

Early-stage returns?

Bruce L Booth

Contrary to conventional thinking, there are compelling reasons for investors to consider early-stage life science ventures, especially in the context of a maturing biotech business 'ecosystem'.

Investing in early-stage life science technologies is a high risk-high return gambit. For the first few decades of biotech, many early-stage investors did exceptionally well by placing smart bets behind new therapeutics, platforms and business models. In recent years, however, poor returns have led many biotech pundits and practitioners to assert that the early-stage venture model is dead, or at least severely broken. This pessimism is unwarranted. The life science sector is transitioning to a more mature business ecosystem, and three emerging themes should support attractive early-stage investing returns going forward: an investor-friendly supply of innovation, greater fundamental demand to support exits and more capital-efficient biotech models to create value.

The past

Over the past five years, in the aftermath of the genomics and technology bubbles, early-stage venture capital returns have been poor, even relative to underwhelming public market returns (Fig. 1a). For biotech in particular, this lackluster performance reflects in large part the lack of alternative routes to liquidity and a weak appetite of the public capital markets for new initial public offerings (IPOs). The IPO process itself may be broken: a case of bankers shopping a development-stage company to a small set of well-connected biotech IPO investors who beat up the company on price, valuation and

the amount of capital raised (Fig. 1b,c). Being considered 'ready' for the public markets now requires late-stage clinical or even commercial products, a far cry from the genomics platform IPOs of the 1990s and clear evidence of a shift toward more fundamentals-driven investing. If a biotech manages to go public, the pricing of the offering has been painful: of the ~50 biotech firms that went public in 2004 to 2006, average pricing was 25% below their expectations. In addition, performance in the 12 months after an IPO has also been brutal for many new issuers: the average return of the 2005 class as of June 2006 was -15%. These market metrics pose a significant challenge to private investors looking to achieve liquidity through secondary offerings on the public markets.

Furthermore, for a traditional biotech company to fund a well-developed pipeline, a *sine qua non* for an IPO today, they are burdened with enormous capital intensity, often spending upwards of \$100 million before an IPO. In short, staying private longer heightens the future financing risk and increases the threat to early-stage investors of having later stage investors reprice a company's stock lower than in the earlier rounds. Because early-stage investors are involved from the beginning, this financing/pricing risk makes the challenge posed by high capital intensity far more acute for them than for later stage investors.

History might suggest that this is just another round of the boom-bust cycle that has characterized biotech investing since the early 1980s: periods of exuberance when many private biotechs went public ('IPO windows') alternating with periods of retrenchment when similar companies struggled to get financing (Fig. 2). During these retrenchments, industry analysts and venture capitalists have always raised questions about the model.

For example, in 1994, times were tough in biotech for several reasons: in the two years

preceding, several spectacular clinical failures wiped out the market capitalizations of several public companies (e.g., Centoxin's failure at Centocor (Malvern, PA, USA) cost them 90% of their value). Furthermore, the threat of socialized medicine and price controls looming in the United States dampened growth forecasts. In this environment, the public markets gave new offerings a very cold reception. During this time, many venture firms talked about new models: 'virtual' company concepts instead of building 'wet labs', shared infrastructure 'incubators', funding fewer new companies with more capital, among others¹.

In 1998, in another period of desolation in the biotech business, the pendulum had swung from virtual companies back to fully integrated biotech companies and to revenue-generating 'pick and shovel' tools providers². In 2002, the hot new model to consider was specialty pharmaceuticals or no-research, development-only companies, which got late-stage and commercial products on the radar of public investors. Today's tough market may just be a continuation of this biotech boom-bust cycle.

The present

Caveat emptor as always; but things appear to be changing. The tough market of the past few years is almost certainly a transition phase, allowing the markets to recover from the exuberant overfunding and capital overhang of 1999-2001. Coming out of that period, companies based on rapidly commoditizing technology platforms, largely without sustainable business models, had to shift their focus or shut down. Therefore, much of the capital invested in the recent 2003-2005 IPO class went to inefficiently hybridizing business models: bringing in-licensed products to these previously platform companies. But this hangover has largely been worked through and most of the carnage is now behind us.

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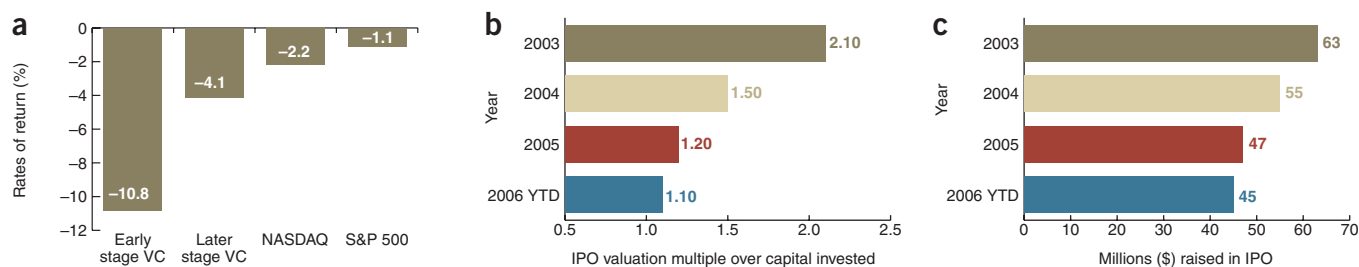


Figure 1 Poor returns and challenging public markets. (a) Early-stage venture capital investing has delivered poor five-year rates of return relative to later stage venture capital and public equity investing (2000–2005)⁸. Although this reflects all sectors, the trends are similar in biotech. The IPO market has been challenging for biotech companies looking to access the public markets: (b) valuations are shrinking relative to the amount of private capital invested; (c) less capital is being raised in the offerings according to investment banks Cowen & Company (New York) and Jefferies & Company (New York). 2006 is a partial year up to June 2006, and excludes Adams Respiratory Therapeutics (Chester, NJ, USA).

Today, real structural changes exist in the market that should support the emergence of a much more favorable early-stage life science investing environment. These changes are the result of the significant evolution of the biotech ecosystem: today, it is more mature, less erratic and far more stable. By analogy, in biological ecosystems, greater species diversity leads to improved overall system function, greater stability and more resilient ‘food webs’ driven by enhanced inter-relationships³. Just as in biology, the biotech universe has evolved in recent years to include a huge number of interrelated players: thousands of private and small-cap public biotech companies, scores of cash-generating big pharma and big biotech companies with strong balance sheets, a myriad of global service providers and contract research organizations (CROs), more innovative product-focused academic laboratories, and a deep set of private and public biotech capital markets. A decade ago, this was certainly not the case.

Three major themes are emerging in this more mature biotech ecosystem and will likely enable early-stage life science investors to achieve superlative returns: first, a unique confluence of innovation supply-side drivers, second, improving demand-side exit fundamentals and alternatives and third, better models for efficiently creating value.

Investor-friendly supply-side drivers

This new biotech ecosystem appears to offer less investor competition for an increasingly abundant and attractive pool of innovation—creating a very investor-friendly environment for early-stage life sciences. This is due to shifts in the sources of innovation, talent and capital.

Sources of innovation becoming more product-focused. Academic research has moved beyond target discovery and novel biology. Increasingly, product-focused translational research activities are being conducted in aca-

demia, including the emergence of university-based high-throughput screening facilities and chemical libraries. Indeed, in the United States, the National Institutes of Health (NIH; Bethesda, MD) has a \$2 billion ‘Roadmap’ initiative focused on translational research, and NIH Director Elias Zerhouni wants the NIH to support research that brings “tangible benefits that touch the lives” of patients rather than solely basic science.

The application of new platform technologies, including both wet-laboratory high-throughput screening and *in silico* modeling, greatly lowers the barrier to entry for academics interested in pursuing modern drug discovery. This moves academic research well beyond simply invention disclosures and publications; as a result, academic institutions are filing more US patents than ever before (the number of US patents filed by academic laboratories has increased over 500% since 1994; ref. 5), and they are increasingly product-focused. By bringing biology, pharmacology and chemistry expertise together in an academic setting, many laboratories are now increasingly focused on generating preclinical and even early clinical therapeutic programs.

In recent years, the Association of University of Technology Transfer Managers (Northbrook, IL, USA) has reported that US academic institutions have formed new startups in general (a majority of which are in the life sciences) at a steady rate of 400–500 companies per year⁵. To help support these efforts, seed and gap funds are being provided by institutions, philanthropists and angel investors to move new discoveries toward classic drug development. Beyond academic laboratories, exciting additional pools of innovation can be found within the known pharmacopeia (e.g., pharmacogenetic targeting or new uses of current therapies) and the convergence of broader disciplines (e.g., nanotech, drug-device combinations, diagnostics). All of this is providing an increasingly product-oriented

supply of discovery, preclinical and early clinical innovations.

Abundance of talent to start/run biotech enterprises. Finding the right drug industry veteran to manage a new company’s R&D program is never easy, but the recent ‘brain drain’ from big pharma has made it a lot less challenging. Chemists and pharmacologists with 15–25 years of deep pharmaceutical experience are leaving the bureaucracies of large R&D organizations (most of their stock options ‘underwater’ and valueless anyway) and are eager to share their expertise in the more exciting, nimble and action-oriented environment of a biotech venture. The same goes for most other disciplines.

The war for experienced talent is being lost by big pharma as managers and executives seek more fulfilling jobs elsewhere; for evidence, one need look no further than announcements of consolidation and reorganization-related departures, which are more common than quarterly reports these days: Johnson & Johnson (New Brunswick, NJ, USA) is shutting down its Alza (Mountain View, CA, USA) and Scios (Fremont, CA, USA) teams; Pfizer (New York) has dumped so many of its acquired R&D staff that it has created a bustling CRO/biotech cluster in several pockets of the Midwest; and Merck (Whitehouse Station, NJ, USA) has let thousands go post-Vioxx (rofecoxib), just to name a few.

In addition to the migration of experienced personnel from big pharma into the biotech startup environment, veterans of big biotech success stories, such as Genentech (S. San Francisco, CA, USA), Amgen (Thousand Oaks, CA, USA) and Biogen-Idec (Cambridge, MA, USA), have been ‘seeding’ most of the major biotech clusters with talented émigrés eager to discover/rediscover more entrepreneurial roles. These pools of available talent are deeper and more receptive to startup biotech than ever before.

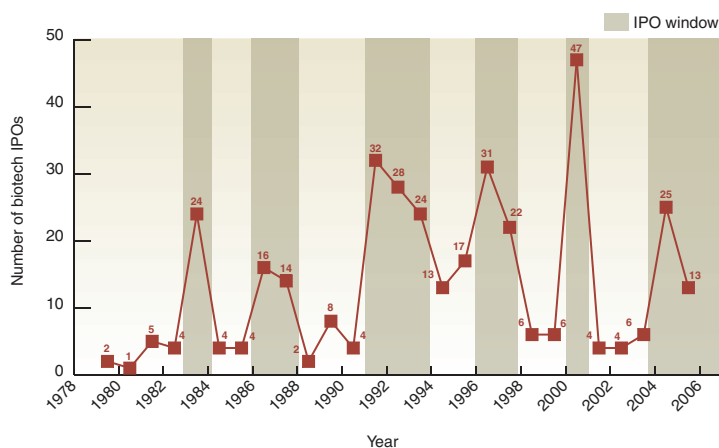


Figure 2 Historic boom and bust cycles in the biotech public markets. There have been six 'windows' (in shading) over the past 25 years when the relative number of biotech IPOs increased dramatically⁸. During these windows, more biotech firms were going public, and their valuations were typically far better than when the window was 'shut'. The parallel trend in valuation multiples over cash during these windows for public and private companies underpins these cycles and has been previously examined⁶. During boom times, early-stage investors have traditionally made disproportionate returns; during 'busts', early-stage investors inevitably question the sustainability of the venture capital model and openly consider the financing of alternative business models.

Less competition for early-stage life science deals. Many of the high-profile venture firms with a strong presence in the life sciences have all raised much larger funds than in the past. Witness 2006 vintage funds from Baltimore-based New Enterprise Associates (\$2.5 billion), Boston-headquartered Polaris Ventures (\$1.0 billion) and Princeton's Domain Associates (\$700 million). Beyond the competitive psychology of being 'one of the biggest', the realities of fundraising increase the pressure to raise bigger funds. Put simply, limited partners, who provide capital to venture firms, are restricted from being >10% of any given fund and want to put \$25–40 million per commitment, which sets a clear floor for fund size of \$250–400 million for many limited partners. Furthermore, as a fee-based business, large funds have more management fees to share among the partners and many find this too alluring to refuse. Because of these pressures, the proportion of large funds versus small and medium-sized funds is increasing dramatically (Fig. 3).

These bigger funds have greater investable capital per partner, and fewer funds maintain the '\$50 million per partner' rule-of-thumb for early-stage investing. Partner 'bandwidth' is the most limited resource at a venture fund, so most large funds aim to hold constant the number of deals (and thus deal bandwidth), but increase the dollars invested per deal. Bigger allocations make doing classic seed (less than \$1 million) and early-stage (\$1–5 million) financings of preclinical and other early-stage programs almost impossible to do. This trend in the venture business, coupled with the generalized malaise toward new life science technologies, make the market for early-stage deals in this area less competitive. Fewer funds looking at a greater number of deals will make for more investor-friendly terms.

Improving demand-side exit fundamentals

The stock of private companies is by definition 'illiquid', and findings ways to convert it into

cash at a good return is central to any form of private equity investing, such as venture capital. Having alternative choices available is important for achieving liquidity at attractive rates of return. In the past, the IPO was a major liquidity event; in today's market, this almost never occurs. However, despite the challenging IPO dynamics, there are several industry and capital market structure reasons to believe exit fundamentals will improve.

Acquisitions are driving more liquidity with good returns. Over the past decade, venture investors have seen the share of liquidity events attributable to mergers and acquisitions (M&As) in biotech increase from <10% to >60% (Fig. 4). There has been an increasing frequency and scale to biotech acquisitions as bigger companies look to strengthen their pipelines and address the R&D productivity challenge⁴. The buyer universe has also greatly expanded in the past decade. Beyond simply big pharma, large and mid-cap biotech firms

are increasingly aggressive acquirers of private companies (e.g., Biogen-Idec's acquisition of San Diego-based Conforma Therapeutics). According to their published financial statements, this buyer universe in 2006 had an annual cash flow from operations of \$105 billion and has cash and liquid reserves of over \$145 billion, which at least in theory is available for acquisitions. To put the latter in perspective, the cash in these profitable biopharmaceutical companies is enough to fund all private biotech venture financings for nearly 30 years at the current rate of ~\$5 billion a year. This gives them enormous buying power today.

The increase in M&A activity is not limited to later stage deals: early clinical and even pre-clinical programs are driving spectacular deal values (e.g., Pfizer's \$567-million acquisition of Angiosyn (San Diego) and Merck's ~\$400-million acquisition of GlycoFi (Lebanon, NH, USA)). A recent study from management consultants Bain & Company (Boston) suggests that median deal values have jumped from \$57

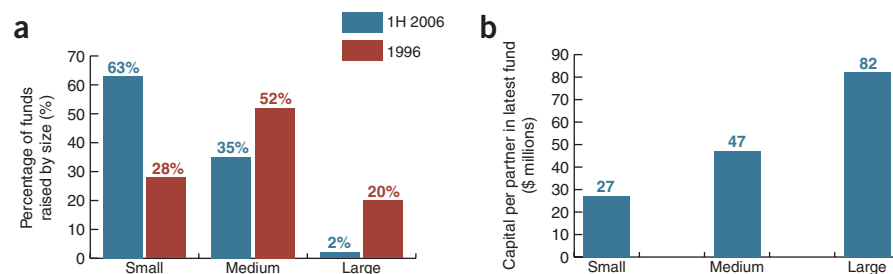


Figure 3 The increase in large venture capital funds is pushing capital toward larger later stage deals. (a) The percentage of venture funds raised in 1995 and 2005 reveals a striking move toward larger funds, with funds greater than \$500 million moving from 2% to 20% of the total number of funds raised. The trend also suggests the disappearance of the small sub-\$100 million fund. As categorized by Dow Jones Venture Source (New York), large funds are those with >\$500 million, medium funds are between \$100 and \$500 million and small funds are <\$100 million. (b) Larger funds require each partner to deploy more capital. Because each partner can only invest and manage four to six new companies in a given fund (a relatively fixed number due to partner bandwidth and time), partners in larger funds need to put more capital in each deal and therefore cannot realistically focus on early-stage life science projects and technologies. Source: National Venture Capital Association and the Private Equity-Holt Compensation Survey.

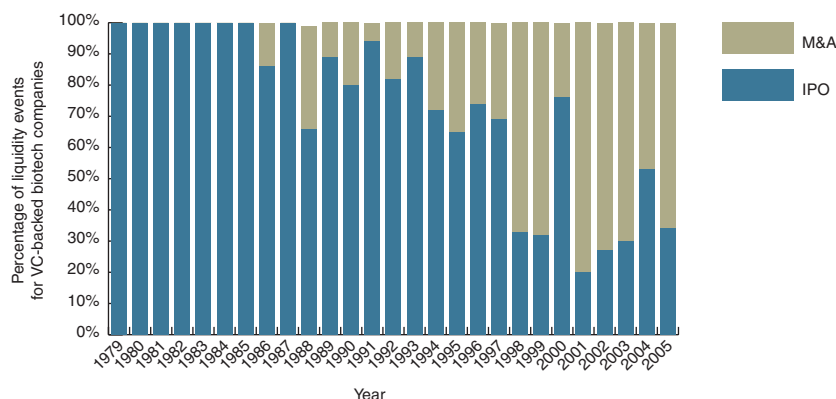


Figure 4 M&As have been an increasingly important driver of venture investor liquidity in biotech. Over the past 20 years, M&A has grown from nothing to ~70% of the liquidity events achieved by venture capital investors in biotech⁶.

million in 2003 to \$170 million in 2005, with an attractive 3.5× median multiple over invested capital⁷. An analysis of recent deals indicates that the top 18 acquisitions of private biotech firms since January 2005 have demanded a 4.1× median multiple over invested capital (Table 1) versus a 2.3× median multiple for a set of comparable IPOs (Table 2)—supporting the premise that acquisitions can and are driving an increasing proportion of returns for early-stage investors. Incrementally, the structure of private securities (e.g., participating

preferred stock) can make, all else being equal, an acquisition-driven exit much more attractive than a public offering to private investors. These trends certainly support the thesis that acquisitions by bigger players will be an increasingly attractive and frequent source of liquidity for early-stage investors.

Credible alternative paths to access public capital market liquidity. The IPO process may be broken today, but alternative public market approaches now exist. Reverse

mergers, in which a private company merges with a publicly traded company (often just a ‘shell’ company), are seen as increasingly credible. Several high-profile reverse mergers have recently occurred, including the merger of public Discovery Partners (San Diego) with Cambridge, Massachusetts-based private firm Infinity Pharmaceuticals (Fig. 5 and Table 3).

Companies are also listing their shares on stock market exchanges without an offering of new shares to the public: Speedel (Basel) and Biovitrum (Stockholm) have both successfully done this on European exchanges. More open and transparent global capital markets are also a viable option for biotech firms, and going public in a foreign market can sometimes be very lucrative. In 2005, for example, MediciNova (San Diego) went public on the Osaka Securities Exchange and raised almost \$170 million. It appears the trend is continuing: in August, Aculogix (Hayward, CA, USA) announced it plans to list on the Tokyo Stock Exchange and is aiming to raise \$101 million. Furthermore, London’s Alternative Investment Market (AIM) has also been aggressive about cultivating its attractiveness to US biotech firms; earlier in 2006, systems biology player Entelos (Foster City, CA, USA) raised \$20 million in an IPO there. It remains to be seen whether US biotechs will benefit from listing overseas or whether this will handicap their

Table 1 Top 18 acquisitions of private VC-backed life science firms since January 2005^a

Acquiring company (location)/target (location)	Deal date	Deal size (\$ millions)	Private capital invested (\$ millions)	Investment multiple ^b
Pfizer/Angiosyn	Jan-05	567	10	56.7×
PDL BioPharma (Redwood City, CA)/ESP Pharma (Edison, NJ, USA)	Mar-05	503	48	10.5×
Pfizer/Rinat Neuroscience (Pittsburgh) ^c	Apr-06	500	58	8.6×
Merck/GlycoFi	May-06	400	29	14.0×
Gilead (Foster City, CA, USA)/Corus Pharma (Seattle)	Jul-06	365	149	2.5×
Pfizer/Idun Pharmaceuticals (San Diego)	Feb-05	298	99	3.0×
Valeant Pharmaceuticals (Costa Mesa, CA, USA)/Xcel Pharmaceuticals (San Diego)	Feb-05	280	118	2.4×
Takeda (Tokyo)/Syrrx (San Diego)	Feb-05	270	136	2.0×
Becton Dickinson (Franklin Lakes, NJ, USA)/GeneOhm Sciences (San Diego)	Jan-06	255	54	4.7×
Biogen-Idec/Conforma Therapeutics	May-06	250	59	4.3×
Ortho-McNeil (Raritan, NJ)/Peninsula Pharmaceuticals (Alameda, CA, USA)	Apr-05	245	93	2.6×
Johnson & Johnson/TransForm Pharmaceuticals (Lexington, MA, USA)	Mar-05	230	60	3.8×
AstraZeneca (London)/KuDOS Pharmaceuticals (Cambridge, UK)	Dec-05	210	64	3.3×
Cephalon (Fraser, PA)/Salmedix (San Diego)	May-05	200	83	2.4×
Roche (Basel, Switzerland)/GlycArt Biotechnology (Zurich)	Jul-05	181	19	9.5×
MedImmune (Gaithersburg, MD, USA)/Collective Therapeutics (Gaithersburg, MD, USA)	Sep-05	158	28	5.7×
Affymetrix (Santa Clara, CA)/ParAllele Bioscience (S. San Francisco, CA, USA)	May-05	120	30	4.0×
Merck/Abmaxis (Santa Clara, CA, USA)	Jun-06	80	9	9.1×
Average				8.3×
Median				4.1×

Data collated from *Windhover* Publications, *BioCentury* and Dow Jones Venture Source.

^aThe acquisitions demonstrate a median multiple of total private capital invested of 4.1×. This multiple is a good proxy for returns, although it does not account for changes in the price of the private company's stock.

^bAssumes full earn-out milestones.

^cEstimate.

Table 2 Top 18 IPOs of private VC-backed life science firms since January 2005

Company (location)	IPO date	Post-IPO valuation (\$ millions)	Private capital invested (\$ millions)	Investment multiple
Altus Pharmaceuticals (Cambridge, MA, USA)	1/26/2006	315	103	3.1x
Osiris (Santa Clara, CA, USA)	8/5/2006	297	148	2.0x
Genomic Health (Redwood City, CA, USA)	9/28/2005	292	104	2.8x
Replidyne (Louisville, CO, USA)	6/28/2006	264	179	1.5x
Renovo (Manchester, UK)	4/7/2006	255	73	3.5x
Accentia Biopharmaceuticals (Morrisville, NC, USA)	10/28/2005	231	53	4.3x
Vanda Pharmaceuticals (Rockville, MD, USA)	4/12/2006	219	62	3.5x
NxStage Medical (Lawrence, MA)	10/27/2005	211	93	2.3x
Somaxon Pharmaceuticals (San Diego)	12/15/2005	198	90	2.2x
Jerini (Berlin)	10/31/2005	188	84	2.3x
BioXell (Milan, Italy)	6/21/2006	188	81	2.3x
Alexza Pharmaceuticals (Palo Alto, CA, USA)	3/8/2006	187	106	1.8x
Targacept (Winston-Salem, NC, USA)	4/12/2006	172	144	1.2x
CombinatoRx (Boston)	11/9/2005	161	132	1.2x
Sunesis Pharmaceuticals (San Francisco)	9/27/2005	150	122	1.2x
Novacea (San Francisco)	5/9/2006	149	108	1.4x
Omrix Biopharmaceuticals (New York)	4/20/2006	148	44	3.4x
Orexo (Uppsala, Sweden)	11/14/2005	147	10	14.8x
Average				3.0x
Median				2.3x

Data collated from *Windhover Publications*, *BioCentury* and Dow Jones Venture Source.

longer-term development, although this alternative exit route seems unlikely to disappear. All of these strategies offer alternative means to tap into lower cost-of-capital financing while opening up future paths to liquidity for private investors.

Less cyclical and more predictable US capital markets. The line between private and public small-cap companies has blurred as biotech firms seek out the lowest cost of capital available to fund the development of their pipelines. Public companies often access private capital (via private investment in public equities, also called 'PIPES'), and some private companies have been able to raise enormous sums of capital without going public (e.g., Fibrogen (S. San Francisco, CA, USA) and Synta Pharmaceuticals (Lexington, MA, USA) have both raised well over \$200 million in private capital).

Furthermore, because most IPOs are simply financing events rather than exits, most private investors end up holding onto their equity for one to three years post-IPO, waiting until a favorable value inflection for the stock. These capital market characteristics make the discrimination between public and private much less relevant. Furthermore, this public-private blurring is reinforced by the emergence of a large number of 'crossover' investors, who invest in pre-IPO private companies as well as publicly traded stocks. These investors get to understand the pipeline and long-term value

creation story of an emerging biotech company before its IPO road show, which involves a much more restricted sharing of information about the prospects for the company. This enables crossover investors to place early bets on likely winners in the public arena. This evolution in the biotech capital markets may make the dramatic ups and downs of the IPO 'windows' of previous years far less pronounced in the future. In fact, the IPO window may now be 'cracked open' all the time for companies with the right attributes, and remain challenging for more tentative stories.

The evidence supporting this market behavior is the prolonged nature of the current window: most historic windows were 18 months or less, but this window has lasted nearly three years. And although in recent financial quarters fewer companies have gone public, there is still a steady stream of offerings. This most likely reflects the continued maturation of the biotech capital markets, and bodes well for a more predictable and less cyclic marketplace.

New capital-efficient models are now viable

With a strong supply of new innovations and a more favorable exit outlook, the third theme supporting attractive early-stage returns is the ability to build value in a capital-efficient manner. As mentioned earlier, the bugbear of biotech investing has always been capital intensity: how much capital did a company need

to burn before it could achieve a significant value inflection and liquidity for its investors. Because of the deepening of the biotech business ecosystem, however, new models of capital efficiency can be achieved.

In particular, virtual biotechs are now a realistic alternative to classic biotech company-building. This breed of biotech is almost exclusively project-focused, has minimal infrastructure and relies solely on external service providers for execution. These three attributes make for both simpler governance and lower cash burn rates. Without the infrastructure and large team

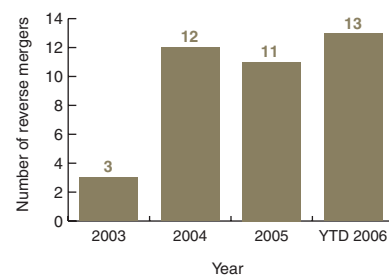


Figure 5 Reverse mergers in biotech are increasing frequent and credible means to access the public markets. Over the three years, >30 biotech reverse mergers (acquisitions by public companies or shells by private companies) have occurred. In the first three quarters of 2006, 13 reverse mergers have occurred. Source: DealFlow Media.

Table 3 Reverse mergers in 2006

Shell company (location)	Private company (location)	Merger date
Neurotech Pharmaceuticals (Redhill, Singapore)	Marco Hi-Tech (New York)	1/7/2006
BTHC II Acquisition (Argyle, TX, USA)	PolyMedix (Philadelphia)	2/22/2006
Integrated Brand Solutions (Vancouver, BC, Canada)	Upstream Biosciences (Vancouver)	3/1/2006
Xcyte Therapies (Seattle, WA, USA)	Cyclacel (Dundee, UK)	3/30/2006
SRKP 4 (Los Angeles)	Cougar Biotech (Los Angeles)	4/10/2006
CancerVax (Carlsbad, CA, USA)	Micromet (Munich)	5/6/2006
Multi-Link Telecommunications (Denver)	Auriga Laboratories (Norcross, GA, USA)	5/17/2006
Castle & Morgan Holdings (New York)	Osteologix (San Francisco)	5/25/2006
Highland Clan Creations (New York)	Raptor Pharmaceutical (Novato, CA, USA)	5/25/2006
Discovery Partners (San Diego)	Infinity Pharma (Cambridge, MA, USA)	9/13/2006
Dauphin Technology (Schaumburg, IL, USA)	GeoVax (Atlanta)	TBD
Axonox (New York)	TorreyPines Therapeutics (La Jolla, CA, USA)	TBD

TBD, to be determined.
Source: DealFlow Media

to support and amortize over the life of the investment, this model allows the titration of capital proportional to the removal of risk from the program and prevents the dilution of decision making that can slow down, or even promote inefficient, program governance. Furthermore, by leveraging external providers, these virtual biotechs can 'rent' a deep pool of less expensive skills and reduce their overall cost base.

In the 1990s, the virtual biotech concept was often discussed, but in practice was limited by the lack of access to and depth of CROs. Today, both broad and specialized CROs cover almost every facet of the drug discovery and development process. Global labor arbitrage enabled by Chinese and Indian CROs make for reduced cash burn rates, and access to deep industry

knowledge from specialty CROs in the United States (largely populated with veterans fleeing big pharma) makes finding high-quality research partners much easier. Furthermore, just as with academic laboratories, access to a plethora of drug discovery tools, such as *in silico* modeling, provides incredible leverage for small, early-stage research companies, especially in lead identification and optimization, that lack the scale of big pharma.

This capital and governance efficiency truly enables early-stage project-based financing and virtual new companies in a manner and scope never before possible. In these models, scarce resources like capital and time are spent on prosecuting an asset, not on more traditional company-building activities. At Atlas, my colleagues and I routinely evaluate plans aiming to

generate investigational new drug applications for well under \$12 million of invested capital, compared with \$40+ million in big pharma. This efficiency, and the increasing interest of big pharma in aggressively sourcing new programs, has opened up a fruitful dialog among venture investors, their portfolio companies and potential partners and acquirers that should support a more welcoming early-stage environment.

Conclusions

Early-stage investing is fraught with challenges, and the past five years have been a struggle. Even so, an abundant, investor-friendly supply of new innovation, favorable exit fundamentals and new models of capital efficiency should provide the foundation for a very attractive environment for early-stage risk capital. Importantly, this more favorable investing environment will ensure that new medical breakthroughs can access the resources and talent required to bring better life-enhancing products to the marketplace.

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