remains largely uncharted territory. However, we think its features may end up looking something like a cross between the drug and biotechnology fields. As with other approaches to small molecules, the drugs themselves should obtain a scope of patent coverage ascertainable by rather well-established criteria of novelty, nonobviousness, utility, and enablement. It seems unlikely that the sort of winner-take-all battles characteristic of recombinant-DNA patents will occur very frequently, if at all, in the field of molecular diversity. However, companies that discover important targets may attempt to claim their use in various drug-discovery methods, including molecular diversity. In addition, several companies have been issued or applied for patents covering certain approaches to molecular diversity. These include, for example, Chiron's (Emeryville, CA) "mimotope" patents on methods of preparing and screening combinatorial peptide and peptoid libraries, Protein Engineering's (Cambridge, MA) patent on the use of phage libraries, and Nexagen's (Boulder, CO) patent applications on the Selex oligonucleotide technology developed by the University of Colorado (Boulder, CO.)

Like other methods of small-molecule drug discovery, molecular-diversity programs follow a different rhythm than protein-based discovery and development. In a prototypical recombinant-DNA project, a novel human protein is postulated to have pharmacologic utility in some disease state. The name of the game is to be the first to isolate, clone, and patent the molecule. Having succeeded in this effort, there is usually very little that can be done to improve upon the natural protein. Thus, such discoveries can be published at an early stage without competitive disadvantage, and their path into clinical development may be comparatively short. By contrast, early disclosure of a small-molecule lead could enable competitors to develop equivalent or superior products, and may only frustrate investors as the compound undergoes one or more years of optimization prior to a decision to begin formal clinical development. ///

Funding through alliances

NEW YORK—Biopharmaceutical firms will increasingly seek funding through corporate alliances, since product development is becoming more difficult and more expensive and since accessing public equity and even private equity is increasingly troublesome. This was one of the themes discussed at a recent conference here that was entitled "Accessing Capital: Innovative Financing Strategies for Biotechnology Companies and Their Financiers" and that was sponsored by International Business Communications (Southborough, MA).

Even the earliest biotech companies relied heavily on corporate alliances for funding. Indeed, the most successful biopharmaceutical firms—including Chiron (Emeryville, CA) and Genentech (S. San Francisco, CA)—used "early corporate partnering not so much to develop specific products, but to furnish early equity following their seed financings," states Linda Cahill, vice president of Johnson & Johnson Development Corporation (New Brunswick, NJ). For instance, of the $14 million raised by Genentech in the three years before its 1979 initial public offering (IPO), just $2 million came from venture capitalists, while fully $12 million came from corporate partners. "And $10 million of the $12 million came from Lubrizol (Wickliffe, OH), which was investing mainly because it was fascinated by the science," says Cahill. In Chiron's case, of the $8 million it raised in the two years preceeding its 1983 IPO, venture capitalists contributed only $1 million and Martin Marietta put up the remaining $7 million. "Again, the bulk of the funding came from a player outside the industry who was simply interested in biotechnology," Cahill states.

The early corporate investors profited handsomely. For Chiron's early investors, the internal rate of return (IRR) following the firm's IPO totaled 97 percent. For Genentech's early investors, the post-IPO IRR came to 52 percent.

These returns far surpass those generated by the 70 biotech firms in the IPO class of 1991-1993, as 60 percent of these firms produced 27 percent IRRs for early investors, on average. Explains Cahill, "Biotech product development has become a much tougher game. Genentech's insulin and Chiron's hepatitis B vaccine were products that, for the most part, were already in the body. They were known therapies, and the only difference with the genetically engineered versions was the production method. These easy targets are gone. Most of the products that the new IPO class are working on are small molecules that aren't in the body and, if they are, they don't have anywhere near the established efficacy profiles of insulin or hepatitis B vaccine."

With product development far more challenging and, thus, far more costly, the newer biopharmaceutical firms will have an even greater need for corporate-alliance funding. "Such funding can be fairly substantial. In fact, it can be about equivalent to an IPO," states Mark Edwards, managing director of Recombinant Capital (San Francisco, CA). Edwards studied a universe of 100 alliances between multinational corporations and biopharmaceutical firms, with fully 74 of these alliances occurring from 1989 to 1992. In 49 of these 100 alliances, the average precommercialization payment to the biopharmaceutical firm totaled $25.1 million. Typically, this payment included a $15 million research-and-development payment, a $10.7 million milestone payment, a $9.3 million equity purchase, and a $3.3 million upfront payment.

The equity-investment component of over 100 strategic alliances involving biotech companies was examined by Tom Smart, associate director of business development at Cell Genesys (Foster City, CA). In fully 80 percent of the alliances, the strategic partner purchased the biotech-company equity at a premium, compared to the biotech company's prior financing. These premiums totaled 67 percent for private companies, on average, and just 19 percent for public companies. "Market cap is the determining factor. Low private-company market caps have a lot more room to rise than high public-company market caps," Smart states.

—B.J. Spalding

Biotech firms need corporate-alliance funding because product development is becoming more costly and accessing public equity is increasingly troublesome.