Biopharmaceutical Sector

Weekly Update – March 25, 2024

Statuary at the Sagrada Familia, Barcelona

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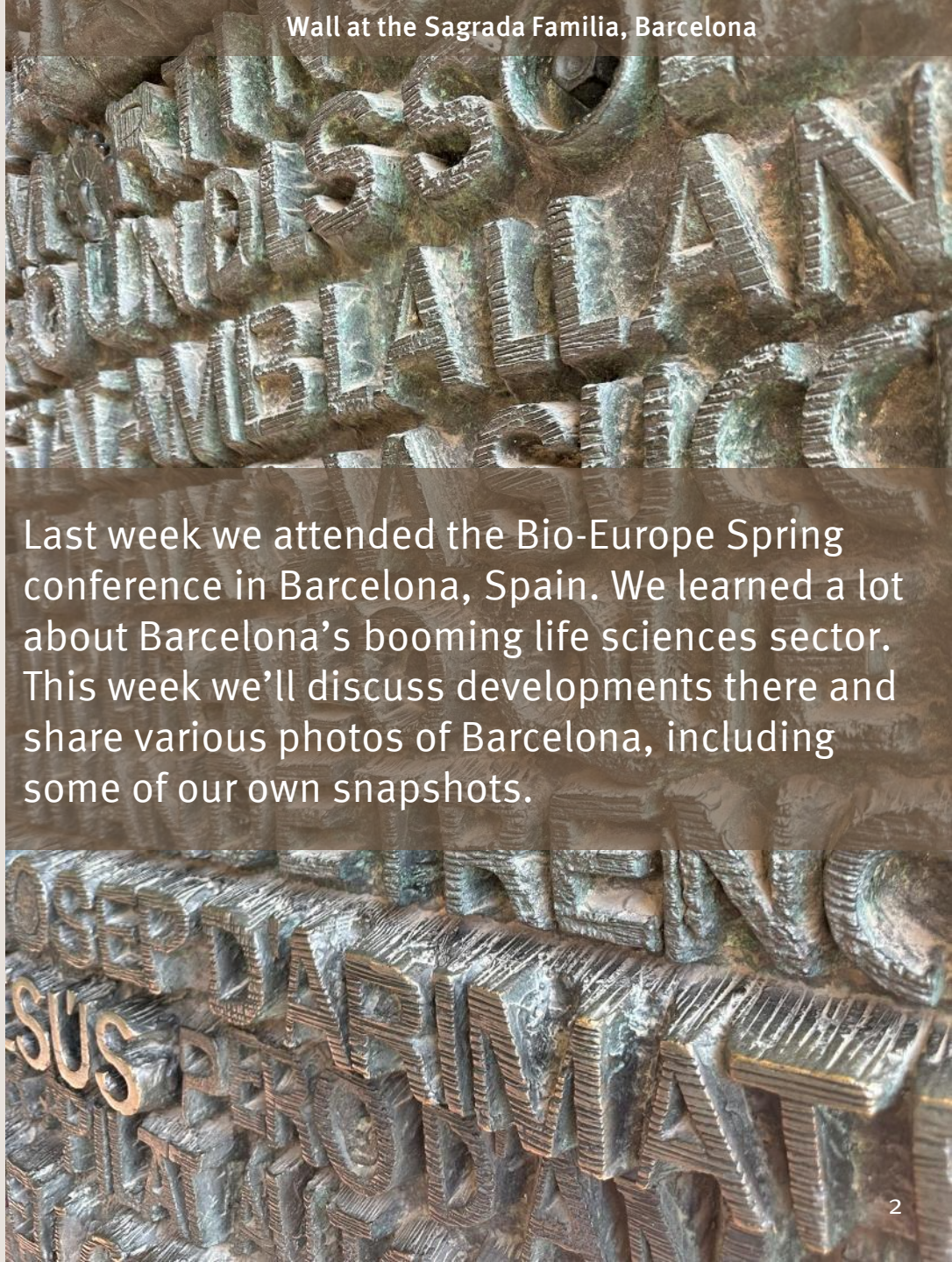
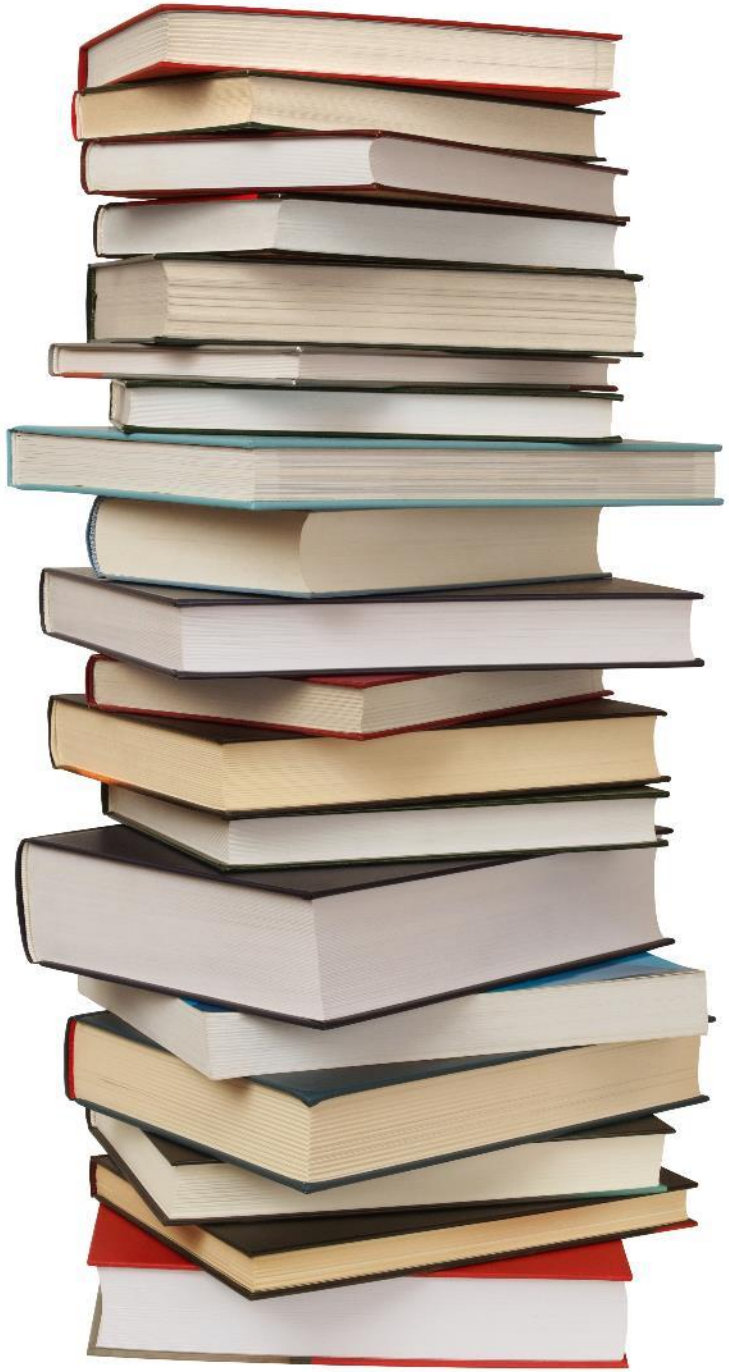


Accessing Past Issues

If you wish to be added to mailing list for this publication, please notify Natasha Yeung (yeungn@stifel.com). Recent issues in case you want to read:

March 18, 2024 (Inflammasome)
March 11, 2024 (IRA, Immunology)
March 4, 2024 (Biotech Employment)
Feb 26, 2024 (Biotech Strategy)
Feb 19, 2024 (Big Drugs, Autoantibodies)
Feb 12, 2024 (Fibrosis, Endometriosis)
Feb 5, 2024 (Severe Disease in Women)
Jan 29, 2024 (Pharma R&D Productivity)
Jan 22, 2024 (AI in medicine)
Jan 15, 2024 (FDA Commissioner Priorities)
Jan 5, 2024 (Sector Outlook for 2024)
Dec 18, 2023 (Expectations for Future)
Dec 11, 2023 (ASH, R&D Days)
Dec 4, 2023 (Big Pharma, CEA)
November 22, 2023 (Bullish on Biotech)
November 20, 2023 (M&A)
November 13, 2023 (AHA, Bear Market)
November 7, 2023 (Unmet Needs)
October 30, 2023 (ADCs)
October 23, 2023 (ESMO Review)
October 16, 2023 (Cancer Screening)
October 9, 2023 (Biosimilars, M&A)
October 2, 2023 (FcRn, Antibiotics)
September 25, 2023 (Target ID)
September 18, 2023 (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 Biotech Hangout This Friday

Biotech Hangout held its latest event on March 22, 2024.

The next event will be on March 29, 2024.

March 22nd Session: https://twitter.com/i/spaces/1OyJAWABYzNKb

Please join us.

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

Please join us for a webinar held by the IQVIA Institute on R&D trends on March 27, 2024 at 10 to 11:30am EST. In addition to Stifel, speakers will be present from Exelixis, Tufts and IQVIA.

For details on joining the webinar please go to:
https://event.on24.com/wcc/r/4534072/098E664C91DB05885F6C524F75A79524

Macro Update

Gaudi Tiles at Parque Guell, Barcelona

Fed Sees Three Rate Cuts in 2024 but a Shallower Easing Path

Howard Schneider and Ann Saphir, *Reuters*, March 21, 2024 (excerpt)

Federal Reserve Chair Jerome Powell said on Wednesday recent high inflation readings had not changed the underlying "story" of slowly easing price pressures in the U.S. as the central bank stayed on track for three interest rate cuts this year and affirmed that solid economic growth will continue. The Fed also left interest rates unchanged and released new quarterly economic projections that showed officials now expect the economy to grow 2.1% this year, above what's considered the U.S. economy's long-run potential and a substantial upgrade from the 1.4% growth seen as of December. At the same time, the unemployment rate is only expected to hit 4% by the end of 2024, barely changed from the current 3.9% level, while a key measure of inflation is projected to keep falling, though at a somewhat slower pace, to end the year at 2.6%.

Source: https://www.reuters.com/markets/rates-bonds/feds-rate-cut-confidence-likely-shaken-not-yet-broken-by-inflation-2024-03-20/

Fed Holds Interest Rates Steady But Signals Cuts Ahead

Natalie Sherman, *BBC*, March 20, 2024 (excerpt)

The US central bank has left its key interest rate unchanged again, while it looks for more evidence that inflation is coming under control.

The decision kept the target range for the Federal Reserve's influential rate in the range of 5.25%-5.5%, the highest in more than two decades.

The Fed is debating whether higher borrowing costs have done enough to ease the pressures pushing up prices. Officials said they still expected to cut rates by the end of the year.

But after raising borrowing costs aggressively in response to soaring prices in 2022, the bank is proceeding cautiously. "We want to be careful and fortunately with the economy growing, the labor market strong and inflation coming down, we can be," Fed chairman Jerome Powell said at a press conference after the Fed's meeting.

Mr. Powell said officials were not overly concerned by some recent data, which has suggested that progress might be stalling.

The inflation rate was 3.2% in the US last month and 3.1% in January.

"We're not going to overreact to these two months of data, nor are we going to ignore them," he said.

Source: https://www.bbc.co.uk/news/business-68619144

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

Biopharma Market Update

Entering Venue at Bio-Europe, Barcelona

Sector Optimism Spreading

The last week of the market saw the XBI move relatively little, and several challenging events hit investors.

For example, Chugai reported negative results on its IL-6 antibody in myasthenia gravis, Enspryng, which was negative for Tourmaline Bio. This one was always a bit of an ambitious hypothesis as myasthenia gravis is thought to be B-cell driven while the IL-6 antibody downregulates the innate pathway.

The level of investment in the PIPE market and the follow-on market remains elevated as investors are focused on putting money to work in better biotech stories. We are also seeing some quality IPO's come up on the calendar.

This week will see us close out the first quarter of the year with the market in a much better place than when the year began.

Importantly, last week saw Fed chairman Powell make it clear that the Fed Funds rate will be coming down barring dramatic negative news. This is the key fundamental that will catalyze change in biotech valuations.

We spoke to several fund groups last week who echoed our own view which is that the rally in biotech is just beginning and that there is huge upside from here. Sentiment is steadily shifting more into the positive column with each week that passes.

A key point is that the Russell 3000 (and other related indices) will be rebalanced based on April values and will become officially changed in June 2024.

Stairwell to the towers of the Sagrada Familia, Barcelona

Sector Tailwinds Picking Up

Because the value of biotech in the market has nearly doubled, this means that the value of biotech in the Russell 3000 will also nearly double when the index is rebalanced.

Countless index funds look to mimic the Russell indices. The likely result is an obvious one: there is *finally* going to be incremental generalist / index buying in our sector.

And it could be a lot given how important index funds have become.

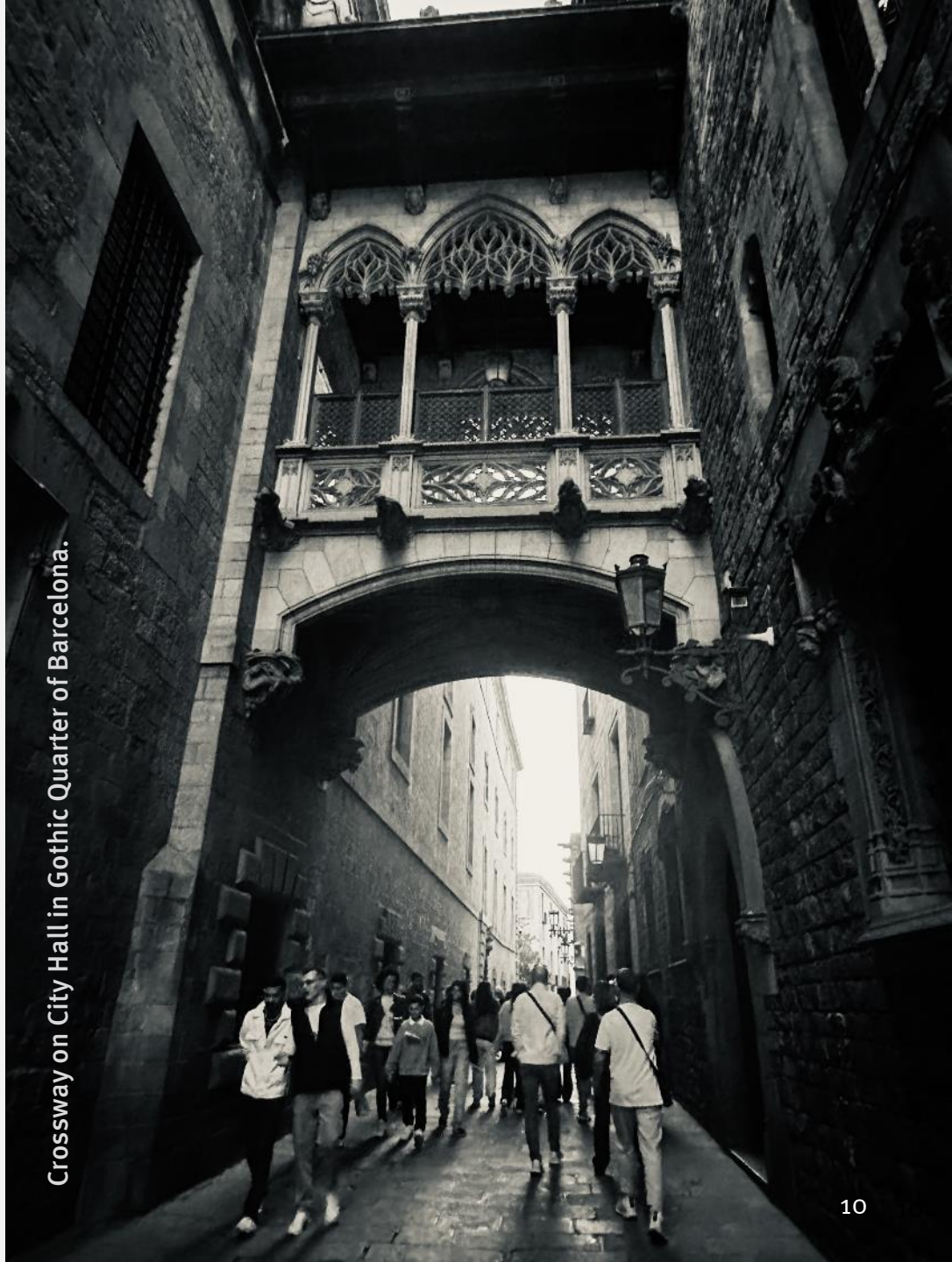
Another key development will be quarterly reports to LP's. Most specialist funds we talk to did quite well in Q1. Like really well. For obvious reasons. The money made on follow-ons and PIPE's alone was plush. (See story on next page).

LP's have already been putting more money to work. Now, with the Q1 reports, we expect even more LP money to come off the sidelines.

What we haven't yet seen is the full impact of the new upcoming crop of IPO's on sector sentiment. The private side of biotech has several interesting stealth companies focused on obesity. Others are working on AI approaches that go well beyond the current crop of AI players in the market.

As these companies go public over the next year, we think the excitement in biotech will only go up.

We will still have some negatives to work through including the China situation and speculative excesses seen in some corners of the market.



Crossway on City Hall in Gothic Quarter of Barcelona.

Biopharma Funds Surge

Stephen Taub, *Institutional Investor*, March 18, 2024 (excerpt)

Most biopharma and life sciences hedge funds fared well in February, extending their winning streak to four months. Several posted double-digit gains for the month, and most others had increases in the mid- to upper single digits. As a result, most of the funds are outperforming the broader market.

The overriding question, of course, is whether these gargantuan gains have peaked or whether this is just the beginning of another extended, prolific upward move reminiscent of the earlier part of the decade. It all depends on a few factors, including whether the Federal Reserve will begin cutting interest rates, which would help small, fledgling companies in general. And will big pharma continue to selectively pay big bucks to acquire companies with promising drug pipelines?

For the moment, fund managers and their investors are savoring the strong showing after biopharma stocks bottomed out in October.

The top performer in February was Avoro Capital Advisors, which rose about 13 percent. It is now up close to 15 percent for the year. Avoro was helped by several of its largest holdings, including No. 3 long Ascendis Pharma, which jumped more than 13 percent last month. Otherwise, two of the four largest longs lost money in February.

Elsewhere, Redmile Group, which lost money in January, gained 11.1 percent in February and is up 8.1 percent for the year. Shares of Krystal Biotech surged 43 percent in February, most of the move coming late in the month when the company reported much better fourth-quarter results than expected. “Our U.S. commercial launch trajectory is tracking closely to that of the best recent rare disease launches, with $50.7 million in net product revenue only six months since approval,” the company stated in a press release. Redmile had gotten a boost from AbbVie’s February acquisition of ImmunoGen, which accounted for more than 17 percent of Redmile’s assets at year-end.

Even Casdin Capital enjoyed a strong February. The hedge fund, which had lagged most of its peers for several years, posted a roughly 11.5 percent gain for the month, matching its return for the year to date. Its largest holdings enjoyed mixed results last month. Among the winners: No. 1 Revolution Medicines, which rose more than 6 percent, and No. 4 Sarepta Therapeutics, up about 7.5 percent.

Meanwhile, RTW Investments surged about 8.75 percent last month and is up nearly 11 percent for the year. This was quite an accomplishment given that most of its largest holdings lost money in February.

RA Capital Management gained 7.2 percent last month and is now up 10.3 percent for the year. Perceptive Advisors jumped 7.1 percent in February, expanding its rise this year to 8.9 percent. It too benefited from Ascendis’s gain; the company was Perceptive’s largest long, accounting for more than 17 percent of assets at year-end.

Soleus Capital Management climbed 6.2 percent for the month, boosting its gain to 14 percent. EcoR1 Capital rose 3.8 percent and is now up 5.7 percent. Averill Partners was up 4.5 percent for the month and nearly 10 percent for the year.

Source: https://www.institutionalinvestor.com/article/2czlsnaonx2mm6iba49og/premium/biopharma-funds-continue-to-surge

Tech Sector Sizzle is an Issue for Biotech

Perhaps the biggest headwind facing stocks in our sector is innovation competition from the tech sector. The generalist manager at a T. Rowe or Fidelity has the choice of which sector to allocate to every day.

Obviously, the tech sector has been offering up some enticing offerings lately. Which may explain the very slow reentry of generalists into our biotech atmosphere. In the last month, us biotech people have given that manager some exciting obesity data from Viking, a new approval in fatty liver disease and some amazing breakthroughs in molecular glues/protein degraders from David Liu's lab. The news this week in mRNA delivery from WangXiao's lab and on the genetic causes of miscarriage is pretty cool too. More broadly, we have amazing innovation underway in a number of fields right now including gene therapy, cell therapy for T1D/neuro conditions, immunology, genetics and cardiometabolism.

However, this type of stuff seems a bit technical and hard to sell to that generalist PM when Nvidia just put out a full suite to make your own humanoid robot. And a freaking good one. Or when rumors last week on OpenAI GPT5 come out and indicate its a lot better than anything we've seen yet in generative AI. It's not too hard to see how this innovation could change our society in a profound way. You can imagine that the generalist PM is paying close attention.

Another interesting development involves Elon Musk's Neuralink –which had a pretty nifty demo last week of a brain-computer interface. You could actually argue that this is a life sciences innovation. After all, companies like GSK are deep in bioelectronics research with their Galvani subsidiary and ActionPotential venture fund. But it's portrayed as tech and our sector has been relatively quiet about the field of bioelectronics. It feels like the next really huge life sciences IPO is going to be Neuralink.

We need to think about how to ramp up the sizzle factor in biotech in order to attract generalists.

Last week saw NVIDIA share GPU technology that will allow anyone to put together their own humanoid robot with it's GPU chips.

The XBI Closed at 93.56 Last Friday (Mar 22), Unmoved for the Week

The XBI is up 5% since the year began. The biotech market was soft again last week as the macro picture weighed on the sector. The yield on the 10-year U.S. Treasury bond was flat while the VIX fell to a sub-13% level.

Biotech Stocks Down Slightly Last Week

Return: Mar 16 to Mar 22, 2024

Nasdaq Biotech Index: -2.1%
Arca XBI ETF: -1.2%
Stifel Global Biotech EV (adjusted): +0.5%*
S&P 500: 2.3%

Return: Jan 1 to Mar 22, 2024

Nasdaq Biotech Index: -0.1%
Arca XBI ETF: +4.8%
Stifel Global Biotech EV (adjusted): +27%*
S&P 500: +9.7%

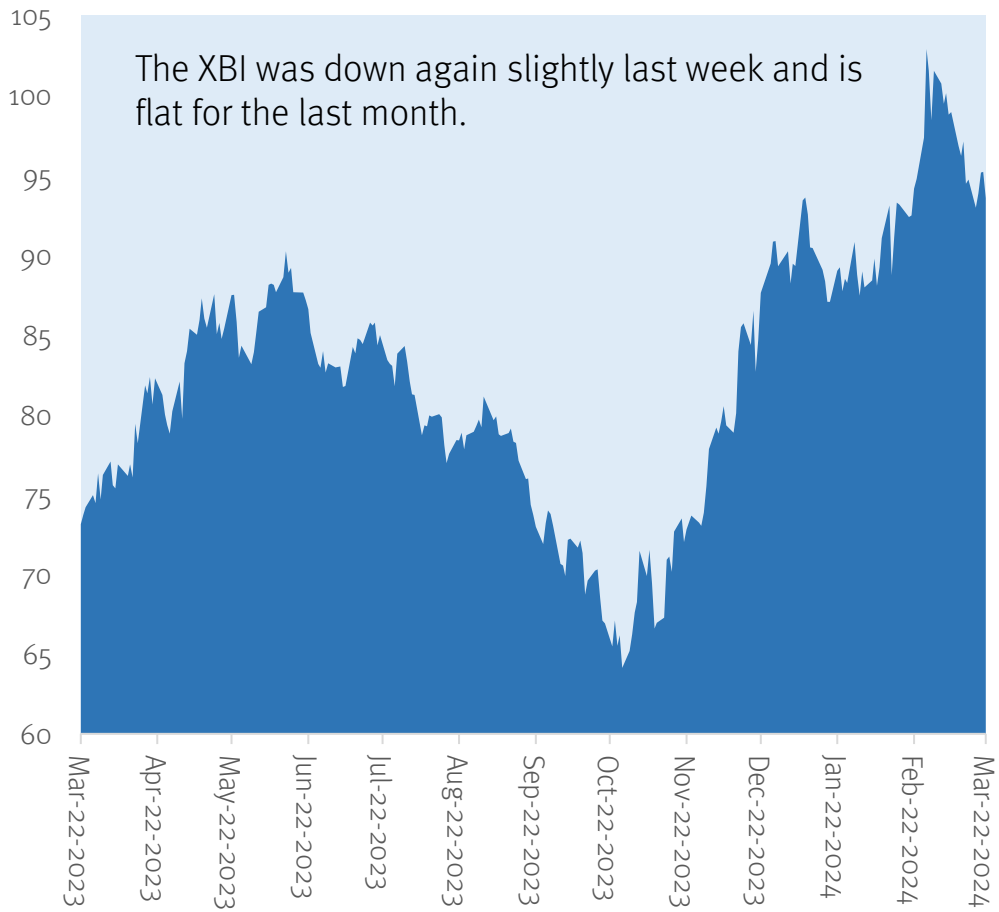
VIX Down

Jan 20, 2023: 19.9%
May 26, 2023: 18.0%
July 21, 2023: 13.6%
Sep 29, 2023: 17.3%
Dec 29, 2023: 12.45%
Jan 26, 2024: 13.26%
Feb 23, 2024: 13.5%
Mar 22, 2024: 12.9%

10-Year Treasury Yield Down

Jan 20, 2023: 3.48%
May 26, 2023: 3.8%
July 21, 2023: 3.84%
Sep 29, 2023: 4.59%
Dec 29, 2023: 3.88%
Jan 26, 2024: 4.15%
Feb 23, 2024: 4.26%
Mar 22, 2024: 4.27%

XBI, March 22, 2023 to March 22, 2024



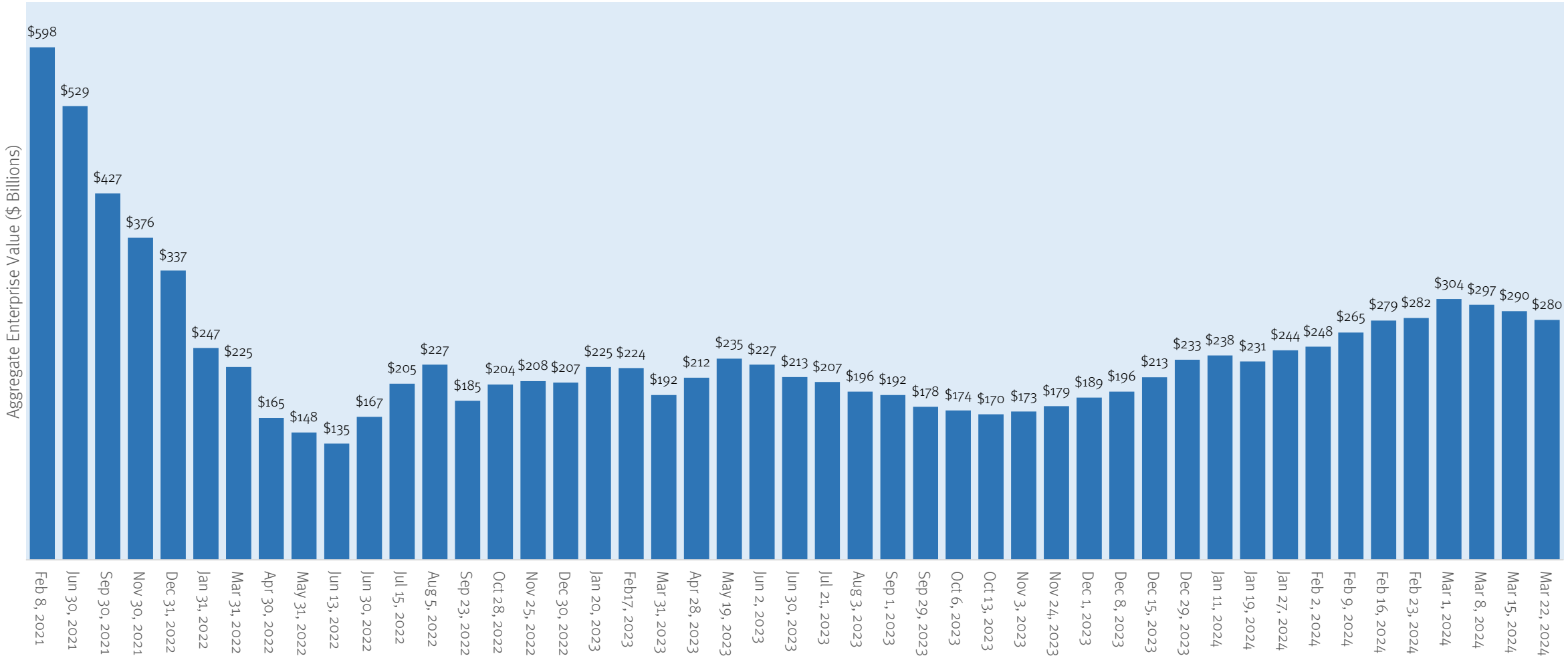
* Change by enterprise value. The adjusted number accounts for the effect of exits and additions via M&A, bankruptcies and IPOs.

Source: S&P Capital IQ and Stifel analysis

Total Global Biotech Sector Value Rose 0.5% Last Week*

The total enterprise value of the global biotech sector is up 27% year-to-date on an addition/exit corrected basis.

Total Enterprise Value of Publicly Traded Global Biotech, Feb 8, 2021 to Mar 22, 2024 ($ Billions)



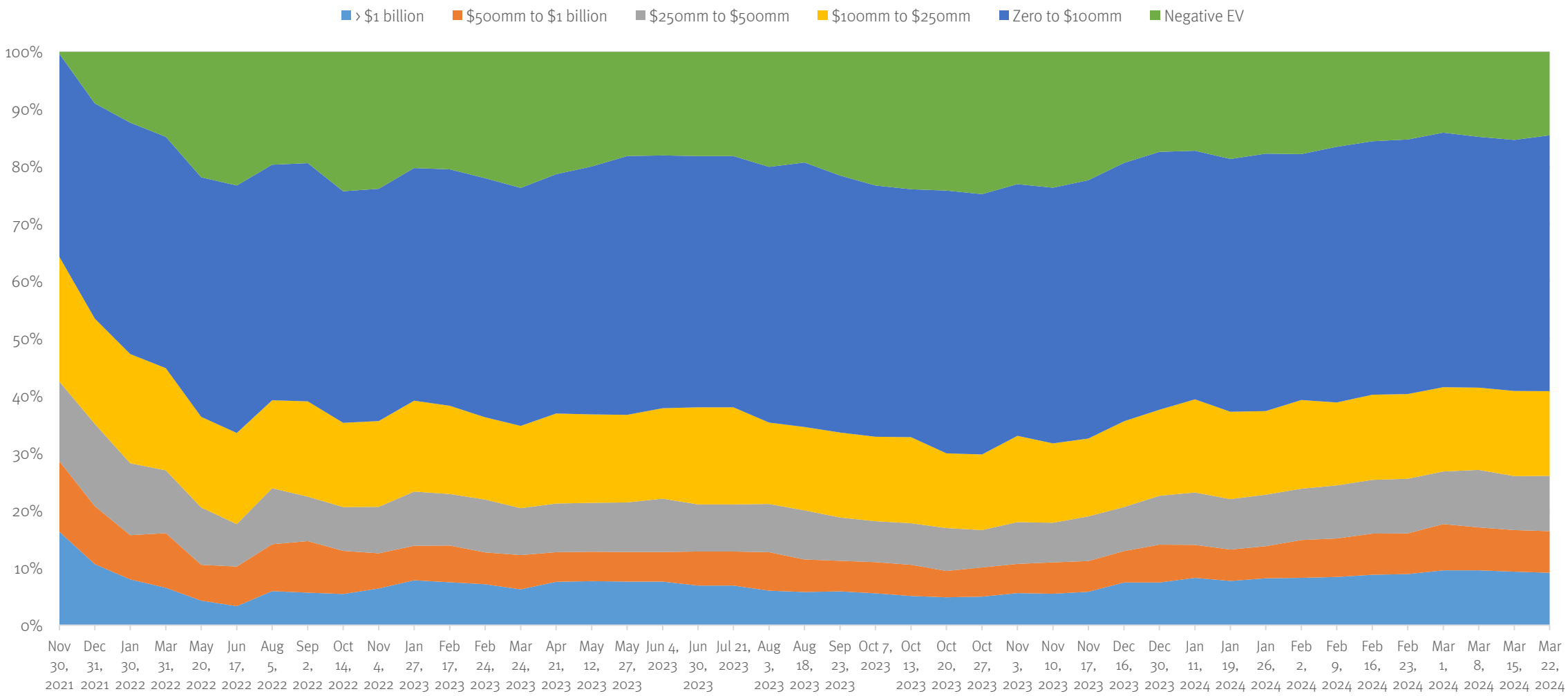
Source: CapitalIQ. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

* The EV shown in the chart would suggest a loss in value, but Karuna and LianBio both came off the list last week. After adjusting for these deletions, the value of the remaining companies rose slightly.

Global Biotech Neighborhood Analysis

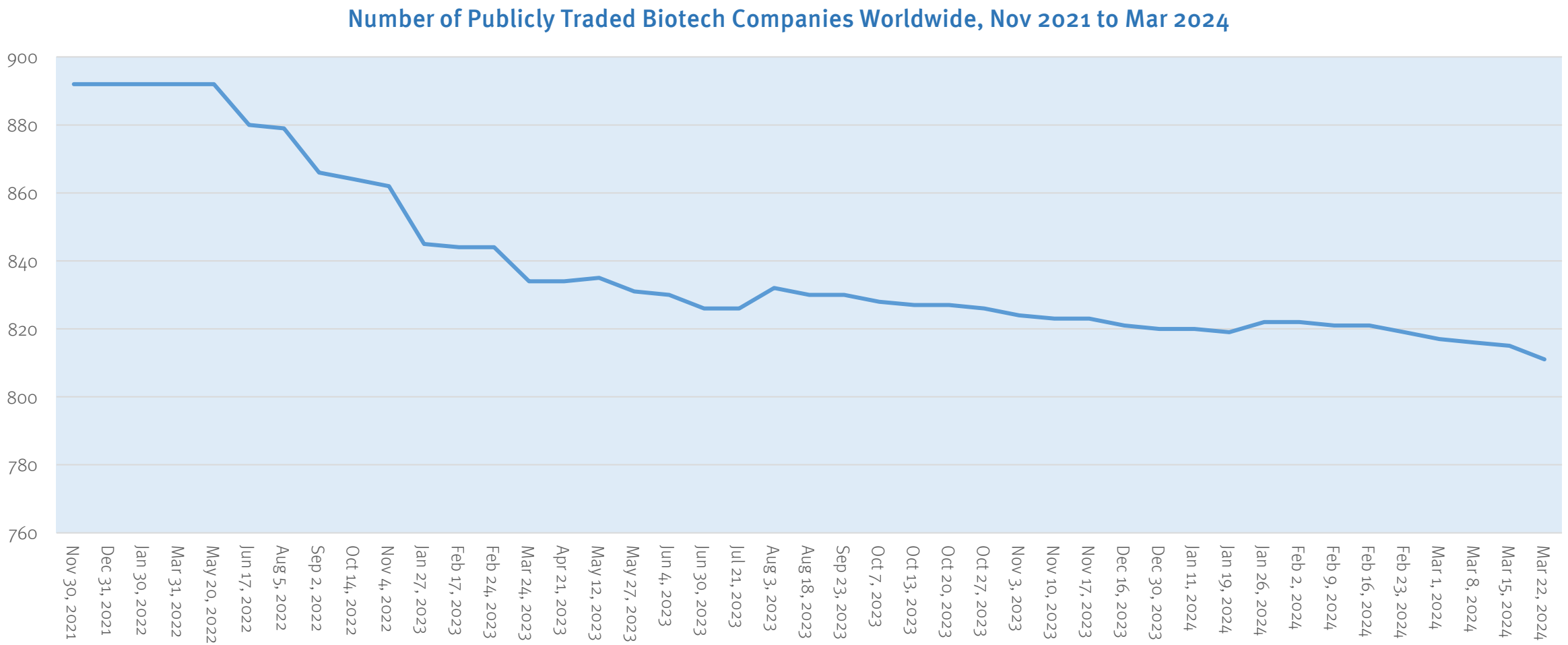
The population of negative EV companies continues to shrink. The population of $1bn+ companies dropped as Karuna came out last week.

Global Biotech Universe by Enterprise Value Category, Nov 30, 2021 to Mar 22, 2024



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

Public Biotech Count Continues to See Attrition



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

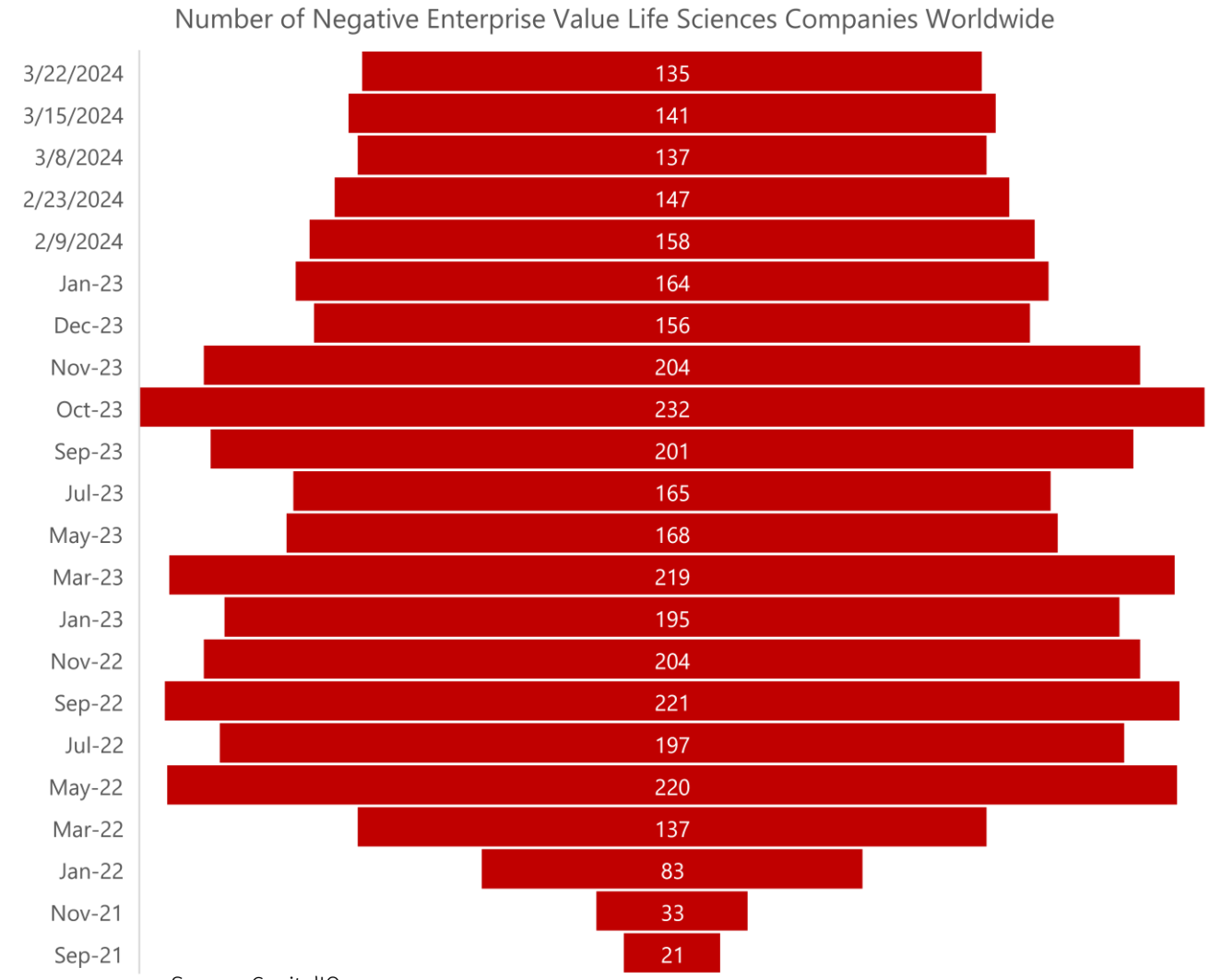
Life Sciences Sector Total Value Dropped 0.2% Last Week

Last week saw the life sciences sector lose $19 billion in value. The worst performing sectors were API, HCIT and pharma services. CDMO's faired relatively well.

Sector	Firm Count	Enterprise Value (Mar 22, 2024, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	81	$78,583	-2.4%	-3.3%	-0.8%
Biotech	800	$279,537	-0.5%	3.4%	-5.1%
CDMO	40	$153,533	2.0%	2.3%	-16.1%
Diagnostics	81	$275,657	0.7%	2.3%	3.5%
OTC	30	$28,288	0.6%	0.7%	-1.9%
Commercial Pharma	719	$6,226,884	-0.3%	-0.3%	12.6%
Pharma Services	39	$198,842	-1.6%	0.8%	-2.3%
Life Science Tools	51	$734,623	1.0%	3.7%	0.7%
Medical Devices	181	$1,707,838	-0.3%	-1.0%	7.7%
HCIT	10	$19,862	-1.8%	-2.5%	-25.8%
Total	**2,032**	**$9,691,630**	**-0.2%**	**0.1%**	**10.2%**

Source: CapitalIQ

Number of Negative Enterprise Value Life Sciences Companies Declined Last Week



Source: CapitalIQ

Despite the flat market, investors are continuing to buy up companies with negative enterprise values.

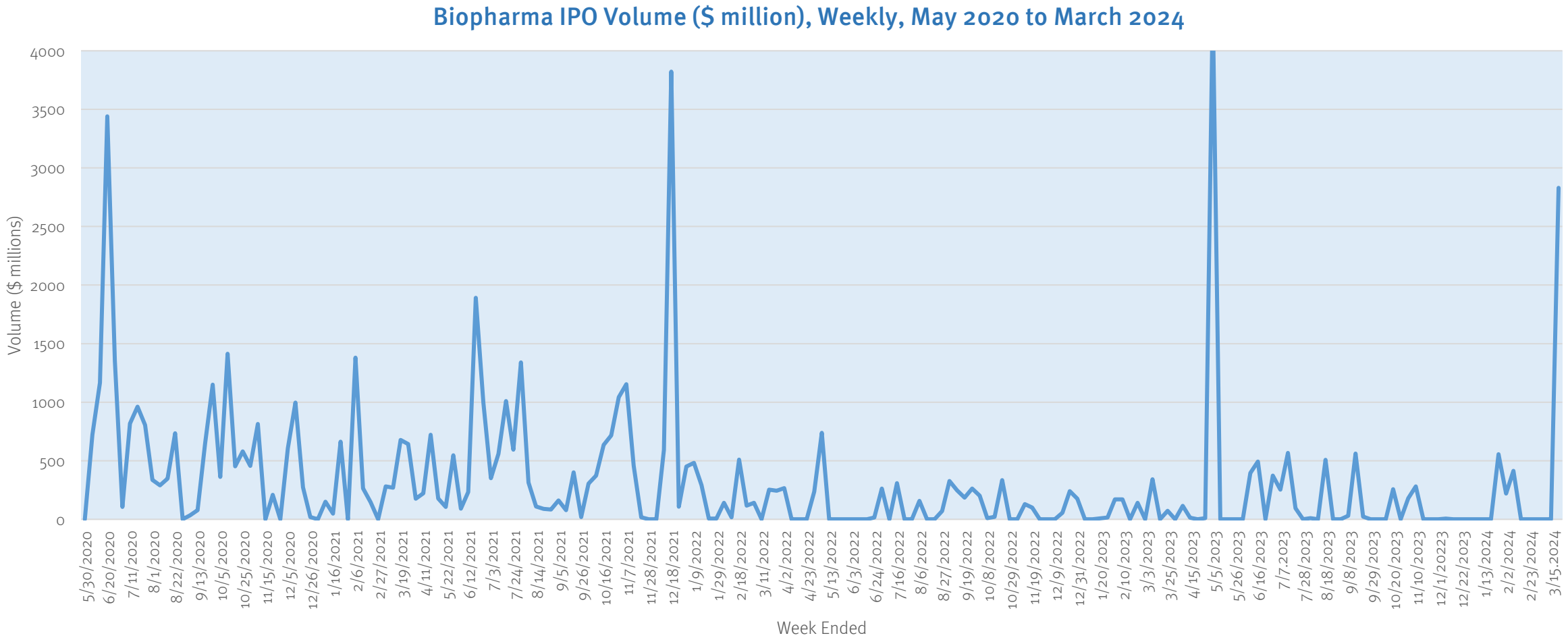
The count of negative EV life sciences companies worldwide fell from 141 from 135 last week.

Capital Markets Update

Stained glass windows, Sagrada Familia, Barcelona.

IPO Market Active Outside the U.S. Last Week

Last week saw Galderma raise $2.8 billion in its market debut on the SIX exchange in Switzerland and Qyuns raise $30mm in its debut on the Hong Kong Stock Exchange.



Source: Data from CapitalIQ and Stifel research.

Galderma Raises $2.8Bn in IPO: Shares Jump 18% on Debut

Zug, Switzerland – March 21, 2024 – Galderma Group AG, the pure-play dermatology category leader, today announces the pricing of its Initial Public Offering at CHF 53 per share, at the top of the announced price range.

Source: https://www.galderma.com/news/galderma-prices-ipo-chf-53-share-and-will-start-trading-six-swiss-exchange-tomorrow

History Suggests Now is a Good Time to Buy IPOs

David Wainer, *Wall Street Journal*, March 14, 2024 (excerpt)

The best time to make money in biotech is usually during periods of cautious optimism. There are strong signs that right now might be one of those moments.

We are now past the downturn but not yet in bubble territory. Biotech stocks started to bounce back during the second half of last year as the Federal Reserve signaled it was done raising interest rates, with cuts penciled in for 2024.

Historically, long-term returns are better when the industry is recovering but not yet sizzling, according to an analysis by University of Florida finance professor Jay Ritter going back to 1983. While there are exceptions, and single-stock performances can skew numbers heavily in any given year, the first-day move, which serves to highlight enthusiasm in the sector, seems to be predictive of long-term performance. When initial demand for IPOs is sky-high and stocks surge on the first day of trading, they tend to perform poorly in subsequent years. When demand is more muted, IPOs tend to do better.

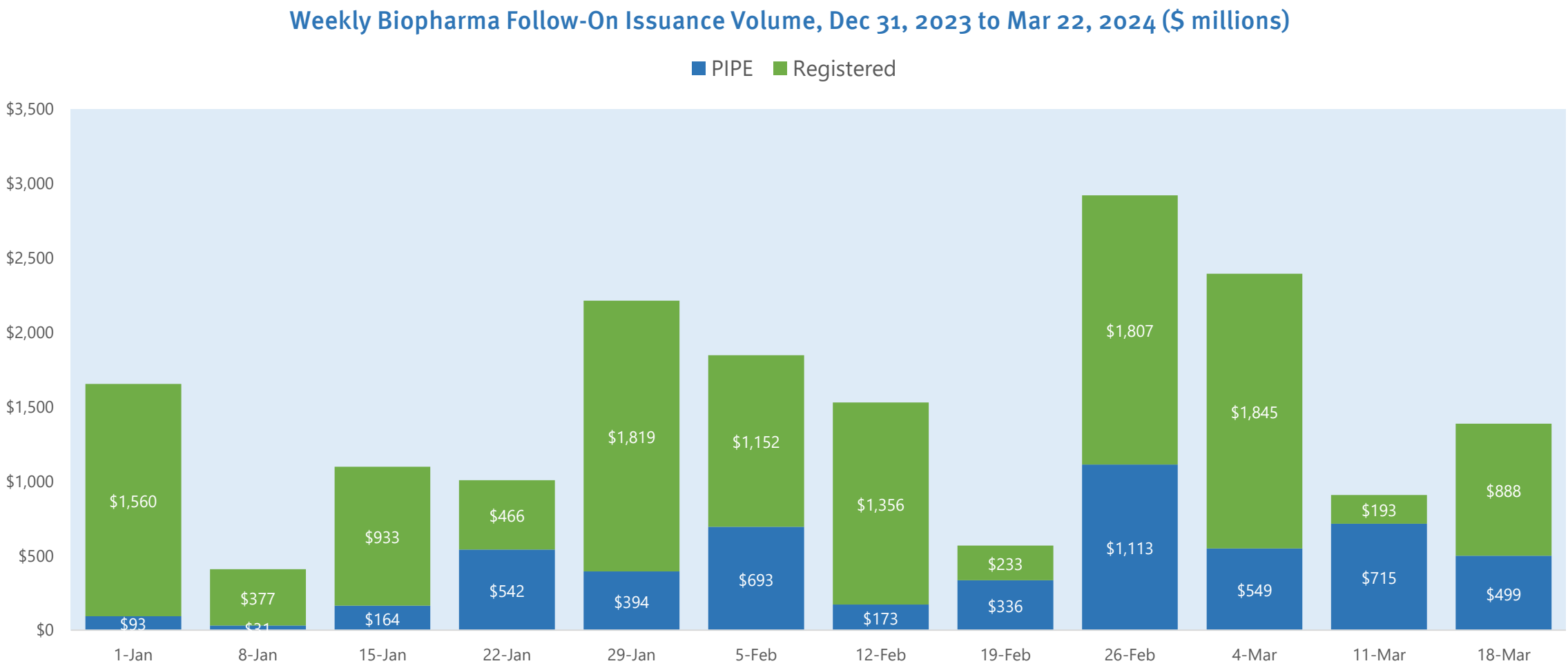
At the height of the dot-com bubble, in 2000, 50 life-science companies went public and rose an average of 32% in their first day of trading. Those stocks went on to deliver negative three-year returns, as measured from the first close, according to Ritter's analysis. Contrast that with 2004, when 30 biotech companies went public. Their initial first-day gain was lower, rising an average of 7.8%. But within three years, investors saw a 48% return from the first close. A similar thing happened after the 2008 crash. In 2010, when financing started to come back, 11 biotech companies went public, rising an average of only 0.9% on their first day. From the first close, though, their three-year return was 51%.

"There does seem to be a pattern," Ritter says. "When public-market investors are enthusiastic, as reflected in big first-day jumps, the long-run results have been very poor."

Source: https://www.wsj.com/tech/biotech/why-that-hot-biotech-ipo-could-be-a-winner-518c3095

Last Week Saw $1.4 Billion in Follow-On Issuance

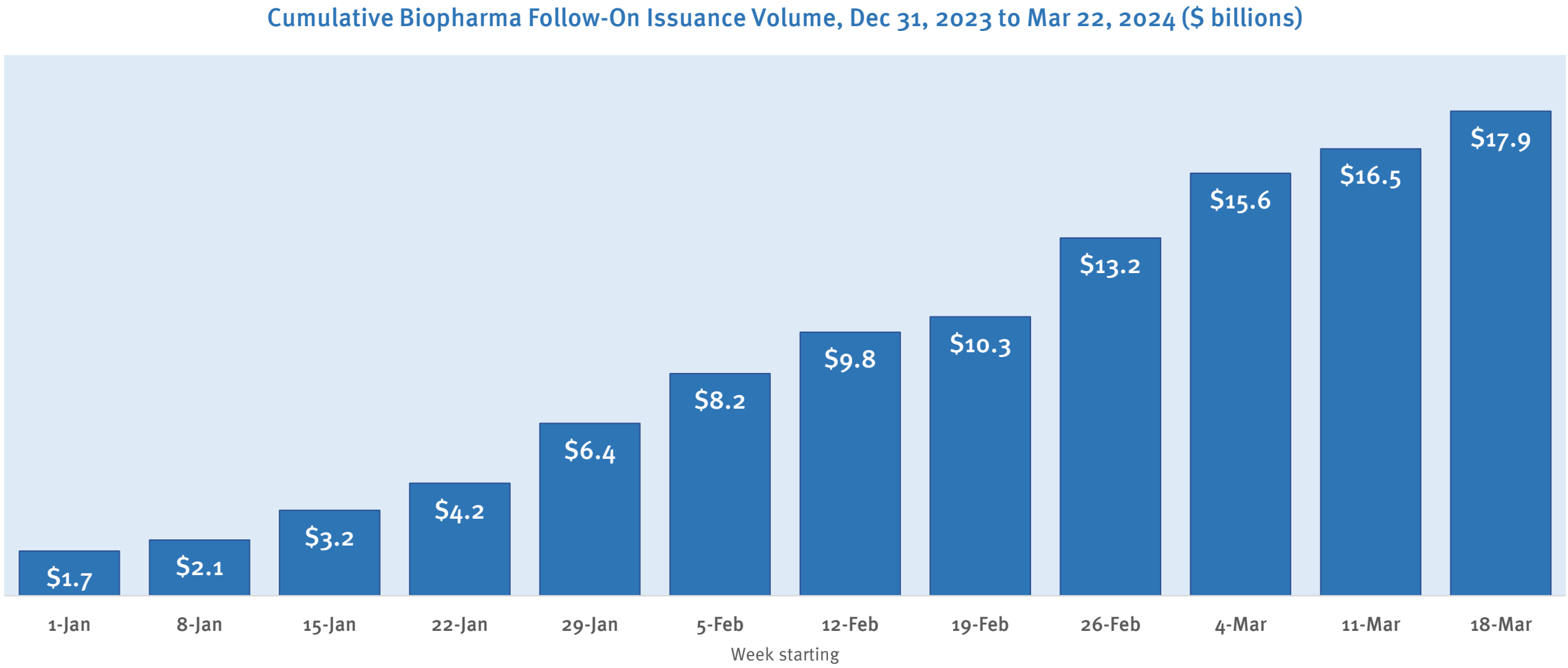
With the XBI flat last week the pace of follow-on offerings picked up from the previous week but is down from the first week of the month when the market was rising. The largest offering was a $600mm raise by Madrigal on the heels of its FDA approval of Rezdiffra for MASH.



Source: Data from CapitalIQ and Stifel research.

Total Follow-On Volume Now at $18 Billion for the Year

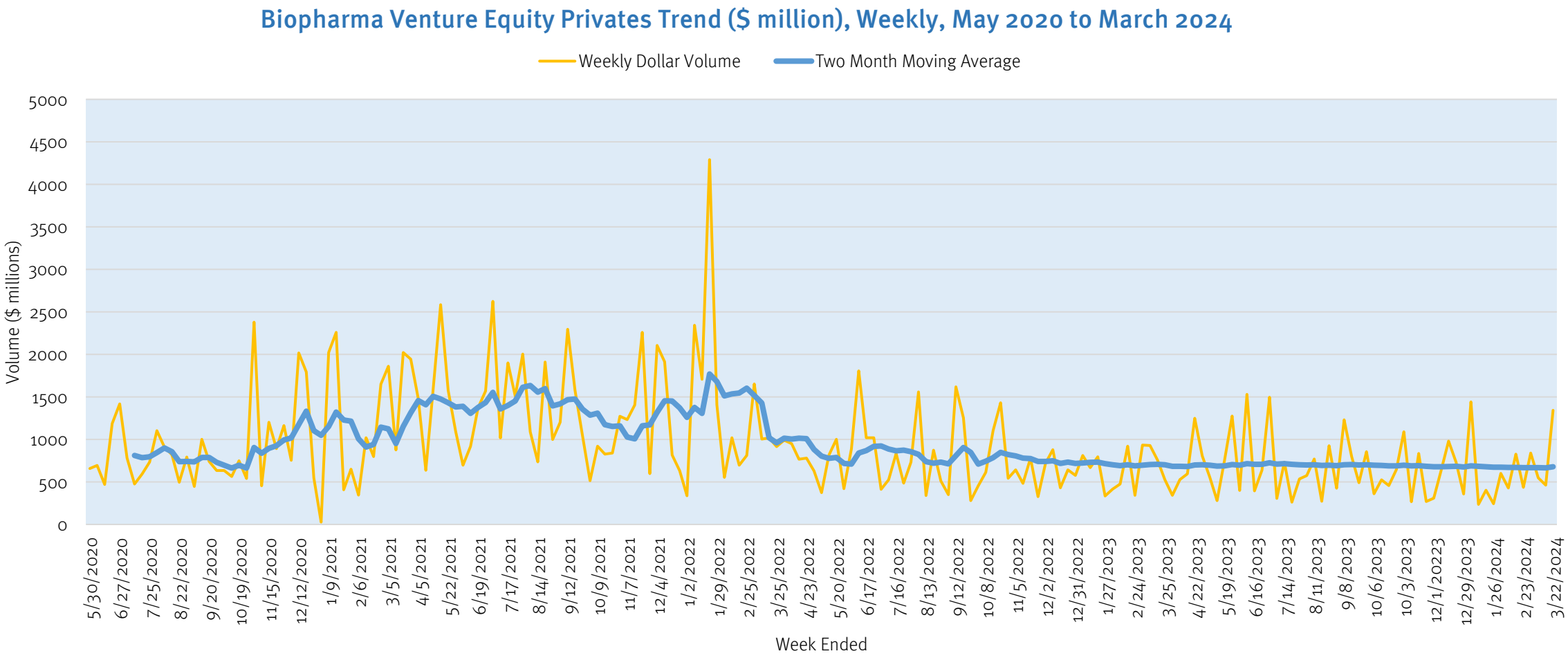
Follow-on Volume has been running at a level of $1.5 billion a week for the first twelve weeks of 2024.



Source: Data from CapitalIQ and Stifel research.

Venture Private Volume Spiked Last Week

We saw $1.4 billion in venture private raises last week. The largest raise was a $400mm+ for Mirador Therapeutics led by Arch Ventures.



Source: Data from CapitalIQ, Crunchbase.

Mirador Therapeutics Raises $400mm+ to Accelerate the Next Generation of Precision Medicines for Immune-Mediated Diseases

SAN DIEGO--(BUSINESS WIRE), March 21, 2024 -- Mirador Therapeutics, Inc. (Mirador) announced its launch today. Founded by Mark C. McKenna and led by several former executives of Prometheus Biosciences (acquired in 2023 by Merck for $10.8 billion), Mirador aims to revolutionize precision medicine for immune-mediated inflammatory and fibrotic diseases by leveraging its proprietary Mirador360TM development engine to rapidly advance multiple programs. Mirador has raised more than $400 million in financing led by ARCH Venture Partners, with early investments from OrbiMed and Fairmount. Other premier life sciences investors also participated, including Fidelity Management & Research Company, Point72, Farallon Capital Management, Boxer Capital, TCGX, Invus, Logos Capital, Moore Strategic Ventures, Blue Owl Healthcare Opportunities, Sanofi Ventures, Woodline Partners LP, Venrock Healthcare Capital Partners, RTW Investments and Alexandria Venture Investments.

“The I&I field is in need of better, novel therapeutics as well as new R&D approaches that target enriched patient populations for improved probability of success in the clinic,” said Kristina Burow, Mirador board member and managing director of ARCH Venture Partners. “The Mirador team has an outstanding track record of success in precision immunology, and we are well on our way to building a company that will make a lasting impact on the lives of millions of patients suffering from a broad range of immune-mediated inflammatory and fibrotic diseases.”

Mirador’s focus is on developing first-in-class or best-in-class precision medicines. To accelerate development, Mirador utilizes Mirador360, its proprietary precision development engine that leverages recent breakthroughs in human genetics and cutting-edge data science.

mirador THERAPEUTICS

“At Mirador, we envision a bold new era of precision medicine for immune-mediated inflammatory and fibrotic diseases driven by speed and superior development accuracy. The industry has only scratched the surface of utilizing advances in human genetics – coupled with exponential progress in machine learning – to accelerate the development of precision therapies for patients who need them the most. With a proven team, distinguished board of directors, leading healthcare investors and proprietary data-driven approach, we aim to create a leading precision medicine company at scale to provide important new treatment options for patients.”

Mark McKenna
Chief Executive Officer
Mirador Therapeutics

Source: https://www.businesswire.com/news/home/20240321262942/en/Mirador-Therapeutics-Launches-to-Accelerate-the-Next-Generation-of-Precision-Medicines-for-Immune-mediated-Diseases

Mirador is the Largest Private Venture Deal in 2024 by Far

Up until last week, private venture deal volume has been slow in 2024. Then, we saw four $100mm deals in rapid succession, capped by Mirador. The statistics below indicate that, at the present run rate, 2024 is shaping up to be #2 in the count of $100mm+ venture rounds.

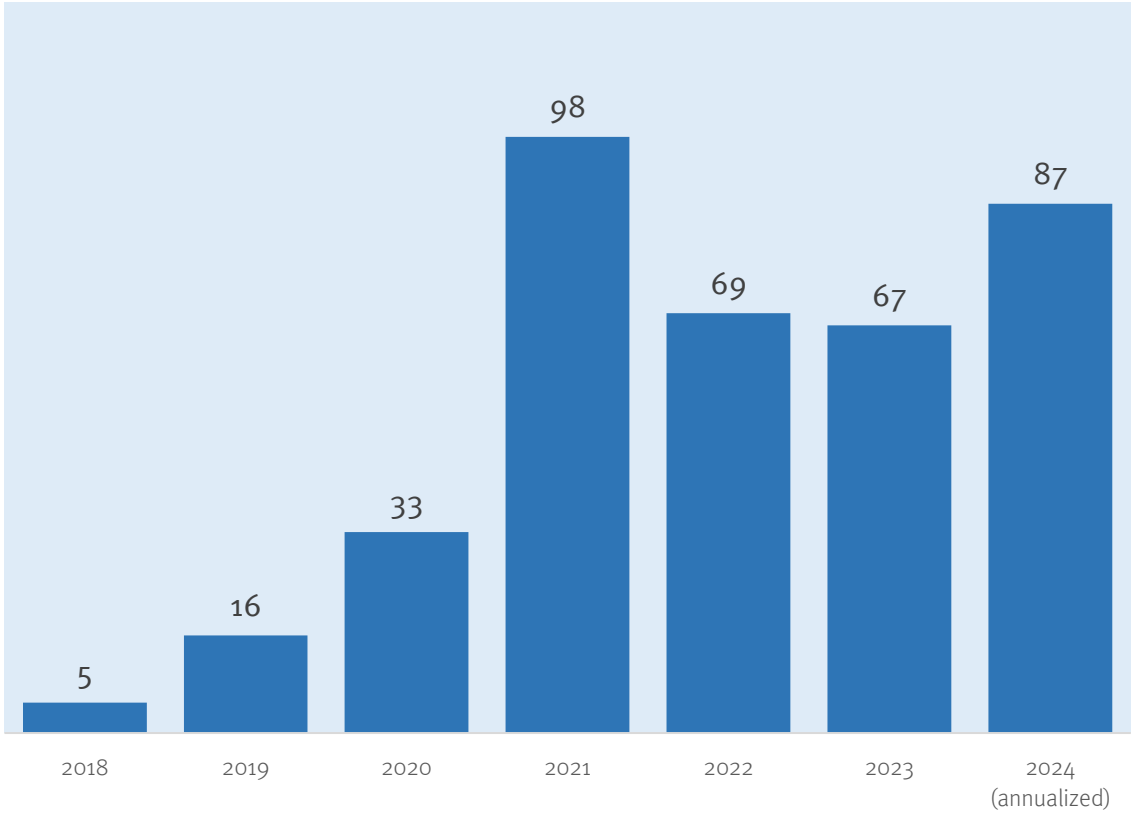
List of private venture deals that raised $100mm or more

Jan 1, 2024 to Mar 22, 2024

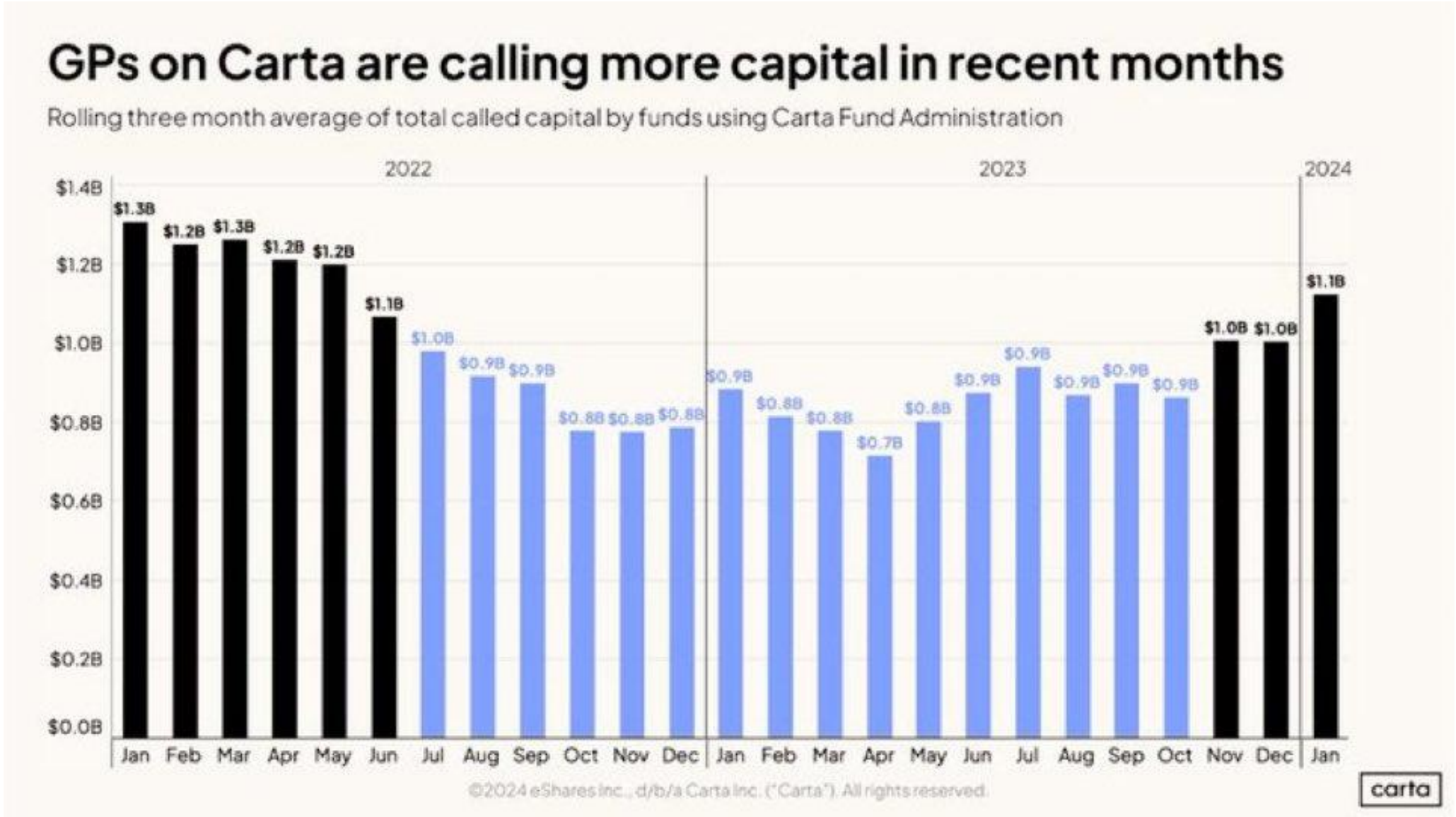
Date	Issuer	Amount ($mm)
3/21/2024	Mirador Therapeutics	$400
3/20/2024	Capstan Therapeutics	$175
3/20/2024	Clasp Therapeutics	$150
3/19/2024	Engrail Therapeutics, Inc.	$157
3/14/2024	Tubulis Technologies	$139
3/6/2024	Sionna Therapeutics, Inc.	$182
3/6/2024	Rakuten Medical	$119
3/1/2024	Fog Pharmaceuticals, Inc.	$145
2/29/2024	Blossomhill	$100
2/28/2024	Simtra BioPharma Solutions	$250
2/14/2024	Latigo Biotherapeutics, Inc.	$135
2/13/2024	BioAge Labs	$170
2/13/2024	ProfoundBio (Suzhou) Co., Ltd.	$112
2/12/2024	Alys Pharmaceuticals	$100
2/8/2024	Neurona Therapeutics, Inc.	$120
1/30/2024	COUR Pharmaceuticals	$105
1/30/2024	Inari Agriculture, Inc.	$103
1/6/2024	Jixing Pharmaceutical Technology	$162
1/4/2024	OnCusp Therapeutics	$100

Source: DealForma, S&P CapitalIQ and Stifel Research

Count of $100mm+ Biopharma Venture Deals, 2018 to March 2024

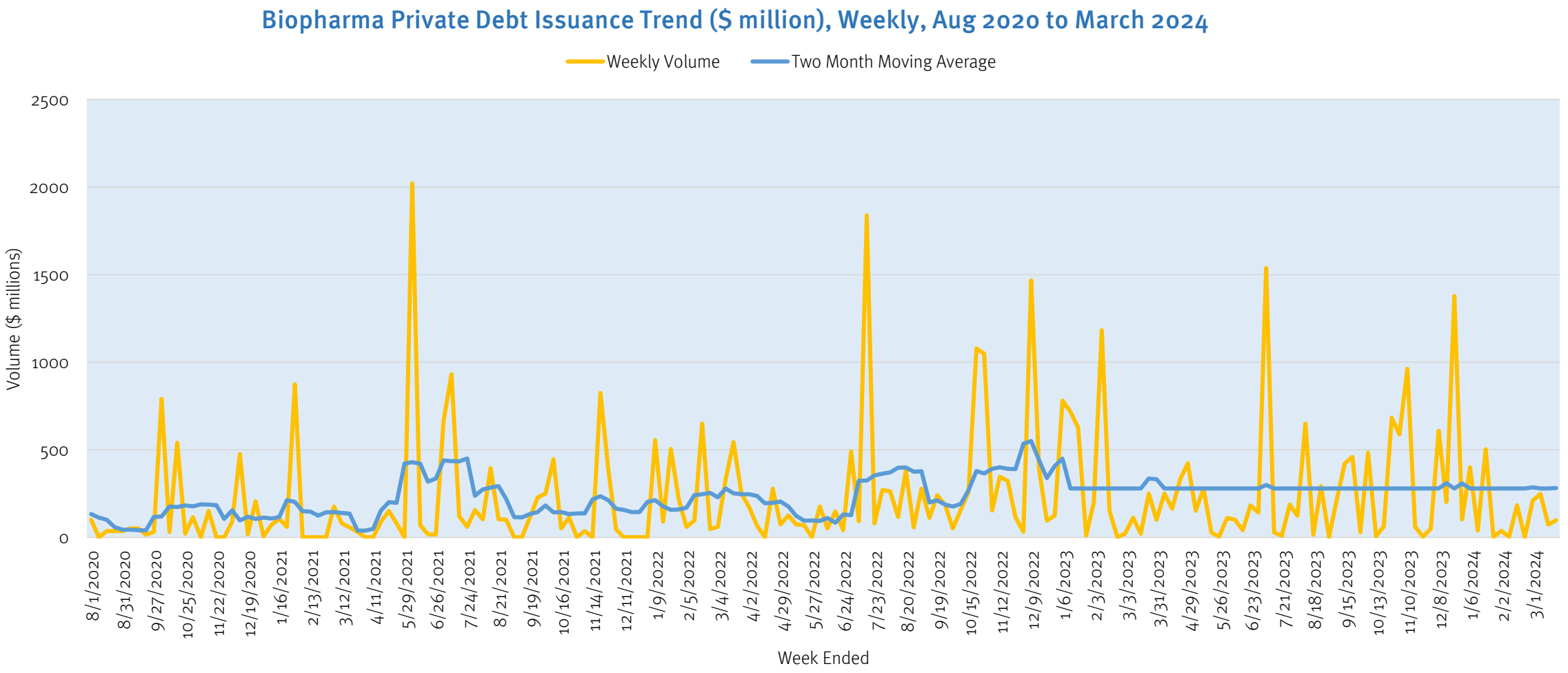


Venture Funding Activity Across U.S. Economy is Picking Up



Biopharma Private Debt Placement Market Did $97 Million in Volume

The debt privates market saw Bluebird raise $75mm via Hercules.



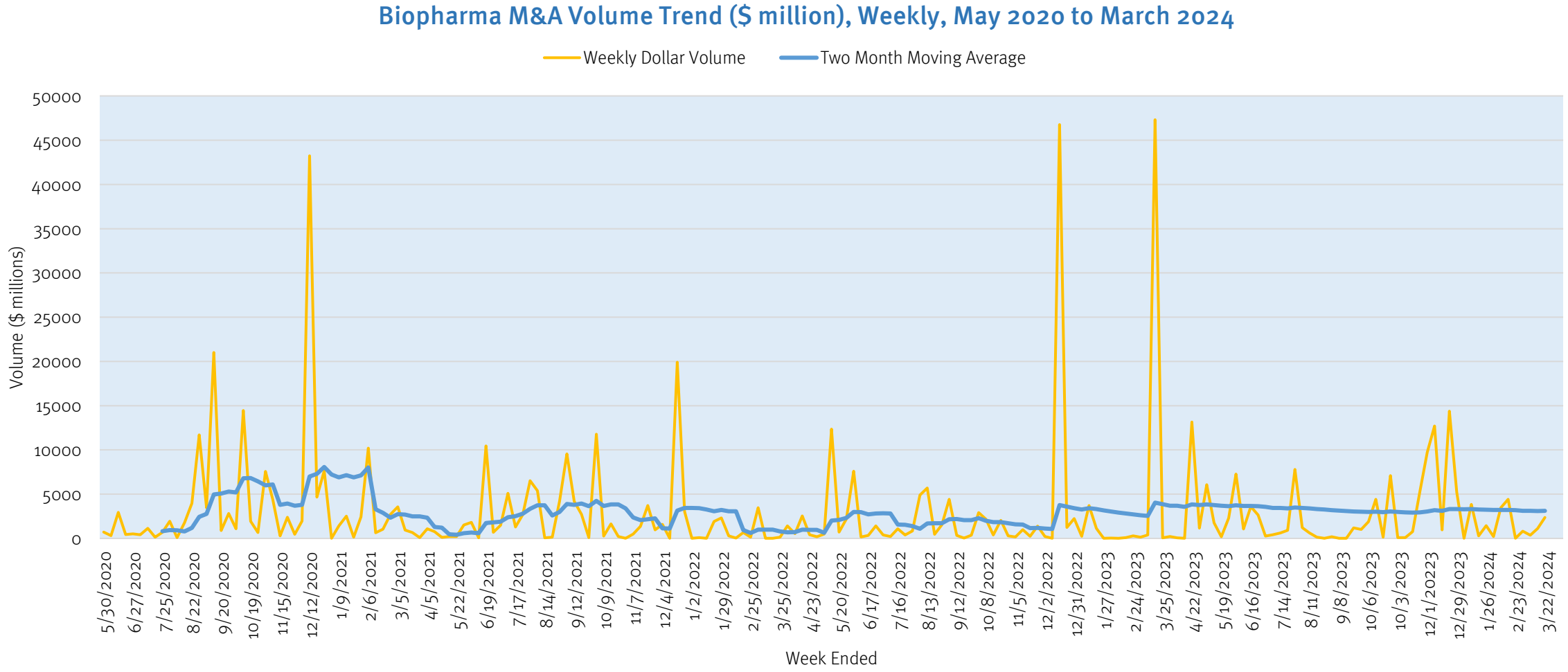
Source: Data from CapitalIQ, Crunchbase.

Deals Update

Barcelona Skyline

Last Week Saw Eight M&A and Asset Deals for Volume of Approximately $3.6 Billion

The largest deals last week were AZ's acquisition of Fusion for $2 billion upfront and Lonza's acquisition of Genentech's Vacaville site for $1.2 billion.



Source: S&P, CapitalIQ

AstraZeneca to Acquire Fusion Pharma

Press Release, Mar 19, 2024

AstraZeneca has entered into a definitive agreement to acquire Fusion Pharmaceuticals Inc., a clinical-stage biopharmaceutical company developing next-generation radioconjugates (RCs). The acquisition marks a major step forward in AstraZeneca delivering on its ambition to transform cancer treatment and outcomes for patients by replacing traditional regimens like chemotherapy and radiotherapy with more targeted treatments.

RCs have emerged as a promising modality in cancer treatment over recent years. These medicines deliver a radioactive isotope directly to cancer cells through precise targeting using molecules such as antibodies, peptides or small molecules. This approach has many potential advantages compared to traditional radiotherapy including minimising damage to healthy cells and enabling access to tumours not reachable through external beam radiation.

This acquisition complements AstraZeneca's leading oncology portfolio with the addition of the Fusion pipeline of RCs, including their most advanced programme, FPI-2265, a potential new treatment for patients with metastatic castration-resistant prostate cancer (mCRPC). FPI-2265 targets prostate-specific membrane antigen (PSMA), a protein that is highly expressed in mCRPC, and is currently in a Phase II trial.

The acquisition brings new expertise and pioneering R&D, manufacturing and supply chain capabilities in actinium-based RCs to AstraZeneca. It also strengthens the Company’s presence in and commitment to Canada.

Source: https://www.astrazeneca.com/media-centre/press-releases/2024/astrazeneca-to-acquire-fusion.html

Fusion Pharmaceuticals Inc.

AstraZeneca is paying nearly a 100% premium to acquire Fusion Pharma.

The total value before CVR is approximately $2 billion.

This is the second major acquisition of a radiopharma player in three months.

Market observers noted that AZ is picking up meaningful manufacturing infrastructure as did BMS with Rayze and Lilly with Point.

This is AstraZeneca’s third significant acquisition in three months.

There is significant scarcity value of remaining radiopharma companies – particularly those with manufacturing infrastructure.

Lonza Signs Agreement to Acquire Large-Scale Biologics Site in Vacaville (US) from Roche for $1.2 Billion

Basel, Switzerland, 20 March 2024

Lonza, a global manufacturing partner to the pharmaceutical, biotech and nutraceutical markets, today announced it has signed an agreement to acquire the Genentech large-scale biologics manufacturing site in Vacaville, California (US) from Roche for USD 1.2 billion.

The acquisition will significantly increase Lonza's large-scale biologics manufacturing capacity to meet demand for commercial mammalian contract manufacturing from customers with existing commercial products, and molecules currently on the path to commercialization within the Lonza network. The Vacaville (US) facility currently has a total bioreactor capacity of around 330,000 liters, making it one of the largest biologics manufacturing sites in the world by volume. Under the agreement, approximately 750 Genentech employees at the Vacaville (US) facility will be offered employment by Lonza.

Demand for capacity for commercial biologics is expected to remain high across the CDMO industry as innovative new therapies reach approval. In this context, the acquisition of the Vacaville (US) site will provide Lonza's customers with immediate access to significant new capacity in the United States, currently the world's largest pharmaceutical market. It will also create a significant West Coast commercial manufacturing presence, complementing Lonza's existing Biologics site on the East Coast, in Portsmouth (US), as well as its international network across Europe and Asia.

Lonza plans to invest approximately CHF 500 million in additional CAPEX to upgrade the Vacaville (US) facility and enhance capabilities to satisfy demand for the next generation of mammalian biologics therapies. The products currently manufactured at the site by Roche will be supplied by Lonza, with committed volumes over the medium term, phasing out over time as the site transitions to serve alternative customers.

Jean-Christophe Hyvert, President, Biologics, Lonza, commented: "The Vacaville site is a highly valuable strategic acquisition that will make capacity immediately available for our customers and unlock future growth for our Biologics division. It will support us in providing a commercialization path to existing customers and incremental large-scale commercial capacity to our partners. We have deep and long-standing industrial expertise in delivering commercial scale manufacturing services for our customers' therapies. In combining this with the strong legacy of the Vacaville facility, its highly skilled colleague community and its proven track record on quality, we are excited to take our leading large-scale mammalian offering to its next chapter of growth."

Source: https://www.lonza.com/news/2024-03-20-07-00

Eliem Cuts in on Tango, Proposing Acquisition After Strategic Review

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

Eliem Therapeutics is sashaying away from the brink of closure, joining hands with a private biotech identified as "Tango" after reviewing strategic alternatives.

RA Capital-backed Eliem is set to snap up Tango, another company that has funds affiliated with RA Capital, according to Securities and Exchange Commission documents filed March 18. Currently, there's no webpage for a private biotech called Tango and the company is not listed as part of RA's portfolio.

According to the proposed transaction, Eliem will issue common stock to Tango's equityholders in exchange for all outstanding equity of Tango, with the company becoming a wholly owned Eliem subsidiary. The proposal means that Tango shareholders would own 15.4% of equity of the company immediately before the deal closes, according to SEC documents.

The proposed exchange ratio values Eliem initially at $110 million right when the deal closes, while Tango valued at $20 million.

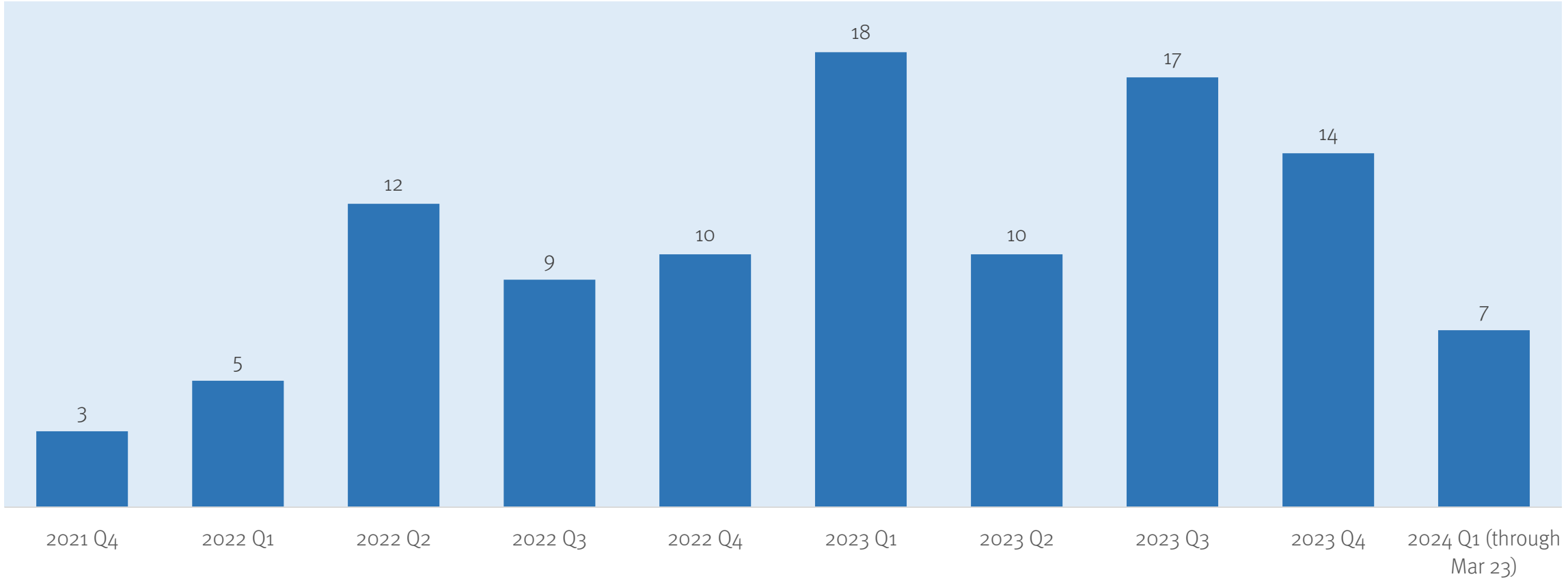
If the acquisition goes through, a concurrent private placement of the new company's common stock would be put into effect. Funds affiliated with RA Capital are expected to purchase a portion of the securities in the concurrent investment, according to SEC filings.

Source: https://www.fiercebiotech.com/biotech/eliem-knows-it-takes-two-tango-dancing-away-closure-new-acquisition

Pace of Biopharma's Exploring Strategic Alternatives is Easing

We count 34 companies exploring strategic alternatives today. This is down substantially from a count of 49 last December (just three months ago). As shown in the chart, fewer companies are announcing that they are seeking strategic alternative this quarter versus previous periods. Shell companies are being used for reverse merger + PIPE deals this year with speed as capital to fund the deals is more abundant.

Announcements that Biopharma Companies Are Exploring "Strategic Alternatives", Q4 2021 to Q1 2024



Source: Stifel analysis of press releases and SEC disclosures.

List of Companies Exploring Strategic Alternatives Today

We count 34 biopharma companies that are exploring strategic options as of Mar 22, 2024. This number is down from levels seen last December

Ticker	Company	Announcement Date	Last Cash ($mm)	Enterprise Value ($mm, Mar 22, 2024)
CYCC	Cyclacel*	3/20/2024	$3.4	-$0.5
KA	Kineta	2/29/2024	$7.6	$1.0
SYBX	Synlogic	2/9/2024	$47.7	-$9.5
WINT	Windtree	1/31/2024	$7.4	$13.1
PULM	Pulmatrix	1/9/2024	$21.3	-$6.6
PRTG	Portage Bio	1/4/2024	$5.3	$4.2
ALVR	Allovir	12/22/2023	$183.9	-$72.5
HEPA	Hepion Pharmaceuticals	12/7/2023	$19.3	-$4.1
KNE	Kane Biotech	11/28/2023	$1.2	$16.9
BCEL	Atreca	11/16/2023	$21.4	-$17.1
ADPT	Adaptive Biotech	11/9/2023	$346.4	$353.0
KTRA	Kintara Therapeutics	10/31/2023	$0.8	$13.1
ATHX	Athersys	10/16/2023	$1.0	$18.0
GLTO	Galecto	9/26/2023	$33.2	-$11.6
TCRT	Alaunos Therapeutics	8/14/2023	$11.9	$19.0
GRTX	Galera Therapeutics	8/14/2023	$28.4	$136.0
SLRX	Salarius Pharmaceuticals	8/8/2023	$5.9	-$3.2
AVTX	Avalo Therapeutics	8/3/2023	$10.2	-$4.3
NBSE	Neubase	8/3/2023	$13.8	-$3.4
VXL	Vaxil Bio	8/2/2023	$0.7	$0.3
RKDA	Arcadia Biosciences	7/20/2023	$15.7	-$12.1
PIRS	Pieris Pharma	7/18/2023	$44.8	-$12.7
SPEX	Spexis	6/30/2023	$1.0	$13.4
AUPH	Aurinia Pharmaceuticals	6/29/2023	$350.4	$466.0
BLPH	Bellorophon Therapeutics	6/24/2023	$4.4	-$3.7
GMDA	Gamida Cell	5/15/2023	$60.4	$76.1
BLCM	Bellicum Therapeutics	3/14/2023	$5.9	$27.2
GTTX	Genetether	2/8/2023	$2.0	$1.0
SNGX	Soligenix	11/10/2022	$17.0	$4.0
HGEN	Humanigen	10/31/2022	$10.9	$57.0
XCUR	Exicure	9/26/2022	$15.6	-$3.0
GLMD	Galmed	6/15/2022	$22.4	-$12.0
ABIO	Arca Bio	4/18/2022	$43.9	-$12.0
ADMA	ADMA Biologics	10/21/2021	$51.4	$1,525.6

Source: Stifel Research of news stories and company press releases.

* Not in press release but indicated on recent conference call.

Industry News

Parque Guell, Barcelona.

Pharma Execs Tell Investors Medicare Negotiations Won't Have a Big Impact

Nathaniel Weixel and Joseph Choi, *The Hill*, Mar 20, 2024 (excerpt)

Since the first offers in the Inflation Reduction Act's Medicare negotiation program went out, high level executives at companies subject to the process have made light of the suggested prices and the impact they'll have.

What they're saying: AstraZeneca CEO Pascal Soriot told reporters last month that the initial offer from the Centers for Medicare and Medicaid (CMS) was "relatively encouraging," while Pfizer CFO David Denton told investors that the impact from negotiations would be "modest."

Far from cooling to the idea of negotiating the prices of their drugs, advocates see these comments as reassuring lip service to potentially anxious shareholders. Merith Basey, executive director of the advocacy group Patients for Affordable Drugs, said, "We were expecting that they would come out and say something like this," noting the pharmaceutical industry could afford to lose a significant amount in the cost of their drugs while still remaining profitable.

These recent comments contrast with what pharmaceutical lawyers have said in court, lamenting the serious harm companies have already begun to experience due to negotiations, a claim that several federal judges have been dubious of.

While some drugmakers may not be anticipating extreme drops in price, at least when talking to investors, advocates stress that the impact on patients would still be immense.

Pharma vs. government price negotiations haven't been as bad as feared (at least for now).

Source: https://thehill.com/newsletters/4545855-pharma-execs-tell-investors-medicare-negotiations-wont-have-a-big-impact/

BioCentury Survey: Cutting Off Access to China CDMO's Problematic for U.S. Biotech

Simone Fishburn, Editor in Chief, *BioCentury*, Mar 21, 2024 (excerpt)

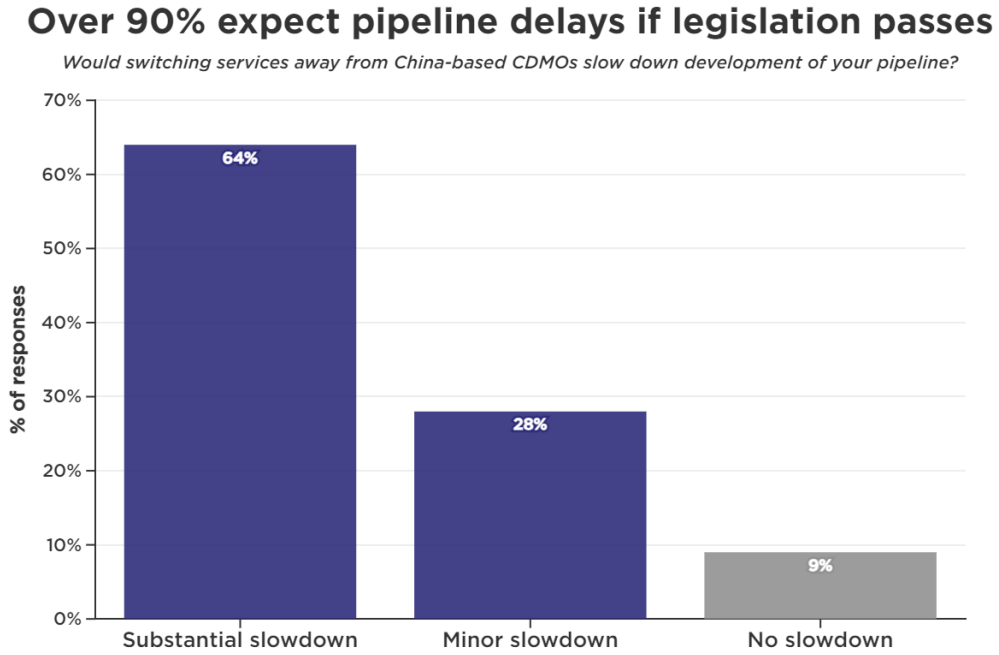
Brace for impact. Legislation targeting Chinese CDMOs and genomics companies that is making its way through Congress, if passed in its current form, will deal a massive blow to biotech companies, with consequences likely to be felt not only throughout the ecosystem but also by patients. The responses to BioCentury's survey signal deep concern, primarily for the ability to replace manufacturing capacity, with views split on the wisdom and rationale of the legislation's goals per se.

BIO's stance on the legislation, which it reversed last week to support the Biosecure Act, also has the community divided. Twice as many oppose the trade organization's new position as agree with it, and many believe the organization has not explained its reasoning.

There's no lack of strong opinions regarding either the legislation or BIO's latest response.

And there is widespread uncertainty about how the legislation will be implemented or the kinds of changes that could be made prior to enactment.

The survey results indicate a potentially devastating headwind for the sector. The dominant concern is for lack of manufacturing capacity, with more than 90% of respondents expecting it would set back their pipelines. The implication is that cutting off access to China CDMOs and forcing companies to find alternatives would translate to slowdowns in clinical trials and, consequently, drug approvals.



Source: https://www.biocentury.com/article/651851/anti-china-bills-portend-massive-blow-to-biotech-biocentury-survey

TB On the Rise for the First Time in Decades

Yolanthe Fawehinmi, *The Independent*, Mar 22, 2024 (excerpt)

A blood test could identify millions of people who unknowingly spread tuberculosis, scientists have said.

More than a million people a year die from tuberculosis (TB), making it the world's deadliest infectious disease, according to the World Health Organisation.

Researchers at the University of Southampton discovered a group of biological markers that are high among infectious patients – and the test could be a significant step in reducing the spread of the disease.

Thankfully, in the UK figures remain low. However, TB cases in the UK increased to around 5,000 in 2023, according to the UK Health Security Agency, and are expecting to continue to rise this year.

Source: https://www.independent.co.uk/news/health/tuberculosis-symptoms-tb-test-blood-b2517110.html

FDA Clears First-Of-Its-Kind Duchenne Drug For Broad Use

Ben Fidler, FierceBiotech, Mar 22, 2024 (excerpt)

The Food and Drug Administration on Thursday approved a first-of-its-kind drug for Duchenne muscular dystrophy, clearing Duvyzat, a medicine developed by Italian pharmaceutical company Italfarmaco and to be sold in the U.S. by its subsidiary ITF Therapeutics.

Duvyzat is the first non-steroidal treatment approved for use in all Duchenne patients who are at least six years of age, regardless of their disease's genetic underpinnings. The drug is a pill designed to slow inflammation and muscle loss. In testing, it was associated with statistically significant benefits, compared to a placebo, on measures of motor function.

The drug's price hasn't been determined yet, according to an ITF spokesperson. Its labeling information requires healthcare providers to evaluate patients' platelet counts and triglycerides before prescribing Duvyzat, and to monitor levels of each afterwards. The most common side effects associated with treatment were diarrhea, stomach pain, nausea and vomiting.

Source: https://www.biopharmadive.com/news/italfarmaco-duchenne-duvyzat-fda-approval/711078/

Obesity Rates in the U.S. on the Rise

Drew DeSilver, March 21, 2024 (excerpt)

Pew Research Center

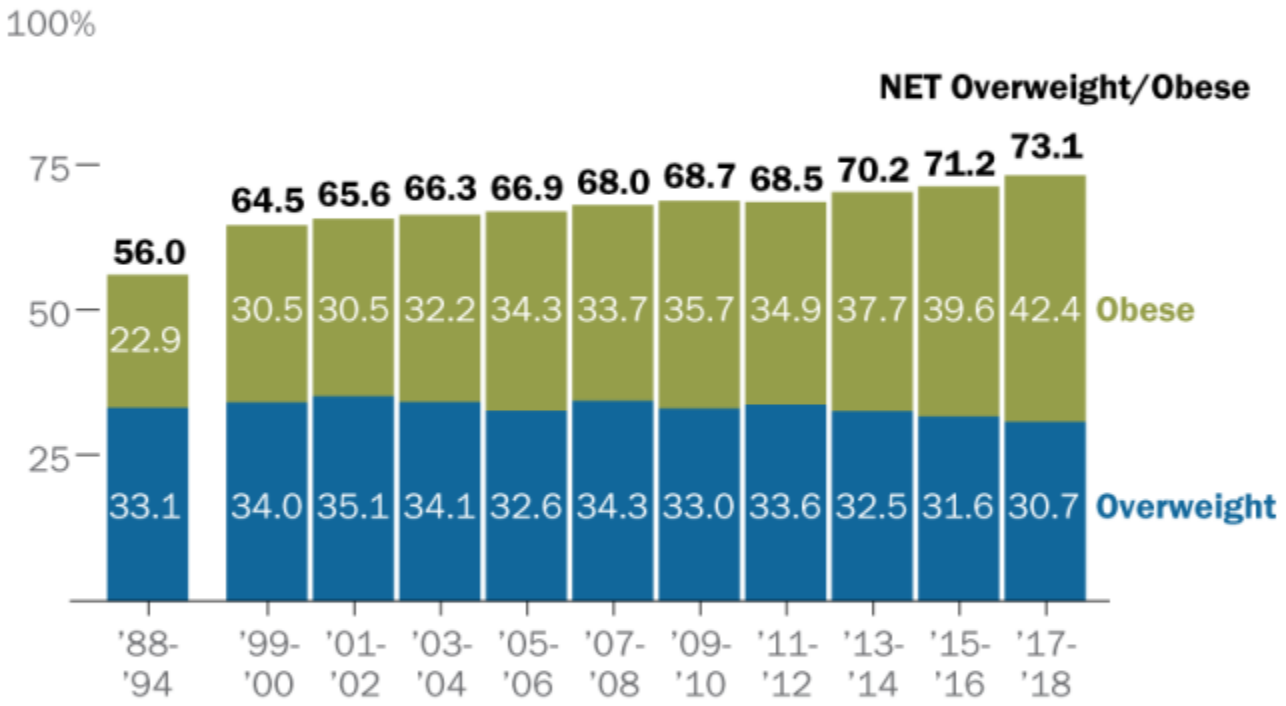
Over the past three decades, the share of Americans categorized as obese (based on body mass index, or BMI, data from the CDC) has risen considerably.

In 2017-18 – the timespan with the most recent data available – about three-quarters of U.S. adults ages 20 and older were considered either overweight (31%) or obese (42%). Just over 9% of adults were considered severely obese. (Note that the CDC survey period spans two years.) About three decades earlier, by comparison, 56% of Americans ages 20 and older were considered overweight or obese, including 3% who were considered severely obese.

Source: https://www.pewresearch.org/short-reads/2024/03/21/as-obesity-rates-rise-in-the-us-and-worldwide-new-weight-loss-drugs-surge-in-popularity/

Share of Americans who are considered overweight or obese has risen over the last 3 decades

% of U.S. adults ages 20 and older whose BMI classifies them as ...



Note: According to the Centers for Disease Control and Prevention, "overweight" is defined as a body mass index (BMI) of 25.0 to 29.9 kg/m^2. "Obese" is defined as BMI greater than or equal to 30 kg/m^2. Figures are age-adjusted.
Source: "Prevalence of Overweight, Obesity and Severe Obesity Among Adults Aged 20 and Over," National Center for Health Statistics (revised Jan. 29, 2021).

PEW RESEARCH CENTER

Medicare to Cover Novo's Weight-Loss Drug Wegovy® for Patients with Heart Disease

Tristan Manalac, *Biospace*, Mar 22, 2024 (excerpt)

The Centers for Medicare and Medicaid Services announced on Thursday that it will cover Novo Nordisk's blockbuster weight-loss medication Wegovy (semaglutide) for the reduction of the risk of heart attack, stroke and other related cardiovascular issues in patients who have preexisting heart disease, according to multiple media reports.

Under this new guidance, private insurers running Medicare prescription drug plans—known as Part D—can pay for anti-obesity medications, such as Wegovy and Lilly's Zepbound (tirzepatide), for additional FDA-approved indications as long as these secondary conditions are covered by the Centers for Medicare and Medicaid Services (CMS).

"CMS has issued guidance to Medicare Part D plans stating that anti-obesity medications that receive FDA approval for an additional medically accepted indication can be considered a Part D drug for that specific use," an agency spokesperson told Reuters in an email.

Source: https://www.biospace.com/article/medicare-to-cover-novo-s-weight-loss-drug-wegovy-for-patients-with-heart-disease/

Here's How Much People are Willing to Spend on Weight Loss Drugs, According to a New Survey

Annika Kim Constantino, *CNBC*, Mar 23, 2024 (excerpt)

A monthly package of a GLP-1 costs between $900 and $1,350 before insurance and other rebates. Both Novo Nordisk and Eli Lilly have savings programs that aim to reduce out-of-pocket costs for weight loss drugs, regardless of whether a patient has commercial insurance coverage.

The majority — nearly 60% — of people surveyed with annual incomes of more than $250,000 said the maximum price they are willing to pay out of pocket for a GLP-1 is more than $300 per month.

Only about 4% of people with annual incomes of less than $75,000 said the same thing. Of that group, 64% said the maximum price they are willing to pay out of pocket for a GLP-1 is $50 per month or less.

The maximum people currently on a GLP-1 said they are willing to pay out of pocket per month was roughly in line with what they actually paid for treatment, according to the survey. The highest price respondents would accept paying skewed lower among those who used to take a GLP-1 or are thinking of taking the drug.

More than half of people currently taking a GLP-1 said they are paying a monthly price of $50 or less out of pocket. Nearly 75% of those who used to take one of the drugs said they spent the same amount.

A small share of both groups paid more than $750 out of pocket per month for a GLP-1.

Source: https://www.cnbc.com/2024/03/23/weight-loss-drug-cost-how-much-people-are-willing-to-spend.html

Willingness to pay for GLP-1 drugs is very much tied to household income.

While not surprising, this article drives home the current societal problem in the market.

There is huge demand for GLP-1 drugs but in a non-reimbursed world, only persons who are well off are able to access the drugs.

First Genetically Engineered Pig Kidney Transplanted into Living Patient: Major Medical Milestone

***Genetic Engineering & Biotechnology News*, Mar 21, 2024 (excerpt)**

eGenesis, a biotechnology company developing human-compatible engineered organs to address the global organ shortage, announced the first ever transplantation of a genetically engineered porcine kidney into a living human recipient.

The transplant was performed by a surgical team at the Massachusetts General Hospital (MGH) led by Tatsuo Kawai, MD, PhD, and Nahel Elias, MD. The patient suffers from end-stage renal disease and lacked other therapeutic options following the loss of vascular access to support continued use of dialysis. Following the procedure, the patient is in good condition and recovering well at MGH.

The eGenesis donor kidney (EGEN-2784) used for this procedure is the company's lead candidate for kidney transplant and carries three classes of genome edits: (1) knock out of three genes involved in the synthesis of glycan antigens implicated in hyperacute rejection, (2) insertion of seven human transgenes involved in the regulation of pathways that modulate rejection: inflammation, innate immunity, coagulation, and complement, and (3) inactivation of the endogenous retroviruses in the porcine genome. Without genetic modification, a porcine kidney would be immediately rejected by a human recipient.

"This successful procedure heralds a new era in medicine in which we have the potential to eliminate organ supply as a barrier to transplantation and realize our vision that no patient dies waiting for an organ," said Michael Curtis, PhD, CEO of eGenesis.

Source: https://www.genengnews.com/topics/translational-medicine/first-genetically-engineered-pig-kidney-transplanted-into-living-patient/

Kelowna Woman Gets 2 Successful Clones of her Cat

Michelle Gomez, *CBC*, Mar 20, 2024 (excerpt)

After two years and four failed attempts, a ragdoll cat that belonged to a Kelowna, B.C., woman has been successfully cloned. Kris Stewart received not one but two kittens cloned using DNA from her beloved cat Bear.

Stewart said she sent Bear's DNA to ViaGen, a Texas-based pet cloning company, after he died at the age of five in a traffic accident in January 2022.

"I just felt like there was more living that needed to be done by Bear," said Stewart. The process of cloning involves putting the animal's DNA into an embryo, which is transferred to the uterus of a surrogate cat who carries and births the babies, according to Kerry Bowman, a bioethicist who works at the University of Toronto.

The kittens, who Stewart has named Bear Bear and Honey Bear, were born on Jan. 10. After staying with their mother in the company's New York facility for eight weeks, Stewart was finally able to pick them up on Wednesday.

"They both seem like Bear," she said. "These guys are bold and sassy." Stewart described Bear as rambunctious and highly intelligent.

Source: https://www.cbc.ca/news/canada/british-columbia/kelowna-cloned-cats-1.7146050

Risk of Autism after Prenatal Topiramate, Valproate, or Lamotrigine Exposure

Hernández-Díaz S, Straub L, Bateman BT, Zhu Y, Mogun H, Wisner KL, Gray KJ, Lester B, McDougle CJ, DiCesare E, Pennell PB, Huybrechts KF. Risk of Autism after Prenatal Topiramate, Valproate, or Lamotrigine Exposure. *N Engl J Med*. Mar 21, 2024;390(12):1069-1079.

The estimated cumulative incidence of autism spectrum disorder at 8 years of age was 1.9% for the full population of children who had not been exposed to antiseizure medication (4,199,796 children). With restriction to children born to mothers with epilepsy, the incidence was 4.2% with no exposure to antiseizure medication (8815 children), 6.2% with exposure to topiramate (1030 children), 10.5% with exposure to valproate (800 children), and 4.1% with exposure to lamotrigine (4205 children). Propensity score–adjusted hazard ratios in a comparison with no exposure to antiseizure medication were 0.96 (95% confidence interval [CI], 0.56 to 1.65) for exposure to topiramate, 2.67 (95% CI, 1.69 to 4.20) for exposure to valproate, and 1.00 (95% CI, 0.69 to 1.46) for exposure to lamotrigine.

The incidence of autism spectrum disorder was higher among children prenatally exposed to the studied antiseizure medications than in the general population. However, after adjustment for indication and other confounders, the association was substantially attenuated for topiramate and lamotrigine, whereas an increased risk remained for valproate. (Funded by the National Institute of Mental Health.)

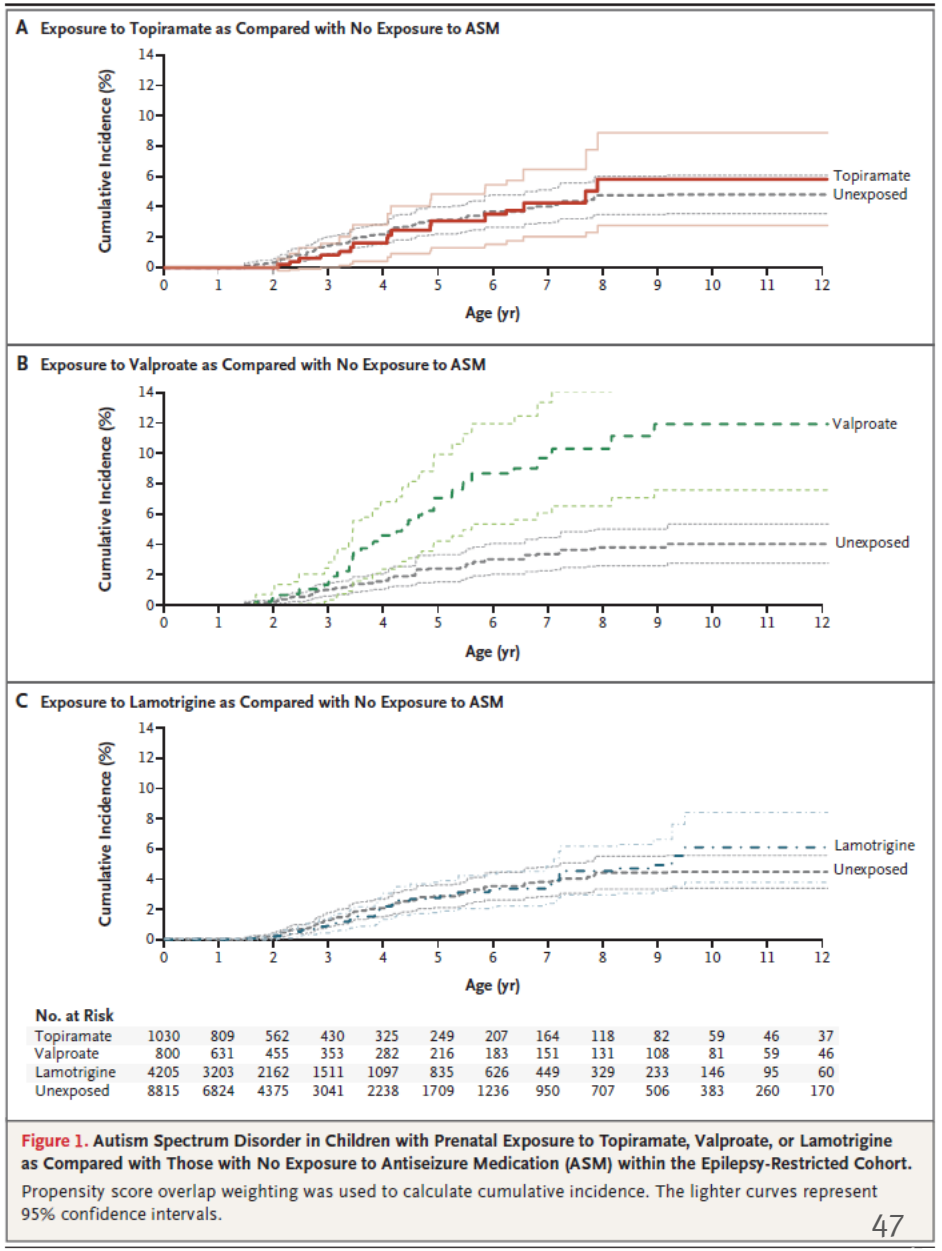


Figure 1. Autism Spectrum Disorder in Children with Prenatal Exposure to Topiramate, Valproate, or Lamotrigine as Compared with Those with No Exposure to Antiseizure Medication (ASM) within the Epilepsy-Restricted Cohort.
Propensity score overlap weighting was used to calculate cumulative incidence. The lighter curves represent 95% confidence intervals.

Source: https://pubmed.ncbi.nlm.nih.gov/38507750/

Inside the Operating Room: Doctors Test a Revolutionary Brain-Computer Implant

Jo Craven McGinty, *Wall Street Journal*, Mar 22, 2024 (excerpt)

Jeffrey Keefer lay on an operating table in the oldest hospital in America surrounded by a surgical team, a group of engineers and a gaggle of spectators hoping to witness the early stages of a healthcare revolution.

Keefer was undergoing brain surgery to relieve symptoms of Parkinson's disease—but since his skull would be open for around four hours anyway, he had also agreed to have an experimental device called a brain-computer interface temporarily implanted.

The unit, developed by Precision Neuroscience, sat on the surface of Keefer's brain for 25 minutes, reading his mind. During that time, he performed a series of exercises with his hands while engineers matched his brain signals to his movements.

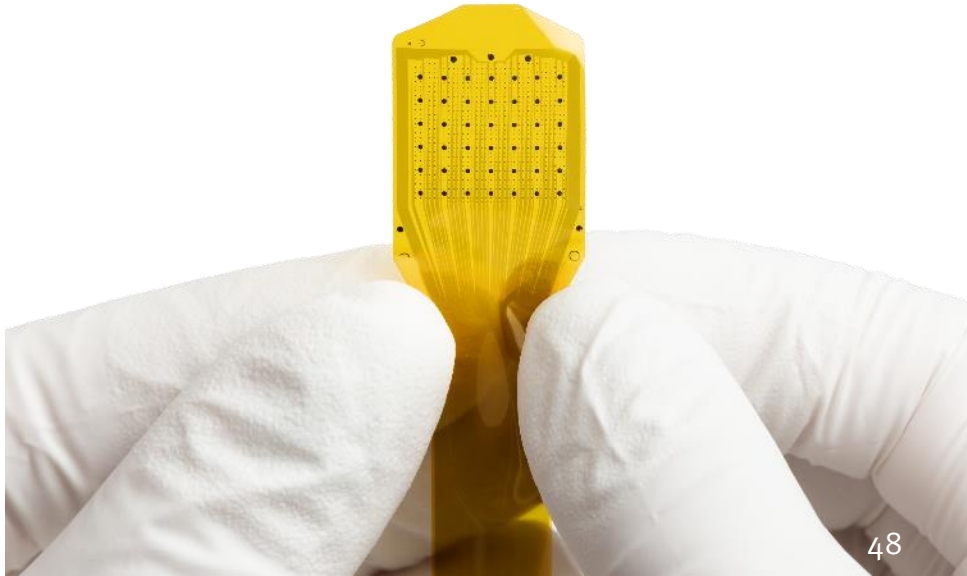
The goal is to train a device that will give paralyzed patients the ability to operate a computer with their thoughts.

Precision is one of several companies vying to commercialize brain-computer interfaces, or BCIs. On Wednesday, Elon Musk's Neuralink introduced the first person implanted with its interface. In a nine-minute presentation streamed on X, Noland Arbaugh, a 29-year-old quadriplegic, used his thoughts to play a game of chess.

Physical movement originates with electrical signals in the brain that are passed through the spinal cord or brain stem, but when someone is paralyzed, the signals hit a dead end. BCIs provide a digital bypass, capturing the signals at the source and relaying the commands to a computer.

The need is massive, according to Dr. Benjamin Rapoport, chief science officer and co-founder of Precision. There are 400,000 severely impaired patients today, he said, and 30,000 or so new patients each year. BCIs could help them win back a measure of independence.

Source: https://www.wsj.com/tech/biotech/inside-the-operating-room-doctors-test-a-revolutionary-brain-computer-implant-f69eboc2



Taysha Shows Off Promising Rett Syndrome Data

Taysha Gene Therapies Press Release, March 19, 2024 (excerpt)

- Data from first adult patient in REVEAL Phase 1/2 trial showed TSHA-102 (low dose, $5.7x10^{14}$ total vg) was well-tolerated with no treatment-emergent SAEs as of 35-week assessment, with sustained improvement across key efficacy measures at decreased steroid levels and new improvement in RSBQ at month six.
- Data from second adult patient showed TSHA-102 (low dose, $5.7x10^{14}$ total vg) was well-tolerated with no treatment-emergent SAEs as of 19-week assessment, with sustained improvement across key efficacy measures, significantly reduced seizure events and new improvement in R-MBA at week 12.
- Principal Investigator observed sustained and new improvements across multiple clinical domains following completion of steroid taper for patient one through 35-weeks post-treatment and for patient two through 19-weeks post-treatment at decreased steroid levels.
- Received Independent Data Monitoring Committee approval of Company's request to proceed to early advancement to cohort two (high dose, $1x10^{15}$ total vg) in REVEAL adolescent and adult trial, and approval to dose second pediatric patient in cohort one (low dose, $5.7x10^{14}$ total vg) in REVEAL pediatric trial

Source: https://ir.tayshagtx.com/news-releases/news-release-details/taysha-gene-therapies-reports-full-year-2023-financial-results

Results of Phase III Study of Enspryng (IL-6 mAb) in Patients with Generalized Myasthenia Gravis

Chugai Press Release, Mar 21, 2024 (excerpt)

Chugai Pharmaceutical Co., Ltd. today announced results from the Phase III LUMINESCE study of Enspryng® (generic name: satralizumab (genetical recombination)), created by Chugai, as an investigational treatment for generalized myasthenia gravis (gMG). Statistically significant data was observed in its primary endpoint, however the results did not reach our expectations on the degree of clinical benefit. Enspryng was well tolerated in gMG, with a safety profile consistent with Enspryng in neuromyelitis optica spectrum disorder (NMOSD) which is the medicine's first indication. Detailed results will be presented as an oral Emerging Science abstract at the American Academy of Neurology (AAN) 2024 Annual Meeting on 15 April in Denver, Colorado.

The results of this study in gMG do not impact Enspryng in NMOSD, in which the medicine is already approved. Chugai, in collaboration with Roche, is committed to developing Enspryng in additional neurological autoimmune and inflammatory diseases that may benefit from the inhibition of interleukin-6 (IL-6) signaling, including autoimmune encephalitis (AIE), myelin oligodendrocyte glycoprotein-associated disorder (MOGAD) and thyroid eye disease (TED).

Source: https://www.chugai-pharm.co.jp/english/news/detail/20240321150000_1059.html

Tourmaline Bio shares dropped 42% last week on this news as the company was also pursuing an IL-6 antibody in myasthenia gravis.

The company's $430mm EV as of Friday close strikes us as being on the low side of things.

Tourmaline is also pursuing Thyroid eye disease and cardiovascular disease where the fundamentals of IL-6 biology are highly favorable.

Past studies of IL-6 mAbs in both diseases have been favorable.

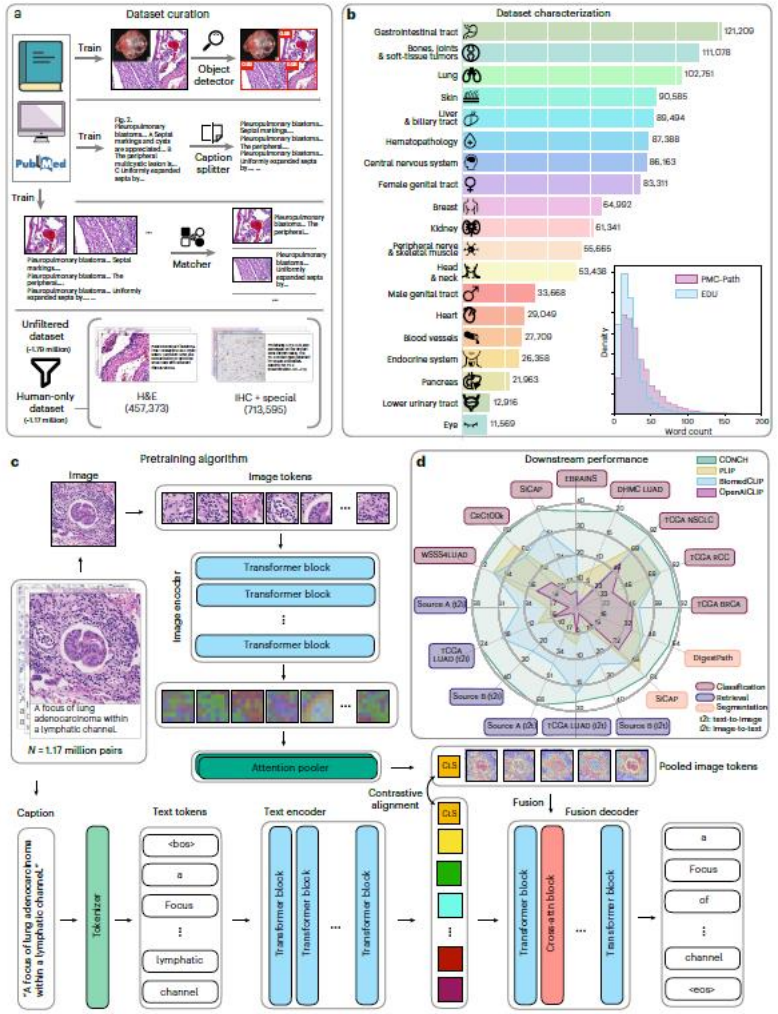
Moreover, Novo is pursuing potentially transformational studies with ziltivekimab, it's IL-6 mAb in CV. As those studies read out, Tourmaline will be offering the market the only late stage IL-6 in a biotech company.

A Visual-Language Foundation Model for Computational Pathology

Lu, M.Y., Chen, B., Williamson, D.F.K. *et al.* A visual-language foundation model for computational pathology. *Nat Med* 30, March 19, 2024, 863–874.

The accelerated adoption of digital pathology and advances in deep learning have enabled the development of robust models for various pathology tasks across a diverse array of diseases and patient cohorts. However, model training is often difficult due to label scarcity in the medical domain, and a model's usage is limited by the specific task and disease for which it is trained. Additionally, most models in histopathology leverage only image data, a stark contrast to how humans teach each other and reason about histopathologic entities. We introduce CONtrastive learning from Captions for Histopathology (CONCH), a visual-language foundation model developed using diverse sources of histopathology images, biomedical text and, notably, over 1.17 million image–caption pairs through task-agnostic pretraining. Evaluated on a suite of 14 diverse benchmarks, CONCH can be transferred to a wide range of downstream tasks involving histopathology images and/or text, achieving state-of-the-art performance on histology image classification, segmentation, captioning, and text-to-image and image-to-text retrieval. CONCH represents a substantial leap over concurrent visual-language pretrained systems for histopathology, with the potential to directly facilitate a wide array of machine learning-based workflows requiring minimal or no further supervised fine-tuning.

Source: https://www.nature.com/articles/s41591-024-02856-4



This article and that on the next page outline pathbreaking work in the field of histopathology.

The Lu et.al. paper builds a foundation model that associates specific visual findings with meaning via image element classification that is context dependent.

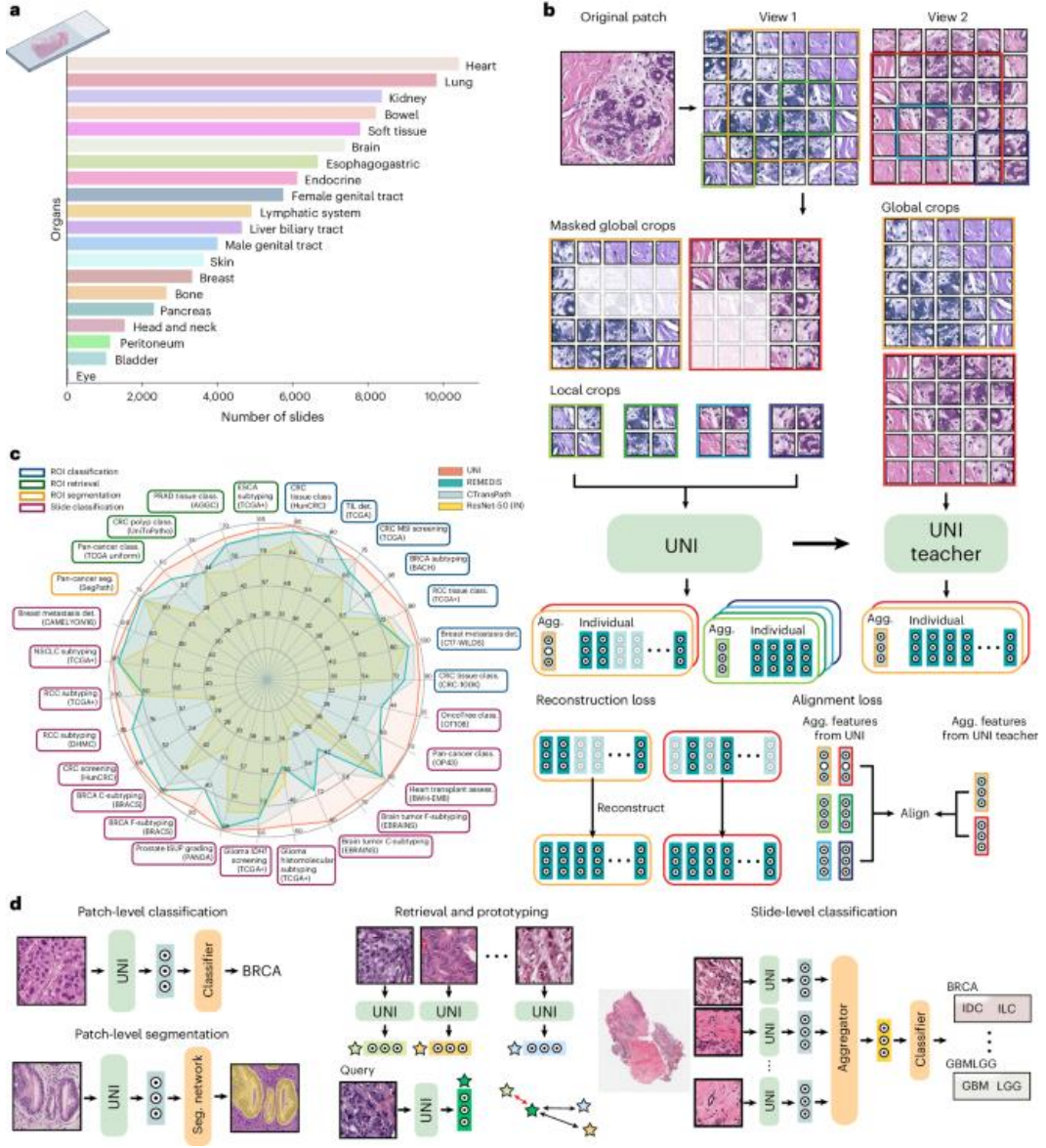
The Chen et.al. paper builds a classifier that looks at much more data and shows impressive out of sample performance.

The core of both papers is an attempt to build an ontology of image elements in histology imagery.

Towards a General-Purpose Foundation Model for Computational Pathology

Chen, R.J., Ding, T., Lu, M.Y. et al. Nat Med 30, March 19, 2024, 850–862.

Quantitative evaluation of tissue images is crucial for computational pathology (CPath) tasks, requiring the objective characterization of histopathological entities from whole-slide images (WSIs). The high resolution of WSIs and the variability of morphological features present significant challenges, complicating the large-scale annotation of data for high-performance applications. To address this challenge, current efforts have proposed the use of pretrained image encoders through transfer learning from natural image datasets or self-supervised learning on publicly available histopathology datasets, but have not been extensively developed and evaluated across diverse tissue types at scale. We introduce UNI, a general-purpose self-supervised model for pathology, pretrained using more than 100 million images from over 100,000 diagnostic H&E-stained WSIs (>77 TB of data) across 20 major tissue types. The model was evaluated on 34 representative CPath tasks of varying diagnostic difficulty. In addition to outperforming previous state-of-the-art models, we demonstrate new modeling capabilities in CPath such as resolution-agnostic tissue classification, slide classification using few-shot class prototypes, and disease subtyping generalization in classifying up to 108 cancer types in the OncoTree classification system. UNI advances unsupervised representation learning at scale in CPath in terms of both pretraining data and downstream evaluation, enabling data-efficient artificial intelligence models that can generalize and transfer to a wide range of diagnostically challenging tasks and clinical workflows in anatomic pathology.



UNI is a general-purpose, self-supervised vision encoder for anatomic pathology based on the vision transformer architecture, achieving state-of-the-art performance across 34 clinical tasks in anatomic pathology. a, Slide distribution of Mass-100K, a large-scale and diverse pretraining dataset of 100 million tissue patches sampled from over 100,000 diagnostic WSIs across 20 major organ types. b, UNI is pretrained on Mass-100K using the DINOv2 self-supervised training algorithm22, which consists of a mask image modeling objective118 and a self-distillation objective25. c, UNI generally outperforms other pretrained encoders across 34 clinical tasks in anatomical pathology (average performance of the 8 SegPath tasks reported). d, The evaluation tasks consist of ROI-level classification, segmentation, retrieval and prototyping, and slide-level classification tasks. Further details are given in Methods. class., classification; seg., segmentation; det., detection; assess., assessment.

Source: https://www.nature.com/articles/s41591-024-02857-3

Progress on Prion-Related Brain Disease

Meredith Wadman, *Science*, Mar 21, 2024 (excerpt)

Ever since neurologist Stanley Prusiner of the University of California, San Francisco identified infectious prions as a cause of neurodegenerative disease in 1982, the quest for treatments has come up short. But on 4 January, a new era was inaugurated. At the University Hospitals Cleveland Medical Center, the first potential participant was screened in the first randomized, placebo-controlled trial targeting prion disease in a dozen years.

The trial will use a strategy already tested, with mixed success, against other neurodegenerative diseases: a snippet of synthetic DNA called an antisense oligonucleotide (ASO) that can reach the brain via an injection into the fluid that bathes the spine and destroy the messenger RNA (mRNA) vital to the production of a disease-causing protein. The ASO in the new trial, made by Ionis Pharmaceuticals and dubbed ION717, targets the mRNA encoding normal prion protein, without which the misfolded form can't arise.

Two other companies aim to remove normal prion protein by different methods. Sangamo Therapeutics is developing zinc finger proteins (ZFPs), tailored to bind to patient DNA and shut down expression of the gene for prion protein, called PRNP. These would be delivered as DNA encoding the ZFPs, packaged in a harmless virus and given as a one-time intravenous injection. Last week, the company reported promising results delivering ZFPs to the brains of nonhuman primates, and it hopes next year to file for permission to launch a human trial in the United Kingdom.

Meanwhile, Gate Bioscience is developing an oral drug that would block the production of prion protein in brain cells. If things go well, the company's small molecule is 3 to 5 years from the clinic, says CEO Jordi Mata-Fink (see graphic, next page).

Source: https://www.science.org/content/article/can-new-drugs-stop-deadly-set-brain-eating-diseases

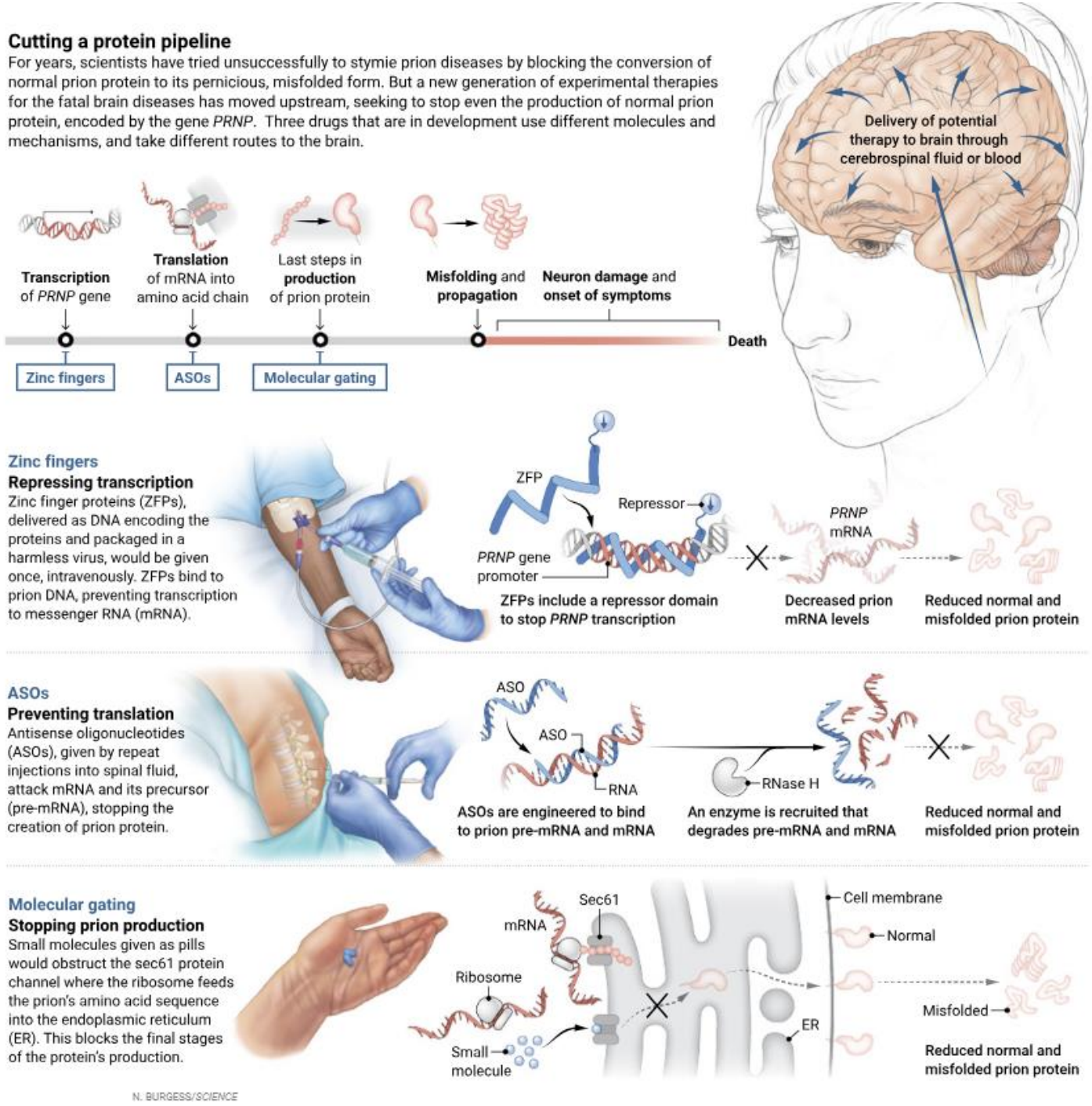
Prion Progress (continued)

Still other groups are seeking to develop small molecules or antibodies that act later in the process, preventing prion protein from misfolding or limiting the damage of the pernicious form. But past attempts have disappointed, and the three firms leading the treatment race argue that the first and essential requirement is to snuff out prion protein before it's ever made. "It's three different approaches for the same therapeutic hypothesis: that elimianating prion protein will be meaningful in slowing, stopping, maybe even reversing the disease," Mata-Fink says. "It feels like the cusp of potentially a really, really, really big change."

"I've been in this field for 17 years. This is the first time I have a treatment trial to offer a patient. … It's hard not to seem excited in front of the families," says Brian Appleby, a neuropsychiatrist who directs the National Prion Disease Pathology Surveillance Center at Case Western Reserve University and is the principal investigator at the Cleveland site of the Ionis trial.

If ION717 works, the payoff might extend beyond prion diseases. It has become clear in the past 2 decades that abnormal proteins propagate in a prionlike way in Alzheimer's disease, Parkinson's disease, and other maladies that destroy neurons.

Source: https://www.science.org/content/article/can-new-drugs-stop-deadly-set-brain-eating-diseases



Why Metformin Causes Weight Loss

Scott, B., Day, E.A., O'Brien, K.L. et al. "Metformin and feeding increase levels of the appetite-suppressing metabolite Lac-Phe in humans," *Nature Metabolism* (2024).

Metformin, a widely used first-line treatment for type 2 diabetes (T2D), is known to reduce blood glucose levels and suppress appetite. Here we report a significant elevation of the appetite-suppressing metabolite N-lactoyl phenylalanine (Lac-Phe) in the blood of individuals treated with metformin across seven observational and interventional studies. Furthermore, Lac-Phe levels were found to rise in response to acute metformin administration and post-prandially in patients with T2D or in metabolically healthy volunteers.

In conclusion, our study demonstrates that metformin, a well-tolerated drug with an excellent safety record, increases Lac-Phe levels. Another paper published in parallel with this work shows that Lac-Phe is increased in both mice and humans upon metformin treatment. The authors experimentally demonstrate, using CNDP2 knockout mice, that metformin inhibits complex 1 in the intestines, causing increased Lac-Phe levels, which contributes to metformin's appetite-suppressing role. Our present work confirms and extends their results, demonstrating that Lac-Phe increases with a single dose of metformin. We clearly demonstrate that Lac-Phe increases are specific to metformin treatment rather than T2D status. In addition, we demonstrate that Lac-Phe increases in response to metformin treatment in both healthy individuals and those with T2D.

Source: https://www.nature.com/articles/s42255-024-01018-7

Scientists Uncover New Secrets to Natural Appetite Control, Offering Promise in the Battle Against Obesity

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

Press Release, Trinity College Dublin, Mar 20, 2024

New research shows the diabetes drug Metformin and solid foods elevate a hunger-reducing factor (Lac-Phe) in the body, whereas sugary drinks have minimal effect. In a ground-breaking study, just published in leading international journal Nature Metabolism, scientists from Trinity and Princeton and Harvard Medical School share newly uncovered secrets to natural appetite control, which offers promise in the battle against obesity and type-2 diabetes.

The scientists today report new insights into how the widely used diabetes drug metformin benefits patients with type-2 diabetes. Metformin is described by some as a “wonder drug” even though we still do not know exactly how it works. This study shows that metformin increases the amount of an appetite suppressing factor called Lactoyl-Phenylalanine (Lac-Phe), identified in 2022 as a natural appetite suppressant, and which is known to be raised by vigorous exercise.

The scientists probed data from other studies involving large numbers of patients, to conclusively demonstrate that Lac-Phe levels rise after individuals take metformin. This work opens a new avenue for developing targeted anti-obesity treatments.

Barry Scott, first author of the research, is a former stock market trader and now a PhD Candidate in Trinity’s School of Biochemistry and Immunology, based in the Trinity Biomedical Sciences Institute (TBSI).

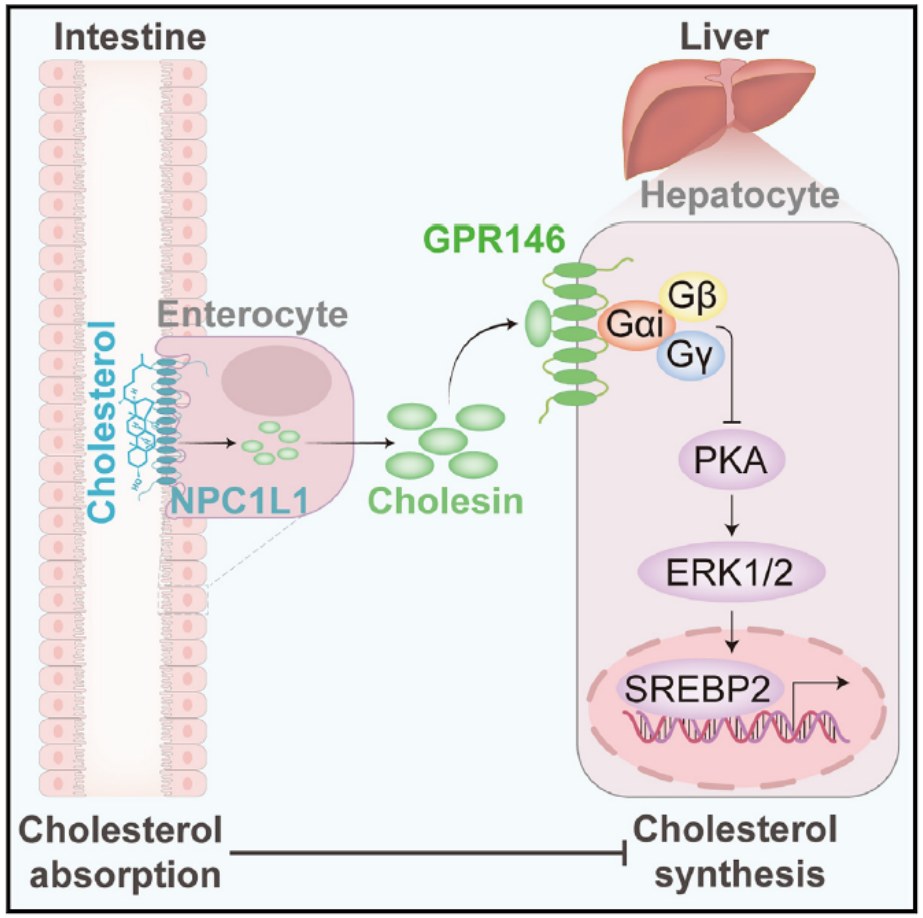
He said: “I’m hopeful our research can have a big impact. Metformin is the most prescribed drug for type-2 diabetes, and it’s very safe and well tolerated. How metformin affects appetite was not known, but this work shows that its influence on Lac-Phe is a key part of its hunger suppressing impact.”

Source: https://www.tcd.ie/news_events/top-stories/featured/scientists-uncover-new-secrets-to-natural-appetite-control-offering-promise-in-the-battle-against-obesity/

Cell March 7, 2024

A gut-derived hormone regulates cholesterol metabolism

Graphical abstract



Authors

Xiaoli Hu, Fengyi Chen, Liangjie Jia, ..., Yan Wang, Huijie Zhang, Yiguo Wang

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In brief

Cholesin, a gut-secreted hormone induced by NPC1L1-mediated cholesterol uptake, binds to GPR146, inhibiting PKA-ERK1/2 signaling in the liver. This Cholesin-GPR146 axis suppresses SREBP2-controlled cholesterol synthesis, ultimately reducing circulating cholesterol levels.

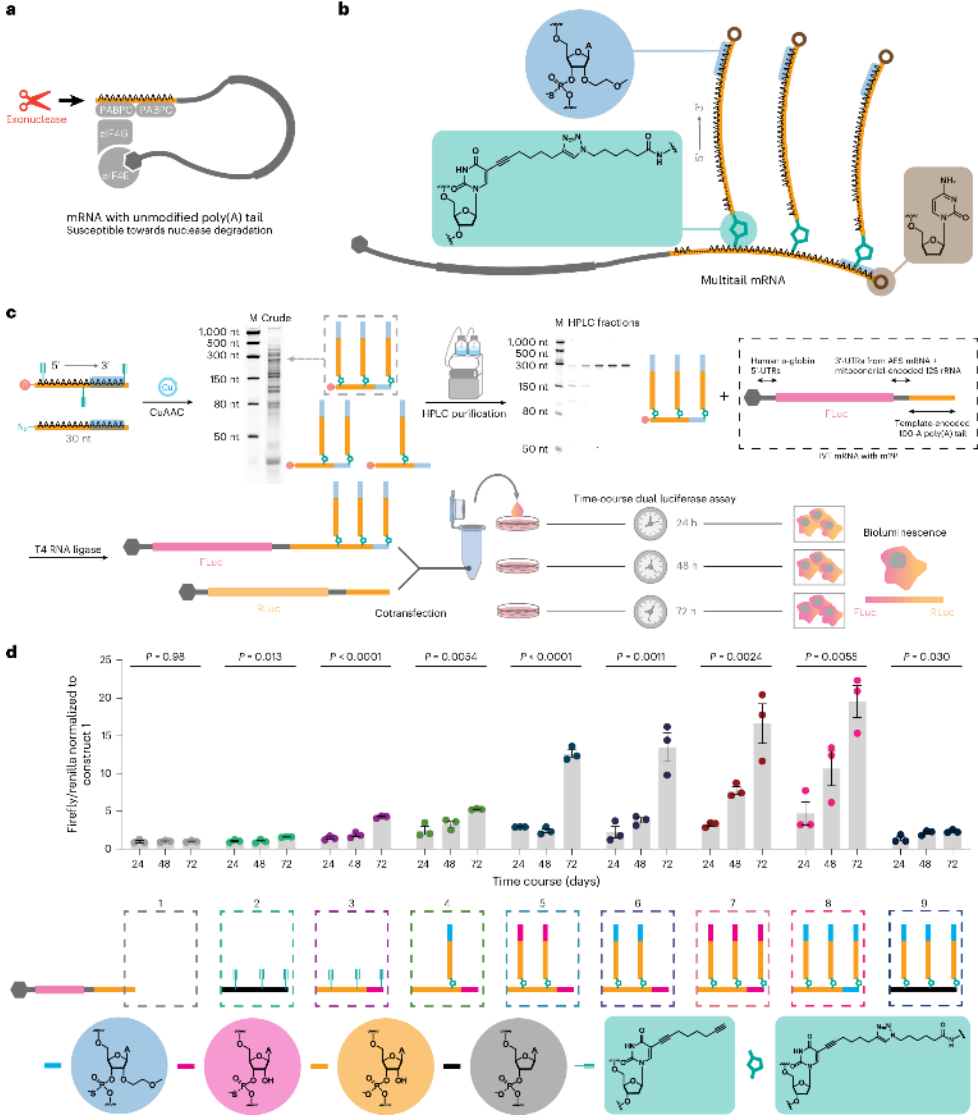
The reciprocal coordination between cholesterol absorption in the intestine and de novo cholesterol synthesis in the liver is essential for maintaining cholesterol homeostasis, yet the mechanisms governing the opposing regulation of these processes remain poorly understood. Here, we identify a hormone, Cholesin, which is capable of inhibiting cholesterol synthesis in the liver, leading to a reduction in circulating cholesterol levels. Cholesin is encoded by a gene with a previously unknown function (C7orf50 in humans; 3110082I17Rik in mice). It is secreted from the intestine in response to cholesterol absorption and binds to GPR146, an orphan G-protein-coupled receptor, exerting antagonistic downstream effects by inhibiting PKA signaling and thereby suppressing SREBP2-controlled cholesterol synthesis in the liver. Therefore, our results demonstrate that the Cholesin-GPR146 axis mediates the inhibitory effect of intestinal cholesterol absorption on hepatic cholesterol synthesis. This discovered hormone, Cholesin, holds promise as an effective agent in combating hypercholesterolemia and atherosclerosis.

Source: https://pubmed.ncbi.nlm.nih.gov/38503280/

New Technique Enhances mRNA Therapies

Chen, H., Liu, D., Guo, J. et al. "Branched chemically modified poly(A) tails enhance the translation capacity of mRNA," *Nat Biotechnology*, Mar 22, 2024.

Although messenger RNA (mRNA) has proved effective as a vaccine, its potential as a general therapeutic modality is limited by its instability and low translation capacity. To increase the duration and level of protein expression from mRNA, we designed and synthesized topologically and chemically modified mRNAs with multiple synthetic poly(A) tails. Here we demonstrate that the optimized multitailed mRNA yielded ~4.7–19.5-fold higher luminescence signals than the control mRNA from 24 to 72 h post transfection in cellulo and 14 days detectable signal versus <7 days signal from the control in vivo. We further achieve efficient multiplexed genome editing of the clinically relevant genes Pcsk9 and Angptl3 in mouse liver at a minimal mRNA dosage. Taken together, these results provide a generalizable approach to synthesize capped branched mRNA with markedly enhanced translation capacity.



a, Pseudo-closed-loop model of translation initiation. **b**, Chemical structures of engineered branched poly(A) tails. Branching oligos are conjugated through triazole linkages. Nuclease-resistant modifications (phosphorothioate and 2′-*O*-methoxyethyl) are incorporated on the last six nucleotides of each branch. Chain-terminating dideoxycytidines are introduced at 3′-end to prevent self-ligation. **c**, Synthesis and screening pipeline of branched mRNA. Alkyne and azide containing oligos were chemically conjugated, HPLC purified and enzymatically ligated to 3′-end of mRNA prepared from IVT with 100% (m1ψ) substitution to produce a branched mRNA-encoding FLuc reporter. 5′-UTRs were adopted from human α-globin 5′-UTR and 3′-UTR from the amino-terminal enhancer of split (AES) mRNA and the mitochondrial-encoded 12S rRNA as used in the Pfizer COVID-19 vaccine, followed by a template-encoded 100-A split poly(A) tail. Constructs were screened in a dual luciferase assay with RLuc as transfection control over a 72-h time course. M, markers. **d**, Barplots of time-course dual luciferase assay screening chemical modifications on multimerized poly(A) tails. Protein expression was measured by FLuc luminescence normalized to RLuc luminescence and the linear mRNA control at 24, 48 and 72 h post transfection. Mean ± standard error of the mean (s.e.m.). $n = 3$ independent transfections for each time point. The *P* values were calculated by an ordinary two-sided one-way ANOVA (comparison of means across time points).

Source: https://www.nature.com/articles/s41587-024-02174-7

Developments in Women's Health

Stained glass windows, Sagrada Familia, Barcelona.

Large Global Gender Gap Remains in Healthcare

Professor Márcia Mendonça Carneiro, *Women & Health*, January 2024

I wonder if 2024 will be the year we make substantial advances in women's health and take fundamental steps toward narrowing the gender gap so that every woman is treated with due respect and receives the essential health care she deserves. 2023 certainly presented huge challenges and reasons to worry, but should we hope 2024 will be any different? Everyone apparently agrees that investing in women's health is a fundamental step to sustainable development, but the reality remains harsh for women.

Efforts to care for the almost four billion women are enormous, and in 2021, the World Health Organization (WHO) defined six priorities for female's health in an attempt to overcome the several challenges women and girls face to obtain proper health care (The World Health Organization Citation2023a). The agenda included access to quality sexual and reproductive health to all, prevention of violence against women, and prevention of noncommunicable diseases (NCDs) such as obesity. Increased female participation in leadership positions both in science and public health is also an important item in the agenda that has not been fulfilled so far.

The available numbers in women's health show the gap remains appalling, despite all the efforts. In fact, finding reliable data is part of the problem. According to McKinsey & Company there are several areas in which the lack of data creates "blind spots" that adversely affect research design, impair investments, and result in unacceptable unmet needs in female health. In fact, defining women's health is the first obstacle as the definition should encompass all aspects of life and should not be confined to reproductive and sexual health. The United Nations Population Fund (UNFPA) defines reproductive and sexual health as "a state of complete physical, mental and social well-being in all matters relating to the reproductive system." The concept involves the ability to make free informed choices on when and how to have children if desired as well as enjoy a safe and fulfilling sex life. Education and access to scientific-based information on effective contraception, sexually transmitted infections (STI), as well as prenatal care are fundamental steps to achieve such goals.

The ghastly reality faced by millions especially for those living in low- and middle-income countries (LMIC) reveals these goals are still a utopia. According to the Guttmacher Institute (https://www.guttmacher.org/global/contraception), more than 100 million unintended pregnancies occur in LMIC which represent almost half (49 percent) of all pregnancies in those nations.

Source: https://www.tandfonline.com/doi/full/10.1080/03630242.2024.2292320

White House Initiative Last Week to Galvanize More Research on Women's Health

The White House, March 18, 2024

In his State of the Union address, President Biden laid out his vision for transforming women's health research and improving women's lives all across America. The President called on Congress to make a bold, transformative investment of $12 billion in new funding for women's health research. This investment would be used to create a Fund for Women's Health Research at the National Institutes of Health (NIH) to advance a cutting-edge, interdisciplinary research agenda and to establish a new nationwide network of research centers of excellence and innovation in women's health—which would serve as a national gold standard for women's health research across the lifespan.

It is long past time to ensure women get the answers they need when it comes to their health—from cardiovascular disease to autoimmune diseases to menopause-related conditions. To pioneer the next generation of discoveries, the President and the First Lady launched the first-ever White House Initiative on Women's Health Research, which aims to fundamentally change how we approach and fund women's health research in the United States.

Today, President Biden is signing a new Executive Order that will direct the most comprehensive set of executive actions ever taken to expand and improve research on women's health. These directives will ensure women's health is integrated and prioritized across the federal research portfolio and budget, and will galvanize new research on a wide range of topics, including women's midlife health.

The President and First Lady are also announcing more than twenty new actions and commitments by federal agencies, including through the U.S. Department of Health and Human Services (HHS), the Department of Defense (DoD), the Department of Veterans Affairs (VA), and the National Science Foundation (NSF). This includes the launch of a new NIH-wide effort that will direct key investments of $200 million in Fiscal Year 2025 to fund new, interdisciplinary women's health research—a first step towards the transformative central Fund on Women's Health that the President has called on Congress to invest in.

Source: https://www.whitehouse.gov/briefing-room/statements-releases/2024/03/18/fact-sheet-president-biden-issues-executive-order-and-announces-new-actions-to-advance-womens-health-research-and-innovation/

Jill Biden in RTP: Heart Attacks and Other Women's Health Issues Need More Research

WRAL News, March 20, 2024

First lady Jill Biden visited Research Triangle Park Wednesday to discuss the Biden administration's effort to prioritize research and funding for women's health, saying health issues affecting women, including osteoporosis, menopause and heart disease, need more scrutiny.

"So many of us and so many of the women in our lives suffer from health conditions for which we don't have answers or solutions," Biden said during remarks at coworking nonprofit Frontier RTP. "We simply don't know about how to prevent, detect and treat the conditions that only affect women, affect women more than men, or affect women differently than men."

Biden also discussed an executive order signed by her husband earlier this week. President Joe Biden, a Democrat who's running for reelection this year, launched the White House Initiative on Women's Health Research, pointing to a historic lack of funding for women's health issues. The executive order increases funding to improve research and data collection across a variety of government agencies and calls for unmet needs to be addressed, including new research on women's midlife health, including conditions such as menopause, arthritis, heart attack and osteoporosis.

"Together we can write a new future for healthcare, where women leave doctors office's with more answers than questions, where no woman or girl has to hear that it's all in your head or it's just stress," she said.

Jill Biden speaks on women's health in Research Triangle Park, NC last week.

Source: https://www.wral.com/story/jill-biden-in-rtp-heart-attacks-and-other-women-s-health-issues-need-more-research/21338693/

Health Execs Applaud Biden's Order on Women's Health

Marissa Plescia, *MedCity News*, Mar 19, 2024

The White House has taken yet another step to advance women's health. After launching a women's health research initiative in November and announcing a $100 million investment in February, President Joe Biden issued an executive order on Monday that will distribute $12 billion to improve women's health research and innovation. Several women's health executives are coming out in support of the series of efforts by the White House.

"It is terrific to see the domino effect of initiatives rolling out from the Biden-Harris administration aimed at driving changes to the women's healthcare system, starting with the First Lady's $100 million funding announcement a few weeks ago," said Anu Sharma, founder and CEO of maternal health company Millie, in an email. "This $12 billion is definitely a more substantial number and gets us closer to what is needed to bridge the gap in women's healthcare."

"At a time when we have become accustomed to outside forces regulating women's health care decisions, it is refreshing to have an administration finally recognize the need for additional research and innovation into women's health, which starts with an influx of funding," said Monica Cepak, CEO of sexual health company WISP. "President Biden has called out specific areas he wants this money to be allocated to, and I am excited to see that menopause, sexual and reproductive health were included within the list."

Source: https://medcitynews.com/2024/03/biden-executive-order-women/

Grace Colon Comments on Biden Administration Initiative

Grace Colon

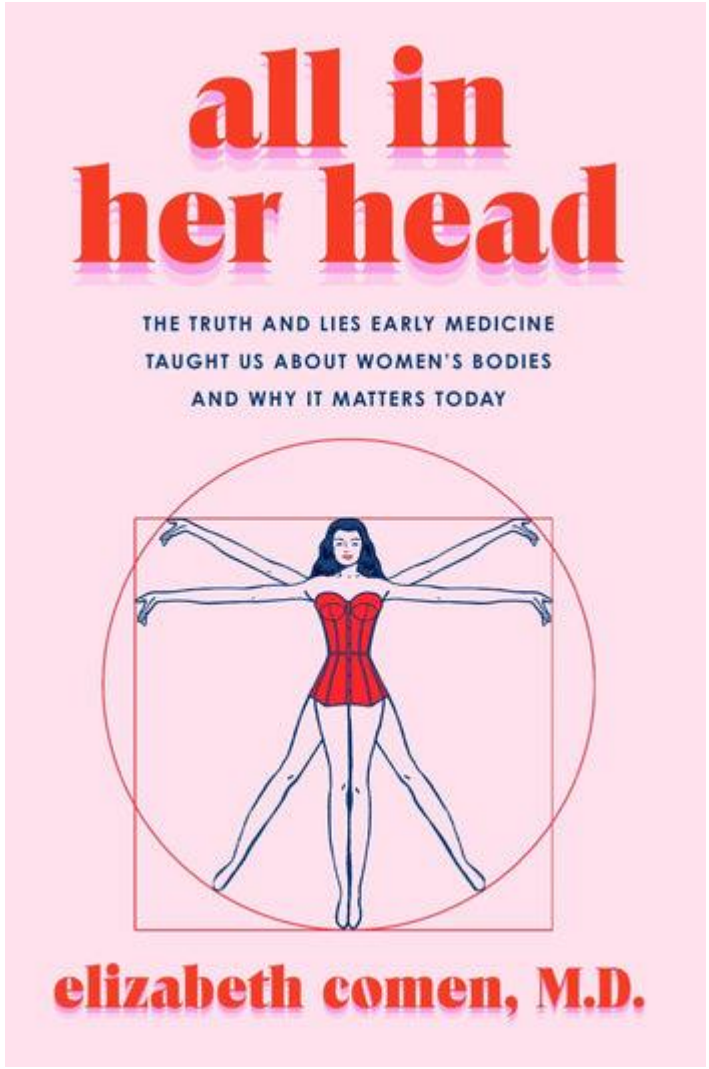
Biotech Industry CEO, Investor and Board Member

"Women's health right now is like the early days of cancer." Colon likens today's treatments to chemotherapy and applying a "broad brush hammer suggesting that until you invest in fundamental research to identify new targets, you're not going to see better drugs."

Biotech Hangout, March 22, 2024

Source: https://twitter.com/BiotechCH/status/1771218264657449012

Recent Book on Women's Health



Memorial Sloan Kettering oncologist and medical historian Dr. Elizabeth Comen draws back the curtain on the collective medical history of women to reintroduce us to our whole bodies—how they work, the actual doctors and patients whose perspectives and experiences laid the foundation for today's medical thought, and the many oversights that still remain unaddressed. With a physician's knowledge and empathy, Dr. Comen follows the road map of the eleven organ systems to share unique and untold stories, drawing upon medical texts and journals, interviews with expert physicians, as well as her own experience treating thousands of women.

Empowering women to better understand ourselves and advocate for care that prioritizes healthy and joyful lives— for us and generations to come—*All in Her Head* is written with humor, wisdom, and deep scientific and cultural insight. Eye-opening, sometimes enraging, yet always captivating, this shared memoir of women's medical history is an essential contribution to a holistic understanding and much-needed reclaiming of women's history and bodies.

Source: https://www.harpercollins.com/products/all-in-her-head-elizabeth-comen

Human GDF-15 Knockouts Are Fertile

Allan Gurtan, Danish Saleheen et.al., *medRxiv*, Mar 18, 2024

Growth differentiation factor 15 (GDF15) is a secreted protein that regulates food intake, body weight, and stress responses in pre-clinical models1. The physiological function of GDF15 in humans remains unclear. Pharmacologically, GDF15 agonism in humans caused nausea without accompanying weight loss2, and the effect of GDF15 antagonism is being tested in clinical trials to treat cachexia and anorexia. Human genetics point to a role for GDF15 in hyperemesis gravidarum, but the safety or impact of complete GDF15 loss, particularly during pregnancy, is unknown. Here, we characterize GDF15 loss-of-function carriers (LOF), including 5 homozygous null carriers ("knockouts") from 75,018 participants enrolled in the Pakistan Genomic Resource (PGR). We tested for the association of GDF15 LOF with 97 quantitative traits and binary outcomes. Further, 3 additional knockouts and 59 heterozygous carriers were identified in recall-by-genotype (RBG) studies accompanied by recruitment of family members. GDF15 knockouts ranged in age from 31 to 75 years, were fertile, and showed no consistent overt metabolic dysfunction. Collectively, our data indicate that (i) complete GDF15 loss is compatible with life and fertility, (ii) chronic therapeutic inhibition of GDF15 may be tolerated, and (iii) GDF15 modulation may not significantly impact body weight or metabolic syndrome.

Source: https://www.medrxiv.org/content/10.1101/2024.03.14.24303793v1.full.pdf

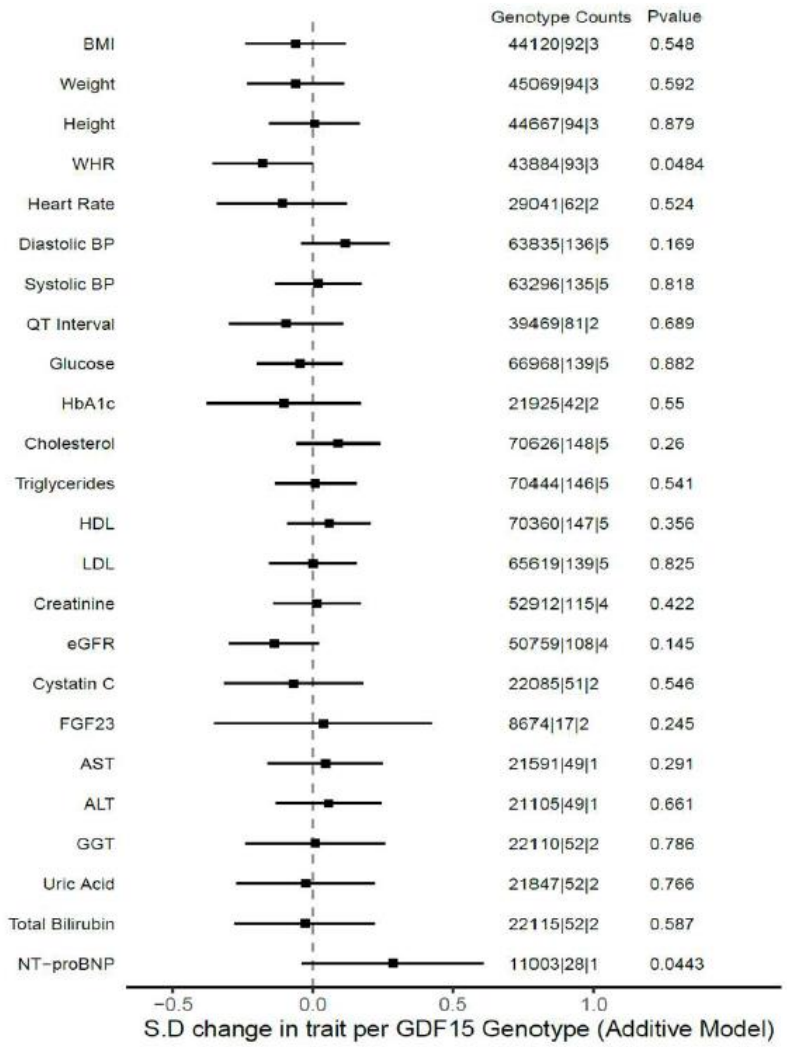
You might recall that we had previously written up a Dec 2023 paper in *Nature* by Marlena Fejzo, Stephen O'Rahilly and colleagues that linked GDF15 levels to vomiting in pregnancy, especially uncontrolled vomiting in pregnancy, hyperemesis gravidarum. Since then, NGM Bio has decided to pursue a GFRAL antibody (cognate receptor of GDF15) for hyperemesis gravidarum.

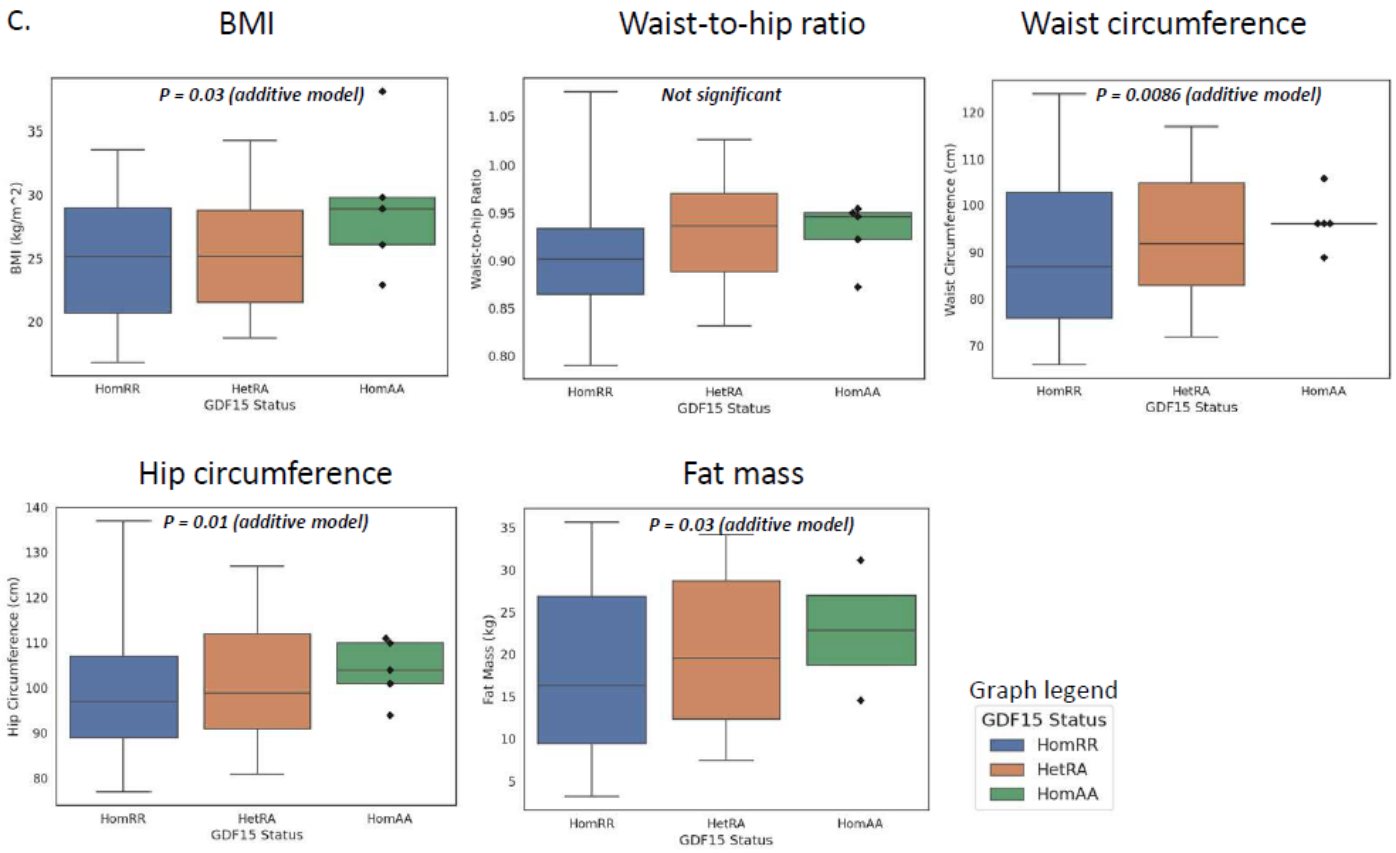
There have always been questions as to whether GDF15 itself is required for fertility and successful pregnancy. A number of papers including that by Lyu et.al. (2023) have argued that GDF15 loss is not good for maintaining pregnancies. Obviously, the GFRAL approach would not involve reducing GDF15 levels, but some have contemplated direct GDF15 control.

Yet others, including Novo Nordisk, have explored GDF15 agonists to induce weight loss, reasoning that if GDF15 induces nausea it might cause you to eat less.

The paper at left is very important in the context of this literature because it shows that GDF15 homozygous null humans were fertile and not different metabolically.

No Overt Metabolic Phenotypes in GDF15 Knockouts





Source: https://www.medrxiv.org/content/10.1101/2024.03.14.24303793v1.full.pdf

Genome-wide Analyses Identify 21 Infertility Loci and over 400 Reproductive Hormone Loci

S Venkatesh, Cecilia Lindgren et.al., *MedRxiv*, March 20, 2024

Genome-wide association studies (GWASs) may help inform treatments for infertility, whose causes remain unknown in many cases. Here we present GWAS meta-analyses across six cohorts for male and female infertility in up to 41,200 cases and 687,005 controls. We identified 21 genetic risk loci for infertility (P≤5E-08), of which 12 have not been reported for any reproductive condition. We found positive genetic correlations between endometriosis and all-cause female infertility (rg=0.585, P=8.98E-14), and between polycystic ovary syndrome and anovulatory infertility (rg=0.403, P=2.16E-03). The evolutionary persistence of female infertility-risk alleles in EBAG9 may be explained by recent directional selection. We additionally identified up to 269 genetic loci associated with follicle-stimulating hormone (FSH), luteinising hormone, oestradiol, and testosterone through sex-specific GWAS meta-analyses (N=6,095-246,862). While hormone-associated variants near FSHB and ARL14EP colocalised with signals for anovulatory infertility, we found no rg between female infertility and reproductive hormones (P>0.05). Exome sequencing analyses in the UK Biobank (N=197,340) revealed that women carrying testosterone-lowering rare variants in GPC2 were at higher risk of infertility (OR=2.63, P=1.25E-03). Taken together, our results suggest that while individual genes associated with hormone regulation may be relevant for fertility, there is limited genetic evidence for correlation between reproductive hormones and infertility at the population level. We provide the first comprehensive view of the genetic architecture of infertility across multiple diagnostic criteria in men and women, and characterise its relationship to other health conditions.

Source: https://www.medrxiv.org/content/10.1101/2024.03.19.24304530v1

This is another really interesting paper shedding light on pregnancy last week – or rather the lack of it.

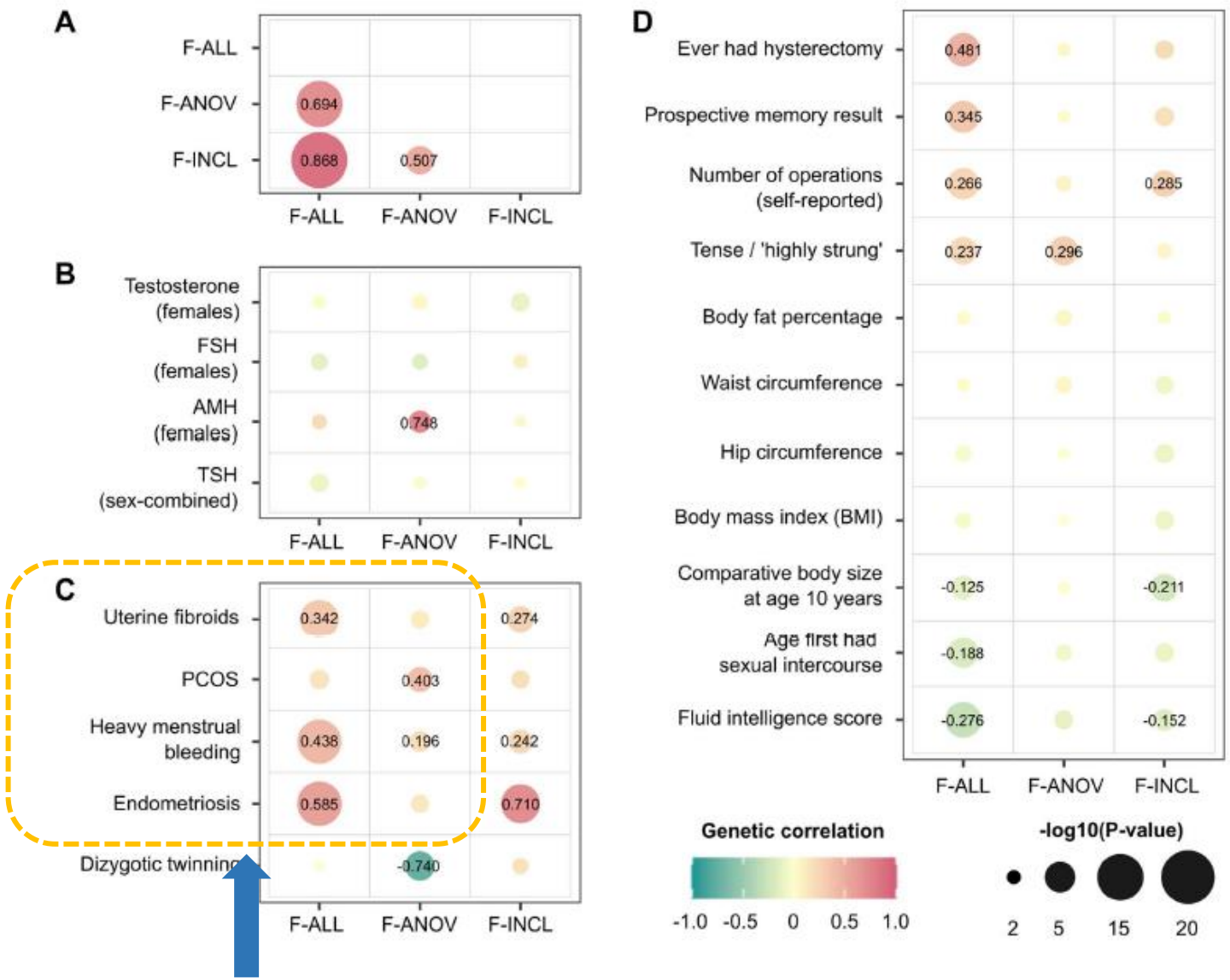
The group of authors from Oxford University compared 41,200 persons with infertility to 687,005 controls.

Female infertility, in general, is not linked to hormone levels, although variants in specific genes including GPC2 (testosterone regulating) and FSHB (FSH hormone) were linked to an inability to ovulate.

More generally, it is thought that only 10% to 15% of infertility is linked to genetic factors (see https://www.genomemedical.com/genetic-testing-pregnancy/is-infertility-genetic/).

One of the most interesting findings in the paper was how closely linked infertility is to endometriosis and polycystic ovary syndrome.

Genome-wide Analyses Identify 21 Infertility Loci (Continued)



Very interesting findings

Figure 3. Genetic correlations between female infertility and other phenotypes. SNP-based genetic correlations (rg) between significantly heritable phenotypes (Z>4) were estimated using LD-score regression, performed using the LDSC software51 on a subset of 1 million HapMap3 SNPs52. Points are coloured by rg estimate, scaled by significance (-log10(P)), and labelled with the associated rg estimate if nominally significant without correction for multiple testing (P<0.05). (A) Genetic correlations among the three significantly heritable definitions of female infertility (all cause=F-ALL, anovulatory=F-ANOV, and idiopathic infertility defined by inclusion=F-INCL). (B) Genetic correlations between female infertility traits and reproductive hormones: testosterone, follicle stimulating hormone (FSH), and anti-Mullerian hormone (AMH, publicly available summary statistics) in female-specific analyses, and thyroid stimulating hormone (TSH, publicly available summary statistics) from sex-combined analysis. (C) Genetic correlations between female infertility traits and female reproductive conditions, with summary statistics generated from the largest available European-ancestry studies for each trait (see Methods). PCOS=polycystic ovary syndrome. (D) Genetic correlations between female infertility traits and selected heritable phenotypes (Z>4) in the UK Biobank, as generated by the Neale lab53. Correlations with all heritable phenotypes can be found in Supp. Table 12.

Source: https://www.medrxiv.org/content/10.1101/2024.03.19.24304530v1

Link Between Endometriosis and Infertility Maybe Mediated by LKF15

Huang Y, Wang Z, Li B, Ke L, Xiong Y, Zhang Y. Loss of KLF15 impairs endometrial receptivity by inhibiting EMT in endometriosis. *J Endocrinol*. Mar 1, 2024:JOE-23-0319

The impaired endometrial receptivity is a major factor contributing to infertility in patients with endometriosis (EM), but the underlying mechanism remains unclear. Our study aimed to investigate the role of Kruppel-like factor 15 (KLF15) in endometrial receptivity and its regulation in EM. We observed a significant decrease in KLF15 expression in the mid-secretory epithelial endometrial cells of EM patients compared to normal females without EM. To confirm the role of KLF15 in endometrial receptivity, we found a significantly reduced KLF15 expression and a significant decrease of embryo implantations number in the rat model via uterine horn infection with siRNA. This highlighted importance of KLF15 as a regulator receptivity. Furthermore, through ChIP-qPCR, we discovered that progesterone receptor (PR) directly binds to KLF15 promoter regions, indicating that progesterone resistance may mediate the decrease in KLF15 expression in EM patients. Additionally, we found that the mid-secretory endometrium of EM patients exhibited impaired epithelial-mesenchymal transition (EMT). Knockdown of KLF15 upregulated E-cadherin and downregulated Vimentin expression, leading to inhibited invasiveness and migration of Ishikawa cells. Overexpression KLF15 promotes EMT, invasiveness, and migration ability, and increased attachment rate of JAR cells to Ishikawa cells. Through RNA-seq analysis, we identified TWIST2 as a downstream gene of KLF15. We confirmed that KLF15 directly binds to the promoter region of TWIST2 via ChIP-qPCR, promoting epithelial cells EMT during the establishment of endometrial receptivity. Our study reveals the involvement of KLF15 in the regulation of endometrial receptivity and its downstream effects on EMT. These findings provide valuable insights into potential therapeutic approaches for treating non-receptive endometrium in patients with EM.

Source: https://pubmed.ncbi.nlm.nih.gov/38513352/

23andMe Study on Genetics of Sporadic and Recurrent Miscarriage

Alexandra Reynoso, Stella Aslibekyan et.al., 23AndMe, *MedRxiv*, March 21, 2024

Miscarriage is a common adverse pregnancy outcome, impacting approximately 15% of pregnancies. Herein, we present results of the largest trans-ancestral genome wide association study for miscarriage to date, based on 334,593 cases of sporadic, and 52,087 cases of recurrent miscarriage in the 23andMe, Inc. Research Cohort.

We identified 10 novel genome-wide significant associations for sporadic miscarriage, and one for recurrent miscarriage. These loci mapped to genes with roles in neural development and telomere length, and to developmental disorders including autism spectrum disorder.

Three variants, with similar directionality and magnitude of effect, replicated in a previously published GWAS. Using Mendelian randomization and triangulation, robust evidence was found for smoking causally increasing the risk of sporadic (genetic liability to ever vs never smoking: OR 1.13; 95%CI: 1.11-1.15; P=2.61e-42) and recurrent (OR 1.25; 95%CI: 1.21-1.30; P=5.47e-34) miscarriage, with moderate, yet triangulating, evidence identified for a potential etiological role of caffeine consumption.

Miscarriage is quite common in pregnancy. In this paper, the research team at 23AndMe asked why.

They find that genes linked to neural development and telomere length predict miscarriage.

There is also robust evidence that smoking is linked to miscarriage risk.

Source: https://www.medrxiv.org/content/10.1101/2024.03.20.24304624v2

Genes Associated with Brain Development Predict Miscarriage

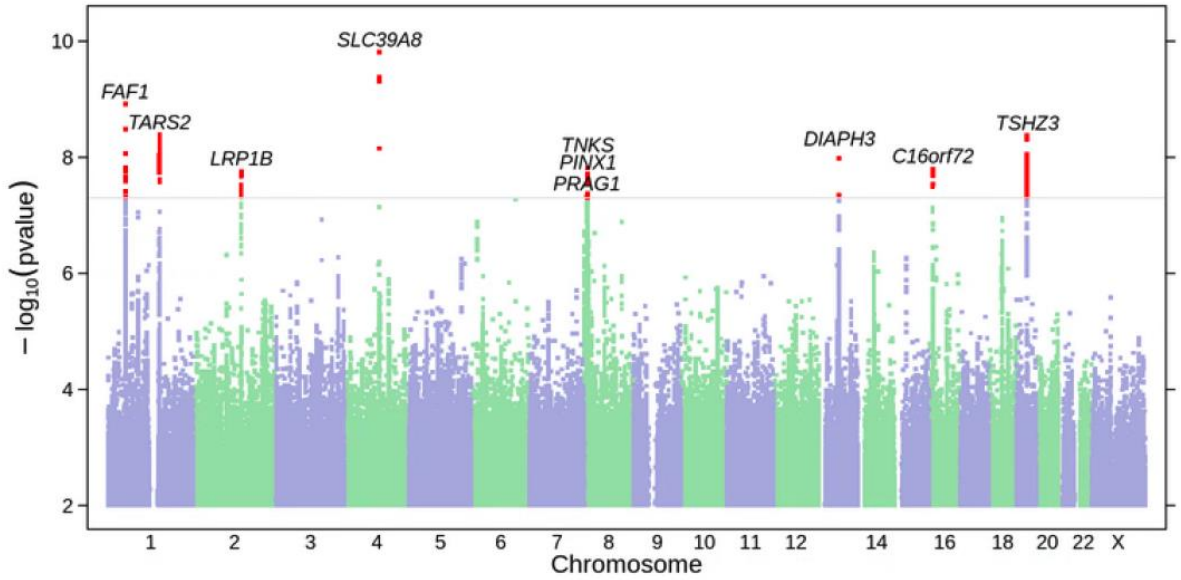
Alexandra Reynoso, Stella Aslibekyan et.al., 23AndMe, *MedRxiv*, March 21, 2024

The top gene predicting sporadic miscarriage is **SLC39A8**. "*SLC39A8* encodes ZIP8, a divalent metal ion transporter. Mutations in the *SLC39A8* gene are associated with congenital disorder of glycosylation type II and Leigh syndrome. Notably, affected patients with both disorders exhibited severe manganese (Mn) deficiency."*

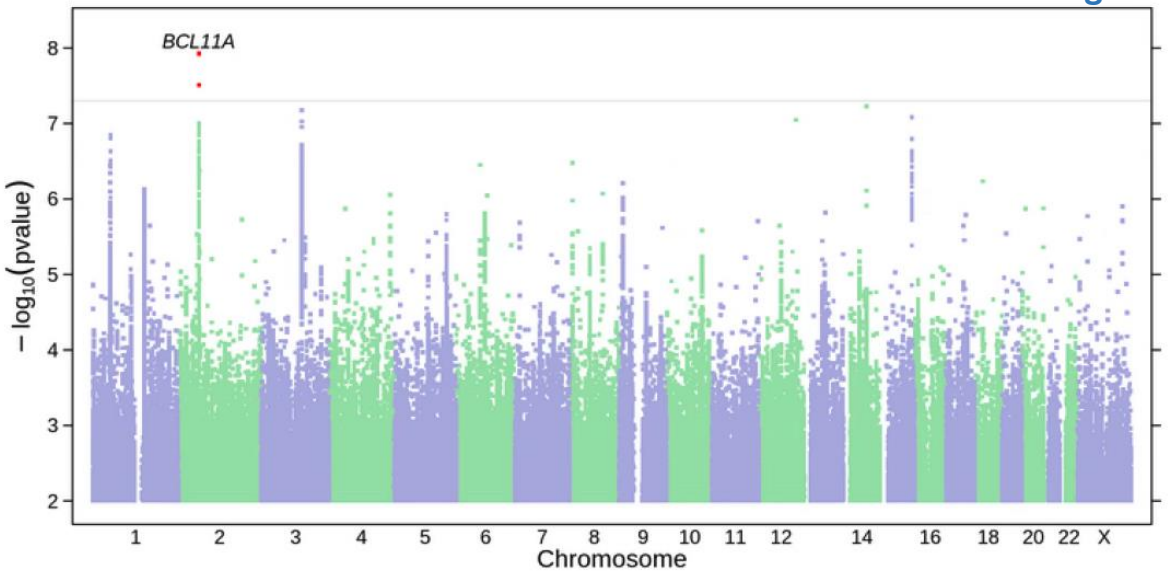
The top gene predicting recurrent miscarriage is **BCL11A**. "Recent studies have identified pathogenic mutations that cause heterozygous loss-of-function of BCL11A and result in a distinct neurodevelopmental disorder that is characterized by persistent HbF expression. "#

a

Manhattan Plot of Genes Associated with Sporadic Miscarriage



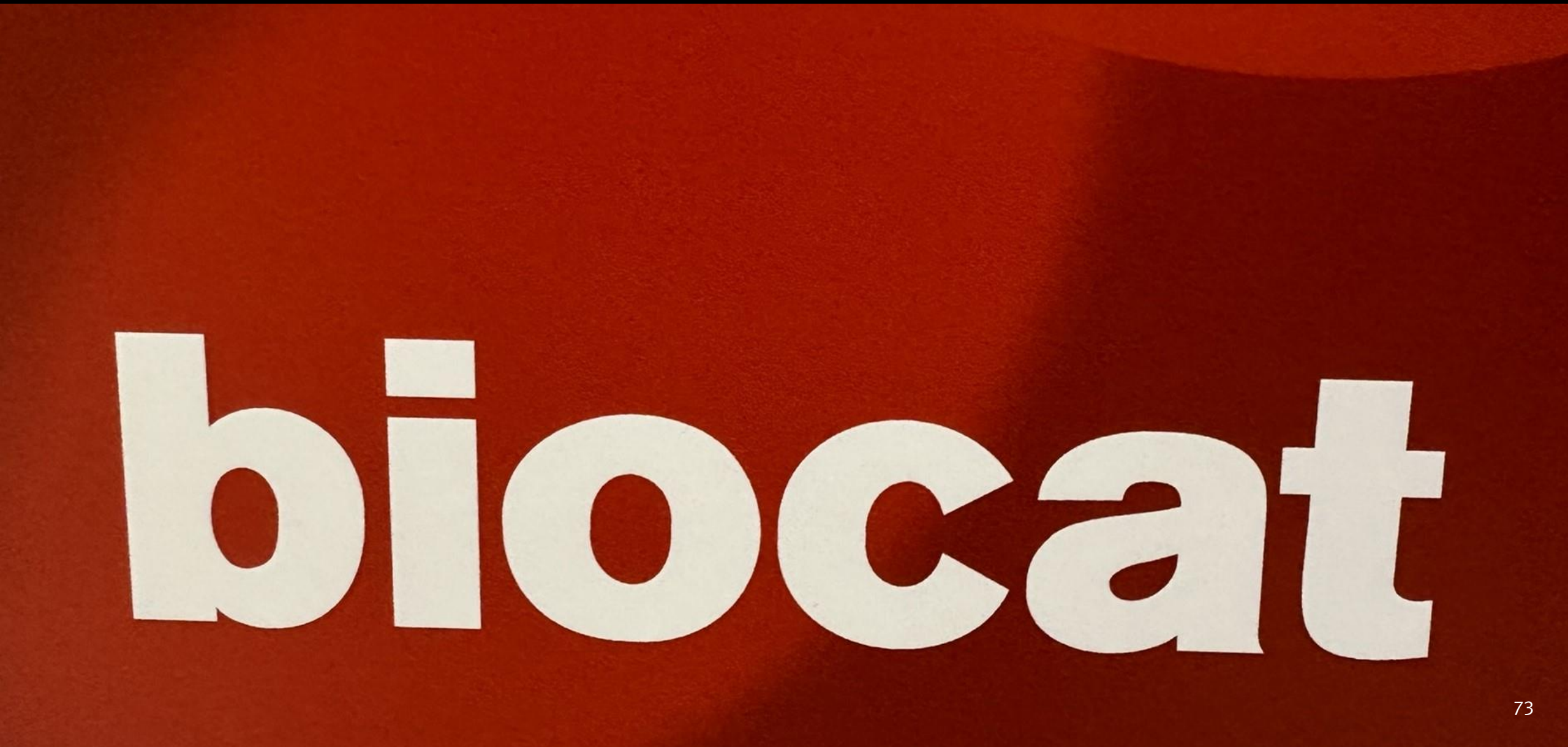
Manhattan Plot of Genes Associated with Recurrent Miscarriage



SNPs achieving genome-wide significance are highlighted in red. The nearest gene to each index SNP is indicated above the relevant association peaks.

* https://www.nature.com/articles/s41598-018-21464-0
\# https://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1009835

Life Sciences in Barcelona



Catalonia Rated A Top Region for Biotech Investment

Last week, we visited Catalonia as part of the Bio-Europe conference and were super-impressed by the quality of the local companies, the hospitality in the region and enterprising attitude of the Catalan people. The local scenery, amazing restaurants and late-night Bio-Europe events didn't hurt in making a great impression. In this section, we hope to give you a sense of what we learned on the visit.

Catalonia was recently voted the second-best place in Europe to invest in biotech, according to a recent industry report. The wider region stakes a claim to fame as Europe's densest pharma environment, with over 1400 life sciences companies, including globally-recognised names such as AstraZeneca, Sanofi, and Novartis. Barcelona's life sciences sector employs over 59,000 people, with a strong pipeline of fresh talent: there are over 52,000 students enrolled in life sciences courses in the Catalonia BioRegion.

Barcelona / Catalonia Region Strong in Life Sciences

1,400

companies and 91 research entities make up Catalonia's life sciences and healthcare sector

The industry's contribution of 4.1%, coupled with the impact of health activities at 3.8%, has yielded a combined economic impact of 7.9% on Catalonia's GDP

Industry and health services provide nearly 264,000 jobs (predominantly highly qualified talent), accounting for 6.5% of Catalonia's employed population.

The sector has seen higher growth than in previous years, with an annual average (CAGR) of 3.81%.

A total of 94% of the sector is concentrated in the province of Barcelona. SMEs make up 89% of the business network.

+€1,025 M

of Foreign Direct Investment in the sector in 2023, up 110% on last year

This boost was driven by the opening of the new R&D hub of the multinational AstraZeneca and Alexion, its rare diseases division. It is the largest foreign R&D investment project in Catalonia to date. Investments by foreign companies from the sector in the BioRegion between 2019 and August 2023 accounted for a total of €1,684 M in direct investment and have created over 4,600 jobs.

Between 2019 and 2023, 25 new hubs of excellence, digital development, tech centres and subsidiaries of large multinationals were established in the BioRegion of Catalonia. They have created and/or announced the creation of +5,000 new jobs.

On this point, +50% of Spain's pharmaceutical industry is based in Catalonia and it is the 2nd region in Spain in exports of life sciences and healthcare products.

+€220 M

in investment raised by startups and scaleups. 52% comes from venture capital (through 37 operations)

Despite the global geopolitical, financial and economic context, the investment has declined but remains above €200 M, a trend perceived prior to (the exceptional) 2022. Venture capital (52%) and subsidies (which have doubled) are the main sources of financing.

58% of venture capital raised had international participation, having a share in 13 operations. Despite declining international participation, +15 new VCs came to the BioRegion in 2023. By contrast, national participation has set new records: 36 VC firms have invested in 25 operations.

Digital health is the only subsector experiencing growing, with a 61% increase compared to the previous year and is coming close approaching its historical maximum with €64 M. Even if decreasing, biotech has exceeded +€110.

The highest operations in 2023 have been for InBrain Neuroelectronics (€20 M), Quida (€18 M) and Som Biotech (€17 M).

#3

in number of publications (per M hab) on advanced therapies in Europe

Catalonia leads the way in terms of capacities in the development of Advanced Therapy Medical Products (ATMP) in Spain. Hospital Clínic, Hospital Vall d'Hebron, Hospital de Can Ruti, Hospital de Sant Pau, Hospital Sant Joan de Déu, Banc de Sang i Teixits, Leitat, the UB and the UAB are stand-out institutions in advanced therapy research in Catalonia.

Catalonia holds 3rd position (per M hab) in terms of the number of scientific publications on ATMP in Europe, only behind Switzerland and the Netherlands, between 2013 and 2022.

In addition, Catalonia is the territory to have recorded a higher percentage of growth (156%) in this period.

For applications for patents in advanced therapies, Catalonia holds 6th position (per M hab) in Europe.

#5 in Europe, #8 worldwide

in participation in active clinical trials

The pharmaceutical industry is firmly committed to Catalan hospitals and institutes for the development of its clinical research and most innovative treatments, as it is here that it can find KOL and highly qualified professionals in many different clinical areas, high-level scientific facilities, a strong healthcare system, favourable regulations, and growing patient recruitment.

In 2023, 88.5% of all clinical trials in Spain were conducted in Catalonia (with 5,308 active trials), which places it 5th in Europe and 8th in the world.

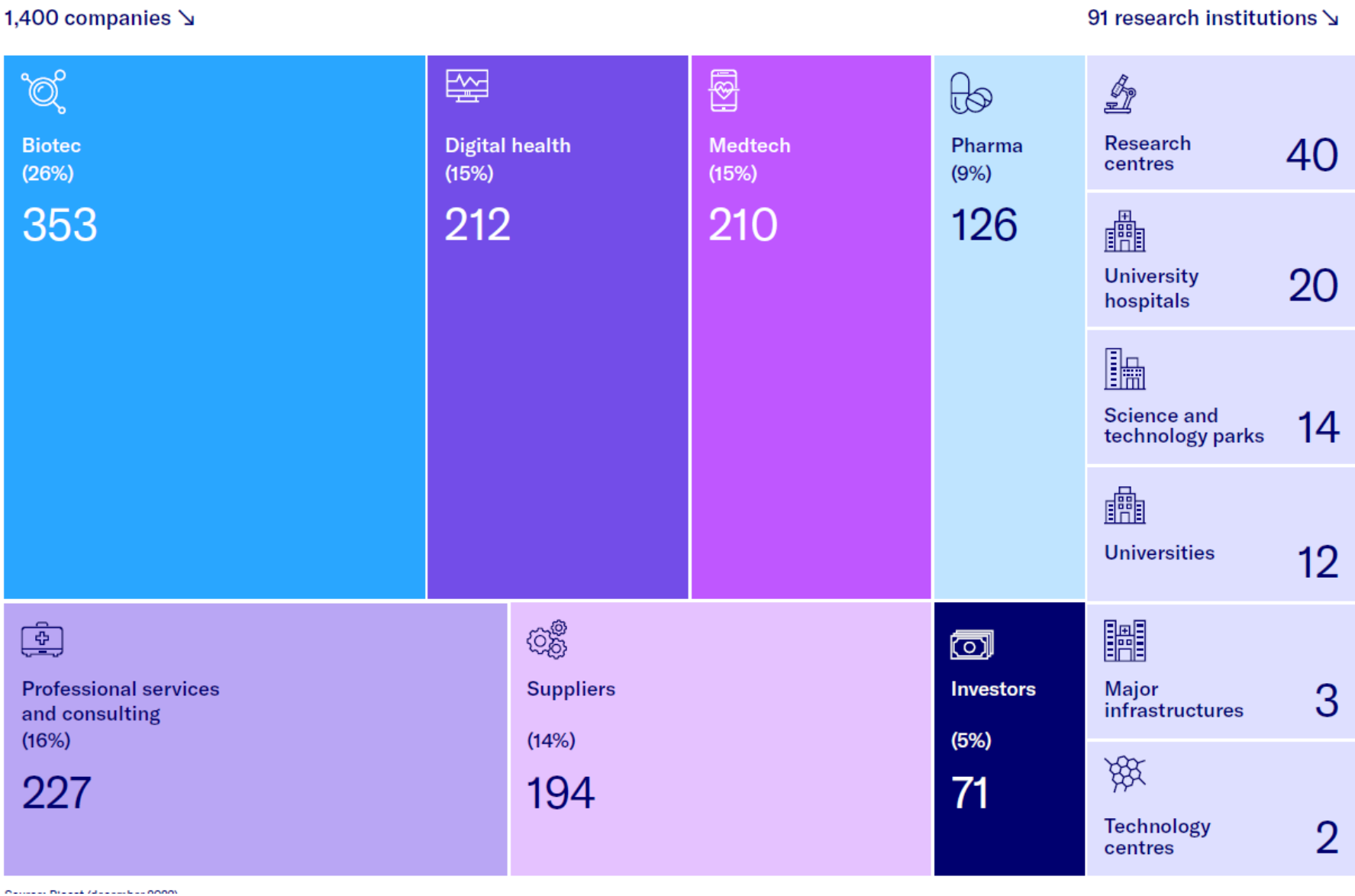
Source: report.biocat.cat

Catalonia's health innovation ecosystem

The life sciences and healthcare sector in Catalonia, commonly referred to as the 'BioRegion', emerges as a key catalyst for innovation, economic and social advancement in the region. Barcelona, hosting 94% of the sector, stands prominently as one of the most dynamic health research and innovation hubs in Europe.

As illustrated, by 2023, the health innovation ecosystem in Catalonia is projected to encompass nearly 1,400 companies and 91 research entities within the region. The collective economic impact of the industry (4.1%) and healthcare activities (3.8%) contributes to a significant economic influence on Catalonia's GDP, accounting for 7.9%. Together, the industry and health services sector generate nearly 264,000 jobs, representing 6.5% of the employed population.

Throughout 2023, most indicators measuring the expansion of the ecosystem evolved moderately or significantly, with the exception, as expected, of investment in venture capital. The sector continues to grow through the development of business initiatives and cutting-edge research projects, the mobilization and attraction of capital, the excellence of science developed in research entities and institutes, the quality and competitiveness of hospitals and the Health System, and the strategic support of the Administration. Ultimately, this growth is attributable to the highly qualified talent, both local and international, driving forward all players of the value chain within this sector.



Source: report.biocat.cat

Record in Foreign Direct Investment due to the attraction of AstraZeneca's R&D hub

Investments by foreign companies in the BioRegion between 2019 and 2023 accounted for a total of €1,684 million in direct investment, resulting in the creation of over 4,600 jobs.

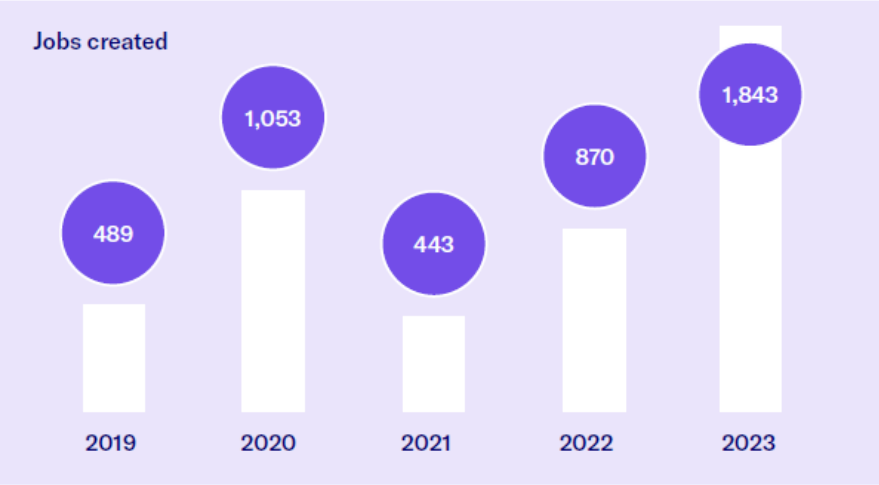
In just the 1st half of 2023, investment increased by 110% ompared to the previous year, and employment by 366%. This boost is the result of the announcement by the Anglo-Swedish multinational AstraZeneca and its division focused on rare diseases, Alexion, regarding the establishment of its Research and Development hub in Barcelona. This is the largest foreign R&D investment project in Catalonia to date, with an investment of nearly €825 million and a goal of creating more than 1,100 jobs.

In fact, as illustrated below, the United Kingdom leads the ranking of the main countries investing in Catalonia in recent years, followed by the United States and Japan.

Top 10 countries in terms of investment and jobs (2019-2023) ↘

Direct Investment (€M)		Jobs created	
United Kingdom	€824 M	United Kingdom	1,105
Japan	€216 M	United States	1,034
United States	€192 M	France	659
Switzerland	€165 M	Japan	510
France	€112 M	Switzerland	475
Germany	€56 M	India	348
India	€53 M	Germany	296
Netherlands	€48 M	Netherlands	117
Belgium	€8 M	Sweden	84
Norway	€3 M	Belgium	30

Foreign Direct Investment in the BioRegion (2019-2023)



Source: ACCIÓ based on FDI Markets. 2023 Data (provisional)

Source: report.biocat.cat

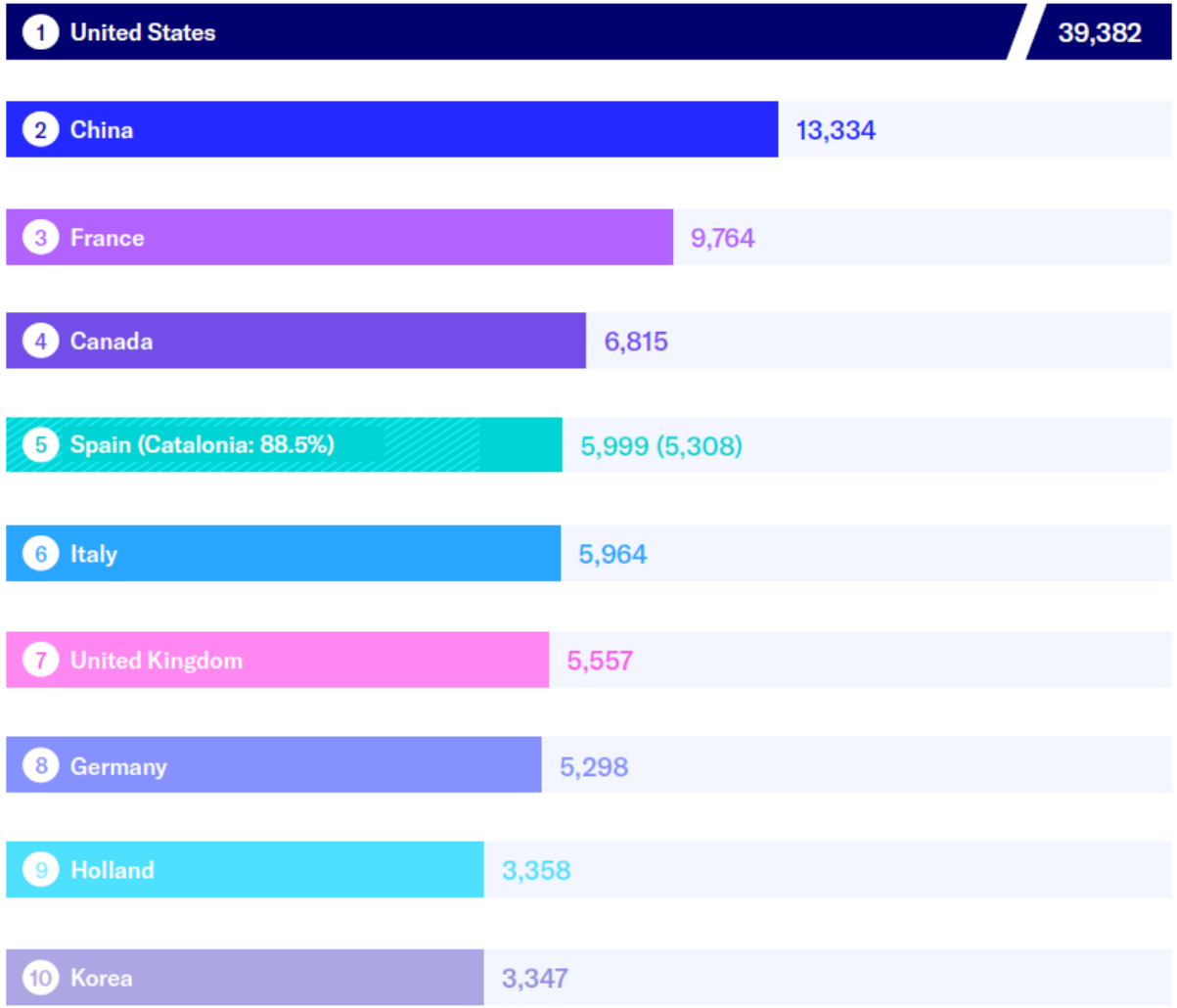
Catalonia ranks 5th in Europe and 8th worldwide in active clinical trials

Catalonia continues to be a preferred destination for attracting and conducting clinical trials. The pharmaceutical industry demonstrates a strong commitment to Catalan hospitals and research institutes for advancing clinical research and developing cutting-edge treatments. Catalonia offers a wealth of KOL and highly skilled professionals across various clinical specialties, state-of-the-art scientific infrastructure, a robust healthcare system, favorable regulatory environment, and growing patient recruitment.

With 88.5% of all clinical trials in Spain conducted in Catalonia, totaling 5,308 active trials, Catalonia holds the 5th position in Europe and the 8th position globally.

Among the various clinical areas, Catalonia particularly excels in oncology trials, which represent 34% of the total, followed by other therapeutic areas such as the immune system and the respiratory system. Catalonia maintains its position within the top 10 in several key therapeutic areas on an international scale.

World top 10
Number of active clinical trials (2023)



Source: Clinicaltrials.gov
Note: Active clinical trials include those in the following recruitment statuses: "Not yet recruiting", "Recruiting", "Enrolling by invitation" and "Active, not recruiting".

Number of trials per clinical area. International comparison (2023)

Clinical area	Active clinical trials	European ranking	World Ranking
Oncology	1,823	#4	#7
Immune system	586	#6	#9
Respiratory system	515	#6	#9
Nervous system	459	#7	#10
Cardiovascular system	457	#7	#11
Dermatology	385	#5	#8
Digestive system	380	#6	#10
Haematology	295	#6	#9
Mental health	157	#6	#9
Metabolic diseases	155	#7	#10

Source: report.biocat.cat

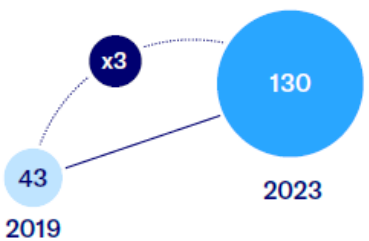
Evolution in attracting investment firms

In 2023, in contrast to the trend of the past four years, national investment firms experienced above-average growth, reaching a total of 36, which is double the number of investors compared to 2019.

Additionally, the presence of individual international investors in 2023 decreased to 25 (14 fewer than in 2022, primarily from Europe), aligning with the decline in the volume of operations observed in previous indicators. American and Asian investors maintained their activity through 6 different operations.

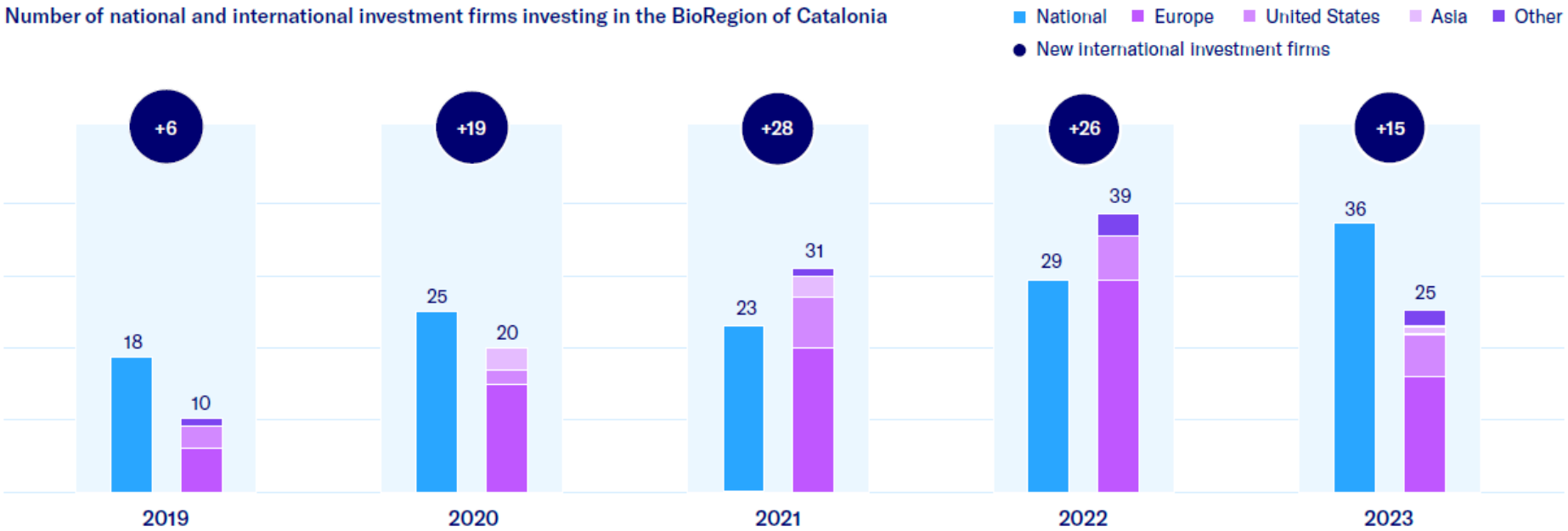
Despite the decrease in 2023, the evident attraction of international capital to the BioRegion is reflected in the consistent annual increase of 15 to 30 new investors since 2020. This trend has culminated in a total of 130 investment firms actively supporting health startups and scaleups established in Catalonia.

Number of international firms that have participated in investment rounds in the BioRegion ↘



Source: Biocat

Number of national and international investment firms investing in the BioRegion of Catalonia



Note: each year, the different investment firms investing in the BioRegion are included. Each investor is counted only once per year.

Most active international investors (2013 - 2022) ↘

AurorA-TT, Boehringer Ingelheim, BoxOne, bpifrance, Bristol Myers Squibb, Chan Zuckerberg Initiative, Chiesi Ventures, European Innovation Council, Fund+, Gilde Healthcare, idinvest Partners, INNOGEST, Kurma Partners, Mangrove Capital Partners, MTIP, NEA, NF, Omega Funds, Philips, Pontifax, Roche, Siemens, Speedinvest, TA Ventures, Takeda, UCB Ventures, UNIQA Ventures, wellingtonpartners

Most active investors 2023 ↘

International

AdBio partners, elaia, European Investment Bank, Philips Ventures, Prevail Partners, Sofinnova partners, USCapital

Established in Catalonia

asabys, Sabadell BStartup, CaixaBank, clavecapital, Fundación Josep Carreras, invivocapital, Lavanda, NARA, Ship2B Ventures, WA4STEAM

Source: report.biocat.cat

Catalonia Home to Nine Pharma Enterprises with More Than $100 Million in Revenue

Source: CapitalIQ and Stifel research.

Catalonia Home to Numerous Promising Biotechs

ABAC Therapeutics
(Precision antimicrobials, PC)

AbilityPharma real medicine for real life
(Autophagy for Cancer, Ph 2b)

accure therapeutics
(Trophic factors in neuro, Ph 2)

AELIX THERAPEUTICS
(HIV Vaccines, Ph 1)

AHEAD THERAPEUTICS
(B-cell therapy for myasthenia, PC)

Aptadel therapeutics
(RNA therapies for cancer, PC)

ARCHIVEL farma
(TB vaccine, Phase 2b)

A&G
(Cancer metabolism, Preclinical)

Integra therapeutics
(Novel gene writing tools, PC)

NUAGE THERAPEUTICS
(biomolecular condensates, PC)

ONA THERAPEUTICS
(ADC's for cancer, Preclin)

ONIRIA® THERAPEUTICS
(Cell dormancy and cancer , PC)

ORYZON
(Epigenetics & CNS, Phase 2)

SOM BIOTECH
(VMAT for Huntington's, Ph 2)

SPLICEBIO
(Novel gene therapies for rare disease, Preclinical)

Source: DealForma

The scale up of rounds, M&A and business exits

In this compilation of transactions, investment rounds, business exits and mergers and acquisitions (M&A) from 2021 to 2023, a notable presence of startups and scaleups is observed across the board. However, in 2023, as previously mentioned, there is a notable absence in the category of large operations (exceeding €40 M) and mega-operations (exceeding €100 M). Additionally, a decline is noted in the number of exits and M&A activities. Noteworthy events include the merger between Amelia and the US company XRHealth, establishing the new entity as a global leader in virtual reality therapies. Furthermore, Palex Medical,
a prominent European group specializing in technology and equipment for the hospital sector, made three acquisitions.

M&A activity in the BioRegion 2023 ↘

Acquirer		Target	
Applus	(CAT)		(FR)
BVI	(US)	MEDICALMIX	(CAT)
Corus	(CAT)	GIRAUD	(FR)
GRIFOLS	(CAT)	Access Biologicals LLC	(US)
Impress	(CAT)	DW	(UK)
Kriya	(US)	TRAMONTANE TX	(CAT)
PANGAEA	(CAT)	PECTUS	(CAT)
Palex	(CAT)	burke&burke	(IT)
Palex	(CAT)	Isoder	(PT)
Palex	(CAT)	MTW Iberica	(ES)
TOPDOCTORS	(CAT)	iWantGreatCare	(UK)
XRHealth	(US)	amelia by XRHealth	(CAT)
ZENDAL	(ES)	MAYMO	(CAT)

Note: refer to page 17 of the BioRegion 2022 Report to see all M&A operations in historical context.

	2021	2022	2023
Exits	GOODGUT, Infinitec, DSR Leading in DAO Deficiency, bioinfogate, DDR, VCN BIOSCIENCES, FISIOPHARMA	mimetis, ALIFARM, MOLOMICS, Vesimin Health, Abamed Pharma, MICROPTIC, vytrus biotech[1], LABIANA[1,2]	amelia by XRHealth, PECTUS, TRAMONTANE TX, MEDICALMIX
€100-250 M		Impress[B]	
€40-100 M	Impress[A,C]	minoryx[C], SPLICEBIO[A]	
€15-40 M	Corus, Koa Health[A,2]	deepull, seqera[A], INBRAIN NEUROELECTRONICS	INBRAIN NEUROELECTRONICS, Qida[A], SOM[B]
€4-15 M	INBRAIN NEUROELECTRONICS, IMIDomics[A], TOPDOCTORS[B], mediktor, VEnvirotech, ANACONDA BIOMED, SEQUENTIA, abzu, BOKA DABA[A], seqera, Integra therapeutics[A], AORTYX	PANGAEA[1,2], PEPTOMYC, Durcal, amelia by XRHealth[A], kriba[2], timeisbrain, MEDSIR[2], oliva, ELEM, NOVA MEAT, cuideo[B]	NUAGE THERAPEUTICS, IOMED[A], OneChain, TOPDOCTORS, KORIKINE BIO, ADMit[A], oliva[A], PEPTOMYC, deepull[B]
€1-4 M	vitaance, NUAGE THERAPEUTICS, HumanITcare, eodyne, devicare[A], mediQuo, telomere therapeutics, oliva, NOVA MEAT, AELIX, in.bio.motion, Aptadel, MIMVRK, amelia by XRHealth[A], cebiotex, Qida[B], ELEM, mjn-neuro, VB DEVICES, Pharmaceiera, KINTSUGI THERAPEUTICS, ima	NANOLIGENT, TECNIC, Methinks, abzu, GATE2BRAIN, vytrus biotech[1], oxolife, innerva, Pulmobiotics, Integra therapeutics, Bioo, Biotest, DyCare, AbilityPharma, OneChain, onalabs, Loop[2], able, VB DEVICES, telomere therapeutics, mediQuo, Floxxics	MIMVRK, NIMBLE Diagnostics, Methinks, IEL, vitaance, Leanbio Pro, acceXible[2], MatchTrial, GATBIO, GLYCO SCIENCE[2], aromics, onalabs, omniscope[2], FreeOx, MANNA MEDTECH, ZYMVOL, ONIRIA THERAPEUTICS, idpharma, mediQuo, CUANTUM MED COG, Genie, renalyse, KAMLEON, Sight

[A] Series A
[B] Series B
[C] Series C

[1] Listed on the BME.
[2] Company headquartered outside of Catalonia but with mainly activity in Catalonia.

Source: Biocat

Note: the companies included are those that have successfully closed an operation (either private or a public grant) with a value equal to or exceeding €1 M. Exit is considered when a company is acquired or undergoes an initial public offering (IPO).

Source: report.biocat.cat

Bacterial Infections and Colon Cancer

Town Square, Barcelona.

Fusobacterium Nucleatum (Fn) is a Common Inhabitant of Human Oral Cavity

Groeger S, Zhou Y, Ruf S, Meyle J. Pathogenic Mechanisms of Fusobacterium nucleatum on Oral Epithelial Cells. Front Oral Health. 2022 Apr 5;3:831607.

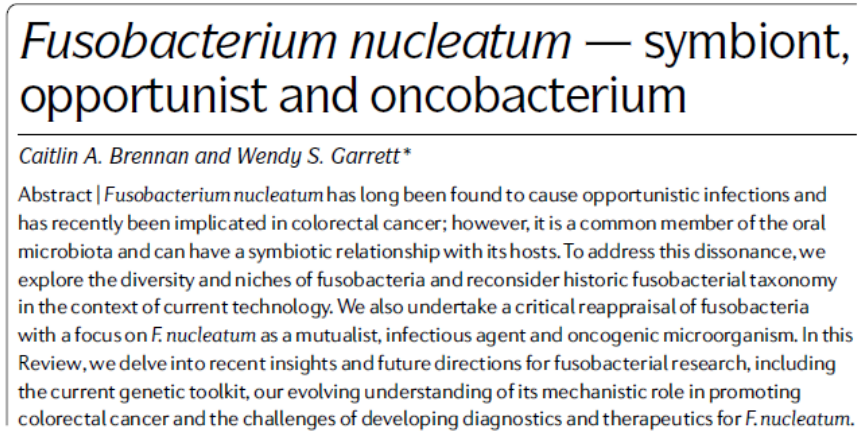
Fusobacterium nucleatum (F. nucleatum) is one of the common inhabitants of the oral cavity and has been identified as a potential etiologic bacterial agent of oral diseases, such as periodontitis and oral carcinomas. F. nucleatum has been shown to be of importance in the development of diverse human cancers. In the dental biofilm, it exhibits a structural role as a bridging organism, connecting primary colonizers to the largely anaerobic secondary colonizers.

It expresses adhesins and is able to induce host cell responses, including the upregulation of defensins and the release of chemokines and interleukins. Like other microorganisms, its detection is achieved through germline-encoded pattern-recognition receptors (PRRs) and pathogen-associated molecular patterns (PAMPs). By identification of the pathogenic mechanisms of F. nucleatum it will be possible to develop effective methods for the diagnosis, prevention, and treatment of diseases in which a F. nucleatum infection is involved.

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9037381/

F. Nucleatum is an Important Oral Bacterial Player

Brennan and Garrett, *Nature Reviews Microbiology*, 2019



Fusobacterium nucleatum — symbiont, opportunist and oncobacterium

*Caitlin A. Brennan and Wendy S. Garrett**

Abstract | *Fusobacterium nucleatum* has long been found to cause opportunistic infections and has recently been implicated in colorectal cancer; however, it is a common member of the oral microbiota and can have a symbiotic relationship with its hosts. To address this dissonance, we explore the diversity and niches of fusobacteria and reconsider historic fusobacterial taxonomy in the context of current technology. We also undertake a critical reappraisal of fusobacteria with a focus on *F. nucleatum* as a mutualist, infectious agent and oncogenic microorganism. In this Review, we delve into recent insights and future directions for fusobacterial research, including the current genetic toolkit, our evolving understanding of its mechanistic role in promoting colorectal cancer and the challenges of developing diagnostics and therapeutics for *F. nucleatum*.

Fusobacteria are Gram-negative anaerobic bacilli with species-specific reservoirs in the human mouth, gastrointestinal tract and elsewhere. An association between the presence of F. nucleatum and human colorectal cancer has emerged across both patient populations and disease stages. F. nucleatum has long been considered as an opportunistic pathogen given its frequent isolation and identification in anaerobic samples from patients with different infections. Although well known to the oral and medical microbiologist, the role of F. nucleatum as a cancer-causing member of the microbiota is still emerging and is revealing the multifaceted ways in which a bacterium can contribute to the development, growth, spread of and treatment response to cancer. Herein, we undertake a critical reappraisal of fusobacteria with a focus on F. nucleatum as a mutualist, infectious agent and oncobacterium.

Main reservoir is oral

Whereas F. nucleatum is fairly ubiquitous in the oral cavity, its usually low levels in the gut are increased in patients with inflammatory bowel disease and can be modulated by factors such as diet.

Source: https://www.nature.com/articles/s41579-018-0129-6

F. Nucleatum is Very Good at Triggering Inflammatory Responses

Brennan and Garrett, *Nature Reviews Microbiology*, 2019

Whereas *F. nucleatum* has a mutualistic relationship with the other members of the oral microbiota, its interactions with human tissues — whether oral or extraoral — span from neutral to pathogenic in nature. Although the oral biofilms it helps coordinate are found on tooth surfaces in healthy individuals, F. nucleatum is also important in periodontitis as it directly shapes host responses and increases the infectivity of other pathogens. Specifically, F. nucleatum can induce expression of the antimicrobial peptide β-defensin 2 and pro-inflammatory cytokines, including IL-6 and IL-8, in the oral epithelium.

Such F. nucleatum-driven inflammation contributes to disease progression in a model of oral tumorigenesis. In these pathogenic settings, F. nucleatum influences the function of immune cells, such as myeloid cells, in which it activates NF-κB, resulting in TNF production. As periodontitis is a polymicrobial disease, unravelling how F. nucleatum interacts with other oral microorganisms to drive disease is of utmost importance. Co-infection of macrophages by both F. nucleatum and P. gingivalis blunts inflammasome activation compared with infection with F. nucleatum alone20. Beyond modulating these host responses, F. nucleatum also increases the invasive potential of P. gingivalis, suggesting that these bacteria act cooperatively to evade destruction by the immune system and to develop an inflammatory-permissive environment during periodontitis.

Source: https://www.nature.com/articles/s41579-018-0129-6

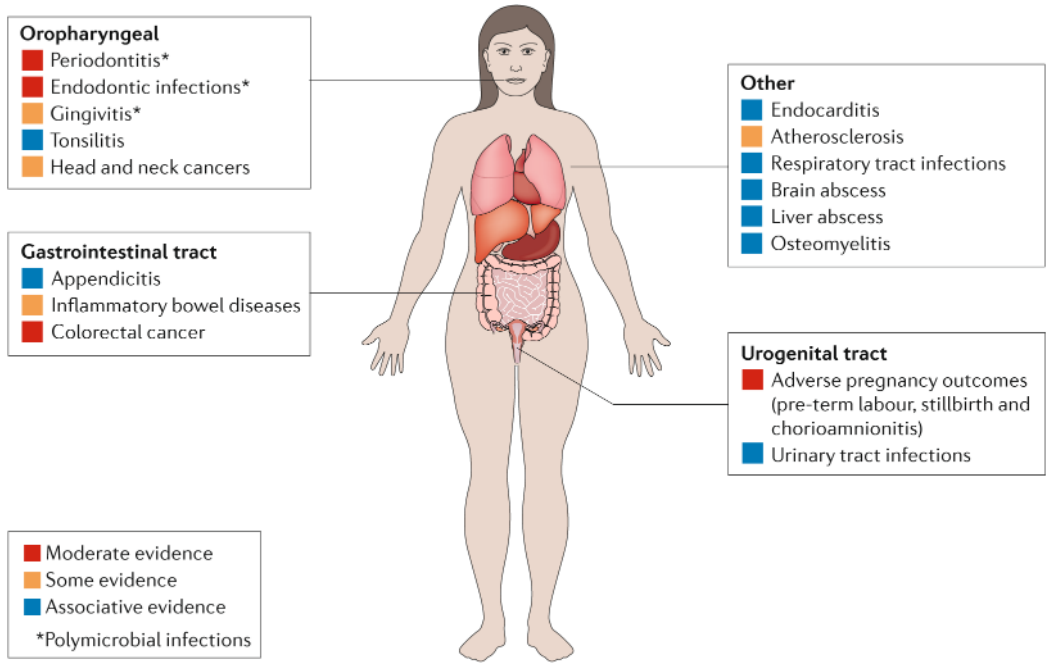
Growing Evidence that *F. Nucleatum* is Causative in a Number of Diseases

Brennan and Garrett, *Nature Reviews Microbiology*, 2019

The contribution of F. nucleatum to extraoral diseases remains rather mechanistically speculative. Although F. nucleatum has been isolated from clinical specimens in a variety of diseases, including appendicitis, brain abscesses, osteomyelitis, pericarditis and adverse pregnancy outcomes such as chorioamnionitis (see figure), the role of F. nucleatum in these pathologies remains unclear. Some have suggested that F. nucleatum is a passenger in these disease states rather than a disease driver. However, F. nucleatum can promote inflammatory responses, as discussed in periodontitis, and can bind and/or invade diverse cell types, including oral, colonic and placental epithelial cells, T cells, keratinocytes and macrophages, among others. Taken together, these observations suggest that F. nucleatum may have a causative role in several infections, but they do not provide evidence to confirm Koch's postulates.

Adverse pregnancy outcomes, such as placental infections and pre-term birth, are the extraoral diseases with the most data supporting a role for F. nucleatum as a driver or causative agent of disease. F. nucleatum is the most common organism isolated from amniotic fluid in pre-term births and can invade the relevant cell type — human umbilical endothelial cells. A specific F. nucleatum adhesin, FadA, has been implicated in these functions.

Oral and extraoral diseases associated with *Fusobacterium nucleatum*.



Source: https://www.nature.com/articles/s41579-018-0129-6

F. Nucleatum Seen Behind Some Colorectal Cancers and Other Cancers

Chen Y, Huang Z, Tang Z, Huang Y, Huang M, Liu H, Ziebolz D, Schmalz G, Jia B, Zhao J. More Than Just a Periodontal Pathogen -the Research Progress on Fusobacterium nucleatum. *Front Cell Infect Microbiol.* 2022 Feb 3;12:815318.

Fusobacterium nucleatum, which exists in the oral cavity and gastrointestinal tract of humans, is an opportunistic pathogen causing different infectious diseases in the oropharynx and other parts of the oral cavity. These include appendicitis (Swidsinski et al., 2011), pericarditis (Truant et al., 1983), brain abscess (Han et al., 2003), osteomyelitis (Gregory et al., 2015), and chorioamnionitis (Altshuler and Hyde, 1988). F. nucleatum was first discovered in periodontal diseases and considered a potential periodontal pathogen (de Andrade et al., 2019). With improvements in microbial detection technology, a higher number of previously neglected microorganisms were found to play an important role in human diseases. Based on recent studies, F. nucleatum was associated with extra-oral malignancies, including colorectal cancer, breast cancer, esophageal squamous cell carcinoma, and gastric cancer (Kostic et al., 2012; Hsieh et al., 2018; Yamamura et al., 2019; Parhi et al., 2020). Moreover, the mechanisms of F. nucleatum affecting colorectal cancer (CRC) are important issues. Its role in extra-oral tumors suggests that it may also be important in oral cancer, and this has aroused a significant interest among scholars. However, its specific carcinogenic mechanisms in the oral field are unclear. Therefore, the role and specific mechanisms of this bacterium in different oral and extraoral diseases were examined.

Source: https://www.frontiersin.org/articles/10.3389/fcimb.2022.815318/full

Most CRC Has F. Nucleatum

Kurt M, Yumuk Z. Diagnostic accuracy of Fusobacterium nucleatum IgA and IgG ELISA test in colorectal cancer. Sci Rep. 2021 Jan 15;11(1):1608.

Colorectal cancer is a serious health problem. The diagnosis of the disease mostly relies on an invasive procedure. A non-invasive diagnostic test such as an immunoassay, may facilitate diagnosis of colorectal cancer. The purpose of the study was to evaluate the use of antibodies against Fusobacterium nucleatum in the diagnosis of colorectal cancer (CRC). Totally 78 patients in three groups were included in the study. F. nucleatum in the tissues was detected using quantitative polymerase chain reaction assay. F. nucleatum IgA and IgG were measured using enzyme linked immunosorbent assay. F. nucleatum was detected in 86.7% and 73.1% cases of CRC and precancerous-benign colon disease (P-BCD), respectively. The OD values from F. nucleatum IgA and IgG ELISA tests were higher in CRC group compared with healthy individuals. The sensitivity of IgA ELISA test varied between 31.8 and 95.5% depending on the chosen cut-off values. The positivity rate of antibodies in patients with high amount of F. nucleatum in tissue was significantly greater than in the negative group. The F. nucleatum IgA and IgG antibodies in CRC were higher than the ones in healthy controls but the discriminative ability of the ELISA test was not adequate to be considered as a diagnostic tool.

Source: https://pubmed.ncbi.nlm.nih.gov/33452405/

F. Nucleatum Levels Linked to Worse Colorectal Cancer Prognosis

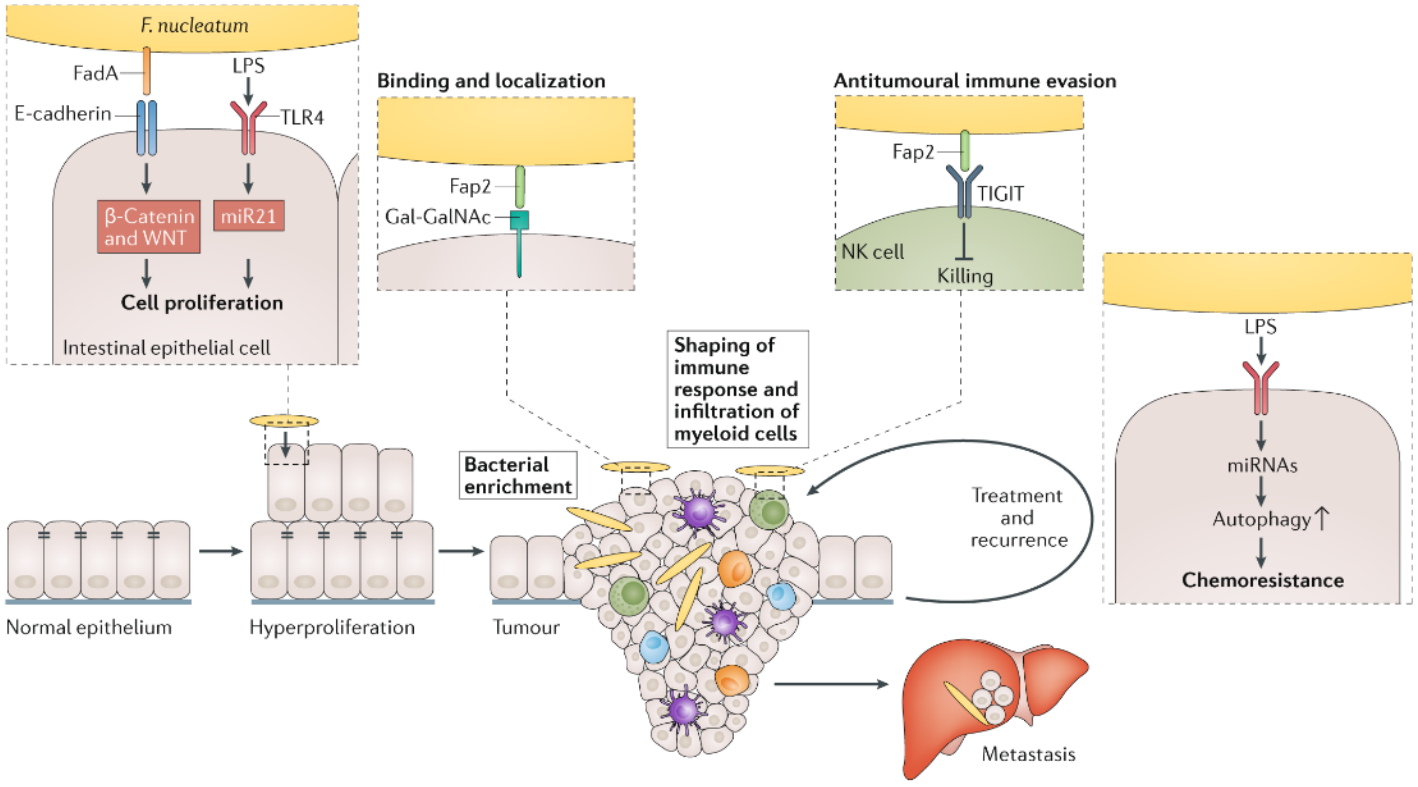
Brennan and Garrett, *Nature Reviews Microbiology*, 2019

Although experimental research into the mechanisms by which F. nucleatum influences colorectal cancer is ongoing, epidemiological studies have enabled timely advances into the connections between intratumoural F. nucleatum levels and colorectal tumorigenesis. The most striking of these observations is that high F. nucleatum abundance is associated with poorer patient prognosis and cancer recurrence owing, in part, perhaps, to F. nucleatum promoting resistance to chemotherapy in colorectal cancer tissues. By linking F. nucleatum abundance to specific tumour phenotypes, such research has further supported the hypothesis that F. nucleatum influences the tumour microenvironment in consistent ways that may be ultimately exploited to shape colorectal cancer treatment. F. nucleatum-high colonic lesions (either malignant or pre-malignant) have further been subtyped according to microsatellite stability, CpG island methylator phenotype (CIMP) status, those bearing certain mutations (BRAF, KRAS, TP53 and others) and localization to the proximal versus transverse or sigmoid colon. Collectively, these data support that there are links between F. nucleatum and tumour genetics and epigenetics that warrant further research. In the near future, tumoural microorganisms might be as influential as tumoural host genetics in guiding prognosis and treatment decisions, and microbial profiling may soon become as routine as tests of the genetic tumour profile. Tumours with a high F. nucleatum burden also have reduced T cell density, supporting experimental research that F. nucleatum contributes to antitumour immunity. Epidemiological studies have also begun to address how exposures and lifestyle, such as diet and antibiotics, may influence F. nucleatum abundance in the setting of colorectal cancer, prompting consideration of whether interventions designed to influence F. nucleatum levels in the body are beneficial for the prevention of colorectal cancer or detrimental to one's native microbiota.

Source: https://www.nature.com/articles/s41579-018-0129-6

F. Nucleatum Levels Linked to Worse Colorectal Cancer Prognosis

Brennan and Garrett, *Nature Reviews Microbiology*, 2019



Source: https://www.nature.com/articles/s41579-018-0129-6

Accumulating evidence suggests that *Fusobacterium nucleatum* influences many stages of colorectal cancer progression. First, *F. nucleatum* can increase cell proliferation in cancer cells through two distinct mechanisms: the binding of FadA to E-cadherin drives activation of the β-catenin and Wnt pathway, and activation of TLR4 and NF-κB results in increased expression of the oncogenic microRNA miR21. These observations are supported by work in the $Apc^{Min/+}$ mouse model of intestinal tumorigenesis, in which *F. nucleatum* administration resulted in more aberrant crypt foci and high-grade dysplasia, both early stages of tumorigenesis. Once the tumour has developed, *F. nucleatum* can localize to the Gal-GalNAc-expressing tumour cells through binding of its Fap2 lectin, which results in enrichment of *F. nucleatum*. *F. nucleatum* functionally modifies the tumour microenvironment by influencing the accumulation of myeloid cells and blocking antitumoural immune responses of natural killer (NK) cells[45]. *F. nucleatum* may also affect metastatic dissemination as it can be isolated from liver and lymph node metastases[40,41,46]. Once colorectal cancer is identified and treated, *F. nucleatum* is associated with increased risk of recurrence and the development of chemoresistance by suppressing specific miRNAs involved in autophagy[59]. LPS, lipopolysaccharide.

Paper Last Week Identifies a Subspecies of *F. Nucleatum* Associated with CRC

Martha Zapeda-Rivera, Christopher Johnson et.al., *Nature*, March 20, 2024

Fusobacterium nucleatum (Fn), a bacterium present in the human oral cavity and rarely found in the lower gastrointestinal tract of healthy individuals is enriched in human colorectal cancer (CRC) tumours. High intratumoural Fn loads are associated with recurrence, metastases and poorer patient prognosis. Here, to delineate Fn genetic factors facilitating tumour colonization, we generated closed genomes for 135 Fn strains; 80 oral strains from individuals without cancer and 55 unique cancer strains cultured from tumours from 51 patients with CRC. Pangenomic analyses identified 483 CRC-enriched genetic factors. Tumour-isolated strains predominantly belong to Fn subspecies *animalis* (Fna). However, genomic analyses reveal that Fna, considered a single subspecies, is instead composed of two distinct clades (Fna C1 and Fna C2). Of these, only Fna C2 dominates the CRC tumour niche. Inter-Fna analyses identified 195 Fna C2-associated genetic factors consistent with increased metabolic potential and colonization of the gastrointestinal tract. In support of this, Fna C2-treated mice had an increased number of intestinal adenomas and altered metabolites. Microbiome analysis of human tumour tissue from 116 patients with CRC demonstrated Fna C2 enrichment. Comparison of 62 paired specimens showed that only Fna C2 is tumour enriched compared to normal adjacent tissue. This was further supported by metagenomic analysis of stool samples from 627 patients with CRC and 619 healthy individuals. Collectively, our results identify the Fna clade bifurcation, show that specifically Fna C2 drives the reported Fn enrichment in human CRC and reveal the genetic underpinnings of pathoadaptation of Fna C2 to the CRC niche.

Source: https://www.nature.com/articles/s41586-024-07182-w

For those of you nerdy enough to get this far, this paper is a stunner.

These authors found that a specific clade of a subspecies of Fn called *Fusobacterium Nucleatum Animalis C2* dominates colorectal cancers.

This does not prove causation. Perhaps only this strain is able to survive in the hypoxic CRC micro-environment.

But this finding sharpens the hypothesis considerably that a strain of fusobacterium plays a causative role in colorectal cancer.

Discussion of Zapeda-Rivera Paper

Medical research

A bacterial strain linked to colon cancer is pinpointed

Cynthia L. Sears & Jessica Queen

Understanding the factors that drive formation of particular types of cancer can aid efforts to develop better diagnostics or treatments. The identification of a bacterial subspecies with a connection to colon cancer has clinical relevance.

Certain types of cancer, such as colon cancers, are associated with the presence of bacteria in the vicinity of the tumour. Writing in *Nature*, Zepeda-Rivera *et al.*[1] reveal new clues in the quest to pinpoint the specific strain of bacterium implicated in human colon cancer.

The bacterium *Fusobacterium nucleatum* is an infrequent, yet potentially lethal, cause of dangerous inflammation (sepsis) and infections of gynaecological tissue. It is present in nearly all human mouths, where it contributes clusters of Fusobacteria. Next-generation DNA sequencing of colorectal cancer from around the globe revealed an even broader array of Fusobacteria species associated with these types of tumour[6].

The link between these species and colorectal cancer was securely established after clinical studies revealed that abundant Fusobacteria in colorectal cancer are associated with disease recurrence, cancer spread (metastasis) and poor outcomes for Fusobacteria, that accelerates the formation of cancer in the colon? Is early growth of abnormal cells (neoplasia) in the colon associated with Fusobacteria colonization? Do specific, bacterially released molecules called virulence factors or the bacterium's metabolic properties mediate Fusobacteria-associated promotion of colorectal cancer?

Zepeda-Rivera and colleagues provide data that narrow the burgeoning complexity of Fusobacteria and colorectal cancer to one culprit, *F. n. animalis*, confirming previous hints[10,11] that this is the subspecies relevant to colorectal cancer. Most unexpected among the authors' detailed studies are their data splitting *F. n. animalis* into two distinct clades (descendants of a common ancestor). Both clades colonize the mouth, but only one is highly prevalent in the tumour microenvironment (Fig. 1). These striking findings arise from the powerful integration of evidence gathered through microbial genetics, sequencing of multiple genomes in colorectal tumours and faecal samples, sampling of colorectal cancer and normal human colon tissues, and model studies in mice.

The most compelling results presented by Zepeda-Rivera *et al.* come from their genetic analyses that identified the two clades of

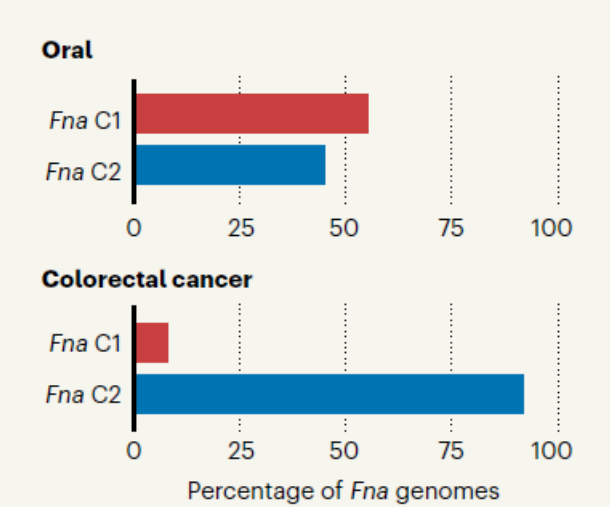


Figure 1 | *Fusobacterium nucleatum animalis* (*Fna*) microbes in the human mouth and in colorectal cancer samples. Zepeda-Rivera *et al.*[1] report that this bacterium associated with colorectal cancer can be divided into two clades. Clade 2 (C2) is highly prevalent in tumours. (Adapted from Fig. 2f of ref. 1.)

Source: https://www.nature.com/articles/d41586-024-00662-z

Disclosure

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