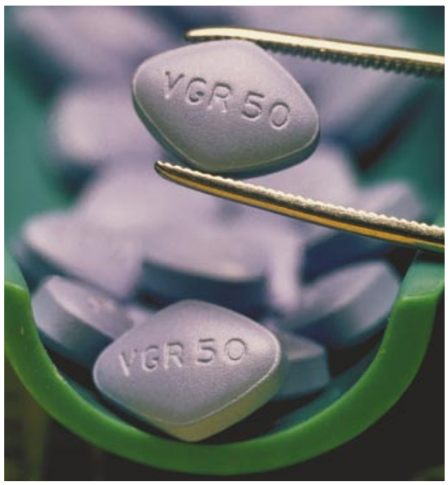
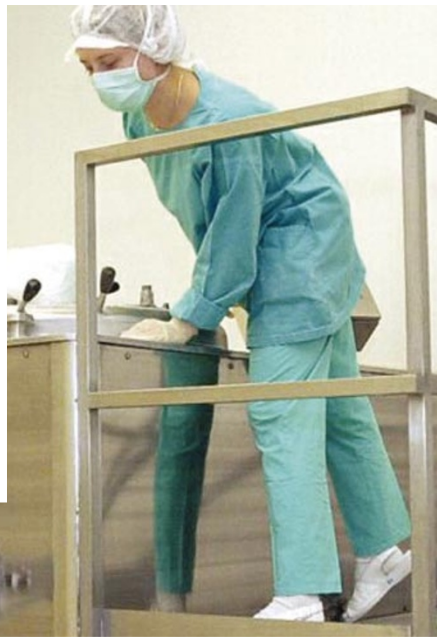
Goliath befriends David

Increasingly, the drugs giants are outsourcing research in drug discovery to start-up companies. Tom Clarke and Helen Pearson analyse an emerging trend, and ask what both sides expect to gain.





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AP

Big business: large firms are desperate for fresh leads to replace current blockbuster therapies.

Eighty-five million dollars — that's how much the drugs arm of German chemicals giant Bayer agreed to pay CuraGen of New Haven, Connecticut, in January this year. In return for this upfront purchase of its stock, the biotech firm signed a deal promising to deliver around 80 obesity and diabetes drug 'targets' mined from human genome data over five years.

This move was seen by industry insiders as confirmation of a growing trend for big pharmaceutical companies to contract start-up firms to do the initial stages of drug development — the discovery of molecules that have the potential to become profitable drugs. "The size of that one deal blew everyone away," says John Hefti of Signature BioScience, a start-up in Hayward, California.

Biotech firms have always sought to sell their ideas to drugs giants. And the giants have also kept a close eye on developments in the biotech sector — on occasion buying companies that have developed a promising product portfolio. For example, in 1990 Swiss-based Roche took a controlling interest in Genentech of South San Francisco, one of the trailblazers of the biotech sector.

But over the past few years, the relationship between start-ups and larger firms has changed. Rather than cherry-picking candidate drugs developed by biotech companies, or swallowing firms that are poised to become profitable, the large firms are contracting out an increasing proportion of drug discovery — work that traditionally would have been done by chemists and pharmacologists in the firms' in-house laboratories. The companies winning these contracts include those in the biotech sector, plus others that are exploiting information technologies or novel approaches to pharmaceutical chemistry.

In part, this trend is driven by mounting economic pressure on the large companies to find replacements for existing blockbuster drugs. At the same time, drugs giants are realizing that the explosion of drug-target data from the human genome is beyond their own capabilities to pursue. But creative new ideas for exploiting such data are feeding numerous start-up companies — and the big firms want to buy into a piece of this action.

Discovery channels

Some within the industry believe that a fundamental shift is under way. Ultimately, they predict that the discovery of new molecular leads may become the preserve of smaller companies, leaving the giants to develop candidate molecules into practical drugs, and putting these through clinical trials. "It's certainly a plausible scenario," says David Floyd, vice-president of discovery chemistry for the US company Bristol-Myers Squibb.

Others argue that the current vogue for outsourcing drug discovery is a sensible strategy while uncertainty reigns over which technologies will be needed to reap a windfall from genomics. Once clear technological winners emerge, these experts contend, the big firms will take the outsourced work back into their own labs.

In any case, argues Ben Shapiro, executive vice-president for worldwide licensing and external research with the US giant Merck, the big companies will need in-house expertise in drug discovery to inform decisions on which start-ups to link with. "The better the internal scientists, the better our decisions about external relationships," he says.

What is clear is that the giants' existing sources of income are drying up. Many of the highest-earning drugs will soon be coming off patent. And the drugs 'pipeline' of compounds awaiting development and testing is running dry. To maintain profits, the big firms need novel drug leads, fast. Start-ups are now getting bigger and better deals with the giants mainly because the latter are "desperate for the drugs", says Joseph Dougherty, a biotech analyst at Lehman Brothers in New York.

So what sorts of technologies are featuring in the current wave of contracts? Rapid and sophisticated versions of structure-based drug design, in which molecules are

DE NOVO PHARMACEUTICALS


SYRRX

Turning genomics into drugs: researchers at De Novo (above) and Ray Stevens of Syrrx (right).

synthesized to fit known sites on proteins involved in disease, are proving popular. Astex Technology, for instance, is a company in Cambridge, UK, that uses X-ray crystallography to determine the structures of drug targets. It then selects fragments of potential drug compounds that look as if they should bind to the active site under investigation. Astex's scientists let these molecules bind to the target site and they then determine the structure of the resulting complex.

This allows Astex to look for weak interactions between the potential drug molecules and their targets that might have been missed using traditional bioassays. Molecules that show promise can then be tweaked to enhance binding. "We're doing intelligent chemistry," says Harren Jhoti, one of the company's founders. The two-year-old firm already has a deal with the Anglo–Swedish firm AstraZeneca to provide crystal structures of cytochrome P450s — enzymes that metabolize drugs — complexed to AstraZeneca's compounds.

Working out which of the estimated 10^{60} potential drug candidates might bind to a protein's active site is a formidable task. And several start-ups are now offering bespoke software to help design molecules with just the right structure. "A computer can generate a far larger number of solutions than a chemist," says David Bailey, chief executive of De Novo Pharmaceuticals in Cambridge, UK.

De Novo, a 1999 spin-off from the University of Cambridge's pharmacology department, feeds known structures of protein binding sites into software that constructs virtual molecules piece-by-piece to fit. To avoid making the mistakes of early structure-based drug designers — whose tailored molecules often proved difficult to produce — each time a fragment is added, the structure is checked for ease of synthesis and similarities to molecules that are known to be toxic. Last year, the company struck a deal — the details of which have not been disclosed — to provide drug leads to the Franco–German company Aventis.


MERCK

On target: Merck uses in-house expertise to help decisions on which projects to outsource.

Binding contract

But Raymond Salemme, chief scientific officer of 3-Dimensional Pharmaceuticals (3DP) in Yardley, Philadelphia, argues that approaches that rely on establishing the structures of potential drug targets are unnecessarily cumbersome. Instead, 3DP is probing changes in the thermodynamics of the bonds between a library of 200,000 drug-like molecules and putative drug targets, before details about the structure of the binding site are known. Essentially, 3DP looks for changes in the temperature at which the protein targets 'denature', or break apart, which increases when molecules are bound tightly to them.

When they spot a promising drug candidate, 3DP's chemists produce a range of related molecules and screen them through iterative rounds of molecular fine-tuning. "If you have a target, we can develop a high-affinity compound," claims Salemme. The company is already doing just that for Bristol-Myers Squibb. In return for producing molecules that bind with high affinity to at least 30 targets, 3DP is getting an upfront fee of $19 million, plus research funding of $14.4 million over the first three years of the collaboration, and a share in subsequent royalties.

Other companies are developing novel high-throughput screens in which thousands of compounds can be tested for biological activity. Signature BioScience, for instance, throws compounds onto a range of cell lines and, by firing radio- and microwaves at them, monitors any physiological effects, such as a change in shape, ion flow or protein movement. "It's quick and dirty," admits Hefti, but by rapidly weeding out compounds that generate unwanted effects the company hopes to home in on potential drugs, again without knowing the target beforehand.

In most of the deals currently being struck, the start-ups get a fee up front and the rest on delivery. The drugs giants "don't pay for much unless we're successful", says Hefti. This allows the start-ups to recoup the investment made in them by venture capitalists. And, in the most part, the start-ups are happy to let the larger firms take over the later stages of drug development: they accept that they lack the financial resources, or familiarity with the regulatory procedures, needed to proceed through preclinical drug development and clinical trials.

Dreams of grandeur

But some of the smaller companies have ambitions to join the ranks of the giants. Vertex Pharmaceuticals of Cambridge, Massachusetts, is one such firm. In May last year, it struck a deal with Swiss-based Novartis promising to deliver eight compounds targeted against protein kinases, a family of enzymes implicated in a wide range of diseases including cancer and cardiovascular disease. Vertex will be responsible for drug development and the first phase of clinical trials — in which drugs are tested on small numbers of patients to check for side effects — before handing over to Novartis. If Vertex meets all of the milestones agreed under the deal, it could earn $800 million.

How the relationship between start-ups and the big firms will develop in the long term is unclear. But given the diversity of drug discovery technologies that are currently emerging, the trend for outsourcing seems set to continue for some time yet.

What the industry is waiting for is a proven technological platform for translating genomics data into candidate drugs on a factory scale. "Some day someone's going to become the Henry Ford of drug discovery," predicts Ray Stevens of the Scripps Research Institute in La Jolla, California, and co-founder of Syrrx, a company that is working on structure-based drug design. Stevens, for one, believes this breakthrough will come from a fleet-footed start-up, rather than from a large pharmaceutical firm. ■

Tom Clarke and Helen Pearson are both members of *Nature*'s science writing team.