Molecular Biomimetics: Genetic Synthesis, Assembly, and Formation of Materials Using Peptides

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Abstract

In nature, the molecular-recognition ability of peptides and, consequently, their functions are evolved through successive cycles of mutation and selection. Using biology as a guide, it is now possible to select, tailor, and control peptide–solid interactions and exploit them in novel ways. Combinatorial mutagenesis provides a protocol to genetically select short peptides with specific affinity to the surfaces of a variety of materials including metals, ceramics, and semiconductors. In the articles of this issue, we describe molecular characterization of inorganic-binding peptides; explain their further tailoring using post-selection genetic engineering and bioinformatics; and finally demonstrate their utility as molecular synthesizers, erectors, and assemblers. The peptides become fundamental building blocks of functional materials, each uniquely designed for an application in areas ranging from practical engineering to medicine.

Introduction

Molecular biomimetics is an emerging key field in science and technology.[1] Through the use of recombinant DNA methods, combinatorial approaches have been developed to select and tailor peptides with properties not present in nature. A peptide is two or more amino acids linked in a chain. Peptides have desirable inorganic-binding and assembly characteristics and can be used as molecular building blocks in practical applications.[2–6] The peptides work either in isolation or when inserted within the structural framework of designer proteins (such as enzymes) that have useful characteristics. The central premise of this interdisciplinary field is that genetically engineered peptides for inorganics (GEPIs)[1] can be utilized as molecular erector sets.[2–6] With molecular biomimetics methods, peptides may direct synthesis, fabrication, assembly, and architecture of hybrid materials, creating materials with programmed composition, phase, and topology. Such materials could have designed and controlled functions at the molecular or nanometer scale. The peptide fabrication and assembly processes take place under ambient and environmentally friendly conditions.[1–11] Gaining the ability to closely manipulate the behavior of peptides to fully control materials formation would be a giant leap toward realizing nanometer-scale building blocks that tailor electronic, optical, mechanical, or magnetic materials properties.[25] Molecular biology and genetics approaches could modify the polypeptides and their molecular-recognition characteristics,[11–15] and traditional and state-of-the-art engineering approaches[16] could create inorganic or synthetic structures such as nanoparticles,[17–20] quantum dots,[20] molecular wires[21] or nanowires,[22] or synthetic molecular systems[23] (e.g., organic semiconductors).[24]

Proteins are long peptide chains that have diverse properties deriving from the specific amino-acid sequences and the physical chain architectures. The wide degree of conformational freedom allows proteins to readily adapt to their environment, and the variability in the genetic sequence and the conformational freedom gives a protein its crucial functionalities.[26,27] Proteins inherently have the largest information content among all the biological macromolecules (including DNA, polysaccharides, and lipids). Therefore, proteins are the "machinery" that accomplish a myriad of functions through their specific recognition and interactions with biomolecules and that are vital to the life of single-celled and multicellular organisms.[26,27]

For example, in the biological hard tissues (Figure 1)[28] in the skeletons of many organisms,[29–31] in bacterial thin films[32] or nanoparticles[33,34] (Figure 1a),[28] in cuticles,[35] spines,[29,36] and spicules (Figure 1b),[37] or in shells[38–40] (Figure 1c),[41] biomolecule–material interaction is accomplished via molecular specificity.[42,43] This leads to the formation of controlled architectures and functions at all scales of dimensional hierarchy.[29,44] A more detailed example is mammalian tooth organ.[45] In this case, of the six tissues present, four (cementum, dentin, enamel, and bone) contain a mineral—hydroxyapatite (HA)—as the *same* inorganic component (Figure 1d).[46] Although the HA particles are the major component in all hard tissues in tooth,[46] as well as in skeletal bone,[47] neither the structure of the individual HA crystallites nor their crystallography or overall organization are the same in any two of these complex composites, which are particle-filled polymeric nanocomposites.[48] Among these tissues, the enamel of the tooth's crown provides the hardest material for the body. Enamel contains almost 99% ceramic

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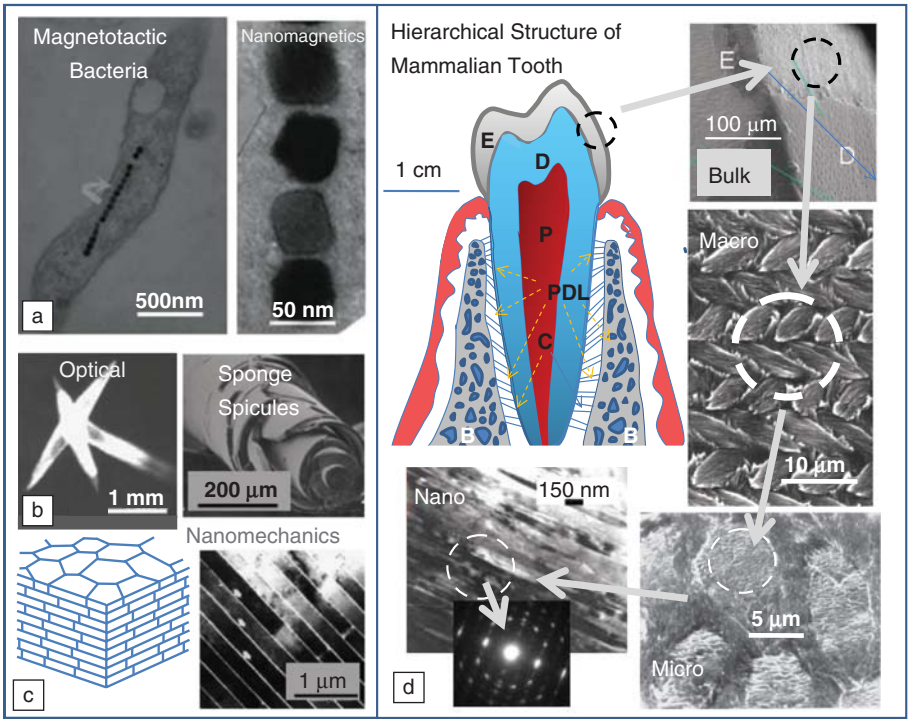

Figure 1. Examples of highly evolved hard tissues from various organisms, controlled by proteins with engineering functions. (a) Magnetite particles in a magnetotactic bacterium, *Aquaspirillum magnetotacticum*, form a magnetic compass (from Reference 28). (b) Spicules of the deep-sea sponge *Rosella* have optical characteristics comparable to synthetic optical fibers (from Reference 37); a light optical image shows a star-shaped lens at the tip of a spicule, and a secondary electron image shows the fractured surface of a spicule revealing layered microstructure. (c) The mother-of-pearl of red abalone shell (*Haliotis Rufescens*) has a highly desirable toughness–strength combination arising from its unique brick-and-mortar nano-/micro-architecture consisting of $CaCO_3$ platelets in the aragonite phase layered with protein/polysaccharide (from Reference 40). (d) Hierarchical architecture of the mammalian enamel at the crown of the tooth (from Reference 46). Enamel (E) forms an integrated structure with the dentin (D) underneath at the bulk scale. The enamel has an architecture of woven enamel rods (3 µm diameter) at the micrometer scale, each rod containing thousands of long HA crystallites (10s of nm thick and several mm long), all spatially and crystallographically well-organized on the nanometer scale.

material and is a protective cover to the dental tissues of all mammalians.[49]

HA has a different architecture in each of the hierarchical scales. The specific structures are controlled by numerous proteins such as amelogenin and tuftelin. Each of these proteins plays a critical role in controlling various structural features in the complex, highly evolved, and functional enamel tissue.[49,50] During the production of the material, the proteins assist or direct the processes of nucleation, growth, morphogenesis, and ordering that lead to enamel rods containing thousands of HA nanoparticles—all organized with well-defined crystallography—and to the final woven architecture of the rods. The latter area is where the overall tissue is integrated with the underlying tougher, bone-like dentin structure—providing a mechanically and structurally smooth and well-integrated transition called the dentin-enamel junction.[46,51] Despite the enormous work invested in isolating many of the proteins and identifying their function in controlling mineralization and buildup of tissues and despite the knowledge that protein absence leads to genetic diseases such as *amelogenin imperfecta*,[52] a thorough understanding of spatial and temporal distributions of the proteins and their isolated or collective roles in forming the complex enamel structure has so far been elusive.[49,50]

Similar to natural, biological proteins that evolve into highly specialized molecules with specific functions, engineered peptides (and designer proteins) in molecular biomimetics could also be of great utility. By design, the peptides could synthesize, assemble, and form solid-containing materials that have controlled molecular-scale organization. Such molecular-scale control could lead to designed functionality with practical implications in a wide range of interdisciplinary fields.[1,28,53–55] Examples include immobilizing nanoinorganic particles on molecular or solid substrates, developing peptide- based molecular probes, and surface engineering of inorganics. If these developments are accomplished, some of current limitations in molecular technology and nanotechnology could be overcome by bridging dissimilar materials components with high complexity and assembling molecular and inorganic nano- components in hybrid systems with specific size, shape, and spatial organization.[56–60] The biomimetic materials field is now mature enough to address fundamental issues at the confluence of materials and biology and to provide practical solutions in engineering and medical fields. This article highlights the selection of peptides that bind to solid substrates, the degree of binding, and the use of peptides as building blocks, and provides a guide for future directions.

Selection of Inorganic-Binding Peptides Using Combinatorial Mutagenesis

For the last two decades, combinatorial biological-display technologies have been developed for a myriad of biological and biotechnological applications. A biological-display technology is a bacteria or phage (a virus that infects a bacteria) engineered to exhibit a peptide sequence on the membrane protein of the bacteria or on the coat protein of the phage. Applications range from the examination of receptor–antibody interactions and the study of protein–ligand interactions to the isolation and directed evolution of enzymes and proteins for enhanced catalysis or altered binding characteristics.[61–65] Among the display technologies, the *in vivo* selection of peptides using cell-surface display (CSD) and phage display (PD) has been used most frequently (Figure 2).[9] CSD is a technology whereby peptides appear on the flagella of a bacterial cell membrane. PD is a technology whereby peptides appear on the coat protein of a phage. These approaches have been adapted to select peptides that bind to solid inorganic materials.[1,3–9,55–59,66] The articles by Evans et al. and Tomczak et al. in this issue explain combinatorial mutagenesis, the method of creating a large set of phage or bacteria—each displaying a peptide with a random sequence—and the biopanning process, the method that culls the set to obtain only the peptide sequences that selectively bind

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to a desired substrate or that have particular binding properties. Figure 2 provides an overview of combinatorial mutagenesis and biopanning, and the article by Sano et al. in this issue provides a specific example of binding to nanoparticles.

Inorganic materials are very different substrates than proteinaceous or general biomolecular ligands.[61–65] Therefore, adapting biological display technologies for the realm of materials science would require a new set of conditions and protocols, though this has not been widely discussed in the literature so far.[55] Inorganic compounds come in a variety of forms, from morphologically uncharacterized powders of various particle sizes to single crystals with crystallographically defined flat surfaces. The chemical or physical nature of the inorganic substrate may disqualify a particular display technology. For instance, since a centrifugation step is necessary during the biopanning process (Figure 2b) when one is working with powder substrates, phage display is suitable for finding peptides that bind to powders,[5–9] but the CSD system is not. Centrifuging a bacterial cell with flagella would shear off the flagella and the attached peptides from the cell. Binding the cells to the powder would not be possible.[9,67] Similarly, while both phage and cell-surface display are normally suitable for panning on single crystals, tightly bound cells or phages may be difficult to recover once they are bound to a material. Thus, it may not be possible to determine the sequences of their high-affinity peptides. In such cases, the use of the CSD system may be advantageous since all binders have an equal likelihood of being recovered following flagellar breakage. Another important factor affecting the efficiency of the display system, and consequently the selection of the strong binders, is monitoring of the stability of the inorganic solid under the selection conditions.[9] Many materials rapidly develop an oxide layer on their surfaces, expose different crystallographic faces to the solvent, and may become chemically or physically modified when incubated in the biological media used during the panning process.

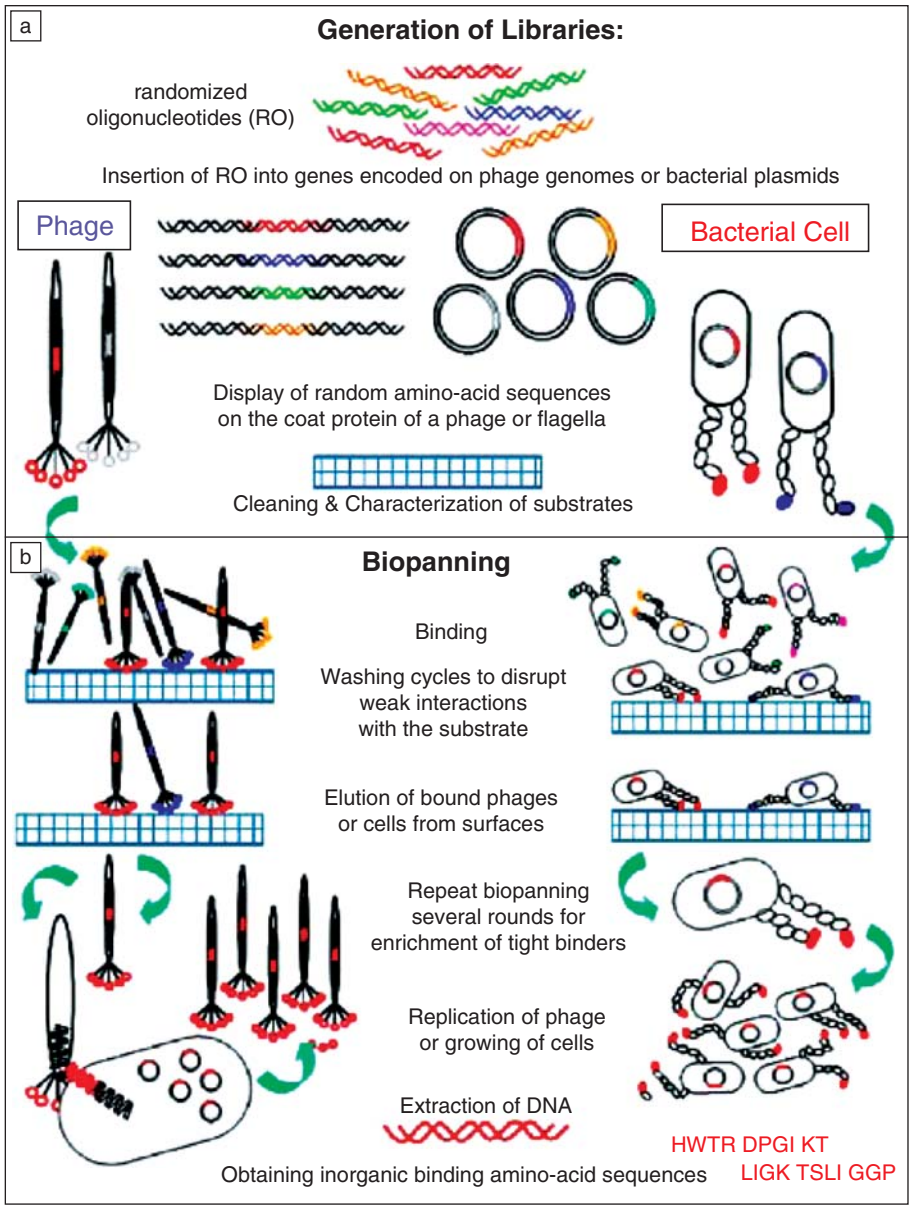

Figure 2. A schematic of the combinatorial mutagenesis, namely phage and cell-surface display, in selecting short amino-acid sequences with affinity for solid inorganic materials (from Reference 55).

Solid Binding and Recognition by Peptides and Assembly

Biocombinatorial techniques provide simple knowledge about a peptide's affinity for an inorganic surface; however, more complete information about the mechanism(s) or the strength of binding and assembly of a genetically selected peptide to a solid will be necessary for the robust use of peptides in practical applications.[55,68] Also, it is essential to evaluate quantitatively the degree of peptide specificity for a given solid as compared to nonspecific interactions with other solids of similar chemical compositions or surface structures (e.g., binding to aragonitic versus calcitic $CaCO_3$, to gold versus platinum or silver, or to silica versus alumina or titania).[68,69] Ideally, the knowledge of the molecular structure and amino-acid sequence of a GEPI and the basis of the peptide's recognition of the solid will allow for further tailoring and manipulation of its functional properties.[70,71] Acquiring this knowledge, therefore, is an essential step in the design and assembly of functional inorganic structures.

Although protein–surface interactions have been the object of considerable research,[72] the fundamental basis of how peptides recognize inorganics remains largely unknown.[42,43,70–77] The specificity of a peptide for a surface may originate from both chemical (e.g., H-bonding, polarity, stereochemistry, and charge effects) and physical (crystallography, topology, size, and morphology) recognition mechanisms.[78,79] Understanding the compositional, sequence, and structural features

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instrumental in binding could eventually result in tailoring the function, recognition, or assembly characteristics of peptides either alone or as a part of designer proteins. Designer proteins include DNA binding proteins, light-emitting/harvesting proteins, self-assembling proteins, and viral capsid.[12–15,55] Chimera (peptide-protein hybrid constructions) of surface-specific peptide binders connected to designer proteins could act as multifunctional linkers having unique physical functionalities such as solid binding proteins with enzymatic function.

Toward the overarching goal of creating multifunctional molecular tools through hybrid GEPI-protein structures, computational biology and materials tools—such as molecular dynamics[70,80] and bioinformatics[81] that draw on experimental parameters[70,82]—are useful instruments to accelerate the process of understanding the molecular recognition of solids by GEPI. These methods are essential for the implementation of chimera in engineering or medical applications. In the absence of complete understanding about the nature of peptide binding, a well-established protocol that involves four basic steps (described in Figure 3) characterizes the binding kinetics, molecular architecture, and surface structure of a GEPI on an inorganic material. The first step evaluates the kinetics of molecular binding involving an assessment of the specificity of the peptide toward various surfaces[55,68,83] using modified surface plasmon resonance (SPR) spectroscopy.[84] It is often coupled with quartz-crystal microbalance (QCM)[85] (Figure 3a).[55,68,83] Significant progress has been made using both SPR[55,68] and QCM.[55,83] However, both of these techniques—especially the latter—have limitations for the study of very small molecules.[86] Once a strong binder is identified, its detailed molecular architecture is characterized by various spectroscopy techniques—most notably with circular dichorism (CD) and nuclear-magnetic-resonance (NMR) spectroscopy (Figure 3b).[70,82,86] The third step involves computational modeling to understand possible peptide recognition of crystallography of the solid surface and is especially useful in the absence of experimental data.[70,79,80] Finally, knowledge of surface coverage, assembly, and supramolecular architectural formation[55] is necessary for rational utility of GEPI for specific applications. Atomic force microscopy (AFM) gives quantitative molecular-level and nanostructure imaging (Figure 3d).[55] The use of AFM imaging here is similar to the evaluation of thiol-based self-assembled monolayers (SAM), ubiquitous among the synthetic molecular linkers.[87,88]

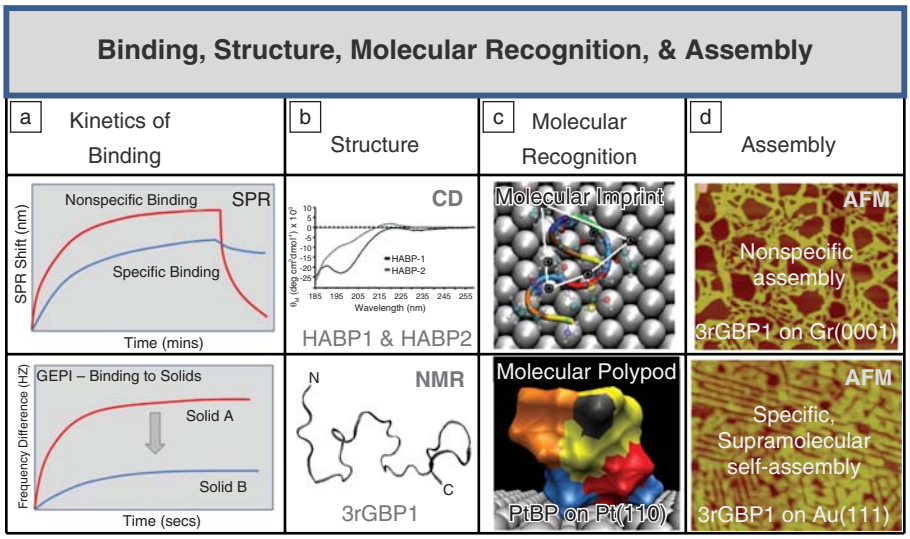

Figure 3. The four established steps for molecular characterization of a genetically engineered polypeptide for inorganics (GEPI) as a viable technological molecular tool. (a) The kinetics of solid binding and specificity of inorganic-binding peptides for a given solid could be determined by surface-plasmon-resonance (SPR) spectroscopy.[83] At the same time, whether a GEPI is specific for a solid surface compared to another solid is determined by quartz-crystal microbalance as well as SPR.[68] (b) Spectroscopy, such as circular dichroism[70] and nuclear magnetic resonance,[70] could provide molecular architecture. HABP1 and HABP2 are two hydroxyapatite binding peptides. 3rGBP1 is a gold binding peptide. (c) In the absence of structural details, computational modeling such as molecular dynamics could provide molecular conformation and shed light on the mechanism of crystallographic surface recognition.[71] Finally, (d) supramolecular self-assembly of the peptide on the crystallographic surface of the inorganic material could be visualized by atomic force microscopy as demonstrated here for a gold-binding peptide on graphite(0001) and Au(111).[55]

GEPI as Molecular Synthesizers, Erectors, and Assemblers in Nanotechnology and Medicine

Three key issues in using peptides to make functional nanomaterials are the synthesis of the individual material components, controlled linking of multicomponent systems, and multidimensional assembly.[55] To make any multicomponent material system ("multimaterial") practically useful—in addition to the intrinsic magnetic, photonic, or electronic properties that are derived from nanometer dimensions[89,90]—each component may need to be chemically modified so as to assemble the system controllably and efficiently.[17–20] As is well-recognized in nanoscience, numerous challenges must be addressed before nanotechnology can be fully implemented successfully into working devices.[89,90] The challenges include synthesizing nanostructures (e.g., particles, rods, and tubes) with uniform size and shape; controlling their composition, bulk structure, and surface characteristics; and organizing them in one, two, and three dimensions with predictable spatial distribution. If biology is to be a guide, some of these challenges could be overcome utilizing the unique opportunities offered by the biomimetic approach at the molecular scale. The approaches used to genetically select and characterize GEPIs are discussed in Figures 2 and 3. Some of the utility is outlined in Figure 4 and also is demonstrated in other articles in this issue.

Controlled binding and assembly of proteins onto inorganic substrates is at the core of bionanotechnology and biological materials engineering.[55,76,91,92] GEPI provides the molecular means to anchor, couple, brace, display, and assemble functional molecules, nanoparticles, and structures.[1] The examples in Figure 4 provide a summary of potential utilizations of GEPI. Once peptides with short amino-acid sequences (7–15 amino acids) are genetically selected, sorted, and categorized, their molecular properties—including structures and binding functions—are characterized (Figures 2 and 3). These include post-selection engineering in which multiple repeats of linear or cyclic architectures for the select sequences are designed and synthesized.[55,68,83] The next step represents a "molecular tool box," which is an inorganic-binding peptide

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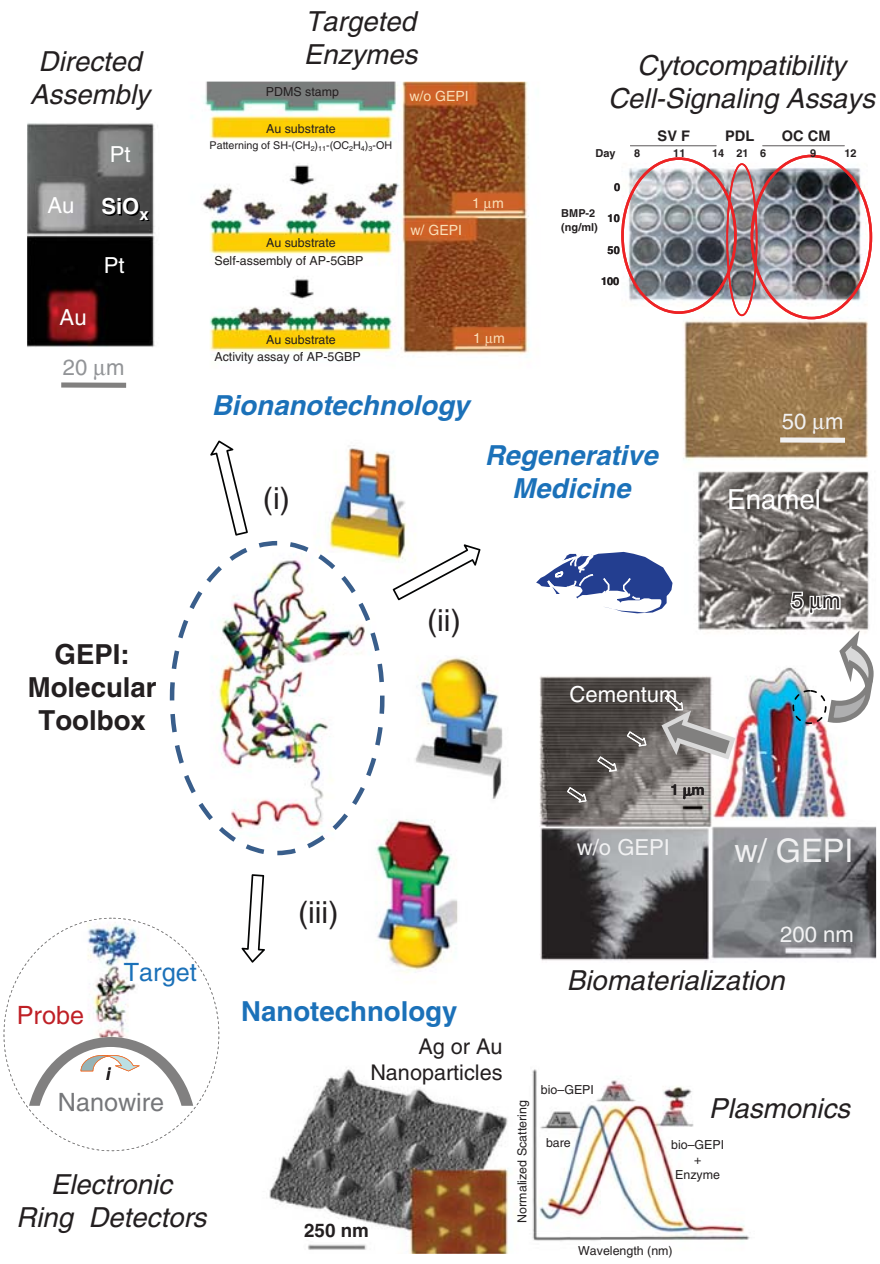

Figure 4. Genetically identified and molecularly characterized genetically engineered peptides for inorganics (GEPIs) could form a molecular toolbox for a wide range of applications from materialization to medicine and nanotechnology. Selected GEPIs from the toolbox could be chosen as building blocks for their specific ability to synthesize, erect, and assemble. (i), (ii), and (iii) represent GEPIs as a nanoparticle immobilizer, a genetic fusing agent, and a bifunctional system, respectively. A bifunctional system could couple two nanoparticles, or a nanoparticle and a functional molecule, simultaneously. The images are sampled experimental results where GEPIs are used in diverse applications: in bionanotechnology to immobilize quantum dots and targeted immobilize enzymes, in regenerative medicine for surface functionalization within cytocompatibility assays and hard-tissue regeneration through materialization using peptides as nucleators and growth modifiers, and in nanotechnology as molecular erectors to immobilize probe molecules in electronic ring detectors and localized surface-enhanced plasmonics.

data bank:[1,9,55] a collection of fully characterized select GEPIs ready to be utilized for a wide range of applications. The practical applications, at the final step, include the utility of GEPI as universal ink in the targeted assembly of nanoparticles—such as quantum dots—at specific regions of multimaterial micropatterned surfaces (for example, an Au and Pt pattern on silica). This is a step toward assembly of nanophotonic entities.[93] Another example involves using GEPIs as molecular erectors. Linking the GEPIs to enzymes with the genes of a virus or bacterium allows for directed self-assembly at specific regions of solid substrates.[94] In bionanotechnology, growth and proliferation of various cell types on solid surfaces as arrays are possible through the cell-signaling characteristics of the hydroxyapatite (HA) binding peptides.[95] It may be possible to regenerate some hard tissues such as enamel and cementum[49,50] using GEPIs and their derivatives to direct nucleation, growth rate, and morphogenesis of HA nanoparticles. One example is the regulation of calcium-phosphate formation using HA binding peptides as synthesizers in biomaterialization.[95] Nanotechnology applications include using GEPIs such as AgBP (Ag-binding peptide) or QBP (quartz binding peptide) as part of a fusion protein assembled on a specific material. These materials include metal (e.g., Ag) nanoparticles[94] or silicon nanowires[96] for target recognition via localized surface-plasmon-resonance spectroscopy[97] or electronic ring detectors,[98] respectively. These platforms, once optimized, could be the basis of new highly sensitive biosensors. (See the article by Chen et al. in this issue regarding the utility of DNA or peptides for these purposes.)

Prospects

The utilization of GEPIs as building blocks and molecular tools in designing, synthesizing, and assembling materials systems necessitates the combination of new concepts from the fields of biology, medicine, computation, informatics, materials science, condensed-matter physics, chemistry, and engineering.[55] Molecular tailoring of specific peptide– solid interactions could have a significant impact in areas in which inorganic materials offer several novel, immediate practical advantages. The attachment of biomolecules in particular proteins onto solid supports is fundamental in the development of advanced biosensors for detection of pathogens, drug screening,[91] bioseparations systems, and diagnostics in medicine[98] such as those used in cancer therapeutics.[92] Protein adsorption and macromolecular interactions at solid surfaces play key roles in the performance of implants and in regenerative medicine.[76,99] (See the article by Rughani et al. in this issue.) Proteins and DNA adsorbed specifically onto solid substrates are used

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to build micro- to nano-arrays suitable for genomics, pharmacogenetics, and proteomics applications.[98,100] Engineered polypeptides hybridized with functional synthetic molecules could be used as heterofunctional building blocks in molecular electronics, ferroelectrics, and photonics. With the aid of genetic-engineering tools, spacing and orientation control of the peptides—which have been major challenges of these fields[89,90,97–100]—can be overcome for desired effects.

With the simultaneous integration of biomacromolecules and functional inorganics, the new multidisciplinary field of *molecular biomimetics* could provide the essential realistic platform to efficiently exploit biological principles for molecular systems design, information, and networking. Through the creation of practical materials using genetically engineered peptides, this field will inevitably demonstrate a high degree of impact on a wide range of applications in the coming years—from fundamental issues in materials science and biology to bio-nanotechnology and medicine.

Acknowledgments

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