Biopharma Market Update

July 14, 2025

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View of Newport Harbor from Stifel Biotech Executive Summit, August 2024

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Antique Medical Books, From the Author's Collection, June 2025

Links to Stifel Biopharma Special Topic Publications

Obesity Drug Update

[July 9, 2025]

Oncology Update

[Jun 5, 2025]

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[Mar 26, 2025]

2025 Biotech Outlook

[Jan 8, 2025]

2024 Biotech Mid-Year Outlook

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Why Invest in Biotech?

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Biotech in a Complex But Improving Policy Environment

Recent Tariff News

Last Friday saw President Trump re-escalate a trade war that had appeared dormant, threatening 30% to 50% tariffs on trading partners.

Given recent progress on the economy and passage of the Big Beautiful Bill, the question, we suppose, is why is he doing this? The more pertinent question might be: why wouldn't he?

Recent economic, market, and policy tailwinds have strengthened his position. Fears of negative consequences from his unpredictable trade agenda have not come to pass, and dire warnings from economic forecasters have, for now, failed to materialize. This favorable environment has emboldened the president to act on his longstanding instinct to use aggressive trade measures as a policy tool to improve the U.S. economic standing.

Our own view is that we will end up with tariffs at the end of the year in the teens, well up from low single digits at the start of the year. There is, of course, some pay off to be had. Last month saw the U.S. report the first budget surplus in a long time, fueled by income from duties on imported goods.

Just a few months ago, the economic outlook was far more uncertain. Markets were plunging, recession fears were widespread, retailers were warning of empty shelves, and Republican tax legislation looked imperiled.

Today, however, the unemployment rate sits at a low 4.1%, inflation has come in below expectations, and the stock market is hovering near record highs. Supply chains, though tested, have largely held, thanks to inventory buildup and the willingness of firms to absorb higher costs.

Outlook for Biotech in a Complex Environment

The successful passage of the One Big, Beautiful Bill Act on July 4 further bolstered the administration's confidence. We weren't so sure that the Bill was going to get through the Congress.

Meanwhile, the Federal Reserve appears increasingly likely to cut rates in September, offering additional support.

Still, the broader economic reality remains complex. Major structural changes to trade policy take time to ripple through supply chains and corporate pricing.

Trump has shown a willingness to soften or delay tariffs when economic pain becomes evident, as seen in adjustments made in April and May. It's not at all obvious what these various policies issues imply for a typical biotech CEO.

Outlook for Biotech

We have seen biotech turn around quite a bit since the surprising announcements of "Liberation Day" on April 8th.

Biotech stocks globally are up more than 60% since hitting a low point on April 8th and are now up nearly 19% for the year. U.S. biotech stocks are up 10% since April 8th and the XBI seems to be headed north. There are quite a few positives, including positive newsflow, and some nagging negatives. Let's start on the negatives before we jump to the positives.

Headwinds Impacting the Biotech Sector

#1. MFN could negatively impact pricing in the U.S. This one looks like a paper tiger at the moment. Rumors are flying that the Trump Administration is going to institute incentives through the CMMI system, allowing companies that keep Medicare drug prices in line with those in other countries to get rebates back from the federal government. Official word of this has not yet arrived but we think some of the run up in the XBI last week was related to the spreading news that this could be on the way.

#2. Talk of pharma tariffs is still with us. Last week saw Trump threaten the pharma industry with 200% tariffs. However, the XLV and XBI went up despite this news. Investors clearly view this tariff threat as "cheap talk" meant to help with negotiations between the Administration and the pharma sector.

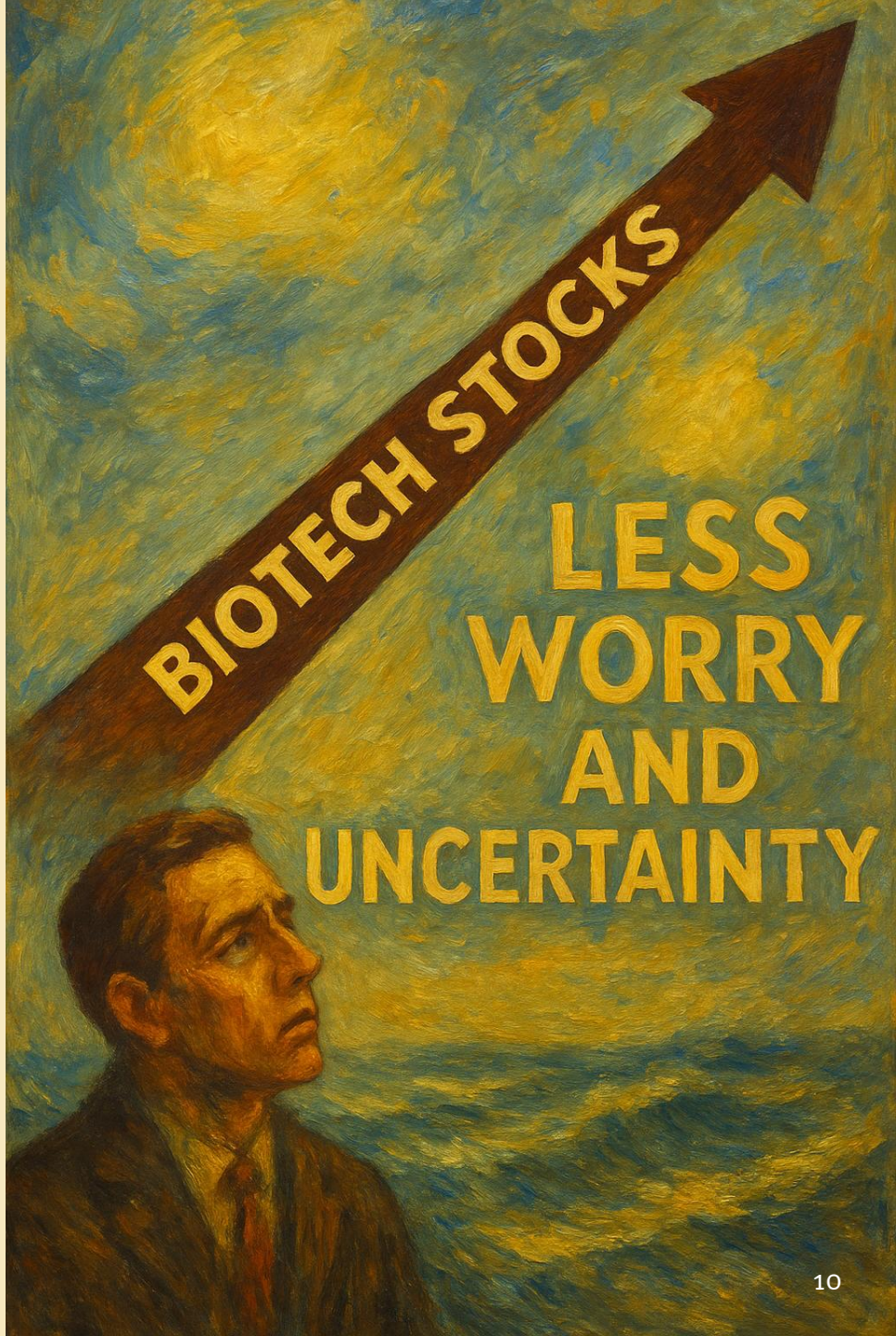
#3. The Big Beautiful Bill isn't great for budget deficits. CBO estimated that the recently passed reconciliation bill will increase the U.S. debt load by three trillion dollars over the next decade. This is likely to add ten to twenty basis points to the ten-year Treasury yield. However, CBO's long-term forecast for the ten-year is actually well below where yields are at present. Our own guess is that other countries are dumping U.S. bonds right now (China perhaps?) and this is part of the reason that Treasury yields have stayed well above four percent in recent months. To state the obvious, lower long-term rates are good for biotech in two respects. First, lower rates are associated with higher values of long duration projects. Second, lower rates are associated with higher risk taking because safe assets return less.

Market Uncertainty Has Greatly Diminished

#4. FDA concerns are turning real (at least somewhat). Despite positive rhetoric from the FDA, there is clear evidence that the agency is struggling to meet its timelines. We have heard a number of sponsors (beyond the obvious cases like Kalvista) indicate that they are facing delays in approvals at FDA. Parenthetically, we find the FDA's recent effort to squelch Kalvista's disclosure of their PDUFA date miss as puzzling and political. It seems odd that in the same month the FDA then dumps on their website 200 CRL's that were previously undisclosed claiming that free speech will be good for industry. By the way, we applaud the idea that the FDA might reveal CRL's but we think this would be much better part of a policy on a forward basis – so that sponsors know it's coming and can adjust accordingly.

Now for the positives:

#1. The Uncertainty and Fear Gripping the Biotech Market Has Greatly Diminished. The main enemy of the market has been uncertainty – the fear that the Trump Administration would in some way hobble the biotech industry. On April 8th, the VIX, the market's "fear gauge" hit 42. Since then, the VIX has dropped to 16% and seems to be dropping more every day. Sentiment in the biotech market is certainly not rosy but is not nearly as despondent as it was three months ago when some investors were wondering aloud as to why anyone would ever put money to work in biotech.



M&A is Back

#2. M&A is back and it's real. We have seen three $10bn type M&A deals so far this year and it's highly likely that more are on the way. By our calculations we are headed for a well above average year for M&A. The Biden Administration's antitrust policies appear to be long forgotten.

We haven't even heard the name "Lina Khan" mentioned in months.

M&A is good for the sector for two reasons: (1) it generates returns to investors – who can attract more outside capital in pursuit of those returns and (2) it returns capital to the sector – where it can be invested in other emerging stories.

#3. The Big Beautiful Bill has become law. While it did not include language changing the pill penalty, language was included that removed disincentives to approve a drug for two orphan indications.

The bill is fiscally expansionary and, while not ideal for deficits, is likely to be beneficial to the market overall and will, very likely, be associated with long-term expansion of risk appetite in the economy – which should be very good for biotech.

#4. Both the FDA and HHS have indicated their support for biosciences. Anti-science perspectives coming out of the Trump Administration have not helped biotech stocks. Pro-industry rhetoric has been heard in recent months that has helped to allay these fears. The FDA has been highly communicative and is listening to the biotech industry. This is a big plus.

Biotech Sector Outlook is Positive

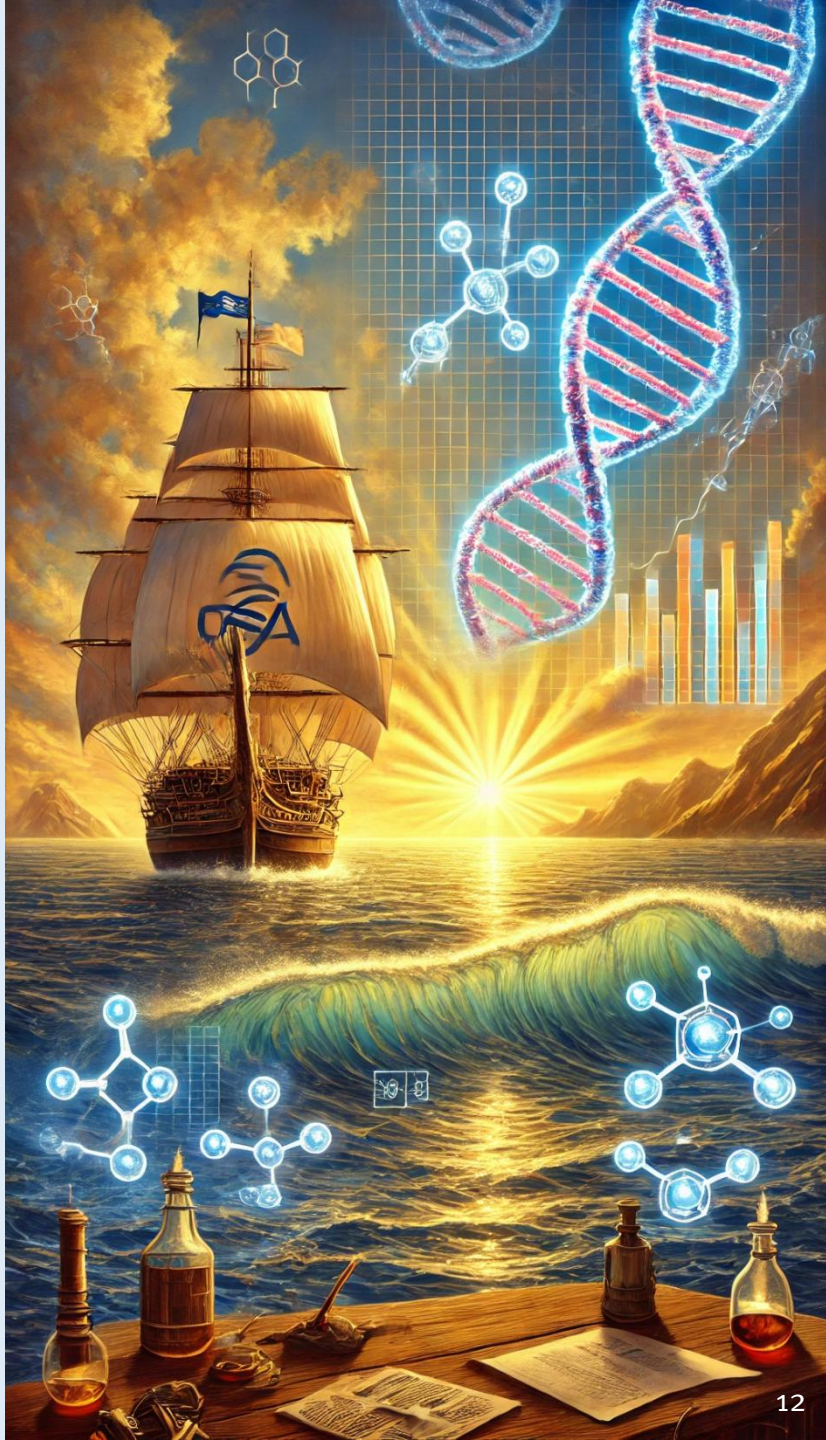
#5. Proposed deep NIH cuts do not seem likely to materialize. The NIH budget has not yet come up for discussion in the Senate Appropriations Committee where it will be discussed. But last week's discussion in that committee on the cuts to the National Science Foundation made it clear that U.S. Senators on both sides of the aisle, including Republican Susan Collins, are committed to maintaining, if not growing, federal science funding. NIH cuts may not take place at all.

Outlook is Positive

On the whole, the negatives do not seem that negative and the positives are quite encouraging. The recent runup in biopharma share prices strikes us as more the beginning of an extended recovery than another blip in the market.

It will, of course, take time for a recovery to take place. The PIPE market and the venture market are still in a bit of a freeze and it will take time for funds to recover from damage caused by LP withdrawals and investor actions to pull money out of biotech mutual funds. Nonetheless, we are seeing quite healthy volumes in the market for follow-on equity offerings in recent weeks and these deals are trading well. This presages a reopening of the PIPEs market, the IPO market and, ultimately, the market for riskier venture stage investments.

There is clear momentum in the biotech market today and we think it's likely that biotech performance is likely to surprise us on the positive in the months ahead.



Trump's Sudden Shifts Make His Policies Baffling to Countries Trying to Negotiate Lower Tariffs

Paul Wiseman, *Associated Press*, July 12, 2025 (excerpt)

WASHINGTON (AP) — In the past week, President Donald Trump has managed to make his erratic trade policies even more baffling to countries desperate to negotiate an escape from his wrath.

Doubling down on his trade wars, Trump is threatening to raise taxes on many goods from Canada, hike his universal tariff on imports from around the world and punish Brazil for prosecuting his friend, the country's former president.

On Saturday, Trump announced more tariffs still, this time on two of the United States' biggest trade partners: the European Union and Mexico, at 30% each.

Former U.S. trade negotiator Wendy Cutler said that Trump's recent moves "underscore the growing unpredictability, incoherence and assertiveness" of his trade policies.

"It's hard for trading partners to know where they stand with Trump on any given day and what more may be coming their way when least expected," said Cutler, now vice president at the Asia Society Policy Institute.

Canada is far from the only target. In an interview Thursday with NBC News Trump suggested that he plans to raise his "baseline" tariff on most imports from an already-high 10% to as much as 20%. Trump sees the baseline tariffs as a way to finance the budget-busting tax cuts in the "One Big Beautiful Bill" he signed into law July 4.

Those tariff threats came after his extraordinary decision Wednesday to impose a 50% import tax on Brazil mainly because he didn't like the way it was treating former Brazilian president Jair Bolsonaro, who is facing trial for trying to overturn his electoral defeat in 2022.

Source: https://apnews.com/article/trump-tariffs-canada-brazil-vietnam-trade-08005b1aedc77736852a90ca3d7c85ae

Trump's 200% Tariff Threat Leaves Pharma Firms Scrambling with Scenario Planning

Karen Gilchrist, *CNBC*, July 11, 2025 (excerpt)

The pharmaceutical industry is scrambling with scenario planning as U.S. President Donald Trump's 200% tariff proposal threatens to drive up drug prices and rip out corporate profit margins.

The president once again warned on Tuesday that long-awaited industry-wide tariffs would be announced "very soon" after the administration launched a so-called 232 investigation into the sector in April.

Trump suggested that those levies would not go into effect immediately, but get a grace period of "about a year, year and a half to come in."

Analysts nevertheless warn that such a rate — even with a delay — will have a detrimental effect on drug prices and profit margins.

"A 200% tariff would inflate production costs, compress profit margins, and risk supply chain disruptions, leading to drug shortages and higher prices for U.S. consumers," Barclays wrote in a note Wednesday.

"That would be potentially disastrous for every person because we need those pharmaceuticals, and it takes those companies a long time to produce them here in the U.S.," Beschloss told CNBC's "Closing Bell."

It is estimated that a tariff of just 25% on pharmaceutical imports would drive up U.S. drug prices by almost $51 billion annually, increasing domestic prices by as much as 12.9% if passed on, according to research from industry trade group Pharmaceutical Research and Manufacturers of America (PhRMA), which on Wednesday lambasted the president's proposals as "counterproductive" to health outcomes.

Source: https://www.cnbc.com/2025/07/11/trump-200percent-pharma-tariffs-threaten-to-push-up-drug-prices-hit-margins.html

Market Volatility Recedes as Investors Brush off Trump's Tariff Threats

Ian Smith and Emily Hebert, *Financial Times*, July 10, 2025 (excerpt)

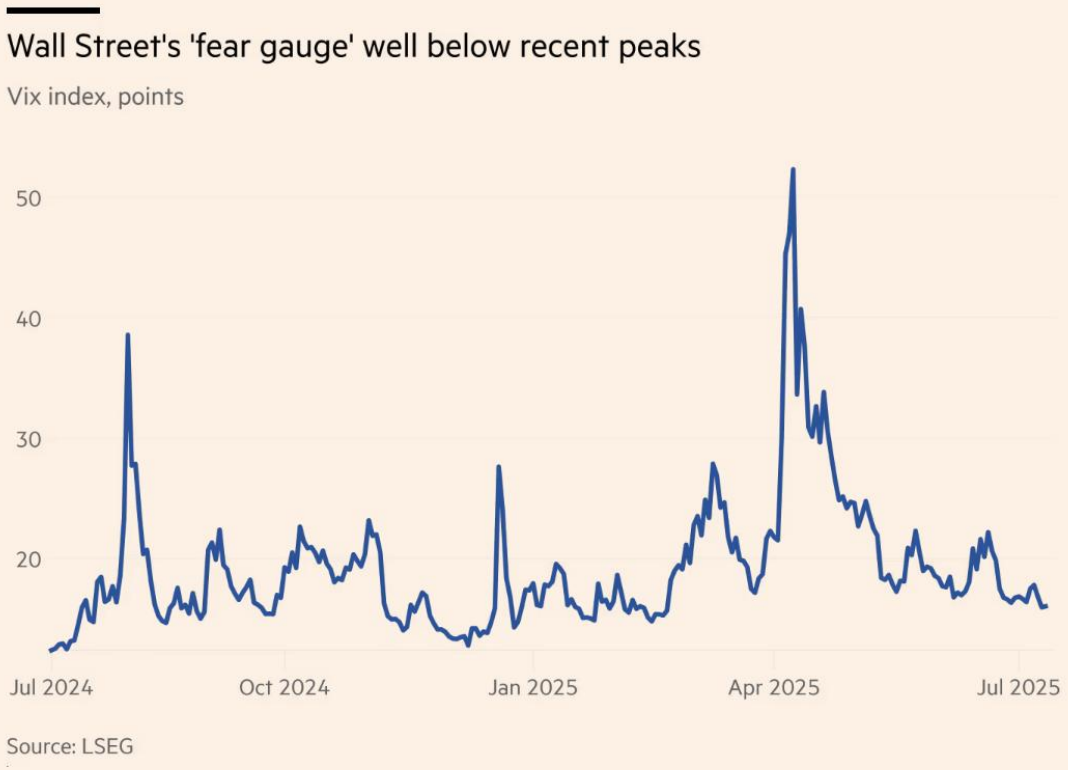
Market volatility has dropped to near its lowest levels of the year and stocks are trading at record highs as anxiety over Donald Trump's tariffs melts away despite the latest escalation of his trade war.

The Vix index, a measure of short-term expected volatility in the S&P 500, has fallen to 16, well below its long-run average of about 20.

At the same time, Nvidia has led a surge in tech stocks as the chipmaker reached an unprecedented $4tn valuation on Wednesday. The moves come even as the US president unleashed a barrage of fresh trade threats this week, including a 50 per cent tariff on copper, 200 per cent on the pharmaceutical sector and levies on countries including Japan, South Korea and the Philippines.

"I don't care about tariffs any more," said Max Kettner, head of multi-asset strategy at HSBC. "This is all self-imposed. What's to stop them saying, let's give it another three months?" Trump's latest moves on tariffs bring their levels closer than some analysts had expected to the steep duties he unveiled in early April on dozens of US trading partners.

However, those initial so-called "reciprocal" tariffs were later postponed and renegotiated after stocks cratered, and Trump then pushed back again the deadline for implementing the duties from July 9 to August.



Source: https://www.ft.com/content/5af6b3eb-1508-4073-bf9c-b60066d0dfc9

Treasury Posts Unexpected Surplus in June as Tariff Receipts Surge

Jeff Cox, *CNBC*, July 11, 2025 (excerpt)

The U.S. government posted a surplus in June as tariffs gave an extra bump to a sharp increase in receipts, the Treasury Department said Friday.

With government red ink swelling throughout the year, last month saw a surplus of just over $27 billion, following a $316 billion deficit in May.

That brought the fiscal year-to-date deficit to $1.34 trillion, up 5% from a year ago. However, with calendar adjustment, the deficit actually edged lower by 1%. There are three months left in the current fiscal year, which ends Sept. 30.

A 13% increase in receipts from the same month a year ago helped bridge the gap, with outlays down 7%. For the year, receipts are up 7% while spending has risen 6%.

The government last posted a June surplus in 2017, during President Donald Trump's first term.

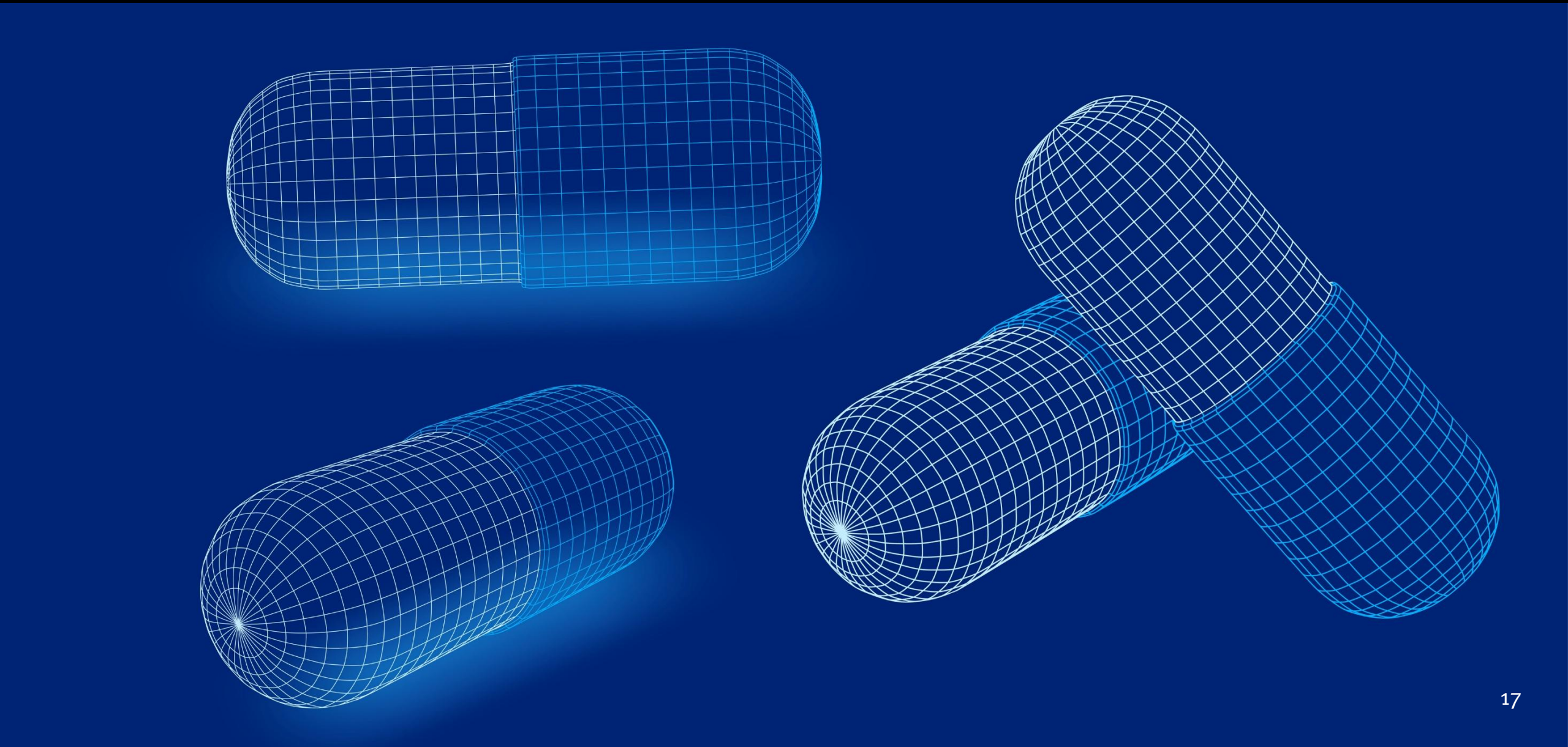
Increasing tariff collections are helping shore up the government finances.

Customs duties totaled about $27 billion for the month, up from $23 billion in May and 301% higher than June 2024. On an annual basis, tariff collections have totaled $113 billion, or 86% more than a year ago.

Persistently high Treasury yields again posed a challenge for federal finances. Net interest on the $36 trillion national debt totaled $84 billion in June, down slightly from May but still higher than any other category with the exception of Social Security. For the year, net interest — what Treasury pays on the debt it issues minus what it earns on investments — is at $749 billion. Total interest payments are projected at $1.2 trillion for the full fiscal year.

Source: https://www.cnbc.com/2025/07/11/treasury-posts-unexpected-surplus-in-june-as-tariff-receipts-surge.html

Biopharma Market Update



The XBI Closed at 87.0 Last Friday (July 11), Up 2.1% for the Week

The Stifel Global Biotech Value Tracker rose by 1.6% last week, less than the XBI and BBC – which both rose. Treasury yields remain stubbornly high. The XBI is down 3.4% for the year while the Stifel Global Biotech Value Tracker is up 19% for the year. The Stifel tracker is global and thus includes China biotech which has performed quite well in 2025.

Biotech Stocks Up Last Week

Return: July 7 to July 12, 2025

Nasdaq Biotech Index: +3.0%
Arca XBI ETF: +2.1%
Virtus LifeSci Biotech ETF (BBC): -+4.3%
Stifel Global Biotech EV (adjusted): +1.6%*
S&P 500: -0.3%

Return: Dec 31, 2024 to July 12, 2025 (YTD)

Nasdaq Biotech Index: +4.0%
Arca XBI ETF: -3.4%
Virtus LifeSci Biotech ETF (BBC): -15.0%
Stifel Global Biotech EV (adjusted): +19%*
S&P 500: +6.4%

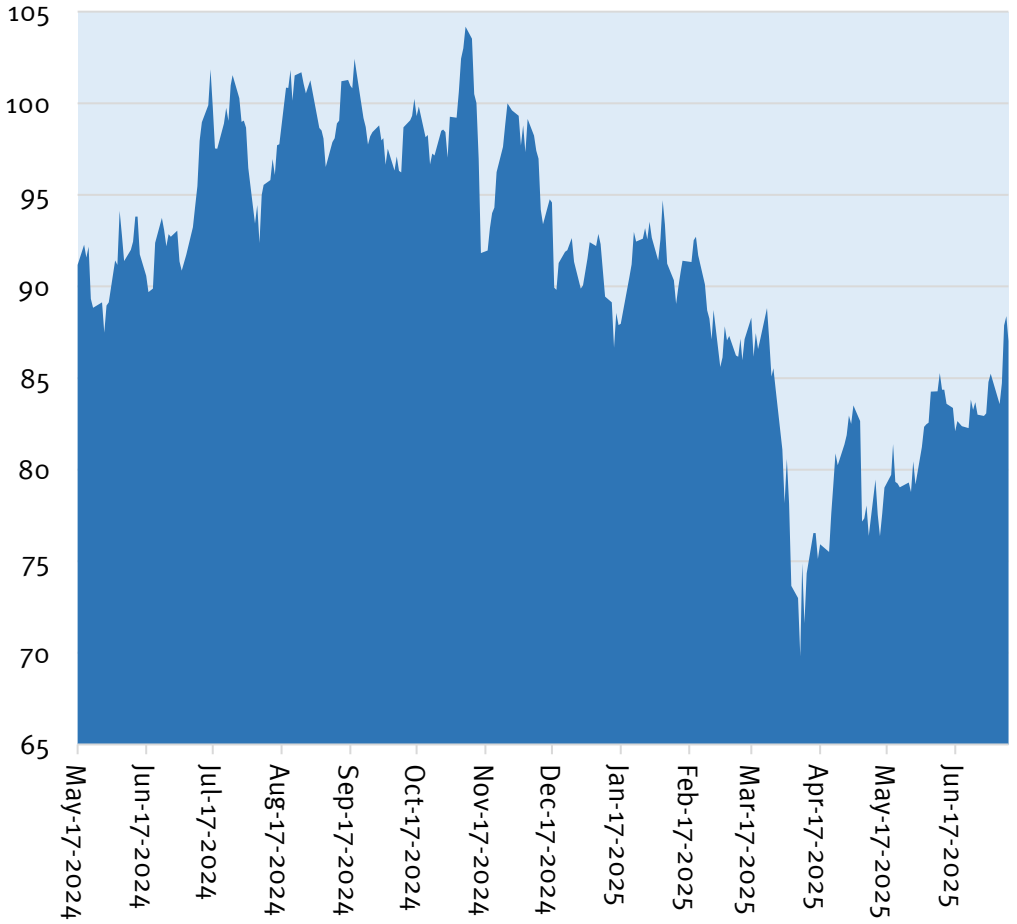
VIX Down

Aug 2, 2024: 23.4%
Dec 13, 2024: 13.8%
Mar 28, 2025: 21.7%
Apr 11, 2025: 37.6%
May 16, 2025: 18.4%
Jun 20, 2025: 20.4%
Jul 12, 2025: 16.4%

10-Year Treasury Yield Up

Aug 2, 2024: 3.80%
Dec 13, 2024: 4.4%
Mar 28, 2025: 4.27%
Apr 11, 2025: 4.48%
May 16, 2025: 4.43%
Jun 20, 2025: 4.3%
Jul 12, 2025: 4.43%

XBI, May 17, 2024 to Jul 12, 2025

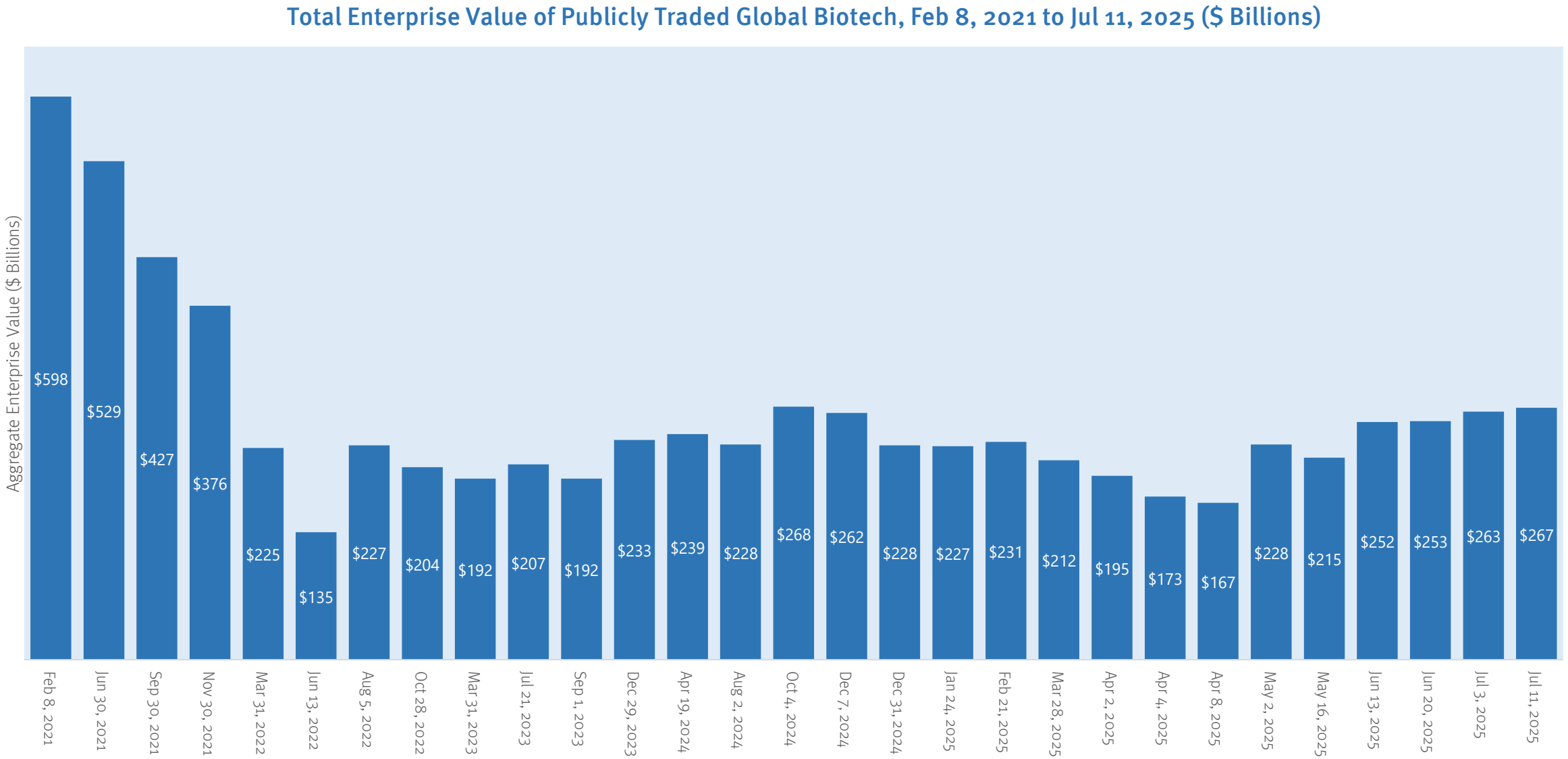


* Change by enterprise value. The adjusted number accounts for the effect of exits and additions via M&A, bankruptcies and IPOs. The annual change by market cap is even higher.

Source: S&P Capital IQ and Stifel analysis

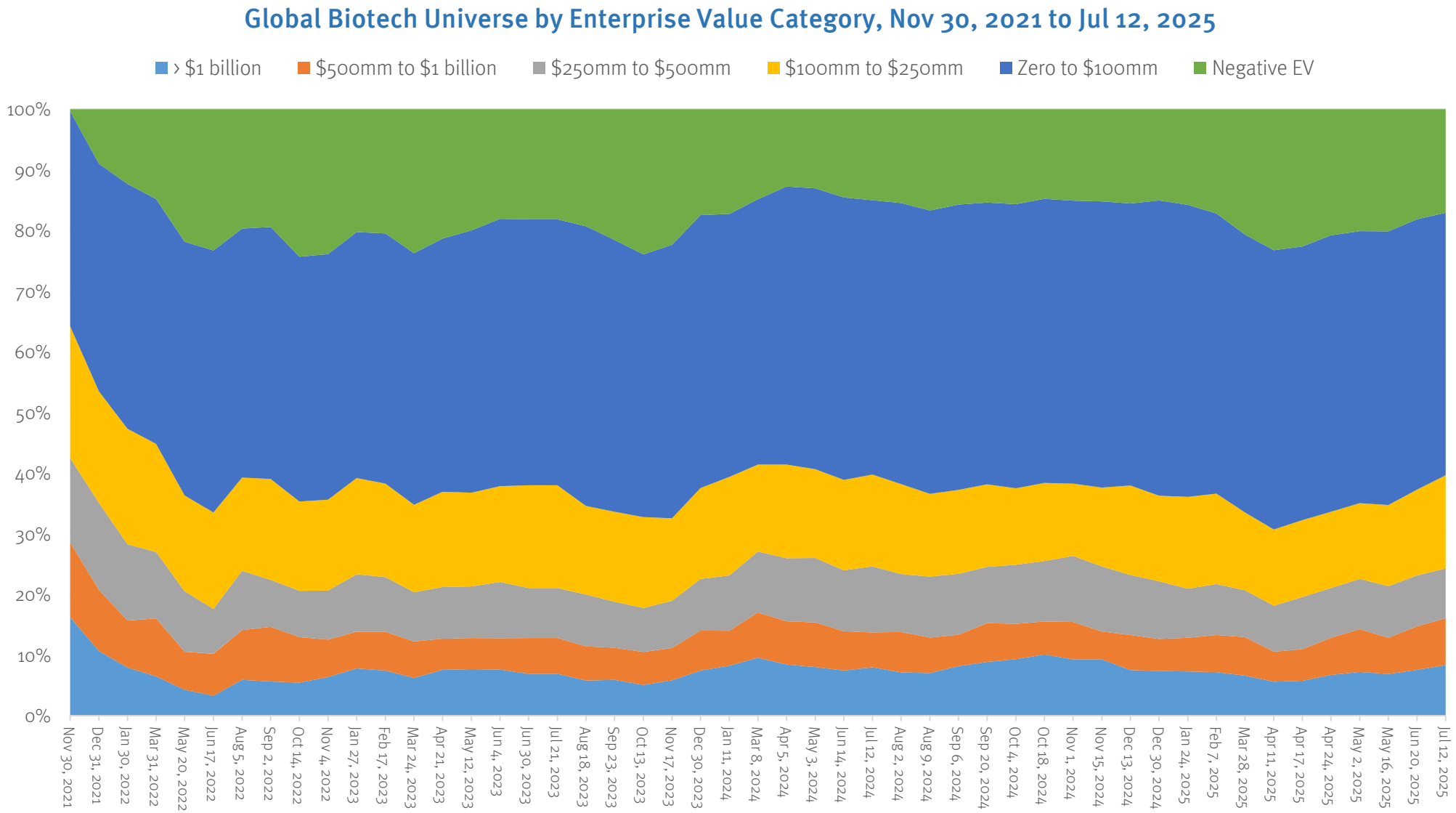
Total Global Biotech Sector Rose 1.6% Last Week

Biotech stocks are up 61% since hitting a low point on Apr 8, 2025. Biotech stocks ended last week up 19% for the year.



Source: CapitalIQ. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

The “Good Neighborhood” in Biotech is Growing Fast

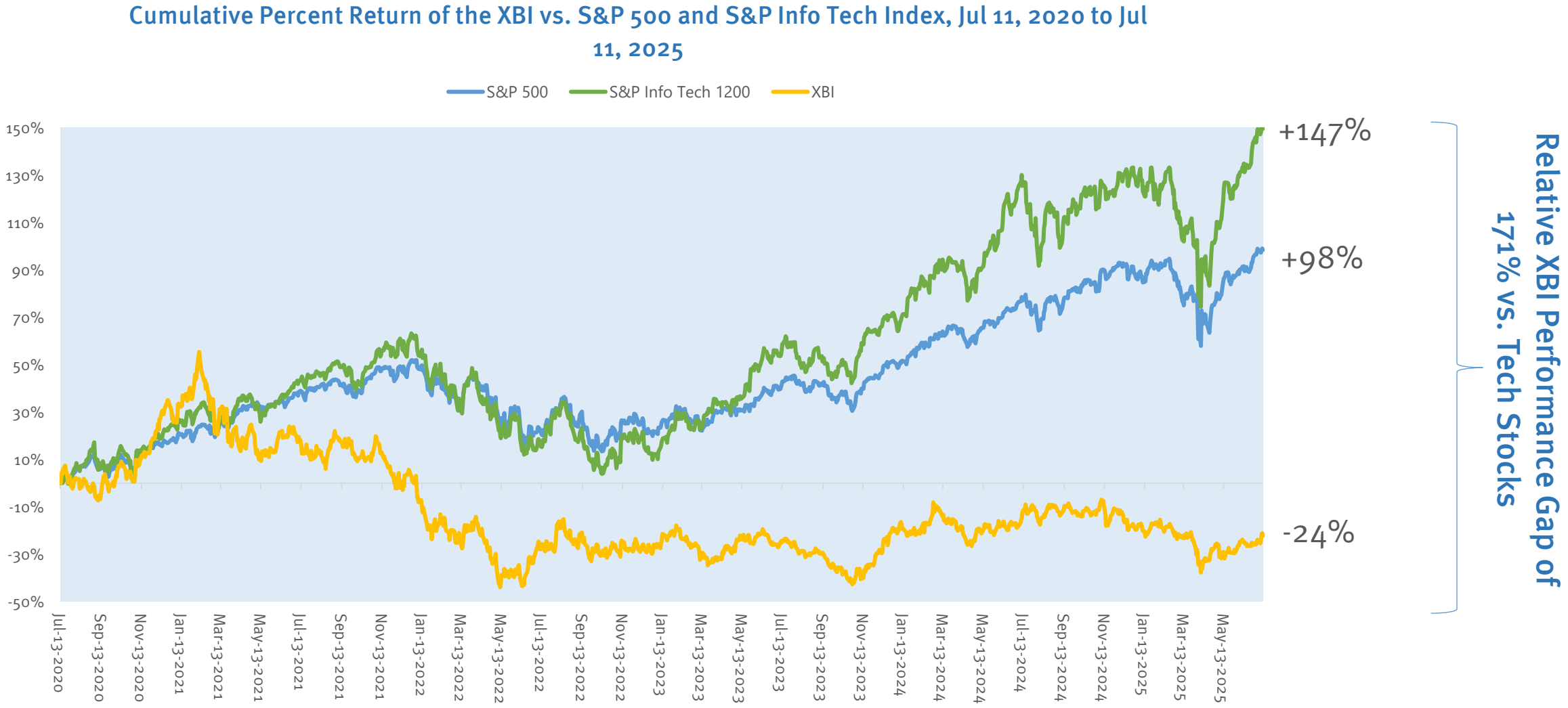


As of last Friday, 40% of biotechs had an EV over $100mm. Compare this to 31% in April. On the other hand, in June 2021, this group comprised 64% of the sector.

Source: CapitalIQ and Stifel analysis. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

Underperformance of Biotech vs. Tech Persists in 2025

The mind-boggling gap in performance between tech and biotech has only widened in recent months.

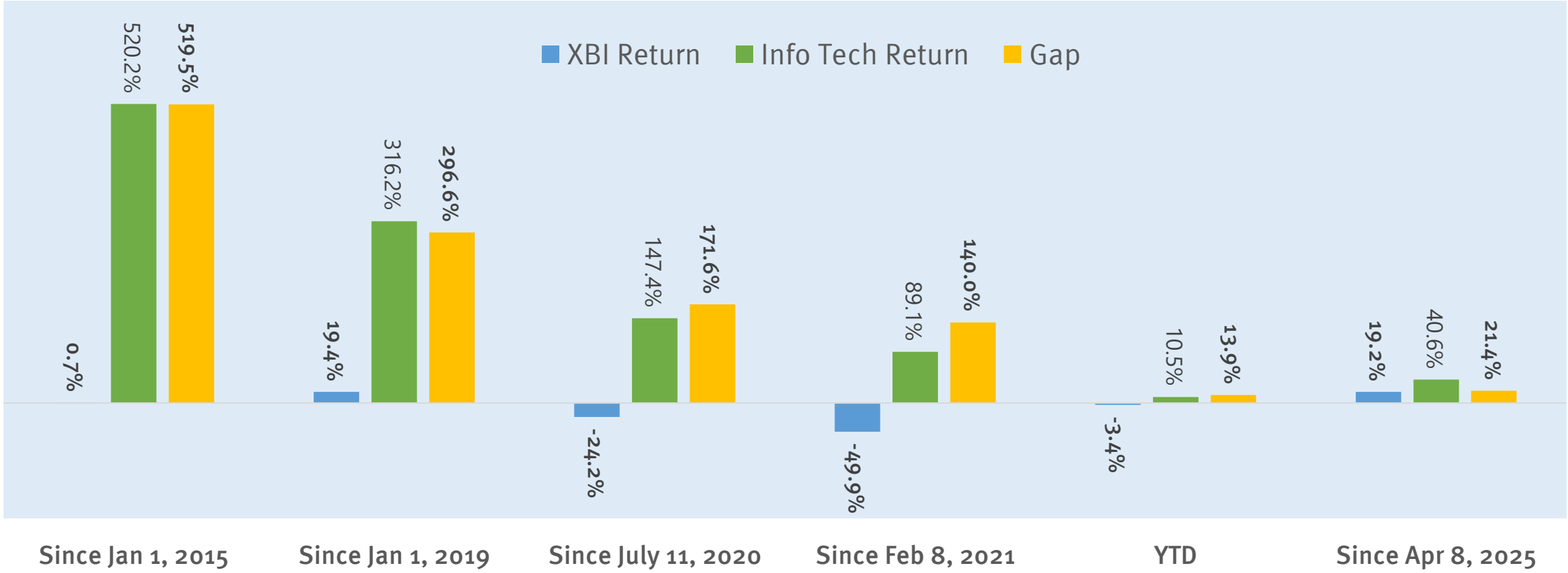


Source: CapitalIQ.

Return Difference Between S&P 1200 Info Tech Index and XBI is Quite Wide

An investment in the XBI ten years ago would have yielded at return of 0.7% whereas an investment in the S&P Info Tech 1200 Index would have yielded a return of 520%. The gap is surprisingly wide and reflects the challenges that the biopharma sector has faced in a challenging pricing, regulatory and R&D environment.

Performance Differential Between XBI and S&P Info Tech 1200 Index at Different Time Intervals

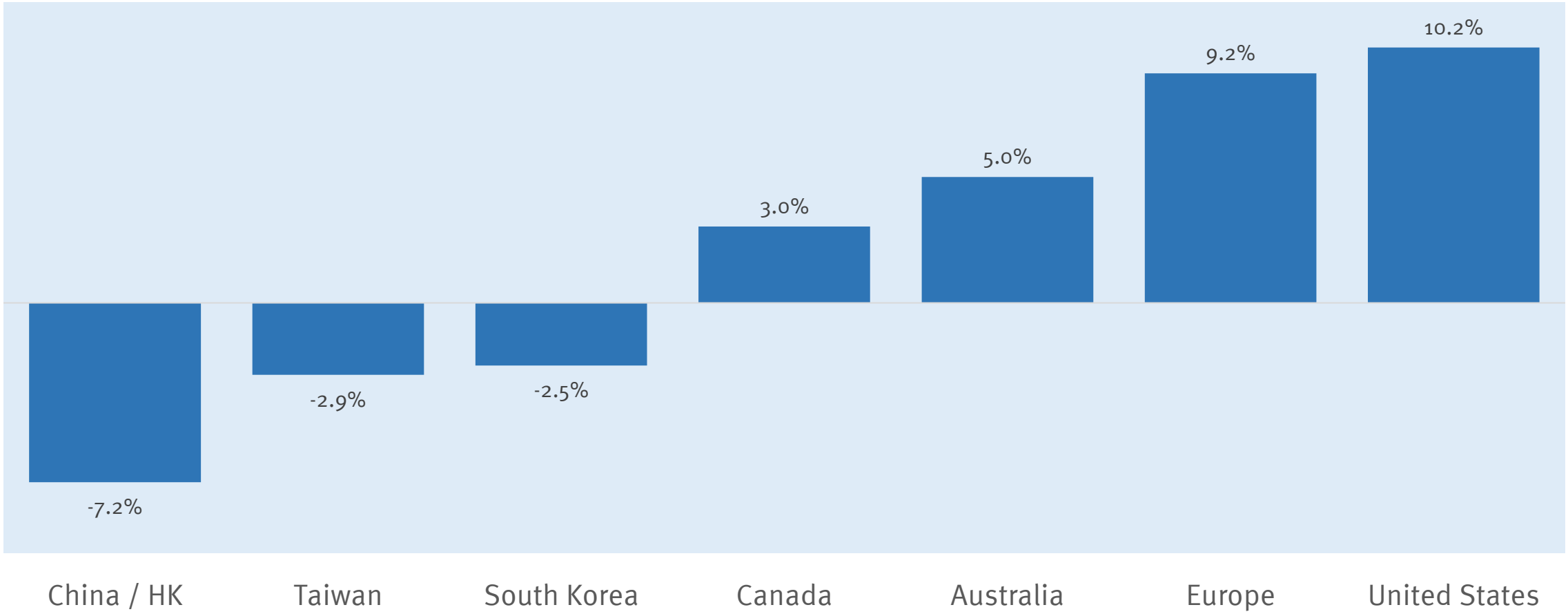


Source: CapitalIQ.

U.S. / Europe Biotech Fared Well in Last Three Weeks

The last three weeks have seen weak performance in the China biotech sector while the U.S. and European sectors have done relatively well.

Percent Change in Total Market Cap of Public Biotech by Country/Region, Jun 20, 2025 to Jul 12, 2025

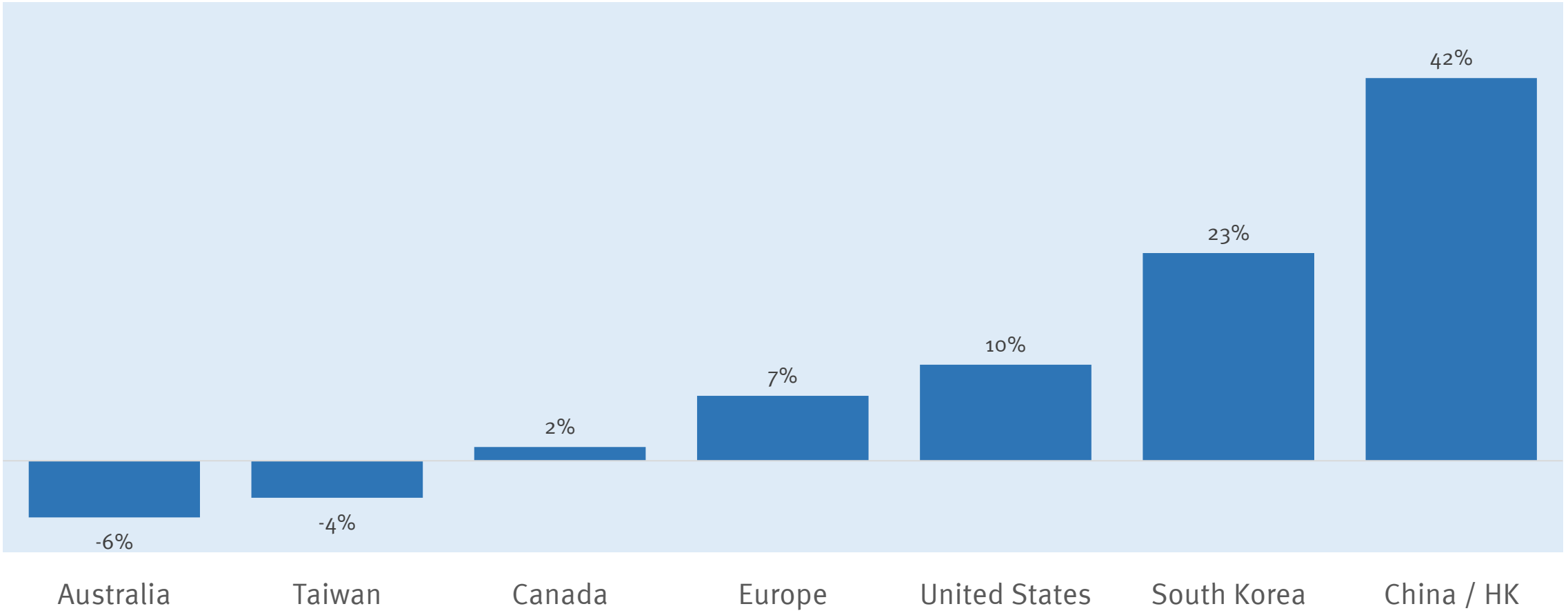


Source: CapitalIQ and Stifel analysis. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange. Europe biotech includes companies from all major EU countries.

China Biotech Has Done Best Since “Liberation Day”

Despite underperformance in recent weeks, the China biotech sector has had stellar performance since early April. U.S. biotech has recovered from sharp losses and is now up 10% since that time.

Percent Change in Total Market Cap of Public Biotech by Country/Region, Apr 3, 2025 to Jul 12, 2025



Source: CapitalIQ and Stifel analysis. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange. Europe biotech includes companies from all major EU countries.

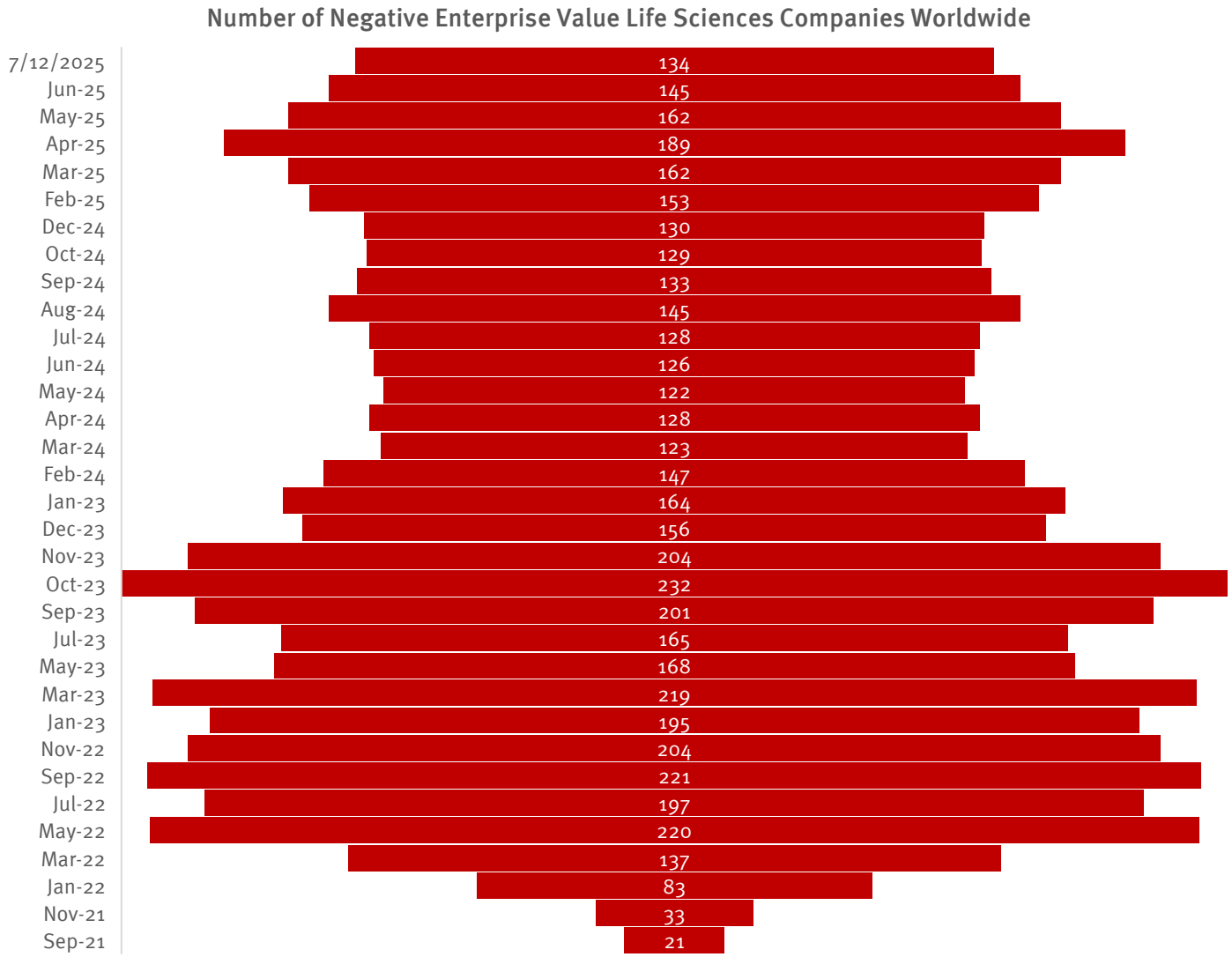
Life Sciences Sector Flat Last Week

The life sciences sector is worth $9.6 trillion and did not change in value last week. Biotech and pharma services were up while medical devices, OTC and diagonstics fell slightly.

Sector	Firm Count	Enterprise Value (Jul 11, 2025, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	79	$97,512	-0.6%	-0.7%	19.0%
Biotech	727	$267,082	1.6%	3.7%	-5.1%
CDMO	37	$162,869	0.6%	-0.5%	26.2%
Diagnostics	75	$270,559	-1.2%	0.4%	1.4%
OTC	29	$24,393	-1.9%	-2.4%	-7.2%
Pharma	695	$6,197,180	0.1%	-1.9%	-7.0%
Services	38	$163,944	2.8%	4.7%	-9.0%
Tools	50	$573,619	0.8%	2.6%	-14.3%
Devices	173	$1,804,417	-1.3%	-0.1%	7.2%
HCIT	7	$24,418	-0.1%	1.7%	36.8%
Total	**1910**	**$9,585,993**	**-0.1%**	**-0.9%**	**-3.8%**

Source: CapitalIQ and Stifel analysis

Number of Negative Enterprise Value Life Sciences Companies Fell in Last Month



The count of negative EV life sciences companies worldwide fell from 145 three weeks ago to 134 last Friday.

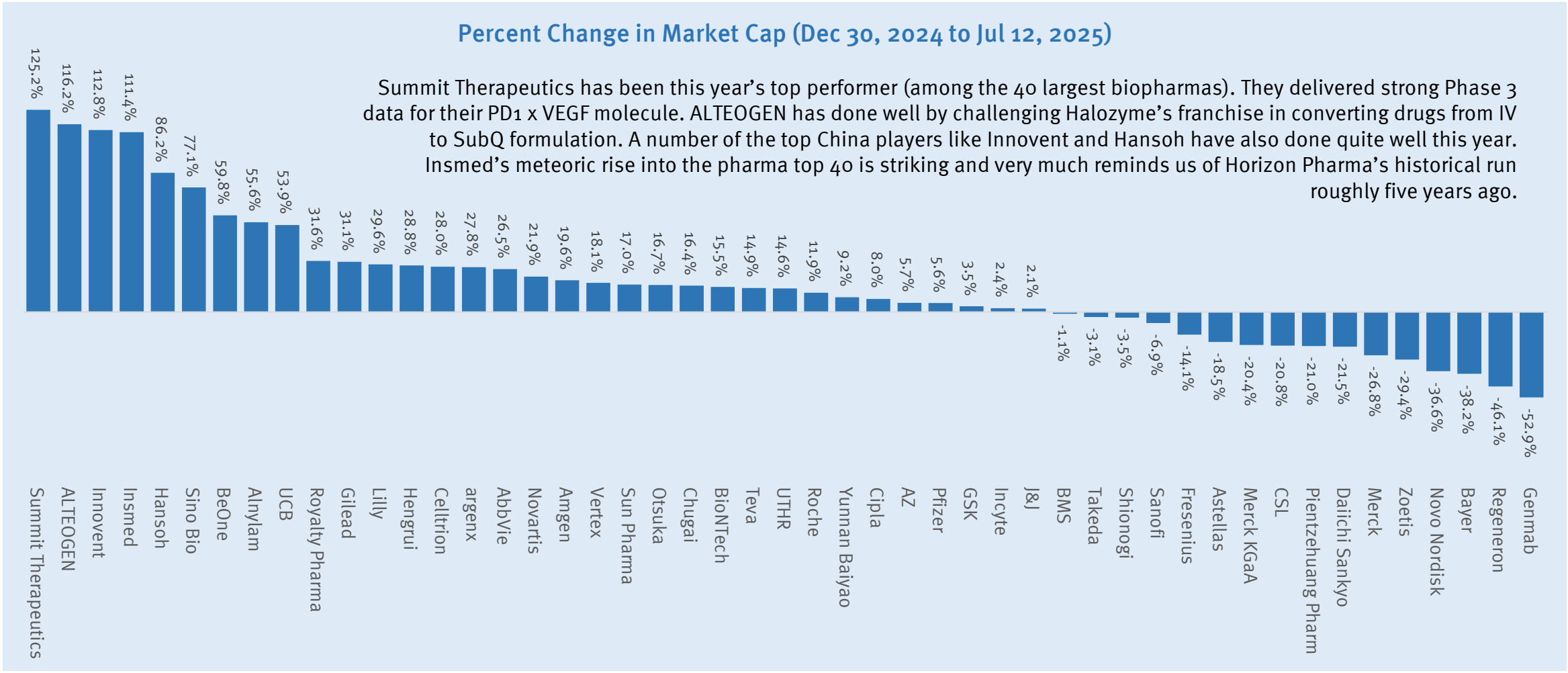
This is the lowest level we have seen since last October.

The biotech sector is very gradually normalizing.

Source: CapitalIQ

How Top Pharma is Evolving in 2025

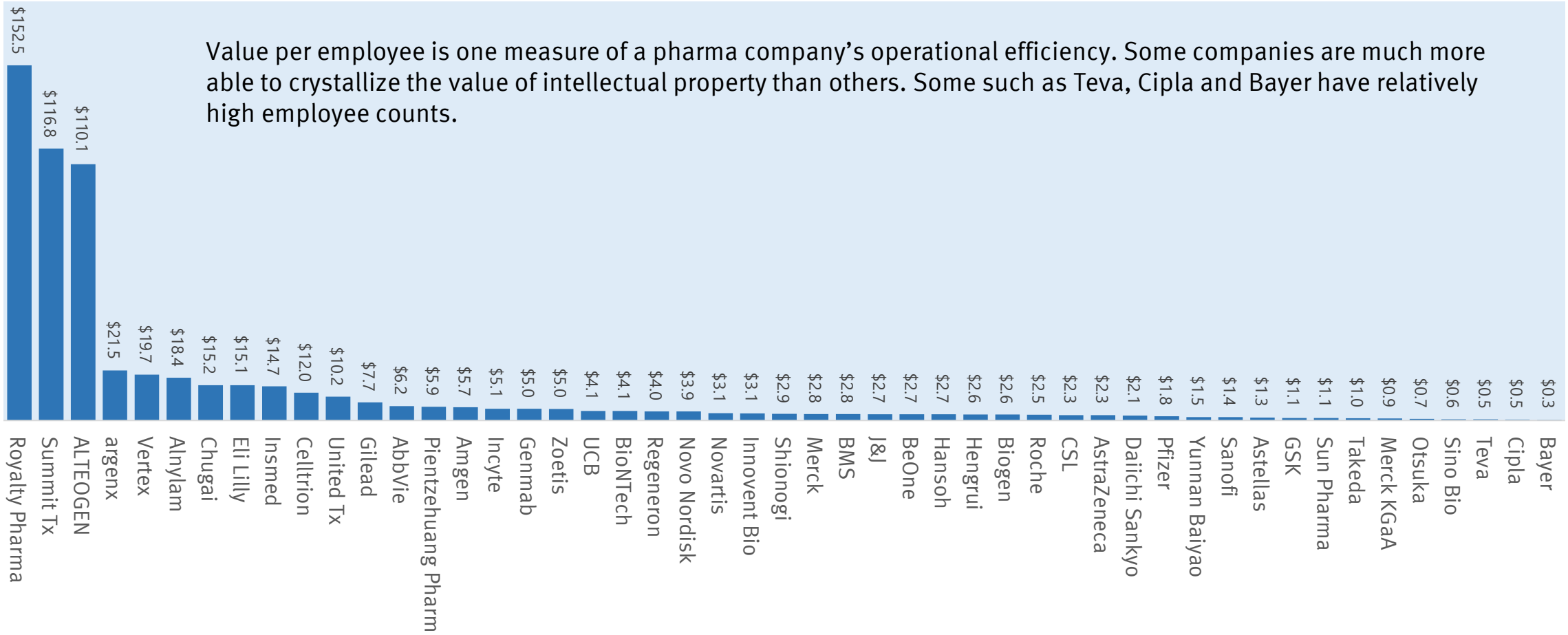
The Median Return YTD of a Top 40 Pharma has Been 13%



Source: S&P CapitalIQ

The Median Pharma Sustains $3 Million in Market Cap Per Employee. Royalty Pharma Exceeds that by 50X. Bayer Has $300K in Market Cap Per Employee

Market Cap $Million Per Employee of the Top 40 Public Biopharma Companies Worldwide, Jul 12, 2025



Source: S&P CapitalIQ

Top 30 Public Biopharma in the World Worth $4.5 Trillion

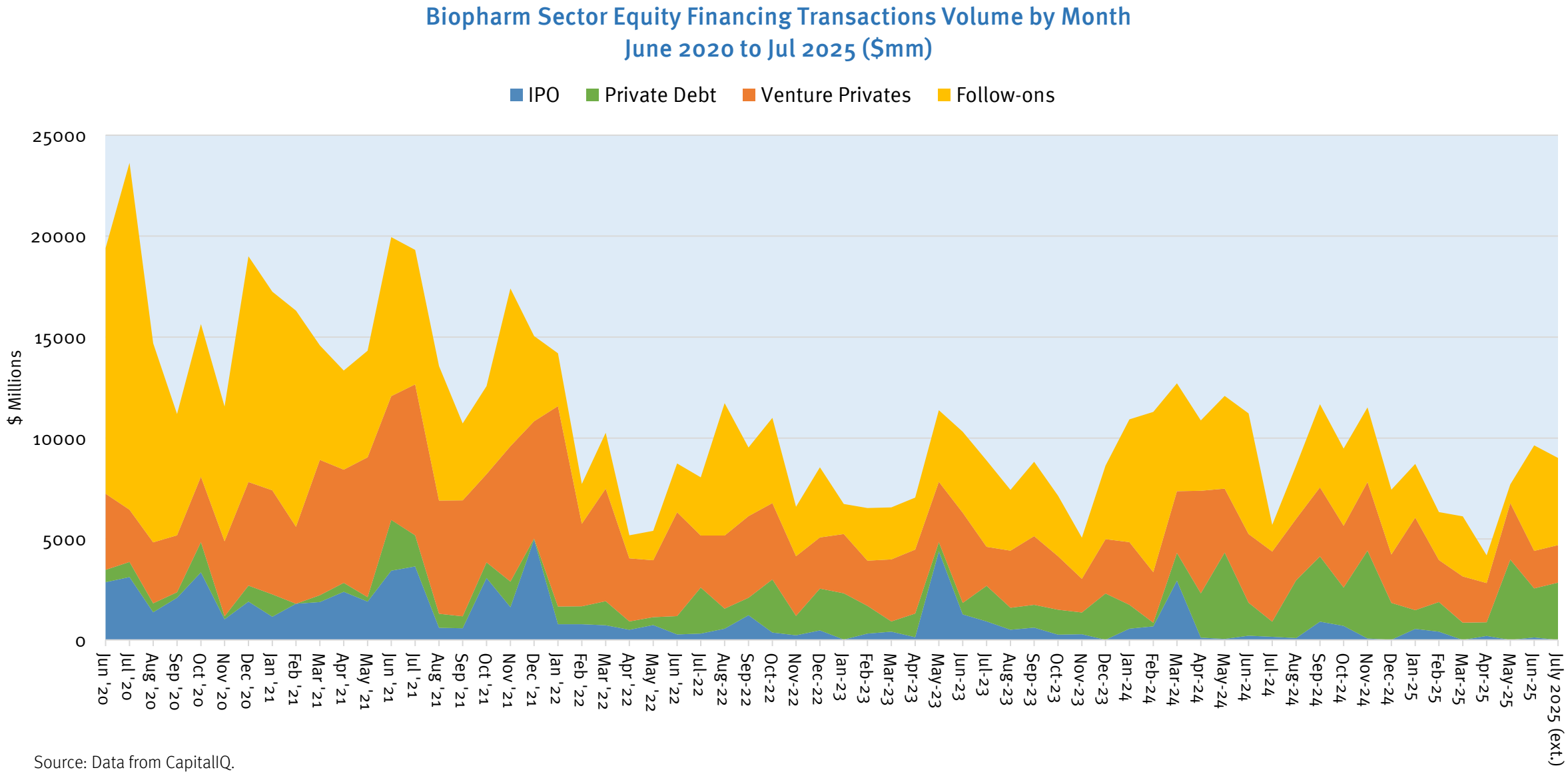
This chart reveals the shifting sands within the pharma sector. Developments that have caught our eye are the resurgence of AbbVie and J&J in 2025. Also of note, argenx is now worth more than Bayer at this point. Vertex is worth more than Sanofi, BMS and GSK. And Hengrui is now worth more than Takeda. Alnylam is twice as valuable as Biogen and Insmed is worth roughly the same as Biogen. Sanofi and BMS are now well outside the industry's top 10 list. It's also interesting to note that at this point, Nvidia is worth more than the top 20 pharmas combined.

Top 30 Public Biopharma Companies by Market Cap, July 12, 2025 ($bn)

Source: S&P CapitalIQ

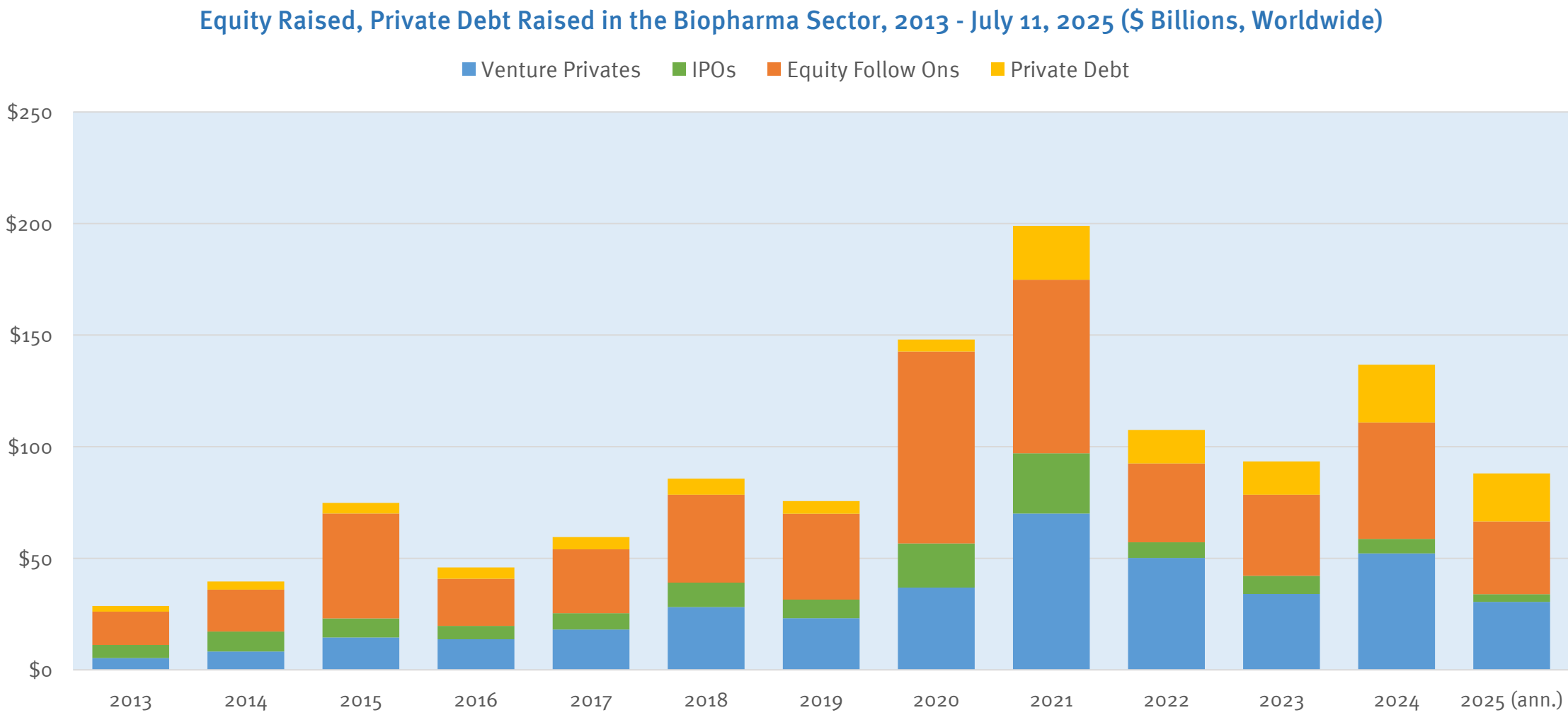
Capital Markets Update

Monthly Financing Volumes Have Picked up in June and July



Source: Data from CapitalIQ.

Capital Raising Pace in 2025 Slower than in Recent Years



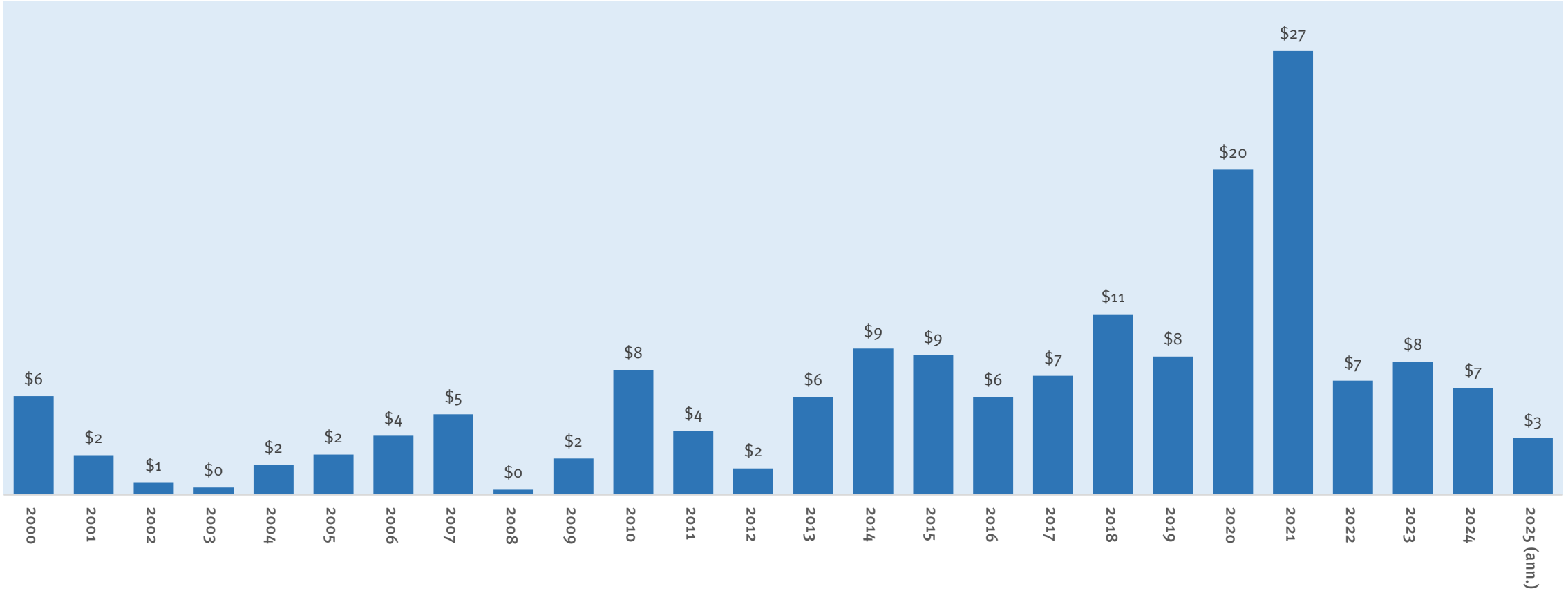
Source: Data from CapitalIQ.

IPO Market Has Remained Quiet Through 2025

The last biotech company to go public on the NASDAQ was Aardvark which priced its deal on Feb 12th (more than five months ago). Since then eleven biotech companies have gone public in other countries (mainly HK).

IPO Volume in the Biopharma Sector, 2000 - 2025 (annualized)

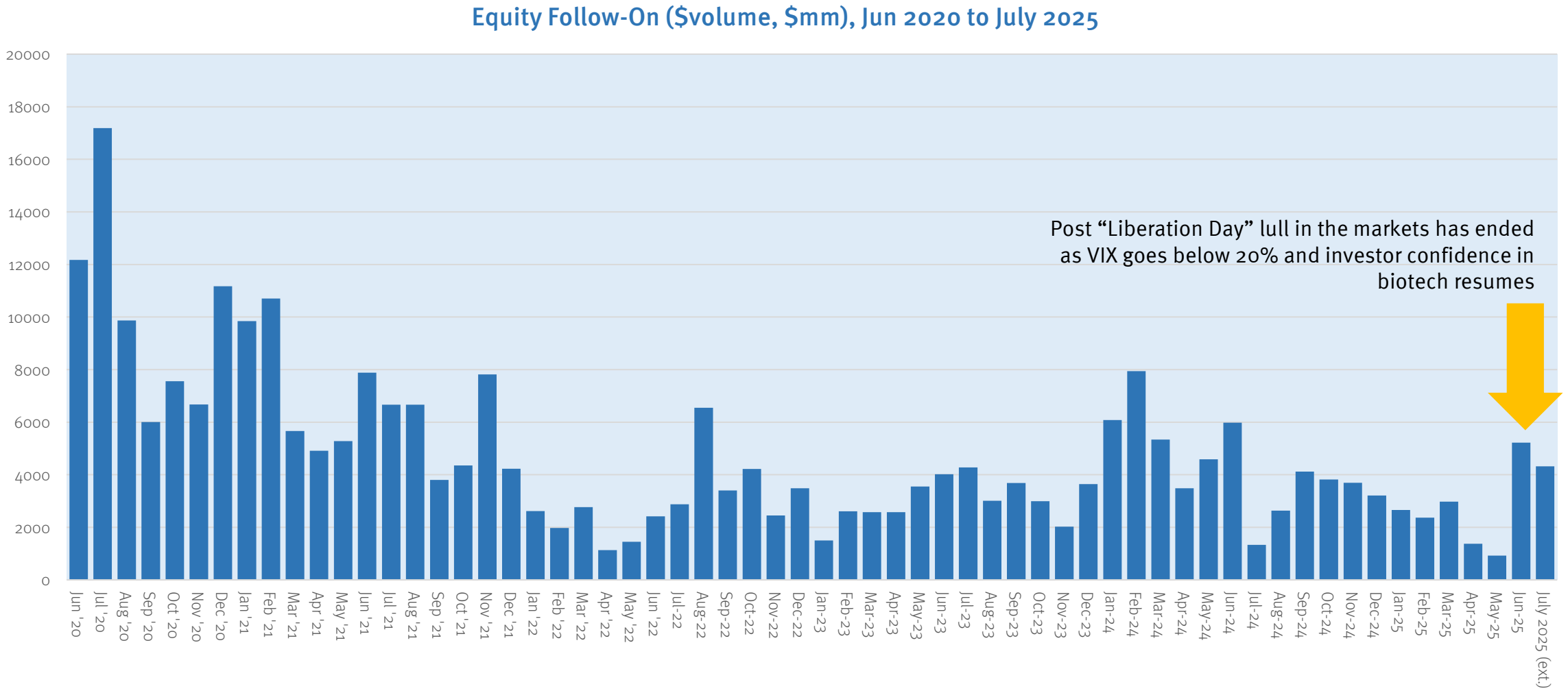
($ Billions, Worldwide)



Source: Data from CapitalIQ.

Global Follow-On Market Has Picked Up in the Last Six Weeks

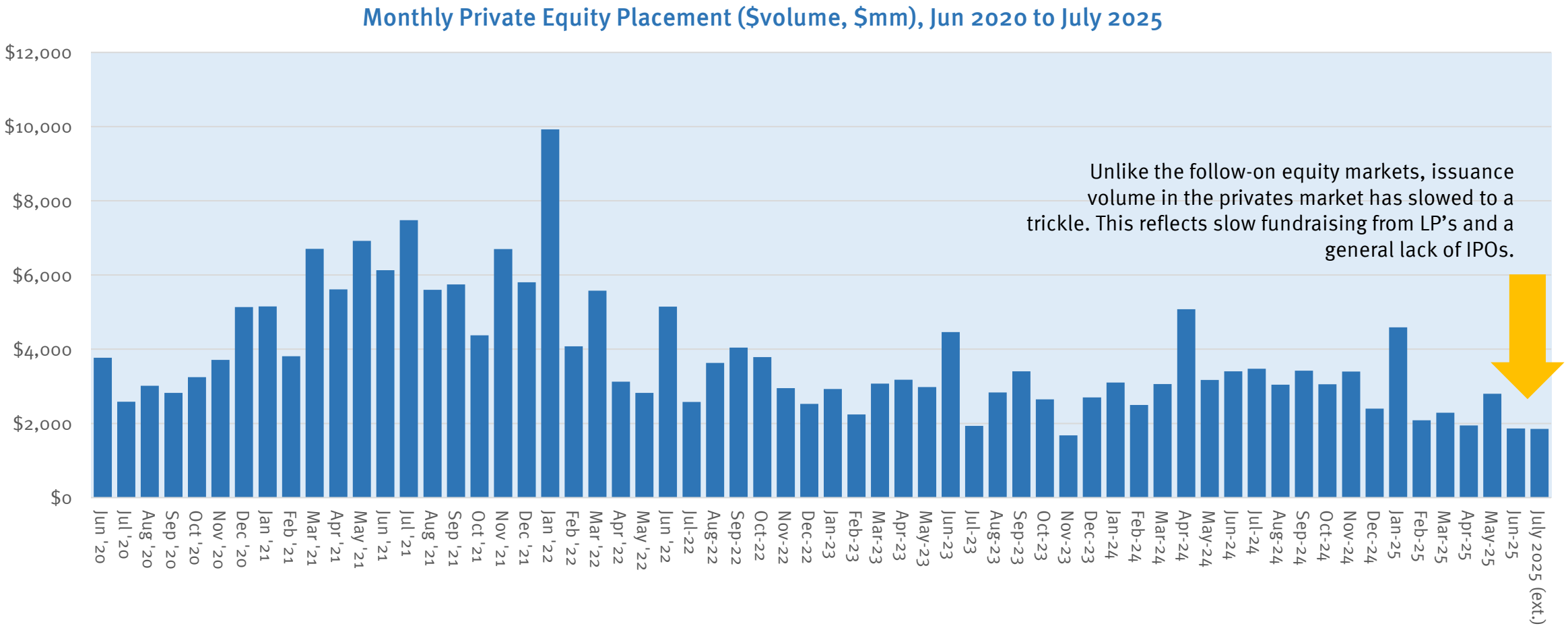
The slowdown in the biopharma follow-on market has reversed in the last six weeks. Volumes have not been this high since Q2 2024.



Source: Data from CapitalIQ, Crunchbase. Data for July 2025 is extrapolated based on results through July 11th.

Venture Equity Private Deal Pace Quite Slow

We are seeing the most extended lull in the privates market since we started keeping statistics. Venture investing has been quite challenging in recent months. We expect this to reverse in the months ahead as exits and IPO's resume for biotech.



Source: Data from CapitalIQ, Crunchbase. Data for May 2025 is extrapolated based on results through May 16th.

Varda Space Raises $187 Million

Brian Gormley, *Wall Street Journal*, July 10, 2025 (excerpt)

Varda Space Industries, which seeks to use microgravity to improve drug development, has raised $187 million in fresh capital and expanded its ability to process pharmaceutical ingredients in orbit.

Because active pharmaceutical ingredients behave differently in microgravity, or near-weightlessness, Varda says its approach could enable improved versions of existing drugs and novel treatments not possible on Earth.

El Segundo, Calif.-based Varda makes unmanned space capsules that are shot into low-Earth-orbit, aboard SpaceX rockets, where they process crystals. These crystals, the building blocks of pharmaceuticals, can be used to manufacture drugs on Earth.

Gravity affects crystal formation. Removing it causes fluids to mix differently, which can lead to more uniformly sized and structured crystals and novel crystals, according to Varda.

Varda has launched three capsules into space and returned them to Earth. A fourth is in orbit and will return later this year, the company says.

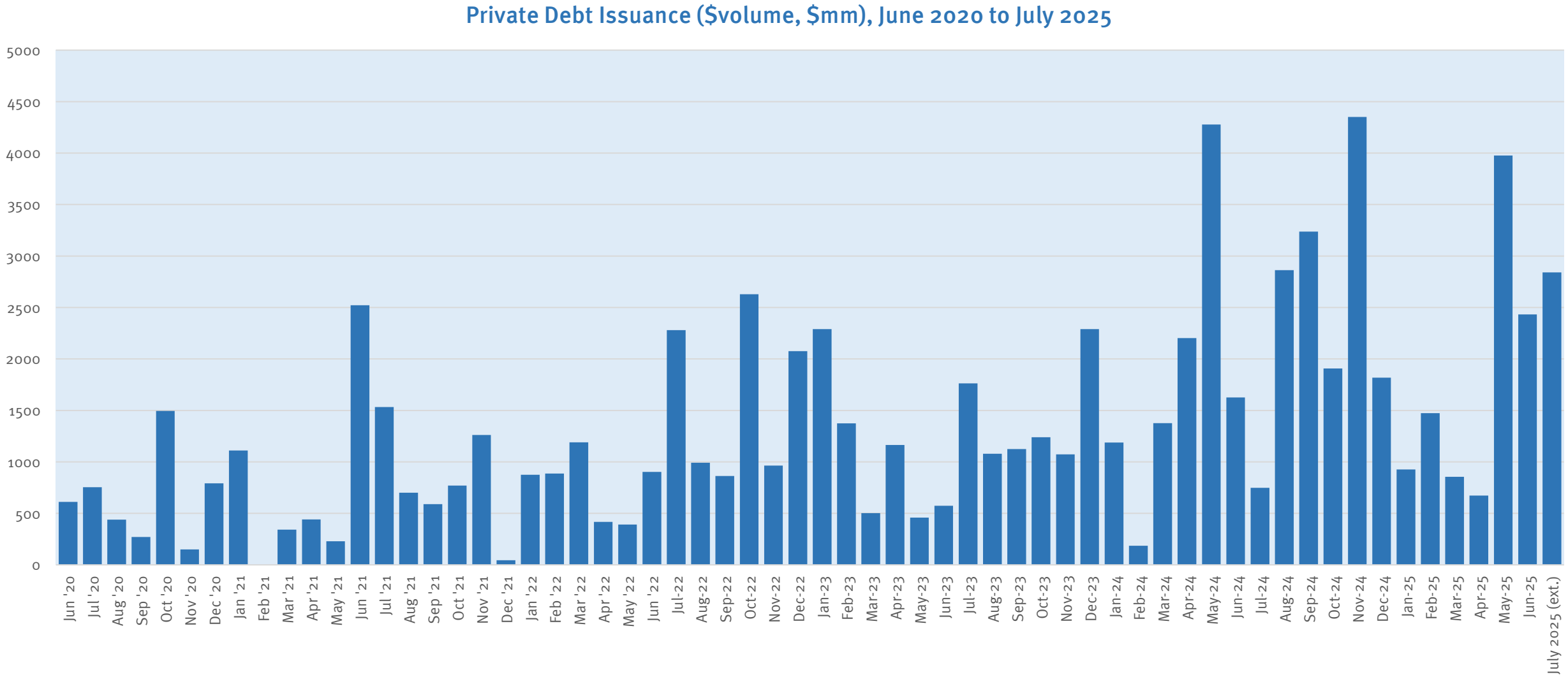
Crystals forming in space retain their structure as they return to Earth, said Chief Executive Will Bruey, who co-founded Varda in November 2020 with President Delian Asparouhov.

Varda in 2023 tested its approach by launching the HIV medication ritonavir into space, a drug that is difficult to formulate on Earth.

In space, a novel form of the ritonavir drug crystals was created. The crystals held their space form on their return to Earth, according to Varda.

Source: https://www.wsj.com/articles/space-medicines-startup-varda-nabs-187-million-financing-ddc44b52

Biopharma Private Debt Placement Volume Strong in Last Quarter

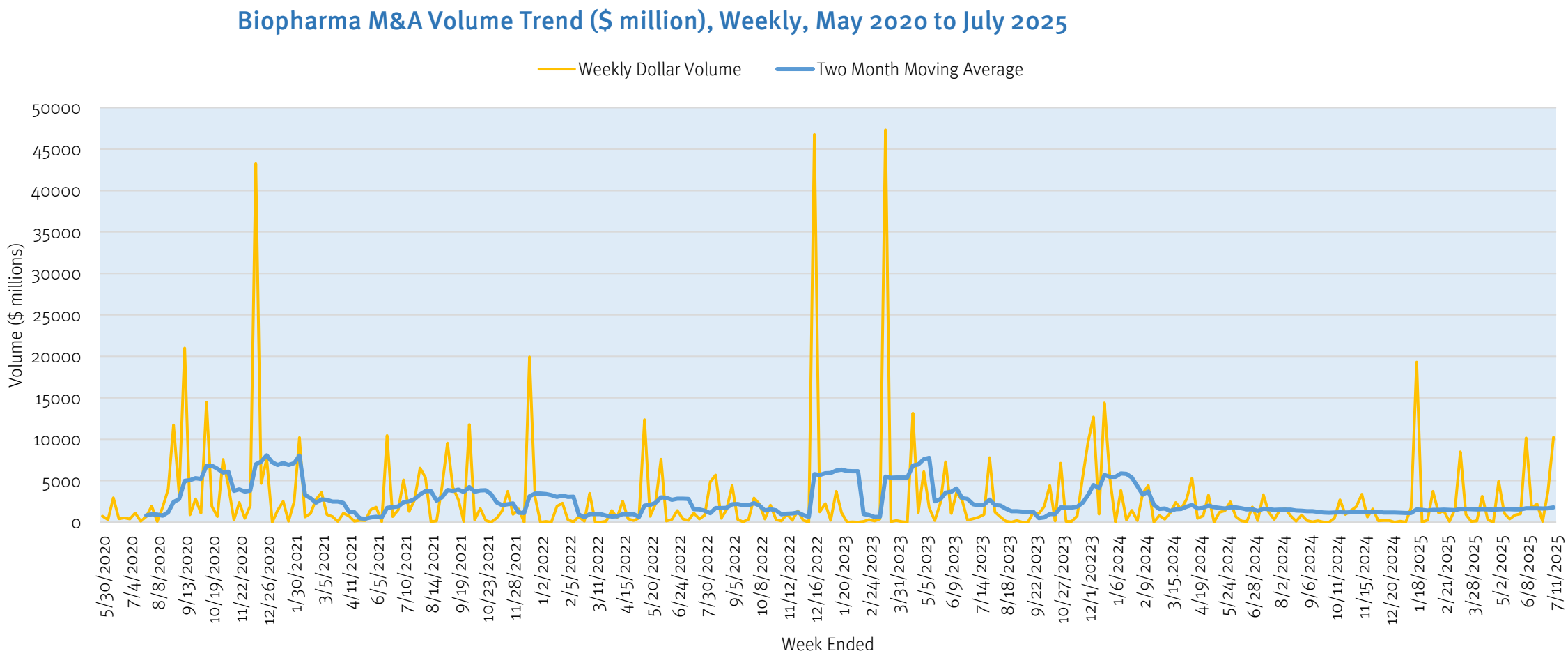


Source: Data from CapitalIQ, Crunchbase. Data for May 2025 is extrapolated based on results through May 16th.

Deals Update

M&A Market Has Been Active in the Last Month

We saw the third $10 billion M&A deal of the year last week with Merck's offer to acquire Verona Pharma. We have also seen a major merger announced between Becton Dickinson and Waters for $17.5 billion and the purchase of PCI Pharma Services by Bain and Kohlberg for $10bn.



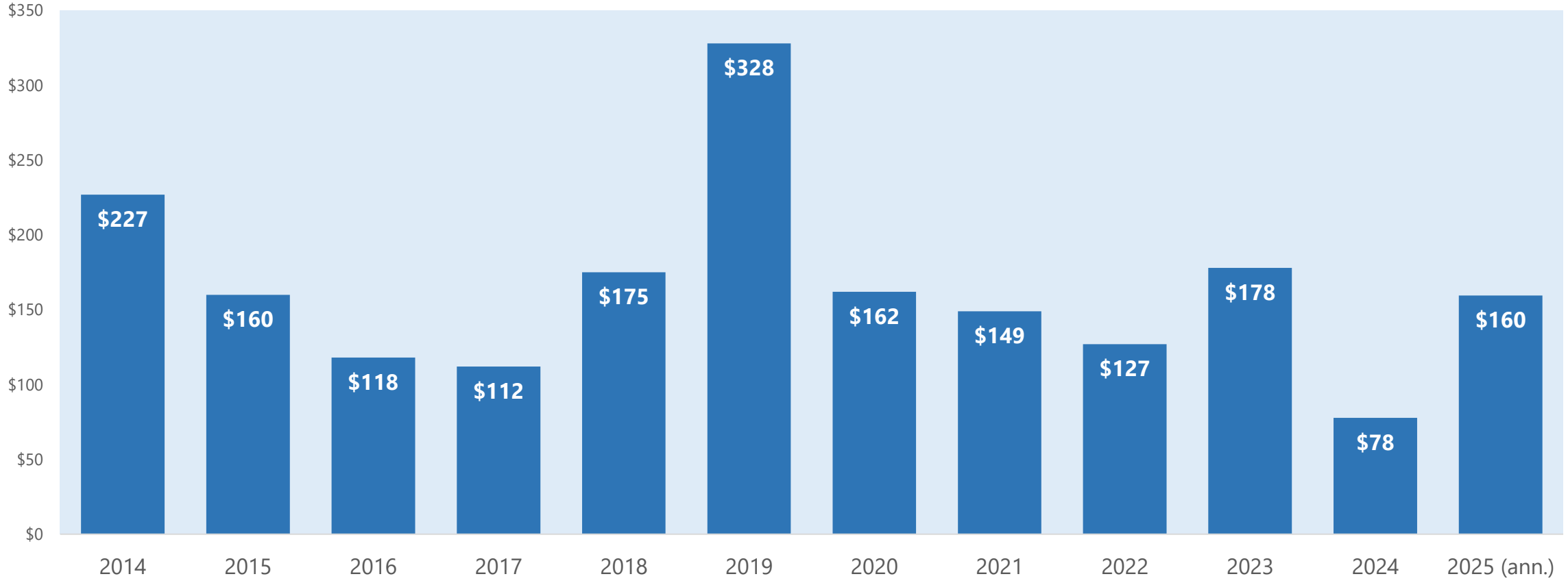
Source: S&P, CapitalIQ

M&A Market Has Been Active in the Last Month

We have seen $32 billion in biopharma M&A volume in the last six weeks. M&A is way up as the uncertainty over Trump's tariffs and MFN policies has been dropping. Overall, the year continues to look like quite a solid year for M&A with the market at a $160 billion run rate. This puts us on pace to have the sixth busiest M&A year in the last 12 years. Impressive because there are no deals over $11 billion.

M&A Volume in the Biopharma Sector, 2014 - 2025

($ Billions, Worldwide)



Source: S&P, CapitalIQ

Merck to Acquire Verona Pharma

RAHWAY, N.J. & RALEIGH, N.C.--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside of the United States and Canada, and Verona Pharma plc (Nasdaq: VRNA) ("Verona Pharma"), a biopharmaceutical company focused on respiratory diseases, today announced that the companies have entered into a definitive agreement under which Merck, through a subsidiary, will acquire Verona Pharma for $107 per American Depository Share (ADS), each of which represents eight Verona Pharma ordinary shares, for a total transaction value of approximately $10 billion.

Through this acquisition Merck will add Ohtuvayre® (ensifentrine), a first-in-class selective dual inhibitor of phosphodiesterase 3 and 4 (PDE3 and PDE4), to its growing cardio-pulmonary pipeline and portfolio. The U.S. Food and Drug Administration approved Ohtuvayre in June 2024 for the maintenance treatment of chronic obstructive pulmonary disease (COPD) in adult patients. Ohtuvayre is the first novel inhaled mechanism for the treatment of COPD in more than 20 years and combines bronchodilator and non-steroidal anti-inflammatory effects. Ohtuvayre is also being evaluated in clinical trials for the treatment of non-cystic fibrosis bronchiectasis.

"This acquisition of Verona Pharma reflects the commitment we have to delivering innovative treatments to patients and our ability to execute on our science-led and value-driven business development strategy," said Robert M. Davis, chairman and chief executive officer, Merck. "Ohtuvayre complements and expands our pipeline and portfolio of treatments for cardio-pulmonary diseases while delivering near- and long-term growth as well as value for shareholders. This novel, first-in-class treatment addresses an important unmet need for COPD patients persistently symptomatic based on its unique combination of bronchodilatory and non-steroidal anti-inflammatory effects. We look forward to welcoming the talented Verona Pharma team to Merck."

"Today's announced agreement with Merck is the culmination of years of focus and determination by the Verona Pharma team advancing Ohtuvayre, the first novel inhaled mechanism for the maintenance treatment of COPD in two decades," said David Zaccardelli, president and chief executive officer, Verona Pharma. "Since launching Ohtuvayre in August 2024 we have seen rapid and accelerating uptake in the U.S. We believe Merck's commercial footprint and industry-leading clinical capabilities will help accelerate the potential of Ohtuvayre to reach more patients living with COPD. This agreement will enable the strong launch trajectory of this important medicine and provides value to Verona Pharma shareholders."

Source: https://www.merck.com/news/merck-to-acquire-verona-pharma-expanding-its-portfolio-to-include-ohtuvayre-ensifentrine-a-first-in-class-copd-maintenance-treatment-for-adults-and-expected-to-drive-growth-into-the-next-dec/

Concentra to Acquire CARGO Therapeutics

SAN CARLOS, Calif., July 08, 2025 (GLOBE NEWSWIRE)-- CARGO Therapeutics, Inc. ("CARGO" or the "Company") (NASDAQ: CRGX), a biotechnology company that has focused on developing CAR T-cell therapies, today announced that it has entered into a definitive merger agreement (the "Merger Agreement") with Concentra Biosciences, LLC ("Concentra"), whereby Concentra will acquire CARGO for $4.379 in cash per share of CARGO common stock, par value $0.001 per share ("CARGO Common Stock"), plus one non-transferable contingent value right ("CVR"), which represents the right to receive: (i) 100% of the closing net cash of CARGO in excess of $217.5 million; and (ii) 80% of any net proceeds received within two years following closing from any disposition of certain of CARGO's product candidates that occurs within two years following closing, each pursuant to a contingent value rights agreement (the "CVR Agreement").

Following a strategic review process conducted with the assistance of CARGO's management and legal and financial advisors and other factors considered, the CARGO board of directors has unanimously determined that the acquisition by Concentra is in the best interests of all CARGO stockholders and has approved the Merger Agreement and related transactions (collectively, the "Transactions").

Pursuant and subject to the terms of the Merger Agreement, Concentra will commence a tender offer (the "Offer") by July 21, 2025, to acquire all outstanding shares of CARGO Common Stock. The closing of the Offer is subject to certain conditions, including the tender of CARGO Common Stock representing at least a majority of the total number of outstanding shares, the availability of at least $217.5 million of cash (net of transaction costs and other liabilities) at closing, and other customary closing conditions. Immediately following the closing of the Offer, CARGO will be acquired by Concentra, and all remaining shares not tendered in the Offer, other than shares owned directly or indirectly by Concentra or the Company or a subsidiary thereof or validly subject to appraisal, will be converted into the right to receive the same cash and CVR consideration per share as is provided in the Offer. CARGO officers, directors and certain Company stockholders holding approximately 17.4% of CARGO Common Stock in the aggregate have signed tender and support agreements under which such parties have agreed to tender their shares in the Offer and support the merger transaction. The merger transaction is expected to close in August 2025.

Source: https://investors.cargo-tx.com/news-releases/news-release-details/cargo-therapeutics-enters-agreement-be-acquired-concentra

Is Biopharma Dealmaking Getting Hot Again?

With pharma's finger on the M&A button, three of the biggest deals of the year are breadcrumbs that could lead to a full-on resurgence.

Michael Gibney, PharmaVoice, July 8, 2025 (excerpt)

Following years of relatively unsubstantial M&A in the biopharma industry, will 2025 be a long-awaited turning point? Signs from the first half of the year are starting to point that direction.

AbbVie's announcement last week that the pharma giant would pick up CAR-T biotech Capstan in a deal worth $2.1 billion gave investors and analysts hope that industry heavyweights are opening their pursestrings to fill gaps in the pipeline. After all, widespread patent cliffs like the one AbbVie faced a couple years ago with Humira necessitate a proactive approach.

As deals like these mount in 2025, the industry's appetite only grows, EY analysts said.

Last year was "a really tough year for M&A," said Ashwin Singhania, principal at EY-Parthenon life sciences, during a recent panel discussion. While deal volume was almost equal in 2024 to the year before, the value of those deals plummeted more than 50% in biopharma, according to an EY report in which analysts called 2024 a "reset year."

Over the last half-decade, the biggest drugmakers have (for the most part) opted for smaller, bolt-on acquisitions over dives into the deeper end of the M&A pool. While the tough environment persists, pharmas with cash to spend and upcoming patent cliffs have waited long enough to pull the trigger, said EY Americas life sciences leader Arda Ural.

"All in all, it continues to be a tough environment, but hopefully as the macro and policy clouds are lifting, it will give biopharma the confidence in their deal models to deploy capital on M&A," Singhania said. "In turn, that will open up other investment vehicles."

Source: https://www.pharmavoice.com/news/pharma-deals-2025-ey-jnj-sanofi-merck/752375/

The Looming "Patent Cliff" Facing Big Pharma

Hannah Kuchler and Patrick Temple-West, *Financial Times*, July 9, 2025 (excerpt)

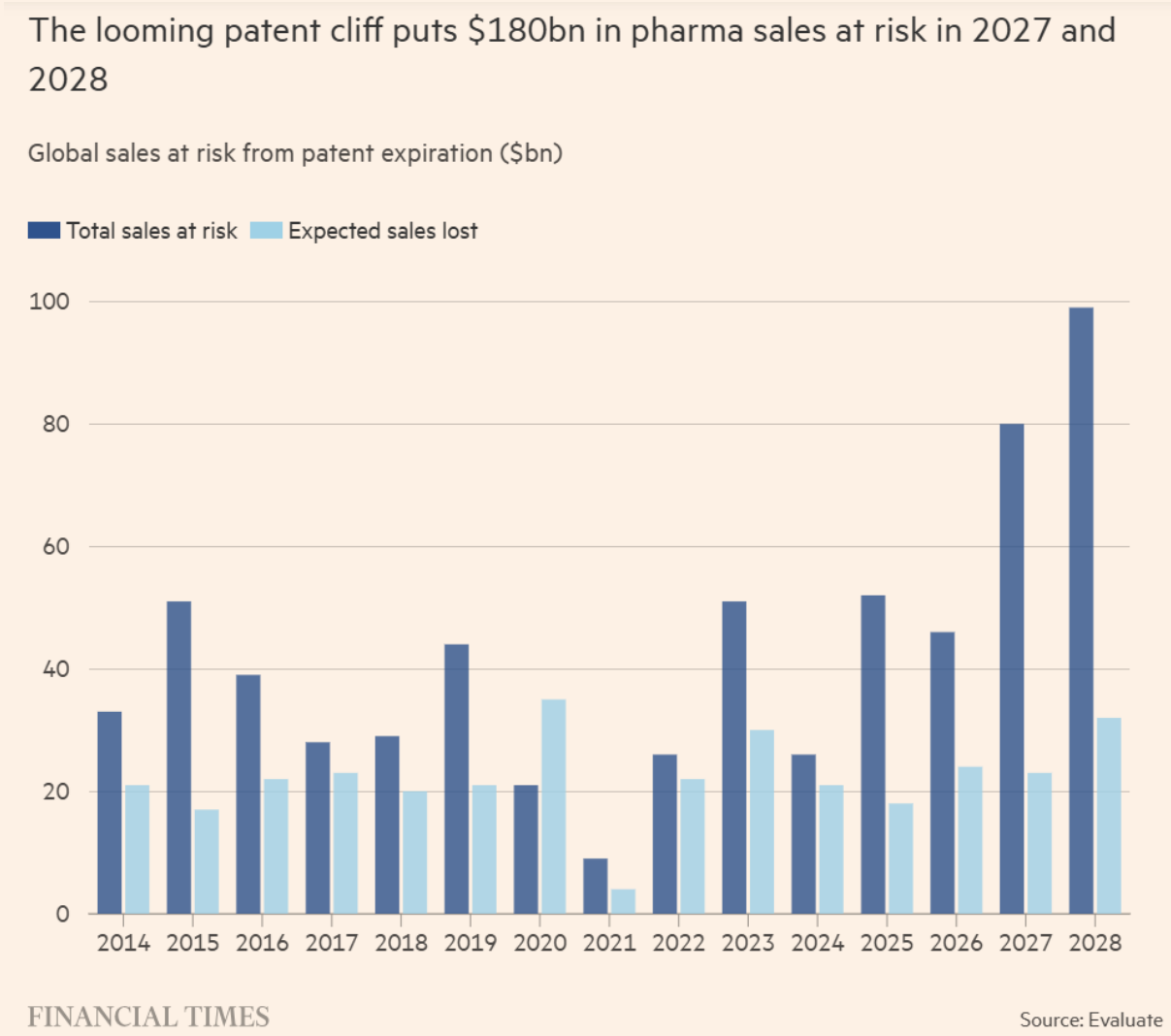
Every year, thousands of patients sit in doctors' offices with needles in their arms receiving a dose of a wonder drug called Keytruda. The cancer medicine is one of the world's best sellers, earning Merck $29.5bn in sales last year. But drip by drip, the US pharmaceutical company's time is running out.

In 2028 Keytruda's patent ends, allowing rivals to sell the same drug at a cheaper price. Investors are spooked and Merck's shares have sunk 35 per cent over the past 12 months.

Merck on Wednesday appeared to take a step towards addressing the looming Keytruda patent cliff. The company is closing in on a $10bn deal to buy London-based biotech Verona Pharma, which has an approved respiratory disease drug that analysts predict could generate peak annual sales of approaching $4bn.

Losing the intellectual property rights for blockbuster drugs is a long-standing ritual for pharmaceutical companies. Drugmakers can earn fortunes when new discoveries are first sold to patients. Governments grant them about 20 years of patent life per drug.

But up to half of that time can be used before the drug gets to market, during development. When the patent is up, competitors are allowed to release generic rivals, potentially wiping out billions of dollars of revenue for the original proprietor. Merck is not alone. The pharmaceutical industry is facing some of its steepest patent cliffs to date. Drugs worth about $180bn of revenue a year are going off patent in 2027 and 2028, according to research firm Evaluate Pharma, representing almost 12 per cent of the global market. Bristol Myers Squibb and Pfizer are also facing 2028 patent expirations for top-selling drugs.



Source: https://www.ft.com/content/360cb65b-a9ab-4fed-b8b3-7c34f2560938

AbbVie Licenses Glenmark Drug Candidate for $700 Million Upfront

NEW YORK, NY and NORTH CHICAGO, IL, July 10, 2025: IGI Therapeutics SA, a wholly owned subsidiary of New York-based Ichnos Glenmark Innovation, Inc. (IGI), and AbbVie (NYSE: ABBV) today announced an exclusive licensing agreement for IGI's lead investigational asset, ISB 2001, developed using IGI's proprietary BEAT® protein platform, for oncology and autoimmune diseases.

"Multispecifics including trispecific antibodies represent a new frontier in immuno-oncology with the potential to deliver deeper, more durable responses by engaging multiple targets simultaneously," said Roopal Thakkar, M.D., Executive Vice-President, Research and Development and Chief Scientific Officer, AbbVie. "This partnership with IGI reflects our unwavering commitment to advancing novel therapies for patients with multiple myeloma, a disease where significant unmet need remains despite recent progress."

"ISB 2001 exemplifies the potential of our BEAT® protein platform to generate effective multispecifics that may overcome resistance and improve outcomes in hard-to-treat cancers," said Cyril Konto, M.D., President and CEO of IGI. "This agreement marks a defining milestone in IGI's scientific journey and reflects our team's deep commitment to delivering meaningful therapies for patients. Our partnership with AbbVie accelerates ISB 2001's path to patients and sharpens our focus on advancing the next generation of BEAT®-enabled assets in oncology."

Under the terms of the agreement, AbbVie will receive exclusive rights to develop, manufacture, and commercialize ISB 2001 across North America, Europe, Japan, and Greater China. Subject to regulatory clearance, IGI will receive an upfront payment of $700 million and is eligible to receive up to $1.225 billion in development, regulatory, and commercial milestone payments, along with tiered, double-digit royalties on net sales.

Source: https://iginnovate.com/2025/07/09/ichnos-glenmark-innovation-igi-and-abbvie-announce-exclusive-global-licensing-agreement-for-isb-2001-a-first-in-class-cd38xbcmaxcd3-trispecific-antibody/

We've become accustomed to seeing nine digit upfronts for China molecules going to big pharma.

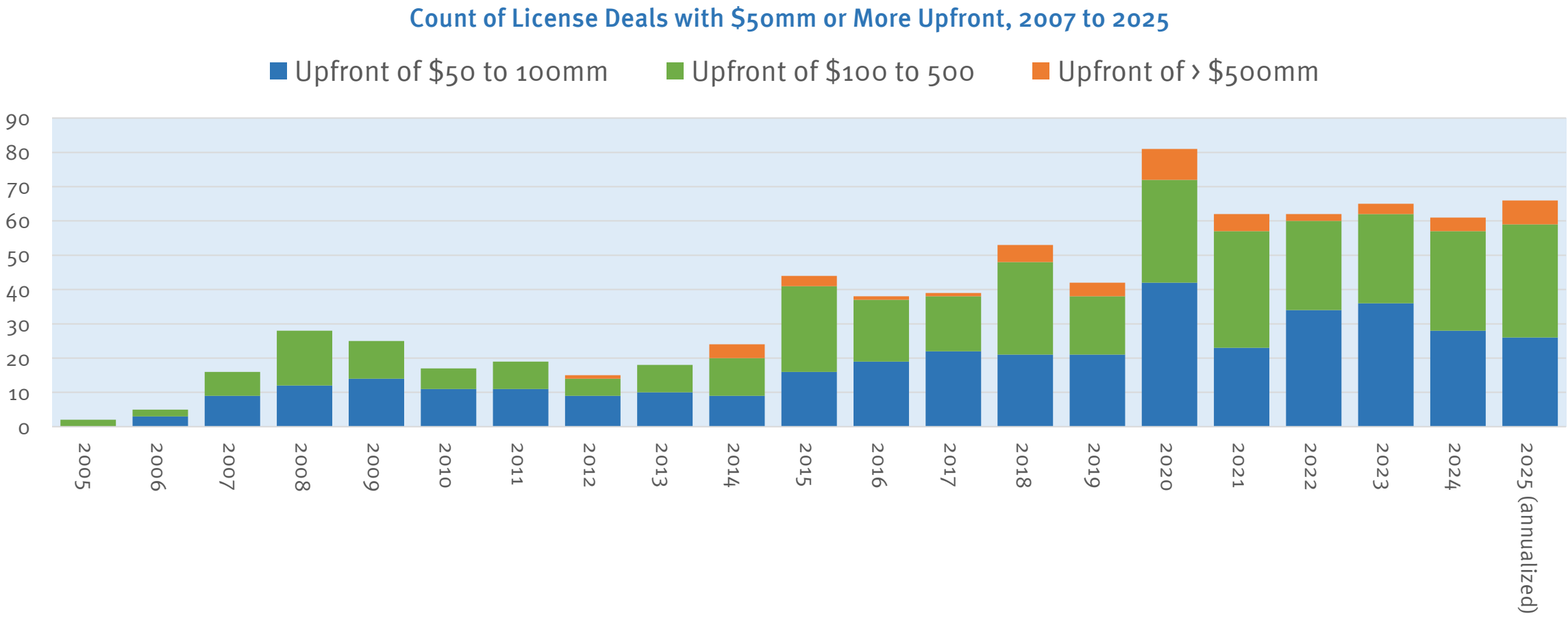
But now we are seeing a $700 million upfront for a molecule developed by a pharmaceutical company based in *India*.

Glenmark has invested heavily into its IGI innovation platform over the last decade and delivered stunningly good data for its triple t-cell engager at last year's ASH meeting in multiple myeloma.

In this deal AbbVie is signing up to develop and commercialize ISB 2001 for both multiple myeloma and autoimmune diseases.

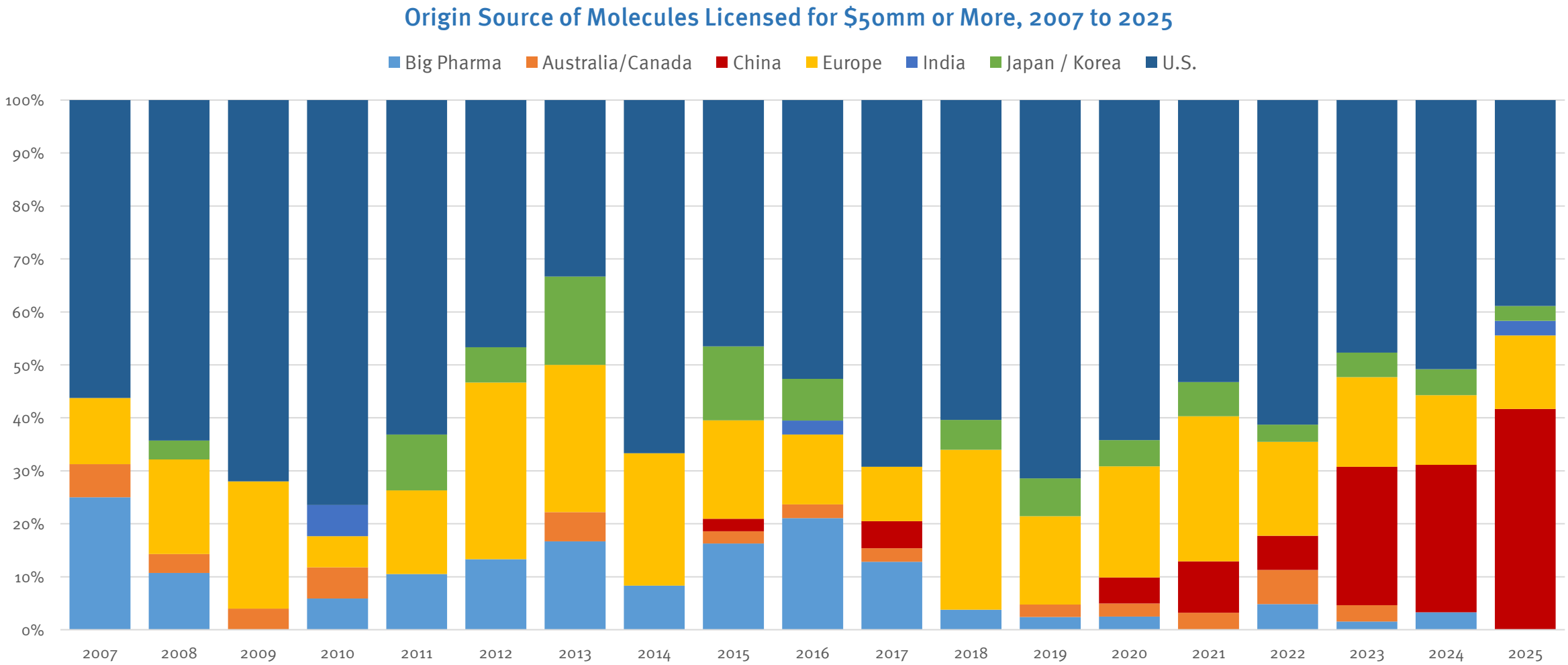
Count of $50mm+ Upfront License Deals in 2025 is In Line with Recent Years

There have been several quite large deals this year including the Glenmark/AbbVie deal, the BioNtech/BMS deal and the 3SBio / Pfizer deal.



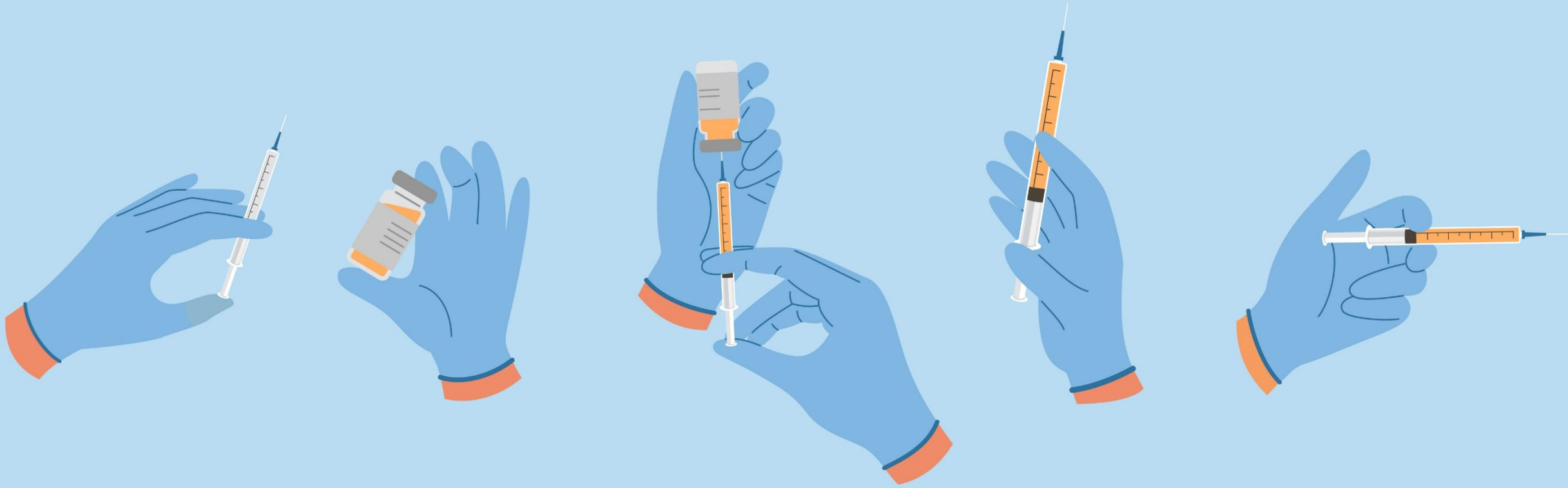
Source: Dealforma

Fewer and Fewer Molecules that are Licensed Out for $50 Million or More Upfront are From U.S. Licensors



Source: Dealforma

Industry Update

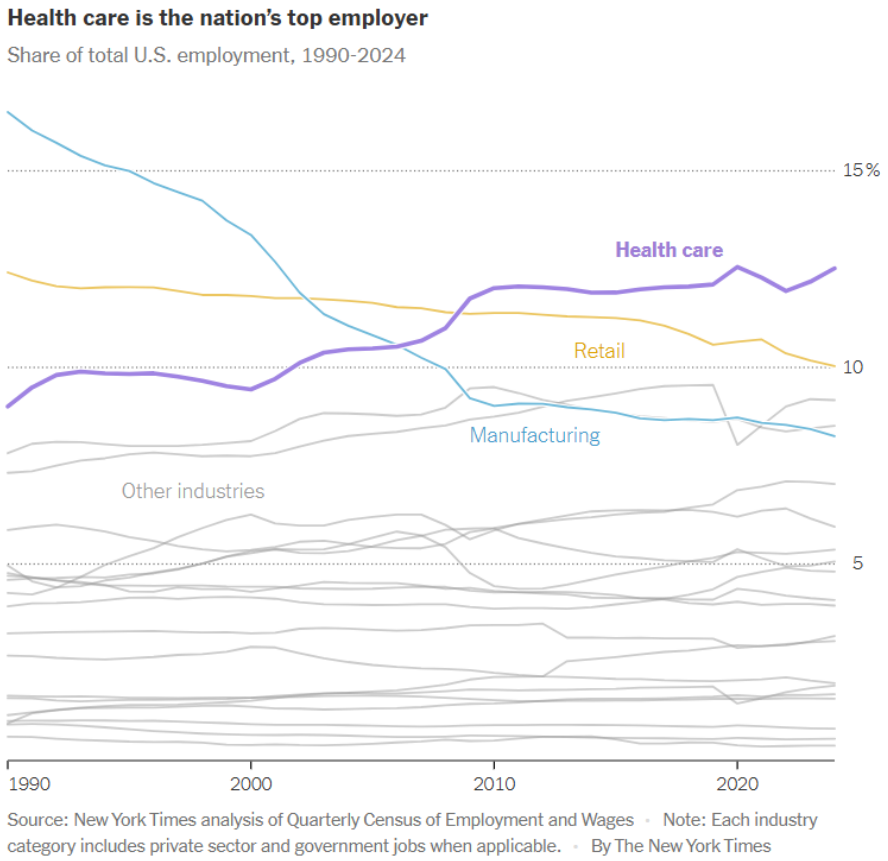


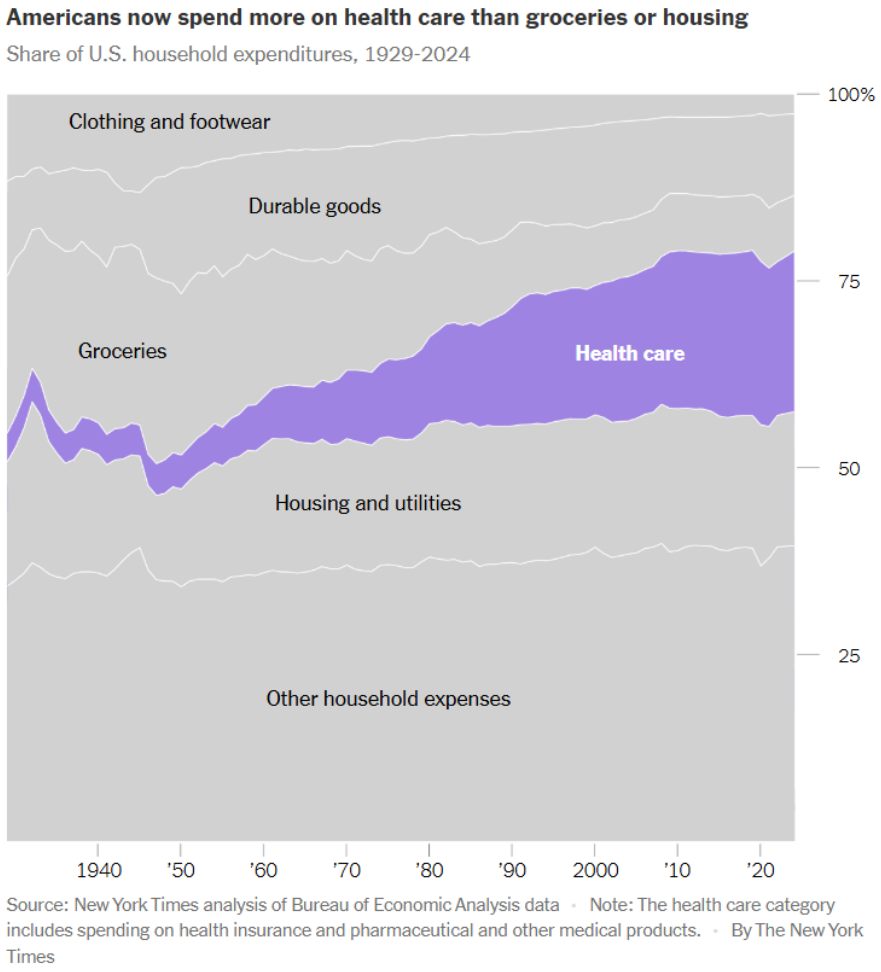
How Health Care Remade the U.S. Economy

Lynda DePillis and Christine Zhang, New York Times, July 3, 2025 (excerpt)

For years, the United States labor market has been undergoing a structural transformation. As jobs in manufacturing have receded, slowly but steadily, the health care industry has more than replaced them.

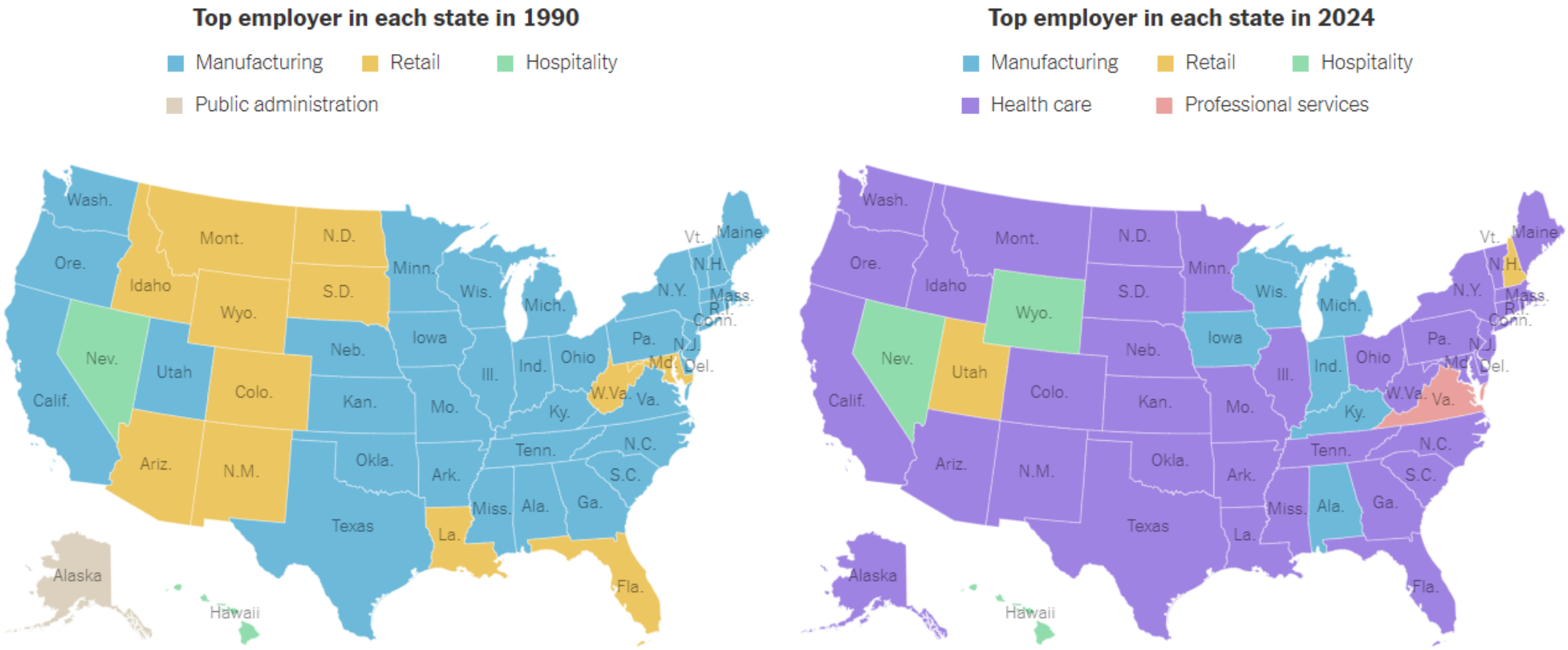
The change has been particularly visible over the past year, during which health care has been responsible for about a third of all employment growth, while other categories, like retail and manufacturing, have stayed essentially flat.





Source: https://www.nytimes.com/interactive/2025/07/03/business/economy/healthcare-jobs.html

How Health Care Remade the U.S. Economy (continued)



Source: New York Times analysis of Quarterly Census of Employment and Wages · Note: Each industry category includes private sector and government jobs when applicable. · By The New York Times

Source: https://www.nytimes.com/interactive/2025/07/03/business/economy/healthcare-jobs.html

The Culprit Impeding Drug Competition Is Not Who The Feds Expected

Sally Pipes, *Forbes*, July 10, 2025 (excerpt)

The Federal Trade Commission and U.S. Department of Justice recently kicked off a series of listening sessions to examine barriers to competition in the drug industry.

The title of the first session—"Anticompetitive Conduct by Pharmaceutical Companies"—made it seem that regulators would chiefly investigate biotech firms. Yet by the end, panelists had refocused the spotlight onto pharmacy benefit managers—and provided striking evidence that PBMs, not biotech companies, deserve most of the blame for the anticompetitive practices that lead to high drug prices.

If the FTC and DOJ heed the panelists' warnings and crack down on this misbehavior, it could tangibly reduce drug costs for patients.

PBMs decide which medicines are included on insurers' formularies, or lists of covered drugs. That gatekeeping authority gives PBMs the power to negotiate prices with manufacturers and secure rebates.

PBMs claim to use those rebates to reduce costs for patients. But the rebate structure actually gives them a strong incentive to prefer higher-priced drugs—even when cheaper and equally effective alternatives are available. That's because their earnings are generally determined as a percentage of a drug's list price.

In cases when PBMs do include biosimilars in their formularies, they're often artificially pricey "private-label" drugs affiliated with the PBMs themselves.

Source: https://www.forbes.com/sites/sallypipes/2025/07/10/the-culprit-impeding-drug-competition-is-not-who-the-feds-expected/

Why Will Health Spending Growth Increase Even While Insurance Coverage Declines?

Thomas Miller, American Enterprise Institute, Post, July 10, 2025 (excerpt)

Late last month, actuaries at the Centers for Medicare and Medicaid Services released their latest projections of 10-year national health care spending trends (from 2024–2033). The June 25 Health Affairs study suggests some manufactured surprise in highlighting "Despite Insurance Coverage Declines, Health to Grow as Share of GDP."

Figuring out the most likely causal chain requires actually reading the data and looking for the lost keys beyond the nearest lamppost of insurance coverage levels. The more powerful underlying causes are Medicare spending growth, increased health care utilization (not health care price inflation), and the continuing long-term decline in the share of health spending paid out of pocket. Declines in the recent high levels of health insurance coverage are relatively modest, at least as projected before final passage last week of Medicaid and ACA marketplace provisions in the Big Beautiful Bill (BBB).

In the near term, annual growth in health spending is up noticeably—8.2 percent in 2024, and a projected 7.1 percent in 2025. Despite some later cooling of those recent highs over the rest of the projection period, national health care spending will continue to outpace GDP growth, 5.8 percent vs. 4.3 percent annually over the entire ten-year period.

The simple math then produces a higher share of the national economy absorbed by the health care sector—growing from 17.6 percent of GDP in 2023 to 20.3 percent in 2033. Caution: Projections are mostly guesses that the future will be roughly similar to the past, with some adjustment for recent years' variations from normal patterns. Actuaries also have to operate within the bounds of current law, rather than assume that better, or worse, policies will be enacted and administered to avert (or accelerate) fiscal collisions ahead. For example, the latest 10-year projections also could not take into account then-yet-to-be-approved changes in health policy made by this month's passage of the BBB via budget reconciliation procedures. (More on that later). However, the projections' reliance on current law also includes expiration next year of enhanced tax subsidies for the Affordable Care Act's individual coverage exchange plans.

Source: https://www.aei.org/health-care/why-will-health-spending-growth-increase-even-while-insurance-coverage-declines/

‘Weak Evidence’ and an ‘Unpleasant’ Odor: FDA Sheds Light on Drug Refusal Process

James Waldron and Frasier Kansteiner, *FiercePharma*, July 11, 2025 (excerpt)

When the FDA unexpectedly uploaded around 200 drug rejection letters this week, the regulator provided a rare glimpse into the high-stakes discussions that decide whether a medicine will ever make it to market.

The FDA claimed it released the complete response letters (CRLs) on Thursday morning as part of an effort to “modernize and increase transparency” at the agency. It’s certainly true that until now, we’ve typically had to rely on the companies themselves to share the reasons for their applications being rejected—assuming they chose to go into any detail at all.

In this context, the haul of documents that have suddenly come to light offers a tantalizing insight into not only the rationale the FDA employs during its reviews, but also the language the agency uses to communicate these decisions.

But if you don’t have a spare weekend to read through hundreds of pages of letters then have no fear, the Fierce Biotech and Fierce Pharma teams have trawled through the documents ourselves and selected some of the examples that we found the most enlightening.

A ‘concerning reduction’ in growth

Pfizer’s rare disease strategy suffered an unexpected setback in 2022 when the FDA rejected Ngenla (somatrogon), a potential treatment for pediatric growth hormone deficiency. The CRL came as a surprise—given the drug had already been approved in Japan, Australia and Canada—and Pfizer’s announcement offered no insight into the agency’s decision. But the FDA’s letter now reveals that one of the key reasons for the agency’s decision was a single individual in a phase 3 open-label trial who developed a “concerning reduction” in annualized height velocity (AHV)—in other words, their growth had slowed.

Source: https://www.fiercepharma.com/pharma/weak-evidence-and-unpleasant-odors-fda-sheds-light-drug-refusal-process

'A Career of Meaning': Chiron Co-Founder Bill Rutter Dies at 97

Ron Leuty, *San Francisco Business Times*, Jul 12, 2025 (excerpt)

William J. "Bill" Rutter — who left a top post at UC San Francisco to shape the biotech industry by co-founding legendary East Bay company Chiron Corp. — died Friday at 97.

Rutter was a well-regarded pioneer on both the academic and commercial sides of biotech. His recruitment by UCSF in the 1960s was a seminal moment that helped establish the graduate-level health care institution as a leading producer of cutting-edge medical research. But it was his founding of Emeryville-based Chiron with Ed Penhoet and Pablo Valenzuela in 1981 that solidified his standing as a biotech legend.

Because of his leading academic position, Rutter's jump to the commercial side of biotech had a long-reaching effect. It effectively opened the door for other academics to pursue for-profit companies that spun out their research.

The company ultimately grew to more than 5,000 employees and revenue of nearly $2 billion, paving the way for groundbreaking work in cancer and hepatitis C. Chiron in 2000 received the Lasker Award for Clinical Medical Research — known as the "American Nobel" — for its hepatitis C research and development of new blood-screening technologies. "Most truly novel approaches go through stages," Rutter told the Business Times in 2008. "There's a technically rich stage where the risk of failure is higher. There's not a high cost, but it needs the maturity, time and a small number of people to muddle through before they find a solution."

Bill Rutter was best known for being involved in the description and discovery of the Hepatitis C virus although Charles Rice and collaborators also get major credit. He was among the first to sequence the HIV virus. Rutter remained interested in virology throughout his life and made major contributions to biology through Chiron, a firm he co-founded. We had the honor of interacting with him well into his advanced age and can attest that his scientific curiosity and gusto never waned.

Source: https://www.bizjournals.com/sanfrancisco/news/2025/07/12/bill-rutter-chiron-ucsf-died.html

Ultragenyx, Mereo Plummet After Late-Stage Trial for Rare Genetic Disorder Appears To Fall Short

Tristan Manalac, *Biospace*, July 10, 2025 (excerpt)

Partners Ultragenyx and Mereo BioPharma saw their stocks drop by 21% and 30%, respectively, after announcing that the Phase II/III study of their osteogenesis imperfecta candidate will proceed to final analysis, implying it did not show sufficiently strong results at an interim analysis.

A Phase II/III study of Ultragenyx and Mereo BioPharma's investigational osteogenesis imperfecta therapy UX143 will proceed to its final analysis, suggesting the trial fell short of an efficacy bar that would have led the companies to end the trial ahead of schedule.

Writing to investors on Thursday morning, analysts at Wiliam Blair said the announcement implies that at the second interim analysis the trial, dubbed Orbit, "did not meet the minimal p-value threshold of $p<0.01$ to end the study early."

The Orbit announcement came after markets closed on Wednesday. In premarket trading Thursday, Ultragenyx was down by 21% and Mereo by 30%.

To preserve the integrity of the study, the partners did not reveal specific efficacy data on Wednesday, only stating that the data monitoring committee for Orbit found that UX143 had an "acceptable" safety profile. The lack of information, according to William Blair, makes it "challenging to speculate why and by how much the second interim [analysis] did not achieve its threshold.

Source: https://www.biospace.com/drug-development/ultragenyx-mereo-plummet-after-late-stage-trial-for-rare-genetic-disorder-appears-to-fall-short

Microglia Replacement Halts the Progression of Microgliopathy in Mice and Humans

J. Wu et.al., *Science*, July 10, 2025 (excerpt)

Microglia are important immune cells in the central nervous system (CNS). The dysfunction of microglia contributes to various CNS disorders. CSF1R is primarily expressed in microglia and is essential for their survival and function. Biallelic CSF1R mutations cause the congenital absence of microglia and are perinatally lethal in both humans and mice, whereas monoallelic mutations cause CSF1R-associated microgliopathy (CAMP), a major form of adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP). ALSP is a fatal disease with no current curative treatment.

Because pathogenic mutations in microglia-specific CSF1R are the cause of ALSP, we reasoned that replacing CSF1R-deficient microglia with wild-type (WT) microglia would halt disease progression. We previously developed efficient strategies for microglia replacement, currently collectively termed microglia intervention strategy for therapy and enhancement by replacement (MISTER), which have since informed and inspired subsequent studies in the field. We thus hypothesized its therapeutic potential for ALSP.

Although traditional bone marrow transplantation (tBMT) alone typically does not achieve efficient microglia replacement in healthy brains, the inherent CSF1R deficiency creates a competitive disadvantage for the recipient's resident microglia, enabling tBMT to achieve effective replacement in our ALSP mouse model and confer therapeutic benefits comparable to those of Mr BMT.

To validate clinical relevance, we conducted tBMT-based treatment in eight individuals with ALSP. By using noninvasive PET imaging with 18F-FDG, we demonstrated increased glucose metabolism in the brain. Notably, MRI and clinical evaluations indicated halted disease progression, preserved motor function, and stabilized cognitive abilities during a 24-month follow-up. This study also provides a mechanistic explanation for a prior clinical case in which an individual with ALSP, initially misdiagnosed with adult-onset metachromatic leukodystrophy, exhibited long-term stabilization after tBMT.

Source: https://www.science.org/doi/10.1126/science.adr1015

Selective Remodelling of the Adipose Niche in Obesity and Weight Loss

Antonio Miranda et.al., *Nature*, July 9, 2025 (excerpt)

Weight loss significantly improves metabolic and cardiovascular health in people with obesity1-3. The remodelling of adipose tissue (AT) is central to these varied and important clinical effects4. However, surprisingly little is known about the underlying mechanisms, presenting a barrier to treatment advances.

Here we report a spatially resolved single-nucleus atlas (comprising 171,247 cells from 70 people) investigating the cell types, molecular events and regulatory factors that reshape human AT, and thus metabolic health, in obesity and therapeutic weight loss.

We discover selective vulnerability to senescence in metabolic, precursor and vascular cells and reveal that senescence is potently reversed by weight loss. We define gene regulatory mechanisms and tissue signals that may drive a degenerative cycle of senescence, tissue injury and metabolic dysfunction. We find that weight loss reduces adipocyte hypertrophy and biomechanical constraint pathways, activating global metabolic flux and bioenergetic substrate cycles that may mediate systemic improvements in metabolic health. In the immune compartment, we demonstrate that weight loss represses obesity-induced macrophage infiltration but does not completely reverse activation, leaving these cells primed to trigger potential weight regain and worsen metabolic dysfunction.

Throughout, we map cells to tissue niches to understand the collective determinants of tissue injury and recovery. Overall, our complementary single-nucleus and spatial datasets offer unprecedented insights into the basis of obese AT dysfunction and its reversal by weight loss and are a key resource for mechanistic and therapeutic exploration.

Source: https://www.nature.com/articles/s41586-025-09233-2

Key Miranda et al. paper illustrations.

Fig. 4: Stressed cells form a spatial niche and enrich for stress-associated signalling pathways.

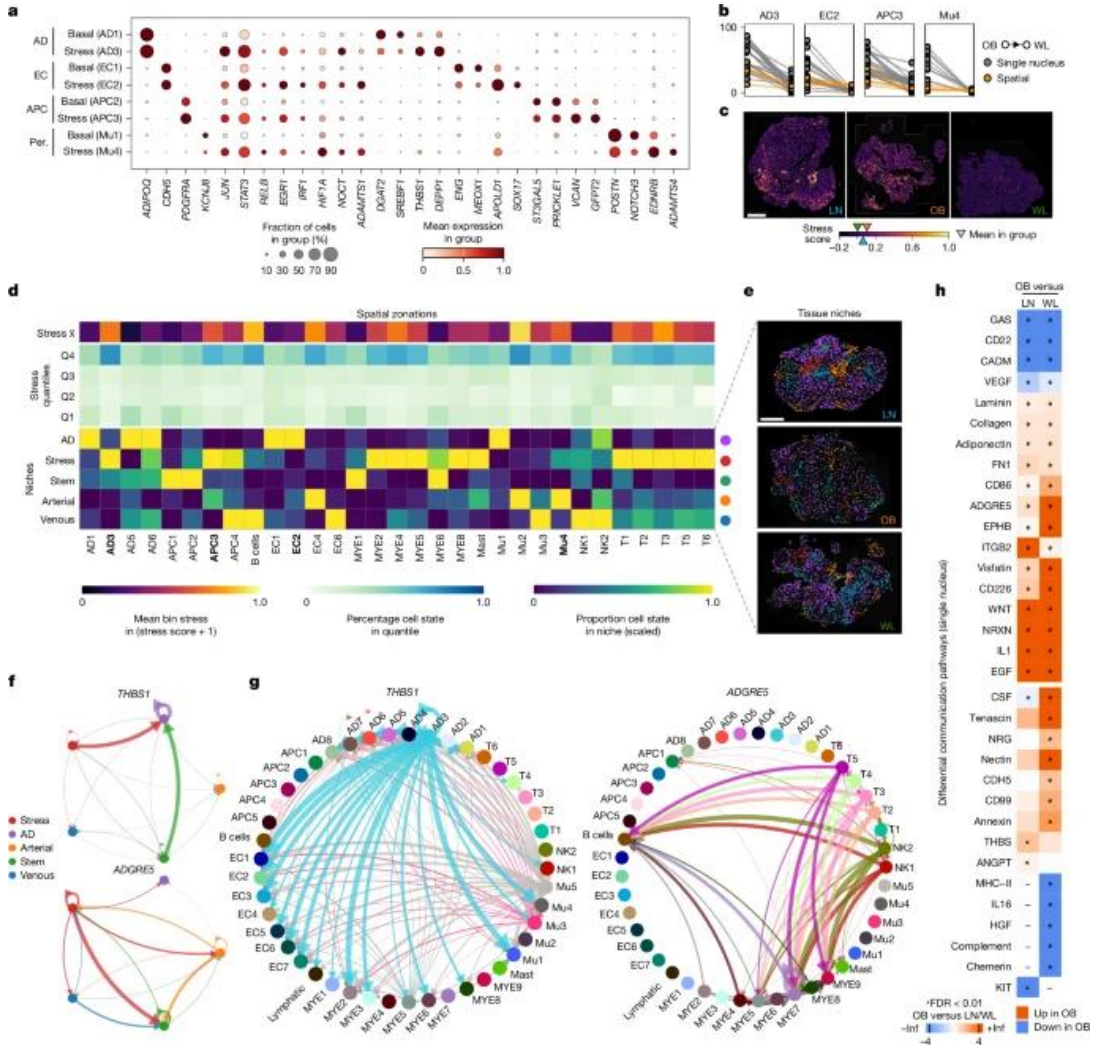
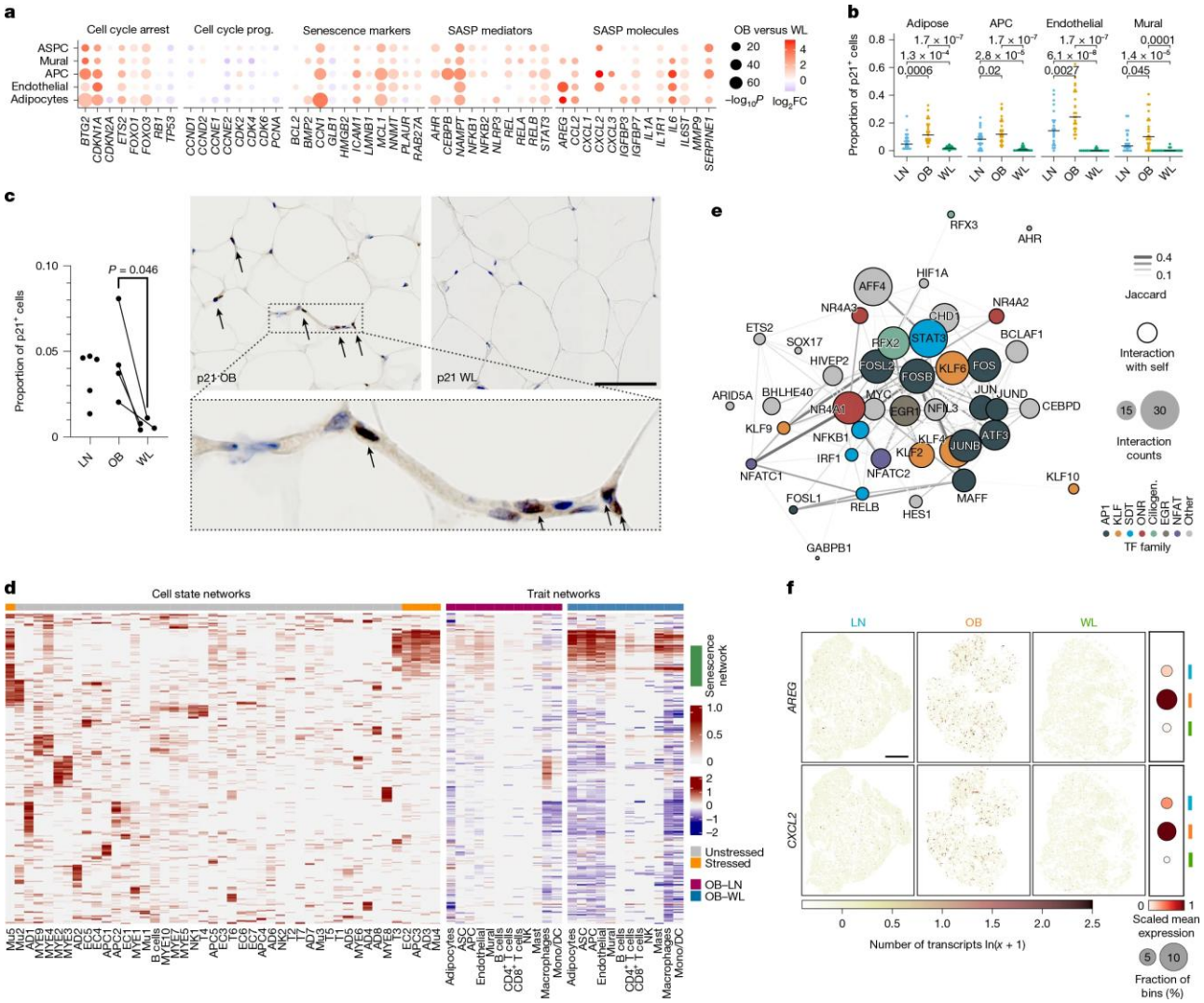


Fig. 5: WL potently reverses senescence and its mediators.



Source: https://www.nature.com/articles/s41586-025-09233-2

Long-Term Obesity and Biological Aging in Young Adults

Paulina Correa-Burrows et.al., *JAMA Network Open*, July 10, 2025 (excerpt)

In this case-control study of 205 participants from a Chilean prospective cohort, long-term obesity was associated with the expression of molecular aging signatures during young adulthood in females and males, including epigenetic modifications and telomere shortening. Exposure to long-term obesity was associated with epigenetic age exceeding chronological age by a mean of 15% to 16%, and in some cases, this difference reached 48%.

In the sample of 205 adults (mean [SD] age, 28.9 [0.6] years; 100 females [49%]), 89 (43%) were in group 1, 43 (21%) in group 2, and 73 (36%) in group 3. Mean (SD) obesity duration was 12.9 (4.8) years in group 2 and 26.6 (2.3) years in group 3. Long-term obesity was associated with adulthood expression of biomarkers denoting antagonistic and integrative aging hallmarks, including mean (SD) hs-CRP (1.69 [2.1] vs 3.67 vs 4.24 [2.4] mg/L; $P < .001$; $f = 0.57$ [95% CI, 0.44-0.70]) and IL-6 (log, 0.69 [0.5] vs 1.03 [0.4] vs 0.99 [0.4]; $P < .001$; $f = 0.53$ [95% CI, 0.41-0.62]), as well as FGF-21, IGF-1, IGF-2, apelin, and irisin. Cohen *f* coefficient indicated a large effect size for the association of long-term obesity with adulthood expression of these markers.

In this multiple-events case-control study, long-term obesity was associated with the expression of biochemical aging markers in adults aged 28 to 31 years, consistent with epigenetic alterations, telomere attrition, chronic inflammation, impaired nutrient sensing, mitochondrial stress, and compromised intercellular communication.

Table 2. Epigenetic Age–Related Phenotype of Participants by BMI Trajectory

	Group (N = 205)[a]			Between-group difference[b]	Cohen *f* (95% CI)[c]
	1 (n = 89)	2 (n = 43)	3 (n = 73)		
Chronological age, y	28.9 (0.8)	28.7 (0.6)	28.8 (0.8)	NS	NA
LTL, kb	8.01 (0.36)	7.46 (0.32)	7.42 (0.26)	ABB	0.81 (0.68-0.95)
Horvath clock					
Age, y	28.5 (2.5)	34.1 (3.8)	34.5 (4.6)	ABB	0.71 (0.58-0.84)
Acceleration, y	−0.4 (2.5)	4.4 (3.7)	4.7 (4.2)	ABB	0.77 (0.64-0.90)
Acceleration, %	−1.4 (8.6)	15.2 (13.2)	16.4 (14.1)	ABB	0.77 (0.63-0.91)
GrimAge clock					
Age, y	26.3 (3.5)	31.6 (3.7)	32.5 (3.9)	ABB	0.65 (0.52-0.78)
Acceleration, y	−2.8 (3.5)	2.2 (3.6)	3.1 (3.8)	ABB	0.71 (0.58-0.85)
Acceleration, %	−10.2 (1.2)	7.7 (1.3)	10.7 (1.3)	ABB	0.71 (0.58-0.85)

Abbreviations: BMI, body mass index; LTL, leukocyte telomere length; NA, not applicable; NS, not significant.

[a] Values for the main outcome, expressed as mean (SD). Models were adjusted for sex and the interaction of sex with BMI trajectory across the life course. Group 1 participants always had a BMI in the healthy range, group 2 had obesity starting in adolescence and remaining into adulthood, and group 3 had obesity in early childhood and remaining into adulthood.

[b] Analysis of covariance with Tukey adjustment (Tukey post hoc analysis for between-group differences). A indicates group 1; and B, group 2; and C, group 3. ABB indicates that group 1 had values significantly different from those of groups 2 and 3, while the mean values in groups 2 and 3 did not differ.

[c] The effect size for the difference was computed as the Cohen *f* coefficient. A small effect size was Cohen *f* of 0.10; moderate, 0.25; and large, 0.40.

Source: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2836386

GPR146 Facilitates Blood Pressure Elevation and Vascular Remodeling via PIEZO1

Zhenzhen Chen et.al., *Circulation Research*, July 10, 2025 (excerpt)

Hypertension is a prevalent chronic disease worldwide. Elevated hydrostatic pressure (HP) is the main feature of hypertension. GPCRs (G-protein–coupled receptors) are crucial for vascular tone and a significant pharmacological target for drug development. Here, we aimed to identify the key GPCR under high HP, and explore its role and mechanism in hypertension and vascular remodeling.

First, RNA-seq was performed under high HP and identified the highly expressed GPCR-GPR146. Furthermore, global knockout GPR146 mice, vascular smooth muscle cell (SMC)–specific knockin and knockout GPR146 mice were used to explore its function in hypertension. Next, an HP loading system ex vivo was established to evaluate the role of GPR146 in response to HP. Vascular SMC–specific Piezo1 mice were constructed to investigate the relationship between GPR146 and PIEZO1.

Under high HP, we identified a highly expressed GPCR-GPR146 in vascular SMCs by RNA-seq and confirmed it in the arterial media of patients with hypertension and animal models. Functionally, overexpression or deletion of Gpr146 in SMCs demonstrated that GPR146 facilitated vascular contraction, promoted vascular SMCs phenotype switching from a contractile phenotype to synthetic phenotype and proinflammation phenotype, and led to blood pressure elevation, vascular remodeling, and cardiac hypertrophy aggravation. In vitro, GPR146 was upregulated in an HP-dependent manner. Mechanistically, GPR146 is a Gαs-coupled GPCR activating the cAMP-CREB1 (cAMP response element–binding protein 1) signaling cascade. Notably, GPR146 upregulated PIEZO1 expression by enhancing CREB1 binding to the PIEZO1 promoter region. Piezo1 deletion in SMCs blocked Gpr146-induced blood pressure elevation and vascular dysfunction. GPR146 neutralization antibody injection markedly alleviates angiotensin II–induced hypertension and vascular remodeling.

Collectively, GPR146 coupled with Gαs and activating the cAMP-CREB1-PIEZO1 signaling pathway contributes to hypertension and vascular remodeling. Blocking GPR146 is an effective therapeutic strategy for hypertension.

Source: https://www.ahajournals.org/doi/10.1161/CIRCRESAHA.125.326288

Metabolic Reprogramming with Aging Drives Cancer

SCIENCE ADVANCES | RESEARCH ARTICLE July 11, 2025

BIOPHYSICS

Proteins with cognition-associated structural changes in a rat model of aging exhibit reduced refolding capacity

Haley E. Tarbox[1], Audrey Branch[2], Stephen D. Fried[1,3]*

Cognitive decline during aging represents a major societal burden, causing both personal and economic hardship in an increasingly aging population. Many studies have found that the proteostasis network, which functions to keep proteins properly folded, is impaired with age, suggesting that there may be many proteins that incur structural alterations with age. Here, we used limited proteolysis mass spectrometry, a structural proteomic method, to globally interrogate protein conformational changes in a rat model of cognitive aging. Specifically, we compared soluble hippocampal proteins from aged rats with preserved cognition to those from aged rats with impaired cognition. We identified a couple hundred proteins as having undergone cognition-associated structural changes (CASCs). We report that CASC proteins are substantially more likely to be nonrefoldable than non-CASC proteins, meaning that they typically cannot spontaneously refold to their native conformations after being chemically denatured. These findings suggest that noncovalent, conformational alterations may be general features in cognitive decline.

Source: https://www.science.org/doi/epdf/10.1126/sciadv.adt3778

Cancer Progression Through the Lens of Age-Induced Metabolic Reprogramming

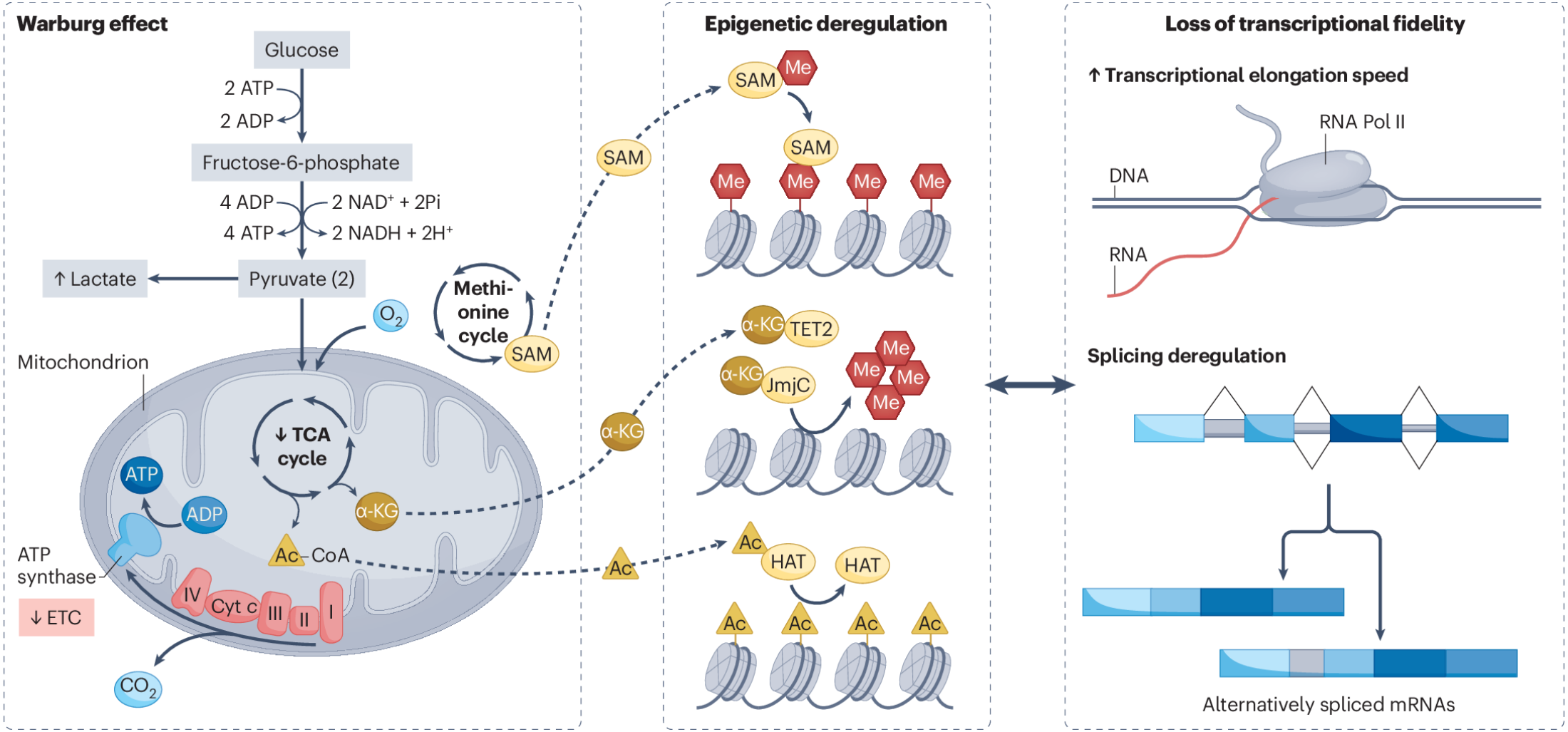
Felicia Lazure and Ana P. Gomes, *Nature Reviews Cancer*, July 11, 2025 (excerpt)

Ageing is an important risk factor for cancer incidence and augments cancer progression. A shared hallmark of ageing and cancer is metabolic reprogramming, which has been suggested to be not only a cause but also a consequence of ageing. Strikingly, many age-regulated pathways are known to also drive tumour progression, suggesting that metabolic reprogramming connects ageing and tumorigenic processes and shapes whether malignant phenotypes manifest, thrive and evolve. With the rising average age of the world population, understanding how age-related changes in the body influence cancer progression is of paramount importance. In this Perspective, we discuss the metabolic changes that occur with ageing and their potential links with tumour initiation and progression and the development of metastatic disease. Finally, we discuss age-induced metabolic divergences that cause racial disparities and their consequences for the tumorigenic process.

Metabolic reprogramming is a fundamental aspect of processes that commit cancer cells to a specific fate and that sustain their growth and survival. Consequently, metabolic flexibility is an essential aspect of tumour initiation, progression and metastatic disease. Importantly, the metabolic rewiring of cancer cells is conditioned by the metabolic landscape of their microenvironment, by their localization in the body, and ultimately by the biology of the patient. Here, we propose that the distinct metabolic landscapes imposed by old age have considerable consequences for cancer. When put into context, a large body of data supports this idea and clearly demonstrates that old age changes the intrinsic metabolic features of cancer cells, as well as their interactions with adjacent tissues, different environments of the metastatic cascade, organ systems and the metabolism of the patient, which collectively dictate cancer cell fate. Although the concepts highlighted herein point to considerable metabolism-mediated consequences of ageing on cancer, including racial disparities in cancer risk and prognosis, they only skim the surface, and a substantial amount of work is needed to solidify our emerging understanding of cancer through the lens of ageing physiology.

Source: https://www.nature.com/articles/s41568-025-00845-4

Lazure and Gomes: Cancer progression through the lens of age-induced metabolic reprogramming



Within the cell of origin, the Warburg effect is a hallmark of ageing that is sufficient to fuel tumorigenesis. Such age-related metabolic shifts may also promote Fe tumorigenesis via their effect on epigenetics. For example, methionine cycle-derived *S*-adenosylmethionine (SAM) mediates DNA and histone methylation, tricarboxylic acid (TCA) cycle-derived α-ketoglutarate (α-KG) controls demethylase function, and acetyl-coenzyme A (acetyl-CoA) contributes to histone acetylation. Ageing is also associated with loss of transcriptional fidelity caused by an increase in RNA polymerase II (RNA Pol II) elongation speed, by deregulated RNA splicing and by epigenetic erosion, which respond to changes in host metabolism. The double-sided arrow indicates the bidirectional and interdependent relationship between epigenetic and transcriptional deregulation. Ac, acetyl group; Cyt *c*, cytochrome *c*; ETC, electron transport chain; HAT, histone acetyltransferase; JmjC, Jumonji domain-containing; Me, methyl group; TET, ten-eleven translocation.

Source: https://www.nature.com/articles/s41568-025-00845-4

Disclosure

STIFEL | Healthcare

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