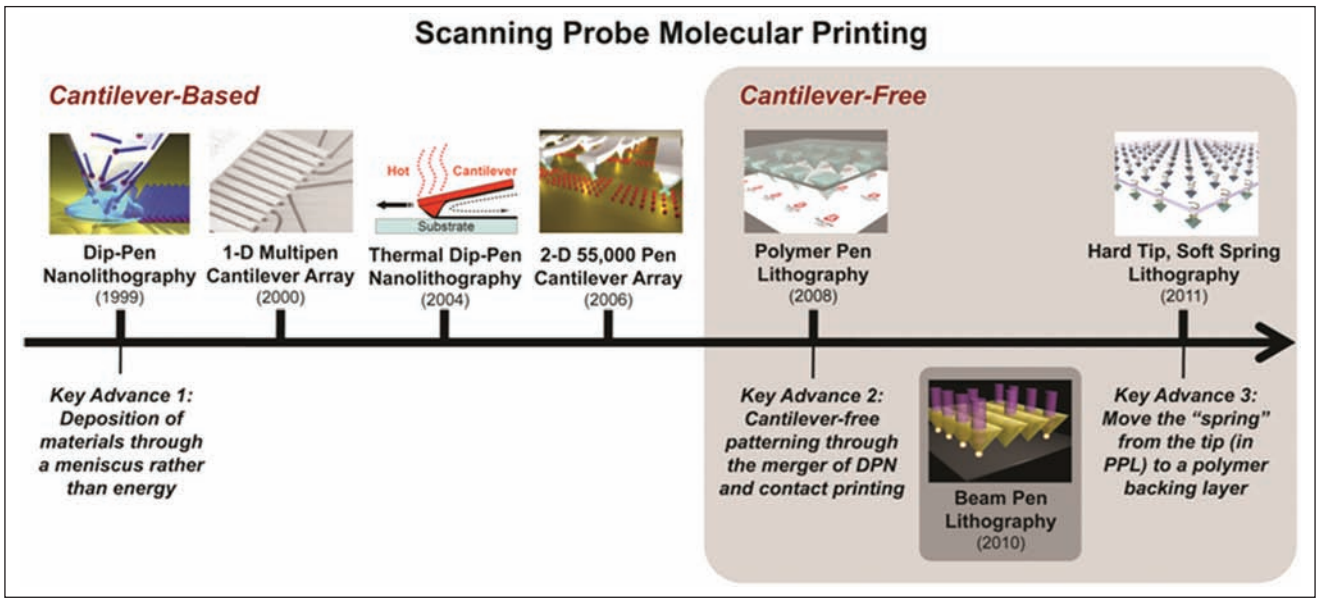

Figure 3. Reprinted with permission from Giam L, Mirkin C. Cantilever-Free Scanning Probe Molecular Printing. *Angew. Chem. Intl. Ed.* **2011**, *33*, 7482–7485.

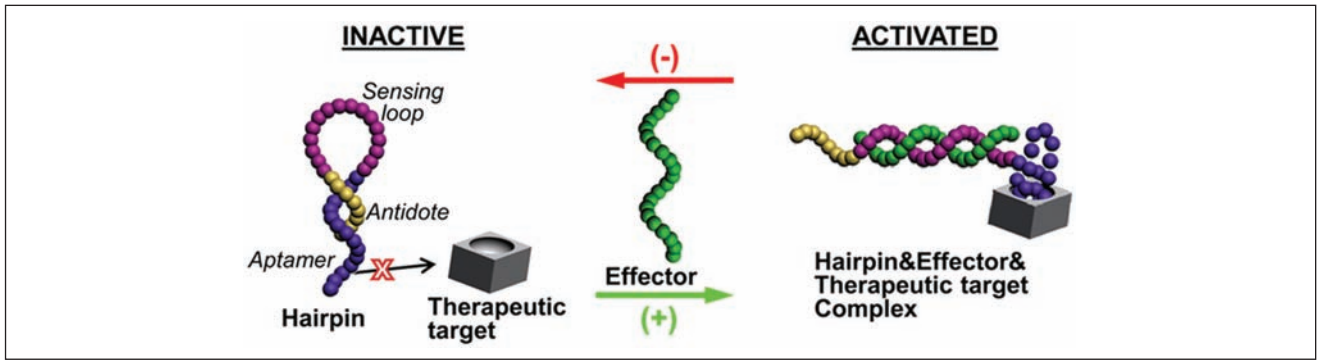

Figure 4. Reprinted with permission from Li N. Reversible Regulation of Aptamer Activity with Effector-Responsive Hairpin Oligonucleotides. *J. Lab Autom*. **2012**. DOI: 10.1177/2211068212448429

microcontact printing to enable parallel and inexpensive printing of molecular features with nanoscale resolution over large areas. The conceptual advance was the elimination of impractical cantilevers and the use of compliant pyramids mounted on a hard transparent backing or, alternatively, the use of hard tips on a soft-backing layer, also mounted on a transparent substrate, as the molecular delivery vehicles in a piezo-driven scanning probe device. These advances have led to all commercialized forms of molecular printing tools (NanoInk).

Reversible Regulation of Aptamer Activity with Effector-Responsive Hairpin Oligonucleotides

By Na Li[1]
[1]University of Miami, Miami, FL, USA

Most of the existing strategies for regulating aptamer activity have a limited specificity and/or reversibility. This work demonstrated a simple, generic strategy to simultaneously achieve specificity and reversibility by exploiting the spontaneous conformational change of hairpin oligonucleotides upon the specific recognition of nucleic acid effectors. This new strategy has been demonstrated with an anticoagulant aptamer. With further optimization and development, this strategy could potentially be used to create on-demand aptamer therapy. The potency of the therapy (the aptamer activity) is continuously adjusted based on the disease status that is indicated by the amount of effectors (mRNA or DNA biomarkers).

Hydrodynamic Stretching of Single Cells for Large Population Mechanical Phenotyping

By Daniel R. Gossett[1], Henry T. K. Tse[1], Serena A. Lee[1], Yong Ying[1], Anne G. Lindgren[1], Otto O. Yang[1], Jianyu Rao[1], Amander T. Clark[1], and Dino Di Carlo[1]
[1]University of California, Los Angeles, Los Angeles, CA, USA

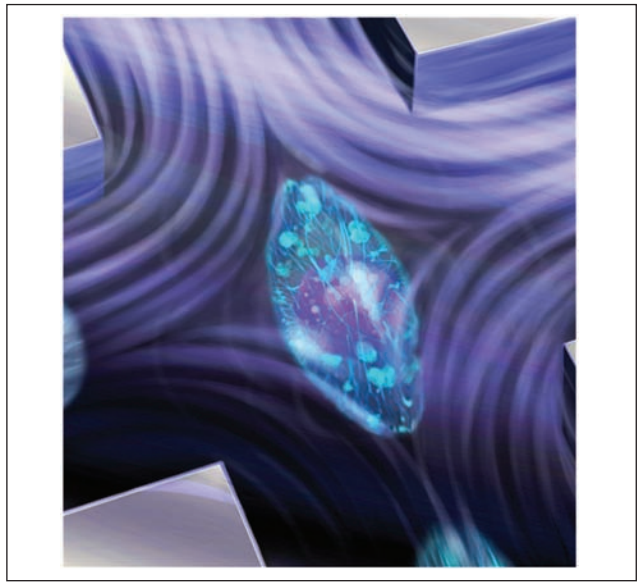

Figure 5. Reprinted with permission from Gossett Daniel R, et al. Hydrodynamic Stretching of Single Cells for Large Population Mechanical Phenotyping. *Proc. Natl. Acad. Sci. U. S. A.* **2012**, *109*, 7630–7635.

Biomarkers for cell type, state, and function enable critical classifications in biological research and medical diagnostics. Recently, biophysical markers have been shown to be attractive, label-free alternatives to conventional biochemical biomarkers. The potential impact of these biophysical markers spans many areas of biomedicine including regenerative medicine, clinical cancer diagnostics, and immune monitoring. However, current methods of probing single-cell mechanical properties are either too labor intensive for clinical adoption or too low in throughput to accurately sample the heterogeneity of biological samples. Dino Di Carlo and his research group have recently developed a technique called *deformability cytometry*, which couples microfluidic hydrodynamic stretching with high-speed imaging and automated image analysis to probe single-cell deformability at a rate of more than 1000 cells/s. This throughput enables thorough sampling of clinically relevant complex and heterogeneous

biological fluids (e.g., blood, pleural effusions, and urine). The limited operational complexity and minimal sample preparation requirements of this method will ease translation as both a research tool and clinical diagnostic tool. Deformability cytometry makes mechanical phenotyping robust and accessible to biomedicine.

Thermal Biosensing with Phase Change Nanoparticles

By Chaoming Wang[1], Zhaoyong Sun[1], Liyuan Ma[1], and Ming Su[7]
[1]University of Central Florida, Orlando, FL, USA

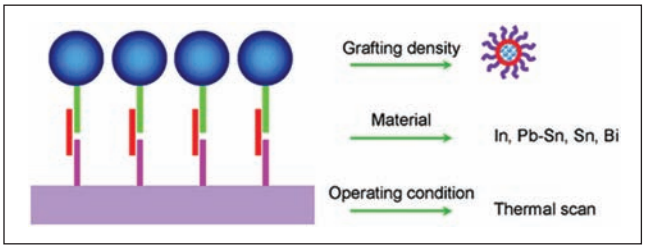

Figure 6. Reprinted with permission from Wang C, et al. Simultaneous Detection of Multiple Biomarkers with Several Orders of Concentration Difference Using Phase Change Nanoparticles. *Anal. Chem*. **2011**, *83*, 2215.

Nanoparticles of optical, magnetic, and electric character can detect biomarkers with high sensitivities but with low multiplicity due to low spectral resolution or nondistinguishable particle property. A panel of nanoparticles of phase-change materials (nano-PCM) has been used to detect multiple biomarkers with differential scanning calorimetry. The nanoparticles are made of either pure metals or eutectic alloys and have sharp and distinct melting peaks during linear temperature rise. After forming one-to-one accordance between each type of nanoparticle and ligand (i.e., antibody or DNA), multiple molecular variations can be detected at the same time for efficient drug discovery and medical diagnosis.

Controlling Spatial Organization of Multiple Cell Types in Defined 3D Geometries

By Halil Tekin[1,2], Jefferson G. Sanchez[1,2], Christian Landeros[1,2], Karen Dubbin[1,2], Robert Langer[1] and Ali Khademhosseini[1,2]
[1]Massachusetts Institute of Technology, Cambridge, MA, USA
[2]Harvard Medical School, Boston, MA, USA

Multicellular communities are structurally and functionally complex. Various spatially distributed cell types in defined microenvironments produce structural complexity. Functional complexity results from the intricate interactions between multiple cell types, which regulate native tissue functions, such as specific organ functions, cancer dynamics, and developmental stages. Recreating these complexities in vitro would be highly useful to fabricate particular tissue constructs for regenerative medicine, create tumor models for drug discovery, and form biomimetic microenvironments to study developmental biology. However, it has remained a challenge to obtain targeted

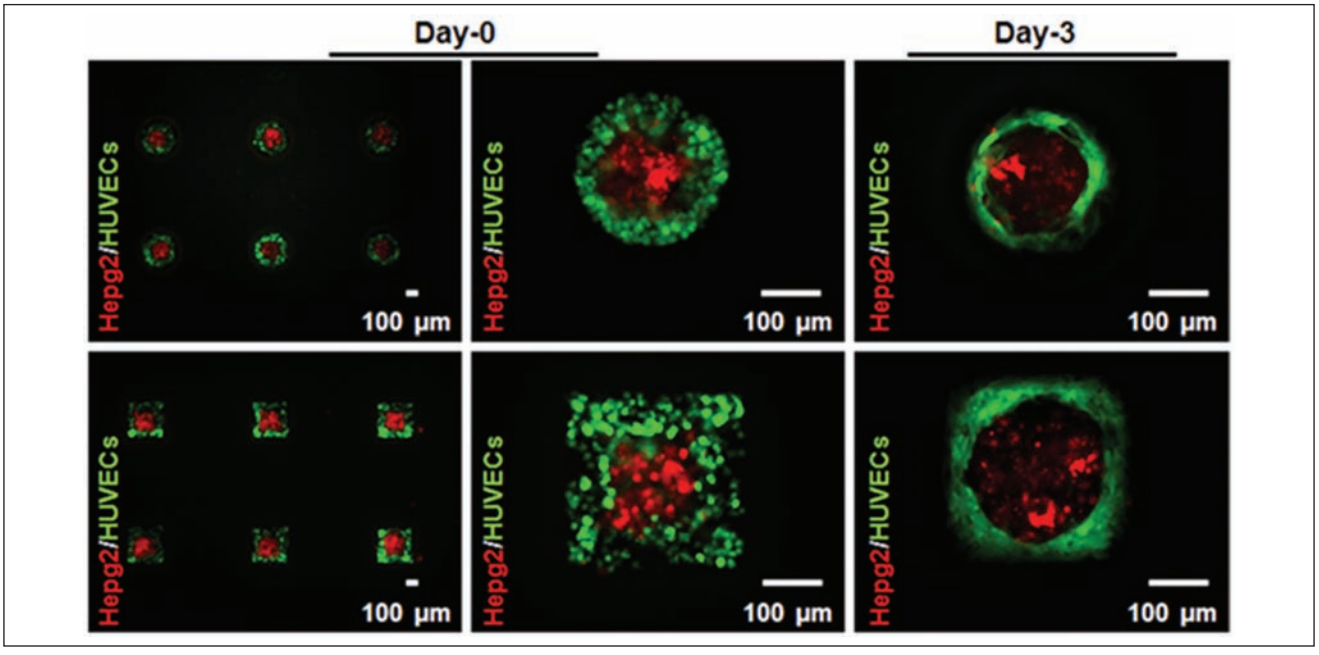

Figure 7. Reprinted with permission from Tekin H, et al. Controlling Spatial Organization of Multiple Cell Types in Defined 3D Geometries. *Adv. Mater*. **2012**. DOI: 10.1002/adma.201201805

spatial organization of various cell types in defined microenvironments. Herein, we introduce poly(N-isopropylacrylamide; PNIPAAm)–based dynamic microwells to spatially arrange multiple cell types in defined 3D geometries by exploiting the shape change properties of microwells at different temperatures. Two biologically relevant different cell types were spatially distributed in square and circular geometries by seeding them at different temperatures. This work is versatile and could potentially be useful for applications in tissue engineering, cancer biology, developmental biology, and drug discovery.

Selective Trapping and Manipulation of Microscale Objects Using Mobile Microvortices

By Li Zhang[1,2], Tristan Petit[1,3], Kathrin E. Peyer[1], Bradley Kratochvil[1], and Bradley J. Nelson[1]
[1]Institute of Robotics and Intelligent Systems, Zurich, Switzerland
[2]The Chinese University of Hong Kong, Hong Kong, China
[3]Diamond Sensors Laboratory, Gif-sur-Yvette, France

This work describes a new technology to trap and manipulate microscale objects, such as microparticles and *Escherichia coli* bacteria, using mobile microvortices generated by a rotating nanowire or self-assembled microspheres. Unlike conventional microfluidic devices, the mobile microvortex performs selective manipulation of individual micro-objects with micrometer positioning precision without the need for fabricating additional features on the manipulation surface. Furthermore, the mobile microvortices, with volumes down to femto-liters, provide noncontact, minimally invasive manipulation of cells and other biological samples in environments

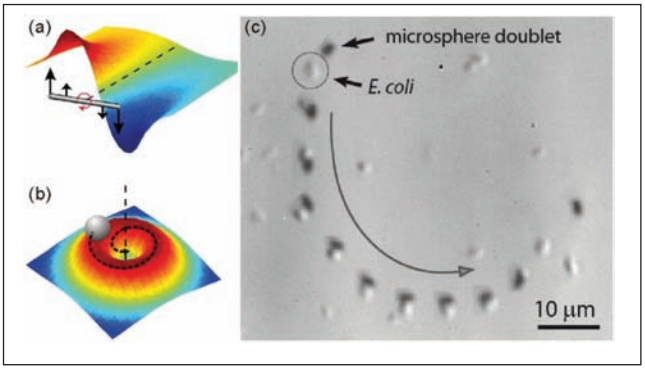

Figure 8. Reprinted with permission from Petit T, Zhang L, Peyer KE, Kratochvil B, Nelson BJ. Selective Trapping and Manipulation of Microscale Objects Using Mobile Microvortices. *Nano Lett*. **2012**, *12*, 156–160.

almost identical to their normal physiological conditions. Another primary advantage of mobile-microvortex–based manipulation is that there is no specific requirement on the material properties of the micro-object.

Acoustic Tweezers: A Noninvasive, Noncontact, Versatile, On-Chip Platform for Cell Manipulation

By Xiaoyun Ding[1], Sz-Chin Steven Lin[1], Brian Kiraly[1], Hongjun Yue[1], Sixing Li[1], I-Kao Chiang[1], Jinjie Shi[1], Stephen J. Benkovic[1], and Tony Jun Huang[1]
[1]The Pennsylvania State University, University Park, PA, USA

Professor Tony Jun Huang's research group at The Pennsylvania State University pioneered the first surface

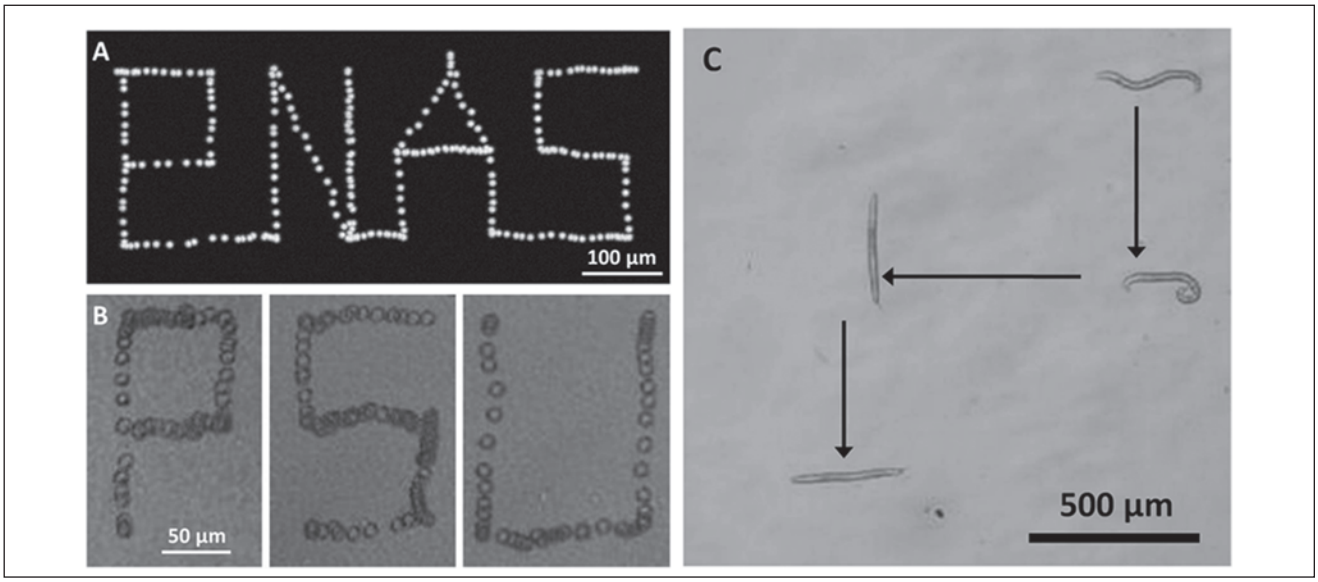

Figure 9. Reprinted with permission from Ding et al. On-Chip Manipulation of Single Microparticles, Cells, and Organisms Using Surface Acoustic Waves. *Proc. Natl. Acad. Sci. U. S. A.* **2012**, *109*, 11105–11109.

acoustic wave-based manipulation platform, so-called "acoustic tweezers," which can trap and dexterously manipulate single microparticles, cells, and entire organisms (i.e., *Caenorhabditis elegans*) along a programmed route in two dimensions within a dime-sized microfluidic chip. The acoustic tweezers can move a 10 µm single polystyrene bead to write the word *PNAS* (fig. 1A), a bovine red blood cell to trace the letters *PSU* (fig. 1B), and a single *C. elegans* in an x-y plane (fig. 1C). It was also the first technology capable of touchless trapping and manipulating *C. elegans*, a 1-mm-long roundworm that is an important model system for studying diseases and development in humans. With its advantages in noninvasiveness, miniaturization, and versatility, our acoustic tweezers will become a powerful tool for many disciplines of science and engineering.

Simultaneous Detection of Ca2+ and Diacylglycerol Signaling in Living Cells

By Paul Tewson[1], Mara Westenberg[1], Yongxin Zhao[2], Robert E. Campbell[3], Anne Marie Quinn[1] and Thomas E. Hughes[1,3]
[1]Montana Molecular, Bozeman, MT, USA
[2]University of Alberta, Edmonton, Alberta, Canada
[3]Montana State University, Bozeman, MT, USA

Cell-based calcium assays have been a mainstay of drug discovery and research since the 1990s. However, Ca2+ is one component of a complex network of interacting pathways that signal via multiple second messengers. Researchers in Montana created a green fluorescent sensor for diacylglycerol and paired it with a red fluorescent Ca2+ sensor, producing a robust, no-wash, multiplex assay that simultaneously detects two second messengers of GPCR signaling. This work demonstrates an approach to producing multiplex assays with improved specificity and more information content. Such assays are suitable for microscopy and use on multimode fluorescence plate readers.

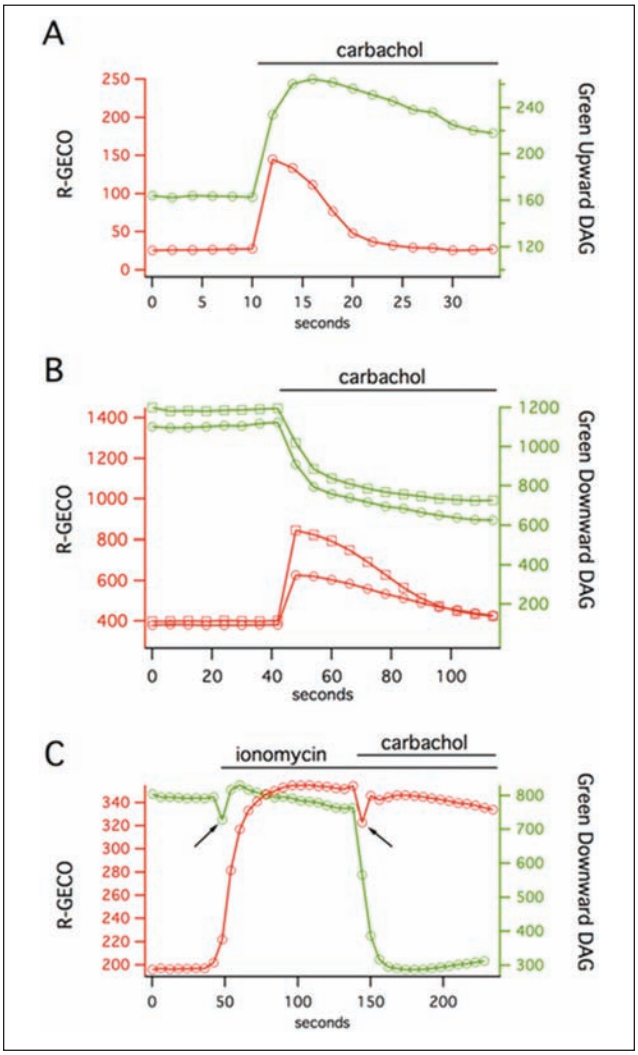

Figure 10. Reprinted with permission from Tewson P, Westenberg M, Zhao Y, Campbell R, Quinn A, Hughes T. Simultaneous Detection of Ca2+ and Diacylglycerol Signaling in Living Cells. *PLoS ONE* **2012**, 7, e42791.