Pharnext

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Pharnext: new therapeutic entities through *ab initio* combinations

Using trait networks (highly complex molecular networks that are perturbed in diseases), the NEXUS platform devises synergistic and patentable drug combinations.

Even though disease biology knowledge is increasing and the amount of money invested in drug development is continuing to rise, there have been few launches of truly innovative drugs over the past few years. So where is the future of drug development? Well, the answer may be somewhat surprising, according to Daniel Cohen, founder and CEO of French drug development company Pharnext. "There may be no such need to develop new chemical entities—there are already enough approved, safe, known therapeutics which could be used to develop patentable breakthrough therapeutics even when these compounds are off patent."

Cohen, a pioneer of genomics and cofounder of Millennium Pharmaceuticals, explained that he does not mean that chemistry innovation should cease but that the industry would need to take a new route—combining lower doses of approved drugs, known to be safe, to treat new indications. He called these new therapeutic entities 'pleodrugs'.

"The industry focuses on single new drugs, but nature does not focus on single targets, either to trigger complex diseases or to maintain health," said Cohen. "We already know that combinations of drugs can be better than single ones at treating diseases, for example, cancer, HIV/AIDS, hypertension or tuberculosis. In addition, the benefit of working with drugs that are already proven to be safe can speed the discovery and preclinical development process and decrease the failure rate, meaning that companies can move to clinical trials much more quickly."

Cohen added, "Drug toxicity poisons the pharmaceutical industry. Paradoxically, network biology suggests that increasing the number of compounds included in combinations could improve safety."

Pharnext's approach takes existing, approved off-patent drugs and natural compounds and formulates synergistic combinations that include doses 5-fold to 100-fold lower than those used for the original indication. The company uses its network biology platform, NEXUS, to create trait networks. It then targets these networks with low-dose combinations (**Fig. 1**). Pharnext has been granted a patent for its use of biological networks to find new drug combinations, and extensive trait networks for 20 diseases have already been created for internal use. These mostly focus on CNS, metabolic and inflammatory conditions.

The company's business model is to identify and develop proprietary pleodrugs with a focus on severe unmet medical needs. Charcot-Marie-Tooth 1A (CMT1A) is a severe neuromuscular disorder that affects peripheral nerves and leads to disabling muscle atrophy in the limbs. Pharnext is developing PXT-3003, a combination of two repurposed, approved off-patent drugs and one nutrient, as a potential disease-modifying drug to treat CMT1A in symptomatic adults. This lead pleodrug completed a positive phase 2 proof-of-concept study.

Figure 1. Pharnext uses its network biology platform known as Nexus to create trait networks (highly complex molecular networks that are perturbed by disease) to guide the development 'pleodrugs' novel, synergistic low-dose drug combinations for the treatment of disease.

"We expect to begin a phase 3 trial soon, after only 6 years of R&D compared with around 12 years for a new chemical entity. This first pleodrug could reach the market as early as 2018," said Cohen.

There have been many failed attempts to improve the treatment of Alzheimer's disease. Pharnext's PXT-864 has potential as both a symptomatic and a disease-modifying treatment. It combines two repurposed, approved off-patent drugs, both at low synergistic doses. After showing improvements in normal and chemically perturbed cognitive function in healthy individuals and requiring only three years of R&D, PXT-864 has now moved into phase 2 clinical trials. The first efficacy results should be available in 2014, with PXT-864 reaching the market in 2019.

Preclinical work suggests that other pleodrugs based on PXT-864 also have strong potential in mild cognitive impairment, amyotrophic lateral sclerosis (ALS) and Parkinson's disease, with efficacy trials planned for these conditions in 2014–2015. The company also has a pleodrug pipeline for the treatment of type 2 diabetes. In parallel, Pharnext is also using trait networks to assess and then validate sets of biomarkers for all these diseases to support clinical trials or as predictive markers for disease prevention.

Pharnext's aim is to become a full-fledged drug development company. "We are confident that we can take our products through to phase 3 trials, so we will soon offer options for commercial rights rather than looking for partners for development deals," Cohen said.

Pharnext has already been granted its first patents for combinations of off-patent drugs. Philippe Becker, patent attorney at Becker & Associés, said, "Patentability is a common and understandable *a priori* question, but even when using off-patent compounds, well-selected pleodrugs offer patentability characteristics that are no different than single new chemical entities." In addition, potential concerns often associated with classical use patents (for example, off-label use and compounding) do not apply in this case.

The company's management team has years of experience in drug development and has worked together for a long time. Philippe Pouletty, general partner of Truffle Capital and cofounder of Pharnext, sees a strong future for the company. "Pharnext's approach to pharmaceutical development is a paradigm change, and we all are very excited," he said. "In a time where drug companies are struggling to get products to the market, and with just 35 employees, this company has already taken its first two pleodrugs from discovery to positive clinical trials after only six years of existence."

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