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Innovations

Speed Dating for Molecules CombinatoRx Looks for That Special Synergy

Coming up with a novel drug can make a company's fortunes, but the overall cost of screening for new candidates is sizeable even before clinical trials. Thus, companies search for any possible shortcuts to the process. Boston-based start-up CombinatoRx (www.combinatorx.com) promises faster and cheaper drug discovery by conducting the equivalent of speed dating for molecules. The company screens paired combinations of generic, pharmacologically active compounds in the hope of stumbling upon desirable interactions that can be turned into therapies.

Curious Liquids

The former Curious Liquids café on the corner of the Boston Common was a grotto-like brick building that looked like an apothecary shop. For a group of young researchers in the late summer of 1999, it was a splendid place to concoct a thoroughly modern pharmaceutical venture. "I got together with Mike Foley and Alexis Borisy, and shortly thereafter we brought Curtis Keith on board," recalled Brent Stockwell, assistant professor of biological sciences at Columbia University, where he researches signaling networks underlying disease phenotypes. "We were looking to start a biotech company. We realized that disease was a multi-factorial process. But most of the pharmaceutical industry, the biotechnology industry, was focused on finding single magic bullets that could reverse a complex disease phenotype. And to us it didn't make sense. We recognized that … when clinicians treat cancer, for example, a cocktail of four drugs is the standard type of regime that is used, or with HIV therapy, a triple cocktail of three drugs is the standard of care."

Stockwell and his colleagues decided to screen combinations of active small molecules to look for synergistic effects. "There are about 2000 drugs approved in the U.S.," said Stockwell. Choosing just pairs, those 2000 compounds would give 2 million potential candidates.

Founded in March 2000, and funded with $2.5 million in angel investments, CombinatoRx has since raised a total of $180 million. This includes $90 million in three rounds from investors such as Boston Millennia Partners, Canaan Venture Partners, and Flagship Ventures; the $44.3 million raised in its IPO in November, 2005; another $48 million from a private placement in March, 2006; and revenue from partnership agreements. As of April 2006, the company had about $90 million left in the bank.

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A Little Agnosticism Goes a Long Way

Using pre-approved compounds, CombinatoRx screens pairs of drugs, bypassing the time-consuming synthesis stage that marks the start of most companies' drug discovery efforts. As the company is working with known drugs, they can tap available data on toxicology, dosing, and formulations. According to Stockwell, the idea was to acquire protectable intellectual property on the combinations and quickly develop them as drugs. "There is a 30- to 40-fold cost savings [over novel molecule screening]," Stockwell said, "Clinical trials will be disease-specific and will cost the same or be even slightly more expensive." By following this strategy, CombinatoRx hopes to reduce the time it takes to bring a drug from discovery to clinical trials.

After CombinatoRx researchers identify a promising match, they then determine the optimal concentration ratio for the two compounds. A dose response matrix is used to quantify the combination effect between each pair in which the concentration of each drug is varied and the corresponding biological activity is monitored. The results of the binary combinations are then analyzed, in the hope that the efficacy of the sum will exceed that of the parts.

CombinatoRx draws inspiration from systems biology. Instead of analyzing individual components or aspects of an organism, systems biologists focus on the overall system. "We believe that biology and, moreover, diseases, are complicated, poorly understood, and that, in most cases, a single agent targeting an individual molecular target is probably not going to be sufficient to address, and certainly not to cure, a particular disease," said Grant Zimmermann, Ph.D, director of Screening and Technology Development at CombinatoRx. "The idea is that we are looking for unanticipated effects. We are looking for novel combinations of approved drugs. We are trying to be very agnostic. We just look at the data."

Unlikely Bedfellows

CombinatoRx's matchmaking produces some odd couplings. For instance, CRx-026, the company's Phase I cancer candidate, is a combination of chlorpromazine, an antipsychotic drug, and pentamidine, an anti-parasitic drug. While ostensibly this combo could help you remain calm and parasite-free, CombinatoRx hopes it will cure you of cancer. By choosing such an unlikely pair of compounds, the company hopes to strengthen their claim on the end product intellectual property. "The vast majority of drugs are

generic," said Alexis Borisy, CombinatoRx president and CEO. "So if you find a surprising, novel, non-obvious combination between a pair, something that you never could have predicted a priori, by that definition of it being novel and non-obvious, it is a patentable invention … The trump patent is the composition of matter of that combination regardless of its use."

CombinatoRx is hoping to graduate from pairs to trios, but since 2000 compounds would produce over 1.3 trillion triplets to be combined and further screened for optimal concentration, the screening and data analysis could be too time-consuming for a company of their size. Moreover, while CombinatoRx's methodology is applicable to novel molecules, the likely consequence of delving into unapproved compounds is the loss of their preclinical cost advantage.

Their basic approach still has risks. While the company is attempting to set up robust intellectual property barriers, they acknowledge in their 2006 10K annual report that doctors can simply prescribe two generic drugs in tandem instead of their drugs. As for the question of why physicians won't do just that, "The formulation, the aligned release products that we create, does not exist on the market place, so there is nothing there for them substitute the products for," said Borisy. "The PK/PD [pharmacokinetic-pharmacodynamic profile] is highly relevant."

Then there is the regulatory risk: while CombinatoRx can bypass preclinical testing with its known compounds, the specter of synergistic side effects might spook the FDA, and the agency might ask for further clinical testing based on the drugs' combined pharmaceutical effects. The agency could also require tests because the drugs used are essentially being applied off-label or for long-term, rather than acute, treatment. "A lot of compounds go through this preclinical testing… to make sure they are 'clean,' meaning they don't significantly interact with those enzymes or receptors associated with hazardous health conditions, even though they might not have anything to do with the activity they are looking for, so these same tests could discover a negative synergistic effect," said Peter Hodder, associate professor of biochemistry at Scripps Institute in Florida. "They can know with reasonable assurance that they are not hitting the most clinically known things. Of course, you can't test absolutely every organ or system with a particular drug, but that is what clinical trials are for."

Molecular Mixology Gains Momentum

Despite the potential risks, other companies and research ventures are eager to try the combinations approach. In 2006, CombinatoRx signed a $250,000 collaboration with Fovea Pharmaceuticals, SA, for candidates to treat eye disease, worth $20 million in potential milestone payments. In 2005, the company cut a $42 million multi-year deal with Angiotech Pharmaceuticals for $27 million upfront and a $15 million purchase of CombinatoRx stock, as well as the possibility of additional millions in milestone payments, and licensed CRx-026 to HenKan Pharmaceutical Company of Taiwan for $500,000 upfront and potentially $23 million in milestone payments. The company also conducted $500,000 in screening work for Novartis.

In a bid to make Singapore a biotech hub, the country's government is disbursing economic development money to lure biotech companies to set up shop there. In August 2005, CombinatoRx launched a subsidiary, CombinatoRx Singapore, in conjunction with Bio*One Capital, to screen for combinations of compounds to treat infectious diseases such as hepatitis, with an initial $2.5 million grant from Singapore's Biomedical Sciences Investment Fund Pte, Ltd. and potentially an additional $17.5 million in milestone payments.

CombinatoRx has also been collaborating with neurodegenerative disease foundations such as CHDI, which focuses on Huntington's Disease, the Spinal Muscular Atrophy Foundation (SMA Foundation), and Accelerate Brain Cure (ABC^2), which is looking for brain cancer therapies. Additionally, the company received a $4.4 million grant in 2005 from the National Institute of Allergy and Infectious Diseases for anthrax toxin research.

Everything but the Kitchen Sink

CombinatoRx currently has six candidates in clinical studies and others in the preclinical pipeline for the treatment of immunoinflammatory diseases and other ailments, including four selective steroid amplifiers, CRx-139, CRx-102, CRx-119 and CRx-170, in Phase II. The company's clinical stage synergistic cytokine modulator, CRx-150, combines an antidepressant and a cardiac drug. CombinatoRx also has early stage metabolic candidates.

In April, the company announced encouraging results for CRx-170, its oral asthma drug in Phase II trials, which combines budesonide, a steroid, with nortriptyline, which amplifies the steroid's effectiveness at treating lung inflammation, so less can be used, reducing side effects. "We reported spectacular results with CRX-102 [an anti-inflammatory arthritis drug]," said Borisy. However, one anti-inflammatory, CRx-119, did not meet its primary endpoint biomarker for periodontal disease, although the company is still testing it for other disease indications, and CRx-140 for psoriasis was discontinued.

According to Borisy's cheery assessments, the company has a 50% rate of success of advancing candidates to Phase II trials, which is above the industry success rate of 20%–30% for Phase II data. "So even if we were only at 25%, we would still be enormously successful because our cost going from the start of a screen to that Phase II data is $10 million or less fully loaded, where the industry average, [according to the Tufts DiMasi Study] without capital weighting adjusting cost and taking the lower number is $150 million," Borisy elaborated, "I would make the strong form of the claim that some time in the future, whether it is fifty years or a hundred years from now, sooner or later, that most new drugs will in fact be combinations, will be multi-targeted in nature, whether with a single molecule or cocktails of molecules. That is the big picture idea behind CombinatoRx. Our approach of the empirical dumb screening today to find these pairs that no one would have predicted is meant as the first small step."

Curious liquids, indeed.

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