From Custom Synthesis To Vast Encoded Libraries: Integrated Support For Lead Generation

Updated 5th Jun 2014

HitGen Introduction

- Contract Research Organization established in 2012 in Chengdu, SW China
  - Focus on hit identification and lead generation using Encoded Library Technology
  - Industry experienced senior management
  - Over 120 skilled scientists and support staff
  - Stable, well trained teams
- Build high quality, drug-like, high diversity DNA encoded libraries and affinity screening capability for lead-finding
- Develop a broader market for DEL technology by virtue of the lower cost and scalability of our highly trained workforce in China

Tianfu Life Science Park

HitGen Business Strategy

- Provide the most diverse and relevant screening library possible for quality hit generation
- Establish broad research support infrastructure for Hit to Lead and Lead Optimization
  - Establish high throughput synthesis capabilities for discrete hit expansion or lead optimization libraries
  - Capabilities in molecular and cell biology and assay development
  - Strategic external network for ADMET and structural biology
- Develop research collaborations with both large and small organizations
  - Partnering of assets generated through screening of our library
  - Screening collaborations for client defined targets
  - Research support for client driven lead optimization programs

High Quality Research Laboratories

Biology Labs

Chemistry Labs

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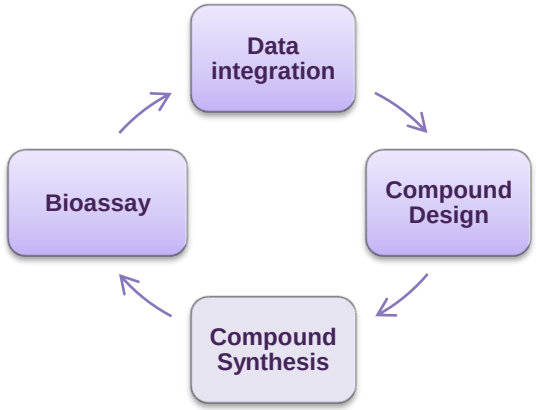
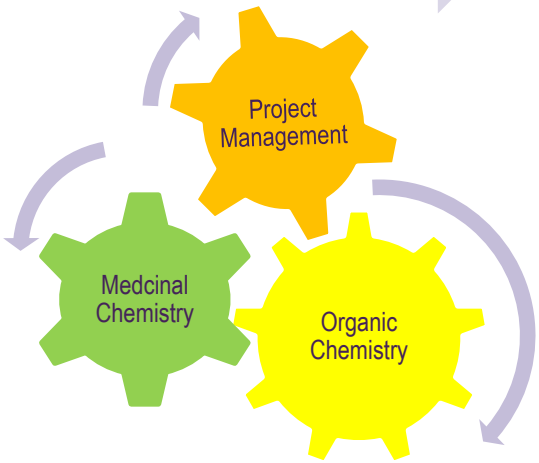
Scientific Activities in Bioscience Team

- Assay development
  - Wide range of detection methods for in-vitro assays
- Library production
  - Coding ligations
- Sequencing (Illumina)
- Phenotypic Target Identification
  - Uses novel bioconjugate and nano-formulation to streamline the process
- Cell and Molecular Biology
  - Custom lentivirus production
  - Protein production

Integrated MedChem Support

Target Identification | **Hit Identification** | **Hit-To-Lead & Lead-Optimization** | Clinical Trial | Launch





Bio-molecules and Bio-conjugates
- ✓Peptide-drug conjugates
- ✓Oligonucleotide-drug conjugates
- ✓Modified Oligo-peptides/nucleotides
- ✓Macrocycles

Libraries
- ✓Encoded libraries
- ✓Conventional small molecule libraries

Small molecules
- ✓Conventional heterocylic compounds
- ✓Nucleosides/Nucleotides
- ✓Tool compounds for bio-assays

Computational Chemistry
- ✓Compound Design SBDD
- ✓QSAR
- ✓Data analysis

Experience in lead optimization in multiple protein classes:
Proteases, Polymerases, Kinases, Phosphatases, Epigenetic proteins

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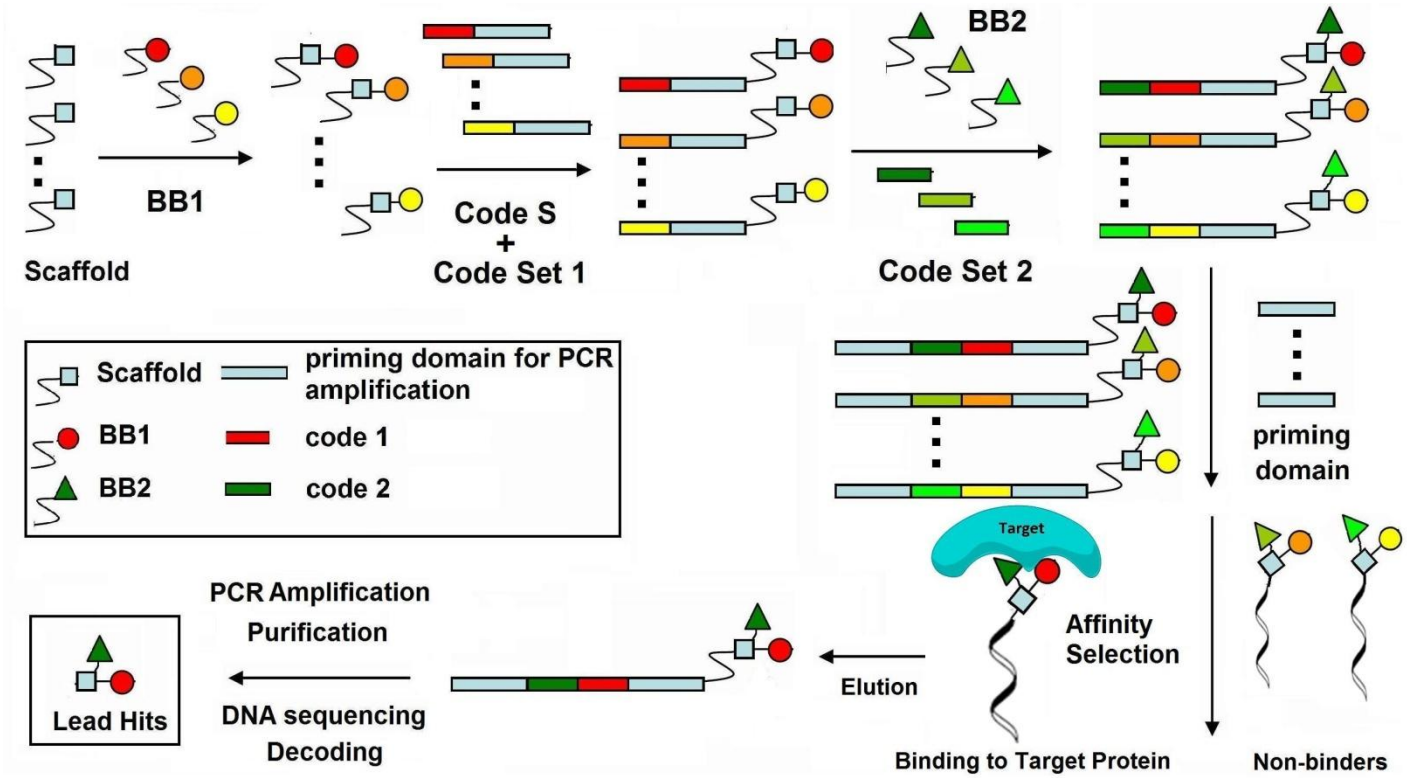
Encoded Library Synthesis & Screening



Benefits of DNA Encoded Library Screening Technology:

- Rapid access to vast chemical libraries
- Less dependency on expensive screening systems
- Far less demand on protein reagents (1-2mg)

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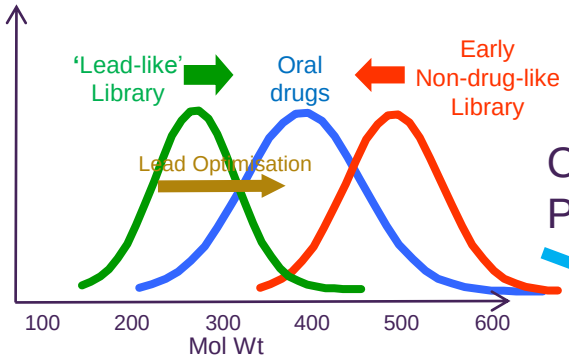
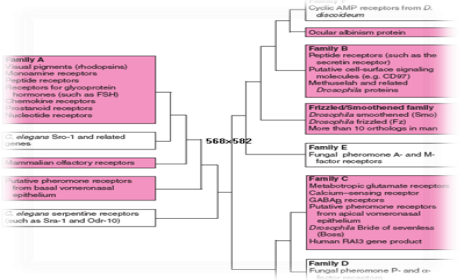
Compound Library Design

- HitGen is producing a highly diverse and drug-like lead-finding library
  - Target 90% of library molecules in oral drug space (Ro5)
  - Select scaffolds and substituent reagents with high average Fsp3
  - Emphasis on diversity by targeting mid-size libraries of 0.3-5 million compounds based on hundreds of different scaffolds
  - Incorporation of a selection of privileged and bioactive fragments

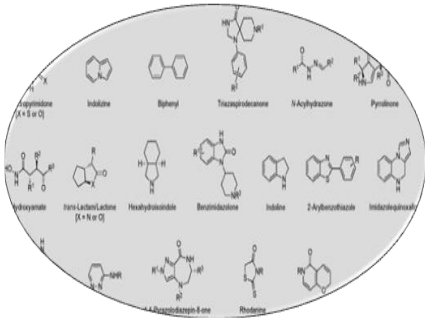


Compound Properties

Target Family

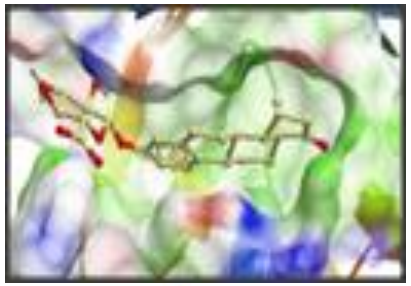


Library Designs

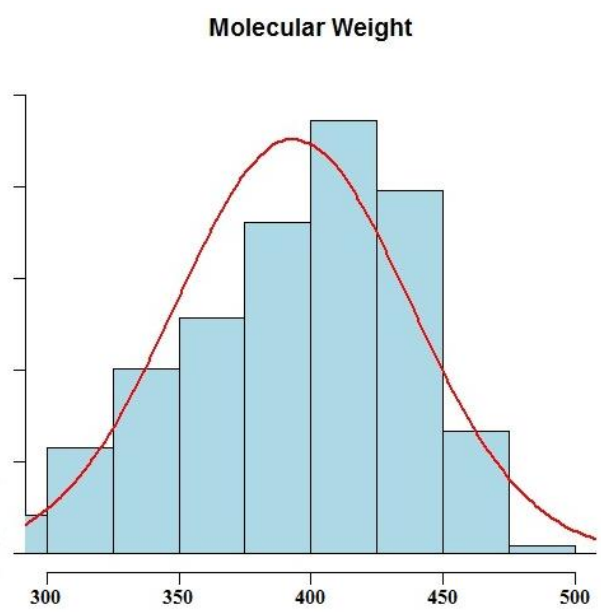


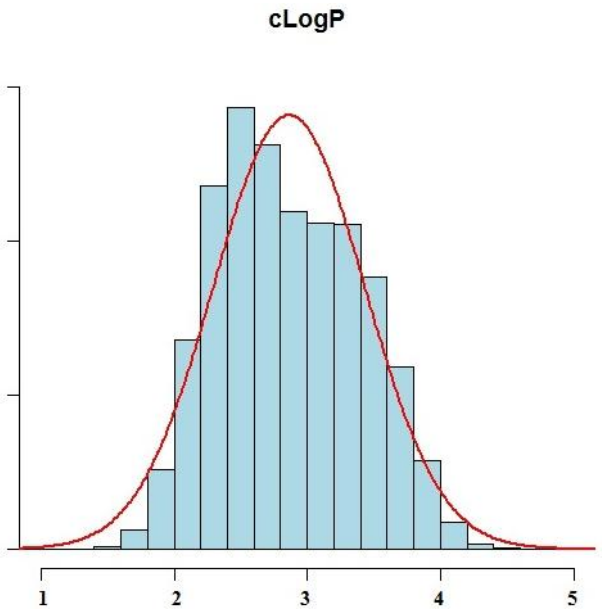
Privileged Structures

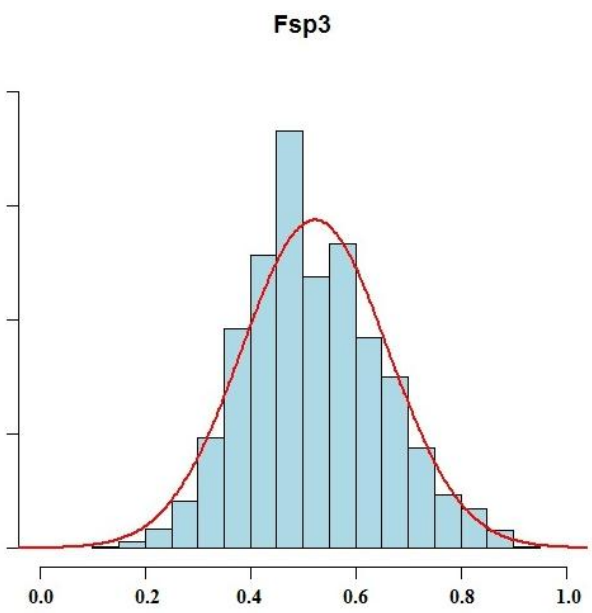
3D Structures

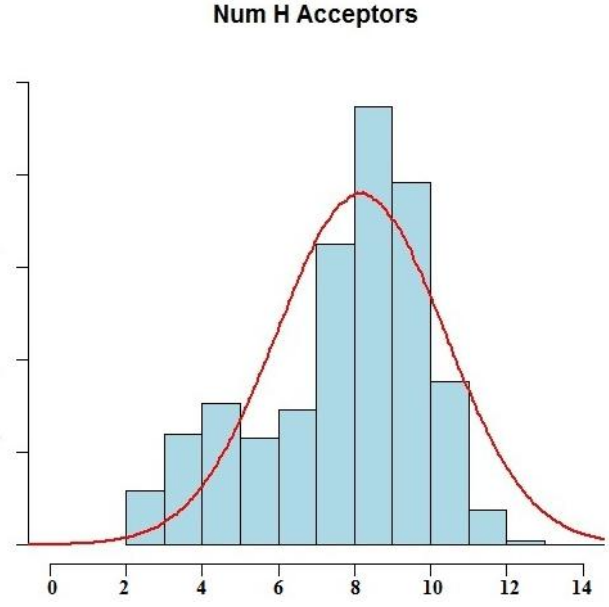


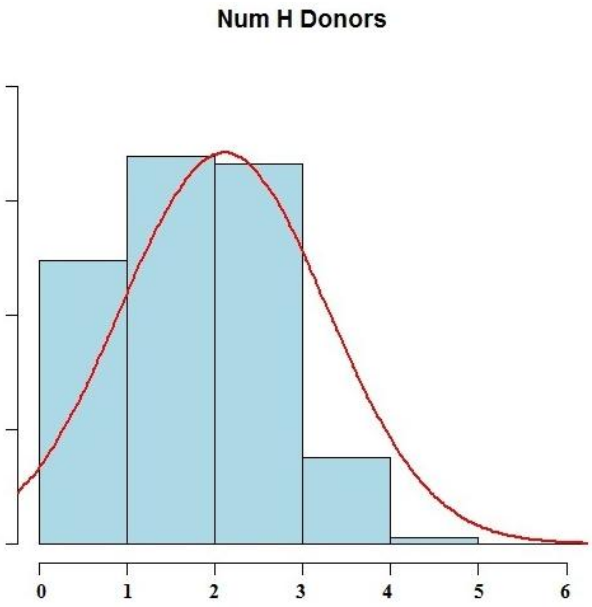
Properties Distribution of 10M Compounds

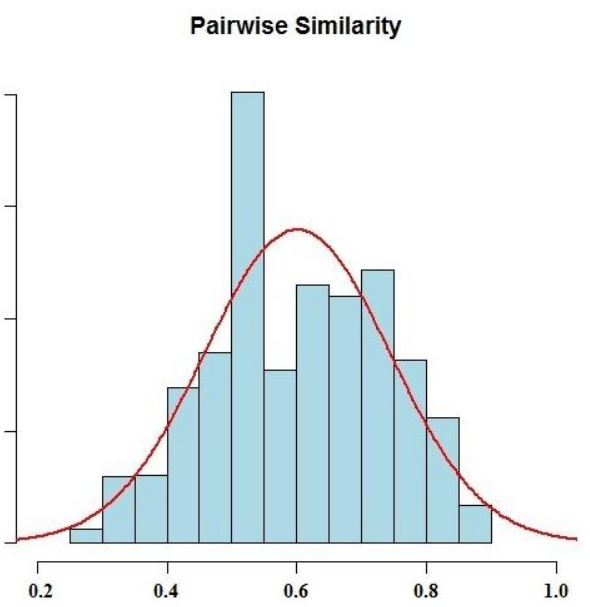












Encoded Library Status

- HitGen has already established a DNA encoded library of >600 million compounds on >320 scaffolds which is available for client screens.
  - Incorporates macrocycles and peptide mimetics targeting PPIs
  - Includes libraries targeting Zn dependant enzymes and GPCRs
- Trial affinity screens on intermediate libraries have already generated novel and interesting hits for a small set of challenging targets:

Target	Protein Class	Size of DEL screened	Activity Range in Biochemical Assay	Properties of best hit MW:cLogP:Fsp3:tPSA
GSK3beta	Kinase	3.6 M	IC50 10-30 uM (Non-ATP competitive)	375 : 1.64 : 0.65 : 85
EGFRm	Kinase	24.5M	IC50 15-60uM (Non-ATP competitive)	442 : 3.58 : 0.50 : 78
LDHA	Dehydrogenase	24.5M	IC50 16 uM (Novel chemotype)	459 : -1.4 : 0.35 : 128
DHODH	Dehydrogenase	24.5M	IC50 7 uM	327 : -0.3 : 0.25 : 109
Factor VIIa	Protease	24.5 M	IC50 30-600 nM	477 : 1.5 : 0.2 : 128

Collaboration Models

Lead Generation

- Partner defines targets and provides materials and protocols as available
- HitGen carries out work for, assay development if not available.
- HitGen screens 200 of its novel encoded libraries for partner's targets exclusively
- Hits identified are licensed to partner exclusively
- **Cost:** small technology access fee and research funding for each target, with milestones for success:
  - Confirmed hit ID
  - LO start
  - Candidate drug nomination
  - Ph2/3 clinical stage initiation,
- **No royalties on sales**

Custom Libraries

- Apply encoded libraries methods for expansion of fragment, hit or lead
- Partner nominates target(s), and provide chemical starting points and design direction
- HitGen designs, makes and screens custom encoded library compounds for customer's target(s)
- Customer owns the libraries exclusively
- **Cost:** research funding based with small success-based milestone.

Research Support

- Protein expression and purifications
- Synthesis of tool or med chem compounds, and reagents, etc
- Hit expansion libraries
- Targeted/LO libraries
- Cell line generation
- Phenotypic Target ID
- **Cost:** FTE based or specific deliverables based milestones

Data Management, Security and Communication

- HitGen uses both physical and electronic lab notebook systems
- Physical lab notebooks has clear log/witness sign off process
- Electronic lab notebook systems are provided by Scilligence Inc
  - RegMol – compound registration, data retrieval and visualization
  - ELN – full experimental protocols and data in English
  - Secure and time-stamped web based system
  - Customers can login remotely to view own project data
  - HitGen staff can only see data from assigned project
- All HitGen staff have signed CDAs and IP assignment
- All documents on HitGen network are encrypted, and unreadable outside the company unless decrypted by authorized manager
- Card access, segregated client labs for larger teams (>4 FTE)
- Weekly reports and TC with team leaders on each project

Thank You!

For further information please contact Steve Young on +44 7920007074 or leadgen.info@hitgen.com