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PHARMA DEAL MAKING: A BRIGHT SPOT AMID THE GLOOM

Biopharma M&A is back and IPOs are possible, but most biotechs aren't out of the woods.

By Melanie Senior

Big pharma's deal-making splurge came later than many hoped, but it's here. After a dismal 2022, biopharma mergers and acquisitions (M&A) value reached over $95 billion by mid-2023, according to BioCentury, putting this year on track to be the strongest since 2019 (Fig. 1). Pfizer's $43 billion Seagen acquisition accounts for the lion's share of M&A dollars so far, but a dozen of 2023's deals are worth $1 billion or more (Table 1). "It's an absolute bumper crop," says Gil Bar-Nahum, managing director at Jefferies' global healthcare investment banking group in London.

Most deals focus on late-stage or marketed assets, as pharma buyers attempt to fill gaps left by blockbusters set to lose patent exclusivity. There's resurgent interest in treatments for chronic, widespread conditions across immunology and cardio-metabolic diseases, although rare diseases remain popular among some buyers. Initial public offerings (IPOs) and follow-on public financings are also reappearing, as investors take confidence from pharma's renewed M&A activity.

Yet this revival is selective and fragile. It offers little comfort for biotechs without late-stage assets or those lacking strong mid-stage clinical data. Biotech stocks are recovering far more slowly from the 2021–2022 downturn than they did from previous troughs in 2016 and 2002, according to investment bank Stifel; blame the flurry of premature listings and outsized valuations during the pandemic-induced biotech bubble, continued

Table 1 | Top mergers and acquisitions of 2023

Target	Acquirer	Deal focus	Value ($ billions)	Date announced
Seagen	Pfizer	Acquires four marketed antibody–drug conjugates and dozens of clinical stage follow-ons	43	13 March
Prometheus Biosciences	Merck	Acquires phase-3-ready monoclonal antibody PRA023, targeted at TNF-L1A in Crohn's disease and ulcerative colitis	10.8	16 April
Reata Pharmaceuticals	Biogen	Acquires therapeutics that regulate cellular metabolism and inflammation in neurologic diseases, including first approved treatment for Friedreich's ataxia	7.3	28 July
Iveric Bio	Astellas Pharma	Acquires complement C5 inhibitor in late-stage development for the treatment of geographic atrophy in age-related macular degeneration, plus some early-stage AAV gene therapy assets for severe ophthalmic indications	5.9	30 April
Chinook Therapeutics	Novartis	Acquires pipeline of small molecules and antibody drugs targeted at rare, severe kidney disorders based on RNA sequencing discoveries in chronic kidney disease cohorts. Lead assets included atrasentan, a phase 3 endothelin receptor inhibitor, and zigakibart	3.2	12 June
Provention Bio	Sanofi	Acquires anti-CD3 monoclonal antibody Tzield (teplizumab), the first disease-modifying treatment for delaying stage 3 T1D	2.9	13 March
Dice Therapeutics	Eli Lilly	Acquires phase 2 small-molecule IL-17 antagonist DC-806 for treatment of psoriasis and a second phase 1 anti-inflammatory agent, DC-853	2.4	20 June
Bellus Health	GSK	Acquires camlipixant, a selective antagonist of P2X3, which is involved in reflexive cough response in respiratory conditions such as COPD	2.0	18 April
CinCor Pharma	AstraZeneca	Acquires phase 2 baxdrostat, an aldosterone synthase inhibitor that may lower blood pressure in patients with treatment-resistant hypertension	1.8	9 January
CTI Biopharma	Swedish Orphan Biovitrum	Adds Vonjo (pacritinib), a JAK1-sparing oral small-molecule kinase inhibitor, to rare blood cancer drug franchise	1.7	10 May
Amryt Pharma	Chiesi Farmaceutici	Acquires handful of marketed niche drugs	1.3	8 January
VectivBio	Ironwood Pharmaceuticals	Adds apraglutide, a GLP-2 analog, to gastrointestinal drug portfolio	1.0	22 May

AAV, adeno-associated virus, COPD, chronic obstructive pulmonary disease; GLP, glucagon-like peptide; JAK, Janus kinase; T1D, type 1 diabetes; TNF-L1A, tumor necrosis factor-like ligand 1A. *Partial year. Source: BCIQ BioCentury Online Intelligence.

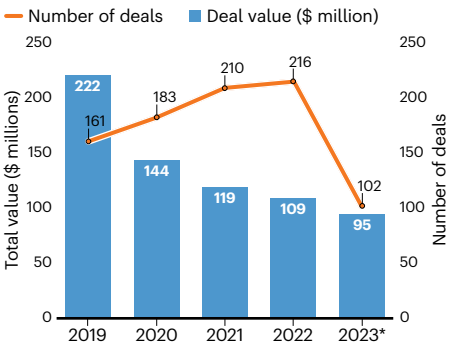

Fig. 1 | Merger and acquisition activity over time. Source: BCIQ BioCentury Online Intelligence.

macroeconomic gloom and generalist investors' current craze for artificial intelligence stocks. At almost a quarter of publicly traded US biotechs, their cash on hand is worth more than their market capitalization (the combined value of their shares), and that cash will last barely more than 18 months on average. With exits hard to come by for all but the chosen few, and muted pharma licensing activity, some venture capitalists are also holding back.

Biotech's slow rebound is set against still-rising interest rates, which curb investors' risk appetite by setting a higher bar for risk-free returns. Dealmakers also have two other sources of uncertainty to contend with: the US Inflation Reduction Act (IRA), which reduces the value of some small-molecule drugs, and a more aggressive Federal Trade Commission (FTC) scrutinizing biopharma acquisitions (Box 1). The FTC's most prominent target so far: Amgen's proposed $84 billion acquisition of Horizon, announced late 2022. (As *Nature Biotechnology* went to press, Amgen agreed to a settlement with the FTC, and the deal is expected to close in the fourth quarter of 2023.)

Late-stage assets top buyers' lists

All but 3 of the top 12 deals announced so far in 2023 involve phase 3, registration-stage or marketed assets: cash-rich pharma acquirors want to boost late-stage pipelines as blockbusters including Merck's anti-PD-1 receptor Keytruda (pembrolizumab), AstraZeneca's diabetes drug Farxiga (dapagliflozin) and Pfizer's oncology drug Ibrance (palbociclib) lose exclusivity this decade. They'll compete – and pay a premium – for the best drugs. Seagen's four marketed antibody–drug conjugates and dozens of clinical stage follow-ons had been on Merck's radar before Pfizer came in with its offer, 40% above Seagen's share price. Snubbed, Merck instead paid a 75% premium for Prometheus, with its phase-3-ready antibody for ulcerative colitis and Crohn's disease, plus a second clinical-stage antibody. Biogen outbid another suitor (said to be Sanofi) for neurology-focused Reata, and Horizon also attracted others besides Amgen.

Plunging post-pandemic biotech share prices, though, turned some apparently hefty deal values into bargains. Ipsen's $925 million deal for Albireo at the start of 2023 was almost double the rare liver disease company's recent

BOX 1

IRA and FTC

The Inflation Reduction Act will subject some top-selling Medicare drugs to negotiated Medicare prices, but small molecules (and other compounds filed as new drug applications) will receive just 9 years' exclusivity, versus 13 for biologics (biologics license application filings). This asymmetry is influencing which assets pharma buys and how those assets are valued. "Small molecules with large Medicare populations are now more difficult to price. We have seen deals fall apart because of this uncertainty," says Joseph Modisett at Morgan Stanley.

Three of the most valuable M&A targets so far this year — Seagen, Prometheus and Provention Bio, acquired by Sanofi — have biologics. Other, small-molecule-focused targets within the top tier, such as Reata (acquired by Biogen for $7.3 billion), Chinook Therapeutics (acquired by Novartis for $3.2 billion) and Amyrt, have rare-disease drugs that are less likely to trigger IRA price curbs, since these will apply only to the most costly Medicare products overall, not necessarily those with the highest individual prices.

The FTC, meanwhile, is spreading its net wider to root out potentially anticompetitive deal-making. Most prominently, it claims that Amgen's proposed acquisition of Horizon might encourage the big biotech to offer insurers product 'bundles' that include Horizon's niche products — Tepezza (teprotumumab) for thyroid eye disease and Krystexxa (pegloticase) for chronic gout — with its own top-sellers, thwarting Horizon competitors. Amgen and Horizon are countersuing the FTC, calling its complaint speculative. On 1 September, the parties agreed to a settlement that forbids Amgen from bundling any of its products with Tepezza or Krystexxa, and prevents the big biotech from using rebates or contract terms that exclude or disadvantage competitors to those Horizon drugs. Amgen must also seek FTC approval if it wants to buy other R&D-stage programs or products for thyroid eye disease or chronic gout.

These added complexities may give buyers pause, even if they don't stop M&A in its tracks: big pharmas face up to $100 billion worth of patent expiries this decade and have a $700 billion M&A war chest. Their "desire to own interesting science remains as strong as ever," says Joseph Modisett, global head of healthcare investment banking at Morgan Stanley. "The fundamentals driving biopharma M&A are robust."

share price, but only a fraction above 2022's price peak. It was a similar story for Chiesi's $1.25 billion acquisition of Amyrt, with its handful of marketed niche drugs. Both deals also included future payments contingent on achieving certain milestones, reflecting a buyers' market. Since then, contingent payments have become less common amid battles for the hottest drugs, yet the focus on de-risked assets continues.

Acquisitions of companies with just one or two assets — so-called 'bolt-on' deals — may remain popular as they are less likely to attract FTC attention. And as phase 3 and later programs are picked off, deals will start to move upstream — though they will still be constrained by buyers' more rigorous data requirements. In June 2023, Eli Lilly paid $2.4 billion for Dice Therapeutics, whose lead oral interleukin (IL)-17 inhibitor is in phase 2; the target is well known, though, and Dice has a potentially more potent phase 1 follow-on compound. Ironwood paid $1 billion for VectivBio before phase 3 data emerge later this year for apraglutide, its long-acting glucagon-like peptide (GLP)-2 analog in development for several rare gastrointestinal diseases. Waiting for the readout would have reduced Ironwood's risk but would also have pushed up the price (and perhaps the competition), notes Dirk Kersten, general partner and manager of Forbion's Growth Opportunities Fund, which invested in Nasdaq-listed VectivBio in mid-2022.

Big diseases are back

Among bigger buyers, drugs treating widespread, chronic immunology and cardiometabolic diseases are more popular. It's hard to fill the multi-billion-dollar-sized shoes of generic-izing blockbusters such as AbbVie's autoimmunity disease drug Humira (adalimumab) or Johnson & Johnson's Stelara (ustekinumab) with niche products.

Three of 2023's top ten acquisitions are in immunology. Prometheus's lead humanized monoclonal antibody is in phase 2 trials for ulcerative colitis and Crohn's disease; it targets tumor necrosis factor-like ligand 1A (TL1A), associated with intestinal inflammation and fibrosis. Provention Bio's anti-CD3 antibody teplizumab was approved in January as Tzield to delay the progression of type 1 diabetes among patients with stage 2 disease; it's also in development for more advanced (stage 3) disease. Dice Therapeutics brings Lilly a platform of oral anti-inflammatory treatment candidates along with the phase 2 IL-17 inhibitor, which is designed to be as effective as antibodies, but more convenient. (Injectable psoriasis drugs generate about $6 billion annually, and Dice's compounds may work across other autoimmune diseases.)

The revolution in obesity treatment, spearheaded by Novo Nordisk's GLP-1 agonist Wegovy (semaglutide, also sold as Ozempic for diabetes) has whet buyers' appetites across cardiometabolic diseases. Lilly's GLP-1 and GIP (glucose-dependent insulinotropic polypeptide) agonist tirzepatide, approved for diabetes as Mounjaro, awaits an obesity approval later this year, and the big pharma has two other phase 2 obesity candidates: retatrutide, a triple GLP, GIP and glucagon agonist, and the oral once-daily GLP-1 agonist orforglipron.

In July 2023, Lilly boosted its obesity pipeline further by acquiring Versanis Bio for up to $1.9 billion (the size of the up-front payment was not disclosed). Versanis's activin and myostatin signaling inhibitor bimagrumab, which slows muscle breakdown, is in phase 2b trials for overweight and obesity. Since it works differently from GLP-1 agonists and other incretins, bimagrumab is also being tested in combination with semaglutide to determine whether the duo could further reduce fat and preserve lean muscle mass. (Bimagrumab was in development at Novartis for muscle-wasting disease.)

AstraZeneca's biggest deal this year so far is in cardio-renal disease: its $1.8 billion acquisition of CinCor. Interest in cardiovascular conditions is likely to continue, given the link between obesity and increased risk of heart disease. Wegovy was recently reported to lower cardiovascular disease risk, and Mounjaro is also in a large cardiovascular outcomes trial. Ozempic already has a cardioprotective claim.

Niche assets still popular

Resurgent interest in big diseases doesn't mean rare conditions are out: half of 2023's top acquisitions so far have involved niche

Table 2 | Top ten IPOs (to end of July 2023)

Company	Amount raised ($ millions)	Date completed	Latest stage and focus	Location
Acelyrin	621	4 May	Phase 3; in-licensing immunology assets; lead program IL-17A for multiple indications, licensed from Affibody	United States
Chongqing Genrix Biopharmaceuticals	488	8 June	Registration; 14 clinical-stage drug candidates in oncology and immunology	China
Apogee Therapeutics	345	13 July	Phase 1; engineered antibodies for autoimmune and inflammatory diseases; lead is extended-half-life IL-13 inhibitor for atopic dermatitis	United States
Mineralys Therapeutics	221	9 February	Phase 2; aldosterone inhibitors for controlling hypertension	United States
Structure Therapeutics	185	2 February	Phase 2; GPCR structure-based drug design. Lead oral GLP-1 receptor agonist for diabetes and obesity	United States
Sichuan Kelun-Biotech Biopharmaceutical	174	10 July	Registration; monoclonal, bispecific antibodies and antibody–drug conjugates	China
Laekna	101	28 June	Phase 2; AKT inhibitor and androgen synthesis inhibitor for various cancers	China
Sagimet Biosciences	85	13 July	Phase 2; fatty acid synthase inhibition for metabolic diseases and cancer	United States
Turnstone Biologics	80	21 July	Phase 1; tumor-reactive TILs	United States
Cutia Therapeutics	59	9 June	Market; customized transdermal drug delivery, alopecia and acne therapeutics	China

GPCR, G-protein-coupled receptor; TIL, tumor-infiltrating lymphocytes. Source: BCIQ BioCentury Online Intelligence.

assets, including Biogen's recent purchase of Reata. That comes with the Friedreich's ataxia drug Skyclarys (omaveloxolone), a synthetic oleanane triterpenoid that works by activating transcription factor Nrf2 and inhibiting pro-inflammatory NF-κB, plus cemdomespib, a phase 1 Hsp90 modulator for diabetic peripheral neuropathic pain, and two preclinical Nrf2 activators.

Buying Chinook brings Novartis two late-stage assets for rare kidney condition immunoglobulin A nephropathy, while rare eye diseases are the focus of Astellas's Iveric deal. The Japanese pharma picks up complement C5 inhibitor Izervay (avacincaptad pegol), approved by US regulators for the treatment of geographic atrophy secondary to age-related macular degeneration and also in the clinic for Stargardt disease, an inherited form of macular degeneration. The crown jewel of Swedish Orphan Biovitrum's $1.7 billion CTI BioPharma buyout is Janus kinase inhibitor Vonjo (pacritinib), which received FDA accelerated approval for the rare bone marrow cancer myelofibrosis. "Rare diseases may be less appealing to some big pharma than five years ago, but they're still attractive," in particular for mid-sized pharma and big biotechs, says Forbion's Dirk Kersten.

Resurgent IPOs reflect big disease theme

Many private biotechs have struggled to raise funds amid an IPO drought in the first half of 2023, which saw just four US biopharma firms go public. Activity has picked up a little since June but remains well below 2018–2021 levels (Fig. 2). The handful of IPOs and follow-on public offerings so far this year mirror the resurgence of drugs for widespread conditions across immunology, cardiology and neurology.

In the biggest US IPO to date of 2023, immunology-focused Acelyrin raised $621 million in May (Table 2) to advance its phase 3 IL-17A inhibitor izokibep, a small protein vying to best monoclonal antibodies across conditions including psoriatic arthritis, uveitis and hidradenitis suppurativa. Structure Therapeutics, which raised $185 million in February, has a pipeline of small-molecule G-protein-coupled receptor (GPCR)-targeting compounds spanning metabolic and respiratory diseases. The company designs its compounds based on visualizations of receptor–ligand binding and simulated signal transduction processes. The most advanced of these is an oral GLP-1 receptor agonist in phase 2 for diabetes and obesity.

Apogee's $345 million IPO in mid-July, which raised more than expected, may signal a more generous IPO environment: Apogee's most advanced program, an optimized IL-13 antibody for atopic dermatitis and asthma, had barely reached the clinic. It's in a hot area, though, and many investors in biotech IPOs so far in 2023 have made money, which builds confidence, says Tim Opler, managing director at Stifel's global healthcare group.

There are also positive signs from follow-on public financing. Almost $12 billion has been raised so far this year, according to BioCentury; on an annualized basis, this would mean a return to pre-pandemic level (Table 3). Most stocks have risen after funding, helping encourage further activity.

Yet public investors, like pharma buyers, are selective. Companies typically need strong mid-stage (or later) clinical data to access follow-on funds. Immunology-focused Argenx's $1.27-billion offering followed positive topline data from a subcutaneous formulation of lead drug Vyvgart (efgartigimod alfa) in chronic inflammatory demyelinating polyneuropathy; the neonatal Fc receptor-targeting antibody fragment is already approved for myasthenia gravis. Zentalis in June pulled in $250 million in a week after announcing data supporting optimal dosing for its phase 2 small-molecule WEE1 inhibitor azenosertib in platinum-resistant ovarian cancer. MoonLake Immunotherapeutics bid for $400 million just one day after announcing positive phase 2 topline data for nanobody sonelokimab in hidradenitis suppurativa, an inflammatory skin condition. Karuna Therapeutics raised $460 million in March 2023 on the back of positive top-line phase 3 results for schizophrenia hopeful xanomeline trospium.

For public companies with phase 1 or preclinical assets, accessing follow-on financing will remain difficult. And not all IPOs take off:

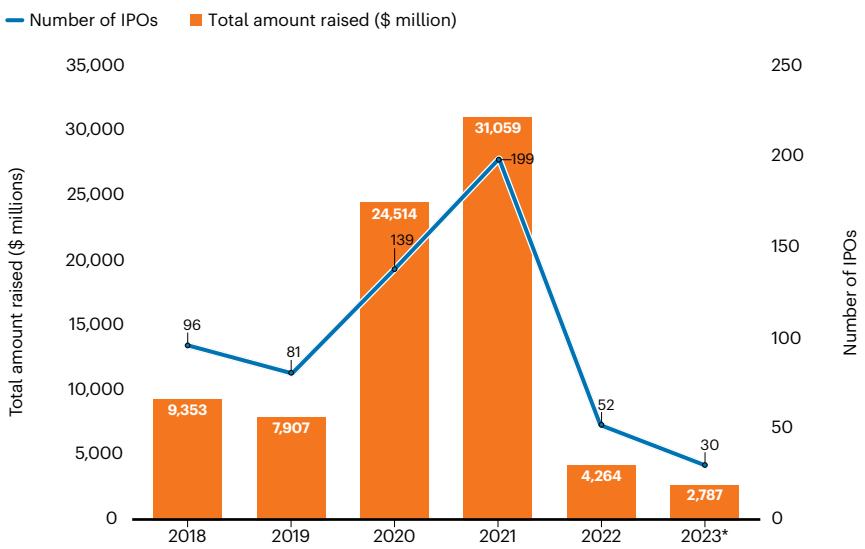

Fig. 2 | IPO activity over time. Weak signs of recovery in the public markets. *As of August 15, 2023. Source: BCIQ BioCentury Online Intelligence.

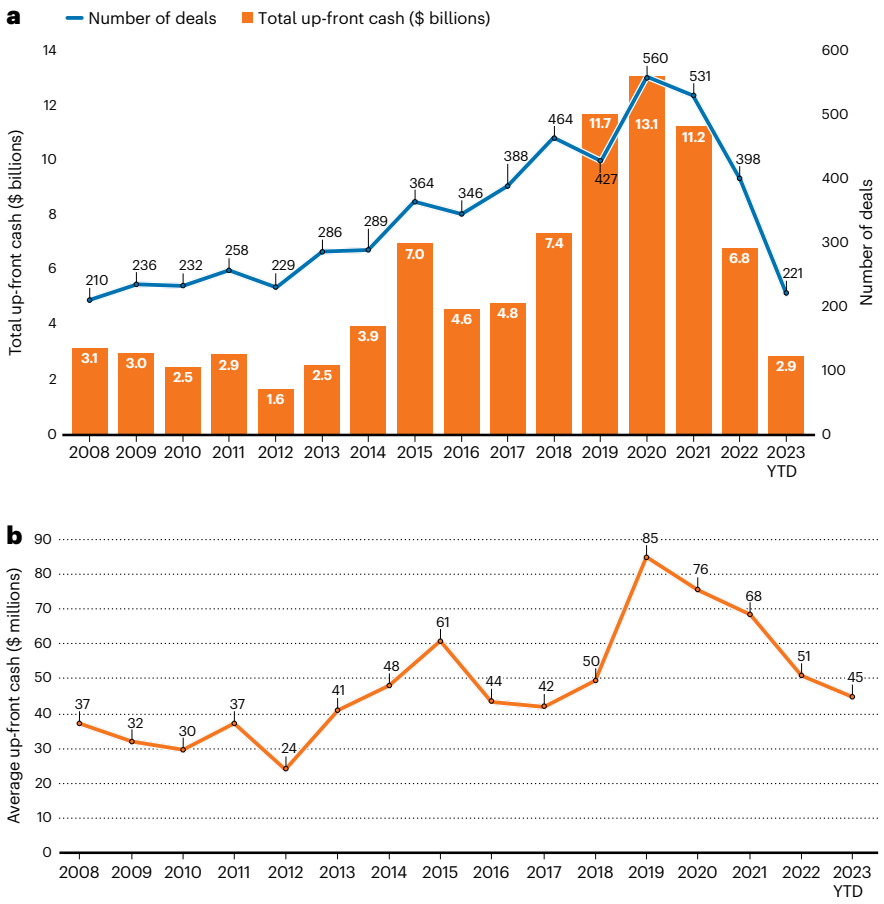

Fig. 3 | Licensing activity over time. a, Deal numbers and up-front cash fall in 2023. **b**, Up-front cash falling in 2023. YTD, year to date. Source: DealForma.

shares have fallen at Turnstone Biologics, which raised $80 million in July to advance its tumor-infiltrating lymphocyte therapies through phase 1 across various cancers, and at cancer drug-delivery-focused Intensity Therapeutics, which raised $22 million in June.

Partnering cools as expectations diverge

In 2022, risk-averse buyers shied away from M&A in favor of partnering. At the start of this year the pendulum swung back. Amid resurgent M&A, licensing deal numbers and values fell, signaling a full year 2023 that may see fewer deals and lower up-front payments than even pre-pandemic 2018 and 2019, according to DealForma (Fig. 3).

In July, though, came one of 2023's biggest partnering deals so far. Roche paid Alnylam $310 million up front for a share of its phase 2 persistent hypertension candidate zilebesiran, which targets liver-expressed angiotensinogen (Table 4). That props up the licensing numbers – and shows that big pharma is still willing to sign opportunistic deals. Roche doesn't have a cardiovascular drug franchise (though its diagnostics division sells cardiac tests), yet it will fund most of a large outcomes study of RNA-targeted zilebesiran, in exchange for a share of US commercial rights and all rights outside the United States.

Divergent expectations on up-front payments and downstream territorial carve-outs may be part of the problem for other would-be licensing partners. Amid still-shaky public markets and reticent venture capitalists, big pharmas have become a much more important source of funds for biotech. That means they often have the upper hand, whether as buyer or licensee. So biotechs seeking the rich up-front rewards available in 2017–2021 may be disappointed, especially as pharma's data demands are also different from those of financial investors (Fig. 3b). "Markets reward biotechs that progress rapidly [toward approval] with small trials," said Novartis's chief strategy and growth officer Ronny Gal at BIO in June. But pharmas prefer to see "larger phase 1 and 2 trials and more robust preclinical packages." Not all biotechs will have such data, leading to delayed or cancelled transactions.

Retaining commercialization rights may also be tricky for would-be biotech licensees (though Alnylam managed). Some companies seeking cash are selling off rights that they would otherwise have kept: in 2023's biggest deal so far, Hong Kong-based Hutchmed, struggling after an FDA rebuff and with its

Table 3 | Top ten follow-on financings

Company	Amount raised ($ millions)	Status at financing	Date completed	Country
Argenx	1,270	Marketed	18 July	Belgium
Vaxcyte	575	Phase 1 / 2	19 April	United States
Karuna Therapeutics	460	Phase 3	21 March	United States
MoonLake Immunotherapeutics	400	Phase 2	28 June	Switzerland
Apellis Pharmaceuticals	403	Marketed	22 February	United States
Guardant Health	403	Market (diagnostic)	22 May	United States
ImmunoGen	374	Marketed	4 May	United States
Revolution Medicines	345	Phase 2	2 March	United States
89bio	316	Phase 2	24 March	United States
Viking Therapeutics	288	Phase 2	30 March	United States

Source: BCIQ BioCentury Online Intelligence.

Table 4 | Top ten licensing deals

Licensee	Licensor	Headline	Stage at signing	Up-front cash ($ millions)	Date
Takeda	Hutchmed	Takeda licenses development and marketing rights to fruquintinib outside China	Marketed	400	23 January
Roche	Alnylam	Roche will co-develop and co-commercialize (in the US) Alnylam's RNAi therapeutic zilebesiran for hypertension in patients with high cardiovascular risk; Roche has exclusive ex-US commercialization rights	Phase 2	310	24 July
Johnson & Johnson (Janssen)	Cellular Biomedicine Group	Janssen licenses development and commercialization rights, outside greater China, to Cellular Biomedicine's anti-CD19/CD20 CAR-Ts for non-Hodgkin lymphoma	Phase 1	245	2 May
BioNTech	OncoC4	BioNTech to co-develop and commercialize anti-CTLA-4 antibody in solid tumor indications	Phase 3	200	20 March
BioNTech	Duality Biologics	BioNTech licenses development and commercialization rights (ex-greater China) to two cancer-focused ADCs from Duality. Deal expands in August to include a third ADC.	Phase 1 / 2	170	3 April
Neurocrine Biosciences	Voyager Therapeutics	Partners collaborate to develop Voyager's preclinical GBA1 program for Parkinson's and other next-generation gene therapies for neurological diseases	Preclinical	136	9 January
Vertex Pharmaceuticals	CRISPR Therapeutics	Vertex and CRISPR Therapeutics partner to accelerate development of Vertex's hypoimmune cell therapies for type 1 diabetes	Preclinical	100	27 March
Novartis	Avrobio	Avrobio sells cystinosis gene therapy program	Phase 1/2	88	22 May
Roche (Genentech)	Belharra Therapeutics	Partners will use Belharra's chemoproteomics platform to discover and develop small molecules for various indications	Discovery	80	4 January
Catalyst Pharmaceuticals	Santhera Pharmaceuticals	Catalyst licenses rights to DMD drug candidate vamorolone in the US, Canada and Mexico	Registration	75	19 July

ADC, antibody–drug conjugate; CAR-T, chimeric antigen receptor-T cell; CTL-A, cytotoxic T-lymphocyte associated; DMD, Duchenne muscular dystrophy, GBA1, glucocerebrosidase; RNAi, RNA interference. Source: BCIQ BioCentury Online Intelligence.

share price languishing, in January accepted $400 million up front from Takeda in exchange for global development and commercialization rights outside China to its colorectal cancer treatment fruquintinib. Fruquintinib, an oral vascular endothelial growth factor (VEGF) inhibitor, was approved in China in 2018 and was recently submitted to US and European regulators (Box 2).

Oncology dominates 2023's licensing deals, but its share has fallen relative to 2022 amid a broader cooling (Fig. 4). Significant treatment advances across a range of cancer-types — akin to those brought about a decade ago by checkpoint inhibitors such as Keytruda — have been lacking, despite promising advances in some subsegments.

Conversely, long sought-after successes in Alzheimer's disease are driving wider interest and investment in neurology, whose share of partnerships has grown in

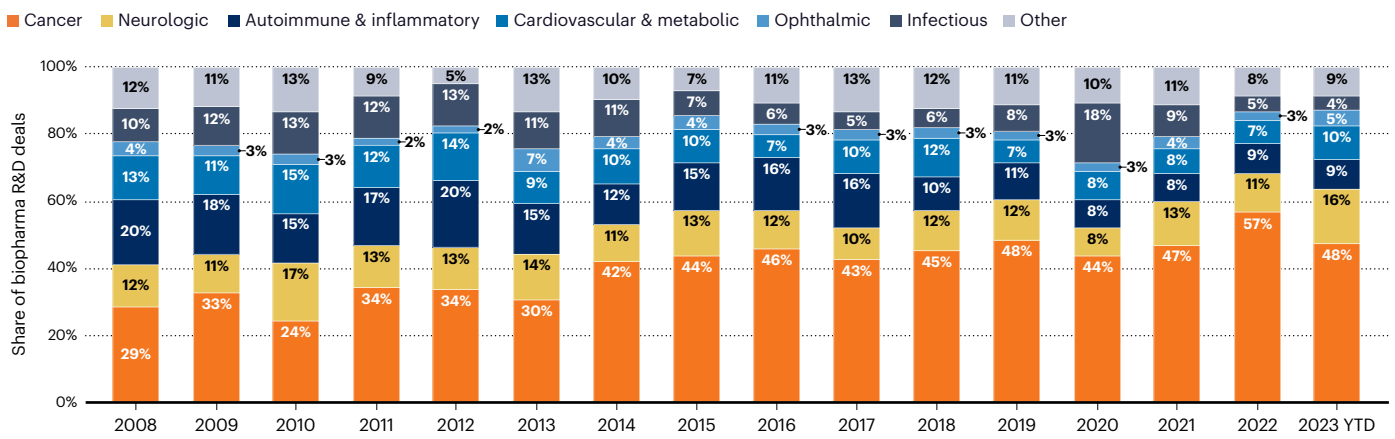

Fig. 4 | Licensing activity by therapeutic area. Oncology's share of deals in 2023 declines in favor of cardiology, neurology and ophthalmology. YTD, year to date. Source: DealForma.

BOX 2

The China conundrum

Geopolitical tensions with the West aren't stopping the growth of China's biopharma industry. Six of the top 15 largest biopharma IPOs in 2023 have been in China. Antibody-focused Chongqing Genrix Biopharmaceutical's $488 million Shanghai IPO is second in size only to Acelyrin. Nor are these tensions curbing Western interest in increasingly innovative Chinese assets and technologies. The pace of such deals, already up substantially over the past three years, could set a high this year, according to BioCentury. Three of the top ten licensing deals in the first half of 2023 — including the biggest — involved a China-based licensor (Table 4). In the second-largest Chinese–Western licensing deal, after Hutchmed's fruquintinib alliance with Takeda, Janssen Biotech paid $245 million up front for global development and sales rights to next-generation chimeric antigen receptor-T (CAR-T) cell assets at Cellular Biomedicine Group. The CD20-directed autologous CAR-T programs, including one in phase 1b, are being developed for diffuse large B-cell lymphoma. Janssen's territorial rights exclude greater China for now, reflecting a broader drop-off in deals for Chinese territory rights, according to Stifel, due to the worsening geopolitical climate. But the partners will negotiate an option for Janssen to sell in China later.

The rise of China-based innovators and China's huge and fast-evolving healthcare market present a conundrum for Western pharma. Few can afford to ignore China, particularly as pricing and drug access pressures rise in the United States. Moderna, facing declining COVID-19 vaccine sales, this year set up a biotech unit in mainland China and in July signed an agreement with the city of Shanghai, China's financial hub, to research, develop and manufacture mRNA-based medicines for China. AstraZeneca, which sells more than any other foreign pharma in China, saw declining sales there in 2022 due to aggressive government-imposed price cuts. But it brushed off rumors that it is selling its Chinese operations and recently forecast a return to growth in China for 2023.

2023; so have those of cardiometabolic and ophthalmology-focused deals, according to DealForma (Fig. 4).

Novo Nordisk in April 2023 paid $75 million up front to Aspect Biosystems to address the root cause of diabetes and obesity through implantable, allogeneic cell-based therapies. Aspect's preclinical 'bioprinted' tissues can be designed to perform various functions — including regenerating damaged insulin-producing pancreatic beta cells. The deal includes up to $650 million in per-product milestones.

Optimism returning?

After a tough couple of years for public biotechs, there are signs of optimism. Venture funding may be muted relative to 2020 and 2021 — Stifel and Capital IQ forecast about $38 billion for the full year 2023 — but it is still healthy compared to pre-pandemic levels. Private investors continue to raise new funds and are on track for the third largest year ever in life sciences venture fundraising, according to Stifel. The $14 billion raised in new venture capital so far this year — including Patient Square Capital's $3.9 billion haul in January — is the same as the total raised during the whole of 2019.

Reverse mergers — in which private companies merge with a listed firm to access public markets without an IPO — are on the rise, according to BioCentury, which reports at least ten so far in 2023. This may signal warmer public markets (or at least the hope thereof). Some reverse merger candidates, such as RNA editing company Korro Bio and gene therapy player Neurogene, raised new funds at the same time.

An end to central banks' raises in interest rates could also encourage public biotech investment.

Granted, the M&A rebound will help only a minority, and public investors are likely to remain highly selective. But the sector has already shown its resourcefulness in the face of funding challenges. Smaller biotechs have consolidated to pool cash and assets. In January, listed precision oncology firm Leap Therapeutics acquired private Flame Biosciences

BOX 3

RNA and gene editing. Nucleic acid-based therapies and technologies, including RNA-based medicines and gene editing tools, are growing fast. But many tools remain relatively early stage. This may help explain 2023's somewhat muted deal numbers so far, with just 20 licensing deals focused on nucleic acid-based assets or technology (including the second-biggest, Roche's $310 million up-front deal with Alnylam) and one acquisition. Novartis in July paid $500 million up front and committed the same in milestones for small interfering RNA (siRNA)-focused, preclinical biotech DTx Pharma.

These numbers are similar to those of 2022, which saw 28 nucleic acid transactions. Yet both years lag the 40+ deals seen during each of 2020 and 2021, according to BioCentury data. Private financing activity remains robust, though. RNA companies ReNAgade Therapeutics and Orbital Therapeutics raised two of this year's biggest series A rounds, worth $300 million and $270 million, respectively. In August, ADARx Pharmaceuticals pulled in a $200 million series C, and in the same month Amber Bio attracted seed funding of $26 million to develop its multi-kilobase gene editing platform.

for its antibody pipeline plus $50 million in cash. Cancer-vaccine-focused Elicio Therapeutics, after failing to go public in 2022, instead merged with listed Angion Biomedica to access the Nasdaq. The pace of royalty monetization deals also remains strong. These provide non-dilutive capital to biotech in exchange for a share of future (or current) product sales royalties. PureTech Health in March sold some of its royalty rights to Karuna Therapeutics' schizophrenia drug xanomeline trospium, due to be filed with the FDA this year, in exchange for $100 million up front in cash and up to $400 million in potential milestones.

Meanwhile, rapid progress across gene editing technologies and RNA-based medicines may soon unleash a large, valuable new treatment category, notes Tim Opler at Stifel, who draws a parallel with antibodies twenty years ago (Box 3). Small molecule and antibody drugs also continue to be optimized, while artificial intelligence promises to shake up everything from R&D timelines to product delivery. All these advances, alongside growing understanding in immunology, neurology, cardiometabolic diseases and more, will continue to drive biopharma deals and funding.

The Inflation Reduction Act (IRA) and FTC loom in larger dealmakers' minds, shrinking the pool of attractive products and intensifying competition. "It's a harder market out there," said Novartis's Gal at BIO in May, weeks before the big pharma declared it couldn't find any more multi-billion-dollar buyout targets and would instead buy back its own shares.

But these regulatory headwinds won't curb all transactions. The IRA has yet to play out; lawsuits launched by pharma firms and providers may delay its implementation. The FTC may lose its case against Amgen and Horizon. A more uncertain, fast-changing environment may make some potential dealmakers more open-minded, willing to follow the science rather than stick to specific therapy areas, suggests Morgan Stanley's Modisett. "Buyers that are too concentrated in one or two areas may be caught off guard" by potential regulatory headwinds, he says. This flexibility could expand some biotechs' pool of potential buyers or partners.

"The pace of M&A will continue to accelerate," predicts Jefferies' Bar-Nahum. Wishful thinking, perhaps, but he is not alone. "I don't think [the IRA] will derail sentiment," agrees Forbion's Kercher. As *Nature Biotechnology* went to press in mid-August, Forbion portfolio company Inversago Pharma, based in Montreal, was acquired by Novo Nordisk for up to $1 billion. The main prize: an oral cannabinoid receptor 1 (CB1) blocker in phase 2 for diabetic kidney disease that Novo thinks may also help fight obesity.

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