DNA-Encoded Chemical Library (DEL)

Tao Liu
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Yu Group Meeting
Conventional High-Throughput Screening (HTS)

DNA-Encoded Chemical Library (DEL)

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Encoded combinatorial chemistry

(chemical repertoire/encoded libraries/commaless code)

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Contributed by Sydney Brenner, March 3, 1992

Design DNA codes for Glycine, Methionine

GGGCCCTATTCTTAG–LINK

CACATGGGGCCCTATTCTTAG–LINK–Gly
ACGGTAGGGCCCTATTCTTAG–LINK–Met

CACATGCACATGGGGCCCTATTCTTAG–LINK–Gly–Gly
CACATGACGGTAGGGCCCTATTCTTAG–LINK–Met–Gly
ACGGTAACCATGGGGCCCTATTCTTAG–LINK–Gly–Met
ACGGTAACGGTAGGGCCCTATTCTTAG–LINK–Met–Met
DNA Sequencing: Chain-Termination Method (Sanger method)

**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
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 a, Xiaopeng Bai a, Ching-Hsuan Tsai a, Hongfang Yang a, Kenneth E. Lind a, Steven R. Skinner a, Zhengrong Zhu a, David I. Israel a, John W. Cuozzo a,‡, Barry A. Morgan a, Koichi Yuki b,‡, Can Xie b,‡, Timothy A. Springer b, Motomu Shimaoka b,‡, Ghotas Evindar a,‡

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

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§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 Wichert¹, Nikolaus Krall¹, Willy Decurtins¹, Raphael M. Franzini¹, Francesca Pretto², Petra Schneider¹, Dario Neri¹* and Jörg Scheuermann¹*
Anti-diabetic activity of insulin-degrading enzyme inhibitors mediated by multiple hormones

Juan Pablo Maianti¹, Amanda McFedries¹, Zachariah H. Foda², Ralph E. Kleiner¹, Xiu Quan Du³, Malcolm A. Leissring⁴, Wei-Jen Tang⁵, Maureen J. Charron³, Markus A. Seeliger², Alan Saghatelian¹ & David R. Liu¹,⁶
**DNA templating**

1. Each molecule is designed as a single-stranded DNA template. BBs are tagged with DNA ‘anti-barcodes’ 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.

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**Chemical Structure**

- **a**
  - 20-atom macrocycle and stereochemistry required
  - Can be reduced
  - Variable (original site of DNA template)
  - Required trans alkene

**Chemical Compound 6b**

- IC$_{50} = 60$ nM

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Thank you