04 Research Activities

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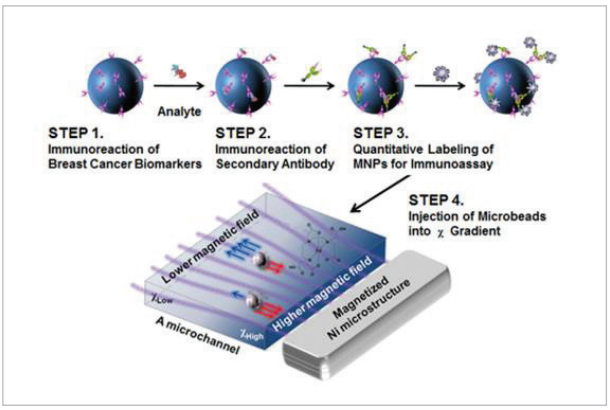
NanoBiotech Laboratory

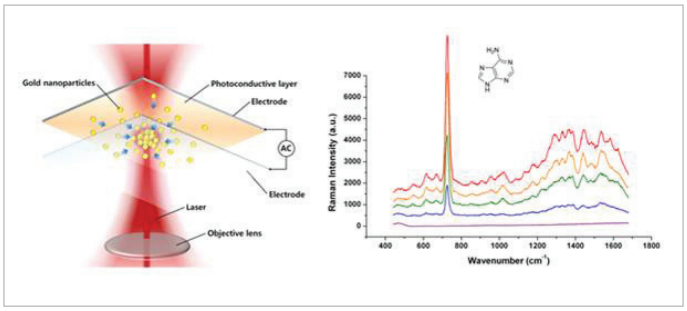
(Prof. Je-Kyun Park, http://nanobio.kaist.ac.kr)

Recent progress of lab-on-a-chip technology is challenging for the development of nanobiotechnology and integrative bioengineering. Particularly, micro/nano fluidics has been a key technology for the realization of micro total analysis systems (μTAS) or lab-on-a-chip as well as the next generation bio-tools for drug discovery, diagnostics, and tissue engineering. This research area covers the design and development of miniaturized devices that manipulate liquid samples at nanoliter volumes, allowing biological assays to be integrated and accomplished on a small scale with minimum time and cost. Prof. Park's research focuses on the development of a nanobiosensor, microfluidic device and lab-on-a-chip as a new platform for biological sample processing, separation, and detection, including optoelectrofluidics, hydrophoretic separation, magnetophoretic assay, and cell-based assay. From June 2008, his laboratory has been selected to receive a National Research Laboratory (NRL) Program grant through the National Research Foundation of Korea funded by the Ministry of Education, Science and Technology (MEST).

Isomagnetophoretic Immunoassay: Isomagnetophoresis can be used to discriminate subtle differences in magnetic susceptibility by using a magnetic susceptibility gradient in a microfluidic channel. In isomagnetophoretic immunoassays, the magnetic nanoparticles are used as labels on microbeads in sandwich-type immunoassay, detecting the amount of bound analytes by isomagnetophoretic focusing the solid-support microbeads under the magnetic susceptibility gradient and magnetic field in a microchannel. One advantage of the method is that the dynamic range of the isomagnetophoretic immunoassay system can be adjusted by altering the magnetic susceptibility gradient. In addition, this isomagnetophoretic immunoassay system can be used to analyze the selected concentration of target analytes in detail by tuning the dynamic ranges. As isomagnetophoresis can reduce signal deviation and discriminate subtle magnetic susceptibility differences, this immunoassay scheme shows an attomolar level of detection limit and a very low coefficient of variance of 1.29% [1]. The proposed immunoassay can be useful to accurately quantify the concentrations of biomarkers over the whole range of analyte concentrations, based on the current status and needs of the patient.

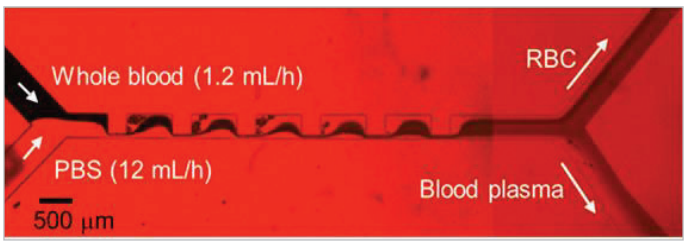


Optoelectrofluidic SERS spectroscopy: Optoelectrofluidic technology allows programmable manipulation of particles or fluids in microenvironments based on optically induced electrokinetics resulted from photochemical,

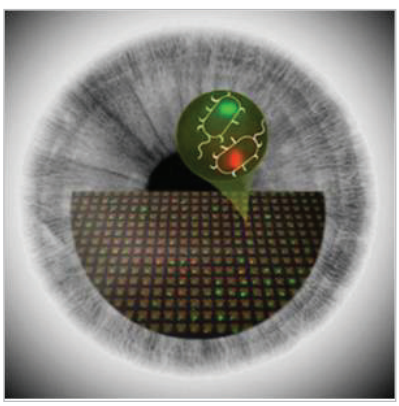


photoconductive, and photothermal effects. This new platform could be applied to develop an integrated system for optoelectrofluidic manipulation of micro- and nanoparticles including living cells and biomolecules [2a]. We recently reported a novel active surface-enhanced Raman scattering (SERS) platform for dynamic on-demand generation of SERS active sites based on optoelectrofluidics [2b]. When a laser source is projected into a sample solution containing metal nanoparticles in an optoelectrofluidic device and an AC electric field is applied, the metal nanoparticles are spontaneously concentrated and assembled within the laser spot, form SERS-active sites, and enhance the Raman signal significantly, allowing dynamic and more sensitive SERS detection. In this simple platform, both dynamic concentration of metal nanoparticles and in situ detection of SERS signal are simultaneously possible with only a single laser source. This approach allows on-demand generation of 'hot spots' at specific regions of interest, and highly sensitive, reliable, and stable SERS measurements of the target molecules in a tiny volume of liquid sample without any fluidic components and complicated systems.

Inertial Microfluidic Separation: Recently, inertial microfluidic separation is of great interest due to its continuous and high throughput separation of cells. To take advantages of high throughput, simple fabrication and high separation resolution, we have developed a new strategy for microfluidic separation using the force balance between inertial lift and Dean drag forces in a contraction-expansion array (CEA) microchannel [3a]. From this modulation of force balance, the particle cutoff size value can be tuned into proper value according to target cell size. In the CEA microchannel, an abrupt change of the cross-sectional area of the expansion regions curves fluid streams and produces a similar effect compared to Dean flows in a curved microchannel of constant cross-section, thereby inducing Dean drag forces acting on particles or cells. In addition, the particles or cells are influenced by inertial lift forces throughout the contraction regions. Accordingly, the force balancing determines whether the particles or cells cross the channel. Continuous inertial blood plasma separation is also demonstrated in a CEA microchannel with a low aspect ratio, which causes the change in magnitudes of the inertial lift forces on the particles [3b].



Microdroplet array for single-cell-based assay: A single-cell-based assay has been demonstrated using a mesh-integrated micro well array which enables easy trapping and consistent addition of droplets in a high-throughput manner [4]. The mesh-integrated droplet array provides a microfluidic platform for simple storage and on-demand merging of droplets. The openness of the system allows easy access to individual droplets and variable integration with other functional modules. By integrating the single-cell droplet-generating channel, the mesh-integrated microarray allows immediate confinement of single cells and total isolation of each chamber throughout the entire droplet manipulation process. With further development of cell-friendlier conditions and automation for parallel handling of droplets, this device may provide a novel screening platform, especially for various microbes directly harvested from a natural environment.



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1. Young Ki Hahn, Je-Kyun Park*, "Versatile immunoassays based on isomagnetophoresis," Lab Chip **2011**, 11 (12): 2045-2048.
2. **a)** Hyundoo Hwang, Je-Kyun Park*, "Optoelectrofluidic manipulation of nanoparticles and biomolecules, Adv. OptoElectronics, **2011**, 2011, Article ID 482483; **b)** Hyundoo Hwang, Dongsik Han, Young-Jae Oh, Yoon-Kyoung Cho, Ki-Hun Jeong, Je-Kyun Park*, "In situ dynamic measurements of the enhanced SERS signal using an optoelectrofluidic SERS platform," Lab Chip, **2011**, 11 (15): 2518-2555.
3. **a)** Myung Gwon Lee, Sungyoung Choi, Je-Kyun Park*, "Inertial separation in a contraction-expansion array microchannel," J. Chromatogr. A, **2011**, 1218 (27): 4138-4143; **b)** Myung Gwon Lee, Sungyoung Choi, Hee-Je Kim, Hee Kyun Lim, Joon-Ho Kim, Nam Huh, Je-Kyun Park*, "Inertial blood plasma separation in a contraction-expansion array microchannel," Appl. Phys. Lett., **2011**, 98 (25), 253702.
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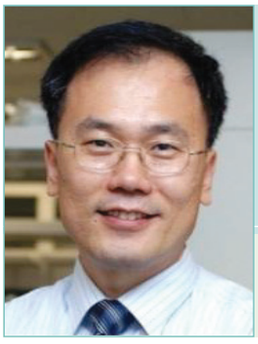

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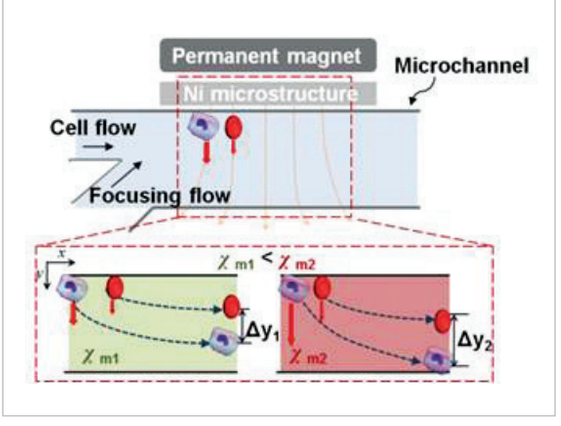
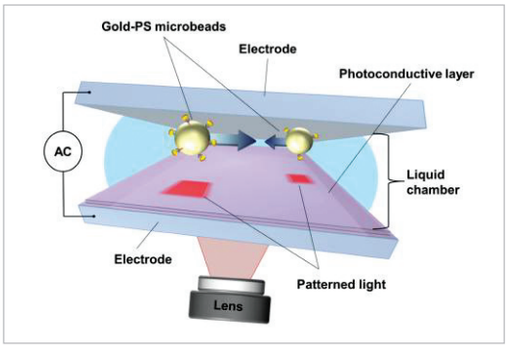
Label-free cell separation using magnetophoresis: We developed a new label-free cell separation using a magnetic repulsion force resulting from the magnetic susceptibility difference between cells and paramagnetic buffer solution in a microchannel [1]. The difference in the magnetic forces acting on different sized cells is enhanced by adjusting the magnetic susceptibility of surrounding medium, which depends on the concentration of paramagnetic salts such as biocompatible gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA) dissolved in the medium. On the basis of this new separation scheme, we demonstrated a label-free separation of U937 cells from red blood cells with > 90% purity and 1 × 10^5 cells/h throughput using a 40 mM Gd-DTPA solution. This work was highlighted in Chemical & Engineering News, entitled "Microfluidic Device Separates Unlabeled Cells (March 12, 2012)"

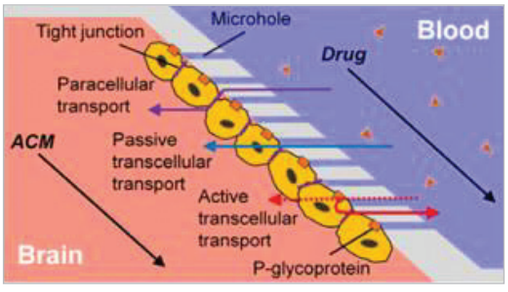


Optoelectrofluidic analysis of colloid particles: Optoelectrofluidic technology allows programmable manipulation of particles or fluids in microenvironments based on optically induced electrokinetics resulted from photochemical, photoconductive, and photothermal effects. Recently, we reported the behavior of metal-polymer hybrid particles in an optoelectrofluidic device [2]. In the application of hundreds of kHz ac voltage, a variety of optically-induced electrokinetic and electrostatic mechanisms affect the movement of gold-coated polystyrene microspheres in concert.



The particles repel from the light pattern and their mobility increases as the amount of gold increases. We apply this model to develop a novel optoelectrofluidic immunoassay, in which the corresponding metal-polymer microparticles are formed by a reaction of antibody-coated gold nanoparticles, antigens, and antibody-coated polystyrene microspheres.

Cell-based assays in a microchannel: An in vivo-like microenvironment may play an important role for drug screening and development. As orally administered drugs must be absorbed from the intestine into the blood circulation, permeability and cytotoxicity assays of drug candidates have been widely used in the early screening stages of drug discovery. To realize the drug permeability assay in a microchannel, a microhole array structure for cell trapping was exploited by mimicking the intestinal epithelial cell membrane, considering the in vivo delivery path of drugs in humans [3]. With the use of trapped cells, the integrated system including toxicity assay could be used as a valuable tool in drug discovery, and its applicability will be extended to include ADME/Tox drug properties.



Cellular hydrogel biopaper: We reported "microarchitectured freestanding cellular hydrogel biopaper" as a novel 3D cell culture or tissue reconstruction module [4]. The biopapers are thin enough to allow adequate diffusion, and they feature both the desired hydrogel microarchitectures and the organized cellular arrangements that can duplicate the native cellular environment. We also developed facile new harvest, transfer, and assembly techniques of the construction of laminated tissue composites of the biopaper with on-demand timing. Using these techniques, we were able to construct stratified 3D hepatic tissue modules with increased liver function. The cellular hydrogel biopaper will provide unprecedented tools to study cell?ECM interaction s, structure?function relationships, tissue morphogenesis, and modular tissue reconstructions.

Key Achievements

1. Y. K. Hahn, J.-K. Park, "Versatile immunoassays based on isomagnetophoresis," Lab on a Chip, 11 (12), 2045-2048, 2011.
2. M. S. Kim, T. Kim, S.-Y. Kong, S. Kwon, C. Y. Bae, J. Choi, C. H. Kim, E. S. Lee, J.-K. Park, "Breast cancer diagnosis using a microfluidic multiplexed immunohistochemistry platform," PLoS One, 5, e10441, 2010.
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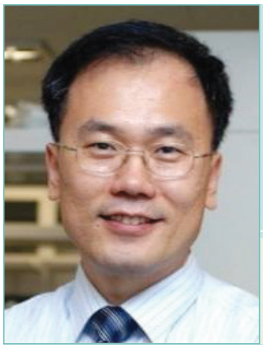
4. J. H. Kang, S. Choi, W. Lee, J.-K. Park, "Isomagnetophoresis to discriminate subtle difference in magnetic susceptibility," Journal of the American Chemical Society, 130 (2), 396-397, 2008.

Achievements 2012/2013

1. F. Shen, H. Hwang, Y. K. Hahn, J.-K. Park, "Label-free cell separation using a tunable magnetophoretic repulsion force," Analytical Chemistry, 84 (7): 3075-3081, 2012.
2. D. Han, H. Hwang, J.-K. Park, "Optoelectrofluidic behavior of metal-polymer hybrid colloidal particles," Applied Physics Letters, 102 (5), 054105, 2013.
3. J. H. Yeon, D. Na, K. Choi, S.-W. Ryu, C. Choi, J.-K. Park, "Reliable permeability assay system in a microfluidic device mimicking cerebral vasculatures," Biomedical Microdevices, 14 (6), 1141-1148, 2012.
4. W. Lee, C. Y. Bae, S. Kwon, J. Son, J. Kim, Y. Jeong, S.-S. Yoo, J.-K. Park, "Cellular hydrogel biopaper for patterned 3D cell culture and modular tissue reconstruction," Advanced Healthcare Materials, 1 (5): 635-639, 2012.



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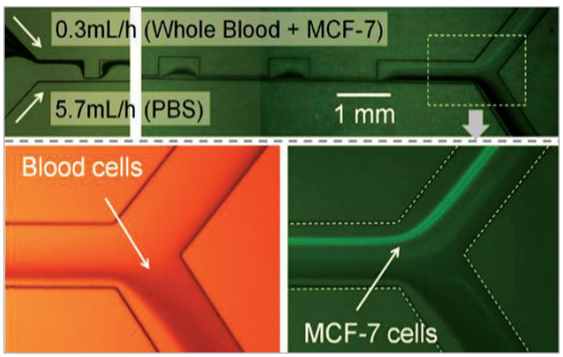
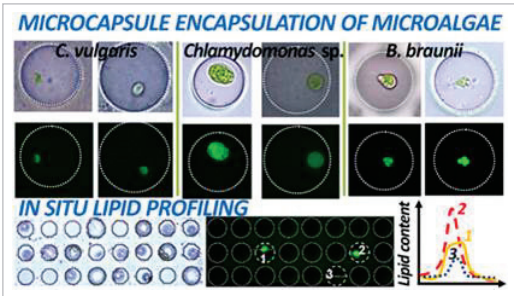
Inertial microfluidics for rare cell separation: The isolation of the circulating tumor cells (CTCs) from the blood is a great challenge because these cells are extremely rare in the peripheral blood. With the recent development of bioMEMS and nanotechnology, traditional cell separation and analytical methods are oriented toward applying their principles to lab-on-a-chip devices or finding a new physical principle for cell separation and detection. Recently, inertial microfluidic separation is of great interest due to its continuous and high throughput separation of cells without chemical cell damages. To take advantages of high throughput, simple fabrication and high separation resolution, a new strategy for microfluidic CTC separation was reported using the force balance between inertial lift and Dean drag forces in a contraction-expansion array microchannel [1]. From this modulation of force balance, the cutoff size value for cell separation can be tuned into proper value according to target cell size.

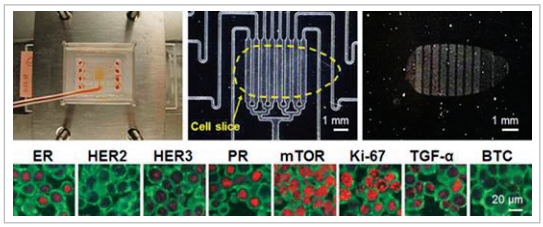


Hydrogel microcapsule array for microalgae screening: Droplet-based microfluidics has recently been applied to a wide range of applications, including biological assay, combinatorial synthesis, and high-throughput screening. Unlike solid-well based systems, microdroplets enables to move or stop, split or merge with others, and select different paths for sorting at timed intervals. However, a precise temporal control of microdroplets such as storage, synchronization and combinatorial pairing of droplets is required to achieve a variety range of chemical and biochemical reactions

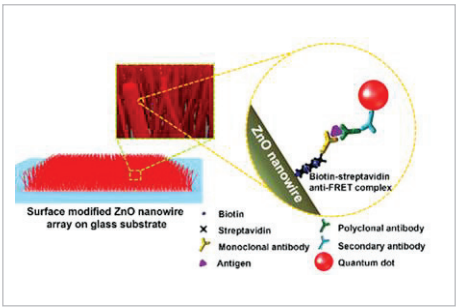


inside microfluidic networks. We developed alginate hydrogel microcapsules containing a green microalga to provide a quantitative analysis of the lipid content of individual alga within the microcapsule [2]. With further development, this device may provide a novel screening platform, especially for various microbes directly harvested from a natural environment.

Microfluidic Immunohistochemistry for breast cancer biomarkers: Immunochemical assay using an antibody-based molecular detection technology can provide information on both cellular morphology and the quantities of molecules within cells (immunocytochemistry) or tissues (immunohistochemistry). In this field, multiplexed protein quantification remains difficult using conventional methods. Recently, we demonstrate a new analytical concept that integrates a microfluidic multiplexing platform and a quantum dot (QD) double-staining method [3]. The microfluidic double-staining method enabled accurate quantification by normalization of biomarker levels to that of β-actin as an internal reference. This novel molecular profiling method will accelerate cancer cell studies and the development of diagnostic tools for personalized medicine.



Quantum dot-based immunoassay: We report an efficient and high-performance immunoassay platform by combining high-density vertical ZnO nanowire array with photostable quantum dot (QD) labeling [4]. The ZnO nanowire array provides a large surface area for the immobilization of biomolecules, which makes it an efficient substrate for the immunoreaction of biomolecules. When a sandwich immunoassay with QD label was conducted on various substrates, the ZnO nanowire substrate showed stronger fluorescence signal than ZnO thin film and bare glass substrates by 3.8 and 8.5 times, respectively. We found that the fluorescence resonance energy transfer (FRET) from QD to ZnO nanowire could be suppressed by extending their distance with multilayer biotin-streptavidin complex. In addition, we demonstrated the QD-based immunoassay of carcinoembryonic antigen on a ZnO nanowire substrate, showing an excellent immunoassay performance with a very low detection limit (0.001 ng/mL) and a large detection range up to 100 ng/mL.



Key Achievements

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Achievements 2013/2014

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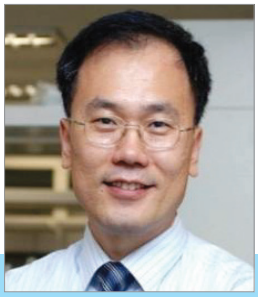

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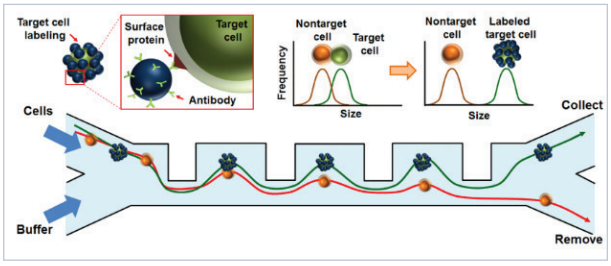
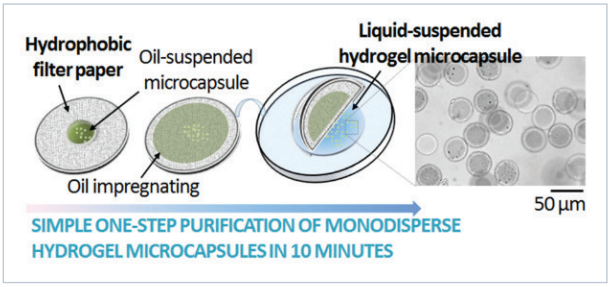
Inertia-activated cell sorting: This paper demonstrates an inertia-activated cell sorting method to separate cells based on their surface protein expression by using inertial microfluidics [1]. Target cells are immune-specifically reacted with antibody-coated microbeads and then separated from nontarget cells. As a proof of concept, separation of MCF-7 breast cancer cells from U937 lymphoma cells was achieved with 97.6% target cell recovery rate, 95% nontarget cell rejection ratio, 73.8% purity, and an enrichment ratio of 93 at a total flow rate of 8.75 mL h–1 without using any external forces.

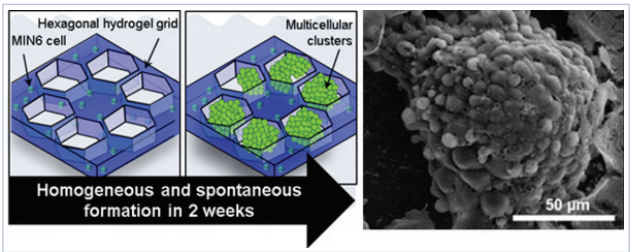


Rapid one-step purification of single-cells: A simple one-step purification method of alginate microcapsules containing a single live cell from oil to aqueous phase was demonstrated by oil impregnation via commercially available hydrophobic filter paper [2]. The filter paper promotes quick depletion of the surrounding oil which guarantees the monodispersity of

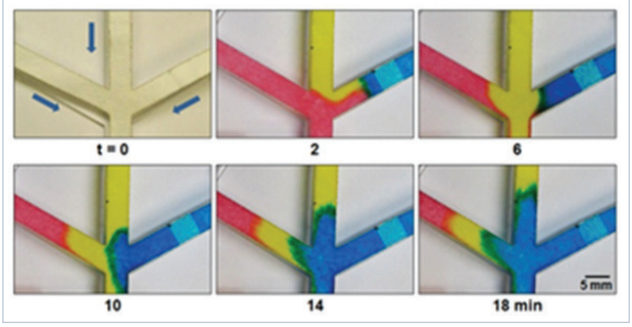


microcapsules, shortens the time required and simplifies the laborious process for washing out the residual oil phase. We expect that this method for the simple and rapid purification of encapsulated single-cell microcapsules will attain widespread adoption, assisting cell biologists and clinicians in the development of single-cell experiments.

In vitro formation of homogeneous MIN6 cell clusters: To effectively form homogeneous cell clusters in vitro, we made cell-containing hydrogel membrane constructs with an adapted grid structure based on a hexagonal micropattern [3]. Homogeneous cell clusters of pancreatic insulinoma (MIN6) cells were spontaneously generated in the floating hydrogel membrane constructs, including a hexagonal grid structure (size of cavity: 100 μm, interval between cavities: 30 μm). Interestingly, 3D clustering of MIN6 cells mimicking the structure of pancreatic islets was coalesced into a merged aggregate attaching to each hexagonal cavity of the hydrogel grid structure. The fate and insulin secretion of homogeneous cell clusters in the hydrogel grid structure were also assessed. The results of these designable hydrogel–cell membrane constructs suggest that facultative in vitro β-cell proliferation and maintenance can be applied to biofunctional assessments.



Programmed sample delivery on a pressurized paper: This paper reports a method to control the fluid flow in paper-based microfluidic devices simply by pressing over the channel surface of paper, thereby decreasing the pore size and permeability of a non-woven polypropylene sheet [4]. As a result, fluid resistance is increased in the pressed region and causes flow rate to decrease. In addition, we demonstrate flow rate control in a Y-shaped merging paper and sequential delivery of multiple color dyes in a three-branched paper. Furthermore, sequential delivery of multiple fluid samples is performed to demonstrate its application in multi-step colorimetric immunoassay, which shows a 4.3-fold signal increase via enhancement step.



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3. W. Lee, C. Y. Bae, S. Kwon, J. Son, J. Kim, Y. Jeong, S.-S. Yoo, **J.-K. Park**, "Cellular hydrogel biopaper for patterned 3D cell culture and modular tissue reconstruction," Advanced Healthcare Materials, 1, 635-639, 2012.
4. H. Hwang, **J.-K. Park**, "Optoelectrofluidic platforms for chemistry and biology," Lab on a Chip, 11, 33-47, 2011.
5. M. S. Kim, T. Kim, S.-Y. Kong, S. Kwon, C. Y. Bae, J. Choi, C. H. Kim, E. S. Lee, **J.-K. Park**, "Breast cancer diagnosis using a microfluidic multiplexed immunohistochemistry platform," PLoS One, 5, e10441, 2010.

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1. J. H. Shin, M. G. Lee, S. Choi, **J.-K. Park**, "Inertia-activated cell sorting of immune-specifically labeled cells in a microfluidic device," RSC Advances, 4, 39140-39144, 2014.
2. D.-H. Lee, M. Jang, **J.-K. Park**, "Rapid one-step purification of single-cells encapsulated in alginate microcapsules from oil to aqueous phase using a hydrophobic filter paper: Implications for single-cell experiments," Biotechnology Journal, 9, 1233-1240, 2014.
3. C. Y. Bae, M.-k. Min, H. Kim, **J.-K. Park**, "Geometric effect of the hydrogel grid structure on in vitro formation of homogeneous MIN6 cell clusters," Lab on a Chip, 14, 2183-2190. 2014.
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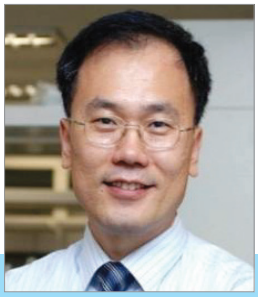

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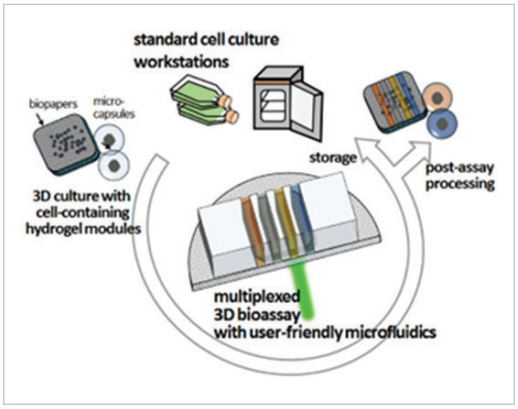
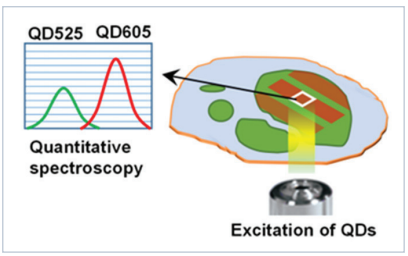
Recent progress of lab-on-a-chip technology is challenging for the development of nanobiotechnology and integrative bioengineering. Particularly, micro/nano fluidics has been a key technology for the realization of micro total analysis systems (μTAS) or lab-on-a-chip as well as the next generation bio-tools for drug discovery, diagnostics, and tissue engineering. This research area covers the design and development of miniaturized devices that manipulate liquid samples at nanoliter volumes, allowing biological assays to be integrated and accomplished on a small scale with minimum time and cost. Prof. Park's research focuses on the development of a nanobiosensor, microfluidic device and lab-on-a-chip as a new platform for biological sample processing, separation, and detection, including optoelectrofluidics, hydrophoretic separation, magnetophoretic assay, and cell-based assay. From June 2008, his laboratory has been selected to receive a National Leading Research Laboratory Program grant through the National Research Foundation of Korea funded by the Ministry of Science, ICT and Future Planning

3D microfluidic bioassays: Recent progress in the development and application of hydrogel-incorporated 3D cell culture and microfluidic bioassays were reviewed [1]. Particularly, 3D bioassay platforms with cell-containing hydrogel modules offer the promise of significant advantages over existing hydrogel-incorporated microfluidic devices, particularly long-term cell maintenance, co-culture of multiple cell types, and organization of cellular arrangements that can duplicate those in vivo. We anticipate that the modular and user-friendly format interfaced with existing laboratory infrastructure will help address several clinical questions in ways that extend well beyond the current 2D cell-culture systems.

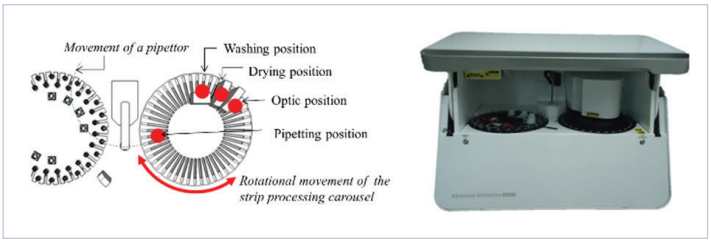


Quantum-dot-based microfluidic immunohistochemistry: An automated multiple biomarker measurement method for tissue from cancer patients was developed using quantum dot (QD)-based protein detection combined with reference-based

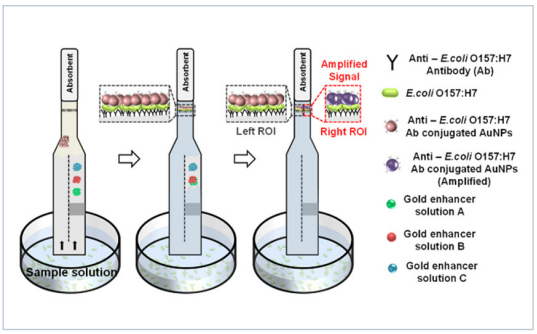


protein quantification and autofluorescence (AF) removal [2]. For the automated measurement of biomarkers, a cytokeratin-based biomarker normalization method was used to measure the averaged expression of proteins. A novel AF-removal algorithm was also proposed and demonstrated to normalize the reference AF spectra reconstructed from unknown AF spectra based on random sampling. This approach ensures accurate removal of the background signal from the original protein signals, which leads to more accurate quantification of QD-labeled biomarkers.

Multiple detection of allergen-specific immunoglobulin E: A multiple allergen-specific IgE test is an efficient way to know a patient's IgE profile. We reported a new clinical laboratory analyzer, which is a fully automated system for multiple allergy tests. For efficient automation of immunoblot procedures, a novel tilting carousel technology was incorporated [3]. In this technology, the strip-processing carousel simply rotates in a tilting state, and other sampling, washing, drying, and reading modules are fixed at the designated positions and do not need three-axis movements. The rotational movement and tilting state of the carousel can locate the immunoblot strips to the required positions, give conditions to shake the reagent vessels, and facilitate the aspiration of wasted reagents. Up to 1860 allergen-specific IgEs can be measured in 3 h and 45 min without manual interruption from sample addition to the final measurement.



Paper fluidic one-step detection of *Escherichia coli*: We developed a pressurized paper-based E. coli O157:H7 detection platform that enables signal enhancement operated by one-step dipping method [4]. After characterization of delayed flow and formation of channel partition in a pressurized paper-based microfluidic device, we detected *E. coli* O157:H7 quantitatively. We expect this platform to be utilized in on-site detection for decreasing limit of detection by increasing sensitivity caused by signal enhancement. Additionally, untrained people are expected to easily use this platform.



Key Achievements

1. M. G. Lee, J. H. Shin, C. Y. Bae, S. Choi, **J.-K. Park**, "Label-free cancer cell separation from human whole blood using inertial microfluidics at low shear stress," Analytical Chemistry, 85, 6213–6218, 2013.
2. F. Shen, H. Hwang, Y. K. Hahn, **J.-K. Park**, "Label-free cell separation using a tunable magnetophoretic repulsion force," Analytical Chemistry, 84, 3075-3081, 2012.
3. H. Hwang, **J.-K. Park**, "Optoelectrofluidic platforms for chemistry and biology," Lab on a Chip, 11, 33-47, 2011.
4. M. S. Kim, T. Kim, S.-Y. Kong, S. Kwon, C. Y. Bae, J. Choi, C. H. Kim, E. S. Lee, **J.-K. Park**, "Breast cancer diagnosis using a microfluidic multiplexed immunohistochemistry platform," PLoS One, 5, e10441, 2010.
5. J. H. Kang, S. Choi, W. Lee, **J.-K. Park**, "Isomagnetophoresis to discriminate subtle difference in magnetic susceptibility," Journal of the American Chemical Society, 130, 396-397, 2008.

Achievement In This Year

1. D.-H. Lee, C. Y. Bae, S. Kwon, **J.-K. Park**, "User-friendly 3D bioassays with cell-containing hydrogel modules: narrowing the gap between the microfluidic bioassays and the clinical end-user's needs," Lab on a Chip, 15, 2379-2387, 2015.
2. S. Kwon, C. H. Cho, E. S. Lee, **J.-K. Park**, "Automated measurement of multiple cancer biomarkers using quantum-dot-based microfluidic immunohistochemistry," Analytical Chemistry, 87, 4177-4183, 2015.
3. J. H. Oh, M. K. Park, S. W. Kim, **J.-K. Park**, "A fully automated analyzer for multiple detection of allergen-specific immunoglobulin E," Analytical Methods, 7, 8889-8895, 2015.
4. J. Park, J. H. Shin, **J.-K. Park**, "One-step detection of *Escherichia coli* O157:H7 by signal enhancement in a pressurized paper-based microfluidic device," Proceedings of μTAS 2015 Conference, Gyeongju, KOREA, pp. 278-280, 2015.