

BioCentury

Emerging Company Profile

Nuevolution: HTS in a tube

By Michael Schuppenhauer
Senior Editor

The ultimate high throughput screen (HTS) would run every possible molecule against a given target in one test tube and identify multiple structurally unique leads. This is what Nuevolution A/S hopes to offer with its Chemetics technology, which tries to eliminate traditional limitations of HTS, including limited library size, time-consuming screening, and a narrow set of leads characterized by high structural similarity. Chemetics mixes the building blocks of small molecules together in one tube and uses DNA as a molecule generator. The result is a large and highly diverse library in a single iteration within one test tube.

One of the main drawbacks of traditional wet HTS lies in the required logistics, such as compound storage and capital expense for the necessary machinery, as well as the time- and therefore cost-consuming process of setting up assays in HTS format in an ultra-pure fashion. Also, Nuevolution CEO Zahed Subhan noted that existing ultra-high throughput systems set high demands on the purity of library compounds, which limits scalability.

In addition, it has become difficult to further optimize assay stringency or accuracy, which is vital in order to limit system noise, such as the occurrence of false positives and false negatives. More precisely, if only a few hits result from a 10^6 compound library, further optimiza-

Nuevolution A/S

Copenhagen, Denmark
Technology: Drug discovery using DNA-directed synthesis of small molecules
Disease focus: N/A
Clinical status: N/A
Founded: May 2001 by Henrik Pedersen, Alex Gouliaev, and Mads Madsen
Corporate partners: N/A
University collaborators: N/A
Number of employees: 30
Funds raised: \$12 million
Investors: Nordic Biotech K/S; Novo A/S; Vaekstfonden
CEO: Zahed Subhan
Patents: None issued

tion of the leads goes for naught if they are actually false positives found by the assay.

One way to avoid the problems of traditional wet chemistry is to employ in silico screening. But Subhan, previously vice president of business development at in silico screening play Locus Pharmaceuticals Inc. (Blue Bell, Penn.), noted that "the results still need verification in the wet chemistry lab – so there's no real gain using that route."

Chemetics uses DNA as a template to direct the synthesis of small molecules, reveal the structure of each small mol-

ecule after binding to a target, and finally serve as a means to amplify the small molecule. The process requires no prior characterization of the DNA template sequence or the small molecule lead, according to Subhan.

In the first step, a large number of DNA fragments of varying sequences are incubated with a number of pharmacophores, essentially oligonucleotides carrying different drug building blocks. The oligos bind to their complementary sequences on the DNA template.

After formation of the complementary DNA strand carrying these various drug building blocks, the drug fragments are brought in close proximity with each other to react — only drug fragments associated on the same DNA template will react. Thus, a unique DNA template directs the synthesis of a unique small molecule. Also, the small molecule remains attached to the DNA template that encoded it and thus becomes traceable. This is important, as the structure of the molecule will be traced and recreated using the underlying DNA template.

The small molecule-DNA template complexes generated in the first step then are run over an immobilized target in a chromatography column. Small molecules that bind to the immobilized targets are held back and later eluted, and the underlying DNA template is amplified using PCR. From the amplified templates the actual small molecule lead structures can be identified.

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Downstream assays are subsequently applied to the eluted small molecules, Subhan said.

Chemetics thus not only does away with the substance library, but also merges all binding assays into a single assay step. By minimizing the assay steps involved, Nuevolution also minimizes the resource-consuming aspects of assays, such as setting them up in HTS format.

Because of the large size of the original DNA-directed library, which is 10^8 to 10^{14} molecules, Subhan said he expects that no further iterations of the process will be necessary to optimize leads.

The library size also minimizes the problem of false positives from assays for two reasons. First, by virtue of its size, it creates more shots on goal in the first run. Second, because the company doesn't build additional molecules off of each hit, including the false positives, it doesn't amplify the number of compounds that would be false positives. Thus, Subhan argued that the quality of the Chemetics leads equals that of optimized leads from traditional processes.

By comparison, Subhan said, the capacity to screen using physical compound libraries is about 10^6 small molecules per month. He believes that the 10^2 - 10^6 times larger libraries created using Chemetics will result in a proportionally larger number of hits with greater structural diversity.

Subhan said Nuevolution's business strategy is to reach early profitability by providing services to pharmaceutical and biopharmaceutical companies on a per target basis. In the medium to long-term, he sees the company out-licensing drug leads from internal drug discovery programs and developing its own drug candidates. Eventually, Subhan hopes Nuevolution will develop and commercialize its own drug candidates.

The company hopes to have DNA templates for creation of a 10^8 compound library available by the end of the summer and expand it to a 10^{14} compound library by summer 2004.

Subhan also hopes to close a series B round of \$13 million by mid-August.