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Amplifiable Novel DNA-Encoded Chemical Libraries on Drug Discovery

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Abstract

The development of DNA-Encoded Chemical Libraries (DELs) has accelerated recently due to the identification of tiny ligands, and the majority of major pharmaceutical companies have adopted the technique. An important issue in biology, chemistry, and the biomedical sciences is the development of chemical ligands that bind to proteins with specificity. By encoding individual organic compounds with unique DNA tags that function as amplifiable identifying bar codes, it is possible to create and transfer unprecedentedly large combinatorial libraries, which in turn makes it easier to find ligands for a wide range of protein targets. Fundamentally, chemical synthesis and genetic abilities are linked. Several experimental implementations of the technique have been reduced to preparation since the first description of DNA-encoded chemical libraries was published in 1992. As a result, a number of ideal DELs with the highest possible percentage of biologically significant chemotypes were selected, each of which covered the chemical space of ChEMBL to the fullest extent. A series of mutually complimentary libraries that enable even greater coverage of ChEMBL than is achievable with a single DEL were discovered through the analysis of various DEL combinations.***Keywords***: ILD, Infection, fibrotic pattern, respiratory tract.

Keywords: DNA-Encoded chemical library, small molecule drug discovery, libraries design and comparison, hit identification, drug discovery, drug design, combinatorial chemistry

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Introduction

Traditional Small Molecule Drug Discovery Small molecule drug discovery has traditionally been pursued by screening conventional, arrayed libraries of small organic molecules, which are screened one-by one by high-throughput screening (HTS) (1). The respective arrayed libraries typically do not exceed a few million compounds, and are produced as individual molecules or as small mixtures of compounds by combinatorial split-and-pool methodology. Typically, due to the necessary large infrastructure, the production of larger libraries and HTS is mainly performed by pharmaceutical companies rather than in an academic context. Interesting strategies for the diversification of chemical structures have been devised, e.g., through diversity-oriented synthesis (DOS) (2) but also these methods suffer from the same restrictions concerning manageable library size and screening infrastructure. On the side of larger compounds, natural display technologies, such as phage display (3), yeast display.(4).mRNA-display (5) or ribosome display (6) have proven useful for the creation of encoded libraries using proteinogenic building blocks. With these natural display technologies, valuable high-molecular weight binders could be identified and developed. (7)

1.2 DNA-Encoded chemical libraries

In analogy to the natural display technologies, DNA-Encoded Chemical Libraries (DELs) feature small molecules individually tagged with a DNA barcode, which allows for the identification of target-binding ligands after PCR amplification and DNA sequencing.(8) A DEL typically comprises 105–108 library members which may all be tested for binding to a target protein in a single experiment. Thanks to the DNA tag a DEL can be stored in a single tube which greatly reduces the need for complicated and expensive infrastructure for storage and screening. Over the last couple of years, DEL technology has been implemented as a tool for small molecule ligand discovery by essentially all big pharmaceutical companies and also by academic groups.(9) While the latter generally focus on the development of novel DNA-compatible chemistries, just a few academic groups practice DEL technology from A-Z, i.e. from DEL generation to in-house screening of targets of interest, hit validation and development.

2. DEL Selections

DNA-Encoded Chemical Libraries (DELs) are collections of small molecules which are individually tagged with DNA fragments encoding the respective small molecule's identity. (8,10) Compared to HTS, where compounds are screened one-by-one, DEL selections can be performed at once for all library members together. This allows for the performance of affinity-based selections against targets of interest in a rapid fashion compared to other small molecule drug discovery methods. To perform DEL selections, the target protein typically is immobilized on a solid support.(11) Proteins used in such DEL selections require a tag such as biotin or poly-histidine for immobilization onto the solid support coated with streptavidin, or nickel/ cobalt, respectively. Magnetic beads or coated tips are often used as the solid support, which also allows for automated DEL selections. (11,12) After immobilization of the target protein on the solid support it is incubated with the DEL. .

Types of DNA encoded chemical libraries:

one can distinguish between single-pharmacophore and dual-pharmacophore DNA-encoded chemical libraries. In the first case, individual molecules (no matter how complex) Schematic representation of (a) single-pharmacophore and (b) dual-pharmacophore DNA-encoded chemical libraries. A linear schematic representation is also displayed next to the double-helix representation of the DNA structure. This graphical representation is used in subsequent figures describing encoding procedures. are attached to distinctive DNA fragments. In most instances, those molecules are coupled to one of the two complementary DNA strands. However, researchers at Praecis [now GlaxoSmithKline (GSK)] had introduced a technology featuring the use of a chemical linker, which would provide a covalent connection between complementary strands and, at the same time, a site for the stepwise growth of organic molecular structures. By contrast, dual-pharmacophore chemical libraries can be produced by coupling pairs of organic molecules at the extremity of complementary DNA strands. If two sub libraries are constructed, featuring two sets of partially complementary oligonucleotides (each modified with organic molecules), these two sub libraries may then be reassembled (i.e., hybridized) to create a large combinatorial diversity.

Encoding and library synthesis strategies: Over the last two decades, various techniques have been used for the tagging of organic molecules with DNA and, consequently, for the construction of encoded combinatorial libraries. Let us consider the construction of a library comprising 1 billion different molecules. Obviously, it would be highly impractical (and prohibitively expensive) to couple 1 billion organic molecules to 1 billion different oligonucleotides (or DNA fragments) one at a time. Luckily, split-and-pool synthesis procedures greatly facilitate the facile and economic assembly of single-pharmacophore chemical libraries. Alternatively, ESAC library technology can also be used to create large molecular repertoires, capitalizing on the combinatorial self-assembly of sub libraries Single-Pharmacophore Chemical Libraries The most commonly used method for the encoding and construction.

single-pharmacophore dna-encoded chemical libraries: The most commonly used method for the encoding and construction of single pharmacophore DNA-encoded chemical libraries relies on DNA-recorded (sometimes also referred to as DNA encoded) synthesis (18,). From a conceptual viewpoint, the simplest way to construct a library relies on the stepwise ligation of double-stranded DNA fragments, which record the identity of individual chemical building blocks. As an example, let us consider a set of 100 different organic molecules, each of which is coupled to a distinctive double-stranded DNA fragment. The set of 100 organic molecules coupled to the cognate DNA fragments can be pooled, as the DNA sequences allow an unambiguous identification of the corresponding building blocks (18,19). The resulting pool can be split into individual reaction vessels (e.g., 100 vessels), each of which is allowed to react with a new chemical moiety. The identity of each building block, which is being added to a nascent molecular structure through a suitable chemical reaction, can then be encoded in a ligation step Schematic representation of encoding strategies for DNA-recorded chemical libraries. In the simplest implementation of this technology, each building block in the synthesis procedure is encoded (i.e., identified) by a distinctive double-stranded DNA fragment. After each chemical reaction, the identity of the newly introduced building block is provided by an additional DNA fragment, which is ligated to the nascent DNA structure.

The procedure described above allows the construction of libraries with relatively short DNA bar codes, which are easy to sequence using modern high-throughput procedures. However, the encoding of n building blocks through ligation of DNA fragments requires 2n oligonucleotides, owing to the heterodimeric nature of DNA. The group of one author (D.N.). encoding procedure that makes use of a set of only n oligonucleotides for the encoding of n building blocks. Let us consider a set of 100 building blocks, each of which is coupled at the 5 ends of a corresponding oligonucleotide (e.g., through the functionalization of an appended linker terminating with a primary amine). The oligonucleotides are designed to have an identical sequence, except for a short central portion, which is distinctive for each building block and acts as bar code. The100-oligonucleotide conjugates can be purified [e.g., by high-performance liquid chromatography (HPLC)] and can be pooled, as each building block can be identified by the bar code to which it is associated. At this stage, splitting of the mixture in individual reaction vessels (e.g., 100 vessels) allows the execution of reactions with a second set of building blocks (e.g., 100 building blocks. The identity of each reaction can be recorded by annealing with a partially complementary oligonucleotide and followed by a Klenow polymerization step. The procedure can be expanded to three or more sets of building blocks by means of splint oligonucleotides and ligation procedures. An alternative way of encoding single-pharmacophore chemical libraries has been pioneered by the group of David Liu and is often referred to as DNA-templated (or DNA-directed) synthesis. In this approach, long preformed oligonucleotides are used to mediate a step wise series of annealing steps with shorter complementary oligonucleotides, carrying chemical moieties that can react with organic structures displayed on the longer oligonucleotide templates. These reaction steps may benefit from the high effective molarity advantage caused by the heterodimerization of the complementary oligonucleotides. Indeed, the Liu group has demonstrated the usefulness of DNA-templated methods for the execution of bimolecular chemical reactions, which would otherwise be inefficient in water solution and in the presence of DNA. The transfer of building blocks onto a nascent molecular structure needs to be followed by a suitable cleavage step, to allow for the next round of coupling to proceed. The procedure appears to be particularly suited for the synthesis of complex macrocyclic structures. In principle, the requirement for high-fidelity annealing between the long oligonucleotide template and the shorter complementary oligonucleotides could represent a limitation for the DNA-directed synthesis methodology. However, Xiaoyu Li and coworkers have described an ingenious optimization of the encoding method featuring the use of an oligonucleotide containing a nascent organic molecule and a polyinosine segment that serves as promiscuous hybridization stretch for short oligonucleotides, and carries transferrable chemical moieties. Two further variations of the DNA-templated synthesis method have been described. The Danish company vipergen has developed an elegant methodology, termed yoctoreactor Schematic representation of encoding strategies for DNA-templated synthesis of chemical libraries. (a) And oligonucleotide template (here depicted for the construction of a molecule based on two building blocks) is annealed with a chemically modified oligonucleotide, which transfers a chemical moiety to the nascent molecule. At the end of the coupling step, a cleavable connection is made between the building block B and the corresponding oligonucleotide (dotted line). In a modified procedure, a general template (containing poly-I stretches for annealing with various coding segments) is sequentially hybridized with oligonucleotide derivatives, which transfer building blocks onto a nascent molecule. In YoctoReactor technology, hairpin structures (containing a coding sequence and a building block) are used to mediate successive cycles of DNA ligation and of chemical reactions. Cleavable linkers are indicated with a dotted line. In DNA routing strategies, long oligonucleotides (containing multiple coding sequences) are sequentially hybridized to columns carrying complementary oligonucleotides. Individual column hybridization steps dictate which chemical reaction (i.e., which building block addition) is performed on a given nascent molecule.

Dual-Pharmacophore Chemical Libraries;

From the beginning, dual-pharmacophore chemical libraries were designed to be compatible with either microarray-based or DNA sequencing–based decoding procedures. In the simplest implementation, two sets of oligonucleotides would be used for library construction, featuring a conserved portion (essential for the self-assembly of the library) and a variable portion (distinctive for each chemical compound. The resulting ESAC libraries can be decoded using microarrays coated with sets of complementary oligonucleotides, but this procedure does not provide information about the enrichment factors of individual pairs of building blocks, since the bar codes are present in different DNA strands. A more elaborate procedure allows the unambiguous identification of pairs of building blocks in ESAC libraries (described in the section titled Decoding Strategies) and in a library that can be decoded by high-throughput DNA sequencing. In this setting, a single oligonucleotide containing a basic site is coupled to various chemical building blocks at the 3 ends, and these reactions are subsequently encoded by ligation with suitable oligonucleotide bar codes (3)

The DNA moiety that directs the assembly of chemically functionalized PNAs allows a PCR amplification Encoding strategies for dual-pharmacophore encoded chemical libraries. (a) General structure of encoded self-assembling chemical (ESAC) library members, which are decoded by hybridization onto oligonucleotide microarrays. (b) In a more powerful procedure, ESAC library members are encoded with a methodology that leads to the simultaneous presence of two codes (identifying building blocks A and B) onto one of the two complementary strands. (c) This encoding strategy is compatible with high-throughput sequencing decoding procedures. Members of the red sub library are constructed by the coupling of building blocks to a general oligonucleotide carrying ana basic site, followed by

encoding by ligation assisted by a splint degradable oligonucleotide (19).

Representative Clinical Candidates and Leads Discovered Using DEL Technology;

Selection experiments against disease-related antigens have resulted in the identification of several lead compounds, some of which later entered clinical development. In2013, GSK published the discovery of 1-(1,3,5-triazin-2-yl) piperidine 4-carboxamide inhibitors against soluble epoxide hydrolase (sEH). Subsequently lead optimization, the kinase inhibitor GSK2982772 reachedanIC50of1.3nM. At present, the compound is in phase1and phase2clinical trials for the treatment of seditious diseases, such as ulcer active colits and rheumatoid arthritis. Furthermore, the FDA recently accepted the application for theautotaxininhibitorX-165, developed by the biotech company X-Chem. The compound was discoveredfroma225million-member DEL, showing inhibitory effects in a mouse model of human lung fibrosis. Additionally, dozen so flow nanomolar leads which have not yet reached clinical trial, were discover design DEL technology Many of them include binders against tumor associated antigens and inflammatory diseases.(15) In the past decade, a collaboration between our group at ETH and the company Philo chem result ed in the development of small molecule drug conjugates(SMDCs)based on the discovery of ligands from de novo andaffinitymaturationexperiments.A99mTc-labeledde rivative of a binder that was previously discovered by affinity maturation experiments from a dual-display DEL is currently examinedina clinical phase1trialfornuclearimaginginrenal cell carcinoma patients [15,16].

Decoding strategies:

The composition of a DNA-encoded chemical library can be characterized by DNA sequencing before and after protein selections, thus providing an experimental determination of relative enrichment factors for all compounds in the library. We assume that the frequency at which a certain DNA sequence is found corresponds to the relative abundance of the corresponding DNA fragment (and hence the associated compound) in the library. Since each base can have four different possibilities (A, C, G, and T), a stretch of 10 bases can encode 410 =220 =1,048,576 different events (17). Considering the iterative nature of most library construction steps, the coding sequences that identify the individual molecules are often found in variable blocks flanked by constant sequences rather than in a single continuous stretch (differing across library members). The use of constant sequence segments facilitates PCR amplification procedures as well as the implementation of certain encoding methods. The advent of high-throughput DNA sequencing technologies (e.g., 454 technology or Illumina sequencing). It has revolutionized the field of DNA-encoded chemistry and per mitted the screening of very large compound collections. The relative abundance of compounds in a library consisting of two sets of building blocks can be depicted as a cube, in which two dimensions are used to determine the identity of pairs of building blocks and the third dimension corresponds to the relative compound frequency (i.e., to the number of times individual sequence tags are read in a high-throughput sequencing experiment). A library based on three sets of building blocks needs four dimensions to display the identity of all compounds and their relative frequencies. In most instances, spheres of different radius or colour are used to graphically represent this pseudo–four-dimensional space. The use of suitable cut-off filters in frequency counts allows the display of the most common molecules in a collection (e.g., the most enriched compounds after a selection procedure). Lines and planes of enriched compounds in libraries based on three sets of building blocks correspond to a set of molecules, for which two or one building blocks (respectively) dominate the selection procedure. It is indeed possible, as we see in the next section, that not all building blocks equally contribute to binding affinity.

Del discovery for hit compounds:

Many different chemical strategies can be considered when constructing an encoded library using multistep synthesis procedures. Some approaches have been inspired by previous combinatorial chemistry approaches, making use of DNA-friendly transformations. Compilations of chemical reactions that can be performed on DNA and are potentially compatible with library construction have been described.

Catch and cap technologies have been proposed as anavenue to achieve higher library purity, but the additional chemical steps may lead to loss in DNA quantities.

A few interesting hits, isolated from DNA-encoded chemical libraries based on two sets of building blocks, have been described. For example, Leimbacheretal. described the synthesis of a combinatorial library featuring a set of amino acids that were subsequently reacted with a set of carboxylic acids, from which specific interleukin-2 inhibitors could be isolated. In those compounds, a methyl indole derivative played a crucial role in the molecular recognition of the cytokine target. In this library and in many other applications, it was convenient to substitute the DNA moiety with a fluorophore to facilitate the determination of dissociation constants in solution using fluorescence polarization methodologies.

The GSK group has reported the isolation of phosphoinositide 3-kinase-α (PI3Kα) inhibitors (IC50 =10 nM) using a library of 3.5 million compounds assembled by the sequential reaction of 191 amino acids with an aromatic multifunctional scaffold, which was subsequently reacted with 96 boronates and 196 amines. Suzuki- and Sonogashira-coupling methodologies are particularly attractive for the formation of carbon–carbon bonds in the presence of DNA. Scientists at GSK also reported the successful isolation of potent inhibitors of the receptor interacting protein 1 (RIP1) kinase from a library of 2.6 billion compounds obtained by the sequential reaction of three sets of compounds. Interestingly, the most potent inhibitors (a set of substituted benzodiazepines) relied on the chemical structure of only the second and third building blocks, whereas the first set of building blocks could be removed without loss of inhibitory potency. This observation suggests that the same inhibitors could have been isolated from libraries based on two sets of building blocks for example, having the design.

Scientists at X-Chem have been very active in the field of DNA-encoded chemical libraries and have reported, among other results, the synthesis of a library containing >300 million compounds resulting from the sequential reaction of 2,259 primary amines, 666 bromoaryl acids, and 667 boronic acids. Fingerprints of selections performed against soluble epoxide hydrolase enabled the synthesis and confirmation of a hit with 2-nM potency and drug-like properties (molecular weight= 431 Da; cLogP=3.1).

Discovery of Covalent Inhibitors

Most applications of DNA-encoded chemical libraries relate to the isolation of noncovalent inhibitors, but the technology is also ideally suited for the discovery of covalent binders. Winssinger and colleagues used a library of 10,000 compounds, based on chemically modified PNAs and featuring suitable Michael acceptors, for the discovery of irreversible covalent binders of MEK2 (mitogen-activated protein kinase. The same group reported the use of PNA-encoded chemical libraries for the discovery of two small molecules that form a covalent bond with cysteine residues conserved across the bromodomain family (epigenetic readers that are important for the regulation of transcriptional programs.

Zimmermann Tal. have recently described the use of ESAC libraries, containing building blocks suitable for the chemical modification of protein targets, to discover a covalent inhibitor of c-Jun N-terminal kinase 1 (JNK1), a protein containing 8 cysteine residues (of which one is in close proximity to the active site). Interestingly, the covalent protein modification was highly selective compared with other kinases with cysteine residues in the active site and proceeded with 1:1 stoichiometry, even in the presence of >1,000-fold excess of glutathione, used to simulate the thiol-rich intracellular-reducing milieu.

On DNA and Off DNA Hit Validation Strategies:

DNA is an invaluable tag for the encoding and decoding of chemical libraries. However, for most applications, it is desirable to use chemical compounds in the absence of DNA. In many cases, the confirmation of hits from library selections proceeds through the resynthesis of the most enriched compounds off-DNA followed by a characterization of their binding proper ties using biochemical or biophysical assays. However, the synthesis and purification of organic molecules can be labor intensive, depending on the structure of the compounds and the number of hits that need to be measured. Furthermore, when the target is not amenable to biochemical characterization (e.g., using an enzyme inhibition assay), it can be difficult to measure binding affinities in the absence of a suitable tag. Surface plasmon resonance methodologies (e.g., BIAcore) may be complex toper form with proteins that lose activity upon immobilization on a solid support or during microsensor chip regeneration procedures. Isothermal titration calorimetry may allow the determination of dissociation constants in solution, but the procedure poses certain requirements on the availability, buffer composition, and solubility for both binding partners. For these reasons, it is often convenient to resynthesize hit compounds with a fluorophore moiety, at the position originally occupied by the DNA tag, and toper form fluorescence polarization measurements in solution. In an initial phase of the hit validation process, it is practical to resynthesize com pounds on-DNA. Zimmermann and colleagues have recently described a general andversatile methodology based on the hybridization of oligonucleotide conjugates with complementary strands, labeled with a suitable fluorophore and/or additional chemical moieties. The technology benefits from the fact that on-DNA synthesis procedures are available from the previously performed library construction steps. Furthermore, oligonucleotides facilitate the purification of the conjugates and their analytical characterization by mass spectrometry while also contributing to the solubilization of lipophilic molecules.

Del genaration with edisigner:

For the generation of chemical space of DELs, the eDESIGNER14 tool was used. At first, based on the list of the most efficient DNA-compatible reactions encoded in the tool (see Supporting Information of respective article14) and a user-provided list of BBs, it generates a special set of instructions for DEL compound enumeration called lib DESIGNs. Each lib DESIGN contains information about the starting headpiece (the whole DNA part for computational convenience is formally represented as a 13C atom), the reaction types, and BBs which will be used in them, as well as deprotection reactions for the final stage of DEL generation. There are also several restrictions that can be applied to control some of the properties of the resulting DEL. They include, for example, the maximum and the median value of heavy atom count in the generated molecules, minimum library size, etc. Once the lib DESIGNs are created, the representative DELs subsets of the selected size can be enumerated by the Lilly Mol tool.23 An example of such enumeration. The isotopic mark on the carbon atom specifies the place of attachment of the DNA tag. For clarity reasons, before physicochemical properties calculation and GTM analysis, the 13C atom is removed, therewith obtaining the compound that would have been resynthesized off-DNA for validation in case of being selected during a real screening campaign.

Genarative Tropographic Mapping (GTM):

In the chemical space molecules are represented as data points, with their position being defined by a vector of numerical values called descriptors. The main idea of GTM16 consists in inserting a flexible hypersurface called manifold into the high dimensional descriptor space with a subsequent projection of these data points into a 2D latent space grid.

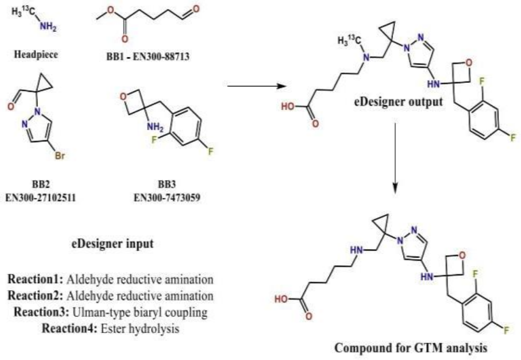

Fig.1 Example of DEL compound generation by eDesigner. The user should provide headpiece and the list of BBs; an appropriate list of reactions will be selected automatically by eDesigner, and respective compounds are generated. The isotopic mark is placed by eDesigner in order to know the position of DNA attachment and is removed prior to GTM analysis and physicochemical properties.

Conclusions:

Using eDesigner, the chemical space of DNA-encoded libraries (DELs) with a total of 2.5 billion compounds

(2.5K libraries, 1M each) was created and generated. GTM was then used to evaluate the data. It was feasible to create a GTM-based method for the rapid selection of DELs occupying the same regions of the chemical space as a reference library because of the probabilistic nature of GTM and the effectiveness of the libraries' analysis and comparison based on the responsibility patterns. Finding the "golden" or "platinum" pool of DELs for primary screening—that is, the libraries with the largest percentage of physiologically significant chemotypes—was the aim of this investigation. So, the best representation of biologically relevant space was provided by ChEMBL, the largest database of dose-response activity assays. Nonetheless, the method presented here might be used with any reference library, for example, actives of a specific biological target.

Author contributions

All authors are contributed equally.

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Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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