Biopharma Market Update

April 14, 2025

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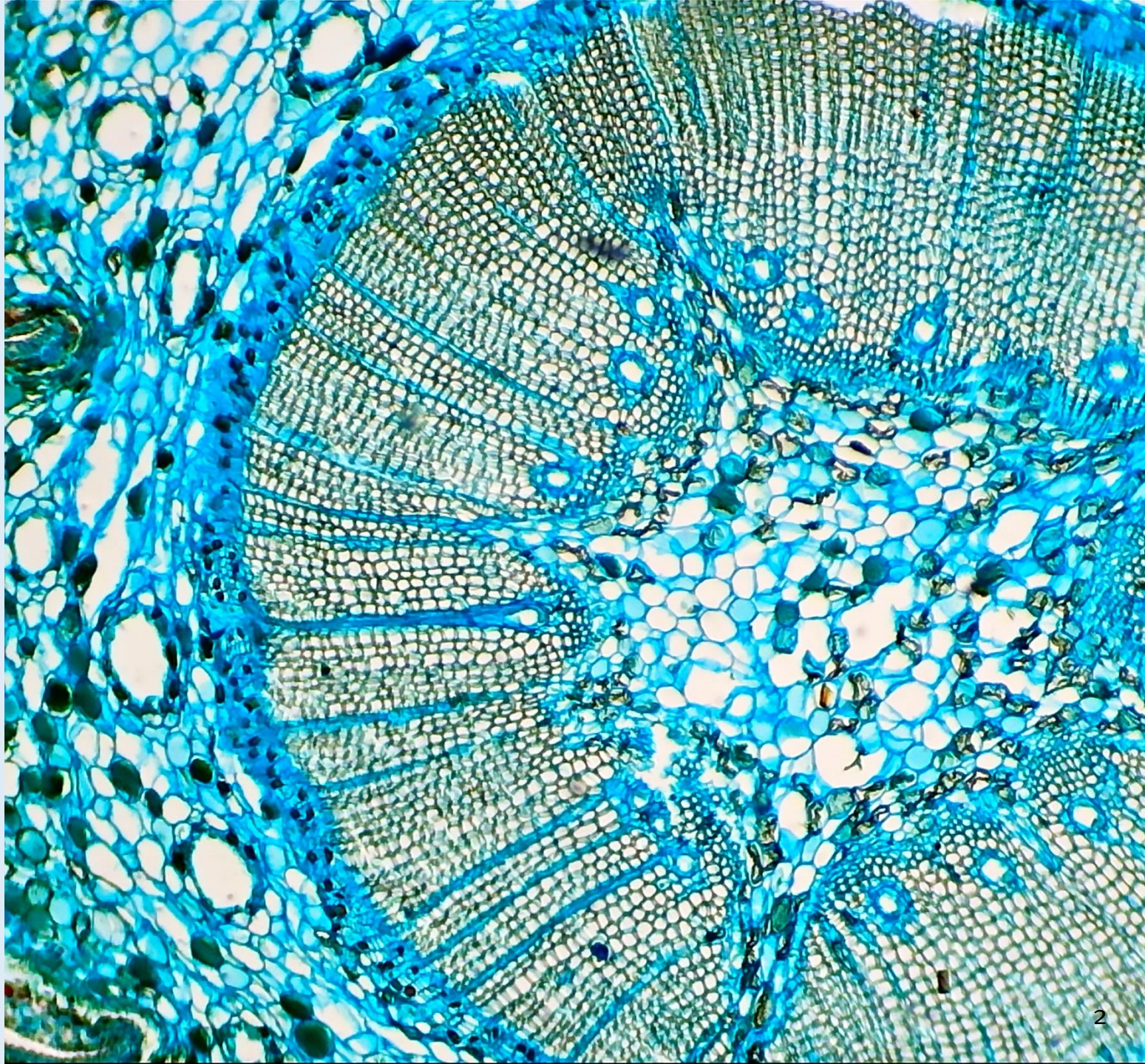

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[July 8, 2024]

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2024 Biotech Outlook

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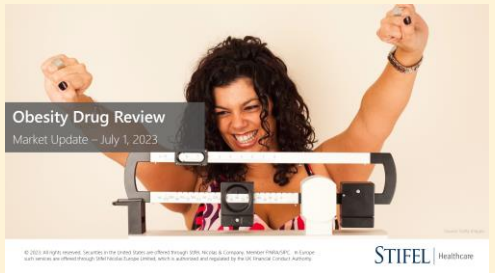
Obesity Drug Review



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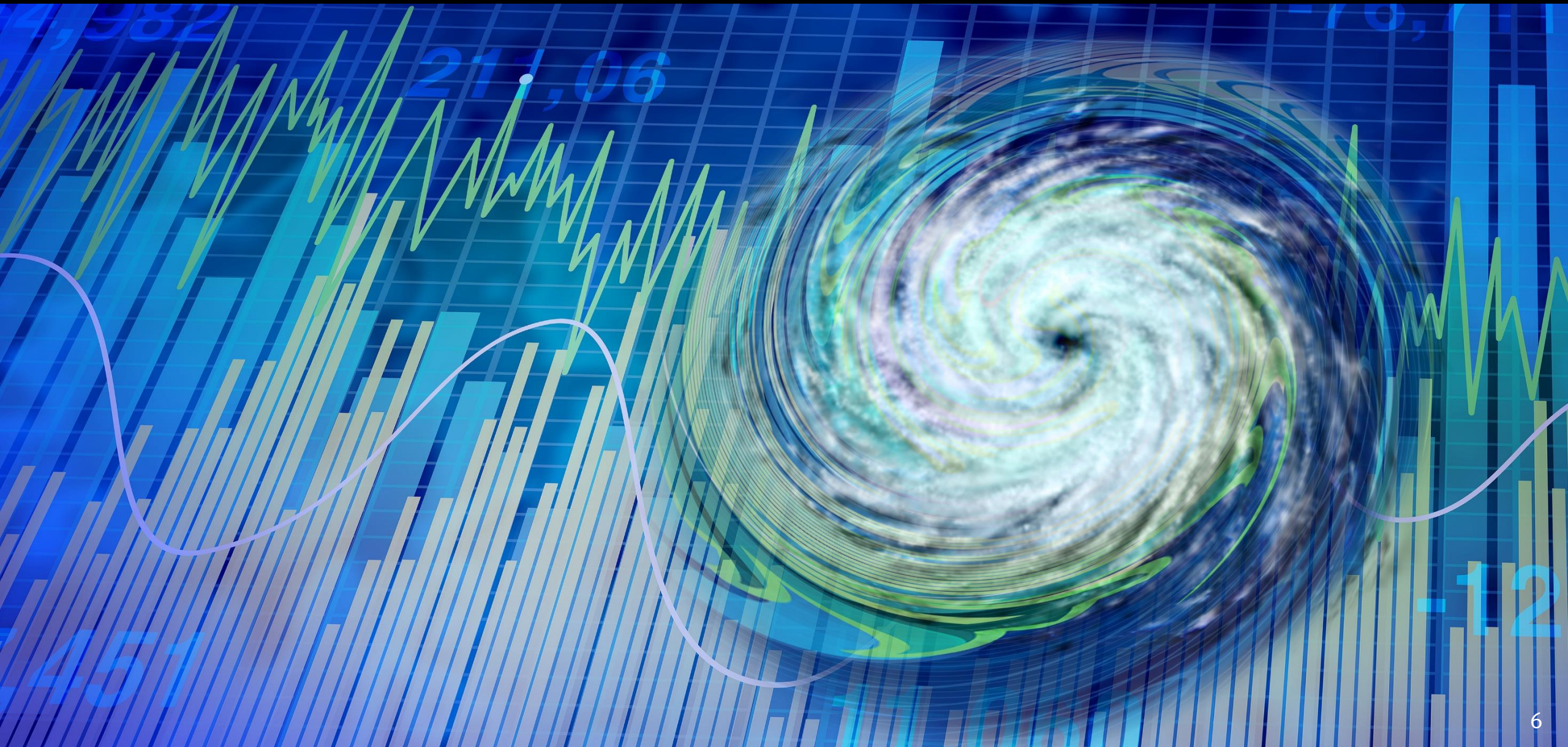
Macro / Tariffs Update



Very Good Inflation News Last Week

Alicia Wallace, "Another inflation report underlines the strength of the US economy before Trump's tariff chaos," *CNN*, April 11, 2025 (excerpt)

US wholesale prices fell last month, new data showed Friday, an indication that inflationary pressures weren't necessarily building before they reach the consumer.

The better-than-expected Producer Price Index reading — which showed that the prices paid to producers **fell 0.4%** in March from the month before and slowed sharply to an annual rate of 2.7%, from 3.2% — provides a snapshot *before* President Donald Trump's aggressive trade policies fully kick in.

Economists were expecting monthly prices to rise by 0.2% and to accelerate to 3.3% on an annual basis.

It followed a similarly encouraging Consumer Price Index report, which on Thursday showed that overall inflation cooled for the goods and services Americans commonly purchase.

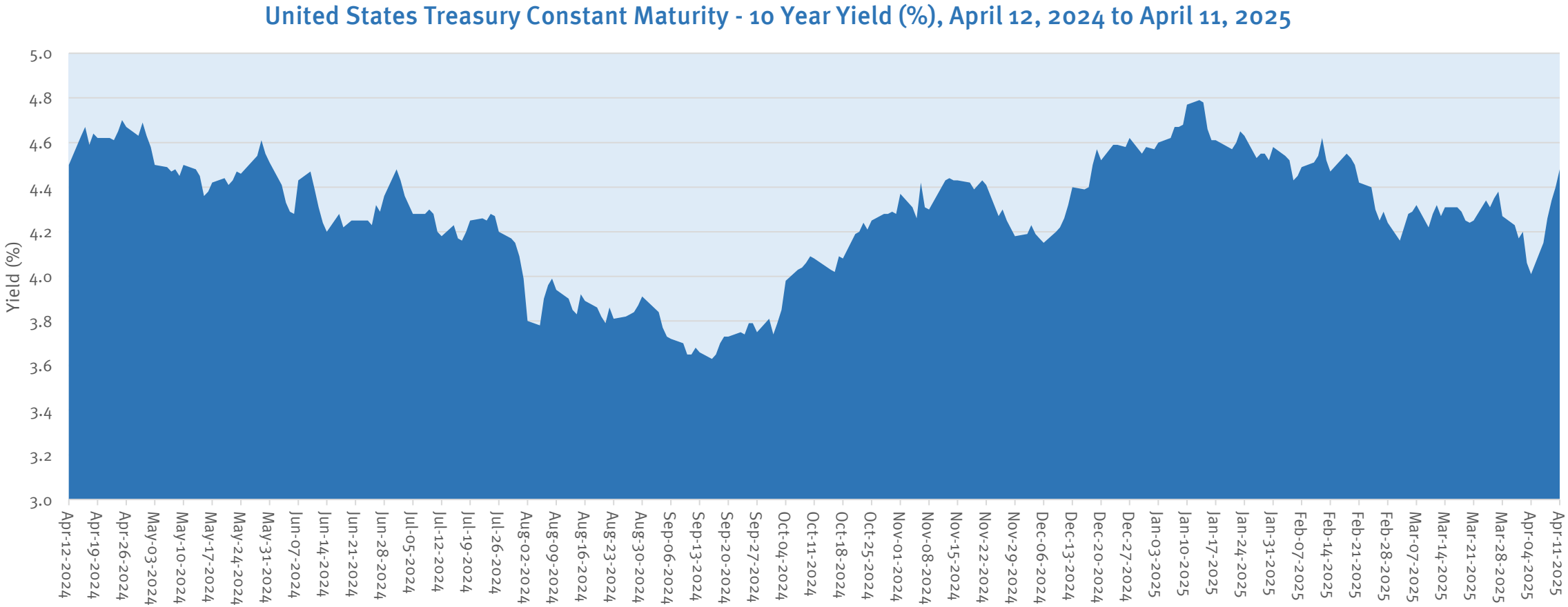
"Inflation was on a cooling course heading into the tariff shock," Oren Klachkin, Nationwide's financial markets economist, wrote in a note to clients Friday. "But like yesterday's CPI report, today's PPI data offer little comfort in the face of significant uncertainty, major trade policy changes and financial market turmoil."

Economists have warned that the sharp escalation in America's effective tariff rate will result in higher prices for businesses and consumers as well as disrupt the global economy, possibly triggering a recession.

Source: https://www.cnn.com/2025/04/11/economy/us-producer-price-index-ppi-inflation-march/index.html

Treasury Yields Spiked Last Week

Long Treasuries initially rose on news of Trump's tariffs as the market sought a safe haven. However, as last week wore on, it became clear that foreign holders were dumping Treasuries on the market. This, ultimately, led to a delay in the tariffs. While the 10-year Treasury yield on Friday ended at 4.5% there was a sense it could have been much higher. Higher yields are not good for biotech stocks which are long duration. Nonetheless, current levels are not different than they were in February.



Source: CapitalIQ.

‘This is Not Normal’: Trump’s Tariffs Upend the Bond Market

Joe Rennison and Colby Smith, *New York Times*, April 11, 2025 (excerpt)

In the usually steady government bond market, the yield on the 10-year Treasury has risen to about 4.5 percent from less than 4 percent at the end of last week.

The bedrock of the financial system trembled this week, with government bond yields rising sharply as the chaotic rollout of tariffs shook investors’ faith in the pivotal role played by the United States in the financial system.

U.S. government bonds, known as Treasuries because they are issued by the U.S. Treasury, are backed by the full faith of the American government, and the market for Treasuries has long been deemed one of the safest and most stable in the world.

But the Treasury market’s erratic behavior all week has raised fears that investors are turning against U.S. assets as President Trump’s trade war escalates.

The yield on the 10-year Treasury, which underpins corporate and consumer borrowing and is arguably the most important interest rate in the world, rose roughly 0.1 percentage points on Friday. The rise added to sharp moves throughout the week that have taken the yield on the 10-year Treasury from less than 4 percent at the end of last week to around 4.5 percent.

Typically, the nearly $30 trillion Treasury market is too large to be significantly affected by shifts in buying appetites, analysts said, highlighting just how severe the current moves in the market have been.

“There has been quite a bit of selling that we have seen,” said Vishal Khanduja, portfolio manager for the total return bond fund at Morgan Stanley Investment Management. **Another worrying sign this week has been the decline in the U.S. dollar**, which tumbled 0.9 percent against a basket of currencies representing its major trading partners on Friday. Every currency of the group of 10 nations rose against the dollar, further pointing to a move away from U.S. assets.

Source: https://www.nytimes.com/2025/04/11/business/economy/treasury-bonds-tariffs.html

Risk of Falling Dollar, Higher Yields and Slowing Economy

Economist, April 13, 2025 (excerpt)

IN 1990S JAPAN the worst days of a market crisis brought about a "triple *yasu*" loss: a fall in stockmarkets, a rise in bond yields and a declining currency. It is now America that must stomach this noxious combination. Although President Donald Trump's tariff pause provided a brief respite, the triple *yasu* has made an unwelcome return. Most alarming lately have been movements in the bond and currency markets. In total since April 1st the dollar has fallen by more than 4% against a basket of major currencies, at the same time as yields on ten-year Treasury bonds have risen by 0.3 percentage points (see chart).

CHART: THE ECONOMIST

In Japan the triple *yasu* was associated with national decline. Yet a flight from all American assets represents a far greater loss. That is because the dollar and Treasury bonds are the world's havens, and the global financial system has been built on the assumption that they are safe.

If bond yields were rising because of stronger American economic growth, they would bring about a stronger greenback. That the dollar is falling instead suggests investors are worried about America's economic stability. It is an ominous repeat of a pattern that struck in Britain after Liz Truss's disastrous "mini-budget" in 2022, which promised unaffordable tax cuts. Although Mr Trump's tariffs raise money for the government, such revenue could be dwarfed by the higher payouts required by rising bond yields.

Trump Has 90 Days to do 150 Trade Deals. Financial Markets Aren't Buying It

By David Goldman and John Towfighi, *CNN*, April 11, 2025 (excerpt)

President Donald Trump and his advisers said this was the plan all along: Scare the bejesus out of the world by announcing astronomically high tariffs, get countries to come to the negotiating table, and — with the exception of China — back away from the most punishing trade barriers as America works out new trade agreements around the globe.

But Trump's 90-day pause on his "reciprocal" tariffs that were never actually reciprocal gives his administration just three months to strike enormously complex trade deals with dozens of countries that it says are lining up to negotiate.

Financial markets aren't buying it. Stocks have whipsawed as volatility has spiked. And other markets, including oil, bonds and the dollar, are sending a clear message of deep skepticism that Trump will be able to pull this one off.

Despite financial markets casting enormous doubt that the Trump administration can salvage the opportunity it created for itself to strike bilateral trade agreements with all 150 countries around the world, the Trump administration remains optimistic.

Treasury Secretary Scott Bessent said this week that more than 70 countries have asked to meet with US representatives to strike a deal that could get them out from under the thumb of Trump's punishing tariffs. Although the administration has provided few details of which countries it is negotiating with, it said it would favor allies like South Korea and Japan first.

But trade deals are incredibly complex arrangements usually negotiated over the course of years, not months. And even if Trump were to negotiate trade with all those countries over a short period — whether full deals or letters of agreement that put a framework of a deal together — China, the world's biggest exporter, remains the elephant in the room.

Source: https://www.cnn.com/2025/04/11/investing/stock-market-dow-tariffs/index.html

China Retaliates Again in Trump's Trade War, Prompting Flight From US Assets

Jeff Mason, Nandita Bose, Joe Cash and Karin Strohecker, Reuters, April 12, 2025 (excerpt)

Beijing increased its tariffs on U.S. imports to 125% on Friday, hitting back against President Donald Trump's decision to raise duties on Chinese goods and increasing the stakes in a trade war that threatens to upend global supply chains.

The retaliation intensified global economic turmoil unleashed by Trump's tariffs. U.S. stocks ended a volatile week higher, but the safe haven of gold hit a record high during the session and benchmark U.S. 10-year government bond yields posted their biggest weekly increase since 2001 alongside a slump in the dollar, signaling a lack of confidence in America Inc.

One U.S. survey of consumers showed inflation fears have mounted to their highest since 1981, while financial institutions have been forecasting an ever greater risk of recession.

Trump downplayed the market turbulence, predicting the dollar would strengthen and saying his 10% across-the-board tariffs represented a floor in most cases as countries strike their own trade deals with Washington.

"When people understand what we're doing, I think the dollar will go way up," he told reporters aboard Air Force One late on Friday. "The bond market's going good. It had a little moment but I solved that problem very quickly."

The $29 trillion Treasury market saw an acute selloff following Trump's initial announcement about what he calls reciprocal tariffs. That turbulence was seen as part of what drove Trump to announce a 90-day pause for countries other than China on Wednesday. The White House has said since then that more than 75 countries have sought trade negotiations with the United States and that future deals would bring certainty.

India and Japan are among the powers to have advanced toward trade talks, but generally foreign leaders have puzzled over how to respond to the biggest disruption to the world trade order in decades.

The tit-for-tat tariff increases by the U.S. and China stand to make goods trade between the world's two largest economies impossible, analysts say. That commerce was worth more than $650 billion in 2024.

Source: https://www.reuters.com/world/trumps-tariff-pause-brings-little-relief-recession-risk-lingers-2025-04-11/

Chinese are Digging in for a Trade War

Joe Leahy, Wenjie Ding, Ryan McMorrow and Nian Liu, *Financial Times*, April 11, 2025 (excerpt)

Donald Trump's tariff war has been wreaking havoc in global markets, but among exporters in China's "trinket town" — the eastern city of Yiwu famous for making everything from Christmas trees to Donald Trump campaign caps — the mood is more of stoic defiance than panic.

Amid government invocations of late dictator Mao Zedong that are intended to project national strength, Chinese business people on the front lines of the trade war said they were confident their nation would prevail.

"Trump wants to steal a slice of China's pie," said exporter Kenny Qi in his small store festooned with "Make American Great Again" T-shirts in a vast Yiwu trade exhibition centre.

But Qi said Trump got a shock when Beijing retaliated with its own 125 per cent tariffs this week. He predicted the US president, whose visage glowered at him from a Maga T-shirt above his desk, would back down "in half a month at most".

Trump's new duties on Chinese goods are more than twice the 60 per cent tariffs he threatened during his election campaign — a level that many economists had at the time considered a worst-case scenario. Beijing has stepped up its nationalist rhetoric to steel the public for the economic fallout from a hard decoupling with the US. Foreign ministry spokesperson Mao Ning posted on the social media site X a video of Mao giving a speech during the 1950-53 Korean war, when Chinese soldiers fought against US-led UN forces.

"No matter how long this war is going to last, we'll never yield, we'll fight until we completely triumph," then-chairman Mao says in the clip.

Source: https://www.ft.com/content/f2073852-b5e7-42a7-b493-f45393992a6

President Trump appears to have his hands full with China given the current trade war. While 15% of its exports go the U.S., the Chinese economy can withstand loss of access to the U.S. market. China has a giant domestic market that its industry can serve.

A recent film in China entitled *The Battle at Lake Changjin*, featured the fighting between the U.S. and China in the Korean war, lionizing the steps taken by Chairman Mao at the time.

The film reminded the hundreds of millions of Chinese viewers that the U.S. bombed China during the Korean War.

Last week's tariffs are being portrayed to the Chinese people in a similar light with social media replays of Mao's speeches during the Korean conflict.

None of this is good, particularly since China holds such a large inventory of dollars and U.S. Treasury bonds.

Why China Thinks it Might Win a Trade War With Trump

***The Economist*, April 10, 2025 (excerpt)**

The trade war is escalating, and fast. On April 8th Chinese officials vowed to "fight to the end" in the face of new threats from Donald Trump, made just hours earlier, having already promised to match American tariffs of 34%. With such an increase, China's tariff rate on American imports will reach 70%. Later the same day, the White House confirmed that it would return fire, with tariffs of 104% applying to Chinese goods from April 9th.

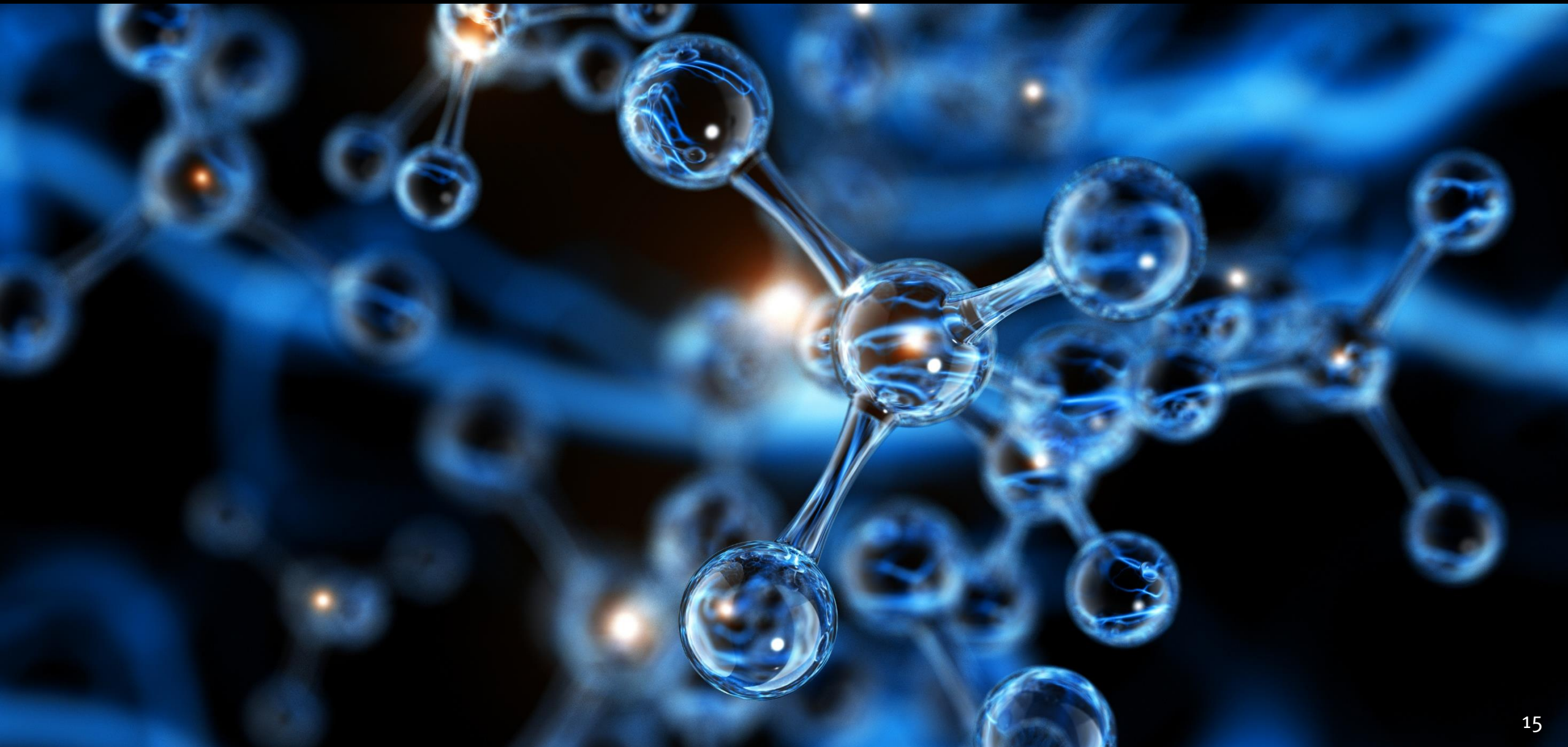
Chinese officials had been eager to show they would not be pushed around; at the same time, they were content to pick their punches, so as to limit self-harm and avoid further escalation. This, the thinking went, would allow for easier negotiations when the time came—a calculation that now appears to have been discarded.

One reason for the shift might be a sense among China's leaders that they could win the trade war. Mr Trump wants a lot from his geopolitical rival, including stemming the flow of fentanyl precursors and help ending Russia's war in Ukraine. America's president has also revealed that he does not want to be responsible for shutting down TikTok, a Chinese-owned short-video app popular among young Americans. Tesla, an electric-vehicle firm owned by Elon Musk, Mr Trump's adviser, is vulnerable to retaliation, since it does about a fifth of its business in China. "This is huge leverage on the us government unless Elon is asked to go," says Alicia Garcia Herrero of Natixis, a French bank.

Chinese officials may also believe that America will be unable to bear the inflation and economic discontent caused by Mr Trump's tariffs. Instead of "fighting to the end", they may only need to fight until American consumer prices begin to rise or employment begins to fall. Senior advisers, government researchers and economists all point to this as the easiest way of bringing Mr Trump to the table.

Source: https://www.economist.com/finance-and-economics/2025/04/08/why-china-thinks-it-might-win-a-trade-war-with-trump

A Wild Week in the Biotech Market



Extreme Volatility in the Broad Market

CNBC, April 11, 2025

Dow jumps 600 points Friday, capping one of the most volatile weeks on Wall Street ever

UM survey: Consumer sentiment tumbles in April as inflation fears spike

Wholesale prices unexpectedly fell 0.4% in March, showing easing inflation backdrop ahead of tariffs

Wall Street Journal, April 11, 2025

Stocks Rally Despite Recession Fears to Cap Tumultuous Week

U.S. stock indexes this week

As of April 11, 4 p.m. ET

Trade war deepens as China lifts U.S. tariff to 125%; 10-year Treasury yield hits 4.5%

Stocks ended higher even as a survey showed consumer sentiment souring to one of the lowest levels in a decade over recession worries. The dollar and Treasurys faced selling pressure after China hit back again in the tariff war.

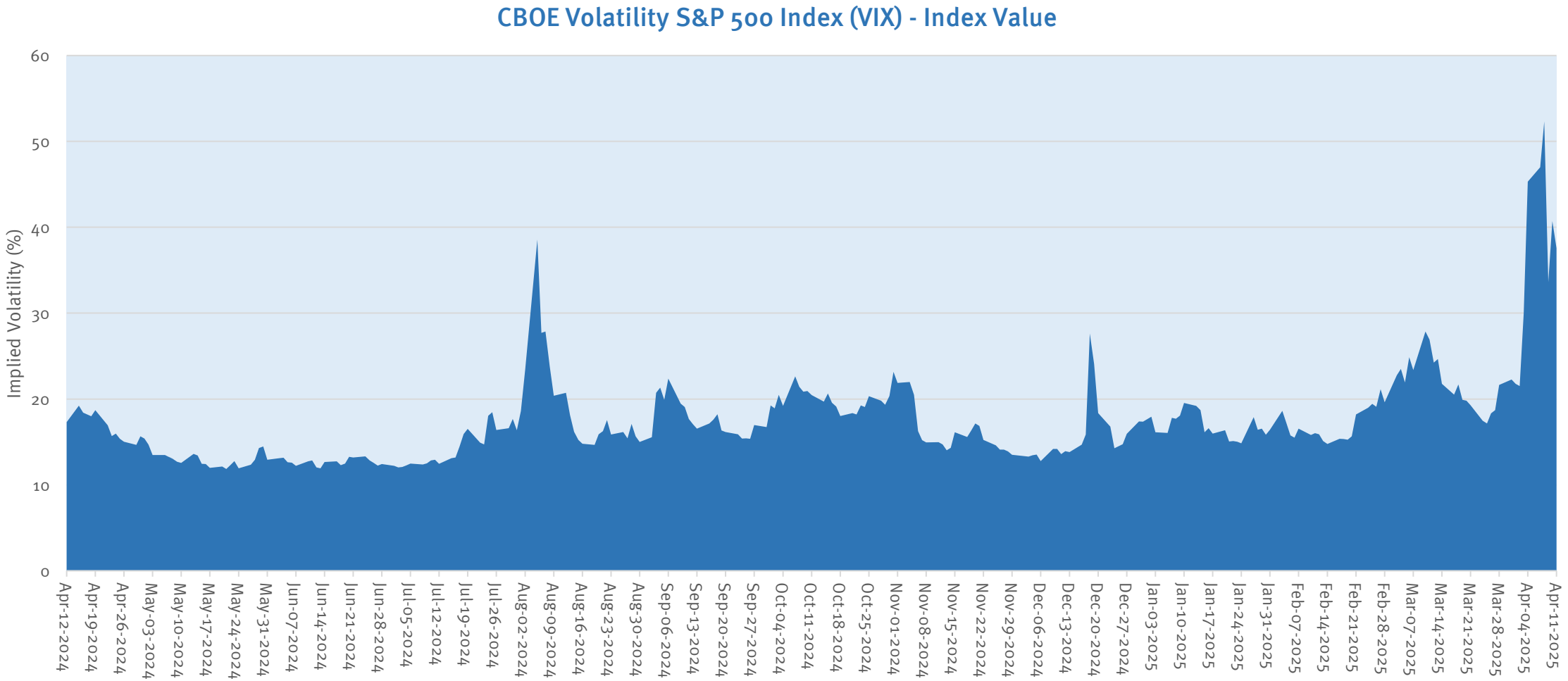
- **Inflation Expectations Reach Highest Level in 44 Years**
- **Analysis | The Simple Explanation for the Treasury Market Mayhem**

Axios, April 10, 2025

Stocks plunge again as volatility reigns despite Trump tariff pause

Last Week Saw Third Biggest Equities Volatility Spike Since 1993

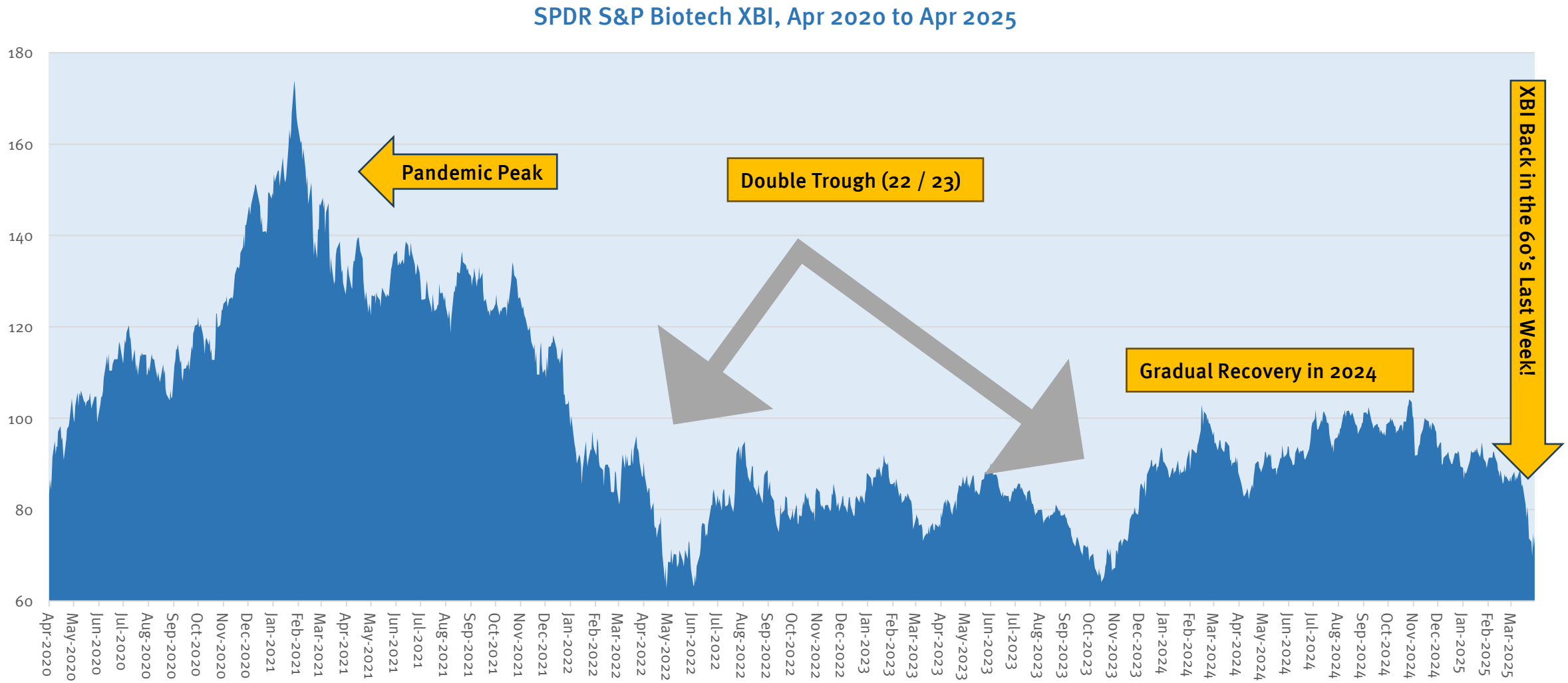
The only time we have seen the market's "fear gauge", the VIX, go higher since its inception in 1993 have been the Global Financial Crisis and the first week of the Pandemic.



Source: CapitalIQ.

Walk on the Wild Side: Biotech Stock Tracker (XBI)

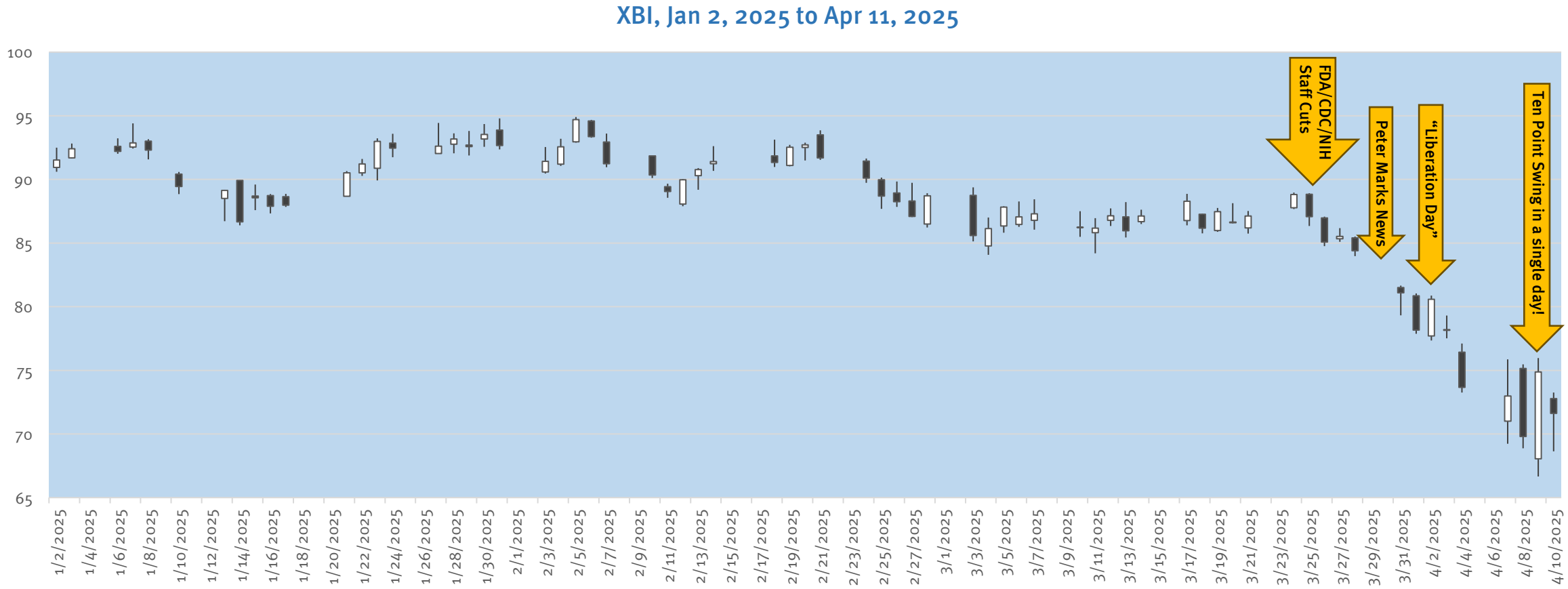
Visions that 2025 would be a consistent year of market recovery were dashed in recent weeks as the XBI bottomed out at 66.6 on Wednesday, very close to previous trough levels hit in 2022 and 2023.



Source: CapitalIQ.

Extreme Intraday Volatility in the XBI Last Week

Trump's escalating trade war unsettled the markets greatly last week – with obvious consequences for biotech. When Trump reversed course on Wednesday on his tariffs, the market jumped wildly. The subsequent day saw very aggressive short-selling coupled with selling from funds in forced liquidation causing wild market swings. Volatility tightened on Friday as funds rushed to take profits while covering their short positions for the weekend.



Source: CapitalIQ.

How One of the Wildest Weeks in Market History Unfolded

Ryan Dezember and Sam Goldfarb, *Wall Street Journal*, April 11, 2025 (excerpt)

… one of the most tumultuous weeks in years for financial markets ended with all three major U.S. indexes up 5% or more. For Wall Street, it was a bruising run. Traders described scenes of tension, where the rapid surges and dives made it difficult to determine the prices of various investments. And the sheer violence of the moves left many exhausted and bracing for more trouble ahead.

With the Dow Jones Industrial Average ending Friday on a 600-plus point gain, Jed Ellerbroek, portfolio manager at Argent Capital Management in St. Louis, said the declines earlier this week and last had clients calling to ask whether or not to buy more shares. Meanwhile, he grew concerned watching individual investors pumping more money than usual into big stock funds.

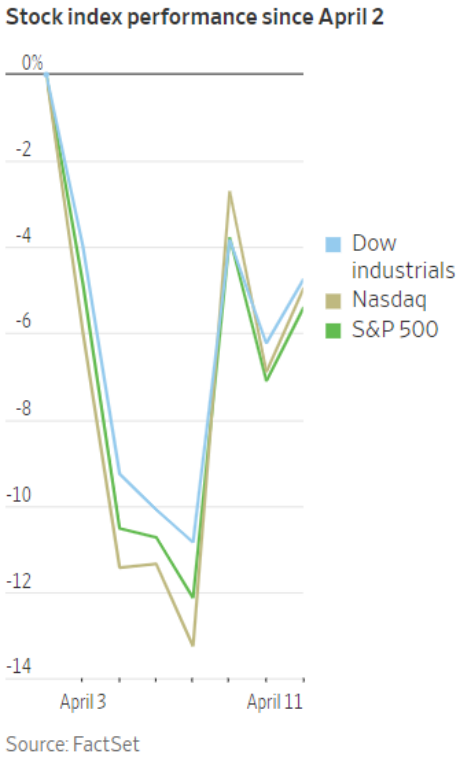
Such investors might be expecting a scenario like the 2020 Covid crash, which was short-lived and led to an epic rally. They might have forgotten how stocks fell more than 50% in the 2008 crash and took years to recoup the losses, Ellerbroek said. “That leaves me feeling like this downturn probably has more to go,” he said.

The S&P 500 rose 1.8% on Friday to end the week up 5.7%. The tech heavy Nasdaq Composite increased 2.1%, for a weekly gain of 7.3%. The blue-chip Dow added 1.6% Friday to lift its weekly rise to 5%. All three indexes remain below where they were trading when President Trump launched his tariff blitz last week from the White House Rose Garden. All three are down on the year.

The volatility began last week after Trump shocked investors, economists, business leaders and trade partners with a barrage of tariffs that were far steeper than anyone expected. A four-day selloff ensued, but it was Wednesday when the wild ride peaked.

A sharp climb in Treasury yields was alarming investors ahead of the opening bell Wednesday when Trump took to social media to say that it was “a great time to buy.” By the day’s end, U.S. stocks had staged a historic rally after another online post from the president announced a 90-day pause on some tariffs and signaled a willingness to negotiate on trade.

The result was a surge so extreme that investors said it echoed prior incidents in which stocks rallied sharply in times of stress, only to tumble to steeper losses.



Source: https://www.wsj.com/finance/investing/how-one-of-the-wildest-weeks-in-market-history-unfolded-41353450

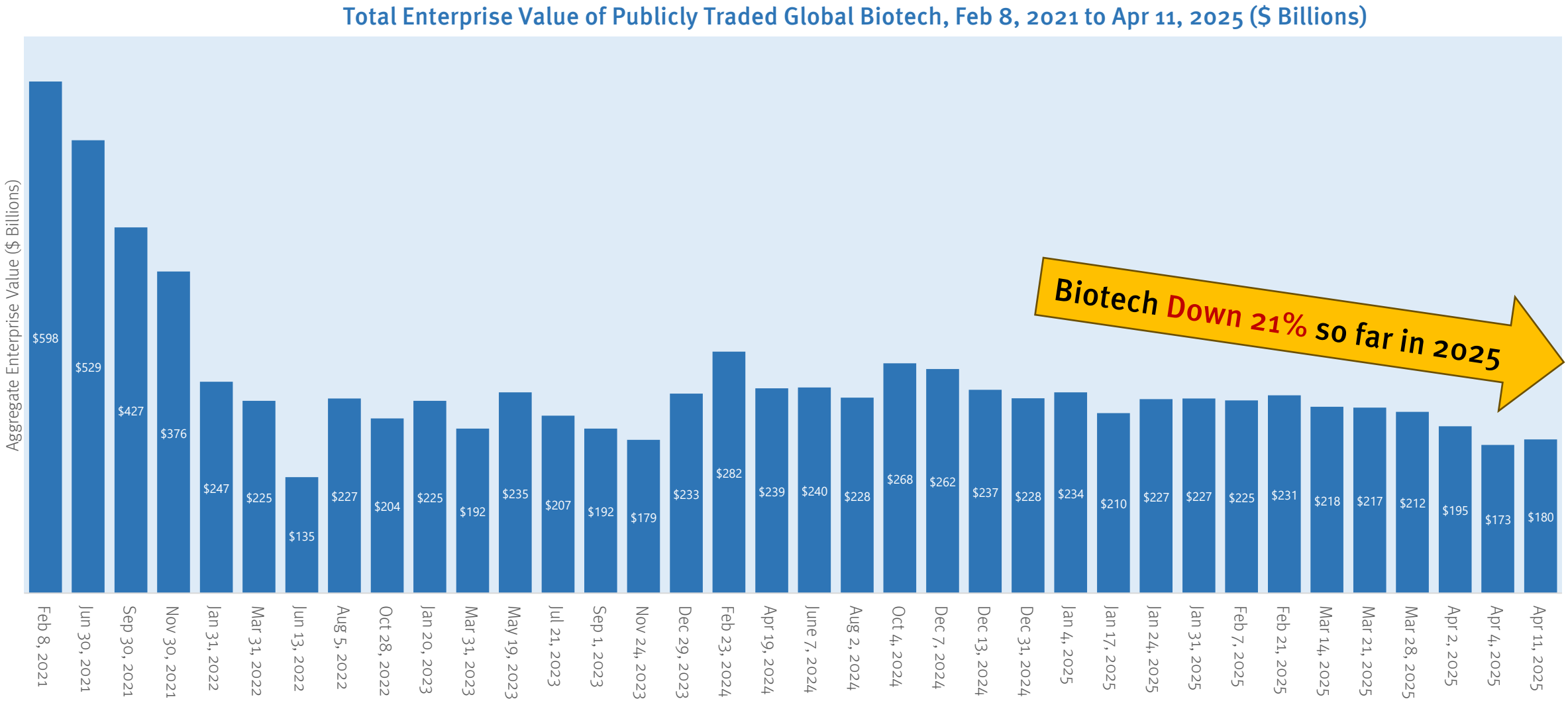
Color from Hedge Funds

One can think of the public markets as involving an ecosystem of players with highly diverse trading styles. Some investors (think Capital Group) buy stocks and hold them typically for ten years or more. Others, in contrast, may buy and sell multiple times in a single day. We spoke to a number of well-known biotech hedge funds last week including some who are willing to trade rapidly and go short on a moment's notice. Some of these managers were themselves shaken by the speed of market movements last Wednesday, noting the increasing rise of automated trading systems in biotech in 2025.

One fund manager described what it was like to be in the market after Trump renounced his tariffs on Wednesday afternoon saying that it was "completely wild". A veritable capitalist jungle. This manager indicated that a number of biotech stocks moved by 20% or more within five minutes. They ascribed this to short-covering in a market where "algo's" were playing heavily. These are quantitative funds that use computerized algorithms to make split second decisions on positioning in a way that is very difficult for mere humans to play. If you will, the algorithms study past behavior in times of extreme volatility and make split second moves before other players can step in. In addition, last week saw heavy use of so-called zero-day options. These allow traders to speculate on intra-day volatility through option positions that last for less than a single day. The purchase and sale of such options can amplify volatility because dealers need to delta hedge their positions. Even though last week ended up not nearly as bad for biotech as one might have feared on Wednesday lunch time, some fund managers remained unsettled going into the weekend – pessimistic on biotech fundamentals, particularly the FDA and Trump's behavior. Others had gained confidence and did well buying up stocks at much lowered prices, particularly on Thursday and Friday.

Total Global Biotech Sector Rose 3.8% Last Week

Biotech stocks rose 3.8% in the last week – a nice bounce after a volatile period. However, without the jump in Summit's value the market would have been flat for the week. By our math, the total global biotech sector is down 21% for the year on an exit-adjusted basis.

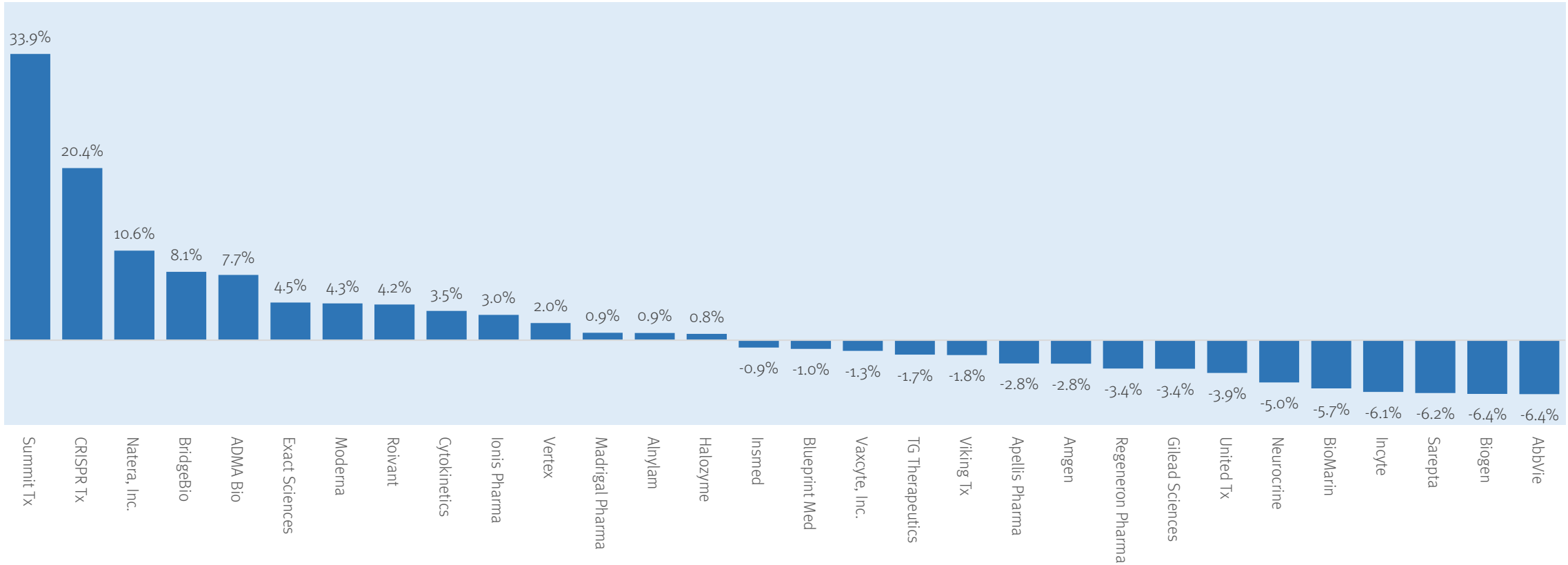


Source: CapitalIQ. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

XBI 30 Performance Mixed Last Week

This chart shows the change in market cap this year for the 30 most influential stocks in the XBI. These 30 stocks comprise 60% of the weight of the XBI (out of 138 stocks total). The mean percentage change in value last week was +1.5%. The median change was -1.0%. Summit jumped the most on heavy insider buying ahead of upcoming ivonescimab data. CRISPR, a heavily shorted stock, jumped substantially as well. Larger cap companies such as AbbVie, Biogen, Gilead, BioMarin, were all down in a volatile market.

Top 30 XBI Influencers, Pecent Change in Market Cap, Week of Apr 4 to Apr 11, 2025

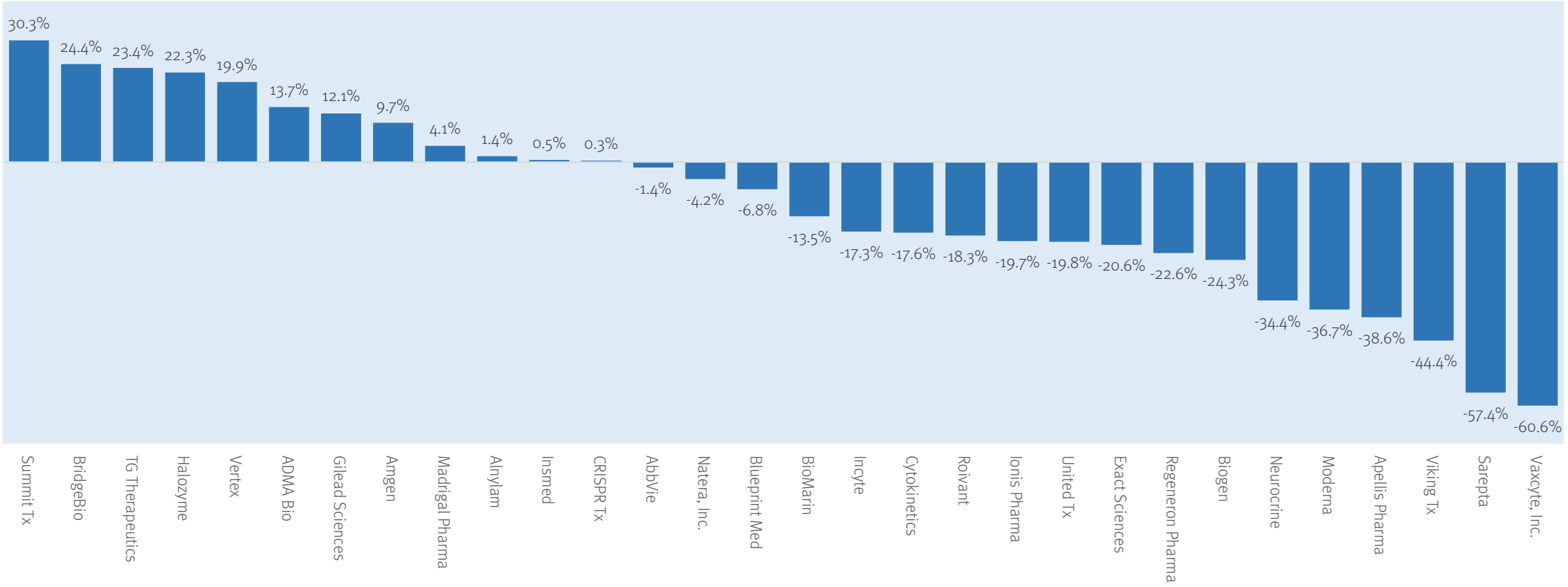


Source: CapitalIQ.

XBI 30 Performance Year to Date

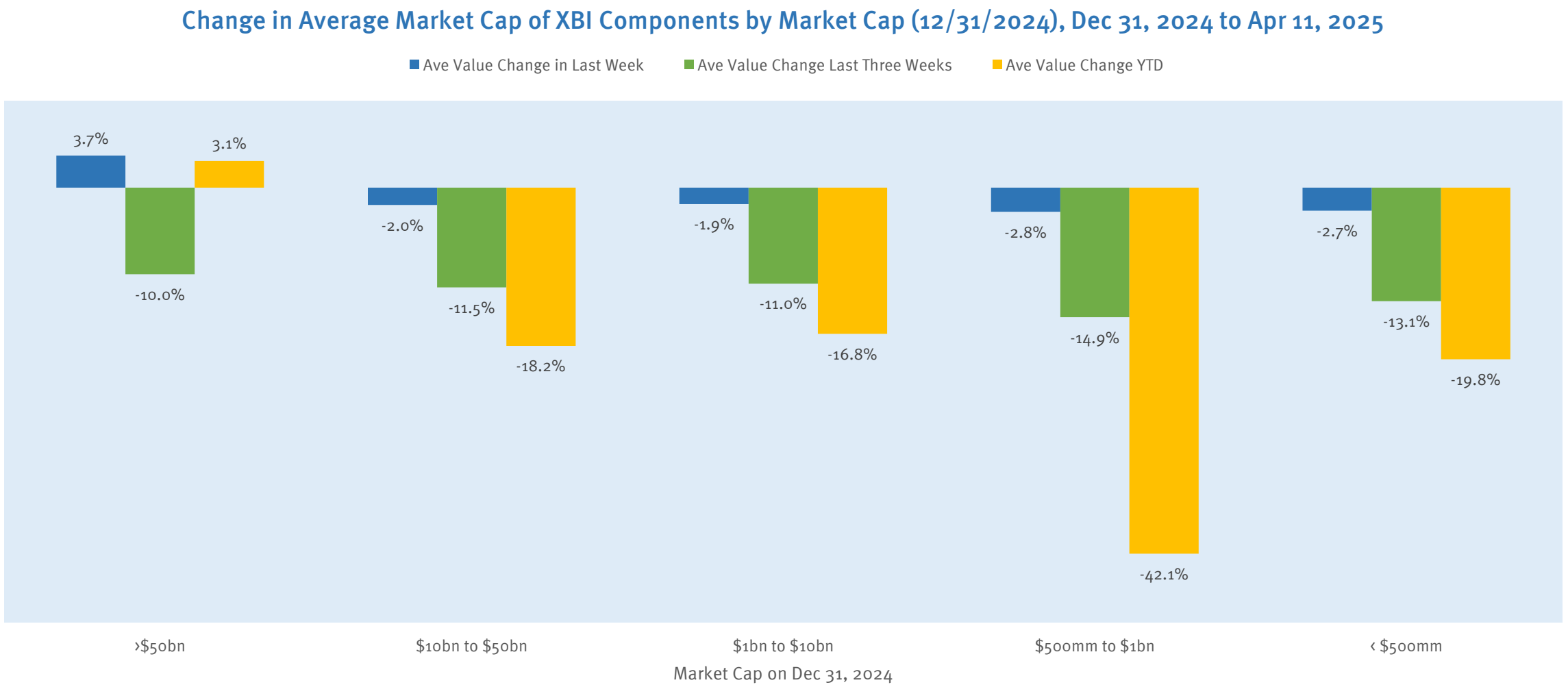
This chart shows the change in market cap this year for the 30 most influential stocks in the XBI. These 30 stocks comprise 60% of the weight of the XBI (out of 138 stocks total). The mean percentage change this year has been -10%. The median change was -9.1%. Summit, BridgeBio, TG Therapeutics and Halozyme have all had returns in the 20%+ category while Neurocrine, Moderna, Apellis, Viking, Sarepta and Vaxcyte have all underperformed their peers.

Top 30 XBI Influencers, Pecent Change in Market Cap, Week of Dec 31, 2024 to Apr 11, 2025



Source: CapitalIQ.

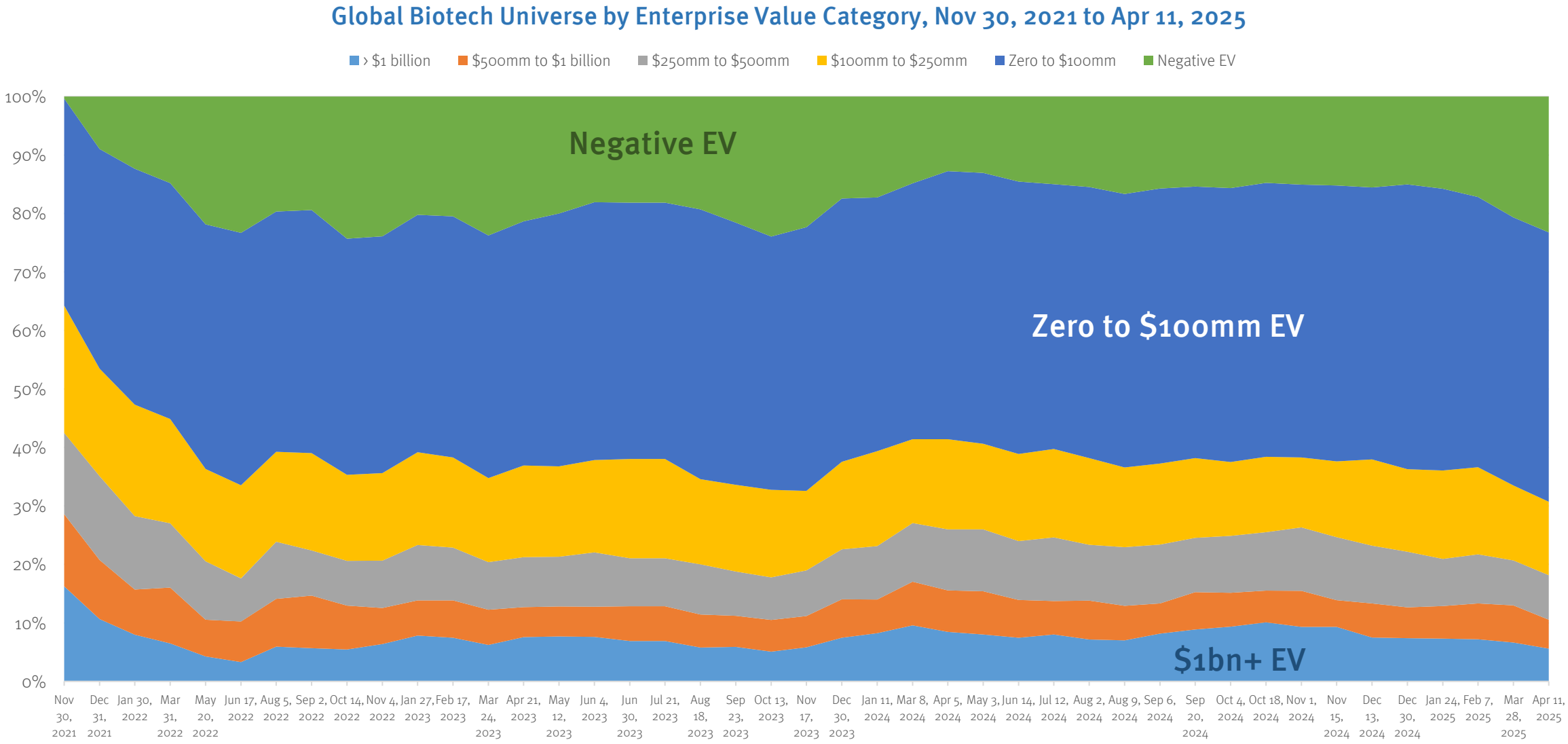
Large Caps in XBI Remain Up for Year While Other Size Categories in XBI Down Big for the Year



Source: CapitalIQ.

Global Biotech Neighborhood Analysis

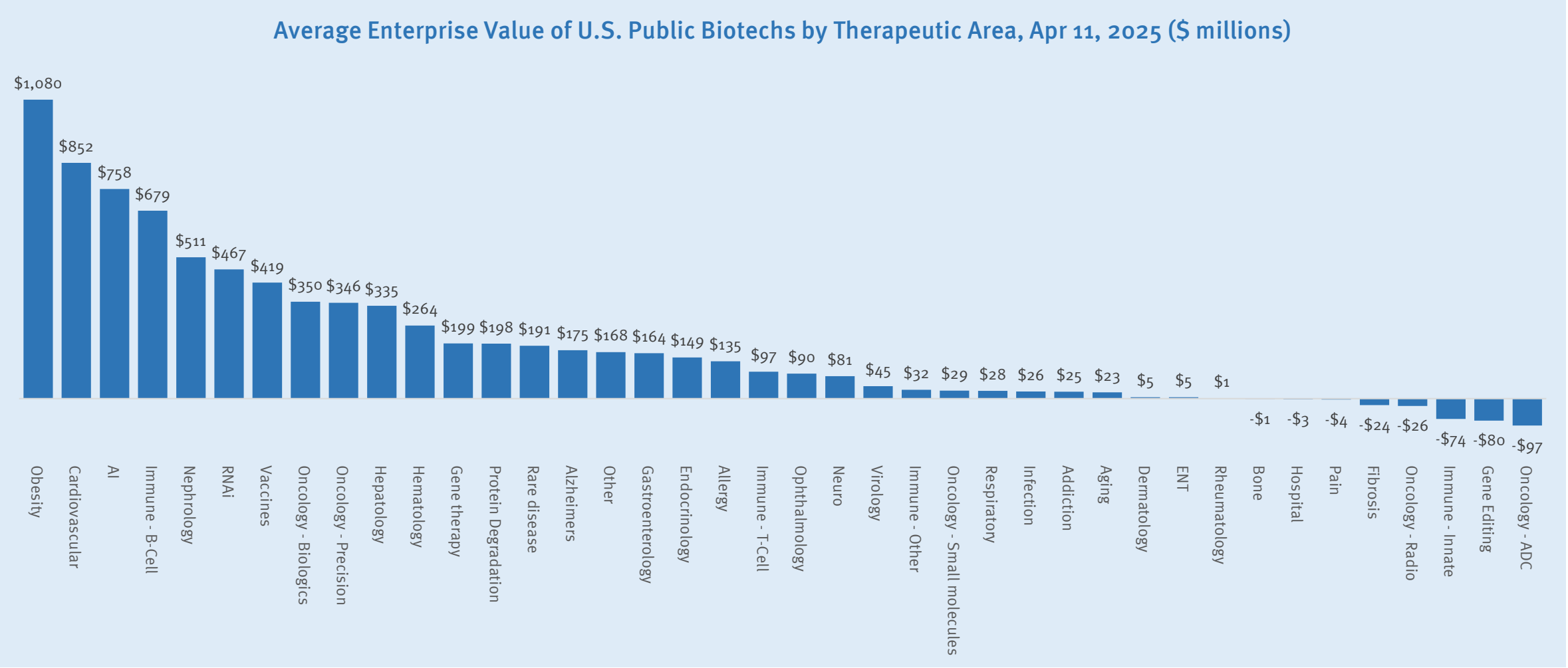
The population of biotechs trading for less than cash continues to expand rapidly.



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

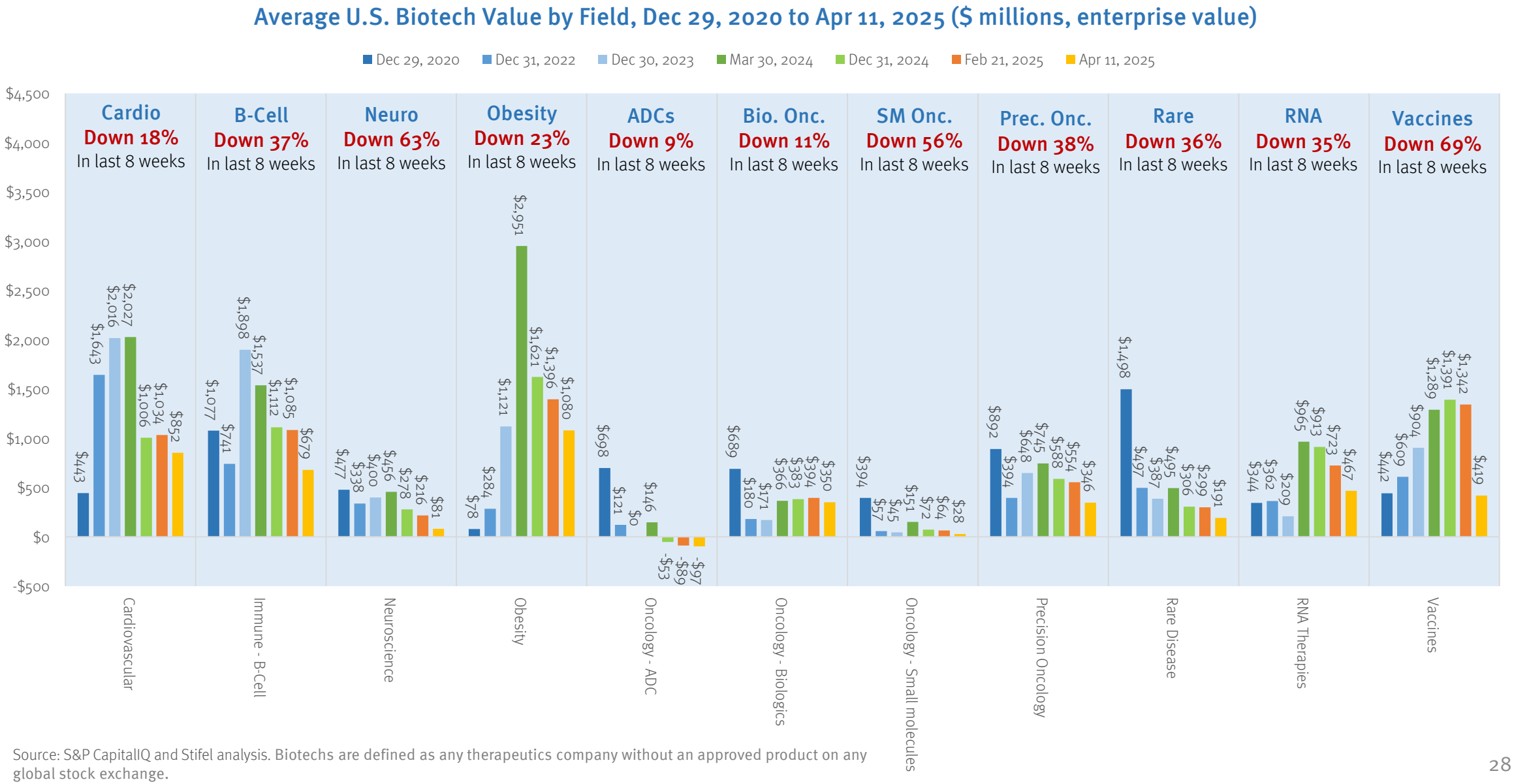
U.S. Biotech Worth the Most in Obesity, CV, AI and B-Cell

The most valued sectors in biotech today are (in order) obesity, cardiovascular and AI. A big change has been the devaluation of vaccine companies in sympathy with less than amazing data from Vaxcyte and somewhat hostile policies from the Trump Administration.



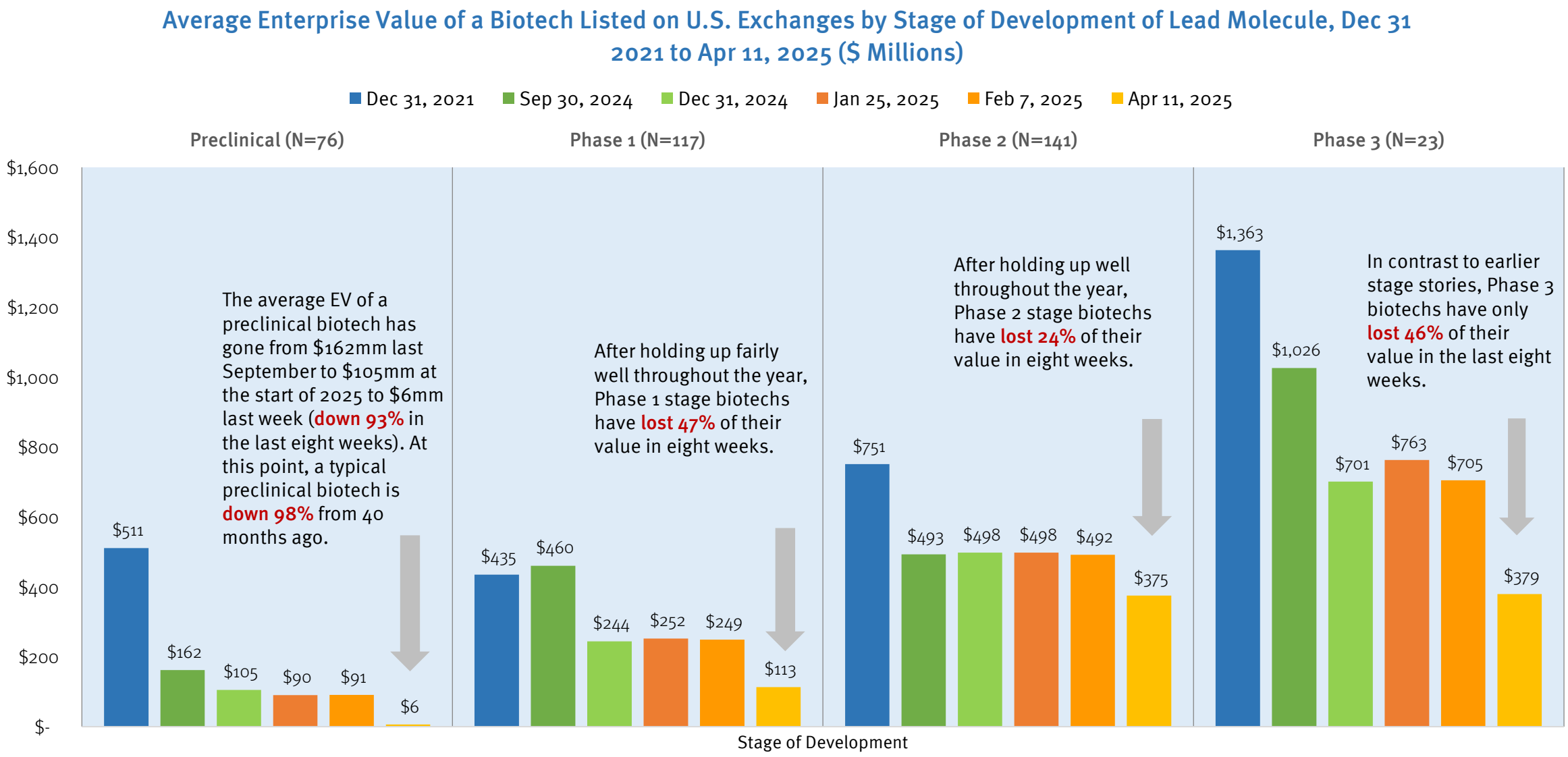
Source: S&P CapitalIQ and Stifel analysis. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

U.S. Biotech Values Down the Most in Vaccines and Neuro



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

Biotech Market is Penalizing Early-Stage Stories



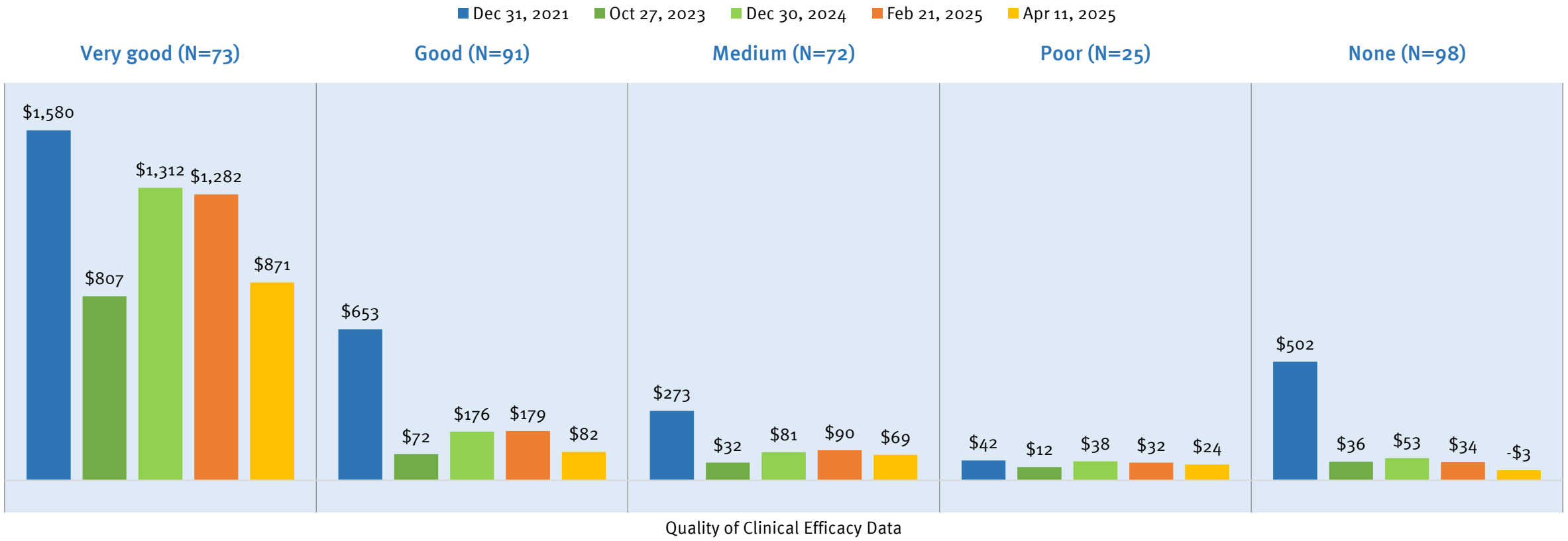
Source: CapitalIQ and Stifel analysis. Phase of development is defined by release of at least some efficacy data from a given stage of clinical development.

Even Highest Quality Biotechs Hit Hard in the Last Two Months

Even companies with a very good dataset have seen their value drop substantially. The percent value drop for companies with “medium” and “poor” datasets in the last eight weeks has been more modest than that for companies with a “very good” dataset. This is likely because the companies in the former baskets already have very low valuations. The value discounts today look very similar to those of Oct 2023, the previous market nadir.

Average Enterprise Value of a Biotech Listed by Quality of Efficacy Data

Dec 31, 2021 to Apr 11, 2025, ($ Millions, US Exchanges Only, N=374)

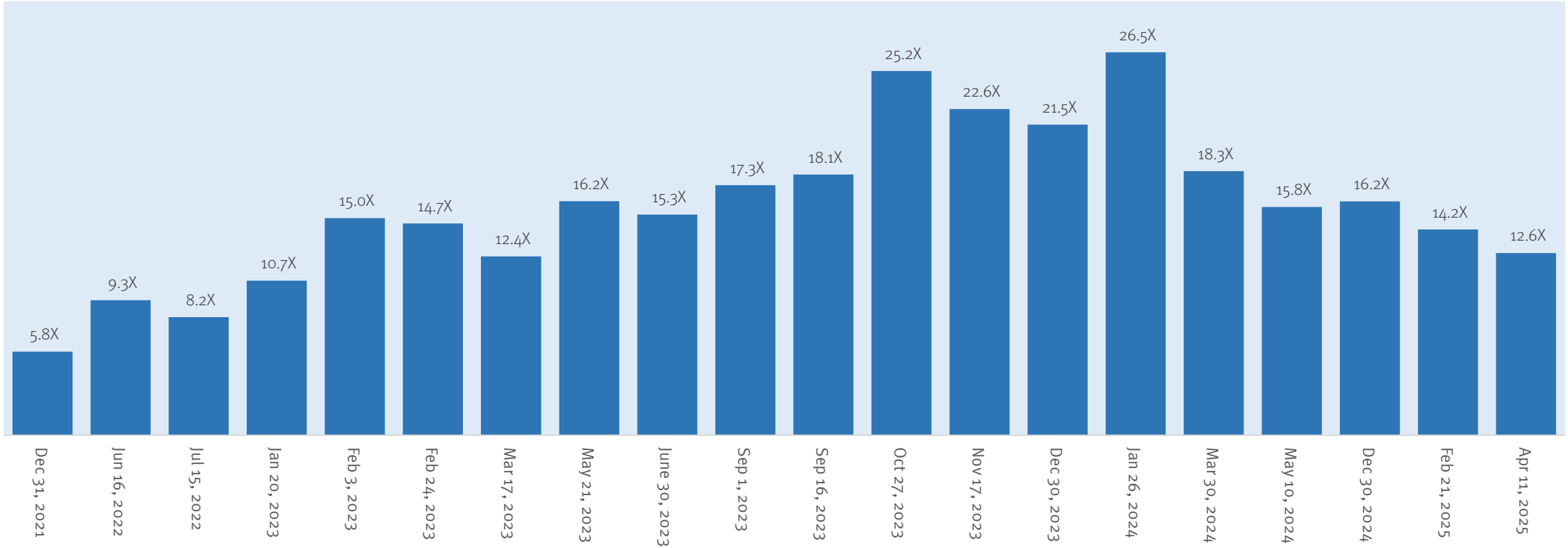


Note: These data are sourced from CapitalIQ and based on Stifel research on the dataset quality for a company’s lead asset. We classified datasets that indicated a high probability that the drug would meaningfully improve on the standard of care for a disease as “very good”. We classified “good” data as data that might beat the standard of care. Medium data was data that was unlikely to beat the standard of care, was very early or came from a study with a mixed signal. Poor data reflects situations where a drug did not perform well at all in a clinical trial.

Quality Premium is Going Down in Current Market

One of the distinctive characteristics of the biotech downturn of 2022 to 2024 has been an extreme quality premium. Companies with “very good” data have traded at a value of five to ten times companies with a “good” dataset. This is starting to change as even companies with a very good dataset have traded down in the last eight weeks. One interpretation of this is that with forced selling in the market, funds have had no choice but to sell their best silver.

Ratio of Average Enteprise Value of a U.S. Biotech with a "Very Good" Dataset to one with a "Medium" Dataset, 2021 to 2025



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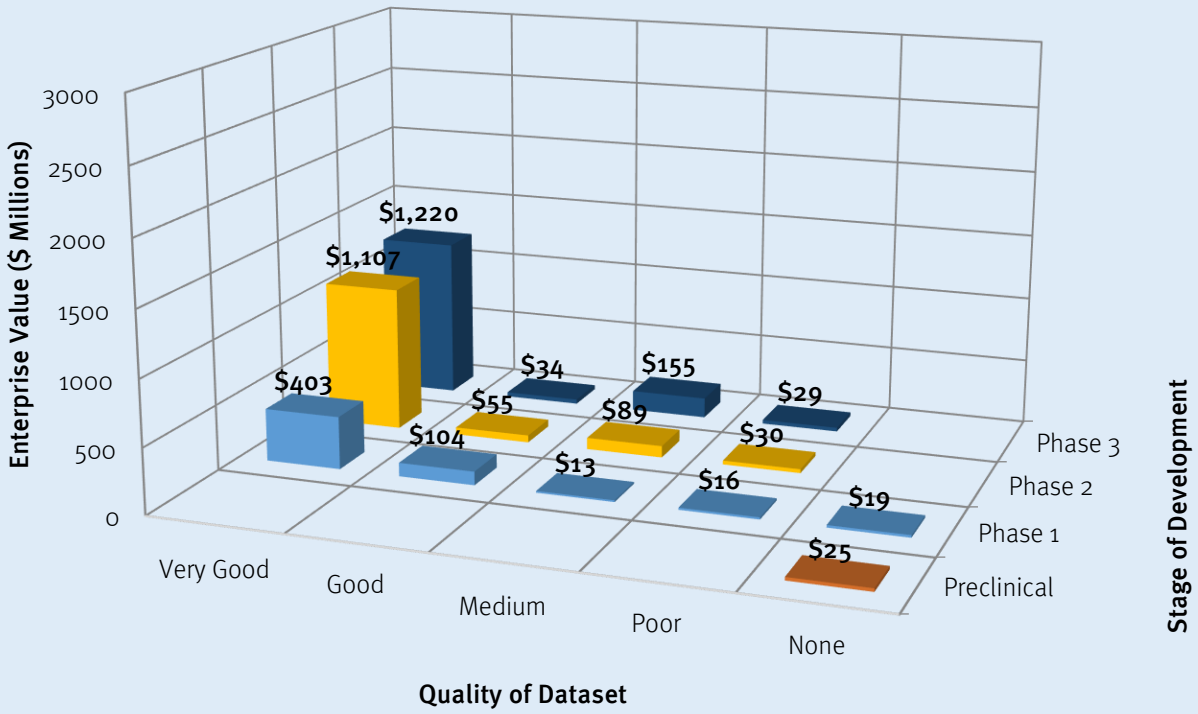
The Most Valued Biotechs are Those With "Very Good" Phase 3 Data

Biotech values have been slashed across the quality and stage of development spectrum since 2025 began.

Average Enterprise Value of a Biotech Listed on U.S. Exchanges by Stage of Development and Quality of Data, Apr 11, 2025



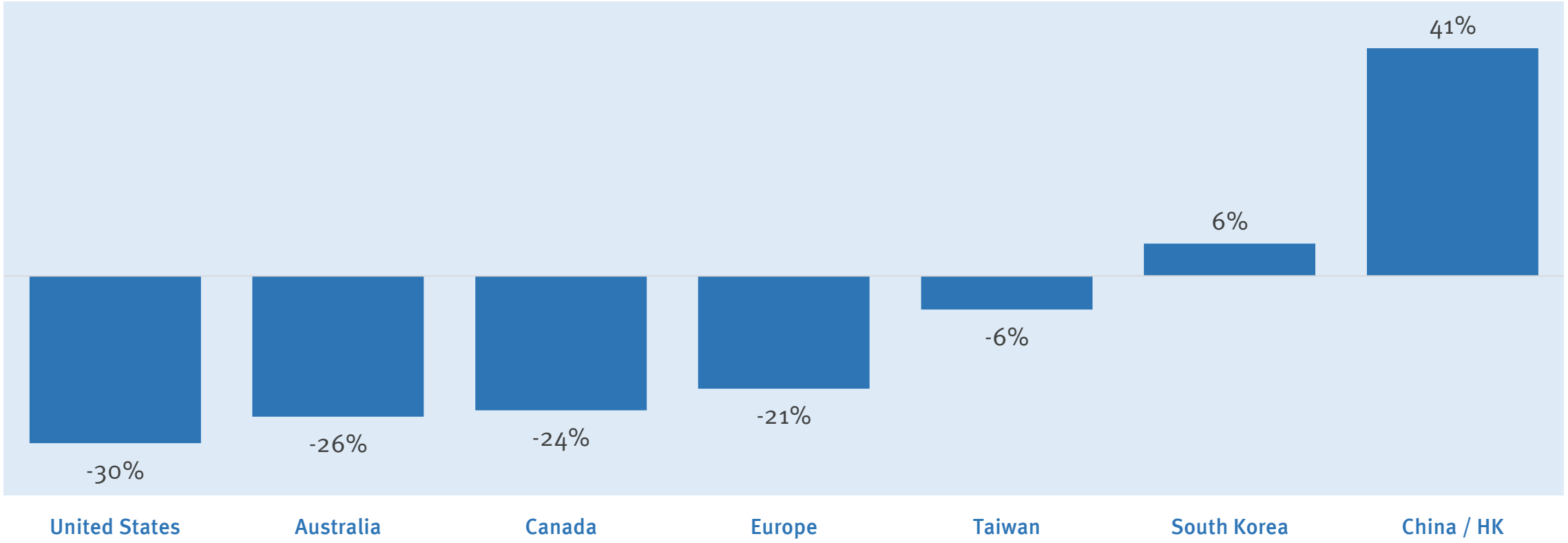
Average Enterprise Value of a Biotech Listed on U.S. Exchanges by Stage of Development and Quality of Data, Dec 31, 2024

Notes: These data are sourced from CapitalIQ and based on Stifel research on the dataset quality for a company's lead asset. We classified datasets that indicated a high probability that the drug would meaningfully improve on the standard of care for a disease as "very good". We classified "good" data as data that might beat the standard of care. Medium data was data that was unlikely to beat the standard of care, was very early or came from a study with a mixed signal. Poor data reflects situations where a drug did not perform well at all in a clinical trial. Stage of development refers to the stage of the last completed trial rather than the stage of ongoing clinical trials.

U.S. Biotech Has Suffered the Most in 2025

The loss of confidence in the biotech market has been highest in the United States where stocks are down 30% in total. We have also seen weakness in Australia, Canada and Europe in 2025. In contrast, both the Taiwan, South Korea and China markets have performed better. The latter three markets have two things in common: (1) they are all in Asia and (2) they are almost completely insulated from U.S. specialist investors which have been suffering LP withdrawals. The U.S. biotech ecosystem has been negative impacted by the cumulative effects of the IRA, increased global competition, persistently high interest rates and persistent poor performance relative to technology stocks.

Percent Change in Total Market Cap of Public Biotech by Country/Region, Dec 31, 2024 to Apr 11, 2025



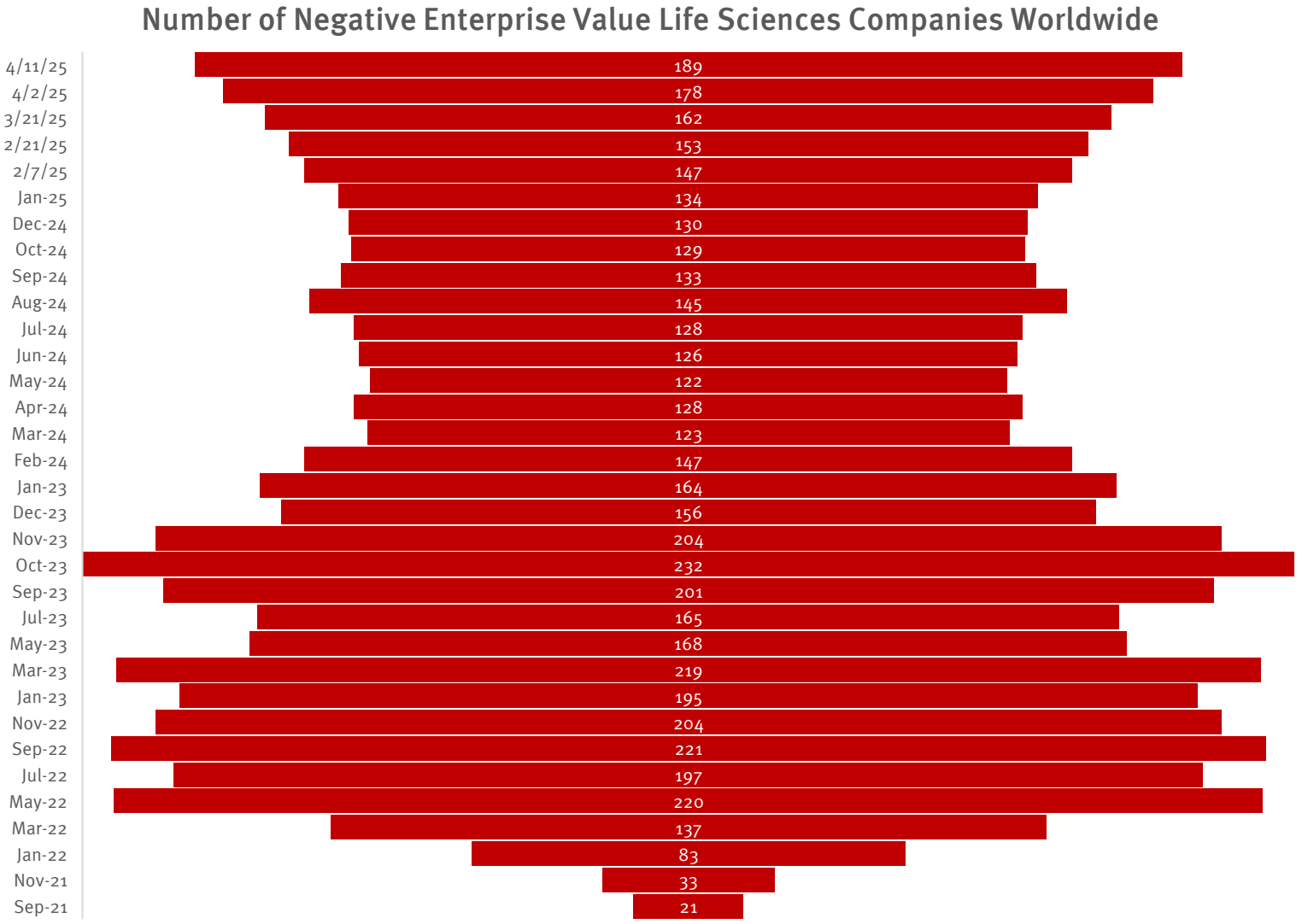
Life Sciences Sector Lost $103 Billion in Value Last Week (-1.2%)

Last week saw strength in biotech and medical devices. Pharma services, API and commercial pharma all lost value.

Sector	Firm Count	Enterprise Value (Apr 11, 2025, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	79	$83,167	-4.0%	-1.1%	6.2%
Biotech	730	$184,412	3.4%	-16.7%	-5.1%
CDMO	37	$147,052	0.4%	-0.4%	13.2%
Diagnostics	76	$235,858	3.5%	-3.4%	-14.2%
OTC	29	$23,301	-0.8%	-1.6%	-11.2%
Pharma	697	$5,685,814	-2.5%	-8.5%	-5.5%
Pharma Services	38	$141,238	-4.7%	-11.6%	-25.4%
LS Tools	50	$533,547	1.0%	-10.5%	-23.3%
Medical Devices	174	$1,697,916	2.0%	-3.1%	3.6%
HCIT	7	$22,984	1.0%	-11.4%	30.5%
Total	**1917**	**$8,755,290**	**-1.2%**	**-7.6%**	**-5.9%**

Source: CapitalIQ and Stifel analysis

Number of Negative Enterprise Value Life Sciences Companies Jumped in Last Week

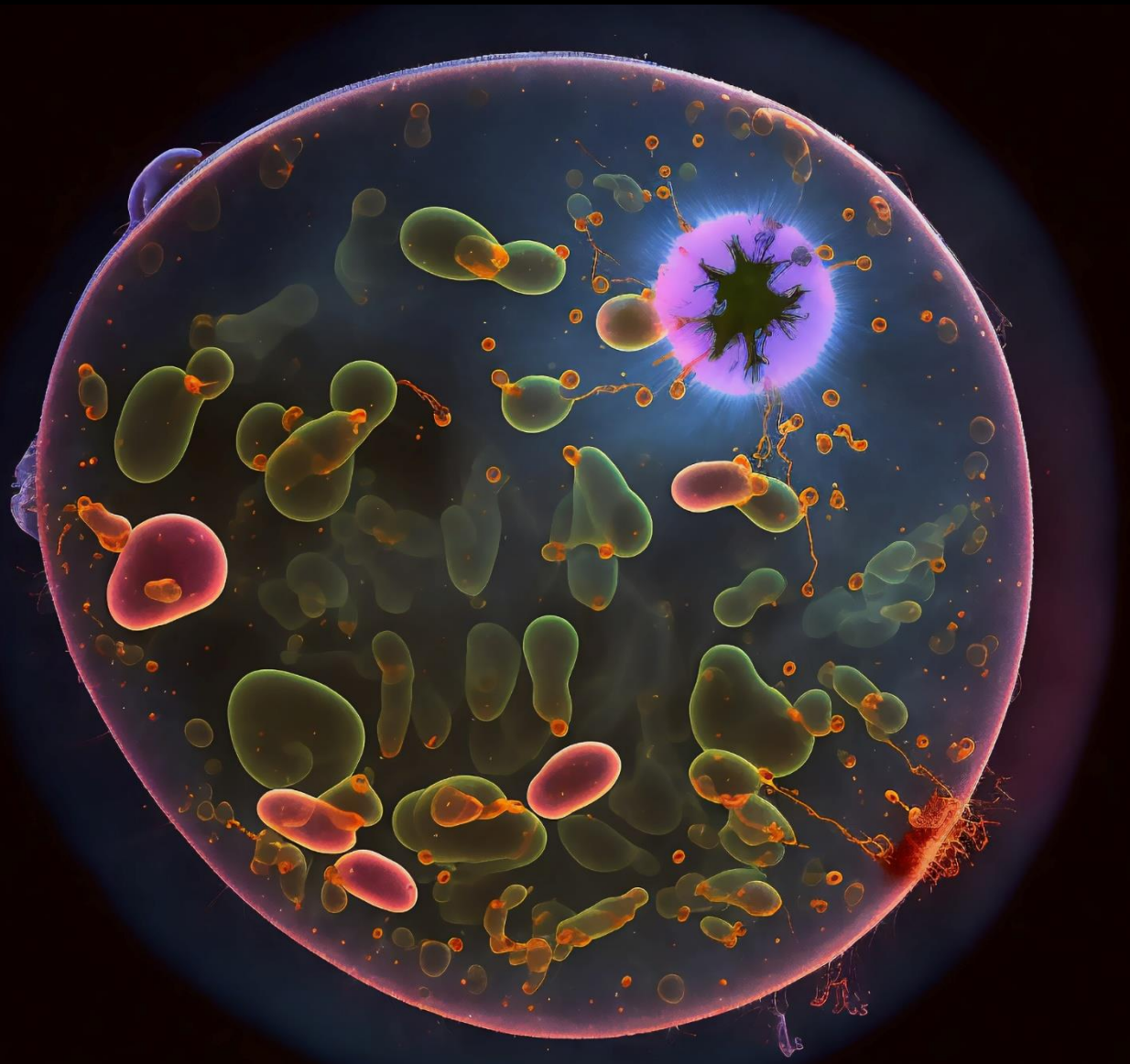


The count of negative EV life sciences companies worldwide rose from 178 a week ago to 189 last Friday.

This measure of sector distress continues to go in the wrong direction.

Source: CapitalIQ

Is Biotech Doomed?



How to Play the Biotech Meltdown in the Age of RFK Jr. and Tariffs

Political pressure and high interest rates have some wondering if the industry's model is broken.

Dave Wainer, *Wall Street Journal*, April 11, 2025 (excerpt)

The U.S. biotech sector had already been through a brutal few years before the latest market crash. Robert F. Kennedy Jr.'s shake-up of the nation's health agencies and persistently high interest rates are prompting it to sink even faster than the broader market, despite so far avoiding the worst of the tariff fallout.

More investors are even wondering if the whole model—risky science, costly funding, political uncertainty and long waits for payoffs—is **simply broken**. For many of the nearly 200 companies trading below their cash value, it probably is. That illustrates the pitfalls of passively investing in an index for this sector. Despite that bleak backdrop, there are still some opportunities for patient investors. After all, the U.S. is still the top spender on drugs by far. And that isn't something RFK Jr. or President Trump is likely to change.

That isn't to play down the overall risk. Even before RFK Jr.'s appointment, biotech was already reeling. **Wave after wave of bankruptcies, shelved drug programs and layoffs had hollowed out the sector.** Dozens of companies that went public during the pandemic-era boom have been locked out of capital markets. Over the past five years, the SPDR S&P Biotech ETF (XBI), which tracks small- and midcap biotech stocks, has lost 14%, while the S&P 500 has gained 89%.

There are also concerns about long-term funding. The Trump administration's budget cuts at the National Institutes of Health are clouding the sector's innovation pipeline, while China's growing biotech industry is siphoning off deals.

Even without direct tariffs, Trump's threat of "sectoral" levies on imported pharmaceuticals is chilling investment. Deal flow, too, has dried up. Eli Lilly Chief Executive David Ricks recently warned that if drugmakers can't raise prices to offset tariffs, they will be forced to scale back research and development.

Conditions at the FDA might also not be as bad as the market fears. Despite RFK Jr.'s purge, the agency is still approving drugs at a normal pace for now, points out John Crowley, CEO of the Biotechnology Innovation Organization, the industry's main trade group. Industry leaders are closely watching whether new Commissioner Marty Makary, a respected Johns Hopkins surgeon, will install strong scientific leadership to replace officials being ousted by RFK Jr.

Source: https://www.wsj.com/tech/biotech/biotech-industry-trump-tariffs-rfk-jr-62a3cfc1

Trump Health Policy Uncertainty Sends Biotech Sector into Deeper Slump

By Maggie Fick and Bhanvi Satija, Reuters, April 14, 2025 (excerpt)

Trump administration cuts across federal health agencies have sent shivers through a biotech industry already struggling through a prolonged downturn, increasing concerns they will have a harder time getting products approved, investors, company executives and analysts said.

Mass firings at the U.S. Food and Drug Administration are particularly risky for small- and mid-cap biotech companies that have innovative treatments in clinical trials but no products on the market to keep them afloat, these sources told Reuters.

Directives from President Donald Trump's administration to freeze grant funding from the National Institutes of Health may also discourage future talent and resources from flowing into the biotech sector, some of them said.

"The sector needs a predictable, science-led regulator to function," said Linden Thomson, senior fund manager at asset manager Candriam, whose biotech fund holds shares in Vertex and Ascendis Pharma. "The future cash flows of the businesses that are used to value stocks are, in biotechnology, in large part based on U.S. commercial sales. If you don't have U.S. approvals you don't have future value," Thomson added.

Source: https://www.wsj.com/tech/biotech/biotech-industry-trump-tariffs-rfk-jr-62a3cfc1

U.S. Health Secretary Robert F. Kennedy Jr. says the layoffs that began last week are needed to streamline the nation's health bureaucracy and will improve agencies' work. But the ouster of top scientists at FDA and other institutions has raised questions over how they will fulfill their missions.

Biotechs have faced delays in scheduling meetings and receiving feedback from the FDA that guides drug development, according to a letter from company executives and investors to Congress this week. "Many have concerns that approval decision deadlines will be missed," the letter said.

"The overwhelming view is that the regulatory agency is impaired, although we have not seen the consequences of it yet since the layoffs and firings have only recently occurred," said Paul Ariano, associate portfolio manager at Thornburg Investment Management, whose fund holds shares in Sarepta Therapeutics and Cytokinetics. **"Sentiment is bad and there is little clarity on the factors that could provide more optimism,"** he said.

Multiple Trump executive orders are blocking funding from the NIH. Funds for early-stage research that NIH has traditionally provided help drive the formation of biotech startups, some of which go on to develop important medicines on their own or in conjunction with large pharmaceutical companies.

"It's a perilous time for small- and mid-cap biotech companies and this will have knock-on effects for the development of new medicines and treatments in years to come," said Tim Opler, managing director in Stifel Investment Bank's Global Healthcare Group.

The climate of uncertainty has left biotechs largely unable to access public capital. Biotech companies have raised $4.2 billion this year compared to $11.1 billion in the same period last year, according to LSEG data.

The Trade War Hits Pause, But the Biotech Doom Loop Carries On

Fund managers and others still see plenty of reason to worry.

Adam Feuerstein, *Stat+*, Opinion, April 10, 2025 (excerpt)

Biotech stocks and the broader markets snapped higher Wednesday after President Trump announced a 90-day pause on reciprocal tariffs for all countries except China, backing down from a trade policy that had triggered a global macroeconomic crisis. The XBI on Wednesday was down more than 4% at 11 a.m. EDT, but shot upward instantly when Trump's tariff retreat was announced in the early afternoon. The index closed 7 % higher — a remarkable 11-percentage point swing.

But biotech stocks are still in a doom loop

Yesterday's development was positive, and might start a longer biotech recovery, but it's too early to stop worrying. This remains the scariest biotech market I can recall since the 2008 global financial crisis.

Tariffs haven't gone away — in fact, we might still see new tariffs specifically targeted at the biopharma sector — and the trade war with China has escalated. The FDA is still a mess and health secretary RFK Jr. still runs HHS. These are not happy days.

Here's the six-month performance of the XBI and the BBC. The latter is a large basket of development-stage biotechs that exemplify the sector's innovation and risk. These are the small- and mid-cap stocks that feature most prominently in biotech investment portfolios.

A 45% plunge in the BBC is shocking. It was -50% before Trump's tariff retreat, so what really changed? Not much.

My sense from conversations with fund managers this week is that they're just trying to survive for another day, and hoping redemptions don't force them to liquidate and shut down.

Source: https://www.statnews.com/2025/04/10/biotech-trade-war-doom-loop/

Is it Time to Get Optimistic?

Feuerstein's opinion piece accurately describes fund manager sentiment and mirrors our "Color From Hedge Funds" comments a few pages back. Feuerstein is not spinning what market participants are thinking right now.

Interestingly, rumors abounded last week, probably with some accuracy, that long-only managers were pulling back and allocating away from biopharma, worried about FDA's stance after Peter Marks resigned from the agency.

We found even hardened investors exhausted and negative on the market late last week. One manager pointed to three great reasons to short the market "all the way down": (1) a dysfunctional FDA, (2) a situation with China that will not end well "anytime soon" and (3) forced hedge fund outflows linked to redemptions and gates that have "already gone down". The manager hastened to add that Trump's "90-day" tariff pause will be up "before we know it" and we'll right back to the "same mess" we faced early last week.

We have no ability to forecast the market for the weeks ahead, but we remain optimistic about biotech in 2025 and think shorting the biotech market right now is likely to be quite dangerous. It's no secret, of course, that we bias to the optimistic side and recent concerns about sector viability are nothing new.

Biotech booms have always been preceded by periods where market participants considered that the sector might be doomed. In addition to previously mentioned positives (upcoming M&A activity, accelerating innovation), there are some potentially interesting more near-term sector dynamics at play.

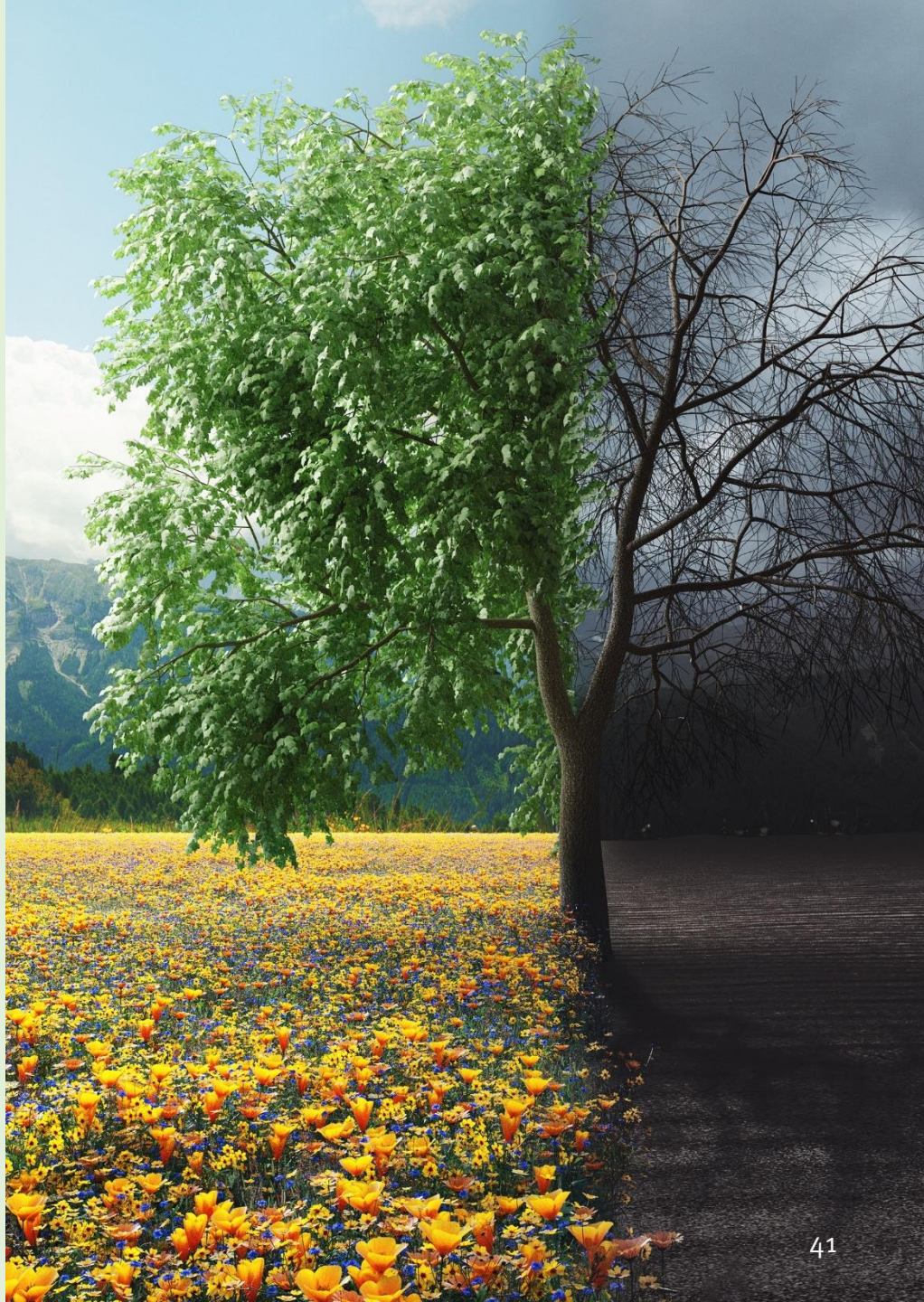
The Ladder of Boom Piercing the Cloud of Doom

We've Seen the Bad and the Ugly But Not the Good

Investors are very focused on FDA and China downside right now and aren't necessarily considering potential upside. We are hearing some potentially quite positive rumors in the market. To be clear, this is *rumor* – passed on in private phone calls without strong substantiation, so take this for what it is worth. Both rumors below are consistent with what people with the Administration's ear, such as Joe Lonsdale, have been saying recently.

First, we are hearing that the FDA is likely to increase the number of approvals this year substantially to show that they can get by with fewer people. Despite this, most of the key people who drive drug approvals, like Nicole Verdun, in groups like CBER and CDER are in place and committed. And, also, RFK wants to create a less administrative, more market-based approach to bringing drugs to the American people. It's interesting that RFK ditched a congressional appearance last week. We are hearing that he is still very much sorting things out and that positive things for industry may come soon, particularly in the rare disease and chronic disease areas.

Second, we are hearing that the Administration may take steps to advantage U.S. biotech given rising Chinese competition. The recent NSCEB report could be the impetus for doing this. This could be tricky, of course. For example, while there is no statutory way to impose tariffs on IP transfers, one could argue that pharma deals with China somehow endanger national security and use Commerce Dept rules to somehow impair or tax China licensing. This may prove to be self-defeating and bad for patients. Further, the global large pharma sector is, well, global. So, it would be hard to stop China licensing to pharmas outside the U.S. who could then be advantaged. A more likely event is that the U.S. would simply provide some type of subsidy or advantage to U.S. biotechs. One could imagine, for example, a transferable tax credit being used.



Data Hold Back is At Play with Some Companies

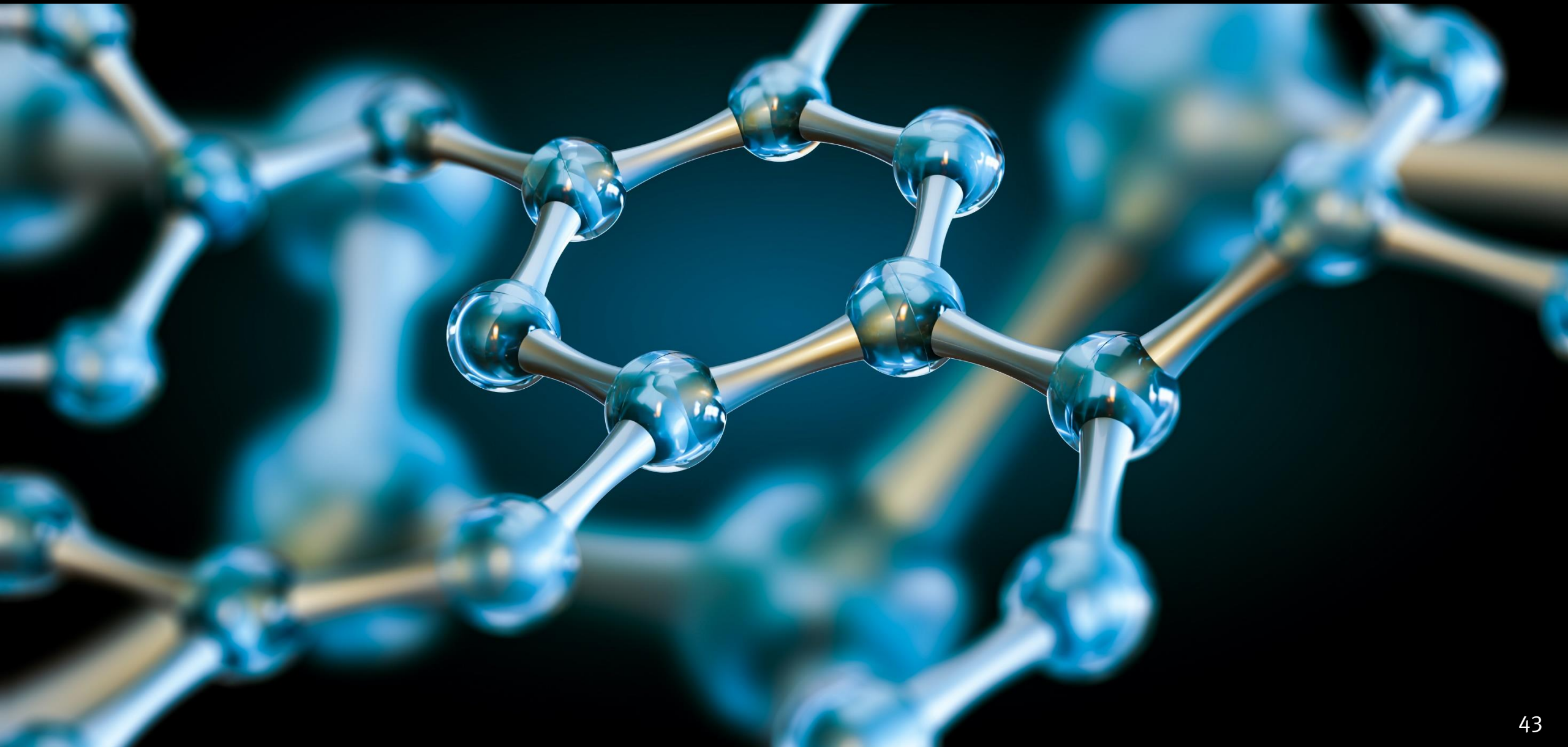
Last week saw Summit signal that they may be sitting on good data for ivonescimab when management stepped up and started buying stock in quantity. They may not be the only company sitting on good data. It's well understood in our industry that most biotechs are quick to release positive data and slow to disclose the negative. We all understand the incentives in a capital-intensive industry. There is always discretion that companies have under SEC rules as to when they release data, particularly when ongoing studies are open label.

But a number of biotech CEOs have said to us that there is "no point" in releasing positive data right now. The market goes down "no matter what you say" so "why say anything?". And with a tough financing market and absurd low valuations, CEOs would rather save their good news to a time when it might be helpful in facilitating a capital raise.

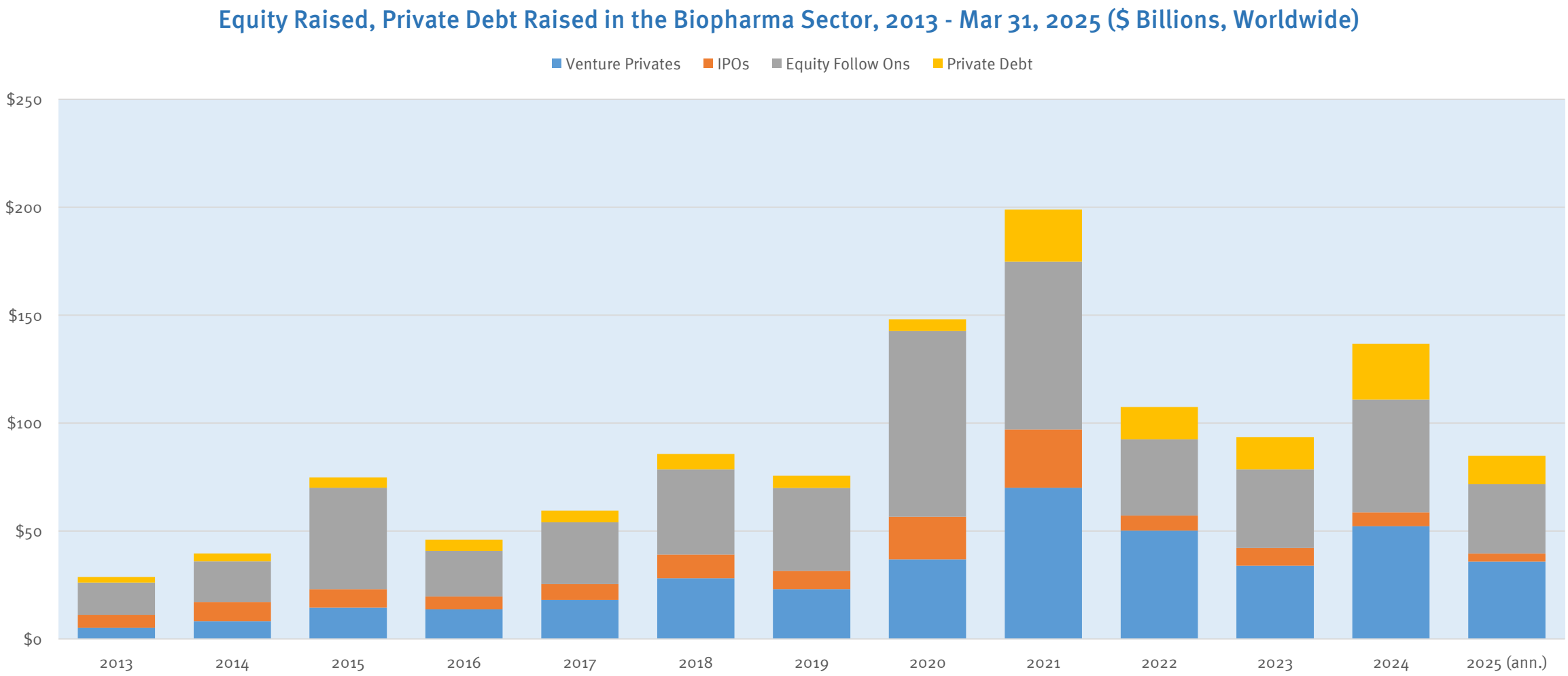
We are aware of at least a handful of small biotechs that are sitting on very good data and focused on the one type of communication that matters: talking to the FDA. And the FDA is sending good signals right now to these companies. And is engaging and meeting with them. We know of two companies where the FDA has unexpectedly pushed them to file for approval for rare disease drugs in recent meetings. We do not wish to imply that dozens of biotechs are sitting on positive data, but we think that industry news is likely to be reasonably positive in the months ahead, once it gets flowing again.

Overall, in the current environment where worries about tariffs and the FDA have sent the sector into a swoon, we think that investors may simply be missing some dynamics that are setting up biotech for a favorable rest of 2025.

Capital Markets Update



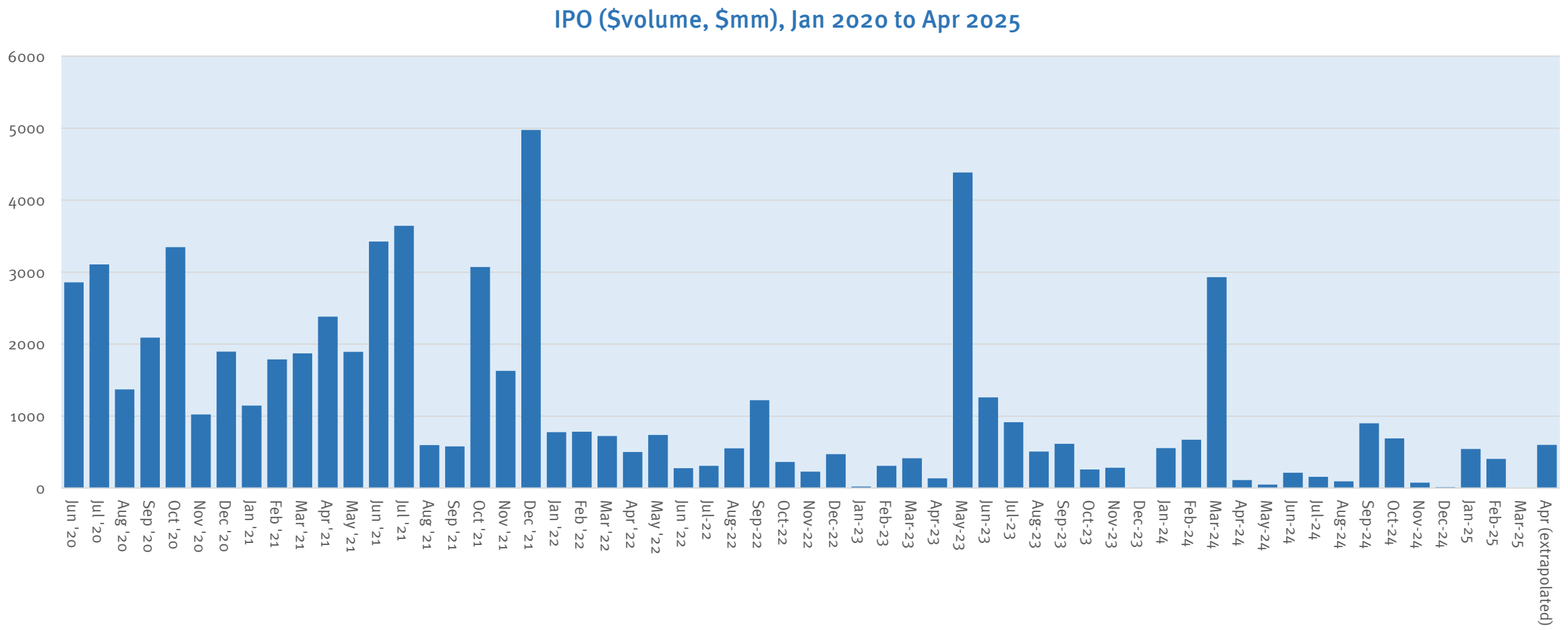
Overall Biopharma Financing Pace Slower in 2025 than the Last Five Years



Source: Data from CapitalIQ and Stifel research.

All Quiet on the U.S. Biotech IPO Front

Last week saw Duality's $200mm IPO get done in HK. With the VIX over 20% and a down market, conditions were not conducive to efforts by companies to go public on the NASDAQ. The IPO market in biotech, for now, has migrated outside the U.S.



Source: Data from CapitalIQ and Stifel research.

Market Volatility Compounds ‘Already Challenging’ Year for Biotech IPOs

James Waldron, *FierceBiotech*, April 11, 2025 (excerpt)

The market turbulence unleashed by President Donald Trump’s tariff policies will likely evaporate the trickle of biotech IPOs that were expected in 2025, a capital markets expert has told Fierce.

While the Nasdaq has recovered from a nosedive triggered by the announcement of President Trump’s global tariffs last week, the stock exchange is still down 15% so far this year. The severity of many of the planned tariffs has been reduced, but fears of an escalating trade war with China and tariffs being introduced for pharmaceutical products still loom large.

The additional volatility these statements have created for the markets in recent days has exacerbated an “already challenging year,” Adam Farlow, Global Chair of Baker McKenzie’s Capital Markets Practice Group, told *Fierce Biotech* in an interview this morning.

“No one was saying 2025 was going to be an awesome year for biotech IPOs, in particular,” he said. “Last week's announcements created additional volatility. Equity markets hate volatility, right?”

“People are going to get their head around what is happening and the volatility will dissipate,” he added. “I do think that's the way it's going to play out—but in the short-to-medium term, there will continue to be volatility,” Farlow said. The early weeks of 2025 saw IPOs from the likes of obesity-focused Aardvark Therapeutics, cystic fibrosis company Sionna Therapeutics, and kidney-focused Maze Therapeutics. Metsera’s $275 million public offering in late January was the largest of the bunch, with the biotech earmarking proceeds for its GLP-1 weight loss asset.

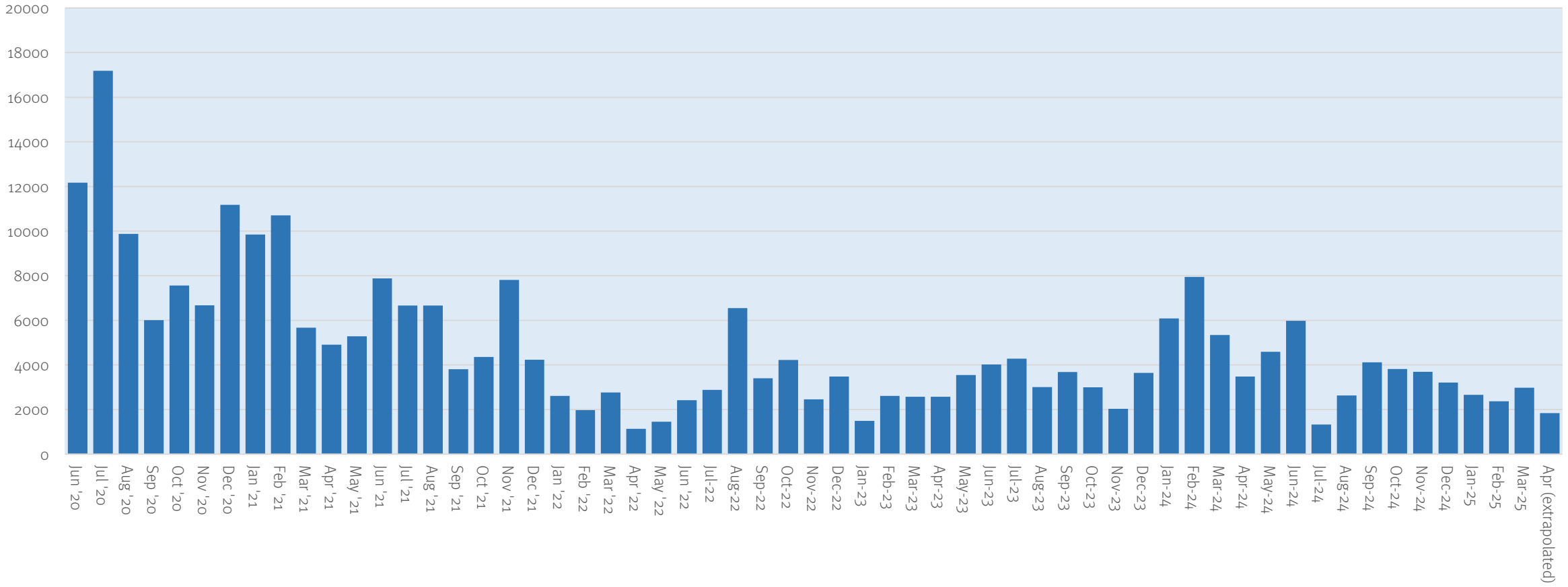
But further Nasdaq debuts look unlikely in the near-term. One consequence of the stock exchange fluctuations has been a loss of equity for investors across all markets, which “can’t possibly be good for the IPO market,” Farlow said.

Source: https://www.fiercebiotech.com/biotech/market-volatility-adds-already-challenging-year-biotech-ipos

Follow-On Equity Financings Very Slow this Month

March was not a bad month for follow-ons. The environment, however, in the last several weeks has been far worse with $498 million in deals done the week before last and $115 million in deals done last week. Our data show global follow-on volume. Much of the uptick in March was caused by volume on the Chinese markets.

Equity Follow-On ($volume, $mm), Jun 2020 to Apr 2025

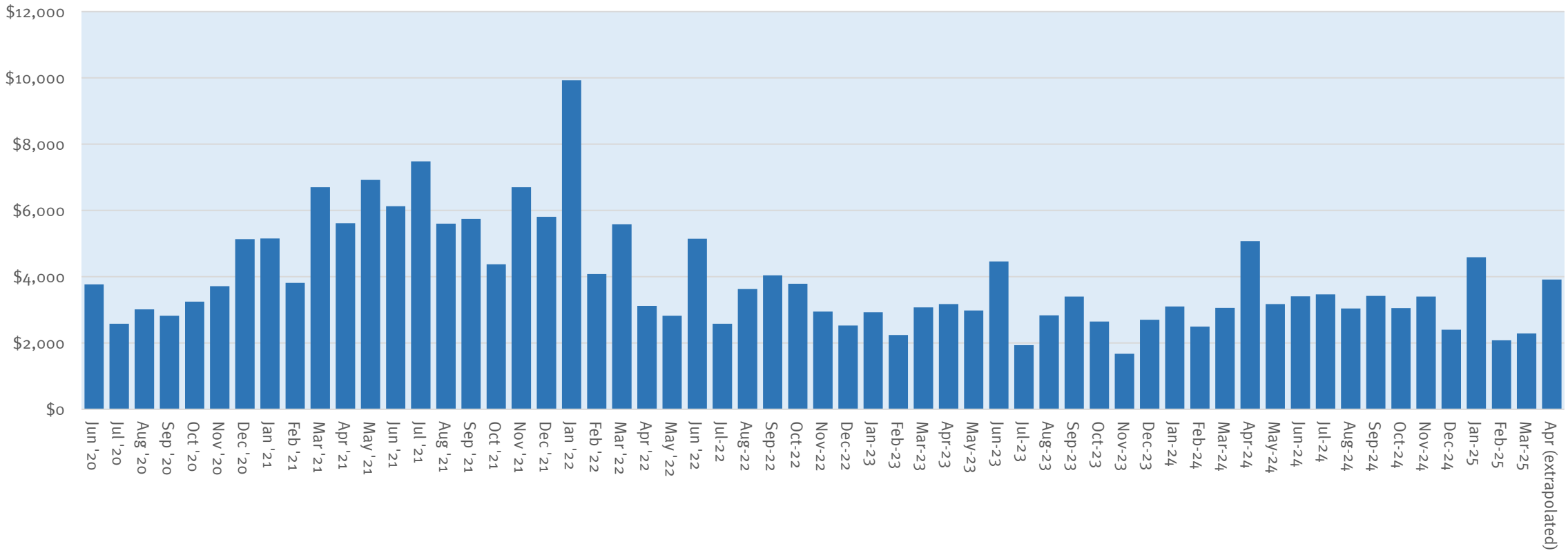


Source: Data from CapitalIQ and Stifel research.

Venture Privates Market Holding Up

The first six weeks of 2024 saw private raises of $900mm a week, on average. The pace of raises fell below this in February and March but has picked up in April, largely due to a $600mm raise by Isomorphic Labs.

Monthly Private Equity Placement ($volume, $mm), Jun 2020 to April 2025



Source: Data from CapitalIQ, Crunchbase.

Biotech Venture Creation: The Benefits Of Scarcity

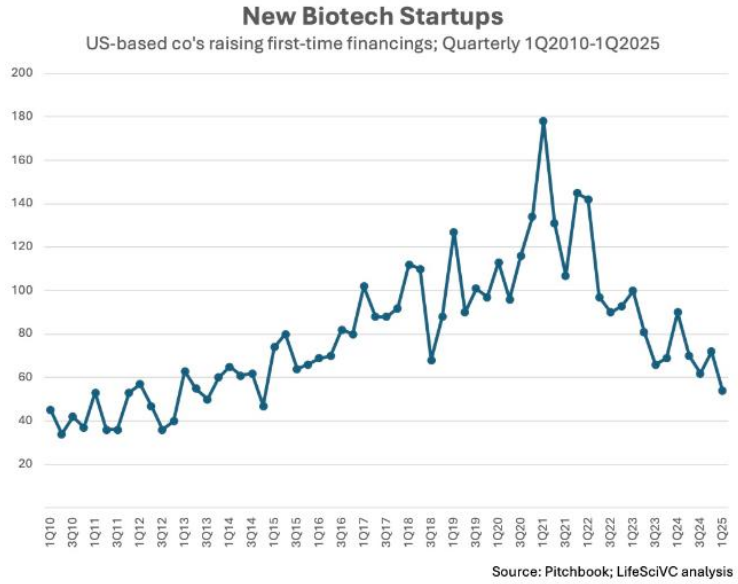
Bruce Booth, *LifeSciVC*, April 8, 2025 (excerpt)

The equity markets have collapsed in 2025, the IPO window is closed, the FDA is in turmoil, the NIH is being gutted… and it's a great time to start new biotech companies.

Why? Because there are so few being created today and there's far less competition for biotech's startup resources.

Here's a snapshot based on the current cut of Pitchbook data: the 1Q 2025 was the lowest quarterly level of new biotech startup formation in the US for a least a decade.

This trendline downwards has been in place for four years, since the all-time-high in 1Q 2021 when the $XBI hit it's peak, and this contraction was the subject of prior blogs in 2023 (Biotech Funding: Times Are Tough, Maybe For The Better) and in 2024 (The Biotech Startup Contraction Continues… And That's A Good Thing), both of which highlighted the value of shrinking the pool of VC-backed biotechs. The pace of new startup formation is now down nearly 70%.



Taking a purely microeconomic viewpoint, startups operate in an "biotech equity" supply-demand environment. When demand to purchase new equity accelerates in frothier markets, tons of supply gets created: over 170 startups got their first financings in 1Q 2021. When demand contracts, supply shrinks: as it has over the past four years. But as a supplier – which venture creation firms like Atlas are – we'd much rather operate in a world of scarce supply as we create our "products". When everyone is creating startups, hyper-competition for resources, patients, and mindshare is a challenge. But with scarce startup supply, when investor demand returns, which it will (as financial cycles are endemic to markets), we'll see value appreciation: by providing a fresh supply of new equity ownership around promising drugs (with clean cap tables), founding/existing equity holders will be rewarded. Paraphrasing an early mentor of mine: as an early stage VC, you need to have an inventory of emerging investments for when the demand part of the cycle accelerates.

Beyond basic supply-demand economics, the three ingredients – or "resources" – required for VC-backed biotech startups are all very favorable today: science, talent, and capital.

Source: https://lifescivc.com/2025/04/biotech-venture-creation-the-benefits-of-scarcity/

LifeSciVC Article Cont. ("Tough Times = Great Biotechs")

Scientific substrate for startups is as strong and mature as ever. As a sector, over the past decade we experimented with and developed a broad toolkit of modalities to address specific drivers of disease with a wide range of therapeutic deliveries. We are now deploying the tools that work best in the context of new medicines addressing real unmet needs, by developing degraders, drugs based on covalency and allostery, genetic medicines, or multi-specific engineered biologics, to name a few. And we're sourcing this startup substrate from all over the globe (from China to the Cambridges, from Italy to Indianapolis) to create NewCo's, often headquartered in our backyard biotech communities.

The market for talent has loosened considerably; great leadership and strong managers are never easy to attract and retain, but things are far more favorable for recruiting teams than back in 2021. Voluntary turnover rates are at decadal lows, and the pool of available talent is deep (and filling with the unfortunate RIFs and belt-tightening). While there's always a "war for talent" for the best teams, the "heat of combat" has come down considerably in this market.

Private capital remains abundant by historic measures, even if more risk-averse today, and more focused on assets than platforms. The first quarter of 2025 saw more than $5B in venture funding for biotech, and over the past twelve months there's been $25B invested. Compared to the same annual period in 2017 and 2018, this is 50% and 25% higher amounts of venture funding, respectively. And it's 300-400% higher than at the start of the secular bull cycles in 2013-2014. Every week there's a new $100M+ mega-round being announced. So there's plenty of dry powder, even though it often feels like firms are just sitting on it. While private valuations for emerging companies seeking Series B and later private rounds remain challenging, funding rounds are getting done (though taking longer to close). And those backlogged private companies waiting to go public need to weigh the deep discounts of raising in the private markets (and the significant equity dilution that implies) with the alternative of selling/partnering assets to strengthen their balance sheets. We've seen a number of those deals lately.

Stepping back and looking at these long-term dynamics when you are in the midst of the bear market part of the financial cycle is often very difficult. And for investors (and management teams) who are being judged on their monthly or quarterly returns, it's brutal. These near-term challenges are not to be taken lightly as they have ripple effects and consequences. Redemptions to funds and capitulation to stock prices raises the cost of capital, sometimes beyond existential levels – as we're seeing in the public markets today.

Big doses of discipline are important medicine for emerging companies to take right now: focusing on portfolio priorities, tightening budgets and belts, exploring partnership alternatives, considering creative mergers, etc….

Multi-year contractions like the one we're in help to recalibrate the overall number of biotech companies. Flux in this ecosystem determines the equilibrium state: startup creation adds to the system, exits and failures subtract. Startup creation is down considerably, and while good exits are constrained (IPOs and mergers / acquisitions), failures have accelerated (shutdowns and liquidations/bankruptcies).

So the "flux" favors a smaller overall ecosystem, though this process takes years to reset. Likes pigs going through the snake, biotechs work their way through the system. After four years of this prevailing flux dynamic, the private VC-backed ecosystem that remains is much healthier: the average health of the herd goes up with scarcity.

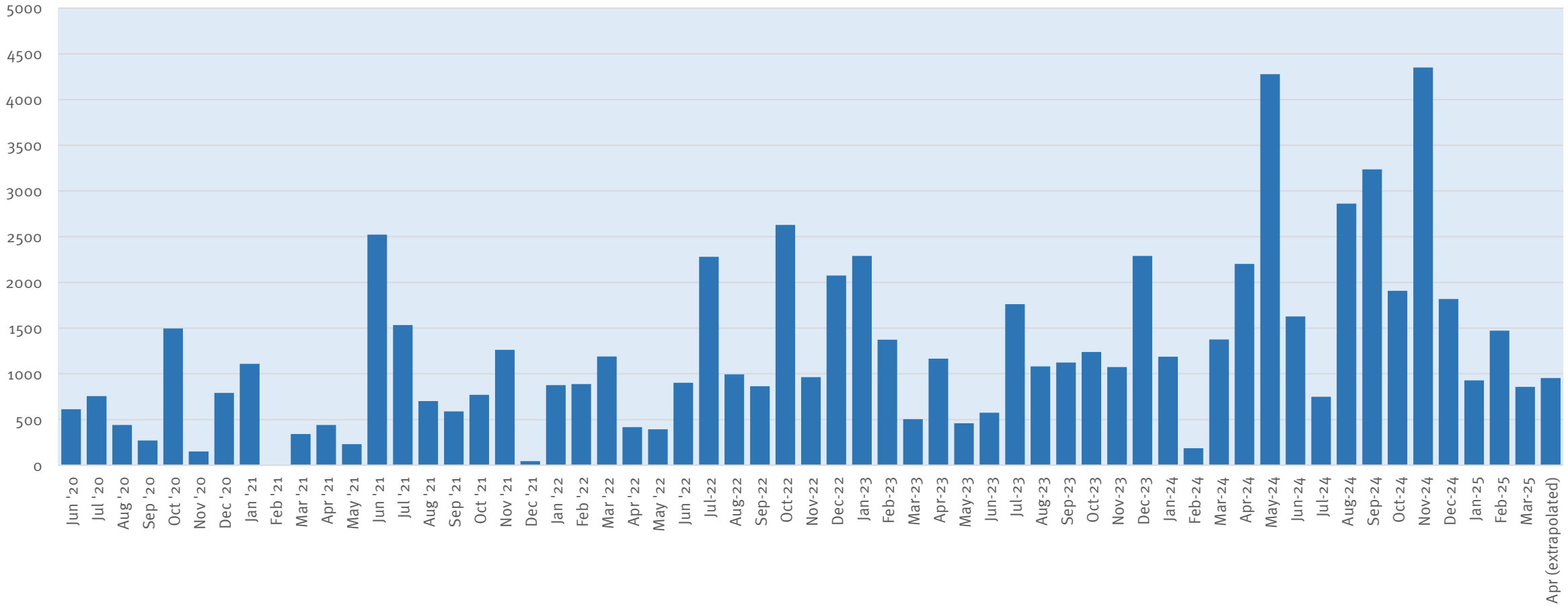
But it's also important to remember that **great companies are often born out of tougher times. Alnylam was started in the nuclear winter of 2002. Nimbus was formed in the spring of 2009, at the bottom of the markets.** Kymera was being formulated in the late 2015/early 2016 bear market.

Source: https://lifescivc.com/2025/04/biotech-venture-creation-the-benefits-of-scarcity/

Global Biopharma Private Debt Placement Volume Has Fallen

The volume of debt deals is running under $1bn a month. This is down considerably from volumes in Q4 2024. Last week saw three companies take down private debt. This was led by Moonlake which raised $75mm from Hercules.

Private Debt Issuance ($volume, $mm), June 2020 to Oct 2024

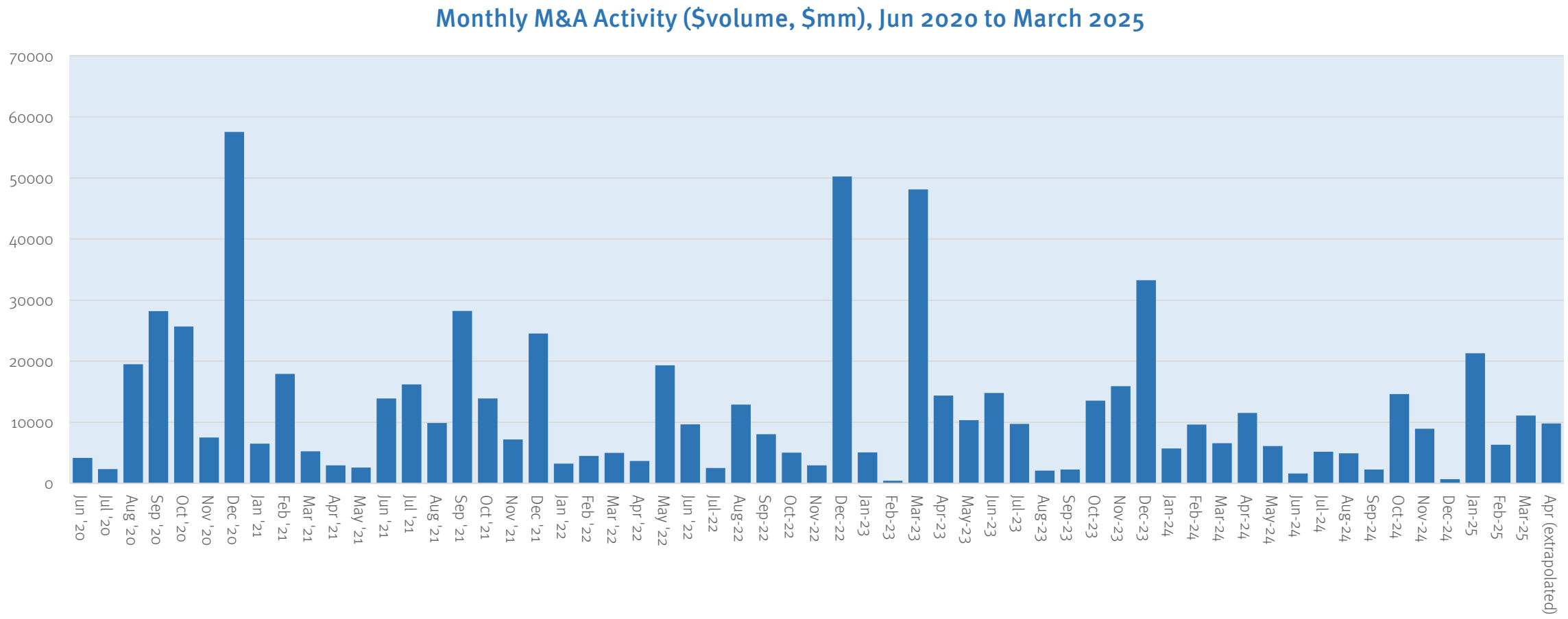


Source: Data from CapitalIQ, Crunchbase.

M&A Update

M&A Market Solid This Year

The M&A market was quite active in March 2025 with two large deals announcing (ENDO/Mallinckrodt and Bain/Tanabe). With the acquisition of Karo Bio by KKR last week, volume remains on a $10bn a month track in April. Interestingly, the overwhelming volume of M&A this year has been late-stage or commercial stage with PE firms undertaking two of the three largest deals in the last 45 days.



Source: S&P, CapitalIQ

Karo Healthcare Announces KKR As New Owner

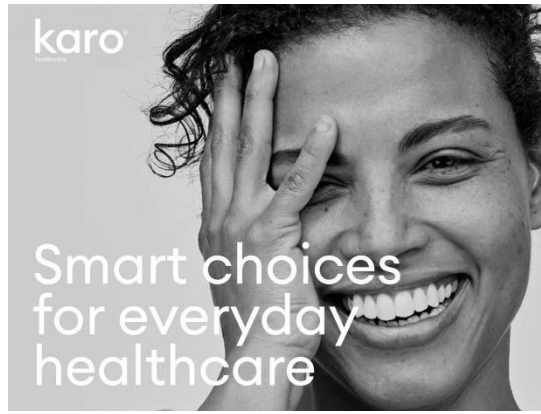
KKR Press Release, April 9, 2025

Karo Healthcare ("Karo") will change owner following the announcement that EQT has agreed to sell Karo to funds managed by KKR, a leading global investment firm. The transaction marks a significant milestone in Karo's journey, following a period of rapid transformation, geographic expansion, and strategic portfolio development. Building on its digitised platform, Karo now welcomes new ownership under KKR to accelerate its next phase of growth. The transaction follows Karo's significant strategic transformation from a Nordic specialty pharma business into a leading pan-European consumer healthcare platform, with an attractive product portfolio spanning core categories such as Skin Health, Foot Health, and Intimate Health, as well as Digestive Health and Vitamins, Minerals & Supplements. During the past five years, Karo has scaled substantially, quadrupling in sales, building leading digital capabilities and establishing market presence to reach consumers in more than 90 countries with top brand positions across European markets.

This rapid growth has been driven by a focused strategy that combines strong organic performance with targeted M&A, enabling Karo to consistently outperform its peers while maintaining industry-leading profitability. M&A has played a central role in Karo's expansion, evidenced by the successful completion of eight acquisitions since 2019, including deals with industry players which have enriched Karo's portfolio, strengthened its presence in key markets, and accelerated its entry into new geographies.

"This is an exciting moment for Karo," said Christoffer Lorenzen, CEO of Karo Healthcare. " We're incredibly proud of what we've achieved in recent years and grateful to EQT for their partnership, which has been instrumental in helping us grow and evolve into the business we are today. With KKR as our new owner, we are entering an exciting next phase in our journey. Their global reach, deep sector understanding, and long-term approach make them the ideal strategic partner as we continue to invest in our brands, expand into new markets and meet the evolving health needs of consumers."

Inaki Cobo, Partner at KKR, said: "Karo is a unique platform with high-quality brands, strong digital and commercial capabilities, and a proven strong leadership team. We are thrilled to invest in this European champion's next phase of growth, drawing on our deep experience in the consumer health space to support continued expansion, innovation, and organic and inorganic growth." Hans Arstad, Managing Director at KKR, added: "Karo operates in a resilient, growing sector supported by long-term demographic trends and increasing consumer focus on wellness and self-care."



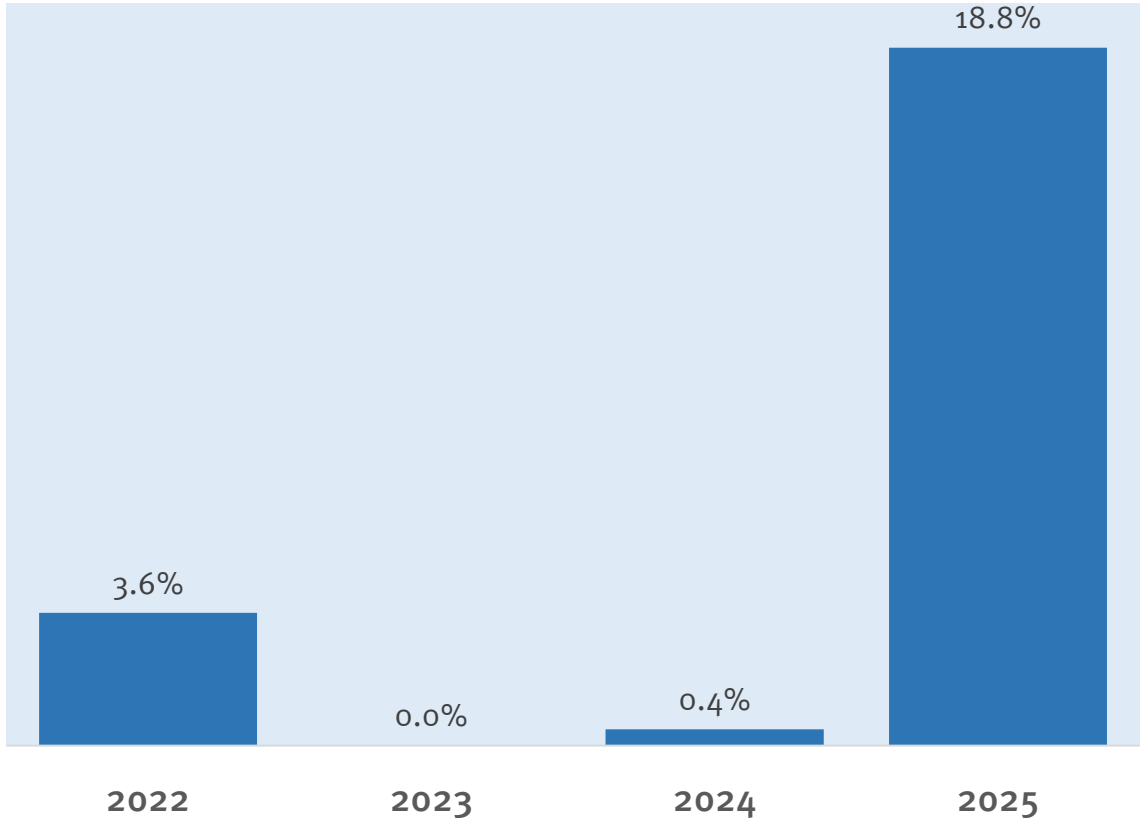
While terms were not disclosed in the press release, it was widely reported in the Swedish press that KKR is paying $2.9 billion to buy Karo Healthcare, a leading OTC firm, from EQT. This is one of the largest M&A deals of the year to date.

Source: https://media.kkr.com/news-details?news_id=7ecc4159-5c35-4da0-b794-ae0027659b8f

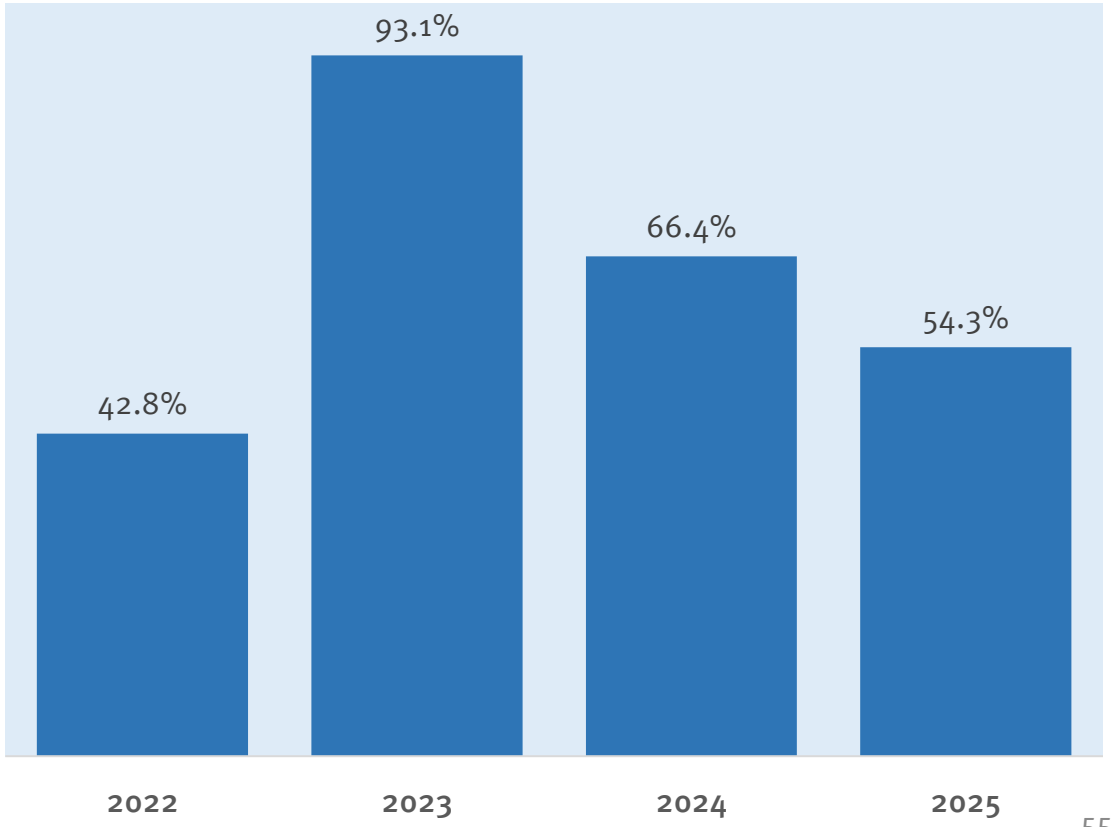
Private Equity Buyers Have Been Unusually Important Thus Far in 2025

This chart shows biopharma buyer type share through the first three and a half months of the year for 2025 and the previous three years. This year, we have seen 18.8% of biopharma M&A volume undertaken by PE firms. This is highly unusual. Big pharma participation have accounted for roughly half the market this year, lower than in the previous two years but higher than in 2022.

Percent of Biopharma M&A Dollar Volume Undertaken by Private Equity Firms (Jan 1 to Apr 12), 2022 to 2025



Percent of Biopharma M&A Dollar Volume Undertaken by Big Pharma Buyers (Jan 1 to Apr 12), 2022 to 2025



Source: DealForma

M&A Recap: Big Pharma Starts the Year Mostly Avoiding Billion-dollar Deals

Jacob Bell, *Biopharma Dive*, April 4, 2025 (excerpt)

The world's largest pharmaceutical companies mostly steered clear of billion-dollar acquisitions in the early months of this year, perhaps indicating how a tumultuous U.S. political environment has led would-be buyers to view bigger deals as too risky for the time being.

Two acquisitions worth $1 billion up front or more — that of psychiatry drugmaker Intra-Cellular Therapies and cancer specialist IDRx — were announced between January and March, according to BioPharma Dive data on the industry's more sizable transactions.

By comparison, six billion-dollar-plus deals were inked during the same three-month period in 2024, though this year's tally is not much lower than the average seen across the starts of the last five years.

It's not just the first quarter, either. Big-ticket biotech buyouts have been getting scarcer for months now. Only four that met BioPharma Dive's criteria were struck across the second half of 2024, which, for the first time in at least seven years, featured no deals worth more than $5 billion.

"We really had a hard time getting through 2024 with regards to deals. It was a depressed environment. Companies were being very, very skittish," said Kristin Ciriello Pothier, Global Deal Advisory and Strategy Leader for KPMG's Healthcare and Life Sciences division. The hope is this year might be different, but "we haven't seen that" yet.

In the first quarter, big pharma was behind five of the 12 deals tracked by BioPharma Dive. The deals included Johnson & Johnson's $14.6 billion purchase of Intra-Cellular; GSK's $1 billion buy of IDRx; Novartis' $925 million acquisition of Anthos Therapeutics; and a couple smaller, cancer-centric offers from AstraZeneca and Bristol-Myers Squibb.

2025 figures through April 3, 2025

Deal value	2018	2019	2020	2021	2022	2023	2024	2025
Up to $500M	11	10	9	15	26	11	13	8
$500M to $999M	5	4	7	4	6	6	8	2
$1,000M to $4,999M	3	9	8	12	8	13	18	1
$5,000M to $9,999M	3	2	1	2	1	4	0	0
$10,000M or more	2	4	3	2	2	4	0	1

Values represent deal count. Acquisitions valued less than $50 million are not included.

Table: Ned Pagliarulo, Jacob Bell / BioPharma Dive • Source: BioPharma Dive • Created with Datawrapper

Source: https://www.biopharmadive.com/news/pharma-biotech-dealmaking-first-quarter-2025-size/744410

Market Volatility to Drive Closer Collaboration Between Biotech Startups, Large Pharma

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

Turbulence in the capital markets is driving biotechnology startups and venture capitalists to consider strategies such as forming closer ties to large pharmaceutical companies.

With optimism budding early this year, biotechs raised $6.3 billion in venture capital in the first quarter, a faster pace than in 2024, when these companies collected $23.6 billion for the full year, according to investment bank William Blair. Biotechs raised $5.4 billion in the first quarter of 2024.

President Trump's shifting tariffs have caused stock market gyrations, postponing the hoped-for revival of initial public offerings, and cuts at the Food and Drug Administration have stoked uncertainty about how the agency will evaluate new drugs.

A lack of clarity on the financial and regulatory fronts is prompting venture investors to align with drugmakers likely to acquire or partner with their companies and sharpen their focus on the commercial potential of startups' drugs. Alignment with pharmaceutical companies takes on added importance when financial markets are uncertain, observers said.

Dr. Simeon George, chief executive and managing partner of venture investor SR One, said he is having more discussions with pharmaceutical companies to understand what they are looking for and update them on what his company is doing, adding that these discussions are about building relationships rather than dealmaking.

"That is where I am spending a ton of time," George said.

Krish Ramadurai, a partner with AIX Ventures, said he is banking on startups' interactions with the FDA taking longer because of turnover at the agency. Startups will have to fund themselves while they wait, which will lead more to consider partnerships with pharmaceutical companies sooner than they otherwise would, Ramadurai said.

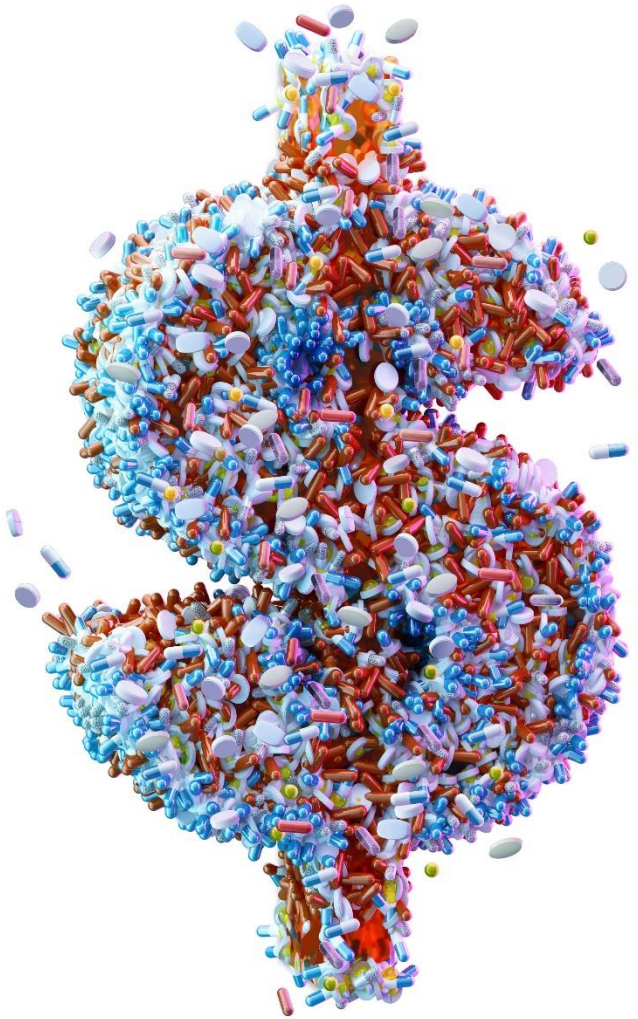
Lee Cooper, managing director of Delos Capital, said volatile markets increase the importance of partnerships that provide know-how as well as capital, adding that in addition to collaborations with drugmakers, startups can gain insights by having the venture arms of these companies as investors. Companies, he said, must examine clinical-trial designs to identify the goals that will drive the most value if achieved.

Source: https://www.wsj.com/articles/market-volatility-to-drive-closer-collaboration-between-biotech-startups-large-pharma-473c0199

Industry Update

Pharma Tariffs Are Coming. Investors Underestimate the Risk

Josh Nathan-Kazis, *Barrons*, April 11, 2025 (excerpt)



While President Donald Trump and his advisers have waffled on the fate of their so-called reciprocal tariff plan, they have remained rock solid on another trade promise: big tariffs for drugmakers.

Trump vowed late Tuesday he would soon impose “a major tariff on pharmaceuticals,” and on Wednesday, after Trump suspended the “reciprocal” tariffs on most trading partners, Treasury Secretary Scott Bessent said during a news conference the pharmaceutical tariffs were still coming.

Later that day, talking to reporters in the Oval Office, Trump suggested the tariffs on pharmaceuticals could be as high as 200%.

“If they have to pay that, they’re going to say, ‘We’re not going to pay that, we’re going to build here,’” Trump said.

Drug stocks have fallen on the tariff threats, but they may not have fallen far enough.

Analysts projecting the potential impact of tariffs seem to be assuming levels of less than 50%. But Trump has indicated the actual tariff levels could be far higher, and recent history suggests that relying on the president to take a moderate course on trade policy would be a bad bet.

It is unclear how the tariffs would even be calculated, so arguing over the details of their impact may not be worth the effort. What’s clear is the threats have significantly dimmed the outlook for biopharma, which was already facing a litany of problems—patent cliffs, drug price reform proposals, and looming worries over the stability of the Food and Drug Administration.

What does seem clear is that there are some biopharma names that would fare relatively better under pharmaceutical tariffs.

Source: https://www.barrons.com/articles/pharma-stocks-tariffs-vertex-pfizer-768bb43b

Trump's Pharmaceutical Tariffs Could Raise Costs for Patients, Worsen Drug Shortages

Annika Kim Constantino, *CNBC*, April 11, 2025 (excerpt)

President Donald Trump's planned tariffs on pharmaceuticals imported into the U.S. could have wide-ranging consequences for drugmakers and American patients, some experts told CNBC.

The duties could disrupt the complex pharmaceutical supply chain, drive up the prices of drugs in the U.S. and exacerbate shortages of critical medicines, some health policy experts said. Drugmakers often rely on a global network of manufacturing sites for different steps of the production process.

"Anything that we change, any trade policies, any tariff policies, anything that further increases the cost of prescription drugs, be it in the supply chain, the distribution network, risks increasing costs to the consumer even further and just worsening the affordability crisis for drugs in America that we've had for a long time," she said.

Trump this week doubled down on plans to impose "major" pharmaceutical-specific tariffs "very shortly," which battered the stocks of some drugmakers early Wednesday. He said he would pause steep tariff rates on dozens of countries following a market fallout that same day, but it does not appear to apply to levies on specific industries like autos, steel, aluminum and pharmaceuticals.

Trump exempted pharmaceuticals from his sweeping tariffs unveiled last week. Still, he has said duties on drugs will encourage drugmakers to move manufacturing operations into the U.S. at a time when domestic production in the industry has shrunk significantly.

The tariffs could worsen the unprecedented shortfall of medicine in the U.S., which is driven by factors such as manufacturing quality control and demand surges. There are 270 active drug shortages in the U.S., which has remained unchanged for the past three quarters, according to data from the American Society of Health-System Pharmacists.

Source: https://www.cnbc.com/2025/04/11/trump-pharmaceutical-tariffs-may-raise-costs-worsen-drug-shortages.html

RTW Opines on FDA Cuts and Pharma Tariffs

Roderick Wong, Chief Investment Officer, RTW, April 10, 2025

The specter of drug tariffs is killing the biotech industry (which was already reeling from RFK FDA fears). Half of biotech companies are trading below cash, an all-time high. In addition to killing innovation (and gifting China future industry leadership), tariffs would mean drug shortages, and higher insurance premiums. That is the future we're facing if drug tariffs look like the others the WH has announced so far. If we must use tariffs, there is a way to bring back manufacturing without killing the industry and even make US biotech the undisputed leader of the world. Here's how:

1. Announce tariffs that take effect in 5 years (the minimum amount of time to set up a new facility) for each drug, which escalate by year, eg 10, 20, 30, 40% etc.
2. Create new programs to reduce the time to set up a new manufacturing plant from 5 to 2 years.
3. Create special industrial zones in the heartland that fast track all local regulatory approvals, eg for construction, energy, environment, etc. Give tax breaks to the businesses, people (no state income tax, vocational scholarships, etc) who decide to live and work there. Give tax breaks to companies that can get their factories built for every year before 5 years.
4. Mandate FDA cut manufacturing review turnaround times to 30 days for new facilities.

On FDA, people are assuming the layoffs will grind things to a halt. That fear alone is killing investment. Reassurance is critical. Here's how:

1. Hire pro-innovation leadership at FDA who supports innovation publicly.
2. Get people excited that leadership not only knows what the current bottlenecks are, but wants to make things go even faster. Here are the problems and solutions:
3. US is now the slowest country to get Phase 1 studies started, and most conservative on Phase 1 design. Bottleneck is FDA pharmtox and manufacturing. Say will match China, the UK, and New Zealand's speed through reform.
4. For product approvals manufacturing approvals are now gating. Shift to risk benefit related framework, cut the list of regulations that don't materially impact safety, and push non-safety related requirements to post-approval.
5. Push academic institutions to speed up their contracting and IRBs, which are huge bottlenecks to trials. Give NIH grant incentives (eg bonus on top of negotiated indirect costs) to universities with the fastest stats and to encourage tech/AI adoption.

Source: https://x.com/docrodwong

Biotech CEOs, VCs Urge Cassidy, Senate to Ease Impact of FDA Cuts

Experts say the layoffs are already causing issues in drug development — and things may get far worse without critical institutional knowledge at the FDA.

Kristin Jensen, *Biopharma Dive*, April 10, 2025 (excerpt)

Health and Human Services Secretary Robert F. Kennedy Jr. has overseen a chaotic round of job cuts in his department. In March, Kennedy announced plans to fire 10,000 people at HHS, including 3,500 at the FDA. The ensuing April 1 layoffs were filled with errors, and Kennedy admitted that about 20% of the personnel let go would need to be rehired.

Key officials at the FDA have also resigned, some in protest over Kennedy's policies. That includes the agency's top vaccine official, Peter Marks, who left on March 28 and cited his concerns with Kennedy's false claims about the dangers of vaccines.

The biotech industry is already feeling the effects, according to the letter. It cited examples like a Massachusetts biotech whose dispute resolution process was suspended because the company's FDA contact "wasn't confident there would be any senior staff to review it." Another drugmaker is trying to work through a clinical hold but isn't sure if any of its FDA project managers are still at the agency.

Larger policy issues are at play as well. The industry is set to begin negotiations with the FDA this year to renew the Prescription Drug User Fee Act, a critical tool that provides funding for the agency and speeds up approvals of medical products. But the FDA has fired key negotiators, and the broad layoffs may put the overall program in jeopardy by violating the statute's minimum staffing levels.

In the letter, some biotech executives and investors laid out recommendations, including the rehiring of specific agency officials. They named Chris Joneckis and Betsy Valenti to keep the user fee program on track, Yaeming Chae and Isaac Dorfman for capacity planning and workload analysis, as well as four other critical employees: Andy Kish, Patrick Zhou, Emily Ewing and Josh Barton.

Peter Kolchinsky of RA Capital Management, the founder of No Patient Left Behind, is the lead signatory on the letter, which follows two others focused on defending science and warning about FDA budget cuts. Cassidy has called on Kennedy to testify about the cuts, but a planned hearing didn't happen this week. HHS staff plan to brief members of a House committee on Friday, *Politico* reported.

Source: https://www.biopharmadive.com/news/biotech-fda-cuts-senate-cassidy-venture-capital-kennedy-fda/745006/

Trump Administration Reinforces Medicare Advantage's Dominant Position

Joshua Cohen, *Forbes*, April 10, 2025 (excerpt)

Privately run Medicare Advantage plans will get a considerable boost in payments from the federal government. The Trump administration announced this week that it would pay the insurers 5.1% more in 2026 than in 2025. This represents a $25 billion increase. The decision made by the Centers for Medicare and Medicaid Services differed from the 2.2% increase that the Biden administration had proposed in January. The difference reflects updated data on spending patterns within the Medicare program. CMS cites rising medical costs.

Medicare serves roughly 68 million elderly and disabled Americans. It also covers people with certain disabilities or illnesses, such as end-stage renal disease. At age 65, most Americans are automatically enrolled in Medicare coverage for hospital and physician visits costs, known as Part A and Part B, respectively.

Altogether, 54% of people enrolled in Medicare are now Medicare Advantage members. Enrollment has almost quadrupled, from eight to 33 million between 2007 and 2024. KFF expects at least 60% of beneficiaries to sign up with a Medicare Advantage plan by the end of the decade. Over the years, there's been bipartisan support for Medicare Advantage, but perhaps a somewhat stronger preference among Republicans as it aligns with their goal to increase the role of the private sector in administering public programs over government-run entities.

The current head of CMS, Mehmet Oz, once said he favored a system of Medicare Advantage for All, which meant not only fully privatizing the program, but also establishing universal healthcare coverage through Medicare Advantage for "every American who is not on Medicaid."

Medicare Advantage plans suffered greatly under Biden who focused on overcoding rather than viability of the program.

The Medicare Advantage program, ultimately, takes the government out of the business of administering healthcare and replaces it with private enterprise.

This policy step to better fund programs is a major step forward for Medicare Advantage plans that have been increasingly underfunded.

It's an interesting move following the national reaction to the assassination of the CEO of UnitedHealthcare last year, reflecting dissatisfaction with health insurance plans in the U.S.

Source: https://www.forbes.com/sites/joshuacohen/2025/04/10/trump-administration-reinforces-medicare-advantages-dominant-position/

High Stakes Showdown Coming Between Pharma and Compounders

J. Edward Moreno, *Sherwood News*, April 11, 2025

OrderlyMeds, an online pharmacy that sells compounded versions of Eli Lilly'sblockbuster weight-loss drug Zepbound, said the drugmaker's cease and desist letter means "nothing." The Food and Drug Administration declared in December that tirzepatide, the active ingredient in Zepbound, is no longer in a shortage, meaning pharmacies like OrderlyMeds that were selling knockoff versions of the drug can't sell exact copies. But OrderlyMeds kept selling compounded tirzepatide.

Lilly told them to 'please stop doing that or we might sue you,' otherwise known as a cease and desist letter. OrderlyMeds responded on Friday saying the letter "only reinforces and reinvigorates OrderlyMeds' mission to provide patients with tailored healthcare solutions, access, and choice." "Rest assured that OrderlyMeds will defend itself and our patients against these attacks that aimed solely at driving shareholder value for Big Pharma, not the individualized needs of you, the patient," the company said in a statement.

OrderlyMeds says that what it sells is "individualized" and "personalized." "So, what does this mean for our patients?" it said in its response to Lilly. "Nothing." A Lilly spokesperson told Sherwood News that it will "continue to take action to stop these illegal actors and urgently call on regulators and law enforcement to do the same."

"The FDA and a federal court have both made clear that compounders 'must cease production' of compounded tirzepatide knockoffs, and anyone continuing to sell mass compounded tirzepatide, including by referring to it as 'personalized,' 'tailored,' or something similar, is breaking the law and deceiving patients," the spokesperson said. The argument that compounding pharmacies can continue selling "personalized" versions of lucrative weight-loss drugs is one that's also being made by Hims & Hers, which has a much larger patient base than OrderlyMeds. Hims sells compounded semaglutide, the active ingredient in Novo Nordisk's Ozempic and Wegovy, not tirzepatide.

There appears to be a **legal challenge brewing** between drugmakers and compounding pharmacies, which may be able to sue for patent infringement. That type of litigation is risky because if a judge were to rule against the drugmakers, it could risk their patent and the billions they make selling those drugs.

The FDA could step in and decide that these pharmacies aren't compliant and need to stop. **The FDA is now run by Marty Makary, who used to work at Sesame, a telehealth company that sold compounded semaglutide**. Also, things seem pretty hectic over at the FDA at the moment.

Source: https://sherwood.news/business/compounding-pharmacy-says-eli-lillys-cease-and-desist-letter-means-nothing/

Akesobio: The Chinese CEO Who Believes Her Cancer Drug Can Beat Merck's Bestseller

Clarence Leong, *Wall Street Journal*, April 11, 2025 (excerpt)

Amid the worst U.S.-China trade clash in modern history, Michelle Xia thinks she has something Chinese that Americans will want.

It isn't a $3 T-shirt or an electronic gadget. It is a cancer drug her company discovered—one that has made her the face of a rising pharmaceutical star.

When Xia founded her company with three colleagues in 2012, China had few labs capable of finding drugs on their own, while U.S. companies filled their research departments with Chinese scientists. Xia, born in China's northwestern province of Gansu, had been one of them: She did cancer research at the University of Louisville and worked in the U.S. for companies including Bayer.

It nagged at her that her home country had little to match the modern medical feats achieved in the West. "The driver was very simple. I thought: Why isn't there innovation in China?" said Xia, 58 years old, in an interview.

Xia's drug could be the biggest of them all, if its promise can be confirmed in U.S. trials. It is an injected therapy called ivonescimab that has shown favorable results versus Merck's $29.5-billion-a-year cancer treatment Keytruda in a Phase 3 trial.

Today, Akeso's headquarters in southern China's Guangdong province is a sprawling campus with spacious factories making dozens of drugs on the market in China or in clinical trials. It has a staff of more than 3,000 and a stock-market value of about $9.5 billion.

Ivonescimab is called a bispecific antibody because it targets two proteins, hitting one to unleash the immune system to kill cancer cells and a second with the goal of starving tumors of their blood supply. Akeso is developing more than a dozen other bispecific antibodies. Traditional cancer drugs, such as Keytruda, typically target one protein.

A study released last September found lung-cancer patients on ivonescimab on average lasted almost twice as long without the disease progressing as patients on Keytruda. The study was conducted only on Chinese patients.

Akesobio

Michelle Xia
Akeso Bio

Source: https://www.wsj.com/health/pharma/ivonescimab-akeso-michelle-xia-cancer-keytruda-d731f982

FDA To Replace Some Animal Testing With AI, Human 'Organoid' Lab Models

Tristan Manalac, *Biospace*, April 11, 2025 (excerpt)

The FDA is phasing out its animal testing requirements for monoclonal antibodies and other therapies, replacing them with "more effective, human-relevant methods," the agency announced Thursday.

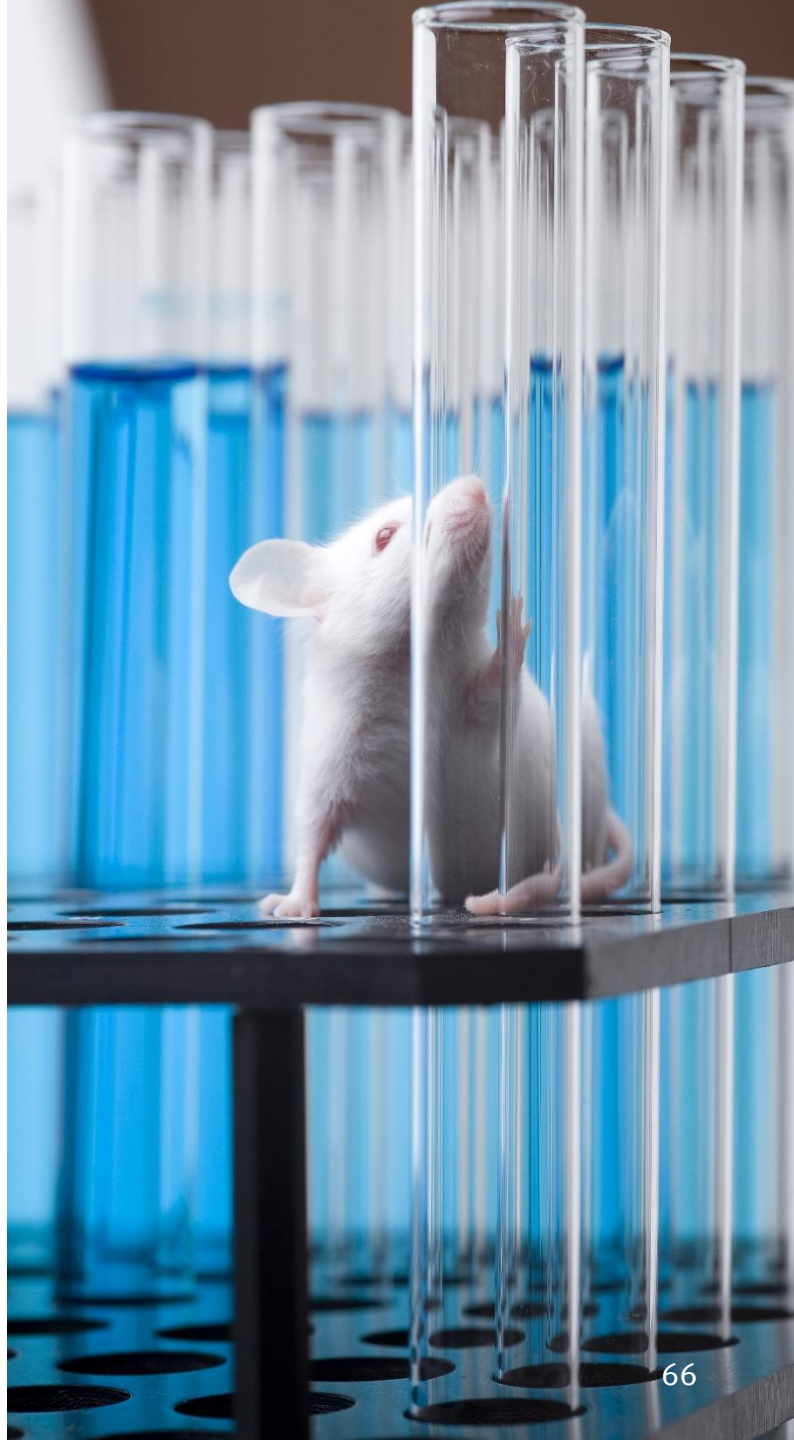
In its press announcement on Thursday, the FDA particularly pointed to "AI-based computational models of toxicity," as an alternative that can be used in place of animal testing. "Software models could simulate how a monoclonal antibody distributes through the human body and reliably predict side effects based on this distribution as well as the drug's molecular composition," the regulator wrote.

Drug sponsors could also use what the FDA calls "human-based lab models," including organ-on-a-chip systems, organoids and other models that can mimic human organs. The FDA will also use existing and real-world safety and efficacy data, including those from other countries, to better assess a drug.

The regulator did not give a detailed timeline for the elimination of its animal study requirements, but it did note that implementation of these new policies will begin "immediately."

"By leveraging AI-based computational modeling, human organ model-based lab testing, and real-world human data, we can get safer treatments to patients faster and more reliably, while also reducing R&D costs and drug prices," FDA Commissioner Marty Makary said in a prepared statement. "It is a win-win for public health and ethics."

Source: https://www.biospace.com/fda/fda-to-replace-some-animal-testing-with-ai-human-organoid-lab-models



Organoids: By Re-Creating Neural Pathway in Dish, Stanford Medicine Research May Speed Pain Treatment

Bruce Goldman, *Stanford University*, April 9, 2025 (excerpt)

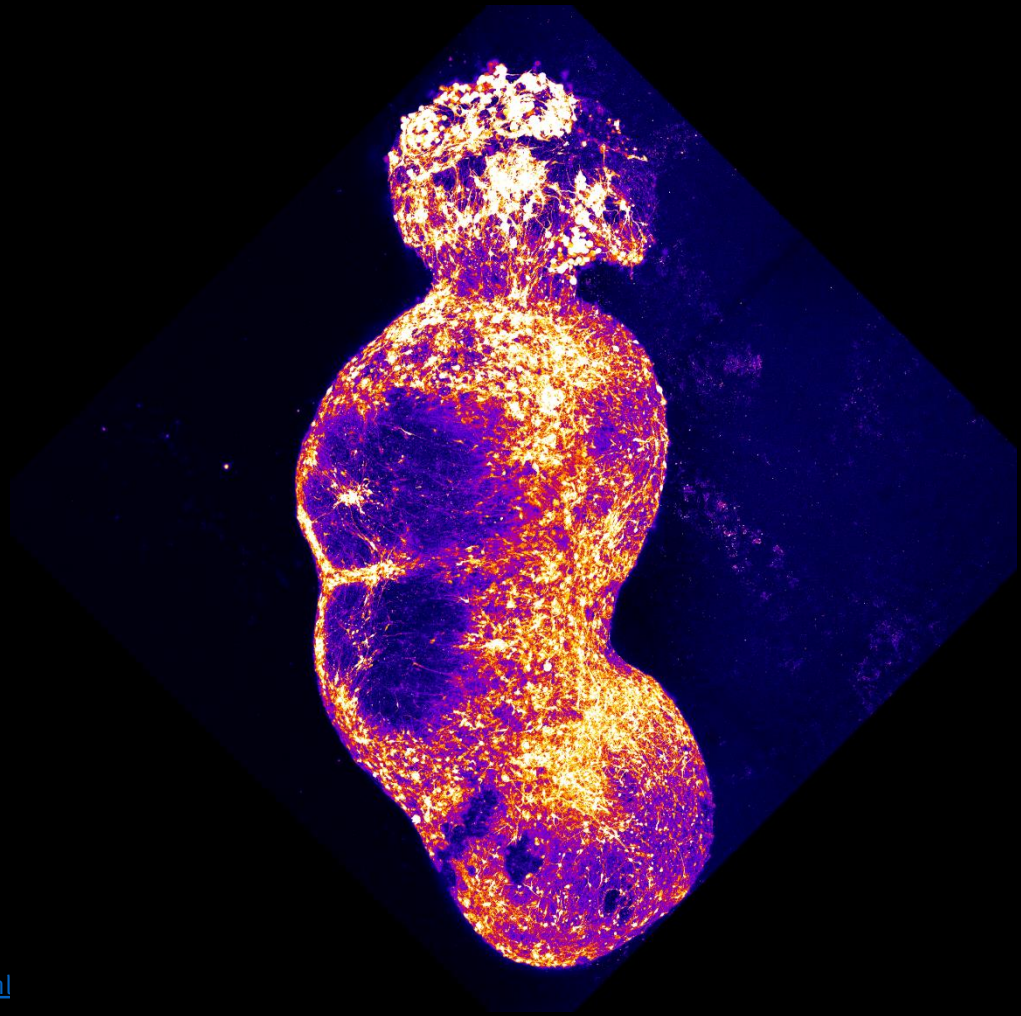
Stanford Medicine investigators have replicated, in a lab dish, one of humans' most prominent nervous pathways for sensing pain. This nerve circuit transmits sensations from the body's skin to the brain. Once further processed in the brain, these signals will translate into our subjective experience, including the uncomfortable feeling of pain.

The advance promises to accelerate what has been slow progress in understanding how pain signals are processed in humans and how best to alleviate pain.

In a study published April 9 in *Nature*, scientists led by Sergiu Pasca, MD, the Kenneth T. Norris, Jr., Professor II of Psychiatry and Behavioral Sciences, describe their successful assembly of four miniaturized parts of the human nervous system to reconstitute what's known as the ascending sensory pathway. The peripheral sensation of pain travels to the brain in a relay involving nerve cells, or neurons, centered in four different regions of the ascending sensory pathway: the dorsal root ganglion, dorsal spinal cord, thalamus and somatosensory cortex.

"We can now model this pathway non-invasively," said Pasca, the study's senior author. "That will, we hope, help us learn how to better treat pain disorders."

Researchers created an assembloid by integrating four organoids that represent the four components of the human sensory pathway.

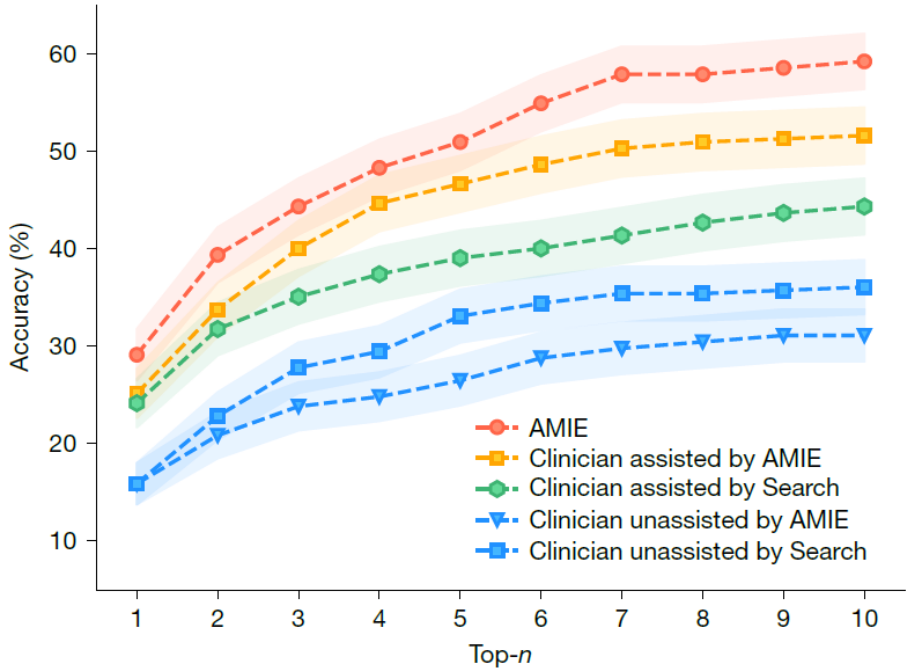


Source: https://med.stanford.edu/news/all-news/2025/04/pain-neural-pathway-dish-speed-treatment.html

Google Research Team: Towards Accurate Differential Diagnosis with Large Language Models

McDuff et.al., *Nature*, April 9, 2025

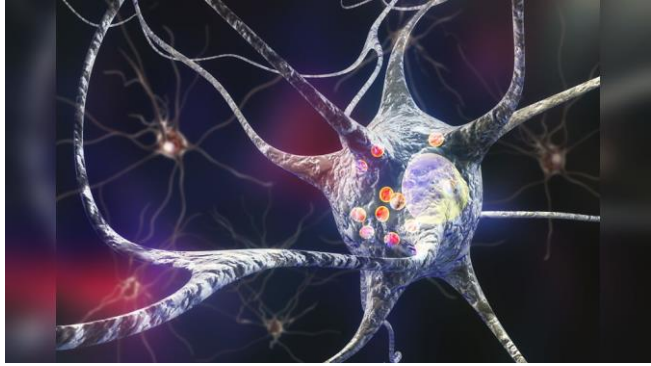
A comprehensive differential diagnosis is a cornerstone of medical care that is often reached through an iterative process of interpretation that combines clinical history, physical examination, investigations and procedures. Interactive interfaces powered by large language models present new opportunities to assist and automate aspects of this process. Here we introduce the Articulate Medical Intelligence Explorer (AMIE), a large language model that is optimized for diagnostic reasoning, and evaluate its ability to generate a differential diagnosis alone or as an aid to clinicians. Twenty clinicians evaluated 302 challenging, real-world medical cases sourced from published case reports. Each case report was read by two clinicians, who were randomized to one of two assistive conditions: assistance from search engines and standard medical resources; or assistance from AMIE in addition to these tools. All clinicians provided a baseline, unassisted differential diagnosis prior to using the respective assistive tools. AMIE exhibited standalone performance that exceeded that of unassisted clinicians (top-10 accuracy 59.1% versus 33.6%, P = 0.04). **Comparing the two assisted study arms, the differential diagnosis quality score was higher for clinicians assisted by AMIE (top-10 accuracy 51.7%) compared with clinicians without its assistance (36.1%; McNemar's test: 45.7, P < 0.01)** and clinicians with search (44.4%; McNemar's test: 4.75, P = 0.03). Further, clinicians assisted by AMIE arrived at more comprehensive differential lists than those without assistance from AMIE. Our study suggests that AMIE has potential to improve clinicians' diagnostic reasoning and accuracy in challenging cases, meriting further real-world evaluation for its ability to empower physicians and widen patients' access to specialist-level expertise.



This study is not the first time that computer's have beaten doctors at diagnosis. But what's impressive is the increased realism of the experiments and the comparison of various AI reasoning engines.

Source: https://www.nature.com/articles/s41586-025-08869-4

Damaged Cell ‘Trash Cans’ May Contribute to Parkinson’s Disease



Isabella Backman, *Yale School of Medicine*, April 10, 2025

Scientists have uncovered more than 20 genes whose mutations cause familial forms of Parkinson’s disease. One of these genes is known as VPS13C, and mutations in this gene may contribute to the disease’s onset by causing the “trash cans” of cells to malfunction, Yale researchers report in a new study. Their findings—which could have implications for new therapeutic targets for Parkinson’s disease—were published April 10 in *Nature Cell Biology*.

Several of the genes associated with Parkinson’s disease are involved in the regulation of lysosomes. These cellular organelles serve as the garbage cans of the cell, accumulating and breaking down waste products and recycling their components. Lysosomal dysfunction may lead to the leakage of toxic substances within brain cells, thus contributing to the onset of Parkinson’s disease.

Pietro De Camilli, MD, John Klingenstein Professor of Neuroscience, professor of cell biology, and Howard Hughes Medical Institute Investigator at Yale School of Medicine (YSM), and his team study the gene VPS13C, which codes for a protein responsible for transferring lipids between organelles. Mutations in VPS13C cause or increase the risk of developing Parkinson’s disease.

As De Camilli and collaborators have previously shown, the VPS13C protein acts as a bridge that transfers lipids from the endoplasmic reticulum—a network of membranes that plays a crucial role in lipid production—to lysosomes. In the latest study they found that when lysosome membranes were damaged, VPS13C proteins rapidly rushed to them, likely to funnel in lipids, an important process in their repair.

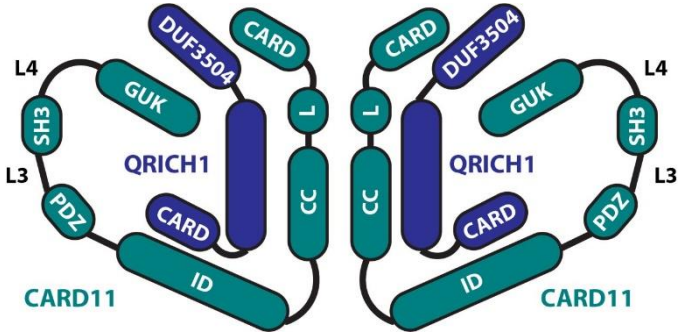
These findings suggest that leakage of lysosomal content may be an explanation for why mutations that cause the loss of function of the VPS13C gene are associated with Parkinson’s disease.

“Imagine a fire truck rushing to the scene to minimize damage—this mechanism is part of an emergency system that prevents leakage from a damaged lysosome,” says De Camilli, who is the paper’s senior author. “A chronic loss of lysosomal integrity could lead to cell toxicity and ultimately neurodegeneration.”

Mutations in the gene LRRK2 are also responsible for Parkinson’s disease, and previous research has shown that these proteins accumulate around damaged lysosomes as well. In the new study, the researchers showed that while VPS13C accumulated rapidly, LRRK2 proteins showed a more delayed response to lysosomal damage, suggesting the two proteins participate in different steps of the lysosome repair process.

Source: https://medicine.yale.edu/news-article/damaged-cell-trash-cans-may-contribute-to-parkinsons-disease/

Immune Cell Research Identifies New Target for Treating Cancer and Autoimmune Disease



Press Release, *Johns Hopkins School of Medicine*, April 8, 2025

In a study of the immune systems of mice, scientists at Johns Hopkins Medicine say they have found a new role for a protein, QRICH1, which could become a target for drugs to dial up or down the activation of T cells to fight cancers and autoimmune diseases.

The research was designed to advance development of immunotherapies that harness the power of the body's immune system to fight disease. Immunotherapies treat cancer by speeding up tumor cell death, and treat autoimmune disorders — in which the body's immune system attacks its own cells — by tamping down such reactions.

"Finding new targets for future drugs that could fine-tune these treatments, making them safer and more effective, is a promising avenue of research," says senior author Joel Pomerantz, Ph.D., associate professor of biological chemistry at the Johns Hopkins University School of Medicine.

The new research findings, supported by funding from the National Institutes of Health, were published March 14 in Science Immunology.

The protein QRICH1 is a recently identified component of a signaling pathway of CD8+ cells, which are T cells that make up the killing machinery of the immune system, says Pomerantz. The scientists say their experiments show that QRICH1 acts as a partial brake that regulates T-cell response, indicating that drugs could be designed to control the protein's activity.

In certain cancers, QRICH1 could be used to increase T-cell activation to fight and kill off cancer cells more effectively. In autoimmune diseases and certain blood cancers, including leukemia and lymphoma, in which overactivation of T cells contributes to worsening of disease, QRICH1 could slow down the activation of T cells, Pomerantz says.

For the new study, the scientists first genetically engineered mice to lack the QRICH1 protein, and conducted experiments demonstrating that the protein is necessary to the CD8+ T cell signaling pathway.

To do so, the scientists extracted T cells from mice genetically engineered to lack QRICH1 and placed the immune cells in a culture dish with a signal that mimics a cancer cell or a virally infected cell.

Source: https://www.hopkinsmedicine.org/research/advancements-in-research

Collagen V Regulates Renal Function after Kidney Injury and Can Be Pharmacologically Targeted to Enhance Kidney Repair in Mice

Su et.al., *Science Translational Medicine*, April 9, 2025

Kidney fibrosis determines clinical outcomes in individuals with chronic kidney disease (CKD). The stoichiometric ratio of collagens in renal scar differs from that of healthy kidney extracellular matrix (ECM), but the functional importance of altered collagen types in injured kidneys remains unclear. Using human population studies, we show that circulating protein and renal mRNA amounts of collagen V A1 (COL5A1) exhibited associations with kidney disease and incident CKD risk. We show that Col5a1 regulates the degree of postinjury fibrosis and renal function. Mice with conditionally knocked out Col5a1 (Col5a1 CKO) exhibited decreased renal function and greater renal fibrosis after dietary adenine- or ureteric obstruction–mediated kidney injury. Renal fibroblasts in Col5a1 CKO animals up-regulated the profibrotic αvβ3 integrin.

Inhibition of αvβ3 signaling with a small molecule, cilengitide, rescued postinjury renal function in Col5a1 CKO animals. Using the hybrid mouse diversity panel that comprises 100 diverse inbred strains of mice, we observed that gene expression of Col5a1 after injury exhibited genetic variation across 100 strains. Strains with low Col5a1 expression after injury exhibited worse renal function compared with animals that had higher degrees of expression. We next measured Col5a1 expression in peripheral blood mononuclear cells in mice to identify nonresponder strains that did not have increased Col5a1 expression after kidney injury. We observed that administration of cilengitide in nonresponder strains significantly rescued postinjury renal fibrosis and function. These studies point to the feasibility of precision medicine approaches to target Col5a1 for enhancing renal repair.

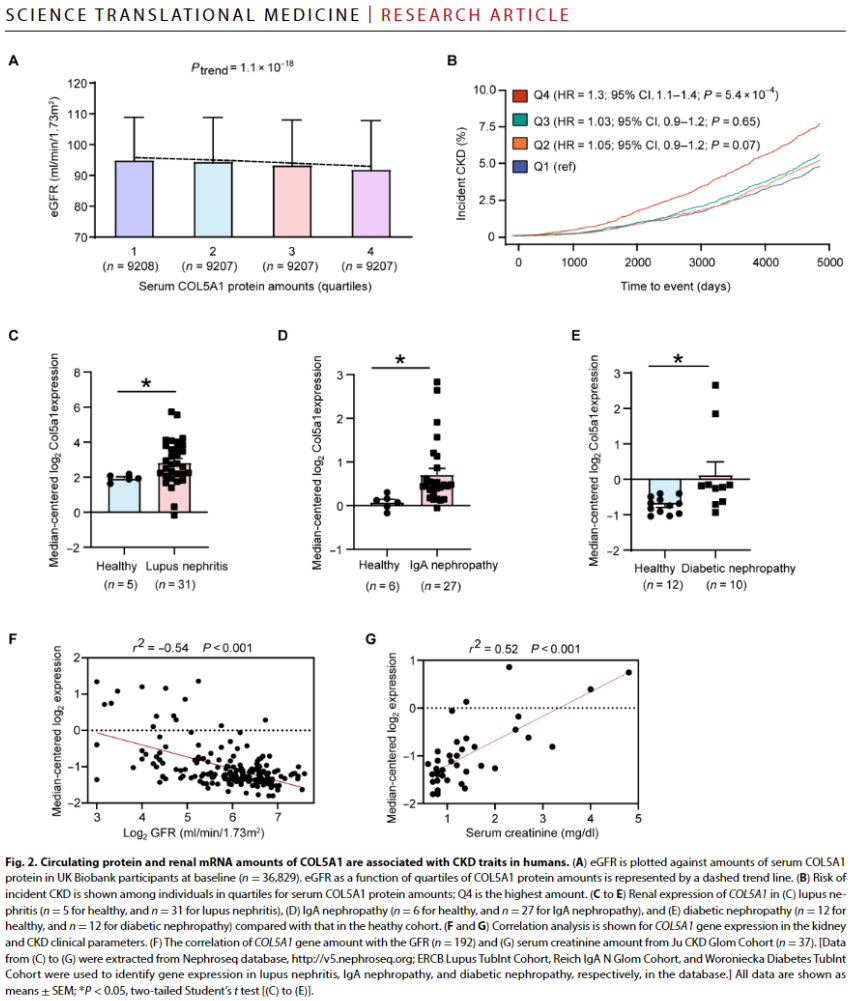


Fig. 2. Circulating protein and renal mRNA amounts of COL5A1 are associated with CKD traits in humans. (**A**) eGFR is plotted against amounts of serum COL5A1 protein in UK Biobank participants at baseline ($n = 36,829$). eGFR as a function of quartiles of COL5A1 protein amounts is represented by a dashed trend line. (**B**) Risk of incident CKD is shown among individuals in quartiles for serum COL5A1 protein amounts; Q4 is the highest amount. (**C** to **E**) Renal expression of *COL5A1* in (C) lupus nephritis ($n = 5$ for healthy, and $n = 31$ for lupus nephritis), (D) IgA nephropathy ($n = 6$ for healthy, and $n = 27$ for IgA nephropathy), and (E) diabetic nephropathy ($n = 12$ for healthy, and $n = 12$ for diabetic nephropathy) compared with that in the heathy cohort. (**F** and **G**) Correlation analysis is shown for *COL5A1* gene expression in the kidney and CKD clinical parameters. (F) The correlation of *COL5A1* gene amount with the GFR ($n = 192$) and (G) serum creatinine amount from Ju CKD Glom Cohort ($n = 37$). [Data from (C) to (G) were extracted from Nephroseq database, http://v5.nephroseq.org; ERCB Lupus TubInt Cohort, Reich IgA N Glom Cohort, and Woroniecka Diabetes TubInt Cohort were used to identify gene expression in lupus nephritis, IgA nephropathy, and diabetic nephropathy, respectively, in the database.] All data are shown as means ± SEM; *$P < 0.05$, two-tailed Student's *t* test [(C) to (E)].

Source: https://www.science.org/doi/10.1126/scitranslmed.ads7714

Immune Checkpoint TIM-3 Regulates Microglia and Alzheimer's Disease

Kimura et.al., *Nature*, April 9, 2025

Microglia are the resident immune cells in the brain and have pivotal roles in neurodevelopment and neuroinflammation. This study investigates the function of the immune-checkpoint molecule TIM-3 (encoded by HAVCR2) in microglia. TIM-3 was recently identified as a genetic risk factor for late-onset Alzheimer's disease, and it can induce T cell exhaustion4. However, its specific function in brain microglia remains unclear. We demonstrate in mouse models that TGFβ signalling induces TIM-3 expression in microglia.

In turn, TIM-3 interacts with SMAD2 and TGFBR2 through its carboxy-terminal tail, which enhances TGFβ signalling by promoting TGFBR-mediated SMAD2 phosphorylation, and this process maintains microglial homeostasis. Genetic deletion of Havcr2 in microglia leads to increased phagocytic activity and a gene-expression profile consistent with the neurodegenerative microglial phenotype (MGnD), also referred to as disease-associated microglia (DAM). Furthermore, microglia-targeted deletion of Havcr2 ameliorates cognitive impairment and reduces amyloid-β pathology in 5×FAD mice (a transgenic model of Alzheimer's disease). Single-nucleus RNA sequencing revealed a subpopulation of MGnD microglia in Havcr2-deficient 5×FAD mice characterized by increased pro-phagocytic and anti-inflammatory gene expression alongside reduced pro-inflammatory gene expression. These transcriptomic changes were corroborated by single-cell RNA sequencing data across most microglial clusters in Havcr2-deficient 5×FAD mice. **Our findings reveal that TIM-3 mediates microglia homeostasis through TGFβ signalling and highlight the therapeutic potential of targeting microglial TIM-3 in Alzheimer's disease.**

Source: https://www.nature.com/articles/s41586-025-08852-z

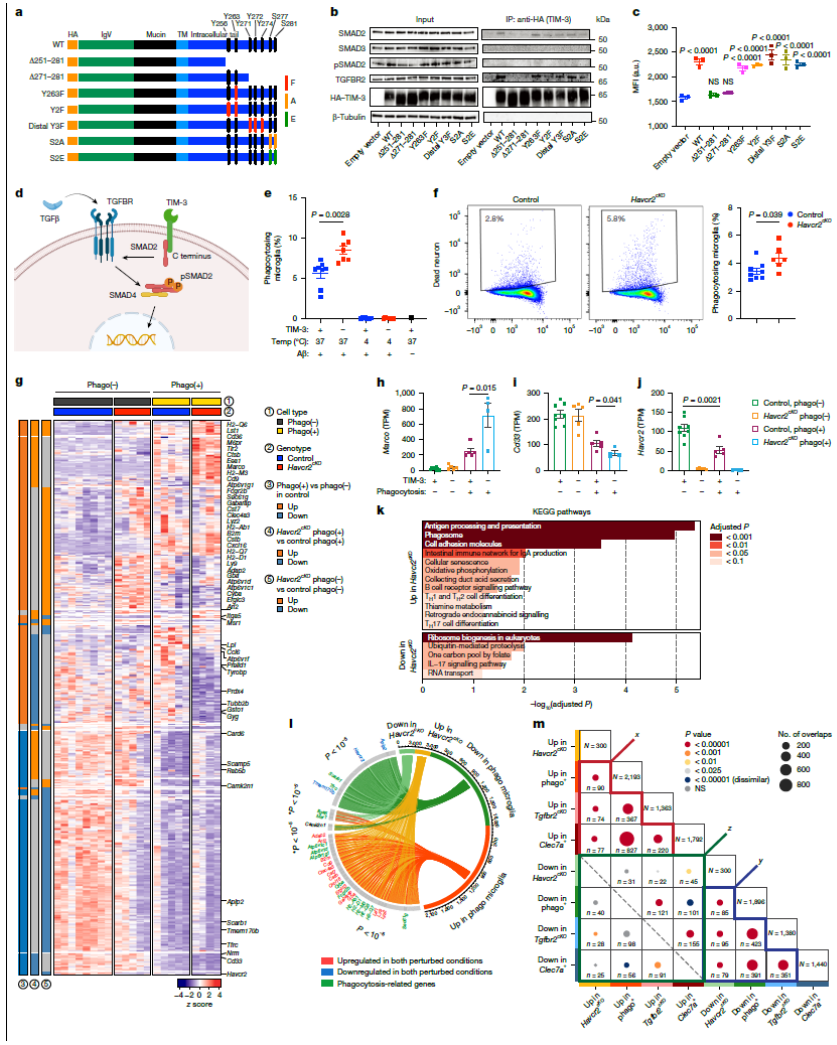


Fig. 3 | *Havcr2*^{cKO} microglia have increased phagocytic ability and share a gene-expression signature with phagocytosing microglia. a, WT and mutant *Havcr2* structures. HA, haemagglutinin; TM, transmembrane. **b**, Blots of HEK293 cells transfected with *Havcr2* constructs co-immunoprecipitated for HA-TIM-3. The samples for the control β-tubulin were run on a separate gel as sample-processing controls (see Supplementary Fig. 1 for gel source data). **c**, Flow cytometry analysis of pSMAD2 in *Havcr2* construct-transfected HEK293 cells. A successfully transfected TIM-3-positive fraction was analysed and compared with all the live cells in the control group (Extended Data Fig. 1c) ($n = 3$ per condition, independent samples). **d**, Schematic of the regulation of SMAD2 phosphorylation by TIM-3. **e**, *Havcr2*^{cKO} microglia were cultured with pH-sensitive dye-stained Aβ for 4 h ($n = 8$ control, 7 *Havcr2*^{cKO}, 1 without Aβ, independent samples). **f**, Fluorescence-stained dead neurons were injected into the cortex and hippocampus of live male mice (3 months old, $n = 8$ control, 6 *Havcr2*^{cKO}, independent mice). The fraction of phagocytosing microglia was analysed 16 h later. **g**, RNA-seq analysis of sorted microglia (live CD45^{low}CD11b^{+} 4D4^{+}Ly6C^{-}) from the same experiment as **f**. The top DEGs shared by at least two of the following three comparisons are shown in the heatmap: (1) control phagocytosing (Phago(+)) versus control non-phagocytosing (Phago(−)); (2) *Havcr2*^{cKO} phagocytosing versus control phagocytosing; (3) *Havcr2*^{cKO} non-phagocytosing versus control non-phagocytosing. Selected genes are highlighted, including the KEGG phagosome pathway gene set (mmu04145), the top 100 DEGs of *Clec7a*$^{+}$ versus *Clec7a*$^{-}$ microglia[10] and selected genes (*Cd9*, *Cd33*, *Cst7*, *Cstb*, *Ccl16*, *Ly9*, *Lyz2* and *H2*). **h**–**j**, The expression of *Marco*, *Cd33* and *Havcr2* in microglia from the same experiment as **g** ($n = 8$, 5, 5 and 4, from the left, independent mice in each genotype). **k**, Pathway analysis of the top DEGs comparing non-phagocytosing *Havcr2*^{cKO} to non-phagocytosing control microglia (FDR < 0.1). Disease pathways (pathways under sections 6.1–6.10 from https://www.kegg.jp/kegg/pathway.html) and ribosomal genes were excluded from the analysis. **l**, Gene-expression signatures of *Havcr2*^{cKO} microglia (DEGs between *Havcr2*^{cKO} non-phagocytosing and control non-phagocytosing microglia) and phagocytosing microglia (DEGs between control phagocytosing and control non-phagocytosing microglia) were compared using the same RNA-seq data as in **g**. The same set of genes is highlighted as in **g**. **m**, The number of overlapping genes (n) between each pair of DEGs upregulated and downregulated in *Havcr2*^{cKO} phagocytosing, *Tgfbr2*^{cKO} and *Clec7a*$^{+}$ microglia compared with control microglia. *N* is the total number of up- or downregulated genes in the condition (row). Results are shown from one experiment, representing at least two independent experiments (**b**,**c**,**e**,**f**). Data are the mean ± s.e.m. Statistical tests: one-way analysis of variance (ANOVA) with Dunnett's multiple comparisons test (**c**) or Student's two-tailed *t*-test (**e**,**f**,**h**–**j**). One-sided permutation test is described in the section 'Circos plot and permutation test' in the Methods for **l** and **m**. The schematic in **d** was created using BioRender (https://biorender.com).

Disclosure

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