Biopharmaceutical Sector

Weekly Update – March 18, 2024

STIFEL | Healthcare

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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 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)
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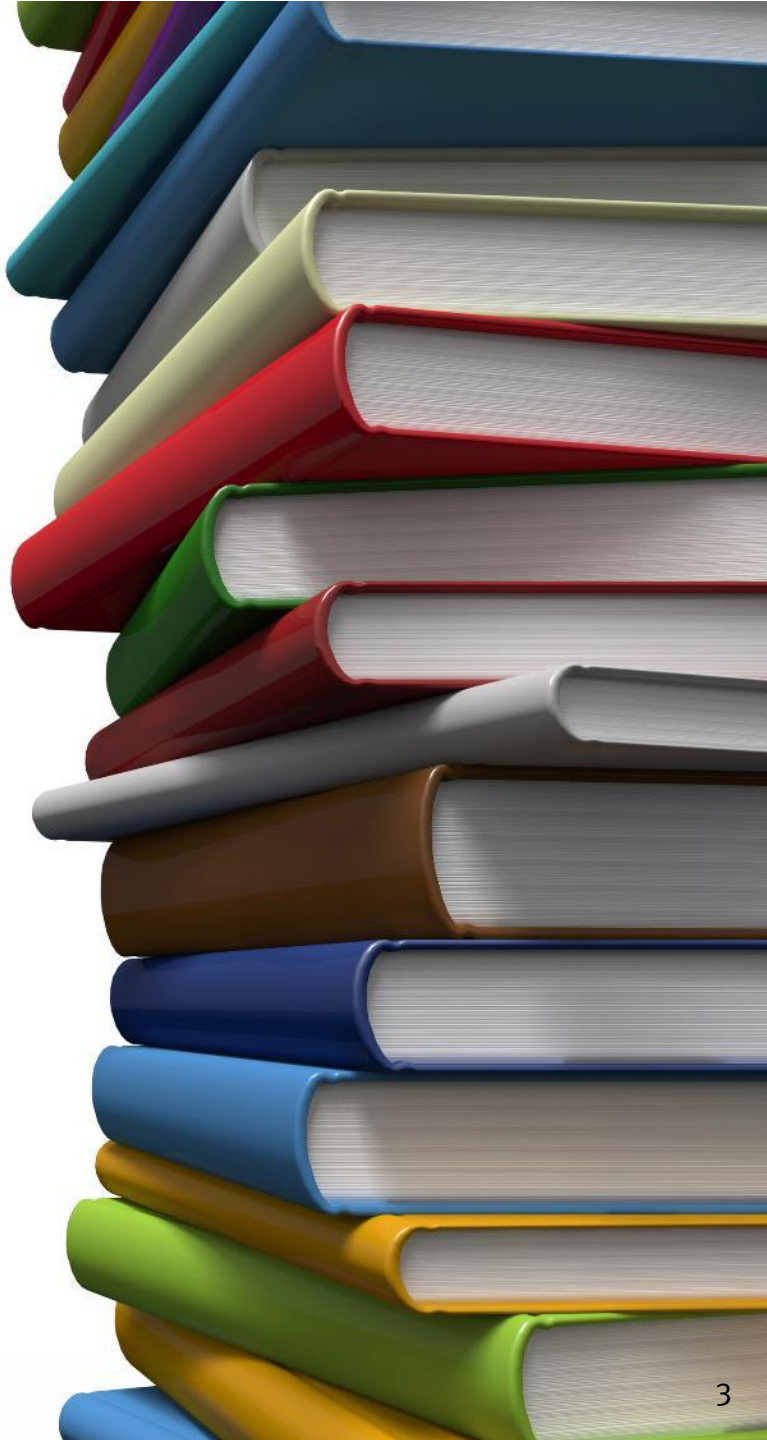
August 21, 2023 (Covid, China)
August 7, 2023 (Employment, Summer reading)
July 24, 2023 (Alzheimer's Disease)
July 7, 2023 (Biotech market review – H1 '23)
July 1, 2023 (Obesity drugs)
June 19, 2023 (Generative AI)
June 12, 2023 (IRA, State of Industry)
May 29, 2023 (Oncology update)
May 22, 2023 (FTC case on Amgen/Horizon)



Join Us at Biotech Hangout This Friday

Biotech Hangout held its latest event on March 15, 2024.

The next event will be on March 22, 2024.

March 15th Replay: https://twitter.com/i/spaces/1nAKEakelZAKL

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

Please join us.

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

The week of March 18 will feature over 5,000 biopharma professionals in Barcelona for Bio-Europe. We hope to meet you there.

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

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

Macro Update

Suspense Builds for Fed as Growth Downshifts and Inflation Lingers

Aaron Back, *Wall Street Journal,* March 16, 2024 (excerpt)

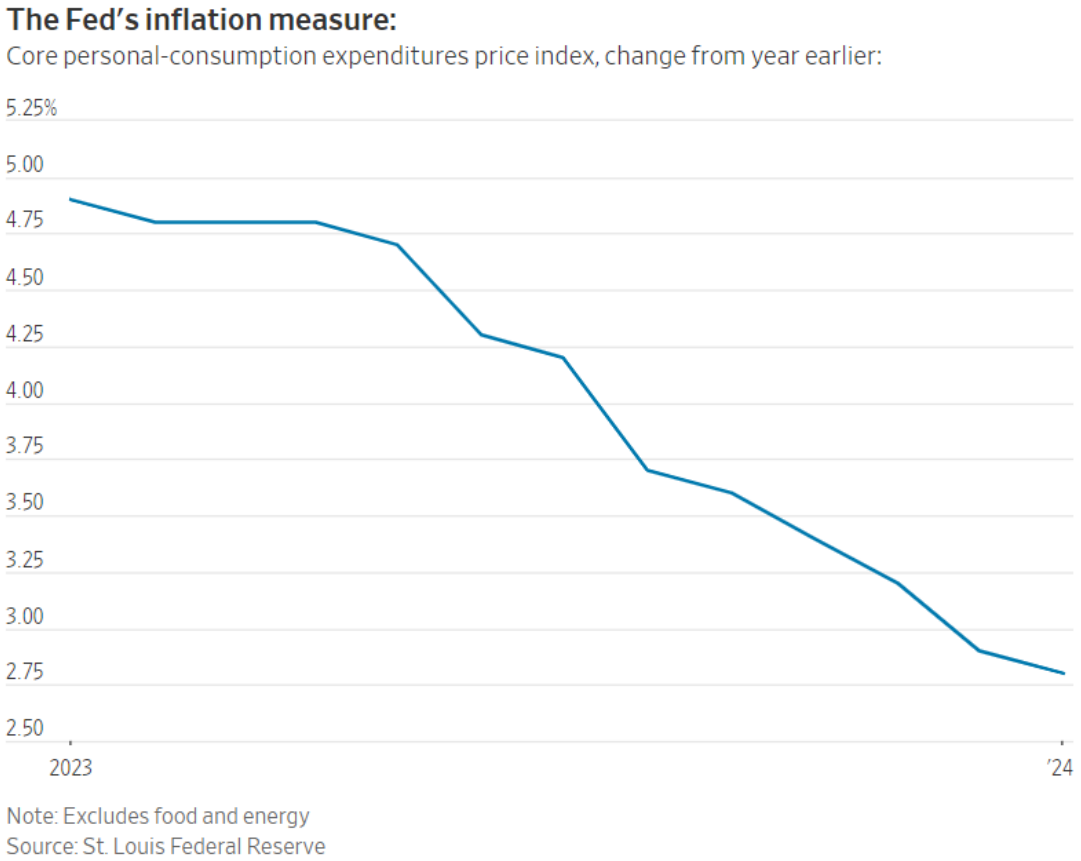
A mixed set of economic data over the past week delivered a whiff of the dreaded S-word: Stagflation. But only a whiff.

First, consumer price inflation in February came in slightly higher than expected. Then retail sales for the month disappointed, with a downward revision to January as well, and February producer prices also came in on the warm side. On Friday, a preliminary reading from the University of Michigan's consumer sentiment survey showed a decline to 76.5 in March from 76.9 previously, against expectations for a slight rise.

Taken together, the data hinted at a possibility that would spook investors: that growth could keep slowing even while inflation plateaus, making it difficult for the Federal Reserve to cut rates this summer. The likelihood of a quarter-point cut by June, as implied by markets, has fallen to 50.4% from 57.4% a week ago, according to the CME FedWatch tool. The implied chance that the Fed could stand pat through its July meeting has risen to 24.1% from just 8.1% a week ago.

Investors should keep the bigger picture in mind. Growth, while coming off the boil, is still solid. And inflation is well below where it was just a few months ago.

Source: https://www.wsj.com/economy/central-banking/suspense-builds-for-fed-as-growth-downshifts-and-inflation-lingers-109b4c3d



Fed Seen Sticking With Three 2024 Cuts Despite Higher Inflation

Steve Matthews and Kyungjin Yoo, Bloomberg, Mar 15, 2024 (excerpt)

A recent pickup in inflation isn't likely to shift Federal Reserve policymakers' forecasts for three interest-rate cuts this year and four in 2025, according to economists surveyed by Bloomberg News.

The Federal Open Market Committee will keep rates steady in the 5.25% to 5.5% range for a fifth consecutive meeting next week, with policymakers reducing rates for the first time in June, economists say.

Fed Chair Jerome Powell and his colleagues will update their economic and rate projections at the March 19-20 meeting for the first time since December, and survey respondents expect only small tweaks to their outlook with no change in the projected rate path.

"We look for the FOMC to nudge up its median forecast for inflation for this year, but otherwise we do not anticipate large changes to the macro or interest-rate projections," said Kathy Bostjancic, chief economist at Nationwide Mutual Insurance Co. Recent sticky inflation "should add to Powell's reticence in sending a green light on a near-term rate cut."

In congressional testimony last week, Powell emphasized the central bank has made good progress in nudging inflation toward its 2% target and needed "just a bit more evidence" before making an initial rate cut. "We're not far from it," he told lawmakers.

Source: https://www.bloomberg.com/news/articles/2024-03-15/fed-seen-sticking-with-three-2024-cuts-despite-higher-inflation

CPI Inflation Overstates Actual Inflation

Jai Kedia, "Inflation is Still Trending in the Right Direction," Cato Institute, March 15, 2024 (excerpt)

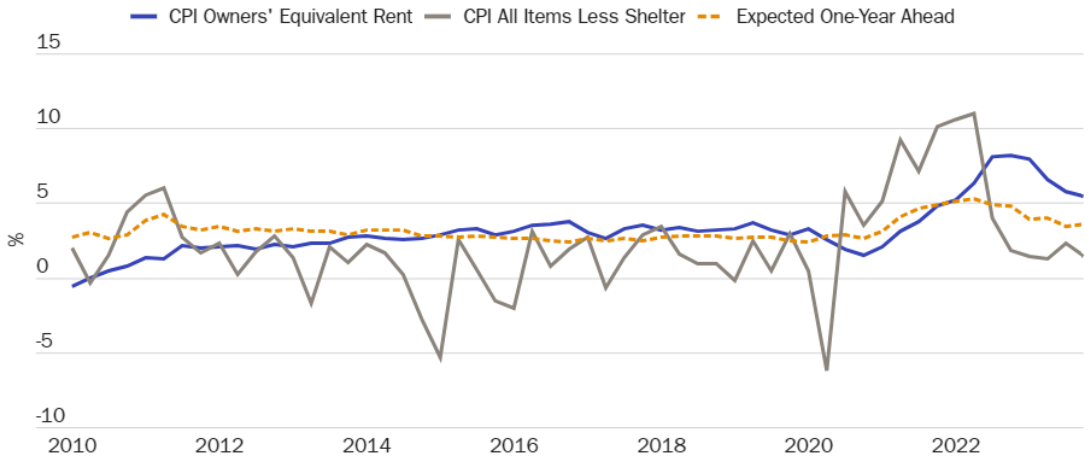
A few months of hotter-than-expected inflation numbers have led to a renewed debate around how entrenched inflation has become. Most recently, the February Consumer Price Index increased 0.4% (4.8% annualized), driven primarily by shelter and gasoline which accounted for 60% of the overall increase in price level. Energy increased by a massive 2.3% in February alone. **Despite these scary numbers, inflation is still trending in the right direction. This article will show that the elevated components of inflation—shelter and energy—do not accurately portray economic conditions.**

Figure 1 shows two measures of CPI inflation—owners' equivalent rent (OER) and the aggregate index less shelter since 2010. Both inflation metrics are computed by calculating the percent change of their respective quarterly price indices and then annualized (multiplied by 4). The aggregate metric was high post-pandemic but eventually started to fall in late 2022. Aggregate inflation less shelter maintained this downward trend and remained below 2% through most of 2023. The graph shows—especially since the pandemic—that shelter inflation as measured through the OER significantly trails the rest of the CPI. (In economist speak, it is a lagged measure.) OER inflation hit its peak 2 quarters after other price measures and similarly lagged in its recovery back towards trend.

Rather than indicating that inflation is entrenched, this increase in the OER is an indicator that shelter prices increased some time back. The problem is that those price increases are just now showing up in the CPI.

Figure 1

Inflation metrics (CPI measures are computed quarterly and annualized)



Sources: U.S. Bureau of Labor Statistics, "Consumer Price Index for All Urban Consumers: Owners' Equivalent Rent of Residences in U.S. City Average," Federal Reserve Bank of St. Louis, 2024. U.S. Bureau of Labor Statistics, "Consumer Price Index for All Urban Consumers: All Items Less Shelter in U.S. City Average," Federal Reserve Bank of St. Louis, 2024. Surveys of Consumers, "Table 32: Expected Change in Prices During the Next Year," University of Michigan, 2024.

Source: https://www.cato.org/blog/inflation-still-trending-right-direction

America's Extraordinary Economy Keeps Defying the Pessimists

***The Economist*, March 14, 2024 (excerpt)**

You have to marvel at America's economy. Not long ago it was widely thought to be on the brink of recession. Instead it ended 2023 nearly 3% larger than 12 months earlier, having enjoyed one of the boomier years of the century so far. And it continues to defy expectations. At the start of this year, economists had been forecasting annualised growth in the first quarter of 1%; that prediction has since doubled. The labour market is in rude health, too. The unemployment rate has been below 4% for 25 consecutive months, the longest such spell in over 50 years. No wonder Uncle Sam is putting the rest of the world to shame. Since the end of 2019 the economy has grown by nearly 8% in real terms, more than twice as fast as the euro zone's and ten times as quickly as Japan's. Britain's has barely grown at all.

America's expansion is all the more striking when you consider the many things that could have killed it. As the Federal Reserve has fought inflation the economy has endured the sharpest rise in interest rates since Jimmy Carter was in the White House. The covid-19 pandemic, an intensifying trade war with China and the fight against climate change have together reshaped supply chains, labour markets and consumer preferences. Wars in Ukraine and Gaza have aggravated geopolitical tensions and worsened the strains on the global trading system.

Strong demand has been met by growing supply. America has 4% more workers than it did at the end of 2019, thanks in part to rising workforce participation, but mainly owing to higher immigration. The foreign-born population is up by 4.4m, a figure which may undercount those who arrived illegally. And the expanding workforce is being put to productive use. America's flexible labour market has almost certainly made it easier for the economy to adapt fast to a changing world.

Other long-standing strengths have made America enviably placed to cope with geopolitical tumult. Its vast internal market encourages innovation and means it depends less on foreign trade than smaller rich economies do. Because the shale boom of the 2010s made America a net energy exporter, it has in aggregate benefited rather than suffered from the high energy prices that hit the wallets of Europeans.

Source: https://www.economist.com/leaders/2024/03/14/americas-extraordinary-economy-keeps-defying-the-pessimists

A Return to the Fundamentals in Biotech Investment?

Barbara Ryan, *Pharmaceutical Executive*, Mar 12, 2024 (excerpt)

Is the recent rally in the biotech market for real? In my last column, I pondered whether the fierce rally for the XBI and biotech sector in the fourth quarter of last year could be the start of something big—and whether the momentum would be sustainable in 2024. I outlined multiple reasons for enthusiasm on this front, including a substantial pivot in investors' expectations for the direction of interest rates (down versus up), compelling clinical data across the sector, strong industry fundamentals, as well as a red-hot M&A market that is unlikely to cool down anytime soon. Well, after surging ahead a whopping 38% in the last quarter of 2023, the XBI was able to close the year with a gain of more than 7%—saving sector specialist investors from a third straight year of losses. As of the end of February, the XBI is up another 15%.

The unshakable bond with interest rates appears to have been broken. What has been recently interesting and new is that biotech stocks (being the longest dated of long dated assets), which have until of late been inexorably and inversely correlated with interest rates and instantly reactive to every economic update—have diverged from this trend. Investors in the sector appear to have shifted their attention to evaluating company fundamentals and valuations versus reading the macro tea leaves. For the first time in two years. Why is that? My sense is that **investors have recognized that the epic surge in Fed-induced interest rates has run its course, and while it may still be a matter of "when," it is no longer a matter of "if"—and that the timeline, while potentially a moving target, is, however, one of inevitability. Hence, the separation and the move to a more focused industry-specific analysis and investment thesis.**

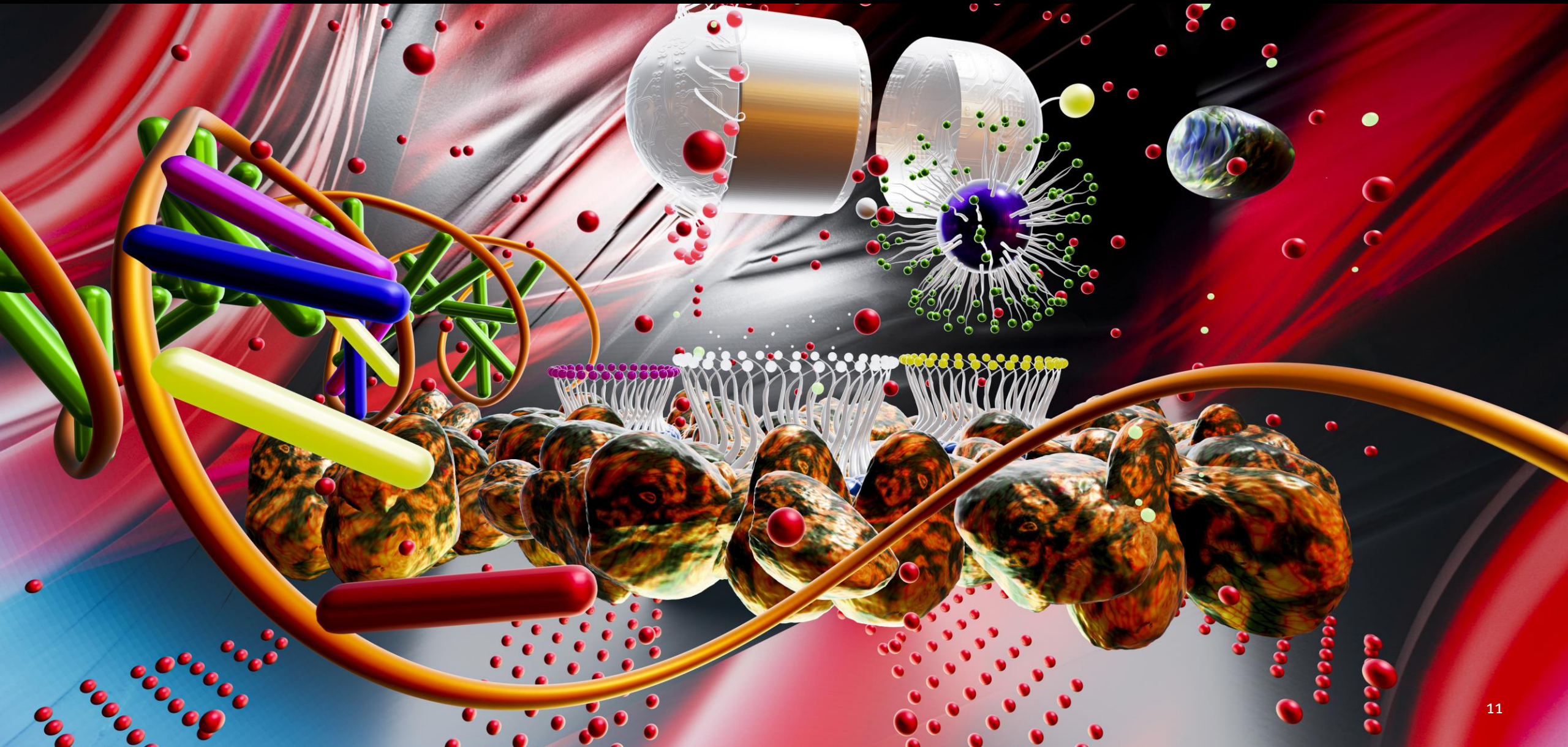
Fundraising is back—with force—due to pent-up demand. With the rise in valuations and increased investor enthusiasm in the sector, biotech companies are racing toward the gates to raise money. In January, drug developers raised $6.2 billion—reflecting the levels during the peak of the COVID-19 pandemic when capital raises achieved all-time highs.

This is a very sharp turnaround from a two-year drought of deals, which forced a record-number of companies to shut down, reprioritize programs, de-emphasize or eliminate potential opportunities, lay off personnel, merge/consolidate, and pursue reverse mergers in an effort to pool resources and extend their cash runways in order to survive and fight another day. The momentum has continued throughout the month of February.

These trends will continue as EY (Ernst & Young) shares that large pharma is armed with over $1.4 trillion in firepower, and the imperative to transact is fueled by impending losses of exclusivity for revenues exceeding $350 billion, which leaves a huge growth gap to fill. This, in turn, puts tens of billions of dollars back into the pockets of the target companies' shareholders, which then, of course, fuels further investments into the companies that remain, driving improved stock-price performance and a healthy appetite for follow-on offerings and IPOs.

Source: https://www.pharmexec.com/view/a-return-to-the-fundamentals-in-biotech-investment-

Biopharma Market Update



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

Biotech Market Softens Up

At the end of October last year, the XBI was at 64. It went as high as 102 on February 27th. That's a 60% rise. Today it's at 94.7. Down 7% in 14 trading days.

You wouldn't exactly say we're in a down market.

The market is now up almost 50% in 18 weeks. That's really good and biotech is definitely back.

So, what's been going on in the last few weeks? Why is the market taking a breather?

There are two reasonable explanations.

First theory: inflation is worse than expected. CPI inflation this week of 3.2% is not great. This is no crisis level to be clear. But the Fed isn't going to be in any rush to lower rates.

Second theory: investors got a bit worried about the speed of the market rise and the risk of excess. You could call it the "too far – too fast theory". If you sprint you will then need to rest for awhile.

One way of thinking about this is to look at the financing market which has taken down $18 billion in ten weeks. When stocks price follow-ons in a normal market, the stock will

(continued on next page)

The XBI has dropped 7% in the last 14 trading days.

Why?

Biotech Market Coffee Break

often get soft and go down.* In this market, instead, stocks are going up after issuance.

Sometimes a lot.

We spoke to one well-known investor last week who said he and his peers got a little scared a few weeks back about all of this and started pulling back.

He blamed speculative excess and said “when people started calling me about the same company that did a PIPE last month – to do another PIPE this month – but at a higher price” I was starting to get worried about the market overheating when I saw those second PIPE’s actually getting done – with the stock still trading up.

The investor then laughed and indicated that he is still excited by the market. He thinks the market will continue to go up and that we’re just taking a bit of a break while past developments consolidate and we sort through the inflation picture and what the Fed is going to do this year.

Other market observers have pointed to the recent macro news as determinative and indicate that market is taking a bit of pause before marching north again.

* See, for example, https://www.nber.org/system/files/chapters/c11475/c11475.pdf

The XBI Closed at 94.71 Last Friday (Mar 15), Down 4.3% for the Week

The XBI is up 6% since the year began. The biotech market was soft last week as the macro picture weighed on the sector. The yield on the 10-year U.S. Treasury bond crept up 28 basis points last week – quite a meaningful move.

Biotech Stocks Down Last Week

Return: Mar 9 to Mar 15, 2024

Nasdaq Biotech Index: -2.1%
Arca XBI ETF: -4.5%
Stifel Global Biotech EV (adjusted): +1.5%*
S&P 500: -0.1%

Return: Jan 1 to Mar 15, 2024

Nasdaq Biotech Index: -0.1%
Arca XBI ETF: +6.1%
Stifel Global Biotech EV (adjusted): +21.5%*
S&P 500: +7.3%

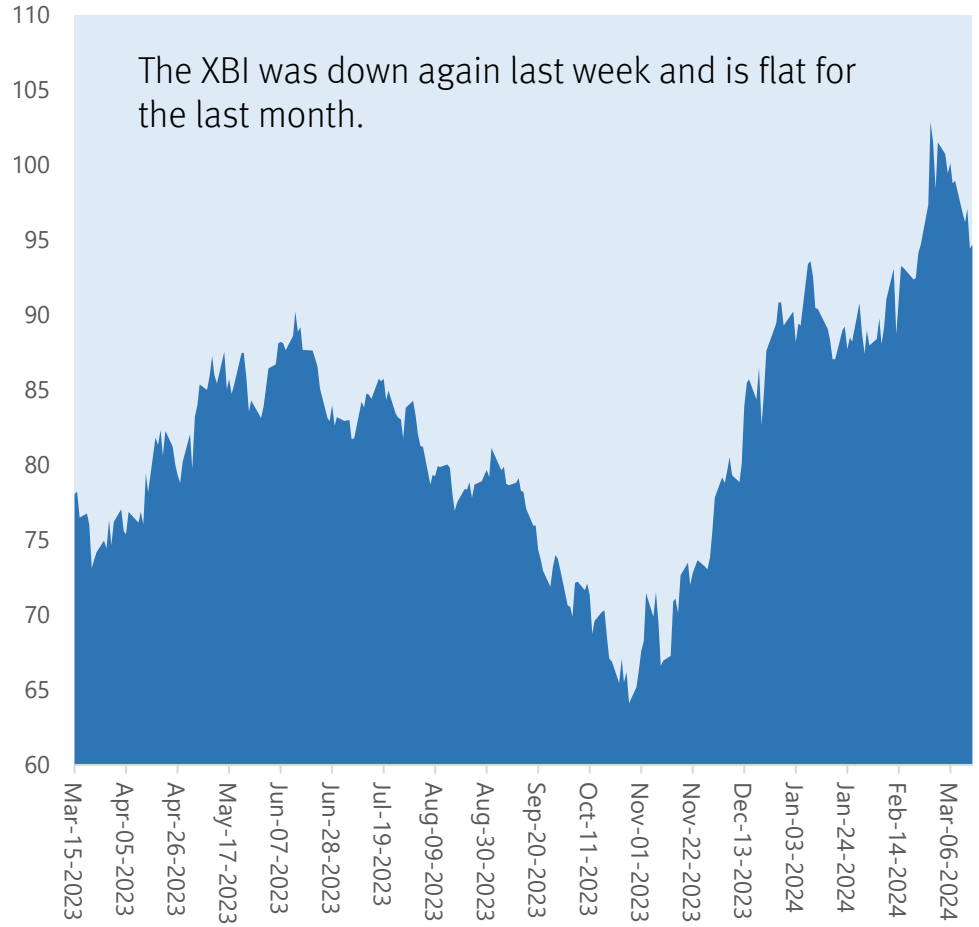
VIX Down

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 8, 2024: 14.7%
Mar 8, 2024: 14.4%

10-Year Treasury Yield Up

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 8, 2024: 4.13%
Mar 15, 2024: 4.31%

XBI, March 15, 2023 to March 15, 2024



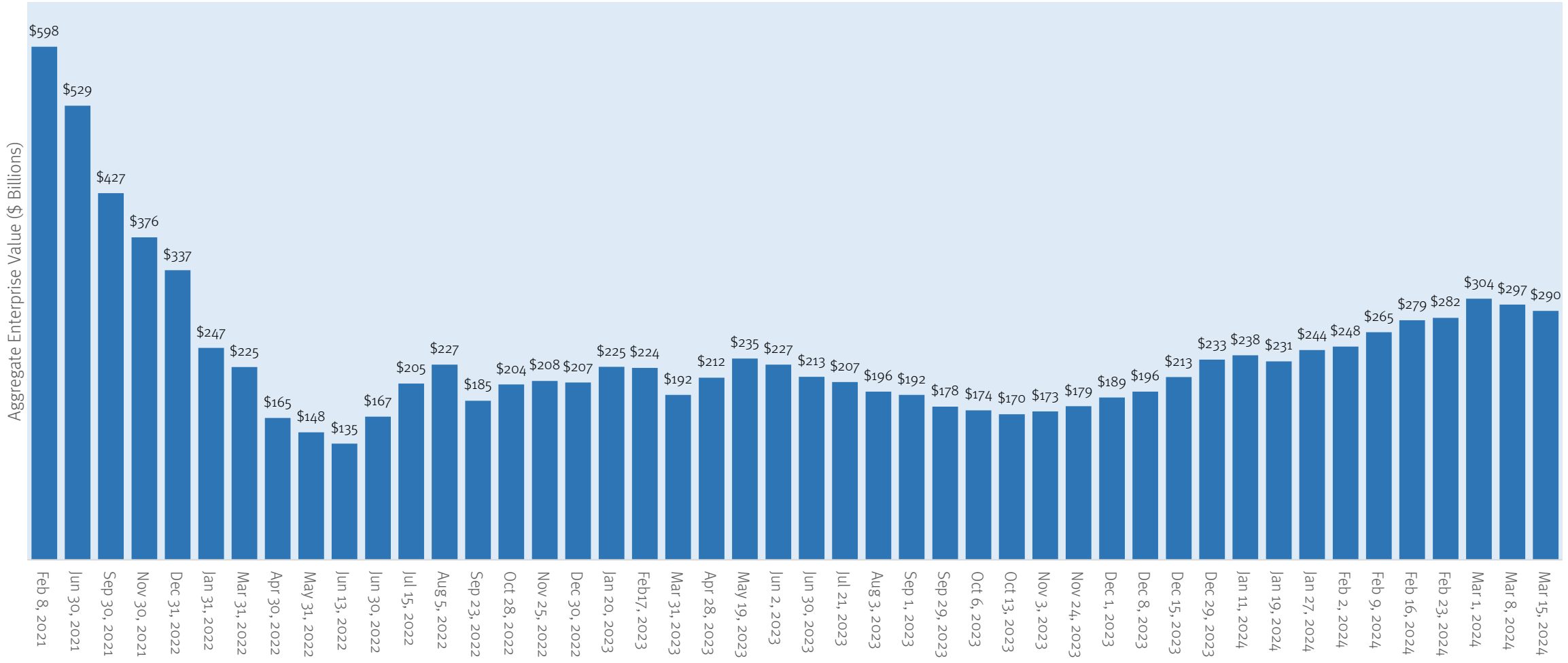
* Change by enterprise value. The adjusted number accounts for the effect of exits and additions via M&A, bankruptcies and IPOs.

Source: S&P Capital IQ and Stifel analysis

Total Global Biotech Sector Value Dropped 2.3% Last Week

The total enterprise value of the global biotech sector is up 27% year-to-date on an addition/exit corrected basis. While the XBI is flat for the last month, the value of total global biotech remains up substantially over the same interval.

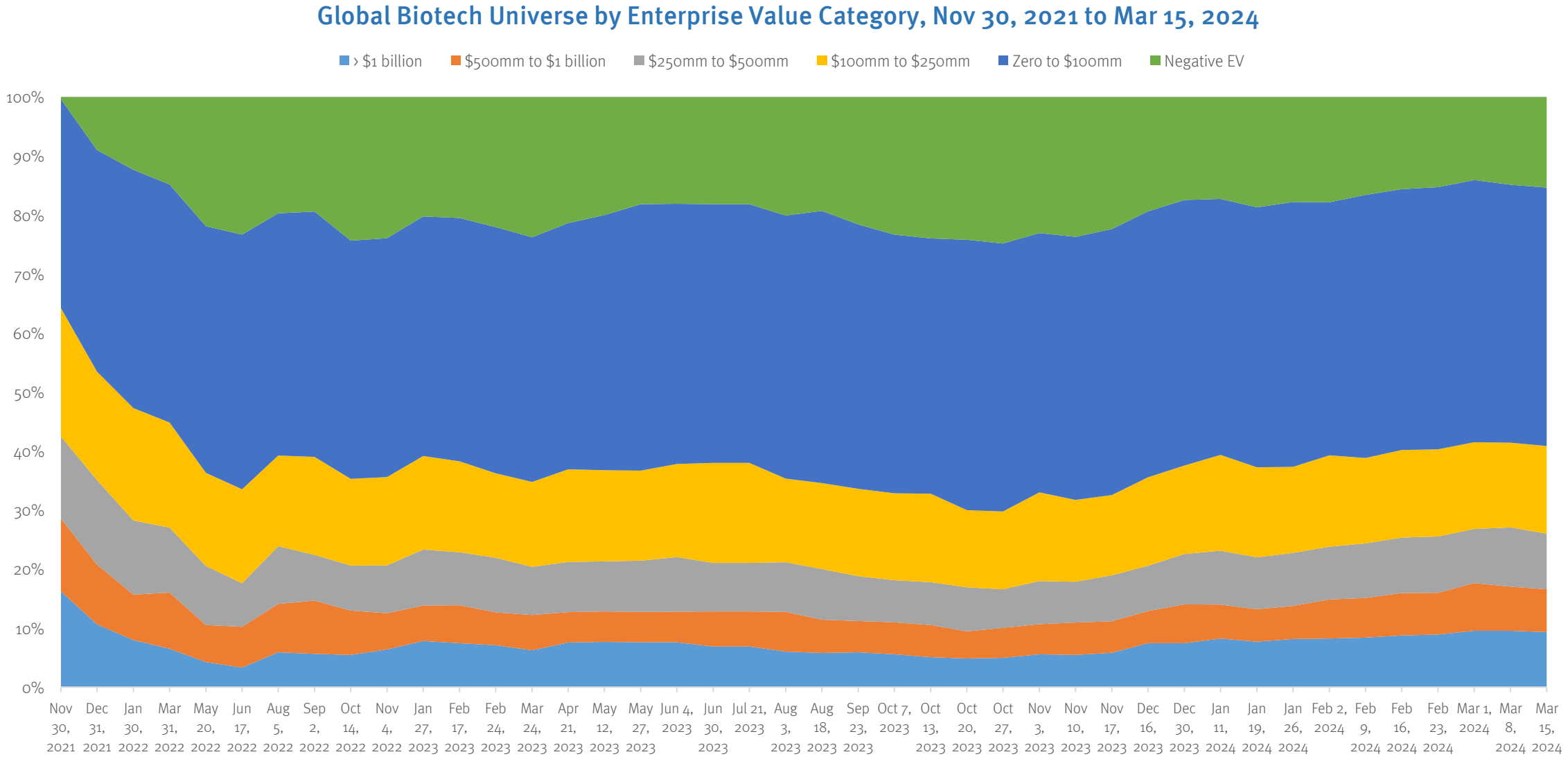
Total Enterprise Value of Publicly Traded Global Biotech, Feb 8, 2021 to Mar 15, 2024 ($ Billions)



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

Global Biotech Neighborhood Analysis

The decline in companies worth $100mm or less in EV has reversed in the last week as market participants have been flocking to larger caps.



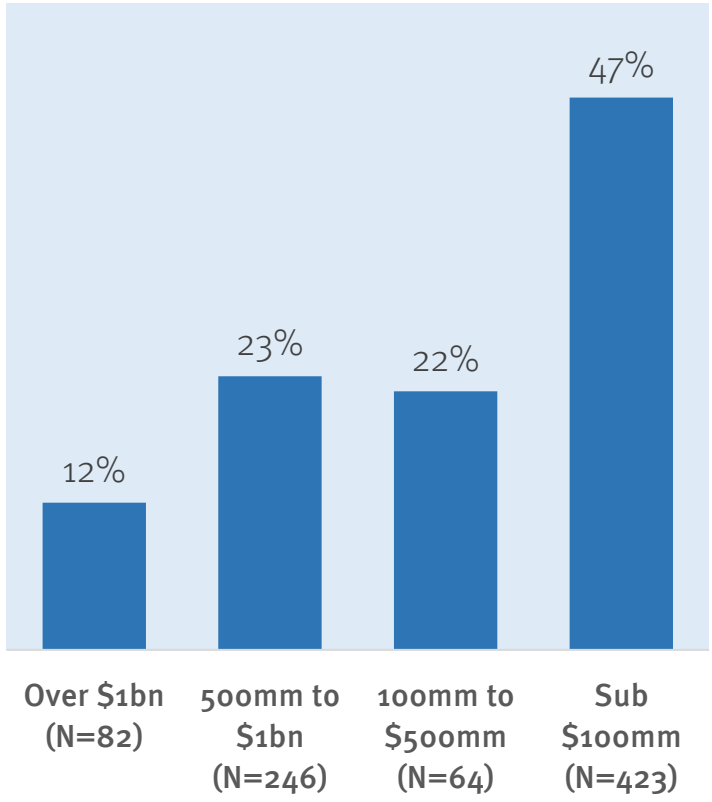
Source: CapitalIQ. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

Biotech Returns by Market Cap Class

While microcaps rocketed up at the start of the year, their ascent stalled a month ago. However, the value of microcaps was so low that the actual dollar change was very modest. Mid and larger cap biotechs have continued to rise over the last month as the market has moved to safer ground. The January small cap rally has stalled for the moment.

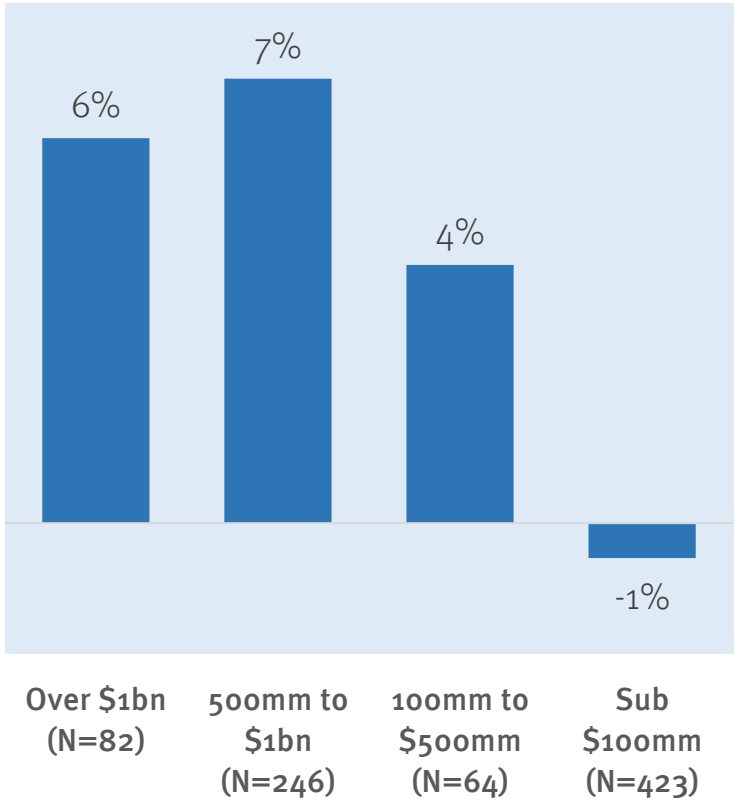
Percent Change in Global Biotech Valuations, Year to Date

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



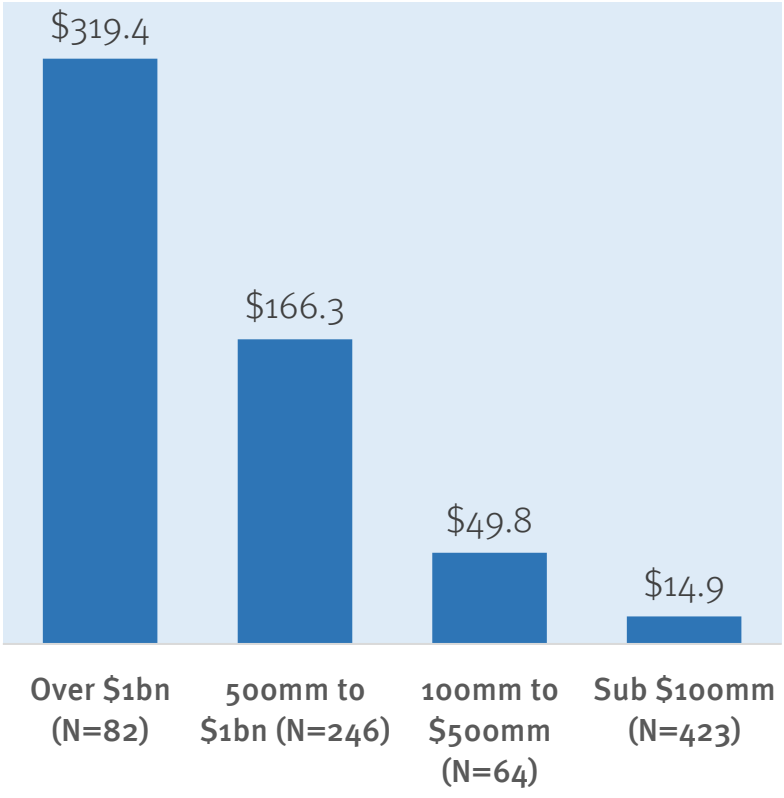
Change in Global Biotech Valuations, Feb 15, 2024 to March 15, 2024

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



Average Change in Global Biotech Valuations, Year to Date

(Dollar Change in Value of Company Group, $mm, N=815)



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

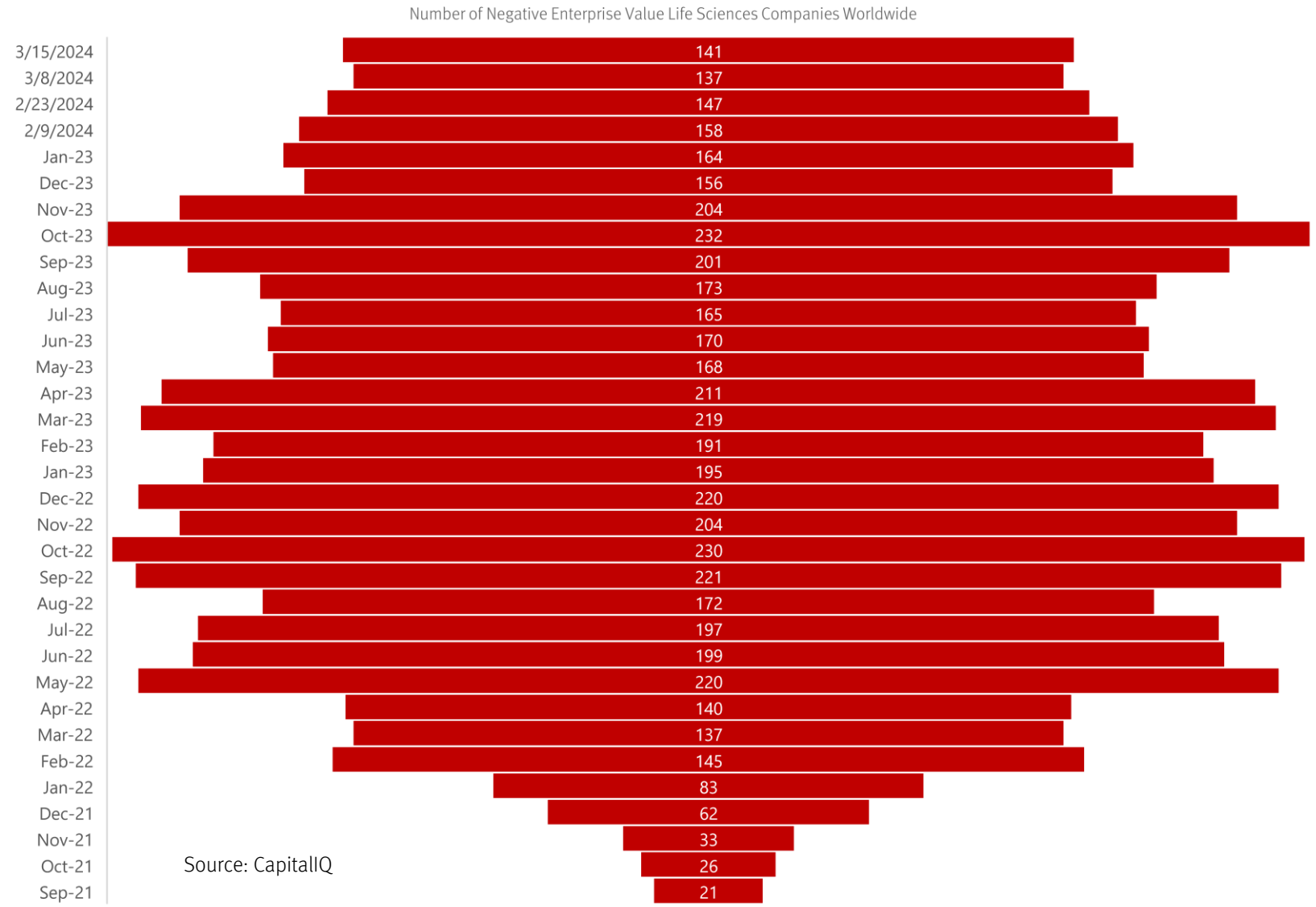
Life Sciences Sector Total Value Dropped Last Week by 1.2%

Last week saw the life sciences sector lost $121 billion in value. The worst performing sectors were diagnostics and biotech.

Sector	Firm Count	Enterprise Value (Mar 15, 2024, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	81	$80,343	-0.8%	1.5%	1.1%
Biotech	803	$290,345	-2.7%	4.4%	-5.1%
CDMO	40	$150,586	-1.1%	1.9%	-17.7%
Diagnostics	81	$273,641	-3.2%	2.3%	3.8%
OTC	30	$28,061	0.5%	1.4%	-3.2%
Commercial Pharma	719	$6,231,396	-0.9%	1.8%	14.3%
Pharma Services	39	$202,109	1.2%	5.3%	1.5%
Tools	51	$727,704	-1.6%	3.8%	0.9%
Devices	181	$1,713,482	-1.9%	1.0%	9.4%
HCIT	10	$20,233	-0.9%	-5.2%	-22.2%
Total	**2035**	**$9,705,899**	**-1.2%**	**2.0%**	**11.4%**

Source: CapitalIQ

Number of Negative Enterprise Value Life Sciences Companies Rose Slightly Last Week



Source: CapitalIQ

The count of negative EV life sciences companies worldwide rose slightly to 141 from 137 last week.

Advice for Private Biotech Firms in 2024

Daniel Sieck and Colleagues, "Ready for the Biotech Bounce Back in 2024?," *Troutman Pepper*, Mar 14, 2024 (excerpted/edited)

After record-shattering years in 2020 and 2021, the relative droughts of 2022 and 2023 left companies and investors scrambling for opportunities. The 2024 forecast, though cautiously optimistic at its outset, has exceeded initial expectations for the biotech and life sciences industry. Fresh capital is providing a much-needed reprieve for existing investors who were largely tapped out from the insider-led rounds that strained cap tables over the last two years.

The year did not exactly start with overly positive expectations. PitchBook had predicted that the biotech and life sciences industry's share of VC and PE deal activity in 2024 would fall further than the 10.8% it clocked in 2023 (the lowest level since 2015). Yet, that bearish sentiment has not played out. Instead, the Wall Street Journal recently reported that biotechs have in fact attracted more than $6 billion in follow-on financing through mid-February, which Jefferies analysts say is a record-setting pace — one that has already exceeded each prior quarter since Q2 2021. Additionally, the IPO window appears to be reopening, with a number of noteworthy IPOs, including: Metagenomi ($100 million) and ArriVent Biopharma ($100 million). Public biotechs are also turning sentiment, with a string of positive data releases and $13.7 billion in secondary raises already in 2024. On the private side, buyouts of companies like Seagen and Cerevel have provided further opportunities for liquidity.

Undoubtedly, the freeing up of the public markets and boost in M&A transactions will continue to trickle down to the private side, likely leading to an uptick in private companies pursuing exit opportunities.

While 2024 is off to an exciting start for biotech and life sciences investments, particularly in AI, weight loss, and cell and gene therapy manufacturing, the funding markets are proceeding with caution. It is worth remembering that although 2022 and 2023 paled in comparison to the booms of 2020 and 2021, the long-term trajectory of the industry remains positive. **Though it would be advisable for companies to temper expectations about any spike in investment and exit opportunities, the first months of 2024 indicate that the bull run for biotech is not over.**

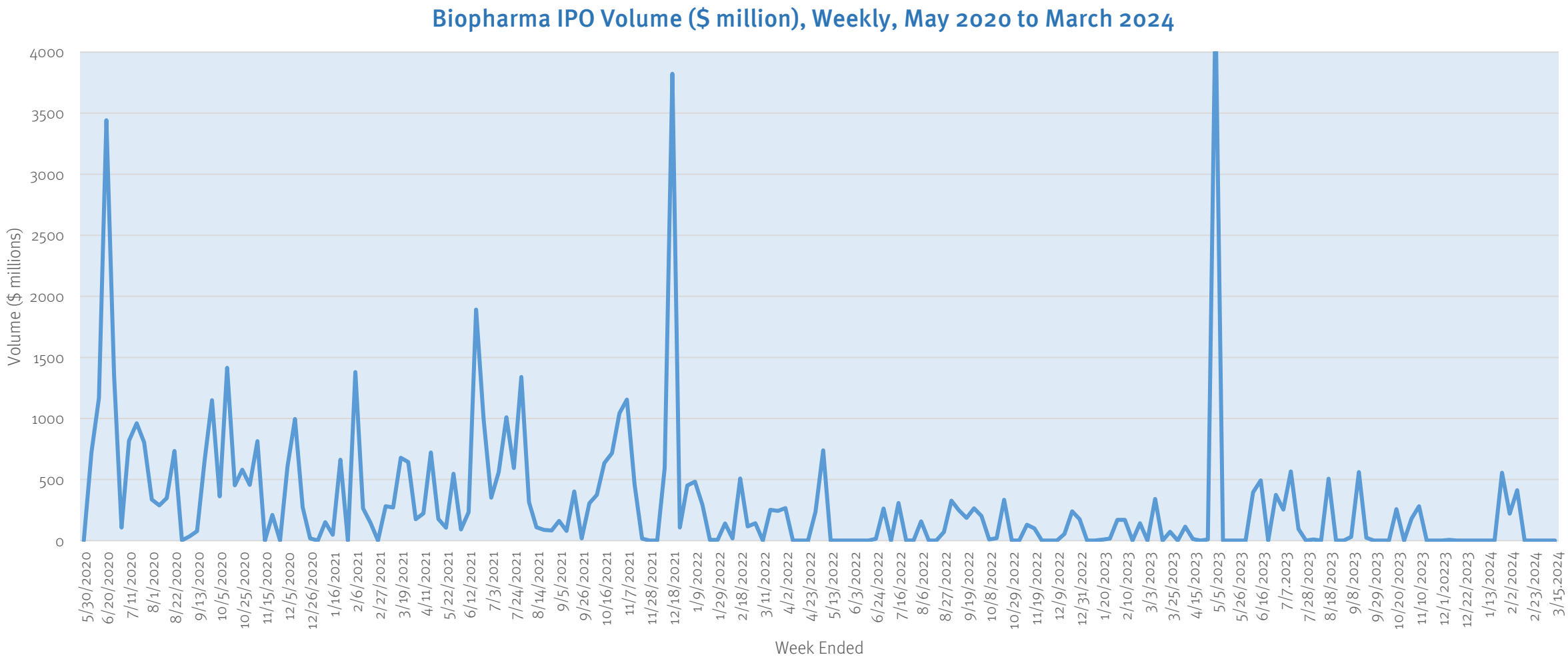
Now is the time for companies to rebuild teams and clean up any deferred maintenance caused by cost-cutting measures over the past years. As exit opportunities re-emerge, companies need to build their investor bases and position themselves for IPOs or M&A transactions. Recent history has repeatedly shown that the windows for these opportunities are short. However, if the start of the year is any indication, a new window is just beginning to open.

Source: https://www.troutman.com/insights/ready-for-the-biotech-bounce-back-in-2024.html

Capital Markets Update

IPO Market Took a Breather Last Week

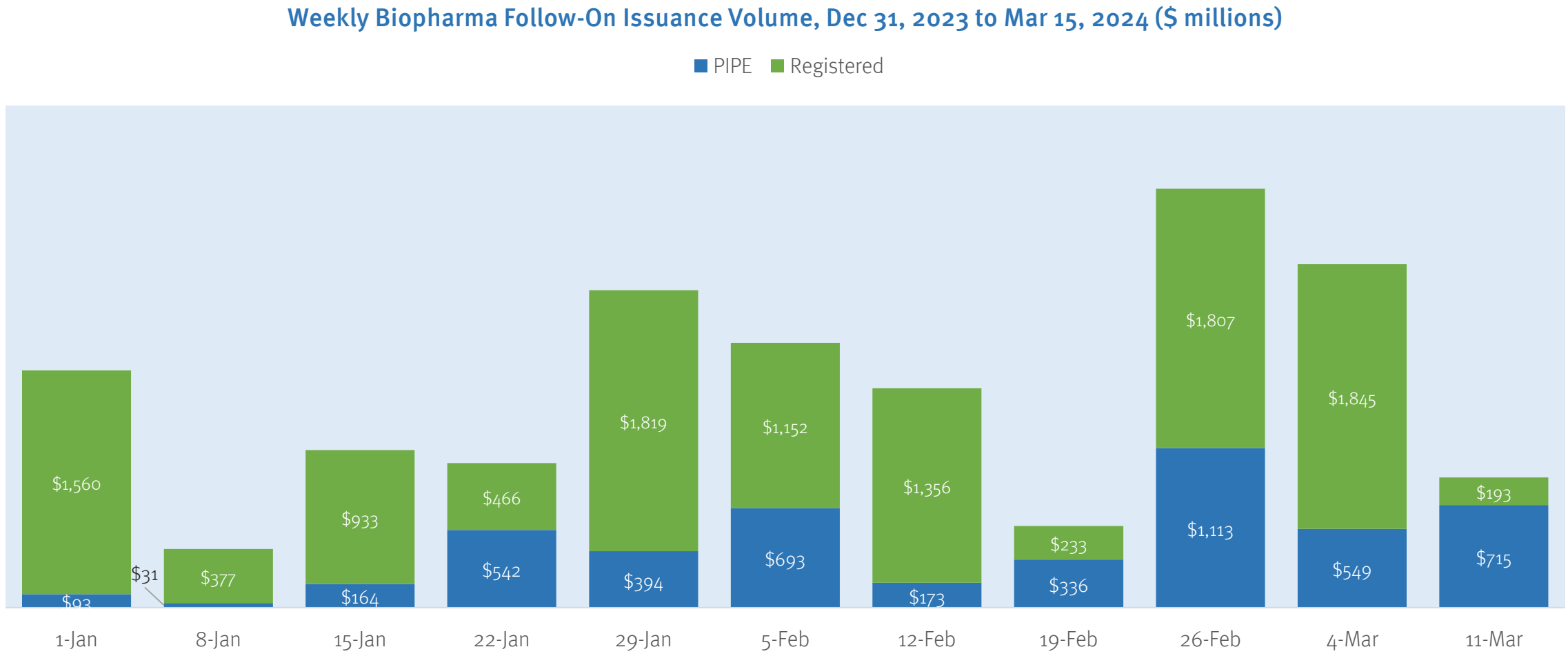
The IPO market took a break last week. We have not seen an IPO price for over a month.



Source: Data from CapitalIQ and Stifel research.

Last Week Saw $908 Million in Follow-On Issuance

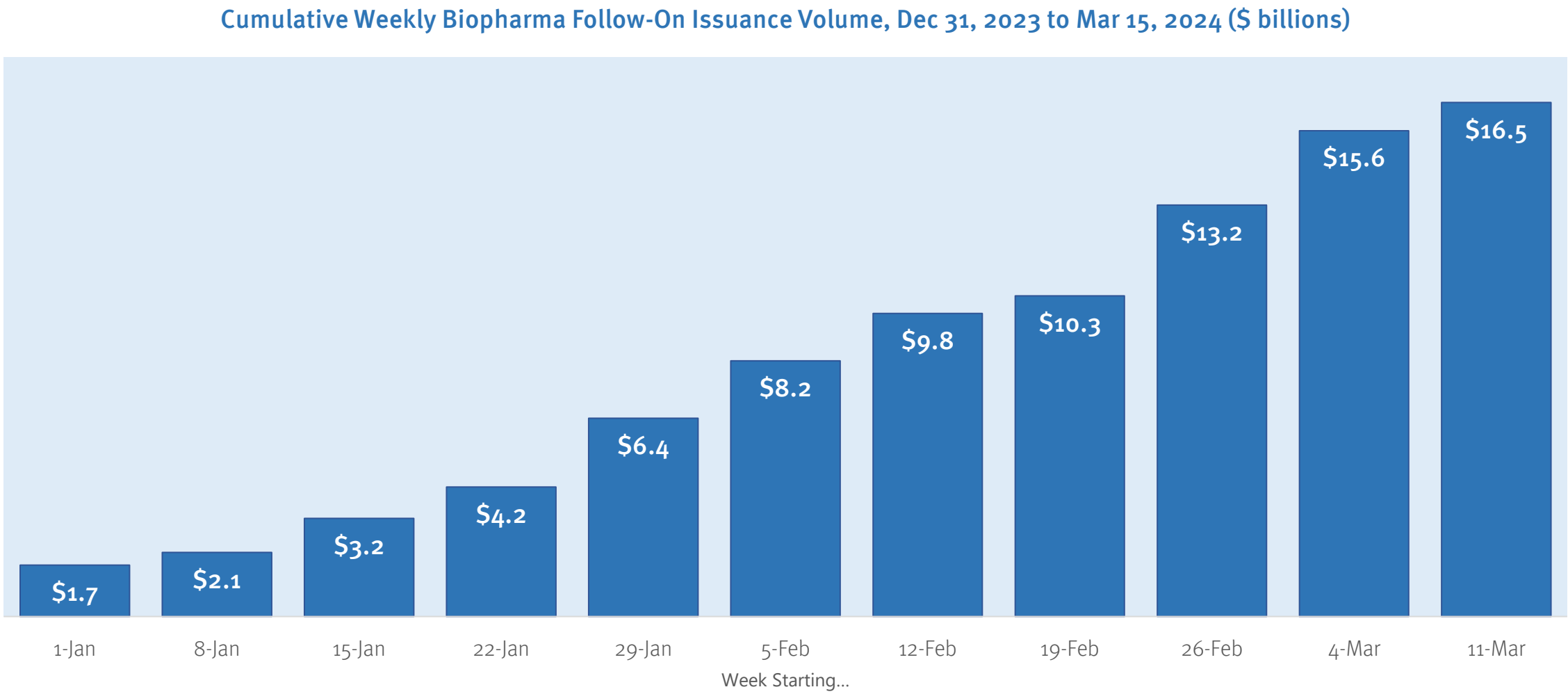
With the XBI down 5% last week the pace of follow-on offerings dropped from previous two weeks. We do not expect this lower volume level to last based on current activity that we are seeing behind the scenes.



Source: Data from CapitalIQ and Stifel research.

Total Follow-On Volume Now Over $16 Billion for the Year

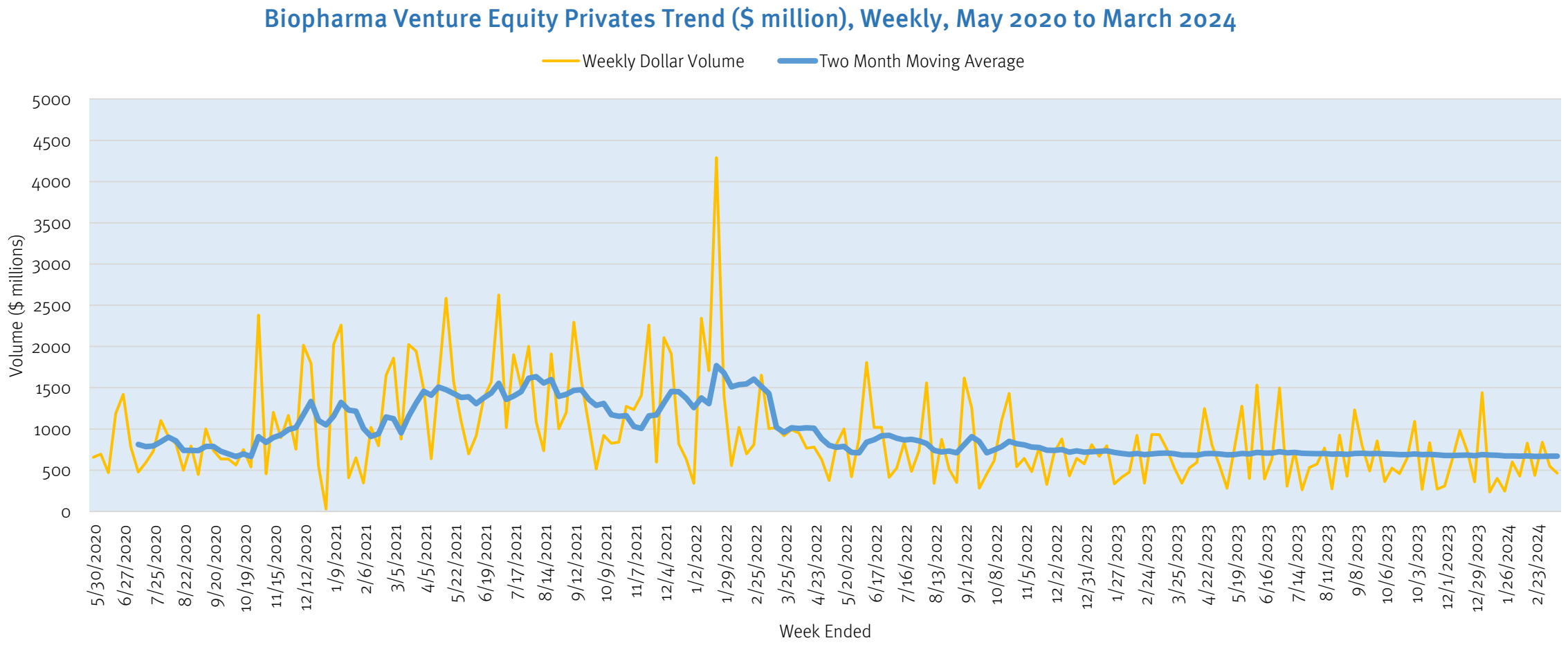
Follow-on Volume has been running at a level of $1.5 billion a week for the first eleven weeks of 2024.



Source: Data from CapitalIQ and Stifel research.

Venture Private Volume Continued to be Quiet Last Week

Last week saw $464 million in privates deal volume. The largest deal was Tubulis raise of $138 million to support ADC development.



Source: Data from CapitalIQ, Crunchbase.

Tubulis Closes Upsized €128 Million Series B2 to Accelerate Clinical Development of Solid Tumor-Focused ADC Pipeline

MUNICH, GERMANY, March 14, 2024 -- Tubulis today announced the successful completion of an upsized and oversubscribed €128 million ($138.8 million) Series B2 financing. The round was co-led by EQT Life Sciences and Nextech Invest Ltd, on behalf of one or more funds managed by it, with participation from new US-based funds, Frazier Life Sciences and Deep Track Capital as well as all existing investors, including Andera Partners, BioMedPartners, Fund+, Bayern Kapital (with ScaleUp-Fonds Bayern), Evotec, coparion, Seventure Partners, OCCIDENT and High-Tech Gründerfonds (HTGF). Tubulis is developing a pipeline of uniquely matched antibody drug conjugates (ADCs) with an indication-tailored targeting molecule and payload combination to develop novel ADCs with superior properties.

The proceeds of the Series B2 will primarily support progress in Tubulis' pipeline of next-generation ADCs toward clinical evaluation and help achieve clinical proof-of-concept for lead candidates, TUB-040 and TUB-030. TUB-040 addresses tumor-antigen Napi2b, a well-characterized target in ovarian and lung cancer and TUB-030 targets 5T4, an antigen often overexpressed in solid tumors. Preclinical proof-of-concept data for these two candidates will be presented at the Annual Meeting of the American Association for Cancer Research (AACR) in April. The company expects to start its first Phase 1/2a clinical trial, including dose escalation and dose optimization cohorts in 2024. The capital will also fund the expansion of Tubulis' suite of technology platforms to unlock novel payloads for the development of versatile and customizable ADCs. In line with the addition of new US investors, Tubulis plans to increase its corporate footprint by establishing a US subsidiary.

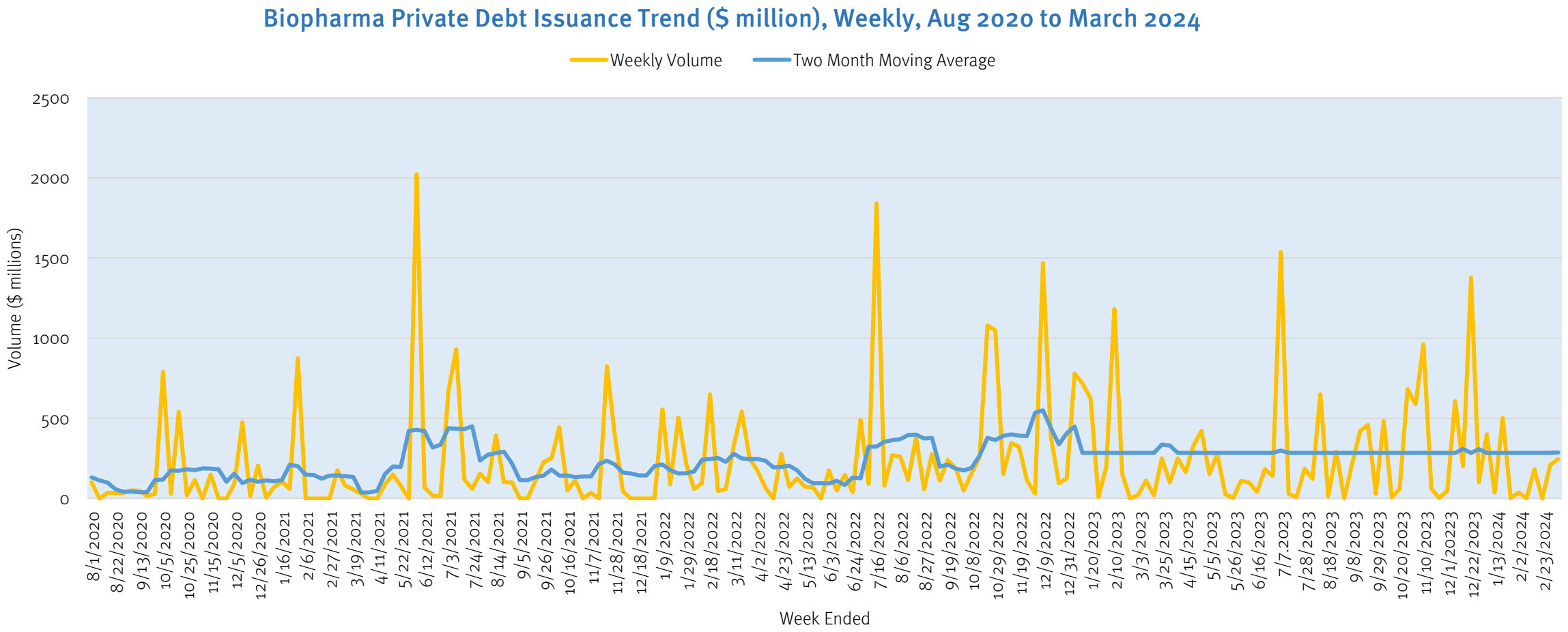
Source: https://tubulis.com/news/tubulis-closes-upsized-e128-million-series-b2-to-accelerate-clinical-development-of-solid-tumor-focused-adc-pipeline/

"This substantial financing from a syndicate of global specialist biotech investors recognizes Tubulis' unique position in the ADC space. Our proprietary platform technologies and internal know-how are the foundation for our pipeline of truly differentiated protein-drug conjugates. "

Dominik Schumacher
Chief Executive Officer
Tubulis

Biopharma Private Debt Placement Market Did $72 Million in Volume

The debt privates market saw Orexo raise $49 million as part of a refinancing deal.



Source: Data from CapitalIQ, Crunchbase.

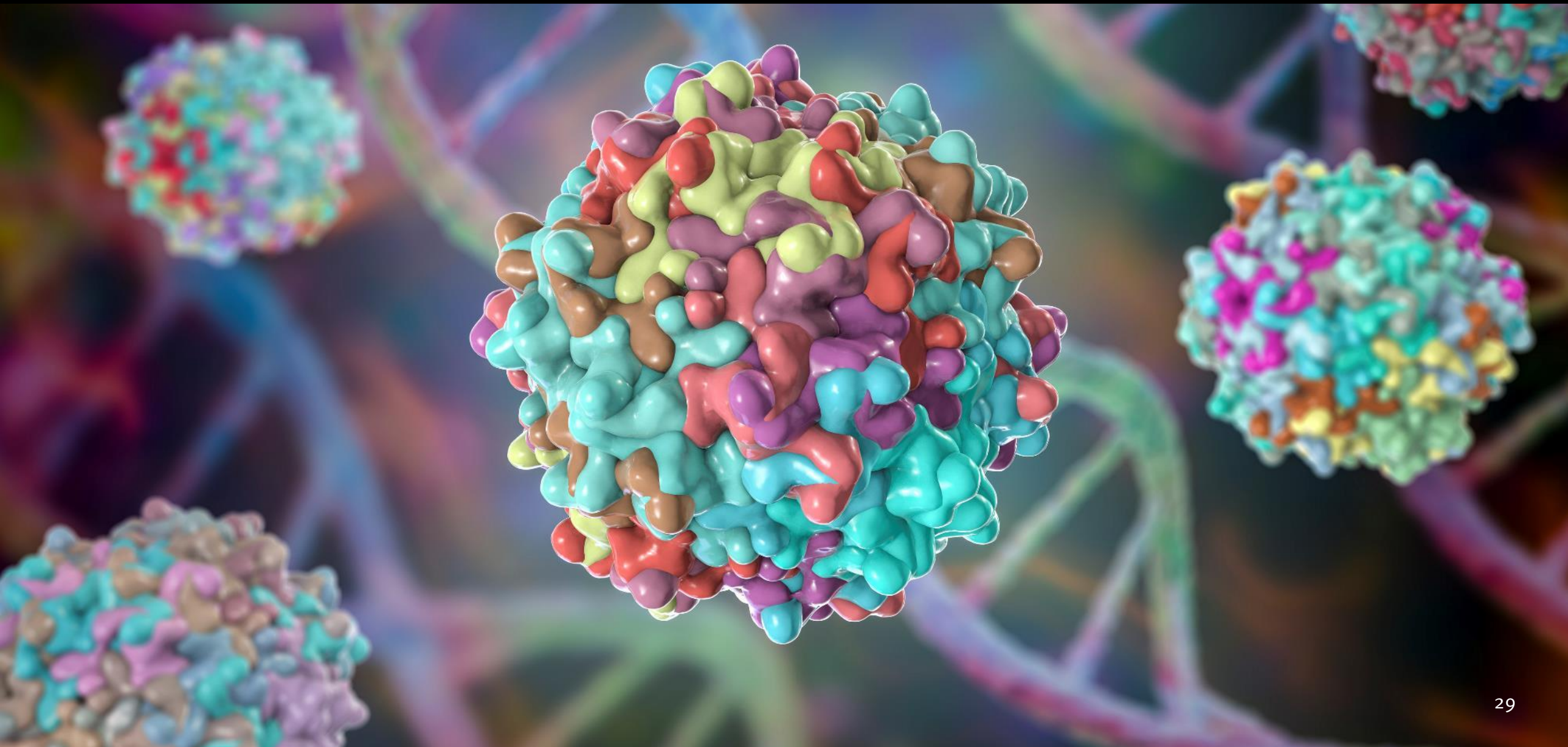
Orexo Contemplates Issuance of Senior Secured Callable Floating Fate Social Bonds and Announces a Conditional Tender Offer for its Existing Bonds

Uppsala, Sweden – March 8, 2024-- Orexo AB (publ), ("Orexo" or the "Company") (STO:ORX) (OTCQX:ORXOY) has mandated ABG Sundal Collier and Carnegie Investment Bank as arrangers and joint bookrunners to arrange a series of fixed income investor meetings commencing on March 11, 2024, to explore the possibility to issue new senior secured callable floating rate social bonds in an expected amount of SEK 500,000,000 and with a tenor of four years (the "New Social Bonds"). Subject to, inter alia, market conditions, a capital markets transaction may follow. The net proceeds from the contemplated issuance of the New Social Bonds will be applied in accordance with the principles set out in Orexo's social financing framework, including but not limited to, refinancing of Orexo's existing senior unsecured callable floating rate bonds of SEK 500,000,000 with maturity in February 2025 (ISIN SE0015193958) (the "Existing Bonds") and financing or refinancing permitted acquisitions or investments under Orexo's social financing framework.

In conjunction with the contemplated issue of the New Social Bonds, Orexo has today announced an invitation to holders of the Existing Bonds to tender any or all of their Existing Bonds for purchase by the Company for cash at a price of 100.750 per cent of the nominal amount plus accrued and unpaid interest (the "Tender Offer"). The Tender Offer will be conditional upon the successful issue of the New Social Bonds and subject to the terms set out in the tender information document dated March 8, 2024, which is available on Orexo's website and attached to this press release (the "Tender Information Document").

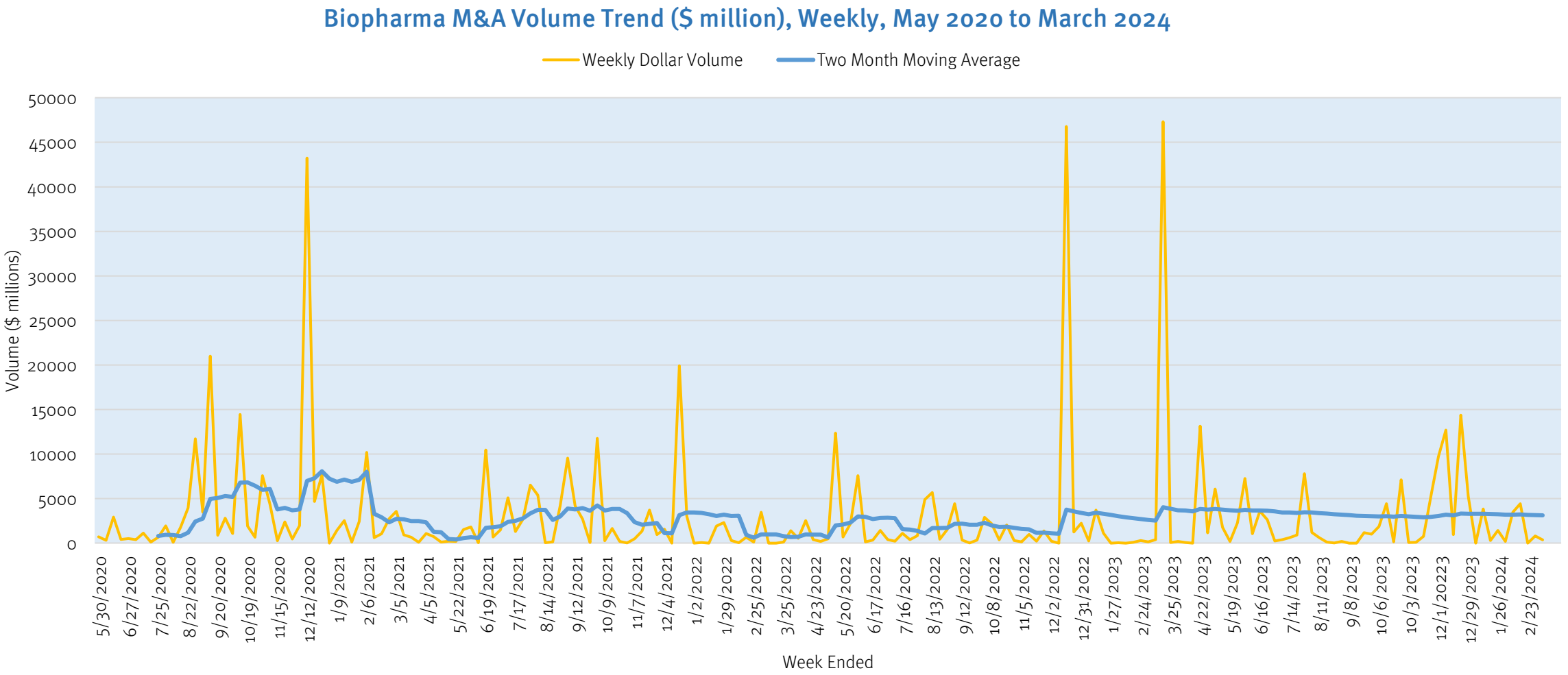
Source: https://orexo.com/news-room/pressreleases-and-news/2024-03-08-orexo-contemplates-issuance-of-senior-secured-callable-floating-rate-social-bonds-and-announces-a-conditional-tender-offer-for-its-existing-bonds

Deals Update



Last Week Saw Six M&A Deals for Volume of Approximately $1.1 Billion

The largest deals last week were AZ's acquisition of Amolyt for $800mm upfront and Linden's acquisition of Alcresta.



Source: S&P, CapitalIQ

AstraZeneca to acquire Amolyt Pharma for $800mm Upfront, Expanding Late-Stage Rare Disease Pipeline

Announcement, Mar 14, 2024

AstraZeneca announced that it has entered into a definitive agreement to acquire Amolyt Pharma, a clinical-stage biotechnology company focused on developing novel treatments for rare endocrine diseases.

The proposed acquisition will bolster the Alexion, AstraZeneca Rare Disease late-stage pipeline and expand on its bone metabolism franchise with the notable addition of eneboparatide (AZP-3601), a Phase III investigational therapeutic peptide with a novel mechanism of action designed to meet key therapeutic goals for hypoparathyroidism. Additionally, Alexion is looking forward to welcoming talent from Amolyt Pharma.

In patients with hypoparathyroidism, a deficiency in parathyroid hormone (PTH) production results in significant dysregulation of calcium and phosphate, which can lead to life-altering symptoms and complications, including chronic kidney disease.1 It is one of the largest known rare diseases, affecting an estimated 115,000 people in the United States and 107,000 people in the European Union, approximately 80% of whom are women.2,3

Marc Dunoyer, Chief Executive Officer, Alexion, AstraZeneca Rare Disease, said: “Chronic hypoparathyroid patients face a significant need for an alternative to current supportive therapies, which do not address the underlying hormone deficiency. As leaders in rare disease, Alexion is uniquely positioned to drive the late-stage development and global commercialisation of eneboparatide, which has the potential to lessen the often debilitating impact of low parathyroid hormone and avoid the risks of high-dose calcium supplementation. We believe this programme, together with Amolyt’s talented team, expertise and earlier pipeline, will enable our expansion into rare endocrinology.”

Eneboparatide is a PTH receptor 1 (PTHR1) agonist with a novel mechanism of action rationally designed to meet the therapeutic goals of hypoparathyroidism.4 Phase II data showed that eneboparatide achieved normalisation of serum calcium levels as well as the potential to eliminate dependence on daily calcium and vitamin D supplementation. In adults with chronic hypoparathyroidism and hypercalciuria, results showed that eneboparatide normalised calcium in urine. In addition, for patients with hypoparathyroidism, eneboparatide preserved bone mineral density, an important potential benefit in patients with an increased risk of osteopenia or osteoporosis.5

Financial considerations

Under the terms of the agreement, AstraZeneca will acquire all of Amolyt Pharma’s outstanding shares for a total consideration of up to $1.05 billion, on a cash and debt free basis. This includes $800 million upfront at deal closing, plus the right for Amolyt Pharma’s shareholders to receive an additional contingent payment of $250 million payable upon achievement of a specified regulatory milestone.

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

Linden Acquires Alcresta Therapeutics

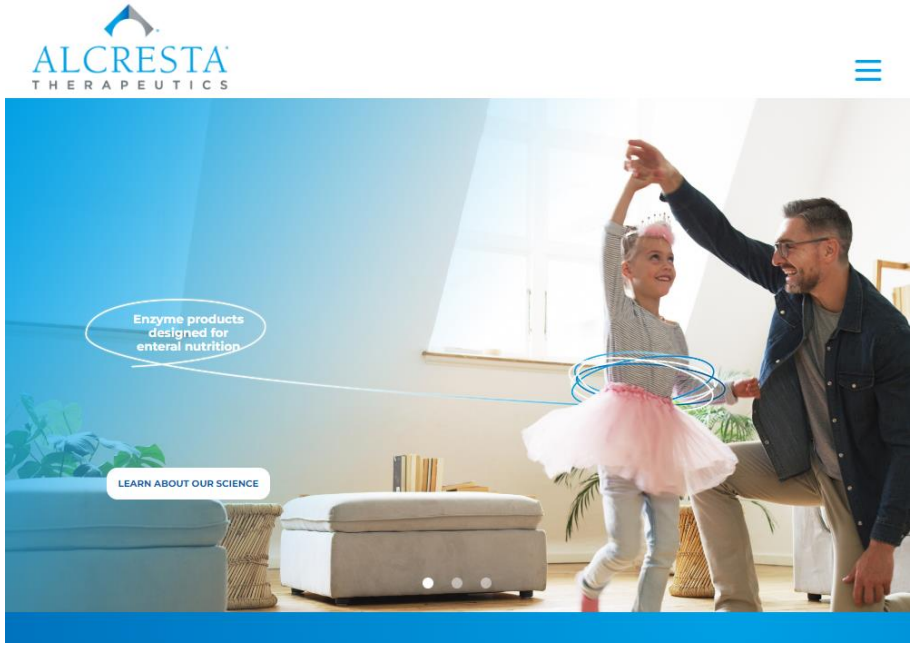
Press Release, Mar 12, 2024

Linden Capital Partners, a Chicago-based private equity firm focused exclusively on the healthcare industry, announced today the completion of its acquisition of Alcresta Therapeutics, a leader in commercializing novel enzyme-based products designed to address challenges faced by patients living with gastrointestinal disorders and rare diseases, from Athyrium Capital, Bessemer Venture Partners, Frazier Healthcare Partners, and HealthQuest Capital. HealthQuest Capital subsequently re-invested in Alcresta and will continue as a minority shareholder and board member.

Alcresta recently announced 510(k) clearance of its next-generation RELiZORB® (iMMOBILIZED LIPASE) cartridge by the Center for Devices and Radiological Health (CDRH) of the U.S. Food and Drug Administration (FDA). The next-generation RELiZORB device was developed to address the enteral nutrition needs of a wider population of patients living with rare diseases and is expected to launch in Q2 2024.

To support Alcresta's growth in the coming years, Linden has assembled a Board of Directors that brings considerable expertise in healthcare, product launches, and commercial execution. The new Board will work closely with the Alcresta team to drive ever improving outcomes for patients and healthcare providers.

"We are grateful to the team of investors, led by Athyrium Capital, that brought significant value creation to Alcresta and guided the sale to Linden," Alcresta CEO Daniel Orlando said, adding, "We have been very impressed with Linden's thoughtful investment approach as we finalize launch plans for the next generation RELiZORB and accelerate R&D efforts for an iteration to treat enterally fed patients in the NICU. We anticipate considerable growth in the years to come and appreciate the added strategic planning and investment expertise Linden and the new Board bring to Alcresta."



Source: https://www.prnewswire.com/news-releases/linden-capital-partners-acquires-alcresta-therapeutics-inc-302086718.html

Novartis Exercises Option to Acquire IFM With First-In-Class STING Antagonist Program Targeting Innate Immune System

Press Release, Mar 13, 2024

IFM Therapeutics (IFM), a privately held biopharmaceutical company focused on developing therapies that modulate novel targets in the innate immune system, announced today that Novartis has exercised its option to acquire all of the outstanding capital stock of IFM Due, a subsidiary company of IFM. Launched in February 2019, with a focus on developing small molecules that inhibit the cGAS-STING pathway, the company entered into an option and collaboration agreement with Novartis in September, 2019 whereby Novartis made fixed payments sufficient to fully finance IFM Due's research and development costs for the cGAS-STING program in exchange for the option to acquire the IFM Due subsidiary. Under the terms of the option exercise, IFM received $90 million in upfront payment and will be eligible for up to $745 million in milestone payments, adding up to $835 million in total consideration.

The acquisition provides Novartis with full rights to IFM Due's portfolio of STING antagonists, which have the potential to treat an array of serious inflammation-driven diseases characterized by excessive interferon and other pro-inflammatory cytokine signaling.

"The acquisition of IFM Due represents the culmination of a highly productive, four-year preclinical collaboration between Novartis and IFM to develop novel small-molecule STING inhibitors with the potential to treat a spectrum of inflammatory diseases," said Richard Siegel, global head of immunology research at Novartis. "We are excited to advance IFM Due's STING program and leverage our deep expertise in inflammation science to bring forward transformative medicines that address major unmet patient needs."

Source: https://www.prnewswire.com/news-releases/novartis-acquires-ifm-due-to-develop-first-in-class-sting-antagonist-program-targeting-innate-immune-system-302087547.html

IFM's Hat Trick and Reflections On Option-To-Buy M&A

Bruce Booth, LifeSciVC, March 13, 2024

Today IFM Therapeutics announced the acquisition of IFM Due, one of its subsidiaries, by Novartis. Back in Sept 2019, IFM granted Novartis the right to acquire IFM Due as part of an "option to buy" collaboration around cGAS-STING antagonists for autoimmune disease.

This secures for IFM what is a rarity for a single biotech company: a liquidity hat trick, as this milestone represents the third successful exit of an IFM Therapeutics subsidiary since its inception in 2015.

Back in 2017, BMS purchased IFM's NLRP3 and STING agonists for cancer. In early 2019, Novartis acquired IFM Tre for NLRP3 antagonists for autoimmune disease, which are now being studied in multiple Phase 2 studies. Then, later in 2019, Novartis secured the right to acquire IFM Due after their lead program entered clinical development. Since inception, across the three exits, IFM has secured over $700M in upfront cash payments and north of $3B in biobucks.

Kudos to the team, led by CEO Martin Seidel since 2019, for their impressive and continued R&D and BD success.

Option-to-Acquire Deals

These days option-based M&A deals aren't in vogue: in large part because capital generally remains abundant despite the contraction, and there's still a focus on "going big" for most startup companies. That said, lean capital efficiency around asset-centric product development with a partner can still drive great returns. In different settings or stages of the market cycle, different deal configurations can make sense.

During the pandemic boom, when the world was awash in capital chasing deals, "going long" as independent company was an easy choice for most teams. But in tighter markets, taking painful levels of equity dilution may be less compelling than securing a lucrative option-based M&A deal.

For historical context, these option-based M&A deals were largely borne out of necessity in far more challenging capital markets (2010-2012) on the venture front, when both the paucity of private financing and the tepid exit environment for early stage deals posed real risks to biotech investment theses. Pharma was willing to engage on early clinical or even preclinical assets with these risk-sharing structures as a way to secure optionality for their emerging pipelines.

Source: https://lifescivc.com/

Reflections On Option-To-Buy M&A (continued)

Bruce Booth, LifeSciVC, March 13, 2024

As a comparison, in 2012, total venture capital funding into biotech was less than quarter of what it is now, even post bubble contraction, and back then we had witnessed only a couple dozen IPOs in the prior 3 years combined. And most of those IPOs were later stage assets in 2010-2012. Times were tough for biotech venture capital. Option-based deals and capital efficient business models were part of ecosystem's need for experimentation and external R&D innovation.

Many flavors of these option-based deals continued to get done for the rest of the decade, and indeed some are still getting done, albeit at a much less frequent cadence. Today, the availability of capital on the supply side, and the reduced appetite for preclinical or early stage acquisitions on the demand side, have limited the role of these option to buy transactions in the current ecosystem.

But if the circumstances are right, these deals can still make some sense: a constructive combination of corporate strategy, funding needs, risk mitigation, and collaborative expertise must come together. In fact, Arkuda Therapeutics, one of our neuroscience companies, just announced a new option deal with Janssen.

Positive anecdotes of acquisition options being exercised over the past few years are easy to find. We've seen Takeda exercise its right to acquire Maverick for T-cell engagers and GammaDelta for its cellular immunotherapy, among other deals. AbbVie recently did the same with Mitokinin for a Parkinson's drug. On the negative side, in a high profile story last month, Gilead bailed on purchasing Tizona after securing that expensive $300M option a few years ago.

But these are indeed just a few anecdotes; what about data since these deal structures emerged circa 2010? Unfortunately, as these are mostly private deals with undisclosed terms, often small enough to be less material to the large Pharma buyer, there's really no great source of comprehensive data on the subject. But a reasonable guess is that the proportion of these deals where the acquisition right is exercised is likely 30%.

This estimate comes from triangulating from a few sources. A quick and dirty dataset from DealForma, courtesy of Tim Opler at Stifel, suggests 30% or so for deals 2010-2020. Talking to lawyers from Goodwin and Cooley, they also suggest ballpark of 30-50% in their experience.

Source: https://lifescivc.com/

Biotech Rally Gets $100 Billion M&A Lift With More Deals to Come

Lisa Pham and Alexandra Muller, *Bloomberg*, March 14, 2024 (excerpt)

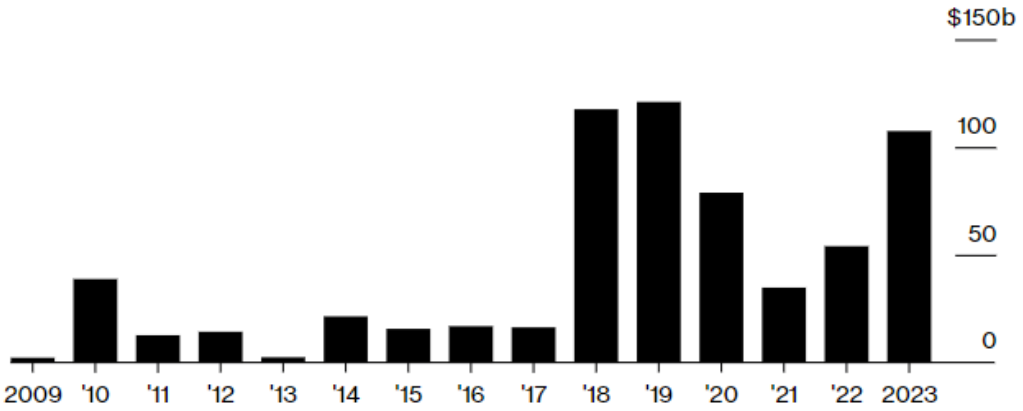
A rash of dealmaking helped reverse the declining fortunes of biotech stocks over the last five months. And as AstraZeneca Plc's $1 billion deal to acquire closely-held Amolyt Pharma illustrates, the likelihood is there's much more to come.

A total of 46 listed biotech transactions worth more than $100 billion were announced across the industry last year, the highest since spending peaked in 2019, according to data compiled by Bloomberg. Chief among them was Pfizer Inc.'s $42 billion acquisition of cancer drug maker Seagen Inc.

The increase in deal activity bodes well for a rally that has seen the Russell 2000 Index Biotechnology Subsector rise nearly 60% since its October low, also boosted by a shift back toward long-duration growth stocks on the prospect of lower interest rates. Many of the world's top pharmaceutical firms are seeking deals to transform often aging drug pipelines, and have billions of dollars to spend on doing so.

"The prospect of further M&A activity looks strong this year," said Ailsa Craig, co-lead manager of the International Biotechnology Trust. "Patent expiries among the larger pharma players continue to be a pressing issue and they will continue to look towards the biotech sector for opportunities to plug the holes in their product shelves and pipelines."

Global Biotech M&A Regains Popularity



Source: Bloomberg
Note: Pending and completed M&A transactions involving public biotech firms as the target

Source: https://www.bloomberg.com/news/articles/2024-03-14/biotech-rally-gets-100-billion-m-a-lift-with-more-deals-to-come

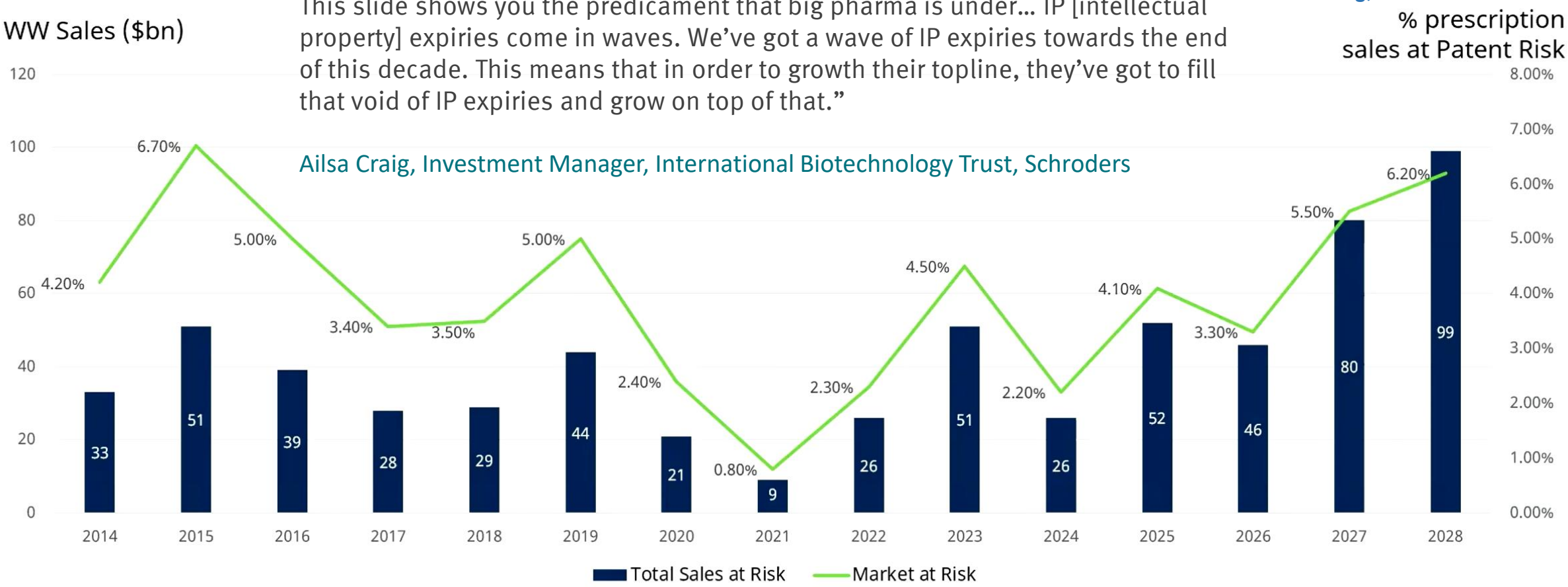
Major biopharma patent expiries

Threat increasing during second half of the decade

Ailsa Craig, Schroders

"I mentioned last year we saw some record numbers of M&A deals. Why is that? This slide shows you the predicament that big pharma is under… IP [intellectual property] expiries come in waves. We've got a wave of IP expiries towards the end of this decade. This means that in order to growth their topline, they've got to fill that void of IP expiries and grow on top of that."

Ailsa Craig, Investment Manager, International Biotechnology Trust, Schroders



Source: Evaluate Pharma August 2023

Source: https://citywire.com/funds-insider/news/ailsa-craig-big-pharma-has-a-problem-and-that-s-driving-biotech-m-and-a/a2438448 -

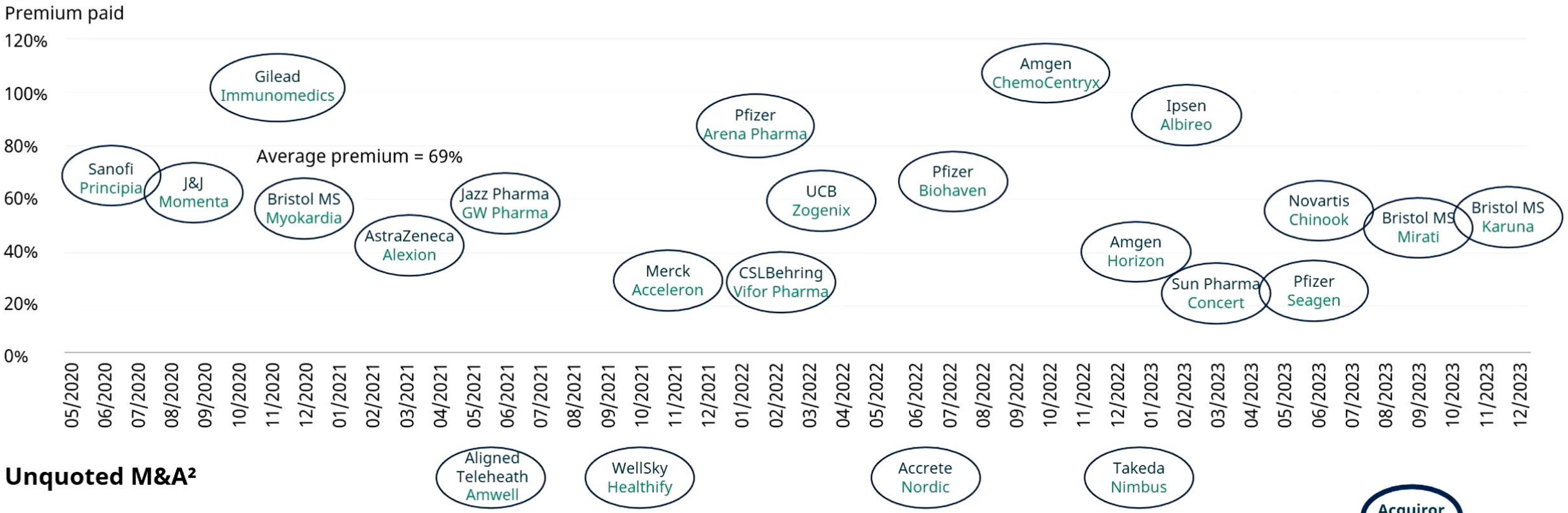
M&A – a major theme of the biotech industry

Strong M&A deal flow for the fund in recent years

Ailsa Craig, Schroders

23 M&A deals among IBT's portfolio companies since 2020[1]

Quoted M&A



Unquoted M&A[2]

Aligned Teleheath Amwell

WellSky Healthify

Accrete Nordic

Takeda Nimbus

Acquiror
Target

Past performance is not a guide to future performance.
Source: Schroders. [1]In some transactions, the market price rose sharply before the announcement. [2]M&A premium not disclosed in unquoted portfolio.
[3]To be confirmed.
Reference to securities are for illustrative purposes only and not a recommendation to buy or sell.

Source: https://citywire.com/funds-insider/news/ailsa-craig-big-pharma-has-a-problem-and-that-s-driving-biotech-m-and-a/a2438448

Industry News

Pharma Dealt a Loss Over 340B Drug Discount Program

Adriel Bettelheim, *Axios*, March 13, 2024 (excerpt)

Pharmaceutical interests lost a closely watched battle over the federal drug discount program on Tuesday when a federal appeals court ruled that Arkansas can block manufacturers from limiting the availability of discounted drugs at certain pharmacies.

The decision from the 8th U.S. Circuit Court of Appeals could encourage look-alike state laws that take aim at restrictions on when providers can use discounts from the 340B program.

The dispute centered on contract pharmacies that dispense discounted drugs to hospitals, community health centers and other safety net providers covered by the program.

As 340B costs have grown, drugmakers have placed restrictions on where hospitals and clinics can use their program discounts.
The providers say the policies threaten patient access while pharmaceutical companies maintain the limits ensure 340B program integrity.

The trade group PhRMA challenged Arkansas' law, saying it was preempted by federal law and improperly empowered a state agency to penalize manufacturers who refuse to distribute to contract pharmacies.

But Judge Michael Melloy wrote that states have some leeway to set requirements since federal 340B law does not mention pharmacies or the delivery of drugs by pharmacies to patients.

"Pharmacy has traditionally been regulated at the state level, and we must assume that absent a strong showing that Congress intended preemption, state statutes that impact health and welfare are not preempted," Melloy wrote.

Source: https://www.axios.com/2024/03/13/drug-discount-340b-appeal

U.S. Healthcare Spend Continues to Outpace GDP

Medpac Report to Congress, Mar 15, 2024

In 2022, $4.5 trillion was spent on health care in the U.S. This spending accounted for 17.3 percent of the U.S.'s gross domestic product (GDP)—up from 14.9 percent 20 years earlier (Figure 1-1).

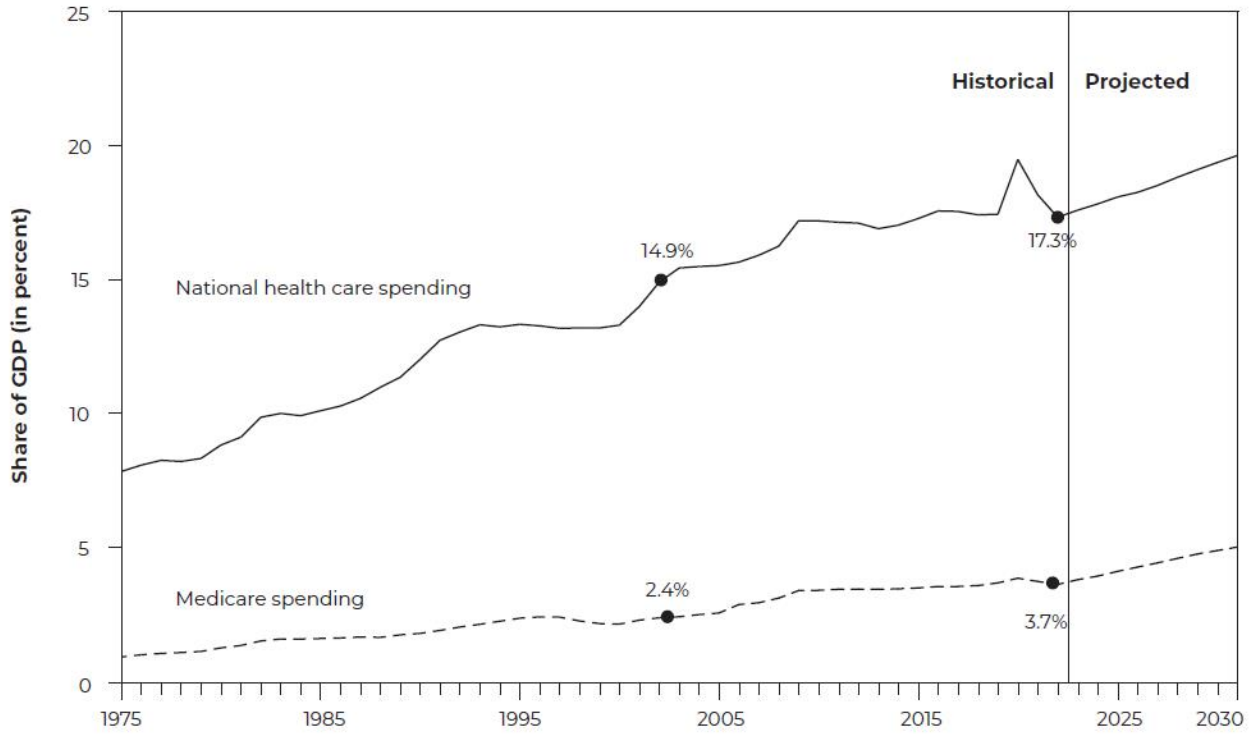
Medicare spending has also grown as a share of GDP over time—making up 3.7 percent of GDP in 2022, up from 2.4 percent 20 years earlier.

National health care spending usually grows faster than GDP, which means this spending as a share of GDP increases over time (Figure 1-1, p. 8). But different spending trends were observed during the recent coronavirus pandemic, with national health care spending as a share of GDP sharply increasing in 2020 and then falling in 2021 and 2022, as it returned to its prepandemic share.

Spending trends in 2023 are estimated to have returned to historical norms, with national health care spending growth (5.1 percent) outpacing GDP growth (4.1 percent) (Keehan et al. 2023). As a result, national health care spending as a share of GDP is expected to have grown slightly to 17.6 percent of GDP (Keehan et al. 2023). CMS expects familiar spending patterns to continue through 2031, with national health care spending growing faster than GDP in part because medical prices are projected to grow faster than economy-wide prices over this period (Keehan et al. 2023).

FIGURE 1–1

Health care spending has grown as a share of the country's GDP



Note: GDP (gross domestic product). The first projected year in the graph is 2023. Pandemic relief funds are counted as national health care spending rather than Medicare spending since they were meant to offset pandemic-related revenue losses from all payers, not just Medicare.

Source: MedPAC analysis of CMS's national health expenditure data (projected data released in July 2023 and historical data released in December 2023), https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/index.html.

Source: https://www.medpac.gov/document/march-2024-report-to-the-congress-medicare-payment-policy/

Medicare Part D Drug Prices Continued to Rise in 2022

Medpac Report to Congress, Mar 15, 2024

TABLE 11–3 **Part D prices, after accounting for generic substitution, continued to rise in 2022**

	2018	2019	2020	2021	2022
	Price index as of 4th quarter (1st quarter 2006 = 1.00)				
All drugs and biologics					
Before accounting for generic substitution	1.90	1.95	2.00	2.09	2.17
After accounting for generic substitution	1.14	1.11	1.13	1.17	1.20
Biologics (excluding insulin)	3.16	3.32	3.51	3.79	4.06
	Annual percentage change*				
All drugs and biologics					
Before accounting for generic substitution	3.6%	2.9%	2.6%	4.1%	3.8%
After accounting for generic substitution	1.7	–2.1	1.3	3.4	2.6
Biologics (excluding insulin)	7.3	5.2	5.7	7.9	7.1
Share of gross Part D spending accounted for by biologics**	9	10	12	13	15

Indexes are calculated using chain-weighted Fisher price indexes and are measured at the median of the distribution relative to prices as of the first quarter of 2006. Prices reflect total amounts paid to pharmacies before rebates or discounts from manufacturers and pharmacies. Indexes shown are rounded. Price indexes reflect changes in the prices of existing products. These indexes do not reflect the effect of launch prices of new products. *Annual percentage changes reflect growth in the price index since the fourth quarter of the previous year, calculated using unrounded data. **Gross spending for biologics excludes insulin. Biologics including insulin accounted for 18 percent of total gross Part D spending in 2018 and rose to 21 percent by 2022.

Source: https://www.medpac.gov/document/march-2024-report-to-the-congress-medicare-payment-policy/

Top 3 Medicare Advantage Insurers Gained Share

Medpac Report to Congress, Mar 15, 2024

TABLE 12–6

Medicare Advantage enrollment share by top three parent organizations increased nationally and locally, July 2019–2023

Top 3 parent organizations, by type of MA plan	Share of MA-eligible beneficiaries living in counties in which insurer offers an MA plan			Percentage point change in share	
	2019	2022	2023	2019–2023	2022–2023
Conventional plans					
UnitedHealth Group Inc.	80%	90%	94%	+14%	+4%
Humana Inc.	85	89	92	+7	+3
CVS Health Corporation	73	83	84	+11	+1

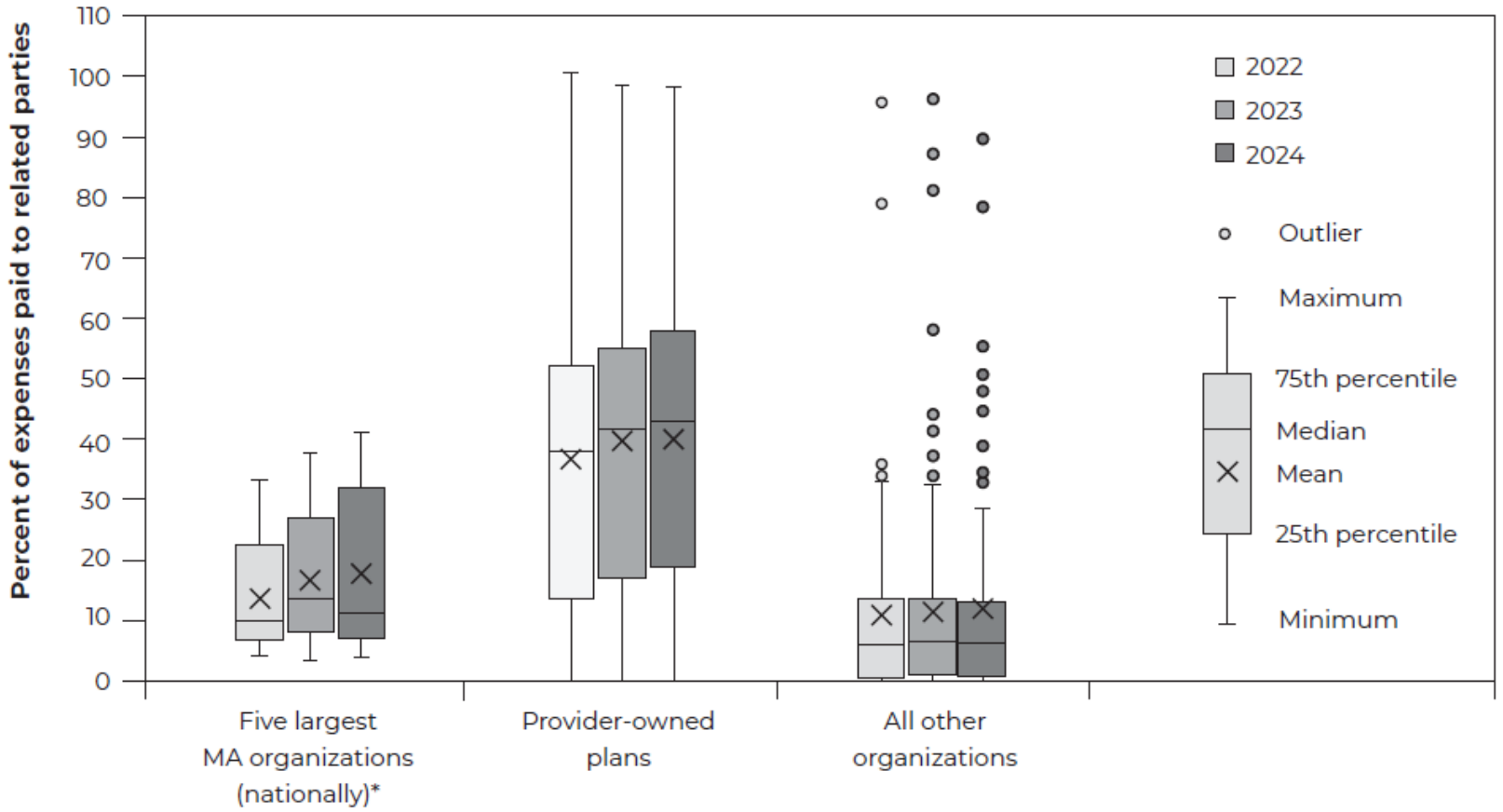
Source: https://www.medpac.gov/document/march-2024-report-to-the-congress-medicare-payment-policy/

Medicare Advantage Insurers Are Vertically Integrating

Medpac Report to Congress, Mar 15, 2024

FIGURE 12–12

Vertical integration is increasing and is highest in plans owned by provider organizations



Note: MA (Medicare Advantage). Excluded are cost-reimbursed plans, Medicare–Medicaid demonstration plans, and employer group plans. *The five largest non-provider-owned plans are UnitedHealth Group, Humana, CVS Health, Elevance Health, and Centene. Kaiser Foundation Health Plan enrolls more beneficiaries than Centene but is categorized as a provider-owned plan in the figure.

Source: MedPAC analysis of data from CMS on plan bids, MMIT Directory of Health Plans.

Source: https://www.medpac.gov/document/march-2024-report-to-the-congress-medicare-payment-policy/

WuXi AppTec Exits BIO Membership Last Week

Sherry Qin, *Wall Street Journal*, March 14, 2024 (excerpt)

WuXi AppTec says it voluntarily left a high-profile biotechnology lobbying group as U.S. legislative efforts were "maligning" its membership in the Washington-based association.

A letter sent by the company to the Biotechnology Innovation Organization's president and CEO, John Crowley, dated March 12, said that "effective immediately, WuXi AppTec, along with our subsidiary WuXi Clinical, will end our associate membership in BIO." The letter was seen Friday by The Wall Street Journal.

WuXi AppTec and its affiliates have been the target of two U.S. bills that seek to prohibit U.S. federal agencies from contracting with or granting funds to certain Chinese biotech companies on the grounds that the companies could threaten national security through actions such as collecting sensitive biometrics information or collaborating with the Chinese military.

WuXi AppTec reiterated in the letter that the U.S. legislative efforts were "preemptively and unfairly targeting the company without due process, a transparent review of the facts, or consideration of their impact on U.S. leadership in biotechnology innovation and patient care."

BIO, an influential trade association whose members include Eli Lilly, Merck, Johnson & Johnson and hundreds of other companies had said Wednesday that it was cutting ties with WuXi AppTec as part of measures to aid U.S. national-security efforts.

Source: https://www.wsj.com/tech/biotech/wuxi-apptec-says-it-left-washington-lobbying-group-voluntarily-33092fb1

Pressure for Sanctions on Wuxi Increasing

Michael Martina, *Reuters*, Feb 12, 2024 (excerpt)

The U.S. should review Chinese biotech firm WuXi AppTec and its affiliate WuXi Biologics for sanctions, a bipartisan group of lawmakers told top Biden administration officials on Monday. In a letter dated Feb. 12 and seen by Reuters, the lawmakers told Treasury Secretary Janet Yellen, Defense Secretary Lloyd Austin and Commerce Secretary Gina Raimondo that the global pharmaceutical giant's links to China's Communist Party and military threatened U.S. national security.

The letter, signed by the Republican chair and Democratic ranking member of the House select committee on China, Representatives Mike Gallagher and Raja Krishnamoorthi, and Senators Gary Peters and Bill Hagerty, is Congress' latest effort to highlight what it says are risks posed by China's biotech leaders.

We continue to be puzzled by last week's concern that Wuxi's ties to the Communist party of China might imply a security risk to the U.S. when the company's services are used by global biotech and pharma companies. Wuxi Apptec provides services such as API. This does not involve collecting private information about patients in any way.

We don't doubt that Wuxi has employees that are involved with or have been involved with the Chinese military. Indeed, because China has a state-controlled economy, all companies must have ties to the government. It's not a choice. And a highly successful company would likely have close ties to the government in order to survive in that society. Nonetheless, Ge Li, founder of Wuxi Apptec is an American-trained chemist.

Similarly, in the U.S., we doubt that there are many successful pharmas that do not take money from the NIH or sell drugs via government programs, including to the military. Most U.S. pharmas have extensive government affairs departments for this very reason and frequently collaborate with DARPA/DoD or use military sites (e.g., VA hospital) for research.

In China, military owned hospitals are used to care for the general populace and are deeply embedded in their society. It would be extremely challenging for any pharma institution in China to not cooperate with such entities and not carry out research with persons at those hospitals. On last week's Biotech Hangout, a number of participants felt that it was inevitable that some form of the *BIOSECURE Act* would pass. There was widespread concern about what this might mean for biotech. It's worth noting that the BIOSECURE Act would not prevent private companies from contracting with Wuxi Apptec, but instead would only prevent U.S. government agencies from doing so.

Source: https://www.reuters.com/business/healthcare-pharmaceuticals/us-lawmakers-call-sanctions-chinas-wuxi-apptec-biotech-firm-2024-02-12/. Also see https://selectcommitteeontheccp.house.gov/media/press-releases/gallagher-issues-statement-biotechnology-innovation-organization-endorsement

WuXi Became a Critical Partner to Biopharma Companies. They're Not Ready if the US Cracks Down

Jared Whitlock, *Endpoints News*, March 13, 2024 (excerpt)

It's hard to disentangle WuXi AppTec's rise from China's. Over the last two decades, the Shanghai-based company grew from nothing into a research superstore for the world's biopharma companies.

But as tensions between the US and China have grown, so have doubts about WuXi's future. It has become so intertwined with US drugmakers and biotech startups that it's now seen as a risk, both by some in Congress and by companies that fear getting caught up in a geopolitical struggle over WuXi's alleged ties to the Chinese military.

In more than a dozen interviews and through the review of securities filings, Endpoints News was able to trace the potential impact of a US crackdown on WuXi and its affiliates. Drugmakers like Amicus Therapeutics, Sound Pharmaceuticals and Eli Lilly would likely face delays and shortages should a bill in Congress or potential US sanctions cut WuXi off from its partners. The reporting disclosed many of these industry risks, and a scramble for backup plans, for the first time.

"If this happens, this will create chaos within the system," said Charles Achibiri, founder of SciRank, a website where scientists review contract manufacturers. "It could potentially drive some biotech companies out of business because the cost of transitioning to a new location could be high."

Biopharma's WuXi reliance

Company	Disclosure	Market cap
Amicus	"The PRC, and WuXi specifically, has faced increased scrutiny by the U.S. government, which could impact our ability to supply Pombiliti™ to meet our forecasted future demand, as WuXi is our sole supplier."	$3.9B
Eli Lilly	"We, and the pharmaceutical industry generally, depend on China-based partners for integral chemical synthesis, reagents, starting materials, and ingredients."	$717B
Iovance Biotherapeutics	"Adding either or both previously mentioned WuXi entities on any or all of the aforementioned lists could materially impact our MSA with WuXi."	$4.1B
Structure Therapeutics	"Our active pharmaceutical ingredients and drug product for our product candidates are currently provided by a single-source supplier, WuXi STA, and we expect to rely on this supplier for the foreseeable future."	$1.7B
Vir Biotechnology	"A group of bipartisan U.S. lawmakers sent a letter to Commerce Secretary Gina Raimondo, Treasury Secretary Janet Yellen, and Defense Secretary Lloyd Austin calling on them to investigate Chinese biotech company WuXi AppTec and its subsidiary, WuXi Biologics, one of our CDMOs."	$1.6B
Fibrogen	"Certain U.S. lawmakers have encouraged sanctions and introduced legislation that could affect WuXi AppTec (Hong Kong) Limited, and our current supplier of FG-3246, WuXi Biologics (Hong Kong) Limited ("WuXi Biologics") and companies that do business with WuXi Biologics."	$190M
AgeX Therapeutics	"Any unfavorable government policies on international trade, such as export controls, capital controls or tariffs, may affect the use of testing facilities in China that we use, including pursuant to Serina's testing arrangements with WuXi AppTec (HongKong) Limited."	$39.3M

Source: https://endpts.com/wuxi-became-a-critical-partner-to-biopharma-companies-theyre-not-ready-if-the-us-cracks-down/

US FDA Panel Backs Expanded Use of J&J, Bristol Myers' CAR-T Therapies

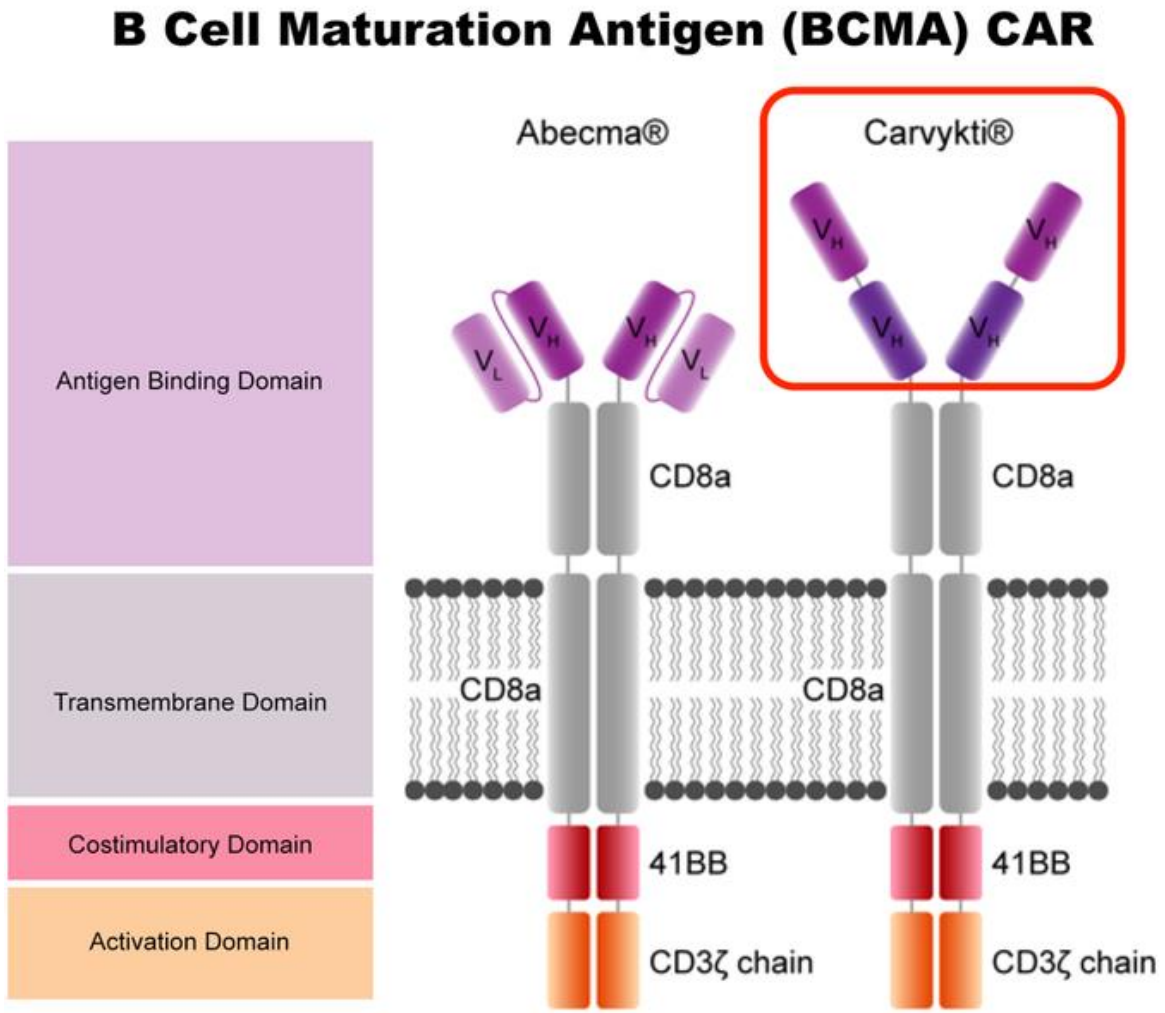
Bhanvi Satija and Sneha S K, *Reuters*, March 15, 2024 (excerpt)

Advisers to the U.S. health regulator voted in favor of allowing the use of Johnson & Johnson and Bristol Myers Squibb's cell therapies as earlier treatments on Friday, paving the way for their use in less severely affected patients with a type of blood cancer.
While all 11 voting members of the panel unanimously agreed the benefits of J&J and Legend Biotech's Carvykti outweighed the risks of the therapy when given as an earlier treatment, only eight voted in favor of Bristol's Abecma.

The therapies are already approved in the U.S. for multiple myeloma patients whose cancer has returned or stopped responding to four prior lines of treatment.

"To be able to give a one-time treatment (to patients) and without requiring them to come back and forth is a really important option," said panelist Mary Kwok.

The FDA's staff reviewers presented concerns about a pattern of early deaths observed in late-stage studies of both the therapies, which they had raised earlier this week.

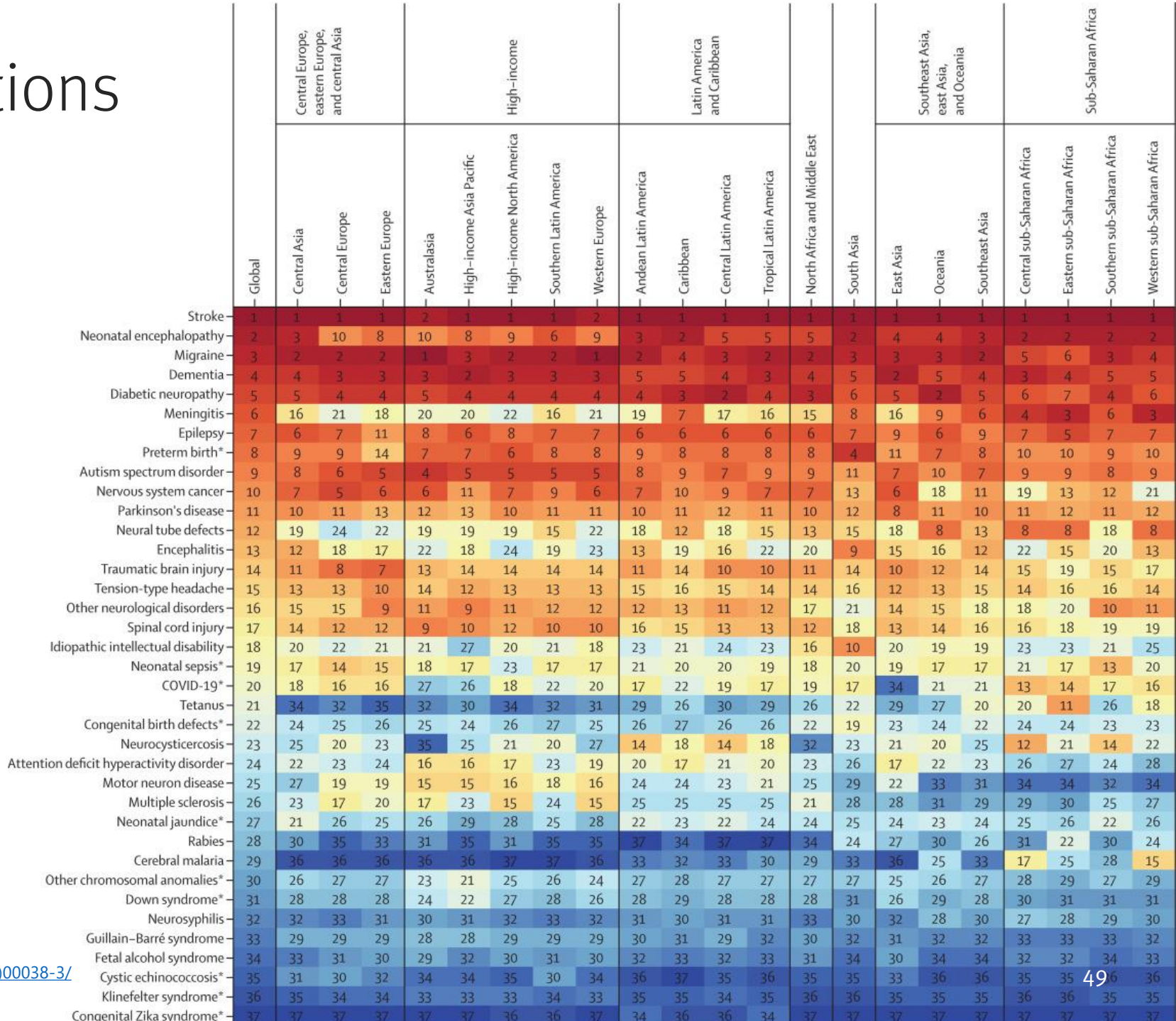


Source: https://www.reuters.com/business/healthcare-pharmaceuticals/us-fda-panel-unanimously-backs-expanded-use-jjs-car-t-therapy-2024-03-15/

Neurological Conditions Leading Cause of Ill Health Worldwide

GBD 2021 Nervous System Disorders Collaborators, *Lancet Neurology*, Mar 14, 2024

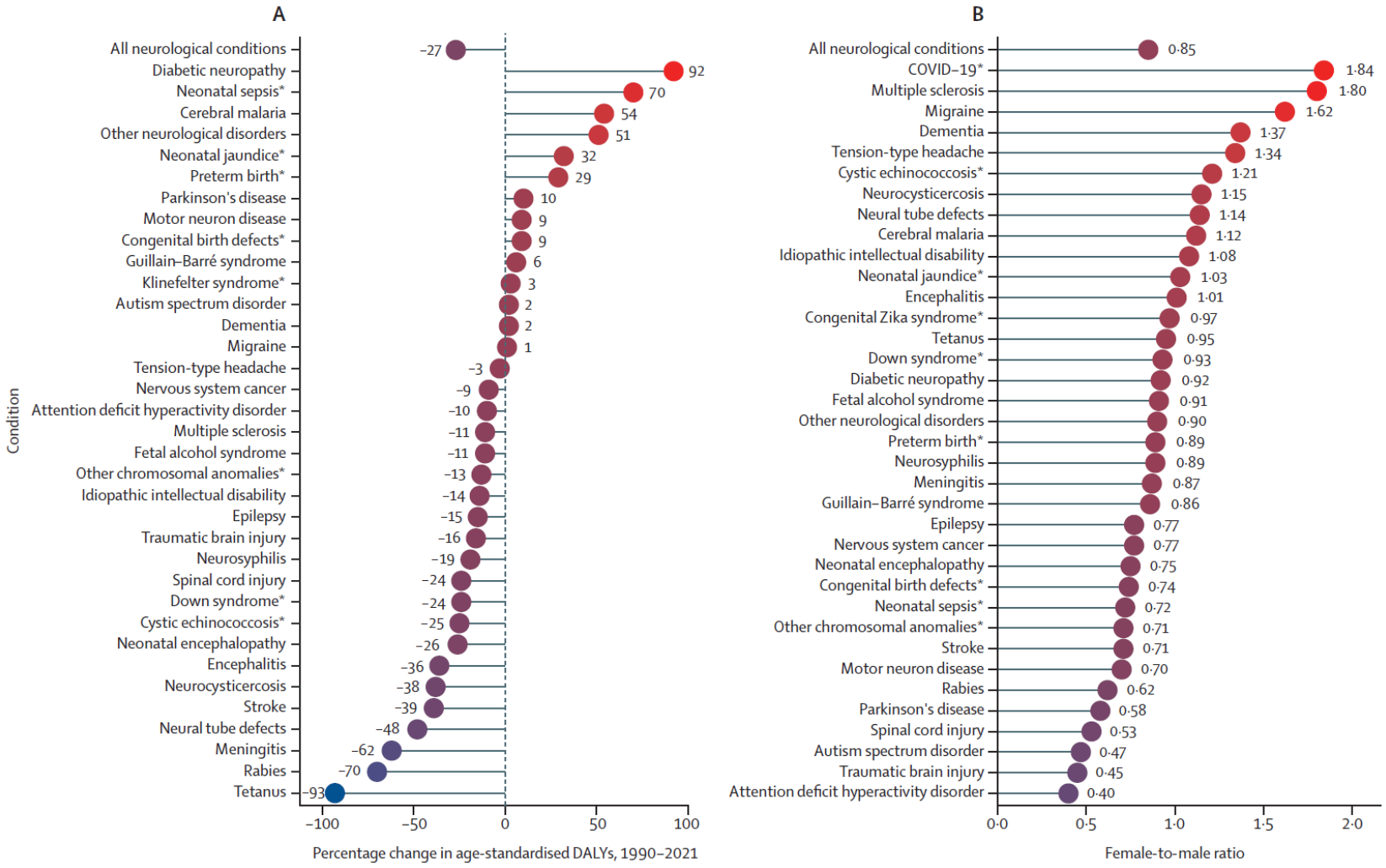
Globally, the 37 conditions affecting the nervous system were collectively ranked as the leading group cause of DALYs in 2021 (443 million, 95% UI 378–521), affecting 3·40 billion (3·20–3·62) individuals (43·1%, 40·5–45·9 of the global population); global DALY counts attributed to these conditions increased by 18·2% (8·7–26·7) between 1990 and 2021. Age-standardised prevalence was almost stable, with a change of 1·5% (0·7–2·4). The ten conditions with the highest age-standardised DALYs in 2021 were stroke, neonatal encephalopathy, migraine, Alzheimer's disease and other dementias, diabetic neuropathy, meningitis, epilepsy, neurological complications due to preterm birth, autism spectrum disorder, and nervous system cancer.



Source: https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(24)00038-3/

Diabetic Neuropathy the Fastest Growing Neurological Problem

GBD 2021 Nervous System Disorders Collaborators, *Lancet Neurology*, Mar 14, 2024



Source: https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(24)00038-3/

Cognitive Components of Aging-Related Increase in Word-Finding Difficulty

Wei HT, Kulzhabayeva D, Erceg L, Robin J, Hu YZ, Chignell M, Meltzer JA. Cognitive components of aging-related increase in word-finding difficulty. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn.* 2024 Feb 14:1-32.

Word-finding difficulty (WFD) is a common cognitive complaint in aging, manifesting both in natural speech and in controlled laboratory tests. Various theories of cognitive aging have addressed WFD, and understanding its underlying mechanisms can help to clarify whether it has diagnostic value for neurodegenerative disease. Two influential "information-universal" theories attribute it to rather broad changes in cognition. The processing speed theory posits a general slowdown of all cognitive processes, while the inhibitory deficit hypothesis (IDH) predicts a specific problem in suppressing irrelevant information. One "information specific" theory of language production, the transmission deficit hypothesis (TDH), posits a breakdown in retrieval of phonological word forms from a corresponding lemma. To adjudicate between these accounts, we administered an online gamified covert naming task featuring picture-word interference (PWI), previously validated to elicit similar semantic interference and phonological facilitation effects as overt naming tasks. 125 healthy adults aged 18 to 85 completed the task, along with a battery of executive function tasks and a naturalistic speech sample to quantify WFD in connected speech. PWI effects provided strong support for the TDH but limited support for IDH, in that semantic interference increased and phonological facilitation decreased across the lifespan. However, neither of these effects on single-word retrieval associated with WFD measured in connected speech. Rather, overall reaction time for word retrieval (controlling for psychomotor slowing) was the best predictor of spontaneous WFD and executive function decline, suggesting processing speed as the key factor, and that verbal reaction time may be an important clinical measure.

Experimental subjects were asked to describe this picture. The speed of the description was much more predictive of cognition decline with age than was the difficulty in word retrieval.

Source: https://pubmed.ncbi.nlm.nih.gov/38353604/

Where Does Fear Come From?

Li HQ, Jiang W, Ling L, Pratelli M, Chen C, Gupta V, Godavarthi SK, Spitzer NC. Generalized fear after acute stress is caused by change in neuronal cotransmitter identity. Science, March 15, 2024;383(6688):1252-1259.

Overgeneralization of fear to harmless situations is a core feature of anxiety disorders resulting from acute stress, yet the mechanisms by which fear becomes generalized are poorly understood. In this study, we show that generalized fear in mice results from a transmitter switch from glutamate to γ-aminobutyric acid (GABA) in serotonergic neurons of the lateral wings of the dorsal raphe. Similar change in transmitter identity was found in the postmortem brains of individuals with posttraumatic stress disorder (PTSD). Overriding the transmitter switch in mice prevented the acquisition of generalized fear. Corticosterone release and activation of glucocorticoid receptors mediated the switch, and prompt antidepressant treatment blocked the cotransmitter switch and generalized fear. Our results provide important insight into the mechanisms involved in fear generalization.

In mice, generalized fear induced by acute stress results from a switch in the neurotransmitters released by a subpopulation of neurons in a specific area of the brain from glutamate to g-aminobutyric acid (GABA). These findings elucidate how fear is generalized in response to stress, provide clues as to how these changes may influence other areas of the brain that modulate fear and open the door for potential future interventions for excess or inappropriate fear.

Source: https://pubmed.ncbi.nlm.nih.gov/38484078/

New Approach to Protein Degradation involving a Zinc Finger Degron

David Liu's lab at Harvard published last week about his laboratory's evolution of compact degrons that enable targeted protein degradation triggered by an otherwise-inert small molecule, a multidisciplinary study that integrates organic chemistry, molecular glues, protein evolution, genome editing, and structural biology.

RESEARCH ARTICLE

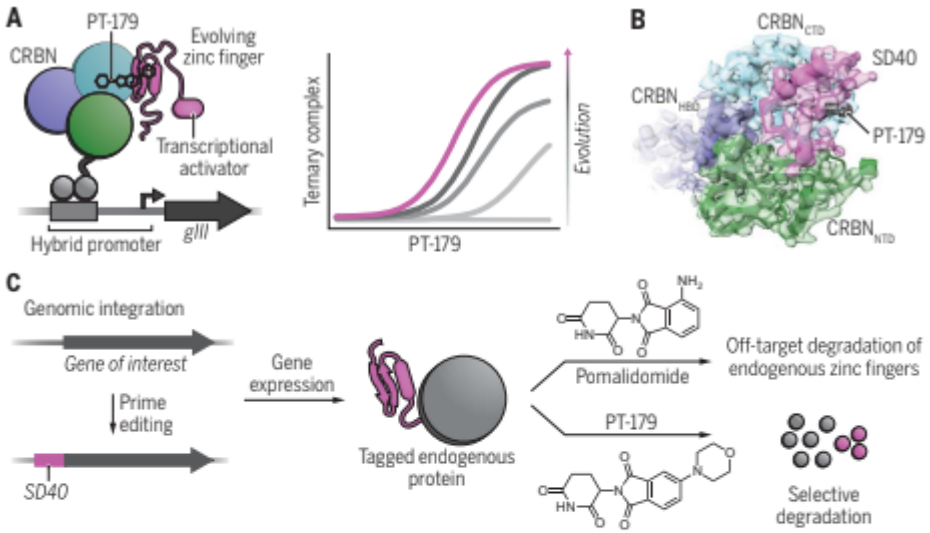
Science, Mar 15, 2024

DEGRON ENGINEERING

Continuous evolution of compact protein degradation tags regulated by selective molecular glues

Jaron A. M. Mercer[1,2,3]†, Stephan J. DeCarlo[1,2,3]†, Shourya S. Roy Burman[4,5]†, Vedagopuram Sreekanth[6,7,8], Andrew T. Nelson[1,2,3], Moritz Hunkeler[4,5], Peter J. Chen[1,2,3], Katherine A. Donovan[4,5], Praveen Kokkonda[6,7], Praveen K. Tiwari[6,7,8], Veronika M. Shoba[6,7], Arghya Deb[6,7], Amit Choudhary[6,7,8]*, Eric S. Fischer[4,5]*, David R. Liu[1,2,3]*

Conditional protein degradation tags (degrons) are usually >100 amino acids long or are triggered by small molecules with substantial off-target effects, thwarting their use as specific modulators of endogenous protein levels. We developed a phage-assisted continuous evolution platform for molecular glue complexes (MG-PACE) and evolved a 36–amino acid zinc finger (ZF) degron (SD40) that binds the ubiquitin ligase substrate receptor cereblon in complex with PT-179, an orthogonal thalidomide derivative. Endogenous proteins tagged in-frame with SD40 using prime editing are degraded by otherwise inert PT-179. Cryo–electron microscopy structures of SD40 in complex with ligand-bound cereblon revealed mechanistic insights into the molecular basis of SD40's activity and specificity. Our efforts establish a system for continuous evolution of molecular glue complexes and provide ZF tags that overcome shortcomings associated with existing degrons.

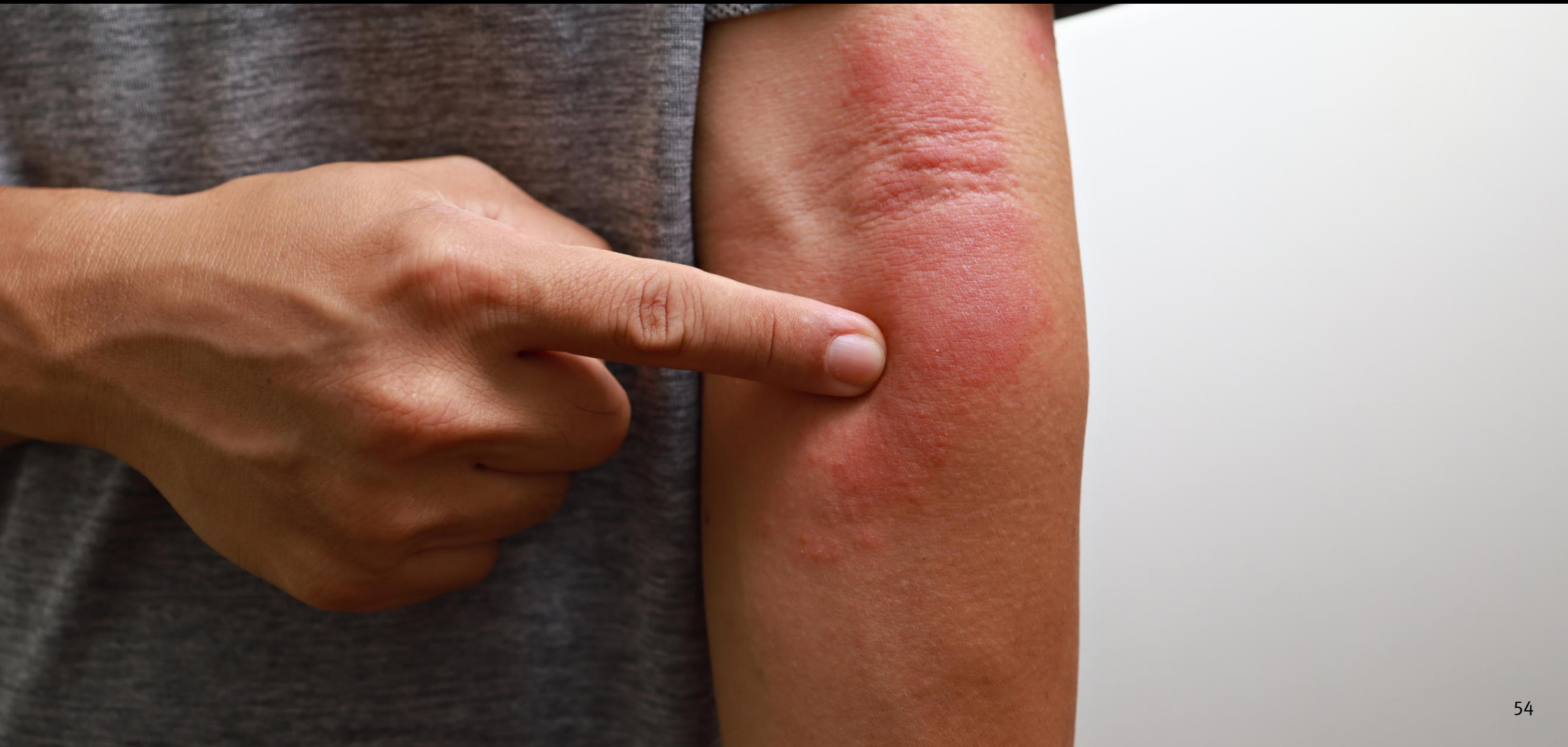


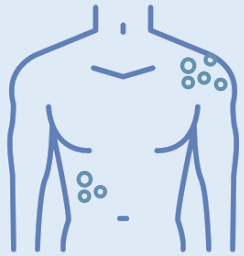
An evolved zinc finger mediates specific degradation of tagged endogenous proteins. (**A**) We developed a selection system for phage-assisted continuous evolution of molecular glue complexes (MG-PACE). We applied MG-PACE to evolve ZF degrons that engage the E3 ubiquitin ligase substrate receptor CRBN only when it is bound to PT-179, a thalidomide derivative that does not exhibit off-target degradation of endogenous human proteins. Assembly of the CRBN•PT-179•ZF ternary complex in host *Escherichia coli* promotes transcription of the essential phage gene *gIII*. (**B**) An ~2.4-Å resolution cryo-EM structure revealed that the evolved ZF protein, SD40 (magenta), engages both CRBN's IMiD-binding C-terminal domain (CRBN$_{CTD}$, cyan) and N-terminal domain (CRBN$_{NTD}$, green) through contacts not previously observed between CRBN and a ZF. (**C**) SD40 is only 36 amino acids long, enabling clean installation of SD40 in-frame into endogenous genomic protein-coding genes in mammalian cell culture with prime editing. SD40-tagged endogenous proteins in human cells are potently, rapidly, and selectively degraded in response to treatment with PT-179.

Mercer *et al.*, *Science* **383**, eadk4422 (2024) 15 March 2024

Source: https://drive.google.com/file/d/18hu15hTnlYaLuXZ7J62ZZu_frEG85ZvP/view

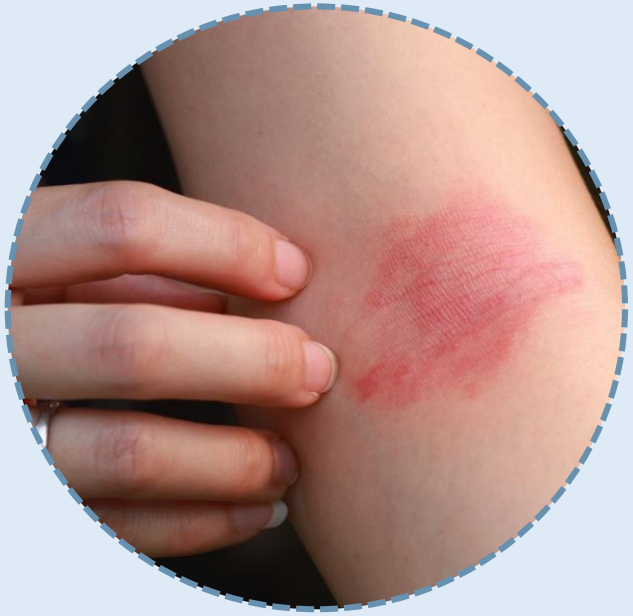
Atopic Dermatitis Update





Atopic Dermatitis

Atopic dermatitis is the most common chronic inflammatory skin disease. Atopic dermatitis manifests as eczema (red inflammatory spotting of the skin). Atopic dermatitis has a complex etiology including genetic and environmental factors which lead to abnormalities in the epidermis and the immune system.



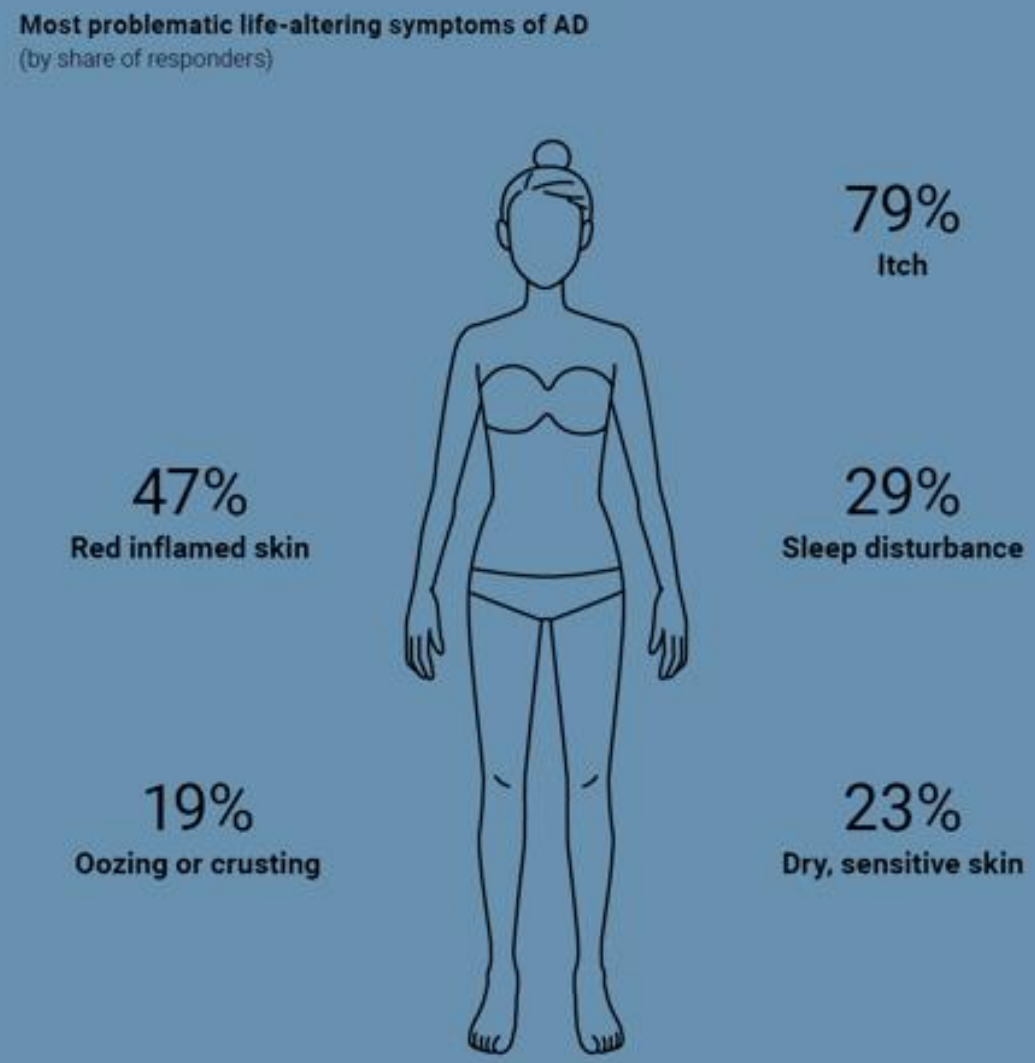
Atopic dermatitis is seen in approximately 10% to 30% of children and 2% to 10% of adults in developed countries. This prevalence has increased two to three-fold in recent decades.

The burden of atopic dermatitis is significant, mainly owing to its high prevalence. Itch, depression, sleep disturbance, and anxiety are the most common manifestations among atopic dermatitis patients.

Managing each patient costs more than

$9,000

In direct and indirect costs per year.



Source: Union Pharma

Substantial Unmet Patient Need

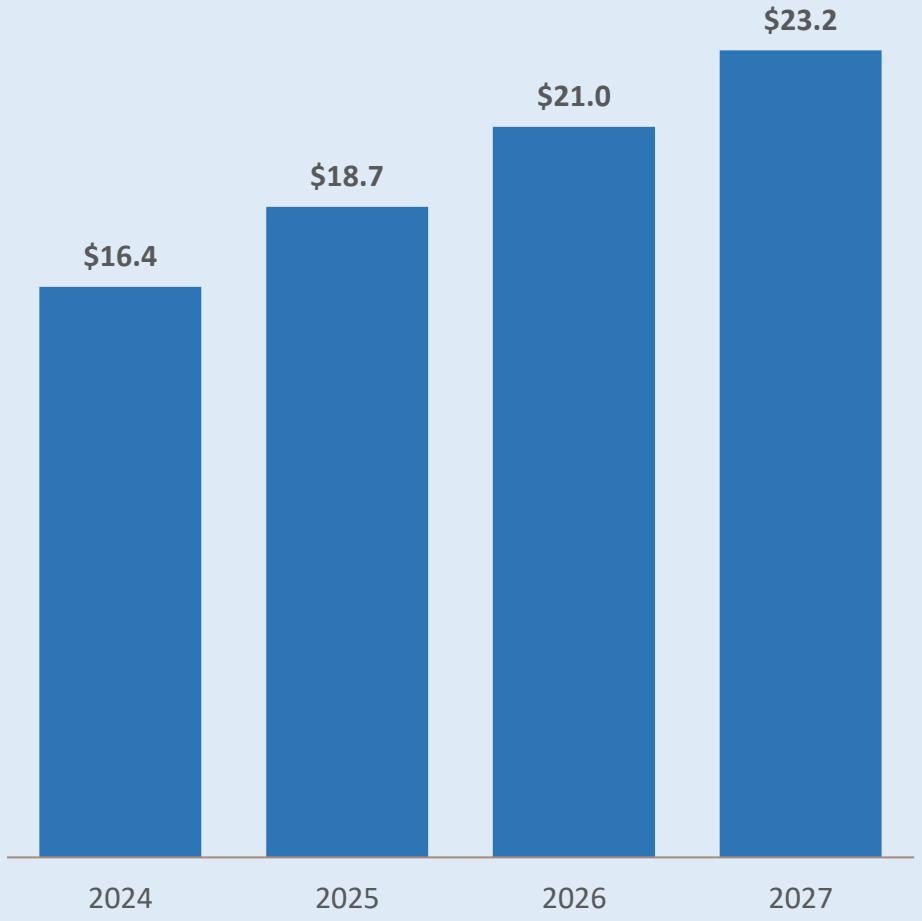
Global Disease Burden

Affects up to	Affects up to
10%	20%
of adults	of children

U.S. Prevalence (moderate to severe)

8.2M	4.2M
adults	Children under 18

Annual Global Sales of Top Ten Atopic Dermatitis Products ($ Billions)



Sources: Silverberg, *Dermatol Clinic* (2017); Sanofi R&D Day, Dec 2023; Evaluate Pharma data on sales of top ten atopic dermatitis products.

Atopic Dermatitis: Field is Highly Competitive

Biologics Pipeline

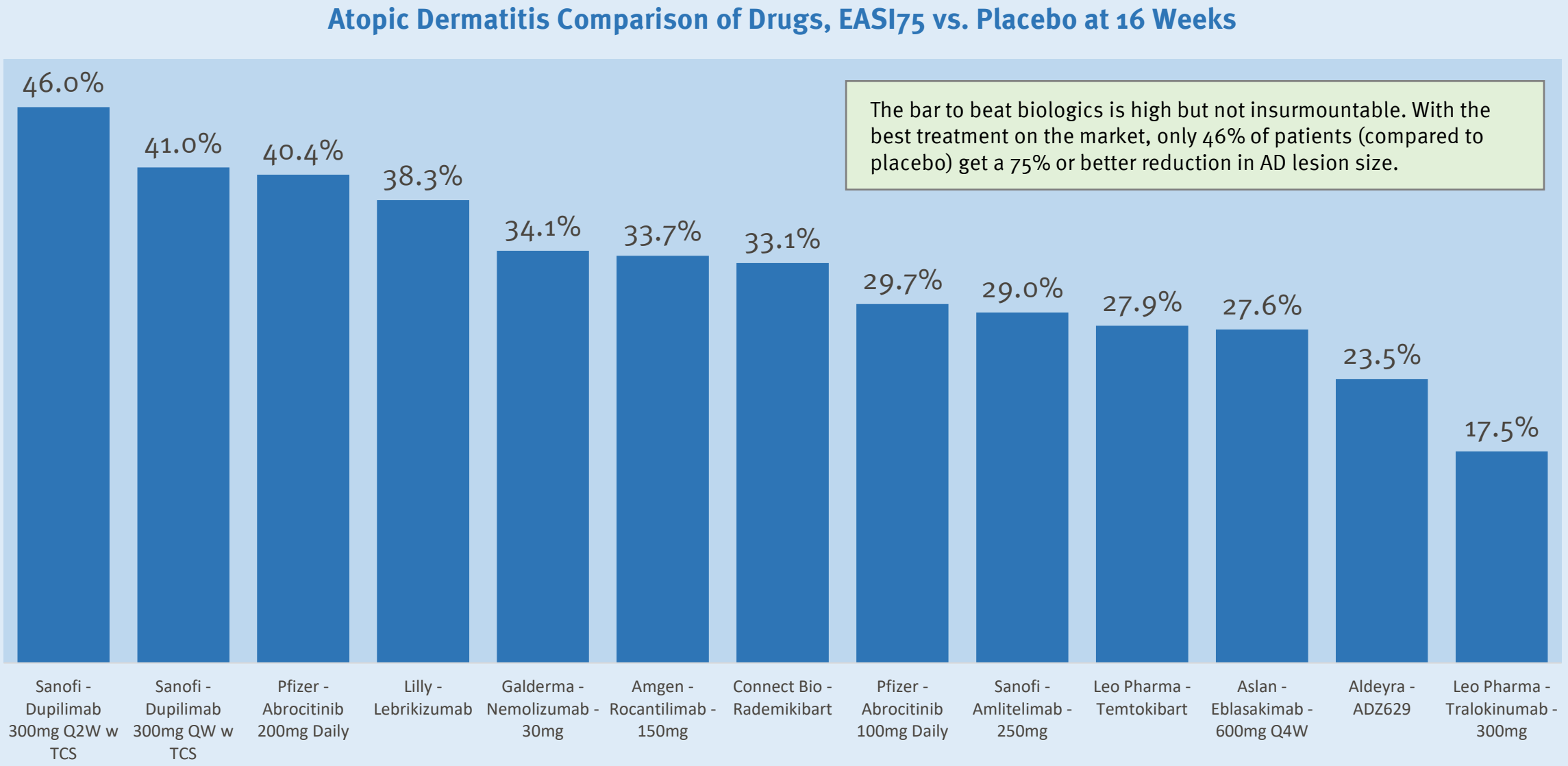
Company	Drug	MOA	Type	Last Completed Stage
Akeso	AK120	IL-4a antibody	Antibody	Phase 1
Amgen	AMG-451	Ox-40 Mab	Antibody	Phase 2
AnaptysBio	ABN-032	BTLA agonist	Antibody	Phase 1
Apogee Tx	APG777	IL-4 / IL-13 Signalling blocker	Antibody	Phase 1
Apogee Tx	APG990	OX-40L antibody	Antibody	Preclin
Apollo Therapeutics	AVTX-007	IL-18 inhibitor	Antibody	Phase 2
Arcutis	ARQ-234	CD200r agonist	Fusion Protein	Preclin
ASLAN	Eblasakimab	IL-13Rα1	Antibody	Phase 2
Astria Therapeutics	STAR-0310	Ox-40 Mab	Antibody	Preclin
Bio-Thera	BAT6026	Ox-40 Mab	Antibody	Phase 2
Biotheus	PM1268	IL-4Rα + IL-31	Bispecific	Preclin
Connect Bio	Rademikibart	IL-4 / IL-13 signalling blocker	Antibody	Phase 2
Eli Lilly	Ucenprubart	Checkpoint Agonist -CD200r	Antibody	Phase 2
Eli Lilly/Almirall	Lebrikizumab	Blocks IL-4 / IL-13 signalling	Antibody	Phase 3
Galderma	Nemoluzumab	Blocks IL-31	Antibody	Phase 2
GSK	GSK1070806	IL-18 inhibitor	Antibody	Phase 1
Hengrui Pharma	SHR-1819	Blocks IL-4 / IL-13 signalling	Antibody	Phase 1
Inmagene	IMG-007	Ox-40 Mab	Antibody	Phase 2
Johnson & Johnson	JNJ-4703	PD-1 agonist	Antibody	Phase 1
Keymed Bio	CM326	TSLP Antagonist	Antibody	Phase 1
LEO Pharma	Tralokinumab	IL-13	Antibody	Approved
LEO Pharma	Temtokibart	IL-22R	Antibody	Phase 2a
Nektar	NKTR-358	IL-2 Agonist	Biologic	Phase 2
Numab Therapeutics	NM26-2198	IL-4Rα / IL-31	Bispecific	Phase 1
Pfizer	PF-07264660	IL4/13/33 antagonist	Biologic	Phase 1
Pfizer	PF-07275315	IL-4/ IL-13/ TSLP antagonist	Biologic	Phase 2
Q32 Bio	ADX-914	IL-7/TSLP antagonist	Antibody	Phase 1
Qyuns Therapeutics	QX005N	Blocks IL-4 / IL-13 signalling	Antibody	Phase 1
Sanofi	Dupilimab	Blocks IL-4 / IL-13 signalling	Antibody	Approved
Sanofi	Amlitelimab	OX40L antagonist	Antibody	Phase 2
SelectION	si-544	KV1.3 Antagonist	Peptide	Phase 1
Tavotek	TAV0101	TSLP Antagonist	Antibody	Phase 1
Triveni Bio	TRIV-509	kallikreins 5 and 7	Antibody	Preclin

Source: Stifel Research

Small Molecule Pipeline

Company	Drug	MOA	Type	Last Completed Stage
AbbVie	Upadacitinib	JAK1 inhibitor	Small Molecule	Phase 2
Aclaris Therapeutics	ATI-1777	Topical JAK1/3 inhibitor	Small Molecule	Phase 2
Akaal Pharma	AK-119	S1P1 receptor modulator	Small Molecule	Phase 1
Aldeyra	ADX-246	RASP Modulator	Small Molecule	Phase 1
Asana Biosciences	ASN002	JAK/SYK inhibitor	Small Molecule	Phase 2
Bayer	BAY-1834845	IRAK4	Small Molecule	Phase 1
CleveXel Pharma	CVXL-0255	Syk and JAk3	Small Molecule	Phase 1
Eli Lilly	Baricitinib	JAK1 / 2 inhibitor	Small molecule	Phase 3
Hengrui Pharma	SHR030	JAK1 inhibitor	Small Molecule	Phase 1
Incyte	Ruxolitinib	JAK1 / 2 inhibitor	Small Molecule	Approved
Innocare	ICP-332	TYK2 JH1 inhibitor	Small Molecule	Phase 1
Kymera	KT-621	Stat6 degrader	Small Molecule	Preclin
LEO Pharma	LP0190	H4R antagonist	Small Molecule	Phase 1
LEO Pharma	LP0133	JAK inhibitor (topical)	Small Molecule	Phase 2
Maruho	Unspecified	KV1.3 Antagonist	Small molecule	Preclin
Minghui Pharma	MH004	JAK Topical (pan-Jak)	Small molecule	Phase 2
Pfizer	Abrocitinib	JAK1 inhibitor	Small Molecule	Phase 3
Pfizer	PF-07038124	Topical PDE4	Small Molecule	Phase 2
Pfizer	PF-07242813	CD1a inhibitor	Small Molecule	Phase 1
Pfizer	Crisaborole	PDE-4 inhibitor	Small Molecule	Approved
RAPT Therapeutics	RPT193	CCR4 antagonist	Small Molecule	Phase 2
Ribon Therapeutics	RBN-343	PARP14	Small Molecule	Preclin
Sanofi	SAR444656	Blocks IRAK4	Small Molecule	Phase 2
Siolta Therapeutics	STMC-103H	Microbiome	Small Molecule	Phase 2
Sitryx	SIT-022	PKM2	Small Molecule	Preclin
Union Therapeutics	Orismilast	PDE-4 inhibitor	Small Molecule	Phase 2
Yirui Pharmaceutical	YR-001	KV1.3 Antagonist	Small Molecule	Phase 1
AbbVie	Upadacitinib	JAK1 inhibitor	Small Molecule	Phase 2
Aclaris Therapeutics	ATI-1777	Topical JAK1/3 inhibitor	Small Molecule	Phase 2
Akaal Pharma	AK-119	S1P1 receptor modulator	Small Molecule	Phase 1
Aldeyra	ADX-246	RASP Modulator	Small Molecule	Phase 1
Asana Biosciences	ASN002	JAK/SYK inhibitor	Small Molecule	Phase 2
Bayer	BAY-1834845	IRAK4	Small Molecule	Phase 1

Efficacy Benchmarks in Atopic Dermatitis at Four Months



Source: Stifel analysis of various Phase 2 and Phase 3 studies.

Opportunities Remain to Capture Share in the AD Market

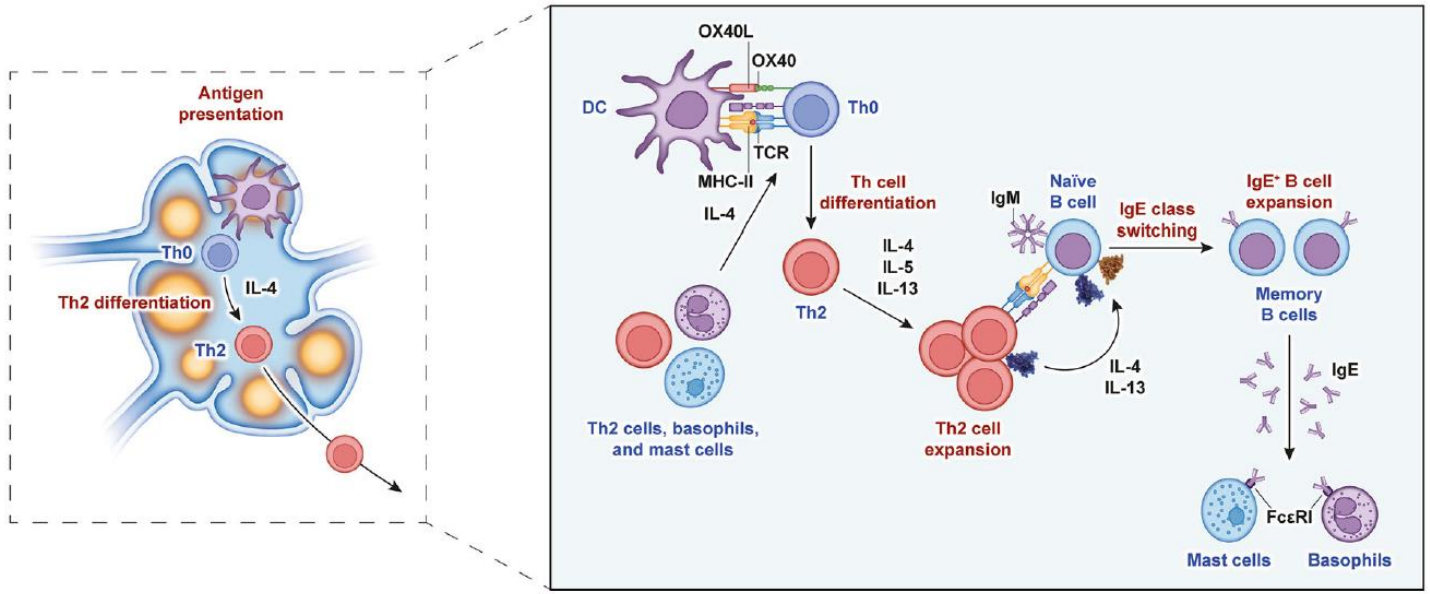
(Adults of Age 18 and Higher)

There are five opportunities commercially to enter and take market share in atopic dermatitis treatments: (1) develop therapies that can treat moderate to severe biologics failures; (2) develop therapies that have an efficacy / safety profile to beat biologics head on and go in front of them; (3) develop therapies that can add value on top of biologics, (4) develop therapies that improve on biologics (e.g., long acting or easier delivery such as oral formulation) or (5) develop therapies that could be used as topicals before biologics are used but after steroids fail.

* See https://www.annallergy.org/article/S1081-1206(22)00497-5/

Today's Approved Drugs Work by Affecting the Type 2 Immune Response Via Th2 Differentiation

Type 2 inflammation leads to defects in the epithelial barrier, allowing entry of allergens/pathogens, where they are taken up by Langerhans cells and other APCs. Disruption to the epithelial barrier also stimulates the release of alarmins (e.g., IL-25, IL-33, TSLP) from keratinocytes. Alarmins induce production of type 2 mediators such as IL-4 and IL-13 by innate immune cells, thereby shaping the immune response toward the type 2 pathway, and the subsequent recruitment of mast cells, basophils, eosinophils, alternatively activated macrophages, and allergen-specific IgE into the dermal layers. Continued activation of type 2 immunity leads to chronic inflammation with emergence of memory Th2 cells, sensitization of sensory neurons to a range.

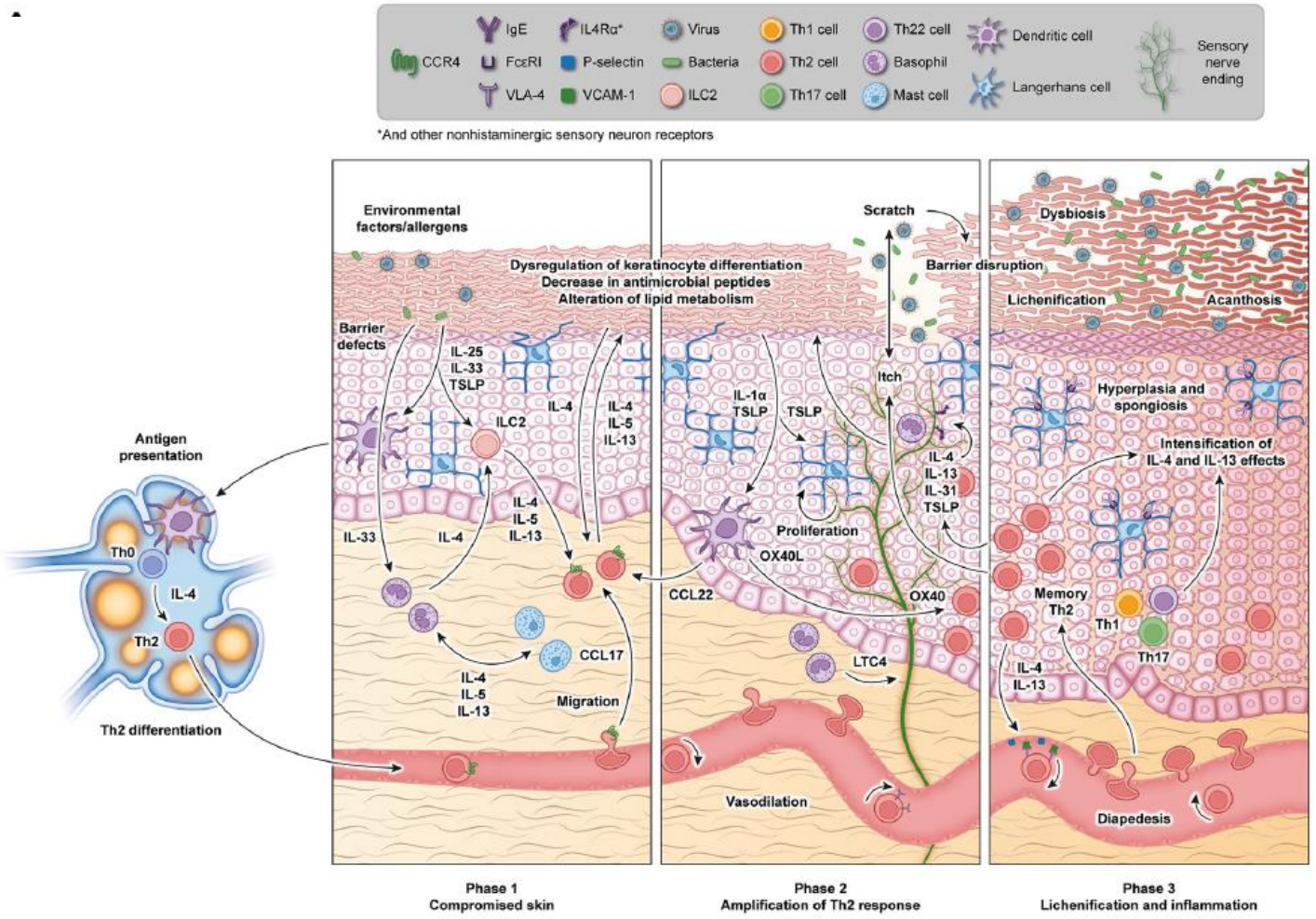


Key: CCL17 C–C motif chemokine ligand 17, DC dendritic cell, Ig immunoglobin, IL interleukin, ILC innate lymphoid cell, LTC_4 leukotriene C_4, MHC-II major histocompatibility complex II, TCR T-cell receptor, TSLP thymic stromal lymphopoietin, VCAM-1 vasopressin-activated calcium-mobilizing receptor 1

Source: Haddad EB, Cyr SL, Arima K, McDonald RA, Levit NA, Nestle FO. Current and Emerging Strategies to Inhibit Type 2 Inflammation in Atopic Dermatitis. *Dermatol Ther* (Heidelb). 2022 Jul;12(7):1501-1533.

How the Type 2 Immune Response Leads to Skin Inflammation

Barrier protein expression is regulated by both external and internal stimuli, including IL-4, IL-1 and IL-31. In AD, excessive IL-4, IL-13, and IL-31 levels downregulate the expression of several skin barrier proteins, including filaggrin (FLG), loricrin, and involucrin. Dysfunction of the epidermal barrier can itself further promote type 2 inflammation through the production of alarmins. Alarmins IL-33 and IL-25 are believed trigger ILC2 activation and overexpression of IL- in the skin; this leads to the recruitment of activated Th2 cells via induction of Th2 cell recruiting chemokines such as CCL17 and furthe increases IL-4/IL-13 expression within the skin. This pathway is believed to play a critical role in chronic inflammation in AD. IL-4 and IL-13 also induce the production of periostin, a matricellul protein that plays a role in chronic inflammation skin fibrosis, and pruritus. Periostin promotes the production of inflammatory cytokines by keratinocytes, amplifying chronic inflammation.



Source: Haddad EB, Cyr SL, Arima K, McDonald RA, Levit NA, Nestle FO. Current and Emerging Strategies to Inhibit Type 2 Inflammation in Atopic Dermatitis. *Dermatol Ther* (Heidelb). 2022 Jul;12(7):1501-1533.

Anaptys Looking to Change the Field By Going Beyond Th2

Initial Disease Efficacy

"Type 2 / Th2" approaches

sanofi

(IL-4/13, Dupilimab)

Lilly

(Lebrikizumab, IL-13)

ASLAN PHARMACEUTICALS

(IL-13Rα1)

LEO

(IL-13, IL-22)

APOGEE THERAPEUTICS

(Long-acting IL-13)

GALDERMA

(IL-31)

Further Improvements in Efficacy On the Way

Focusing on agonizing an inhibitory pathway

AnaptysBio

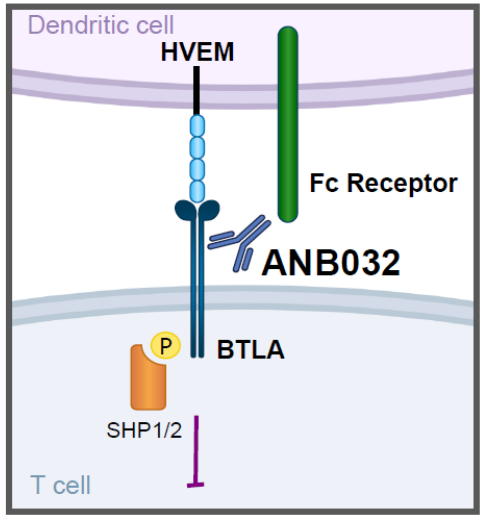
(BTLA agonist)

The HVEM-BTLA pathway plays an important role in regulating DC homeostasis. The lymphotoxin β receptor signaling pathway triggers the proliferation of dendritic cells, while the HVEM-BTLA signaling pathway suppresses dendritic cell proliferation.

Anaptys Positioning in AD Market

The story of ANB032 is straightforward. This is a potential best-in-class BTLA agonist that inhibits activated effector T-cells, induces T-regs and agonizes beneficial Th1 and Th2 cells.

ANB032 has potential to treat wide range of systemic inflammatory diseases[1]



BTLA is key node of immune regulation

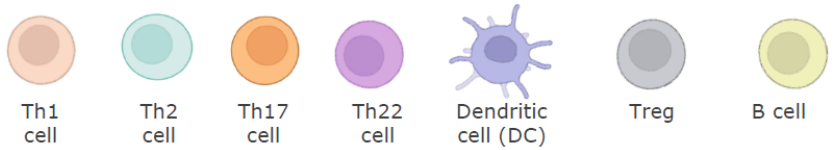
- B and T lymphocyte attenuator (BTLA) is a potent checkpoint receptor
- Expressed only on immune cells and preferentially on activated immune cells
- Dysregulation of BTLA pathway accelerates onset and exacerbates disease

ANB032: IgG4 antibody (non-depleting)

- Binds BTLA proximal to immune cell
- Fc receptor binding contributes to differentiated potency
- Non-blocking of HVEM engagement

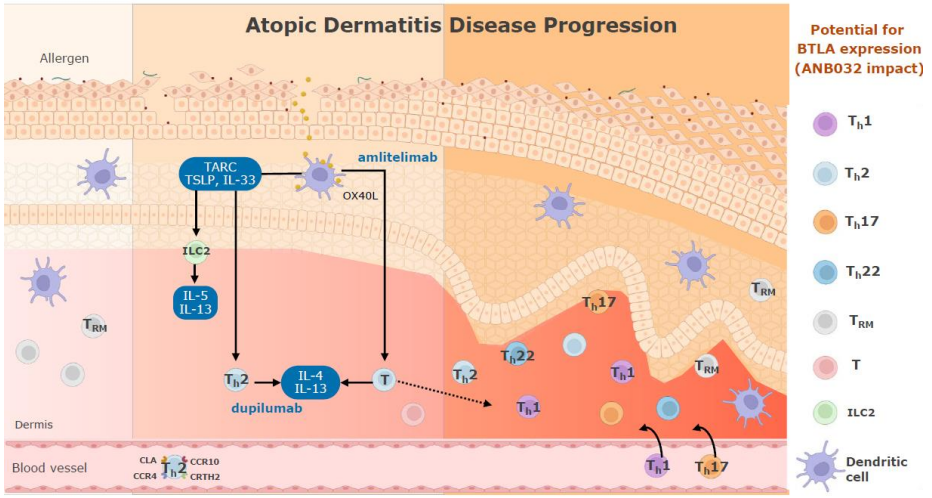
ANB032 modulates immune cells:

inhibit activated T cell proliferation, reduce inflammatory cytokine secretion and modulate DC function including inducing Tregs



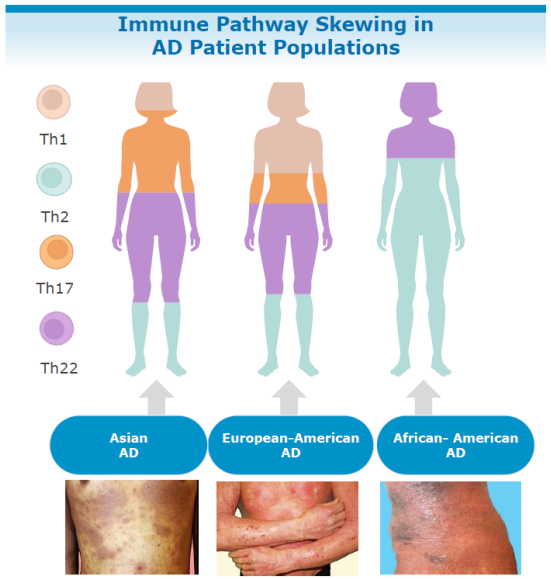
Source of picture: AnaptysBio corporate presentation, March 2024

Th1, Th2, Th17, Th22 and dendritic cells in tissue and periphery drive atopic dermatitis pathogenesis



Immune pathway skewing in atopic dermatitis patient populations highlights the need for new therapies

SOC only directly targets Th2 pathway



AD is highly heterogeneous involving multiple immune cytokines

- Immune activation can vary by ethnicity resulting in a highly heterogeneous presentation
- Substantial unmet need across all patient populations

Expect ANB032 to drive deeper responses across broader patient population

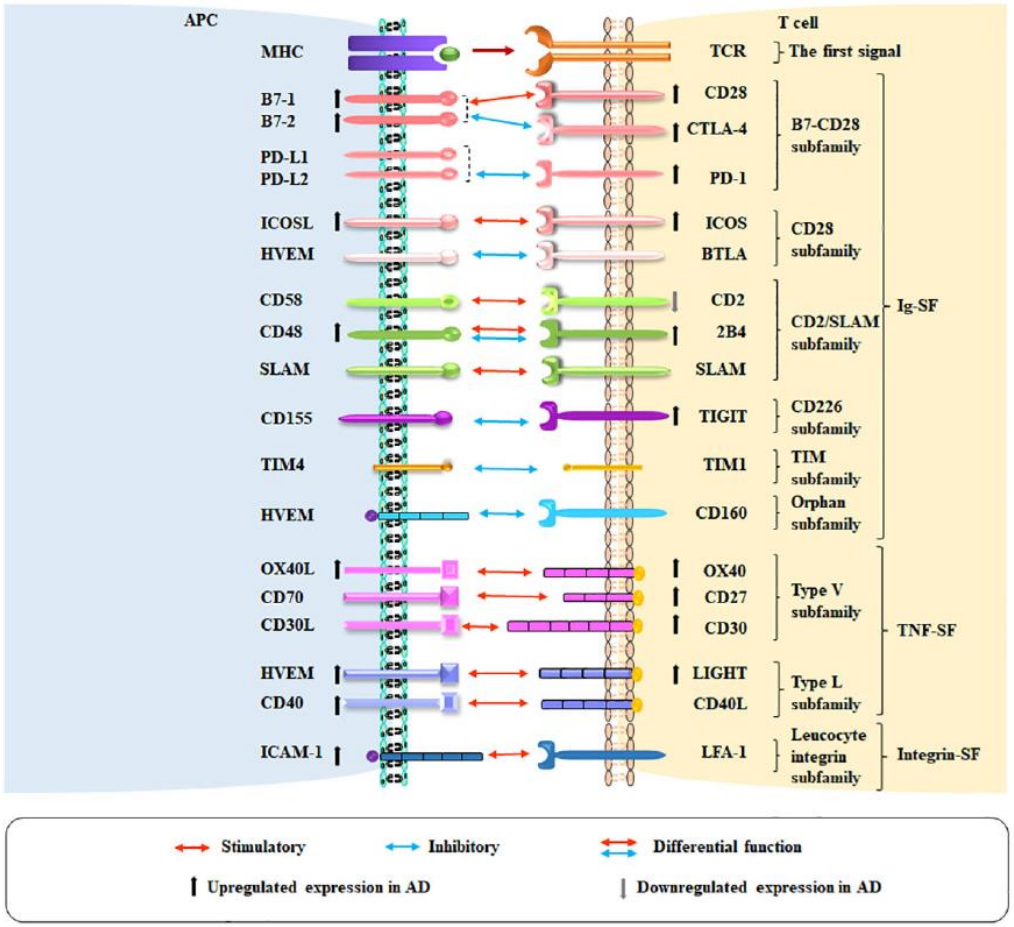
- Restore immune balance

Adapted from Renert-Yuval Y, et al. Ann Allergy Asthma Immunol 2020;124:28–35; Czarnowicki T, et al. J Allergy Clin Immunol 2019;143:1–11.

Substantial Scientific Rationale for Looking at Role of Checkpoint and Co-Stimulatory Pathways in Atopic Derm

Zheng C, Shi Y, Zou Y. T cell co-stimulatory and co-inhibitory pathways in atopic dermatitis. Front Immunol. 2023 Mar 13;14:1081999.

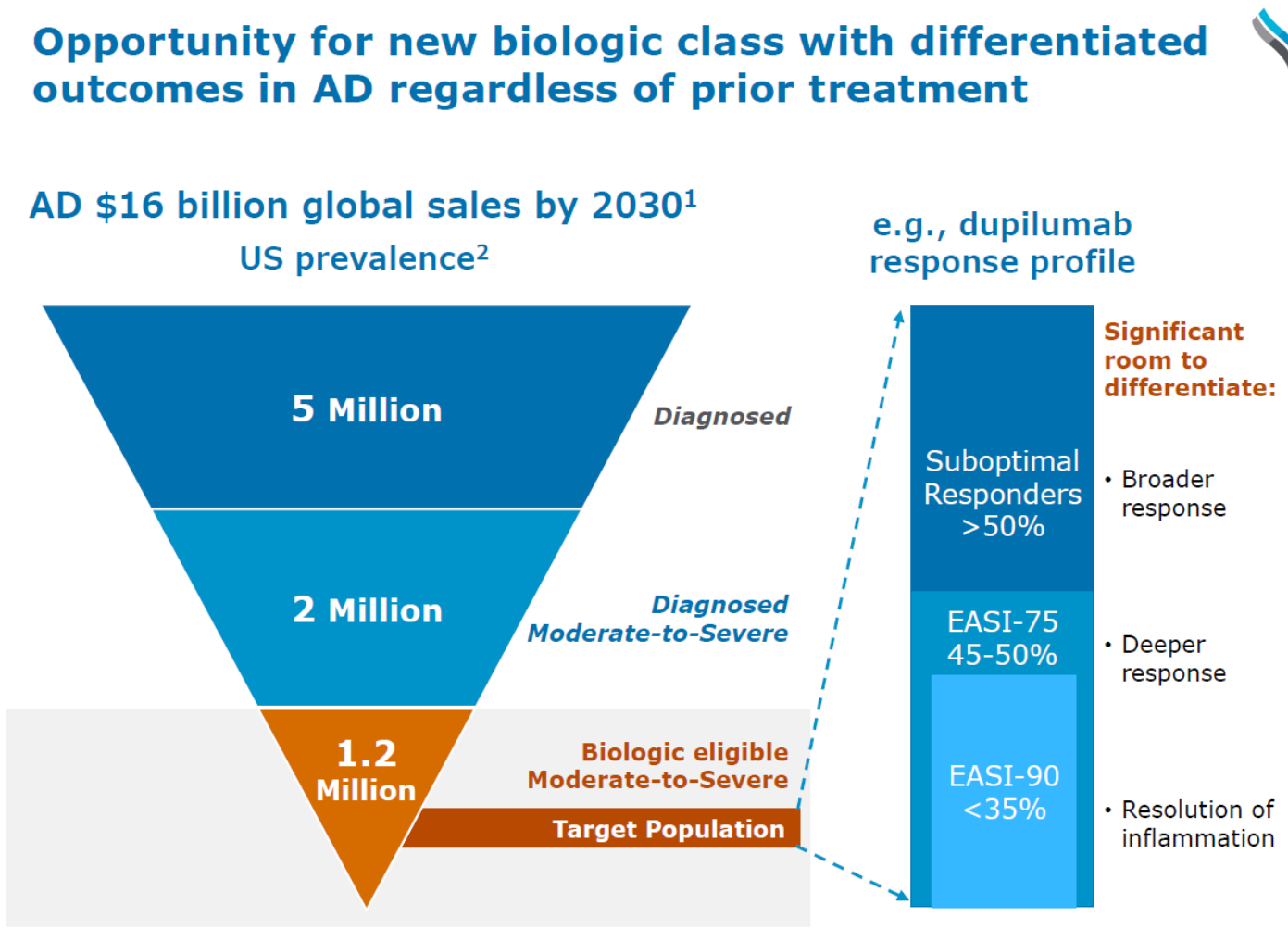
The use of immune checkpoint inhibitors (ICIs) targeting the T cell inhibitory pathways has revolutionized cancer treatment. However, ICIs might induce progressive atopic dermatitis (AD) by affecting T cell reactivation. The critical role of T cells in AD pathogenesis is widely known. T cell co-signaling pathways regulate T cell activation, where co-signaling molecules are essential for determining the magnitude of the T cell response to antigens. Given the increasing use of ICIs in cancer treatment, a timely overview of the role of T cell co-signaling molecules in AD is required. In this review, we emphasize the importance of these molecules involved in AD pathogenesis. We also discuss the potential of targeting T cell co-signaling pathways to treat AD and present the unresolved issues and existing limitations. A better understanding of the T cell co-signaling pathways would aid investigation of the mechanism, prognosis evaluation, and treatment of AD.



Co-stimulatory and co-inhibitory pathways in AD. The co-stimulatory and co-inhibitory molecules on APCs and T cells in AD are shown. Red arrows indicate co-stimulation, blue arrows indicate co-inhibition, and red and blue arrows together indicate molecules with co-inhibitory and costimulatory functions. Ascending and descending arrows indicate the increase and decrease of co-stimulatory and co-inhibitory molecules in AD, respectively.

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10040887/

AnaptysBio Positioning in Atopic Derm Market



Anaptys is telling a classic differentiation story versus the market leader dupilimab in atopic dermatitis.

They see the drug as having a commercial opportunity in:

a. Dupi non-responders
b. Dupi suboptimal responders
c. Beating dupi with a broader, better response

With a price of $30k / year there is market opportunity that is more than $30 billion in size. Anaptys doesn't need to take much share to win in this market.

Source of picture: AnaptysBio corporate presentation, March 2024

Inflammasome / NRLP3 / IL-1 Drug Update

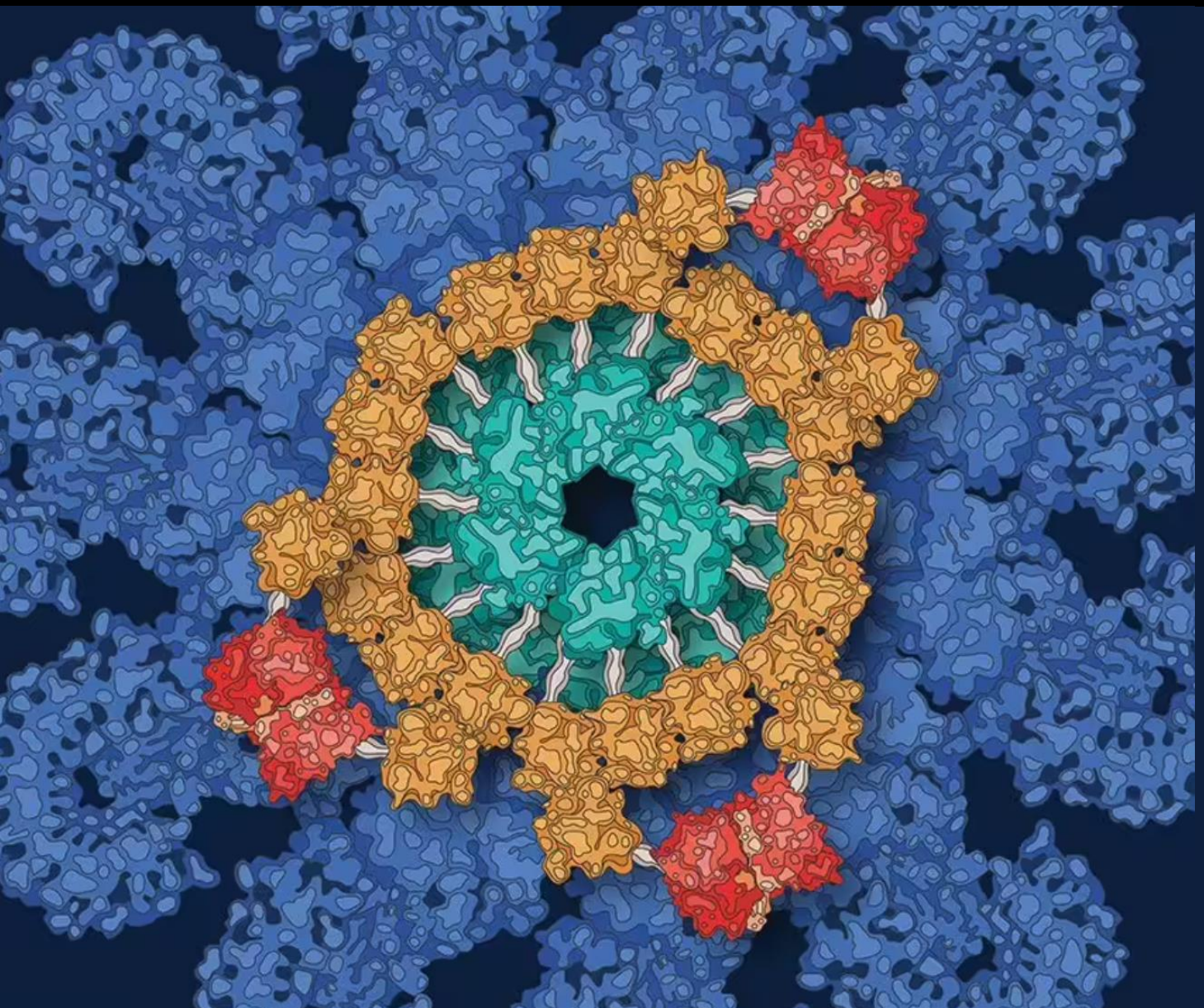


Illustration of NLRP3 complex
Kate Schroeder
University of Queensland

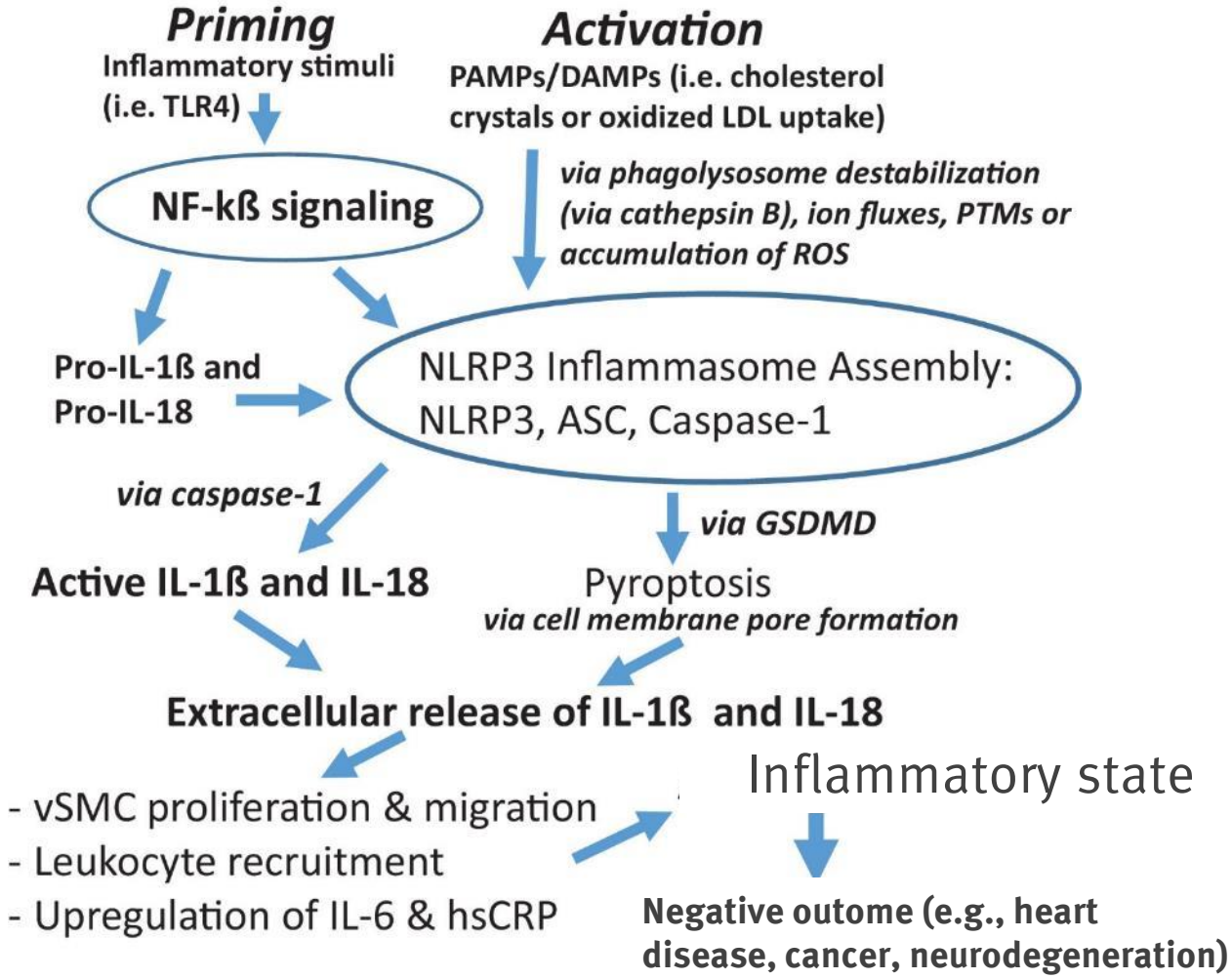
High Market Potential For Inflammasome Inhibitors

- Drugs that inhibit the IL-1 pathway can play a critical role in offering a well-tolerated therapy to break the cycle of aberrant inflammatory progression.
- As shown at right, the role of IL-1β signaling, downstream of inflammasome activation, has been validated in over 50 chronic inflammatory disorders with the clinical use of biologics targeting this pathway.
- This is a classic area in which to develop “pipeline in a pill” type drug candidates.
- The potential of this class is substantially larger than that for JAK inhibitors (currently projected to have revenues exceeding $30 billion):
  - Higher likelihood of safety
  - Broader set of indications impacting more patients

Disease States Where there Is Supportive Evidence of Efficacy of an Inflammasome Inhibitor

AA Amyloidosis
Acute Behcet's disease
Acute Decompensated Heart Failure
All-Cause Mortality
ANCA-Associated Vasculitis
Anemia
Ankylosing Spondylitis
Autoimmune Disease of the Inner Ear
Cancer - Lung
CAPS
Cardiovascular Mortality
Castleman's Disease
Chondrocalcinosis
Congestive Heart Failure
Crohn's Disease
CV Mortality in CKD
Cytokine Release Syndrome / CAR-t
Erdheim-Chester disease
Familial Mediterranean fever
Giant Cell Arteritis
Gout
Graves Orbitopathy
Henoch–Schonlein purpura
Hidradenitis Suppurativa
Hip / Knee replacement
Inflammatory Myopathies (Myositis)
Kawasaki Disease
Lung serositis
Macrophage Activation Syndrome
Majeed Syndrome
Melanoma
Mevalonate kinase deficiency / Hyper IGD
Myocarditis
NASH
Osteoarthritis
Osteomyelitis
PAPA Syndrome
Parkinson’s Disease
Periarthritis of the shoulder
Pericarditis
PFAPA Syndrome
Post-MI Recovery / ACS
Primary Sjögren syndrome fatigue
Psoriatic arthritis
Pyoderma Gangrenosum
Rheumatoid Arthritis
SAPHO Syndrome
Schnitzler Syndrome
Sepsis
Silicosis
Status Epilepticus
Stills Disease
Sweet Syndrome
Systemic-Onset Juvenile Idiopathic Arthritis
TBI
TRAPS
Ulcerative Colitis
Urticarial vasculitis

Innate Immune System Biology: IL-1 Pathway



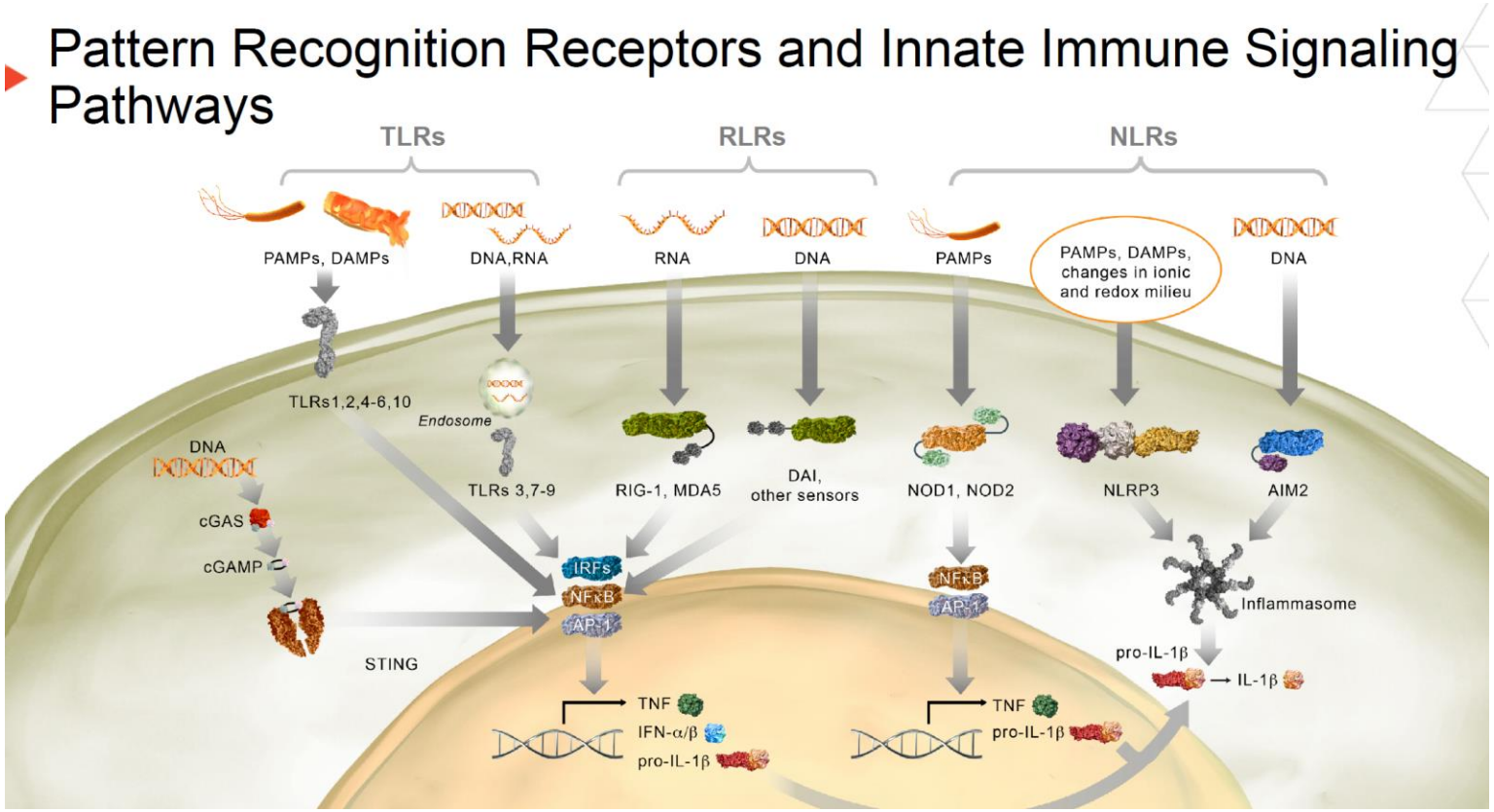
The innate immune system is complex and features multiple actors including macrophages, neutrophils and NK cells. A key pathway is the IL-1 pathway. This pathway operates through priming and activation. Once primed and activated in response to a foreign invader or tissue insult (e.g., smoking), the system generates the NRLP3 assembly via Caspase-1 and ASC and products active IL-1 and IL-18. These in turn transcribe numerous cytokines and pro-inflammatory factors including IL-6, IL-33 and NF-κB.

Source: https://www.translationalres.com/article/S1931-5244(19)30166-5/fulltext

Innate Immune Biology Dendrogram: Macrophages and Neutrophils

Source: Stifel research and analysis

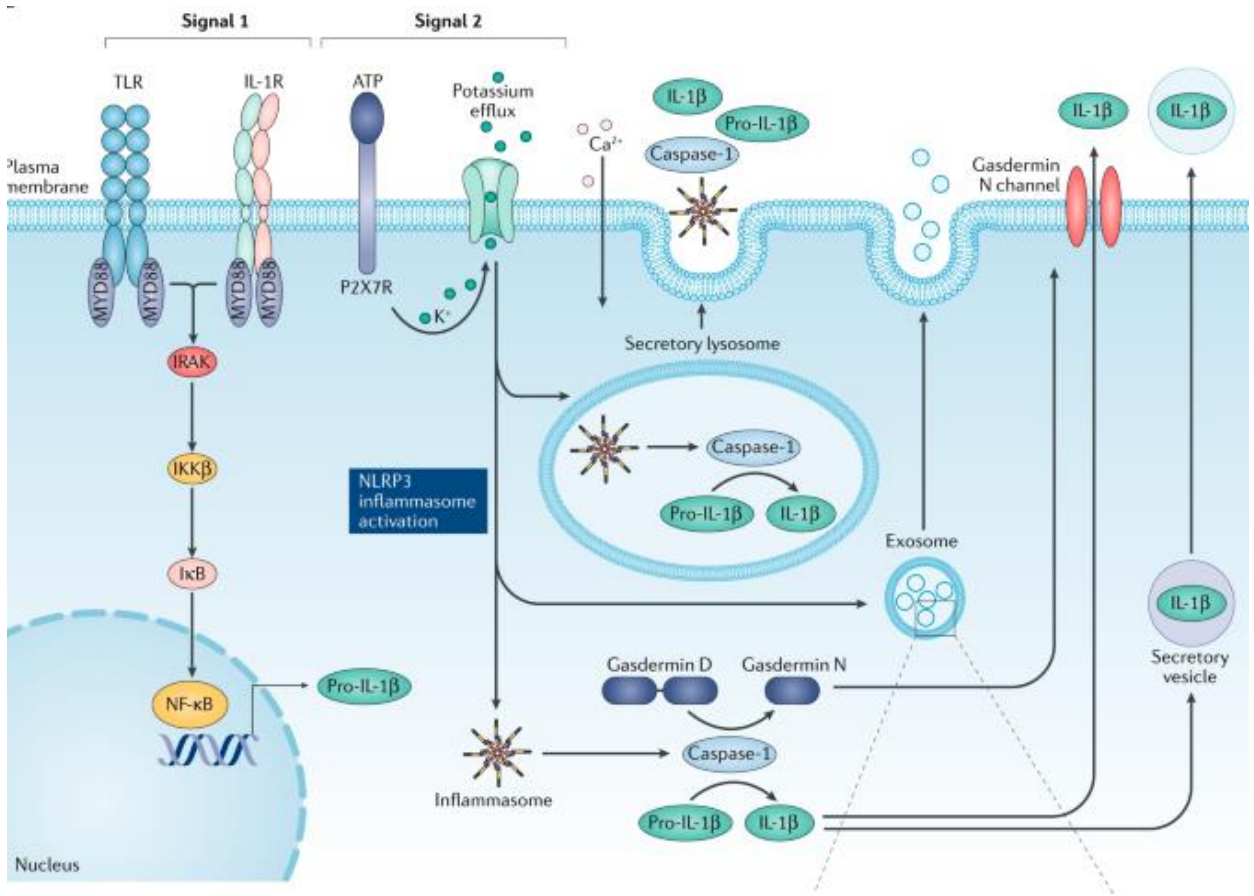
TLR's, NLR's and RLR's are Upstream of Key Innate Immune Cytokines (e.g., IL-1) and Respond to DAMPs and PAMPs



Source: IFM Tre Corporate Presentation, 2018

IL-1/NRLP3 Are Master Regulators of Innate Immunity

- The main functions of the IL-1 family are innate immune reaction and inflammation
- IL-1β is a product of blood monocytes, tissue macrophages, and dendritic cells
- Following the binding of pro-inflammatory cytokines in the IL-1 family downstream signaling cascade leads to activation of NFkB
- Inactive IL-1β precursor accumulates in the cytosol until processed by NLRP3 & caspase 1 into active cytokine
- The rate-limiting step in the processing and secretion of IL-1β takes place with activation of the inflammasome



Source: https://www.nature.com/articles/s41584-019-0277-8

Current Landscape: Approved Drugs for IL-1 and IL-6 Modulation

Target	Drug	INN Name	Sponsor	Delivery Format	U.S. Price / Year	Revenue in 2023 ($mm)	Efficacy	Dosing / Half Life
il-1	Kineret	Anakinra	SOBI	SC	$250,000	$220	Highly effective	Daily / 5 hours
il-1β	Ilaris	Canakinumab	Novartis	IV/SC	$124,000	$1400	Highly effective	Every 2 months / 26 days
IL-6r	Actemra	Tocilizumab	Roche	SC	$78,000	$3000	Highly effective	Monthly / 13 days
il-1β, IL-6	Colchicine	Colchicine	Various	Oral	$50	‹ $100	Works in gout	Daily / 30 hours
IL-6	Sylvant	Siltuximab	Recordati	IV	$74,000*	‹ $100	Highly effective	Every 3 weeks / 18 days
IL-1 trap	Arcalyst	Rilonacept	Kiniksa	IV	$230,000	$223	Highly effective	Weekly / 8.6 days
IL-6r	Kevzara	Sarilumab	Sanofi/Regeneron	SC	$75,000	$390	Highly effective	Twice monthly / 8 days

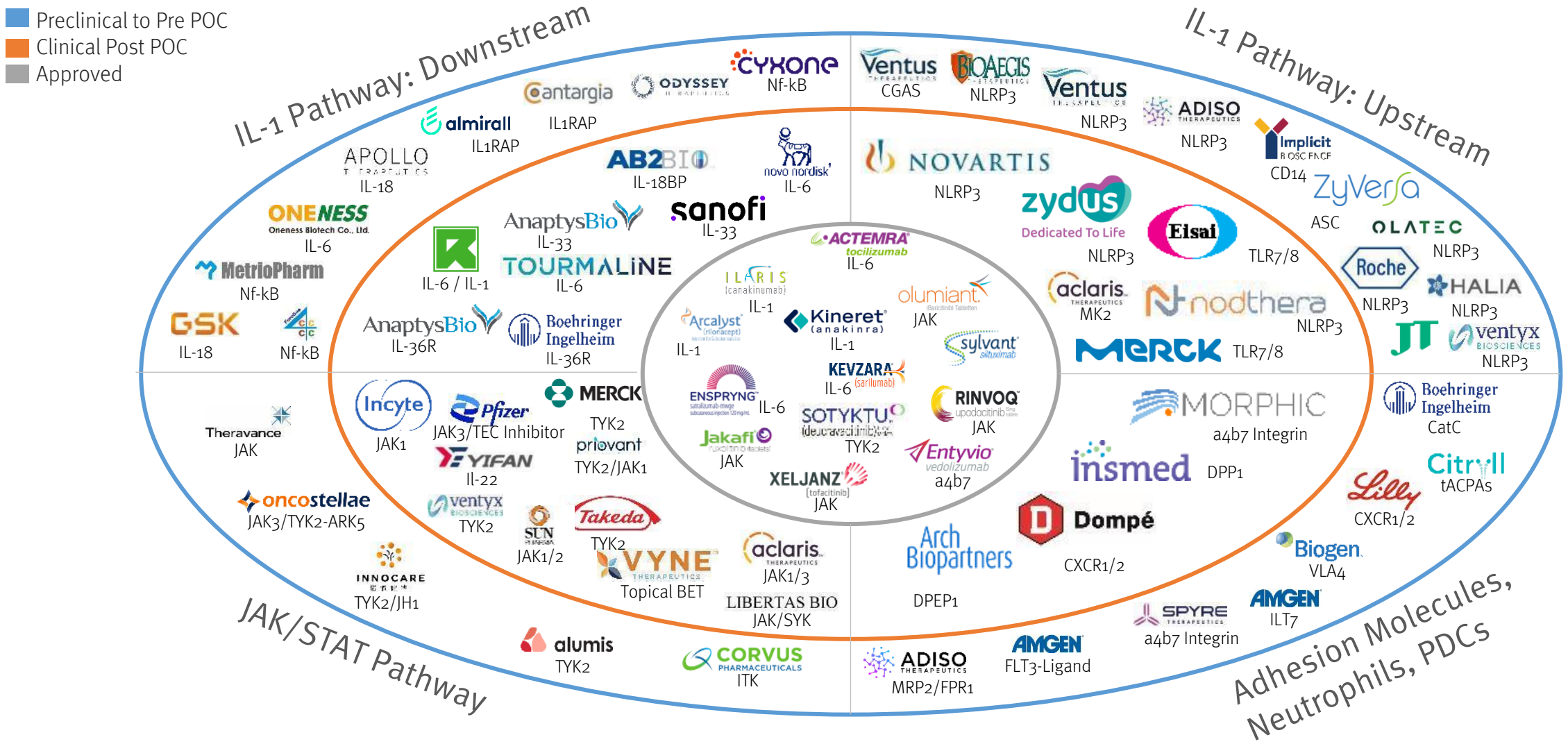
- Existing approved drugs in the IL-1 pathway are quite expensive and, except for colchicine, are targeted at rare diseases or very high-priced uses.
- The two most successful drugs from a commercial perspective are Actemra® with sales of $3 billion in 2023 and Ilaris® with sales of $1.4 billion in 2023.
- Actemra has significant sales from its use in rheumatoid arthritis and is heavily discounted through U.S. Medicaid and Medicare. In contrast, Ilaris sells for over $100,000 per year of use and is largely used in rare disease indications.

* 400mg IV on drugs.com is $6,667. We assume that one IV dose is given per year to derive a $74,000 price.

Approved Indications for Each Drug

Drug	Rheumatoid Arthritis	CAPS	PJIA / SJIA / DIRA / Hyper-IGD / AOSD	Giant Cell Arteritis	Castleman's Disease	FMF	Pericarditis	Gout / Pseudogout	PBC / Cirhhosis
Kineret	Yes		Yes						
Ilaris		Yes	Yes			Yes		Yes	
Actemra	Yes			Yes					
Colchicine						Yes	Yes	Yes	Yes
Sylvant					Yes				
Arcalyst		Yes	Yes				Yes		
Kevzara	Yes								

Pipeline of Selected Drugs that Modulate Innate Immunity



Source: Stifel Research

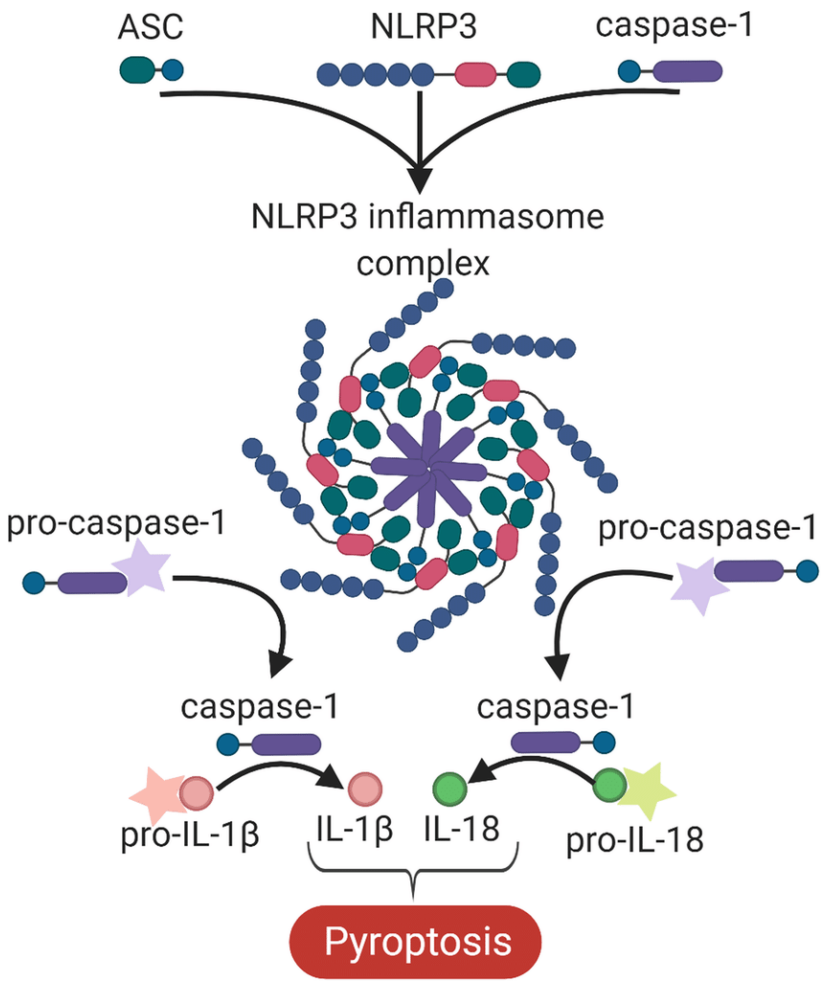
NLRP3 Biology

NLRP3 is a key part of the inflammasome that triggers release of IL-1β and other pro-inflammatory cytokines

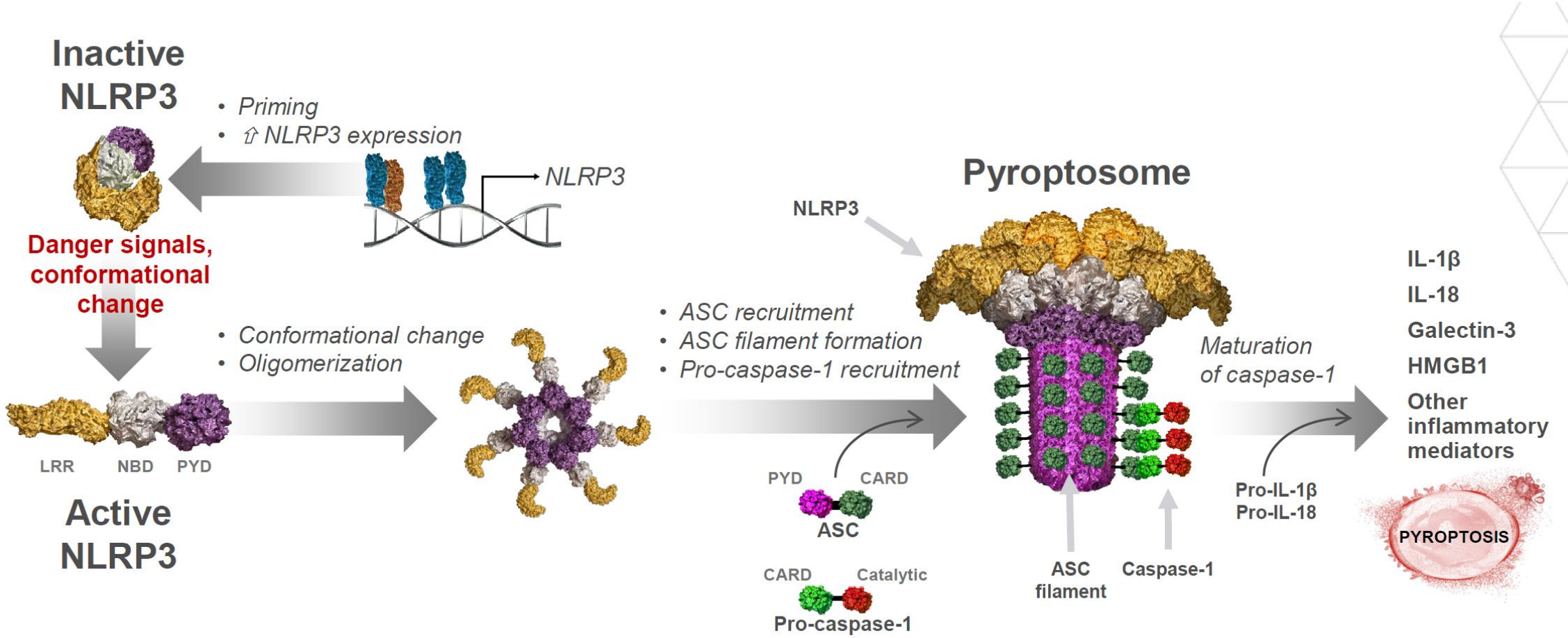
The NLRP3 inflammasome complex regulates the release of important pro-inflammatory cytokines, which function as key elements of the body's innate immune response to infections and tissue injury. However, overactivation of the NLRP3 inflammasome can lead to a chronic state of inflammation that underlies a wide range of human diseases.

As illustrated at right, formation of the NLRP3 inflammasome involves the constituent molecules of the NLRP3 inflammasome (i.e. NLRP3, ASC and caspase-1) binding to form a complete NLRP3 inflammasome complex.

This inflammasome complex allows the cleavage of pro-caspase-1 into its active isomer, caspase-1, which in turn cleaves pro-IL-1β and pro-IL-18 to their active isomers IL-1β and IL-18 respectively. The increase in these pro-inflammatory proteins ultimately leads to pyroptosis



NLRP3 is a Sensor of Danger Signals



Source: IFM Tre Corporate Presentation

NLRP3 is a Highly Validated Target

NLRP3 is a key part of the inflammasome that triggers release of IL-1β and other pro-inflammatory cytokines

Preclinical pharmacology with knockouts and tool compounds

- Dozens of published studies from different labs in many disease models

Genetics

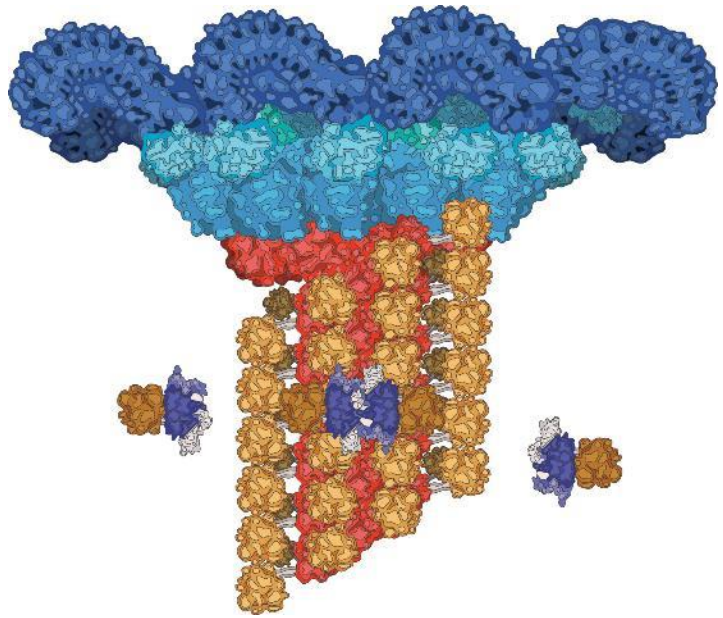
- Gain-of-function mutations
- Risk-associated genetic variants increase that NLRP3 activity, including CHIP

Efficacy established in several diseases

- Diseases associated with NLRP3 triggers and/or genetic variants
- IBD, cardiovascular and metabolic disease, lung cancer, gout, CAPS, dry eye etc.

Activation mechanism and stimuli

- NLRP3 is the *only* inflammasome activated via a two-step mechanism
- Danger signals that activate NLRP3 are *specific* to NLRP3; they do *not* activate other inflammasomes



Side view of NLRP3 Complex

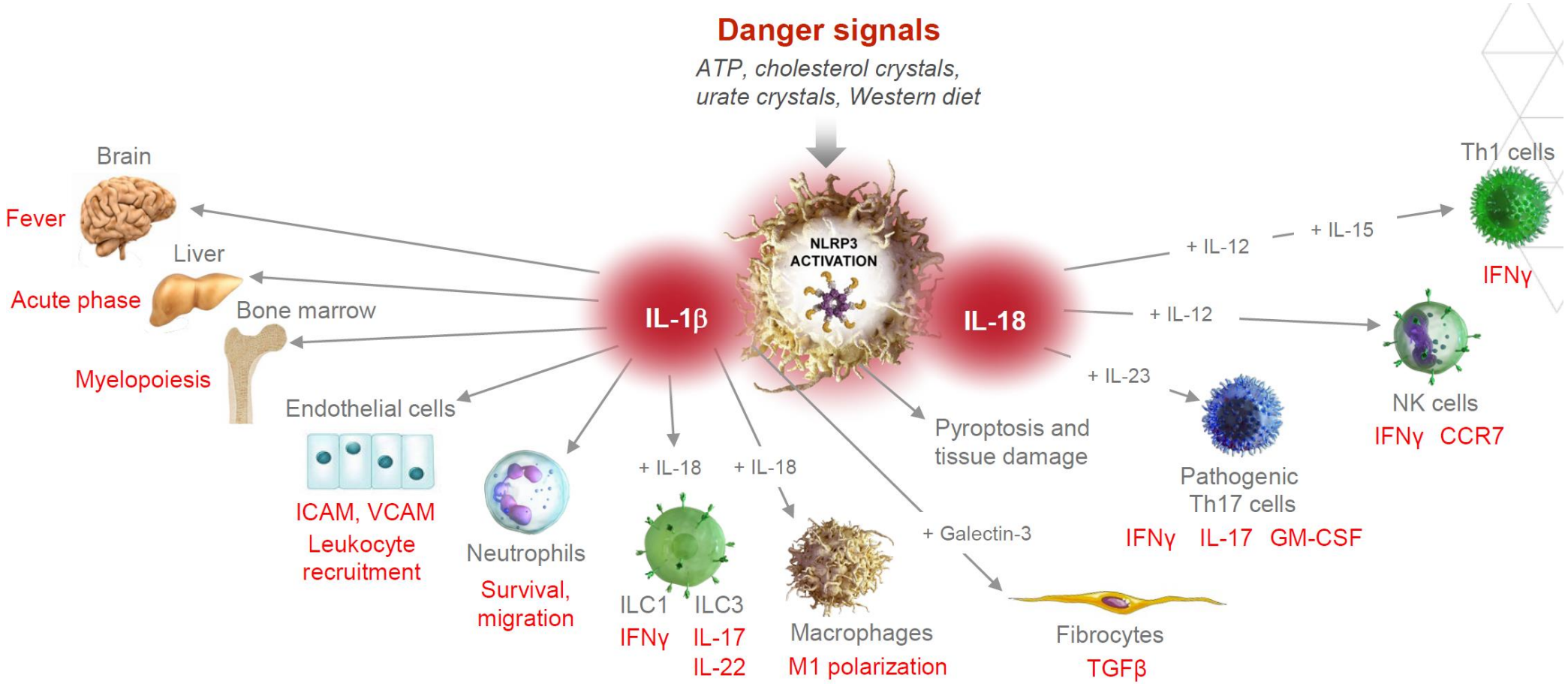
Rationale for Targeting NLRP3

NLRP3 is known to be activated by a range of non-infectious tissue damage signals associated with injury, aging, physical inactivity and obesity. When activated, NLRP3 initiates immune responses and stimulates production of inflammatory cytokines IL-1β and IL-18, as well as pyroptosis. Based on both animal model studies and clinical data, NLRP3 has been shown to be associated with a diverse range of diseases and conditions, including genetic NLRP3-dependent auto-inflammatory diseases (CAPS and related conditions), systemic diseases (cardiovascular, dermatologic and rheumatic conditions) and neuroinflammatory diseases (Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and multiple sclerosis), among others.

While the NLRP3 inflammasome historically has been a challenging drug target, the therapeutic potential of NLRP3 inhibitors in autoimmune disease has been validated by clinical and preclinical data and genetic evidence generated by third parties. Several clinical therapies targeting NLRP3-dependent cytokine anti-IL-1β have been approved, providing validation for its role in a broad range of inflammatory disorders. Approved therapies include Ilaris (canakinumab) for the treatment of Still's disease and multiple periodic fever syndromes, Kineret (anakinra) for the treatment of Neonatal onset multisystem inflammatory disease (NOMID) and Arcalyst (rilonacept) for the treatment of CAPS. However, the therapeutic window of these drugs is limited by an increased risk of serious infections.

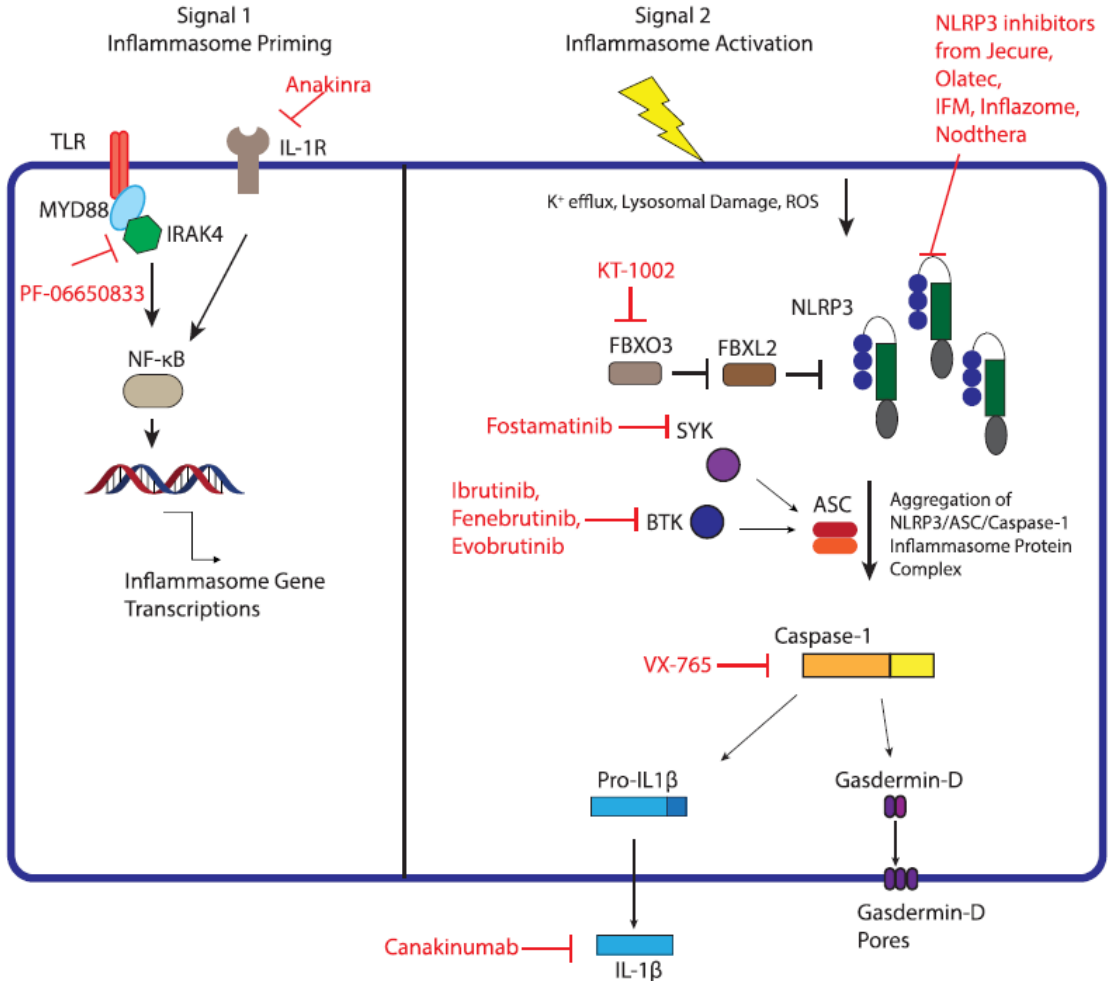
An NLRP3 inhibitor may be less immunosuppressive and better tolerated than an anti-IL-1β therapy because (a) other pathogen-recognizing inflammasomes can be engaged to produce IL-1β, and (b) risk of infection may be lower as the effects of a small molecule therapy are easily reversible upon discontinuation of therapy (hours to days) compared to an antibody, which clears the body very slowly (days to weeks).

Activation of NLRP3 Drives a Complex Multifactorial Response



Source: IFM Tre Corporate Presentation

NLRP3 Inhibitor Pharmacology



Source: https://pubs.acs.org/doi/full/10.1021/acs.jmedchem.0c01307

Inflammasome activation is mediated by two key steps: priming, often called signal 1, and activation, often called signal 2 (figure at left). Priming consists of upregulation of inflammasome-related proteins including inflammasome sensor proteins, IL-1β and IL-18 through upregulation of NF-κB transcriptional activity. NF-κB transcriptional activity is highly regulated by numerous intracellular and extracellular mechanisms. NF-κB is held in an inactive state in the cytosol by IκB proteins. Post-translational modification or ubiquitination of IκB in response to signal transduction from extracellular stimuli leads to nuclear localization and activation of NF-κB. Bacterial components will activate NF-κB transcriptional activity through TLR binding and signal transduction through Myd88, IRAK, and TRAF6. Cytokines such as IL-1β and TNFα also activate NF-κB transcriptional activity as do other DAMPs such as S100a8/a9. In the absence of NF-κB priming, many cells do not express enough inflammasome components for inflammasome activation upon signal 2 treatment. In particular, many cells do not express high levels of pro-IL-1β in the absence of signal 1. This leads to ASC speck formation upon signal 2, but without concomitant secretion of IL-1β.

Chronic Activation of NLRP3 Drives Multiple Diseases

Specific NLRP3 triggers drive distinct inflammatory pathologies

Danger Associated Molecular Patterns ("DAMPs")									
Uric acid crystals	Silica, asbestos	Cholesterol crystals	Aβ, lipofuscin	Amylin, lipids	Aberrant lipids	Oxalate crystals	Microbiota	Hyperosmolarity	Gain-of-function mutations

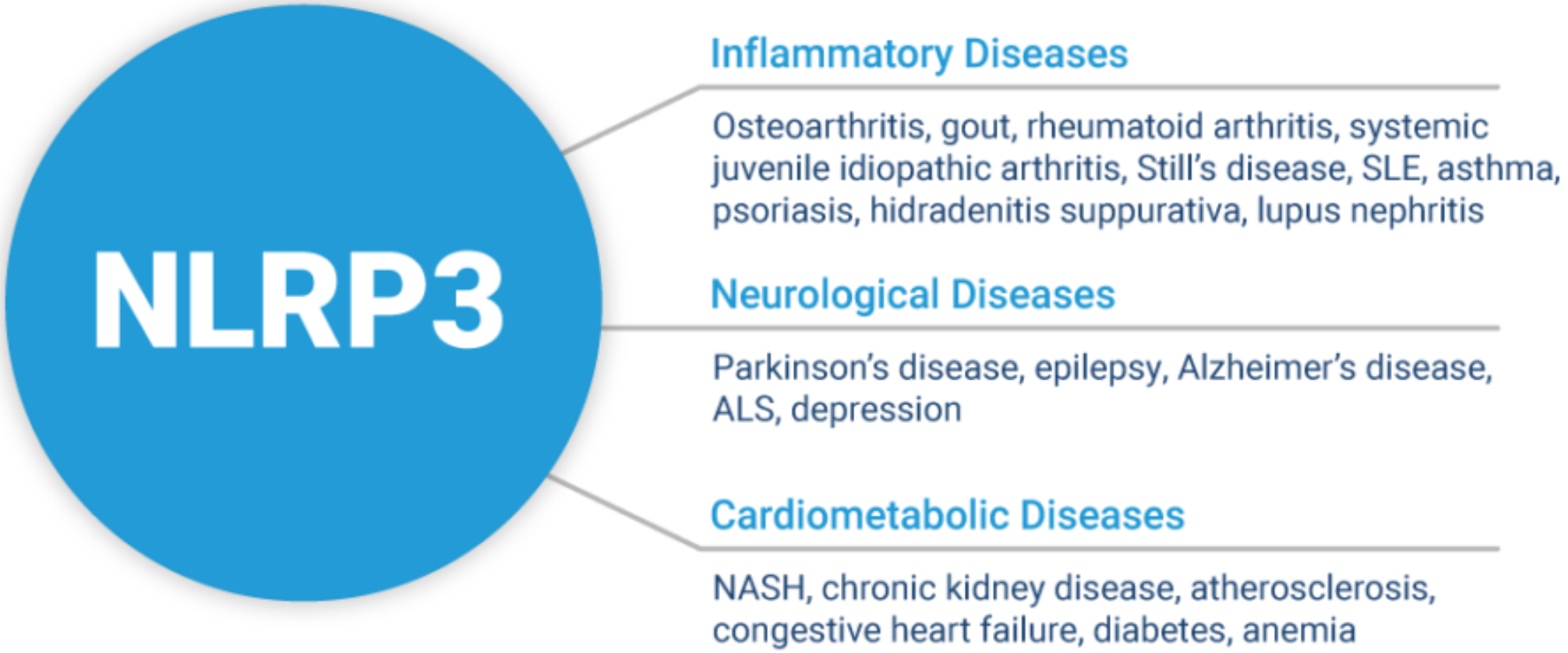
In specific tissues										
Joint	Lung	Circulation	Brain	Pancreas	Adipose	Liver	Kidney	Intestine	Eye	Skin

Enable multiple therapeutic opportunities for both orphan and large-market diseases

Gout, RA, SLE	asthma, asbestosis, lung cancer	Atherosclerosis	Alzheimer's disease	Type II diabetes	Obesity	NASH, fibrosis	Nephropathy	IBD (CD, UC)	AMD, Dry Eye	CAPS, scleroderma

Source: IFM Tre Corporate Presentation

Numerous Therapeutics Opportunities for an NLRP3 Modulator



Source: https://www.ventustx.com/pipeline/nlrp3/

Comparison of Selected NLRP3 Inhibitors in Development

	NOVARTIS	Roche	ventyx BIOSCIENCES	nodthera
Product	NP3-562	Solfulast	VTX2735	NT-0796 / NT-0249
Source	Internal R&D	Inflazome acquisition	Zomagen acquisition	Internal R&D
Stage	Preclin	Phase 2	Phase 1	Phase 1
Indication	OA, FACS, CV, MDS	Cardio, CKD, IPF	IPF, MS	Neuroinflammation
Patent Filing Date	1/13/2022	7/4/2018	3/15/2021	7/31/2018
IC_{50} in LPS induced IL-1b production	10*	NA	80 nM	11nm
Preclinical and clinical evidence	NP3–562 demonstrated excellent potency in human whole blood and full inhibition of IL-1β release in a mouse acute peritonitis model at 30 mg/kg po dose. An X-ray structure of NP3–562 bound to the NLRP3 NACHT domain revealed a unique binding mode as compared to the known sulfonylurea-based inhibitors.	Roche tested this compound in ulcerative colitis and obtained negative results. This is not surprising given that UC is more of a T-cell than an IL-1 driven disease. There was an imbalance of AE's against the NLRP3 compound versus placebo in the study.	Ventyx's peripheral NLRP appears attractive with good data in CAPS. Company has not disclosed half life of compound and is working on an ER version. Safety findings impressive.	Reported positive Phase 1 data in 2022. In 2024 showed reductions in inflammation in a Parkinson's study including drops in nFL and Trem2 Has also provided evidence that NT-0249 and NT-0796, reduce obesity in the DIO mouse model and that brain exposure appears necessary for efficacy.

Comparison of Selected NLRP3 Inhibitors (continued)

	zydus Dedicated To Life	ADISO THERAPEUTICS	JT	Ventus THERAPEUTICS
Product	ZYIL1	ADS031	JTE-162 / JT-002	VENT-02
Source	Internal R&D	Internal R&D	Internal R&D	Internal R&D
Stage	Phase 2	Preclin	Phase 2	Phase 1
Indication	CAPS, rare disease	Ssc, IPF	AD, HS, Psoriasis	Neuroinflammation
Patent Filing Date	6/8/2018	NA	12/20/2020	2/24/2022
IC_{50} in LPS induced IL-1b production	13nm	NA	3nm	NA
Preclinical and clinical evidence	Showed strong Phase 1 results. Showed excellent results in CAPS study. Ongoing studies in rare disease indications.	Adiso is pursuing dual inhibition of the of both NLRP 1 and NLRP 3, as NLRP1 is expressed predominantly in barrier cells, while NLRP3 is found in infiltrating immune cells. Both cell types are directly implicated in respiratory and dermal inflammation. Adiso is planning to pursue IND-enabling studies for ADS032 in 2023.	JT002 reduced proinflammatory cytokine production across a number of cellular assays and prevented pyroptosis, an inflammatory form of cell death triggered by active caspase-1. JT002 demonstrated in vivo target engagement at therapeutically relevant concentrations when orally dosed in mice and prevented body weight loss.	Based on the exceptional safety margins demonstrated in IND-enabling studies, the Phase 1 trial is designed to fully explore VENT-02's pharmacodynamics, safety, and tolerability across a broad range of single and multiple ascending doses. Ventus expects preliminary results from the trial in the first half of 2024.

Other NRLP3 candidates not shown here are from AC Immune, Apaxen, BioAegis, Changchun GeneScience Pharma, Halia Therapeutics, J&J, Olatec, Pfizer, PTC Therapeutics, Secarna, University of Manchester and Novo Nordisk / Ventus (VENT-01). Other companies developing promising drugs in the inflammasome field include BioAge, BMS, Cerevance, Enveda, EpiCentRx, ExScientia, Monte Rosa, Omass, Paratus Sciences, Pyrotech, Shaperon and ZyVersa.

ZYIL1 is an Attractive Development Candidate

Daily oral dosing with short half life

IB-101 has a half life less than three hours. Kinetically, this half life is like that of Anakinra®.

The benefit of a short half-life is that it is still possible to achieve immune responses but to avoid long-term suppression of the inflammasome with its attendant risk of infection.

Profound reduction of IL-1β

90%+ of reduction of IL-1β seen in Phase 1 studies at 3 hours (using LPS challenge on blood in an *ex vivo* setting)**

Substantially less inhibition seen at 24 hours (dose dependent)

Strong binding characteristics

Potential inhibitor of NLRP3 complex. IC_{50} = 13nm vs. IL-1β. IC_{50} = 9nm vs. IL-18 (both in THP-1 monocyte line)

Good clinical data

Strong data in CAPS from an initial Phase 1b clinical study

Excellent Safety and tolerability

There is always some IL-1β produced by sites that are not NLRP3 dependent so a person would not have full ablation of innate immune system function with an NLRP3 inhibitor*

IB-101 exhibited excellent safety and tolerability in a Phase 1 study. No significant laboratory abnormalities (including liver). No QTc prolongation observed.

In a 14-day MAD study, BID dose at 12.5mg and 50mg was well-tolerated without SAEs.

Safety fold established in preclinical studies

Very good oral bioavailability

Strong animal data

Excellent efficacy seen in animal models of IBD, MS, sepsis, lung inflammation and neuroinflammation

* See Mangan et. al. Targeting the NLRP3 inflammasome in inflammatory diseases. *Nat Rev Drug Discov.* 2018 Sep;17(9):688.
** See Primiano et. al., Efficacy and Pharmacology of NLRP3 Inflammasome Inhibitor CP-456,777 (CRID3) in Murine Models of Dermal and Pulmonary Inflammation, *The Journal of Immunology*, Aug 12, 2016.

VTX2735 is an Attractive Development Candidate

Profound reduction of CRP*

High exposures & target coverage achieved in Phase 1

90%+ of reduction of CRP although a number of subjects already had low CRP because they were on canakinumab before entering study

CRP went up when subjects were taken off of study drug

Similar reductions in IL-6. Company has not shown IL-1b reductions

Strong binding characteristics

Potent inhibitor in PBMC from CAPS (FCAS) patients

Potential inhibitor of NLRP3 complex. IC_{50} = 80nm

Good clinical data

Strong data in CAPS from an initial Phase 1b clinical study (see chart at right)

Future clinical plans include secondary prevention of MACE in post-MI patients and the treatment of recurrent pericarditis

Excellent Safety and tolerability

Promising clinical safety profile: (1) No signals that raise safety concerns that require further nonclinical study for genetox, safety pharmacology and phototoxicity, (2) Current tox data support 3 months of human dosing

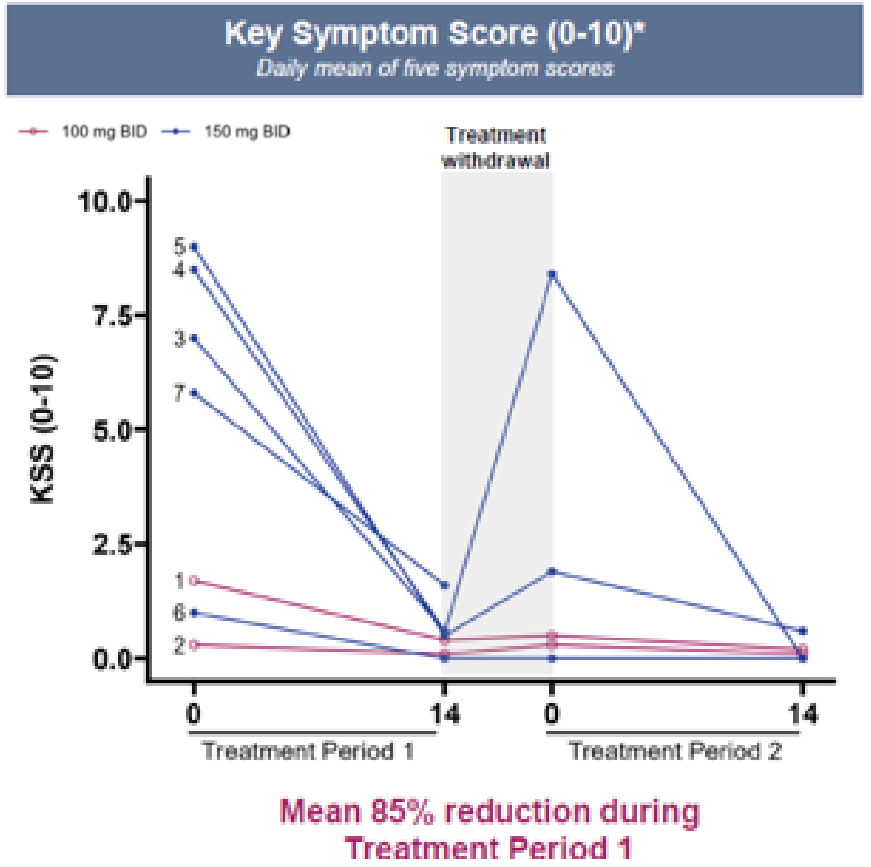
Strong animal data

Demonstrated PD and *in vivo* efficacy in rodent models.

Long patent life

LOE in 2041. With Hatch-Waxman, coverage into mid-2040's possible.

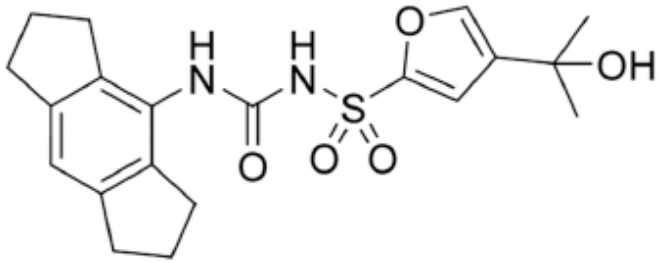
CAPS data from Ventyx



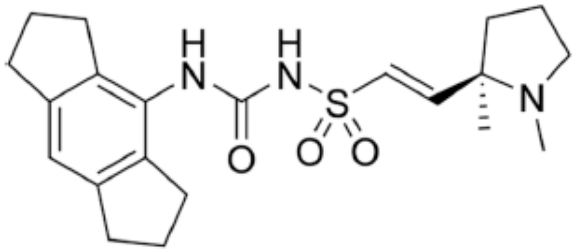
* See Ventyx Investor Presentation, March 2024 (https://ir.ventyxbio.com/static-files/39023798-4d89-49d0-9aa6-46b9820d8a61).

Comparison of Molecules to Pfizer's First Generation MCC950 NLRP3 Sulfonylurea Type Structure

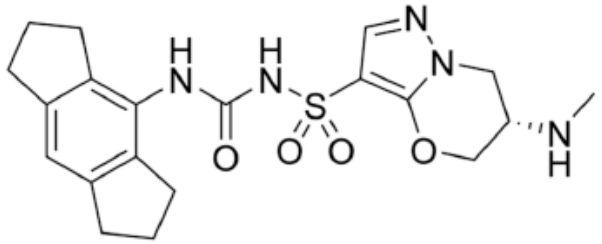
MCC950 (Pfizer) (1)



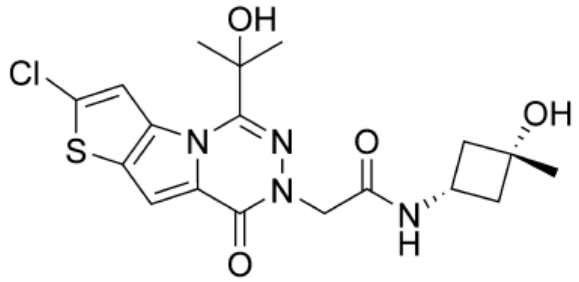
ZYIL1 (Zydus) (1)



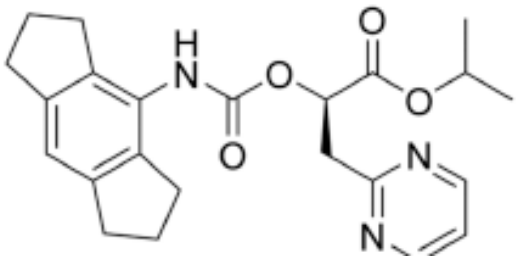
GDC-2394 (Roche) (1)



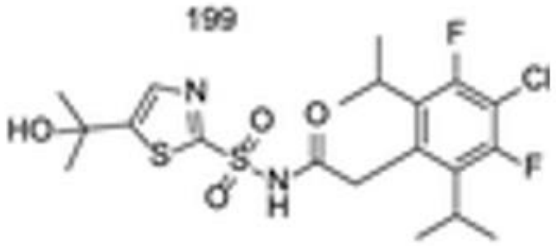
NP3-562 (Novartis) (1)



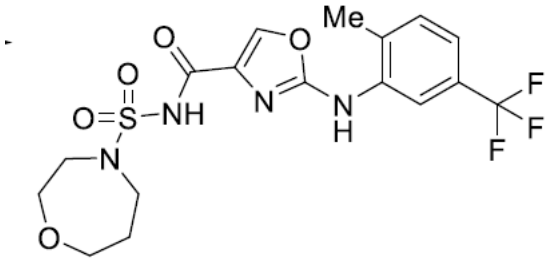
NT-0796 (Nodthera) (1)



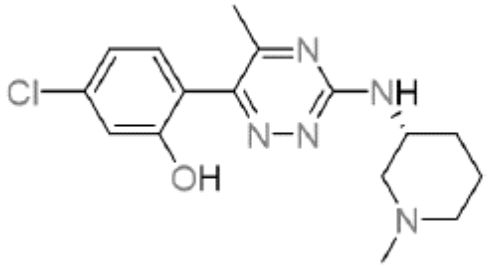
IFM Tre / Novartis Structure 199 (2)



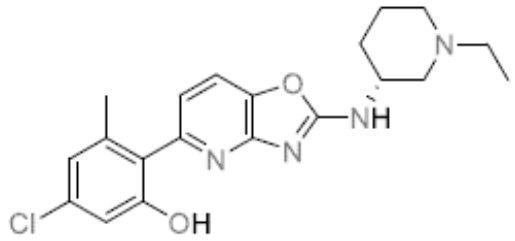
JTE-162 (Japan Tobacco) (3)



PTC Therapeutics I-8 (4)

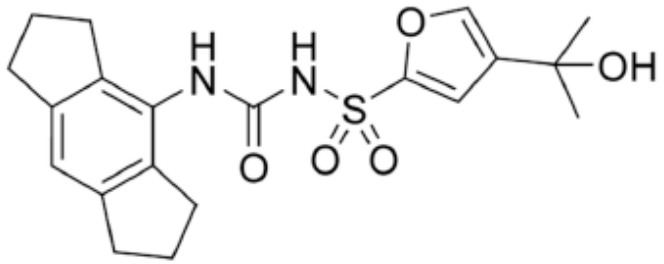


Roche Compound 19 (5)

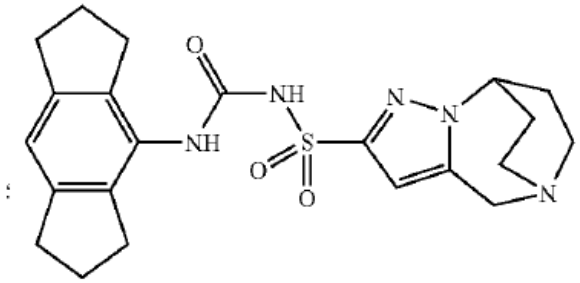


Comparison of Molecules (Continued)

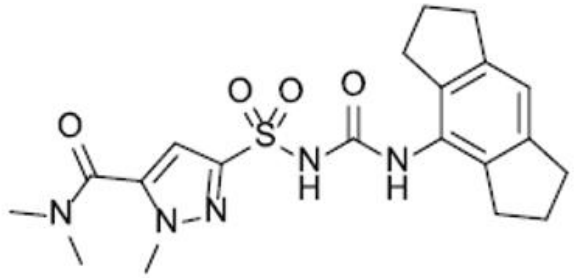
MCC950 (Pfizer) (1)



Illustrative Ventyx Structure (6)



Illustrative Inflazome / Roche Structure (7)



Commentary

While Novartis acquired an NLRP3 library from IFM Tre, it is also taking NP3-562 forward in development. This product has a highly distinct chemotype relative to Pfizer MCC950 tool molecule. In contrast, the two most clinically advanced NLRP3 inhibitors today, ZYIL1 and VTX2735, have structures that are quite similar to MCC950 and have performed well thus far in clinical studies.

Japan Tobacco's JTE-162 and PTC Therapeutics' family are somewhat more novel but involve as yet untested scaffolds.

While Roche acquired both Jecure and Inflazome, they also appear to have an internal development effort underway. We assume that GDC-2394 is the Jecure molecule and, while, structurally similar to MCC950, it's use was associated with severe liver injury in a Phase 1 study (8).

References: (1) https://pubs.acs.org/doi/10.1021/acs.jmedchem.3c02098; (2) https://pubs.acs.org/doi/full/10.1021/acs.jmedchem.0c01307; (3) https://pubs.acs.org/doi/10.1021/acsmedchemlett.3c00433; (4) https://pubs.acs.org/doi/10.1021/acsmedchemlett.3c00122 (5) https://pubs.acs.org/doi/10.1021/acsmedchemlett.3c00236; (6) https://patents.google.com/patent/US20230183258A1; (7) https://pubs.acs.org/doi/full/10.1021/acs.jmedchem.0c01307; (8) https://pubmed.ncbi.nlm.nih.gov/37350225/.

Looking for Indications in the Inflammasome Pathway:

Genetics and Proteomics

- As one might imagine, investigators have not tested approved IL-1 drugs like canakinumab or anakinra in every indication where IL-1 therapy might work. Thus, prior investigator studies would be likely to miss some promising indications.
- An important opportunity is to look at indications where trials have not been run using an IL-1 modulator but where there is genetic evidence that such a trial should be run.
- There are three types of evidence to look at in this regard:

Mendelian randomization studies	Mutation studies	Proteomic, RNA, DNA association studies
Persons which specific polymorphisms in IL-1 relevant genes may be more likely to have a specific disease in large GWAS studies.	Mutations in genes in the IL-1 pathway are associated with specific disease states or, alternatively, protection from disease.	Associations between genes, transcriptomics, proteins and phenotype may point to activity in a certain disease state.

Indications with Good Demonstrated Efficacy in IL-1 Pathway

We surveyed diseases where clinical studies or case reports have been made using drugs targeting the inflammasome using Pubmed. The results are shown below.

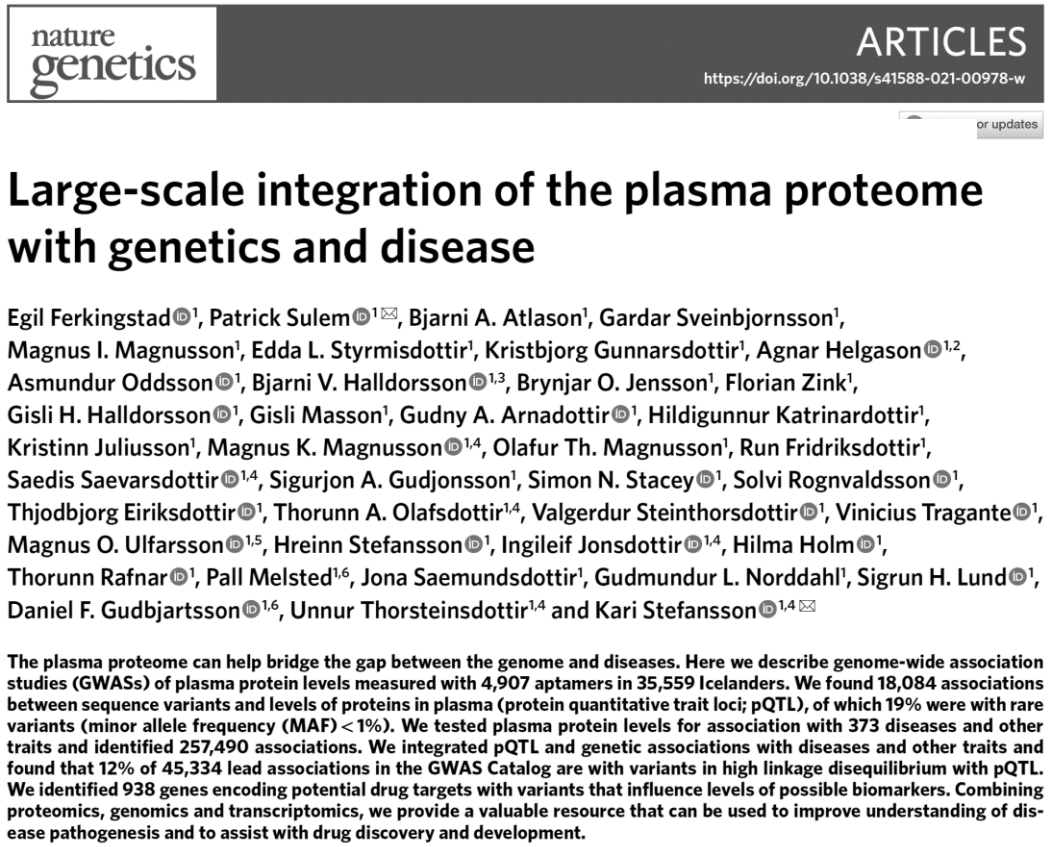
Status	Indications with Good Efficacy		Indications Lacking Good or Better Efficacy	
Disease	Acute Behcet's disease ANCA-Associated Vasculitis AA Amyloidosis Acute Dec Heart Failure Atherosclerosis Autoimmune Disease of Inner Ear CAPS Castleman's Disease Chondrocalcinosis CPPD Crohn's Disease Cytokine Release Syndrome Erdheim-Chester disease Familial Mediterranean fever Graves orbitopathy Gout, refractory Hidradenitis Suppurativa	Kawasaki Disease Macrophage Activation Syndrome Majeed Syndrome Mevalonate kinase deficiency Myocarditis NASH / metabolic syndrome OA / Knee replacement Osteomyelitis Periarthritis of the shoulder Pericarditis PFAPA Syndrome Psoriatic arthritis Rheumatoid Arthritis Schnitzler Syndrome Status Epilepticus Stills Disease Systemic-Onset Juvenile Id. Arthritis Urticarial vasculitis	Acute Severe Colitis Alcoholic Hepatitis All-Cause Mortality ALS Atrial Fibrillation Bursitis Cancer - Lung Cancer - Ovarian Cancer - Prostate Cancer - Renal Cardiovascular Mortality Chronic Fatigue Syndrome CKD Mineral and Bone Disorder Congestive Heart Failure COPD COVID-19 CV Mortality in CKD Diabetes Dry Eye GVHD Hemorrhagic Stroke	Hypertension Ischemic Stroke Lupus Melanoma NOMID Osteoarthritis Peripheral Artery Disease (PAD) Polymyalgia rheumatica Post-MI Recovery / ACS Pulmonary Arterial Hypertension Pyoderma Gangrenosum Schizophrenia Sepsis Sjögren's syndrome Sporadic inclusion body myositis Stroke Prevention Subarachnoid Hemorrhage Systemic Sclerosis / scleroderma Takayasu arteritis Urticaria (Hives)

Genomic or Proteomic Findings

We surveyed the literature to identify diseases where clinical studies or case reports have been made using drugs targeting the inflammasome. We employed Pubmed as a tool for conducting literature search. The results are shown below.

Approach	GWAS / Mendelian Randomization	Mutational Analysis	Transcriptomic / Proteomic Studies
Positive Findings	ALS Alzheimer's Disease Atherosclerosis Asthma Cancer Celiac Disease COPD Focal epilepsy Gout Graves Disease Graves Orbitopathy IBD Kawasaki Disease Lupus Rheumatoid Arthritis Schizophrenia Sickle Cell Anemia sJIA	Atherosclerosis Autoimmune Disease of the Inner Ear CAPS Familial Mediterranean Fever NOMID/CINCA PAAND Sweet Syndrome	Anemia Gout Lupus nephritis Rheumatoid arthritis
Negative Findings	Ankylosing Spondylitis Diabetes Heart Failure Ischemic stroke Metabolic syndrome Multiple sclerosis		Blood pressure Cholesterol

Decode Looked at over 4900 Proteins and their Association with Phenotype



nature genetics

ARTICLES

https://doi.org/10.1038/s41588-021-00978-w

or updates

Large-scale integration of the plasma proteome with genetics and disease

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The plasma proteome can help bridge the gap between the genome and diseases. Here we describe genome-wide association studies (GWASs) of plasma protein levels measured with 4,907 aptamers in 35,559 Icelanders. We found 18,084 associations between sequence variants and levels of proteins in plasma (protein quantitative trait loci; pQTL), of which 19% were with rare variants (minor allele frequency (MAF) < 1%). We tested plasma protein levels for association with 373 diseases and other traits and identified 257,490 associations. We integrated pQTL and genetic associations with diseases and other traits and found that 12% of 45,334 lead associations in the GWAS Catalog are with variants in high linkage disequilibrium with pQTL. We identified 938 genes encoding potential drug targets with variants that influence levels of possible biomarkers. Combining proteomics, genomics and transcriptomics, we provide a valuable resource that can be used to improve understanding of disease pathogenesis and to assist with drug discovery and development.

Decode, a subsidiary of Amgen, published the paper at left in December 2021.

As part of this paper, they looked at the correlation of many blood proteins with phenotypes.

This included many proteins in the innate immune pathway.

Many of these had pQTL's (basically genetic – proteomic – phenotypic) associations that were quite strong.

Source: https://www.nature.com/articles/s41588-021-00978-w

Decode Data on Proteomic Associations With IL1

Phenotypic Associations with IL-1 pathway among the Icelandic people.

Phenotype	Protein	SeqId	Pvalue	Effect (SD)
Rheumatoid Arthritis	IL1RAP	14048_7	2.80E-21	-0.37
Autoimmune Disease	IL1RAP	14048_7	1.00E-13	-0.14
Uric Acid	IL1RN	5353_89	1.70E-265	0.24
Fibromyalgia	IL1RN	5353_89	1.80E-17	0.20
Cholelithiasis	IL1RN	5353_89	9.40E-31	0.26
Gallstones	IL1RN	5353_89	6.00E-26	0.24
Diverticular disease	IL1RN	5353_89	7.50E-09	0.17
Systemic_Lupus_Erythematosus	IL1B	3037_62	1.40E-13	0.61
Anemia	IL1R1	2991_9	2.00E-09	0.32
Depression	IL1RN	5353_89	4.10E-09	0.11
Cancer_All_Types	IL1R1	2991_9	7.40E-43	0.19
Breast_Cancer	IL1RL2	2994_71	6.20E-18	0.19
Gout_Disease	IL1RN	5353_89	2.60E-13	0.39
Metabolic_acidosis	IL1RN	5353_89	1.20E-16	0.19
Alzheimers_disease_or_Dementia	IL1R1	2991_9	1.60E-13	0.15
Dementia_other_than_Alzheimers	IL1RL1	4234_8	1.70E-15	0.20
Breast_Cancer	IL1B	3037_62	3.40E-10	0.14

There is a lot of interesting data here. The incredibly tight p-value on uric acid helps to explain the strong IL-1 / gout linkage. The effect size on gout is also notable.

Perhaps more surprising to us was the high p-value on Cholelithiasis (gallstones) and cancer.

The effect size on lupus is striking as is the effect size on anemia. One normally does not think of anemia as an inflammatory disease.

The links to depression, dementia and Alzehimer's are interesting.

Source: supplementary appendices to https://www.nature.com/articles/s41588-021-00978-w

Disclosure

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