

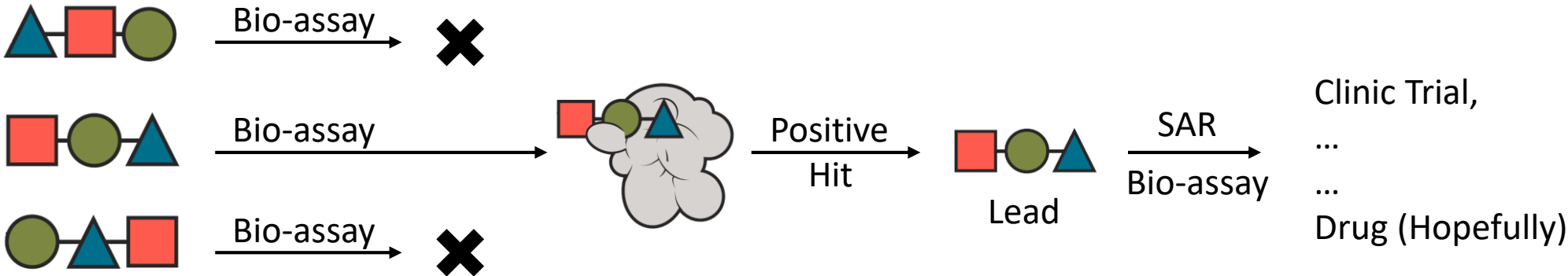
# DNA-Encoded Chemical Library (DEL)

Tao Liu

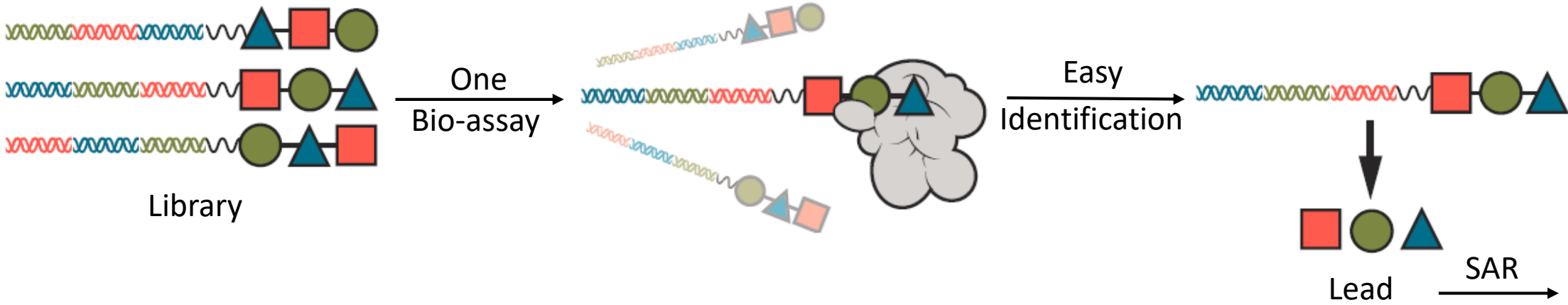
4/29/2016

Yu Group Meeting

# Conventional High-Throughput Screening (HTS)



# DNA-Encoded Chemical Library (DEL)



# Encoded combinatorial chemistry

(chemical repertoire/encoded libraries/commaless code)

**SYDNEY BRENNER** AND **RICHARD A. LERNER**

Departments of Chemistry and Molecular Biology, **The Scripps Research Institute**, 10666 North Torrey Pines, La Jolla, CA 92037

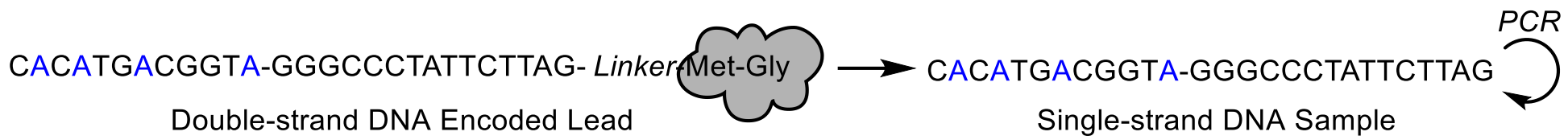
*Contributed by Sydney Brenner, March 3, 1992*

**GGGCCCTATTCTTAG-LINK**

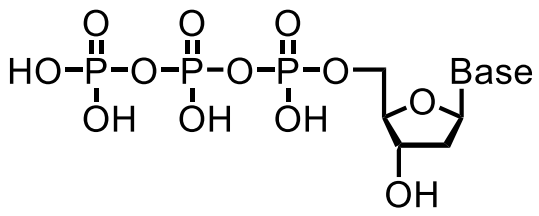
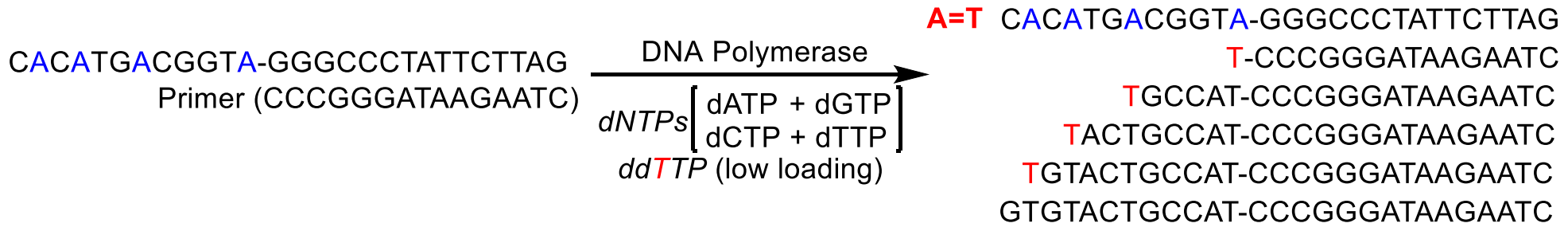
Design DNA codes for  
Glycine, Methionine

**CACATGGGGCCCTATTCTTAG-LINK-Gly**  
**ACGGTAGGGCCCTATTCTTAG-LINK-Met**

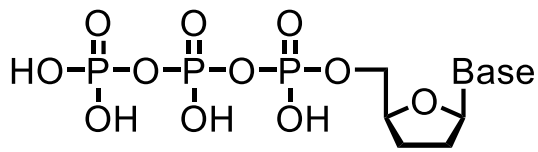
**CACATGCACATGGGGCCCTATTCTTAG-LINK-Gly-Gly**  
**CACATGACGGTAGGGCCCTATTCTTAG-LINK-Met-Gly**  
**ACGGTACACATGGGGCCCTATTCTTAG-LINK-Gly-Met**  
**ACGGTACGGTAGGGCCCTATTCTTAG-LINK-Met-Met**



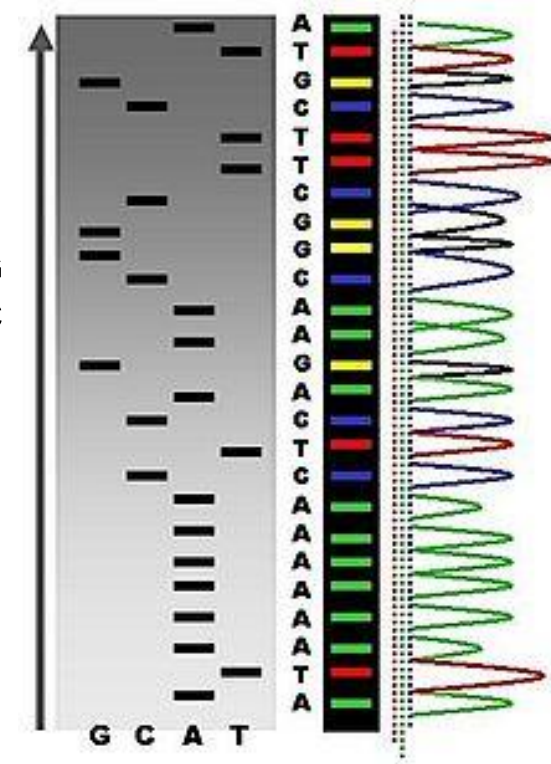
**DNA Sequencing: Chain-Termination Method (Sanger method)**



Deoxyribonucleotide triphosphate (dNTP)



Dideoxynucleotide triphosphate (ddNTP)



Automated Chromatography

**DNA Sequencing:** High Accuracy (99.9%), Fast (6 h/million bases), Low Cost (0.05-0.15 USD/million bases).

**DNA-Encoded Library: Automated Synthesis, Automated Sequencing, Automated Data Interpretation.**

# Applications of DNA-Encoded Chemical Library (DEL)

Small Molecule Library

Double DNA-Encoded Library

Cyclic Macromolecule Library



ELSEVIER

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# Bioorganic & Medicinal Chemistry

journal homepage: [www.elsevier.com/locate/bmc](http://www.elsevier.com/locate/bmc)

## Application of **encoded library technology (ELT)** to a protein–protein interaction target: Discovery of a potent class of integrin lymphocyte function-associated antigen 1 (LFA-1) antagonists

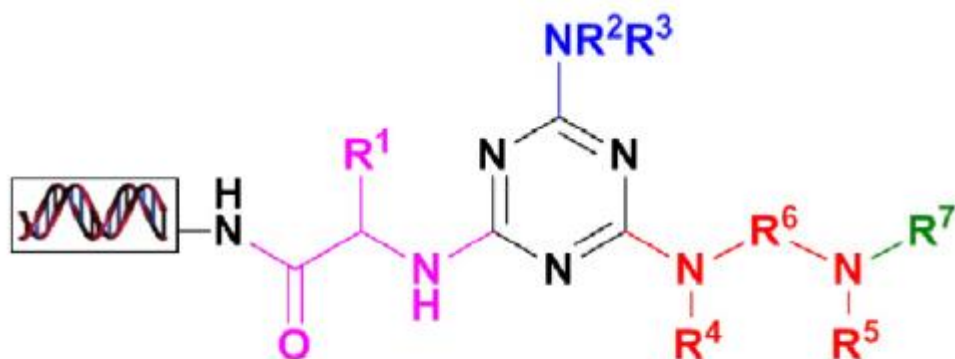


Christopher S. Kollmann<sup>a</sup>, Xiaopeng Bai<sup>a</sup>, Ching-Hsuan Tsai<sup>a</sup>, Hongfang Yang<sup>a</sup>, Kenneth E. Lind<sup>a</sup>, Steven R. Skinner<sup>a</sup>, Zhengrong Zhu<sup>a</sup>, David I. Israel<sup>a</sup>, John W. Cuzzo<sup>a,†</sup>, Barry A. Morgan<sup>a</sup>, Koichi Yuki<sup>b,‡</sup>, Can Xie<sup>b,§</sup>, Timothy A. Springer<sup>b</sup>, Motomu Shimaoka<sup>b,¶</sup>, Ghotas Evindar<sup>a,\*</sup>

<sup>a</sup> **GlaxoSmithKline**, Platform Technology & Science, MDR Boston, 830 Winter Street, Waltham, MA 02451, USA

<sup>b</sup> Immune Disease Institute, Children's Hospital Boston, Harvard Medical School, Program in Cellular and Molecular Medicine, Department of Biological Chemistry and Molecular Pharmacology, 3 Blackfan Circle, Rm. 3100, Boston, MA 02115, USA

# Allosteric inhibitor of protein-protein interactions



**Cycle 1:** 192 Fmoc-Amino Acids

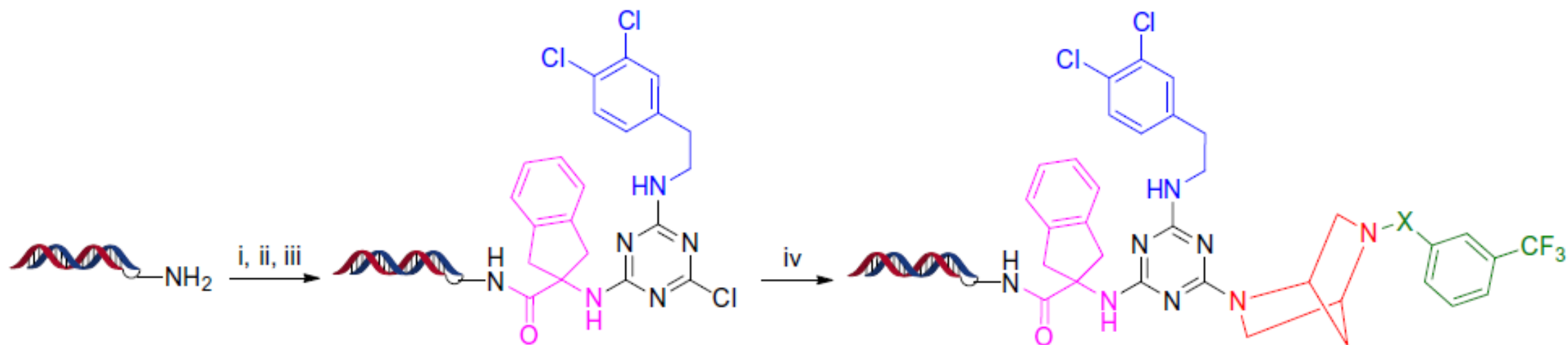
**Cycle 2:** 479 amines

**Cycle 3:** 96 diamines

**Cycle 4:** 459 amine-capping BBs (carboxylic acids, aldehydes, sulfonyl chlorides, isocyanates) + 4 blanks

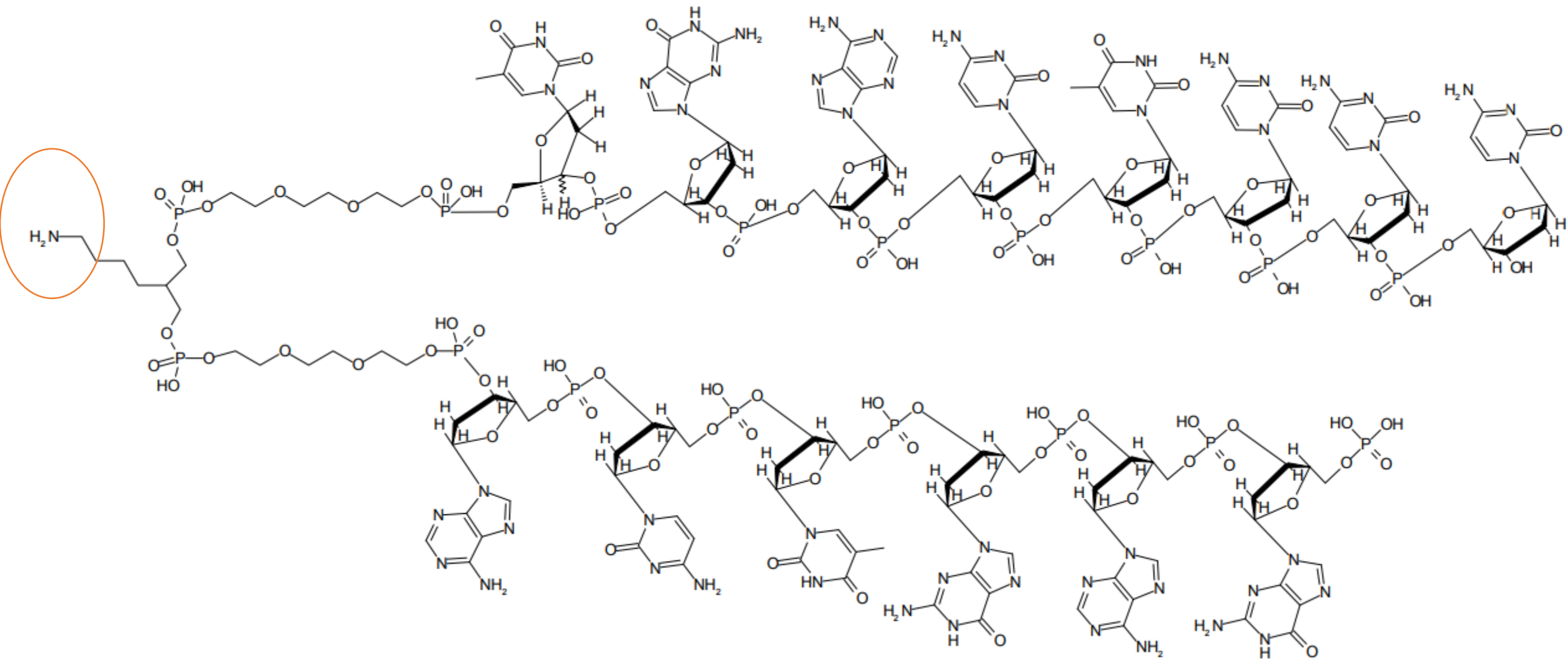
**Library diversity: 4.1 billion**

**Figure 1.** Design of DEL-A.





# GSK DNA-Headpiece





## Encoded Library Technology as a Source of Hits for the Discovery and Lead Optimization of a Potent and Selective Class of Bactericidal Direct Inhibitors of *Mycobacterium tuberculosis* InhA

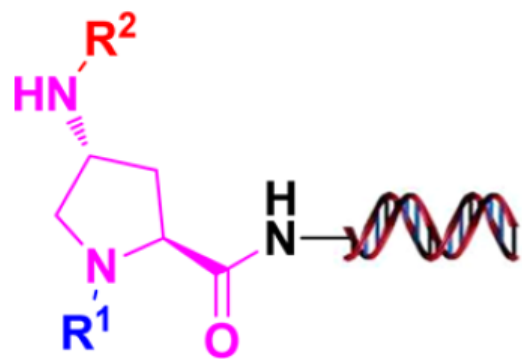
Lourdes Encinas,<sup>‡</sup> Heather O’Keefe,<sup>†</sup> Margarete Neu,<sup>§</sup> Modesto J. Remuiñán,<sup>‡</sup> Amish M. Patel,<sup>†</sup> Ana Guardia,<sup>‡</sup> Christopher P. Davie,<sup>†</sup> Natalia Pérez-Macías,<sup>||</sup> Hongfang Yang,<sup>†</sup> Maire A. Convery,<sup>§</sup> Jeff A. Messer,<sup>†</sup> Esther Pérez-Herrán,<sup>‡</sup> Paolo A. Centrella,<sup>⊥</sup> Daniel Álvarez-Gómez,<sup>‡</sup> Matthew A. Clark,<sup>⊥</sup> Sophie Huss,<sup>‡</sup> Gary K. O’Donovan,<sup>†</sup> Fátima Ortega-Muro,<sup>‡</sup> William McDowell,<sup>#</sup> Pablo Castañeda,<sup>‡</sup> Christopher C. Arico-Muendel,<sup>†</sup> Stane Pajk,<sup>∞</sup> Joaquín Rullás,<sup>‡</sup> Iñigo Angulo-Barturen,<sup>‡</sup> Emilio Álvarez-Ruíz,<sup>×</sup> Alfonso Mendoza-Losana,<sup>‡</sup> Lluís Ballell Pages,<sup>‡</sup> Julia Castro-Pichel,<sup>\*,‡</sup> and Ghotas Evindar<sup>\*,†</sup>

<sup>†</sup>ELT Boston, Platform Technology & Science, **GlaxoSmithKline**, Waltham, Massachusetts 02451, United States

<sup>‡</sup>Diseases of the Developing World, Tres Cantos Medicines Development Campus, **GlaxoSmithKline**, Severo Ochoa 2, 28760 Tres Cantos, Madrid, Spain

<sup>§</sup>Computational and Structural Chemistry, Platform Technology & Science, **GlaxoSmithKline**, Stevenage SG1 2NY, Hertfordshire, U.K.

# Target: InhA, enoyl-ACP reductase from Mycobacterium Tuberculosis (TB)



**Cycle 1:** 22 diamino acids (1 shown)

**Cycle 2:** 855 amine-capping BBs (carboxylic acids, aldehydes, sulfonyl chlorides, isocyanates)

**Cycle 3:** 857 amine-capping BBs (carboxylic acids, aldehydes, sulfonyl chlorides, isocyanates)

**Library diversity: 16.1 million**

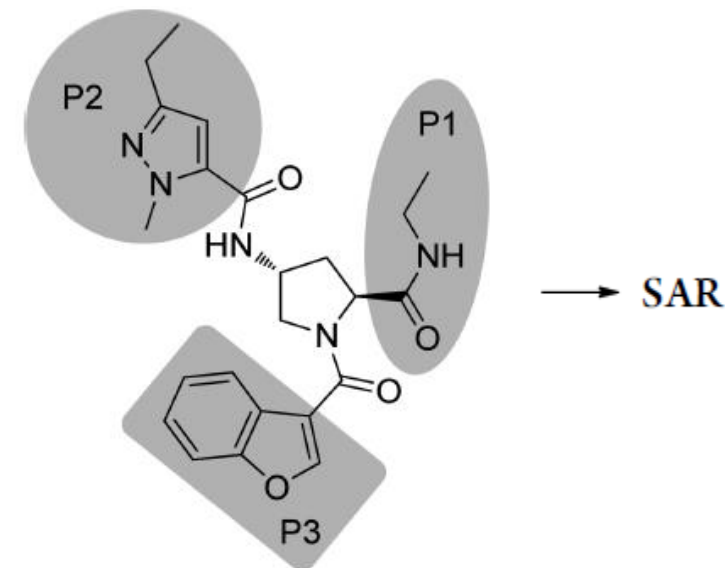
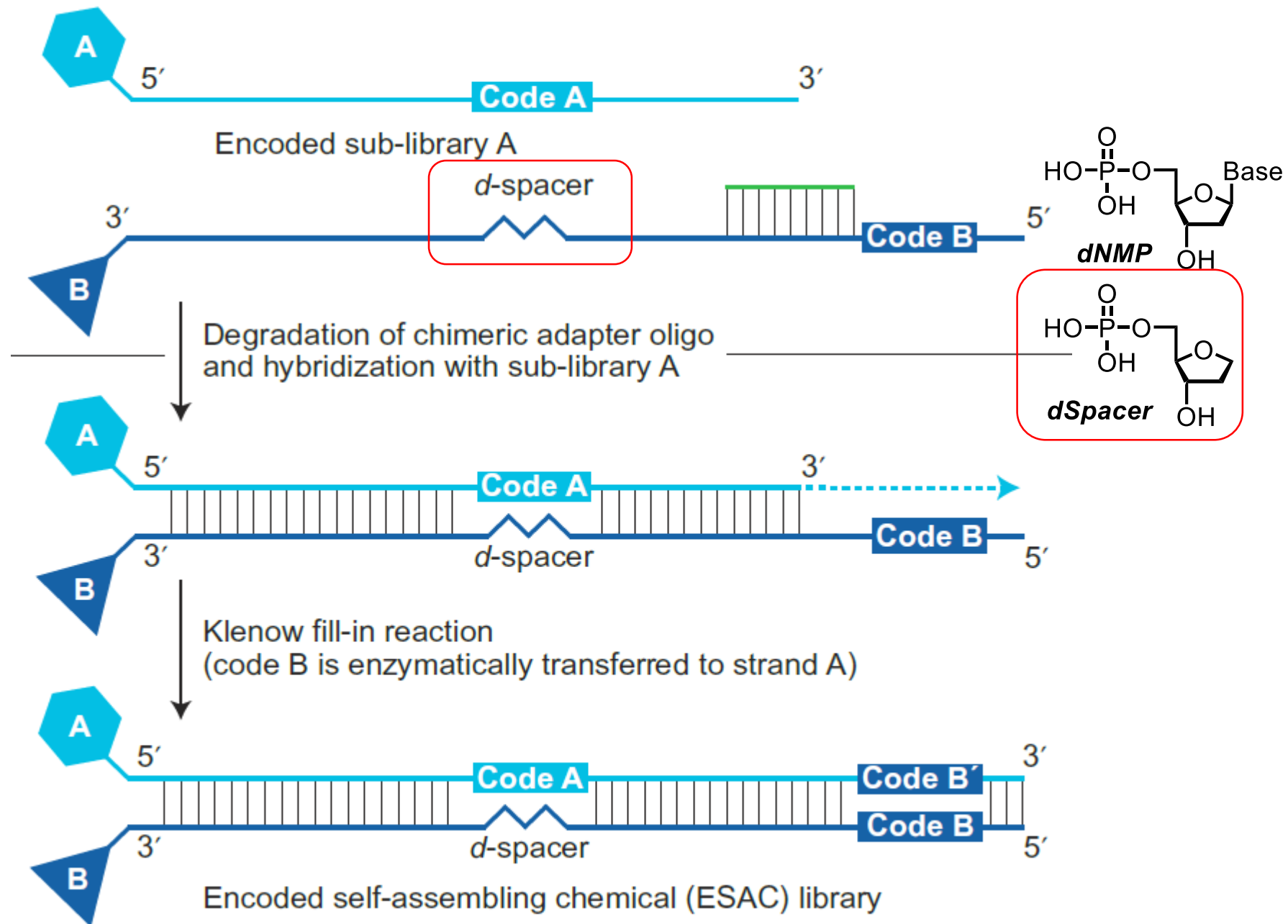
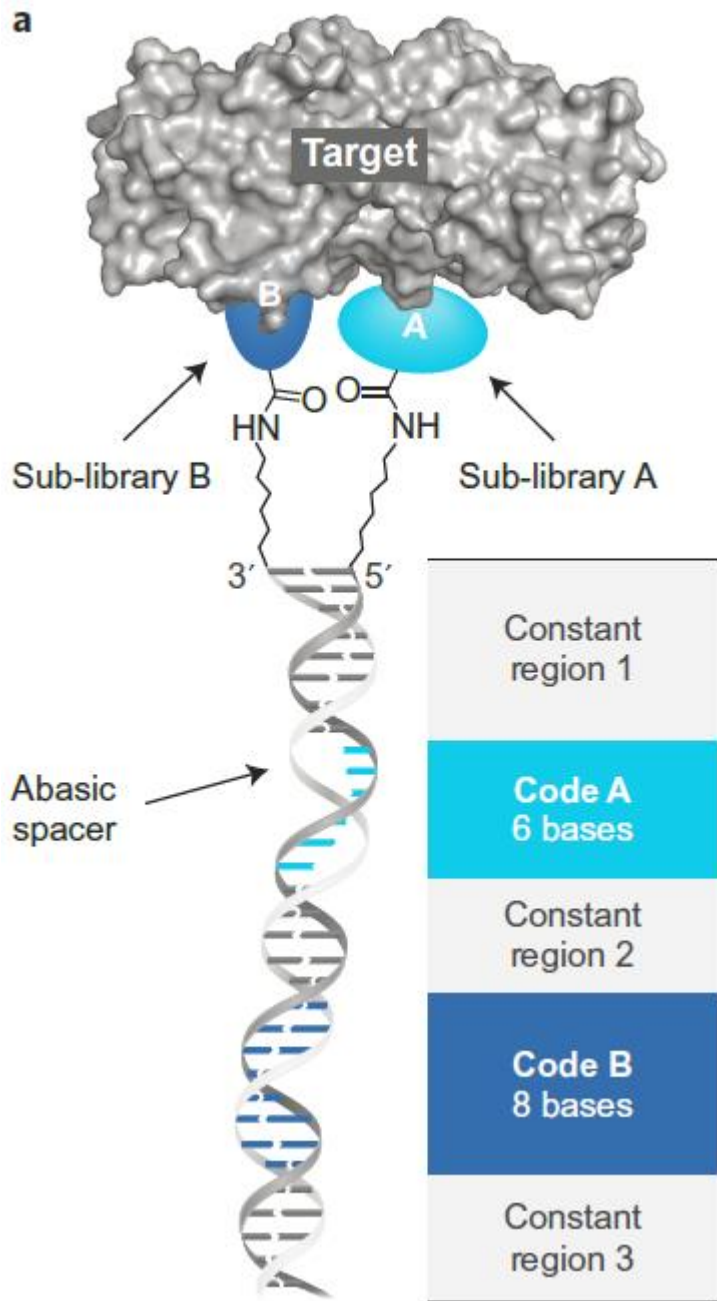


Figure 1. Design of DNA-encoded library (DEL).

# Dual-display of small molecules enables the discovery of ligand pairs and facilitates affinity maturation

Moreno Wichert<sup>1</sup>, Nikolaus Krall<sup>1</sup>, Willy Decurtins<sup>1</sup>, Raphael M. Franzini<sup>1</sup>, Francesca Pretto<sup>2</sup>, Petra Schneider<sup>1</sup>, Dario Neri<sup>1\*</sup> and Jörg Scheuermann<sup>1\*</sup>





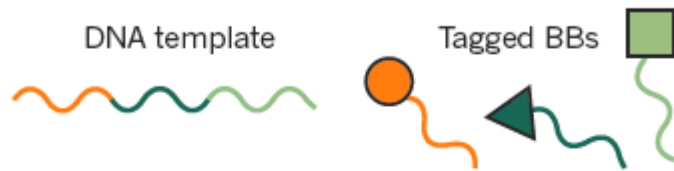
## **Anti-diabetic activity of insulin-degrading enzyme inhibitors mediated by multiple hormones**

Juan Pablo Maianti<sup>1</sup>, Amanda McFedries<sup>1</sup>, Zachariah H. Foda<sup>2</sup>, Ralph E. Kleiner<sup>1</sup>, Xiu Quan Du<sup>3</sup>, Malcolm A. Leissring<sup>4</sup>, Wei-Jen Tang<sup>5</sup>, Maureen J. Charron<sup>3</sup>, Markus A. Seeliger<sup>2</sup>, Alan Saghatelian<sup>1</sup> & David R. Liu<sup>1,6</sup>

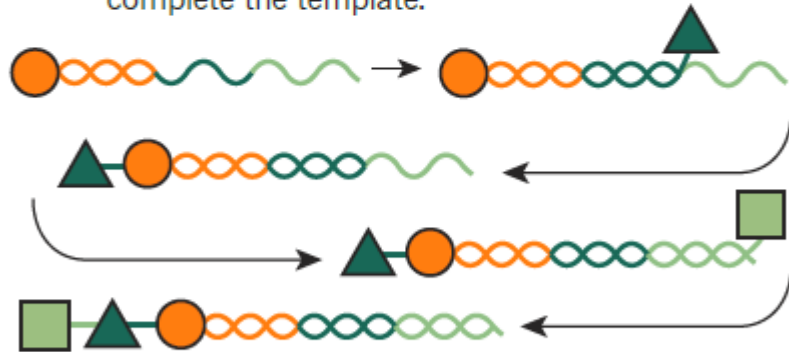


## DNA templating

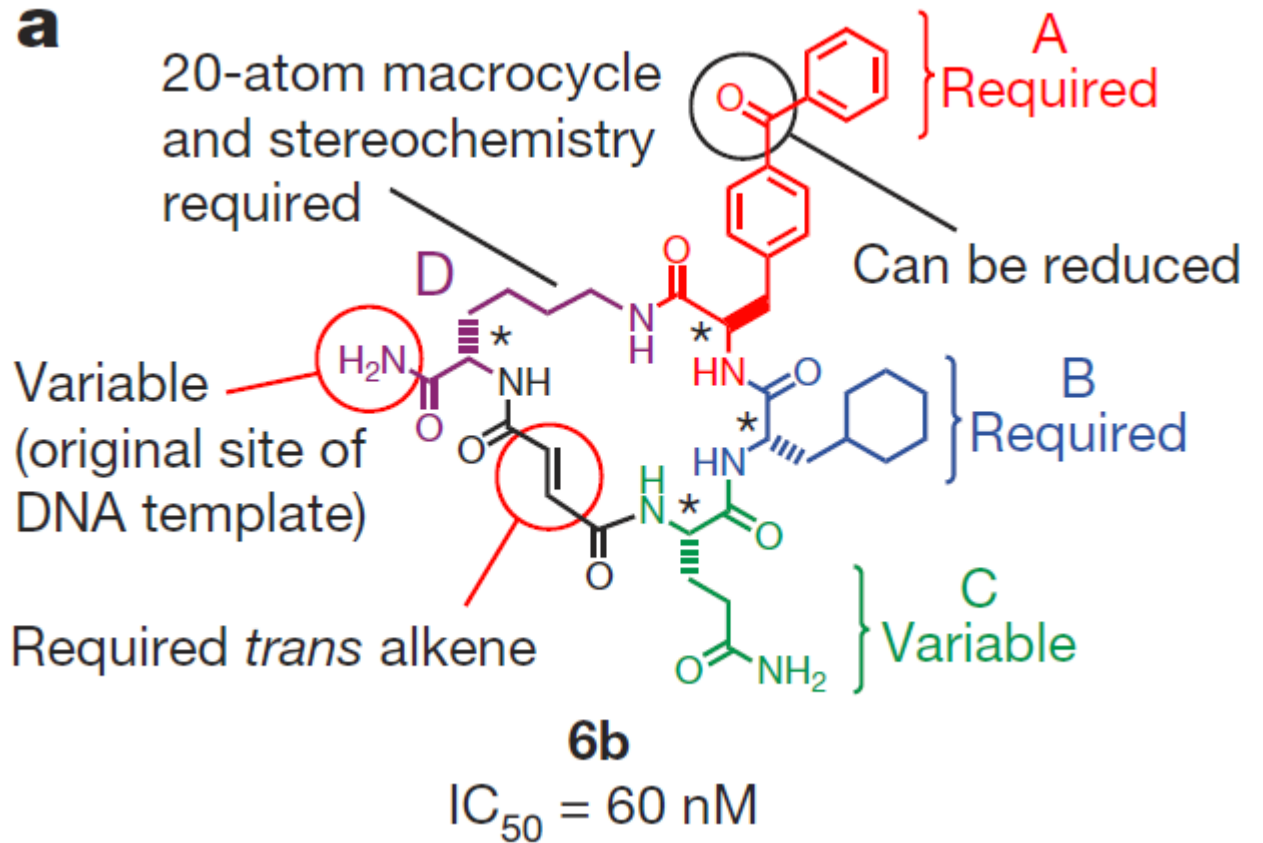
- 1 ▶ Each molecule is designed as a single-stranded DNA template. BBs are tagged with DNA 'anti-barcode' that are complementary to regions on the planned molecule's template.



- 2 ▶ A DNA-tagged BB binds to its corresponding section on the template. A second DNA-tagged BB is added and binds to its corresponding template position, and the two BBs join in a chemical reaction. More BBs are added to complete the template.



- 3 ▶ A final chemical reaction can convert a string of building blocks into a ring, producing barcoded macrocycles.





Thank you