

Nuevolution: Size Matters

Nuevolution (Copenhagen, Denmark) has set out to revolutionise traditional drug discovery. With a unique platform based on a hybrid of wet chemistry and molecular biology, the company is able to rapidly synthesise billions of drug-like compounds in a single test tube and select the most potent drug candidates in weeks. *BVW* speaks to CEO Dr Zahed Subhan about creating the only library you'll ever need.

The company, founded in May 2001 by Drs Henrik Pedersen (CSO), Alex Haahr Gouliaev (EVP of drug discovery) and Mads Nørregaard-Madsen (director of molecular design), plans to use its proprietary Chemetics technologies to cost effectively synthesise and screen many billions of drug leads to virtually any target in weeks.

chemical efficiency

Subhan says Chemetics, a suite of sub-technologies, represents the ultimate drug discovery tool. "It is the only technology available today that successfully combines ultra-large libraries of billions to trillions of drug-like small molecules with a stringent screening method that can efficiently handle such huge numbers of compounds."

The company says that traditional approaches to drug lead identification and optimisation have severe limitations with regard to small molecule library sizes and screening capacity. Even with combinatorial chemistry and highly optimised ultra high-throughput screening systems, it has proven difficult to scale up library sizes beyond a million molecules screened per month, even for the largest pharma. Consequently, current drug discovery approaches typically generate hits of low micromolar affinity. Often, these hits are devoid of selectivity and important drug-like characteristics and have to undergo further iterative cycles of secondary library formation and screening, leading to a time-consuming process that generates few, often structurally related, optimised leads. "In the midst of the genomics boom a few years ago, people seemed to forget just how important chemistry is to early drug discovery. The pendulum is swinging back in the post-genomics era. We have combined a new wet chemistry method with molecular biology in a way that hasn't been attempted before, allowing us to produce high quality leads in a very short period of time."

The key to the company's platform

involves the synthesis of an enormously diverse library of 10^{12} – 10^{14} drug-like molecules, containing hundreds to thousands of leads. "Current technologies do not allow the screening of such large libraries, making it impossible to identify the leads in this immense pool of small molecules," states Subhan.

Nuevolution has filed broad patent applications covering its concepts of DNA-directed synthesis of small molecules and the application of these to drug discovery.

The first step in the Chemetics process involves the DNA-directed synthesis of a highly diverse library of many billions of small molecules. The library is based on building blocks that each consist of a chemical moiety (a drug-like fragment) linked to a specific DNA strand (oligonucleotide). The chemical moieties, which can either be of the scaffold type or of the substituent type, are synthesised by conventional organic chemistry. Importantly, the chemical moieties used in Chemetics are designed to have drug-like properties and generally known and used medicinal structures/fragments will be included.

The library of small molecules is generated in a single test tube. Drug-like fragments attached to DNA are mixed with single-stranded DNA templates. During this incubation phase, the oligonucleotide parts of the drug-like fragments bind specifically to their complementary DNA sequences on the template. Library compounds are formed when a chemical reaction is initiated between drug fragments associated with the same template.

Once library molecules are screened against a target, the binding molecules are isolated and a new library composed of the highest affinity ligands is generated. First, the specific DNA templates to which the binding ligands are linked are amplified by PCR. The amplified DNA fragments are then used to re-initiate the library-generating process. By using multiple rounds of screening and amplification, Chemetics can select the most

potent and specific drug-like leads in a process that mimics 'natural' evolution.

Unlike competing small molecule discovery companies, Subhan says Nuevolution does not need to produce different libraries depending on the target on interest. "Because our library is so big, we won't need specific versions for particular targets or disease areas, – the ultra-large library theoretically contains all the compounds needed for drug leads for any target." Nuevolution is refining its platform, and has not yet started to offer its services commercially, although expects to conclude its first major drug discovery partnership in mid-2004.

location, location, location

The company is headquartered in the heart of the Medicon Valley, one of the fastest growing biotechnology hubs in Europe. There are several reasons for locating the company here, according to Subhan: "It is possible to recruit highly qualified and motivated scientists relatively easily and the region boasts an excellent infrastructure ideally suited to a rapidly growing company."

To date, Nuevolution has received approximately €12.2M in funding, from venture capital investors including Novo, Nordic Biotech and the Danish Investment Fund, and is planning a €20.0M series B financing round this year.

"The multi-partnering opportunity offered by Chemetics will allow Nuevolution to become profitable by the end of 2006. We will also use Chemetics to accelerate our in-house drug discovery activities and generate a pipeline of drug candidates that may be out-licensed or co-developed with pharmaceutical company partners. Drug discovery is a numbers game and we simply have a lot more than anybody else – size really does matter," concludes Subhan. **SC**

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