Original Article

Multiyear patterns regarding the relative availability of venture capital for the US biotechnology industry

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ABSTRACT **Venture capital (VC) funding of US biotechnology companies was analysed relative to total VC investments placed in US companies from 1995 to 2007. During those years, except for a spike because of the dot-com bubble from 1999 to 2001, VC funding of US biotechnology companies grew at a faster rate percentagewise than total VC funding of US companies, with respect to annual dollars invested, number of deals closed and the mean dollar investment. Start-up and early-stage VC funding of US biotechnology companies also grew at a faster rate percentagewise, with respect to all three parameters, than total start-up and early-stage VC funding of US companies. It was further observed that long-term trends in the availability of VC for biotechnology do not appear to be affected by perturbations in the financial markets and short-term fluctuations in the availability of VC. It was concluded that the biotechnology industry should continue to attract VC over the long run particularly because of the emerging impact of personalised medicine and the coming of age of bioenergy.**
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INTRODUCTION

This study emanated from the author's consulting practice, where from time to time he has observed the difficulties that a few seemingly promising biotechnology companies have had in securing venture capital (VC). Presumably not every firm with an exciting technology or product platform will be successful in its attempts to raise VC. Moreover, papers occasionally appear portending a decline in the availability of VC for the biotechnology industry. For example, Dellenbach recently reported that during the second quarter of 2008, investments made by VC firms in US biotechnology companies were lower by more than 40 per cent, and

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the number of such investments declined by almost 50 per cent, as compared to the first quarter of 2008.[1] The availability of VC for the US biotechnology industry may fluctuate from quarter to quarter, but as a practical matter, it would be useful to ascertain long-term trends in the availability of VC for the biotechnology industry.

Previous reports on funding for biotechnology have appeared,[2–5] but their usefulness is limited in a number of ways, such as not breaking out VC funding from other types of funding, reporting on VC funding for periods shorter than a decade, reporting on VC funding for periods ending over 5 years ago, not comparing VC funding for biotechnology with total VC funding for all industries, not breaking out start-up and early-stage financing from expansion and later-stage financing, and not reporting on the number of investments made each year.

Comprehensive data have been reported recently on VC funding for the US biotechnology industry, as well as total VC funding for all US industries.[6] The data, however, were not presented as annual figures, but rather as quarterly numbers in lengthy tables, making it difficult to discern patterns. A preliminary review of these data suggests that over the long term the biotechnology industry has been relatively successful in obtaining VC and is likely to maintain its track record in attracting such funds.[7] The current study analyses multiyear patterns in VC funding for US biotechnology companies relative to total VC funds available and concludes that this sector has performed reasonably well in securing such funds.

METHODOLOGY

Quarterly data were obtained from the MoneyTree™ Report[6] for the first quarter of 1995 through the fourth quarter of 2007, regarding the level of VC funding and the number of such investments in US companies, broken out as follows: all investments, all start-up and early-stage investments, all biotechnology investments, and all start-up and early-stage biotechnology investments. Annual totals were then calculated, as were annual mean VC investments for each of the above categories.

The annual totals calculated from the MoneyTree™ Report[6] for the level of VC funding for all investments, all start-up and early-stage investments, and all biotechnology investments agreed closely with the corresponding annual figures reported in *Science and Engineering Indicators 2008*[5] (except that the latter publication did not list data for 2007). Data for the level of VC funding for all start-up and early-stage biotechnology investments, as well as all data regarding numbers of VC investments for all categories were not reported in *Science and Engineering Indicators 2008*.[5]

RESULTS

Figure 1 plots total VC investments in US companies from 1995 to 2007, with respect to dollars invested and number of deals closed. Such investments increased from US $8.0 billion funding 1842 deals in 1995 to $31 billion funding 3914 deals in 2007, except for a spike because of the dot-com bubble when VC investments amounting to $54 billion, $106 billion and $41 billion funded 5503, 7905 and 4478 deals in 1999, 2000 and 2001, respectively. The percentage increases in the dollars invested and the number of deals closed in 2007, as compared to the dollars invested and the number of deals closed in 1995, amounted to 288 and 112 per cent, respectively.

Figure 2 plots total VC investments in US biotechnology companies from 1995 to 2007, also with respect to dollars invested and number of deals closed. Such investments increased from $0.83 billion funding 170 deals in 1995 to $5.2 billion funding 488 deals in 2007. The percentage increases in the dollars invested and the number of deals closed in 2007, as compared to the dollars invested and the number of deals closed in 1995, amounted to 527 and 187 per cent, respectively. These percentage increases

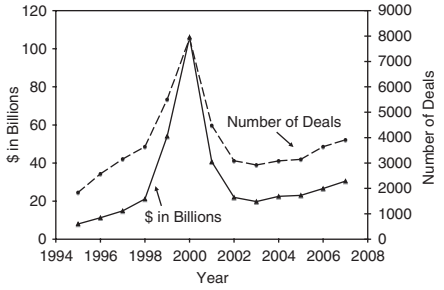

Figure 1: Venture capital investments in US companies.

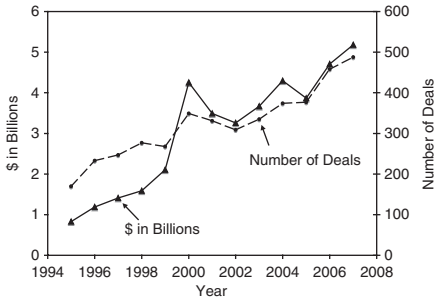

Figure 2: Venture capital investments in US biotechnology companies.

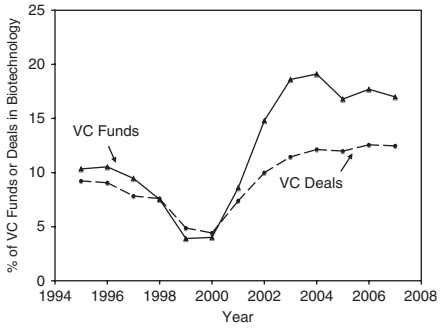

Figure 3: Percentages of venture capital (VC) funds invested and deals closed by VC firms in biotechnology companies.

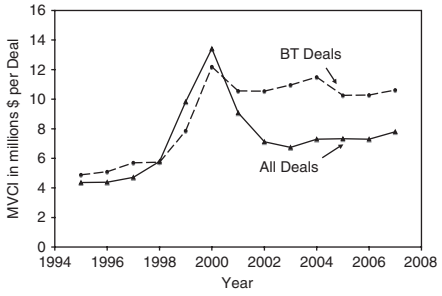

Figure 4: Mean venture capital investments (MVCI) in biotechnology (BT) deals and in all deals.

for VC investments in US biotechnology companies were 83 and 67 per cent larger than the corresponding percentage increases for all VC investments in US companies.

Figure 3 plots VC funds invested and deals closed in US biotechnology companies as percentages of all VC funds invested and deals closed in all US companies. Except during the dot-com years, when these percentages fell to around 4 and 5 per cent, respectively, they increased from an average of around 9.5 and 8.5 per cent, respectively, in the period from 1995 to 1998, to an average of around 17.5 and 11.7 per cent, respectively, in the period from 2002 to 2007.

Figure 4 shows that from 1995 to 2001, the mean VC investment for biotechnology deals was similar to the mean VC investment for all deals. From 1995 to 1998, the annual mean VC investment averaged $5.4 million for biotechnology deals and $4.8 million for all deals. During the dot-com era, the mean VC investment for both biotechnology deals and all deals rose sharply, peaking in 2000 at $12.2 million for biotechnology deals and $13.4 million for all deals. From 2002 to 2007, the annual mean VC investment averaged $10.7 million for biotechnology deals or 47 per cent greater than the corresponding average of $7.3 million for all deals.

The prior figures demonstrate that over the years the biotechnology sector has performed relatively well in maintaining and even increasing its share of VC funding. Moreover, it is not uncommon for the biotechnology sector to experience annual increases in VC funding even though one or two quarterly declines in such funding also occur in the same year showing an overall increase. Table 1 demonstrates that even in years in

Table 1: Quarterly decreases greater than 30 per cent in US VC biotechnology investments, compared to prior quarter, in years when US VC biotechnology investments increased compared to prior year

$ in millions invested per quarter			*$ in billions invested per year*		
Quarter – year	*$ in millions*	*% Decrease*	*Year*	*$ in billions*	*% Increase*
	Quarter 3 – 1996 vs. Quarter 2 – 1996			*1996 vs. 1995*	
Q3 – 1996	142	−60	1996	1.19	43
Q2 – 1996	351	—	1995	0.83	—
	Quarter 1 – 1997 vs. Quarter 4 – 1996			*1997 vs. 1996*	
Q1 – 1997	243	−36	1997	1.41	18
Q4 – 1996	379	—	1996	1.19	—
	Quarter 3 – 1997 vs. Quarter 2 – 1997			*1997 vs. 1996*	
Q3 – 1997	277	−31	1997	1.41	18
Q2 – 1997	399	—	1996	1.19	—
	Quarter 2 – 2000 vs. Quarter 1 – 2000			*2000 vs. 1999*	
Q2 – 2000	730	−34	2000	4.25	101
Q1 – 2000	1110	—	1999	2.11	—

which quarterly VC funding of biotechnology decreased by more than 30 per cent, compared to the prior quarter, there was annual growth in such funding. In fact, in 1997, there were two quarters characterised by a downturn in such funding, but annual VC funding of biotechnology in 1997 was 18 per cent higher than in 1996.

The following figures demonstrate the relative availability of VC for start-up and early-stage biotechnology companies. Figure 5 plots total VC investments in start-up through early-stage US companies from 1995 to 2007, with respect to dollars invested and number of deals closed. Such investments increased from $3.1 billion funding 940 deals in 1995 to $6.6 billion funding 1438 deals in 2007, except for the spike during the dot-com era when VC investments amounting to $15 billion, $29 billion and $9.4 billion funded 2518, 3536 and 1543 deals in 1999, 2000 and 2001, respectively. The percentage increases in the dollars invested and the number of deals closed in 2007, as compared to the dollars invested and the number of deals closed in 1995, amounted to 113 and 53 per cent, respectively.

Figure 6 plots total VC investments in start-up through early-stage US biotechnology companies from 1995 to 2007, also with respect to dollars invested and number of deals closed. Such investments increased from $0.46 billion funding 106 deals in 1995 to $1.5 billion funding 222 deals in 2007. The percentage increases in the dollars invested and the number of deals closed in 2007, as compared to the dollars invested and the number of deals closed in 1995, amounted to 226 and 109 per cent, respectively. Again, these percentage increases for VC investments in start-up through early-stage US biotechnology companies were larger than the corresponding percentage increases for all VC investments in US companies.

Figure 7 shows that the percentage of all VC funds committed to biotechnology that were invested in start-up through early-stage companies decreased from a high of 56 per cent in 1995 to an average of 22 per cent for the period from 2002 to 2007. This is similar to the pattern for all start-up through early-stage companies, in which the percentage of total VC funds that were invested in all start-up through early-stage companies gradually declined from 1995 to 2002, resulting in an average of 20 per cent for the period from 2002 to 2007. In contrast, the percentage of all VC funds committed to start-up through early-stage companies that were invested in

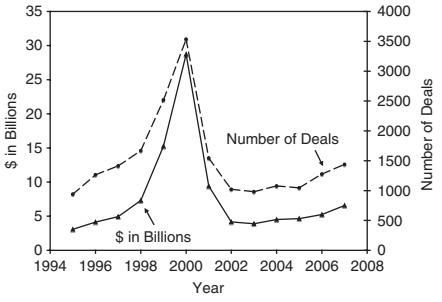

Figure 5: Start-up through early-stage venture capital investments in US companies.

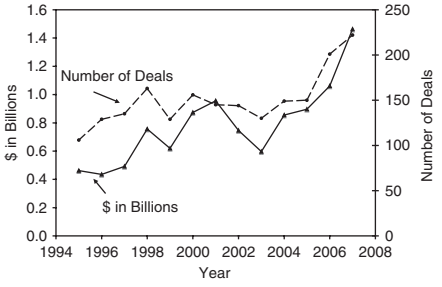

Figure 6: Start-up through early-stage venture capital investments in US biotechnology companies.

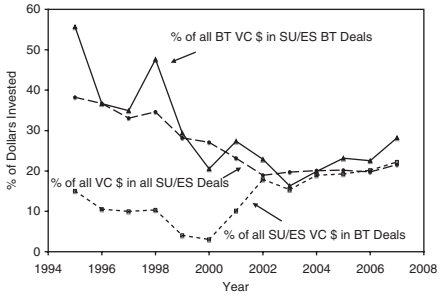

Figure 7: Relative amounts of venture capital (VC) invested in start-up through early-stage (SU/ES) biotechnology (BT) deals and in all SU/ES deals.

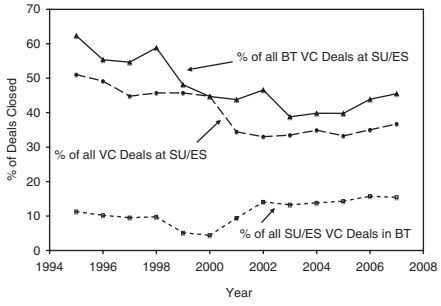

Figure 8: Relative numbers of venture capital (VC) deals characterised as start-up through early-stage (SU/ES) or as SU/ES in biotechnology (BT).

biotechnology increased from an average of 11.5 per cent for the period from 1995 to 1998 to an average of around 19 per cent for the period from 2002 to 2007. During the dot-com years of 1999 and 2000, however, the percentage of all VC funds committed to start-up through early-stage companies that were invested in biotechnology averaged just 3.5 per cent.

Figure 8 shows that the percentage of all VC deals in biotechnology that pertained to start-up through early-stage companies decreased from an average of almost 58 per cent for the period from 1995 to 1998 to an average of 42.5 per cent for the period from 2002 to 2007. This too is similar to the pattern for all start-up through early-stage companies, in which the percentage of all VC deals that pertained to start-up through early-stage companies decreased from an average of almost 48 per cent for the period from 1995 to 1998 to an average of around 33 per cent for the period from 2002 to 2007. On the other hand, the percentage of all VC deals in start-up through early-stage companies that pertained to biotechnology increased from an average of 10 per cent for the period from 1995 to 1998 to an average of 14 per cent for the period from 2002 to 2007. However, during the dot-com years of 1999 and 2000, the percentage of all VC deals in start-up through early-stage companies that pertained to biotechnology averaged just 4.5 per cent.

Figure 9 shows that from 1995 to 1999, the mean VC investment for start-up through early-stage biotechnology deals was similar to the mean VC investment for all start-up

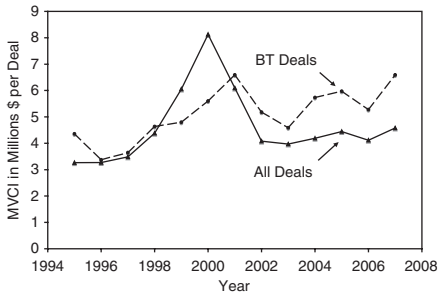

Figure 9: Mean venture capital investments (MVCI) in start-up through early-stage biotechnology (BT) deals and in all start-up through early-stage deals.

through early-stage deals. For that 5-year period the annual mean VC investment averaged $4.2 million for start-up through early-stage biotechnology deals and $4.1 million for all start-up through early-stage deals. In 2000, the mean VC investment for all start-up through early-stage deals spiked at $8.1 million, as compared to a mean VC investment of $5.6 million for start-up through early-stage biotechnology deals. Subsequently, from 2002 to 2007, the annual mean VC investment averaged $5.6 million for start-up through early-stage biotechnology deals or 33 per cent greater than the corresponding average of $4.2 million for all start-up through early-stage deals. Clearly, the start-up and early-stage segment of the biotechnology sector has also performed relatively well in competing for its share of start-up and early-stage VC funding.

DISCUSSION AND CONCLUSIONS

The current study demonstrates that VC funding of the US biotechnology industry has thrived over the years. Angel investors have also contributed substantially to the growth of the industry. As reported in *Science and Engineering Indicators 2008*,[5] total angel investments in US companies encompassing all industries grew from $18 billion in 2003 to $23 billion in 2004, $23 billion in 2005 and $26 billion in 2006, and 11, 10, 12 and 18 per cent, respectively, of these totals were invested in biotechnology companies. This means that angel investments in US biotechnology companies grew from $2.0 billion in 2003 to $2.3 billion in 2004, $2.8 billion in 2005 and $4.7 billion in 2006. Thus, from 2003 to 2006, angel investments in biotechnology increased 135 per cent, vs. 44 per cent for all angel investments.

The relative success of the biotechnology industry in obtaining VC and angel funds is reflected in the industry's growing demonstration of commercial success and in the corresponding market performance of public biotechnology stocks. It has previously been observed that 48 per cent of all biopharmaceuticals receiving US regulatory approval from 1982 to 2005 occurred in the period 2001 to 2005, which represented only 21 per cent of that 24-year period, and that from 1990 to 2005, the revenues of the 10 largest US biotechnology companies specialising in biopharmaceuticals increased from a total of around $1 billion to almost $32 billion, with the corresponding bottom line switching from a combined loss to a combined net profit exceeding $6 billion.[8] Moreover, from 1995 to 2005, the annual returns for the NASDAQ Biotechnology Index and the AMEX Biotechnology Index averaged just over 20 per cent, compared to the annual returns for the S&P 500 Index, the Dow Jones Industrial Average and the NASDAQ Composite averaging just under 10 per cent.[9]

An interesting question not explained by the results reported herein is why VC funding of US biotechnology companies has grown at a faster pace than total VC funding of US companies. The current study was not designed to answer this question. However, recapitulation of some relevant history coupled with data reported elsewhere may provide a four-part explanation.

First, a series of radical innovations in research methodologies, escalating in the 1970s and 1980s, provided the underpinnings

for accomplishing the basic research that led to the birth and fuelled the growth of the modern biotechnology industry.[10,11] These innovations made it possible to undertake novel experimental studies that revealed the molecular mechanisms by which normal cells function and how diseased cells differ and enabled researchers to produce highly purified quantities of macromolecules for further investigation.

Second, recognising the importance of potential applications emanating from advances in fundamental biology research, the US government tended since 1970 to increase its spending on such research from year to year, both in current and constant dollars, and to increase it relative to funding other research disciplines. The budget of the National Institutes of Health, the agency responsible for funding most biological research in the United States, grew from 7 per cent of total US government funds spent on R&D in 1970 to 30 per cent in 2005.[12,13] Total life sciences research funded by the US government grew from 36 per cent of all US government-funded research in 1980 to 53 per cent in 2005.[13] The pivotal role of the US government in funding both basic and applied biotechnology-related research was a powerful inducement for venture capitalists to invest in biotechnology. The ever-expanding biotechnology-related knowledge base funded by the government and residing mostly in the public domain was recognised as a true resource, freely available to commercial biotechnology R&D operations, providing some hedge against the considerable risks associated with biotechnology product development.[10,14]

Third, the founders of the early biotechnology companies, in the late 1970s and early 1980s, played a major role in generating both public awareness and public acceptance of biotechnology in the United States.[15,16] As discussed elsewhere, 'They appeared on radio and television, met with the press, educated members of the executive and legislative branches of government, spoke at town meetings and public conferences, and held open house at their laboratories. This proactive stance preceded the formation of an industry trade association and helped make possible the exponential growth of biotech companies during that era. In the early 1980s two trade associations were formed, the Industrial Biotechnology Association and the Association of Biotechnology Companies, which merged into the Biotechnology Industry Organization a decade later. These trade associations made it a priority to continue to address the concerns of the public regarding biotechnology'.[15] Venture capitalists were very much aware of the communication activities and outreach efforts of the early biotechnology entrepreneurs.[17,18] By 1981, 430 US biotechnology companies were open for business, the vast majority of which were not around in 1970, and by 1994, there were over 1300 biotechnology companies in the United States.[16] Outside of the United States, there were fewer than 100 biotechnology companies in 1981, but by 1994, the number of European biotechnology companies had grown to 475. As of 2006, there were over 5000 biotechnology companies worldwide.[3]

Fourth, the fundamental advances in molecular and cell biology made possible by government funding did lead to numerous applications in pharmaceuticals, diagnostics, agriculture and industrial processes. The cumulative number of biotechnology drug and vaccine indication approvals alone increased from 0 in 1980 to 366 in 2005.[8] The cumulative number of biotechnology patents awarded by the US Patent and Trademark Office (USPTO) to US applicants from 1980 to 2005 was 120 times larger than the number of such patents awarded in 1980.[5] In contrast, the cumulative number of patents pertaining to information and communications technologies that were awarded by the USPTO to US applicants from 1980 to 2005 was only 53 times larger than the number of such patents awarded

in 1980. In 2005, with respect to the top three industries in the United States receiving VC, information technology, biotechnology and communications technology received the first, second and third largest shares of VC.

Past performance would suggest that the outlook is positive regarding the biotechnology industry's long-term prospects for continuing to attract VC funds in order to fuel innovation and product development. However, in view of the global financial crisis that escalated rapidly beginning in September 2008, one might question the applicability of inferring prospects based on past performance. There is some precedent, nevertheless, for discounting the impact of perturbations in the financial markets on long-term trends in the availability of VC. In October 1987, the Dow Jones Industrial Average fell almost 23 per cent, and the closing high for that year, in August, was not reached again until almost 2 years later.[19] Yet, as noted by Andrews and Paytas,[4] VC funding of biotechnology companies was higher in 1987 than in 1986, and while it declined slightly in 1988, it was still greater than in 1986 and then increased significantly in 1989.

There are two major reasons why the biotechnology industry should continue to attract VC over the long run – the future impact of personalised medicine and the growing need to develop alternative sources of energy.

Personalised medicine represents targeted therapy based on genotype-dependent diagnostic results.[20] Research clinicians are now individualising 'diagnoses of people suffering from what would now be considered one disease into a number of related disorders',[7] each disorder diagnosed for the expression of a specific biomarker. As just one example, atherosclerosis may ultimately be diagnosed by detecting the expression of one or more of 38 biomarkers, any one of which that may trigger the symptoms. Rader and Daugherty[21] have identified 38 clinical and preclinical trials, each trial directed at a different therapeutic target, where each therapeutic target represents one of the 38 biomarkers for atherosclerosis or its risk factors.

It is explained elsewhere why personalised medicine represents a new paradigm that should be particularly attractive to VC firms seeking to invest in this technology.[7,20] In summary, the target population for each new therapeutic will be less heterogeneous and therefore smaller than in current pharmaceutical markets, but because of the customised features of these therapeutics, they are expected to achieve better clinical results with fewer side effects than current alternatives and with a lower probability of recall by the Food and Drug Administration (FDA). R&D costs should drop significantly because of smaller clinical trials with higher success rates than have been experienced previously, thereby leading to high rates of return on niche market-directed therapeutics. Experience thus far indicates that the length of time required to complete clinical trials and obtain FDA approval, typically 10–12 years for non-personalised therapeutics, can be reduced by 50–70 per cent for personalised medicines.[22]

Other compelling reasons for VC firms investing in companies focusing on personalised medicine are that in the United States alone over $250 billion are spent on prescription medicines, but '50 per cent of [the] drugs are not efficacious as prescribed', and 'adverse drug reactions [are the] 6th leading cause of death'.[23] Therapeutics and diagnostic procedures representative of personalised medicine are increasingly entering the marketplace. The number of such FDA-approved therapeutics, most of which presently pertain to the treatment of various cancers[24,25] and hereditary diseases[26] is still relatively small, but there are over 1000 genetic tests currently available.[23]

Genzyme Corporation provides an excellent example of a biotechnology company that has secured a foothold in the hereditary disease niche of personalised medicine.[26] Genzyme provides four enzymes

for treating four different genetic disorders, in which the natural enzymes are absent, defective or deficient. It also provides genetic diagnostic services. Founded in 1981, Genzyme first reported annual revenues exceeding $1 billion only 20 years later.[8] In 2008, its annual revenues totalled $4.6 billion, of which $2.2 billion and $0.5 billion were attributed to therapeutic enzyme revenues and genetics diagnostics revenues, respectively.[26]

With respect to the need to develop alternative sources of energy, it is clear that energy consumption continues to increase worldwide,[27,28] yet the quantity of fossil fuel resources is finite,[29] and there is an urgent need to develop alternative sources of energy with lower greenhouse gas emissions than from fossil fuels.[28–30] For example, annual US oil production decreased 35 per cent from 1970 to 2004, but annual US oil consumption increased 36 per cent in that same time period.[29] US oil production provided for 79 per cent of US oil consumption in 1970, but only 38 per cent by 2004. Regarding the long-term outlook worldwide, global primary energy demand is expected to increase 43–55 per cent from 2005 to 2030.[27,28]

Among the alternative sources of energy being developed are biofuels, which presently satisfy only around 0.2 per cent of energy demand worldwide.[27] The major biofuel produced today is ethanol. In 2006, 13.5 billion gallons were produced worldwide, mostly from corn in the United States and sugarcane in Brazil.[28] In the United States alone, ethanol made from corn increased from 1.7 billion gallons in 2001 to 2.8 billion gallons in 2003 and 4.8 billion gallons in 2006, and is expected to have reached 9 billion gallons in 2008.[28,29] Yet, ethanol made from corn and sugarcane is only a first generation biofuel, which is hardly expected to satisfy more than 1 per cent of future energy requirements.

To better meet future energy needs will require the deployment of genetic and biochemical engineering technologies to enable the development of advanced biofuels, such as ethanol derived from ligno-cellulosic feedstocks, higher chain alcohols produced by bacteria, biogasoline resulting from fermentation of waste feedstocks, biodiesel produced by algae, hydrogen produced by algae or cyanobacteria and ultimately microbial fuel cells to generate electricity.[30,31] It has recently been estimated that these new biofuels will ultimately result in satisfying 5–40 per cent of the world's energy needs by 2050.[30] This implies that somewhere between 47 and 377 times the amount of energy that is now being consumed from first generation biofuels in 2008 would be consumed from advanced biofuels in 2050.[27]

To illustrate the reality of the potential bioenergy marketplace, one needs only to address just one of the advanced biofuels under development – cellulose-derived ethanol, and the technical progress made by just one company – Verenium Corporation. Verenium is among the two dozen companies that have been identified as leaders in developing processes for manufacturing ethanol from a variety of cellulosic feedstocks.[32] In 2008, Verenium became the first company to start up a demonstration-scale, cellulosic ethanol plant in the United States, which is capable of producing 1.4 million gallons of ethanol per year.[33] Also in 2008, Verenium reported starting up a 3 million-litre-per-year cellulosic ethanol plant in Thailand in a joint venture with Marubeni Corporation. Verenium had previously partnered with Marubeni and Tsukishima Kikai Co., Ltd., in Japan in producing cellulosic ethanol from construction wood waste in a 1.4 million-litre-per-year plant. In January 2009, Verenium announced its plans to build the first commercial-scale, cellulosic ethanol plant in the United States, which would be capable of producing up to 36 million gallons of ethanol derived from renewable grasses. The plant is expected to be operating in 2011. Verenium believes that by 2022, cellulosic ethanol producers

will be supplying 16 billion gallons of the fuel for the US marketplace alone.

Most of the early R&D efforts of biotechnology companies focusing on advanced biofuels were funded by government grants and contracts and by alliances with large industrial partners. The VC community has only relatively recently begun to invest in the development of advanced biofuels. VC investments in US biotechnology companies focusing on advanced biofuel development increased from under $1 million in 2004 to $20.5 million in 2005 to $813 million in 2006.[34] Clearly, as important milestones are increasingly being met by companies developing advanced biofuels, more and more VC firms will recognise the coming of age of bioenergy and invest their dollars accordingly.

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