Biopharma Market Update

May 19, 2025

STIFEL | Healthcare

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Kellen Medical Research Building, Mayo Clinic, May 12, 2025

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AI in medicine

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2024 Biotech Outlook

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Why Invest in Biotech?

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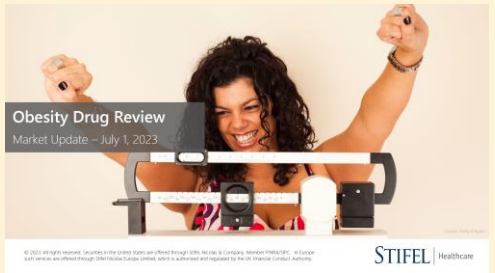
Obesity Drug Review



[July 1, 2023]

Feel Free to Join Us at Biotech Hangout

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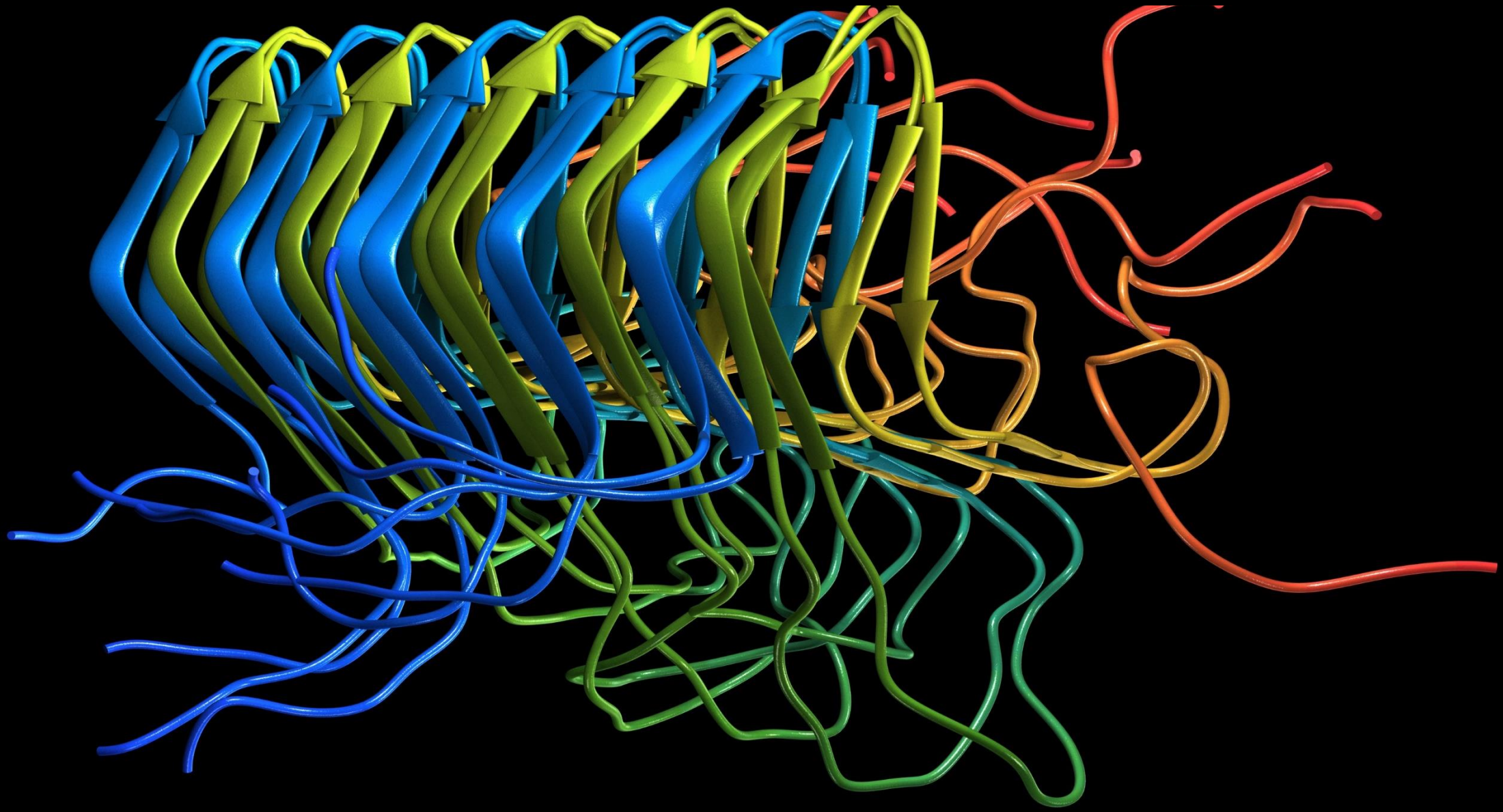
To Learn More
https://www.biotechhangout.com/

Macro Update



Alzheimer's Protein Fibril

US Producer Prices Fell Unexpectedly in April as Margins Shrank

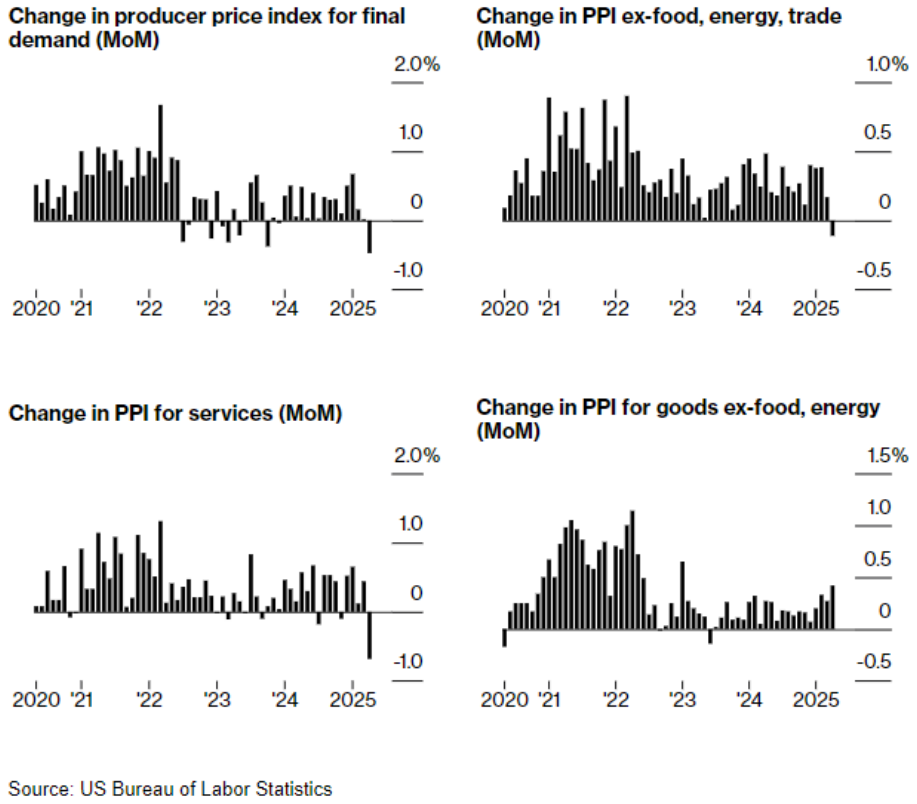
Augusta Saraiva, Bloomberg, May 15, 2025

Prices paid to US producers unexpectedly declined in April by the most in five years, largely reflecting a slump in margins, suggesting companies are absorbing some of the hit from higher tariffs.

The 0.5% decrease in the producer price index followed no change in March, Bureau of Labor Statistics data showed Thursday. The median forecast in a Bloomberg survey of economists called for a 0.2% gain. Excluding food and energy, the PPI declined 0.4% — the most since 2015.

Stripping out food, energy and trade, a less-volatile measure favored by many economists, prices fell 0.1%, the first decline in five years. Compared with a year ago, the gauge rose 2.9%.

The figures suggest American manufacturers and service providers are so far refraining from passing along higher US duties on imports. The impact on consumers has also been modest even as producers are feeling the pinch from aggressive levies on imported materials and other inputs.



Source: US Bureau of Labor Statistics

Source: https://www.bloomberg.com/news/articles/2025-05-15/us-producer-prices-fall-unexpectedly-as-margins-decline

Moody’s Downgrade Intensifies Investor Worry About US Fiscal Path

NEW YORK, May 18 (Reuters) - A U.S. sovereign downgrade by Moody's has exacerbated investor worries about a looming debt time-bomb that could spur bond market vigilantes who want to see more fiscal restraint from Washington.

The ratings agency cut America's pristine sovereign credit rating by one notch on Friday, the last of the major ratings agencies to downgrade the country, citing concerns about the nation's growing $36 trillion debt pile.

The move came as Republicans who control the House of Representatives and the Senate seek to approve a sweeping package of tax cuts, spending hikes and safety-net reductions, which could add trillions to the U.S. debt pile. Uncertainty over the final shape of the so-called "Big Beautiful Bill" has investors on edge even as optimism has emerged over trade. The bill failed to clear a key hurdle on Friday even as U.S. President Donald Trump called for unity around the legislation.

"The bond market has been keeping a sharp eye on what transpires in Washington this year in particular," said Carol Schleif, chief market strategist at BMO Private Wealth, who said that Moody's downgrade may make investors more cautious.

Source: https://www.reuters.com/world/us/moodys-downgrade-intensifies-investor-worry-about-us-fiscal-path-2025-05-18/

S&P 500 Posts Fifth Winning Day, Notches 5% Weekly Gain as U.S.-China Trade Tensions Ease

Brian Evans, Pia Singh and Tanaya Macheel, CNBC, May 16, 2025

The S&P 500 rose Friday for a fifth session and posted a sharp weekly gain, as investors looked past the release of disappointing consumer sentiment data and persistent inflation worry.

The broad market index climbed 0.70% to end at 5,958.38, while the Nasdaq Composite gained 0.52% to close at 19,211.10. The Dow Jones Industrial Average gained 331.99 points, or 0.78%, settling at 42,654.74. Friday's advance put the 30-stock benchmark into positive territory for 2025.

For the week, the S&P 500 surged 5.3%, and the Dow gained 3.4%. The Nasdaq Composite jumped 7.2% this week. Technology stocks also had a strong week. Shares of Nvidia gained about 16%, while Meta Platforms advanced 8%. Shares of Apple climbed 6%, while Microsoft popped 3%.

The major averages rose even after the University of Michigan's consumer sentiment index came in at its second-lowest level on record. Consumers also see prices rising 7.3% over the next year, up from 6.5% last month.

Stocks have made a strong comeback since U.S. and Chinese officials earlier this week agreed on a 90-day truce in their tariff measures, which eased investors' fears of escalating global trade tensions and rising risk to the economy.

"Markets are repricing the stagflation risk right now — what was once the base case for folks who were sure that tariffs were going to shoot inflation skyward immediately, really hasn't been supported in the data," said Jamie Cox, managing partner at Harris Financial Group. "The U.S. consumer may say he/she is worried, but they aren't spending like they are. Consumption trumps all once you filter out all the noise." Wall Street is also hoping that there will be more clarity on the trade front in the weeks ahead.

Source: https://www.cnbc.com/2025/05/15/stock-market-today-live-updates.html

Biotech, Healthcare and Policy Developments

Biotech is Showing Signs of Life

Biotech itself showed some signs of life last week with two M&A deals, a series of remarkably positive clinical developments and several follow-ons. The XBI even rose despite the MFN announcement on Monday.

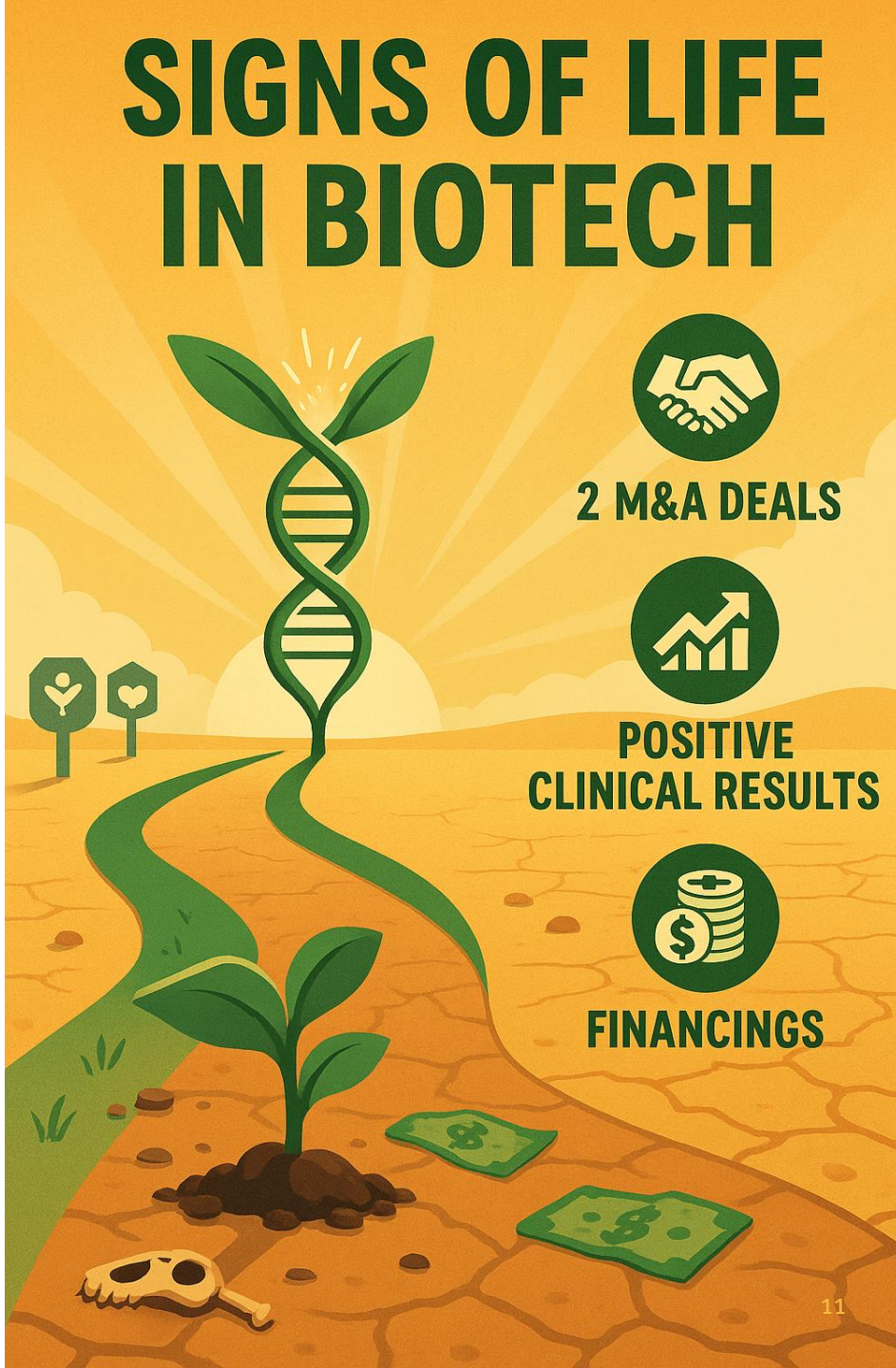
However, the macro backdrop remains decidedly mixed. We heard from RFK Jr. in his Senate testimony. The content of what he said did not necessarily cause investors to want to leap into the healthcare and biopharma sector.

Further, at last week's ASGTC conference sentiment towards new CBER head Vinay Prasad was not great.

We spoke at events last week at the Mayo Clinic in Rochester MN and the *FT/Endpoints* conference in NYC.

We continue to be optimistic on the FDA (more on that below), however managers continue to report that getting capital into specialist funds is challenging as we scrape bottom in a period of extended policy uncertainty.

Normally, we don't hear so much as to what is going on with healthcare systems but can report that listening to a prominent HC lobbyist speak at Mayo, there is just as much uncertainty now on the provider side as what is going in Washington DC. Changes in Medicaid rules are not likely to be good for healthcare providers, and the changes are likely to put major pressure on state governments. There are numerous potential changes in store for the healthcare system under the Trump administration and the lobbyist indicated that we are in early innings of the developments there.

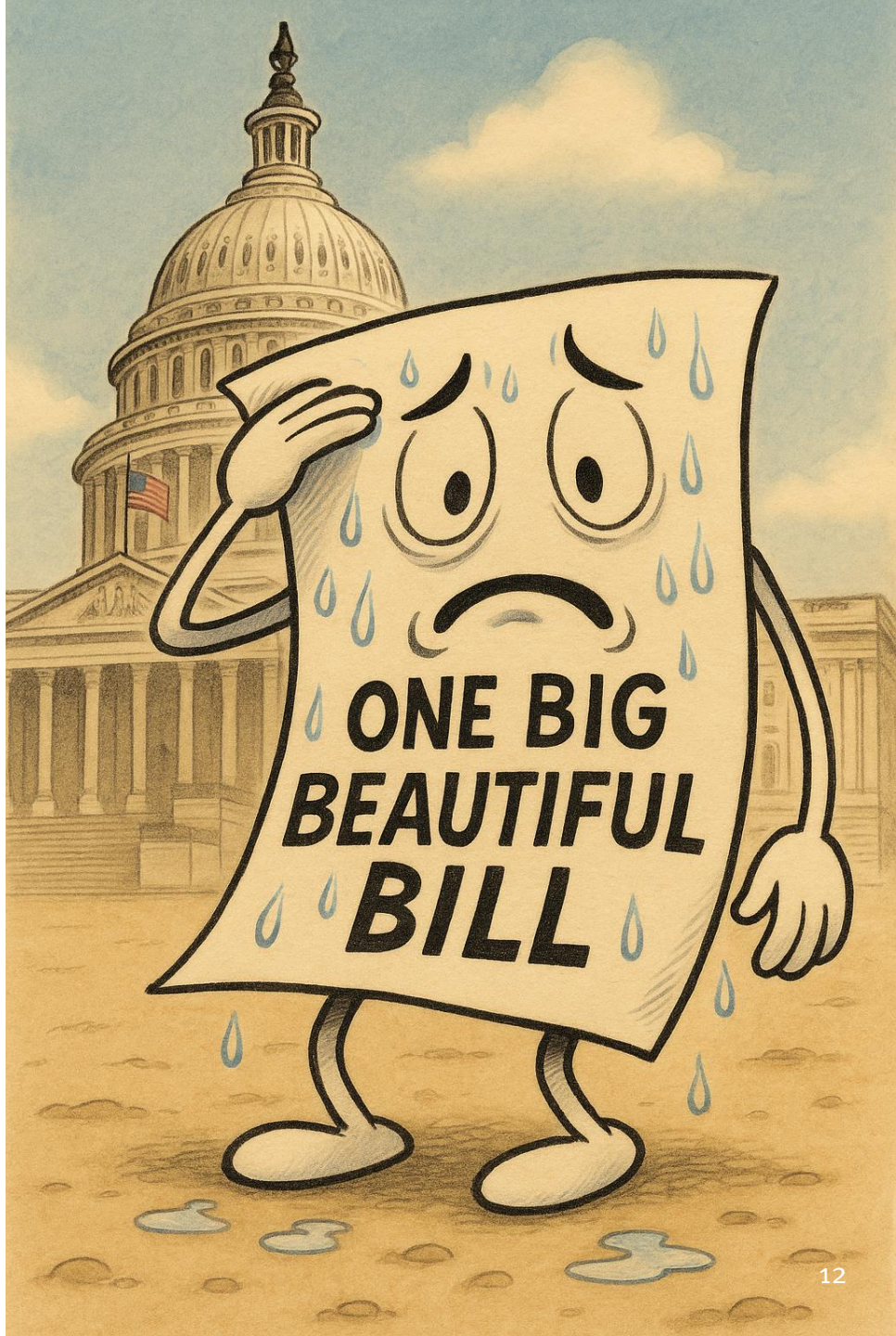


Reconciliation Bill Challenges

President Donald Trump's "One Big Beautiful Bill" faced challenges last week when it first failed to advance out of the House Budget Committee. The bill, encompassing tax cuts, increased defense and border security funding, and spending reductions in programs like Medicaid and green energy subsidies, was rejected in a 16–21 vote. Notably, five Republicans joined Democrats in opposing the measure, highlighting internal divisions within the GOP. By Sunday night this bill got out of committee with the conservatives abstaining.

Key challenges facing the bill include demands from fiscal conservatives for deeper immediate spending cuts, particularly to Medicaid and food assistance programs. These lawmakers criticized the bill for delaying significant reforms until 2029, arguing that it would exacerbate the national debt, projected to increase by $3.3 to $5.2 trillion over the next decade. Additionally, Republicans from high-tax states expressed dissatisfaction with the proposed cap on state and local tax (SALT) deductions, seeking higher limits to benefit their constituents. This all coincided with Moody's downgrade of the U.S. credit rating, intensifying concerns over fiscal responsibility. As negotiations continue, GOP leaders aim to reconcile these differences to advance the legislation.

We have previously noted that President Trump is acutely aware of his popularity ratings, and we believe that his policy actions are, in part, linked to how he is doing in the polls. Last week’s abysmal University of



Politics Linked to MFN Policies

Michigan consumer sentiment data highlight the populace's broad fears of inflation linked to tariffs. It is striking to us that in the so-called "China negotiations" the Trump Administration essentially unilaterally backed off its previous tariffs. The *Economist* ran a story last week entitled "America Has Given China a Surprisingly Good Tariff Deal" in which it noted:

> "The financial chaos following Liberation Day included a bond-market revolt and a plunging dollar. This disturbance persuaded Mr Trump to offer a 90-day reprieve to most of America's trading partners on April 9th. After the Geneva talks, China has now been added to the list. Its reciprocal tariff of 10% is as low as any country enjoys. Moreover, this low rate applies even though China, unlike other countries, still has a 10% retaliatory tariff in place."

Recent approval tracking polls from Ipsos and Bullfinch Group show that Trump's approval numbers improved after the China tariff retreat but barely.

This, in our opinion, is why Trump is now trying to beat on the pharma industry with the MFN announcement. The idea we think is to improve his perceived legitimacy as a leader and to help get his tax cuts through Congress. As one might imagine Trump's MFN initiative received more than a little discussion at last week's *FT/Endpoints* event – which, by the way, was very nicely done. Chris Boerner, CEO of BMS, noted the history pricing and policies in Europe and said "we should not import failed policies" into the United States.

BMS CEO Comments on Trump 2.0

Boerner, a superb speaker, avoided criticism of the Trump Administration but artfully noted the risks inherent in ongoing policy reforms saying, “It’s relied on, for decades, an interaction between government and academia, academia and industry. And so, as we look for opportunities to improve components of that ecosystem, we’ve got to recognize that while we’re looking to advance and fix things, we don’t break them at the same time. Let’s also remember that while the US is in a leadership position today, that’s not an inalienable right. This is a global ecosystem.”*

We agree with his comments wholeheartedly.

U.S. success in biosciences is not preordained in any way.

As the policy laser pointer is increasingly focusing on the role of middlemen in the pharma supply system, we are seeing weakness in PBM stocks. While pharma stocks held up well after his MFN announcement last week, we saw the shares of both CVS and Cigna (owners of PBMs) drop. This was linked to the discussion of the need to limit PBM abuses in the MFN executive order.

Even more disastrous was the peremptory dismissal of Andy Witty as CEO of UnitedHealthcare. We learned why a day later when the *WSJ* announced that United is facing a criminal Medicare fraud investigation. United stock is down more than 50% in the last month.

* See https://endpts.com/bristol-myers-ceo-says-americas-biopharma-pole-position-is-not-guaranteed/

RFK Jr. In Front of Senate Last Week

The board of UnitedHealthcare is bringing back former CEO Stephen Hemsley, who is widely credited as the architect of the company's previous growth and integrated strategy. UNH responded to the news story indicating that it stands "by the integrity of our Medicare Advantage program."

In congressional hearings before both the Senate HELP Committee and the House Appropriations Committee, RFK Jr. addressed a wide array of health policy topics tied to the HHS budget, including vaccine safety, domestic manufacturing, MFN drug pricing, staffing reorganization at HHS, and the role of AI in regulatory science.

He praised Eli Lilly and other companies for recent investments in U.S. manufacturing capacity, suggesting that the administration is considering new "incentives" to further boost domestic pharmaceutical production. While RFK did not specify what these incentives might entail, he emphasized close collaboration with industry leaders and expressed optimism about bringing more drug production onshore.

On drug pricing, RFK signaled support for aggressive measures to lower costs, invoking President Trump's executive order on Most Favored Nation (MFN) pricing as a model. He stated that the president "doesn't care how we get there," reinforcing the administration's flexibility on mechanisms to reduce prices.

Medicaid Cuts on the Menu

Notably, he suggested MFN could apply broadly, including to 340B drugs (supplied to non-profit hospitals and health centers for the poor), which surprised observers given past assumptions that MFN reforms would be confined to Medicare or Medicaid. Meanwhile, pharma stocks have rallied recently, interpreting the latest MFN developments as less menacing than initially feared. However, uncertainties persist, especially around how implementation would work and whether a 180-day negotiation period would be preserved.

RFK also made controversial remarks on vaccine safety, claiming that most vaccines aside from COVID had not been tested against placebo—a statement quickly challenged by Senator Cassidy, who cited placebo-controlled trials for rotavirus, HPV, and measles vaccines. RFK Jr. also said that only the sickest kids “die of measles” implying that the vaccine might not be needed. Ouch. On staffing, RFK declined to comment due to a federal court order but indicated the intent was consolidation, not elimination, of HHS roles. He also voiced support for incorporating AI into drug development, particularly Phase III clinical trials, and potentially for use in expediting FDA approvals, though he offered few specifics.

There has been significant concern of prospective Medicaid Cuts. Robert Greenstein, Visiting Fellow of the Brookings Institution last week said: “40 years ago, one of every four children in America, about 25%, had no health insurance, today it’s 5%. Among the population as a whole, the share of the population that’s uninsured has been cut in half primarily because of the

Healthcare Investor Concerns Remain

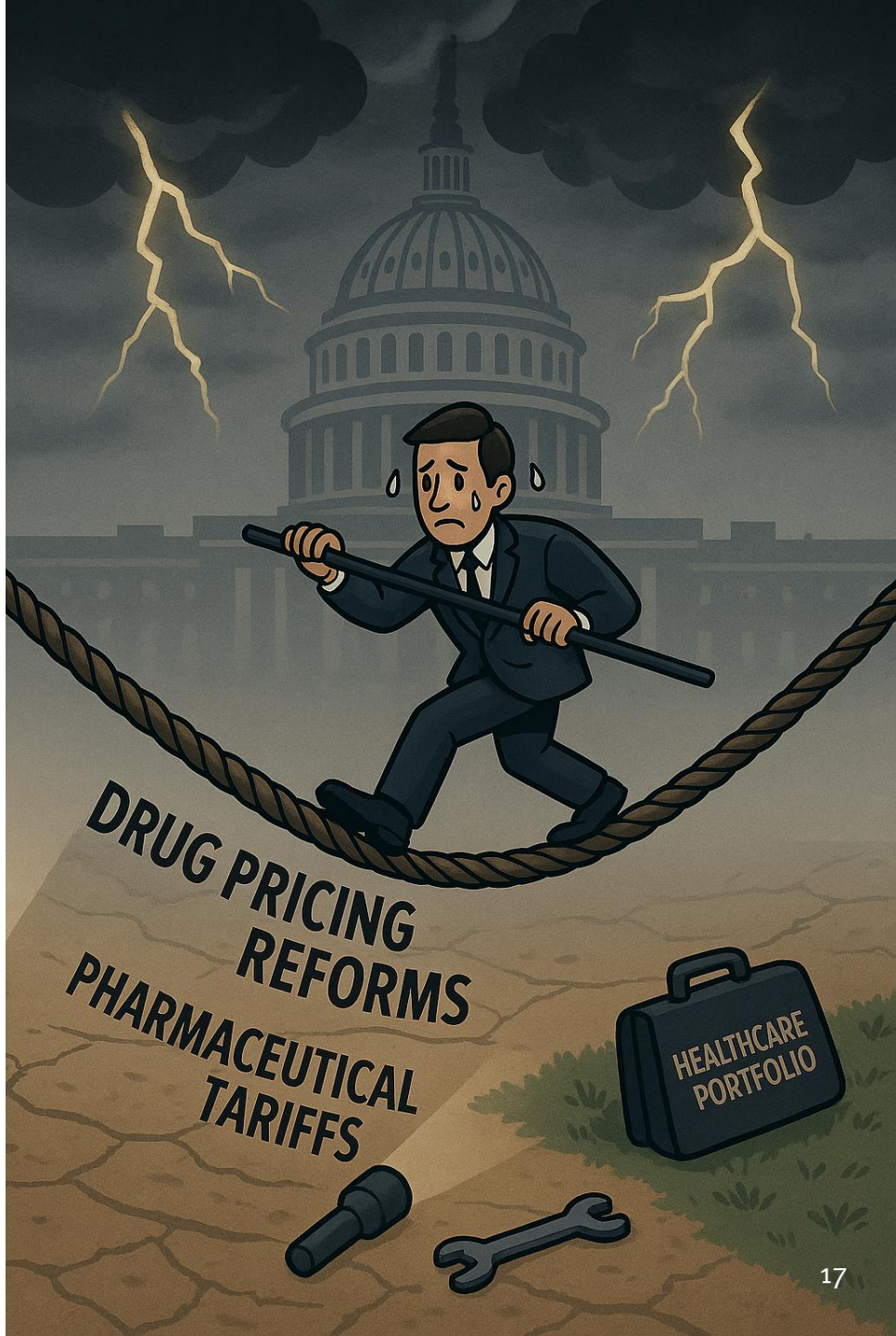
Affordable Care Act enacted back in 2010. We'll see poverty go back up, and we will clearly see, if you cut Medicaid substantially, you're going to have millions more people who lack health insurance."

Separately, the House Energy & Commerce Committee advanced a budget proposal including $912 billion in cuts, with $715 billion targeting Medicaid. The proposal includes new work requirements (80 hours) for adult enrollees, though parents of dependent children are excluded—a key exemption that benefits companies like Vertex Pharmaceuticals, which has substantial Medicaid exposure through cystic fibrosis patients.

Additionally, Trump hinted at softening his stance on pharma tariffs, noting that companies like Lilly might avoid them due to recent U.S. investments. However, Roche warned it might reconsider U.S. manufacturing if MFN pricing is enacted, renewing focus on the role of PBMs ("middlemen") in the pricing debate.

If there was a takeaway from the RFK Jr. Senate hearings last week it was that there is high policy uncertainty in healthcare with the current Trump Administration. This is not attracting investors to our sector.

One fund manager who has been in conversations to pick up additional LP money last week said to us: "Pension funds, endowments and wealthy individuals listened to those RFK hearings and don't want to put their dollars into the harm's way of the healthcare sector right now."



Likely Effect of Work Requirements on Medicaid Enrollment

Matthew Fiedler, Brookings Institution, May 16, 2025

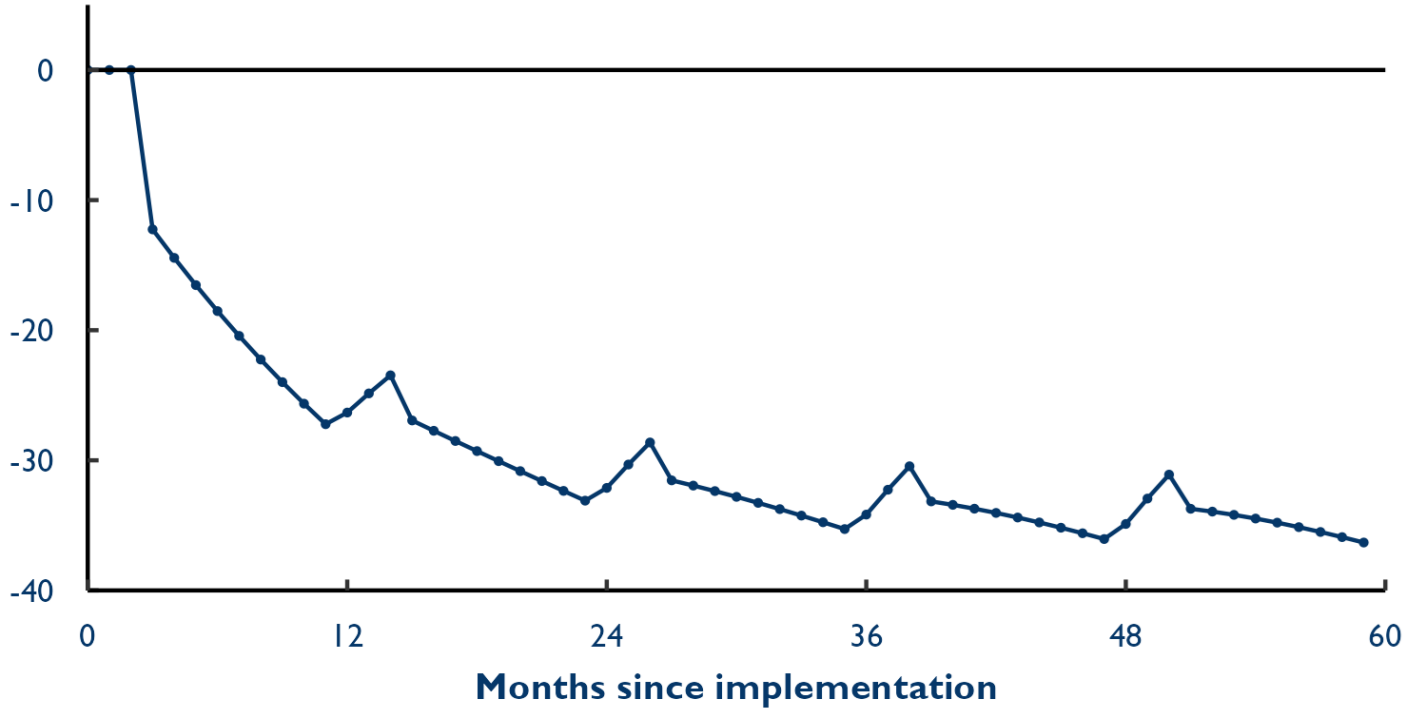
In June 2018, Arkansas received a waiver under the first Trump administration to implement a work requirement for some people receiving Medicaid benefits, which is similar in some respects to the requirement being considered in reconciliation.

Based on the Arkansas experience, Fiedler estimates that a similar federal work requirement would reduce Medicaid enrollment by an estimated 27% at the end of the policy's first year and by 34%, on average, over the long run.

Fiedler notes that other research examining Arkansas' experience has found that most enrollees lost coverage due to challenges in reporting information to the state, not true non-compliance with the policy, and that policy did not increase employment.

Figure ES.1. Effect of Work Requirement on Enrollment

Change in enrollment due to work requirement (%)



Note: The figure plots the percent difference between monthly enrollment with and without a work requirement when simulating the model using the base parameter estimates. The work requirement is assumed to be implemented in January of an unspecified year. See text for details.

Source: https://www.brookings.edu/collection/reconciliation-health-care/

FDA Developments

Photo Taken of Part of a Lonza Advertisement, Milan Italy, March 19, 2025

FDA Developments Paramount

We have previously argued that the FDA under Martin Makary will work hard to accelerate approvals for drugs that could meaningfully impact the lives of patients with intractable diseases.

Our own view is that FDA headwinds have gotten far too much attention in comparison to tailwinds.

This administration has been attempting to reform the FDA and there is no doubt a lot of change underway.

Some have said that the FDA will not be serious about accelerating approvals and, if anything, under Vinay Prasad, at CBER, the FDA will be tougher on industry. And more erratic to boot.

Tim Hunt, CEO of the Alliance for Regenerative Medicine spoke at the *FT / Endpoints* Conference, indicating that none of their members have complained of FDA delays under Makary.

Others have noted that a tough FDA is essential and that accelerating approvals will turn important drugs into “nutritionals” – with light labels that cheapen pharma.

It feels like no matter what it does, the FDA can’t win. There is incredible anxiety in many quarters about any change in the FDA’s regulatory frameworks.

FDA Has Been Evolving in its Thinking

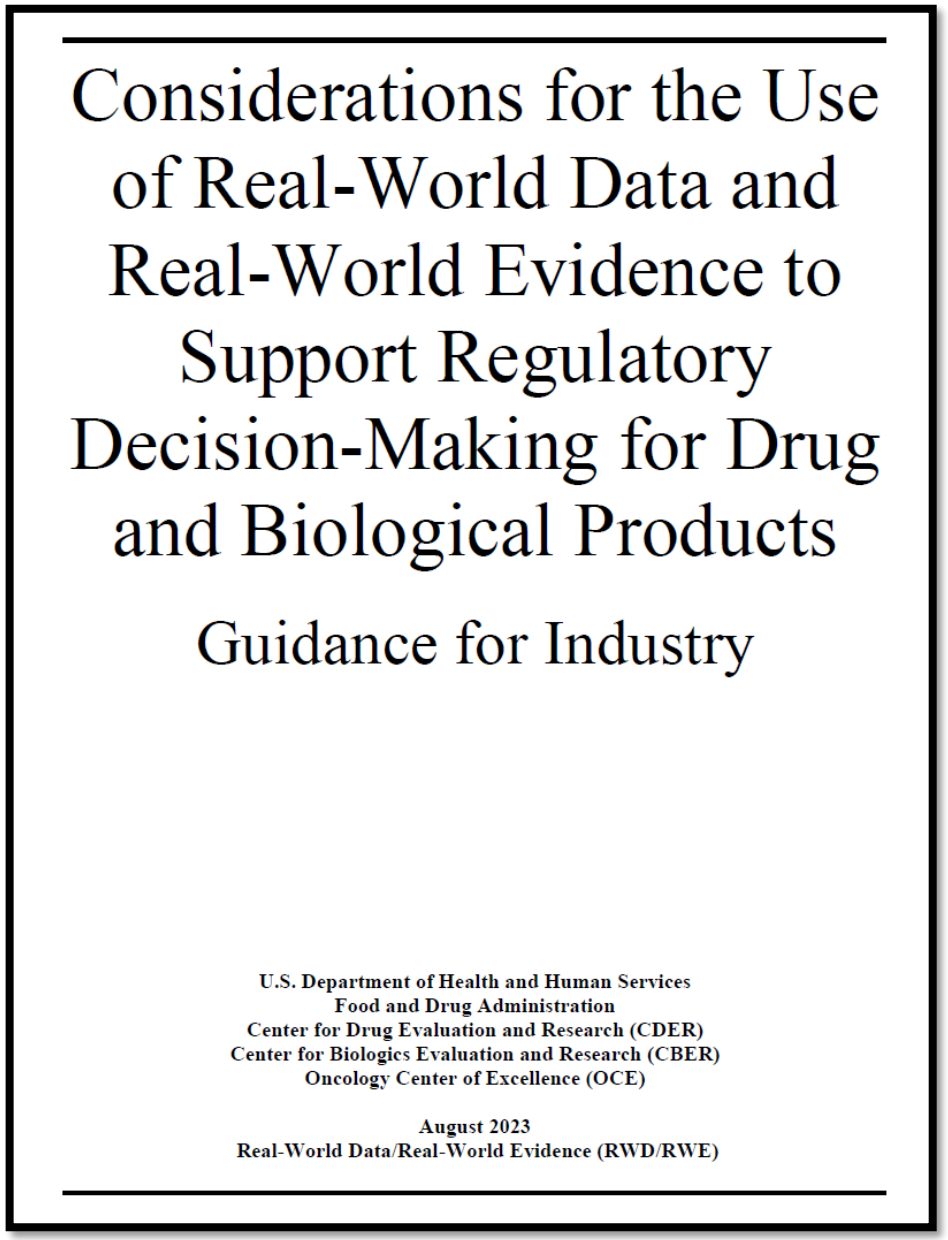
As important backdrop, it has been argued for years that the FDA's criteria for approving new medicines don't necessarily work as well as they could for patient's benefit. One might recall that former FDA Commissioner Mark McLellan previously argued that the FDA should try to titrate requirements to make sure that drug approvals balance patient interest with industry interest in developing products at the least burdensome cost.

Implied and later discussed was the notion that efficacy and safety requirements shouldn't be cookie cutter but instead could be thought of in a Bayesian perspective and might also be able to leverage real world evidence.

The FDA has been open to this type of idea since issuing guidance shown at right in Aug 2023 on the use of real-world data, particularly when the number of patients with a disease is small.

One needs to obtain enough data for an investigational drug to rule out the hypothesis that it might not be safe or effective.

In theory, one could use an incredibly small dataset to make inferences that a drug is working. For example, one would never expect to see a child with osteogenesis imperfecta get up and win a 100-meter race. So, if a kid gets treated and runs the race well three months later you wouldn't need to see that much more. OK, perhaps, three kids might be enough. As for safety, one would like to see more than three kids, but probably thousands of cases would not be needed.


Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

August 2023
Real-World Data/Real-World Evidence (RWD/RWE)

Prasad and Makary Views Compatible

Our own view is that there is an opportunity to improve FDA regulatory frameworks, and we believe that the FDA communications in recent months on the topic have been constructive. It feels to us that there are so many diseases like Parkinson's, lupus and countless rare conditions where drugs could and should be getting to patients more rapidly.

Many observers appear to believe that new CBER head Vinay Prasad's views on past approvals from companies like Sarepta are incompatible with those expressed recently by Commissioner Martin Makary.

In a rapidly evolving regulatory landscape, two of the most prominent voices in medical policy, Dr. Vinay Prasad and Dr. Martin Makary, are increasingly aligned in their views on drug approvals, particularly for rare diseases. Both have been critical of inefficiencies in the current approval process and have advocated for a more rational, transparent and patient-centered approach. Their compatibility lies in a shared belief that evidence standards must remain rigorous, but also adaptive enough to accommodate innovative science and real-world constraints.

Dr. Prasad has long emphasized the importance of evidence quality, calling out approvals based on surrogate endpoints or weak trials. He supports Bayesian adaptive methods, especially in rare disease trials where traditional large-scale randomized controlled trials may not be feasible. Similarly, Dr. Makary has championed efficiency in medicine and has been outspoken about regulatory waste. He argues that reforms are needed at the FDA to reduce time-to-approval for treatments where the unmet need is severe and the risk-to-benefit ratio is favorable.

No Paradox at FDA

So, our argument is that the FDA will be more Bayesian in considering approvals (weighing the strength of dataset signal versus numbers of patients).

High patient need always matters but may not be so important as it was when Peter Marks waved through Sarepta's first approval based on a dataset with a relatively weak signal. His argument was that patient need was paramount.

Makary and Prasad, in contrast, are looking for drugs that have *strong signals* from clinical trials – even from small datasets.

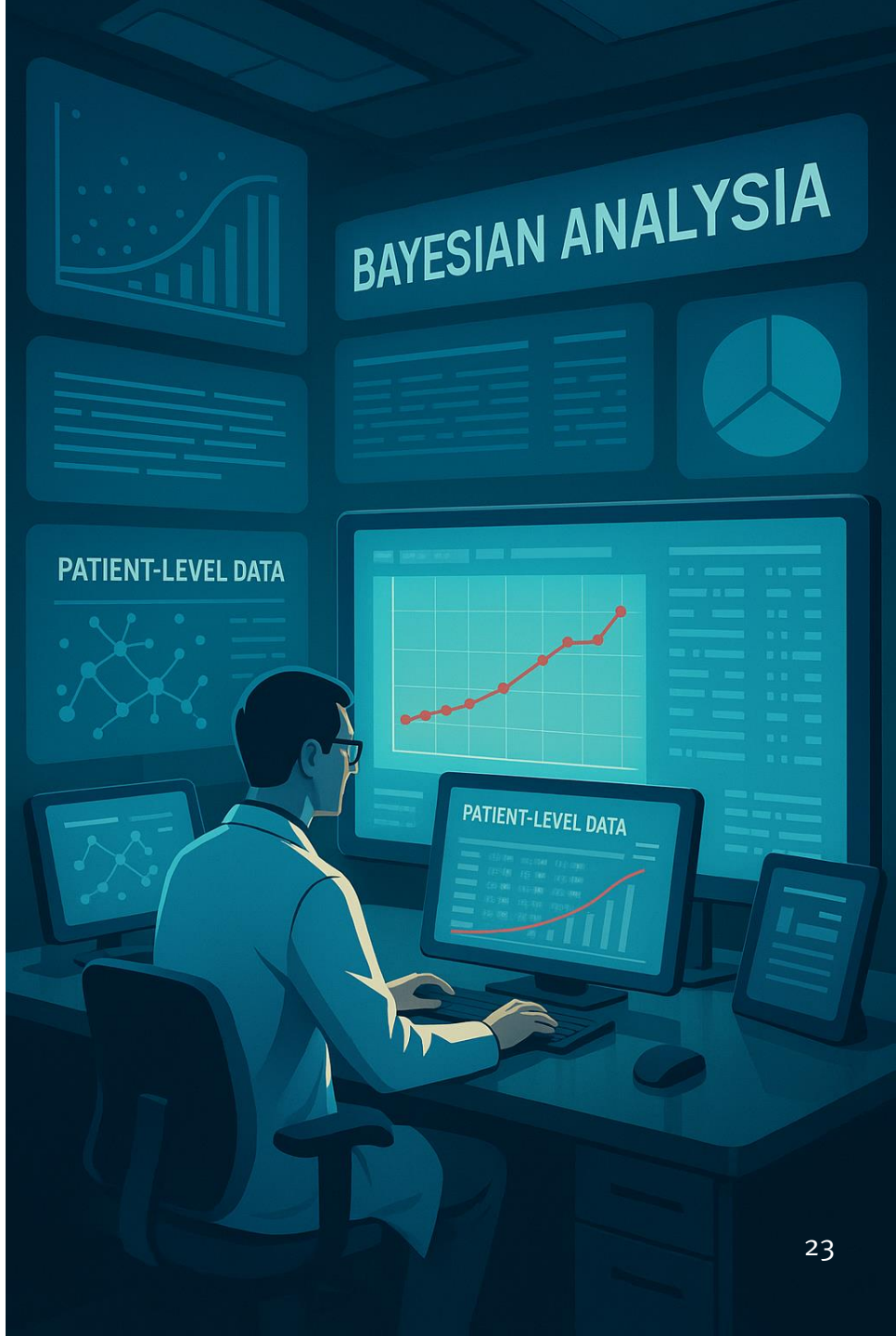
Of course, it is easy to sit in the banker's study and pontificate about how friendly the FDA is going to be this year. But the question that matters is how has the FDA been behaving in recent months?

Well, we don't have a huge dataset to work from so we are going to have to be Bayesian about it.

Here is a compilation of anecdotal data that should, *in totum*, give a view of the agency's current functionality and thought process.

Bayer's Late-Stage Pipeline

Sebastian Guth, President Bayer US, spoke at a panel last week at the *FT Endpoints p*harma conference and indicated that Bayer has multiple pending approvals at the agency and that none of these packages are behind schedule with this FDA. Bayer's PDUFA dates are for Elinzanetant for menopausal symptoms (July); Finerenone for heart failure (June) and HD Eylea (August).



FDA Has Been Largely Constructive in Recent Sponsor Dialogue

Longeveron (Laromestrocel for Alzheimer's)

Longeveron announced a positive Type B meeting held on March 20th with the FDA, achieving alignment on the design of a single, pivotal Phase 2/3 adaptive clinical trial. The FDA indicated that, if interim results are positive, the trial could support a Biologics License Application (BLA) submission. Laromestrocel has received both Regenerative Medicine Advanced Therapy (RMAT) and Fast Track designations for this indication.

Cabaletta (rese-cell for myositis)

Cabaletta is developing CAR T cells to address autoimmune diseases such as myositis, SLE/LN and scleroderma. Cabaletta last week announced that it has entered into what we hope is the first of many agreements with the FDA under Commissioner Martin Makary to achieve rapid market authorization for an important drug candidate initially for myositis, a disabling autoimmune disease that affects ~80,000 patients in the US. Cabaletta has previously shared data on a patient with this disease who achieved a rapid, very deep response. They will soon share additional data across multiple diseases in three oral presentations at EULAR. Cabaletta had earlier said that it would align with FDA on myositis registrational trial designs for rese-cel. While Cabaletta doesn't have that many patients the responses are deep, consistent and impressive – what the FDA is looking for.

Cabaletta disclosed the following last week: "Following a Type C meeting with the FDA and receipt of meeting minutes in April 2025, Cabaletta is planning to implement the following design for two single-arm, disease-specific registrational cohorts in the ongoing RESET-Myositis trial, either of which, if successful, enable a future Biologics License Application (BLA) submission for rese-cel in myositis: One cohort will evaluate approximately 15 patients with either dermatomyositis (DM) or antisynthetase syndrome (ASyS) and one cohort will evaluate approximately 15 patients with immune-mediated necrotizing myopathy (IMNM)."

Cabaletta stock rose more than 70% on this news.

The company does need to complete manufacturing work and build a 100-patient database (>40% already enrolled) but it's clear to us (and other investors apparently) that the company has a very good chance to get to an FDA approval in the next three years with a reasonable resource commitment.

The required efficacy dataset size and safety database requirement is less onerous than what previous sponsors have had to fulfill for 25,000+ prevalence population drug candidates.

FDA Has Been Constructive (continued)

The bottom line is that the total cost of getting a therapy to market has come down. Perhaps to give a point of comparison, Trikafta was approved by FDA for cystic fibrosis among patients who had at least one copy of the F508del mutation in the CFTR gene. Vertex undertook three Phase 3 studies with a total of 768 participants as part of its approval package. There have been other gene and cell therapies addressing somewhat smaller markets that have agreed to more modest approval packages (but not as modest as Cabaletta's). However, these therapies (think Gamida Cell) have not delivered the dramatic type of complete responses seen with Cabaletta's rese-cell.

Cereno Scientific

Cereno is developing a PAH drug and met with the FDA in a Type C meeting to discuss its approval pathway on April 21, 2025. The signal seen in Phase 2a for their HDAC drug was present but not as strong as what had been seen by Cabaletta (positive impact on exploratory biomarkers). FDA responded by requiring that they complete a placebo-controlled Phase 2b trial. This strikes us as appropriate and responsive to the quality of the underlying data.

Dyne Therapeutics

Dyne participated in a Type C meeting with CDER at the Food and Drug Administration in May 2025 and discussed the path to regulatory approval, including U.S. Accelerated Approval, for DYNE-101 in DM1.

FDA and Dyne agreed that it would carry out one additional placebo-controlled Registrational Expansion Cohort to wrap up its registrational program.

Full details on this registrational program were not provided but the bottom line is that Dyne does not have to do a Phase 3 program but instead can wrap up an expanded Phase 2 study and file for approval.

Impressive given that there are more than 35,000 patients in the US with DM1.

John Cox, CEO of Dyne said of the FDA's stance: "Our two lead programs continue to demonstrate compelling and favorable data, including evidence of functional improvement across multiple measures in DM1 and DMD. We are urgently advancing both programs toward potential U.S. Accelerated Approval submissions in 2026 and possible commercial launches in 2027…"

FDA Not a Pushover

These five recent examples are highly consistent with our characterization of the agency. Constructive, flexible and appropriately cautious about making sure that safety databases are built out.

It is fair to say that the FDA is not a pushover in any sense. This agency isn't, in any way, abandoning traditional evidentiary standards for drug approvals. They are simply saying to sponsors: once you have proven that your drug works beyond a reasonable doubt there is no need to run up the score with more and more trial enrollment. Once we know the drug is working let's do what we can to get it to patients ASAP.

Upcoming Oncology AdComm

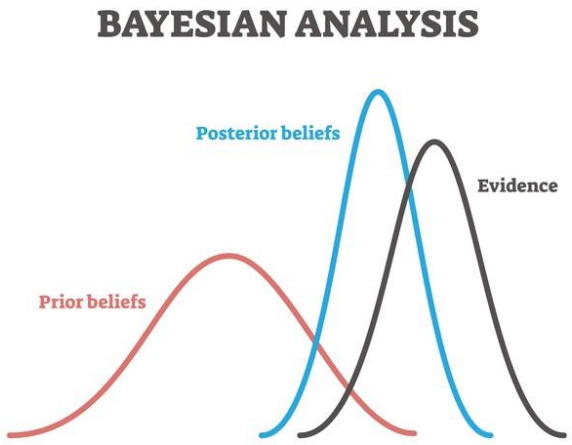
Next week's May 21st ODAC will feature a series of important questions: (1) should Genentech be able to get *Columvi* approved for refractory DLBCL with a study that only has 9% of its patients from within the U.S.? Our sense is that the bar is more like 25% required so this application could run into trouble (2) should Urogen be able to get an approval with a single arm study? Is their data compelling enough to warrant not doing a two-arm study? Notably, ImmunityBio, Ferring and Genentech all used single arm studies before in applications for BCG-unresponsive NMIBC. (3) is Pfizer's PARP/ARPI inhibitor Phase 3 data strong enough in prostate cancer to warrant an approval.

These are all good topics for discussion. The rigor of the old FDA that you have known and loved is still very much around.

Note on Analyzing Clinical Datasets: Extraction of Signal

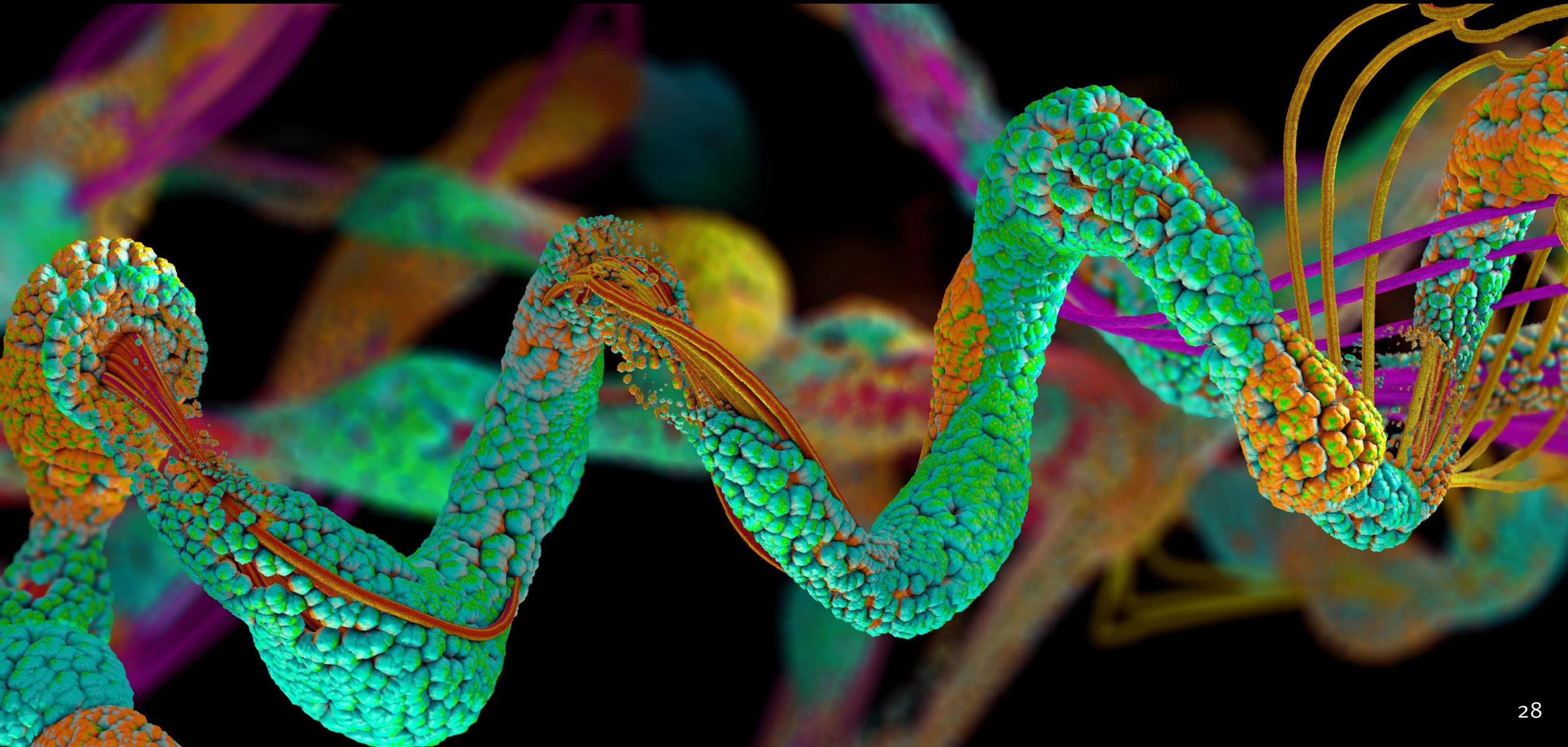
Analysis of clinical datasets is all about looking for signal amidst noise while identifying patient show-stoppers.

- The FDA analyzes countless datasets looking for meaningful applications for drugs that work.
- But how do you spot opportunity amidst noise?
- One might start by looking only for clinical trial data that had statistically significant results.
- This is not necessarily the right approach. One might end up approving a drug that is clinically marginal with safety liabilities. Or, alternatively, one might reject a drug that really works but the efficacy dataset is too small to deliver a statistically significant finding.
- Bayes' Theorem says that we should consider prior beliefs when evaluating evidence and we should also update our beliefs based on the underlying probability distribution of an event if a hypothesis were not true.
- To illustrate, FibroGen raised substantial capital in 2004 based on six patients of data for a HIF-2a inhibitor. All six patients had anemia at baseline and all six no longer had anemia after treatment with drug. Because the probability of spontaneous resolution of anemia is close to zero, this meant that the probability that the drug was active was very high even though the results were not statistically significant.
- Signal extraction from small datasets, single-arm studies, anecdotal data and circumstantial evidence is a critical skill in pharmaceutical regulatory science.



Statistical significance in a clinical trial is much less important than how much we update our beliefs after a clinical trial based on observed data and an understanding of how likely the observed data could have been due to chance. One should always ask: what are the odds based on our prior beliefs that this dataset would have been generated by chance?

Biopharma Market Update



The XBI Closed at 79.02 Last Friday (May 16), Up 3.4% for the Week

The Stifel Global Biotech Value Tracker rose by 2.4% last week, slightly less than the XBI (+3.4%) and the BBC (up 3.4%). Treasury yields remain stubbornly high. The XBI is down 12.2% for the year while the Stifel Global Biotech Value Tracker is down 5% for the year.

Biotech Stocks Up Last Week

Return: May 9 to May 16, 2025

Nasdaq Biotech Index: +4.1%
Arca XBI ETF: +3.4%
Virtus LifeSci Biotech ETF (BBC): +3.4%
Stifel Global Biotech EV (adjusted): +2.4%*
S&P 500: +5.3%

Return: Dec 31, 2024 to May 16, 2025 (YTD)

Nasdaq Biotech Index: -12.3%
Arca XBI ETF: -12.2%
Virtus LifeSci Biotech ETF (BBC): -25.4%
Stifel Global Biotech EV (adjusted): -4.9%*
S&P 500: +1.3%

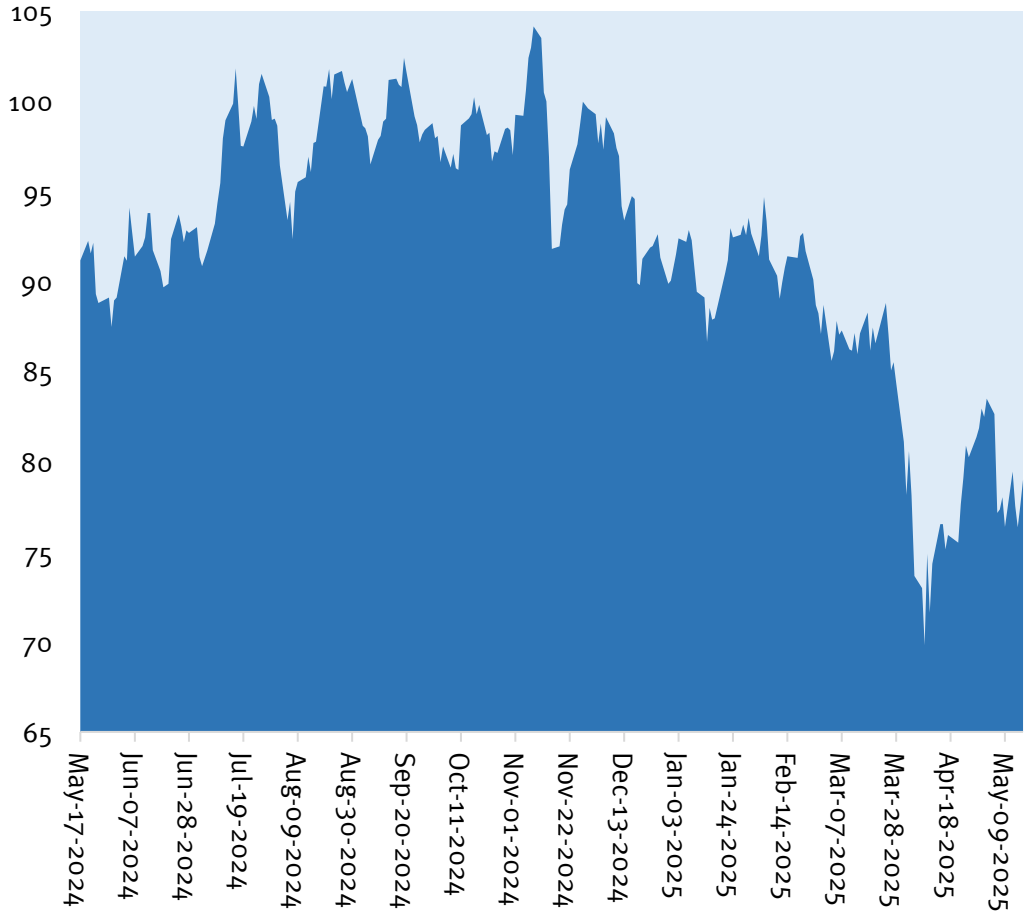
VIX Down

Aug 2, 2024: 23.4%
Dec 13, 2024: 13.8%
Jan 24, 2025: 14.2%
Feb 21, 2025: 18.2%
Mar 28, 2025: 21.7%
Apr 11, 2025: 37.6%
May 2, 2025: 22.6%
May 16, 2025: 18.4%

10-Year Treasury Yield Up

Aug 2, 2024: 3.80%
Dec 13, 2024: 4.4%
Jan 24, 2025: 4.6%
Feb 21, 2025: 4.4%
Mar 28, 2025: 4.27%
Apr 11, 2025: 4.48%
May 2, 2025: 4.33%
May 16, 2025: 4.43%

XBI, May 16, 2024 to Apr 24, 2025



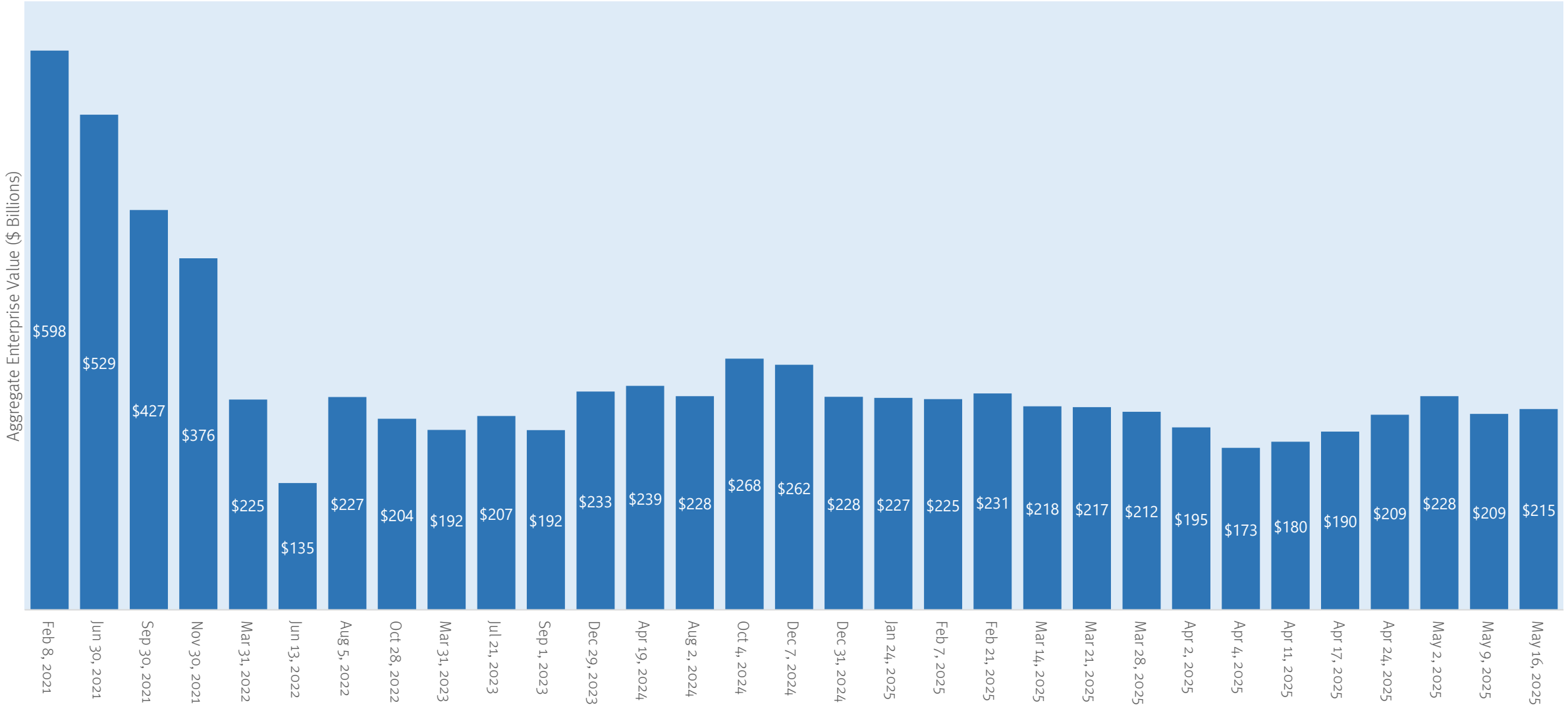
* Change by enterprise value. The adjusted number accounts for the effect of exits and additions via M&A, bankruptcies and IPOs. The annual change by market cap is even higher.

Source: S&P Capital IQ and Stifel analysis

Total Global Biotech Sector Rose 2.4% Last Week

Biotech stocks are up 24% since hitting a low point six weeks ago. Biotech stocks ended last week *down 5%* for the year.

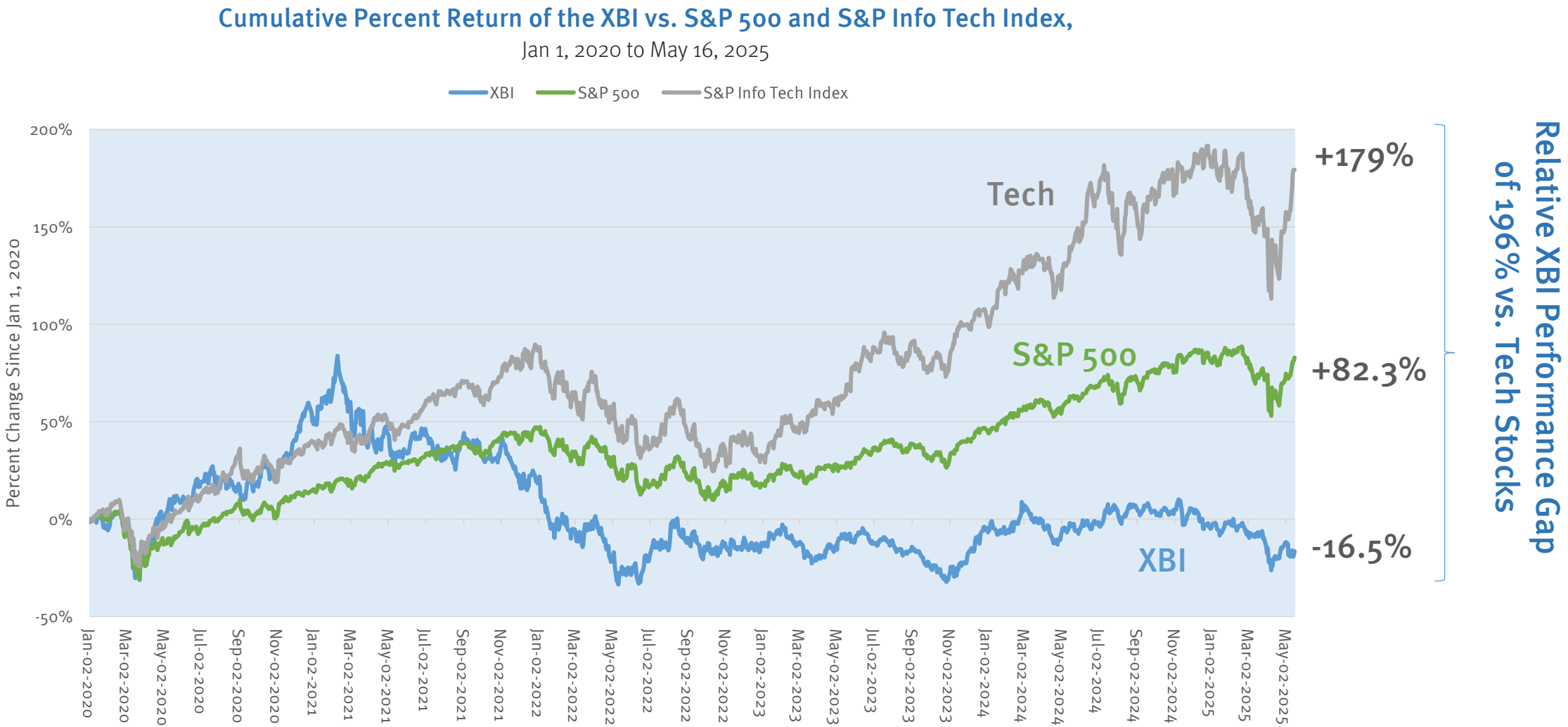
Total Enterprise Value of Publicly Traded Global Biotech, Feb 8, 2021 to May 17, 2025 ($ Billions)



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

Biotech Underperformance Has Deepened in 2025

We began 2023 with a 106% differential between the S&P IT Index and the XBI since the start of 2020. By the start of 2025 it had hit 186%. As of last Friday, the gap stood at a difficult to comprehend 197%.

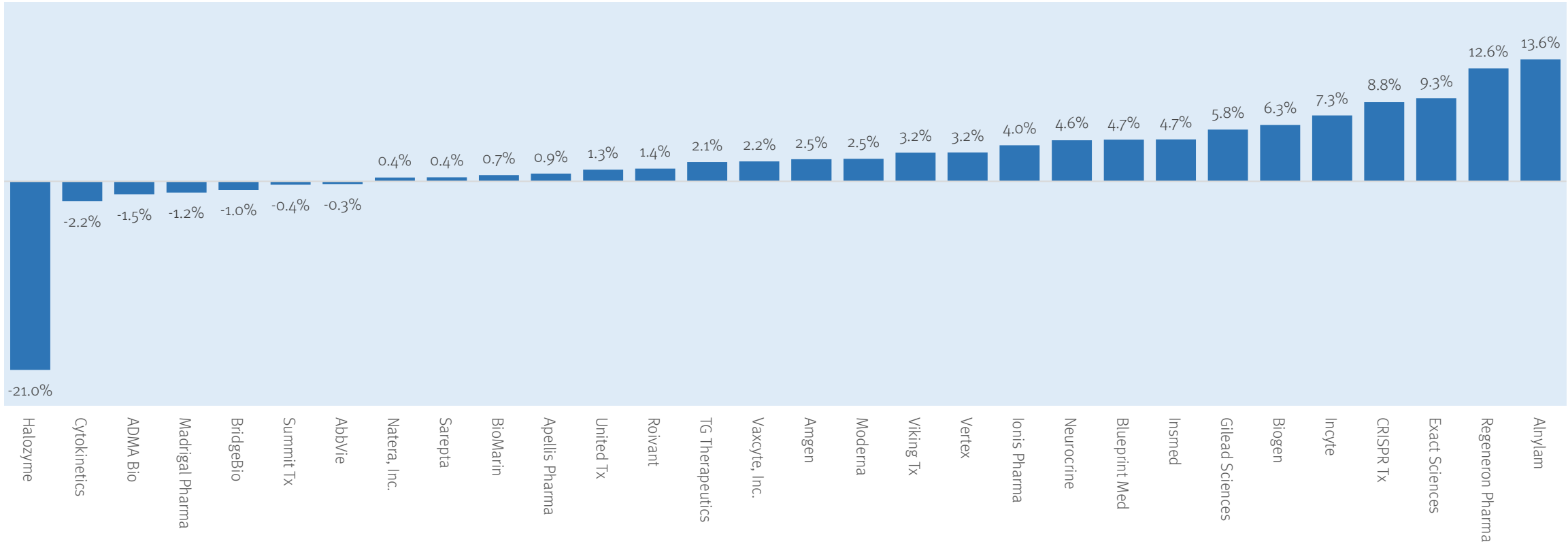


Source: CapitalIQ.

XBI 30 Performance Up 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 +2.5%. The median change was +2.3%. Alnylam did well based on outstanding mortality data in Phase 3 Helios-B trial for its Amvuttra. Regeneron did well after receiving a positive judgement in a lawsuit on PCSK9 IP with Amgen. Halozyme shares were hit hard after Medicare announced that changes to a root molecule would not provide additional protection from the negotiation provisions of the IRA.

Top 30 XBI Influencers, Pecent Change in Market Cap, Week of May 9 to May 16, 2025



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

Big Pharma Counted on This Loophole. It May Be Closing.

Josh Nathan-Kazis, *Barron's*, May 13, 2025 (excerpt)

Buried in a 200-page technical document released by the Centers for Medicare and Medicaid Services late Monday was a short, convoluted paragraph that could translate to big problems for Johnson & Johnson, Merck, Bristol Myers Squibb, and a handful of their big pharma peers.

The paragraph could spell the end of a strategy the drugmakers had believed would allow them to put off the impact of Medicare price cuts for some of their top-earning cancer drugs.

The plan had been to shift patients to newer injectable versions of the cancer drugs, and then keep charging Medicare high prices for the injectable versions even after the original versions were subject to the new price negotiation program.

The paragraph on page 13 of Monday night's guidance document suggests that the Trump administration might be planning to put an end to that workaround. The problem for investors is that a lot of drugmakers had bet heavily on the gambit, building it into their strategies to blunt the impact of the inevitable revenue drops that are coming as a wave of monoclonal antibody cancer therapies approaches the end of its patent life.

For Merck, the new guidance could disrupt the company's plans to drag out revenue from Keytruda, the cancer megablockbuster responsible for nearly half its sales. For Johnson & Johnson, it would mean that revenue from their cancer drug Darzalex Faspro would drop sharply in 2029, five years earlier than expected. And for Bristol, it might be bad news for Opdivo Qvantig, which could see its sales drop in 2028, also earlier than expected.

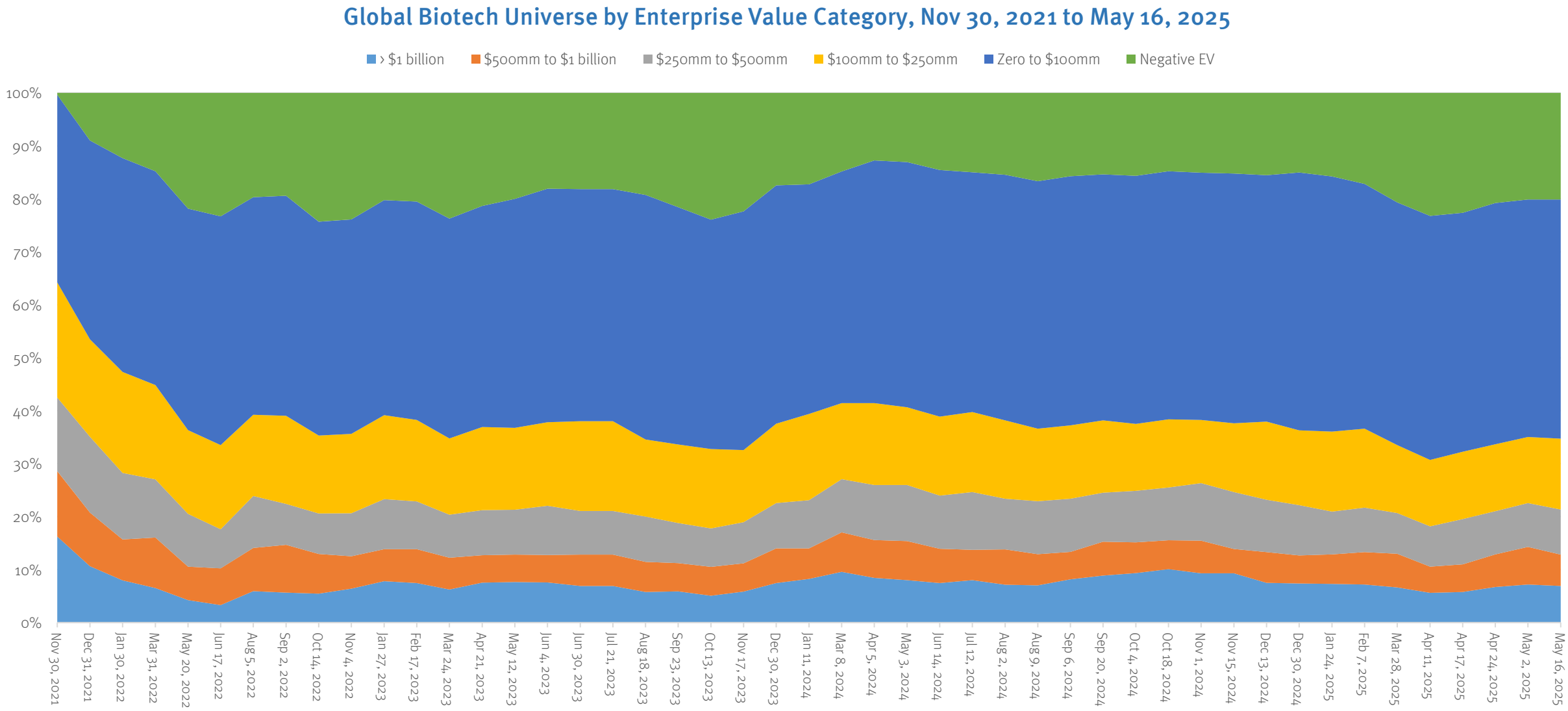
Shares of all three of the drugmakers fell on Tuesday. Merck was down 4.7%, Johnson & Johnson was down 3.7%, and Bristol was down 3.3%. The S&P 500 was up 0.7%.

Also down was Halozyme, the biotech that makes the ingredient that allows Opdivo Qvantig, Darzalex Faspro, and other medicines to be quickly injected, rather than slowly infused. Its shares were down 25%.

Source: https://www.barrons.com/articles/merck-jnj-bristol-pharma-drug-price-loophole-b6881c80

Global Biotech Neighborhood Analysis

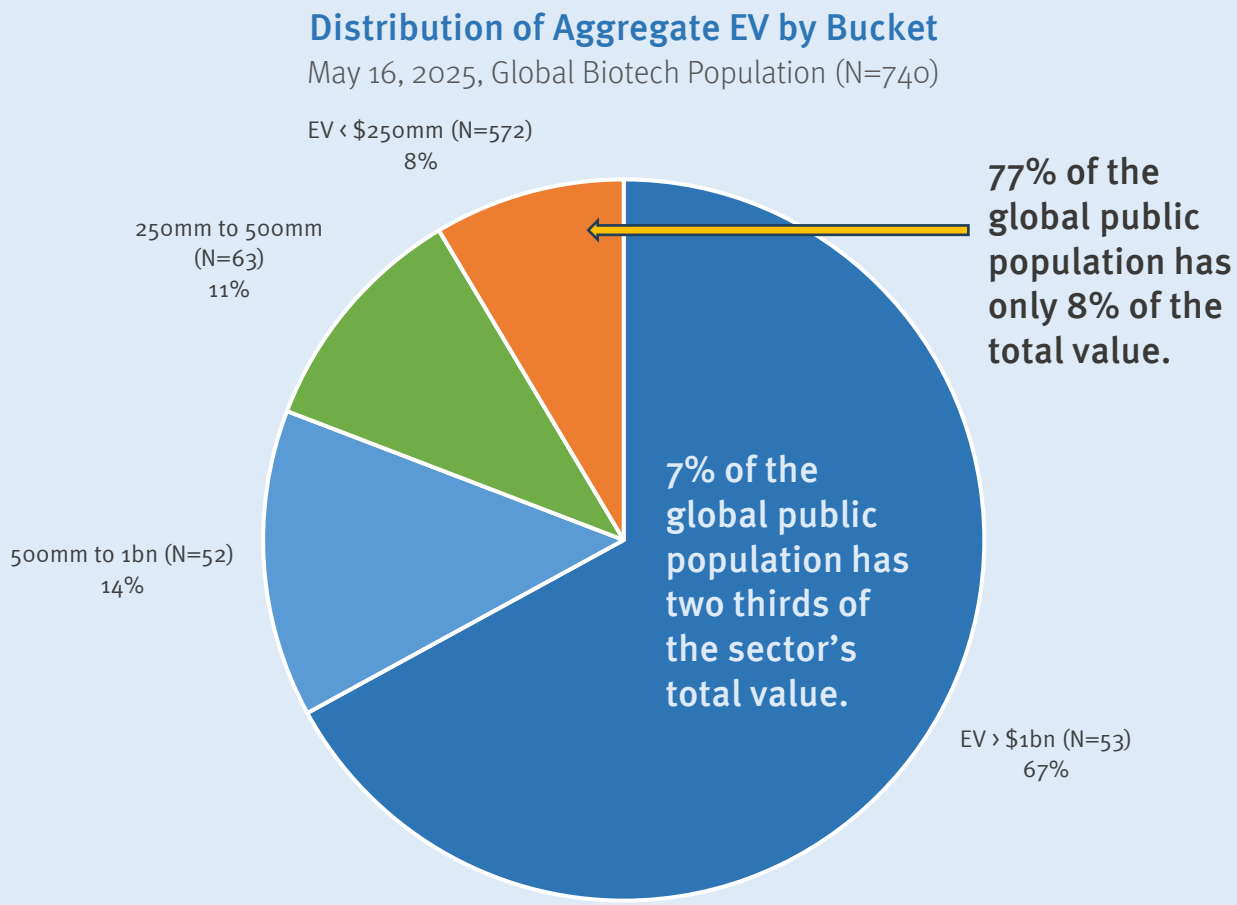
We saw shrinkage in the negative EV population last week.

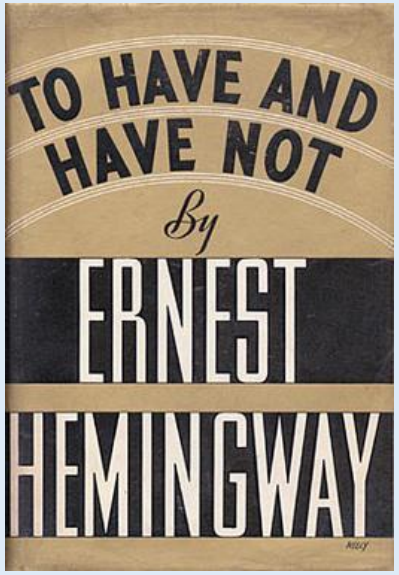


Source: CapitalIQ and Stifel analysis. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

“Have and Have Not” Biotech Market Still Stands

It’s nowhere close to the 80/20 rule in biotech. The bottom 77% of biotechs by value have only 8% of the total EV of the global sector.





“Now is no time to think of what you do not have. Think of what you can do with that there is.”

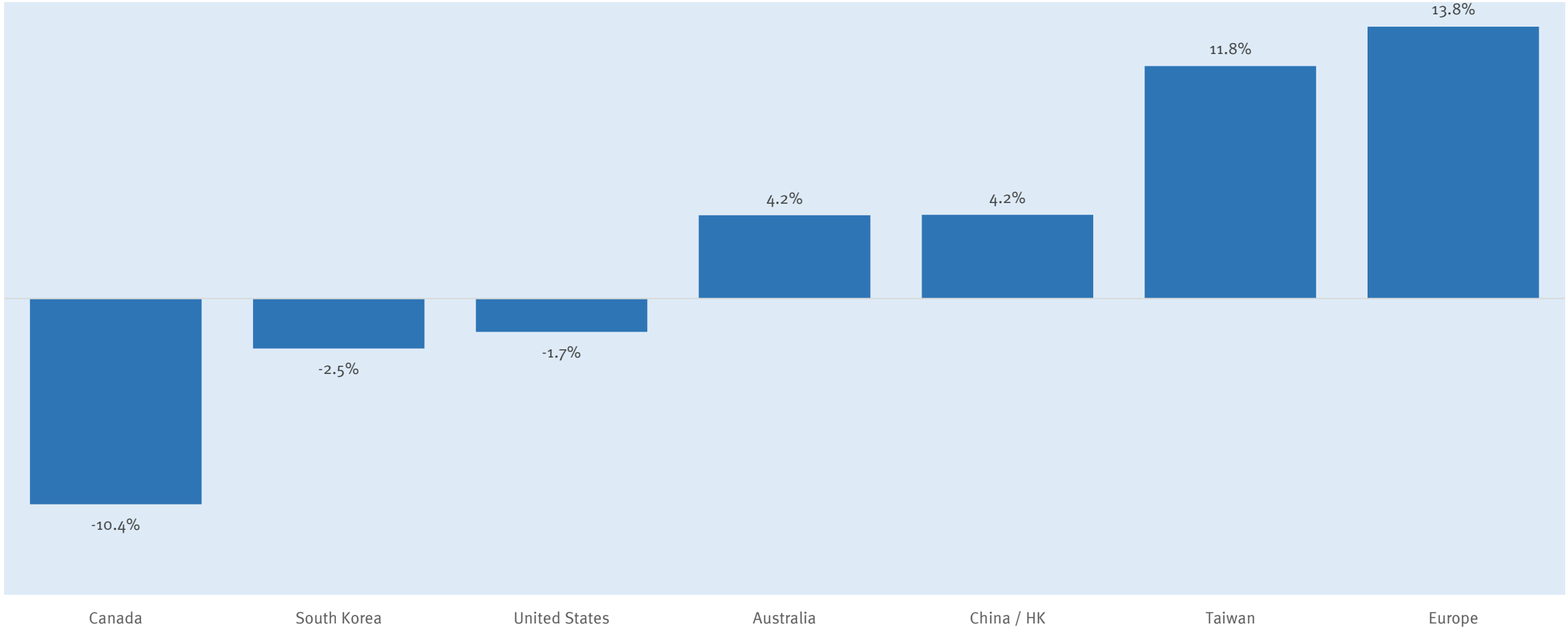
Ernest Hemingway

Source: CapitalIQ and Stifel analysis. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange. The buckets are those for enterprise value on May 16, 2025.

Europe and Taiwan Biotech Fared Well Last Week

Last week saw a strong recovery take place in Europe and Taiwan while U.S. biotech was down slightly. Canada biotech shed 10% of its value last week.

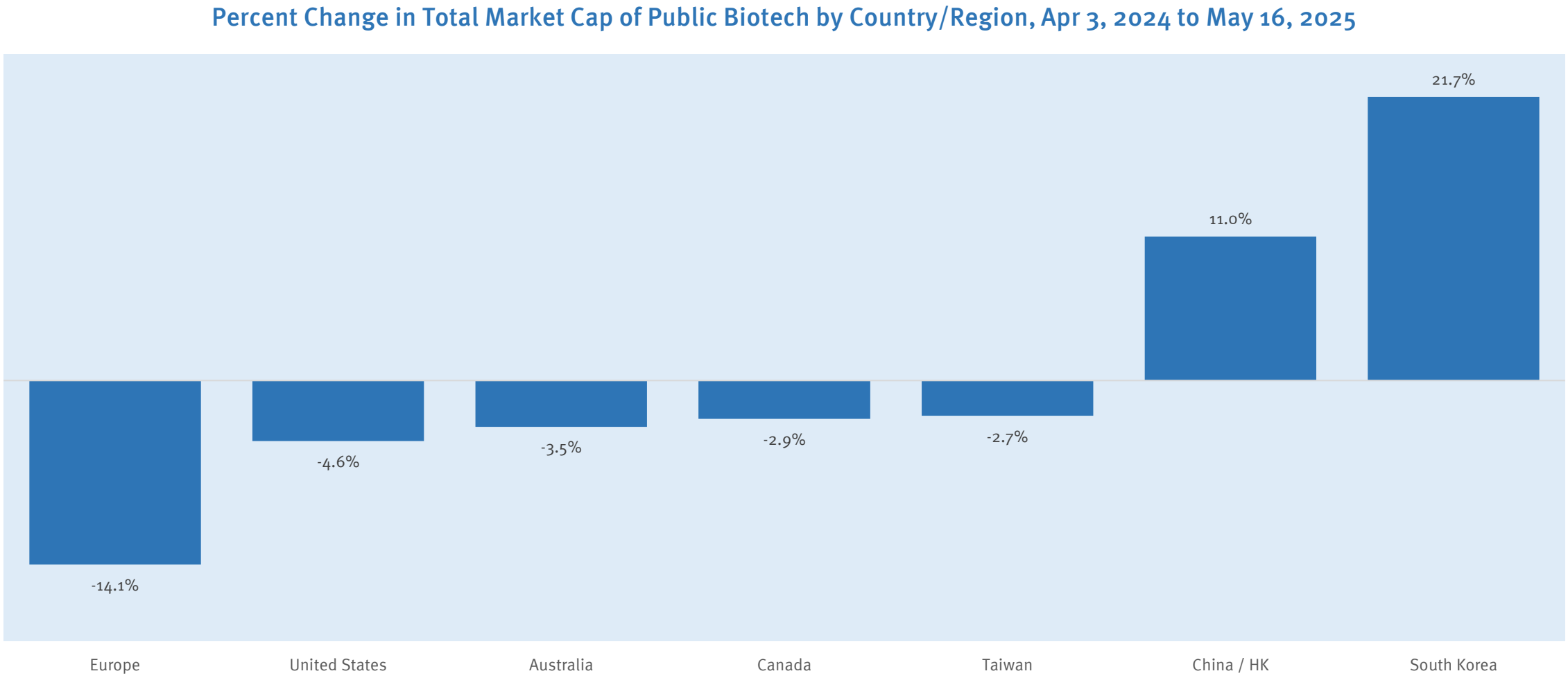
Percent Change in Total Market Cap of Public Biotech by Country/Region, May 9, 2024 to May 16, 2025



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

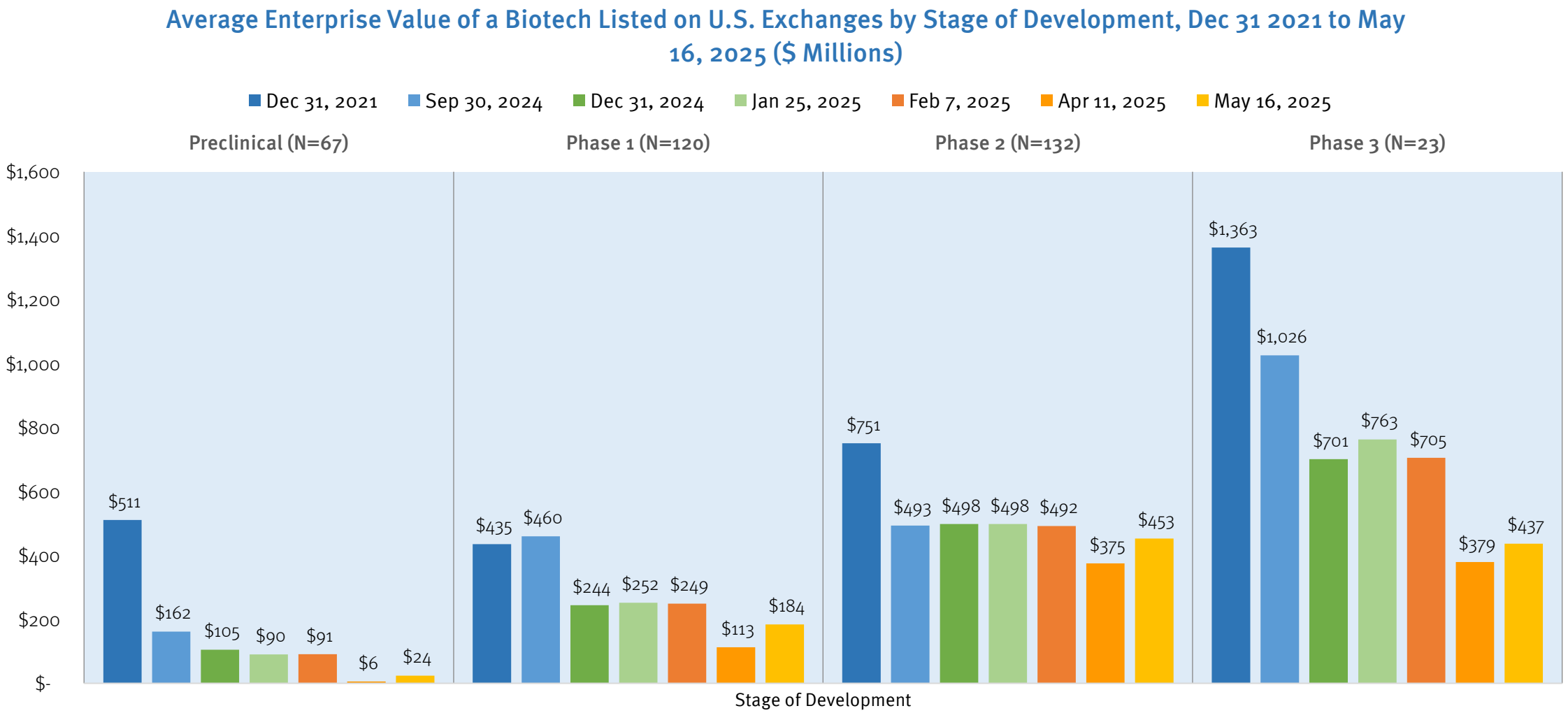
Biotech Performance by Region Last Six Weeks

This chart tracks post-Liberation Day biotech performance. U.S. biotech is down 5% while Europe is down 14% since then. China and South Korea have fared the best since then.



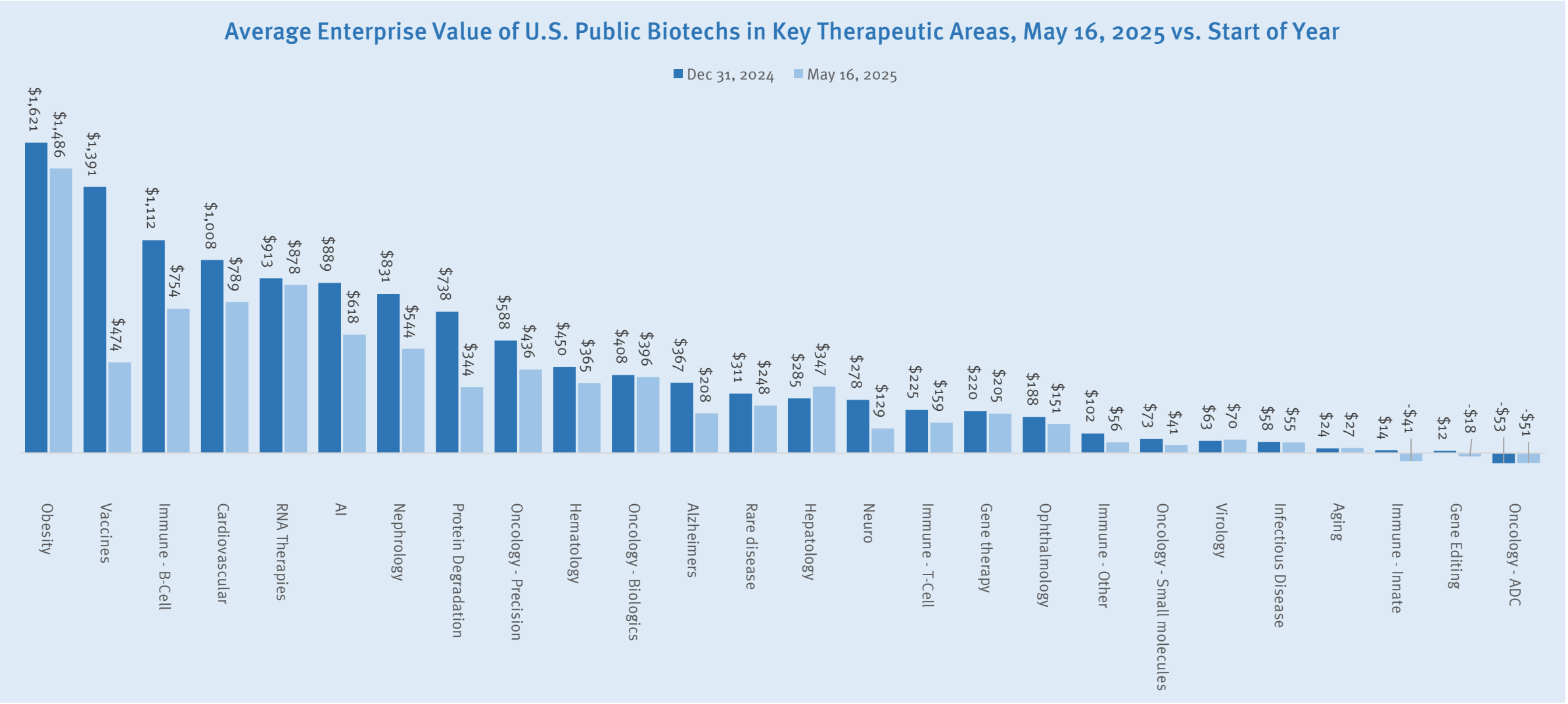
Source: CapitalIQ and Stifel analysis. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

Phase 3 U.S. Biotech Values Continue to Soften Relative to Phase 1 and Phase 2 Stocks



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

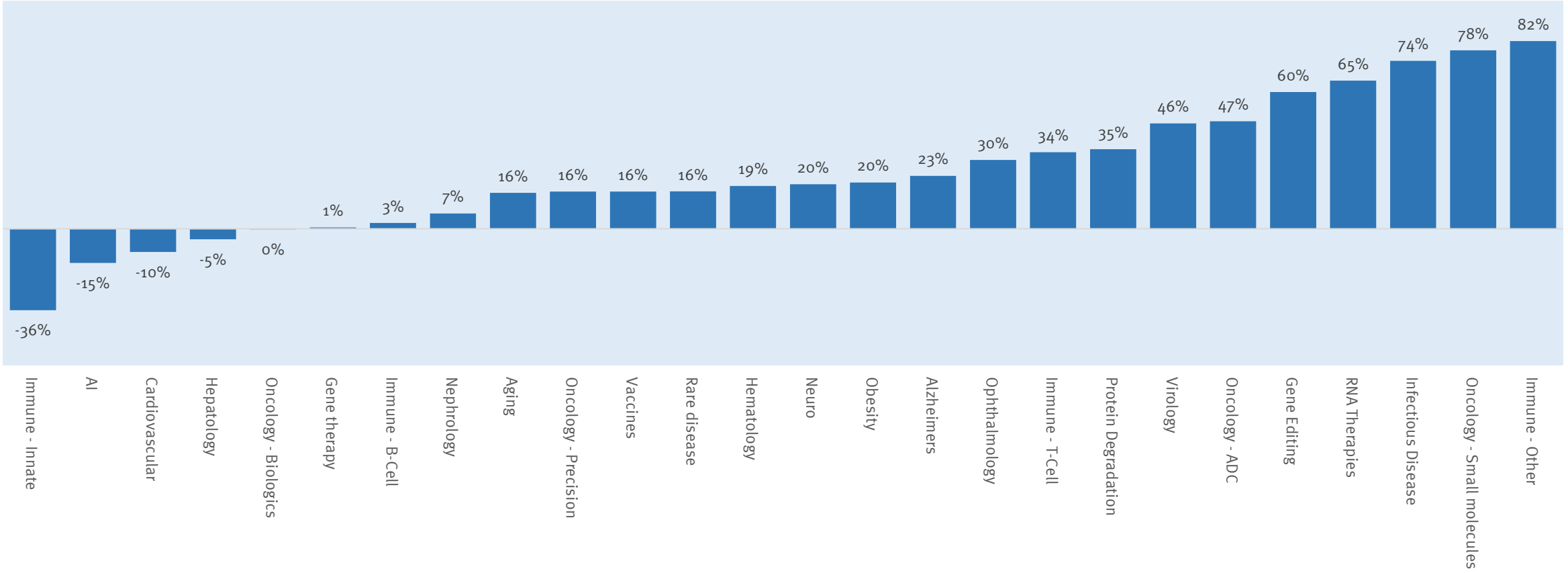
Since Year Began Obesity and RNA Biotechs Have Held Their Values Most While Other Sectors Including Immunology and Vaccines Are Down



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

We are Seeing Beaten Down Fields Like ADC's, Gene Editing, ID, RNA and Small Molecule Oncology Performed Well in Last Month

Four Week in Change Average Enterprise Value of U.S. Public Biotechs in Key Therapeutic Areas, Apr 17 vs May 16, 2025 ($ millions)



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

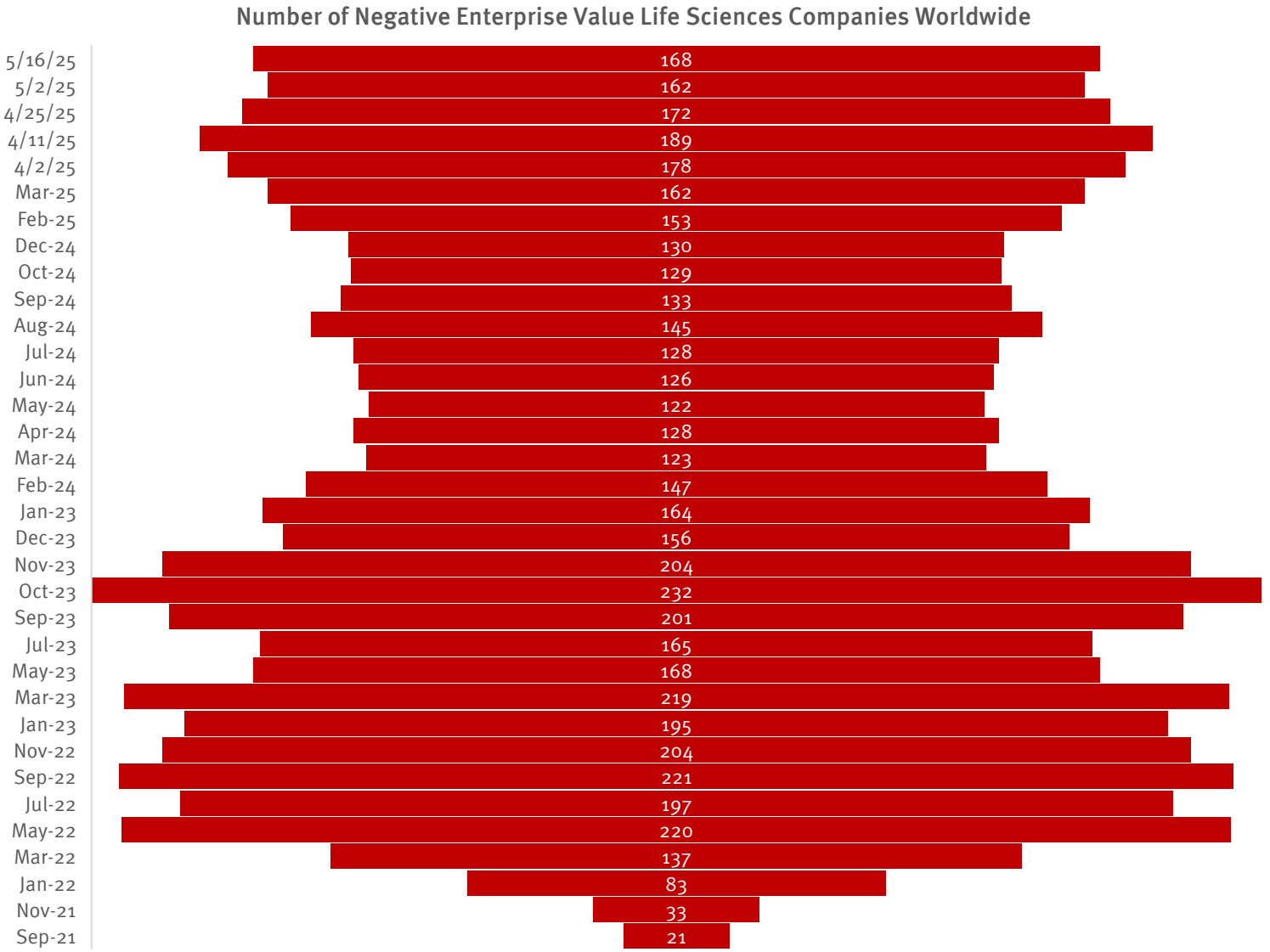
Life Sciences Sector Gained $82 Billion in Value Last Week (+0.9%)

Last week saw strength in the API, life science tools and diagnostics sectors while CDMOs and pharma services companies were weak.

Sector	Firm Count	Enterprise Value (May 16, 2025, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	79	$91,140	4.4%	6.9%	9.4%
Biotech	723	$215,302	2.4%	10.0%	-5.1%
CDMO	37	$151,771	-1.8%	1.2%	14.5%
Diagnostics	75	$264,923	2.7%	10.6%	-4.5%
OTC	29	$24,676	-1.3%	5.1%	-5.7%
Pharma	694	$5,854,504	0.4%	0.0%	-7.8%
Services	38	$145,262	-0.3%	3.8%	-22.7%
Tools	50	$543,765	2.9%	3.0%	-25.2%
Devices	173	$1,827,241	2.0%	6.9%	8.3%
HCIT	7	$24,069	-3.6%	6.1%	30.2%
Total	**1905**	**$9,143,653**	**0.9%**	**2.2%**	**-6.0%**

Source: CapitalIQ and Stifel analysis

Number of Negative Enterprise Value Life Sciences Companies Rose in Last Two Weeks



The count of negative EV life sciences companies worldwide fell from 162 two weeks ago to 168 last Friday.

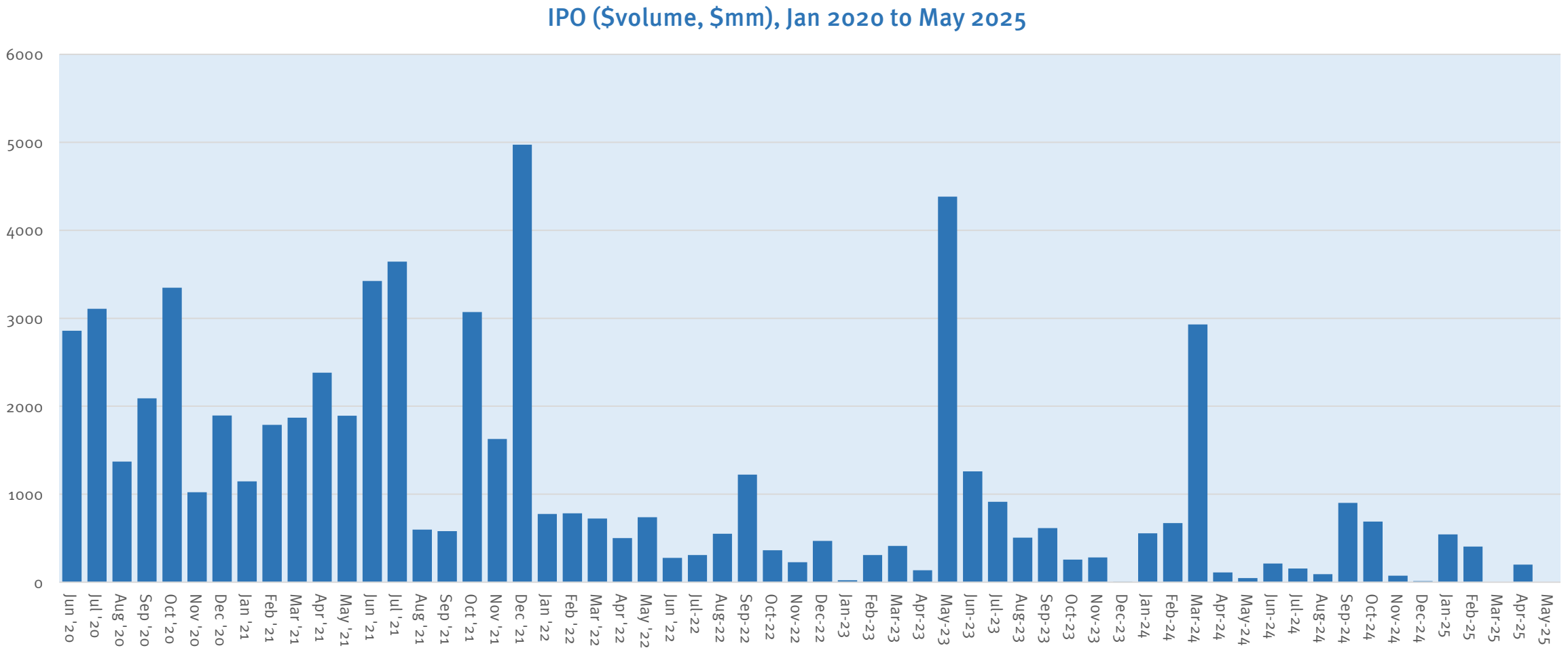
This metric has been stubbornly high in recent weeks.

Source: CapitalIQ

Capital Markets Update

IPO Market Quiet This Month

The last company to go public in the biopharma sector was Duality Biologics which went out in Hong Kong in early April. We are now slated to see Hengrui do a $1.27 billion IPO in HK next week. The U.S. biotech IPO market remains largely closed.



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

It’s Been Three Months Without a Biotech IPO

Kyle LaHucick, *Endpoints News*, May 16, 2025 (excerpt)

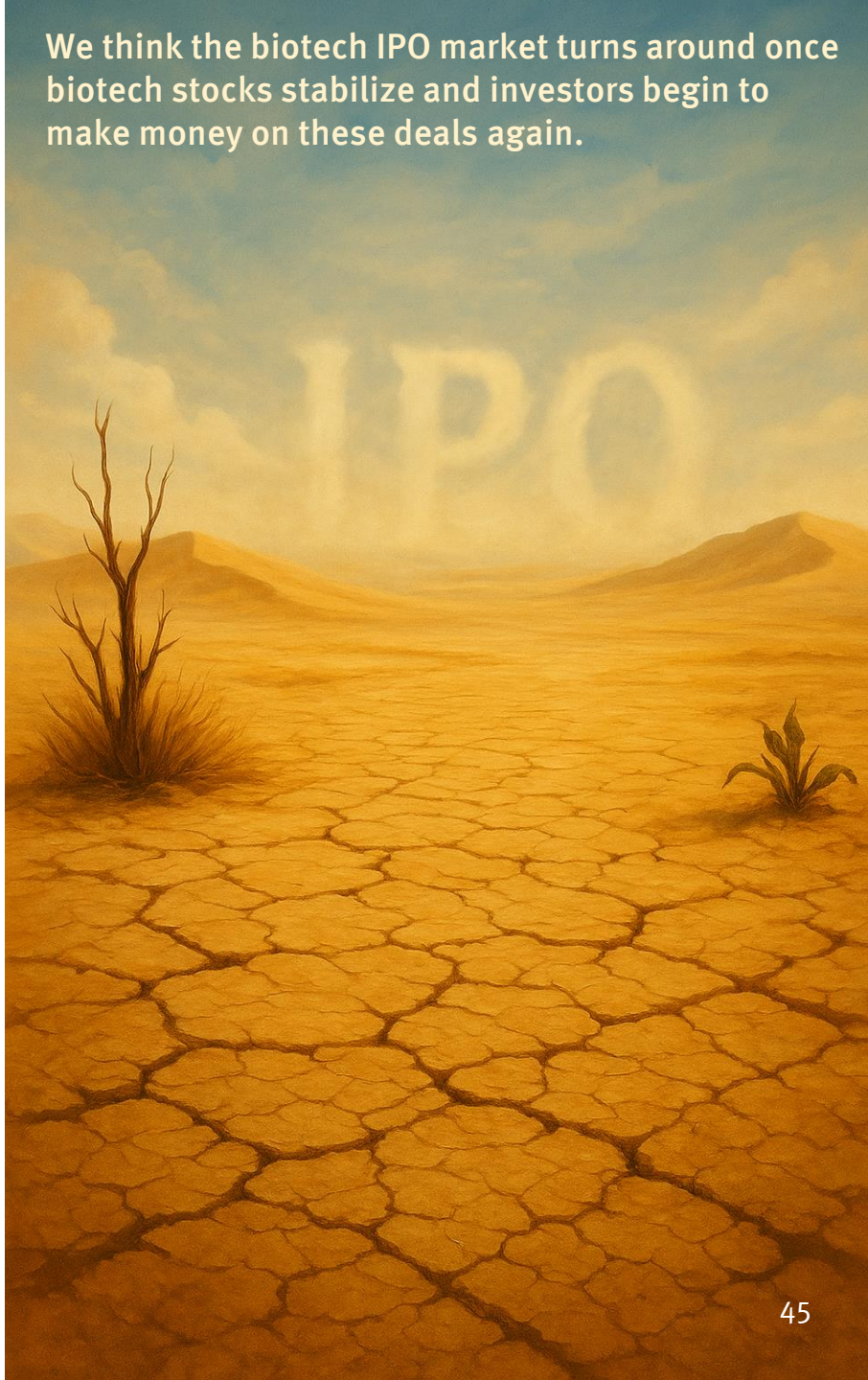
The last time a biotech went public on a US stock exchange, people were buying flowers for Valentine’s Day. Those petals withered long ago. It’s been 13 weeks since Aardvark Therapeutics’ $94 million initial public offering on Feb. 13 in the bleakest streak for biotech IPOs since 2022.A few Chinese biotechs have been successful with listings in Hong Kong, but there’s been no activity for private biotechs eyeing the public markets in the US.

“The last time we saw an IPO market as slow as that of 2025 was in 2012,” Stifel banker Tim Opler and his team wrote May 5.

A few hopefuls like immunology biotech Odyssey Therapeutics and cell therapy maker Aurion appear to have stalled and have not disclosed any updates to their previously revealed IPO pitches. No other biotechs have publicly submitted paperwork for a new listing on the Nasdaq or NYSE. (There was one small IPO last week — Apimeds Pharmaceuticals bagged $13.5 million in its debut — though Endpoints News generally tracks IPOs above $50 million).

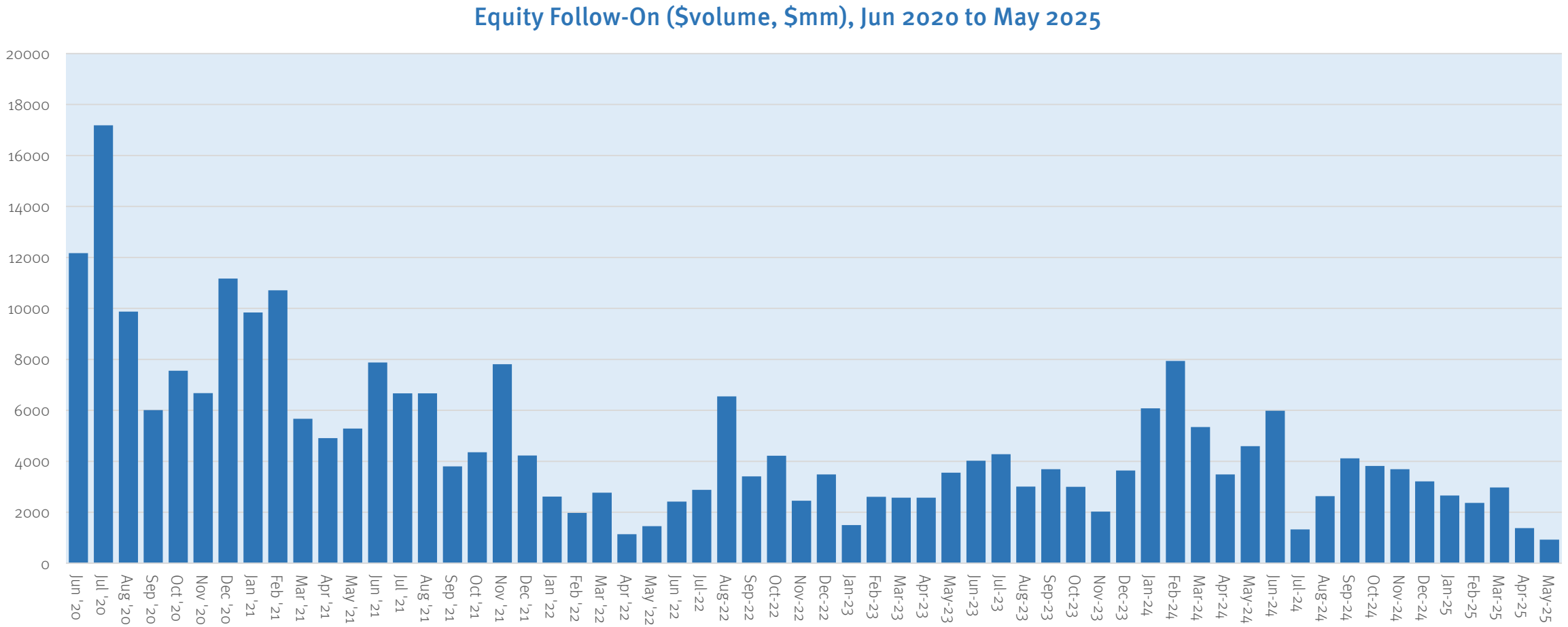
The last time there was this long of a quiet spell was in 2022, when there was a 19-week period between PepGen’s IPO on May 6 and Third Harmonic Bio’s debut on the Nasdaq on Sept. 15. It was a short run for Third Harmonic. The company’s stockholders are set to vote next month on whether to dissolve the anti-inflammatory drug developer. For the last three years, industry insiders have hoped for a more consistent and active slate of IPOs. A confluence of factors have dried up the IPO landscape, including macro uncertainties, potential pharmaceutical tariffs and few signs of generalist investor interest. Plus, the performance of the biotech IPOs of 2023, 2024 and early 2025 doesn’t paint a pretty picture and lends little confidence for future prospects. As of a May 4 report by Raymond James banker Brian Gleason and his team, 27 of the 33 IPOs since 2023 are currently trading below their issue price. The median performance was negative 58%.

Source: https://endpts.com/its-been-three-months-without-a-biotech-ipo/



Global Follow-On Market Continuing to Slow This Month

The slowdown in the biopharma follow-on market is continuing this month. The last three weeks have seen $556 million of volume, making it one of the slowest periods in recent years. This said, the market is not closed. Companies with good data like CytomX are still able to come to market.

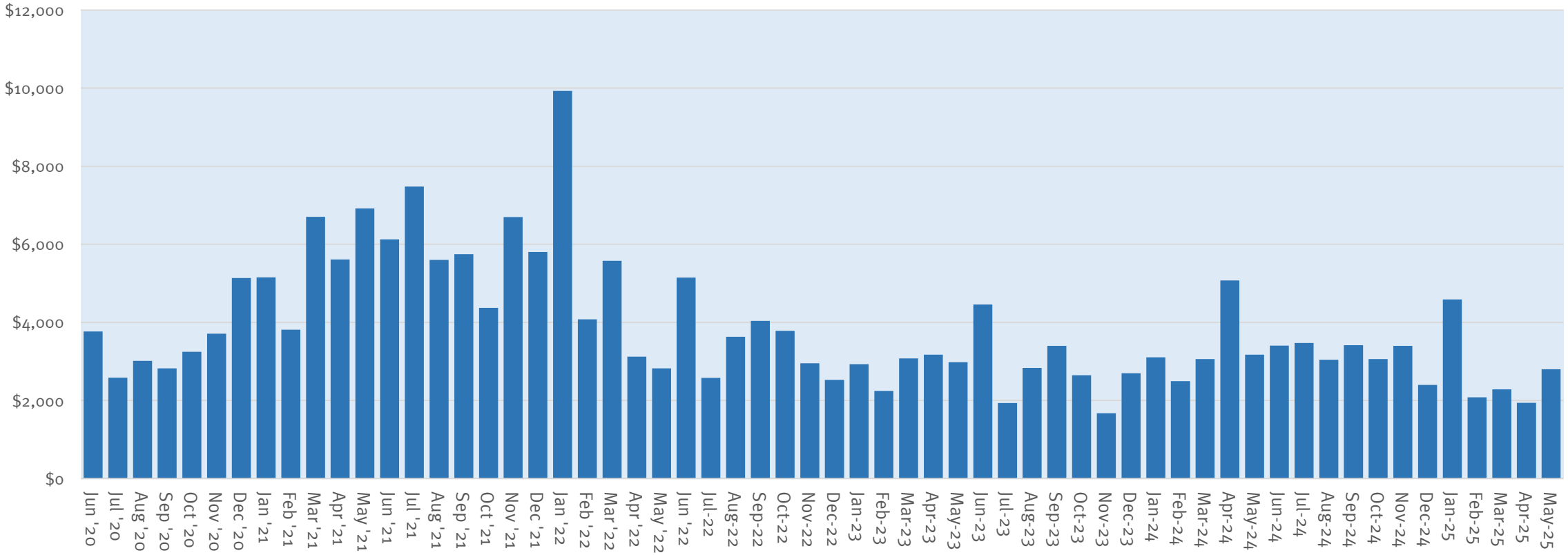


Source: Data from CapitalIQ, Crunchbase. Data for May 2025 is extrapolated based on results through May 16th.

Venture Privates Picking Up (a Bit)

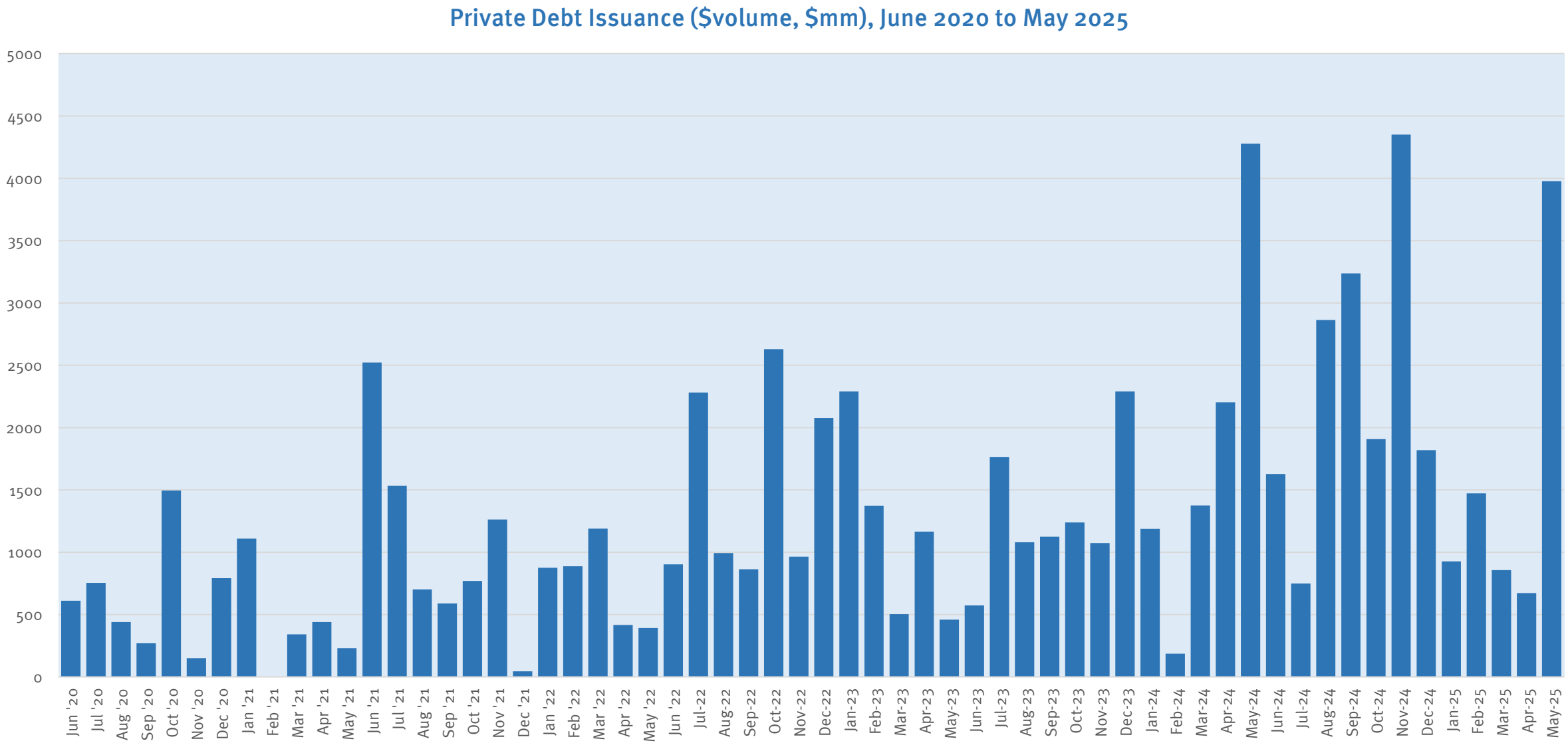
Recent months have seen modest activity in the venture privates market. The market was particularly slow last week with less than $200mm in deals pricing in the market. For the year, we are on pace to a $33bn volume year, which would be the slowest since 2019.

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



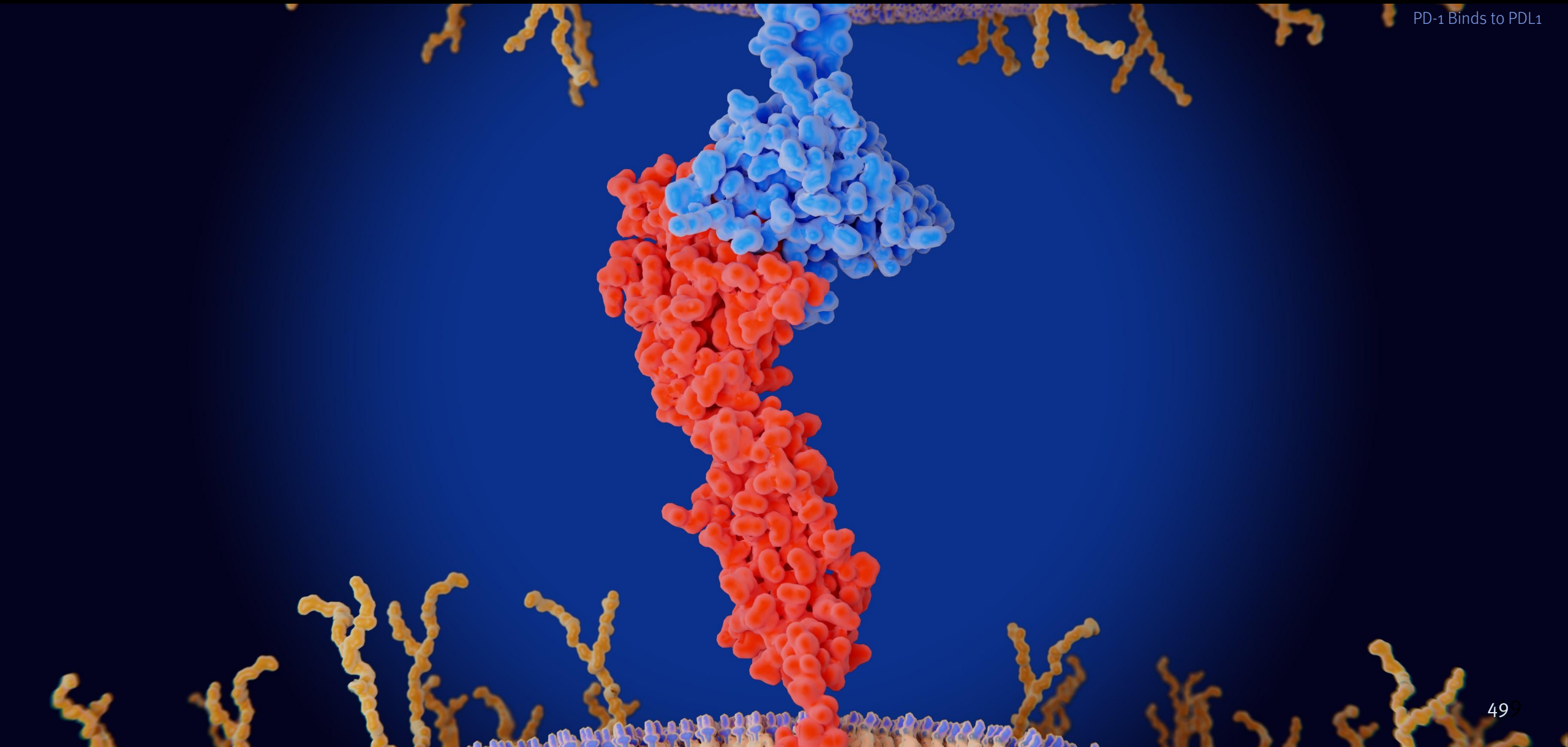
Source: Data from CapitalIQ, Crunchbase. Data for May 2025 is extrapolated based on results through May 16th.

Global Biopharma Private Debt Placement Volume Strong This Month



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

Deals Update

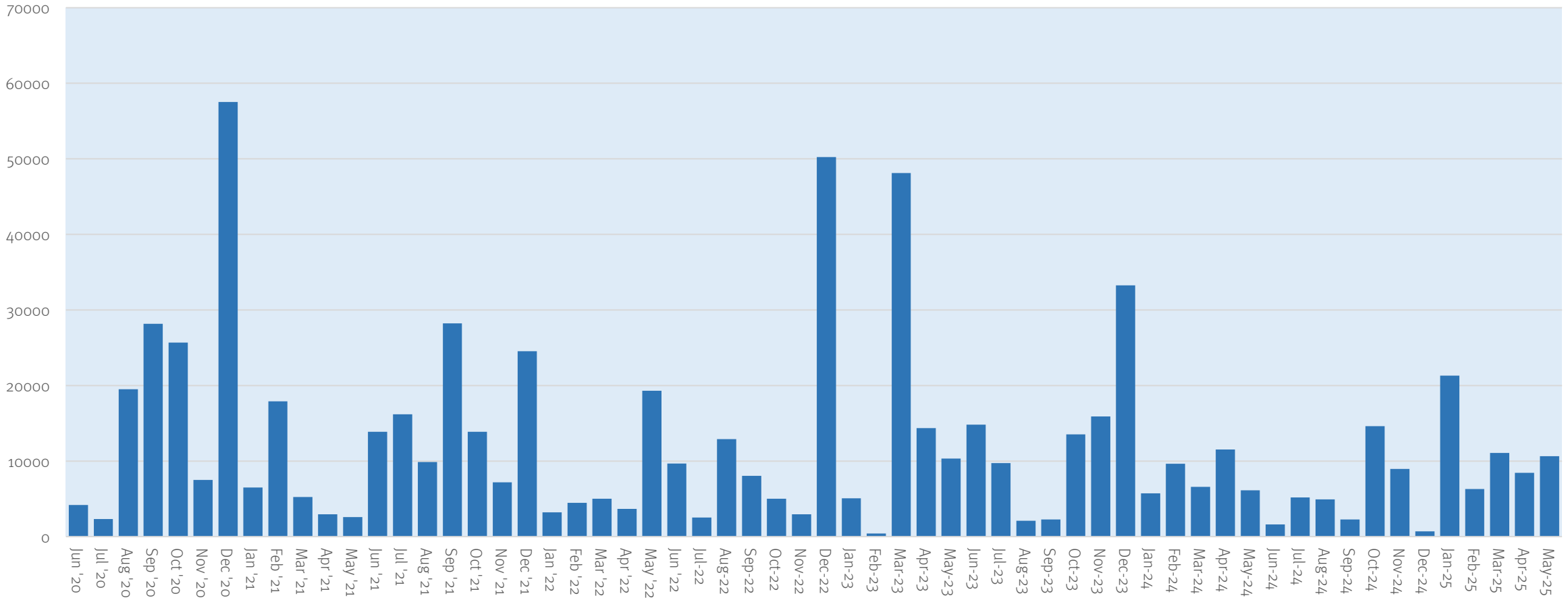


PD-1 Binds to PDL1

M&A Market Continues to be Highly Active in May 2025

We have seen $6.5 billion in biopharma M&A volume so far this month. If we extrapolate this, we are on track for an $11 billion month. Overall, the year continues to look like quite a solid year for M&A. Last week saw GSK buy a Phase 3 ready liver disease drug from Boston Pharma for $1.2 billion and BioMarin step in to buy Inozyme for $260 million (a 180% premium).

Monthly M&A Activity ($volume, $mm), Jun 1, 2020 to May 2025



Source: S&P, CapitalIQ

GSK to Acquire Efimosfermin to Treat and Prevent Progression of Steatotic Liver Disease (SLD)

GSK Press Release, May 14, 2025 (excerpt)

GSK plc (LSE/NYSE: GSK) and Boston Pharmaceuticals, a leading clinical stage biopharmaceutical company developing highly targeted therapies for patients with serious liver diseases, today announced that they have entered into an agreement under which GSK will acquire Boston Pharmaceuticals' lead asset, efimosfermin alfa. Efimosfermin is a phase III-ready, potential best-in-class, investigational specialty medicine to treat and prevent progression of steatotic liver disease (SLD). Under the agreement, GSK will pay $1.2 billion upfront, with potential for additional success-based milestone payments totalling $800 million.

Efimosfermin is a novel, once-monthly fibroblast growth factor 21 (FGF21) analog therapeutic in clinical development for the treatment of metabolic dysfunction-associated steatohepatitis (MASH), including cirrhosis, and future development in alcohol-related liver disease (ALD), both forms of SLD. Given efimosfermin's direct antifibrotic mechanism of action and GSK's data-driven insights from work in human genetics and disease phenotyping, it has potential to address more advanced stages of SLD and opportunity in combination with GSK'990, a siRNA therapeutic in development for other subsets of patients with SLD.

Recent data from a phase II trial of efimosfermin, designed to assess the efficacy and safety of a monthly subcutaneous dose in participants with biopsy-confirmed moderate-to-advanced (F2 or F3) MASH, showed that efimosfermin rapidly and significantly reversed liver fibrosis and stopped its progression, with a manageable tolerability profile. These data suggest potentially greater fibrosis improvement compared to that seen with other therapeutic approaches and with benefit expected independent of background glucagon-like peptide-1 (GLP-1) therapy. In addition, efimosfermin could offer triglyceride reduction and improved glycaemic control, important considerations for MASH patients who frequently face cardiometabolic co-morbidities. Efimosfermin's unique properties, including low immunogenicity and an extended half-life, also offer the potential for a monthly dosing regimen and improved patient convenience. Full data from the trial was presented at the American Association for the Study of Liver Diseases (AASLD) Meeting in November 2024.

Source: https://www.gsk.com/en-gb/media/press-releases/gsk-to-acquire-efimosfermin-a-phase-iii-ready-potential-best-in-class-specialty-medicine-to-treat-and-prevent-progression-of-steatotic-liver-disease-sld/

Comparison of Efimosfermin to Other FGF21's in Development

Key points of differentiation include monthly dosing and competitive efficacy in MASH resolution.

Drug Candidate	Company	Mechanism / Format	Dosing	Clinical Stage	Key Efficacy Highlights	Notable Features
Efimosfermin	GSK	Long-acting FGF21 analog	Monthly SC injection	Phase III-ready	Phase II: 45.2% achieved ≥1-stage fibrosis improvement; 67.7% MASH resolution without fibrosis worsening	Potential best-in-class; direct antifibrotic action; low discontinuation rates; being explored for ALD as well
Pegozafermin	89bio	PEGylated FGF21 analog	Weekly or biweekly SC injection	Phase III (ENLIGHTEN trials)	Phase IIb: Significant fibrosis regression and MASH resolution; improvements in lipid and glycemic profiles	First FGF21 analog in Phase III for cirrhotic MASH; strong metabolic benefits; favorable safety profile
Efruxifermin	akero	Fc-FGF21 fusion protein	Weekly SC injection	Phase III (SYNCHRONY program)	Phase IIb: 39% achieved ≥1-stage fibrosis improvement without MASH worsening; notable cirrhosis reversal	Demonstrated efficacy in advanced fibrosis (F4); potential for combination therapy with GLP-1 agents

Source: Company Press Releases

BioMarin Acquires Inozyme Pharma

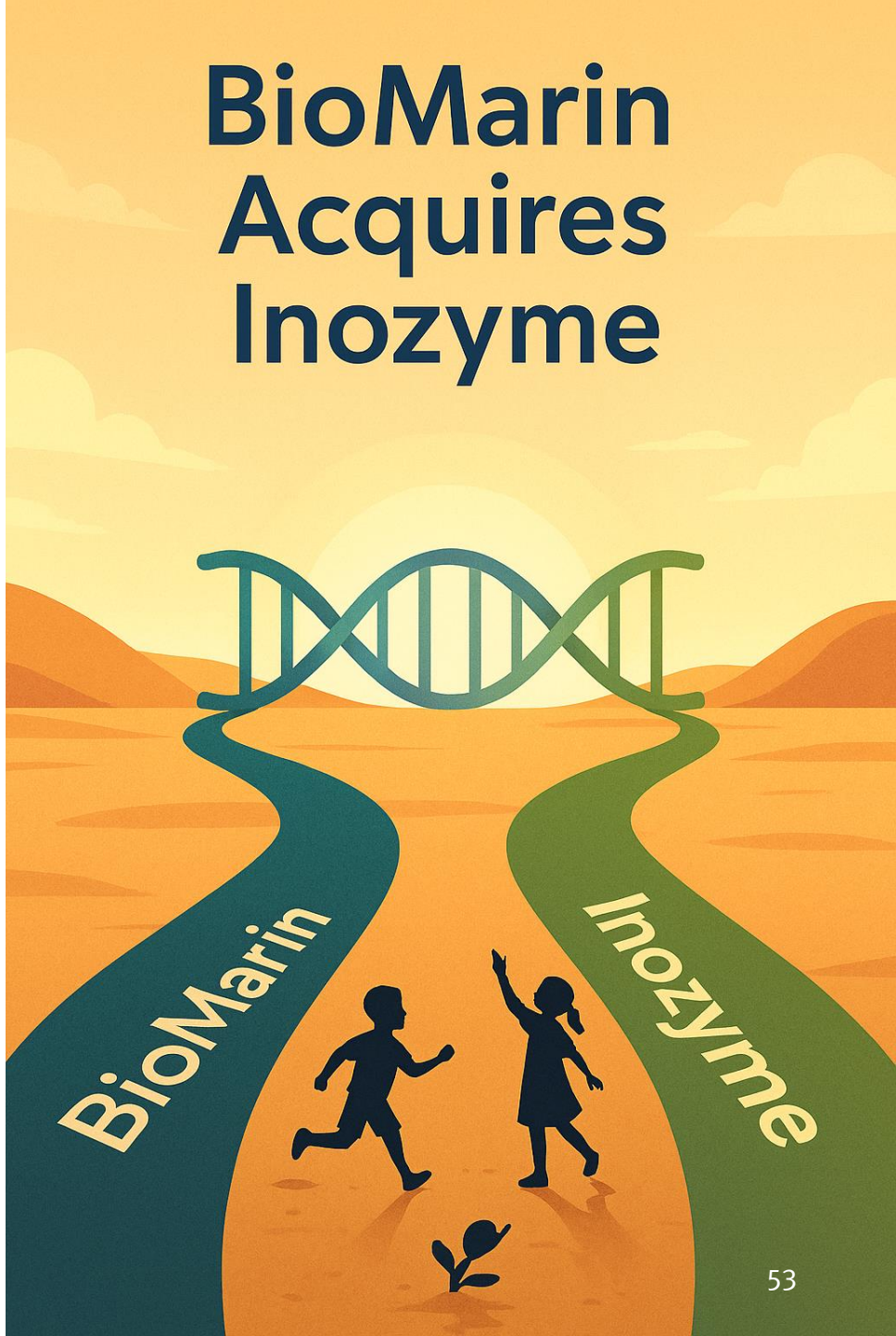
BioMarin Press Release, May 16, 2025 (excerpt)

SAN RAFAEL, Calif. and BOSTON, May 16, 2025 /PRNewswire/ -- BioMarin Pharmaceutical Inc. (Nasdaq: BMRN) and Inozyme Pharma, Inc. (Nasdaq: INZY) announced today that BioMarin has entered into a definitive agreement to acquire Inozyme for $4.00 per share in an all-cash transaction for a total consideration of approximately $270 million. The transaction has been unanimously approved by the Boards of Directors of both companies and is expected to close in the third quarter of 2025, subject to regulatory approval, successful completion of a tender offer and other customary closing conditions.

The acquisition will strengthen BioMarin's enzyme therapies portfolio, adding a late-stage enzyme replacement therapy, INZ-701, which is currently being assessed for the treatment of ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) Deficiency, a rare, serious and progressive genetic condition that affects blood vessels, soft tissues and bones. The condition is associated with increased cardiovascular mortality risk across all age groups, especially in infants. It is also associated with severe rickets and osteomalacia in children and adults. Data from the first Phase 3 pivotal study of INZ-701 in children is expected in early 2026, with potential regulatory approval in 2027.

"Today's announcement gives greater hope to patients who may benefit from INZ-701, a potentially transformative therapy that aims to address the underlying causes and systemic impacts of ENPP1 Deficiency," said Douglas A. Treco, Ph.D., Chief Executive Officer and Chairman of Inozyme. "BioMarin has paved the way over the past two and a half decades, successfully launching five first-in-disease enzyme therapies. I'd like to thank the team at Inozyme and our partners for their outstanding work and dedication, as we pass this important potentially life-changing therapy to the leading innovator in genetically defined conditions."

Source: https://www.gsk.com/en-gb/media/press-releases/gsk-to-acquire-efimosfermin-a-phase-iii-ready-potential-best-in-class-specialty-medicine-to-treat-and-prevent-progression-of-steatotic-liver-disease-sld/



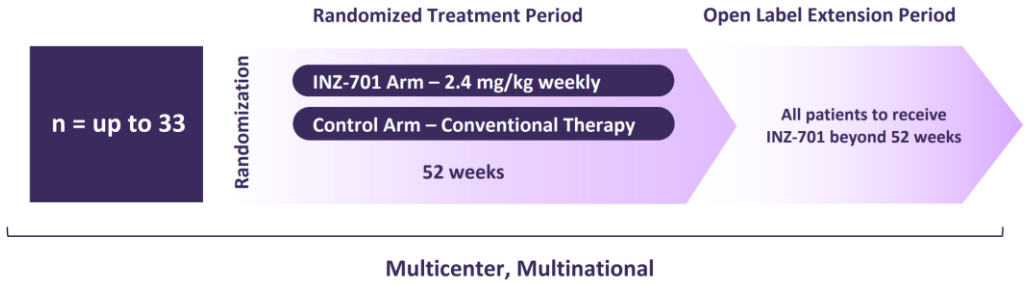
Inozyme Program for ENPP1 Deficiency Impressive

Rapid, significant and sustained increase in PPi observed at all doses (Ph1/2)

Population: *Pediatric*

- Confirmed genetic diagnosis
- Radiographic evidence of skeletal abnormalities
- ≥1 year and <13 years
- Low plasma PPi

Design: Randomized (2:1), Open Label



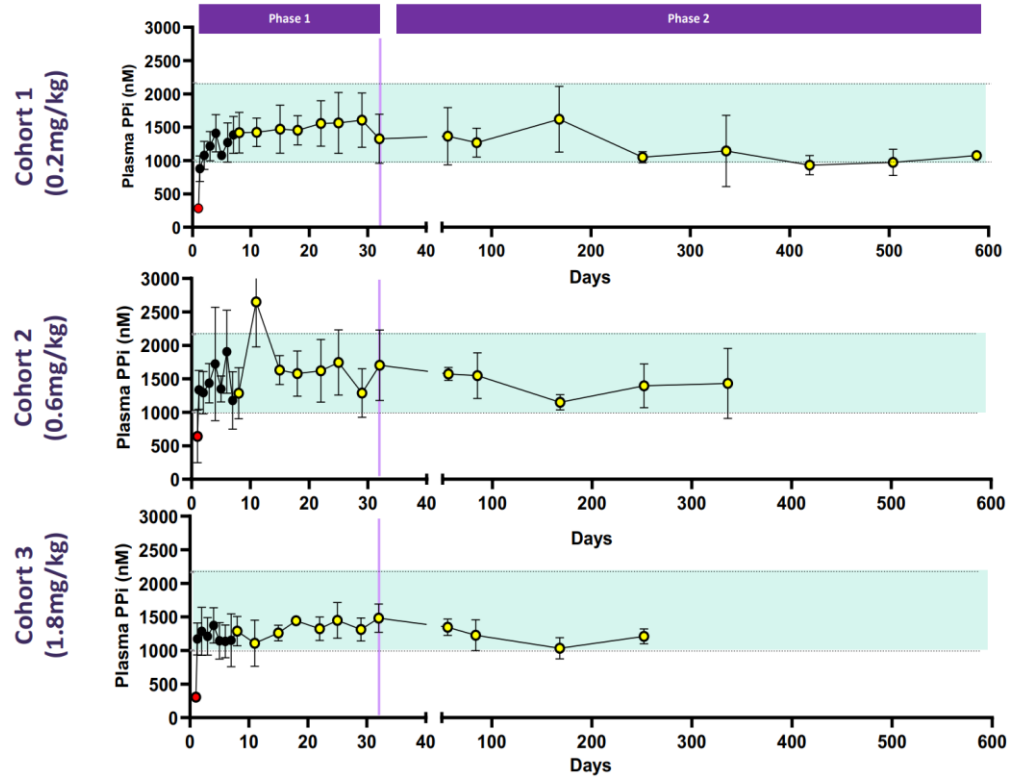
Endpoints

US

- **Primary**: Change in plasma PPi from baseline over time
- **Secondary**: Trends in RGI-C score, RSS, Growth Z-score; PK

EU

- **Co-Primary**:
  - Change in plasma PPi from baseline over time
  - RGI-C score (with p<0.2)
- **Secondary**: RSS, Growth Z-score; PK



Source: Company Investor Presentation

Industry Update

Biden Is Diagnosed With an Aggressive Form of Prostate Cancer

Tyler Pager, *New York Times*, May 18, 2025 (excerpt)

Former President Joseph R. Biden Jr. was diagnosed on Friday with an aggressive form of prostate cancer that has spread to his bones, his office said in a statement on Sunday.

The diagnosis came after Mr. Biden reported urinary symptoms, which led doctors to find a "small nodule" on his prostate. Mr. Biden's cancer is "characterized by a Gleason score of 9 (Grade Group 5) with metastasis to the bone," the statement said.

"While this represents a more aggressive form of the disease, the cancer appears to be hormone-sensitive which allows for effective management," according to the statement from Mr. Biden's office, which was unsigned. "The president and his family are reviewing treatment options with his physicians."

Mr. Biden, 82, left office in January as the oldest-serving president in American history. Throughout his presidency, Mr. Biden faced questions about his age and his health, which ultimately led him to abandon his re-election campaign.

Mr. Biden and his family have faced numerous health challenges throughout their lives. In 1988, Mr. Biden battled two brain aneurysms that threatened to end his political career. His son Beau died in 2015 from glioblastoma, an aggressive form of brain cancer.

Source: https://www.nytimes.com/2025/05/18/us/politics/biden-prostate-cancer.html

We wish former President Biden Biden well as he grapples with advanced prostate cancer. There are a number of positive items of note including the fact that the cancer appears to be hormone responsive.

Further, with today's drug options for metastatic disease such as Pluvicto®, Biden likely has good prospects.

Interestingly, the Biden Administration invested heavily in cancer and championed a major early cancer detection project through the NIH.

Biden has also been a major supporter of the Cancer Moonshot Initiative.

The Trump administration's approach to cancer research funding has been marked by significant budgetary reductions, raising concerns among scientists, healthcare professionals, and patient advocates.

Novo CEO to Depart as Obesity Drugmaker's Challenges Rise

Ned Pagliarulo, *Biopharma Dive*, May 16, 2025 (excerpt)

Novo Nordisk CEO Lars Fruergaard Jørgensen, who led the Danish drugmaker to new heights through its development of powerful medicines for diabetes and obesity, will step down from his position, the company said Friday.

While the runaway success of Novo's GLP-1 drugs Ozempic and Wegovy made it for a time the second most valuable pharmaceutical company in the world, its stock has slumped amid supply chain bottlenecks, clinical trial setbacks and encroaching competition from rival Eli Lilly. Shares are worth less than half what they were one year ago.

Lars Rebien Sørensen, who chairs the board of the Novo Nordisk Foundation and was Jørgensen's predecessor at Novo, will join the company's board. (The Novo Nordisk Foundation owns a controlling stake in Novo Nordisk through a holding company.)

"Novo Nordisk's strategy remains unchanged, and the board is confident in the company's current business plans and its ability to execute on the plans," Novo board chair Helge Lund said in a statement. "I would like to thank Lars Fruergaard Jørgensen for his outstanding contributions to Novo Nordisk's success during his tenure as CEO."

Source: https://www.biopharmadive.com/news/novo-nordisk-ceo-step-down-jorgensen-market-challenges/748337/

Lars Fruergaard Jørgensen has been an incredibly well-liked CEO and gets credit for pushing to turn semaglutide into a major obesity drug. In many ways Novo has created today's booming obesity drug market. While Novo has partially gone outside to build up its next generation pipeline in obesity, it has fallen short of Lilly by sticking to next generation internal candidate Cagrisema. In retrospect, Novo was quite optimistic about its pipeline and walked away from a triple drug candidate that looks a lot like Eli Lilly's retatrutide. Novo is now in preclinical testing of UBT251, an emerging triple incretin drug candidate. The company under Jørgensen was slow to react to the manufacturing capacity challenges posed by semaglutide's success. This has allowed both Lilly and a large compounded market to emerge. The compounded market persists in a personalized format despite ending the semaglutide shortage. Evidation reports to us that half of the semaglutide market is now compounded – which has not been good for Novo shares. Despite these failures, the company has a formidable, albeit early obesity pipeline and is in Phase 3 with ziltivekimab for the control of inflammation in atherosclerosis. This drug is late stage and has potential to be huge.

The MAGA Revolution Threatens America's Most Innovative Place

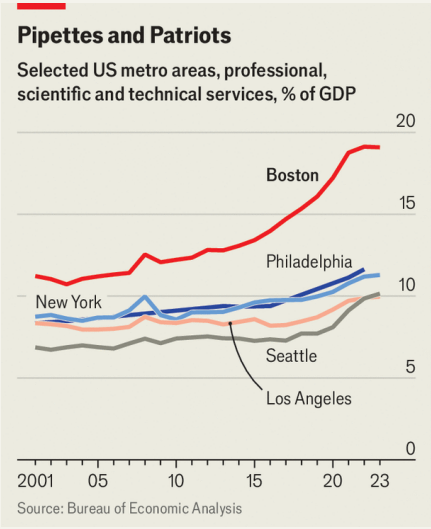
The Economist, May 19, 2025 (excerpt)

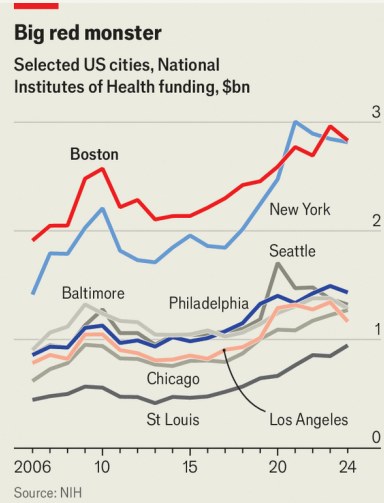
Science sometimes advances not by design but by happenstance. Thirty years ago a graduate student in chemical engineering at the Massachusetts Institute of Technology was describing a bottleneck in his work over drinks at a bar in Cambridge, Massachusetts. A Harvard student heard and suggested a solution using microchip manufacturing technology that his lab had recently developed. The casual exchange led to a collaboration under the guidance of Donald Ingber, a Harvard cell biologist, that eventually helped pioneer organ-chip technology—lab-grown models of human organs on tiny chips. Dr Ingber would go on to found a biotech firm in Boston that commercialised the technology. The story's arc is very Boston: federally funded academic research and serendipitous encounters among brainiacs spawning innovation and biotech firms. If science in America has a centre of gravity it is along the Charles River, which snakes between Boston and Cambridge, where MIT, Harvard, world-class hospitals and venture-capital firms all share a riverbank. Yet that same concentration of science makes the area vulnerable to politics. President Donald Trump's policies on universities and his administration's proposed cuts to science funding threaten not only Massachusetts's sprawling research and biotech ecosystem, but also the country's competitive edge in innovation.

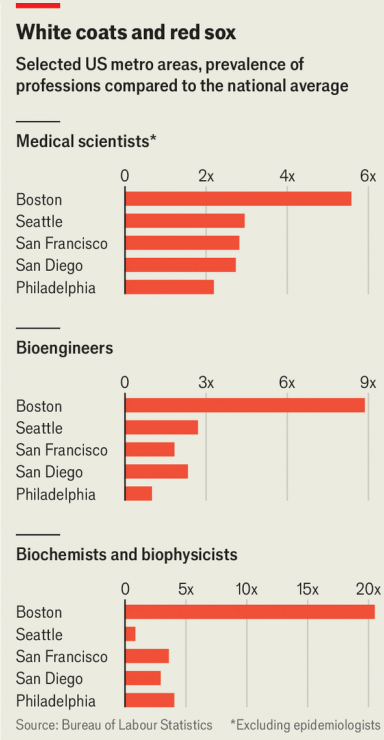
For 17 of the past 19 years universities and hospitals in Boston have received more funding from the National Institutes of Health (nih) than those anywhere else (see chart). Roughly one in eight of America's top 40 research universities call the area home. Of all these institutions no place has drawn Mr Trump's ire quite like Harvard. Just hours after Harvard refused to comply with federal demands to restructure the university, Dr Ingber was among the first of its scientists to receive a stop-work order on his grants. Then on May 5th Linda McMahon, the education secretary, sent a rambling letter to Harvard with an extraordinary threat: the university will no longer receive any new federal research grants.

Biotech and pharmaceutical firms rely on a stream of discoveries from federally funded university labs doing open-ended research. But the more federal money flows into university labs, the greater the chances that scientists stumble upon discoveries that industry can turn into the next life-saving drug. Sekar Kathiresan, the head of the Boston-based biotech firm Verve Therapeutics, expects to spend $2bn developing a drug that could treat heart disease, which is the leading cause of death in the world. "The technology we're using to turn off a cholesterol-raising gene in the liver to lead to lifelong cholesterol-lowering", he says, was made possible by scientists at the Broad Institute in Cambridge who invented base editing in 2016. "Generous federal funding for science is critical for the next generation of ideas and cures," he adds.

With the fight raging most fiercely inside Massachusetts, the state has in many ways led the resistance against Mr Trump's funding cuts and woo-woo approach to science. Since February the state's attorney-general has filed two lawsuits against cuts to NIH funding. Others have joined both suits. Harvard, too, is pushing back in court.







Source: https://www.economist.com/united-states/2025/05/18/the-maga-revolution-threatens-americas-most-innovative-place

Art Levinson: Seek Truth and Don’t Fear Failure

Ron Leuty, “Biotech at 50,” *San Francisco Business Times*, May 15, 2025 (excerpt)

Leading Bay Area biotech companies are people like Levinson, who with Google in 2013 started Calico in South San Francisco, and many of his disciples. That list includes [Hal] Barron, now the CEO of Redwood City-based Altos Labs, a "life-extending" company of more than 450 people whose investors have included Amazon chief Jeff Bezos and longtime tech investor Yuri Milner.

"One of the most incredible gifts I've been given in my life is when I am challenged by a problem, I can very easily go, 'So what would this person do?'" Barron said, noting his time with former Genentech and Roche colleagues like Levinson, the former UCSF chancellor and former head of the Bill & Melinda Gates Foundation Susan Desmond-Hellmann, AstraZeneca CEO Pascal Soriot, BioMarin Pharmaceutical Inc. Chief Business Officer James Sabry and Gilead Sciences Inc. CEO Dan O'Day.

"I can hear them. I know them well. But the most important one is the voice of Art," Barron said. "I spend my entire life trying to be like Art. But you could try to be like Art or you could be Art. It's a big difference."

One of Levinson's biggest lessons? Seek truth, Barron said.

"Sometimes the truth is inconvenient, maybe even really bad, but you take the long view. He ensured balance — the short-term means, the long-term perspective," Barron said. "It's often a luxury that CEOs say they don't have. He rejected that false choice: You always have the option. … He would always instill in people this sense of understanding how to balance those things.“ It's a lesson as the Bay Area biotech industry faces the headwinds of cuts to basic science research support reduced funding for emerging companies and the loss of talent.

"Great leaders don't fear failure," Barron said. "(Art) would be the first to say, 'I'm not encouraging anyone to fail, but you can't fear failure or you won't be doing anything meaningful.'"

Art Levinson was CEO of Genentech from 1995 to 2009, a period in which he shaped the modern biotech industry.

Source: https://www.bizjournals.com/sanfrancisco/news/2025/05/15/biotech-50-genentech-art-levinson.html

Women's Health Faces Growing Headwinds, Despite Jump in Venture Investment

Delilah Alvarado, *Biopharma Dive*, May 13, 2025 (excerpt)

The women's health field has a long way to go addressing persistent deficits in research and treatment. Common conditions that affect women like endometriosis and polycystic ovarian syndrome remain misunderstood, while maternal mortality in the U.S. remains higher than in similarly wealthy countries.

Yet there are green shoots. Startups focused on women's health drew a record amount of venture funding in 2024, extending a run of recent momentum. Researchers at Silicon Valley Bank, which tracks startup funding, tabulated in a report last month $2.6 billion in women's health venture investment last year, up from $1.7 billion in 2023. Notably, biopharma-related investments made up 34% of the total sum, indicating rising interest in new treatments over the sector's past focus on "healthtech" solutions.

But the outlook may be shakier in academia, which is so often the source of ideas that later blossom into future drugs. The Biden administration launched the White House Initiative in Women's Health Research at the end of 2023 to help spur investment in the field. But while $113 million was distributed across startups, universities and health institutions, the initiative began at the tail end of Biden's presidency and has an unclear future under President Donald Trump.

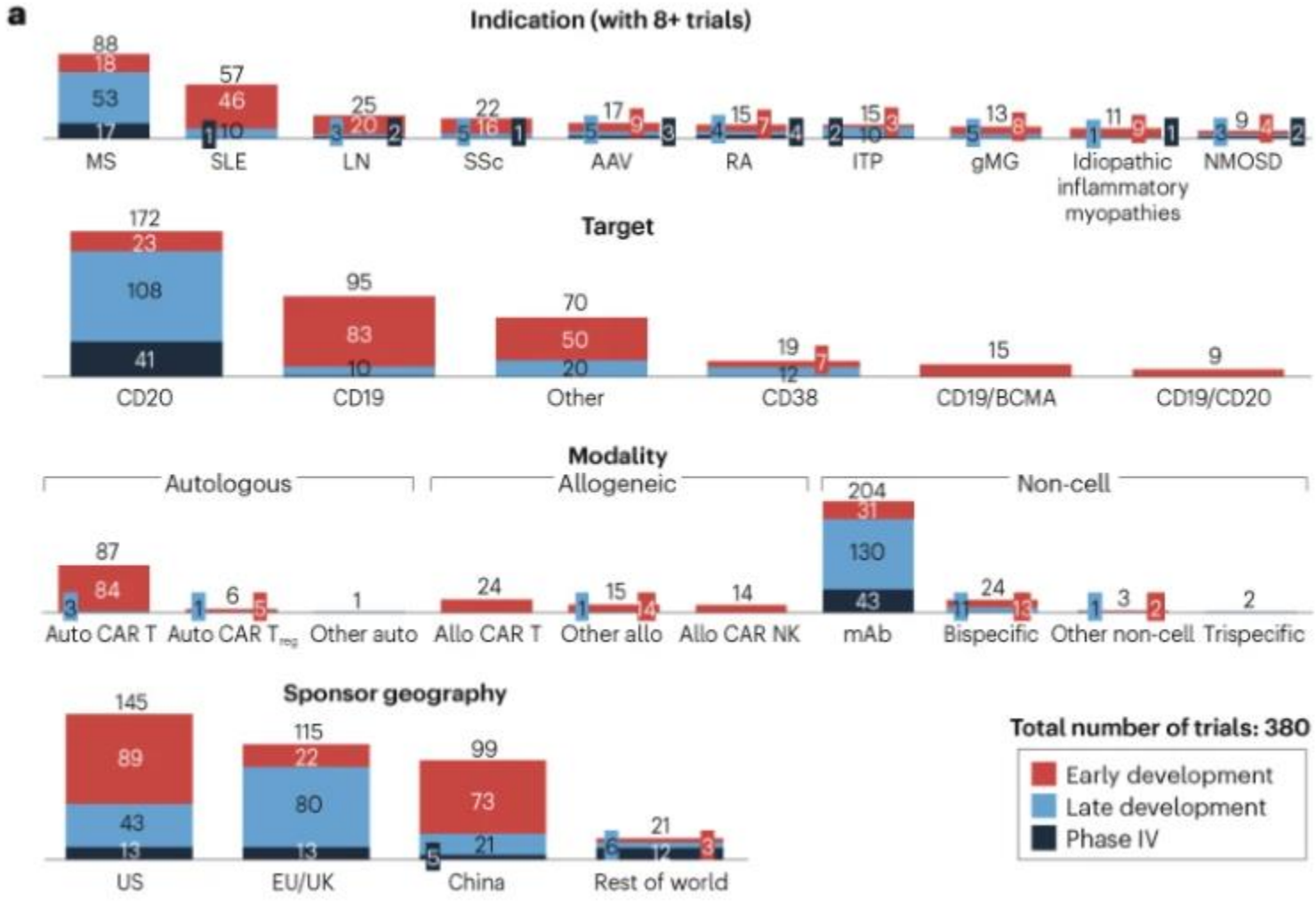
"By the time it got going, they lost the election — and it's over," said Sabra Klein, professor of molecular microbiology and immunology at the Johns Hopkins Bloomberg School of Public Health and co-director of the Johns Hopkins Center for Women's Health, Sex and Gender Research. "A year is not dedicated investment."

The Trump administration has also implemented several actions that could further impede already neglected areas of research or hamper adoption of existing treatments. "The field of women's health is already underserved, so we can't really afford further slowdown," said Sabrina Johnson, CEO of women's health-focused company Daré Biosciences.

Source: https://www.biopharmadive.com/news/womens-health-venture-funding-increase-headwinds-barriers/747969/

Characteristics of Drug Candidates Aiming to Reset Autoimmune Diseases

Bhandari M, Smith JF, Capra E, Yang G. The race to reset autoimmune diseases. Nat Rev Drug Discov. May 12, 2025

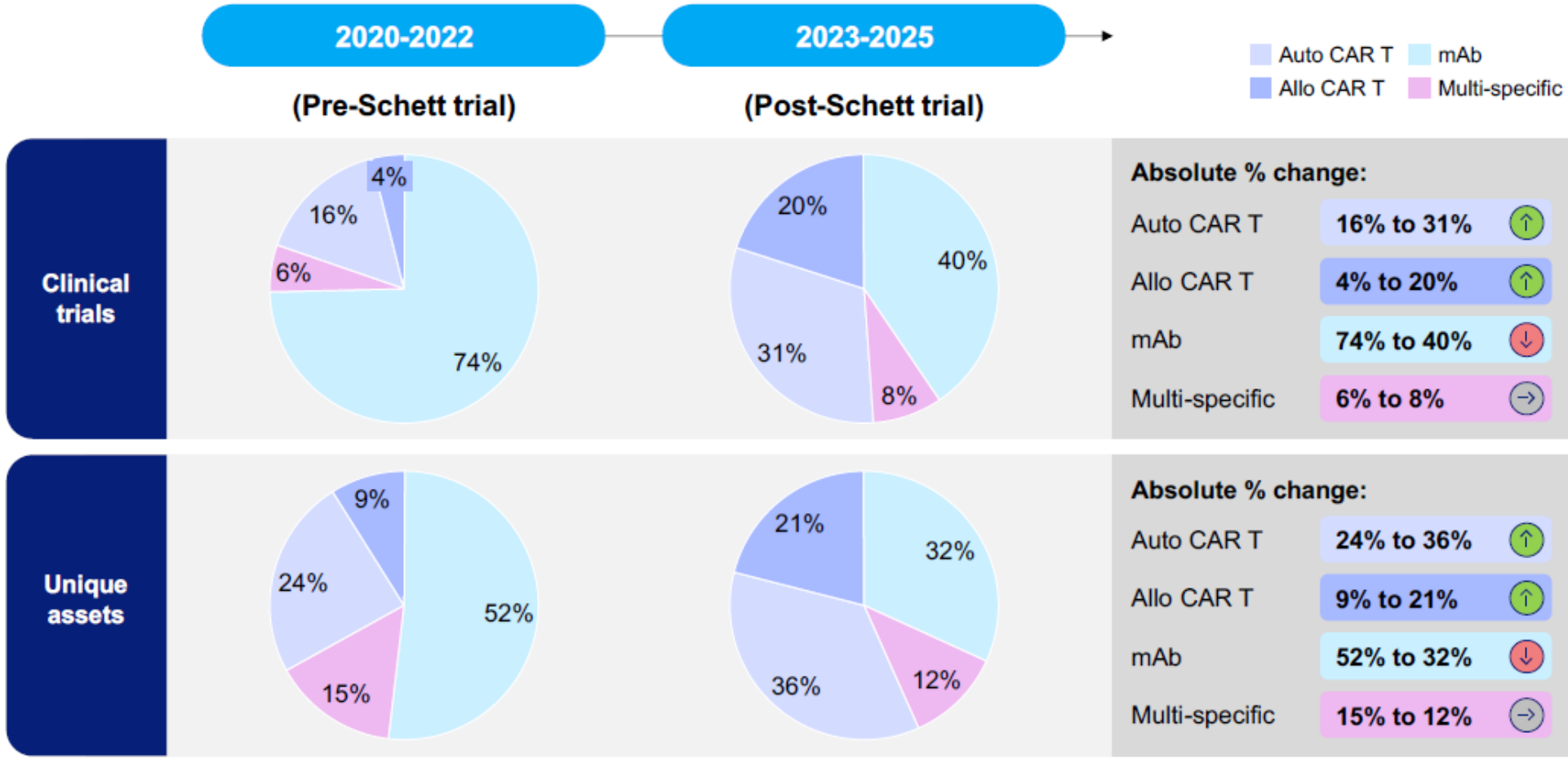


There are a total of 380 interventional-stage trials in this landscape analysis, sourced from ClinicalTrials.gov (see Supplementary Box 1 for details). Monoclonal antibodies (mAbs) are included for comparison, although these do not provide sustained B-cell depletion from a single treatment. 'Other' refers to single/multiple target assets not listed separately in the graph and undisclosed targets. AAV, ANCA-associated vasculitis; gMG, generalized myasthenia gravis; ITP, idiopathic thrombocytopenic purpura; LN, lupus nephritis; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

Source: https://www.nature.com/articles/d41573-025-00085-z

Georg Schett's CAR-T Autoimmunity Studies Triggered Massive Interest in Running Clinical Studies in T-cell Therapies in Autoimmunity

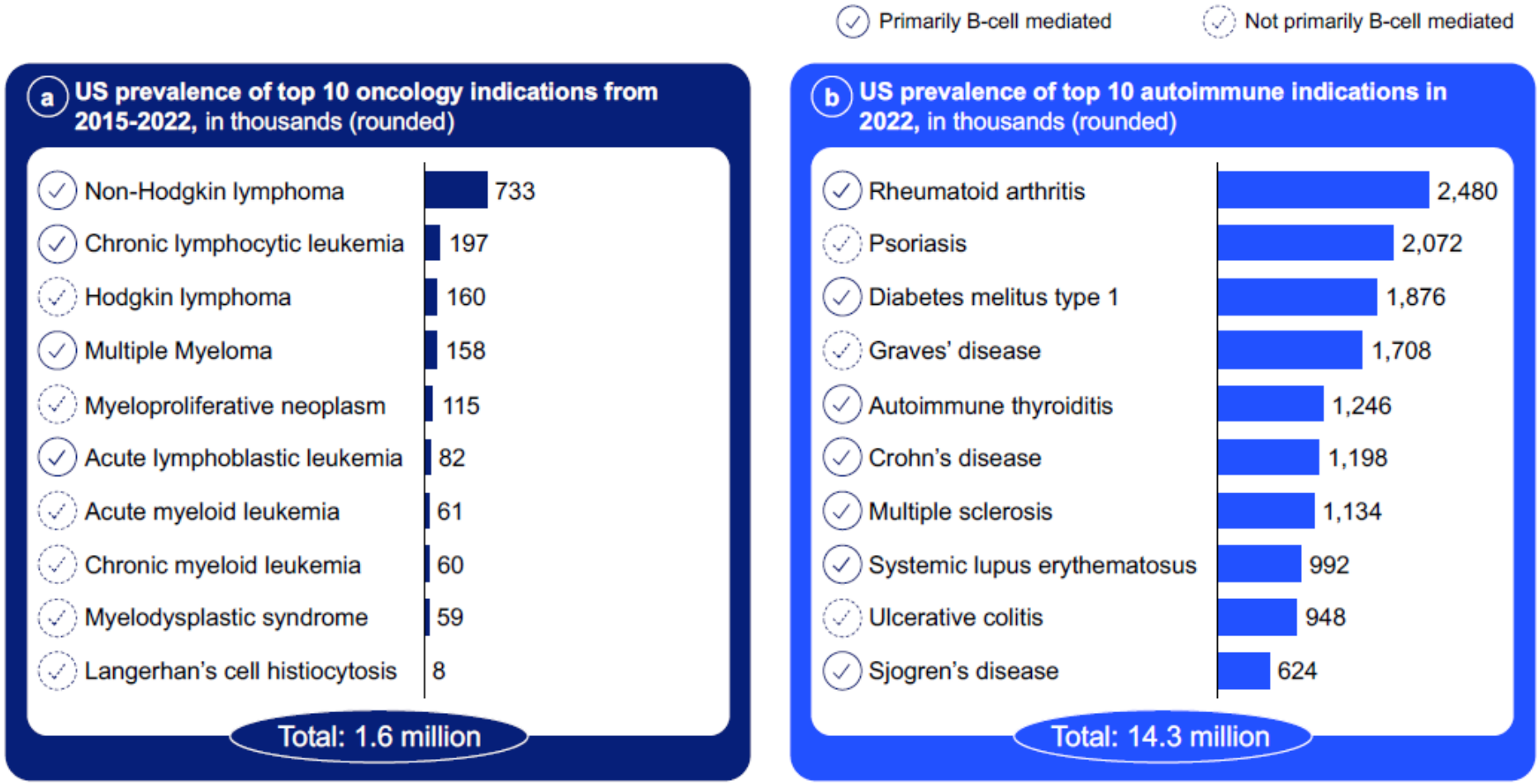
Bhandari M, Smith JF, Capra E, Yang G. The race to reset autoimmune diseases. Nat Rev Drug Discov. May 12, 2025



Source: https://www.nature.com/articles/d41573-025-00085-z

Opportunity for B-Cell mediated Autoimmunity Much Larger than Similar Opportunity in Cancer

Bhandari M, Smith JF, Capra E, Yang G. The race to reset autoimmune diseases. Nat Rev Drug Discov. May 12, 2025



Source: https://www.nature.com/articles/d41573-025-00085-z

In Memoriam: Charlotte Dravet

Written by the International Child Neurology Association: Dr. Charlotte Dravet (July 14, 1936 – May 10, 2025), the esteemed French pediatric psychiatrist and epileptologist, renowned globally for her pioneering contributions to epilepsy research, passed away, leaving behind a profound legacy in the field of child neurology. Her groundbreaking identification and description of Severe Myoclonic Epilepsy of Infancy in 1978, later named Dravet Syndrome, transformed the understanding and management of severe childhood epilepsies.

Charlotte Dravet

Born in 1936, Dravet graduated in medicine from Aix-Marseille University in 1961 and subsequently completed her residency training in Pediatrics in Marseille from 1962 to 1965. She earned her MD with a thesis titled "Encéphalopathie Épileptique de l'Enfant avec Pointe-onde lente diffuse ("petit mal variant")" in 1965 and was certified as a psychiatrist in 1971.

Dravet's meticulous observations led to her initial description of Severe Myoclonic Epilepsy of Infancy (SMEI) in 1978, distinguishing it from Lennox-Gastaut Syndrome. In 1981, together with Michelle Bureau, she described benign myoclonic epilepsy of infancy. **Her work significantly advanced the understanding of genetic epilepsies, notably through the discovery in 2001 that mutations in the SCN1A gene were present in most Dravet Syndrome cases.**

Throughout her career, Dravet actively participated in the delineation of epileptic syndromes and contributed extensively to epilepsy literature, co-authoring influential books and numerous scientific articles. Her major publications include seminal works such as "Severe Myoclonic Epilepsy in Infants and its Related Syndromes" (2000), and "The Core Dravet Syndrome Phenotype" (2011).

After her retirement in 2000, Dravet continued to advocate passionately for children with epilepsy, regularly attending the Childhood Epilepsy Unit at the Policlinico A. Gemelli of the Università Cattolica del Sacro Cuore in Rome, Italy, as an Honorary Consultant. **Dr. Charlotte Dravet's extraordinary contributions to pediatric epilepsy will forever be remembered and honored.**

Source: https://www.icnapedia.org/education/news/11072-charlotte-dravet-july-14-1936-may-10-2025

Impressive Update from Intellia in ATTR Amyloidosis

Intellia Announces Positive Two-Year Follow-Up Data from Ongoing Phase 1 Study of Nexiguran Ziclumeran (nex-z), in Patients with Hereditary Transthyretin (ATTR) Amyloidosis with Polyneuropathy at Peripheral Nerve Society Annual Meeting

CAMBRIDGE, Mass., May 18, 2025 (GLOBE NEWSWIRE) -- Intellia Therapeutics, Inc. (NASDAQ:NTLA), a leading clinical-stage gene editing company focused on revolutionizing medicine with CRISPR-based therapies, today announced positive two-year follow-up data from the ongoing Phase 1 trial of investigational nexiguran ziclumeran (nex-z) for the treatment of hereditary ATTR amyloidosis with polyneuropathy (ATTRv-PN). Results were shared in an oral presentation on Sunday, May 18 at the 2025 Peripheral Nerve Society (PNS) Annual Meeting in Edinburgh, United Kingdom. The Phase 3 MAGNITUDE-2 trial design of nex-z in ATTRv-PN was also exhibited in a poster presentation.

"We are pleased to share new findings at PNS, which continue to support our growing body of evidence that a single dose of nex-z leads to deep, durable and consistent reductions in serum TTRs, with evidence of disease stability or clinically meaningful improvements in neuropathic impairment measures through two years," said Intellia President and Chief Executive Officer John Leonard, M.D. "These data are also the first to show improvement in patients who had previously progressed on patisiran, further validating the hypothesis that increasingly deep reductions in TTR levels may lead to improved outcomes in ATTR amyloidosis."

Clinical and Biomarker Measures	Change from Baseline at Month 12	Change from Baseline at Month 24
Part 1: Dose-escalation portion N=15*		
NIS, mean (SD)	-2.0 (5.3)	-4.5 (7.4)
Part 2: Dose expansion portion N=21*		
NIS, mean (SD)	-2.1 (10.2)	-5.2 (10.7)
mNIS+7, mean (SD) (overall)	-0.6 (11.1)	-8.5 (9.6)
mNIS+7, mean (SD) (patients previously on patisiran) †	-6.3 (11.6)	-6.5 (9.8)
Full cohort N=36‡		
Norfolk QoL-DN, mean (SD)**	-3.5 (21.0)	-8.5 (19.3)
NfL (% change from baseline)***	-8.6 (41.7)	N/A
mBMI, mean (SD)**	13.4 (93.2)	39.0 (87.1)

* Data cutoff April 11, 2025; ** Data cutoff August 21, 2024; *** Data cutoff April 12, 2024; † N=6; ‡ 24-month data in 19 patients; N/A: Data not available at Month 24

Source: https://www.globenewswire.com/news-release/2025/05/18/3083534/0/en/Intellia-Announces-Positive-Two-Year-Follow-Up-Data-from-Ongoing-Phase-1-Study-of-Nexiguran-Ziclumeran-nex-z-in-Patients-with-Hereditary-Transthyretin-ATTR-Amyloidosis-with-Polyneu.html

Intellia's Nex-Z Compares Favorably to Other Agents in ATTR Polyneuropathy

Therapy	Company	Mechanism	Dosing	Clinical Stage	Key Efficacy Highlights	Data in ATTR Polyneuropathy?	Notable Features
Nexiguran Ziclumeran (Nex-Z)	Intellia Therapeutics	In vivo CRISPR-Cas9 gene editing	Single IV dose	Phase 1 (ATTRv-PN)	90% mean serum TTR reduction sustained at 24 months; 14 of 18 patients showed ≥4-point improvement in mNIS+7; benefits observed even in patients previously treated with patisiran	Phase 1 trial in ATTRv-PN showed 90% mean TTR reduction sustained over 24 months, and improvement in mNIS+7 scores (≥4 points in 14 of 18 patients).	Potential for one-time treatment; durable TTR suppression; favorable safety profile with mild/moderate reactions
Patisiran (Onpattro)	Alnylam	RNA interference (RNAi)	IV infusion every 3 weeks	Phase 3 (APOLLO-B)	Statistically significant improvement in 6-minute walk test and quality of life at 12 months; sustained benefits observed in open-label extension	Approved for hATTR-PN. The Phase 3 APOLLO trial showed significant improvement in neuropathy symptoms, quality of life, and walking ability.	First FDA-approved RNAi therapeutic for hATTR-PN; well-established safety profile
Eplontersen (Wainua)	IONIS AstraZeneca	Antisense oligonucleotide	Monthly SC injection	Phase 3 (NEURO-TTRansform)	Sustained TTR reduction and improvements in neuropathy and quality of life through 66 weeks	The NEURO-TTRansform trial in hATTR-PN showed sustained TTR knockdown, improvement in mNIS+7, and better quality of life. FDA-approved for hATTR-PN.	Ligand-conjugated design for enhanced delivery; favorable safety and tolerability
Acoramidis (Attruby)	bridgebio	TTR stabilizer	Oral, twice daily	Phase 3 (ATTRibute-CM)	Significant improvement in composite endpoint (all-cause mortality, cardiovascular hospitalization, NT-proBNP, 6-minute walk distance); 15.2% absolute risk reduction in composite outcome at 30 months	Primarily studied in ATTR cardiomyopathy (ATTR-CM). No reported data in polyneuropathy.	Oral administration; FDA-approved for ATTR-CM; potential alternative to existing stabilizers
Tafamidis (Vyndaqel)	Pfizer	TTR stabilizer	Oral, once daily	FDA Approved (ATTR-CM)	30% reduction in all-cause mortality and 32% reduction in cardiovascular-related hospitalizations over 30 months in ATTR-ACT trial	Tafamidis was studied for hATTR-PN in Europe (approved under the name Vyndaqel for PN), but not approved for PN in the U.S. Focus is now on ATTR-CM.	First FDA-approved treatment for ATTR-CM; established safety and efficacy profile; once-daily dosing

Source: Company Press Releases

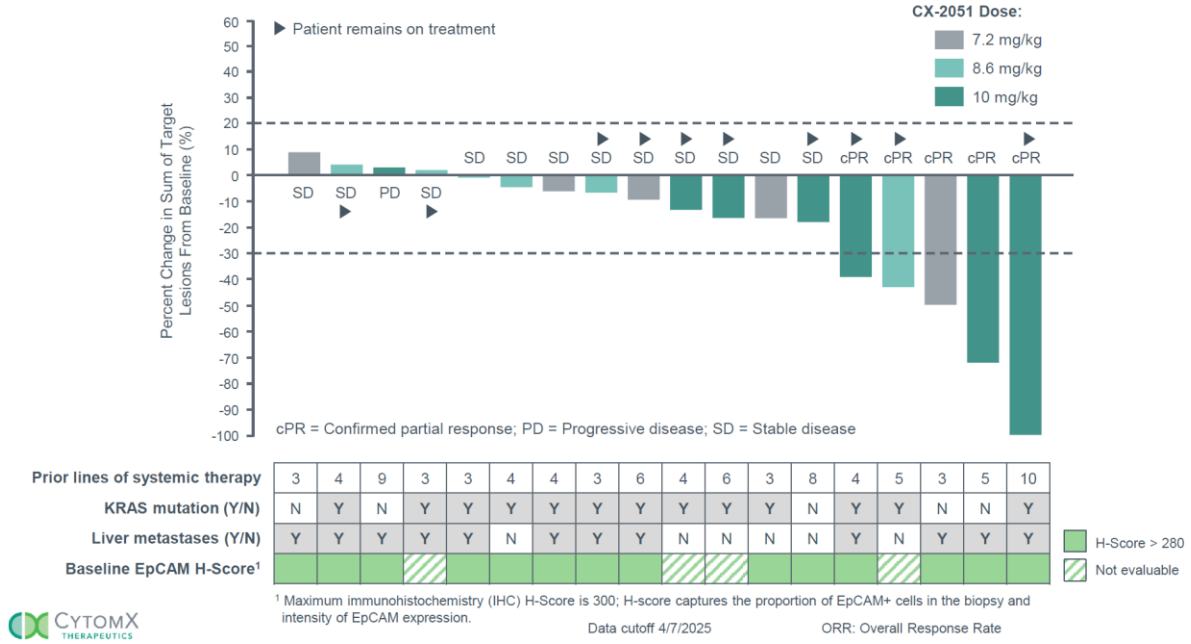
Impressive Update from CytomX in CRC

A 28% ORR rate is highly impressive in fifth line CRC. EpCAM has long been a pan-cancer target of interest and CytomX may have cracked the code on how to drug it with its CX-2051 candidate. This drug has a masking domain which is designed to reduce EpCAM binding in normal tissues. Cytomx shares rose 183% last week on the news.

SOUTH SAN FRANCISCO, Calif., May 12, 2025 (GLOBE NEWSWIRE) -- CytomX Therapeutics, Inc. (Nasdaq: CTMX), a leader in the field of masked, conditionally activated biologics, today announced positive interim Phase 1 data for its EpCAM PROBODY® ADC candidate, CX-2051, in advanced, late-line CRC. The data are as of an April 7th 2025 data cutoff from the ongoing CTMX-2051-101 Phase 1 study.

"EpCAM is a high potential and broadly expressed cancer target that has been challenging to drug historically due to expression on normal tissues. We believe we have broken important new ground with our data announced today, which show potential for markedly improved outcomes for CRC patients," said Sean McCarthy, D. Phil, chief executive officer and chairman of CytomX. "CX-2051 is showing impressive, durable anti-tumor activity in late line metastatic CRC, an area of high unmet need and a very difficult tumor to treat. Furthermore, CX-2051 has been generally well tolerated, highlighting the power of CytomX PROBODY® masking technology."

Dr. McCarthy added, "Importantly, we believe these results validate EpCAM as an oncology target and unlock a broad development opportunity for CX-2051 in CRC and potentially many other cancer types where EpCAM is expressed. We are excited to rapidly advance CX-2051 for the benefit of CRC patients and to explore the full potential of this novel ADC."

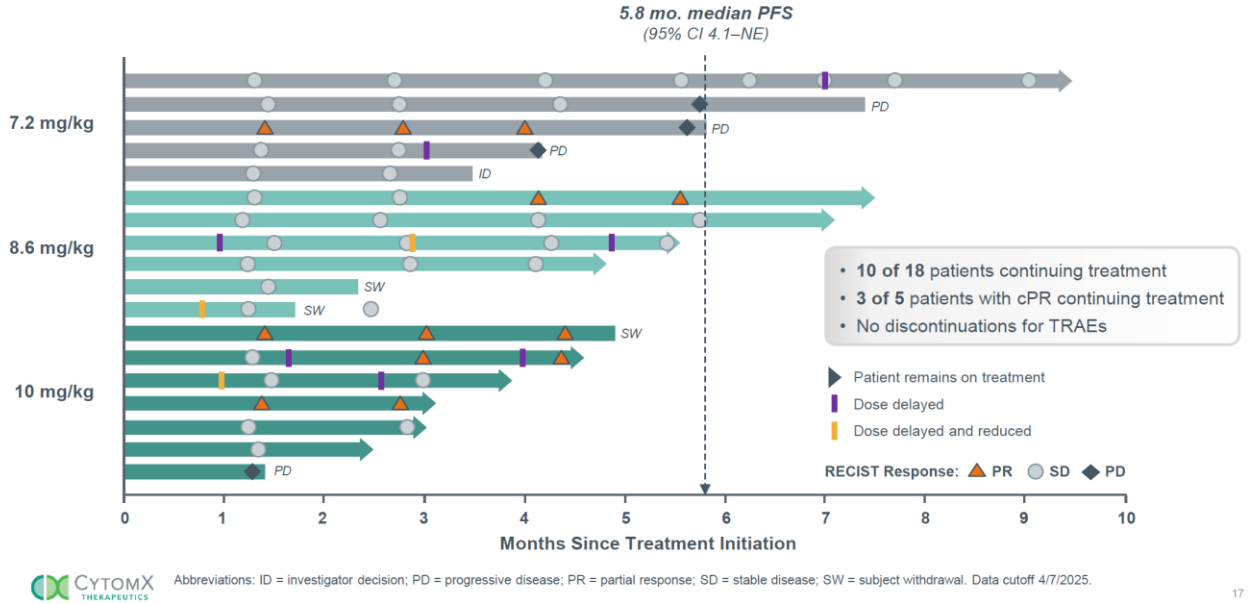


Source: https://ir.cytomx.com/news-releases/news-release-details/cytomx-announces-positive-interim-data-phase-1-dose-escalation

Encouraging Durability / Comparison to SOC for CX-2051

Emerging Durability Results with CX-2051

Preliminary median progression free survival 5.8 months



CytomX Therapeutics

Abbreviations: ID = investigator decision; PD = progressive disease; PR = partial response; SD = stable disease; SW = subject withdrawal. Data cutoff 4/7/2025.

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3L+ CRC Landscape

Treatment	ORR (%)	DCR (%)	Median PFS (months)	Median OS (months)
CX-2051 (7.2–10 mg/kg)	**28%**	**94%**	**5.8** [1]	**N/A**
Fruquintinib	2%	56%	3.7	7.4
Regorafenib	1%	41%	2.0	6.4
Trifluridine/tipiracil	2%	44%	2.0	7.1
Trifluridine/tipiracil + *Bevacizumab*	6%	77%	5.6	10.8

[1] Preliminary PFS as of 4/7/2025 data cutoff.

Abbreviations: DCR = disease control rate; ORR = overall response rate; OS = overall survival; PFS = progression free survival.

Sources: Lonsurf® (trifluridine and tipiracil) Fruzaqla® (fruquintinib), Stivarga® (regorafenib) package inserts; Dasari et al. 2023; Grothey et al. 2013; Prager et al. 2023.

Source: https://ir.cytomx.com/events-and-presentations

First Ever Bespoke CRISPR Therapy Shown Last Week

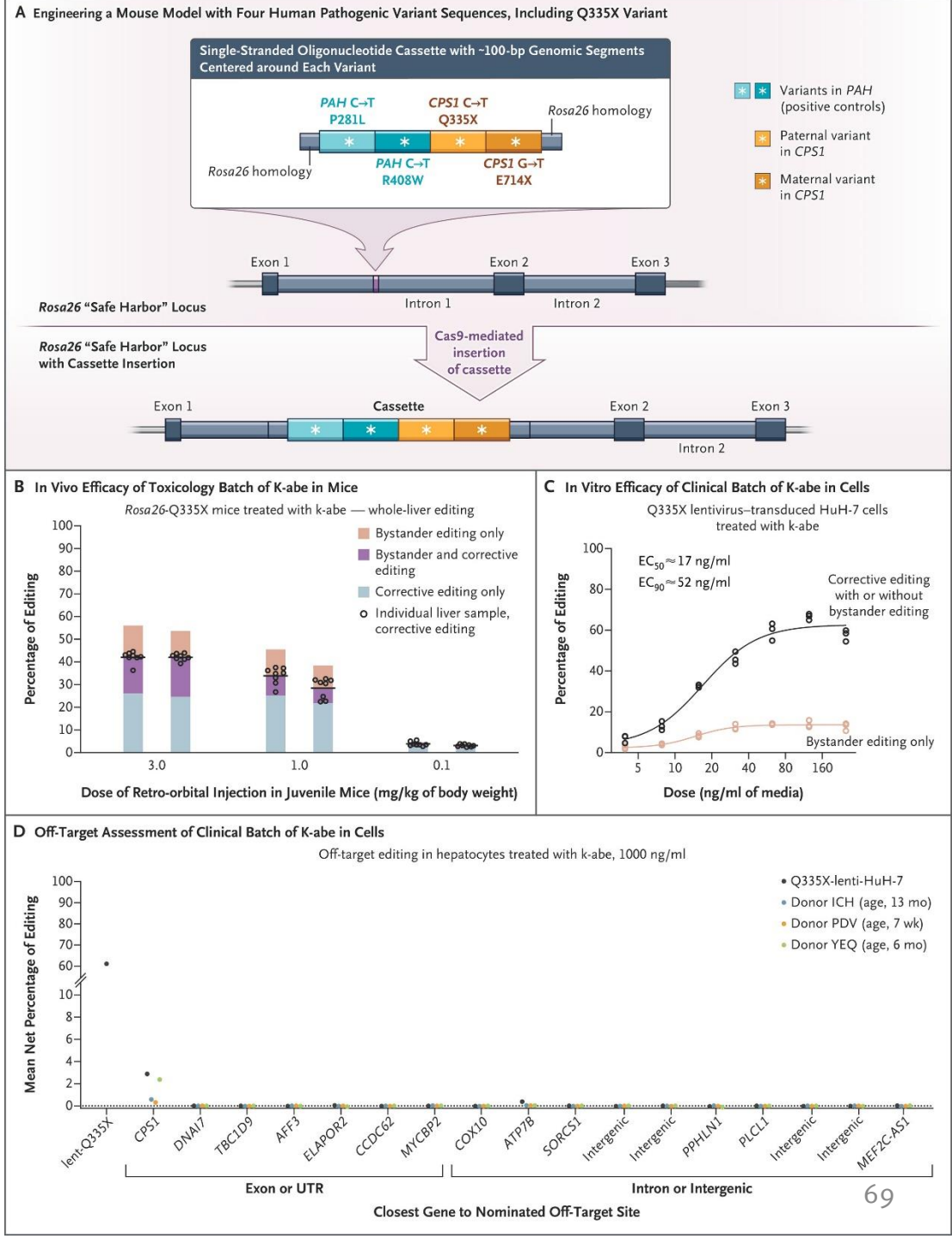
Musunuru K et.al., "Patient-Specific In Vivo Gene Editing to Treat a Rare Genetic Disease," *N Engl J Med*. May 15, 2025

Base editors can correct disease-causing genetic variants. After a neonate had received a diagnosis of severe carbamoyl-phosphate synthetase 1 deficiency, a disease with an estimated 50% mortality in early infancy, we immediately began to develop a customized lipid nanoparticle–delivered base-editing therapy. After regulatory approval had been obtained for the therapy, the patient received two infusions at approximately 7 and 8 months of age. In the 7 weeks after the initial infusion, the patient was able to receive an increased amount of dietary protein and a reduced dose of a nitrogen-scavenger medication to half the starting dose, without unacceptable adverse events and despite viral illnesses. No serious adverse events occurred. Longer follow-up is warranted to assess safety and efficacy.

We developed a workflow for the rapid development of customized, corrective gene-editing therapies for patients with ultrarare or unique "N-of-1" variants. More specifically, we developed a base-editing therapy, delivered in vivo to hepatocytes through lipid nanoparticles, for a single patient who at birth received a diagnosis of neonatal-onset carbamoyl-phosphate synthetase 1 (CPS1) deficiency, an ultrarare inborn error of metabolism affecting the urea cycle. CPS1 deficiency affects 1 in 1,300,000 persons and has an estimated mortality of 50% in early infancy.

In this study, we describe a personalized base-editing therapy wholly developed in the 6-month span after a patient's birth. The patient was able to receive an increased amount of dietary protein and a reduced dose (to half the starting dose) of a nitrogen-scavenger medication, despite the "stress tests" presented by consecutive viral infections. The short follow-up is a limitation of this study; longer follow-up is needed to assess the safety and efficacy of k-abe, as well as the patient's neurologic health.

Source: https://www.nejm.org/doi/full/10.1056/NEJMoa2504747



Programmable Gene Insertion in Human Cells with a Laboratory-Evolved CRISPR-Associated Transposase

Witte et.al. *Science*. May 15, 2025;388(6748):eadt5199.

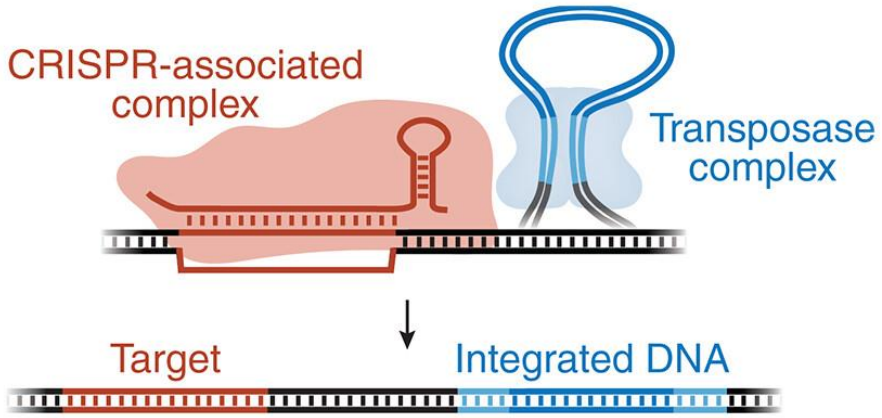
The efficient insertion of gene-sized DNA sequences at user-specified genomic sites is a long-standing goal in genome editing. Although current editing methods can correct most disease-causing mutations, the genetic diversity underlying many disorders will require the design and regulatory approval of many mutation-specific strategies—substantially limiting the number of patients who can benefit from therapeutic genome editing. Programmed genomic integration of a healthy gene copy could offer a mutation-agnostic treatment for loss-of-function genetic diseases. Additionally, targeted gene integration enables other applications, including cancer immunotherapies, transgenic cell and animal models for basic research, and metabolic engineering.

CRISPR-associated transposases (CASTs) are naturally occurring bacterial systems that exploit nuclease-deficient CRISPR machinery to integrate DNA at genomic locations specified by guide RNAs. CASTs offer many attractive qualities as a genome editing tool, including facile programmability, compatibility with multi-kilobase-scale DNA cargo, and avoidance of genomic double-strand DNA breaks. Despite this promise, wild-type CASTs reported to date support minimal integration in human cells (often ≤0.1% of treated cells). We reasoned that this low efficiency may stem from naturally evolved, suboptimal transposition catalysis that mitigates mobilization-induced fitness cost to the host. To enable efficient CAST integration in human cells, we developed a phage-assisted continuous evolution (PACE) system that rapidly evolves CAST variants capable of fast targeted transposition and applied CAST-PACE to a prototypical Type I-F CAST system from Pseudoalteromonas.

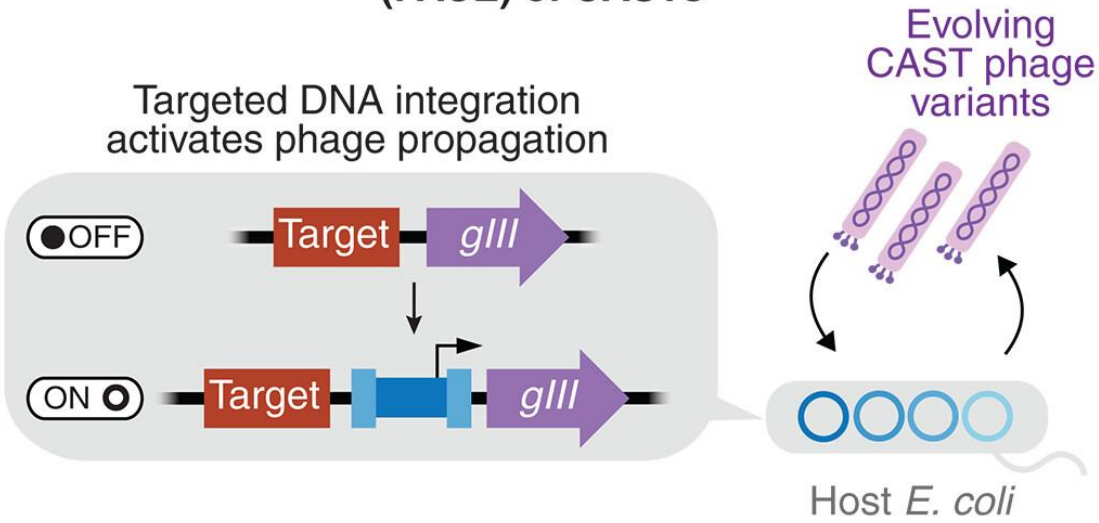
We linked on-target DNA integration in Escherichia coli to the propagation of continuously mutating phage genomes encoding evolving CAST components. After hundreds of generations of continuous selection, replication, and mutation in which the resulting phage survived an overall 10322-fold dilution, we generated an evolved variant of the CAST transposase protein TnsB that mediated ›200-fold improved integration activity in human cells. The evolved TnsB contains 10 activity-enhancing mutations located throughout the protein, which likely modulate several distinct interactions with other CAST components. Notably, the evolved TnsB mediated efficient integration activity in human cells without requiring codelivery of the bacterial CAST accessory protein, ClpX, which is cytotoxic. We combined this evolved TnsB with other PACE-evolved and rationally engineered CAST components to yield evoCAST, a system optimized for human-cell integration activity. EvoCAST achieved 10 to 30% integration efficiencies across 14 genomic targets in human cells, representing a 420-fold average improvement over wild-type CAST. EvoCAST supported large DNA cargoes ›10 kb and mediated the integration of several therapeutic payloads at disease-relevant genomic sites, including safe harbor loci, sites for cancer immunotherapy engineering, and genes implicated in loss-of-function genetic diseases. EvoCAST also performed targeted integration in multiple human cell types, including primary human fibroblasts, and exhibited high product purity, with no detected insertions and deletions (indels), predominantly unidirectional cargo insertion, single–base pair precision of integration, and low levels of off-target integration.

Source: https://www.science.org/doi/10.1126/science.adt5199

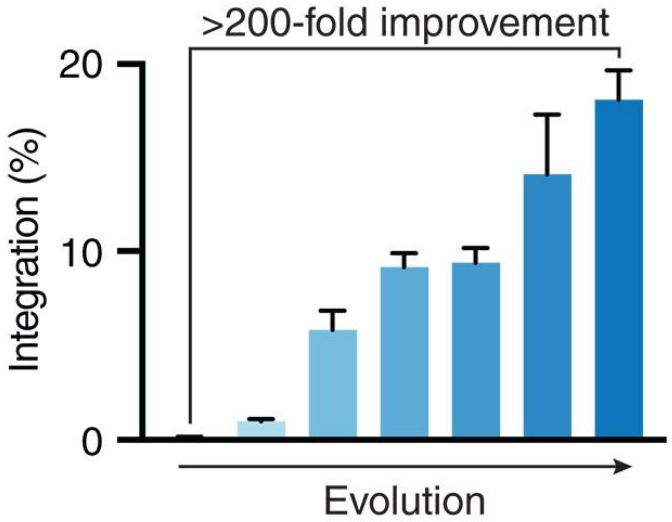
DNA integration by CRISPR-associated transposases (CASTs)



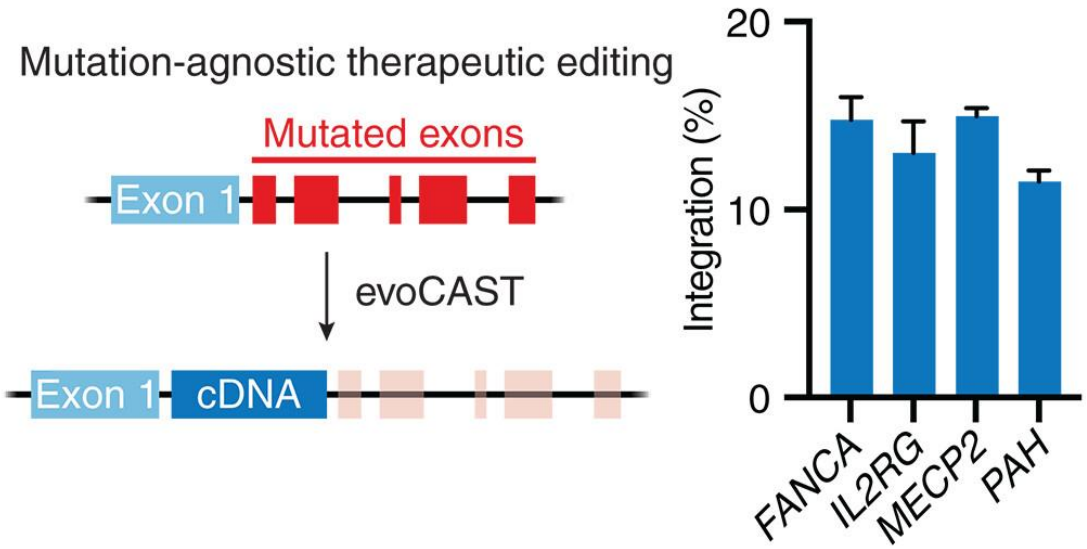
Phage-assisted continuous evolution (PACE) of CASTs



Evolved CAST variants in human cells



Applications of evoCAST



Source: https://www.science.org/doi/10.1126/science.adt5199

Promising Data ANGPTL4 Antibody from Marea Therapeutics

Cummings et.al., "Safety and efficacy of a novel ANGPTL4 inhibitory antibody for lipid lowering: results from phase 1 and phase 1b/2a clinical studies, *Lancet*, May 15, 2025

Genetic studies have established angiopoietin-related protein 4 (ANGPTL4) as a key regulator of triglyceride metabolism and a promising target to reduce atherosclerotic cardiovascular disease (ASCVD) risk beyond traditional risk factors.

We found no evidence of clinical adversity in human germline ANGPTL4 loss-of-function, adding to preclinical support for initiating human studies. Between Nov 20, 2017, and Sept 10, 2019, in the first-in-human, randomised, placebo-controlled, single-ascending-dose phase 1 study, part 1A enrolled 32 healthy participants: six each received 15 mg, 50 mg, 150 mg, or 450 mg of MAR001, and eight received placebo. Part 1B enrolled 12 participants: nine received 450 mg of MAR001 and three received placebo. Part 1C enrolled 12 participants: eight received 450 mg of MAR001 and four received placebo. Between Nov 24, 2013, and July 1, 2024, in the multidose phase 1b/2a randomised, double-blind, placebo-controlled study, 55 participants were randomly assigned to receive subcutaneous injections of placebo (19 participants) or MAR001 at doses of 150 mg (ten participants), 300 mg (nine participants), or 450 mg (17 participants), followed by a 12-week safety follow-up period. MAR001 was safe and generally well tolerated, and we observed no treatment-related systemic inflammatory biomarker elevations or changes in mesenteric lymph node size or inflammation assessed by MRI. MAR001 (450 mg) yielded placebo-adjusted week 12 mean reductions in triglycerides of 52·7% (90% CI −77·0 to −28·3) and in remnant cholesterol of 52·5% (−76·1 to −28·9).

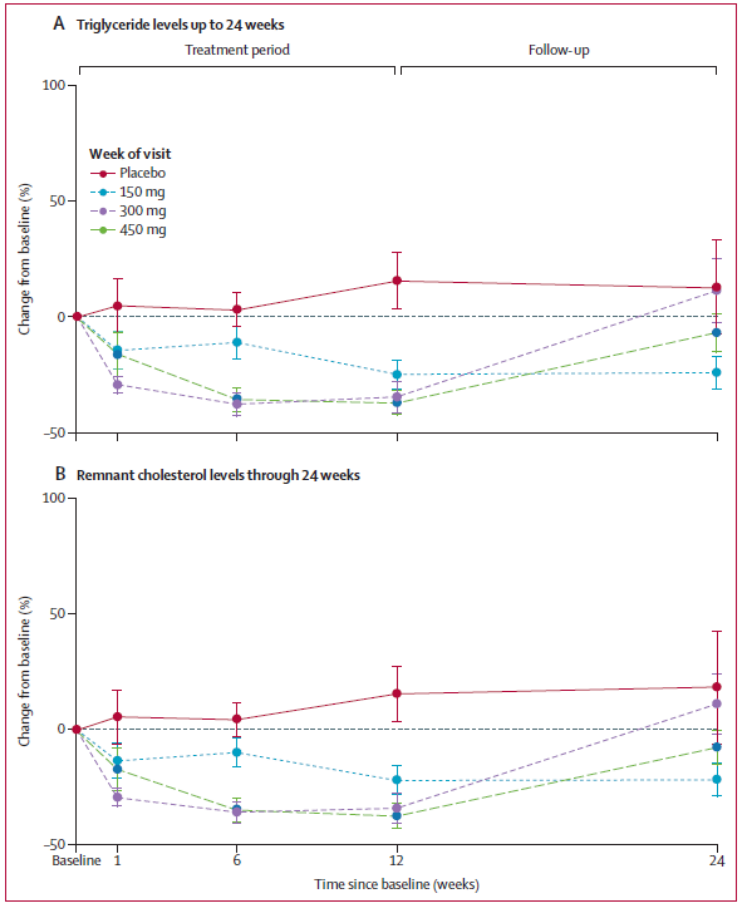


Figure 2: **Effect of MAR001 on triglyceride and remnant cholesterol levels up to 24 weeks in the multidose clinical study**
Error bars indicate SE of the mean.

Source: https://www.sciencedirect.com/science/article/abs/pii/S0140673625008256

STAT5 and STAT3 Balance Shapes Dendritic Cell Function and Tumour Immunity

Zhou, J., Tison, K., Zhou, H. et al., *Nature*, May 14, 2025.

Immune checkpoint blockade (ICB) has transformed cancer therapy. The efficacy of immunotherapy depends on dendritic cell-mediated tumour antigen presentation, T cell priming and activation. However, the relationship between the key transcription factors in dendritic cells and ICB efficacy remains unknown. Here we found that ICB reprograms the interplay between the STAT3 and STAT5 transcriptional pathways in dendritic cells, thereby activating T cell immunity and enabling ICB efficacy. Mechanistically, STAT3 restrained the JAK2 and STAT5 transcriptional pathway, determining the fate of dendritic cell function. As STAT3 is often activated in the tumour microenvironment5, we developed two distinct PROTAC (proteolysis-targeting chimera) degraders of STAT3, SD-36 and SD-2301. STAT3 degraders effectively degraded STAT3 in dendritic cells and reprogrammed the dendritic cell–transcriptional network towards immunogenicity. Furthermore, STAT3 degrader monotherapy was efficacious in treatment of advanced tumours and ICB-resistant tumours without toxicity in mice. Thus, the crosstalk between STAT3 and STAT5 transcriptional pathways determines the dendritic cell phenotype in the tumour microenvironment and STAT3 degraders hold promise for cancer immunotherapy.

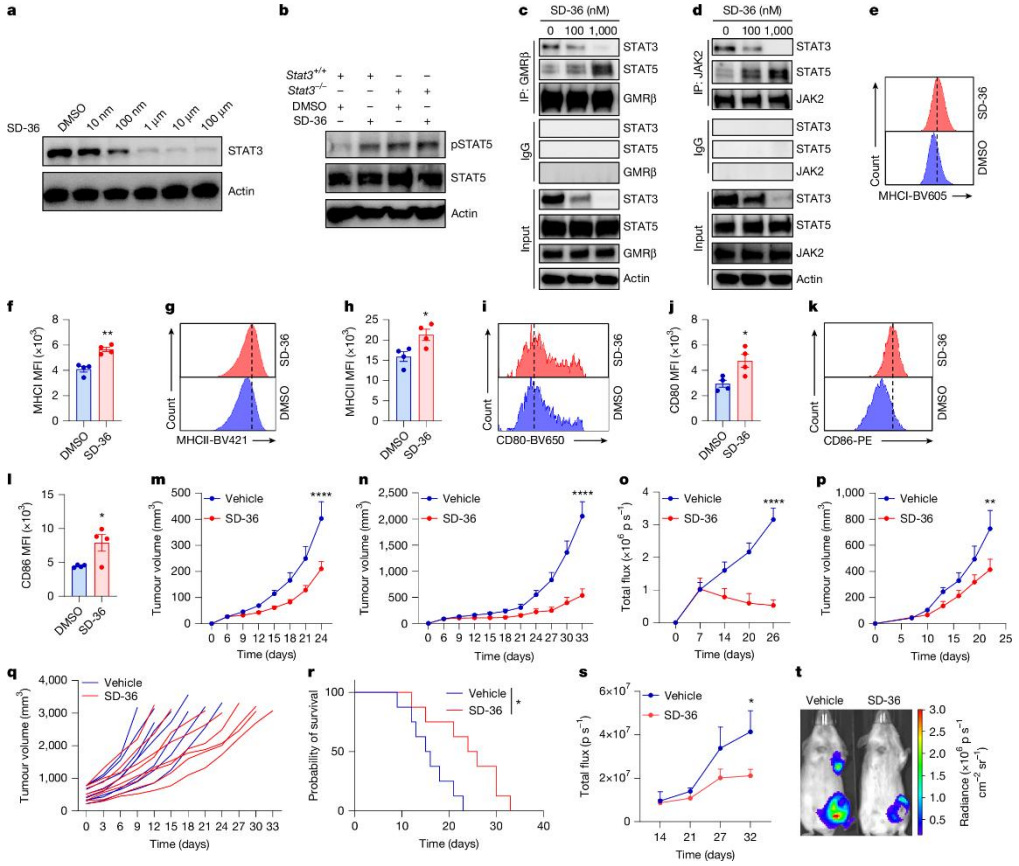
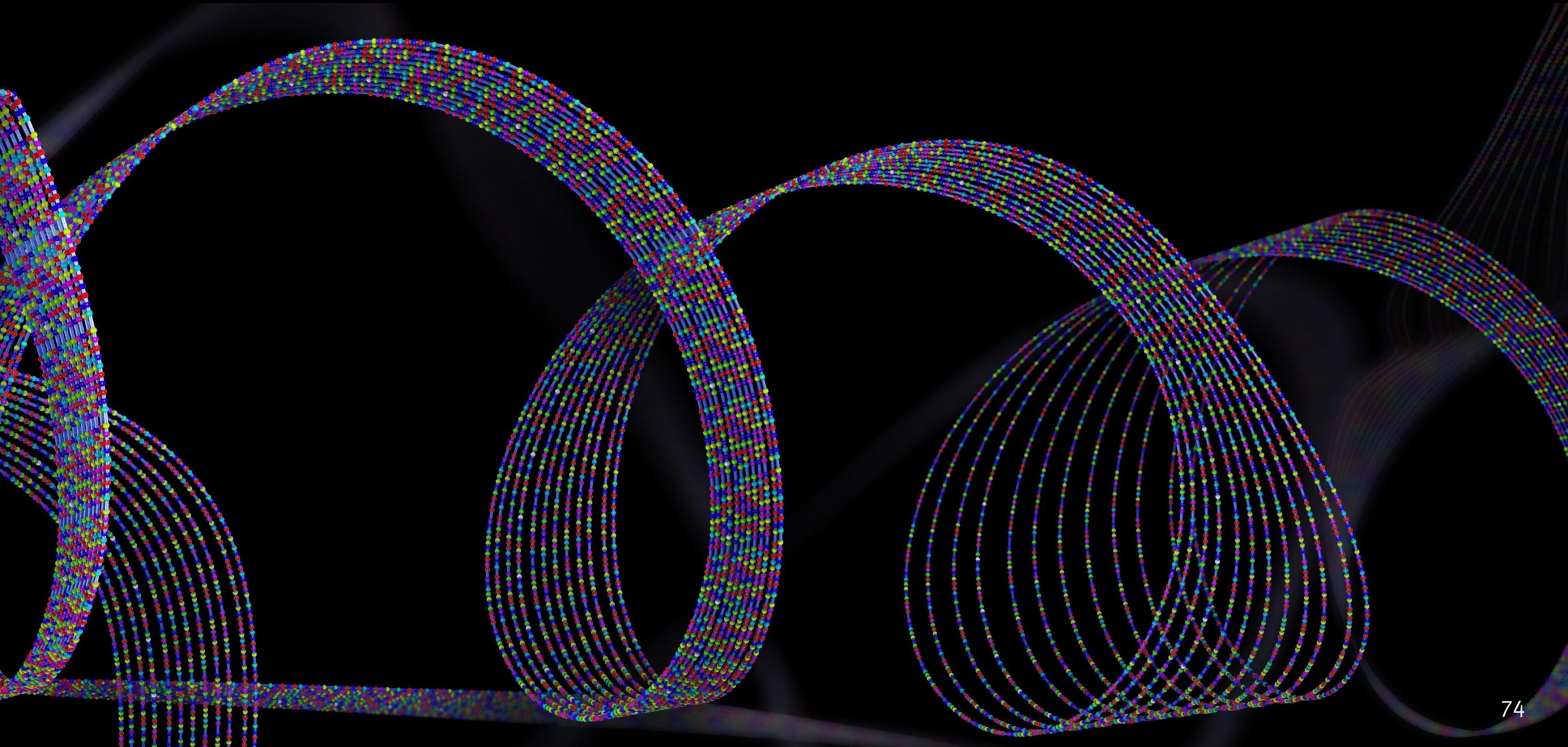


Fig. 4: STAT3 degraders for treatment of advanced tumours.

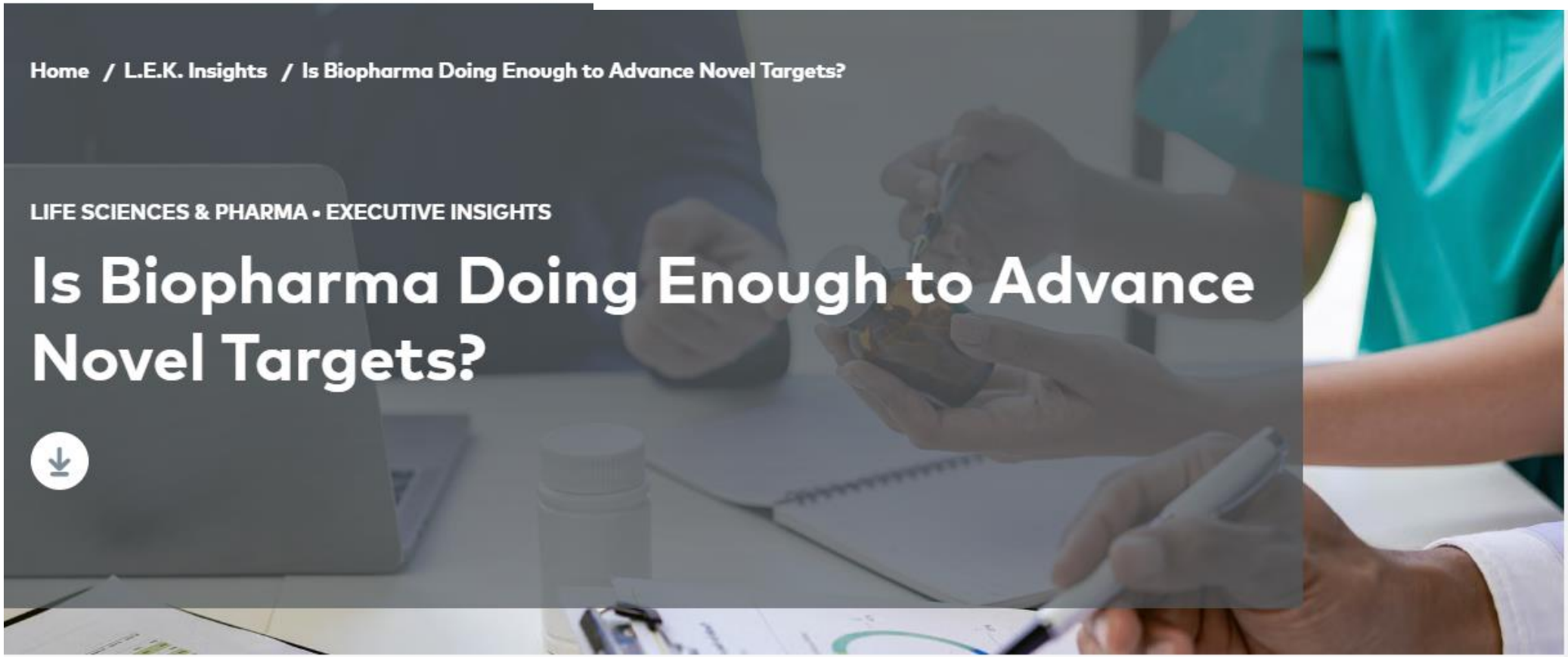
a, Immunoblot showing STAT3 expression in mouse cDC1s treated with different concentrations of SD-36 in vitro. **b**, Immunoblot showing expression of pSTAT5 and STAT5 in cDC1s from *Stat3*$^{+/+}$ and *Stat3*$^{-/-}$ mice treated with SD-36 (200 nM) for 48 h and LPS (20 ng ml^{-1}) for 1 h. In **a**,**b**, one of three experiments is shown. **c**,**d**, cDC1s were treated with different doses of SD-36 for 24 h and were immunoprecipitated (IP) with anti-GMRβ (**c**) or anti-JAK2 (**d**). The immunoprecipitation shows the interaction between GMRβ, JAK2, STAT3 and STAT5 in cDC1s. One of two experiments with repeats is shown. **e**–**l**, FACS analysis of MHCI (**e**,**f**), MHCII (**g**,**h**), CD80 (**i**,**j**) and CD86 (**k**,**l**) on cDC1s treated with SD-36 (**e**–**h**) and SD-36 plus LPS (**i**–**l**). Representative histograms are shown. Data are mean ± s.e.m., $n = 4$; $^{*}P = 0.0241$ (**h**), $^{*}P = 0.023$ (**j**), $^{*}P = 0.0329$ (**l**) and $^{**}P = 0.0015$ (**f**), unpaired two-tailed *t*-test. **m**–**p**, Mice were inoculated with 4T1 (**m**), MC38 (**n**), ID8 (**o**) or LLC (**p**) cells and were treated with SD-36 (20 mg kg^{-1}) every 3 days, and tumour volumes were monitored. Data are mean ± s.e.m.; $n = 6$ (**m**,**p**) and $n = 5$ (**n**,**o**); $^{**}P = 0.0021$ (**p**) and $^{****}P < 0.0001$ (**m**–**o**), two-way ANOVA. **q**–**r**. Mice bearing CT26 tumours (500 mm³ per tumour) were treated with SD-36 or vehicle and tumour volumes.

Source: https://www.nature.com/articles/s41586-025-09000-3

LEK Study of Biological Targets and Pharma R&D



LEK™



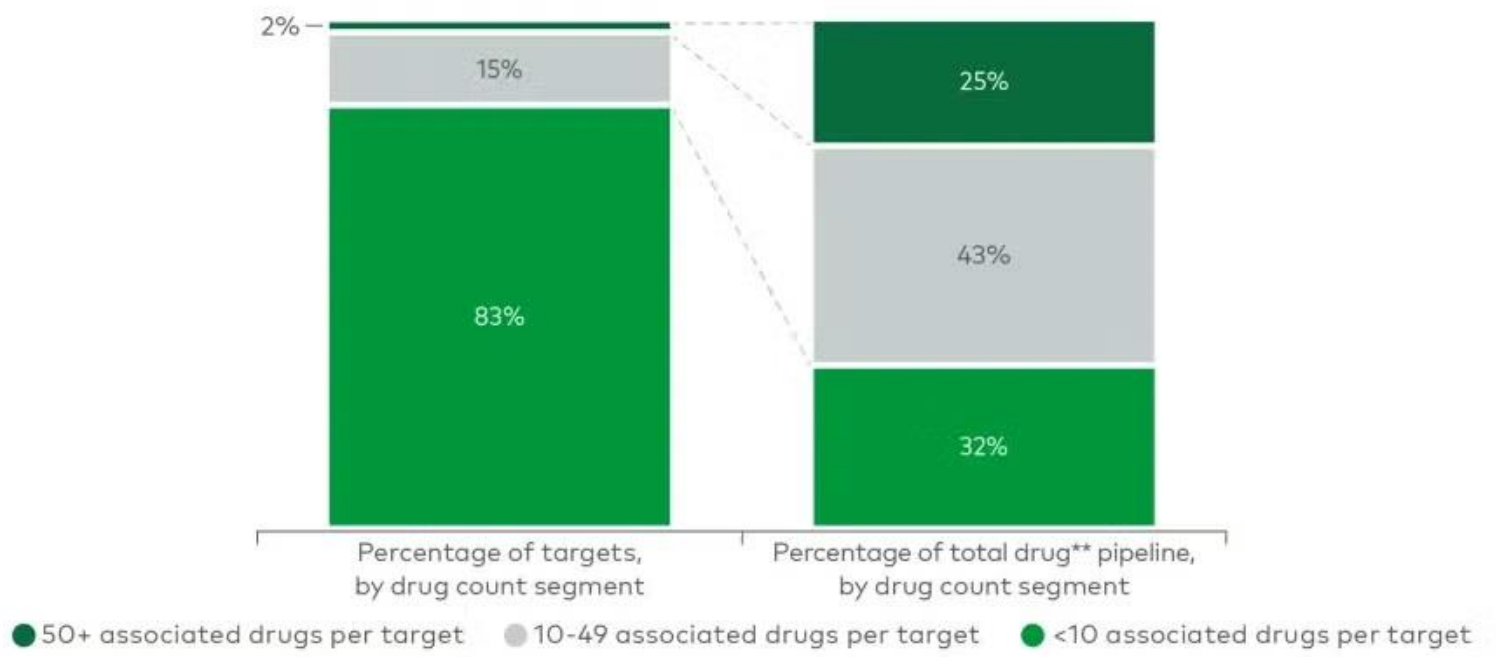
Volume XXVII, Issue 33 | May 15, 2025

Matt Mancuso
Pierre Jacquet, M.D., Ph.D.
Ricardo Brau
Anne Dhulesia
Ananth Srinivasan

Source: https://www.lek.com/insights/hea/us/ei/biopharma-doing-enough-advance-novel-targets

LEK Study: High Target Crowding in Pharma R&D

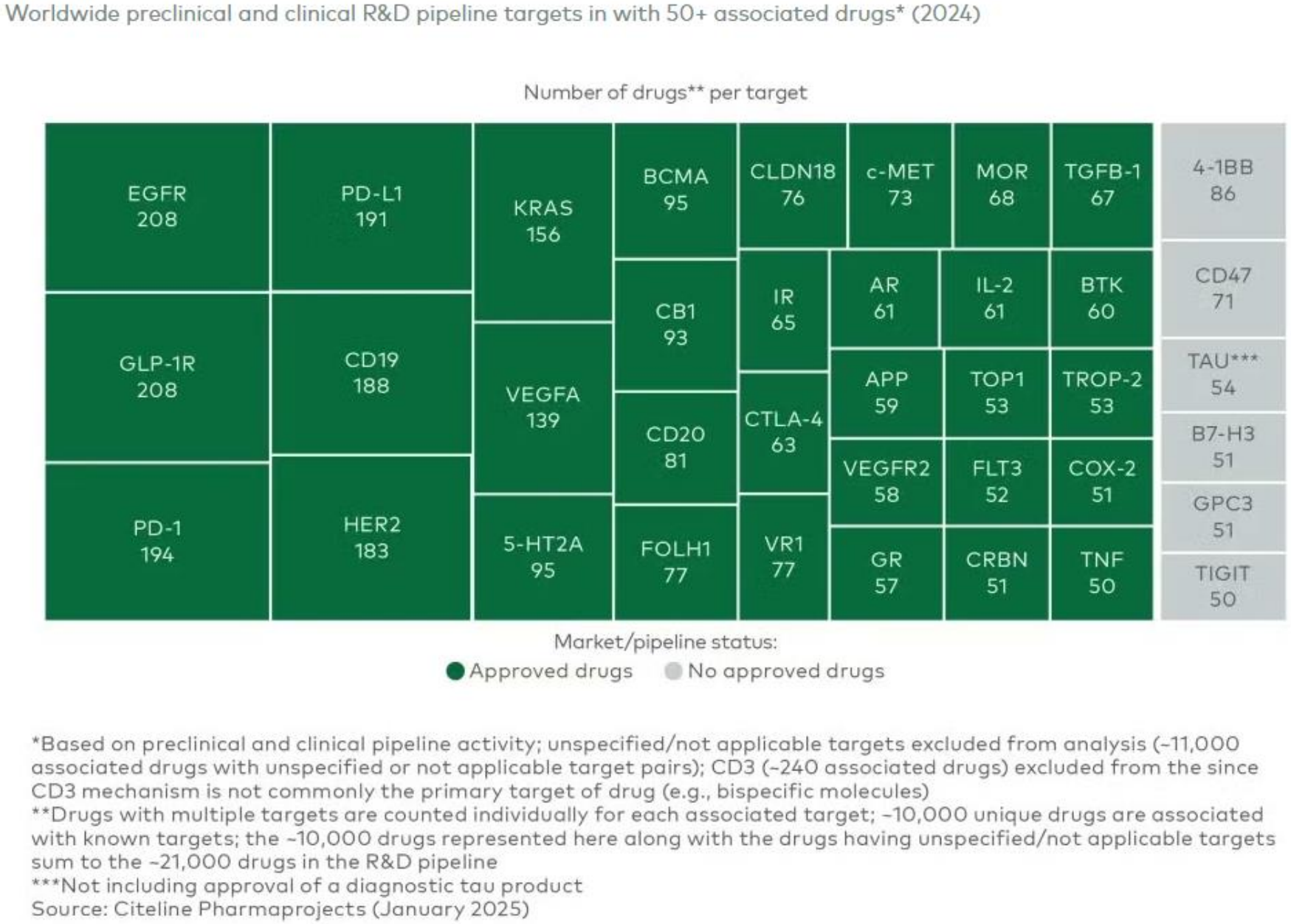
About 2% of active R&D targets — 38 targets in total — were associated with 50 or more drugs. Despite representing a small number of total targets, the 38 highly developed targets account for roughly one quarter of the entire preclinical and clinical R&D pipeline — highlighting substantial crowding among a limited set of biological mechanisms (see Figures 1a and 1b).



Note: *Based on preclinical and clinical pipeline activity. Unspecified / Not applicable targets excluded from analysis (~11,000 associated drugs with Unspecified or Not applicable target pairs). CD3 (~240 associated drugs) excluded from the since CD3 mechanism is not commonly the primary target of drug (e.g., bispecific molecules); **Drugs with multiple targets are counted individually for each associated target. ~10,000 unique drugs are associated with known targets. The ~10,000 drugs represented here along with the drugs having Unspecified / Not applicable targets sum to the ~21,000 drugs in the R&D pipeline
Source: Citeline Pharmaprojects (January 2025)

Source: https://www.lek.com/insights/hea/us/ei/biopharma-doing-enough-advance-novel-targets

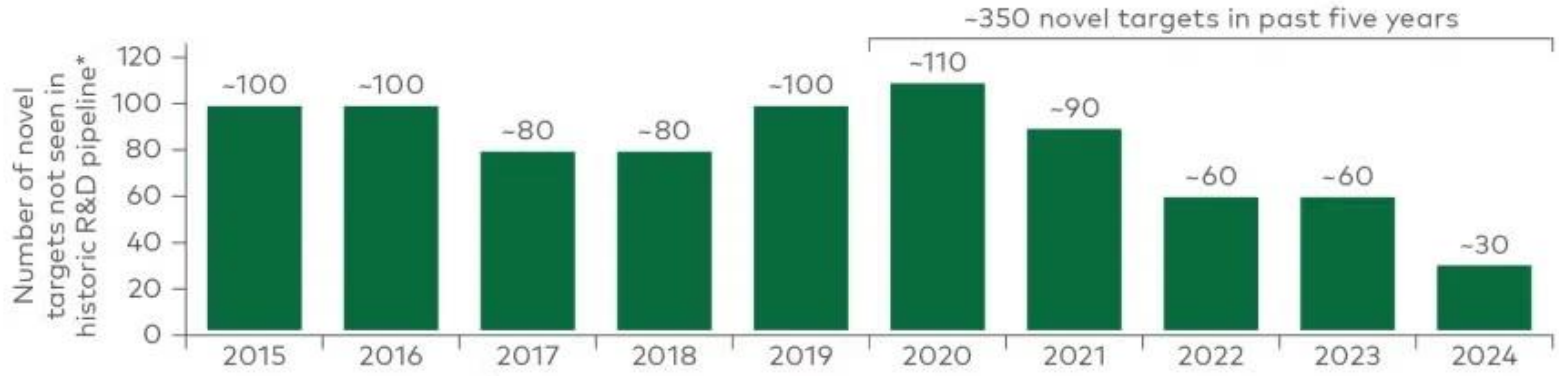
Most Crowded Targets



*Based on preclinical and clinical pipeline activity; unspecified/not applicable targets excluded from analysis (~11,000 associated drugs with unspecified or not applicable target pairs); CD3 (~240 associated drugs) excluded from the since CD3 mechanism is not commonly the primary target of drug (e.g., bispecific molecules)
**Drugs with multiple targets are counted individually for each associated target; ~10,000 unique drugs are associated with known targets; the ~10,000 drugs represented here along with the drugs having unspecified/not applicable targets sum to the ~21,000 drugs in the R&D pipeline
***Not including approval of a diagnostic tau product
Source: Citeline Pharmaprojects (January 2025)

Source: https://www.lek.com/insights/hea/us/ei/biopharma-doing-enough-advance-novel-targets

LEK: Slowdown in Novel Targets Has Coincided with Less Series A VC Investment



	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
Total R&D drug pipeline**	~10.8K	~12.1K	~13.0K	~13.5K	~14.8K	~15.8K	~17.1K	~18.4K	~19.4K	~20.8K
Series A biopharma investment***	$4B	$4B	$5B	$9B	$8B	$11B	$17B	$12B	$10B	$11B
Series A funded companies***	298	327	335	454	428	503	684	486	387	304

*A novel target is defined as a target first identified in the preclinical/clinical pipeline during the recorded year
**Represents the total number of drugs with active preclinical Phase 1, Phase 2 and Phase 3 presence
***Includes all completed and announced/in progress Series A, B and C global venture capital investor deals (primary investor type only) classified within the life sciences industry
Source: Citeline Pharmaprojects (January 2025); PitchBook Data Inc. (January 2025)

Source: https://www.lek.com/insights/hea/us/ei/biopharma-doing-enough-advance-novel-targets

Pipeline gap in novel targets

The annual rate at which novel targets enter the pipeline has dropped significantly — from around 100 a decade ago to just 30 in 2024. This decline in early-stage innovation isn't due to a lack of new drugs in development or reduced early-stage venture capital funding. In fact, the overall R&D pipeline has nearly doubled in size, growing from approximately 11,000 active drug programs in 2015 to about 21,000 by the end of 2024, even after accounting for product launches, program pauses and terminations.

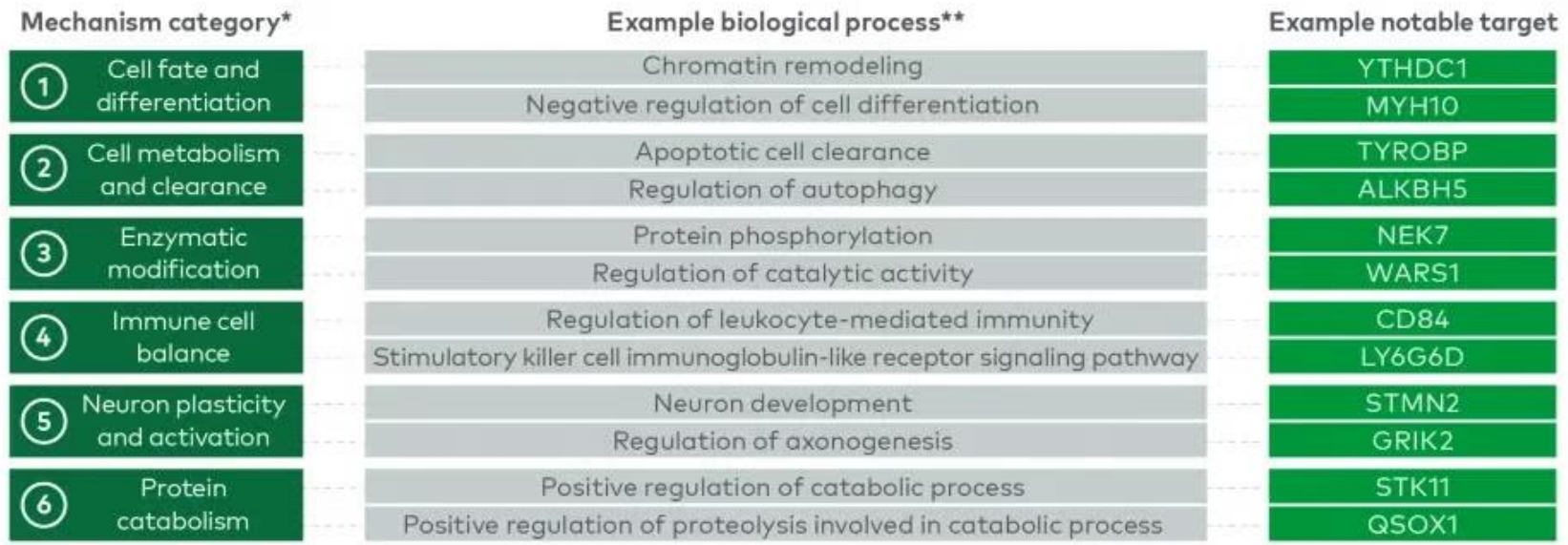
At the same time, Series A investment in early-stage life sciences companies has grown steadily, averaging around 18% annual growth over the past 10 years, with increasing average investment across a smaller number of companies being funded (see Figure 2).

LEK: Most Interrogated Areas of Novel Biology

Roughly 350 novel targets entered the R&D pipeline between 2020 and 2024, with most being pursued in oncology, immunology, metabolism and neuroscience. A closer look reveals six core mechanistic categories driving this wave of biological innovation:

1.Cell fate and differentiation
2.Cell metabolism and clearance
3.Enzymatic modification
4.Immune cell balance
5.Neuron plasticity and activation
6.Protein catabolism

These mechanisms span diverse biological functions, but the targets associated with them remain largely early-stage — about 70% are still in preclinical development, including examples such as ALKBH5 and YTHDC1. The remaining approximately 30% have advanced to the clinic, primarily in Phase 1 trials, with targets such as LY6G6D and NEK7. As this biology continues to mature, deeper scientific assessment of these mechanistic areas is warranted to uncover high-potential innovation opportunities (see Figure 3).



Note: *Mechanism categories have been developed by leveraging a Gene Ontology (GO) Term analysis of 2020-2024 new R&D pipeline targets with the Panther 19.0 database. Identified GO biological processes were characterized and grouped into the six shown mechanism categories; **Targets may have biological overlap between different mechanism categories
Source: Citeline Pharmaprojects (January 2025); PubMed Journal Archive; Ashburner et al. Nat Genetics. 2000; The Gene Ontology Consortium. Genetics. 2023

Source: https://www.lek.com/insights/hea/us/ei/biopharma-doing-enough-advance-novel-targets

LEK: Toward a More Balanced R&D Portfolio

Our data shows that the **biopharma industry is becoming increasingly cautious in its clinical target selection**. While refining known biology remains valuable, the current focus on a narrow set of well-characterized targets is leading to inefficient capital deployment. This crowding signals a broader imbalance — prioritizing familiar, lower-risk mechanisms over novel approaches that may offer greater long-term potential. As a result, even technically strong programs often struggle to differentiate clinically or commercially, with true differentiation emerging only after significant late-stage investment — raising the risk of redundancy.

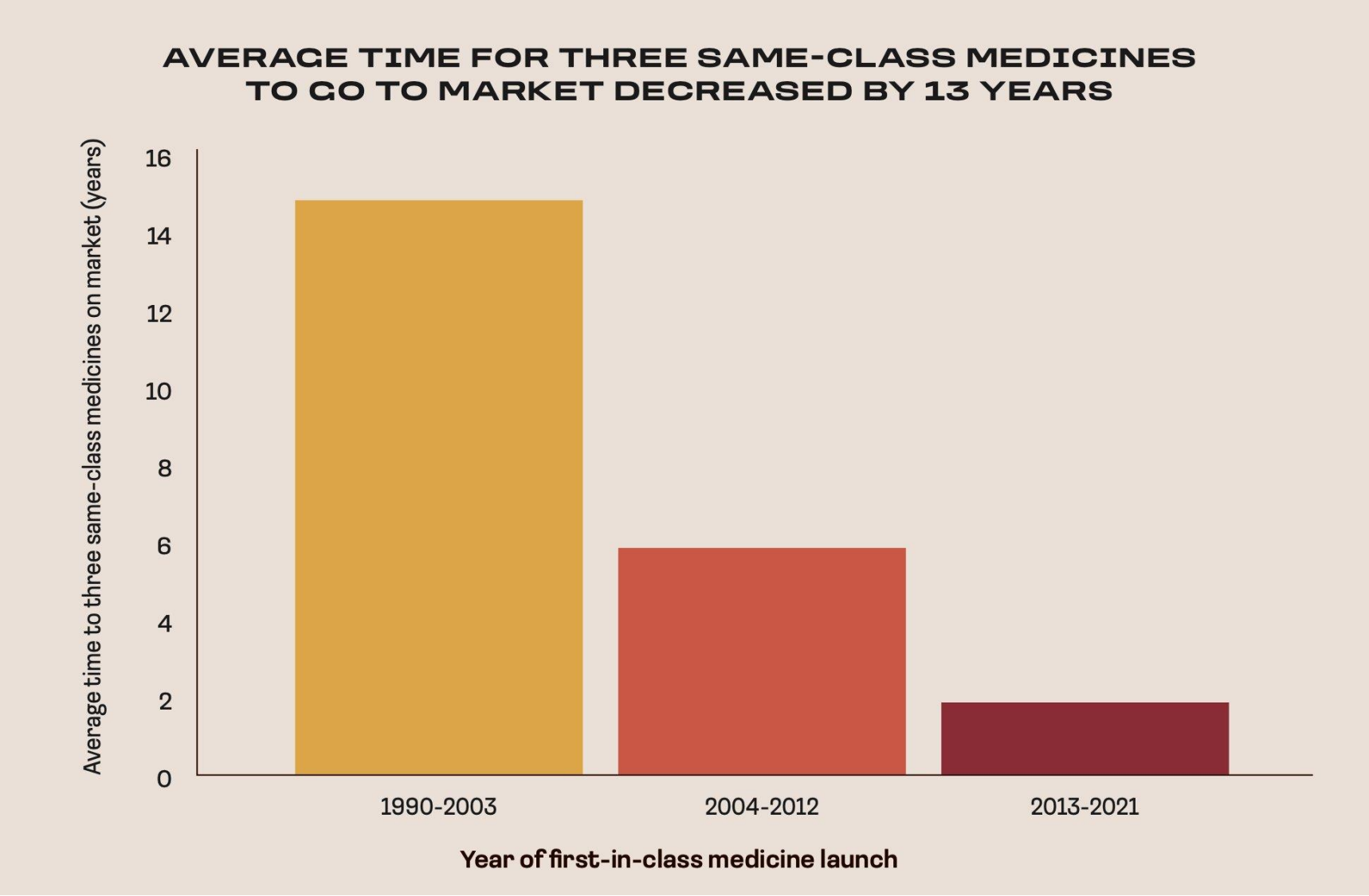
The upside? There's still **significant untapped potential in novel and underexplored targets**. Despite persistent unmet needs, around 55% of the 4,500 druggable proteins in the human genome remain untouched by drug development (Finan et al., 2017). While not all will prove viable, scientific advances are steadily expanding the boundaries of druggable space.

Realizing this potential will require rigorous scientific vetting and targeted investment. Emerging technologies — such as artificial intelligence-driven discovery and in silico experimentation — provide powerful tools for derisking novel biology earlier and more cost-effectively. Equally critical is strategic collaboration among leading biopharma companies, emerging biotechs and academic institutions to foster smarter risk-taking and increase pipeline momentum around novel, first-in-class targets.

To remain competitive and deliver meaningful innovation, the industry must rebalance its approach — embracing bold science, advanced technologies and collaborative models that unlock the next wave of high-impact targets and transformative therapies.

Source: https://www.lek.com/insights/hea/us/ei/biopharma-doing-enough-advance-novel-targets

PHRMA: Period of Branded Exclusivity Dropping Fast with Increased Crowding



Source: https://innovation.org/wp-content/uploads/2025/02/PhRMA-InnovationReport.pdf

Disclosure

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