


The 2017 SLAS Technology Ten: Translating Life Sciences Innovation

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Along with a new name, this issue introduces a new annual feature that honors groundbreaking achievements in translating life sciences innovation. For the past 21 years, this journal has provided a unique forum for the presentation of new technologies that advance life sciences and biomedical research. This tradition continues with the first *SLAS Technology Ten*, celebrating the best of the great work published in this journal throughout the previous year. The collection represents achievements from nine countries – China, Finland, France, Germany, Japan, Sweden, Switzerland, UK, and USA.

The reports showcased in this 2017 *SLAS Technology Ten* collection reflect a diversity of technological advances that make significant contributions to life sciences and biomedical research and applications. From being able to move liquid with sound to dispense primary cells and DNA to microfluidic-based immunoassays, the 2017 *SLAS Technology Ten* illustrate the ingenuity that is improving how patients are diagnosed and treated. In this past year, we have had the opportunity to report on how 3D printing can empower researchers to rapidly develop the tools to affect a wide range of applications, including regenerative medicine and diagnostic assay development. This year's highlighted articles also continue to push the envelope of what is possible with automation, integrating new functions into high-throughput sample preparation and screening to further drive efficiencies in research.

We are proud and appreciative that the authors of the 2017 *SLAS Technology Ten* chose to share their outstanding work with this journal, contributing to its value as a hallmark and ever-evolving resource for translating life sciences innovation.

Precision Cancer Medicine in the Acoustic Dispensing Era: Ex Vivo Primary Cell Drug Sensitivity Testing

By Evgeny Kuleskiy, Jani Saarela, Laura Turunen, and Krister Wennerberg

Cancer therapy is increasingly becoming individualized, but there are also big gaps between the molecular knowledge of individual cancers we can generate today and what can be applied in the clinic. In an attempt to bridge this knowledge gap between cancer genetic and molecular profiling and clinically useful information, an individualized systems medicine program has been established at the Institute for Molecular

Medicine Finland (FIMM), University of Helsinki, and the Helsinki University Hospital. Central to this program is drug sensitivity and resistance testing (DSRT), in which responses of primary cancer cells to a comprehensive clinical oncology and signal transduction drug collection are monitored. The drug sensitivity information is used with molecular profiling to establish hypotheses on individual cancer-selective targeting drug combinations and their predictive biomarkers, which can be explored in the clinic. Here, we describe how acoustic droplet ejection is enabling DSRT in our cancer individualized systems medicine program to (1) generate consistent but configurable assay-ready plates and determine how this affects data quality, (2) flexibly prepare drug combination testing plates, (3) dispense reagents and cells to the assay plates, and (4) perform ultra-miniaturized follow-up assays on the cells from DSRT plates.

Smart DNA Fabrication Using Sound Waves: Applying Acoustic Dispensing Technologies to Synthetic Biology

By Paulina Kanigowska, Yue Shen, Yijing Zheng, Susan Rosser, and Yizhi Cai

Acoustic droplet ejection (ADE) technology uses focused acoustic energy to transfer nanoliter-scale liquid droplets with high precision and accuracy. This noncontact, tipless, low-volume dispensing technology minimizes the possibility of cross-contamination and potentially reduces the costs of reagents and consumables. To date, acoustic dispensers have mainly been used in screening libraries of compounds. In this article, we describe the first application of this powerful technology to the rapidly developing field of synthetic biology, for DNA synthesis and assembly at the nanoliter scale using a Labcyte Echo 550 (Labcyte, Sunnyvale, CA)

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acoustic dispenser. We were able to successfully downscale PCRs and the popular one-pot DNA assembly methods, Golden Gate and Gibson assemblies, from the microliter to the nanoliter scale with high assembly efficiency, which effectively cut the reagent cost by 20- to 100-fold. We envision that acoustic dispensing will become an instrumental technology in synthetic biology, particularly in the era of DNA foundries.

Automated High-Throughput Fluorescence Lifetime Imaging Microscopy to Detect Protein-Protein Interactions

By Camilo Guzmán, Christina Oetken-Lindholm, and Daniel Abankwa

Fluorescence resonance energy transfer (FRET) is widely used to study conformational changes of macromolecules and protein-protein, protein-nucleic acid, and protein-small molecule interactions. FRET biosensors can serve as valuable secondary assays in drug discovery and for target validation in mammalian cells. Fluorescence lifetime imaging microscopy (FLIM) allows precise quantification of the FRET efficiency in intact cells, as FLIM is independent of fluorophore concentration, detection efficiency, and fluorescence intensity. We have developed an automated FLIM system using a commercial frequency domain FLIM attachment (Lambert Instruments, Groningen, Netherlands) for wide-field imaging. Our automated FLIM system is capable of imaging and analyzing up to 50 different positions of a slide in less than 4 min or the inner 60 wells of a 96-well plate in less than 20 min. Automation is achieved using a motorized stage and controller (Prior Scientific, Cambridge, UK) coupled with a Zeiss (Jena, Germany) Axio Observer body and full integration into the Lambert Instruments FLIM acquisition software. As an application example, we analyze the interaction of the oncoprotein Ras and its effector Raf after drug treatment. In conclusion, our automated FLIM imaging system requires only commercial components and may therefore allow for a broader use of this technique in chemogenomics projects.

Fully Automated One-Step Production of Functional 3D Tumor Spheroids for High-Content Screening

By François Monjaret, Mathieu Fernandes, Eve Duchemin-Pelletier, Amelie Argento, Sébastien Degot, and Joanne Young

Adoption of spheroids within high-content screening (HCS) has lagged behind high-throughput screening (HTS) due to issues with running complex assays on large 3D structures. To enable multiplexed imaging and analysis of spheroids, different cancer cell lines were grown in 3D on micropatterned 96-well plates with automated production of nine uniform

spheroids per well. Spheroids achieve diameters of up to 600 μm , and reproducibility was experimentally validated (interwell and interplate $\text{CV}_{\text{diameter}}$ ($<5\%$). Biphoton imaging confirmed that micropatterned spheroids exhibit characteristic cell heterogeneity with distinct microregions. Furthermore, central necrosis appears at a consistent spheroid size, suggesting standardized growth. Using three reference compounds (fluorouracil, irinotecan, and staurosporine), we validated HT-29 micropatterned spheroids on an HCS platform, benchmarking against hanging-drop spheroids. Spheroid formation and imaging in a single plate accelerate assay workflow, and fixed positioning prevents structures from overlapping or sticking to the well wall, augmenting image processing reliability. Furthermore, multiple spheroids per well increase the statistical confidence sufficiently to discriminate compound mechanisms of action and generate EC_{50} values for endpoints of cell death, architectural change, and size within a single-pass read. Higher quality data and a more efficient HCS work chain should encourage integration of micropatterned spheroid models within fundamental research and drug discovery applications.

Fully Automated Quantification of Insulin Concentration Using a Microfluidic-Based Chemiluminescence Immunoassay

By Ping Yao, Zhu Liu, Steve Tung, Zaili Dong, and Lianqing Liu

A fully automated microfluidic-based detection system for the rapid determination of insulin concentration through a chemiluminescence immunoassay has been developed. The microfluidic chip used in the system is a double-layered polydimethylsiloxane device embedded with interconnecting micropumps, microvalves, and a micromixer. At a high injection rate of the developing solution, the chemiluminescence signal can be excited and measured within a short period of time. The integral value of the chemiluminescence light signal is used to determine the insulin concentration of the samples, and the results indicate that the measurement is accurate in the range from 1.5 to 391 pM. The entire chemiluminescence assay can be completed in less than 10 min. The fully automated microfluidic-based insulin detection system provides a useful platform for rapid determination of insulin in clinical diagnostics for diabetes, which is expected to become increasingly important for future point-of-care applications.

Standardized 3D Bioprinting of Soft Tissue Models with Human Primary Cells

By Markus Rimann, Epifania Bono, Helene Annaheim, Matthias Bleisch, and Ursula Graf-Hausner

Cells grown in 3D are more physiologically relevant than cells cultured in 2D. To use 3D models in substance testing and regenerative medicine, reproducibility and standardization are important. Bioprinting offers not only automated standardizable processes but also the production of complex tissue-like structures in an additive manner. We developed an all-in-one bioprinting solution to produce soft tissue models. The holistic approach included (1) a bioprinter in a sterile environment, (2) a light-induced bioink polymerization unit, (3) a user-friendly software, (4) the capability to print in standard labware for HTS, (5) cell-compatible inkjet-based print-heads, (6) a cell-compatible ready-to-use BioInk, and (7) standard operating procedures. In a proof-of-concept study, skin as a reference soft tissue model was printed. To produce dermal equivalents, primary human dermal fibroblasts were printed in alternating layers with BioInk and cultured for up to 7 weeks. During long-term cultures, the models were remodeled and fully populated with viable and spreaded fibroblasts. Primary human dermal keratinocytes were seeded on top of dermal equivalents, and epidermis-like structures were formed as verified with hematoxylin and eosin staining and immunostaining. However, a fully stratified epidermis was not achieved. Nevertheless, this is one of the first reports of an integrative bioprinting strategy for industrial routine application.

Open-Source Wax RepRap 3-D Printer for Rapid Prototyping Paper-Based Microfluidics

By J. M. Pearce, N. C. Anzalone, and C. L. Heldt

The open-source release of self-replicating rapid prototypers (RepRaps) has created a rich opportunity for low-cost distributed digital fabrication of complex 3D objects such as scientific equipment. For example, 3D printable reactionware devices offer the opportunity to combine open hardware microfluidic handling with lab-on-a-chip reactionware to radically reduce costs and increase the number and complexity of microfluidic applications. To further drive down the cost while improving the performance of lab-on-a-chip paper-based microfluidic prototyping, this study reports on the development of a RepRap upgrade capable of converting a Prusa Mendel RepRap into a wax 3D printer for paper-based microfluidic applications. An open-source hardware approach is used to demonstrate a 3D printable upgrade for the 3D printer, which combines a heated syringe pump with the RepRap/Arduino 3D control. The bill of materials, designs, basic assembly, and use instructions are provided, along with a completely free and open-source software tool chain. The open-source hardware device described here accelerates the potential of the nascent field of electrochemical detection combined with paper-based microfluidics by dropping the marginal cost of

prototyping to nearly zero while accelerating the turnover between paper-based microfluidic designs.

Ultra-High-Throughput Sample Preparation System for Lymphocyte Immunophenotyping Point-of-Care Diagnostics

By David I. Walsh III, Shashi K. Murthy, and Aman Russom

Point-of-care (POC) microfluidic devices often lack the integration of common sample preparation steps, such as preconcentration, which can limit their utility in the field. In this technology brief, we describe a system that combines the necessary sample preparation methods to perform sample-to-result analysis of large-volume (20 mL) biopsy model samples with staining of captured cells. Our platform combines centrifugal-paper microfluidic filtration and an analysis system to process large, dilute biological samples. Using commercialization-friendly manufacturing methods and materials, yielding a sample throughput of 20 mL/min, and allowing for on-chip staining and imaging bring together a practical yet powerful approach to microfluidic diagnostics of large, dilute samples.

Automated Device for Asynchronous Extraction of RNA, DNA, or Protein Biomarkers from Surrogate Patient Samples

By Anna L. Bitting, Hali Bordelon, Mark L. Baglia, Keersten M. Davis, Amy E. Creecy, Philip A. Short, Laura E. Albert, Aditya V. Karhade, David W. Wright, Frederick R. Haselton, and Nicholas M. Adams

Many biomarker-based diagnostic methods are inhibited by nontarget molecules in patient samples, necessitating biomarker extraction before detection. We have developed a simple device that purifies RNA, DNA, or protein biomarkers from complex biological samples without robotics or fluid pumping. The device design is based on functionalized magnetic beads, which capture biomarkers and remove background biomolecules by magnetically transferring the beads through processing solutions arrayed within small-diameter tubing. The process was automated by wrapping the tubing around a disc-like cassette and rotating it past a magnet using a programmable motor. This device recovered biomarkers at ~80% of the operator-dependent extraction method published previously. The device was validated by extracting biomarkers from a panel of surrogate patient samples containing clinically relevant concentrations of (1) influenza A RNA in nasal swabs, (2) *Escherichia coli* DNA in urine, (3) *Mycobacterium tuberculosis* DNA in sputum,

and (4) *Plasmodium falciparum* protein and DNA in blood. The device successfully extracted each biomarker type from samples representing low levels of clinically relevant infectivity (i.e., 7.3 copies/ μ L of influenza A RNA, 405 copies/ μ L of *E. coli* DNA, 0.22 copies/ μ L of tuberculosis DNA, 167 copies/ μ L of malaria parasite DNA, and 2.7 pM of malaria parasite protein).

Automated Patch Clamp Meets High-Throughput Screening: 384 Cells Recorded in Parallel on a Planar Patch Clamp Module

By Alison Obergrussberger, Andrea Brüggemann, Tom A. Goetze, Markus Rapedius, Claudia Haarmann, Ilka Rinke, Nadine Becker, Takayuki Oka, Atsushi Ohtsuki, Timo Stengel, Marius Vogel, Juergen Steindl, Max Mueller, Johannes Stiehler, Michael George, and Niels Fertig

We have developed an automated patch clamp module for high-throughput ion channel screening, recording from 384 cells simultaneously. The module is incorporated into a laboratory pipetting robot and uses a 384-channel pipettor head for application of cells and compounds. The module contains 384 amplifier channels for fully parallel recordings using a digital amplifier. Success rates for completed experiments (1- to 4-point concentration-response curves for cells satisfying defined quality control parameters) of greater than 85% have been routinely achieved with, for example, HEK, CHO, and RBL cell lines expressing hNaV1.7, hERG, Kir2.1, GABA, or glutamate receptors. Pharmacology experiments are recorded and analyzed using specialized software, and the pharmacology of hNaV1.7 and hERG is described. Fast external solution exchange rates of 200 M Ω and recordings of voltage-gated Na⁺ and Ca²⁺ are shown.

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