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Biopharmaceutical Sector

Update – Sep 9, 2024

STIFEL | Healthcare

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Gene Sequencing Vending Machine, Boston Children's Hospital, Aug 2024

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If you wish to be added to the mailing list for this publication, please notify Natasha Yeung (yeungn@stifel.com). Past issues:

Aug 12, 2024 (Biotech Market)
July 15, 2024 (Halftime Report)
July 8, 2024 (Obesity Market Update)
June 17, 2024 (Lab Market)
June 8, 2024 (Oncology Review)
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New York Public Library, Main Reading Room

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And meet us at a number of upcoming conference events:

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https://www.biotechhangout.com/

biofuture™

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

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

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

https://www.sachsforum.com/

To meet with Stifel @ Sachs
yeungn@stifel.com

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

https://informaconnect.com/bioeurope/

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

September 2024 Life Sciences Market Outlook

Emory Medical School and Hospital, Atlanta, GA

What's Next for the Life Sciences Market?

It feels like we are in a critical moment for the life sciences market. We are seeing a confluence of events define the market going forward:

1. The start of monetary easing – linked to declining inflation across the world;
2. A near-term set of life science market catalysts driven by major clinical trial readouts at large pharma and small biotech; and
3. A presidential election in the United States with important implications for the value of sector investments and the M&A market.

This moment is accompanied by an acceleration of the underlying fundamental driver of the life sciences sector: innovation. In this and a previous issue we have shared photographs of medical research powerhouses around the world with the intent of conveying our growing collective commitment to fund life sciences research.

While perhaps less visible, we believe that this fundamental driver of our sector's momentum is far more important than what fiddling the White House might cook up for drug prices or what moves the Fed makes next. To be clear, we aren't suggesting complacence on drug pricing. Anything but.

Nonetheless, research drives value for humankind: avoidance of disease, quality of life and extension of lifespan. And, of course, value for investors. This will continue.

The Macro Picture

Let's start with a look at the macro picture. We have heard investors recently say that the upcoming Fed rate cut is already "priced in" to biotech stocks.

We find this hard to believe. The XBI started the year at 90 and has bounced around between 80 and 103 ever since. The XBI hasn't budged for two months and stands at 96 today. The reality is that inflation and higher rates have been capping biotech stocks since late 2022.

We liken the recent sector mood to that of the morning after a wild party. We are going through a multi-billion-dollar hangover in which retail and generalist investors left our sector. Many remaining investors remain face down on the sofa – hoping for a better day ahead. Specialists are locked into a war to out analyze the other, to find the killer short or get long a breaking biotech story. But it's been hard to ride the big value wave up – due to the paucity of generalist entry into stocks.

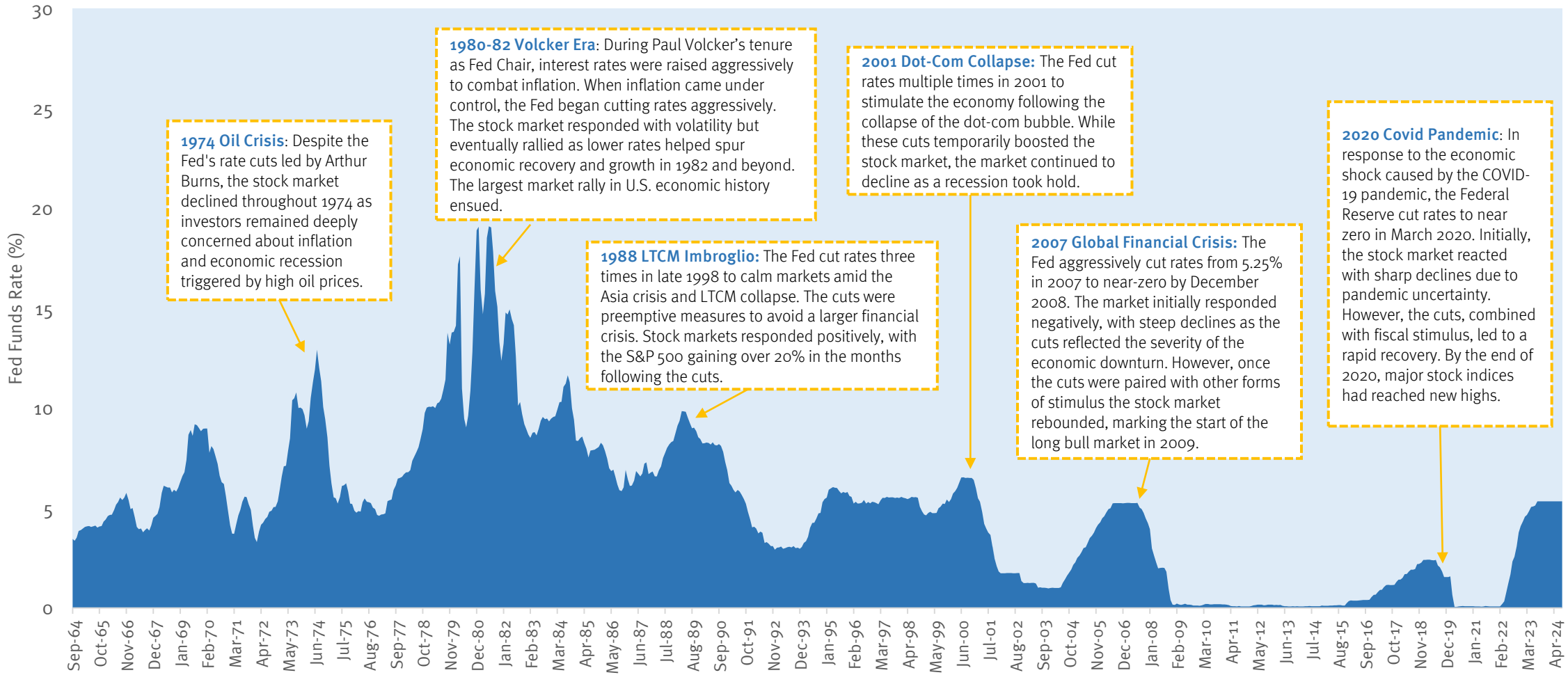
We think that the better day is coming. The chart on the next page reviews market moves following the Fed rate cut moves over the last sixty years.

Key takeaways are: (1) the market went down and stayed down only one time in six and went up and stayed up four times in six, (2) these market moves were generally big but weren't necessarily overnight and (3) the most relevant historical analogue for today (the Volcker Period) saw the biggest up move in life sciences stocks in history.

How Has the Stock Market Reacted to Past Fed Rate Cuts?

Over the last sixty years we have seen major Fed rates cuts six times. The stock market has performed well following cuts two-thirds of the time and only performed poorly once (1974).

U.S. Fed Funds Rate (%), September 1964 to September 2024

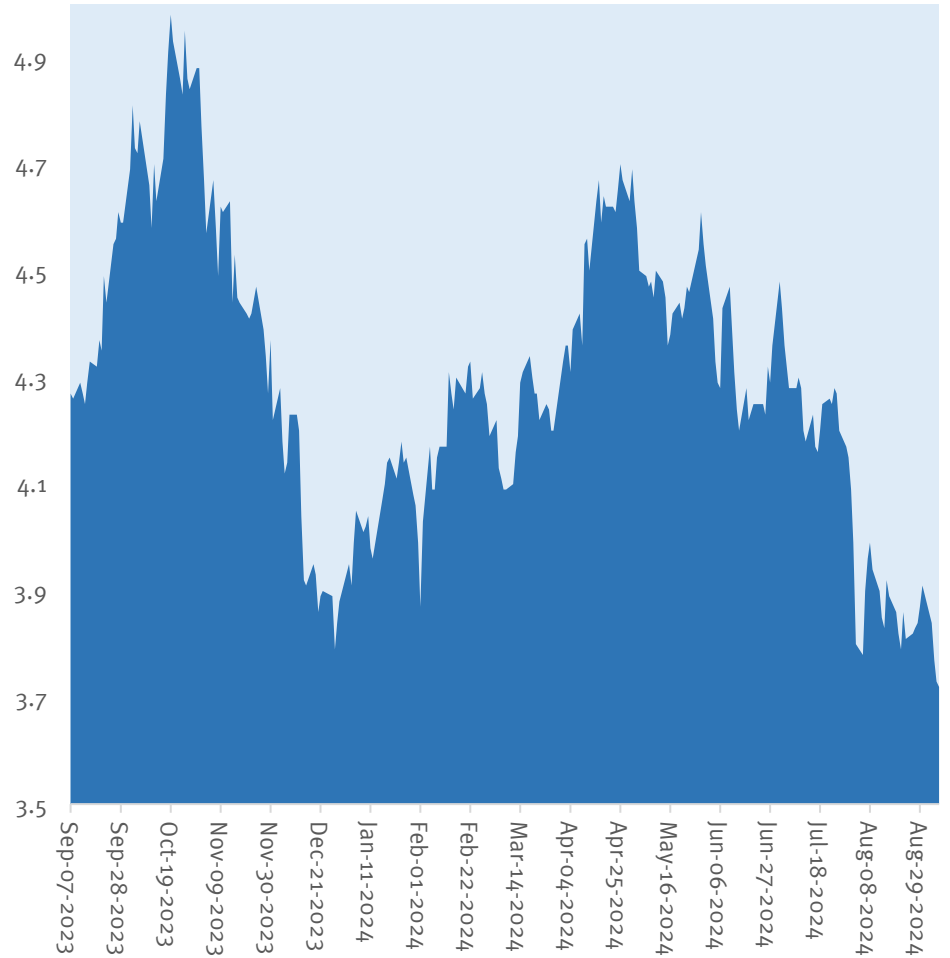


Source: Federal Reserve Bank of St. Louis (FRED Database). Note: The federal funds rate, also known as the federal funds target rate, is the interest rate that commercial banks charge each other to borrow or lend money overnight. The Federal Open Market Committee, a branch of the Federal Reserve, sets the federal funds rate.

The Case for Sector Optimism

- In past issues we have said, perhaps foolishly, that we will see the XBI hit 120 this year.
- We still think that is likely to happen.
- This weekend's data from Summit and upcoming readouts will help.
- Yet, the big opportunity will come after 2024. The upside opportunity isn't about a 20% move in the market.
- Rather, we ask whether life sciences stocks can double or triple from here.
- History would suggest that this as a realistic medium-term possibility.
- As happened in 1982, we can reasonably expect to see sector fundamentals drive (1) major growth in capital pools for life sciences, (2) substantial increases in valuations for life science investments, and (3) expansion of the sector into new areas.
- A key prerequisite for this type of move is already in place: a big drop in long interest rates. As illustrated at right, long Treasury rates have fallen from 5% to around 3.7%. This is a substantial positive for the long-duration biotech sector.
- When rates were headed up you will recall biotech stocks were crushed, but we haven't seen the opposite occur after the recent rate decline. Yet.
- It will take time for this dynamic to fully play out.

United States Treasury Ten Year Yield (%), Sep 7, 2023 to Sep 6, 2024



Source: S&P CapitalIQ

Fall Investor Season Upon Us

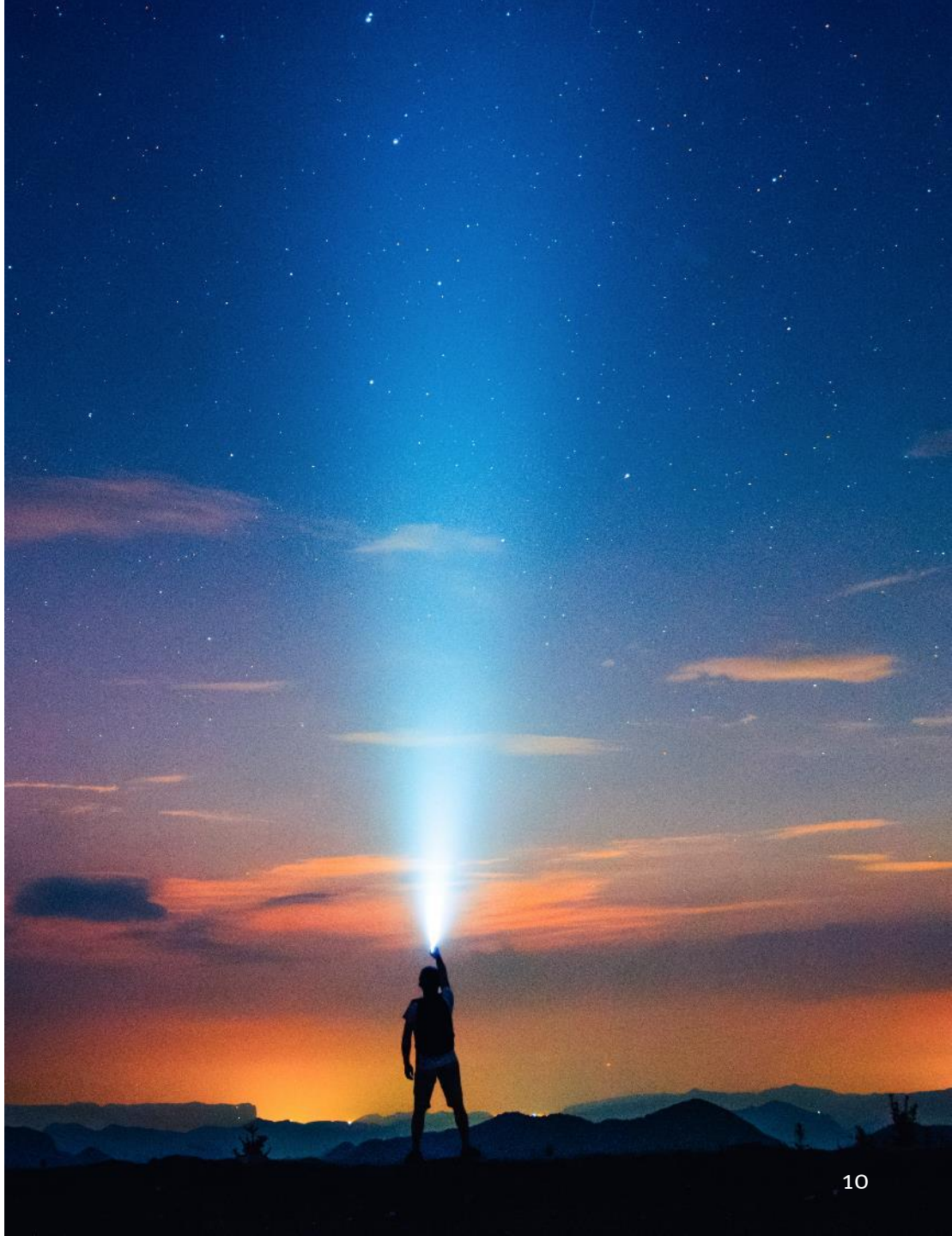
With New York City filling with market participants for the many ongoing life sciences post-Labor Day conferences we have had the chance to sit down and talk with a broad range of investors.

Optimism is in the air and investors are highly focused on the ideas that will drive value for patients.

So many investors are looking for future star companies with detailed analyses and number-crunching to figure out what is going to matter.

Here are some recent conversational snippets:

- “Whether Harris wins or Trump wins the election – it’s not going to change our outlook on the sector. Bottom line, the real winner is innovation, and neither candidate is going to stop it.”
- “I think the Kymera STAT6 program is going to redefine what degraders can do and what is next in immunology. This program could create a viable oral alternative to Dupixent.”
- “I expect that M&A will pick up after the election, particularly if Trump wins. Lower rates, M&A momentum and positive catalysts are going to make for great kick at year end.”
- “We see the obesity market moving well beyond the GLP-1’s and are optimistic about a range of small molecule alternatives like the Rivus mitochondrial decoupler.”



Market Chatter

Further points from recent conversations with investors and life sciences CEO's:

- We spoke to an LP who directs billions to funds – large and small. He views event driven funds as less attractive than those that make bets on fundamentals – especially with a long/short approach. He is looking for funds that can generate steady returns while managing risk well and thinks that we need to see better returns in the SMID Cap biotech sector before he ups his bet on funds in this area.
- So many people we spoke to last week mentioned the explosion in activity following the August hiatus. The sheer volume of current business activity has been striking and has caught many off guard.
- Investors keyed into data readouts associated with ESMO, WCLC, EEC and EASD. Multiple obesity readouts coming up at EASD will impact the market.
- Investors are skittish on perceived mixed datasets in recent weeks from Alnylam, Neurocrine and some others. We see upside in these names.
- There is a strong sense that the market will pick up more after the election rather than right after the upcoming Fed rate cut.
- Worries about a recession are impacting the overall market which is shifting to more defensive asset classes (not good for biotech).
- Even with the possibility of a 50-basis point cut (highlighted on the next page), the view is that the election will remove uncertainty from the market and make it easier to place bets on stocks whoever wins.
- Biotech investors highly interested than getting the election behind us.

Recent Economic Headlines Highlight Possibility of Larger Fed Rate Cut This Month and Risks of Weakening Economy

ECONOMIC REPORT

Decaying jobs market overtakes inflation as U.S. economy's biggest threat

Hiring slows dramatically and unemployment is rising

Marketwatch, Sep 7, 2024

Top Federal Reserve officials leave door open for large interest rate cuts if data worsens

Comments from policymakers follow report showing US economy added fewer jobs than expected

Financial Times, Sep 6, 2024

Jobs Slowdown Frustrates Investors Who Wanted Certainty on the Fed

Revisions and other distortions mean monetary policy outlook remains hazier than Wall Street would have liked

Wall Street Journal, Sep 7, 2024

Fed Must Decide If Quarter-Point Cut Will Be Enough for Workers

- Jobs report leaves investors uncertain about Fed's next move
- Officials set for a heated debate at upcoming policy meeting

Bloomberg, Sep 7, 2024

Summit / Akeso Sunday Ivonescimab Data at WCLC

HONGKONG and CALIFORNIA, Sept. 8, 2024 /PRNewswire/ -- Akeso (9926. HK) is thrilled to unveil groundbreaking data on its internally developed ivonescimab (a first-in-class PD-1/VEGF bispecific antibody) at the IASLC 2024 World Conference on Lung Cancer (WCLC24). The data, presented as a Late-Breaking Abstract (LBA) with an oral presentation, comes from a registration Phase III head-to-head clinical trial comparing ivonescimab monotherapy to pembrolizumab monotherapy as a first-line treatment for PD-L1 positive (PD-L1 TPS ≥1%) locally advanced or metastatic non-small cell lung cancer (NSCLC). Ivonescimab as first-line treatment for PD-L1 positive NSCLC significantly extends median progression-free survival (mPFS) compared to pembrolizumab, with both statistical and clinical significance.

In the ITT population, ivonescimab demonstrated a median progression-free survival (mPFS) of 11.14 months compared to 5.82 months for pembrolizumab. The PFS hazard ratio (HR) was 0.51 (P<0.0001), indicating a significant 49% reduction in the risk of disease progression or death.

Ivonescimab significantly improved the objective response rate (ORR) and disease control rate (DCR) compared to pembrolizumab in the first-line treatment of PD-L1 positive non-small cell lung cancer (NSCLC) patients. The ORR for ivonescimab was 50.0%, versus 38.5% for pembrolizumab, while the DCR was 89.9% for ivonescimab versus 70.5% for pembrolizumab. These results highlight ivonescimab's effective anti-tumor effect.
Overall survival data was not yet mature at the time of the data cutoff and will be evaluated in the future.

Source: https://www.prnewswire.com/news-releases/akesos-ivonescimab-head-to-head-phase-iii-data-against-pembrolizumab-unveiled-at-wclc-2024-302241266.html

One would not normally refer to a single company's data readout when looking at the entire market.

However, these aren't ordinary data.

Summit Therapeutics reported on Sunday an HR of 0.51 against Keytruda in front line advanced NSCLC.

Two relatively small biotechs just clobbered Keytruda®, the largest selling drug of 2023, in a late-stage clinical trial.

Of course, we will ultimately want to see OS data and outcomes from further indications, particularly in the U.S. But these PFS data are a big step.

Summit's data, coupled, with recently released positive data from Vaxcyte set up the market with some of the most positive catalysts seen in years.

With further readouts ahead, we expect market momentum to accelerate.

What We Think is Likely to Work in Public Biotech Markets

What Has Worked

We believe that the public market has largely understood and discounted the implications of promising therapeutic areas such as:

1. Cardiometabolic disease, especially GLP-1's for obesity
2. Immunology
3. Genetically-targeted oncology
4. Effective, rare disease therapeutics
5. Pneumococcal vaccines
6. T-cell engagers and ADCs
7. RNA therapeutics

What Is Likely to Work

We believe that the public market has yet to properly value the implications of emerging therapeutics in areas that include:

1. Small molecules and drugs that modulate GIP, GPR75 and other novel targets for obesity
2. Novel targets in neuroscience, particularly muscarinics, mutation-targeted therapies (e.g., TREM2), selected cell therapeutics and orexins
3. Degraders in immunology and cardiology
4. Drugs that improve on PD-1/CTLA4's in oncology
5. Muscle targeting drugs, particularly myostatin inhibitors, in a consumer driven market
6. Further developments in Fc gamma receptors and IgG depleting therapeutics

What We Think is Likely to Work in the Commercial-Stage Life Sciences and Biopharma Field

In a declining rate environment, we initially expect to see particularly good returns associated with **lower risk, medium duration assets** that include:

- **Private equity plays (have been bottled up for awhile)**
- **Credit plays**
- **Commercial growth equity plays**
- **Specialty pharma / Gx plays (have performed well lately)**

It's notable to us that a number of specialty pharma stocks have responded particularly well to recent asset acquisitions. A similar trend foretold a large spec pharma boom in 2014.

The scenario discussed herein where biotech can double or triple will come more in the medium-term as risk-premia shrink

Private Venture Market Themes for Future

Approaching Translational Readiness

Just as obesity shifted into a translationally ready field around five years ago, we expect to see translational readiness hit a number of gigantic areas with strong implications for returns in the decade ahead:

1. Pan-tumor Therapeutics (e.g., Myc/Elane)
2. Drugs to increase lifespan
3. Bioelectronics
4. Fibrosis
5. Programmable cell therapies
6. Hair regrowth therapies
7. Female-predominant diseases
8. Gene editing for agriculture

Giant IPOs of the Future (ex-Pharma)

Other commercial areas where explosive growth (and large IPOs) may lay ahead include:

1. Innovative value-based care delivery models that leverage biosciences know-how
2. Applications of 'Omics technologies to areas like healthcare and life insurance
3. AI-enabled consumer-driven comprehensive care, particularly for patients that do not have good access to care
4. AI-enabled hospitals and urgent care ambulatory clinics (e.g., emergency department decision-making)

Biotech Capital Markets Outlook

- We have seen September kick off the secondary issuance market in biotech with a boom. $1.5 billion hit the market in just four days after Labor Day.
- A considerable amount of additional secondary biotech paper is likely to come to market in the next six weeks.
- This will likely be driven by companies reporting data and a desire of biotech CEO's to avoid having to raise money around the election.
- We are seeing high quality issuers and those with good datasets able to complete financings while non catalyst driven financings for smaller cap names remain tough to get done in today's market.
- As rates dropped in the Spring and returns started to turn positive after issuance we saw very high activity in the PIPEs market. It feels likely that we will see a repeat of heavy PIPE deal flow in the Fall.
- There is a very good chance that September and early October issuance volume challenges the record volume seen in February and March.
- A similar dynamic is at play in the IPO market where the visible queue of companies seeking to go public has lengthened considerably in recent weeks.

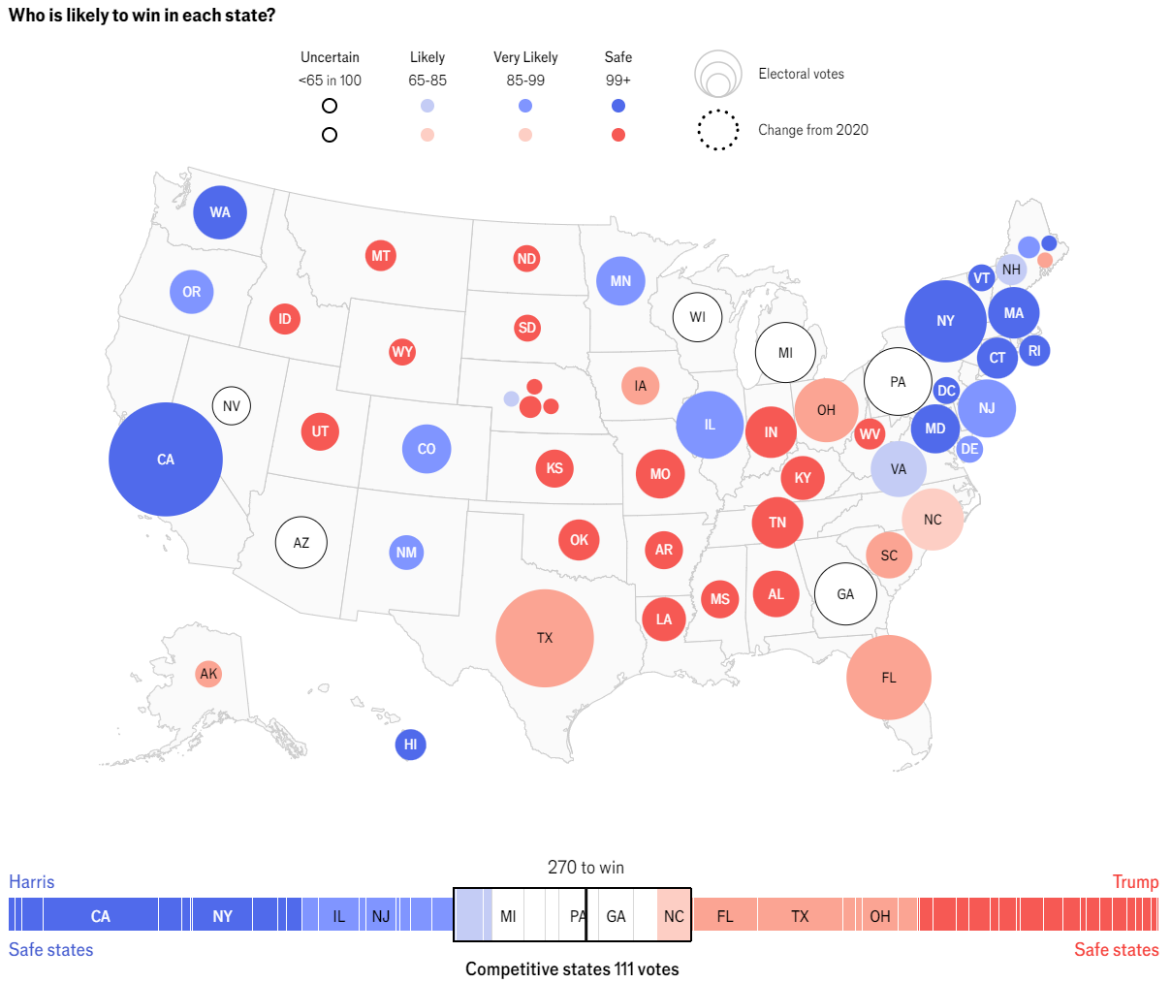
The Economist Forecasting U.S. Election as a Dead Heat

The Economist, Sep 6, 2024 (excerpt)

Chance of winning the electoral college

Kamala Harris has about a 1 in 2 chance

Donald Trump has about a 1 in 2 chance



Source: https://www.economist.com/interactive/us-2024-election/prediction-model/president/

For Pharma, Trump vs. Harris Is a Showdown Between Two Industry Foes

KFF Health News, Aug 26, 2024 (excerpt)

Former President Donald Trump and Vice President Kamala Harris have a rare point of agreement in their otherwise bitter and divisive contest: It's up to the government to cut high U.S. drug prices.

Harris cast the tie-breaking Senate vote in 2022 for legislation that allows Medicare to negotiate drug prices for its more than 60 million beneficiaries. Before that, she was an aggressive regulator of the drug industry as California attorney general.

As president, Trump would likely retain Medicare price negotiations unless the pharmaceutical industry can come up with something more compelling that they'd put on the table, people close to him say. In his first term, he proposed various policies aimed at reducing prescription costs but had limited success with their implementation.

The drug industry could benefit, though, if Trump remains unable to advance such proposals.

"His efforts were largely fragmented and faced resistance from both the industry and lawmakers," said Sergio Jose Gutierrez, a political strategist who has primarily worked with Democrats in the U.S. "The lack of a cohesive strategy and the limited ability to implement significant changes made his approach less effective compared to what a Harris-Walz administration could offer."

The industry is increasingly under attack by lawmakers from both parties for drug prices most Americans regard as unreasonable, according to KFF polling, so the election outcome could be pivotal to drug companies' fortunes. Their predicament is a sharp reversal from years past, when the firms enjoyed a reputation as being almost untouchable. For more than a decade, manufacturers successfully fended off proposals to let Medicare negotiate lower drug prices before losing the battle two years ago.

At the Democratic National Convention in Chicago last week, Harris and fellow Democrats touted their records on curbing drug prices. Harris supporters point to her past and present.

While she was California's attorney general, she joined cases that resulted in nearly $7.2 billion (about $22 per person in the U.S.) in fines for drug companies.

"In the United States of America, no senior should have to choose between either filling their prescription or paying their rent," Harris said Aug. 15 in her first joint appearance with Biden since he exited the presidential race.

She has promised to extend both the annual drug spending cap and the insulin price cap to all Americans with insurance, not just those on Medicare, if elected president.

Harris also backed a contentious policy that, in some instances, would empower the federal government to inject more competition into the marketplace by seizing the patents on some high-cost drugs developed with federal funds.

While Republicans as a party remain more friendly to the pharmaceutical industry, Trump has been willing to challenge GOP orthodoxy by taking action to combat high drug costs.

He sought during his administration to tie drug prices in Medicare to lower international prices, a proposal that the PricewaterhouseCoopers health research institute estimated would cost five drugmakers as much as $500 million a year. What was known as the "most favored nation" interim final rule was blocked because of legal challenges and later rescinded by the Biden administration.

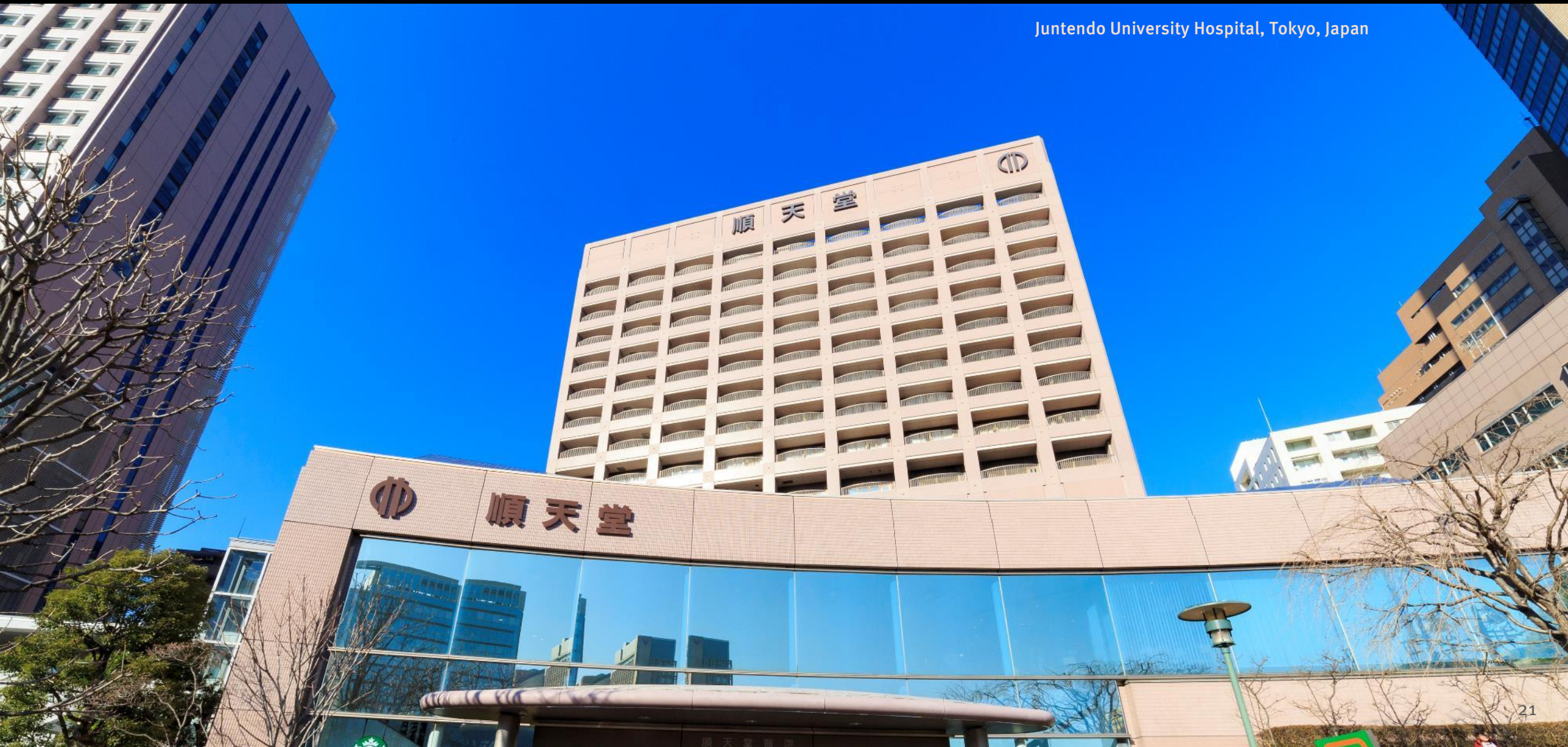
Source: https://kffhealthnews.org/news/article/trump-versus-harris-showdown-big-pharma-foes-drug-pricing/

How Biotech Investors View the U.S. Election

- With an election two months away, most investors prefer not to discuss politics and are resigned to moving forward no matter what the outcome. A minority express strong views.
- Several see the political showdown between Harris and Trump as less sector relevant than one might think because the healthcare card doesn't differ that much by side.
- Many investors worry about Trump in a large macro sense. His friendship with Russia, swaggering style and the like concerns them.
- The "anti-Trump" investors see Trump as a threat to democratic values and argue that Kamala Harris is likely to be more pragmatic than Joe Biden when it comes to the economy, taxes and biotech.
- These investors note that Harris is likely to be a big supporter of the NIH and by capping Medicare spend will likely be an indirect "friend" of pharma.
- Specifically, Medicare out of pocket spending caps take the brakes off of medicine usage for beneficiaries and will likely drive demand over time.
- In contrast, anti-Harris investors note that she has strong tendencies toward regulating the pharma industry and cast the tie-breaking vote for the IRA. These investors note that Harris has been quick to decry the pharma industry and prices after announcing her candidacy.
- Further, anti-Harris investors note that Trump should be much better for the biotech sector by being less vigilant on antitrust matters – which would stimulate greater returns among small and midcap pharma/biotechs due to heightened M&A.
- There is a further sense that the executive branch has substantial discretion in how aggressively it negotiates drug prices under the IRA. The feeling is a Trump presidency will be more relaxed on these negotiations than a Harris presidency.
- There is also a sense that with such a close election it is likely that we will not have any party control both the executive branch and both houses of Congress. As a result, there is a sense that we will are likely to see status quote type policies prevail – which will, ultimately, be good for the pharma sector.
- Anti-Harris investors worry about capital gains tax rates under Harris and how this will impact investment flows across the economy, including biotech.

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

Biopharma Market Statistics



Juntendo University Hospital, Tokyo, Japan

The XBI Closed at 96.5 Last Friday (Sep 6), Down 4.7% for the Week

The XBI was down last week as the jobless numbers reduced the expected chance of an aggressive Fed rate cut. The XBI is up 8% for the year to date. The VIX has risen steadily in recent weeks as investors have fretted over the size of a Fed rate cut. There was also a flight to defensives last week, depressing the S&P, as investors became more fearful of a recession.

Biotech Stocks Down Last Week

Return: Sep 1 to Sep 7, 2024

Nasdaq Biotech Index: -3.8%
Arca XBI ETF: -4.7%
Stifel Global Biotech EV (adjusted): -3.6%*
S&P 500: -4.2%

Return: Dec 29, 2023 to Sep 7, 2024 (YTD)

Nasdaq Biotech Index: +7.4%
Arca XBI ETF: +8.1%
Stifel Global Biotech EV (adjusted): +23.7%*
S&P 500: +13.4%

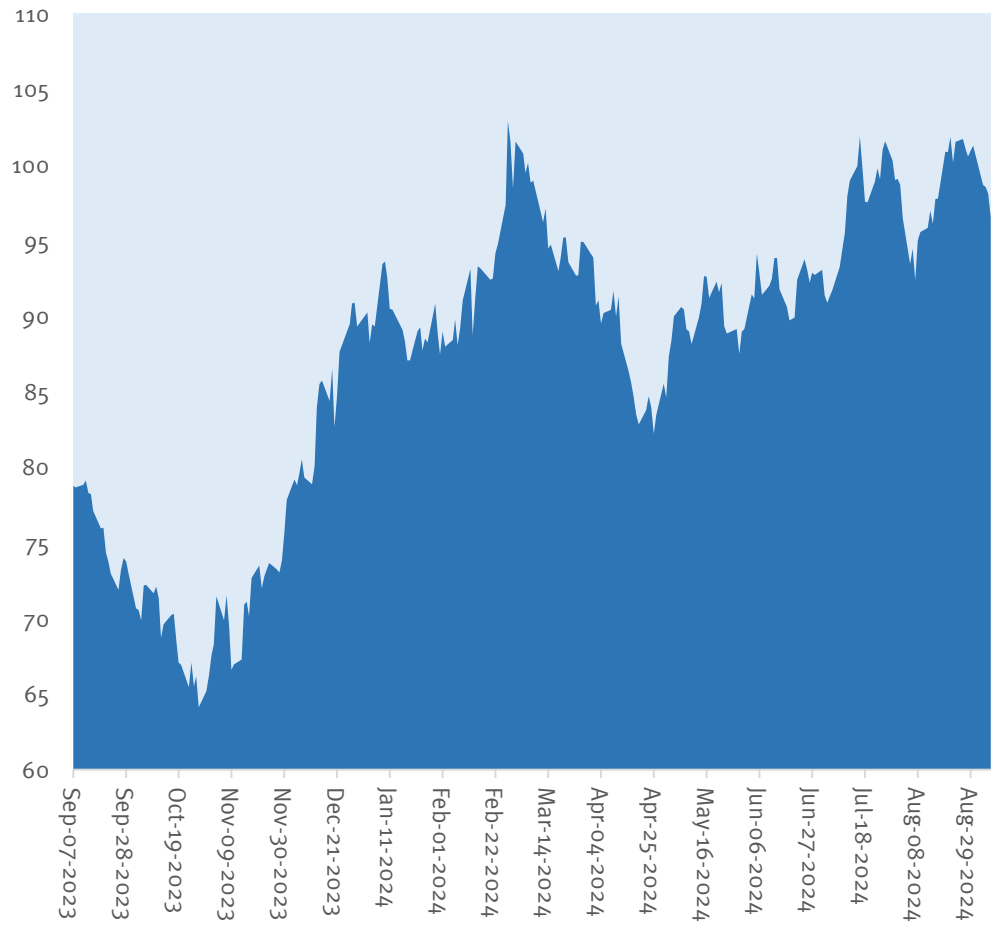
VIX Rose

Sep 29, 2023: 17.3%
Dec 29, 2023: 12.45%
Mar 29, 2024: 13.0%
May 17, 2024: 12.0%
Jun 14, 2024: 12.7%
Aug 2, 2024: 23.4%
Aug 9, 2024: 20.4%
Sep 6, 2024: 22.4%

10-Year Treasury Yield Down

Sep 29, 2023: 4.59%
Dec 29, 2023: 3.88%
Mar 29, 2024: 4.20%
May 17, 2024: 4.42%
Jun 14, 2024: 4.2%
Aug 2, 2024: 3.80%
Aug 9, 2024: 3.94%
Sep 6, 2024: 3.72%

XBI, Sep 7, 2023 to Sep 6, 2024



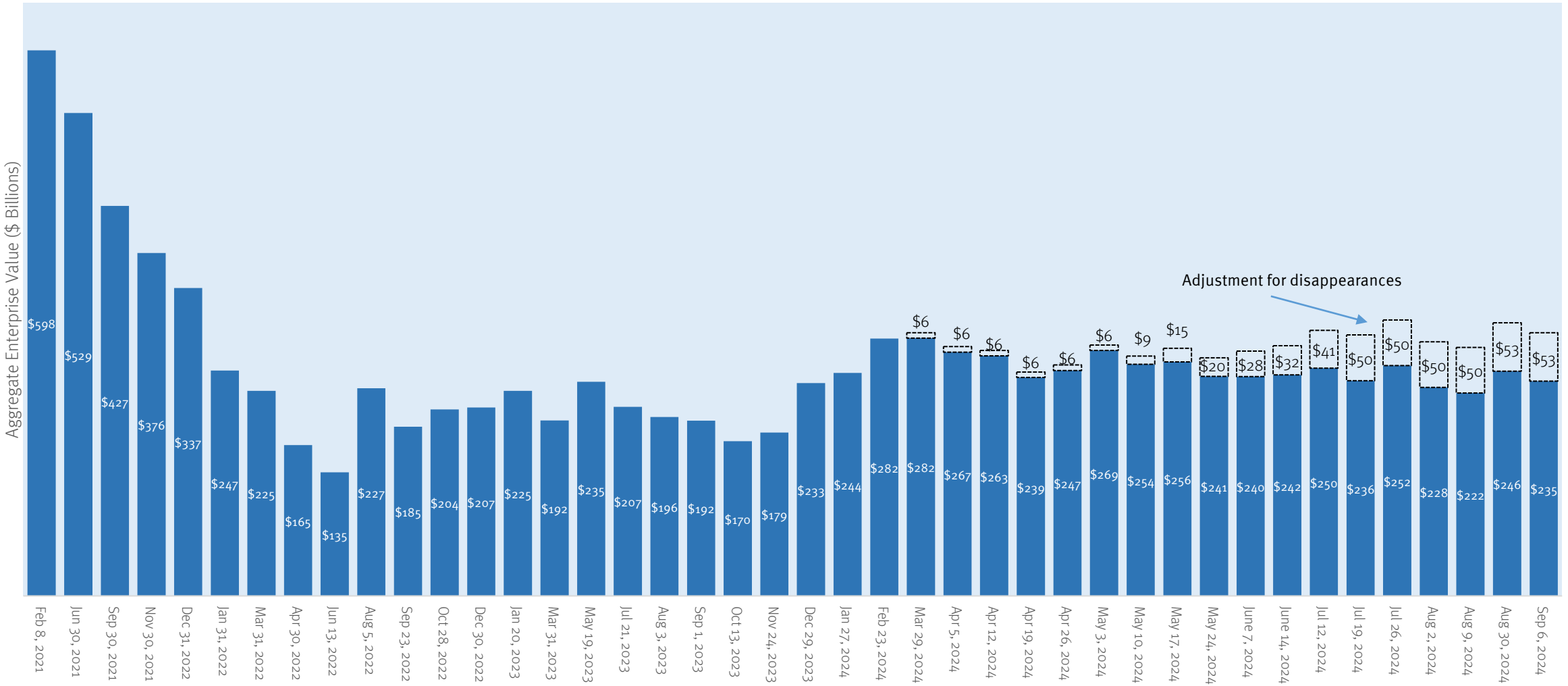
* Change by enterprise value. The adjusted number accounts for the effect of exits and additions via M&A, bankruptcies and IPOs.

Source: S&P Capital IQ and Stifel analysis

Total Global Biotech Sector Down 3.6% Last Week

Biotech stocks were down 3.6% in the last week but have risen 7% over the last three months. On a disappearance adjusted basis, biotech is up 23.7% for the year to date. It's been quite a strong year for biotech.

Total Enterprise Value of Publicly Traded Global Biotech, Feb 8, 2021 to Sep 6, 2024 ($ Billions)

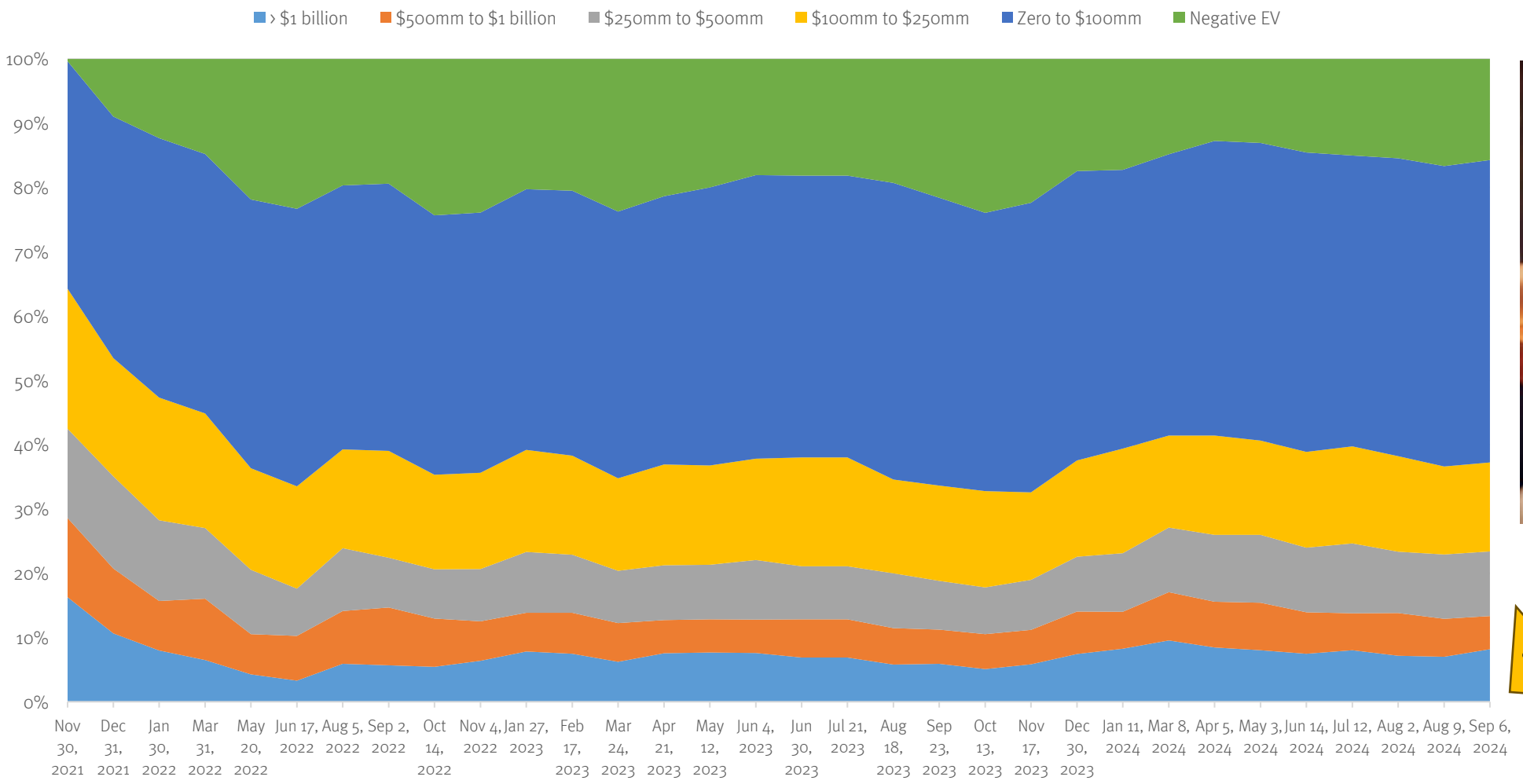


Source: CapitalIQ. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

Global Biotech Neighborhood Analysis

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

Global Biotech Universe by Enterprise Value Category, Nov 30, 2021 to Sep 6, 2024



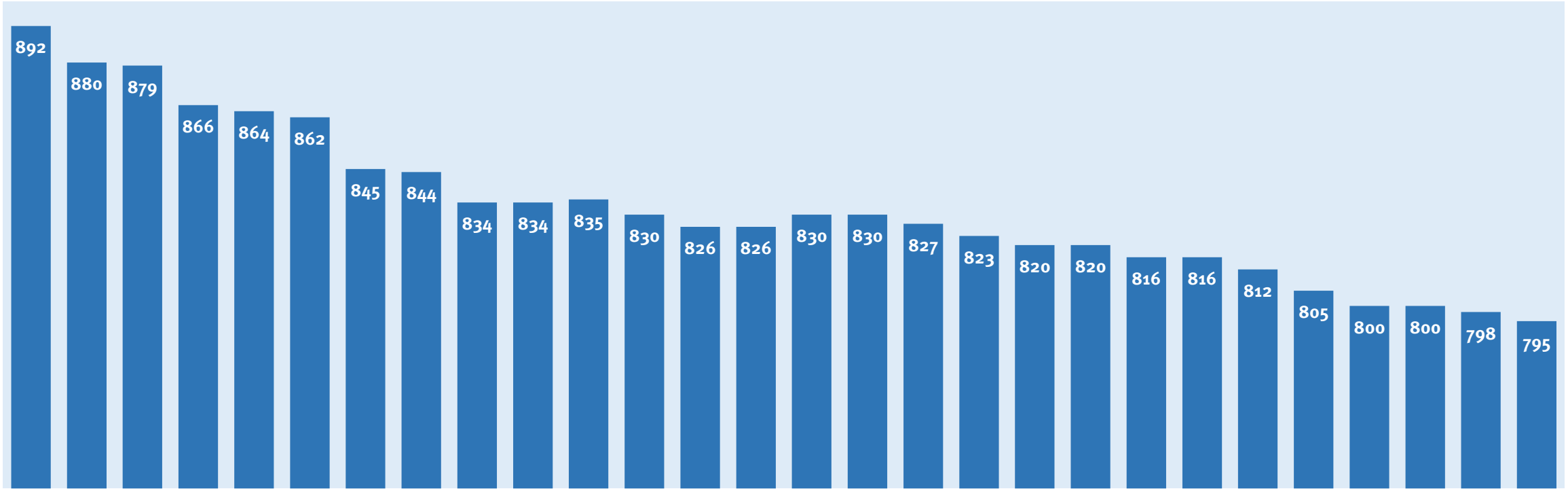
"Upper classes" of biotech doing well now

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

Public Biotech Population Continues to Shrink

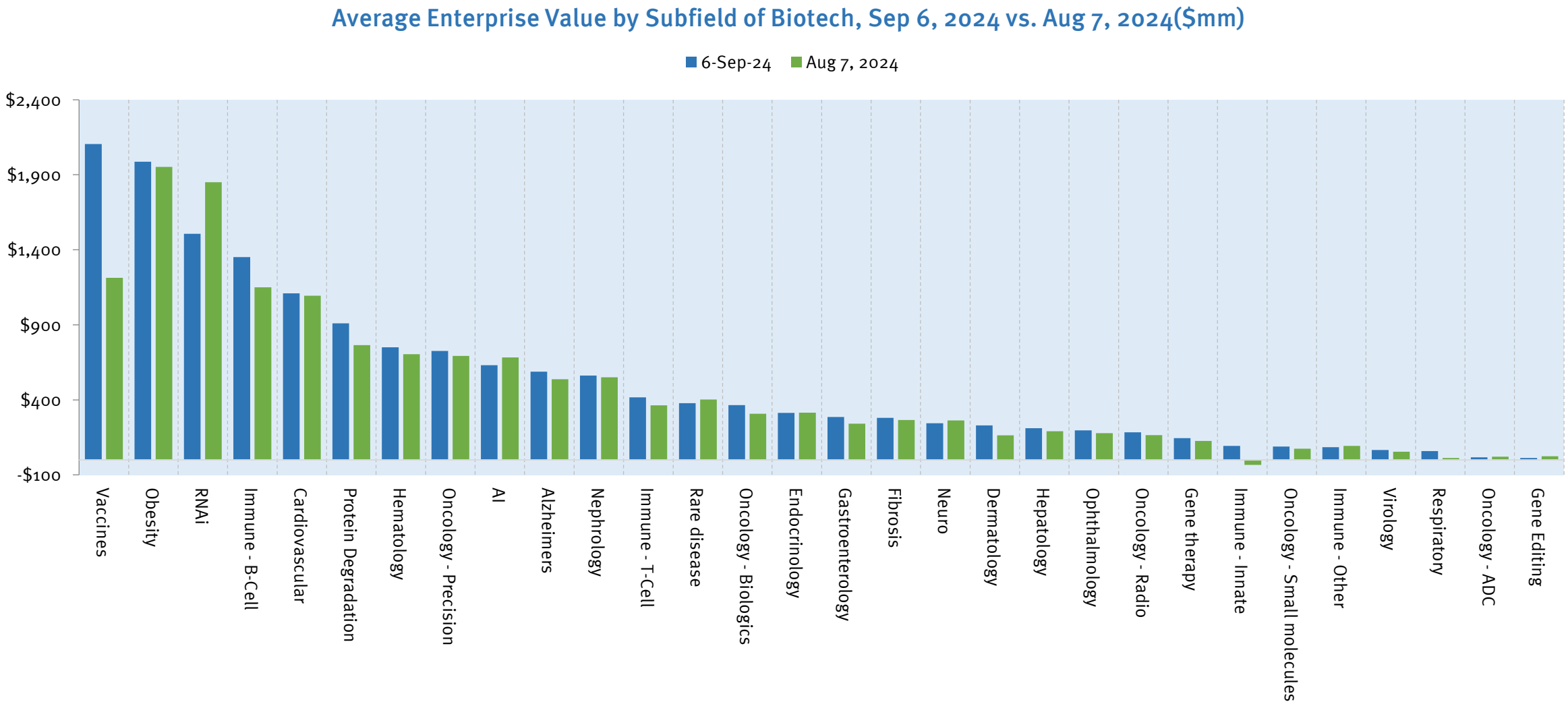
The public biotech universe has dropped by roughly 100 companies (net) since May 2022. We would expect the upcoming "mini-wave" of IPO's to help reverse this trend.

Number of Publicly Traded Biotech Companies Worldwide, May 2022 to Sep 2024



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

Rise in Vaxcyte Stock Powers Vaccine Field Ahead of Obesity Area and RNA. B-Cell and Degraders Also Are Perfoming Well

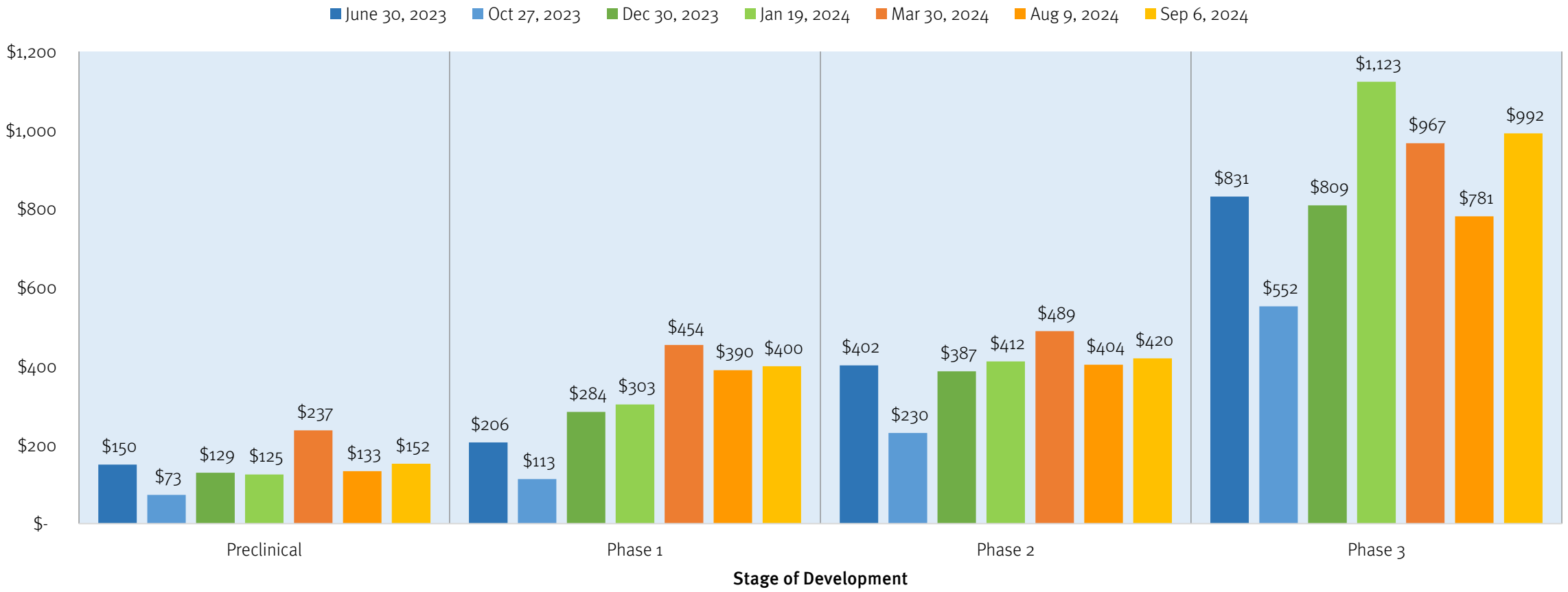


Notes: Data from CapitalIQ. Stifel categorized companies by therapeutic area.

Late-Stage Biotech Values Have Rebounded in Last Month

The average value of a Phase 3 biotech today is $992 million – up from $781 million just a month ago. Compare this to $1 billion at the end of Q1 and $809 million at the start of 2024. We have also seen bumps up in the value of pre-clinical companies over the last month.

Average Enterprise Value of a Biotech Listed on U.S. Exchanges by Stage of Development, June 30 2023 to Sep 6, 2024 ($ Millions)



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

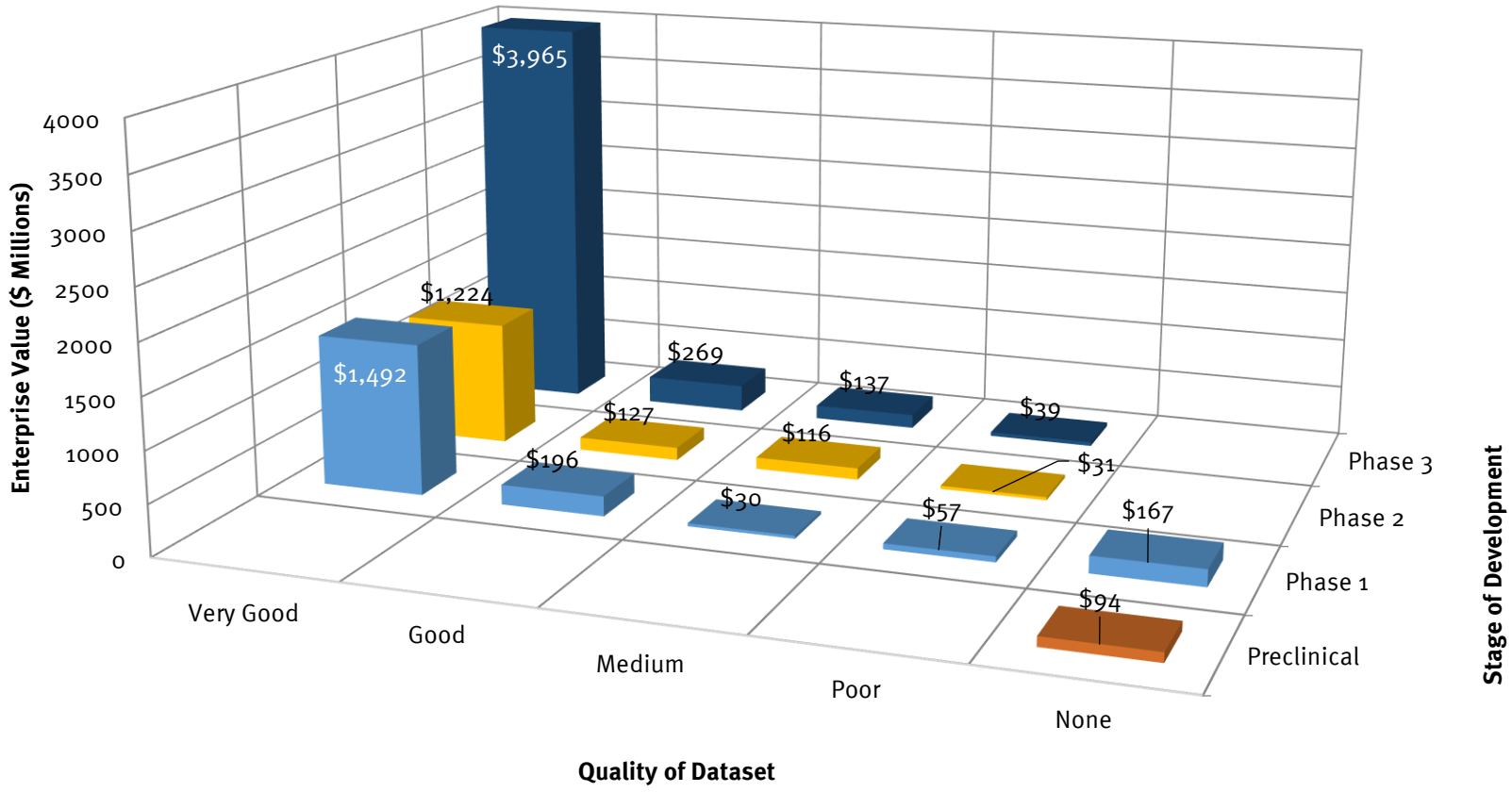
“Winner-Take-All” Mindset Re-Emerging in Biotech

Driven in part by Vaxcyte and Summit, we are seeing the average EV of Phase 3 stocks with very good datasets come close to $4 billion.

The of average value of a company with a great Phase 3 dataset today is *forty-two times higher* than a company with no data.

We have not seen a quality premium like this before in biotech.

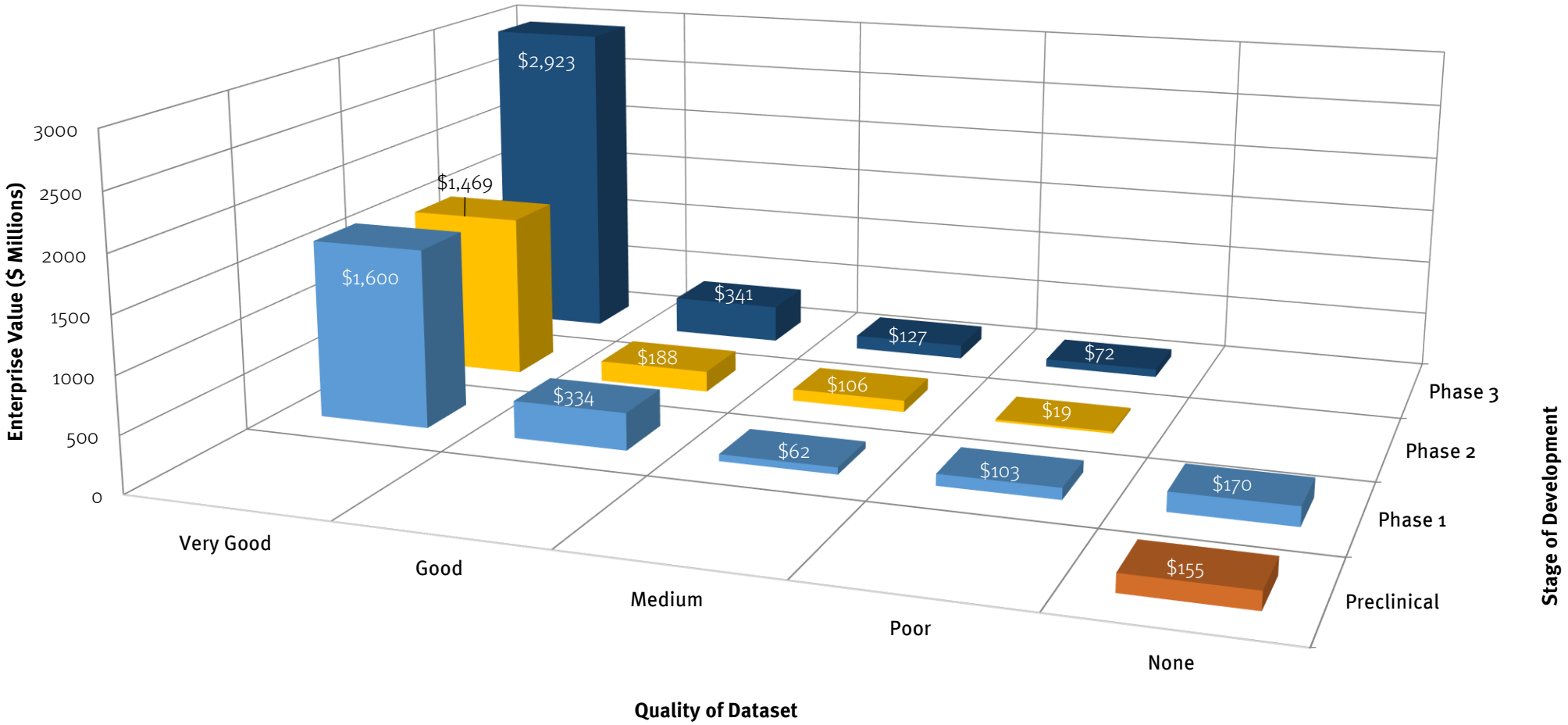
Average Enterprise Value of a Biotech Listed on U.S. Exchanges by Stage of Development and Quality of Data, Sep 6, 2024 ($ millions)



Source: CapitalIQ and Stifel analysis. We classified datasets that indicated a high probability that the drug would meaningfully improve on the standard of care for a disease as “very good”. We classified “good” data as data that might beat the standard of care. Medium data was data that was unlikely to beat the standard of care, was very early or came from a study with a mixed signal. Poor data reflects situations where a drug did not perform well at all in a clinical trial.

For Comparison - Quality x Stage Value Matrix, End of Q1 2024: The Ratio of Biotechs with Very Good Phase 3 Data to No Data Was 15X (vs 42X Today)

Average Enterprise Value of a Biotech Listed on U.S. Exchanges by Stage of Development and Quality of Data
March 28, 2024 ($ millions)



Source: CapitalIQ and Stifel analysis.

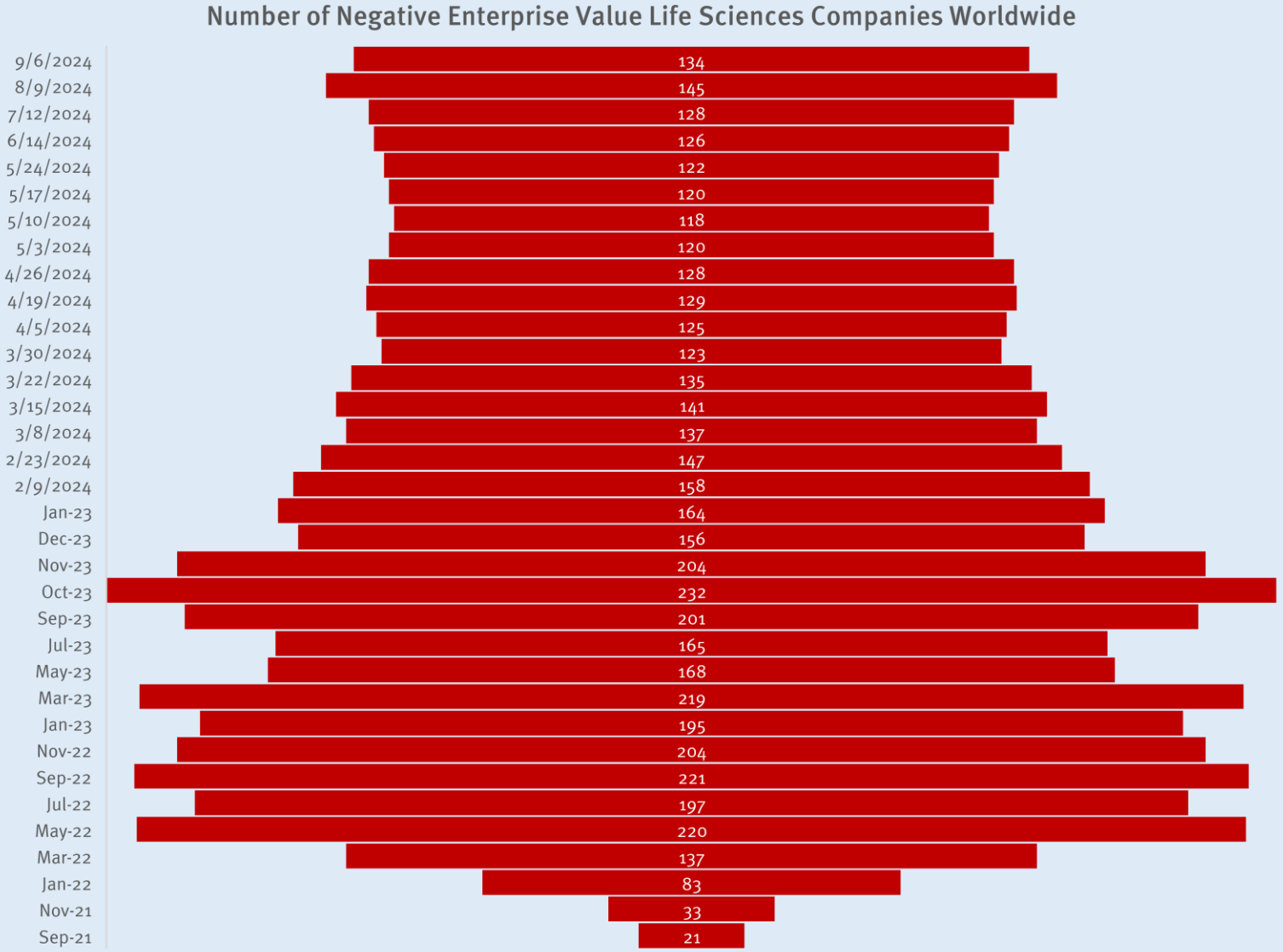
Life Sciences Sector Total Value Down 2.5% Last Week

Performance was weak the life sciences sector last week as biotech, commercial pharma, diagnostics and pharma services dropped.

Sector	Firm Count	Enterprise Value (Sep 6, 2024, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	80	$88,962	-0.3%	0.4%	14.5%
Biotech	770	$232,967	-3.6%	6.2%	-5.1%
CDMO	39	$160,413	-1.9%	0.0%	-2.1%
Diagnostics	81	$246,337	-2.6%	0.6%	1.7%
OTC	29	$27,698	1.6%	4.2%	-6.1%
Pharma	716	$6,839,000	-2.8%	3.1%	16.9%
Pharma Services	38	$177,894	-3.0%	-1.1%	-10.7%
Life Sciences Tools	50	$715,982	-1.8%	-0.1%	5.8%
Medical Devices	179	$1,768,737	-1.2%	5.0%	13.3%
HCIT	10	$19,996	-2.5%	16.1%	-2.4%
Total	**1992**	**$10,277,986**	**-2.5%**	**3.1%**	**14.5%**

Source: CapitalIQ and Stifel analysis

Drop in Count of Negative Enterprise Value Life Sciences Companies in Last Four Weeks



We have seen a drop in the number of life science companies trading with a negative EV in the last few weeks.

This metric indicates that the sector is starting to look less distressed than it was a month ago.

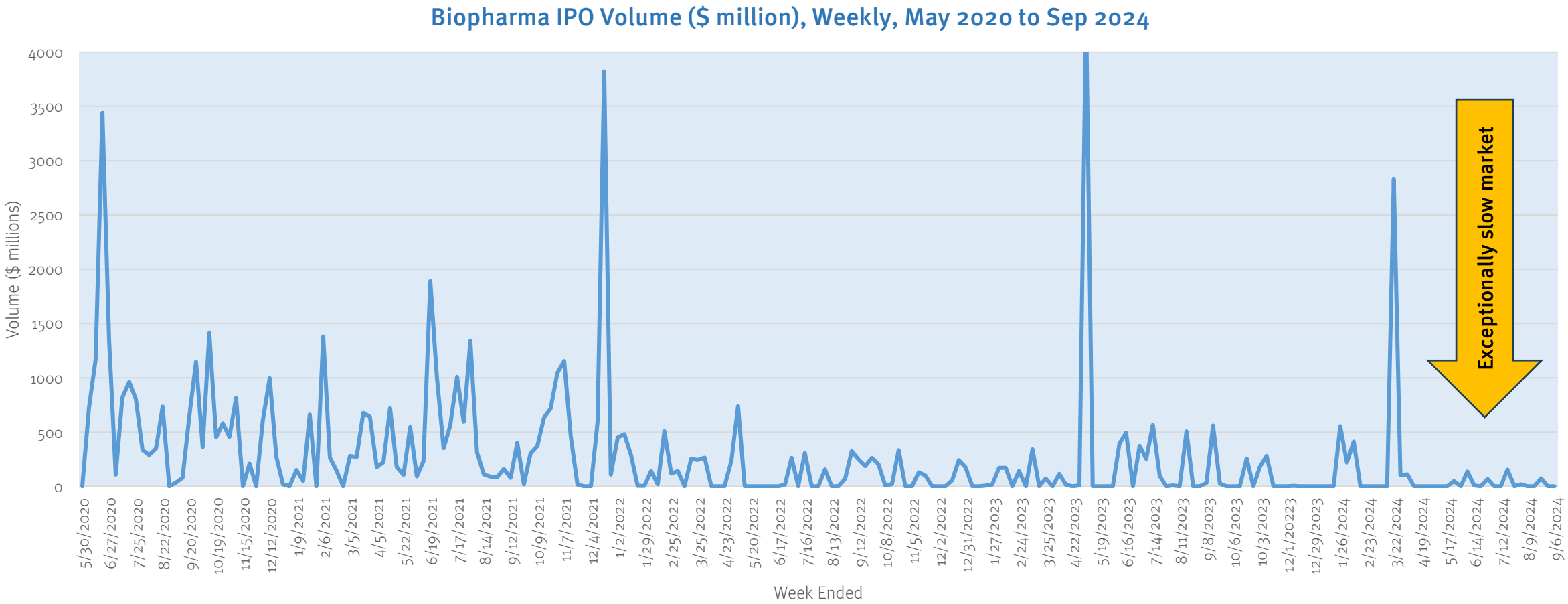
Source: CapitalIQ and Stifel analysis

Capital Markets Update

Max Planck Institut, Munich, Germany

IPO Market Eerily Quiet in Recent Months

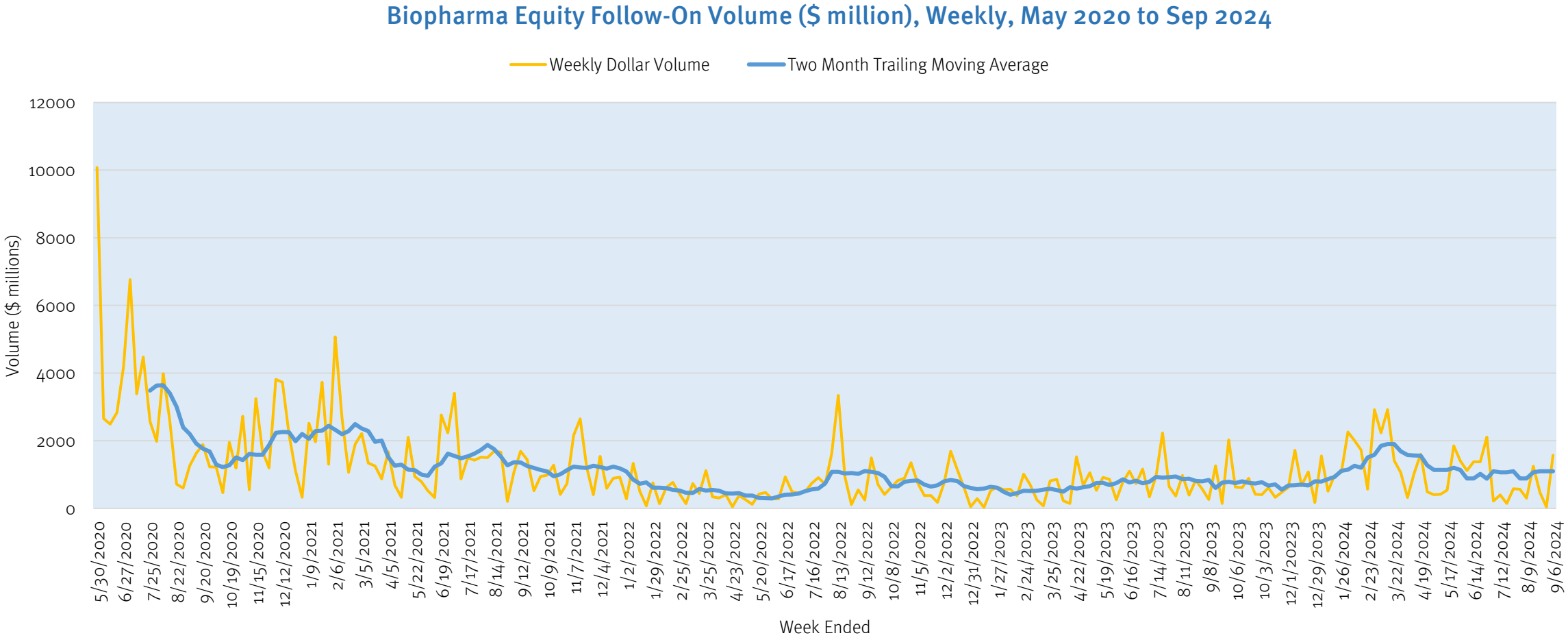
The U.S. IPO market has remained inactive for several months. The most recent company to go public was TYK Medicines of China on August 19th. The last U.S. IPO was that of Artiva which priced a $167 million offering on July 18th. There is a slate of companies scheduled to hit the road this week. This week will be an important test for the market.



Source: Data from CapitalIQ and Stifel research.

Follow-On Market Picked up Substantially Last Week

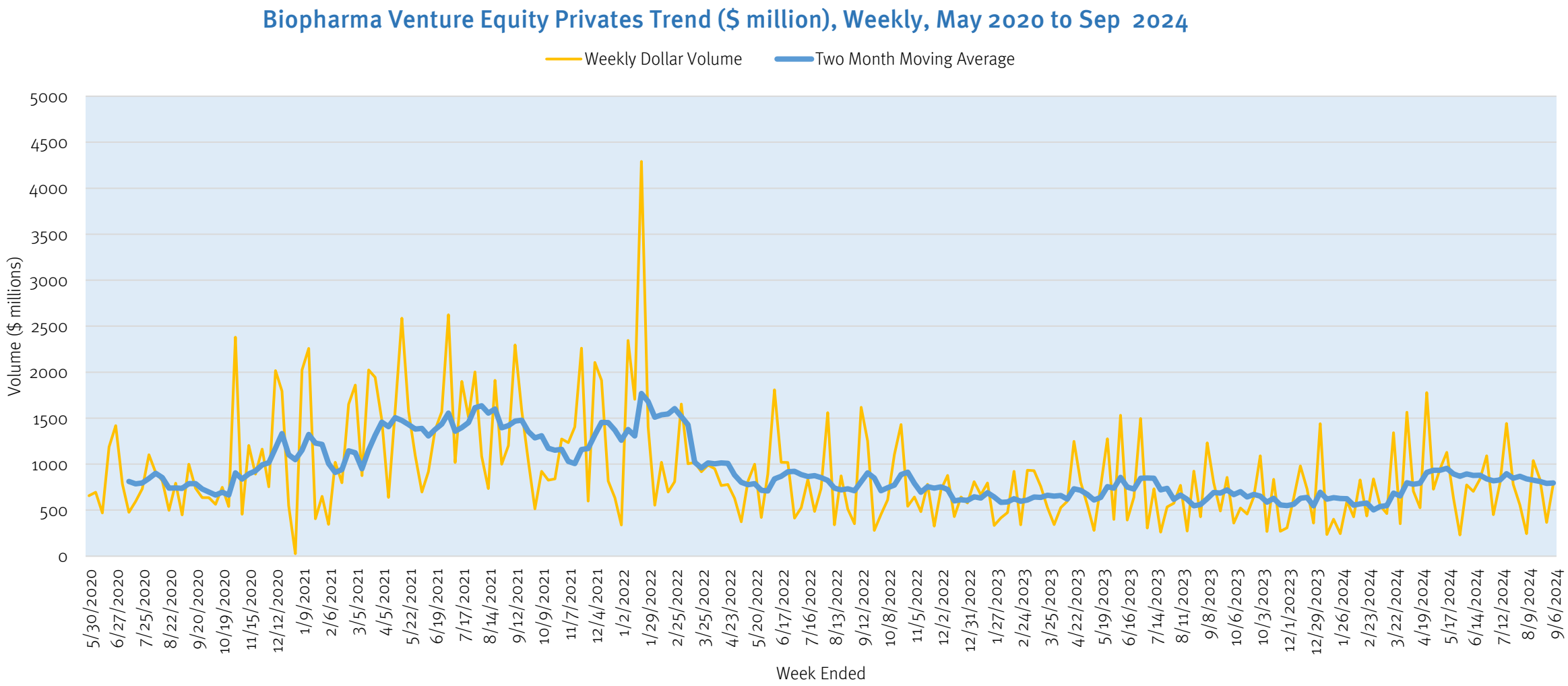
August was quite slow month for follow-ons. The recent return from holidays combined with the prospect of Fed easing sparked a strong kick to the market last week with $1.5 billion in deals pricing, led by a large deal from Vaxcyte. We expect to see volumes continue to run strong throughout this month.



Source: Data from CapitalIQ.

Private Venture Equity Market Normal Last Week

Weekly volume of venture privates this year has averaged $750mm. Last week saw $789 million raised in the market.



Source: Data from CapitalIQ, Crunchbase.

ArsenalBio Announces $325 Million Financing to Advance Programmable Cell Therapy Programs through Clinical Development

South San Francisco, Calif. – September 4, 2024: Arsenal Biosciences, Inc. (ArsenalBio), a clinical stage programmable cell therapy company focused on engineering advanced CAR T-cell therapies for solid tumors, today announced the close of an oversubscribed $325 million Series C financing round. The funding round included new investors ARCH Venture Partners, Milky Way Investments Group, Regeneron Ventures, NVentures (NVIDIA's venture capital arm), Luma Group, funds and accounts advised by T. Rowe Price Associates, Inc., Rock Springs Capital, among others, with ongoing support from existing investors the Parker Institute for Cancer Immunotherapy (PICI), SoftBank Vision Fund 2, Bristol-Myers Squibb Company, Westlake Village BioPartners, Kleiner Perkins, Byers Capital, and Hitachi Ventures.

Proceeds from the financing will be used to advance ArsenalBio's lead programs through development as the company continues to build its pipeline of therapeutic candidates for solid tumor cancers based on its proprietary T cell engineering technology, including logic gating. The funds will also drive further innovation in developing tools and processes for identifying new candidate cell therapies, helping ArsenalBio remain at the forefront of the rapidly evolving field of cell therapy, and bringing it closer to its goal of addressing unmet needs across the oncology category.

ArsenalBio's robust pipeline includes potential therapies in development for ovarian, kidney, and prostate cancers, as well as other solid tumors being co-developed through a collaboration with Bristol-Myers Squibb Company. The fundraising follows ArsenalBio's recent entry into clinic with its second T cell product candidate, AB-2100, being studied in a Phase 1/2 clinical trial for clear-cell renal cell carcinoma (ccRCC). The candidate has been granted Fast Track designation by the U.S. Food and Drug Administration.

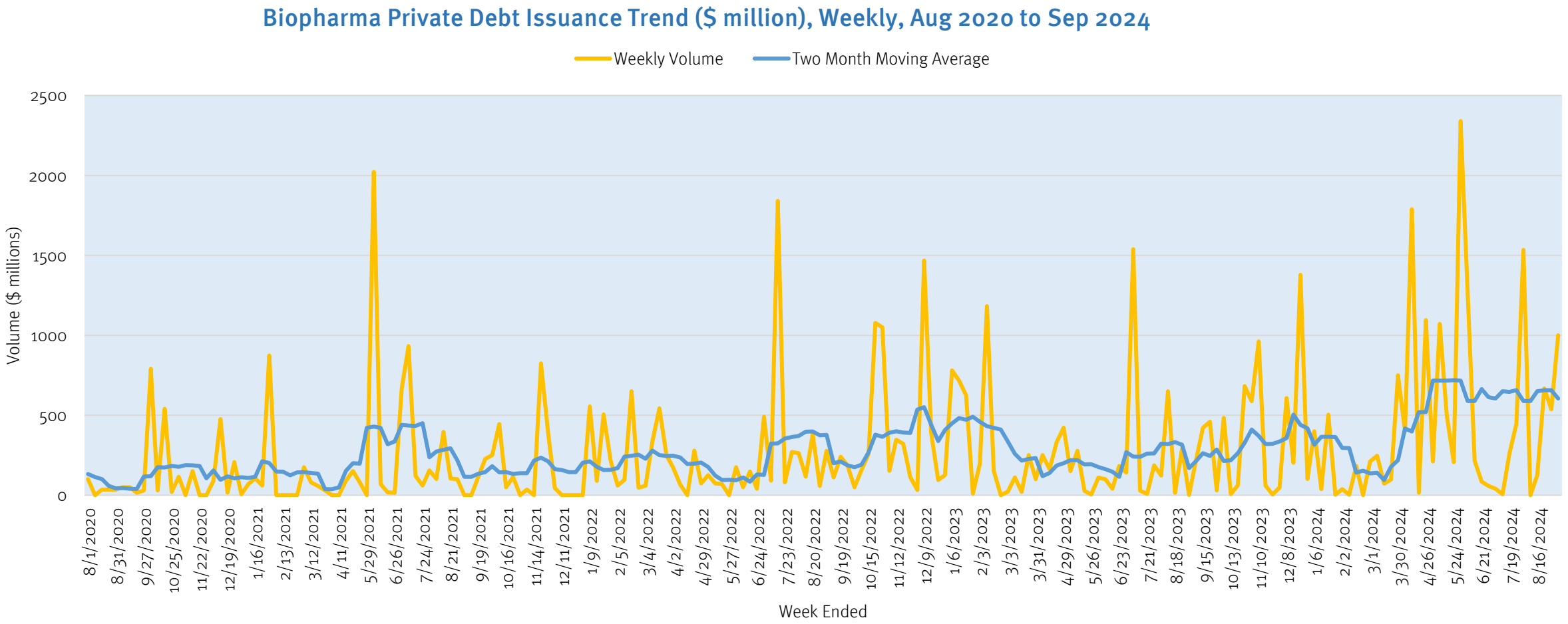
"Our initial clinical trials and preclinical studies have shown the promise of our T cell engineering approach and have given us the confidence to broaden the application of our technology to address additional cancer types. This new investment enables us to continue our development roadmap, scale up our manufacturing capabilities, and invest in new avenues for innovation in T cell medicine"

Ken Drazan
Chief Executive Officer, ArsenalBio

Source: https://arsenalbio.com/2024/09/04/arsenalbio-announces-325-million-financing-to-advance-programmable-cell-therapy-programs-through-clinical-development/

Biopharma Private Debt Market Remains Elevated

Volumes in the private debt market have remained elevated in the last several months. We have been averaging around $700mm a week in this market – the same volume as seen in the venture equity market. Last week saw $1bn in issuance volume anchored by an offer of $850 million in exchangeable senior notes from Jazz Pharma.



Source: Data from CapitalIQ, Crunchbase, Stifel research.

Jazz Pharmaceuticals Announces Pricing of Private Offering of $850 Million of 3.125% Exchangeable Senior Notes due 2030 and Concurrent Ordinary Share Repurchases

DUBLIN, Sept. 4, 2024 /PRNewswire/ -- Jazz Pharmaceuticals plc (Nasdaq: JAZZ) ("Jazz Pharmaceuticals") today announced the pricing of $850 million aggregate principal amount of 3.125% exchangeable senior notes due 2030 (the "notes") in a private offering (the "offering") by Jazz Investments I Limited, its wholly-owned subsidiary (the "Issuer"), to qualified institutional buyers pursuant to Rule 144A under the Securities Act of 1933, as amended (the "Securities Act"). The Issuer also granted the initial purchasers of the notes an option, exercisable within a period of 13 days from and including the date the notes are first issued, to purchase up to an additional $150 million aggregate principal amount of notes. The sale of the notes is expected to close on September 6, 2024, subject to customary closing conditions.

The notes will be general unsecured obligations of the Issuer and will accrue interest payable semiannually in arrears on March 15 and September 15 of each year, beginning on March 15, 2025, at a rate of 3.125% per year. The notes will mature on September 15, 2030, unless earlier exchanged, redeemed or repurchased. Prior to June 15, 2030, the notes will be exchangeable only upon satisfaction of certain conditions and during certain periods, and thereafter, at any time until the close of business on the second scheduled trading day immediately preceding the maturity date. The Issuer will settle exchanges by paying cash up to the aggregate principal amount of the notes to be exchanged. The remainder, if any, of the Issuer's exchange obligation in excess of the aggregate principal amount of the notes will be settled in cash, ordinary shares of Jazz Pharmaceuticals ("ordinary shares") or a combination of cash and ordinary shares, at the Issuer's election. The initial exchange rate will be 6.5339 ordinary shares per $1,000 principal amount of notes (equivalent to an initial exchange price of approximately $153.05 per ordinary share, which represents a premium of approximately 40.0% above the closing sale price per ordinary share on the Nasdaq Global Select Market on September 3, 2024), subject to adjustment in some events but not for any accrued and unpaid interest.

The Issuer's obligations under the notes will be fully and unconditionally guaranteed on a senior unsecured basis by Jazz Pharmaceuticals; will rank pari passu in right of payment with the Issuer's existing 2.000% exchangeable senior notes due 2026; will be effectively subordinated to the Issuer's guarantees of the indebtedness under Jazz Pharmaceuticals' credit agreement (the "credit agreement") and Jazz Pharmaceuticals' 4.375% senior secured notes due 2029 (the "senior secured notes") to the extent of the value of the assets securing such guarantees; and will be structurally subordinated to the indebtedness and guarantees under the credit agreement and the senior secured notes of Jazz Pharmaceuticals' other subsidiaries that are borrowers or have provided guarantees of such indebtedness.

How does this structure work? Ordinarily, the term "exchangeable note" gives the investor the right to exchange their note for shares of a third company that are owned by the issuer. Such exchangeables are rare, in general, and almost unheard of in the biopharma sector. This deal looks and feels more like a traditional convertible except that the investor does not control how Jazz settles its securities upon triggering an exchange. Specifically, Jazz can settle the principal amount in cash or stock at its election. If you will, Jazz gets to decide when to issue stock to investors rather than the other way around as is typically the case with a convertible. One could call this structure a "reverse convertible" as it transfers some optionality to the issuer.

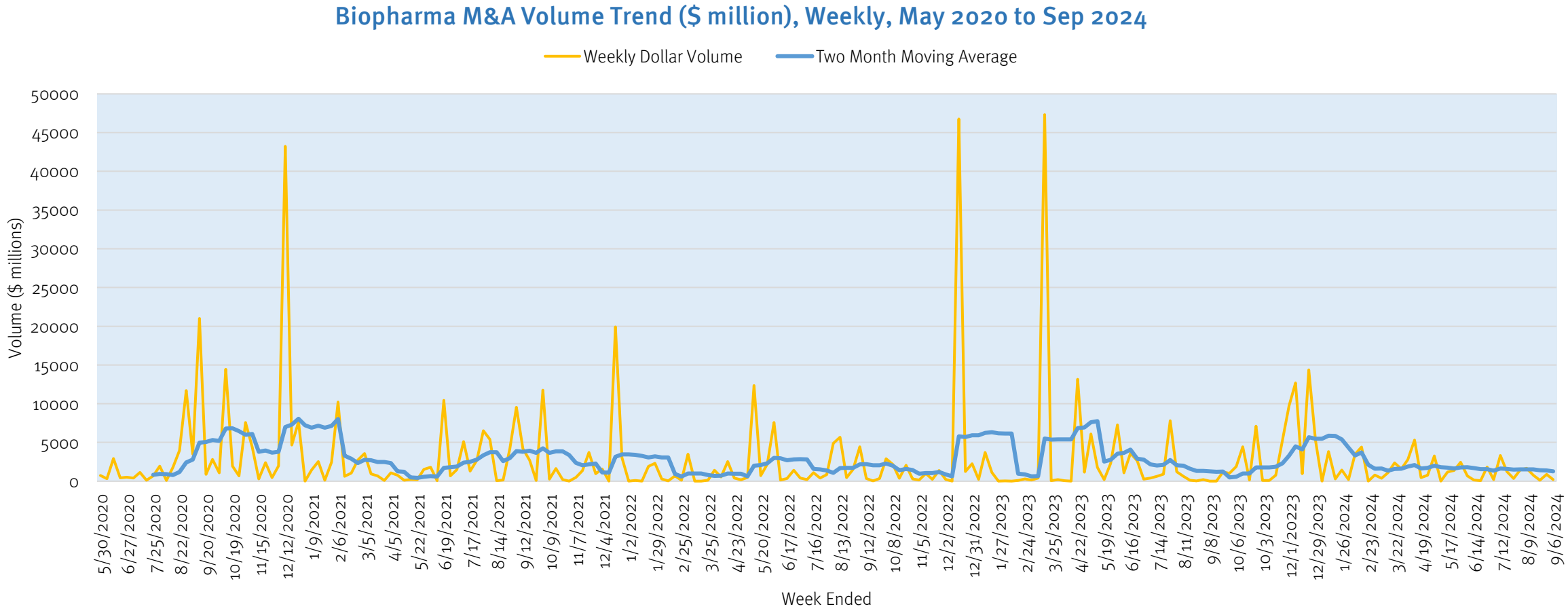
Source: https://investor.jazzpharma.com/news-releases/news-release-details/jazz-pharmaceuticals-announces-pricing-private-offering-850-o

Deal News

University of Paris, René Descartes, Top Ranked Medical School in France

Last Week Saw No Meaningful Biopharma M&A Volume

Last week saw $198 million in M&A volume. M&A volume overall has been slow by historical standards throughout 2024. As Q3 2024 is coming into its final weeks we are looking at an $11bn quarter. The market has printed $50bn in total volume all year – which is well below volumes in any year to date over the last decade. Conversations with pharma lead us to believe that the volume drought is very much linked to antitrust fears and a desire by buyers to get beyond the election.



Source: S&P CapitalIQ

Naoki Okamura of Astellas Pharma on Inorganic Growth

Ryan Cross, *Endpoints News*, Sept. 6, 2024 (excerpt)

"We kind of stopped thinking that internally-developed product is the best product," Okamura said. "Going forward, there would be very few, if any, compounds that we say that this is our internally-discovered, developed product."

The company has been striking partnerships with smaller biotechs and academic centers, many focused on cell and gene therapies. In January, the company announced a five-year collaboration with Mass General Brigham in Boston, although details about that partnership are sparse.

These efforts are small compared to its $5.9 billion acquisition Iveric Bio and its eye drug Izervay last summer. It was the company's largest acquisition ever. And while Okamura said Astellas will remain "opportunistic," another Iveric-sized purchase isn't happening anytime soon.

"We had been watching the compound for more than eight years until we made the final decision to acquire," Okamura said. "Six billion dollars is somewhat the limit for our financial capacity. So if you ask me, are you going to do a similar size M&A in three years? I don't think so."

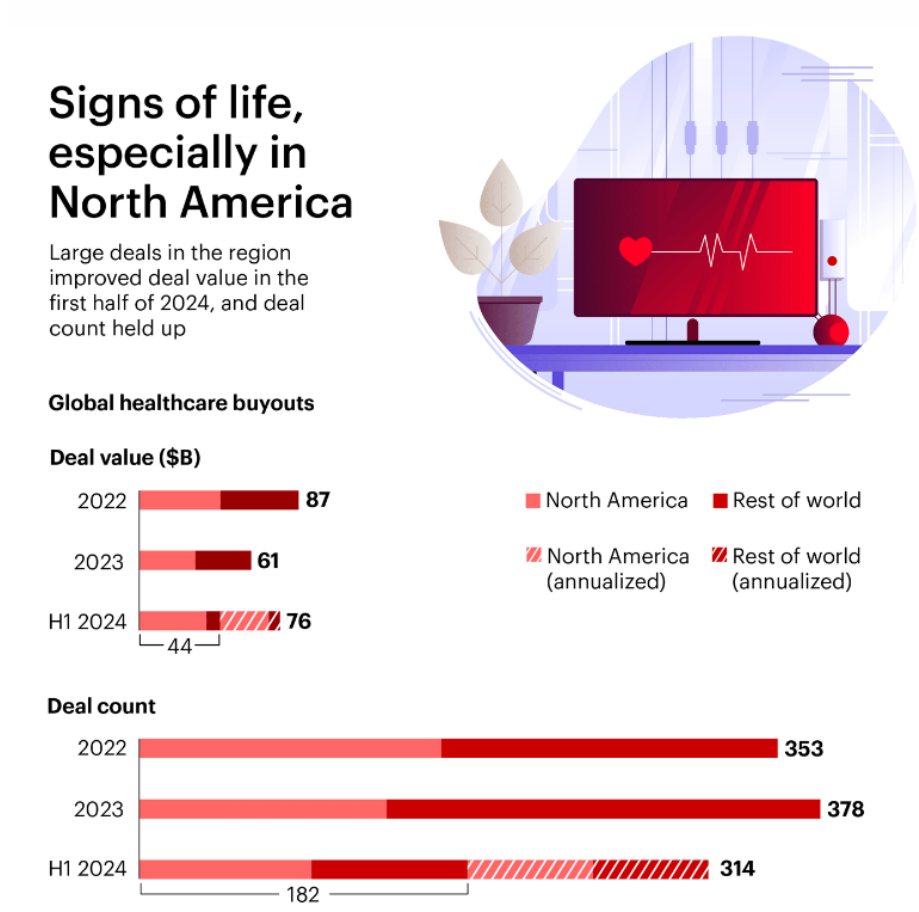
At a time when many pharma companies are abandoning gene therapy programs, especially for rare diseases, Astellas insists that it has no plans to give up on the medicines, even in the face of one of the industry's most tragic failures.

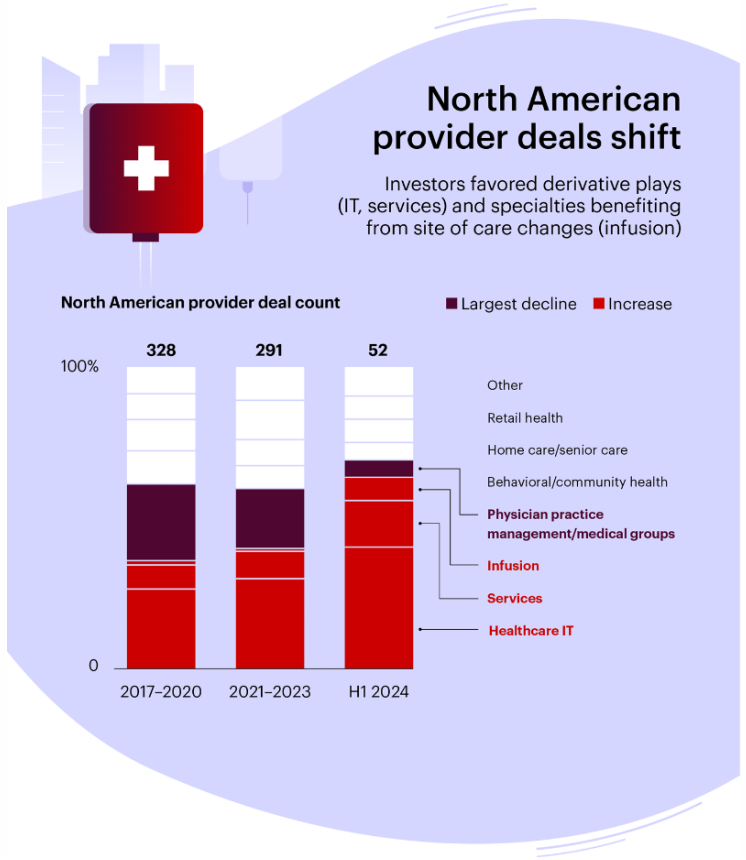
Naoki Okamura
CEO, Astellas Pharma

Source: https://endpts.com/astellas-ceo-talks-future-beyond-xtandi-as-japanese-drugmaker-puts-roots-in-boston/. Photo from Getty Images.

Big Deals Rule: Healthcare Private Equity Midyear Update

Bain and Company, August 29, 2024





"As we pulled together the deal trends for our midyear report," says Kara Murphy, coleader of Bain's Global Healthcare Private Equity group, "healthcare PE is having one of its top three to five years ever."

While she cautions that healthcare deals are still off from their 2021 highs, there's a case to be made for optimism. Nirad Jain, who coleads the Global Healthcare Private Equity group, sees pockets of deal activity everywhere.

"Even in the month of August, we saw Carlyle announce the large Vantive carve-out from Baxter for almost $4 billion," Nirad says, "and I think these are very important markers for the broader market to have confidence that dealmaking is getting back to a new normal."

Sources: https://www.bain.com/insights/big-deals-rule-healthcare-private-equity-midyear-update-infographic/, https://www.bain.com/insights/the-case-for-guarded-optimism-in-the-healthcare-sector-podcast/

Industry News

Indiana Biosciences Research Institute, Indianapolis, IN

Biotechs Are in Focus as Congress Looks to Get Tougher on China

Reshma Kapadia, *Barron's*, Sep 8, 2024 (excerpt)

As Congress embarks on what has been billed as "China Week," a bipartisan bill targeting Chinese biotech companies is among the most likely of a myriad of proposals to move ahead.

While more China-oriented restrictions are expected from the Biden administration, this week was expected to be the culmination of months of negotiations in Congress on other proposals on that front. But internal divisions about the structure and scope of some of the legislation have derailed other initiatives for the moment, highlighting how difficult it is to come to agreement despite broad-based bipartisan talk about getting tough on Beijing.

People who track trade and national-security policy say that the bipartisan BIOSECURE Act, which targets Chinese life science companies, is most likely to be voted on. If passed, the bill would restrict federal contractors from working with five Chinese biotechs, including Wuxi Apptec, which is critical in drug development. That could have broader ripples through the industry.

"The BIOSECURE Act could significantly disrupt biotechnology-related supply chains and bring biotechnology fully into the U.S. China technology competition arena," says Paul Triolo, a partner at Albright Stonebridge Group who leads the consultancy's work on China and technology policy.

Source: https://www.barrons.com/articles/china-week-congress-exports-biotech-aa93788e

Influential Democrat Will Oppose Biosecure Act Ahead of House Vote

Jared Whitlock, *Endpoints News*, Sep 6, 2024 (excerpt)

An influential member in Congress is slated to publicly disavow the closely watched Biosecure Act ahead of a planned House vote next week, according to a letter reviewed by Endpoints News.

The legislation would force drugmakers to restrict their work with two popular Chinese contractors: WuXi Biologics and its sister company, WuXi AppTec, by 2032. It also names three genomics companies: BGI, MGI and Complete Genomics.

James McGovern (D-MA), ranking member of the House Rules Committee, said in the letter that the bill would essentially ban companies without due process.

“In short, with no due process for named companies, Congress is relying on questionable data to make important national security decisions. It may be that some of the companies named should be on the list. But others may be punished that should not be,” he wrote in a letter to members of the House that is slated to be sent soon.

McGovern has been publicly quiet on the legislation, but this week, he asked some of his colleagues to vote against the bill, according to three sources familiar with the matter. A spokesman for his office confirmed his advocacy against the bill.“ Over the last several months, I’ve participated in a number of briefings and conversations related to this bill — in both classified and unclassified settings,” he wrote in the letter. “And all of those have led me to believe that HR 8333, as currently drafted, is a shortsighted way to address the real problem of foreign exploitation of the US biopharmaceutical industry.”

It’s unclear if McGovern’s letter will sway the vote on the bill. In McGovern’s district, WuXi Biologics planned to build a $300 million biomedical plant in Worcester, MA, that’s at the center of last-minute lobbying against the legislation.

Source: https://endpts.com/exclusive-influential-democrat-will-oppose-biosecure-act-ahead-of-house-vote/

Catenion Study Shows R&D Productivity Champs

Industry R&D Productivity Driven By Mega Trends – From COVID-19 To Obesity

By Markus Thunecke, Erika Kuchen and Alexander Wallroth

Catenion Study, Sep 1, 2024

Executive Summary

The overall R&D productivity of the 30 largest public biopharma companies has increased despite a challenging global environment for investment and growth. Will hype cycles impact this picture in coming years?

Novo Tops Ranking Again – The Gift That Keeps On Giving

After winning the crown in Catenion's longitudinal study that reviewed R&D productivity from 2013 until 2022, Novo Nordisk A/S also claimed the #1 position in R&D Productivity and Company Performance for the 2023-2024 period (*see Exhibit 2*) – not surprising given its strength in obesity, which has easily become the industry's hottest area. The GLP-1 agonist franchise consisting of Ozempic, Wegovy and Rybelsus combine for $181bn in NPV. In addition, the Phase III amylin receptor agonist combo with semaglutide, CagriSema, more than doubled in value since last year to $74bn, which is reflecting its potential best-in-class weight loss properties.

Given Novo's high market cap of $450bn which is approximately the size of the entire Danish economy, the company will have to deliver outstanding growth over the next years to meet investors' expectations.

Exhibit 2: R&D Productivity And Corporate Growth Ranking Of The Top 30, Showing The Top 10 Companies

R&D PRODUCTIVITY				COMPANY PERFORMANCE			
R&D Rank	Company	Momentum (Pipeline NPV)	Longterm (All NPV)	Corp. Growth Rank	Company	Past Performance	Forecast Performance
1	Novo Nordisk	2	1	1	Novo Nordisk	4	3
2	Vertex	1	3	1	Vertex	1	6
3	Eli Lilly	5	2	3	Eli Lilly	7	2
4	Moderna	3	4	4	Regeneron	2	9
5	Daiichi Sankyo	4	5	5	Daiichi Sankyo	12	4
6	BioNTech	6	6	6	Ipsen	6	14
7	AstraZeneca	7	8	7	AbbVie	3	18
8	Regeneron	11	7	7	Jazz	10	11
9	Amgen	8	10	9	AstraZeneca	9	13
10	Jazz	15	9	10	Merck & Co	17	8
				10	UCB	15	10

Top 5

Source: Catenion; Data As Of July 2024

Vertex Sits Comfortably At Number Two In R&D Productivity

The cystic fibrosis (CF) franchise of Vertex Pharmaceuticals Incorporated still dominates its valuation with 75% of attributable value stemming from this area. CF-blockbuster Trikafta does not lose exclusivity before 2037, but the sales are expected to move over to new drug Vanzacaftor triple that is under FDA-review. In addition, Vertex has successfully started to diversify its portfolio. Casgevy, recently the first-ever approved CRISPR/Cas9 product for sickle cell disease, stems from a deal with CRISPR Therapeutics ($900m upfront, $200 milestone payments) and is currently valued at $4bn.

Vertex claims the #1 spot in the momentum ranking and, in its pipeline, has demonstrated internal capabilities. Its Phase III non-opioid pain killer targeting the NaV1.8 ion channel is valued at $11bn.

In April 2024, Vertex announced the acquisition of Alpine Immune Sciences Inc. for $4.9bn to access povetacicept, a Phase II BAFF/APRIL inhibitor with best-in-class potential in IgA nephropathy. Based on its steady growth and high profitability Vertex has quietly (no mega deals, no hype-chasing activities but lots of bolt-on and product focused deals) turned into one of the most valuable biopharma companies in the world with a market cap of ca. $125bn and a highly diversified portfolio spanning multiple different diseases from very rare indications to mass markets such as neuropathic pain.

Source: https://catenion.com/2023-2024-global-biopharma-rd-productivity-and-growth-ranking/

Travere Therapeutics Announces Full FDA Approval of FILSPARI® (sparsentan), the Only Non-Immunosuppressive Treatment that Significantly Slows Kidney Function Decline in IgA Nephropathy

SAN DIEGO, Sept. 05, 2024 (GLOBE NEWSWIRE) -- Travere Therapeutics, Inc., (Nasdaq: TVTX) today announced that the U.S. Food and Drug Administration (FDA) has granted full approval to FILSPARI® (sparsentan) to slow kidney function decline in adults with primary IgAN who are at risk of disease progression. FILSPARI was granted accelerated approval in February 2023 based on the surrogate marker of proteinuria. Full approval is based on positive long-term confirmatory results from the PROTECT Study demonstrating that FILSPARI significantly slowed kidney function decline over two years compared to irbesartan.

"We know that most people living with IgAN are at risk of disease progression and are seeking a safe, effective and convenient treatment option that can help preserve their kidney function. Full approval now enables physicians to confidently prescribe FILSPARI more broadly as a once-daily, oral, non-immunosuppressive treatment, that can provide superior preservation of kidney function and replace current standard of care," said Eric Dube, Ph.D., president and chief executive officer of Travere Therapeutics.

FILSPARI is the only oral, once-daily, non-immunosuppressive medication that directly targets glomerular injury in the kidney by blocking two critical pathways of IgAN disease progression (endothelin-1 and angiotensin II).

The two-year efficacy data contained in the FDA-approved label is a modified intention to treat (ITT) analysis, and as preferred by the FDA, evaluates data from all patients regardless of treatment discontinuation. In the final analysis of the 404 randomized patients, FILSPARI significantly reduced the rate of decline in kidney function from baseline to Week 110 compared to irbesartan. In the ITT analysis included in the label, the mean eGFR slope from baseline to Week 110 was -3.0 mL/min/1.73 m2/year for FILSPARI and -4.2 mL/min/1.73 m2/year for irbesartan, corresponding to a statistically significant treatment effect of 1.2 mL/ min/1.73 m2/year (p=0.0168).

Eric Dube
Chief Executive Officer
Travere Therapeutics

Source: https://ir.travere.com/news-releases/news-release-details/travere-therapeutics-announces-full-fda-approval-filsparir

Vaxcyte's "Best-Case" Data for Pneumococcal Vaccine Boost Shares

Delilah Alvarado, *Biopharma Dive*, Sep 3, 2024 (excerpt)

Investors and analysts have been closely tracking Vaxcyte's candidate. While Tuesday's results are from a mid-stage test, the stock market reaction indicates Wall Street sees it as a potential competitor to pneumococcal vaccines from Pfizer, Merck & Co. and GSK.

Pfizer, in particular, has been dominant with its Prevnar 20 shot. In an Aug. 14 note to clients, Mizuho Securities analyst Salim Syed noted how Vaxcyte could "disrupt Pfizer's 20-year [plus] near monopoly" on an $8 billion market.

Approved in 2021 for adults 18 years or older, Prevnar 20 was more recently cleared to include use in infants and children. It has become the go-to option over others, including an earlier shot from Pfizer and two others from Merck.

New competitors have advanced, however. In June, Merck gained approval from the Food and Drug Administration for its latest shot, called Capvaxive. That vaccine protects against 21 serotypes, including eight that are not covered by other approved shots. Advisers to the Centers for Disease Control and Prevention have since recommended Capvaxive in adults 65 years and older and young adults who have not previously received a shot and who have certain underlying health conditions.

While Vaxcyte's competing product has a ways to go before reaching market, the early data has set high expectations. "Essentially, what we got today was the best-case scenario with zero misses," Syed wrote in a Tuesday morning note to investors.

Vaxcyte's study enrolled 1,015 healthy adults 50 years or older and tested three doses of the company's shot against placebo.

The highest dose produced the strongest immune response, matching the efficacy of Prevnar 20 on all serotypes covered by that shot. Across seven of those serotypes, the immune response spurred by Vaxcyte's product was statistically greater than those produced by Pfizer's.

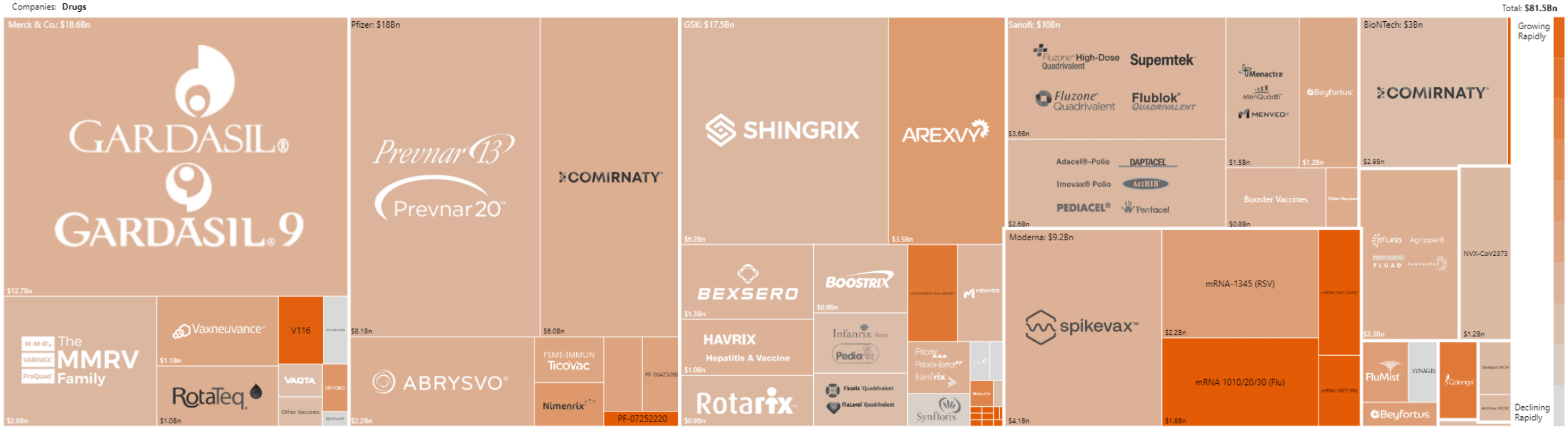
Source: https://www.biopharmadive.com/news/vaxcyte-shares-soar-early-stage-readout-pneumococcal-vaccine/725888/

Vaccine Market Map (Revenue in 2023)

Source: Pharmasights

Vaccine Market Map in 2028

This chart shows analyst consensus estimates of revenue by product in 2028. Total revenue is expected to grow from $70bn in 2023 to $82bn by 2028. This chart does not necessarily reflect the strength of Vaxcyte's data and its potential disruption to the pneumococcal vaccine marketplace.



Source: Pharmasights

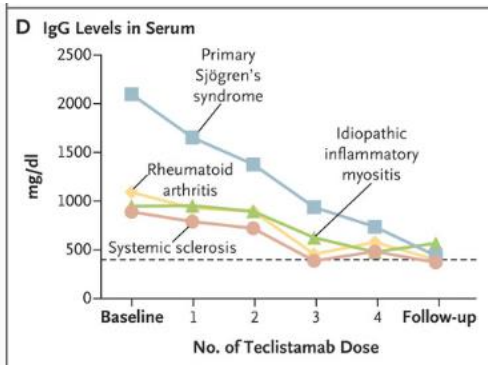
BCMA T-Cell Engager Shows Impressive Results in Four Refractory Autoimmune Patients

Hagen et al., *New England Journal of Medicine*, Sep 4, 2024.

The T-cell engager teclistamab acts on T cells through CD3 (the defining marker of T cells) and targets plasmablasts and plasma cells through BCMA. Teclistamab has been shown to be highly effective in patients with multiple myeloma.4 Thus, we hypothesized that teclistamab may be effective for targeting severe autoimmune diseases, even after failure of conventional B-cell depletion. We administered teclistamab subcutaneously to four patients with autoimmune diseases that were resistant to more than five immunosuppressants, including rituximab (Figure 1A and Table S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). Patient 1 had systemic sclerosis with calcinosis cutis and interstitial lung disease. Patient 2 had primary Sjögren's syndrome with xerostomia and xerophthalmia (dryness of mouth and eyes), arthritis, enthesitis, myositis, inflammatory rash, and interstitial lung disease. Patient 3 had MDA5-positive idiopathic inflammatory myositis with arthritis, inflammatory rash, digital ulcers, and interstitial lung disease. Patient 4 had seropositive rheumatoid arthritis.

Teclistamab improved disease activity in all four patients. In Patient 1, skin disease (as measured by the modified Rodnan skin score) improved from 39 to 24. In Patient 2, the score on the EULAR Sjögren's Syndrome Disease Activity Index improved from 34 to 15. In Patient 3, the skin inflammation score on the Cutaneous Dermatomyositis Disease Area and Severity Index improved from 22 to 6 points, the arthritis score on the Disease Activity Score 28 for Rheumatoid Arthritis with CRP (DAS28-CRP) improved from 3.6 to 1.6, and the lung diffusion capacity improved from 44% to 57%. In Patient 4, the arthritis score on the DAS28-CRP improved from 5.9 to 1.9 (Figure 1F). In Patient 2, imaging performed with the use of positron-emission tomography–computed tomography with gallium 68–labeled fibroblast activation protein inhibitor (FAPI-PET-CT) revealed resolution of arthritis in the hands and knees (Fig. S1I). Skin inflammation and ulcerations were markedly reduced in Patient 3 (Fig. S1J). Taken together, these data show that the targeting of the plasma-cell compartment by a BCMA-targeted T-cell engager is feasible in patients with autoimmune disease. Whether such therapy results in sustained clinical remission warrants further study.

Source: https://www.nejm.org/doi/full/10.1056/NEJMc2408786



E Changes in Serum Autoantibodies at Latest Follow-up

	Autoantibody	Baseline	Follow-up
Patient 1 (systemic sclerosis)	ANA — titer	1:3200	1:100
	PM-Scl-75 — RU (normal <15)	30	1
	PM-Scl-100 — RU (normal <15)	35	3
Patient 2 (primary Sjögren's syndrome)	ANA — titer	1:10,000	1:3200
	SS-A/Ro-52 — U/ml (normal <25)	129.7	55.3
	SS-A/Ro-60 — U/ml (normal <25)	189.5	131.3
	SS-B/La — U/ml (normal <25)	222.5	165.2
	PL-7 — RU (normal <15)	122	91
Patient 3 (idiopathic inflammatory myositis)	ANA — U/ml (normal <25)	1:100	1:100
	MDA5 — RU (normal <15)	38	18
Patient 4 (rheumatoid arthritis)	RF — U/ml (normal <25)	507.2	18.4
	CCP2 — U/ml (normal <25)	2.7	0.9
	MCV — U/ml (normal <25)	82.9	3.0

F Clinical Efficacy Analysis

	Patient 1 (systemic sclerosis)		Patient 2 (primary Sjögren's syndrome)		Patient 3 (idiopathic inflammatory myositis)		Patient 4 (rheumatoid arthritis)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Visual analogue scale (patient global) — mm	90	50	50	10	50	20	60	40
Modified Rodnan skin score — units	39	24	N/A	N/A	N/A	N/A	N/A	N/A
ESSDAI (Sjögren's syndrome activity) — units	N/A	N/A	34	15	N/A	N/A	N/A	N/A
CDASI (skin inflammation) — units	N/A	N/A	N/A	N/A	22	6	N/A	N/A
MMT-8 (diffusion capacity of lung) — units	N/A	N/A	N/A	N/A	138	150	N/A	N/A
DAS28–CRP (arthritis) — units	N/A	N/A	N/A	N/A	3.6	1.6	5.6	1.9
Health assessment questionnaire — units	2.5	2.1	1.3	1.1	1.8	1.0	3.0	1.6
DLCOSB (single-breath diffusion capacity of lung for carbon monoxide) — percent of predicted	34	33	23	27	44	57	76	72

Shown are the characteristics of the patients at baseline (Panel A), a schematic view of the treatment protocol (Panel B), safety results (Panel C), IgG levels in serum (Panel D), changes in serum autoantibodies at the latest follow-up (Panel E), and clinical efficacy (Panel F). ANA denotes antinuclear antibodies, CCP2 second-generation cyclic citrullinated peptide, CDASI Cutaneous Dermatomyositis Disease Area and Severity Index, CRS cytokine release syndrome, CUT cutaneous, DAS28 Disease Activity Score 28, ESSDAI EULAR Sjögren's Syndrome Disease Activity Index, GI gastrointestinal, HSV herpes simplex virus, ICANS immune effector-cell–associated neurotoxicity syndrome, MCV mutated citrullinated vimentin, MDA5 anti–melanoma differentiation-associated gene 5, MMT-8 manual muscle testing 8, N/A not applicable, PM-Scl polymyositis–scleroderma, PSS primary Sjögren's syndrome, RA rheumatoid arthritis, RF rheumatoid factor, RU relative units, and URTI upper respiratory tract infection.

CD3 x BCMA T-Cell Engager Shows Disease Remission in Lupus

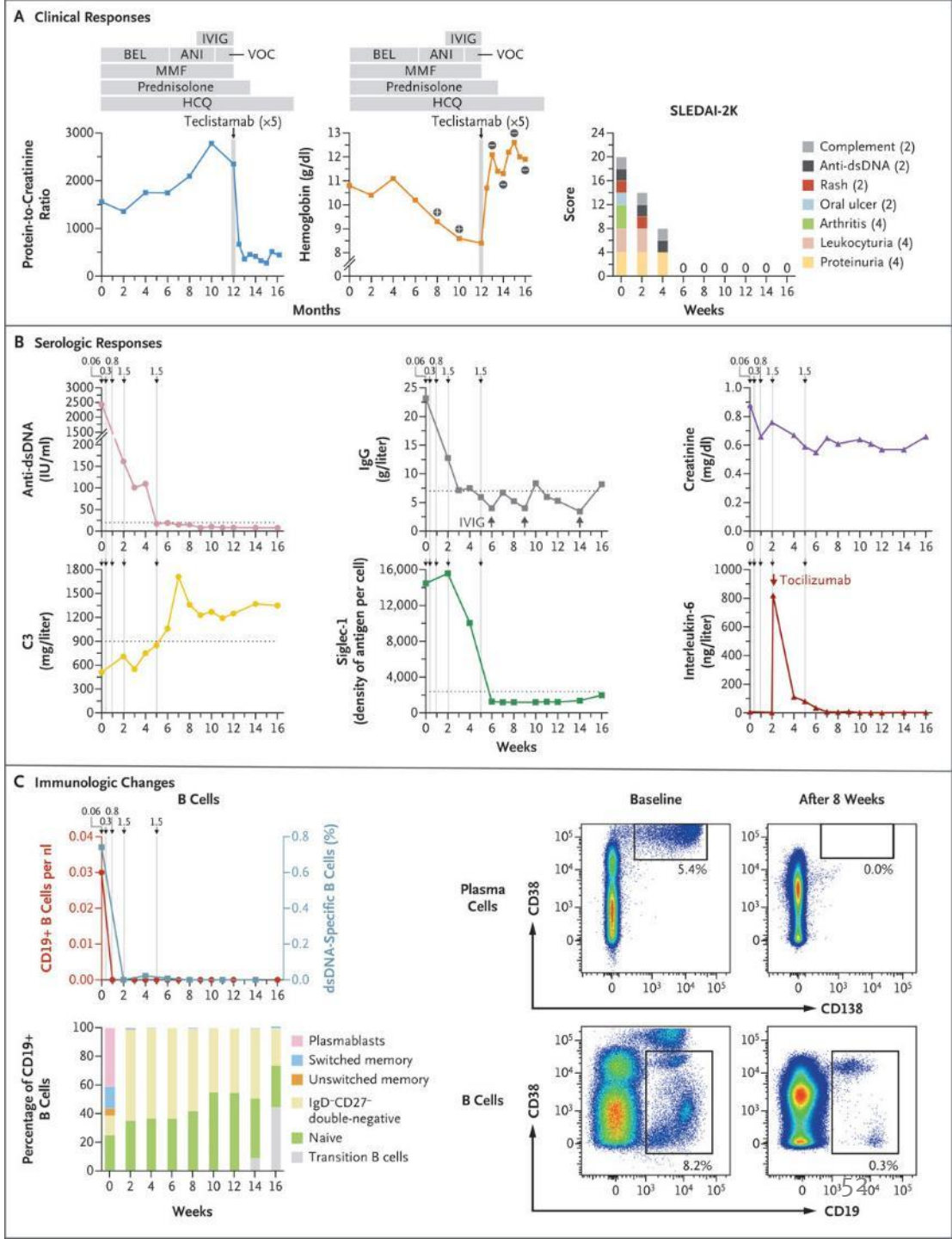
Alexander et al., *New England Journal of Medicine*, Sep 4, 2024.

Anti-CD19 chimeric antigen receptor (CAR) T-cell therapies have shown substantial therapeutic efficacy in patients with autoimmune diseases such as systemic lupus erythematosus (SLE) by inducing deep B-cell depletion.1 However, their expensive and time-consuming manufacturing process, the necessity of conditioning regimens, and a limited ability to modify the dose of CAR T cells once administration has begun, preclude their widespread use. Bispecific antibodies that engage T cells have dual binding sites targeting both CD3 and a target B-cell antigen; this attribute results in CD3+ T-cell activation and the subsequent destruction of target cells. We now report on the use of the CD3 and B-cell maturation antigen (BCMA)–bispecific antibody teclistamab, which is approved for the treatment of multiple myeloma, in a patient with severe SLE. Teclistamab was selected for use in our patient to exploit its capacity to deplete B cells and plasma cells,3 both of which express BCMA and are implicated in driving autoimmunity in patients with SLE.

A 23-year-old woman with a 6-year history of SLE presented with active lupus nephritis (World Health Organization class II and V), autoimmune hemolytic anemia, vesiculobullous lesions, and polyarthritis. Previous treatment with hydroxychloroquine, methotrexate, azathioprine, dapsone, mycophenolate mofetil, voclosporin, belimumab, and anifrolumab had not sufficiently controlled her symptoms. After written informed consent was obtained, the patient received subcutaneous injections of the recommended step-up doses of teclistamab (0.03 and 0.6 mg per kilogram of body weight), followed by an additional step-up dose of 0.8 mg per kilogram on day 7; she subsequently received the full dose of 1.5 mg per kilogram at weeks 2 and 5 (final doses).

This case shows that short-term treatment with a bispecific BCMA-directed antibody induced a rapid and drug-free complete remission of SLE by depleting long-lived plasma cells and memory B cells. The response in our patient was remarkable and could position bispecific BCMA-directed antibodies as a future off-the-shelf treatment, potentially with incidences of response similar to those obtained with anti-CD19 CAR T-cell therapies. However, a longer follow-up period, particularly until the occurrence of B-cell repopulation, and treatment of a larger patient population are needed to determine the incidence and duration of response.

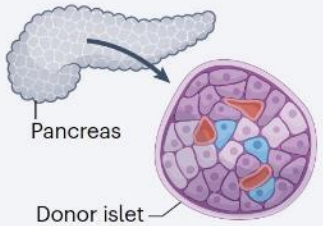
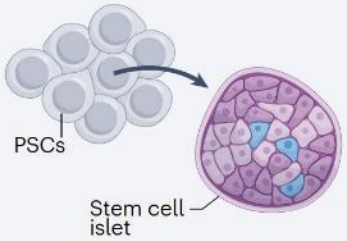
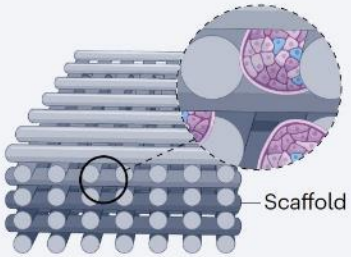
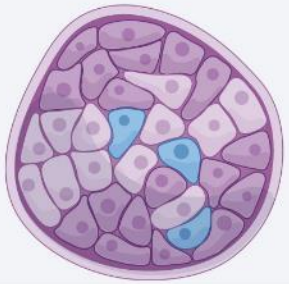
Source: https://www.nejm.org/doi/full/10.1056/NEJMc2407150



Harnessing Cellular Therapeutics for Type 1 Diabetes Mellitus: Progress, Challenges, and the Road Ahead

Grattoni et.al., *Nature Reviews Endocrinology*, Sep 3, 2024

Table 1 | Proposed iterative developments of β cell replacement products

	Current islet transplantation	First-generation naked β cell therapy	Second-generation β cell therapy: encapsulation	Second-generation β cell therapy: other protections	Future β cell therapy
Product schematics					
Cell source	Donor islet transplant	Renewable source	Renewable source	Renewable source	Renewable source
Immune suppression	Broad suppression	Broad suppression	No broad suppression	Reduced/no broad suppression	No broad suppression
Glycaemic control	Improved (HbA_{1c}, hypos, TIR)	Improved (HbA_{1c}, hypos, TIR)	Improved (HbA_{1c}, hypos, TIR)	Improved (HbA_{1c}, hypos, TIR)	Physiological glucose regulation restored
Daily insulin requirement	50–100% reduction	50–100% reduction	70–100% reduction	70–100% reduction	100% reduction (insulin independence)
Duration of efficacy	Variable	6–24 months	6–24 months	6–24 months	>24 months

hypos, hypoglycaemic events; PSC, pluripotent stem cell; TIR, time in range.

Source: https://www.nature.com/articles/s41574-024-01029-0

Happy Birthday, Baby! What the Future Holds for Those Born Today

An intelligent digital agent could be a companion for life—and other predictions for the next 125 years.

Kara Platoni, *MIT Technology Review*, September/October 2024

Happy birthday, baby.

You have been born into an era of intelligent machines. They have watched over you almost since your conception. They let your parents listen in on your tiny heartbeat, track your gestation on an app, and post your sonogram on social media. Well before you were born, you were known to the algorithm.

Your arrival coincided with the 125th anniversary of this magazine. With a bit of luck and the right genes, you might see the next 125 years. How will you and the next generation of machines grow up together? We asked more than a dozen experts to imagine your joint future. We explained that this would be a thought experiment. What I mean is: We asked them to get weird.

Just about all of them agreed on how to frame the past: Computing shrank from giant shared industrial mainframes to personal desktop devices to electronic shrapnel so small it's ambient in the environment. Previously controlled at arm's length through punch card, keyboard, or mouse, computing became wearable, moving onto—and very recently into—the body. In our time, eye or brain implants are only for medical aid; in your time, who knows?

Source: https://www.technologyreview.com/2024/08/15/1096178/125-years-predictions-babies-digital-agents/

nature reviews immunology

https://doi.org/10.1038/s41577-024-01077-7

Review article

Check for updates

The renaissance of oral tolerance: merging tradition and new insights

Sep 6, 2024

Vuk Cerovic[1] ✉, Oliver Pabst[1] & Allan McI Mowat[2] ✉

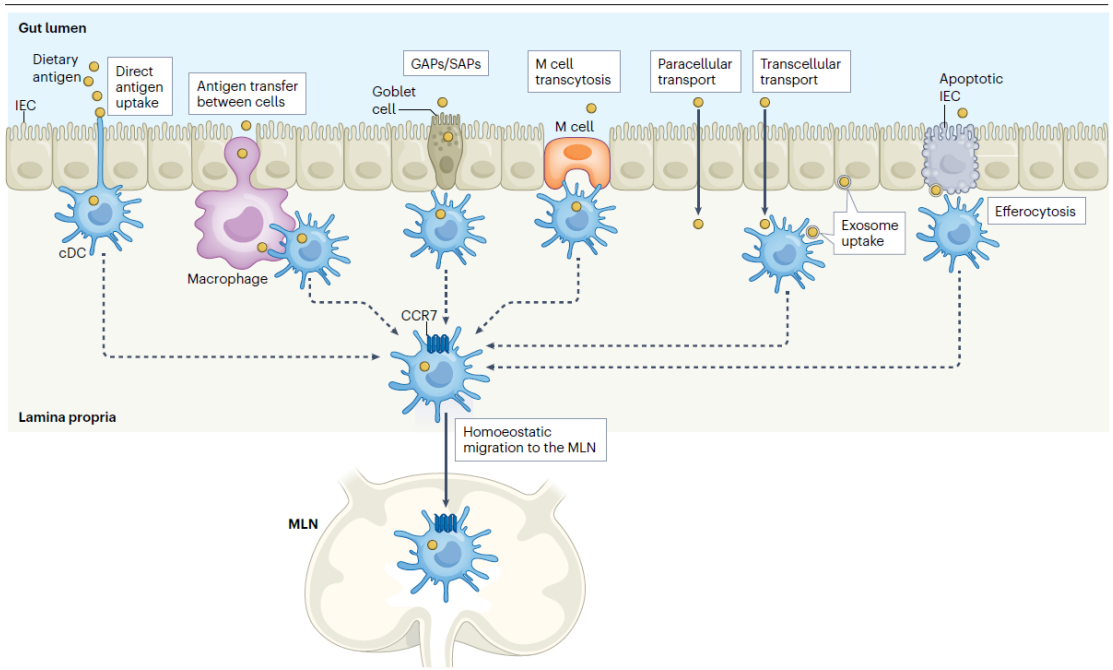
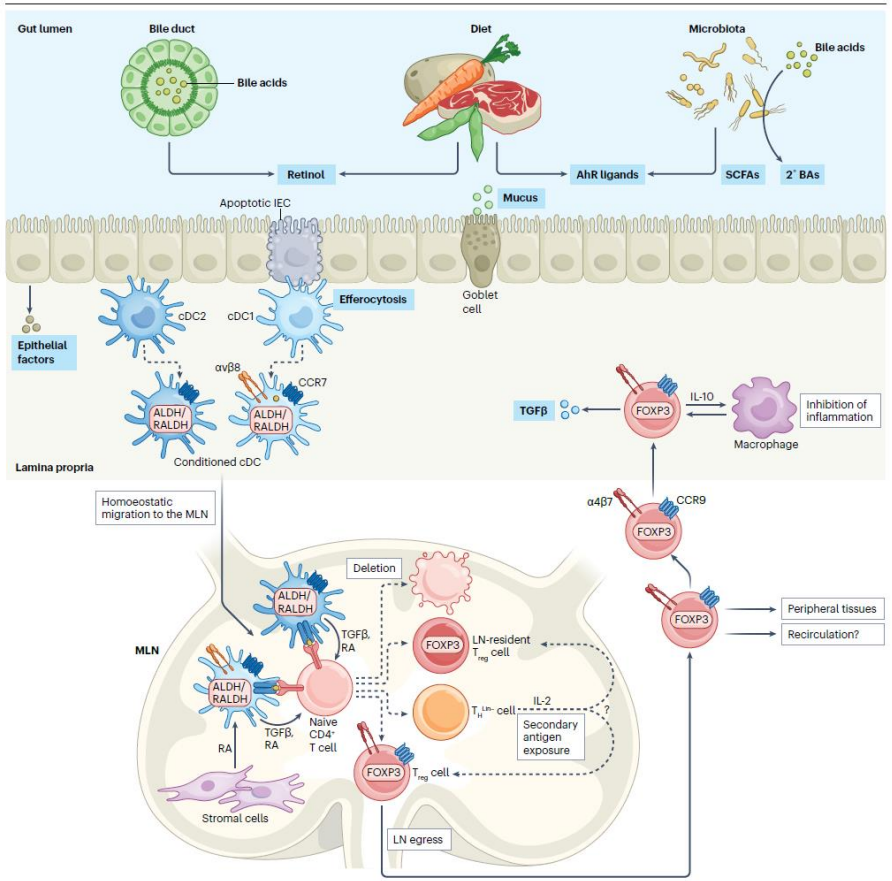


Fig. 1 | Routes of antigen uptake in the intestine. A variety of mechanisms have been proposed to account for the transport of dietary antigen (yellow circles) across the intestinal epithelium. These mechanisms lead to antigen uptake, transport and presentation by migrating conventional dendritic cells (cDCs) that is necessary for the induction of oral tolerance. Potential routes that have been proposed include the direct uptake of luminal antigen by lamina propria cDCs or macrophages followed by transfer of antigen to neighbouring cDCs. Antigen may also gain access to CD103$^+$ cDCs in the lamina propria via goblet cell-associated passages (GAPs) or secretory cell-associated passages (SAPs), or after transcytosis via microfold (M) cells in the villus epithelium. Conventional intestinal epithelial cells (IECs) may allow paracellular or transcellular antigen transport to underlying cDCs. Luminal antigen taken up by IECs may also be transferred to cDCs via generation of exosomes or after uptake of apoptotic IECs by efferocytic cDC1s. MLN, mesenteric lymph node.

Oral tolerance is the process by which feeding of soluble proteins induces antigen-specific systemic immune unresponsiveness. Oral tolerance is thought to have a central role in suppressing immune responses to 'harmless' food antigens, and its failure can lead to development of pathologies such as food allergies or coeliac disease. However, on the basis of long-standing experimental observations, the relevance of oral tolerance in human health has achieved new prominence recently following the discovery that oral administration of peanut proteins prevents the development of peanut allergy in at-risk human infants. In this Review, we summarize the new mechanistic insights into three key processes necessary for the induction of tolerance to oral antigens: antigen uptake and transport across the small intestinal epithelial barrier to the underlying immune cells; the processing, transport and presentation of fed antigen by different populations of antigen-presenting cells; and the development of immunosuppressive T cell populations that mediate antigen-specific tolerance.



Source: https://www.nature.com/articles/s41577-024-01077-7

Original Investigation | Nutrition, Obesity, and Exercise

June 5, 2024

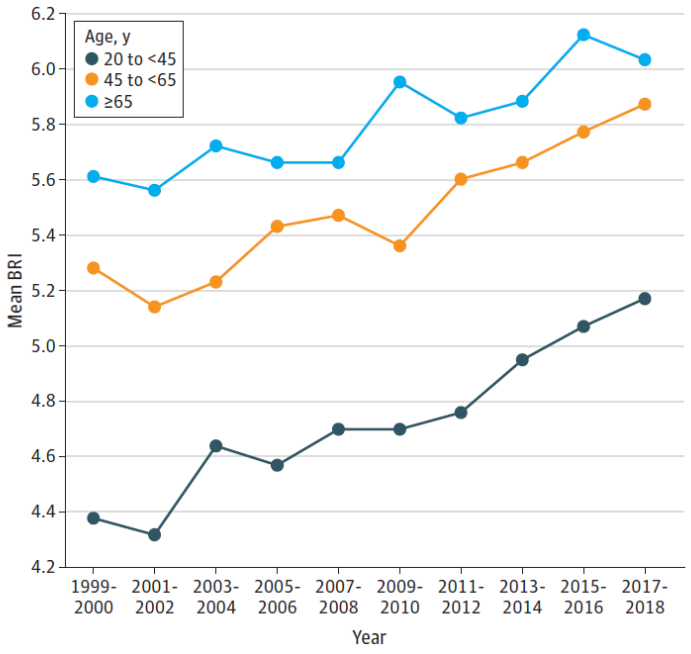
Body Roundness Index and All-Cause Mortality Among US Adults

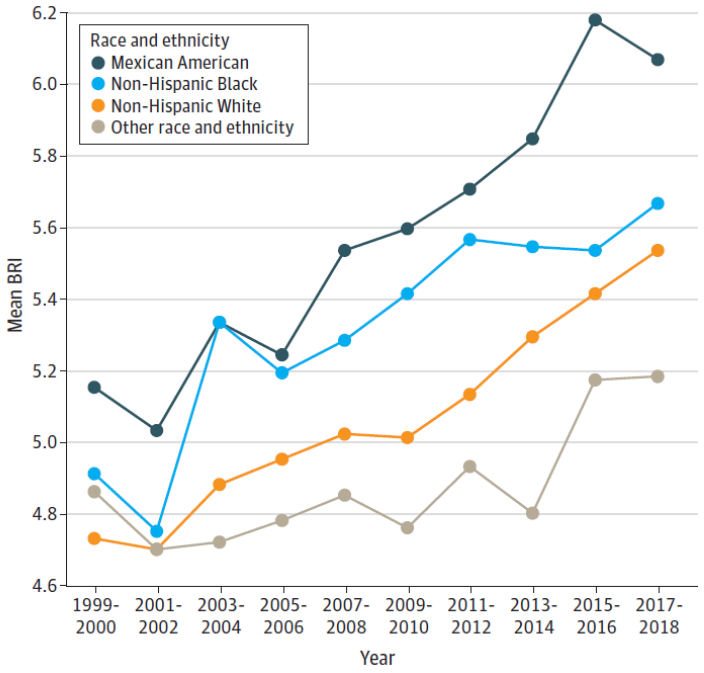
Xiaoqian Zhang, MD[1,2]; Ning Ma, MD[1,3]; Qiushi Lin, MD, PhD[4]; et al

» Author Affiliations | Article Information

JAMA Netw Open. 2024;7(6):e2415051. doi:10.1001/jamanetworkopen.2024.15051

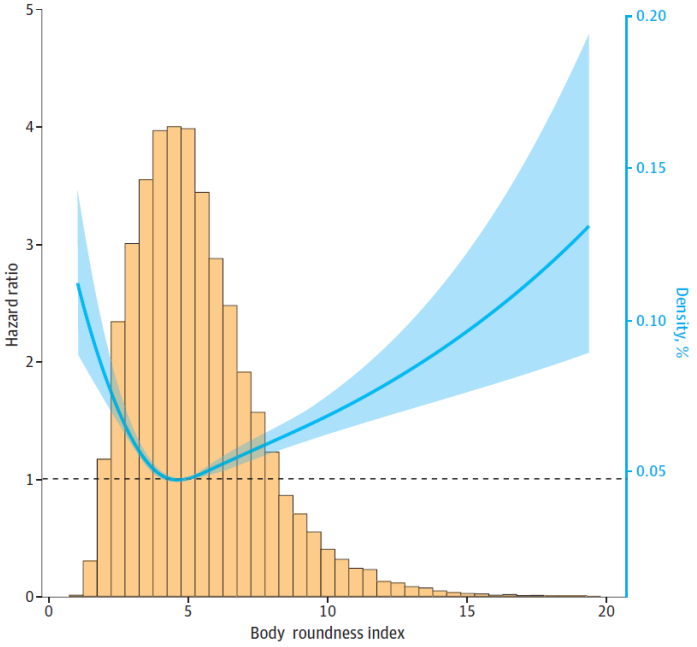
We are getting rounder by the year in the U.S.





Excess "body roundness" kills

Figure 2. The Association Between Body Roundness Index and All-Cause Mortality Risk After Full Adjustment



Source: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2819558

A New Artificial Intelligence Pathology Tool for Cancer

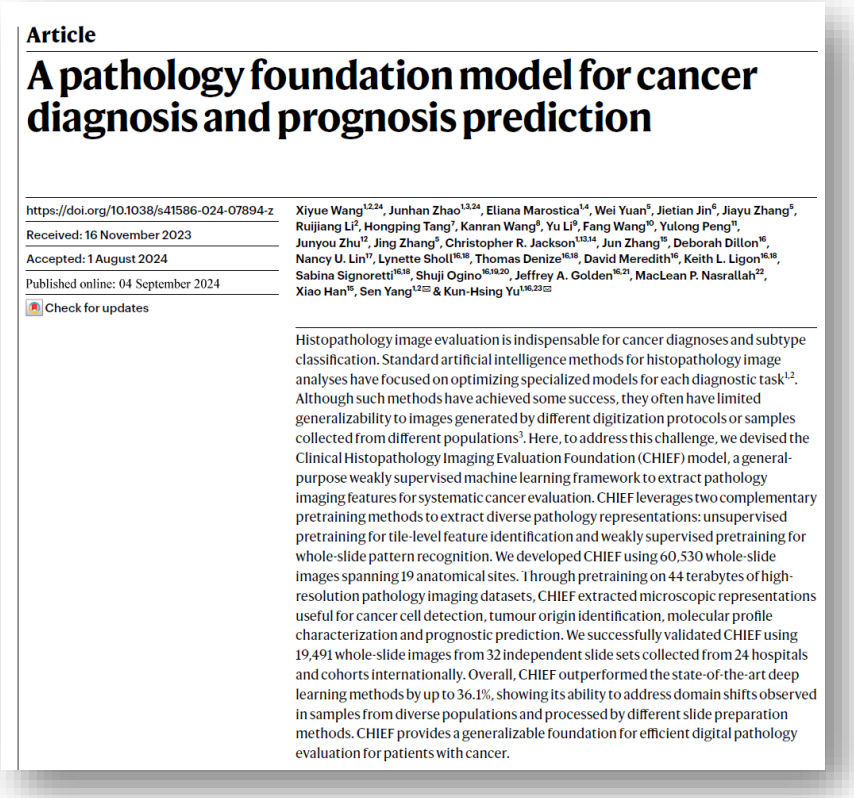
Harvard Medical School Press Release, Sep 5, 2024

Scientists at Harvard Medical School have designed a versatile, ChatGPT-like AI model capable of performing an array of diagnostic tasks across multiple forms of cancers. The new AI system, described Sept. 4 in *Nature*, goes a step beyond many current AI approaches to cancer diagnosis, the researchers said.

Current AI systems are typically trained to perform specific tasks — such as detecting cancer presence or predicting a tumor's genetic profile — and they tend to work only in a handful of cancer types. By contrast, the new model can perform a wide array of tasks and was tested on 19 cancer types, giving it a flexibility similar to that of large language models such as ChatGPT.

While other foundation AI models for medical diagnosis based on pathology images have emerged recently, this is believed to be the first to predict patient outcomes and validate them across several international patient groups. The AI model, which works by reading digital slides of tumor tissues, detects cancer cells and predicts a tumor's molecular profile based on cellular features seen on the image with superior accuracy to most current AI systems. It can forecast patient survival across multiple cancer types and accurately pinpoint features in the tissue that surrounds a tumor — also known as the tumor microenvironment — that are related to a patient's response to standard treatments, including surgery, chemotherapy, radiation, and immunotherapy. Finally, the team said, the tool appears capable of generating novel insights — it identified specific tumor characteristics previously not known to be linked to patient survival.

The findings, the research team said, add to growing evidence that AI-powered approaches can enhance clinicians' ability to evaluate cancers efficiently and accurately, including the identification of patients who might not respond well to standard cancer therapies.



Article

A pathology foundation model for cancer diagnosis and prognosis prediction

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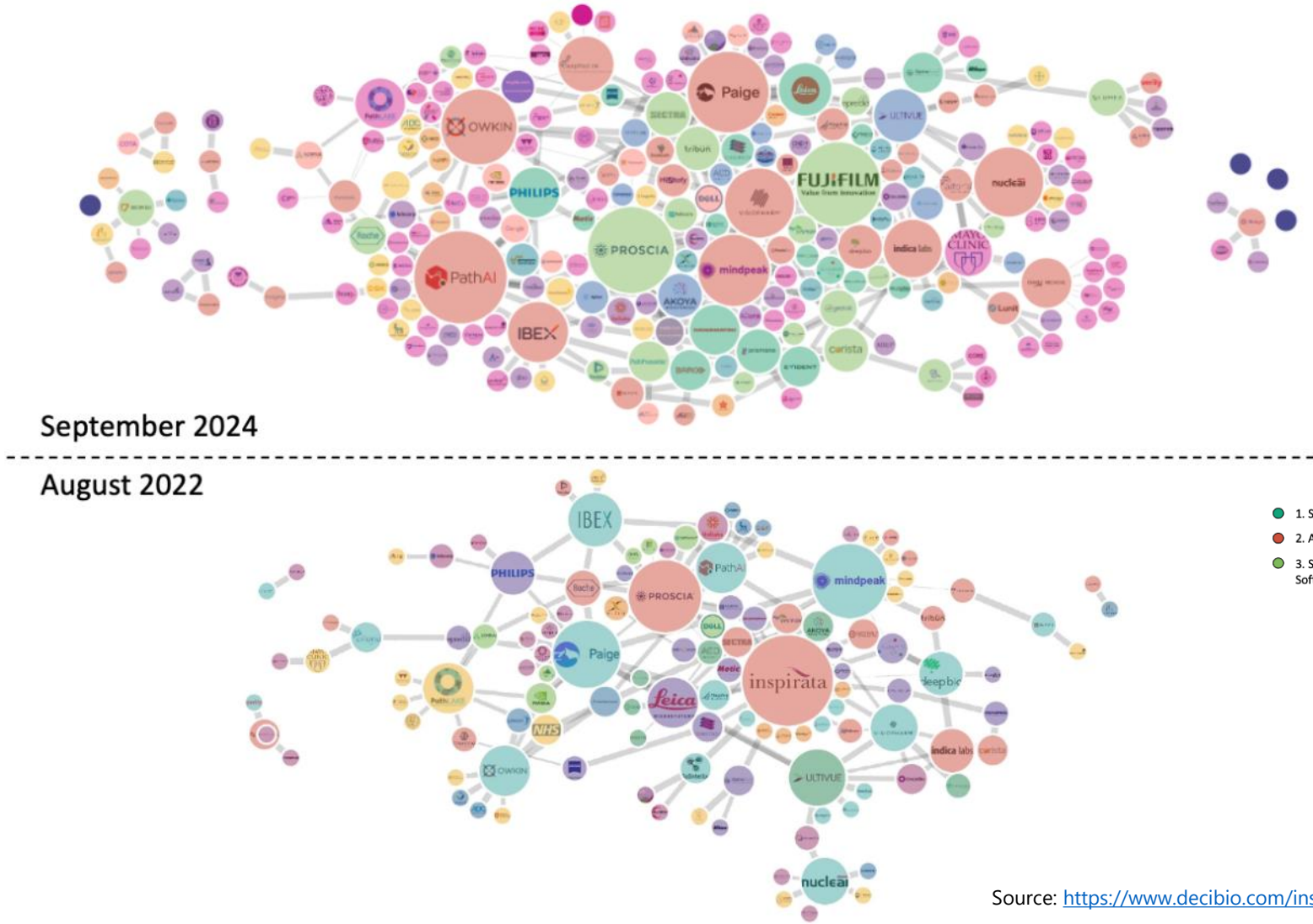
Check for updates

Xiyue Wang[1,2,24], Junhan Zhao[1,3,24], Eliana Marostica[1,4], Wei Yuan[5], Jietian Jin[6], Jiayu Zhang[5], Ruijiang Li[5], Hongping Tang[7], Kanran Wang[8], Yu Li[9], Fang Wang[10], Yulong Peng[11], Junyou Zhu[12], Jing Zhang[5], Christopher R. Jackson[1,13,14], Jun Zhang[15], Deborah Dillon[16], Nancy U. Lin[17], Lynette Sholl[16,18], Thomas Denize[16,18], David Meredith[16], Keith L. Ligon[16,18], Sabina Signoretti[16,18], Shuji Ogino[16,19,20], Jeffrey A. Golden[16,21], MacLean P. Nasrallah[22], Xiao Han[15], Sen Yang[1,2] & Kun-Hsing Yu[1,16,23]

Histopathology image evaluation is indispensable for cancer diagnoses and subtype classification. Standard artificial intelligence methods for histopathology image analyses have focused on optimizing specialized models for each diagnostic task[1,2]. Although such methods have achieved some success, they often have limited generalizability to images generated by different digitization protocols or samples collected from different populations[3]. Here, to address this challenge, we devised the Clinical Histopathology Imaging Evaluation Foundation (CHIEF) model, a general-purpose weakly supervised machine learning framework to extract pathology imaging features for systematic cancer evaluation. CHIEF leverages two complementary pretraining methods to extract diverse pathology representations: unsupervised pretraining for tile-level feature identification and weakly supervised pretraining for whole-slide pattern recognition. We developed CHIEF using 60,530 whole-slide images spanning 19 anatomical sites. Through pretraining on 44 terabytes of high-resolution pathology imaging datasets, CHIEF extracted microscopic representations useful for cancer cell detection, tumour origin identification, molecular profile characterization and prognostic prediction. We successfully validated CHIEF using 19,491 whole-slide images from 32 independent slide sets collected from 24 hospitals and cohorts internationally. Overall, CHIEF outperformed the state-of-the-art deep learning methods by up to 36.1%, showing its ability to address domain shifts observed in samples from diverse populations and processed by different slide preparation methods. CHIEF provides a generalizable foundation for efficient digital pathology evaluation for patients with cancer.

Source: https://hms.harvard.edu/news/new-artificial-intelligence-tool-cancer

Explosion in Digital Pathology Partnership Activity



By Katie Maloney
Principal
DeciBio
September 2024

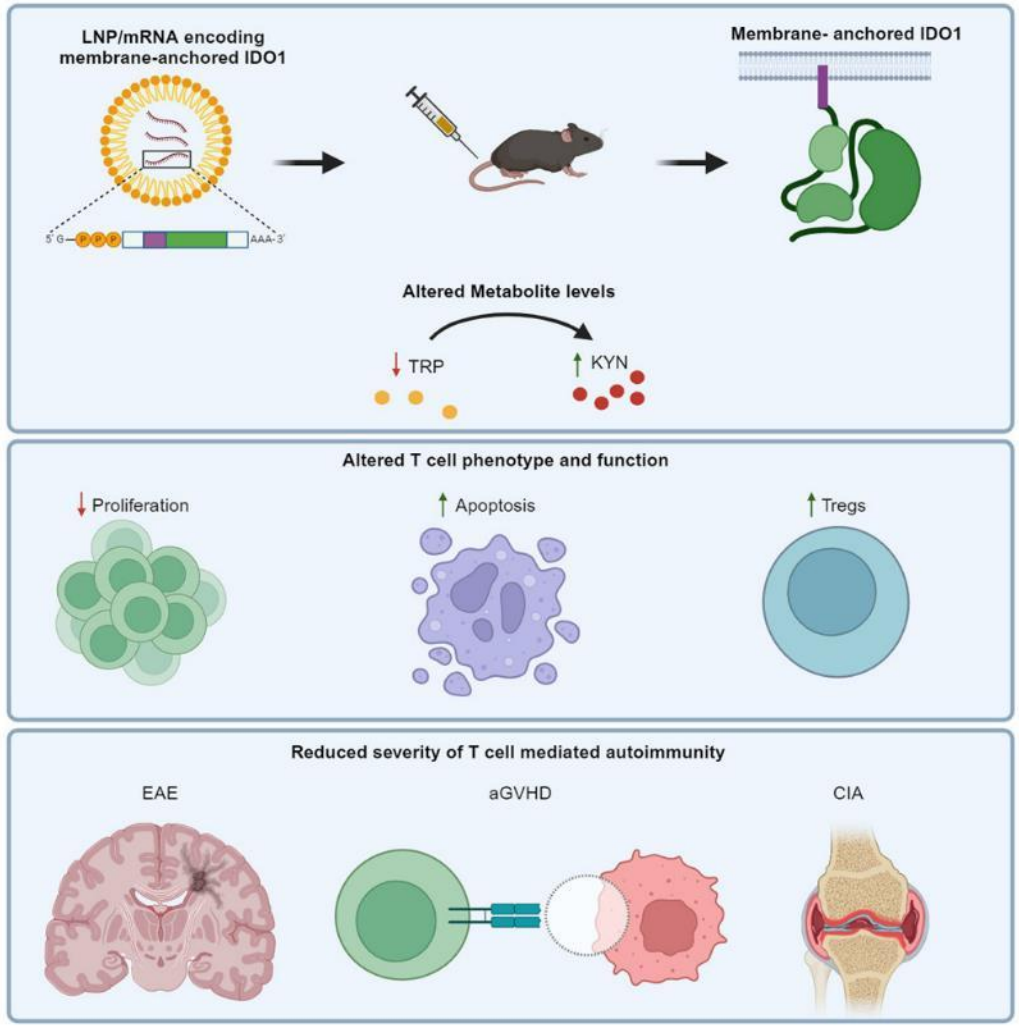
Company size corresponds with number of partnerships, link thickness corresponds with recency of the partnership (thicker lines are more recent; partnerships for which a year could not be established are set at minimum thickness).

Source: https://www.decibio.com/insights/a-busy-two-years---digital-pathology-landscape-update.

mRNA-delivery of IDO1 Suppresses T Cell-Mediated Autoimmunity

Kenney et al., *Cell Reports Medicine*, Sep 6, 2024.

Indoleamine-2,3-dioxygenase (IDO)1 degrades tryptophan, obtained through dietary intake, into immunoregulatory metabolites of the kynurenine pathway. Deficiency or blockade of IDO1 results in the enhancement of autoimmune severity in rodent models and increased susceptibility to developing autoimmunity in humans. Despite this, therapeutic modalities that leverage IDO1 for the treatment of autoimmunity remain limited. Here, we use messenger (m)RNA formulated in lipid nanoparticles (LNPs) to deliver a human IDO1 variant containing the myristoylation site of Src to anchor the protein to the inner face of the plasma membrane. This membrane-anchored IDO1 has increased protein production, leading to increased metabolite changes, and ultimately ameliorates disease in three models of T cell-mediated autoimmunity: experimental autoimmune encephalomyelitis (EAE), rat collagen-induced arthritis (CIA), and acute graft-versus-host disease (aGVHD). The efficacy of IDO1 is correlated with hepatic expression and systemic tryptophan depletion. Thus, the delivery of membrane-anchored IDO1 by mRNA suppresses the immune response in several well-characterized models of autoimmunity.



Source: https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(24)00438-5

Monoclonal B-cell Lymphocytosis Linked to Melanoma

ROCHESTER, Minn. Sep 5, 2024 — About 8 to 10 million Americans over age 40 have an overabundance of cloned white blood cells, or lymphocytes, that hamper their immune systems. Although many who have this condition — called monoclonal B-cell lymphocytosis (MBL) — do not experience any symptoms, a new study shows they may have an elevated risk for several health complications, including melanoma, a form of skin cancer. The findings, by Mayo Clinic researchers, are published in a new paper in the Journal of Clinical Oncology.

People with MBL fall along a spectrum that spans from a low amount to a high amount of these dysfunctional lymphocytes. Previous research has shown that MBL is a precursor to a type of blood and bone marrow cancer known as chronic lymphocytic leukemia (CLL). People with CLL also have a heightened risk of melanoma.

"Our study is the first to show that people with this pre-cancerous stage of MBL have a 92% elevated risk of developing melanoma. The risk of melanoma is similar to what we see among people with chronic lymphocytic leukemia," says Susan Slager, Ph.D., researcher with the Mayo Clinic Comprehensive Cancer Center and senior author of the study.

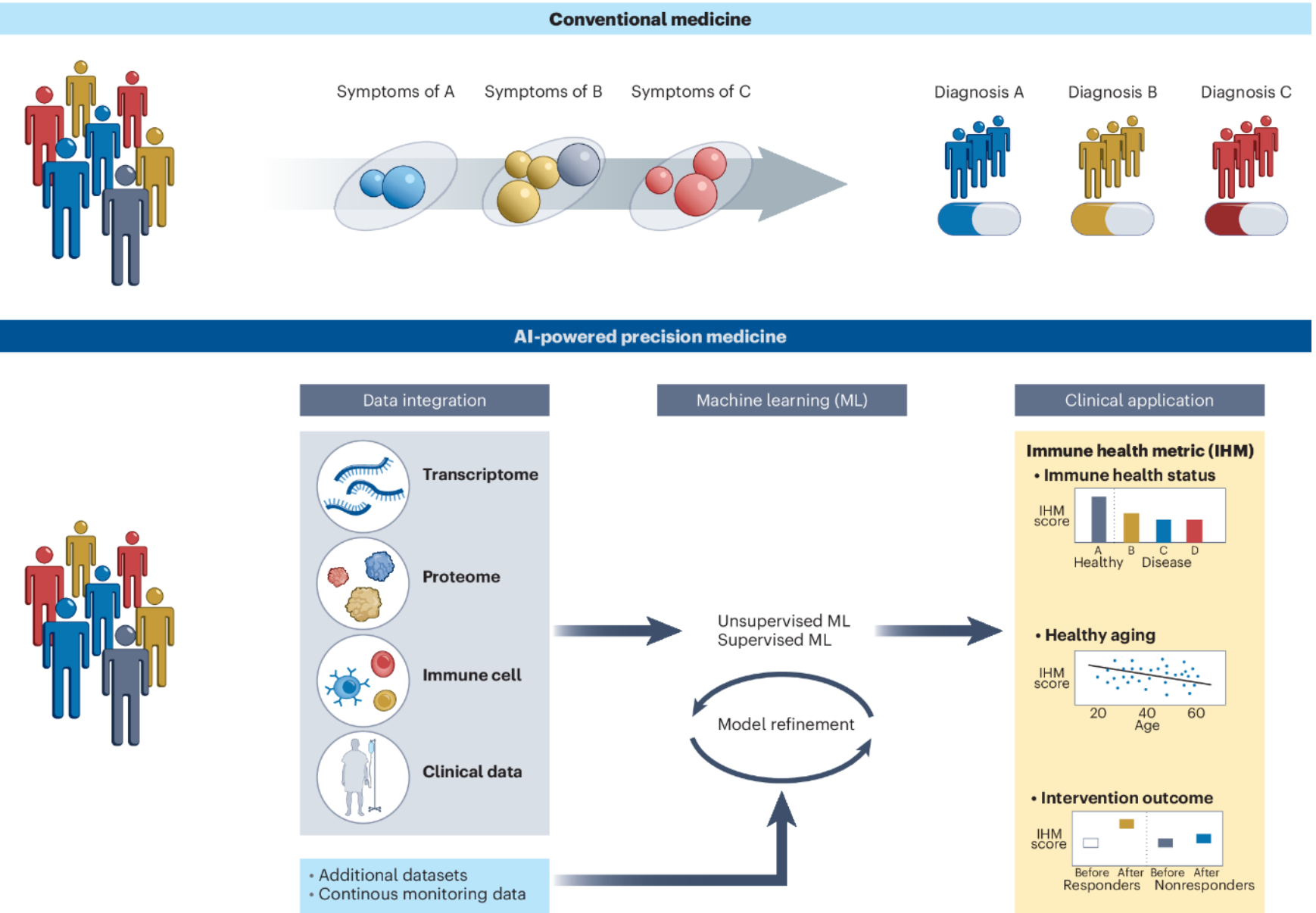
The findings suggest that having MBL, even at low levels, can serve as a biological signal, or biomarker, for early detection of melanoma, which is increasing worldwide.

Dr. Slager and her research team have been studying the largest available cohort of individuals — more than 7,000 people screened for MBL through the Mayo Clinic Biobank. The researchers have now followed these individuals for about four years and are finding a collection of potentially related diagnoses among those who screened positive for MBL.

Susan Slager
Professor of Biostatistics
Mayo Clinic

Source: https://newsnetwork.mayoclinic.org/discussion/mayo-clinic-study-finds-dysfunctional-white-blood-cells-linked-to-heightened-melanoma-risk/

A Global Metric of Immune Health



Vinuesa et.al., *Nature Medicine*, Sep 5, 2024

Conventional diagnosis of immune-related conditions has largely relied on a combination of clinical manifestations and a small set of laboratory parameters. The '-omics' revolution means this approach of distinguishing healthy individuals from those with immune disease can be amplified massively using results from genome sequencing, transcriptomics, metabolomics and deep cellular phenotyping. The integration of artificial intelligence (AI) and multi-omics data establishes a unified human IHM. The IHM is mechanism agnostic but can distinguish between healthy and diseased individuals, track aging and response to treatment, and predict antibody responses. ML, machine learning.

Source: https://www.nature.com/articles/s41591-024-03210-4

Upper Gastrointestinal Mucosal Damage and Subsequent Risk of Parkinson Disease

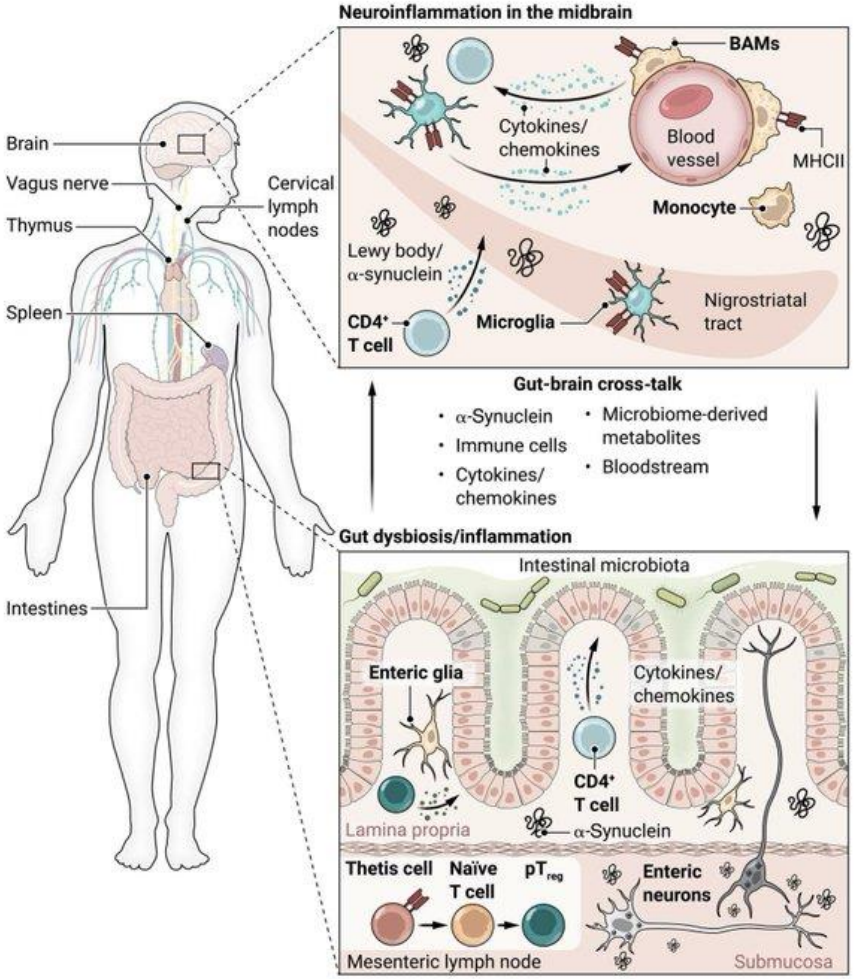
Jocelyn Chang, Tufts and colleagues, *JAMA Open Network*, Sep 5, 2024 (excerpt)

The gut-first hypothesis of Parkinson disease (PD) has gained traction, yet potential inciting events triggering Parkinson pathology from gut-related factors remain unclear. While Helicobacter pylori infection is linked to mucosal damage (MD) and PD, it is unknown how upper gastrointestinal MD from any source increases PD risk.

Of 9350 patients, participants had a mean (SD) age of 52.3 (20.3) years; 5177 (55.4%) were male; and 269 (2.9%) were Asian, 737 (7.9%) Black, and 6888 (73.7%) White. Most participants underwent endoscopy between the ages of 50 and 64 years (2842 [30.4%]). At baseline, patients with MD were more likely to have a history of H pylori infection, proton-pump inhibitor use, chronic nonsteroidal anti-inflammatory drug use, gastroesophageal reflux disease, smoking, constipation, and dysphagia. The mean (SD) follow-up time was 14.9 (6.9) years for the whole cohort, during which patients with MD were more likely to develop PD (IRR, 4.15; 95% CI, 2.89-5.97; P < .001) than those without MD, even after covariate adjustment (HR, 1.76; 95% CI 1.11-2.51; P = .01).

The findings of our investigation corroborate our hypothesis that upper gastrointestinal MD would be associated with clinical PD development, reinforcing the theory of a gut-first progression in PD in a subset of patients. These findings likely suggest 1 of 2 possibilities: first, that MD may serve as an inciting event that could precipitate pathologic alpha-synuclein misfolding in the gut. Second, as dopamine is known to play a key gastroprotective role,18 it may be that patients with subclinical dopaminergic signaling reduction are at higher risk of MD and that alpha-synuclein pathology preceded this event. Understanding these mechanisms is of great interest in future research endeavors.

Our comprehensive analysis indicates a marked escalation in PD risk among individuals with MD (IRR, 4.15; 95% CI, 2.89-5.97; P < .001). This association persisted even after adjustment for established covariates (HR, 1.76; 95% CI, 1.11-2.51; P = .01), underpinning the pivotal role of the gut-brain axis in neurodegenerative conditions and highlighting GI factors as potential early biomarkers and contributors to PD pathogenesis. The substantial 14.2-year mean lead-time between detection of MD and diagnosis of PD likewise strengthens the hypothesis that MD precedes motor symptoms of PD.



Source: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2823250

SCIENCE ADVANCES | RESEARCH ARTICLE Sep 4, 2024

NEUROSCIENCE

Cerebrospinal fluid flow extends to peripheral nerves further unifying the nervous system

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Cerebrospinal fluid (CSF) is responsible for maintaining brain homeostasis through nutrient delivery and waste removal for the central nervous system (CNS). Here, we demonstrate extensive CSF flow throughout the peripheral nervous system (PNS) by tracing distribution of multimodal 1.9-nanometer gold nanoparticles, roughly the size of CSF circulating proteins, infused within the lateral cerebral ventricle (a primary site of CSF production). CSF-infused 1.9-nanometer gold transitions from CNS to PNS at root attachment/transition zones and distributes through the perineurium and endoneurium, with ultimate delivery to axoplasm of distal peripheral nerves. Larger 15-nanometer gold fails to transit from CNS to PNS and instead forms "dye-cuffs," as predicted by current dogma of CSF restriction within CNS, identifying size limitations in central to peripheral flow. Intravenous 1.9-nanometer gold is unable to cross the blood-brain/nerve barrier. Our findings suggest that CSF plays a consistent role in maintaining homeostasis throughout the nervous system with implications for CNS and PNS therapy and neural drug delivery.

Source: https://www.science.org/doi/10.1126/sciadv.adn3259

A unit of life

The major structures within an animal cell at rest

A - Nucleus
The control center of the cell that contains the cell's genetic material, which is composed of DNA molecules. The DNA in the nucleus is packed into structures called chromosomes.

B - Ribosome
Ribosomes are molecular machines that follow genetic instructions to build proteins. They can sometimes be picky about which genetic instructions they follow.

C - Mitochondrion
Known as the cell's powerhouse, mitochondria generate energy through a process called cellular respiration. More than a billion years ago they were free-living bacteria and were engulfed by an ancestor of an animal cell, leading to a mutually beneficial relationship.

D - Endoplasmic reticulum (ER)
A network of membranes involved in the synthesis of proteins and fats. There are two types: smooth and rough. Smooth ER produces fats, like phospholipids used in cells' membranes, and plays a role in detoxifying drugs and toxins. Rough ER provides a platform for ribosomes to construct proteins. It's rough because ribosomes dot its surface.

E - Golgi apparatus
Groups of flattened membrane-enclosed sacs that process, sort and deliver proteins and lipids to their proper destinations within the cell or for secretion outside of the cell.

F - Lysosome
Membrane-bound sacs containing digestive enzymes that break down and recycle cellular waste and foreign materials. Think of them as the cell's garbage disposal or recycling center.

G - Cytoskeleton
A network of protein filaments that provide structure, support and help in cell movement and division. It can quickly reorganize to change cell shape and enable movement.

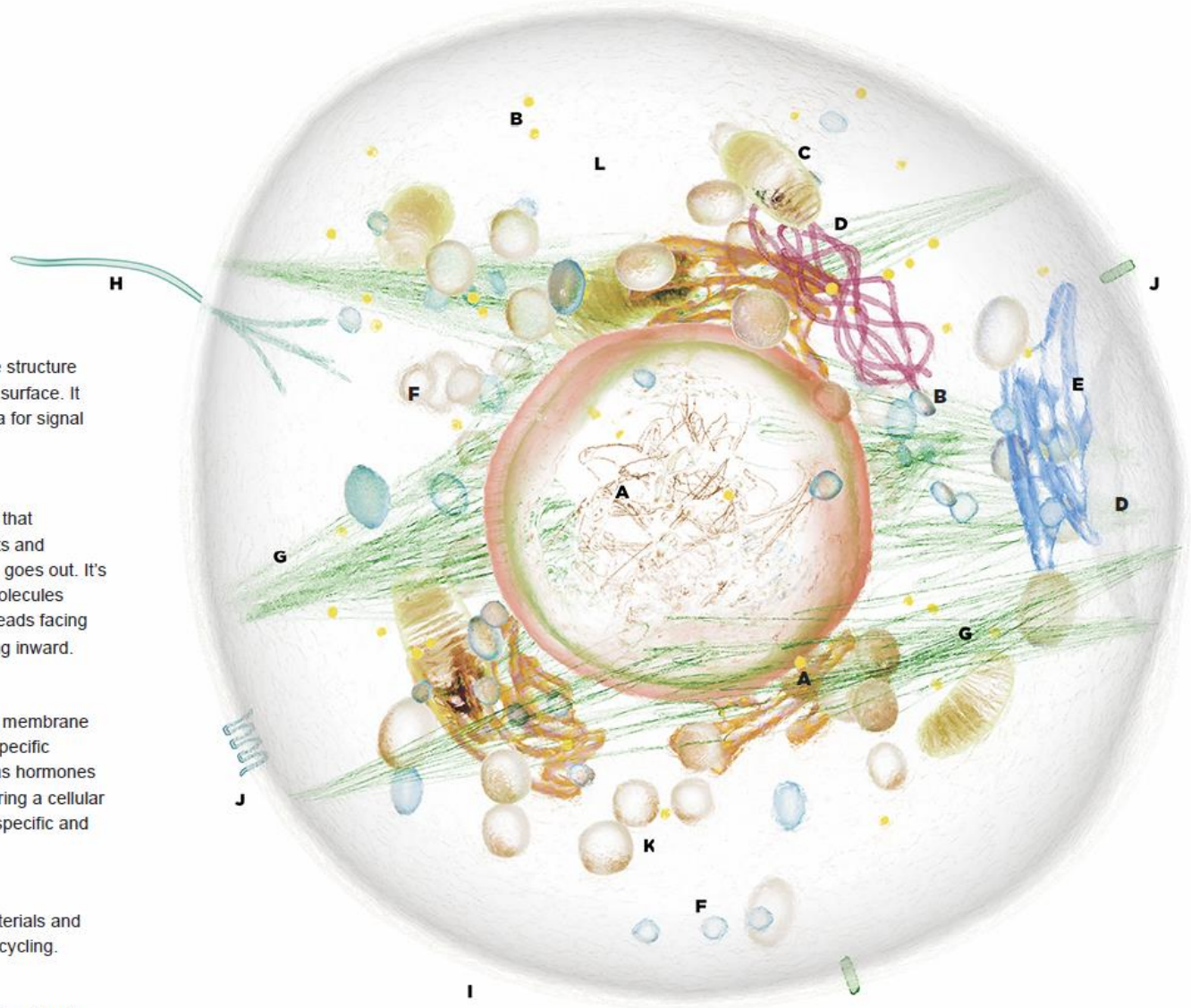
H - Primary cilium
A single, unbending hairlike structure that extends from the cell's surface. It serves as a cellular antenna for signal reception.

I - Cell membrane
A flexible and dynamic wall that surrounds the cell's contents and controls what comes in and goes out. It's made of two layers of fat molecules (phospholipids) with their heads facing outward and their tails facing inward.

J - Receptor
Proteins located on the cell membrane or within the cell that bind specific signaling molecules, such as hormones or neurotransmitters, triggering a cellular response. They are highly specific and selective.

K - Vacuole
A sac that stores waste materials and aids in cell digestion and recycling.

L - Cytoplasm
The gel-like substance enclosed by the cell membrane that houses the cell's structures. It's mainly composed of water, salts and organic molecules and is where many cellular activities occur.



Source: Stanford on the cell (Aug 2024): https://stanmed.stanford.edu/issue/2024issue2/

Disclosure

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