Perspective

Protein and Peptide Biomimicry: Gold-Mining Inspiration from Nature's Ingenuity

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Introduction: Biomimicry

Biomimicry, a word derived from the Greek words "bios", meaning "life", and "mimesis", meaning "to imitate", has been accurately described by the Biomimicry Institute as a design principle that uses Nature as model, mentor, and measure. Nature's elegant processes, refined over the course of evolution, provide myriad examples of systems that operate with unparalleled simplicity, efficiency, and durability. It is the essence of elegance in engineering. Through careful observation and dedicated study, Nature's secrets begin to unfold and the fundamental principles underlying natural phenomena can become clear. Recognizing the wisdom that Nature has to offer, biomimetic researchers derive inspiration from or attempt to mimic directly the form and/or function of natural designs.

The field of biomimicry has enjoyed a long and rich history spanning many decades, and has influenced a variety of disciplines, ranging from architecture and economics, to materials science and bioengineering. A particularly notable example of bioinspired design is Velcro®, the hook-and-eye fastener invented by George de Mestral and modeled after the microscopic hooks on seed-bearing burrs that enable them to cling to animal fur and become dispersed. What began as natural curiosity in the mind of a Swiss mountaineer has today become a multimillion dollar global industry.

State-of-the-art technology is enabling biomimeticists to examine Nature with an eye capable of resolving structures well below the macro-and micro-scales; the concerted efforts of microbiologists, chemists, physicists, and engineers have made observation at the nano and even the molecular scale a reality.

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Technological advances are continually expanding the frontier of what is possible in this field, which remains in its infancy. In particular, interdisciplinary research in biomimetic polymer engineering is poised to make lasting contributions to both the fundamental science and engineering applications of the basic building blocks of life—proteins. Hence, we focus here on the mimicry of these natural molecules, in particular.

Mimicry of protein function

In the post-genomic era (so called, even while genomes and their organization still offer us much to learn), we are only beginning to understand the exquisite array of complex functions that proteins facilitate. Proteins not only comprise extraordinarily strong and versatile cellular structures, but also very precisely control nearly all cellular functions, including molecular recognition, catalysis, regulation of growth cycles, and structural stabilization. In short, proteins constitute the basic currency of life. The prospect of being able to control cellular function predictably at the molecular level is in many ways the holy grail of drug discovery, and promises tremendous impact on scientific research, the medical industry, and human health worldwide.

In biological systems, form and function are intimately intertwined; properly designed structural mimics of a molecule will often be able to perform analogous functions. While protein engineers are making real strides in designing *de novo* tailor-made proteins to perform specific functions, the complexity of protein folding mechanisms has limited the ability to reliably engineer a specific tertiary structure, even for just average-size proteins.[1] As an alternative approach to circumventing the "protein folding problem", there is growing interest in recapitulating protein function in simplified synthetic scaffolds, or "foldamers". Foldamers are typically oligomeric or polymeric molecules (up to ~50mers), based on a non-natural backbone, and are able to mimic a variety of simple sec-

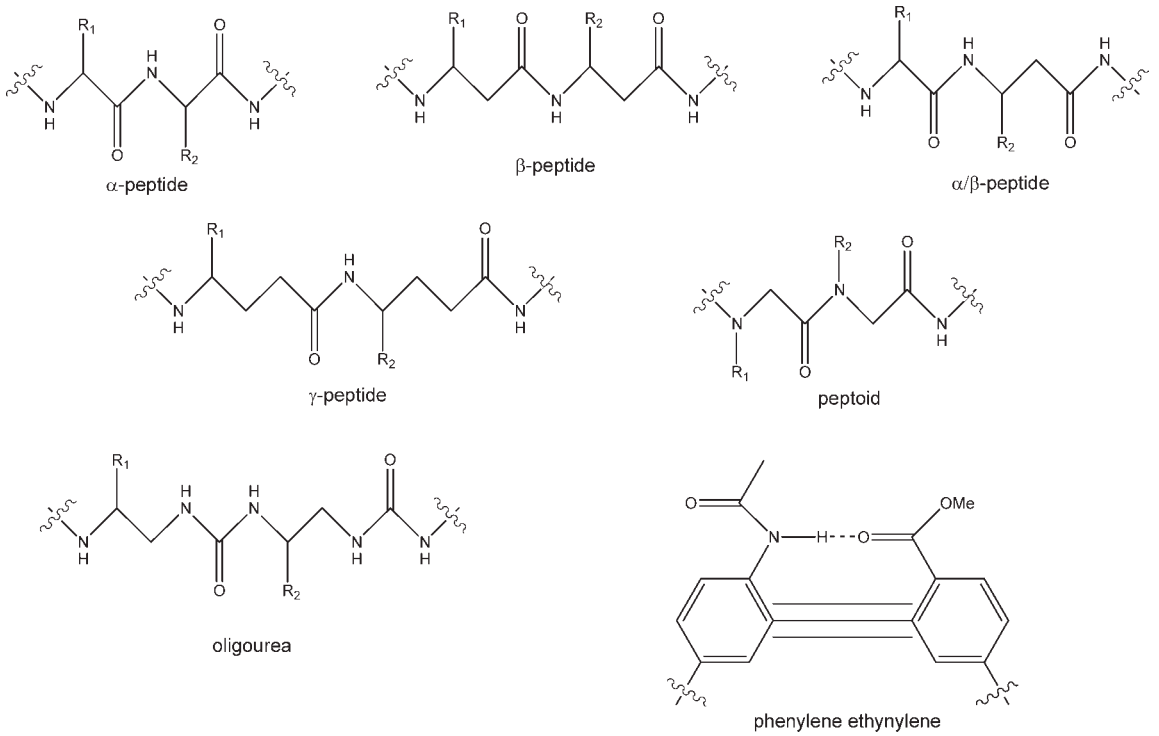

Figure 1. Structures of selected foldamer backbone scaffolds.

ondary structures.[2] Beyond strictly achieving the same result using non-natural molecules, foldamers are uniquely advantageous for mimicking biological systems. While synthetic analogs are typically simpler structures that can often be produced more efficiently and in a more cost-effective manner, they also can "transcend Nature" by imparting improvements in biostability and bioavailability compared to their natural counterparts. Additionally, a simple foldamer-based biomimetic system in which parameters can be precisely and independently controlled is well-suited for interrogating structure-activity relationships. Furthermore, as conclusions from these studies are often transferable back to the natural system, more broadly applicable knowledge may result. Last, many researchers that derive inspiration from Nature conceive of entirely new and useful applications for the technology being developed. For all of these reasons, the use of foldamers to mimic bioactive proteins and protein domains continues to be a very active area of research.

Many types of foldamer backbone scaffolds have been found to mimic simple helical, turn, and sheet-like peptide secondary structures. Examples of well-characterized foldamer scaffolds, shown in Figure 1, include α/β peptides,[3] β-peptides and γ-peptides,[4] *N*-substituted glycines (peptoids),[2,5] phenylene ethynylenes,[6] and urea derivatives.[7] All of these classes of non-natural oligomers have been shown to exhibit kinetic and thermodynamic stability, and can mimic some functions of bioactive peptides. Interestingly, despite the overall complexity of protein function, several bioactive peptides exhibit surprisingly short and simple architectures that are amenable to biomimicry. The literature provides abundant examples of simple proteins that have been mimicked including antimicrobial peptides, lung surfactant proteins, protein binding domains, cell penetrating mediators, and proteins that target a variety of biologically relevant targets (for a recent review, see[8]).

While notable progress has been made in mimicking simple protein/peptide secondary structures, the prospect of creating foldamer-based supramolecular assemblies that adopt discrete tertiary and quaternary structures opens up the possibility of regulating far more complex protein-like functions. Since the average protein length is approximately 250 amino acids, and contains two 15-kilodalton domains,[9] engineering of a stably folded supramolecular foldamer structure has proven to be a formidable challenge. As will be discussed, however, significant progress has been realized in the case of β-peptides, α/β-peptides, and peptoids. These three classes of foldamers, which have demonstrated potential for use as pharmaceutical agents, are the primary focus of this discussion. Recent advances in foldamer biomimicry are ushering in a new era in the design of functional protein mimics; as our ability to use synthetic monomers to construct complex structures is improved, so too will be our ability to mimic their function.

β-peptides, α/β- peptides, and peptoids

As shown in Figure 1, the extended backbone of β-peptides contains an "extra" methylene group between amide groups, in comparison to natural α-peptides. β-peptides are capable of adopting a variety of structures, including helices, turns, and sheet-like architectures (for reviews see[4,8]). A hybrid structure with a heterogeneous backbone can also be formed using a combination of α-peptide and β-peptide monomers in the same molecule.[3] Sporadic inclusion of β-peptide residues can induce turns, and can cause minor changes to foldamer structure.[10] Molecules with a regularly repeating arrangement of α-

and β-peptide monomers have been made and found to form stable structures closely related to those of natural peptides.[3]

Peptoid structure is isomerically related to that of peptides, in that the side chains are attached to amide nitrogens rather than to α-carbons, as shown in Figure 1.[5] The conformational and stereochemical ramifications of the *N*-substituent on the peptoid backbone (which is identical to a peptide backbone in its sequence of atoms) are significant.[2] The lack of amide protons and chiral centers in the peptoid backbone results in the absence of backbone-mediated hydrogen bonding in a fully substituted peptoid chain, and also precludes the formation of intrinsic backbone handedness. It has been shown, however, that incorporation of α-chiral side chains generates steric and, in some cases, electronic repulsions that can induce the formation of a helical backbone conformation reminiscent of the polyproline type I helices like those found in collagen ($\sim$3 residues per turn, pitch of $\sim$6 Å), stabilizing the secondary structure.[2]

The structural differences between these classes of foldamers, and the natural peptides that inspired them have important implications for biomimicry. The non-natural backbone renders them impervious to protease activity, thereby increasing bioavailability and reducing specific recognition by the immune system.[11,12] These foldamers, so far, have been shown to induce only very low-level antibody response, and certain peptoids have been found to be bioactive, nontoxic, and nonimmunogenic.[13,14]

Here we discuss how foldamer biomimicry has evolved from a curiosity involving a few peptide chemists to a highly interdisciplinary field that has the potential to significantly improve our ability to understand and treat disease. We highlight accomplishments of using β-pepides, α/β-peptides, and peptoids to mimic small bioactive molecules, as well as more recent work demonstrating foldamers' ability to adopt more complex supramolecular tertiary and quarternary structures. We conclude with an outlook on the interdisciplinary character of the field, and postulate future directions in the pursuit of making non-natural protein-like assemblies.

Enabling technology for foldamer-based biomimicry

The foundation of foldamer science is deeply rooted in the achievements of peptide chemistry's founding fathers over the past century. Since the first report of α-peptide synthesis in 1901, great strides in technology development have been made that now make routine the synthesis of long biopolymers (for review see[9]). Over the past one hundred years, improvements in protecting group design and coupling agents have greatly increased product yields and coupling efficiencies. A major breakthrough occurred in 1963 with the introduction of solid-phase α-peptide synthesis by R. B. Merrifield.[15] This innovative approach of building molecules on solid support enabled the easy removal of byproducts, and reagents through washing and filtration between subsequent couplings, and made the process amenable to automation using a single reaction vessel. The development of improved resin solid supports was key, along with parallel advancements in purification and analysis technology, and together have made synthesis of linear, sequence-specific α-peptide polymers up to 50 monomers long easily achievable with the use of careful procedure and best practices.[9]

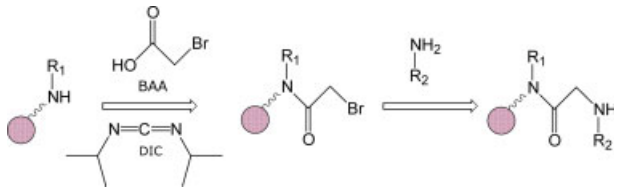

Figure 2. Submonomer approach to peptoid synthesis.

A second milestone was achieved in the development of chemical ligation, a technology that enables the solution-phase coupling of unprotected peptide fragments.[16] The basis for this technique is the use of two components with unique, mutually reactive functionalities resulting in a "chemoselective" reaction. Since the first demonstration of this technique, this methodology has seen the benefit of several generations of improvements and variations.[17] The approach is still not widely used, but recent developments suggest that it will soon become more practical.

Synthetic methods to make foldamers have been adapted from solid-phase methods used for conventional peptides. While short sequences of β-peptides can be made using a standard fluorenyl-methoxy-carbonyl (Fmoc) protecting group-based solid-phase synthesis protocol, the yield of longer molecules is significantly reduced due to incomplete deprotection and the need for extended coupling times.[9] Recently, however, Seebach et al. developed a thioligation strategy that can be used to construct longer β-peptides and α/β-peptides in improved yields.[9] A method to efficiently synthesize β-peptide combinatorial libraries has been reported, which is an important step for screening the bioactivity of several drug candidates.[18]

Peptoid synthesis was revolutionized by the work of Zuckermann et al., who reported the "submonomer" approach shown in Figure 2.[19] Using a solid-phase protocol and an automated peptide synthesizer, this novel synthetic route gives access to a diversity of functionalized peptoids at modest cost and effort;[20] the high submonomer coupling efficiencies (comparable to those attained in Fmoc peptide synthesis) coupled with the low cost of production from inexpensive, and readily available starting reagents set peptoids apart. Diverse, sequence-specific peptoids up to at least 50 residues in length can be readily synthesized in high yields.

Peptoids are a highly suitable family of foldamers for use in commercializable medical applications for a variety of reasons. A robotic synthesizer can be used to make many peptoid chains in parallel, or to create large combinatorial libraries of peptoids to quickly screen thousands of molecules for bioactivity.[21] One can also alternate between submonomer and monomer protocols (whereby peptoids are made by coupling of activated Fmoc-protected monomers[5,22] within a single, automated solid-phase synthesis, enabling the facile creation of peptoid-peptide hybrid sequences. Incorporation of natural and non-natural sequences in the same molecule can be used to achieve the optimal balance of good bioactivity and an appropriate rate of biodegradation.

Peptide and peptoid chemists have, therefore, laid the fundamental groundwork on which the field of molecular biomimicry is being built. The establishment of these enabling technologies began over one-hundred years ago, and innovations are continuing to be made today. This work has paved the way for researchers from many disciplines to ponder ways to

design and control foldamer structure and to consider potential applications of these versatile materials.

Mimics of short elements of peptide secondary structure

The establishment of robust methods to synthesize non-natural peptide and peptoid foldamers has enabled researchers to probe a few practical applications of sequences designed to adopt stable secondary structures. This work has involved the joint efforts of chemists, chemical biologists, microbiologists, clinicians, and chemical engineers. Among the many classes of bioactive peptides that have been mimicked,[8] antimicrobial peptides (AMPs) are one of the most active areas of study due, in part, to their relatively simple structural requirements and their potential to meet a pressing clinical need.

Antimicrobial peptides (AMPs) are a ubiquitous class of short (<40 amino acids), amphipathic, naturally occurring molecules that defend organisms against a broad spectrum of bacterial invaders through a generalized membrane permeabilization mechanism of action. Because AMPs do not operate through specific receptor-mediated events, bacteria have been largely unable to develop resistance to AMPs over the course of evolution, making them attractive candidates as lead compounds in the development of novel antibiotic agents. However, AMPs suffer from proteolytic susceptibility and a resultant poor *in vivo* bioavailability, which has curtailed their clinical use. The non-natural, protease-stable foldamer backbone offers a means for recapitulating these peptides' function while circumventing their shortcomings.

The linear, cationic, mostly helical class of antimicrobial peptides, such as the magainins and cecropins, exhibit an amphipathic structure that is readily recapitulated in a foldamer helix. The work of several laboratories has shown that β-peptides and α/β peptides can exhibit potent and selective antimicrobial activities (reviewed in[8]). Structure-activity relationship studies have demonstrated that several parameters including molecular hydrophobicity, sequence length, and amphipathicity modulate the selectivity. It has also been shown that while the amphipathicity of a molecule once it is in the membrane environment is important for activity, a rigid structure outside of a membrane is not. Moreover, α-peptides and their non-natural peptide counterparts appear to share a common mechanism of action, as they both appear to be bounded by a low-micromolar minimum inhibitory concentrations (MICs).

Our laboratory has focused on designing peptoids to be potent and selective antimicrobial agents. The helicity induced by incorporating α-chiral side chains results in a regular periodicity of three monomers per turn, which is highly amenable to designing amphipathic structures. We have synthesized, designed, and characterized over 50 sequences with diverse side chain functionalities, and have found many of them to be potent and selective antibiotics, killing bacteria with low-micromolar MICs while not harming mammalian cells until their concentrations are well above the respective MICs.[23] In tests of broad-spectrum activity, it is interesting how the activity of a given peptoid against certain strains will often closely parallel that of the natural peptide it mimics. Moreover, structure-activity relationship studies have also determined that peptoid-based AMP mimics appear to utilize a mechanism of action strikingly similar to that of AMPs themselves.[24]

Whereas AMP function is related to overall molecular architecture (e.g., amphipathicity, hydrophobicity, overall charge), the proper function of other types of proteins depends on more precise replication of a particular monomer arrangement in space. Non-natural peptides have been used to mimic a variety of structurally specific proteins, including inhibitors of protein-protein interactions, HIV fusion inhibitors, inhibitors of fat and cholesterol uptake, and RNA binding (for reviews see[8,25,26]). Similarly, peptoids have also been used to inhibit protein interactions and receptor binders, as well as to mimic the "physical catalysis" of lipid film behavior that is naturally accomplished by the hydrophobic lung surfactant proteins, SP-B and SP-C, which enable normal breathing.[27–29]

An aspect of foldamer biomimicry that has been championed primarily by engineers is the use of synthetic polymers, often derivatized with small peptides, to create novel biomaterials and "smart" devices. The impetus of this line of research resides in the fact that cell behavior is affected by stimulation from its external environment, as well as by specific signaling molecules. Specifically, integrins have been shown to influence cell growth, differentiation, adhesion, and motility. Research in this area is directly applicable to the design of biomaterials for tissue engineering, reactive coatings, and smart surfaces. The ability to control the properties of biomaterials as they morph in time and space adds a new dimension that until now has set natural materials apart. Advances in these areas have been focused in the areas of tissue engineering, the development of diagnostic tools, and surface engineering.[30]

Foldamers have also been created to mimic a variety of different structures. β-peptides have been assembled to form a variety of helical conformations, as well as stacks, sheets, and turns.[4] Because the typically bulky nature of peptoid side chains limits the conformational freedom of a peptoid backbone, peptoids are usually contorted to form polyproline type I-like helices, which are longer in pitch than α-helices, with helix handedness being directed by the side chain enantiomers used. Fully substituted peptoids are also precluded from forming sheet-like or hairpin structures due to the lack of hydrogen bonding. Well-designed peptoid helices are stable in a variety of organic solvents. While peptoids that incorporate α-chiral side chains typically form these collagen-like helices, a novel "threaded loop" structure, adopted by a particular family of nonamers in acetonitrile solution only, has been reported.[31] A very interesting aspect of this structure is that it is stabilized by hydrogen bonds involving the C-terminus, as well as backbone carbonyl groups, and in essence shows a structure that is folded "inside out", with a burial of hydrophilic surface area and exposure of side-chain hydrophobes to the nonhydrogen bonding, polar organic solvent acetonitrile; yet these nonamers form regular peptoid helices in methanol. As in natural proteins, the *N*- and *C*-termini end up very close in space in the threaded loop structure (which, interestingly, was discovered in a study of many different peptoids in solution, not designed). It has also been shown that peptoids can be made to form cyclic structures easily and efficiently.[32]

Foldamers as mimics of tertiary and quarternary structures

As has been discussed, foldamers designed to mimic simple secondary structures have proven to offer some interesting

biological functions, and to exhibit promise as mimics of small bioactive proteins. The ability to mimic a protein's tertiary and quarternary structure is a further level of sophistication that would unmask the potential to mimic even more complex functions. While this represents a tremendous challenge, exciting progress has already been made in many areas just in the past year. Recent work from the Schepartz laboratory reports the first high-resolution structure of a stable, discrete, and compact β-peptide assembly, Zwit-1F.[33] This β-dodecamer spontaneously self-assembles into an octameric, bundled β-peptide quarternary structure driven by noncovalent inter-residue interactions. Biophysical characterization of the Zwit-1F structure confirmed that the kinetic and thermodynamic properties of the β-peptide analogue are strikingly similar to those of natural peptide bundles.[34]

The Gellman laboratory has reported the first helix bundle architecture created using the heterogeneous α/β-peptide scaffold.[35] Indeed, direct translation of a protein GCN4 known to self assemble into the α/β-peptide scaffold retained its ability to self-assemble, albeit with somewhat altered stability and helix association geometry.[35] Helix bundles composed of both α/β-peptides and α-peptides have also been demonstrated.[36] This report opens the door to entirely new conformational possibilities; the prospect of being able to fine-tune tertiary structure by using a combination of different foldamer backbones may be the key step in mimicking more complex protein functions, since each scaffold offers its own unique limitations and possibilities.

A recent report also demonstrates the potential for foldamers to adopt a zinc finger-like architecture found in a class of transcription factors that recognize and bind specific DNA.[37] A β-peptide 16mer consisting of a turn and helix structure was designed with strategically placed histidine and cysteine residues that have a strong affinity for binding zinc. It was found that indeed the β-peptide folds in the presence of Zn^2, as was hoped.

Quaternary helix bundle architectures have also been reported for peptoid scaffolds.[38,39] A library of 3,400 amphipathic 15mers was screened for the presence of a hydrophobic core using a 1,8-ANS binding assay. Several sequences were found that appear to self-associate. In a subsequent study, one of the sequences showing a high-propensity to self-assemble was selected to determine the effect of coupling four repeats of the 15mer sequence together.[39] Indeed it was found that peptoids can assemble to form a hydrophobic core and to display apparently cooperative folding transitions.

An impressive and beautiful accomplishment was reported by the Raines laboratory in which synthetic collagen was created by the self-assembly of chemically synthesized α-peptide fragments into a triple-helix.[40] Three separate peptide fragments were connected in a precise chemical architecture through disulfide bonds that facilitated self-assembly. This landmark achievement marks the first reporting of mimics with lengths ($>$400 nm) that rival and even exceed that of natural collagen assemblies ($\sim$300 nm).

Outlook

While biomimicry is a design principle that has been utilized successfully for decades, the advancement of technologies to probe Nature on the molecular level has initiated a new era in the field; the potential of biomimicry is now becoming less constrained by technological capability and tempered primarily by the capacity of our imaginations. The use of non-natural foldamers to mimic the function of bioactive proteins is an active area of research that was founded by peptide chemists and has grown into a discipline that also benefits from the work of microbiologists, chemical biologists, clinicians, and chemical engineers. While there have been many significant successes in foldamer biomimicry to date, the potential of this field is only beginning to be realized, and the possibilities only beginning to be explored. It is notable, for example, that most of the sequences of peptoids and β-peptides to date have sequences that are dominated by repeating motifs; this is not necessarily always dictated by limitations of the synthesis, but clearly, also by the fears of the molecular engineers of creating a system that cannot be predicted nor understood. If we are taking our inspiration from Nature's ingenuity as we design the first truly functional peptide and protein mimics, it must be admitted that we have only succeeded, so far, in scratching our way down a few feet into the dirt, and gaining our first glimpses of the riches that lie below to be further excavated, by years of back-breaking work that remains ahead of us.

Combining the precepts of a selection process with a relatively high-throughput, parallel synthesis, as Dill and Zuckermann have done, will allow unfettered imaginations to find the proverbial "needle in a haystack"—the structured foldamer that has not been precisely designed to form a discrete structure from *de novo* principles, but instead, painted in soft focus with water colors (as a family of sequence motifs, with diversity in specific side chains) to offer the chance to collapse into a reasonably well-ordered structure that has some function, such as metal binding. Successful *in vivo* testing of bioactivity of foldamers in animals, and eventually humans, will put some real wind behind our sails and attract even more researchers and funding to the area.

A highly effective means of accelerating the rate of progress in this area will be through knowledge sharing and collaborations that cross disciplines. For example, it is important for those who perform physical experiments to have an understanding of the work of those who use computer modeling to address similar questions; limited collaborations across these disciplines have benefited the foldamer field to date. Those who work on the engineering design and synthesis of more subtly bioactive foldamer designs can only benefit from knowing about advances in microbiology and structural biology that could inform their work. Engineers that are searching for new biomaterial applications of biomimetic designs need to stay in close contact with clinicians who best understand the needs of patients. Maintaining an awareness of ongoing work across disciplines, and participating in collaborations, such as those that have been funded in the past five—eight years by the NIH's Bioengineering Research Partnership funding program, and the NSF's Collaborative Research in Chemistry program, will facilitate the most efficient and effective advancement of biomimicry and its application to medicine and biotechnology.

Another change that is presently occurring, which facilitates the development of interdisciplinary studies, such as these, is the burgeoning extent of cross-training that is now included in scientific and engineering curricula. Today, in addition to core

chemistry and engineering classes, many chemical engineering departments require at least an introductory level class in biology and biochemical engineering. Deeper training in the methods of organic synthesis and the purification of particular molecules can put powerful tools in the hands of chemical engineers, who naturally have a keen focus on applications and wonder immediately what a molecule may "be good for". As we have all noticed, many chemical engineering departments have changed their names to reflect the increasingly biological focus of their research activities; at this point, 8 of the top 25 chemical engineering departments in the U.S. have been renamed to reflect a more biological thrust (Chemical & Biological Engineering, and Chemical & Biomolecular Engineering are popular choices), and 16 of these departments now have faculty members actively doing research in the field of biomimicry, broadly defined.

As the frontiers of science expand at an apparently ever-increasing rate, the boundaries between individual scientific disciplines are becoming less and less distinct; and it becomes increasingly challenging for any one of us to keep up with each other's work, and with the literature as a whole. As chemical engineers, we begin to feel that we are part of scientific communities other than the close-knit world of chemical engineers (in my case, my students and I skirt the borders of chemical biology and biophysics), and that is good. Many chemical engineers are well trained and well poised to catalyze a revolutionary blending of fundamental science and applied engineering that promises to transform the way in which research is done over the next 10–20 years. This is no coincidence. Rather, it is only although the concerted efforts of scientists and engineers that interdisciplinary fields, such as foldamer-based biomimicry can emerge. Over time, the contributions that chemical engineers can make, even at the molecular synthesis and discovery stages of protein biomimicry, will increasingly be recognized.

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