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Editorial

High throughput strategies for the design, discovery, and analysis of biomaterials

Biomaterials found in nature have evolved from a multifactorial and combinatorial process involving a number of distinct molecular components and processing steps. The resultant materials have a complex structure with hierarchical organization and systems-level function that is frequently the result of more than the sum of the individual parts. Scientists and engineers are aiming to dissect these structure-activity relations by designing high throughput platforms for screening the individual versus combined effects of multivariate biological cues. Computational tools and high content screening methods have provided additional insights into synergies that can emerge between materials properties and environmental parameters and how these shape specific biological endpoints. In order to recapitulate the complexity inherent to natural biomaterials, engineered biomaterials are being increasingly designed and elucidated based on an emerging technology triad that couples combinatorial methods, high throughput screening, and high content analysis.

The fifteen contributions in this special issue of *Acta Biomaterialia* include review articles and original research papers that cover the spectrum from high-throughput and combinatorial techniques, to high content screening and analysis. Throughout the special issue, emphasis will be placed on the marriage of combinatorial materials development and computational tools for imaging and analysis, towards platforms that shorten the time and effort to functional biomaterials. The articles herein fall within and often across the following topical sub-areas: *biomolecule microarrays*, *polymeric biomaterials for discovery and screening*, *hydrogel platforms for screening multivariate cues*, and *biomaterials driven assays for high-content analysis*.

As elaborated further below, this special issue highlights recent advances in (a) enhanced throughput designs for biological screening of biomaterials and (b) high biological content studies of cell-biomaterial interactions. Under (a), we focus on developments in array technologies for combinatorial engineering and analyses of synthetic and naturally-inspired biomaterials, and three-dimensional micro-engineered platforms presenting multivariate biological signals. Under (b), we expand the focus to emerging areas in biomaterials driven assays for high-throughput discovery, and high dimensional screens and imaging technologies for material interactions with biology.

Biomolecule microarrays. Tissue microenvironments play host to a rich assortment of biological molecules that are presented to cells in a context dependent fashion, with broad variability in composition across tissue. Exploring the interdependence of extracellular biomolecular and matrix composition and tissue form and function *in vivo* is inherently challenging. To this end, high-throughput assays are being proposed to deconstruct the multitude of biochemical cues that cells integrate to adopt a specific outcome. In this issue, the Habibovic laboratory reports on high-throughput screening approaches to enable combinatorial "reconfiguration" of biomaterials using microfluidics. A contribution from the Hwang laboratory explores the current state of high-throughput platforms used in studying cellular processes. To demonstrate the power of extracellular matrix microarray approaches, Bhatia, Underhill and colleagues report the combinatorial discovery of matrix signals that promote endoderm specification, while a study from the Voelker laboratory demonstrates how stem cells are responsive to both matrix protein and growth factors when presented together during differentiation. Similarly, but using short peptides, Derda and colleagues show how arraying combinations of peptides derived from matrix proteins and growth factors can influence epithelial to mesenchymal transitions in mammary epithelial cells. Taken together, these reports demonstrate the strength in combinatorial microarray strategies to decipher the links between adhesion, growth factor activity, and strategic cellular outcomes.

Polymeric biomaterials for combinatorial discovery and screening. While nature has optimized materials with a high level of complexity for specific biological requirements, the toolbox of the synthetic materials chemist has often provided comparable solutions with the benefit of synthetic control at the molecular level. In this issue, Mei and colleagues review the progress and promise of synthetic polymer microarraying approaches for stem cell engineering. As an example of high-throughput materials design, a contribution from the Sung laboratory reports the combinatorial development of shape memory polymers for applications in vascular biology. Combinatorial approaches for polymer development have benefitted other areas of biomaterials science and engineering. For instance, a review article by Alexander and colleagues discusses the use of polymer microarrays to discover surfaces that are resistant to bacteria growth. Both synthetic and natural biomaterials have advantages and disadvantages; high-throughput arraying strategies enable the broad space of both classes to be assessed separately and together for optimization of a desired application.

Hydrogel platforms for screening multivariate cues. The extracellular matrix *in vivo* is a dynamic viscoelastic material. Combinatorial screening approaches using hydrogel biomaterials pose several advantages to conventional approaches on rigid substrates, including the ability to tune both biochemical and biophysical properties.

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A study from the Murphy laboratory explores the interplay between these parameters using a platform involving differential wettability to fabricate hydrogel microarrays with variable stiffness and presentation of short peptide ligands while an article from the Bradley laboratory proposes innovative double-networked hydrogels for discovery of bioactive materials. Dynamic stimulation is demonstrated by a study from the Simmons laboratory, where hydrogel biomaterials are integrated with stretchable membranes to study cellular response to temporal mechanical stimulation. Revzin and colleagues take an alternative combinatorial approach to presenting multivariate cues in 3D by fabricating microgels and exploring the cues that influence differentiation of stem cell spheroids. Whether using a 2D or 3D platform, synthetic hydrogel biomaterials in high-throughput assays are proving a powerful approach to screen multiple biochemical and biophysical cues together.

Biomaterials driven assays for high-content analysis. Alongside the need to develop highly parallel strategies for biomaterials discovery, there is a complementary need to couple computation and high-content analysis in order to extract materials-specific biological informatics. This is particularly important considering subtle changes in biological activity that may prove critical for an application, and the enormous data sets generated from high-throughput assays that need to be analyzed in a time-efficient manner with meaningful output. To underscore this important area, a review by Groen, Kohn, and de Boer explore the emergence of "materiomics" and the coupling of genomics with combinatorial materials design strategies. As an example of how biomaterials and high-content imaging can drive next-generation assays for biotechnology and medicine, a contribution from the Saha laboratory couples microcontact printing with high content imaging to yield multi-parametric data on CRISPR-Cas9 gene editing for optimizing delivery strategies. A paper from the Dalby and Reid laboratories elucidates ways in which nanoscale mechanical stimulation can steer cell biological fates.

Collectively, the articles in this special issue serve to frame the current state of high-throughput assays and high-content analyses, the integration of which we believe is reshaping not only fundamental biology research but also the design and implementation of biomaterials across multiple fields. If the ultimate goal is to match the complexity observed in natural biomaterials, high-throughput/high-content approaches are necessary to expand the parameter space, towards defining structure-activity relationships between materials and biological systems. Innovative combinatorics, advanced imaging, and new analysis and screening methods are positioned to further accelerate the pace of the ideation and realization of new biology-encoding materials.

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