BioBlocks, Inc.: Transforming the process of lead discovery

BioBlocks CEO Dr Peter Pallai discusses how BioBlocks is making drug discovery more straightforward, faster and more economical using data-driven approaches

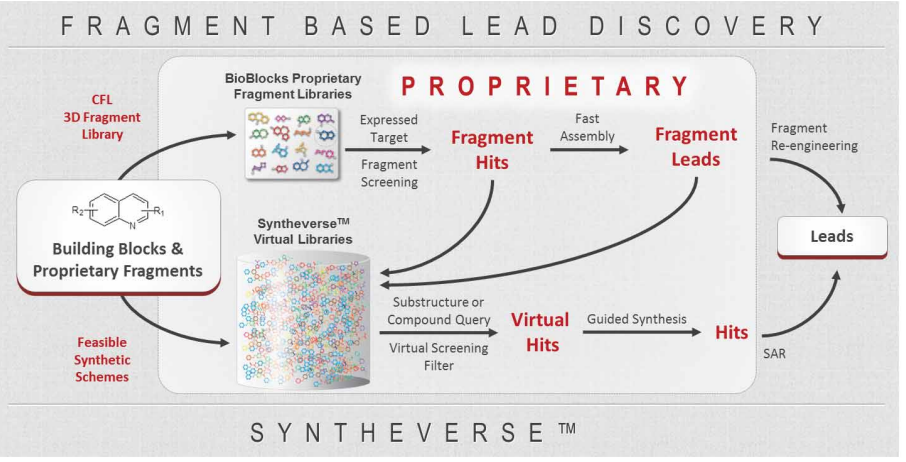
BioBlocks is a medicinal chemistry company specialised in compound synthesis and lead discovery for preclinical customers. Over the past 16 years, the company has developed numerous preclinical assets for their partners. Their new Leap-to-Lead™ platform combines BioBlocks' medicinal chemistry expertise with advanced cheminformatic tools.[1]

Building the BioBlocks hallmark collaborative lead discovery engine

"BioBlocks was founded in San Diego in 2002. Through my 30 years of experience in the biotech and pharma industry, I developed a vision of reinventing the lead discovery 'game' and assembling a team of top scientific talent to achieve this goal.

"After the typical humble beginning, initially in a home office and a garage fitting to a California startup, we soon established our laboratory and headquarters in the San Diego biotech hub just east of UCSD with the mission to provide chemistry tools and services to the drug discovery community," said CEO Dr Peter Pallai.

"Over the years we've grown our team with top talent in medicinal/synthetic chemistry and cheminformatics. These capabilities have helped numerous biotech/pharma partners to develop preclinical leads. Our success led to the opening of our Budapest laboratories in 2006 where our scientists, well trained in synthetic and medicinal chemistry, make crucial contributions to medicinal chemistry projects. Working in a highly integrated manner the two teams, including eight scientists in San Diego and 45 in Budapest, created the BioBlocks hallmark collaborative lead discovery model that is helping our partners to navigate the complex process of lead discovery and to meet their project objectives.



"Through our work, we identified significant challenges in the current drug discovery paradigm, including a high attrition rate due to lack of high-quality IND [investigational new drug] candidates and eroding IP positions due to patent expirations. We concluded that this required a serious rethinking of how drug candidates are discovered.

"We recognised that the answer lies in innovation that can effectively address these pitfalls. Having on board the best talent in both locations we were able to answer the call of this market opportunity. In an internally funded R&D effort over half a dozen years, we developed the Leap-to-Lead platform to provide new solutions for the discovery process itself and opened up new chemical space that can be effectively navigated to create new chemical matter."

Leap-to-Lead: the cost-effective alternative to high-throughput screening (HTS)

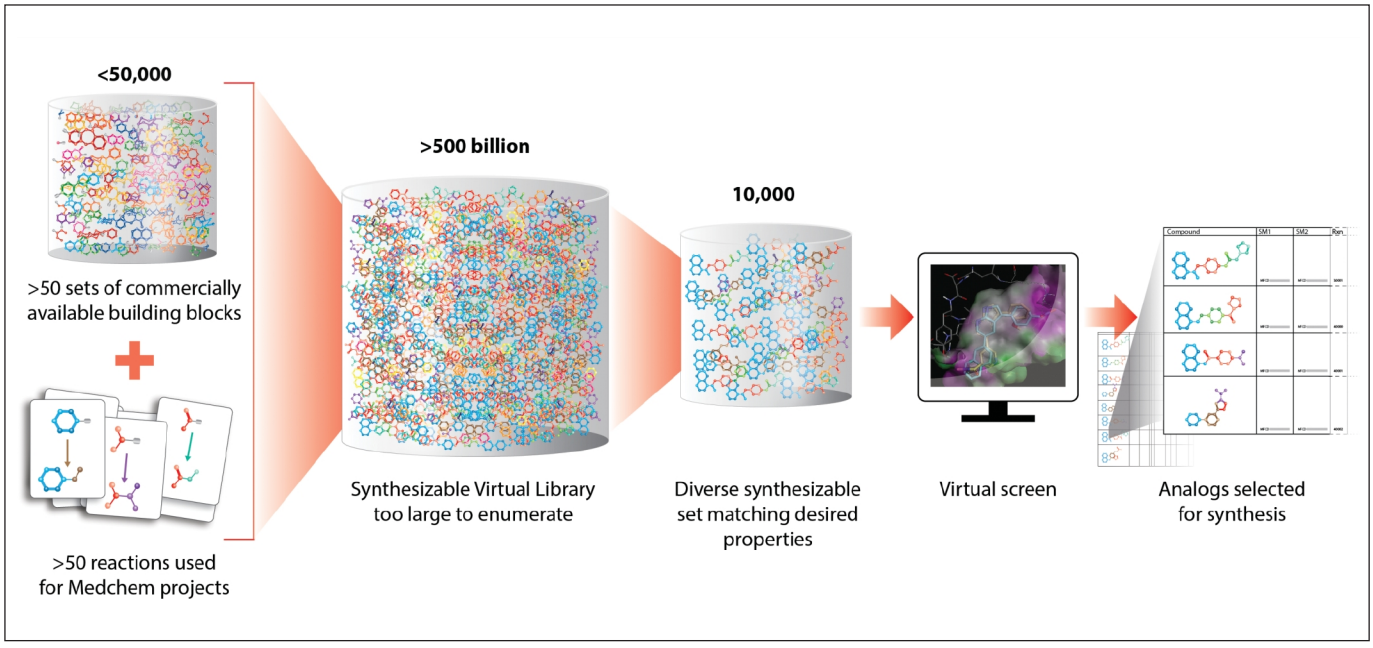
The Leap-to-Lead platform radically improves lead generation and optimisation for our partners. It begins with a screen of our Comprehensive Fragment Library (CFL) to find high-quality initial hits.[2] We then convert those or previous hits into proprietary leads through our analog-generating Syntheverse™ technology.[3] This process allows us to create strategic value for our partners by providing novel quality leads for their targets.

CFL: medicinally enriched fragment library

Our fragment-based lead discovery (FBLD) process is differentiated by the CFL, a proprietary collection of over 35 million diverse fragments selected using strict quality and pharmaceutical value criteria. We've carefully curated our library to maximise representation of medically relevant chemical space to prepare two CFL plates available immediately for partners to screen for no charge in their assays. Through our proprietary clustering algorithms, we connect hits to novel fragments in the CFL Select Set. The expanded, enhanced hit set from the CFL is carried forward using the Syntheverse to develop analogs for the next phase of the partnership.

Syntheverse: intelligent lead creation

The Syntheverse is an advanced cheminformatics algorithm capable of generating over 500 billion



compounds of target molecules trained with pre-coded feasible reaction schemes and curated reagent sets, including our proprietary fragments.

The CFL screening hits identified are used as inputs by the proprietary Syntheverse process to rapidly identify promising analogs from a virtual screen. The resulting analogs are selected for synthesis or purchase if commercially available. BioBlocks' medicinal chemistry expertise is encoded in the Syntheverse to provide accurate selections of reaction schemes and thus immediate synthesis.

Additionally, the Syntheverse has powerful capabilities in cases where a lead requires optimisation of some set of properties (i.e. toxicity, solubility, stability, etc.). The Syntheverse can quickly identify improved alternatives for groups needing replacement and provide schemes for their synthesis. Starting from CFL screening hits or an existing lead, the iterative Syntheverse process can generate novel leads for partners.

Leap-to-Lead partnership programme

A Leap-to-Lead FBLD partnership project consists of three phases, with BioBlocks delivering novel leads enabling optimisation and patent filing as the overall goals. Each phase is iterative, with clear milestones and expectations from both parties at each phase. A typical partnership begins with the CFL Fragment Screen (Phase 1) to identify hits using a fragment-friendly assay from either the partner or a qualified biology CRO. Using connections between fragments designed into the CFL, BioBlocks generates Fragment Analogs (Phase 2) in two rounds, both commercially available and newly synthesised, to produce families of analogs suitable for lead finding. The Leap-to-Lead process then continues to Fragment Evolution (Phase 3), where fragment families from Phase 2 will be optimised to leads using a combination of BioBlocks' Syntheverse technology and the partner's assays. During Phase 3, the identification of fragment leads transitions the primary assay to a typical activity-based biochemical assay, enabling a hit-to-lead campaign from a superior starting point. The Phase 3 process will entail sustained synthesis of analogs generated by the Syntheverse by BioBlocks, and testing by the partner in an assay cascade over several rounds.

"The goal of fragment-based lead discovery is to build high-quality leads from the ground up, beginning with high-quality starting points," said Pallai. "The Leap-to-Lead platform, which includes the CFL and Syntheverse, combines our years of medicinal chemistry expertise with powerful cheminformatics to leverage FBLD's advantages."

Phases 1 and 2: from screen to analogs

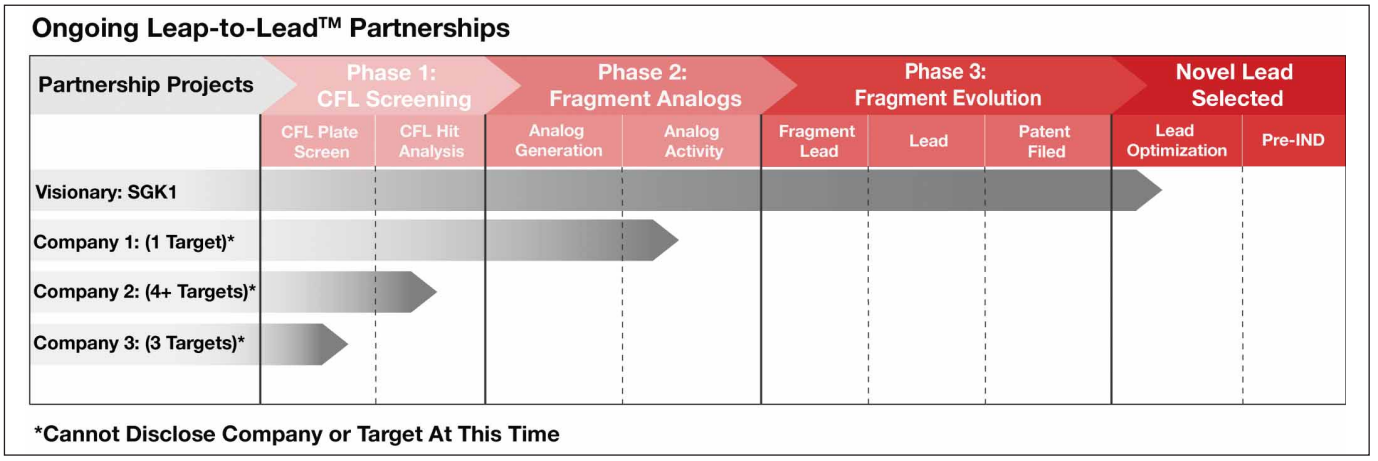
In Phase 1, BioBlocks provides a physical set of fragments from the Comprehensive Fragment Library, representing the large virtual clusters in the BioBlocks repertoire. The selected compounds are provided as high concentration solutions in DMSO, allowing for screening at up to mM concentrations in the partner's assay. This screening phase takes about one to two months (depending on the partner's assay).

In Phase 2, BioBlocks will use information on the hits identified from Phase 1 to generate fragment analogs. Through proprietary clustering algorithms, BioBlocks connects hits to novel fragments in the CFL Select Set to identify both commercially available and synthetic analogs in two rounds. Each round will involve the generation of analog samples by purchase or synthesis by BioBlocks, incorporation into new plates and screening by the partner in the same (or additional) assay(s) as Phase 1.

The first round of analogs will contain mostly commercially available compounds that take less time to evaluate than synthetic ones. The second round will contain a higher proportion of synthesised analogs based on the results of the first round. This also ensures that synthesis is kept to a minimum, efficient set to avoid unnecessary synthesis time and cost. Hits from this phase will be clustered into structural families, an early indicator of successful fragment evolution. This analoging phase takes three to four months, given repeated assay experiments by the partner, fragment analoging by BioBlocks, and purchase and synthesis of analogs. From here, partners will have the chance to evaluate their families of active analogs and proceed to the next phase.

Leap-to-Lead platform partnerships

From many years of lead discovery experience, the BioBlocks team understands that the search for novel, effective leads is at the forefront of drug discovery. Accessing an expanded chemical space to identify those leads with high efficacy, IP novelty, and medicinally favourable properties remains a major challenge. BioBlocks is excited to announce the launch of Leap-to-Lead platform partnerships, a highly efficient alternative to traditional, typically HTS-driven, approaches for drug discovery. Building on our 16 successful years creating multiple quality commercialisable leads, we are now seeking partnerships to utilise Leap-to-Lead for generating proprietary, high-quality leads for IND-enabling studies and development.



Phase 3: fragment evolution

Phase 3 introduces the second arm of Leap-to-Lead: the Syntheverse, which was trained with feasible reaction schemes to utilise BioBlocks' proprietary fragments. BioBlocks' medicinal chemistry expertise is encoded in the Syntheverse to provide accurate selections of reaction schemes and thus immediate synthesis. The CFL analog families from Phase 2 are used as inputs by the proprietary Syntheverse process to rapidly select informative analogs from a virtual screen. The resulting compounds are selected for synthesis.

Once the compounds generated in Phase 3 are determined to be active in a biochemical assay, these fragment leads are optimised to leads using a combination of BioBlocks' Syntheverse technology and the partner's assays. This process will entail sustained synthesis of analogs generated by the Syntheverse, by BioBlocks employees, and testing by the partner over several rounds.

Revamping suboptimal leads

The Leap-to-Lead process is designed be used in other situations as well. The CFL virtual library can provide a diverse array of alternative options for the parts of a lead molecule with a biological or patent liability, and the Syntheverse provides chemistry options that allow rapid scaffold replacement and alternative chemistries to make re-engineering of key target interactions possible.

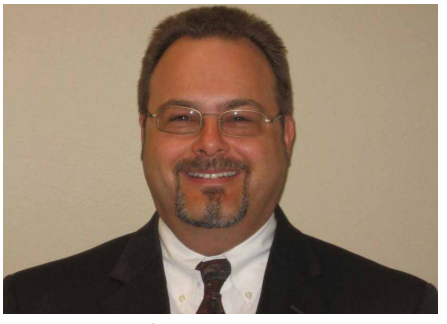
The Syntheverse also has powerful capabilities to provide alternatives in cases where a lead requires improved pharmaceutical properties (i.e. toxicity, solubility, stability, etc.). The Syntheverse can quickly identify structural replacements for problematic groups and provide synthetic schemes for the replacements.

The BioBlocks team

The San Diego and Budapest BioBlocks teams include several members with significant expertise in the drug discovery realm. BioBlocks' leadership team is composed of Dr Peter V Pallai, CEO, Dr Warren Wade, VP, Chemistry, and Dr Janos Gerencser, COO, all industry veterans who have held therapeutic project leadership positions in pharma/biotech companies and key leadership positions at drug discovery chemistry CROs. Dr Todd Meyer, principal scientist at BioBlocks San Diego, is the chemistry project leader for the SGK1 project and has been instrumental in developing the practical procedures used in the Leap-to-Lead platform. Balazs Gyimóthy, senior manager, head of chemistry and technology development at BioBlocks Budapest, has a great deal of experience in library design and parallel synthesis. This combination of experience and knowledge makes this an ideal team to create new technologies that have the potential to fundamentally change the process of drug discovery.

As the chief architect of the Leap-to-Lead platform, Wade combines his experience advancing two small molecule candidates for IND filings while a director of medicinal chemistry at Neurocrine Biosciences, Inc with FBLD experience from his time as a research investigator at Abbott. While working on the discovery of preclinical compounds for obesity, acute and neuropathic pain, multiple sclerosis and insomnia indications for a variety of target classes, he recognised the value of computer-assisted synthetic chemistry to provide new ideas for drug discovery projects, which has become the core of the platform.

"It is always easier to pick from a set of solutions to a problem than think of the best solution in the first place. By using computational methods to provide diverse possibilities for any chemically based project, I aim to expand the imagination beyond its typical limitations so that truly novel solutions can be discovered," Wade said.



Dr Warren Wade

Case study: Leap-to-Lead technology in action

Targeting SGK1 for TNBC indication with Visionary Pharmaceuticals

Visionary and BioBlocks formed a partnership to identify novel inhibitors of SGK1. Using the Leap-to-Lead platform we were able to deliver an active lead with novel chemical space, leading to a recent patent application.

Collaboration workflow

- CFL plates screened in SGK1 assay
- Hits identified from CFL screen
- Analogs selected from relevant clusters
- Efficient hit-to-lead process completed with only two Syntheverse runs.

Collaboration milestones

- Developed a lead series that has improved properties compared to literature leads
- Developed novel IP – patent application filed
- Advanced partnership to lead optimisation
- Partnered with a public biotech to explore alternative indication.

Read about this case at https://www.bioblocks.com/case-study-syntheverse

Leap-to-Lead™ addresses common Drug Discovery problems

PROBLEM		IMPROVEMENT		L2L MODULE		APPROACH
HTS not informative or not practical	>>	Better Screening Hits	>>	CFL	>>	Fragment Screen Requires fragment friendly assay
Literature Lead or lack of IP	>>	New Hit to Lead Path	>>	SVS	>>	Scaffold hopping with known chemistry
Lead with unacceptable properties	>>	New Chemical Matter	>>	CFL SVS	>> >>	Replace core with novel CFL options Identify high quality products from any reaction scheme
Difficult targets, e.g. epigenetics	>>	New Interaction Motifs	>>	CFL	>>	Wider range of fragment shapes allows for non-traditional targets

Current collaborations

As the amount of data and literature knowledge steadily increases from the medical, scientific and economic fields, forming strategic partnerships and scientific collaborations is more important now than ever to harness the strengths and possible synergies of each party for the best outcomes while minimising costs. To achieve these goals, BioBlocks currently provides its CFL screening plates to partners with no upfront costs.

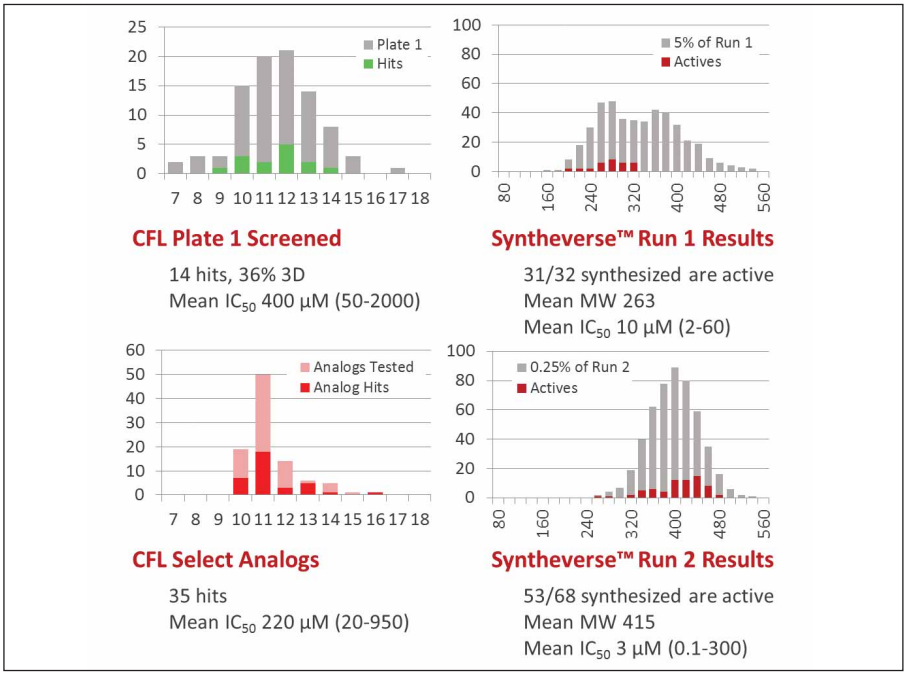
BioBlocks has demonstrated the economic value of the Leap-to-Lead technology through several collaborations since 2014, and is now opening its doors to a new set of partnerships. In 2014 BioBlocks initiated its first partnership with Visionary Pharmaceuticals to target SGK1 for TNBC indication. The partnership successfully produced a novel lead series resulting in a patent application and embarked on lead optimisation and IND-enabling studies. BioBlocks systematically evolved the Leap-to-Lead technologies to reproducibly generate novel leads with potent activity and selectivity. The advanced algorithms in the Syntheverse ensure that leads developed have good property profiles and filter out candidates that are at risk of failing approval for known safety issues.

BioBlocks is currently using the technology to focus on early discovery phases; however, the innovative Leap-to-Lead methodologies also show promise for projects in later stages of drug development and could 'rescue' candidates by identifying viable alternative molecules that lack identified liabilities, including patentability. BioBlocks has initiated three new partnership projects that are generating promising results. We are planning to add new projects and partnerships in 2018.

Partnering benefits

Leap-to-Lead partnerships create strategic value by providing novel quality leads cost efficiently for partners' valuable targets:

- Efficient generation of patentable preclinical leads
- Better activity and patent coverage via advanced cheminformatics algorithms
- Rescue patent position of known leads using novel scaffolds
- Access to large virtual set (more than 500 billion) of synthesisable structures
- Improve your compounds at any stage using chemical evolution processes
- Successful lead discovery by aligning the partner's expertise with our technologies.[4]



About Us

BioBlocks is a medicinal chemistry company specialised in preclinical lead discovery. Over the past 16 years, we have developed numerous preclinical assets for our partners. BioBlocks focuses on creating proprietary, high-quality leads by combining its expertise in medicinal chemistry with its cutting-edge Leap-to-Lead platform. For more information on how to partner with BioBlocks, please send an email to ppallai@bioblocks.com or follow us on LinkedIn at linkedin.com/company/bioblocks-inc.

Limited number of collaborations now available

Leap-to-Lead partnerships aim to generate patentable preclinical leads, placing our partners in a position of strength moving into preclinical development and clinical trials. We are seeking partnerships with research-driven drug discovery/development entities at all stages to utilise Leap-to-Lead.

With your target expertise and our advanced platform, we can lower the challenging hurdles of drug discovery. Together we can create de-risked assets with market value for your organisation.

References

1 https://www.bioblocks.com/l2loverview/#leap-to-lead-overview
2 http://www.bioblocks.com/cfl-overview/
3 http://www.bioblocks.com/syntheverse/
4 http://www.bioblocks.com/typical-project-outcomes/

BioBlocks
A CHEMISTRY PARTNER IN DRUG DISCOVERY

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