Case Study

Assessing the history and value of Human Genome Sciences

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ABSTRACT

Human Genome Science (HGS) aspired to dominate the emergent field of genomics by discovering expressed gene sequences and developing therapeutic and diagnostic products based on proprietary genes. While HGS' accomplishments fell short of their own lofty expectations, by the time HGS was acquired by GlaxoSmithKline, the company had extensive intellectual property and had launched a product with >$1 billion market potential. Nevertheless, HGS' acquisition price was less than the total capital investments in the company. This work examines HGS' history and accomplishments in the context of the business plan described by the company at their IPO. We focus specifically on the company's valuation over time, which was highly correlated with general market indices, but negatively correlated with metrics of technical or clinical progress. The history of HGS points to the challenge of accounting for the value created by a science-based business plan. Earnings-based metrics, present value calculations, and "fair value" assessments did not account for HGS' progress in executing their stated business plan. This work highlights the critical need for accounting practices that credit value to the progress of translational science and enable investors to profit from such investments.

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INTRODUCTION

Human Genome Sciences (HGS) was not a company with normal ambitions. At its founding in 1992, HGS aspired to dominate the newly emergent field of genomics by being the first to sequence and patent all of the genes expressed from the human genome and develop a pipeline of therapeutic and diagnostic products based on these genes. The company's outsized ambitions were advertised in elaborate annual reports, which featured Greek gods and saints as metaphors for the company's search for knowledge and fight against disease. By the time HGS was acquired by GlaxoSmithKline (GSK) in 2012 for $3.6 billion,[1] the company could claim many accomplishments, but had ultimately failed to fulfill its own lofty expectations. The story of HGS is an exemplar of the ambitions and aspirations of the biotechnology industry in general, and its denouement provides insight into the challenges that prevent this industry from fulfilling its promise. What happened to HGS? What was its value? What can the biotechnology industry learn that will be of value in the future?

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A SHORT HISTORY

The history of HGS begins with Craig Venter's ambitious proposition that all of the genes expressed by the human genome could be discovered by shotgun sequencing of

expressed messenger RNA sequences, termed "expressed sequence tags" (EST). In 1992, two investors, Alan Walton and Walter Steinberg, who were among the first to recognize the commercial potential of Venter's approach, arranged for the founding of two organizations. The Institute for Genetic Research (TIGR), a non-profit scientific enterprise led by Venter, would undertake high-throughput sequencing of ESTs. Human Genome Sciences (HGS), a commercial enterprise led by William Hazeltine, would provide financial support for TIGR, and have commercial rights to its discoveries. Within a year, HGS completed a landmark partnership with SmithKline Beecham, which provided additional capital investment, research funding, and experience in drug discovery and development.

In 1993, HGS filed for its IPO. The Company's S-1 filing described the company's goals as: "The Company's principal objective is to discover rapidly and obtain proprietary rights to a substantial portfolio of novel genes and to commercialize products based on those genes either alone or in collaboration with corporate partners."[2] The strategy, as described in the S-1 filing, was "to identify rapidly the majority of the genes that comprise the human genome through partial sequencing and to select for further development those genes which have potential commercial value." Already by 1993, the S-1 stated that "…the Company believes it has, together with TIGR, identified approximately 25,000 human genes (including approximately 20,000 novel genes) of a total of 50,000–100,000 genes believed to exist."[2]

The relationship between TIGR and HGS was terminated in June 1997, and Venter turned his attention to sequencing the entire human genome through his association with a new company, Celera Genomics. By then, more than 162,000 non-overlapping ESTs had been sequenced. Of these ESTs, 82% were thought to represent the transcripts of previously unknown genes.[3] HGS' 1998 annual report summarized its gene discovery efforts thus: "Between 1993 and 1995, HGS' scientists isolated messenger RNAs corresponding to what is estimated to be more than 95 percent of all human genes."[4] The report also described an emphasis on a "functional genomics" program, which included gene expression profiling to "analyze gene expression of each of the more than 11,000 newly discovered secreted protein genes" as well as "high-throughput, robotic-cloning method to produce small amounts of each newly discovered secreted protein" and the analysis of 12,000 genes using this method.[4]

On the business development front, HGS assembled a "Human Gene Consortium" of pharmaceutical companies including SmithKline Beecham, Schering-Plough, Takeda Chemical, Synthelabo, and Merck KGaA, to partner in drug discovery and development. These companies provided HGS with financial and technical support, and integrated HGS' intellectual property and methods into their partner's internal development programs. When the consortium agreement expired in June 2001, an HGS press release noted that "Consortium members have identified approximately 460 research programs for the creation of small molecule, protein, and antibody drugs, involving about 280 different genes. We believe there is substantial value in these partnerships"

The first clinical trials with proteins discovered through EST sequencing began in the late 1990s. In 1995, HGS initiated clinical development of repifermin, a recombinant Keratinocyte Growth Factor-2 protein (KGF-2), to accelerate the healing of ulcers. In 1998, it initiated clinical trials for mirostipen, a recombinant Myeloid Progenitor Inhibitory Factor-1 protein (MPIF-1) for the treatment of neutropenia. Also in 1998, a third candidate product, a gene therapy incorporating the gene sequence for Vascular Endothelial Growth Factor-2 protein (VEGF-2) to treat atherosclerosis, was spun out to a newly formed gene therapy company, Vascular Genetics. None of these trials would proceed beyond Phase 2 (Table 1). In addition to using newly discovered gene sequences and their gene products as therapeutic entities, HGS entered into a partnership in 1999 with Cambridge Antibody Technology to develop monoclonal antibodies that would inhibit the function of the gene products discovered by HGS.

As the stock market started its exuberant climb in 1999 and Craig Venter joined Francis Collins at the White House to announce completion of the Human Genome Project in 2000, HGS was well positioned to capitalize on investor enthusiasm for genomics. The company had more than 100 issued patents, a robust clinical development pipeline, multiple corporate partners, and a high profile in the scientific and business community. The company raised a total of $1.4 billion dollars through two secondary offerings in 2000, and closed Q3 2000 with a market capitalization in excess of $8.5 billion. This financing bonanza allowed HGS to grow to over 1100 employees and purchase Principia Pharmaceutical for $150 million. This acquisition provided HGS with an expanded clinical pipeline of 20 candidate products based on existing, patent-expiring biological products as well as a technology applicable to pharmaceuticalizing gene products identified through HGS' gene discovery platform. Despite its formidable technical position and strengthening clinical pipeline, the end of the "dot.com" bubble caused HGS' stock to collapse. By the end of 2002, the company's market capitalization had dropped to $1.1 billion, only 13% of its peak value (Figure 1a).

HGS had limited revenues from 1993–2008, mostly from research relationships, and continued to invest

Table 1: Human Genome Sciences clinical portfolio 1993-2012. Phase 1: date of initiation of phase 1 trial; Phase: most advanced phase achieved; Status: status as of September 2013; Target: therapeutic protein or target; Gene #: sequence comprising product or target; Type: RP = recombinant protein, MAB = monoclonal antibody, CE=chemical entity, RP-alb=albumin fusion. Clinical status, target, gene #, and lead indication were identified in Pharmaprojects

Product	Phase 1	Phase	Status	Target	Gene #	Type	Indication
repifermin	1995	2	D/C	fibroblast growth factor receptor 2	2263	RP	UC/ulcers
raxibacumab (Abthrax)	2003	Launch	Launch	antigen, Bacillus anthracis, anthrax toxin receptor 1	84168	MAB	anthrax
streptococcus vaccine	2003	1	D/C			vaccine	infection
mirostipen	1998	2	D/C	myeloid progenitor inhibitory factor-1	6368	RP	neutropenia
ardenermin	2000	1	D/C	tumour necrosis factor superfamily, member 13b	10673	RP	immunodeficiency
darapladib	2001	3	Active	phospholipase A2, group VII	7941	CE	atherosclerosis
albinterferon alfa-2b	2001	3	D/C	interferon (alpha, beta and omega) receptor 2	3455	RP-alb	hepatitis C
belimumab (Benlysta)	2001	Launch	Launch	tumour necrosis factor superfamily, member 13b	10673	MAB	lupus
albumin-IL-2 fusion (Zalbin)	2002	FDA	D/C	interleukin 2 receptor, alpha	3559	RP-alb	cancer
BLyS radiolabelled	2002	1	D/C	tumour necrosis factor superfamily, member 13b	10673	RP	cancer
HGS-TR2J	2002	1	D/C	tumour necrosis factor receptor superfamily, 10b	8795	RP	cancer
mapatumumab	2002	2	Active	tumour necrosis factor receptor superfamily, 10a	8797	MAB	cancer
albutropin	2002	1	D/C	growth hormone receptor	2690	RP-alb	GH Deficiency
lexatumumab	2003	1	D/C	tumour necrosis factor receptor superfamily, 10b	8795	MAB	cancer
CCR5mAb004	2005	1	D/C	chemokine (C-C motif) receptor 5	1234	MAB	UC, HIV/AIDS
albiglutide	2005	3	Active	glucagon	2641	RP-alb	diabetes
SSR-411298	2005	2	D/C	fatty acid amide hydrolase	2166	CE	pain/depression
rilapladib	2006	2	Active	phospholipase A2, group VII	7941	CE	Alzheimer's
FP-1039	2008	2	Active	fibroblast growth factor receptor 1	2260	RP	cancer
HGS-1029	2008	1	D/C	baculoviral IAP repeat containing 3	330	CE	cancer
SAR-115740	2009	1	D/C	transient receptor potential cation channel, subfamily V1	7442	CE	pain

heavily in R&D (Figure 1b-c). The company would ultimately invest more than $2.7 billion in R&D, which resulted in consistent growth of a product pipeline, as estimated by the number of Predicted Product Approvals (PPA) (Figure 1d). PPA estimates the number of products likely to be approved based on the number of candidates in each stage of clinical development and the historical approval probability for candidates at that stage.[6] HGS continued to expand its intellectual property with steady growth in the number of issued patents (Figure 1e). Nevertheless, HGS' market capitalization tracked below the cumulative capital investment in the company for most of the decade. By end of 2008, its market capitalization would be only $264 million, less than 3% of its peak value and only 11% of the total capital raised (Figure 1a).

In 2009, HGS had three applications before the FDA. One was for Zalbin (albinterferon alpha-2b), a fusion protein that had been tested in two pivotal phase 3 trials for chronic hepatitis C. The second was Benlysta (belimumab), a monoclonal antibody against BLyS (B-lymphocyte stimulator, or BLyS tumor necrosis factor

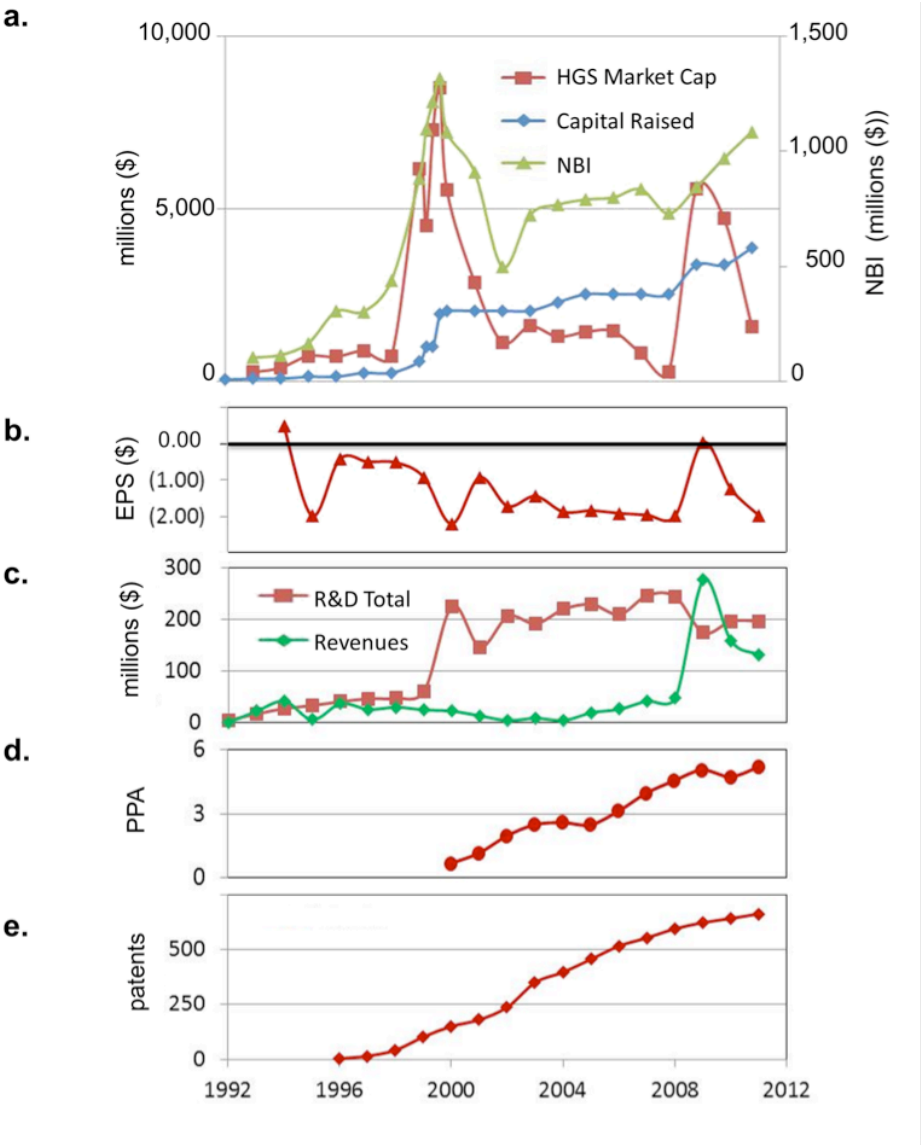

Figure 1: Human Genome Sciences: technical and financial metrics from 1992-2012. (a) left axis: market capitalization, total capital raised; right axis: NASDAQ Biotech Index (NBI) (b) earnings per share (EPS) (c) annual R&D spending and revenues (d) Predicted Product Approval (PPA) (e) number of patents issued to HGS. Financial data is from Standard & Poor's Capital IQ, patent data from www.uspto.gov, and clinical data is from Pharmaprojects

superfamily, member 13b), which achieved its primary endpoints in two pivotal phase 3 trials for Systemic lupus erythematosus (SLE). The third was ABthrax (raxibacumab), a monoclonal antibody intended to provide passive immunity against anthrax toxin, a product HGS had already begun to produce for the U.S. Strategic National Stockpile (Table 1). HGS' market capitalization began to rise precipitously from its nadir in 2008, reaching a peak of over $5.5 billion by the end of 2009. During this period, the company reportedly rejected a $7 billion acquisition offer from Amgen[7], choosing instead to raise over $850 million in additional capital through secondary offerings.

After many years of net negative earnings, HGS achieved profitability in 2009 (Figure 1a), largely due to revenues from the manufacture of ABthrax for the U.S. Strategic National Stockpile. The company anticipated positive earnings after 2012, based on the approval of the drug applications then before the FDA, but in June 2010, Zalbin received unfavorable reviews from an FDA advisory committee. A review committee also asked HGS to provide additional data on ABthrax, which was submitted in July 2012. The FDA's review of Benlysta in November 2010 highlighted questions about the safety and efficacy of the drug, leading to a 10% drop in the company's stock price the next day. When the drug was finally approved for the treatment of SLE in March 2011, HGS had a market capitalization of $6 billion. By year end, however, HGS stock had dropped precipitously based, in part, on disappointing early sales of Benlysta and negative earnings reports, and closed the year with a market capitalization of $2 billion.

It is worth noting that SLE is a challenging target for drug development and potentially a blockbuster market. Benlysta was the first drug to be approved explicitly for treatment of this indication since corticosteroids and Plaquenil in 1955, and Aspirin in 1948. SLE affects as many as 1.5 million people in the U.S. annually,[8] and analysts have variously estimated the market for Benlysta to be between $3.1 billion and $7 billion annually.[9]

In April 2012, GSK made a hostile offer to acquire HGS, offering $13 per share, an 81% premium on the company's stock price of $7.17 per share, a 52-week low. Although it initially rejected the offer, HGS ultimately was acquired for $14.25/share, or $3.6 billion, less than the $3.9 billion in capital investments that had been made in the company since its inception. The net acquisition price, $3 billion less cash and debt, included $2.6 billion in net operating loss carry-forwards and R&D tax credits, and allowed GSK to recapture 50% of Benlysta profits owed HGS through their alliance. Moreover, at acquisition, HGS had seven additional candidate products in clinical development including ABthrax, which was approved in December 2012.

DID HGS ACHIEVE ITS PLAN?

While few companies have so articulately or artistically captured the expectations for the nascent field of genomics in the 1990s, HGS' aspirations were not unique. Many entrepreneurs and investors believed that companies like HGS would not only be able to establish meaningful proprietary positions in human genes, but radically reform the processes for validating drug targets and drug discovery. It was widely expected that genomics would not only provide new targets for drug discovery, but accelerate the pace and efficiency of drug development. These expectations were evident in HGS' S-1 filing which described plans to "discover rapidly and obtain proprietary rights to a substantial portfolio of novel genes"[2] and commercialize "products based on those genes,"[2] as a means of creating economic value for its shareholders. Did HGS succeed in achieving these goals?

"a substantial portfolio of novel genes"

By the sheer number of genes sequenced, the combined gene discovery platforms of HGS and TIGR were successful. Early data from TIGR described the discovery of as many as 100,000 novel genes.[3] While these observations overestimated the number of genes in the human genome (later determined to number less than 30,000), it is likely that the sequences identified by HGS, in fact, included a substantial number of previously unknown genes. By the time HGS was acquired, more than 600 patents would be issued, testifying to their apparent novelty and utility.

HGS was not, however, the only enterprise engaged in EST sequencing in the early 1990s. Incyte Pharmaceuticals, founded in 1991, had an identical strategy of gene discovery by high-throughput EST sequencing and, by 2012, had more issued patents (>800). Also in 1994, Merck launched the Integrated Molecular Analysis of Genomes and its Expression (IMAGE) Consortium designed to place EST sequences in the public domain and systematically prevent companies like HGS and Incyte from establishing blocking, proprietary positions through gene discovery. Moreover, EST sequencing was widely practiced in investigator-initiated research through the early 1990s. Thus, while HGS did establish a substantial portfolio of intellectual property, it did not dominate the intellectual property landscape of the human genome.

"commercializing products based on those genes"

The initial optimism of scientists that genomics would radically advance drug discovery was short-lived. By 2001, a report from Lehman Brothers titled

"The Fruits of Genomics" called attention to the fact that genomic approaches to target discovery and validation were not sufficiently robust to add near-term value to pharmaceutical development, and that the novel targets provided by genomics were less-well characterized than previous drug targets.[10] The report predicted that the initial impact of investments in genomic technologies would be to slow productivity, increase costs, and decrease the present value of products in development. HGS' experience conforms to this prediction.

From 1992–2012, HGS commenced clinical trials of 21 candidate products (Table 1). HGS' first clinical trials of candidate products arising from its gene discovery and functional genomics platforms failed. It was not until 2001 that HGS began clinical development of Benlysta.

Benlysta is a monoclonal antibody targeted against tumor necrosis factor (TNF) superfamily member 13b, a protein involved in B-cell activation. The *TNFSF13B* gene, which expresses this protein, was described by HGS contemporaneously with papers from four other institutions describing the same target, referred to variously as B Lymphocyte Stimulator (BLyS), B-cell Activating Factor (BAFF), APOL-related leukocyte expressed ligand (TALL), or the Dendritic cell-derived TNF-like molecule.[11-15] Moreover, by the time Benlysta was approved, three other monoclonal antibody products targeted against different TNF homologues had already been approved including Remicade (1998) for Crohn's disease and both Humira (2002) and Simponi (2009) for Rheumatoid Arthritis. Moreover, two other monoclonal antibody products against the same target, Eli Lilly's tabalumab and Anthera Pharmaceuticals' blisibimod, were in late stage development as of 2012. Thus, while HGS was successful in commercializing at least one product related to its gene discovery and target validation platforms, it was not far ahead of the forefront of drug discovery or development.

At the acquisition in 2012, HGS had a product pipeline that would be predicted to produce 4–5 commercial products based on a calculated PPA. Significantly, many of these products are not genome-related and involve microbial targets or are albumin fusions of existing biological products (glucagon, growth hormone, interferon, and IL-2) designed to extend patient life and improve pharmacokinetics. These development programs did not originate with HGS' genomic platforms, but were enabled by HGS' ability to raise large amounts of capital based on the promise of genomics. HGS' experience in this regard is similar to that of other genomics companies such as Millennium and Incyte, which ultimately created less value from the gene sequences they discovered, than from their ability to raise capital based on the promise of their genomics platforms, which would subsequently be invested in more traditional drug discovery projects or acquisition of late stage products.

Return on investment

The $3.6 billion paid for HGS was less than the $3.9 billion of capital investments that had been made in the company. Thus, even without taking into account the inflation adjusted value of early investments or dilution from noncapital transactions, HGS provided a net negative return on shareholder investments.

A closer examination of HGS' market capitalization over time, however, provides a more nuanced picture. This analysis shows that each round of private or public investment provided investors with an opportunity to exit with a positive return (Figure 2). For venture capital investors, the IPO only 18 months after the initial investment provided a substantial step-up in valuation and the opportunity for liquidity. While HGS' stock traded below the IPO price for almost five years, the bull market of 1999–2000 offered opportunities for positive returns. Even investors who participated in two financings at the peak of the 2000 tech bubble had a window, though limited, to exit with a positive return before the stock collapsed in late 2000. Thus, venture investors, institutional investors, and investment banks had an opportunity to make money from HGS, even though the company failed to create long-term value. On average, however, investors who bought shares through public markets lost value.

ASSESSING THE VALUE OF HGS

At its inception, HGS was explicitly an R&D-stage, science-based business committed to a long-term program of discovery that was expected to identify product development opportunities. As such, HGS exemplified both the biotechnology industry's ambition and its ability to mobilize large amounts of capital for translational science. Throughout its history, HGSs valuation exemplified the greatest challenge facing the biotechnology industry, namely the absence of a rational relationship between market or accounting-based metrics of corporate value and the technical progress of companies focused on translating science for product development.

Like many start-up biotechnology companies, HGS overestimated the potential of its core technologies, the impact that genomics would have on the efficiency of drug development, and the timeline required to translate nascent science into approved products. Nevertheless, HGS ultimately did exactly what it promised investors; establishing a substantial portfolio of intellectual

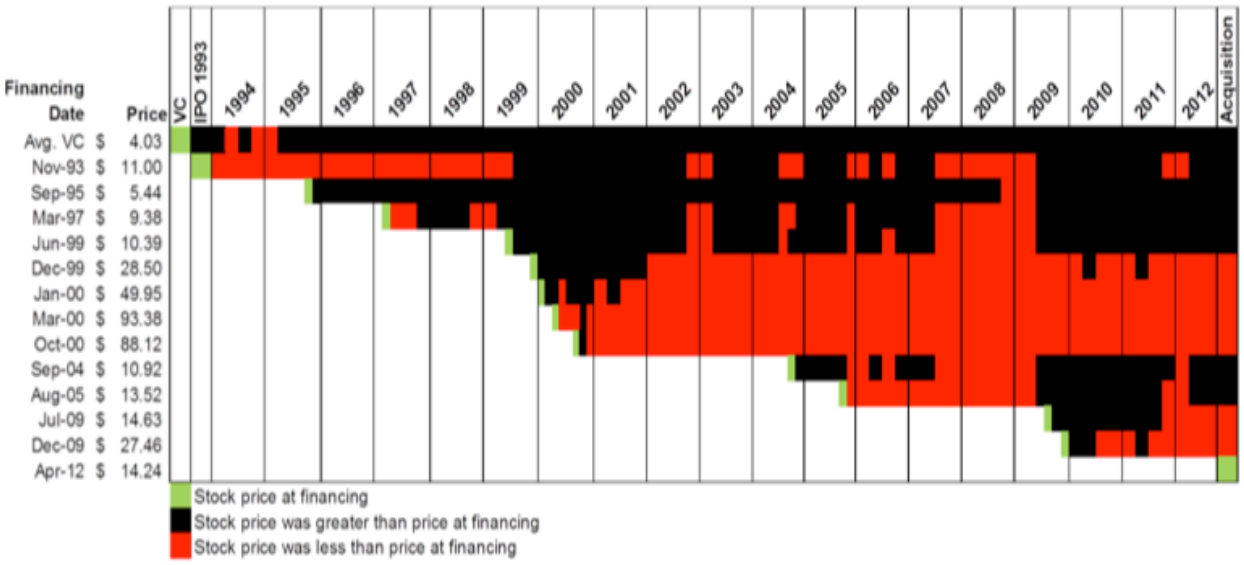

Figure 2. Return on Investment in HGS. Opportunities to exit with a positive return (black) or negative return (red) at the end of each quarter 1992–2012. Investment dates and prices are shown at left and indicated by green boxes. The average price of venture capital investments was determined from HGS' S-1A filed in November 1993. Other financial data is from Standard & Poor's Capital IQ.

property and a pipeline of promising products, as well as successfully launching an important product with billion-dollar potential. These accomplishments, however, were never reflected in HGS' valuation, and the company was ultimately acquired for a "fair value" that was less than the total capital investment in the company, and little more than the sum of its cash, R&D tax credits, and royalties owned on jointly-developed products.

HGS' market capitalization between 1993 and 2012 correlated significantly with general market conditions, as measured by the NASDAQ or NBI indices, but exhibited a significant negative correlation with the accumulation of intellectual property and maturation of its product pipeline, as measured by PPA (data not shown). Similarly, HGS' technical progress did not contribute to the 10-fold increase in valuation during the 1999-2000 "dot-com" bubble, the subsequent 30-fold decrease in valuation to a nadir in 2008, nor the fact that HGS' valuation was 3-fold higher in 2009, with no products on the market, than it was at the end of 2011, after Bentlysta was approved. The fact that HGS stock tracked with the NADAQ index, whose components are valued primarily by the economic performance of commercial products and consumer behavior, is counterintuitive given HGS' business plan focused on the advancement of translational science. The discordance between HGS' accomplishments and its valuation was highlighted in the disconnect between GSK's justification of its offer to acquire HGS for $13/share as reflecting the "fair value" of HGS,[16] while HGS argued that this offer failed to "reflect the value inherent in Human Genome Sciences."[1]

What is the "value inherent" in a biotechnology company such as HGS? Can this even be defined or measured? Earning-based value metrics are not relevant to research-stage companies that operate at a net loss. Moreover, such metrics systematically devalue R&D expenses of revenue-generating companies by decreasing earnings. Present value calculations can ascribe *de minimis* value to long-term development programs. Accounting standards that define the "fair value" of assets, including intellectual property, are heavily influenced by temporal market conditions. Most financial analysts focus on near-term fluctuations in stock price, which often reflect technical milestones, but not the steady technical progress that enables seminal milestones to be reached. Without minimizing the expertise and complexity inherent in evaluating intellectual property, intangible assets, alliances, management, tax credits, cash positions and other critical aspects of a company's strategic and financial position, a macroscopic analysis of HGS history suggests that such analyses failed to account for the technical progress of the company towards its goals. At acquisition, much of HGS' progress and intellectual property would have been accounted for simply as goodwill.

Pisano has argued that biotechnology is, at its core, a science-based business that requires distinct architecture and business models from other businesses.[17] One critical component of such architecture would be standards for valuing science-based companies that provide for a rational appreciation of value in parallel with a company's technological successes and failures.

Investors should be able to invest in the strategic goals of early-stage companies with the expectation that the company's technical success towards achieving these goals will be reflected in increasing valuations. The fact that such success may not be reflected in economic metrics of value creation constitutes a systematic disincentive for investment and entrepreneurial activity in general. This is evident in the current climate of investment activity, which increasingly eschews investments in translational science, in favor of investments in products whose value can be formally measured by traditional market-based metrics. Mechanisms that credit value to the course of translational science would enable investors to realize positive returns on investments in effective translational science and ensure that the industry continues to attract the capital required for groundbreaking research and development.

HGS is a conspicuous exemplar of both the promise of the biotechnology industry and also the challenges facing an industry focused on creating value through the translation of nascent scientific discoveries into successful products and sustainable companies. For the industry to continue mobilizing the large amounts of capital investment required for translational science, there needs to be greater alignment between milestones of translational progress and measures of the value that can be realized by investors.

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