Innovators take cover as market bubble bursts

Can biotech’s cash cushion soften the blow as public markets tumble?

Melanie Senior

After a record-breaking couple of years for life science company financing, the party is over. “Biotech is correcting after an unprecedented run-up,” says Jean-François Formela, managing partner at Atlas Venture in Boston (Fig. 1). The S&P index of biotech stocks is down >40% since the start of 2021, even though the broader index is up. Most of 2021’s biotech initial public offering (IPO) class is trading below listing price; some biotechs are now worth no more than their cash. So far this year, IPOs are down to a trickle or being pulled, public biotech investors are licking their wounds, and private investors are nervous. The longer and deeper the hangover, the more likely it is to affect venture financing. Money is already moving away from later-stage rounds.

The good news: biotech coffers are stuffed with enough money to cushion the blow, at least for a while (Fig. 2). Many venture capital firms (VCs) have raised new funds to sustain company growth or creation, and venture debt has expanded. Biotech’s investor base has widened, bringing in many more long-term backers. “Capital markets look very different to ten or even five years ago,” says Formela. Company creation continued strongly through 2021, with talent, not money, now the bottleneck. And investors and biotech CEOs are looking hopefully to big pharma to re-engage in acquisitions this year, after overheated biotech valuations tempered deal-making in 2021. The mood is concern and caution, rather than panic.

But as the pandemic enters a new stage and wider macro-economic and geopolitical uncertainties take hold, it is unclear how quickly, or how high, biotech will bounce back. Companies with cash reserves must rediscover spending discipline, set clear milestones, generate data and restart conversations with potential partners and acquirers. But those that missed the fund-raising party may struggle. “If anyone thinks they can still go out, raise a crossover round and then do an IPO in 2022, they’re delusional,” says Antoine Papiernik, managing partner at Sofinnova Partners.

Bye-bye bonanza

Biotech was already attracting more and deeper-pocketed investors before COVID-19 hit. The pandemic turbocharged this trend as generalists, retail investors, hedge funds and even private equity investors piled in. Private fund sizes ballooned into the billions: Arch Venture Partners raised >$1.5 billion; OrbiMed and Flagship Pioneering each hauled in over $2 billion. Bigger funds meant bigger funding rounds.
For VCs, average series A rounds reached $41 million in 2021; B and C rounds reached ≥$500 million — for example, at drug-price-focused EQRx and cell- and gene-therapy technology company ElevateBio (Fig. 3). Even seed deals reached the tens of millions.

In a historical reversal of roles, investors competed for deals, rather than biotech CEOs competing for capital. The endgame to this bonanza became the IPO, whose average $160 million haul in 2021, though lower than 2020’s, was nevertheless double that of 2017 (Fig. 4). “Private companies saw that they were more valuable when public, so they rushed to list,” recalls one VC. Public investors reached back into private crossover (pre-IPO) rounds to ensure a spot at the IPO table; some later-stage investors moved upstream to avoid missing out. “Series Bs became crossovers. Later-stage investors got interested in earlier-stage companies,” recalls Hakan Goker, managing director at corporate venture firm M Ventures.

Intervals between venture rounds narrowed as traditional series A, B and C rounds were compressed into one (Table 1). Half of the 20 biggest biopharma Nasdaq listings in 2021 were companies founded in or after 2018 (Table 2). In January 2021, investment firm Medicxi bundled ten of its smaller portfolio companies into Centessa Pharmaceuticals, pulling in over a dozen other investors into a $250 million A round. Just four months later, UK-based Centessa, with four clinical-stage assets, raised $380 million in a Nasdaq IPO (Table 1 and Box 1). Others were even more ambitious. Flagship-backed Sana Biotechnology, promising a new generation of gene- and cell therapies, and SoftBank-backed synthetic biology firm Zymergen each raised over half a billion dollars via Nasdaq listings, despite the former having no clinical assets and the latter working in the traditionally lower-value industrial sector (Box 2). A faster, supposedly less complex route to market opened for biotechs willing to merge with special-purpose acquisition companies (Box 3), public shells that raise funds in advance.

The largesse was not limited to the United States. Europe’s biotechs also cashed in during 2021, smashing public and private fundraising records (Fig. 5). UK-based biotechs raised $3.6 billion, triple 2020’s haul, according to BioCentury. The $1.3 billion raised through UK biotech IPOs included two in the Nasdaq 2021 top ten, Centessa and Exscientia, the latter tapping into excitement around the potential for artificial intelligence to accelerate drug discovery. Exscientia’s $510 million IPO (including a concurrent private placement) came just months after the company raised >$600 million in series C and D rounds that same year (Table 2). Oxford Nanopore Technologies’ $474-million London listing was the city’s largest-ever biotech IPO, hot on the heels of the company raising the UK’s biggest private round in 2021, worth $271 million.

The reckoning
When the public market for biotech stocks went south, it wasn’t pretty. The rout saw 2021’s biotech IPO class fall by 37% on average by year’s end, according to Refinitiv data. Many newly listed companies fared much worse, and the decline has continued in 2022. It’s unclear why biotech, the pandemic savior sector, has been hit so hard relative to the rest of the market, but a few factors were at play (Fig. 5).

Some of the falls reflect unrealistic initial valuations, including for firms that shouldn’t have been anywhere near the public market. “When the wind blows hard enough, even turkeys can fly,” is how one VC puts it. Abundant capital removed almost all barriers to company formation, says one fund manager; many lacked operational maturity. A quarter of those that listed in 2021 were preclinical. They have been punished harshly, as have those issuing bad clinical news.

Even companies with untainted clinical-stage assets have been hit. Centessa’s shares halved (Table 2). Cullinan Oncology, whose portfolio includes a phase 2 epidermal growth factor receptor (EGFR) inhibitor for exon-20-mutated non-small-cell lung cancer, has fallen 70% since its $287 million IPO. So has LianBio, just a few months after its $325 million Nasdaq IPO. The company sources candidates globally for Asian markets; lead mavacamten, licensed from Bristol Myers Squibb, has just started a phase 3 trial in obstructive hypertrophic cardiomyopathy in China, where it recently
received breakthrough designation. Vor Biopharma, whose engineered allogeneic hematopoietic stem cell candidate VOR33 is on the cusp of a phase 1/2 trial in acute myeloid leukemia patients at high risk of relapse after hematopoietic stem cell therapy, listed in February 2021 at $20 a share. The pop to $40 was unjustified, according to some analysts. But none felt it was worth as little as the current $8 a share. "At first, companies with late-stage assets were more immune," says Sally Bennett, co-head private and syndicate investment at New York-based investment firm HealthCor Management. "But as the rout went on, it became more indiscriminate." Many investors sold out after six-month lockup periods — typically imposed on existing investors (VCs and crossover investors) that buy into an IPO — began to expire. Some observers point to rising concerns over drug pricing, a leaderless US Food and Drug Administration (FDA) during 2021 and site-inspection delays. The number of FDA-imposed clinical holds rose sharply in 2021, while the share of positive news from small and mid-sized biotechs fell, according to data from Jefferies and Morgan Stanley, respectively. Yet approvals continued apace through 2021, despite the pandemic. And most of the US drug price reform options that were circulating in government circles have retreated.

For Medici co-founder and partner Francesco de Rubertis, the sell-off is driven less by judgment than by market mechanics — funds forced by covenants or sector allocation rules to sell when losses reach a certain level. "It can't be that everything is worth cash," he says. But risk went out of fashion as spooked generalists, opportunistic retail investors and other 'tourists' unaccustomed to biotech cycles rushed to withdraw money.

A cushion — for some
Collapsing share prices — whatever their precise cause — don't affect R&D until the money runs out. Centessa has enough cash through to 2024, according to CEO Saurabh Saha, along with clinical-stage assets that may generate positive news.

Many private firms also look flush: Atlas's portfolio companies also each have at least two years’ worth of cash, according to Formela. If things haven't improved by then, some may benefit from Atlas's second $300 million Opportunity fund, raised in October 2021. It was initially an offensive move, allowing the VC to play in its portfolio companies' precocious crossover rounds and IPOs. As those options have faded, the fund has become defensive, says Formela, allowing the VC to support its own companies for longer — and benefit from lower buy-in valuations. Khosla Ventures also raised a $550-million opportunity fund in early 2022.

Company creation and earlier-stage investing has so far remained insulated from the public market spiral. In March 2022, Atlas raised another $450-million early-stage fund and Frazier Healthcare raised one worth $987 million. "It will take a while before the public market correction impacts our willingness to start companies," says Atlas's Formela. Other VCs agree: "The fundamentals remain intact: great science, unmet need, and lots more [drug development] modalities to pursue," says Soren Møller, managing partner of Novo Seeds, which creates and builds companies in the Nordic region. It kept up its usual pace in 2021, seeding five new companies from its evergreen fund. Cambridge, Massachusetts-based Flagship Pioneering plans to use its $3.4-billion war chest to build 20–25 companies over next 2.5–3 years. "That's about the rate at which we've operated historically, and I don't see that slowing down," founder Noubar Afeyan told *Forbes* in June.

Already, though, money is moving away from later-stage rounds as crossover and

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**Fig. 3 | Trends in private financing rounds, 2017–2021.** All trend lines are up. **a,** Series A rounds. **b,** Series B rounds. **c,** Series C rounds.
IPO plans are ditched, reports Roel Bulthuis, managing partner at Amsterdam-based INKEF Capital, which invests in early-stage European healthcare and technology companies. “Investors are starting to behave differently.”

Not all firms are protected. Biotechs with late-stage, cash-hungry programs or issuing bad news have had to downsize or raise debt. Biogen is cutting staff following dismal late-stage, cash-hungry programs or issuing debt. Biogen is cutting staff following dismal sales of its Alzheimer’s drug Aduhelm (aducanumab), whose reimbursement was limited to trial participants following 2021’s controversial FDA approval.

Microbiome-focused Kaleido Biosciences shrank its workforce early in 2022 and cut a mid-stage program. Gamida Cell, facing a clinical hold on an earlier program, pared back its headcount to eke out its cash until mid-2023, by which time it hopes the FDA will have approved its lead bone marrow transplant graft omniducel. And Ardelyx, whose shares are trading at around the $1 mark, the lowest since its 2014 IPO, secured $27.5 million in debt financing from SLR Capital in February 2022 to fund the launch of its sodium–hydrogen exchanger subtype 3 (NHE3) inhibitor Ibsrela (tenapanor). Although this was approved for irritable bowel syndrome with constipation back in 2019, last year, the FDA turned down the same drug for the more lucrative indication of controlling serum phosphorus in patients with chronic kidney disease on dialysis.

**A necessary correction?**

Some long-standing biotech investors welcome the correction — and not just for the buying opportunities. Excess capital and undiscerning public markets created a flood of listings from low-quality, undercooked or undifferentiated companies whose subsequent struggles could affect the broader sector reputation. All biotechs, even those with sufficient cash today, face the prospect of future ‘down-rounds’ — financings based on a lower valuation, which dilutes existing shareholders and damages confidence.

Frantic competition in private rounds meant firms were being financed not according to how much they needed to reach certain milestones, but by investors’ drive to invest as fast as possible, “so they could move on to raising the next, even bigger fund,” says INKEF’s Bulthuis. Traditional metrics for valuing companies — an art rather than science, even in earlier times — were abandoned. That made it difficult for seed- and early-stage investors to benchmark valuations at a realistic level that would keep acquisition or partnership options open and avoid future down-rounds.

Some corners of the market, such as allogeneic cell therapies, gene therapies or antibody–drug conjugates, began to look uncomfortably crowded, with many companies chasing similar narrowly defined commercial opportunities. There are now hundreds of chimeric antigen receptor (CAR)-T cell therapy companies, for example, although the handful of therapies on the market have yet to make a mark commercially. In February 2022, Janssen and Legend Biotech’s Carvykti (ciltaclabtagene autoleucel) became the sixth approved CAR-T cell therapy in the United States, and the second directed at B cell maturation antigen (BCMA), for refractory or relapsed multiple myeloma. “I see lots of people going after similar indications, with versions of the same modality,” says one investor. There are concerns that each inch of progress is being packaged into a standalone company, in some cases reflecting at best incremental innovation, rather than step changes. This dilutes investor interest and may mean less capital and undiscerning public markets for the buying opportunities. Excess capital is invested.

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Now it's back to basics. “Teams need to pace themselves,” put their heads down and focus on generating good data, says Papiernik. Spending and strategy will differentiate winners from losers. In the end, there are two ways for biotechs to create value, he continues. “By partnering or selling to pharma.”

Mergers and acquisitions to the rescue? With so much cheap capital swilling around, biotechs didn’t need to pay much attention to business development in 2021. Partnering held up, but there were just $108 billion worth of biopharma acquisitions, down 15% on 2020 and less than half of 2019’s figure, according to EY (Table 3). The top ten deals included...
Box 2 | Industrial and synthetic biology ventures — a new dawn?

Biotech’s pandemic prominence also revived interest in its applications beyond healthcare and medicine, after several false dawns in previous decades (such as biofuels in the 2000s). Synthetic biology firms aim to use DNA, bacteria or eukaryotic cells to make almost anything — fuel, industrial chemicals, foods or fabrics — more cleanly and efficiently. Bill Gates-backed synthetic biology company Ginkgo Bioworks raised $2.5 billion via a special-purpose acquisition company (SPAC) in November 2021, valuing the company at $17 billion. But symbio ventures have suffered from the same hangover as health biotech ventures: 14-year-old Ginkgo hasn’t got a product on the market yet and is down 60% since the SPAC deal; Zymergen, whose tagline is “we make tomorrow,” has lost 90% of its stock value since IPO (in part because a promised optical film for foldable LED screens failed to materialize).

But with climate change, transition to green (and local) energy sources, and sustainable foods and agriculture front-of-mind, these emergent industries have arrived and aren’t going away. And specially health VCs are taking note. Following in the footsteps of funds like Breakout Ventures (Modern Meadow and Twelve) and Khosla Ventures (Impossible Foods), Flagship Pioneering is expanding from therapeutics to invest part of its new $3.4 billion fund in agriculture and nutrition.

Box 3 | The super SPACs

Special-purpose acquisition companies (SPACs) were popular in biotech through 2020, but slowed in 2021 (as they did in the rest of the market). They involve ‘blank check’ or shell companies raising money in an IPO and using the proceeds to find and buy a business afterwards, often in conjunction with private investment in public equity (PIPE) financing. SPACs allegedly provide a faster route to market than conventional IPOs and skirt some lengthy disclosure and roadshow processes associated with IPOs.

But the shine has come off. The average share performance after ‘de-SPAC-ing’ — finding a target private company to buy — was ~32% by the end of 2021, even worse than for normal IPOs, according to PitchBook. Going public via SPAC still involves wooing investors and agreeing on a valuation; and the way SPACs are structured means that they aren’t always cheap for new investors. Regulators have also been circling, with talk of new rules to ensure the price of a SPAC is more tightly tied to that of the underlying company. So far, such threats have not materialized.

Opinions differ on the value that SPACs have brought to biotech. One Boston-based VC dismisses them as “a distraction” and “the manifestation of exuberance and excess capital.” Another believes SPACs could offer an alternative for some companies this year, as conventional IPOs dwindle. SPAC sponsors have two years, after raising capital, to find a private merger partner. Dozens of healthcare-focused SPACs have yet to find a target. Already in 2022, PureTech Health-founded Gelseis, which sells a weight management aid, raised about $100 million in a SPAC deal — though its stock has since fallen 40%. Another PureTech-founded entity, Akili Interactive (which sells a video-game-based treatment for attention deficit hyperactivity disorder), announced plans to complete a $400 million SPAC transaction mid-year.

Others have failed to launch: Valo Health terminated a $750 million deal with a SPAC sponsored by Khosla Ventures in November. UK-headquartered BenevolentAI which uses AI to speed drug discovery, in December 2021 announced a merger with the Amsterdam-listed SPAC Odyssey Acquisition, anticipated to raise >$400 million. The deal would be among Europe’s largest SPAC mergers — if it completes.

Merck’s $11.5 billion acquisition of Acceleron Pharma, with its late-stage pulmonary arterial hypertension drug sotatercept; Jazz Pharmaceuticals’ $7.2 billion takeover of cannabis-based medicine maker GW Pharmaceuticals; and Sanofi’s $3.2 billion purchase of mRNA-focused startup Translate Bio (Table 3). Sanofi, the Paris-based big pharma, was one of the most active dealmakers in 2021: it spent a further combined $4 billion on New York-based Kadmon, with its approved graft-versus-host disease drug Rezurock (belumosudil); Cambridge, UK-based Kymab, whose OX40L-targeting monoclonal antibody is in phase 2 trials for atopic dermatitis; and California-based Amunix Pharmaceuticals, with a preclinical pipeline of T-cell engagers and cytokines therapies designed to activate only in disease-specific microenvironments.

Several of 2021’s deals and financings reflected broader trends shaping biotech: the drive to streamline R&D with an expanding suite of digital and biology-based tools, and growing interest in biopharma from private equity — a group traditionally focused on large, revenue-generating businesses. There was consolidation among contract research organizations, as Thermo Fisher Scientific acquired Pharmaceutical Product Development (PPD) for $17.4 billion and Dublin-based Icon paid $12 billion for PRA Health Sciences. Stockholm-headquartered firm EQT Private Equity and Goldman Sachs Asset Management bought contract research organization Parexel for $8.5 billion — the biggest private equity buyout of a healthcare firm, according to PitchBook. EQT then snapped up Amsterdam-based early-stage investment firm Life Science Partners in November 2021 for approximately $500 million (Box 4).

In December 2021, Utah-based Recursion announced a drug-hunting partnership with Basel, Switzerland-based Roche with $150 million up front and a potential value of $1 billion. Recursion is among a growing cohort of well-financed biotechs seeking to industrialize drug discovery using artificial intelligence (AI)-powered algorithms and scaled-up molecular data analysis. Like Exscientia, Recursion scored a large IPO in 2021, after a hefty Series D the year before. “Biotech is becoming more of an engineering than an empirical science,” reflected Westlake Village BioPartners’ founding managing director Beth Seidenberg during a J.P. Morgan Endpoints panel. The explosion of gene editing and delivery tools, visualization methods and computer-powered data analysis is allowing scientists to tame biology in ways that weren’t possible just ten or even five years ago.

These approaches haven’t — yet — delivered new drugs faster. They also come with challenges, including the risk that
an R&D-supporting technology becomes obsolete before any drug gets to market. But their promise is compelling; and big pharma knows it needs a seat at the table. The Roche deal involves identifying and developing up to 40 new medicines for cancer or neurological disorders.

As prices come down, biotechs are dusting off their deal-making handbooks and looking expectantly at big pharma. “Pharma are desperate to fill their pipelines with more innovative approaches and will be looking for biotech for those opportunities,” says Daphne Zohar, CEO of London- and Nasdaq-listed PureTech, whose pipeline includes four clinical-stage immunomodulatory drugs. Big pharma is collectively sitting on over $500 billion cash or equivalent, according to EY, and many face near-term patent-expiries on key drugs.

Novo Seeds’ Møller reports increased interest: in February 2022, AbbVie paid $130 million up front for portfolio company Syndesi Therapeutics of Louvain-la-Neuve, Belgium, whose synaptic vesicle protein 2A program, spun out of Brussels-based UCB, recently entered trials for cognitive impairment. In March 2022, UCB bought California-based Zogenix, focused on drugs for rare forms of epilepsy, in a deal worth up to $1.9 billion.

Some biotechs that missed the IPO gravy train have turned to transactions. Neuromuscular rare diseases-focused Dynacure of Strasbourg, France, withdrew a planned $100 million IPO in July 2021, and in November signed a deal with Kyoto-based Nippon Shinyagu for development and commercialization in Japan of its phase 1/2 antisense oligonucleotide candidate for myotubular and centronuclear myopathies, in exchange for $5 million up front and up to $82 million in milestones.

Even if vigorous merger and acquisition activity does return, it can’t entirely replace a buoyant public market: there are too few buyers. A hawkish US Federal Trade Commission may also continue to put a damper on very large acquisitions. But some exciting deals “could re-inject confidence,” says de Rubertis.

What’s next?
Venture and private equity investors still want to put money into biotech. In February 2022, European life sciences VC Life Science Partners (LSP) — now owned by EQT — closed Europe’s largest life sciences venture fund ever, worth over $1.1 billion. Although venture capital remains abundant (if now a little harder to access), talent, rather than money, has become the main bottleneck to company creation. That’s a big shift for Europe, where biotech growth was long hampered by insufficient venture funding.

So biotech CEOs and other senior management are hot property. Investors report that CEOs, as well as chief medical officers, chief financial officers and, in the cell and gene therapy space, heads of CMC (chemistry, manufacturing and controls) are now demanding a greater share of equity in the company — sometimes totaling as much as 20%, double what was previously considered the norm. Even in Europe, biotech CEOs are taking a page out of their technology counterparts’ books in daring to ask for more money and have more say in how their company is financed, says INKEF’s Bulthuis. And healthcare entrepreneurs now come fresh from their PhDs or postdocs, rather than first building a distinguished academic career.

Public investors are still cowering. Biotech, with dozens of new, early-stage companies, now looks much riskier than
many other sectors. Bad news pummels share prices, yet good news barely lifts them. So “everyone's hunkering down or moving towards lower-risk investments,” says one fund manager. “No one wants to see anything new.” Nor can the sector rely on COVID-19-like boosts: newer investors in the sector are realizing “there won’t be a COVID-19 every five years,” reflects de Rubertis.

Still, few predict lasting damage from this downturn. At worst, it’s a necessary correction and at best, it creates bargain buys and sparks the flow of deals in a sector whose relevance, across healthcare and beyond, has never been greater (Box 2).

Newer biotech CEOs who have yet to live through a down cycle must lean on experienced board members. “When the sea gets rough, they [management teams] have people on the bridge that have seen it before,” says Papiernik. His advice for 2022? Act purposefully, and above all, “do not panic.”

**Box 4 | Private equity comes to the life sciences**

Private equity (PE) investors typically focus on buying and restructuring revenue-generating companies. But a new ‘growth equity’ subsector is looking more closely at pre-revenue companies expected to launch a product or undergo another value-creating event, such as an acquisition, in the near term. PE and growth equity has boomed over the past few years amid low interest rates and as investors sought exclusive alternatives to public stocks. Biotech got plenty of attention during the pandemic. In 2021, growth equity investment in healthcare reached its highest level in over a decade, according to PitchBook. EQT’s acquisitions of Parexel and venture firm Life Science Partners (see main text) are just the latest examples of PE’s growing interest.

In November 2021, PE firm Blackstone Life Sciences took a $100 million equity stake in UK-based Autolus Therapeutics, whose CD19 CAR-T therapy, obecabtagene autoleucel, is in a pivotal trial in adult acute lymphoblastic leukemia due to read out this year. Autolus’s shares had more than halved since its 2018 IPO, so Blackstone spotted opportunity, providing $50 million in up-front cash (in addition to the $100 million private placement) and negotiating a royalty share on future sales of the therapy. The collaboration and financing deal, one of largest investments in a UK biotech, funds Autolus through mid-2023.

General Atlantic has stakes in Centessa, Immunocore (another Nasdaq-listed UK-based biotech, whose bispecific T-cell receptor immunotherapy Kimmtrak (tebentafusp) was approved by the FDA in January), and synthetic biology firm Ginkgo Bioworks.

PE firm NovaQuest Capital Management was involved in Roivant Sciences’ acquisition of computational physics company Silicon Therapeutics, before Roivant’s private investment in public equity (PIPE) and SPAC merger with Montes Archimedes Acquisition in October 2021, which raised >$600 million.

For Sofinnova’s Papiernik, these deals are just the early tremors of what will soon become another “tectonic” force shaping biotech. With trillions of dollars of private money at its disposal, PE provides another source of capital if public markets do remain muted.

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