Biopharmaceutical Sector

Update – Sep 23, 2024

STIFEL | Healthcare

Table of Contents

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Past Issues

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Sep 9, 2024 (Sector Outlook)
Aug 12, 2024 (Biotech Market)
July 15, 2024 (Halftime Report)
July 8, 2024 (Obesity Market Update)
June 17, 2024 (Lab Market)
June 8, 2024 (Oncology Review)
May 27, 2024 (GLP-1's)
May 20, 2024 (Returning Capital)
May 13, 2024 (Brain, AlphaFold 3)
May 6, 2024 (Earnings, Obesity)
April 29, 2024 (M&A, Japan)
April 22, 2024 (Pharma Pricing)
April 15, 2024 (AI in Pharma)
April 8, 2024 (The Buyside)
April 1, 2024 (Biotech Balance Sheets)
March 25, 2024 (Women's Health)
March 18, 2024 (Inflammasome)
March 11, 2024 (IRA, Immunology)
March 4, 2024 (Biotech Employment)
Feb 26, 2024 (Biotech Strategy)
Feb 19, 2024 (Big Drugs, Autoantibodies)
Feb 12, 2024 (Fibrosis, Endometriosis)
Feb 5, 2024 (Severe Disease in Women)
Jan 29, 2024 (Pharma R&D Productivity)
Jan 22, 2024 (AI in medicine)
Jan 5, 2024 (Sector Outlook for 2024)
Dec 18, 2023 (Expectations for Future)
Dec 11, 2023 (ASH, R&D Days)
Dec 4, 2023 (Big Pharma, CEA)
November 22, 2023 (Bullish on Biotech)
November 20, 2023 (M&A)
November 13, 2023 (AHA, Bear Market)
November 7, 2023 (Unmet Needs)
October 30, 2023 (ADCs)
October 23, 2023 (ESMO Review)
October 16, 2023 (Cancer Screening)
October 9, 2023 (Biosimilars, M&A)
October 2, 2023 (FcRn, Antibiotics)
September 25, 2023 (Target ID)
September 18, 2023 (Pharma Strategy)
September 11, 2023 (US Health System)
September 5, 2023 (FTC, IRA, Depression)
August 21, 2023 (Covid, China)
August 7, 2023 (Employment, Reading)
July 24, 2023 (Alzheimer's Disease)
July 7, 2023 (Biotech market review – H1 '23)
July 1, 2023 (Obesity drugs)
June 19, 2023 (Generative AI)
June 12, 2023 (IRA, State of Industry)
May 29, 2023 (Oncology update)
May 22, 2023 (FTC case on Amgen/Horizon)

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And meet us at a number of upcoming conference events:

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

biofuture™

New York City
October 28-30, 2024
https://biofuture.com/

To meet with Stifel at BioFuture:
yeungn@stifel.com

The week of Sep 24 features a gathering of biotech industry power players in Basel at the Sachs Associates Europe conference.

https://www.sachsforum.com/

To meet with Stifel @ Sachs
yeungn@stifel.com

The week of Nov 4 will feature over 5,000 biopharma professionals in Stockholm for Bio-Europe. We'd love to meet you there.

https://informaconnect.com/bioeurope/

To meet with Stifel @ Bio-Europe
yeungn@stifel.com

The Fed Rate Cut and Biotech

Federal Reserve Rate Cut

50

Basis Points in Fed Funds Rate
On Sep 18, 2024

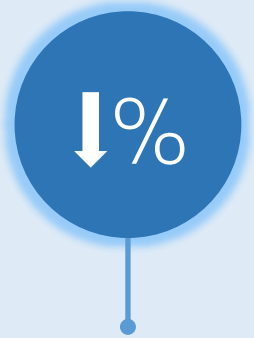
Fed Cuts Rates for the First Time in Four Years

Good News for Biotech

The cut “will be very positive for the biotech capital markets,” said John Maraganore, the former CEO of Alnylam Pharmaceuticals who is currently an advisor to drug startups. “I expect to see a meaningful strengthening of the biotech tape as interest rates decline.”

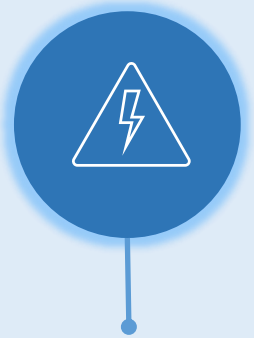
Source: https://www.biopharmadive.com/news/biotech-interest-rates-impact-startups-venture-capital/727479/

Four Reasons Why Rate Cuts are Good for Biotech



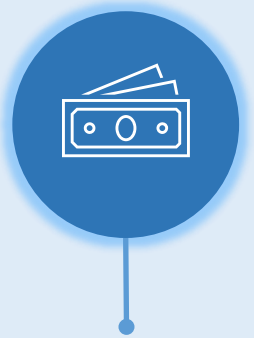
1 Lower Discount Rate

Biotech firms have long timelines before they generate revenue, making their value dependent on long-dated cash flows. The cash flow timelines are far longer for biotech than most other industries and these are often referred to as “long duration”. A rate cut reduces the discount rate used in valuation models, substantially increasing the present value of those future cash flows, in turn driving up valuations.



2 Lower Risk Premia

Historically, periods of low interest rates have led to greater risk taking by investors – who are always looking to maximize return. If safe assets have low returns, investors will seek greater risk – which is often associated with biotech stocks. In recent issues we have highlighted the high value differential between late stage biotechs with good data and those with no data that are early stage. This is emblematic of a high risk premium caused by risk aversion on the part of investors.



3 Increase in Spend

Lower interest rates can stimulate the broader economy by encouraging spending and investment by consumers and businesses.

If the overall economic environment improves, biotech firms can benefit from higher consumer confidence and increased healthcare spending, which can further drive demand for innovative treatments.

4 M&A Activity

Lower rates can encourage larger pharmaceutical or biotech firms to engage in mergers and acquisitions. This is related to financing costs, confidence and willingness to take on longer-dated projects.

Companies with stronger balance sheets may be more inclined to acquire smaller, innovative biotech firms, boosting activity in the sector.

Fed's Rate Cut Sends Stocks to Record Highs. Where are Markets Headed from Here?

Max Zahn, *ABC News*, Sept. 20, 2024 (excerpt)

Stocks rallied to record highs this week in the aftermath of a jumbo-sized interest rate cut at the Federal Reserve, presenting investors with a key question: Where is the market headed from here?

Experts who spoke to ABC News voiced cautious optimism about the outlook for the stock market, since rate cuts typically boost economic performance and buoy corporate earnings.

They warned that stocks already stand at elevated prices after a year of strong gains, leaving the market vulnerable to a downturn if the economy continues to slow.

"We're in for some volatility," Steve Sosnick, chief strategist at Interactive Brokers, told ABC News. "It wouldn't surprise me if the move higher is more of a grind than it is an escalator."

On Thursday, the S&P 500 soared 1.7% and the Dow Industrial Average jumped 1.2%, catapulting both indexes to record highs one day after the Fed handed down a half-point interest rate cut.

Along with the rate cut, the central bank forecasted two quarter-point cuts over the remainder of this year and a series of cuts next year totaling one percentage point.

The topsy-turvy response owes in part to a run-up in stock prices that preceded the rate cut, experts said. Prior to the rate cut, the S&P 500 had already soared about 18% this year, in part due to anticipation of a lowering of rates.

Source: https://abcnews.go.com/Business/feds-rate-cut-sends-stocks-record-highs-markets/story?id=113868539

Can the Fed's Rate Cut Change Biotech's 'New Normal'?

Ben Fidler, *Biopharma Dive*, Sept. 19, 2024 (excerpt)

The biotechnology sector got what many in the industry expect will be a substantial lift Wednesday when the Federal Reserve lowered interest rates for the first time in more than four years.

After a two-day meeting, the Fed cut its benchmark interest rate by half a percentage point. While the Fed's target, at 4.75% to 5%, remains near 15-year highs, the move could spur investment in biotech companies, which are typically seen as the kind of risky bet investors tend to disfavor when interest rates are elevated.

Investors and executives interviewed by BioPharma Dive cautioned the Fed's decision won't solve all that ails the sector, however. Other macroeconomic potholes, like the U.S. presidential election, still lay ahead. And within the industry, other factors could remain brakes on any stock bounce. Dealmaking involving public companies, which spiked last year and rekindled interest in biotech, has cooled, for instance.

By its nature, biotech is a fraught investing endeavor, with busts more frequent than booms. Drug startups need many years and often hundreds of millions — if not billions — of dollars to invent a new medicine and bring it to market. Financial losses accumulate in the meantime, meaning young companies need investors patient enough to stick with them for a lengthy journey. At the end of the day, most companies still fail.

Source: https://www.biopharmadive.com/news/biotech-interest-rates-impact-startups-venture-capital/727479/

"Falling interest rates will clearly be better for riskier segments of the markets like ours."

Mike Gilman

CEO of Arrakis Therapeutics

VC's Applaud the Fed

Marc Vartabedian, *Wall Street Journal*, Sept. 18, 2024 (excerpt)

Venture capitalists applauded the Federal Reserve's decision to cut interest rates by a half percentage point, saying the move was a long-awaited step toward kick-starting a slumping venture industry.

Investors said the cut on Wednesday isn't likely to have an immediate effect on the venture market, but that over months lower interest rates could improve access to capital for startups and spur more initial public offerings, a key way investors cash out of startups. The IPO market has been in the doldrums for the better part of two years.

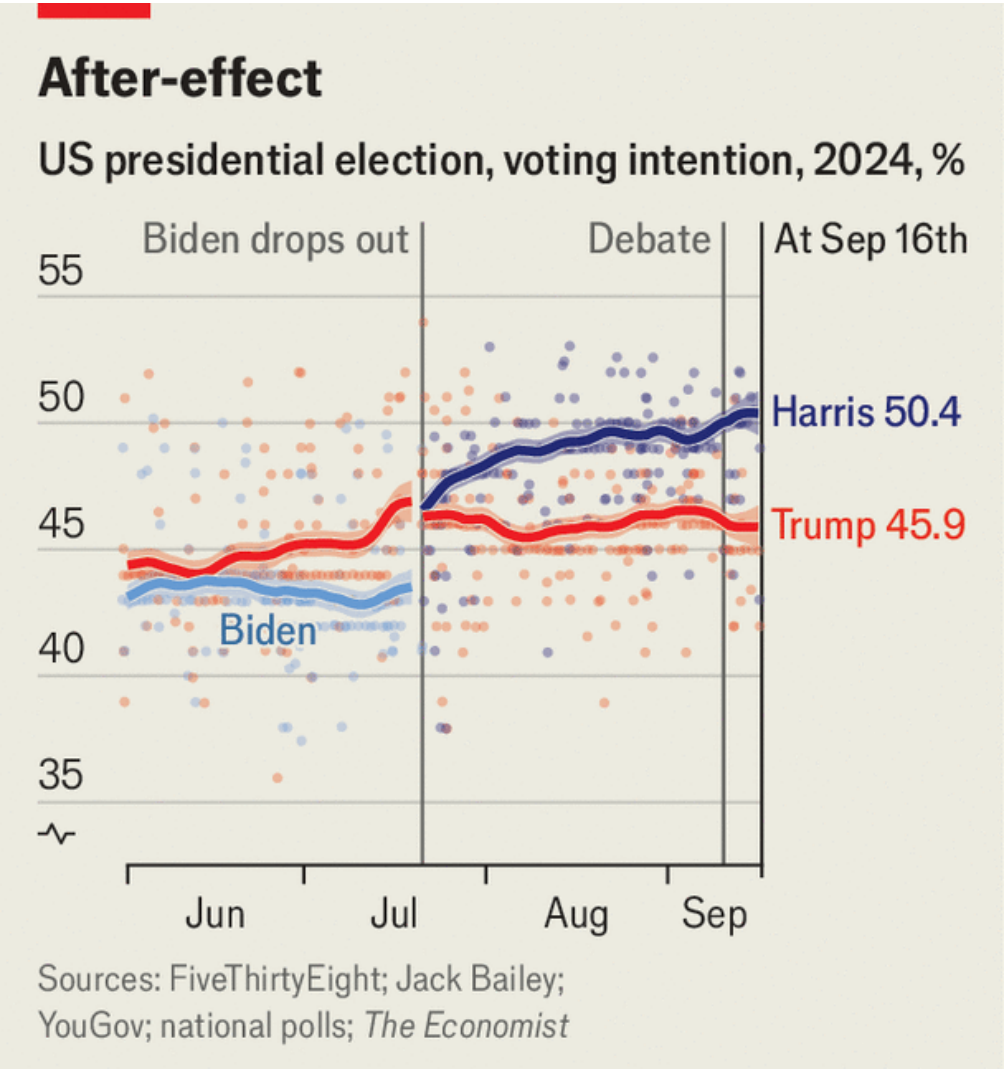
The Fed's decision marks its first rate cut since 2020 and brings the benchmark federal-funds rate to a range between 4.75% and 5%.

Anna Garcia, managing partner at Altari Ventures, said the size of the rate cut matters less to the venture world than the broader confirmation that interest rates are entering a dovish phase. She said it would take several quarters for the effects to be felt while the sentiment of limited partners, which invest in venture funds, would improve relatively soon.

"I believe LPs will become more active and serious in their conversations with new venture fund managers into 2025," Garcia said. "I will shift the timing of my next fundraise according to the changing LP sentiment and LP capital availability."

Source: https://www.wsj.com/articles/venture-capital-industry-cheers-fed-rate-cut-6e6edb4f

The Economist: Kamala Harris Gets Post-Debate Bounce in Polls



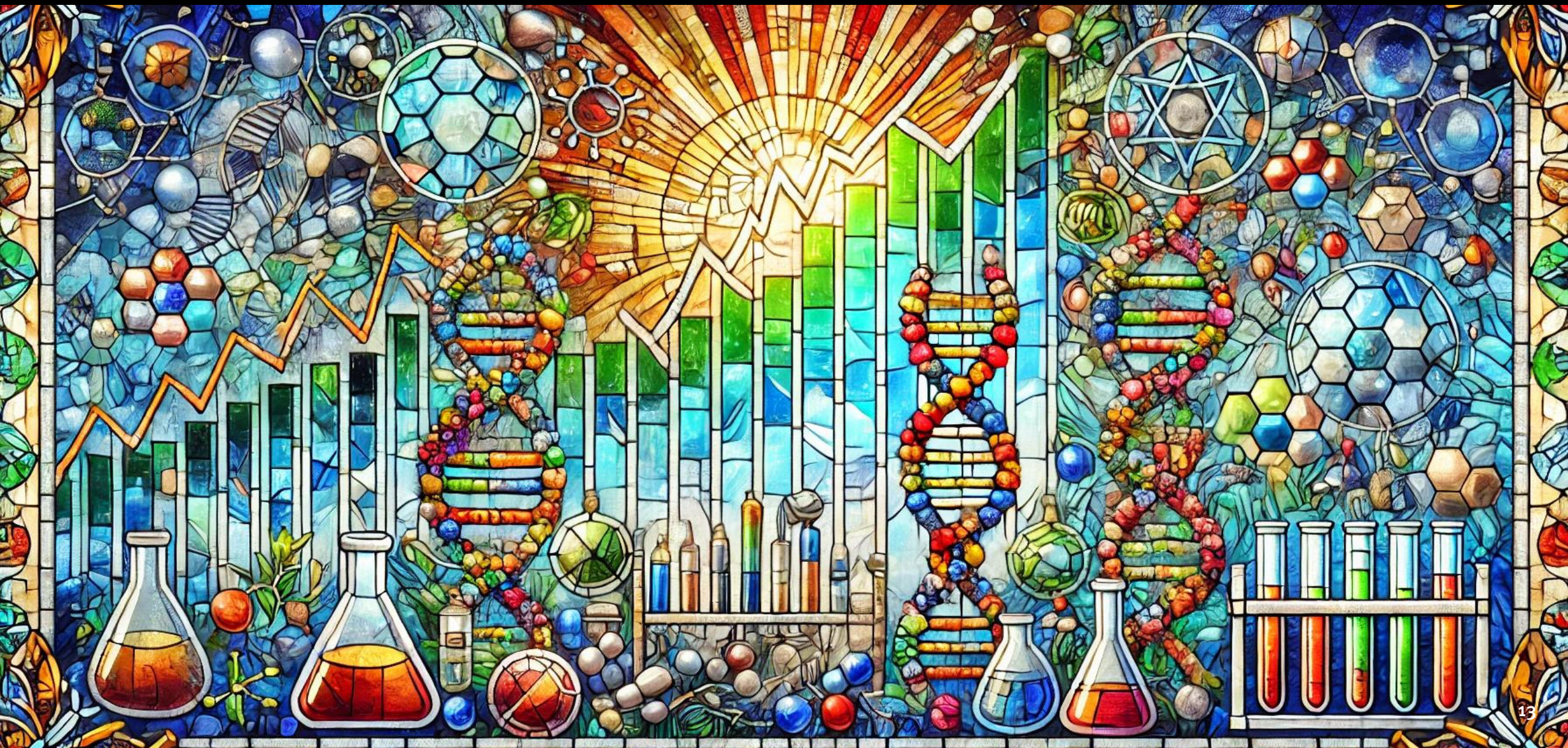
The Economist, Sep 18, 2024 (excerpt)

According to The Economist's poll tracker, Kamala Harris's nationwide lead over Donald Trump has widened to 4.5 percentage points, from 3.8 points on September 10th, the day of their debate. A 0.7-point improvement is small but potentially significant, and gives Ms Harris her biggest lead yet in our tracker (see chart).

Contrary to Mr Trump's claims, Ms Harris clearly won the debate. Several surveys have confirmed what cnn's flash poll suggested on the night: that a large majority of Americans thought Ms Harris bested Mr Trump, who repeatedly waded into the traps his rival laid for him and came across as angry and rambling. A YouGov poll reported that 55% of debate-watchers thought Ms Harris won, against 25% for Mr Trump; abc's scored it 58% to 36% for Ms Harris. A good night for the Democrat was capped by an endorsement from Taylor Swift.

Source: https://www.economist.com/united-states/2024/09/18/kamala-harriss-post-debate-bounce-is-now-visible-in-the-polls

Biopharma Market Update



Alexandria Center for Life Sciences, South San Francisco, CA. Source: Stifel

The XBI Closed at 101.6 Last Friday (Sep 20), Up 2.6% for the Week

The XBI was up last week on the news of a big Fed rate cut. The XBI is up 13.8% for the year to date. The VIX has fallen while the 10-year Treasury bond yield is flat.

Biotech Stocks Up Last Week

Return: Sep 14 to Sep 20, 2024

Nasdaq Biotech Index: -0.4%
Arca XBI ETF: +2.6%
Stifel Global Biotech EV (adjusted): -0.8%*
S&P 500: +1.4%

Return: Dec 29, 2023 to Sep 20, 2024 (YTD)

Nasdaq Biotech Index: +11.6%
Arca XBI ETF: +13.8%
Stifel Global Biotech EV (adjusted): +37.3%*
S&P 500: +19.6%

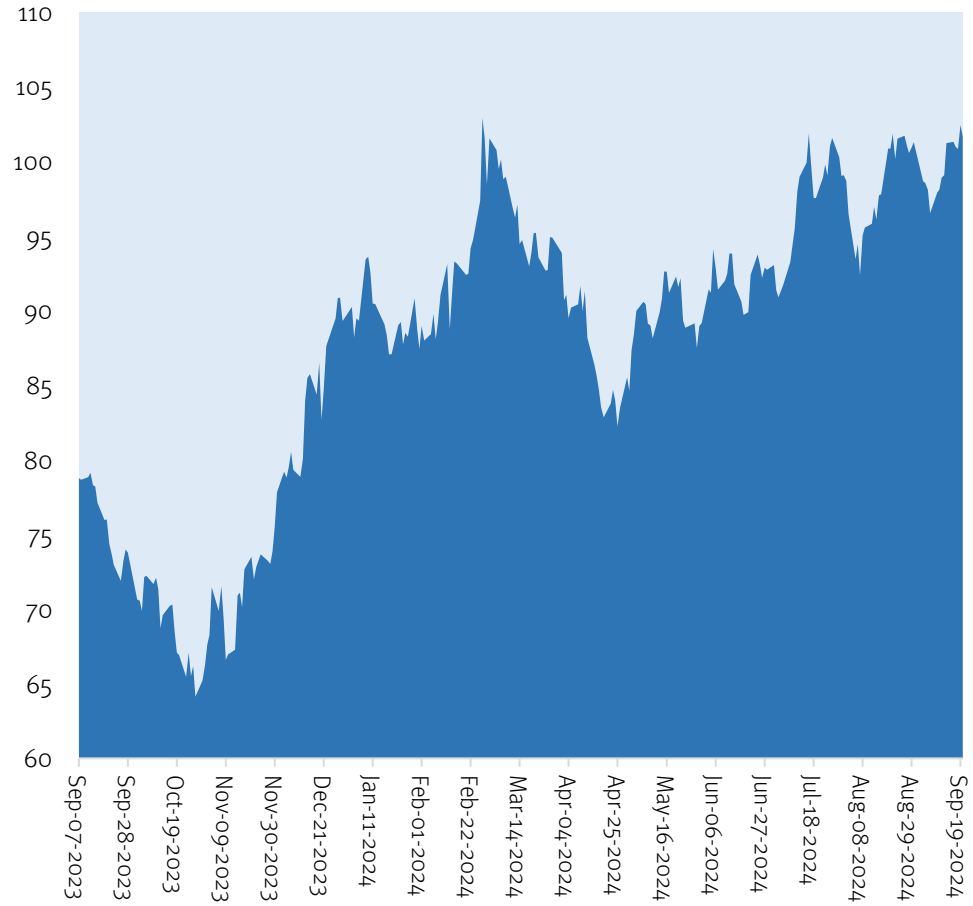
VIX Fell Significantly

Sep 29, 2023: 17.3%
Dec 29, 2023: 12.45%
Mar 29, 2024: 13.0%
May 17, 2024: 12.0%
Jun 14, 2024: 12.7%
Aug 2, 2024: 23.4%
Sep 6, 2024: 22.4%
Sep 20, 2024: 16.1%

10-Year Treasury Yield Flat

Sep 29, 2023: 4.59%
Dec 29, 2023: 3.88%
Mar 29, 2024: 4.20%
May 17, 2024: 4.42%
Jun 14, 2024: 4.2%
Aug 2, 2024: 3.80%
Sep 6, 2024: 3.72%
Sep 20, 2024: 3.73%

XBI, Sep 7, 2023 to Sep 20, 2024



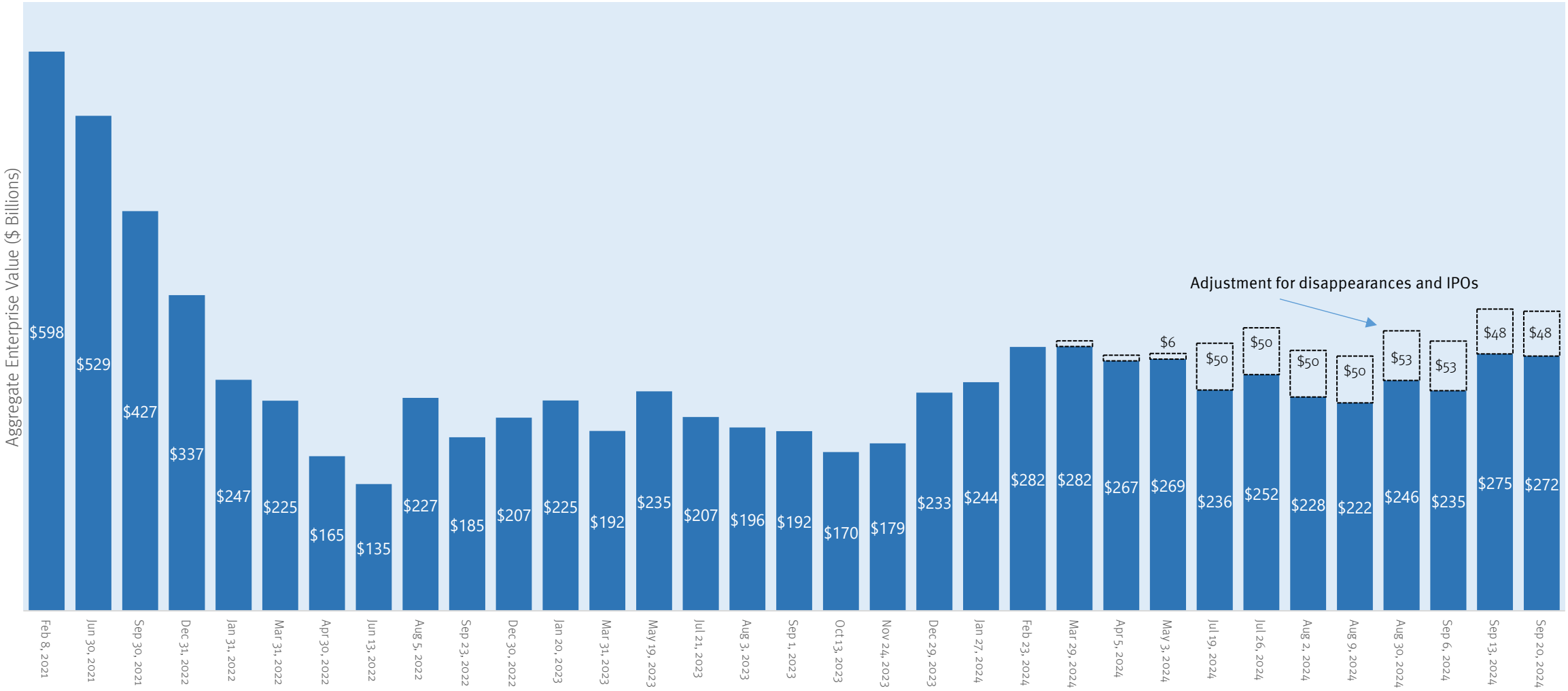
* Change by enterprise value. The adjusted number accounts for the effect of exits and additions via M&A, bankruptcies and IPOs. The annual change by market cap is even higher. The aggregate market cap of all biotechs was $271bn on Dec 31, 2023 and is now $355bn. But there has been net disappearances of $48bn. That is, the adjusted total biotech market has gone up by $132 bn in value thus far in 2024 (over 40%).

Source: S&P Capital IQ and Stifel analysis

Total Global Biotech Sector Down 0.8% Last Week

Biotech stocks were down 0.8% in the last week despite the Fed rate cut but have risen 8% over the last two months. On a disappearance adjusted basis, biotech is up 37.3% for the year to date. It's been quite a strong year for biotech. The market's aggregate EV is now up well over 100% from trough.

Total Enterprise Value of Publicly Traded Global Biotech, Feb 8, 2021 to Sep 20, 2024 ($ Billions)

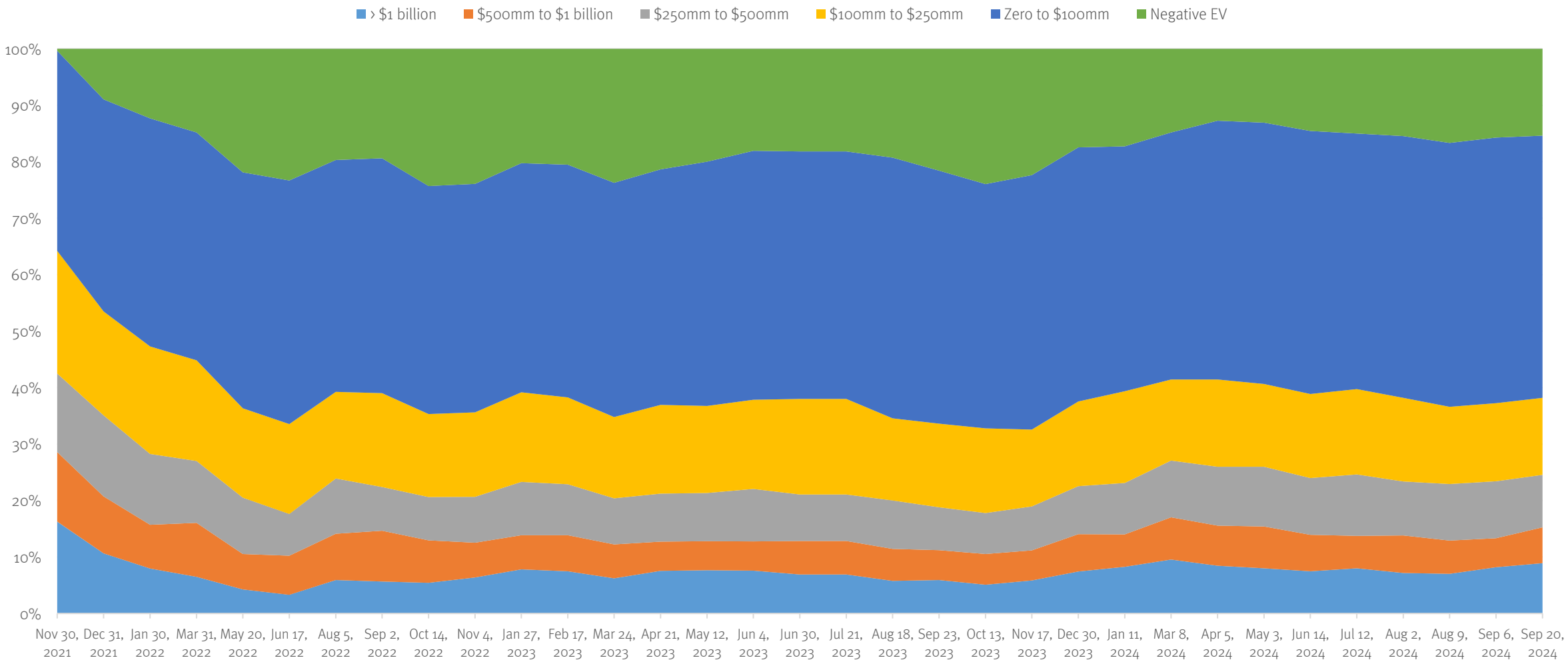


Source: CapitalIQ. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

Global Biotech Neighborhood Analysis

The population of high value companies has been growing nicely lately as companies like Vaxcyte and Summit have attracted investor interest.

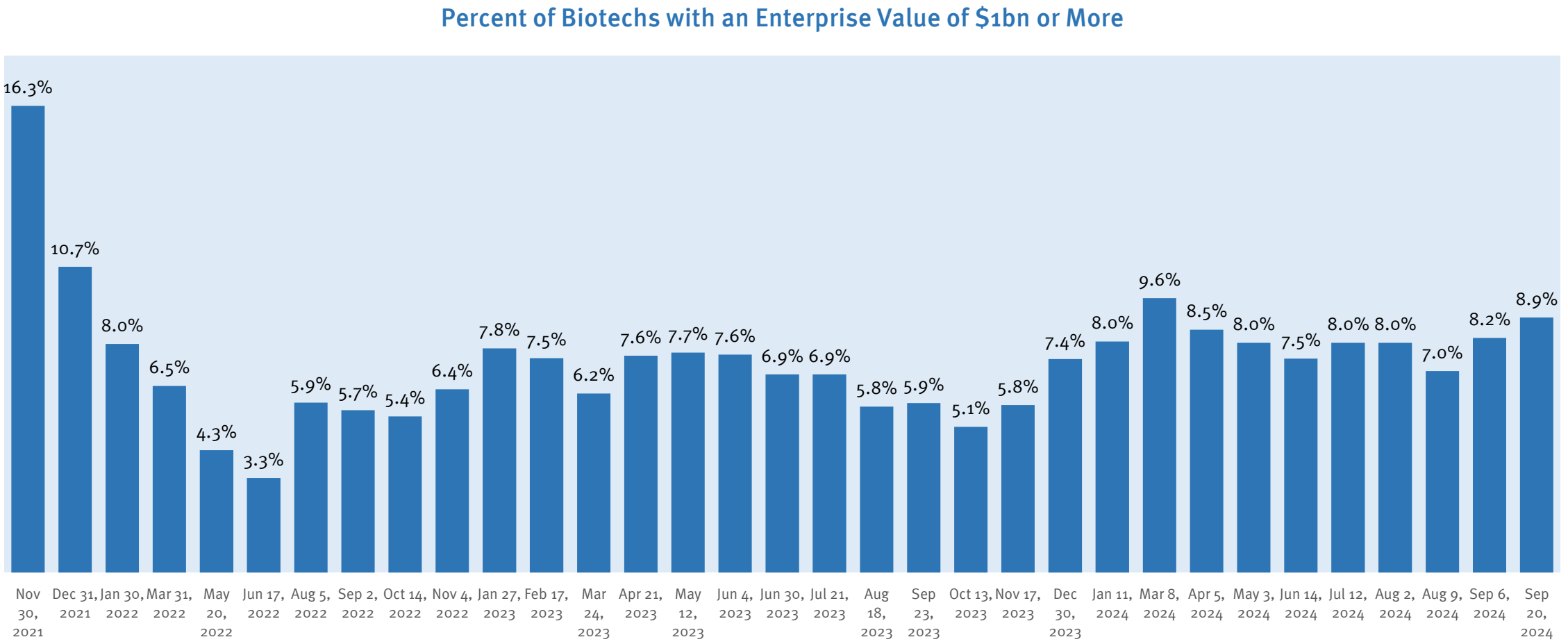
Global Biotech Universe by Enterprise Value Category, Nov 30, 2021 to Sep 20, 2024



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

The Percent of Biotechs Worth More than a Billion is Up Nicely So Far in 2024

On August 9th, 2024 there were 56 biotechs with an EV › $1 billion. As of last Friday, there were 71 such companies.

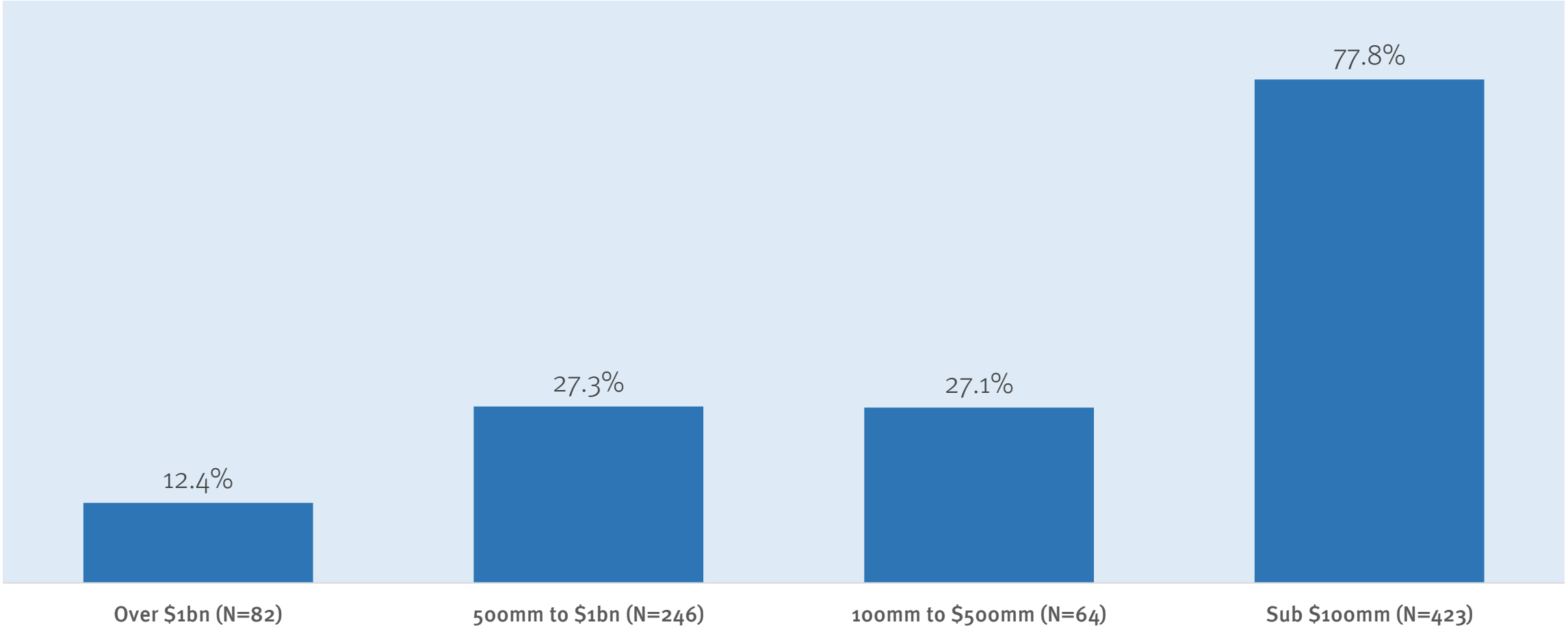


Source: CapitalIQ and Stifel analysis. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

Small Cap Biotech Continues to Outperform in 2024

Change in Global Biotech Valuations, Dec 31, 2023 to Sep 20, 2024

(Percent Change in Value of Company Group, N=815)



Source: CapitalIQ and Stifel analysis

Biotech Hedge Funds Performing Well

Stephen Taub, *Institutional Investor*, Sept. 12, 2024 (excerpt)

Most life sciences and biopharma hedge funds made money in August. Strong gains enabled several funds to return to the black for the year.

One of the top performers in 2024 remains Janus Henderson's Biotechnology Innovation Fund, a pure play on biotech stocks. The fund gained 3.9 percent in August and is up 38.7 percent for the year, according to a hedge fund database. Janus's hedge fund is more diversified than many of the other biopharma specialists. It includes longs, often smaller and less-liquid companies, private companies, and shorting, which helped performance when the sector was selling off in recent years.

Casdin Capital's share class that invests only in public securities is likely the top performer for the year, up about 40 percent, says an investor.

Elsewhere, Soleus Capital gained 4.7 percent in August and is up 13.8 percent for the year, an investor says. Soleus benefited from the performance of TG Therapeutics, which surged about 19 percent last month.

Suvretta's Averill Partners gained 1.6 percent in August and is up 18.5 percent so far in 2024, per an investor. RA Capital Management jumped 60 basis points and is now up 13.7 percent for the year, according to an investor.

At least two funds moved into the black after posting strong gains last month. Perceptive Advisors climbed 5 percent in August and is now up 3.5 percent for the year.

Source: https://www.institutionalinvestor.com/article/2dr3zh8dob6vbopp7b9j4/hedge-funds/biopharma-hedge-funds-extend-gains

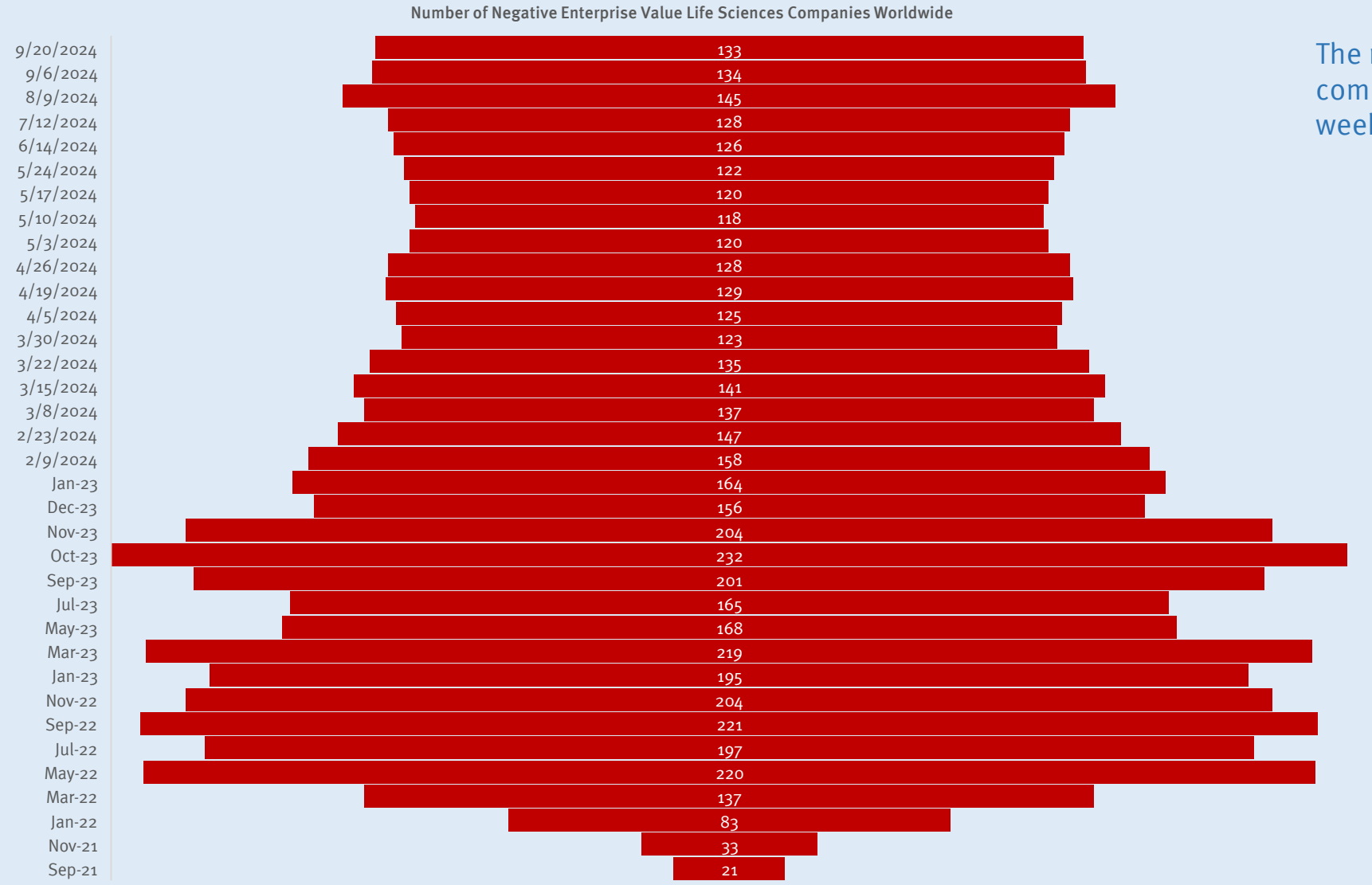
Life Sciences Sector Total Value Down 0.7% Last Week

Performance was flat in the life sciences sector last week. The best performing sectors were HCIT and pharma services. Commercial pharma, medical devices and biotech were all down slightly.

Sector	Firm Count	Enterprise Value (Sep 20, 2024, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	79	$89,066	-1.4%	2.9%	13.1%
Biotech	777	$267,417	-0.7%	10.9%	-5.1%
CDMO	39	$165,956	1.3%	2.8%	6.3%
Diagnostics	81	$252,941	-0.1%	0.0%	9.9%
OTC	29	$27,401	-1.8%	1.1%	-6.6%
Pharma	713	$6,814,636	-0.8%	-1.7%	18.3%
Pharma Services	38	$181,471	1.6%	1.2%	-7.5%
LS Tools	50	$728,885	0.4%	1.6%	10.3%
Devices	180	$1,789,141	-0.7%	1.9%	17.7%
HCIT	10	$21,315	4.5%	4.7%	8.8%
Total	1996	$10,338,229	-0.7%	-0.3%	17.5%

Source: CapitalIQ and Stifel analysis

Count of Negative Enterprise Value Life Sciences Companies Has Changed Little in Recent Weeks



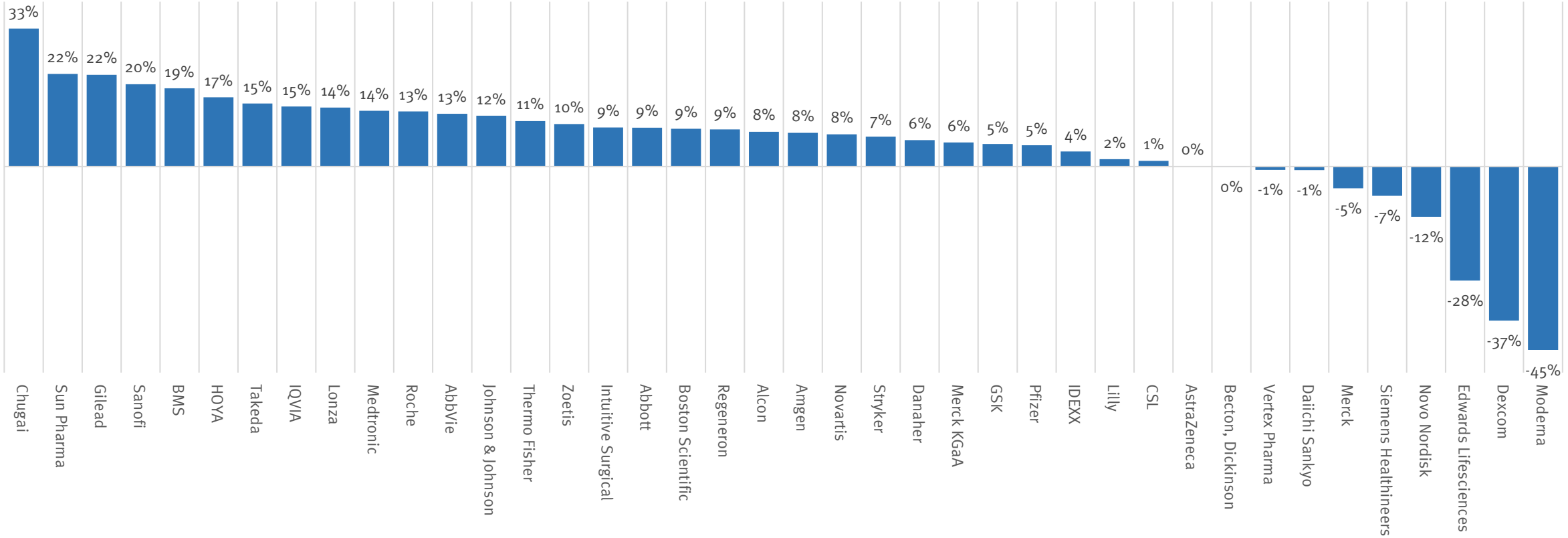
The number of negative EV life sciences companies has been relatively flat in recent weeks.

Source: CapitalIQ and Stifel analysis

How the World Turns: Life Cap Life Science Share Price Returns in the Quarter to Date

In recent quarters, Lilly and Novo have dominated large cap players in returns. In the quarter to date, the story is very different with a number of less heralded companies performing well including Gilead, BMS, Chugai and Sun Pharma. Moderna, Dexcom and Edwards Life Sciences have all done relatively poorly in the last quarter. Chugai, BMS and Gilead have all posted strong performance numbers and are seeing their growth stories come together.

Top 40 Life Science Players: Percent Change in Market Cap, June 30 to Sep 20, 2024 ($ Billions)



Source: CapitalIQ and Stifel analysis

Good News for a Change from Gilead and Sanofi

sanofi

Sanofi's tolebrutinib drug delays progressive MS by 31% in trial

By **Ludwig Burger**

September 20, 2024 10:07 AM EDT · Updated a day ago

Reuters

Sanofi's drug tolebrutinib has shown highly encouraging results in treating non-relapsing secondary progressive multiple sclerosis (nrSPMS), a form of MS that lacks effective treatments. In the Phase 3 HERCULES study, tolebrutinib was able to delay disability progression by 31% compared to placebo. Additionally, it nearly doubled the rate of confirmed disability improvement among patients, from 5% in the placebo group to 10% in those taking the drug. This promising data provides hope for nrSPMS patients, and Sanofi plans to file for regulatory approval later in 2024. If successful, tolebrutinib could represent a major breakthrough in MS treatment.

Gilead says its twice-yearly shot cut HIV infections by 96% in trial

CNBC

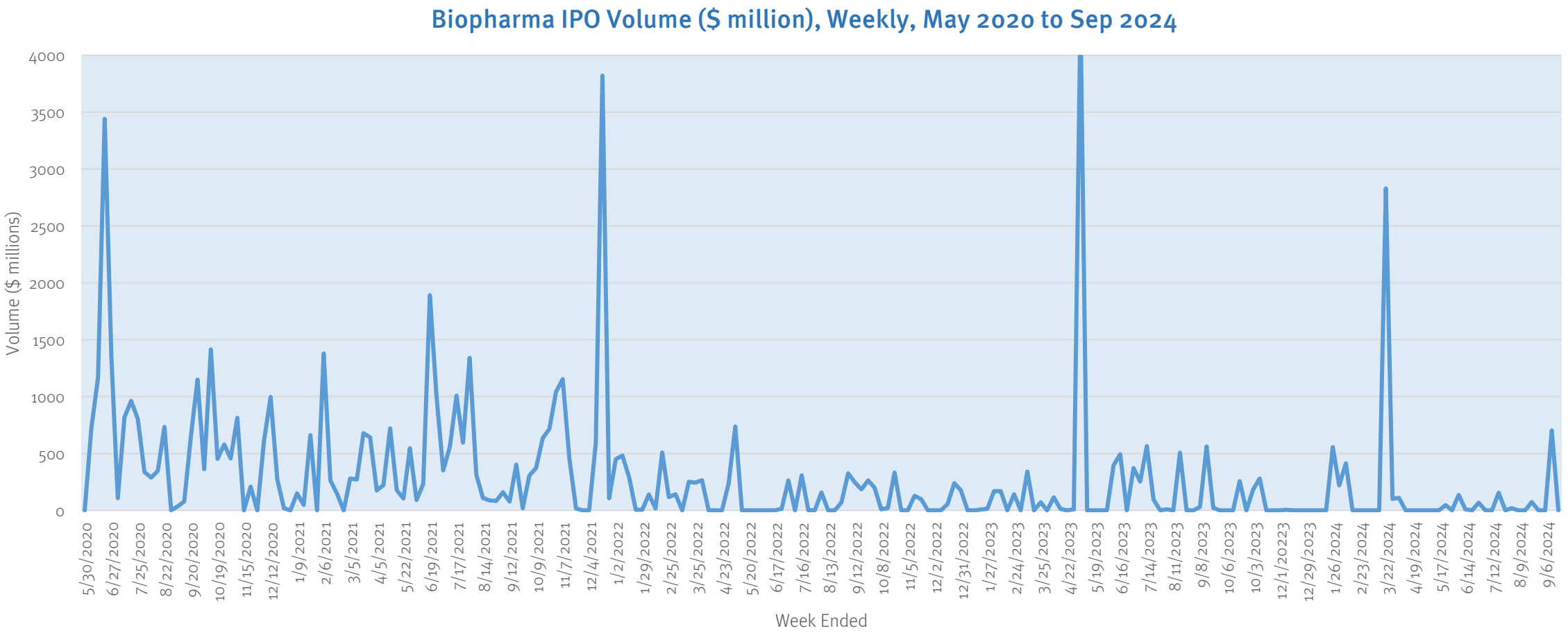
PUBLISHED THU, SEP 12 2024•9:29 AM EDT | UPDATED THU, SEP 12 2024•11:49 AM EDT

Gilead's HIV prevention drug, lenacapavir, has shown highly promising results, cutting the risk of infection by 96% in clinical trials. This twice-yearly injectable medication is a significant advancement compared to daily oral PrEP like Truvada. In trials involving over 3,200 participants, lenacapavir showed near-complete protection against HIV, with only two cases of infection in the group taking the injection. The convenience of fewer doses makes it an appealing option, though concerns remain about its potential cost and accessibility

Capital Markets Update

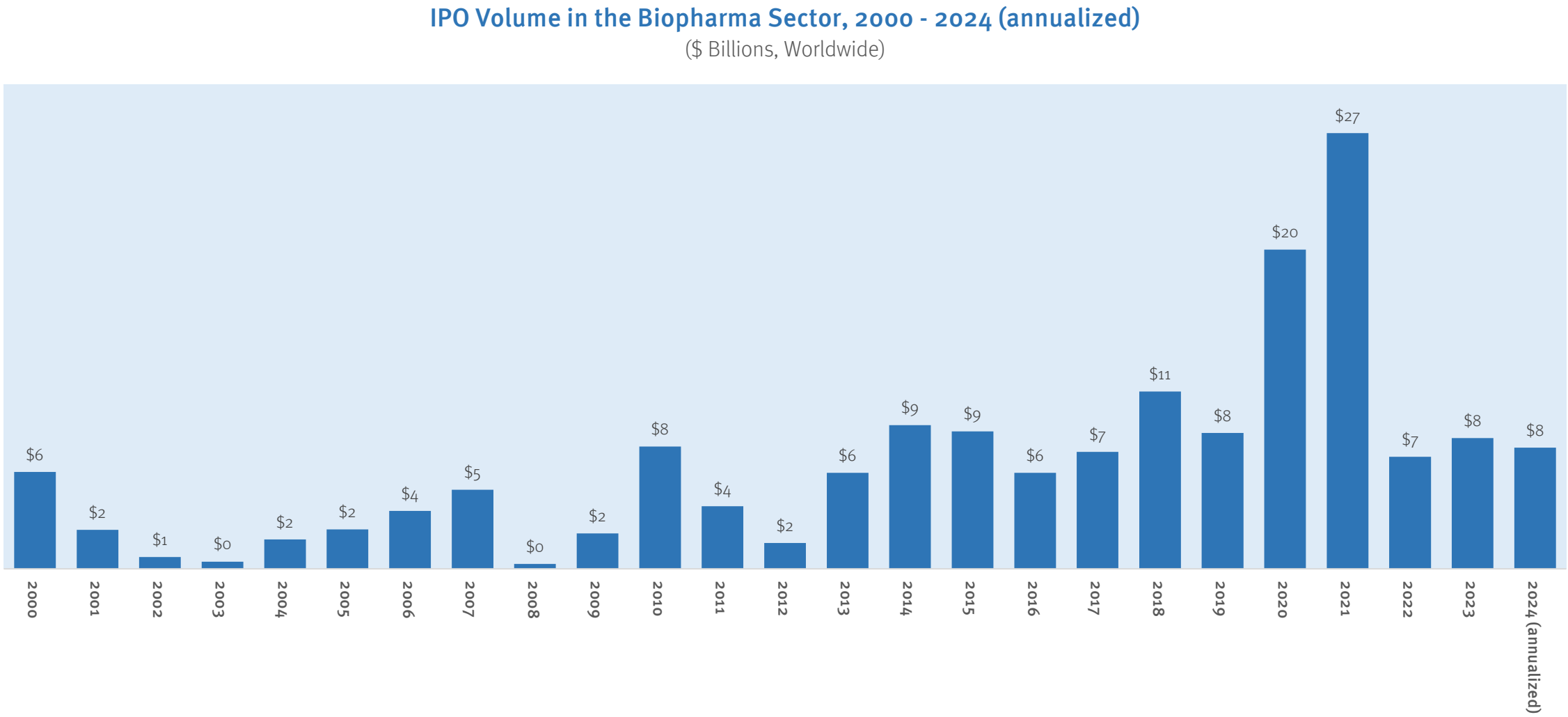
IPO Market Activity Up

After months of inactivity the U.S. IPO market priced three offerings two weeks ago (Bicara, MBX and Zenas). We saw two other companies flip to visible filings last week (Upstream and Camp4). The IPO market is perking up and is open for strong stories.



Source: Data from CapitalIQ and Stifel research.

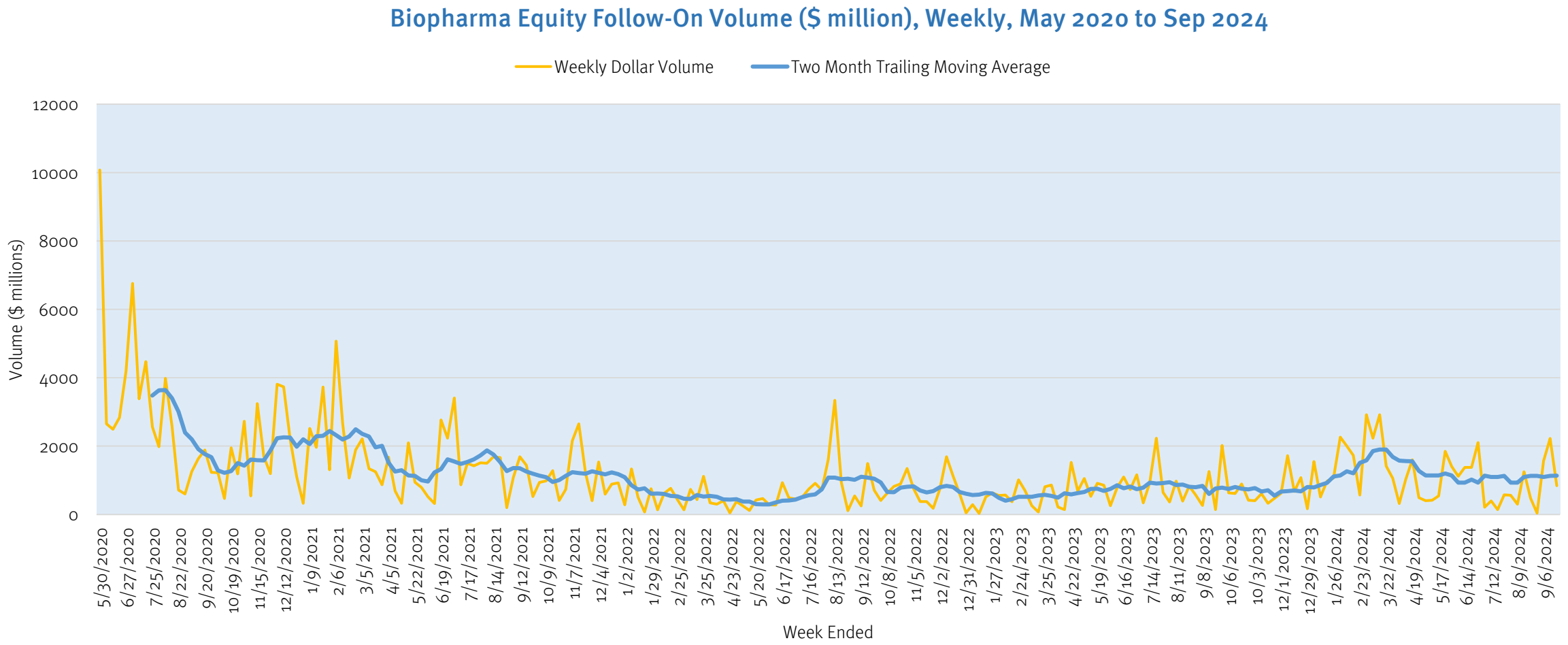
We are Tracking to a Slow Year for Biopharma IPO Volume



Source: Data from CapitalIQ, Stifel research.

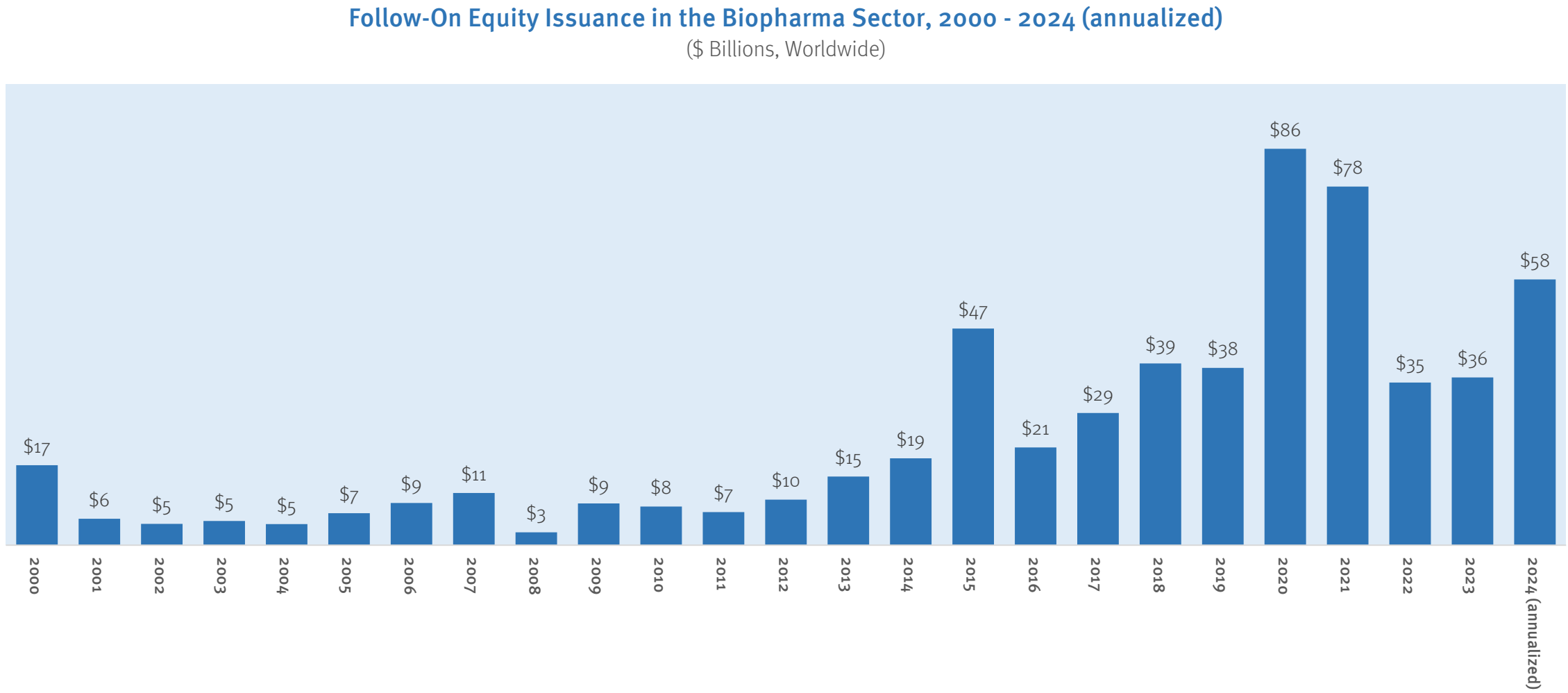
Follow-On Market Very Strong This Month

After a very slow August the follow-on equity market for biotech has been exceptional in September. Since Labor Day we have seen more than $4.5 billion of issuance in the market. We are on track to match the blistering offering pace seen in January and February of this year. We expect the secondaries market to continue to be active in the weeks ahead.



Source: Data from CapitalIQ.

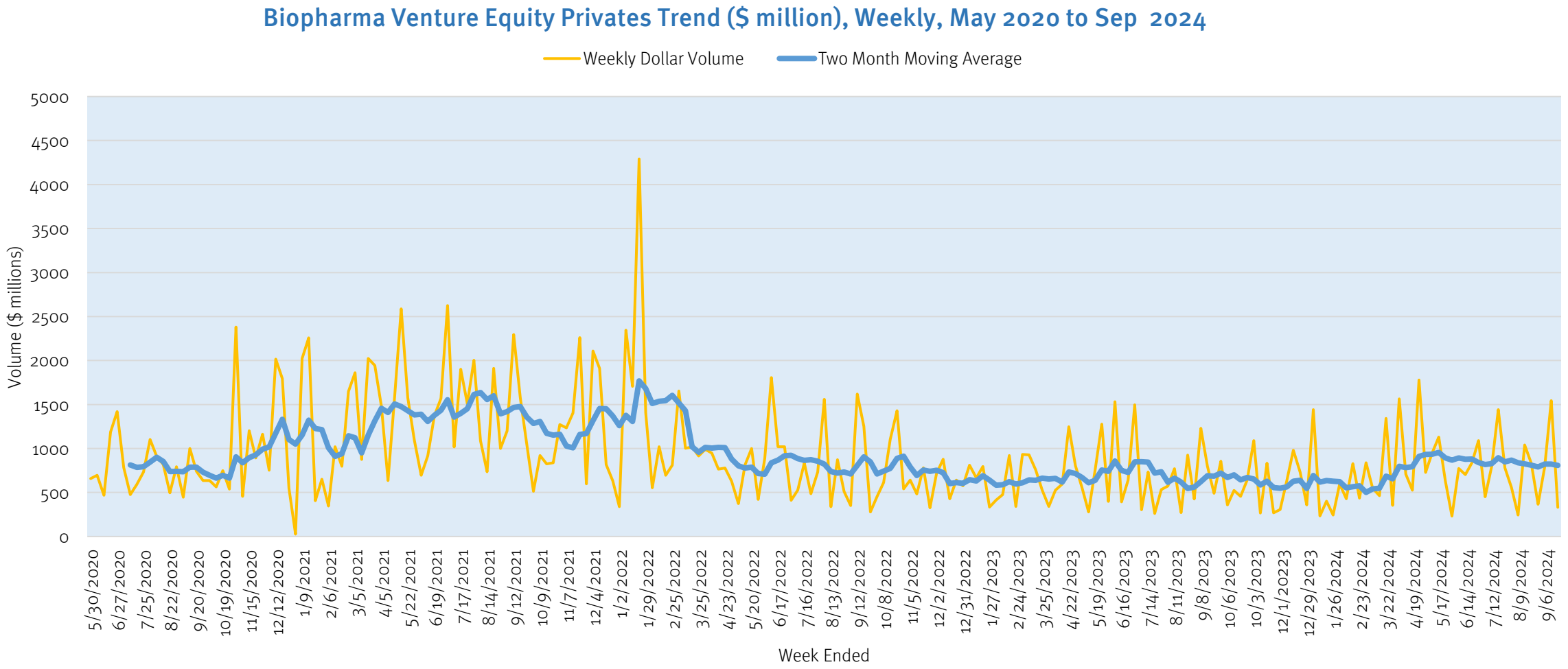
We are Tracking to a Very Strong Year for Biopharma Follow-On Equity Issuance Volume



Source: Data from CapitalIQ, Stifel research.

Private Venture Equity Market Normal This Month

Weekly volume of venture privates this year has averaged $750mm. This month's volume has been in line with this average.



Source: Data from CapitalIQ, Crunchbase.

From ‘Science Fiction to Reality': New George Church-Founded Biotech Raises $65M for Cell Therapy Platform

Gabrielle Masson, *FierceBiotech*, Sep 19, 2024 (excerpt)

GC Therapeutics has entered gameplay with the mission of unlocking a new generation of cell therapies, uploading with $75 million for its “plug-and-play” tech developed in the lab of—and with cells from—George Church, Ph.D.

“George donated his skin cells, which were reprogrammed into the stem cells that were used. So, he truly has skin in the game,” GCTx co-founder and Chief Scientific Officer Alex Ng, Ph.D., told Fierce Biotech. “Along with this deep contribution, we're really proud to have his initials on our door. Of course, GC Therapeutics could also mean gene and cell therapeutics, or the letters of DNA.”

The biotech has capped off a $65 million series A financing led by Cormorant Asset Management with participation from Mubadala Capital and Andreessen Horowitz (a16z) Bio + Health, among others. That brings the company’s total capital raised since its 2019 inception to $75 million, according to a Sept. 19 release.

GCTx is based around TFome, a cellular programming platform built to “plug and play”—that is, to deliver off-the-shelf induced pluripotent stem cell (iPSC)-based medicines up to 100 times faster than conventional methods. The single-step process combines synthetic biology, gene editing, cell engineering and machine learning in efforts to boost potency, efficiency and quality, according to the company.

“This approach harnesses the transformative potential of transcription factor biology to guide iPSC cell fate into any differentiated cell type in a single, seamless step,” GCTx co-founder Church said in the company release. “By transcending the limitations of natural processes, it holds the promise to create cells that surpass the capabilities of those found in nature, generating a groundbreaking new class of SuperCell medicines to address diverse disease areas and reduce healthcare burdens.”

Parastoo Khoshakhlagh, Ph.D.; Alex Ng, Ph.D.; and George Church, Ph.D. of GC Therapeutics

Source: https://www.fiercebiotech.com/biotech/science-fiction-reality-new-george-church-founded-biotech-raises-75m-cell-therapy-platform

Andreesen Horowitz on the GC Therapeutics Pitch

Vineeta Agarwala, "Investing in GC Therapeutics," Sep 20, 2024

Transcription factors (TFs) are powerful "master regulators" inside the cell, directing the cell's machinery to express certain genes, and keep others turned off. During development, TFs are known to play a key role in determining cell 'fate,' and driving differentiation of stem cells into more specialized cell types. The status quo for iPSC differentiation research, therefore, has been focused on hypothesis-driven approaches to testing the role of different TFs, at different timepoints, in different artisanal lab protocols. But there are thousands of TFs in the cell—the space of possible differentiation protocols is simply too large to manually traverse with only 'educated guesses.'

GCTx is flipping the entire iPSC differentiation paradigm on its head. Rather than manually iterating through a limited set of differentiation protocols, the Human TFome technology platform instead deploys large-scale combinatorial screening to discover new hypotheses and better methods that are as-yet unknown to even the best biologists. Importantly, TFome screening is fundamentally unbiased, and unshackled by prior knowledge—and could instead blow open new biological insights regarding how best to differentiate and develop different cell types of interest.

Every day, GCTx is discovering previously unknown cocktails of transcription factors whose exposure to iPSCs can induce rapid differentiation into many different cell types of interest. These cocktails are then refined, optimized, and further tailored to produce precise cellular phenotypes. And differentiated cells can then be further engineered (into what GCTx calls "SuperCells") in a variety of ways to improve their ability to modify disease, engraft into the human body, avoid immune rejection, etc.

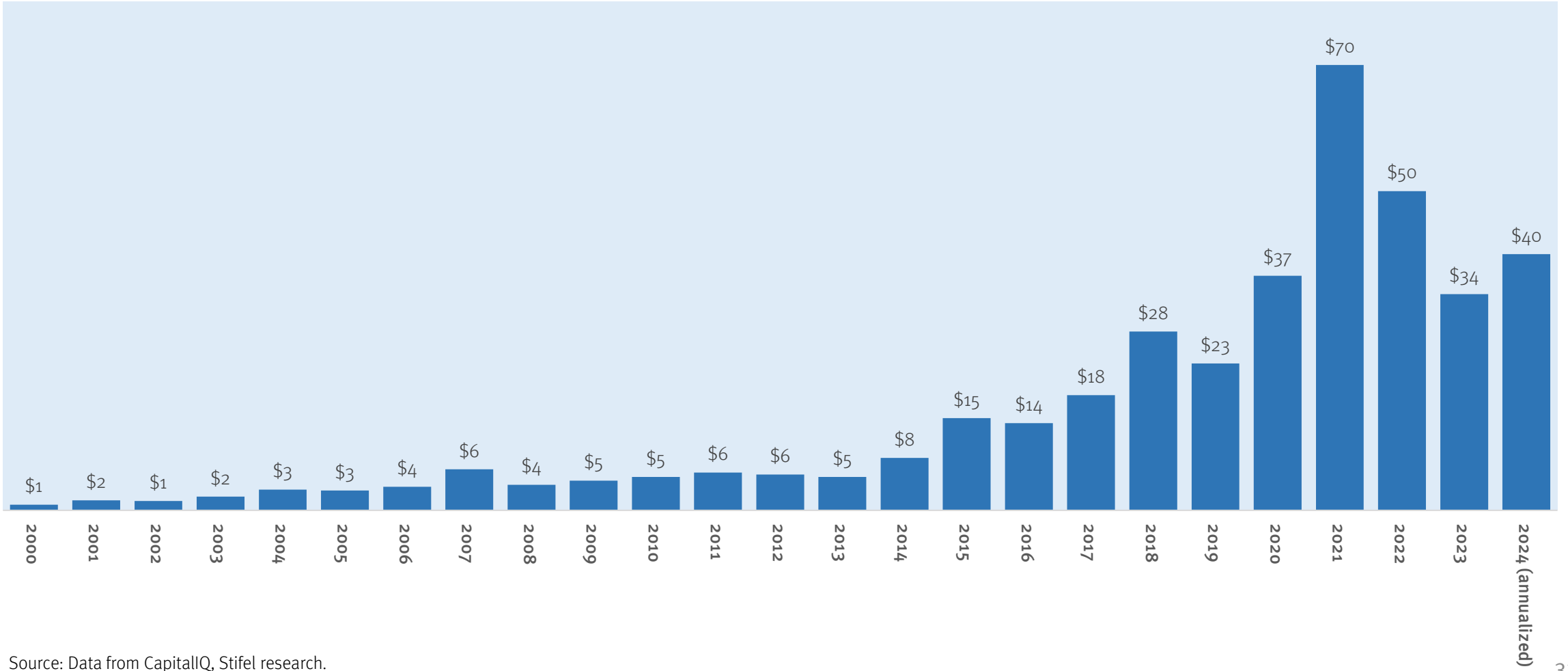
When we first heard the GC Therapeutics pitch, the opportunity to build a suite of truly "off the shelf" (e.g., scalable, not patient-specific, accessible to all) cellular medicines for a wide range of diseases caught our eye. The cell therapy industry is in need of more capital- and time-efficient approaches, and GCTx promises to deliver exactly that. The early differentiation protocols identified by TFome can produce differentiated human cells in a single-step, four-day process—in sharp contrast to many current iPSC differentiation protocols which can take weeks or even months to complete.

Source: https://a16z.com/announcement/investing-in-gc-therapeutics/

We are Tracking to a Meaningfully Improved Year in Biotech Venture Financing

Venture Equity Private Rounds in the Biopharma Sector, 2000 - 2024 (annualized)

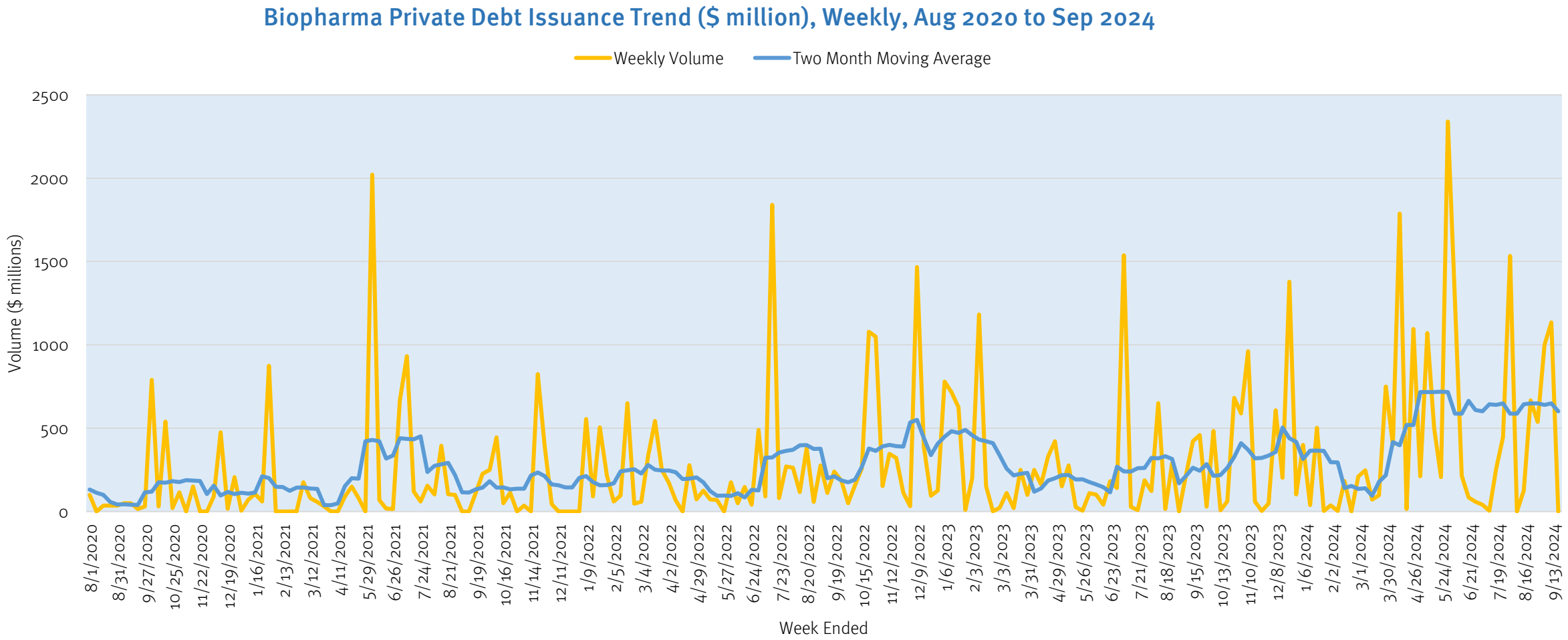
($ Billions, Worldwide)



Source: Data from CapitalIQ, Stifel research.

Biopharma Private Debt Market Robust

Volumes in the private debt market have been elevated in the last several months. The issuance volume seen thus far in September has been in line with the levels seen since May.

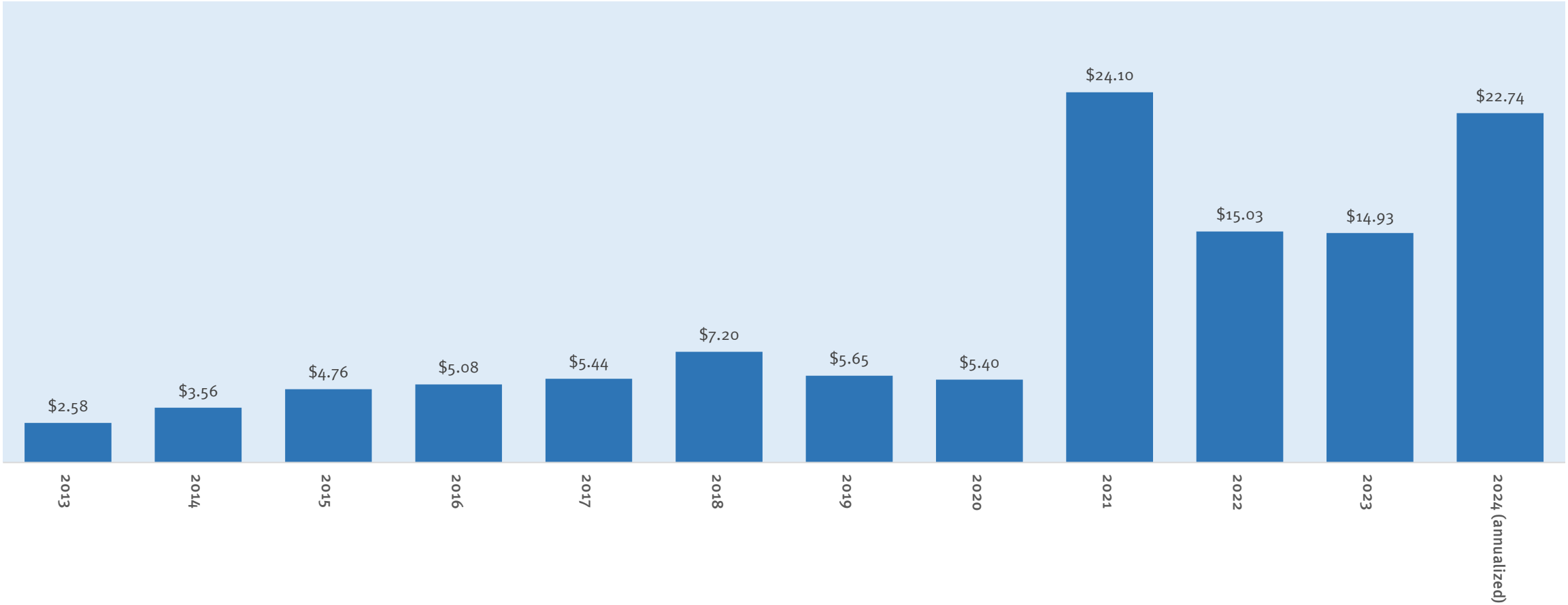


Source: Data from CapitalIQ, Crunchbase, Stifel research.

We are Tracking to a Near Record Year in Life Sciences Private Debt Issuance

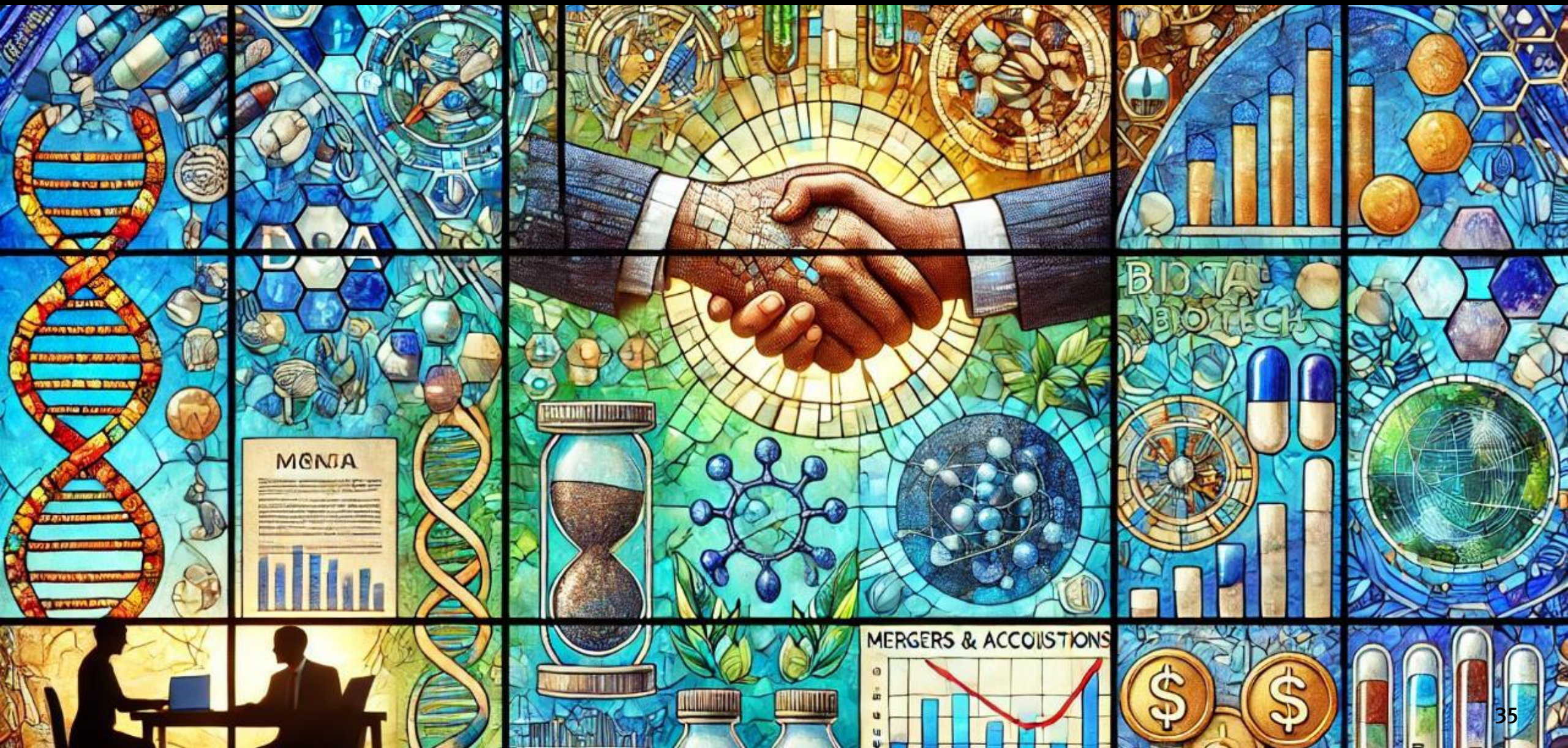
Private Debt Market Volume in Life Sciences, 2013 - 2024 (annualized)

($ Billions, Worldwide)



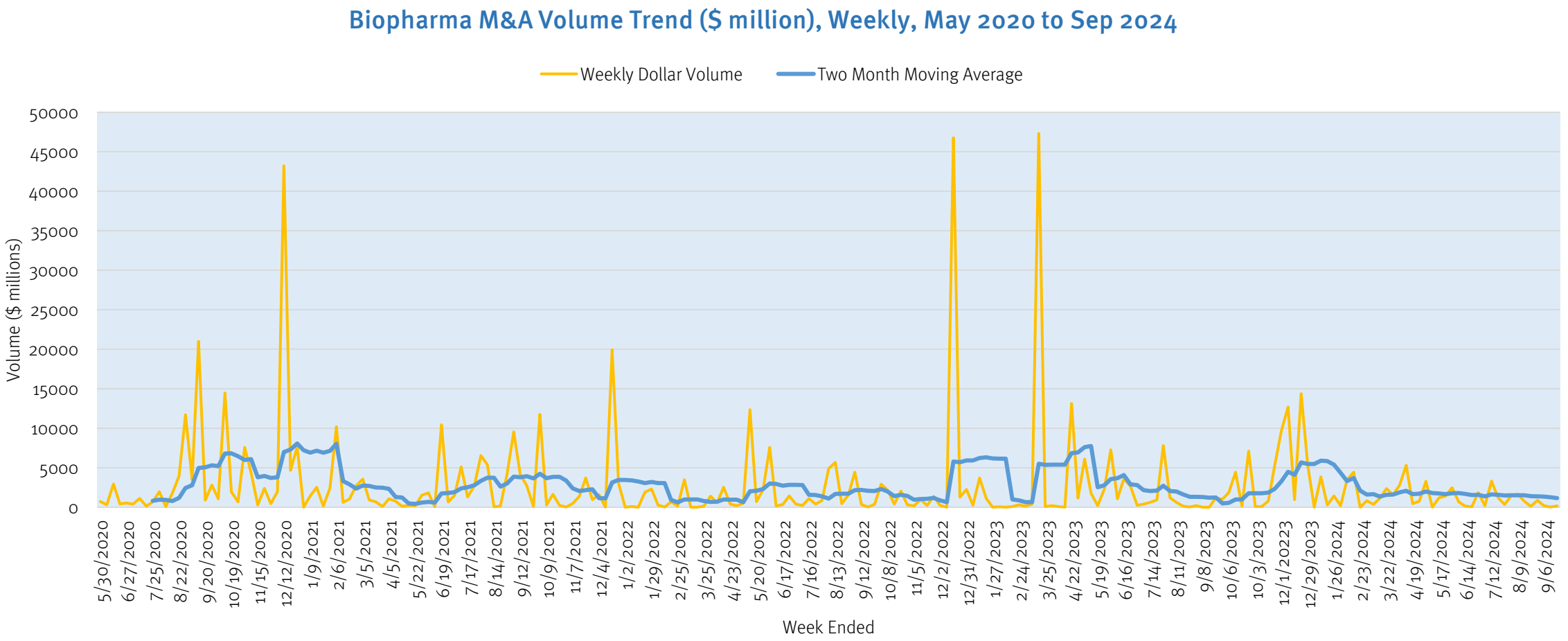
Source: Data from CapitalIQ, Stifel research.

Deal News



Last Week Saw No Meaningful Biopharma M&A Volume

M&A volume has been very muted in September. Last week saw Philip Morris sell its Vectura subsidiary to Molex Asia for $198 million upfront. Also, Organon entered into an agreement to buy Dermavant for $175 million upfront and a package of milestones (approval and commercial).



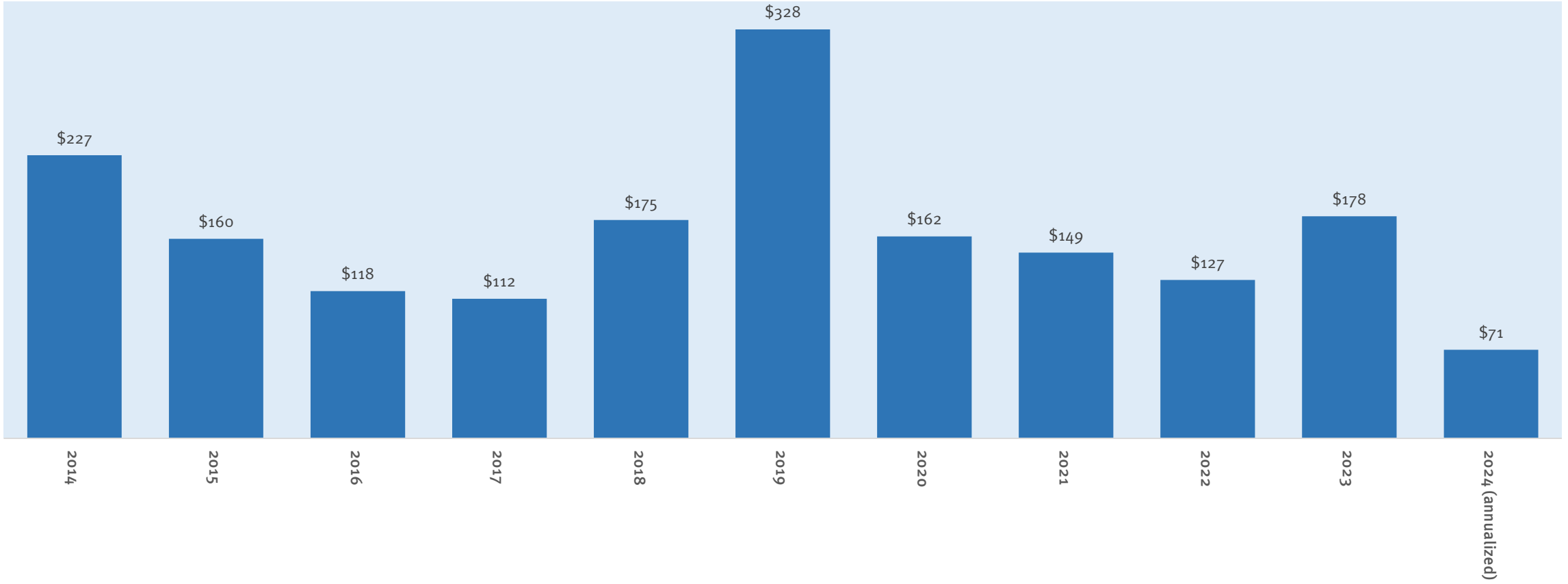
Source: S&P CapitalIQ

We are Tracking to a Very Slow Year in Biopharma M&A Volume

M&A volume has been slow throughout 2024. We are not only on track for record low volume since 2014 but appear on track to break that dubious record by a wide margin. We expect this to change in the post-election environment of 2025.

M&A Volume in the Biopharma Sector, 2014 - 2024 (annualized)

($ Billions, Worldwide, Counts Upfront Payments)



Source: Data from CapitalIQ, Stifel research.

Marlboro Maker Sells Asthma Inhaler Group at Discount After Health Backlash

Eri Sugiura, *Financial Times*, Sep 17, 2024 (excerpt)

Philip Morris International has agreed to sell its Vectura asthma inhaler maker for only a third of what it paid, after PMI's tobacco interests prompted pharmaceutical clients to shun the healthcare biotech.

PMI announced on Tuesday that Vectura, a UK-based pharmaceutical outsourcer specialising in making asthma inhalers and medicines, had been sold to Molex for up to £298mn. Molex's pharmaceutical unit Phillips Medisize would operate Vectura, it added.

The deal comes just three years after PMI, maker of Marlboro cigarettes, paid £915mn enterprise value, including net debt, to buy the UK-based contract manufacturer, as part of an attempted pivot away from tobacco. PMI is set to receive an initial £150mn and then up to £148mn more, depending on Vectura's achieving certain performance targets. As a result, at most PMI will recoup only a third of its original acquisition cost."

Despite the investment and commitment to developing products and therapies vital to patients, unwarranted opposition to PMI's transformation has impacted Vectura's scientific engagement," PMI said.

Vectura, which also develops products for smoking-related conditions, had faced strong backlash from doctors and other public health professionals following PMI's takeover.

The European Respiratory Society also said it was "very alarmed" by the deal, criticising PMI for obscuring its image as a company that profited from "getting people addicted to its dangerous products".

Source: https://www.ft.com/content/b4890310-7ad7-42fd-9dea-9a562ed4f6f3

M&A: Creating An AI-first Drug Discovery Engine

Asher Mullard, *Nature Reviews Drug Discovery*, Sep 13, 2024 (excerpt)

When Recursion launched in 2013, the fledgling biotech's goal was to turn machine vision loose on images of cells, at scale, to better understand the biology of disease. Exscientia, founded the year before, set out by contrast to code algorithms that would enable medicinal chemists to better explore chemical space. Over the past decade, both firms have leaned into expectations that these and related computational approaches will make drug discovery better, faster and cheaper. The two companies now want to become one, betting that an AI-first, 'full-stack' small-molecule discovery engine can deliver the drug discovery goods.

Najat Khan, Chief R&D Officer and Chief Commercial Officer at Recursion, sees an opportunity. Khan — a chemist by training, and then a consultant with Boston Consulting Group — spent the past 6 years at Johnson & Johnson overseeing the pharmaceutical behemoth's data science efforts and its R&D strategy and portfolio organization. She joined Recursion in July, just weeks before the proposed deal was announced. And with ten candidates in the firm's pipeline in or about to enter the clinic, if the merger goes through, Khan looks forward to building out Recursion's drug development infrastructure to make it an end-to-end AI-first enterprise.

When did you learn that the Exscientia deal was on the table, and why did it appeal?

Najat Khan: The teams worked really hard to get the deal done in the month or so before it was announced. And I think it's a complementary match for both companies.

We have to prioritize and focus on the areas that offer the biggest opportunity to change our probability of success. Recursion's origins were in decoding biology — really understanding it at a much more granular and interconnected level, and creating digital maps of biology. Recursion has been looking for first-in-class molecules. Exscientia was really more focused on chemistry and best-in-class molecules. This potential combination gives us the convergence of these two approaches, which is excellence in biology and excellence in chemistry, to get to both first-in-class and best-in-class programmes. Lead optimization, especially, is one of the biggest challenges in small-molecule design, and of course predicting toxicity and so forth takes a lot of work. So having precision chemistry, leveraging active learning, and using automated approaches to do this at scale, that's what Exscientia potentially brings to the table.

Najat Khan
Chief R&D Officer and CCO, Recursion

Source: https://www.nature.com/articles/d41573-024-00149-6

Oncology BD&L: Winning in an Increasingly Competitive Environment

Anne Dhulesia, Sean Dyson and Guy Stephens, LEK Report, September 12, 2024

1. Oncology leads biopharma business development and licensing (BD&L), accounting for about 50% of global deal volume. Growing oncology pipelines provide a rich set of BD&L targets, with emerging biopharma now accounting for 60% of all oncology trials.

2. Since 2020, large pharmas have shifted to later-stage dealmaking to secure near-term, de-risked revenues in response to upcoming patent cliffs and the impact of the US Inflation Reduction Act.

3. BD&L is crucial for accessing innovation, with antibody drug conjugates (ADCs) and multispecifics now representing 35% of early-stage transactions, up from 11% in 2019. BD&L is often more viable than in-house origination of these modalities.

4. China has become a significant source of oncology innovation, contributing around 30% of all oncology licensing deals in 2023 as its R&D increasingly focuses on novel mechanisms.

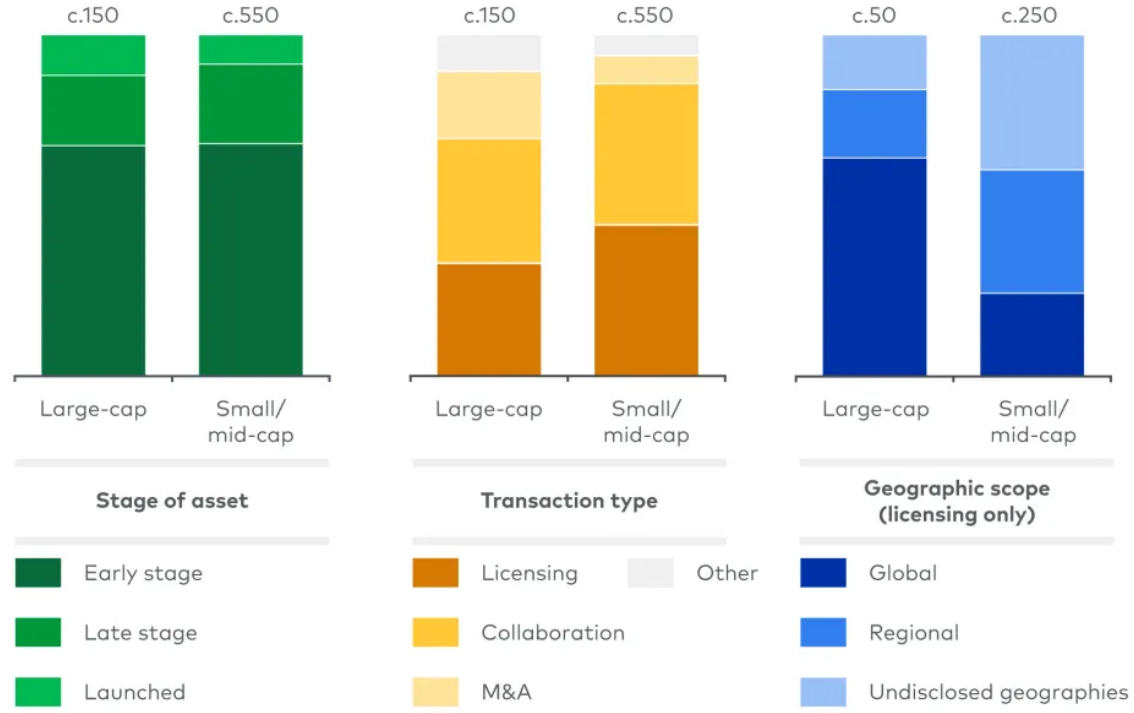
Trends in deal volume/value (2019-23)

Notes: *Total deal value at signing, excludes deals with undisclosed values
Source: L.E.K. research and analysis of Cortellis, company investor materials and press releases

Source: https://www.lek.com/insights/hea/global/ei/oncology-bdl-winning-increasingly-competitive-environment

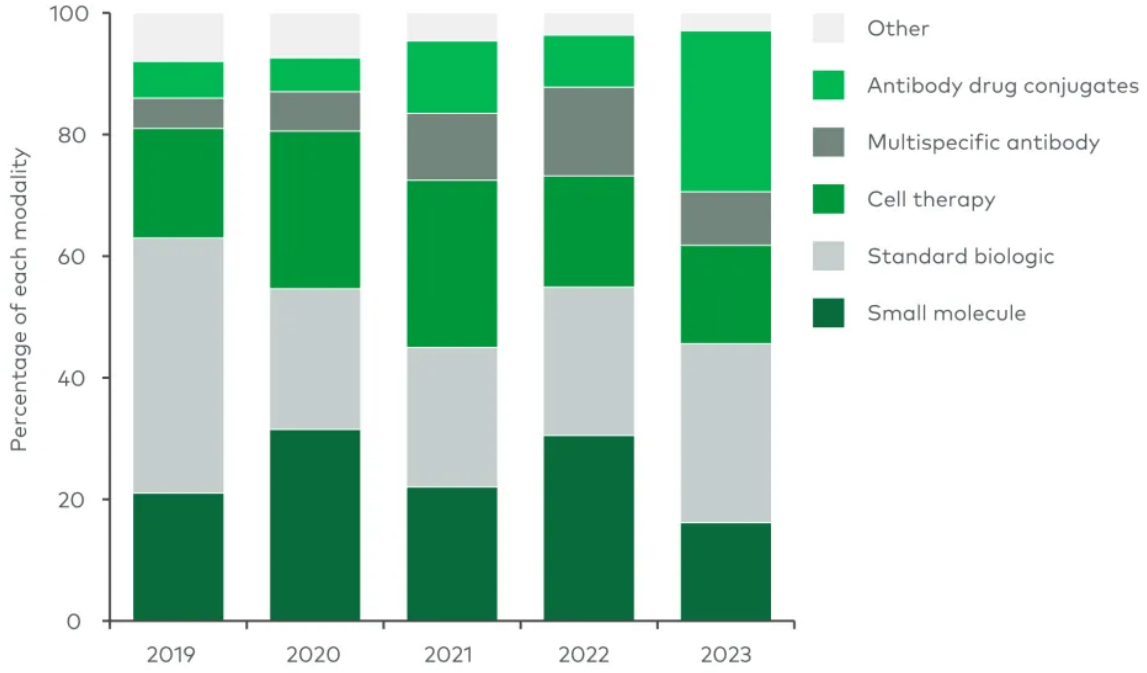
LEK Oncology BD&L Report: Key Charts & Conclusion

Oncology BD&L transactions, by company size (2019-23)



Source: L.E.K. research and analysis of Cortellis, company investor materials and press releases

Early-stage BD&L deals, by type of modality (2019-23)



Source: L.E.K. research and analysis of Cortellis, company investor materials and press releases

The oncology transaction landscape is becoming increasingly competitive, characterised by fewer but more expensive deals commanding higher premiums. Innovation sources are evolving, increasingly coming from novel modalities and geographies. Successful execution in this rapidly evolving environment requires well-structured scouting and screening processes. Teams wishing to transact in oncology must consistently monitor the landscape and upcoming events of companies of interest. They should be ready to move quickly after key readouts to appraise the asset and approach the company with an up-to-date, attractive offer. Success in this context demands that all biopharmas adopt robust, well-structured diligence processes to ensure they can offer their most competitive, yet still affordable, deal terms. For small/mid-cap pharmas that cannot compete with the deep pockets of large pharmas for global deals, strategic focus is crucial. This requires careful determination of specific assets, deal types and geographical areas where they can offer competitive terms. This may involve focusing on specific tumour types or call points for licensing deals in select geographies.

Source: https://www.lek.com/insights/hea/global/ei/oncology-bdl-winning-increasingly-competitive-environment

Andrew Pannu Comments on Single-Asset Driven M&A Deals

X Post, Sep 18, 2024

Grading Notable Biopharma Single-Asset Driven M&A Deals, 2016 - 2019[1]

Key Asset	TA	Acquirer	Target	Deal Size ($M)	Est. Peak Sales ($M)	Current Sales (FY23, $M)	Phase at Deal	Date	Deal Rationale	Deal Outcome	Grade
ARQ 531 (nemtabrutinib)	Oncology	MERCK	ARQULE	$2,700	>$2,000	Not Approved	Phase 1	December 2019	BTK inhibitors were hot given potential in patients refractory to Imbruvica - Lilly (Loxo) had just shown solid early data	Recorded >$2B in asset impairment charges due to extended R&D timeline; fell behind Lilly (already approved)	C-
Leqvio (inclisiran)	CV / Metabolic	NOVARTIS	The Medicines Company	$7,446	>$2,000	$355	Phase 3	November 2019	Synergies with Novartis' CV infrastructure (i.e. Entresto); massive market with differentiated dosing profile (2x a year)	Slow launch; EU blocked until CV outcomes data from ORION-4 comes; US "buy and bill" model facing resistance amongst CV docs	C
Otezla (apremilast)	Immunology	AMGEN	Celgene	$13,400	$2,500	$2,188	Marketed	August 2019	Growth potential into new indications / markets + complementary to existing portfolio	Solid product, but hasn't met ambitious growth targets that justified big takeout price	B-
Xiidra (lifitegrast)	Ophthalmology	NOVARTIS	Takeda	$5,300	$1,000	2022: $487	Marketed	July 2019	In-line with Novartis' increased focus on ophthalmology, following transfer of Alcon's ophthalmic products to its Pharma division	Overpaid; Growth slowing; Sold the asset to Bausch + Lomb in July 2023 for $1.75B upfront + $750M in sales milestones	D
Welireg (belzutifan)	Oncology	MERCK	Peloton Therapeutics	$2,333	$386	$218	Phase 2	May 2019	Solidify position in 1L RCC with potential to own a leading combo (with Keytruda); comparable efficacy and superior safety vs. other TKIs	Launched in US in 2021 (under review in EU) and expanded label via LITESPARK-005 trial; grew 77% in 2023	A-
Cablivi (caplacizumab)	Hematology	SANOFI	Ablynx	$4,800	$500	~$250	Registration	June 2018	Fits Sanofi's strategy of de-risked, bolt-on deals in rare disease (i.e. Bioverativ deal)	Sanofi has haircut peak sales closer to $400M; overall commercially the asset has struggled	C
Zolgensma (onasemnogene abeparvovec)	Rare Disease	NOVARTIS	AveXis	$8,700	$1,500 - $2,000	$1,214	Pivotal	April 2018	Strong data in emerging modality (gene therapy) with pathway to approval in ~1 year	Overpaid; solid product with good long-term data; space is competitive and sales have started to slow	B
Eucrisa (crisaborole)	Immunology	Pfizer	ANACOR	$5,200	$2,000	Undisclosed, just $138 in 2019	Registration	May 2016	Synergies with existing commercial infrastructure and end markets (primary care / pediatric)	Has gotten crushed by Dupixent; Pfizer never cracked the dermatology space & reimbursement was a constant challenge	D-
Rova-T	Oncology	abbvie	Stemcentrx	$9,800	$5,800	Discontinued	Pivotal	April 2016	Foothold into ADC space with a promising asset + platform that could churn out several more	Rova-T failed in clinical trials (data began underwhelming right after the deal closed)	F
Calquence (acalabrutinib)	Hematology	AstraZeneca	Acerta Pharma	$4,000	$5,000	$2,514	Phase 2/3	February 2016	Skate towards where SoC was trending and potentially own 2/3 of a combo, with a BTK and PD-L1	Strong market share in lymphoma with some follow-on clinical wins; growing >20% YoY, ahead of est. Anchor combo product in onc	A

Andrew Pannu @andrewpannu

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(1) As of 9/17/2024, **non-exhaustive**, includes single-asset driven M&A deals with >$1B deal values

Andrew Pannu Comments:

1. BD is tough. Not only do you have to manage clinical risk, but even if the asset works well, you could get steamrolled by a slightly better positioned competitor or be unable to secure favorable reimbursement. Suddenly an asset that years / hundreds of millions of $ were invested into could be DOA

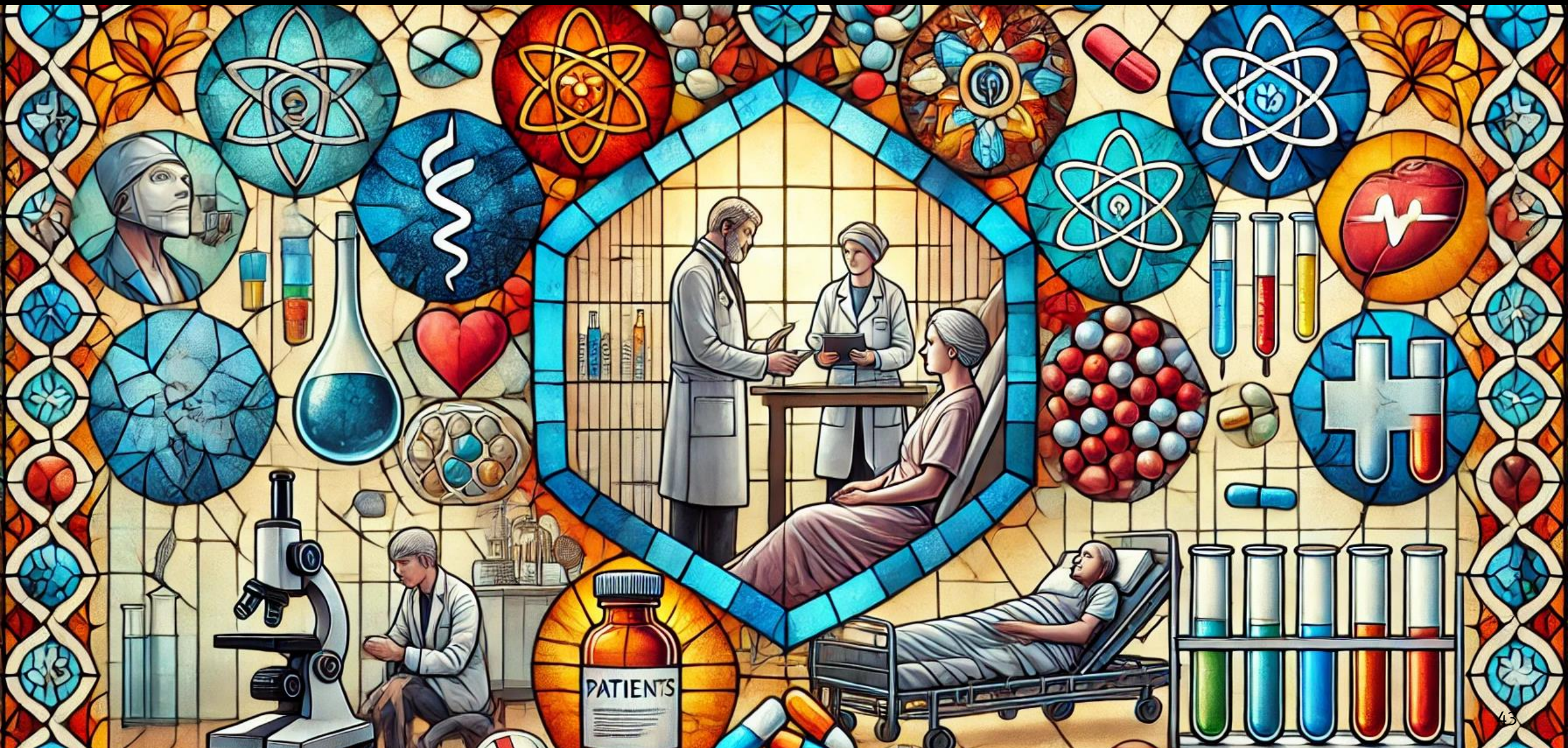
2. Launches are critical to get right. It's rare to see a floundering asset have a sudden revival. There's some practical reasons for this (i.e. the company diverts S&M resources elsewhere), but first impressions are really hard to break with many physicians and KOLs

3. Operating in a "zone of competency" seems to generate higher success rates. This can be explained by not having to build the commercial infrastructure to support an asset on the fly - you already have relationships with the right prescribers / KOLs and might have leverage through other assets in the portfolio for reimbursement discussions (see: AbbVie in I&I with Humira --› Skyrizi & Rinvoq). It's tough for a company to thrive in an entirely new space unless the asset is a gamechanger

4. Competitive intelligence is critical. It's baseline to know all the other assets out there, the nuanced design decisions they made, how they differ vs. yours and so forth. Simulating commercial / clinical outcomes at scale and layering that into your view of the world is also valuable

Source: https://x.com/andrewpannu/status/1836397919542640719/photo/1

Industry News



The Drug Lobby's Lawsuit Against the IRA Finds a Sign of Life After Appeals Court Ruling

Zachary Brennan, *Endpoints News*, Sep 20, 2024 (excerpt)

The US Court of Appeals for the Fifth Circuit is reviving PhRMA's legal attack on Medicare drug price negotiations.

On Friday, the appeals court reversed a lower court's ruling from earlier this year that had dismissed PhRMA's lawsuit before it even took shape. Back in June 2023, PhRMA, the National Infusion Center Association and the Global Colon Cancer Association sued CMS over its new drug price negotiation program, claiming the penalties were unconstitutional, among other issues. In February, however, the west Texas federal district court threw out the case, saying NICA lacked standing and that the court was an improper venue.

Now the Fifth Circuit is saying NICA does have standing, and that the district court has the appropriate subject-matter jurisdiction over NICA's claims, according to the opinion.

Part of the argument that had to be overturned has to do with claims arising under the Medicare Act, which must be "channeled" through the relevant agency (i.e. HHS) before they can be challenged in federal court. The district court said PhRMA needed to take this channeling route. But the Fifth Circuit ruled that NICA didn't need to, partly because it's challenging a provision of the Inflation Reduction Act, not the Medicare Act.

Circuit Judge Irma Carrillo Ramirez, who wrote an opinion concurring in part and dissenting in part, countered that "even if NICA had standing, its claims cannot be disentangled from the Medicare Act. For providers, the IRA has no significance outside of Medicare reimbursements. The Medicare Act therefore provides both the standing and the substantive basis for NICA's due process claim, and because it arises under the Medicare Act, it must be channeled through HHS."

NICA NATIONAL INFUSION CENTER ASSOCIATION

versus

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA ·

Source: https://endpts.com/the-drug-lobbys-lawsuit-against-the-ira-finds-a-sign-of-life-after-appeals-court-ruling/

Appeals Court Ruling

Before ELROD, DUNCAN, and RAMIREZ, *Circuit Judges*.

JENNIFER WALKER ELROD, *Circuit Judge*:

The Inflation Reduction Act directs the Department of Health and Human Services to establish a Drug Price Negotiation Program that shifts the price-setting mechanism for many of America's highest-selling drugs from the free market to a government-run process. The program requires HHS to select "negotiation-eligible drugs," and then negotiate a "maximum fair price" with the manufacturers of those drugs. HHS is statutorily required to offer a price between 40% and 75% of the existing market price. Manufacturers who fail to reach an agreement with HHS are subject to escalating fines ranging from 187.5% to 1,900% of the drug's price that can only be suspended if the manufacturer terminates Medicare coverage for all drugs that it produces.

National Infusion Center Association, whose members provide infusion treatments for cancer and chronic diseases, filed this lawsuit challenging the constitutionality of the Drug Pricing Program.

NICA claims that the Program violates its members' due process rights, contains an unconstitutional delegation of legislative power to HHS, and coerces compliance using excessive fines. The district court dismissed NICA's lawsuit for lack of subject-matter jurisdiction, reasoning that 42 U.S.C. § 405 required NICA to "channel" its constitutional claims through HHS. Channeling means having one's claims decided by the relevant agency before bringing them in federal court. Because NICA has standing to challenge the Drug Pricing Program and because NICA's claims arise under the IRA, not the Medicare Act, and therefore need not be channeled, we REVERSE.

(concluding that a claim challenging the Secretary's alleged failure to comply with the rulemaking requirements of the APA in issuing instructions and a rule were "inextricably intertwined" with a party's claims for Medicare benefits). NICA's claims arise at least in part under the Medicare Act because it provides the standing and substantive basis of it claims, and that's enough to require channeling.[11]

* * *

NICA does not have standing to bring its due process claim because it has not established the existence of an imminent injury in fact. I concur with the majority's holding that NICA lacks standing to bring its nondelegation and excessive fines claims. Even if NICA had standing, its claims cannot be disentangled from the Medicare Act. For providers, the IRA has no significance outside of Medicare reimbursements. The Medicare Act therefore provides both the standing and the substantive basis for NICA's due process claim, and because it arises under the Medicare Act, it must be channeled through HHS. I respectfully dissent.

Source: https://litigationtracker.law.georgetown.edu/litigation/national-infusion-center-association-et-al-v-becerra-et-al-2/

As Biosecure Bill Advances, Drugmakers Prepare for Prospect of China Pivot

Amy Baxter, *Biopharma Dive*, Sep 16, 2024 (excerpt)

Some of the most widely used drug contractors are based in China. But the U.S. biopharmaceutical industry may eventually be pushed to cut ties with those partners if the Biosecure Act, which passed in the House of Representatives last week, becomes law.

The act would effectively prohibit U.S. companies from doing business with five Chinese firms, including WuXi AppTec, Complete Genomics and MGI Tech. In the House's version, companies with existing contracts are given eight years to sever ties. The bill also allows Congress to add more companies to its list as it weighs perceived connections between the Chinese government and U.S. drug industry, as well as cybersecurity and intellectual property concerns.

Still, the path forward for the bill isn't entirely secure. There were more "no" votes than in expected in the House's 306-81 passage, which could suggest a tougher path in the Senate.

"It did not pass as overwhelmingly as it had passed out of committee," said Nielsen Hobbs, an analyst with Citeline. "It's both an indication of some softness of support, as well as an invitation for folks [who] want to make modifications to try and do so."

It's unclear if the Senate plans to vote on the bill or if there's enough time left in the year for the legislation to make its way into law. A lame duck Congress is less likely to push through substantive bills after the U.S. elections in November, too.

"This is probably not going to pass before the election," Hobbs predicted.

Even with a murky future, U.S. biotechs are preparing for a potential disentanglement from some of their largest Chinese contractors.

Source: https://www.biopharmadive.com/news/drug-industry-china-biosecure-act-wuxi-cdmo-cro/727108/

FTC Sues Drug Middlemen for Allegedly Inflating Insulin Prices

Annika Kim Constantino, *CNBC*, Sep 20, 2024 (excerpt)

The Federal Trade Commission on Friday sued three large U.S. health companies that negotiate insulin prices, arguing the drug middlemen use practices that boost their profits while "artificially" inflating costs for patients.

The suit targets the three biggest so-called pharmacy benefit managers, UnitedHealth Group's Optum Rx, CVS Health's Caremark and Cigna's Express Scripts. All are owned by or connected to health insurers and collectively administer about 80% of the nation's prescriptions, according to the FTC. The FTC's lawsuit also includes each PBM's affiliated group purchasing organization, which brokers drug purchases for hospitals and other health-care providers. The agency said it could recommend suing drugmakers Eli Lilly, Sanofi and Novo Nordisk in the future as well over their role in driving up list prices for their insulin products.

A UnitedHealth spokesperson said the suit "demonstrates a profound misunderstanding of how drug pricing works, noting that Optum RX has "aggressively and successfully" negotiated with drug manufacturers. A CVS spokesperson said Caremark is "proud of the work" it has done to make insulin more affordable for Americans, adding that "to suggest anything else, as the FTC did today, is simply wrong."

And, a spokesperson for Express Scripts said the suit "continues a troubling pattern from the FTC of unsubstantiated and ideologically-driven attacks" on PBMs. It comes three days after Express Scripts sued the FTC, demanding that the agency retract its allegedly "defamatory" July report that claimed that the PBM industry is hiking drug prices.

PBMs sit at the center of the drug supply chain in the U.S. They negotiate rebates with drug manufacturers on behalf of insurers, large employers and federal health plans. They also create lists of medications, or formularies, that are covered by insurance and reimburse pharmacies for prescriptions. The FTC has been investigating PBMs since 2022.

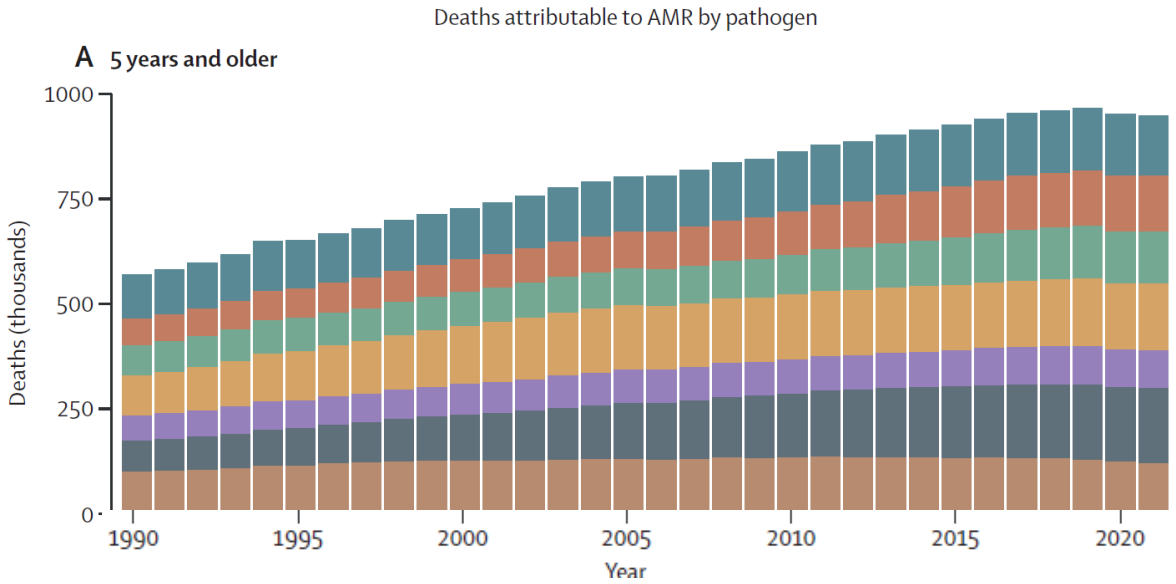
Source: https://www.cnbc.com/2024/09/20/ftc-sues-drug-middlemen-for-allegedly-inflating-insulin-prices.html

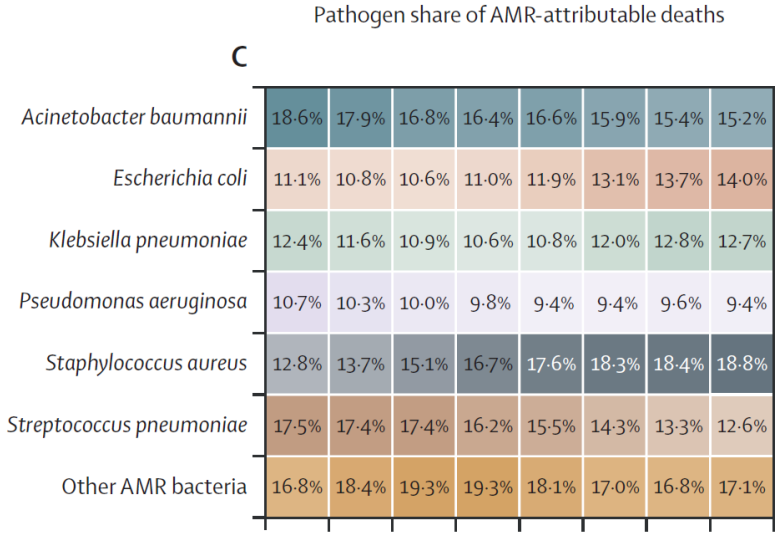
Global burden of bacterial antimicrobial resistance 1990–2021: a systematic analysis with forecasts to 2050

*GBD 2021 Antimicrobial Resistance Collaborators** Lancet, Sep 16, 2024

Summary

Background Antimicrobial resistance (AMR) poses an important global health challenge in the 21st century. A previous study has quantified the global and regional burden of AMR for 2019, followed with additional publications that provided more detailed estimates for several WHO regions by country. To date, there have been no studies that produce comprehensive estimates of AMR burden across locations that encompass historical trends and future forecasts.





Source: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(24)01867-1/

AMR Deaths Headed in One Direction: Up

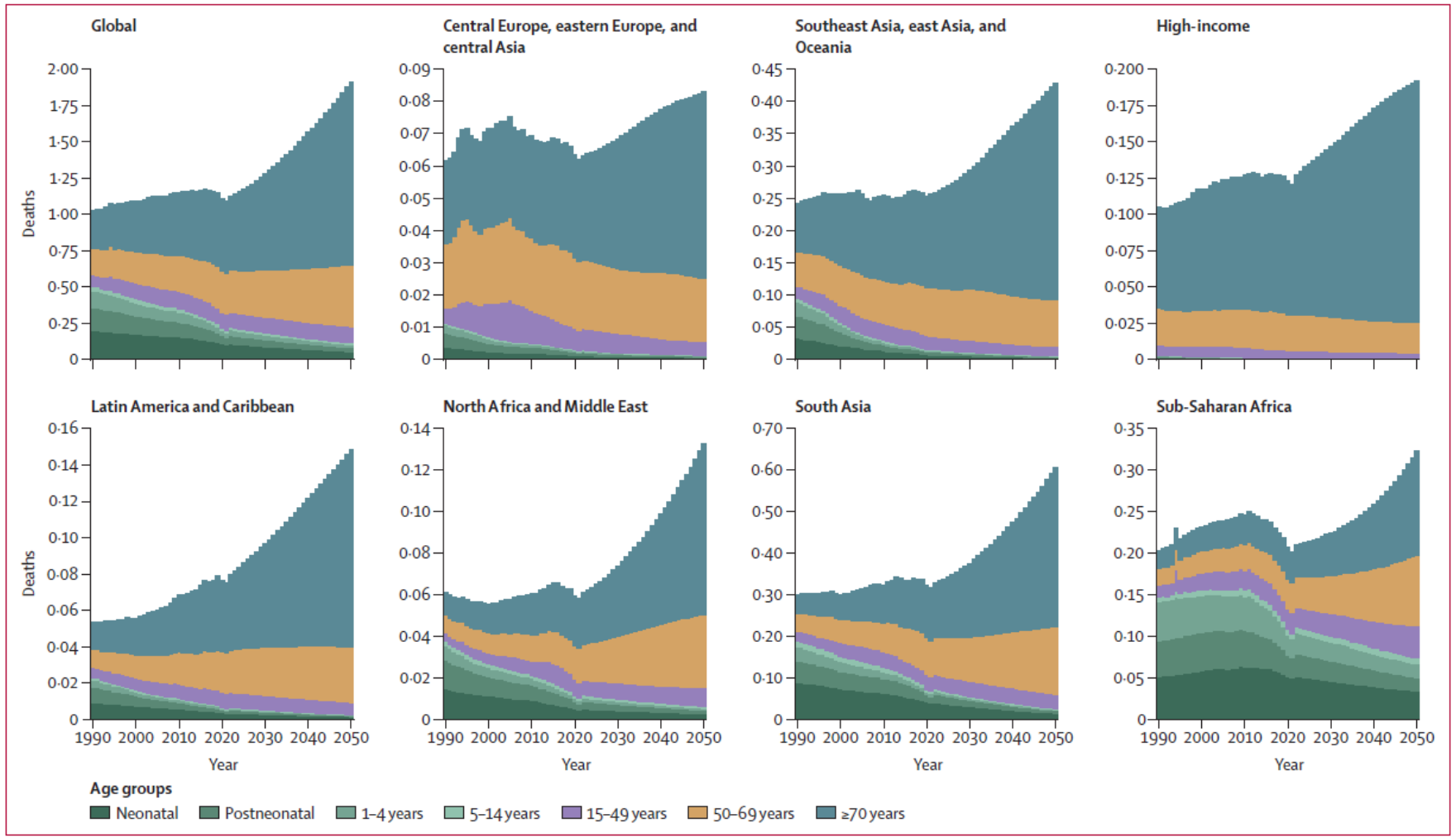


Figure 7: **Deaths attributable to AMR by age group and location in the reference scenario, 2022–2050 Units are in millions.**

Source: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(24)01867-1/

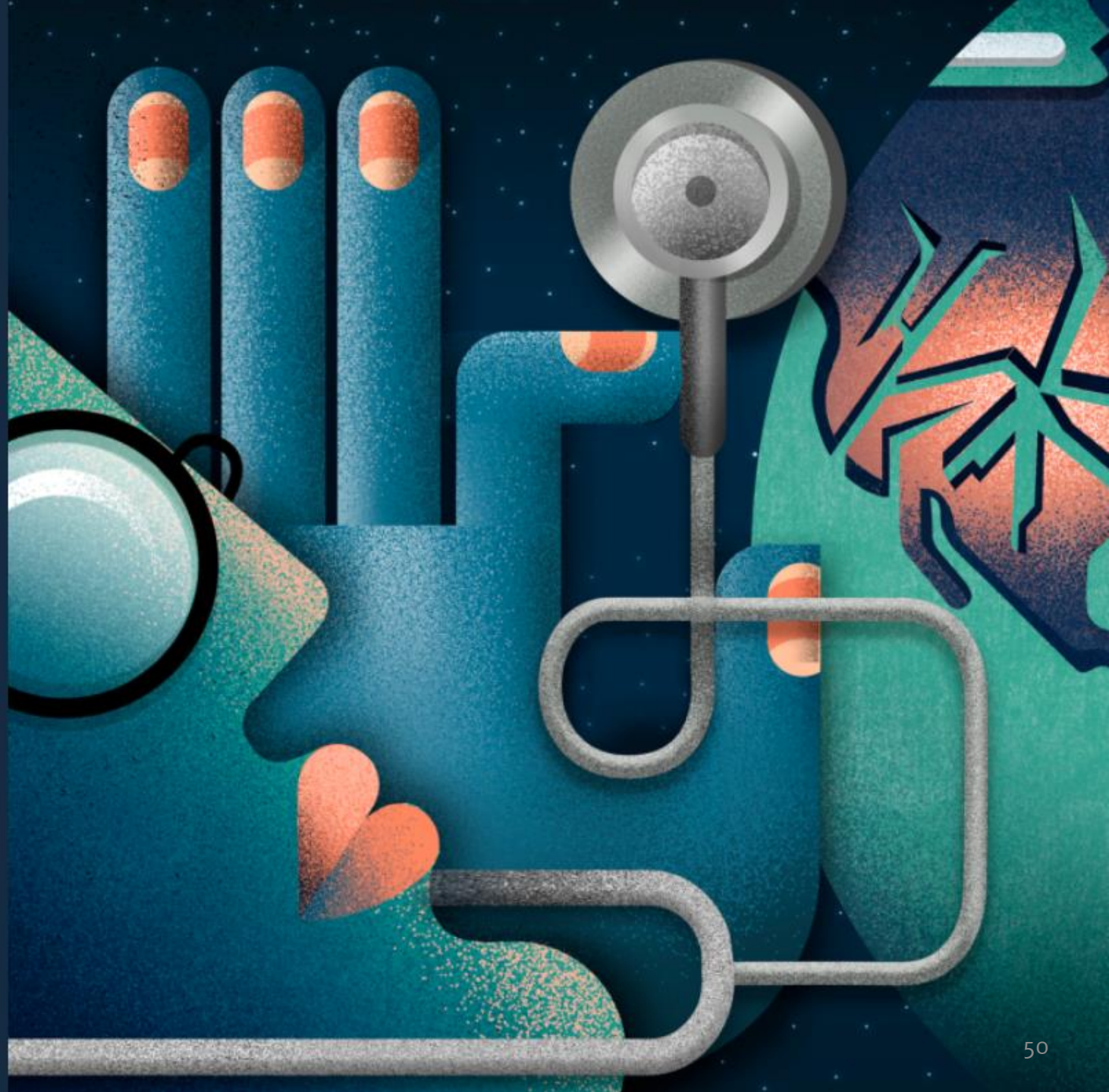
FUND REPORTS
SEPTEMBER 19, 2024

Source: https://www.commonwealthfund.org/publications/fund-reports/2024/sep/mirror-mirror-2024

The Commonwealth Fund

Mirror, Mirror 2024: A Portrait of the Failing U.S. Health System

Comparing Performance in 10 Nations



Commonwealth Fund Finds U.S. in Last Place of Major Countries in Healthcare Quality

Commonwealth Fund Report, *September 19, 2024* (excerpt)

Mirror, Mirror 2024 is the Commonwealth Fund's eighth report comparing the performance of health systems in selected countries. Since the first edition in 2004, our goal has remained the same: to highlight lessons from the experiences of these nations, with special attention to how they might inform health system improvement in the United States.

While each country's health system is unique — evolving over decades, sometimes centuries, in tandem with shifts in political culture, history, and resources — comparisons can offer rich insights to inform policy thinking. Perhaps above all, they can demonstrate the profound impact of national policy choices on a country's health and well-being.

In this edition of Mirror, Mirror, we compare the health systems of 10 countries: Australia, Canada, France, Germany, the Netherlands, New Zealand, Sweden, Switzerland, the United Kingdom, and the United States. We examine five key domains of health system performance: access to care, care process, administrative efficiency, equity, and health outcomes.

Despite their overall rankings, all the countries have strengths and weaknesses, ranking high on some dimensions and lower on others. No country is at the top or bottom on all areas of performance. Even the top-ranked country — Australia — does less well, for example, on measures of access to care and care process. And even the U.S., with the lowest-ranked health system, ranks second in the care process domain.

Nevertheless, in the aggregate, the nine nations we examined are more alike than different with respect to their higher and lower performance in various domains. But there is one glaring exception — the U.S.

Especially concerning is the U.S. record on health outcomes, particularly in relation to how much the U.S. spends on health care. The ability to keep people healthy is a critical indicator of a nation's capacity to achieve equitable growth. In fulfilling this fundamental obligation, the U.S. continues to fail.

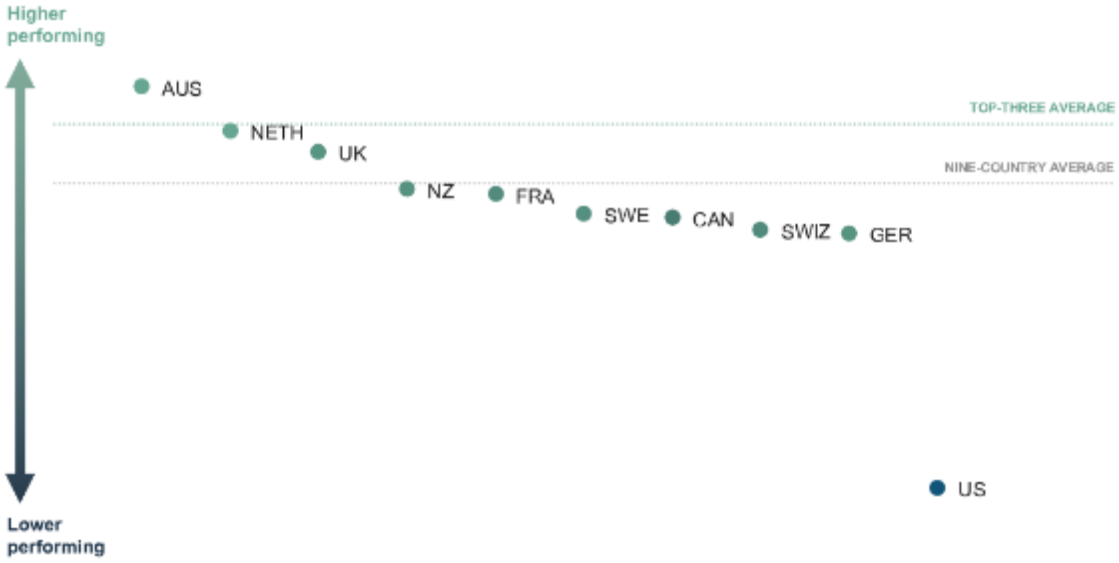
"The top three countries are Australia, the Netherlands, and the United Kingdom, although differences in overall performance between most countries are relatively small. The only clear outlier is the U.S., where health system performance is dramatically lower. The U.S. continues to be in a class by itself in the underperformance of its health care sector."

Source: https://www.commonwealthfund.org/publications/fund-reports/2024/sep/mirror-mirror-2024

Commonwealth Fund Study Charts

EXHIBIT 2 — *Overall Performance Ranking*

The United States lags its international peers considerably on health system performance.



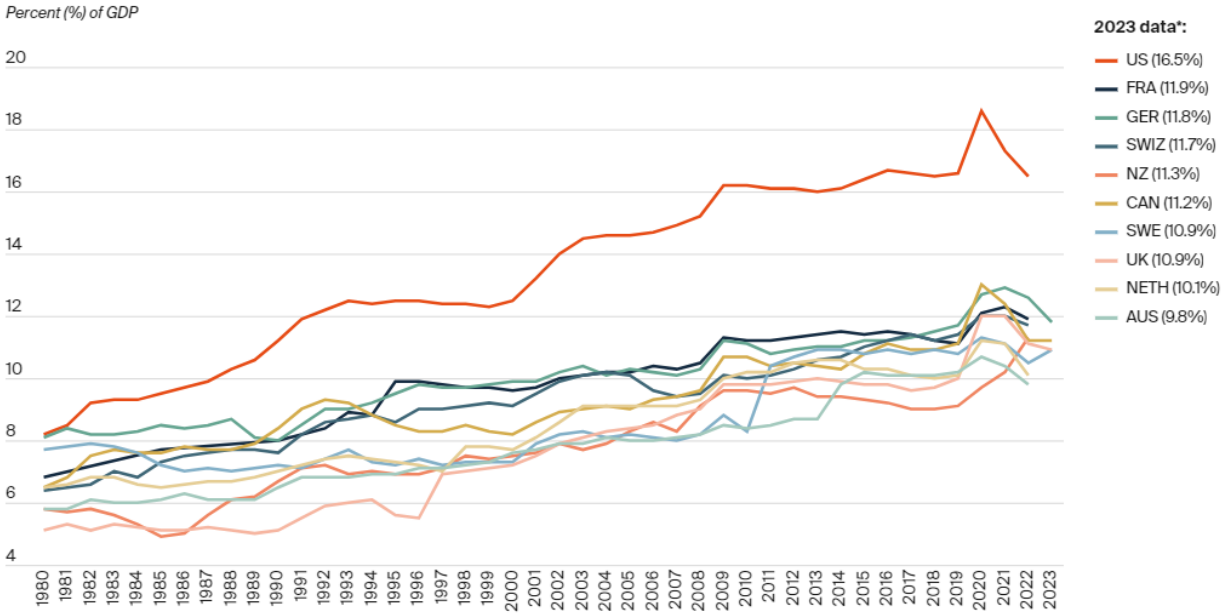
Note: To normalize performance scores across countries, each score is the calculated standard deviation from a nine-country average that excludes the US. See "How We Conducted This Study" for more detail.

Data: Commonwealth Fund analysis.

Source: David Blumenthal et al., *Mirror, Mirror 2024: A Portrait of the Failing U.S. Health System — Comparing Performance in 10 Nations* (Commonwealth Fund, Sept. 2024). https://doi.org/10.26099/ta0g-zp66

EXHIBIT 3 — *Health Care Spending*

Health Care Spending as a Percentage of GDP, 1980–2023



Notes: GDP = gross domestic product. Current expenditures on health. Based on System of Health Accounts methodology, with some differences between country methodologies.
* Data for CAN, GER, SWE, and the UK from 2023; data for AUS, FRA, NETH, NZ, SWIZ, and the US from 2022.

Data: OECD Health Data, July 2024.

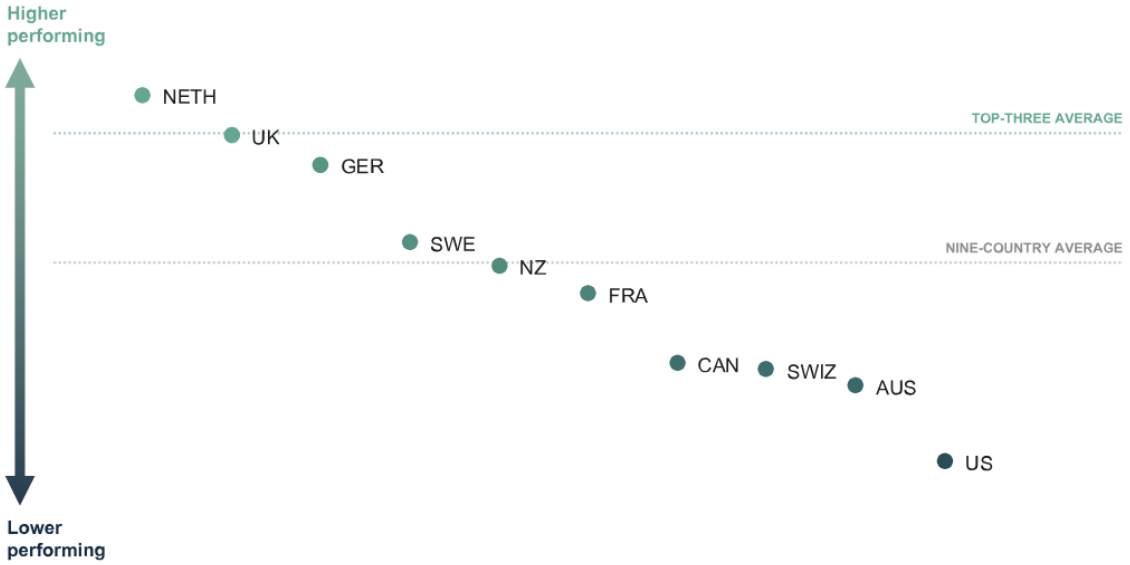
Source: David Blumenthal et al., *Mirror, Mirror 2024: A Portrait of the Failing U.S. Health System — Comparing Performance in 10 Nations* (Commonwealth Fund, Sept. 2024). https://doi.org/10.26099/ta0g-zp66

Source: https://www.commonwealthfund.org/publications/fund-reports/2024/sep/mirror-mirror-2024

Commonwealth Fund Study Charts (Continued)

EXHIBIT 5 — *Access to Care*

Americans face the most barriers to accessing and affording health care.



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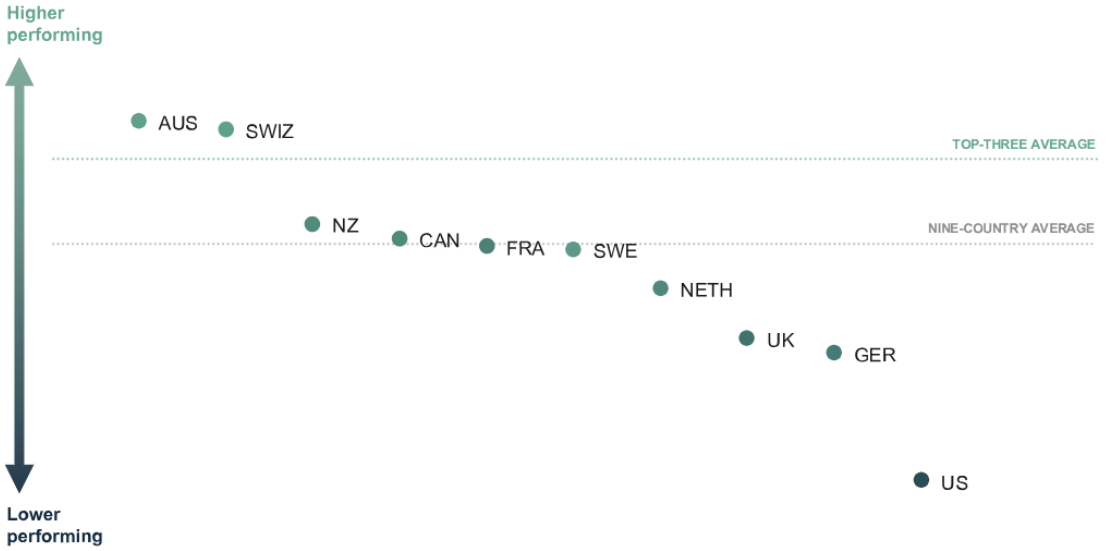
Data: Commonwealth Fund analysis.

Source: David Blumenthal et al., *Mirror, Mirror 2024: A Portrait of the Failing U.S. Health System — Comparing Performance in 10 Nations* (Commonwealth Fund, Sept. 2024). https://doi.org/10.26099/ta0g-zp66

EXHIBIT 9 — *Health Outcomes*

Americans live the shortest lives and have the most avoidable deaths.



Note: To normalize performance scores across countries, each score is the calculated standard deviation from a nine-country average that excludes the US. See "How We Conducted This Study" for more detail.

Data: Commonwealth Fund analysis.

Source: David Blumenthal et al., *Mirror, Mirror 2024: A Portrait of the Failing U.S. Health System — Comparing Performance in 10 Nations* (Commonwealth Fund, Sept. 2024). https://doi.org/10.26099/ta0g-zp66

Source: https://www.commonwealthfund.org/publications/fund-reports/2024/sep/mirror-mirror-2024

Athena Institute Study: Pharma R&D Productivity Deteriorating

The pharmaceutical productivity gap – Incremental decline in R&D efficiency despite transient improvements

Kenneth D.S. Fernald *, **Philipp C. Förster, Eric Claassen, Linda H.M. van de Burgwal**

Vrije Universiteit Amsterdam, Athena Institute, De Boelelaan 1085, 1081 HV Amsterdam, the Netherlands

Drug Discovery Today, Oct 2024

Rising research and development costs, currently exceeding $3.5 billion per novel drug, reflect a five-decade decline in pharmaceutical R&D efficiency. While recent reports suggest a potential turnaround, this review offers a systems-level analysis to explore whether this marks a structural shift or transient reversal. We analyzed financial data from the 200 largest pharmaceutical firms, novel drug approvals, and more than 80 000 clinical trials between 2012 and 2023. Our analysis revealed that despite recent stabilization, the pharmaceutical industry continues to face challenges, particularly due to elevated late-stage clinical attrition, suggesting that a sustained turnaround in R&D efficiency remains elusive.

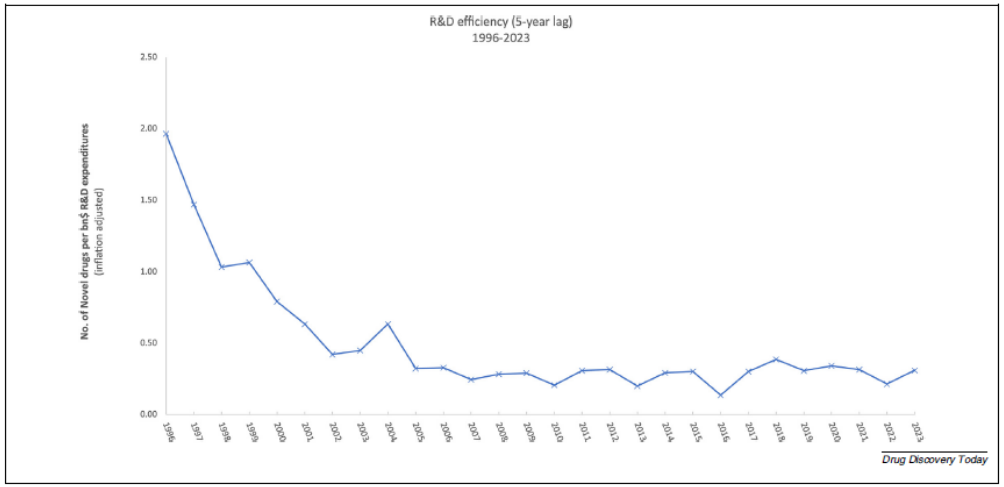


FIGURE 2
R&D efficiency, expressed as the number of novel drug introductions per $1bn of R&D expenditures 5 years prior – adjusted for inflation (in 2023 US$).

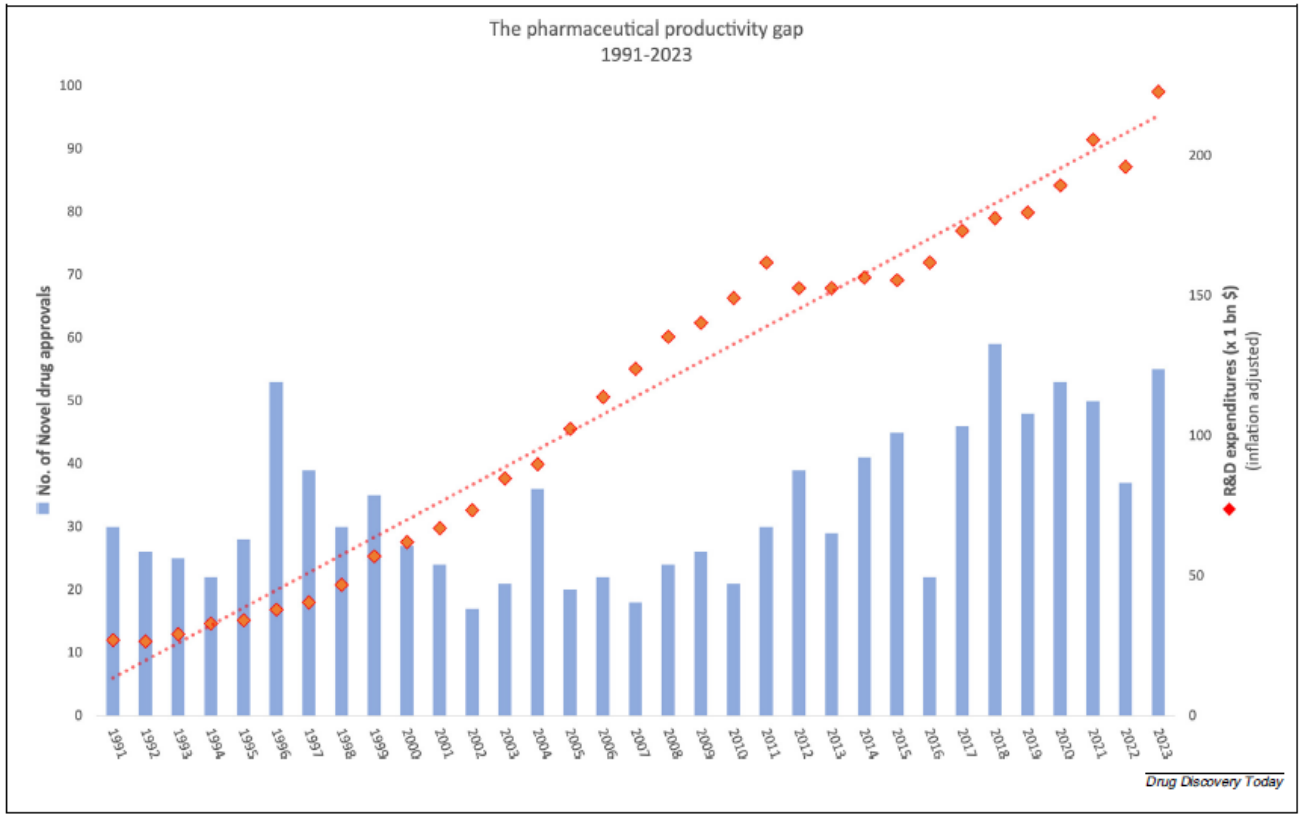


FIGURE 1
The pharmaceutical 'productivity gap', updated from Fernald *et al.*[p13] A steady rise of R&D expenditures compared to a stagnant pattern of novel drug introductions. [Data obtained from fda.gov, Market Data (Datastream) and literature.]

Source: https://www.sciencedirect.com/science/article/pii/S135964462400285X

Compounded GLP-1 Obesity Market Thriving in U.S.

Julia Ingram and Alex Clark, *CBS News*, Sep 21, 2024 (excerpt)

Prescription weight loss drugs have become so popular in the United States that suppliers have struggled to keep up. Jean Readdy, a retired teacher living in Sinking Spring, Pennsylvania, is among the one in eight Americans who have tried a GLP-1 drug for weight loss or diabetes, more commonly known by brand names like Ozempic and Wegovy. Now, she's one of a growing number of people turning to compounded drugs: reformulated versions the FDA has permitted pharmacies to distribute during an ongoing shortage of brand-name drugs.

Readdy's decision to switch from a name brand to a compounded drug came down to price and availability. Paying $1,200 a month for the name-brand drug Zepbound wasn't sustainable, and it was becoming impossible to find, she said.

Readdy turned to online communities where thousands of people shared resources and where to find the drugs in short supply. On a Reddit forum, she read about the side effects, learned about alternatives, and eventually came across a spreadsheet with dozens of telehealth providers for prescription drugs used for weight loss. After weighing the risks and calling dozens of pharmacies, she eventually found one that provided her with injectable tirzepatide, the same active ingredient found in Zepbound. Readdy now pays $399 a month for her compounded medication.

CBS News identified more than 100 companies advertising access to tirzepatide or semaglutide, both active ingredients in name-brand GLP-1 drugs that regulate insulin and suppress appetite.

LegitScript, an organization that monitors and certifies online businesses, said it saw a 94% increase in companies applying for its healthcare certification since 2023. More than half of its recent applicants had a weight-loss focus on their website.

However, compounded drugs aren't reviewed for efficacy and safety by the FDA.

"There is not a tremendous amount of oversight," said CBS News medical contributor Dr. Celine Gounder. "There is a wide range in terms of the quality and the risks.“

Readdy, who has lost more than 50 pounds, said she intends to continue using her compounded medication.

Source: https://www.cbsnews.com/news/compound-drug-market-weight-loss-ozempic-wegovy/

Lilly Suing FDA Claiming that Retatrutide is a Biologic

Steve Usdin, *Biocentury*, Sep 12, 2024 (excerpt)

Eli Lilly has filed a lawsuit seeking to force FDA to reverse its decision to classify retatrutide as a drug. Classifying the investigational anti-obesity product as a biologic could extend the duration of its exemption from Medicare drug price negotiation by four years, which could increase Lilly's revenues by billions of dollars.

The lawsuit could also provide clues about how vulnerable FDA regulatory decisions will be to legal challenges in the aftermath of the Supreme Court's recent decision *in Loper Bright Enterprises v. Raimondo* that overturned the Chevron doctrine and scrapped the deference courts have traditionally given federal agencies to interpret ambiguous laws.

Retatrutide is a 39 amino acid peptide (see https://acs.digitellinc.com/p/s/synthesis-of-retatrutide-by-native-chemical-ligation-ncl-a-once-weekly-gip-glp-1-and-glucagon-receptor-triagonist-532522).

Lilly is arguing that it should be a biologic even though the threshold for a biologic under the FDA guidance is 40 amino acids. See https://www.fda.gov/about-fda/economic-impact-analyses-fda-regulations/definition-term-biological-product-final-regulatory-impact-analysis.

Lilly's point is that the law requires the FDA to interpret the meaning of "biologic" and it should not be up to the FDA to decide how to classify a peptide.

This is based on the recent *Loper* case which led to the overturn of the Chevron doctrine.

This will be an important case to watch for both (1) the peptide market and (2) the FDA's authority to issue rulemakings interpreting current laws.

Source: https://www.biocentury.com/article/653532/lilly-asks-court-to-force-fda-to-classify-obesity-product-as-biologic

Novo Nordisk A/S: Monlunabant Phase 2a Trial in Obesity Successfully Completed

Bagsværd, Denmark, 20 September 2024 – Novo Nordisk today announced headline results from a phase 2a clinical trial with monlunabant, a small molecule oral cannabinoid receptor 1 (CB1) inverse agonist. Monlunabant, formerly INV-202, was part of the acquisition of Inversago Pharmaceuticals Inc. announced in August 2023.

The trial investigated the efficacy and safety of a once-daily 10 mg, 20 mg and 50 mg dose of monlunabant compared to placebo on body weight after 16 weeks in 243 people with obesity and metabolic syndrome1. People were equally randomised among the four treatment arms.

From a baseline body weight of 110.1 kg, all doses of monlunabant achieved a statistically significant weight loss compared to placebo. After 16 weeks of treatment, people treated with a once-daily 10 mg dose of monlunabant achieved a weight loss of 7.1 kg compared to a reduction of 0.7 kg with placebo. Limited additional weight loss was seen at higher doses of monlunabant.

In the trial, the most common adverse events were gastrointestinal, with the vast majority being mild to moderate and dose dependent. **Reporting of mild to moderate neuropsychiatric side effects, primarily anxiety, irritability, and sleep disturbances, was more frequent and dose dependent with monlunabant compared to placebo. No serious adverse events were reported in relation to neuropsychiatric side effects.**

“The phase 2a results indicate the weight-lowering potential of monlunabant and that further work is needed to determine the optimal dosing to balance safety and efficacy,” said Martin Holst Lange, executive vice president and head of Development at Novo Nordisk. “Obesity is a complex disease with a significant unmet need, and as an oral small molecule having a new mechanism of action, monlunabant is one of the novel projects in our pipeline with the potential of treating obesity.”

Based on the results, Novo Nordisk expects to initiate a larger phase 2b trial in obesity to further investigate dosing and the safety profile of monlunabant over a longer duration in a global population. The phase 2b trial is expected to be initiated in 2025.

Source: https://www.novonordisk.com/news-and-media/news-and-ir-materials/news-details.html?id=170501

Novo has said that patients could lose 15% to 20% of body weight with a CB1 agonist in a year. The 6% weight loss at 16 weeks is consistent with this prediction. Novo has also said that it will need to watch CNS side effects carefully.

The news that there were psychiatric side effects with monlunabant was not well received by the market. Novo shares dropped 5% on the news. Skye shares dropped 42% on the news and Corbus shares dropped 62%.

We appear to be missing something because the efficacy of the CB1 MOA is clearly established in this trial and previous Sanofi trials.

Further, the Skye drug is an antibody that cannot cross the BBB at all. Thus, it strikes us that, if anything, this stock should have *gone up* on the news. Perhaps investors believe that peripheral CB1 agonism causes CNS issues.

A key point is that the CB1 MOA should be additive to other classes such as GLP-1s. CB1’s don’t have to beat GLP-1’s to matter.

Metabolism and Diet are Linked to Root of Bipolar Depression, Say Researchers

Robin McKie, *The Guardian*, Sept. 21, 2024 (excerpt)

Iain Campbell, a researcher based at Edinburgh University, has a special perspective on bipolar depression. He lives with the condition and has lost family members who have taken their own lives because of their depression. It remains an intractable, devastating health problem, he says.

More than a million people in the UK have bipolar depression, of whom a third are likely to attempt suicide. Yet the condition's roots remain unknown – despite significant efforts to understand them.

However, a major new approach to the illness has recently been adopted by psychiatrists to uncover its causes and highlight possible treatments. Rather than viewing bipolar depression as a mood disorder, it should be seen as a metabolic disturbance that can be tackled through diets and other interventions that can change bodily processes.

"We should be thinking of bipolar depression, not as a primary emotional problem, but as a malfunctioning of energy regulation in the body," said Campbell, who has played a key role in setting up Edinburgh University's Hub for Metabolic Psychiatry, which opened last week. "It is a very different way of thinking about mental illness."

Backed by the Baszucki Foundation, a Canadian charity, and UK Research and Innovation, the national funding agency, the hub will investigate bipolar depression's links to metabolic disorders, such as diabetes and obesity, and will also investigate how it is affected by disruptions to circadian rhythms.

"Systems involving energy, metabolism and light are all interlinked in our bodies and one outcome to their disruption is bipolar depression, we believe," said Professor Danny Smith, head of the new Hub for Metabolic Psychiatry.

Bipolar depression was originally known as manic depression, a label that catches its progression, Smith added. "At times, people have no energy. At others, they simply have too much. They are manic. They don't need sleep. They are really active and do things that are out of character. Psychiatrists will say to them: how are you feeling? In fact, they should be asking: what are you doing?"

One approach is developing metabolic treatments that could curtail their bouts of mania and lethargic depression, said Campbell. "Ketogenic diets, in which a person eats no carbohydrates but lots of fats, are quite common. They are used to cut weight but also to treat epilepsy in some cases. However, it is now becoming clear they can help alleviate bipolar depression."

A recent study carried out at Edinburgh University involved 27 individuals with bipolar depression who were put on a keto diet for eight weeks.

"A third of them did very well. Their mood was more stable, they were less impulsive, and their depression lifted," said Smith. "[Finding] out why some responded and others did not will be one of the first undertakings for researchers at the new hub."

Source: https://www.theguardian.com/society/2024/sep/21/metabolism-diet-linked-bipolar-depression-scientists-edinburgh

Pilot Clinical Study Tries Ketogenic Diet in Psychiatric Disorders

Psychiatry Research (335) 2024

Ketogenic Diet Intervention on Metabolic and Psychiatric Health in Bipolar and Schizophrenia: A Pilot Trial

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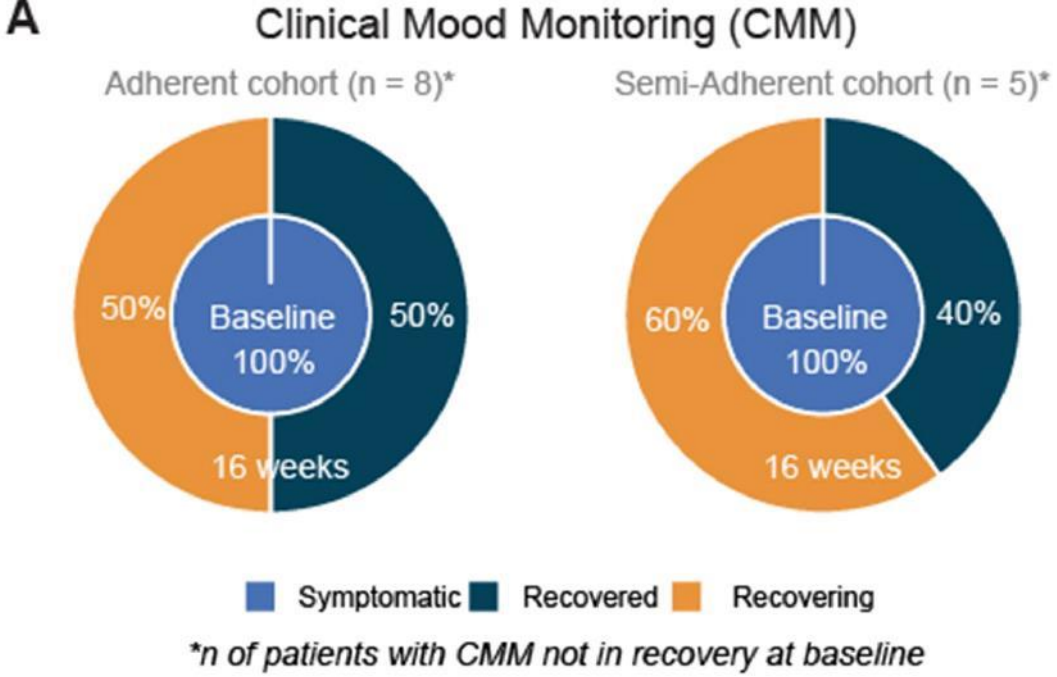
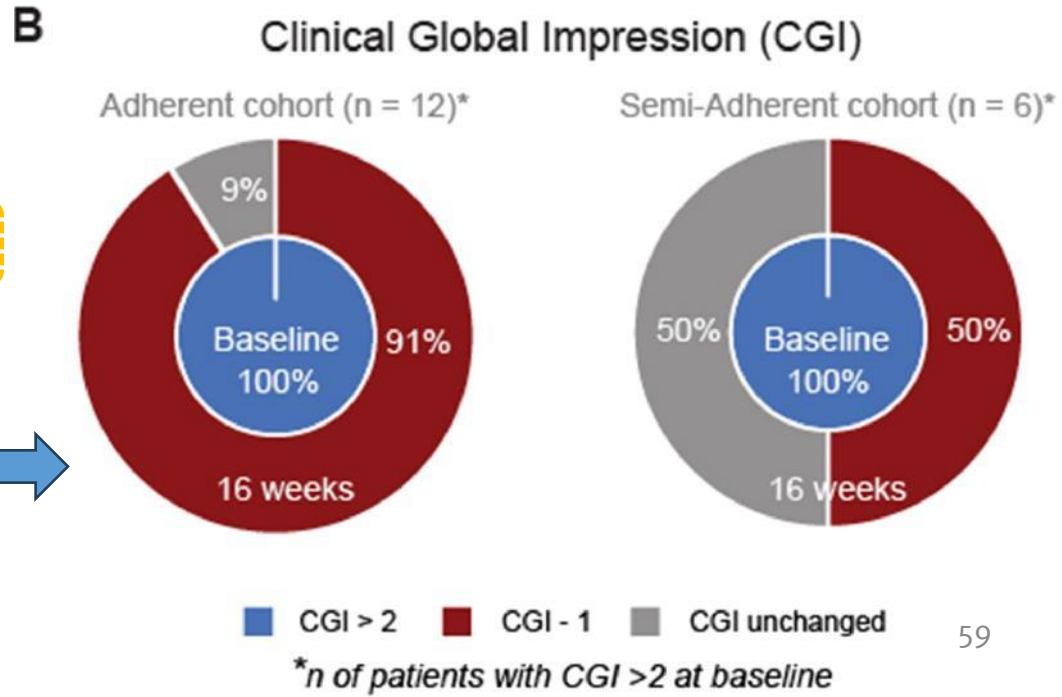
ARTICLE INFO

Keywords:
Bipolar illness
Schizoaffective disorder
Ketogenic diet metabolic therapy
Insulin resistance
Obesity
Metabolic psychiatry
Metabolic syndrome
Psychiatric disease
Clinical trial
Mental health

ABSTRACT

The ketogenic diet (KD, also known as metabolic therapy) has been successful in the treatment of obesity, type 2 diabetes, and epilepsy. More recently, this treatment has shown promise in the treatment of psychiatric illness. We conducted a 4–month pilot study to investigate the effects of a KD on individuals with schizophrenia or bipolar disorder with existing metabolic abnormalities. Twenty–three participants were enrolled in a single–arm trial. Results showcased improvements in metabolic health, with no participants meeting metabolic syndrome criteria by study conclusion. Adherent individuals experienced significant reduction in weight (12 %), BMI (12 %), waist circumference (13 %), and visceral adipose tissue (36 %). Observed biomarker enhancements in this population include a 27 % decrease in HOMA–IR, and a 25 % drop in triglyceride levels. In psychiatric measurements, participants with schizophrenia showed a 32 % reduction in Brief Psychiatric Rating Scale scores. Overall Clinical Global Impression (CGI) severity improved by an average of 31 %, and the proportion of participants that started with elevated symptomatology improved at least 1–point on CGI (79 %). Psychiatric outcomes across the cohort encompassed increased life satisfaction (17 %) and enhanced sleep quality (19 %). This pilot trial underscores the potential advantages of adjunctive ketogenic dietary treatment in individuals grappling with serious mental illness.





Sunburst graph depicting final Clinical Mood Monitoring and Clinical Global Impressions of individual with elevated symptomatology at baseline across adherent and semi–adherent populations (A) Inclusion criteria was baseline Clinical Mood Monitoring assessment of "not in a recovered or recovering state" (B) inclusion criteria was baseline Clinical Global Impressions›2.

Source: https://www.sciencedirect.com/science/article/pii/S0165178124001513

Psychiatry Drug Market Map (Revenue in 2023)

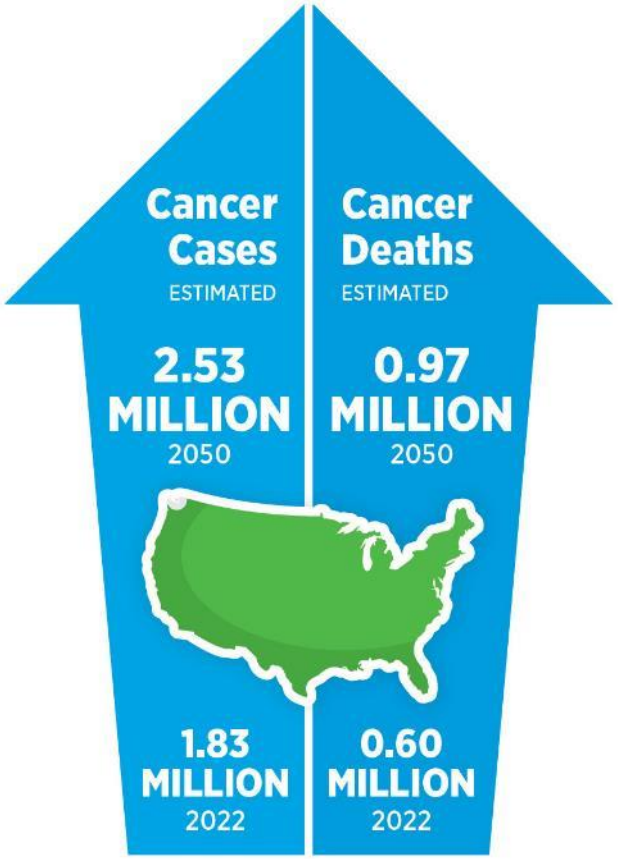
Source: Pharmasights

AACR Cancer Progress Report Released

- In the United States (US), the overall cancer death rate has been steadily declining since the 1990s, with the reductions between 1991 and 2021 translating into more than 4.1 million cancer deaths avoided.
- The decline in overall US cancer death rate is attributable to reduction in smoking rates, as well as improvements in treatment and early detection of certain cancers.
- Roughly half of cancers are preventable.
- More than 18 million cancer survivors were living in the United States as of January 1, 2022.
- Progress has not been even against all cancer types or all stages of a given cancer type.
- Many segments of the US population experience stark inequities in the cancer burden; these inequities are largely driven by structural and social factors.
- It is imperative that all stakeholders work together to implement evidence-based interventions including public policies that guarantee equitable access to quality health care for all patients, regardless of their race, ethnicity, age, sexual orientation, gender identity, socioeconomic status, or geographic location.
- The economic burden of cancer on individuals and the US health care system is expected to rise in the coming decades.

Source: https://cancerprogressreport.aacr.org/

AACR Cancer Progress Report Charts



Source: (46).

TABLE 1

Estimated Burden of Common Types of Cancer in the United States in 2024

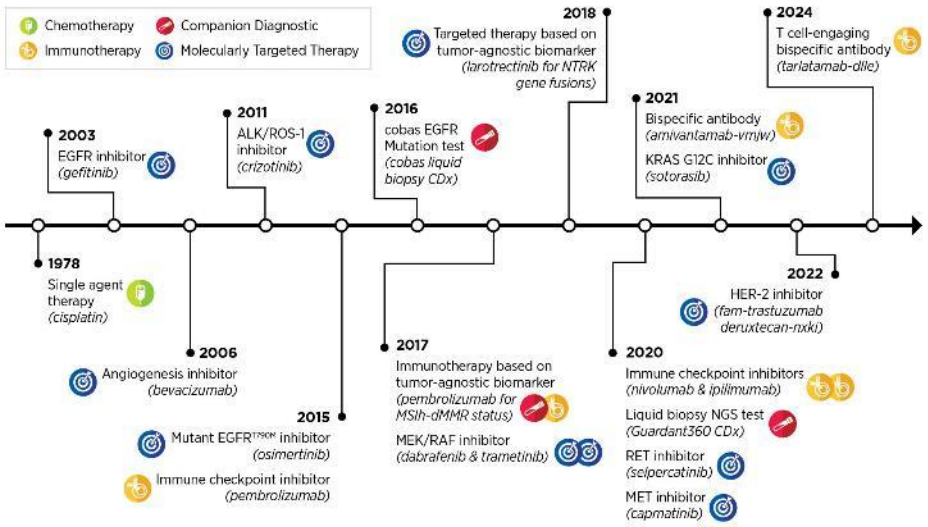
	NEW CASES	DEATHS
All Cancers Combined	**2,001,140**	**611,720**
Breast	313,510	42,780
Prostate	299,010	35,250
Lung and Bronchus	234,580	125,070
Colorectal	152,810	53,010
Melanoma (Skin)	100,640	8,290
Bladder	83,190	16,840
Kidney and Renal Pelvis	81,610	14,390
Non-Hodgkin Lymphoma	80,620	20,140
Uterine	67,880	13,250
Pancreatic	66,440	51,750
Thyroid	44,020	2,170
Liver and Intrahepatic bile duct	41,630	29,840
Myeloma	35,780	12,540

Source: (3).

FIGURE 1

Research Driving Progress Against Lung Cancer

FIRST FDA APPROVALS OF THERAPEUTICS WITH DISTINCT MECHANISMS OF ACTION



Thanks to research-driven clinical breakthroughs and steep reduction in US smoking rate, lung cancer mortality is declining rapidly. In fact, the decrease in lung cancer mortality per year accelerated from 2 percent between 2005 and 2013 to 4 percent between 2013 and 2021 (4). Basic research discoveries have identified numerous cellular pathways that are associated with lung cancer development. Key components of these pathways include proteins such as KRAS, EGFR, FGFR, ALK, ROS1, RET, MET, NTRK, HER2, and DLL3. Research has also shown that cancer cells evade destruction by the immune system because they have high levels of proteins that can attach to and trigger brakes on immune cells, stopping them from attacking cancer cells. Collectively, this knowledge has laid the foundation for personalized treatments for patients with lung cancer, in particular, molecularly targeted therapeutics and immunotherapeutics, which have resulted in remarkable lasting responses. Indicated on the timeline are important milestones in lung cancer precision medicine, including first US Food and Drug Administration (FDA) approvals for molecularly targeted therapeutics or immunotherapeutics that have distinct mechanism of action. While not included in the figure, large scale clinical studies such as the National Lung Screening Trial and Nederlands–Leuvens Longkanker Screenings Onderzoek have demonstrated that early detection using low-dose computed tomography (LDCT) screening can lower lung cancer mortality (5,6). Population-level implementation of LDCT use (current uptake of which is extremely low) among eligible individuals can further reduce the burden of lung cancer in the United States.

Source: https://cancerprogressreport.aacr.org/

Research That Led to Obesity Drugs Wins Major Medical Prize

Gina Kolata and Stephanie Nolen, *New York Times*, Sep 19, 2024 (excerpt)

The Lasker Awards, a prestigious set of prizes given for advances in medicine and public health research, were given on Thursday to scientists whose research helped lead to the discovery of a new class of obesity drugs, infectious disease specialists who worked on the drivers of H.I.V. infection and how to stop it, and a scientist who discovered a way the body protects itself from infectious diseases and cancer.

The Laskers are highly regarded in the fields of biomedicine and are sometimes seen as foretelling recipients of the Nobel Prizes in the sciences.

This year's Lasker-DeBakey Clinical Medical Research Award went to three scientists for their work on GLP-1, the hormone that led to drugs like Wegovy (the same compound is the basis for Ozempic), which have transformed the treatment of obesity. They are Dr. Joel Habener, Svetlana Mojsov and Lotte Bjerre Knudsen.

Each of the three honorees played a role at a key moment: finding the new hormone; finding the biologically active shorter form of GLP-1; and, finally, showing that the shorter form elicits weight loss. The story of GLP-1 begins with Dr. Habener, an endocrinologist who arrived in the mid-1970s at Massachusetts General Hospital, where he decided to work on diabetes.

Most of the focus had been on insulin, which lowers blood sugar levels. But there is another hormone, glucagon, that raises it. Dr. Habener decided to try to find the gene for glucagon, hoping it would lead to a way to squelch the hormone and so lower blood sugar. Working with anglerfish, he discovered a gene for another mysterious protein that resembles glucagon.

A young scientist at Massachusetts General Hospital, Dr. Mojsov, was intrigued by GLP-1. She realized that after GLP-1 was made, it was cut by enzymes in the cell to make it into a form that was biologically active. But where was it cut? And after it was cut, where in the body was the active protein found?

Dr. Mojsov speculated, based on her deep knowledge of protein chemistry, that the first six amino acids of the protein chain were sliced off after GLP-1 had been made. Then she proved her speculation using what was, for the time, a very sophisticated chemical methodology.

Next, she synthesized this shorter molecule, the active form of GLP-1. Collaborating with Dr. Gordon Weir, and others in Dr. Habener's lab, she discovered that GLP-1 acts only on the insulin-producing cells of the pancreas and that it exquisitely regulates blood sugar.

"Gordon called me and said, 'You won't believe how active this is,'" she recalled. "'Very, very small amounts still stimulate insulin production. I have never seen that before.'" "The final excitement," she said, was when a colleague, Dr. David Nathan, infused her GLP-1 into patients. He gave her blood samples from the patients to analyze. Some received GLP-1, and others did not.

It was absolutely clear which patients had received GLP-1. Dr. Mojsov recalled looking at her research assistant and saying, "This is going to be a drug." But there was one problem: GLP-1 lasted only fleetingly in the body. "Its half life was about three minutes," said Dr. Jeffrey Friedman, an obesity researcher at Rockefeller University and a member of the Lasker committee.

No one, at the time, was thinking of obesity. That changed when Lotte Bjerre Knudsen, a researcher for Novo Nordisk, saw a research paper by Dr. Stephen Bloom of Hammersmith Hospital in London. In his paper, published in 1996, he reported that when he had injected GLP-1 into rats' brains, they lost their appetites. GLP-1 molecules, she realized, had an effect — weight loss — that was separate and distinct from their effect on blood sugar. And that effect could be demonstrated if only the hormone could be made to last longer.

She set to work, coupling GLP-1 to a fatty acid that binds to albumin. The result was liraglutide, a drug that lasted 13 hours in the body. At first, Novo Nordisk tested it as a diabetes treatment. But Dr. Knudsen insisted on testing it separately as a treatment for obesity.

Source: https://www.nytimes.com/2024/09/19/health/2024-lasker-awards-ozempic-wegovy-glp-1.html

Lasker Winner Reflects on GLP-1 Evolution

Lotte Bjerre Knudsen, Novo Nordisk, "GLP-1 for Treating Obesity—Origin, History, and Evolution," *JAMA*, Sep 19, 2024 (excerpt)

Obesity has long lacked effective and safe treatments, in contrast with type 2 diabetes (T2D), for which treatments have flourished since the 1950s aided by the shared understanding of T2D as a disease. Obesity has not been understood as such, even with the rising number of people with obesity reaching epidemic proportions. Efficacious treatments now exist for obesity based on the biology of glucagon-like peptide-1 (GLP-1).

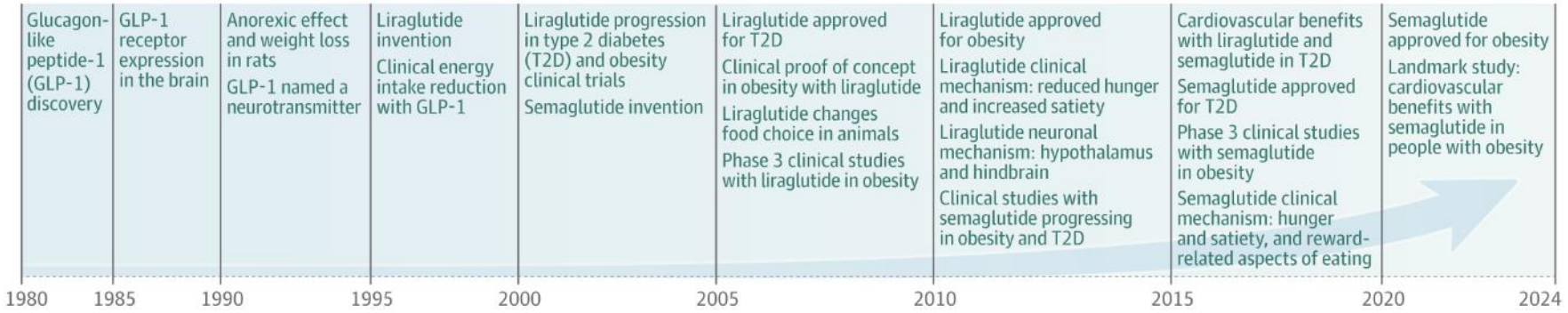
The discovery of GLP-1 was focused on diabetes, and GLP-1 receptor agonists (GLP-1RAs) are important treatments for T2D. Interesting and less well known science suggesting GLP-1 as a potential treatment for obesity developed relatively early, with studies from the 1980s showing broad receptor expression in the rodent brain. Ole Madsen of the Hagedorn Research Institute in Denmark used a tumor-driven animal model producing high levels of glucagon, GLP-1, and peptide YY and found these animals to have profound anorexia with high levels of circulating GLP-1. Stephen Bloom of Hammersmith Hospital in the UK injected GLP-1 directly into the brain of fasting rats, observed profound reduction in food intake, and called out GLP-1 as a neurotransmitter.

Unfortunately, native GLP-1 was not a good drug candidate. The pharmacokinetics and the pharmacodynamics for GLP-1 are clear: the best efficacy for lowering blood glucose or body weight requires pharmacological concentrations 24 hours per day, irrespective of drug administration intervals. Native GLP-1 is rapidly degraded and cleared, resulting in a very short half-life. Furthermore, the molecule is difficult to formulate. Long-acting formulations of GLP-1 or simple analogs of GLP-1 were taken into clinical trials but failed due to skin reactions. Another solution was needed. The first long-acting GLP-1RA was liraglutide, a fatty acid acylated analogue of GLP-1 with 97% homology to native GLP-1. I led this work at Novo Nordisk (coinventors Per Franklin Nielsen and Per Olaf Huusfeldt) and proposed liraglutide be taken into clinical development for obesity as well as T2D. If liraglutide could solve the challenges in making GLP-1 receptor agonism a viable drug target for T2D, the solution would apply to obesity as well.

At the time of liraglutide approval for T2D in Europe (2009) and the US (2010), essentially all major pharmaceutical companies had abandoned new drug discovery for obesity, either because they lacked belief that efficacious medicines could be made or because of concerns regarding cardiovascular or neuropsychiatric safety. Novo Nordisk pursued an ambitious program for the treatment of obesity, resulting in the 2014 FDA approval of liraglutide for obesity. Because of general concerns surrounding the safety of obesity medications, understanding the mechanism was critical.

Semaglutide was the second GLP-1RA approved for the treatment of obesity and the first to deliver double-digit weight loss. The semaglutide coinventors are Jesper Lau, Thomas Kruse, and Paw Bloch (Novo Nordisk). **The impact of an effective treatment for an underappreciated, underrecognized disease has increased exponentially. It makes sense that people want these treatments.**

Figure. Inflection Points in the Journey to GLP-1–Based Medicines for Obesity and Related Complications



Source: https://jamanetwork.com/journals/jama/fullarticle/2823791

Obesity is Driven by a Build-up of Molecular Mesh Around Hunger Neurons

Alexander Dityatev, *Nature*, Sep 18, 2024 (excerpt)

After eating a meal, the concentration of glucose in the blood rises and triggers β-cells in the pancreas to secrete more of the hormone insulin, which circulates in the blood and reaches the brain. A region of the brain called the arcuate nucleus of the hypothalamus (ARC) is responsible for sensing insulin levels, adjusting food intake and controlling related physiological processes such as burning fat and expending energy. If neurons in the ARC lose sensitivity to insulin, we start to eat more, accumulate fat and develop problems with our metabolic health. Writing in *Nature*, Beddows et al. report that a build-up of a molecular meshwork called the extracellular matrix around neurons stops insulin from reaching its receptor, driving insulin resistance in the brains of obese mice. Freeing neurons from this meshwork restores insulin signalling and drastically reduces body weight.

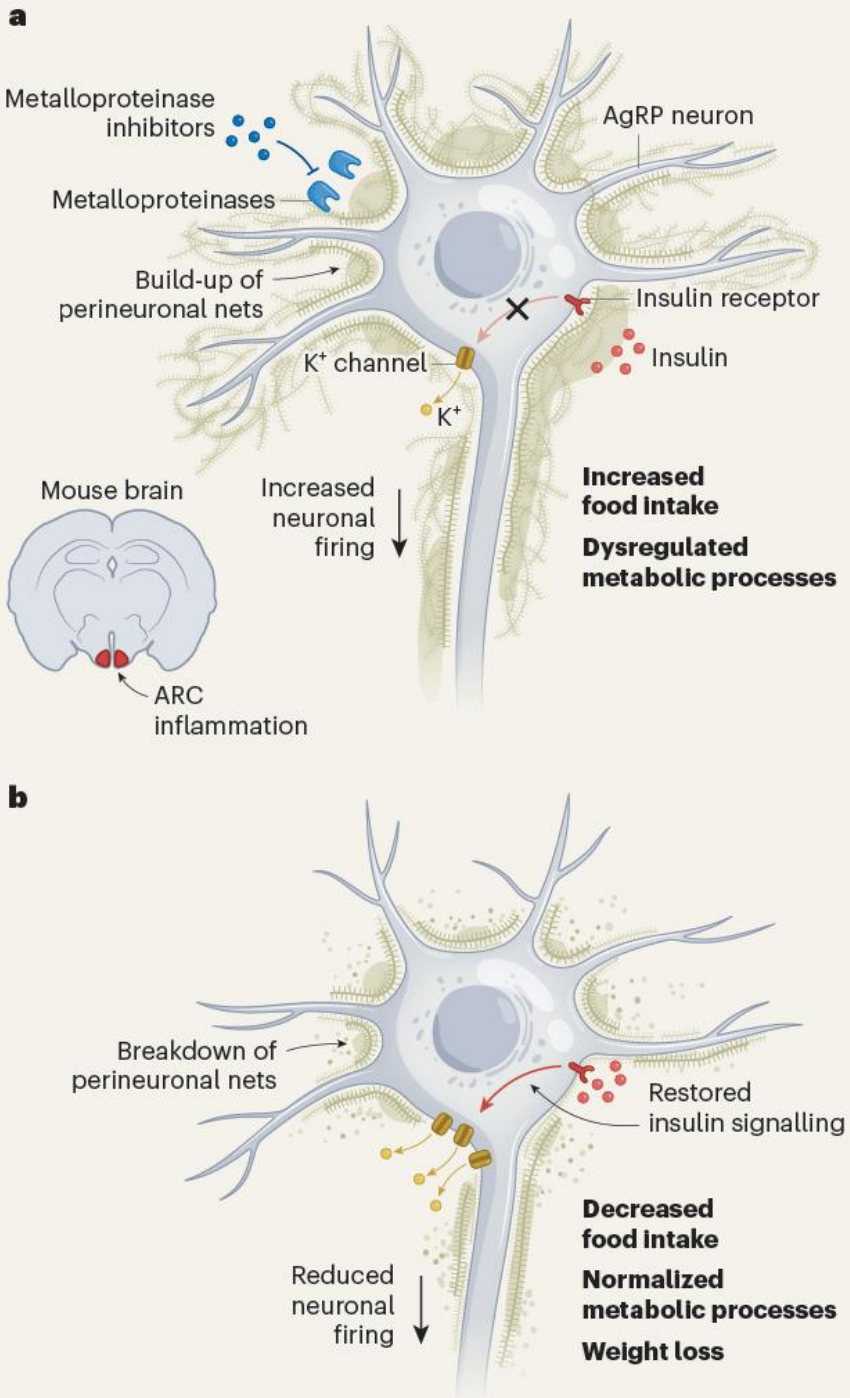


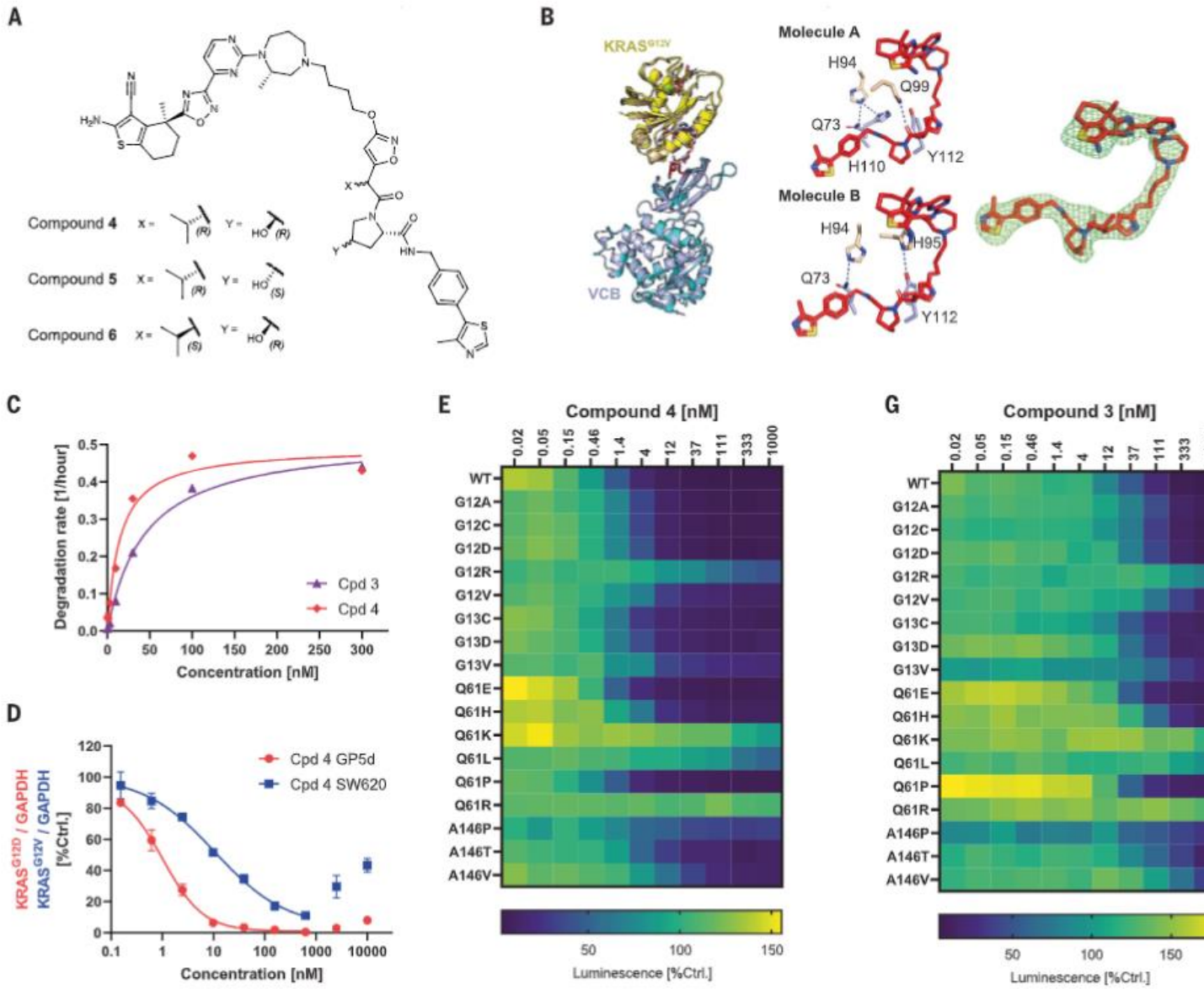
Figure 1 | Insulin resistance in the brain during metabolic disease. a, A part of the brain called the arcuate nucleus of the hypothalamus (ARC) responds to insulin after a meal and regulates metabolic processes. Beddows *et al.*[1] find that, during the progression of metabolic diseases (such as obesity) in rodents, inflammation in the ARC leads to the dysregulation of proteins (metalloproteinase enzymes and their inhibitors) that control the turnover of a meshwork of proteins and sugars called the extracellular matrix. This accumulates, in the form of perineuronal nets, around neurons that express the neuropeptide AgRP, preventing insulin from reaching its receptor. Disrupted insulin signalling leads to downregulation of channels that conduct potassium ions (K^+), which increases the firing rate of AgRP neurons. This increases inhibition of nearby neurons in another part of the hypothalamus (not shown), disrupting metabolic processes. b, Breaking down perineuronal nets restores insulin signalling, causing obese mice to eat less and lose body weight.

Source: https://www.nature.com/articles/d41586-024-02325-5

Boehringer Team Touts Pan-KRAS Inhibitor in *Science*

Popow J. et.al., "Targeting cancer with small-molecule pan-KRAS degraders," *Science,* Sep 20, 2024, pp. 1338-1347.

Mutations in the Kirsten rat sarcoma viral oncogene homolog (KRAS) protein are highly prevalent in cancer. However, small-molecule concepts that address oncogenic KRAS alleles remain elusive beyond replacing glycine at position 12 with cysteine (G12C), which is clinically drugged through covalent inhibitors. Guided by biophysical and structural studies of ternary complexes, we designed a heterobifunctional small molecule that potently degrades 13 out of 17 of the most prevalent oncogenic KRAS alleles. Compared with inhibition, KRAS degradation results in more profound and sustained pathway modulation across a broad range of KRAS mutant cell lines, killing cancer cells while sparing models without genetic KRAS aberrations. Pharmacological degradation of oncogenic KRAS was tolerated and led to tumor regression in vivo. Together, these findings unveil a new path toward addressing KRAS-driven cancers with small-molecule degraders.



Source: https://pubmed.ncbi.nlm.nih.gov/39298590/

Prostate Cancer Progression Tied to MYC Gene

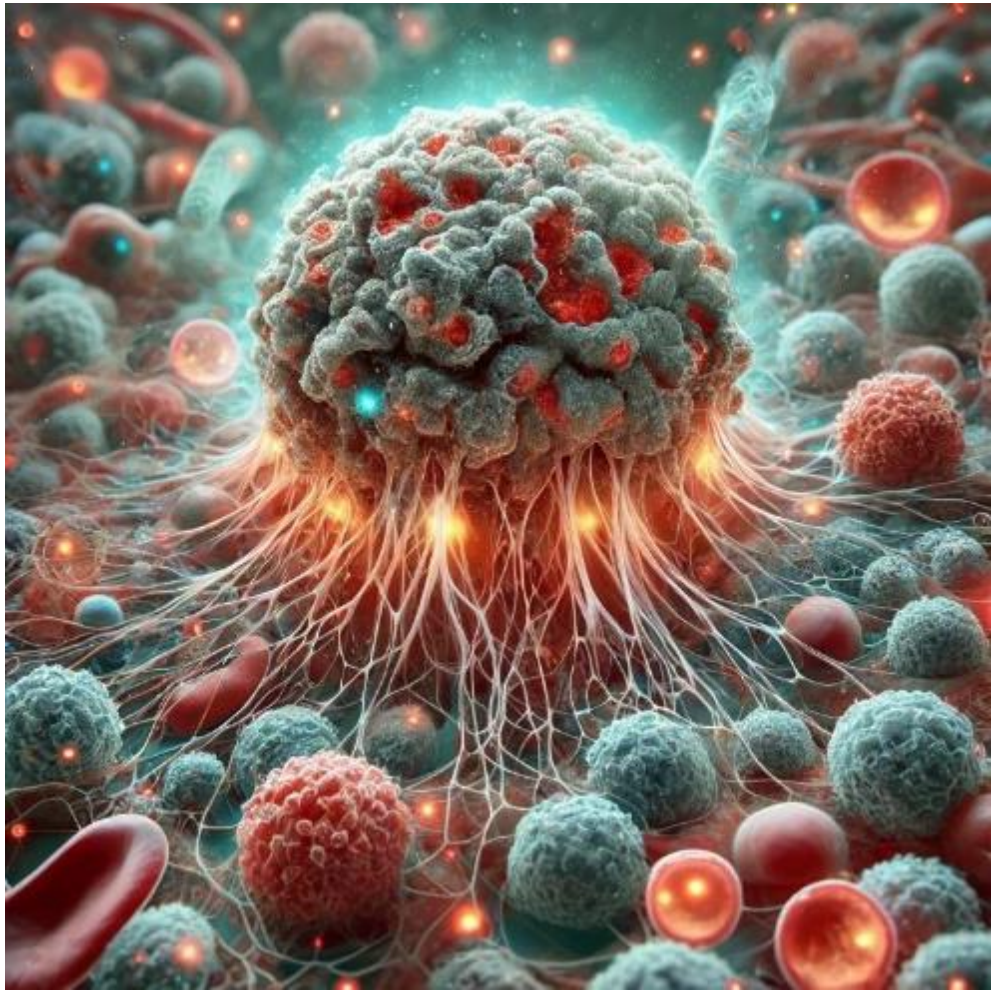
Johns Hopkins Press Release, Sep 19, 2024

By tracking the changes in prostate cancer cells over time, researchers at the Johns Hopkins Kimmel Cancer Center have found that activation of the MYC gene — a well-known cancer-causing gene — sets off a cascade of events that leads to both initiation and progression of the disease.

Scientists have learned that prostate cancers can vary significantly among patients and that there are often differences within each patient's tumor. However, the study published Aug. 28 in *Nature Communications* identifies the MYC gene as a common denominator across prostate cancers. The work demonstrates that initial MYC activation attracts immune cells to the tumor but later helps hide the tumor from immune cells. This discovery is the first step toward identifying potential therapeutic targets along the pathway.

"This is a very powerful oncogenic pathway set off by MYC activation," says Srinivasan Yegnasubramanian, M.D., Ph.D., professor of oncology, pathology, and radiation oncology and molecular radiation sciences, and director of the inHealth precision medicine initiative at Johns Hopkins. "We need to understand this complex cascade of events in detail to find out more effective ways to manage the disease."

Studies of human tumor tissues can help scientists investigate prostate cancer, but they only provide a snapshot. To get a sense of the changes that occur over time in prostate cancer, scientists turn to animal models. Yegnasubramanian and his colleagues married the two approaches to get a detailed look at prostate cancer initiation and progression.



Source: https://www.hopkinsmedicine.org/news/newsroom/news-releases/2024/09/a-common-culprit-drives-prostate-cancer-progression

Cancer, the Master of Hijacking

Eric Topol, *Substack*, Sep 15, 2024 (excerpt)

Recently, we learned about another type of LLM—lipid-laden macrophages—and their role in brain cancer (not large language models!) The resident macrophages of the brain, known as microglia, and monocyte-derived macrophages, form LLMs by scavenging cholesterol lipid from the myelin sheath of neurons.

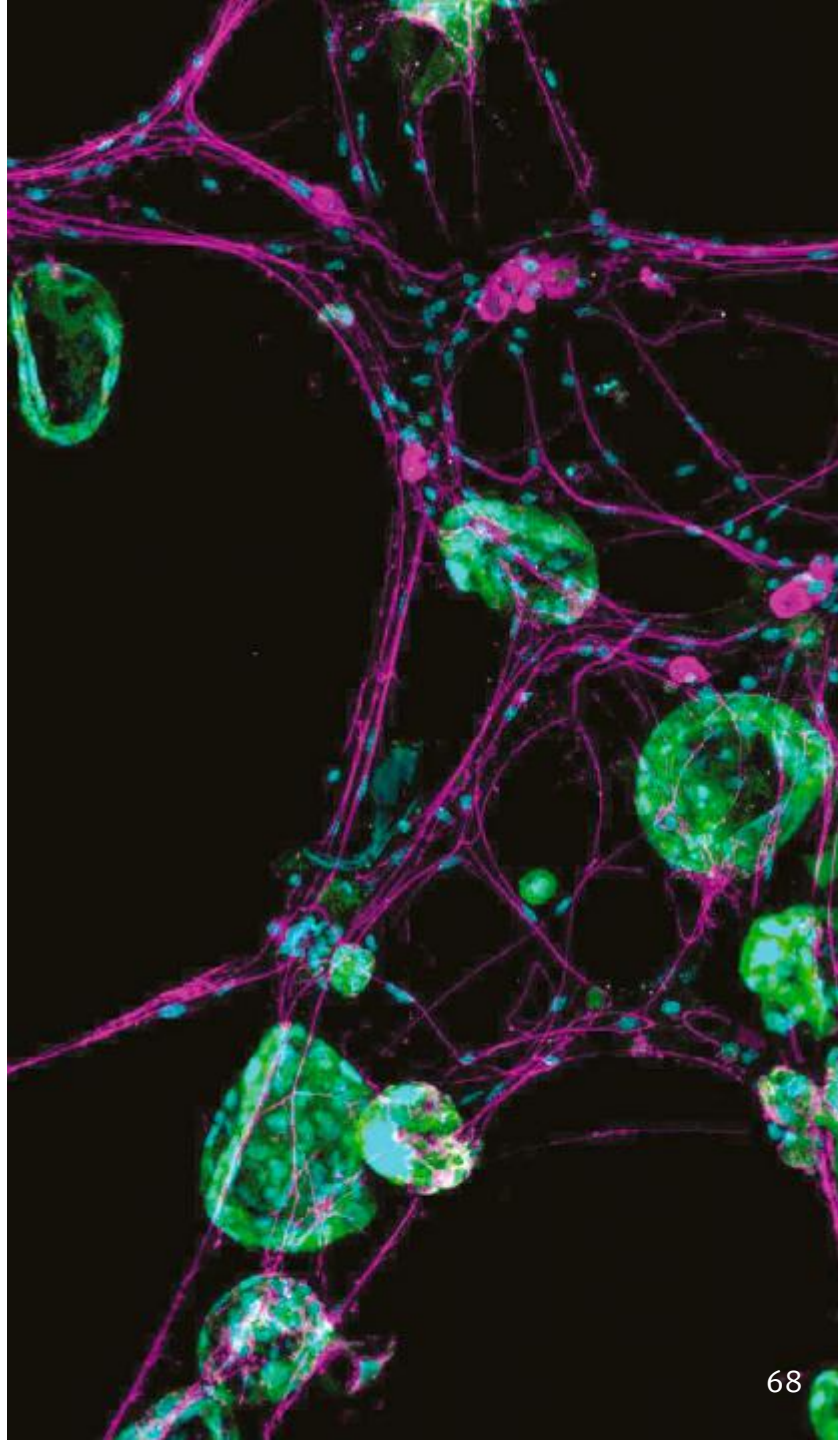
As a result, there's a triple whammy. Not only do the LLMs suppress our immune response to the cancer, such as by changes in gene expression and blunted T cell capacity, but they transfer cholesterol to the mesenchymal glioblastoma cells which enhances their proliferation. Beyond that, if the myelin debris was not picked up by LLMs, it would otherwise have toxic effect to limit tumor progression.
Back in 2019, also in brain cancer, Venkataramani and colleagues, Venkatesh et al, and Zeng et al, simultaneously reported that direct synapses were formed between neurons and cancer cells. The functional significance of these synapses, as shown below, is to promote tumor growth and migration. Although some connections between cancer and neurons had between reported many years previously, as reviewed here, the 3 papers laid the foundation for the field of cancer neuroscience.

As demonstrated by elegant single-cell resolution, cancer cells hijack the mitochondria from T cells! This is remarkable because it simultaneously takes down the immune response to the tumor and empowers cancer cells with their stolen powerhouse fuel supply.

I've tried here to take you through some of the numerous (and fascinating) ways that cancer can take over various types of cells, sub-cellular components (mitochondria), and tissue (neural, blood vessel) in our body, evading our immune system, breaking down our defense, promoting its growth and metastasis. No wonder cancer is often so challenging to achieve durable treatment success.

Many of the mechanisms mentioned are recent discoveries which have laid the foundation for new (often repurposed) therapies, not previously considered as candidates to treat cancer. Collectively, they highlight the importance of basic science to provide new insights for potential therapies. It takes years from such work to translate to effective, validated treatments, but hopefully illuminating this multi-dimensional hijacking capability of cancer will eventually enrich our armamentarium.

Source: https://erictopol.substack.com/p/cancer-the-master-of-hijacking



Disclosure

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