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Precision financing

Private biotech financing in 2023 is more discriminate, disciplined and demanding. Strong data and efficiency are de rigueur.

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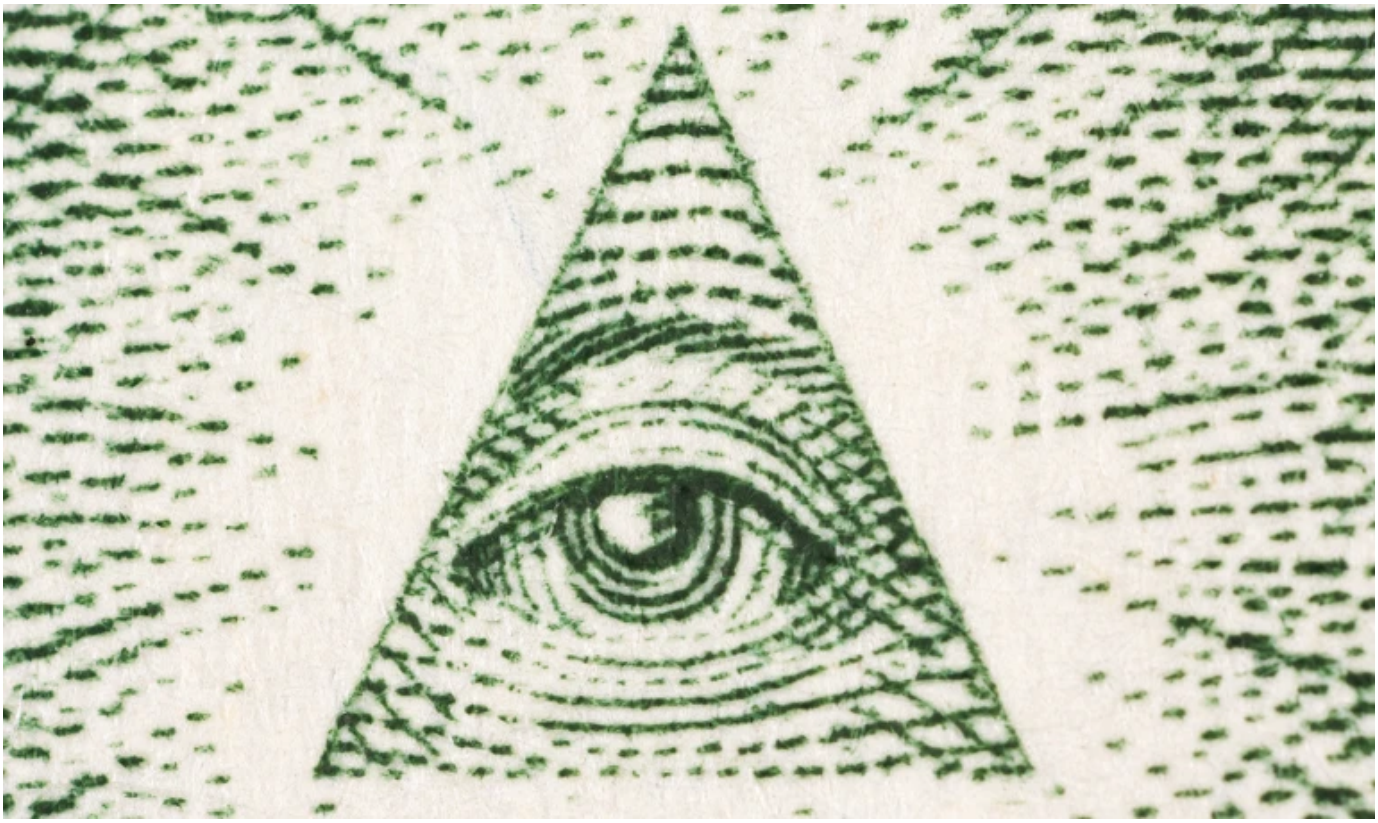

The 2020s have flung biotech from the heights of pandemic exuberance, when cash grew on trees and anyone with a lab coat could take a company public, to the belt-tightening lows of 2022, with layoffs, liquidations and falling valuations.

As the dust settles in 2023, a more discriminate financing environment is emerging. There is still plenty of private money about: $35 billion of venture capital was raised in 2022, more than during pre-pandemic 2019. But investors aren't giving it away so easily. With little insight into when the wider economic malaise will end, many venture capitalists continue to face tough decisions about which of their portfolio companies to support. A quick exit via an initial public offering (IPO) is no longer an option: IPOs in 2022 fell to just 25% of pre-pandemic levels, and few expect much change this year (Fig. 1). Pharma acquirers haven't picked up the slack, either: mergers and acquisitions during 2022 were smaller, and rarer, than many anticipated at the start of the year (*Nat. Biotechnol.* **40**, 1546–1550; 2022). Pfizer's proposed $43 billion acquisition of Seagen in March 2023 may catalyze more action, but several pharma CEOs are talking down mega-mergers. Raising new venture capital (VC) funds has become tougher, too. Limited partners (who fund the VC funds) are shutting off the taps as they nurse their public holdings and want evidence of payback on their invested funds before putting more money to work. The collapse of Silicon Valley Bank in March 2023 hasn't helped confidence in biotech fundraising (or bank stocks), even if federal action does secure companies' existing deposits.

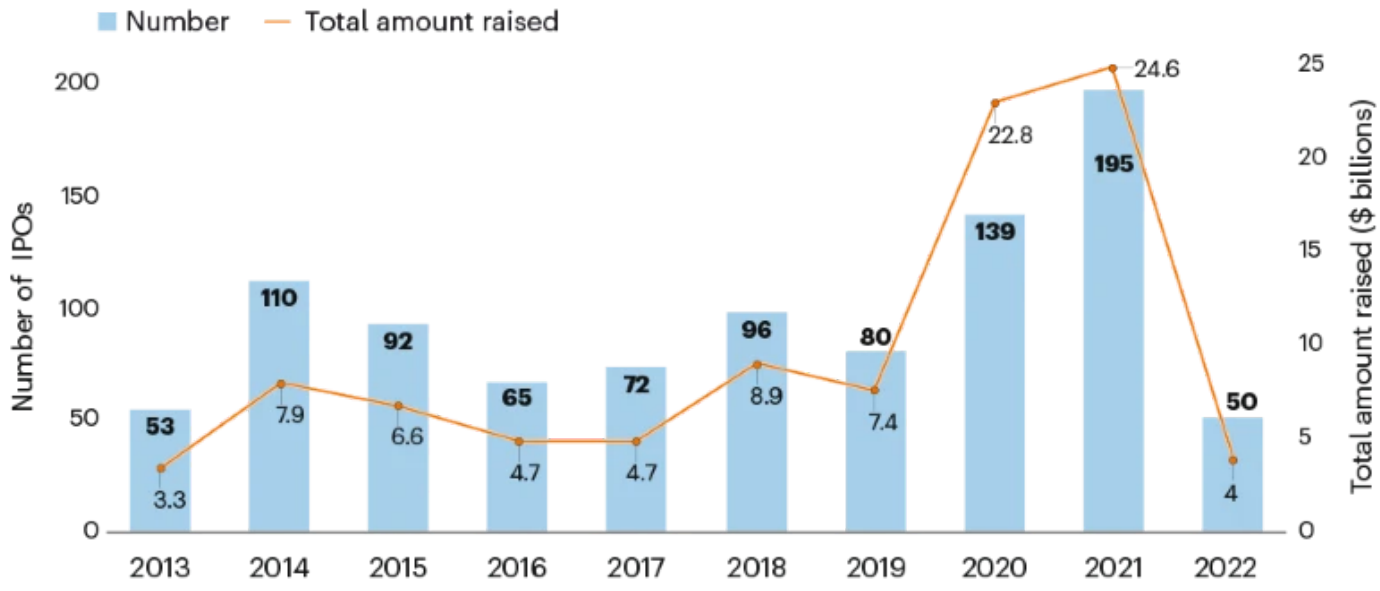

Fig. 1 Historical biotech IPOs. The IPO window slammed shut in 2022, leaving no exits for private companies. Source: BioCentury BCIQ Database.

To attract funding in 2023, biotechs need strong data (ideally clinical data), a differentiated asset or technology, disciplined spending, sensible time frames and

realistic valuation expectations. Such basics were forgotten during the upturn, and inflated private valuations persisted beyond it — partly explaining the lower investment and merger and acquisition activity during 2022.

Haves and have-nots

The chosen few can still win large rounds. In the first few weeks of 2023, Danish biotech Hemab Therapeutics, chaired by Alnylam's former founder CEO John Maraganore, raised a $135 million series B to support a phase 1/2 study of a bispecific antibody for a rare clotting disorder, Glanzmann thrombasthenia, and Lyon, France-based Amolyt Pharma, run by serial entrepreneur Thierry Abribat, pulled in $138 million in a series C on the back of positive phase 2a data for long-acting parathyroid hormone receptor-1 agonist eneboparatide for hypoparathyroidism. Both are well above the average B and C rounds raised in 2022, and even beat heady 2021's averages (Fig. 2). So, by far, did Cargo Therapeutics' $200 million series A , raised on the back of phase 1 results for its autologous CD22 chimeric antigen receptor (CAR)-T cell therapy, in development for large B cell lymphomas that are relapsed or refractory to CD19 CAR-T cell therapy.

A couple of biotechs have even pulled off successful IPOs, thanks to clinical-stage assets and buyers lined up in advance: Structure Therapeutics, designing small molecules targeting G-protein-coupled receptors for metabolic and pulmonary diseases, raised $185.3 million on the NASDAQ in February, followed days later by Mineralys's $192 million IPO that will fund phase 2/3 trials of lorundrastat, an aldosterone synthase inhibitor, for resistant hypertension. Listings remain a rarity, though: the BioCentury BCIQ

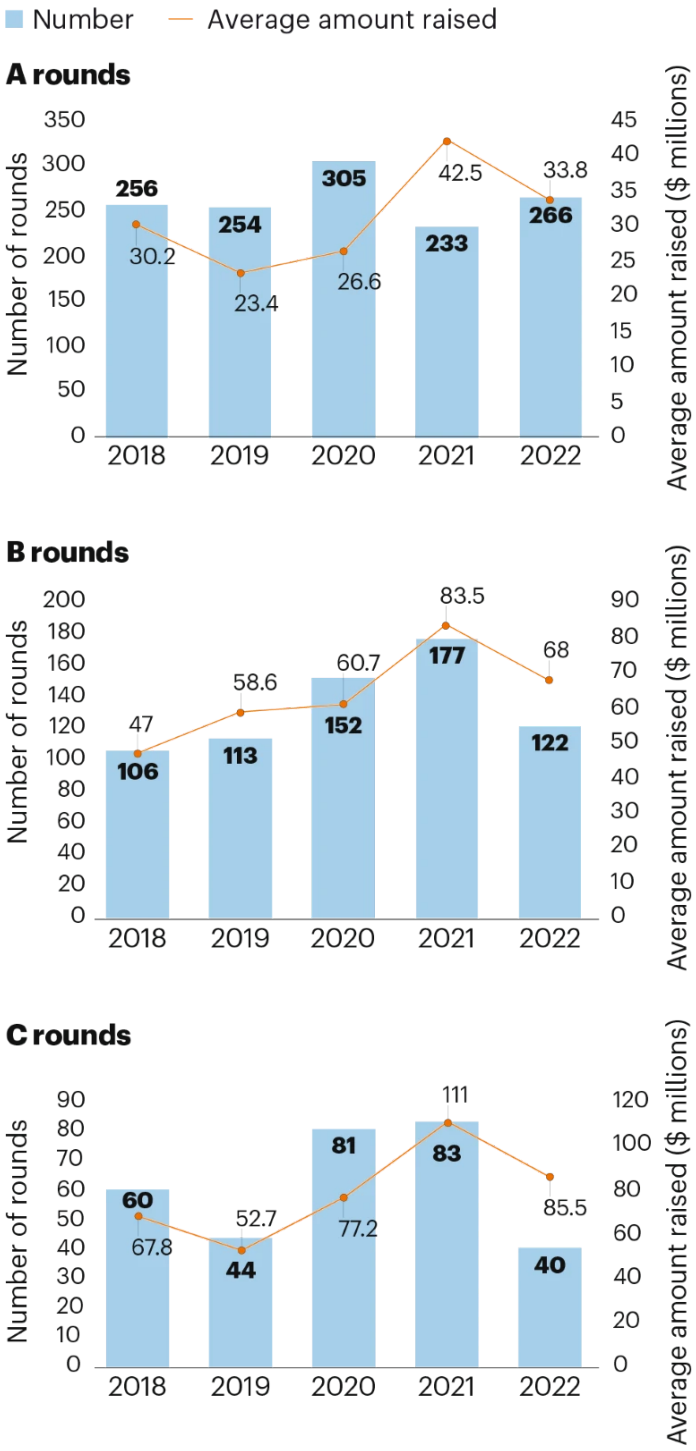

Fig. 2 | Trends in biotech private financing over five years. Private funding round averages fell in 2022; C rounds slumped sharply in number and size. Top, series A rounds. Middle, series B rounds. Bottom, series C rounds. Source: BioCentury BCIQ Database

database records just five biotech IPOs in 2023 so far, raising a total of just over $430 million.

"It's a moment of separation – between the 'haves' and have-nots'," says Antoine Papiernik, managing partner at Sofinnova Partners, which co-led the Amolyt deal.

In this ruthless meritocracy, the 'haves' needn't necessarily be clinical-stage companies. Platform technologies that promise multiple novel programs are fashionable. RNA-based discovery engines have become hot property since the runaway successes of Moderna and BioNTech, with five $100 million-plus financings during 2022 and 2023, including MPM Capital- and BioImpact Capital-founded Orna Therapeutics' $221 million series B in 2022 (Box 1).

Box 1 Taking RNA therapeutics mainstream

The 23 RNA-based company financings in 2022 were double 2019's count. Before 2022, no single one had surpassed $100 million. Inspired by Moderna and BioNTech's mRNA-based COVID-19 vaccines, researchers are digging into various forms and designs of RNA to unlock new therapeutic opportunities.

Orna's circular RNA-based medicines (*Nat. Biotechnol.* https://doi.org/10.1038/d41587-022-00005-1; 2022) may be more effective, more stable and simpler to produce. Merck signed up with $150 million up front in an August 2022 deal that could be worth up to $3.65 billion. Arch Ventures-backed Nutcracker Therapeutics raised a $167 million series C on its promise of faster RNA therapeutics design, development and manufacturing, while six-month-old Orbital is trying to extend RNA therapeutics' delivery to more cell types and prolong half-life. ReCode Therapeutics, which is optimizing mRNA and gene correction for precision genetic medicines, including for cystic fibrosis, bumped up an earlier $80 million series B to $120 million in mid-2022 with funding from Bayer and Amgen's venture arms. Other companies are attempting to drug RNA using small molecules; Atomic AI, for example, raised a $35 million series A in January*Nat. Biotechnol.* **41**, 305; 2023).

There's seed-stage action, too: in 2023, Italy's Resalis Therapeutics, which targets non-coding micro-RNA to tackle metabolic disease, attracted €10 million ($11 million) in seed funding from local VC firm Claris Ventures and angels.

Gene-editing groups are also on the right side of the line. Chroma Medicine's epigenetic editing approach targets innate gene regulation processes like methylation, rather than cutting or nicking DNA. It attracted a $135 million series B on March 1, led by GV (Google Ventures), Alphabet's venture arm. Metagenomi, inspired by CRISPR's provenance in bacteria, is mining microbes to help build novel precision editing tools. In early 2023 it added $100 million to a $175 million series B begun the year before. This wasn't a distressed extension round; investors were competing for a share of potential next-generation gene-edited therapies. "We wanted to increase our holding" and couldn't get enough the first time around, says Naveed Siddiqi, senior partner, venture investments at Novo Holdings, which co-led the 2023 tranche. The company is still preclinical, but animal gene editing models offer the prospect of good translation into the clinic, notes Siddiqi. With sufficient cash to get to proof of concept and cash-generating deals with antisense pioneer

Ionis and with Moderna, Metagenomi will be "ready to go public once the market opens," says Siddiqi.

Synthekine's cytokine engineering platform pulled in a $100 million series C at the start of this year, led by The Column Group, fresh with two $615 million funds, one for early-stage and one for later-stage ventures, raised in June 2022. Synthekine's PEGylated α/β–biased interleukin-2 partial agonist STK-012, engineered to preferentially stimulate tumor-antigen activating T cells, is only in phase 1 (for advanced solid tumors), but the biotech has four further preclinical immuno-oncology programs, including cytokine-empowered CAR-T cells designed to be more potent, more durable and less toxic.

Cell- and gene-therapy companies in 2022 raised just over $3 billion in private investment. That's only half of 2021's bumper $6 billion, reflecting manufacturing and commercial challenges in the field, overcrowding, and the broader slowdown. But 2022 still brought 11 deals worth more than $100 million (top ten in Table 1), including a $270 million series C for gene therapy player Kriya Therapeutics, led by Patient Square Capital, and $300 million series C for Flagship Pioneering-backed Tessera Therapeutics, seeking to simplify CAR-T cell therapy using its 'gene writing' platform. This uses mobile genetic elements (also called transposable elements, or 'jumping genes') to 'write' therapeutic messages into the genome, potentially enabling RNA-based CARs to be inserted into T cells in vivo, skirting the need for complex, burdensome T cell extraction and re-infusion processes. The 2022 cell- and gene-therapy funding total was level with 2020's and well ahead of 2019's ($1.88 billion) and 2018's ($1.16 billion). So far in 2023, about a dozen private gene- and cell-therapy companies have raised a combined $525 million, according to BioCentury. Flagship Pioneering-founded Ring Therapeutics added an $86.5 million series C to that total on March 9; funds will help advance preclinical nucleic acid-based medicines harnessing anellovirus-based vectors.

The winner–loser triage can be drawn out. Strong companies that need cash but haven't quite reached data readout may get a down round — investment at a lower valuation than in the previous round, leaving existing investors (and management)

with smaller shares of a smaller pie. But at least there will still be a pie. Luckier ones may achieve the same valuation as at their last financing; such flat rounds are, in the current climate, "the new up rounds," says Novo's Siddiqi. Bridge financing (often a cash loan that converts into equity) can help firms reach a specific milestone, like a data readout or licensing deal. But beware shifting goalposts as investors demand more progress before funding the next round (Box 2).

Box 2 Who are your investors?

Not all investors are equal, and that's especially true during troubled times. Multiple backers are better than one, as they offer more flexibility in subsequent rounds. Investors with longer time horizons are better positioned to weather a storm; that includes those, like Hellerup, Denmark-based Novo Holdings (backers of Hemab and Amolyt), with open-ended or 'evergreen' funding structures. These are not tied to generating returns over a specific time period, as fixed funds are.

If fixed funds are involved, investors with a several fund types and flexibility in where they invest also bring advantages. Naarden, Netherlands-based Forbion, for instance, can use up to a third of its $500 million Growth Opportunities fund to support firms across its Forbion Ventures Fund franchise or that of seed- and early-stage partner BioGeneration Ventures (subject to external validation). Similarly, Third Rock Ventures can tap its newest (2022) $1.1 billion Fund VI to support the strongest companies from its previous two funds. In challenging markets like today's, "it's important to show strong insider backing," says Sander Slootweg. Investors unable to prop up their own projects will struggle to attract outside money.

Venture debt — loans to venture-backed companies — are another option, but rising interest rates make this an expensive last resort. Royalty-based financing deals have also accelerated, as companies seek cash today in exchange for a share of sales-linked royalties later. These deals are more common among public companies.

Other biotechs have had little option but to shutter shop or eke out the cash they have, including by cutting programs and staff. Layoffs seen in 2022 are continuing, with over a dozen so far this year, according to Fierce Biotech's Layoff Tracker.

In times like these, though, one biotech's distress can be another's opportunity — both to seize assets and to attract new money. Disc Medicine in December 2022 scooped up struggling Gemini Therapeutics' cash and its NASDAQ listing, raising an additional $53.5 million from existing and new investors Access Biotechnology and OrbiMed along the way. Disc has three clinical-stage programs for various hematological diseases, including bitopertin, a small-molecule glycine transporter 1 inhibitor, for erythropoietic porphyrias. Since listing, it has raised another $62.5 million, mostly from Bain Capital Life Sciences, betting on positive clinical data readouts later this year.

Private precision oncology firm Enliven Therapeutics played a similar reverse-merger trick with listed Imara, which had run out of road. Thanks to a concurrent $165 million in private financing, along with Imara's leftover cash, newly public Enliven found itself with $300 million — enough to see it through to early 2026. (Plus, CEOs are recycled: Imara's leader Rahul Ballal is now running new fibrosis-focused Mediar Therapeutics, which raised an $85 million series A on March 15.) Private biotech mergers can also trigger fresh funding, not always on disadvantageous terms: when cell-therapy company Ensoma bought gene-editing minnow Twelve Bio in January 2023, Twelve's founding investor Arix Bioscience co-led an $85 million financing round in the enlarged group at a modest premium, according to Arix CEO Robert Lyne.

Whatever the funding strategy, and however high-profile the company, failed data means game over. Liquidation plans emerged in February 2023 for Flagship-backed Rubius Therapeutics, which had been trying to turn red cells into therapeutics. Rubius was worth almost $2 billion at its 2019 IPO despite having no clinical assets. A further crunch is expected during the second half of 2023 as biotechs that raised money at the start of the bull market in 2020 run out of road and investor reserves are

depleted. “There will be difficult decisions” during 2023 for even top-tier VC portfolios, says one investor.

Early-stage insulation

There are positives. Innovation isn’t slowing, and early-stage (seed and series A) investing remains relatively unscathed, says Edward van Wezel, managing partner at Naarden, Netherlands-based BioGeneration Ventures. The number of A rounds remained steady in 2022, and their average size dipped much less than that of C rounds (Fig. 2). BioGeneration maintained its (mostly European) deal flow through 2022 despite the shock in the rest of the market; for example, with a $5.7 million seed financing for Complement Therapeutics, a preclinical Manchester University spin-out working on new therapies for complement-mediated diseases through knowledge of factor H-related proteins. “Current market conditions are irrelevant to the outcomes of companies created today,” says Jean-François Formela, partner at Atlas Venture, also focused on seed and early-stage funding. Sofinnova expects to do more seed and early-stage activity over next 24 months. Third Rock is putting more money and time into seed development to generate more data and thereby enable meatier series A’s, says partner Jeffrey Tong, which, in turn, give firms some wiggle room to produce the value-inflecting clinical or proof-of-platform data they’ll need for the next stage. Look no further than Cargo, funded to take its lead through phase 2 and advance its pipeline, or Rapport Therapeutics, which raised a $100 million series A in March 2023 from Third Rock, Arch Venture Partners and Johnson & Johnson Innovation to progress its central nervous system pipeline. Rapport is using regional receptor-associated proteins to develop small molecules that target neurotransmitter receptors specifically, potentially enabling greater efficacy and fewer side effects than current treatments.

For investors with money to spare, now is a great time to invest, whatever the stage. “We make more money starting companies during down cycles,” said Arch Venture Partners’ co-founder and managing director Robert Nelsen in January 2023. Arch closed a $3 billion biotech-creation Fund XII at the end of June 2022, barely 18 months after its previous, $1.9 billion fund. And this time, the quality and experience of

companies, entrepreneurs, boards and investors is streets ahead of what it was in the downturns of 2001 and 2008, adds Sofinnova's Papiernik. New funds have emerged, helping build "the largest ever war chest of investable capital" in biotech, according to PitchBook data cited in a report from Silicon Valley Bank before its demise (Box 3).

Box 3 Bigger money.

Inaugural healthcare funds from Patient Square Capital ($3.9 billion) and tech-focused B Capital ($500 million from two funds), both announced this year, highlight the growing interest in biotech of private equity and large investment firms. Like all investors, they seek to buy low and sell high, but with many with tens of billions of dollars under management, these groups put large sums to work: Patient Square has deployed $3 billion since the downturn really took root in mid-2021, including leading a $270 million C round to fund Kriya Therapeutics' machine learning-powered discovery-to-manufacturing gene therapy platform. Patient Square joins the likes of Apollo, Blackstone, Carlyle and Intermediate Capital Group, which have bought or allied with life-sciences-focused VC funds over the last few years.

Meanwhile, tech–biotech convergence is carving out a new segment: newcomer Dimension (founded by two experienced venture capitalists, from Obvious Ventures and Lux Capital) in January announced a $350 million fund targeting the tech–life sciences interface, with four biology-software ventures already under its wing, including machine learning-powered drug discoverer Enveda Biosciences.

This sector maturity is also reflected in a broadening range of investment strategies. Founder-entrepreneurs have new options to help them get out of the blocks, tailored to today's straitened times. Curie.Bio, unveiled in February by serial entrepreneurs Alexis Borisy and Zach Weinberg, describes itself as a "drug discovery copilot and seed investor." It offers founders $5–8 million in seed money and targeted drug discovery support in exchange for only 40% of equity, rather than the 60–90% that early investors typically pocket. The promise of greater control has added sweetness, as many biotech teams are forced into flat or down rounds that dilute their holdings

even further. Curie.Bio's top-tier backers, including GV, Casdin Capital and Arch Venture Partners, have put in $520 million, of which $270 million will be invested in early-stage companies. The rest will help build an R&D services arm via a network of almost 100 contract research organizations and alliance management professionals. Curie.Bio's 60-person-strong team of experienced drug discoverers and developers, spanning medicinal chemists, structural biologists and more, will copilot founders along a capital-efficient route "from idea to industrial-grade drug embodiment," says Borisy. That means potent, selective drug candidates ready to be tested in appropriate physiological systems and to progress through development. Successful founders get a 12- to 24-month "industrial grade" plan, access to facilities and resources (without having to build or buy them) and, if their idea works, an open door to Curie.Bio's network of follow-on investors. Four ventures are already up and running; the Curie.Bio team is agonistic on modality, and ideas can come from anywhere — academia or industry, US or global.

A European story?

In 2022, Europe's share of global venture financing and IPOs fell while Asia's grew. European companies accounted for barely more than 10% of global private financing in 2022 — $3.5 billion, down from 15% in 2021 (Fig. 3). Yet overlooking Europe is unwise, says Novo's Siddiqi. The region's biotech valuations didn't bubble over as much as those in the United States during the pandemic, and still today, "Europe offers great value for the science it's producing," he says.

Siddiqi claims it's now possible to finance a European company through to a regulatory filing, with a nod to Amolyt, aiming to start phase 3 studies of eneboparatide this year. (Novo Holdings' ventures investment group co-led Amolyt's 2019 series A when the drug was preclinical.) Another nod goes to Basel, Switzerland-based

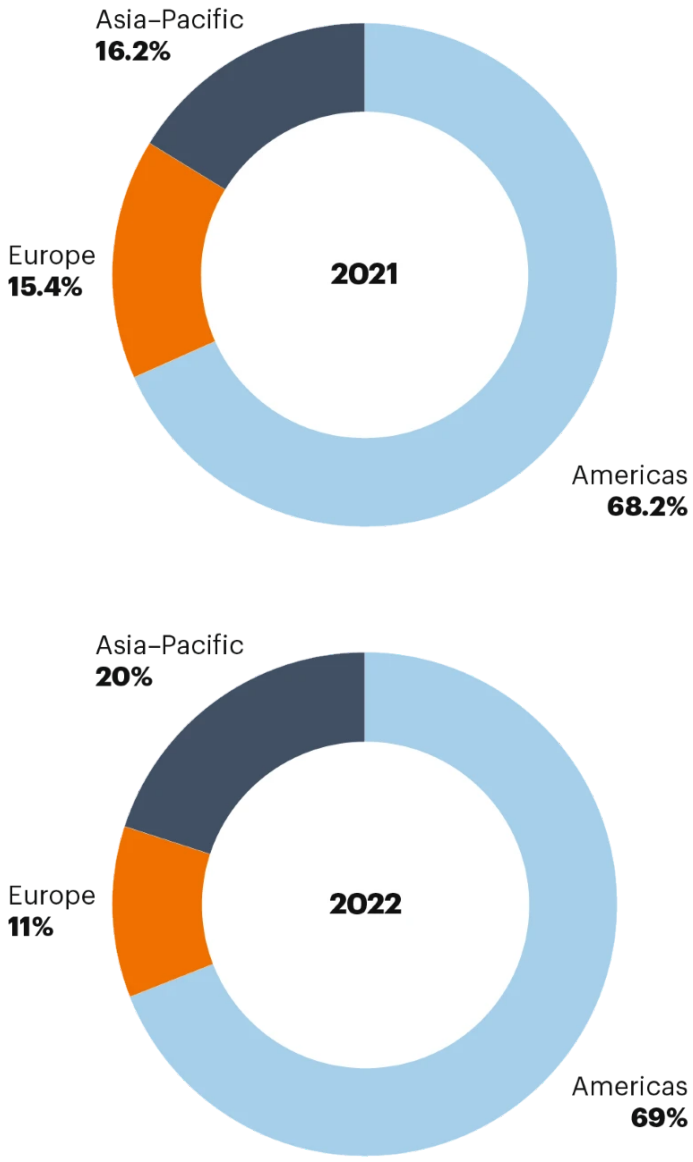

Fig. 3 | Regional private investing in biotech. Europe falls below Asia–Pacific as the Americas remain strong. Source: BioCentury BCIQ Database.

Noema Pharma, which in March raised a $112 million series B, co-led by Forbion and Jeito Capital, to advance its clinical-stage neuroscience pipeline. Sofinnova-founded Noema, built around discarded assets from Roche, has three phase 2b trials, including ones for basimglurant, an mGluR5 inhibitor for severe pain in trigeminal neuralgia and seizures in tuberous sclerosis complex, and gemlapodect, a phosphodiesterase-10a inhibitor for Tourette's syndrome and stuttering. "For me, the 2023 story is about Europe," says Siddiqi.

Early-stage financing has improved in Europe over the last decade, and later stage growth funds now exist. But not all investors are optimistic about Europe's chances of growing full-sized biotechs. A lack of functioning public markets for biopharma and insufficient growth capital continue to hold it back, according to one trans-Atlantic investor. With moving to the United States almost a sine qua non for European biotechs, money and talent drain away. Most damagingly, so does the chance of a local champion to help spawn follow-on success stories. There may also be pickings for overseas buyers: in January 2023, Nanjing, China-based ReLive Biotechnologies bought German-listed Co.Don, including rights to its European Medicines Agency-approved regenerative cell therapy, Spherox, used to treat articular cartilage defects, plus GMP (good manufacturing practice)-standard manufacturing facilities. Co.Don's technology hadn't taken off, but the company provides a foothold for

ReLive and its global ambition. Founded in 2021, ReLive concurrently raised a $35 million series A from Shanghai Healthcare Capital (Table 1).

Still, Europe's strong science base means companies will continue to be created, even if they do later leave. Dresden, Germany-based Seamless Therapeutics emerged mid-March with $12.5 million in seed money from Wellington Partners and Forbion to build reprogrammable recombinase enzymes that can edit a wide range of gene sequences. The technology stems from Frank Buchholz' lab at the University of Dresden. "The best opportunities may lie in the very early stages, at the academic–industry interface," says David Schilansky, CEO of Home Biosciences.

Home Biosciences is doing something similar to Curie.Bio, on a smaller scale, with academic founders in Europe. Seeded in 2021 with $15 million from Redmile Group and Sofinnova, Home identifies promising academic science and brings the skills and resources to take it to a proof-of-concept-stage, VC-ready venture with its own pipeline. These skills, housed centrally, include a contracting approach that tech transfer offices can readily understand, plus management, due diligence and access to experts. "Great science is there, at the right price, though European technology transfer offices can be hard to decipher," especially in France and Germany, says Schilansky. "Lots of people think they can buy European science, but can't 'talk European'," adds the trans-Atlantic investor.

Home's innovation hunt is focused on underinvested areas including kidney disease, fibrosis, bone and muscle disorders. Home has two ventures up and running: One Biosciences, a single-cell and artificial intelligence (AI) platform backed by the Paris-based Institut Curie; and a fibrosis venture, Sequantrix, from Universitätsklinikum Aachen in Germany. Two more are in the works.

Home is seeking a €30–35 million ($33–38 million) series A. Schilansky is more positive about its chances this year than he was in 2022, when many investors were struggling to support their existing flock. Yet, with Curie.Bio pulling in half a billion dollars in half the time, it's clear that the trans-Atlantic funding chasm remains.

Efficiency rules

Efficiency is a common thread spanning biotech investment strategies and R&D in 2023.

Curie.Bio can offer founders a better deal because they're not building a new set of infrastructure around each project. Asset-centric approaches that accelerate programs to the next data point with minimal capital and overheads are multiplying along the R&D spectrum as external funding sources become more discriminating — and with no end in sight.

TVM Capital's "project-focused company" approach was born out of necessity after the 2008 crash. Then, as now, many investors had veered away from risky biotech, recalls Luc Marengère, managing partner. TVM's limited partners challenged them to come up with a faster, cheaper and more predictable drug development format. So TVM teamed up with Eli Lilly, whose Chorus subsidiary was already taking a 'fail-fast' approach to in-house programs, running experiments that could quickly rule assets out (or in). TVM initially sourced programs from big pharma, including Lilly, but now the bulk of the deal flow is from biotechs looking to raise money. "We cherry-pick what we like, put it in a de novo company and develop it," with each project-focused company having preferred access to Chorus, says Marengère.

It's an attractive solution for biotechs that can't fund everything (or anything) themselves. On 1 February, TVM committed up to $24 million to Recurv Pharma, set up to take the novel taxane cancer chemotherapy RP-001 through phase 2a proof of concept in solid tumors. RP-001, originally licensed from Stony Brook University (part of the State University of New York system) by TargaGenix, is an omega-3 polyunsaturated fatty acid–taxoid conjugate, encapsulated in an oil-in-water drug delivery system that may provide a safer, more efficacious treatment alternative to regular taxane therapy. TargaGenix has since shut down. Recurv is the eighth project-focused company from TVM's $478 million Life Science Innovation Fund II.

"We bring the capital, a development partner and a motivated buyer," says Marengère, referring to Lilly's option rights to the programs. The model "is as

relevant in 2023 as it was in 2008."

Blackstone Life Sciences-backed operating company Neurvati offers tailored partnering options to biopharma companies with promising clinical-stage neuroscience assets. It accelerates selected programs through later-stage development, with committed capital from Blackstone Life Sciences. Neurvati's team designs studies to de-risk the assets, which are dropped into independent subsidiaries. The trick is matching the resources to the assets: "The structure, strategy and clinical development plan that you put around a Duchenne's muscular dystrophy (DMD) program is very different to what you'd require for a schizophrenia" asset, says president and CEO Bruce Leuchter, who also co-founded digital therapeutics company Click Therapeutics. Neurvati's first subsidiary, GRIN Therapeutics, is developing radiprodil, an NR2B-selective *N*-methyl-D-aspartate (NMDA) negative allosteric modulator, for genetically defined developmental epileptic encephalopathies. Radiprodil failed phase 2 trials of diabetic peripheral neuropathic pain in 2010, and a trial in infantile spasms was stopped in 2016.

Neurvati's emergence in late 2021, plus the recent financings by Rapport and Noema Pharma, reflect growing interest in central nervous system-related conditions. High failure rates have burned investors, but also left massive unmet need. The attention on newer treatments like Biogen's Aduhelm (aducanumab) and Eisai and Biogen's Leqembi (lecanemab) in Alzheimer's disease offer a glimpse into the demand for new neurology therapies.

Computing new drugs

Computational biology firms applying AI or other in silico tools to drug discovery and development attracted $1.6 billion in 2022, according to data from PitchBook and Silicon Valley Bank — less than in 2021 ($2.8 billion) but more than in 2020 ($1.1 billion). Financing deals for such firms also achieved some of 2022's highest post-money valuations, even though many are preclinical. High-profile advances like OpenAI's chatbot (ChatGPT) or, in the sector, DeepMind's AlphaFold technology for predicting 3D protein structure, continue to attract investment into the AI–biopharma interface.

Excitement is warranted: these computational tools aren't just accelerating and expanding regular R&D activities — for instance, by trawling through and screening massive chemical spaces. Together with molecular biology tools, they are helping scientists uncover entirely new drug target estates and more precise ways of drugging them. They allow molecular behavior to be visualized and explored in detail: Eikon Therapeutics, whose platform tracks individual proteins inside living cells, set 2022's high-water mark in January with a half-a-billion-dollar series B. AI is also being used to generate brand new proteins or molecular structures. "We create drugs, straight out of the computer, that can either hit new or challenging targets," said Alex Snyder, chief medical officer at Flagship-backed Generate Biomedicines, during a J.P. Morgan Healthcare Conference panel in January 2023. "The goal is to design them, test them, learn and repeat." Generate Biomedicines and Hong Kong-based Insilico Medicine, also using generative AI, both raised large rounds in 2021 (a $370 million series B for Generate Biomedicines, a $255 million C round for Insilico); Insilico topped up with a $60 million D round last year. New startups continue to emerge.

So far, the promised drastically increased success rates and reduced R&D timelines haven't materialized. "AI has not found" a new drug, as Atlas's Formela notes. But it has helped redirect some therapies: UK-based BenevolentAI redirected Lilly's Janus-associated kinase inhibitor Olumiant (baricitinib) during the pandemic, making it the first approved immunomodulatory medicine for COVID-19. In February 2023, Insilico Medicine received US Food and Drug Administration (FDA) orphan drug designation for a small molecule inhibitor discovered by its generative AI platform, which has completed Phase 1 trials in idiopathic pulmonary fibrosis. Chinese regulators also granted investigational new drug authorization for an oral 3-chymotrypsin-like protease (3CLpro) inhibitor for Covid-19, designed using Insilico's generative chemistry platform. The platform generated a suite of 3CLpro-like compounds that were tweaked to optimize binding. (3CLpro is key to SARS-CoV-2 replication.)

AI will not, on its own, revolutionize drug R&D. "We're going through a bit of a phase where the tool [AI] is enshrined as the differentiated element that will change everything," says OrbiMed general partner Peter Thompson, acknowledging some

hype around the space. It's a useful tool that will be applied with others: Flagship-backed Treeline Biosciences, for instance, uses computational science alongside structural biology and medicinal chemistry to uncover and drug difficult or previously unknown oncology drug targets. It raised $261 million in October 2022. Nimbus Therapeutics used computer modeling and structure-based design to develop an oral, highly selective allosteric tyrosine kinase 2 inhibitor for which Takeda, in December 2022, paid $4 billion up front. Nimbus would never have produced that drug — in phase 2b for psoriasis and other autoimmune diseases — without a large medicinal chemistry team, notes Atlas's Formela.

Hence, "we currently invest in companies that use these tools, but not ones that brand themselves exclusively as AI discovery companies," says Forbion managing partner Sander Slootweg. "The proof of the pudding is [getting a new drug into] the clinic" and beyond.

Precision financing

That expression captures most investors' mood in 2023 (and perhaps beyond): they want much firmer proof that an approach or asset is working before they put dollars behind it.

Precision financing will replace generalizations: the IPO window will be open for the winners but closed for the rest. Large private rounds will be available to those with compelling clinical data — or a highly productive platform — but out of reach of the rest.

Few expect markets to bounce back anytime soon. "It may take another two years," suggests Sofinnova's Papiernik.

While the shakeout continues, companies focused on developing products that serve patients will find money, Papiernik says. They may also be part of a more resilient sector thereafter. As TVM's Marengère puts it, "sometimes even a forest fire is good for the landscape."

Table 1 Top financings in cell and gene therapy

Company	Round	Amount raised ($ M)	Date	Country
2022				
Tessera Therapeutics	C	300	19 April	United States
Kriya Therapeutics	C	270	16 May	United States
Arsenal Biosciences	B	220	6 Sept	United States
Affini-T Therapeutics	Uncategorized	175	22 March	United States
Metagenomi	B	175	25 Jan	United States
Frontera Therapeutics	B	160	19 July	United States
Aspen Neuroscience	B	147	9 May	United States
Tessa Therapeutics	A	126	9 June	Singapore
OriCell Therapeutics	B	125	1 Aug	China
Aurion Biotechnologies	Uncategorized	120	12 April	United States
2023				
Synthekine	C	100	6 Jan	United States

Company	Round	Amount raised ($ M)	Date	Country
Metagenomi	B	100	5 Jan	United States
Perceive Biotherapeutics	B	78	6 Jan	United States
Nanjing Iaso Biotherapeutics	C	74.3	17 Jan	China
OriCell Therapeutics	B	45	28 Feb	China
Eluminex Biosciences	B	40	27 Fab	China
ReLive Biotechnologies	A	36	25 Jan	China
Immune-Onc Therapeutics	B	25	5 Jan	United States

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