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Efficient synthetic methods have been generated for the (i) synthesis of libraries of unnatural oligomers, (ii) methods have been developed for the generation and screening of libraries of electronic, magnetic and optical materials, (iii) miniantibodies have been generated which share some of the properties of antibodies themselves.

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FINAL REPORT

GRANT#: N00014-93-1-0380 R&T CODE: 341u011

PRINCIPAL INVESTIGATOR: Peter G. Schultz

INSTITUTION: University of California, Berkeley

GRANT TITLE: Novel Biopolymeric Materials

AWARD PERIOD: 1 March 1993 - 28 February 1996

OBJECTIVE: (i) To design, synthesize and characterize new classes of biopolymers with novel physical, conformational or biological properties; (ii) To develop a new framework, relative to the antibody molecule, for the selective binding of molecules and (iii) To initiate a program for the combinatorial synthesis and evaluation of large libraries of solid state materials for novel electronic, magnetic and optical properties.

APPROACH AND ACCOMPLISHMENTS:

(i) A Combinatorial Approach to Materials Discovery

A method that combines thin film deposition and physical masking techniques has been used for the parallel synthesis of spatially addressable libraries of solid state materials. Arrays containing different combinations, stoichiometries and deposition sequences of $BaCO_3$, Bi_2O_3, CaO, CuO, PbO, $SrCO_3$ and Y_2O_3 were generated using a series of binary masks. The arrays were sintered and BiSrCaCuO and YBaCuO superconducting films were identified. Samples down to 200 μm x 200 μm in size were generated, corresponding to library densities of 10,000 sites/inch^2. The ability to generate and screen combinatorial libraries of solid state compounds, when coupled with theory and empirical observations, may significantly increase the rate at which novel electronic, magnetic and optical materials are discovered and theoretical predictions tested.

(ii) The Solid Phase Synthesis of *N*-Alkylcarbamate Oligomers

An efficient method for the solid phase synthesis of *N*-alkylcarbamate oligomers from alternating carboxylic acid and N^{α}-Fmoc protected chiral *p*-nitrophenylcarbonate monomers has been developed. The general synthetic scheme involves four steps per coupling cycle: deprotection of the terminal amino group of the growing oligomer, acylation of the free amine with a carboxylic acid monomer, reduction of the resulting amide bond with borane and coupling of the secondary amine to a N^{α}-Fmoc protected *p*-nitrophenyl carbonate monomer. This novel biopolymer which has two side chain residues per backbone carbamate linkage and no backbone hydrogen bond donors may provide new frameworks for drug design as well as folded domains with novel physical and biological properties.

(iii) The Solid Phase Synthesis of Oligoureas

An efficient method for solid phase synthesis of oligoureas from readily prepared optically active azido 4-nitrophenyl carbamate monomers is described.

(iv) Synthesis of a Cyclic Urea as a Nonnatural Biopolymer Scaffold

A cyclic urea trimer was synthesized from readily available amino acid derivatives using a simple, iterative approach. A selective amide reduction using borane (BH_3-THF) and a triphosgene-mediated cyclization are the key features in a synthesis of the cyclic urea trimer **2**.

(v) Novel Biopolymers for Drug Discovery

The natural biopolymers, oligopeptides, nucleic acids and oligosaccharides, have evolved to carry out specific cellular functions such as biocatalysis, signal transduction, and information storage. Chemistry and molecular biology have significantly advanced our ability to synthesize and manipulate the structures of these molecules. However, the question arises whether we can design whole new classes of "synthetic biopolymers" with properties or functions not found in the natural biopolymers. One such opportunity may be in the search for new therapeutic agents.

(vi) An Unnatural Biopolymer for Drug Discovery

In an effort to determine whether "unnatural" polymeric backbones exist with improved pharmacological properties relative to those of peptides, we have developed a highly efficient method for the solid phase synthesis of oligocarbamates and oligocarbamate libraries. Oligocarbamates were synthesized from a pool of optically active, *N*-protected aminocarbonate monomers with greater than 99% overall coupling efficiencies. A spatially defined library of oligocarbamates was generated using photochemical methods and screened for binding affinity to a monoclonal antibody. A number of high affinity ligands were then synthesized and analyzed in solution with respect to their IC_{50} values, water/octanol partitioning coefficients, and proteolytic stability. The synthesis and characterization of these and other unnatural polymers may not only facilitate the development of new drugs, they may also provide new frameworks for testing theories of protein/peptide folding and structure.

CONCLUSIONS: Efficient synthetic methods have been generated for the (i) synthesis of libraries of unnatural oligomers, (ii) methods have been developed for the generation and screening of libraries of electronic, magnetic and optical materials, (iii) miniantibodies have been generated which share some of the properties of antibodies themselves.

SIGNIFICANCE: (i) The above work may provide new classes of unnatural biopolymers with improved properties relative to polypeptides for molecular recognition and catalysis; (ii) Combinatorial methods should increase the rate at which new materials are discovered and our ability to test and refine theory.

AWARD INFORMATION: Harrison Howe Lectureship Award, Rochester Section of the American Chemical Society (1993); National Academy of Sciences, USA (1993); Wolf Prize in Chemistry (1994); Honorary Doctor of Sciences, Uppsala University of Sweden (1994); California Scientist of the Year Award (1995); Discover Magazine Awards for Technological Innovation (1996).

PUBLICATIONS AND REPORTS:

1. Xiang, X.-D.; Sun, X.; Briceño, G.; Lou, Y.; Wang, K.-A.; Chang, H.; Wallace-Freedman, W.G.; Chen, S.-W.; Schultz, P.G. "A Combinatorial Approach to Materials Discovery" *Science* **1995**, *268*, 1738-1740.

2. Paikoff, S.J.; Wilson, T.E.; Cho, C.Y.; Schultz, P.G. "The Solid Phase Synthesis of N-Alkylcarbamate Oligomers" *Tetrahedron Letters* in press

3. Kim, J.-M.; Paikoff, S.J.; Schultz, P.G. "The Solid Phase Synthesis of Oligoureas" *Tetrahedron Letters* in press.

4. Kim, J.-M.; Wilson, T.E.; Norman, T.C.; Schultz, P.G. "Synthesis of a Cyclic Urea as a Nonnatural Biopolymer Scaffold" *Tetrahedron Letters* in press.

5. Moran, E.J.; Wilson, T.E.; Cho, C.Y.; Cherry, S.R.; Schultz, P.G. "Novel Biopolymers for Drug Discovery" *Peptide Science* **1995**, *37*, 213-219.

6. Cho, C.Y.; Moran, E.J.; Cherry, S.; Stephans, J.; Fodor, S.P.A.; Adams, C.; Sundaram, A.; Jacobs, J.W.; Schultz, P.G. "An Unnatural Biopolymer" *Science* **1993**, *261*, 1303-1305.