Smart Biomaterials

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A bird's eye view of the mighty Amazon. The confluence of the Amazon River (mainstem, brown) and the Rio Negro River (tributary, black) at the city of Manaus. From space, most of the forested areas (green) appear homogeneous, as do many of the rivers. However, large-scale evidence points to the heterogeneous nature of the Amazon basin and the effects of this heterogeneity on distribution patterns of terrestrial and aquatic biodiversity. For freshwater systems, major tributaries join the mainstem Amazon River and increase species diversity immediately downstream of the confluence, but not upstream. This may be due to the river confluence providing conditions enabling both fish faunas (tributary and mainstem) to coexist over certain distances. The image suggests this possibility: The two rivers meet but remain distinct for a large distance downstream.

ing of such biotas, together with increased food availability and habitat stability, suggests that species should accumulate in a downstream direction.

Their extremely large sample enabled Fernandes *et al.* to carry out a test of this hypothesis on an unprecedented scale. They combined upstream and downstream samples at each confluence to obtain comprehensive estimates of richness at each site, and used rarefaction methods to estimate species richness in each section of the 2000-km stretch of river that they studied. They did not find any evidence to support the species accumulation hypothesis. Inspection of the species × site matrix data (kindly provided by the authors) shows that 18 electric fish species (41.2%) drop out progressively as one proceeds downstream, whereas only 5 species (11.6%) are added to the overall list from downstream stations. Despite the spikes in species richness below the confluence points where the tributaries enter the Amazon mainstem, diversity apparently returns to a lower state in the reaches between tributaries.

The pattern of electric fish diversity across a transect of the Amazon basin is strikingly similar to the general patterns of species richness seen in small terrestrial vertebrates of the Amazon basin. For example, amphibian species richness shows the greatest diversity on the flanks of the Andes, with attenuation eastward, that is, downstream (*7*). An increase in diversity from one site to another also characterizes much of the Amazon fauna, both terrestrial and aquatic, from the foothills to the lowlands. The exact driving forces behind these diversity patterns may vary by taxa (ancient geologic ridges in the case of some amphibians and small mammals, major rivers in the case of many primates, and tributaries in the case of freshwater fishes), but the biogeography and conservation implications are the same. First, we need to better bridge our evolutionary and ecological understanding of the forces driving species diversity for each group of taxa in order to better inform conservation planning. Second, freshwater aquatic biodiversity (especially that of fishes) is understudied and needs priority research like the Fernandes *et al*. study to establish a better and more comprehensive understanding of species distribution patterns. Finally, this and other studies continue to emphasize that lowland Amazonia is a very heterogeneous region and that its biodiversity is not evenly distributed, nor does it follow neat and clear overlapping patterns across taxonomic groups.

If we are to better manage the Amazon, we need to decide where to conserve biodiversity. We can only answer that question with detailed species-based information and analyses of distribution patterns of the kind presented by Fernandes and colleagues. Any other approach will be like trying to go up a river without a paddle.

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MATERIALS SCIENCE

Smart Biomaterials

Daniel G. Anderson, Jason A. Burdick, Robert Langer

More than 2000 years ago, the Romans, Chinese, and Aztecs used biomaterials such as gold for dentistry. Yet it is only with the development of synthetic polymer systems in the past few decades that biomaterials have begun to find broad applications in modern medicine (*1*). A new wave of advances in cell biology, chemistry, and materials science is enabling the production of a new generation of smart biomaterials.

Minute nanofibers of various structures and chemistries are formed through simple self-association and organization of peptides and proteins (*2*). Several bioactive extracellular protein domains have been identified that can be incorporated as small peptides into nanofibers through simple modification of the peptide amino acid sequence. Nanofibers can be designed to present these peptide sequences at high density. Three-dimensional (3D) macroscopic gel-like solids can also present high densities of such bioactive peptides.

Applying molecular self-assembly, Silva *et al*. report a new 3D material capable of directing the differentiation of neural progenitor cells to a specific lineage without the help of growth factors (*3*) (see the figure, A). Stem and progenitor cells have the ability to differentiate into derivative tissues and have great potential for tissue repair or replacement. Typically, differentiation is controlled by soluble compounds such as growth factors. Silva *et al*. synthesized self-assembling peptide amphiphiles that present the pentapeptide epitope isoleucine-lysine-valine-alanine-valine (IKVAV). IKVAV is an amino acid sequence found in laminin, which promotes neurite adhesion, sprouting, and growth. These peptide amphiphiles self-assemble in aqueous media to form nanofibers with diameters of 5 to 8 nm and lengths several orders of magnitude higher. Macroscopically, these intermeshed fibers form highly hydrated 3D gels that are able to direct the rapid differentiation of encapsulated neural progenitors into neurons while discouraging the production of astrocytes. The inhibition of astrocyte prolifera-

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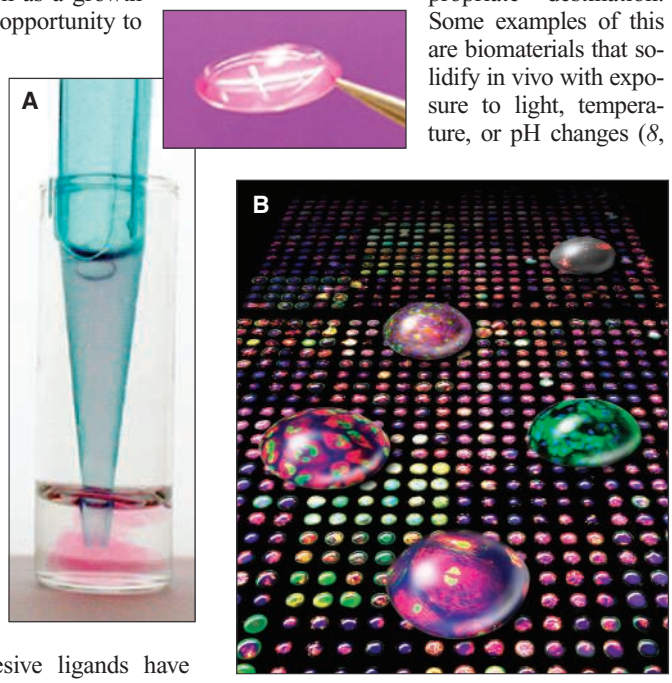
tion may prevent glial scar formation, which inhibits the regeneration and elongation of axons after central nervous system trauma.

Although the discovery of specific bioactive peptides has enabled the rational design of materials with the ability to control cell behavior, it is often unclear which chemical properties are necessary to provide this control. A high-throughput synthesis and screening platform for the testing of polymer-cell interactions can accelerate the discovery of such materials (*4*) (see the figure, B). Researchers have screened a library of polymers synthesized in nanoliter volumes for their effects on human embryonic stem (hES) cell growth and differentiation. There were numerous unexpected interactions: Some materials supported high levels of hES cell differentiation into epithelial-like cells, and others supported hES cell growth only in the absence of certain growth factors. Future studies combining rationally designed combinatorial libraries of biomaterials and high-throughput screening methods should allow the identification of new methods to control cellular behavior in tissue-engineered constructs. The ability to induce specific cellular behaviors (such as differentiation) with a material, as opposed to a diffusible compound such as a growth factor, provides the first opportunity to control precisely where differentiation occurs in an engineered tissue. In the future, this positional control of cellular behavior may facilitate the production of tissues composed of multiple lineages derived from a single stem cell type.

In addition to biomaterials that direct specific cellular behaviors, researchers are also developing smart biomaterials that respond to specific cellular signals. Hydrogels containing both matrix metalloproteinase (MMP) degradable sites and tethered adhesive ligands have been manufactured (*5*). The presence of these MMP sites allows native cells to control gel remodeling such that these cells replace the synthetic gel material with tissue. When these biomaterials are further supplemented with specific growth factors, such as bone morphogenetic proteins, these gels support the infiltration of cells and the formation of mineralized tissue for the healing of critical-sized cranial defects in rats. These materials exhibit many of the benefits of naturally derived gels such as collagen (for example, the ability to be remodeled and biocompatibility), yet avoid some undesirable properties of natural extracellular matrix gels (such as nonspecific protein adsorption).

Advances in microfabrication have also provided new approaches for developing smart biomaterials and drug delivery systems. For example, implantable silicon microchips with 100 drug-containing wells have been created (*6*). Each well can release drug on demand by application of a low voltage. Fully degradable versions of drug delivery microchips have also been reported (*7*). The incorporation of sensors into computer-controlled drug delivery systems like these may lead to responsive, fully automated drug therapies.

From a clinical standpoint, many of the advantages of these next-generation biomaterials are lost if the material cannot be implanted correctly. For example, proper contact between bone and implant is extremely important for the apposition and integration of bone tissue. To this end, biomaterials are being developed to allow easy application in one form (such as a liquid) that is rapidly converted into another (a solid or gel) at the appropriate destination. Some examples of this are biomaterials that solidify in vivo with exposure to light, temperature, or pH changes (*8*, *9*). Biodegradable shape-memory polymers (*10*) are also under development. These materials are composed of at least two separated phases, each with a different thermal transition temperature. These distinct phase transition temperatures allow the materials to "memorize" a permanent shape at body temperature that can be substantially different from a temporary shape at room temperature. Materials such as these may greatly simplify the use of biomaterials in surgical procedures, as they can be implanted at room temperature in a minimally invasive form (for example, laparoscopically) and then expand to a final shape after reaching body temperature.



Smart biomaterials get smarter. (**A**) A gel is formed by mixing a 1:1 volume ratio of murine neural progenitor cells suspended in culture medium and a 1% (by weight) solution of peptide amphiphile molecules that self-assemble into nanofibers. The cells remain viable after their encapsulation by the nanofibers and proceed to differentiate rapidly and selectively into neurons. (**B**) Polymeric microarray with fluorescently labeled human embryonic stem cells. Several individual spots with different cell types are magnified.

In addition to materials with responsive bulk properties, researchers are also developing smart surfaces. One example is a surface that can reversibly switch between hydrophilic and hydrophobic in response to an electric potential (*11*). A key design feature of this surface is the carefully controlled intermolecular spacing of a molecule with a negative terminus—(16-mercapto)hexadecanoic acid (2-chlorophenyl)diphenylmethyl ester (MHAE)—on a gold surface. With the proper spacing, the surface responds to negative electric potential by extending itself to display the hydrophilic, negatively charged terminus. Upon application of a positive charge, the gold surface attracts the negatively charged terminus, bending MHAE molecules to display their hydrophobic moieties. In the future, coatings such as these may enable production of medical devices and sensors with digitally responsive surfaces.

The work described here shows that we are no longer limited to off-the-shelf materials for biomedical applications. We have moved beyond the days of the first artificial heart created from polyetherurethanes, the same material originally used in ladies' girdles (*12*). We expect that biomaterials will become increasingly influenced by advances in cell biology and chemistry, and that the combination of these smart biomaterials with biosensors (*13*), new drug delivery systems (*14*), growth factors (*15*), and DNA (*16*) will boost the development and clinical application of new medical devices.

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