Biopharmaceutical Sector

Weekly Update – December 4, 2023

STIFEL | Healthcare

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Eukaryotic cell stock illustration

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Client Partnership When it Counts

The biopharma industry environment has not been an easy place in 2023.

Stifel's Global Healthcare Group has remained focused on supporting our clients in achieving their long-term goals throughout the market downturn.

As shown at right, we remain active across the board. We have supported our clients in achieving notable recent successes in M&A, licensing and capital markets transactions.

Stifel's full-service healthcare investment banking practice offers a best-in-class combination of deep sector knowledge, strong industry relationships, and broad product expertise.

Stifel's Global Healthcare Group is comprised of over 100 professionals covering all segments of the healthcare industry. The team, located in New York, San Francisco, London, Mumbai, Toronto, and Montreal, has substantial experience in assisting companies with all types of financing and M&A assignments. The Global Healthcare Group is dedicated to building long-term relationships with its clients through senior level attention. Since the formation of the Global Healthcare Group in Q4 2010, the team have helped raise over $115 billion for almost 300 healthcare companies in over 600 transactions. Over the same period, members of the Global Healthcare Group have advised on over 350 announced M&A transactions, including over 160 cross-border assignments.

$300,000,000

XENON

Confidentially Marketed Follow-on Offering

Joint Bookrunner

November 2023

$245,000,000

TEIJIN

In-Licensing of the Japan Rights to Three Rare Endocrinology Drugs from

ascendis pharma

Advisor to Licensee

November 2023

$175,000,000

PROPELLA

Has Agreed to be Acquired by

astellas

Advisor to Seller

Pending

$185,000,000

VIRIDIAN

PIPE

Co-Lead Placement Agent

October 2023

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All transaction announcements appear as a matter of record only. Stifel collectively refers to Stifel, Nicolaus & Company, Incorporated and other affiliated broker-dealer subsidiaries of Stifel Financial Corp.

Past Issues / Mailing List

If you are not on the mailing list for this publication and wish to be added, please notify Natasha Yeung (yeungn@stifel.com).

Recent issues in case you missed and want to read:

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 (Changing Pharma Strategy)
September 11, 2023 (US Health System)
September 5, 2023 (FTC, IRA, Depression)
August 21, 2023 (Covid, China)
August 7, 2023 (Employment, Summer 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)

Join Us at These Upcoming Events

Biotech Hangout held its latest event on December 1, 2023.

The next event will be on December 8, 2023.

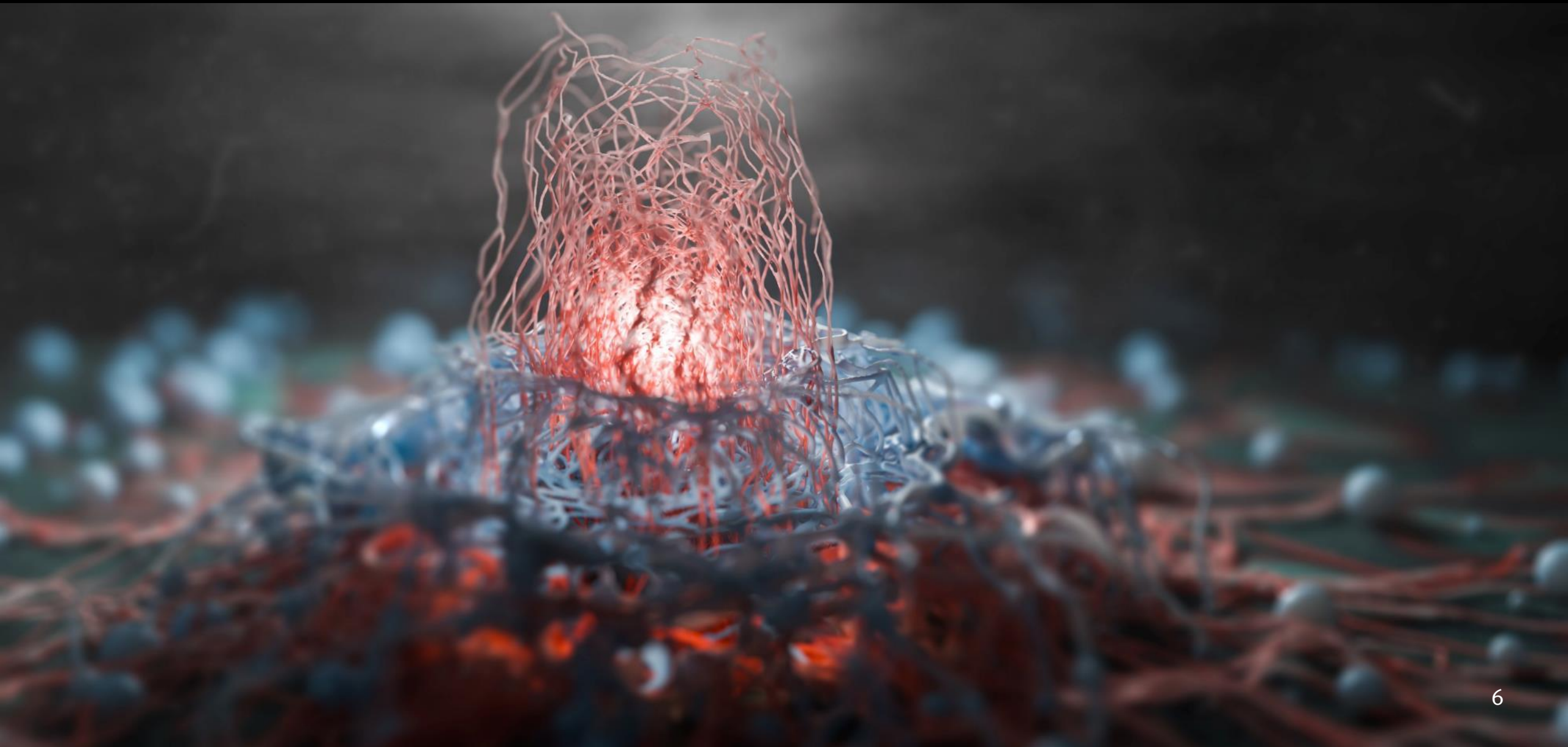
Please join us.

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

The week of Jan 7, 2024 will feature over 30,000 biopharma professionals in SF for JPM, Biotech Showcase and many other events. Stifel will be hosting an industry cocktail party on Jan 7th.

To meet with Stifel
yeungn@stifel.com

Macro Update



Excellent PCE Inflation Number Last Week

Personal Income and Outlays, October 2023

Personal income increased $57.1 billion (0.2 percent at a monthly rate) in October, according to estimates released today by the Bureau of Economic Analysis (tables 2 and 3). **Disposable personal income** (DPI), personal income less personal current taxes, increased $63.4 billion (0.3 percent) and **personal consumption expenditures** (PCE) increased $41.2 billion (0.2 percent).

The **PCE price index** increased less than 0.1 percent. Excluding food and energy, the PCE price index increased 0.2 percent (table 5). **Real DPI** increased 0.3 percent in October and **real PCE** increased 0.2 percent; goods increased 0.1 percent and services increased 0.2 percent (tables 3 and 4).

	2023				
	June	July	Aug.	Sept.	Oct.
	Percent change from preceding month				
Personal income:					
Current dollars	0.2	0.3	0.5	0.4	0.2
Disposable personal income:					
Current dollars	0.1	0.1	0.4	0.4	0.3
Chained (2017) dollars	-0.1	-0.1	0.0	0.0	0.3
Personal consumption expenditures (PCE):					
Current dollars	0.4	0.7	0.4	0.7	0.2
Chained (2017) dollars	0.3	0.6	0.0	0.3	0.2
Price indexes:					
PCE	0.2	0.2	0.4	0.4	0.0
PCE, excluding food and energy	0.2	0.2	0.1	0.3	0.2
Price indexes:	Percent change from month one year ago				
PCE	3.2	3.4	3.4	3.4	3.0
PCE, excluding food and energy	4.3	4.3	3.8	3.7	3.5

PCE inflation for the month of October was 0%. If food and energy were excluded it was 0.2% (2.4% run rate). This is vast improvement from where we've been in the last 18 months.

Source: https://www.bea.gov/news/2023/personal-income-and-outlays-october-2023

Fed's Favorite Gauge Shows Inflation Rose 0.2% in October and 3.5% From a Year Ago, as Expected

Jeff Cox, *CNBC*, November 30, 2023 (excerpt)

Inflation as measured by personal spending increased in line with expectations in October, possibly giving the Federal Reserve more incentive to hold rates steady and perhaps start cutting in 2024, according to a data release Thursday.

The personal consumption expenditures price index, excluding food and energy prices, rose 0.2% for the month and 3.5% on a year-over-year basis, the Commerce Department reported. Both numbers aligned with the Dow Jones consensus and were down from respective readings of 0.3% and 3.7% in September.

Personal income and spending both rose 0.2% on the month, also meeting estimates and indicating that consumers are keeping pace with inflation. However, both numbers fell on the month; income rose 0.4% in September while spending was up 0.7%. Slower spending growth, though, aligns with the Fed's goal of cooling the economy so inflation can recede.

Stocks rallied following the news, as the Dow Jones Industrial Average hit a 2023 high. Bonds sold off, with Treasury yields popping as the rate-sensitive 2-year note moved up more than 6 basis points (0.06 percentage point) to 4.71%.

While the public more closely watches the Labor Department's consumer price index as an inflation measure, the Fed prefers the core PCE reading. The former measure primarily looks at what goods and services cost, while the latter focuses on what people actually spend, adjusting for consumer behavior when prices fluctuate. Core CPI was at 4% in October while headline was at 3.2%.

Source: https://www.cnbc.com/2023/11/30/pce-inflation-report-october-2023-.html

Goods Deflation Is Back. It Could Speed Inflation's Return to 2%.

David Harrison, *Wall Street Journal*, Dec 3, 2023 (excerpt)

After a historic run-up in inflation, Americans are now starting to see something they haven't in three years: deflation.

To be sure, deflation—that is, falling prices—is largely confined to appliances, furniture, used cars and other goods. Economywide deflation, when prices of most goods and services continuously fall, isn't in the cards.

But economists say goods prices likely have further to fall, which will ease inflation's return to the Federal Reserve's 2% target, perhaps as early as the second half of next year.

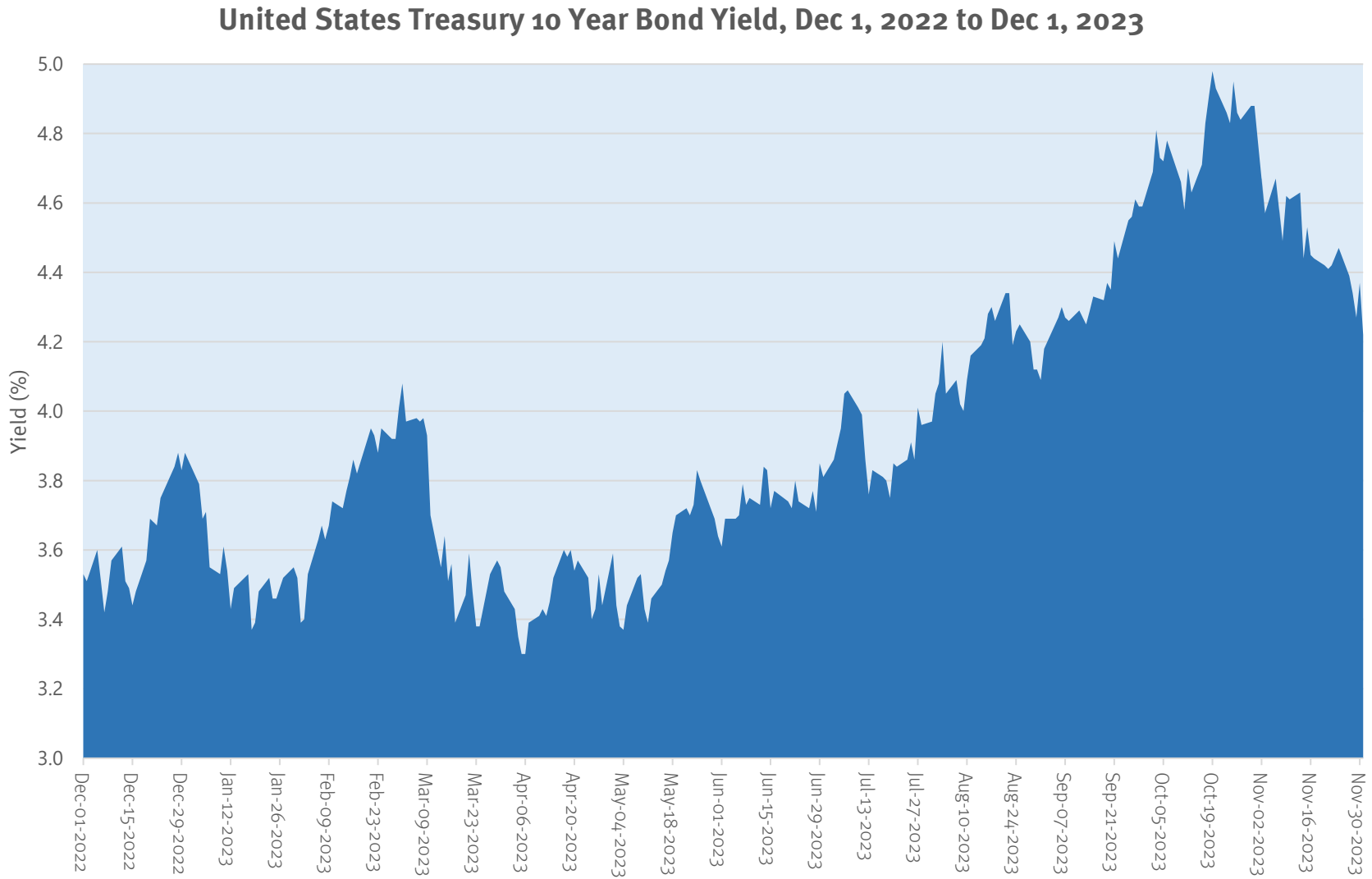
Prices for long-lasting items, known as durable goods, have fallen on a year-over-year basis for five straight months. In October, they were down 2.6% from their peak in September 2022, according to data released Thursday by the Commerce Department.

That has helped bring down core inflation, which excludes the volatile food and energy categories, to 3.5% in October, from 5.5% in September 2022, as measured by the personal-consumption expenditures price index, the Fed's preferred inflation gauge.

The prices of services such as home rental and car insurance continue to climb, albeit at a slowing pace. They were up 4.4% in October from a year earlier, slower than 4.7% in September but well above their pace before the pandemic.

Source: https://www.wsj.com/economy/goods-deflation-is-back-it-could-speed-inflations-return-to-2-c782d434?mod=hp_lead_pos3

Climb in Long Treasury Yields Has Reversed

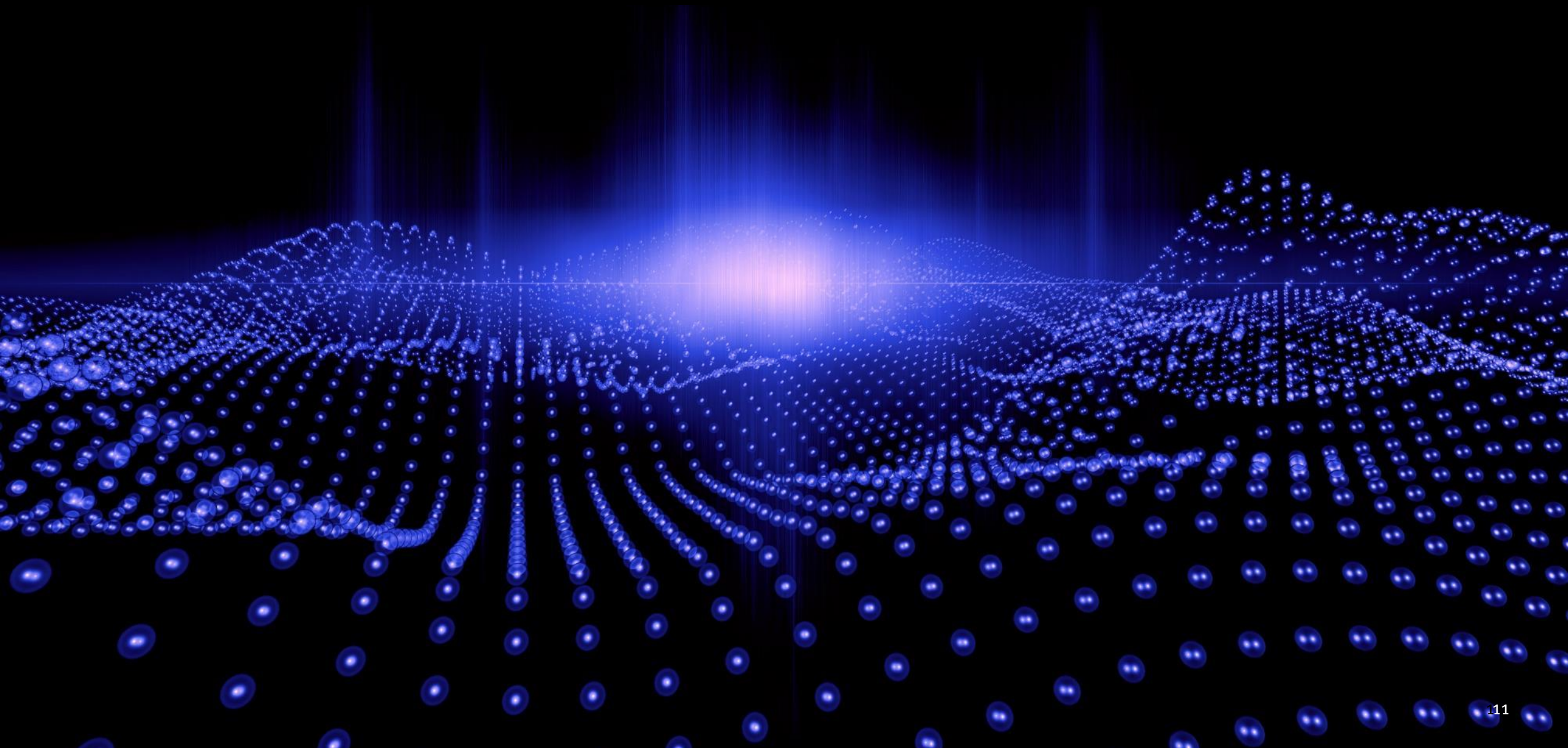


Ten-Year US Treasury Bond Yields have dropped by 80 basis points since peaking in October

That's a huge move and a giant positive for biotech.

Source: S&P CapitalIQ.

The Market Rally

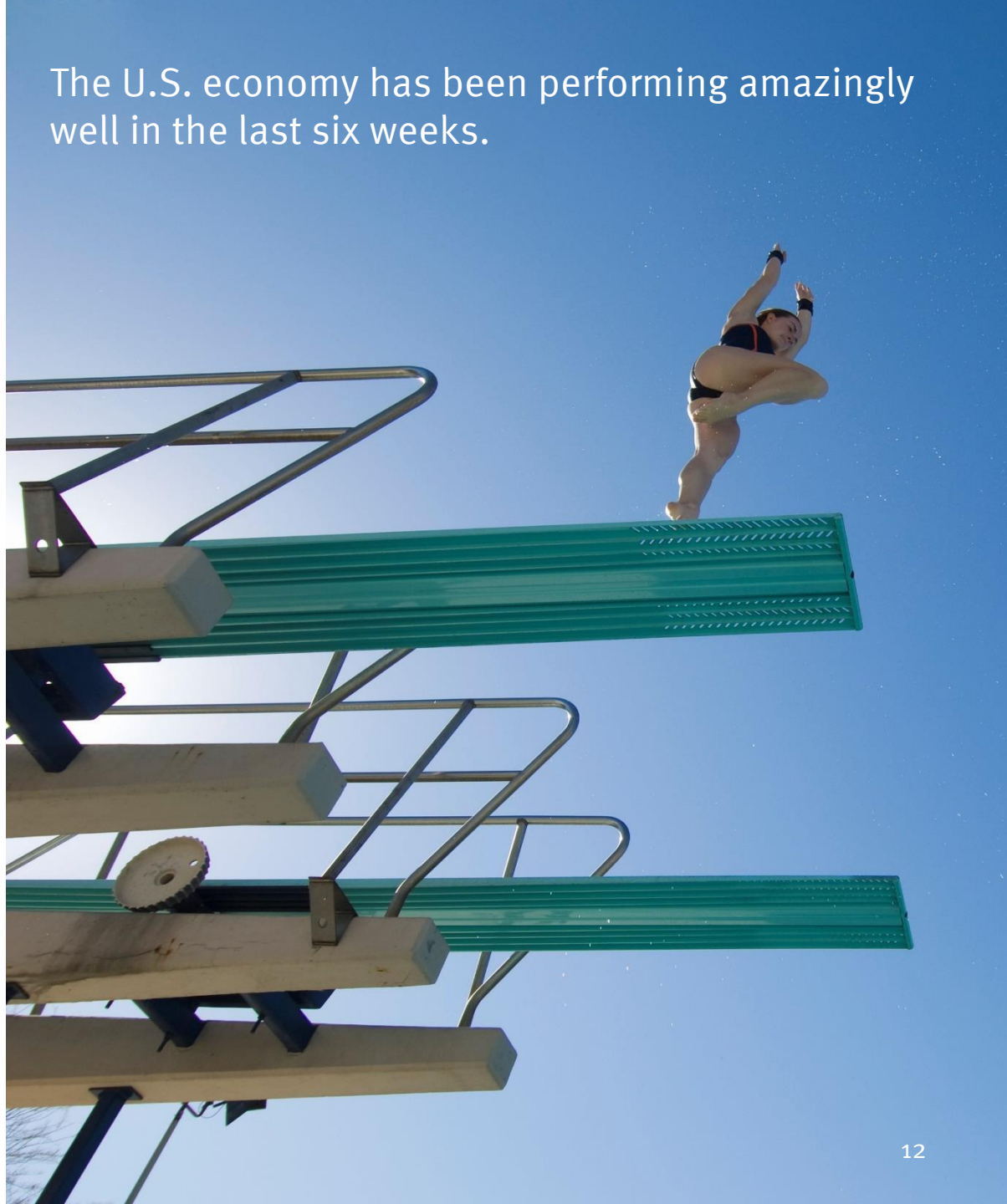


The Risk On Trade, the Rally and What's Happening Now

The XBI has jumped 21% in five short weeks and other risky asset classes have also rallied rapidly. We are seeing a "quadruple macro flip" take place off the shaky diving board called the U.S. economy. First, the U.S. Treasury has signalled limited borrowing for Q4 2023 in its Quarterly Refunding Announcement (QRA). This was unexpected and has fed the rally as more than $300 billion in expected Treasury borrowings got taken off the table. Second, inflation numbers have come in much better than expected. Third, the economy is slowing down but not crashing. Fourth, oil prices have gotten a lot weaker. All super positive for risk-taking in stocks. And all at once.

In a year where it has seemed at times to biotech investors that nothing could go right, we have seen a **dramatic and sudden turn** for the better.

Given how positive the fundamentals have become, we are surprised that the biotech market is only up 21% at this point. We have now moved well beyond that "negative sentiment" funk we were talking about just four and five weeks ago. But we think it's most likely going to be a gradual process of capital appreciation from here as opposed to a "melt up" scenario. The reason is that one can still do quite well by keeping capital in money markets. Also, savvy investors want to see that next QRA report and next inflation report. Digging out of this macro hole is going to take time. Investor confidence does not reverse on a dime. Our general sense is that the biotech market direction in 2024 is going to be driven by a gradual shift away from an insanely high-quality premium in biotech, a gradual realization that biotech actually is a great asset class to own (as we discussed last week). The big positives ahead are continued likely declines in oil prices (wars create incentives for countries like Russia to keep pumping oil aggressively), continued slowdown in inflation and positive biopharma sector fundamentals. The negatives will come from election year uncertainties, continued geopolitical risk and potentially voracious borrowing needs of the U.S. government. On the whole, we are quite optimistic about the year ahead of us in biotech but don't expect a smooth, linear ride up from here.



Dow Rallies to Year's Highest Close, Caps Blockbuster Month

Stephen Culp, *Reuters*, Nov 30, 2023 (excerpt)

The Dow Jones Industrial Average closed at its highest level since January 2022 as investors crossed the finish line of a banner month for stocks and viewed cooling inflation data as a harbinger of easing Federal Reserve monetary policy.

The Dow was the clear outperformer, with a solid boost from Salesforce on the heels of its consensus-beating earnings report.

The S&P 500 closed modestly green, while tech and tech-adjacent momentum stocks, led by Nvidia, pulled the Nasdaq into negative territory.

Still, the S&P 500 and the Nasdaq notched their largest monthly percentage gain since July 2022. November was the Dow's best month for percentage gains since October 2022.

"We're putting the cherry on top of a banner month," said Ryan Detrick, chief market strategist at Carson Group in Omaha. "It's a nice reminder for investors how worried everyone was a month ago, and we just finished one of the best months in history for stocks."

The improving inflation picture has left its mark on stocks with the S&P pulling up substantially for the year.

It's been a great month (for once) in stocks.

Source: https://www.reuters.com/markets/us/wall-st-futures-edge-higher-easing-inflation-hopes-2023-11-30/

Tech Giants Lead Surge in Global Mega-caps as Inflation Eases

***Reuters*, Dec 1, 2023 (excerpt)**

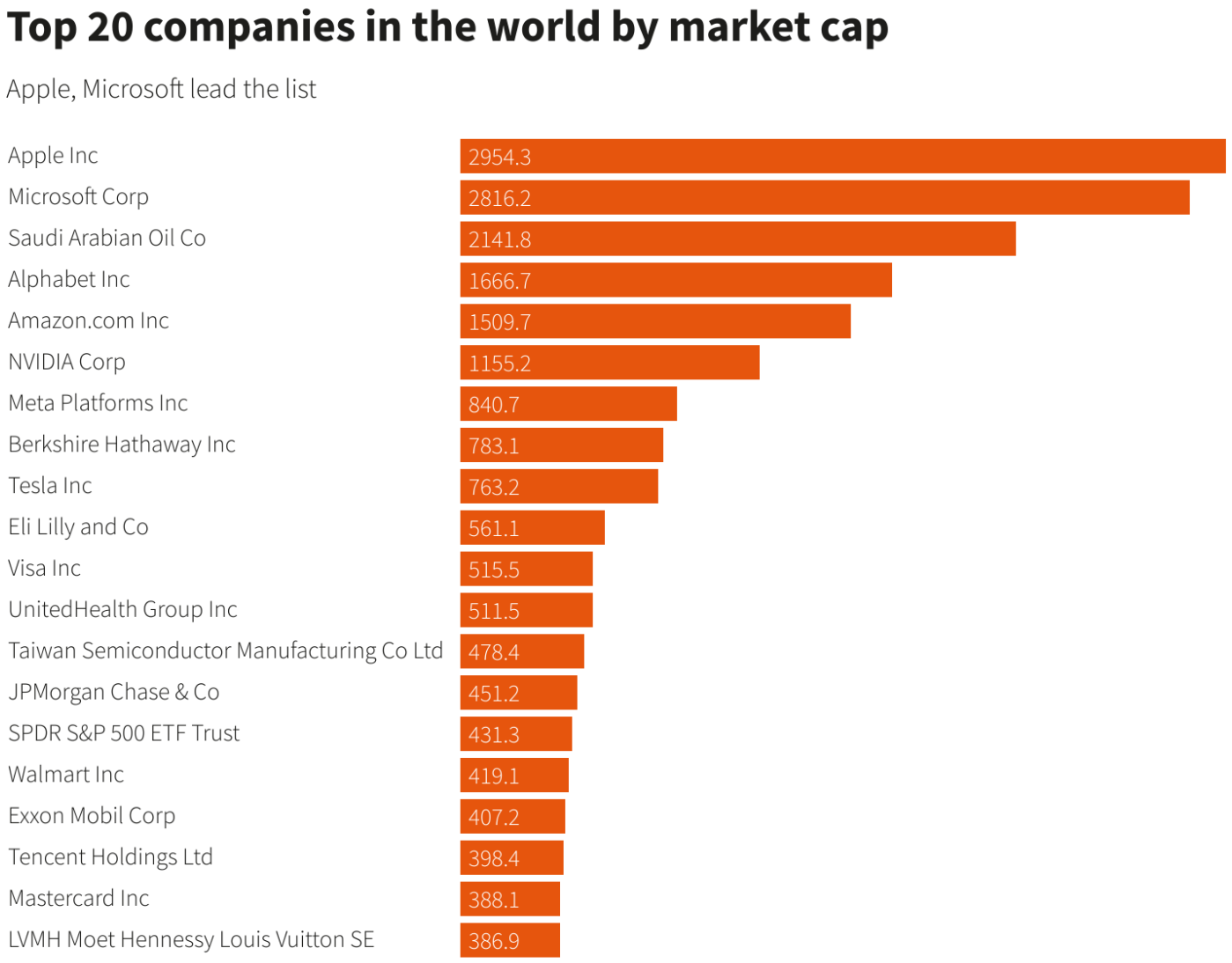
Market capitalisations of global mega-cap companies, led by prominent technology firms, surged in November, buoyed by a decline in U.S. yields and growing anticipation of potential rate cuts by global central banks amid diminishing worries about inflation.

Apple Inc's market value jumped 11.2% to $2.95 trillion over the past month, while Microsoft Corp saw a 12.1% increase in its market cap, reaching $2.8 trillion.

Nvidia Corp's market cap soared 14.7% to $1.15 trillion, following its announcement of a 206% year-over-year revenue increase to $18.1 billion in the third quarter. The firm also projected higher-than-expected revenue for the fiscal fourth quarter, citing improved supply chain conditions and robust demand for its AI chips.

Easing inflation concerns also gave a big boost to banking stocks. JPMorgan Chase & Co saw its market cap increase by 12.2% to $451 billion by the end of November.

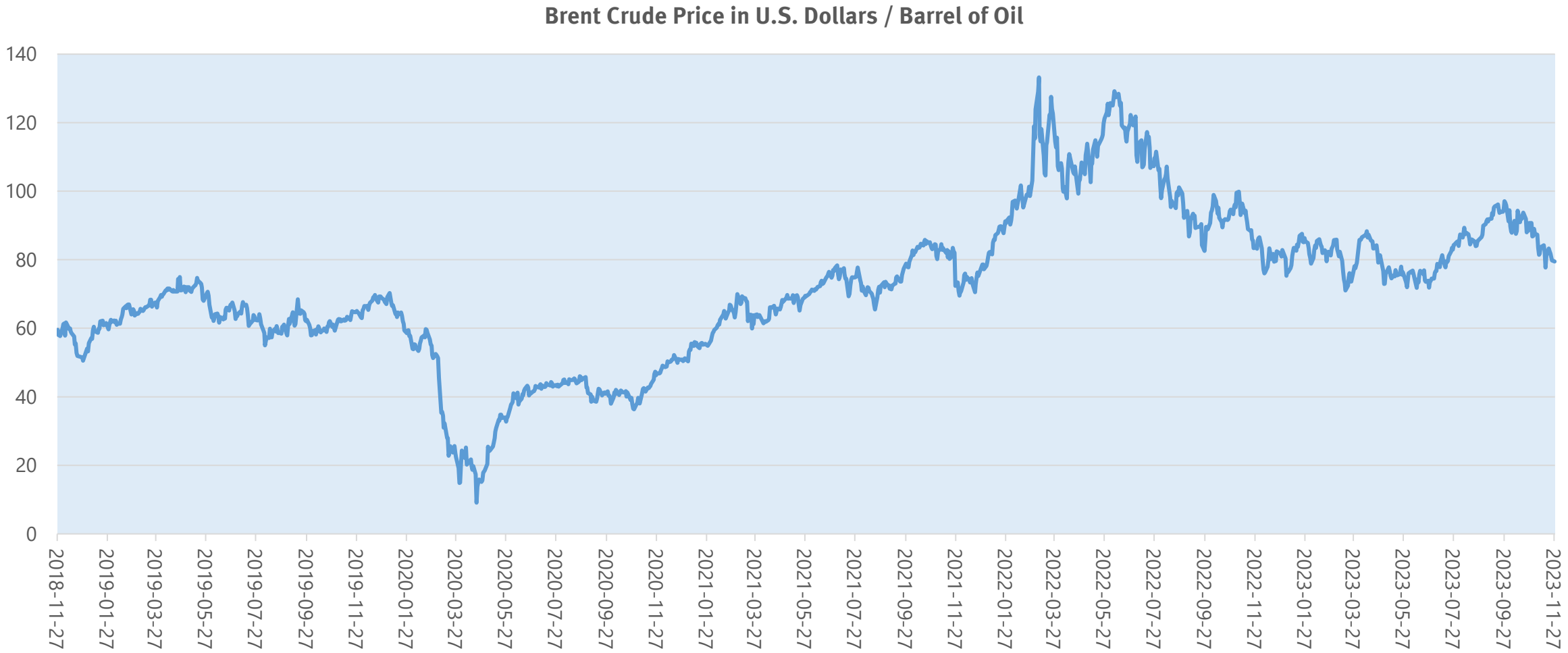
Source: https://www.reuters.com/markets/global-markets-marketcap-2023-12-01/



Note: Amount in $ billions; Data as of Nov 30, 2023
Source: LSEG Eikon

Oil Prices Went Below $80 / Barrel Last Week

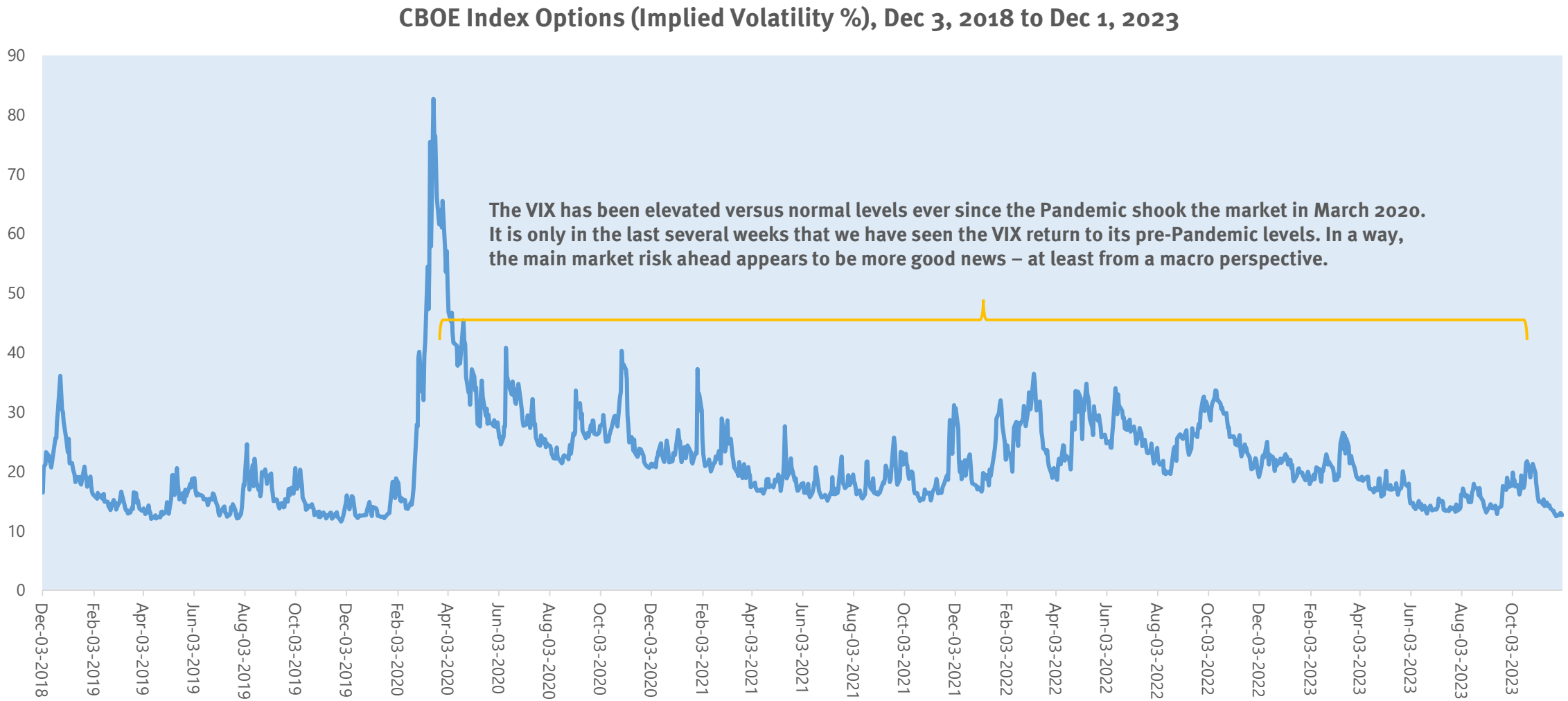
Some market observers are seeing oil prices going well below $60 / BBL next year. This would be a huge positive for the U.S. economy, inflation and biotech.



Source: FRED, Federal Reserve Bank of St. Louis.

Halcyon Days: VIX At Lowest Level Since 2019

The VIX is the market's "fear gauge" and is a reasonably good index of macro uncertainty. It's way down in recent weeks.



Source: S&P CapitalIQ

The Stock Market Had an Impressive November. What Comes Next

Teresa Rivas, *Barron's*, Dec 1, 2023 (excerpt)

"When November wrapped up, the stock market said goodbye to the best month—so far—of a good year. That understandably leaves investors to wonder whether there's is enough juice (or milk and cookies) left for a Santa rally. There's good news for those who want to believe.

The S&P 500 closed the month up just shy of 9%, while the Nasdaq gained almost 11%. That's a swift reversal from the third-quarter selloff, but follows the pattern that has held in 2023, with Big Tech leading the way.

And barring any huge disruption, even a lackluster December won't derail this year's winning streak. So far in 2023, through Thursday's close, the S&P 500 is up within a fraction of 19% and the Nasdaq has gained nearly double that.

There is hope that December can still add to the year's gains. Putting aside down years for the market, the month historically tends to be a good one for investors.

That's especially true because the S&P 500 tends to hang onto gains after big consecutive up weeks. Plus, at this point, there seems little fundamentally that would cause Big Tech leaders to falter—at least in the very near term. Technical indicators also support gains to close the year.

Nonetheless, even those predicting the economy will deteriorate next year don't believe a recession will keep stocks down for long, and there is historical precedent for that thinking.

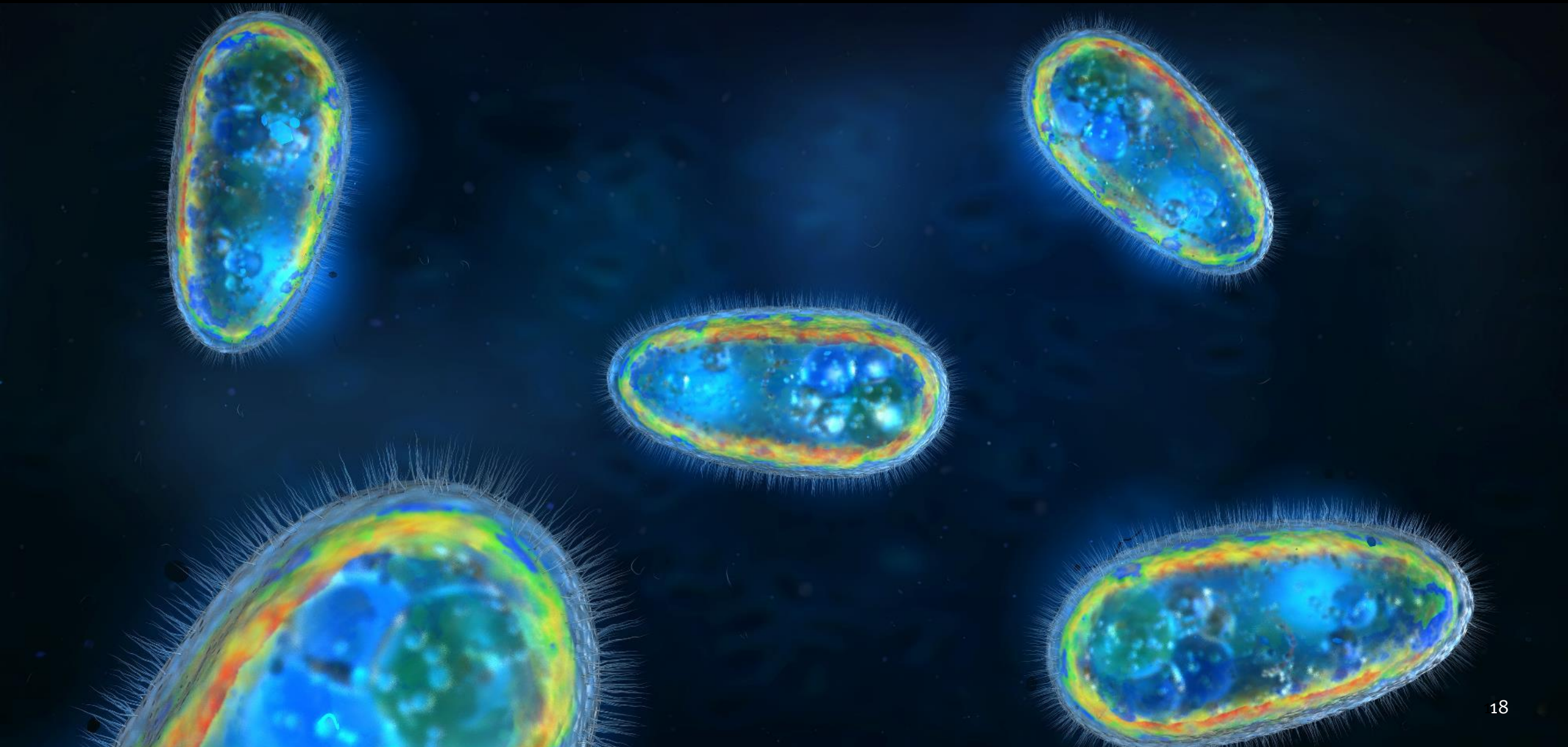
Still, the Federal Reserve will keep driving the market's moves in the new year, as it has this year.

Fed speakers are sounding more dovish in the past week, and yields keep drifting lower; lower yields in general can be see as less of a headwind for stocks.

Any indication—by the Federal Open Market Committee at its December meeting next week—that interest rates could come down for any reason other than a recession would be one less thing for the market to worry about."

Source: https://www.barrons.com/articles/stock-market-november-december-performance-e2c11b82

Biopharma Market Update



The XBI Closed at 77.83 Last Week (Up 5.7%)

The XBI headed up last week for the fourth time in five on the back of a very good PCE Inflation number, the acquisition of Immunogen and heavy short covering in the market. The XBI is now down 6.2% for the year (much better than -22.7% five weeks ago).

Biotech Stocks Up Last Week

Return: Nov 25 to Dec 1, 2023

Nasdaq Biotech Index: +2.9%
Arca XBI ETF: +5.7%
Stifel Global Biotech EV (adjusted): 5.5%*
S&P 500: +0.8%

Return: Jan 1 to Dec 1, 2023

Nasdaq Biotech Index: -5.7%
Arca XBI ETF: -6.2%
Stifel Global Biotech EV (adjusted): 2.2%*
S&P 500: +19.7%

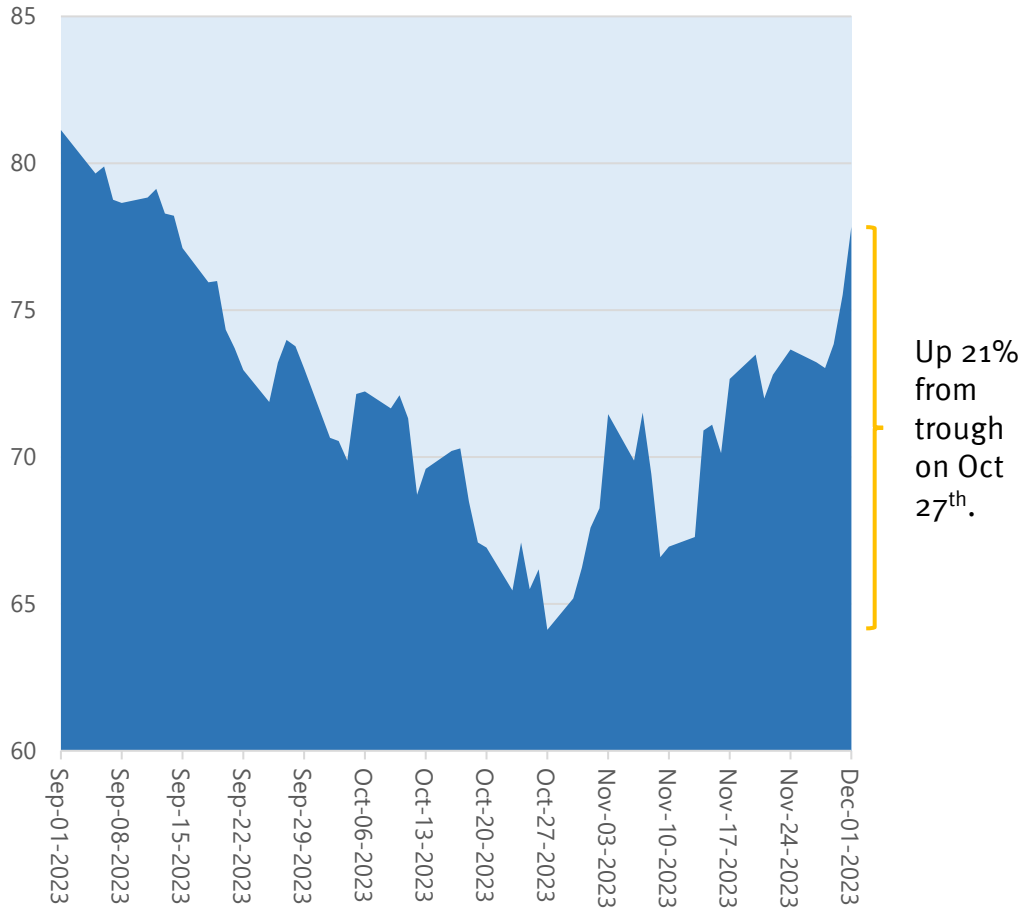
VIX Down

Oct 21: 29.7%
Jan 20: 19.9%
May 26: 18.0%
July 21: 13.6%
Sep 29: 17.3%
Oct 27: 21.2%
Nov 17: 13.8%
Dec 1: 12.6%

10-Year Treasury Yield Down

Oct 21: 4.2%
Jan 20: 3.48%
May 26: 3.8%
July 21: 3.84%
Sep 29: 4.59%
Oct 27: 4.86%
Nov 17: 4.44%
Dec 1: 4.24%

XBI, Sep 1 to Dec 1, 2023



* Change by enterprise value. The adjusted number accounts for the effect of exits and additions via M&A, bankruptcies and IPOs.

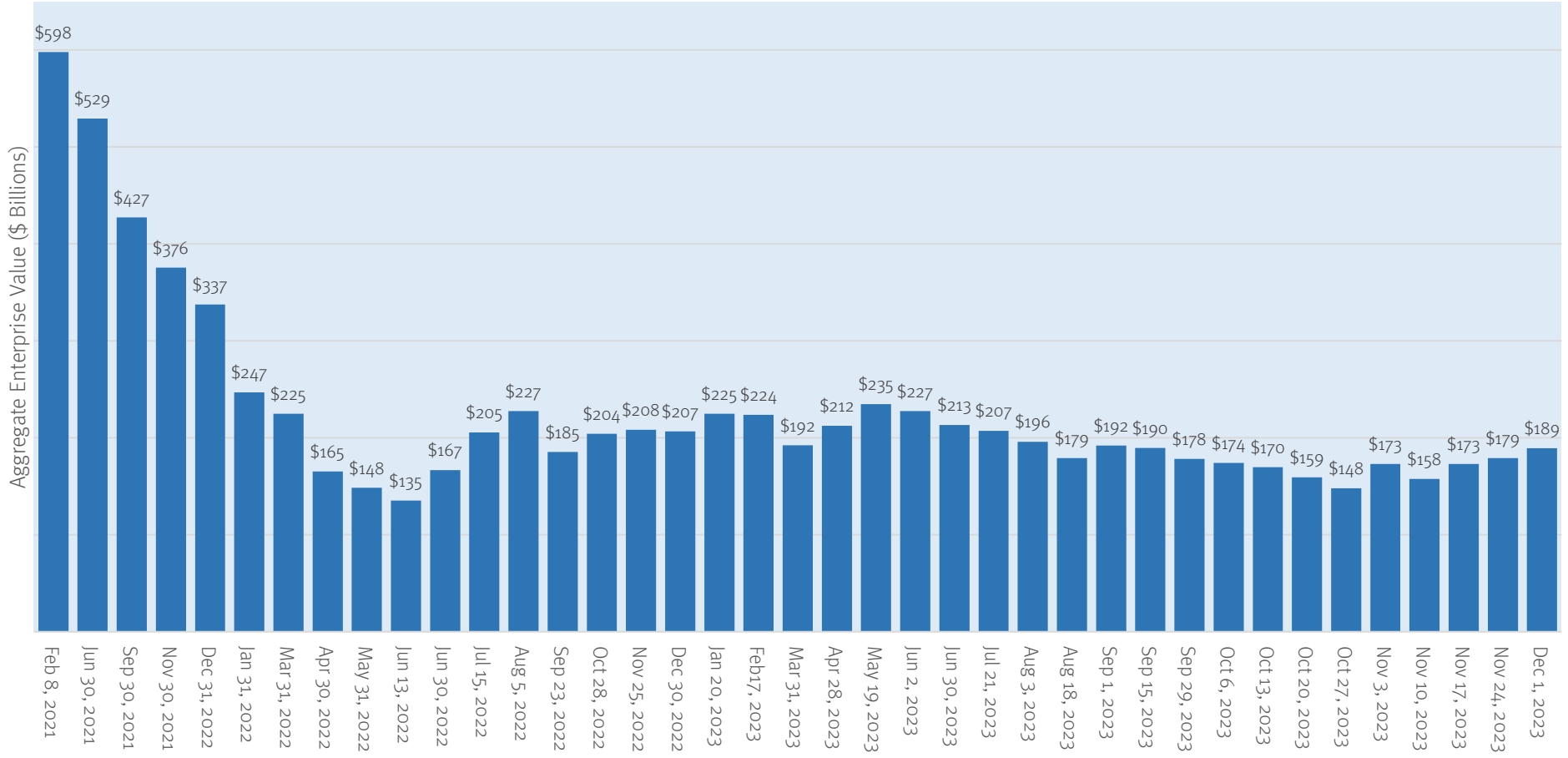
Source: S&P Capital IQ and Stifel analysis

Total Global Biotech Sector is Now Up 29% in Recent Rally

The total enterprise value of the global biotech sector rose by 5.5% last week and is now up 2.2% for the year after adjusting for exits and entries. This is the first time since September where we have had an up market for the year in biotech. Biotech values are up 29% since their recent trough on October 27, 2023.

Total Enterprise Value of Publicly Traded Global Biotech

Feb 8, 2021 to Dec 1, 2023 ($ Billions)

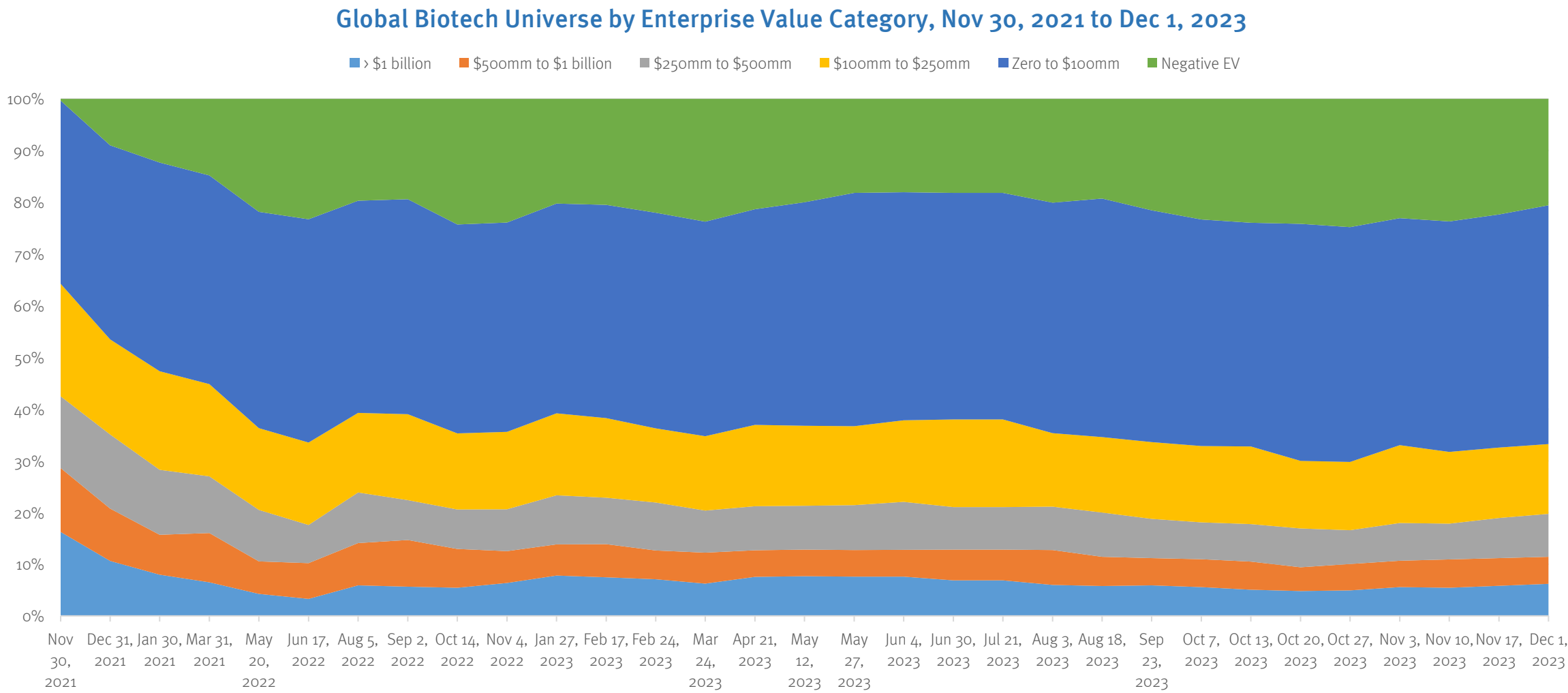


While biotech is up 29% since trough, this rally is still in its early days.

It's clear from this chart that the market would need to rally 50% to 100% from here to get anywhere near where it was at the end of 2022.

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

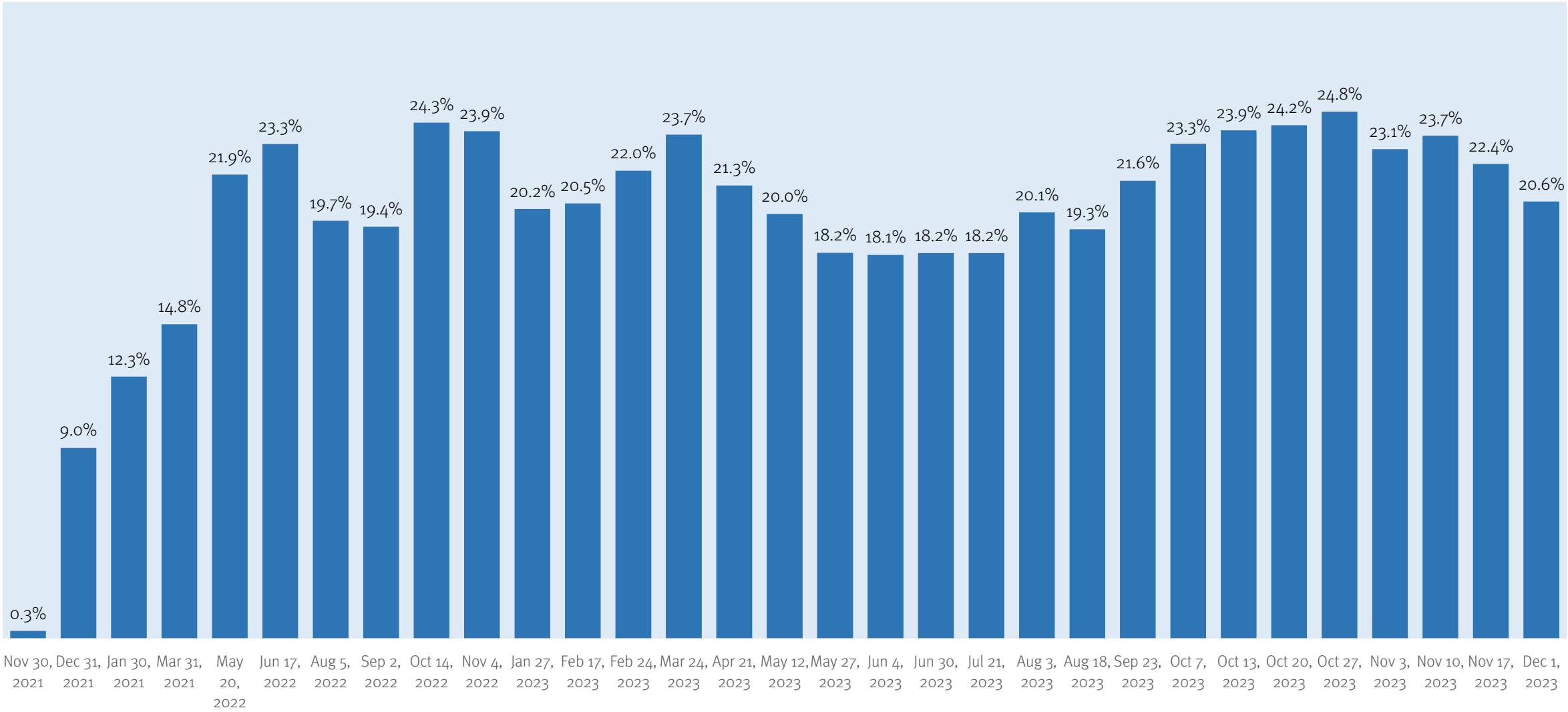
We are Seeing Meaningful Growth in the Population of Biotechs Worth Over $100 Million in EV Since Oct 27th



Source: CapitalIQ and Stifel analysis.

Negative EV Biotech Count Has Dropped in Recent Weeks

Percent of Global Biotechs with Negative Enterprise Value, Nov 2021 to Dec 2023 (N=821)



Source: CapitalIQ and Stifel analysis.

Bruce Booth Says Biotech Consolidation Not Happening

Bruce Booth, Atlas Venture, *LifeSciVC*, November 30, 2023

After the bursting of the pandemic biotech bubble, talk of industry consolidation was ubiquitous. The sector had pushed out too many IPOs during the go-go years, leading to too many public biotech companies, with sub-scale enterprises, and wasteful crowding in lots of therapeutic categories. And too many inexperienced management teams leading those newly-minted public companies. There's certainly some truth in those claims.

Many industry insiders tried to push for consolidation, including encouraging both outright acquisitions and mergers of equals, to try to streamline and "right-size" the sector. And if consolidation didn't work, struggling companies were encouraged to consider just throwing in the towel and move to shutdown, returning the remaining cash to shareholders via liquidation. White papers were written and shared widely about these points. Some investors even hosted "brainstorming" events with groups of CEOs to try to facilitate dialogues about meaningful and productive combinations. Such was the prevailing sentiment in early 2022.

So what happened in the nearly two years since then? Well, very little consolidation, if any.

Several years into the post-bubble bear market, the public biotech sector has only contracted by 4.5% since early 2022.

Shutdowns were only 2% of the sector: declaring failure and closing up shop just hasn't happened often. M&A, including by Pharma or via mergers of equals, only happened for 7% of the companies in the sector. It's worth noting that reverse mergers don't shrink the sector – they just put a private surviving story into the public shell of a dying one. Furthermore, reverse mergers are often seen as an attractive alternative to shutting down as it keeps hope alive – and pays bankers some fees during this IPO famine (that typically aren't paid in liquidations or wind-downs).

Source: https://lifescivc.com/2023/11/biotech-consolidation-not-really-happening/

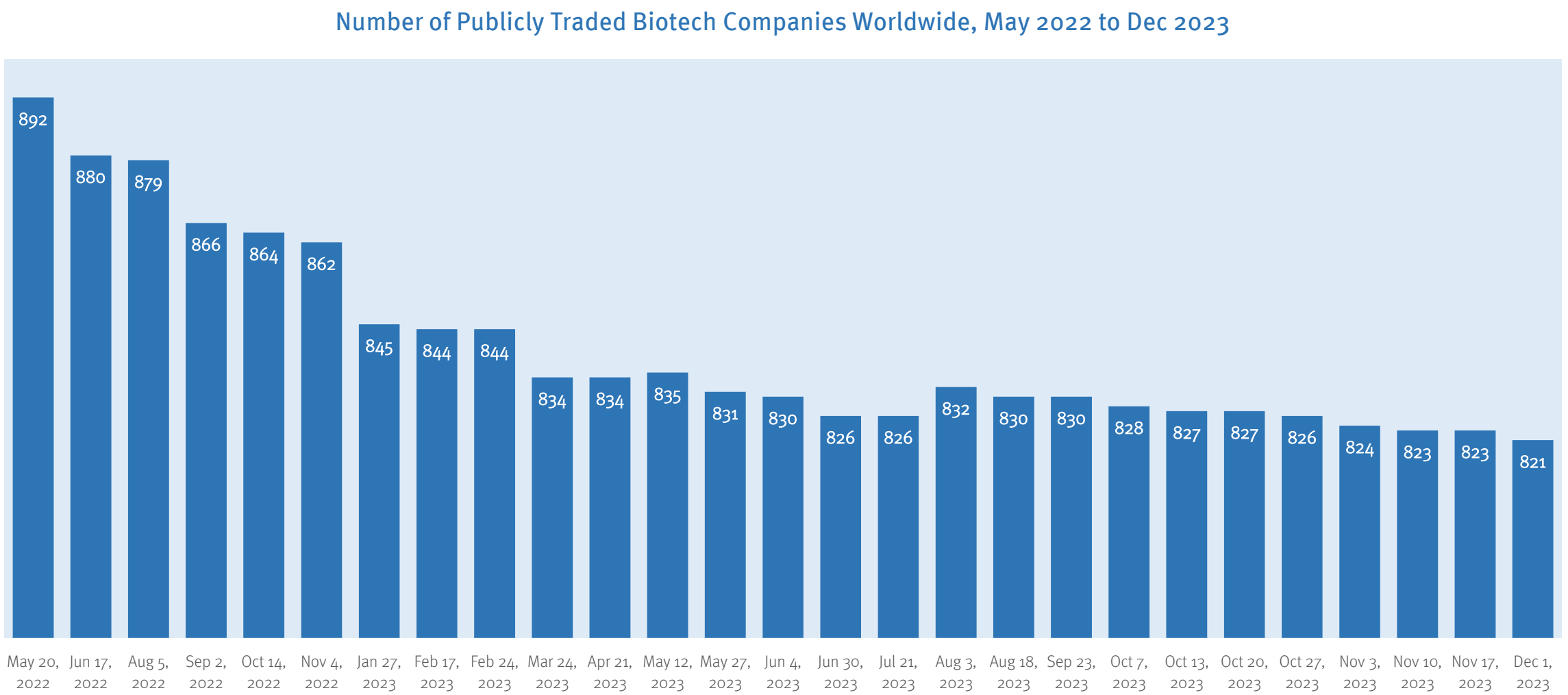
As a historical comparison, in the post-Genomics-Bubble aftermath from 2001-2003, the public biotech sector only shrank 7% despite similarly loud calls for consolidation, according to data in E&Y Reports from that time. A much bigger drop happened in the Great Financial Crisis, where we saw a net reduction of nearly 20% of the public biotech arena between 2007-2009. A hangover from an overly euphoric technology bubble is very different, perhaps, than the contagion of a financial system meltdown, at least in terms of driving biotechs to disappear.

So why has it been so hard to drive consolidating deals or liquidations, either now or in the post-2001 aftermath? Perhaps the sector just isn't well-suited to broad restructuring and consolidation. Hype, hope, and finding a way just keep companies going (even if it's not great for existing shareholders). The only time a big shift in the number of biotechs happened was when the financial markets ground to a halt, with banks going under, in the GFC – and that was only 20%, as noted above. My guess is most industry insiders would like to see 30-40% fewer public biotechs. I'm fairly confident that's not going to happen anytime soon.

While there's little to show for two years of the "we need fewer public biotech" sentiment, there's obviously going to be some temporal dynamic in these data. Companies that raised follow-on financings in the better days of 2021 are likely running on fumes now; they will either raise capital or fall into one of these other categories: Acquisition, Reverse Mergers, MOEs, shutdowns, or bankruptcies – or they will have to partner their prize assets and start over. And many have been "kicking the can down the road" through RIFs and portfolio prioritizations, which may or may not "work" at creating a path to successful survival during this challenging period. So there's still some time left for the public biotech world to meaningfully shrink.

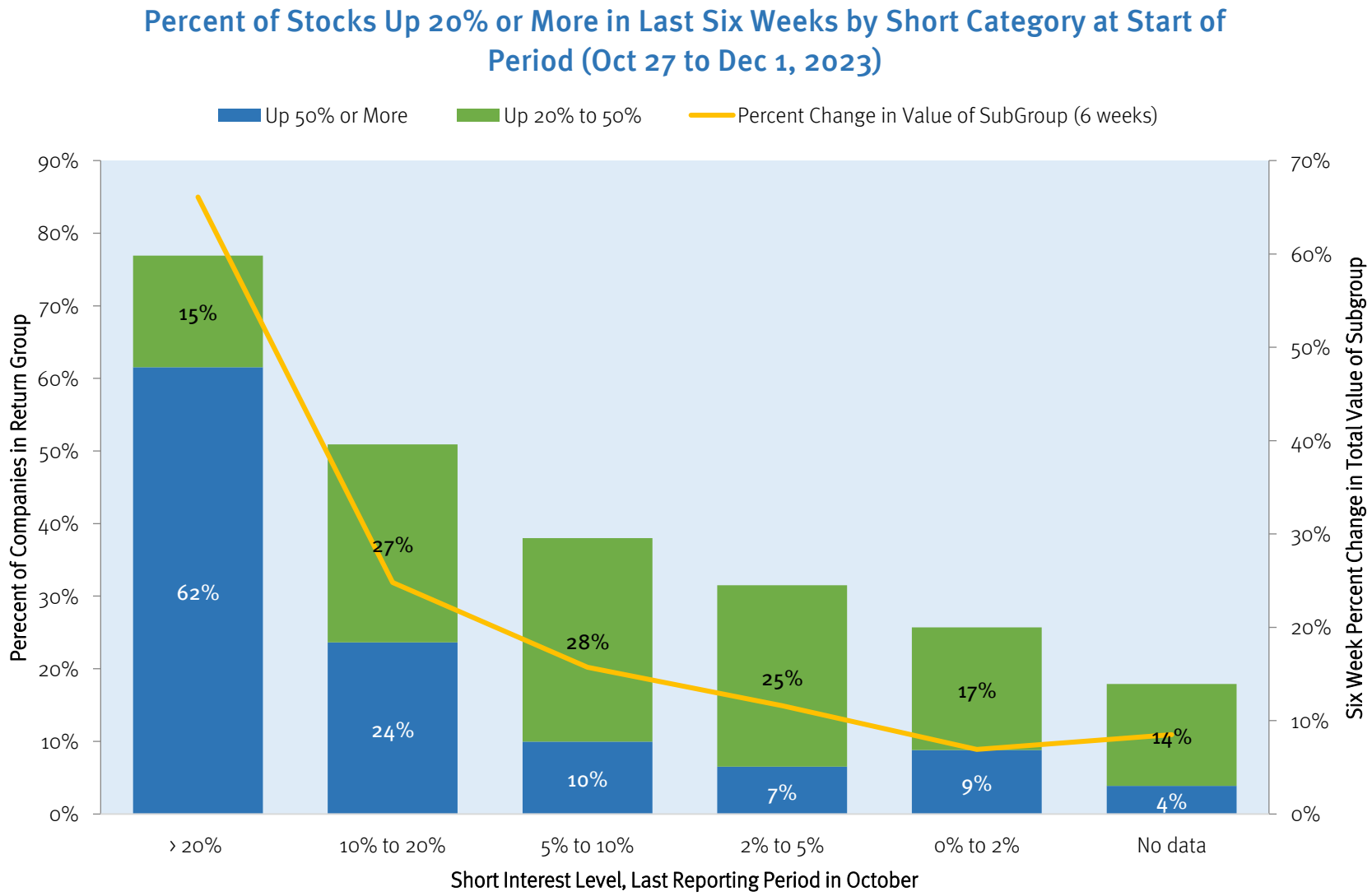
The bottom line is that big changes in industry numbers via consolidation/shutdowns are rather unlikely to happen. Convincing a management team and/or their Board to just shut down or hand the keys to someone else is superbly hard. It happens sometimes, but nowhere near as much as it probably should. Which is why we're likely stuck with a big universe of small cap public biotech companies for the foreseeable future.

Our Tracker Consistent with Bruce Booth Conclusion: Global Public Biotech Population Has Shrunk Only 8% in Last 18 Months



Source: CapitalIQ and Stifel analysis.

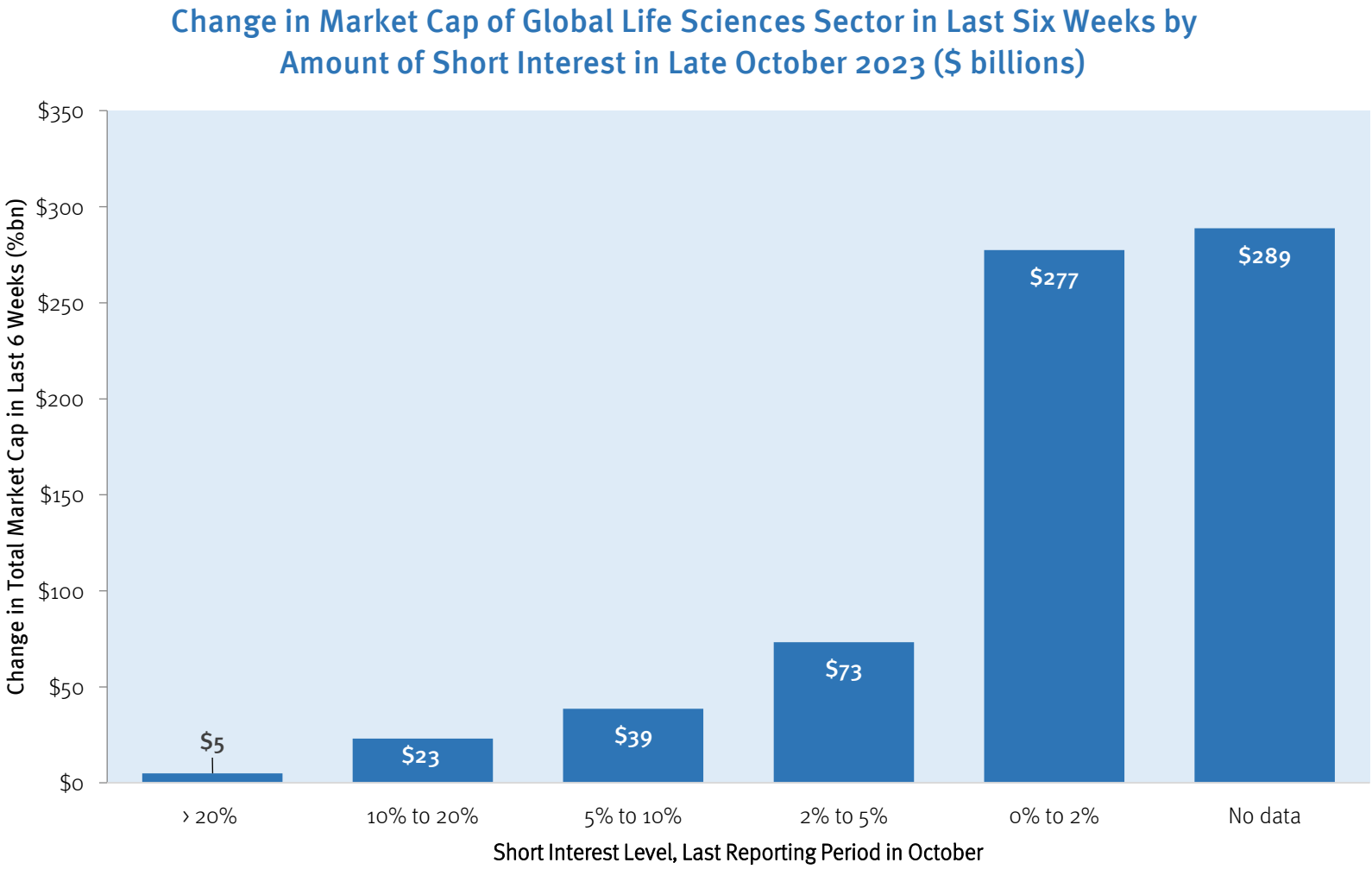
Short Selling Can be Highly Risky



Over 60% of companies that had short interest of 20% or more in late October have risen by 50% or more in the last six weeks. The average percent change in market cap over the last six weeks of this highly shorted group has been 66%. In contrast, companies with zero to 2% short interest at the time are up 6.9% over the same interval. It's clear from this chart that short-selling can be very dangerous when the market turns.

Source: S&P CapitalIQ and Stifel analysis. Short interest is defined as number of shares short divided by total shares outstanding.

Has This Been a Fundamental Rally or One Just Caused by Short Covering?



Even though returns have been much higher for highly shorted stocks in the last six weeks, 91% of the value accretion in the life sciences sector has been for companies where there was less than 5% baseline short interest.

The reason is an obvious one. Short positions of 5% or more are relatively rare.

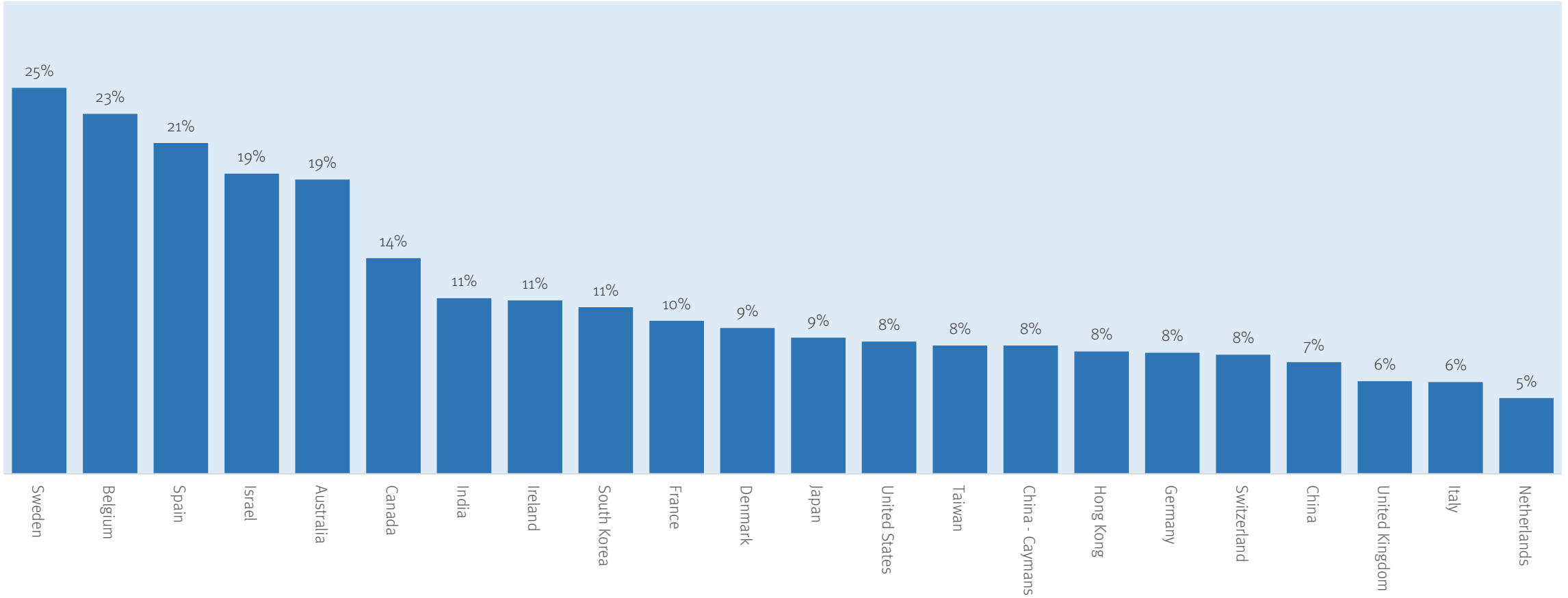
For this reason, one can say that overwhelmingly the recent rally has been a function of "real" buying rather than technically driven short covering.

Source: S&P CapitalIQ. Short interest is defined as number of shares short divided by total shares outstanding.

In Which Countries Has the Rally Been Strongest?

Life science companies in Sweden, Belgium, Spain, Israel and Australia have bounced the most in the recent rally. Life sciences stocks in the U.S. are up 8% in aggregate while those in China are up 7%.

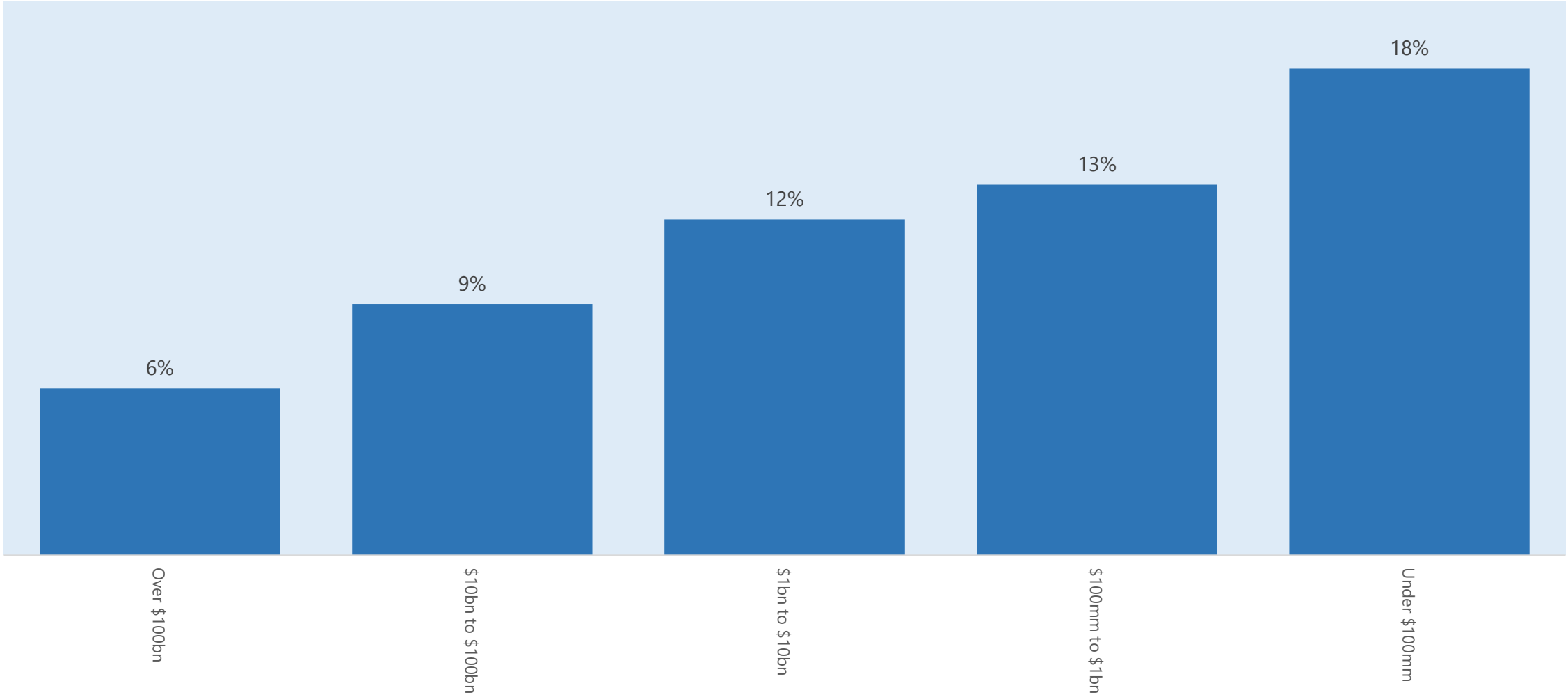
Percent Change in Aggregate Global Market Cap of HQ Country in Life Sciences Industry, Oct 27, 2023 to Dec 1, 2023



Source: CapitalIQ and Stifel analysis.

Small Caps Have Done Best in the Recent Rally

Percent Change in Aggregate Global Market Cap of Market Cap on Oct 27th, Oct 27, 2023 to Dec 1, 2023

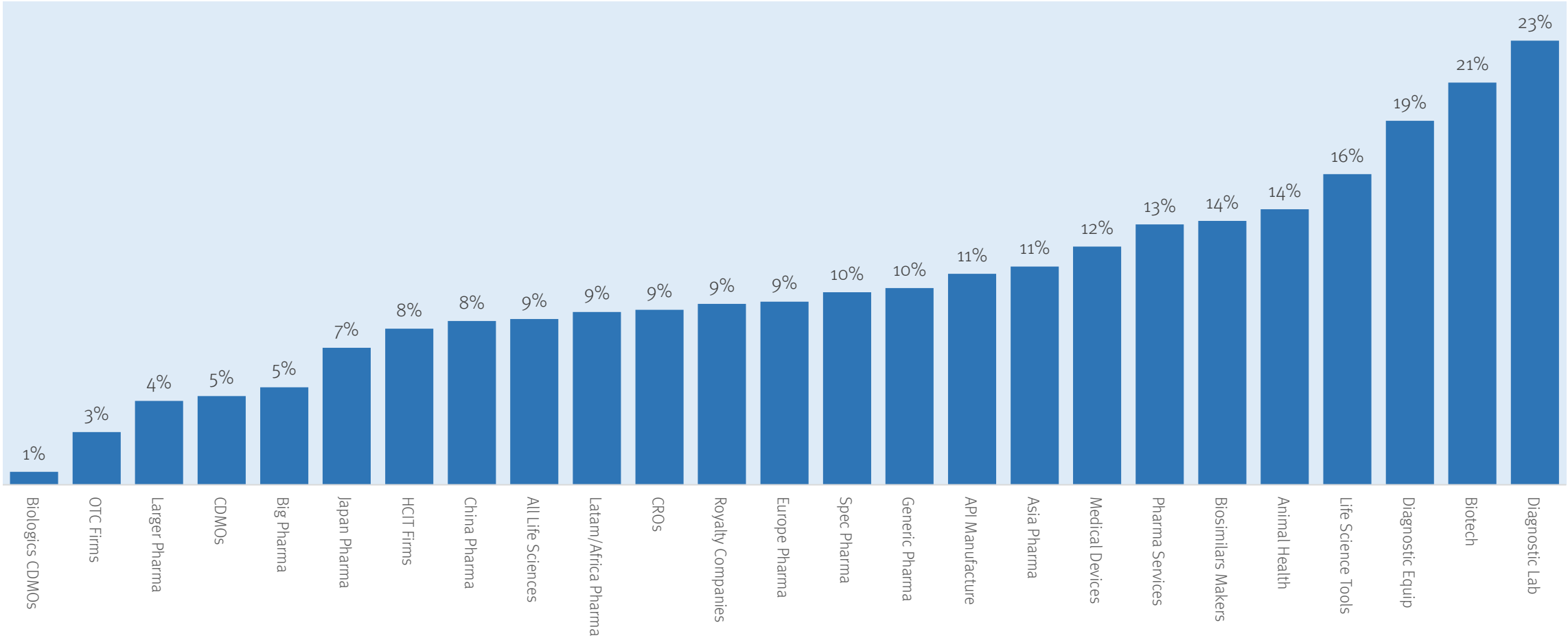


Source: CapitalIQ and Stifel analysis.

In Which Life Sciences Segments Has the Rally Been Strongest?

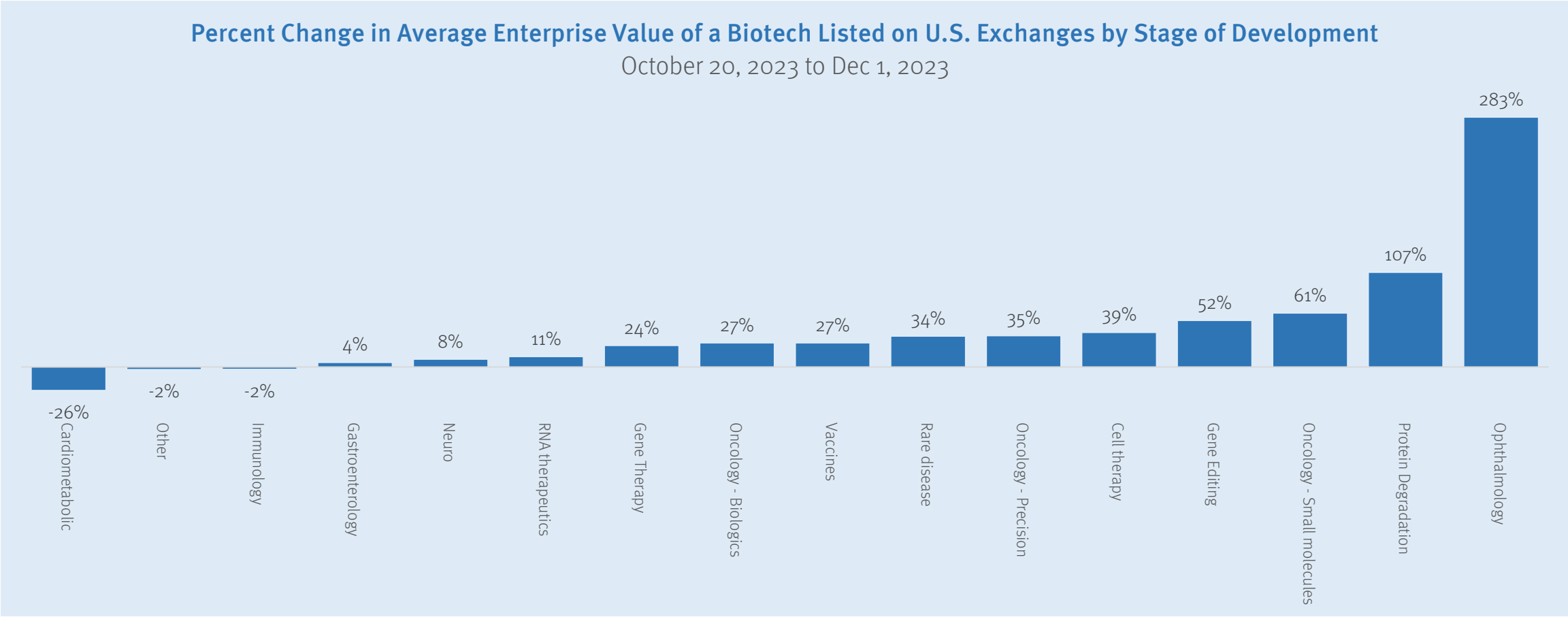
The valuations of biotechs, diagnostics companies, life science tools makers and animal health players are up 14% to 23% in the market rally of the last six weeks. The effect of the rally has been strong across the market and no subsector has traded down in aggregate over the last six weeks.

Percent Change in Aggregate Global Market Cap of Segment of Life Sciences Industry, Oct 27, 2023 to Dec 1, 2023



Source: CapitalIQ and Stifel analysis.

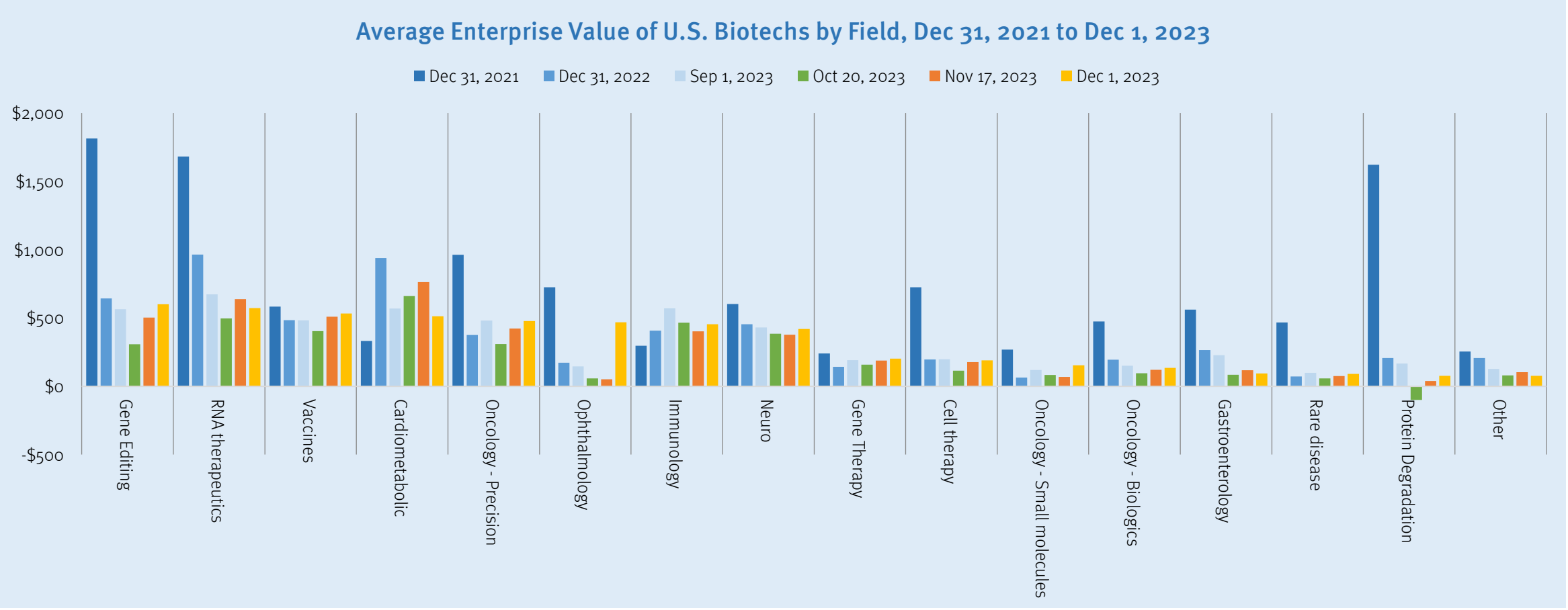
Biotech Rally Over Last Six Weeks: Ophthalmology, Protein Degraders and Oncology Bouncing Back. CVM and I&I Down



Source: CapitalIQ and Stifel analysis.

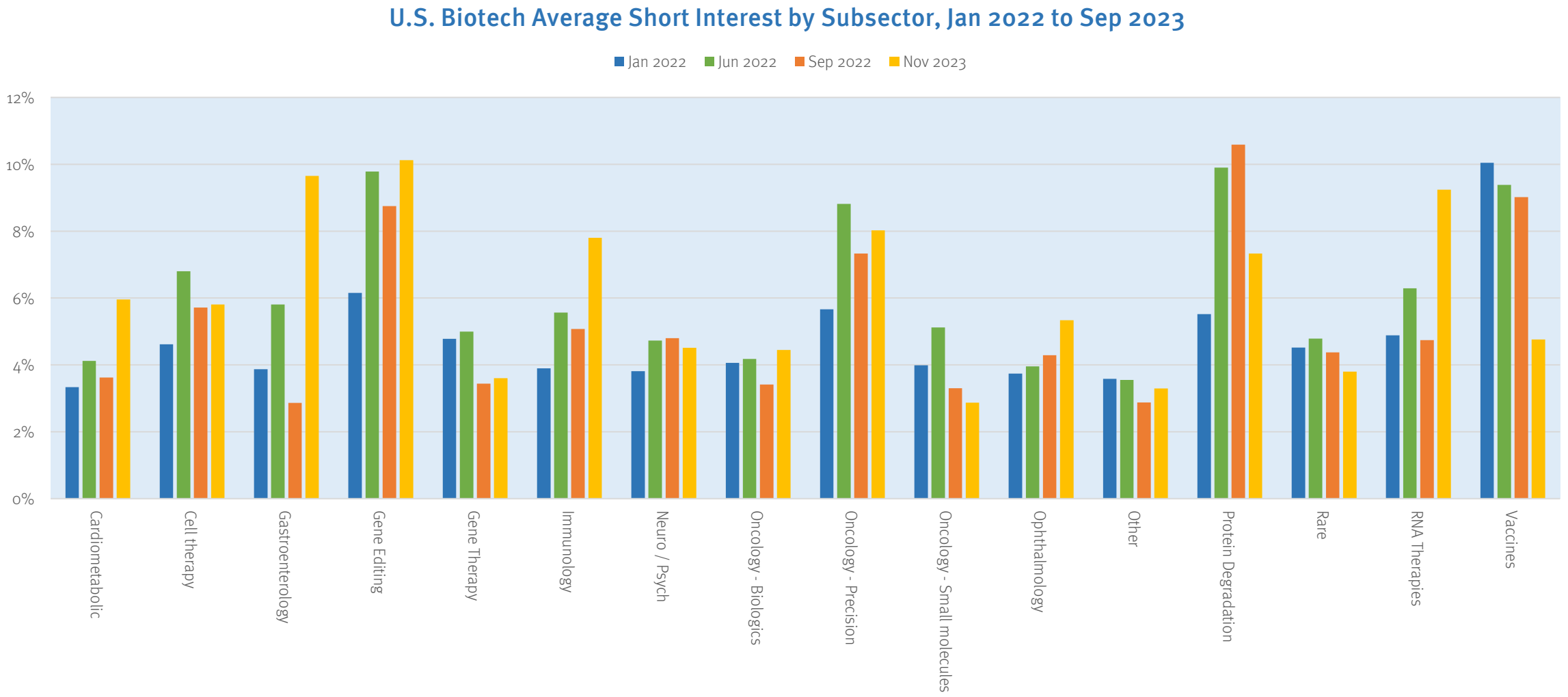
Highest Average US Biotech Valuations Today Found in Gene Editing, RNA, Vaccines and Cardiometabolic

Certain therapeutic areas have been deeply impacted in the post-pandemic biotech swoon. These include protein degraders, rare disease, oncology biologics (particularly IO antibodies), oncology small molecules, cell therapy and gene therapy. The rally is having an effect in these areas, but the value recoveries seen have been minor relative to the valuation declines since 2021.



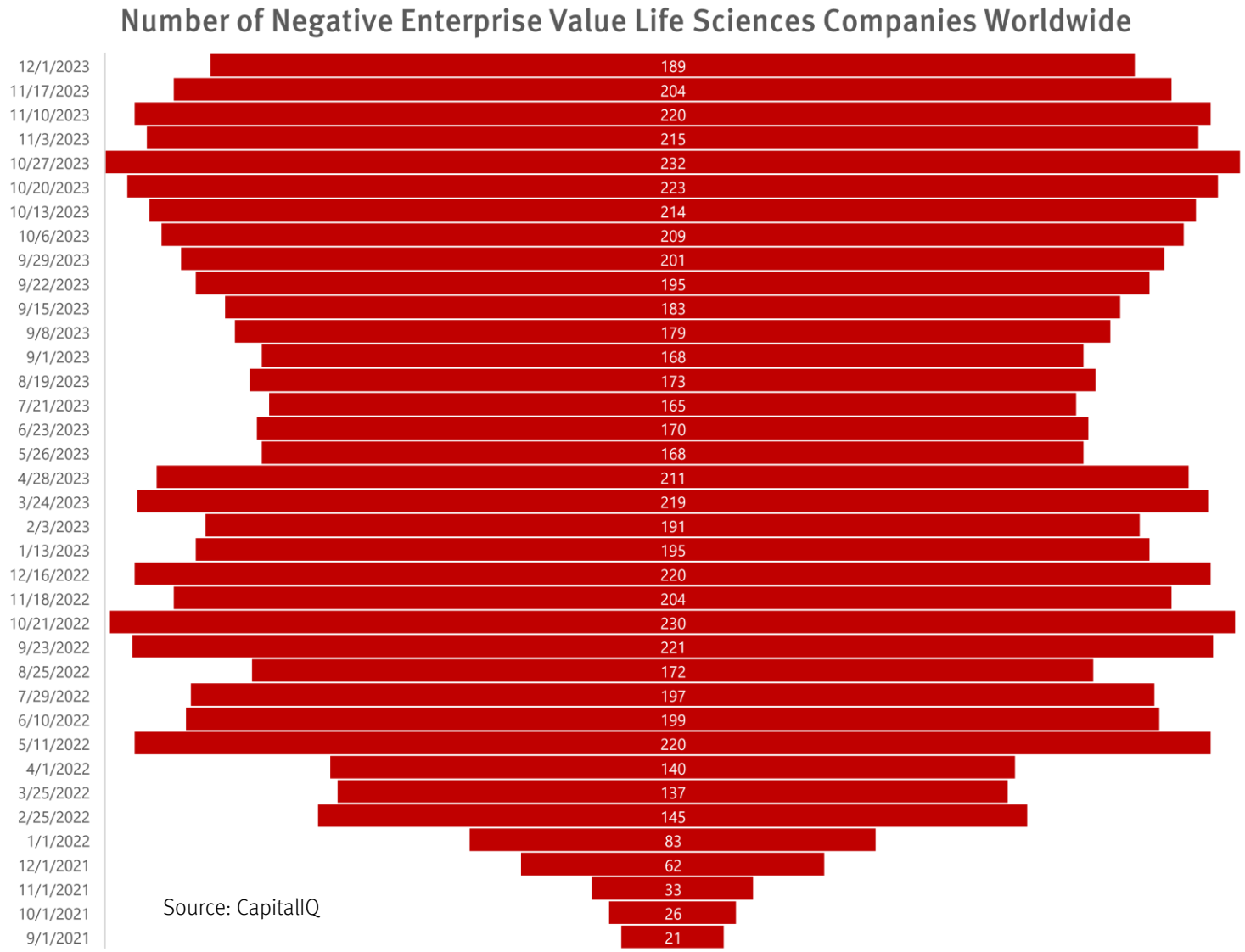
Source: CapitalIQ and Stifel analysis.

Short Interest Down Big in Protein Degraders and Vaccines While Creeping Up in Gene Editing, RNA, Immunology & GI



Source: CapitalIQ. Short interest is defined as number of shares short according to the most recent NASDAQ short interest report (typically, about a 3 week lage) and total shares outstanding.

Number of Negative Enterprise Value Life Sciences Companies Fell to 189 in Last Week



Source: CapitalIQ

The count of negative EV life sciences companies worldwide fell from 204 two weeks ago to 189 last Friday.

The negative EV life science company population has shrunk by 19% since peaking on Oct 27, 2023.

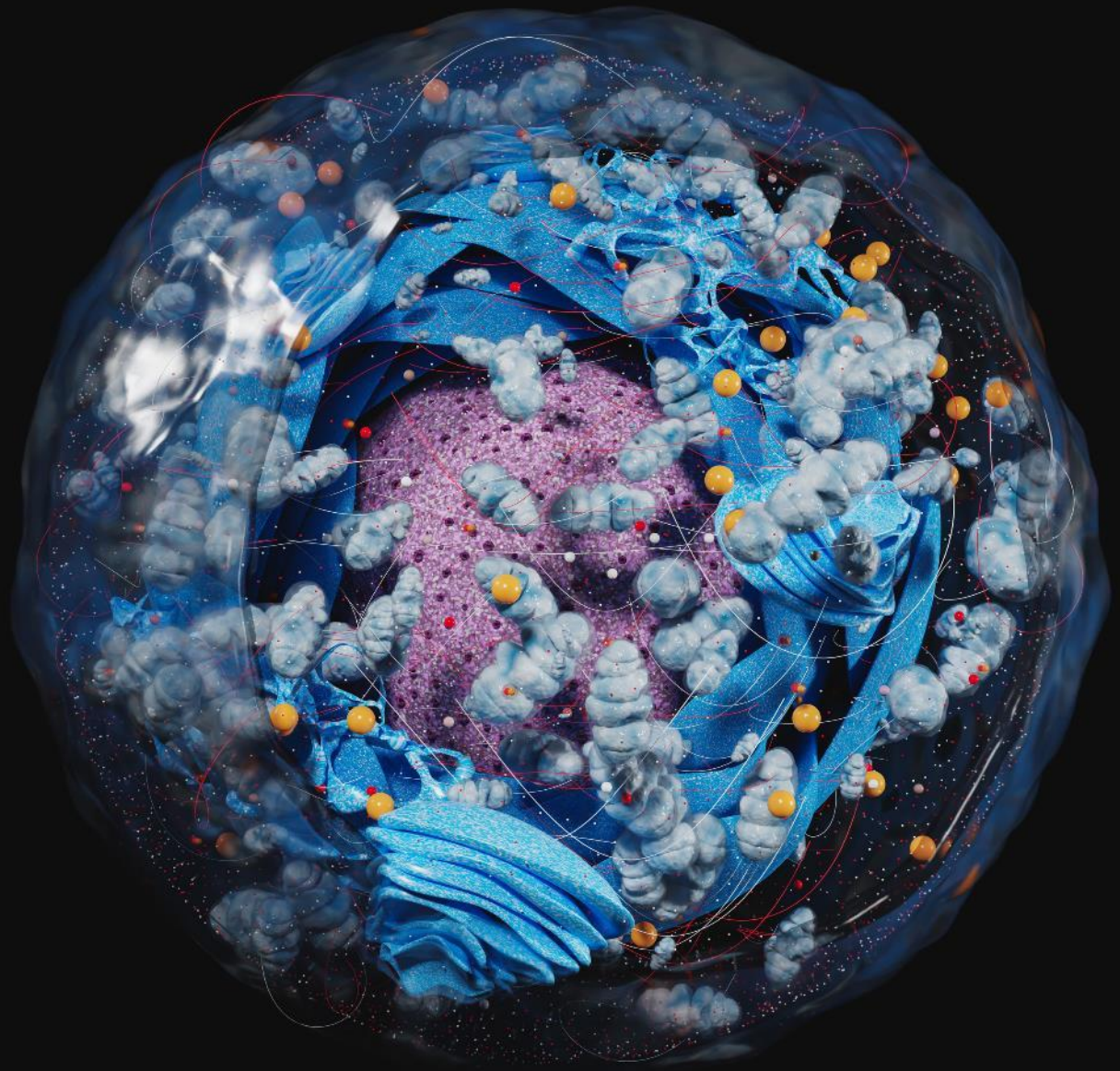
Life Sciences Sector Up 0.7% Last Week

Last week saw a 2.7% rise in life sciences stocks worldwide. The sector's value rose by $61 billion. Biotech was up the most. CDMO's were down 2.1%.

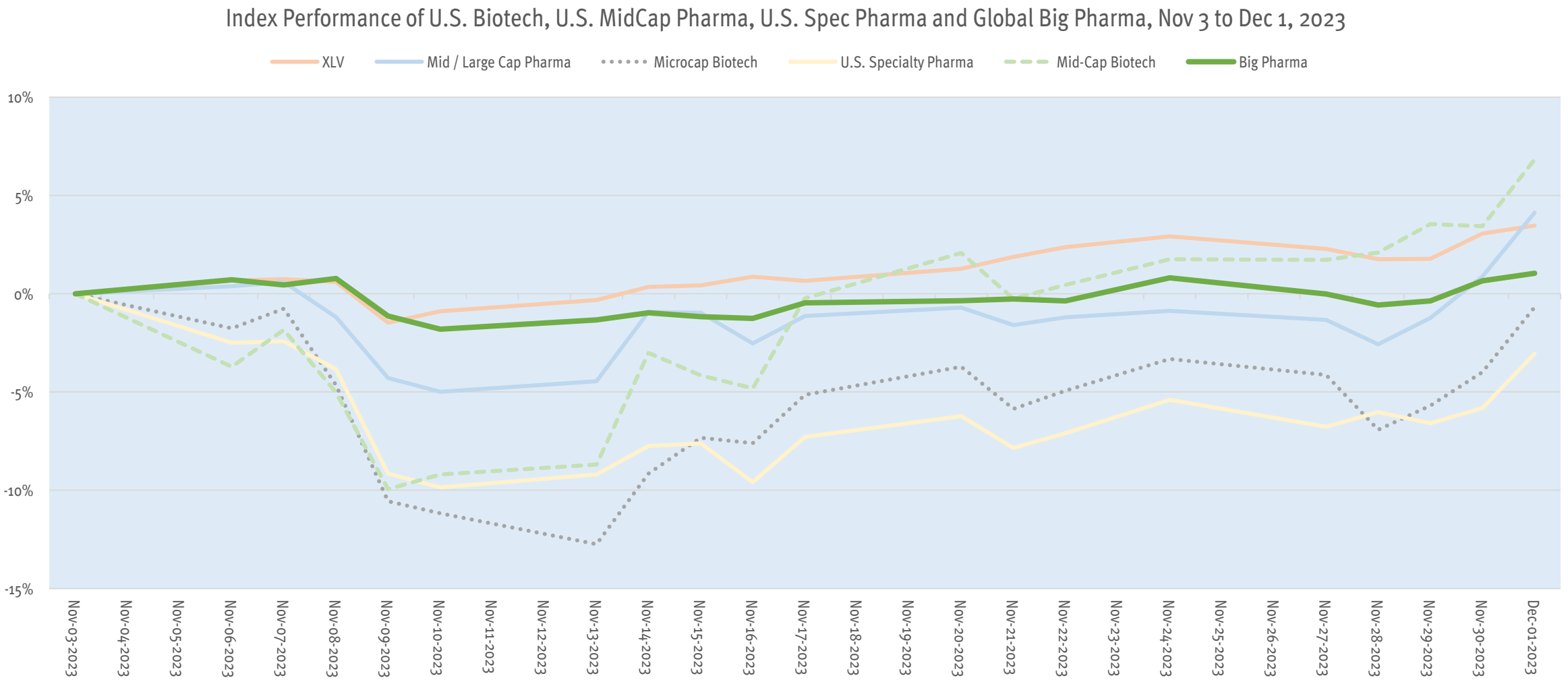
Sector	Firm Count	Enterprise Value (Dec 1, 2023, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	81	$86,228	0.9%	8.6%	3.6%
Biotech	808	$189,368	5.5%	19.8%	-5.1%
CDMO	40	$147,627	-2.1%	2.2%	-19.0%
Diagnostics	83	$261,747	2.1%	15.3%	-2.6%
OTC	30	$27,789	-0.4%	1.6%	-3.1%
Commercial Pharma	726	$5,776,836	0.5%	2.8%	-2.2%
Pharma Services	39	$204,168	0.0%	5.8%	3.4%
Tools	53	$642,688	1.2%	11.1%	-17.7%
Devices	181	$1,556,249	1.0%	7.4%	-2.5%
HCIT	11	$21,502	-0.5%	6.1%	-31.2%
Total	**2052**	**$8,915,201**	**0.7%**	**4.9%**	**-3.8%**

Source: CapitalIQ

Big Pharma Updates



Big Pharma Up 1% Over Last Month



Notes: These data are from S&P CapitalIQ and are compiled into equal-weighted indices. Big pharma includes PFE, LLY, MRK, ABBV, NOVO B, ROG, JNJ, AMGN, AZN, NOVN and SAN. Midcap / large pahrma includes VRTX, ARGX, ALNY, BMRN, INCY, NBIX, OGN, IONS, EXEL, ALKS, ITCI, HRMY, INDV, BPMC, MRTX, SAGE, IDIA, APLS. US specialty pharma includes SUPN, EGRX, CPRX, PCRX, IRWD, JAZZ, COLL, BHC, BLCO, ARQT, HLS, ASRT, OPTN, GTHX, ANIK, HROW, PHAT, ESPR, CALTX, AMARIN, OPK, LQDA, RIGL, EYPT, MRNS, ALIM, TRVN. Midcap biotech biotech includes KRTX, MDGL, CERE, CYTK, ARWR, PCVX, DNLI, VIR, CRSP, PRTA, BEAM, AKRO, IMVT, VRNA, VTYX, SWTX, SNDX and Microcap biotech includes LCTX, GLSI, GRPH, CYDY, OMER, SVRA, THRD, EVLO, TCRT, CMRX, TSHA, DTIL, OVID, TNYA, VXRT, CUE, XFOR, ATHA, TRVI, CTXR, SELB, CRMD, MTNB, AKBA.

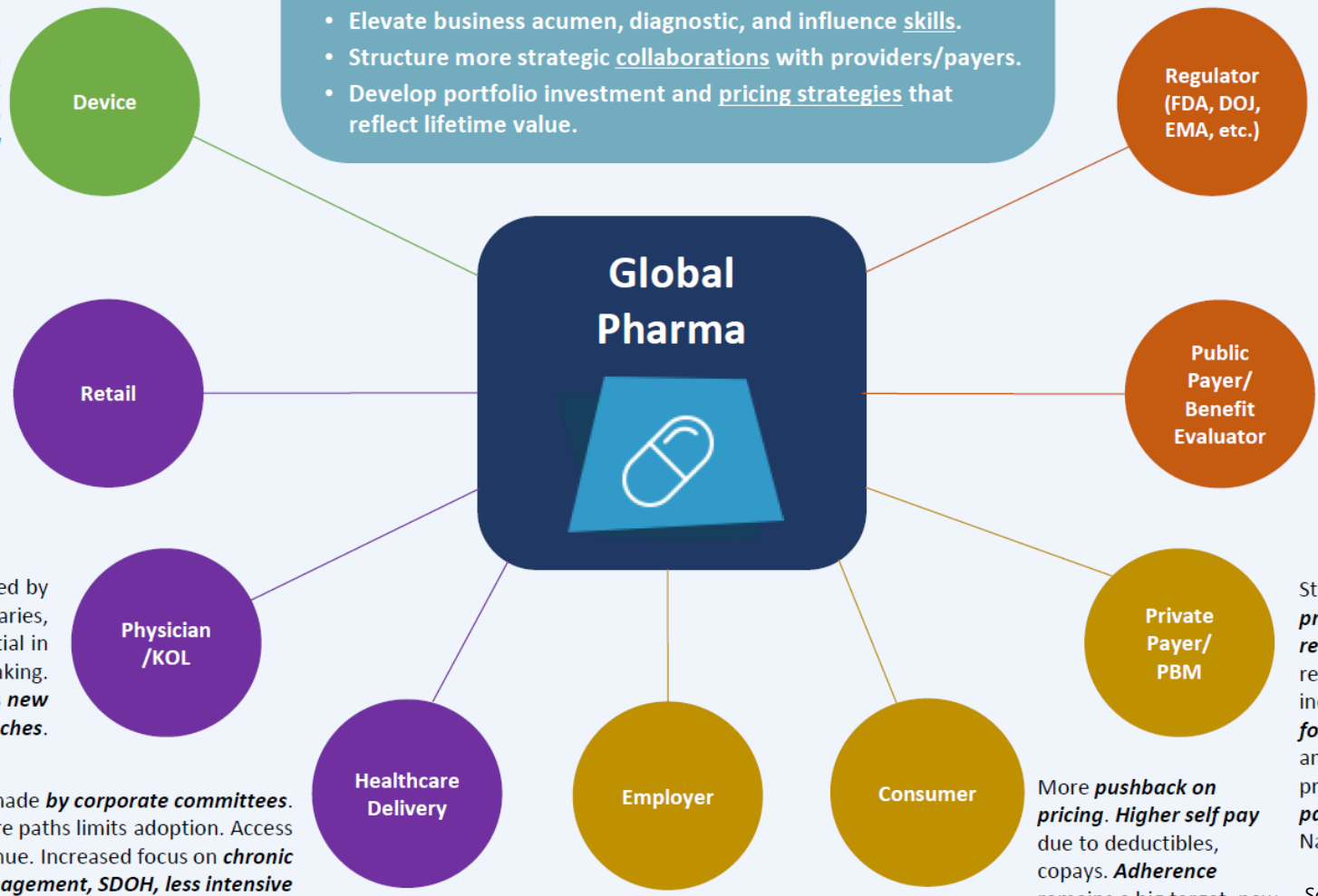
Numerof & Associates Highlights Large Pharma Challenges for 2024

Especially in the U.S., the consolidation of healthcare delivery into fewer, more complex and powerful healthcare systems is a growing challenge. This dynamic is changing who makes purchasing decisions, the criteria used, and the kinds of questions that get asked. Manufacturers are struggling to adapt their marketing and market access processes to this ongoing trend. We see continued innovation here – in engagement methods and in the way companies' structure and support their commercial model. Both technology as an enabler, and on more sophisticated approaches to major accounts management are increasingly being used to address the evolving way in which purchase decisions are made in healthcare. The search for new and effective ways to engage with stakeholders and differentiate products in a crowded field is here to stay.

The passage of the Inflation Reduction Act (IRA) in the U.S. shattered management's complacency regarding the political landscape. Similar regulatory actions are moving forward in the EU as well, with direct pricing agreements, price controls, reference and risk-based pricing increasingly being adopted.

Key Action Steps

- Reevaluate investments, R&D priorities, launch sequencing.
- Redesign commercial models, targeting/segmentation.
- Align R&D, Medical Affairs, Commercial functions.
- Craft compelling databased economic & clinical value narratives that resonate with key stakeholders.
- Elevate business acumen, diagnostic, and influence skills.
- Structure more strategic collaborations with providers/payers.
- Develop portfolio investment and pricing strategies that reflect lifetime value.



Explosion in AI and predictive analytics. More product development collaborations, ***combining drugs, devices, and diagnostics***.

Retail clinics continue to expand, and pharmacies increase primary care role. Growing disruption from ***new distribution models***. Focus on chronic disease management, medication adherence.

Physicians guided by institutional formularies, care paths, less influential in decision making. Engagement requires ***new omnichannel approaches***.

Product decisions made ***by corporate committees***. Adherence to care paths limits adoption. Access restrictions continue. Increased focus on ***chronic disease management, SDOH, less intensive settings, including home***.

Strong support for ***restricted formularies***, pushback on high price specialty drugs and ***high cost therapeutic areas***. Increased interest in reducing total cost of care/improving outcomes.

More ***pushback on pricing***. ***Higher self pay*** due to deductibles, copays. ***Adherence*** remains a big target, new consumer apps. More interest in ***clinical trial*** participation, outcomes.

Strong pushback on ***drug prices***. More ***access restrictions***. Evidence requirements increasing, including RWE. ***Restricted formularies***. Exploring risk and indication-based pricing. ***Increased partnerships*** with delivery. Narrow networks continue.

Price controls, ***reference/ risk-based pricing, access limits, harmonization***. More EU direct ***drug pricing agreements***. ***More RWE, CER***. National pricing impacting ***global pricing***. In the US, ***political and legislative action*** creates greater risk and opportunity.

IRA and EU initiatives challenge *launch sequencing, evidentiary requirements*, and *risk*. Strategic rethinking of ***global supply chains and reshoring***. ***Tougher enforcement*** of rules.

NUMEROF & Associates

Source: https://nai-consulting.com/the-numerof-global-pharma-outlook/

Can a Big Pharma Ever Be Worth $1 Trillion?

David Wainer, *Wall Street Journal*, Nov 29, 2023

There are five tech companies valued at over $1 trillion. In healthcare, the closest contender is Eli Lilly.

This year it became the first big pharmaceutical to surpass a market capitalization of $500 billion thanks to the popularity of its obesity and diabetes medications and, to a lesser extent, its experimental Alzheimer's drug. But hanging over Lilly and rival Novo Nordisk is a reality that puts the brakes on big pharma's ascent: the patent cliff.

There are several reasons why there isn't a big pharma company in the trillion dollar club, but the boom-and-bust nature of drug development is high on the list. Unlike Apple, which hypothetically can make huge margins off the iPhone for perpetuity, U.S. drug companies have a limited period from which to profit from their innovation. As their patents expire and generic competitors enter the market, sales plunge. Pharma executives, overly focused on short-term growth, don't often prepare their companies for that.

As Lilly soars into the pharma stratosphere, a big question is whether it can avoid the fate that has befallen its competitors (and itself in the past). The company's chief scientific and medical officer, Daniel Skovronsky, says he wants to avoid a key error much of the industry tends to make.

"When a company has a mega blockbuster drug that is doing really well, every investment on the margin goes towards that instead of towards something that's untested and unproven," he says in an interview. "And that drug overshadows the rest of the portfolio and everything else is starved for people, money and attention."

Once the big blockbuster runs out, he added, "they find out their cupboard is bare, and there's nothing else coming." The predicament Skovronsky describes ails nearly every drug company at the moment to varying degrees. The industry is staring down a $200 billion cliff in annual sales by the end of the decade. And because companies need to keep their top and bottom lines growing, they wind up having to sacrifice long-term innovation for short-term growth. Rather than making bets on edgier science, they shell out billions of dollars on proven therapies, where investment returns are lower. Another way to put it, says Skovronsky, is that they are moving money from the balance sheet to the income statement.

"We think about that as going to the grocery store when you're hungry. You end up buying things you don't really need," he says.

"We're going at business development from a longer-term perspective of what could pay off in the decades to come or more," Skovronsky says. "So some of our recent deals reflect that we're acquiring not just molecules but also a team, a technology, and a platform that we think can expand our capabilities."

Source: https://www.wsj.com/health/pharma/can-a-big-pharma-ever-be-worth-1-trillion-703583ae

Bayer Chief Blames Thin Drug Pipeline on ‘Years of Under-investment’

Olaf Storbeck, *Financial Times,* Nov 26, 2023

Bayer’s chief executive has blamed an “old chemistry mindset” and a chronic lack of investment in research by his predecessors for a thin drug pipeline that has dragged down the group’s share price.

“We had several years of under-investment up until about 2018. Bayer was not sourcing novel, cutting-edge molecules [and was not] going for really important targets,” Bill Anderson told the Financial Times in an interview after the German group shocked shareholders by abandoning a late-stage trial of one of its most promising new drugs.

As a consequence, “the late-stage pipeline is thin relative to the patent losses we have in the next years”, he said. “I can’t fix what didn’t happen eight or 10 years ago.”

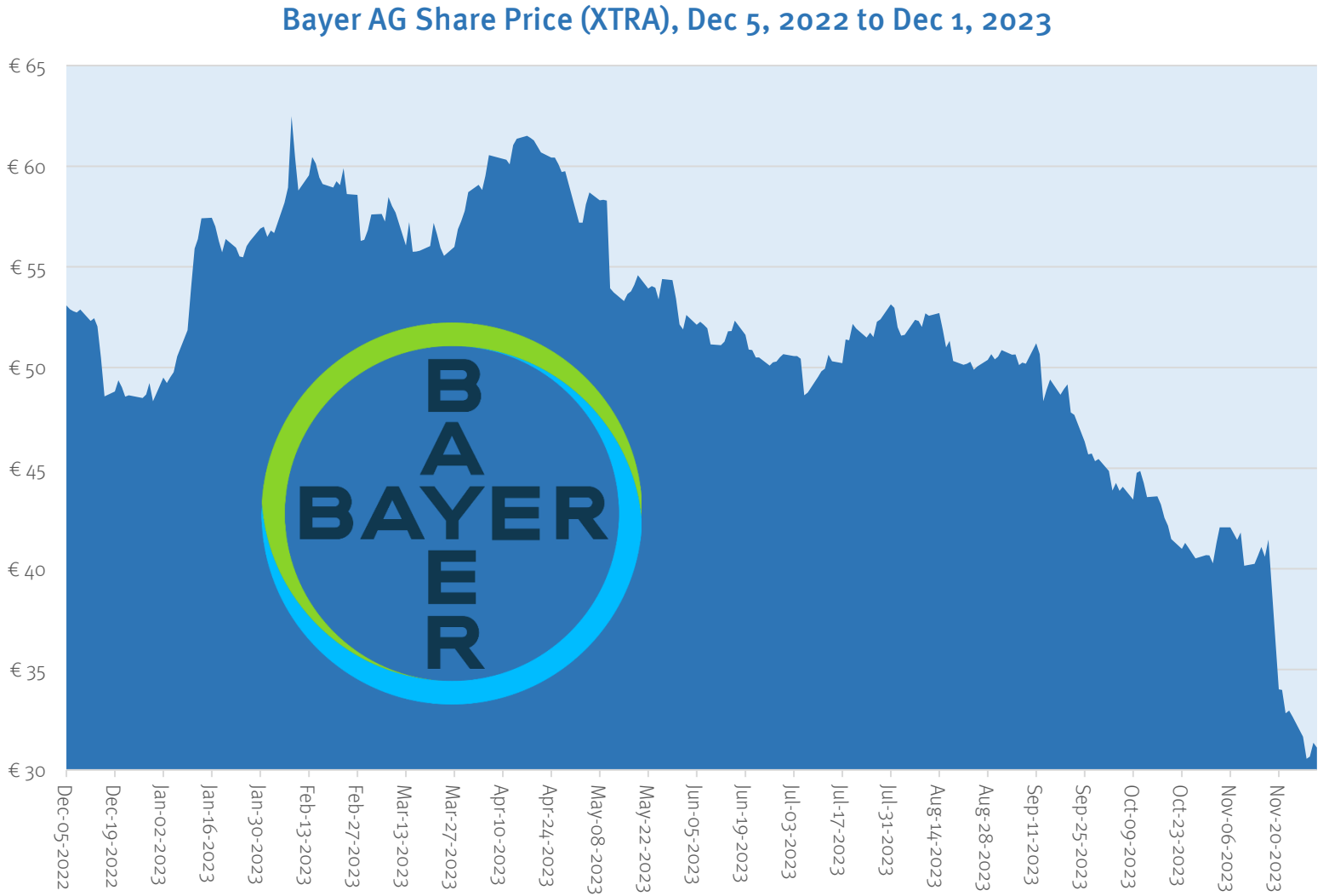
Bayer last week abandoned a trial of blood-thinner asundexian after it did not work as hoped to treat heart disease. The setback over a drug that was supposed to generate up to €5bn in annual sales at its peak caused Bayer’s already struggling stock to fall 18 per cent in a day. Patents for its two best-selling drugs are also expiring over the next three years.

Bayer is left with three prospective blockbusters that it hopes will generate more than €1bn in annual sales each: a treatment for prostate cancer, for chronic kidney disease and to treat menopause symptoms.“

I like the late-stage assets that we have,” Anderson said but added that the lack of new market-ready drugs was caused by an “old chemistry mindset” that was prevalent at Bayer until five years ago when the company made radical changes to its R&D strategy. But until then, he said, Bayer’s thinking was: “If we had enough chemists and labs, then eventually they’d come up with something. That’s not a strategy.”

Source: https://www.ft.com/content/ffce99b0-7fd6-4b47-94f4-45d03cd68882

Bayer Market Cap Down to $33 Billion



We should probably stop referring to Bayer as a “big pharma” as their cap today is less than that of companies like Seagen and Sun Pharma.

The company is trading with an EV / EBITDA ratio of 6.8x. The largest generator of EBITDA is their glyphosate franchise in crop sciences. The bad news is that this is vulnerable to near term patent expiry. The good news is that there is no such thing as generic substitution in the crop world and glyphosate sales should be strong for years to come. Further good news comes from an early pipeline which includes products like BlueRock’s IPSC product for cancer.

Luke Miels Sheds Light on GSK Internal Changes, 'Very Busy' BD Scene

Amber Tong, *Endpoints News*, Nov 30, 2023

GSK has been reworking its R&D process, complete with a recent revamp on the research side. And according to chief commercial officer Luke Miels, the overhaul has had an impact on his team, too.

The entire organization has changed "a lot" over the past few years, Miels said at a fireside chat during the Redburn Atlantic CEO Conference. The key idea? To make sure that people on the commercial side who are working with the R&D team on projects are both "scientifically fluent" and "commercially credible" — and vice versa within the R&D unit.

The commercial group has also been deeply involved in deals, according to Miels, who says he spends about 20% of his time looking at business development opportunities as it's an attractive and "very busy" environment.

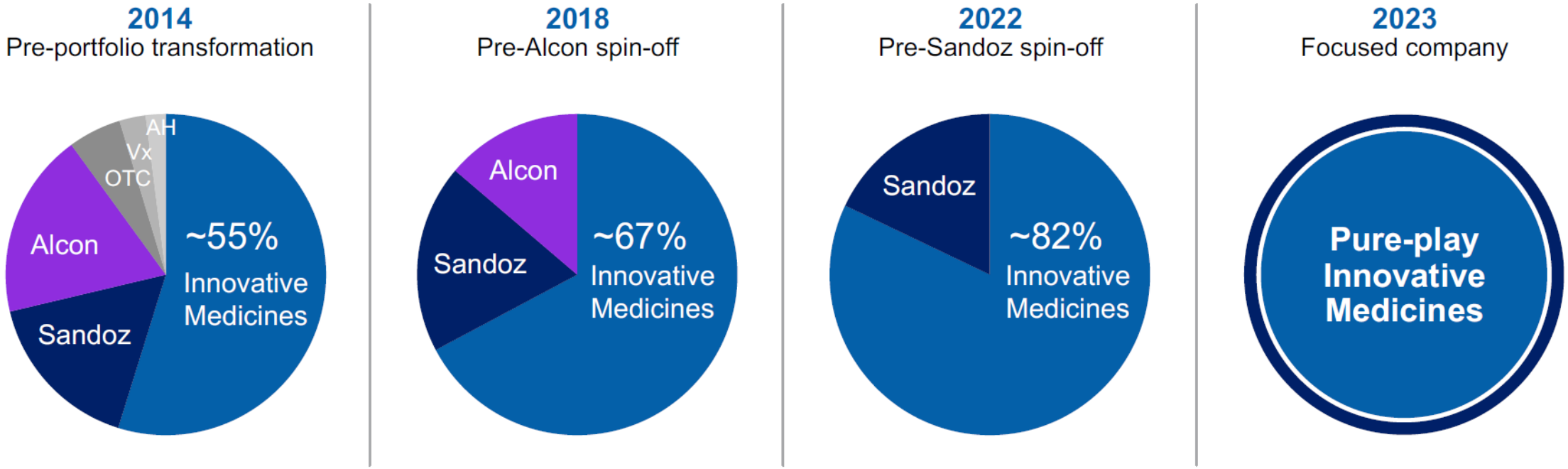
He offered the acquisitions of Bellus Health and Sierra Oncology as examples, where GSK would buy a company for the potential of their late-stage programs — and future deals will similarly be "in that couple of billion range, not mega-deals." Then there are the even smaller tuck-in deals in the hundreds of millions.

Luke Miels, Chief Commercial Officer, GSK

Source: https://endpts.com/luke-miels-on-gsk-internal-changes-very-busy-bd-scene/

Novartis R&D Day

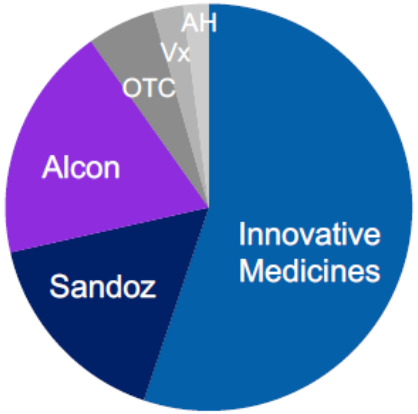
Novartis R&D Day (Nov 28):
Radical Transformation of Company Since 2014



Source: https://www.novartis.com/news/media-releases/novartis-upgrades-mid-term-sales-growth-guidance-showcases-its-differentiated-innovative-medicines-strategy-and-robust-pipeline-rd-day

Novartis Has Improved Margins and Cash Flow Through Portfolio Transformation

9M 2014
Pre-portfolio transformation



9M 2023
Focused company

	9M 2014 Pre-portfolio transformation	9M 2023 Focused company
Group core margin	26.0%	36.9%
Group FCF (USD) as % of sales	6.8bn Q1-Q3 2014 15.6%	11.0bn Q1-Q3 2023 32.4%

9M 2014 figures reflecting revised free cash flow definition, 2023 figures reflect Continuing Operations.

Source: https://www.novartis.com/news/media-releases/novartis-upgrades-mid-term-sales-growth-guidance-showcases-its-differentiated-innovative-medicines-strategy-and-robust-pipeline-rd-day

NOVARTIS

We are raising our mid-term sales guidance to +5% CAGR and core margin of ~40%+ by 2027...

Barring unforeseen events

Novartis (Continuing operations)

Net sales expected to grow
+5% cc CAGR 2022-2027

Raised from expected to grow +4% cc CAGR 2022-2027

Core operating income margin
~40%+ by 2027

Absorbing corporate costs & low margin contract manufacturing sales to Sandoz

Source: https://www.novartis.com/news/media-releases/novartis-upgrades-mid-term-sales-growth-guidance-showcases-its-differentiated-innovative-medicines-strategy-and-robust-pipeline-rd-day

NOVARTIS

Three breakthrough technology opportunities could potentially unlock substantial mid-to-long-term growth for Novartis

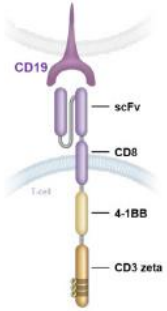
Radioligand therapies in solid tumors

RLT therapies achieving **better efficacy** with **lower side effects** e.g. prostate, neuroendocrine

Promising platform due to more **effective patient selection** (imaging) and **precision targeting** tumor cells

Significant market opportunity with **potential in other solid tumors**: e.g. lung, breast, GI

CAR-T in immunology



Promising early data for **CD19 CAR-T in SLE**[1]

Potential cures in a range of refractory **B-cell driven autoimmune diseases**

Potential in SLE, Sjögren's, severe rheumatoid arthritis, and other neurological diseases

siRNA in neuroscience and cardiovascular

Improving **adherence** whilst **maintaining efficacy** in cardiovascular

Technologies delivering **nucleic assets to the brain** have shown promising early data

Major market **opportunities** in **neurodegenerative**, **neuromuscular** and **cardiovascular** diseases

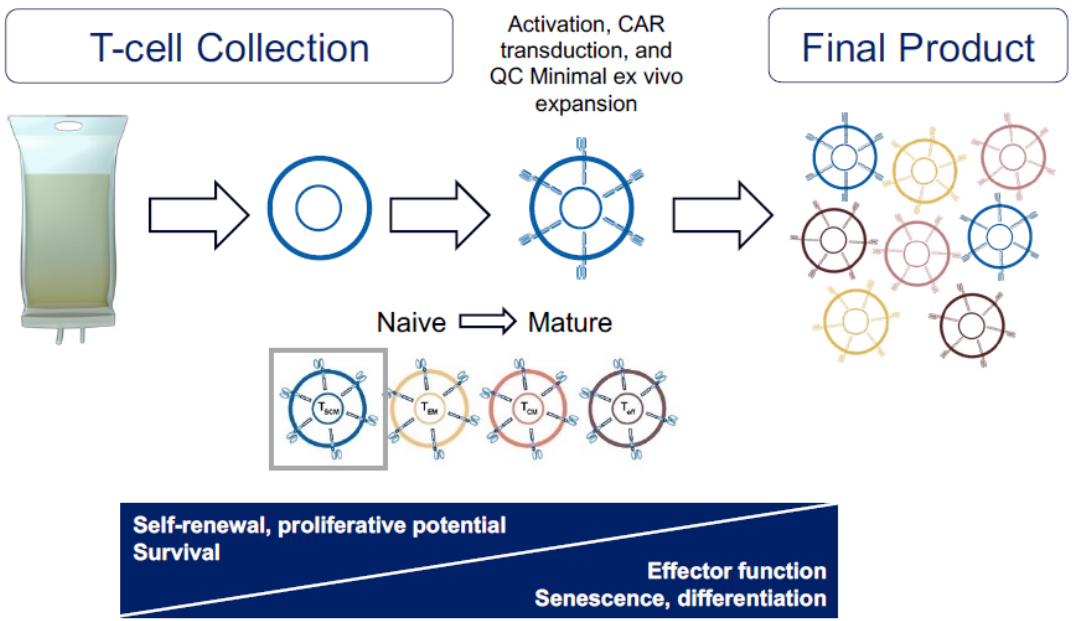
1. Hernandez, JC, Barba, P, Alberich, ML, et al. (2023) An Open-Label, Multicenter, Ph1/2 Study to Assess Safety, Efficacy and Cellular Kinetics of YTB323 (rapcabtagene autoleucel), a Rapidly Manufactured CAR-T Therapy Targeting CD19 on B Cells, for Severe Refractory Systemic Lupus Erythematosus: Preliminary Results; [abstract]. Arthritis Rheumatol. 75 (suppl 9).

Source: https://www.novartis.com/news/media-releases/novartis-upgrades-mid-term-sales-growth-guidance-showcases-its-differentiated-innovative-medicines-strategy-and-robust-pipeline-rd-day

Novartis: Impressive Progress on Cell Therapy Platform

Moving to a differentiated second-gen platform in cell therapy...

T-Charge™ second generation rapid manufacturing...



...differentiated from first-gen CAR-T

1. **Younger T-cells preserving stemness**[1,2,3]
   increasing the stem and central memory T cells[3]

2. **Enhances in vivo expansion**[2,3]
   with the potential to improve efficacy and durability of response 25-fold lower CAR-T cell count infused compared to traditional CAR-T

3. **<2 days manufacturing time**[2,3]
   aim of <10 days door-to-door time in the US

1. Engels, B. et al. Blood 138 (Suppl. 1): 2848 (2021). 2. Barba P, et al. Blood (2022) 140 (Supplement 1): 1056–1059. 3. Sperling A, et al. EHA 2022 Congress; June 9-12, 2022; Vienna, Austria. Poster P1446.

Source: https://www.novartis.com/news/media-releases/novartis-upgrades-mid-term-sales-growth-guidance-showcases-its-differentiated-innovative-medicines-strategy-and-robust-pipeline-rd-day

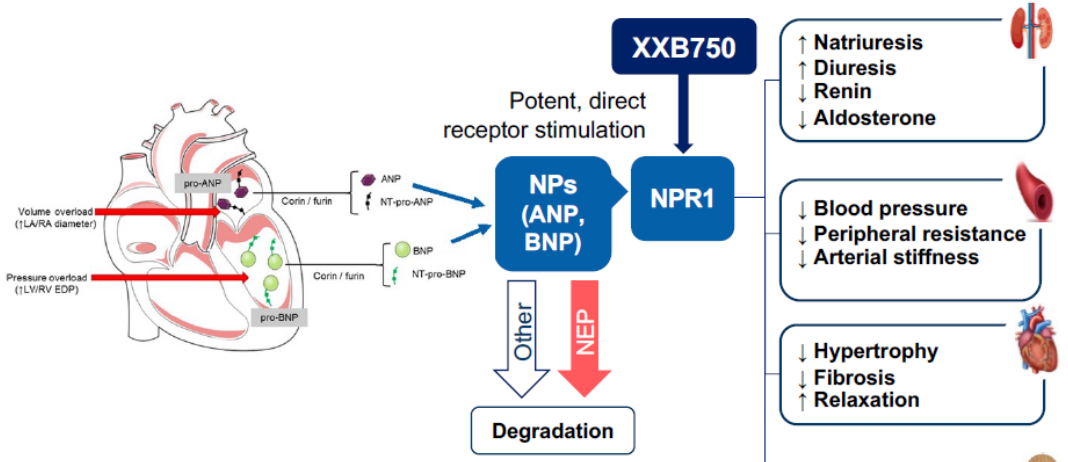
Novartis' NPR1 Activator Making Progress

XXB750: Innovating in natriuretic peptide (NP) biology for refractory HFrEF and resistant hypertension

- Building on our strengths in heart failure research, development and commercialization of Entresto with XXB750
- XXB750 is a fully human monoclonal antibody, activates NPR1 directly via a novel ANP-noncompetitive mechanism
- NPR1 is expressed in multiple organ systems and plays a central role in hypertension and heart failure
- Pre-clinical and early clinical data support potential benefit of XXB750 due to stimulation of the NPR1 receptor

Ph2 in rHTN ongoing; Ph2 HF FPFV H1 2024

XXB750 fully leverages the benefits of the NP system by direct receptor stimulation



Advantages of direct receptor stimulation:

- ✓ Bypasses natriuretic peptide (NP) degradation pathways
- ✓ Overcomes inactive BNP isoforms issue
- ✓ Evidence suggesting ANP as main mediator of cGMP increase by Entresto

HFrEF – heart failure with reduced ejection fraction. (r)HTN – (resistant) hypertension. NPR1 – natriuretic peptide receptor 1. ANP – atrial natriuretic peptide. FPFV – first patient first visit.

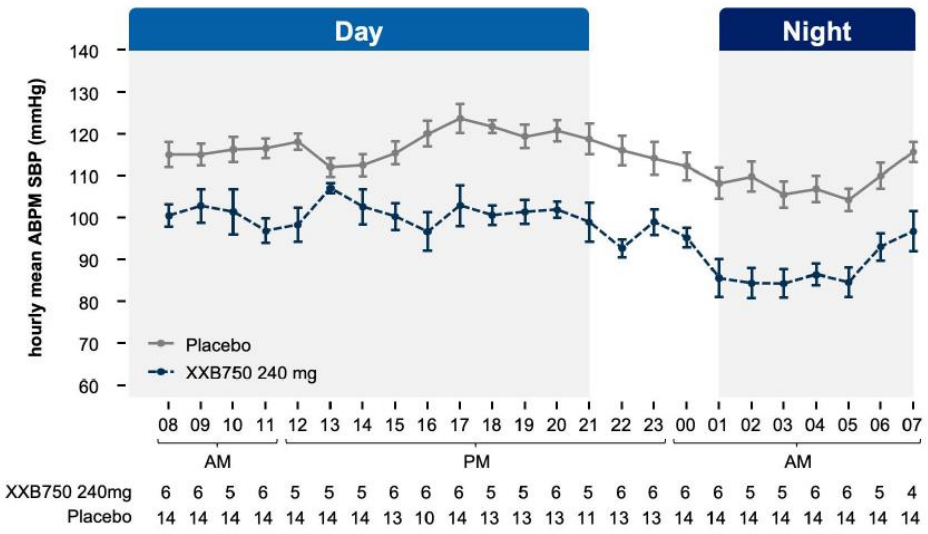
Source: https://www.novartis.com/news/media-releases/novartis-upgrades-mid-term-sales-growth-guidance-showcases-its-differentiated-innovative-medicines-strategy-and-robust-pipeline-rd-day

NPR1 Activator Data to Date Impressive

Ph1, healthy volunteer data 24-hr ABPM SBP at day 2

Placebo vs. XXB750 240mg

Day 2 after XXB750 240mg single dose



- Approximately 10% of hypertensive patients are not well-controlled despite concurrent use of ≥ 3 classes of antihypertensive agents[1]

XXB750

- ✓ Novel mechanism of action orthogonal to RAS inhibition
- ✓ Highly efficacious in healthy volunteers: mean SBP lowering of ~18mmHg
- ✓ Sustained BP lowering over 24 hours
- ✓ Improvement in night time dipping
- ✓ Progressing in Ph2b study in resistant hypertension

Wow Factor

SBP – systolic blood pressure (BP). ABPM – ambulatory blood pressure monitoring. RAS – renin-angiotensin system. 1. Sheppard JP, Martin U, McManus RJ, Diagnosis and management of resistant hypertension, Heart 2017;103:1295-1302.

Source: https://www.novartis.com/news/media-releases/novartis-upgrades-mid-term-sales-growth-guidance-showcases-its-differentiated-innovative-medicines-strategy-and-robust-pipeline-rd-day

NOVARTIS

Strong pipeline across our core therapeutic areas with planned submissions by 2027

Select examples

Kisqali®
●●●
Adjuvant breast cancer filed in EMA in **Q3 2023.** FDA regulatory submission expected in **Q4 2023**

Pluvicto®
●●
mCRPC (post-ARDT, pre-taxane), FDA regulatory submission expected in **2024**

mHSPC readout expected in **2025**

Iptacopan
●●●
PNH filed with FDA and EMA in **Q2 2023**

IgAN submission expected in **2024**[1]

C3G readout expected in **Q4 2023**

Atrasentan
●
IgAN submission expected in **2024**[1]

Remibrutinib
●●●
CSU submission expected in **2024**

Multiple sclerosis and CINDU readouts expected in **2026**

Lutathera®
●
GEP-NET 1L G3 EU submission expected in **2024**

Scemblix®
●●
1L CML-CP readout expected in **2024**

OAV-101
●●
SMA IT readout expected in **2024**

Pelacarsen
●●●
CVRR readout expected in **2025**

Ianalumab
●●●
1L and 2L ITP readouts expected in **2025**

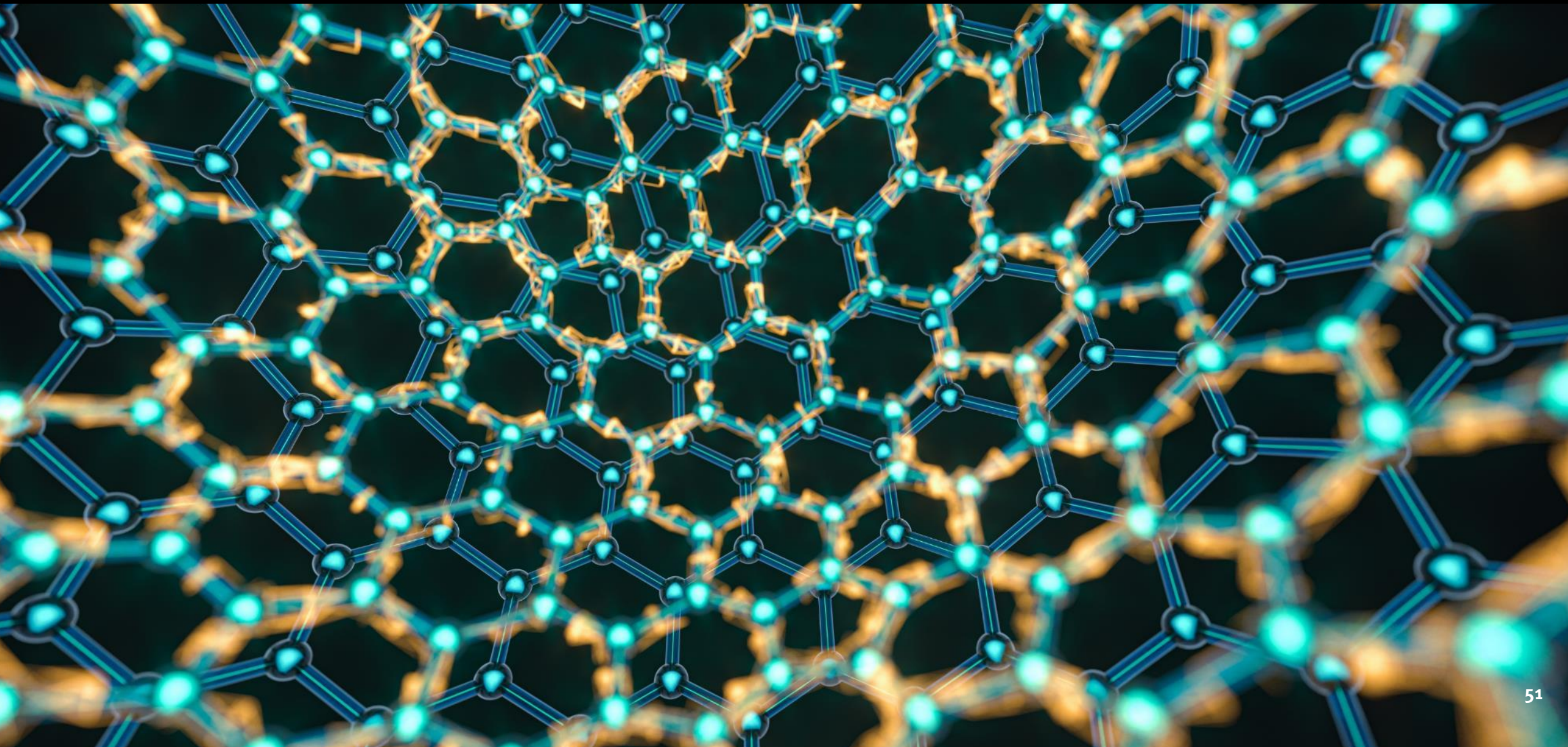
Sjögren's readout expected in **2026**

Zigakibart
●
IgAN readout expected in **2026**

1. US submission for accelerated approval. Unprobabilized estimated peak sales of all asset indications in late-stage development: ● > USD 1bn ●● > USD 2bn ●●● > USD 3bn

Source: https://www.novartis.com/news/media-releases/novartis-upgrades-mid-term-sales-growth-guidance-showcases-its-differentiated-innovative-medicines-strategy-and-robust-pipeline-rd-day

Peter Kolchinsky of RA Capital on Cost Effectiveness Analysis



To read the full slide deck:
https://nopatientleftbehind.docsend.com/view/y6m6fz6umi9e4chk

RACAPITAL

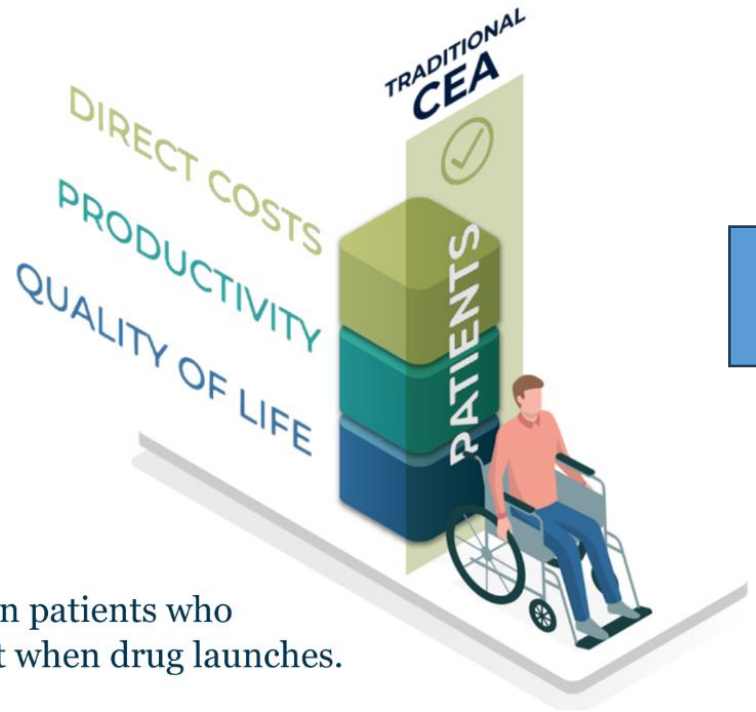
Do Fish Know About Water?

PETER KOLCHINSKY, PhD
Managing Partner, RA Capital Management
Co-Founder, No Patient Left Behind

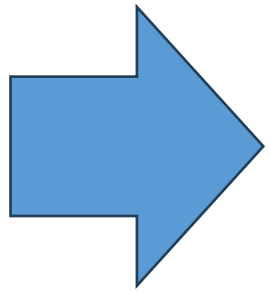
CVCT CONFERENCE
NOVEMBER 2023
WASHINGTON D.C.

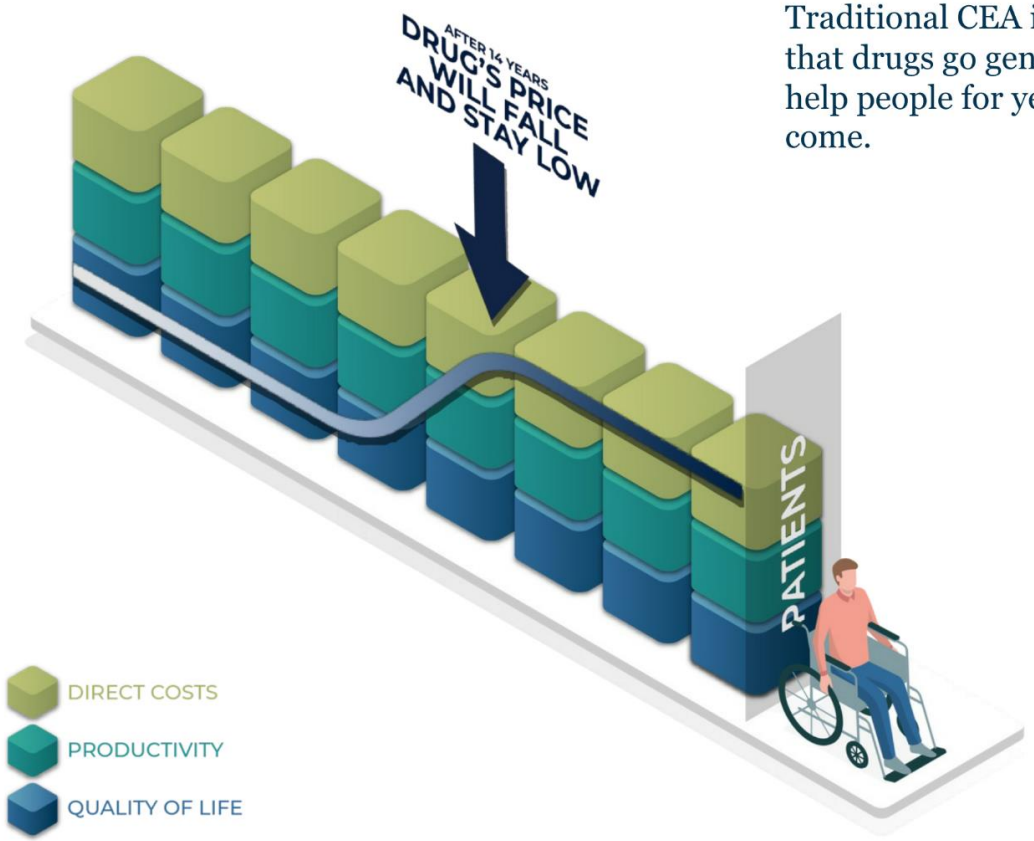
RA CAPITAL MANAGEMENT
200 BERKELEY STREET • 18TH FLOOR • BOSTON, MA 02116 • WWW.RACAP.COM

Cost Effectiveness Analysis Such as that Proposed in the IRA Ignores Numerous Benefits of Drug Innovation Including the Social Dividend from a Generic Drug



Focus on patients who start treatment when drug launches.

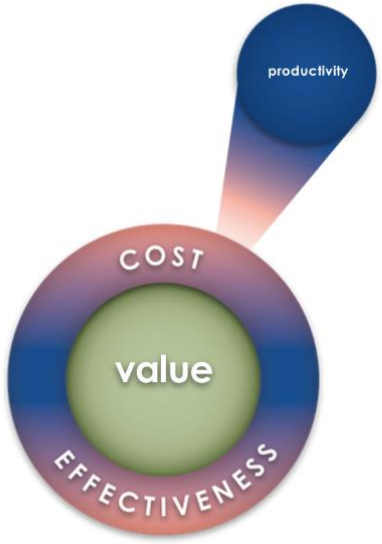




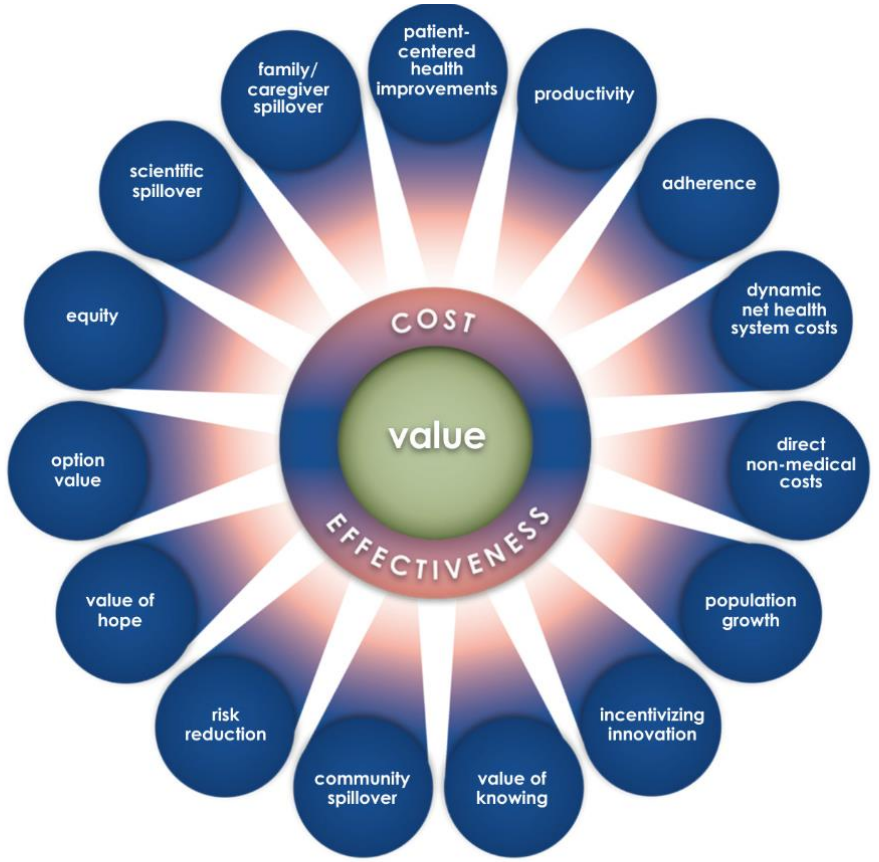
Traditional CEA ignores that drugs go generic and help people for years to come.

Source: https://nopatientleftbehind.docsend.com/view/y6m6fz6umi9e4chk

RA Capital Proposing a Generalized Approach to Cost Effectiveness Analysis



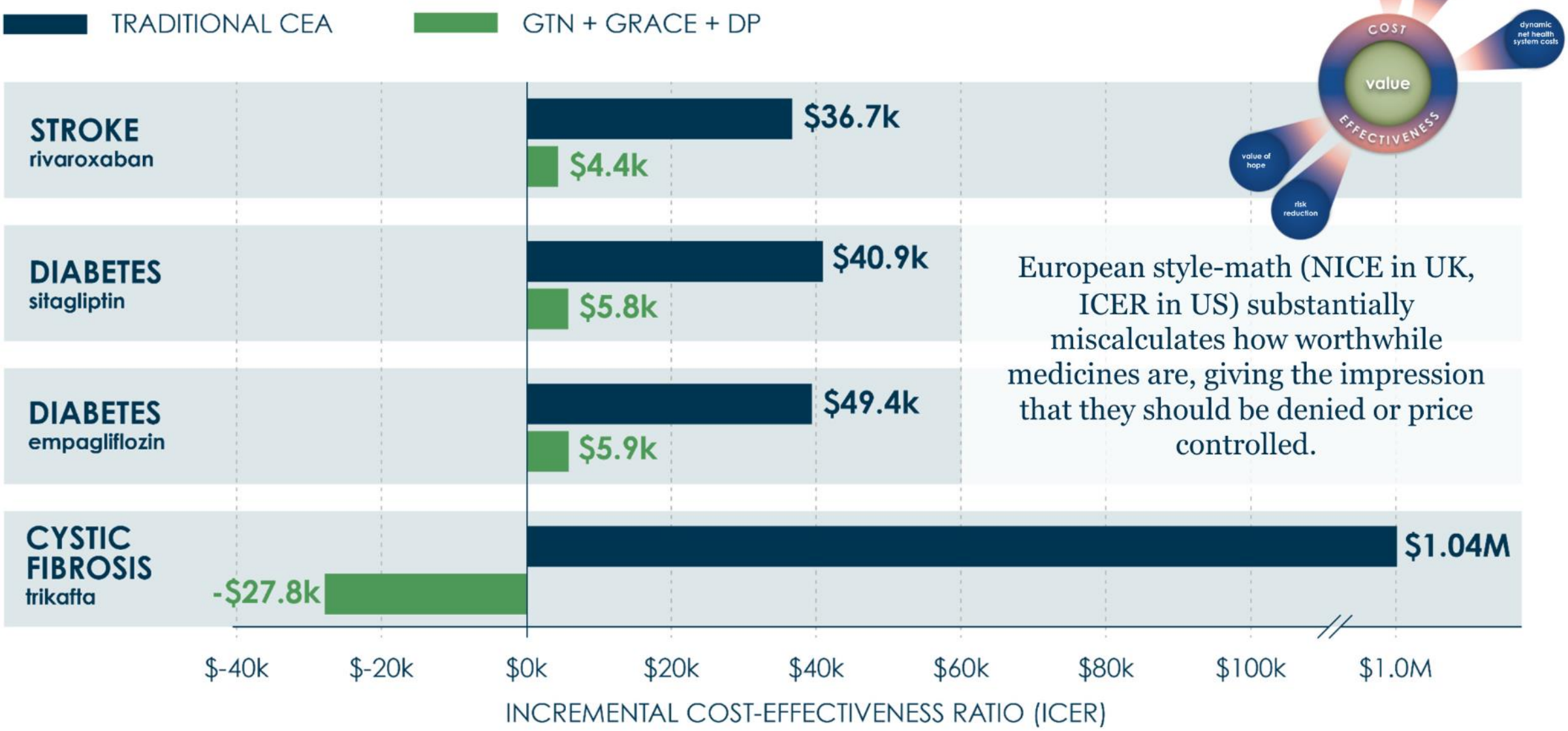
Traditional CEA
(and even then, often excludes productivity)



Generalized CEA
"The Value Flower"

Source: https://nopatientleftbehind.docsend.com/view/y6m6fz6umi9e4chk

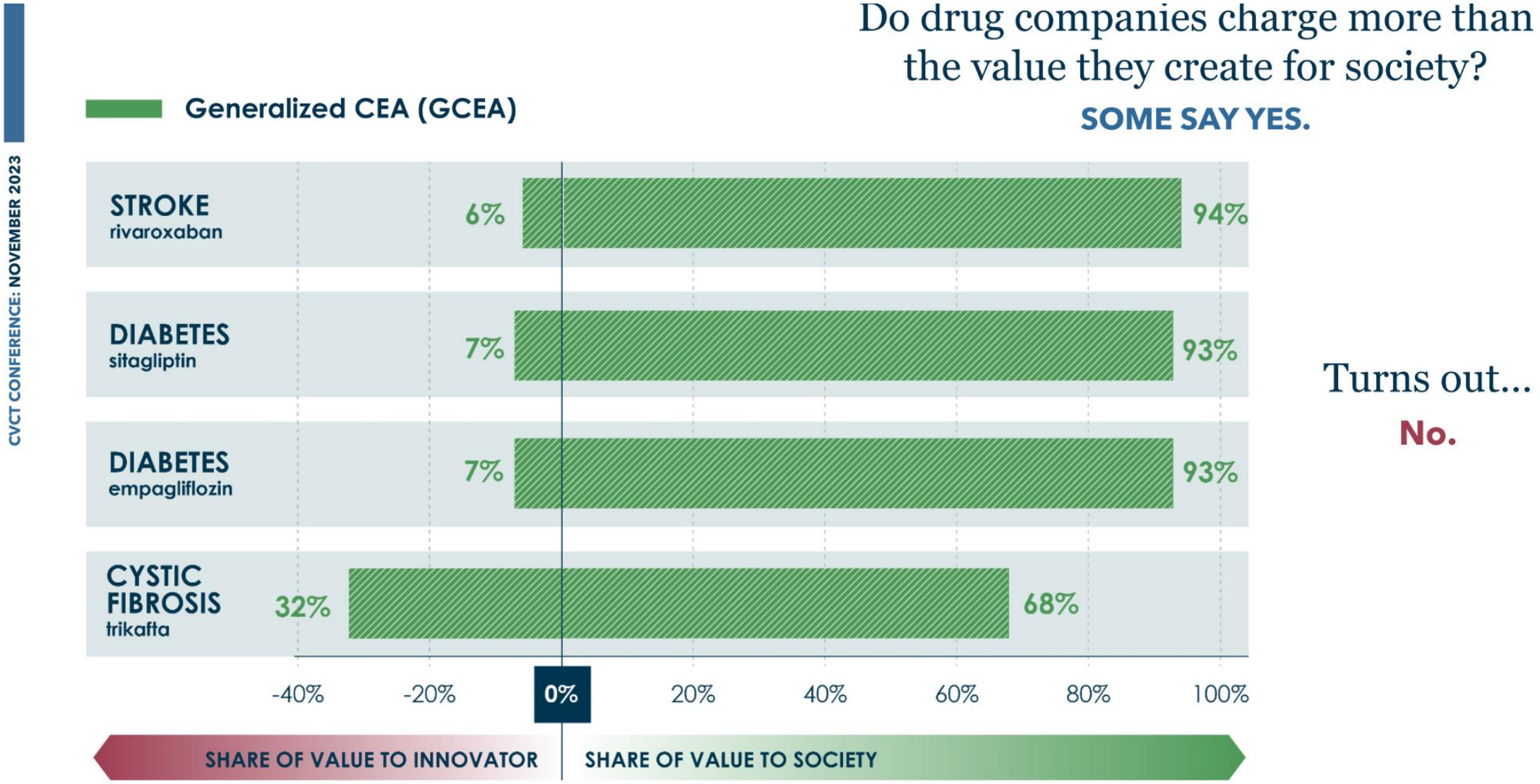
Illustration of Missed Drug Value with Traditional CEA



European style-math (NICE in UK, ICER in US) substantially miscalculates how worthwhile medicines are, giving the impression that they should be denied or price controlled.

Source: https://nopatientleftbehind.docsend.com/view/y6m6fz6umi9e4chk

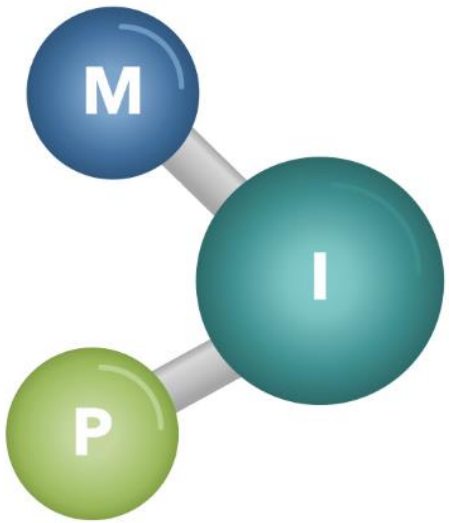
Huge Societal Externalities from Drug Discovery Activity

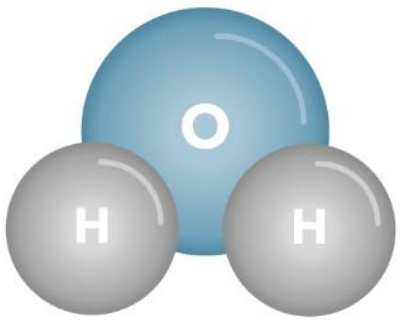


Source: https://nopatientleftbehind.docsend.com/view/y6m6fz6umi9e4chk

Affordable Innovation requires:

Market-based pricing with a **Patent-intended period of exclusivity** made **affordable via proper Insurance**, which means low out-of-pocket costs.

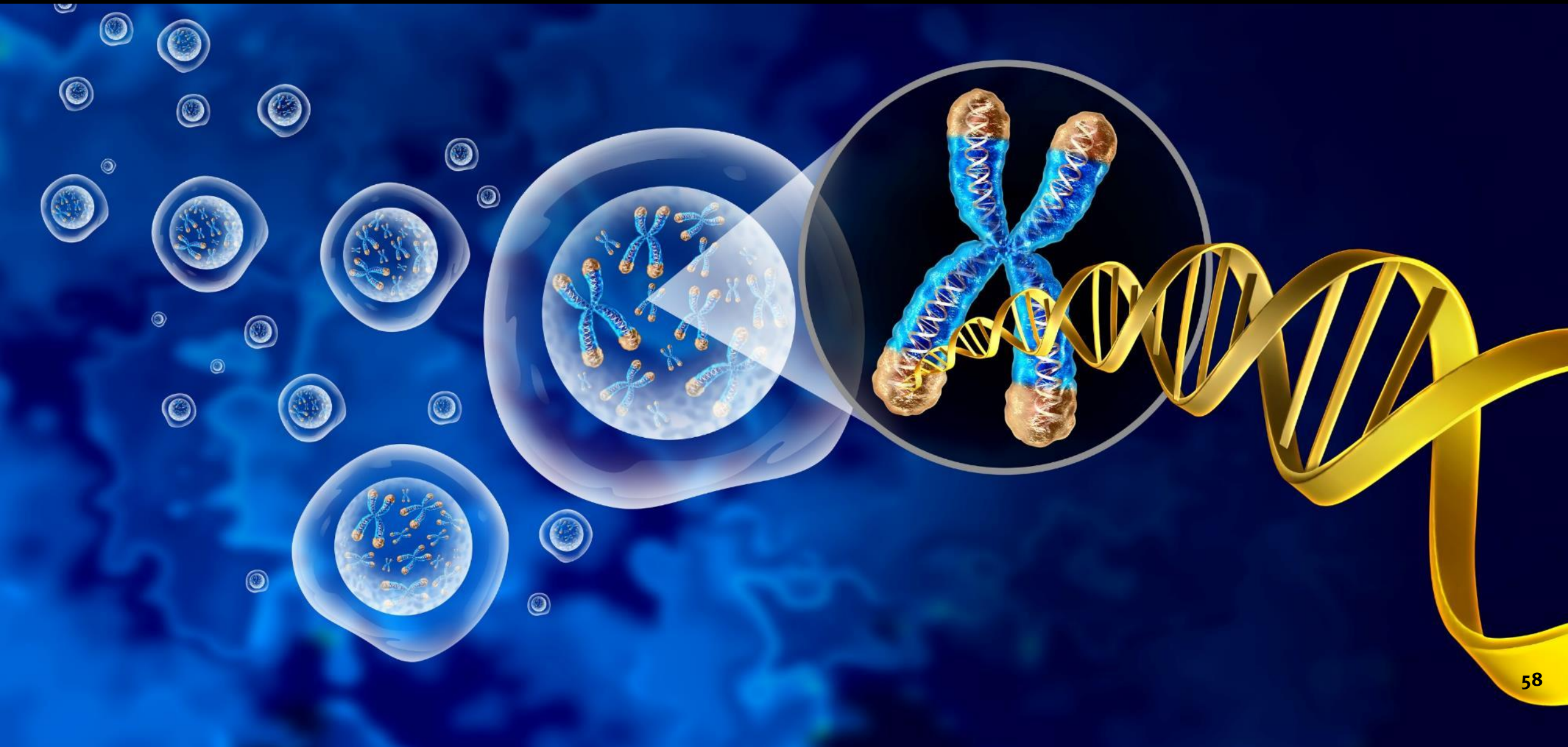




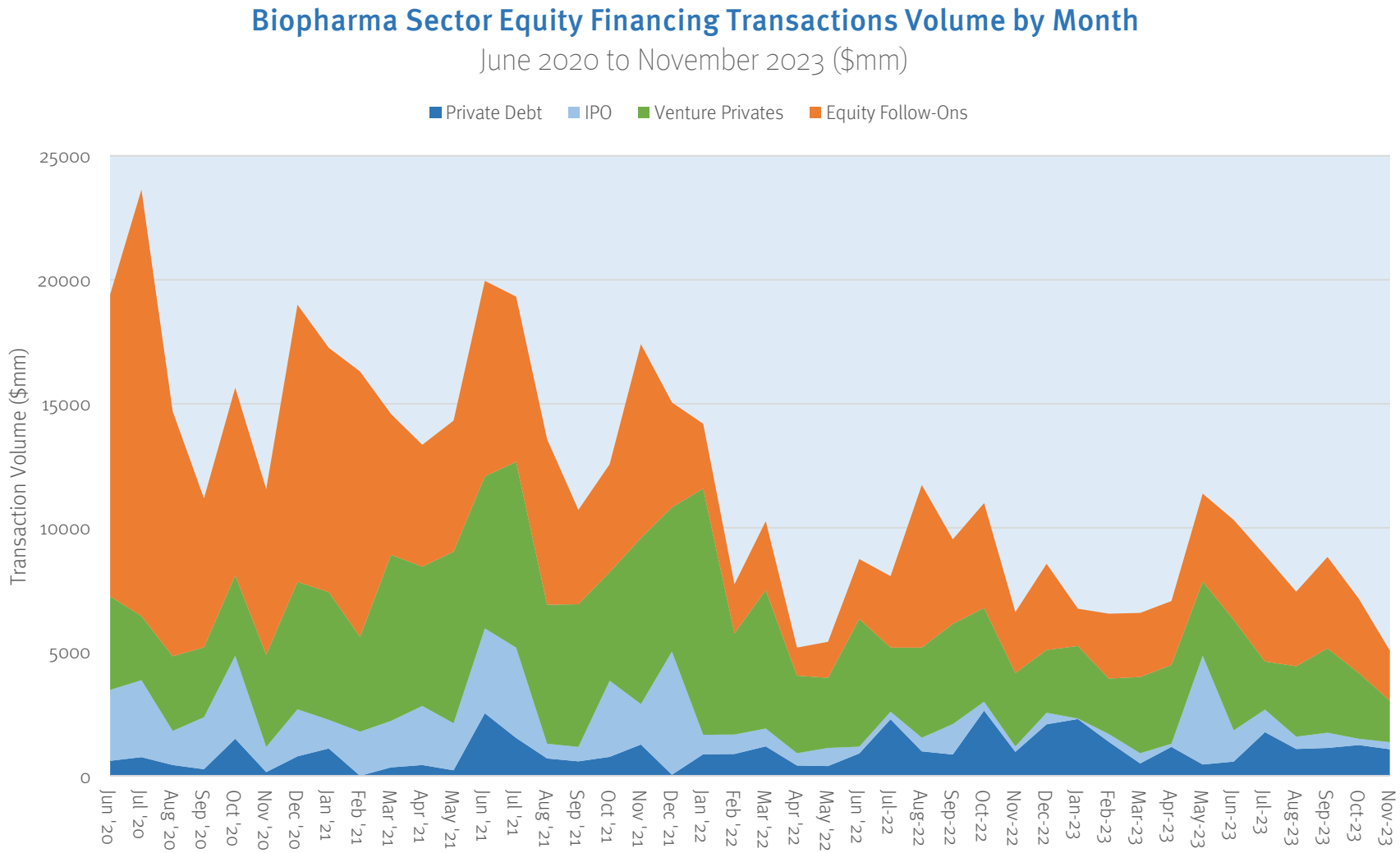
- **SOLVE AFFORDABILITY BY LOWERING OOP COSTS**
  Europe does this pretty well… when it's covered, it's covered.

- **GET VALUE FOR SOCIETY BY ENSURING ALL DRUGS GO GENERIC**
  after their patent-intended period of exclusivity (~14 years)

Capital Markets Update



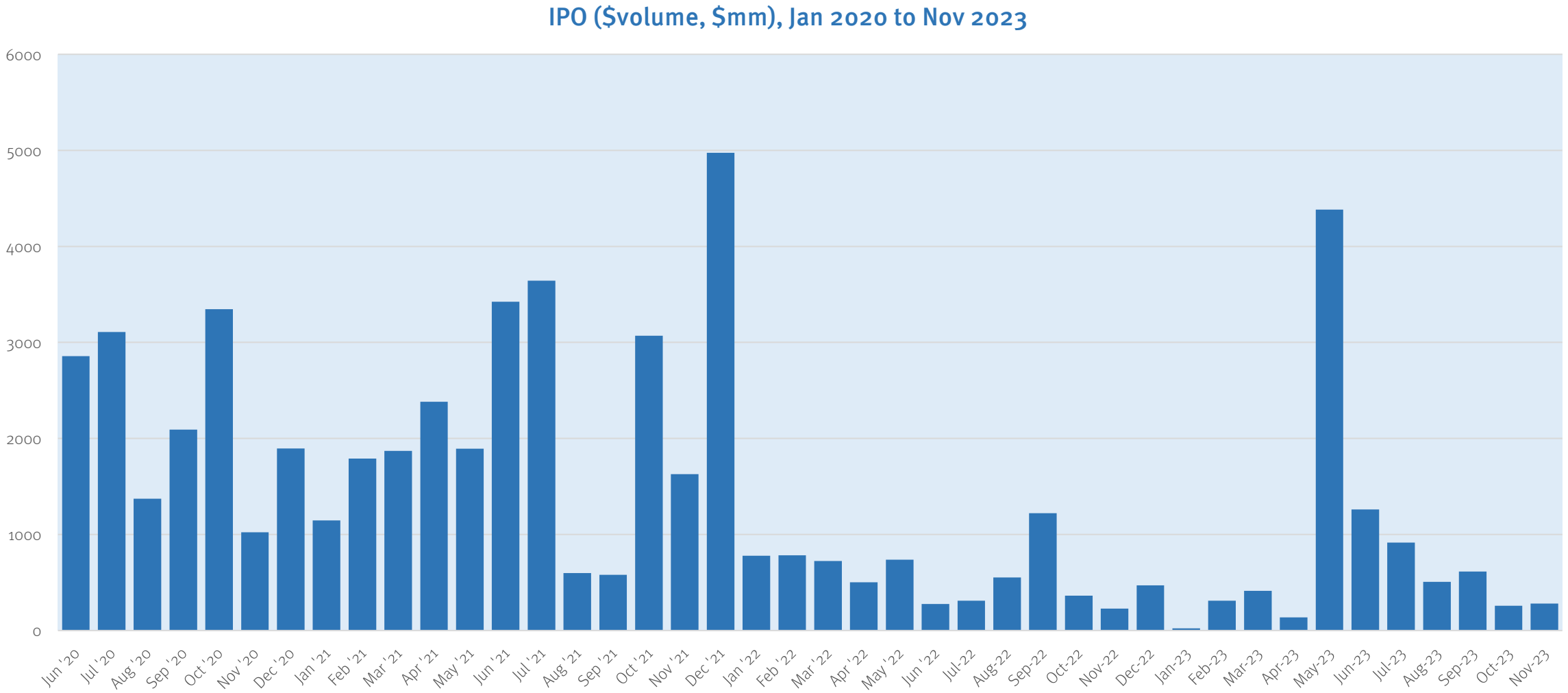
November the Third Slowest Month for Financing Volume Since the Pandemic Began



November was a month of market recovery from terrible sentiment that was concentrated at the start of the month. This coincided with a short-day count and the Thanksgiving holiday to result in relatively low financing volume.

Source: Data from CapitalIQ and Stifel research.

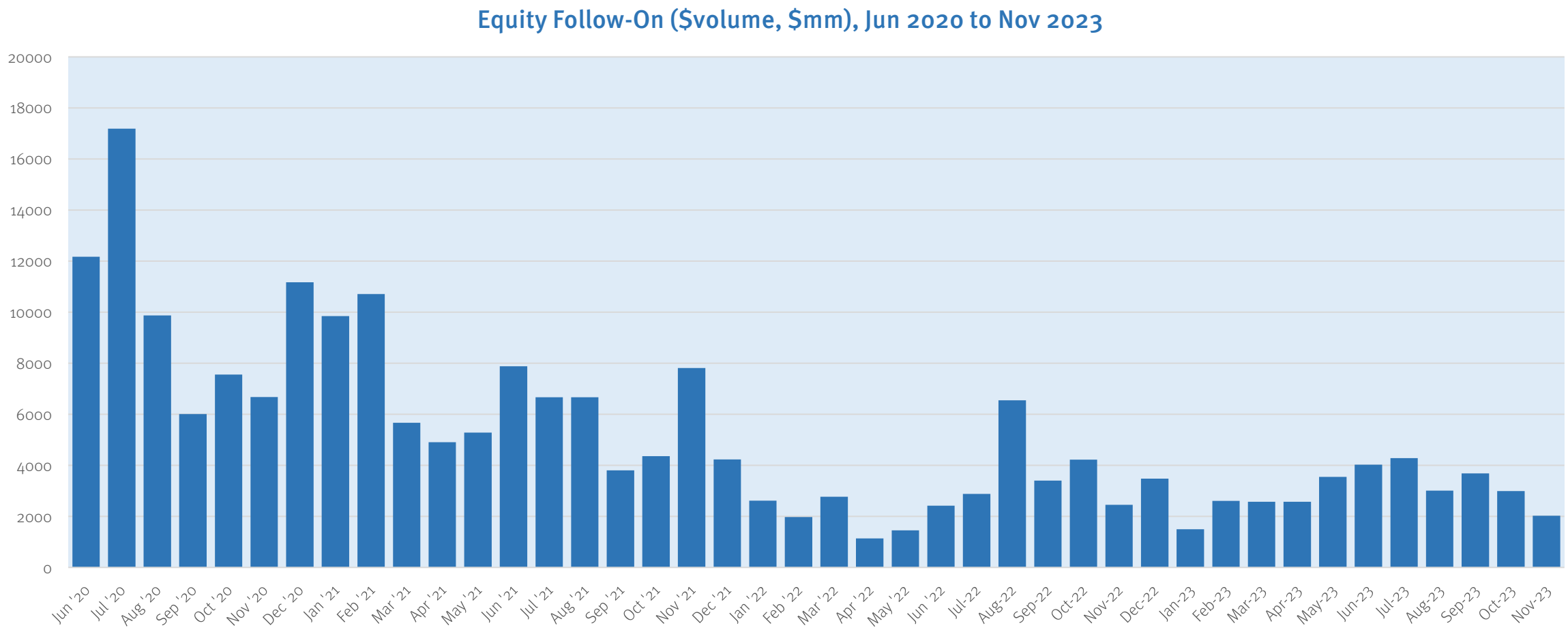
IPO Market Saw No Transactions Last Week and Just One Deal (CARGO) for the Entire Month



Source: Data from CapitalIQ and Stifel research.

Last Month Was Light for Follow-On Offerings

Last month saw very light follow-on offering as the market remained in some disarray due to sentiment issues and high Treasury yields. We expect to see a busier calendar in December despite the usual holiday break.



Source: Data from CapitalIQ and Stifel research.

Xenon Raises a $300 Million Follow-On

VANCOUVER, British Columbia, Nov. 29, 2023 (GLOBE NEWSWIRE) -- Xenon Pharmaceuticals Inc. (Nasdaq:XENE) ("Xenon"), a neurology-focused biopharmaceutical company, today announced the pricing of its upsized underwritten public offering of 8,461,542 common shares and, in lieu of common shares to certain investors, pre-funded warrants to purchase up to 769,230 common shares pursuant to its existing shelf registration statement. The common shares are being offered at a public offering price of $32.50 per common share and the pre-funded warrants are being offered at a price of $32.4999 per pre-funded warrant. The gross proceeds to Xenon from the offering, before deducting underwriting discounts and commissions and other offering expenses payable by Xenon, are expected to be approximately $300.0 million. In addition, Xenon has granted to the underwriters of the offering an option for a period of 30 days to purchase up to an additional 1,384,615 common shares at the public offering price, less the underwriting discounts and commissions. The offering is expected to close on or about December 4, 2023 subject to customary closing conditions.

J.P. Morgan, Jefferies, BofA Securities, Stifel, and RBC Capital Markets are acting as joint book-running managers for the offering.

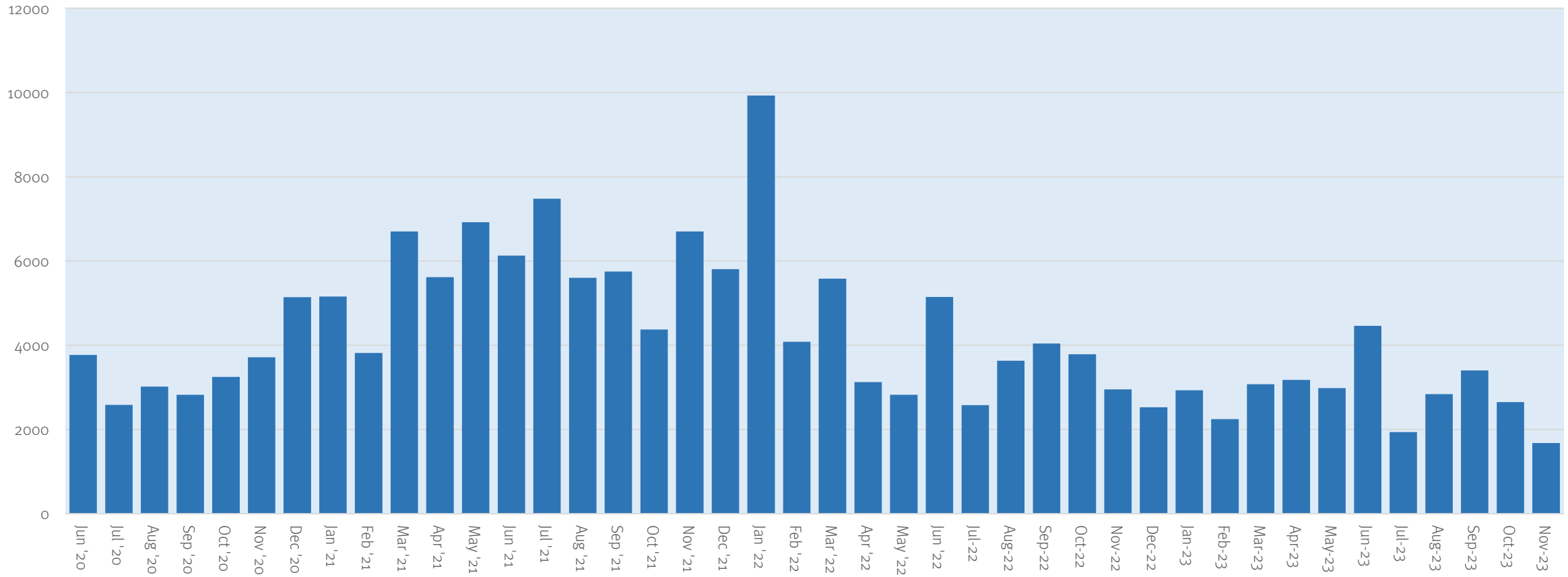
Stifel was pleased to act as a joint bookrunner on Xenon's financing last week.

Source: https://investor.xenon-pharma.com/news-releases/news-release-details/xenon-pharmaceuticals-announces-pricing-upsized-3000-million

Venture Equity Market Slow in November

November was the slowest month for venture equity financings since the start of the Pandemic. This reflects the very difficult financing environment faced up to mid-month. We expect the market to pick up significantly in Q1 2024 following the recent revival of the equity market.

Monthly Private Equity Placement in Venture Biopharma Market ($volume, $mm), Jan 2020 to Nov 2023



Source: Data from CapitalIQ, Crunchbase.

Startup Ajax Health Extends Medtech Innovation Model to Hologic

Brian Gormley, *Wall Street Journal*, Nov 30, 2023 (excerpt)

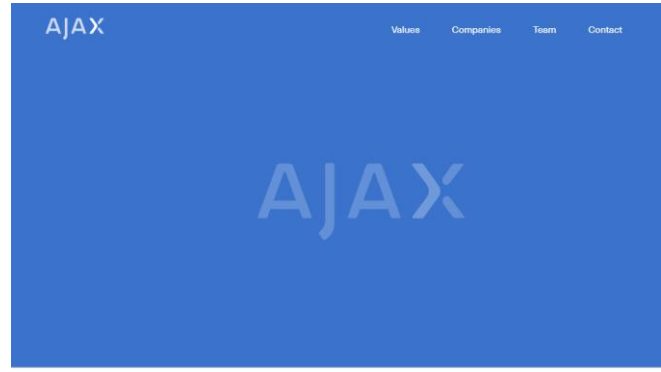
Menlo Park, Calif.-based Ajax creates turnkey innovation platforms for commercial-stage medtech players, and it has teamed with investment firm KKR and medtech company Hologic to launch Maverix Medical, a startup formed to advance diagnostics and medical devices to treat lung cancer.

Maverix is independent but intends to work with Hologic to bring lung-cancer products to market, said Ali Satvat, a KKR partner and co-head of the firm's Americas healthcare unit and global head of health care strategic growth.

Large companies often struggle to innovate while startups are better at inventing products than bringing them to market. Ajax aims to pair the agility of startups with the commercial infrastructure of larger businesses. Maverix is the second such platform Ajax has launched and it intends to develop more, said founder and Chief Executive Duke Rohlen.

Ajax has had success with its first platform, Cordis-X, an accelerator for inventing new products for medical-device company Cordis. But as the Cordis experience shows, the model isn't easy to execute.

Rohlen, who founded Ajax in 2017, seeks to fill a gap he sees in the medtech industry. Startups develop transformative medical devices that can command top dollar from companies seeking acquisitions. Large companies can acquire transformational products by purchasing startups, but they also need incremental improvements to existing products and new products to pair with existing medical devices.

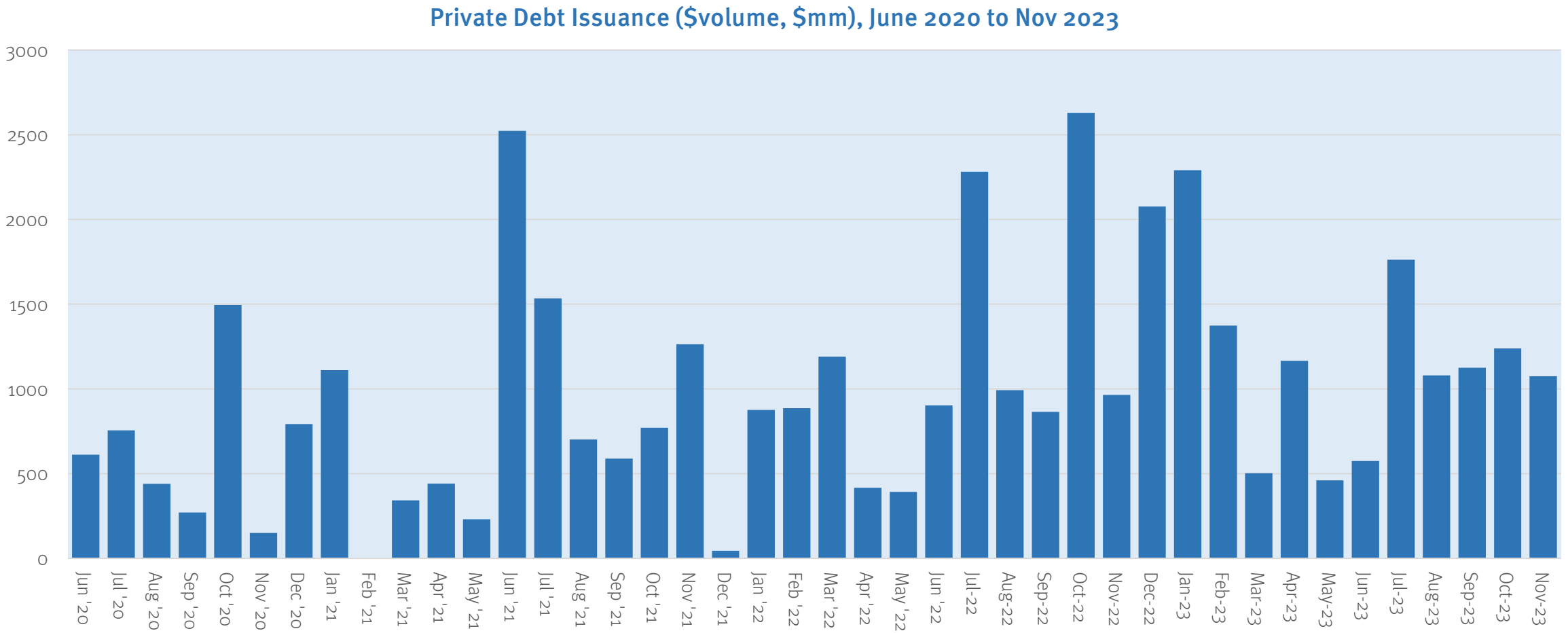


Ajax Health is a turnkey growth solution for commercial-stage medtech companies that creates value for its strategic partners with an impactful model for product and portfolio development.

Source: https://www.wsj.com/articles/startup-ajax-health-extends-medtech-innovation-model-to-hologic-7002fada

Weekly Global Biopharma Private Debt Placement Volume Solid in November

We saw a billion dollars in private debt deals get done in November. This was impressive in light of the high interest rate environment and underlying macro picture.



Source: Data from CapitalIQ, Crunchbase.

Flagship Outlines Plans to Raise $3B for New Fund

Gwendolyn Wu, *Biopharma Dive*, Nov 30, 2023

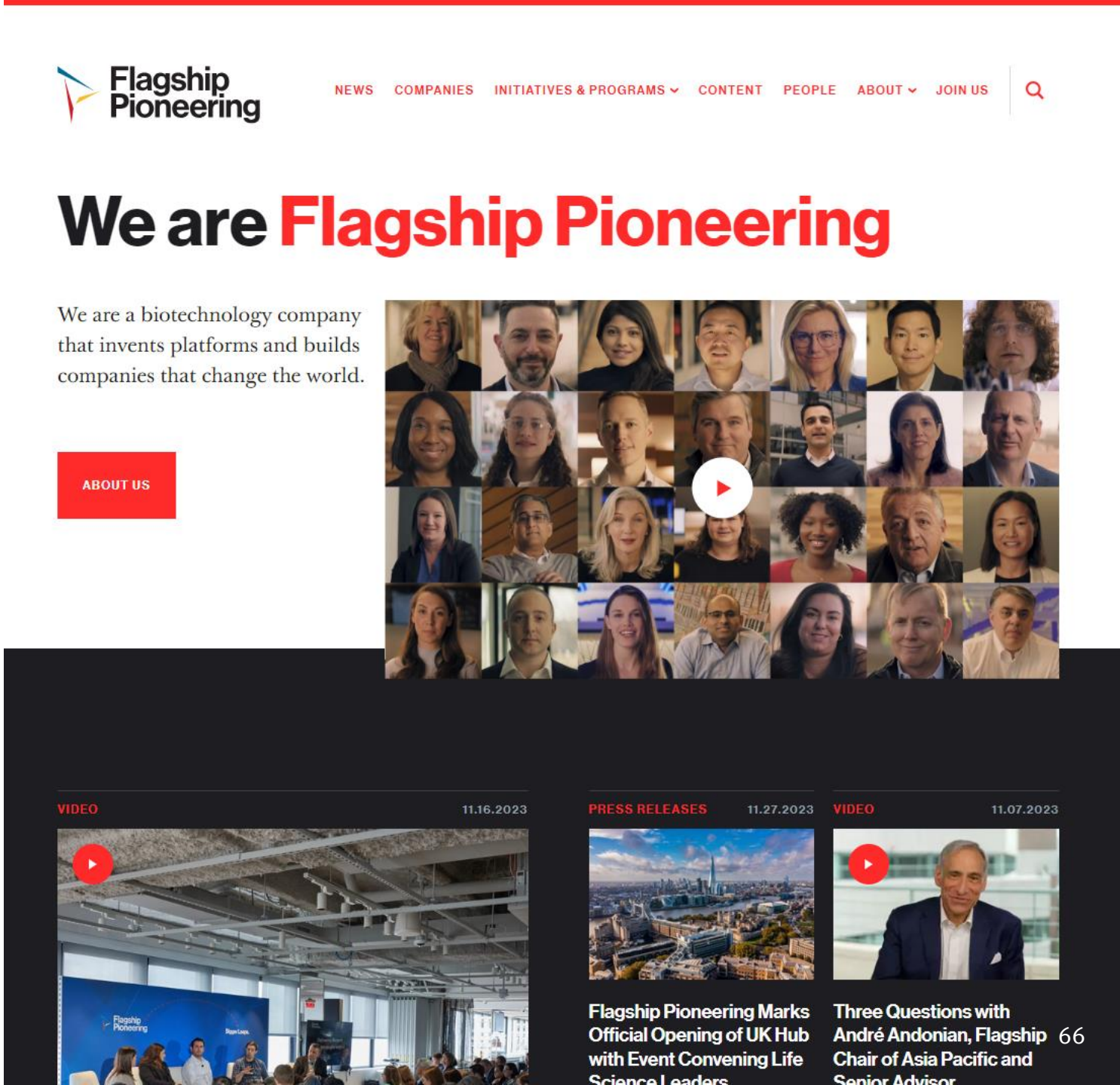
Flagship Pioneering is looking to raise $3 billion for its eighth venture fund, a sign the high-profile company creator continues to see investor interest in the biotechnology sector despite a turbulent market.

The plans were outlined in a securities document signed by Flagship's chief financial officer Charles Carelli and filed with federal regulators Wednesday. Boston Business Journal earlier reported the news.

Based in Cambridge, Massachusetts, Flagship has launched a number of biotech startups this year, including Empress Therapeutics, Metaphore Biotechnologies and, most recently, Quotient Therapeutics. It closed its Fund VII in 2021, bringing in a little more than $3.3 billion for life sciences investing.

The firm declined to comment on Wednesday's filing, citing Securities and Exchange Commission regulations.

Source: https://www.biopharmadive.com/news/flagship-fund-viii-biotech-raise-3-billion/701204/



Ono Pharma Expands Venture Fund to $200mm

OSAKA, Japan, Dec. 1, 2023 /PRNewswire/ -- Ono Pharmaceutical Co., Ltd. (Osaka, Japan; President and CEO: Gyo Sagara; "Ono") today announced that in order to accelerate the open innovation, it has increased its investment pool from US$100 million to US$200 million to continue strategic investment in Ono Venture Investment Fund I, L.P. ("OVI FI"), which was established as a corporate venture capital fund in CA, USA in May 2020.

With the aim of accessing and partnering on drug discovery targets and cutting-edge technologies for the generation of innovative medicines, Ono established Ono Venture Investment, Inc. (South San Francisco, CA, USA: "OVI"), as well as OVI FI as local subsidiaries in the U.S. in May 2020. OVI manages the investment fund and invests in bio-ventures and startup companies.

Since the establishment in 2020, OVI and OVI FI have been supporting the drug discovery activities through strategic investments in 11 bio-venture companies to date, including the most recent investment in Photys Therapeutics (Waltham, MA, USA).

Source: https://www.prnewswire.com/news-releases/ono-expands-investment-in-ono-venture-investment-fund-i-lp-to-us200-million-302001666.html

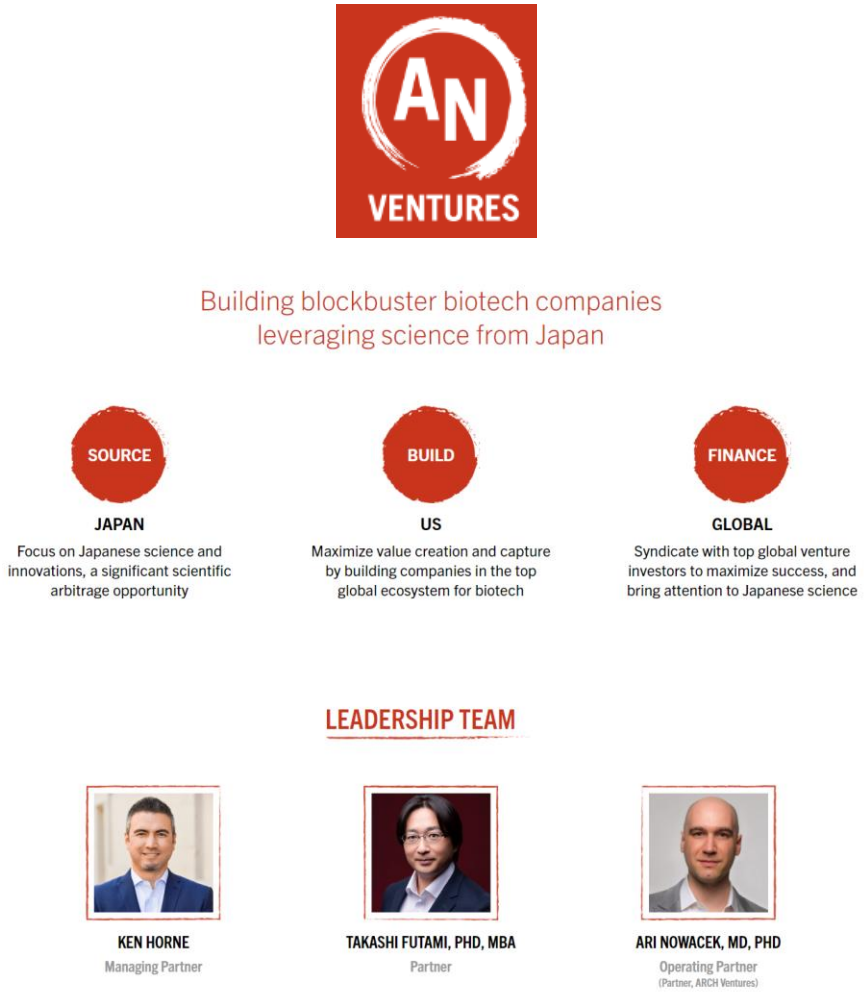
ARCH-allied AN Venture Partners Raises $200M to Build Biotechs out of Research from Japan

Kyle LaHucick, *Endpoints News*, Dec 1, 2023 (excerpt)

A new investment firm affiliated with ARCH Venture Partners has raised $200 million for its first fund as it seeks to back scientific research out of Japan to create new global biotech startups.

AN Venture Partners' financing haul was disclosed in a Thursday SEC filing and comes the same week Osaka-based drugmaker Ono Pharmaceutical said it had doubled its own corporate VC arm to $200 million after having already backed 11 startups, including Photys Therapeutics.

Tokyo and San Francisco-based AN has "an agreed alliance with ARCH," per the fund's website, and aims to create new companies and back other early-stage life sciences startups with a focus on science out of Japan. ARCH is one of the most prolific names in the life sciences investment arena, having helped start many blue-chip names in biotech, diagnostics and other technologies.



Source: https://endpts.com/arch-allied-an-venture-partners-raises-200m-to-build-biotechs-out-of-research-from-japan/

Dallas Investing in Biotech Infrastructure

Shelly Hagan, *Bloomberg*, Dec 1, 2023 (excerpt)

A Texas oil heir's quest to make Dallas a hub for biotech is showing signs of paying off, potentially paving the way for scientific discoveries ranging from reviving the woolly mammoth to treatments for cancer.

Lyda Hill, the 81-year-old granddaughter of wildcatter H.L. Hunt, has funneled millions of philanthropic and investment dollars into developing the industry in her hometown. In September, her marquee project, an office campus modeled after the Kendall Square innovation district near MIT, scored a big win when it was named one of the three headquarters for the federal government's new health research institutes.

Hill has done just that in the life sciences industry, partly motivated by her own battle with breast cancer. Her charitable donations include $50 million to the University of Texas MD Anderson Cancer Center's Moon Shots Program; $50 million to the UT Southwestern Medical Center that was partly used to create the Lyda Hill Department of Bioinformatics; $20 million to the Hockaday School, a private all girls school in Dallas, to fund science-focused programs; and $30 million to the Dallas-based Meadows Mental Health Policy Institute.

"The very beginning of what's happening here is quite encouraging and I think bodes well for this next chapter," said Case, who now runs investment firm Revolution, which focuses on investments in places outside of traditional venture hubs like San Francisco and Boston.

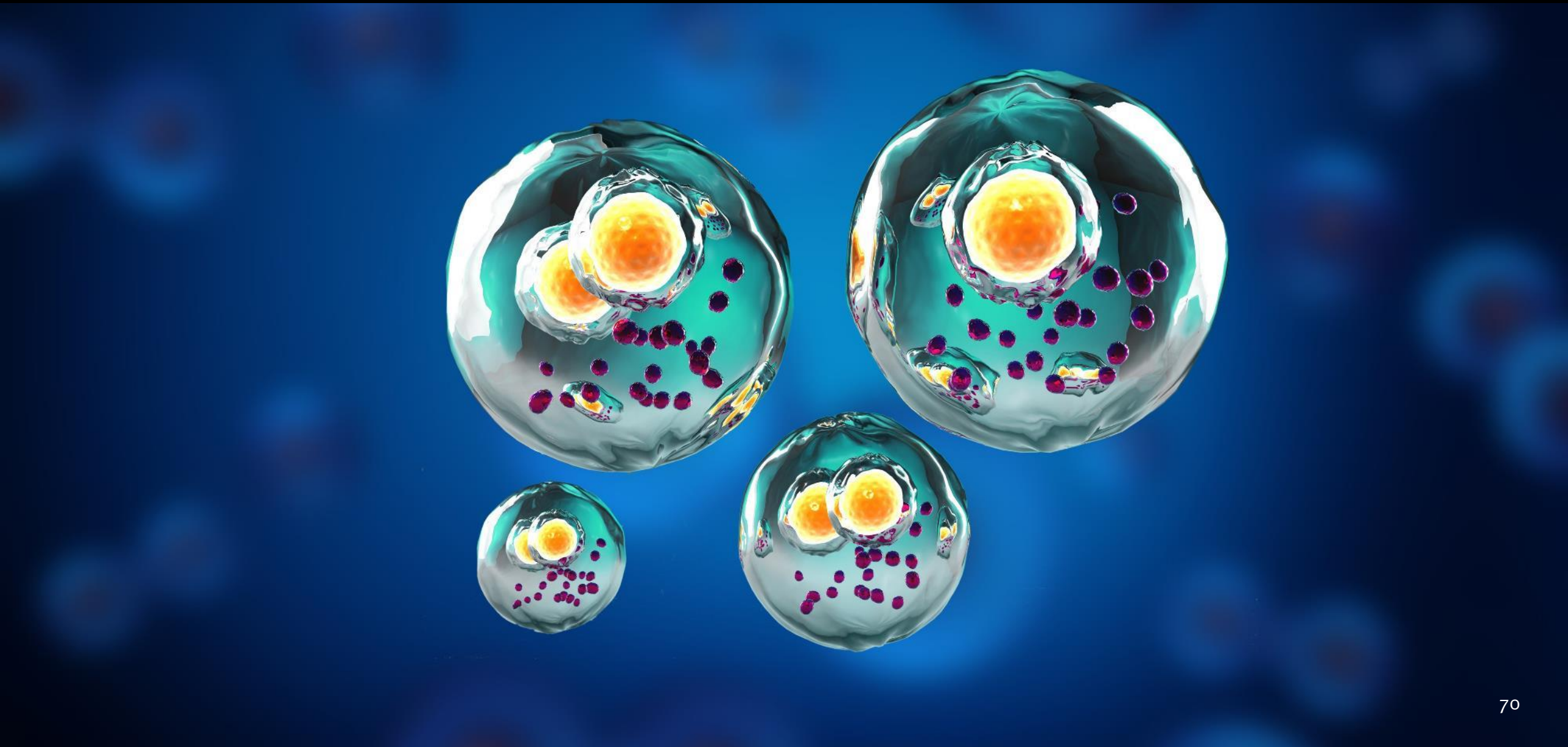
What Dallas lacks, and what Case's firm is trying to solve, is access to capital. Venture capital funding in Dallas was $157 million in the third quarter, versus $10.2 billion in San Francisco and $3.5 billion in Boston, according to PitchBook data.

A rendering of NexPoint's Texas Research Quarter development.

BioLabs has been hosting informal meetings at Old Parkland, an office park in Dallas that houses asset management firms, to tout investment opportunities at Pegasus Park. Gabby Everett, a scientist and director of the Dallas Biolabs site, said there are ongoing discussions between some founders and investors.Another developer is looking to cash in on the biotech industry in North Texas. NexPoint founder James Dondero has proposed a $4 billion project that would convert Ross Perot's former Electronic Data Systems campus in the Dallas suburb of Plano into a life sciences hub. NexPoint received rezoning approval from the Plano city council in November.

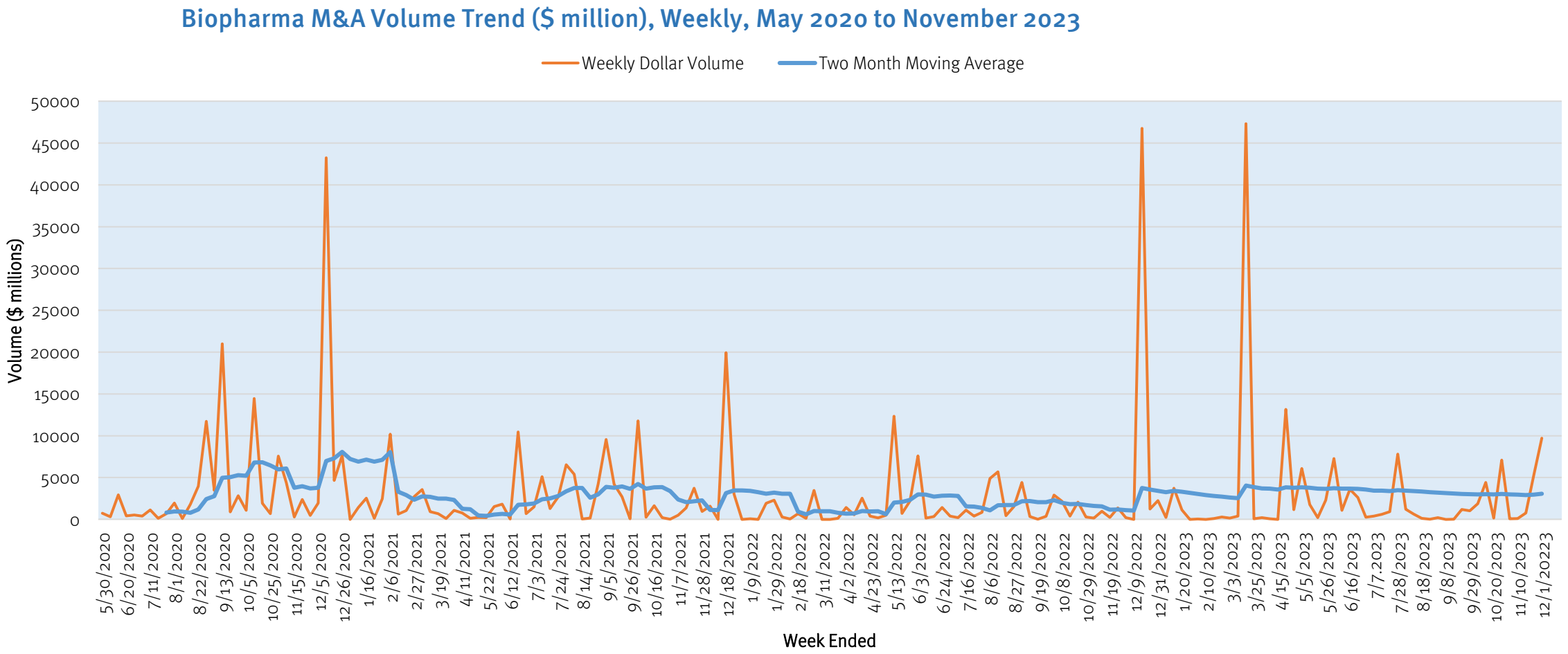
Source: https://www.bloomberg.com/news/articles/2023-12-01/billionaire-oilman-s-heir-is-driving-dallas-innovation-push

Deals Environment Update



M&A Market Active Over Last Two Weeks

The last two weeks have featured brisk M&A levels with an offer by AbbVie to buy Immunogen for $10bn, an offer by the ownership group of Taisho Pharma to acquire the company for $4 billion and two offers by Kevin Tang's Concentra to buy biotechs.



Source: S&P, CapitalIQ

AbbVie to Acquire ImmunoGen for $10.1 Billion

NORTH CHICAGO, Ill., and WALTHAM, Mass., Nov. 30, 2023 /PRNewswire/

AbbVie Inc. (NYSE: ABBV) and ImmunoGen, Inc. (NASDAQ: IMGN) today announced a definitive agreement under which AbbVie will acquire ImmunoGen, and its flagship cancer therapy ELAHERE® (mirvetuximab soravtansine-gynx), a first-in-class antibody-drug conjugate (ADC) approved for platinum-resistant ovarian cancer (PROC). The acquisition accelerates AbbVie's commercial and clinical presence in the solid tumor space. Additionally, ImmunoGen's follow-on pipeline of promising next-generation ADCs further complements AbbVie's ADC platform and existing programs.

Under the terms of the transaction, AbbVie will acquire all outstanding shares of ImmunoGen for $31.26 per share in cash. The transaction values ImmunoGen at a total equity value of approximately $10.1 billion. The boards of directors of both companies have approved the transaction. This transaction is expected to close in the middle of 2024, subject to ImmunoGen shareholder approval, regulatory approvals, and other customary closing conditions.

"The acquisition of ImmunoGen demonstrates our commitment to deliver on our long-term growth strategy and enables AbbVie to further diversify our oncology pipeline across solid tumors and hematologic malignancies," said Richard A. Gonzalez, chairman and chief executive officer, AbbVie. "Together, AbbVie and ImmunoGen have the potential to transform the standard of care for people living with cancer."

ImmunoGen's oncology portfolio has the potential to help drive long-term revenue growth for AbbVie's oncology franchise. Ovarian cancer is the leading cause of death from gynecological cancers in the U.S. ELAHERE is the first targeted medicine to show meaningful survival benefit in PROC. As a fast-growing solid tumor therapy, ELAHERE provides AbbVie with a potential multi-billion-dollar on-market medicine with expansion opportunities in earlier lines of therapy and larger segments of the ovarian cancer market.

The ADC field has been very strong in recent years and AbbVie is moving to beef up its presence in this important area.

AbbVie is paying 8.4 times analyst consensus 2030 revenue. Compare this to Pfizer's price of 4.6 times analyst consensus 2030 revenue for Seagen.

Source: https://news.abbvie.com/2023-11-30-AbbVie-to-Acquire-ImmunoGen,-including-its-Flagship-Cancer-Therapy-ELAHERE-R-mirvetuximab-soravtansine-gynx-,-Expanding-Solid-Tumor-Portfolio

After Targeting Struggling Biotechs, Tang's Concentra Shifts Gears with Unsolicited Bid for LianBio

Ayisha Sharma, *Endpoints News*, Dec 1, 2023 (excerpt)

Tang Capital Management has made its fifth unsolicited acquisition bid of the year, this time for US-Chinese company LianBio.

The choice of target marks a notable change in strategy for the California investment group, which had opted to proposition struggling early-stage biotechs in 2023.

LianBio is in a relatively strong position compared with Tang's previous targets, which include Atea Pharmaceuticals, Jounce Therapeutics, Rain Oncology and Theseus Pharmaceuticals.

LianBio has several partnered products on the market and has benefited from a recent spate of clinical successes.

Tang Capital Partners, Tang Capital Management and leader Kevin Tang each currently own 8.6% worth of LianBio shares, according to a Nov. 30 SEC filing. The same document revealed that Tang's shell company Concentra has offered to buy 100% of the equity of LianBio for $4.30 per share plus a contingent value right (CVR) for 80% of net proceeds from any license or divestment of the biotech's programs.

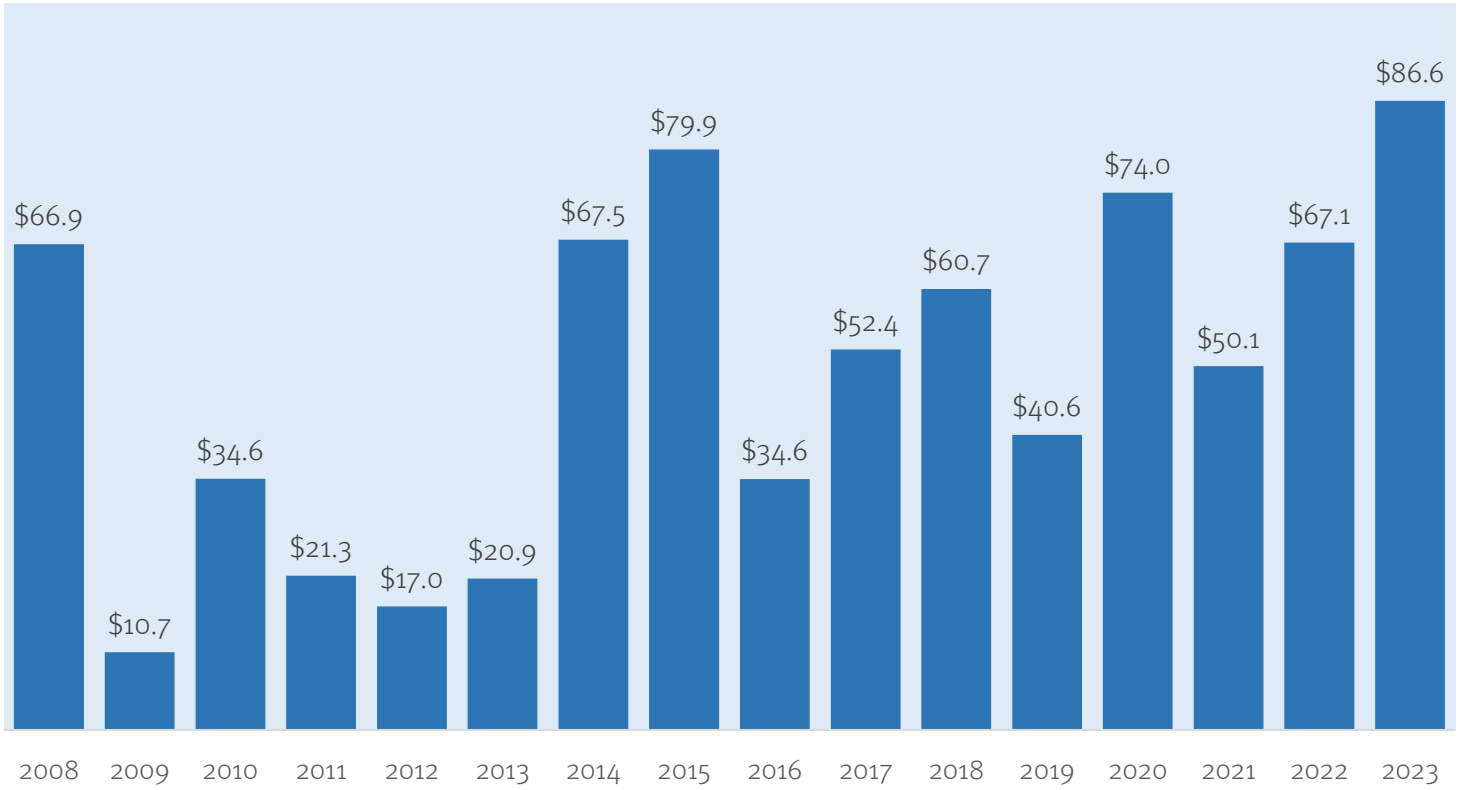
Source: https://endpts.com/tangs-concentra-shifts-gears-with-unsolicited-bid-for-lianbio-after-previously-targeting-struggling-biotechs/

Big Pharma Biotech M&A Volume at Record Level in 2023

Big Pharma Acquisition Volume in 2023 of Biotechs Has Surpassed Record Levels Despite IRA/FTC Uncertainties. The Immunogen deal officially pushed 2023 into the Record Books.

Dollar Volume of Big Pharma M&A Acquisitions of Biotechs for Between $50 Million and $50 Billion

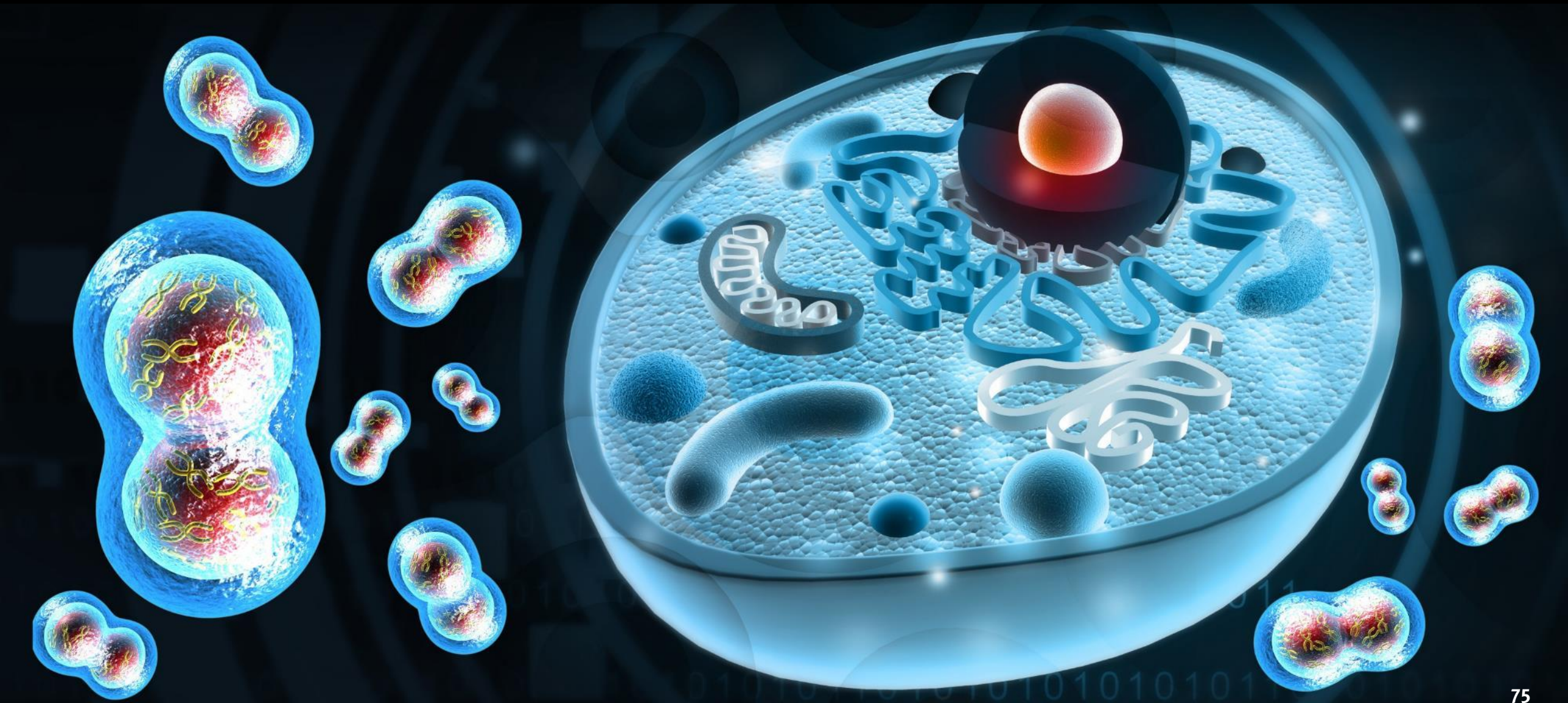
$ Billions, 2008 to 2023 (YTD)



Source: DealForma and Stifel analysis.

This chart measures sub-$50 billion M&A which we called “Biotech”, leaving out the horizontal “mega deals” like AbbVie / Allergan and BMS / Celgene. With those larger deals out of the calculus, one can see the cumulative effect of pharma acquisitions of biotech. What becomes apparent is that 2023 has been an exceptionally busy year by any historic measure.

Industry News



U.S. Life Expectancy Improved in 2022

CDC, Nov 29, 2023

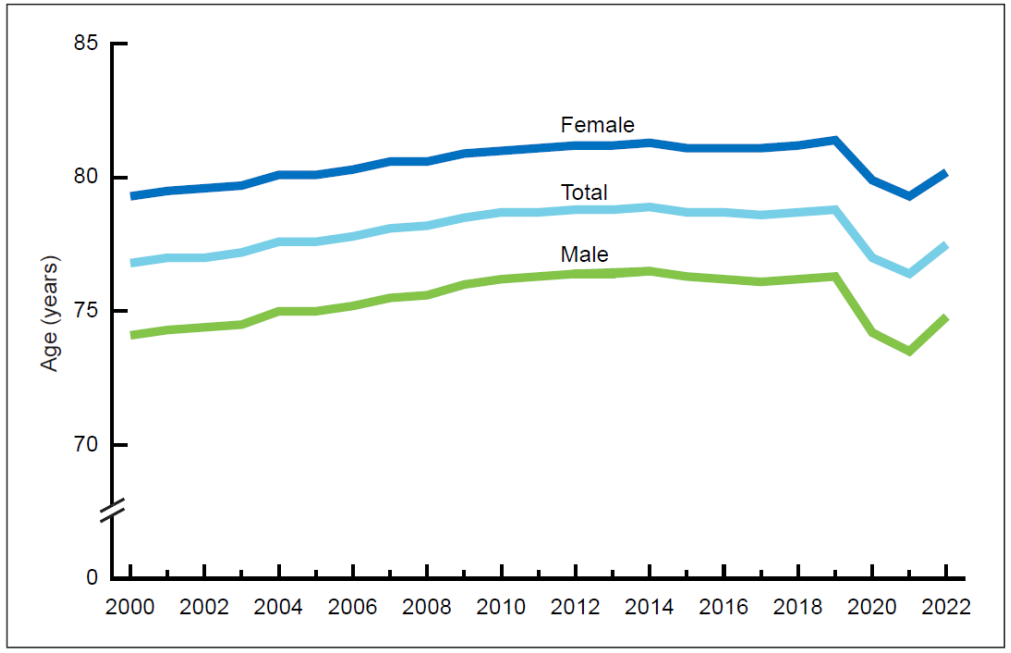
Vital Statistics Rapid Release

Report No. 31 ■ November 2023

Provisional Life Expectancy Estimates for 2022

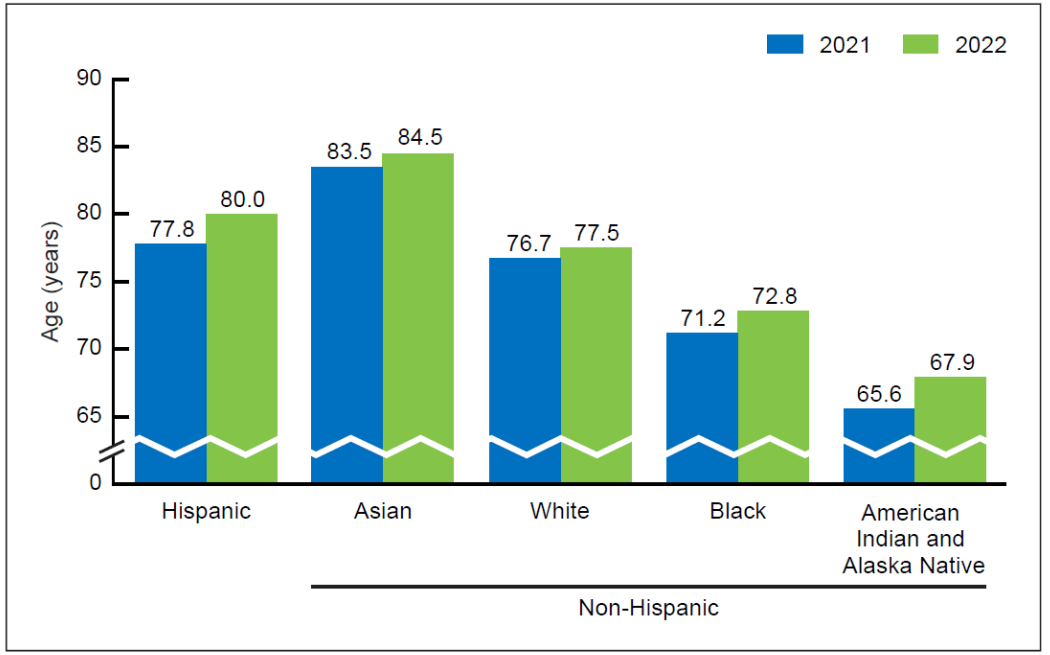
Elizabeth Arias, Ph.D., Kenneth D. Kochanek, M.A., Jiaquan Xu, M.D., and Betzaida Tejada-Vera, M.S.

Figure 1. Life expectancy at birth, by sex: United States, 2000–2022



NOTES: Estimates are based on provisional data for 2022. Provisional data are subject to change as additional data are received. Estimates for 2000–2021 are based on final data.
SOURCE: National Center for Health Statistics, National Vital Statistics System, mortality data file.

Figure 2. Life expectancy at birth, by Hispanic origin and race: United States, 2021-2022



NOTES: Estimates are based on provisional data for 2022. Provisional data are subject to change as additional data are received. Estimates for 2021 are based on final data. Life tables by Hispanic origin and race are based on death rates that have been adjusted for Hispanic-origin and race misclassification on death certificates; see Technical Notes in this report.
SOURCE: National Center for Health Statistics, National Vital Statistics System, mortality data file.

Source: https://www.cdc.gov/nchs/data/vsrr/vsrr031.pdf

Cigna, Humana in Talks for Blockbuster Merger

Lauren Thomas, Anna Wilde Mathews and Laura Cooper, *Wall Street Journal*, Nov 29, 2023

Cigna and Humana are in talks for a combination that would create a new powerhouse in the health-insurance industry.

The companies are discussing a stock-and-cash deal that could be finalized by the end of the year, assuming the talks don't fall apart, according to people familiar with the matter.

While the structure and terms under discussion couldn't be learned, a merger of the managed-care providers would be huge, and give rise to a company worth some $140 billion given Cigna's market value Wednesday morning of about $83 billion and Humana's of roughly $62 billion.

Cigna shares fell more than 8% by the close on Wednesday, while Humana lost about 5.5%, as investors digested news of the possible deal, reported earlier in the day by The *Wall Street Journal.*

Joining forces would give the pair scale to rival that of UnitedHealth Group and CVS Health and vault the combined company into the top tier of integrated healthcare firms. Cigna, which had revenue of about $181 billion last year, would be able to marry its huge pharmacy-benefit unit, which manages drug plans, and its strength in commercial insurance with Humana's big position in the fast-growing Medicare segment, something Cigna has long sought.

Source: https://www.wsj.com/business/deals/cigna-humana-in-talks-for-blockbuster-merger-c5c7f1bo

Soleus Goes Activists on Theratechnologies

Stephen Taub, *Institutional Investor*, Nov 30, 2023 (excerpt)

A life sciences hedge fund has gone activist on one of its smaller holdings.

Soleus Capital Management converted its 13G filing, which suggests a passive investment, to a 13D document for Montreal-based Theratechnologies, a biopharmaceuticals company focused on the development and commercialization of innovative therapies. In the filing, Soleus disclosed it had boosted its stake to nearly 5.2 million shares, or 10.5 percent of the total outstanding.

The stock is currently trading at about $1.70 a share, down from nearly $9 a year ago and way down from its all-time high of nearly $45, in May 2018. Just a month ago, the company sold 12.5 million shares for a buck apiece in a secondary offering, so those buyers have already seen a 70 percent gain.

In the 13D filing, Soleus said the shares are attractive and that it has communicated with management and the board of directors about "opportunities to enhance stockholder value." These include the potential appointment to the board of directors of an individual designated by Soleus and the engagement of an investment bank to help the company "explore strategic transactions that may involve the sale" of some or all of its assets and/or a change of control.

Theratechnologies has two HIV medicines and research programs in HIV, nonalcoholic steatohepatitis, and oncology.

Source: https://www.institutionalinvestor.com/article/2cirg80d29lkyhzln2b5s

FDA Investigating Serious Risk of T-Cell Malignancy Following BCMA-Directed or CD19-Directed Autologous Chimeric Antigen Receptor (CAR) T Cell Immunotherapies

FDA Press Release, Nov 28, 2023

The Food and Drug Administration (FDA) has received reports of T-cell malignancies, including chimeric antigen receptor CAR-positive lymphoma, in patients who received treatment with BCMA- or CD19-directed autologous CAR T cell immunotherapies. Reports were received from clinical trials and/or postmarketing adverse event (AE) data sources.

FDA has determined that the risk of T-cell malignancies is applicable to all currently approved BCMA-directed and CD19-directed genetically modified autologous CAR T cell immunotherapies. T-cell malignancies have occurred in patients treated with several products in the class. Currently approved products in this class (listed alphabetically by trade name) include the following:
Abecma (idecabtagene vicleucel)
Breyanzi (lisocabtagene maraleucel)
Carvykti (ciltacabtagene autoleucel)
Kymriah (tisagenlecleucel)
Tecartus (brexucabtagene autoleucel)
Yescarta (axicabtagene ciloleucel)

Although the overall benefits of these products continue to outweigh their potential risks for their approved uses, FDA is investigating the identified risk of T cell malignancy with serious outcomes, including hospitalization and death, and is evaluating the need for regulatory action.

As with all gene therapy products with integrating vectors (lentiviral or retroviral vectors), the potential risk of developing secondary malignancies is labeled as a class warning in the U.S. prescribing information (USPIs) for approved BCMA-directed and CD19-directed genetically modified autologous T cell immunotherapies. The initial approvals of these products included postmarketing requirements (PMRs) under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) to conduct 15-year long term follow-up observational safety studies to assess the long-term safety and the risk of secondary malignancies occurring after treatment.

Source: https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/fda-investigating-serious-risk-t-cell-malignancy-following-bcma-directed-or-cd19-directed-autologous

Volatile Day for CAR-T Biotechs After FDA Announces Cancer Safety Review

Annalee Armstrong, *FierceBiotech*, Nov 28, 2023 (excerpt)

As if biotechs needed any more bad news, CAR-T therapy companies saw shares tumble on the news that the FDA will investigate the "serious risk" of subsequent, secondary cancers that can occur after treatment with the therapies.

Autolus Therapeutics, developer of autologous T-cell therapies, dropped down to $3.05 per share after opening at $4.78, before recovering to $4.55 at close. Natural killer cell biotech Nkarta was volatile throughout the day, but only lost about 1% of its value, closing at $2.46 compared to $2.54 at open. Arcellx started at $52.95, fell to $48.37 and leveled out to finish the day at $51.10.

Meanwhile, companies with already approved therapies cratered. Legend Biotech, which developed Carvykti with Johnson & Johnson, fell to a low of $57.38 after the FDA news dropped, before recovering to $59.99 at close. This compares to $61.69 at open.

The agency said today that it has received reports of T-cell malignancies—including CAR-positive lymphoma—among patients who received BCMA- or CD19-directed CAR-T immunotherapies. Some of those patients were hospitalized or later died. The events are from clinical trials as well as post-marketing surveillance programs.

Approved BCMA-directed and CD19-directed genetically modified autologous T-cell immunotherapies that use integrating vectors, such as lentiviral or retroviral vectors, already have this potential risk listed as a class-wide warning on their labels. Companies have been required to monitor patients for 15 years following treatment.

But the FDA may now take even more direct regulatory action. In announcing the review, the agency stated that the overall benefit of the approved product still outweighs the risks. The FDA's investigation applies to all approved CAR-Ts, which currently totals six. Dozens of companies have follow-ups in the clinic that hope to improve on certain aspects of the CAR-T process.

Source: https://www.fiercebiotech.com/biotech/volatile-day-car-t-biotechs-after-fda-announces-secondary-cancer-safety-review

Thinking Through the CAR-t Cancer Risk Story

We spoke last week to a number of market participants and immunologists to try to gain perspective on the FDA's surprising note about the risk of T-cell malignancy following administration of CAR-t.

It's important to start by noting that number of these malignancies reported in the FDA Adverse Event database (FAERS) has been quite modest – a little over a dozen events in total. And over 30,000 patients have been dosed with CAR-t so far. Obviously, not all AE's get reported but, presumably, the event rate is not off by an order of magnitude. We would say something like an upper limit of 3x. So, the risk here is 12/30000 to 36/30000 (0.04% to 0.1%). While very low, the FDA note tells us that there have been some fatal T-cell malignancies after CAR-t treatment.

The question quickly becomes "why" are we seeing these malignancies and how relevant might this be for applications of CAR-t outside of cancer. The risk/benefit assessment from a regulatory perspective might be less favorable for a less fatal disease. For example, Immix is applying CAR to treat a rare disease with great effect (AL Amyloidosis). Gracell is using CAR to treat autoimmunity and others, as yet undeclared, are using CAR to treat serious viral infections.

To start, it's worth noting that a CAR-t is a T-cell that is typically engineered using a lentivirus to express an antigen encoded with a transduced genetic sequence. It's well known that lentiviral transfer of genetic data is not 100% accurate so it's theoretically possible that a CAR-t lentivirus could somehow cause a cancer. A lentiviral vector presumably breaks a promoter protein. It has long been hypothesized, in fact, that T-cell lymphomas have a viral origin.* Cases of viral-vector insertional mutagenesis have been seen with gene therapies where lentiviral vectors are also used.

The FDA has gone on to approve relevant gene therapies (e.g., Bluebird) even though underlying diseases are not necessarily fatal. Further, there is substantial evidence that lentiviral vectors are particularly low risk for causing insertional mutagenesis.**

It's also well known that T-cells themselves do not cause cancer. Of course, they are part of the solution to the disease. T-cell leukocyte extracts, for example, have been used for decades to treat diseases outside the U.S. and in thousands of patients treated there are zero records of cancers – much less T-cell lymphomas.***

We spoke with one sponsor last week who had an IND go through FDA for a CAR-t for a non-cancer disease just last month without comment, so it appears that the FDA is either newly sensitized to the T-cell lymphoma risk from a specific case or is not particularly worried about the risk. This company did not receive any special instructions from FDA to carry out batch release testing in a different way. Also, Gracell's IND for SLE was cleared last Monday.

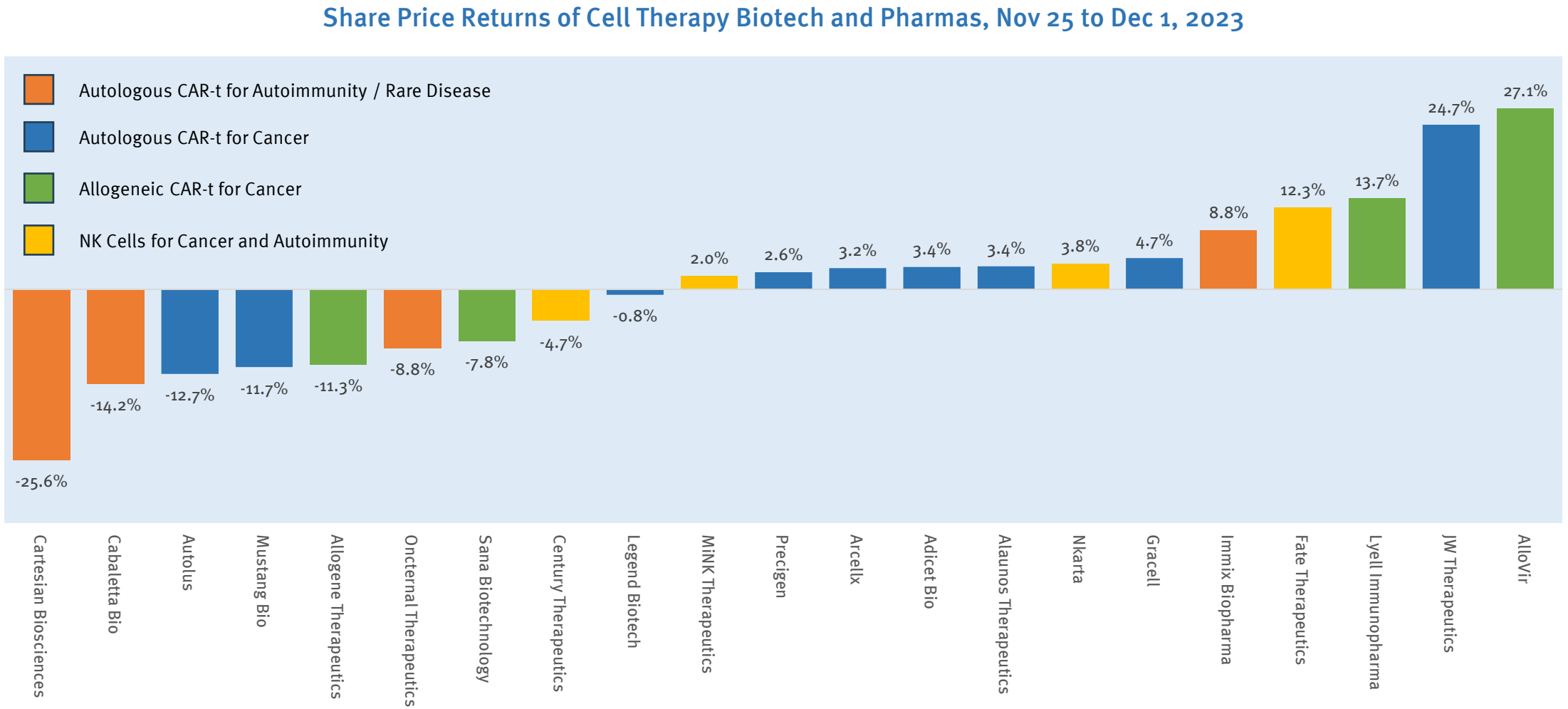
One might expect FDA to impose new rules involving manufacturing controls on CAR manufacturing etc. but it's clear that this has not yet happened and may not happen.

Our own view is that the market sizing of applications of CAR-t for diseases like lupus or AL amyloidosis might become a bit smaller but that the risk of T-cell lymphomas is not going to significantly change the potential of these therapies outside of cancer. That is, it's possible that one might not want to use CAR-t for a routine case of lupus or myasthenia gravis but instead save the therapy for more expensive cases. But we are not aware of sponsors today that have contemplated such routine use in any case.

Overall, the lymphoma risk factor appears to be a minor one in this context. The market appears to agree. With one exception, no relevant stock was down more than 20% on the news. See next page for details.

* See, for example, Au WY, Liang R. Peripheral T-cell lymphoma. Curr Oncol Rep. 2002 Sep;4(5):434-42.
** See, for example, Sarkis C, Philippe S, Mallet J, Serguera C. Non-integrating lentiviral vectors. Curr Gene Ther. 2008
*** See, for example, https://www.scirp.org/journal/paperinformation.aspx?paperid=53910

Share Price Reaction in Cell Therapy Biotechs Last Week After FDA Note on CAR-t Cancer Risk



Source: CapitalIQ and Stifel Analysis

Does It Pay to Go Vegan?

Blackie K, Bobe G, Takata Y. Vegetarian diets and risk of all-cause mortality in a population-based prospective study in the United States. J Health Popul Nutr. 2023 Nov 23;42(1):130.

The popularity of vegetarian diets has increased the need for studies on long-term health outcomes. A limited number of studies, including only one study from a non-vegetarian population, investigated the risk of mortality with self-identified vegetarianism and reported inconsistent results. This study evaluated prospective associations between vegetarian diets and all-cause mortality among 117,673 participants from the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial cohort study. Vegetarian diet status was self-identified on the questionnaire. Deaths were ascertained from follow-up questionnaires and the National Death Index database. Multivariable Cox regression models were used to estimate the risk of all-cause mortality in hazard ratio (HR) and 95% confidence intervals (CI). By diet group, there were 116,894 omnivores (whose diet does not exclude animal products), 329 lacto- and/or ovo-vegetarians (whose diet excludes meat, but includes dairy and/or eggs), 310 pesco-vegetarians (whose diet excludes meat except for fish and seafood) and 140 vegans (whose diet excludes all animal products). After an average follow-up of 18 years, 39,763 participants were deceased. **The risk of all-cause mortality did not statistically significantly differ among the four diet groups. Comparing with the omnivore group, the HR (95% CI) were 0.81 (0.64-1.03) for pesco-vegetarian group, 0.99 (0.80-1.22) for lacto- and/or ovo-vegetarian group and 1.27 (0.99-1.63) for vegan group, respectively.** Similarly, mortality risk did not differ when comparing lacto- and/or ovo-vegetarians plus vegans with meat/fish eaters (omnivores and pesco-vegetarians) (HR [95% CI] = 1.09 [0.93-1.28]). As this study is one of the two studies of vegetarianism and mortality in non-vegetarian populations, further investigation is warranted.

A very large study published last week showed no evidence that supports veganism as a way to live longer.

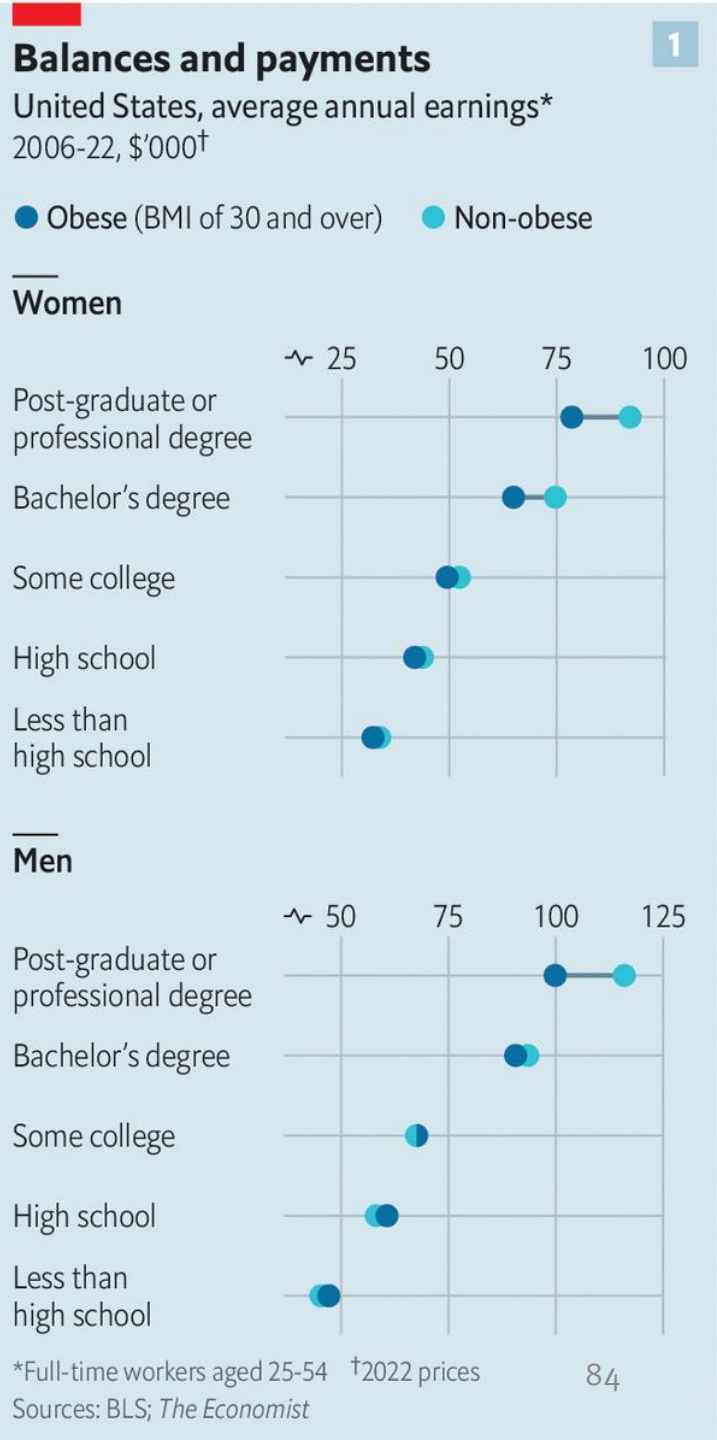
Source: https://pubmed.ncbi.nlm.nih.gov/37996932/

Scale Economics: The Obesity Pay Gap is Worse Than Previously Thought

Economist, Nov 23, 2023

Obese people experience discrimination in many parts of their lives, and the workplace is no exception. Studies have long shown that obese workers, defined as those with a body-mass index (bmi) of 30 or more, earn significantly less than their slimmer counterparts. In America, several state and local governments are contemplating laws against this treatment. On November 22nd, one such ban came into force in New York City.

Yet the costs of weight discrimination may be even greater than previously thought. “The overwhelming evidence,” wrote the Institute for Employment Studies, a British think-tank, in a recent report, “is that it is only women living with obesity who experience the obesity wage penalty.” They were expressing a view that is widely aired in academic papers. To test it, The Economist has analysed data concerning 23,000 workers from the American Time Use Survey, conducted by the Bureau of Labour Statistics. Our number-crunching suggests that, in fact, being obese hurts the earnings of both women and men.



Source: https://www.economist.com/finance-and-economics/2023/11/23/the-obesity-pay-gap-is-worse-than-previously-thought

Altimmune Announces Positive Topline Results From MOMENTUM 48-Week Phase 2 Obesity Trial Of Pemvidutide

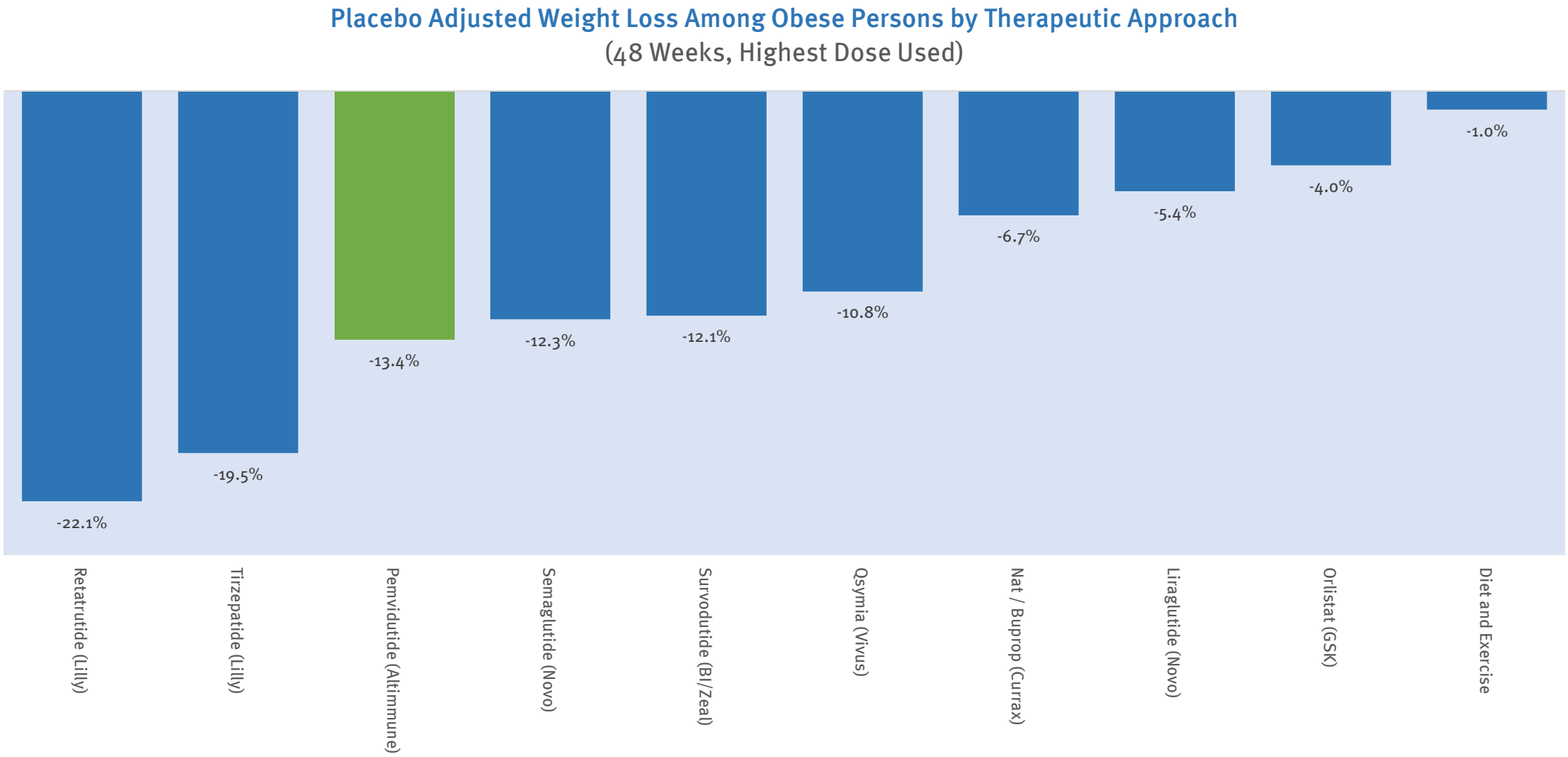
GAITHERSBURG, Md., Nov. 30, 2023 (GLOBE NEWSWIRE) -- Altimmune, Inc. (Nasdaq: ALT), a clinical-stage biopharmaceutical company (the "Company"), today announced topline results from its 48-week MOMENTUM Phase 2 obesity trial of pemvidutide. The trial enrolled 391 subjects with obesity or overweight with at least one co-morbidity and without diabetes. Subjects were randomized 1:1:1:1 to 1.2 mg, 1.8 mg, 2.4 mg pemvidutide or placebo administered weekly for 48 weeks in conjunction with diet and exercise. The 1.2 mg and 1.8 mg doses were administered without dose titration, while a short 4-week titration period was employed for the 2.4 mg dose. At baseline, subjects had a mean age of approximately 50 years, mean body mass index (BMI) of approximately 37 kg/m2 and mean body weight of approximately 104 kg. Approximately 75% of subjects were female.

At Week 48, subjects receiving pemvidutide achieved mean weight losses of 10.3%, 11.2%, 15.6% and 2.2% at the 1.2 mg, 1.8 mg, and 2.4 mg doses and placebo, respectively, with a near-linear trajectory of continued weight loss observed on the 2.4 mg dose at the end of treatment. Over 50% of subjects achieved at least 15% weight loss and over 30% of subjects achieved at least 20% weight loss on the 2.4 mg dose. As in prior clinical trials, pemvidutide resulted in robust reductions in serum lipids and improvements in blood pressure without imbalances in cardiac events, arrhythmias or clinically meaningful increases in heart rate. Glucose homeostasis was maintained, with no significant changes in fasting glucose or HbA1c.

More subjects receiving pemvidutide stayed on study compared to those receiving placebo, with 74.1% of pemvidutide subjects completing the trial compared to 61.9% of placebo subjects. Nausea and vomiting comprised the majority of adverse events (AEs) and were predominantly mild to moderate in severity. Only one (1.0%) subject experienced a drug-related serious adverse event (SAE), a case of vomiting at the 2.4 mg dose. Rates of AEs leading to treatment discontinuation were 6.2% in subjects receiving placebo and 5.1%, 19.2%, and 19.6% in subjects receiving 1.2 mg, 1.8 mg and 2.4 mg of pemvidutide, respectively. Study discontinuations related to study drug occurred in 2.1% of placebo subjects and 4.1%, 16.2% and 15.5% in subjects receiving 1.2 mg, 1.8 mg and 2.4 mg of pemvidutide, respectively, with most discontinuations due to AEs in the pemvidutide groups occurring in the first 16 weeks of treatment. No AEs of special interest or major adverse cardiac events (MACE) were observed, and there were low rates

Source: https://ir.altimmune.com/news-releases/news-release-details/altimmune-announces-positive-topline-results-momentum-48-week

Pemvidutide Weight Loss Results Beat Semaglutide and Survodutide But Behind Lilly Molecules



Source: Stifel analysis of results of various trials.

Pfizer Announces Topline Phase 2b Results of Oral GLP-1R Agonist, Danuglipron, in Adults with Obesity

Dec 1, 2023 -- NEW YORK--(BUSINESS WIRE)-- Pfizer Inc. (NYSE: PFE) today announced topline data from the Phase 2b clinical trial (NCT04707313) investigating its oral Glucagon-like peptide-1 receptor agonist (GLP-1RA) candidate, danuglipron (PF-06882961), in adults with obesity and without type 2 diabetes. The study met its primary endpoint demonstrating statistically significant change in body weight from baseline.

Twice-daily dosing of danuglipron showed statistically significant reductions from baseline in body weight for all doses, with mean reductions ranging from -6.9% to -11.7%, compared to +1.4% for placebo at 32 weeks, and -4.8% to -9.4%, compared to +0.17% for placebo at 26 weeks. Placebo-adjusted reductions in mean body weight ranged from -8% to -13% at 32 weeks and -5% to -9.5% at 26 weeks. Depending on titration schedule, participants were at target dose levels for 6 to 24 weeks.

While the most common adverse events were mild and gastrointestinal in nature consistent with the mechanism, high rates were observed (up to 73% nausea; up to 47% vomiting; up to 25% diarrhea). High discontinuation rates, greater than 50%, were seen across all doses compared to approximately 40% with placebo. No new safety signals were reported and treatment with danuglipron was not associated with increased incidence of liver enzyme elevation compared to placebo. Data from this study will be presented at a future scientific conference or published in a peer-reviewed journal.

“We believe an improved once-daily formulation of danuglipron could play an important role in the obesity treatment paradigm, and we will focus our efforts on gathering the data to understand its potential profile,” said Mikael Dolsten, MD., PhD., Chief Scientific Officer & President, Pfizer Research and Development. “Results from ongoing and future studies of the once-daily danuglipron modified release formulation will inform a potential path forward with an aim to improve the tolerability profile and optimize both study design and execution.”

Future development of danuglipron will be focused on a **once-daily formulation**, with pharmacokinetic data anticipated in the first half of 2024.

Source: https://investors.pfizer.com/Investors/News/news-details/2023/Pfizer-Announces-Topline-Phase-2b-Results-of-Oral-GLP-1R-Agonist-Danuglipron-in-Adults-with-Obesity

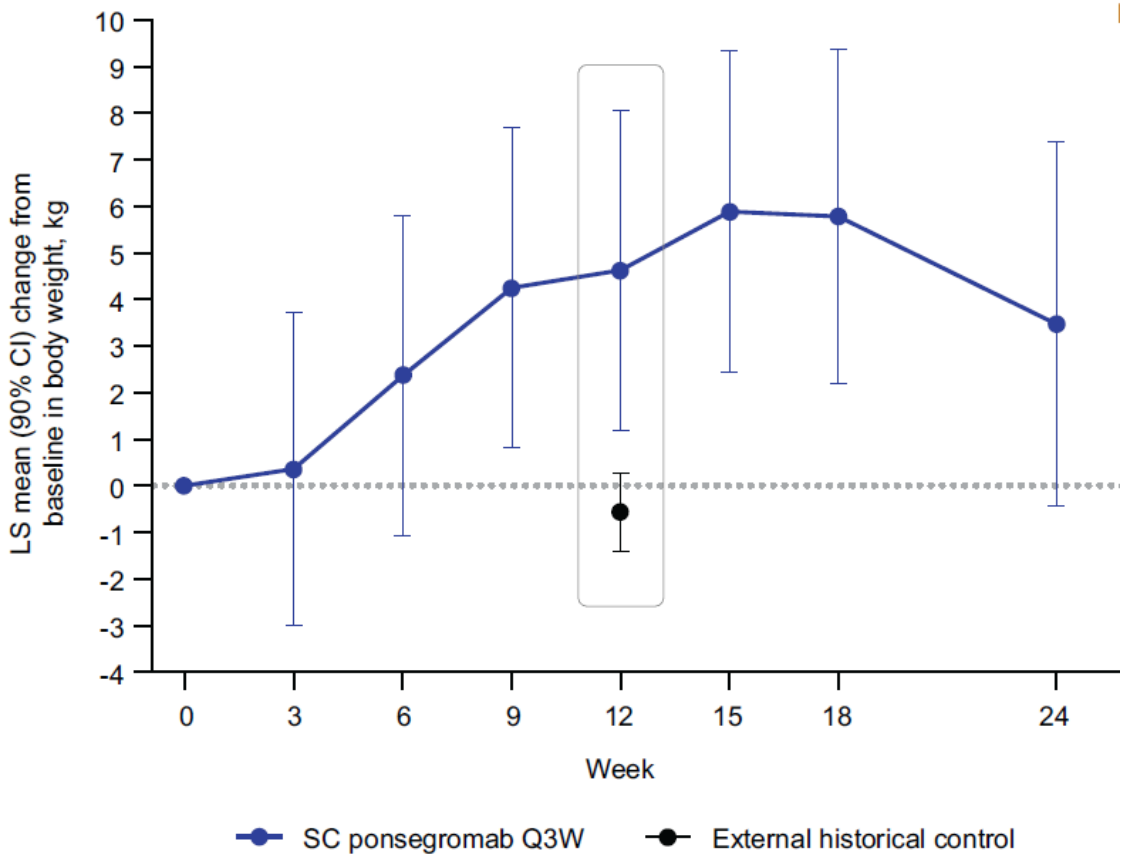
Pfizer Ponsegromab Weight Gain Data in Cancer Cachexia Highly Impressive

RESEARCH ARTICLE | NOVEMBER 20 2023 Clinical Cancer Research

A Phase 1b First-In-Patient Study Assessing the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Ponsegromab in Participants with Cancer and Cachexia

Jeffrey Crawford ; Roberto A. Calle ; Susie M. Collins ; Yan Weng ; Shannon L. Lubaczewski ; Clare Buckeridge ; Ellen Q. Wang ; Magdalena A. Harrington ; Anil Tarachandani ; Michelle I. Rossulek ; James H. Revkin

This first-in-patient (phase Ib), 24-week study assessed use of ponsegromab, a monoclonal antibody against GDF-15, in adults with advanced cancer, cachexia, and elevated GDF-15 serum concentration. Experimental Design: Participants (n = 10 received open-label ponsegromab subcutaneous 200 mg every 3 weeks for 12 weeks in addition to standard-of-care anti-cancer treatment No treatment-related treatment-emergent adverse events, injection site reactions, or adverse trends in clinical laboratory tests, vital signs, or electrocardiogram parameters attributable to ponsegromab were identified A least-squares mean (standard error) increase of 4.63 kg (1.98) was observed at week 12, an increase of approximately 6.6% relative to baseline Ponsegromab-mediated improvements in actigraphy-based assessments of physical activity and in quality of life, including appetite as assessed by Functional Assessment of Anorexia-Cachexia Therapy total and subscale scores, were also observed.



Source: https://aacrjournals.org/clincancerres/article/doi/10.1158/1078-0432.CCR-23-1631/730198/A-Phase-1b-First-In-Patient-Study-Assessing-the

Biomea Shares Up 42% Last Week on Abstract Titles Released for ATTD Conference

REDWOOD CITY, Calif., Nov. 27, 2023 (GLOBE NEWSWIRE) -- Biomea Fusion, Inc. ("Biomea") (Nasdaq: BMEA), a clinical-stage biopharmaceutical company dedicated to discovering and developing novel covalent small molecules to treat and improve the lives of patients with genetically defined cancers and metabolic diseases, today announced the acceptance of three abstracts presenting new clinical data from the ongoing escalation portion of its COVALENT-111 trial, evaluating BMF-219 as a potential treatment for people with type 2 diabetes, at the 17th International Conference on Advanced Technologies & Treatments for Diabetes (ATTD) taking place in Florence, Italy, 6-9 March 2024. This new clinical data from all dosing cohorts initiated to date from the escalation portion of COVALENT-111 will be featured during a Poster Discussion Presentation and two Poster Viewing Presentations at ATTD.

These abstracts further validate the mechanism of action of covalently inhibiting menin in people with type 2 diabetes to potentially provide long-term improvement in glycemic control through beta cell regeneration.

Accepted 2024 ATTD Abstract Titles

Abstract Submission Number: 101
Abstract Title: Durable Glycemic Control with BMF-219 during off-Treatment Period at Week 26: a Phase 1/2 Trial of BMF-219 in Patients with Type 2 Diabetes (COVALENT-111)

Abstract Submission Number: 751
Abstract Title: Key Observations from the Dose – Escalation Portion of COVALENT-111, a Phase 1/2 Trial of the Covalent Menin Inhibitor BMF-219 in Patients with Type 2 Diabetes

Abstract Submission Number: 722
Presentation Session: E-Poster Viewing Session
Abstract Title: Case Studies from COVALENT-111, a Phase 1/2 Trial of BMF-219, a Covalent Menin Inhibitor, in Patients with Type 2 Diabetes in COVALENT-111

Source: https://investors.biomeafusion.com/news-releases/news-release-details/biomea-fusion-announces-acceptance-three-abstracts-its-novel

Normally, one would not expect to see a stock jump 42% on the release of abstract titles for a conference taking place in four months.

However, in this case, Biomea is one of the five most shorted stocks in biotech on the NASDAQ. For whatever reason, the company's MENIN approach to T2D has attracted its share of skeptics.

And the company's first abstract title "let the cat out of bag" by referencing durable glycemic control. The durability of response with Biomea's drug, BMF-219, has been a key question raised by company skeptics.

Six ways large language models are changing healthcare

Check for updates

Nature Medicine asks six leading AI researchers to explain how LLM-powered chatbots are having an impact on health, from virtual nurses to detecting cancer progression.

The public debut in late 2022 of ChatGPT, a large language model (LLM) chatbot able to write well-informed and precise texts on just about any topic, galvanized a huge surge of interest in LLMs – including in many areas of healthcare research. Investment in LLMs is now exploding, as is research into other innovations for artificial intelligence (AI) in health.

Nature Medicine asked six leading researchers to explain how LLMs are beginning to transform healthcare.

Virtual nurses

68 million adults in the USA have two or more chronic diseases. To meet their demands for future healthcare, care capacity will have to increase at least tenfold, estimates Munjal Shah, co-founder and CEO of Hippocratic AI, based in Palo Alto, California. At present, he says, "we only have the resources to provide chronic care support to the top 20% of the sickest of the sick. Put simply, we don't have enough nurses."

With this in mind, Shah's company (which has received US$50 million in venture capital support) is using LLMs to help nurses do their work. Such administrative support is "a safer use case for LLMs than diagnostic use cases," Shah explains, and he believes that AI tools "can be scaled to truly solve the healthcare staffing crisis."

The aim is to create virtual nurses for chronic care that use an automated 'voice' to speak to, and listen to, patients. Although the virtual nurses will not be involved in clinical diagnosis, says Shah, they could remind patients to take their medicine, follow through with care plans, schedule follow-up appointments, review medication issues and help patients navigate care-access issues.

An LLM-backed chronic-care nurse can pass the NCLEX licensing exam for nurses and the NAPLEX licensing exam for pharmacists, says Shah. An LLM nurse can "speak every language, and remember every conversation with each patient," he says.

To train its LLM nurse, Hippocratic AI built its own model using text from care plans, regulations and other medical manuals. The company then trained the model on how to speak like a chronic-care nurse using conversations between registered chronic-care nurses and patient actors.

To safety-check its LLM nurse, Hippocratic AI has set up a safety council, and it has recruited more than a thousand nurses to evaluate the model in a double-blind randomized trial. The product, says Shah, will be released one sub-condition or procedure at a time – for example, for patients with chronic kidney disease, then for patients with arthritis, and so on.

Clinical note-taking

LLMs are poised to create huge efficiencies for clinicians by liberating them from their keyboards, says David Bates, a professor of medicine at Harvard Medical School.

"One problem we have is the inbox," says Bates. "Most physicians are now using electronic health records, and these generate a lot of email and most physicians don't have good strategies for managing this." An LLM can help categorize emails and can be trained to respond to basic messages, Bates says. "The trick is to ensure it doesn't say anything stupid."

LLMs could also prove good at checking in with patients with chronic conditions during the time between conventional encounters with caregivers, writing notes in patients' records and summarizing patients' issues. All of this "could make care much faster," says Bates.

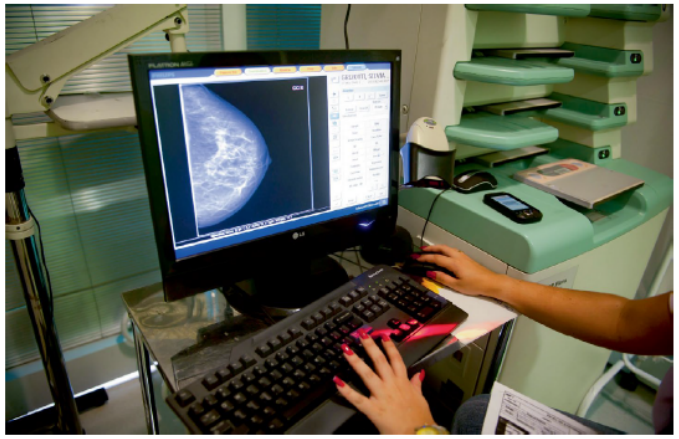
Bates's musings are far from academic. In September, Oracle Computer (based in Austin, Texas) announced that it is poised to market an AI-powered voice- and screen-based Clinical Digital Assistant that can conduct administrative tasks in response to conversational voice commands. Oracle says it aims to make its digital assistant available by the end of 2024.

Adverse-event detection

Vivek Rudrapatna is a gastroenterologist at the University of California, San Francisco, who has been working with the US Food and Drug Administration on unearthing adverse-event data from clinical notes within electronic health record systems. "Clinical notes have been underutilized because we lack tools to effectively examine them," says Rudrapatna.

Thanks to LLMs, this is no longer the case, Rudrapatna enthuses. There have been impressive advances in understanding natural language processing, initially following the release of context-aware deep learning models such as BERT (bidirectional encoder representations from transformers) and now using GPT-4. However, the presence of identifiable patient information in clinical notes has hindered research in this area.

Rudrapatna tackled this challenge with the automated redaction of protected health information from 75 million clinical notes, together with the extraction of serious adverse events[1]. The BERT model that Rudrapatna and his team used was fine-tuned to extract only events that resulted in hospitalization and were also associated with the use of biologic immunosuppressants for inflammatory bowel disease – Rudrapatna's specialty.



AI can analyze hundreds of mammogram images to predict metastatic cancer.

Rudrapatna is now hopeful that LLMs can automate the detection of adverse events from electronic health records and "may someday support the surveillance of drug safety in the post-marketing setting using new data sources," he says.

Predicting cancer metastasis

LLMs are being used to predict metastatic cancer and to assist in devising clinical treatment responses, says Amber Simpson, Canada Research Chair in Biomedical Computing and Informatics at Queens University, Canada, who collaborates with a research team at Memorial Sloan Kettering Cancer Center in New York City.

Her research on LLM-assisted cancer diagnosis includes a set of studies in which cancer-progression patterns were extracted from vast numbers of computed tomography reports (714,454 structured radiology reports were used in the most recent study[2]) and were analyzed by a natural language processing model that was then used to predict metastatic disease in multiple organs. The models used features from consecutive structured text radiology reports to predict the presence of metastatic disease.

By offering oncologists a predictive pathway of how cancer will progress, the LLM shifts treatment strategies toward a more targeted, deliberate approach.

"Currently, we treat everyone to help a few," Simpson explains. "With this type of model, if you add the treatment data, you can start saying the next treatment this patient should receive is this specific therapy – and that's really the holy grail of precision medicine."

Such an approach helps to elucidate cancer drugs beyond clinical trials, in real-world settings, Simpson adds. "This type of analysis allows us to understand population-level analysis of cancer patients and how drugs work in the wild."

Unusually for an AI model, this is already in clinical use. "We're already showing this approach can be used clinically. We're already targeting patients," says Simpson.

Social determinants of health

LLMs can deliver useful information on the social determinants of health to clinicians, says Maxim Topaz, a professor of nursing at Columbia University. He has spent years refining LLM-based methods that deliver hard-to-find, unstructured, non-medical information that has an impact on health.

CREDIT: PULSARIMAGES/ALAMY STOCK PHOTO

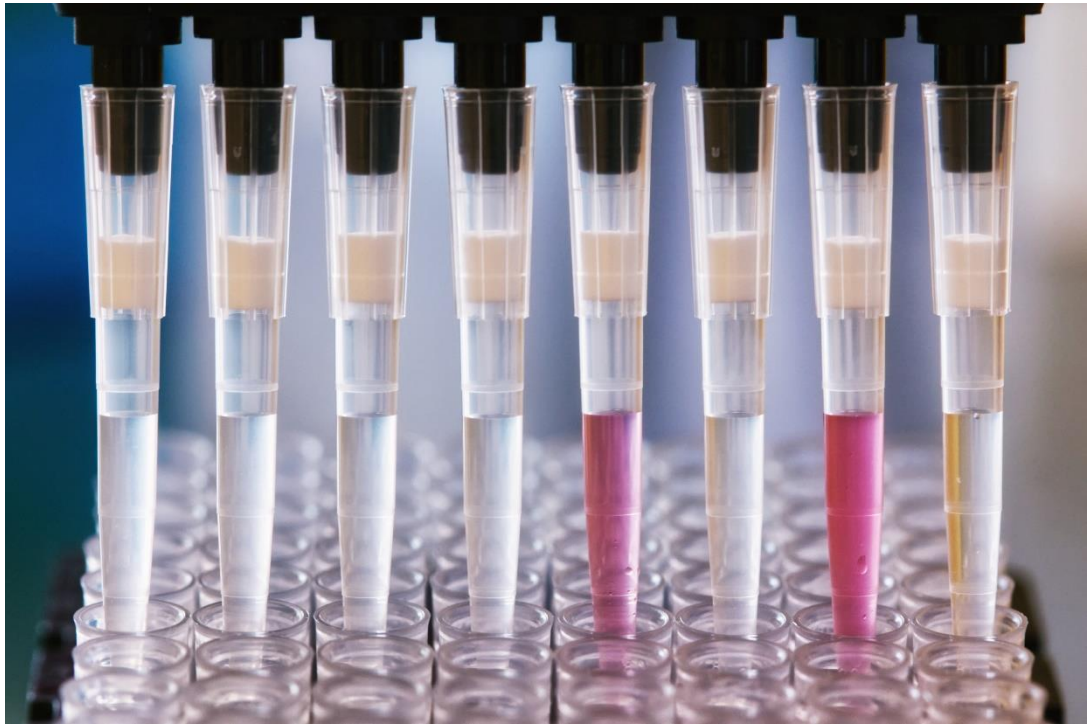
We like the ideas shown here of using LLM's to virtualize nursing and address the social determinants of health.

Source: https://www.nature.com/articles/s41591-023-02700-1

UK Biobank Releases Half a Million Whole-Genome Sequences for Biomedical Research

Catherine Offord, *Science*, Nov 29, 2023

One of the world's largest databases of whole genomes has just become a lot larger. The British health study known as the UK Biobank today made the full genetic sequences of nearly 500,000 people available to scientists for analysis, more than doubling the size of an earlier data set. Combined with long-term health data on participants, this "treasure trove" has the potential to transform biomedical science, organizers say.



Geneticists are excited by the news. Such a large set of sequences provides a uniquely rich resource for studying the biological underpinnings of human health and disease, says Eleftheria Zeggini, director of the Institute of Translational Genomics at Helmholtz Munich. "In the field of human genomics, sample size is queen."

Since its founding in 2006, the UK Biobank has collected biological samples, whole-body scans, and data on the health and lifestyle of half a million middle-age and elderly volunteers. It has also, with participants' consent, tracked those people's incidence of cancer, dementia, and other conditions through records maintained by the country's National Health Service.

Source: https://www.science.org/content/article/uk-biobank-releases-half-million-whole-genome-sequences-biomedical-research

J&J Hired Thousands of Data Scientists. Will The Strategy Pay Off?

Peter Loftus, *Wall Street Journal*, Nov 30, 2023

Johnson & Johnson is making one of the biggest bets in the healthcare industry on using data science and artificial intelligence to bolster its work. The 137-year-old pharmaceutical and medical-device company has hired 6,000 data scientists and digital specialists in recent years, and spent hundreds of millions of dollars on their work, such as using machines to scour massive health-record datasets. Last year the company opened a state-of-the-art research site near San Francisco that houses advanced data science.

Some early efforts focus on diagnostics, like an algorithm that analyzes heart tests to spot a deadly type of high blood pressure much sooner than humans can, and voice-recognition technology to analyze speech for early signs of Alzheimer's disease. There's a virtual-reality goggle set to help train surgeons on procedures like knee replacements.

The long game, though, is a goal that has seen a lot of hype but less concrete proof that it will become a reality: using AI for drug discovery. Startup biotechs are in the early days of human testing of AI-discovered drugs. Google this year introduced cloud-based AI tools to assist drugmakers in finding new treatments. But it could still be years before an AI-discovered drug is approved for sale by regulators.

Some pharmaceutical leaders have expressed skepticism that AI could ever discover new drugs any better than humans can.

J&J says it has an edge: a massive database called med. AI that it can sift for patterns to help speed up drug development. The info includes "real-world data"—anonymized information collected from everyday patient visits to doctors and hospitals—and years of clinical-trial results.

"AI and data science are going to be the heart of how we are transforming and innovating," says Najat Khan, chief data science officer and global head of strategy and operations for J&J's pharmaceutical research unit. "The amount of data is increasing, the algorithms are getting better, the computers are getting better."

J&J says it has already used machine learning to help design an experimental cancer drug that is scheduled to start human testing next year.

A few things make J&J's effort different, Khan says. Its data-science workers are tightly integrated into the company's strategic decisions on drug research. The company's massive datasets—med. AI has more than three petabytes of information—are made available to tens of thousands of employees. And it has hired people who aren't just data scientists but also have skills in chemistry, biology or drug development.

Source: https://www.wsj.com/tech/biotech/johnson-johnson-hiring-data-scientists-ai-ccbf2c07

Tiny Robots Made From Human Cells Heal Damaged Tissue

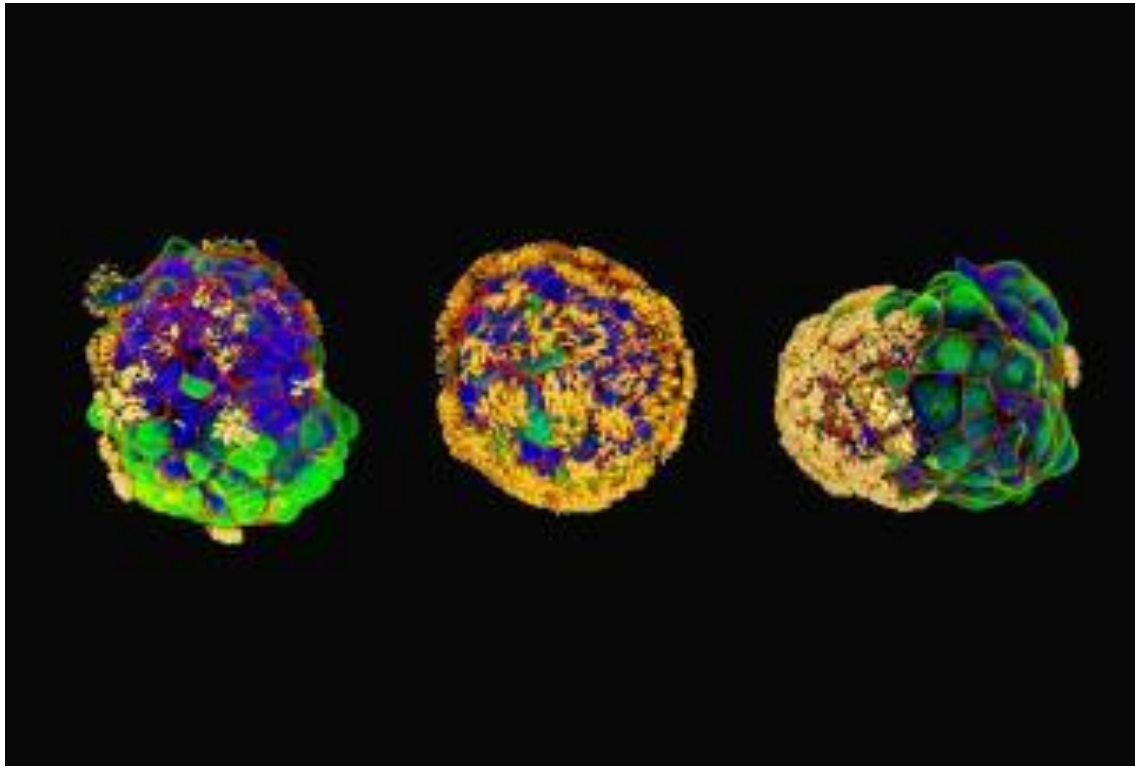
Matthew Hutson, Nature, Nov 30, 2023 (excerpt).

“Scientists have developed tiny robots made of human cells that are able to repair damaged neural tissue. The ‘anthrobots’ were made using human tracheal cells and might, in future, be used in personalized medicine.

The research "points the way to a ’tissue engineering 2.0’ that synthetically controls a range of developmental processes,” says Alex Hughes, a bioengineer at the University of Pennsylvania, in Philadelphia.

Developmental biologist Michael Levin at Tufts University in Medford, Massachusetts, and his colleagues had previously developed tiny robots using clumps of embryonic frog cells. But the medical applications of these ‘xenobots’ were limited, because they weren’t derived from human cells and because they had to be manually carved into the desired shape. The researchers have now developed self-assembling anthrobots and are investigating their therapeutic potential using human tissue grown in the laboratory. They published their findings in Advanced Science.

Levin and his team grew spheroids of human tracheal skin cells in a gel for two weeks, before removing the clusters and growing them for one week in a less viscous solution. This caused tiny hairs on the cells called cilia to move to the outside of the spheroids instead of the inside. These cilia acted as oars, and the researchers found that the resulting anthrobots — each containing a few hundred cells — often swam in one of several patterns. Some swam in straight lines, others swam in circles or arcs, and some moved chaotically.”



Three examples of Anthrobots with hair-like cilia in yellow. “It is fascinating and completely unexpected that normal patient tracheal cells, without modifying their DNA, can move on their own and encourage neuron growth across a region of damage,” said Michael Levin. Images: Gizem Gumuskaya

Source: https://www.nature.com/articles/d41586-023-03777-x

Loyal's Drug for Dogs, IGF1 and Death

Emily Anthes, "Could a Drug Give Your Pet More Dog Years?," *New York Times*, Nov 28, 2023 (excerpt)

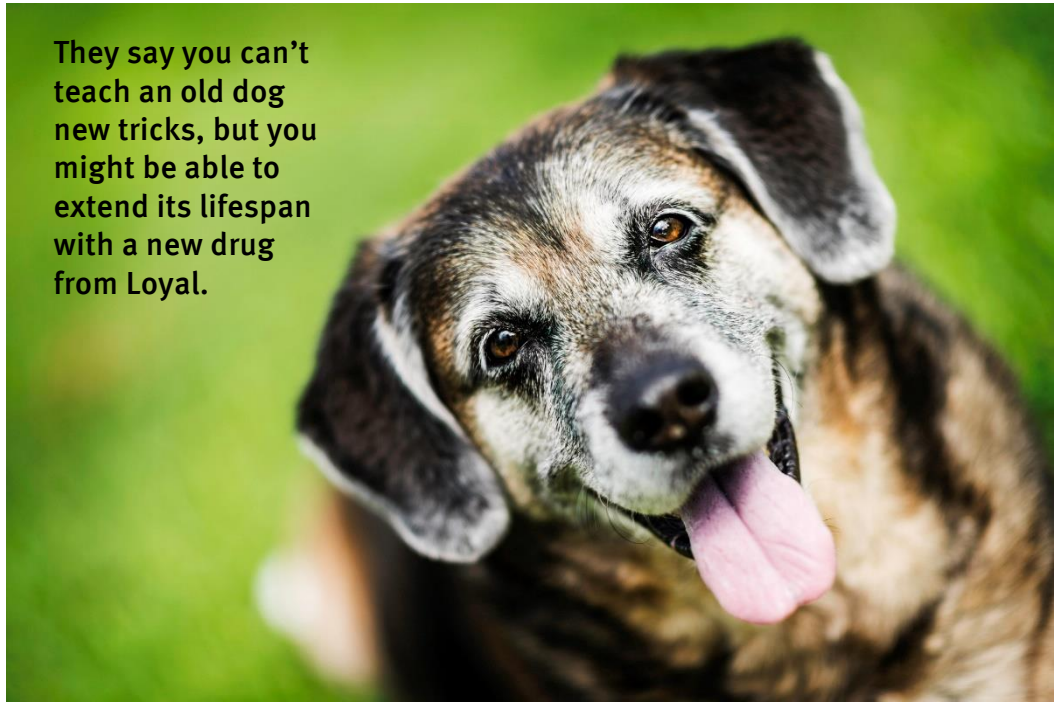
"When you adopt a dog, you're adopting future heartbreak," said Emilie Adams, a New Yorker who owns three Rhodesian Ridgebacks. "It's worth it over time because you just have so much love between now and when they go. But their life spans are shorter than ours."

In recent years, scientists have been chasing after drugs that might stave off this heartbreak by extending the lives of our canine companions. On Tuesday, the biotech company Loyal announced that it had moved one step closer to bringing one such drug to market. "The data you provided are sufficient to show that there is a reasonable expectation of effectiveness," an official at the U.S. Food and Drug Administration informed the company in a recent letter.

That means that the drug, which Loyal declined to identify for proprietary reasons, has met one of the requirements for "expanded conditional approval," a fast-tracked authorization for animal drugs that fulfill unmet health needs and require difficult clinical trials. The drug is not available to pet owners yet, and the F.D.A. must still review the company's safety and manufacturing data. But conditional approval, which Loyal hopes to receive in 2026, would allow the company to begin marketing the drug for canine life extension, even before a large clinical trial is complete.

"We're going to be going for claiming at least one year of healthy life span extension," said Celine Halioua, the founder and chief executive of Loyal. Whether the drug will actually deliver on that promise is unknown. Although a small study suggests LOY-001 might blunt metabolic changes associated with aging, Loyal has not yet demonstrated that it lengthens dogs' lives.

Source: https://www.nytimes.com/2023/11/28/science/longevity-drugs-dogs.html



LOY-001, an extended-release implant intended for large, adult dogs, is designed to modulate a different growth-related compound: insulinlike growth factor-1, or IGF-1. The IGF-1 pathway has been associated with aging and longevity in several species; in dogs, it is known to play a key role in determining body size. Although the idea remains unproven, some scientists hypothesize that high IGF-1 levels drive both rapid growth and accelerated aging in large dogs, which generally have shorter life spans than small ones."

IFG1 and Humans

ROLE of IGF-1 System in the Modulation of Longevity: Controversies and New Insights From a Centenarians' Perspective

Front. Endocrinol., 01 February 2019

Giovanni Vitale[1,2], Giuseppe Pellegrino[3], Maria Vollery[4] and Leo J. Hofland[5]*

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Human aging is currently defined as a physiological decline of biological functions in the body with a continual adaptation to internal and external damaging. The endocrine system plays a major role in orchestrating cellular interactions, metabolism, growth, and aging. Several *in vivo* studies from worms to mice showed that downregulated activity of the GH/IGF-1/insulin pathway could be beneficial for the extension of human life span, whereas results are contradictory in humans. In the present review, we discuss the potential role of the IGF-1 system in modulation of longevity, hypothesizing that the endocrine and metabolic adaptation observed in centenarians and in mammals during caloric restriction may be a physiological strategy for extending lifespan through a slower cell growing/metabolism, a better physiologic reserve capacity, a shift of cellular metabolism from cell proliferation to repair activities and a decrease in accumulation of senescent cells. Therefore, understanding of the link between IGF-1/insulin system and longevity may have future clinical applications in promoting healthy aging and in Rehabilitation Medicine.

Source: https://www.frontiersin.org/articles/10.3389/fendo.2019.00027

Too much insulin-like growth factor appears to accelerate death in dogs. In humans, the data on this topic is confounded at best although GWAS data suggest that higher expression of IGF-1 is also associated with somewhat lower survival rates.

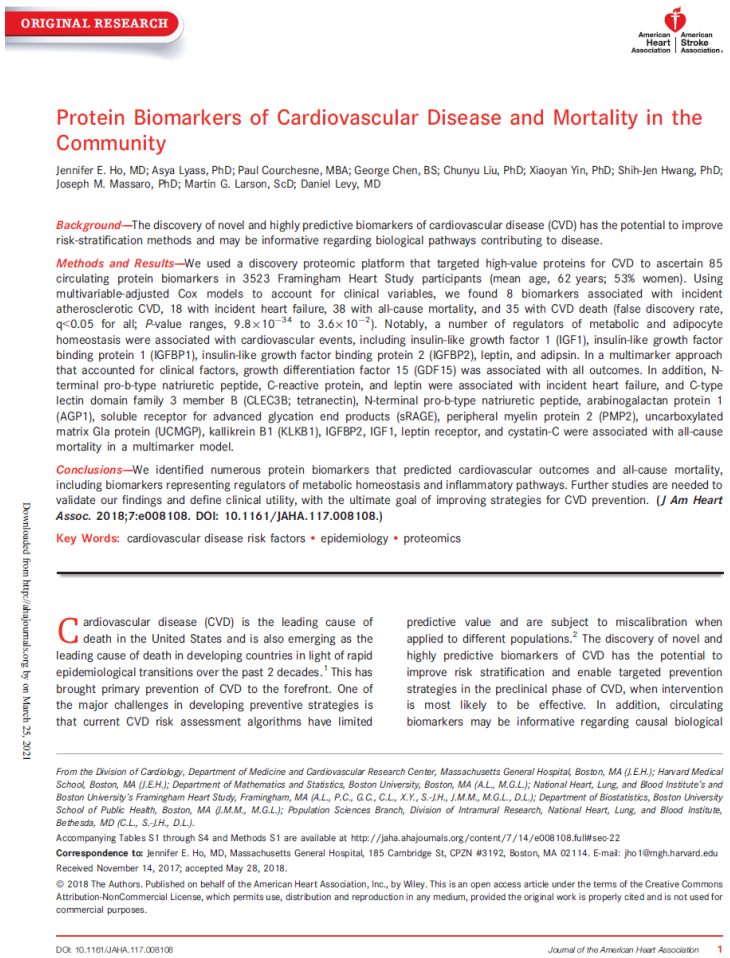
"Suh et al. (64) evaluated serum IGF-1 levels in Ashkenazi Jewish centenarians' offspring and in age-matched controls. Female centenarians' offspring had 35% higher serum IGF-1 levels than that controls. This difference may represent a compensatory response to reduced IGF-1 receptor signaling. Indeed, female offspring showed shorter stature than controls. In addition, an overrepresentation of heterozygous mutations in the IGF-1 receptor gene together with relatively high serum IGF-1 levels and weakened activity of the IGF-1 receptor has been described in Ashkenazi Jewish centenarians compared to controls without familial longevity.

In order to study longevity, other authors characterized these pathways in nonagenarian siblings and their offspring. In the Leiden Longevity Study, 421 families were recruited consisting of at least two long-lived Caucasian siblings, their offspring and partners of the offspring as control. In these populations serum glucose, insulin and triglycerides were the best biomarker of healthy aging (glucose and insulin low levels were considered healthy) (65). Nonagenarians in the lowest circulating IGF-1/IGFBP-3 ratio were associated with a better survival (66).

Preclinical models have provided a great insight into the aging process with consistent data considering the role of the GH/IGF-1/insulin system in the modulation of lifespan. While it is well known that enhanced insulin sensitivity and low insulin levels are associated with an improved survival, there are several evidences showing that attenuation of the GH/IGF-1 axis may have beneficial effects in extending lifespan in humans. However, it is still unknown which are the optimal IGF-1 levels during life to live longer and healthier. In addition, IGF-1 receptor sensitivity and activation of the post-receptor pathway were not evaluated in the majority of the study enrolling long-lived subjects. Therefore, it is not possible to define the real activation status of the IGF-1 receptor signaling through the mere dosage of circulating IGF-1 levels. This renders more difficult the identification of pharmacological or environmental strategies targeting this system for extending lifespan and promoting healthy aging."

Data Don't Support Drugging IGF-1 for Longevity in Humans

This thorough Framingham analysis paper shows that humans with higher IGF-1 live longer – not shorter.



ORIGINAL RESEARCH

American Heart Association | American Stroke Association.

Protein Biomarkers of Cardiovascular Disease and Mortality in the Community

Jennifer E. Ho, MD; Asya Lyass, PhD; Paul Courchesne, MBA; George Chen, BS; Chunyu Liu, PhD; Xiaoyan Yin, PhD; Shih-Jen Hwang, PhD; Joseph M. Massaro, PhD; Martin G. Larson, ScD; Daniel Levy, MD

Background—The discovery of novel and highly predictive biomarkers of cardiovascular disease (CVD) has the potential to improve risk-stratification methods and may be informative regarding biological pathways contributing to disease.

Methods and Results—We used a discovery proteomic platform that targeted high-value proteins for CVD to ascertain 85 circulating protein biomarkers in 3523 Framingham Heart Study participants (mean age, 62 years; 53% women). Using multivariable-adjusted Cox models to account for clinical variables, we found 8 biomarkers associated with incident atherosclerotic CVD, 18 with incident heart failure, 38 with all-cause mortality, and 35 with CVD death (false discovery rate, $q<0.05$ for all; P-value ranges, 9.8×10^{-34} to 3.6×10^{-2}). Notably, a number of regulators of metabolic and adipocyte homeostasis were associated with cardiovascular events, including insulin-like growth factor 1 (IGF1), insulin-like growth factor binding protein 1 (IGFBP1), insulin-like growth factor binding protein 2 (IGFBP2), leptin, and adipsin. In a multimarker approach that accounted for clinical factors, growth differentiation factor 15 (GDF15) was associated with all outcomes. In addition, N-terminal pro-b-type natriuretic peptide, C-reactive protein, and leptin were associated with incident heart failure, and C-type lectin domain family 3 member B (CLEC3B; tetranectin), N-terminal pro-b-type natriuretic peptide, arabinogalactan protein 1 (AGP1), soluble receptor for advanced glycation end products (sRAGE), peripheral myelin protein 2 (PMP2), uncarboxylated matrix Gla protein (UCMGP), kallikrein B1 (KLKB1), IGFBP2, IGF1, leptin receptor, and cystatin-C were associated with all-cause mortality in a multimarker model.

Conclusions—We identified numerous protein biomarkers that predicted cardiovascular outcomes and all-cause mortality, including biomarkers representing regulators of metabolic homeostasis and inflammatory pathways. Further studies are needed to validate our findings and define clinical utility, with the ultimate goal of improving strategies for CVD prevention. (*J Am Heart Assoc.* 2018;7:e008108. DOI: 10.1161/JAHA.117.008108.)

Key Words: cardiovascular disease risk factors • epidemiology • proteomics

Cardiovascular disease (CVD) is the leading cause of death in the United States and is also emerging as the leading cause of death in developing countries in light of rapid epidemiological transitions over the past 2 decades.[1] This has brought primary prevention of CVD to the forefront. One of the major challenges in developing preventive strategies is that current CVD risk assessment algorithms have limited predictive value and are subject to miscalibration when applied to different populations.[2] The discovery of novel and highly predictive biomarkers of CVD has the potential to improve risk stratification and enable targeted prevention strategies in the preclinical phase of CVD, when intervention is most likely to be effective. In addition, circulating biomarkers may be informative regarding causal biological

From the Division of Cardiology, Department of Medicine and Cardiovascular Research Center, Massachusetts General Hospital, Boston, MA (J.E.H.); Harvard Medical School, Boston, MA (J.E.H.); Department of Mathematics and Statistics, Boston University, Boston, MA (A.L., M.G.L.); National Heart, Lung, and Blood Institute's and Boston University's Framingham Heart Study, Framingham, MA (A.L., P.C., G.C., C.L., X.Y., S.-J.H., J.M.M., M.G.L., D.L.); Department of Biostatistics, Boston University School of Public Health, Boston, MA (J.M.M., M.G.L.); Population Sciences Branch, Division of Intramural Research, National Heart, Lung, and Blood Institute, Bethesda, MD (C.L., S.-J.H., D.L.).

Accompanying Tables S1 through S4 and Methods S1 are available at http://jaha.ahajournals.org/content/7/14/e008108.full#sec-22

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Received November 14, 2017; accepted May 28, 2018.

Source: https://pubmed.ncbi.nlm.nih.gov/30006491/

This fascinating paper buries the headline. A population of persons in Southern Ecuador are born with congenital IGF-1 deficiency and make a lot less insulin. While they almost never get cancer or diabetes, their mortality rates are similar to those of control. There is, unfortunately, no compelling evidence that drugs which reduce IGF-1 might improve human life expectancy.

AGING

Growth Hormone Receptor Deficiency Is Associated with a Major Reduction in Pro-Aging Signaling, Cancer, and Diabetes in Humans

Jaime Guevara-Aguirre,[1*†] Priya Balasubramanian,[2,3*] Marco Guevara-Aguirre,[1] Min Wei,[3] Federica Madia,[3] Chia-Wei Cheng,[3] David Hwang,[4] Alejandro Martin-Montalvo,[5,6] Jannette Saavedra,[1] Sue Ingles,[7] Rafael de Cabo,[5] Pinchas Cohen,[4] Valter D. Longo[2,3,8†]

Science Translational Medicine, Feb 16, 2011

Mutations in growth signaling pathways extend life span, as well as protect against age-dependent DNA damage in yeast and decrease insulin resistance and cancer in mice. To test their effect in humans, we monitored for 22 years Ecuadorian individuals who carry mutations in the growth hormone receptor (*GHR*) gene that lead to severe GHR and IGF-1 (insulin-like growth factor–1) deficiencies. We combined this information with surveys to identify the cause and age of death for individuals in this community who died before this period. The individuals with GHR deficiency exhibited only one nonlethal malignancy and no cases of diabetes, in contrast to a prevalence of 17% for cancer and 5% for diabetes in control subjects. A possible explanation for the very low incidence of cancer was suggested by in vitro studies: Serum from subjects with GHR deficiency reduced DNA breaks but increased apoptosis in human mammary epithelial cells treated with hydrogen peroxide. Serum from GHR-deficient subjects also caused reduced expression of *RAS*, *PKA* (protein kinase A), and *TOR* (target of rapamycin) and up-regulation of *SOD2* (superoxide dismutase 2) in treated cells, changes that promote cellular protection and life-span extension in model organisms. We also observed reduced insulin concentrations (1.4 μU/ml versus 4.4 μU/ml in unaffected relatives) and a very low HOMA-IR (homeostatic model assessment–insulin resistance) index (0.34 versus 0.96 in unaffected relatives) in individuals with GHR deficiency, indicating higher insulin sensitivity, which could explain the absence of diabetes in these subjects. These results provide evidence for a role of evolutionarily conserved pathways in the control of aging and disease burden in humans.

Source: https://www.science.org/doi/epdf/10.1126/scitranslmed.3001845

A review of the data does not support the use of an IGF-1 reducing drug in humans such as that proposed by Loyal for dogs.

Nonetheless, there is overwhelming evidence in the literature that avoiding diabetes and improving insulin sensitivity is associated with longer and healthier human life spans.

High-Dimensional Multi-pass Flow Cytometry via Spectrally Encoded Cellular Barcoding

Kwok SJJ, Forward S, Fahlberg MD, Assita ER, Cosgriff S, Lee SH, Abbott GR, Zhu H, Minasian NH, Vote AS, Martino N, Yun SH. High-dimensional multi-pass flow cytometry via spectrally encoded cellular barcoding. *Nat Biomed Eng.* 2023 Nov 30.

Advances in immunology, immuno-oncology, drug discovery and vaccine development demand improvements in the capabilities of flow cytometry to allow it to measure more protein markers per cell at multiple timepoints. However, the size of panels of fluorophore markers is limited by overlaps in fluorescence-emission spectra, and flow cytometers typically perform cell measurements at one timepoint. Here we describe multi-pass high-dimensional flow cytometry, a method leveraging cellular barcoding via microparticles emitting near-infrared laser light to track and repeatedly measure each cell using more markers and fewer colours. By using live human peripheral blood mononuclear cells, we show that the method enables the time-resolved characterization of the same cells before and after stimulation, their analysis via a 10-marker panel with minimal compensation for spectral spillover and their deep immunophenotyping via a 32-marker panel, where the same cells are analysed in 3 back-to-back cycles with 10–13 markers per cycle, reducing overall spillover and simplifying marker-panel design. Cellular barcoding in flow cytometry extends the utility of the technique for high-dimensional multi-pass single-cell analyses.

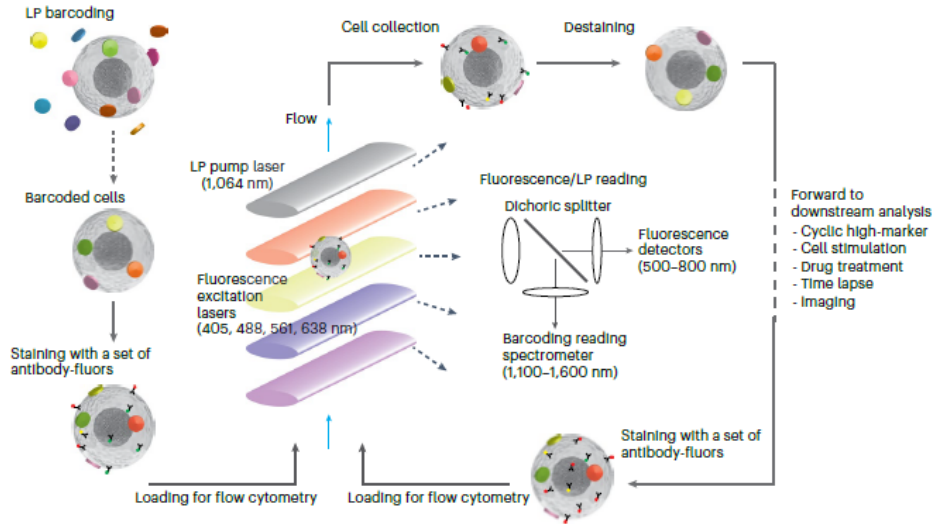

Fig. 1 | Schematic of multi-pass flow cytometry. The major steps include: tagging cells with LPs to yield LP-barcoded cells which typically have 3+ LPs; staining cells with a first set of fluorophore-conjugated antibodies; loading the barcoded and stained cells into a flow cytometer that detects fluorescence signals using multiple excitation lasers and LP lasing signals using a pump laser and spectrometer; then collecting the cells, destaining (for example, photobleaching of the fluorophores or chemical release of antibodies), restaining the cells with another set of antibodies and measuring them again in the flow cytometer. In addition to flow cytometry, this technology can be expanded to further downstream and upstream analysis of the barcoded cells.

Source: https://pubmed.ncbi.nlm.nih.gov/38036616/

New Technology Improves on Cryo-EM Called Cryo-LM

Mazal H, Wieser FF, Sandoghdar V. Insights into protein structure using cryogenic light microscopy. *Biochem Soc Trans.* 2023 Nov 28:BST20221246.

Fluorescence microscopy has witnessed many clever innovations in the last two decades, leading to new methods such as structured illumination and super-resolution microscopies. The attainable resolution in biological samples is, however, ultimately limited by residual motion within the sample or in the microscope setup. Thus, such experiments are typically performed on chemically fixed samples. Cryogenic light microscopy (Cryo-LM) has been investigated as an alternative, drawing on various preservation techniques developed for cryogenic electron microscopy (Cryo-EM). Moreover, this approach offers a powerful platform for correlative microscopy. Another key advantage of Cryo-LM is the strong reduction in photobleaching at low temperatures, facilitating the collection of orders of magnitude more photons from a single fluorophore. This results in much higher localization precision, leading to Angstrom resolution. In this review, we discuss the general development and progress of Cryo-LM with an emphasis on its application in harnessing structural information on proteins and protein complexes.

Source: https://pubmed.ncbi.nlm.nih.gov/38015555/

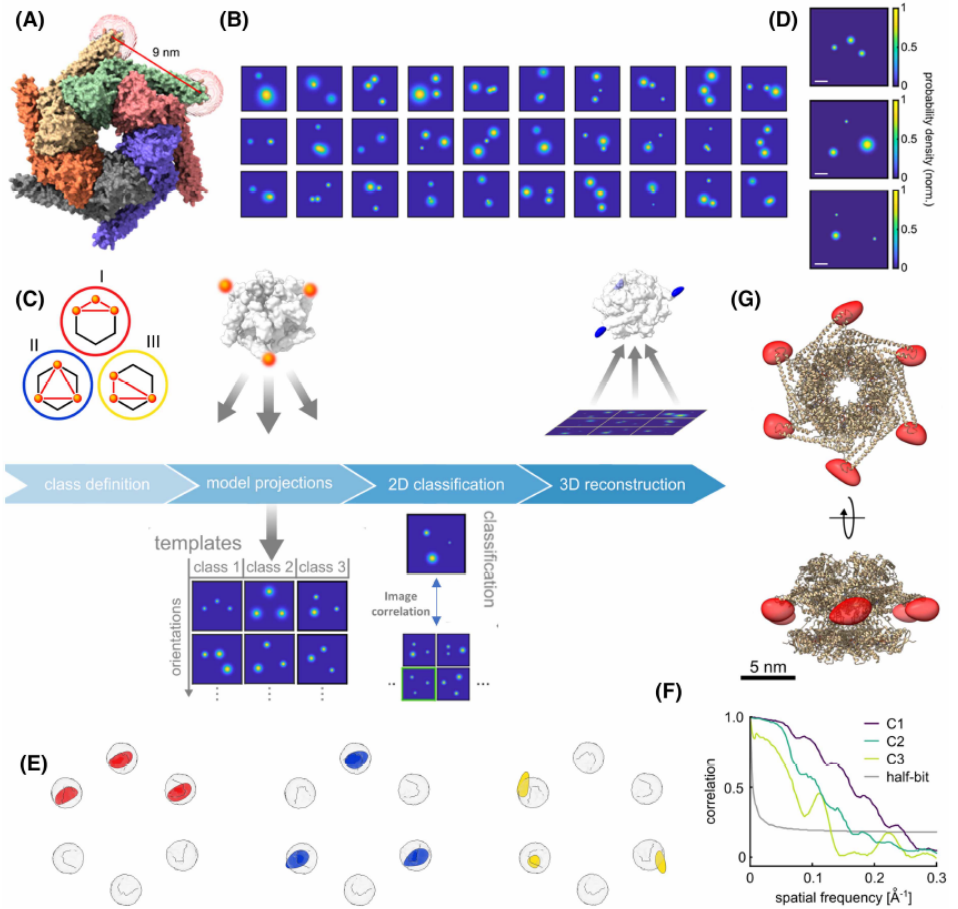

Figure 6. Single-particle classification and reconstruction in a model-system.
(**A**) Crystal structure of hexamer protein, ClpB (PDB: 1QVR). The labeling positions and the distance between them are marked. (**B**) 50% labeling efficiency of the protein inherently yields three different classes of different configurations and distances due to the C6 symmetry of the hexamer (**C**). (**B**) Examples of 2D super-resolved particle images in a 30 nm × 30 nm box with 0.15 nm pixel size emerge from the heterogeneous particles in the sample. (**C**) A strategic pipeline for classifying the images obtained in (**B**) to three classes. An approach based on template matching is employed here. Initially, an extensive library of images is generated for each class, encompassing all possible 3D orientations. Subsequently, each experimental image is cross-correlated with the image library of all classes. The experimental images are assigned to the class that yielded the highest correlation score. (**D**) A near-top view projection of each class. The images for each class are subsequently employed for separate 3D reconstruction. (**E**) The reconstructed fluorophores' positions (red, blue, yellow) align with their expected theoretical accessible volumes (gray spheres). (**F**) Fourier shell correlation curves of the reconstructed fluorophore volumes. The intersection with the half-bit criterion determines resolutions of 4.0, 7.9 and 6.4 Å, respectively. (**G**) By combining the partially resolved classes, a full structure can be resolved. Panels **D**, **E**, **F** and **G** adapted from Reference [131] with permission; copyright 2022 eLife.

Comparison of Cryo-LM to Other Structural Biology Resolution Tools

Mazal H, Wieser FF, Sandoghdar V. Insights into protein structure using cryogenic light microscopy. *Biochem Soc Trans.* 2023 Nov 28:BST20221246.

'In the drama of life on a molecular scale, proteins are where the action is'. Proteins adopt complicated three-dimensional (3D) structures, and assemble into homogenous or heterogenous quaternary structures, ranging from small cellular components up to large assemblies such as viruses. Their 3D arrangement is a part of their dynamic mechanisms of action, governing and orchestrating every aspect of cellular physiology in both health and disease. As such, understanding their structure and function has been a major focus in molecular biology. X-ray crystallography and NMR spectroscopy have successfully been used for this purpose, albeit with limitations, especially when dealing with large and complex biological macromolecules. More recently, cryogenic electron microscopy (Cryo-EM) has emerged as a revolutionary method, allowing the determination of near-atomic and even atomic resolution structures of isolated macromolecules (see Figure 1). The low contrast in this method, however, brings about challenges in identifying individual proteins and target molecules, thus, compromising the quality of attainable structural information in a native cell membrane or identifying target molecules in situ.

Some of the first studies of protein conformational dynamics, in particular the structures underlying their potential energy surface, came from spectroscopic measurements at cryogenic temperatures (CTs). High-resolution spectroscopy of single proteins, for instance, has revealed the dynamics of hydrogen bonds in cofactor binding sites. The advantages of fluorescence studies at CT also gave way to the first single-molecule detection and high-resolution spectroscopy as well as the first demonstrations of SR microscopy through spectral selection and localization of individual molecules.

Cryogenic measurements offer two major advantages over RT imaging. First, the superior sample preservation strongly reduces thermal fluctuations and allows spectroscopy and microscopy at very high spectral and spatial resolutions. The second advantage is that photochemistry is considerably slowed down, leading to about three orders of magnitude more emitted photons from a fluorophore than at RT. Together with the great asset of specific fluorescence labeling, these features promote the development of cryogenic light microscopy (Cryo-LM) for correlative imaging with other cutting-edge techniques such as Cryo-EM that suffer from less specificity. Here, a biological sample is preserved in its near-native state via shock-freezing or high-pressure freezing, where the fast cooling rate preserves water molecules in their random structure, generating amorphous ice (vitreous ice)

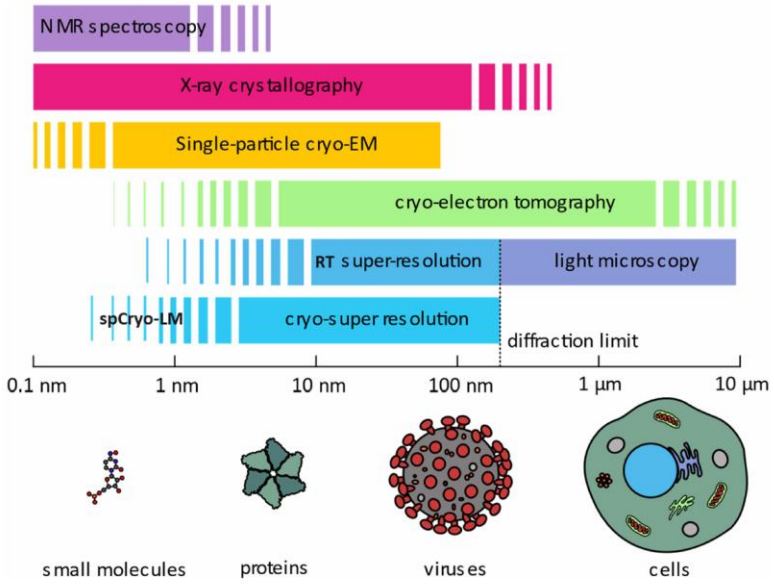

Figure 1. An overview of the resolving capability of different methods for studies in structural biology.
Different methods have been developed to investigate biological structures at various scales, ranging from a few Angstroms (small molecules) up to µm scales (cellular structures), not to scale. Light microscopy is unique in its wide coverage of scales, spanning from the Angstrom scale up to the millimeter scale.

Source: https://pubmed.ncbi.nlm.nih.gov/38015555/

Disclosure

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