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Embracing simplicity in biomaterials design

Matthew J. Webber

University of Notre Dame Department of Chemical & Biomolecular Engineering, 205B McCourtney Hall, Notre Dame, IN 46556 United States of America

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ABSTRACT

Biomaterials offer elegant frameworks to uncover mysteries of biology and vital tools to treat diseased or damaged tissues. Complex natural materials in the living world inspire the design of many engineered biomaterial constructs. Yet, complexity in materials design introduces practical, functional, and economic constraints. These challenges point to some virtues for a simplified approach in the design of biomaterials, especially when intended for clinical impact. But what is simplicity, and how can simple synthetic systems interface and intervene with application-specific complexities in the living world? Herein, both the philosophy and inherent benefits of simplicity in biomaterials design are discussed.

Simplicity vs. complexity

The living world abounds with elegant and complex materials and systems. The extracellular matrix offers spatiotemporal cues organizing tissues and organs, while the function of cells and tissues—and indeed the entire organism—entails a coordinated and highly regulated network of systems and signaling molecules. As biomaterials scientists, inspiration from living materials drives the creative pursuit of our own synthetic analogues. Profs. Azevedo and Mata have offered compelling support for complexity in biomaterials design[1]; complexities of the living world are indeed aspirational. Herein, however, an alternate view is presented illustrating practical, functional, and economic considerations that may dictate a reductionist approach to biomaterials design (Figure 1). In seeking biomaterials with scalable, reproducible function, and with the intent of translational impact, there are certain situations where Einstein's paradoxical advice is fitting: "*everything should be made as simple as possible, but not simpler.*"

Translational implications of complexity

Biomaterials offer elegant frameworks to study cellular processes, uncover knowledge about biology or disease, and prepare model tissues for drug discovery. In these applications, recapitulating the complexity of natural materials may be ideal. The realization of clinical impact is another important objective of engineered biomaterials. Here, complexity may introduce impediments to translation. Complex or multi-component biomaterials can present challenges in the context of scalable manufacturing and distribution. Each component of a biomaterial—some designs also include recombinant proteins or living cells—must be reproducibly synthesized or sourced and fully characterized. New processes or infrastructure may need to be invented, with each stage of development adding time and cost. For technology used in humans, it is of vital importance to understand the safety, biocompatibility, toxicology, and mechanism of clearance of both the biomaterial and its primary degradation products; more components can compound such efforts. Though accelerated by necessity of an ongoing pandemic, the design of mRNA-based lipid nanoparticle (LNP) vaccines against SARS-CoV-2 captured simplicity with a system of five discrete and defined components, each with necessary purpose. Four of these were simple lipids[2], and each component leveraged established protocols for Good Manufacturing Practice (GMP) production. Added features, such as targeting, may further augment or improve LNP function, though was not necessary in this case.

Regulatory approval processes must also be navigated for clinical translation[3]. Biomaterials based on clinically approved natural or synthetic materials may benefit from paths for accelerated approval, known in the United States as the 510(k) process, on the basis of being "substantially equivalent" to an existing device. Conversely, novel biomaterials with engineered activity or responsive function, or which include cell or biologic components, may be categorized as combination products and required to traverse parallel regulatory approval paths—as would be required for a device, drug, or biologic—simultaneously. This tortuous, and sometimes case-specific, regulatory process increases the likelihood of unexpected or unpredictable outcomes in technology validation and approval. Unfortunately, these challenges can serve to disincentivize complexity and stifle innovation in translational biomaterials design.

Successful development and regulatory approval of a new biomaterial is capital-intensive. As such, a product that emerges must have a clearly defined (*ideally large*) market, with prospects to address a truly unmet clinical need or substantially improve the standard of care.

E-mail address: mwebber@nd.edu

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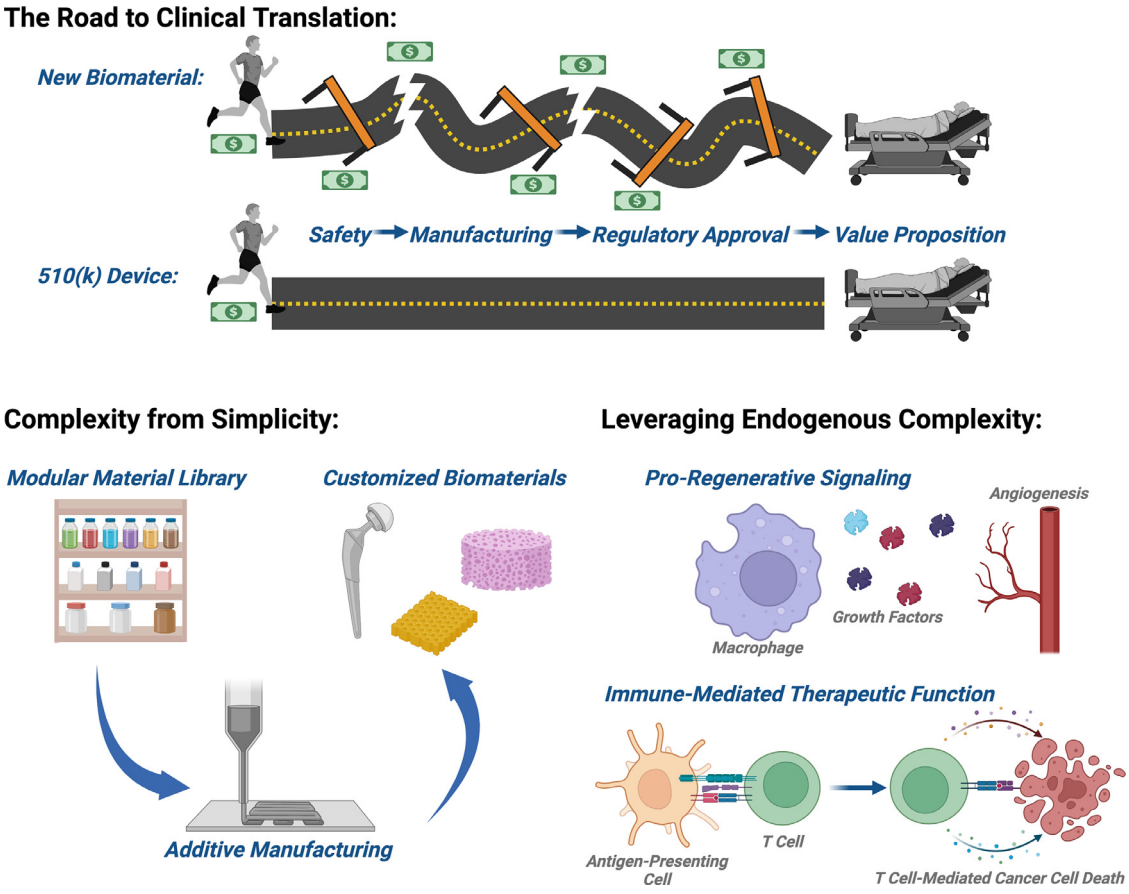

Fig 1. The virtues of a simplified approach to biomaterials design should include considerations for the path to clinical translation (*top*). For instance, a new biomaterial entails a more complex path to clinical translational than repurposing an already-approved device, known by the US FDA as the 510(k) pathway. However, a simple or reductionist approach to biomaterials design does not entail a simple end-product. This is exemplified in the complex functional biomaterials that are realized from modular strategies for additive manufacturing (*bottom left*) or in routes to use simple biomaterials to harness complex endogenous, and often immune-linked, processes in tissue repair or disease mitigation (*bottom right*).

Healthcare economics, whether in a multi-payer or socialized framework, dictates that incremental improvements in function compared to the existing standard of care may limit adoption. This is especially true if new technology comes with significant added cost, more complex administration, and/or increased pain and discomfort. Accordingly, a clear value proposition must be offered, regardless of the complex or elegant engineering that went into developing a biomaterial.

Complexity born of simple modularity

Simple building blocks enable modular or combinatorial approaches to achieve complexity. Cheap, reliable, and reproducible platforms may be more easily implemented or adapted to a task at hand, and unlock the creativity of scientists and engineers to solve problems with confidence from validated underlying material technologies. Some of the most awe-inspiring architecture in human history, examples that have stood for hundreds of years or more, were created by stacking rocks. Similarly, simple “stackable” or modular technologies may empower complex and hierarchically structured biomaterials customized for a specific task. One such example with increasing impact in biomaterials design is the expansion of additive manufacturing, including 3D printing[4]. The (bio)materials underlying these techniques are typically simple and reliable, beginning from a requirement that they be molded or printed in three dimensions with acceptable feature size. From libraries of these materials, spanning metallic and soft polymeric forms, new biomaterials can be created at the point-of-use for digitally directed mass customization and personalization to meet the needs of a specific application, regenerating or replacing hard and soft tissues alike.

Modularity in biomaterials design can also be captured on the molecular scale. One such example is found using synthetic recognition motifs[5], resembling a lock-and-key mechanism. These predictable and tunable molecular-scale interactions can be used to prepare simple, modular, and application-agnostic biomaterial platforms, later tuned for a specific task by modifying discrete and defined sites with cargo or active agents. For example, a generic drug carrier could be conceived that presents sites to load an assortment of modified therapeutics specific to a desired indication or in response to patient-specific data. Likewise, a scaffold could be designed with sites for precise presentation of desired cell- or tissue-specific active signals[6]. In this way, simple and reliably produced material frameworks enable molecular-scale customization for a specific application.

Simple approaches to complex physiology

It has been suggested that the injection of virtually any hydrogel into the myocardium following an infarct will elicit some regenerative function. As we increasingly appreciate the role of endogenous pro-regenerative stem and immune cell populations[7,8] many of which are involved in resorption and clearance of a biomaterial, we may find aspects of truth in this statement. Including highly active recombinant factors into a biomaterial may enhance tissue regeneration, but entails added cost; over the years, certain of these factors have also been associated with an increased risk of cancer. Multicomponent pro-regenerative biomaterials may also be more difficult to define and reliably produce. Naturally sourced materials such as Matrigel® consist of both matrix

and signaling molecules with extremely potent regenerative function, yet sourcing, isolation, and batch-to-batch variability introduce complexity and heterogeneity that prevents clinical use. Accordingly, biomaterials design may instead seek to promote the complexity of endogenous pro-regenerative mechanisms, ideally achieving this goal without need for overly complex, over-engineered, or multi-component materials.

In a related way, the field of cancer nanotechnology has accumulated (*at least*) hundreds of papers of novel bespoke nanoparticle technologies that successfully combat cancer in various rodent models. The composition of the underlying nanoparticles varies from metallic to polymeric, with optional inclusion of active modes of targeting and different classes of therapeutic or diagnostic agent on board. Though unique features of different cancers may dictate some degree of material specification, it may also be wise to reevaluate the design of such systems in light of the increased development costs and the translational hurdles presented by complex and/or multicomponent nanotechnologies[9]. The underlying objectives in using such technologies must be clearly elucidated, to include considerations for more efficient and effective diagnosis and/or delivery coupled with improved safety and tolerability. As with tissue regeneration, there is also an expanding appreciation for the complex innate and adaptive immune-based mechanisms to combat diseases such as cancer[10], and new technologies may instead seek to harness these complex immune-based processes without being complex themselves.

Conclusions

In designing synthetic biomaterials to better treat disease or regenerate damaged tissues, it is tempting—and indeed even inspiring—to look to living materials and systems for direction[1]. Yet, a variety of other considerations and boundary conditions must be addressed so as to realize technologies that achieve their intended impact. Importantly, complexity in biomaterials design may dictate a tortuous and costly path to develop and scalably manufacture an eventual product, with added regulatory hurdles along the way. As adoption of new technologies often contends with an existing standard of care, those with only incremental improvement are not likely to justify increased cost. One should also be mindful that a simple approach to biomaterials design does not necessarily imply a simple end-product. Indeed, from simple or "stackable" modular building blocks, it is possible for highly complex and creative technologies to emerge. Finally, as living systems possess a variety of innate and immune-linked mechanisms to achieve tissue regeneration or combat pathologies such as cancer, a possible role for biomaterials may be to harness these complex endogenous mechanisms, without requiring the synthetic biomaterial be overly complex itself. Simplicity is difficult to define and perhaps even paradoxical; it may be dictated by a specific case, or even subject to the eye of the beholder. Given this, biomaterials scientists may remember the design advice of Antoine de Saint-Exupéry: "*perfection is achieved, not when there is nothing more to add, but when there is nothing left to take away*."

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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