Ascendancy of semi-synthetic biomaterials from design towards democratization

Semi-synthetic goldilocks material design integrates the tunable characteristics of synthetic materials and the refined complexity of natural components, enabling for the progress of biomaterials across length scales. Accelerated translational success may thus be possible for more personalized and accessible products.

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Over the past 20 years, the biomaterial repertoire has expanded rapidly alongside progress in synthetic biology and our deepening understanding of biological systems across many length scales. Refined synthetic strategies reach new levels of biomimicry, and novel methods to engineer naturally derived materials increasingly blur the lines between synthetic and natural approaches. This confluence of advances has given rise to a 'goldilocks' design class of biomaterials: optimized blends that aim to unite the benefits of both the synthetic and the natural. Synthetic components are often more controllable, modular and easily characterized, while natural materials are often more familiar to the host system, better able to replicate native complexity, and allow for personalized variability. Such hybrid designs are now becoming increasingly accessible and scalable, and have begun to gain translational traction (Fig. 1).

The asymptotic progression towards an engineered balance of synthetic and natural materials has driven the field from first-generation static material systems and second-generation bioactive materials towards biomimetic and cell- and gene-activating three-dimensional (3D) systems. In the past 20 years, biomaterial designs have moved towards more sophisticated spatiotemporally controlled (4D-responsive) systems. As the understanding of the immune system and underlying biology of disease has improved in parallel, today's biomaterial systems have also evolved to accommodate for more advanced synthetic biology methods, enabling advances such as gene replacement and gene-editing therapies that trend towards addressing the root causes of disease. With this increasing complexity, opportunities are ripe for further personalization of these materials, but difficulties inherently arise from regulatory hurdles and manufacturing these systems at scale. Consequently, the field must not lose sight of the ever-widening accessibility gap inherent with sophisticated diagnostics and therapeutics. Concomitant efforts to promote democratization and curb disparity will amplify the benefits of technical progress in a global context.

Here, we highlight several representative goldilocks materials across length scales that have risen above the fold and demonstrate this convergence of synthetic and natural, while considering how current trajectories might guide the field towards the parallel goals of improved efficacy, translatability, personalization and accessibility.

Molecular-scale designs for therapeutics and diagnostics

Synthetic biology is the full embodiment of the goldilocks approach, employing careful selection and synthetic modification of natural biological systems to produce, in effect, biomaterials that exert a targeted effect. Combined with the omics revolution and artificial intelligence (AI)-driven methods that decode protein folding, such as the recent efforts of Google's DeepMind AlphaFold or the Baker group's recent work in designing protein binders de novo from isolated knowledge of the corresponding target structure[1], synthetic biology approaches have provided versatile platforms for the identification of numerous gene and protein diagnostic targets, as well as providing powerful methods to improve sensitivity of diagnostics systems.

In particular, the recent discovery of the bacterial immune system's RNA-guided CRISPR–Cas endonuclease systems has not only provided new gene-editing methods and resurrected gene therapy approaches with new clinical trials underway[2], but has also created opportunities for personalized diagnostics systems through the development of the SHERLOCK[3] (specific high-sensitivity enzymatic reporter unlocking) and DETECTR (DNA endonuclease-targeted CRISPR trans reporter)[4] platforms. Cas12 and Cas13 family nucleases exhibit 'collateral RNase' activity, which can cleave carefully engineered fluorescent or colorimetric RNA reporters when activated with sequence-specific RNA guides. The SHERLOCK diagnostic platform can be engineered to specifically identify RNA or DNA biomarkers in a patient sample. As the platform recognizes specific sequences of nucleic acids, these systems can be easily personalized to identify even single-nucleotide variations, which may enable sensitive and early disease detection. The system can be multiplexed and adapted as a fluorescence assay read-out or for a lateral flow format[5]. The method is designed for facile personalization independent of disease prevalence, is cheap, is compatible with longitudinal monitoring, and can be run in constant temperature conditions without the need for bulky equipment, making it accessible and well-poised for promoting democratization of diagnostics.

Harnessing knowledge of the immune system and synthetic biology yielded early monoclonal antibody production methods, which powered the rise of blockbuster antibody-based therapeutics, revolutionized our understanding of the diverse cell types that compose our bodies' tissues through identification of specific cell marker proteins, and contributed to the development of various diagnostic methods, including the lateral flow test. As synthetic biology methods improved, a number of smaller and more efficient binder designs have been engineered (aptamers, affibodies and nanobodies), providing powerful methods to improve sensitivity of diagnostics systems and potentially unlocking more efficient targeting means for drug delivery carriers. Clinically, some of these binders have also already shown promise independently as therapeutic agents[6]. Through bioorthogonal chemistry, these binders can be manipulated and added to a surface in a controlled manner that preserves and does not obscure the bioactive site[7]. Identification of further bioactivity and bioorthogonal handles may soon be possible through AI-driven methods[1], opening the opportunity to

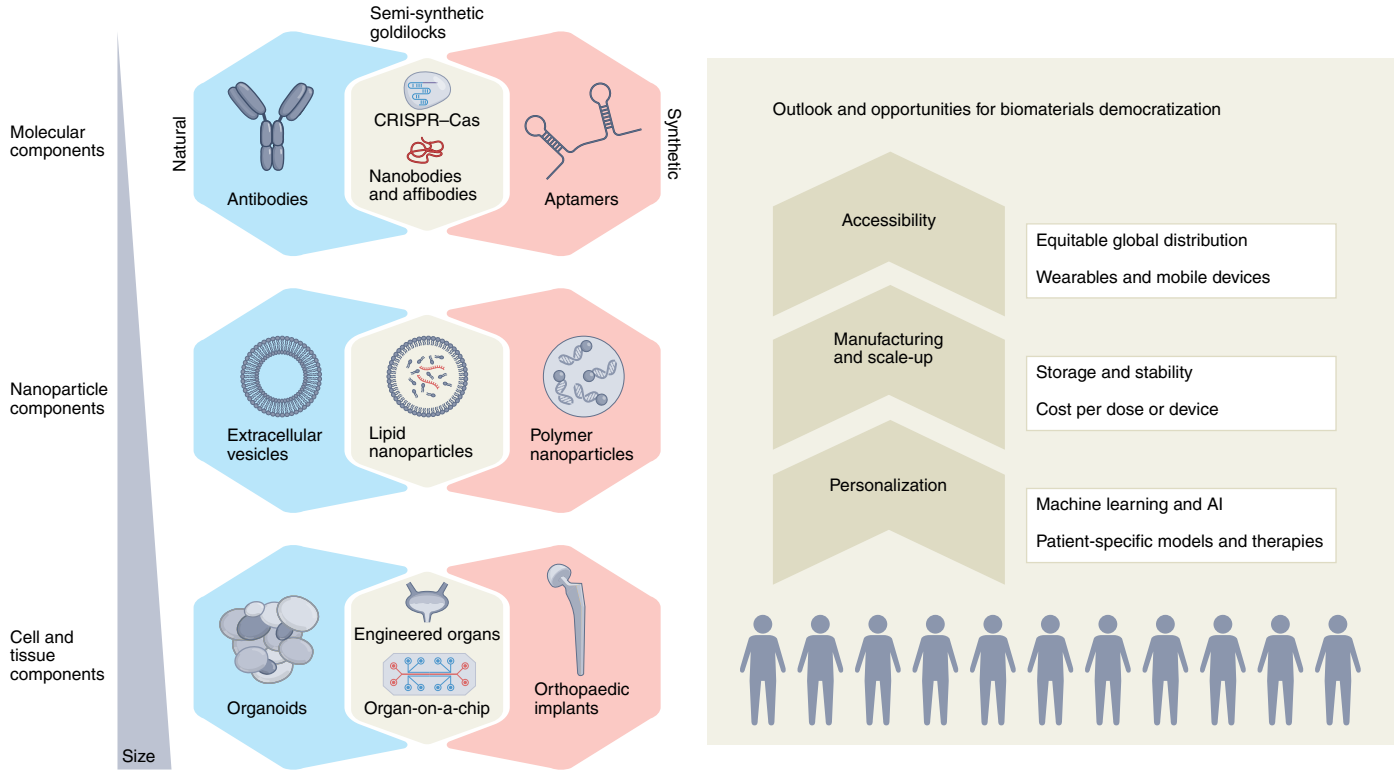

Fig. 1 | Goldilocks semi-synthetic biomaterials optimally blend synthetic and natural components. Goldilocks biomaterials have gained clinical traction across length scales and across the diverse diagnostic, drug delivery and tissue-engineering domains of biomaterials. These materials are well-poised to address key obstacles in democratization.

help exert further semi-synthetic control for novel, more efficient binding designs that could facilitate more nuanced and personalized biomaterial design.

Nanoscale platforms for drug delivery

In the drug delivery space, several major milestones have been reached in the treatment of acquired and inherited disease. Exciting recent nanoparticle-based clinical progress has been seen with the development of lipid nanoparticles (LNPs), semi-synthetic blends of lipids that are designed to mimic low-density lipoproteins. Optimized lipid compositions have been gradually refined over the past several decades, enabled by the rise of high-throughput screening approaches[8]. LNPs have become the starlets of the blossoming RNA delivery field, with the approval of the small interfering RNA therapeutic Onpattro for hereditary transthyretin amyloidosis[9] and, more recently, as the most effective vaccination method against COVID-19 with the Pfizer–BioNTech and Moderna vaccines.

LNPs uniquely lie in the goldilocks zone between more fully natural drug delivery strategies, such as extracellular vesicles, and fully synthetic systems such as polymersomes, which debuted in 1995. LNP systems present advantageous modularity of synthetic components and carefully controlled ratios of the lipid components, while often balancing beneficial natural components (often cholesterol in the formulation and as adsorbed apolipoprotein E (ApoE) in vivo), which may contribute to safe ushering of the particles into cells for the delivery of their therapeutic cargo. Semi-synthetic polyethylene glycol-modified (PEGylated) lipid components are included to stabilize the particles, modulate the protein corona and temporarily 'mask' the vector from the immune system, as well as lengthen circulation.

The messenger RNA (mRNA) cargo itself is also typically semi-synthetic. In the case of the approved COVID-19 mRNA vaccines, the mRNA sequence encoding the spike protein from SARS-CoV-2 was carefully selected and modified to include stabilizing proline amino acids to ensure sufficient structural similarity with the native virus spike protein antigen. Additionally, chemical and non-natural nucleoside modifications increase stability and tune immunogenicity[10].

Semi-synthetic strategies to modify drug delivery carriers with engineered constituent molecules (selective organ targeting[11]), antibodies and other binder designs (affibodies and aptamers) for cell-[12] and organ-specific targeting promise to usher in a new era of tailored therapeutics and provide opportunities for personalization. Experience with the COVID-19 pandemic has demonstrated that mRNA vaccines have a promising profile in terms of production cost, volume and speed — all of which are critical in ensuring broadly equitable access[13]. With the infrastructure developed through the pandemic and the ability to easily substitute disease-target-specific mRNA cargo, mRNA therapeutics may become an even cheaper and potentially easily democratized class of therapeutics. Future designs should strive for thermostability, single administration, needleless delivery (oral and transdermal formulations), tailored targeting, fewer side effects and long shelf life to further expand access. The arrival of AI and big data approaches hold promise towards the further tailoring, personalization and democratization of these approaches[14].

Semi-synthetic tissue-scale systems as personalized models

A key focus of the tissue-engineering field has been the creation of replacement

tissues and organs to address the donor crisis. Clinical progress in this area will benefit from ongoing efforts to achieve better vascularization, hierarchical order and immune profile; nevertheless, products have emerged for some simple flat or hollow soft tissues, such as skin grafts (Integra), small blood vessels (Humacyte), bladder[15] and cartilage (Anika), building on the early success of inert and bioactive glass orthopaedic implants. Progress in the regenerative strategies for more complex tissues and organ systems, such as the brain and liver, have been slower, correlated with their more complex functionality. Although our understanding of the immune response to implanted materials and the factors that can instigate the foreign body response have improved over the past several decades, these phenomena remain major barriers in the efficient translation of biomaterial therapies for most tissue-engineering applications.

Despite the challenges involved in translating tissue-engineering strategies, we have gained broader knowledge around the complex array of instructions embedded in a 3D native extracellular matrix through mechanical, structural and chemical signals and the cellular response to such microenvironmental cues[16]. These insights have fuelled a steady shift towards improved 3D-representative semi-synthetic biomimetic culture materials, inspiring the further growth of various bioreactor systems and bioprinting of cell-instructive scaffolds[17], and laying the foundation for burgeoning organoid technology[18] and organ-on-a-chip (organ–chip) systems[19] as promising models for complex organs and multi-organ systems.

Organ–chip systems have blossomed into an exemplary goldilocks model system for personalized drug screening and disease modelling[20]. Organ–chip systems employ synthetic microfluidic channels that are coated with cells or self-assembled tissue structures under a physiologically relevant dynamic flow environment to semi-synthetically recapitulate complex organ and multi-organ level functions in vitro. Since the first soft lithography-based lung alveolus model organ–chip system was presented in 2010[19], numerous model systems with different chip configurations have become commercially available — some employing 3D extracellular-matrix-based matrices or precise structural control now possible through 3D-printing methods[20]. These systems could possibly replace animal models in many instances and, by employing cells derived from specific patients, provide more clinically relevant models and opportunities for personalized drug screening or modelling of disease. These systems provide platforms to meaningfully screen the growing number of promising human-specific drug targets identified through the omics revolution that may not exist in animal models, or human–microbiome interactions, which are challenging to meaningfully replicate in animal models. Further, these platforms could provide the opportunity to screen and model diseases or drug treatments for commonly under-represented groups in clinical trials, such as pregnant persons or minority populations[21,22].

Outlook

Most current regulations for emerging biomaterials are adapted from existing legislation for older pharmacological systems and are not necessarily attuned to the complexity or variability common in more recent biomaterial designs. However, the easy control and characterization of some semi-synthetic materials can be viewed favourably by regulatory bodies. In particular, in the diagnostics space, naturally occurring DNA sequences are not patentable in the United States, Australia and the European Union, but semi-synthetic versions of genetic material (that is, complementary DNA) are. This limitation on patentability has allegedly limited the economic motivation required to drive more rapid innovation in the diagnostics space, but has been argued necessary to maintain equitable access to diagnostic testing.

Some countries, such as the United States, Japan and those in the European Union, have expedited pathways available for some regenerative therapies, but non-standardized regulatory processes for the translation of drug and biomaterial therapies result in slow patchwork adaptation. The translation of the COVID-19 vaccines shows that accelerated approval of therapeutics around the world is possible without compromising safety[23], but the inequitable global distribution of the vaccines remains a hurdle that was poorly navigated throughout the pandemic, with richer countries claiming disproportionate amounts of the available vaccines[24]. The stark inequality in accessibility of testing and vaccination resources during the COVID-19 pandemic has clarified the need for more accessible therapeutics and cheap home diagnostics[25]. Wearables and near ubiquitous global use of mobile devices[26] could present an opportunity for remote evaluation and diagnosis of patients that could improve treatment access and equity. The huge amount of funding that facilitated the development of the COVID-19 vaccines also democratized the opportunity for smaller biotech companies to contribute, a welcome trend that could improve innovation and competitively reduce the prices of therapeutics in the future, making access more equitable.

We propose that current shifts towards finding the goldilocks biomaterial design point towards an imminent new generation of biomaterials where personalized considerations around individuals' needs (sex[27], age and genome) are now possible and should be incorporated into biomaterial design. AI, machine-learning and data-driven methods promise to lead this next generation of materials, just as their foundational computational methods have fuelled the sequencing revolution that has already contributed to our foundational understanding of disease, the immune system and developmental biology. However, depending on the research questions, there may be challenges arising due to limited data availability, leading to overfitting or data imbalance. That said, strategies may be available that can help mitigate these effects such as data augmentation, transfer learning or the use of generative models to supplement the available data. In turn, the promise of AI and machine learning and the associated implementation pathway should be evaluated on a project-by-project basis. The predisposition of computational fields towards open-access data-sharing practices may help drive the future democratization of efforts in the biomaterials field. The sequencing field itself has rapidly evolved in the past 20 years with the arrival of next-generation sequencing methods, facilitating high-throughput bulk methods such as RNA-Seq[28], before moving towards more resolved frameworks with single-cell approaches[29] and multiplexed spatial resolution[30], now with multidisciplinary efforts seeking integration with other omics methods or systems biology approaches[31]. Historically, many goldilocks materials have been discovered through serendipity, but machine-learning and data-driven methods might aid more efficient design and deeper understanding of essential design parameters for future materials. Applying these computational approaches to understanding the underlying biology and the underpinnings of disease, along with drug and material design, is itself a goldilocks approach, as these approaches are synthetic systems designed to parse the natural variety found in biological systems and will lead development towards identifying essential personalized therapeutics and diagnostics. ❐

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M.M.S. invested in, consults for (or was on scientific advisory boards or boards of directors) and conducts sponsored research funded by companies related to the biomaterials field; is co-inventor on multiple patents and patent applications describing nanomaterials for therapeutic delivery, regenerative medicine and diagnostics; and is co-founder of start-up companies in the biomedical field. A.T.S. and C.L.G. declare no competing interests.

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