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BIOPHARMACEUTICALS

The engineering of drug discovery

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Present-day industrialized drug discovery is built on a technological foundation consisting of combinatorial chemistry, genomics, and high-throughput screening—a source of novel molecules, a source of novel targets, and a method to assay one against the other, respectively. These core technologies are still evolving rapidly at most major pharmaceutical companies, but one can begin to see a paradigm that will likely be with us for decades. New opportunities are emerging downstream of the foundation trinity. These include automated medicinal chemistry, high-throughput forms of toxicology, drug metabolism, and pharmacogenomics as a high-throughput form of pharmacology. This broadening drug discovery paradigm is leading to innovation from a broader base of professionals drawn from many disciplines, especially engineering.

I have worked at the interface between drug discovery and engineering for nearly 15 years—enough time to see trends and to conclude that a legitimate role will soon be served by engineering contributions to the industrialization of drug discovery. Engineers come in all forms, including mechanical, electrical, and chemical engineers; software developers; material scientists; spectral/optical scientists; and semiconductor physicists. They come from many other industrial areas and are already being pursued by biopharmaceutical companies with the foresight to realize the importance of their skills to drug discovery. There is also a growing demand for scientific professionals in biology and chemistry with an aptitude in or inclination toward engineering. The migration of process development chemists and engineers to drug discovery is an indication of the opportunities that lie ahead.

In many ways, this is nothing new—this industry has had engineers producing various bits and pieces for years—but their new role will go well beyond designing synthesizers, sequencers, and plate washers. Functional blocks of laboratory processes are now finding their way into miniature versions and into massively parallel arrays. These functional blocks are being linked in larger numbers and in more complex systems than at any previous time.

The design of the discovery operations of any pharmaceutical company employing enlightened industrialized drug discovery technologies is now more the object of engineering than of chemistry or biology. *Design requirements* and *functional specifications* are foreign to most scientists in the pharmaceutical industry, at least as they apply to their drug discovery operations. A catch-up process is now under way, as exemplified by the creation of enterprise-wide informatics infrastructures. Schematics, schemas, and specifications are the emerging trade secrets of the industry.

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Big science is coming to drug discovery, and the strategic high ground requires a new vocabulary: screening-synthesis autonomous feedback loops, inventory access, just-in-time synthesis, data mining engines, search agents, microfluidics, process bottlenecks, and even enterprise-wide informatics with push technology. These are all coming on-line and will change drug discovery forever. Such processes will free up time that scientists can apply to experimental design as well as to finding answers to questions that otherwise would be impossible to obtain.

If we benefit from 100 automated sequencers producing a few megabases per day, then what will the world be like when we can get a few gigabases per day? When it takes 8 weeks from request to receipt to synthesize 96 new analogs, what will the world be like when this happens in 8 hours? When it takes a human, aided by software, several hours to decide what screening results mean and what analogs might be worthwhile synthesizing in the next iteration, then what will the world be like when a dozen such decisions are made and integrated through synthesis and screening without any human intervention at all? It now takes a day just to physically write out nested BLAST searches with match-contingent search branching; what will the world be like when millions of branch searches take place in an hour guided by automated inputs from diverse, self-annotated databases, including protein information and screening data?

As in the computer industry, where computing power has doubled every 18 months, engineers will make huge leaps in drug-discovery power possible. Executives in the pharmaceutical industry, particularly those from the disciplines of biomedicine, biology, and chemistry need to take very serious note of what is happening.

This is not a claim that chemists and biologists will become obsolete—clearly not. Rather, the claim is that most companies are sitting on human resources and expertise that are in need of liberation to pursue significantly improved forms of drug discovery. If you observe the activities of the average high-performing, top-notch, bench-level PhD chemists at a big pharmaceutical company while they are physically working in the lab, and ask what exactly do these highly trained individuals do with their time, the answer is that they watch beakers, or perform some other equally mundane task. They should be more creatively engaged.

In most of the world, production tooling often makes more creativity possible. Automation does not automatically lead to a reduction in quality—it often makes it possible to get more from our human resources, to gain strategic advantage by innovative industrialization. The pharmaceutical industry just happens to be the latest industry to industrialize its core processes.

We live in exciting times in the drug discovery industry. At the moment, throughput is the word of the day. I think *effective throughput* will become increasingly important. For example, as more and more of the genome is sequenced, the means of sequencing new read-frames are important (unless polymorphisms are the objective). Otherwise, even as your sequencing throughput increases, the effective new throughput can decrease. One of the biggest areas for the future is the integration of synthesis with screening, eventually replaced by pharmacogenomic screening, which will move to become a primary screen from its current role well downstream. I also look to miniaturization technologies and microchemistry to bring new capabilities at higher throughputs and lower costs.

From all this emerging capability and infrastructure, I think we can expect high-quality compounds and screening data, along with new molecular targets, which will yield many compounds ready for the march through clinical trials. I am optimistic that freeing up high-quality time for scientists will make it possible to address unmet medical needs as never before. ///

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