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Liu, David R.

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Harvard University
Department of Chemistry and Chemical Biology
12 Oxford Street
Cambridge, MA 02138

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14. ABSTRACT We have developed a new approach to (*i*) controlling chemical reactivity and (*ii*) discovering functional synthetic molecules that is based on biosynthesis and molecular evolution in nature. Our approach uses DNA-templated organic synthesis as a surprisingly general means of translating an amplifiable information carrier into a synthetic structure. We have integrated insights into DNA-templated synthesis with synthetic organic chemistry and molecular biology to develop (*a*) new modes of controlling reactivity that are not possible using existing synthetic methods, (*b*) multistep small molecule syntheses programmed by DNA sequences, (*c*) a model for stereoselectivity in DNA-templated synthesis, (*d*) DNA-templated *library* synthesis of complex small molecules, and (*e*) selections for DNA-linked synthetic molecules with protein binding affinity and specificty. These studies have enabled synthetic molecules to participate in powerful processes including translation, selection, and amplification previously available only to biological macromolecules. Our studies represent an entirely new approach to synthesis and discovery that may lead to new synthetic small molecules and polymers with desired properties, as well as to the discovery of new chemical reactions.

15. SUBJECT TERMS
DNA-templated organic synthesis, evolving synthetic molecules

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FINAL REPORT

GRANT #: N00014-00-1-0596

PRINCIPAL INVESTIGATOR: Dr. David R. Liu

INSTITUTION: Harvard University

GRANT TITLE: The Development of Amplifiable and Evolvable Unnatural Molecules

AWARD PERIOD: 1 May 2000-30 April 2003

OBJECTIVE: To develop methods of translating, amplifying, and selecting DNA sequences encoding synthetic molecules with desired properties, paralleling the natural evolution of biological molecules.

APPROACH: We have used DNA-templated organic synthesis as a means of translating DNA sequences into synthetic molecules. This artificial translation is the key step that has enabled us to develop powerful new approaches to the creation and discovery of synthetic molecules.

ACCOMPLISHMENTS: We have developed a new approach to (*i*) controlling chemical reactivity and (*ii*) discovering functional synthetic molecules that is based on biosynthesis and molecular evolution in nature. Our approach uses DNA-templated organic synthesis as a surprisingly general means of translating an amplifiable information carrier into a synthetic structure. We have integrated insights into DNA-templated synthesis with synthetic organic chemistry and molecular biology to develop (*a*) new modes of controlling reactivity that are not possible using existing synthetic methods, (*b*) multistep small molecule syntheses programmed by DNA sequences, (*c*) a model for stereoselectivity in DNA-templated synthesis, (*d*) DNA-templated *library* synthesis of complex small molecules, and (*e*) selections for DNA-linked synthetic molecules with protein binding affinity and specificty. These studies have enabled synthetic molecules to participate in powerful processes including translation, selection, and amplification previously available only to biological macromolecules.

CONCLUSIONS: DNA-templated organic synthesis is a general phenomenon that enables chemical reactivity to be controlled by effective molarity. In addition, the use of

DNA-templated synthesis as a means of translating amplifiable nucleic acid sequences into synthetic molecules enables the latter to undergo powerful manipulations that were previously only available to biological macromolecules.

SIGNIFICANCE: Our studies represent an entirely new approach to synthesis and discovery that may lead to new synthetic small molecules and polymers with desired properties, as well as to the discovery of new chemical reactions.

PATENT INFORMATION: A patent application on DNA-templated organic synthesis has been filed by Harvard University.

AWARD INFORMATION: Promoted to John L. Loeb Associate Professor of the Natural Sciences and Associate Professor of Chemistry and Chemical Biology, Harvard University (2003); American Chemical Society Young Cope Scholar Award (2003); Roslyn Abramson Award for undergraduate teaching at Harvard (2003); AstraZeneca Pharmaceuticals Excellence in Chemistry Award (2003); Merck Genome-Related Pilot Research Award (2003); *Synlett* and *Synthesis* Editorial Board Assistant Professor Journal Award (2003); Arnold and Mabel Beckman Foundation Young Investigator (2002); Alfred P. Sloan Foundation Research Fellow (2002); American Cancer Society Research Scholar (2001); NSF CAREER Award Recipient (2001); Searle Scholars Program Awardee (2000)

PUBLICATIONS:

1. "Highly Sensitive *In Vitro* Selections for DNA-Linked Synthetic Small Molecules with Protein Binding Affinity and Specificity" Doyon, J. B.; Snyder, T. M.; Liu, D. R. **submitted** (2003).

2. "Stereoselectivity in DNA-Templated Organic Synthesis and Its Origins" Li, X. and Liu, D. R. *J. Am. Chem. Soc.* **in press** (2003).

3. "Two Enabling Architectures for DNA-Templated Organic Synthesis" Gartner, Z. J.; Grubina, R.; Calderone, C. T.; Liu, D. R. *Angew. Chem. Int. Ed.* **42**, 1370-1375 (2003). A Science and Technology Concentrate describing this work appears in *Chem. & Eng. News* **81** [13] 24 (2003).

4. "Directing Otherwise Incompatible Reactions in a Single Solution Using DNA-Templated Organic Synthesis"

Calderone, C. T.; Puckett, J. W.; Gartner, Z. J.; Liu, D. R. *Angew. Chem. Int. Ed.* **41**, 4104-4108 (2002). This work is featured as an Editor's Choice in *Science* **298** [5598] , 1517 (2002).

5. "Multistep Small-Molecule Synthesis Programmed by DNA Templates" Gartner, Z. J.; Kanan, M. W.; Liu, D. R. *J. Am. Chem. Soc.*, **124**, 10304 (2002). News stories describing this work appear in *Chem. & Eng. News* **80** [34] 12 (2002), and in *Science*, **300**, 242 (2003).

6. "Expanding the Reaction Scope of DNA-Templated Synthesis" Gartner, Z, J.; Kanan, M. W.; Liu, D. R. *Angew. Chem. Int. Ed.*, **41**, 1796 (2002). This work is featured in an online *Nature* Science Update (http://www.nature.com/nsu/nsu_pf/020527/020527-1.html)

7. "The Generality of DNA-Templated Synthesis as a Basis for Evolving Non-Natural Small Molecules" Gartner, Z. J. and Liu, D. R. *J. Am. Chem. Soc.* **123**, 6961-6963 (2001). A Highlight describing this work appears in *Angew. Chem. Int. Ed.* **41**, 89 (2002).