

# This time may be different

Bruce L Booth

The markets may be softening on biotech, but overall the sector remains in an incredibly strong environment.

Biotech has been witnessing the greatest five-year bull run in the industry's history. The optimism for the sector and for new biomedical product innovation has manifested itself across the public and private markets, fundraising metrics, initial public offerings (IPOs) and secondary offerings and partnering activity. A quick review of the summary data underscores that exuberance: as of October 2015, the public markets, as measured by the NASDAQ Biotech Index, were up some 200% relative to the S&P 500 and other equity indices; over 140 biotech companies had closed successful and substantial IPOs since the spring of 2013, marking the most prolific IPO window in history; and tens of billions in proceeds have been recycled in the sector via robust private and public R&D-stage merger-and-acquisition (M&A) activity (**Fig. 1**).

It's no wonder that that burgeoning markets like this lead to superlative commentary from analysts, media and investors alike. Here are a few great quotes from Ernst & Young (E&Y)'s *Annual Report on Biotech*<sup>1,2</sup>:

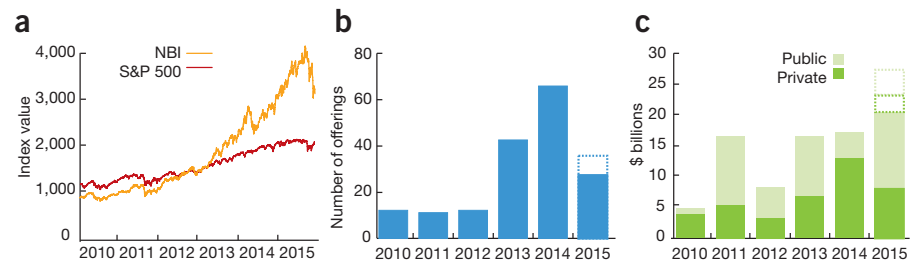
"This year... the largest biotech bull market ever..."

"For most of its history, biotechnology has been... built on promise... Companies are now turning that promise into reality..."

"...[T]here was a tidal wave of public financings. Even relatively young companies...found a receptive audience in the public markets."

"With a decent trading record in recent transactions and industry fundamentals stronger than ever, the future looks bright for continuing interest on the part of investors as they search for the next Amgen..."

Bruce L. Booth (@LifeSciVC; <http://www.lifescivc.com>) is a partner at Atlas Venture, Cambridge, Massachusetts, USA.  
e-mail: [bruce@atlasventure.com](mailto:bruce@atlasventure.com)



**Figure 1** Biotech's five-year bull market. (a) The NASDAQ Biotech Index (NBI) has outperformed the S&P 500 over the past five years by over 200%. Data from Yahoo! Finance. (b) Number of VC-backed biotech IPOs over the past five years. Data annualized from the National Venture Capital Association. (c) Deal value for R&D-stage M&A transactions of private and publicly traded biopharma companies from Thomson Reuters. Outlined area represents data annualized for 2015 from 30 September 2015 numbers.

And a second set from *CNN Money*:

"[I]nvestors fell head over heels for biotechnology stocks, infatuated with the promise of miracle breakthroughs...Wall Street has fallen in love again."

"Overall market conditions also are propelling more money into biotech. The biotech sector is relatively immune to the effects of an interest rate increase...leading many investors to funnel their money into the sector as the threat of more rate hikes by the Federal Reserve looms..."

These quotes almost certainly could have been said or written about the current investment environment for biotech, but instead they come from very different periods in biotech history. The first set appear in E&Y's 1992 report<sup>1</sup> and the second pair from a CNN online article in the heady days of 2000, at the height of the genomics bubble<sup>2</sup>. The quotes are instructive for two reasons: they foreshadow a coming dialog about the current biotech investment cycle, and they help put into context the current bull market.

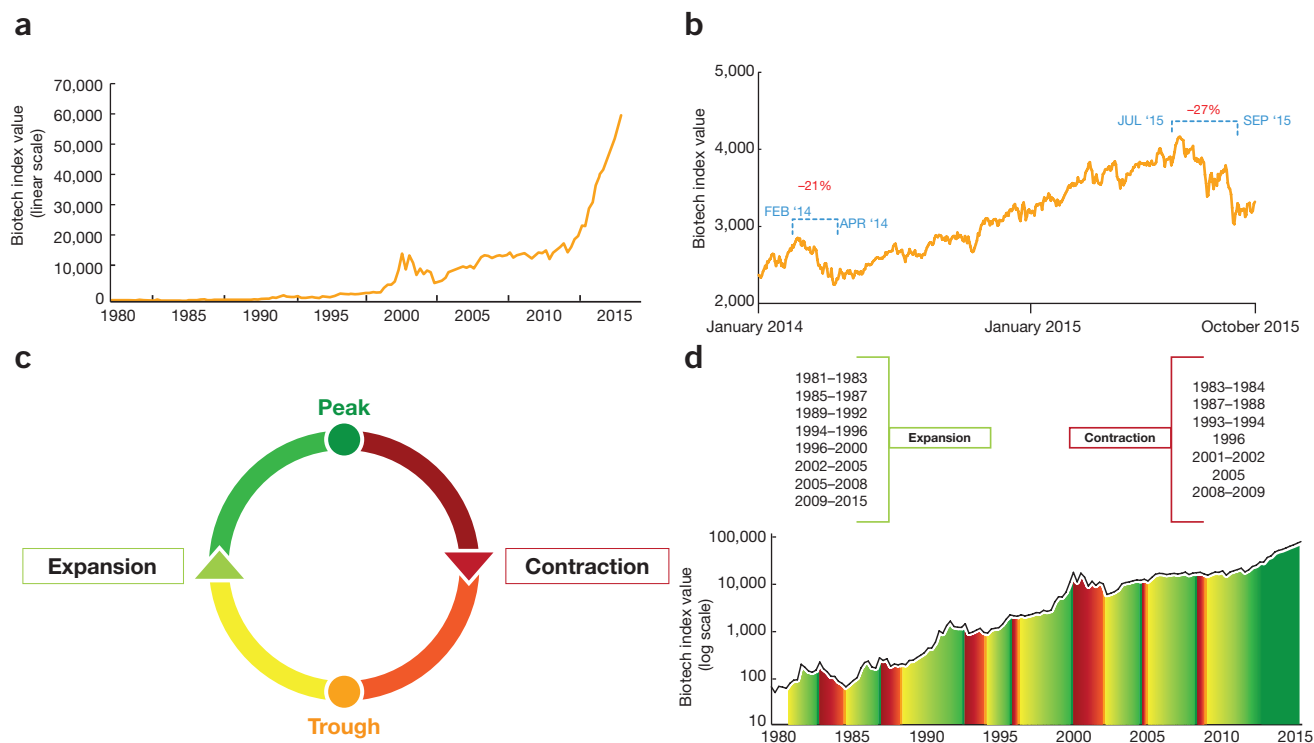
In the following Commentary, I summarize biotech investment at the end of 2015; I look back on some key landmark events in the sector's history, discuss some key and possibly

structural differences in today's environment, and share some perennial truths that remain the same as ever about biotech investment. To set the context, it is worth repeating the maxim usually attributed to Mark Twain: "History doesn't repeat itself, but it does rhyme."

## Current environment in context

The bull markets of 1992 and 2000 that gave rise to the comments above have been dwarfed by the optimism of the past five years (**Fig. 2a**). Given the recent negative sentiment in the biopharma sector, with the 3Q15 delivering a 27% peak-to-trough move in the NASDAQ Biotech Index, it's easy to forget this historical background (**Fig. 2b**). The markets may indeed be softening on a relative basis, but we remain in an incredibly strong overall investment environment for biotech. At least three observations support this premise.

First, sentiment appears disconnected from relative valuation. In January 2015, when the NASDAQ Biotech Index moved upward through 3,200 for the first time in history, pundits were excited about the markets and, if anything, worried that we might be entering into a biobubble of 'irrational exuberance'; compare that to the end of September, when



**Figure 2** Biotech's current performance in context of long-term investment cycles. (a) Datastream Global Biotech Index plotted since 1980, as tracked by Thomson Reuters (New York, NY), showing the steep rise in the biotech markets over past few years. (b) Recent two-year performance of the NASDAQ Biotech Index. There have been two corrections >20% in the index during this period. (c) Illustration of the investment cycle in which periods of contraction to a trough are followed by periods of expansion to a peak; this cycle is intrinsic to most asset classes in the investment world. (d) The biotech industry has experienced nearly eight full turns of the investment cycle since the early 1980s. Date ranges are approximate. Data from Datastream Biotech Index (a, d) and NASDAQ (b) and is through October 2015.

the same index dropped to 3,200, following a more than 25% decline; investor sentiment was incredibly negative, the 'bubble had burst' and the bloom was off the biotech rose. The same absolute valuations were met with a 180-degree difference in sentiment.

Second, even during this period of negative sentiment, the sector delivered nine substantial biotech IPOs that priced their offerings in the six-week period following 15 September 2015. Nine IPOs in six weeks is an incredibly robust pace, only matched by a dozen or so six-week periods in the history of the industry. Several more IPOs closed in November, underlining the continued 'open' aspect of the current IPO window. Furthermore, many of these offerings were made at premium valuations, especially for companies without any clinical data; in fact, the median IPO valuation in September and October was 33% higher than the median valuation of offerings in 2013–2014. It's fair to say that several of these offerings were 'club IPOs,' given the absence of significant new demand, with most of the stocks' IPO buyers being prior crossover investors; but they still raised public capital at very attractive prices.

Lastly, although investor anxiety has been widespread, it has been punctuated by two

large stock losses that damaged the returns of large public equity funds. Valeant (Laval, Canada), a specialty pharma company, has been under considerable scrutiny for its revenue and pricing strategies and lost over \$60 billion in market capitalization in 3Q15. Biogen also faces headwinds on its revenue forecasts and lost nearly \$20 billion. Combined, these two stocks eliminated \$80 billion of stock market value, held largely by healthcare-focused investors, in 3Q15; for context, this is roughly equivalent to the aggregate market capitalization of all ~140 companies that have gone public since 2013. Wiping out that much value in a single quarter certainly dented the prevailing investor psychology; it remains to be seen how persistent the resulting negative sentiment is likely to be.

However, keeping the current investing environment in context is important, especially relative to four decades of history in biotech—which is why it is valuable to understand the investment cycle.

**Investment cycles**

Every asset class is defined by periods of expansion and contraction; buoyant markets typically lead to inflows of capital in the former, and vice versa (Fig. 2c). Biotech has gone

through nearly eight of these cycles since its birth as an industry in the early 1980s, with the Datastream Biotech index plotted on a logarithmic scale to see the trends in the early years (Fig. 2d).

During its nascent years, a bull market in the early 1980s emerged that was supported by new technologies, such as recombinant protein expression, and marked the first real IPO 'window,' with companies like Amgen (Thousand Oaks, CA) entering the public markets. Later in the 1980s, markets again entered an expansion; in early 1987, Celgene (Summit, NJ) went public; shortly afterward things cooled down again with the stock market crash in the fall of that year. Biotech exploded in the early 1990s with the largest bull market of the sector's short history; Gilead (Foster City, CA) went public during this window, with its S-1 focused on nucleotides, aptamers and antisense, only one of which has matured into products for them. The spectacular phase 3 failure of Centoxin (nebacumab), Centocor's anti-sepsis human IgM antibody, and anxiety due to Hillary Clinton's single-payer health insurance system dialog in Washington combined to bring an end to that bull market in 1993.

The genomics bubble was a short but very active period of expansion in the summer of

2000, as sequencing technology propelled the ‘gold rush’ around expressed sequence tags (ESTs) and the Human Genome Project as well as an explosion of novel drug-discovery technologies (such as combinatorial chemistry, high-throughput crystallography, tandem mass spectrometry and functional genomics). As that market collapsed into a contraction in 2001, biotech entered its ‘nuclear winter’: for seven straight quarters, the NASDAQ Biotech Index moved downward, by >70% from peak to trough. In late 2002, the market very tepidly returned, and most of the next six years was marked by very muted cycles.

Emerging from the 2008–2009 global financial crisis, the biotech market began to firm up in 2010–2012, supported largely by strong M&A as big pharma and big biopharmaceutical companies sought to secure more innovation for their pipelines. A full acceleration of the expansion began in early 2013 as the current IPO window opened. Since that time, the markets have seen two brief periods of ‘correction,’ with the NASDAQ Biotech Index dropping by >20%. With that whirlwind of biotech financing and market history, the key takeaway is that investment cycles have been, and will continue to be, a part of the business—and that the expectation is that over time the trendline for the sector will move upward and to the right (Fig. 2).

Another observation from Figure 2 is the uniqueness of the current period; since the spring of 2009, the sector has largely been in expansion, first strengthening through confidence in the large-cap biotech companies, and then accelerating in 2013 into the small-cap and new issuance markets as well. This period constitutes by far the longest and largest bull market in biotech history. So the big question is whether there is something different going on today in comparison to prior periods.

### This time is different

Sir John Templeton once said that the four most dangerous and expensive words in investing are “This time it’s different.” At the risk of running afoul of history and Templeton’s advice, this time in biotech may indeed be different from past cycles. There are at least four major elements I would put forward to support this assertion.

### Advancing products over promise.

As the fruits of biomedical science and bioengineering continue to ripen, ever more prospects are emerging for new therapeutic interventions in disease (Fig. 3a); this translation is being facilitated by an ever-maturing base of management and R&D talent and by

a regulatory environment more conducive to innovation than in the past (including, for example, the Food and Drug Administration’s (Rockville, MD) breakthrough therapy designation). For example, in the past three years, Gilead has brought to market not only the world’s first curative hepatitis C therapy in Sovaldi (sofosbuvir, a nucleotide polymerase inhibitor), but also Zydelig (idelalisib), a phosphoinositol 3-kinase delta (PI3K $\delta$ ) inhibitor against refractory B cell malignancies such as relapsed follicular B cell non-Hodgkin lymphoma and relapsed chronic lymphocytic leukemia. Similarly, Amgen and Regeneron (Tarrytown, NY)/Sanofi (Paris) have brought two antibodies to market targeting the proprotein convertase subtilisin/kexin type 9 (PCSK9) in hypercholesterolemia—only ten years after the discovery of PCSK9’s genetic association with cholesterol. Alnylam Pharmaceuticals (Cambridge, MA) has several RNA interference therapies under testing in phase 3. Even certain gene and cell therapy programs are advancing into registration studies after proof-of-concept results in the clinic, especially in the field of chimeric antigen receptor (CAR) T cells. Indeed, the industry’s pipeline has never been as deep or as innovation rich as it is today, with over 3,400 active clinical-stage projects, 70% of which are being advanced by small companies<sup>3</sup>. Few would dispute that, after nearly four decades of promise, the biotech industry has begun delivering in earnest on its potential for transformative products; this is one way in which today’s environment departs from that of past cycles, which were built primarily on often ephemeral promises.

**Maturing industry players.** Related to the delivery of real products, the biotech industry is no longer a ‘nascent’ sector as it was in its first few decades. In the United States alone, there are over 2,500 biotech companies, including over 400 traded on major public market exchanges; European biotech doubles that number to add to the statistics<sup>4</sup>, and the beginnings of an innovative sector are forming in Asia. Furthermore, the biotech industry is moving from purely loss-making R&D stories toward compelling financial metrics.

If one takes the approximately 150 companies in the NASDAQ Biotech Index in aggregate, for example, the industry’s revenues and earnings have more than doubled over the past five years (Fig. 3b). The larger, more established players are clearly driving several of these financial metrics, but the trickle-down effect across the biotech sector is certainly helping to support demand. In addition, the number of biotech companies

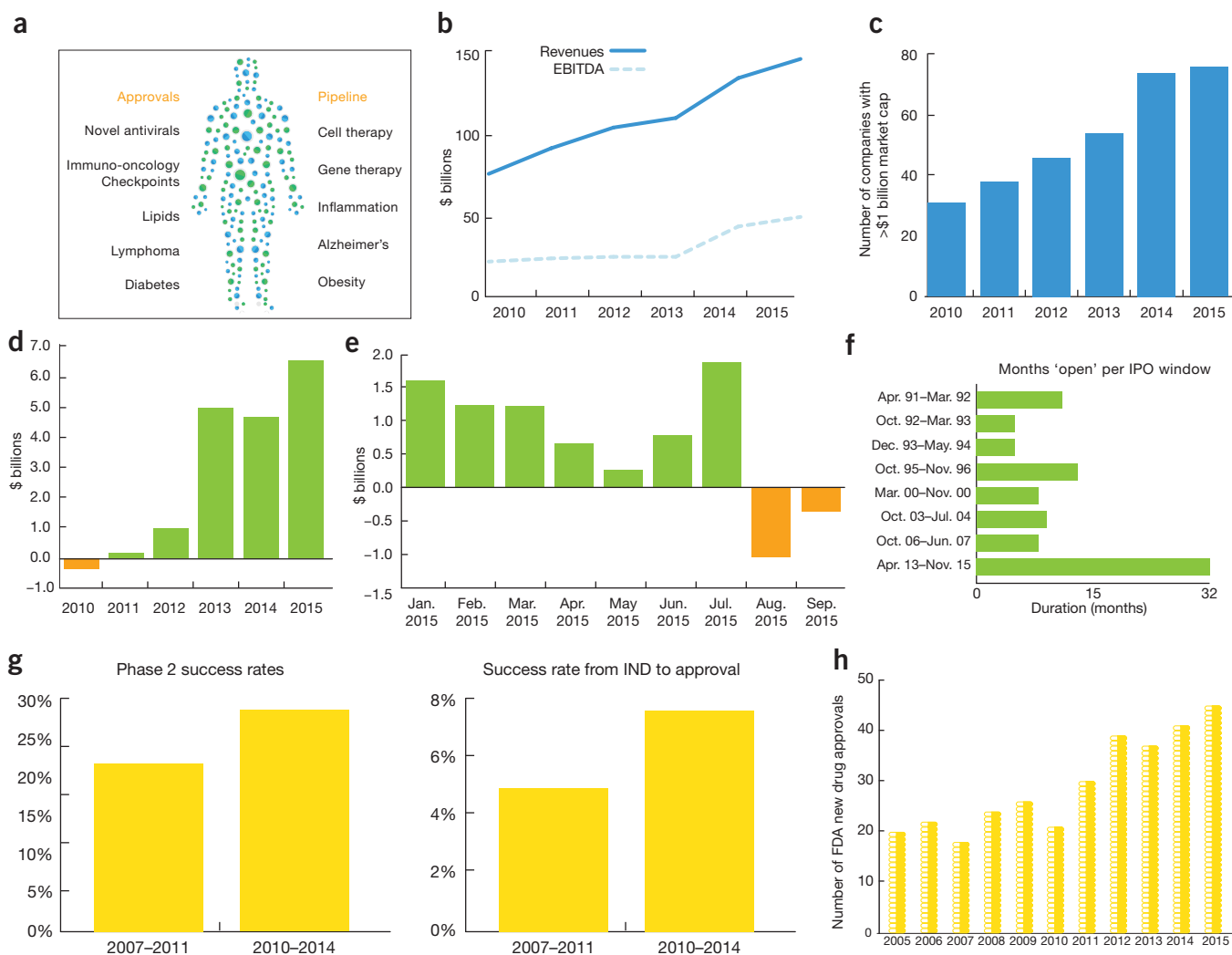
with >\$1 billion in market capitalization has nearly tripled over that period (Fig. 3c), a clear indication of how robustly capitalized the sector is today.

**Deepening capital markets.** Past expansionary cycles in biotech have been characterized by very shallow institutional investor pools focused on biotech; when this core group of investors got skittish on the markets, sentiment rapidly went negative. This led to a feast-or-famine environment. Today’s equity capital markets for biotech are very different. The breadth and depth of the public market investor base has never been more extensive, across both significant specialist investors such as Orbimed (New York, NY) and RA Capital (Boston, MA) and large generalist firms like Janus (Denver, CO) or Fidelity (Boston, MA) that have dedicated biotech funds and portfolio managers. The number of major institutional buyers in the IPOs of the past three years number in the hundreds of accounts, not dozens as in past cycles.

Further evidence for this deepening capital base is the flow of funds in the equity markets into biotech. As shown in Figure 3d, using data from consultancy Informa’s (London, UK) business intelligence division EPFR Global, the net capital flows into the biotech sector have been close to \$20 billion over the past few years. The first seven months of 2015 were also quite strong. The negative sentiment in 3Q15, discussed above, then led to net outflows, representing about \$1.5 billion in aggregate, according to EPFR (Fig. 3e).

However, as a reflection of how strong the capital markets are today, during this recent period of net outflows the sector managed to price nearly a dozen IPOs at premium valuations, as noted before. This robust IPO activity reflects the resiliency of the current equity capital markets. In fact, the IPO window continues to be active, marking the longest open cycle in biotech’s history—31 months and counting (Fig. 3f). Defining an IPO window as one in which at least four offerings get priced per month on average, the industry has witnessed eight such windows since 1990, with the prior seven having an average duration of only 6–8 months. The current cycle’s depth and breadth strongly highlights a structural change in the biotech equity capital markets.

**Improving R&D productivity.** The fourth and final element that may be different about the current markets is that after a multi-decadal decline in industry R&D productivity, the sector may be seeing a glimmer of hope: return on R&D invest-



**Figure 3** This time is different. At least four current features of the industry support this premise: advancing products over promise, maturing biotech industry, deepening capital markets and improving industry R&D. **(a)** Advancing products over promise. Selected examples of areas in which medical advances are delivering major impact through innovation. **(b)** Maturation of the biotech industry. Aggregate revenue and EBITDA figures for all the companies in the NASDAQ Biotech Index have increased twofold over the past five years. Data from company annual and quarterly filings. **(c)** Number of biotech companies in the NASDAQ Biotech Index with market capitalizations above \$1 billion. Data as of year end for 2010–2014 and as of 30 September 2015 for 2015. **(d)** Deepening capital markets. Annual net fund flows into the biotech sector; data according to EPFR reflecting Biotech Global Sector Equity flows. **(e)** Monthly net fund flows for 2015 (data from same source as in **d**). **(f)** The duration of the current IPO window is unprecedented. Open windows defined as greater than four IPOs per month on average. Chart shows number of months of an open window. Current period is at 32 months and counting. Data from NASDAQ. **(g)** Improving R&D productivity. Phase 2 project survival rates and success rates from IND application to approval have both seen favorable trends in the recent cohort of KMR benchmarking data, according to global assessment management firm Alliance Bernstein (New York, NY). **(h)** FDA new drug approvals reached an 19-year high in 2015 with 44 new drugs (data from FDA).

ments may be improving, according to analysts at business consultancies, such as Boston Consulting Group (Boston, MA)<sup>5</sup> and McKinsey (New York, NY)<sup>6</sup>. Furthermore, recent data from consultants KMR (New York, NY) suggest that phase 2 attrition rates have also improved, with project survival up nearly 20% in the recent cohort; applying all the changes in attrition, the success rate from investigational new drug (IND) application to approval has moved from 5%, or 1 in 20, to close to 1 in 12 in the recent KMR dataset (**Fig. 3g**). As a lagging indicator, the number of US Food and Drug Administration (FDA)

approvals reached a 19-year high in 2015, with 44 new therapeutics (**Fig. 3h**).

These favorable trends in R&D productivity may be a reflection of better decision-making by the industry as a whole as well as a shift by big pharma towards more 'external R&D' strategies, as externally sourced assets often have higher rates of clinical development success both historically<sup>7</sup> and more recently (Boston Consulting Group; M. Ringel, personal communication).

Thus, the above four elements, among potentially many others, support the idea that this investment cycle may present some struc-

tural differences from past periods in biotech history.

**What's not different**

However, as George Santayana admonished, "Those who cannot remember the past are condemned to repeat it." At least three elements of the current biotech markets are as true now as they've been in the investment cycles of the past.

**Valuation inflation.** Every expansionary phase involves an upward trend in valuations. Optimism about the future leads to net present value assumptions that are often rosier



than reality. Specific companies and sometimes entire sectors can see their valuations inflate beyond what can reasonably be supported by future cash flows. When valuations overshoot, there are really only two possible outcomes: either companies quickly grow into their valuations by advancing products or accelerating financial performance, or they see their valuations reset downward.

The bull market we have been witnessing over the past five years is no exception to this cyclic inflation of valuations. The price-to-earnings (P/E) multiples (a metric for relative valuations) of the profitable companies in the NASDAQ Biotech Index have increased twofold over the past five years, from 16 to 32 (Fig. 4a). This expansion in valuation multiples probably accounts for close to half of the gains in the index overall (the other half is due to an increase in revenues and earnings).

In addition, an examination of private and IPO valuations suggests similar inflation, in particular in the period 2014–2015. Normalizing the median and top quartile valuations of late-stage private rounds (such as Series B–C–D financings) and IPOs to 2010, the uptick in recent years is apparent, up at least twofold over the past year or two (Fig. 4b).

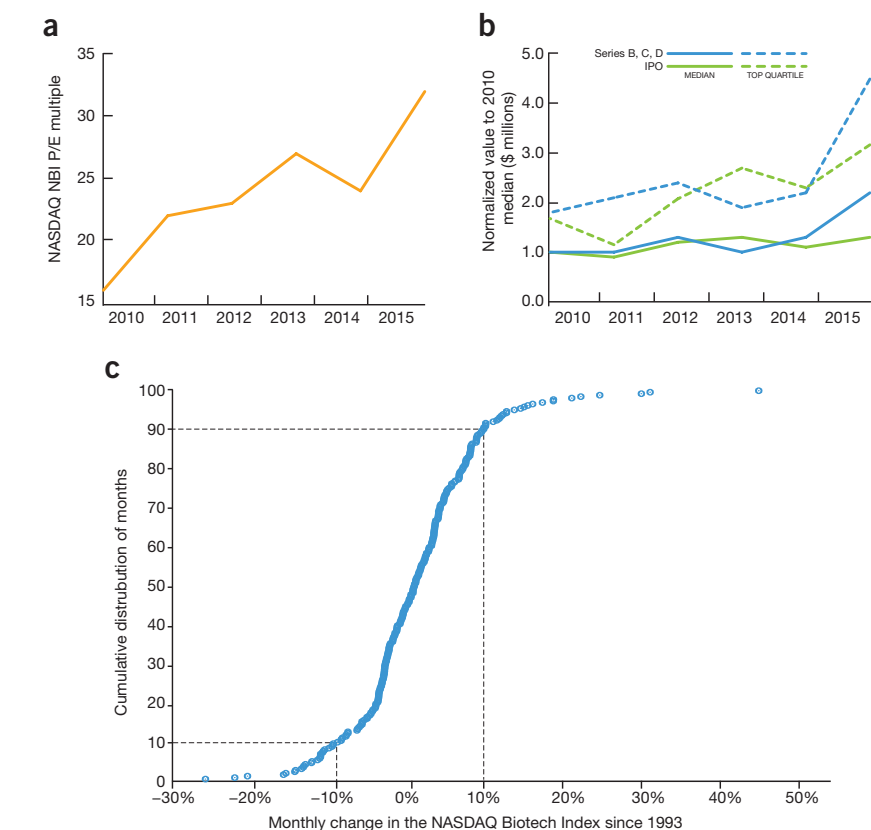
This upswing in valuations is certainly to be expected after over five years of an accelerating bull market; what is unclear is whether small-cap biotechs in particular will be able to grow into those valuations with positive clinical data, given their sizeable cash war chests enabled by these more favorable valuations.

**Event-driven hypervolatility.** Biotech has and will continue to be an event-driven business: as even large companies get defined by single or a few blockbuster programs, clinical data news flow is a major driver for valuations. This is intrinsic to our R&D-heavy, product innovation-focused industry.

Examining the monthly changes in the NASDAQ Biotech Index since its inception in 1993 reveals that approximately one out of every five months (20%) have had either a 10% move upwards or downwards in the index (Fig. 4c). This is massive volatility for an index representing an entire sector. By comparison, it is roughly 100% more volatility than the S&P 500.

As in prior cycles, we should anticipate that this hypervolatile investing environment will continue to characterize the biotech sector.

**Payer and reimbursement challenges.** The third element that has perennially been an issue for the biopharma industry is drug pricing, with public debate most often trig-



**Figure 4** Three things that are not different in biotech today. (a) Valuation inflation. As in all expansionary periods, relative valuation metrics have risen in recent years. P/E multiples of the profitable biotech companies in the NASDAQ Biotech Index have doubled over the past five years. Data from Yahoo! Finance and NASDAQ. (b) The relative valuations of private and new issuance (IPO)-stage companies have also inflated over time. This chart plots the normalized data for the median (solid) and top quartile (dotted) valuations for later stage rounds (Series B, C and D financing rounds) as well as pre-money valuations of IPOs. Data normalized in each group to median in 2010. A clear uptick in valuations can be seen, especially in top-quartile valuations in the recent window 2013–2015. (c) Event-driven hypervolatility. Biotech remains a very volatile sector. This chart plots the monthly changes in the NASDAQ Biotech Index since its inception in 1993, arranged from most negative changes to most positive changes. Roughly 10% of the months witnessed greater than 10% declines in the index, and another 10% witnessed greater than 10% increases. Data from Pitchbook as of September 2015 (a,b) and from NASDAQ as of October 2015 (c).

gered by bad behavior (such as that of Turing Pharma (New York, NY) and Valeant in 3Q15) or healthcare policy (for example, for HillaryCare in 1993). Historically, when pricing debates begin, investors get anxious and the markets cool. The pricing dynamic in the industry is likely to continue to be a source of anxiety over the next decade, especially given the low likelihood and slow pace of change in Washington, DC.

Although this is a topic worthy of an article itself, the industry as a whole needs to get out in front of the pricing discussion, putting forward models of pay for performance and value-based pricing that help align incentives for better care and overall cost reduction. Until these topics get more resolution, the pricing discussion will continue to unnerve the investment community.

## Final thoughts

Where the biotech market indices and sentiment will end up in 2016 is only a speculator's guess, and this author won't go there. Although ample evidence supports the likelihood of some structural changes in the industry compared with past periods, that doesn't negate the axiomatic nature of the investment cycle.

Rather than making predictions, it is worth emphasizing a few market certainties: first, biotech markets will cycle through periods of expansion and contraction; second, the cost of capital and ability to finance biotech companies will move with those cycles; and third, drug R&D will remain a long-term, high-risk and high-reward endeavor.

Smart investors embrace those certainties and, especially for early-stage company investing, adopt a patient capital approach that spans

across investment cycles. Take advantage of opportunities to accelerate young companies in bull markets, without overcapitalizing them inefficiently. And plant the seeds for great young companies during less bullish periods so that they can be well positioned when markets change for the better.

Five key components underpin most early-stage investing strategies to this effect, and these certainly embody the approach at Atlas Venture (Cambridge, MA): focus on transformative potential innovation, embrace a market-agnostic capital efficiency for financing startups through cycles, diversify the business model even within biotech (for example, both asset-centric and platform plays), constructively engage the ecosystem via partnering and collaboration, and—most important of all—recruit,

retain and reward the fantastic people who build and run these biotech companies.

The past five years have been an exceptional time for the biotech industry—yielding more medicines for patients, better-funded companies and an ecosystem supportive of fostering further innovation. As the industry enters its fifth decade as a sector, it's nice to see it finally maturing to deliver on its promise.

#### ACKNOWLEDGMENTS

The author would like to thank his colleagues at Atlas Venture for their helpful perspectives and input into the sector, and both K. Margeson and E. Silva for data and graphical support.

#### COMPETING FINANCIAL INTERESTS

The author declares competing financial interests: details accompany the online version of the paper (doi:10.1038/nbt.3452).

1. Ernst & Young. *Biotech '92: Promise to Reality*. Ernst & Young Annual Biotech Report. 1992 (Ernst & Young, New York, 1992).
2. Slud, M. Boom time for biotech. *CNNMoney* (22 February 2000). <http://money.cnn.com/2000/02/22/companies/biotech/>
3. Thomas, D. & Wessel, C. Emerging therapeutic company investment and deal trends (Biotechnology Industry Organization, 11 June 2015). <https://www.bio.org/sites/default/files/BIO%20Emerging%20Therapeutic%20Company%20Report%20June%2011%202015.pdf>
4. Ernst & Young. *Beyond Borders: Reaching New Heights*. Ernst & Young Annual Biotech Report 2015 (Ernst & Young, New York, 2015). [http://www.ey.com/Publication/vwLUAssets/EY-beyond-borders-2015/\\$FILE/EY-beyond-borders-2015.pdf](http://www.ey.com/Publication/vwLUAssets/EY-beyond-borders-2015/$FILE/EY-beyond-borders-2015.pdf)
5. Schulze, U. *et al.* *Nat. Rev. Drug Discov.* **13**, 331–332 (2014).
6. Smietana, K. *et al.* *Nat. Rev. Drug Discov.* **14**, 455–456 (2015).
7. Booth, B. *et al.* *Improving the Pharma Research Pipeline McKinsey Quarterly*, Web Exclusive August 2004 (McKinsey, New York, 2004)