

BUSINESS

The right combination

Instead of the painstaking process of developing new drugs, one Boston-based company is making its mark by pairing up those we already have. **Meredith Wadman reports.**

Drug research largely boils down to the search for ‘magic bullets’ — molecules that act against single, specific biological targets. But putting each candidate bullet through its paces is a laborious and expensive business. Flying in the face of convention, a young biotech company in Boston, Massachusetts, has adopted a very different approach, and has so far been well rewarded for its efforts.

CombinatoRx (pronounced Combinatorix) is the brainchild of Harvard chemistry PhD dropout Alexis Borisy and several pals, all of whom worked in the lab of leading chemical biologist Stuart Schreiber.

In 1999, over hot chocolate in a favourite cafe, Borisy, Michael Foley and Brent Stockwell dreamed up a scheme to abandon the search for new molecules in favour of redeploying existing drugs. They planned simply to fire combinations of existing drugs at a range of biological targets that mimic diseases to see which proved effective, and then patent and sell the successful pairings. Back-of-the-envelope maths told them that the 2,000 unique drugs already approved by the US Food and Drug Administration — most of which are off-patent — would yield some 2 million two-drug combinations to be tested.

It was a “very simple, dumb, empirical, brute-force approach” to drug discovery, says Borisy. But it made intuitive sense. Single drugs usually modify a particular cell signal involved in a disease. Yet the body rarely sends a cellular signal using just one molecule — instead several signalling networks are typically acted on by lots of molecules at multiple points. So rather than trying to knock out one point on a pathway, Borisy and his friends reckoned it might be possible to use two drugs to hit the right combination of targets.

Business-wise, this search for molecular synergy had a lot in its favour. By testing approved drugs — whose chemistry and pharmacology are already understood — the company could, they hoped, catapult itself through the early stages of drug discovery, saving tens of millions of dollars.

“The discovery process was reduced to

chief scientific officer at Infinity Pharmaceuticals in nearby Cambridge. “That’s the coolest part of the whole enterprise.”

Within nine months, the trio — joined by Curtis Keith, also from Schreiber’s lab — had secured seed funding and hired their first employees. They began building a prototype screening system in a basement lab in downtown Boston. That involved adapting existing systems to accommodate pairs of compounds, instead of individual agents. They ended up with a proprietary system that evaluates 36 different dosing configurations at once for many pairs of compounds. The first million or so combinations they screened produced 300 interesting pairs. Seven of these are now in clinical trials, with a much larger group in the pre-clinical pipeline, according to Borisy, who is now the company’s chief executive.

In their spare time, the group raised \$90 million in venture capital (most of it now spent) and signed licensing deals with other companies worth \$58 million. CombinatoRx went public in November, adding another \$44 million to its coffers (see chart).

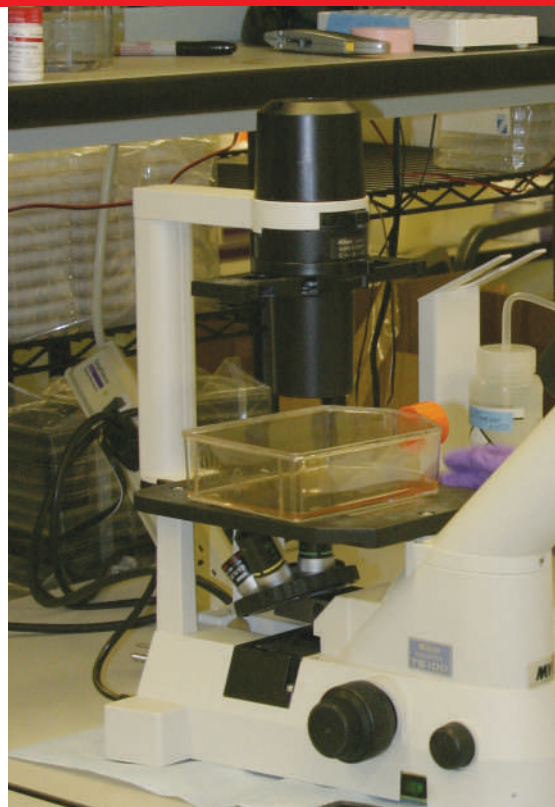
“Most people would have said: ‘This is crazy, these four kids right out of grad school starting a publicly traded company,’” muses Stockwell, a co-founder and adviser to the company, who is now at Columbia University in New York. “But here we are with \$100 million in the bank.”

The current phase I and II clinical trials are testing combinations against rheumatoid arthritis, psoriasis, asthma and metastatic cancers such as colon and lung. The mixtures involved are nothing if not unconventional. For one, the anticlotting agent dipyridamole is

“The company is doing something really unique.”

— **Danny Cummings**

paired with the steroid prednisolone to treat rheumatoid arthritis. The idea is that the dipyridamole boosts the effect of the steroid, allowing a lower dose of prednisolone and so causing fewer side effects. In another, the anti-fungal pentamidine is battling cancer aided by the antipsychotic chlorpromazine.



Joint effort: a CombinatoRx researcher tests a drug combination on cancerous cells.

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Dynamic duos

“They’re doing something really unique,” says Danny Cummings, an analyst who reports on CombinatoRx for Hoover’s, a business information service in Austin, Texas. “In five years, they’ve got seven products into clinical trials for a total cost of less than \$50 million. The average cost to develop a new prescription drug is \$802 million.”

But some observers have expressed concerns about safety, arguing that uncharted toxicities could emerge just as easily as unpredicted therapeutic effects. Borisy counters that the company’s safety testing is thorough. “Synergy is rare, whether good or bad,” he adds. “We will certainly be safer than any new chemical entity.”

Nevertheless, investors in the company face two big questions. What will stop doctors from writing separate prescriptions for cheap, generic versions of the components that make up the products? And will US health insurers pay out for a combination when the generics are each available more cheaply?

“It’s the most obvious concern,” says Adams. “The only way I can think around it is that they are using different doses of the drugs than are currently manufactured, making a combination drug more convenient.”

CombinatoRX share price





more besides, to protect its carefully patented combinations. The company is, for instance, using timed-release formulations that make its two-part recipes difficult to mimic.

His arguments have certainly swayed some investors. "They've gone to great lengths to refine the timing of the combinations and the dosage," says William Hunter, chief executive of Angiotech Pharmaceuticals, a biotech firm in Vancouver, Canada. Last October, Angiotech agreed to pay CombinatoRx \$42 million — plus up to \$460 million in downstream milestone and royalty payments — for access to its database and the rights to develop active combinations for specific applications, such as preventing internal scarring after surgery.

Simple considerations of convenience may also play a big role, argues Ted Ashburn, head of business development at Dynogen Pharmaceuticals in Waltham, Massachusetts. "It is inherently easier for doctors to write, and for insurers to reimburse, one prescription versus two — and for patients to take a single tablet versus two."

One precedent suggests that CombinatoRx will be able to charge reasonable, if not exorbitant, rates for its pills. NitroMed, of Lexington, Massachusetts, makes BiDil, a congestive heart-failure drug targeted at African-Americans. Based on two off-patent components, BiDil costs up to \$11 per day — roughly double the cost of the generics.

That, the CombinatoRx crew hopes, is a harbinger of things to come. "I obviously have a personal, financial and emotional stake in the company," says Stockwell. "But if you really believe in the approach, then CombinatoRx should by rights become the largest and most successful pharmaceutical company in the

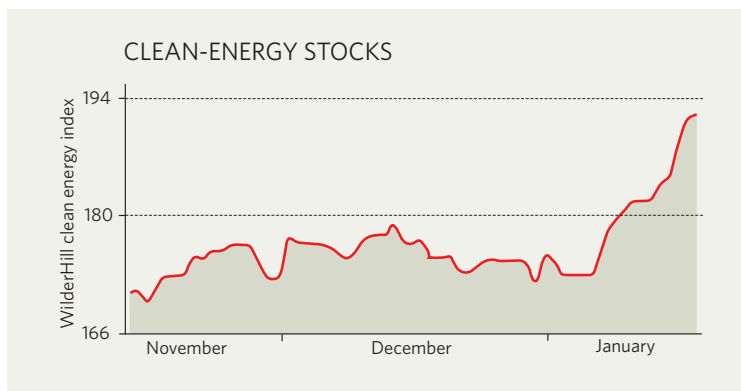
IN BRIEF

BIOCRIST BUOYED The US Food and Drug Administration last week agreed that potential flu drug peramivir can be fast-tracked through the approval process. Made by BioCryst Pharmaceuticals of Birmingham, Alabama, peramivir is an injectable drug that may be able to treat avian flu. News of its fast-track status sent BioCryst's share price soaring — it closed up 17.6%, at \$22.41, on the day of the announcement. The fast-track process means that fewer data have to be shown before the drug's approval for use in humans. BioCryst's shares have more than doubled in value since the start of October, boosted not only by peramivir but also by the launch of an anticancer drug trial and a licensing deal with Roche (see *Nature* 438, 737; 2005).

CHIPPING AWAY Just one day after Intel disappointed Wall Street with fourth-quarter results that were weaker than expected, its chief competitor revealed record sales for the same period. On 18 January, Advanced Micro Devices of Sunnyvale, California, the second-largest manufacturer of the chips that run personal computers, announced sales of \$1.84 billion for the fourth quarter, up 45% on the previous year. This suggests that despite being the world's leading semiconductor maker, Intel may be losing more market share to its arch-rival than it has acknowledged.

PFIZER STRUGGLES Hounded by generic competition, Pfizer, the world's largest drug-maker, reported lacklustre results for the fourth quarter of 2005. At \$2.73 billion, net income was down 3.3% on the previous year. Fourth-quarter revenues fell 8.9% from 2004, to \$13.59 billion. In a statement, Henry McKinnell, Pfizer's chief executive, called 2005 "one of the most difficult years in memory". But the latest results weren't as bad as investors had feared, and the firm's share price closed up 4% at \$24.97 on 19 January, the day the results were announced.

MARKET WATCH



SOURCE: ECO

Stocks in companies with interests in alternative energy sources breezed into the new year, with investors particularly excited by the prospects for solar power.

The WilderHill Clean Energy Index (ECO on the American Stock Exchange) moved forward on the back of news about successful share offerings in a couple of solar-panel companies. The sector is also benefiting from a general sense that the uncertainty about oil and gas supplies that dogged major nations in 2005 won't dissipate any time soon — leaving people more positive about energy sources that were once considered to be on the fringe.

"Solar stocks are taking off," says Robert Wilder, whose company, WilderShares in Encinitas, California, maintains the ECO index. An initial public offering (IPO) for SunPower, a solar-panel maker spun off by California-based Cypress

Semiconductor in November, raised \$139 million. Then last month, an IPO for China's Suntech Power netted \$455 million — not bad at a time when many young companies are struggling to get initial public offerings off the ground. "Solar-panel companies are growing at 30-40% each year, and they are typically selling everything they can produce," Wilder says.

But it's not all rosy for alternative-energy suppliers. Companies working with hydrogen or fuel cells "continue to disappoint", Wilder says. Many of the smaller ones, he adds, are now "running out of money".

This week, WilderHill and London-based New Energy Finance will launch a new market index tracking more non-US companies than ECO, reflecting the strength of demand for energy from renewable sources in Europe and Asia. ■

Colin Macilwain