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Stepping into the omics era: Opportunities and challenges for biomaterials science and engineering☆

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Abstract

The research paradigm in biomaterials science and engineering is evolving from using low-throughput and iterative experimental designs towards high-throughput experimental designs for materials optimization and the evaluation of materials properties. Computational science plays an important role in this transition. With the emergence of the omics approach in the biomaterials field, referred to as materiomics, high-throughput approaches hold the promise of tackling the complexity of materials and understanding correlations between material properties and their effects on complex biological systems. The intrinsic complexity of biological systems is an important factor that is often oversimplified when characterizing biological responses to materials and establishing property-activity relationships. Indeed, *in vitro* tests designed to predict *in vivo* performance of a given biomaterial are largely lacking as we are not able to capture the biological complexity of whole tissues in an *in vitro* model. In this opinion paper, we explain how we reached our opinion that converging genomics and materiomics into a new field would enable a significant acceleration of the development of new and improved medical devices. The use of computational modeling to correlate high-throughput gene expression profiling with high throughput combinatorial material design strategies would add power to the analysis of biological effects induced by material properties. We believe that this extra layer of complexity on top of high-throughput material experimentation is necessary to tackle the biological complexity and further advance the biomaterials field.

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Keywords

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1. Introduction

Regenerative medicine requires an understanding of the complexity of life science principles and biomaterials for the successful development of new therapeutic approaches. The biomaterial field has evolved over the past decades witnessing important successes using the classical design and engineering approaches. However, when looking into the future, clinical translation could be more efficient and rapid. For the field to undergo this transition, with faster developments we foresee that the scientific complexity at both sides of the interface – the material on the one hand and the organism on the other – needs to be addressed simultaneously. Fortunately, it seems that both material and biological complexity can be addressed using similar approaches.

1.1. Classical biomaterial research

Classically, biomaterial design and optimization are largely confined to a low-throughput and iterative experimental approach. Using this 'trial and error' methodology, hundreds of clinically used medical implants (using a wide range of biomaterials) have been successfully developed. A few prominent examples are coronary stents, orthopedic implants, and intraocular lenses. However, the exponentially growing body of scientific work on biomaterials is not proportional to the low number of truly fundamental clinical breakthroughs. Typically, a biomaterial is subject to iterative engineering, at different property scales (*e.g.* chemistry, structural or mechanical), driven by hypotheses emerging from biological concepts or practical intuition. For instance, scientists argue that the *in vitro* cell phenotype is more functional when the natural *in vivo* extracellular matrix is structurally mimicked using electro-spinning techniques [1] or that osteoblastic function is enhanced on rougher surfaces because it mimics that of osteoclastic resorption during bone remodeling [2–4]. The inevitable consequence of trial and error approaches is that variations to one property alter other properties, yet at different scales. A good example is the iterative design of osteoinductive materials over the past 25 years, in spite of the fact that the exact properties enabling osteoinduction are still undefined. Doing so, the tridimensional macrostructure, interconnected pore structure and surface micro-topography have all shown (separately or in combination) their valuable contribution to the osteoinductivity of calcium phosphate ceramics [5–8]. However, attempts at improving the mechanical properties of osteoinductive ceramics resulted in a decrease in the osteoinductive capacity [6,9].

Importantly, adequate *in vitro* models to test biomaterials are still largely lacking. *In vitro* assays characterizing the biological effect of designed biomaterials are similarly inspired by biology yet based on intuition rather than proven effectiveness. Biomaterials for bone regeneration applications are mostly characterized using *in vitro* assays without proven predictable efficacy such as osteogenic differentiation to address the bone forming capacity of cells or materials [10–12]. That being said, advances in developmental and (stem) cell

biology may provide a solid basis for hypothesis-based biomaterial research. Candidate approaches have indeed been successful. The *in vivo* bone forming capacity of human mesenchymal stem cells (MSCs) was enhanced by specifically targeting protein kinase A signaling, selected based on its reported implications in vascular calcification and bone mineral density [13]. Alternatively, when targets for aimed signaling pathways are unknown, a high-throughput screening approach can be employed to, for example, identify small molecules mimicking hypoxia to modulate angiogenic responses in MSCs [14]. Furthermore, *in vitro* cell based assays often involve assessing a whole population using for instance qRT-PCR techniques or ELISAs, where valuable single cell, subpopulation or spatial information, obtained by techniques such as immunohistochemistry or flow cytometry, is lost.

The aforementioned approach has led to successful clinical translation to some extent. For instance, calcium phosphate based products are available on the market for orthopedic or maxillofacial applications, however, for minimal weight bearing applications. Also, the available products are mainly, but not exclusively, osteoconductive and progress achieved with osteoinductive materials has yet to reach the clinic [15,16]. Clearly, the biomaterials field requires a different approach to enable further, more effective and rapid developments. Considering the complexity of both biological and material systems seems a fundamental necessity herein. Successful engineering of biomaterials for biomedical purposes might need a reverse engineering approach in order to decompose and understand the biological systems.

1.2. Complexity of biomaterials and biological systems

Tissue engineering aims at implanting a temporary scaffold that permits and promotes regeneration of the damaged tissue through stimulation of the body to heal itself. Therefore, the intrinsic complexity of biological systems is a crucial concept to acknowledge. Nature has built 'diversity', complex systems, using smart combinations of relatively few 'universal' components at different hierarchical scales. Using a small number of building blocks, either chemical elements or four nucleotides, Nature has created structural and functional diversity. Unraveling this complexity (*e.g.* ENCODE project; identifying all functional elements in the genome) at one single scale already seems a meticulous and interminable job.

Similarly, a (synthetic or natural) material should be considered as a complex system composed of a hierarchical combination of properties (from elemental, through structural to functional). An osteoinductive calcium phosphate ceramic is hierarchically composed of, naturally, calcium and phosphate, a crystal structure, a surface charge, grain and pore sizes, surface topography, microporosity and all together with its macro-porosity determine its final clinical effectiveness in inducing and promoting bone formation. As such, improving the mechanical properties of osteoinductive ceramics by the addition of mechanically more stable polymers is successful in improving the mechanical properties but it is at the expense of the osteoinductivity. Not only are different properties interrelated to and influencing each other, yet but at different scales, also different properties might converge to the same biological effect.

The challenge to design smart materials to regenerate biological tissues is intrinsically multifaceted, yet highly intertwined. The scientific complexity at both sides of the interface – the material on the one hand and the organism on the other – needs to be considered. Such multi-scale complexities make any single-scale analysis and prediction a hypothesis at best and hence argue for a multi-scale approach.

2. Biomaterial development

Biomaterials represent a uniquely challenging design and optimization problem. The biomaterials community faces myriad difficulties, perhaps foremost the need to develop standard test methods that will enable comparability of data, the lack of high-throughput screening methods, and the almost universal dearth of computational models that can predict biological outcomes based on material properties. In a review a few years ago, Kohn et al. already pointed out that “the imagination of biomedical engineers and clinicians and advances in biology have outpaced the ability of material scientists to provide the new generation of biomaterials that is critically needed for the full clinical implementation of the tissue engineering approach” [17]. While biomedical engineers explore the need for resorbable polymer scaffolds that promote a variety of regenerative therapies, the most commonly used scaffold materials in all tissue engineering research are the well-known copolymers of lactic acid and glycolic acid. So far, only a small number of studies explore polymers that have complex monomer structures, and simple “trial and error” seems to be the most common approach to match a specific polymer to a target application.

However, research efforts in biomaterials development are now shifting to the use of increasingly complex material systems to facilitate the *de novo* design, synthesis and fabrication of novel biomaterials with properties tailored to specific biological needs and clinical applications. This requires a major shift from time-consuming trial-and-error based conventional methods (*i.e.*, one sample and one experiment-at-a-time) to combinatorial and computational approaches allowing creation and high-throughput screening of libraries of materials [18].

2.1. Combinatorial approaches

It is important for the biomedical community to have a wide range of biomaterials options available. Yet, over the last 40 years only five fundamentally new, degradable polymers have reached wide clinical use in the US (1969: poly(glycolic acid), 1971: lactide-glycolide copolymers; 1982: polydioxanone; 1996: polyanhydride; 1998: acrylate terminated PLA-PEG)); the rate of entry of new, synthetic polymers into clinical use has historically been about one per decade. The traditional mode of biomaterial design follows synthesis of a new material, its characterization, processing of the material into a desired shape or form (fabrication of the biomaterial), and characterization of intrinsic and extrinsic properties relevant to the target (biological) application. This chain of events starts all over again if the material does not meet the required specifications for the desired application. The interplay among (i) synthesis and processing, (ii) structure, and (iii) properties such as the cellular response to a biomaterial follows the form of the classic materials science paradigm. Taking advantage of this set of relationships for the ultimate control of cellular responses is a powerful approach to advancing clinical applications of biomaterials.

The development efforts for biomaterials in the past were not only too slow but also did not result in a sufficient diversity of chemical structures. Combinatorial methods accelerate the discovery of new biomaterials by increasing the number of available candidate materials for any specific application, and by allowing systematic studies of correlations between structure, material properties and performance [19]. Combinatorial approaches also lower the cost and the amount of material used during discovery. For instance, combinatorial chemistry had great success to identify lead compounds for discovery of new drugs [20,21]. Combinatorial chemistry was also successfully applied to obtain polymer libraries with predictable and systematically varied material properties [22]. For instance, we developed a combinatorial library of 112 polymers that allowed structure-property correlations and as such reported predictable changes in glass transition temperature (T_g), surface wettability and cellular response (highlighted in Fig. 1) [23]. In general, combinatorial approaches can be used to elicit fundamentally different biological responses by systematically varying the polymer chemistry and blends thereof [24,25]. For instance, depending on the PEG block length and the prevalence of these blocks within the polymer chains, chemically identical PEG-containing tyrosine-based segmented terpolymers led to tunable bioresorption times (within hours [26] up to at least 3 years [27] *in vivo*), protein adsorption and cell migration behavior [28,29], formation of nano- and micro-domains [30,31], exogenous production of reactive oxygen species (ROS) [32], cell–cell vs. cell–substrate adhesivity [33], cytoskeletal organization and differentiation of stem cells [34]. The requirement for increased chemical complexity of new biomaterials goes hand-in-hand with the requirement for more sophisticated analytical tools to characterize and quantify the material and its biological properties.

2.2. High-throughput experimentation (HTE) as a materials design and optimization strategy

Over the last 30 years, combinatorial chemistry and high throughput screening led to significant changes in the drug discovery process. This was due to the ability to simultaneously synthesize millions of random moieties and to identify the most active compounds [21]. This approach was often described as searching for “a needle in a haystack”, indicating that identifying the small number of active compounds within the millions of useless compounds present in the reaction mixture is the real challenge of this approach. The search for active drug candidates was facilitated by the fact that for drug activity the compound's chemical structure is the single most important parameter. Unfortunately, for polymers there is no simple correlation between chemical composition and potential utility. This is due to the fact that the utility of a polymer is affected by its average molecular weight and molecular weight distribution, as well as by the way the polymer is processed into a shaped object. Through polymer processing, the same polymer can be endowed with different end use properties. For instance, a Styrofoam cup, used to dispense hot coffee, and a transparent overhead projection sheet can both be made of polystyrene. Once the Styrofoam cup and the overhead projection sheet have been dissolved in methylene chloride, no chemical structure differences can be detected between these two polystyrene solutions. Therefore, the methodology developed for drug discovery cannot be directly applied to polymer discovery.

Indeed, polymer discovery is preferably based on parallel synthesis where each polymer candidate is prepared in its own reaction vessel (Fig. 1) [22]. The exploration of the wide range of structure-property correlations represents the first commercial success of the use of HTE in biomaterials discovery; a number of polymers were identified that are now used in medical implants world-wide [35]. Similarly, a semi-automated methodology was developed to synthesize and screen a polymer library of about 400 individual polymers for gene delivery [36,37]. In this work, the polymers were spotted in an array and the utility of each of the polymers in gene delivery was examined.

The need to create individual polymers in a parallel synthesis setup tends to limit the number of individual polymers included in a polymer library to a few hundred at most. Scientists, used to working on millions of moieties in a typical drug discovery library, would not normally regard the exploration of tens or hundreds of individual compounds as “high throughput experimentation”. To address this point, the innovative concept of creating property gradients by changing the blend composition along the length of a microscopy slide was implemented. As such high-throughput screening platforms were developed (both in 2D and 3D) to specifically characterize and analyze material properties and cell-material interactions along gradients. In this way, continuous physical property gradients (such as composition, phase separation, crystallinity, nanotopography, etc.) and biological property gradients (*e.g.*, density of biologically active ligands such as fibronectin, RGD-peptide, laminin peptide) were created [38–43]. Furthermore, inkjet printing has been used to deposit biologically active proteins (*e.g.*, collagen) for high throughput cell patterning [44]. Other techniques for developing cellular patterns include, but are not limited to, soft lithography, laser-directed cell printing, and photolithographic techniques [45–48]. In the recent years, technological advances enabled the fabrication of miniaturized platforms assembling physical surface properties of biomaterials, which beside chemical composition play an important role in cellular behavior [49]. We developed an algorithm based library of over 2000 topographical features assembled on a chip, which allows high-throughput assessment of cell behavior on the separate topographical features (Fig. 2) [50]. Moreover, this and similar platforms allow direct comparison design characteristics to phenotypical read-outs such as cell shape or the expression of differentiation markers [51].

3. Biological evaluation

Biomaterials are being developed for specific clinical applications for which accurate evaluation of the material's performance within the biological context is crucial. However, specialized *in vitro* tests to determine *in vivo* biomaterial performances are still largely lacking. This is a crucial step in testing anything; without an appropriate readout or biological hypothesis, the evaluation of materials and the effect of their properties are difficult to interpret. For example, the necessity of *in vivo* assessment to test the osteoinductivity of a material for bone regeneration is due to the fact that only poorly predictive *in vitro* models are available today. So far we were not able to assemble, simplify or predict the biological complexity of tissues in an *in vitro* model. We therefore need to better understand the biology of the tissue of interest. Concepts from developmental biology have been used, for instance in the field of cartilage repair [52]. In the case the intended tissue has regenerative capacities, the mechanisms during healing may be studied and used.

While the classical selection criterion for a safe, stable implant dictated choosing a passive, inert material, it is now understood that any such device will elicit a cellular response. It is now widely accepted that a biomaterial must interact with tissue rather than act simply as a static implant. Today the principal criterion for biomaterials performance becomes a desirable, controlled cellular response. Consequently, a major focus of biomaterial research centers is on control of cellular interactions between the artificial material and the surrounding living tissue.

3.1. Genomics to tackle biological complexity

In order to unite the biological complexity in an *in vitro* model, we propose the use of another omics approach: transcriptomics. Historically, gene expression profiling has been useful to unveil biological signaling pathways, study mechanisms involved in development or to study stem cell niches. Furthermore, genomics is commonly used in the pharmacological field to investigate the effect of many different therapeutics and small molecules [53]. The gene expression profile represents, *via* a global measurement, the cell's transcriptional state; giving a clue about its response to external factors and hinting towards its phenotype. External stimuli from surrounding cells and extracellular matrix substantially define cellular identity and behavior (*e.g.*, differentiation) *via* the gene expression profile of each cell.

In tackling the biological complexity, gene expression profiling is a useful tool not only to study and understand the biology of the intended tissue but also to monitor the biological effects of a biomaterial (both *in vivo* and *in vitro*). Hitherto, transcriptomics have been applied in the biomaterials field (as summarized in Table 1). Indeed the cellular responses to different surface structures of biomaterials have been investigated using gene expression profiling [54,55]. Also, gene expression and networks were analyzed on ceramic/collagen composites, materials based on various fabrication techniques, and different ceramics in order to understand the cellular response to the presented physico-chemical stimuli [56–59].

In fact, whole cellular profiles may reveal additional information otherwise hidden when a specific biological readout of interest (*e.g.* BMP2 up regulation or secretion) is assessed [60]. Similarly, Autefage et al., studied the effect of dissolution products from strontium incorporated bioglass on hMSCs using *in vitro* transcriptomics [61]. The incorporation of strontium into bioglass for bone regeneration applications has been shown previously to upregulate osteogenic markers *in vitro* and osteoconduction *in vivo* without fully understanding the mechanism. Genes contributing the most to the measured response were extracted from the transcriptional profiles and revealed a strong regulation of the sterol and steroid synthesis pathway. Additionally, the expected effect on genes related to bone development and osteogenic differentiation was only mild. This study and these results illustrate the added value of global phenotypic measurements such as transcriptional profiling while focusing on a presumed effect or specific genes clusters limits the outcome.

3.2. Converging multiple omics approaches

As aforementioned, the omics approaches, materiomics and transcriptomics are already applied separately in several fields including the biomaterials field. As illustrated in Table 1,

most of the genomics studies applied to biomaterials studies involve low sample number or only one material property. However, the key to success for future advances in the biomaterials field may be to integrate or converge multiple omics fields by addressing the double-sided complexity presented by biomaterials for tissue regeneration. Therefore, the convergence of the two omics fields seems a natural choice. Herein materiomics deals with the complexity presented by material systems and genomics addresses the biological complexity at gene expression level – as illustrated in Fig. 3. Then, using a systematic approach, libraries containing a large variety of materials properties on the one hand and corresponding genome-wide gene expression profiles on the other hand can be built. Such libraries with high throughput data on both scales (biological/transcriptome and material/materiome) would allow powerful correlation analyses to define the biological functionality of material properties and, furthermore, to understand and improve materials for biological applications. Importantly and as mentioned before, an *in vitro* model with a biological question is crucial when addressing these libraries. Indeed in such large datasets, “fishing” presents a major pitfall. Without any biological readout correlations between material properties and gene expression profiles are endless and meaningless. For instance the *in vivo* performance of a biomaterial in an application specific model may be used to enrich the correlations. However, the convenient existence of a successful material with known *in vivo* application is herein a prerequisite. Also, the significance of the correlation between *in vitro* cellular behavior and *in vivo* bioactivity is achieved when different and varying *in vivo* performances can be compared. Also, integration of multi-scale experimental analyses may present the future key to improve our understanding how structure and properties are linked as most properties (biological and material) are strongly dependent on the scale of observation. Similarly, the dynamic nature of gene expression argues in favor of continuous assessment of the transcriptional variation in time in response to a biomaterial. Time courses or at least multiple time points would allow a more complete picture of the biological response.

An illustrative example of convergence of multiple omics approaches is the Connectivity Map [62,63]. This effort has assembled the transcriptional profiles of cells exposed to a large set of bioactive molecules. The response to the compounds is reflected in the transcriptional profiles of the cultured cells. High throughput screening of compounds enables not only identification of hit compounds with aimed effects but also formulation of structure-function relationships. Indeed connections between molecules sharing a molecular response allow exploration of the chemical-functional relationships thereby modeling and designing molecules with improved biological properties.

We recently explored the potential of converging materiomics and transcriptomics [64]. We reported the transcriptional profiles that an osteoblast can adopt in response to a set of 23 materials with varying properties. The diversity of the set of materials, ranging from polymers, to composites to synthetic ceramics and titanium with wide range of properties allowed evaluating the effect of separate properties. By correlating specific properties and known *in vivo* performances to gene expression profiles, we showed for instance that TGF- β and WNT signaling may play a role the response to osteoinductive materials along with differential cell adhesion kinetics via attenuated FAK signaling. We have also showed that the addition of calcium and phosphate to a biomaterial affected BMP2 expression and TGF-

β signaling. This type of approach helps understanding cellular responses in relation to material properties, which will promote the development of more effective biomaterials for applications in tissue regeneration. Increasing the number of materials with concomitant variations in properties allows for more significant and robust property-effect relationships which would lead to improved biomaterial design criteria.

Further developments within this field could be foreseen as genomics is brought to single cell scale with the development of single cell RNA sequencing [65,66]. Even a spatio-temporal dimension is acquired with the emergence of *in situ* RNA detection [67,68]. *In situ* RNA detection combines imaging techniques with RNA probes, allowing the assessment of increasing number genes simultaneously [69]. However, major advances are necessary to upscale the detection of transcripts. For instance, this method would allow addressing the transcriptional responses of all different cells in the vicinity of an implanted material revealing the biological responses. This might be masked when using a population-wide tool such as gene expression profiling. Moreover, other omics fields could be used alongside or instead of genomics to tackle the biological complexity. Proteomics, for instance, analyses the entire set of proteins translated or modified by a biological system. Alternatively, morphological and cytoskeletal descriptors may be used to screen materials [70,71]. However, unless correlated to a biological functionality, cytoskeletal and morphological parameters do not directly reveal biological functionality [72]. This imaging-based approach allows for live-monitoring where gene expression profiling demands an end-point measurement *via* cell lysis. Naturally, antibody-based screening targeting a protein of interest is a functional readout, however, belongs to the candidate rather than holistic or high-content approaches.

3.3. Computational modeling

In recent years, the technical capability to synthesize libraries of biomaterials has outpaced the ability to test the properties of the individual polymers and materials for potential applications. While many publications report on high-throughput approaches for biomaterial development, the exploration of physical and biological properties of materials remains complex, time-consuming, and costly [73]. Aiming at the most efficient strategy to extract biological information from cellular or tissue responses to arrays of generated libraries of materials, computational modeling of material properties may be an attractive alternative to high throughput experimentation, or be used in combination with high throughput experimentation to limit the number of materials that need to be evaluated [74,75].

Current computational approaches for managing and modeling the bounty of data arising from combinatorial synthesis, HTE and ultimately (gen)omics approaches in biomaterials development generally aim to explore and quantify the relationship between the biomaterial *in vitro* and *in vivo* properties (the outputs) and pre-computed physico-chemical properties commonly known as descriptors (the inputs). This conceptual scheme is borrowed from Quantitative Structure–Activity Relationship (QSAR) methods employed successfully by the pharmaceutical industry in rational (*i.e.*, computer-aided) drug design. When translated to the materials and biomaterials realm, these same methods have adopted the sobriquet Quantitative Structure–Property Relationship or Quantitative Structure–Performance

Relationship (QSPR) [76]. Our work of the past decade exemplifies the broad utility of QSPR models in biomaterials discovery and property prediction [17,77–83]. Coupled with virtual high-throughput screening (vHTS), QSPR and related *in silico* quantitative approaches have contributed immensely to our fundamental understanding of the complex relationships between biomaterials and their *in vitro* and, in some cases, *in vivo* properties. Moreover, these studies have established a new paradigm for managing large biomaterial data sets and for predicting new, but as-yet unknown, properties of biomaterials. With the more recent emergence of “omics” technologies such as genomics, transcriptomics, and proteomics, scientists now enjoy unparalleled opportunities for looking into the hierarchical levels of biological complexity from the perspective of the receptor, cell, tissue, organ, whole organism, and beyond to the ambient environmental conditions. However, the sheer size and complexity of data sets emanating from these omics-based approaches complicate an already substantial challenge in biomaterials discovery and optimization. A case in point is the scenario described above, combining multiple omics technologies, that would amalgamate the vast amount of data on a library of biomaterials with the even larger amount of omics data on the biomaterials-tissue interaction. The resulting size of such data sets would almost certainly overwhelm standard methods of data analysis like partial least-squares (PLS) regression. We must also remember that such real-world biomaterials and omics-based data sets are typically plagued by experimental uncertainties, outliers, missing data and, particularly for omics data, issues about signal-to-noise ratio. Even non-linear approaches such as artificial neural networks (ANNs) would do little to alleviate this “big data” dilemma. What is needed is a fresh approach to computational modeling and data analysis that adapts, and scales, well to such ultra-high multi-dimensional multivariable problems.

One promising solution may be found in the emerging high dimensional model representation (HDMR) approach, which has been successfully employed in applications as diverse as aircraft and vehicle design, atmospheric physics and chemistry, and bioengineering. The HDMR algorithm [84–86] is a general function-mapping technique that expresses the output of a multivariate system in terms of a hierarchy of cooperative effects among its input variables. The coauthors Rabitz and Welsh with their coworkers have recently illustrated the utility of HDMR in constructing a single analytical model that reliably predicted the performance for all possible binary and ternary component mixtures for a solution mixture containing all permissible combinations of 10 solvents from just a modest number of experiments [84]. HDMR rests on the general observation that, for many physical systems, only relatively low-order input variable cooperativity is significant [87]. HDMR is adept at handling high and ultra-high dimensional problems such as envisioned here in which multiple outputs (dependent variables) and 10 s, 100 s, or even 1000 s of inputs (independent variables). There is no need for pre-computed molecular descriptors as in QSAR/QSPR modeling, since HDMR relies solely on the “raw” inputs and outputs to identify possible functional relationships. Unlike conventional regression methods like PLS and ANN that either assume a specific analytical form or impose simplifying conditions, HDMR requires no assumptions or special conditions to uncover the full input–output relationship. HDMR lets the analysis naturally determine the precise input–output relationship in terms of each of the independent variables and their key interactions. HDMR

is especially designed to address complex multi-dimensional problems as would be encountered when combining multiple omics approaches. Importantly, HDMR scales well as the number of input variables as well as the dimensionality of the problem increases. This important advantage enables HDMR to build statistically robust quantitative models with only sparse sampling of the full multi-dimensional property space. Data analysis tools such as HDMR will facilitate the coming integration of large combinatorial libraries of advanced biomaterials with omics-based data to accelerate and streamline the development of advanced biomaterials for applications in tissue regeneration applications and beyond.

4. Conclusion

In our opinion, combining multiple omics approaches to address both the biological and the material complexity simultaneously would facilitate the development of innovative, new tissue regeneration applications. New insights in biology and full cellular response assessments are necessary in order to adequately address the effect of material properties on the organism. Moreover, the different omics fields require collaboration between experts in their respective fields; without material sciences, biological knowledge or bioinformatics analyses, the proposed approach is not viable. Indeed, the multidisciplinary required for tissue engineering is even more necessary when trying to converge multiple omics approaches.

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Statement of Significance

In this opinion paper, we postulate that converging genomics and materiomics into a new field would enable a significant acceleration of the development of new and improved medical devices. The use of computational modeling to correlate high-throughput gene expression profiling with high throughput combinatorial material design strategies would add power to the analysis of biological effects induced by material properties. We believe that this extra layer of complexity on top of high-throughput material experimentation is necessary to tackle the biological complexity and further advance the biomaterials field.

Fig. 1.

Combinatorial methods accelerate the discovery of new biomaterials. A library of 112 degradable polymers were fabricated using a strictly alternating A–B type copolymer design with 14 distinct tyrosine-derived diphenols and eight different aliphatic diacids in all possible combinations. The first monomer contained a functionalizable pending chain, for attachment of a series of chemical groups, while the second monomer allowed copolymerization of n different monomers A with m different monomers B, by giving rise to an array of $m \times n$ structurally related copolymers. The diphenols introduced a variety of pendent chains into the polymer structure, while the diacids controlled the flexibility and hydrophobicity of the polymer backbone. This systematic approach allows studying numerous polymeric candidate materials for medical applications thereby facilitating the identification of correlations between polymer structure and (biological) properties. Indeed further studies showed structure-property correlations using this combinatorial library and reported predictable changes in glass transition temperature (T_g), surface wettability and cellular response. This library of 112 discreet polymers exhibited predictable correlations between polymer structure and a wide range of polymer properties, including biological properties such as protein surface adsorption and cell proliferation. As an example, the glass transition temperature of all 112 polymers is shown here as function of the structure of the diacid and diphenol [22,23].

Fig. 2.

High-throughput platform to assess cell behavior on topographical features. A library of surface features were randomly generated using mathematical algorithms and produced into chips with 2176 different and unique topographies. Cellular responses to these unique surface features are assessed by high content imaging of morphological parameters or the expression of typical proliferation or differentiation markers (such as EDU incorporation or ALP expression). These libraries of topographical features can be broadly applied to reveal cell-surface interaction aiming at improved biomaterial and implant surfaces [50,51]. (Figure adapted from Unadkat et al. and Hulsman et al.)

Fig. 3.

Converging materiomics with transcriptomics. This graphical representation illustrates the proposed approach of combating the complexity of biomaterials with the complexity offered by transcriptomic data. On the one hand, the “materiome” assembles the numerous properties that builds up a biomaterial (1). On the other hand, a cell's transcriptome captures the biological response to a biomaterial (2). Increasing the number of materials to be evaluated ($1 \dots n$) leads to a concomitant increase in the set of properties or materiomes ($1 \dots x$) and the number of corresponding transcriptomes ($1 \dots y$). As such, libraries containing a large variety of materials properties on the one hand and corresponding genome-wide gene expression profiles on the other hand can be built. Herein correlations between the effect of the various biomaterial properties and the biological responses reflected in the transcriptional profiles are key to new insights for improved biomaterial design (3).

Table 1

Studies using gene expression profiling as a tool to study the biological effect material properties on cellular behaviour.

Publication		Number of materials	Material property	Details	Refs.
Dalby et al.	2008	2 Material surfaces vs 1 flat reference	Topography	Evaluating the osteogenic property of surface nanotopographies in comparison to osteogenic (dexamethasone-treated) human mesenchymal stromal cells over 2 time points (14 and 28 days)	[54]
Tsimbouri et al.	2013 2014	2 Material surfaces vs 1 flat reference	Topography	The effect of nanotopography on stem cell fate and proliferation studied in human mesenchymal stromal cells using gene expression profiling	[55]
Eyckmans et al.	2013	2 Materials	Calcium phosphate	Gene expression profiling to identify molecular mechanisms involved in calcium phosphate-mediated bone formation of human periosteum derived cells	[56]
Baker et al. + Kumar et al.	2014 2011	4 Materials vs 2 flat references	Chemical composition Material structure	Gene expression profiling of primary human bone marrow stromal cells to evaluate the influence of scaffold structure in comparison to chemical composition	[57,59]
Barradas et al.	2013	2 Materials	Calcium phosphate	Study the effect of calcium dissolution from ceramics on the gene expression profile of human bone marrow-derived mesenchymal stromal cells	[58]
Autefage et al.	2015	3 Materials (medium containing released ions) vs 1 control	Ion release	Aiming at understanding the osteogenic effect of the dissolution of incorporated strontium into bioglass	[61]
Groen et al.	2015	23 Materials vs 1 flat reference	Surface structure Chemical composition Molecular weight Calcium phosphate	Gene expression profiling on materials with a variety of properties to understand cell-biomaterial interactions i relation to the biophysical and biochemical cues provided by materials and material surfaces	[64]