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MOLECULAR RECOGNITION IS CENTRAL TO BIOLOGY, and the discovery and characterization of interacting partners are major endeavors of biological scientists. Phage display, largely developed in the 1980s, has begun to make critical contributions to these endeavors. The approach is based on two pivotal concepts. The first is that phage, viruses that infect bacteria, can be used to link protein recognition and DNA replication. The protein (or peptide) is displayed on the surface of the phage particle and the genes encoding it are contained within the particle. The second concept is that large libraries of the DNA sequences encoding these molecules can be cloned into phage. Individual phage can then be rescued from libraries by virtue of interaction of the displayed protein with the cognate ligand, and the phage can be amplified by infection of bacteria.

The broad strategy is one that was adopted long ago by nature in the immune system. There, vast immune repertoires or libraries of molecules (antibodies, T-cell receptors) permit recognition of virtually any foreign entity. Protein recognition and replication are then linked, for example, when specific antibody-producing cells are stimulated to divide by interaction of antigen and antibody cell-surface receptors for antigen. The result is a system for efficiently generating molecular species capable of specifically recognizing almost any molecular shape.

In 1985, George Smith first showed that the linkage between phenotype and genotype could be established in filamentous bacteriophage and gave birth to the new technology of phage display. Smith showed that foreign DNA fragments could be inserted into filamentous phage gene III, which codes for the phage coat protein pIII, to create a fusion protein with the foreign sequence in the amino-terminal domain. The fusion protein was incorporated into the virion, which retained infectivity and displayed the foreign peptide in a form accessible to specific antibody to the peptide. This "fusion phage" could be greatly enriched relative to ordinary phage by affinity selection on immobilized antibody (a process usually termed "panning"). Subsequently, in 1990, Scott and Smith, Dower and colleagues, and Devlin and colleagues independently cloned libraries of peptides and showed that peptides of specific activity could be retrieved from these libraries by panning. Concurrent with these developments, in 1989, Richard Lerner and colleagues reported that libraries of randomly recombined