Organizers’ Welcome

The practice of encoded library synthesis and screening continues to evolve with increased numbers of practitioners as well as reported successes and innovations. Our guiding intent for this meeting has been to assemble in the Boston area world experts and passionate followers of encoded library based platforms to share in a day of presentations, posters and discussions of this fastmoving field of science. Based on the success of the First Boston Symposium of Encoded Library Platforms as well as the enduring success of the International Symposium on DNA-Encoded Chemical Libraries in Zürich, we were confident of a good response for this meeting. Indeed, attendance has grown from approximately 150 participants in 2015 to more than 200 today. We have arranged for industrial and academic speakers addressing themes that highlight recent developments in chemistry, selection biology, informatics and new applications of encoded library platform technologies. We are pleased to organize this meeting around eight world expert speakers and twenty-two posters. We are grateful for the generosity of several sponsors who make this meeting more comfortable with the funding of food and refreshments. We hope this symposium will enhance common understanding of the latest developments of this technology and its application in drug discovery, and connect scientists for knowledge sharing and possible collaborations.

Sincerely meeting organizers,

Christopher P. Davie
GlaxoSmithKline, Waltham MA

Robert Goodnow, Jr.
Pharmaron, Boston

Isaac Krauss
Brandeis University, Waltham MA

Ninad Prabhu
GlaxoSmithKline, Waltham MA

Letian Kuai
GlaxoSmithKline, Waltham MA
Many Thanks to Our Generous Sponsors

Brandeis University is gratefully acknowledged for the use of the Shapiro Campus Center, as is Brandeis Chemistry, for logistical and financial assistance. Food and drink are provided based on the financial contributions of the following organizations.

DECLTech

LGC BIOSEARCH TECHNOLOGIES

X-CHÊM PHARMACEUTICALS

Tyger

Acknowledgements for Meeting Logistics

The following faculty, staff and students of Brandeis University have been very helpful for organizing various aspects of this meeting:

Professor Barry Snider, Anna Esposito, Courtney Maurer, Meghan Hennelly, Robert Steinberg, Mary Jasset, Elizabeth Atwood, the Krauss Group.
# Symposium Agenda

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<td>Break, poster session, and networking – Atrium</td>
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<td>Vitamin C can also be Good for Reactions. Development of a Mild and Practical N-arylation for DNA-Encoded Libraries</td>
<td>Yves Ruff, Novartis</td>
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<td>5:15 – 5:30</td>
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<td>5:30 – 6:30</td>
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<td>All invited</td>
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Speaker Abstracts and Biography

Isaac J. Krauss
Directed evolution of DNA- and RNA-supported carbohydrate clusters

Dr. Isaac J. Krauss
Associate Professor
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Waltham, MA USA
kraussi@brandeis.edu

In this presentation, we will discuss the development of SELMA (SELection of Modified Aptamers) for selection of functional nucleic acids bearing large modifications, such as oligosaccharides. In particular, we have utilized SELMA to obtain carbohydrate-decorated aptamers, in which the nucleic acid portion is able to present glycans in a multivalent configuration that mimics a broadly-neutralizing HIV epitope. Glycan cluster mimics of the HIV gp120 glycoprotein surface are of interest as potential HIV vaccine candidates.

Isaac Krauss grew up in Fairbanks, Alaska and attended college at Stanford University, where he did research on π-allyl chemistry with Prof. Barry Trost. He then moved to the New York City to attend the Ph. D. program in chemistry at Columbia University, where he worked in Jim Leighton’s group on the development of ligands for stereoselective hydroformylation and conjugate addition reactions. He then did a postdoc in the lab of Sam Danishefsky at Memorial Sloan-Kettering Cancer Center, working on the synthesis of carbohydrate vaccines and natural products with cell migration inhibitory properties. He began his independent career at Brandeis in 2008, where he became interested in directed evolution as a means to design carbohydrate vaccines against HIV. His research program now spans organic synthesis and chemical glycobiology.
Identification and prioritization of chemically tractable therapeutic targets remains a major challenge in early drug discovery process. Herein we present the use of DNA-encoded library technology (ELT) that allows for rapid and efficient screening of targets not only to prioritize targets of interest but also to reduce early attrition in early drug discovery. In tackling this challenge, we screened 100 antibacterial targets from *A. baumannii* and *S. aureus* in parallel to prioritize the proteins by chemical tractability. The success of this program led to the hypothesis that ELT selection signal alone could be used to assess the ligandability of large sets of target proteins. A comparison of ELT selection outcome with past HTS screens for several of these targets revealed that this new tractability concept would have predicted HTS outcome >70% of the time. This target tractability assessment paradigm was further evaluated through screening 42 targets from *M. tuberculosis*. In this presentation, we will highlight the need for understanding chemical tractability along with the experimental data for large panels of target proteins prioritized using ELT selections to support the conclusion that ELT allows for target prioritization, improved decision making and resource allocation.

Ghotas is a site manager and chemistry group leader in the DNA encoded library technology (ELT) division of GlaxoSmithKline (GSK) in Waltham, Massachusetts. He was born and raised in Kurdistan mountains before migrating to Canada. He completed his undergraduate and MSc degrees at the University of Waterloo, concentrating on synthesis and structure-activity studies of antifungal natural products aureobasidins. He then joined Vertex Pharmaceuticals, in Boston, as a medicinal chemist. While at Vertex, he was instrumental in the success of P38 MAP Kinase (first and second generation), ICE-1 inhibitors (second generation), and early ZAP-70 programs. These efforts led to discovery of four clinical candidates, VX-745, VX-765, VX-954 and VX-702. After 4 years at Vertex, he then moved to the University of Toronto to pursue a PhD degree in organic chemistry with focus on “Novel Approaches to Synthesis of Nitrogen Containing Heterocycles”. After completing his PhD he moved back to Boston to join Praecis Pharmaceuticals as a staff scientist to lead the medicinal chemistry sphingosine-1-phosphate (S1P) receptor agonist discovery program. His team’s efforts led to candidate selection of GSK1842799A that was transitioned into GSK as part of Praecis acquisition in 2007. He has worked on DNA encoded library technology from the inception of the platform and has led different group activities within the platform over the past 14 years. Ghotas has authored well 40 publications and patents in the area of drug discovery and platform development over the last 20 years.
The *in vitro* selection of encoded molecule populations allows a collective assessment of function for many molecules simultaneously. This has several advantages over typical laboratory assays, such as improved throughput and dramatically lower cost. This presentation will focus on a new approach, which we call selection-based sensing, that extends use of the *in vitro* selection to assessing function of samples not just encoded molecules. Selection-based sensing encodes sample stimuli information within populations of DNA sequences via the exposure and selection of DNA-linked synthetic probes. Inspired by natural selection-driven evolution, the signal for these assays is DNA allele frequency change within a population in response to selection. Probes have been designed for detection of enzymatic activities and allow activity detection by DNA sequence analysis (qPCR or DNA sequencing). Probes are composed of enzyme substrates or covalently-labeling, activity based probes (ABPs) linked to encoding DNAs. We describe the development of this approach and present its application in proteomic activity detection and in the screening of conventional (off-DNA) small molecule libraries by DNA analysis.
Peter Dandliker
“Small Molecule Affinity Selection at Merck”

Peter Dandliker, Ph.D.
Director - Pharmacology
Merck Research Laboratories
Boston MA, USA
peter.dandliker@merck.com

Affinity selection mass spectrometry (ASMS) is a general, high-throughput method to select and identify small molecule ligands from complex compound mixtures. Merck has advanced a specific ASMS approach termed ALIS (Automated Ligand Identification System), a two-dimensional LC/MS system in line with high-resolution mass spectrometry, to routinely assess one million compound / target encounters per day. This high throughput capability, while traditionally employed for small molecule hit identification, has been recently adapted to deconvolute molecular targets of phenotypically active compounds of unknown mechanism, in an approach termed Protein Array ALIS (PA-ALIS), and to quantitatively rank order the binding affinity of medicinal chemistry analogs in complex mixtures (Protein Titration or PT-ALIS). The PT-ALIS method, when combined with nanoscale parallel or mixture synthesis permits identification of analogs most likely to exhibit potent functional activity starting from very small quantities of material and without need for compound purification prior to biological assay. An introduction to ALIS and the novel application to medicinal chemistry and target identification will be presented.

Dr. Dandliker leads the MSD ALIS affinity screening group, located in Boston. In 20 years of pharmaceutical discovery research, Peter has held a range of leadership roles at the chemistry / biology interface, establishing teams dedicated to hit-to-lead medicinal chemistry and biology, high-throughput ADME, and founding a research lab on behalf of a western pharma company in Shanghai. He enjoys purposeful technical innovation in the areas of target & lead discovery, pharmacological characterization, and chemical optimization, and applying those new capabilities to discovery programs. He holds a Ph.D. in organic chemistry from UCLA and performed his postdoctoral work at the California Institute of Technology.
The NIH Molecular Libraries Program (MLP) was founded to translate the discoveries of the Human Genome Project into therapeutics through a network of high-throughput screening (HTS) centers. A decade of discovery produced hundreds of probes — highly selective small molecules that modulate cellular function — but centralized compound screening bears the same cost and infrastructure burdens of millennial DNA sequencing centers, which has limited access to the technology and, more significantly, the rate of small molecule discovery. We are building a distributable drug discovery platform analogous to next-generation DNA sequencing. We have adapted DNA-encoded library synthesis strategies to solid phase, yielding ultra-miniaturized compound libraries of microscopic beads each displaying many copies of a small molecule library member and a corresponding amplifiable DNA encoding its structure. In parallel, we have engineered microfluidic integrated circuits that load individual compound library beads into picoliter-scale droplets of assay reagent, photochemically cleave the compound from the bead into the droplet in a UV dose-dependent fashion (0.01–10 μM compound), incubate the dosed droplets, detect activity using laser-induced confocal fluorescence, and sort hit-containing droplets for PCR amplification and high-throughput sequencing. To demonstrate the feasibility of the platform, we synthesized a modest (~50k-member) DNA-encoded library of protease inhibitors and developed droplet-scale biochemical assays of HIV-1 protease, ZIKV NS2B-NS3 protease, and cathepsin D. This presentation will discuss our discovery and optimization of hits from these screens, the development of laser-induced fluorescence polarization assay detection, novel droplet incubation circuit architectures, and mechanism-based rapid assay development as a suite of new applications for DNA-encoded library technology.

Brian M. Paegel is associate professor in the Department of Chemistry at The Scripps Research Institute. He is interested in the assembly of cell-like compartments and the unique chemistry and biology that can be conducted in their confines. He studies cellular membrane assembly, evolution of new proteases for mass spectrometry-based proteomics, DNA-encoded compound library design and synthesis, and ultra-miniaturized compound screening toward distributed drug discovery. Paegel earned his undergraduate degree in chemistry from Duke University and his doctoral degree in chemistry from UC Berkeley as a student of Richard Mathies. He pursued postdoctoral studies in chemical biology and molecular evolution under the mentorship of Gerald Joyce at The Scripps Research Institute, where he was the recipient of both a NIH National Research Service Award and a Pathway to Independence Award. In 2008 he was appointed to the chemistry faculty and relocated to TSRI’s new east coast campus in South Florida where he received a NIH Director’s New Innovator award and a NSF CAREER award for his work in directed evolution and membrane assembly.
John P. Guilinger
X-Chem’s development of DNA-encoded libraries and selection methodology for identifying irreversible covalent inhibitors

Dr. John P. Guilinger
Senior Research Scientist, Lead Discovery
X-Chem Pharmaceuticals
Waltham, MA USA
jguilinger@x-chemrx.com

X-Chem’s proprietary DNA-encoded library of >100 billion compounds and selection platform has generated novel lead compounds to some of the most difficult and intractable therapeutic targets with thirty-four programs licensed to collaboration partners. X-Chem continues to advance and enhance its drug discovery capability and technology for discovery of novel small-molecule therapeutics. One example of X-Chem’s technology advancements is the development of irreversible covalent libraries and selection techniques to uncover lead compounds with covalent mechanisms of action.

John is from Boulder, CO and received his BS/MS from Brandeis University and PhD in Molecular Biology from Harvard University. In Dr. David Liu’s group at Harvard, he developed and applied high-throughput sequencing based selections to profile and improve the specificity of multiple types of genome-editing technologies. Joining X-Chem in 2014, he has supported and led collaborative projects resulting in discovery of multiple lead compounds to a variety of therapeutic targets. He has also been a principle contributor in advancing X-Chem’s technology to uncover inhibitors with irreversible mechanisms of action.
DNA-encoded libraries are used in a powerful form of affinity selection that enables screening of small/medium molecules. It is an exciting time for this technology, as candidate molecules identified using this method are entering clinical trials. Here we show that libraries can be freed from their DNA tags by converting that encoding to a spatial array and cleaving the DNA. This is accomplished by: 1) Preparing a one-bead-one-compound library; 2) Immobilizing beads on a silica chip; 3) Using next generation sequencing-based techniques to read the sequence of DNA on each bead; 4) Removing the DNA bar codes; 5) screening against targets of interest.

Transforming DECLS in this fashion results in several advantages. On the synthetic side, the fact that the DNA is eventually removed allows for the use of standard protecting groups that require acidic deprotection and the opportunity for one final non-DNA compatible reaction. The ability to interrogate large numbers of compounds at each step in library synthesis also allows for quality control checks on synthetic efficiency. On the screening side, multiple conditions can be tested against the same compound collection and collections as large as 1 billion compounds can be screened in one day on a given system. Moreover, targets that interact with DNA can be screened and since binding information is collected for every compound, we expect SAR will be enhanced.

Jacob grew up in Wayland, just down the road from the meeting site, and his dad actually worked at Brandeis for many years. Jacob received his bachelor’s degree, magna cum laude, in chemistry from Harvard University where he worked in the Jacobsen lab. He received his Ph.D. from the California Institute of Technology where he worked with Bob Grubbs. He did a postdoc with Greg Fu at MIT. In all three cases, he worked on enantioselective catalysis. He then shifted fields to the use of nanomaterials for health applications during a postdoc at Rice University with James Tour.

Jacob joined the Department of Molecular Medicine, Beckman Research Institute of City of Hope (Duarte, CA) in 2010 as an Assistant Professor and he was promoted to Associate Professor in 2016. His group’s work on using nanoparticles to detect and treat cancer has been featured on the covers of several journals, including Advanced Healthcare Materials and Bioconjugate Chemistry. Jacob was noted as one of the “Rising Stars and Young Nanoarchitects in Materials Science” by the Royal Society of Chemistry and was nominated for the Kabiller Young Investigator Award in Nanoscience and Nanomedicine. In 2011, he teamed up with Greg Copeland to develop the DNA-Free DNA-encoded library screening platform described above.
**Yves Ruff**  
*Vitamin C can also be good for reactions. Development of a mild and practical N-arylation for DNA encoded libraries*

Dr. Yves Ruff  
NIBR Postdoctoral researcher  
Novartis Institutes For Biomedical Research, Global Discovery Chemistry  
Basel, Switzerland  
yves.ruff@novartis.com

DNA Encoded Libraries (DELS) consist in a collection of hundreds of millions to billions of synthetic small molecules each conjugated to a unique DNA sequence, or DNA tag. These vast collections of synthetic compounds can be screened in mixtures for binding to immobilized proteins by selection processes, making them an attractive tool for the discovery of ligands for pharmaceutical targets. To build these libraries, synthetic small molecules have to be constructed directly on DNA. Therefore, DEL synthesis rests on the development of novel methodologies for the formation of covalent chemical bonds under mild conditions that are compatible with the solubility and stability of the nucleic acid tags. This requires adapting standard organic chemistry protocols in order to go from single reaction under controlled atmosphere in organic solvents, towards hundreds if not thousands of parallel small-scale reactions under mild aqueous conditions. In particular, transition metal catalyzed N-arylation reactions are one of the most used transformations in medicinal chemistry, and are not yet described for the preparation of DNA encoded libraries. In this context, we describe the development of effective and practical protocols for the copper and palladium catalyzed N-arylation of amines on synthetic DNA conjugates. By parallel screening of known and newly synthesized ligands at the nanomole scale, we have identified three unprecedented and complementary catalytic systems for the N-arylation of DNA encoded aryl iodides. All of these reactions extend our ability to design new library setups, and give us access to new sets of building blocks that are relevant for medicinal chemistry.

Yves graduated from the University of Strasbourg (France) where he conducted his PhD under the supervision of Professor Jean-Marie Lehn on dynamic combinatorial chemistry and its application to the preparation of dynamic polymers analogs of polysaccharides. He then joined the Stupp laboratory in Northwestern University (Chicago, IL) to develop new ways to generate artificial viruses using the controlled self-assembly of peptides and DNA molecules. Yves then joined the laboratory of Prof. Nicolas Giuseppone in Strasbourg with a European Marie Curie Career Integration grant to develop an unprecedented methodology to make peptide bonds reversible under physiological conditions. Since 2014, Yves is part of the Hit Generation Sciences group in NIBR to develop new methodologies for DNA encoded libraries (DELS), and in particular new chemical transformations for DELs synthesis.
Post #1 Comparative analysis of target immobilization methods and their influence on enrichment levels in DNA-encoded chemical library affinity selections

Moreno Wichert\textsuperscript{1}, Ann Petersen\textsuperscript{1}, Dominique Burger\textsuperscript{1}, Felix Gruber\textsuperscript{1}, Jianping Cai\textsuperscript{1}, Quentin Strebel\textsuperscript{1}, Oliv Eidam\textsuperscript{1}, Daniel Schlatter\textsuperscript{1}, and Alex Satz\textsuperscript{1}

\textsuperscript{1}Roche Pharma Research and Early Development, Roche Innovation Center, Basel, Switzerland

DNA-encoded chemical library technology has developed to a valuable screening tool for hit or lead identification in the drug discovery process. Different methods for affinity-based selections using DNA-encoded chemical libraries have been reported. In this article, we describe and compare different target immobilization techniques on solid support and their influence on enrichment levels. In our selection protocol, the encoded libraries and the tagged target of interest is incubated in solution, and the formed complexes are then captured on resin in pipet tips. Various stringent washing steps remove non-binding library members, whereas binding molecules are removed from the target at the final elution step, amplified by PCR and identified by high-throughput DNA sequencing. We further show how we routinely assess the degree of target immobilization on solid support upfront selection by quantitative HPLC analysis. Finally, we highlight important criteria for protein characterization and qualification for the successful use in DNA-encoded library selections.
Library design has been an important part of DNA-encoded library technology (DEL). Efficiency of the design depends on chemical building blocks (BBs) utilized to assemble the library. Therefore, availability of novel diverse BBs with high reactivity and specific structural features, i.e. small size, not lipophilic, and 3D shape, is of importance to succeed in producing high quality DELs. This is especially critical while selecting core BBs with two or three orthogonal functions complied with DEL chemistry. Indeed, these polyfunctional BBs have been underrepresented on the market thus requiring approaches to make them synthetically and economically accessible.

For more than 25 years, we have been working on synthesis of BBs, intermediates, and screening compound libraries accumulating the knowledge of manual and parallel synthetic chemistry. We applied this knowledge to the inventory of BB’s that allowed to generate a set of polyfunctional BBs on a multimilligram-to-gram scale readily accessed via validated synthetic approaches, i.e., alkylation, arylation, protective group addition. Novelty, exclusivity and favorable physicochemical profiles of starting reagents support production of high quality core BBs.
Attachment of molecules to DNA bound to the solid support is an attractive small-molecule conjugation method that permits the use of organic solvents, rigorous reaction conditions, and simple workup. However, the conjugated structures must be resistant to the harsh DNA deprotection/cleavage conditions and the stabilities of building blocks under various deprotection conditions are mostly unexplored. Amide structures are ubiquitous in the construction of DNA-encoded chemical library, yet the stability of most of these compounds under the deprotection/cleavage conditions are mostly unexplored. In the present study, we analyzed the stability of 131 structurally diverse fragments that contain amides and amide-like elements during DNA deprotection protocols. Structural features susceptible to decomposition in DNA deprotection conditions were identified and a protocol that enabled the synthesis of DNA conjugates with labile fragments on solid support was identified.
Post #4 Application of DNA Programmed Combinatorial Chemistry to Discovery of Affinity Ligands for Proteins

Laila Dafik, Bobby O’Brien, Alex Shulman, Oliver Zahn and Pat Brown

Impossible, 525 Chesapeake Drive, Redwood City, CA 94063, United States.

Many natural sources, such as extracts from plants or microbes, contain a diversity of potentially valuable proteins and small molecules, but to date there has been no general, scalable way to purify multiple high-value components from such a complex source. Directed evolution of large combinatorial chemistry libraries is an emerging approach for identifying small molecules with desirable properties. We used a DNA programmed combinatorial chemistry technique to identify novel pH-regulated affinity reagents for isolation and purification of selected protein targets from a crude extract. Multiple selections were carried out in parallel by assigning DNA barcodes to each of the parallel selections. We applied a purifying selection to a naive DNA-programmed library comprising over a hundred million distinct compounds. The identities of the molecules that satisfied each selection condition were determined by high-throughput sequencing. We used this method to identify novel pH-regulated affinity reagents for purification of high-value proteins from a crude extract. DNA programmed combinatorial chemistry techniques can substantially increase global access to small-molecule reagents for efficiently isolating the many high-value molecular components commonly found in abundant natural materials.
BINDING AFFINITY MEASUREMENT OF COMPOUNDS IN MIXTURES USING AFFINITY SELECTION – MASS SPECTROMETRY


GlaxoSmithKline, NCE Waltham, 830 Winter Street, Waltham, Massachusetts, USA 02451

Affinity selection-mass spectrometry (AS-MS) techniques directly identify protein-bound components from complex mixtures, making it possible to simultaneously evaluate multiple ligands from compound mixtures/libraries. AS-MS has been developed and applied in early stage drug discovery by the pharmaceutical industry. Here, we describe application of AS-MS in early stage drug discovery at GSK Boston site.

Encoded Library Technology (ELT) is an affinity-based selection system that utilizes large combinatorial libraries of small molecule warheads encoded by a unique combination of DNA tags. Binders to a molecular target are then selected from library pools and sequenced using next generation DNA sequencing. The raw sequencing data is then translated to count the unique warheads and grouped by families based on shared building blocks. Exemplar compounds from families of binders are synthesized off-DNA to confirm their binding and activity.

We present a case study focused on screening potent inhibitors of SIRT1/2/3. These pan SIRT1/2/3 inhibitors, representing a novel chemotype, are significantly more potent than currently available inhibitors. The combination of ELT and ASMS was a valuable tool for understanding the binding affinity and activity of these molecules and determining whether compounds discovered through ELT selections bind to the target protein. Following the first round of AS-MS experiments on the test compounds in which TRUE/FALSE binders are determined, we have developed a mixture based competition ASMS method to rank the TRUE binders. The affinity competition experiment 50% inhibitory concentration (ACE50 value) of the binding curves generated with this method are used to rank the relative potencies of the compounds. Providing relative ranking data to ELT post selection chemistry (PSC) chemists would potentially allow them to prioritize which chemotypes to further pursue.
DyNAbind GmbH/Technische Universität Dresden

DyNAbind GmbH is a start-up company which spun out from the TU Dresden. Our focus is on reshaping the core DNA-Encoded Library workflow in order to expand the scope, reliability and speed of the process while enabling the use of a fragment-based discovery approach. We have developed three key innovations: Dynamic Chemical Libraries, DNA encoding and rapid selection benchmarking with our Path-Coding Algorithm, and automated fully kinetic hit validation with our Binding Profiler system.

Dynamic DNA-Encoded Libraries (D-DELS) are dual pharmacophore libraries built up on a novel Y-shaped DNA architecture. The universally complementary annealing region is designed to be intrinsically unstable in selection conditions, constantly reshuffling the fragment pairs in solution. The pairs are stabilized upon binding to the target protein. The D-DEL approach improves the signal-to-noise ratio in selection, producing fewer, but more reliable hits compared to a traditional single pharmacophore or static dual-pharmacophore library. Moreover, our dual display of small molecule fragments allowed an in-situ affinity maturation, resulting in new pairs of supporting binders which increased affinity.

The Path-Coding Algorithm developed by our team represents a new approach to encoding library members. We generate longer codes to take advantage of the large information space present. The algorithm generates highly diverse codes which are compliant with specific relationships between adjacent bases. This confers the codes with two special properties. The first is a degree of built-in error proofing, which allows the algorithm to detect impossible reads, and attempt to correct them based on the information contained in neighbouring bases. The second is the possibility of diversity analysis via qPCR. We have prepared a qPCR calibration which presents information on the diversity of the DNA pool amplified. This allows us to benchmark selection quality (degree of enrichment and signal-to-noise ratio) and rapidly determine optimum selection conditions. Moreover, specific primers can be used to verify the presence of known binding molecules.

Our third innovation is the Binding Profiler system for hit validation. This system is based on modifying a biosensor surface with a universally conserved DNA segment, loading on detected hit compound pairs, measuring kinetic behavior (Kd, k_on, k_off) against the target, and then regenerating the DNA-functionalized surface for the next round of binders. The system offers a high degree of automation, with over 300 reads per day achieved, and requires no chemical resynthesis of hit compounds off-DNA. Moreover, the Binding Profiler allows dual pharmacophore hits to be quickly validated before chemical efforts must be put into optimizing the linkage between the compounds.

Here these innovations are demonstrated in a selection and validation campaign run against human Carbonic Anhydrase II with a fragment-based DNA-Encoded Library consisting of ~100,000 members.
The evolution of sequence-defined synthetic polymers made of building blocks beyond those compatible with polymerase enzymes or the ribosome has the potential to generate new classes of receptors, catalysts, and materials. We used a ligase-mediated DNA-templated polymerization system and \textit{in vitro} selection to evolve highly functionalized nucleic acid polymers (HFNAPs) made from 32 building blocks containing eight chemically diverse side-chains on a DNA backbone. Through iterated cycles of polymer translation, selection, and reverse translation, we discovered HFNAPs that bind PCSK9 and IL-6, two protein targets implicated in human diseases. Mutation and reselection of an active PCSK9-binding polymer yielded evolved polymers with high affinity ($K_D = 3$ nM). This evolved polymer potently inhibited binding between PCSK9 and the LDL receptor. Structure-activity relationship studies revealed that specific side-chains at defined positions in the polymers are required for binding to their respective targets. Our findings expand the chemical space of evolvable polymers to include densely functionalized nucleic acids with diverse, researcher-defined chemical repertoires.
Post #8  Development of an ELT Selection Method for Irreversible Inhibitors

Zhengrong Zhu
GlaxoSmithKline, NCE Waltham, 830 Winter Street, Waltham, Massachusetts, USA 02451

Traditionally drug discovery has been focused on reversible inhibitors; however, irreversible inhibitor may offer advantages for some therapeutic targets. High biochemical efficiency of irreversible inhibitors may translate into lower dose and reduced off-target effects. Uncoupling pharmacokinetics and pharmacodynamics and prolonging duration of action by irreversible inhibitors may result in less-frequent drug dosing. So it is not surprising many approved drugs are irreversible inhibitors. Encoded library technology (ELT) is a powerful technology platform for identifying small molecule compounds that bind protein targets using DNA tagged combinatorial libraries. Standard ELT selection process is very effective in finding reversible inhibitors but may not be so for irreversible inhibitors. In this project we used tool compounds with DNA tag to develop a new ELT selection method for irreversible inhibitors. ELT selection conditions were optimized for this new method. The new method was validated by identifying tool compounds that were spiked in an ELT compound library at the same concentration of individual compound in the library. This new method of ELT selection will offer an enabling tool for drug discovery targets that may be undruggable for reversible inhibitors.
Technology-enabled synthesis of unique building blocks for DNA-encoded libraries

Balazs Gyimóthy, Krisztián Niesz

ComInnex Inc., Zahony u. 7., 1031 Budapest, Hungary

Over the last few years there has been increasing intention to improve the physical chemical properties (e.g. logP, logD and solubility) of test molecules developed in early phase drug discovery. Several recent publications have described that increasing the sp3 character of N-containing heterocyclic compounds significantly improves such physical chemical properties. Thus, the need for the rational design and synthesis of 3D compounds -instead of purely aromatic and flat ones- is growing rapidly.

High fsp3 templates could easily be generated via partial hydrogenation of aromatic compounds. ComInnex, using its long-standing knowledge and experience in the fields of both reduction and synthesis of aromatic molecules, has developed a platform using its internal cheminformatics infrastructure together with state-of-the-art flow technology instrumentation to design unique and diverse compounds, including bi- and trifunctional building blocks used for building DNA-encoded libraries.
Discovery of small molecule protease-activated receptor 2 (PAR2) antagonists and agonists using DNA-encoded library (DEL) screening technologies

Dean G. Brown,1 Andrew Ferguson,1 Hongming Chen,2 Linda Sundström,2 Stefan Geschwinder,2 Arjan Snijder,2 Maria Saxin,2 Jing Zhang,1 Ye Wu,1 Holly Souter,3 Dawn Troast,3 Christoph Dumelin,3 Giles A. Brown,4 Robert K.Y. Cheng,4 Cedric Fiez-Vandal,4 Oliver Schlenker,4 Robert Cooke,4 Rudi Prihandoko,4 Benjamin Tehan,4 Giselle Wiggin,4 Andrei Zhukov,4 Miles S. Congreve,4 Barry Teobald,4 Shawn Johnstone,5 Qingqi Liu,6 Wenzhen Yang,6 Rongfeng Chen6 Roland Burli,1 and Niek Dekker2

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PAR2 is a G-protein coupled receptor (GPCR) known to mediate inflammatory pathways and is implicated in several diseases such as pain, airway inflammation, and skin disorders. We report a novel series of antagonists discovered by DEL screening of purified and stabilized PAR2. Optimization of this series resulted in potent and selective compounds which demonstrated antagonism across a range of PAR2 cellular models. The crystal structure of the stabilized receptor in complex with a member of this series revealed an allosteric binding mode at the surface of the receptor within the hydrophobic membrane spanning region. In addition, another series was identified by DEL screening of an unknown binding mode. Chemical expansion of this series resulted in potent and selective agonists of PAR2. Thus, DEL screening in combination with GPCR stabilization technology and crystallography, has led to novel antagonists and agonists of PAR2. These compounds have proven to be useful tools in helping to understand the complex pharmacology of this receptor.
Screening miniaturization using solid-phase DNA-encoded libraries

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DNA-encoded libraries provide an efficient and vast source of diversity for screening and are often deployed against targets that are unsuited for, or have failed to produce ligands using traditional HTS style screens. We have demonstrated the synthesis of 2 unique one-bead-one-compound (OBOC) DNA-encoded solid-phase libraries for the discovery of ligands via multiple screening strategies. A low-diversity (29k member) HIV-1 protease inhibitor library, composed of variations on known FDA-approved inhibitor themes, was designed to screen for inhibitors of 6 drug resistant HIV-1 protease mutants in order to generate pan-library structure activity relationship profiles against a rapidly mutating viral target. A serum-antibody binding library, designed to mimic unknown antigens, featured much larger diversity (500k members) and benefited from truncations and reaction side-products to further increase library diversity. DNA-encoded solid-phase libraries were then either screened for target-binding to beads by FACS (serum screening) or for modulation of enzymatic activity using functional assays (HIV-1 protease) in microfluidic droplets. The hit beads were collected in each case, the DNA encoding tags amplified in PCR, and the resulting amplicons were sequenced in bulk. The next-generation sequencing output was used to elucidate hit structures and prioritize hits for resynthesis based on homology and redundancy. DNA-encoded solid-phase combinatorial libraries and miniaturizing high-throughput screening (by microfluidics or FACS) provides a distributable and economical platform for small molecule discovery and facilitates efficient exploration of unconventional targets and chemical spaces.
Post #12  Directed evolution of DNA and RNA supported carbohydrate clusters

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At the center of the HIV vaccine research efforts lay a class of broadly neutralizing antibodies (bNAbs), e.g. 2G12 and PGT128, that block viral fusion to the host cell by binding to 2-4 N-linked Man₉(GlcNAc)₂ carbohydrates on the HIV envelope spike protein gp120. SELMA (SELection with Modified Aptamers) is a directed evolution technique used to discover glycosylated-DNA aptamers with the specific goal of studying the HIV envelope glycoprotein gp120 and the carbohydrate-binding antibodies that have been discovered to bind the ‘glycan shield’ of gp120. Our high temperature application of SELMA using synthetic high mannose carbohydrates has been successful in identifying glycosylated aptamers that bind to 2G12 with low nanomolar Kds, similar to the known 2G12-gp120 binding. We are working to expand our DNA-based method to study other broadly neutralizing HIV antibodies. We have also developed a carbohydrate-modified RNA scaffold display technology with the goal of developing structures which might be useful as vaccines to elicit broadly-neutralizing antibodies.
It has been observed that individual targets have distinct patterns of ELT binders. These ELT binding patterns could, potentially, be used as a poly-ligand based tool for identification of individual targets. We hypothesized that ELT with its billions of DNA-encoded probes, can also be used as a tool to describe more complex systems, like cells, that are expressing multiple targets. The project set out to investigate the feasibility of profiling human cells with ELT molecules. We first assessed whether ELT could identify a consistent profile of cell ELT binders (descriptors) across different cell lines. In parallel, we developed a new analytical method, adapting an established method from the RNA sequencing field to our needs. By running cell-based ELT selections in multiple replicates and applying the new analytical method, we were able to reproducibly identify differential ELT descriptors for 5 tested human cell lines: Ramos, Raji, Daudi, K562 and Molt4. The Molt4 or Ramos cell-specific descriptors were synthesized on-DNA and tested for binding in cell-based selections. These selections confirmed that re-synthesized on-DNA descriptors do preferentially bind either Molt4 or Ramos in correlation with original selections. Given the current progress of the technology development, we envision the possibility of utilizing ELT profiling in areas such as target/off-target engagement, monitoring changes of cells in manufacturing process, and identification of potential biomarkers.
DNA-free DNA Encoded Libraries

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DNA-Encoded Library based drug discovery can be drastically enhanced with a spatial encoding platform enabling removal of the DNA identifier prior to screening drug targets. DNA-encoded combinatorial libraries (DECLs) are becoming increasingly important as drug discovery platforms, leveraging powerful affinity based screening of many different drug targets. Multiple candidate molecules discovered with this technique are now entering clinical trials. Here, we demonstrate DNA-free DNA-Encoded Libraries can overcome traditional limitations of DECL, allowing a wider range of targets (such as DNA binding biomolecules) and fewer false positives. This combined with a nanofabricated spatial platform and step-wise synthetic quality control process, enables robust screening of over a billion compounds in a single day.
ChemPass has developed a powerful in silico forward-reaction-based technology that enables the design of synthesizable scaffolds or building blocks using a chemist-oriented software. The heart of the system is a fully customizable synthesis know-how database and a design engine combined with a proprietary artificial intelligence technology to generate novel chemical matter with associated data including the synthesis scheme, synthesis cost and time, reagent availability information as well as physicochemical, functional group and other properties. The platform also includes a regularly updated reagent database from eMolecules, a constantly growing synthesis know-how database, embedded novelty check in eMolecules and SureChEMBL databases and customizable med-chem filters. The interface has specifically been developed for organic or medicinal chemists therefore they can use it without any cheminformatics knowledge or extensive training.

The software is ideally suited to DEL-based technologies because the user can easily control the acceptable protecting groups or the functional group count and type present in the designed scaffolds or building blocks to direct the design towards suitably protected mono-, bi- or trifunctional molecules as scaffolds or building blocks. Moreover, the software’s synthetic reaction list can be limited to or enhanced to include all organic reactions validated for DNA-encoded chemistry and thereby it is possible to explore the different molecular frameworks that can be created using multi-step DNA-encoded synthesis.

The poster will feature key examples of the design method and the resulting novel libraries that are suitable for discovery of novel hit and lead structures.
Ligand discovery was one of the first applications of one-bead-one-compound (OBOC) combinatorial libraries. However, the conventional on-bead binding-based screens exhibit high false positive rates during off-bead validation of re-synthesized hit compounds, often negating the economy of combinatorial library synthesis and screening. These false positive signals putatively originate from artificially enhanced target binding potency due to the polyvalent display of ligand on the bead surface. Off-bead OBOC library screening is now possible using droplet microfluidics, but detection has been limited to homogenous fluorescence. Here, we explore fluorescence polarization (FP) as an alternative assay detection modality for microfluidic DNA-encoded combinatorial library screens. In these screens, library beads are loaded into droplets containing the macromolecular screening target, a fluorophore-labelled library member is photochemically cleaved from the bead, the dosed droplet is incubated, and the laser-induced FP is measured. Droplets containing a target binding ligand will exhibit a higher degree of polarization and the device sorts the droplet for collection and sequencing. Unbound ligands rotate freely in solution, the droplet fluorescence is depolarized, and the device shunts the droplet to waste.

Polarization-activated droplet sorting (PADS) is being prototyped using fluorescein-tagged biotin as a control ligand of control target streptavidin. Fluorescein-biotin (5 nM) in droplets containing streptavidin (50 nM) exhibited $\text{FP} = 42 \pm 6 \text{ mP}$, normalized to FP of droplets without target. Integrating PADS with light-induced and graduated high-throughput screening after bead release ($\text{hvSABR}$) will permit direct interrogation of DNA-encoded compound bead libraries for affinity binding without the DNA-encoding tag attached to the small molecule library member and enable ligand displacement as a new assay format for distributed drug discovery.
Don’t Forget About the Tag!

Neil Carlson, Ninad Prabhu, Ken Lind, Svetlana Belyanskya, Chris Dimitri, Chris Phelps, Kathleen Newcomer, Jeff Messer

GlaxoSmithKline, NCE Waltham, 830 Winter Street, Waltham, Massachusetts, USA 02451

When performing affinity selections with DNA encoded libraries, one needs to keep in mind that the small molecule is only a portion of the entire complex – the DNA itself may partially or entirely drive target engagement. Additionally, the PCR and sequencing processes that allow us to read the tags can impact the results (e.g. mutation and PCR amplification bias). This poster will describe approaches we use to identify when the DNA is playing an unintended role in the selection process and how we use that information as we interpret our results.
DNA-templated Photo-crosslinking for Library Selection and Target Identification

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Sensitive and specific labelling of small-molecule-binding proteins is of high significance in chemical biology and drug discovery. We have developed a novel method named DNA-programmed Photo-Affinity Labelling (DPAL). DPAL’s unique dual-probe system provides simple, flexible and modular affinity labelling of small molecule’s protein targets. Importantly, the introduction of DNA encoding and template effect enable multiplexed protein labelling by multiple probes in a single solution. We show that DPAL can be implemented in the selection of DNA-encoded chemical libraries directly against soluble protein targets, as well as in target identification of bioactive small molecules.
DNA-encoded library technology is a cutting-edge technology for hit identification of biological targets of interest. It provides both an ultra-high-throughput and a cost-efficient tool for the discovery of small molecules that bind to protein targets of pharmaceutical interest. The success of ELT relies heavily on the chemical diversity accessed through DNA-Encoded Library (DEL) synthesis. Although progress has been made for some commonly employed reactions in medicinal chemistry, there is still a large need for additional on-DNA reactions with a wide range of synthetic regents for ELT library synthesis. This poster summarised recent on-DNA reaction development progress and discussed the future challenges and opportunities in DNA encoded chemistry.
DNA Encoded Library Technology (DEL) is a technology based on affinity selection with DNA encoded small molecule library. Each DEL molecule has a small molecule warhead tethered with a unique DNA sequence. In ELT selection process, the DNA is sequenced to facilitate recognition and quantification of each small molecule warhead. Despite the obvious application in drug discovery, where the off-DNA chemical warhead is the desired product, it is long recognized that the DNA also serves as a payload. The DEL library is indeed a small molecule-macro molecule conjugate library, allowing the screening for drug delivery vehicle since each selected warhead is readily conjugatable. Here we describe a direct selection methodology based on functionally partitioning library members that internalize live cells and remain intact. The selected exemplars demonstrate strong cell-binding and internalization effect with varying cell specificity. The molecular mechanisms of the internalization require more investigation. Preliminary result demonstrates that the internalization is endocytosis-dependent and at least a part of the delivered DNA remains intact inside the cell. It is also encouraging that the warhead not only delivers DNA but also large protein complexes.
mRNA display selection of glycopeptides that bind to HIV neutralizing antibodies for vaccine design

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A number of broadly neutralizing antibodies (bnAbs) against HIV have been discovered to recognize carbohydrates on gp120, a viral envelope glycoprotein, and are of great interest as targets for HIV vaccine design. Immunogens designed to bind to those bnAbs and elicit antibodies similar to them have potential to serve as vaccines. To design glycopeptides that mimic bnAb epitopes on gp120 through directed evolution, we developed a glycopeptide selection system using mRNA display. In the system, we introduced alkyne groups into peptides and those alkyynes are used to attach synthetic sugar azides by click chemistry. Using this technology, we created glycopeptide libraries containing 10 trillion sequences, and successfully selected glycopeptides that bind to bnAb 2G12 with sub nM to low nM $K_D$’s. The immunogenicity of those glycopeptides is currently under investigation in animal studies.

We will also present current attempts to apply this selection system for other carbohydrate-binding bnAbs including PGT Abs, which are more attractive targets since they neutralize a broader range of HIV strains, as well as further modifications of this selection system. Since we utilize AUG (start) codons to incorporate homopropargylglycine (HPG), which is an alkyne-containing methionine analog, for glycan attachment, all peptides produced in this system have a glycan at the N-terminus, which is not intentional yet may be an obstacle in binding to selection targets. Thus, we added peptidyl formyl transferase (PDF) and methionine aminopeptidase (MAP) in the translation reaction, and confirmed that those enzymes can successfully remove N-terminal formyl HPG when the penultimate amino acid is small, such as alanine and serine. Furthermore, utilizing enzymatically generated N-terminal serine, we introduced an additional modification at N-terminus by periodate oxidation followed by oxime ligation. Combining these technologies, we are also working on the mRNA display of peptides that have multiple modifications installed by different types of chemistry.
Identification of PAD4-specific Reversible Inhibitors Through DNA Encoded Library Technology (ELT)

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Abstract and figures (figures are optional)

Protein arginine deiminase 4 (PAD4) has been strongly linked to diverse diseases such as autoimmune, cardiovascular and oncological diseases. Novel selective PAD4 inhibitors binding a calcium-deficient form of the PAD4 enzyme have been successfully identified through screening GlaxoSmithKline’s DNA-encoded small-molecule libraries with and without added calcium. These highly selective, new tool molecules will enable future research on the therapeutic potential of PAD4 inhibitors. In this poster, we will describe the selection results that led to the potent, cellular penetrant PAD4-specific reversible Inhibitors with excellent physicochemical properties.

Figure Binding site in crystal structure of GSK199 with PAD4
Meeting Participant Associations

Abbvie
Amgen Asia R&D Center, Amgen Inc.
AMRI
Aquilo Capital
Astellas Pharma Inc.
AstraZeneca
Bayer AG
Baylor College of Medicine
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UCB
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Uppsala University
Vertex Pharmaceuticals
Warp Drive Bio
WuXi Apptec
X-Chem Pharmaceuticals
Future Meeting Announcements

1) ACS session on Encoded Technologies in Washington DC, Monday, Aug 21, 2017, MEDI: Encoded Technologies for Lead Generation, Successes & Challenges, Room 146B - Walter E. Washington Convention Center, MEDI004a, 1:30pm - 4:55pm

2) DELT Symposium 2018 in Chengdu: The 2018 symposium will be organized by HitGen, LTD and will feature a 2-day event, which will include not only scientific presentations and a poster session but also sightseeing tours of Chengdu. (contact: Alex Shaginian; alex.shaginian@hitgen.com)

3) DELT Symposium 2019 in ETH Zurich

4) DELT Symposium 2020 in Waltham/Boston
**Special Edition of MedChemComm dedicated to DNA-encoded methods**

Similar to what was done following the 2015 Boston Symposium on Encoded Library Platforms (BSELP), there will be an Encoded Library Platform themed collection hosted by the Royal Society of Chemistry journal *MedChemComm* following the 2017 BSELP. Meeting participants are encouraged to submit scientific manuscripts. Disclosure of new research results or informative reviews will be considered. Please note that all articles submitted will undergo the normal peer-review process for the journal.

For reviews, authors are requested to inform the managing editor in advance of their review topics so as to avoid overlap with other submissions and/or already published, similar material. The deadline for submissions is **October 31st 2017**. For further details, please communicate with James Anson (Deputy Editor, *MedChemComm*, mmedchemcomm-rsc@rsc.org)

The 2015/2016 “DNA Encoded Libraries” collection ([link](#)) includes the 8 papers below. We hope to see even more in the next edition.

**2015 First Boston Symposium of Encoded Library Platforms**

Robert A. Goodnow Jr. and Christopher P. Davie

**From haystack to needle: finding value with DNA encoded library technology at GSK**

Christopher C. Arico-Muendel

**Crosslinking of DNA-linked ligands to target proteins for enrichment from DNA-encoded libraries**

Kyle E. Denton and Casey J. Krusemark

**Design and synthesis of DNA-encoded libraries based on a benzodiazepine and a pyrazolopyrimidine scaffold**

M. Klika Škopić, O. Bugain, K. Jung, S. Onstein, S. Brandherm, T. Kalliokoski and A. Brunschweiger

**Screening for covalent inhibitors using DNA-display of small molecule libraries functionalized with cysteine reactive moieties**

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* pg. 37
C. Zambaldo, J.-P. Daguer, J. Saarbach, S. Barluenga and N. Winssinger

**Novel p38α MAP kinase inhibitors identified from yoctoReactor DNA-encoded small molecule library**

**Analysis of the productivity of DNA encoded libraries**
Oliv Eidam and Alexander L. Satz

**Development and design of the tertiary amino effect reaction for DNA-encoded library synthesis**
Xia Tian, Gregory S. Basarab, Nidhal Selmi, Thierry Kogej, Ying Zhang, Matthew Clark and Robert A. Goodnow Jr.

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