HGS drug flop latest genomics setback

In April, Human Genome Sciences (HGS; Rockville, MD) abandoned development of Mirostipen, a phase 2 drug designed to fight low white blood cell levels in chemotherapy patients. In 1997, the myeloid progenitor inhibitor factor-1 received a lot of attention as the first genomics-derived drug to move into clinical trials (*Nat. Biotechnol.* **16**, 129, 1998). Its biological activity was found to be unsatisfactory, however, and the company is now shifting it resources to another, non-genomics-based, protein drug for the same use. Investors drove down HGS stock more than 20% after the announcement, pushing shares to $14.25 in mid-May—down 80% from the 52-week high of $77.00. The drop reflects additional concern on the part of investors that genomics-derived drugs, once touted as following a quicker, less risky path to drug approval, will face the same hurdles in development as do other biotechnology products.

The promise of genomics technology helped drive the biotechnology sector to record heights two year ago, but analysts have since realized that the potential of genomics for drug development is not likely to be fulfilled any time soon. And although biotechnology share prices as a whole are struggling, with the Amex Biotechnology Index down more than 40% from its highs of last June, genomics companies are faring especially poorly. In addition to HGS, Celera Genomics (Rockville, MD) is down 72% from its 52-week high, and Millennium Pharmaceuticals (Cambridge, MA) is down 63% from its 52-week high. "There was a huge set of goods that was promised that hasn't been delivered," says John McCamant, the editor of the Medical Technology Stock Letter (Berkeley, CA). "It really was over-promise, under-deliver."

Indeed, despite securing financing during the peak of the genomics frenzy in early 2000, so-called genomics companies are unable to rely on genomics-derived drugs to fuel their businesses. For example, HGS's stated aim is to discover, develop, manufacture, and sell its own genomics-based drugs, yet of the seven drugs HGS is testing in humans, three are not derived from genomics technology but are rather improved, extended-release versions of existing proteins. HGS chief executive William Haseltine says the focus on the extended-release products, a technology it acquired in 2000, represents only an effort to "spread the risk" of drug development, not a move away from genomics, which carries the highest risk of failure but the highest potential payoff. "I think every responsible pharmacy company tries to balance risk," says Haseltine, adding, "At this point, people are down on genomics. People have counted it out way too soon."

Likewise, Millennium, which boomed on the promise of its "gene-to-patient platform," has only one drug in clinical trials aimed at a genomics-derived target. The company, however, has guided one non-genomics-derived drug, the cancer treatment Campath, to US Food and Drug Administration (Rockville, MD) approval, and Millennium derives most of its revenue from Integrilin, a non-genomics-derived anticlotting agent it acquired when it bought Cor Therapeutics in December 2001 for $2 billion in shares, almost an 80% premium (*Nat. Biotechnol.* **20**, 11, 2002). Still, Millennium says it remains committed to using genetic information to find drugs. "It's happening," says John Maraganore, the company's senior vice president for strategic product development. Maraganore acknowledges that "the expectations far exceeded the reality from a timing standpoint" but says the company will start clinical trials of three or four other drugs later this year.

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And Celera, which is seeking to turn its human genome–decoding prowess into new therapies (see p. 536), does not yet have any drugs of any kind in clinical trials. In fact there are no blockbuster genomics candidates on the cusp of approval anywhere. Analysts have only modest expectations for Repifermin, the wound-healing drug (keratinocyte growth factor-2) in phase 2 trials that is now HGS's most advanced candidate. And although Millennium and Amgen (Thousand Oaks, CA) have both announced that they are testing genomics-derived drugs, little data on those products, still in the earliest phases of testing, are available. "The market definitely overestimated the rate at which products come out," says Erick Noensie, an analyst at Thomas Weisel Partners (New York). "It's not going to be a bolus of product, but more of a slow trickle."

Nevertheless, companies ranging from pharmaceutical giants such as GlaxoSmithKline (London) to biotech firms like Incyte Genomics (Palo Alto, CA) are continuing to comb through genetic data in hopes of improving drug development, and analysts insist that despite the disappointments, the technology should not be disregarded. "I don't think it [recent setbacks] invalidates the idea behind it," says Michael King, an analyst at Robertson Stephens (New York). "You go through a reality period. Every new technology goes through this." Even McCamant, who says that biotech investors are still "feeling the pain" of excessively high expectations from the technology, thinks that genomics will eventually bear fruit.

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Genta strikes bumper deal with Aventis

On April 29, cancer therapeutics firm Genta (Berkeley Heights, NJ) and Aventis (Frankfurt, Germany) announced an agreement to jointly develop and commercialize Genta's lead antisense therapeutic, Genasense. The deal provides Genta with $480 million in cash, equity, milestones, and convertible debt—the second-highest amount a large life science company has ever paid for a single biotech drug. Analysts say the high price boosts Genta as a business and further validates antisense as a technology, and deny that it is a sign of desperation on the part of Aventis to fill its depleted pipeline.

Genasense would be the first oncology drug to use an antisense mechanism to target mRNA in the apoptotic pathway. It reduces the production of Bcl-2, a protein that is expressed in over 70% of all cancers and is known to block the effects of chemotherapy. The drug's ability to enhance the effectiveness of chemotherapy (by promoting apoptosis) is being tested in patients with melanoma, multiple myeloma, and chronic lymphocytic leukemia, and phase 3 trials are expected to be completed in summer 2002, with a launch anticipated in the third quarter of 2003. Analysts at Needham & Co. (New York) say Genta has positioned itself well by choosing a highly relevant target and testing it for 12 indications—a huge potential market justifying the value of the deal. Genasense is also