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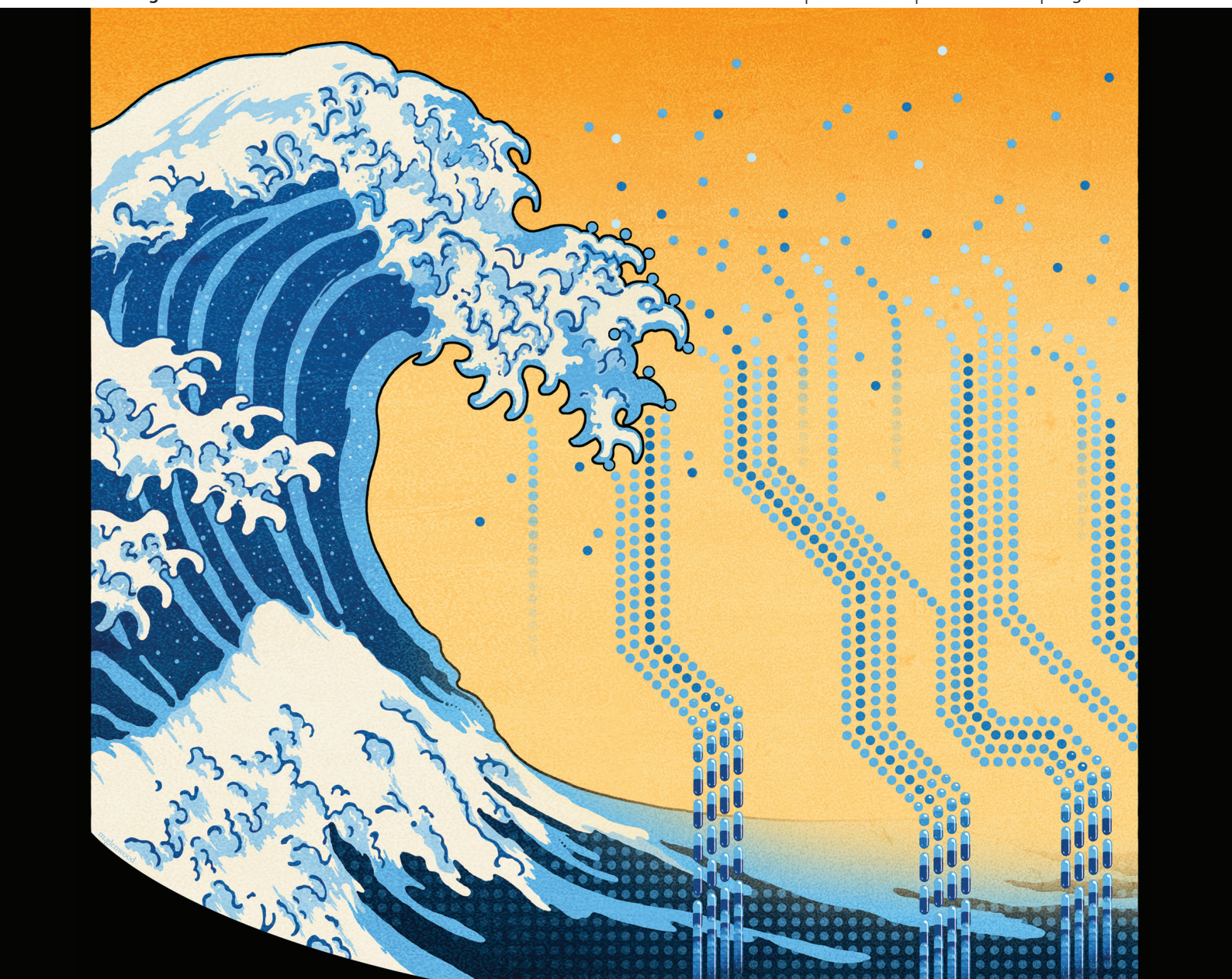

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EDITORIAL

Lab on a Chip: United States of America

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This United States of America themed issue of *Lab on a Chip* presents an overview of work at the leading edge of microsystems engineering in the USA today. The issue is partly based on work presented in a symposium on "Microfluidics and Medicine: Accelerating the flow from lab to clinic" that was sponsored by the Wyss Institute for Biologically Inspired Engineering at Harvard University and convened in Boston, Massachusetts in May 2011. The focus of this symposium was on research and technology development at the leading edge of the microfluidics field that promises to have a transformative impact on medicine and clinical care. However, this issue covers more ground and includes fundamental articles that describe new microsystem components, fabrication methods and microassays for single molecules, single cells and complex living tissues and embryos, as well as microdevices designed to meet a variety of medical challenges in areas ranging from cancer diagnostics to organ-on-chip replacements for animal testing in drug development.

An Emerging Theme. It is difficult to identify a single, *most* important theme from a meeting designed to provide a broad overview of advances in a field. Nonetheless, one obvious area of rapid development to emerge from these papers concerns the use of microfluidic systems—in combination with cells—to provide new approaches to the solution of important problems in biomedical analysis. This theme is at least in part an effort to answer a question that has become increasingly important for microfluidics, that is: what does it, uniquely, bring to science and technology? What can microfluidics do, and for which there is a compelling, large-scale application, that *no* other technique can? The papers, and discussions surrounding them, suggest rapidly growing interest in the ability of microfluidic systems to enable manipulation of mammalian cells in "life-like" circumstances.

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The growth of this interest in fusing microfluidics with mammalian cell culture—and especially in cell culture involving human cells—has several roots, of which two are based in the pharmaceutical industry. i) *Decreasing the probability of failure of drug candidates in clinical trials.* The pharmaceutical industry, globally, has (to express the problem in an understated way) encountered "growing difficulties" in evaluating toxicity and efficacy using its present techniques. A part of the difficulty—and perhaps much of it—has to do with the very incompletely understood differences between humans and animal models for humans (mice, rats, dogs, pigs, and so on). A human patient is not a large mouse, and drugs that seem to be safe and effective in animals are not necessarily equally so in humans. By this analysis, expanded testing of drug candidates for intended use in humans, using *human* cells and tissues—although also certainly not able to predict outcomes completely in intact humans, and certainly not to predict outcome across the broad phenotypic and genetic range of humans—would provide one additional and particularly relevant type of information to use in selecting *against* compounds that are likely to fail in human clinical trials. Microfluidic systems of some design will probably be *required* for these types of studies, since primary human cells will always be expensive and in short supply, and since certain processes important in tissues (for example, ensuring that delivery of nutrients from medium to the cells is not limited by mass transport) *require* small systems. ii) *Patient-specific Medicine.* A second, growing awareness in the pharmaceutical industry is that the range of human response to xenobiotics can be very broad, and developing economical, timely ways of testing the response of individual humans, or members of particular genetic subpopulations, to pharmaceuticals has the potential to increase the safety and efficacy of drugs. This type of bioassay will, again, often *require* microfluidic systems, since tissue samples will frequently—if not always—be small: the tissue available from a needle biopsy of a tumor or from circulating tumor cells isolated from a patient's blood are simple examples.

The blending of microfluidic systems, cell biology, tissue engineering and organ physiology suggests a new direction for microfluidic technology: away from complex systems of valves, channels, and microscale incubation chambers, and toward systems of sufficient simplicity to be useable with the great technical complexity required to grow, dose, and analyze cells and tissues. Microfluidics (as a field, and by the nature of the individuals who have worked in it) has tended, implicitly, to model itself on integrated circuits, and to assume that "more complexity is more capability." In fact, the right model may be the opposite: "The simpler (when combined with complex biology) the better." A movement toward simplicity of microsystem design and compatibility with complex biology would be a new one for the field: that is, toward technology guided by biomedical science, rather than technology grown from physical science.

At the same time, as microengineers find themselves selecting living cells as system components, they need to learn the design principles that govern how cells become organized and function within living tissues, as well as how tissues join together to form functional organs. Combination of different types of cells and linkage of different tissues and micro-organs to study whole organism physiology will require new types of pumps, channels and sensors—ones that are designed with physiological relevance and simplicity of operation constantly in mind. In addition to maintaining cell viability and permitting real-time analysis of mammalian cells, another important advantage of microsystems engineering is that our methods enable us to fabricate microdevices with precise geometry, topography, mechanics, chemistry and flow dynamics on the same scale as that which determines cell organization with living tissues. Recent advances in using microtechnologies to build organ-on-chip microsystems that reconstitute tissue–tissue interfaces and to recapitulate organ-level functions *in vitro* demonstrate the potential value that this approach offers as an alternative to conventional cell-based systems for validation of drug candidates, as well as for toxicity screening of chemicals, cosmetics and toxins.

The final issue that was addressed in the meeting, and in this issue, centers on the many obstacles that still need to be overcome when it comes to translation and commercialization of microfluidics technologies for high-value medical applications. When it comes to commercializing a microsystems technology, the reality in the trenches is far worse than what we see from our optimistic perspectives at the lab bench at universities and research institutes around the world. As researchers, we strive to push the envelope, to incorporate as many 'bells and whistles' as possible, and, very simply, to impress, without regard to materials, robustness, scale-up or cost. When trying to commercialize a technology, the major technical focus is on rigidifying the design, selecting cost-effective materials optimized for the specific application, finalizing processes and procedures, and developing scalable manufacturing—basically, this represents starting from scratch. More importantly, technical advances are meaningless if they are not driven by a commercialization plan led by an entrepreneur who is focused on a single, high value application that is best suited to the technology at hand. In the past, academics worked at the bench in isolation, and hoped that someday if technical success was demonstrated, an entrepreneur or corporate partner would drop from the sky and make their vision into a reality. This model has not worked. It's time for all of us to think of the long-term challenges that must be overcome for our inventions to have an impact on the world, and to redesign how we carry out research at the bench to ensure that these microtechnologies take the shortest path to success.

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